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Review Article

A REVIEW ON MICROCAPSULES

***Krishna Sailaja A. and Jyothika M.**
RBVRR Women's College of Pharmacy, Hyderabad, India
**Author for Correspondence*

ABSTRACT
The controlled release drug delivery system, releases the active drug or medicament at a predetermined rate targeting the drug to specific site over a prolonged period of time. Microencapsulation provides a promising drug delivery system since it provides unlimited combinations of core and shell materials, targeting to the specific areas of gastrointestinal tract. The review of microcapsules includes the definition of microcapsule, reasons for micro encapsulation, types of micro capsules, the mechanism of drug release, types of coating materials, techniques for the preparation of microcapsule and its applications.

Keywords: *Microcapsules, Miniature, Shell, Core, Applications*

INTRODUCTION
Microencapsulation is the process of enclosing a substance inside a miniature called capsule. Microcapsules are 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. The microcapsule size range from 1 µ -7mm.All the 3 states i.e. solid, liquid and gases may be encapsulated which may affect the size and shape of capsules (Leon and Herbert, 1990).

- If the solid or crystalline material is used as the core, the resultant capsule may be irregularly shaped.
- If the core material is liquid, simple spherical capsules containing a single droplet of encapsulate may be formed.

Reasons for Microencapsulation

- It is mainly used to increase the stability, and sustained/prolonged release of the product.
- Controlling the release rate of the drug from the microcapsules.
- This technique was widely used for masking taste and odour of many drugs and to improve patient compliance.
- For converting liquid drugs into a free flowing powder.
- To reduce the toxicity and GI irritation and many major side effects of the drugs
- Alteration in site of absorption can be achieved by microencapsulation (James, 2002; Bansode *et al.*, 2010).

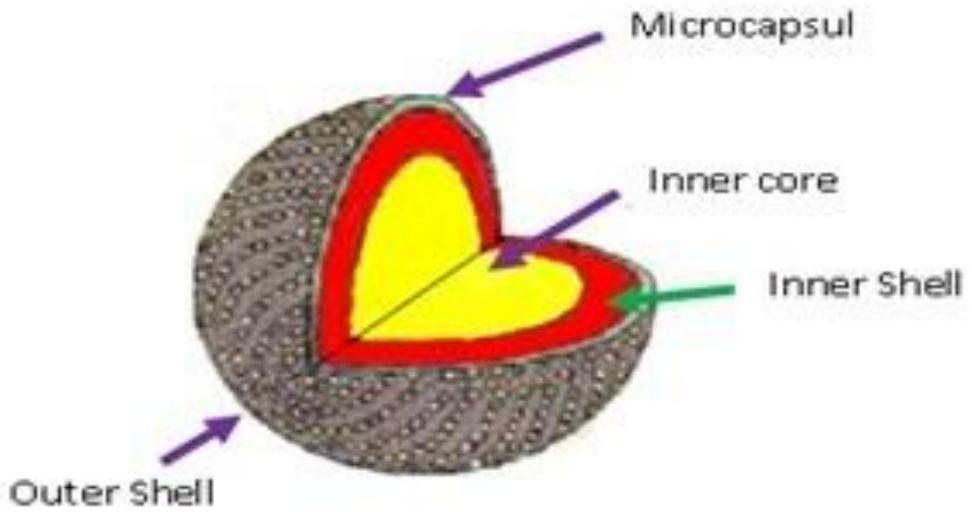

Figure 1: Structure of microcapsule

Types of microcapsules*:* The microcapsules are divided into three types
1. Mononuclear / single core.
2. Polynuclear/ multiple core.
3. Matrix type (Jyothi, 2012).

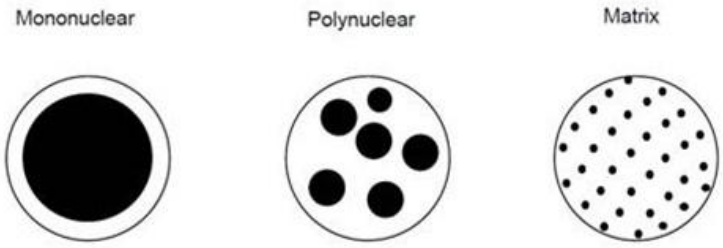

Figure 2: Types of microcapsules

Mechanism of Drug Release from Microcapsules
It involves 4 different mechanisms (Brazel and Peppas, 2000).
1. Diffusion controlled monolithic system**:** It is the most common mechanism of drug release from core material in which the dissolution fluid penetrates the shell then the core comes into contact with dissolution fluid and leaks through interstitial channels or pores. The drug release depends upon
a) The rate of drug dissolution in dissolution fluid**.**
b) Rate of penetration of dissolution fluid to the microcapsules and rate at which the dissolved drug escapes from the microcapsules.
The rate kinetics of drug release follows higuchi equation

$$Q=[D/J\ (2A- € CS)CSt\ ]½$$

Q = Amount of drug release per unit area of exposed surface in time t.
J = Tortuosity of the capillary system in the wall.
D = Diffusion co-efficient of solute in solution.
A = Total amount of drug per unit volume.
€ = Porosity of the wall of microcapsules.
CS = Solubility of the drug in permeating dissolution fluid.
2. Dissolution**:** The rate of drug release depends upon the dissolution rate of polymer coat, when coat is soluble in dissolution fluid. It also depends upon the solubility in the dissolution fluid and thickness of coat material. The release of the drug occurs by dissolution of the coat or by melting the wall of the capsule.
3. Degradation controlled monolithic system: The drug is dissolved in matrix and is distributed throughout the core. The drug is attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow when compared to degradation of the matrix.
4. Erosion: The release of the drug by erosion mechanism occurs due to pH or enzymatic hydrolysis of the coat. The drug release from microcapsules has become complex. Difference in physical forms of microcapsules such as size, shape and arrangement of core and coat materials. The physico-chemical properties of core material like solubility, diffusibility, partition co-efficient and for coating materials like thickness, porosity. The drug release from microcapsules follow zero order kinetics i.e. the release rate is constant they deliver fixed amount of drug per time period. Microcapsules of monolithic type have the t½ dependent release for first half of total drug release and turn down exponentially thereafter (Sachan, 2005).
Development of Microcapsules
1. Core material: The core material is defined as the specific material to be coated whether it can be a solid or liquid. The solid core can be the active ingredient, stabilizers, diluents, excipients, release rate retardants whereas liquid core include the dissolved materials.

2. Coating material: Coating materials are defined as a layer of substance covered over the core for production of the drug. The coating material should possess properties such as

- It should have controlled release under specific conditions, soluble in aqueous media/solvent.
- It should possess sufficient properties such as flexibility, strength, impermeability, stability and optical properties.
- It should be chemically compatible with the core and non-reactive.
- It should be capable of forming a film.

Types of coating materials: Depending upon origin (Shekhar *et al*., 2010).

Table 1: Types Of Coating Materials

POLYMERS	EXAMPLES
1. **1.NATURAL POLYMERS**:	
A.Proteins:	Albumin Gelatin Collagen.
B.Carbohydrates:	Agarose Chitosan Starch Carragenan
C.Chemically modified carbohydrates	polystarch Polydextran
2.SYNTHETIC POLYMERS:	
A.Biodegradable:	Lactides Glycolides and co polymers Poly alkly cyanoacrylates Poly anhydrides
B.Non biodegradable :	poly methyl methacrylate (PMMA) Acrolein Glycidyl methacrylate Epoxy polymers

POLYMERS ..	EXAMPLES
DEPENDING UPON SOLUBILITY: **1.Water soluble resins:**	Gelatin Gum arabic Starch Poly vinyl pylorridine Methyl cellulose Carboxy methyl cellulose Hydroxy ethyl cellulose Poly vinyl alcohol Arabinogalactan Polyacrylic acid.
2.Water insoluble resins :	Ethyl cellulose Poly ethylene Polymethacrylate Polyamide (Nylon) Poly (Ethylene vinyl acetate) Cellulose nitrates Silicones Poly (lactide-co-gylcolide)
3.Waxes and Lipids :	paraffin Carnauba. Spermaceti Bees wax Stearic acid Stearyl alcohol Glyceryl stearate
4.Enteric resins :	Shellac Cellulose acetate phthalate Zein

Factors Influencing Properties of Microcapsules

1. Properties of material

a. Dispersed phase

b. Continuous phase

The polymer plays an important role in encapsulating the drug which depends on

i. The solubility of the polymer.
ii. The concentration of polymer.
iii. The organic solvent used.
iv. Rate of solvent removal.
v. Dispersed and continuous phase ratio.
vi. Nature of the drug –hydrophilic /hydrophobic

If the polymer concentration is increased the encapsulation efficiency of the drug also increases and if the dispersed phase is highly viscous it reduces porosity of the microcapsules thus sustaining the drug release.

Dispersed and continuous phase ratio effect the rate of solidification of microcapsules .If the volume of continuous phase is large it causes a high concentration gradient of the organic solvent across the phase boundary by diluting the solvent, leading to fast solidification of the microcapsules. This rate of solidification in turn affects the particle size of the microcapsules; increase in the volume of continuous phase increases the particle size.

Rate of solvent removal is temperature dependent, a rapid increase in temperature results in the formation of thin wall and a large hollow core resulting in burst release of the drug whereas step wise increase in temperature reduces the core size leading to control drug release.

The solubility of the polymer depends on the cloud point (Cs) of the organic solvent used ,higher the cloud point of the organic solvent higher the solubility of the polymer and hence requires more amount of organic solvent to precipitate out from the polymeric solution.

Parameters to Be Considered for the Formulation

- Viscosity of dispersed phase.
- Volume fraction of dispersed phase to continuous phase.
- Quantity of drug in dispersed phase.
- Concentration of surfactant.
- Operating parameters:
- Agitation rate
- Temperature
- Pressure
- Geometry of reactor and agitator.

Techniques for Preparation of Microcapsules

1. *Physical Methods*

2. Chemical Methods

3. Physicochemical Methods

1. Physical Methods

A. Air suspension coating*:* In this method the core material which is a solid is dispersed into supporting air stream and these suspended particles are drug coated with polymers in volatile solvent release leaving a very thin layer/film of a polymer on core. The process is repeated for several times until required parameters such as coating thickness are achieved. The air stream which supports particles also helps to dry the particles. The rate of drying is directly proportional to the temperature of air stream. The coating chamber is arranged such that particles move upwards through coating zone, then disperse into moving air and back to the base of coating chamber making repeated passes until desired thickness is achieved (Jackson *et al.*, 1991).

Process variables to be considered during formulation:

- Concentration of coating material.
- Solubility, Melting point, Surface area, Density, Volatility of core material.
- Temperature of air stream, amount of air stream required to fluidize.

B. Coacervation process*:* In this process, the core material is dispersed in the solution of coating material such that the Core material doesn't dissolve/react in solvent. Coacervation occurs when there is a change of pH value of the dispersion which is done either by adding sulphuric acid, Hcl, organic acids as a result it decreases the solubility of the dispersed phase (shell material) and proceeds to form precipitate from the solution. The shell material forms a continuous coating around core and shell cools down to harden and forms a microcapsule. The hardening agents such as formaldehyde may be added to the process. The suspension was the dried in spray drier / fluidized bed dryer (Nihant *et al.*, 1995).

Disadvantage

* Spray drying is only suitable for heat sensitive drugs.

C. Pan coating: It is the one of the oldest method used in pharmaceutical industry. In this method, the particles are tumbled in a pan while the coating material is applied slowly. The solution is applied from the atomized spray to the core material, hot air is passed to remove coating solvent. Particles > 600µm in size are essentially effective for pan coating (Kasturagi *et al.*, 1995).

D. Centrifugal extrusion process: This process is suitable only for liquid/slurries. In this process the encapsulation occurs using a rotating extrusion head which contains concentric nozzles. The jet of core liquid is surrounded by sheath of solution. As the jet moves through the air breaks owing into droplets of core each coated with wall solution. While the droplets are in fluidized/flight molten wall is hardened/solvent may be evaporated from wall solution. Since, the droplets are within ±10% mean diameter, they settle as a narrow ring around the spray nozzle. So, capsule can be hardened after formation by holding them in a ring shaped hardening bath. This process is suitable for forming particles of 400-2000µm.

E. Spray drying and congealing method*:* This method is suitable for labile drugs because of less contact time in dryer & it is economical. In this process active material is dissolved/suspended in polymer solution and trapped in the dried particle. Both the methods are similar in process of dispersion of core & coating substance but there is a difference in rate of solidification of coating.

In spray drying, there is a rapid evaporation of solvent in which coating material is dissolved whereas in case of spray congealing solidifying occurs by thermal congealing/introducing a non solvent. Removal of non solvent is by sorption, extraction and evaporation (Re, 1998; Poshadri and Aparna, 2010).

A. Solvent evaporation method: This method is widely used for water soluble and water insoluble materials to produce solid and liquid core materials.

A variety of film forming agents or polymers can be used. In this method, the coating material (polymer) is dissolved in a volatile solvent which is immiscible with the liquid vehicle phase. A core material (drug) which is to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture or dispersion is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The solvent is evaporated either by continuous agitation or by application of external heat supply (Jain, 2002).

B. Interfacial Polymerisation*:* In this method, the reactants join at the interphase and react rapidly. The reaction involves an acid chloride and a compound containing an active hydrogen atom such as amine or alcohol, polyesters, polyuria. As a result, thin flexible walls are rapidly formed at the interface; the acid formed is neutralized by the base formed during the reaction.

C. Interfacial cross linking: In this method, the monomer containing active hydrogen is replaced by a polymer such as protein. As a result, reaction occurs at the interface of emulsion, the acid chloride reacts with various functional groups of protein which leads to formation of a membrane. This method was developed to avoid the use of toxic diamines.

D. Insitu polymerisation*:* This method involves direct polymerization of a single monomer is carried out on the particle surface. The coating thickness ranges from 0.2-75µm.

E. Matrix polymerisation*:* In this method, a core material is embedded in a polymeric matrix during formation of particles. This method is similar to that of spray drying, in which particle is formed by evaporation of the solvent from matrix material.

3. Physico-chemical Methods

A. Coacervation phase separation: It includes 3 stepshttps://en.wikipedia.org/wiki/Micro-encapsulation.

i. Formation of 3 immiscible phases (core material, coating material phase, liquid phase)
ii. Deposition of polymer on core material.
iii. Rigidisation of coating material.

Core material is dispersed in solution of coating polymer, solvent for polymer is vehicle.

↓

Deposition of polymeric solution onto core material.

↓

Deposition of liquid polymer occur when polymer is absorbed at interface between core material and liquid vehicle phase

↓

Rigidisation

↓

Microcapsule

B. Ionotropic gelation method: This method is based on the ability of polyelectrolytes to crosslink in the presence of counter ions to form hydrogels. Ionotropic gelation is produced when units of uric acid of the chains in the polymer alginate, crosslink with multivalent cations. These may include calcium, zinc, iron and aluminum.

Applications (Benita, 1996)

- Microencapsulation has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat.
- A great degree of protection can be provided by microencapsulation. For ex: Vitamin A, K has been shown to be protected from moisture and oxygen.
- In the field of agriculture microencapsulation has been used to decrease potential danger of handling toxic/noxious substances. Toxicity occurred due to handling of fumigants, herbicides, insectides and pesticides which has been decreased by the use of microencapsulation techniques.
- *To reduce gastric irritation.

In Food Industry (Jackson and Lee, 1991)

- In conventional drug delivery system, the ingredients react and slowly degrade and lose activity or become hazardous by oxidation reactions and limits bioavailability. Hence microencapsulation can overcome all these challenges by providing texture, colour, blending, odour and masking taste, appealing aroma release.
- By microencapsulation liquids are converted to solid powder at low cost and stabilize the shelf life of active ingredients.

In Vaccine Delivery

* Microcapsules have been used as carriers as they stabilize and modulate the antigen release.
*The drug reduces the multiple dosing, increasing patients' convenience. For Ex: LUCRIN depot which contains lyophilized polymer made from lactic acid. The core contains leuprolide acetate which is analog of gonadotropin releasing hormone for the treatment of prostate cancer, breast cancer and endometriosis (Thies and Bissey, 1983). *Novel drug delivery system has potential applications in controlled/sustained delivery of the drugs. Microencapsulation has proven to be potential for the replacement of therapeutic agents, gene therapy, for treatment of AIDS, tumors, diabetes.

CONCLUSION

As the concept of controlled drug delivery system was introduced in the year 1970's much more progress and promising results were made in microencapsulation. In this process, three phases of matter can be encapsulated such as solid, liquids and gases. It converts the liquid drugs into free flowing powder. It reduces the toxicity and GI irritation and side effects. Micro capsules proved to be a better delivery system for sustaining the drug release and targeting to the specific site there by reducing the toxicity and adverse effects of the drugs.

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