



## Microencapsulation – A Novel Approach in Drug Delivery: A Review

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**ABSTRACT:** The review of Microencapsulation is a well-established dedicated to the preparation, properties and uses of individually encapsulated novel small particles, as well as significant improvements to tried-and-tested techniques relevant to micro and nano particles and their use in a wide variety of industrial, engineering, pharmaceutical, biotechnology and research applications. Its scope extends beyond conventional microcapsules to all other small particulate systems such as self-assembling structures that involve preparative manipulation. The review covers encapsulation materials, physics of release through the capsule wall and / or desorption from carrier, techniques of preparation, many uses to which microcapsules are put. © 2011 IGJPS. All rights reserved.

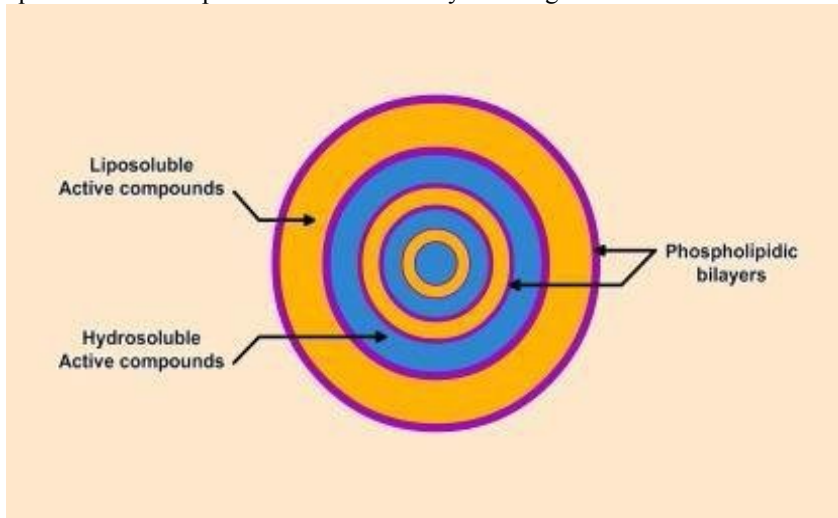
**KEYWORDS:** Microencapsulation; Core Materials; Coating Materials.

### INTRODUCTION

Microencapsulation is a process by which solids, liquids or even gases may be enclosed in microscopic particles formation of thin coatings of wall material around the substances. The process had its origin in the late 1930s as a cleaner substitute for carbon paper and carbon ribbons as sought by the business machines industry. The ultimate development in the 1950s of reproduction paper and ribbons that contained dyes in tiny gelatin capsules released on impact by a typewriter key or the pressure of a pen or pencil was the stimulus for the development of a host of microencapsulated materials, including drugs [1, 2].

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having particle size less than 200  $\mu\text{m}$ . 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 Bio encapsulation 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 life [3, 4].

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 macro packaging 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 feasible.



**Fig. 1: Microencapsulation process**

- 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 stability.

### **The reasons for microencapsulation**

The reasons for microencapsulation are countless. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack. In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides. The problem may be as simple as masking the taste or odor of the core, or as complex as increasing the selectivity of an adsorption or extraction process.

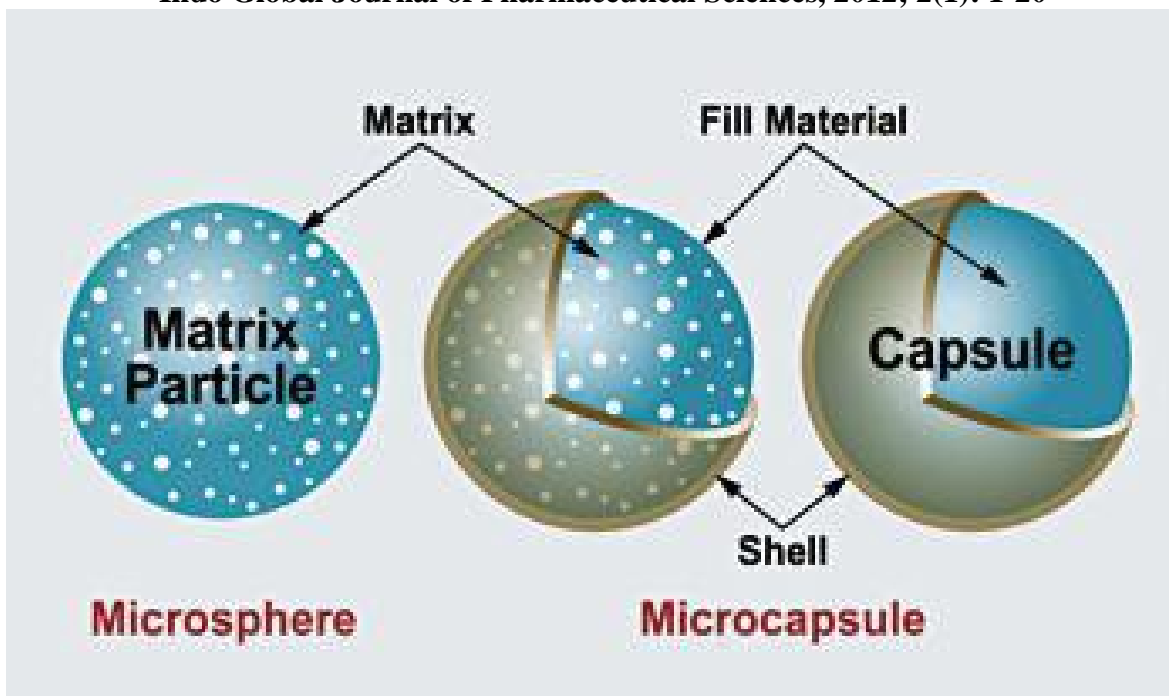


Fig. 2: Microsphere & microcapsule

#### Fundamental considerations

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods [5, 6].

#### Release mechanisms

Mechanisms of drug release from microspheres are

##### 1. Degradation controlled monolithic system

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

##### 2. Diffusion controlled monolithic system

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous or heterogeneous mechanism.

##### 3. Diffusion controlled reservoir system

Here the active agent is encapsulated by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

##### 4. Erosion

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like glyceryl mono stearate, beeswax and steryl alcohol etc. [7-9].

#### Core materials

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 materials. The solid core be active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators. The ability to vary the core material composition provides definite

flexibility and utilization of these characteristics often allows effectual design and development of the desired microcapsule properties [10].

### **Coating materials**

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. While selecting a polymer the product requirements ie. 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.

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 [11]. The microcapsules 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.

The coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and nonreactive with the core material; and provide the desired coating properties, such as strength, flexibility, impermeability, optical properties, and stability. The coating materials used in microencapsulation methods are amenable, to some extent, to in situ modification [12].

The selection of a given coating often can be aided by the review of existing literature and by the study of free or cast films, although practical use of free-film information often is impeded for the following reasons:

- Cast or free films prepared by the usual casting techniques yield films that are considerably thicker than those produced by the microencapsulation of small particles; hence, the results obtained from the cast films may not be extrapolate to the thin microcapsule coatings.
- The particular microencapsulation method employed for the deposition of a given coating produces specific and inherent properties that are difficult to simulate with existing film-casting methods.
- The coating substrate of core material may have a decisive effect on coating properties. Hence, the selection of a particular coating material involves consideration of both classic free-film data and applied results [13].

### **Coating material properties**

- Stabilization of core material.
- Inert toward active ingredients.
- Controlled release under specific conditions.
- Film-forming, pliable, tasteless, stable.
- Non-hygroscopic, no high viscosity, economical.
- Soluble in an aqueous media or solvent, or melting.
- The coating can be flexible, brittle, hard, thin etc.

### **Examples of coating materials:**

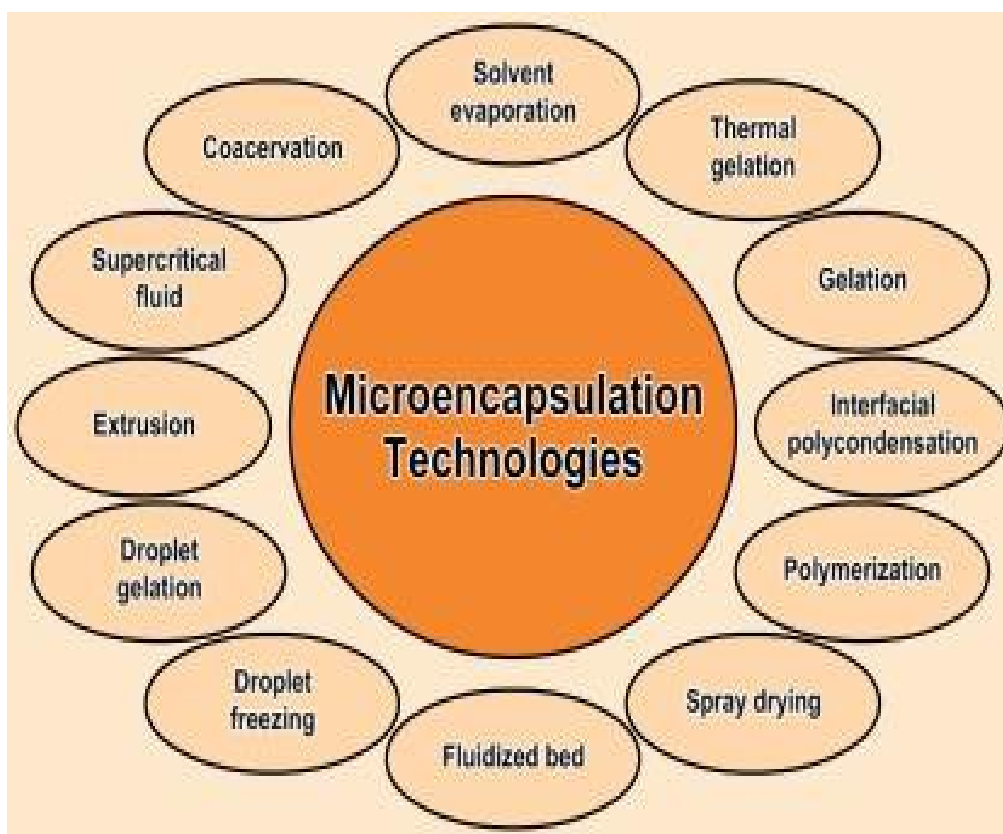
- **Water soluble resins** – Gelatin, Gum Arabic, Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxyethylcellulose, Methylcellulose, Arabinogalactan, Polyvinyl alcohol, Polyacrylic acid.

- **Water insoluble resins** – Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene Vinyl acetate), cellulose nitrate, Silicones, Poly lactideco glycolide.
- **Waxes and lipids** – Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.
- **Enteric resins** – Shellac, Cellulose acetate phthalate, Zein [14].

#### **Techniques to manufacture microcapsules**

Preparation of microspheres should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and Susceptibility to chemicalmodification [15].



**Fig. 3: Microencapsulation techniques**

#### **Physical methods**

##### **Air-suspension coating**

Microencapsulation by air suspension technique consist of the dispersing of solid, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particles are suspended on an upward moving air stream. The design of the chamber and its operating parameters effect a recirculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is spray applied to the moving particles.

During each pass through the coating zone, the core material receives an increment of coating material. The cyclic process is repeated, perhaps several hundred times during processing, depending on the purpose of microencapsulation the coating thickness

desired or whether the core material particles are thoroughly encapsulated. The supporting air stream also serves to dry the product while it is being encapsulated. Drying rates are directly related to the volume temperature of the supporting air stream.

Air-suspension coating of particles by solutions or melts gives better control and flexibility. The particles are coated while suspended in an upward-moving air stream. They are supported by a perforated plate having different patterns of holes inside and outside a cylindrical insert.

Just sufficient air is permitted to rise through the outer annular space to fluidize the settling particles. Most of the rising air (usually heated) flows inside the cylinder, causing the particles to rise rapidly. At the top, as the air stream diverges and slows, they settle back onto the outer bed and move downward to repeat the cycle. The particles pass through the inner cylinder many times in a few minutes methods.

The air suspension process offers a wide variety of coating materials candidates for microencapsulation. The process has the capability of applying coatings in the form of solvent solutions, aqueous solution, emulsions, dispersions or hot melts in equipment ranging in capacities from one pound to 990 pounds. Core materials comprised of micron or submicron particles can be effectively encapsulated by air suspension techniques, but agglomeration of the particles to some larger size is normally achieved.

### **Coacervation and microencapsulation**

Coacervation is a colloid phenomenon. If one starts with a solution of a colloid in an appropriate solvent, then according to the nature of the colloid, various changes can bring about a reduction of the solubility of the colloid. As a result of this reduction a large part of the colloid can be separated out into a new phase. The original one phase system becomes two phases. One is rich and the other is poor in colloid concentration. The colloid-rich phase in a dispersed state appears as amorphous liquid droplets called coacervate droplets. Upon standing these coalesce into one clear homogenous colloid-rich liquid layer, known as the coacervate layer which can be deposited so as to produce the wall material of the resultant capsules.

Coacervation may be initiated in a number of different ways. Examples are changing the temperature, changing the pH or adding a second substance such as a concentrated aqueous ionic salt solution or a non-solvent.

As the coacervate forms, it must wet the suspended core particles or core droplets and coalesce into a continuous coating for the process of microencapsulation to occur. The final step for microencapsulation is the hardening of the coacervate wall and the isolation of the microcapsules, usually the most difficult step in the total process [16].

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-

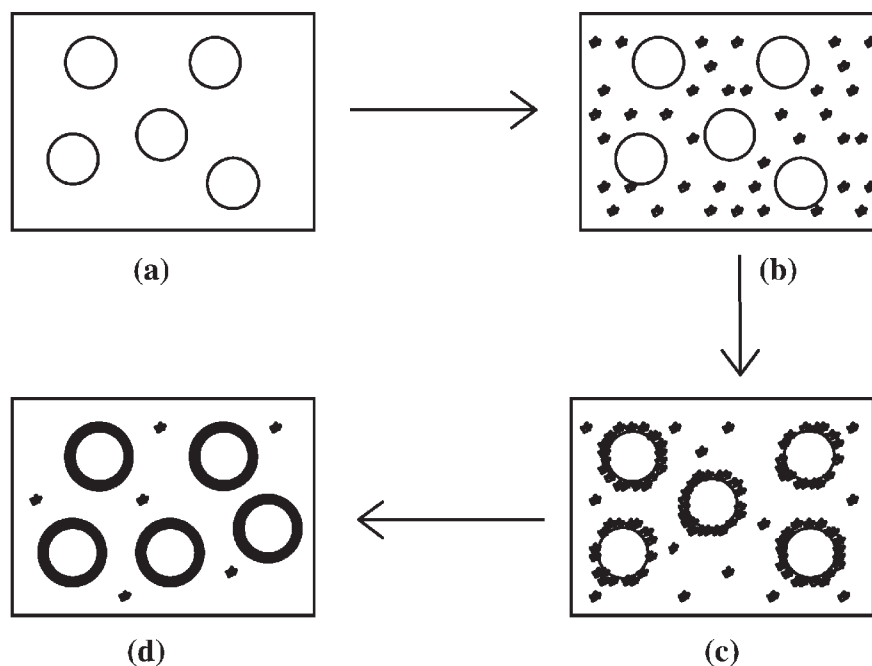
- Formation of three immiscible phases; a liquid manufacturing phase, a core material phase and a coating material phase
- Deposition of the liquid polymer coating on the core material
- Rigidizing of the coating material

**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.



**Fig. 4: Coacervation process:** (a) Core material dispersion in solution of shell polymer; (b) Separation of coacervate from solution; (c) Coating of core material by micro droplets of coacervate; (d) Coalescence of coacervate to form continuous shell around core particles.

### Simple coacervation

Simple coacervation involves the use of either a second more-water soluble polymer or an aqueous non-solvent for the gelatin. This produces the partial dehydration/desolvation of the gelatin molecules at a temperature above the gelling point. This results in the separation of a liquid gelatin-rich phase in association with an equilibrium liquid (gelatin-poor) which under optimum separation conditions can be almost completely devoid of gelatin.

Simple coacervation can be effected either by mixing two colloidal dispersions, one having a high affinity for water, or it can be induced by adding a strongly hydrophilic substance such as alcohol or sodium sulfate [17]. The water soluble polymer is concentrated in water by the action of a water miscible, non-solvent for the emerging polymer (gelatin) phase. Ethanol, acetone, dioxane, isopropanol and propanol have been used to cause separation of coacervate of gelatin, polyvinyl alcohol and methyl cellulose. Phase separation can be effected by the addition of an electrolyte such as an inorganic salt to an aqueous solution of a polymer such as gelatin, polyvinyl alcohol or carboxymethyl cellulose.

A typical simple coacervation using gelatin colloid is as follows: to a 10 percent dispersion of gelatin in water, the core material is added with continuous stirring and at a temperature of 40°C. Then a 20 percent sodium sulfate solution or ethanol is added at 50 to 60 percent by final total volume, in order to induce the coacervation. This system is cooled to 50°C; then, it is necessary to insolubilize the coacervate capsules suspended in the equilibrium liquid by the addition of a hardening agent such as glutaraldehyde and adjusting the pH. The resulting microcapsules are washed, dried and collected [18].

### **Complex coacervation**

Complex coacervation' can be induced in systems having two dispersed hydrophilic colloids of opposite electric charges. Neutralization of the overall positive charges on one of the colloids by the negative charge on the other is used to bring about separation of the polymer-rich complex coacervate phase.

The gelatin-gum arabic (gum acacia) system is the most studied complex coacervation system. Complex coacervation is possible only at pH values below the isoelectric point of gelatin. It is at these pH values that gelatin becomes positively charged, but gum arabic continues to be negatively charged. A typical complex coacervation process using gelatin and gum arabic colloids is as follows: The core material is emulsified or suspended either in the gelatin or gum arabic solution. The aqueous solution of both the gelatin and gum arabic should each be below 3 percent by weight. Then, the gelatin or the gum arabic solution (whichever was not previously used to suspend the core material) is added into the system. The temperature of the system must be higher than the gel point of an aqueous gelatin solution (greater than 35°C). The pH is adjusted to 3.8-4.3 and continuous mixing is maintained throughout the whole process. The system is cooled to 50°C and the gelled coacervate capsule walls are insolubilized by either adding glutaraldehyde or another hardening agent or adjusting the pH. The microcapsules are washed, dried and collected [19, 20].

### **Aqueous phase separation**

The term aqueous phase separation is often more simply described as "oil-in-water" microencapsulation. The two encapsulation processes described above are examples of this "oil-in-water" encapsulation. In this process the core material is the oil and it should be immiscible in the continuous phase, namely water. A commercial example of aqueous phase separation would be the microencapsulation of an oily flavor such as sour cream with a gelatin wall. These microcapsules would then be dispersed in a dry cake mix. The mechanism of release would be during the moist baking cycle of the cake, moist-heat causing the capsule walls to first swell and then rupture [21].

### **Organic phase separation**

The term organic phase separation' is sometimes more simply referred to as "water-in-oil" microencapsulation. In this case the polar core is dispersed into an oily or non-polar continuous medium. The wall material is then dissolved in this continuous medium. A simple technique for encapsulation consists of dissolving ethyl cellulose in cyclohexane at a temperature of 50°C with continuing mixing. Only one phase is present. The cyclohexane is the oily, continuous phase and the ethyl cellulose will later form the coacervative wall. The temperature is elevated to 70°C over a period of 20 to 30 minutes. The core material is added and the temperature raised to 80°C over a period of time and is held at that temperature for one hour. The system is allowed to cool rapidly to 20-40°C. Upon cooling, the ethyl cellulose will gradually emerge as a separated coacervate phase which will then gradually solidify by the time 20°C is reached (unlike hot cyclohexane, the cold material is a non-solvent). The capsules are washed, filtered and air dried. It should be noted that ethyl cellulose is generally approved for use in the pharmaceutical industry. However, for its use in the food industry the "Code of Federal Regulations" should be consulted under the categories of both microencapsulation and ethyl cellulose [22].

Another ethyl cellulose wall encapsulation system involves the addition of polyisobutylene to the ethyl cellulose/cyclohexane. The procedure begins with the addition of ethyl cellulose to a mixture of cyclohexane and polyisobutylene at room temperature. Polyisobutylene, which is more soluble in cyclohexane than is ethyl cellulose, is more effective in causing the latter to emerge as a separate liquid coacervate than would be the case with merely cooling the cyclohexane. The solution is then heated to 80°C and the core material added. The system is cooled to 40°C in 60 minutes and cooled quickly to 20-25°C. Microcapsules are filtered, washed and dried. A modification of this system involves the following procedure: The polyisobutylene is dissolved in cyclohexane at a temperature of 70°C and with continuous stirring. After cooling the system to 40°C, ethyl cellulose is added and



dissolved. The core is dispersed in this solution and the system again heated to 78°C and held for 10 minutes at this temperature. Then it is slowly cooled to room temperature followed by cooling to 10°C over two hours. Besides polyisobutylene, other coacervation inducing agents have been used such as polyethylene and butyl rubber [23].

#### **Designing the process--process and material selection**

Coacervation is a very complicated physical phenomenon. And, many factors affect the properties of the resulting microcapsules. Coacervation and phase separation from organic and aqueous media involve many properties, materials and processes such as: phase inducing agents, stirring rates, core to wall ratios, polymer characteristics, core characteristics (wet ability, solubility), cooling rates and rates of addition.

The basic production of microcapsules actually involves three distinct steps as discuss above. The hardening of the microcapsules sufficient for isolation of them into a dry free-flowing powder remains as a persistent problem. One of the earliest attempts is the gelatin-tannin reaction. Tannic acid is recognized as a means for "hardening" gelatin walled capsules. It should be noted that a particular encapsulation system, such as would be described in any one of the patents in the literature, is not necessarily effective in encapsulating a given flavor. Consequently it is often necessary to develop or modify an encapsulation system for each flavor. This is particularly true when one looks at the multitude of requirements related to storage and release of the microcapsule core [24]. Example: Coacervation Microencapsulation of Talc Particles with Poly (methyl methacrylate) by Pressure-Induced Phase Separation of CO<sub>2</sub>-Expanded Ethanol Solutions

#### **Polymer encapsulation by rapid expansion of supercritical fluids**

Supercritical fluids are highly compressed gasses that possess several advantageous properties of both liquids and gases. These fluids have attracted much attention in recent years, the most widely used being supercritical CO<sub>2</sub>, alkanes (C<sub>2</sub> to C<sub>4</sub>), and nitrous oxide (N<sub>2</sub>O). They have low hydrocarbon-like solubility for most solutes and are miscible with common gases such as hydrogen (H<sub>2</sub>) and nitrogen. A small change in temperature or pressure causes a large change in the density of supercritical fluids near the critical point a property which enhances their use in several industrial applications. Supercritical CO<sub>2</sub> is widely used for its low critical temperature value, in addition to its nontoxic, non flammable properties; it is also readily available, highly pure and cost-effective. It has found applications in encapsulating active ingredients by polymers. Different core materials such as pesticides, pigments, pharmaceutical ingredients, vitamins, flavors, and dyes are encapsulated using this method. A wide variety of shell materials that either dissolve (paraffin wax, acrylates, polyethylene glycol) or do not dissolve (proteins, polysaccharides) in supercritical CO<sub>2</sub> are used for encapsulating core substances [25].

#### **The most widely used methods are as follows:**

- Rapid expansion of supercritical solution (RESS)
- Gas anti-solvent (GAS)
- Particles from gas-saturated solution (PGSS)

#### **Rapid expansion of supercritical solution**

In this process, supercritical fluid containing the active ingredient and the shell material are maintained at high pressure and then released at atmospheric pressure through a small nozzle. The sudden drop in pressure causes desolvation of the shell material, which is then deposited around the active ingredient (core) and forms a coating layer. The disadvantage of this process is that both the active in- gradient and the shell material must be very soluble in supercritical fluids. In general, very few polymers with low cohesive energy densities (e.g., polydimethylsiloxanes, polymethacrylates) are soluble in supercritical fluids such as CO<sub>2</sub>. The solubility of polymers can be enhanced by using co-solvents. In some cases nonsolvents are used; this increases the solubility in supercritical fluids, but the shell materials do not dissolve at atmospheric pressure. A schematic of the microencapsulation process using supercritical CO<sub>2</sub>

It had very recently carried out microencapsulation of TiO<sub>2</sub> nanoparticles with polymer by RESS using ethanol as a non solvent for the polymer shell such as polyethylene glycol (PEG), poly(styrene)-b-(polymethyl methacrylate)-copoly(glycidal methacrylate) copolymer (PS-b-(PMMA-co-PGMA) and polymethyl methacrylate) [26].

#### Gas anti-solvent (GAS) process

This process is also called supercritical fluid anti-solvent (SAS). Here, supercritical fluid is added to a solution of shell material and the active ingredients and maintained at high pressure. This leads to a volume expansion of the solution that causes super saturation

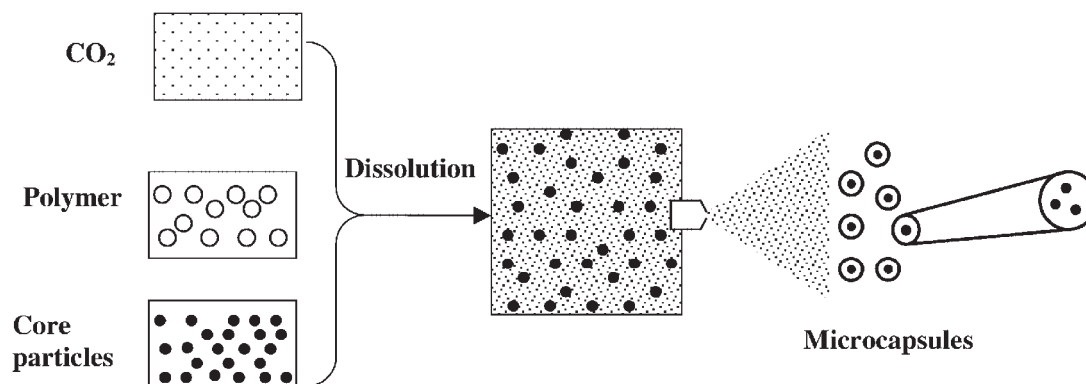


Fig. 5: Microencapsulation by rapid expansion of supercritical solutions

such that precipitation of the solute occurs. Thus, the solute must be soluble in the liquid solvent, but should not dissolve in the mixture of solvent and supercritical fluid. On the other hand, the liquid solvent must be miscible with the supercritical fluid. This process is unsuitable for the encapsulation of water-soluble ingredients as water has low solubility in supercritical fluids. It is also possible to produce submicron particles using this method [27].

#### Particles from a gas-saturated solution (PGSS)

This process is carried out by mixing core and shell materials in supercritical fluid at high pressure. During this process supercritical fluid penetrates the shell material, causing swelling. When the mixture is heated above the glass transition temperature the polymer liquefies. Upon releasing the pressure, the shell material is allowed to deposit onto the active ingredient. In this process, the core and shell materials may not be soluble in the supercritical fluid. Within the pharmaceutical industry, preformed microparticles are often used for the entrapment of active materials using supercritical fluids under pressure.

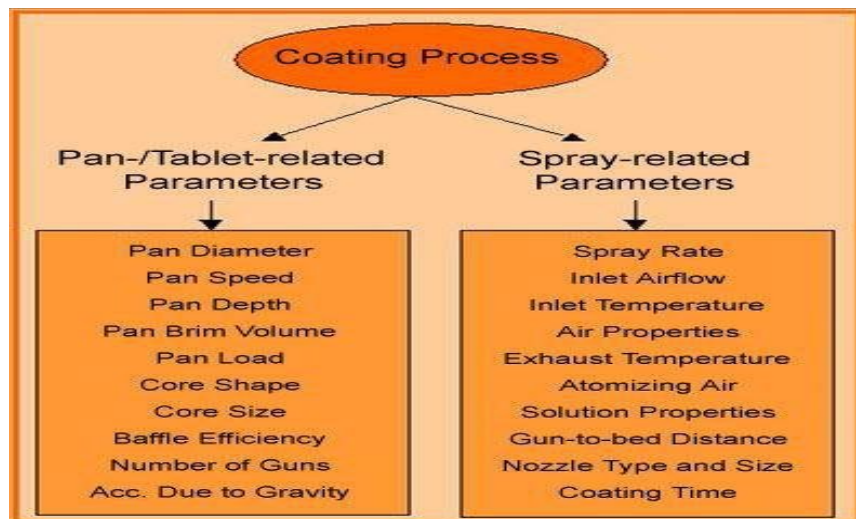
When the pressure is released, the microparticles shrink and return to their original shape and entrap the ingredients [28].

#### Centrifugal extrusion

Liquids are encapsulated using a rotating extrusion head containing concentric nozzles. In this process, a jet of core liquid is surrounded by a sheath of wall solution or melt. As the jet moves through the air it breaks, owing to Rayleigh instability, into droplets of core, each coated with the wall solution. While the droplets are in flight, a molten wall may be hardened or a solvent may be evaporated from the wall solution. Since most of the droplets are within  $\pm 10\%$  of the mean diameter, they land in a narrow ring around the spray nozzle. Hence, if needed, the capsules can be hardened after formation by catching them in a ring-shaped hardening bath. This process is excellent for forming particles 400–2,000  $\mu\text{m}$  (16-79 mils) in diameter. Since the drops are formed by the breakup of a liquid jet, the process is only suitable for liquid or slurry. A high production rate can be achieved, i.e., up to 22.5 kg (50 lb) of microcapsules can be produced per nozzle per hour per head. Heads containing 16 nozzles are available [29].

**Pan coating**

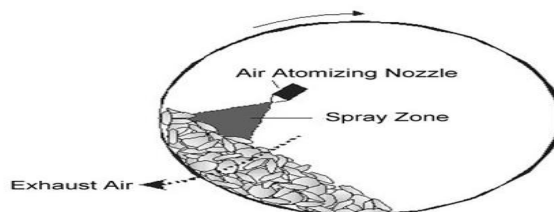
The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets.



**Fig. 6: Representation of typical Pan Coating**

The particles are tumbled in a pan or other device while the coating material is applied slowly 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 beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds, and then coated with protective layers 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 pans. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans. In some cases, final solvent removal is accomplished in a drying oven [30].



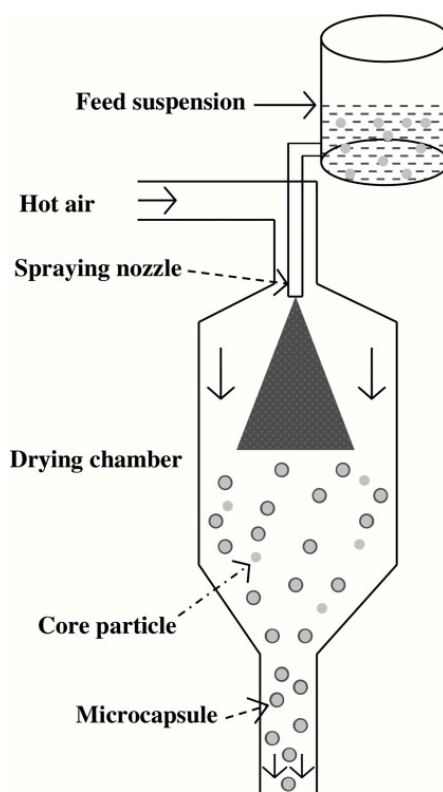
**Fig. 7: List of variables affecting pan coating**

**Spray-drying**

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages is the ability to handle labile materials because of the short contact time in the dryer, in addition, the operation is economical. In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300 m Pa.s.

Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected. The principal 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 a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, however, is accomplished by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating - core material mixture into a non-solvent. Removal of the non-solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques.

In practice, microencapsulation by spray drying is conducted by dispersing a core material in a coating solution, in which the coating substance is dissolved and in which the core material is insoluble, and then by atomizing the mixture into air stream. The air, usually heated, supplies the latent heat of vaporization required to remove the solvent from the coating material, thus forming the microencapsulated product [31].



**Fig. 8: Spray Dryer**

The equipment components of a standard spray dryer include an air heater, atomizer, main spray chamber, blower or fan, cyclone and product collector. Microencapsulation by spray congealing can be accomplished with spray drying equipment when the protective coating is applied as a melt. General process variables and conditions are quite similar to those already described, except that the core material is dispersed in a coating material melt rather than a coating solution.

Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a cool air stream. Waxes, fatty acids and alcohols, polymers and sugars, which are solids at room temperature but meltable at reasonable temperatures, are applicable to spray congealing techniques. Typically, the particle size of spray congealed products can be accurately controlled when

spray drying equipment is used, and has been found to be a function of the feed rate, the atomizing wheel velocity, dispersion of feed material viscosity, and variables [32].

### **Airflow**

The initial contact between spray droplets and drying air controls evaporation rates and product temperatures in the dryer. There are three modes of contact:

- **Co-current**

Drying air and particles move through the drying chamber in the same direction. Product temperatures on discharge from the dryer are lower than the exhaust air temperature, and hence this is an ideal mode for drying heat sensitive products. When operating with rotary atomizer, the air disperser creates a high degree of air rotation, giving uniform temperatures throughout the drying chamber. However, an alternative non-rotating airflow is often used in tower or FILTERMAT-type spray dryers using nozzle atomizers with equal success.

- **Counter-current**

Drying air and particles move through the drying chamber in opposite directions. This mode is suitable for products which require a degree of heat treatment during drying. The temperature of the powder leaving the dryer is usually higher than the exhaust air temperature.

- **Mixed-flow**

Particle movement through the drying chamber experiences both co-current and counter-current phases. This mode is suitable for heat stable products where coarse powder requirements necessitate the use of nozzle atomizers, spraying upwards into an incoming airflow, or for heat sensitive products where the atomizer sprays droplets downwards towards an integrated fluid bed and the air inlet and outlet are located at the top of the drying chamber, eg. Study on microencapsulation of lycopene by spray drying [33].

### **Fluidized-bed technology**

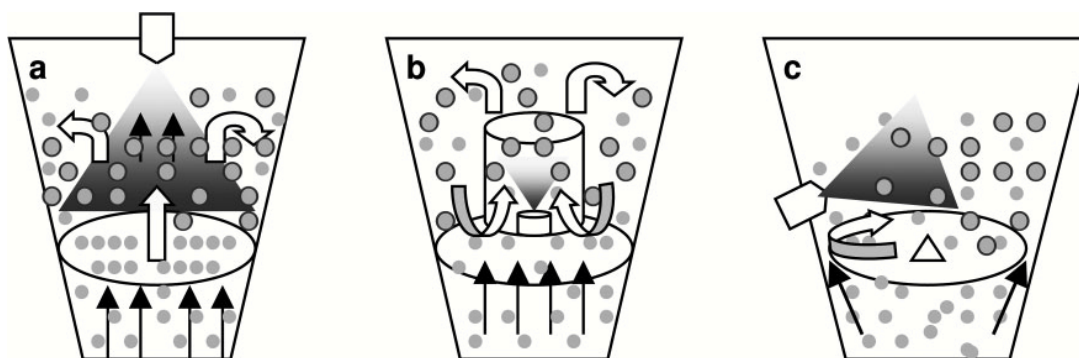
With the high demand for encapsulated materials in the global market, fluid-bed coaters have become more popular. They are used for encapsulating solid or porous particles with optimal heat exchange. The liquid coating is sprayed onto the particles and the rapid evaporation helps in the formation of an outer layer on the particles. The thickness and formulations of the coating can be obtained as desired [34].

### **Different types of fluid-bed coaters include top spray, bottom spray, and tangential spray**

- (a) Top spray
- (b) Bottom spray
- (c) Tangential spray.

In the top spray system the coating material is sprayed downwards on to the fluid bed such that as the solid or porous particles move to the coating region they become encapsulated. Increased encapsulation efficiency and the prevention of cluster formation is achieved by opposing flows of the coating materials and the particles. Dripping of the coated particles depends on the formulation of the coating material. Top spray fluid-bed coaters produce higher yields of encapsulated particles than either bottom or tangential sprays.

The bottom spray is also known as “Wurster’s coater” in recognition of its development by Prof. D.E. Wurster. This technique uses a coating chamber that has a cylindrical nozzle and a perforated bottom plate. The cylindrical nozzle is used for spraying the coating material. As the particles move upwards through the perforated bottom plate and pass the nozzle area, they are encapsulated by the coating material.



**Fig. 9: Fluid bed coaters**

The coating material adheres to the particle surface by evaporation of the solvent or cooling of the encapsulated particle. This process is continued until the desired thickness and weight is obtained. Although it is a time consuming process, the multilayer coating procedure helps in reducing particle defects [35].

The tangential spray consists of a rotating disc at the bottom of the coating chamber, with the same diameter as the chamber. During the process the disc is raised to create a gap between the edge of the chamber and the disc. The tangential nozzle is placed above the rotating disc through which the coating material is released. The particles move through the gap into the spraying zone and are encapsulated. As they travel a minimum distance there is a higher yield of encapsulated particles [36].

### **Chemical methods**

#### **Solvent evaporation**

This technique has been used by companies including the NCR Company, Gavaert Photo Production NV, and Fuji Photo Film Co., Ltd. to produce microcapsules. The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent for the polymer. In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core. In the case in which core material is dissolved in the coating polymer solution, a matrix - type microcapsule is formed. Once all the solvent for the polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders.

The solvent evaporation technique to produce microcapsules is applicable to a wide variety of liquid and solid core materials. The core materials may be either water soluble or water insoluble materials. A variety of film forming polymers can be used as coatings [37]. Example: Evaluation of sucrose esters as alternative surfactants in microencapsulation of proteins by the solvent evaporation method [38].

#### **Polymerization**

In this technique the capsule shell will be formed at or on the surface of the droplet or particle by polymerization of the reactive monomers. The substances used are multifunctional monomers. Generally used monomers include multifunctional isocyanates and multifunctional acid chlorides. These will be used either individually or in combination. The multifunctional monomer dissolved in liquid core material and it will be dispersed in aqueous phase containing dispersing agent. A coreactant multifunctional amine will be added to the mixture. This results in rapid polymerization at interface and generation of capsule shell takes place. A poly urea shell

will be formed when isocyanate reacts with amine, polynylon or polyamide shell will be formed when acid chloride reacts with amine. When isocyanate reacts with hydroxyl containing monomer produces polyurethane shell. Like IFP the capsule shell formation occurs because of polymerization monomers added to the encapsulation reactor. In this process no reactive agents are added to the core material, polymerization occurs exclusively in the continuous phase and on the continuous phase side of the interface formed by the dispersed core material and continuous phase. Initially a low molecular weight prepolymer will be formed, as time goes on the prepolymer grows in size, it deposits on the surface of the dispersed core material there by generating solid capsule shell. Example: encapsulation of various water immiscible liquids with shells formed by the reaction at acidic pH of urea with formaldehyde in aqueous media [39].

#### **Interfacial polymer**

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 [40].

#### **In-situ polymerization**

In a few microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface. In one process, E.g. Cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rates are about 0.5 $\mu$ m/min. Coating thickness ranges 0.2-75 $\mu$ m. The coating is uniform, even over sharp projections [41].

#### **Matrix polymer**

In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles. A simple method of this type is spray-drying, in which the particle is formed by evaporation of the solvent from the matrix material. However, the solidification of the matrix also can be caused by a chemical change. Using this phenomenon, Chang prepares microcapsules containing protein solutions by incorporating the protein in the aqueous diamine phase. Chang has demonstrated the permselectivity, by their ability to convert blood urea to ammonia, the enzyme remaining within the microcapsules when incorporated within an extracorporeal shunt system. Numerous groups are utilizing polymerization techniques to accomplish microencapsulation. Examples are the National Lead Corporation, Eurand Americ [42].

#### **Application of microencapsulation**

There are many reasons why drugs and related chemicals have been microencapsulated. The technology has been used widely in the design of controlled release and sustained release dosage forms [43-45].



Fig. 9: Applications of microencapsulation

- To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.
- Many drugs have been microencapsulated to reduce gastric and other G.I. tract irritations. Sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding than conventional preparations.
- A liquid can be converted to a pseudo-solid for easy handling and storage. eg. Eprazinone.
- Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride.
- Carbon tetra chlorides and a number of other substances have been microencapsulated to reduce their odor and volatility.
- Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g. vitamin A palmitate.
- Separation of incompatible substance has been achieved by encapsulation.
- 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.
- Protection of liquid crystals.

#### Characterization of microcapsule

The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.



### **Sieve analysis**

Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker (Sieving machine, Retsch, Germany). A series of five standard stainless steel sieves (20, 30, 45, 60 and 80 mesh) are arranged in the order of decreasing aperture size. Five grams of drug loaded microspheres are placed on the upper-most sieve. The sieves are shaken for a period of about 10 min, and then the particles on the screen are weighed [46].

### **Morphology of microspheres**

The surface morphologies of microspheres are examined by a scanning electron microscope (XL 30 SEM Philips, Eindhoven, and The Netherlands). The microspheres are mounted onto a copper cylinder (10 mm in diameter, 10 mm in height) by using a double-sided adhesive tape. The specimens are coated at a current of 10 mA for 4 min using an ion sputtering device (JFC-1100E, Jeol, Japan) [47].

#### ➤ **Atomic force microscopy (AFM)**

A Multimode Atomic Force Microscope from Digital Instrument is used to study the surface morphology of the microspheres. The samples are mounted on metal slabs using double-sided adhesive tapes and observed under microscope that is maintained in a constant-temperature and vibration-free environment [48].

### **Particle size**

Particle size determination approximately 30 mg microparticles is redispersed in 2–3 ml distilled water, containing 0.1% (m/m) Tween 20 for 3 min, using ultrasound and then transferred into the small volume recirculating unit, operating at 60 ml/s. The microparticle size can be determined by laser diffractometry using a Malvern Mastersizer X (Malvern Instruments, UK) [49].

### **Polymer solubility in the solvents**

Solution turbidity is a strong indication of solvent power. The cloud point can be used for the determination of the solubility of the polymer in different organic solvent.

### **Viscosity of the polymer solutions**

The absolute viscosity, kinematic viscosity, and the intrinsic viscosity of the polymer solutions in different solvents can be measured by a U-tube viscometer (viscometer constant at 40°C is 0.0038 mm<sup>2</sup>/s/s) at 25 ± 0.1°C in a thermostatic bath. The polymer solutions are allowed to stand for 24 h prior to measurement to ensure complete polymer dissolution [50].

### **Density determination**

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and density of the microsphere carrier is determined [51].

### **Bulk density**

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an auto trap (Quantach- Rome, FL, USA) until the microsphere bed volume is stabilized. The bulk density is estimated by the ratio of microsphere weight to the final volume of the tapped microsphere bed.

### **Capture efficiency**

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

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

### **Angle of contact**

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200° within a minute of deposition of microspheres [52].

### **In vitro methods**

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating *in vivo* conditions has led to development of a number of *in vitro* release methods for buccal formulations; however no standard *in vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed [53].

### **Beaker method**

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed from 60-300 rpm [54].

### **Dissolution apparatus**

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements (paddle and basket). Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

### **Advantages**

- 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*.
- Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly [55].

## **CONCLUSION**

Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimeters. The capsule protects the active ingredient from its surrounding environment until an appropriate time. Then, the material escapes through the capsule wall by various means, including rupture, dissolution, melting or diffusion. Microencapsulation is both an art and a science. There's no ONE way to do it, and each new application provides a fresh challenge. Solving these riddles requires experience, skill and the mastery of many different technologies.

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