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SCHOOL OF BIO & CHEMICAL ENGINEERING

DEPARTMENT OF BIOMEDICAL ENGINEERING

UNIT – I – BIOMEMS AND NANOTECHOLOGY – SBM1606

UNIT 1 – BIOMEMS AND NANOTECHNOLOGY

1 DEFINITION:

Microelectromechanical systems (**MEMS)**, *MicroElectroMechanical* or *microelectronic and microelectromechanical systems* and the related *micromechatronics* is the technology of very small devices; it merges at the nano-scale into nanoelectromechanical systems (NEMS) and nanotechnology.

MEMS are separate and distinct from the hypothetical vision of molecular nanotechnology or molecular electronics. MEMS are made up of components between 1 to 100 micrometres in size (i.e. 0.001 to 0.1 mm), and MEMS devices generally range in size from 20 micrometres to a millimetre (i.e. 0.02 to 1.0 mm). They usually consist of a central unit that processes data (the microprocessor) and several components that interact with the surroundings such as microsensors. At these size scales, the standard constructs of classical physics are not always useful. Because of the large surface area to volume ratio of MEMS, surface effects such as electrostatics and wetting dominate over volume effects such as inertia or thermal mass.

MEMS or Micro Electro Mechanical Systems are Semiconductor ICs that have combined the electrical and mechanical property of Silicon. There are actual moving mass, springs, cavities, dampers etc inside a MEMS structure. MEMS can detect motions such as acceleration, gravity, angular motion, magnetic field and pressure etc. Typical MEMS is SIP (system in package) IC consisting of two ICs. First IC senses the desired parameter and converts it into equivalent capacitance. Second IC converts the capacitance into equivalent voltage or digitally onto I2C bus.

Two principal components of MEMS:

A sensing or actuating element and a signal transduction unit. MEMS as a microsensor:

2 ORIGIN:

Manufactured on to semiconductor material.
Used to make sensors, actuators, accelerometer,switches and light.
Used in automobiles, aerospace, biomedical app wireless,optical communication.

(1) 1947-invention of the point contact transistor uses electrical current (or) a small amt of voltage to control a larger change in current (or) voltage
-Transistor is a building blocks of computers, cellular phones other modern electronics .

(2) 1954-Discovery of the piezoresistive effect in silicon and germanium to sense air (or) H2O pressure,better then metal.

Eg. Strain gauges, pressure sensor and accelerometer utilize piezoresistive effect in silicon

(3) 1958-First integrated circuit (IC). IC includes transistors, resistors, capacitors and wires.

(4) 1968-The resonant gate transistor patented this device . It joined a mechanical component with an electronic element and is called a resonant gate. 1mm size, it serves as a frequency filter in IC.

(5) 1971-Invention of µ processor.

Single chip microprocessor . -Paved the way for the personal computer

(6) 1979-HP micro machined inkjet nozzle thermal inkjet technology (TIJ).

TIJ-heats ink-creating tiny bubbles, tiny bubbles collapse – ink squirts through an array of nozzle onto the paper

(7) 1982-LIGA process – manufacturing microstructure

(8) 1986-AFM – scans the surface of an atomic structure by measuring the force acting on the tip of a micro scale cantilever

(9) 1992 – Grating light modulator .

-It is a micro opto electro mechanical system (mems)

-Graphic printing, lithography and optical communication. **(10)1993-**Multi user mems processes (MUMPs) a three layer poly silicon surface micro machining process to create their own design (1cm)

. **(11)1993-**First manufactured accelerometer. The automotive industry used this accelerometer in automobiles for airbag deployment sensing, highly reliable, very small, inexpensive .

(12)1994-Deap reactive ion etching patened.

-DRIE – highly an isotropic etch process used to create deep,steep sided holes and trenches in to H2o.

(13) Late 1990s early 2000 -biomem. -Scientist are combining sensors and actuators with emerging biotechnology.

Application includes,

- -Drug delivery system
- -DNA array
- -Insulin pump
- -Lab – on – a – chip (LOC)
- -Glucometers
- -Neural probe arrays
- -Microfluidics

3 Summary

Mems devises measured things as pressure in engines and motion in cars mems are controlling our communication network mems travel through human body to a monitor blood pressure.

The application and growth of mems and memes are endless. Mems are even getting smaller now have nano electro mechanical systems (nems).

4. TYPES:

4.1MATERIALS USED FOR MEMS MANUFACTURING

The fabrication of MEMS evolved from the process technology in semiconductor device fabrication, i.e. the basic techniques are deposition of material layers, patterning by photolithography and etching to produce the required shapes.

4.1.1Silicon

Silicon is the material used to create most integrated circuits used in consumer electronics in the modern industry. The economies of scale, ready availability of cheap high -quality materials and ability to incorporate electronic functionality make silicon attractive for a wide variety of MEMS applications. Silicon also has significant advantages engendered through its material properties.

In single crystal form, silicon is an almost perfect Hookean material, meaning that when it is flexed there is virtually no hysteresis and hence almost no energy dissipation. As well as making for highly repeatable motion, this also makes silicon very reliable as it suffers very little fatigue and can have service lifetimes in the range of billions to trillions of cycles without breaking.

4.1.2 Polymers

Even though the electronics industry provides an economy of scale for the silicon industry, crystalline silicon is still a complex and relatively expensive material to be produced. Polymers on the other hand can be produced in huge volumes, with a great variety of material characteristics. MEMS devices can be made from polymers by processes such asinjection molding, embossing or stereolithography and are especially well suited to microfluidic applications such as disposable blood testing cartridges.

4.1.3 Metals

Metals can also be used to create MEMS elements. While metals do not have some of the advantages displayed by silicon in terms of mechanical properties, when used within their limitations, metals can exhibit very high degrees of reliability. Metals can be deposited by electroplating, evaporation, and sputtering processes. Commonly used metals include gold, nickel, aluminium, copper, chromium, titanium, tungsten, platinum, and silver.

4.1.4 Ceramics

The nitrides of silicon, aluminium and titanium as well as silicon carbide and other ceramics are increasingly applied in MEMS fabrication due to advantageous combinations of material properties. AlN crystallizes in the wurtzite structure and thus shows pyroelectric and piezoelectric properties enabling sensors, for instance, with sensitivity to normal and shear forces. TiN, on the other hand, exhibits a high electrical conductivity and large elastic modulus allowing to realize electrostatic MEMS actuation schemes with ultrathin membranes. Moreover, the high resistance of TiN against biocorrosion qualifies the material for applications in biogenic environments and in biosensors.

5. MEMS TECHNOLOGY:

Micro-Electro-Mechanical Systems, or MEMS, is a technology that in its most general form can be defined as miniaturized mechanical and electro-mechanical elements (i.e., devices and structures) that are made using the techniques of microfabrication. The critical physical dimensions of MEMS devices can vary from well below one micron on the lower end of the dimensional spectrum, all the way to several millimeters. Likewise, the types of MEMS devices can vary from relatively simple structures having no moving elements, to extremely complex electromechanical systems with multiple moving elements under the control of integrated microelectronics. The one main criterion of MEMS is that there are at least some elements having some sort of mechanical functionality whether or not these elements can move. The term used to define MEMS varies in different parts of the world. In the United States they are predominantly called MEMS, while in some other parts of the world they are called

“Microsystems Technology” or “micromachined devices”.

While the functional elements of MEMS are miniaturized structures, sensors, actuators, and microelectronics, the most notable (and perhaps most interesting) elements are the microsensors and microactuators. Microsensors and microactuators are appropriately categorized as

“transducers”, which aredefined as devices that convert energy from oneform to another. In the

case of microsensors, the device typically converts a measured mechanical signal into an electrical signal.

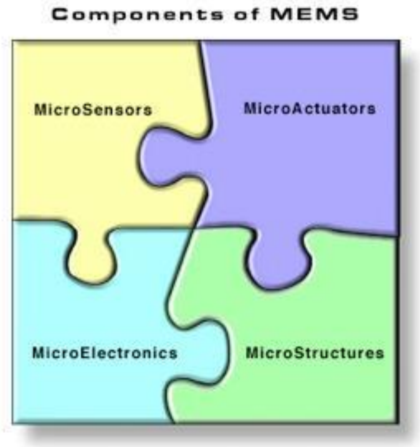

Fig. 1.1 Components of MEMS

Over the past several decades MEMS researchers and developers have demonstrated an extremely large number of microsensors for almost every possible sensing modality including temperature, pressure, inertial forces, chemical species, magnetic fields, radiation, etc. Remarkably, many of these micromachined sensors have demonstrated performances exceeding those of their macroscale counterparts. That is, the micromachined version of, for example, a pressure transducer, usually outperforms a pressure sensor made using the most precise macroscale level machining techniques. Not only is the performance of MEMS devices exceptional, but their method of production leverages the same batch fabrication techniques used in the integrated circuit industry – which can translate into low per-device production costs, as well as many other benefits. Consequently, it is possible to not only achieve stellar device performance, but to do so at a relatively low cost level. Not surprisingly, silicon based discrete microsensors were quickly commercially exploited and the markets for these devices continue to grow at a rapid rate.

More recently, the MEMS research and development community has demonstrated a number of microactuators including: microvalves for control of gas and liquid flows; optical switches and mirrors to redirect or modulate light beams; independently controlled micromirror arrays for displays, microresonators for a number of different applications, micropumps to develop positive fluid pressures, microflaps to modulate airstreams on airfoils, as well as many others. Surprisingly, even though these microactuators are extremely small, they frequently can cause effects at the macroscale level; that is, these tiny actuators can perform mechanical feats far larger than their size would imply. For example, researchers have placed small microactuators on the leading edge of airfoils of an aircraft and have been able to steer the aircraft using only these microminiaturized devices.

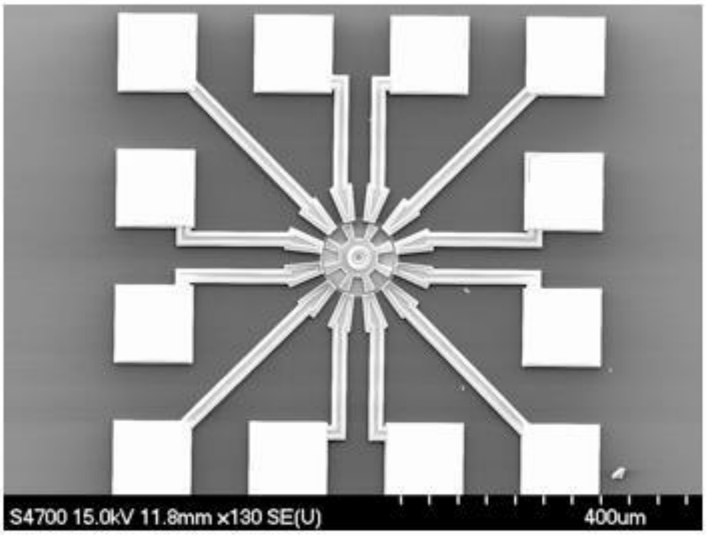

Fig:1. 2. A surface micromachined electro-statically-actuated micromotor fabricated by the MNX.

This device is an example of a MEMS-based microactuator.

The real potential of MEMS starts to become fulfilled when these miniaturized sensors, actuators, and structures can all be merged onto a common silicon substrate along with integrated circuits (i.e., microelectronics). While the electronics are fabricated using integrated circuit (IC) process sequences (e.g., CMOS, Bipolar, or BICMOS processes), the micromechanical components are fabricated using compatible "micromachining" processes that selectively etch away parts of the silicon wafer or add new structural layers to form the mechanical and electromechanical devices. It is even more interesting if MEMS can be merged not only with microelectronics, but with other technologies such as photonics, nanotechnology, etc. This is sometimes called “heterogeneous integration.” Clearly, these technologies are filled with numerous commercial market opportunities.

The present MEMS involves a single discrete microsensor, a single discrete microactuator, a single microsensor integrated with electronics, a multiplicity of essentially identical microsensors integrated with electronics, a single microactuator integrated with electronics, or a multiplicity of essentially identical microactuators integrated with electronics.

This vision of MEMS whereby microsensors, microactuators and microelectronics and other technologies, can be integrated onto a single microchip is expected to be one of the most important technological breakthroughs of the future. This will enable the development of smart products by augmenting the computational ability of microelectronics with the perception and control capabilities of microsensors and microactuators. Microelectronic integrated circuits can be thought of as the "brains" of a system and MEMS augments this decision-making capability with "eyes" and "arms", to allow microsystems to sense and control the environment. Sensors gather information from the environment through measuring mechanical, thermal, biological, chemical, optical, and magnetic phenomena. The electronics then process the information derived from the sensors and through some decision making capability direct the actuators to respond by moving, positioning, regulating, pumping, and filtering, thereby controlling the environment for some desired outcome or purpose. Furthermore, because MEMS devices are manufactured using batch fabrication techniques, similar to ICs, unprecedented levels of functionality, reliability, and sophistication can be placed on a small silicon chip at a relatively low cost. MEMS technology is extremely diverse and fertile, both in its expected application areas, as well as in how the devices are designed and manufactured.

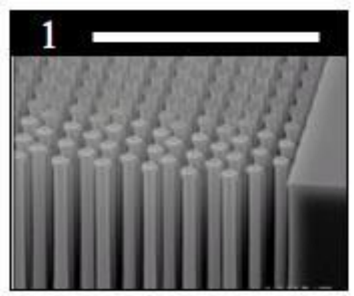

Fig:1. 3 An array of sub-micron posts made using top-down nanotechnology fabrication methods.

Although MEMS and Nanotechnology are sometimes cited as separate and distinct technologies, in reality the distinction between the two is not so clear-cut. In fact, these two technologies are highly dependent on one another. The well-known scanning tunneling-tip microscope (STM) which is used to detect individual atoms and molecules on the nanometer scale is a MEMS device. Similarly the atomic force microscope (AFM) which is used to manipulate the placement and position of individual atoms and molecules on the surface of a substrate is a MEMS device as well. In fact, a variety of MEMS technologies are required in order to interface with the nanoscale domain.

Likewise, many MEMS technologies are becoming dependent on nanotechnologies for successful new products. For example, the crash airbag accelerometers that are manufactured using MEMS technology can have their long-term reliability degraded due to dynamic in-use stiction effects between the proof mass and the substrate. A nanotechnology called Self-Assembled Monolayers (SAM) coatings are now routinely used to treat the surfaces of the moving MEMS elements so as to prevent stiction effects from occurring over the product’s life.

6.MEMS IN HEALTH CARE

Healthcare has emerged as one the biggest and fastest growing Industry around the World. The growing importance of Human life, increase in individual disposal income and awareness of preventative measures are driving the growth of this Industry. Increase in life expectancy and ageing of world population has made Healthcare as a very lucrative Industry.

MEMS has evolved as one of the most revolutionized Semiconductor components in personal Healthcare. The advent of MEMS is opening new ventures of application in Healthcare. This article will address some of the applications MEMS in medical electronics system design to serve the healthcare needs. Semiconductor are used in core medical electronic Instruments such as CT scan, X-ray machines, ECG, Ultrasound, Blood pressure and Glucose monitoring etc. Semiconductor plays function such as sensing, signal conditioning, data conversion & processing, controlling the machines & robots etc.

Bulky and centralized hospital equipments now have a new substitute – handheld personalized healthcare equipments. As firsthand healthcare is shifting from Hospitals to individual, the need of miniaturization, cost-effectiveness, robustness and battery operation has evolved. After creating a new wave of revolution in consumer and mobile phone Industry, MEMS is all set to give healthcare a new definition. Some typical applications of MEMS in Healthcare are pedometer, blood pressure monitoring, ECG, hearing aids etc. MEMS can also be used in complex procedures such as DNA Analysis.

Motions MEMS such as accelerometer have made it possible to accurately measure motion by consuming minimal power with a very compact form factor. As MEMS can detect both linear and angular motion in all 3-axis, a complete inertial state of body or body part can be detected. MEMS can be used in not only wearable device such as pedometer or mobile ECG machine but also penetrative gadgets such as blood pressure monitors or miniaturized robots.

6.1 APPLICATION OF MEMS

6.1.1.Pedometer

Pedometer is perhaps one of the simplest application yet very useful application of MEMS. MEMS can detect the jerk body is facing while a user is running or walking at each step. The jerk experienced by MEMS IC. This feature can be used to measure accurately number of steps taken. MEMS can be used to calculate Step count, Speed, Distance, Calories. Some parameters such as step length, height and weight may be needed for calibration. Accurately Pedometer can be developed keeping in mind the locations where user is wearing them (attached to belt, shirt/pant pocket etc). A 3-axis accelerometer can detect acceleration in all the three axis so a single MEMS can detect the change independent of the way pedometer is worn by the user. MEMS can also be used to detect the swing in centre of gravity of person. This data can be used by doctor to suggest the right posture or even wear right equipment to the patient.

6.1.2HearingAid

MEMS microphone has made it possible to make small size hearing aid with high sound quality, reliability and affordability. MEMS microphones meet price points set by the traditional electret condenser microphones (ECM), while boasting superior reliability and robustness. MP45DT microphone is less susceptible to mechanical vibration, temperature variations and electromagnetic interference. The sensing element, capable of detecting acoustic waves, is manufactured using a specialized silicon micromachining process to produce audio sensors. MEMS microphone based hearing aid can be designed in such a way that it becomes invisible to external world thus avoiding apparent social issues.

6.1.3 Early Diagnosis of Glaucoma

MEMS microphone and a transmitter antenna when mounted on a 24-hour silicon disposable lens can be used for early diagnosis of glaucoma. As the MEMS sensor is ultra miniaturized, it can be mounted at the peripheral of lens without impacting normal viewing. Also a small antenna will transmit relevant data to the receiving station. The Sensor is capable of measuring cornea deformations due to Intra-Ocular-Pressure (IOP) variations. The IOP Sensor is a wireless sensor that acts as a transducer, antenna and mechanical support for additional read-out electronics. This information can be monitored and analyzed by Hospital to take necessary action and diagnose glaucoma in its early stage.

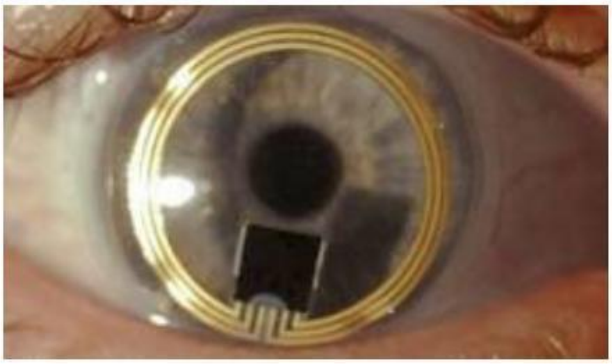

Fig1.4. Early diagnosis of Glaucoma

6.1.4 Blood Pressure

The human circulatory system generates pressure which can be measured by miniaturized and biocompatible BioMEMS. The generated pressure is complex and varies by a large value and change by the current situation of human body so it require very specific MEMS to do the task. The BioMEMS can be inserted into the body and moved to the specific places near the heart. By measuring pressure gradients across heart valves, doctors can access valve disease. It will be to diagnose and monitor heart failure and measuring cardiac output.

6.1.5 Body Gateway

Body gateway is a wearable device used for measuring physiological parameters such as ECG, heart rate, breathing rate etc. It can also detect person's movement and if there is a abnormal movement such as falling down on floor can be detected. The measured data or alarms can be sent via Bluetooth to internet gateway device which can send the data to Hospital control rooms. MEMS is the key enablers for this, it can detect person movement and change is blood pressure to measure the breathing rate. The small size and ultra low power consumption has made it possible. This application of MEMS can also lead to revolution of telemedicine where hospitals can monitor patients in real time scenario and take necessary action remotely. It can also reduce the cost of treatment drastically as patients no longer have to admit in Hospitals for monitoring reliable information.

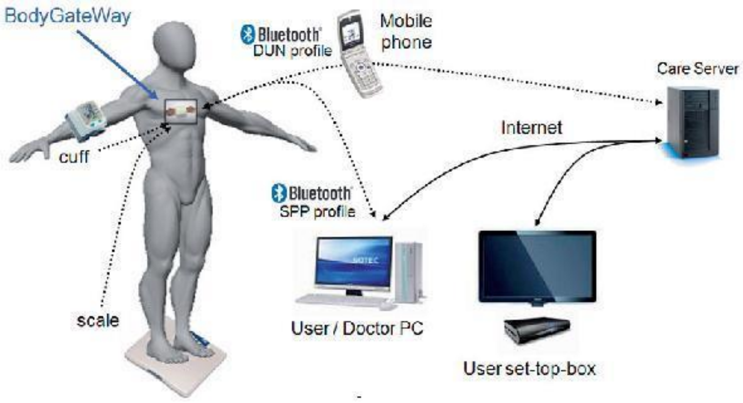

Fig1.5. Body Gateway

6.1.6 Lab on Chip

Lab-on-a-chip allows small amounts of bodily fluids to be tested in seconds. All chemical reactions occur inside thebiochip's buried channels or on its surface. And because the cartridge that carries the chip is self-contained and disposable, the system strongly reduces the cross-contamination risks of conventional multi-step protocols. The ST Lab-on-chip is designed to handle micro fluidics and some of the knowledge is based on expertise in MEMS inkjet printer chips. The Lab-on-chip can amplify or multiply DNA sample in approx 15 minutes thus requires very small amount of fluid, saves time and is economical.

7.INTEGRATED MEMS

The majority of microelectromechanical system (MEMS) devices must be combined with integrated circuits (ICs) for operation in larger electronic systems. A MEMS device typically interacts with a physical, chemical or optical quantity and has an electrical interface to the outside world. For MEMS sensors, the electrical output signal correlates with the physical, optical or chemical input quantity that is sensed. In the case of MEMS actuators, an electrical input signal is used to control one or more physical, optical or chemical quantities. To enable the MEMS transducer to perform useful functions, the electrical interface with the outside world is, in most cases, realized through integrated circuits (ICs) that provide the system with the necessary intelligence. ICs may provide signal conditioning functions such as analog-to-digital conversion, amplification, temperature compensation, storage or filtering as well as system testing and logic and communication functions

MEMS and ICs can be integrated using two basic methods:

(1)In the general approach referred to here as a multi-chip solution, MEMS and IC components are manufactured on separate substrates using dedicated MEMS and IC processes and are subsequently hybridized in the final system. Two-dimensionally or side-by-side integrated systems are often referred to as multi-chip modules. When chips are vertically stacked in a package in this way, such a system is also referred to as a system-in-package or a vertical multi-chip module2. Devices created through vertical stacking of several IC chips are also referred to as three-dimensional integrated circuits (3D ICs).

(2) In the general approach referred to here as a system-on-chip (SoC) solution, MEMS and IC components are manufactured on the same substrate, using consecutive or interlaced processing schemes.

8.MICROSYSTEMS

Microsystems are miniaturized (silicon or polymer) devices which perform non-electronic functions: typically sensing and actuation. Typical microsystems have mechanical parts, like microbridges in RF switches or bending cantilevers in atomic force microscopes (AFMs); electrical parts like piezoresistors in airbag sensors or capacitors in pressure sensors; or thermal, optical and fluidic structures like heaters and nozzles in inkjet printer or flow sensors. In biomicrosystems (BioMEMS) cells or microbeads are handled by fluidic streams, magnetic and electric fields, thermal gradients etc. In chemical microsystems operations like sample pretreatment, separation and detection are built on microchips. This field is also known as microfluidics or lab-on-a-chip. Today it is possible to build up microsystems without any tooling needed by computer-aided direct parallel batch processing technologies called RMPD Rapid Micro Product Development.

A microsystem is an engineering system that contains MEMS components that are designed to perform specific engineering functions. 3 components : micro sensors, actuators, and a processing unit.

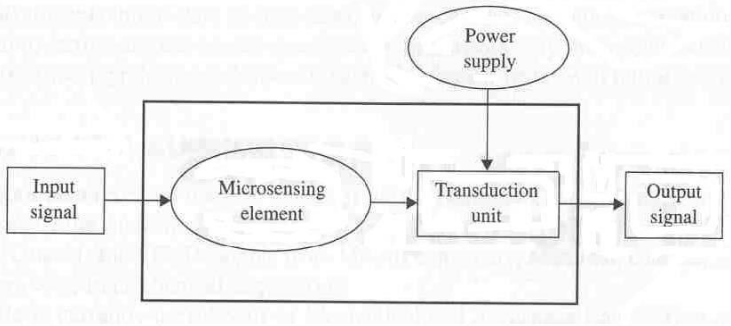

Fig1. 6 Components of a Microsystem

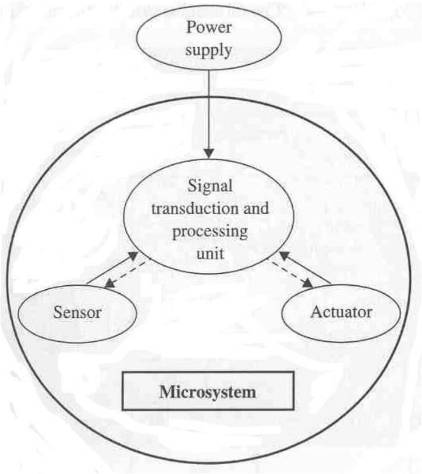

Fig1.7 Microsystems

An intelligent microsystem incorporates signal processing and closed-loop feedback control systems into a microsystem.

Examples – Micro gears, Micro mixer, Micro mirrors

TEXT / REFERENCE BOOKS

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DEPARTMENT OF BIOMEDICAL ENGINEERING

UNIT – II – Processing : Micro Machining Technology – SBM1606

UNIT 2

PROCESSING: MICRO MACHINING TECHNOLOGY

2.LITHOGRAPHY

Lithography in MEMS context is typically the transfer of a pattern into a photosensitive material by selective exposure to a radiation source such as light. A photosensitive material is a material that experiences a change in its physical properties when exposed to a radiation source. If a photosensitive material is selectively exposed to radiation (e.g. by masking some of the radiation) the pattern of the radiation on the material is transferred to the material exposed, as the properties of the exposed and unexposed regions differ.

This exposed region can then be removed or treated providing a mask for the underlying substrate. Photolithography is typically used with metal or other thin film deposition, wet and dry etching.

2.1.1Electron beam lithography

Electron beam lithography (often abbreviated as e-beam lithography) is the practice of scanning a beam of electrons in a patterned fashion across a surface covered with a film (called the resist) ("exposing" the resist) and of selectively removing either exposed or non-exposed regions of the resist ("developing"). The purpose, is to create very small structures in the resist that can subsequently be transferred to the substrate material, often by etching. It was developed for manufacturing integrated circuits, and is also used for creating nanotechnology architectures.

The primary advantage of electron beam lithography is that it is one of the ways to beat the diffraction limit of light and make features in the nanometer region. This form of maskless lithography has found wide usage in photomask- making used in photolithography, low -volume production of semiconductor components, and research & development.

The key limitation of electron beam lithography is throughput, i.e., the very long time it takes to expose an entire silicon wafer or glass substrate. A long exposure time leaves the user vulnerable to beam drift or instability which may occur during the exposure. Also, the turn-around time for reworking or re-design is lengthened unnecessarily if the pattern is not being changed the second time.

2.1.2**Ion beam lithography**

It is known that focused-ion-beam lithography has the capability of writing extremely fine lines (less than 50 nm line and space has been achieved) without proximity effect. However, because the writing field in ion-beam lithography is quite small, large area patterns must be created by stitching together the small fields.

2.1.3**Ion track technology**

Ion track technology is a deep cutting tool with a resolution limit around 8 nm applicable to radiation resistant minerals, glasses and polymers. It is capable to generate holes in thin films without any development process. Structural depth can be defined either by ion range or by material thickness. Aspect ratios up to several 10^4 can be reached. The technique can shape and texture materials at a defined inclination angle. Random pattern, single-ion track structures and aimed pattern consisting of individual single tracks can be generated.

2.1.4**X-ray lithography**

X-ray lithography, is a process used in electronic industry to selectively remove parts of a thin film. It uses X-rays to transfer a geometric pattern from a mask to a light-sensitive chemical photoresist, or simply "resist," on the substrate. A series of chemical treatments then engraves the produced pattern into the material underneath the photoresist.

2.1.5Diamond patterning

A simple way to carve or create patterns on the surface of nanodiamonds without damaging them could lead to a new photonic devices.

Diamond patterning is a method of forming diamond MEMS. It is achieved by the lithographic application of diamond films to a substrate such as silicon. The patterns can be formed by selective deposition through a silicon dioxide mask, or by deposition followed by micromachining or focused ion beam milling.

2.2ETCHING:

Etching processes

There are two basic categories of etching processes: wet etching and dry etching. In the former, the material is dissolved when immersed in a chemical solution. In the latter, the material is sputtered or dissolved using reactive ions or a vapor phase etchant.

2.2.1Wet etching

Wet chemical etching consists in selective removal of material by dipping a substrate into a solution that dissolves it. The chemical nature of this etching process provides a good selectivity, which means the etching rate of the target material is considerably higher than the mask material if selected carefully.

2.2.2Isotropic etching

Etching progresses at the same speed in all directions. Long and narrow holes in a mask will produce v-shaped grooves in the silicon. The surface of these grooves can be atomically smooth if the etch is carried out correctly, with dimensions and angles being extremely accurate.

2.2.3Anisotropic etching

Some single crystal materials, such as silicon, will have different etching rates depending on the crystallographic orientation of the substrate. This is known as anisotropic etching and one of the most common examples is the etching of silicon in KOH (potassium hydroxide), where Si <111>planes etch approximately 100 times slower than other planes (crystallographic orientations) .Therefore, etching a rectangular hole in a (100)-Si wafer results in a pyramid shaped etch pit with 54.7° walls, instead of a hole with curved sidewalls as with isotropic etching.

2.2.4HF etching

Hydrofluoric acid is commonly used as an aqueous etchant for silicon dioxide (SiO_2, also known as BOX for SOI), usually in 49% concentrated form, 5:1, 10:1 or 20:1 BOE (buffered oxide etchant) or BHF (Buffered HF). They were first used in medieval times for glass etching. It was used in IC fabrication for patterning the gate oxide until the process step was replaced by RIE.

Hydrofluoric acid is considered one of the more dangerous acids in the cleanroom. It penetrates the skin upon contact and it diffuses straight to the bone. Therefore, the damage is not felt until it is too late.

2.2.5Electrochemical etching

Electrochemical etching (ECE) for dopant-selective removal of silicon is a common method to automate and to selectively control etching. An active p-n diode junction is required, and either type of dopant can be the etch-resistant ("etch-stop") material. Boron is the most common etch-stop dopant. In combination with wet anisotropic etching as described above, ECE has been used successfully for controlling silicon diaphragm thickness in commercial piezoresistive silicon pressure sensors. Selectively doped regions can be created either by implantation, diffusion, or epitaxial deposition of silicon.

2.3 Dry etching

2.3.1Vapor etching

Xenon difluoride -Xenondifluoride (XeF) is a dry vapor phase isotropic etch for silicon originally applied for MEMS in 1995 at University of California, Los Angeles.Primarily used for releasing metal and dielectric structures by undercutting silicon, XeF has the advantage of a stiction-free release unlike wet etchants. Its etch selectivity to silicon is very high, allowing it to work with photoresist, SiO , silicon nitride, and various metals for masking. Its reaction to silicon is "plasmaless", is purely chemical and spontaneous and is often operated in pulsed mode. Models of the etching action are available, and university laboratories and various commercial tools offer solutions using this approach.

2.3.2Plasma etching

Modern VLSI processes avoid wet etching, and use plasma etching instead. Plasma etchers can operate in several modes by adjusting the parameters of the plasma. Ordinary plasma etching operates between 0.1 and 5 Torr. (This unit of pressure, commonly used in vacuum engineering, equals approximately 133.3 pascals.) The plasma produces energetic free radicals, neutrally charged, that react at the surface of the wafer. Since neutral particles attack the wafer from all angles, this process is isotropic.

Plasma etching can be isotropic, i.e., exhibiting a lateral undercut rate on a patterned surface approximately the same as its downward etch rate, or can be anisotropic, i.e., exhibiting a smaller lateral undercut rate than its downward etch rate. Such anisotropy is maximized in deep reactive ion etching. The use of the term anisotropy for plasma etching should not be conflated with the use of the same term when referring to orientation-dependent etching.

The source gas for the plasma usually contains small molecules rich in chlorine or fluorine. For instance, carbon tetrachloride (CCl4) etches silicon and aluminium, and trifluoromethaneetches silicon dioxide and silicon nitride. A plasma containing oxygen is used to oxidize ("ash") photoresist and facilitate its removal.

Ion milling, or sputter etching, uses lower pressures, often as low as 10−4 Torr (10 mPa). It bombards the wafer with energetic ions of noble gases, often Ar+, which knock atoms from the substrate by transferring momentum. Because the etching is performed by ions, which approach the wafer approximately from one direction, this process is highly anisotropic. On the other hand, it tends to display poor selectivity. Reactive-ion etching (RIE) operates under conditions intermediate between sputter and plasma etching (between 10–3 and 10−1 Torr). Deep reactive-ion etching (DRIE) modifies the RIE technique to produce deep, narrow features.

Sputtering

2.3.4 Reactive ion etching (RIE)

In reactive-ion etching (RIE), the substrate is placed inside a reactor, and several gases are introduced. Plasma is struck in the gas mixture using an RF power source, which breaks the gas molecules into ions. The ions accelerate towards, and react with, the surface of the material being etched, forming another gaseous material. This is known as the chemical part of reactive ion etching. There is also a physical part, which is similar to the sputtering deposition process. If the ions have high enough energy, they can knock atoms out of the material to be etched without a chemical reaction. It is a very complex task to develop dry etches processes that balance chemical and physical etching, since there are many parameters to adjust. By changing the balance it is possible to influence the anisotropy of the etching, since the chemical part is isotropic and the physical part highly anisotropic the combination can form sidewalls that have shapes from rounded to vertical.

Deep RIE (DRIE) is a special subclass of RIE that is growing in popularity. In this process, etch depths of hundreds of micrometres are achieved with almost vertical sidewalls. The primary technology is based on the so-called "Bosch process" named after the German company Robert Bosch, which filed the original patent, where two different gas compositions alternate in the reactor. Currently there are two variations of the DRIE. The first variation consists of three distinct steps (the original Bosch process) while the second variation only consists of two steps. In the first variation, the etch cycle is as follows:

(i) SF6 isotropic etch;

(ii) C4F8 passivation;

(iii) SF6 anisoptropic etch for floor cleaning. In the 2nd variation, steps (i) and (iii) are combined.

Both variations operate similarly. The C4F8 creates a polymer on the surface of the substrate, and the second gas composition (SF6 and O2) etches the substrate. The polymer is immediately sputtered away by the physical part of the etching, but only on the horizontal surfaces and not the sidewalls. Since the polymer only dissolves very slowly in the chemical part of the etching, it builds up on the sidewalls and protects them from etching. As a result, etching aspect ratios of 50 to 1 can be achieved. The process can easily be used to etch completely through a silicon substrate, and etch rates are 3–6 times higher than wet etching.

2.4 ION IMPLANTAION

An ion-implantation material-modification technique was applied to a micro-electro mechanical systems (MEMS) fabrication technique in order to enhance the functionality of MEMS. Ion implantation, which is well known as doping technology in semiconductor and surface modification technology, can alter the characteristics of a substrate by the addition of ions. However, when the object is a microscale device such as MEMS, such implantation involves metallurgy of the micro material, because size, depth, and area of the modified area are on the same order as the size of the microscale device. When the characteristics that can be controlled by ion implantation are combined with other properties, such mechanical, electrical, optical, and chemical, a wide range of characteristics can be easily controlled simply by changing the operating parameters, such as ion species, energy, dose, and substrate temperature. By effectively utilizing region selectivity, which is an advantage of ion implantation, the local physical properties of a micro device can be controlled. Consequently, in the design of MEMS devices, material properties can be controlled to enhance the functionality of the device. In this study, we used this ion implantation technique, which only involved injection of ions and etching that changed the chemical property of the substrate material, to fabricate a micro device, e.g., a microcantileverbeam, that has low elasticity and electric conductance.

2.5 WAFER BONDING

Wafer bonding is a packaging technology on wafer- level for the fabrication of microelectromechanical systems (MEMS), nanoelectromechanical systems (NEMS), microelectronics and optoelectronics, ensuring a mechanically stable and hermetically sealed encapsulation. The wafers' diameter range from 100 mm to 200 mm (4 inch to 8 inch) for MEMS/NEMS and up to 300 mm (12 inch) for the production of microelectronic devices

In microelectromechanical systems (MEMS) and nanoelectromechanical systems (NEMS), the package protects the sensitive internal structures from environmental influences such as temperature, moisture, high pressure and oxidizing species. The long-term stability and reliability of the functional elements depend on the encapsulation process, as does the overall device cost. The package has to fulfill the following requirements:

- protection against environmental influences
- heat dissipation
- integration of elements with different technologies
- compatibility with the surrounding periphery
- maintenance of energy and information flow

2.5.1TECHNIQUES:

The commonly used and developed bonding methods are as follows:

 Direct bonding Plasma activated bonding Anodic bonding Eutectic bonding Glass frit bonding Adhesive bonding Thermo compression bonding Reactive bonding Transient liquid phase diffusion bonding

2.5.2REQUIREMENTS:

The bonding of wafers requires specific environmental conditions which can generally be defined as follows:

1) substrate surface
    - flatness
    - smoothness
    - cleanliness
2) bonding environment
    - bond temperature
    - ambient pressure
- applied force
3) materials
    - substrate materials
- intermediate layer materials

The actual bond is an interaction of all those conditions and requirements. Hence, the applied technology needs to be chosen in respect to the present substrate and defined specification like max. bearable temperature, mechanical pressure or desired gaseous atmosphere.

2.5.3EVALUATION:

The bonded wafers are characterized in order to evaluate a technology's yield, bonding strength and level of hermeticity either for fabricated devices or for the purpose of process development. Therefore, several different approaches for the bond characterization have emerged. On the one hand non-destructive optical methods to find cracks or interfacial voids are used beside destructive techniques for the bond strength evaluation, like tensile or shear testing. On the other hand the unique properties of carefully chosen gases or the pressure depending vibration behavior of micro resonators are exploited for hermeticity testing.

2.6INTEGRATED PROCESSING

With the integrated process option the wafers are removed from the standard line and after the addition of micromachining steps return to the standard line. The position of the additional process steps is extremely important. In some cases the additional depositions are added after the main thermal processing but before the aluminium. Depending on the sensitivity of the electronics devices to thermal budget, a maximum thermal budget for the micromachining is determined.

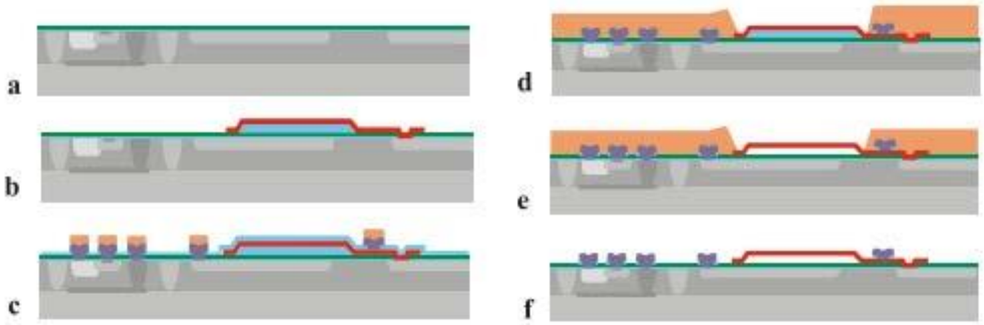

Fig2.1 integrated processing

2.7BULK MICROMACHINING

Bulk micromachining is the oldest paradigm of silicon based MEMS. The whole thickness of a silicon wafer is used for building the micro-mechanical structures.Silicon is machined using various etching processes. Anodic bonding of glass plates or additional silicon wafers is used for adding features in the third dimension and for hermetic encapsulation. Bulk micromachining has been essential in enabling high performance pressure sensors and accelerometers.

The term bulk micromachining comes from the fact that this type of micromachining is used to realize micromechanical structures within the bulk of a single-crystal silicon wafer by selectively removing (‘etching’) wafer material. The microstructures fabricated using bulk micromachining may cover the thickness range from submicron to full wafer thickness (200–500 μm), and the lateral size range from submicron to the lateral dimensions of a full wafer. Bulk micromachining technique allows to selectively remove significant amounts of silicon from a substrate to form membranes on one side of a wafer, a variety of trenches, holes, or other

Bulk micromachining technique can be divided into wet etching and dry etching of silicon according to the phase of etchants. Liquid etchants, almost exclusively replying on aqueous chemicals, are referred to as wet etching. Vapor and plasma etchants are referred to as dry etching. For etching such thick silicon substrate, anisotropic wet etchants such as solutions of potassium hydroxide (KOH), ethylene diamine and pyrocatechol (EDP), tetramethylammonium hydroxide (TMAH), and hydrazine-water are used. These etchants have different etch rates in different crystal orientation of the silicon . Wet etching in mostcase is done from the back side of the wafer while the plasma etching is being applied to front side.Etch process can be made selective by the use of dopants (heavily doped regions etch slowly) or may even be halted electrochemically (e.g., etching stops upon encountering a region of different polarity in a biased p–n junction). A region at which wet etching tends to slow down or diminish is called an etch-stop. Wet etching occurs by dipping substrate into an etching bath or spraying it with etchants that may be acid or alkaline. Wet etching can either be isotropic etching or anisotropic etching depending on the structure of the materials or the etchants used. If the material is amorphous or polycrystalline, wet etching is always isotropic etching. During isotropic etching (etchants used are acid solution), resist is always undercut, implying that the deep etching is not practical for MEMS.

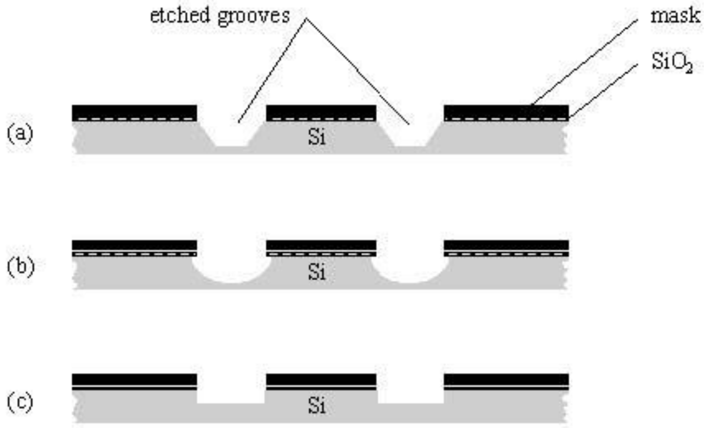

Fig.2.2 Etched grooves using (a) anisotropic etchants, (b) isotropic etchants, (c) Reactive Ion Etching (RIE)

2.7.1 Isotropic Etching

Isotropic etching uses very strong acids for attacking the Si, resulting in rounded patterns grooved into the substrate material because of the equal etch rate in all directions. Rates of up to 50 microns per minute can be achieved (about 100 times faster than anisotropic etching). The rate depends on the concentration of the acid used and the processing temperature as well as on the grade of agitation applied to the sample while etching. Because the etch rate depends on agitation, difficulties occur when controlling the exact extend of the etched structure.

The most common etchants are mixtures of hydrofluoric acids (HF) and nitric acid (HNO3) with either water or rather acetic acid being used as diluent. A solution of this kind is often referred to as *HNA*system. Since the etch rate of SiO2 is high (300 to 800 Å/min), either thick layers of oxide or alternative masking layers like silicon nitride (Si3N4) are needed when etching deeper patterns into the substrate. Otherwise the accuracy of the mask could be affected in a negative way, resulting in poor resolution of the etched profile.

Since the etchant attacks the Si equally in every direction, it takes away the material horizontally as well, thus undercutting the masking layer on top. The longer the sample remains in the etch bath, the stronger this effect, since the etch rate is all the same in every direction, making masking a difficult task when etching isotropically.

A common means for cleaning a plain wafer before doing any kind of process is immersing it in a piranha etch (H2O2:H2SO4, concentration varying between 1:1 and 4:1) to remove impurities on top of the sample. The acid does not affect Si itself, developing a thin film of oxide instead when brought in contact.

The *BHF* solution mentioned above for patterning the oxide mask also belongs to the category of isotropic etchants.

2.7.2Anisotropic Etching

Anisotropic etching techniques were developed later than their isotropic relatives. The most important attribute of anisotropic etch is their ability to control the lateral extensions of the etched profile. In contrast to the isotropic etchants, anisotropic etchants attack the substrate material depending on its crystalline structure, thus revealing very precise structures when applied correctly. They were developed in the 1960s by Bell Laboratories.

Common chemicals used in anisotropic etching processes are:

Potassium hydroxide (KOH)/H2O solutions, sometimes with ispropyl alcohol (IPA) additive at 65-85°C

Ethylene diaminepyrocatechol (EDP), diluted with water at 115ºC

Tetramethylammmonium hydroxide (TMAH) and water at 90ºC

Hydrazine N2H4/H2O/IPA at 115ºC

The etchants differ with respect to their specifications regarding handling, toxicity, and appropriate masking material. Again, the etch rate depends on the concentration of the solution used, higher concentrations generally slow down the etching process, since the water is needed in the etching process as an oxidizing agent for silicon.

KOH is the most popular etchant. It can be used in near saturated solutions with processing temperatures of up to 80ºC; higher temperatures affect the etch uniformity and produce unwanted fumes. A disadvantage of this chemical is the fact that its etch selectivity between Si an SiO2 is too low, resulting in mask layers made of oxide being attacked quickly. Therefore, for this process, alternative masking materials are needed, adding additional process steps to the fabrication process. Like applying to the isotropic HNA etching system, Si3N4 is an appropriate material for masking, staying untouched by the KOH etchant. While the etching is in progress, the development of bubbles that consist of hydrogen set free by the reaction occurs. When too great in numbers, these bubbles can prevent parts of the solution from keeping in touch with the substrate's surface, leading to an increase in surface roughness. This especially happens at long etch times when using solutions of high concentration. Agitation of the immersed sample reduces this problem. KOH can cause blindness in contact with the eyes, but is less hazardous than most of the other etching solutions.

TMAH is the newest of the etching solutions mentioned above. Being non-toxic, its handling is easy compared to the other etchants. The appropriate concentration is chosen by weighing surface smoothness against etch rate, since the first is better with more saturated solutions, whereas the latter rises with the amount of water present in the solution. A value of approximately 22 wt% is usually a reasonable compromise between these two factors. The disadvantage of TMAH is its lower etch rate of Si, compared to the other chemicals.

Hydrazine was the first anisotropic etchant. It is explosive at concentrations of 50 % and above in solution with water and very toxic (suspected to cause cancer). For this reason it is hardly in use anymore, having been replaced by EDP in most cases which is less hazardous. The surface quality of the produced structures is very good, depending on the water concentration and the temperature of the solution. Silicon oxide nearly is not attacked and therefore often used as masking material, as well as many metallic films.

The organic etchant EDP was developed to replace the hard to handle hydrazine, providing a more stable and less toxic means for anisotropic etching processes. SiO2 can be used as masking material, since with EDP the etch selectivity between Si and its oxide is very good. Selectivity is also good between Si and various other materials, e. g., gold, chromium, silver, copper or silicon nitride, making this etchant pretty flexible in this respect. But the solution is toxic and has to be handled with great care. It ages fast, especially in the presence of oxide, resulting in an optically denser liquid with considerably lower etch activity.

In general, etch rates of anisotropic etchants are considerably lower than those of isotropic processes, mostly being slower than 1 µm/s. Etching deep structures of some 100 microns into the bulk of a substrate material therefore is far more time consuming when using anisotropic etchants, demanding processing times of several hours. This requires a careful choice of the masking material to prevent the etched structure to get too imprecise due to the mask layer being attacked to hard by the etchant. In some cases, surface roughness is too high, making a short isotropic etch advisable after the anisotropic process for smoothing purposes.

For both isotropic and anisotropic etching proper protection of the backside of the wafer is required. This can be done mechanically by keeping it in a special holder that prevents the backside to get exposed to the liquid. Or, it is possible to coat it with a chemical protection layer,

e. g., waxes.

2.8.SURFACE MICRO MACHINING

In contrast to the bulk micromachining described above, where three-dimensional structures are etched into the substrate wafer, surface micromachining consists of building them by layering thin films of new material onto the surface of the substrate. Usually, sacrificial spacer layers are used to create freestanding structures like air-bridges; after depositing such a sacrificial layer and patterning it using microlithographic steps described above, the material for the final structure is deposited. Afterwards, the spacer layer is removed by an appropriate etchant, freeing the desired structure.

Surface micromachining was invented in the late 1960s, when a cantilever beam was produced by underetching the applied material on top of a sacrificial layer. The techniques used in this area emerged in the early 1980s, using polysilicon as structural material. Many different structures created using surface micromachining have been demonstrated, e. g., springs, gears, sliders and sealed cavities. However, the first commercial application based on this process was announced 1991 by Analog Devices (an accelerometer for the automobile industries).

Surface micromachining uses layers deposited on the surface of a substrate as the structural materials, rather than using the substrate itself. Surface micromachining was created in the late 1980s to render micromachining of silicon more compatible with planar integrated circuit technology, with the goal of combining MEMS and integrated circuits on the same silicon wafer. The original surface micromachining concept was based on thin polycrystalline silicon layers patterned as movable mechanical structures and released by sacrificial etching of the underlying oxide layer. Interdigital comb electrodes were used to produce in-plane forces and to detect in-plane movement capacitively. This MEMS paradigm has enabled the manufacturing of low cost accelerometers for e.g. automotive air-bag systems and other applications where low performance and/or high g-ranges are sufficient. Analog Devices has pioneered the industrialization of surface micromachining and has realized the co-integration of MEMS and integrated circuits.

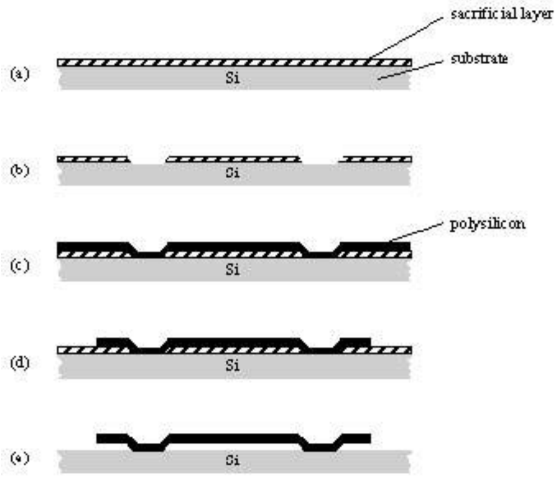

Fig2.3 Basic surface micromachining process. (a) Spacer layer deposition. (b) Pattering of the spacer layer. (c) Deposition of the microstructure layer. (d) Patterning of desired structure.

2.8.1Stripping of the spacer layer resolves final structure.

The steps for producing the air-bridge are clearly visible. Different materials can be used for the spacer layer, with photoresist being the simplest choice, reducing the steps necessary for patterning. Photoresist can be exposed with an appropriate mask and simply developed, revealing the structure needed for the following deposition of the microstructure layer. If a metallic material is used for this purpose, often a seed layer is deposited in order to enable the final structure to be applied via electrodeposition. This seed layer can be evaporated to a thickness of ~100 Å; afterwards, the sample is electroplated for an appropriate time in order to achieve the desired thickness of the final structure.

A variation of the standard surface micromachining process is called lift-off. Its aim is to apply a (metallic in most cases) layer to the substrate only in specific areas. Therefore, a sacrificial layer (usually photoresist) is applied and patterned, opening the regions that are to be covered with the metal film. After deposition of the metal, it contacts the substrate only in those regions. By removing the photoresist with a solvent that does not attack the metal layer, the material on top of the sacrificial layer is "lifted off", leaving the metal only at the desired areas

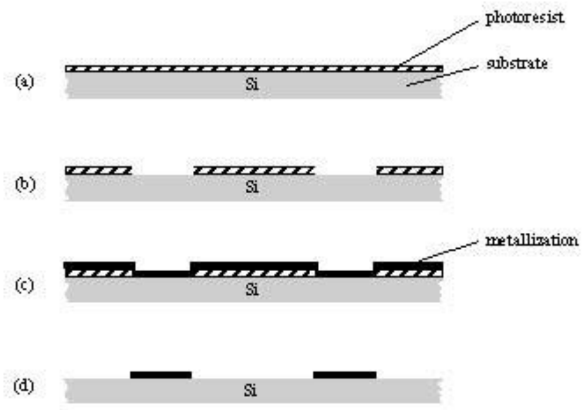

Fig. 2.4.Principle of the lift-off process

Important for the success of the lift-off procedure is the use of relatively thick photoresist in order to provide a very thin metallic layer on the sidewalls of the opening. This allows the lift-off to be completed without breaking the metallic film too easily. This is also the main difference between lift-off and normal surface micromachining, where thicker sidewalls are required in order to provide stability of the free structure.

The advantage of the lift-off procedure is the ability to work with metallic layers such as platinum or gold that are difficult to pattern by etching directly.

2.9COATING TECHNOLOGY

Stiction is a major problem in MEMS devices. Stiction (i.e.,unintentional adhesion) occurs when surface adhesion forces (viz., capillary, van derWaals and electrostatic) are higher than the mechanical restoring force of the miniaturized surfaces of the structural components. As a result of stiction, surfaces can permanently adhere to each other causing device failure-a phenomenon known as in-use stiction.

The application of low-energy surface coatings would be required to eliminate or reduce capillary, chemical bonding and electrostatic forces between the contacting microstructure surfaces of the MEMS device.

Coatings should have the following characteristics.-

 The coating should have excellent adhesion on the surfaces of the micro-components It should be hydrophobic in nature and thin enough not to bridge structural features of the MEMS device. The coating also has to permeate through microscopically small openings and diffuse onto under surfaces. The coating film should have stability in MEMS operating environments (viz. air and vacuum) It should retain its lubricating properties for longer periods. This is specially critical in MEMS devices for biomedical applications.

2.9.1Techniques:

2.9.2Spin coating

Spin coating of photoresist is the standard coatingmethod for flat wafers in MEMS technology. First, photoresist is flooded onto thewafer in order to cover the whole surface. A pause afterthe dispense step allows additional time for the solutionto flow into the deep features. A slow acceleration andspin speed is applied in the first step. This allows timefor the solution to flow and spread prior to drying. Asecond step with a fast spin speed promotes the drying ofthe film and reduces the further flowing of photoresistthat can result in non-uniformal coating.

2.9.3Spray Coating

The direct spray system includes an ultrasonic spray nozzle, which generates a distribution of droplets of micrometer size. It can reduce the effect of fluid dynamics of photoresist on the wafer as the resist droplets are supposed to stay where they are being deposited. The central part of the aerosol is forwarded to the dispense nozzle which is constructed to reduce the carrier gas pressure and to redirect the resist spray perpendicular to the substrate surface. During spray coating, the wafer is rotated slowly while the swivel arm of the spray coating unit is moved across the wafer. The low spinner speed (30-60rpm) is to minimize the centrifugal force. The rotating also allows resist coverage in all the angle of the cavities. Photoresist AZ4562 diluted with a solvent is used for this spray system as it results in good coverage and uniform layer

2.9.4Electrodeposition

It requires a special plating equipment and cataphoretic resist emulsion. To deposit a photoresist layer, the wafer surface must be coated with an electrically conductive material. The wafer to be coated faces an inert, planar stainless steel anode at a distance of 50 mm.

2.10CVD-LIGA PROCESS

The LIGA Fabrication process provides the possibility to produce micromechanical structures with very high aspect ratios compared to other microelectromechanical technologies (up to 300:1). The height of the manufactured pieces can be 100 microns to a couple of millimeters. By using molding, different materials (metal, ceramics as well as plastic) can be used to produce the final structure.

LIGA is a German abbreviation and stands for Lithographie, Galvanoformung and Abformung (lithography, electrodeposition and molding). The process was developed in the 1980s by the Kernforschungszentrum Karlsruhe, Germany (KfK) to provide a technique for producing large numbers of micron sized nozzles.

The principle of the LIGA process consists of depositing a relatively thick layer of a polymer sensitive to X-rays on top of a conductive substrate or one covered with a conductive seed layer. This can be done by applying multiple coats of photoresist during spinning the substrate wafer for thicknesses of up to a few hundred microns. For thicker polymer layers (millimeters) it is common to buy prefabricated plates of PMMA (polymethylmethacrylate, a polymer often used as photoresist), attach them to the substrate plate and mill them back to the desired thickness.

After exposure through an appropriate X-ray-mask, a developer removes either the exposed (positive photoresist) or the unexposed (negative) areas of polymer, and metal layers are grown by electroplating in the spaces now free from cover. Often the metal is grown higher than needed and then milled back to the desired thickness together with the photoresist. Having removed the unwanted areas of the polymer, the resulting metallic structure can be used. Free mechanical structures can be manufactured by using a sacrificial layer between the wafer substrate and the grown metal film and dissolving this layer, thus yielding the structure in the end of the process; this technique is called sacrificial LIGA (SLIGA).

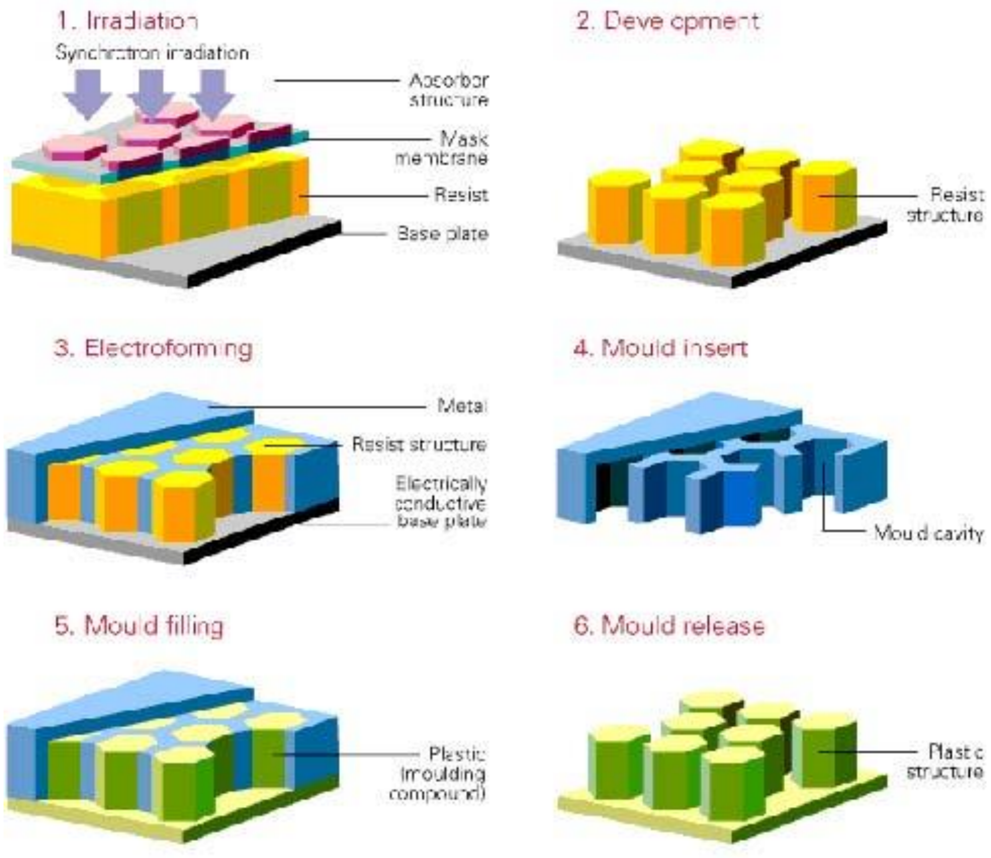

Fig2.5. LIGA process

For the purpose of mass production, the metal can serve as a mould or embossing tool for pieces made of various materials such as metals, polymers, ceramics or glass.

The major advantages of the LIGA process are the high aspect ratios made possible and therefore the larger heights of the pieces, very sharp vertical sidewalls as well as the possibility to produce three-dimensional structures by using a sacrificial layer as described above.

The main disadvantage of LIGA is the need of high-energy X-rays that can only be achieved with a synchrotron. This and the expensive X-ray masks needed for exposure make the cost for the process high. On the other hand, the mass production of microstructures by using the produced structures as mold for other materials becomes very inexpensive per produced device, since the expensive exposure step only needs to be done once in the beginning of the fabrication process.

To reduce the cost of LIGA, especially the investment costs for the synchrotron, the usage of traditional lithography light sources in the UV range is being investigated in combination with other photoresist materials (rather polyamides or standard photoresists than the polymers used in X-ray lithography). Using these processes, structures of up to 80 microns in height can be produced with this technique.

Alternatively companies providing the necessary tools for LIGA to multiple users can reduce the production cost, too. MCNC in Research Triangle Park, NC offers LIGAMUMPs™, a "Multi-user MEMS Process that involves the fabrication of high aspect ratio MEMS in a low-cost environment"

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DEPARTMENT OF BIOMEDICAL ENGINEERING

UNIT – III – MICROSYSTEMS AND MICROFLUIDS– SBM1302

UNIT-3- MICROSYSTEMS AND MICROFLUIDS

3.1 Micro systems:

Microsystems are miniaturized (silicon or polymer) devices which perform non-electronic functions typically sensing and actuation

3.1.1Microfluidics:

Microfluidics is a multidisciplinary field intersecting engineering, physics, chemistry, biochemistry, nanotechnology, and biotechnology, with practical applications to the design of systems in which low volumes of fluids are processed to achieve multiplexing, automation, and high-throughput screening.

3.2.Microsensors

Sensors used in MEMS are termed microsensors. They have physical dimensions in the submicrometer to millimeter range. They have lower manufacturing cost (mass-production, less materials),wider exploitation of IC technology (integration),wider applicability to sensor arrays, less weight.

Sensors in mems are classified as

3.2.1Acoustic wave sensor

These generally measure chemical composition in gas.

Generate acoustic wave by converting mechanical energy into electrical energy.

3.2.2Biomedical sensors

It has bio-sensors, bio-instruments, surgery tools and system for analysing quick, accurate and low cost testing of biological substance.

They are used to measure biological substance as well as for diagnostic purpose.

Eg: glucose + O_2gluconaldehyde +H_2O_2.

3.2.3Chemical sensors

Used to sense particular chemical compound Very simple

Eg: metals are vulnerable to oxidation when exposed to air for long, oxide on the metal change in properties such as electrical resistance, based on this principle the microsensors are designed and developed.

Chemi-resistors

Polymers used in this sensors can cause change in electrical conducting of metal

Eg:NH_3

3.2.4Optical sensors

Principle of interaction between photons in light and electron in solid that receive the light have been well developed to sense the intensity of light.

Solid state material that provide strong photon electron interaction are used as sensing material.

Selection of this material are based on the quantum efficiency.

3.2.5Pressure sensors:

They are generally used in automotive and aerospace industry.

Human body is a complex system of pumps, valves,vessels and interconnections.health monitoring of a patient requires knowledge of blood pressure,bladder pressure and cerebral spinal fluid pressure.

Pressure sensors are inserted in the human body to monitor the above, these sensors should be small and ideally disposable.

Sensors are inserted to catheter and then to the arteries.

3.2.6Thermal sensors

Thermocouple are most common transducer used to sense heat.

The principle is when electromotive force produced at the open end of 2 dissimilar metallic wires,the junction of the wire is heated. Temperature produced at junction due to heating can be correlated to magnitude of produced emf or voltage.

3.3Actuators

An actuator is a type of motor that is responsible for moving or controlling a mechanism or system.

It is operated by a source of energy, typically electric current, hydraulic fluid pressure, or pneumatic pressure, and converts that energy into motion.

3.1Types:

There are four main types of actuators: Hydraulic, Pneumatic, Electric and Mechanical.

3.1.1Hydraulic actuator:

Hydraulic actuators consist of a cylinder or fluid motor that utilizes hydraulic power to facilitate mechanical process. The mechanical motion gives an output in terms of linear, rotary or oscillatory motion. Since liquids are nearly incompressible, they take longer to gain speed and power and also slow back down, but they can exert great force. The hydraulic actuator also allows for very precise control of the movement produced. In linear hydraulic actuators, a typical set-up is made up of a hollow cylinder that contains a liquid, usually oil, and a piston that is inserted in it. When pressure is applied onto the piston, objects can be moved by the force produced. Hydraulic actuators can be operated manually, such as a hydraulic car jack, or they can be operated through a hydraulic pump, which can be seen in construction equipment such as cranes or excavators.

3.1.2Pneumatic actuator:

Pneumatic actuators work on the same concept as hydraulic actuators except compressed gas is used instead of liquid. Energy, in the form of compressed gas, is converted into linear or rotary motion, depending on the type of actuator. Pneumatic energy is more desirable for main engine controls because it can quickly respond in starting and stopping as the power source does not need to be stored in reserve for operation. Also, pneumatic actuators are preferred in places where cleanliness is important, since the fluid in hydraulic actuators might leak and contaminate the surroundings. However, pneumatic actuators are still likely to leak, making them less efficient compared to mechanical actuators. Another downside is that they take up a lot of space, create a lot of noise and are difficult to transport once installed in a place.

3.1.3Electric actuator:

Electric actuators are devices powered by motors that convert electrical energy to mechanical torque. The electrical energy is used to create motion in equipment that require multi-turn valves like gate or globe valves. Since no oil is involved, electrical actuators are considered to be one of the cleanest and readily available forms of actuators. Electric actuators are typically installed in engines, where they open and close different valves. There are many designs of electric actuators and this depends on their function in the engine that they are installed in.

3.1.4Mechanical actuator:

Mechanical actuators function through converting rotary motion to linear motion.When a rotary motion. Devices such as gears, rails, pulley, chain and others are used to help convert the motion. Some of the simple mechanisms used to convert motion are screws, where the rotation of the actuator's nut causes the screw shaft to move in a straight line, the wheel and axle, where the rotating motion of a wheel causes a belt or something similar to move in a linear motion.

3.2Electrostatic Forces

Electrostatic force is the phenomenon that results from slow-moving or stationary electrical charges. electrostatic force is the physical reaction that holds together the electromagnetic field created by subatomic particles, such as electrons and protons.Electrostatic force between electrons and protons is one of the strongest forces in the universe, even more powerful than gravity. A hydrogen atom, which contains only one electron and one proton, has the fundamental force of gravity keeping it together.As two surfaces come in contact with each other, charge exchange occurs, resulting in the development of electrostatic forces.

3.3Intelligent/ Smart Materials

A smart material is one which reacts to its environment all by itself. The change is inherent to the material and not a result of some electronics. The reaction may exhibit itself as a change in volume, a change in colour or a change in viscosity and this may occur in response to a change in temperature, stress, electrical current, or magnetic field.

These smart materials include shape memory alloys, piezoelectric materials, magneto-rheological and electro-rheological materials, magnetostrictive materials and chromic materials which change their colour in reaction to various stimuli.

A smart structure incorporates some form of actuator and sensor (which may be made from smart materials) with control hardware and software to form a system which reacts to its environment. Such a structure might be an aircraft wing which continuously alters its profile during flight to give the optimum shape for the operating conditions at the time.

The current generation of smart structures featuring piezoelectric materials is generally synthesized with polymeric fibrous composite laminates which readily accommodate embedded piezoelectric actuators and sensors. Any external force applied on the structure will set vibrations and cause deformations in the structure. These deformations will cause stresses and strains in the structure. If the structure is embedded with smart crystals, the effects of the vibration can be controlled using a feedback mechanism. Since piezoelectrics undergo surface elongation when an electric field is applied and produce charge when surface strain is applied, they can be used as both actuators and sensors. Some commonly used actuation materials are lead zirconatetitanate (PZT) and polyvinylidenefluoride (PVDF). Some ceramic electrostrictive materials are also used as actuation materials among them are lead magnesium niobate(PMN),Terfenol, a rare earth magnetic like material and Nitinol (nickel titanium alloy). They are available in the form of wires or sheets. These substances have the ability to change the shape, natural frequency,damping or other mechanical characteristics in response to change in environment.

3.3.1Shape Memory Alloys

Shape memory alloys (SMAs) are one of the most well known types of smart material. The SME describes the process of a material changing shape or remembering a particular shape at a specific temperature (i.e. its transformation or memory temperature).

Shape memory alloys have found a large number of uses in aerospace, medicine and the leisure industry.

Medical applications- Nitinol is biocompatible, that is, it can be used in the body without an adverse reaction, so it has found a number of medical uses. These include stents in which rings of SMA wire hold open a polymer tube to open up a blocked vein, blood filters, and bone plates which contract upon transformation to pull the two ends of the broken bone in to closer contact and encourage more rapid healing. SMAs also find use in dentistry for orthodontic braces which straighten teeth.

SMAs can be used as actuators. They can be used in cut out switches for kettles and other devices, security door locks, fire protection devices such as smoke alarms and cooking safety indicators.

3.3.2 Piezoelectric Materials

The piezoelectric effect and electrostriction are opposite phenomena and both relate a shape change with voltage.

An electrical field is generated if a mechanical force is applied to the material to change its shape. This is the piezoelectric effect. When a electric field is applied to the piezoelectric material it changes its shape very rapidly and very precisely in accordance with the magnitude of the field.

The piezoelectric effect was first observed in quartz and various other crystals such as tourmaline. Barium titanate and cadmium sulphate have also been shown to demonstrate the effect but by far the most commonly used piezoelectric ceramic today is lead zirconium titanate (PZT).

The main use of piezoelectric ceramics is in actuators, in the microbiology field in microscopic cell handling systems, in fibre optics and acoustics, in ink-jet printers where fine movement control is necessary and for vibration damping. The most well known application is in the sensors which deploy car airbags. The material changes in shape with the impact thus generating a field which deploys the airbag. Ionic polymers work in a similar way to piezoelectric ceramics, However they need to be wet to function. An electrical current is passed through the polymer when it is wet to produce a change in its crystal structure and thus its shape. Muscle fibres are essentially polymeric and operate in a similar way, so research in this field has focussed on potential uses in medicine.

3.3.3Magnetostrictive Materials

Magnetostrictive materials are similar to piezoelectric and electrostrictive materials except the change in shape are related to a magnetic field rather than an electrical field.

Magnetostrictive materials convert magnetic to mechanical energy or vice versa.

The most common magnetostrictive material today is called TERFENOL-D (terbium (TER), iron (FE), Naval Ordanance Laboratory (NOL) and dysprosium (D)). This alloy of terbium, iron and dysprosium shows a large magnetostrictive effect and is used in transducers and actuators. Magnetic materials contain domains which can be likened to tiny magnets within the material. When an external magnetic field is applied the domains rotate to align with this field and this result in a shape change. Conversely if the material is squashed or stretched by means of an external force the domains are forced to move and this causes a change in the magnetisation. Magnetostrictive materials can be used as both actuators (where a magnetic field is applied to cause a shape change) and sensors (which convert a movement into a magnetic field).Ultrasonic magnetostrictive transducers have been used in ultrasonic cleaners and surgical tools. Other applications include hearing aids, razorblade sharpeners, linear motors, damping systems, positioning equipment, and sonar.

3.3.4Magneto- And Electro Rheological Materials

Electro-rheological (ER) materials change their properties with the application of an electrical field and consist of insulating oil such as mineral oil containing a dispersion of solid particles. Magnetorheological materials (MR) are again based on a mineral or silicone oil carrier but this time the solid dispersed within the fluid is a magnetically soft material (such as iron) and the properties of the fluid are altered by applying a magnetic field. In both cases the dispersed particles are of the order of microns in size. In both cases the smart fluid changes from a fluid to a solid with the application of the relevant field. The small particles in the fluid align and are attracted to each other resulting in a dramatic change in viscosity.

The effect takes milliseconds to occur and is completely reversible by the removal of the field. The first industries to identify uses were the automotive and aerospace industries where the fluids are used in vibration damping and variable torque transmission. MR dampers are used to control the suspension in cars to allow the feel of the ride to be varied. Dampers are also used in prosthetic limbs to allow the patient to adapt to various movements for example the change from running to walking.

3.4LAB ON CHIP

A s (LOC) is a device that integrates one or several laboratory functions on a single chip of only millimeters to a few square centimeters to achieve automation and high-throughput screening. LOCs deals with the handling of extremely small fluid volumes down to less than picoliters. Lab-on-a-chip devices are a subset of Micro-electro-mechanical systems (MEMS) devices and often indicated by "Micro Total Analysis Systems" (µTAS) as well. LOC is closely related to, and overlaps with, microfluidics which describes primarily the physics, the manipulation and study of minute amounts of fluids. However, strictly regarded "Lab-on-a- Chip" indicates generally the scaling of single or multiple lab processes down to chip-format, whereas "µTAS" is dedicated to the integration of the total sequence of lab processes to perform chemical analysis.

The first real lab-on-a-chip was created in 1979 at Stanford University for gas chromatography. However, major lab-on-a-chip research only began in the late 80s with the development of microfluidics and the adaptation of microfabrication processes for the production of polymer chips. The ability to easily fabricate polymer microchips enabled many research laboratories to start their own investigations into lab-on-a-chip technologies. Today, it is even possible to fabricate fully customized lab-on-a-chip devices in any lab without the need of a clean room

3.4Applications

3.4.1Lab-On-A-Chip And Cell Biology

Lab-on-a-chip demonstrates the ability to control cells at the single-cell level while dealing with a large amount of cells in seconds. At the microscale level flow switch can be very fast and goes down to just tens of milliseconds. Using fast optical detectors (such as the Opto Reader, for example) one can detect and isolate a given cell (such as cancerous cell made fluorescent using antibodies) with high throughput. There are several other applications for lab-on-a-chip in cell biology, including micro patch clamp, control of stem cell differentiation, high-speed flow cytometry and cell sorting.

3.4.2Lab-On-A-Chip and Chemistry

The ability to perform fast heating and cooling at the microscale enables higher efficiency in some chemical reactions. Therefore, much research has been conducted on using labs-on-a-chip as microsized and highly parallelized micro chemical reactors. Lab-on-a-chip devices can also be of interest when dealing with dangerous and explosive compounds in that they contain risk by dealing with smaller volumes at a time.

3.4.3Fabrication Technologies

Lab-on-a-chip uses the most common microfluidic device fabrication technologies, and depending on their applications, various polymers.

PDMS lab-on-a-chip: PDMS (polydimethylsiloxane) is a transparent and flexible elastomer. PDMS is widely used because it is very easy and cheap to fabricate PDMS labs-on-a-chip by casting .Moreover, labs-on-a-chip made of PDMS take advantage of the easy integration of quake microvalves for fast flow switch and permeability of air for cell culture and studies. Widely used for lab-on-a-chip prototyping, PDMS shows severe limitations for industrial production. Because the material is subject to ageing, and because PDMS absorbs hydrophobic molecules, it is hard to integrate electrodes into a PDMS

Thermopolymers (PMMA PS…) lab-on-a-chip: Thermoplastics are good candidates for the fabrication of labs-on-a-chip since they are transparent, compatible with micrometer-sized lithography and more chemically inert than PDMS.

Glass lab-on-a-chip: Transparent, compatible with micrometer sized machining, chemically inert, with a wide range of well-known chemical surface treatments and reproducible electrode integration, glass is a very good candidate for the industrialization of labs-on-a- chip. From a research point of view, the fabrication of glass labs-on-a-chip require clean rooms and researchers with a strong knowledge of microfabrication..

Silicon lab-on-a-chip: The first lab-on-a-chip was done in silicon, and it seems like quite a normal choice since microtechnologies are based on the micromachining of silicon. Silicon is expensive, it is not optically transparent (except for IR) and it requires a clean room as well as a strong knowledge of microfabrication. Moreover, the electrical conductivity of silicon makes it impossible to use for lab-on-a-chip operations requiring high voltage (like electrophoresis). Still, even if nowadays silicon seems like an obsolete candidate for the industrialization of lab-on-a-chip, it is not commonly used unless very necessary.

3.4.4Advantages

Low cost, High parallelization,Ease of use and compactness, Reduction of human error, Faster response time and diagnosis, Low volume samples, Real time process control and monitoring increase sensitivity, Expendable.

3.4.5Limitations

Industrialization, Signal/noise ratio, Ethics and human behaviour, Lab-on-a-chip needs an external system to work.

3.5 Silicon And Glass Micromachining For Micro Total Analysis Systems (µ TAS)

Micro total analysis system is a sub set of devices comprising the lab on the chip. It uses both hard and soft microfabrication techniques. It can be a hybrid of several chips. It is an integrated and miniaturised chemical analysis system.

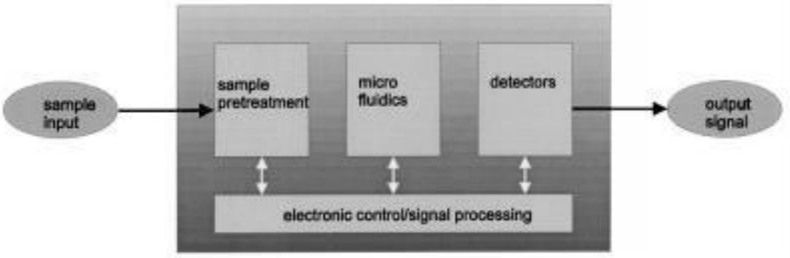

Fig. 3.1 Elements of a µ TAS

In general, four types of subsystems are thought to comprise amTAS: a sampling unit, a microfluidic unit, a detector system and an electronic controller. .An important aspect is the very small size required for the sensing element operating in a microchannel of a few hundreds of microns width.

A single chip includes sample preparation, separation and detection system.

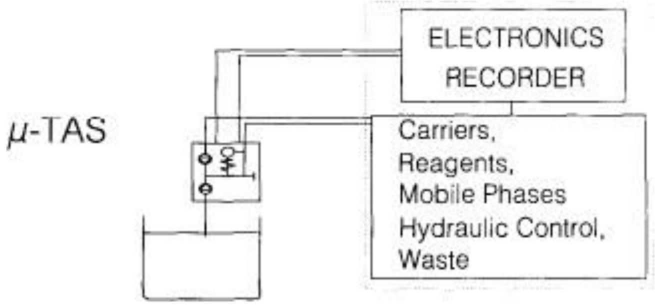

Fig.3.2 MICROTOTAL ANALYSIS SYSTEM

3.5.1Fabrication

μTAS fabrication has matured, affording microstructure generation from a wide range of materials (e.g. glass, silicon, elastomers, plastics, thermosets, paper) and using an equally broad set of microfabrication methods (e.g. photolithography, soft lithography, injection molding, hot embossing, laser micromachining).

Recent innovations in fabrication explored unconventional materials and fabrication strategies. Corn protein (zein) was processed by soft lithography and bonded to both a glass slide and another zein film by ethanol vapor deposition to form green microfluidic devices.

An origami (paper folding) method was developed to fabricate three-dimensional (3D) paper devices from single sheets of flat paper in a single photolithographic step.

Curved microfluidic networks were built from the self-assembly of differentially photo-crosslinked SU-8 films, which spontaneously and reversibly curled on film de-solvation and re-solvation .

Advantages

- Limited mixing of fluids
- Portability
- Automation
- Reduction of sample
- Low cost
- Fast

Disadvantages

- Blockages due to gas bubbles
- Contamination

3.5.2Silicon micromachining

Bulk Etching- Anisotropic wet chemical etching.

Surface micromachinig- Build structures on top of the substrate surface. Wafer bonding – Direct bonding, Anodic bonding

3.5.3Glass Micromachining

Glass is often considered a more desirable material for particular MEMS device applications due to its unique properties, such as optical transparency and biological compatibility.

MEMS applications where micro-machined glass is used include:

* sensors, such as those incorporating pressure, accelerometer, gyroscope transducers

* bioMEMS devices enabled by lab-on-chip and microfluidics technologies

* membranes

* spacers for cell phone cameras

Different glass micromachinig methods are powder blasting, laser, wet etching, ultrasonic and DRIE.

3.5.4Powder Blasting

Powder blasting is also referred to as sandblasting, impact abrasive machining or abrasive jet machining (AJM). In this process, fine abrasive particles are propelled by compressed air at the workpiece and these particles mechanically remove material by small chipping.

Powder blasting can be used to create membranes in glass for MEMS applications. The process can be controlled to leave as thin as 75-100 um of glass material with a depth uniformity within 15 microns.

Advantages

- It can quickly create through-holes in brittle materials without creating burrs on the surface.
- Process is anisotropic
- All surfaces are fully protected throughout the manufacturing process

Disadvantages

- The machined surface finish is slightly rough unless is it is wet etched after powder blasting.

3.5.5Laser Machining

With the laser machining process, glass material removal is from thermal shock or ablation by directed optical energy. There are several sources of lasers for machining glass and their selection is based on the type of application. The laser systems that are available for glass include CO2, Nd:YAG and excimer. The wavelength of the laser needs to be such that it doesnot pass through the glass without etching it. Computer-controlled equipment (most commonly an X-Y table) directs the beam to the desired location.

Advantages

- Easy to create a pattern from a CAD drawing and there is no mask, tooling or tool wear.
- The process can be easily automated.
- This process has a low taper angle and can be used on large pieces.

Disadvantages

- Laser machining creates subsurface micro-cracks and also creates a HAZ (Heat Affected Zone) which results in a kerf or damaged area at the top surface of the hole.
- Laser machining can crack or break thin glass pieces.

3.5.6 Ultrasonic Machining

This is a non-impact process in which a mechanical tool oscillates above the workpiece at a high frequency, roughly 20,000 cycles per second. The tool end (horn) is formed in the shape of the desired feature. The tool end (horn) and workpiece are submerged in abrasive slurry. The majority of the machining occurs by the tool end and abrasive particles hitting the workpiece.

Advantages

- Ability to drill straight sidewalls and produce very fine features.
- High aspect ratios that can be achieved.
- It is also easily repeatable until tool wear.
- Also, multiple depths and contoured surfaces (2-1/2 D) can be achieved.

Disadvantages

- A slow process with a large capital investment.
- The tooling needs to be redressed for every 25-50 pieces to avoid feature degradation.
- It is more difficult to engrave contoured and interior surfaces.

3.5.7Wet Etch

Wet etching involves the creation of a pattern in glass by immersing the wafer in an acid, most commonly hydrofluoric. An acid-resistant mask material can be used for selective material removal and the part can be etched to multiple levels. Common mask materials are Cr-Au and/or an acid resistant photoresist.

Advantages

- Wet etching can create very high detailed features and works well for removing thin films

- The shape and size of the part is not usually limited.
- Produced features have a low surface roughness and therefore this process can be used with applications where near optical clarity is desired.

Disadvantages

- The wet etch process is isotropic and there is undercutting of the photoresist that is equal in distance to the etch depth. This gives the process a low aspect ratio.
- The acid material is extremely hazardous to humans and the environment.

3.5.8 Deep Reactive Ion Etching (DRIE)

A dry etch micro-machining method is Deep Reactive Ion Etching, or DRIE. The process uses directional plasma ions to hit the glass causing erosion. A metal mask can be used to direct the ions and create the desired features. The process can be used on glass, but the gas chemistry is geared more toward silicon etching.

Advantages

- The process can be extremely accurate with feature creation and can achieve very small features.
- There is a low amount of surface roughness and it is a highly anisotropic process.

Disadvantages

- Depending on the number and type of features, the DRIE process can be very slow and because of this, it is not good for removing material across a wide area.
- Ion etching works well for etching silicon, but the process is extremely slow for etching glass. In fact, since it etches so slowly, glass is often used as a mask for etching silicon.

3.6.Surface Chemistry in Polymer Micro Fluidic System

Polymers exhibit comparatively low material cost and feature a wide range of (customizable) material characteristics. Furthermore, their thermally induced castability makes polymers amenable to commercially very well-established, high-fidelity replication schemes such as hot embossing and injection molding, thus covering the full scope for upscale from small- series to mass production.

3.6.1Materials

The most frequently used polymers include poly(methyl methacrylate) (PMMA), polycarbonate (PC), cyclic olefin materials, SU-8 and poly(dimethylsiloxane) (PDMS) which is commonly processed by the so-called ‘soft lithography’ fabrication scheme.

PMMA has been one of the most widely used polymers formicrofluidics. It is particularly useful for microfluidic chips due to its comparatively low cost, high optical transparency, and well definable electric and mechanical properties.PMMA is the least hydrophobic polymer, and can directly generate stable EOF in the microchannels . Owing to its unique absorption characteristics in the infrared regime, PMMA is also amenable to direct-write microstructuringby common CO2 laser ablation systems. These favorable physicochemical properties frequently make PMMA the material of choice for the fabrication of microfluidic devices.

PC is a widely used thermoplastic polymer which is,for instance, used for the fabrication of optical data storage media such as compact disks. Its high durability, strength, temperature resistance, lowdensity and good optical properties have also made PC a popular material for the fabrication of microfluidic devices.

Cyclic olefin polymer (COP) and cyclic olefin copolymer (COC) high optical clarity, even into the deep-UV range, low water absorption and, compared to other polymers, an exceptionally high resistance to organic solvents.

SU-8 is a UV-sensitive epoxy-based negative photoresist known from surface micromachining which can be obtained with range of viscosities for forming high thickness films (∼100 μm) by spin coating. It has also been shown that the SU-8 native resin itself or through suitable functionalization procedures is compatible with a range of chemical and biological assays

PDMS, an elastomeric material, has been widely used for the fabrication of microfluidic devices by ‘soft lithography. Features on the micron scale can be replicated with high fidelity in PDMS using replica molding from a microstructured, e.g. SU-8,master. The replica can be sealed reversibly or irreversibly without disfeaturing of the microchannels. PDMS substrates have been utilized with biological samples because of their low toxicity and their rather high optical transparency down to 280 nm, making PDMS compatible to a number of detection methods.

3.6.2Processing

There is a variety of machining techniques used for the fabrication of polymeric microfluidic devices, which can be coarsely categorized into direct/serial writing and replication schemes Often used direct structuring methods comprise (ultra-)precision milling, laser ablation photolithography, hot embossing, and injection molding,

3.6.3Surface Modification

Several coating techniques are available.

Common techniques include vapor-, plasma- and liquid-phase techniques. These techniques result in different levels of process control, layer thickness uniformities, and bring about certain restrains about the topology of surfaces to be coated. Surface treatments can lead to deposition of new and/or conversion of native surface layers.

Techniques include- Chemical vapour deposition, plasma activation, UV irradiation, sol gel chemistry, dynamic coatings, serial writing, mask based techniques

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DEPARTMENT OF BIOMEDICAL ENGINEERING

UNIT – IV – TRENDS IN MEMS FOR HEALTH CARE – SBM1606

UNIT – 4: TRENDS IN MEMS FOR HEALTH CARE

4. **There are many applications of MEMS in human body which are being implanted in the huma**n.

4.1 Pacemaker

- It is also known as artificial pacemaker of heart.
- It is small device implanted onto the heart which uses the battery.
- It sends electrical impulses which helps in heart beat rhythm.
- It is used when the heart natural pacemaker is defective and makes the heart to beat in regular rhythm.

4.2 Capsule Endoscopy

- It is used for imaging the digestive tract.
- It poses video, light source and transmitter.
- 50,000 images can be transferred during 8 hours of exposure
- It does not require skill technician
- It follows natural peristaltic movements of digestive tract.

4.3 Cochlear Implant

- It is a prosthetic device which is used as a hearing aid.
- It consists of microphone, signal processor RF transmitter, implant KF receiver, converter and electrode array.
- It can stimulate cochlear nerve and produces high quality device.

4.4 Artificial Retina

- It is a electronic device implanted in eye which restores the vision.
- This device captures visual signal and send to brain in form of electrical impulses.
- Video camera mounted on glass which captures images and are converted to a signal on a implanted material and they relay to the optic nerve.

4.5 Heart Tissue Production

- Heart cells are grown and subjected to electrical current, so they react like heart muscles.
- They can be grafted upon where heart muscles are weak end.
- It will produce heart rhythm in a regular waveform.

4.2 DRUG DELIVERY SYSTEM

- Drug delivered systems are engineered technology for the targeted delivery or controlled release of therapeutic agent.
- Drugs have long been used to improve health and extent life.
- The practice of drug delivery has changed dramatically in last few decades and even greater changes or anticipated in a near future.
- Biomedical engineers are contributed to the development of number of new models of drug delivery that have entered clinical practice.
- Side effect have been limited by this drug delivery method for many diseases such as cancers, neutrodegenerative disease and infectious diseases.
- Drug delivery system controls the rate at which a drug is released and location in the body where it is released.

Different modes of drug delivery system.

- Conventional route
- Sustained drug delivery system
- Controlled drug delivery system
- Implantable drug delivery system
- Transdermal drug delivery system

4.2.1Conventional route

- Conventional dosage form compromises solution, suspension and emulsion (liquid dosage form).
- Capsule, tablet etc. (solid dosage form)

4.2.2..1Mode of action

- When rapid efficient absorption of drug is desired for GI tract it represents the oral dosage form of choice.
- Drugs in suspension are also readily disorders the large available surface area of the dispersed solid facilitates rapid dissolution and absorption.

4.2.2 Sustained drug delivery system

- Sustained release dosage form are designed to release a drug at a pre-determined rate by maintaining a constant drug level for a specific period of time with minimal side effect.

- This can be achieved through a variety of formulation including liposome and drug polymer conjugates.
- Liposome have been used via a variety of administration route including intravenous, intramuscular, intraperitoneal and oral
- The half life of liposome ranges from few minutes to few hours depending upon the size and lipid composition.

4.2.2.1Mode of action

- Active agents are coated with the carrier molecule such as liposome which resulted in the complex called hapten carrier molecule. This complex by macrophage results in phagocog** carrier molecule forms a phagolysosome complex by fusing with lysosome. This phagolysosome fuses with the phagocytic cell and releases the drug towards the target site of a predetermined level.

4.3 Controlled drug delivery system

- Controlled release system have become very useful tool in medical practice.
- Controlled release system maintains constant therapeutic concentration of the drug within a therapeutic range of drug over prolonged period.
- Controlled delivery system offers an alternative approach to regulate both duration and localization of therapeutic agents in control delivery the active agents combined with a synthetic components to produce a delivery system.
- It frequently involves combination of active agents with inert polymeric material for the release of the drug. eg: chemically controlled system.
- Drug molecule is chemically linked to the backbone of the polymer
- In the body, in the presence of enzymes and biological fluid, chemical hydrolysis or enzymatic cleavage occurs with concomitant release of the drug at a control rate.

4.4 Implantable drug delivery system: eg. Program controlled insulin dosing

- It is also known as artificial pancreas
- This insulin pump delivers insulin through a catheter inserted in the body
- This device can deliver insulin in two ways: i) The fixed program unit with the pre-set 24 hour rate per time profile ii) The demand program unit which is basal rate preselected and a supplementary dose is trigger at mean time.
- Treatment drug delivery patch in contact to the skin for iontophoretic delivery.
- An electrode of the same polarity at a charge of the drug is placed in the reservoir.
- The electrical circuit is completed by the application of second electrode of the opposite polarity at different skin site.

4.5 Bio-Chip

- Bio-Chip is the collection of microarray arranged on a solid substrate
- It can perform millions of mathematical operations.
- A micro-chip can also perform thousands of biological operations.
- It increases the speed of identification of genes.

4.5.1Components of Bio-Chip

- There are 2 components of bio-chip i) Transponder ii) Reader / scanner.

4.5.2 Transponder

- It is a device for receiving a radiosignal and automatically transmit it to a different signal.

4.5.3 Reader / Scanner

- It consist of an exciter coil which creates electromagnetic signals.
- It provides energy to activate the implanted chip
- It also carrier a receiver coil to receive ID number.
- It contains the software and components to decodes and all this is done in milliseconds.

4.5.4Working

Reader transmits a low power radio signal and activate the implanted bio-chip

↓

ID numbers are transmitted by transponder and received by reader

↓

Reader displays the ID number on the readers LCD display

4.5.5 Bio-Chip Implant

- It is injected by the hypodermic syringe beneath the skin
- Injection is safe and simple
- Anesthesia is not required
- Route of injection depends upon the type of implanted material and their application.

4.5.6Application

- In the bio-chip, tracing of any person in the world is very easy.

- It stores all the data information and has the potential to replace passport, medical records etc.
- Medicinal implementation of bio-chip are glucose detector, oxygen sensor, blood pressure sensor etc (explain all the sensor briefly).

4.5.7Advantages

- It is smaller in size
- It performs of biological reaction in few seconds
- It increases the speed of diagnosis
- It is very faster and powerful technique

4.6Needle Electrode (Micro needle)

- It is used to record peripheral nerves action potential
- It is used to reduce movement artifacts and interface impedance.
- These electrodes merely penetrate skin and are placed parallel to the skin surface.
- Basic needle consists of a solid needle made up of stainless steel (SS) with sharp point.
- Needle insulated with varnish and tip is left exposed.
- Lead wire attached to the other end of needle and encapsulated in a plastic hub to protect it.
- It is mainly used in EMG.

2nd type

- Used to monitor ECG continuously during surgery
- Has SS hypodermic needle placed subcutaneously an each limb
- Lead wires with connectors connects the electrode to the monitor
- Epoxy resin fills the human and once it is set, needle is inserted card serves as active electrode.

3rd type

- Bipolar coaxial electrode

4th type

- It has a fine wire made of SS with diameter 25 – 125 µm insulated with varnish
- Lip is introduced into lumen for needle
- It is inserted through skin into muscle.
- Coiled wire also used.
- If one monopolar needle electrode → one wire is used for measuring electrode and other a separate reference electrode.

- The bipolar needle electrode → 2 wires are used, one as reference and other as measuring electrode.

4.7 Neuroprothetics

- Neuroprosthetics is a discipline related to neuroscience and biomedical engineering concerned with developing neural prosthesis.
- There are sometimes contrasted with a brain computer interface which connects the brain to a computer rather than a device meant replace missing biological functionality
- Neural prosthetics are a series of device that can substitute a motor, sensory or cognitive mortality that might have been damaged as a result of an injury or a disease.

4.7.1Visual prosthetics

- The visual prosthetics can create a sense of image by electrically stimulating neurons in the visual system.
- A camera would wirelessly transmit to an implants the implant would map the image across an array of electrode.
- The array o electrodes has effectively stimulate 600 – 1000 locations, stimulating optic neuron in the retina thin creating an image.
- A visual prostheses system consists of an external or implantable imaging system which acquires and process the video.
- Power and data will be transmitted to the implant wirelessly by the external unit.
- The implant uses the received power / data which converts the digital data into analog output which will be delivered to the nerve via microelectrode.
- Photoreceptors are the specialized neurons that convert photons into electrical signal.

4.7.2Auditory prosthetics: eg. Cochlear implant these devices substitute the function performed by the ear drum.

- A microphone on external unit gathers the sound and process it, the processed signal is then transferred to an implanted unit that stimulated the auditory nerve via a microelectrode array.
- Three main categories for auditory prosthetics cochlear implant cochlear electrode arrays are implanted.
- Auditory brain stem implant – ABI electrode array stimulates the cochlear nuclear complex.
- Auditory mid brain implant – AMI stimulates auditory neurons in the inferior colliculus.

4.7.3Motor Prosthetics

- Devices which supports the function of autonomous nervous system includes the implant for bladder control.
- In the attempts to gain conscious control of the movement which includes electrical stimulation.

4.7.4Bladder control implant.

- When the spinal cord injury leads to paraplegia, patients have difficult in empting their bladder and this can cause infection.
- This device is implanted over sacral anterior route ganglia of the spinal cord controlled by an external transmitter.
- It delivers intermitter stimulation which improved bladder implying.

4.7.5Cognitive prosthetics

- Cognitive prosthetics can store the function to individuals with brain tissue loss due to injury, disease etc.
- The function of the damaged tissue can be rectified with integrated tissue.
- Brain plasticity suggest that the brain is capable of rewiring itself so that an area of the brain associated with a particular function can even perform function associated with another portion of brain. Eg: Auditory cortex can perform function simultaneous improves the auditory process cortex visual information.
- Implants could take advantage of brain plasticity to restore cognitive function even if the native tissue has been destroyed.

4.7.6Spinal cord injury

- It consists of an implanted receiver stimulator, an external shoulder position sensor and a terminal electrode.
- The terminal electrode is placed on the motor point of a muscle. This enables a low electrical threshold to the utilized.
- The external sensor measures voluntary movement that occur in the countralteral shoulder and basis motor output command on this information.
- A radio frequency signal is then transmitted to the implanted receiver stimulator which converts to an electrical stimuli that depolarizes the peripheral nerve.

4.8Shape Memory Implant

- Shape memory is a terms which dendex a material ability to return from a program frozen temporary shape the original permanent shape as a result of external physical stimulate (temp, tight, radiation etc) or chemical factor (pH change, ionic strength and solvents).

- The first materials in which the shape memory effect has been where metal alloys are in particular on alloy of nickel and titanium which has been applied in medical practice.
- Implant made up on an alloy have been applied in the bone surgery as a self blocking material for bond bones coral, maxillofacial surgery spine surgery.

4.8.1Drawback

- Inflammation, corrosion, difficult removal after complete bone adhesion.
- SMA can be replaced by polymers due to the lower production cost, shape stability, widal range of shape change and production of complicated shape.

4.8.2Shape Memory Effect

- Shape memory effect which conilines the right morphology of a polymer and the technology process is associated with its finer molecular structure
- For a polymer to have specific property it has to have atleast two molecular elements in its structure net points and switching segments.
- Two categories of shape memory polymers are distinguish in terms of the nature of bond which fix the original and temporary shapes.

4.8.3Net points

- It determine the permanent shape
- Nature of bond: chemical, covlanet bond, physical – intermolecular intraction.

4.8.4Switching segments

- It is responsible for fixing the temporary shape
- It possess the nature of reversible bond.
- Chemical → covalent bond physical → intermolecular interaction.

4.8.5 Biodegradable shape memory polymer

- Degradable shape memory materials have been found to be especially useful in low invasive tissue surgery.
- A shape memory implant of a temporary shape could be placed inside the body by requiring only a minimum surgery.
- After a pre-determined period or responding to an external stimulus it would assume permanent shape meeting the therapeutic requirements.
- After a period to heal the lesion the material would be reabsorbed which would prevent long term cellular response and other delayed undesired interaction between the body and the implant.

- Biocompatible shape memory polymer successfully replaced previously used implant made of metal alloys.
- They can be used to make surgical devices such as self locking staples and surgical pins.

4.8.6Biocompatibility of polymers (in vivo)

- Synthetic materials which are foreign substances in a human body can be applied in vivo if they need fundamental criterion of the biocompatibility.
- This means that they have to remain non-toxic throughout the period of contact with tissues that they cannot induce inflammation, allergy, carcinogensis or mutagenic.
- Biocompatable shape memory implants or materials it is extremely difficult to get rid of certain compounds which are found in a finished product.
- Traces of such low molecule compound are released from implant polymer to the human body and have toxic effect on it as well as induce inflammation at te implant site.
- Toxic components should be avoided when designing the synthesis method and the composition of such material.
- Biocompatability is not only a result of the composition but also of the dimension and the shape of the material which induces cellular response (in vivo) for eg: large fragments of materials they induces a inflammatory condition if the dimension enable endocytosis by macrophages.
- It is also extremely important to make the right choice of the type of material from which the implant is to be made and to select the right shape so that its mechanical properties are appropriate for its role at the implant site.
- Synthesis involves introducing functional group into the skeleton of the degraded polyester chain which can cross link the materials when treated with the UV radiation.

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DEPARTMENT OF BIOMEDICAL ENGINEERING

UNIT – V – MEDICAL APPLICATIONS IN NANOTECHNOLOGY – SBM1606

UNIT – 5 - MEDICAL APPLICATIONS IN NANOTECHNOLGOY

5.1 Introduction

- In the day today life various disease like diabetes, cancer, sparkinsen diseases, Alzheimer disease, cardiovascular disease and multiple sclerosis.
- As well as different kinds of serious inflammatory or infectious disease.
- Nanomedicine is an application of nanotechnology which works in the field of health and medicine
- Nanomedicine makes use of nanomaterials and nanoelectronic biosensor.
- Nanomedicine helps in earlier detection, prevention, ** and effective therapeutic regime.

5.1.1Drug delivery

- Nanoparticles are used for site specific drug delivery.
- In this technique the required drug dose is used and side effects are lowered significantly as the active agents is deposited in the morbid region only.
- This highly selective approach can reduce cost and pain to the patients.
- There are variety of nanoparticles such as dendrimers, nanoporous material, are used for drug encapsulation.
- They transport small drug molecules to the desired location for the active release of the drug.
- In or gold nanoparticles are finding important application in the cancer treatment.
- The targeted medicine reduces the drug consumption and treatment expensive making a treatment of patient cost effective.

5.1.2 Protein / Peptide Delivey

- Nanoparticles were found useful in delivery the myclin antigen which induce immune tolerance in a mouse model with relapsing multiple sclerosis.
- In this technique biodegradable polyesterinemicroparticles coating with the myclin sheath peptide will reset the mouse immune system and this prevents the reoccurrence of disease and reduces the symptom.
- Protective myclin sheath forms protein on the nerve flues of the central nervous system.
- This method of treatment can potentially be used in the treatment of various other autoimmune disorder.

5.1.3 Oncology

- Due to the small size of nanoparticles, it can be great use in particularly in imaging
- Nanoparticles such as quantum dots with quantum confinement properties such as light emission can be used in conjunction with MRI to produce exceptional images tumor size.
- They also used in cancer therapy.
- Ex:

1.	Carbon nanotubes:	0.5 – 3 nm in diameter 20 – 1000 nm in length Used for detecting DNA mutastion. Detection of disease protein biomaker
2.	Dendrimers	Less than 10 nm in size Useful for release drug delivery Image contrast agent
3.	Nano crystals	2 – 9.5 nm in size It improves formulation for poorly soluble drugs. Labelling of breast cancer marker
4.	Nano particles	10 – 100 nm in size It is used in MRI Ultrasound images as a image contrast agents. Targetted drug delivery Reporters of apoptosis and angiogenesis.
5.	Nanoshells	Application in tumour specific imaging Deep tissue thermal ablation.
6.	Nanowires	Useful for disease protein biomarker detection DNA mutation detection Gene expression detection
7.	Quantum dots	2 – 9.5 nm in size Cell assays

5.1.4Modified Medicated Textiles :

- Using nanotechnology newer antibacterial cotton has been developed and used for antibacterial textiles.

- Developmental works during nanotechnology new modified antibacterial textiles have been developed to inhibit the growth bacteria, fungi etc.

5.1.5Nanopharmaceuticals

- Nanopharmaceuticals can be used to detect disease at much earlier stages and the diagnostic application could build upon convenient procedure using nanoparticles.
- Nanopharmaceuticals are an emerging field where the size of the drug particle or a therapeutic delivery system work at the nano scale.
- Delivering the appropriate dose of a particular active agent to specific disease still remains difficult in the pharmaceutical industry.

5.1.6 Antibiotic resistance

- Antibiotic resistance can be decreased by use of nanoparticle in combination therapy.
- Zinc oxide nanoparticle can decrease the antibiotic resistance and enhance the antibacterial activity of ciprofloxacin against microorganism by interfering with various protein that are interacting with antibiotic resistance.

5.1.7 Tissue engineering

- In tissue engineering, nanotechnology can be applied to reproduce or repair damaged tissue.
- By using suitable nanomaterial paste scaffolds and growth factor which artificially stimulant cell proliferation in organ transplant or artificial implant therapy.
- Nanotechnology can be useful which can lead to life extension

5.2.Synthesis of Nanomaterials

5.2.1 Introduction

There are a large number of techniques available to synthesize different types of nanomaterials in the form of colloids, clusters, powders, tubes, rods, wires, thin films etc. There are various physical, chemical, biological and hybrid techniques available to synthesize nanomaterials. The technique to be used depends upon the material of interest, type of nanostructure viz., zero dimensional, one dimensional, or two dimensional material size, quantity etc.

5.2.2Physical methods:*(a) mechanical:* ball milling, melt mixing

(*b)Vapor:* physical vapor deposition, laser ablation, sputter deposition, electric arc deposition, ion implantation

5.2.3**Chemical methods:** colloids, sol-gel, L-B films, inverse micelles.

5.2.4Biological methods:biomembranes, DNA, enzymes, microorganisms.

5.3 Physical methods

5.3.1 Ball milling: It is used in making of nanoparticles of some metals and alloys in the form of powder. Usually the mill contains one or more containers are used at a time to make fine particles. Size of container depends upon the quantity of interest. Hardened steel or tungsten carbide balls are put in containers along with powder or flakes (<50 um) of a material of interest. Initial material can be of arbitrary size and shape. Container is closed with tight lids. The containers are rotated at high speed (a few hundreds of rpm) around their own axis. Additionally they may rotate around some central axis and are therefore called as 'planetary ball mill'. When the containers are rotating around the central axis, the material is forced to the walls and is pressed against the walls. But due to the motion of the containers around their own axis, the material is forced to other region of the container. By controlling the speed of rotation of the central axis and container as well as duration of milling, it is possible to ground the material to fine powder whose size can be quite uniform. Some of the materials like Co, Cr, W, Ni-Ti, Al-Fe, Ag-Fe etc. are made nanocrystalline using ball mill.

Large balls, used for milling, produce smaller grain size and larger defects in the particles. The process may add some impurities from balls. The container may be filled with air or inert gas. However, this can be an additional source of impurity. A temperature rise in the range of 100 to 1100 C is expected to take place during the collisions. Cryo-cooling is used to dissipate the generated heat.

5.3.2 Melt Mixing: It is possible to form or arrest the nanoparticles in glass. Structurally, glass is an amorphous solid, lacking long range periodic arrangement as well as symmetry arrangement of atoms/molecules. When a liquid is cooled below certain temperature, it forms either a crystalline or amorphous solid (glass). Nuclei are formed spontaneously with homogenous (in the melt) or inhomogeneous (on the surface of other materials) nucleation, which can grow to form ordered, crystalline solid. Usually, metals form crystalline solids but, if cooled at very high cooling rate, they can form amorphous solids. Such solids are known as metallic glasses. Even in such cases the atoms try to reorganize themselves into crystalline solids. Addition of elements like B, P, Si etc. helps to keep the metallic glasses in amorphous state. It is possible to form nanocrystals within metallic glasses. It is also possible to form some nanoparticles by mixing the molten streams of metals at high velocity with turbulence. On mixing thoroughly, nanoparticles are formed.

5.3.3 Physical Vapor Deposition: It involves material for evaporation, an inert gas or reactive gas for collosion of material vapor, a cold finger on which clusters or nanoparticles can condense, a scraper to scrape the nanoparticles and piston- anvil (an arrangement in which nanoparticle powder can be compacted). All the processes are carried out in a vacuum chamber so that the desired purity of the end product can be obtained.

Metals or high vapor pressure metal oxides are evaporated or sublimated from filaments or boats of refractory metals like W, Ta, Mo in which materials to be evaporated are held. Size, shape and even the phase of evaporated material can depend upon the gas pressure in deposition chamber. Clusters or nanoparticles condensed on the cold finger (water or liquid nitrogen cooled) can be scraped off inside the vacuum system. The process of evaporation and condensation can be repeated several times until enough quantity of material falls through a funnel in which a piston-anvil arrangement has been provided.

5.3.4 Ionized Cluster Beam Deposition: It is useful to obtain adherent and high quality single crystalline thin films. The set up consists of a source of evaporation, a nozzle through which material can expand into the chamber, an electron beam to ionize the clusters, an arrangement to accelerate the clusters and a substrate on which nanoparticle film can be deposited, all housed in a suitable vacuum chamber. Small clusters from molten material are expanded through the fine nozzle. The vapor pressure, ~10 torr to 10-2 torr needs to be created in the source and the nozzle needs to have a diameter larger than the mean free path of atoms or molecules in vapor form in the source to form the clusters. On collision with electron beam clusters get ionized. Due to applied accelerating voltage, the clusters are directed towards the substrate. By controlling the accelerating voltage, it is possible to control the energy with which the clusters hit the substrate. Thus it is possible to obtain the films of nanocrystalline material using ionized cluster beam.

5.3.5 Laser Vaporization: In this method, vaporization of the material is effected using pulses of laser beam of high power. The set up is aultra high vacuum or high vacuum system equipped with inert or reactive gas introduction facility, laser beam, solid target and cooled substrate. Clusters of any material of which solid target can be made are possible to synthesize. Usually laser giving UV wavelength such as excimer laser is necessary because other wavelengths like IR or visible are often reflected by some of the metal surface. A powerful beam of laser evaporates the atoms from a solid source, atoms collide with inert gas atoms (or reactive gases) and cool on them forming clusters. They condense on the cooled substrate. The method is often known as laser ablation. Gas pressure is very critical in determining the particle size and distribution. Simultaneous evaporation of another material and mixing the two evaporated materials in inert gas leads to the formation of alloys or compounds.

5.3.6 Laser Pyrolysis or Laser Assisted Depositon: Here a mixture of reactant gases is decomposed using a powerful laser beam in presence of some inert gas like helium or argon. Atoms or molecules of decomposed reactant gases collide with inert gas atoms and interact with each other, grow and are then get deposited on cooled substrate. Many materials like Al_2O_3, WC, Si_3Ni_4 etc. are synthesized in nanocrystalline form by this method. Here too, gas pressure plays an important role in deciding the particle size and their distribution.

5.3.7 Sputter Deposition: In sputter deposition, some inert gas ions like Ar are incident on a target at a high energy. The ions become neutral at the surface but due to their energy, incident ions may get implanted, get bounded back, create collision cascades in target atoms, displace some of the atoms in the target creating vacancies, interstitials and other defects, desorb some adsorbents, create photons while loosing energy to target atoms or even sputter out some target atoms/molecules, clusters, ions and secondary electrons. Sputter deposition is a widely used thin film deposition technique, specially to obtain stoichiometric thin films from target material. Target material may be some alloy, ceramic or compound. It is a very good technique to deposit multilayer films for mirrors or magnetic films for spintronic applications. Sputter deposition can be carried out using Direct Current (DC) sputtering, Radio Frequency (RF) sputtering or magnetron sputtering. In all these methods, one uses discharge or plasma of some inert gas atoms or reactive gases. The deposition is carried out in a required gas pressurized high vacuum or ultra high vacuum system equipped with electrodes, one of which is a sputter target and the other is a substrate, gas introduction facility etc.

In DC sputtering, the target is held at high negative voltage and substrate may be at positive, ground or floating potential. Substrates may be simultaneously heated or cooled depending upon the requirement. Once the required base pressure is attained in the vacuum system, usually argon gas introduced at a low pressure. A visible glow is observed and current flows between anode and cathode indicating the deposition onset. When sufficiently high voltage is applied between anode and cathode with a gas in it, a glow discharge is set up with different regions as cathode glow, Crooke's dark space, negative glow, Faraday dark space, positive column, anode dark space and anode glow. These regions are the result of plasma. Plasma is a mixture of free electrons, ions and photons. Plasma is overall neutral but there can be regions, which are predominantly of positive or negative charge. The density of various particles and the length over which they are spread and distributed depends upon the gas pressure.

In RF sputtering 5-30 MHz frequency is used and the electrodes can be insulating. However, 13.56 MHz is a commonly used frequency for deposition. Target itself biases to negative potential becoming cathode.

RF and DC sputtering efficiency can be further increased using magnetic field. When both electric and magnetic fields act simultaneously on a charged particle, force is acted upon it. Electrons moves in a helical path and is able to ionize more atoms in the gas. In practice, both parallel and magnetic fields to the direction of electric field are used to further increase the ionization of the gas, increasing the efficiency of sputtering. By introducing gases like O2, N2, NH3, CH4, H2S etc. while metal targets are sputtered, one can obtain metal oxides like Al2O3, nitrides, carbides etc., This is known as reactive sputtering.

The plasma density can be further enhanced using microwave frequency and coupling the resonance frequency of electrons in magnetic field. Ionization density using Electron Cyclotron Resonance plasma is about 2-3 orders of magnitude larger. Thin films and nanoparticles of Si2O3, SiN, GaN etc. have been obtained using this technique.

5.3.8 Chemical Vapour Deposition (CVD): It is a hybrid method using chemicals in vapour phase. Basic CVD process can be considered as a transport of reactant vapour or reactant gas towards the substrate kept at some high temperature where the reactant cracks into different products which diffuse on the surface, undergo some chemical reaction at appropriate site, nucleate and grow to form the desired material film. The by-products created on the substrate have to be transported back to the gaseous phase removing them from the substrate. Vapours of desired material may be often pumped into reaction chamber using some carrier gas. In some cases the reactions may occur through aerosol formation in gas phase. There are various processes such as reduction of gas, chemical reaction between different source gases, oxidation or some disproportionate reaction by which CVD can proceed. However, it is preferable that the reaction occurs at the substrate rather than in the gas phase. Usually temperature ~ 300 to 1200 C is used at the substrate. There are two ways viz., hot wall and cold wall by which substrates are heated. In hot wall set up the deposition can take place even on reactor walls. This is avoided in cold wall design. Besides this, the reaction can take place in gas phase with hot wall design,which is suppressed in cold wall set up. Further, coupling of plasma with chemical reaction in cold wall set up is feasible. Usually gas pressures in the range of 0.1 torr to 1.0 torr are used. Growth rate and film quality depend upon the gas pressure and the substrate temperature. When the growth takes place at low temperature, it is limited by the kinetics of surface tension.

CVD is widely used in industry because of relatively simple instrumentation, ease of processing, possibility of depositing different types of materials and economic viability. Under certain deposition conditions nanocrystalline films or single crystalline films are possible. There are many variants of CVD like metallo organic CVD (MOCVD), atomic layer epitaxy (ALE), vapor phase epitaxy (VPE), plasma enhanced CVD (PECVD) etc. They differ in source gas pressure, geometrical layout, temperature used etc.

5.3.9 Electric Arc Deposition: This is one of the simplest and useful methods, which leads to mass scale production of fullerenes and carbon nanotubes. It requires water cooled vacuum chamber and electrodes to strike an arc between them. The positive electrode itself acts as the source of material. If some catalyst are to be used, there can be some additional thermal source of evaporation. Inert gas or reactive gas introduction is necessary. Usually the gap between the electrodes is ~1mm and high current ~50 to 100 amperes is passed from a low voltage power supply (~12-15 volts). Inert gas pressure is maintained in the vacuum system. When an arc is set up, anode material evaporates. This is possible as along as the discharge can be maintained. By striking the arc between the two graphite electrodes, it is possible to get fullerenes in large quantity. In case of fullerenes, the formation occurs at low helium pressure as compared to that used for nanotube formation. Also, fullerenes are obtained by purification of soot collected from inner walls of vacuum chamber, whereas nanotubes are found to be formed only at high He gas pressure and in the central portion of the cathode. No carbon nanotubes are found on the chamber walls

5.3.10 Ion Implantation: In this method high energy (few keV to hundereds of keV) or low energy (<200 eV) ions are used to obtain nanoparticles. Ions of interest are usually formed using an ion gun specially designed to produce metal ions, which are accelerated to high or low energy towards the substrate heated to few hundered of C. Depending upon the energy f the incident ions, various other processes like sputtering and generation of electromagnetic radiation may take place. It is possible to obtain single element nanoparticles or compounds and alloys of more than one element. In some experiments it has been possible to even obtain doped nanoparticles using ion implantation. There is possibility of making nanoparticles using swift heavy ions (few MeV energy) employing ion accelerators like a pelletron.

5.3.11 Molecular beam epitaxy (MBE): This technique of deposition can be used to deposit elemental or compound quantum dots, quantum wells, quantum wires in a very controlled manner. High degree of purity in materials is achievable using ultra high vacuum (better than torr). Special sources of deposition known as Kundsen cell (K-cell) or effusion cell are employed to obtain molecular beams of the constituent elements. The rate of deposition is kept very low and substrate temperature is rather high in order to achieve sufficient mobility of the elements on the substrate and layer by layer growth to obtain nanostructures.

5.3.12Thermolysis: Nanoparticles can be made by decomposing solids at high temperature having metal cations, and molecular anions or metal organic compounds. The process is called thermolysis. For example, small lithium particles can be made by decomposing lithium azide, LiN3. The material is placed in an evacuated quartz tube and heated to 400 C. At but 370 C LiN3 decomposes, releasing N2 gas, which is observed by an increase in the pressure on the vacuum gauge. In a few minutes the pressure drops back to its original low value, indicating that all the N2 has been removed. The remaining lithium atoms coalesce to form small colloidal metal particles. Particles less than 5nm can be made by this method. Passivation can be achieved by introducing an appropriate gas.

5.3.13Pulsed laser method: Pulsed lasers have been used in the synthesis of nanoparticles of silver. Silver nitrate solution and a reducing agent are flowed through a blenderlike device. In the blender there is a solid disk, which rotates in the solution. The solid disk is subjected to pulses from a laser beam creating hot spots on the surface of the disk. Silver nitrate and the reducing agent react at these hot spots, resulting in the formation of small silver particles, which can be separated from the solution using a centrifuge. The size of particles is controlled by the energy of the laser and rotation speed of the disk. This method is capable of a high rate of production.

5.4Chemical Methods (Wet Chemical route)

There are numerous advantages of using chemical methods, which are –

- Inexpensive, less instrumentation compared to many physical methods
- Low temperature (< 350 C) synthesis
- Doping of foreign atoms (ions) possible during synthesis
- Variety of size and shapes are possible
- Self assembly or patterning is possible

5.4.1Colloids and Colloids in solutions: A class of materials in which two or more phases (solid, liquid, gas) of same or different materials co-exist with at least one dimension less than a micrometer is known as colloids. Colloids may be particles, plates, or fibers. Nanomaterials are a sub-class of colloids, in which one of the dimensions of colloids is in about 1 to 100 nm range. Colloids are the particles suspended in some host matrix.

5.4.2Interactions: Colloids are particles with large surface to volume ratio. Therefore atoms on the surface are in a highly reactive state, which easily interact to form bigger particles or tend to coagulate. It is thus necessary to understand the stability of colloids i.e., how the colloids dispersed in a medium can remain suspended particles. In general there are a number of interactions involved. There are two types of interactions: attractive and repulsive. Repulsive interaction involves short distance of Born repulsive interaction and long range attractive interaction van der Waals attraction. Repulsive part arises due to repulsion between electron clouds in each atom and attractive part is due to interaction between fluctuating or permanent dipoles of atoms/molecules. The attractive forces between colloidal particles reduced in colloids in a liquid medium. Colloids in liquid may be positively charged, negatively charged or even neutral. But in most cases they are charged. As there are some charges on particles, ions of opposite charges accumulate around them. Oppositely charged ions are known as counter ions. This accumulation of counter ions leads to formation of an electric double layer. Stability of colloids can be increased by stearic hinderance or repulsion. By adsorbing some layers of a different material on colloidal particles eg.polymer it is possible to reduce the attractive forces between them..

5.4.3Synthesis: Chemical reactions in which colloidal particles are obtained are carried out in glass reactor of suitable size. Glass reactor usually has a provision to introduce some precursors, gases as well as measure temperature, pH etc. during the reaction. It is usually possible to remove the products at suitable time intervals. Reaction is usually carried out under inert atmosphere like argon or nitrogen gas so as to avoid any uncontrolled oxidation of the products. There is also provision made to stir the reactants during the reaction by using Teflon coated magnetic needle.

Although chemical synthesis of nanoparticles is a complex process, by understanding how nucleation and growth of particles takes place, it is possible to control the various steps and try to achieve monodispersed nanoparticles. This can be done with the help of LaMer diagram. As we keep on increasing the concentration of the reactants in the solution, at certain concentration, say C_O, the formation of nuclei begins. There is no precipitate at this concentration. Further increase in concentration increases nuclei formation up to a concentration C_N, above which there is ‘super saturation’ between C_N and C_S. Concentration C_N denotes the maximum rate of nuclei formation. When nuclei formation reduces, again C_O the minimum concentration for nucleation is reached. No new nuclei can be formed and crystal growth reduces the concentration. At this concentration C_S, an equilibrium is obtained. If new nuclei are formed during the growth of particles, particle with large size distribution are obtained. Therefore it is very important that concentration of solute and its diffusion to dissolve species be adjusted properly in order that no fresh nuclei are formed once the concentration of solute and its diffusion to dissolve species be adjusted properly in order that no fresh nuclei are formed once the concentration has reached C_N. Particles can grow even at the expense of smaller particles. Larger particles are more stable and grow at the expense of smaller particles. This growth mode is known as Ostwald ripening. The driving force for large particles is the reduction in surface free energy.

5.4.4Colloidal metal nanoparticles are often synthesized by reduction of some metal salt or acid. For example highly stable gold particles can be obtained by reducing choloroauric acid (HAuCl4) with tri sodium citrate ($Na_3C_6H_5O_7$). The reaction takes place as follows –

HAuCl4 + Na3C6H5O7 ⟶ Au+ +C6H5O- + HCl + 3NaCl.

Au atoms are formed by nucleation and condensation. They grow bigger in size by reduction of more Au+ ions on the surface. These atoms are stabilized by oppositely charged citrate ions. Metal gold nanoparticles exhibit intense red, magenta etc., colours, depending upon the particle size. Gold nanoparticles are stabilized by repulsive Coulomb interaction. It is also possible to stabilize gold nanoparticles using thiol or some other capping molecules. In a similar manner, silver, palladium, copper and other metal nanoparticles can be synthesized using appropriate precursors, temperature, pH, duration of synthesis etc., Particle size, size distribution and shape strongly depend on the reaction parameters and can be controlled to achieve desired results. It is also possible to synthesize alloy nanoparticles using appropriate precursors.

5.4.5Compound semiconductor nanoparticles can be synthesized by wet chemical route using appropriate salts. Sulphide semiconductors like CdS and ZnS can be synthesized easily by what is known as co-precipitation. For example to obtain ZnS nanoparticles any zinc salt like Zinc sulphate (ZnSO4), zinc chloride (ZnCl2) can be dissolved in aqeous (or nonaqeous) liquid and Na2S is added to the solution. Following simple reaction results to give particles of ZnS.

$ZnCl_2 + Na_2S \rightarrow ZnS + 2NaCl$

To obtain zinc oxide particles one can use following reactions:

$ZnCl_2 + 2NaOH \rightarrow Zn(OH)_2 + 2NaCl$

$Zn(OH)_2 \rightarrow ZnO + H_2O$

Selenide particles can be obtained using appropriate selenium giving salt. However, all these nanoparticles need to be surface passivated as colloids formed in liquids have a tendency to coagulate or ripen due to attractive forces existing between them. The electrostatic and other repulsive forces may not be sufficient to keep them apart. However, stearic hindrance can be created by appropriately coating the particles to keep them apart. This is often known as 'chemical capping' and has become a widely used method in the synthesis of nanoparticles. Advantage with this chemical route is that, one can get stable particles of variety of aterials not only in the solution, but even after drying off the liquid. Coatings may be part of post-treatment or a part of the synthesis reactions to obtain nanoparticles. If it is a part of the synthesis reaction, the concentration of capping molecules can be used in two ways, to control the size as well as to protect the particles from coagulation. Chemical capping can be carried out at high or low temperature depending on the reactants. In high temperature reactions, cold organometallic reactants are injected in some solvent like triocylphosphineoxide held at temperature >300 C.

5.4.6 Langmuir-Blodgett (L-B) method: This technique to transfer organic layers at air-liquid interface onto solid substrates is known for nearly 70 years. The technique was developed by the two scientists Langmuir and Blodgett. In this technique one uses amphiphilic long chain molecules like that in fatty acids. An amphiphilic molecule has a hydrophilic group (water loving) at one end and a hydrophobic group (water hating) at the other end. As an example consider the molecule of arachidic acid, which ahs a chemical formula $[CH_3(CH_2)_{16} COOH]$. There are many such long chain organic chains with general chemical formula $[CH_3(CH_2)_nCOOH]$, where n is a positive integer. In this case, $-CH_3$ is hydrophobic and $–COOH$ is hydrophilic in nature.

Usually molecules with $n>14$ are candidates to form L-B films. This is necessary in order to keep hydrophobic and hydrophilic ends well separated from each other. When such molecules are put in water, the molecules spread themselves on surface of water in such a way that their hydrophilic ends, often called as heads, are immersed in water, whereas the hydrophobic ends called as tails remain in air. They are also surface active agents or surfactants. Surfactants are amphiphilic molecules i.e. an organic chain molecule in which at one end there is polar, hydrophilic (water loving) and at the other a nonpolar, hydrophobic (water hating) group of atoms. Using a movable barrier, it is possible to compress these molecules to come close together to form a monolayer and align the tails. It is however necessary that hydrophilic and hydrophobic ends are well separated. Such a monolayer is two dimensionally ordered and can be transferred on some suitable solid substrates like glass, silicon etc. This is done by dipping the solid substrate in the liquid, in which ordered organic molecular monolayer is already formed.

Deposition of L-B films is done by following steps: (1) A monolayer of amphiphilic molecules is formed (2) A substrate is dipped in the liquid (3) The substrate is pulled out, during which ordered molecules get attached to the substrate (4) When the substrate is again dipped, molecules again get deposited as the substrate forming a second layer on the substrate (5) As the substrate is again pulled out a thin layer gets deposited. By repeating the procedure large number of ordered layers can be transformed on a substrate.

In general there are three types of L-B films with different multilayer sequence. These are known as X, Y, and Z type. (1) X-type: Deposition only during insertion of substrate (2)Y-type: Deposition both the times except no deposition during first immersion (3) Z-type: Deposition only during removal of substrate. Y type of films are most common. Although the layers are ordered, there is only the van der Waals interaction between different layers. Thus L-B films are good examples of nanostructured materials.

It is possible to obtain nanoparticles using L-B technique. A metal salt like CdCl2 or ZnCl2 is dissolved in water on surface of which a compressed uniform monolayer of surfactant is spread. When H2S gas is passed in the solution, CdS or ZnS nanoparticles of few tens of nanometers can be formed. Particles are uniform in size. If surfactants are not present, uniform nanoparticles are not formed.

5.4.7 Sol-Gel Method: As the name implies sol-gel involves two types of materials or components ‘sol’ and ‘gel’. There are several advantages of sol-gel: All sol-gel formation process is usually a low temperature process. This means less energy consumption and less pollution too. Some of the benefits like getting unique materials such as aerogels, zeolites, ordered porous solids by organic-inorganic hybridization are unique to sol-gel process. It is also possible to synthesize nanoparticles, nanorods, nanotubes etc., using sol-gel technique.

Sols are solid particles in a liquid. They are thus a subclass of colloids. Gels are nothing but a continuous network of particles with pores filled with liquid (or polymers containing liquid). A sol-gel process involves formation of ‘sols’in a liquid and then connecting the sol particles (or some subunit capable of forming a porous network) to form a network. By drying the liquid, it is possible to obtain powders, thin films or even monolithic solid.

Synthesis of sol-gel in general involves hydrolysis of precursors, condensation followed by polycondensation to form particles, gelation and drying process by various routes. Precursors (starting chemicals) are to be chosen so that they have a tendency to form gels. Both alkoxides or metal salts can be used. Alkoxides have a general formula M(ROH)n, where M is a cation, R an alcohol group, and n is the number of (ROH) groups with each cation. Salts are denoted as MX, in which M is a cation and X is an anion. Although it is not mandatory that only oxides be formed by a sol-gel process, often oxide ceramics are best synthesized by a sol-gel route. For example in silica, SiO4 group with Si at the centre and four oxygen atoms at the apexes of tetrahedron are very ideal for forming sols with interconnectivity through the corners of tetrahedrons, creating some cavities or pores. By polycodensation process (i.e., many hydrolyzed units coming together by removal of some atoms from small molecules like OH) sols are nucleated and ultimately solgel is formed. Sol-gel method is particularly useful to synthesize ceramics or metal oxides although sulphides, borides and nitrides also are possible.

5.4.8 Microemulsion: Synthesis of nanoparticles in the cavities produced in microemulsion is a widely used method. Advantage of this method is the biocompatibility and biodegradability of synthesized materials. Biocompatability is useful in drug delivery of nanomaterials and biodegradability is environmentally useful. Whenever two immiscible liquids are mechanically agitated or stirred together, they are known to form what is called ‘emulsion’. The tendency of the liquids is such that the liquid is smaller quantity tries to form small droplets, coagulated droplets or layers so that they are all separated from the rest of the liquid (for example droplets of fat in milk). The droplet sizes in emulsion are usually larger than 100 nm upto even few millimeters. Emulsions are usually turbid in appearance. On the other hand, there is another class of immiscible liquids, known as microemulsions which are transparent and the droplets are in the range of ~1 to 100 nm. This is size needed for the synthesis of nanomaterials. Microemulsions are stabilized using surfactants (surface stabilized active agents). When an organic liquid or oil (O), water (W) and surfactant (T) are mixed together, under some critical concentration, ‘micelles’ or inverse micelles are formed, depending upon the concentration of water and organic liquid. Micelles are formed with excess water and inverse micelles are formed in excess of organic liquid or oil. The ratio of water, oil and surfactant is important to decide which type of micelle will be formed and can be represented in a ternary phase diagram, using a triangle. Composition can be determined by drawing lines parallel to all three sides of the triangle. A modified phase diagram known as ‘Winsor Diagram’ also can be constructed for finer details. The critical micelle concentration (CMC) depends upon all W, O and T concentrations. Effect of T is to reduce the surface tension of water dramatically below CMC and remain constant above it, as the organic solvent concentration is kept on increasing. There are four types of surfactants in general:

Cationic: eg. CTAB

Anionic: eg. R-SO3-Na+

Nonionic: R-(CH2-CH2-O)20-H

Amphoeric: eg. betaines.

A large number of nanoparticles of (metals, semiconductors and insulators) cobalt, copper, CaCO3, BaSO4, CdS, ZnSetc, have been synthesized using microemulsions or inverse micelles. Eg.synthesis of cobalt nanoparticles – A reverse miceller solution of water and oil can be stabilized using a monlayer of surfactant like sodium bis (2-ethylhexyl) sulfosuccinate or Na(AOT). The droplet diameter is controlled simply by controlling the amount of water. Two micellar solutions having same diameter of droplets can be formed. Thus one solution shuld have Co(AOT)2 i.e., cobalt bis (2-ethylhexyl) sulfosuccinate and the other should have sodium tetrahydroborate (NaBH4). When two solutions are mixed together the solution appears clear but the color changes from pink to black. One can find by electron microscopy analysis that cobalt nanoparticles are formed.

5.4.9 Other Chemical Methods: Several types of reducing agents can be used to produce nanoparticles such as NaBEt3H, LiBEt3H, and NaBH4 where Et denotes ethyl (-C2H5) radical. For example, nanoparticles of molybdenum (Mo) can be reduced in toluene solution with NaBEt3H at room temperature, providing a high yield of Mo nanoparticles having dimensions of 1-5 nm.

Nanoparticles of aluminum have been made by decomposing Me2EtNAlH3 in toluene and heating the solution to 105 C for 2 h (Me is methyl, -CH3). Titanium isopropoxide is added to the solution. The titanium acts as a catalyst for the reaction. The choice of catalyst determines the size of the particles produced. For instance, 80 nm particles have been made using titanium. A surfactant such as oleic acid can be added to the solution to coat the particles and prevent aggregation.

5.5Biological Methods

Synthesis of nanomaterials using biological ingredients can be roughly divided into following three types:

- use of microorganisms
- use of enzymes or plant extracts
- use of templates like DNA, membranes, viruses

5.5.1Synthesis using microorganisms: Microorganisms are capable of interacting with metals coming in contact with them through their cells and form nanoparticles. Different processes of metal-microorganism interactions are: (i) Some microorganisms produce hydrogen sulfide (H2S). It can oxidize organic matter forming sulphate, which in turn acts like an electron acceptor for metabolism. This H2S can, in presence of metal salt, convert metal ions into metal sulphide, which deposits extracellulary. (ii) In some cases, metal ions from a metal salt enter the cell. The metal ions are then converted into a nontoxic form and covered with proteins in order to protect the remainder of cell from toxic environment. (iii) certain microorganisms are capable of secreting some polymeric materials like polysaccharides. They have some phosphate, hydroxyl and carboxyl anionic groups which complex with metal ions and bind extracellularly (iv) cells are also capable of reacting with metals or ions by processes like oxidation, reduction, methylation, demethylation etc.

Examples:

- Pseudomonas stutzeri Ag259 bateria are found in silver mines and are capable of accumulating silver inside or outside of their cells walls. Using this fact these bacterial strains can be challenged with high concentration of silver salt like AgNO3. Numerous silver nanoparticles of different shapes can be produced having size <200 nm intracellularly.
- Low concentrations of metal ions (Au+, Ag+ etc.) can be converted to metal nanoparticles by Lactobacillus strain present in butter milk. By exposing the mixture of two different metal salts to bacteria, it is indeed possible to obtain alloys under certain conditions.
- Fusariumoxysporum challenged with gold or silver salt for approximately three days produces gold or silver particles extracellularly..ExtremophilicactinomyceteThermomonospora sp. produces gold nanoparticles extracellularly.
- When silver metal salt is treated with fungus Verticillium sp. the nanoparticles can be produced intracellularly. Changes in biomass colour from initial yellow to final brown, after exposure to silver salt, is a visual indication of silver nanoparticles formation. Particles can be recovered by washing with some suitable detergent or

ultrasonication. In a similar way, gold nanoparticles can be produced using Verticillium sp. However, the colour of biomass is from pink to blue depending upon the particle size.

- Semiconductor nanoparticles like CdS, ZnS, PbS etc. can be produced using different microbial routes. Desulfobacteriaceae can form 2-5 nm ZnS nanoparticles. Bacteria Klebsillapneumoniae can be used to synthesize CdS nanoparticles. When Cd(NO3)2 is mixed in a solution containing bacteria and solution is shaked for about one day at ~38 C, then the CdS nanoparticles in the size range ~5-200 nm can be formed. CdS nanoparticles with narrow size distribution can be synthesized using the yeasts like Candida glabrata and Schizosaccharomycespombe. Similarly it is possible to synthesize PbS by challenging Torulopsis sp. with lead salt like PbNO3.

5.5.2 Synthesis using plant extracts: It has been reported that live alfalfa plants are found to produce gold nanoparticles from solids. Leaves from geranium plant (pelargonium graveolens) have also been used to synthesize nanoparticles of gold. Nanoparticles obtained using Collectotrichum sp. Fungus related to geranium plant has a wide distribution of sizes and particles are mostly spherical. On the other hand, geranium leaves produce rod and disk shaped nanoparticles. Synthesis procedure to obtain gold nanoparticles form geranium plant extract is as follows: Finely crushed leaves are put in Erlenmeyer flask and boiled in water just for a minute. Leaves get ruptured and cells release intracellular material. Solution is cooled and decanted. This solution is added to HAuCl4 aqueous solution and nanoparticles of gold start forming within a minute.

5.5.3 Use of templates: DNA, S-layers or some membranes have long range periodic order in terms of some molecular groups of their constituents. Therefore on some periodic active sites preformed nanoparticles can be anchored. Alternatively, using certain protocols nanoparticles can be synthesized using DNA, membranes etc., as templates. Such ordered arrays are formed as a result of various interactions that take place between the templates and the particles.

Ferritin is a colloidal protein of nanosize. It stores iron in metabolic process and is abundant in animals. It is also capable of forming uniform three dimensional hierarchical architechture. There are 24 protein (peptides) subunits in a ferritin, which are arranged in such a way that they create a central cavity of ~6nm. Diameter of polypeptide shell is 12 nm. Ferritin can accommodate 4500 Fe atoms. They are in Fe3+ state as hydrated iron oxide mineral, ferrihydrite. The protein subunits are composed of light as well as heavy chains having dinuclearferroxidecentres. These centres are catalysts for in vitro oxidation of Fe2+ ions. The ferritin without inorganic matter in its cavity is known as apoferritin and can be used to entrap desired nanomaterial inside the protein cage. Therefore, first step is to remove iron from ferritin to form apoferritin and then introduce metal ions to form metal nanoparticles inside the cavity or carry out some controlled reaction with metal ions to make a compound inside the cavity. In any case, ions can be removed or introduced inside the ferritin, through some available channels.

Horse spleen ferritin, diluted with sodium acetate buffer, should be placed in dialysis bag. A solution of sodium acetate and thioglycolic acid is made in which dialysis bag is kept under nitrogen gas flow for 2-3hours. Solution needs to be replaced from time to time for total 4-5 hours. Further dialysis of apoferritin solution should be done against saline for one hour and in refreshed saline for ~15-20 hours. Apoferriting should then be mixed with solution having sodium chloride (NaCl) and N-tris (hydroxymethyl) methyl-2-aminoethanosuphonic acid (TES). Aqueous cadmium acetate is added to this solution and stirred continuously with constant N2 gas purging. Process of CdS formation is stepwise with Cd loading of 55 atoms per apoferritin colloid taking place in each step. Higher loading like 110, 165, 220 are possible. Due to remarkably constant size of ferritin colloids and apoferritin derived from them, it is possible to obtain nanoparticles of very uniform size. Besides CdS there ae several other examples like controlled iron oxide, manganese, uranyl oxide, cobalt, cobalt-platinum alloy etc., being synthesized inside ferritin. It is possible to fabricate ordered arrays of ferritin as well as of nanoparticles inside them.

DNA can be used for preformed charged nanoparticles can get bonded with phosphate group of DNA and even form organized arrays of nanoparticles. CdS (or other sulfide) nanoparticles can be synthesized using DNA. Organic molecules can cap the surfaces of nanoparticles growing in solutions. Similarly one can use DNA to bind with surface of growing nanoparticles. For example, double stranded Salmon sperm DNA can be sheared to an average size of 500 bp. Cadmium acetate can be added to desired medium like water, dimethylformamide, ethanol, propanol etc., and reaction carried out in a glass flask with facility to purge the solution and flow with an inert gas like nitrogen. Addition of DNA should be made and then Na2S can be added dropwise. Depending upon the concentrations of cadmium acetate, sodium chloride and DNA nanoparticles of CdS with size less than ~10 nm can be obtained. DNA probably bonds through its negatively charged phosphate group to positively charged (Cd+) nanoparticle surface.

5.6NANOFABRICATION

5.6.1 Introduction

One of the widely used method for the fabrication of nanostructures is lithography, which makes use of radiation-sensitive layer to form well-defined patterns on a surface. Current technologies for the fabrication of nanoscale structure are limited in terms of the minimum feature size that can be achieved. Natural macromolecules and the processes through which their highly controlled assembly is carried out have become a source of interest to create novel devices and materials.

5.6.2Strategies for nanoarchitecture

One approach to the preparation of nanostructure, called the *bottom-up approach*, is to collect, consolidate, and fashion individual atoms and molecules into the structure. This is carried out by a sequence of chemical reactions controlled by catalysts. It is a process that is widespread in biology where catalysts called enzymes assemble amino acids to construct living tissue that forms and supports the organs of the body. It is the process of self-assembly.

The opposite approach to the preparation of nanostructure is called the *top-down method*, which starts with large-scale object or pattern and gradually reduces its dimension or dimensions

. 5.6.3 **Lithography**

Conventional ‘Lithography’ is a top down approach. The word lithography has its origin in the Greek work ‘litho’ which means stone. Lithography therefore literally means carving a stone or writing on a stone. It is now used now to mean a process in which a sample is patterned by removing some part of it or sometimes even organizing some material on a suitable substrate. Lithography is extensively used in electronics industry so as to obtain integrated circuits (IC) or very large scale integration (VLSI) on small piece of semiconductor substrate often called a ‘chip’.

Different lithography techniques like optical lithography, x-ray lithography, electron beam lithography and some other have been developed. They depend upon using photons or particle radiations for carving the materials. The lithography technique involve transfer of some pre-designed geometrical pattern (called master or mask) on a semiconductor (silicon) or directly patterning (often known as writing) using suitable radiation. Mask is usually prepared by creating radiation opaque and transparent regions on glass or some other material. Pre-designed patterns can be transferred on a substrate much faster as compared to direct writing. Direct writing being a slower process is overall expensive.

Common principle in most of the lithographic technique is to expose a material sensitive to either electromagnetic radiation or to particles at some regions. Such a radiation sensitive material is known as resist. The selection of area is made using a mask, which is transparent is some regions and opaque in the other regions. This causes selective exposure of the resist, making it weaker or stronger compared to unexposed material depending upon the type of the resist being used. By removing the exposed or unexposed material in suitable chemicals or plasma, desired pattern is obtained.

Various steps involved in photolithography to transfer a pattern on some semiconductor surface: A thin film coating of a metal (like chromium) is deposited on a suitable substrate (for example glass or silicon). A positive or a negative photoresist, usually some polymer, is coated on metal thin film. Positive photoresist material has the property that when exposed to the appropriate radiation it degrades or some chemical bonds are broken. Negative resist on the other hand is a material, which hardens (crosslinks) on exposure to a radiation. A mask is placed between the resist coated substrate and the source of light. By using a suitable chemical (developer) the weakened portion is removed (or image is developed). Remaining unexposed part also can be removed by appropriate chemical treatment. The remaining material can be dissolved in one step and the hardened material in another step.

Depending upon the radiation used like visible light, X-rays, electrons, ions etc., the lithography name is tagged with it.

Nanolithography is the art and science of etching, writing, or printing at the microscopic level, where the dimensions of characters are on the order of nanometers (units of 10^{-9} meter, or millionths of a millimeter). This includes various methods of modifying semiconductor chips at the atomic level for the purpose of fabricating integrated circuits (ICs). Instruments used in nanolithography include the scanning probe microscope (SPM) and the atomic force microscope (ATM). The SPM allows surface viewing in fine detail without necessarily modifying it. Either the SPM or the ATM can be used to etch, write, or print on a surface in single-atom dimensions.

5.6.4 Lithography using photons

It is possible to use visible, ultraviolet, extreme ultraviolet (EUV) or X-rays to perform lithography. Highest resolution of the generated features ultimately depend upon the wavelength of radiation used and interaction of radiation with matter as well as mask and optical elements used. Smaller the wavelength used smaller can be feature size. Depth of focus depends upon the penetration of incident radiation. In the visible range glass lenses and masks can be used. In the UV range fused silica or calcium fluoride lenses are used.

There are three methods used to pattern a substrate viz., proximity, contact and projection. In proximity method, mask is held close to the photoresist coated metallized substrate, whereas in contact method the mask is in contact with photoresist. In both proximity and contact methods a parallel beam of light falls on the mask, which transmits the radiation through some windows but blocks through opaque parts. Although better resolution is achieved with contact method as compared to proximity method, in contact method the mask gets damaged faster. In case of projection method a focused beam is scanned through the mask, which allows good resolution to be achieved along with the reduced damage of the mask. However, scanning is a slow process and also requires scanning mechanism adding to the cost.

5.6.5 UVlight and Laser Beams: Using monochromatic light in the visible to UV range, features as small as 1 to 1.5 um size can be routinely obtained. Often g-line (436 nm) from mercury lamp is used. Laser beam of KrF (248 nm) or ArF (193 nm) also are employed reaching ~150 nm as the smallest feature size.

5.6.6 X-ray lithography: Smaller features are possible to obtain by employing X-rays also. However, it is difficult to make suitable masks for X-ray lithography. X-rays in the 0.1-5nm range are used with appropriate metal masks in proximite geometry. Absorption of X-rays in materials not only depends upon the thickness of the material but is also complicated by the presence of adsorption edges. Metal masks are fabricated in such a way that through thin portions they are transmitted and absorbed in thicker regions. Gold masks are often used.

X-ray lithography is a next generation lithography that has been developed for the semiconductor industry. Batches of microprocessors have already been produced. The short wavelengths of 0.8 nm X-rays overcome diffraction limits in the resolution of otherwise competitive optical lithography. The X-rays illuminate a mask placed in proximity to a resist-coated wafer. No lenses are used, and only rudimentary collimating mirrors. The X-rays are broadband, typically from a compact synchrotron radiation source, allowing rapid exposure. Deep X-ray lithography uses yet shorter wavelengths, about 0.1 nm with modified procedures, to fabricate deeper structures, sometimes three dimensional, with reduced resolution. The mask consists of an X-ray absorber, typically of gold or compounds of tantalum or tungsten, on a membrane that is transparent to X-rays, typically of silicon carbide or diamond. The pattern on the mask is written by direct write electron beam lithography onto a resist that is developed by conventional semiconductor processes. The membrane can be stretched for overlay accuracy.

Most X-ray lithography demonstrations have been performed by copying with image fidelity, i.e. without magnification, 1x, on the line of fuzzy contrast as illustrated in the figure. But with the increasing need for high resolution, X-ray lithography is now performed on the Sweet Spot, using local “demagnification by bias.” Dense structures are developed by multiple exposures with translation. Many advantages accrue from the application of 3x “demagnification": the mask is more easily fabricated; the mask to wafer gap is increased; and the contrast is higher. The technique is extensible to dense 15 nm prints. The resulting printing has high contrast. X-rays generate secondary electrons as in the cases of extreme ultraviolet lithography and electron beam lithography. While the fine pattern definition is due principally to secondaries from Auger electrons with a short path length, the primary electrons will sensitize the resist over a larger region than the X-ray exposure. While this does not affect the pattern pitch resolution (determined by wavelength and gap), the image exposure contrast $(max - min) / (max + min)$ is reduced since the pitch is on the order of the primary photo-electron range. Several prints at about 20 nm have been published. Another manifestation of the photoelectron effect is exposure to X-ray generated electrons from thick gold films used for making daughter masks. Simulations suggest that photoelectron generation from the gold substrate may affect dissolution rates.

5.6.7Lithography using particle beams

Optical lithography is an important manufacturing tool in the semiconductor industry. However, to fabricate semiconductor devices smaller than 100nm, ultraviolet light of short wavelengths (193 nm) is required, but this will not work because the materials are not transparent at these wavelengths. Electron beam and X-ray lithography can be used to make nanostructures, but these processes are not amenable to the high rate of production that is necessary for large-scale manufacturing. Electron-beam lithography uses a finely focused beam of electrons, which is scanned in a specific pattern over the surface of a material. It can produce a patterned structure on a surface having 10-nm resolution. Because it requires the beam to hit the surface point by point in a serial manner, it cannot produce structures at sufficiently high rates to be used in assembly-line manufacturing processes. X-ray lithography can produce pattern on surfaces having 20nm resolution, but its mask technology and exposure systems are complex and expensive for practical applications.

All the moving particles are associated with wavelength known as de Broglie wavelength. All kinds of particles can in principle be used. But to achieve high resolution wavelength should be as small as possible. Thus large mass and large velocity of particle makes is possible to get adequate resolution. In fact it is possible using neutral atoms, ions or electrons to bring down the particle associated wavelength to any desired value, even as small as 0.1 nm.

5.6.8 Electron Beam Lithography: It is very similar to a scanning electron microscope and requires vacuum. Sometimes SEM is modified in order to use it as a lithography set up. Electron beam lithography is a direct writing method i.e., no mask is required to generate a pattern. Rather, pattern or masters required for other lithography processes like optical lithography and soft lithography can be generated using electron beam lithography. Electrons with high energy (~5KeV) are incident on the photoresist. Here also positive or negative photoresists can be used. Common positive resists are polymethylmethacrylate (PMMA) and polybutane-1-sulphone (PBS). Negative resist often used in electron beam lithography is polyglycidylmethacrylatecoehylacrylate (COP). Developers used are methylisobutylkeone (MIBK) and isopropylalcohal (IPA) in 1:1 ratio. A focused electron beam in electron beam lithography is used in two modes viz., vector scan and raster scan. In vector scan the electron beam writes on some specified region. After one region is completed the X-Y scanning stage on which substrate to be patterned is mounted, moves. During its movement electron beam is put off. Then a new region is selected and written with the beam. This is continued until whole pattern is generated. In raster scan the beam is rastered or moved continuously over a small area, line by line. The X-Y stage of sample moves at right angles to the beam. The beam is turned off or turned on depending on the pattern. Although very high resolution (~50 nm) is routinely possible using this lithography, due to scanning mode it is rather slow.

The practice of using a beam of electrons to generate patterns on a surface is known as Electron beam lithography. The primary advantage of this technique is that it is one of the ways to beat the diffraction limit of light and make features in the sub-micrometre regime. Beam widths may be on the order of nanometers. This form of lithography has found wide usage in research, but has yet to become a standard technique in industry. The main reason for this is speed. The beam must be scanned across the surface to be patterned -- pattern generation is serial. This makes for very slow pattern generation compared with a parallel technique like photolithography (the current standard) in which the entire surface is patterned at once. As an example, to pattern a single layer of semiconductor containing 60 devices (each device consists of many layers) it would take an electron beam system approximately two hours; compared with less than two minutes for an optical system.

One caveat: While electron beam lithography is used directly in industry for writing features, the process is used mainly to generate exposure masks to be used with conventional photolithography. However, when it is more cost-effective to avoid the use of masks, e.g., low volume production or prototyping, electron-beam direct writing is also used.

For commercial applications, electron beam lithography is usually produced using dedicated beam writing systems that are very expensive. For research applications, it is very common to produce electron beam lithography using an electron microscope with a home-made or relatively low cost lithography accessory. Such systems have produced linewidths of ~20 nm since at least 1990, while current systems have produced linewidths on the order of 10 nm or smaller. These smallest features have generally been isolated features, as nested features exacerbate the proximity effect, whereby electrons from exposure of an adjacent feature spill over into the exposure of the currently written feature, effectively enlarging its image, and reducing its contrast, i.e., difference between maximum and minimum intensity. Hence, nested feature resolution is harder to control. For most resists, it is difficult to go below 25 nm lines and spaces, and a limit of 20 nm lines and spaces has been found.

With today's electron optics, electron beam widths can routinely go down to a few nm. This is limited mainly by aberrations and space charge. However, the practical resolution limit is determined not by the beam size but by forward scattering in the photoresist and secondary electron travel in the photoresist. The forward scattering can be decreased by using higher energy electrons or thinner photoresist, but the generation of secondary electrons is inevitable. The travel distance of secondary electrons is not a fundamentally derived physical value, but a statistical parameter often determined from many experiments or Monte Carlo simulations down to < 1 eV. This is necessary since the energy distribution of secondary electrons peaks well below 10 eV. Hence, the resolution limit is not usually cited as a well-fixed number as with an optical diffraction-limited system. Repeatability and control at the practical resolution limit often require considerations not related to image formation, e.g., photoresist development and intermolecular forces. In addition to secondary electrons, primary electrons from the incident beam with sufficient energy to penetrate the photoresist can be multiply scattered over large distances from underlying films and/or the substrate. This leads to exposure of areas at a significant distance from the desired exposure location. These electrons are called backscattered electrons and have the same effect as long-range flare in optical projection systems. A large enough dose of backscattered electrons can lead to complete removal of photoresist in the desired pattern area.

5.6.9 Ion Beam Lithography: Very small features (~5-10 nm) can be written using high-energy ion beams. Major advantage of using ion beams is that resists are more sensitive to ions as compared to electron and have low scattering in the resist as well as from the substrate. Commonly used ions are He+, Ga+ etc., with energy in the 100-300 KeV range.

5.6.10Neutral Beam Lithography: Neutral atoms like argon or cesium have been allowed to impinge on substrates to be patterned through the mask. Such beams cause less damage to the masks. Self assembled monolayers on gold substrate have been often patterned using neutral beams.

5.6.11 Scanning Probe Lithography

STM and AFM microscopes using sharp tips or probes for imaging can be used for lithography purpose. This has evolved scanning probe lithography (SPL). One major advantage is that like optical lithography it is also carried out in air. There are different ways in which SPL can be carried out viz., mechanical scratching or movement, optical, thermomechanical and electrical.

5.6.12Mechanical Lithography: In mechanical lithography there are different modes like scratching, pick up and pick down or dip pen lithography.

(i) Scratching: Pits or lines can be produced using either STM tip or AFM tip on surface of bulk material or surface of a thin film. Formation of pits or lines by scratching is like ploughing, in which scratched material is piled up around the indented region. Variety of materials like nickel, gold, copper, polymers, Langmuir Blogett films, high temperature superconductors are possible to scratch. Often diamond tips can be used. Pits as small as 30 nm diameter and 10 nm depth are possible to make.

(ii) Pick-up and Pick-down: Atoms are picked up one by one and arranged in desired pattern on a substrate. STM/AFM tips can be used to move atoms or molecules. Systematic work by IBM scientists made it possible for them to pile up xenon atoms on a metal substrate and write a letter patter IBM for the first time. Some scientists moved 30 nm GaAs particles on a GaAs substrate. Letter patterns as high as 50 nm in height were made using AFM tip. Now the technique is used to fabricate some circuits.

(iii) Dip-pen lithography: The method bears a similarity to writing on a piece of paper with ink. That is why the name dip pen lithography is given. An AFM tip is used as a pen and molecules are used as ink. Appropriate molecules picked up by the tip from the source of molecules can be transported and transferred at desired place on the substrate. Letters with line thickness as small as 15nm have been written. Overwriting and erasing capability of dip pen lithography is quite a unique feature.

Dip Pen Nanolithography (DPN) is a scanning probe lithography technique where an atomic force microscope tip is used to transfer molecules to a surface via a solvent meniscus. This technique allows surface patterning on scales of under 100 nanometres. DPN is the nanotechnology analog of the dip pen (also called the quill pen), where the tip of an atomic force microscope cantilever acts as a "pen," which is coated with a chemical compound or mixture acting as an "ink," and put in contact with a substrate, the "paper." DPN enables direct deposition of nanoscale materials onto a substrate in a flexible manner. The vehicle for deposition can include pyramidal scanning probe microscope tips, hollow tips, and even tips on thermally actuated cantilevers. Applications of this technology currently range through chemistry, materials science, and the life sciences, and include such work as ultra high density biological nanoarrays, additive photomask repair, and brand protection for pharmaceuticals. The technique was discovered in 1999 by a research group at Northwestern University led by Chad Mirkin. The company NanoInk, Inc. holds a patent on Dip Pen Nanolithography, and "DPN" and "Dip Pen Nanolithography" are trademarks or registered trademarks of NanoInk.

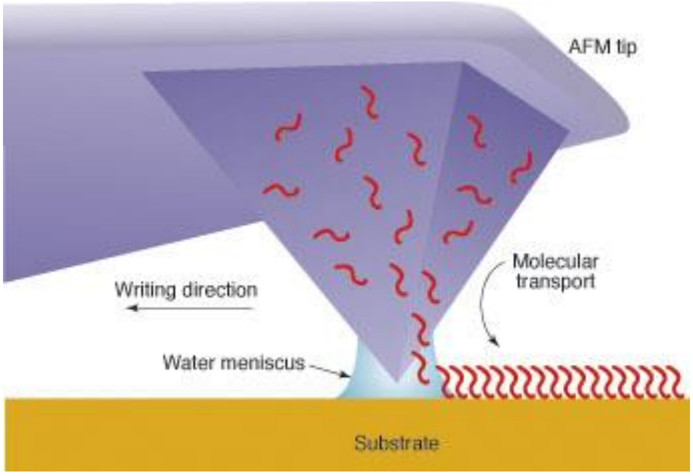


Fig.5.1 ATOMIC FORCE MICROSCOPE

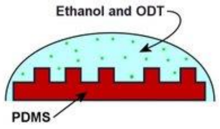
5.6.13Optical scanning probe lithography: Very high resolution ~20-50 nm is possible, overcoming the diffraction limit, with visible light using Scanning Near-Field Optical Microscope (SNOM). This is attributed to near-field component of electromagnetic radiation. In SNOM, a fine spot of light emerging through an aperture, scans on the surface within a distance of less than wavelength of light used for scanning. By placing the aperture close to the photoresist coated substrate, it is possible to obtain as small as ~50nm size features routinely.

5.6.14 Thermo-mechanical lithography: It is also possible to use an AFM tip along with a laser beam and carry out nanolithography. While the AFM tip is in contact with a coating like polymethylmethaacrylate (PMMA), laser beam strikes the same point of the coating. This heats the film locally enabling the tip to penetrate in the material and make a pit. This thermo-mechanical method is capable of producing resolution as high as ~30nm.

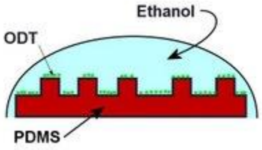
5.6.15Electrical Scanning Probe Lithography: In this method, a voltage is applied between the SPM tip and the sample. Above some critical voltage if large current flows between the tip and the sample, an irreversible change can occur in sample surface. Variety of bulk solid and think films surfaces has been patterned using this method. In silicon or modified silicon surface ~30 -60 nm wide and ~5-10 nm deep lines have been engraved.

5.6.16 Soft Lithography

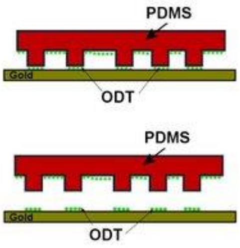
The name soft lithography is used to mean the techniques using materials like polymers, organic materials or self assembled films. It is a useful alternative to obtain resolution better than ~100nm at low cost. Moreover, the method is applicable from few nm to few um size features. In general, soft-lithography technique involves fabrication of a patterned master, molding of master and making replicas. A master is usually made using X-ray or electron beam lithography. It is supposed to be quite rigid. A mold is usually made using a polymer like polydimethylsiloxane (PDMS), epoxide, polyeurethane etc., PDMS is most common amongst the polymers used for molding due to its attractive properties like thermal stability (~150 C), optical transparency, flexibility (~160% elongation), capability of cross-linking using IR or UV radiation etc. However, during molding, some distortions can take place and adequate control has to be practiced to achieve reproducible and required results.



"Inking" a stamp. PDMS stamp with pattern is placed in Ethanol and ODT solution



ODT from the solution settles down onto the PDMS stamp. Stamp now has ODT attached to it which acts as the ink.



The PDMS stamp with the ODT is placed on the gold substrate. When the stamp is removed, the ODT in contact with the gold stays stuck to the gold. Thus the pattern from the stamp is transferred to the gold via the ODT "ink."

In technology, ***soft lithography*** refers to a set of methods for fabricating or replicating structures using "elastomeric stamps, molds, and conformable photomasks. It is called "soft" because it uses elastomeric materials. Soft lithography is generally used to construct features measured on the nanometer scale. ***Soft lithography*** includes the technologies of Micro Contact Printing (µCP), replica molding (REM), microtransfer molding (µTM), micromolding in capillaries (MIMIC) and solvent-assisted micromolding (SAMIM). One of the soft lithography procedures is as follows:

1. The steps of any of your favorite micro- or nano- scale lithography procedures (photolithography, EBL, etc.) are followed to etch a desired pattern onto a substrate (usually silicon)
2. Next, the stamp is created by pouring a degassed resin overtop of the etched wafer. Common resins include PDMS and Fluorosilicone.
3. Removing the cured resin from the substrate, a stamp contoured to your pattern is acquired.
4. The stamp is then "inked" by placing it, pattern-up, in a bath of inking solution (for example, ODT in ethanol) for a short period of time. The ink molecules will fall and

adhere to the surface of the stamp creating a single-molecule layer of the ink on the stamp.

5. The inked stamp is then pressed on the substrate and removed, leaving the desired single-molecule thick pattern on the substrate
6. Steps 4 and 5 are repeated for each substrate on which the pattern is desired

Advantages: Soft lithography has some unique advantages over other forms of lithography (such as photolithography and electron beam lithography). They include the following:

- Lower cost than traditional photolithography in mass production
- Well-suited for applications in biotechnology
- Well-suited for applications in plastic electronics
- Well-suited for applications involving large or nonplanar (nonflat) surfaces
- More pattern-transferring methods than traditional lithography techniques (more "ink" options)
- Does not need a photo-reactive surface to create a nanostructure
- Smaller details than photolithography in laboratory settings (~30nm vs ~100nm)

5.6.17 Nanoimprint lithography: It has been developed that may provide a low-cost, high-production rate manufacturing technology. Nanoimprint lithography patterns a resist by physically deforming the resist shape with a mold having a nanostructure pattern on it, rather than by modifying the resist surface by radiation, as in conventional lithography. A resist is a coating material that is sufficiently soft that an impression can be made on it by a harder material. A mold having a nanoscale structured pattern on it is pressed into a thin resist coating on a substrate, creating a contrast pattern in the resist. After the mold is lifted off, an etching process is used to remove the remaining resist material in the compressed regions. The resist is a thermoplastic polymer, which is a material that softens on heating. It is heated during the molding process to soften the polymer relative to the mold. The polymer is generally heated above its glass transition temperature, thereby allowing it to flow and conform to the mold pattern. The mold can be a metal, insulator or semiconductor fabricated by conventional lithography methods. Nanoimprint lithography can produce patterns on a surface having 10 nm resolution at low cost and high rates because it does not require the use of sophisticated radiation beam generating pattern for the production of each structure.

5.6.18Microcontact Printing (uCP): A PDMS stamp is dipped in an alanethiol solution and pressed against the metallized (Au, Ag, Cu) substrate. Those parts of substrate, which come in contact with the PDMS receive layers of alkanethiol. The monolayers do not spread on the substrate. Further, these self assembled monolayers can be used as resists for selective etching or deposition. The printing being simulateous, it is a fast method.

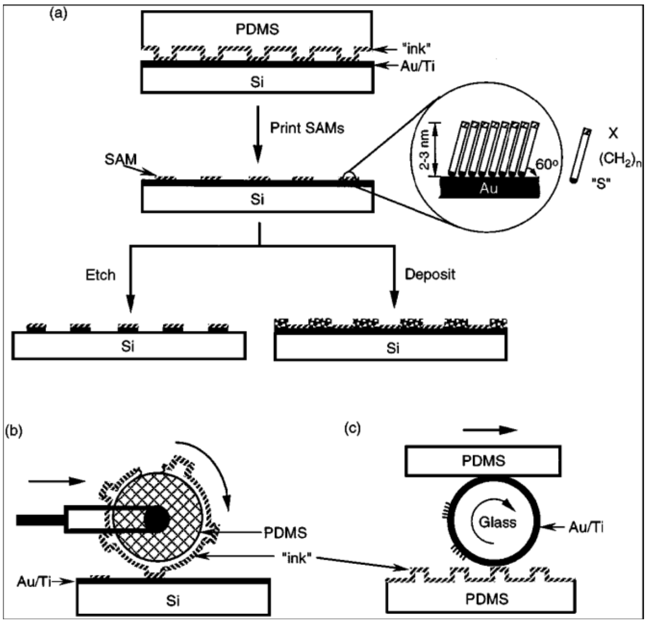


Fig.10 Schematic procedures for ^{1}uCP of hexadecanethiol (HDT) on the surface of gold: (*a*) printing on a planar surface with a planar stamp (*b*) printing on a planar surface over large areas with a rolling stamp, and (*c*) printing on a nonplanar surface with a planar stamp.

5.6.19 Relica Molding: In this method, a PDMS master or stamp is used to replicate a number o copies. For example a solution of polyurathene is poured in PDMS and cured using UV light or thermal treatment so that polyurathene becomes solid. PDMS can be easily removed so that a pattern opposite to that is produced in polyurathene. By applying small pressure on PDMS, it is possible to further reduce the size o the features smaller than in the original pattern. Nanostructure ~30 nm have been achieved using this method.

5.6.20Micro Transfer Molding (uTM): A preformed polymer is poured in PDMS stamp. Excess polymer is removed and the stamp is pressed against a substrate. Using thermal treatment polymer is imprinted on the substrate and mould is removed.

5.6.21Micromolding in Capilleries (MIMIC): In this technique, a PDMS stamp is placed on a substrate to be patterned. A low viscocity polymer is then placed in contact with PDMS. The liquid flows into channels of PDMS by capillary action. After thermal treatment of curing with UV radiation the polymer gets solidified. PDMS stamp is then removed to obtain the patterned substrate.

5.6.20 Solvent-Assisted Micromolding (SAMIM): A PDMS stamp coated with a solvent is pressed against the substrate coated with a polymer film. Solvent softens the polymer surface in contact. PDMS can be removed after the solvent has evaporated. PDMS stamp itself is not affected by the solvent. Volatile and substrate dissolving solvents, but not PDMS stamp dissolving, need to be used. Polymethylmethacrylate (PMMA), cellulose acetate, polyvinyl chloride etc., are used as polymers.

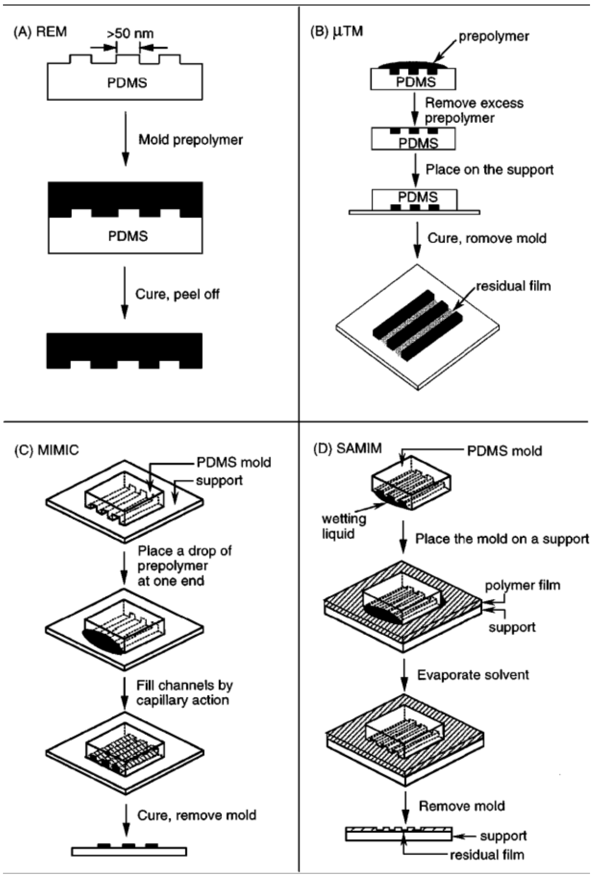


Fig.5.2 Schematic illustration of procedures for (*a*) replica molding (REM), (*b*) microtransfer molding (uTM), (*c*) micromolding in capillaries (MIMIC), and (*d*) solvent-assisted micromolding (SAMIM).

5.7 Self Assembly

The ‘bottom up’ approach of nanofabrication proposes to overcome the limitations of traditional ‘top down’ lithographic techniques by relying on the self-organization of molecular building blocks into higher order assemblies having a desired configuration. A variety of molecular building blocks with programmed non-covalent recognition sites have been designed and produced by organic synthesis. Nature has been working on nanoscale self-assembly. Consequently, today biological materials are used as building blocks for self-assembly applications. These biological materials include DNA nanostructures, small peptides, S-layer glycoproteins, viral proteins and even whole bacteriophages.

5.7.1Process of self-assembly: The spontaneous organization of small molecules into larger well-defined, stable, ordered molecular complexes or aggregates is known as self assembly. Self assembly takes place spontaneously by adsorption of atoms or molecules onto a substrate in a systematic, ordered manner. This process involves the use of weak, reversible interactions between parts of molecules without any central control, and the result is a configuration that is in equilibrium. The procedure is automatically error-checking, so faulty or improperly attached subunits can be replaced during the growth.

The traditional organic synthesis of very large molecules called macromolecules comprises a number of time-consuming steps that involve breaking and remaking strong covalent bonds, and these steps are carried out under kinetic control. They yields are small, and errors are not readily recognized or corrected. In contrast to this, self-assembly variety of synthesis makes use of weak, noncovalent bonding interactions such as those involving hydrogen bonds and van der Waals forces, which permit the reactions to proceed under thermodynamic control, with continual correction of errors. The initial individual molecules or subunits are usually small in size and number and easy to synthesize, and the final product is produced in a thermodynamically equilibrium state.

On one hand, fabrication methods in micro- and nanoscience allow for batch processing. That is, we have the ability to make many copies of the same device simultaneously. How do we design these devices so that they spontaneously assemble themselves into a useful working structure? On the other hand, traditional fabrication methods are limited in resolution. To make smaller structures, i.e., true nanoscale structures, requires the development of new methods. Taking their cue from nature, coaxing nanostructures into self assembling is an avenue many scientists are exploring. Ultimately, a deeper understanding of self assembly may shed light on the nature of life itself.

Assembly by capillary forces: G.M. White sides and his group at Harvard University have designed and studied various self assembling systems. Many of these are based on the so-called "capillary bond." This "bond" exploits two properties of objects in water. First, small objects resting on the surface of water attract one another. In this way, interacting particles feel a force of attraction. Second, when two hydrophobic surfaces come into contact they remain in contact. In other words, they bond. In their experiments Whitesideset. al. have used the polymer polydimethylsiloxane (PDMS) to fabricate their self assembling shapes. PDMS is naturally hydrophobic and its surface properties can be easily changed from hydrophobic to hydrophilic by treating with an oxygen plasma. In this way interacting particles with varying surface properties can be fabricated. Whitesideset. al. have designed planar systems that self assemble to tile the plane, tile the plane with gaps, and form chain-like structures.

Assembly by electrostatic forces: Assembly by capillary forces relies upon particle-particle interaction and interaction between particles and their enviornment. The particles have surface properties (hydrophobic or hydrophillic) and the enviornment is water.

Assembly by magnetic forces: simple to construct self assembling system involves magnets. In its simplest incarnation, the system is no more than a collection of disk shaped magnets randomly strewn about a inside a container. Here, simple shaking is enough to cause formation of a more highly ordered state

5.7.2Interactions governing self-assembly: Self organization and self-assembly are ubiquitous in nature, ranging from the simplest chemical reactions to the formation of living organisms. Self-assembly is synonymous for the spontaneous occurrence of order in a given open system. Any spontaneous process is irreversible and is accompanied by an increase in the combined entropy for both the system and its environment. The basic thermodynamic quantity, which dictates these processes at constant pressure, is system’s Gibbs free energy change.

$\Delta G=\Delta H-\Delta TS$, where ΔH and ΔS are the changes of enthalpy and entropy, respectively, after the reaction or self-assembly processes. For spontaneous process, ΔG must to be <0. One major contribution to ΔH comes from the potential attractive interactions. The forces that determine

ΔH include: van der Waals, hydrogen bonding, electrostatic, hydrophobic, and other non-bonding interactions. Entropy is related to quality of energy and order in any given system and is measured by the statistical probability. In the process of self-organization and self-assembly of the inorganic materials, major contributions to ΔG come from the system's enthalpy change, because entropy change is generally of less importance due to the limited freedom of inorganic compounds in condensed phase.

Self assembly is the organization of molecules or materials into order from disorder. Quantum mechanics determines the forces that organize the system on the nanometer scale. There are only four forces known in nature, these are the strong and weak forces existing in the nuclei, gravitational forces, and electromagnetic forces. Of these only the electromagnetic force will be relevant for the self-assembly. The chemical bonding interaction is one the strongest among all electromagnetic forces. Since self-assembly does not involve the breaking or the formation of chemical bonds, only non-bonding interactions are important. The non-bonding electromagnetic force is expressed in various forms e.g van der Waals forces, hydrogen bonding, electrostatic forces, magnetic interactions and others such as cation- and metal complexation interactions. In some cases, one type of interaction dominates, in others, several interactions may be of equal importance and these interactions may be cooperative instead of additive.

Van der Waals interaction is a weak short-range attractive force due to the temporary dipole-dipole moment interaction that results from electron movement surrounding the nuclei. It is non-discriminate and contributes to less than 2kcal/mol for each pair of interacting dipole moments. It is a high order interaction. Electrostatic interaction is Columbic in nature. Its interacting energy is inversely proportional to the distance between the charged particles. Electrostatic interaction is strong and constitutes one of the major forces. Temperature does not have a strong effect on electrostatic interactions. The hydrogen bonding interaction very unique interaction between hydrogen bond donors (e.g N-H, O-H) and acceptors (eg. N, O). Hydrogen bonding plays an important role in hydrophobic interactions and in molecular recognition of proteins because of its directionality. It was originally thought that hydrogen bonding interaction is mostly electrostatic in nature, but it is now generally accepted that the hydrogen bond consists of many different interactions, including Coulombic attraction, exchange repulsion, polarization and charge transfer and dispersion. The hydrogen bonding interaction contributes to about 2-20 kcal/mol to the total energy. If one or both of the donor and acceptor are charged, the interaction becomes much stronger. Hydrophobic interactions between the non-polar solutes in aqueous solution arises from the stronger attraction between the water-water molecules than between the solute-water molecules. Metal complexation is due mostly to a combination of electronic, electrostatic, charge transfer, van der Waals interactions and the polarization effect. In the case of complexation between transition metal ions and ligands, four or six coordinates is generally found.

5.7.3Examples of self-assembly: (i) Semicondutor islands: One type of self-assembly involves the preparation of semiconductor islands. It can be carried out by a technique called heteroepitaxy, which involves the placement or deposition of the material that forms the islands on a supporting substrate called a substrate made of a different material with a closely matched interface between them. It involves bringing atoms or molecules to the surface of the substrate where they do one of three things. They either are adsorbed and diffuse about on the surface until they join or nucleate with another adatom to form an island, attach themselves to or aggregate into an existing island, or desorb and thereby leave the surface. Small islands can continue to grow, migrate to other positions, or evaporate. There is critical size at which they become stable, and no longer experience much evaporation. Thus there is an initial nucleation stage when the number of islands increases with the coverage. This is followed by an aggregation stage when the number of islands levels off and the existing ones grow in size. Finally there is the coalescence stage when the main events that take place involve the merge of exisiting islands with each other to form larger clusters.

It is possible to spontaneously create quantum dots of Ge on Si, InAs on GaAs etc. The origin of self assembly is strain induced. For example germanium and silicon have only 4% lattice mismatch. Therefore Ge can be deposited epitaxially on Si single crystal upto 3-4 monolayers. This results into spontaneous formation of nanosized islands or quantum dots. However, temperature of substrate has to be >350 C during deposition or post deposition annealing is required. Size of the islands depends upon growth temperature as well as substrate plane on which it grows.

5.7.4 Monolayers: A model system that well illustrates the principles and advantages of the self-assembly process is a self-assembled monolayer. The Langmuir-Blodgett technique, had been widely used for the preparation and study of optical coatings, biosensors, ligand-stabilized Au clusters, antibodies and enzymes. It involves starting with clusters, forming them into monolayer at an air-water interface, and then transferring the monolayer to a substrate in the form of what is called a Langmuir-Blodgett film. Self assembled monolayers, are stronger, are easier to make, and make use of a wide variety of available starting materials.

Self-assembled monolayers and multilayers have been prepared on various metallic and inorganic substrates such as Ag, Au, Cu, Ge, Pt, Si, GaAs, SiO2, and other materials. This has been done with aid of bonding molecules or ligands such as alkanethiols RSH, sulfides RSR’, disulfides RSSR’, acids RCOOH, and siloxanes RSiOR3, where the symbols R and R’ designate organic molecule groups that bond to a thiol radical –SH or an acid radical –COOH. The binding to the surface for the thiols, sulfides, and disulfides is via the sulfur atom; that is, the entity RS-Au is formed on a gold substrate, and the binding for the acid is RCO2-(MO)n where MO denotes a metal oxide substrate ion, and the hydrogen atom H of the acid is released at the formation of the bond. The alkanethiols RSH are the most widely used ligands because of their greater solubility, their compatibility with many organic functional groups, and their speed of reaction. They spontaneously adsorb on the surface; hence the term self-assemble is applicable.

For self-assembled monolayers to be useful in commercial microstructures, they can be arranged in structured regions or pattern on the surface. An alkaenthio ‘ink’ can systematically form or write pattern on a gold surface with alkanethiolate. The monolayer-forming ‘ink’ can be applied to the surface by a process called microcontact printing, which utilizes an elastomer, which is a material with rubber like properties, as a ‘stamp’ to transfer the pattern. The process can be employed to produce think radiation-sensitive layers called resists for nanoscale lithography. The monolayers themselves can serve for a process called passivation by protecting the underlying surface from corrosion.

Self-assembled monolayer: Self assembled monolayers (SAMs) are surfaces consisting of a single layer of molecules on a substrate. Rather than having to use a technique such as chemical vapor deposition or molecular beam epitaxy to add molecules to a surface (often with poor control over the thickness of the molecular layer), self assembled monolayers can be prepared simply by adding a solution of the desired molecule onto the substrate surface and washing off the excess.

A common example is an alkane thiol on gold. Sulfur has particular affinity for gold, with a binding energy in the range of 20–35 kcal/mol (85–145 kJ/mol). An alkane with a thiol head group will stick to the gold surface and form an ordered assembly with the alkyl chains packing together due to van der Waals forces. For alkyl thiols on gold, the extended alkyl chains typically orient with an angle of ~30 degrees from the perpendicular of the substrate, and are assumed to be in a fully extended linear arrangement. There has been a great deal of work done determining the process by which alkyl thiol on gold assemblies are produced. It is generally thought that alkyl thiol molecules first bind to the gold surface in a 'lying down' position, where the alkyl chain tails of the molecules lie flat on the gold surface. The thiol interaction provides about 20–30 kcal/mol (85–130 kJ/mol) of driving force for the initial binding, which is modeled as a Langmuir binding isotherm. These binding events continue until the lying down molecules are dense enough on the surface to interact with each other. At some point the alkyl chains lift off the substrate and point outwards, tethered by the thiol anchor to the surface. There is a shift to a mixture of lying down molecules and island domains of upright alkyl chains, tilted at 30 degrees to the normal. At this stage binding kinetics become more complex and can no longer be modeled with a simple Langmuir binding isotherm. Over time the island domains merge and cover the bulk of the substrate, and the process can be compared to a 2-D crystallization process on a surface. Alkyl thiol SAMs exhibit grain boundaries and defects even after long periods of assembly. The initial stage of SAM formation usually takes minutes or less under the normal conditions of 0.1-10 mmol/L thiol concentration in a solvent. More ordering of the assembly can take place over days or months, depending on the molecules involved.

A variety of other self-assembled monolayers can be formed, although there is always debate about the degree to which systems self-assemble. Alkyl thiols are known to assemble on many metals, including silver, copper, palladium, and platinum. Alkyl silane molecules (e.g. octadecyltrichlorosilane) are another well-known example of self-assembly on silicon oxide surfaces and potentially be of greater technical relevance than alkyl thiol assembly on metals. Alkyl carboxylates are known to assemble on a variety of surfaces, such as aluminium and mica. Silicon has been used through the reaction of silicon hydride surface and a radical generator, such as heat, UV or radical initiator molecule, or with reagents such as Grignard and chlorosilanes. Once assembly has been accomplished, chemistry can be performed on the layer, especially if self-assembly places a reactive functional group on the outside of the monolayer.

SAMs have several applications in scientific research; they tend to have quite different chemical kinetics than the same molecules in another form, because of their exposed, 2-dimensional distribution, and as such are useful for some chemical and biochemical experiments. They can also be used for simulation of biological membranes and as substrates for cell culture. As technology develops to control the functional groups present in SAMS, either by direct deposition of molecules with those groups or by chemical modification of the layer, many other applications are also developing, for example in nanoscale fabrication of electronics.

5.7.5 Protein folding and aggregation: Protein folding is a typical example of self-assembly regulated by many subtle interacting forces. Protein folding is the process by which the polypeptide is folded into a functional three-dimensional protein structure based on the amino-acid sequence. When polypeptides are newly produced under physiological conditions, their folding is based on the interacting forces and the laws of thermodynamics. However, in some cases, molecular chaperones have to be employed to assist protein folding to prevent incorrect interactions within and between non-native polypeptides.

Molecular recognition means that there is specific interaction between protein and ligand, or between antibody and antigen. As was observed experimentally, topography (conformational match seems to play an essential role in protein-ligand recognition. Because hydrophobic and van der Waals interactions are not specific; they cannot alone be responsible for molecular recognition. Directional hydrogen bonding and electrostatic interactions play an important role.

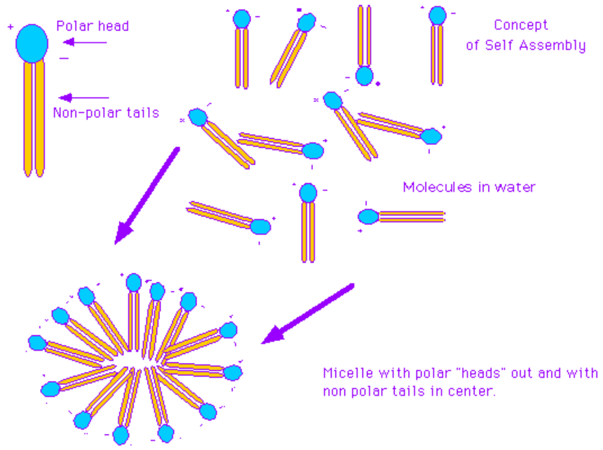


Fig.5.3 PROTEIN FOLDING AGGREGATION

Hydrophobic and hydrophilic interactions are important because many molecules in biology such as proteins and the molecules that make up the cell membrane have hydrophilic and hydrophobic regions on the same molecule. When put in water these molecules automatically organize themselves into more complex and biologically useful structures. This process is termed self assembly. It is illustrated in the diagram for a molecule with a polar head and a non polar tail.

5.7.6Applications: (i) Self assembly using biological templates: There are many examples of self assembly at biological templates like S-layers, proteins, DNA, lipids etc. When organized arrays of inorganic crystals are embedded in biological systems they are often referred to as biomineralized systems.

Mangetotactic bacteria are small bacteria, ~35 to 120 nm sized permanent magnets are present inside them. The magnets are of either iron sulphide (Fe3S4-gregite) or iron oxide (Fe3O4 – magnetite). Such magnetic particles make a chain of nanomagnets. It is useful for navigation of bacteria. Earth's magnetic field has a dip in the north and south hemisphere which helps bacteria to seek direction.

Another example of self-assembly in biological systems is S-layers. They are part of cell envelope of prokaryotic organisms. They are two dimension, crystalline single proteins or glycoprotein monomers organized in hexagonal, oblique or square lattices. These lattices have ordered pores. The periodicity of pores can vary, depending upon the protein, from 3-35 nm. Such S-layers after extraction from bacterial cells have been transferred on some metallic substrates (or grids). When treated with cadmium salt and subsequently with Na2S, ordered arrays of CdS nanoparticles could be formed. S-layers have been used to assemble Au, Pt, Fe, Ni etc., metal nanoparticles. In general, S-layers extracted from the biological cells can be directly used to deposit nanoparticles from liquid phase.

Ferritins are protein colloids of 12 nm size found in all animals. Ferritins have a cavities ~6-8 nm in size filled with iron oxide. It is possible to remove iron oxide and replace it with metal or other nanoparticle. Further it is possible to make a two dimensional array of ferritins in solution. For example, ferritin solution in NaCl and phosphate at ~5.8 pH can be filled in a trough. Chloroform containing dichloroacetic acid can be used to dissolve poly-1-benzal-L-histidine (PBLH) and spread over ferritin solution in trough. After about two hours the solution can be heated at 38 C for one hour and cooled back to room temperature. This produces ordered layer of ferritin at liquid-air interface. The layer can be transferred on silicon substrate by dipping in the solution.

DNA is a long helical molecule. It has large aspect ratio and acts like a long one dimensional template in its simplest form. Its four nucleotide bases viz., guanine, cytosine, adenine, and thymine can form a rich variety of sequences and structures. Thus, cirucular, square, branched etc. long or short DNA templates are possible. Besides planar geometry, they can adopt even three dimensional structures. As DNA has alternate sugar and phosphate groups on its strands, it is possible to anchor metal, semiconductor or oxide particles by different bonding on DNA to have assembly of particles.

5.7.7 Self assembly using organic molecules: Preformed inorganic nanoparticles can be assembled on solid substrates through some organic molecules adsorbed on their surfaces. CdS nanoparticles functionalized with carboxylic group can be transferred to aluminium thin films. Dithiols adsorbed on metals surface also could adsorb CdS nanoparticles to form layers of them. Silver particles have been adsorbed on oxidized aluminium layers using bifunctional molecule such as 4-carboxythiophenol. These molecules bind to aluminium oxide layer by carboxylic group and thiol attaches to silver particles.

Using a two phase reaction alkanethiol or alkylamine capped gold, silver and palladium nanoparticles have been self assembled. Here chemical reaction takes place in an aqueous medium. The particles are then transferred into an organic solvent. Solvent is allowed to evaporate which leaves self-assembled layer.

Using Langmuir Blodgett technique it is possible to transfer organic layers along with the attached nanoparticles in liquid subphase to form ordered monolayer or multiple layers on solid substrate. It is possible to order different bilayers of nanoparticles by simply dipping the same substrate alternately in different baths.

5.7.8 Others

(a) Sputtering (a bottom-up approach): One method used to make thin layers of material that are only a few atoms thick is called "sputtering." Sputtering involves transferring atoms from a block of source metal over to a surface waiting to be coated. The atoms are knocked loose from the source metal by bombarding them with other high-energy particles. The common aproachtaken when explaining sputtering is to imagine billiard balls being struck by the cue ball. The cue ball is rather like the hihg-energy incident particle. As it strikes a bunch of billiard balls (atoms in a block of source metal) they scatter from one another. This is where the analogy breaks down, though, as there is no second surface that the billiard balls attach to besides the pool table. In sputtering, however, the loose atoms are free to deposit on some material that needs to be coated.

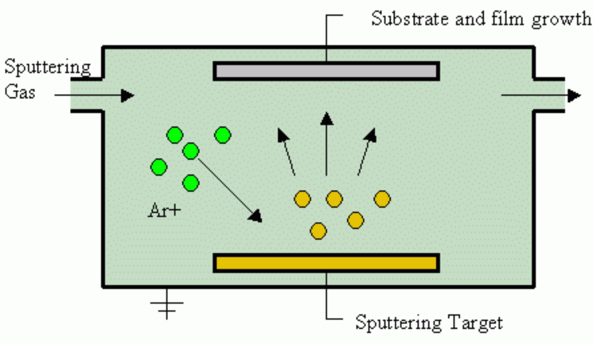


Fig.5.4 SPUTTERING-BOTTOM TO TOP APPROACH

5.7.9*Nanoscale Crystal Growth (a bottom-up approach):* Just like it sounds, this method involves rather tricky selection of seed crystals and growing conditions with the hopes of creating crystals that have unusual shapes. Nanowires, which happen to exhibit tremendous conductivity, are typically created in this way.

5.7.10Focused ion beam: Focused ion beam, also known as FIB, is a scientific instrument that resembles a scanning electron microscope. However, whereas the SEM uses a focused beam of electrons to image the sample in the chamber, a FIB instead uses a focused beam of gallium ions. Gallium is chosen because it is easy to build a gallium liquid metal ion source (LMIS). In a Gallium LMIS, gallium metal is placed in contact with a tungsten needle and heated. Gallium wets the tungsten, and a huge electric field (greater than 10^8 volts per centimeter) causes ionization and field emission of the gallium atoms. These ions are then accelerated to an energy of 5-50 keV (kiloelectronvolts), and then focused onto the sample by electrostatic lenses. A modern FIB can deliver tens of nanoamps of current to a sample, or can image the sample with a spot size on the order of a few nanometers.

Unlike an electron microscope, the FIB is inherently destructive to the specimen. When the high-energy gallium ions strike the sample, they will sputter atoms from the surface. Gallium atoms will also be implanted into the top few nanometers of the surface, and the surface will be made amorphous. Because of the sputtering capability, the FIB is used as a micro-machining tool, to modify or machine materials at the micro- and nanoscale. A FIB can also be used to deposit material via ion beam induced deposition. FIB-assisted chemical vapor deposition occurs when a gas, such as tungsten carbonyl ($W(CO)_6$) is introduced to the vacuum chamber and allowed to chemisorb onto the sample. By scanning an area with the beam, the precursor gas will be decomposed into volatile and non-volatile components; the non-volatile component, such as tungsten, remains on the surface as a deposition. This is useful, as the deposited metal can be used as a sacrificial layer, to protect the underlying sample from the destructive sputtering of the beam. Other materials such as platinum can also be deposited.

FIB is often used in the semiconductor industry to patch or modify an existing semiconductor device. For example, in an integrated circuit, the gallium beam could be used to cut unwanted electrical connections, or to deposit conductive material in order to make a connection. The FIB is also commonly used to prepare samples for the transmission electron microscope. The TEM requires very thin samples, typically ~100 nanometers. Other techniques, such as ion milling or electropolishing can be used to prepare such thin samples. However, the nanometer-scale resolution of the FIB allows the exact thin region to be chosen. This is vital, for example, in integrated circuit failure analysis. If a particular transistor out of several million on a chip is bad, the only tool capable of preparing an electron microscope sample of that single transistor is the FIB. The drawback to FIB sample preparation is the above-mentioned surface damage and implantation. However, this is usually only noticeable in high-resolution "lattice imaging" TEM. By lightly ion-milling the sample after completing the FIB preparation, much of this damage can be removed. In short, the FIB is a useful and versatile tool in the materials sciences and semiconductor fields.

5.8 NANOMATERIALS IN HUMANS: Exposure of environment and humans

Exposure of nanomaterials to workers, consumers, and the environment seems inevitable with the increasing production volumes and the increasing number of commercially available products containing nanomaterials or based on nanotechnology exposure is a key element in risk assessment of nanomaterials since it is a precondition for the potential toxicological and ecotoxicological effects to take place. If there is no exposure – there is no risk. Nanoparticles are already being used in various products and the exposure can happen through multiple routes.

Human routes of exposure are:

- Dermal (for instance through the use of cosmetics containing nanoparticles);
- Inhalation (of nanoparticles for instance in the workpiece);
- Ingestion (for instance food products containing nanoparticles);
- And injection (for instance medicine based on nanotechnology).

5.8.1Hazard Identification

In order to complete a hazard identification of nanomaterials, the following is ideally required.

- ecotoxicological studies
- Data about toxic effects
- Information on physical – chemical properties
    - Solubility

  - Sorption
- Biodegrability
- Accumulation

And all likely depending on the specific size and detailed composition of the nanoparticles.

In addition to the physical – chemical properties normally considered in relation to chemical substances, the physical chemical properties of nanomateials is dependent on a number of additional factors such as size structure, shape, and surface area. Opinions on, which of these factors are important differ among scientists, and the identification of key properties is a key gap of our current knowledge.

There is little doubt that the physical – chemical properties normally required when doing a hazard identification of chemical substances are not representative for nanomaterials, however there is at current no alternative methods. In the following key issues in regards to determining the destiny and distribution of nanoparticles in the environment will be discussed, however the focus will primarily be on fullerenes such as C60.

5.8.2Interaction in the environment

Nanoparticles can be used to enhance the bioavailability of other chemical substances so that they are easily degradable or harmful substances can be transported to vulnerable ecosystems.

Besides the toxicity of the nanoparticeles itself, it is furthermore unclear whether nanoparticles increases the bioavailability or toxicity of other xenobiotics in the environment or other substances in the human body. Nanoparticles such as C60 have many potential uses in for instance in medicine because of their ability to transport drugs to parts of the body which are normally hard to reach. However, this property is exactly what also may be the source to adverse toxic effects. Furthermore research is being done into the application of nanoparticles or spreading of contaminants already in the environment. This is being pursued in order to increase the bioavailability for degradation of microorganism, however it may also lead to increase uptake and increased toxicity of contaminants in plants and animals, but to the best of our knowledge, no scientific information is available that supports this.

5.8.3Conclusion

It is still too early to determine whether nanomaterials or nanoparticles are harmful or not however the effects observed lately have made many public and governmental institutions aware of the lack of knowledge concerning the properties of nanoparticles the urgent need for a systematic evaluation of the potential adverse effect of Nanotechnology. Furthermore, some guidance is needed as to which precautionary measures are warranted in order to encourage the development of “green nanotechnologies” and other future innovative technologies, while at the same time minimizing the potential for negative surprises in the form of adverse effects on human health and/or the environment, it is important to understand that there are many different nanomaterials and that the risk they pose will differ substantially depending on their properties. At the moment it is not possible to identify which properties or combination of properties make some nanomaterials harmful and which make them harmless, and property it will depend on the nanomaterial is question. This makes it is extremely difficult to do risk assessments and life-cycle assessment of nanomaterials because, in theory, you would have to do a risk assessment for each of the specific variation of nanomaterials – a daunting task!

5.9Nanotoxicology

Nanotoxicology is the study of the toxicity of nanomaterials. Because of quanum size effects and large surface area to volume ratio, nanomaterials have unique properties compared with their larger counterparts.

Nanotoxicology is a branch of bionanoscience which deals with the study and application of toxicity of nanomaterials.

Nanomaterials, even when made of inert elements like gold, become highly active at nanometer dimensions.

Nanotoxicological studies are intended to determine whether and to what extent these properties may pose a threat to the environment and to human beings. For instance, diesel nanoparticles have been found to damage the cardiovascular system in a mouse model.

Nanotoxicology is a sub-speciality of particle toxicology. It addresses the toxicology of nanoparticles (particles <100 nm diameter) which appear to have toxicity effects that are unusual and not seen with larger particles. Nanoparticles can be divided into combustion-derived nanoparticles (like diesel soot), manufactured nanoparticles like carbon nanotubes and naturally occurring nanoparticles from volcanic eruptions, atmospheric chemistry etc.

Typical nanoparticles that have been studied are titanium dioxide, alumina, zinc oxide, carbon black, and carbon nanotubes, and "nano-nC60". Nanoparticles have much larger surface area to unit mass ratios which in some cases may lead to greater pro-inflammatory effects (in, for example lung tissue). In addition, some nanoparticles seem to be able to translocate from their site of deposition to distant sites such as the blood and the brain. This has resulted in a sea-change in how particle toxicology is viewed – instead of being confined to the lungs, nanoparticle toxicologists study the brain, blood, liver, skin and gut.

5.9.1Toxicity of QDs

There are different opinions about the toxicity of QDs; therefore, we investigated their toxicity in amoeba as primary eukaryotes, in plant, and in animal.

5.9.2 In amoeba

It has been determined that QD labeling had no detectable effect on cell growth and had no deleterious effects on cellular signaling and motility during development of the Dictyosteliumdiscoideum cells.

5.9.3in plant

The ratio of reduced glutathione levels (GSH) relative to the oxidized glutathione (GSSG) in plants suggests that QDs caused oxidative stress on the plant at this condition.

5.9.4 In animal

Yan et al. investigated the potential vascular endothelial toxicity of mercaptosuccinic acid (2-sulfanylbutanedioic acid) – capped QDs in vitro.

Their results suggested that QDs could not only impair mitochondria but also exert endothelial toxicity through activation of mitochondrial death pathway and induction of endothelial apoptosis.

More recently, Chen et al. have studied the cytotoxicity of CdTe/CDs (core-shell) structured and also CdTe/CDs/ZnS (core-shell-shell) structured aqueous synthesized QDs, and their results suggest that the cytotoxicity of CdTe QDs not only comes from the release of Cd^{2+} ions but also intracellular distribution of QDs in cells and the associated nanoscale effects.

5.9.5Metal nano particles

Nanomaterials are consistently being released into the environmental via spillages, wear washing and disposal at a rate proportional to their level of use. We don't know where the go or what happens to them after they are released: they may accumulate on land or water and enter the food chain via plants and aquatic life, where they could exist harmlessly or react. They might enter the human body: routes include inhalation, ingestion or even possibly through our skin.

It has been suggested that once inside the body, the smallness of nanomaterials allows them to easily could allow them to penetrate living cells, where they can amass, disrupt cell activity or corrupt genes. They can also bypass the visual transportation channels, cross the blood-brain barrier.

5.9.6Lungs

There has been much interest in the health effects of airborne particles, specifically PM10 (thoracic fraction).

PM2.5 (respirable fraction), PM1, and ultrafine particles (PM0.1), which are = 10, 2.5, 1, and 0.1 µm (100 nm), respectively. One to 5 nm air suspended ENMs that enter the lungs are not predicted to reach the alveoli; instead a high percentage is likely to deposit in the mucus – lined upper airways (tracheobronchial region) due to their strong diffusion properties. On the other hand -45% of 10 nm, - 50% of 20 nm, and – 25% of 100 nm ENMs deposit in the alveoli. Deposition is greater during exercises. Chronic obstructive pulmonary and decreases alveolar particle deposition.

5.9.7 Nasal cavity

Uptake from the nasal cavity into the olfactory nerve, followed by retrograde axonal transport to the olfactory bulb and beyond, was shown in studies of the polio virus (30 nm) and colloidal silver coated gold (50 nm). Uptake of -35 nm 13C particles along the olfactory pathway to the olfactory bulb, and to a lesser extent into the cerebrum and cerebellum, was shown 1 to 7 days later. Exposure to ~30 nm agglomerates of Mn by inhalation resulted in upto a 3.5 fold increase of Mn in the olfactory bulb, and lower (but significant) increases in 4 rat brain regions. The increase of Mn in brain regions other than the olfactory bulb may have resulted from translocation to the brain by route(s) other than via the olfactory nerve, such as through cerebrospinal fluid or across the blood-brain barrier. The nasal cavity is the only site where the nervous system is exposed directly to the environment. This is an often overlooked potential route of small amounts of ENMs into the brain.

5.9.8 Dermal exposure

Skin is composed of 4 primary layers, the outermost epidermis (which contains the stratum corneum, stratum granulosum and stratum spinosum), dermis, and hypodermis. The hair follicle is an invagination of the stratum comeum, lined by a horny layer (acroinfundibulum). Dermal uptake routes are intercellular, intracellular, and follicular penetration. Uptake is primarily by diffusion. Materials that diffuse through the lipid-rich intercellular space of the stratum comeum typically have a low molecular weight (< 500 Da) and are lipophilic.

Materials that penetrate to the stratum corneum into the stratum granulosum can induce the resident keratinocytes to release proinflammatory cytokines. Materials that penetrate to the stratum spinosum, which contains langerhands cells (dendritic cells of the immune system), can initiate an immunological response.

This is mediated by the Langerhans cells, which can become antigen-presenting cells and can interact with T-cells. Once materials reach the stratum granulosum or stratum spinosum there is little barrier to absorption into the circulatory and lymphatic systems. Whereas dry powder ENMs pose a greater risk for inhalation exposure than those in liquids, liquid dispersed ENMs present a greater risk for dermal exposure.

Consumer materials most relevant to dermal exposure include quntum dots, titania, and zinc oxide in sunscreens, and silver as an anti-microbial agent in clothing and other products. Prolonged dermal application of microfinetitania sunscreen suggested penetration into the epidermis and dermis. However, subsequent studies did not verify penetration of titania from sunscreens into epidermis or dermis of human, porcine or psoriatic skin or find evidence of skin penetration of zinc oxide from sunscreen or positively or negatively – changed iron containing ENMs. Nanoparticles with dye penetrated deeper into hair follicles of massaged porcine skin in vitro and persisted thirty nm carbodylated quantum dots applied to the skin of mice were localized in the folds and defects in the stratum corneum and hair follicles. A small amount penetrated as deep as the dermis. Ultraviolet radiation increased penetration, raising concern that these results might generalize and enter the central nervous system. The high surface area and surface activity of nanomaterials means they may have amplified effects tests on human cells grown in laboratories have shown immune reactions and inflammations in lung tissue. However, it is important to remember that many of these dangers are still speculative, man made nanoparticles are relatively simple, and existing materials are not considered to have the complexity of systems like viruses that themselves struggle to enter and corrupt cells, and are of a similar size to nanomaterials. There is only one way to find out whether these risks are realistic or speculative at normal nanomaterial concentrations – testing. But this is rather difficult.

5.9.9Problems with Testing

Toxicity is not only idiosyncratic to the chemical composition and structure of each nanomaterial, but is also dependent upon other factors in particular, shape and solubility. Shape may affect interactions with binding sites on enzymes, and sphercity or regularity may affect surface reactivity and mobility.

Surface charge fundamentally changes reactivity negatively charged membranes interact with positively charged particles, but not negative ones. Even size matters. After all, a 100 nm diameter particles is one million times bigger (in volume) than a 1 nm diameter particles – and even across the nanosclae, transitions may occur between fundamental properties.

Whether the tests are carried out n plants, cells, or organisms can also affect the conclusions of testing, as can the materials used during nanomaterial synthesis to direct the nano size and shape since most of these are toxic themselves and might contaminate products. These factors all depend on the experimental conditions under which the nanomaterial was synthesized and tested, making comparison between research groups almost impossible.

For the toxicity of nanomaterials to be meaningful, they need to be compared with the toxicity of the bulk material, but not all materials can exist when the same chemical structure for nano and bulk types. Even if they do, we can't be sure nanomaterials retain their dimensions under testing they might form chains, aggregate lumps, or break down into smaller nanoparticles. Without accounting for these variations, we can't be sure how the "nano" factor affects toxicity, and whether nanomaterials pose us any risk. This is wahy no regulatory guidelines exist, and why nanomaterials are so freely used. But precisely because they are being freely used, we really need to know the answers.

5.9.10Metal oxide nanomaterials

The knowledge on potential harmful effects of metallic nanomaterials lags behind their increased use in consumer products and therefore, the safety data on various nanomaterials applicable for risk assessment are urgently needed. In this study, 11 metal oxide nanoparticles (MeOx NPs) prepared using flame pyrolysis method were analysed for their toxicity nanoscale sunscreens. PEG-coated ~37 nm quantum dots accumulated in the lymphatic duct system after intra-dermal injection in mice. Cadmium, determined by ICP-MS, from cadmium-containing quantum dots was seen in liver, spleen, and heart, however, it is uncertain if this was from cadmium or translocation of the quantum dots because methods were not used to show the presence of quantum dots. The above results suggest topically applied ENMs that penetrate to the dermis might enter the lymphatic system, and the ENMs or dissolved components distribute systematically. To address these concerns ENMs intended for dermal application such as titania, are often surface coated, eg. With silica, alumina, or manganese. One goal of the surface treatment is to minimize toxicity by trapping the free radicals of reactive oxygen species (ROS).

An in vitro study showed that mechanical stretching of human skin increased penetration of 500 and 100 nm fluorescent dextran particles through the stratum corneum, with some distribution into the epidermis and dermis. Similarly, mechanical flexing increased penetration of a 3-5 nm phenylalanine based C60 amino acid ENM through porcine skin in vitro. The contribution of skin flexing and immune system response was further addressed wit three titania formulations applied to minipigs. There was some ENM penetration into epidermis and abdominal and neck dermis, but no elevation of titanium in lymph nodes or liver. Topical exposure of mice to SWCNTs resulted in oxidative stress in the skin and skin thickening, demonstrating the potential for toxicity not revealed by in vitro studies of ENM skin penetration. There are no reports of long-term studies with topical ENM exposure.

In the absence of organic solvents, the above suggests that topically applied ENMs do not penetrate normal skin. Not surprisingly, organic solvents (chloroform >coclohexane> toluene) increased penetration of fullerene into skin that had the stratum corneum removed by tape stripping. As the fullernes were not detected in systemic circulation, there was no evidence of systemic absorption.

5.9.11 Oral exposure

Little is known about the bioavailability of ENMs from the buccal cavity or the sub-lingual site, or possible adverse effects from oral ingestion.

Particle absorption from the intestine results from diffusion though the mucus layer, initial contact with enterocytes or M (microfold or membranous specialized phatocytic enterocyte) cells, cellular trafficking, and post-translocation events . Colloidal bismuth subcitrate particles (4.5 nm at neutral pH) rapidly penetrated the mucosa of dyspeptic humans, resulting in bismuth in the blood. Particles appeared to penetrate only in regions of gastric epithelial disruption. Greater uptake of 50 to 60 nm polysterene particles was seen through Peyer's patches and enterocytes in the villous region of the GI tract than in non-lymphoid tissue, although the latter has a much larger intestinal surface area. Peyer's patches are one element of gut-associated lymphoid tissue, which consist of M cells and epithelial cells with a reduced number of goblet cells, resulting in lower mucin production. It was estimated that ~7% of 50 nm and 4% of 100 – nm polysterene ENMs were absorbed.

Fifty nm polystyrene ENMs fed to rats for 10 days by gavage showed 34% absorption, of which about 75% was in the liver, spleen, blood and bone marrow, no ENMs were seen in heart or lung. After oral administration of 50 nm fluorescence – labeled polystyrene ENMs, 18% of the dose appeared in the bile within 24 h and 9% was seen in the blood at 24h, none was observed in urine. The mechanism of GI uptake of 4, 10, 28 or 58 nm colloidal (maltodextran) gold ENMs from the drinking water of mice was shown to be penetration through gaps created by enterocytes that had died and were being extruded from the villus. Gold abundance in peripheral organs inversely correlated with particle size.

In summary, there appears to be significant absorption of some ENMs from the GI tract, with absorption inversely related to ENM size. The absorption site seems to be regions of compromised gastric epithelial integrity and low mucin content.

5.9.12Ocular and mucous membrane exposure

Ocular exposure might occur from ENMs that are airborne, intentionality placed near the eye (e.g. cosmetics), accidently splashed onto the eye, or by transfer from the hands during rubbing of the eyes, which was shown to occur in 37% of 124 adults every hour. This route of exposure could result in ENM uptake through the cornea into the eye or drainage from the eye socket into the nasal cavity through the nasolacrimal duct. Other than a study that found uptake of a polymer ENM into conjuctival and corneal cells, this route has been largely ignored in research studies of ENM exposure.

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