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A REVIEW ON MICROENCAPSULATION

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ABSTRACT

Microencapsulation is a process by which very tiny droplets or particles of liquid, solid or gas are enclosed or coated with a continuous film of polymeric material. It includes Bio encapsulation which is more restricted to the entrapment of a biologically active substance generally to improve its performance and to enhance its shelf life. This technique has been employed in a diverse range of fields from chemicals and pharmaceuticals to cosmetics and printing. For this reason, widespread interest has developed in microencapsulation technology. The most significant feature of microcapsules is their microscopic size that allows for a huge surface area. The large surface area is available for sites of adsorption and desorption, chemical reactions, light scattering, etc. This review paper highlights the major reasons behind microencapsulation, important techniques of microencapsulation and application of microencapsulated products in different areas of science and technology.

INTRODUCTION

Microencapsulation is basically a process of encoating an active agent, which is in the form of tiny individuals particles or droplets (micron sized) of the diameter of 1-1000 micron to produce small capsules. These capsules are referred to as microcapsules, sometimes the term microspheres is used synonymously. Microencapsulation is a very good example of novel drug delivery system, as it not only allows controlled or prolonged release and can also employ pellets, which are of their numerous advantages in themselves, but also several other advantages, including protection of the " active agent " from the "could be" harsh internal environment for it. The microcapsules serve as the reservoir for the active agent and so controlled or later release is achieved. Food ingredients, enzymes, cells, or several other materials including solids, liquids or gases can be incorporated in these capsules using the various microencapsulation techniques. This process is efficiently being used in textiles, food industry and of course pharma industry. In recent times, microencapsulation has turned out to be of great importance as it is a group of technologies covering and promoting so many various novel aspects of the drug delivery system. In some literature, it is defined as a packaging technology of solids, liquids and gases. Because it does involve the surrounding of the particles and give them a kind of finishing, hence packaging.

This technology is a grant of 'Chester Carlson', who invented this is the late 1940s. He used this to encapsulate dyes in his new copying process, well known as xerography.

Microcapsules

Generally, capsules are classified

A) On the basis of their sizes

CAPSULES	SIZE
Nanocapsules	< 0.2 micron
Microcapsules	0.2nm - 5000 micron
Macrocapsules	> 5000 micron

B) On the basis of their size and construction

(i) Microcapsules (ii) Microspheres

(i) Microcapsules are then divided as,
a) Mononuclear b) Polynuclear

Depending on whether the core is divided.
(ii) Whereas, Microspheres can be distinguished as,
a) Homogenous b) Heterogenous

Depending on whether the core is in the molecular state (dissolved) or in the form of particles (suspended).

IUPAC defines microcapsules as

"Hollow micro particles composed of a solid shell surrounding a core forming space available to permanently or temporarily entrapped substances, where the substances can be drugs, particles, dyes and similar materials."

It can be well understood as a solid inner core (the core contains the active substance) which is covered or coated by a polymer layer (this layer constitutes the capsule

membrane), the solid core substantially being the central part of the capsule, the core can be a single or group of particles either of solids, liquids or gases, these could even be present in combinations. The polymer is inert in nature. Microcapsules, in the same way as pellets, can be formulated into various dosage forms. These could be dispersed into hard/soft gelatin capsules, which may be enteric coated, or suspended in liquids giving rise to suspension dosage form. Wherein all of these dosage forms allow dispersion of individual microcapsules on release.

Well, if microspheres are considered, the core and polymer is not distinguished, in fact, the core is evenly dispersed and or dissolved in a polymer network, so these are matrix systems.

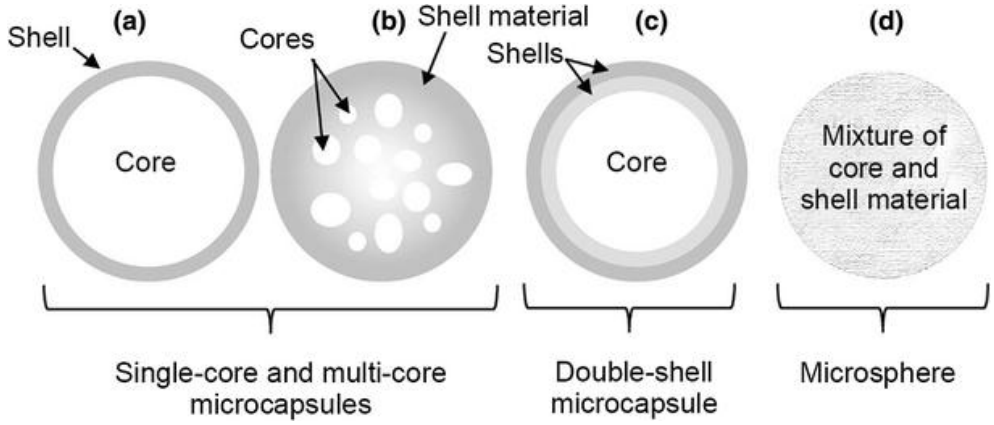

Fig. 1:

1. The single core microcapsules are categorized as 1.microcapsules with solid core 2.microcapsules with non-solid core.
2. The multi-core microcapsules are categorized as: 1. Microcapsules with solid micro domains or nano domains 2. Microcapsules with non-solid micro domains or nano domains.
3. Whereas, microspheres are molecular mix of matrix and encapsulated active agent, which could be either Homogenous or Heterogenous.

Composition of Microcapsules

The composition of microcapsules is very simple to study. Going by the structure, the 3 basic elements are;

1. Core material
2. Polymer material (coating material)
3. Vehicle (for formulation)

These are discussed in detail below,

(i) Core Material: As discussed in the previous sections, core material is the active agent or ingredient. Also, the core material could be solids, liquids, gases or dispersions. The composition of the core varies and thus is an important factor in the designing of the whole microcapsule, because it is the core material that ultimately has to be coated and encapsulated. The flexibility of the choices and design completely depends on the core material. It is to be noted, that the core material is actually our desired drug. And this drug may be micro encapsulated for so many reasons. These could be protection of the reactive drug material or its component, modification and enhancement of the physical properties of the drug, to serve controlled or prolonged release and many more.

(ii) Coating Material (Polymer): These are generally polymers. A broad range of polymers including novel and innovative polymer, that are under patent and traditional polymers are available for microencapsulation. There are certain inert and pH sensitive polymers. The coating polymers play barrier between the drug (core) and the external environment. These are protective films, which prevents the inadequate exposure. The polymers form a membrane, which dissolves in reaction to specific stimuli. The coating material must be appropriate and wisely chosen as it greatly affects the chemical and physical properties of the microcapsules. It is to be kept in mind that apart from the chemical and physical compatibility between the coating and the drug, the overall appearance must also be elegant for the customer satisfaction. Before the selection of any polymer for this purpose, the release behavior, strength, rigidity (or flexibility), chemical compatibility more appropriately inertness, stability, optical characteristics must be well studied. There are so many polymers that are preferred including ethyl cellulose, polyvinyl alcohol, gelatin, cellulose acetate pthalate, styrene maleic anhydride etc. The polymers could be hydrophobic, hydrophilic or both in nature. The film thickness depends completely on the core material and its physical properties.

(iii) VEHICLE: A vehicle can be described as any component or solvent which facilitates the drug formulation by increasing the bulk of the drug and also patient compliance. The addition of vehicle in the microcapsule formulation is optional.

The vehicles are (I) aqueous (II) non-aqueous.

The above discussion is summarized in the table as below:

CORE MATERIALS	COATING MATERIAL		VEHICLE
(a) Solid	(a) Polymers	(b) Waxes	(a) Aqueous
(b) Liquid	(c) Resins	(d) Proteins	(b) Non- Aqueous
	(e) Polysaccharides		

Microencapsulation Techniques

There are numerous techniques of microencapsulation. The selection of the technique, is again very crucial. The efficiency of the chosen technique has to be taken into consideration.

(A) PHYSICAL OR PHYSICO-MECHANICAL METHODS	(B) PHYSICO-CHEMICAL METHODS	(C) CHEMICAL METHODS
Air suspension (wurster)	Ionotropic gelation	Solvent evaporation
Centrifugal extrusion	Coacervation-phase separation process	Polymerization
Pan coating	Super critical CO2 assisted microencapsulation	Poly condensation
Spray drying and Congealing		
Vibrational nozzle (Nozzle Vibration Technology)		

(A) Physical Or Physico Mechanical Methods

(i) Air Suspension (Wurster): The solid particulate core materials, which are the drug particles (or call it active ingredient) are dispersed in a stream of air and thus the air suspended particles are spray coated.

(ii) Centrifugal Extrusion: This is also called multi-orifice centrifugal process. This process was developed by the Southwest Research Institute. Microcapsules are produced by utilizing centrifugal force which impels the core particles with force, into an enveloping membrane, thereby micro encapsulating the same. This process is capable of micro encapsulating liquids and solids of varied size ranges, with diverse coating materials.

(iii) Pan Coating: Pan coating is generally preferred for relatively large particles. This method is effectively used for the production of controlled release microcapsules. This process goes on with core particles placed in the coating pan, where the coating is either in solution form or as an atomized spray.

(iv) Spray Drying And Spray Congealing: These two techniques are similar to each other except in the coating solidification. These two are very popular and cost effective methods. Considering the spray dryer equipment, the core material is dispersed in the liquefied coating substance/ polymer substance (solution form) termed feed suspension. This is then sprayed in the drying chamber (hot air chamber) with the aid of atomizer. The coating-core mixture is turned into small particles (micro particles) which upon drying give microcapsules.

The same equipment is employed in the spray congealing process, here the core material is dispersed in a coating melt. Coating solidification is achieved by spraying the hot core-coating material mixture into the stream of cool air.

(v) Vibrational Nozzle Technology: This technology is based on the concept of Rayleigh Instability concept. The microencapsulation is accomplished by introducing the fluid stream of the liquid core-coating material mixture in laminar flow into the nozzle which consists of concentric tubes. As the nozzle is vibrational, the liquid mixture forms droplets. These droplets are allowed to travel through an electrostatic field to get charged. This is a novel technique.

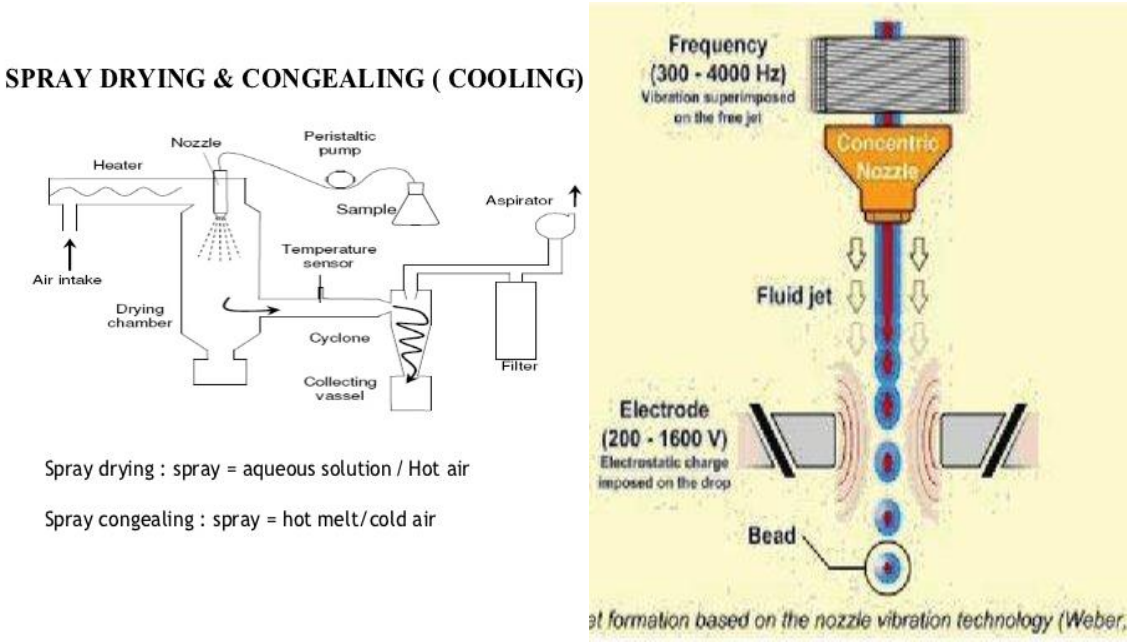

Fig: Figure showing Microencapsulation through spray drying and congealing; Figure showing Microencapsulation through Vibrational Nozzle Technology.

(B) Physico Chemical Methods

(i) IONOTROPIC GELATION: It is the most extensively used technique in microencapsulation. The aqueous solutions of sodium alginate, gellan or carrageenan are gelated by adding divalent cations like chloride salts of calcium, barium or potassium. This induces the polymer cross linking, which gives rise to discrete solid micro particles.

(ii) COACERVATION - PHASE SEPARATION: The liquid phase of the coating material from a polymeric solution separates and wraps around the core particles. This process is coacervation and as the liquid phase separates and encases the particle, the process is also termed phase separation. Contemporarily, there are two methods of coacervation viz. Simple and Complex processes. Both the processes are almost identical with only one difference i.e., the simple process employs desolvating agents for phase separation, while complex process involves complexation between two oppositely charged polymers.

(iii) SUPERCRITICAL CO2 ASSISTED MICROENCAPSULATION: Supercritical fluids are nothing but highly compressed gases. These are substances whose liquid and gas phases are indistinguishable above critical point. The critical point includes 1. Critical temperature (Tc) 2. Critical pressure (Pc).

Thus, the supercritical fluids possess several advantageous properties of both liquids and gases. For many processes, including microencapsulation supercritical CO2 is used because it is cost effective, non-toxic, non-flammable and most importantly has low critical temperature value.

There are 3 methods which are widely used and they are;

1. Rapid Expansion of Supercritical Solutions (RESS)
2. Gas Anti Solvent Method (GAS)
3. Particles from Gas Saturated Solution (PGSS)

(C) CHEMICAL METHODS

(i) SOLVENT EVAPORATION: This method is efficiently used for not only microencapsulation but also the preparation of nano particles. In this method, the polymer compounds (coating material) are dissolved in volatile organic solvents such as chloroform, ethyl acetate, dichloromethane to form an emulsion. This emulsion is converted into a core micro particles suspension by dispersing the core particles in it. The solvent is then evaporated with the help of vacuum, application of high temperature or by constant and continuous stirring.

(ii) POLYMERIZATION: This heading covers two major aspects they are;

1. ***Interfacial Polymerization:*** A monomer mixture along with the core particles is dispersed in a stirring tank. Another monomer mixture is introduced in the tank. The polymerization reaction occurs by a chemical reaction between the two monomers. The reaction is supported by the changes in the pH (upon addition of acids or bases) and/or temperature, use of catalysts. The polymer consolidation is achieved by the addition of additives. The reaction between the two monomers causes cross linking and formation of the polymer around the core particle at the interface.

2. ***In situ Polymerization:*** The core particles to be encapsulated are dispersed in water in liquid form. The mixture is stirred in a stirring tank which gives rise to droplets. After which two different monomer mixtures

are added to it. The polymerization reaction occurs by the chemical reaction between the two monomers. The polymer so formed gets deposited around the droplets thus encapsulating them.

(iii) POLYCONDENSATION: This process requires two complimentary monomers in a two phase suspension system, which have to undergo poly-condensation. Each of the two monomers resides largely in one of the two immiscible phases in the suspension system. The polymer thus formed at the interface, is either soluble or insoluble in the droplets. The soluble polymer gives particulate microcapsules (monolithic in nature), if insoluble then the polymer surrounds individual droplets to produce microcapsules.

Factors affecting encapsulating efficiency

The micro encapsulating efficiency gets influenced by various factors:-

1. Concentration of Polymer
2. Solubility of Polymer in the Solvent
3. Rate of Solvent Removal
4. Solubility of Organic Solvent in Water

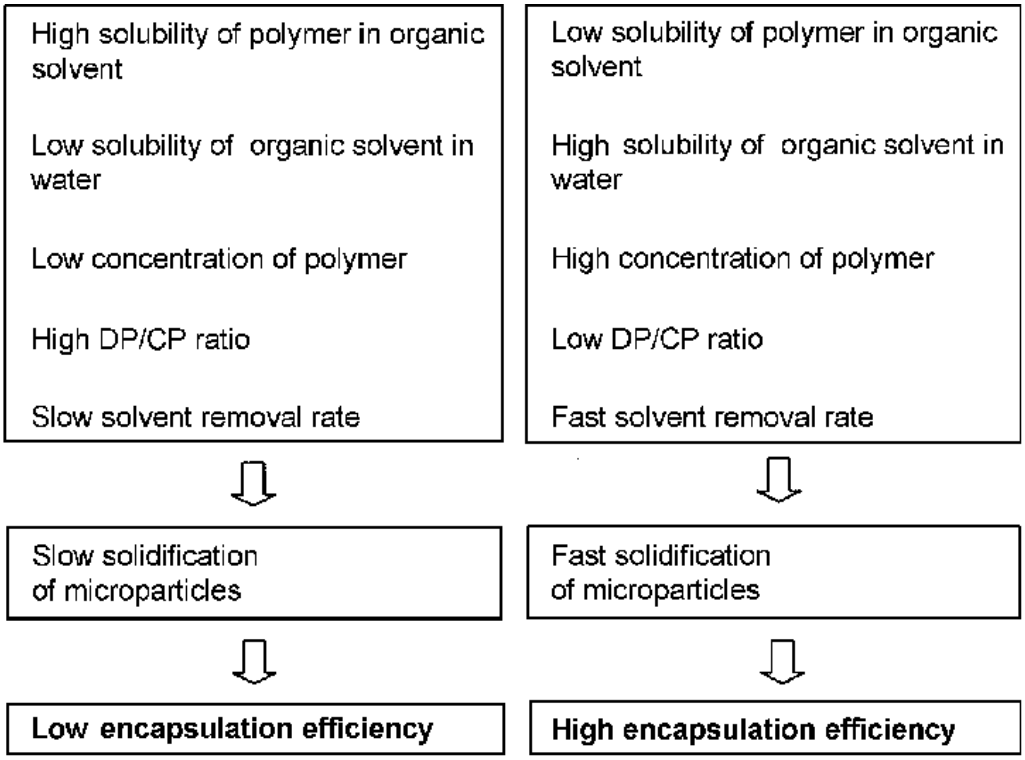

Fig. Figure depicts various factors affecting microencapsulating efficiency.

Release Patterns and Methods

Drug Release: Mechanisms of drug release from microcapsule (MC) are categorized as follows, these mechanisms are either functional side by side or one of them plays the key role in drug release.

1. Diffusion: Diffusion is the most common mechanism of drug release from MC. The core of the microcapsule is dissolved by dissolution fluid as it penetrates the outer shell, causing the dissolved drug in the core to leak out through the pores or interstitial channels.

The kinetics of such release obeys Higuchi's equation:

$Q = [D/J (2A – \varepsilon CS) CS t] ½$

Q=the amount of drug released per unit area of exposed surface in time't'.

D=the diffusion coefficient of solute in solution.
A=Total amount of drug per unit volume.
Cs=Solubility of the drug in penetrating dissolution fluid.
ε =the porosity of the wall of microcapsule.
J=the tortuosity of the capillary system in the wall

The rate of drug release depends on:

1. The rate at which the penetration fluid penetrates the wall of microcapsule i.e. the rate of penetration.
2. The rate at which the drug forms solution with the dissolution fluid i.e. the rate of drug dissolution.
3. The rate at which dissolved drug disperses from the pores.

Diffusion controls drug release from both- monolithic and reservoir system but the mechanism involved differs.

- In monolithic system the diffusion of active drug and its release occurs prior to or concurrent to degradation of polymer metrics, also Rate of release is affected whether Degradation of polymer occurs by homogeneous or heterogeneous mechanism.
- In reservoir system the drug release in this case is controlled by a rate controlling membrane through

which agent diffuses (this membrane stays intact until drug delivery is completed).

The matrix degradation occurs irrespective of drug release.

2. ***DISSOLUTION:*** The Rate determining step in the release of drug from the micro capsule is the dissolution rate of polymer from micro capsule which is soluble in the dissolution fluid.

Rate of release is influenced by:
A) Polymer's solubility in the given dissolution fluid.
B) Thickness of coat.
The drug release can also occur by melting the wall of capsule.

3. ***OSMOSIS:*** The Polymer coat of micro capsule imitates the role of a semi permeable membrane favoring the development of osmotic pressure difference across the inside out of micro capsule, which acts as a driving force for the drug solution to move out of microcapsules through pore formation in the coat.
For a water soluble drug; in presence of aqueous medium i.e. water- The water uptake through pores causes' polymer chain to swell causing osmotic pressure difference and also initiate new pore formation.

4. ***EROSION***: Coat materials like glyceryl monostearate, bees wax and stearyl alcohol undergo coat erosion due to pH/ enzymatic hydrolysis causing drug release.

5. ***DEGRADATION:*** Basically degradation plays role in drug release from monolithic system. Dissolution of active drug in its matrix leads to its distribution throughout the core and drug release occurs when this matrix degrades. The rate of matrix degradation for drug release is faster when compared to its release through diffusion.

Release Pattern
Release patterns are majorly influenced by difference in physical form of microcapsule and physico chemical properties of core materials such as shape, size, coat material of microcapsule and solubility, partition coefficient, thickness, porosity of coating material respectively. Also other factors like formulation, properties of drug and dissolution medium plays a crucial role in drug release pattern.

A micro capsule can be modeled as both are constant and non-constant activity source i.e,

1. ***NON CONSTANT ACTIVITY SOURCE:*** The one which follows 1st order kinetics that is the rate of release decreases exponentially with time until drug is exhausted.

Such system can be modeled in case a micro capsule in its initial interaction/ contact with an aqueous solution allows water permeation through its membrane which would dissolve only a fixed amount of drug present in its core to its solution state. Such arrangement facilitates drug diffusion across membrane in perfect sync which leads to decrease in concentration gradient gradually as drug diffuses, this reduces the rate of diffusion leading to exponential decay of drug release over time.

2. ***CONSTANT ACTIVITY SOURCE:*** This follows zero order kinetics (the release rate is constant) i.e. microcapsule delivers a fixed amount of drug per min or hour until drug is exhausted or the solid reservoir of undissolved drug is maintained in microcapsule.
Such systems can be modeled in case of a drug dissolution with limited solubility i.e. only a part of drug dissolves initially, acting as a constant source which follows zero order kinetics. Due to such an arrangement the concentration gradient remains constant until undissolved drug resides in the reservoir.

Need of Microencapsulation
Microencapsulation is an extremely promising technique especially designed to ensure patients compliance. The aim of microencapsulation is isolation of its core containing the bio active agents, from its surrounding and ensuring its rupture at time of use. Microspheres with unique release profile can be designed but slight changes in certain aspects for example by change of polymer one can transform microspheres from a matrix to reservoir system , because a change in polymer will affect the diffusion coefficient of drug leading to changes in its degradation kinetics. Similarly a change in initial concentration of drug inside microsphere can lead to transformation of activity source from non-constant to constant. Various shapes and sizes also contribute in modifying release profile of a microcapsule. A microcapsule need not to be a sphere only it can be a micro-cylinder or micro-slab. Each of which depicts their own release profile. Increase in radius of a microsphere will allow a larger concentration of drug to be delivered over a longer period of time.

Though microencapsulation is basically considered a reliable technique for sustained drug release at its specific targets example there tendency to target the drug to pathogens with resides intracellularly. But this method also have potential for controlled drug release which involves solid biodegradable microspheres. Such arrangements facilitates the idea of less frequent drug administration which eliminates the risk of high plasma peak concentration of drug followed by avoiding the risk of any adverse effects. Microencapsulation helps to ensure time controlled pulsatile release of entrapped drug in the core of microsphere. Not only pharmacodynamics of any drug its affected but also pharmacokinetic property of drug. Such as with the aid of microencapsulation there is increase in a drug's stability, its dissolution and bioavailability.

Due to such promising potential of this method it has got priority over the conventional drug delivery system. Because of the endless possibilities of combination of core and shell material plus its endeavour to respond to physiological stimuli by release of drug as per the body's need microencapsulation finds its huge application extending from food, agricultural industry to pharma industry.

Applications of Microencapsulation

Microencapsulation technique founds its infinite application not only in pharma industry but also in food, biotechnology and agricultural industry.

In dosage designing and its delivery pattern, microencapsulation permits designing such a delivery system which aids with patients compliance such as:

1. Microencapsulation shows potential in designing a targeted and controlled/sustained/prolonged release dosage form with the use of correct biodegradable polymer.
2. This methods helps in decreasing the GI tract irritation particularly caused by large dose administration, microencapsulation ensures less frequent dose administration decreasing gastric irritation.
3. It helps in handling incompatible substances like eutectic mixtures (ones which converts to liquid form when they come in direct contact to each other) e.g.: Administration of mixture of aspirin and chlorpheniramine was being accomplished by the use of microencapsulation technique.
4. It helps in masking of bitter taste of drugs like paracetamol and nitrofurantoin.
5. For core materials like sodium chloride their hygroscopic property is reduced by use of microencapsulation.
6. Microencapsulation is used to convert liquid to solid (e.g.: castor oil) or from liquid to pseudo solid (e.g.: Eprazinone) to ease the handling of liquid substances in formulation.
7. Microencapsulation ensures the protection of its core material against factors like humidity, light, heat and oxygen.
8. This methods allows easy handling of volatile substances by reducing their volatility e.g.: methyl salicylate.
9. Intrauterine contraceptive devices can be easily designed using this technique
10. To ensure release of any drug in intestine i.e. to avoid gastric irritation or its degradation at gastric pH an enteric dosage form can be designed using this method.
11. In treatment of genetic disorders like haemophilia or cystic fibrosis, a corrective gene sequence in form of plasmid DNA can be delivered by use of microencapsulation.
12. Microencapsulation also finds its usage in gene therapy and in vaccines used for AIDS, diabetes etc.
13. Handling of toxic substances like herbicides, insecticides becomes easier with microencapsulation.
14. Formulation of a multi-layered tablet for controlled release of medicament contained in different layers of dosage form is achieved by this method.
15. Microencapsulation also finds its use in biotechnology e.g.: cell immobilization – in plant cell culture to increase efficiency in production of various metabolites.

Similarly for the treatment of severe hormone deficient diseases like hepatic failure and diabetes by use of microencapsulation human tissues are transformed into bio-artificial organs and transplant in human body to fulfil hormone deficiency.

To increase production of ethanol and other solvents this method is employed along with continuous fermentation process.

Microencapsulation technique also finds its enormous usage in nutraceuticals (to increase nutritional value of food products), food industries (beverage production) and agricultural industry.

With the various applications discussed above and also the flexibility, ease and advantages of microencapsulation technique one can be ensured that this technique has a huge scope for development of more precise and targeted delivery techniques for prevalent clinical ailments and also it has great potential to serve as a Novel drug delivery system in the coming future.

CONCLUSION

In Microencapsulation process solid, liquid and gas can be entrapped. It has got more popularity in drug delivery system and has been shown most advantageous than conventional drug delivery system. Since it is not only used in pharmaceutical field only but it is also used in other fields like agricultural field, analysis field in food industry as well as in building construction material also. As there are many method of encapsulation but still it is on research to develop more method to encapsulate different matter and better than previous method.

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