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# Microencapsulation (Part a)

## Definition:

As a process it is a means of applying relatively thin coating to small particles of solids or droplets of liquids and dispersion.

## Size:

There are from several 10ths of micron .....5000 micron in size.

## Characteristics:

- Taste and odor masking
- Conversion of oils and other liquids to solids for the ease of handling.
- Protection of drug against environment (moisture, light, heat and oxidation)
- Prevention of pain on injection
- Delay of volatization
- Separation of incompatible materials (other drug and excipients such as buffer).
- Improvement of flow property of powders
- Safe handling of toxic substance
- Aid in depression of water insoluble substances I aqueous media.
- Production of SR, CR and targeted medication.
- Reduced dose dumping potential compared to large implantable devices

## Properties of coating material:

- Should form film that is cohesive with core material.
- Should be chemical compatible
- Non-reactive with core material
- Provide desired coating properties. Such as strength, flexibility, impermeability, optical properties and stability.

## Benefits of encapsulation:

- Sustained release and prolonged action medication , taste masked chewable tablets, powders and suspensions, single layer tablets containing chemically incompatible ingredients and new formulation except for creams, ointments, aerosols, dressings, plasters, suppositories and injectable.
- Pharmaceutically related areas, such as hygiene, diagnostic aids and medical equipment design also are amenable to microencapsulation.

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## Disadvantages/Drawbacks/ Limitations of Microencapsulation:

- Incomplete or discontinuous coating.
- Inadequate stability or shelf life of sensitive pharmaceuticals.
- Non reproducibility.
- Unstable release characteristics of coated products.
- Economic limitation/high cost product.

## Microcapsule:

Has a drug located centrally within the particle, cohere it is encased within a unique polymeric membrane.

## Microsphere:

Has its drug dispersed throughout the particle that is the internal structure is a matrix of drug and polymeric excipients?

## Types of processes used for microencapsulation:

Each process has its capabilities and limitation

1. Coacervation- phase separation.
2. Spray drying and congealing.
3. Polymerization.
4. Air suspension/solvent evaporation technique.

## Fundamental consideration:

- Involves a basic understanding of general properties of core material and coating material.
- Methods employed in the manufacture of microcapsules of may well result in products of varied composition, quality and utility.

## Things which we must know:

i. What are the specific dosage or product requirements stabilization, reduced volatility, release characteristics, environmental conditions etc.?
ii. Which coating material will satisfy the product objectives and requirements?
iii. Which microencapsulation method is best suited to accomplish the coated product objective?
iv. What is the physical and chemical properties of core material?

## Coacervation or Phase separation technique:

## Definition:

The word coacervation derived from the Latin word acervus which means aggregation and the prefix "co" indicates the preceding union of the colloidal particles.

This term was first used to describe the phenomena of phase separation in colloidal system and thus it was defined as a process in which aqueous colloidal solution separate upon alteration of thermodynamic condition of state into two liquid phase, one rich in colloid i.e the coacervate and the other containing little colloid."

Deposition of this coacervate around drug or core material form the embryonic capsule and then appropriate gelling of coacervate resulted in microencapsulation. (This gelling can be brought about by using appropriate gelling agents (e.g. formaldehyde or glutraldehyde) or by bringing the PH to isoelectronic point.

## Core Material:

- The core material or drug which can be encapsulated by coacervation can be solid, liquid, gas, liquid slurry, suspension or emulsion.
- Also pharmaceuticals from different pharmacological classes which can be microencapsulated by coacervation include analgesic, antibiotics and antihistamines, tranquillizers iron salts and vitamins.

## Wall Material:

- Coating material can be selected from the variety of natural and synthetic polymers depending on the core material to be encapsulated and the desired characteristics.
- The amount of the coating material used range from 3%-30% of the total weight which gives film thickness ranges from 1-200μm.
- Also coating of drug which possesses sharp peaks and depression is difficult. Whereas spherical particles can be uniformly encapsulated.
- Both natural and synthetic colloid can be used microencapsulation of drugs.
  Hydrophobic colloids are used encapsulating water soluble or hydrophilic drugs whereas hydrophilic colloids are used for encapsulating water insoluble or hydrophobic drug.

**Example of hydrophilic and hydrophobic colloids used for microencapsulation by coacervation is given below:**

| Natural | Synthetic |
|---|---|
| • Agar<br>• Albumin<br>• Casein<br>• Gelatin<br>• Chitosan<br>• Starch<br>• Pectin<br>• waxes | • **acrylic polymers:**<br>▪ polyacrylamide<br>▪ polyacrylic acid<br>▪ poly lactic acid<br>▪ poly glycolic acid<br>• **cellulose derivatives**<br>▪ Methyl cellulose<br>▪ Ethyl cellulose<br>▪ Hydroxyethyl cellulose<br>▪ Hydroxy propyl cellulose<br>• **Polyamides:**<br>▪ Nylon-6,10<br>▪ Nylon-6<br>• **Poly styrene**<br>• **Polyvinyl alcohol**<br>• **Polyvinyl**<br>• **Pyrrolodine**<br>• **Shellac** |

## Methods employed for coacervation / phase separation:

There are various means and methods which can be used for coacervation phase separation. The choice of method depend upon the polymer and the set of conditions which are being used. Following methods can be used:

- Temperature
- Salt addition
- Non solvent addition
- Incompatible polymer addition
- Polymer-polymer interaction

## Temperature changes:

By temperature changes, phase separation of disperse polymer takes place in the form of immiscible liquid, droplets and if drug or core substance is present into the system, these droplets surround the core and for the microcapsules.

A system that utilizes the ethyl cellulose and cyclohexane at high temperature is an example of thermally induced microencapsulation. Ethyl cellulose is soluble in cyclohexane at elevated temperature but insoluble at the room temperature. For microencapsulation, first of all ethyl cellulose is dispersed in the cyclohexane and then mixture is heated to boiling point so that a homogenous polymer solution is formed. Then core material is added in the solution with continuous stirring and mixture is allowed to cool. This results in phase separation of ethyl cellulose and microencapsulation of the core material. Further cooling of mixture at room temperature cause gelation and solidification of the coating.

## Salt addition:

Soluble inorganic salts can be added to aqueous solutions of water soluble polymers to cause phase separation. A gelatin-water-sodium sulfate is an example. In this system, phase separation /coacervation is induced by adding drop wise 20% solutions of sodium sulfate.

## Non solvent addition:

A liquid that is a non-solvent for a given polymer or does not dissolve the given polymer can be added to a solution of polymer to induce phase separation. The resulting immiscible liquid polymer is used for encapsulation of an immiscible core.

## For example:

**Cellulose acetate+ methyl ethyl ketone** ⟶ **solution of polymer** ⟶
(polymer) (solvent for polymer)

**Addition of drug (Scopolamine)** ⟶ **Addition of isopropyl ether** (non-solvent for the polymer) ⟶ **phase separation and microencapsulation of suspended drug occur.**

## Incompatible polymer interaction:

Microencapsulation can be carried out by using the incompatibility of two dissimilar polymers present in a common solvent.

e.g. Methylene blue- ethyl cellulose-liquid polybutadiene is an example of the microencapsulation by incompatible polymer addition.

Ethyl cellulose dissolved in toluene to form polymer solution. Then methylene blue (drug) is dispersed in the polymer solution. Phase separation is carried out by adding liquid polybutadiene which is soluble in toluene but incompatible with ethyl cellulose, thus causes demixing of ethyl cellulose and phase separation occur.

## Polymer-polymer interaction:

The interaction of two oppositely charged polyelectrolyte can result in the formation of a complex having such reduced solubility that phase separation occur.

e.g. Gelatin and acacia are examples of oppositely charged polyelectrolyte because gelatin has a positive charge whereas acacia possesses a negative charge. Gelatin-Gelatin, Gelatin-CMC are examples of other oppositely charged polyelectrolyte used in microencapsulation.

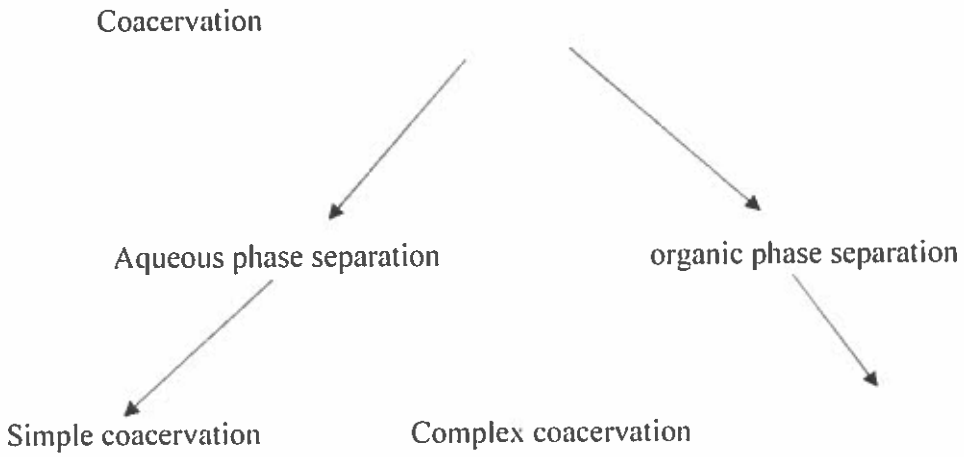
## Description of coacervation/phase separation methods:

Coacervation and phase separation methods divided into two main group's i.e.

- Aqueous phase separation
- Organic phase separation

Aqueous phase separation is further divided into

i. Simple coacervation
ii. Complex coacervation




## Aqueous phase separation:

- This method is used for the encapsulation of water insoluble or hydrophobic drugs, both in liquid and solid state and the polymer or wall former used in this technique is hydrophilic in nature.
- In the first step an aqueous colloidal solution of hydrophilic polymer which has film forming properties is prepared and then drug or core material is added in it.
- When liquid are to be microencapsulated an oil in water (W/O) type emulsion is prepared, with the liquid to be coated occupying the disperse phase and the aqueous colloidal solution, the continuous phase. When solids are to be coated, suspension of the particulate solid in the aqueous colloidal solution is prepared.

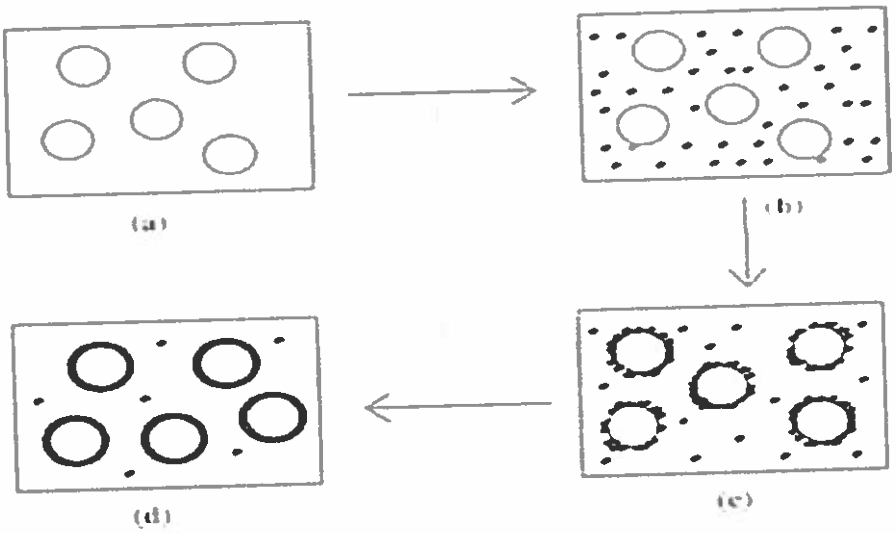
- Then phase separation is produced either by addition of precipitating agent or by the reduction in temperature or PH change. Encapsulation occurs when the coating material is salted out and encases the drug substances.
- This method further consist of simple and complex coacervation. Simple coacervation deals with a system containing only one colloid solute whereas complex coacervation deals with a system containing more than one colloid solutes (and involves charges on the colloid and their neutralization).

## Simple coacervation:

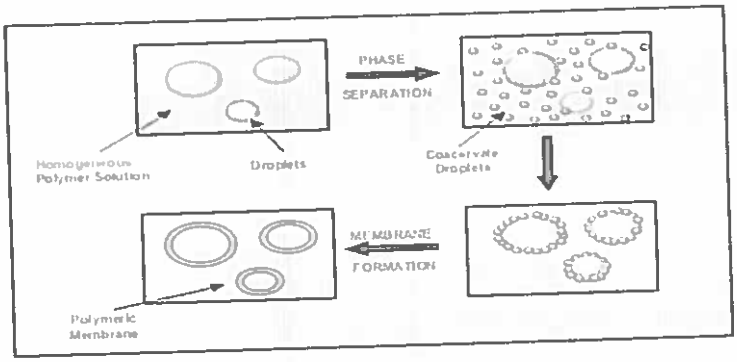
It consist of following steps;

1. Dispersion of the core material in aqueous solution of the polymer
2. Creation of insufficiency of water for the hydrophilic colloid and the disposition of the coacervate around the core.
3. Gelation of the coacervate and hardening of the microcapsules

In the simple coacervation, the single colloid which is present in the continuous phase deposited on the surface of the disperse particles as a result of physical influences such as salting out effect or the addition of another solvent. Such influences results in the dehydration of hydrophilic colloid. For example gelatin is most commonly used hydrophilic-colloid in simple coaservation and in this case phase separation is produced by the addition of highly soluble salt such as sodium sulfate or ammonium sulfate or by the addition of alcohol.




## COACERVATION / PHASE SEPARATION




1. Formation of three immiscible phase
2. Deposition of coating
3. Rigidization of coating.

**Diagram of simple coacervation:**

## Complex coacervation:

- In contrast to simple coacervation, complex coacervation requires at least two hydrophilic colloids in the continuous phase of the fluid system.
- The general procedure consist of neutralization of the charges on the colloid and the formation of coacervate, which can be shown as:

[Colloid 1]+ [colloid2] ⟶ [colloid1] + [colloid 2]

The encapsulation process in complex coacervation consist of following

1. Preparation of the hydrophilic colloid solution
2. Addition of second hydrophilic colloid solution of opposite charge to induce coacervation
3. Deposition of the coacervate around the core
4. Gelation of coacervate and hardening of microcapsules

A combination of acacia and gelatin at neutral PH (below the isoelectric point of gelatin) fulfills the requirement of complex coacervation. At that PH gelatin carries a appositive charge because of protonation of basic group whereas acacia carries a negative charge because of ionization of glucuronic acid group. The two colloid attract each other and separate into distinct liquid phase cause coacervate. Then deposition of coacervate occur around the core and then gelation of coacervate and hardening of microcapsules is carried out by the addition of the hardening agents e.g. formaldehyde.

## Flow chart of simple coacervation process:

Water –immiscible liquid

Or

Water –insoluble solid particles

Aqueous coating solution (gelatin in water)

O/W emulsion or

Aqueous suspension of solid particles

Then add 20% w/w $Na_2SO_4$ solution with continuous

Stirring to produce coacervation

Gel the colloid by pouring coacervate mixture in to 7% -20% w/w $Na_2SO_4$ solution

Filter and wash coacervate with cold water to remove salt

Treat filter material with formaldehyde to harden the coacervate

Filter and wash particles with cold water to remove hardening agent

Dry to remove remaining solvent

## Flow chart for complex coacervation process:

Water –immiscible liquid

Or

Water –insoluble solid particles

Aqueous coating solution (acacia in water)

O/W emulsion or

Aqueous suspension of solid particles

Add gelatin solution with stirring

Add warm water until coacervate is produced

Pour coacervate mixture into cold water

Then treat coacervate with formaldehyde solution

Remove aggregates of encapsulated material

And wash with water

Dry and comminute aggregated material

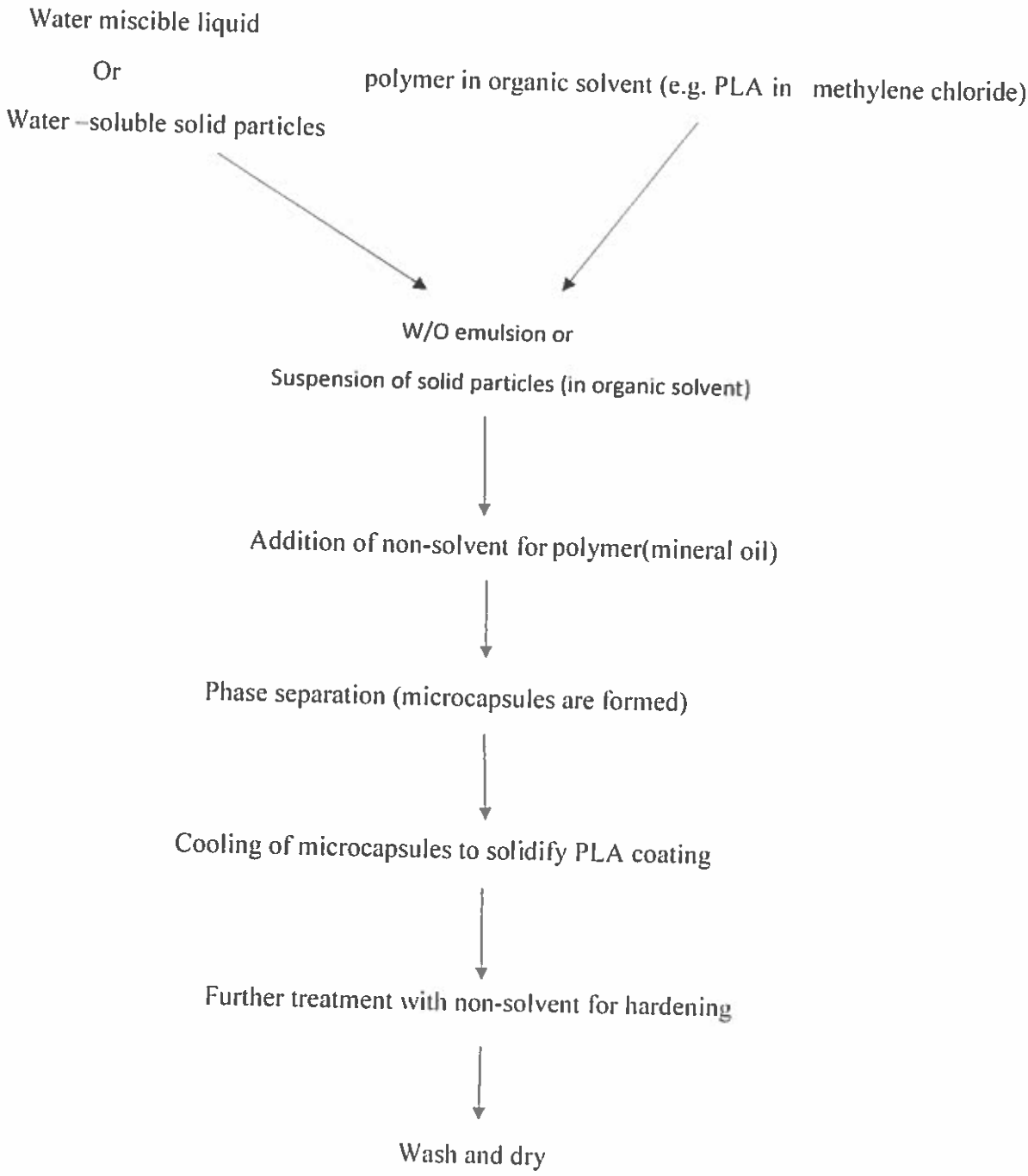
**Organic phase separation:**

- This method is the inverse of the aqueous phase separation process in that:
  It is used for encapsulation of water soluble and the hydrophilic drugs (both in liquid and solid state) and the wall containing phase is hydrophobic in nature.
- In the first step polymer and the coating material is dissolved in the organic solvent phase (continuous phase). Then drug is added in the above phase.
- When liquid are to be microencapsulated, water in oil (W/O) type emulsion is prepared, with the liquid to be coated occupying the disperse phase and the organic solution, the continuous phase. When solids are to be microencapsulated then either they are suspended in the organic solvent or they are dissolve (because hydrophilic in nature) in the internal phase of the W/O type emulsion.
- Phase separation and coating of the solid or liquid disperse particles by the polymer is carried out by adding the solvent which is miscible with the continuous organic phase but which is non solvent for the polymer or by adding second incompatible polymer.
- Hardening of the polymer coating on the drug particles is usually carried out either by the addition of the more of the non-solvent or by separating the coated particles from the system, washing them with non-solvent liquid and drying.

**Example:**

Organic phase separation method by nonsolvent addition has been used for encapsulation of hydrocortisone. In this method, hydrocortisone is first suspended in PLA-methylene chloride solution. When mineral oil is added in this suspension, it results in precipitation of polymer (PLA) around the solid hydrocortisone.

**Flow chart for complex coacervation process:**



## Storage:

During storage of microcapsules, factor such as pressure, temperature, light, humidity, air and pollutants should be considered.

Excess pressure can cause fusion of microcapsules leading to non-free flowing product. Also microcapsules containing volatile materials must be protected from excessive temperature to avoid decomposition and evaporation of core material.

## Application of coacervation:

### 1. Antibiotics:

Examples of antibiotics which are encapsulated by coacervation technique include:

- Amoxicillin, ampicillin and bacampicillin (pencillins)
- Cephalexin and cephradine ( Cephalosporins)
- Erythromycin and clarithromycin ( Quinolones)
- Chloramphenicol

Amoxicillin was encapsulated to produce sustained release effect and to improve patient compliance. Also the unpleasant taste of clarithromycin and erythromycin was masked by simple coacervation using gelatin and sodium sulfate.

### 2. Anti-inflammatory drug:

Example of anti-inflammatory drugs which are encapsulated by coacervation technique:

- Diclofenac sodium
- Ibuprofen
- Naproxen
- Mefenamic acid and flufenamic acid

These NSAIDs are microencapsulated not only for sustained release effect but also to reduce the gastric ulcerogenic activity.

### 3. Bronchodilators:

Bronchodilators which are encapsulated by coacervation technique include:

- Theophylline
- Terbutaline sulphate

Theophylline was encapsulated for sustained release effects, for extending absorption, to decrease gastric irritation and to mask the bitter taste of the drug.

### 4. Sulfa drugs:

Examples of sulfa drugs which are encapsulated by coacervation technique include:

- Sulfadiazine
- Sulfamerazine
- Sulfamethoxazole

### 5. Diuretics:

Diuretics for example furosemide, chlorothiazide and sulphonamide were encapsulated to produce sustained release formulation that offers the advantage of avoiding short period of peak diuresis observe with the conventional formulation.

### 6. Urinary antiseptics:

Sustained release microcapsules of nitrofurantoin and nalidixic acid were also prepared.

### 7. Antiepileptic drugs:

Examples of antiepileptic drugs prepared by coacervation technique include:

- Phenytoin sodium
- Beclamide

Phenytoin sodium was encapsulated to produce the sustained release effect and to improve the patient compliance whereas beclamide was encapsulated to mask the unpleasant taste of the drugs and for separating incompatible substances.

### 8. Antihypertensive:

Antihypertensive for examples, isosorbide mononitrate, captopril, propranolol and nicardipine were encapsulated to maintain suitable blood level for a longer period of time with minimum frequency of administration and also to overcome the tolerance develop in conventional preparations.

### 9. Analgesics

Analgesics e.g. acetyl salicylic acid (aspirin) was encapsulated to mask the bitter taste and to produce sustained release effect. Acetaminophen (paracetamol) was also encapsulated by this technique.

### 10. Anticancers:

Anticancer drugs for example mitomycin, bleomycin and mercaptopurin were encapsulated to produce sustained release formulations with minimum side effects.

### 11. Tranquilizers:

For example

- Diazepam
- Oxazepam

### 12. Electrolyte replenisher:

Microencapsulation of sodium chloride and potassium chloride give better control release as compared to standard tablet and powder form.

### 13. Vitamins and metal salts:

Vitamins such as A, B1, B2,B6, B12, C and D and mineral salts e.g. zinc sulfate are encapsulated by this technique.

### 14. Converting liquid to free flowing powders:

Cod liver oil, benzaldehyde and other citrus essential oils were coated to obtained fine powder in order to prevent their vaporization and oxidation.

### Applications of coacervation (table form):

| Serial No. | Pharmacological class | Drugs | Reason for Microencapsulation |
|---|---|---|---|
| 1 | **Antibiotics** | • Amoxicillin, ampicillin and bacampicillin (pencillins)<br>• Cephalexin and cephradine ( Cephalosporins)<br>• Erythromycin and clarithromycin ( Quinolones)<br>• Chloramphenicol | **SR** |
| 2 | **Anti-inflammatory drugs** | • Diclofenac sodium<br>• Ibuprofen<br>• Naproxen<br>• Mefenamic acid and flufenamic acid | **SR,RGI** |
| 3 | **Bronchodilators** | Theophylline | **SR, RGI, MUT** |
| 4 | **Sulfa drugs** | • Sulfadiazine<br>• Sulfamerazine<br>• Sulfamethoxazole | **SR, MUT** |

| | | | |
|---|---|---|---|
| 5 | **Diuretics** | • Furosemide<br>• Chlorothiazide<br>• sulphonamide | **SR** |
| 6 | **Urinary antiseptics** | • Nitrofurantoin<br>• Nalidixic acid | **SR** |
| 7 | **Antiepileptic agent** | • Phenytoin sodium<br>• Beclamide | **SIS/MUT, SR** |
| 8 | **Analgesics** | • Acetyl salicylic acid (aspirin)<br>• Paracetamol | **SIS/MUT, RGI, SR** |
| 9 | **Antihypertensive** | • Isosorbide mononitrate<br>• captopril<br>• propranolol | **SR, IT** |
| 10 | **Anticancer** | • Mitomycin<br>• Bleomycin<br>• Mercaptopurin | **SR, IT** |
| 11 | **Tranquilizers** | • Diazepam<br>• Oxazepam | **SR** |
| 12 | **Electrolyte replenisher** | • sodium chloride<br>• potassium chloride | **SR, RGI, SIS** |
| 13 | **Vitamins** | A, B1, B2,B6, B12, C and D | **SR, EP, MUT** |
| 14 | **Metal salts** | | **SR** |
| 15 | **Volatile liquids** | • Cod liver oil<br>• Benzaldehyde | **CLP, EP** |

**Where:**

**SR=** sustained release

**MUT=** Masking unpleasant taste**Roll No.Sadia Batool 02**

**SIS=** separating incompatible substances**Amna Lodhi 25**

**IT=** improved tolerability **Afreen Naqvi 35**

**EP=** Environmental protection**Arifa Islam 38**

**CLP=** Converting liquids to powders**(Final Prof. Eve)**