International Journal for Multidisciplinary Research (IJFMR)
E-ISSN : 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

The Review on Microencapsulation: A Promising Technique for Controlled Drug Delivery

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Abstract:
Microencapsulation is a well-established process of enveloping or surrounding one substance into another substance which gives capsules having range from less than one micron to several hundred microns in size. One of the highly efficiently method is micro encapsulation, micro particles or microspheres rely upon various factors like solubility of polymer in solvent, concentration of polymer, solubility of organic solvent in water, rate of solvent removal etc. Microparticulate drug delivery systems are an interesting and promising option when developing an oral controlled release system. The objective of this paper is to take a closer look at microparticles as drug delivery devices for increasing efficiency of drug delivery, improving the release profile and drug targeting. In order to appreciate the application possibilities of microcapsules in drug delivery, some fundamental aspects are briefly reviewed. The controlled release drug delivery system, releases the active drug or medicament at a predetermined rate targeting to specific site over a prolonged period of time.

Keywords: Drug delivery systems, Microcapsules, Controlled release, Microencapsulation, Shell, Core, Miniature.

INTRODUCTION

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Microencapsulation includes Bioencapsulation which is more restricted to the entrapment of a biologically active substance (from DNA to entire cell or group of cells for example) generally to improve its performance &/or enhance its shelf life1 . 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. Several of these properties can be attained by macropackaging techniques; however, the uniqueness of microencapsulation is the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms and not has been technically feasible2

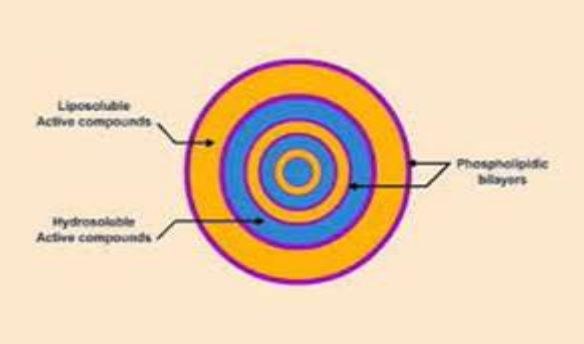


Figure 1: Microencapsulation process

REASONS FOR MICROENCAPSULATION

• The primary reason for microencapsulation is found to be either for sustained or prolonged drug release.

• This technique has been widely used for masking taste and odor of many drugs to improve patient compliance.

• This technique can be used for converting liquid drugs in a free-flowing powder.

• The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.

• Incompatibility among the drugs can be prevented by microencapsulation.

• Vaporization of many volatile drugs e.g., methyl salicylate and peppermint oil can be prevented by microencapsulation.

• 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.

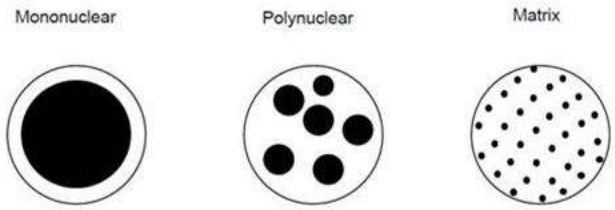
• Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.

• Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability3 .

1. Mononuclear / single core.

2. Polynuclear/ multiple core.

3. Matrix type .



Composition of microcapsules

Coating materials

A wide variety of coating materials are available for microencapsulation. Some patent innovative coating polymers have also been developed for some special applications particularly among the bioadhesives and mucoadhesives. However, many traditional coating materials are satisfactory for the use in the gastrointestinal tract. They include inert polymers and pH sensitive ones as carboxylate and amino derivatives, which swell or dissolve according to the degree of cross-linking(15–19)

The selection of appropriate coating material from a long list of candidate materials needs consideration of the following general criteria by the research pharmacist:

1. What are the specific dosage forms or product requirements, such as stabilization, reduced volatility, release characteristics, and environmental conditions?
2. What coating material will satisfy the product objective and requirements?
3. What microencapsulation method is best suited to accomplish the coated product objectives?

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/ microspheres. While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability(1,5,20–22)

Generally hydrophilic polymers, hydrophobic polymers or a combination of both are used for the microencapsulation process. A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The micro-capsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms(23,26)

Core materials

The core material is the material over which coating has to be applied to serve the specific purpose. Core material may be in form of solids or droplets of liquids and dispersions. The composition of core material can vary and thus furnish definite flexibility and allow effectual design and development of the desired

microcapsule properties. A substance may be microencapsulated for a number of reasons. Examples may include protection of reactive material from their environment, safe and convenient handling of the materials which are otherwise toxic or noxious, taste masking, means for controlled or modified release properties means of handling liquids as solids, preparation of free flow powders and in modification of physical properties of the drug(5,27–32)

Technologies used for the 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:

1. Concentration of coating material.
2. Solubility, Melting point, Surface area, Density, Volatility of core material.
3. 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. CIBTech Journal of Pharmaceutical Sciences ISSN: 2319–3891 (Online) An Open Access, Online International Journal Available at http://www.cibtech.org/cjps.htm 2015 Vol.4 (2) April-June, pp.26-33/Sailaja and Jyothika

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.

Mechanism and kinetics of drug release

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion.

Diffusion

Diffusion is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores. Thus, the overall release depends on, (a) the rate at which dissolution fluid penetrates the wall of microcapsules, (b) the rate at which drug dissolves in the dissolution fluid, and (c) the rate at which the dissolved drug leak out and disperse from the surface(3,4,16). The kinetics of such drug release obeys Higuchi's equation as below(4,5,8,50,51):

$$Q = [D/J \ (2A - \varepsilon C_S) \ C_S \ t]^{1/2}$$

Where, Q is the amount of drug released per unit area of exposed surface in time t; D is the diffusion coefficient of the solute in the solution; A is the total amount of drug per unit volume; C_S is the solubility of drug in permeating dissolution fluid; ε is the porosity of the wall of microcapsule; J is the tortuosity of the capillary system in the wall. The above equation can be simplified to Q = vt where, v is the apparent release rate.

Dissolution

Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid. Thickness of coat and its solubility in the dissolution fluid influence the release rate(5,6,52)

Osmosis

The polymer coat of microcapsule acts as semi permeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat(7,53)

Erosion

Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol(13,54)

Attempts to model drug release from microcapsules have become complicated due to great diversity in physical forms of microcapsules with regard to size, shape and arrangement of the core and coat materials(1,4,6,55). The physiochemical properties of core materials such as solubility, diffusibility and partition coefficient, and of coating materials such as variable thickness, porosity, and inertness also makes modeling of drug release difficult. However, based on various studies concerning the release characteristics, the following generalizations can be made:

1. Drug release rate from microcapsules conforming to reservoir type is of zero order.

2. Microcapsules of monolithic type and containing dissolved drug have release rates that are $t_{1/2}$ dependant for the first half of the total drug release and thereafter decline exponentially.
3. However, if a monolithic microcapsule containing large excess of dissolved drug, the release rate is essentially $t_{1/2}$ dependant throughout almost the entire drug release.

In monolithic capsules the path traveled by drug is not constant; the drug at the center travels a large distance than the drug at the surface. Therefore, the release rate generally decreases with time.

Applications of microcapsules and microspheres

Some of the applications of microencapsulation can be described in detail as given below:

1. Prolonged release dosage forms. The microencapsulated drug can be administered, as microencapsulation is perhaps most useful for the preparation of tablets, capsules or parenteral dosage forms (3)
2. Microencapsulation can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach (56)
3. It can be used to mask the taste of bitter drugs(6,57)
4. From the mechanical point of view, microencapsulation has been used to aid in the addition of oily medicines to tableted dosage forms. This has been used to overcome problems inherent in producing tablets from otherwise tacky granulations and in direct compression to tablets(58,59)
5. It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microencapsulation does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided(60,61)
6. The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation. The stability enhancement of incompatible aspirin-chlorpheniramine maleate mixture was accomplished by micro-encapsulating both of them before mixing(6)
7. Microencapsulation can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation(6)
8. Microencapsulation has also been used to decrease potential danger of handling of toxic or noxious substances. The toxicity occurred due to handling of fumigants, herbicides, insecticides and pesticides have been advantageously decreased after microencapsulation(61)
9. The hygroscopic properties of many core materials may be reduced by microencapsulation(62)
10. Many drugs have been microencapsulated to reduce gastric irritation(62)
11. Microencapsulation method has also been proposed to prepare intrauterine contraceptive device(12,63)
12. In the fabrication of multilayered tablet formulations for controlled release of medi-cament contained in medial layers of tableted particles(1,7,10,63)

CONCLUSION

Microfabricated system offers potential advantages over conventional drug delivery systems. Microspheres and microcapsules are established as unique carrier systems for many pharmaceuticals and can be tailored to adhere to targeted tissue systems. Hence, micro-capsules and microspheres can be used not only for controlled release but also for targeted delivery of drugs to a specific site in the body. Therefore, the development of safe and efficient particular systems will require, in the future, indepth investigations of both the biological and technological aspects of these systems. 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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