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# CURRENT TRENDS IN PHARMACEUTICAL MICROENCAPSULATION TECHNOLOGIES: A REVIEW

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## ABSTRACT

Microencapsulation are multi-particulate drug transport classifications, prepared to get extended, sustained or controlled drug delivery to increase bioavailability, stability and target the drug, to exact site at a preset rate. Every minute droplets or particles of liquid or solid material that are surrounded or coated with a continuous film of polymeric material is known as microencapsulation process. Microencapsulation techniques used to improve stability, cover unpleasant taste, improve the release properties of drugs, and deliver specific drug delivery in pharmaceutical industries. The contest of microencapsulation is in selecting the suitable conditions for producing extremely active microcapsules. This paper is a complete review of microencapsulation and its applications, various drug release mechanisms and latest developments in the pharmacy field. It provides an inclusive overview of technology, main goals of microencapsulation and discusses the various processes and techniques involved in microencapsulation including physical, chemical, physicochemical, and other methods involved.

**KEYWORDS**: Microencapsulation, Release Mechanisms, Preparation techniques, Applications.

## INTRODUCTION

A finely intended controlled drug delivery system can defeat some of the problems of traditional therapy and improve the therapeutic efficacy of a given medication. Inorder to get the most extreme therapeutic efficacy, it is important to deliver the drug to the objective tissue in the optimal amount in the correct period of time there by causing little toxicity and insignificant side effects. 'There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microencapsule as carriers for drugs'.[1]

"Generally Multiparticulate drug delivery systems are intended for oral, parentral and topical formulations and approaches include formulations in the form of pellets, granules, beads, gelispheres, microcapsules, microspheres, lipospheres, microparticles and nanoparticles".[2,3] "Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials".[4] Microencapsulation is a process by which very little droplets or particles of liquid or solid material are enclosed or coated with a constant film of polymeric material.[5]

Microencapsulation has been used to increase stability, to mask bitter taste, to improve the release properties of drugs, and to provide specific drug delivery in pharmaceutical industries.[6] The first research leading to the development of micro encapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kass in 1931and dealt with the preparation of gelatin spheres and the use of gelatin coacervation process for coating.[6] In the late 1930s, Green and co-workers of National cash register co. Dayton, Ohio, developed the gelatin coacervation process.[7]

Then may other coating materials and processes of application have been developed by the pharmaceutical industry for the microencapsulation of medicines. Over the last 25 years pharmaceutical companies for microencapsulated drugs have taken out numerous patents.[8, 9]

### Need of microencapsulation in drug delivery system

The primary reason for microencapsulation is found to be either for sustained or prolonged drug release.[10] This technique has been widely used for masking taste and odor of many drugs to improve patient compliance.[10] This technique can be used for converting liquid drugs in a free flowing powder.[10] The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.[10] Incompatibility among the drugs can be prevented by microencapsulation.[10]

Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.[10] Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl. Alteration in site of absorption can also be achieved by microencapsulation.[10]

The main cause for microencapsulation is due to sustained or prolonged drug release. This is mainly used for masking taste and odor in many drugs as it helps to improve patient compliance. Besides this, it is used for converting liquid drugs to free flowing powder; also, it stabilizes drugs that are sensitive to oxygen, moisture or light. Microencapsulation further prevents incompatibility among drugs, vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil, reduces toxicity and GI irritation including ferrous sulphate and KCI and also, alteration in site of absorption.[10]

**Drug release mechanism of microencapsulation**

Drug release from the microparticulate formulation occurs by general mechanism including diffusion, dissolution, osmosis and erosion.[11] Major mechanisms of drug release from microcapsules include:

**1. Dissolution Controlled System:** Dissolution process is the rate controlling step. 'Using the polymer, the drug is embedded in slow dissolving or erodible matrix or by coating with slow dissolving substance. There are two types, encapsulation and matrix'.[12]

**a) Encapsulation:** Slow dissolving materials like cellulose, polyethylene glycol, polymethacrylates, and waxes were used as coating material for drug particle or encapsulated by microencapsulation techniques. It is based on the solubility and thickness of coating as the dissolution rate will vary.[13,15]

**b) Matrix or Monoliths:** We can control the rate of dissolution fluid penetration into matrix by altering the rate of porosity. Drug dissolution is controlled by waxes such as beeswax, carnauba wax, hydrogenated castor oil. The wax embedded drug is prepared by dispersing drug in molten wax and congealing and granulating the same.[14,15](Fig.1)

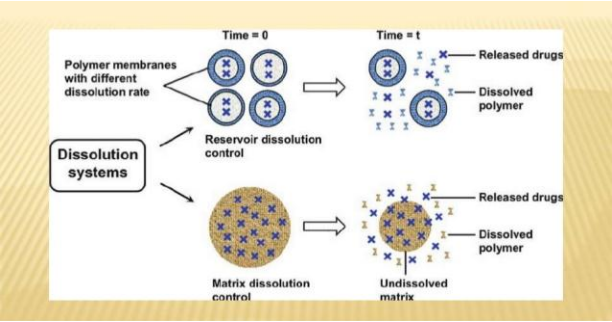


**Fig 1: Release mechanism Dissolution controlled system.[33]**

**2. Diffusion Controlled System:** Diffusion of drug through inert water insoluble membrane barrier is the rate controlling step.[15] In the case of a polymer matrix, the diffusion of the active ingredient can be through the intact polymer network or through the pores filled with water.[16] Water-soluble drugs may also dissolve in the aqueous pore networks. Due to water uptake, polymer chains swell, representing the formation of new pores and/or osmotic pressure. Through swelling, the volume increases, the effective diffusion coefficient of the drug is increased, and more pharmacon molecules enter the aqueous part.[16] Drug release rate also depends upon where the polymer degradation occurs due to either homogeneous or heterogeneous mechanism.[17]

The drug release depends on three factors like:

- Rate of drug dissolution in the dissolution fluid
- Rate of penetration of dissolution fluid to the microbeads
- Rate at which the dissolved drug escapes from the microbeads.[18](Fig 2)

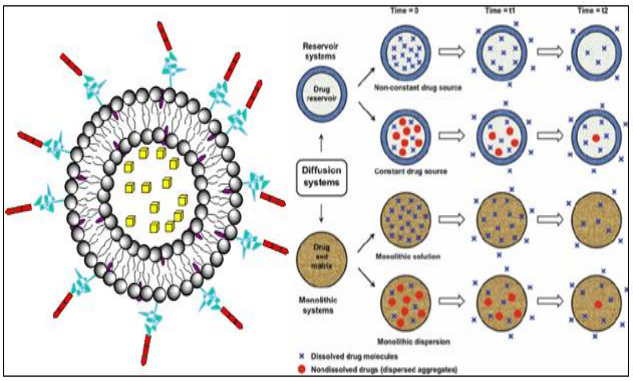


**Fig 2: Release mechanism Diffusion controlled system.[34]**

**3. Osmosis:** Another method of drug release is through osmosis. The essential requirement of osmosis is semi-permeable membrane. As the process progresses an osmotic pressure is created between the outside and inside membrane of microcapsule which results in the release of drug through small pores.

**4. Erosion:** Some coatings can be designed to erode gradually with time, thereby, releasing the drug contained within the particle. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as the water penetrates within it leading to the plasticization of the matrix.

**Microencapsulation technique**

Microencapsulation techniques involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, stability and release characteristics of the coated materials and the microencapsulation methods. The intended physical characters of the encapsulated product

and the intended use of the final product must also be considered.[19-21]

**Core Material:** 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 liquid core or can include dispersed and/or dissolved material. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or accelerators.[19-21]

**Coating Materials:** The coating material should be capable of forming a film that is cohesive with the core materials, chemically compatible and non-reactive with the core material. It should provide the desired coating properties such as strength, flexibility impermeability, optical properties and stability. The total thickness of the coatings achieved with microencapsulation techniques is microscopic in size. A numbers of different substances both biodegradable as well as non-biodegredable have been investigated for the preparation or microcapsules. Coating materials include the polymers of natural and synthetic origin and also modified natural substances. Also, coating material inert substance which coats on core with desired thickness. Composition of coating are Inert polymer Plasticizer Coloring agent Resins, waxes and lipids Release rate enhancers or retardants.[19-21]

**Stability, release and other properties**: Three important areas of current microencapsulation application are the stabilization of core materials, control of the release or availability of core materials and separation of chemically reactive ingredients within a tablet or powder mixture. A wide variety of mechanisms is available to release encapsulated core materials, such as disruption the coating which can occur by pressure, shear or abrasion forces, permeability changes brought about enzymatically etc., improved gastro tolerability of drugs can be obtained by microencapsulation.[19-21] (Fig 3)

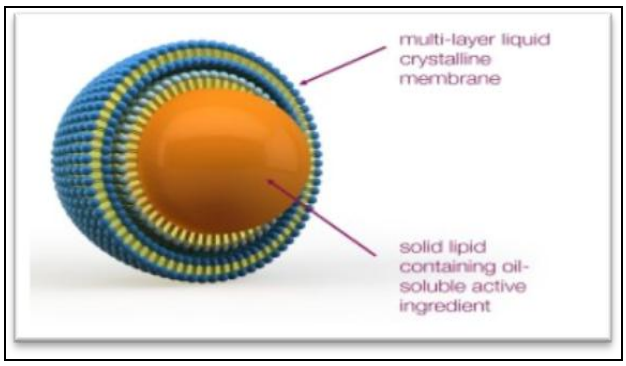


**Fig 3: Microcapsule with Core material and Coating material.**[29]

**Methods of microencapsulation**

Various techniques are used in preparation of Microencapsulation.[22-27,28,30]

1. Coacervation phase separation
2. Multi orifice centrifugal process
3. Pan coating
4. Air suspension coating
5. Spray drying and spray congealing
6. Polymerization
7. Melt dispersion technique

**1. Coacervation Phase Separation**: Coacervation is a colloid phenomenon. If one starts with a solution of a colloid in an appropriate solvent, then according to the nature of the colloid, various changes can bring about a reduction to the solubility of the colloid. As a result of this reduction a large part of the colloid can be separated into a new phase. The original phase one system becomes two phases. This process consists of three steps and leads to the formation of three immiscible phases- 1. Liquid manufacturing phase 2. Core material phase and 3. Coating material phase. Deposition of the liquid polymer coating on the core material.

The process of coacervation involves the core material that will be added to the solution. The core material should not react or dissolve in water and it should be dispersed in the solution. The particle size will be defined by dispersion parameter, as stirring speed, stirrer shape, surface tension and viscosity. Size range 2µm - 1200µm. Coacervation starts with a change of the pH value of the dispersion, e.g. by adding H2SO4, Hcl or organic acids. The result is a reduction of the solubility of the dispersed phases[22-23,30,24] (shell material). (Fig 4) The shell material

1. (coacervate) starts to precipitate from the solution.
2. Forms a continuous coating around the core droplets.
3. cooled down to harden and forms the final capsule.

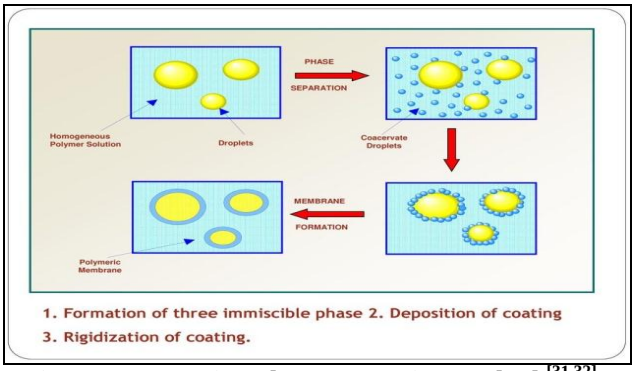


**Fig 4: Coacervation phase separation method.**[31,32]

**2. Multi orifice centrifugal process**: The South-West Research Institute (SWRI) has developed a mechanical process for producing microcapsules that utilizes centrifugal forces to hurl, a core material particle through an enveloping microencapsulation membrane therapy effecting mechanical microencapsulation. The processing variables include the rotational speed of the cylinder, flow rate of the core and coating materials, concentration and viscosity of the coating material and the viscosity and surface tension of the core material. This method is

capable of microecapsulating liquids and solids of varied size ranges, with diverse coating materials.[22,23,30] (Fig 5)

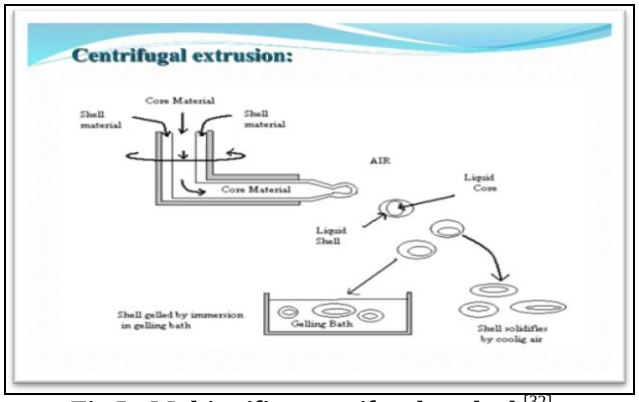


**Fig 5: Multi orifice centrifugal method.**[32]

**3. Pan Coating:** The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. As far as microencapsulation is considered the solid particles greater than 600 microns in size are generally considered essential for effective coating, and the process has been extensively employed for the preparation of controlled - release beads.[13,14,15] (Fig 6)

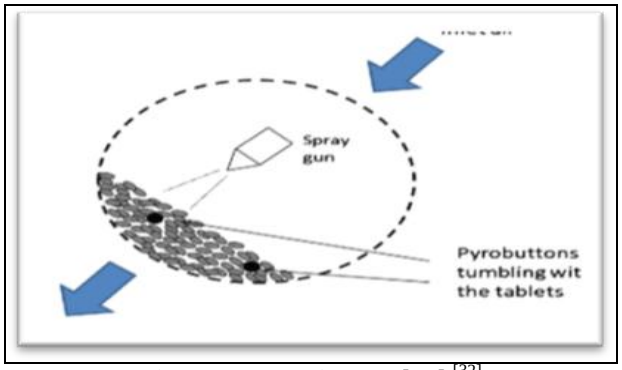


**Fig 6: Pan Coating method.**[32]

**4. Air Suspension Coating**: Air-suspension coating of particles by solutions or melts gives better control and flexibility. The particles are coated while suspended in an upward-moving air stream. They are supported by a perforated plate having different patterns of holes inside and outside a cylindrical insert. Sufficient air is permitted to rise through the outer annular space to fluidize the settling particles. Most of the rising air (usually heated) flows inside the cylinder, causing the particles to rise rapidly. At the top, as the air stream diverges and slows, they settle back onto the outer bed and move downward to repeat the cycle. The particles pass through the inner cylinder many times in a few minutes methods. The air suspension process offers a wide variety of coating materials candidates for microencapsulation. The process has the capability of applying coatings in the form of solvent solutions, aqueous solution, emulsions and dispersions or hot melts in equipment ranging in capacities from one pound to 990 pounds. Core materials comprised of micron or submicron particles can be effectively encapsulated by air suspension techniques, but agglomeration of the particles to some larger size is normally achieved.[19-20,22] (Fig 7)

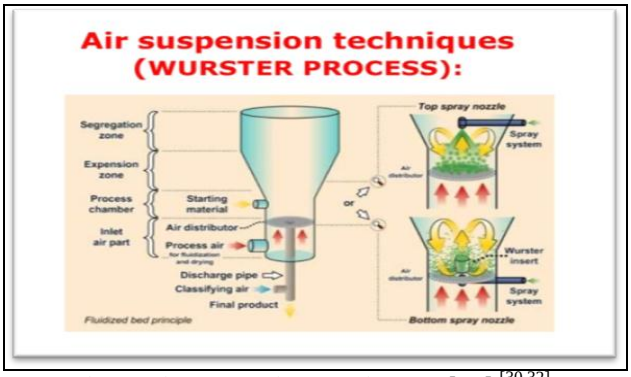


**Fig 7: Air suspension coating method.**[30,32]

**5. Spray Drying and Spray Congealing**: Spray-drying is a widely used technique in the food and pharmaceutical industry, because it presents several advantages including those of low cost, easy adaptation to the industrial scale, and high drug-loading efficiency. In the spray-drying process, core material is mixed or homogenized in a solution of wall material, to form a stable emulsion. This emulsion is fed into a spray dryer and formed into a dried particle. Wall materials can be selected from a variety of polymers, depending on the core material and the desired characteristics of the final product. In the spray congealing process, the coating solidification is effected by thermally congealing a molten coating material. For the spray-drying process, the wall material must be soluble in water at an acceptable level and possess good properties of emulsification, film forming, and drying.[24-26] (Fig 8)

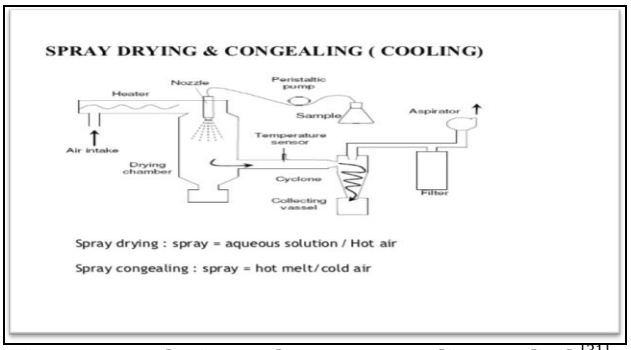


**Fig 8: Spray drying and spray congealing method.**[31]

**6. Polymerization**: This method involves the reaction of monomeric unit located at the interface existing between a core material and a continuous phase in which the core material is dispersed. The continuous or core material

supporting phase is usually a liquid or gas and therefore the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid or solid-gas interface e.g., microcapsules containing protein solutions by incorporating the protein in the aqueous diamine phase.[20,21,23,30]

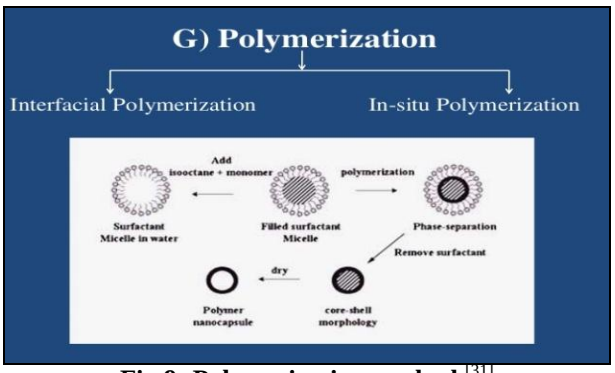


**Fig 9: Polymerization method.**[31]

**a. Interfacial Polymer:** Interfacial polymerization, the two reactants in a polycondensation meet at an interface and react rapidly. The basis of this method is the classical Schotten Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea and polyurethane; under the right conditions, thin flexible walls form rapidly at the interface.[23]

**b. In-situ Polymerization**: In a few microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface. This method is similar to interfacial polymerization that shell form by polymerization, but in this process no reactive agent is added to the core material. The polymerization starts in continuous phases and it is deposited at interface, as the time progress the pre-polymer grows in size.[25,29,31,32]

**7. Melt Dispersion Technique:** In this technique the coating material is melted by heating upto 80$^{o}$C. The drug is suspended in it and then emulsified in water containing emulsifying agent at 80$^{o}$C under stirring. Microcapsules are formed as the temperature of the system reaches room temperature.[27-30]

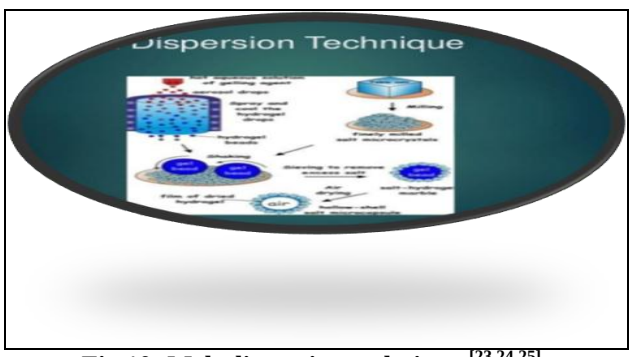


**Fig 10: Melt dispersion technique.**[23,24,25]

**Applications of microencapsule in pharmaceutical industry**

1. Reduces hazards e.g. insecticides
2. Reduces possibilities of sensitization e.g. ampicillin trihydrate
3. Reduces hygroscopic properties e.g. sodium chloride
4. Improve flow properties of vitamins e.g. riboflavin, niacin, thiamine
5. Production of sustained release dosage forms
6. Reduces gastric irritation e.g. aspirin, potassium chloride
7. Used to mask unpleasant taste of drugs. e.g. acetaminophen
8. Prevents incompatibilities between drugs e.g. aspirin & chlorpheniramine maleate
9. Provides protection to core material against environmental conditions
10. Enhances stability of fat soluble vitamins
11. Prolonged release dosage forms. The microencapsulated drug can be administered as microencapsulation as it is useful for the preparation of tablets, capsules or parental dosage forms.[27, 28, 32]

## CONCLUSION

Microencapsulation is one of the quality preservation techniques of sensitive substances and a method to produce materials with new valuable properties. The popular microencapsulation technique is the most convenient way of protection and masking, reduce dissolution rate, facilitation of handling, and spatial targeting of active ingredients. Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimeters. The capsule protects the active ingredient from its surrounding environment until an appropriate time. Then, the material escapes through the capsule wall by various means, including rupture, dissolution, melting or diffusion. The microencapsulation approach is also beneficial for those drugs which require dissolving into the intestine and not in the stomach.

## ACKNOWLEDGMENTS

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