

INTERNSHIP AND TRAINING PROGRAM

AN INTERNSHIP REPORT

Submitted by

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I'm one of those fortunate student whose path is enlightened by expertise and competent guidance of Mr.P.MAHENDRAN(PRODUCTION HEAD) for completing this intership successfully.

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INTRODUCTION:

An overall view of various departments which run an entire pharmaceutical company and the technology induced in the formulation of pharmaceuticals.



INDUSTRY OVERVIEW

Started in the year 2000, Kausikh Therapeutics is a manufacturing organization, having 2 manufacturing facilities, 500 employees, covering all dosage forms and selling products in India and across the globe.

Kausikh Therapeutics (P) Ltd is one of the most respected contract research and manufacturing (CRAMS) organizations in India. Apart from marketing their own brands in India, a B2B business that out-licenses the generic products also are developed by in-house R&D to the pharmaceutical marketing companies against a supply agreement.

MOTTO OF THE COMPANY

Consistent growth and sustainability is a multidimensional aspiration for all at Kausikh. We remain focused on providing quality and affordable medicines to

billions of ailing patients across geographies and bridging the gap of unmet needs of the medical fraternity through continuous innovation.

AIM & OBJECTIVE

- To be a global player in the contract manufacturing space working with the innovators.
- To have manufacturing sites outside India and be a global player.
- To be a globally recognized manufacturing organization (CMO) of quality pharmaceutical drugs in different dosage forms
- Offering the best customer service by being a one stop shop for all our customer drug needs and let us make sure we deliver the highest quality product in a timely manner.

PRODUCTS

1. Gabapentin Capsules IP 300 mg (anticonvulsant)
2. Phenytoin BP 300 mg (anticonvulsant)
3. Haloperidol IP 10 mg
4. Fluoxetine USP 20 mg
5. Metformin BP 500 mg
6. Itraconazole capsules 200 mg
7. Nifedipine
8. Enalapril
9. Telsartan 40 mg
10. Gastro-resistant Omeprazole capsules BP 20 mg
11. Metformin Hydrochloride SR Tablet USP 500mg

PLANT 1 TABLET AND CAPSULES PRODUCTION

DEPARTMENTS OF INDUSTRY :

- Warehouse
 - Raw material area
 - Quarantine area
 - Finish Good store
- Quality Control Department
- Quality analysis Department
- Production department
- Microbiology department
- Packaging Department
- Research and development department
- Accounts department
- Business development department

Warehouse:

It receives raw material. Until this material is cleared, it remains there. Temperature and humidity is kept under control.

PREMISES:

- It was well situated, well laid down, tidy, clean and well secured enabling good preservation of raw material packaging material and finished products.
- Humidity was set between 35 to 60%.

Raw Material Store:Raw material store was for the divided into the following

- ★ quarantine area
 - Packing material quarantine
 - Raw material Quarantine
- ★ Excipient area
- ★ Active pharmaceutical ingredients
- ★ Dispensing area
- ★ Chiller area

Quarantine :

All raw materials, packaging and labeling materials are held in our quarantine area until they are sampled, tested or examined and released for use by our quality control laboratory. The sampling is performed according to specific procedures by trained personnel.

This area is divided into two sections

Packing material Quarantine: In this section packing material for different dosage forms is kept under recommended and controlled atmosphere.

Raw material Quarantine: In this section raw material is kept under normal conditions, active Pharmaceutical ingredients is kept in 15-25°C, excipients are kept at 25°C in subsection of this area.

Chiller Area:

In this area normally temperature sensitive products are kept in separate areas to prevent them from damage or deterioration.

Dispensing area : Dispensing area is also present in the raw material section where dispensing is performed under manufacturing order of a product at time of dispensing 4 personnel should be present there to check the process of dispensing

according to SOP.

- Production pharmacist
- QA pharmacist
- Raw material store pharmacist
- Raw material dispenser

PURCHASE ORDER FOR RAW MATERIAL:

Stock delivery report is prepared. Checking of documentation is done. COA is issued. The assistant store manager receives the raw materials and transfers it to the Quarantine with the label '**quarantined**' before transferring the bulk after clearance from QCD. The QCD collects the sample and reports for its release, it is according to the specifications or rejection if not. After rejection from quality control DEPARTMENT, red **rejected** slip is pasted on each of the quarantined material and the quarantined slip is removed. After release by the quality control department, green **released** slip is pasted on each of the quarantined material and the quarantined slip is removed. The material released information's is entered in the material log sheet. The store keeper manages to transfer the RM to the bulk with necessary information pasted on it. Two copies of GRN after release of RM from QC are proposed. One copy of GRN is retained by store keeper and one copy is sent to the Accounts Department for costing. The store keeper (raw material) transfers the whole of the consignment of the material with the help of section workers by means of trolley, lifter to the bulk Store.

Documentation:

Following documentation that done in warehouse a different stages

- Temperature/Humidity charts
- Dispensing log book
- Raw materials requisition
- Raw material analysis report
- Request for retest
- Certificate of Analysis
- Issuance of slips (Pink slip: material identification, Yellow slip : Sampled at QC, Green slip : passed From QC)

PRODUCTION DEPARTMENT:

Production team is committed to produce highest quality products which can satisfy the needs of both doctors and patients. The production team endeavors to manufacture products that are cost effective through best utilization of their resources. While entering the production area, cap, overall and change of shoes) are worn.

In kaushik therapeutics, the production area is divided into following sections

Procedure for manufacturing in Production area :

- ★ Generation of M.O(manufacturing order) under instructions of the business development department that pass buyers order of medicine to the production department
- ★ M.O is checked by QC department .API quantity is checked and signed by QC if quantity is within reign otherwise it will be rejected.
- ★ M.O is sent to raw material store and dispensed according to cGMP.
- ★ Dispensed material is shifted into production area for further processing and manufacturing of medicine

STEPS INVOLVED IN TABLET MANUFACTURING :

1.Dispensing of raw material :

Tabletting process starts with dispensing of active ingredients. Weigh and dispense system begins with a pharmacist getting a bill of materials for ingredients that make up a recipe for a batch to be manufactured. Each material must be gathered from the warehouse. Then, it is verified as a proper material, carefully weighed, checked again, and finally readied for mixing in the recipe.

2.Dry Mixing:

Mixing is defined as a process that tends to result in a randomization of dissimilar particles within a System.

Mixing process - Steps:

In the solid-solid mixing operation, four steps are involved. These are

1. Expansion of the bed of solids
2. Application of three dimensional shear forces to the powder bed.
3. Mix long enough to permit true randomization of particles.
4. Maintain randomization (No segregation after mixing)

Based on the flow properties of the powders, appropriate mixers should be selected.

- Free Flowing solids - V cone blender, Double cone blender
- Cohesive solids - Sigma blender, Planetary blender

Mixing equipment-Criteria:

- ❖ The equipment should never be filled more than 60% so as to leave sufficient mixing volume.
- ❖ The shearing force should be sufficient to prevent aggregation.
- ❖ There should be no centrifugal effect so that the powder doesn't get

separated according to their weights.

- ❖ The forces should not cause breakage of the particles which results in demixing due to different particle size.

MECHANISMS OF MIXING SOLIDS:

A. Convective Mixing

It is achieved by the inversion of the powder bed using blades or paddles or screw elements. A large mass of material moves from one part to another. Convective mixing is referred to as macromixing .

B. Shear Mixing:

In this type, the forces of attraction are broken down so that each particle moves on its own between regions of different composition and parallel to their surfaces. Shear forces reduce These attractions and reduce the scale of segregation.

C. Diffusive Mixing:

It involves the random motion of particles within the powder bed, thereby particles change their positions relative to one another. It is sometimes referred to as micromixing. It occurs at the interfaces of dissimilar regions.

Sigma Blade Mixer:

Principle :

The mechanism of mixing is shearing. The inter-meshing of sigma shaped blades creates high shear and kneading actions. Convective mixing is achieved by cascading the material.

Working : Different powders are introduced from the top of the trough. The body is covered because considerable dust may be evolved during dry blending.

Through the fixed speed drive, the sigma blades are allowed to rotate. The blades move at different speeds. They turn towards each other so that the powders move from the sides to the center of the bowl. The material then moves downwards over the point and then sheared between the blades and the wall of the trough. Thus cascading action(convective) as well as shear action can be achieved. The perforated blades help in breaking lumps and aggregates. Thus high shear forces are set up. By means of a rack-and-pinion drive the bowl is tilted to empty the blend.

3.Wet Mixing:

Ribbon Blender:

Principle : The mechanism of mixing is shear. Shear is transferred to the powder bed by moving blades (ribbon shaped) in a fixed (non movable) shell. High Shear rates are effective in breaking lumps and aggregates. Convective mixing also occurs as the powder bed is lifted and allowed to cascade to the bottom of the container. An equilibrium state of mixing can be achieved.

Working : Through the fixed speed drive, ribbons are allowed to rotate. One blade moves the solids slowly in one direction and the other moves them quickly in opposite direction. Different powders are introduced from the top of the trough. The body is covered because granulating solution may evaporate during wet granulation.

The powders are lifted by a centrally located vertical screw and allowed to cascade to the bottom of the container (tumbling action). The counteracting blades set up high shear and are effective in breaking up lumps or aggregates. Helical blades move the powders from one end to another. The final stage of mix

represents an equilibrium state. The blend is discharged from the bottom opening.

4.Wet Granulation: *Wet granulation is required to avoid destruction of active components in the powder.*

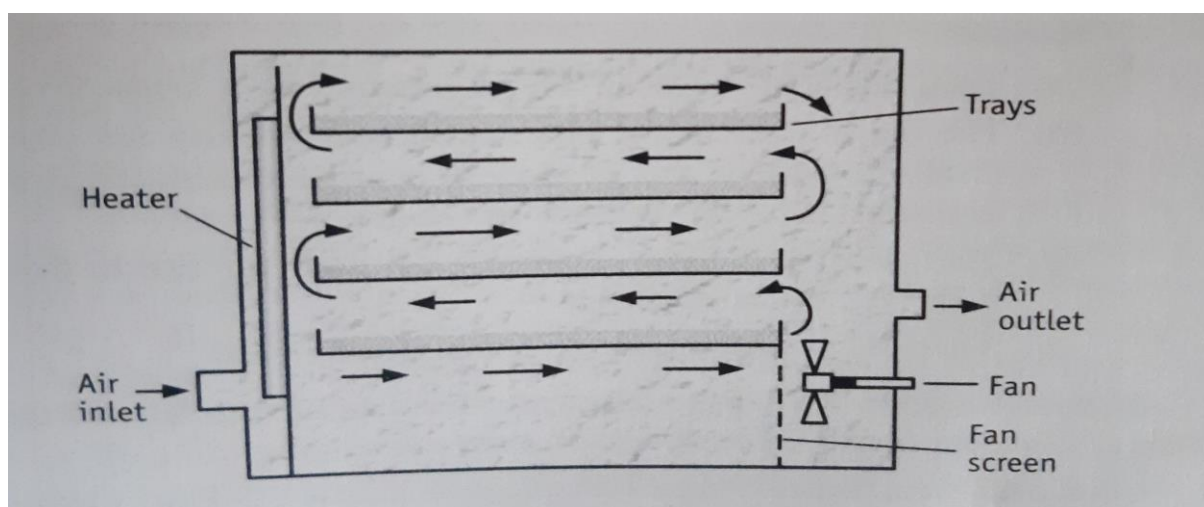
Rapid Mixer Granulator(RMG):

It is also called a high shear mixer that mixes ingredients to make the granules before compression. *Impellers* and *Choppers* are mainly responsible for wet granulation in the RMG.

Principle : A mechanical impeller moves the powder while a liquid binder is applied onto the moving powder bed. Addition of liquid binder starts the formulation of granules. Thus Wet granulation is accomplished.

Working:

The formation of granules occurs by rising, whirling and tumbling motion of the material. Dry mixing is done by adding all the ingredients into the RMG by rotation of the impeller and chopper at a high speed. During the addition of binder solutions to the powder bed, the impeller and chopper are operated at low speed. After the formation of wet mass, impeller and chopper are operated at high speed to form the granules of the required size.



5.Drying:

Tray dryer :

Principle : In a tray dryer, hot air is continuously circulated. Forced convection heating takes place to remove moisture from the solids placed in trays. Simultaneously, the moist air is removed partially.

Working :

Wet solid is loaded into trays. Trays are placed in the chamber. Fresh air is introduced through inlet, which passes through the heaters and gets heated up. The hot air is circulated by means of fans at 2 to 5 metre per second. Turbulent flow lowers the partial vapour pressure in the atmosphere and also reduces the thickness of the air boundary layer. The water is picked up by air. As water evaporates from the surface, the water diffuses from the interior of the solid by capillary action. These events occur in the single pass of air. The time of contact is short and the amount of water picked up in a single pass of air is small. Therefore the discharged air to the tune of 80 to 90% is circulated back through fans. Only 10 to 20% of air is introduced. Moist air is discharged through the outlet. Thus constant temperature and uniform airflow over the material can be maintained for achieving uniform drying.

In case of wet granules (in case of tablets and in capsules), drying is continued until the desired moisture content is obtained. At the end of drying, the trays are pulled off the chamber and taken to a tray dumping station.

Advantages:

- In tray dryer, handling of materials (loading and unloading) can be done without losses.
- It is operated batch-wise.

(OR)

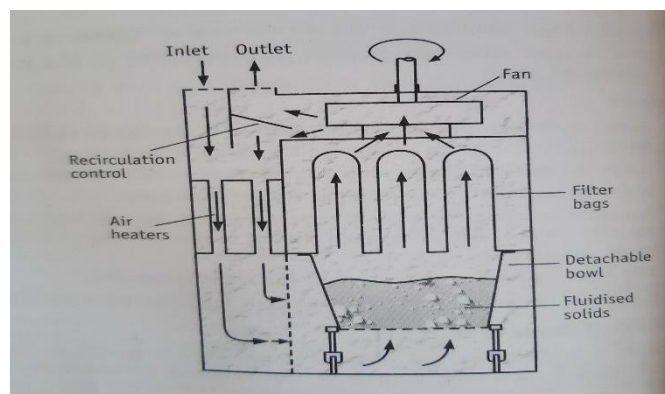
VERTICAL FLUIDIZED BED DRYER:

Principle: In fluidized bed dryer, hot air(gas) is passed at high pressure through a perforated bottom of the container containing granules to be dried. The granules are lifted from the bottom and suspended in the stream of air. This condition is called *fluidized state*. The hot gas is surrounding every granule to completely dry them. Thus materials or granules are uniformly dried.

Dryer capacity:

Width	12-57 inches
Length	10-50 feet
Depth	3 inch
Speed	5-25 ft/min

Working: The wet granules to be dried are placed in the detachable bowl. The bowl is pushed into the dryer. Fresh air is allowed to pass through a pre-filter, which subsequently gets heated by passing through a heat exchanger. The hot air flows through the bottom of the bowl. Simultaneously, fan is allowed to rotate.



The air velocity is gradually increased.

When the velocity of the air is greater than settling velocity of granules, the granules remain partially suspended in the gas stream. After some time, a point of pressure is reached at which frictional drag on the particles is equal to the force of gravity. The granules rise in the container because of high velocity gas (1.5 to 7.5 metres per minute) and later fall back in a random boiling method. This condition is said to be *fluidized state*. The gas surrounds every granule to completely dry them. The air leaves the dryer by passing through the bag filter. The entrained particles remain adhered to the inside surface of the bags. Periodically the bags are shaken to remove the entrained particles.

Intense mixing between granules and hot gas provides uniform conditions of temperature, Composition, and particle size distribution. Drying is achieved at constant rate and falling rate period is very short. Any attempt to increase the air velocity may result in entrainment.

The residence time for drying is about 40 minutes. The material is left for some time in the dryer for reaching ambient temperature. The bowl is taken out for discharging. The end product is free flowing.

Advantages:

- It can be used for three operations such as mixing, granulation and drying.
- It is 15 times faster than the tray dryer.
- The thermal efficiency is 2 to 6 times than tray dryer.
- It facilitates the drying of thermolabile substances, since the contact time

for drying is short.

6.LUBRICATION AND FINAL MIXING :

Double cone Blender :

Working : As the blender rotates, the material loaded undergoes tumbling motion. When the shell is inverted, the material splits into two portions. This process of dividing and recombining continuously yields an ordered mixing by mechanical means. The powdered mass is converted shock-wise, so that no demixing due to density differences will occur. It is rotated so that the material alternatively is collected in the bottom of shell.

It is an efficient design for mixing powders of different densities. The rate of rotation should be optimum depending on the size and shape of the tumbler, nature of material to be mixed. Commonly the range is 30 to 100 revolutions per minute.

7.COMPRESSION:

Tablet Compression Machines (Tablet Press)

Tablets are made by compressing a formulation containing a drug or drugs with excipients on stamping machines called *presses*. Tablet compression machines are designed with the following basic components;

- Hopper(s) for holding and feeding granulation to be compressed.
- Dies that define the size and shape of the tablet.
- Punches for compressing the granulation within the dies.
- Cam tracks for guiding the movement of the punches.
- A feeding mechanism for moving granulation from the hopper into the dies.

SINGLE STATION PRESS:

MULTI-STATION PRESS:

They are termed as *rotary* because the head of the tablet machine that holds the upper punches, dies, and lower punches in place rotates. As the head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression, and ejection. The portions of the head that hold the upper and lower punches are called the upper and lower turrets respectively, and the portion holding the dies is called the *die table*. At the start of compression cycle, granulation stored in a hopper, empties into the feed frame(A), which has several compartments. These compartments spread the granulation over a wide area to provide time for the dies(B) to fill. The pull-down Cam(C) guides the lower punches to the bottom of their vertical travel, allowing the dies to overfill. The punches then pass over a weight- control cam(E), which reduces the fill in the dies to the desired amount. A wipe-off blade(D) at the end of the feed frame removes the excess granulation and directs it into the front of the feed-frame.

Next, the lower punches travel over the lower compression roll(F) while simultaneously the upper punches ride beneath the upper compression roll(G). The upper punches enter a fixed distance into the dies, while the lower punches are raised to squeeze and compact the granulation within the dies. To regulate the upward movement of the lower punches, the height of the lower pressure roll is changed. After the moment of compression, the upper punches are withdrawn as they follow the upper punch raising cam(H) ;the lower punches ride up the cam(I),which brings the tablets above the surface of the dies. The exact position is determined by a threaded bolt called the *ejector* Knob. The tablets strike a

sweep-off blade affixed to the front of the feed-frame(A) and slide down a chute into a receptacle. At the same time, the lower punches re-enter the pull down cam(C) and the cycle is repeated.

A tablet machine's output is regulated by three basic characteristics of its design:

1. Number of tooling sets
2. Number of compression stations
3. Rotational speed of the press.

COMPRESSION MACHINE TOOLING:

The most common tools employed are referred to as BB tooling and are 5.25 inches in length, and have a nominal barrel diameter of 0.75 inches and 1-inch head diameter. B tooling is identical to the BB type except that the lower punch is only 3.16 inches long. D tooling is popular for large tablets, utilizing a 1-inch barrel diameter, 3.4-inch head diameter, and 5.25-inch length. The dies that are used with the above punches are either a 0.945-inch outside diameter (OD) die capable of making a 16-inch round tablet or 16-inch capsule-shaped tablet; or a 13/16 inch OD die capable of handling a 16-inch round or 3/4-inch capsule shaped tablet.

Several types of steel are normally used in the manufacture of compression tooling. These steels differ in toughness, to withstand the cyclic compacting forces (ductility), and in wear resistance. Unfortunately, no single steel type has a high resistance to abrasive wear and a high ductility. Therefore, the selection of the best steel for a specific Application must be based on experience and an accumulated history of the product being letted.

To avoid tooling damage, compressive loads or pressures at the pressure rolls must be translated into a calculation of pressure at the punch tips. As tablet punch diameter decreases, less force is required to produce the same pressure at the

punch face, since the face represents a smaller fraction of a unit area (square inch). The formula for the area of a circle is $\pi * r^2$ where r is the radius of the circle. Given a flat punch face, the area of a 1/4-inch diameter punch would thus be $3.14 * (1/8)^2$ or $3.14 * 1/16$ or approximately 1/20 square-inch. If a 1-ton load is being applied by the pressure roll, this area is translated as 2000 pounds on 1/20 square inch, or 40,000 pounds on 1 square -inch, a gross overload.

8.COATING PROCESS:

In most cases, the coating process is the last critical step in the tablet production cycle. Tablet coating is the application of a coating composition to a moving bed of tablets with the concurrent use of heated air to facilitate evaporation of the solvent. The distribution of the coating is accomplished by the movement of the tablets either perpendicular (coating pan) or vertical (air suspension coater) to the application of the coating composition. The coating process can be divided into two types; i.e. sugar coating and film coating. The type of process chosen depends on the type of coating that is to be applied, the durability (toughness) of the tablet core, and the economics of the process. Sugar coating is still a widely used coating process because of the excellent tablet appearance it achieves.

COATING EQUIPMENTS :

Conventional Pan System:

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand. The pan is 8 to 60 inches in diameter and is rotated on its horizontal axis by a motor. Heated air is directed into the pan and onto the tablet bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are tablets by ladling or spraying the material onto the rotating tablet bed. Use of atomizing systems to spray the liquid coating material onto the tablets produces a faster, more even distribution of the

solution or suspension.

Perforated Pan System:

In general, all equipment of this type consists of a perforated or partially perforated drum that is rotated on its horizontal axis in an enclosed housing. In the Accela-Cota and Hi Coater systems, drying air is directed into the drum, is passed through the tablet bed, and is exhausted through perforations in the drum. The Driacoater introduces drying air through hollow perforated ribs located on the inside periphery of the drum. As the pan rotates, the ribs dip into the tablet bed, and drying air passes up through and fluidizes the tablet bed. Exhaust is from back of the pan. As the coating pan rotates, the ribs dip into the tablet bed, and drying air passes up through and fluidizes the tablet bed. Exhaust is from the back of the pan.

The Glatt coater is the latest perforated pan coater to be introduced in the industry. In the Glatt coater, drying air can be directed from inside the drum through the tablet bed and out an exhaust duct; alternatively, with an optional split-chambered plenum, drying air can be directed in the reverse manner up through the drum perforations for partial fluidization of the tablet bed. Several airflow configurations are possible. In all four of these perforated pan systems the coating solution is applied to the surface of the rotating tablet bed through spraying nozzles that are positioned inside the drum.

Fluidized Bed (Air Suspension) Systems:

Fluidized bed coaters are also highly efficient drying systems. Fluidization of the tablet mass is achieved in a columnar chamber by the upward flow of drying air. The airflow is controlled so that more air enters the center of the column, causing the tablets to rise in the center. The movement of tablets is upward through the center of the chamber. They then fall toward the chamber wall and move

downward to re-enter the air stream at the bottom of the chamber. In some units, 8 smaller column(s) is used to direct tablet movement within the main column. Coating solutions are continuously applied from a spray nozzle located at the bottom of the chamber or are sprayed onto the top of the cascading tablet bed by nozzles located in the upper region of the chamber.

Spray Application Systems:

The two basic types of systems used to apply a finely divided (atomized) spray of coating solutions or suspensions onto tablets are

(1) high-pressure, airless

(2) low-pressure, air-atomized. The principal difference in the two types is the manner in which atomization of the liquid is achieved.

In the airless spray system, liquid is pumped at high pressure (250 to 3,000 pounds per square inch gauge (psig) through a small orifice (0.009 inch to 0.020 inch id) in the fluid nozzle, which results in a finely divided spray. The degree of atomization and the spray rate are controlled by the fluid pressure, orifice size, and viscosity of the liquid. Because of the small orifice, suspended solids in the coating composition must be finely milled or filtered to prevent orifice blockage.

In the low-pressure air-atomized system, liquid is pumped through a somewhat larger orifice (0.020 inch to 0.060 inch id) at relatively low pressures (5 to 50 psig) . Low pressure (10 to 100 psig) air contacts the liquid stream at the tip of the atomizer, and a finely divided spray is produced. The degree of atomization is controlled by the fluid pressure, fluid cap orifice, viscosity of the liquid, air pressure, and air cap design.

Coated tablet Evaluation /Quality control:

- *Water vapor permeability*

- *Film strength*

For film coating,

- *Adhesion test*
- *Diametral crushing strength*
- *Disintegration test*
- *Dissolution test*
- *Stability studies*
- *Tests for resistance to chipping and cracking.*

9.LABELING AND PACKAGING :

Labels should be stored in an air-conditioned room, and in winter, the air should be humidified to maintain a relative humidity of 50% to avoid over drying of labels. The room should have sufficient space for storage.

The following package configurations have been identified by the FDA as examples of packaging systems that are capable of meeting the requirements of tamper-resistant packaging as defined by the FDA regulation.

- Film wrappers
- Blister package
- Strip package
- Bubble pack
- Shrink seals and bands
- Foil, paper, or plastic pouches
- Bottle seals
- Tape seals
- Breakable caps
- Sealed tubes
- Aerosol containers

- Sealed cartons

Film Wrapper:

End-folded wrapper:

The end-folded wrapper is formed by pushing the product into a sheet of over wrapping film, which forms the film around the product and folds the edges in a gift-wrap fashion. The folded areas are sealed by pressing against a heated bar. Because of the overlapping folding sequence of the seals, the film used must be heat-sealable on both surfaces. Materials commonly used for this application are cellophane and polypropylene. Cellophane, which is regenerated cellulose, is not inherently heat-sealable but requires a heat-seal coating to impart heat-sealing characteristics to the film. This is usually accomplished by coating the cellophane with either polyvinylidene chloride (PVdC) or nitrocellulose. Since PVdC also provides a durable moisture barrier, PVdC coated cellophane is often used for the over wrapping of products that are sensitive to moisture.

Fin-Seal Wrapper:

Unlike the end-folded wrapper configuration, fin seal packaging does not require the product to act as a bearing surface against which the overwrap is sealed. The seals are formed by crimping the film together and sealing together the two inside surfaces of the film, producing a "fin" seal. Since the seals are formed by compressing the material between two heated bars (or nipping the film between pressure rollers) rather than sealing against the package, much greater and more consistent sealing pressure can be applied, and consequently, better seal integrity can be accomplished. For this reason, fin sealing has primarily been used when protective packaging is critical. Since the surface of the heat seal does not come in contact with the heated sealing bars on the packaging equipment, much more tenacious heat sealants, such as polyethylene or Surlyn can be used. With

good seal integrity, the overwrap can be removed or opened only by tearing the wrapper.

Shrink Wrapper:

The shrink wrap concept involves the packaging of a product in a thermoplastic film that has been stretched and oriented during its manufacture and that has the property of reverting back to its unstretched dimensions once the molecular structure is "unfrozen" by the application of heat. The shrink film is used in roll form, with the center folded in the direction of winding. As the film unwinds on the overwrapping machine, a pocket is formed in the centerfold of the sheet, into which the product is inserted. An L-shaped sealer seals the remainder of the overwrap and trims off the excess film. The loosely wrapped product is then moved through a heated tunnel, which shrinks the over wrap into a tightly wrapped unit. The materials commonly used are *heat shrinkable grades of polypropylene, polyethylene, and PVC*. The major advantages of this type of the wrapper are the *flexibility and low cost* of the packaging equipment required.

Blister package:

The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic softening into a contoured mold. After cooling, the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with product and lidded with a heat-sealable backing material. The backing material, or lidding, can be of either a push through or peelable type. For a push-through type of blister, the backing material is usually heat-seal-coated aluminum foil. The coating on the foil must be compatible with the blister material to ensure satisfactory sealing, both for product protection and for tamper resistance. Peelable backing materials have been used to meet the requirements of child-

resistant packaging. This type of backing must have a degree of puncture resistance to prevent a child from pushing the product through the lidding and must also have sufficient tensile strength to allow the lidding to be pulled away from the blister even when the lidding is strongly adhered to it. To accomplish this, a material such as polyester or paper is used as a component of the backing lamination. Foil is generally used as a component of backing lamination if barrier protection is a critical requirement; however, metallized polyester is replacing foil for some barrier applications.

Materials commonly used for the thermo-formable blister are *PVC*, *PVC/polyethylene combinations*, *polystyrene*, and *polypropylene*.

Strip Package:

A strip package is a form of unit dose packaging that is commonly used for the packaging of tablets and capsules. A strip package is formed by feeding two webs of a heat-sealable flexible film through either a heated crimping roller or a heated reciprocating platen. The product is dropped into the pocket formed prior to forming the final set of seals. A continuous strip of packets is formed. The strip of packets is cut to the desired number of packets in length. The strips are usually packaged into a folding carton. The product between the two sheets of film usually has a seal around each tablet, with perforations usually separating adjacent packets.

For high barrier applications, a *paper/polyethylene/foil/polyethylene lamination* is commonly used. When product visibility is important, a heat-sealable *cellophane* or a *polyester* can be used.

PRODUCT-PACK VALIDATION :

NON STERILE PRODUCT-PACK VALIDATION :

- *Water Vapor permeability*
- *Light transmission*
- *Stability*

STERILE PRODUCT-PACK VALIDATION :

- *Compatibility*
- *Seal integrity /Immersion test*

REGULATORY REQUIREMENTS :

The main requirements are as follows :

1.New drug application (NDA): NDA must be submitted and approved prior to the sale of the product on the market. The details that need to be included are as follows:

- a. Primary component formulation details, critical dimensions and drawings
- b. Primary and secondary component artwork such as labels, leaflets and cartons.
- c. Primary component quality standards, testing methods and compatibility data.
- d. Product-pack validation data.
- e. In-process operations and facility details of filling and packaging operations.
- f. List of primary component manufacturers

2. Supplemental NDA type I: This is submitted when major process changes are required. The supplemental NDA require FDA approval prior to implementation. The type of changes include:

- a. Relaxing or deletion of primary component specification limit or critical dimensions that will not affect component quality.
- b. Changing a testing method of a primary component.
- c. Any change in artwork test.
- d. The use of different facility for filling or packaging where the facility has not received a cGMP inspection.

3. Supplemental NDA type II: These changes can be implemented prior to FDA approval. Adding a new testing methodology to ensure better quality control, changes in artwork to strengthen safe use of a product, deletion of artwork giving false indications and small changes (cGMP approved) in filling or packaging process are included in supplemental NDA Type II changes.

4. Annual NDA reports: Annual NDA reports detail the minor changes (that do not require a supplemental application) that take place within a year after approval of NDA.

5. Drug master file (DMF): A DMF is a submission to FDA that provide detailed information about processes and facilities used in manufacturing, packaging and storing of pharmaceutical products. The complete file in relation to packaging component consists of two types (Type I and III), out of five types of DMF. DMF type I details manufacturing site and facility whereas, DMF type III details data supporting the suitability of the component for their intended use.

In the case of packaging materials, most packaging material manufacturers maintain DMF with the FDA. Upon request from the manufacturer, the FDA uses this file as a reference to support a New Drug Application that which a drug manufacturer files.

CAPSULE SECTION:

HARD GELATIN CAPSULES FILLING :

Filling machines are differentiated by the means by which they measure and feed the dose of material. The feeding mechanism commonly employed in filling machines are of two types: (a) Dependent type-powder is transferred from a hopper directly to the capsule body and flow of the powder is aided either by a revolving auger or by a vibrating plate. The powder inside these capsules is a loose fill. From auger machines higher fill weights are often achievable, (b) Independent type-compress the measured amount of powder to form a plug. The plug is formed inside a dosator or dosing tube with the help of a moveable piston that controls the dosing volume. Dosator type feeding units are very versatile because the fill weight can be varied over the wide range. Filling machines are available with a range of outputs, from bench-scale to high-output industrial scale and from manual to fully automatic.

Semi automatic Filler Machine:

The empty capsules are fed from the storage hopper and through the rectifying unit, into the two-piece filling ring. Rectification is based on dimensional differences between the outside diameters of the cap and body portions of the capsule. The ring containing separable portions, lower portion and upper portion, is rotated and a vacuum is applied on its underside. This vacuum seats the bodies into the lower portion of the ring, while the caps are retained in the upper portion. The two portions of the ring are then separated, and the upper (cap-containing) portion is set aside. The lower (body containing) portion of the ring is placed on a variable speed turntable and is mechanically rotated under the powder hopper, which contains an auger for the forced delivery of the powder. After one (or more) complete rotation of the ring, the powder hopper is removed, and the two portions

of the ring are rejoined. The intact ring is positioned in front of the peg ring, and the closing plate is pivoted to a position approximately 180 degrees from that. Pneumatic pressure is applied to the peg ring, which forces the capsule body into the cap, and the closing plate holds the caps in position. Ejection of the filled capsules from the rings cannot occur with the plate in the closing position. For ejection of the capsules, the pressure is released, the closing plate is restored to its original position, and the capsules are expelled through the upper portion of the ring. Normal closing and ejection occur with the peg ring in a vertical position with the filled capsules being collected through a chute into the collection chamber.

EVALUATION /QUALITY CONTROL TEST:

- Weight variation test
- Content Uniformity
- In Vitro testing

Type of dosage forms for filling into hard gelatin capsules

Solid	Semisolid	Liquids
Powders	Paste	NON-aqueous solutions
Granules	Thermosoftening	Oily liquids
Pellets	Thixotropic mixtures	
Tablets		
Capsules		

QUALITY ASSURANCE DEPARTMENT :

Quality assurance is a part of quality management focused on providing confidence that quality requirements will be fulfilled.

Quality assurance therefore incorporates GMP and other factors, such as product design and development. The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that

- a. Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as good laboratory practice (GLP) and good clinical practice (GCP).
- b. Managerial responsibilities are clearly specified in job descriptions.
- c. All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.
- d. Production and control operations are clearly specified in a written form and GMP requirements are adopted.
- e. The finished product is correctly tested and checked, according to the defined procedures and are sold or supplied after the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements.
- f. Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer. distributed, and handled so that quality is maintained throughout their shelf-life.
- g. There is a procedure for self-inspection and/or quality audit that regularly raises the effectiveness and applicability of the quality assurance system.

- h. Deviations are reported, investigated and recorded.
- i. Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

Raw material quality assurance monograph:

A. (Raw material name)

1. Structural formula, molecular weight
2. Chemical name(s)
3. Item number
4. Date of issue
5. Date of superseded, if any, or new material
6. Signature of writer
7. Signature of approval

B. Samples

1. Safety requirement
2. Sample plan and procedure
3. Sample size and sample container to be used
4. Preservation sample required

C. Retest program

1. Retesting schedule
2. Reanalysis to be performed to assure identity, strength, quality, and purity

D. Specifications (wherever applicable)

1. Description
2. Solubility
3. Identity
 - a. Specific chemical tests such as related alkaloids, organic nitrogen basis, acid moiety, or inorganic salt tests; sulfate, chloride, phosphate, sodium, and potassium tests; or other spot organic and inorganic chemical tests as needed.
 - b. Infrared absorption
 - c. Ultraviolet absorption
 - d. Melting range
 - e. Congealing point
 - f. Boiling point or range
 - g. Thin-layer, paper, liquid, or gas chromatography
4. Purity and quality
 - a. General completeness of solutions, pH, specific rotation, nonvolatile residue, ash, acid-insoluble ash, residue on ignition, loss on drying, water content, heavy metals, arsenic, lead, mercury, selenium, sulfate, chloride, carbonates, acid value, iodine value, saponification value.
 - b. Special quality tests, particle size, crystallinity characteristics, and

polymorphic forms

c. Special purity tests, ferric and ferrous salts, peroxides and aldehydes in ether and related degradation products

5. Assay, calculated either on anhydrous or hydrous basis.

6. Microbial limits, especially for raw materials from natural sources

E. Test procedures

1. Compendial, USP, or NF references

2. Non Compendial, detailed analytical procedure, weights; dilutions; extractions; normality; reagents; instrumentation used and procedure, if any; calculations

F. Approved suppliers

1. List of prime suppliers and other approved alternative suppliers, if any.

MICROBIOLOGY DEPARTMENT :

The microbial flora associated with various raw materials can vary considerably. Standard plate-counting procedures are familiar and popular methods. In addition, broth enrichment procedures are used to detect low levels of microorganisms. The following categories of raw materials are often contaminated with various microbial flora and should be thoroughly investigated: processed water, colors, dyes, pigments, talcs, starches, clays, fillers, natural gums, and thickening agents. It is important to consider the pharmaceutical process when a limit is established for the number of microorganisms per gram of raw material. Sample should be taken throughout the Production cycle on a random basis. The final dosage form is often statistically sampled and tested for

microbiological attributes. Here again, the absence of pathogens is important, and the total count gives a measure of microbiologic normality. The hazard of microbial contamination is related to the intended area of use for the product. For parenteral products, the dictum is that any viable microorganism is a health hazard. Even for orally administered products, the presence *E. coli* and *Salmonella* species are always objectionable, and the presence of *Pseudomonas* species, *C. albicans*, *Enterobacter* species and mycotoxin-producing fungi are usually objectionable since these organisms have been implicated foods.

PLANT 2-LIQUID PRODUCTION AREA

1. Dedusting
2. Quarantine
3. Approve area
4. Cold room
5. Dispensing room
6. Sugar storage room
7. Bottle washing area
8. FG store
9. Liquid filling area
10. Liquid manufacturing room
11. Label and Packaging

APPROVED STORES:

Raw material is stored in temperature control room. Various raw material include

- Potassium iodide
- PVP

- Ferrous ascorbate
- Ascorbic acid
- Vitamin acetate IP
- Cholecalciferol
- Niacinamide
- Vitamin E Dry powder
- Salbutamol sulphate

DISPENSING ROOM:

The raw material dispersed is from two booth. They are active material(drugs) booth and inactive material booth(excipients).They both contains two separate weighing machine.

Excipients:

- MCCP
- Crose carmellose sodium
- Purified talc
- Ferrous gluconate
- Polymeg 4000
- Zinc gluconate
- Kyron
- Calcium stearate

LIQUID PRODUCTION AREA

DAY STORE



1000 l TANK



4000 l TANK



2000 l TANK



2000 l TANK



2000 l TANK



1000 l TANK



1000 l TANK(BOILER)



BOTTLE WASHING



FILLING SEALING



VISUAL INSPECTION



LABELING MACHINE



MEASURING CAP MACHINE



CARTON PRINTING MACHINE

(PRINTING ROOM)

SUMMARY:

Kausikh therapeutics pvt ltd is Manufacturing formulations in wide range of dosage forms, including; dispersible, bi-layered, coated, uncoated, enteric coated, Hard gelatin capsules, Granules and Liquid Orals. It also manufactures beta lactams (dispersible tablets, uncoated tablets, coated and dry syrups). Various departments of the manufacturing unit are Quality Assurance, Quality Control, Warehouse, Production, research and development.

1. Raw materials are quarantined in quarantine area for a few days in order to carry out test by QC department and are labelled in yellow label, red and green labels.
2. Instrumental Methods used to ensure the quality of raw materials; punched tablets and packed tablets. It provides COA-Certificate of analysis and Sop (standard operating procedure) for instruments.
3. In granulation process the components used are Rapid Mixer Granulator (RMG), fluid bed dryer (FBD), sifter, Multi miller, blender.
4. Compression of tablet involves hopper to hold feed granules, feed frame Carries granules from hopper to die cavity, die Cavity is the space meant for tablet to be punched, Punches- upper and lower punch compreses tablet.
5. Coating of tablets carried out in ganscoater with perforated coating pan,hot air inlet,exhaust and coat solution inlet.
6. In QC department:

Disintegration test, dissolution test, hardness test,friability tests,weight variation tests are carried out.

- 7.In microbiology laboratory, quantitative and qualitative tests are carried to

indicate presence of colonies growth of E.COLI and other bacterial strains.

8.Packing department comprises of strip packing, blister packing, ALULU packing and packing primary packages to cartons.

Industrial Contacts:

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CONCLUSION:

Through serving on humanity is not only a person's responsibility but also of community. And this community comprises of all the members starting from very first of disposal of quality products. No work is penniless rather the knowledge it keeps in, internship at any working areas is a great learning experience in itself. KAUSHIK THERAPEUTICS enhanced understanding of my academic knowledge and experience. Through this internship, I not only got the opportunity to experience but I also learnt the applications of theories in actual application. I got to observe the whole working environment of pharmaceutical industry & the important aspects regarding the production of high-quality pharmaceuticals & carrying out during production are according to GMP.