Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

CHAPTER-2- Unit:1- MICROENCAPSULATION

SYLLABUS:

Microencapsulation:

- ✓ **Definition,**
- ✓ **Advantages and disadvantages,**
- ✓ **Microspheres/microcapsules,**
- ✓ **Microparticles,**
- ✓ **Methods of microencapsulation, applications**

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

Upon completion of the course the student shall be able to

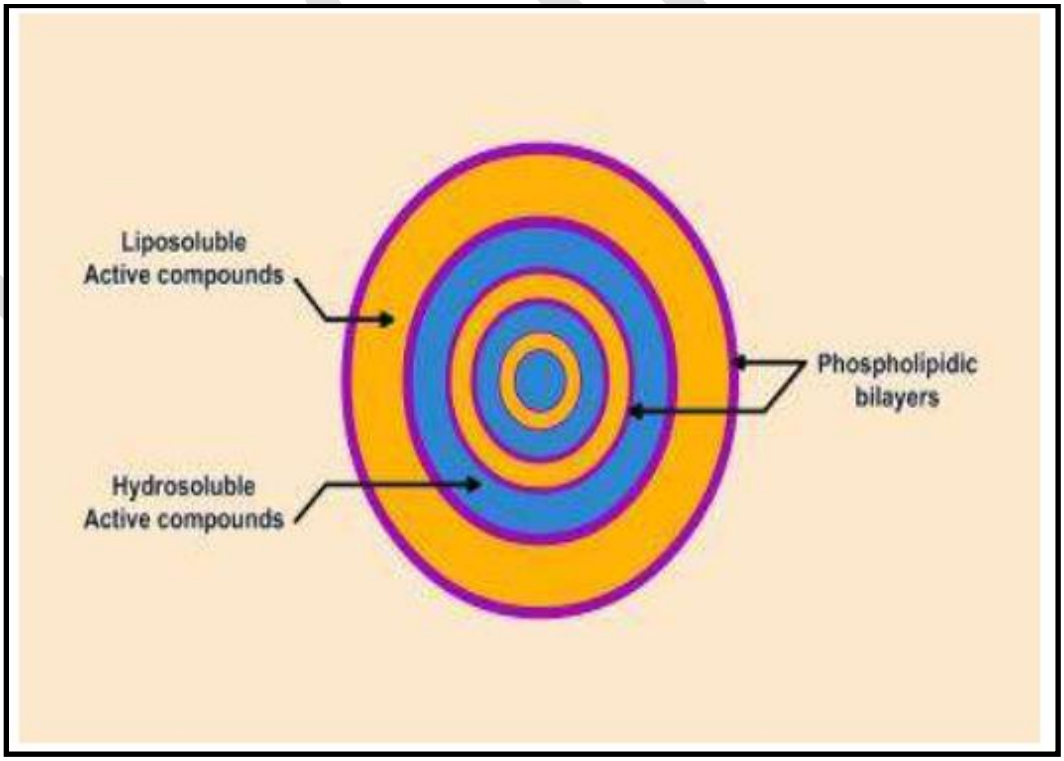
1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

MICROENCAPSULATION

Definition: ***Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material.***

- Microencapsulation can also be used to enclose solids, liquids, or gases inside a micrometric wall made of hard or soft soluble film.
- The product obtained by this process is called as micro particles, microcapsules, Macro-particle.
- Particles having diameter between 3 – 800 µm are known as micro particles or microcapsules or microspheres. Particles larger than 1000 µm are known as Macro-particles.

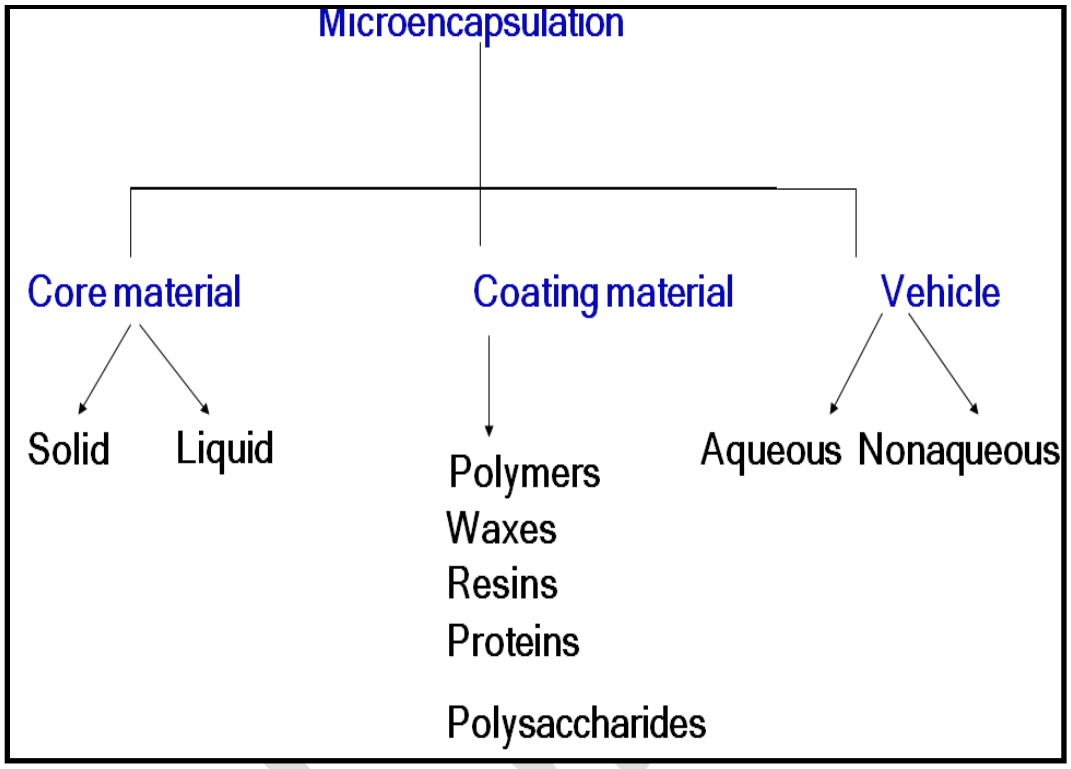
IUPAC Definition: ***Hollow micro particle composed of a solid shell surrounding a core forming space available to permanently or temporarily entrapped substances.***



- In a relatively simple form, a microcapsule is a small sphere with a uniform wall around it.

- The material inside the microcapsule is referred to as the core, internal phase, whereas the wall is sometimes called a shell, coating, or membrane.

Fundamental and Consideration



Materials for Microencapsulation

Core Materials

- The core material, defined as the specific material to be coated, can be liquid or solid in nature.
- The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved materials. Core be active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators.

Coating Materials

The coating material should be capable of forming a film that is cohesive with the core Material.

Coating Material Properties

- ✓ Stabilize the core material.
- ✓ Controlled release under specific conditions.
- ✓ Film-forming, tasteless, stable.
- ✓ Non-hygroscopic, no high viscosity, economical.
- ✓ Soluble in an aqueous media or solvent.
- ✓ The coating can be flexible, brittle, hard, thin etc.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Particles having diameter between 3 – 800 µm are known as?	Microparticles
2	Particles larger than 1000 µm are known as ?	Macroparticles
3	The substance in which enclose solids, liquids, or gases inside a micrometric wall made of hard or soft soluble film.	Microencapsulation
4	The material inside the microcapsule is referred to as?	Core material
5	The substance forming a film that is cohesive with the core Material?	Coating material
6	Flexible, brittle, thin are properties of?	Coating material

Examples of Coating Materials

1. Water soluble resin–

- Gelatine, Gum Arabic, Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxyethylcellulose, Methylcellulose, Polyvinyl alcohol.

2. Water insoluble resins

- Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon),Poly (Ethylene- Vinyl acetate),cellulose nitrate,Silicones, Poly(lactideco-glycolide).

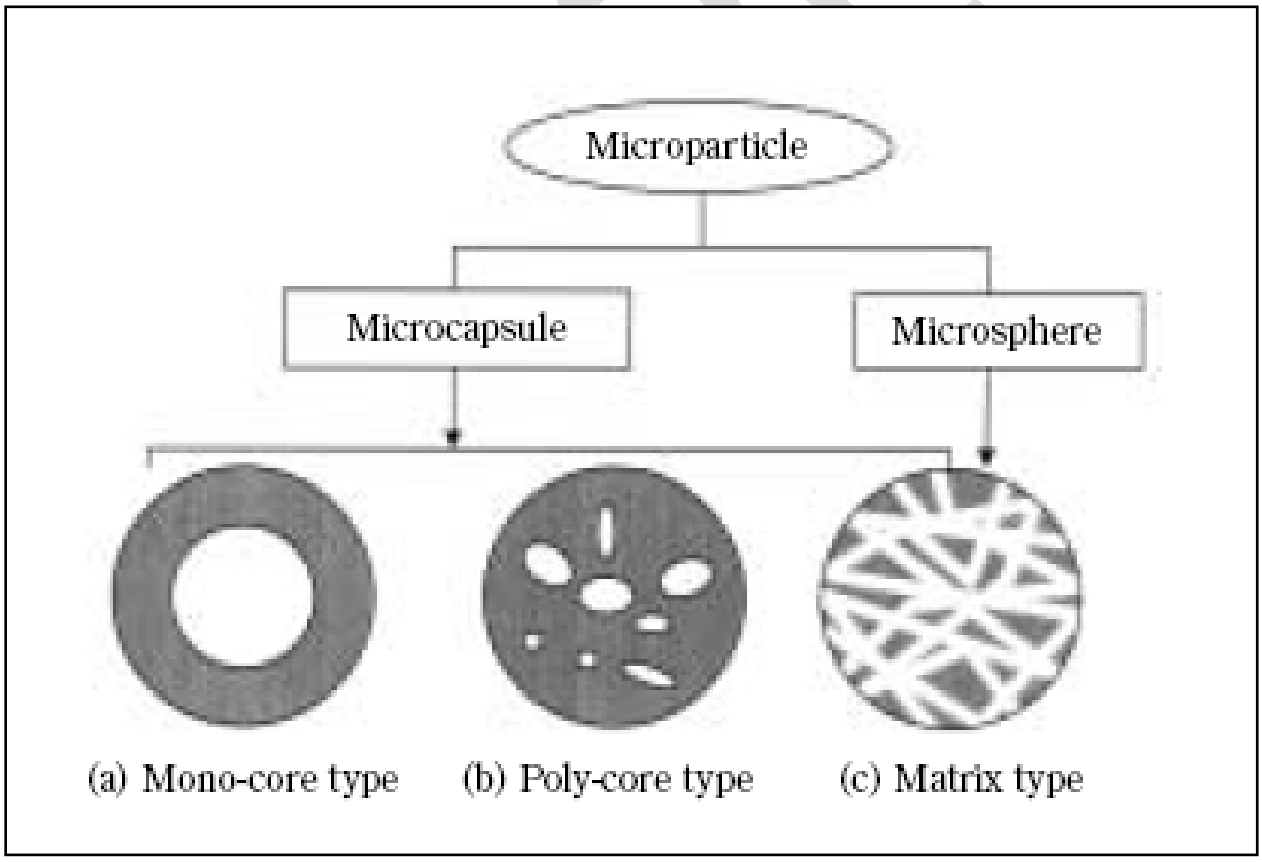
3. Waxes and lipids

- Paraffin, Carnauba, Spermaceti,Beeswax, Stearic acid, Stearyl alcohol, Glyceryl tearates.

4. Enteric resins

- Shellac, Cellulose acetate phthalate, Zein.

Classification of Microparticle

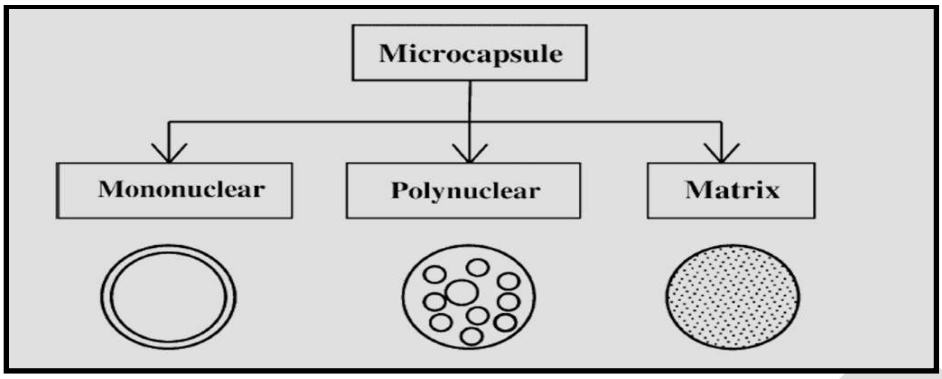


1. Microcapsules:

- The active agent forms a core surrounded by an inert diffusion barrier.

2.Microspheres:

- The active agent is dispersed or dissolved in an inert polymer.



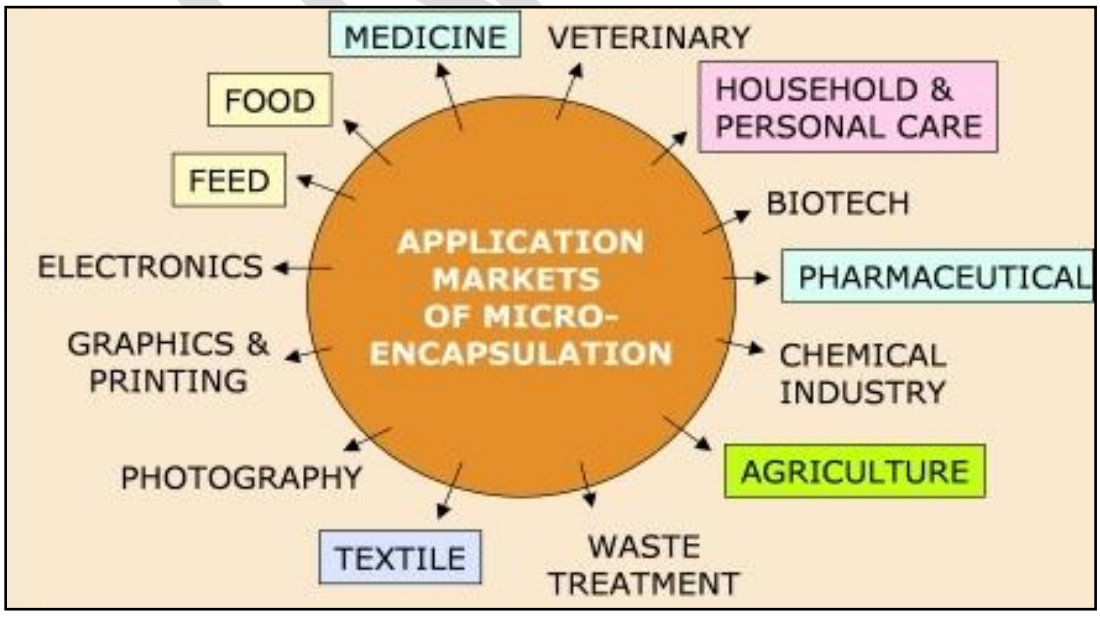
Advantages

- To Increase of bioavailability
- To alter the drug release
- To improve the patient's compliance
- To produce a targeted drug delivery
- To reduce the reactivity of the core in relation to the outside environment
- To decrease evaporation rate of the core material.
- To convert liquid to solid form & To mask the core taste.

Disadvantages

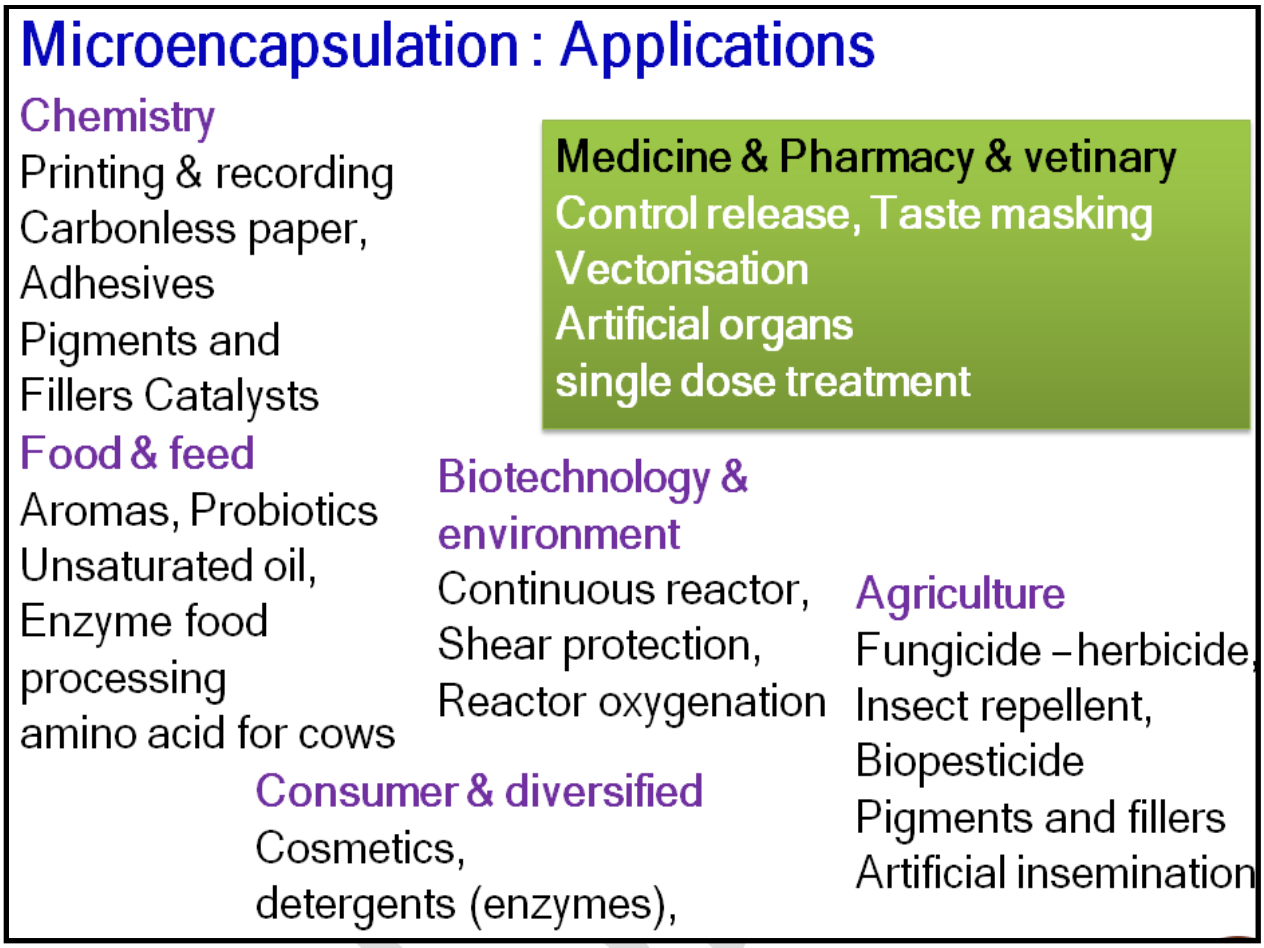
- Possible Cross reaction between core and shell material
- Difficult to achieve continuous and uniform film.
- Shelf life of hygroscopic drugs is reduced.
- More production costs.
- More skill and knowledge is required.

Application of Microencapsulation Techniques



One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Gelatine, Gum Arabic, Starch are example of?	Water soluble resin
2	Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon) are example of?	Water insoluble resin
3	Paraffin, Carnauba, Spermaceti,Beeswax, Stearic acid are example of?	Wax and Lipid
4	Shellac is category of?	Enteric resin
5	Microparticles are classified in?	Two types
6	Microcapsules are classified into?	Three types



The techniques of microencapsulation depends of the physical and chemical properties of the **material to be encapsulated.**

- The stability and the biological activity of the drug should not be affected.
- Yield and drug encapsulation efficiency should be high.
- Microsphere quality and drug release profile should be reproducible within time period.
- Microsphere should not exhibit aggregation.
- Process should be usable at an industrial scale.

Techniques for Manufacturing of Microencapsulation

A. Physical Methods

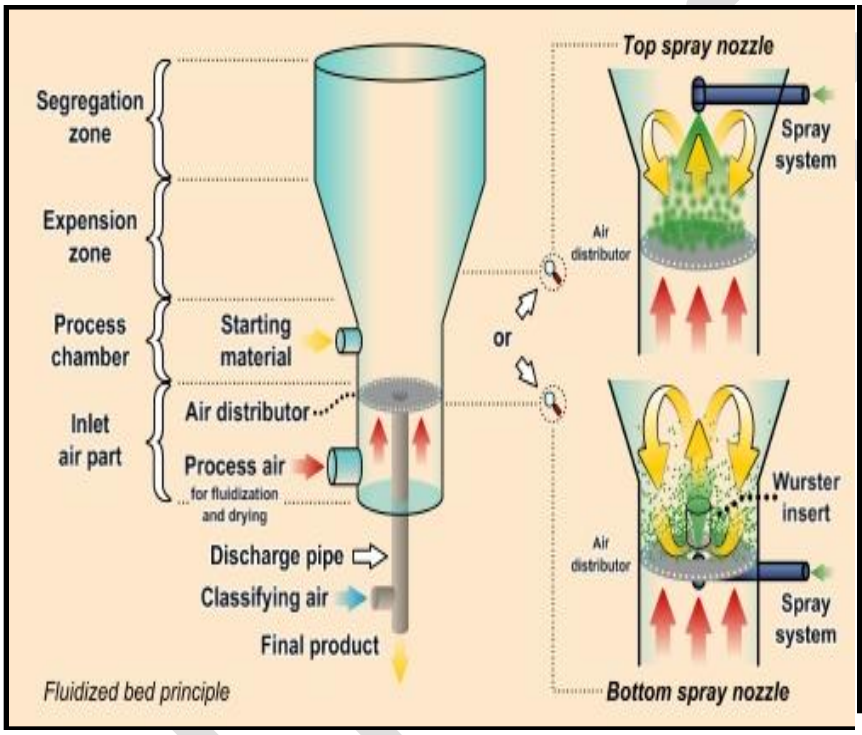
Spray Drying, Spray Chilling, Fluid Bed Coating, Multi-orifice Centrifugal Process, Pan Coating, Air Suspension Coating , Centrifugal Extrusion

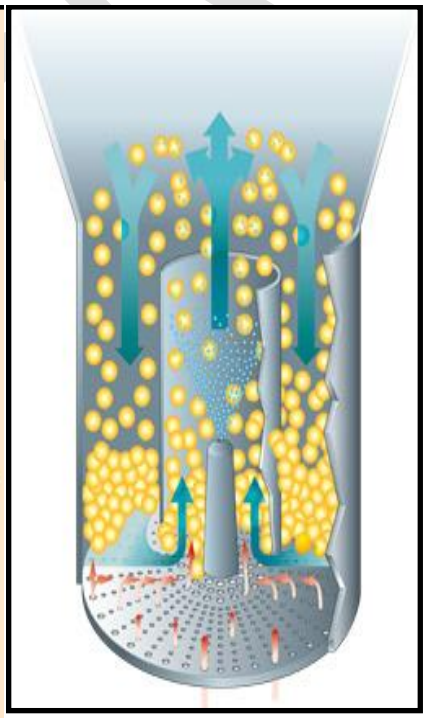
B. Chemical Methods

Coacervation Phase Separation, Solvent evaporation, Solvent Extraction, Interfacial Polymerization, *In-Situ* Polymerization, Matrix polymerization

Air-Suspension Coating

- Air suspension coating, first described by Professor Dale Erwin Wurster at the University of Wisconsin in 1959, gives improved control and flexibility compared to pan coating.
- In this process, the particulate core material, which is solid, is dispersed into the supporting air stream and these suspended particles are coated with polymers in a volatile solvent leaving a very thin layer of polymer on them.
- The dispersing of solid, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particles are suspended on an upward moving air stream.





- The design of the chamber and its operating parameters effect a recalculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is spray applied to the moving particles.
- During each pass through the coating zone, the core material receives an increment of coating material.
- The cyclic process is repeated, perhaps several hundred times during processing, depending on the purpose of microencapsulation the coating thickness desired or whether the core material particles are thoroughly encapsulated.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	How many types of techniques for manufacturing microcapsule?	Physical & Chemical
2	Spray drying technique is type of?	Physical method
3	Coacervation phase separation is type of?	Chemical method
4	Air suspension coating, first described by?	Prof. Erwin wurster
5	In which process the particulate core material, which is solid, is dispersed into the supporting air stream and these suspended particles are coated with polymers in a volatile solvent leaving a very thin layer of polymer on them.	Wurster technique
6	Air suspension technique is one type of?	Cyclic process

- The supporting air stream also serves to dry the product while it is being encapsulated. Drying rates are directly related to the volume temperature of the supporting air stream.

Processing variables for efficient, effective encapsulation by air suspension techniques:

1. Density, surface area, melting point, solubility, friability, volatility, Crystallinity, and flow-ability of core the core material.
2. Coating material concentration (or melting point if not a solution).
3. Coating material application rate.
4. Volume of air required to support and fluidizes the core material.
5. Amount of coating material required.
6. Inlet and outlet operating temperatures.

Coacervation-phase separation

The general outline of the processes consists of ***three steps*** carried out under continuous agitation.

1. Formation of Three Immiscible Chemical Phases
2. Deposition of the Coating
3. Rigidization of the Coating

Formation of Three Immiscible Chemical Phases

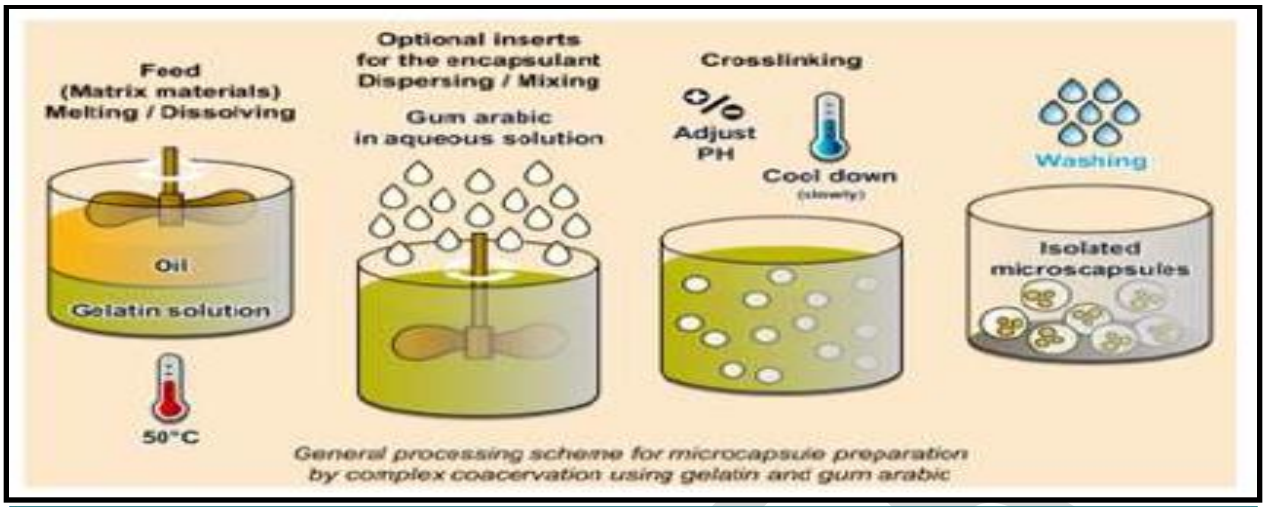
- A liquid manufacturing vehicle phase, a core material phase, and a coating material phase.
- To form the three phases, the core material dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase.

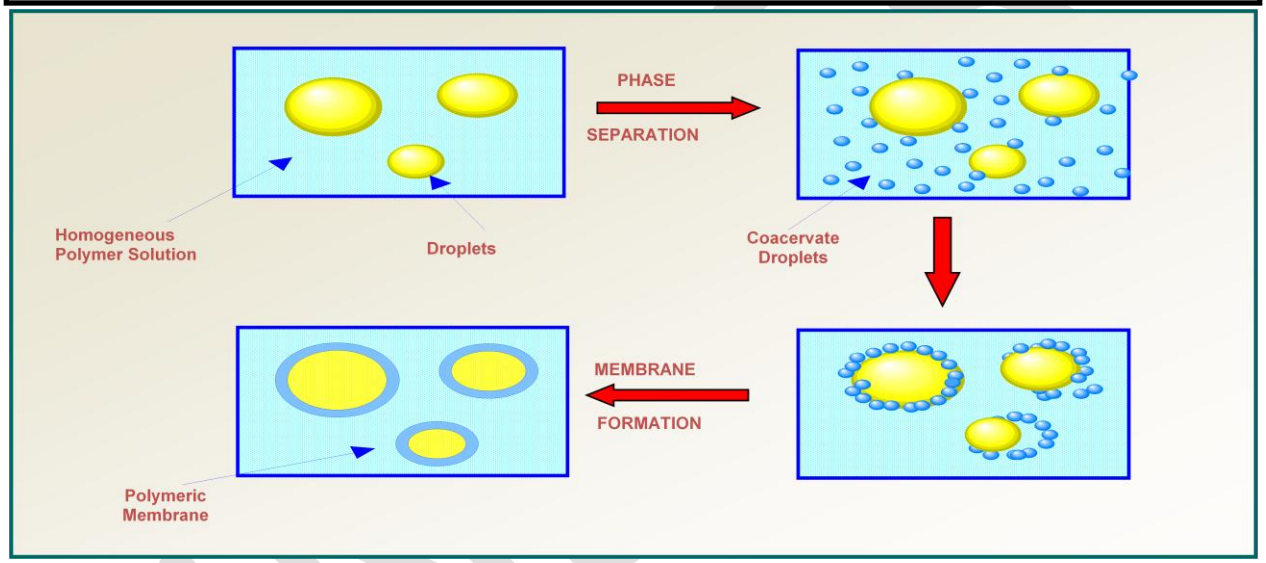
Deposition of the Coating

- It consists of depositing the liquid polymer coating upon the core material. Deposition if the liquid polymer coating around then core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to effective coating.
- The continued deposition of the coating material is promoted by a reduction in the total free interfacial energy of the system, brought about by the decrease of the coating material surface area during clearance of the liquid polymer droplets.

Rigidization of the Coating

- It involves rigid the coating, usually by thermal, cross-linking, or desolvation techniques, to form a self-sustaining microcapsules.





Spray-Drying & Spray-Congealing

- Microencapsulation by spray-drying is a low-cost commercial process which is mostly used for the encapsulation of fragrances, oils and flavors.

Steps:

1- Core particles are dispersed in a polymer solution and sprayed into a hot chamber.

2- The shell material solidifies onto the core particles as the solvent evaporates.

- The microcapsules obtained are of polynuclear.

- Spray Drying is the most commonly used encapsulation method in the food industry.
- The process is economical and flexible uses equipment that is readily available, and produces particles of good quality.

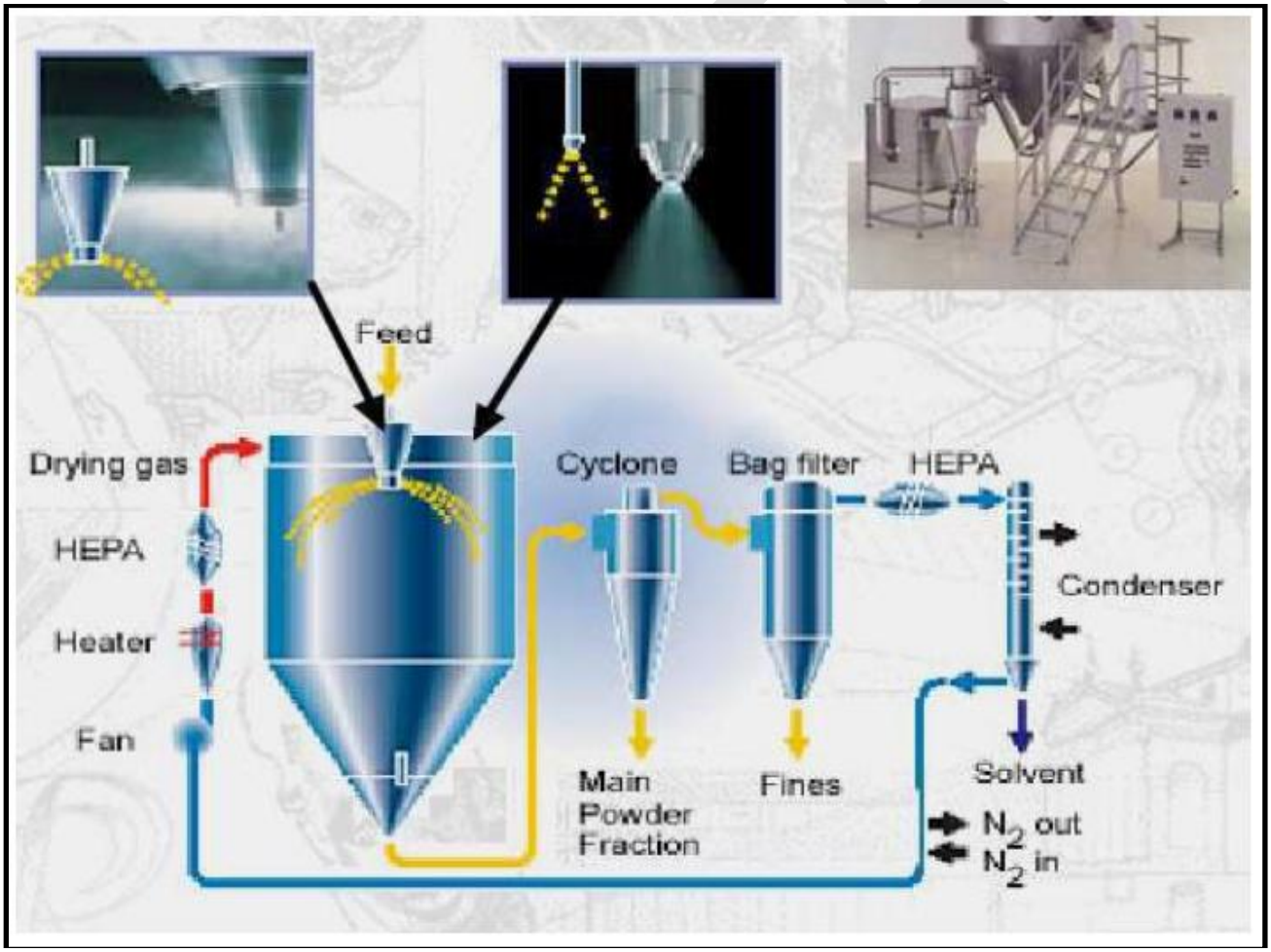
- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	How many processes consist of coacervation technique?	Three steps
2	First phase of coacervation technique contain?	Three immiscible phase
3	Give the name of third phase which consists of depositing the liquid polymer coating upon the core material?	Deposition of coating
4	Regidization of coating usually carried out by?	Desolvation technique
5	Which technique is commonly found in food industry?	Spray drying
6	In which technique, the shell material solidifies onto the core particles as the solvent evaporates.	Spray drying

The process involves three basic steps:

1. **Preparation of a dispersion or emulsion to be processed**
2. **Homogenization of the dispersion and**
3. **Atomization of the mass into the drying chamber.**

- Spray dried ingredients typically have a very small particle size (**generally less than 100 µm**) which makes them highly soluble.
- Typical shell materials include gum acacia, maltodextrins, hydrophobically modified starch and mixtures. Other polysaccharides like alginate, carboxymethylcellulose and guar gum.
- Proteins like whey proteins, soy proteins, sodium caseinate can be used as the wall material in spray drying.



Spray-Congealing

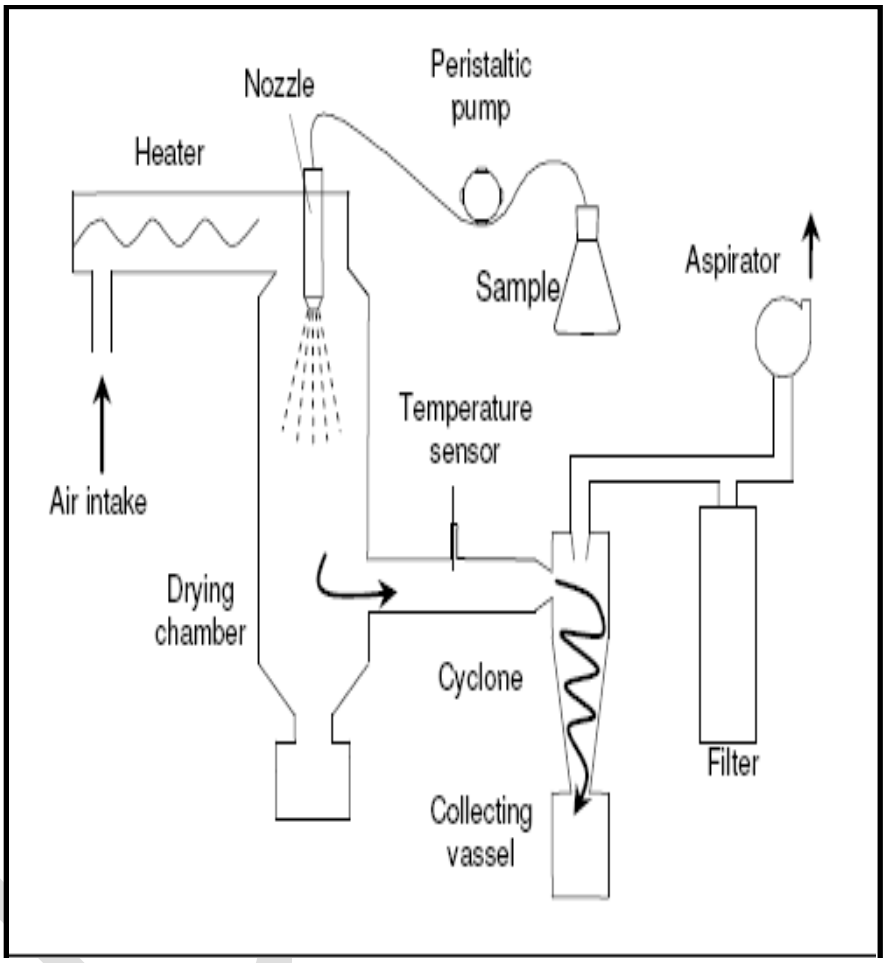
This technique can be accomplished with spray drying equipment when the protective coating is applied as a melt.

1- The core material is dispersed in a coating material melt.

2- Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a cool air stream.

- e.g. microencapsulation of vitamins with digestible waxes for taste masking.

Spray cooling or congealing
spray = hot melt
cold air
> high yield, fast process

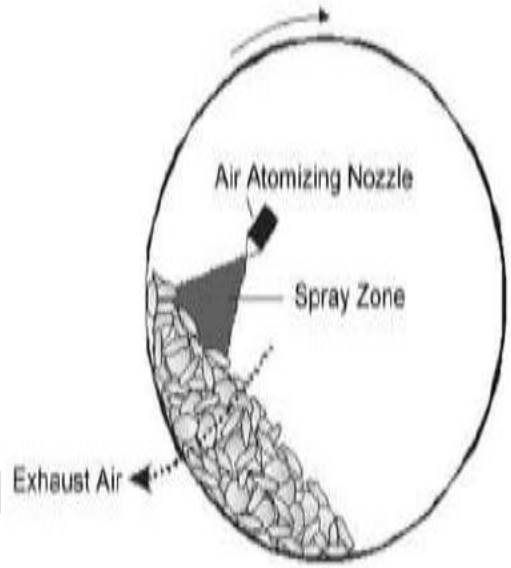


Pan Coating

- The pan coating process widely used and the oldest industrial procedures for forming small, coated particles or tablets.
- The particles are tumbled in a pan or other device.
- The coating material is applied slowly with respect to microencapsulation.
- Solid particles greater than 600 microns in size are generally considered essential for effective coating, and the process extensively employed for the preparation of controlled - release beads.
- ***1- Solid particles are mixed with a dry coating material.***
- ***2- The temperature is raised so that the coating material melts and encloses the core particles, and then is solidified by cooling***.
- Or The coating is applied as a solution, or as a In atomized spray, to the desired solid core material in the coating pans.
- Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans.

- **One Word Question Answer**

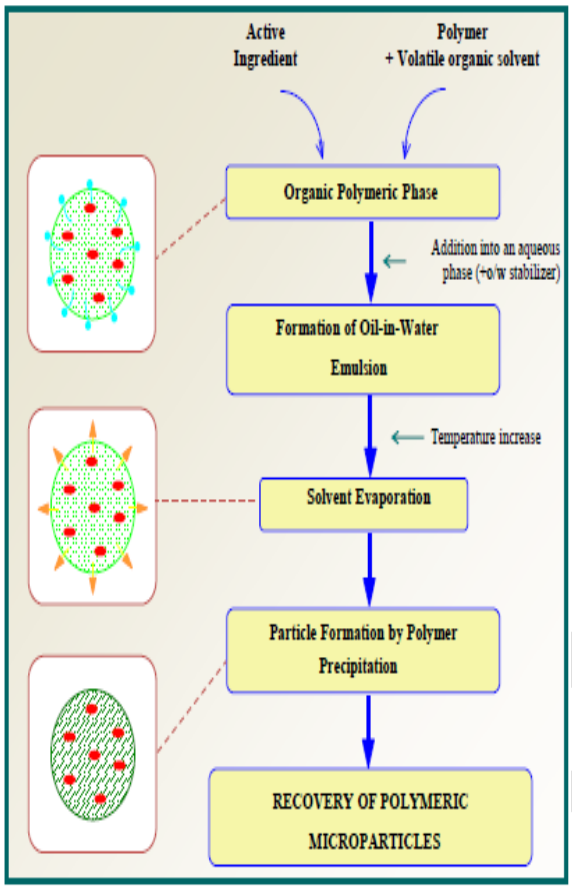
SR NO.	QUESTION	ANSWER
1	How many process steps is found in spray drying?	Three
2	Spray dried ingredients typically have a very small particle size, how much?	less than 100 µm
3	In spray dryer the typical shell materials are composed of?	Acacia gum, Maltodextrin
4	Which technique can be accomplished with spray drying equipment when the protective coating is applied as a melt?	Spray-congealing
5	How much size of solid particles are generally considered essential for effective pan coating?	600 microns
6	In which technique, the liquid is atomized in no. of small droplets?	Spray drying



- Medicaments are usually coated onto various spherical substrates and then coated with protective layers of various polymers.

Solvent Evaporation Technique

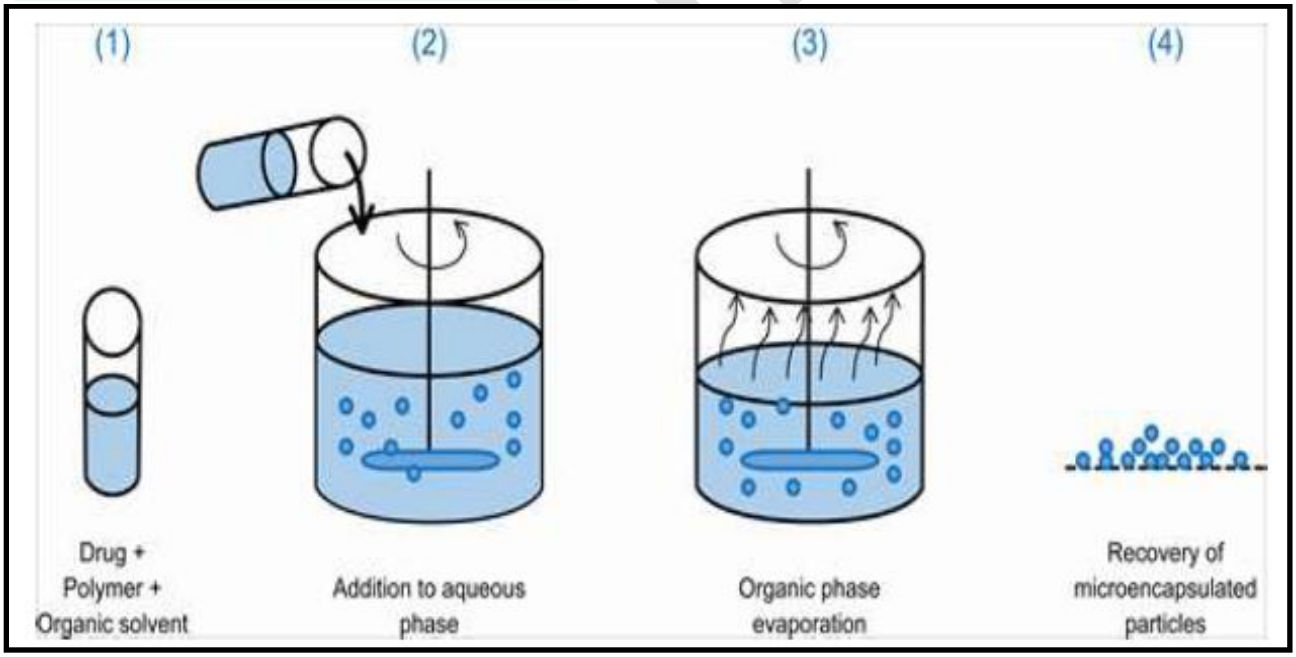
- The polymer is dissolved in a water immiscible volatile organic solvent like dichloromethane or chloroform, into which the core material is also dissolved or dispersed.



Step 1:
Formation of a solution/dispersion of the drug into an organic polymer phase.

Step 2:
Emulsification of the polymer phase into an aqueous phase containing a suitable stabilizer, thus, forming a o/w emulsion.

Step 3:
Removal of the organic solvent from the dispersed phase by extraction or evaporation leading to polymer precipitation and formation of the microspheres.



- The resulting solution is added drop wise to a stirring aqueous solution having a suitable stabilizer like poly (vinyl alcohol) or Polyvinylpyrrolidone, etc. to form small polymer droplets containing

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	In which technique, the polymer is dissolved in a water immiscible volatile organic solvent	Solvent evaporation
2	Solution or dispersion of Active ingredients are prepared in which phase?	Organic phase like chloroform
3	Which type of emulsion produce in solvent evaporation method?	o/w emulsion
4	Organic phase is removed by which method?	Extraction
5	Higher temperature leads to produce how much quantity of yield?	Greater as compared to lower temperature

- encapsulated material. With time, the droplets are hardened to produce the corresponding polymer microcapsules.
- This hardening process is accomplished by the removal of the solvent from the polymer droplets either by solvent evaporation (by heat or reduced pressure).

Polymerization

- The method involve the reaction of monomeric unit located at the interface existing between a core material substance and continuous phase in which the core material is disperse.
- The core material-supporting phase is usually a liquid or gas, and therefore polymerization reaction occurs at liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface. E.g. In the formation of polyamide (Nylon) polymeric reaction occurring at liquid-liquid interface existing between aliphatic diamine & dicarboxylic acid halide.
- Monodisperse microgels in the micron or submicron size range. Precipitation polymerization starts from a homogeneous monomer solution in which the synthesized polymer is insoluble.
- The particle size of the resulting microspheres depends on the polymerization conditions, including the monomer/co monomer composition, the amount of initiator and the total monomer concentration.

Applications of Microcapsules and Microspheres

1. Agricultural Applications

- Reduce insect populations by disrupting their mating process.
- Protects the pheromone from oxidation and light during storage and release.

2. Catalyst

- Safe handling, easy recovery, reuse and disposal at an acceptable economic cost.
- Metal species such as palladium (II) acetate and osmium tetroxide have been encapsulated in polyurea microcapsules and used successfully as recoverable and reusable catalysts without significant leaching and loss of activity.

3. Food Industry

- Adding ingredients to food products to improve nutritional value can compromise their taste, colour, texture and aroma.
- Sometimes they slowly degrade and lose their activity, or become hazardous by oxidation reactions.

- Ingredients can also react with components present in the food system, which may limit bioavailability.

4. Pharmaceutical Application

- Potential applications of this drug delivery system are replacement of therapeutic agents (not taken orally today like insulin), gene therapy and in use of vaccines for treating AIDS, tumors, cancer and diabetes.
- The delivery of corrective gene sequences in the form of plasmid DNA could provide convenient therapy for a number of genetic diseases such as cystic fibrosis and hemophilia.
- Lupin has already launched in the market world's first Cephalexin (Ceff-ER) and Cefadroxil (Odoxil OD) antibiotic tablets for treatment of bacterial infections.
- Aspirin controlled release version ZORprin CR tablets are used for relieving arthritis symptoms.
- Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythms.
- Niaspan CR tablet is used for improving cholesterol levels and thus reducing the risk for a heart attack.
- Glucotrol (Glipizide SR) is an anti diabetic medicine used to control high blood pressure.
- Some of the applications of microencapsulation can be described in detail as given below:

1. Prolonged release dosage forms.
2. Prepare enteric-coated dosage forms selectively absorbed in the intestine rather than the stomach.
3. It can be used to mask the taste of bitter drugs.
4. To reduce gastric irritation.
5. Used to aid in the addition of oily medicines to tableted dosage forms.

- To overcome problems inherent in producing tablets from otherwise tacky granulations.
- This was accomplished through improved flow properties. eg. The non-flowable multicomponent solid mixture of niacin, riboflavin, and thiamine hydrochloride and iron phosphate may be encapsulated and made directly into tablets.

6. To protect drugs from environmental hazards such as humidity, light, oxygen or heat. eg. vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation.

7. The separations of incompatible substances, eg. pharmaceutical eutectics.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which method involve the reaction of monomeric unit located at the interface existing between a core material substance and continuous phase in which the core material is disperse.	Polymerization
2	The core material-supporting phase in polymerization phase is usually available in?	Liquid or gas state
3	Which technique is reduce the gastric irritation?	Microencapsulation
4	Drug protection, incompatibilities can be avoided by which technique?	Microencapsulation
5	In which field, microencapsulation technique that improve nutritional value?	Food Industry
6	Which technique is reduced volatility?	Microencapsulation

The stability enhancement of incompatible aspirin-chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing.

8. Microencapsulation can be used to decrease the volatility.
9. The hygroscopic properties of many core materials may be reduced by microencapsulation.
10. In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tableted particles.
11. Microencapsulation has also been used to decrease potential danger of handling of toxic or noxious substances. Such as fumigants, herbicides, insecticides and pesticides