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MICROENCAPSULATION TECHNIQUES IN PHARMACEUTICAL FORMULATION

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ABSTRACT

Essentially microencapsulation is a process or technique by which thin coatings can be applied reproducibly to small particles of solids, droplets of liquids, or dispersion, thus forming microcapsules. It can be differentiated readily from other coatings methods in the size of the particle involved; these range from several tenths of a micron to 5000µ in size. A number of microencapsulation processes have been discussed in the literature. Some are based on chemically processes and involve a chemical or phase change; others are mechanical and require special equipment to produce the physical change in the system require. The microencapsulation process provides answers for problem such as masking the taste of bitter drugs, a means of formulating prolonged action dosage forms, a means of separating incompatible material's, a method of protecting chemicals against moisture or oxidation and a means of modifying a materials' physical characteristics for ease of handling in formulation and manufacture.

KEYWORDS: Microencapsulation, Pan coating, Coacervation, Fluidized bed coating, Multi-orifice centrifugal technique.

I. INTRODUCTION

Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules of many useful properties. Microencapsulation can also be used to enclose solids, liquids, or gases inside a micrometric wall made of hard or soft soluble film, in order to reduce dosing frequency and prevent the degradation of pharmaceuticals. In a relatively simple 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. Some materials like lipids and polymers, such as alginate, may be used as a mixture to trap the material of interest inside. Most microcapsules have pores with diameters between a few micrometers and a few millimeters.

The technique of microencapsulation (Figure 1), depends on the physical and chemical properties of the material to be encapsulated.[1,3] The core may be a crystal, a jagged adsorbent particle, an emulsion, a Pickering emulsion, a suspension of solids.

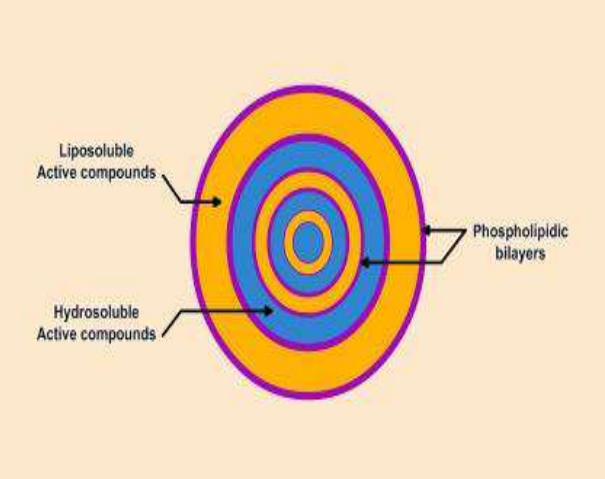

Figure. 1: Microencapsulation process.

Iupac Definition: *Microencapsulation: Hollow micro particle composed of a solid shell surrounding a core-forming space available to permanently or temporarily entrapped substance*s.[1]

II. Advantages Of Microencapsulation[2,3]

1. Protection against UV, heat, bio-oxidation, acids, bases.
2. Improved shelf life due to preventing degradation reactions.
3. Masking of bitter taste and odours.
4. Control of hygroscope.

5. Enhance flow ability, Enhance solubility and permeability.
6. Handling liquids as solids.

III. Classification: Microcapsules can be classified on three basic categories according to their morphology as follows (Figure 2).[2]

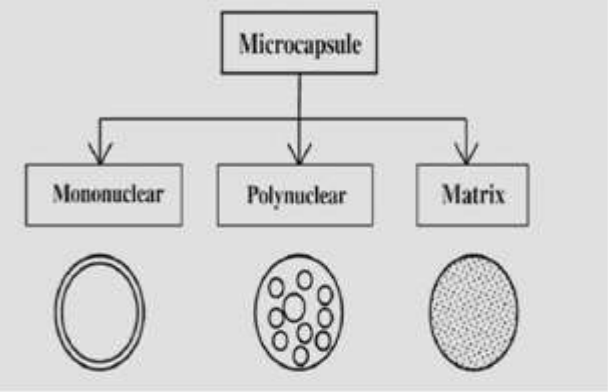

Figure. 2: Classification of Microencapsulation.

A. Mononuclear- Mononuclear (core-shell) microcapsules contain the shell around the core.
B. Polynuclear- While poly nuclear capsules have many cores enclosed within the shell.
C. Matrix types- In matrix encapsulation, the core material is distributed homogeneously into the shell material.

IV. Important Features of Microcapsules

1. The total surface area is inversely proportional to the diameter [4]
2.This large surface area is available for sites of adsorption and desorption, chemical reactions, light scattering, etc. [for example, the total surface area of 1mm of hollow microcapsules having a diameter of 0.1 mm has been reported to be about 60 m^2].

Reasons for Encapsulation[5]

1. It is mainly used to increase the stability and life of the product.
2. To control the rate at which it leaves the microcapsule, as in the controlled release.
3. A liquid can be converted to a pseudo-solid for easy handling and storage.
4. Microencapsulation has been employed to provide protection to the core materials against atmospheric condition.
5. Retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack.

V. Materials for Microencapsulation

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.[3, 5]

Coating Materials: 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.[3,5]

Coating Material Properties[4]

1. Stabilize the core material.
2. Controlled release under specific conditions.
3. Film-forming, pliable, tasteless, stable.
4. Non-hygroscopic, no high viscosity, economical.
5. Soluble in an aqueous media or solvent, or melting.
6. The coating can be flexible, brittle, hard, thin etc.

Examples of Coating Materials

1. Water soluble resin– Gelatine, Gum Arabic, Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxyethylcellulose, Methylcellulose, Arabinogalactan, Polyvinyl alcohol, Polyacrylic acid.
2. Water insoluble resins – Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene- Vinyl acetate),cellulose nitrate, Silicones, Poly(lactideco- glycolide).
3. Waxes and lipids – Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.
4. Enteric resins – Shellac, Cellulose acetate phthalate, Zein.

VI. Techniques for Manufacturing of Microencapsulations[6]

A. Physical Methods

a) Spray Drying
b) Spray Chilling
c) Fluid Bed Coating
d) Multi-orifice Centrifugal Process
e) Pan Coating
f) Air Suspension Coating
g) Centrifugal Extrusion

1. Pan coating

The pan coating process widely used and the oldest industrial procedures for forming small, coated particles or tablets.[7] 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 extensively employed for the preparation of controlled - release beads. Coating process is described in figure 3.[6]

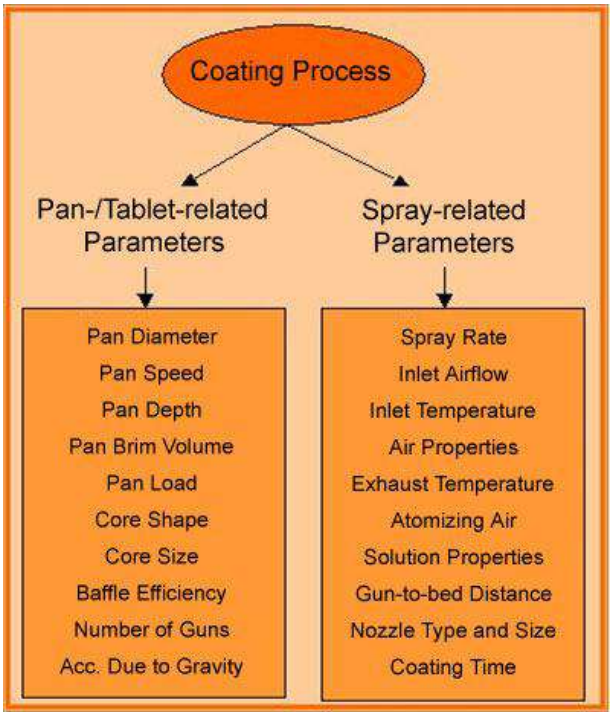

Figure. 3: List of variables affecting pan coating process.

In practice, the coating is applied as a solution, or as a In 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 show on figure 4. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds and then coated with protective layers of various polymers.

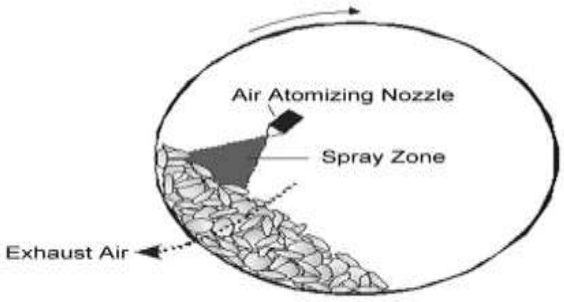

Figure. 4: Representation of a typical pan coating.

2. Air-suspension coating

Air suspension coating, (as shown in figure 5)[7] first described by Professor Dale Erwin Wurster at the University of Wisconsin in 1959, gives improved control and flexibility compared to pan coating. In this process the particulate core material, which is solid, is dispersed into the supporting air stream and these suspended particles are coated with polymers in a volatile solvent leaving a very thin layer of polymer on them. This process of air-suspension is repeated several hundred times until the required parameters such as coating thickness, etc., is achieved. The air stream which supports the particles also helps to dry them, and the rate of drying is directly proportional to the temperature of the air stream which can be modified to further affect the properties of the coating.[8]

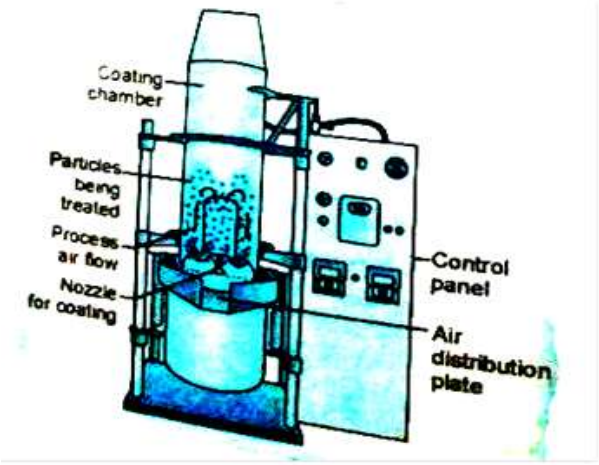

Figure. 5: Air suspension coating.

3. 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.[8] As the jet moves through the air it breaks, owing to Rayleigh instability, into droplets of core, each coated with the wall solution as shown in figure 6. While the droplets are in flight, the molten wall may be hardened or a solvent may be evaporated from the wall solution.

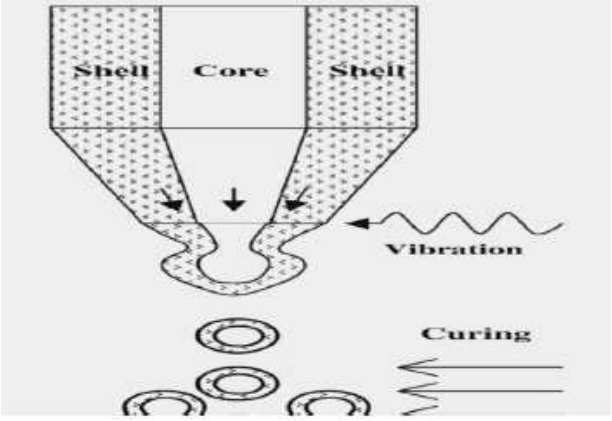

Figure. 6: Centrifugal extrusion.

Since most of the droplets are within ± 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 µm (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 slurries. A high production rate can be achieved, up to 22.5 kg (50 lb.) of microcapsules can be produced per nozzle per hour. Heads containing 16 nozzles are available.

4. Spray–drying

Spray drying (as shown in figure 7) 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 300mPa.

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.

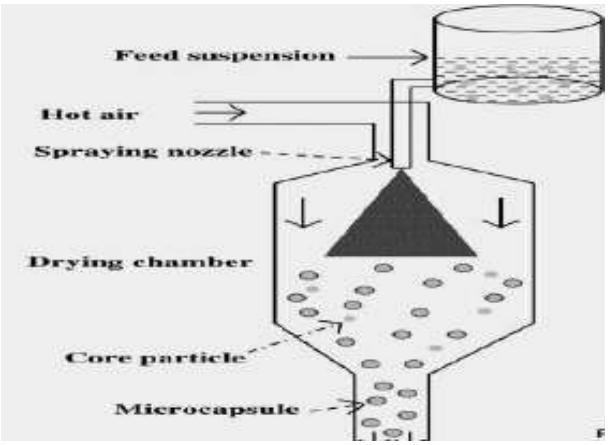

Figure. 7: Spray Drying.

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.

6. Fluidized-bed technology: Fluid bed coating, (as shown in figure 8) another mechanical encapsulation method, is restricted to encapsulation of solid core materials, including liquids absorbed into porous solids. This technique is used extensively to encapsulate pharmaceuticals. Solid particles to be encapsulated are suspended on a jet of air and then covered by a spray of liquid coating material. The capsules are then moved to an area where their shells are solidified by cooling or solvent vaporization. The process of suspending, spraying, and cooling is repeated until the capsules' walls are of the desired thickness. This process is known as the Wurster process when the spray nozzle is located at the bottom of the fluidized bed of particles. Both fluidized bed coating and the Wurster process are variations of the pan coating method.

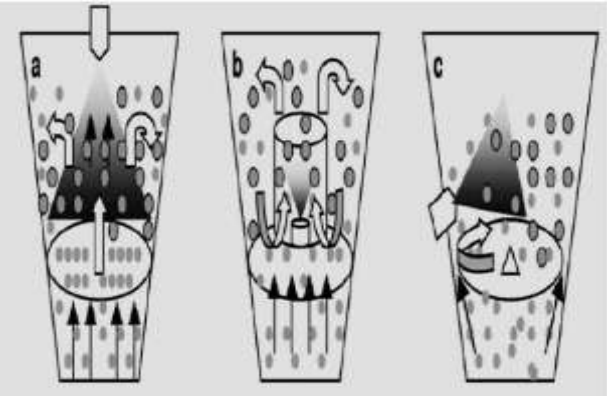

Figure. 8: Fludized bed Technology.

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

7. Multi-orifice Centrifugal Process

The Southwest Research Institute (SWRI) has developed a mechanical process for producing microcapsules that utilizes centrifugal forces to hurl a core material particle trough an enveloping microencapsulation membrane thereby effecting mechanical microencapsulation Processing variables include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity and surface tension of the core material.

The Multi-orifice centrifugal (as shown in figure 9) process is capable for microencapsulating liquids and solids of varied size ranges, with diverse coating materials. The encapsulated product can be supplied as slurry in the hardening mediator s a dry powder. Production rates of 50 to 75 pounds per our have been achieved with the process.

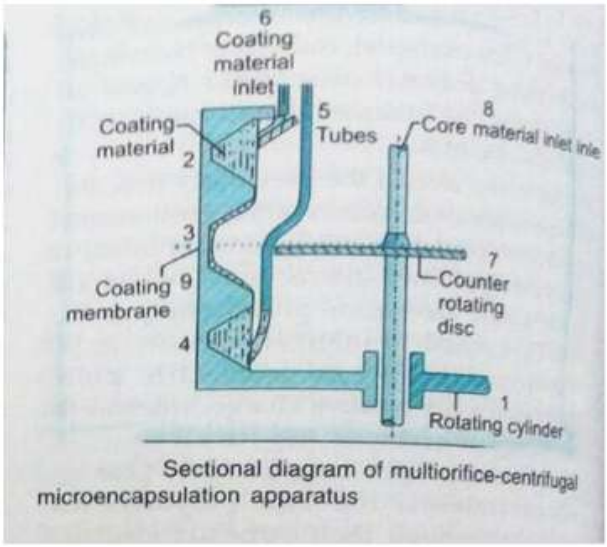

Figure. 9: Multi-orifice Centrifugal Process.

C. Chemical Methods[13,14]

a) Coacervation Phase Separation
b) Solvent evaporation
c) Solvent Extraction
d) Interfacial Polymerization
e) In-Situ Polymerization
f) Matrix polymerization

1. Coacervation-phase separation: The general outline of the processes consists of three steps carried out under continuous agitation, as shown in figure 10.

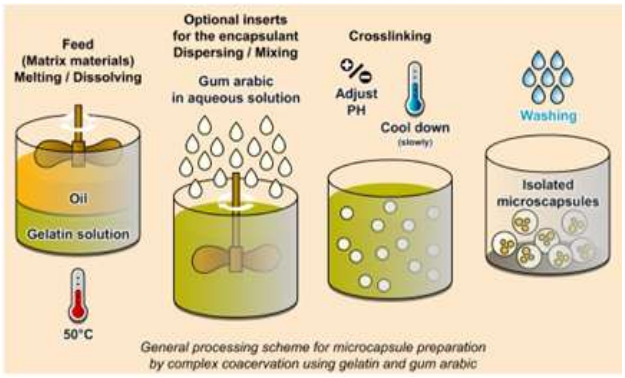

Figure. 10: Coacervation Phase Separation.

a. Formation of Three Immiscible Chemical Phases – A liquid manufacturing vehicle phase, a core material phase, and a coating material phase. To form the three phases, the core material dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase.

The coating material phase, an immiscible polymer in a liquid state, is formed by utilizing one of the methods of the methods of phase separation-coacervation, i.e., by changing the temperature of the polymer solution; or by adding a salt, non-solvent, or incompatible polymer to the polymer solution; or by inducing a polymer - polymer interaction.

b. Deposition of the Coating – It consists of depositing the liquid polymer coating upon the core material. This is accomplished by controlled, physical mixing of the material in the manufacturing vehicle. Deposition if the liquid polymer coating around then core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to effective coating. The continued deposition of the coating material is promoted by a reduction in the total free interfacial energy of the system, brought about by the decrease of the coating material surface area during clearance of the liquid polymer droplets.

c. Rigidization of the Coating – It involves rigid the coating, usually by thermal, cross-linking, or de-solvation techniques, to form a self-sustaining microcapsules.

E.g. Coacervation Microencapsulation of Talc Particles with Poly (methyl methacrylate) by Pressure-Induced Phase Separation of CO_2-Expanded Ethanol Solutions.

2. Interfacial Polycondensation

In interfacial Polycondensation, the two reactants in a Polycondensation meet at an interface and react rapidly. The basic 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 di-acid 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.

3. Interfacial Cross-Linking: Interfacial cross-linking is derived from interfacial polycondensation, and was developed to avoid the use of toxic diamines, for pharmaceutical or cosmetic applications. In this method, the small bifunctional monomer containing active hydrogen atoms is replaced by a biosourced polymer, like a protein. When the reaction is performed at the interface of an emulsion, the acid chloride reacts with the various functional groups of the protein, leading to the formation of a membrane. The method is very versatile, and the properties of the microcapsules (size, porosity, degradability, mechanical resistance).

4. 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 µm/min. Coating thickness

ranges 0.2–75 µm (0.0079–2.9528 mils). The coating is uniform, even over sharp projections. Protein microcapsules are biocompatible and biodegradable, and the presence of the protein backbone renders the membrane more resistant and elastic than those obtained by interfacial polycondensation.

5. Matrix Polymerization: In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles (Figure 11). 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.

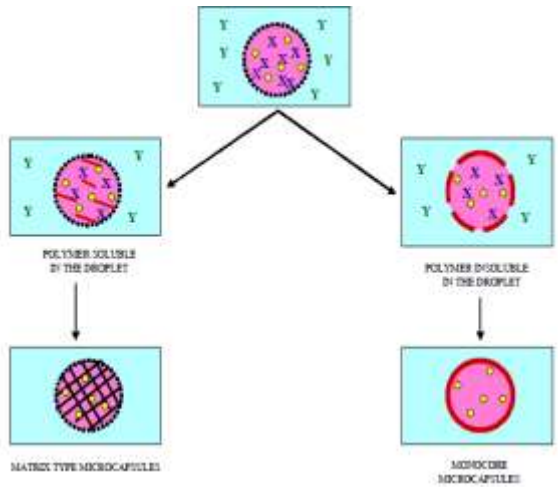

Figure. 11: Mechanism of matrix type or mono core type microcapsule formation by interfacial polymerization (X and Y are bi functional monomers).

According to this technique the monomer (alkyl acrylate) is added drop wise to the stirred aqueous polymerisation medium containing the material to be encapsulated (core material) and a suitable emulsifier. The polymerisation begins and initially produced polymer molecules precipitate in the aqueous medium to form primary nuclei. As the polymerisation proceeds, these nuclei grow gradually and simultaneously entrap the core material to form the final microcapsules.[15]

6. Solvent Evaporation/Solvent Extraction

Microcapsule formation by solvent evaporation/solvent extraction is very similar to suspension cross linking, 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 drop wise to a stirring aqueous solution having a suitable stabilizer like poly (vinyl alcohol) or Polyvinylpyrrolidone, etc. to form small polymer droplets containing encapsulated material.[15]

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. A schematic representation of microencapsulation by solvent evaporation technique is shown in Figure 12. Solvent evaporation/extraction processes is suitable for the preparation of drug loaded microcapsules based on the biodegradable polyesters such as polylactide, poly (lactideco- glycolide) and polyhydroxybutyrate.

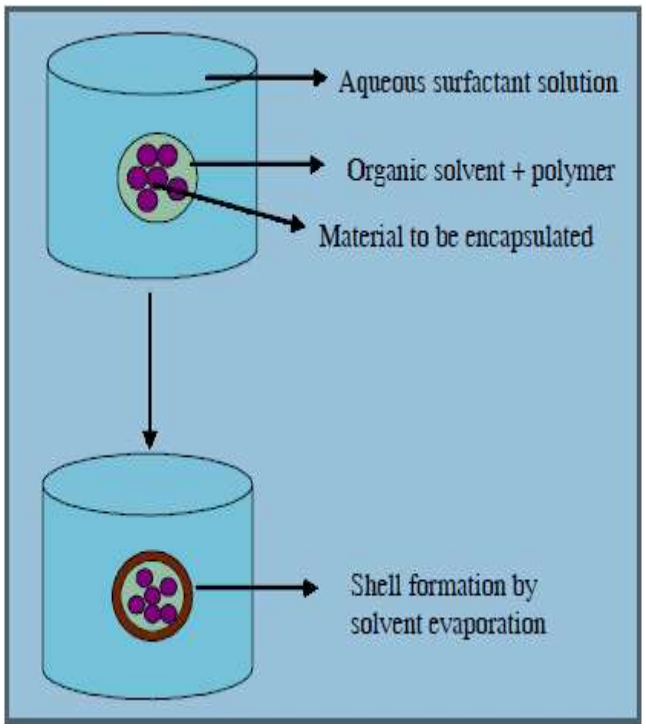

Figure. 12: Solvent Evaporation/Solvent Extraction.

VII. Evaluation of Microcapsules

The size and shape of the prepared micro particles can be determined by light and scanning electron microscope.[16,17]

A. Microcapsule solvation can be predicted using following formula;

Microcapsule solvation (%) = $(M_1 / M_2) \times 100$

M_1 - Microcapsules weighed immediately

M_2 - After drying to a constant weight

B. Bulk density is determined by following formula;

Bulk Density = Sample weight / Sample volume

C. Tap density is measured by employing the conventional tapping method using 10 ml measuring cylinder and the number of tapings will reduced to 100 as it is sufficient to bring about a plateau condition.

Taped density is calculated by following formula
Tapped density = Weight of microcapsules /Volume of microcapsules after 100 tappings

D. Compressibility index can be calculated using following formula;
C_i = {(Initial volume – Final volume) / Initial volume} × 100

E. Hausner's ratio, another index of flow ability of microcapsules, is calculated by following formula;
Hausner's ratio = Volume before tapping / Volume after tapping

F. Angle of repose is measured by passing microcapsules through a funnel on the horizontal surface. The height (h) of the heap formed was measured and radius (r) of cone base is also determined.[18, 19, 20]
The angle of repose (Ø) is calculated by following formula;
Ø = tan -1 h / r
Where *r* is the radius and *h* is the height

VIII. Release Mechanisms
Mechanisms of drug release are-[21]

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 Stearyl alcohol etc. the following considerations can be made:

- Drug release rate from microcapsules follow the zero order kinetic.
- Microcapsules of monolithic type have thet1/2 dependant release rate for the first half of the total drug release and thereafter turndown exponentially.
- Microcapsules of monolithic type containing excess of dissolved drug, the release rate are t1/2 dependant throughout almost the entire drug release.
- The path travelled by drug is not constant in monolithic capsules; as the drug at the
- Centre travels a large distance than the drug at the surface. Therefore, the release rate in monolithic capsules generally decreases with time.[22,23]

IX. Applications of Microencapsulation[24,25]
The applications of micro-encapsulation are numerous. The ones mentioned below are some of the most common ones.

A. Agriculture
➢ Crop protection.
➢ Pheromones can reduce insect populations by disrupting their mating process.

B. Pharmaceutics
➢ One of the major applications area of technique is pharmaceutical/ biomedical for controlled/sustained encapsulation drug delivery.

C. Food Industry
➢ Improve nutritional value can compromise their taste, colour, texture and aroma. Sometimes they slowly degrade and lose their activity, or become hazardous by oxidation reactions.

D. Energy generation
➢ Hollow plastic microspheres loaded with gaseous deuterium (a fusion fuel) are used to harness nuclear fusion for producing electrical energy. The capsules are multi-layered.

F. Defence
➢ One of the important defence applications of microencapsulation technology is in self-healing polymers and composites.

Some examples of microencapsulated drugs have been shown in Table 1.

Table. 1: Some examples of Microencapsulated Drug.

Drug / Core material	*Characteristic property*	*Purpose of encapsulation*	*Final product form*
Actaminophen	Slightly water soluble solid	Taste masking	Tablet
Aspirin	Slightly water soluble solid	Taste masking, sustained release, reduced gastric irritation, separation of incompatibles	Tablet or capsule
Islet of Langerhans	Viable cells	Sustained normalization of diabetic condition	Injectable
Isosorbide dinitrate	Water soluble solid	Sustained release	Capsules
Menthol	Volatile solution	Reduction of volatility, sustained release	Lotion
Progesterone	Slightly water soluble solid	Sustained release	Varied
Potassium chloride	Highly water soluble solid	Reduced gastric irritation	Capsule
Urease	Water soluble enzyme	Permselectivity of enzyme, substrate, and reaction products.	Dispersion
Vitamin A palmitate	Nonvolatile liquid	Stabilization to oxidation	Dry powder

XI. CONCLUSION

The microencapsulation technique offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling and spatial targeting of the active ingredient.

This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action. In future by combining various other approaches, microencapsulation technique will find the vital place in novel drug delivery system.

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