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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – I - SBT1302 – PHARMACEUTICAL BIOTECHNOLOGY

COURSE OUTCOMES;
At the end of the course the student would be able to;

- CO1-Identify the prospects of applying Biotechnological concepts in drug discovery
- CO2-Inspect the kinetics, dynamics of drugs relating to the routes of administration
- CO3-Categorize the unit operation principles involved in the bulk drug manufacturing process
- CO4-Compare the product development of various drug formulations Tablets, Capsules, parentrals, oral liquids and topical applications.
- CO5-Appraise the mode of action of various drugs, laxatives, nonsteroidal contraceptives, antiseptics, antacids, analgesics, vitamins and hormones
- CO6-Elaborate the regulatory aspects involved in preclinical and clinical testing of drugs

Introduction

Development of Drug and Pharmaceutical Industry

The modern era of the pharmaceutical industry—of isolation and purification of compounds, chemical synthesis, and computer-aided drug design—is considered to have begun in the 19th century, thousands of years after intuition and trial and error led humans to believe that plants, animals, and minerals contained medicinal properties. The unification of research in the 20th century in fields such as chemistry and physiology increased the understanding of basic drug-discovery processes. Identifying new drug targets, attaining regulatory approval from government agencies, and refining techniques in drug discovery and development are among the challenges that face the pharmaceutical industry today. The continual evolution and advancement of the pharmaceutical industry is fundamental in the control and elimination of disease around the world.

HISTORY

THE ORIGIN OF MEDICINES

MEDICINES OF ANCIENT CIVILIZATIONS

The oldest records of medicinal preparations made from plants, animals, or minerals are those of the early Chinese, Hindu, and Mediterranean civilizations. An herbal compendium, said to have been written in the 28th century BC by the legendary emperor Shennong, described the antifever capabilities of a substance known as *chang shan* (from the plant species *Dichroa febrifuga*), which has since been shown to contain antimalarial alkaloids (alkaline organic chemicals containing nitrogen). Workers at the school of alchemy that flourished in Alexandria, Egypt, in the 2nd century BC prepared several relatively purified inorganic chemicals, including lead carbonate, arsenic, and mercury. According to *De materia medica*, written by the Greek physician Pedanius Dioscorides in the 1st century AD, verdigris (basic cupric acetate) and cupric sulfate were prescribed as medicinal agents. While attempts were made to use many of the mineral preparations as drugs, most proved to be too toxic to be used in this manner.

Many plant-derived medications employed by the ancients are still in use today. Egyptians treated constipation with senna pods and castor oil and indigestion with peppermint and caraway. Various plants containing digitalis-like compounds (cardiac stimulants) were employed to treat a number of ailments. Ancient Chinese physicians employed ma huang, a plant containing ephedrine,for a variety of purposes. Today

ephedrine is used in many pharmaceutical preparations intended for the treatment of cold and allergy symptoms. The Greek physician Galen (*c.*130–*c.* 200 AD) included opium and squill among the drugs in his apothecary shop (pharmacy). Today derivatives of opium alkaloids are widely employed for pain relief, and, while squill was used for a time as a cardiac stimulant, it is better known as a rat poison. Although many of the medicinal preparations used by Galen are obsolete, he made many important conceptual contributions to modern medicine. For example, he was among the first practitioners to insist on purity for drugs. He also recognized the importance of using the right variety and age of botanical specimens to be used in making drugs.

PHARMACEUTICAL SCIENCE IN THE 16TH AND 17TH CENTURIES

Pharmaceutical science improved markedly in the 16th and 17th centuries. In 1546 the first pharmacopoeia, or collected list of drugs and medicinal chemicals with directions for making pharmaceutical preparations, appeared in Nürnberg, Ger. Previous to this time, medical preparations had varied in concentration and even in constituents. Other pharmacopoeias followed in Basel (1561), Augsburg (1564), and London (1618). The *London Pharmacopoeia* became mandatory for the whole of England and thus became the first example of a national pharmacopoeia. Another important advance was initiated by Paracelsus, a 16th-century Swiss physician-chemist. He admonished his contemporaries not to use chemistry as it had widely been employed prior to his time in the speculative science of alchemy and the making of gold. Instead, Paracelsus advocated the use of chemistry to study the preparation of medicines.

In London the Society of Apothecaries (pharmacists) was founded in 1617. This marked the emergence of pharmacy as a distinct and separate entity. The separation of apothecaries from grocers was authorized by King James I, who also mandated that only a member of the society could keep an apothecary's shop and make or sell pharmaceutical preparations. In 1841 the Pharmaceutical Society of Great Britain was founded. This society oversaw the education and training of pharmacists to assure a scientific basis for the profession. Today professional societies around the world play a prominent role in supervising the education and practice of their members.

In 1783 the English physician and botanist William Withering published his famous monograph on the use of digitalis (an extract from the flowering purple foxglove, *Digitalis purpurea*). His book, *An Account of the Foxglove and Some of Its Medicinal Uses: With Practical Remarks on Dropsy and Other Diseases*, described in detail the use of digitalis

preparations and included suggestions as to how their toxicity might be reduced. Plants containing digitalis-like compounds had been employed by ancient Egyptians thousands of years earlier, but their use had been erratic.

Withering believed that the primary action of digitalis was on the kidney, thereby preventing dropsy (edema). Later, when it was discovered that water was transported in the circulation with blood, it was found that the primary action of digitalis was to improve cardiac performance, with the reduction in edema resulting from improved cardiovascular function. Nevertheless, the observations in Withering's monograph led to a more rational and scientifically based use of digitalis and eventually other drugs.

ISOLATION AND SYNTHESIS OF COMPOUNDS

In the 1800s many important compounds were isolated from plants for the first time. About 1804 the active ingredient, morphine, was isolated from opium. In 1820 quinine (malaria treatment) was isolated from cinchona bark and colchicine (gout treatment) from autumn crocus. In 1833 atropine (variety of uses) was purified from *Atropa belladonna*, and in 1860 cocaine (local anesthetic) was isolated from coca leaves. Isolation and purification of these medicinal compounds was of tremendous importance for several reasons. First, accurate doses of the drugs could be administered, something that had not been possible previously because the plants contained unknown and variable amounts of the active drug. Second, toxic effects due to impurities in the plant products could be eliminated if only the pure active ingredients were used. Finally, knowledge of the chemical structure of pure drugs enabled laboratory synthesis of many structurally related compounds and the development of valuable drugs.

Pain relief has been an important goal of medicine development for millennia. Prior to the mid- 19th century, surgeons took great pride in the speed with which they could complete a surgical procedure. Faster surgery meant that the patient would undergo the excruciating pain for shorter periods of time. In 1842 ether was first employed as an anesthetic during surgery, and chloroform followed soon after in 1847. These agents revolutionized the practice of surgery. After their introduction, careful attention could be paid to prevention of tissue damage, and longer and more-complex surgical procedures could be carried out more safely. Although both ether and chloroform were employed in anesthesia for more than a century, their current use is severely limited by their side effects; ether is very flammable and explosive and chloroform may cause severe

liver toxicity in some patients. However, because pharmaceutical chemists knew the chemical structures of these two anesthetics, they were able to synthesize newer anesthetics, which have many chemical similarities with ether and chloroform but do not burn or cause liver toxicity.

Development of Anti-Infective agents- Discovery of antiseptics and vaccines

Prior to the development of anesthesia, many patients succumbed to the pain and stress of surgery. Many other patients had their wounds become infected and died as a result of their infection. In 1865 the British surgeon and medical scientist Joseph Lister initiated the era of antiseptic surgery in England. While many of the innovations of the antiseptic era are procedural (use of gloves and other sterile procedures), Lister also introduced the use of phenol as an anti-infective agent.

In the prevention of infectious diseases, an even more important innovation took place near the beginning of the 19th century with the introduction of smallpox vaccine. In the late 1790s the English surgeon Edward Jenner observed that milkmaids who had been infected with the relatively benign cowpox virus were protected against the much more deadly smallpox. After this observation he developed an immunization procedure based on the use of crude material from the cowpox lesions. This success was followed in 1885 by the development of rabies vaccine by the French chemist and microbiologist Louis Pasteur. Widespread vaccination programs have dramatically reduced the incidence of many infectious diseases that once were common. Indeed, vaccination programs have eliminated smallpox infections. The virus no longer exists in the wild, and, unless it is reintroduced from caches of smallpox virus held in laboratories in the United States and Russia, smallpox will no longer occur in humans. A similar effort is under way with widespread polio vaccinations; however, it remains unknown whether the vaccines will eliminate polio as a human disease.

IMPROVEMENT IN DRUG ADMINISTRATION

While it may seem obvious today, it was not always clearly understood that medications must be delivered to the diseased tissue in order to be effective. Indeed, at times apothecaries made pills that were designed to be swallowed, pass through the gastrointestinal tract, be retrieved from the stool, and used again. While most drugs are effective and safe when taken orally, some are not reliably absorbed into the body from the gastrointestinal tract and must be delivered by other routes. In the middle of the 17th

century, Richard Lower and Christopher Wren, working at the University of Oxford, demonstrated that drugs could be injected into the bloodstream of dogs using a hollow quill. In 1853 the French surgeon Charles Gabriel Pravaz invented the hollow hypodermic needle, which was first used in the treatment of disease in the same year by Scottish physician Alexander Wood. The hollow hypodermic needle had a tremendous influence on drug administration. Because drugs could be injected directly into the bloodstream, rapid and dependable drug action became more readily producible. Development of the hollow hypodermic needle also led to an understanding that drugs could be administered by multiple routes and was of great significance for the development of the modern science of pharmaceutics, or dosage form development.

NEW CLASSES OF PHARMACEUTICALS

In the latter part of the 19th century a number of important new classes of pharmaceuticals were developed. In 1869 chloral hydrate became the first synthetic sedative-hypnotic (sleep- producing) drug. In 1879 it was discovered that organic nitrates such as nitroglycerin could relax blood vessels, eventually leading to the use of these organic nitrates in the treatment of heart problems. In 1875 several salts of salicylic acid were developed for their antipyretic (fever-reducing) action. Salicylate-like preparations in the form of willow bark extracts (which contain salicin) had been in use for at least 100 years prior to the identification and synthesis of the purified compounds. In 1879 the artificial sweetener saccharin was introduced. In 1886 acetanilide, the first analgesic- antipyretic drug (relieving pain and fever), was introduced, but later, in 1887, it was replaced by the less toxic phenacetin. In 1899 aspirin (acetylsalicylic acid) became the most effective and popular anti-inflammatory, analgesic-antipyretic drug for at least the next 60 years. Cocaine, derived from the coca leaf, was the only known local anesthetic until about 1900, when the synthetic compound benzocaine was introduced. Benzocaine was the first of many local anesthetics with similar chemical structures and led to the synthesis and introduction of a variety of compounds with more efficacy and less toxicity.

TRANSITIONS IN DRUG DISCOVERY

In the late 19th and early 20th centuries, a number of social, cultural, and technical changes of importance to pharmaceutical discovery, development, and manufacturing

were taking place. One of the most important changes occurred when universities began to encourage their faculties to form a more coherent understanding of existing information. Some chemists developed new and improved ways to separate chemicals from minerals, plants, and animals, while others developed ways to synthesize novel compounds. Biologists did research to improve understanding of the processes fundamental to life in species of microbes, plants, and animals. Developments in science were happening at a greatly accelerated rate, and the way in which pharmacists and physicians were educated changed. Prior to this transformation the primary means of educating physicians and pharmacists had been through apprenticeships. While apprenticeship teaching remained important to the education process (in the form of clerkships, internships, and residencies), pharmacy and medical schools began to create science departments and hire faculty to teach students the new information in basic biology and chemistry. New faculty was expected to carry out research or scholarship of their own. With the rapid advances in chemical separations and synthesis, single pharmacists did not have the skills and resources to make the newer, chemically pure drugs. Instead, large chemical and pharmaceutical companies began to appear and employed university-trained scientists equipped with knowledge of the latest technologies and information in their fields.

As the 20th century progressed, the benefits of medical, chemical, and biological research began to be appreciated by the general public and by politicians, prompting governments to develop mechanisms to provide support for university research. In the United States, for instance, the National Institutes of Health, the National Science Foundation, the Department of Agriculture, and many other agencies undertook their own research or supported research and discovery at universities that could then be used for pharmaceutical development. Nonprofit organizations were also developed to support research, including the Australian Heart Foundation, the American Heart Association, the Heart and Stroke Foundation of Canada, and H.E.A.R.T UK. The symbiotic relationship between large public institutions carrying out fundamental research and private companies making use of the new knowledge to develop and produce new pharmaceutical products has contributed greatly to the advancement of medicine.

DISCOVERY OF PENICILLIN

The first description of penicillin was published in 1929 by the Scottish bacteriologist Alexander Fleming. Fleming had been studying staphylococcal bacteria in the laboratory at St. Mary's Hospital in London. He noticed that a mold had contaminated one of his cultures, causing the bacteria in its vicinity to undergo lysis (membrane rupture) and die. Since the mold was from the genus *Penicillium*, Fleming named the active antibacterial substance penicillin. At first the significance of Fleming's discovery was not widely recognized. It was more than 10 years later before British biochemist Ernst Boris Chain and Australian pathologist Howard Florey, working at the University of Oxford, showed that a crude penicillin preparation produced a dramatic curative effect when administered to mice with streptococcal infections.

The production of large quantities of penicillin was difficult with the facilities available to the investigators. However, by 1941 they had enough penicillin to carry out a clinical trial in several patients with severe staphylococcal and streptococcal infections. The effects of penicillin were remarkable, although there was not enough drug available to save the lives of all the patients in the trial.

In an effort to develop large quantities of penicillin, the collaboration of scientists at the United States Department of Agriculture's Northern Regional Research Laboratories in Peoria, Ill., was enlisted. The laboratories in Peoria had large fermentation vats that could be used in an attempt to grow an abundance of the mold. In England the first penicillin had been produced by growing the *Penicillium notatum* mold in small containers. However, *P. notatum* would not grow well in the large fermentation vats

available in Peoria, so scientists from the laboratories searched for another strain of *Penicillium*. Eventually a strain of *Penicillium chrysogenum* that had been isolated from an overripe cantaloupe was found to grow very well in the deep culture vats. After the process of growing the penicillin-producing organisms was developed, pharmaceutical firms were recruited to further develop and market the drug for clinical use. The use of penicillin very quickly revolutionized the treatment of serious bacterial infections. The discovery, development, and marketing of penicillin provides an excellent example of the beneficial collaborative interaction of not-for-profit researchers and the pharmaceutical industry.

ISOLATION OF INSULIN

The vast majority of hormones were identified, had their biological activity defined, and were synthesized in the first half of the 20th century. Illnesses relating to their excess or deficiency were also beginning to be understood at that time. Hormones, produced in specific organs, released into the circulation, and carried to other organs, significantly affect metabolism and homeostasis. Some examples of hormones are insulin (from the pancreas), epinephrine (or adrenaline; from the adrenal medulla), thyroxine (from the thyroid gland), cortisol (from the adrenal cortex), estrogen (from the ovaries), and testosterone (from the testes). As a result of discovering these hormones and their mechanisms of action in the body, it became possible to treat illnesses of deficiency or excess effectively. The discovery and use of insulin to treat diabetes is an example of these developments.

In 1869 Paul Langerhans, a medical student in Germany, was studying the histology of the pancreas. He noted that this organ has two distinct types of cells—acinar cells, now known to secrete digestive enzymes, and islet cells (now called islets of Langerhans). The function of islet cells was suggested in 1889 when German physiologist and pathologist Oskar Minkowski and German physician Joseph von Mering showed that removing the pancreas from a dog caused the animal to exhibit a disorder quite similar to human diabetes mellitus (elevated blood glucose and metabolic changes). After this discovery, a number of scientists in various parts of the world attempted to extract the active substance from the pancreas so that it could be used to treat diabetes. We now know that these attempts were largely unsuccessful because the digestive enzymes present in the acinar cells metabolized the insulin from the islet cells when the pancreas was disrupted.

One of the first successful attempts to isolate the active substance was reported in 1921 by Romanian physiologist Nicolas C. Paulescu, who discovered a substance called pancrein in pancreatic extracts from dogs. Paulescu found that diabetic dogs given an injection of pancrein experienced a temporary decrease in blood glucose levels. Although he did not purify pancrein, it is thought that the substance was insulin. That same year, working independently, Frederick Banting, a young Canadian surgeon in Toronto, persuaded a physiology professor to allow him use of a laboratory to search for the active substance from the pancreas. Banting guessed correctly that the islet cells secreted insulin, which was destroyed by enzymes from the acinar cells. By this time Banting had enlisted the support of Charles H. Best, a fourth-year medical student. Together they tied off the pancreatic ducts through which acinar cells release the digestive enzymes. This insult caused the acinar cells to die. Subsequently, the remainder of the pancreas was homogenized and extracted with ethyl alcohol and acid. The extract thus obtained decreased blood glucose levels in dogs with a form of diabetes. Banting and Best worked with Canadian chemist James B. Collip and Scottish physiologist J.J.R. Macleod to obtain purified insulin, and shortly thereafter, in 1922, a 14-year-old boy with severe diabetes was the first human to be treated successfully with the pancreatic extracts.

After this success other scientists became involved in the quest to develop large quantities of purified insulin extracts. Eventually, extracts from pig and cow pancreases created a sufficient and reliable supply of insulin. For the next 50 years most of the insulin used to treat diabetes was extracted from porcine and bovine sources. There are only slight differences in chemical structure between bovine, porcine, and human insulin, and their hormonal activities are essentially equivalent. Today, as a result of recombinant DNA technology, most of the insulin used in therapy is synthesized by pharmaceutical companies and is identical to human insulin.

IDENTIFICATION OF VITAMINS

Vitamins are organic compounds that are necessary for body metabolism and, generally, must be provided from the diet. For centuries many diseases of dietary deficiency had been recognized, although not well defined. Most of the vitamin deficiency disorders were biochemically and physiologically defined in the late 19th and early 20th centuries. The discovery of thiamin (vitamin B_1) exemplifies how vitamin deficiencies and their treatment were discovered.

Thiamin deficiency produces beriberi, a word from the Sinhalese meaning "extreme weakness." The symptoms include spasms and rigidity of the legs, possible paralysis of a limb, personality disturbances, and depression. This disease became widespread in Asia in the 19th century because steam-powered rice mills produced polished rice, which lacked the vitamin-rich husk. A dietary deficiency was first suggested as the cause of beriberi in 1880 when a new diet was instituted for the Japanese navy. When fish, meat, barley, and vegetables were added to the sailor's diet of polished rice, the incidence of beriberi in the navy was significantly reduced. In 1897 the Dutch physician Christiaan Eijkman was working in Java when he showed that fowl fed a diet of polished rice developed symptoms similar to beriberi. He was also able to demonstrate that unpolished rice in the diet prevented and cured the symptoms in fowl and humans. By 1912 a highly concentrated extract of the active ingredient was prepared by the Polish biochemist Casimir Funk, who recognized that it belonged to a new class of essential foods called vitamins. Thiamin was isolated in 1926 and its chemical structure determined in 1936. The chemical structures of the other vitamins were determined prior to 1940.

EMERGENCE OF MODERN DISEASES AND TREATMENT

The rapid decline in the number of deaths from infections due to the development of vaccines and antibiotics led to the unveiling of a new list of deadly diseases in the industrialized world during the second half of the 20th century. Included in this list are cardiovascular disease, cancer, and stroke. While these remain the three leading causes of death today, a great deal of progress in decreasing mortality and disability caused by these diseases has been made since the 1940s. As with treatment of any complex disease, there are many events of importance in the development of effective therapy. For decreasing death and disability from cardiovascular diseases and stroke, one of the most important developments was the discovery of effective treatments for hypertension (high blood pressure)—i.e., the discovery of thiazide diuretics. For decreasing death and disability from cancer, one very important step was the development of cancer chemotherapy.

HYPERTENSION

Hypertension has been labeled the "silent killer." It usually has minimal or no symptoms and typically is not regarded as a primary cause of death. Untreated hypertension increases the incidence and severity of cardiovascular diseases and stroke. Before 1950 there were no effective treatments for hypertension. U.S. Pres.Franklin D. Roosevelt died

after a stroke in 1945, despite a large effort by his physicians to control his very high blood pressure by prescribing sedatives and rest.

When sulfanilamide was introduced into therapy, one of the side effects it produced was metabolic acidosis (acid-base imbalance). After further study, it was learned that the acidosis was caused by inhibition of the enzyme carbonic anhydrase. Inhibition of carbonic anhydrase produces diuresis (urine formation). Subsequently, many sulfanilamide-like compounds were synthesized and screened for their ability to inhibit carbonic anhydrase. Acetazolamide, which was developed by scientists at Lederle Laboratories (now a part of Wyeth Pharmaceuticals, Inc.), became the first of a class of diuretics that serve as carbonic anhydrase inhibitors. In an attempt to produce a carbonic anhydrase inhibitor more effective than acetazolamide,chlorothiazide was synthesized by a team of scientists led by Dr. Karl Henry Beyer at Merck & Co., Inc., and became the first successful thiazide diuretic. While acetazolamide causes diuresis by increasing sodium bicarbonate excretion, chlorothiazide was found to increase sodium chloride excretion. More importantly, by the mid-1950s it had been shown that chlorothiazide lowers blood pressure in patients with hypertension. Over the next 50 years many other classes of drugs that lower blood pressure (antihypertensive drugs) were added to the physician's armamentarium for treatment of hypertension. Partially as a result of effective treatment of this disease, the death rate from cardiovascular diseases and stroke decreased dramatically during this period.

The discovery of chlorothiazide exemplifies two important pathways to effective drug development. The first is screening for a biological effect. Thousands of drugs have been developed through effective screening for a biological activity. The second pathway is serendipity—i.e., making fortunate discoveries by chance. While creating experiments that can lead to chance outcomes does not require particular scientific skill, recognizing the importance of accidental discoveries is one of the hallmarks of sound science. Many authorities doubt that Fleming was the first scientist to notice that when agar plates were contaminated with *Penicillium* mold, bacteria did not grow near the mold. However, what made Fleming great was that he was the first to recognize the importance of what he had seen. In the case of chlorothiazide, it was serendipitous that sulfanilamide was found to cause metabolic acidosis, and it was serendipitous that chlorothiazide was recognized to cause sodium chloride excretion and an antihypertensive effect.

EARLY PROGRESS IN CANCER DRUG DEVELOPMENT

Sulfur mustard was synthesized in 1854. By the late 1880s it was recognized that sulfur mustard could cause blistering of the skin, eye irritation possibly leading to blindness, and severe lung injury if inhaled. In 1917 during World War I, sulfur mustard was first used as a chemical weapon. By 1919 it was realized that exposure to sulfur mustard also produced very serious systemic toxicities. Among other effects, it caused leukopenia (decreased white blood cells) and damage to bone marrow and lymphoid tissue. During the interval between World War I and World War II there was extensive research into the biological and chemical effects of nitrogen mustards (chemical analogs of sulfur mustard) and similar chemical-warfare compounds. The toxicity of nitrogen mustard on lymphoid tissue caused researchers to study the effect of nitrogen mustard on lymphomas in mice. In the early 1940s nitrogen mustard (mechlorethamine) was discovered to be effective in the treatment of human lymphomas. The efficacy of this treatment led to the widespread realization that chemotherapy for cancer could be effective. In turn, this realization led to extensive research, discovery, and development of other cancer chemotherapeutic agents.

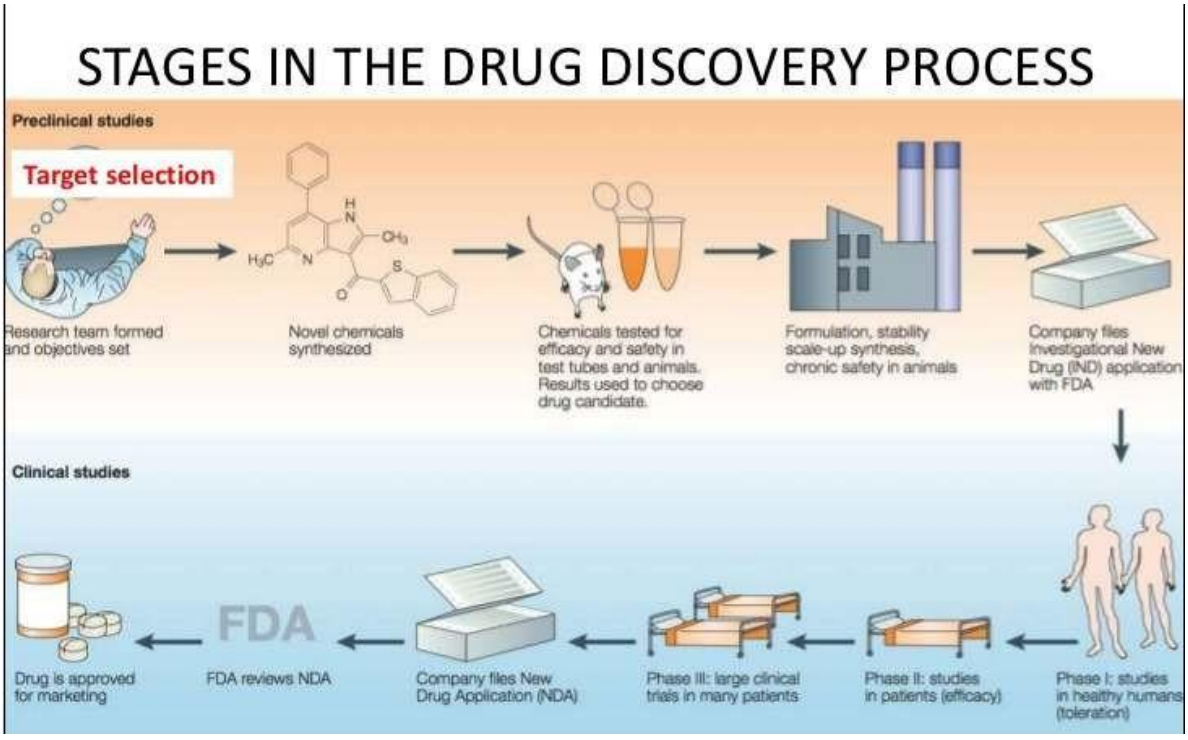
PHARMACEUTICAL INDUSTRY IN THE MODERN ERA

The pharmaceutical industry has become a large and very complex enterprise. At the end of the 20th century, most of the world's largest pharmaceutical companies were located in North America, Europe, and Japan; many of the largest were multinational, having research, manufacturing, and sales taking place in multiple countries. Since pharmaceuticals can be quite profitable, many countries are trying to develop the infrastructure necessary for drug companies in their countries to become larger and to compete on a worldwide scale. The industry has also come to be characterized by outsourcing. That is, many companies contract with specialty manufacturers or research firms to carry out parts of the drug development process for them. Others try to retain most of the processes within their own company. Since the pharmaceutical industry is driven largely by profits and competition—each company striving to be the first to find cures for specific diseases—it is anticipated that the industry will continue to change and evolve over time.

DRUG DISCOVERY & DEVELOPMENT

INTRODUCTION

New drugs begin in the laboratory with scientists, including chemists and pharmacologists, who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects. Out of every 5,000 new compounds identified during the discovery process, approximately five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds on average is ultimately approved as a marketed drug for treatment. The following sequence of research activities begins the process that results in development of new medicines:



- Target Identification. Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Scientists use a variety of techniques to identify and isolate individual targets to learn more about their functions and how they influence disease. Compounds are then identified that have various interactions with the drug targets that might be helpful in treatment of a specific disease.

- Target Prioritization/Validation. To select targets most likely to be useful in the development of new treatments for disease, researchers analyze and compare each drug target to others based on their association with a specific disease and their ability to regulate biological and chemical compounds in the body. Tests are conducted to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells. Research scientists can then identify compounds that have an effect on the target selected.

- Lead Identification. A lead compound or substance is one that is believed to have potential to treat disease. Laboratory scientists can compare known substances with new compounds to determine their likelihood of success. Leads are sometimes developed as collections, or libraries, of individual molecules that possess properties needed in a new drug. Testing is then done on each of these molecules to confirm its effect on the drug target.

- Lead Optimization. Lead optimization compares the properties of various lead compounds and provides information to help biopharmaceutical companies select the compound or compounds with the greatest potential to be developed into safe and effective medicines. Often during this same stage of development, lead prioritization studies are conducted in living organisms (*in vivo*) and in cells in the test tube (*in vitro*) to compare various lead compounds and how they are metabolized and affect the body.

  In the preclinical stage of drug development, an investigational drug must be tested extensively in the laboratory to ensure it will be safe to administer to humans. Testing at this stage can take from one to five years and must provide information about the pharmaceutical composition of the drug, its safety, how the drug will be formulated and manufactured, and how it will be administered to the first human subjects.

- Preclinical Technology. During the preclinical development of a drug, laboratory tests document the effect of the investigational drug in living organisms (*in vivo*) and in cells in the test tube (*in vitro*).

- Chemistry Manufacturing and Controls (CMC)/Pharmaceutics. The results of preclinical testing are used by experts in pharmaceutical methods to determine how to best formulate the drug for its intended clinical use. For example, a drug that is intended to act on the sinuses may be formulated as a time-release capsule or as a nasal spray. Regulatory agencies require testing that documents the characteristics -- chemical composition, purity, quality and potency -- of the drug's active ingredient and of the formulated drug.

- Pharmacology/Toxicology. Pharmacological testing determines effects of the candidate drug on the body. Toxicology studies are conducted to identify potential risks to humans.

  The results of all testing must be provided to the Food and Drug Administration (FDA) and/or other appropriate regulatory agencies to obtain permission to begin clinical testing in humans. Regulatory agencies review the specific tests and documentation required to proceed to the next stage of development. Testing of an investigational new drug begins with submission of information about the drug and application for permission to begin administration to healthy volunteers or patients.

- Investigational New Drug (IND)/Clinical Trial Exception (CTX)/Clinical Trial Authorization (CTA) Applications. INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed.

  In addition to obtaining permission from appropriate regulatory authorities, an institutional or independent review board (IRB) or ethical advisory board must approve the protocol for testing, as well as the informed consent documents that volunteers sign prior to participating in a clinical study. An IRB is an independent committee of physicians, community advocates and others that ensures a clinical trial is ethical and the rights of study participants are protected.

  Clinical testing is usually described as consisting of Phase I, Phase II and Phase III clinical studies. In each successive phase, increasing numbers of patients are tested.

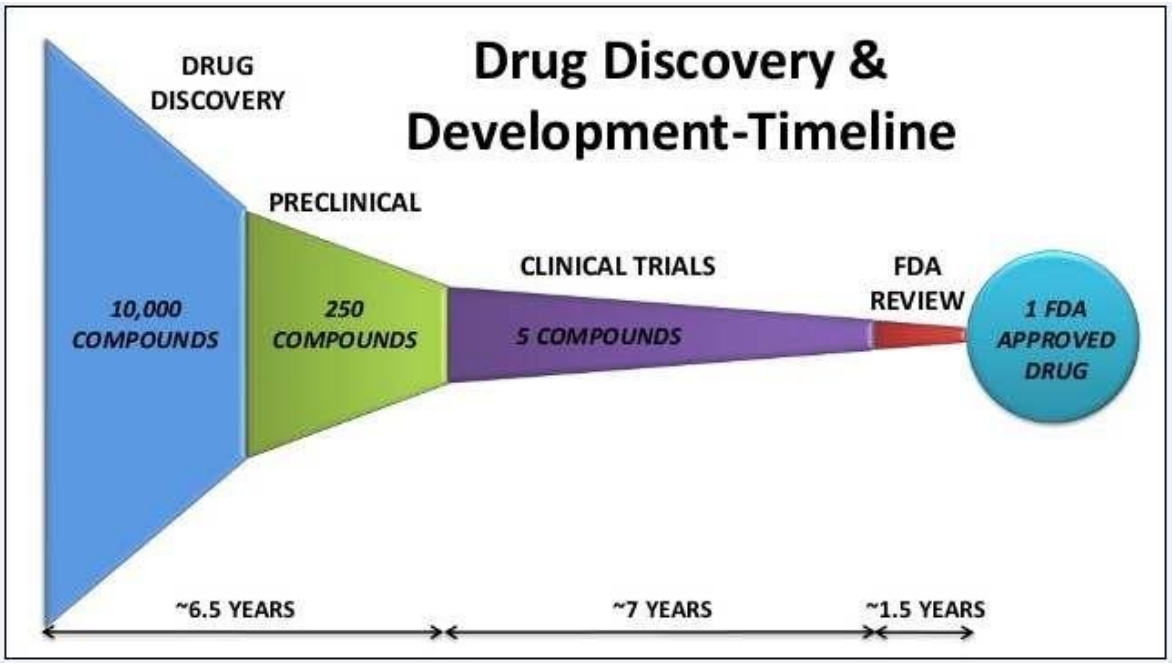
- Phase I Clinical Studies. Phase I studies are designed to verify safety and tolerability of the candidate drug in humans and typically take six to nine months. These are the first studies conducted in humans. A small number of subjects, usually from 20 to 100 healthy volunteers, take the investigational drug for short periods of time. Testing includes observation and careful documentation of how the drug acts in the body -- how it is absorbed, distributed, metabolized and excreted.
- Phase II Clinical Studies. Phase II studies are designed to determine effectiveness and further study the safety of the candidate drug in humans. Depending upon the type of investigational drug and the condition it treats, this phase of development generally takes from six months to three years. Testing is conducted with up to several hundred patients suffering from the condition the investigational drug is designed to treat. This testing determines safety and effectiveness of the drug in treating the condition and establishes the minimum and maximum effective dose. Most Phase II clinical trials are randomized, or randomly divided into groups, one of which receives the investigational drug, one of which gets a placebo containing no medication and sometimes a third group that receives a current standard treatment to which the new investigational drug will be compared. In addition, most Phase II studies are double-blinded, meaning that neither patients nor researchers evaluating the compound know who is receiving the investigational drug or placebo.
- Phase III Clinical Studies. Phase III studies provide expanded testing of effectiveness and safety of an investigational drug, usually in randomized and blinded clinical trials. Depending on the type of drug candidate and the condition it treats, this phase usually requires one to four years of testing. In Phase III, safety and efficacy testing is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats.
- New Drug Application (NDA)/Marketing Authorization Application (MAA)NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such applications document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities in other countries. The application must present substantial evidence that the drug will have

the effect it is represented to have when people use it or under the conditions for which it is prescribed, recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes six months to two years.

After the FDA (or other regulatory agency for drugs marketed outside the U.S.) approves a new drug, pharmaceutical companies may conduct additional studies, including Phase IIIb and Phase IV studies. Late-stage drug development studies of approved, marketed drugs may continue for several months to several years.

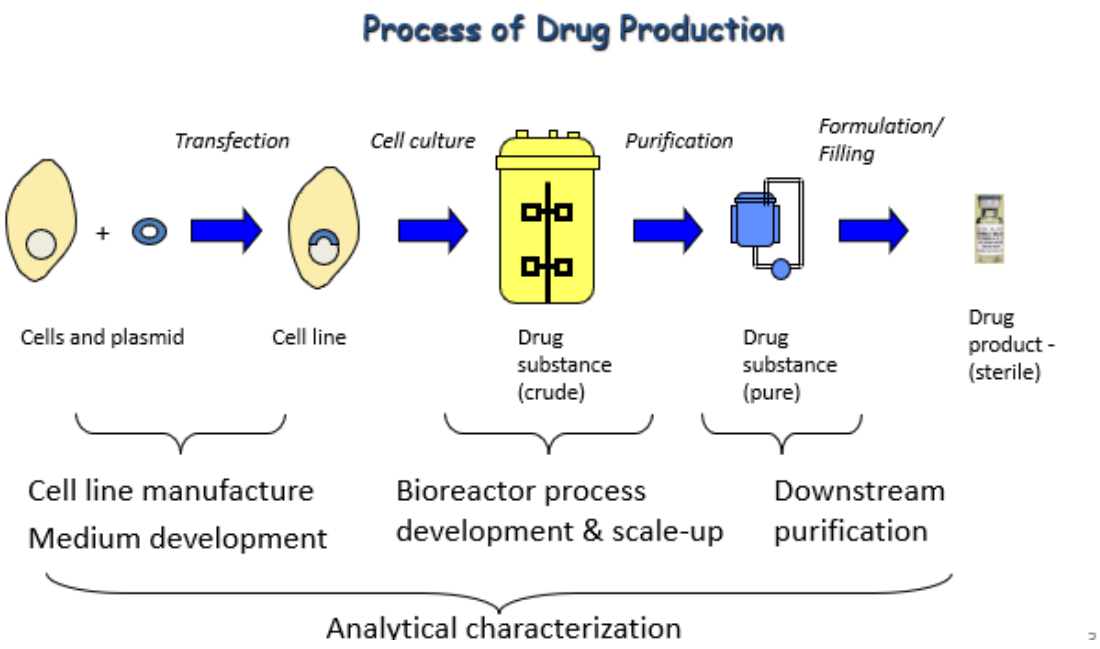
- Phase IIIb/IV Studies. Phase IIIb trials, which often begin before approval, may supplement or complete earlier trials by providing additional safety data or they may test the approved drug for additional conditions for which it may prove useful. Phase IV studies expand testing of a proven drug to broader patient populations and compare the long-term effectiveness and/or cost of the drug to other marketed drugs available to treat the same condition.

- Post-Approval Studies. Post-approval studies test a marketed drug in new age groups or patient types. Some studies focus on previously unknown side effects or related risk factors. As with all stages of drug development testing, the purpose is to ensure the safety and effectiveness of marketed drugs.



THERAPEUTIC AGENTS

- Before the advent of molecular biotechnology most **human proteins** were available in only **small** (limited) quantities.
- Today hundreds of genes (~1000) for human proteins have been cloned, sequenced, expressed in the host cells and are being tested as therapeutic agents (drugs) in humans.
- Over 140 biopharmaceuticals on the market; over 400 in clinical trials
- Biopharmaceuticals include:
  - Proteins (made in bacterial, fungal or mammalian cell culture)
    - erythropoietin (EPO)
    - insulin
    - interferon (Intron A)
    - granulocyte-colony stimulating factor (G-CSF)
    - human growth hormone (HGH, human somatotropin)
    - tissue plasminogen activator (tPA)
  - Monoclonal antibodies (made in mammalian cell culture)
  - Vaccines
    - live and inactivated viruses and bacteria
    - subunit vaccines
    - recombinant vaccines
  - Gene Therapy Products (viral and non-viral)



RECOMBINANT PROTEINS

INTERFERONS

Scientists discovered an antiviral protein in 1957 that inhibited growth of influenza virus in chicken embryos. It was named interferon because it interfered with the growth of influenza virus.

- Anti viral proteins released by host cells (part of the immune system)
- Interfere with viral multiplication
- Host cell specific but not virus specific

Different types of cells in animals produce different interferons

- 3 types of human interferon:
  - alpha interferon (13 genes)
  - beta interferon (2 genes)
  - gamma interferon (1 gene)
  - Alpha & beta usually produced early in viral infections (viruses or viral RNA) - Gamma appears later

-> Presence of double-stranded RNA indicates cell is infected

Viral infected cells release alpha and beta interferons

Diffuse to neighboring cells -> Virus can't replicate

Human Interferons -> to fight viral infections

Interferon therapy

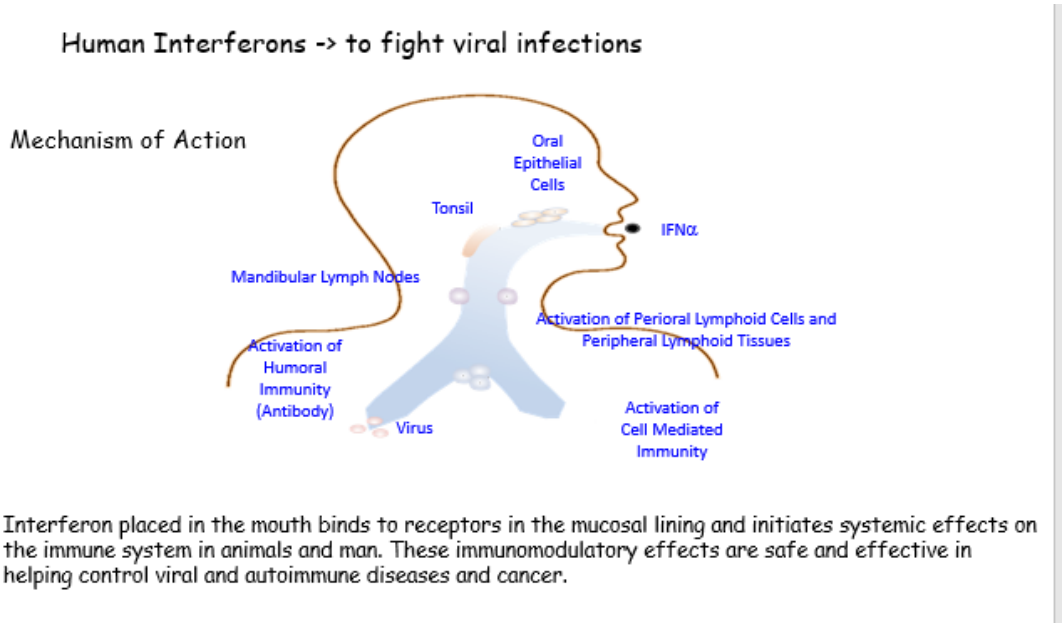
Limited lifetime, short lasting effect

Recombinant interferons

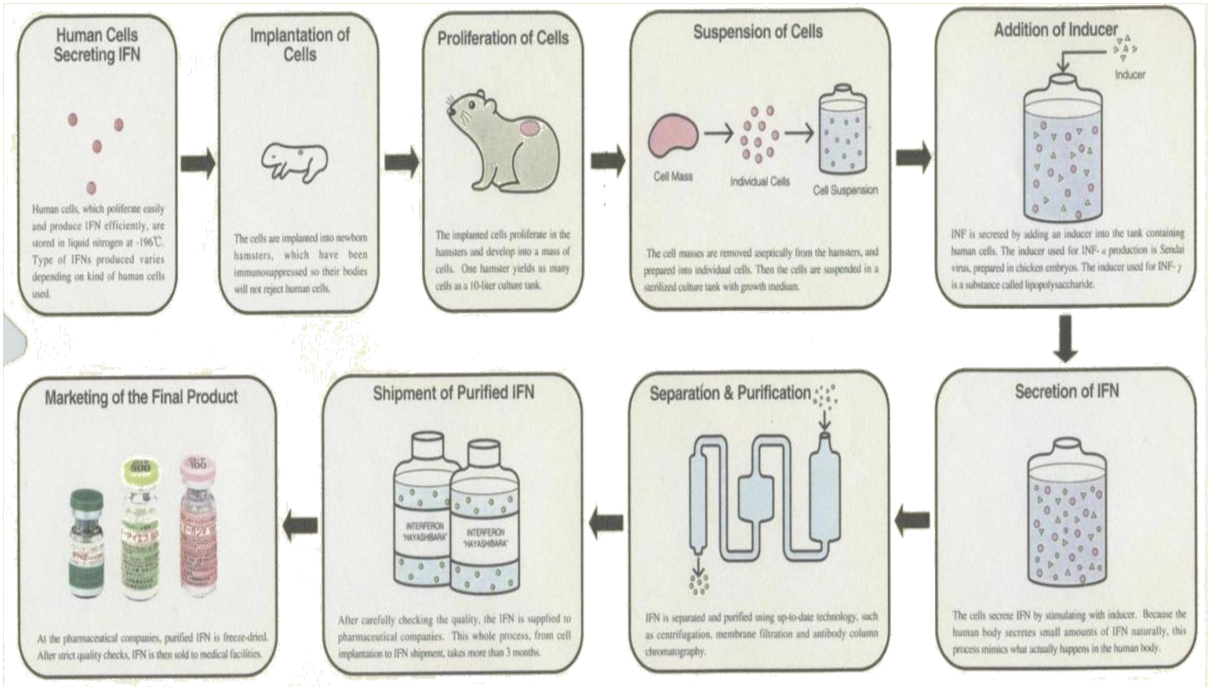
- Pure and fast
- Hybrid genes for enhanced/new activity
- Oral administration

Injectable interferon (beta) is approved world-wide (FDA) for the treatment of various cancers and viral diseases.Interferon is a protein readily eliminated from the blood by the kidney. To counteract the kidney's clearance of interferon from the blood injectable interferon must be given in doses much higher than what occur naturally. Side effects include flu-like symptoms, poor results on liver function tests, and blood cell abnormalities. More serious side effects include depression, epileptic seizures, or liver problems.

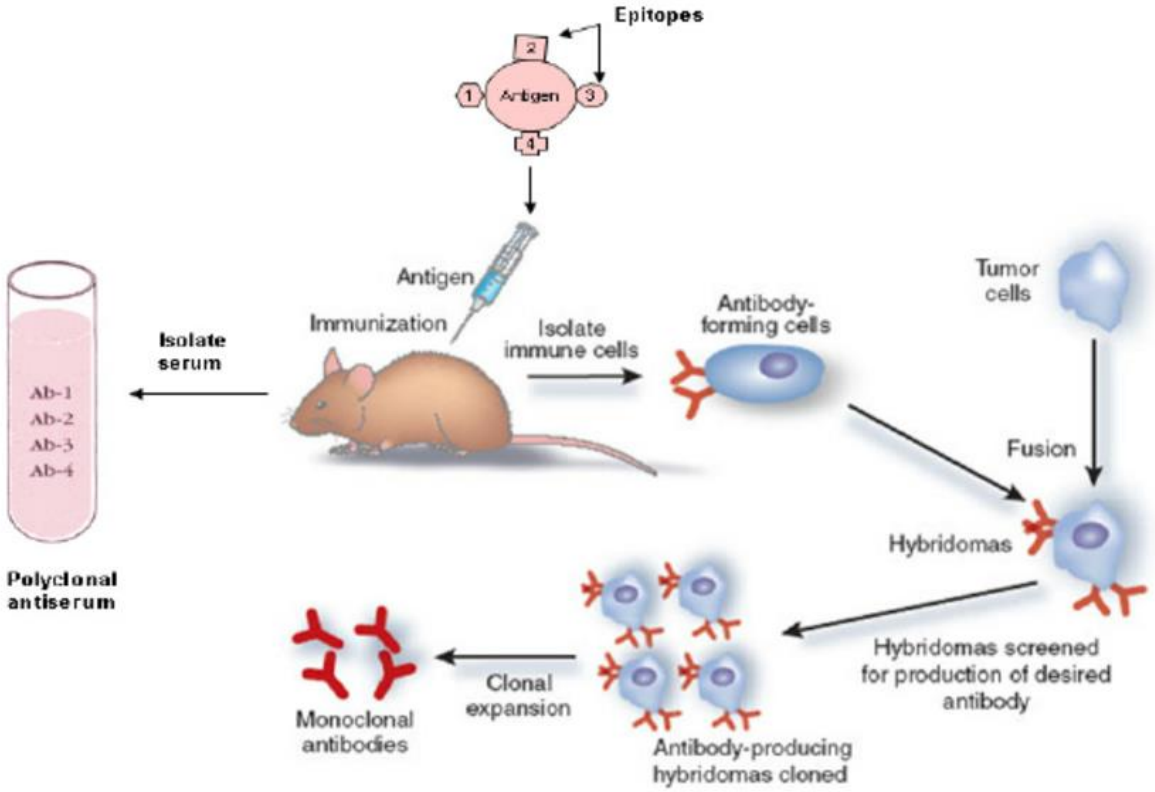
Low-dose oral interferon is given in doses 10 thousand times less than injectable interferon. Therefore, side effects are dramatically reduced.Oral interferon is human interferon alpha administered in a small tablet (lozenge) to humans or in powder to animals.Oral interferon binds to surface (mucosal) cells in the mouth and throat resulting in stimulation of white blood cells and activates hundreds of genes affecting the immune system in the peripheral blood of man, cattle and mice.Studies show oral interferon is effective against disorders such as cancer, viral diseases and autoimmunity.



Manufacturing steps for interferon



MONOCLONAL ANTIBODY



Clinical applications- Examples

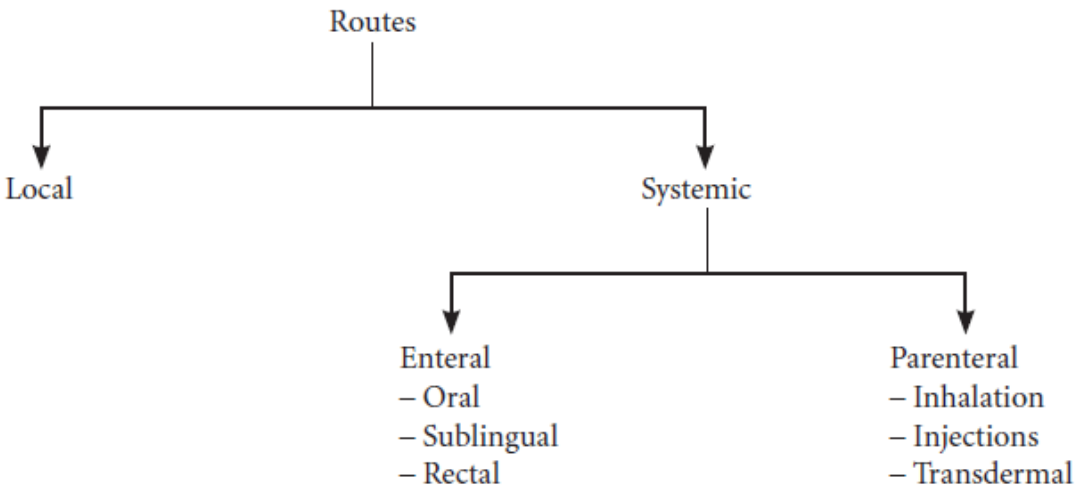
- Transplantation – muronomab (OKT3) 1986, basiliximab 1998
- Cardiovascular disease – abciximab 1994
- Cancer – rituximab 1997, trastuzumab 1998
- Viral infection – palivizumab 1998
- Inflammatory diseases – infliximab 1998, etanercept 1999

ROUTES OF DRUG ADMINISTRATION

Most of the drugs can be administered by different routes. Drug- and patient-related factors determine

the selection of routes for drug administration. The factors are:

1. Characteristics of the drug.
2. Emergency/routine use.
3. Site of action of the drug—local or systemic.
4. Condition of the patient (unconscious, vomiting, diarrhoea).
5. Age of the patient.
6. Effect of gastric pH, digestive enzymes and fi rst-pass metabolism.
7. Patient's/doctor's choice (sometimes).



ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – II - SBT1302 – PHARMACEUTICAL BIOTECHNOLOGY

COURSE OUTCOMES;

At the end of the course the student would be able to;

- CO1-Identify the prospects of applying Biotechnological concepts in drug discovery
- CO2-Inspect the kinetics, dynamics of drugs relating to the routes of administration
- CO3-Categorize the unit operation principles involved in the bulk drug manufacturing process
- CO4-Compare the product development of various drug formulations Tablets, Capsules, parentrals, oral liquids and topical applications.
- CO5-Appraise the mode of action of various drugs, laxatives, nonsteroidal contraceptives, antiseptics, antacids, analgesics, vitamins and hormones
- CO6-Elaborate the regulatory aspects involved in preclinical and clinical testing of drugs

DRUG ABSORPTION, DISTRIBUTION AND ELIMINATION PHARMACOKINETICS

DRUG ADMINISTRATION

Often the goal is to attain a therapeutic drug concentration in plasma from which drug enters the tissue (therapeutic window between toxic concentration and minimal effective concentration).

A. Enteral Routes

1. Sublingual (buccal)

Certain drugs are best given beneath the tongue or retained in the cheek pouch and are absorbed from these regions into the local circulation. These vascular areas are ideal for lipid-soluble drugs that would be metabolized in the gut or liver, since the blood vessels in the mouth bypass the liver (do not undergo first pass liver metabolism), and drain directly into the systemic circulation. This route is usually reserved for nitrates and certain hormones.

2. Oral

By far the most common route. The passage of drug from the gut into the blood is influenced by biologic and physicochemical factors and by the dosage form. For most drugs, two- to five-fold differences in the rate or extent of gastrointestinal absorption can occur,depending on the dosage form. These two characteristics, rate and completeness of absorption, comprise bioavailability. Generally, the bioavailability of oral drugs follows the order: solution > suspension > capsule > tablet > coated tablet.

3. Rectal

The administration of suppositories is usually reserved for situations in which oral administration is difficult. This route is more frequently used in small children. The rectum is devoid of villi; thus, absorption is often slow.

B. Parenteral Routes

1. Intravenous injection

Used when a rapid clinical response is necessary, e.g., an acute asthmatic episode. This route allows one to achieve relatively precise drug concentrations in the plasma, since bioavailability is not a concern. Most drugs should be injected over 1-2 minutes in order to prevent the occurrence of very high drug concentrations in the injected vein, possibly causing adverse

effects. Some drugs, particularly those with narrow therapeutic indices or short half-lives, are best administered as a slow IV infusion or drip.

2. Intra-arterial injection

Used in certain special situations, notably with anticancer drugs, in an effort to deliver a high concentration of drug to a particular tissue. Typically, the injected artery leads directly to the target organ.

3. Intrathecal injection

The blood-brain barrier limits the entry of many drugs into cerebrospinal fluid. Under some circumstances, usually life-threatening, antibiotics, antifungals and anticancer drugs are given via lumbar puncture and injection into the subarachnoid space.

4. Intramuscular injection

Drugs may be injected into the arm (deltoid), thigh (vastus lateralis) or buttocks (gluteus maximus). Because of differences in vascularity, the rates of absorption differ, with arm > thigh > buttocks. Drug absorption may be slow and erratic. The volume of injection, osmolality of the solution, lipid solubility and degree of ionization influence absorption. It should not be assumed that the IM route is as reliable as the IV route.

5. Subcutaneous injection

Some drugs, notably insulin, are routinely administered SC. Drug absorption is generally slower SC than IM, due to poorer vascularity. Absorption can be facilitated by heat, massage or vasodilators. It can be slowed by coadministration of vasoconstrictors, a practice commonly used to prolong the local action of local anesthetics. As above, arm > thigh.

6. Inhalation

Volatile anesthetics, as well as many drugs which affect pulmonary function, are administered as aerosols. Other obvious examples include nicotine and tetrahydrocannabinol (THC), which are absorbed following inhalation of tobacco or marijuana smoke. The large alveolar area and blood supply lead to rapid absorption into the blood. Drugs administered via this route are not subject to first-pass liver metabolism.

7. Topical application

a. Eye

For desired local effects.

b. Intravaginal

For infections or contraceptives.

c. Intranasal

For alleviation of local symptoms.

d. Skin

Topical drug administration for skin disorders minimizes systemic exposure. However, systemic absorption does occur and varies with the area, site, drug, and state of the skin. Dimethyl sulfoxide (DMSO) enhances the percutaneous absorption of many drugs, but its use is controversial because of concerns about its toxicity.

e. Drug patches (drug enters systemic circulation by zero order kinetics – a constant amount of drug enters the circulation per unit time).

DRUG ABSORPTION

A. Biologic Factors

1. Membrane structure and function

The cell membrane is a semipermeable lipoid sieve containing numerous aqueous channels, as well as a variety of specialized carrier molecules.

a. For most tissues, passive aqueous diffusion through channels occurs only for molecules less than 150-200 MW. A notable exception is the endothelial capillary lining, whose relatively large pores allow molecules of 20-30,000 to pass. However, the capillaries of most of the brain lack these large pores.

b. Passive lipid diffusion is probably the most important absorptive mechanism. Lipid-soluble drugs dissolve in the membrane, and are driven through by a concentration gradient across the membrane.

c. Carrier-mediated facilitated transport occurs for some drugs, particularly those which are analogs of endogenous compounds for which there already exist specific membrane carrier systems. For example, methotrexate, an anticancer drug which is structurally similar to folic acid, is actively transported by the folate membrane transport system.

2. Local blood flow is a strong determinant of the rate of absorption because it continuously maintains the concentration gradient necessary for passive diffusion to occur. For orally administered drugs, remember that the blood supply draining the gut passes through the liver before reaching the systemic circulation. Since the liver is a major site of drug metabolism, this first-pass effect may reduce the amount of drug reaching the target tissue. In some cases, the first-pass effect results in metabolic activation of an inert pro-drug.

3. Gastric emptying times vary among patients and contribute significantly to intersubjective variability in drug absorption.

4. Drug binding

Many drugs will bind strongly to proteins in the blood or to food substances in the gut. Binding to plasma proteins will increase the rate of passive absorption by maintaining the concentration gradient of free drug. For many drugs, the gastrointestinal absorption rate, but not the extent of absorption, is reduced by the presence of food in the gut. Some drugs are not affected by food, while the absorption of a third group of drugs is enhanced by food (bile secretion by liver in response to food in GI tract increases drug absorption). Some drugs are irritating and should be administered with meals to reduce adverse effects.

DRUG DISTRIBUTION

Once in the blood, drugs are simultaneously distributed throughout the body and eliminated. Typically, distribution is much more rapid than elimination, is accomplished via the circulation, and is influenced by regional blood flow.

A. Compartments

1. Central Compartment

The central compartment includes the well-perfused organs and tissues (heart, blood, liver, brain and kidney) with which drug equilibrates rapidly.

2. Peripheral Compartment(s)

The peripheral compartment(s) include(s) those organs (e.g., adipose and skeletal muscle) which are less well-perfused, and with which drug therefore equilibrates more slowly. Redistribution from one compartment to another often alters the duration of effect at the target tissue. For example, thiopental, a highly lipid-soluble drug, induces anaesthesia within seconds because of rapid equilibration between blood and brain. Despite the fact that the drug is slowly metabolized, however, the duration of anaesthesia is short because of drug redistribution into adipose tissue, which can act as a storage site, or drug reservoir.

3. Special Compartments

Several special compartments deserve mention. Entry of drug into the cerebrospinal fluid (CSF) and central nervous system (CNS) is restricted by the structure of the capillaries and pericapillary glial cells (the choroid plexus is an exception). The blood-brain barrier limits the success of antibiotics, anticancer drugs and other agents used to treat CNS diseases. Drugs also have relatively poor access to pericardial fluid, bronchial secretions and fluid in the middle ear, thus making the treatment of infections in these regions difficult.

B. Protein Binding

Many drugs bind to plasma proteins. Weak acids and neutral drugs bind particularly to albumin, while basic drugs tend to bind to alpha-1-acid glycoprotein (orosomucoid). Some drugs even bind to red cell surface proteins.

1. Effects on drug distribution

Only that fraction of the plasma drug concentration which is freely circulating (i.e., unbound) can penetrate cell membranes. Protein binding thus decreases the net transfer of drug across membranes. Drug binding to plasma proteins is generally weak and rapidly reversible, however, so that protein-bound drug can be considered to be in a temporary storage compartment. The protein concentration of extravascular fluids (e.g., CSF, lymph, synovial fluid) is very low. Thus, at equilibrium (when the concentrations of free drug are equal), the total drug concentration in plasma is usually higher than that in extravascular fluid. The extent of protein binding must be considered in interpreting "blood levels" of drugs.

2. Effects on drug elimination

The effects of plasma protein binding on drug elimination are complex. For drugs excreted only by renal glomerular filtration, protein binding decreases the rate of elimination since only the free drug is filtered. For example, the rates of renal excretion of several tetracyclines are inversely related to their extent of plasma protein binding. Conversely, however, if drug is eliminated by hepatic metabolism or renal tubular secretion, plasma protein binding may promote drug elimination by increasing the rate that that drug is presented for elimination.

3. Tissue binding

Binding to tissue proteins may cause local concentration of drug. For example, if a drug is bound more extensively at intracellular than at extracellular sites, the intracellular and extracellular concentrations of free drug may be equal or nearly so, but the total intracellular drug concentration may be much greater than the total extracellular concentration.

C. Apparent volume of distribution (AVD or Vd).

The volume of distribution, or more properly the apparent volume of distribution, is calculated from measurements of the total concentration of drug in the blood compartment after a single IV injection. Suppose that we injected someone IV with 100 mg of a drug, and measured the blood concentration of the drug repeatedly during the next several hours.

DRUG BIOTRANSFORMATION

The body is exposed to a wide variety of foreign compounds, called xenobiotics. Exposure to some such compounds is unintentional (e.g., environmental or food substances), while others are deliberately used as drugs. The following discussion of drug biotransformation is applicable to all xenobiotics, and to some endogenous compounds (e.g., steroids) as well. The kidneys are capable of eliminating drugs which are low in molecular weight, or which are polar and fully ionized at physiologic pH. Most drugs do not fit these criteria, but rather are fairly large, unionized or partially ionized, lipophilic molecules. The general goal of drug metabolism is to transform such compounds into more polar (i.e., more readily excretable) water soluble products. For example, were it not for biotransformation to more water-soluble products, thiopental, a short-acting, lipophilic anaesthetic, would have a half-life of more than 100 years! Imagine, without biotransformation reactions, anaesthesiologists might grow old waiting for patients to wake up.

Most products of drug metabolism are less active than the parent compound. In some cases, however, metabolites may be responsible for toxic, mutagenic, teratogenic or carcinogenic effects. For example, overdoses of acetaminophen owe their hepatotoxicity to a minor metabolite which reacts with liver proteins. In some cases, with metabolism of so-called prodrugs, metabolites are actually the active therapeutic compounds. The best example of a prodrug is cyclophosphamide, an inert compound which is metabolized by the liver into a highly active anticancer drug.

A. Sites of drug metabolism

1. At the organ level

The liver is the primary organ of drug metabolism. The gastrointestinal tract is the most important extrahepatic site. Some orally administered drugs (e.g., isoproterenol) are conjugated extensively in the intestinal epithelium, resulting in decreased bioavailability. The lung, kidney, intestine, skin and placenta can also carry out drug metabolizing reactions. Because of its enormous perfusion rate and its anatomic location with regard to the circulatory system, the lungs may exert a first-pass effect for drugs administered IV.

2. At the cellular level

Most enzymes involved in drug metabolism are located within the lipophilic membranes of the smooth endoplasmic reticulum (SER). When the SER is isolated in the laboratory by tissue homogenation and centrifugation, the SER membranes re-form into vesicles called microsomes. Since most of the enzymes carry out oxidation reactions, this SER complex is referred to as the microsomal mixed function oxidase (MFO) system.

3. At the biochemical level

Phase I reactions refer to those which convert a drug to a more polar compound by introducing or unmasking polar functional groups such as - OH, -NH2, or -SH. Some Phase I products are still not eliminated rapidly, and hence undergo Phase II reactions involving conjugation of the newly established polar group with endogenous compounds such as glucuronic acid, sulfuric acid, acetic acid, or amino acids (typically glycine). Glucuronide formation is the most common phase II reaction. Sometimes, the parent drug may undergo phase II conjugation directly. In some cases, a drug may undergo a series of consecutive reactions resulting in the formation of dozens of metabolites. Most phase I MFO biotransformation reactions are oxidative in nature and require a reducing agent (NADPH), molecular oxygen, and a complex of microsomal enzymes; the terminal oxidizing enzyme is called cytochrome P450, a hemoprotein so named because its carbon monoxide derivative absorbs light at 450 nm. We now know that cytochrome P450 is actually a family of enzymes which differ primarily with regard to their substrate specificities. Advances in molecular biology have led to the identification of more than 70 distinct P450 genes in various species. The nomenclature of the P450 reductase gene products has become complex. Based upon their amino acid homologies, the P450 reductases have been grouped into families such that a cytochrome P450 from one family exhibits < 40% amino acid sequence identity to a cytochrome P450 in another gene family.

Table 1: **Major Cytochrome P450 Gene Families**

P_{450} Gene Family/Subfamily	Characteristic Substrates	Characteristic Inducers	Characteristic Inhibitor
CYP 1A2	Acetominophen Estradiol Caffeine	Tobacco Char-Grilled Meats Insulin	Cimetidine Amiodarone Ticlopidine
CYP 2C19	Diazepam, Omeprazole Progesterone	Prednisone Rifampin	Cimetidine Ketoconazole Omeprazole
CYP 2C9	Tamoxifen Ibuprofen Fluoxetine	Rifampin Secobarbital	Fluvastatin Lovastatin Isoniazid
CYP 2D6	Debrisoquine Ondansetron Amphetamine	Dexamethasone? Rifampin?	Cimetidine Fluoxetine Methadone
CYP 2E1	Ethanol Benzene Halothane	Ethanol Isoniazid	Disulfiram Water Cress
CYP 3A4, 5, 7	Cyclosporin Clarithromycin Hydrocortisone Vincristine Many, many others	Barbiturates Glucocorticoids Carbamazepine St. John's Wort	Cimetidine Clarithromycin Ketoconazole Grapefruit Juice Many others

B. Enzyme Induction

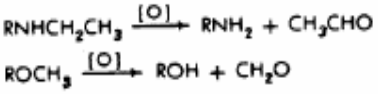
An interesting and important feature of the cytochrome P450 mixed function oxidase system is the ability of some xenobiotics to induce the synthesis of new enzyme. Microsomal enzyme induction is a complex and poorly understood process associated with an increase in liver weight, proliferation of the SER, and synthesis of P450 enzymes. For example, phenobarbital induces the P450IIB subfamily, while polycyclic aromatic hydrocarbons (e.g., found in cigarette smoke or charcoal broiled foods) induce the P450IA subfamily.Obviously, the dose and frequency of drug administration required to achieve therapeutic drug concentrations in blood may vary enormously from person to person, depending upon the degree of exposure to microsomal inducers. For example, consider patients who routinely ingest barbiturates or tranquilizers (P450 inducers) who must, for medical reasons, be treated with warfarin or dicumarol (oral anticoagulants). Because of a faster rate of drug metabolism, the dose of warfarin will need to be high. If the patient should for some reason discontinue the barbiturates, the blood level of warfarin will rise, perhaps leading to a bleeding disorder.

C. Enzyme Inhibition

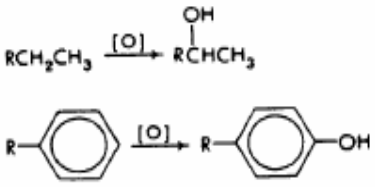
Relatively few xenobiotics are known to inhibit microsomal enzymes. Some drugs are used therapeutically because they inhibit specific enzyme systems (e.g., monoamine oxidase inhibitors for depression, xanthine oxidase inhibitors for gout, etc.). Sometimes such drugs are not totally specific and inhibit other enzyme systems to some extent. However, cimetidine, a widely used anti-ulcer drug, is an important, potent inhibitor of microsomal drug metabolism which retards the metabolism of many other drugs, including warfarin and similar anticoagulants, theophylline and caffeine, phenobarbital, phenytoin, carbamazepine, propranolol, diazepam, and chlordiazepoxide. Other inhibitors are erythromycin and ketonazole.

I. *Oxidative Reactions* (Microsomal)

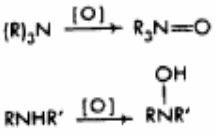
(1) N- and O-Dealkylation



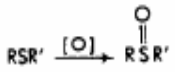
(2) Side Chain (Aliphatic) and Aromatic Hydroxylation



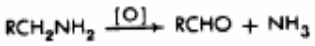
(3) N-Oxidation and N-Hydroxylation



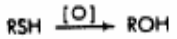
(4) Sulfoxide Formation



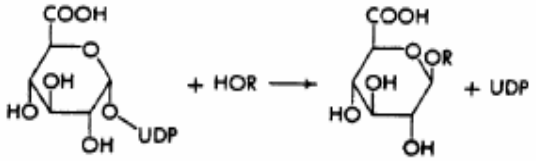
(5) Deamination of Amines



(6) Desulfuration



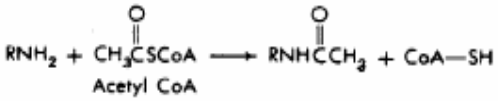
II. *Glucuronide Synthesis* (Microsomal)



UDP–Glucuronic Acid

III. *Other Conjugation Reactions*

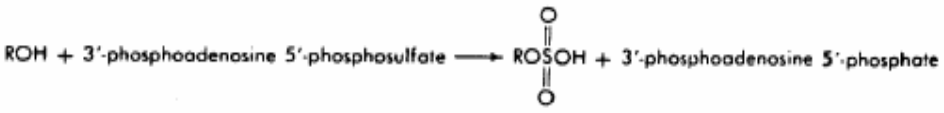
(1) Acetylation



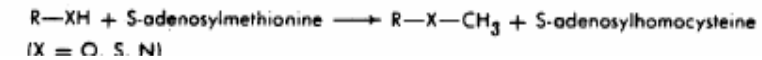
Acetyl CoA

(2) Conjugation with Glycine

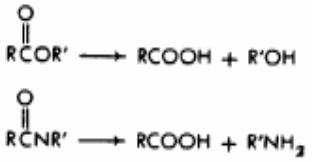
(3) Conjugation with Sulfate



(4) O-, S-, and N-Methylation

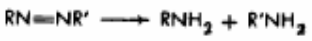


IV. *Hydrolysis of Esters and Amides*

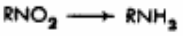


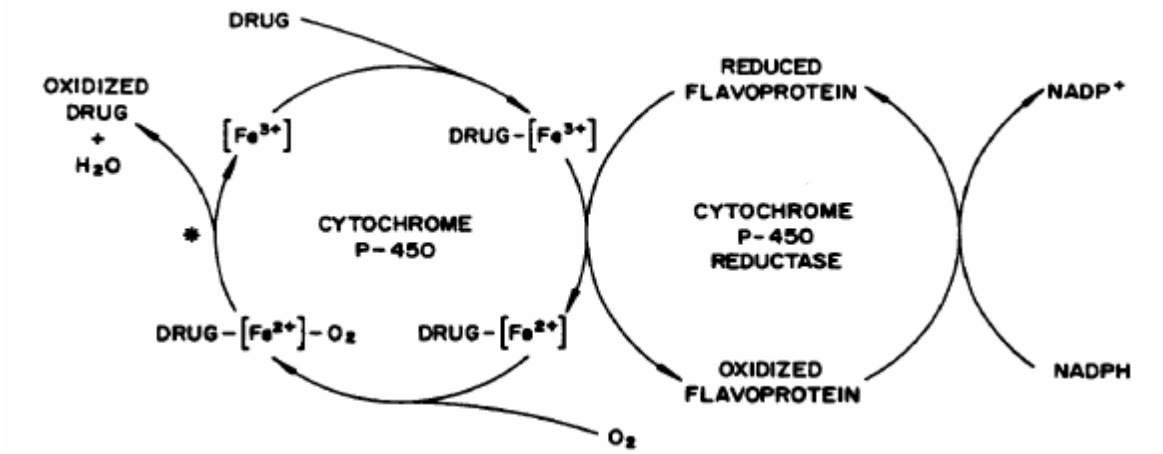
V. *Reduction*

(1) Azo Reduction



(2) Nitro Reduction





DRUG ELIMINATION

The kidney is the most important organ for the excretion of drugs and/or their metabolites. Some compounds are also excreted via bile, sweat, saliva, exhaled air, or milk, the latter a possible source of unwanted exposure in nursing infants. Drug excretion may involve one or more of the following processes.

A. Renal Glomerular Filtration

Glomeruli permit the passage of most drug molecules, but restrict the passage of protein-bound drugs. Changes in glomerular filtration rate affect the rate of elimination of drugs which are primarily eliminated by filtration (e.g., digoxin, kanamycin).

B. Renal Tubular Secretion

The kidney can actively transport some drugs (e.g., dicloxacillin) against a concentration gradient, even if the drugs are protein-bound. (Actually, only free drug is transported, but the protein-drug complex rapidly dissociates.) A drug called probenecid competitively inhibits the tubular secretion of the penicillin, and may be used clinically to prolong the duration of effect of the penicillin.

C. Renal Tubular Reabsorption

Many drugs are passively reabsorbed in the distal renal tubules. Reabsorption is influenced by the same physicochemical factors that influence gastrointestinal absorption: nonionized, lipid-soluble drugs are extensively reabsorbed into plasma, while ionized and polar molecules will remain in the renal filtrate and be excreted via urine. Thus, as in the gut, urine pH plays an important role, as does urine volume. Urine pH may vary widely from 4.5 to 8.0, may be influenced by diet, exercise, or disease, and tends to be lower during the day than at night. It is

sometimes clinically useful, particularly in drug overdose cases, to alter the pH of the urine (of the patient). For drugs which are weak acids, urine alkalinization favors the ionized form and promotes excretion. Alternatively, acidification promotes the renal clearance of weak bases.

D. Biliary Excretion

Comparatively little is known about hepatic drug elimination. Many drugs and metabolites are passed into the small intestine via bile and may undergo enterohepatic cycling. Recent studies have attempted to interrupt enterohepatic cycling of drugs, pesticides and heavy metals through the oral administration of non-absorbable, nonspecific adsorbents such as charcoal or cholestyramine. The results, generally a decrease in drug half-life, have been surprising in that they suggest that many more drugs undergo enterohepatic cycling than previously suspected.

PHARMACOKINETICS

Pharmacokinetics is concerned with the variation in drug concentration with time as a result of absorption, distribution and elimination.

The time course of drug action depends on:

1. Drug dose, route of administration, rate and extent of absorption, distribution rate (particularly to site of action) and rate of elimination.
2. The minimum effective concentration and concentration-effect relationship. Consideration of the time course of drug action is important since usually it is necessary to maintain a certain concentration of drug at its site of action for a finite period of time. Since effect usually is proportional to plasma (or tissue) concentration, the objective of therapy is to attain and maintain the needed plasma concentration for the period needed, whether this is days or years. To do this, one need understand something about pharmacokinetics. Most of the pharmacokinetic concepts we will deal with describe the behaviour of a simple one-compartment model in which drug equilibrates so rapidly in the entire volume that the dominant factors are the rates of absorption (input) and elimination (output).

Factors Which Modify Dose and Dose Interval

1. Altered absorption.
2. Altered elimination
3. Altered volume of distribution.

The presence of food in the GI tract and altered GI motility and absorptive properties can influence the rate and extent of absorption. For parenteral administration, changes in local

perfusion can have the same effect. Drug elimination can be strongly influenced by disease. Altered hepatic perfusion (as in shock or heart failure) and altered renal function cause frequent problems. The change in renal clearance of drug can be estimated from the endogenous creatinine clearance (or, less accurately, from serum creatinine or BUN).

Factors that influence metabolism

- Age
    - older animals less efficient at metabolism
- Sex
    - Linked to hormonal differences
- Heredity
    - Genetic differences can influence amounts and efficiency of metabolic enzymes
- Disease states
    - Liver, cardiac, kidney disease
- Enzyme induction and Enzyme inhibition

Factors: Genetic Differences

- Man vs. Monkey vs. Rabbit vs. Rat vs. Guinea pig
- Differences can even be where in the drug metabolism occurs
    - Meta vs. para in aromatic rings and which of two aromatic rings
- Example: Cats
    - Can't conjugate phenols by glucuronic acid
    - Sulfate conjugate instead → Aspirin *BAD* for kitty!
- Example: Pigs
    - Lack Sulfotransferase but very efficient glucoronic acid conjugation
- Example: Rabbits
    - Cottontail met. hexobarbitol 10X faster than New Zealand
- Humans: Genetic/hereditary differences account for huge differences seen in the rate of enzyme metabolism
-

<u>Enzyme inhibition and inhibition of metabolism</u>

- Leads to drug accumulation and toxicity
- Mechanisms
    - Substrate competition

- interference with protein synthesis
- Interference with drug metabolizing enzymes
- Hepatotoxicity leading to decreased metabolism

“Enzyme induction”

- Results from drug or chemical exposure
- *Very important* source of drug-drug interactions
- Caused by the increased rate of enzyme production
- Often drugs can increase their own rate of metabolism
- Compounds that enhance metabolism:
    - Phenobarbital and other barbiturates,
    - glutethimide, phenylbutazone,
    - meprobamate, ethanol,
    - phenytoin, rifampin, griseofulvin, carbamazepine

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT –III - SBT1302 – PHARMACEUTICAL BIOTECHNOLOGY

COURSE OUTCOMES;

At the end of the course the student would be able to;

- CO1-Identify the prospects of applying Biotechnological concepts in drug discovery
- CO2-Inspect the kinetics, dynamics of drugs relating to the routes of administration
- CO3-Categorize the unit operation principles involved in the bulk drug manufacturing process
- CO4-Compare the product development of various drug formulations Tablets, Capsules, parentrals, oral liquids and topical applications.
- CO5-Appraise the mode of action of various drugs, laxatives, nonsteroidal contraceptives, antiseptics, antacids, analgesics, vitamins and hormones
- CO6-Elaborate the regulatory aspects involved in preclinical and clinical testing of drugs

Bulk drug Manufacturing

Introduction

The pharmaceutical industry is an important component of health care systems throughout the world; it is comprised of many public and private organizations that discover, develop, manufacture and market medicines for human and animal health. The pharmaceutical industry is based primarily upon the scientific research and development (R&D) of medicines that prevent or treat diseases and disorders. Drug substances exhibit a wide range of pharmacological activity and toxicological properties. Modern scientific and technological advances are accelerating the discovery and development of innovative pharmaceuticals with improved therapeutic activity and reduced side effects. Molecular biologists, medicinal chemists and pharmacists are improving the benefits of drugs through increased potency and specificity. These advances create new concerns for protecting the health and safety of workers within the pharmaceutical industry.

Many dynamic scientific, social and economic factors affect the pharmaceutical industry. Some pharmaceutical companies operate in both national and multinational markets. Therefore, their activities are subject to legislation, regulation and policies relating to drug development and approval, manufacturing and quality control, marketing and sales. Academic, government and industry scientists, practising physicians and pharmacists, as well as the public, influence the pharmaceutical industry. Health care providers (e.g., physicians, dentists, nurses, pharmacists and veterinarians) in hospitals, clinics, pharmacies and private practice may prescribe drugs or recommend how they should be dispensed. Government regulations and health care policies on pharmaceuticals are influenced by the public, advocacy groups and private interests. These complex factors interact to influence the discovery and development, manufacturing, marketing and sales of drugs.

The pharmaceutical industry is largely driven by scientific discovery and development, in conjunction with toxicological and clinical experience (see figure:1). Major differences exist between large organizations which engage in a broad range of drug discovery and development, manufacturing and quality control, marketing and sales and smaller organizations which focus on a specific aspect. Most multinational pharmaceutical companies are involved in all these activities; however, they may specialize in one aspect based upon local market factors. Academic, public and private organizations perform scientific research to discover and develop new drugs. The biotechnology industry is becoming a major contributor to innovative

pharmaceutical research. Often, collaborative agreements between research organizations and large pharmaceutical companies are formed to explore the potential of new drug substances. Bulks are active drug substances used to manufacture dosage- form products, process medicated animal feeds or compound prescription medications.

Figure :1 Drug development in the pharmaceutical industry

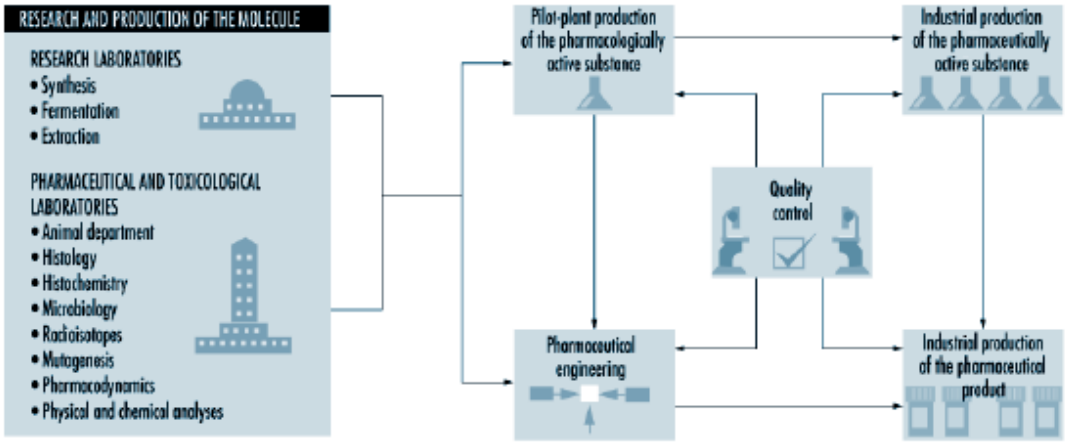


Figure :1 Drug development in the pharmaceutical industry

Many countries have specific legal protections for proprietary drugs and manufacturing processes, known as intellectual property rights. In instances when legal protections are limited or do not exist, some companies specialize in manufacturing and marketing generic drugs. The pharmaceutical industry requires large amounts of capital investment due to the high expenses associated with R&D, regulatory approval, manufacturing, quality assurance and control, marketing and sales. Many countries have extensive government regulations affecting the development and approval of drugs for commercial sale. These countries have strict requirements for good manufacturing practices to ensure the integrity of drug manufacturing operations and the quality, safety and efficacy of pharmaceutical products.

International and domestic trade, as well as tax and finance policies and practices, affect how the pharmaceutical industry operates within a country. Significant differences exist between developed and developing countries, regarding their needs for pharmaceutical substances. In developing countries, where malnutrition and infectious diseases are prevalent, nutritional supplements, vitamins and anti-infective drugs are most needed. In developed countries, where the diseases associated with ageing and specific ailments are primary health concerns,

cardiovascular, central nervous system, gastrointestinal, anti-infective, diabetes and chemotherapy drugs are in the greatest demand.

Human and animal health drugs share similar R&D activities and manufacturing processes; however, they have unique therapeutic benefits and mechanisms for their approval, distribution, marketing and sales. Veterinarians administer drugs to control infectious diseases and parasitic organisms in agricultural and companion animals. Vaccines and anti-infective and antiparasitic drugs are commonly used for this purpose. Nutritional supplements, antibiotics and hormones are widely employed by modern agriculture to promote the growth and health of farm animals. The R&D of pharmaceuticals for human and animal health are often allied, due to concurrent needs to control infectious agents and disease.

Types of Reactions in Bulk drug Manufacture and Processes.

Many different biological and chemical agents are discovered, developed and used in the pharmaceutical industry. Some manufacturing processes in the pharmaceutical, biochemical and synthetic organic chemical industries are similar; however, the greater diversity, smaller scale and specific applications in the pharmaceutical industry are unique. Since the primary purpose is to produce medicinal substances with pharmacological activity, many agents in pharmaceutical R&D and manufacturing are hazardous to workers. Proper control measures must be implemented to protect workers from industrial chemicals and drug substances during many R&D, manufacturing and quality control operations

The pharmaceutical industry uses biological agents (e.g., bacteria and viruses) in many special applications, such as vaccine production, fermentation processes, derivation of blood-based products and biotechnology. Chemical agents may be categorized as industrial chemicals and drug-related substances. These may be raw materials, intermediates or finished products. Special situations arise when industrial chemicals or drug substances are employed in laboratory R&D, quality assurance and control assays, engineering and maintenance, or when they are created as by-products or wastes.

Industrial chemicals

Industrial chemicals are used in researching and developing active drug substances and manufacturing bulk substances and finished pharmaceutical products. Organic and inorganic chemicals are raw materials, serving as reactants, reagents, catalysts and solvents. The use of

industrial chemicals is determined by the specific manufacturing process and operations. Many of these materials may be hazardous to workers. Since worker exposures to industrial chemicals may be hazardous, occupational exposure limits, such as threshold limit values (TLVs) have been established by government, technical and professional organizations.

Pharmaceutical manufacturing Operations

Pharmaceutical manufacturing operations may be categorized as basic production of bulk drug substances and pharmaceutical manufacturing of dosage form products. Figure:2 illustrates the manufacturing process.

Figure :2 Manufacturing process in the pharmaceutical industry

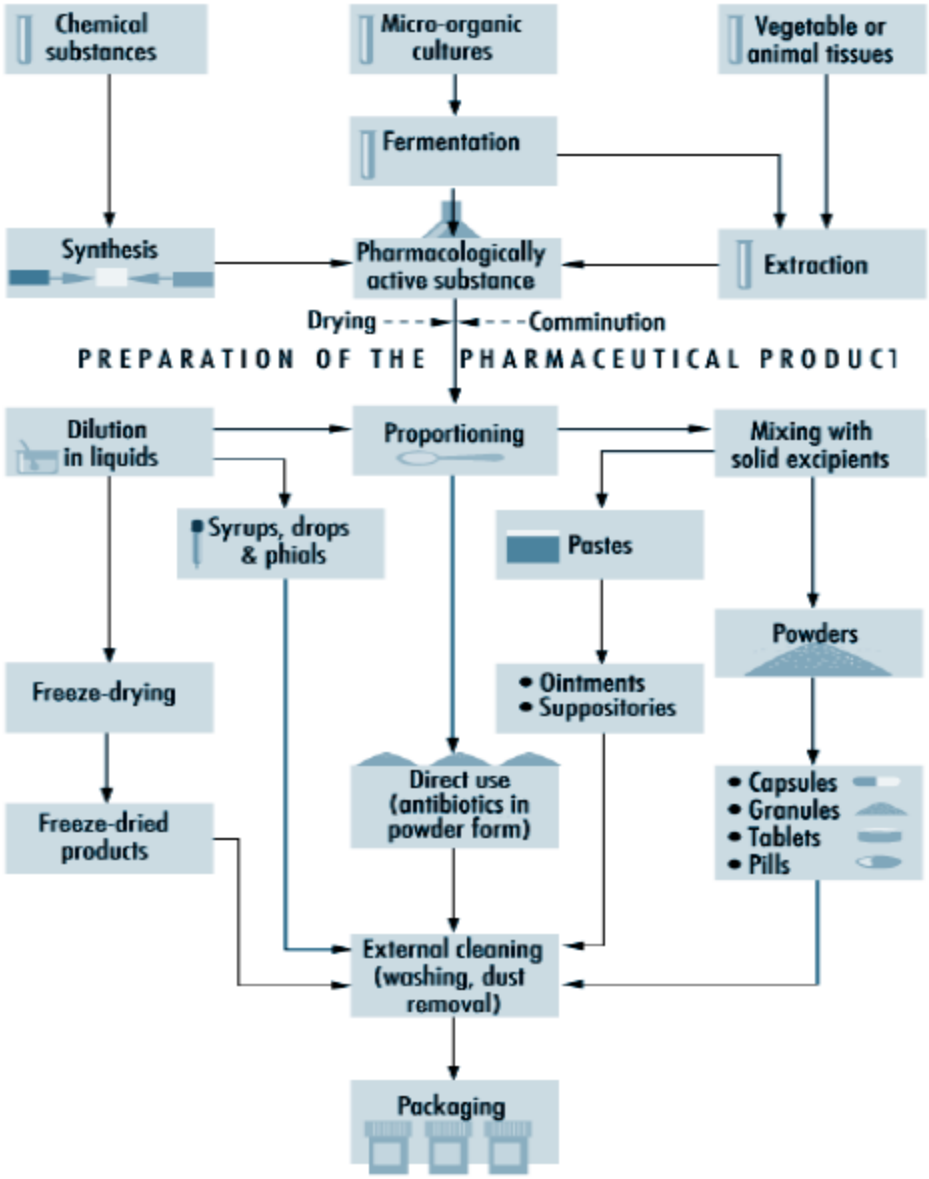


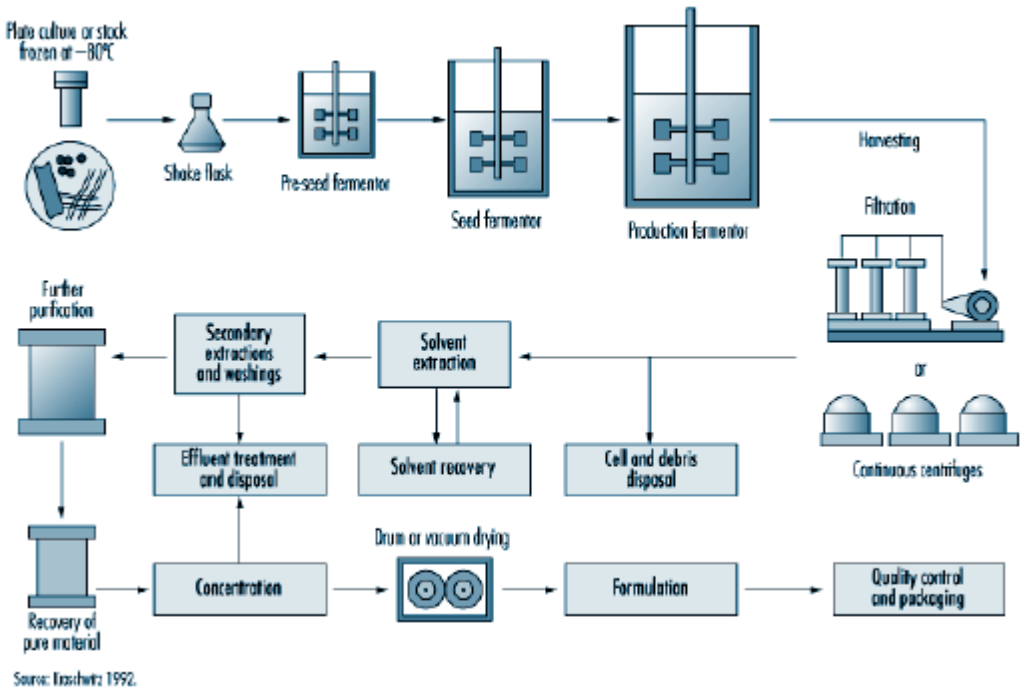
Figure :2 Manufacturing process in the pharmaceutical industry

Basic production of bulk drug substances may employ three major types of processes: fermentation, organic chemical synthesis, and biological and natural extraction. These manufacturing operations may be discrete batch, continuous or a combination of these processes. Antibiotics, steroids and vitamins are produced by fermentation, whereas many new drug substances are produced by organic synthesis. Historically, most drug substances were derived from natural sources such as plants, animals, fungi and other organisms. Natural medicines are pharmacologically diverse and difficult to produce commercially due to their complex chemistry and limited potency

Fermentation

Fermentation is a biochemical process employing selected micro-organisms and microbiological technologies to produce a chemical product. Batch fermentation processes involve three basic steps: inoculum and seed preparation, fermentation, and product recovery or isolation (Theodore and McGuinn 1992). A schematic diagram of a fermentation process is given in figure : 3 . Inoculum preparation begins with a spore sample from a microbial strain. The strain is selectively cultured, purified and grown using a battery of microbiological techniques to produce the desired product. The spores of the microbial strain are activated with water and nutrients in warm conditions. Cells from the culture are grown through a series of agar plates, test tubes and flasks under controlled environmental conditions to create a dense suspension.

Figure :3 Diagram of a fermentation process



The cells are transferred to a seed tank for further growth. The seed tank is a small fermentation vessel designed to optimize the growth of the inoculum. The cells from the seed tank are charged to a steam sterilized production fermentor. Sterilized nutrients and purified water are added to the vessel to begin the fermentation. During aerobic fermentation, the contents of the fermentor are heated, agitated and aerated by a perforated pipe or sparger, maintaining an optimum air flow rate and temperature. After the biochemical reactions are complete, the fermentation broth is filtered to remove the micro-organisms, or mycelia. The drug product, which may be present in the filtrate or within the mycelia, is recovered by various steps, such as solvent extraction, precipitation, ion exchange and absorption.

Solvents used for extracting the product generally can be recovered; however, small portions remain in the process wastewater, depending upon their solubility and the design of the process equipment. Precipitation is a method to separate the drug product from the aqueous broth. The drug product is filtered from the broth and extracted from the solid residues. Copper and zinc are common precipitating agents in this process. Ion exchange or adsorption removes the product from the broth by chemical reaction with solid materials, such as resins or activated carbon. The drug product is recovered from the solid phase by a solvent which may be recovered by evaporation.

Worker health and safety

Worker safety hazards may be posed by moving machine parts and equipment; high pressure steam, hot water, heated surfaces and hot workplace environments; corrosive and irritating chemicals; heavy manual handling of materials and equipment; and high noise levels. Worker exposures to solvent vapours may occur when recovering or isolating products. Worker exposures to solvents may result from uncontained filtration equipment and fugitive emissions for leaking pumps, valves and manifold stations during extraction and purification steps. Since the isolation and growth of micro-organisms are essential for fermentation, biological hazards are reduced by employing non-pathogenic microbes, maintaining closed process equipment and treating spent broth before its discharge.

Generally, process safety concerns are less important during fermentation than during organic synthesis operations, since fermentation is primarily based upon aqueous chemistry and requires process containment during seed preparation and fermentation. Fire and explosion hazards may arise during solvent extractions; however, the flammability of solvents is reduced by dilution with water in filtration and recovery steps. Safety hazards (i.e., thermal burns and scalding) are posed by the large volumes of pressurized steam and hot water associated with fermentation operations.

Chemical synthesis

Chemical synthesis processes use organic and inorganic chemicals in batch operations to produce drug substances with unique physical and pharmacological properties. Typically, a series of chemical reactions are performed in multi-purpose reactors and the products are isolated by extraction, crystallization and filtration (Kroschwitz 1992). The finished products are usually dried, milled and blended. Organic synthesis plants, process equipment and utilities are comparable in the pharmaceutical and fine chemical industries. A schematic diagram of an organic synthesis process is given in figure :4 .

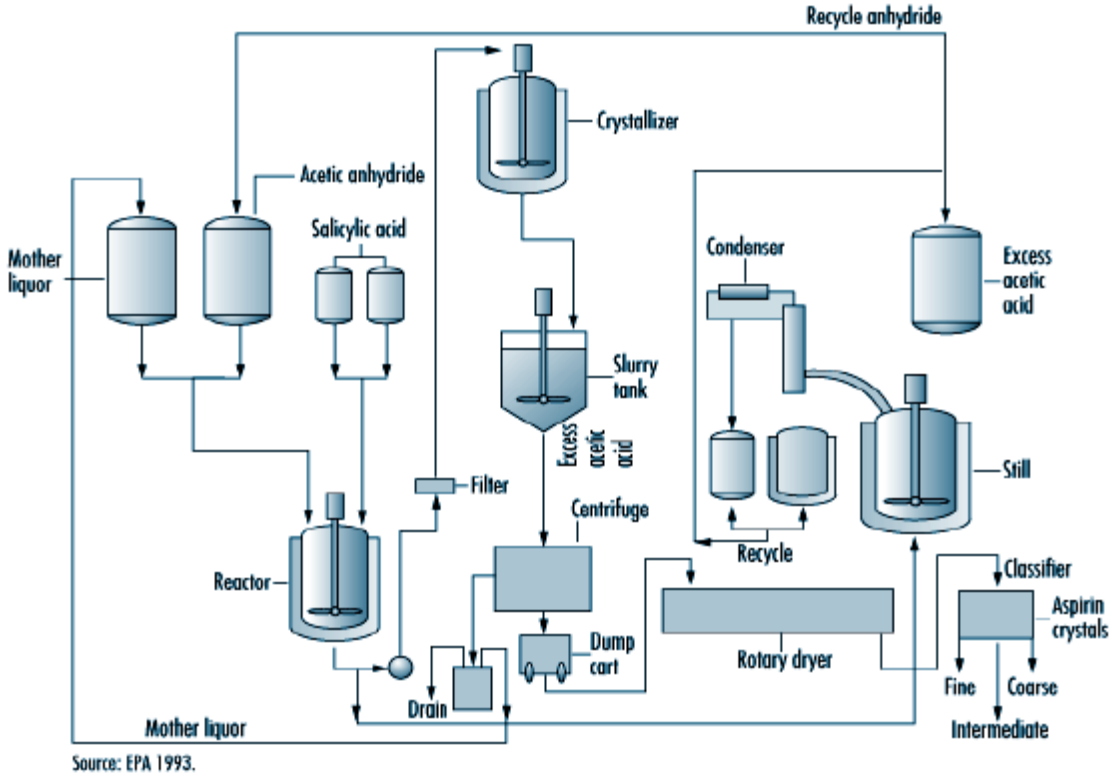


Figure :4 Diagram of an organic synthesis process

Pharmaceutical chemistry is becoming increasingly complex with multi-step processing, where the product from one step becomes a starting material for the next step, until the finished drug product is synthesized. Bulk chemicals which are intermediates of the finished product may be transferred between organic synthesis plants for various technical, financial and legal considerations. Most intermediates and products are produced in a series of batch reactions on a campaign basis. Manufacturing processes operate for discrete periods of time, before materials, equipment and utilities are changed to prepare for a new process. Many organic synthesis plants in the pharmaceutical industry are designed to maximize their operating flexibility, due to the diversity and complexity of modern medicinal chemistry. This is achieved

by constructing facilities and installing process equipment that can be modified for new manufacturing processes, in addition to their utility requirements.

Multi-purpose reactors are the primary processing equipment in chemical synthesis operations (see figure :5). They are reinforced pressure vessels with stainless, glass or metal alloy linings. The nature of chemical reactions and physical properties of materials (e.g., reactive, corrosive, flammable) determine the design, features and construction of reactors. Multi-purpose reactors have external shells and internal coils which are filled with cooling water, steam or chemicals with special heat-transfer properties. The reactor shell is heated or cooled, based upon the requirements of the chemical reactions. Multi-purpose reactors have agitators, baffles and many inlets and outlets connecting them to other process vessels, equipment and bulk chemical supplies. Temperature-, pressure- and weight-sensing instruments are installed to measure and control the chemical process in the reactor. Reactors may be operated at high pressures or low vacuums, depending upon their engineering design and features and the requirements of the process chemistry.

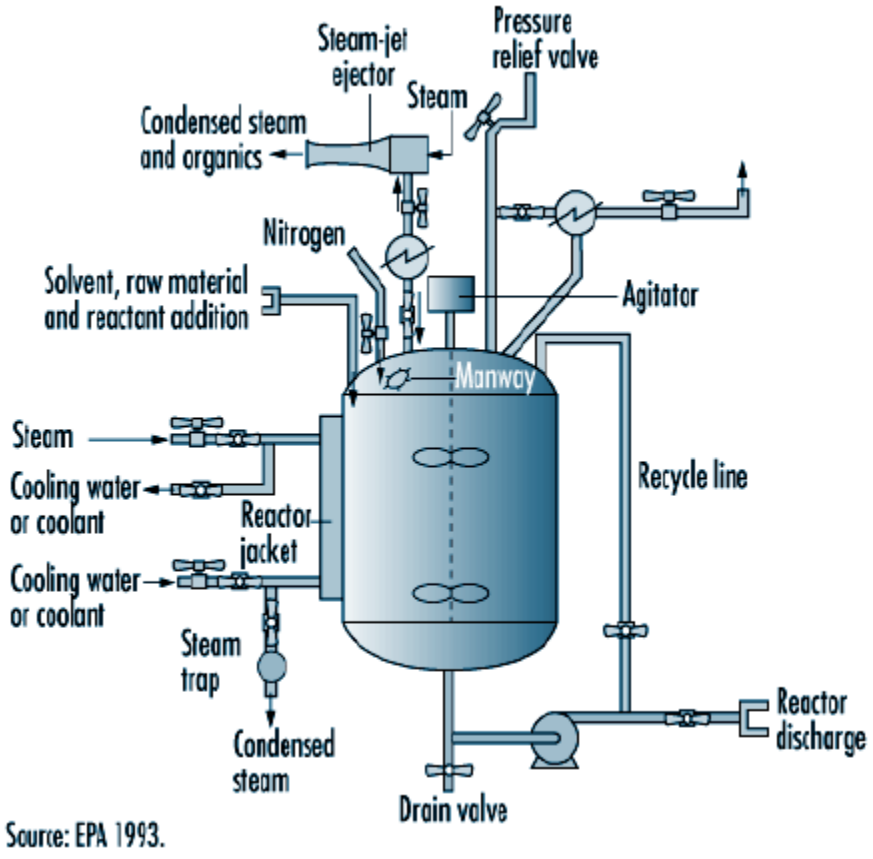


Figure :5 Diagram of a chemical reactor in organic synthesis

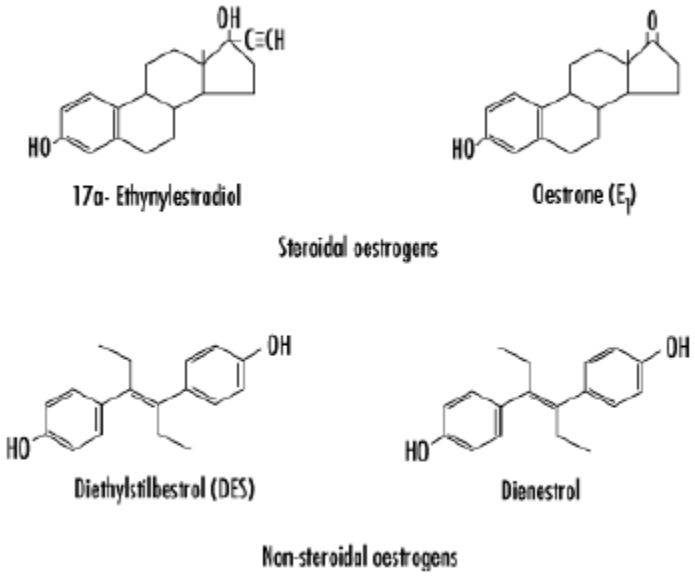


Figure :6 Examples of steroidal and non-steroidal oestrogen structure

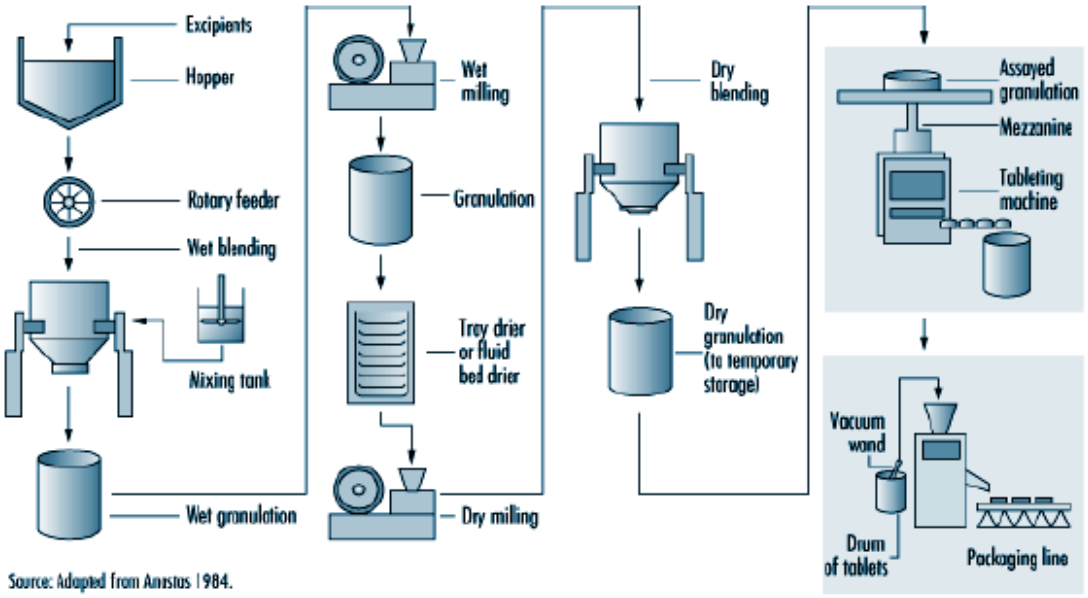


Figure :7 Typical oral contraceptive tablet manufacturing process flow

Heat exchangers are connected to reactors to heat or cool the reaction and condense solvent vapours when they are heated above their boiling point, creating a reflux or recycling of the condensed vapours. Air pollution control devices (e.g., scrubbers and impingers) can be connected to the exhaust vents on process vessels, reducing gas, vapour and dust emissions (EPA 1993). Volatile solvents and toxic chemicals may be released to the workplace or atmosphere, unless they are controlled during the reaction by heat exchangers or air control devices. Some solventsand reactants are difficult to condense, absorb or adsorb in air control devices (e.g., methylene chloride and chloroform) due to their chemical and physical properties.

Bulk chemical products are recovered or isolated by separation, purification and filtration operations. Typically, these products are contained in mother liquors, as dissolved or suspended solids in a solvent mixture. The mother liquors may be transferred between process vessels or equipment in temporary or permanent pipes or hoses, by pumps, pressurized inert gases, vacuum or gravity. Transferring materials is a concern due to the rates of reaction, critical temperatures or pressures, features of processing equipment and potential for leaks and spills. Special precautions to minimize static electricity are required when processes use or generate flammable gases and liquids. Charging flammable liquids through submerged dip tubes and grounding and bonding conductive materials and maintaining inert atmospheres inside process equipment reduce the risk of a fire or explosion (Crowl and Louvar 1990).

Worker health and safety

Many worker health and safety hazards are posed by synthesis operations. They include safety hazards from moving machine parts, pressurized equipment and pipes; heavy manual handling of materials and equipment; steam, hot liquids, heated surfaces and hot workplace environments; confined spaces and hazardous energy sources (e.g., electricity); and high noise levels.

Acute and chronic health risks may result from worker exposures to hazardous chemicals during synthesis operations. Chemicals with acute health effects can damage the eyes and skin, be corrosive or irritating to body tissues, cause sensitization or allergic reactions or be asphyxiants, causing suffocation or oxygen deficiency. Chemicals with chronic health effects may cause cancer, or damage the liver, kidneys or lungs or affect the nervous, endocrine, reproductive or other organ systems. Health and safety hazards may be controlled by implementing appropriate control measures (e.g., process modifications, engineering controls, administrative practices, personal and respiratory protective equipment).

Organic synthesis reactions may create major process safety risks from highly hazardous materials, fire, explosion or uncontrolled chemical reactions which impact the community surrounding the plant. Process safety can be very complex in organic synthesis. It is addressed in several ways: by examining the dynamics of chemical reactions, properties of highly hazardous materials, design, operation and maintenance of equipment and utilities, training of operating and engineering staff, and emergency preparedness and response of the facility and local community. Technical guidance is available on process hazard analysis and management activities to reduce the risks of chemical synthesis operations (Crowl and Louvar 1990; Kroschwitz 1992).

Biological and natural extraction

Large volumes of natural materials, such as plant and animal matter, may be processed to extract substances which are pharmacologically active. In each step of the process, the volumes of materials are reduced by a series of batch processes, until the final drug product is obtained. Typically, processes are performed in campaigns lasting a few weeks, until the desired quantity of finished product is obtained. Solvents are used to remove insoluble fats and oils, thereby extracting the finished drug substance. The pH (acidity) of the extraction solution and waste products can be adjusted by neutralizing them with strong acids and bases. Metal compounds frequently serve as precipitating agents, and phenol compounds as disinfectants.

Worker health and safety

Some workers may develop allergic and/or skin irritation from handling certain plants. Animal matter may be contaminated with infectious organisms unless appropriate precautions are taken. Workers may be exposed to solvents and corrosive chemicals during biological and natural extraction operations. Fire and explosion risks are posed by storing, handling, processing and recovering flammable liquids. Moving mechanical parts; hot steam, water, surfaces and workplaces; and high noise levels are risks to worker safety.

Process safety issues are often reduced by the large volumes of plant or animal materials, and smaller scale of solvent extraction activities. Fire and explosion hazards, and worker exposures to solvents or corrosive or irritating chemicals may occur during extraction and recovery operations, depending upon the specific chemistry and containment of process equipment.

Pharmaceutical manufacturing of dosage forms

Drug substances are converted into dosage-form products before they are dispensed or administered to humans or animals. Active drug substances are mixed with pharmaceutical necessities, such as binders, fillers, flavouring and bulking agents, preservatives and antioxidants. These ingredients may be dried, milled, blended, compressed and granulated to achieve the desired properties before they are manufactured as a final formulation. Tablets and capsules are very common oral dosage forms; another common form is sterile liquids for injection or ophthalmic application. Figure:8 illustrates typical unit operations for manufacturing of pharmaceutical dosage-form products.

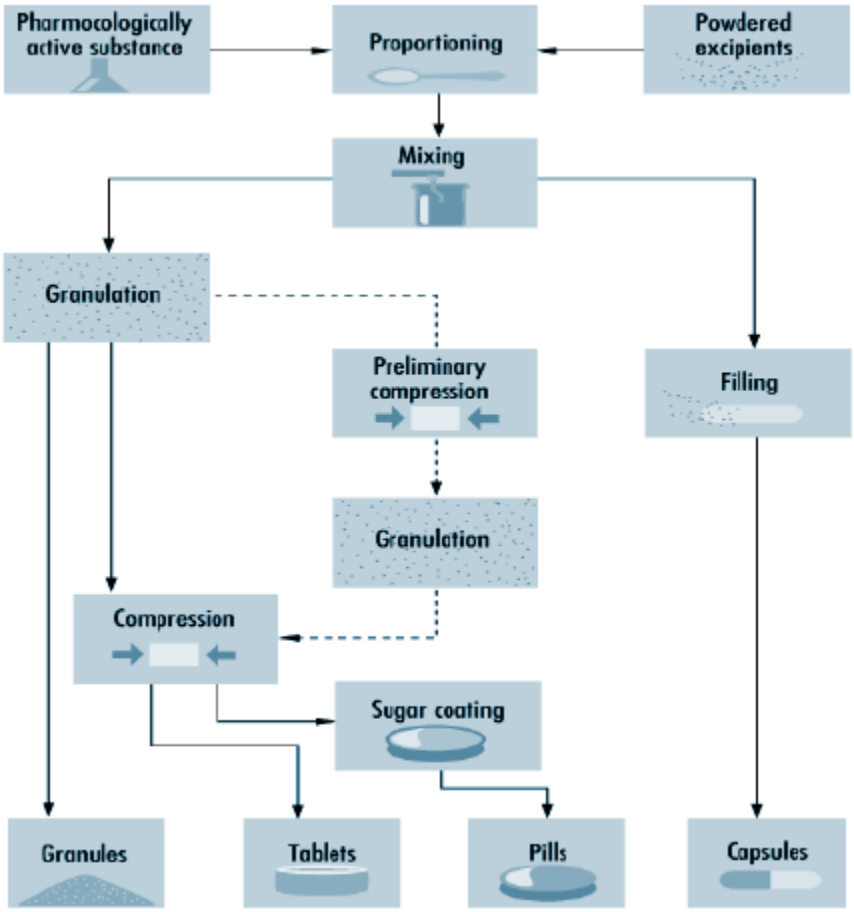


Figure :8 Pharmaceutical manufacturing of dosage-form products

Pharmaceutical blends may be compressed by wet granulation, direct compression or slugging to obtain the desired physical properties, before their formulation as a finished drug product. In wet granulation, the active ingredients and excipients are wetted with aqueous or solvent solutions to produce course granules with enlarged particle sizes. The granules are dried, mixed with lubricants (e.g., magnesium stearate), disintegrants or binders, then compressed into tablets. During direct compression, a metal die holds a measured amount of the drug blend while a punch compresses the tablet. Drugs that are not sufficiently stable for wet granulation or cannot be directly compressed are slugged. Slugging or dry granulation blends and compresses relatively large tablets which are ground and screened to a desired mesh size, then recompressed into the final tablet. Blended and granulated materials may also be produced in capsule form. Hard gelatin capsules are dried, trimmed, filled and joined on capsule-filling machines. Liquids may be produced as sterile solutions for injection into the body or administration to the eyes; liquids, suspensions and syrups for oral ingestion; and tinctures for application on the skin. Highly controlled environmental conditions, contained process equipment and purified raw materials are required for manufacturing sterile liquids to prevent

microbiological and particulate contamination. Facility utilities (e.g., ventilation, steam and water), process equipment and workplace surfaces must be cleaned and maintained to prevent and minimize contamination. Water at high temperatures and pressures is used to destroy and filter bacteria and other contaminants from the sterile water supply when making solutions for injection. Parenteral liquids are injected by intradermal, intramuscular or intravenous administration into the body. These liquids are sterilized by dry or moist heat under high pressure with bacteria-retaining filters. Although liquid solutions for oral or topical use do not require sterilization, solutions to be administered to the eyes (ophthalmic) must be sterilized. Oral liquids are prepared by mixing the active drug substances with a solvent or preservative to inhibit mold and bacterial growth. Liquid suspensions and emulsions are produced by colloid mills and homogenizers, respectively. Creams and ointments are prepared by blending or compounding active ingredients with petrolatum, heavy greases or emollients before packaging in metal or plastic tubes.

Worker health and safety

Worker health and safety risks during pharmaceutical manufacturing are created by moving machine parts (e.g., exposed gears, belts and shafts) and hazardous energy sources (e.g., electrical, pneumatic, thermal, etc.); manual handling of material and equipment; high-pressure steam, hot water and heated surfaces; flammable and corrosive liquids; and high noise levels. Worker exposures to airborne dusts may occur during dispensing, drying, milling and blending operations. Exposure to pharmaceutical products is a particular concern when mixtures containing high proportions of active drug substances are handled or processed. Wet granulation, compounding and coating operations may create high worker exposures to solvent vapours.

Process safety issues primarily relate to the risks of fire or explosion during pharmaceutical manufacturing of dosage forms. Many of these operations (e.g., granulation, blending, compounding and drying) use flammable liquids, which may create flammable or explosive atmospheres. Since some pharmaceutical dusts are highly explosive, their physical properties should be examined before they are processed. Fluid bed drying, milling and slugging are a particular concern when they involve potentially explosive materials. Engineering measures and safe work practices reduce the risks of explosive dusts and flammable liquids (e.g., vapour- and dust-tight electrical equipment and utilities, grounding and bonding of equipment, sealed containers with pressure relief and inert atmospheres).

Control measures

Fire and explosion prevention and protection; process containment of hazardous substances, machine hazards and high noise levels; dilution and local exhaust ventilation (LEV); use of respirators (e.g., dust and organic vapour masks and, in some cases, powered air-purifying respirators or air-supplied masks and suits) and personal protective equipment (PPE); and worker training on workplace hazards and safe work practices are workplace control measures applicable during all of the various pharmaceutical manufacturing operations described below. Specific issues involve substituting less hazardous materials whenever possible during drug development and manufacturing. Also, minimizing material transfers, unsealed or open processing and sampling activities decreases the potential for worker exposures.

The engineering design and features of facilities, utilities and process equipment can prevent environmental pollution and reduce worker exposures to hazardous substances. Modern pharmaceutical manufacturing facilities and process equipment are reducing environmental, health and safety risks by preventing pollution and improving the containment of hazards. Worker health and safety and quality control objectives are achieved by improving the isolation, containment and cleanliness of pharmaceutical facilities and process equipment. Preventing worker exposures to hazardous substances and pharmaceutical products is highly compatible with the concurrent need to prevent workers from accidentally contaminating raw materials and finished products. Safe work procedures and good manufacturing practices are complementary activities.

Facility design and process-engineering issues

The engineering design and features of pharmaceutical facilities and process equipment influences worker health and safety. The construction materials, process equipment and housekeeping practices greatly affect the cleanliness of the workplace. Dilution and LEV systems control fugitive vapours and dust emissions during manufacturing operations. Fire and explosion prevention and protection measures (e.g., vapour- and dust-tight electrical equipment and utilities, extinguishing systems, fire and smoke detectors and emergency alarms) are needed when flammable liquids and vapours are present. Storage and handling systems (e.g., storage vessels, portable containers, pumps and piping) are installed to move liquids within pharmaceutical manufacturing facilities. Hazardous solids can be handled and processed in enclosed equipment and vessels, individual bulk containers (IBCs) and sealed drums and bags. The isolation or containment of facilities, process equipment and hazardous materials promotes worker health and safety. Mechanical hazards are controlled by installing barrier guards on moving machine parts.

The process equipment and utilities may be controlled by manual or automatic means. In manual plants, chemical operators read instruments and control process equipment and utilities near the process equipment. In automated plants, the process equipment, utilities and control devices are controlled by distributed systems, allowing them to be operated from a remote location such as a control room. Manual operations are often employed when materials are charged or transferred, products are discharged and packaged and when maintenance is performed or nonroutine conditions arise. Written instructions should be prepared, to describe standard operating procedures as well as worker health and safety hazards and control measures.

Verification of workplace controls

Workplace control measures are evaluated periodically to protect workers from health and safety hazards and minimize environmental pollution. Many manufacturing processes and pieces of equipment are validated in the pharmaceutical industry to ensure the quality of products. Similar validation practices may be implemented for workplace control measures to ensure that they are effective and reliable. Periodically, process instructions and safe work practices are revised. Preventive maintenance activities identify when process and engineering equipment may fail, thereby precluding problems. Training and supervision informs and educates workers about environmental, health and safety hazards, reinforcing safe work practices and the use of respirators and personal protective equipment. Inspection programmes examine whether safe workplace conditions and work practices are maintained. This includes inspecting respirators and to ensure they are properly selected, worn and maintained by workers. Audit programmes review the management systems for identifying, evaluating and controlling environmental, health and safety hazards.

Pharmaceutical unit operations

Weighing and dispensing

Weighing and dispensing of solids and liquids is a very common activity throughout the pharmaceutical industry. Usually workers dispense materials by hand-scooping solids and pouring or pumping liquids. Weighing and dispensing are often performed in a warehouse during bulk chemical production or in a pharmacy during pharmaceutical dosage-form manufacturing. Due to the likelihood of spills, leaks and fugitive emissions during weighing and dispensing, proper workplace control measures are necessary to protect workers. Weighing and dispensing should be performed in a partitioned workplace area with good dilution ventilation. The work surfaces in areas where materials are weighed and dispensed should be smooth and sealed, permitting their proper cleaning. LEV with backdraft or sidedraft hoods

prevents the release of air contaminants when weighing and dispensing dusty solids or volatile liquids. Weighing and dispensing highly toxic materials may require additional control measures such as laminar ventilation hoods or isolation devices (e.g., glove boxes or glove bags).

Charging and discharging solids and liquids

Solids and liquids are frequently charged and discharged from containers and process equipment in pharmaceutical manufacturing operations. Charging and discharging of materials are often performed manually by workers; however, other methods are employed (e.g., gravity, mechanical or pneumatic transfer systems). Contained process equipment, transfer systems and engineering controls prevent worker exposures during charging and discharging of highly hazardous materials. Gravity charging from enclosed containers and vacuum, pressure and pumping systems eliminate fugitive emissions during charging and discharging operations. LEV with flanged inlets captures fugitive dusts and vapours which are released at open transfer points.

Liquid separations

Liquids are separated based upon their physical properties (e.g., density, solubility and miscibility). Liquid separations are commonly performed during bulk chemical production and pharmaceutical manufacturing operations. Hazardous liquids should be transferred, processed and separated in closed vessels and piping systems to reduce worker exposures to liquid spills and airborne vapours. Eyewashes and safety showers should be located near operations where hazardous liquids are transferred, processed or separated. Spill control measures and fire and explosion prevention and protection are needed when using flammable liquids.

Transferring liquids

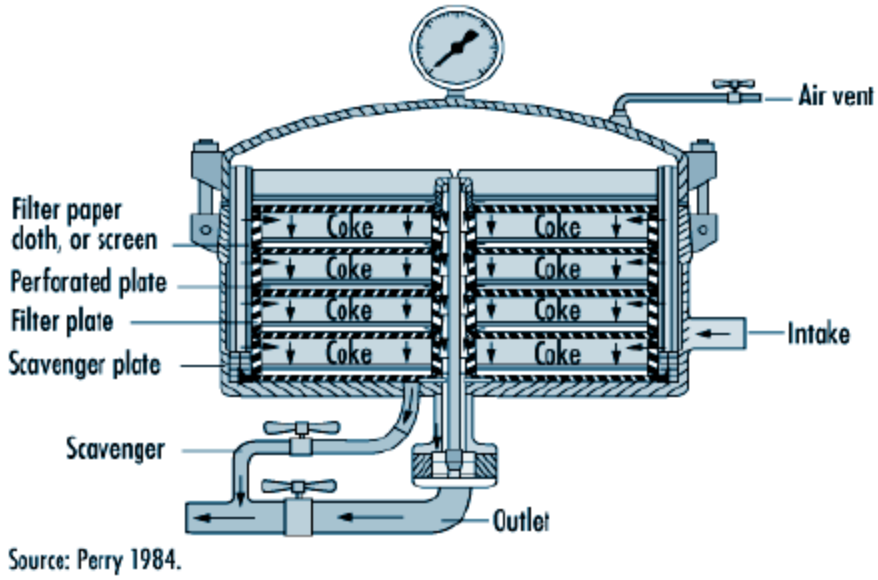
Liquids are often transferred between storage vessels, containers and process equipment during pharmaceutical manufacturing operations. Ideally, facility and manufacturing processes are designed to minimize the need for transferring hazardous materials, thereby decreasing the chance of spills and worker exposures. Liquids may be transferred between process vessels and equipment through manifold stations, areas where many pipe flanges are located close together. This allows temporary connections to be made between piping systems. Spills, leaks and vapour emissions may occur at manifold stations; therefore proper gaskets and tight seals on hoses and pipes are needed to prevent environmental pollution and workplace releases. Drainage systems with sealed tanks or sumps capture spilled liquids so they can be reclaimed and recovered. Sealed vessels and containers and piping systems are highly desirable when transferring large volumes of liquids. Special precautions should be taken when using inert

gases to pressurize transfer lines or process equipment, since this may increase the release of volatile organic compounds (VOCs) and hazardous air pollutants. Recirculation or condensation of exhaust gases and vapours reduces air pollution.

Filtration

Solids and liquids are separated during filtration operations. Filters have different designs and features with varying containment and control of liquids and vapours. When open filters are used for hazardous materials, workers may be exposed to liquids, wet solids, vapours and aerosols during loading and unloading operations. Closed process equipment can be used to filter highly hazardous materials, reducing vapour emissions and preventing worker exposures (see figure:9). Filtration should be performed in areas with spill control and good dilution and LEV. Volatile solvent vapours can be exhausted through vents on sealed process equipment and controlled by air emissions devices (e.g., condensers, scrubbers and adsorbers).

Figure :9 A sparkler filter



Source: Perry 1984.

Compounding

Solids and liquids are mixed in compounding operations to produce solutions, suspensions, syrups, ointments and pastes. Contained process equipment and transfer systems are recommended when compounding highly hazardous materials (Kroschwitz 1992; Perry 1984). Buffering agents, detergents and germicides that are neutralizing, cleaning and biocidal agents may be hazardous to workers. Eyewashes and safety showers reduce injuries, if workers accidentally contact corrosive or irritating substances. Due to the wet surfaces in compounding areas, workers need to be protected from electrical hazards of equipment and utilities. Thermal hazards are posed by steam and hot water

during compounding and cleaning activities. Worker injuries from burns and falls are prevented by installing insulation on hot surfaces and maintaining dry non-slip floors.

Granulation

Dry and wet solids are granulated to change their physical properties. Granulators have different designs and features with varying containment and control of mechanical hazards and airborne dusts and vapours (Perry 1984; Swarbick and Boylan 1996). Enclosed granulators can be vented to air-control devices, reducing emissions of solvent vapours or dusts to the workplace and atmosphere (see figure :10). Material-handling concerns arise when loading and unloading granulators. Mechanical equipment (e.g., elevated platforms, lift tables and pallet jacks) assists workers to perform heavy manual tasks. Eyewashes and safety showers are needed, if workers accidentally contact solvents or irritating dusts.

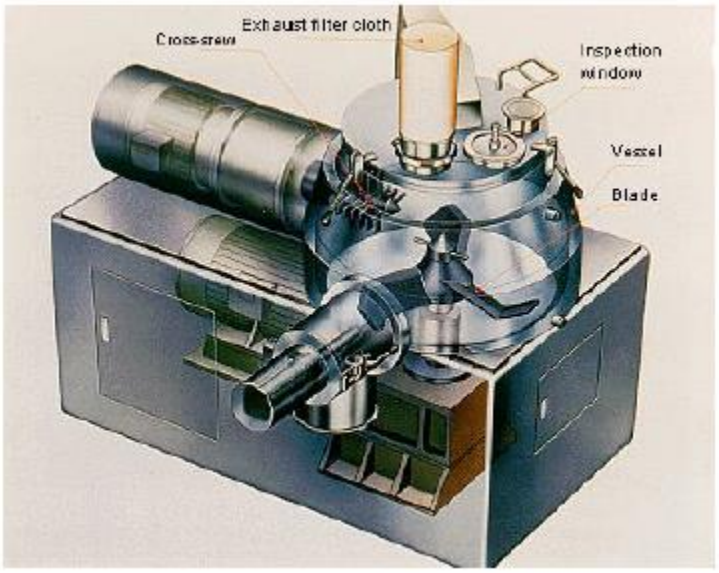


Figure :10 A high steam granulator

Drying

Water- or solvent-wet solids are dried during many pharmaceutical manufacturing operations. Dryers have different designs and features with varying containment and control of vapours and dusts . Flammable solvent vapours and explosive airborne dusts may create flammable or explosive atmosphere; explosion relief venting is particularly important on contained dryers. Dilution and LEV reduces the risk of fire or explosion, in addition to controlling worker exposures to solvent vapours when handling wet cakes, or to airborne dusts when unloading dried products. Heavy material handling may be involved when loading or unloading dryer trays, bins or containers Mechanical equipment (e.g., drum jacks, lifts and work platforms)

assists these manual tasks. Eyewashes and safety showers should be located nearby, in case workers accidentally contact solvents and dusts.

Glatt Air Techniques, Inc

Figure :11 A rotary vacuum dryer

Figure :12 A vacuum shelf dryer

Figure :12 A vacuum shelf dryer

Milling

Dry solids are milled to change their particle characteristics and produce free-flowing powders. Mills have different designs and features with varying containment and control of mechanical hazards and airborne dusts. Prior to milling materials, their physical properties and hazards should be reviewed or tested. Explosion prevention and protection measures involve installing dust-tight electrical equipment and utilities, grounding and bonding equipment and accessories to eliminate electrostatic sparking, installing safety relief valves on enclosed mills, and constructing blast relief panels in walls. These measures may be necessary due to the explosivity of some drug substances and excipients, high dust levels and energies associated with milling operations.

Blending

Dry solids are blended to produce homogeneous mixtures. Blenders have different designs and features with varying containment and control of mechanical hazards and airborne dusts. Worker exposures to drug substances, excipients and blends may occur when loading and unloading blending equipment. LEV with flanged inlets reduces fugitive dust emissions during blending. Heavy material handling may be required when charging and discharging solids from blenders. Mechanical equipment (e.g., work platforms, hoists and drum and pallet jacks) reduces the physical demands of heavy material handling.

Compression

Dry solids are compressed or slugged to compact them, changing their particle properties. Compression equipment has different designs and features with varying containment and control of mechanical hazards and airborne dusts. Compression equipment may pose serious mechanical hazards if inadequately guarded. High noise levels may also be produced by compression and slugging operations. Enclosing impact sources, isolating vibrating equipment, rotating workers and using hearing-protective devices (e.g., ear muffs and plugs) reduce the impact of noise exposures.

Solid dosage-form manufacturing

Tablets and capsules are the most common oral dosage forms. Compressed or moulded tablets contain mixtures of drug substances and excipients. These tablets may be uncoated or coated with solvent mixtures or aqueous solutions. Capsules are soft or hard gelatin shells. Tablet presses (see figure :13), tablet-coating equipment and capsule-filling machines have different designs and features with varying containment and control of mechanical hazards and airborne dusts (Cole 1990). Workers may be exposed to solvent vapours when spray-coating tablets. Modern tablet-coating equipment is highly contained; however, LEV can be installed in older

open coating pans to control fugitive solvent vapours. Tablet-coating equipment can be vented to air emission devices to control VOCs from the process (see figure :14). Whenever possible, recovered solvents should be reused by the process or aqueous mixtures substituted for solvent mixtures for tablet coating. Modern tablet presses and capsule-filling machines are enclosed by interlocked panels, reducing the hazards of fast-moving parts, high noise levels and dust emissions during their operation. Hearing-protective devices can reduce worker noise exposures during tablet and capsule operations.

Figure :13 Tablet press with load hopper and spiral dust pickups for product recovery

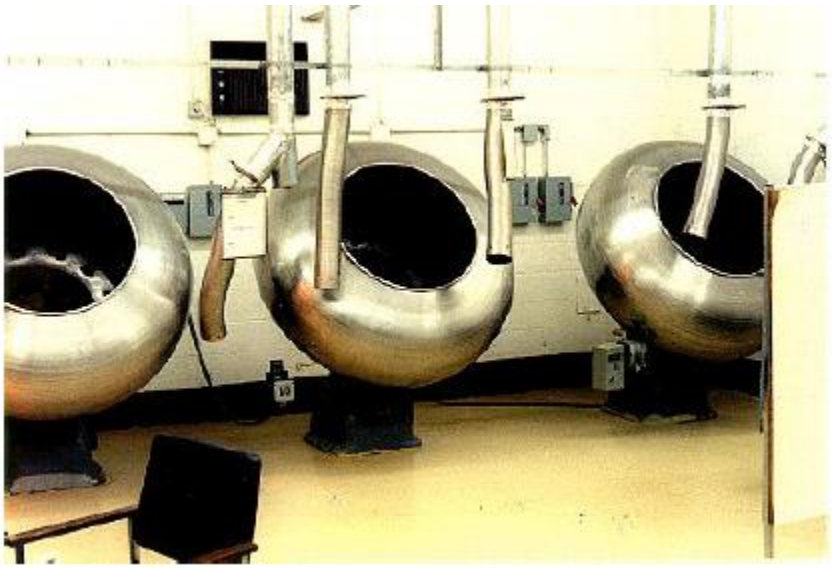


Figure :14 A tablet coating machine

Sterile manufacturing

Sterile products are manufactured in pharmaceutical manufacturing plants with modular design (see figure :15), clean workplace and equipment surfaces, and high efficiency particulate air (HEPA) filtered ventilation systems. The principles and practices of controlling contamination in sterile liquid manufacturing are similar to those in the microelectronics industry. Workers wear protective clothing to prevent them from contaminating products during sterile manufacturing operations. Sterile pharmaceutical technologies to control contamination involve freeze-drying products, using liquid germicides and sterilizing gases, installing laminar flow ventilation, isolating modules with differential air pressures and containing manufacturing and filling equipment.

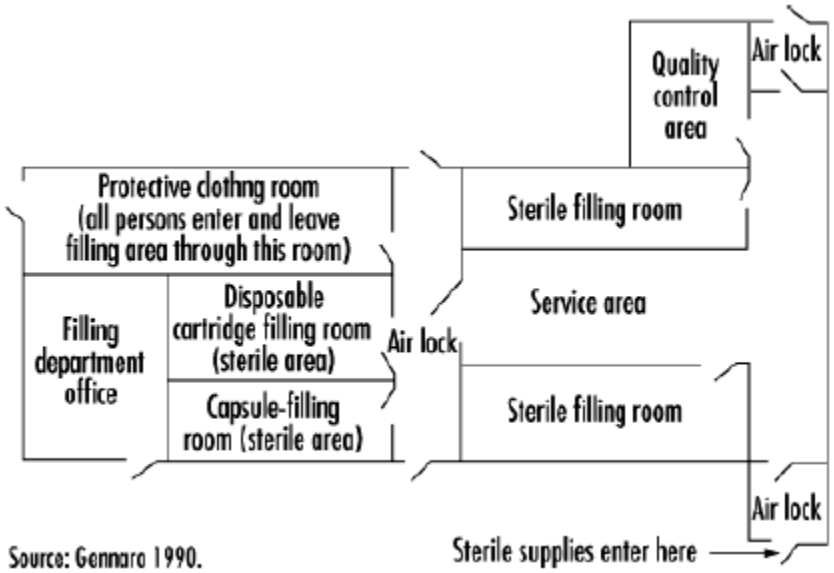


Figure :15 Diagram of a sterile liquid manufacturing facility

Chemical hazards are posed by toxic germicides (e.g., formaldehyde and glutaraldehyde) and sterilizing gases (i.e., ethylene oxide). Whenever possible, less hazardous agents should be selected (e.g., alcohols, ammonium compounds). Sterilization of raw materials and equipment may be performed by high-pressure steam or toxic gases (i.e., diluted ethylene oxide gas mixtures) (Swarbick and Boylan 1996). Sterilization vessels can be located in separate areas with remote instrument and control systems, non-recirculated air and LEV to extract toxic gas emissions. Workers should be trained on standard operating instructions, safe work practices and appropriate emergency response. Gas sterilization chambers should be fully evacuated under vacuum and purged with air to minimize fugitive workplace emissions before sterilized goods are removed. Gas emissions from sterilization chambers can be vented to air control devices (e.g., carbon adsorption or catalytic converters) to reduce atmospheric emissions. Occupational hygiene monitoring measures worker exposures to chemical germicides and

sterilizing gases, helping to assess the adequacy of control measures. Safety hazards involve high-pressure steam and hot water, moving machine parts in washing, filling, capping and packaging equipment, high noise levels and repetitive manual tasks.

Cleaning and maintenance activities

Non-routine tasks may occur when cleaning, repairing and maintaining equipment, utilities and workplaces. Although unique hazards may arise during non-routine tasks, recurring health and safety concerns are encountered. Workplace and equipment surfaces may be contaminated by hazardous materials and drug substances, requiring them to be cleaned before unprotected workers conduct servicing or maintenance work. Cleaning is performed by washing or wiping liquids and sweeping or vacuuming dusts. Dry sweeping and blowing solids with compressed air are not recommended, since they create high worker exposures to airborne dusts. Wet mopping and vacuuming reduce worker exposures to dusts during cleaning activities. Vacuum cleaners with HEPA filters may be needed when cleaning hazardous substances and high-potency drugs. Explosion-proof equipment and conductive materials may be required in vacuum systems for explosive dusts. Eyewashes and safety showers and PPE reduce the effect of workers' accidental contact with corrosive and irritating detergents and cleaning liquids.

Hazardous mechanical, electrical, pneumatic or thermal energy may need to be released or controlled before equipment and utilities are serviced, repaired or maintained. Contract workers may perform special production or engineering tasks in pharmaceutical plants without adequate training on safety precautions. Careful supervision of contract workers is important, so they do not violate safety rules or perform work that creates a fire, explosion or other serious health and safety hazards. Special contractor safety programmes are required when working with highly hazardous materials (e.g., toxic, reactive, flammable or explosive) and processes (e.g., exothermic or high pressure) in bulk pharmaceutical and dosage-form manufacturing facilities.

Packaging

Pharmaceutical packaging operations are performed with a series of integrated machines and repetitive manual tasks (Gennaro 1990; Swarbick and Boylan 1996). Finished dosage-form products may be packaged in many different types of containers (e.g., plastic or glass bottles, foil blister packs, pouches or sachets, tubes and sterile vials). The mechanical equipment fills, caps, labels, cartons and packs the finished products in shipping containers. Worker proximity to packaging equipment necessitates barrier guarding on moving machine parts, accessible control switches and emergency stop cables and employee training on machine hazards and safe work practices. Enclosure and isolation of equipment reduces sound and vibration levels in packaging areas. Use of hearing-protective devices (e.g., ear muffs and plugs) reduces

worker exposures to noise. Good industrial design promotes the productivity, comfort and safety of employees, by addressing ergonomic hazards from poor body postures, material handling and highly repetitive tasks.

Laboratory operations

Laboratory operations in the pharmaceutical industry are diverse. They may pose biological, chemical and physical hazards, depending upon the specific agents, operations, equipment and work practices employed. Major distinctions exist between labs which conduct scientific research and product and process development and those which evaluate quality assurance and control activities (Swarbick and Boylan 1996). Lab workers may conduct scientific research to discover drug substances, develop manufacturing processes for bulk chemical and dosage-form products or analyze raw materials, intermediates and finished products. Lab activities should be evaluated individually, although good lab practices apply to many situations (National Research Council 1981). Clearly defined responsibilities, training and information, safe work practices and control measures and emergency response plans are important means for effectively managing environmental, health and safety hazards.

The health and safety hazards of flammable and toxic materials are reduced by minimizing their inventories in labs and storing them in separate cabinets. Lab assays and operations which may release air contaminants can be performed in ventilated exhaust fume hoods to protect workers. Biological safety hoods provide downward and inward laminar flow, preventing the release of micro-organisms (Gennaro 1990; Swarbick and Boylan 1996). Worker training and information describes the hazards of lab work, safe work practices and proper emergency response to fires and spills. Food and beverages should not be consumed in lab areas. Lab safety is enhanced by requiring supervisors to approve and manage highly hazardous operations. Good lab practices separate, treat and dispose of biological and chemical wastes. Physical hazards (e.g., radiation and electromagnetic energy sources) are often certified and operated, according to specific regulations.

General Health and Safety Hazards

Ergonomics and material handling

The materials shipped, stored, handled, processed and packaged in the pharmaceutical industry range from large quantities of raw materials to small packages containing pharmaceutical products. Raw materials for bulk chemical production are shipped in bulk containers (e.g., tank trucks, rail cars), metal and fibre drums, reinforced paper and plastic bags. Pharmaceutical production uses smaller quantities of raw materials due to the reduced scale of the operations. Material-handling devices (e.g., fork-lift trucks, pallet lifts, vacuum hoists and drum jacks)

assist material handling during warehousing and production operations. Heavy manual work may create ergonomic risks when moving materials and equipment if mechanical devices are not available. Good industrial engineering and facility management practices reduce injuries from material handling by improving the design and features of equipment and the workplace and decreasing the size and weight of containers (Cole 1990). Engineering control measures (e.g., ergonomic design of tools, materials and equipment) and administrative practices (e.g., rotating workers, providing worker training) reduce the risks of cumulative trauma injuries during highly repetitive production and packaging operations.

Machine guarding and control of hazardous energy

Unguarded moving machine parts in pharmaceutical manufacturing and packaging equipment create mechanical hazards. Exposed "crush and nip points" in open equipment may seriously injure workers. Mechanical hazards are exacerbated by the large numbers and different designs of equipment, crowded workplace conditions and frequent interactions between workers and equipment. Interlocked guards, control switches, emergency stop devices and operator training are important means of reducing mechanical hazards. Loose hair, long-sleeved clothing, jewellery or other objects may become trapped in equipment. Routine inspection and repair activities identify and control mechanical hazards during production and packaging operations. Hazardous electrical, pneumatic and thermal energy must be released or controlled before working on active equipment and utilities. Workers are protected from sources of hazardous energy by implementing lockout/tagout procedures.

Noise exposures

High sound levels may be generated by manufacturing equipment and utilities (e.g., compressed air, vacuum sources and ventilation systems). Due to the enclosed design of pharmaceutical workplace modules, workers are often located close to machines during manufacturing and packaging operations. Workers observe and interact with production and packaging equipment, thereby increasing their exposure to noise. Engineering methods reduce sound levels by modifying, enclosing and dampening noise sources. Employee rotation and use of hearing-protective devices (e.g., ear muffs and plugs) reduce workers' exposure to high noise levels. Comprehensive hearing conservation programmes identify noise sources, reduce workplace sound levels, and train workers on the hazards of noise exposure and proper use of hearing-protective devices. Noise monitoring and medical surveillance (i.e., audiometry) assess worker exposures to noise and their resulting loss of hearing. This helps to identify noise problems and evaluate the adequacy of corrective measures.

Solvent vapour and potent compound exposures

Special concerns may arise when workers are exposed to toxic solvent vapours and potent drugs as airborne dusts. Worker exposures to solvent vapours and potent compounds may occur during various manufacturing operations, which need to be identified, evaluated and controlled to ensure that workers are protected. Engineering controls are the preferred means of controlling these exposures, due to their inherent effectiveness and reliability (Cole 1990; Naumann et al. 1996). Enclosed process equipment and material handling systems prevent worker exposures, while LEV and PPE supplement these measures. Increased facility and process containment is needed for controlling highly toxic solvents (e.g., benzene, chlorinated hydrocarbons, ketones) and potent compounds. Positive-pressure respirators (e.g., powered-air purifying and supplied-air) and PPE are needed when highly toxic solvents and potent compounds are handled and processed. Special concerns are posed by operations where high levels of solvent vapours (e.g., compounding, granulating and tablet coating) and dusts (e.g., drying, milling and blending) are generated. Locker and shower rooms, decontamination practices and good sanitary practices (e.g., washing and showering) are necessary to prevent or minimize the effects of worker exposures inside and outside the workplace.

Process safety management

Process safety programmes are implemented in the pharmaceutical industry due to the complex chemistry, hazardous materials and operations in bulk chemical manufacturing (Crowl and Louvar 1990). Highly hazardous materials and processes may be employed in multi-step organic synthesis reactions to produce the desired drug substance. The thermodynamics and kinetics of these chemical reactions must be evaluated, since they may involve highly toxic and reactive materials, lachrymators and flammable or explosive compounds.

Process safety management involves conducting physical hazard testing of materials and reactions, performing hazard analysis studies to review the process chemistry and engineering practices, examining preventive maintenance and mechanical integrity of the process equipment and utilities, implementing worker training and developing operating instructions and emergency response procedures. Special engineering features for process safety include selecting proper pressure-rated vessels, installing isolation and suppression systems, and providing pressure relief venting with catch tanks. Process safety management practices are similar in the pharmaceutical and chemical industries when manufacturing bulk pharmaceuticals as speciality organic chemicals (Crowl and Louvar 1990; Kroschwitz 1992).

Environmental Issues

The different pharmaceutical manufacturing processes each have their own environmental issues, as discussed below.

Fermentation

Fermentation generates large volumes of solid waste which contains mycelia and spent filter cakes (EPA 1995; Theodore and McGuinn 1992). Filter cakes contain mycelia, filter media and small amounts of nutrients, intermediates and residual products. These solid wastes are typically non-hazardous, yet they may contain solvents and small amounts of residual chemicals depending upon the specific chemistry of the fermentation process. Environmental problems may develop if fermentation batches become infected with a viral phage which attacks the micro-organisms in the fermentation process. Although phage infections are rare, they create a significant environmental problem by generating large amounts of waste broth.

Spent fermentation broth contains sugars, starches, proteins, nitrogen, phosphates and other nutrients with high biochemical oxygen demand (BOD), chemical oxygen demand (COD) and total suspended solids (TSS) with pH values ranging from 4 to 8. Fermentation broths can be treated by microbiological wastewater systems, after the effluent is equalized to promote the stable operation of the treatment system. Steam and small amounts of industrial chemicals (e.g., phenols, detergents and disinfectants) maintain the sterility of the equipment and products during fermentation. Large volumes of moist air are exhausted from fermentors, containing carbon dioxide and odours which may be treated before they are emitted to the atmosphere.

Organic synthesis

Wastes from chemical synthesis are complex due to the variety of hazardous materials, reactions and unit operations (Kroschwitz 1992; Theodore and McGuinn 1992). Organic synthesis processes may generate acids, bases, aqueous or solvent liquors, cyanides and metal wastes in liquid or slurry form. Solid wastes may include filter cakes containing inorganic salts, organic by-products and metal complexes. Waste solvents in organic synthesis are usually recovered by distillation and extraction. This allows the solvents to be reused by other processes and reduces the volume of liquid hazardous wastes to be disposed of. Residues from distillation (still bottoms) need to be treated before they are disposed. Typical treatment systems include steam stripping to remove solvents, followed by microbiological treatment of other organic substances. Volatile organic and hazardous substance emissions during organic synthesis operations should be controlled by air pollution control devices (e.g., condensers, scrubbers, venturi impingers).

Waste water from synthesis operations may contain aqueous liquors, wash water, discharges from pumps, scrubbers and cooling systems, and fugitive leaks and spills (EPA 1995). This waste water may contain many organic and inorganic substances with different chemical compositions, toxicities and biodegradabilities. Trace amounts of raw materials, solvents and by-products may be present in aqueous mother liquors from crystallizations and wash layers from extractions and equipment cleaning. These waste waters are high in BOD, COD and TSS, with varying acidity or alkalinity and pH values ranging from 1 to 11.

Biological and natural extraction

Spent raw materials and solvents, wash water and spills are the primary sources of solid and liquid wastes (Theodore and McGuinn 1992). Organic and inorganic chemicals may be present as residues in these waste streams. Usually, waste waters have low BOD, COD and TSS, with relatively neutral pH values ranging from 6 to 8.

Pharmaceutical manufacturing of dosage forms

Pharmaceutical manufacturing of dosage-form products generates solid and liquid wastes during cleaning and sterilization, and from leaks and spills and rejected products (Theodore and McGuinn 1992). Drying, milling and blending operations generate atmospheric and fugitive dust emissions. These emissions can be controlled and recycled to the manufacturing of dosage form products; however, quality control practices may prevent this if other residues are present. When solvents are used during wet granulation, compounding and tablet coating, VOCs and hazardous air pollutants may be released to the atmosphere or in the workplace as process or fugitive emissions. Waste waters may contain inorganic salts, sugars, syrups and traces of drug substances. These waste waters usually have low BOD, COD and TSS, with neutral pH values. Some antiparasitic or anti-infective drugs for humans and animals may be toxic to aquatic organisms, requiring special treatment of liquid wastes.

Environmental pollution prevention

Waste minimization and pollution prevention

Good engineering and administrative practices minimize the environmental impact of bulk chemical production and pharmaceutical manufacturing operations. Pollution prevention employs modifying processes and equipment, recycling and recovering materials and maintaining good housekeeping and operating practices (Theodore and McGuinn 1992). These activities enhance the management of environmental issues, as well as worker health and safety.

Process modifications

Processes may be modified to reformulate products by using materials that are less hazardous or persistent or changing manufacturing operations to reduce air emissions, liquid effluents and solid wastes. Reducing the amount and toxicity of wastes is wise, since it improves the efficiency of manufacturing processes and reduces the costs and impacts of waste disposal. Government drug approval regulations may limit the ability of pharmaceutical manufacturers to change hazardous materials, manufacturing processes, equipment and facilities (Spilker 1994). Drug manufacturers must anticipate the environmental, health and safety impacts of selecting hazardous materials and designing manufacturing process at an early stage. It becomes increasingly difficult to make changes during the later stages of drug development and regulatory approval, without considerable loss of time and expense.

It is very desirable to develop manufacturing processes with less hazardous solvents. Ethyl acetate, alcohols and acetone are preferable to highly toxic solvents such as benzene, chloroform and trichloroethylene. Whenever possible, some materials should be avoided due to their physical properties, ecotoxicity or persistence in the environment (e.g., heavy metals, methylene chloride) (Crowl and Louvar 1990). Substituting aqueous washes for solvents during filtrations in bulk chemical production reduces liquid wastes and vapour emissions. Also, substituting aqueous for solvent-based solutions during tablet coating reduces environmental, health and safety concerns. Pollution prevention is promoted by improving and automating process equipment, as well as performing routine calibration, servicing and preventive maintenance. Optimizing organic synthesis reactions increases product yields, often decreasing the generation of wastes. Incorrect or inefficient temperature, pressure and material control systems cause inefficient chemical reactions, creating additional gaseous, liquid and solid wastes.

The following are examples of process modifications in bulk pharmaceutical production (Theodore and McGuinn 1992):

· Minimize the quantities of hazardous materials used and select materials whose wastes can be controlled, recovered and recycled, whenever possible.

· Develop and install systems for recycling raw materials (e.g., solvents), intermediates, wastes and utility materials (e.g., cooling water, heat transfer liquids, lubricants, steam condensate).

· Examine reactants, solvents and catalysts to optimize the efficiency of chemical reactions.

· Modify the design and features of processing equipment to minimize pollution and wastes.

· Improve processes to maximize product yields and desired properties, eliminating additional processing (e.g., re-crystallization, drying and milling). Consider using multi-purpose

equipment (e.g., reactors, filters and dryers) to reduce pollution and wastes during transfers, cleaning and additional process steps.

· Use appropriate instruments, automated control systems and computer programs to maximize the efficiency of processes and reduce pollution and wastes.

Resource recovery and recycling

Resource recovery uses waste products and reclaims materials during processing by separating waste impurities from desired materials. Solid wastes from fermentation (e.g., mycelia) may be added to animal feeds as a nutritional supplement or as soil conditioners and fertilizers. Inorganic salts may be recovered from chemical liquors produced during organic synthesis operations. Spent solvents are often recycled by separation and distillation. Air emission control devices (e.g., condensers, compression and refrigeration equipment) greatly reduce emissions of volatile organic compounds to the atmosphere (EPA 1993). These devices capture solvent vapours by condensation, enabling the reuse of solvents as raw materials or for cleaning vessels and equipment. Scrubbers neutralize or absorb acid, caustic and soluble gases and vapours, discharging their effluents to waste treatment systems.

Recycled solvents may be reused as media for performing reactions and extractions, and cleaning operations. Different types of solvents should not be mixed, since this reduces their ability to be recycled. Some solvents should be segregated during processing (e.g., chlorinated and non-chlorinated, aliphatic and aromatic, aqueous and flammable solvents). Dissolved and suspended solids are extracted or separated from the solvents, before the solvents are recovered. Laboratory analysis identifies the composition and properties of waste solvents and recycled raw materials. Many new waste prevention and control technologies are being developed for solid, liquid and gaseous wastes.

General housekeeping and operating practices

Written operating procedures, material-handling instructions and waste management practices reduce the generation and improve the treatment of wastes (Theodore and McGuinn 1992). Good operating and housekeeping practices identify specific responsibilities for generating, handling and treating wastes. Training and supervision of operating staff increases their ability to improve and maintain efficient manufacturing and waste management operations. Workers should be trained on the hazards of waste management practices and the proper means of responding to emergency spills, leaks and fugitive emissions. Worker training should address material handling, cleaning or neutralizing wastes and wearing respirators and PPE. Spill and leak detection devices prevent pollution by routinely monitoring production equipment and utilities, identifying and controlling fugitive emissions and leaks. These activities may be

successfully integrated with preventive maintenance practices to clean, calibrate, replace and repair equipment that creates pollution.

Written instructions describing normal operating procedures, as well as start-up, shut-down and emergency procedures, prevent pollution and reduce risks to worker health and safety. Careful management of material inventories decreases the excessive purchasing of raw materials and generation of wastes. Computer systems can assist the effective management of plant operations, maintenance practices and material inventories. Automatic weighing, monitoring and alarm systems can be installed to improve the management of materials and equipment (e.g., storage tanks, process equipment and waste treatment systems). Modern instrument and control systems often increase the productivity of operations, reducing pollution and health and safety hazards. Comprehensive pollution prevention programmes examine all wastes generated at a facility and examine the options for eliminating, reducing or treating them. Environmental audits examine the strengths and weaknesses of pollution prevention and waste management programmes, seeking to optimize their performance.

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT –IV - SBT1302 – PHARMACEUTICAL BIOTECHNOLOGY

COURSE OUTCOMES;

At the end of the course the student would be able to;

- CO1-Identify the prospects of applying Biotechnological concepts in drug discovery
- CO2-Inspect the kinetics, dynamics of drugs relating to the routes of administration
- CO3-Categorize the unit operation principles involved in the bulk drug manufacturing process
- CO4-Compare the product development of various drug formulations Tablets, Capsules, parentrals, oral liquids and topical applications.
- CO5-Appraise the mode of action of various drugs, laxatives, nonsteroidal contraceptives, antiseptics, antacids, analgesics, vitamins and hormones
- CO6-Elaborate the regulatory aspects involved in preclinical and clinical testing of drugs

PRODUCT FORMS AND DEVELOPMENT

Tablets

A **tablet** is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose.

Excipients

The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive.

Coating the tablet

A **polymer coating** is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

Compressed tablets

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered **sublingually, buccally, rectally or intravaginally.**

Forms of tablets

The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. Medicinal tablets were originally made in the shape of a disk of whatever color their components determined, but are now made in many shapes and colors to help distinguish different medicines.

Stamping of tablets

Tablets are often stamped with **symbols, letters,** and **numbers**, which enable them to be identified.

Size of tablets

Sizes of tablets to be swallowed range from a **few millimeters** to about a **centimeter.**

Shape of tablets

Some tablets are in the shape of capsules, and are called **"caplets".** Other products are manufactured in the form of tablets which are designed to dissolve or disintegrate; e.g. cleaning and deodorizing products.

Medicinal tablets and capsules are often called **"pills",** though originally, "pill" referred specifically to a **soft mass rolled into a ball shape,** rather than a compressed powder.

Compressed tablets

A tablet prepared, usually as a large-scale production, by means of great pressure; most compressed tablets consist of the active ingredient and a diluent, binder, disintegrator, and lubricant.

Tablet formulation

In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or **active pharmaceutical ingredient (API)** content uniformity but granulation should prevent this. Content uniformity ensures that the same API dose is delivered with each tablet.

Some **APIs** may be tableted as pure substances, but this is rarely the case; most formulations include excipients. Normally, a pharmacologically inactive ingredient (excipient) termed a *binder* is added to help hold the tablet together and give it strength.

Binders / binding agent

A wide variety of binders may be used, some common ones including **lactose, dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, povidone polyvinylpyrrolidone** and **modified cellulose** (for example hydroxypropyl methylcellulose and hydroxyethylcellulose).

Often, an ingredient is also needed to act as a **disintegrant** to aid tablet dispersion once swallowed, releasing the API for absorption. Some binders, such as **starch** and **cellulose**, are also excellent disintegrants.

Advantages and disadvantages

Tablets are **simple** and convenient to use. They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to **protect unstable medications** or **disguise unpalatable ingredients. Colored coatings, embossed markings** and **printing** can be used to aid **tablet recognition.** Manufacturing processes and techniques can provide tablets special properties, for example, sustained release or fast dissolving formulations.

Some drugs may be unsuitable for administration by the oral route. For example, **protein drugs** such as **insulin** may be **denatured** by **stomach acids.** Such drugs **cannot be made** into **tablets.** Some drugs may be deactivated by the liver when they are carried there from the gastrointestinal tract by the hepatic portal vein (the "first pass effect"), making them unsuitable for oral use.

Drugs which can be taken sublingually are absorbed through the oral mucosae, so that they bypass the liver and are less susceptible to the first pass effect. The oral bioavailability of some drugs may be low due to poor absorption from the gastrointestinal tract. Such drugs may need to be given in very high doses or by injection.

For drugs that need to have rapid onset, or that have severe side effects, the oral route may not be suitable. For example salbutamol, used to treat problems in the pulmonary system, can have effects on the heart and circulation if taken orally; these effects are greatly reduced by inhaling smaller doses direct to the required site of action.

A proportion of the population have difficulties swallowing tablets either because they just don't like taking them or because their medical condition makes it difficult for them (dysphagia, vomiting). In such instances it may be better to consider alternative dosage form or administration route

Granulation

Granulation is the act or **process of forming or crystallizing into grains.** Granules typically have a size range between **0.2 to 4.0 mm** depending on their subsequent use.

Pharmaceutical industry

In the pharmaceutical industry, granulation refers to the act or process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules.

It is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Granulation is extensively used in the manufacturing of tablets and pellets (or spheroids).

The granulation process combines one or more powder particles and forms a granule that will allow tableting or spheronization process to be within required limits. This way predictable and repeatable process is possible and quality tablets or pellets can be produced using tabletting or spheronization equipment.

Purpose of granulation

o Granulation is carried out for various reasons, one of those is to prevent the segregation of the constituents of powder mix. Segregation is due to differences in the size or density of the component of the mix.

o Normally, the smaller and/or denser particles tend to concentrate at the base of the container with the larger and/or less dense ones on the top. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of granules will not occur.

o Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

o Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same powders are often more easily compacted. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule.

For example, if one were to make tablets from granulated sugar versus powdered sugar, powdered sugar would be difficult to compress into a tablet and granulated sugar would be easy to compress. Powdered sugar's small particles have poor flow and compression characteristics. These small particles would have to be compressed very slowly for a long period of time to make a worthwhile tablet. Unless the powdered sugar is granulated, it could not efficiently be made into a tablet that has good tablet characteristics such as uniform content or consistent hardness.

Granulation techniques

In pharmaceutical industry, two types of granulation technologies are employed, namely,

1. Wet granulation and

2. Dry granulation.

Wet granulation

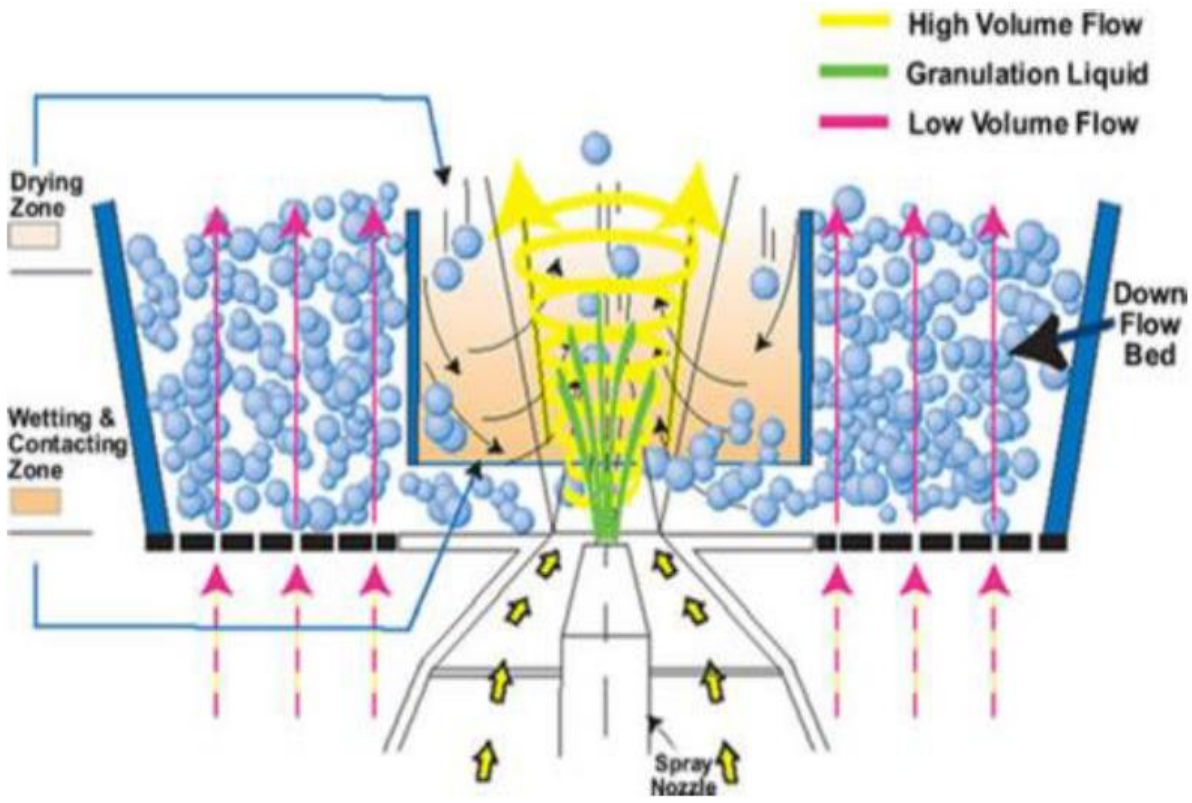
In wet granulation, granules are formed by the addition of a granulation liquid onto a powder bed which is under the influence of an impeller (in a High shear granulator, screws (in a twin screw granulator) or air (in a fluidized bed granulator). The agitation resulting in the system along with the wetting of the components within the formulation results in the aggregation of the primary powder particles to produce wet granules.

The granulation liquid (fluid) contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol either alone or in combination. The liquid solution can be either aqueous based or solvent based. Aqueous solutions have the advantage of being safer to deal with than solvents.

Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together. However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required.

Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules.

The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules, which is subsequently dried.



Dry granulation

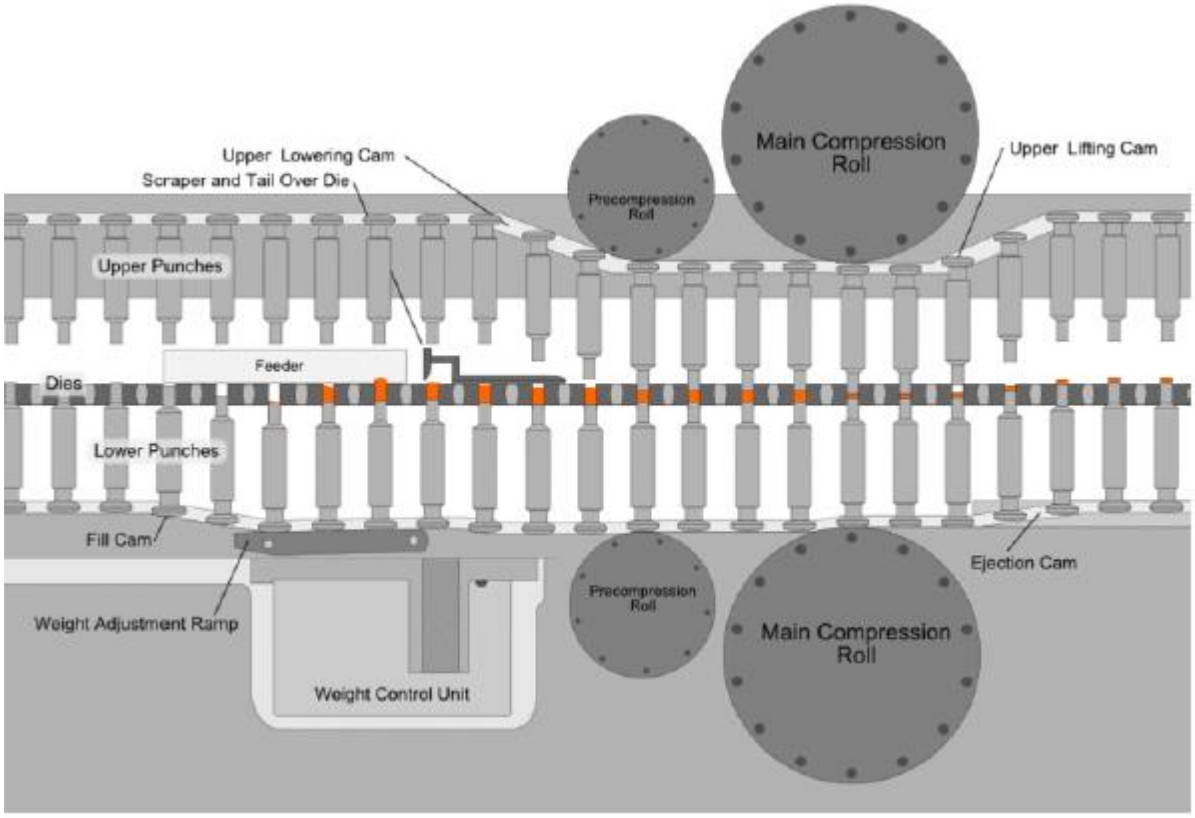
The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. Sweying granulator or high shear mixer-granulator can be used for the dry granulation. Dry granulation can be conducted under two processes; either a large tablet (slug) is produced in a heavy duty tabletting press or the powder is squeezed between two counter-rotating rollers to produce a continuous sheet or ribbon of materials (roller compactor, commonly referred to as a chilsonator).

When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. The roller compactor (granulator-compactor) uses an auger-feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into a ribbon or small pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression.

Tablet Presses

A tablet press is a mechanical device that compresses powder into tablets of uniform size and weight. A press can be used to manufacture tablets of a wide variety of materials, including pharmaceuticals, illicit drugs such as MDMA, cleaning products, and cosmetics. To form a tablet, the granulated material must be metered into a cavity formed by two punches and a die, and then the punches must be pressed together with great force to fuse the material together.

Working principle of tablet press



A tablet is formed by the combined pressing action of two punches and a die. In the first step of a typical operation, the bottom punch is lowered in the die creating a cavity into which the granulated feedstock is fed.

The exact depth of the lower punch can be precisely controlled to meter the amount of powder that fills the cavity. The excess is scraped from the top of the die, and the lower punch is drawn down and temporarily covered to prevent spillage.

Then, the upper punch is brought down into contact with the powder as the cover is removed. The force of compression is delivered by high pressure compression rolls which fuse the granulated material together into a hard tablet.

After compression, the **lower punch** is **raised** to **eject** the **tablet.**

Types of tablet presses

1. Single-punch press and

2. Rotary tablet press

Most high speed tablet presses take the form of a rotating turret that holds any number of punches. As they rotate around the turret, the punches come into contact with cams which control the punch's vertical position. Punches and dies are usually custom made for each application, and can be made in a wide variety of sizes, shapes, and can be customized with manufacturer codes and scoring lines to make tablets easier to break. Depending on tablet size, shape, material, and press configuration, a typical modern press can produce from **250,000 to over 1,000,000 tablets an hour.**

Single-punch press

Rotary tablet press

Single-punch press Rotary tablet press

Die

A **die** is a specialized too used in manufacturing industries to cut or shape material using a press.

MDMA

3,4-methylenedioxy-*N*-methylamphetamine is an empathogenic drug of the phenethylamine and amphetamine classes of drugs. The terms empathogen and entactogen are used to describe a class of psychoactive drugs that produce distinctive emotional and social effects similar to those of MDMA (ecstasy).

MDMA can induce, Euphoria, A sense of intimacy with others, Diminished anxiety and Mild psychedelia. Many studies, particularly in the fields of psychology and cognitive therapy, have suggested MDMA has therapeutic benefits and facilitates therapy sessions in certain individuals, a practice for which it had been formally used in the past. Clinical trials are now testing the therapeutic potential of MDMA for post-traumatic stress disorder, anxiety associated with terminal cancer and addiction.

Euphoria

Euphoria is medically recognized as a mental and emotional condition in which a person experiences intense feeling of well-being, elation, happiness, excitement, and joy.

psychedelia Psychedelic states are an array of experiences including changes of perception such ashallucinations, synesthesia, altered states of awareness or focused consciousness, variation in thought patterns, trance or hypnotic states, mysticalstates, and other mind alterations.

Coating of tablets

Many tablets today are coated after being pressed. Although sugar-coating was popular in the past, the process has many drawbacks.

Modern tablet coatings

Modern tablet coatings are polymer and polysaccharide based, with plasticizers (dispersants are additives that increase the plasticity or fluidity of a material). The dominant applications are for plastics, especially polyvinyl chloride (PVC) and pigments included.

Nature of tablet coatings

Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets.

Merits of tablet coatings

Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow. Tablet coatings are also useful to extend the shelf-life of components that are sensitive to moisture or oxidation. Special coatings (for example with pearlescent effects) can enhance brand recognition.

Enteric coatings

 If the active ingredient of a tablet is sensitive to acid, or is irritant to the stomach lining, an enteric coating can be used, which is resistant to stomach acid, and dissolves in the less acidic area of the intestines.

 Enteric coatings are also used for medicines that can be negatively affected by taking a long time to reach the small intestine, where they are absorbed.

 Coatings are often chosen to control the rate of dissolution of the drug in the gastrointestinal tract. Some drugs will be absorbed better at different points in the digestive system.

 If the highest percentage of absorption of a drug takes place in the stomach, a coating that dissolves quickly and easily in acid will be selected.

 If the rate of absorption is best in the large intestine or colon, then a coating that is acid resistant and dissolves slowly would be used to ensure it reached that point before dispersing.

Tablet coating machines

There are two types of coating machines used in the pharmaceutical industry:

1. Coating pans and

2. Automatic coaters.

Coating pans are used mostly for sugar coating of pellets. Automatic coaters are used for all kinds of coatings; they can be equipped with remote control panel, dehumidifier, dust collectors. The explosion-proof design is required for alcohol containing coatings.

Pill splitters

It is sometimes necessary to split tablets into halves or quarters. Tablets are easier to break accurately if scored, but there are devices called pill-splitters which cut unscored and scored tablets. Tablets with special coatings (for example enteric coatings or controlled-release coatings) should not be broken before use, as this will expose the tablet core to the digestive juices, circumventing the intended delayed-release effect.

Scored and unscored tablets

A scored tablet is any tablet that has an indentation where it looks like the tablet has been pre-cut. An unscored tablet has no pre-cut line.

Capsules

In the manufacture of pharmaceuticals, **encapsulation** refers to a range of techniques used to enclose medicines in a relatively stable shell known as a **capsule**, allowing them to, for example, be taken orally or be used as suppositories.

Types of capsules

The two main types of capsules are:

 Hard-shelled capsules, which are typically made using gelatin and contain dry, powdered ingredients or miniature pellets made by, e.g. processes of extrusion or spheronisation.

 Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Both of these classes of capsules are made from aqueous solutions of gelling agents like:

 Animal protein mainly **gelatin;**

 Plant polysaccharides or **their derivatives** like **carrageenans** and **modified forms** of **starch** and **cellulose.**

Ingredients added to capsule

Other ingredients can be added to the gelling agent solution like

 Plasticizers such as glycerin and/or sorbitol to decrease the capsule's hardness,

 Coloring Agents,

 Preservatives,

 Disintegrants,

 Lubricants and

 Surface treatment

Since their inception, capsules have been viewed by consumers as the most efficient method of taking medication. For this reason, producers of drugs such as OTC analgesics wanting to emphasize the strength of their product developed the "caplet" or "capsule-shaped tablet" in order to tie this positive association to more efficiently-produced tablet pills. After the 1982 Tylenol tampering murders, capsules experienced a minor fall in popularity as tablets were seen as more resistant to tampering.

Single piece gel encapsulation

In 1834, Mothes and Dublanc were granted a patent for a method to produce a single-piece gelatin capsule that was sealed with a drop of gelatin solution. They used individual iron moulds for their process, filling the capsules individually with a medicine dropper.

Later on, methods were developed that used sets of plates with pockets to form the capsules. Although some companies still use this method, the equipment is not produced commercially any more. All modern soft-gel encapsulation uses variations of a process developed by R.P. Scherer in 1933. His innovation was to use a rotary die to produce the capsules, with the filling taking place by blow molding. This method reduced wastage, and was the first process to yield capsules with highly repeatable dosage. The current owner of the RPS cherer technology is Catalent Pharma Solutions, the world's largest manufacturer of prescription pharmaceutical softgels.

Softgels

Softgels can be an effective delivery system for oral drugs, especially poorly soluble drugs. This is because the fill can contain liquid ingredients that help increase solubility or permeability of the drug across the membranes in the body.

Liquid ingredients are difficult to include in any other solid dosage form such as a tablet. Softgels are also highly suited to potent drugs (for example, where the dose is <100 μg), where the highly reproducible filling process helps ensure each softgel has the same drug content, and because the operators are not exposed to any drug dust during the manufacturing process.

In 1949, the Lederle Laboratories division of the American Cyanamid Company developed the "Accogel" process, allowing powders to be accurately filled into soft gelatin capsules.

Two-piece gel encapsulation

The capsules are made in two parts by dipping metal pins in the gelling agent solution. Two-piece gelatin capsule machinery is manufactured by R&J Engineering Corporation of Canada. The capsules are supplied as closed units to the pharmaceutical manufacturer. Before use, the two halves are separated, the capsule is filled with powder or more normally pellets made by the process of Extrusion & Spheronization (either by placing a compressed slug of powder into one half of the capsule, or by filling one half of the capsule with loose powder) and the other half of the capsule is pressed on.

With the compressed slug method, weight varies less between capsules. However, the machinery required to manufacture them is more complex. The powder or spheroids inside the

capsule contains the active ingredient(s) and any excipients, such as binders, disintegrants, fillers, glidant, and preservatives.

Manufacturing materials

 Gelatin capsules, informally called **gel caps** or **gelcaps**, are composed of **gelatin** manufactured from the **collagen** of **animal skin** or **bone.**

 Vegetable capsules are composed of **hypromellose,** a **polymer formulated** from **cellulose.**

Manufacturing equipment

 The process of encapsulation of hard gelatin capsules could be done on manual, semi-automatic and automatic machines.

 Softgels are filled at the same time as they are produced and sealed on the rotary die of fully automatic machine.

Dosage forms preferred by the public to consume

Dosage forms

Dosage forms (also called **unit doses**) are essentially pharmaceutical products in the form in which they are marketed for use, typically involving a mixture of active drug components and nondrug components (excipients), along with other non-reusable material that may not be considered either ingredient or packaging (such as a capsule shell, for example).

Parenteral nutrition

Parenteral nutrition (PN) is feeding a person intravenously, bypassing the usual process of eating and digestion. The person receives nutritional formulae that contain nutrients such as glucose, amino acids, lipids and added vitamins and dietary minerals.

It is called **total parenteral nutrition** (TPN) or **total nutrient admixture** (TNA) when no significant nutrition is obtained by other routes. It may be called **peripheral parenteral nutrition** (PPN) when administered through vein access in a limb, rather than through a central vein.

Mechanical pumps to administer TPN

A mechanical pump under computer control is used to dispense the TPN fluid. Pumps are available that allow TPN administration at home, usually with the preparation and attachment by a family member. These pumps operate on an external dispensing line, part of a single-use dispensing cassette. Connection of the dispensing line to the patient is via a valve on a semi-permanent attached venous port whose closure is displaced by a connection on the dispensing

line. Preparation, attachment, and valve replacement require care in sanitation and sterile techniques at specific locations. The use of a rechargeable battery and a portable component pack allows a convenient household mobility for many patients during administration periods, these being typically from twelve to sixteen hours a day.

Indications

 Total parenteral nutrition (TPN) is provided when the gastrointestinal tract is nonfunctional because of an interruption in its continuity (it is blocked, or has a leak - a fistula) or because its absorptive capacity is impaired.

 It has been used for comatose patients, although enteral feeding is usually preferable, and less prone to complications.

 Parenteral nutrition is used to prevent malnutrition in patients who are unable to obtain adequate nutrients by oral or enteral routes.

Gastrointestinal disorders

TPN may be the only feasible option for providing nutrition to patients who do not have a functioning gastrointestinal tract or who have disorders requiring complete bowel rest, including bowel obstruction, short bowel syndrome, Gastroschisis, prolonged diarrhea regardless of its cause, high-output fistula, very severe Crohn's disease or ulcerative colitis, and certain pediatric GI disorders including congenital GI anomalies and necrotizing enterocolitis**.**

Duration

Short-term PN may be used if a person's digestive system has shut down (for instance by peritonitis), and they are at a low enough weight to cause concerns about nutrition during an extended hospital stay.

Long-term PN is occasionally used to treat people suffering the extended consequences of an accident, surgery, or digestive disorder. PN has extended the life of children born with nonexistent or severely deformed organs.

Complications

TPN fully by-passes the GI tract and normal methods of nutrient absorption. Possible complications, which may be significant, are listed below.

Infection

TPN requires a chronic IV access for the solution to run through, and the most common complication is infection of this catheter. Infection is a common cause of death in these patients,

with a mortality rate of approximately 15% per infection, and death usually results from septic shock.

Blood clots

Chronic IV access leaves a foreign body in the vascular system, and blood clots on this IV line are common. Death can result from pulmonary embolism wherein a clot that starts on the IV line but breaks off and goes into the lungs.

Fatty liver and liver failure

Fatty liver is usually a more long-term complication of TPN, though over a long enough course it is fairly common. The pathogenesis is due to using linoleic acid (an omega-6 fatty acid component of soybean oil) as a major source of calories.

Solutions

The nutrient solution consists of water and electrolytes; glucose, amino acids, and lipids; essential vitamins, minerals and trace elements are added or given separately. Previously lipid emulsions were given separately but it is becoming more common for a "three-in-one" solution of glucose, proteins, and lipids to be administered.

Emulsifiers Only a limited number of emulsifiers is commonly regarded as safe to use for parenteral administration, of which the most important is lecithin. **Lecithin** can be **biodegraded** and **metabolized,** since it is an **integral part** of **biological membranes,** making it virtually **non-toxic.** Other emulsifiers can only be **excreted** via the **kidneys, creating a toxic load.** The emulsifier of choice for most fat emulsions used for parenteral nutrition is a highly purified egg lecithin, due to its **low toxicity** and **complete integration** with **cell membranes.**

Total parenteral nutrition Examples of total parenteral nutrition solutions			
Substance	**Normal patient**	**High stress**	**Fluid-restricted**
Amino acids	85 g	128 g	75 g
Dextrose	250 g	350 g	250 g
Lipids	100 g	100 g	50 g
Na+	150 mEq	155 mEq	80 mEq
K+	80 mEq	80 mEq	40 mEq
Ca2+	360 mg	360 mg	180 mg
Mg2+	240 mg	240 mg	120 mg
Acetate	72 mEq	226 mEq	134 mEq
Cl-	143 mEq	145 mEq	70 mEq
P	310 mg	465 mg	233 mg
MVI-12	10 mL	10 mL	10 mL
Trace elements	5 mL	5 mL	5 mL

Solutions for total parenteral nutrition may be customized to individual patient requirements, or standardized solutions may be used. The use of standardized parenteral nutrition solutions is cost effective and may provide better control of serum electrolytes.

Ideally each patient is assessed individually before commencing on parenteral nutrition, and a team consisting of specialised doctors, nurses, clinical pharmacists and Registered Dietitians evaluate the patient's individual data and decide what PN formula to use and at what infusion rate.

For energy only, intravenous sugar solutions with dextrose or glucose are generally used. This is not considered to be parenteral nutrition as it does not prevent malnutrition when used on its own. Standardized solutions may also differ between developers. The solution for normal patients may be given both centrally and peripherally.

Individual components

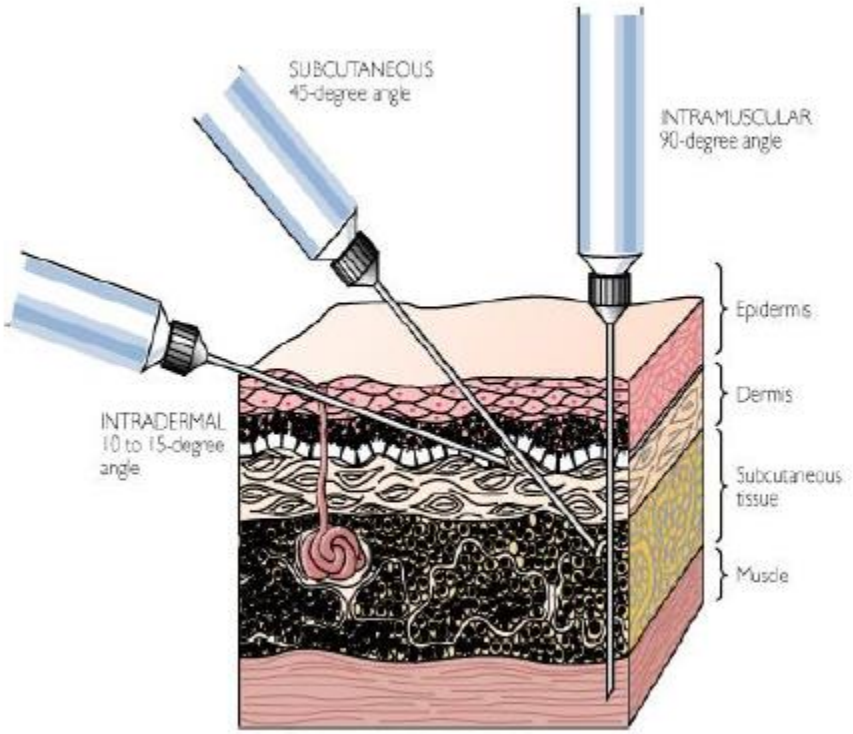
Individual nutrient components may be added to more precisely adjust the body contents of it. That individual nutrient may, if possible, be infused individually, or it may be injected into a bag of nutrient solution or intravenous fluids that is given to the patient. Administration of individual components may be more hazardous than administration of pre-mixed solutions

such as those used in total parenteral nutrition, because the latter are generally already balanced in regard to e.g. osmolarity and ability to infuse peripherally. For example, incorrect IV administration of concentrated potassium can be lethal, but this is not a danger if the potassium is mixed in TPN solution and diluted.

Vitamins may be added to a bulk premixed nutrient immediately before administration, typically in two doses, one fat soluble, the other water soluble, this since the additional vitamins can promote spoilage of stored product.

Route of administration of parenteral solutions

1. Intradermal (Id) – into dermis
2. Intramuscular (Im) – into muscle
3. Intraosseous (Io) - injecting directly into the marrow of a bone
4. Intraperitoneal (Ip) – into peritoneum
5. **Intravenous (Iv) – into vein**
6. Subcutaneous (Sc) – into subcutaneous tissue
7. Intrathecal (It) injection into the spinal column



Oral Liquids

Oral administration is a route of administration where a substance is taken through the mouth. Many medications are taken orally because they are intended to have a systemic effect, reaching different parts of the body via the bloodstream, for example.

Scope

Oral administration is a part of enteral administration, which also includes

 Buccal (dissolved inside the cheek)

 Sublabial (dissolved under the lip) and

 Sublingual administration (dissolved under the tongue). Note that due to rapid absorption many consider SL a parenteral route.

Buccal administration

Buccal administration refers to a Route of administration. Topical route of administration by which drugs held or applied in the buccal area (in the cheek) diffuse through the oral mucosa (tissues which line the mouth) and enter directly into the bloodstream. Buccal administration may provide better bioavailability of some drugs and a more rapid onset of action compared to oral administration because the medication does not pass through the digestive system and thereby avoids first pass metabolism.

As of May 2014, buccal forms of the psychiatric drug, asenapine; the opioid drugs buprenorphine, naloxone, and fentanyl; the cardiovascular drug nitroglycerin; the nausea medication Prochlorperazine; the hormone replacement therapy testosterone, and nicotine as a smoking cessation aid, were commercially available in buccal forms, as was midazolam, an anticonvulsant, used to treat acute epileptic seizures. Buccal administration of vaccines has been studied, but there are challenges to this approach due to immune tolerance mechanisms that prevent the body from over-reacting to immunogens encountered in the course of daily life.

Sublabial, literally 'under the lip', from Latin, refers to the pharmacological route of administration by which the active substance is placed between the lip and the gingiva. The frenula may be irritated when in contact with corrosive materials but can be avoided with this route.

It is usually used for drugs such as Glyceryl trinitrate, for example, in angina pectoris.

Upper lip administration

Some drugs are inactive in the digestive tract, but this can be avoided if held between the upper lip and gum. This prevents the substances from getting swallowed with salivation, as would normally occur between the lower lip and gum, permitting slow release of the drug to prolong the duration of action.

Sublingual (abbreviated **SL**), from the Latin for "under the tongue", refers to the pharmacological route of administration by which drugs diffuse into the blood through tissues under the tongue. Many drugs are designed for sublingual administration, including cardiovascular drugs, steroids, barbiturates, opioid analgesics with poor gastrointestinal bioavailability, enzymes and, increasingly, vitamins and minerals.

Principle

When a chemical comes in contact with the mucous membrane beneath the tongue, it diffuses through it. Because the connective tissue beneath the epithelium contains a profusion of capillaries, the substance then diffuses into them and enters the venous circulation. In contrast, substances absorbed in the intestines are subject to "first-pass metabolism" in the liver before entering the general circulation.

Sublingual administration has certain advantages over oral administration. Being more direct, it is often faster, and it ensures that the substance will risk degradation only by salivary enzymes before entering the bloodstream, whereas orally administered drugs must survive passage through the hostile environment of the gastrointestinal tract, which risks degrading them, either by stomach acid or bile, or by the many enzymes therein, such as monoamine oxidase (MAO). Furthermore, after absorption from the gastrointestinal tract, such drugs must pass to the liver, where they may be extensively altered; this is known as the first pass effect of drug metabolism. Due to the digestive activity of the stomach and intestines and the solubility of the GI tract, the oral route is unsuitable for certain substances, such as salvinorin A.

Forms

Pharmaceutical preparations for sublingual administration are manufactured in the form of:

 Sublingual tablets—tablets which easily melt in the mouth, dissolve rapidly and with little or no residue. Nitroglycerine tablets are an example, the anti-emeticondansetron is another.

 Sublingual strips—similar to that tablets in that they easily melt in the mouth and dissolve rapidly. Suboxone is an example of medication that comes in a sublingual strip.

 Multi-Purpose Tablets—Soluble tablets for either oral or sublingual (or buccal) administration, often also suitable for preparation of injections, Hydrostat (hydromorphone) and a number of brands of morphine tablets and cubes.

 Sublingual Drops—a concentrated solution to be dropped under the tongue, as with some nicocodeine cough preparatations,

 Sublingual Spray—spray for the tongue; certain human and veterinary drugs are dispensed as such.

 Lozenge—effects a metred and patient-controlled-rate combination of sublingual, buccal, and oral administration, as with the Actiq fentanyl lozenge-on-a-stick (lollipop).

 Effervescent Buccal or Sublingual Tablets—this method drives the drug through the mucous membranes much faster (this is the case in the stomach with carbonated or effervescent liquids as well) and is used in the Fentora fentanyl buccal tablet.

Injections

An **injection** is an infusion method of putting fluid into the body, usually with a syringe and a hollow needle which is pierced through the skin to a sufficient depth for the material to be administered into the body. An injection follows a parenteral route of administration; that is, administration via a route other than through the digestive tract. Since the process inherently involves a small puncture wound to the body (with varying degrees of pain depending on injection type and location, medication type, needle gauge and the skill of the individual administering the injection), fear of needles is a common phobia.

There are several methods of injection or infusion used in humans, including intradermal, subcutaneous, intramuscular,intravenous, intraosseous, intraperitoneal, intrathecal, epidural, intracardiac, intraarticular, intracavernous, and intravitreal. Rodents used for research are often administered intracerebral, intracerebroventricular, or intraportal injections as well. Long-acting forms of subcutaneous/intramuscular injections are available for various drugs, and are called depot injections.

Injections are among the most common health care procedures, with at least 16 billion administered in developing and transitional countries each year. 95% of injections are administered in curative care, 3% are for immunization, and the rest for other purposes, such as blood transfusions. In some instances the term *injection* is used synonymously with inoculation even by different workers in the same hospital. This should not cause confusion; the focus is on what is being injected/inoculated, not the terminology of the procedure.

Intramuscular injection

In an **intramuscular injection**, the medication is delivered directly into a muscle. Many vaccines are administered intramuscularly, as are codeine, metoclopramide, and many other medications. Many drugs injected intramuscularly are absorbed into the muscle fairly and quickly, while others are more gradual. Injections to the buttocks are known to reach the

bloodstream quickly due to the large amount of muscular tissue and corresponding blood supply. Generally, intramuscular injections are administered by a trained medical professional; however, prescribed self-administered intramuscular injections are becoming more common for patients who require these injections routinely.

Depot injection

A **depot injection** is an injection, usually subcutaneous, intradermal, or intramuscular, that deposits a drug in a localized mass, called a depot, from which it is gradually absorbed by surrounding tissue. Such injection allows the active compound to be released in a consistent way over a long period. Depot injections are usually either solid or oil-based. Depot injections may be available as certain forms of a drug, such as decanoate salts or esters. Examples of depot injections include Depo Provera and haloperidol decanoate. Prostate cancer patients receiving hormone therapy usually get depot injections as a treatment or therapy. Zoladex is an example of a medication delivered by depot for prostate cancer treatment or therapy.

The advantages of using a long-acting depot injection include increased medication compliance due to reduction in the frequency of dosing, as well as more consistent serum concentrations. A significant disadvantage is that the drug is not immediately reversible, since it is slowly released.

In psychiatric nursing, a short acting depot, zuclopenthixol acetate (Clopixol Acuphase), which lasts in the system from 24 – 72 hours, is now more regularly used for rapid tranquillisation

Infiltration

The pharmaceutical injection type of infiltration involves loading a volume of tissue with the drug, filling the interstitial space. Local anesthetics are often infiltrated into the dermis and hypodermis.

Hypodermic injections in nature

Various animals, and some plants, have been injecting for various reasons long before humans began doing so in a process commonly called stinging. Some examples include:

- Snakes, wasps, scorpions: poison, to kill prey and self-defense.
- Some bees: poison, to defend themselves and their nests.
- Cnidaria (jellyfish, etc.): poison, to kill prey.
- Stinging nettles: poison, to try to avoid being eaten.
- Stingrays: poison, defense mechanism when provoked

Injection pain

The pain of an injection may be lessened by prior application of ice or topical anesthetic, or simultaneous pinching of the skin. Recent studies suggest that forced coughing during an injection stimulates a transient rise in blood pressure which inhibits the perception of pain. Sometimes, as with an amniocentesis, a local anesthetic is given.[4] The most common technique to reduce the pain of an injection is simply to distract the patient.

Babies can be distracted by giving them a small amount of sweet liquid, such as sugar solution, during the injection, which reduces crying.

Injection safety

40% of injections worldwide are administered with unsterilized, reused syringes and needles, and in some countries this proportion is 70%, exposing millions of people to infections.

Another risk is poor collection and disposal of dirty injection equipment, which exposes healthcare workers and the community to the risk of needle stick injuries. In some countries, unsafe disposal can lead to re-sale of used equipment on the black market. Many countries have legislation or policies that mandate that healthcare professionals use a safety syringe (safety engineered needle) or alternative methods of administering medicines whenever possible.

Open burning of syringes, which is considered unsafe by the World Health Organization, is reported by half of the non-industrialized countries.

According to one study, unsafe injections cause an estimated 1.3 million early deaths each year.

To improve injection safety, the WHO recommends:

1. Changing the behavior of health care workers and patients

2. Ensuring the availability of equipment and supplies

3. Managing waste safely and appropriately

A *needle tract infection* is an infection that occurs when pathogenic micro-organisms are seeded into the tissues of the body during an injection. Such infections are also referred to as *needlestick infections*.

Topical applications

A **topical medication** is a medication that is applied to a particular place on or in the body, as opposed to systemically. Most often this means application to body surfaces such as the skin or mucous membranes to treat ailments via a large range of classes including but not limited to creams, foams, gels, lotions, and ointments.

Many topical medications are epicutaneous, meaning that they are applied directly to the skin. Topical medications may also be inhalational, such as asthma medications, or applied to the surface of tissues other than the skin, such as eye drops applied to the conjunctiva, or ear drops placed in the ear, or medications applied to the surface of a tooth. As a route of administration, topical medications are contrasted with enteral (in the digestive tract) and intravascular/intravenous (injected into the circulatory system).

A topical effect, in the pharmacodynamic sense, may refer to a local, rather than systemic, target for a medication. However, many topically administered drugs have systemic effects, because they reach the circulation after being absorbed by the tissues.

Topical medications differ from many other types of drugs because mishandling them can lead to certain complications in a patient or administrator of the drug.

Some hydrophobic chemicals, such as steroid hormones, can be absorbed into the body after being applied to the skin in the form of a cream, gel, or lotion.Transdermal patches have become a popular means of administering some drugs for birth control, hormone replacement therapy, and prevention of motion sickness. One example of an antibiotic that may be applied topically is chloramphenicol.

Choice of base formulation

A medication's potency often is changed with its base. For example, some topical steroids will be classified one or two strengths higher when moving from cream to ointment. As a rule of thumb, an ointment base is more occlusive and will drive the medication into the skin more rapidly than a solution or cream base.

The manufacturer of each topical product has total control over the content of the base of a medication. Although containing the same active ingredients, one manufacturer's cream might be more acidic than the next, which could cause skin irritation or change its absorption rate. For example, a vaginal formulation ofmiconazole antifungal cream might irritate the skin less than an athlete foot formulation of miconazole cream. These variations can, on occasion, result in different clinical outcomes, even though the active ingredient is the same. No comparative potency labeling exists to ensure equal efficacy between brands of topical steroids (percentage of oil vs water dramatically affect the potency of topical steroid). Studies have confirmed that

the potency of some topical steroid products may differ according to manufacturer or brand. An example of this is the case of brand name Valisone cream and Kenalog cream in clinical studies have demonstrated significantly better vasoconstrictions than some forms of this drug produced by generic drug manufacturers. However, in a simple base like an ointment, much less variation between manufacturers is common.

In dermatology, the base of a topical medication is often as important as the medication itself. It is extremely important to receive a medication in the correct base, before applying to the skin. A pharmacist should not substitute an ointment for a cream, or vice versa, as the potency of the medication can change. Some physicians use a thick ointment to replace the waterproof barrier of the inflamed skin in the treatment of eczema, and a cream might not accomplish the same clinical intention.

Classes of topical medications

There are many general classes, with no clear dividing line between similar formulations. As a result, what the manufacturer's marketing department chooses to list on the label of a topical medication might be completely different from what the form would normally be called. For example, Eucerin "cream" is more appropriately described as an ointment than as a cream.

Topical solution

Topical solutions are of low viscosity and often use water or alcohol in the base. The solution can cause drying of the skin if alcohol is used in the base.[4] These are usually a powder dissolved in water, alcohol, and sometimes oil. Alcohol in topical steroids can frequently cause drying if it is used as a base ingredient. There is significant variability between brands. There is a risk of irritation, depending on the preservative(s) and fragrances used in the base. Some examples of topical solutions are given below:

1. Aluminium acetate topical solution: This is colorless, with a faint acetous odour and sweetish taste. It is applied topically as an astringent after dilution with 10-40 parts of water. This is used in many types of dermatologic lotions, creams, and pastes. Commercial premeasured and packed tablets and powders are available for this preparation.

2. Povidone iodine topical solution: This is a chemical complex of iodine with polyvinylpyrrolidone, the agent being a polymer having an

average molecular weight of 40,000. The povidone iodine contains 10% available iodine, slowly released when applied to skin. This preparation is employed topically as a surgical scrub and non irritating antiseptic solution, with its effectiveness being directly attributed to the presence and release of iodine from the complex. Commercial product: Betadine solution.

Lotion

Lotions are similar to solutions but are thicker and tend to be more emollient in nature than solution. They are usually oil mixed with water, and more often than not have less alcohol than solutions. Lotions can be drying if they contain a high amount of alcohol. There is a significant variability in the ingredients between different lotions.

Lotions can be used for the delivery to the skin of medications such as:

- Antibiotics
- Antiseptics
- Antifungals
- Corticosteroids
- Anti-acne agents
- Soothing, smoothing, moisturizing or protective agents (such as calamine)

Shake lotion

A mixture that separates into two or three parts with time. Frequently oil mixed with a water-based solution needs to be shaken into suspension before use. "Shake well before use".

Cream

A cream is an emulsion of oil and water in approximately equal proportions. It penetrates the stratum corneum outer layer of skin wall.. Cream is thicker than lotion, and maintains its shape when removed from its container. It tends to be moderate in moisturizing tendency. For topical steroid products, oil-in-water emulsions are common. Creams have a significant risk of causing immunological sensitization due to preservatives. It has a high rate of acceptance by patients. There is a great variation in ingredients, composition, pH, and tolerance among generic brands.

Uses of creams

- The provision of a barrier to protect the skin
- This may be a physical barrier or a chemical barrier as with sunscreens
- To aid in the retention of moisture (especially water-in-oil creams)
- Cleansing
- Emollient effects

 As a vehicle for drug substances such as local anaesthetics, anti-inflammatories (NSAIDs or corticosteroids), hormones, antibiotics, antifungals or counter-irritants.

Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base. This term has traditionally been applied to semisolids that possess a relatively fluid consistency formulated as either water-in-oil (e.g., Cold Cream) or oil-in-water (e.g., Fluocinolone Acetonide Cream) emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable. Creams can be used for administering drugs via the vaginal route (e.g., Triple Sulfa Vaginal Cream). Creams are used to help sun burns

Composition: There are four main ingredients of the cold cream 1: Water 2: Oil 3: Emulsifier 4: Thickening agent

Oinments

An **ointment** is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (oil 80% - water 20%) with a high viscosity, that is intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that it can contain.They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired.

Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye(an *eye ointment*), chest, vulva, anus, and nose. An ointment may or may not be medicated.

Ointments are usually very moisturizing, and good for dry skin. They have a low risk of sensitization due to having few ingredients beyond the base oil or fat, and low irritation risk. There is typically little variability between brands of drugs. They are often disliked by patients due to greasiness.

The vehicle of an ointment is known as the *ointment base*. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are:

 Hydrocarbon bases, e.g. hard paraffin, soft paraffin, microcrystalline wax and ceresine

 Absorption bases, e.g. wool fat, beeswax

 Water-soluble bases, e.g. macrogols 200, 300, 400

 Emulsifying bases, e.g. emulsifying wax, cetrimide

 Vegetable oils, e.g. olive oil, coconut oil, sesame oil, almond oil and peanut oil.

The medicaments are dispersed in the base and are divided after penetrating the living cells of the skin.

` The water number of an ointment is the maximum quantity of water that 100g of a base can contain at 20 °C.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. They can also be derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases.

Evaluation of ointments

1. Drug content
2. Release of medicament from base
3. Medicament penetration
4. Consistency of the preparation
5. Absorption of medicament into blood stream
6. Irritant effect

Properties which affect choice of an ointment base are:

1. Stability
2. Penetrability
3. Solvent property
4. Irritant effects
5. Ease of application and removal

Methods of preparation of ointments

Trituration

In this, finely subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base followed by dilution with gradually increasing amounts of the base.

Fusion In this method the ingredients are melted together in descending order of their melting points and stirred to ensure homogeneity.

Transdermal patch

Transdermal patches can be a very precise time released method of delivering a drug. Cutting a patch in half might affect the dose delivered.

The release of the active component from a transdermal delivery system (patch) may be controlled by diffusion through the adhesive which covers the whole patch, by diffusion through a membrane which may only have adhesive on the patch rim or drug release may be controlled by release from a polymer matrix. Cutting a patch might cause rapid dehydration of the base of the medicine and affect the rate of diffusion.

Gel Gels are thicker than a solution. Gels are often a semisolid emulsion in an alcohol base. Some will melt at body temperature. Gel tends to be cellulose cut with alcohol or acetone. Gels tend to be drying. Gels tend to have greatly variable ingredients between brands. Gels carry a significant risk of inducing hypersensitivity due to fragrances and preservatives. Gel is useful for the scalp and body folds. In applying gel one should avoid fissures and erosions due to the drying and stinging effect of the alcohol base. Gel enjoys a high rate of acceptance due to its cosmetic elegance.

Foam

Foam can be seen with topical steroid marketed for the scalp.

Eg: Desonide is a synthetic nonfluorinated corticosteroid; topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of these properties, however, is unclear for the dermal route of administration. Following absorption through the skin, corticosteroids follow pharmacokinetic pathways similarly to intravenously administered corticosteroids. The mechanism of corticosteroids is thought to induce phospholipase A2 inhibitory proteins (lipocortins). Lipocortins control the biosynthesis of inflammation mediators, likes prostaglandins and leukotrienes. Lipocortins can inhibit the common precursor of inflammation mediators, arachidonic acid.

Biofrequency chip

A topical dosage form that is programmed with low frequencies recognized by the body and complements topical medication adhered to the backing of the chip.

Powder

Powder is either the pure drug by itself (talcum powder), or is made of the drug mixed in a carrier such as corn starch or corn cob powder (Zeosorb AF - miconazole powder). Can be used as an inhaled topical (cocaine powder used in nasal surgery).

Eg: Miconazole is an imidazole antifungal agent, developed by Janssen Pharmaceutica, commonly applied topically to theskin or to mucous membranes to cure fungal infections. It works by inhibiting the synthesis of ergosterol, a critical component of fungal cell membranes. It can also be used against certain species of *Leishmania* protozoa which are a type of unicellular parasites that also contain ergosterol in their cell membranes. In addition to its antifungal and antiparasitic actions, it also has some antibacterial properties. It is marketed in various formulations under various brand names.

Solid

Medication may be placed in a solid form. Examples are deodorant, antiperspirants, astringents, and hemostatic agents. Some solids melt when they reach body temperature (e.g. rectal suppositories).

Eg: Action of antiperspirants

Antiperspirants contain ingredients that control sweat and body odour safely and effectively. They are readily available on the market as sprays (aerosol), sticks, creams or roll-ons.

When an antiperspirant is applied to the skin surface, its anti-perspirant ingredients – usually aluminium salts – dissolve in the sweat or moisture on the skin surface of the armpit. The dissolved substance forms a gel, which creates a small temporary 'plug' near the top of the sweat gland, significantly reducing the amount of sweat that is secreted to the skin surface. Bathing and washing will remove the antiperspirant gel.

Re-application of antiperspirants can be beneficial to help reduce sweating and keep fresh throughout the day. Antiperspirants reduce underarm sweating but they do not impact on the natural ability of the body to control its temperature (thermoregulation).

Paste

Paste combines three agents - oil, water, and powder. It is an ointment in which a powder is suspended.

Eg: Toothpaste is a paste or gel dentifrice used with a toothbrush as an accessory to clean and maintain the aesthetics and health of teeth. Toothpaste is used to promote oral hygiene: it serves as an abrasive that aids in removing the dental plaque and food from the teeth, assists in suppressing halitosis, and delivers active ingredients (most commonly fluoride) to help prevent tooth decay (dental caries) and gum disease (gingivitis). Salt and sodium bicarbonate (baking soda) are among materials that can be substituted for commercial toothpaste. Toothpaste is not intended to be swallowed due to the fluoride content, but is generally not very harmful if accidentally swallowed in small amounts; however, one should seek medical attention after swallowing abnormally large amounts

In addition to 20–42% water, toothpastes are derived from a variety of components, the three main ones being abrasives, fluoride, and detergents.

Abrasives

Abrasives constitute at least 50% of typical toothpaste. These insoluble particles help remove plaque from the teeth. The removal of plaque and calculus helps minimize cavities and periodontal disease. Representative abrasives include particles of aluminum hydroxide (Al(OH)3), calcium carbonate (CaCO3), various calcium hydrogen phosphates, various silicas and zeolites, and hydroxyapatite (Ca5(PO4)3OH).

Abrasives, like the dental polishing agents used in dentists' offices, also cause a small amount of enamel erosion which is termed "polishing" action. Some brands contain powdered white mica, which acts as a mild abrasive, and also adds a cosmetically pleasing glittery shimmer to the paste. The polishing of teeth removes stains from tooth surfaces, but has not been shown to improve dental health over and above the effects of the removal of plaque and calculus.

Fluorides Fluoride in various forms is the most popular active ingredient in toothpaste to prevent cavities. Fluoride occurs in small amounts in plants, animals, and some natural water sources. The additional fluoride in toothpaste has beneficial effects on the formation of dental enamel and bones. Sodium fluoride (NaF) is the most common source of fluoride, but stannous fluoride (SnF2), olaflur (an organic salt of fluoride), and sodium monofluorophosphate (Na2PO3F) are also used. Stannous fluoride has been shown to be more effective than sodium fluoride in reducing the incidence of dental caries and controlling gingivitis.

Much of the toothpaste sold in the United States has 1,000 to 1,100 parts per million fluoride. In European countries, such as the UK or Greece, the fluoride content is often higher; a NaF content of 0.312% w/w (1,450 ppm fluoride) is common.

Surfactants

Many, although not all, toothpastes contain sodium lauryl sulfate (SLS) or related surfactants (detergents). SLS is found in many other personal care products, as well, such as shampoo, and is mainly a foaming agent, which enables uniform distribution of toothpaste, improving its cleansing power.

Other components in tooth paste

Antibacterial agents

Triclosan, an antibacterial agent, is a common toothpaste ingredient in the United Kingdom. Triclosan or zinc chloride prevent gingivitis and, according to the American Dental

Association, helps reduce tartar and bad breath. A 2006 review of clinical research concluded there was evidence for the effectiveness of 0.30% triclosan in reducing plaque and gingivitis.

Flavorants

Toothpaste comes in a variety of colors, and flavors intended to encourage use of the product. Three most common flavorants are peppermint, spearmint, and wintergreen. Toothpaste flavored with peppermint-anise oil is popular in the Mediterranean region. These flavors are provided by the respective oils, e.g. peppermint oil. More exotic flavors include Anethole anise, apricot, bubblegum, cinnamon, fennel, lavender, neem, ginger, vanilla, lemon, orange, and pine. Alternatively, unflavored toothpastes exist.

Remineralizers

Hydroxyapatite nanocrystals and a variety of calcium phosphates are included in formulations for remineralization, i.e. the reformation of enamel.

Miscellaneous components

Agents are added to suppress the tendency of toothpaste to dry into a powder. Included are various sugar alcohols, such asglycerol, sorbitol, or xylitol, or related derivatives, such as 1,2-propylene glycol and polyethyleneglycol. Strontium chloride or potassium nitrate is included in some toothpaste to reduce sensitivity. Sodium polyphosphate is added to minimize the formation of tartar.

Tincture

A **tincture** is typically an alcoholic extract of plant or animal material or solution of such or of a low volatility substance (such as iodine and mercurochrome). Herbal tinctures are not always made using ethanol as the solvent, though this is most commonly the case. Other solvents include vinegar, glycerol, diethyl ether and propylene glycol, not all of which can be used for internal consumption. Ethanol has the advantage of being an excellent solvent for both acidic and basic (alkaline) constituents.

A tincture is a skin preparation that has a high percentage of alcohol. It would normally be used as a drug vehicle if drying of the area is desired.

Preservation of drugs

Profit making

Products, metabolites formation

Action of preservatives

Mechanism of action of antimicrobial agents

Cost effectiveness

Time factor

Pharmaceutical product

It is substance or mixture of substances, for use in human beings or animals for:

 The diagnosis, treatment, mitigation or prevention of a disease or its symptom

 The diagnosis, treatment, mitigation of any abnormal physical or physiological state or its symptoms or

 Altering, modifying, correcting or restoring any organic function.

Microbial spoilage

It is defined as “deterioration of pharmaceutical products by the contaminant microbe”.

Preservation

Inhibiting or minimizing preferably during the storage and multi-dose application the risk of microbial contamination of pharmaceutical products.

Microorganisms involved in the spoilage of pharmaceutical products

 Pseudomonas aeruginosa

 Salmonella cavaban

 Escherichia coli

 Staphylococcus aureus

 Clostridium botulinum

 Clostridium perfingens

 Streptococcus faecalis

 Proteus sp.

Sources of contamination

In manufacture

 Raw materials (water and materials with natural origin), microbiological quality

 Pharmaceutical industry environment – wet sites, cleaning equipment

 Packaging Eg: Cardboard, Corks, Papers are unsuitable packaging materials

 Containers those are frequently re-used

 Contamination of disinfectant due to re-used containers

 Repackaging of products purchased in bulk into smaller containers

 Processing

 Storage

 Transportation

In use

a. Human source

→ Normal flora of the patients

→ Highest risk of contamination in topical products – Staphylococcus, Micrococcus, Pseudomonas, Diphtheroids

→ Dispobable applicators and spoons for topical and oral products

→ In hospital – cross contamination between patients during use

→ Hand washing and creams used by staff-source of cross infection

→ Improper handling

b. Environmental source

→ Small number of airborne contaminants may settle in product

→ Water borne contaminants – Pseudomonas

c. Equipment source

→ Equipment for pharmaceutical drug administration

→ Hospital equipments – breathe tubes, ventilator, humidifiers and incubators. May be the living habitats of opportunistic pathogens colonizing wet sites (Pseudomonas)

Susceptibility of pharmaceutical products to microbial degradation

Therapeutic drugs

Alkaloids (morphine, atropine), Painkillers (aspirin, paracetamol), Thalidomide, Barbiturates, Steroid esters may serve as nutrients. Examples include:

Metabolism of atropine in eye drops by contaminating fungi

Inactivation of penicillin injections by Beta lactamase producing bacteria.

Chloramphenicol deactivation in an oral medicine by a chloramphenicol acetylase producing contaminant.

Microbial hydrolysis of aspirin in suspension by esterase producing bacteria.

Sweetening, flavoring and colouring agents

Many of the sugars and other sweetening agents used in pharmacy are ready substrates for microbial growth.

At one time, colouring agents (tartrazine and amaranth) and flavouring agents (Peppermint water) were kept as stock solution for extemporaneous dispensing exhibit support for the growth of Pseudomonas sp. Including P. aeruginosa.

Humectants

Glycerol, sorbitol can be metabolized thoroughly

Resistant when in high concentration

Organic polymers

Pectin, cellulose, dextran-microbial depolymerisation by a number of extracellular enzymes.

Agar-gar inert polymer

PEG - easily degraded

Synthetic polymers (nylon, polystyrene, polyester) – extremely resistant

Preservatives and disinfectants

Many preservatives and disinfectants can be metabolized by a wide variety of gram negative bacteria but at concentration below their effective use levels.

Pseudomonas has outstanding degradative capacity.

Surface active agents

Visible signs of microbial degradation

 Loss of viscosity and sedimentation due to depolymerisation of suspending agents.

 pH change

 Gas production

 Unpleasant smelling and tasting metabolites such as “sour” fatty acids, “fishy” amines, “bad eggs” bitter, earth or sticky taste or smell indicates the spoilage.

 Products may become unappealingly discoloured by microbial pigments of various shades.

 Microbial polymerization of sugars and surfactant molecules can produce shiny, viscous masses in syrups, shampoos and creams.

 Fungal growth in creams has produced gritty textures.

 Metabolism of surfactant in o/w emulsions reduce stability and accelerate creaming of the oil globules. Release of fatty acids lower ph and encourage coalescence of oil globules and cracking of emulsion.

Factors affecting microbial spoilage of pharmaceutical products

 Type and size of contaminant innoculum

 Nutritional factors

 Moisture contents – water activity

 Redox potential

 Storage temperature

 pH

 Packaging design

 Protection of microorganisms within pharmaceutical products.

Preservatives

Inhibit or minimize the risk of microbial contamination of pharmaceutical products preferably during the storage and multi-dose application.

Their inclusion may not be needed in case of tablets, powders and capsules.
They should never be added to mask the poor manufacturing process.

Features of the ideal preservative

 Should be free of toxic or irritant effects at the concentrations used

 Should be effective in preventing the growth of micro-organisms most likely to contaminate the preparation.

 Should be soluble in water to achieve adequate concentrations in the aqueous phase of a system of two or more phases.

 Has adequate stability to heat and prolonged storage, with no chemical decomposition or volatilization during the desired shelf life.

 Should be chemically compatible with all other formulation components and should retain the undissociated form at the ph of the preparation.

 Should not be adversely affected by the product's container or closure

 Should have an acceptable odour and colour.

 Should be cheap.

Types of preservatives

Cationic detergents

 Benzalkonium chloride

 Alky, trimethyl ammonium chloride

 Applied in cosmetics and contact lens solution

Alcohols

 chlorbutanol

 Dichlorobenzyl and benzyl alcohol

 Phenyl and phenoxy ethanol

 2-bromo-2-nitropropane-1,3-diol (bronopol)

Phenolic compounds

 Chlorinated and isopropyl derivatives of meta-cresol

Organic acids

 Acetic acid, lactic acid, citric acid, propionic acid.

 Benzoic acid and hydroxyl-benzoic acid

 Salicylic acid and salts

 Sorbate and salts

 Sulphur dioxide, sulphites and metabisulphites.

Factors affecting the efficacy and availability of preservatives

→ Chemical structure of the preservatives

→ Temperature

→ Capacity of preservatives

→ Presence of inactivating agents-dirty condition

→ Changes of concentration

→ Great inoculums size

→ Effects of product ph

→ Efficiency of multiphase systems

→ Effect of container and packaging

→ Type and initial level of contamination

Methods of preservation of pharmaceutical products

The 5 basic methods of preservation are as follows:

Physical protection

Preservative coating only

Water proof protection

Water vapour proof protection

Water vapour proof protection with desiccant

Analytical methods and test for various drugs and pharmaceuticals

Guided by pharmacology and clinical sciences, and driven by chemistry, pharmaceutical research in the past has played a crucial role in the progress of development of pharmaceuticals. The contribution of chemistry, pharmacology, microbiology and biochemistry has set a standard in the drug discovery where new drugs are no longer generated only by the imagination of chemists but these new drugs are the outcome of exchange of ideas between biologists and chemists.

The process of drug development starts with the innovation of a drug molecule that has showed therapeutic value to battle, control, check or cure diseases. The synthesis and characterization of such molecules which are also called active pharmaceutical ingredients (APIs) and their analysis to create preliminary safety and therapeutic efficacy data are prerequisites to identification of drug candidates for further detailed investigations .

The investigations on the pre drug discovery are based on knowing the basic cause of the disease to be treated, the information on how the genes are altered that cause the disease, the interaction of proteins and the affected cells and changes brought by these affected cells and how they affect these cells. Phase 1	50–200 healthy subjects (usually) or patients who are not expected to benefit from the IMP	Is the IMP safe in humans?
What does the body do to the IMP? (pharmacokinetics)		
What does the IMP do to the body? (pharmacodynamics)		
Will the IMP work in patients?		
Phase 2	100–400 patients with the target disease	Is the IMP∗ safe in patients?
Does the IMP seem to work in patients?		
Phase 3	1000–5000 patients with the target disease	Is the IMP really safe in patients?
Does the IMP really work in patients		

Phase 4	Many thousands or millions of patients with the target disease	Just how safe is the new medicine? (pharmacovigilance)
How does the new medicine compare with similar medicines?		

Analytical techniques

2.1. Titrimetric techniques

Origin of the titrimetric method of analysis goes back to somewhere in the middle of the 18th century. It was the year 1835 when Gay–Lussac invented the volumetric method which subsequently leads to the origin of term titration. Although the assay method is very old yet there are signs of some modernization, i.e., spreading of non-aqueous titration method, expanding the field of application of titrimetric methods to (very) weak acids and bases as well as potentiometric end point detection improving the precision of the methods. With the development of functional group analysis procedures titrimetric methods have been shown to be beneficial in kinetic measurements which are in turn applied to establish reaction rates. There are many advantages associated with these methods which include saving time and labor, high precision and the fact that there is no need of using reference standards

Chromatographic techniques

2.2.1. Thin layer chromatography

Although an old technique yet it finds a lot of application in the field of pharmaceutical analysis. In thin layer chromatography, a solid phase, the adsorbent, is coated onto a solid support as a thin layer usually on a glass, plastic, or aluminum support. Several factors determine the efficiency of this type of chromatographic separation. First the adsorbent should show extreme selectivity toward the substances being separated so as to the dissimilarities in the rate of elution be large. For the separation of any given mixture, some adsorbents may be too strongly adsorbing or too weakly adsorbing.

High performance thin layer chromatography

With the advancement of the technique, high performance thin layer chromatography (HPTLC) emerged as an important instrument in drug analysis. HPTLC is a fast separation technique and flexible enough to analyze a wide variety of samples. This technique is advantageous in many means as it is simple to handle and requires a short analysis time to analyze the complex or the crude sample cleanup. HPTLC evaluates the entire chromatogram with a variety of parameters

without time limits. Moreover, there is simultaneous but independent development of multiple samples and standards on each plate, leading to an increased reliability of results

High-performance liquid chromatography (HPLC)

HPLC is an advanced form of liquid chromatography used in separating the complex mixture of molecules encountered in chemical and biological systems, in order to recognize better the role of individual molecules

Gas chromatography

Moving ahead with another chromatographic technique, gas chromatography is a powerful separation technique for detection of volatile organic compounds. Combining separation and on-line detection allows accurate quantitative determination of complex mixtures, including traces of compounds down to parts per trillions in some specific cases. Gas liquid chromatography commands a substantial role in the analysis of pharmaceutical product.

Spectroscopic techniques

Spectrophotometry

Another important group of methods which find an important place in pharmacopoeias are spectrophotometric methods based on natural UV absorption and chemical reactions. Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength.

The advantages of these methods are low time and labor consumption. The precision of these methods is also excellent. The use of UV–Vis spectrophotometry especially applied in the analysis of pharmaceutical dosage form has increased rapidly over the last few years

Nuclear magnetic resonance spectroscopy (NMR)

Since the first report appeared in 1996 (Shuker et al., 1996) describing the use of NMR spectroscopy to screen for the drug molecules, the field of NMR based screening has proceeded promptly. Over the last few years, a variety of state-of-the-art approaches have been presented and found a widespread application in both pharmaceutical and academic research. Recently NMR finds its application in quantitative analysis in order to determine the impurity of the drug, characterization of the composition of the drug products and in quantitation of drugs in pharmaceutical formulations and biological fluids.

Pharmaceutical labelling

A **prescription drug** is a pharmaceutical drug that legally requires a medical prescription to be dispensed. In contrast, **over-the-counter drugs** can be obtained without a prescription. The reason for this difference in substance control is the potential scope of misuse, from drug abuse to practicing medicine without a license and without sufficient education. Different jurisdictions have different definitions of what constitutes a prescription drug.

"**Rx**" is often used as a short form for prescription drug in North America. Prescription drugs are often dispensed together with a monograph (in Europe, a Patient Information Leaflet or PIL) that gives detailed information about the drug.

Why is labeling of drug is so important?

- Inherent risks
- Risks due to interactions with other drugs
- Risks due to disease states
- Risk of over and under dosage

Label – I

“Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference)”.

Label – II

“For use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the FD&C Act.”

Need of a label

Label means a display of written, printed or graphic matter upon immediate container or the wrapper of a drug package.

Types of label

1. Manufacturer label
2. Dispensing label

Manufacturer label

A label, which contains drug information for the use of medical practitioners, pharmacists, or nurse supplied by the manufacturer, packer or distributor of the drug (FDA).

Legal requirements of a Manufacturer label

- The name of preparation
- Strength and dosage form
- Quantity
- Instruction for the use
- Precautions and warnings
- Registration number
- Batch number
- Manufacturing and expiry date
- Price
- The name and address of pharmaceutical industry

The name of preparation

Generic name:

According to drug labeling and packaging rules 1986: "International non-proprietary name means the name of a drug as recommended by WHO or may be notified by the federal government in the official gazette"

Brand name:

- Brand name is used to market the drug
- Property of drug company

Strength

It is amount of active drug / unit dose

Eg: Amoxicillin, 250mg capsules and Amoxicillin, 500mg capsules

Specification

- U.S.P
- B.P

USP specifications

The **United States Pharmacopeia** (**USP**) is a pharmacopeia (compendium of drug information) for the United States published annually by the **United States Pharmacopoeial Convention** (usually also called the USP), a nonprofit organization that owns the trademark and copyright.

The USP is published in a combined volume with the National Formulary (a formulary) as the **USP-NF**.[2] If a drug ingredient or drug product has an applicable USP quality standard (in the form of a USP-NF monograph), it must conform in order to use the designation "USP" or "NF." Drugs subject to USP standards include both human drugs (prescription, over-the-counter, or otherwise), as well as animal drugs.

USP-NF standards also have a role in U.S. federal law; a drug or drug ingredient with a name recognized in USP-NF is deemed adulterated if it does not satisfy compendial standards for strength, quality or purity. USP also sets standards for dietary supplements, and food ingredients (as part of the Food Chemicals Codex). USP has no role in enforcing its standards; enforcement is the responsibility of FDA and other government authorities in the U.S. and elsewhere.

BP Specifications

The **British Pharmacopoeia** (**BP**) is the national pharmacopoeia of the United Kingdom. It is an annual published collection of quality standards for UK medicinal substances. It is used by individuals and organizations involved in pharmaceutical research, development, manufacture and testing.

Pharmacopoeial standards are publicly available and legally enforceable standards of quality for medicinal products and their constituents. The British Pharmacopoeia is an important statutory component in the control of medicines which complements and assists the licensing and inspection processes of the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom. Along with the British National Formulary (BNF), it defines the UK's pharmaceutical standards.

Pharmacopoeial standards are compliance requirements; that is, they provide the means for an independent judgment as to the overall quality of an article and apply throughout the shelf-life of a product. Inclusion of a substance in a pharmacopoeia does not indicate that it is either safe or effective for the treatment of any disease.

Dosage form

Dosage form of the medicine should be mentioned on the label.

Eg: different dosage forms of amoxicillin

Quantity

Quantity / volume present per a packaging unit

The container holds 20 tablets and each tablet has a dosage strength of 500mg / tablet.

Instructions

Shake well before use:

Necessary to all disperse systems.

 Emulsions

 Suspensions Eg: Liniments, Lotions, Tinctures

Warning

Do not shake the patient

Shake the bottle well before use

Precautions

Storage conditions

Store in a cool place – not >0oC-8 oC is necessary for many products.

Protect from light

 Necessary for light sensitive preparations.

 Light resistive containers should be used.

Keep out of the reach of children

All dispensed medicines should carry this information on label.

Warnings

For external use only

Inflammable

If the preparation contains 50% or more alcohol or any other inflammable solvent, then the label should contain the word inflammable.

Not to be taken

 Liquid preparation that are not administered by mouth

 For nasal drops, enemas and nasal sprays

 Unit dosage forms Eg: Pessaries and rectal suppositories

 Help to administer drugs safely

 Types of warning

o If hypersensitivity to a drug

 For controlled substances

 About combining with other drugs or products

Registration number

A number given to a specific drug, when it is registered according to specific rules by registration board set up by federal government.

Batch number

According to drug act 1976, "A designation printed on label of a drug that identifies the batch and permits the production history of the batch including all stages of manufacturer and control to be traced and are viewed"

Manufacturing date

Liscense number

Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The act requires a firm, who manufactures a biologic for sale in interstate commerce to hold a license for the product.

Expiry date

According to drug Act 1976 S3, "Date stated on the label of a drug after which a drug is not expected to retain its claimed efficacy, safety, quantity or potency or after which it is no permissible to sell the drug"

Manufacturer information

 Name

 Address

Price

Barcodes

It is an optical machine readable representation of data, which shows data about the object to which it attaches.

Dispensing label

It includes:

Drug name and quantity

Patient name

Prescription number

Phone number

Instruction for use

Pharmacy name and address

Special instructions

Packing

Pharmaceutical packaging has to be carried out for the purpose of the safety of the pharmaceutical preparations in order to keep them free from contamination, hinder microbial growth, and ensure product safety through the intended shelf life for the pharmaceuticals. Packaging is a critical tool in the pharmaceutical industry.

Blister pack

 Blister pack is a term for several types of pre-formed plastic packaging used for small consumer goods, foods, and for pharmaceuticals.

 The primary component of a blister pack is a cavity or pocket made from a formable web, usually a thermoformed plastic. This usually has a backing of paperboard or a lidding seal of aluminum foil or plastic. A blister that folds onto itself is often called a clamshell.

 Blister packs are useful for protecting products against external factors, such as humidity and contamination for extended periods of time. Opaque blisters also protect light-sensitive products against UV rays.

Production Process

Thermoforming

In the case of thermoforming, a plastic film or sheet is unwound from the reel and guided though a pre-heating station on the blister line. The temperature of the pre-heating plates (upper and lower plates) is such that the plastic will soften and become pliable. The warm plastic will then arrive in a forming station where a large pressure (4 to 8 bar) will form the blister cavity into a negative mold.

The mold is cooled such that the plastic becomes rigid again and maintains its shape when removed from the mold. In case of difficult shapes, the warm film will be physically pushed down partially into the cavity by a "plug-assist" feature. Plug-assist results in a blister cavity with more uniform wall distribution and is typically used when the cavity size and shape is larger than a small tablets and capsules.

Cold forming

In the case of cold forming, an aluminum-based laminate film is simply pressed into a mold by means of a stamp. The aluminum will be elongated and maintain the formed shape. In the industry these blisters are called cold form foil (CFF) blisters. The principal advantage of cold form foil blisters is that the use of aluminum offers a near complete barrier for water and oxygen, allowing an extended product expiry date. The principal disadvantages of cold form

foil blisters are: the slower speed of production compared to thermoforming; the lack of transparency of the package (a therapy compliance disadvantage); and the larger size of the blister card (aluminum cannot be formed with near 90 degree angles).

Uses of blister pack

Blister packs are commonly used as unit-dose packaging for pharmaceutical tablets, capsules or lozenges. Blister packs can provide barrier protection for shelf life requirements, and a degree of tamper resistance. In the US, blister packs are mainly used for packing physician samples of drug products, or for Over The Counter (OTC) products in the pharmacy. In other parts of the world, blister packs are the main packaging type since pharmacy dispensing and re-packaging are not common. A series of blister cavities is sometimes called a blister card or blister strip as well as blister pack. The difference between a strip pack and blister pack is that a strip pack does not have thermo-formed or cold formed cavities; the strip pack is formed around the tablet at a time when it is dropped to the sealing area between sealing moulds. In some parts of the world the pharmaceutical blister pack is known as a Push-Through-Pack (PTP), an accurate description of two key properties (i) the lidding foil is brittle making it possible to press the product out while breaking the lidding foil and (ii) a semi-rigid formed cavity being sufficiently collapsable to be able to dispense the tablet or capsule by means of pressing it out with the thumb. The main advantages of unit-dose blister packs over other methods of packing pharmaceutical products are the assurance of product/packaging integrity (including shelflife) of each individual dose and the ability to create a compliance pack or calendar pack by printing the days of the week above each dose. Blister packs are created by means of a form-fill-seal process at the pharmaceutical company or designated contract packer. A form-fill-seal process means that the blister pack is created from rolls of flat sheet or film, filled with the pharmaceutical product and closed (sealed) on the same equipment. Such equipment is called a **blisterline.** There are two types of blister machine' design: rotary and flat-plate.

Paperboard Box containing tablets A carton is a box or container usually made of paperboard and sometimes of corrugated fiberboard. Many types of cartons are used in packaging. Sometimes a carton is also called a box. Eg: Carton box containing 1(PVC/AL) strip of 7 F.C tablets &an inner leaflet. Cartons can be made from many materials: paperboard, duplex, white kraft, recycled and many more various plastics, or a composite. Some are "food grade" for direct contact with foods. Many cartons are made out of a single piece of paperboard. Depending on the need, this paperboard can be waxed or coated with polyethylene to form a moisture barrier. This may serve to contain a liquid product or keep a powder dry. An **ampoule** is a small sealed vial which is used to contain and preserve a sample, usually a solid or liquid. Ampoules are commonly made of glass, although plastic ampoules do exist. Modern ampoules are most commonly used to contain pharmaceuticals and chemicals that must be protected from air and contaminants. They are hermetically sealed by melting the thin top with an open flame, and usually opened by snapping off the neck. If properly done, this last operation creates a clean break without any extra glass shards or slivers; but the liquid or solution may be filtered for greater assurance. The space above the chemical may be filled with an inert gas before sealing. The walls of glass ampoules are usually sufficiently strong to be brought into a glovebox without any difficulty. Glass ampoules are more expensive than bottles and other simple containers, but there are many situations where their superior imperviousness to gases and liquids and all-glass interior surface are worth the extra cost. Examples of chemicals sold in ampoules are: Injectable pharmaceuticals, Air-sensitive reagents like tetrakis (triphenylphosphine) palladium(0), Hygroscopic materials like deuterated solvents and trifluoromethanesulfonic acid, and Analytical standards. Ampoules often have colored rings of paint or enamel around their necks. Color coding of modern ampoules is done during the manufacturing process. A machine paints colored rings on the ampoule shortly after it has been sealed. The rings are made of a substance that is readable by other machines. These color codes identify the substance inside the ampoule so that it does not need to be tested to verify the contents. The machine-readable color codes allow for accurate handling of the substance for the purposes of storage, labeling, and secondary packaging. The dot above the neck identifies the location of a small cut in the glass to help breaking/opening the ampoule.

IV bags

About 25% of all plastic hospital products, including IV bags, are made of a plastic called polyvinyl chloride, or PVC. By itself, PVC is hard and brittle. But in the 1960s, manufacturers began adding chemicals called pthalates to make their products soft and flexible. Most IV bags contain a phthalate called DEHP (diethylhexyl phthalate).

Tubes for ointments, tooth paste, creams, lotion

A **tube** is a soft squeezable container which can be used for thick liquids such as adhesive, caulking, ointment, and toothpaste. Basically, a tube is a cylindrical, hollow piece with a round or oval profile, made of plastic, paperboard, or aluminum. Both ends of this tube are treated differently during the manufacturing process and filling. In general, on one end of the tube body there is a round orifice, which can be closed by different caps and closures. The orifice can be shaped in many different ways. Plastic nozzles in various styles and lengths are just one good example.

To attach caps and closures, in most cases a thread is tapped onto the opening structure. Furthermore, something all aluminium tubes have in common is that the other open end is folded several times after the contents have been added. The tube is thus hermetically sealed and nearly germ-free due to the high temperatures during the production process. Furthermore, it is possible to coat the inside of the tube with special coatings to prevent the material from reacting with the contents.

Tubes are not poured from liquid aluminium; they are produced by the process of impact extrusion. In this process, the tube body is extruded from a small piece of aluminium with the round shape of a coin. Unlimited printing designs can be applied to the tube, thanks to the wet-in-wet offset printing method. Six tones can be printed with this printing procedure, which gives packaging designers great opportunities to express their creativity.

The filled content can be easily squeezed out by the pressure of two fingers. The main characteristic of aluminium tubes is the total separation of the contents from the surrounding atmosphere; therefore, such tubes are especially suitable for the packaging of highly perishable contents. Aluminium tubes are used as packaging technology for cosmetics, pharmaceuticals, food, and technical products.

Plastic Tubes : Tube containers can also be produced in plastic, most commonly PE. The use of plastic tubes is very popular for the storage of Cosmetics such as hand creams etc. and also some food stuffs. The plastic tube retains its shape after each "squeeze" unlike laminate tubes such as toothpaste tubes. Plastic tubes can also be highly decorated or have a special additive such as soft touch to make the tube more appealing during use or point of sale (POS).

Plastic tubes are produced using the extrusion process. A "sleeve" is first produced using a very specialised extrusion line. The "Sleeve" must be produced to a very high standard (for decoration purposes) and also to very tight tolerances as automated processes are required post the extrusion operation. Once the "sleeve" is produced the tube head is fitted using an automated heading machine. Tube printing using complex and specialised printing machines such as silk screen printing applies the desired decoration. The open tubes are then most likely packed and despatched to another facility for filling and sealing.

Good manufacturing practices (GMP)

Good manufacturing practices (**GMP**) are the practices required in order to conform to the guidelines recommended by agencies that control authorization and licensing for manufacture and sale of food, drug products, and active pharmaceutical products. These guidelines provide minimum requirements that a pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public. Good manufacturing practices, along with good agricultural practices, good laboratory practices and good clinical practices, are overseen by regulatory agencies in the United States, Canada, Europe, China, and other countries.

High level details

Good manufacturing practice guidelines provide guidance for manufacturing, testing, and quality assurance in order to ensure that a food or drug product is safe for human consumption. Many countries have legislated that food,and pharmaceutical and medical device manufacturers follow GMP procedures and create their own GMP guidelines that correspond with their legislation.

All guidelines follow a few basic principles:

 Manufacturing facilities must maintain a clean and hygienic manufacturing area.

 Controlled environmental conditions in order to prevent cross contamination of food or drug product from adulterants that may render the product unsafe for human consumption.

 Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.

 Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.

 Instructions and procedures are written in clear and unambiguous language. (Good Documentation Practices)

 Operators are trained to carry out and document procedures.

 Cross contamination with unlabelled major allergens is prevented.

 Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the food or drug was as expected. Deviations are investigated and documented.

 Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.

 The distribution of the food or drugs minimizes any risk to their quality.
 A system is available for recalling any batch from sale or supply.

 Complaints about marketed products are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective products and to prevent recurrence.

Practices are recommended with the goal of safeguarding the health of consumers and patients as well as producing good quality food, medicine, medical devices, or active pharmaceutical products. In the United States, a food or drug may be deemed "adulterated" if it has passed all of the specifications tests, but is found to be manufactured in a facility or condition which violates or does not comply with current good manufacturing guideline. Therefore, complying with GMP is mandatory in all pharmaceutical manufacturing, and most food processing.
GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfil GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.
The quality is built into the product and GMP is the most essential part of ensuring this product quality.

Guideline versions

GMPs are enforced in the United States by the U.S. Food and Drug Administration (FDA), under Title 21 CFR. The regulations use the phrase "current good manufacturing practices" (cGMP) to describe these guidelines. Courts may theoretically hold that a product is adulterated even if there is no specific regulatory requirement that was violated as long as the process was not performed according to industry standards. Since June 2010, a different set of cGMP requirements have applied to all manufacturers ofdietary supplements.

The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world. The European Union's GMP (EU-GMP) enforces similar requirements to WHO GMP, as does the FDA's version in the US. Similar GMPs are used in other countries, with Australia, Canada, Japan, Saudi Arabia, Singapore, Philippines, Vietnam and others having highly developed/sophisticated GMP requirements. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", which is named so because of the color of its cover; it is officially known as *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*.[2]

Since the 1999 publication of *GMPs for Active Pharmaceutical Ingredients*, by the International Conference on Harmonization (ICH), GMPs now apply in those countries and trade groupings that are signatories to ICH (the EU, Japan and the U.S.), and applies in other countries (e.g., Australia, Canada, Singapore) which adopt ICH guidelines for the manufacture and testing of active raw materials.

GMC is part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization or product specification.

Enforcements

Within the European Union, GMP inspections are performed by National Regulatory Agencies (e.g., GMP inspections are performed in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA)); in the Republic of Korea (South Korea) by the Korea Food & Drug Administration (KFDA); in Australia by the Therapeutical Goods Administration (TGA); in Bangladesh by the Drug Administration (DGDA); in South Africa by the Medicines Control Council (MCC); in Brazil by the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil) (ANVISA); in Iran, in India gmp inspections are carried out by state FDA and these FDA report to Central Drugs Standard Control Organization [3] and Pakistan by the Drug Regulatory Authority of Pakistan;, Nigeria has NAFDAC and by

similar national organisations worldwide. Each of theinspectorates carry out routine GMP inspections to ensure that drug products are produced safely and correctly; additionally, many countries perform pre-approval inspections (PAI) for GMP compliance prior to the approval of a new drug for marketing.

Regulatory agencies (including the FDA in the U.S. and regulatory agencies in many European nations) are authorized to conduct unannounced inspections, though some are scheduled. FDA routine domestic inspections are usually unannounced, but must be conducted according to 704(a) of the FD&C Act (21 USCS § 374), which requires that they are performed at a "reasonable time". Courts have held that any time the firm is open for business is a reasonable time for an inspection.

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT –V - SBT1302 – PHARMACEUTICAL BIOTECHNOLOGY

COURSE OUTCOMES;

At the end of the course the student would be able to;

- CO1-Identify the prospects of applying Biotechnological concepts in drug discovery
- CO2-Inspect the kinetics, dynamics of drugs relating to the routes of administration
- CO3-Categorize the unit operation principles involved in the bulk drug manufacturing process
- CO4-Compare the product development of various drug formulations Tablets, Capsules, parentrals, oral liquids and topical applications.
- CO5-Appraise the mode of action of various drugs, laxatives, nonsteroidal contraceptives, antiseptics, antacids, analgesics, vitamins and hormones
- CO6-Elaborate the regulatory aspects involved in preclinical and clinical testing of drugs

PHARMACEUTICAL PRODUCTS

Therapeutic categories such as vitamins, laxatives, analgesics, non-steroidal contraceptives, Antibiotics, biological, hormones examples with respect to system.

Therapeutic vitamins towards human system

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol

Food sources of vitamin D include:

- Cod liver oil
- Salmon (sockeye)
- Mackerel
- Tuna fish canned in water
- Milk, non-fat, reduced-fat, and whole, vitamin D-fortified
- Orange juice fortified with vitamin D
- Yogurt fortified with 20 percent of the daily value of vitamin D
- Eggs, vitamin D is found in the yolk
- Swiss cheese
- Fortified cereals

Metabolic pathway of Vitamin D

Vitamin D3 (VD3), the most physiologically relevant form of vitamin D, is synthesized in the skin (Stratum spinosum and Stratum basale) from 7-dehydrocholesterol, a process which depends on sunlight, specifically ultraviolet B radiation (wavelengths of 270–300 nm). Alternatively, it can be acquired in the diet or in vitamin supplements. VD3 is then converted in the liver by VD3-25 hydroxylase to 25-dihydroxyvitamin D3 (25(OH)VD3), which is the main circulating form of VD3. Finally, 25(OH)VD3 is metabolized in the kidneys by the cytochrome P450 protein CYP27B1 (Its enzyme,25-Hydroxy Vit D3- 14,1α Hydroxylase) to 1,25(OH)2VD3, the most physiologically active VD3 metabolite. In addition to being processed in the liver and the kidneys, VD3 can also be metabolized by cells of the immune

system. In this way, 1,25(OH)2VD3 is concentrated locally in those lymphoid microenvironments that contain physiologically high concentrations of VD3, thereby increasing its specific action and also limiting potentially undesirable systemic effects, such as hypercalcaemia and increased bone resorption. Cells of the immune system, including macrophages, dendritic cells (DCs), T and B cells express the enzymes CYP27A1 and/or CYP27B1, and therefore can also hydroxylate 25(OH)VD3 to 1,25(OH)2VD3. 1,25(OH)2VD3 acts on immune cells in an autocrine or paracrine manner by binding to the vitamin D receptor (VDR). Finally, the enzyme 24-hydroxylase, which is most abundant in the kidney and intestine10, catabolizes 1,25(OH)2VD3 to its inactive metabolite,calcitroic acid, which is then excreted in the bile.

Dosage

The following doses have been studied in scientific research:

By Mouth:

 For preventing osteoporosis and fractures: 400-1000 IU per day has been used for older adults. Some experts recommended higher doses of1000-2000 IU daily.

 For preventing falls: 800-1000 IU/day has been used in combination with calcium 1000-1200 mg/day.

 For preventing multiple sclerosis (MS): long-term consumption of at least 400 IU per day, mainly in the form of a multivitamin supplement, has been used.

 For preventing all cancer types: calcium 1400-1500 mg/day plus vitamin D3 (cholecalciferol) 1100 IU/day in postmenopausal women has been used.

 For muscle pain caused by medications called "statins": vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) 50,000 units once a week or 400 IU daily.

 For preventing the flu: vitamin D (cholecalciferol) 1200 IU daily.

 Most vitamin supplements contain only 400 IU (10 mcg) vitamin D.

 The Institute of Medicine publishes recommended daily allowance (RDA), which is an estimate of the amount of vitamin D that meets the needs of most people in the population. The current RDA was set in 2010. The RDA varies based on age as follows: 1-70 years of age, 600 IU daily; 71 years and older, 800 IU daily; pregnant and lactating women, 600 IU daily. For infants ages 0-12 months, an adequate intake (AI) level of 400 IU is recommended.

 Some organizations are recommending higher amounts. In 2008, the American Academy of Paediatrics increased the recommended minimum daily intake of vitamin D to 400 IU daily for all infants and children, including adolescents. Parents should not use vitamin D liquids dosed as 400 IU/drop. Giving one dropperful or mL by mistake can deliver 10,000 IU/day. The US

Food and Drug Administration (FDA) will force companies to provide no more than 400 IU per dropperful in the future.

 The National Osteoporosis Foundation recommends vitamin D 400 IU to 800 IU daily for adults under age 50, and 800 IU to 1000 IU daily for older adults.

 The North American Menopause Society recommends 700 IU to 800 IU daily for women at risk of deficiency due to low sun (e.g., homebound, northern latitude) exposure.

 Guidelines from the Osteoporosis Society of Canada recommend vitamin D 400 IU per day for people up to age 50, and 800 IU per day for people over 50. Osteoporosis Canada now recommends 400-1000 IU daily for adults under the age of 50 years and 800-2000 IU daily for adults over the age of 50 years.

 The Canadian Cancer Society recommends 1000 IU/day during the fall and winter for adults in Canada. For those with a higher risk of having low vitamin D levels, this dose should be taken year round. This includes people who have dark skin, usually wear clothing that covers most of their skin, and people who are older or who don't go outside often.

 Many experts now recommend using vitamin D supplements containing cholecalciferol in order to meet these intake levels. This seems to be more potent than another form of vitamin D called ergocalciferol.

Effective for:

Low levels of phosphate in the blood due to an inherited disorder called familial hypophosphatemia. Taking vitamin D (calcitriol or dihydrotachysterol) by mouth along with phosphate supplements is effective for treating bone disorders in people with low levels of phosphate in the blood. Low levels of phosphate in the blood due to a disease called Fanconi syndrome. Taking vitamin D (ergocalciferol) by mouth is effective for treating low levels of phosphate in the blood due to a disease called Fanconi syndrome. Low blood calcium levels due to low parathyroid hormone levels. Low levels of parathyroid hormone can cause calcium levels to become too low. Taking vitamin D (dihydrotachysterol, calcitriol, or ergocalciferol) by mouth is effective for increasing calcium blood levels in people with low parathyroid hormone levels. Softening of the bones (osteomalacia). Taking vitamin D (cholecalciferol) is effective for treating softening of the bones. Also, taking vitamin D (calcifediol) is effective for treating softening of the bones due to liver disease. In addition, taking vitamin D (ergocalciferol) is effective for treating softening of the bones caused by medications or poor absorption syndromes. Psoriasis. Applying vitamin D or calcipotriene (a synthetic form of vitamin D) to the skin treats psoriasis in some people. Applying vitamin D to the skin together

with cream containing drugs called corticosteroids seems to be more effective for treating psoriasis than using just vitamin D or the corticosteroid creams alone.

Side effects

Special Precautions & Warnings:

Pregnancy and breast-feeding: Vitamin D is **likely safe** during pregnancy and breast-feeding when used in daily amounts below 4000 units. do not use higher doses. vitamin d is **possibly unsafe** when used in higher amounts during pregnancy or while breast-feeding. Using higher doses might cause serious harm to the infant.

Kidney disease: Vitamin D may increase calcium levels and increase the risk of ―hardening of the arteries‖ in people with serious kidney disease. This must be balanced with the need to prevent renal osteodystrophy, a bone disease that occurs when the kidneys fail to maintain the proper levels of calcium and phosphorus in the blood. Calcium levels should be monitored carefully in people with kidney disease.

High levels of calcium in the blood: Taking vitamin D could make this condition worse.

"Hardening of the arteries" (atherosclerosis): Taking vitamin D could make this condition worse, especially in people with kidney disease.

Sarcoidosis: Vitamin D may increase calcium levels in people with sarcoidosis. This could lead to kidney stones and other problems. Use vitamin D cautiously.

Histoplasmosis: Vitamin D may increase calcium levels in people with histoplasmosis. This could lead to kidney stones and other problems. Use vitamin D cautiously.

Over-active parathyroid gland (hyperparathyroidism): Vitamin D may increase calcium levels in people with hyperparathyroidism. Use vitamin D cautiously.

Lymphoma: Vitamin D may increase calcium levels in people with lymphoma. This could lead to kidney stones and other problems. Use vitamin D cautiously.

Tuberculosis: Vitamin D might increase calcium levels in people with tuberculosis. This might result in complications such as kidney stones.

Laxatives

Introduction

Laxatives (**purgatives**, **aperients**) are substances that loosen stools and increase bowel movements. They are used to treat and prevent constipation. Laxatives vary based on how they work and the side effects they have. Certain stimulant, lubricant and saline laxatives are used to evacuate the colon for rectal and bowel examinations, and may be supplemented by enemas under certain circumstances. Sufficiently high doses of laxatives may cause diarrhoea.

Some laxatives combine more than one active ingredient. Laxatives may be oral or suppository in form.

Uses

 Acute and chronic constipation

 Bowel preparation

 Chronic immobility

Types of laxatives

Bulk-forming agents

Bulk-forming laxatives, also known as roughage, are substances, such as **fiber** in food and **hydrophilic agents**

in over-the-counter drugs, that add bulk and **water to stools** so that they can pass more easily through

the intestines (lower part of the digestive tract).

Properties

 Site of action: small and large intestines

 Onset of action: 12–72 hours

 Examples: Dietary Fiber, Metamucil, Citrucel, FiberCon

Bulk-forming agents absorb water and should be taken with plenty of water. Bulk-forming agents generally have the gentlest of effects among laxatives and can be taken for long-term maintenance of regular bowel movements.

Dietary fiber

Foods that help with laxation include fiber-rich foods. Dietary fiber includes insoluble fiber and soluble fiber, such as:

 Fruits, such as bananas, kiwifruits, prunes, apples (with skin), pears (with skin), and raspberries.

 Vegetables, such as broccoli, string beans, kale, spinach, cooked winter squash, cooked green peas, and baked potatoes (with skin).

 Whole grains

 Bran products.

 Nuts

 Legumes, such as beans, peas, and lentils.

Emollient agents (stool softeners)

Emollient laxatives, also known as stool softeners, are anionic surfactants that enable **additional water and fats** to be incorporated in the stool,

making it easier for them to move through the gastrointestinal tract.

Properties

 Site of action: small and large intestines

 Onset of action: 12–72 hours

 Examples: Docusate (Colace, Diocto), Gibs-Eze

Emollient agents should be taken with plenty of water. Emollient agents prevent constipation rather than

treat long-term constipation.

Lubricant agents

Lubricant laxatives are substances that coat the stool with **slippery lipids** and **retard colonic absorption of water** so that the stool slides through the colon more easily. Lubricant laxatives also increase the weight of stool and decrease intestinal transit time.

Properties

 Site of action: colon

 Onset of action: 6–8 hours

 Example: mineral oil

Mineral oil is the only nonprescription lubricant. Mineral oil may **decrease the absorption of fat-soluble vitamins and some minerals.**

Hyperosmotic agents

Hyperosmotic laxatives are substances that cause the intestines to hold more water within and create an **osmotic effect that stimulates a bowel movement**.

Properties

 Site of action: colon

 Onset of Action: 12–72 hours (oral) 0.25 - 1 hour (rectal)

 Examples: glycerin suppositories, sorbitol, lactulose,

and PEG (Colyte, MiraLax).

Glycerin suppositories

Lactulose works by the osmotic effect, which retains water in the **colon, lowering the pH through bacterial fermentation to lactic, formic and acetic acid, and increasing colonic peristalsis.** Lactulose is also indicated in portal-systemic encephalopathy. Glycerin suppositories work mostly by **hyperosmotic action,** but the **sodium stearatein** in the preparation also causes local irritation to the colon. Solutions of polyethylene glycol and electrolytes (sodium chloride, sodium bicarbonate, potassium chloride, and sometimes sodium sulfate) are used for whole bowel irrigation, a process designed **to prepare the bowel for**

surgery or colonoscopy and to treat certain types of poisoning. Brand names for these solutions include GoLytely, GlycoLax, CoLyte, Miralax, Movicol, NuLytely, Suprep, and Fortrans. Solutions of sorbitol (SoftLax) have similar effects.

Saline laxative agents

Saline laxatives are **non-absorbable osmotic substances** that attract and retain water in the intestinal lumen, **increasing intraluminal pressure** that mechanically stimulates evacuation of the bowel. **Magnesium-containing agents** also cause the release of **cholecystokinin,** which increases intestinal motility and fluid secretion. Saline laxatives may alter a patient's fluid and electrolyte balance.

Properties

 Site of action: small and large intestines

 Onset of action: 0.5–3 hours (oral), 2–15 minutes (rectal)

 Examples: sodium phosphate (and variants), magnesium citrate, magnesium hydroxide (milk of magnesia), and magnesium sulfate (Epsom salt) Saline laxatives should be taken with plenty of water.

Stimulant agents

Stimulant laxatives are substances that act on the intestinal mucosa or nerve plexus, altering water and electrolyte secretion. They also stimulate peristaltic action and can be dangerous under certain circumstances.

Properties

 Site of action: colon

 Onset of action: 6–10 hours

 Examples: senna, bisacodyl

They are the most powerful among laxatives and should be used with care. Prolonged use of stimulant laxatives can create drug dependence by damaging the colon's haustral folds, making a user less able to move feces through the colon on their own. A study of patients with chronic constipation found that 28% of chronic stimulant laxative users lost haustral folds over the course of one year, while none of the control group did.

ANALGESICS

An **analgesic** or **painkiller** is any member of the group of drugs used to achieve analgesia, relief from pain. Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anaesthetics, which reversibly eliminate sensation. Analgesics include paracetamol (known in North America as acetaminophen or simply APAP), the

nonsteroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and oxycodone.

Mild analgesics

1. Aspirin

Aspirin, also known as **acetylsalicylic acid** (**ASA**), is a medication, often used to treat

- Pain,
- Fever, and
- Inflammation.

Aspirin is also used long-term, at low doses, to help prevent **heart attacks, strokes, and blood clot** formation in people at high risk of developing blood clots.Low doses of aspirin may be given immediately after a heart attack to reduce the risk of another heart attack or the death of heart tissue. Aspirin may be effective at preventing certain types of cancer, particularly **colorectal cancer.**

Mechanism of action

Suppression of prostaglandins and thromboxanes

Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its **irreversible inactivation** of the **cyclooxygenase** (COX; officially known as prostaglandin-endoperoxide synthase, PTGS) enzyme required for prostaglandin and thromboxane synthesis. Aspirin acts as an **acetylating agent** where an **acetyl group is covalently attached** to a **serine residue** in the active site of the **PTGS enzyme**. This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors. Low-dose aspirin use **irreversibly blocks the formation of thromboxane A2 in platelets**, producing an **inhibitory effect on platelet aggregation** during the lifetime of the affected platelet (8–9 days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks. 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition. Prostaglandins, local hormones produced in the body, have diverse effects, including the **transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation**. Thromboxane are responsible for the aggregation of platelets that form blood clots. Heart attacks are caused primarily by blood clots, and **low doses of aspirin** are seen as an effective medical intervention for **acute myocardial infarction.**

COX-1 and COX-2 inhibition

At least two different types of cyclooxygenase occur: COX-1 and COX-2. Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are proinflammatory. Aspirin-modified PTGS2 produces lipoxins, most of which are anti-inflammatory. Newer NSAID drugs, COX-2 inhibitors (coxibs), have been developed to inhibit only PTGS2, with the intent to reduce the incidence of gastrointestinal side effects.

However, several of the new COX-2 inhibitors, such as rofecoxib (Vioxx), have been withdrawn in the last decade, after evidence emerged that PTGS2 inhibitors increase the risk of heart attack and stroke. Endothelial cells lining the microvasculature in the body are proposed to express PTGS2, and, by selectively inhibiting PTGS2, prostaglandin production (specifically, PGI2; prostacyclin) is downregulated with respect to thromboxane levels, as PTGS1 in platelets is unaffected. Thus, the protective anticoagulative effect of PGI2 is removed, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new PTGS once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

Additional mechanisms

Aspirin has been shown to have at least three additional modes of action.

 It **uncouples oxidative phosphorylation in cartilaginous (and hepatic) mitochondria,** by diffusing from the inner membrane space as a proton carrier back into the mitochondrial matrix, where it ionizes once again to release protons. In short, **aspirin buffers and transports the protons**. When **high doses** of aspirin are given, it may actually cause **fever**, owing to the heat released from the electron transport chain, as opposed to the antipyretic action of aspirin seen with lower doses.

 In addition, aspirin induces the formation of **NO-radicals** in the body, which has been shown in mice to have an independent mechanism of reducing inflammation. This reduced leukocyte adhesion, which is an important step in immune response to infection; however, evidence is insufficient to show aspirin helps to fight infection.

 More recent data also suggest **salicylic acid** and **its derivatives** modulate signaling through **NF-κB**. NF-κB, a transcription factor complex, plays a central role in many biological processes, including inflammation.

 Aspirin is readily **broken down** in the body to **salicylic acid**, which itself has anti-inflammatory, antipyretic, and analgesic effects. In 2012, salicylic acid was found to activate AMP-activated protein kinase, which has been suggested as a possible explanation for some of

the effects of both salicylic acid and aspirin. The acetyl portion of the aspirin molecule has its own targets. Acetylation of cellular proteins is a well-established phenomenon in the regulation of protein function at the post-translational level. Aspirin is able to acetylate several other targets in addition to COX isoenzymes. These acetylation reactions may explain many hitherto unexplained effects of aspirin.

Aspirin dosage

1. Aspirin comes as a regular tablet, a **delayed-release tablet, a chewable tablet, a powder, a gum, and a rectal suppository**.

2. It's typically taken every four to **six hours** to treat **fever and pain**. It's usually taken once a day to lower the risk of a heart attack or stroke. Typical
dosages range from **50 milligrams** (mg) to **6,000 mg**, daily.

3. You should swallow the delayed-release tablets with a full glass of water. These tablets don't work immediately after they are taken, so you
shouldn't use them for quick pain relief.

4. The chewable tablets can be crushed, chewed, or swallowed whole. You should drink a full glass of water right after taking this form of the
medication.

Medical uses

Aspirin is used in the treatment of a number of conditions, including

- Rheumatic fever, and
- Fever,
- Pain,
- Inflammatory diseases, such as
- rheumatoid arthritis,
- pericarditis, and
- Kawasaki disease.

Lower doses of aspirin have also shown to reduce the risk of death from a heart attack, or the risk of stroke in some circumstances. There is some evidence that aspirin is effective at preventing colorectal cancer, though the mechanisms of this effect are unclear

Side effects

The main side effects of aspirin are gastric ulcers, stomach bleeding, and ringing in the ears, especially with higher doses. While daily aspirin can help prevent a clot-related stroke, it may increase risk of a bleeding stroke (hemorrhagic stroke). In children and adolescents, aspirin is

not recommended for flu-like symptoms or viral illnesses, because of the risk of Reye's syndrome.

Aspirin Warnings

Before taking aspirin, tell your doctor if you have or have ever had:

- Asthma
- Frequent stuffed or runny nose
- Nasal polyps (growths on the linings of the nose)
- Frequent heartburn, upset stomach, or stomach pain
- Ulcers
- Anemia
- Gout
- Diabetes
- Liver or kidney disease
- Hemophilia (a bleeding disorder) or any other bleeding conditions

2. Paracetamol / acetaminophen

Paracetamol, also known as acetaminophen or APAP, is a medication used to treat pain and fever.[9] It is typically used for mild to moderate pain

Medical uses

- Fever
- Pain
- Osteoarthritis
- Low back pain
- Headaches
- Postoperative pain

Liver damage

3. Ibuprofen

Ibuprofen, from **i**so**bu**tyl**phen**yl**pro**panoic acid, is a nonsteroidal anti-inflammatory drug (NSAID) used for treating pain, fever, and inflammation. This includes **painful menstrual periods, migraines, and rheumatoid arthritis.** About 60% of people improve with any given NSAID, and it is recommended that if one does not work then another should be tried. It may also be used to close a patent ductus arteriosus in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.

Mechanism of action of Ibuprofen

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the COX enzymes, which convert arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A2 (which stimulates platelet aggregation, leading to the formation of blood clots). The exact mechanism of action of ibuprofen is unknown. Ibuprofen is a nonselective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. Its pharmacological effects are believed to be due to inhibition of cyclooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Inhibition of COX-1 is thought to cause some of the side effects of ibuprofen including gastrointestinal ulceration. Ibuprofen is administered as a racemic mixture. The R-enantiomer undergoes extensive interconversion to the S-enantiomer *in vivo*. The S-enantiomer is believed to be the more pharmacologically active enantiomer.

Like aspirin and indometacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for unwanted effects on the gastrointestinal tract.[36] However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage.

Medical uses

Ibuprofen is used primarily for fever (including post immunisation fever), mild-to-moderate pain (including pain relief after surgery), painful menstruation, osteoarthritis, dental pain, headaches and pain from kidney stones. It is used for inflammatory diseases such as juvenile idiopathic arthritis and rheumatoid arthritis. It is also used for pericarditis and patent ductus arteriosus.

Side effects

Common side effects include heartburn and a rash. Compared to other NSAIDs it may have fewer side effects such as gastrointestinal bleeding. It increases the risk of heart failure, kidney failure, and liver failure. At low doses it does not appear to increase the risk of myocardial infarction; however, at higher doses it may. It may result in worsened asthma. While it is unclear if it is safe in early pregnancy, it appears to be harmful in later pregnancy. Like other

NSAIDs, it works by inhibiting the making of prostaglandins by decreasing the activity of the enzyme cyclooxygenase.Ibuprofen might be a weaker anti-inflammatory than other NSAIDs.

Miscarriage

A study of pregnant woman suggests those taking any type or amount of NSAIDs (including ibuprofen, diclofenac and naproxen) were 2.4 times more likely tomiscarry than those not taking the drugs. However, an Israeli study found no increased risk of miscarriage in the group of mothers using NSAIDs.

STRONG ANALGESICS

OPIUM

Opium contains two main groups of alkaloids. Phenanthrenes such as morphine, codeine, and thebaine are the main psychoactive constituents. Isoquinolines such as papaverine and noscapine have no significant central nervous system effects, and are not regulated under the Controlled Substances Act. Morphine is the most prevalent and important alkaloid in opium, consisting of 10%–16% of the total, and is responsible for most of its harmful effects such as lung edema, respiratory difficulties, coma, or cardiac or respiratory collapse. Morphine binds to and activates mu opioid receptor in the brain, spinal cord, stomach and intestine. Regular use can lead to drug toleranceor physical dependence. Chronic opium addicts in 1906 China or modern-day Iran consume an average of eight grams of opium daily. A narcotic is an addictive drug that reduces pain, induces sleep and may alter mood or behaviour. In medicine, an analgesic narcotic means opioid, which refers to all natural, semi-synthetic and synthetic substances that behave pharmacologically like morphine, the primary constituent of natural opium. The opioids are classified on the WADA List as narcotics. Pain killers (morphine, heroine, codeine) are, sometimes, used by athletes or competitors engaged in violent sports. Increased threshold for pain tolerance, adjusted by opioids application, allows a better sport performance. Opioids are drugs with great potential of physical and psychic dependence. Tolerance of the drugs develop quickly. The main biomedical effects of analgesic narcotics on central nervous system are euphoria, lethargy, apathy and inability to concentrate. Sudden withdrawal of opioid drugs, or application of opioid antagonists, causes a withdrawal syndrome in addicted persons. The opioid hunger is badly tolerated by addicted persons.

2. Heroine

Heroin is an opioid painkiller and the **3,6-diacetyl ester** of morphine. Heroin is prescribed as an **analgesic, cough suppressant** and as an **antidiarrhoeal**. It is also used as a recreational drug for its euphoric effects. Frequent and regular administration is associated with tolerance and physical dependence. In some countries it is available for prescription to long-term users

as a form of opioid replacement therapy alongside counseling. It was originally synthesized by C. R. Alder Wright in 1874 by adding two acetyl groups to the molecule morphine, a natural product of the opium poppy. Internationally, heroin is controlled under Schedules I and IV of the Single Convention on Narcotic Drugs. It is generally illegal to manufacture, possess, or sell heroin without a license. In 2004, Afghanistan produced roughly 87% of the world supply in illicit raw opium. However, the production rate in Mexico rose six fold from 2007 to 2011, making Mexico the second largest opium producer in the world.

Administered **intravenously** by injection, heroin is two to four times more potent than morphine and is faster in its onset of action. Illicit heroin is sometimes available in a matte-white powder freebase form. Because of its lower boiling point, the freebase form of heroin is smokable.

The ill effects of the drug may include:

 Reduced sex drive and loss of sensation in the genitals. Inability to achieve orgasm

 Impotence in men and infertility in women

 Inability to focus

 Severe weakening of the body‘s immune system

 Loss of memory

 Inability to think coherently, loss of intellectual capacity

 Rotting of teeth and inflammation in the gums

 Inability to succeed in any aspects of life – be it social, professional, personal, emotional or spiritual.

 Extreme depression

 Insomnia

 Cold sweats

 Digestive issues – the most common being constipation

 Pustules on the face

 Respiratory problems – difficulty breathing.

 Loss of appetite

Seriously, this list can extend into multiple pages! Heroin addiction can cause a person to lose absolutely everything – friends, parents, family, job, money. Users may even lie or steal in order to get their fix; they lose their self-respect and feel that their life becomes totally meaningless. Some people are of the opinion that you should try everything in life at least once – well, that certainly does not apply to heroin and other drugs.

3. Codeine

Codeine, also known as **3-methylmorphine**, is an opiate used to treat pain, as a cough medicine, and for diarrhoea. It is typically used for mild to moderate degrees of pain. Greater benefit may occur when combined with paracetamol (acetaminophen) or aspirin. Evidence for use for cough is poor. In Europe it is not recommended as a cough medicine in those under twelve years of age. It is taken by mouth. It typically starts working after half an hour with maximum effect at two hours. Effects last for about four to six hours. Common side effects include vomiting, constipation, itchiness, and light-headedness. Serious side effects may include a decreased effort to breathe and addiction. It is unclear if its use in pregnancy is safe. Care should be used during breast feeding as it may result in opiate toxicity in the baby. Codeine works following being broken down by the liver into morphine. How quickly this occurs depends on a person's genetics.

Formulations

Codeine is marketed as both a single-ingredient drug and in combination preparations with paracetamol (as co-codamol: *e.g.*, brands Paracod, Panadeine, and the Tylenol-with-codeine series, including Tylenol 3 and 1,2,4); with aspirin (as co-codaprin); or with ibuprofen (as Nurofen Plus).These combinations provide greater pain relief than either agent alone (drug synergy).

Codeine is also commonly marketed in products containing codeine with other pain killers or muscle relaxers, as well as codeine mixed with phenacetin (Emprazil With Codeine No. 1, 2, 3, 4 and 5), naproxen, indomethacin, diclofenac, and others, as well as more complex mixtures, including such mixtures as aspirin + paracetamol + codeine ± caffeine ± antihistamines and other agents, such as those mentioned above.

Codeine-only products can be obtained with a prescription as a time release tablet (*e.g.*, Codeine Contin 100 mg and Perduretas 50 mg). Codeine is also marketed in cough syrups with zero to a half-dozen other active ingredients, and a linctus (*e.g.*, Paveral) for all of the uses for which codeine is indicated. Injectable codeine is available for subcutaneous or intramuscular injection only; intravenous injection is contraindicated as this can result in nonimmune mast-cell degranulation and resulting anaphylactoid reaction. Codeine suppositories are also marketed in some countries.

Medical uses

Codeine is used to treat mild to moderate pain and to relieve cough. Codeine is also used to treat diarrhea and diarrhea-predominant irritable bowel syndrome, although loperamide (which is available OTC for milder diarrhea), diphenoxylate, paregoric or even laudanum (also known

as *Tincture of Opium*) are more frequently used to treat severe diarrhea. It is weak evidence that it is useful in cancer pain but it is associated with increased side effects.

Adverse effects

Common adverse effects associated with the use of codeine include drowsiness and constipation. Less common are itching, nausea, vomiting, dry mouth, miosis, orthostatic hypotension, urinary retention, euphoria, dysphoria, and coughing. Rare adverse effects include anaphylaxis, seizure, acute pancreatitis, and respiratory depression. As with all opiates, longer-term effects can vary, but can include diminished libido, apathy, and memory loss. Some people may also have an allergic reaction to codeine, such as the swelling of skin and rashes. Codeine and morphine, as well as opium, were used for control of diabetes until relatively recently, and still are in rare cases in some countries, and the hypoglycemic effect of codeine, although usually weaker than that of morphine, diamorphine, or hydromorphone, can lead to cravings for sugar. Tolerance to many of the effects of codeine develops with prolonged use, including to its therapeutic effects. The rate at which this occurs develops at different rates for different effects, with tolerance to the constipation-inducing effects developing particularly slowly for instance.

A potentially serious adverse drug reaction, as with other opioids, is respiratory depression. This depression is dose-related and is a mechanism for the potentially fatal consequences of overdose. As codeine is metabolized to morphine, morphine can be passed through breast milk in potentially lethal amounts, fatally depressing the respiration of a breastfed baby. In August 2012, the United States Federal Drug Administration issued a warning about deaths in pediatric patients < 6 years old after ingesting "normal" doses of paracetamol with codeine after tonsillectomy.

Some patients are very effective converters of codeine to its active form, morphine, resulting in lethal blood levels. The FDA presently is recommending very cautious use of Codeine in young tonsillectomy patients: use the drug in the lowest amount that can control the pain, use "as needed" and not "around the clock", and seek immediate medical attention if a child on codeine exhibits excessive sedation or abnormally noisy breathing.

Non steroidal contraceptives

Birth control, also known as **contraception** and **fertility control**, is methods or devices used to prevent pregnancy. Planning, provision and use of birth control is called family planning. Birth control methods have been used since ancient times, but effective and safe methods only became available in the 20th century. Some cultures limit or discourage access to birth control because they consider it to be morally, religiously, or politically undesirable.

Ormeloxifene

Ormeloxifene (also known as **centchroman**) is one of the selective estrogen receptor modulators, or SERMs, a class of medication which acts on the estrogen receptor. It is best known as a non-hormonal, non-steroidal oral contraceptive which is taken once per week. In India, ormeloxifene has been available as birth control since the early 1990s, and it is currently marketed there under the trade name

Saheli. Ormeloxifene has also been licensed under the trade names **Novex-DS**, **Centron** and **Sevista**.

Medical uses

Ormeloxifene is primarily used as a contraceptive but may also be effective for dysfunctional uterine bleeding and advanced breast cancer.

Birth control

Ormeloxifene may be used as a weekly oral contraceptive. The weekly schedule is an advantage for women who prefer an oral contraceptive, but find it difficult or impractical to adhere to a daily schedule required by other oral contraceptives. For the first twelve weeks of use, it is advised to take the ormeloxifene pill twice per week. From the thirteenth week on, it is taken once per week. The consensus is that backup protection in the first month is a cautious but sensible choice. A standard dose is 30 mg weekly, but 60 mg loading doses can reduce pregnancy rates by 38%. It has a failure rate of about 1-2% with ideal use which is slightly less effective than found for combined oral contraceptive pills.

Other indications

- Ormeloxifene has also been tested in experimental setting as a treatment for menorrhagia.
- Use in treatment of mastalgia and fibroadenoma has also been described.

Adverse effect

There are concerns that ormeloxifene may cause delayed menstruation.

Mode of action

Ormeloxifene is a SERM, or selective estrogen receptor modulator. In some parts of the body, its action is estrogenic (e.g., bones), in other parts of the body, its action is anti-estrogenic (e.g., uterus, breasts.) It causes an asynchrony in the menstrual cycle between ovulation and the development of the uterine lining, although its exact mode of action is not well defined. In clinical trials, it caused ovulation to occur later than it normally would in some women, but did not affect ovulation in the majority of women, while causing the lining of the uterus to build more slowly. It speeds the transport of any fertilized egg through the fallopian tubes more

quickly than is normal. Presumably, this combination of effects creates an environment such that if fertilization occurs, implantation will not be possible.

Marketing

Ormeloxifene is only legally available in India as of 2009.Ormeloxifene has been tested and licensed as a form of birth control, as well as a treatment for dysfunctional uterine bleeding.

 It was first manufactured by Torrent Pharmaceuticals, and marketed as birth control under the trade name **Centron**. Centron was discontinued.

 A new license for ormeloxifene was issued to Hindustan Latex Ltd., which now manufactures ormeloxifene as birth control under the trade name **Saheli**, **Novex** and **Novex-DS**.

 Torrent Pharmaceuticals has resumed manufacture of ormeloxifene under the trade name **Sevista**, as a treatment for dysfunctional uterine bleeding.

Antibiotics

Antibiotics or **antibacterials** are a type of antimicrobial used in the treatment and prevention of bacterial infection. They may either kill or inhibit the growth of bacteria. Several antibiotics are also effective against fungi and protozoans, and some are toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately. In 1928, Alexander Fleming identified penicillin, the first chemical compound with antibiotic properties. Fleming was working on a culture of disease-causing bacteria when he noticed the spores of little green mold in one of his culture plates. He observed that the presence of the mold killed or prevented the growth of the bacteria.

Classes of antibiotics

Antibacterial antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity. Most target bacterial functions or growth processes.Those that target the bacterial cell wall (penicillins and cephalosporins) or the cell membrane (polymyxins), or interfere with essential bacterial enzymes (rifamycins, lipiarmycins, quinolones, and sulfonamides) have bactericidal activities. Those that target protein synthesis (macrolides, lincosamides and tetracyclines) are usually bacteriostatic (with the exception of bactericidal aminoglycosides).Further categorization is based on their target specificity. "Narrow-spectrum" antibacterial antibiotics target specific types of bacteria, such as Gram-negative or Gram-positive bacteria, whereas broad-spectrum antibiotics affect a wide range of bacteria.

Production

With advances in medicinal chemistry, most modern antibacterials are semisynthetic modifications of various natural compounds. These include, for example, the beta-lactam antibiotics, which include,

- The penicillins (produced by fungi in the genus *Penicillium*),
- The cephalosporins, and
- The carbapenems.

Compounds that are still isolated from living organisms are the aminoglycosides, whereas other antibacterials—for example, the sulfonamides, the quinolones, and the oxazolidinones—are produced solely by chemical synthesis.

Many antibacterial compounds are relatively small molecules with a molecular weight of less than 2000 atomic mass units.

Since the first pioneering efforts of Florey and Chain in 1939, the importance of antibiotics, including antibacterials, to medicine has led to intense research into producing antibacterials at large scales. Following screening of antibacterials against a wide range of bacteria, production of the active compounds is carried out using fermentation, usually in strongly aerobic conditions.

Administration

Oral antibiotics are taken by mouth, whereas intravenous administration may be used in more serious cases, [*citation needed*] such as deep-seated systemic infections. Antibiotics may also sometimes be administered topically, as with eye drops or ointments.

The topical antibiotics are:

- Erythromycin
- Clindamycin
- Gentamycin
- Tetracycline
- Meclocycline
- (Sodium) sulfacetamide

While topical medications that act as Comedolytics as well as antibiotics are:

- Benzoyl peroxide
- Azelaic acid

Side Effects

- Antibiotics are screened for any negative effects on humans or other mammals before approval for clinical use, and are usually considered safe

and most are well tolerated. However, some antibiotics have been associated with a range of adverse side effects. Side-effects range from mild to very serious depending on the antibiotics used, the microbial organisms targeted, and the individual patient. Safety profiles of newer drugs are often not as well established as for those that have a long history of use.

 Adverse effects range from fever and nausea to major allergic reactions, including photodermatitis and anaphylaxis.

 Common side-effects include diarrhea, resulting from disruption of the species composition in the intestinal flora, resulting, for example, in overgrowth of pathogenic bacteria, such as *Clostridium difficile*.

 Antibacterials can also affect the vaginal flora, and may lead to overgrowth of yeast species of the genus *Candida* in the vulvo-vaginal area.

 Additional side-effects can result from interaction with other drugs, such as elevated risk of tendon damage from administration of a quinolone antibiotic with a systemic corticosteroid.

 Some scientists have hypothesized that the indiscriminate use of antibiotics alters the host microbiota and this has been associated with chronic disease.

Resistance Mechanisms

Resistance may take the form of biodegradation of pharmaceuticals, such as sulfamethazine-degrading soil bacteria introduced to sulfamethazine through medicated pig feces. The survival of bacteria often results from an inheritable resistance, but the growth of resistance to antibacterial also occurs through horizontal gene transfer. Horizontal transfer is more likely to happen in locations of frequent antibiotic use. Antibiotics such as penicillin and erythromycin, which used to have a high efficacy against many bacterial species and strains, have become less effective, due to the increased resistance of many bacterial strains Resistance may take the form of biodegradation of pharmaceuticals, such as sulfamethazine-degrading soil bacteria introduced to sulfamethazine through medicated pig faeces. The survival of bacteria often results from an inheritable resistance, but the growth of resistance to antibacterial also occurs through horizontal gene transfer. Horizontal transfer is more likely to happen in locations of frequent antibiotic use.

Several molecular mechanisms of antibacterial resistance exist. Intrinsic antibacterial resistance may be part of the genetic makeup of bacterial strains. For example, an antibiotic target may be absent from the bacterial genome. Acquired resistance results from a mutation in the bacterial chromosome or the acquisition of extra-chromosomal DNA. Antibacterial-producing bacteria have evolved resistance mechanisms that have been shown to be similar to,

and may have been transferred to, antibacterial-resistant strains. The spread of antibacterial resistance often occurs through vertical transmission of mutations during growth and by genetic recombination of DNA by horizontal genetic exchange. For instance, antibacterial resistance genes can be exchanged between different bacterial strains or species via plasmids that carry these resistance genes. Plasmids that carry several different resistance genes can confer resistance to multiple antibacterial. Cross-resistance to several antibacterial may also occur when a resistance mechanism encoded by a single gene conveys resistance to more than one antibacterial compound.

Example – 1: Penicillin

Penicillin (**PCN** or **pen**) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (oral use), procaine penicillin, and benzathine penicillin (intramuscular use). They are derived from *Penicillium* fungi. Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci. Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use. All penicillins are β-lactam antibiotics. About 10% of people report that they are allergic to penicillin; however, up to 90% of this group may not actually be allergic. Serious allergies only occur in about 0.03%.

Production

Penicillin is a secondary metabolite of certain species of *Penicillium* and is produced when growth of the fungus is inhibited by stress. It is not produced during active growth. Production is also limited by feedback in the synthesis pathway of penicillin.

o α-ketoglutarate + AcCoA → homocitrate → L-α-aminoadipic acid → L-lysine + β-lactam

The by-product, L-lysine, inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production. The *Penicillium* cells are grown using a technique called fed-batch culture, in which the cells are constantly subject to stress, which is required for induction of penicillin production. The available carbon sources are also important: Glucose inhibits penicillin production, whereas lactose does not. The pH and the levels of nitrogen, lysine, phosphate, and oxygen of the batches must also be carefully controlled. The biotechnological method of directed evolution has been applied to produce by mutation a large number of *Penicillium*strains. These techniques include error-prone PCR, DNA shuffling, ITCHY, and strand-overlap PCR. Semisynthetic penicillins are prepared starting from the penicillin nucleus 6-APA.

Therapeutic hormones towards human system

Insulin (medication) is the use of insulin and similar proteins as a medication to treat disease. Insulin comes in a number of different types including short acting (such as regular insulin) and long acting (such as NPH insulin). Insulin is used to treat a number of diseases including diabetes and its acute complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic states.It is also used along with glucose to treat high blood potassium levels.Side effects may include: low blood sugar levels, skin reactions at the site of injection and low potassium levels among others.Insulin was first used as a medication in Canada by Charles Best and Frederick Banting in January 1922.

Types

Medical preparations of insulin are never just 'insulin in water'. Clinical insulins are specially prepared mixtures of insulin plus other substances including preservatives. These delay absorption of the insulin, adjust the pH of the solution to reduce reactions at the injection site, and so on. Slight variations of the human insulin molecule are called insulin analogues, (technically "insulin receptor ligands") so named because they are not technically insulin, rather they are analogues which retain the hormone's glucose management functionality. They have absorption and activity characteristics not currently possible with subcutaneously injected insulin proper. They are either absorbed rapidly in an attempt to mimic real beta cell insulin, or steadily absorbed after injection instead of having a 'peak' followed by a more or less rapid decline in insulin action, all while retaining insulin's glucose-lowering action in the human body. However, a number of meta-analyses, including those done by the Cochrane Collaboration in 2002, Germany's Institute for Quality and Cost Effectiveness in the Health Care Sector [IQWiG] released in 2007, and the Canadian Agency for Drugs and Technology in Health (CADTH) also released in 2007 have shown no unequivocal advantages in clinical use of insulin analogues over more conventional insulin types.

Choosing insulin type and dosage/timing should be done by an experienced medical professional working closely with the diabetic patient.

The commonly used types of insulin are:

 Fast-acting: Includes the insulin analogues *aspart*, *lispro*, and *glulisine*. These begin to work within 5 to 15 minutes and are active for 3 to 4 hours. Most insulins form hexamers which delay entry into the blood in active form; these analog insulins do not, but have normal insulin activity. Newer varieties are now pending regulatory approval in the U.S. which are designed to work rapidly, but retain the same genetic structure as regular human insulin.

 Short-acting: Includes *regular* insulin which begins working within 30 minutes and is active about 5 to 8 hours.

 Intermediate-acting: Includes *NPH insulin* which begins working in 1 to 3 hours and is active 16 to 24 hours.

 Long acting: Includes the analogues *glargine* and *detemir*, each of which begins working within 1 to 2 hours and continue to be active, without
major peaks or dips, for about 24 hours, although this varies in many individuals.

 Ultra-long acting: Currently only includes the analogue *degludec*, which begins working within 30–90 minutes, and continues to be active for
greater than 24 hours.

 Combination insulin products – Includes a combination of either fast-acting or short-acting insulin with a longer acting insulin, typically an *NPH insulin*. The combination products begin to work with the shorter acting insulin (5–15 minutes for fast-acting, and 30 minutes for short acting), and remain active for 16 to 24 hours. There are several variations with different proportions of the mixed insulins (e.g. Novolog Mix 70/30 contains 70% aspart protamine [akin to NPH], and 30% aspart.)

Yeast-based

In late 2003, Wockhardt commenced manufacture of a yeast-based insulin costing $3.25 in India claiming it eliminated the risk of contracting diseases such as BSE and CJD associated with insulin derived from pigs and cattle. However, the company continues to manufacture insulin derived from pigs and cows in the United Kingdom under the Hypurin/CP Pharmaceuticals brand name.

Methods of administration

Unlike many medicines, insulin cannot be taken orally at the present time. Like nearly all other proteins introduced into thegastrointestinal tract, it is reduced to fragments (even single amino acid components), whereupon all 'insulin activity' is lost. There has been some research into ways to protect insulin from the digestive tract, so that it can be administered in a pill. So far this is entirely experimental.

Subcutaneous

Insulin is usually taken as subcutaneous injections by single-use syringes with needles, an insulin pump, or by repeated-use insulin pens with needles. Patients who wish to reduce repeated skin puncture of insulin injections often use an injection port in conjunction with syringes.

Administration schedules often attempt to mimic the physiologic secretion of insulin by the pancreas. Hence, both a long-acting insulin and a short-acting insulin are typically used.

Insulin pump

Insulin pumps are a reasonable solution for some. Advantages to the patient are better control over background or 'basal' insulin dosage, bolus doses calculated to fractions of a unit, and calculators in the pump that may help with determining 'bolus' infusion dosages. The limitations are cost, the potential for hypoglycemic and hyperglycemic episodes, catheter problems, and no "closed loop" means of controlling insulin delivery based on current blood glucose levels. Insulin pumps may be like 'electrical injectors' attached to a temporarily implanted catheter or cannula. Some who cannot achieve adequate glucose control by conventional (or jet) injection are able to do so with the appropriate pump. Indwelling catheters pose the risk of infection and ulceration, and some patients may also develop lipodystrophy due to the infusion sets. These risks can often be minimized by keeping infusion sites clean. Insulin pumps require care and effort to use correctly.

Inhalable insulin

In 2006 the U.S. Food and Drug Administration approved the use of Exubera, the first inhalable insulin. It was withdrawn from the market by its maker as of third quarter 2007, due to lack of acceptance. Inhaled insulin claimed to have similar efficacy to injected insulin, both in terms of controlling glucose levels and blood half-life. Currently, inhaled insulin is short acting and is typically taken before meals; an injection of long-acting insulin at night is often still required. When patients were switched from injected to inhaled insulin, no significant difference was observed in HbA1c levels over three months. Accurate dosing was a particular problem, although patients showed no significant weight gain or pulmonary function decline over the length of the trial, when compared to the baseline. Following its commercial launch in 2005 in the United Kingdom, it was not (as of July 2006) recommended by National Institute for Health and Clinical Excellence for routine use, except in cases where there is "proven injection phobia diagnosed by a psychiatrist or psychologist". In January 2008, the world's largest insulin manufacturer, Novo Nordisk, also announced that the company was discontinuing all further development of the company's own version of inhalable insulin, known as the AERx iDMS inhaled insulin system. Similarly, Eli Lilly and Company ended its efforts to develop its inhaled Air Insulin in March 2008. However, MannKind Corp. (majority owner, Alfred E. Mann) remains optimistic about the concept.

Transdermal

There are several methods for transdermal delivery of insulin. Pulsatile insulin uses microjets to pulse insulin into the patient, mimicking the physiological secretions of insulin by the pancreas. Jet injection had different insulin delivery peaks and durations as compared to needle injection. Some diabetics find control possible with jet injectors, but not with hypodermic injection. Both electricity using iontophoresis and ultrasound have been found to make the skin temporarily porous. The insulin administration aspect remains experimental, but the blood glucose test aspect of "wrist appliances" is commercially available. Researchers have produced a watch-like device that tests for blood glucose levels through the skin and administers corrective doses of insulin through pores in the skin. A similar device, but relying on skin-penetrating "microneedles", was in the animal testing stage in 2015.

Intranasal insulin

Intranasal insulin is being investigated. CPEX Pharmaceuticals reported phase 2a clinical trial preliminary results for its intranasal drug, Nasulin, on March 19, 2010; there's no word on when it might be expected on the market.

Oral insulin

The basic appeal of oral hypoglycemic agents is that most people would prefer a pill to an injection. However, insulin is a protein, which is digested in the stomachand gut and in order to be effective at controlling blood sugar, cannot be taken orally in its current form. The potential market for an oral form of insulin is assumed to be enormous, thus many laboratories have attempted to devise ways of moving enough intact insulin from the gut to the portal vein to have a measurable effect on blood sugar. A number of derivatization and formulation strategies are currently being pursued to in an attempt to develop orally available insulin. Many of these approaches employ nanoparticle delivery systems and several are being tested in clinical trials.

Dosage units

One international unit of insulin (1 IU) is defined as the "biological equivalent" of 34.7 μg pure crystalline insulin. This corresponds to the old USP insulin unit, where one unit (U) of insulin was set equal to the amount required to reduce the concentration of blood glucose in a fasting rabbit to 45 mg/dl (2.5 mmol/L). The unit of measurement used in insulin therapy is not part of the International System of Units (abbreviated SI) which is the modern form of the metric system. Instead the pharmacological international unit (IU) is defined by the WHO Expert Committee on Biological Standardization.

Detection in biological fluids

Insulin is often measured in serum, plasma or blood in order to monitor therapy in diabetic patients, confirm a diagnosis of poisoning in hospitalized persons or assist in a medicolegal investigation of suspicious death. Interpretation of the resulting insulin concentrations is complex, given the numerous types of insulin available, various routes of administration, the presence of anti-insulin antibodies in insulin-dependent diabetics and the *ex vivo* instability of the drug.

Other potential confounding factors include the wide-ranging cross-reactivity of commercial insulin immunoassays for the biosynthetic insulin analogs, the use of high-dose intravenous insulin as an antidote to antihypertensive drug over dosage and postmortem redistribution of insulin within the body.

The use of a chromatographic technique for insulin assay may be preferable to immunoassay in some circumstances, to avoid the issue of cross reactivity affecting the quantitative result and also to assist identifying the specific type of insulin in the specimen.

Combination with other antidiabetic drug

A combination therapy of insulin and other antidiabetic drugs appears to be most beneficial in diabetic patients who still have residual insulin secretory capacity. A combination of insulin therapy and sulphonylurea is more effective than insulin alone in treating patients with type 2 diabetes after secondary failure to oral drugs, leading to better glucose profiles and/or decreased insulin needs.

Allergy

Allergy to Insulin products is rare with a prevalence of about 2%, of which most reactions are not due to the insulin itself but to preservatives added to insulin such as zinc, protamine, and meta-cresol. Most reactions are Type I hypersensitivity reactions and rarely cause anaphylaxis. A suspected allergy to insulin can be confirmed by skin prick testing, patch testing and occasionally skin biopsy. First line therapy against insulin hypersensitivity reactions includes symptomatic therapy with antihistamines. The affected persons are then switched to a preparation that does not contain the specific agent they are reacting to or undergo desensitization.

Problems associated with insulin

There are several problems with insulin as a clinical treatment for diabetes:

- Mode of administration.
- Selecting the 'right' dose and timing. Usually one unit of insulin is ~15grams of CHO.

 Selecting an appropriate insulin preparation (typically on 'speed of onset and duration of action' grounds).
 Adjusting dosage and timing to fit food intake timing, amounts, and types.
 Adjusting dosage and timing to fit exercise undertaken.
 Adjusting dosage, type, and timing to fit other conditions, for instance the increased stress of illness.
 Variability in absorption into the bloodstream via subcutaneous delivery
 The dosage is non-physiological in that a subcutaneous bolus dose of insulin alone is administered instead of combination of insulin and Cpeptide
being released gradually and directly into the portal vein.
 It is simply a nuisance for patients to inject whenever they eat carbohydrate or have a high blood glucose reading.
 It is dangerous in case of mistake (most especially 'too much' insulin).