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A REVIEW ON MICROENCAPSULATION- A NOVEL DRUG DELIVERY SYSTEM

Preeti Joshi* and G. Gnanarajan

Shri Guru Ram Rai Institute of Science and Technology, Dehradun.

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***Corresponding Author**
Preeti Joshi
Shri Guru Ram Rai Institute of Science and Technology, Dehradun.

ABSTRACT

The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Recent development in technology has provided viable alternatives that can be administered via different routes of administration. Various routes that are used include oral, topical, nasal, rectal, vaginal and ocular etc, but nowdays microcapsules provide drug delivery at a controlled rate for a desired period of time. An ideal Controlled drug delivery system is one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time.

KEYWORDS: Granules formulation, microencapsulation, controlled release.

1. Microencapsulation

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) generally to improve its performance &/or enhance its shelf life. Microencapsulated products (microparticles or microcapsules) are small entities that have an active agent know as the core material surrounded by a shell known as the coating material or embedded in a matrix structure. Most of the microparticle shells consist of organic polymers, but waxes and lipids are also used.

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 the liquid core can include

dispersed and/or dissolved. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or accelerators.

Coating materials

The coating material should be capable of forming a film that is cohesive with the core materials, be chemically compatible and non reactive with the core material and 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 size5.

Microencapsulation is the creation of a barrier to avoid chemical reactions and/or to enable the controlled release of the ingredients. It involves mass transport behaviour in some way between the core (the ingredient) and the shell (capsule or coating). The entrapped material is usually a liquid but may be a solid or a gas.[1][2]

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 odour 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.

Table no. 1-Difference between conventional and controlled drug delivery

S.NO	Conventional	Control drug delivery system
1.	Poor patient compliance	Improved patient convenience and

		compliance
2.	Drug fluctuation can lead adverse effect	Reduction in fluctuation and reduce side effects
3	Frequency of drug increases	Decrease in dosing frequency
4.	Decreased safety margin	Increase safety margin due to better control at plasma levels
5.	Greater amount of drug dose	Less amount of drug dose

Advantages of microencapsulation

- Reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effects.
- Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
- Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.
- Microencapsulated ingredients do not interfere with other ingredients
- Shelf life may be increased
- The microencapsulated ingredients can be added at any time in the processing and remain unaltered
- Consumers are unable to taste the added capsules.[3][4]

Disadvantages of microencapsulation

- Due to foreign ingredients in foods, customers with allergies may not be aware
- More skill and knowledge is required to use this advanced and complex technology
- Production cost
- Shelf life of hygroscopic drugs is reduced
- Difficult to achieve continous and uniform film
- Possible cross-reaction that may occur between the core and wall material selected.

Application of microencapsulation

- Cell immobilization: In plant cell cultures, Human tissue is turned into bio-artificial organs, in continuous fermentation processes.
- Beverage production
- Protection of molecules from other compounds

- Drug delivery: Controlled release delivery systems.
- Quality and safety in food, agricultural & environmental sectors.
- Soil inoculation.
- In textiles: means of imparting finishes.
- Microencapsulation has been employed to provide protection to the core materials
- 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.
- Microencapsulation can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than in the stomach.
- It can be used to mask the taste of bitter drugs.
- It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microencapsulation does not yetprovide 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. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation.
- 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 microencapsulating both of them before mixing.
- 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.
- The hygroscopic properties of many core materials may be reduced by microencapsulation.
- Many drugs have been microencapsulated to reduce gastric irritation.
- Microencapsulation method has also been proposed to prepare intrauterine contraceptive device.
- In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tabletted particles. [5][6]

MECHANISM OF RELEASE METHOD OF MICROENCAPSULATION

Even when the aim of microencapsulation application is the isolation of the core from its surroundings,the wall must be ruptured at the time of use. Many walls are ruptured easily by pressure of shear stress, as in case of breaking dye particles during writing to form a copy. Capsule contents may be released by melting the wall, or dissolving it under particular conditions, as in case of an enteric drug coating. In other system the wall is broken by solvent action, enzyme attack, chemical reaction, hydrolysis, or slow disintegration.

Microencapsulation can be used to slow the release of a drug into the body. This may permit one controlled release dose to substitute for several doses of non-encapsulated drug and also may decrease side effects for some drugs by preventing high initial concentrations in the blood. There is usually a certain desired release pattern. In some cases, it is zero-order, i.e the release rate is constant. In this case, the micoencapsules deliver a fixed amount of drug per minute or hour during the period of their effectiveness. This can occur as long as a solid reservoir or dissolving drug is maintained in the microcapsule.

A more typical release pattern is first-order in which the rate decrease exponentially with time until the drug source is exhausted. In this situation, a fixed amount of drug is in solution inside the microcapsule. The concentration difference between the inside and the outside of the capsule decrease continually as the drug diffuses.

Nevertheless, there are some other mechanism that may take place in the liberation of the encapsulated material. These include biodegradation, osmotic pressure, diffusion etc. Each one will depend on the composition of the capsule made and the environment it is in. Therefore, the liberation of the material may be affected by various mechanism takes place simultaneously.

CLASSIFICATION OF MICROENCAPSULATION

Microcapsules can be classified on three basic categories according to their morphology as follows,

1. Mononuclear
2. Polynuclear and
3. Matrix types

Mononuclear (core-shell) microcapsules contain the shell around the core, while polynuclear capsules have many cores enclosed within the shell. In matrix encapsulation, the core material is distributed homogeneously into the shell material. In addition to these three basic morphologies, microcapsules can also be mononuclear with multiple shells, or they may form clusters of microcapsules.[7]

Microencapsulation Technique

- Air suspension
- Solvent evaporation techniques
- Coacervation phase separation
- Polymerization
- Pan coating
- Spray drying and congealing

Air Suspension

The air suspension technique involves the dispersion of the core materials in a supporting air stream and the spray coating on the air suspended particles. The moving air stream suspends the particles on an upward within the coating chamber. The design of the coating chamber and its operating parameters should be in such a way that could effect the flow of the particles through the coating zone of chamber, where a coating material (polymer solution) is applied to the moving particles. As the moving particles passed through the coating zone repeatedly, the core material receive more of coating material. The cyclic process is repeated about several time depending on the coating thickness desired or whether the core material particles are thoroughly encapsulated. The encapsulated product is dried by passing the stream air. Drying rates are directly depending to the temperature of the supporting air stream. The process variables that can affect the process.

1) Concentration of the coating material or if in solution form then melting point.
2) Solubility, surface area, density, melting point volatility, volatility of core material.
3) Application rate of coating material.
4) Temperature of air stream.
5) The amount of air required to fluidize the core material.[8]

Solvent Evaporation/Solvent Extraction

Microcapsule formation by solvent evaporation/solvent extraction 53-60 is very similar to suspension crosslinking, but in this case the polymer is usually hydrophobic polyester. The polymer is dissolved in a water immiscible volatile organic solvent like dichloromethane or chloroform, into which the core material is also dissolved or dispersed. The resulting solution is added dropwise to a stirring aqueous having a suitable stabilizer like poly (vinyl alcohol) or polyvinylpyrrolidone, etc. to form small polymer droplets containing encapsulated material. With time, the droplets are hardened to produce the corresponding polymer microcapsules. This hardening process is accomplished by the removal of the solvent from the polymer droplets either by solvent evaporation (by heat or reduced pressure),or by solvent\ extraction (with a third liquid which is a precipitant for the polymer and miscible with both water and solvent). Solvent extraction produces microcapsules with higher porosities than those obtained by solvent evaporation of microencapsulation by solvent evaporation technique. Solvent evaporation/extraction processes is suitable for the preparation of drug loaded microcapsules based on the biodegradable polyesters such as polylactide, (lactideco-glycolide) and polyhydroxybutyrate.

Coacervation Phase Separation

This process consist of three steps.

a) Formation of three immiscible phases; a liquid manufacturing phase, a core material phase and a coating material phase.

b) Deposition of the liquid polymer coating on the core material.

c) Rigidizing of the coating material.

Step-1: The first step of coacervation phase separation involves the formation of three immiscible chemical phases: a liquid vehicle phase, a coating material phase and a core material phase. The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for polymer. The coating material phase consists of a polymer in a liquid phase, is formed by using one of the of phase separation- coacervation method, i.e. .by changing the temperature of the polymer solution, by adding a solution, or by inducing a polymer-polymer interaction.

Step-2: It involves the deposition of the liquid polymer coating upon the core material. This is done by controlled mixing of liquid coating material and the core material in the manufacturing vehicle. The liquid coating polymer deposited on the core material if the

polymer is adsorbed at the interface formed between the core material and liquid phase. The reduction in the total free interfacial energy of the system help to promote the deposition of the coating material, brought by the decrease of the coating material surface area during coalescence of the liquid polymer droplets.

Step-3: In the last step rigidizing of the coating material done by the thermal, cross linking desolvation techniques, to forms a self supporting microcapsule.

Polymerization

A relatively new microencapsulation method utilizes polymerization technique to form protective microcapsules coating in situ. The method involves the reaction of monomeric units located at the interface existing between a core material substance 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 reactions occurs at a liquid-liquid, liquid-gas, solid- liquid, or solid gas interphase. In Interfacial polymerization, the two reactants in a poly condensation 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,\ polyurethane. Under the right conditions, thin flexible walls form rapidly at the interface. A solution of the pesticide and a diacid chloride are emulsified in water and an aqueous solution containing an amine and a polyfunctional isocyanate is added. Base is present to neutralize the acid formed during the reaction. Condensed polymer walls form instantaneously at the interface of the emulsion droplets.

Pan coating

The microencapsulation of relatively large particles by pan methods has become wide spread in the pharmaceutical industry. With respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating and there process has been extensively employed for the of controlled release preparation. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds and the coated with protective lagers of various polymers. In practice, the coating is applied as a solution or as an atomized spray to the desired solid core material in the coating pan. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans.

Spray drying and spray congealing

Spray drying and spray congealing processes are similar in that both involve dispersing the core material in liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby relatively rapid solidification of the coating is affected. The principle difference between the two methods is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of solvent in which the coating material is dissolved. Coating solidification in spray congealing method, however, is accomplished by thermally congealing a molten coating material or by solidifying the dissolved coating by introducing the coating core material mixture into a non solvent. Removal of the nonsolvent or solvent from the coated product is then accomplished by sorption extraction or evaporation techniques.[14][15]

Materials used in microencapsulation

Coating materials

A number of different substances both biodegradable as well as non- biodegradable have been investigated for the preparation or microcapsules. These materials include the polymers of natural and synthetic origin and also modified natural substances. Some of the polymers used in the preparation of the microcapsules are classified and listed below.

Synthetic Polymers

Non-biodegradable

PMMA, Acrolein, Glycidyl methacrylate, Epoxy polymers

Biodegradable

Lactides and glycolides and their copolymers, Polyalkyl cyano acrylates, Polyanhydrides, carbopol.

Natural Materials

Proteins**,** Albumins, Collagen, Carbohydrates, Starch, Agar Carrageenan, Chitosan.

Chemically modified carbohydrates

DEAE cellulose**,** Poly (acryl) dextran.[9][10]

EVALUATION OF MICROENCAPSULES

1. Particle size and shape

The most widely used procedure to visualize microcapsule is conventional Light microscopy, and scanning electron microscopy (SEM). Both techniques can be used to determine the shape and outer structure of microcapsule. SEM provides higher resolution in contrast to the light microscopy. It allows investigation of the microsphere surfaces and after particles are cross sectioned, it can also be used for the investigation of double walled systems. Confocal laser scanning microscopy (CLSM) is applied as a nondestructive visualization technique, which allows characterization of structures not only on surface, but also inside particle.

2. FourierTransform–infrared spectroscopy: (FTIR)

FTIR is used to determine the degradation of the polymeric matrix of the carrier system, and also interaction between drug and polymer system if present.

3. Density determination

The density of the microcapsule can be measured by using a multi volume\ pychnometer. Accurately weighed sample in a cup is placed in pychnometer, helium is introduced at a constant pressure in chamber and allowed to expand. The expansion results in a decrease in pressure within the chamber. From two pressure readings the volume and hence density of microcapsule can be determined.

4. Isoelectric point

The micro electrophoresis is an apparatus used to measure electrophoretic mobility of microsphere from which the isoelectric point can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behavior or ion absorption nature of microsphere.

5. Capture efficiency

The capture efficiency of microcapsule or the percent drug entrapment can be determined by allowing washed microcapsule to lyse. The lysate is then subjected to determination of active constituents as per monograph. The percent encapsulation efficiency is calculated using following equation

$$\%\text{Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100$$

6. Contact angle

The angle of contact is measured to determine the wetting property of microcapsule. It determines the nature of microsphere in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water surface by placing a droplet in circular cell mounted above the objective of inverted microscope. Contact angle is measured at 200C within a minute of decomposition of microsphere.

7. Hausner's ratio

It is the ratio of tapped to bulk density and was calculated by using the eq:

Hausner's ratio=TD/BD

8. In-vitro release studies

Release studies for microcapsules can be carried out in different pH condition like pH 1.2 and pH 7.4 using USP rotating basket or paddle apparatus. The samples are taken at specific time intervals and are replaced by same amount of fresh medium. The samples withdrawn are analyzed as per the monograph requirement and release profile is determined using the plot of amount released a function of time.[11]

FUTURE CONSIDERATION

Microencapsulation is a technique currently has been using for the delivery of many microbial, mammalian cells, drugs. But the technology needs to be further enhanced and use of this technology in diseases models, such as models of tumors for developing pharmaceutical formulations.

CONCLUSION

This article reveals the need of microencapsulation technique which deliver the drugs at a controlled rate for a desired period of time. It is a promising technique for wide range of diseases**.**

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