MICROENCAPSULATION: A NEW ERA IN NOVAL DRUG DELIVERY

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Abstract

This review paper gives a general overview of microencapsulation technology. A microcapsule is a very small capsule and its preparation procedure, called microencapsulation. Microencapsulation is one of the highly efficient method. Many different active materials like drugs, pesticides, flavours, enzymes, vitamins and catalysts have been successfully encapsulated microcapsules made from a variety of polymeric and non-polymeric materials like poly(ethylene glycol), poly(methacrylate), poly(styrene), cellulose, poly(lactide), poly(lactide-co-glycolide), gelatin and acacia, etc. This technology has been used in many fields like pharmaceutical, agriculture, food, printing, cosmetic, textile and defence. In defence sector this technology has introduced the concept of self-healing composites as well as chemical decontaminating fabrics.
INTRODUCTION:

Micro encapsulation rapidly expanding technology. It is the process of applying relatively thin coatings to tiny particles of solids or droplets of liquids and dispersions. It 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. Microencapsulation is a relieving considerable attention fundamentally, commercially\(^1\). Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules many useful properties. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters\(^2\). The controlled drug delivery system has used to reduce the problems associated with conventional therapy and to improve the therapeutic efficacy of a given drug. The maximum therapeutic efficacy can be achieved by delivering of the active agent in the optimal rate to the target tissue, then causing little toxicity and minimum side effects. To deliver a therapeutic substance to the target site in a sustained controlled release fashion various approaches are used\(^3\). Microencapsulation is a technique by which solid, liquid or gaseous active ingredients are packaged within a second material for the purpose of shielding the active ingredient from the surrounding environment. Thus the active ingredient is designated as the core material whereas the surrounding material forms the shell\(^4\).
Diagram of two representations of microcapsules: (A) continuous core surrounded by continuous shell; (B) core material dispersed in a matrix of shell material.

**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 size.

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.

**ADVANTAGES:**

1) 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.
2) Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.

3) Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.

4) The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in vivo.

5) Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.

6) Microorganism and enzyme immobilization.
   a) Enzymes have been encapsulated in cheeses to accelerate ripening and flavor development. The encapsulated enzymes are protected from low pH and high ionic strength in the cheese.
   b) The encapsulation of microorganisms has been used to improve stability of starter cultures.

7) Protection against UV, heat, oxidation, acids, bases (e.g. colorants and vitamins).
   E.g. Vitamin A monosodium glutamate.
   Appearance (white) protection (water, T, light).

8) Improved shelf life due to preventing degradative reactions (dehydration, oxidation).

9) Masking of taste or odours.

10) Improved processing, texture and less wastage of ingredients.
   - Control of hygroscopy.
   - enhance flow ability and dispersibility.
   - dust free powder
- enhance solubility

11) Handling liquids as solids.

12) There is a growing demand for nutritious foods for children which provides them with much needed vitamins and minerals during the growing age. Microencapsulation could deliver the much needed ingredients in children friendly and tasty way.

13) Enhance visual aspect and marketing concept.

14) Carbonless copy paper was the first marketable product to employ microcapsules. A coating of microencapsulated colourless ink is applied to the top sheet of paper, and a developer is applied to the subsequent sheet. When pressure is applied by writing, the capsules break and the ink reacts with the developer to produce the dark colour of the copy.$^6$

**CLASSIFICATION:**

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.

- **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.

**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, (lactide-co- glycolide) and polyhydroxybutyrate.

**Coacervation Phase Separation:**

This process of microencapsulation is generally referred to The National Cash Register (NCR) Corporation and the patents of B.K. Green. This process consists 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. Microencapsulation by coacervation phase separation process.

**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 polycondensation meet at an interface and react rapidly. The basis of this method is the classical Schotten-
Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea, 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 widespread in the pharmaceutical industry. With respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating and the process has been extensively employed for the preparation of controlled release medicaments. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds and the coated with protective layers of various polymers. In practice, the coating is applied as a solution or as a 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 liquified 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 nonsolvent. Removal of the nonsolvent or solvent from the coated product is then accomplished by sorption extraction or evaporation techniques.

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

**EVALUATION:**

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. **Fourier Transform 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 pychnomete, 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

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\% \text{ Entrapment} = \frac{\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 20°C within a minute of decomposition of microsphere.

7. **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.

CONCLUSION:

The research in the area of microencapsulation has huge potential to give raw material advantageous traits resulting in superior products. The very much popular microencapsulation technique is the most convenient way of protection and masking, reduce dissolution rate, facilitation of handling, and spatial targeting of active ingredient. Although significant advantage have been made in the field of microencapsulation, still many challenges need to be rectified during the appropriate selection of core materials, coating materials and process techniques. The microencapsulation approach also beneficial for those drugs which required to dissolved into the intestine not in the stomach. Therefore, this safe and efficient particular system should be developed in future.

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