Microencapsulation: A Review

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Abstract- *Microencapsulation is the technique of surrounding and enclosing small discrete solid particles or small liquid droplets in an unbroken shell. Microencapsulation is a technique for modifying and delaying the release of drugs from pharmaceutical dosage forms. A well-designed controlled drug delivery system can solve some of the drawbacks of conventional therapies while also improving a medicine's therapeutic efficacy. The controlled release drug delivery system delivers the active drug or medicament at a predetermined rate over a prolonged period of time, targeting the medicine to a specific site. The review of microcapsules includes the types of microcapsules, preparation and evaluation.*

Keywords- microencapsulation, drug, micro capsule, coacervation, polymerization

I. INTRODUCTION

The technique of encapsulating a substance inside a miniature capsule is known as microencapsulation. Microcapsules are small spheres surrounded by an uniform wall. Bungen burg de Jong and Kan reported the first research leading to the development of microencapsulation processes for pharmaceuticals in 1931, and it dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process. A well-designed controlled drug delivery system can solve some of the problems of traditional therapy while also improving a drug therapeutic efficacy.To achieve optimum therapeutic efficacy, the agent must be delivered to the target area in the optimal amount and at the proper time, resulting in minimal toxicity and adverse effects. [36] Microencapsulation is the process of surrounding or coating very tiny droplets or particles of liquid or solid material with a continuous film of polymeric material [37].

Reasons for Microencapsulation[3]

1. The main reason for microencapsulation is to give the drug a prolonged or sustained release.
2. This technique has been widely utilised to mask the organoleptic properties of many drugs, such as taste and odour, and thereby enhance patient compliance. For example, paracetamol and nitrofurantoine have been used to mask the bitter taste.
3. Liquid drugs can be transformed into a free-flowing powder utilising microencapsulation techniques.
4. Microencapsulation can protect medications that are susceptible to moisture, light, or oxygen. For example, nifedipine is protected from photo instability.
5. The microencapsulation technology can also helpful to prevent drug incompatibility.
6. Drugs that are naturally volatile can evaporate at normal temperature. Microencapsulation can prevent drugs like aspirin and peppermint oil from being absorbed into the body.
7. Microencapsulation can reduce toxicity and GI irritation, for example with KCL and ferrous sulphate.
8. Microencapsulation has also been used to alter the absorption site. This application has proven to be beneficial for drugs that are toxic at lower pH levels.
9. Bakan and Anderson discovered that microencapsulated vitamin A palmitate was more stable and less prone to oxidation.
10. In addition, the microencapsulation process has been used to prepare intrauterine contraceptive devices.

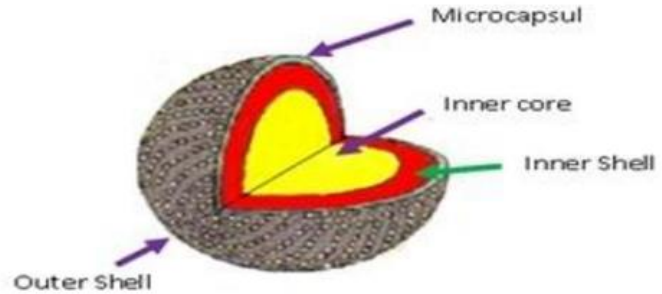

Figure 1: Structure of microcapsule

II. TYPES[1]

Microcapsules can be classified into three types;

1. Mononuclear/Single core.
2. Poly nuclear/Multiple core.
3. Matrix type

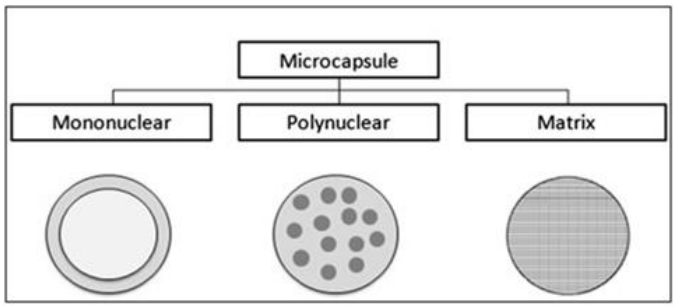

Figure 2:- Types of microcapsules (2)

III. METHOD OF PREPARATION (3,4,5,6,7)

There are various methods of microencapsulation. The methods are divided into three types

1. Physical methods
2. Physico-chemical methods
3. Chemical methods

1. Physical Methods

- Fluidized bed technology
- Spray drying
- spray congealing
- Air suspension coating
- Pan coating
- Spinning disk
- Centrifugal extrusion

2. Physico-Chemical Methods

- Solvent evaporation
- Coacervation
- Hydrogel microspheres
- Polymer-polymer incompatibility
- Polymer encapsulation

3. Chemical Methods

- Interfacial polycondensation
- Interfacial polymerization
- Interfacial cross-linking
- Matrix polymerization

1. Physical Methods

Fluidized Bed Technology

Solids and liquids are absorbed into the porous material using this process. The solid external material is blown away by jet air. Then a liquid-coated material is sprayed on top of it. An external layer is formed over the material by an accelerated evaporation process. The procedure is repeated until the desired weight and thickness are obtained [8]. The fluid-bed coater comes in a variety of configurations [9].

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

a) Top-Spray Units

In a heated atmosphere, fat and wax collide. That is why this form of spraying material is being introduced over the previously fluidized solid material bed. The capsules are manufactured with solid shells using this approach. This approach is widely used in the manufacturing of water-soluble drugs and foods. The top-spray approach has limits when it comes to solution spraying on the shell part. The solution droplets move in the opposite direction of the gas stream during spraying, disappearing from the fluidized bed. This method is ideal for a surface covering of shell element deposition and evaporation[8].

b) Bottom-Spray Units

This unit was first improved by Professor D.E. Wurster. Wurster's Coater is the alternate name for this unit. This device primarily uses a chamber for coating purposes, which has a cylindrical nozzle and a plate with a perforated bottom. The coating elements are sprayed with the cylindrical shaped nozzle. 6 The medicine is injected into the perforated plate and subsequently into the nozzle.The drug is encapsulated with the coating ingredient in this manner. Following that, the coating element adjusts over the drug due to the evaporation of the coating solvent and a decreasing thermal condition. A thick and sufficient shell is obtained after multiple repeats of this technique [8,10].

c) Tangential-Spray Units

The operation is described in the unit's name. From a tangential angle with the circle, the coating element is applied to the circular bottom of the container. A rotating disc creates a uniform coating shell that is equally distributed. For a uniform coating, the rotation speed must remain constant. For fluidization, a Consider flow bed ensures steady air circulation. The rest of the techniques are identical to those used in the other approaches. This device can provide a homogeneous and appropriate coating shell.The active ingredient in the drug must be released. A regulated release of an active agent drug can be manufactured in this unit. The

spray material is driven to a nozzle connected to the manufacturing bed to avoid an unfavourable drying.

Spray Drying

The core drag components are dispersed in a polymer solution, and spraying is done in a hot chamber. The outer membrane material solidifies when the applied solvent evaporates. Finally, a polynuclear or matrix microcapsule is created[11]. The method of encapsulation is cost-effective. The drag oil's purity, smell, and flavour are all unchanged during this process.

Spray-Congealing

The core element is dispersed in the coating material, which has been melted. When a solution is sprayed in a cold air stream, a solid coating shell forms [12].

Air Suspension Coating

This approach was first introduced by Professor Dale E. Wurster of the University of Wisconsin. In this case, solid drug components are dispersed in an auxiliary air stream. The coating procedure takes place in a chamber where the drug particle is separated by a stream of airflow. The chamber's operating condition has a significant impact on coating performance. For improved coated shell manufacture, this process is repeated up to a hundred times. The product's drying process is accelerated by the thermal state of the applied air stream. As a result, the airflow and temperature of the air directly accelerate the product's drying process [31].

Pan Coating

It is a physical microencapsulation approach. It is a frequently used commercial technology for producing small-sized coated particles. The coating element is used in this case in a dry state with the requisite solid particles. The coating element melts as the heating energy rises, and the space between the coating material and the core element disappears. When the temperature drops below a certain point, the shell material solidifies [12].

Spinning Disk or Rotational Suspension Separation

This method is particularly efficient for manufacturing because it is quick, low-cost, and simple to implement. The solution of the core material is poured onto a revolving disc. The membrane forms a shell over the core element as a result of the spinning process. The undesirable particles are flung away by the centrifugal force of the disc rotation when the shell forming mechanism is completed. Finally, when the temperature drops, the coated element becomes rigid and firm over the core agent's surface.

Centrifugal Extrusion

It has nozzles that allow two types of solution to pass through while spinning at the same time. The liquid can be forced through the nozzle by a pump for the core and shell elements. A metal rod or column is utilised here for two-fluid mechanisms. When the solution flows through the nozzle, the solution is divided into droplets by this metal column, which are mostly spherical in shape. The way capsules are converted from droplets is determined by the shell membrane element [12, 14].

2. Physico-Chemical Methods

Solvent Evaporation or Drying of In-Liquid [15]

Microencapsulation has also been widely adapted using this method. The introduction of an additional medium to emulsify the active ingredient and polymer does not dissolve during the emulsification process. It is a simple approach for microcapsules containing a variety of polymers and different types of chemical components [16, 17]. The characteristics of microspheres can be altered by the entire evaporation procedure. The emulsion and production process are accelerated by the dispersing element, the active element-to-polymer ratio, core material solubility, and stir rate [17, 18]. The hydrophilic or hydrophobic nature of the drug determines whether it can be encapsulated effectively. The oil-in-water technique is commonly employed to create hydrophobic drug materials. This oil-in-water approach is simple to use, and it is followed by some other method. The oil-in-water process has four important stages:

1. In a polymer organic solvent, a hydrophobic drug is dissolved.
2. The dispersed phase shows that the organic constituent has been emulsified. Aqueous phase also denotes a continuous phase.
3. In a continuous phase, the solvent is extracted from the dispersed phase, where the solvent evaporates and solidifies into droplets.
4. The drying and recovery process can help to get rid of remaining solvent.

A different technique is required for highly hydrophilic drug material. There is a possibility that the highly hydrophilic drug will not dissolve in the organic solvent. The

active agent may reach the continuous phase during the emulsion period, resulting in drug loss [19,20].

The following is a viable alternative:

a) Water-oil-water double emulsion method: In an aqueous solution, hydrophilic drag emulsifies in the organic phase. For a second emulsion layer, an emulsion process will take place in an aqueous solution.
b) Oil-water co-solvent method: If the drag does not dissolve in the organic solvent, an auxiliary is added to make the drug soluble.
c) Oil-water dispersion method: The drug is dispersed in a polymer and an organic solvent using a powder and solid form of the drug.
d) Evaporation of an oil-oil non-aqueous solvent: The oil replaces the aqueous phase.

The drug should be in an aqueous state at initially. In addition, a viscosity booster and stabiliser should be included in the arrangement. Dichloromethane, chloroform, and other solvents are required for the production of water in a high-stirring process.

In the water-oil-water approach, PVA or PVP is used as an emulsifier in a large amount of water for the emulsion process. The emulsion is subsequently sent to a vigorous, stirring procedure for the evaporation of the organic part in the solvent. After that, the final microspheres are manufactured using a washing and drying process.

Coacervation

There are two methods for carrying out coacervation. One is a straightforward process, whereas the other is a complex one. The phase separation is maintained in the basic technique by introducing a dissolvation-type agent. Furthermore, two polymers with differing charges are integrated throughout the complex procedure [21]. First and foremost, the polymer solution is mixed with the core element (typically oil) (a cationic aqueous polymer, gelatin). Following that, a polymer solution (anionic, water-soluble gum arabic) is added to the resulting dispersion. When the two polymers combine, the coating material settles on top of the core particle. The process is speed up by adding salt, changing the pH, changing the temperature, or diluting the medium. Finally, the microcapsules are stabilised using formaldehyde cross-linking, dissolvation, or thermal adaptation. Complex coacervation, which includes fragrant oils, liquid crystals, tastes, dyes, or inks as the core material, is used to make microcapsules.

Hydrogel Microspheres

Microspheres produced of gel-type polymers, for example, from the polymer dissolved method in aqueous solution, are the constituent elements of the microsphere. The active element must then be separated from the overall mixing volume. To generate micro-level droplets, the elements require a precision mechanism that uses a stirring process to gradually harden the element. Then plunge into a hardening bath containing a calcium chloride solution that is slowly stirred [22]. This approach is based on an aqueous solution. In the microspheres, the residual elements are separated.

The particle size is controlled by the following factors:

- Changing extruders measurement.
- Changing flow rate of the polymer.

Polymer-Polymer Incompatibility

A phase separation process occurs when two polymers are incompatible with each other. Two types of polymer were utilised in this method, both of which are soluble in a common solvent but do not combine. One of the two phases of the polymer constitutes the capsule's shell, while the other serves as a separator. Furthermore, the capsule shell does not contain the second phase polymer. The shell is dissolved by a cross-linking of chemical or non-solvent substance. Microcapsules are manufactured in this manner.During the manufacturing process, the capsules have a tendency to stick together [21]. The encapsulation of polymer and polymer incompatibility takes place in an aqueous or aqueous-free environment. Furthermore, organic media is critical in the early stages.

Polymer Encapsulation

Supercritical fluids, such as highly compressed gases, have a variety of features in addition to their liquid and gaseous forms. Carbon-dioxide and Nitrous-oxide are the most prevalent in the applied section of these criteria. For the density of the fluid, the thermal state and operating pressure are critical game changers [23]. The coated element and the effective agent material are kept under high pressure, while the element release is kept at normal room pressure via a specific nozzle. These pressure variations cause the coating material to dissolve and adhere to the core element, forming the coating membrane [23, 24].This technique encapsulates active factors such as taste, vitamin and mineral content, colour, pigment, and insecticides. The outer shell membrane is mostly made of paraffin wax and polyethylene glycol. One

condition must be met: the active element and the shell element must both be soluble in supercritical fluids [23].

3. Chemical Methods

Interfacial Polymerization (IFP)

Reactive monomer polymerization will build a coated shell over the active core's outer surface [21]. The monomer is a form of polymer that has multiple functions. Monomers can be utilised in either a single or mixed form. The multifunctional monomer is dissolved in the liquid core material, resulting in dispersion in the aqueous phase that holds the dispersing element. An additional amine-type reactant will be added to the mix. The coated shell will be created after an accelerated polymerization.

Polyuria membrane is formed when isocyanate reacts with amine. As a result, a reaction between acid chloride and amine produces polynylon or polyamide, whereas a reaction between isocyanate and hydroxyl produces polyurethane shell. Polyurethane-urea encapsulates diammonium hydrogen phosphate through the Interfacial polymerization process. The elemental analysis yields DAHP at a weight of 62 %, which will be used as fill. This fill will generate powdered microcapsules with a 22% microcapsule content. The usual particle size of DAHP is 13.35mm, and the average particle size of 95% is 30.1mm.

Polymerization

The addition of polymerization monomers to the encapsulation reactor results in a capsule covered shell that is identical to IFP. There are no reactive ingredients combined with the core element in this procedure. Polymerization occurs in the continuous phase of the dispersed core element. The weight of the polymer used to make the shell will be less at first. After that, as time passes, the polymer's thickness will increase, and the polymer will eventually become a capsule shell. Polymerization takes place in the aqueous state, which is a unique aspect of in situ encapsulation technique. This criterion distinguishes the in situ encapsulation method from other methods.As a result, a condensed material shell is produced over the dispersed type core element. The coated capsule membrane has a greater cross-linked vale and water insolubility in this method. Because the entire polymerization process takes place in water, the reactive material does not dissolve in the core element. This approach has become a frequently used method for mass capsule production.

Interfacial Cross-Linking

Interfacial polycondensation is used to investigate this form of cross-linking [25]. This approach is used to decrease the toxic effects of Diamines. Furthermore, this approach is commonly utilised in commercial pharmaceutical manufacture and the cosmetic industry. Biosource's polymer replaces a tiny bifunctional monomer in the same way that protein does. Reactive hydrogen is present in this form of monomer. The reaction mechanism takes place on the emulsion's surface. The membrane shell is formed by the interaction of several types of protein functional groups with acid chloride [26].

Matrix Polymerization

There is an embedded process for the core element in the matrix of the polymer at the moment of particle formation. The solvent evaporation in the matrix material is accelerated by a spray and drying mechanism. The solid shape of the matrix can be improved by changing the chemical environment [27].

IV. EVALUATION

1) Morphology of microspheres

A scanning electron microscope is used to analyse the surface morphologies of microspheres (XL 30 SEM Philips, Eindhoven, and The Netherlands). A double-sided adhesive tape is used to adhere the microspheres to a copper cylinder (10 mm in diameter, 10 mm in height). Using an ion sputtering equipment, the specimens are coated for 4 minutes at a current of 10 mA. (JFC-1100E, Jeol, Japan)[28].

2) Sieve analysis

A mechanical sieve shaker can be used to separate the microspheres into various size fractions (Sieving machine, Retsch, Germany). In order of decreasing aperture size, a set of five standard stainless steel sieves (20, 30, 45, 60, and 80 mesh) are positioned. On the upper-most sieve, five grammes of drug-loaded microspheres are inserted. After shaking the sieves for roughly 10 minutes, the particles on the screen are weighed[29].

3) Particle size

Approximately 30 mg microparticles are redispersed in 2–3 ml distilled water containing 0.1 % (m/m) Tween 20 for 3 minutes using ultrasound and then transferred into the small volume recirculating unit, which operates at 60 ml/s. A Malvern Mastersizer X (Malvern Instruments, UK) can be

used to determine the microparticle size using laser diffractometry (Malvern Instruments, UK) [30].

4) Atomic force microscopy (AFM)

A Multimode Atomic Force Microscope The surface morphology of the microspheres is studied using a microscope from Digital Instrument. The samples are adhered to metal slabs with double-sided adhesive tapes and examined under a microscope in a constant temperature and vibration-free environment [31].

5) Polymer solubility in the solvents

The turbidity of a solution is a strong indicator of its solvent strength. The cloud point can be used to determine the polymer's solubility in different organic solvents.

6) Viscosity of the polymer solutions

A U-tube viscometer (viscometer constant at 400C is 0.0038 mm2/s/s) at 25 0.10C in a thermostatic bath can be used to measure the absolute viscosity, kinematic viscosity, and intrinsic viscosity of polymer solutions in various solvents. To ensure complete polymer dissolution, the polymer solutions are allowed to stand for 24 hours before being measured [32].

7) Density determination

A multi volume pychnometer can be used to determine the density of the microspheres. The multi volume pychnometer is placed into a precisely weighed sample in a cup. Helium is introduced into the chamber at a steady pressure and allowed to expand. The pressure within the chamber decreases as a result of this expansion. There are two successive readings of pressure reduction at different initial pressures. The volume and density of the microsphere carrier are calculated using two pressure readings[33].

8) Bulk density

The constructed microspheres are weighed and transferred to a 10-ml graduated glass cylinder. The microsphere bed volume is stabilised by tapping the cylinder with an auto trap (Quantach- Rome, FL, USA). The bulk density is calculated using the ratio of microsphere weight to the tapped microsphere bed's final volume.

9) Capture efficiency

Allowing washed microspheres to lyse can be used to measure the microspheres capture efficiency or percent entrapment. The active ingredients in the lysate are subsequently determined according to the monograph's requirements.

10) Angle of contact

The wetting property of a micro particle carrier is determined by measuring the angle of contact. It influences whether microspheres are hydrophilic or hydrophobic in nature. This thermodynamic feature is unique to solids and is influenced by the adsorbed component's existence. At the solid/air/water interface, the angle of contact is measured. A droplet is placed in a circular cell set above the objective of an inverted microscope to measure the advancing and receding angle of contact. Within a minute of microsphere deposition, the contact angle is measured at 200°[34].

11) In vitro methods

There is a need for experimental procedures that can be used to determine the release characteristics and permeability of a medication via a membrane. A variety of in vitro and in vivo approaches have been reported for this purpose. In vitro drug release studies have been used in pharmaceutical production, product development, and other areas as a quality control tool. It's crucial to have sensitive and reproducible release data produced from physic-chemically and hydro-dynamically defined conditions.A number of in vitro release methods for buccal formulations have been created because to the influence of technologically defined circumstances and the difficulties of simulating in vivo settings; nevertheless, no standard in vitro method has yet been developed. Depending on the shape and application of the dosage form generated, different workers used apparatus of diverse designs and under varying conditions [35].

12) Beaker method

In this procedure, the dosage form is made to adhere to the bottom of the beaker containing the medium and is consistently stirred with an over head stirrer. The stirrer speed in the literature for the studies ranges from 60 to 300 rpm, and the volume of the medium utilised in the studies ranges from 50 to 500 ml.

13) Dissolution apparatus

In vitro release profiles have been studied utilising both rotating elements and standard USP or BP dissolution apparatus (paddle and basket). The study's dissolution media

ranged from 100 to 500 ml, with rotation speeds ranging from 50 to 100 rpm.

V. CONCULSION

Microencapsulation is the most convenient method for protecting and masking active ingredients, reducing dissolution rates, facilitating handling, and spatial targeting. This method is also useful for medications that dissolve in the intestine rather than the stomach. Micro capsules have proven to be a better delivery strategy for sustaining drug release and targeting to a specific site, lowering drug toxicity and side effects. The most widely used solvent extraction/evaporationbased approach using a beaker/stirrer for producing large amounts of microcapsule in a cost-effective or well-controlled manner is solvent extraction/evaporation based technique using a beaker/stirrer.

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