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Micro Particles: A Review of Recent Developments, Microencapsulation Method, and Therapeutic Strategies

Abstract

A targeted drug delivery system has a great impact on patience health minimizing the side effect and enhancing therapeutic outcomes, so modern research come towards particulate drug delivery system. Microparticle and nanoparticle are key tools for targeted sustained, delayed, and tissue-specific drug delivery. In this review article, I will discuss microparticle drug delivery system, types of microparticles how drug release from microparticulate system, Materials required for microparticulate drug delivery system, polymers used for micro particles drug delivery system, and procedures employed for the formulation of microparticulate drug delivery systems, Microencapsulation method, and treatment plan depend on Polymeric Microparticles.

Key Words: Microparticle; Targeted Delivery, Microencapsulation Method

Introduction

Microparticles are tiny solid particles with a size range of 1-1000um (N. Jyothi, Harekrishna, Lakshami, & Sari, 2016; Kataria, Middha, Sandhu, Ajay, & Bhawana, 2011). On the basis of microparticle preparation method, drug dissolved, entrapment and encapsulation into the microparticle matrix. The microparticle drug delivery systems are a consistent way to administer the drug into target site without side effects and to achieve the effective therapeutic concentration at specific site (D. A. Padalkar, Shahi, & Thube patil, 2011). Different types of pharmacologically active drug moieties show low water solubilities that requires the fabrication of different delivery vehicle for targeting delivery (Koroleva, Nagovitsina, Bidanov, Gorbachevski, & Yurtov, 2016).

In recent years, particle delivery systems for drugs have shifted from scientific inquisitiveness to more dynamic research safeties, clinical applications. It has many advantages over a convenient method of drug administration. The main advantage of microparticle drug delivery is that they are easily injecting into the tissue or applied either topically by using an appropriate vehicle (Kohane, 2007).

Microparticles have many advantages, they are formulated are formed to protect the drug from environmental degradation, masking bitter taste, preserving volatile, a reduced side effects of the drug, and enhance drug targeting. Microparticles are divided into two types' microsphere and microcapsule. In microsphere drug is homogeneously dispersed in matrix system, the drug may be suspended or dissolved while in microcapsule heterogeneous particle cover by a membrane shell core and forming a reservoir. Microspheres contain lipid or solid active constituents either in dispersed (Lengyel, Kállai-Szabó, Antal, Laki, & Antal, 2019).

Microparticles deliver easily through different ways in the body and control the release pattern of a drug for a different period due to entrapment of drug protection against degradation. This method of drug delivery is helpful in the controlled delivery of drug moiety. The maximum effect of the drug is achieved by sustaining the dose at the therapeutic level through a constant period by microparticles,

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especially for those drugs which have high potent drugs like anticancer drugs. Microparticle has the advantage and some limitation due to small size that leads to aggregation of a particle (A. N. Padalkar, Shahi, & Thube, 2011). In this review article, we will discuss types of nanoparticle like microsphere, microcapsule, and their types, different method of preparation, drug release mechanism from nanoparticle, advantages, and disadvantages of nanoparticle and future aspects of modern drug delivery system.

Types of Microparticles

Microparticles are of two types;

Microcapsules

Microcapsules consist of core material that is completely surrounded by film or polymeric material. The coat of microcapsule is continuous, porous and sometimes non porous polymeric type (N. Jyothi et al., 2016; Sharma & Lewis, 2010). Microcapsules can be classifying into three categories on the basis of morphology such as

Monocored

Monocored microcapsules contain single hollow chamber within the capsule.

Polycored

Polycored microcapsules consist of number of diverse sized chambers present in shell.

Matrix Type

In matrix type microcapsules, active ingredient is incorporate in the matrix of shell material (Dubey, 2009).

Microspheres

Microspheres are matrix-based systems. In microsphere drug is added within a rate controlled polymer matrix (Yang & Pierstorff, 2012).

Advantages of Microparticles

a) By administering subcutaneous and intramuscular to bypass gastric environment.
b) Administer safely by using standard needles
c) Possibility of directly administer the drug in the target tissues which are not by convenient dosage form e.g., central nervous system
d) No need of surgical removal of empty fragments if biodegradable matrix former is used. PLGA is most commonly used matrix former because it is biocompatible and degraded to natural substances present in human body (Siepmann & Siepmann, 2006)

Mechanism of Drug Release from Microparticulate System

The basic object of drug release from any targeting drug delivery system is to achieve the drug concentration at therapeutic level at the site of action of which must be in therapeutic window (Bajpai, Shukla, Bhanu, & Kankane, 2008; Ostrovidova, Makeev, & Shamtsian, 2003). Drug release from system is depend upon different factors that effect on the drug release from the carrier that comprise composition of the drug delivery system, their ratio, physicochemical interaction among the components and their method of preparation (J. H. Lee & Yeo, 2015). Drug release from the drug delivery system is categorized into four categories on the basis of mechanism of drug escape from the carrier;

Diffusion Controlled Drug Delivery System

For the targeted drug delivery of drug, diffusion plays an important role for the release of drug in a controlled manner. It is a dominant mechanism of drug release pattern from the system as compared to other mechanism of drug release (Siepmann, Siegel, & Siepmann, 2012). Diffusion controlled system releases the drug from a reservoir by infiltration from inner to outer medium on the basis of concentration gradient across the membrane. Diffusion of drug from system is the rate limiting step. Drug Diffusion from reservoir are typically either reservoir diffusion or matrix-based systems. By following the reservoir system, first drug dissolves in the core of the system and then diffuses out from the polymeric shell. In the matrix system, drug is homogeneously dispersed in the polymer matrix without any outer membrane barrier: therefore initially drug is released rapidly, followed by slow release as a function of time and distance for drug molecules present in the inner carrier of the system (X. Huang & Brazel, 2001; J. H. Lee & Yeo, 2015).

Dissolution

Dissolution process refers to the detachment of the active drug moiety from the surface of their solid structure followed by the diffusion into surrounding bulk liquid medium. Desired drug release profile can be attained by exploitation of this process. Matrix and membrane-based systems can be fabricated to slow the drug release. If the water soluble polymer is used then dissolution is the rate limiting step (Wang & Shmeis, 2005).

Osmosis

In osmosis movement of solute particle across the semipermeable membrane from lower concentration to higher solute concentration. Osmotic flow through the semipermeable membrane is directed to compensate the difference in concentrations of the impermeable solutes on either side of the semipermeable membrane. It results in a hydrostatic pressure difference across semipermeable membrane that causes solvent to move in opposite direction (Herrlich, Spieth, Messner, & Zengerle, 2012; Siegel & Rathbone, 2012).

Degradation and Erosion

The biodegradable polymers such as polyesters, polyamides and polysaccharides are used in different drug delivery system and drug release occur by enzymatic degradation or hydrolytic of amide, ester and hydrazone bonds in the structure (W. C. Lee & Chu, 2008; Yoo & Park, 2001). polymer degradation proportion determines the release of drug kinetics and it is based on molecular weight of polymer, end group crystallinity and monomer composition (Fredenberg, Wahlgren, Reslow, & Axelsson, 2011). Biodegradation of polymers are preferred because these are converted into substances that are easily excreted from body without causing any toxic effects in the body (J. H. Lee & Yeo, 2015).

Swelling

Swelling is a mechanism of up taking water by a polymer system and result in increased the system volume. The rate of swelling mechanism is depending on the water polymer interaction i.e, hydrophilicity of the polymer the crosslinker density in the polymer chains. When hydrophilic polymeric materials come in contact with aqueous solutions such as water imbibes, or body fluids into the system, the water uptake by system resulting in swelling of the polymer shell and drug is released from the polymer system (Peppas, Bures, Leobandung, & Ichikawa, 2000).

Materials Required for Micro Particulate Drug Delivery System

Core Material

The material which is coated known as core. It may be a solid or liquid in nature.

Composition of Core

- Active ingredients
- Stabilizers
- Diluents
- Release rate retardants
- Release rate accelerators

Coating Material

Depending upon the nature of core material coating material is selected from different types of natural and synthetic materials.

Desired Characteristics of Coating Material

- Coating material have ability to form thin film
- Coating material have compatibility physically and chemically
- It should be non-reactive with core material
- After coating it must show desired properties of coating such as flexibility, strength, stability and optical properties (Palanivel, Manavalan, & Valliappan, 2009).

Table 1. Examples of Coating Materials (Radhika, Sai, Evangelin, & Balaji, 2012)

Coating material	Examples
Water soluble resins	Gelatin, gum arabica, starch, PVP, PVA, hydroxyl ethylcellulose, methyl cellulose
Water insoluble resins	Ethyl cellulose, polyethylene, polymethacrylate, polyamides, silicones
Waxes and lipids	Bees wax, paraffin, carnauba, spermaceti, stearyl alcohol
Enteric resins	Shellac, zein, cellulose acetate phthalate

Polymers used in Microparticulate Drug Delivery System

Waxy nature polymer and different protective materials such as natural, semi synthetic and synthetic polymers are used in micro particulate drug delivery (Kadam & Suvarna, 2015). Natural polymers are bio decomposable, biocompatible, and also bio adhesive in nature. Biodegradable property can prolong the mean time when come inContact with mucous membrane because they have high degree of swelling property in aqueous medium and form gel. The frequency at which the drug is release from reservoir is governed by polymer concentration and the pattern of drug release in a sustained manner. The main disadvantage in clinical setting is drug loading efficacy is complex and difficult for biodegradable and it effect the control drug release. Besides this they give extensive range of uses in microsphere based drug delivery (Park, Ye, & Park, 2005).

Synthetic polymeric microspheres have many applications in many fields such as in clinical setup also as bulking agent, filler, drug delivery vehicles etc. and consider as proved safe , biocompatible but they have disadvantage that they tend move away from the site of injection and show side effects, embolism and organ damage (Kadam & Suvarna, 2015).

Table 2. Natural Polymers used in Microparticulate Drug Delivery Systems

Natural Proteins	Natural Polysaccharides
Collagen	Starch
Gelatin	Dextran
Albumin	Chitosan
Silk	Hyaluronic acid
	Pectin
	Guar gum
	Chitin

Table 3. Synthetic Polymers (Biodegradable) used in Microparticulate Drug Delivery Systems (Kadam & Suvarna, 2015; Kipper, Shen, Determan, & Narasimhan, 2002; Park et al., 2005)

Polyesters	Polyanhydrides	Polyphosphazenes	Others
Poly lactic-co-glycolic acid (PLGA)	Poly (Sebaic acid)	Aminated polyphosphazenes	Poly phosphoesters
Poly(glycolic acid)	Poly (fatty acid dimers)	Alkoxy polyphosphazenes	Poly orthoesters
Poly lactic acid (PLA)	Poly[1,6 bis(p-carboxyphenoxy0 hexane] (poly CPH)		Poly (alkyl cyanoacrylates)
Poly-e-caprolactone (PCL)	Poly adipic acid		Poly amides
Polyalkonates	Poly terphthalic acid		polyurethanes
Poly(3 hydroxybutyrate) (PHB)			Polyacetals

Table 4. Synthetic Polymers (non-biodegradable) used in microparticulate Drug Delivery Systems (Carien, Alvaro, & Josias, 2009; Pillai & Panchagnula, 2001)

Cellulose derivatives	Silicone	Acrylic polymers	Others
Hydroxypropyl methylcellulose (HPMC)	polydimethysiloxane	polymethacrylates	Polyvinyl pyrrolidine
Carboxymethyl cellulose (CMC)	Colloidal silica	Poly (methyl methacrylate)	Ethyl vinyl acetate
Cellulose acetate		Poly hydro (ethyl methacrylate)	Poloxamers
Cellulose acetate phthalate (CAP)			Poloxamines

Formulation of microparticulate drug delivery systems

In the literature different types of microencapsulation techniques exist that can be employed to prepare polymeric microspheres.

Chemical Methods

Interfacial Polymerization

This technique has been widely applied to the microencapsulation of different types of core materials such as aqueous solutions, water immiscible liquids and solids. In interfacial polymerization capsule shell is formed on the droplet surface at the reactive monomers by polymerization. For that purpose, multifunctional monomers are used. Multifunctional isocyanate and multifunctional acid chloride are used either separately or in combine form. First in liquid core multifunctional monomer is dissolved and then dispersed in dispersing agent in aqueous phase (N. V. N. Jyothi et al., 2010).

Emulsion Polymerization

In emulsion polymerization, monomers are adding to stirred aqueous medium contain surfactant and drug which is to be encapsulated. As polymerization begin molecules of polymer in aqueous medium precipitate and form primary nuclei. The nuclei grow slowly and the drug encapsulated to form microcapsules. Mostly hydrophobic materials are used for encapsulation by this technique (Tiarks, Landfester, & Antonietti, 2001).

In situ Polymerization

In this method shell is formed around core material

due to addition of monomers into reactor. Polymerization occurs at the interface of continuous phase and core of material without addition of reactive agent. The process involves the formation of pre-polymer that grows with time and results in the formation of coat around the core material. For preparation of Carboxyl functionalized magnetic microspheres by this technique, the methacrylic acid and styrene are heated at 85 ºC by using lauryl peroxide as initiator in the presence of nano Fe_3O_4. Hydrophobic liquid materials are encapsulated by *in situ* polymerization by the reaction of urea and formaldehyde at acidic pH in aqueous solution (N. V. N. Jyothi et al., 2010).

Physico-Chemical Methods

Coacervation

This process has two types one is simple coacervation and other is complex coacervation. In Single polymers ethyl cellulose or gelatin are used as aqueous or organic solvent. In complex coacervation two oppositely charged polymers, both having aqueous solubility is used. In both types, coacervation is carried out by desolvation of fully solvated polymer materials. In coacervation microencapsulation is carried out by aqueous solution prepared at 40-50 ºC then core material is dispersed. A suitable desolvating agent is added to the solution which leads to desolvated polymer molecules. This mixture is cooled to and crosslinking agent is added for hardening the microcapsule walls around the core material (Arshady, 1990).

Emulsion Solvent Evaporation

Emulsion solvent evaporation technique is mainly investigated to encapsulation various drugs especially lipophilic drugs (Yeo, Baek, & Park, 2001). Emulsion solvent evaporation (Olerile et al.) consists of two steps. In First polymer is dissolved in water immiscible organic solvent, second drug is incorporate in solution of polymer. Mainly used organic solvents in emulsion solvent evaporation technique are dichloromethane and chloroform. Then final solution is adding dropwise to nonsolvent of polymer solution have a appropriate amount of surface-active agent to form tiny polymer droplets which contain encapsulated drug. The droplets are hardened to produce the desired polymer of microcapsules. The hardening process is proceed by the removal of the solvent from the polymer droplets by solvent evaporation (Nava-Arzaluz, Pinon-Segundo, Ganem-Rondero, & Lechuga-Ballesteros, 2012). There are various technique of microencapsulation of drug by emulsion solvent evaporation method (Deshmukh, Wagh, & Naik, 2016).

O/W Emulsion Solvent Evaporation

Oil in water emulsion is commonly used for poorly water-soluble drugs. It is a simplest method and consists of four steps. Those drugs which are insoluble in water are dissolved in the water immiscible solvent solution of polymer known as internal phase. Second step is the emulsification of the internal phase in an aqueous phase called external phase. Third step is the separation of solvent from internal phase by solvent evaporation and formation of discrete droplets of internal phase into solid particles. Last step is the collection and drying of solid particles to separate out the remaining solvent. This technique is not useful for encapsulation of water-soluble drugs. It is due to that water soluble drug is not dissolved in non polar solvent, and other one is that water soluble drug will diffuse to external phase which will cause drug loss (Li, Rouaud, & Poncelet, 2008).

W/O Emulsion

Water in oil emulsion is used for encapsulation of hydrophilic drugs. In W/O emulsion, internal phase is water and oil is used as external phase. Drug is dissolved in internal water phase and emulsified in external oil phase containing emulsifying agent such as spans, cholesterol and wool fat (Madaan, Chanana, Kataria, & Bilandi, 2014). Khalid *et al* encapsulated the highly water soluble substance (ascorbic acid) into water in oil emulsion to make it controlled release for prolonged effects (Khalid, Kobayashi, Neves, Uemura, & Nakajima, 2013).

Multiple Emulsion

Multiple emulsions are known as 'emulsion of emulsion' is a complex method in which both O/W and W/O emulsion exists simultaneously. Multiple emulsion are of two types water-oil-water (w/o/w) emulsion and oil-water-oil (o/w/o) emulsion (Iqbal, Zafar, Fessi, & Elaissari, 2015). Water-oil-water type emulsion has wider application and has been extensively investigated for encapsulation of pharmaceutical ingredients. Water soluble drugs can be easily encapsulated in water-oil-water emulsion because internal phase is water and exploited for sustained delivery of hydrophilic drugs. This technique has advantage of being used for parenteral administration because of the external water phase which makes it less viscous and easy to handle.

Multiple emulsions are formulated by two step emulsification process. In this method re-emulsification of primary o/w or w/o emulsion into the outermost continuous phase. In first step primary o/w or w/o emulsion is formed by using hydrophilic or hydrophobic surfactant respectively. This primary emulsion is then re-emulsified into continuous oil or water phase containing hydrophobic or hydrophilic surfactant respectively (Khan, Talegaonkar, Iqbal, Ahmed, & Khar, 2006).

Ion-Gelation

Ionic gelation process extensively utilized in the formation of microparticle for controlled drug delivery. In this method the capability of polyelectrolytes to interact with multivalent ions to produce hydrogels. For example the ionic gelation of alginate and calcium ion to form calcium alginate microcapsules.

Sol Gel Method

In sol gel method, molecular precursors in liquid phase are transformed into oxide network (gel) by the polycondensation reaction. Mild conditions are required for ionotropic gelation method so, it is the preferred method for microencapsulation but microcapsules prepared by this method are not stable and require further modifications to improve stability (H.-J. Huang, Yuan, & Chen, 2006). According to this method, microspheres are formed by adding drug loaded alginate solution in calcium chloride solution. 3D lattice of ionically cross-linked alginate is formed when calcium ions move into alginate drop. Oppositely charged polyelectrolytes are incorporated to improve the strength of coating on the core material (Yeo et al., 2001).

Physico-Mechanical Methods

Fluidized Bed Coating

Fluidized bed technique mainly adopted for encapsulation of solid core materials. This process is commonly used to encapsulate pharmaceutical ingredients. In this process solid particles that want to encapsulate are suspended in a jet of air and then apply liquid spray of coating material. Spray nozzle is used to spray coating solution on solid particle. Gas which carries the coating solution is applied under high pressure. Strong shear force interaction is developed at the gas-liquid interface generates waves that split the solution into droplets. Several cycles of wetting-drying result in formation of continuous film around particles. Then capsule core is hardened by cooling or vaporization of solvent. This whole cyclic process is repeated until the capsule walls get desired thickness (Guignon, Duquenoy, & Dumoulin, 2002; Knezevic, Gosak, Hraste, & Jalsenjak, 1998). Various types of fluid bed coaters include top spray, bottom spray and tangential spray.

Spray Drying and Spray Congealing

This method is mainly used for thermo labile drugs in this process rapid evaporation of solvent is occur from the droplet. It protects the environmental degradation of the product by multistage drying and improves the quality of product. It is also employed as an encapsulation technique when it entraps active moiety with coating material (Mahdavi, Jafari, Ghorbani, & Assadpoor, 2014; Shu, Yu, Zhao, & Liu, 2006). Spray drying process is divided into four basic steps: atomization of liquid, blending of liquid with the drying gas, removal of the liquid and segregation of dried particles from gas. Atomization converts the liquid stream into fine droplets. Efficient drying of droplets is ensured due to high surface area. Various nozzles are used for generation of fine droplets most commonly used is pneumatic nozzle in which liquid stream is split into discrete droplets by interaction with pressurized air. Liquid spray is then mixed with drying gas and drying of particles occurs with evaporation of solvent from droplets. After drying solid particles are collected by separation from the drying gas chamber. Cyclone collector and/or bag filtration is used for particles collection. Major advantage of microencapsulation by spray drying is the production of free flowing solid particles (Paudel, Worku, Meeus, Guns, & Van den Mooter, 2013). Spray congealing also known as spray chilling, includes dispersion of active moiety in melted coating material without use of solvent. This mixture is then sprayed into stream of cold air to get solid droplets by cooling at temperature below the melting point of coating material. This method was used to encapsulate bovine somatotropin by dispersing it in molten wax and spraying through nozzle. Microspheres were formed by cooling the molten coating material and desired size was achieved by passing through sieve (Yeo et al., 2001).

Pan Coating

This technique is mainly employed in pharma sector to get small coated particles. The size of particles more than 600 micron are suitable for pan coating (Bansode, K Banarjee, D Gaikwad, L Jadhav, & M Thorat, 2010). Coating material is mixed with solid core and temperature of the pan is increased so that coating material melts and form a coat around core

material and then cooled to obtain solid coated particles. In this process, melting point of core must be higher than the melting temperature of coat. In another method, coating material in form of solution or in atomized spray form apply to the desired core material in the coating pan. Hot air is applied to remove solvent for a specific period of time by rotating pan at constant rate, (Jamekhorshid, Sadrameli, & Farid, 2014; Venkatesan, Manavalan, & Valliappan, 2009).

Conclusion and Future Perspectives

Microparticles and nanoparticles are emerging areas for drug deliver and research for drug administration to patients in convenient way besides of conventual method. Different types of anatomical, physicochemical and physiological factors give them different characteristics and prove that these are the future of medicine. There need to do a lot of work in field of microfluid and nanofluid drug delivery system when novelty in these fields comes true then the goal of developing multifunctional, precise targeting controlled, and biocompatible drug delivery will be near to reality.

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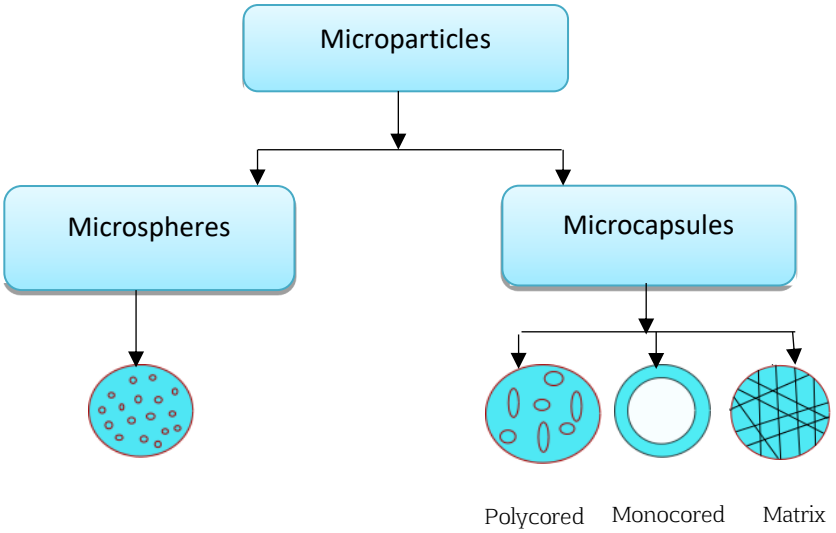

Figure 1: Types of Microparticles

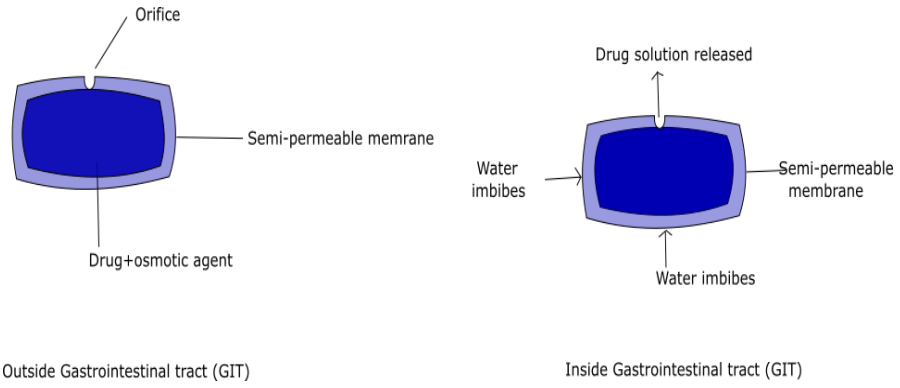

Figure 2: Mechanism of Drug Release by Osmotic Drug Delivery System

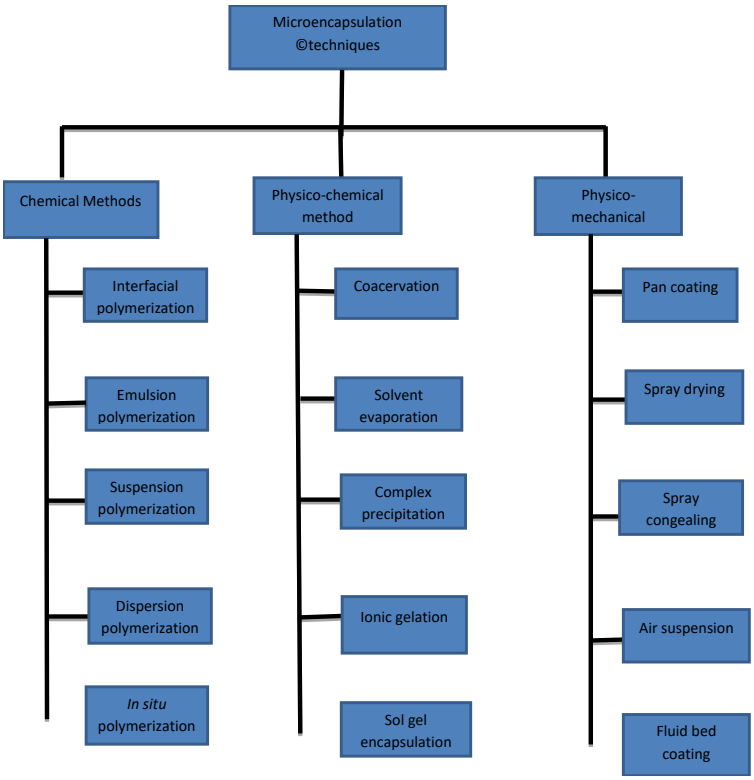

Figure 3: Methods of Microencapsulation

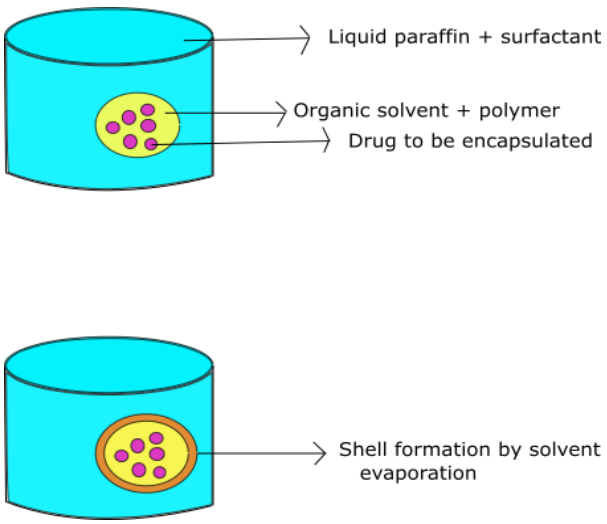

Figure 4: Schematic Diagram of Microencapsulation by Emulsion Solvent Evaporation