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Micro Encapsulation

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ABSTRACT:The process of enclosing one substance namely core material into another substance that is coating material is called as microencapsulation which gives capsules in the size range from less than one micron to several hundred microns in size. Microencapsulation is one of the highly effective method. Various factors like solubility of polymer in solvent, concentration of polymer, solubility of organic solvent in water, rate of solvent removal etc. affects the encapsulation efficiency of microparticles. Substances can be encapsulated in such a way that the core material is enclosed within coating material for specific interval of time. This technique of microencapsulation has been used in different fields like pharmaceutical, agriculture, textile, food, printing and defence. This article covers review on microencapsulation advantages, disadvantages, applications, polymer characteristics, ideal characteristics of drugs suitable for microencapsulation and its methods.

KEYWORDS: Microencapsulation, Microcapsule, Core material, Coating material, Natural polymers, synthetic polymers.

I. INTRODUCTION

Microencapsulation is the process of enclosing a substance inside a miniature capsule. Extremely tiny droplets, or particles of liquid or solid material, are packed within a second material or coated with a continuous film of polymeric material for the purpose of shielding the active ingredient from the surrounding environment. These capsules, which range in size from one micron to seven millimetres, release their contents at a later time by means appropriate to the application. The ingredients to be coated are referred to as core, internal phase (IP), encapsulate or fill, whereas terms applied to the coating of the microcapsules include the wall, shell, external phase or membrane [1].

Microencapsulation provides the means of converting liquids to solids, altering colloidal surface properties, providing environmental protection and 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 there subsequent use and adaptation to a wide variety of dosage forms and product application. The materials to be coated are referred to as core, internal phase, active ingredient, fill, payload or nucleus, whereas the coatings of microcapsules are termed as wall, shell, external phase,membrane or coating. Microcapsules may have one or multiple coatings arranged in strata of varying thicknesses around core material. All the three states of material i.e. solid, liquid and gas, may be encapsulated and affect shape and size of resultant capsules[2].

There are four typical mechanisms by which the core material is released from a microcapsule: Mechanical rupture of the capsule wall

- Dissolution of the wall
- Melting of the wall
- Diffusion through the wall [1].

II. REASONS FOR MICROENCAPSULATION[3]:

1. The primary reason for microencapsulation is found to be either for sustained or prolonged drug release.
2. This technique has been widely used for masking taste and odour of many drugs to improve patient compliance.
3. This technique can be used for converting liquid drugs in a free flowing powder.
4. The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
5. Incompatibility among the drugs can be prevented by microencapsulation.

III. CLASSIFICATION OF MICROCAPSULES[4]:

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On the basis of morphology, microcapsules are classified into 3-types: 1.Monocore 2.Polycore 3.Matrix

Monocore microcapsules consist of only one core enclosed in the shell, while polycore capsules have many cores enclosed within the shell. On the other hand, in matrix encapsulation, the core material is distributed homogeneously into the shell material. In addition to these three basic morphologies, microcapsules can also be mononuclear with multiple shells.

IV. ADVANTAGES[5]:

i) To Increase of bioavailability.
ii) To alter the drug release.
iii) To improve the patient's compliance.
iv) To produce a targeted drug delivery.
v) To reduce the reactivity of the core in relation to the outside environment.
vi) To decrease evaporation rate of the core material.
vii) To convert liquid to solid form & to mask the core taste.

V. DISADVANTAGES[6]:

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

VI. MATERIALS USED FOR MICROENCAPSULATION:

1) Core material: It is defined as material to be coated. The liquid core include dissolved materials whereas the solid core belongs to active ingredients, excipients, stabilizers, release rate retardants or diluents. The core material provides flexibility and allows effective design and development of microcapsules[7].
2) Coating Material: It can be defined as layer of substance which forms a cover over core for production of microcapsules. Desired properties for coating material;
   - It should be soluble in aqueous media/solvent and also provide controlled release under specific conditions.
   - It should have properties like flexibility, strength, stability, impermeability and optical properties.
   - It should be chemical compatible.
   - It should have capability to forming a film.
   - It should be pliable, tasteless, stable, non hygroscopic, economic and should not have high viscosity.

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, Carboxymethyl-cellulose, Hydroxyethylcellulose, Methylcellulose, Arabinogalactan, Polyvinyl alcohol, Polyacrylic acid.
- ♦ Water insoluble resins – Ethyl-cellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (EthyleneVinyl acetate), Cellulose nitrate, Silicones, Poly(lactidecoglycolide).
- ♦ Waxes and lipids – Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.
- ♦ Enteric resins – Shellac, Cellulose acetate phthalate, Zein[8].

VII. FACTORS INFLUENCING PROPERTIES OF MICROCAPSULES:

Material properties.
* Dispersed phase:-
The polymer used plays a vital role for drug encapsulation which further depends upon-

- Solubility of polymer.
- Concentration of polymer.
- The organic solvent used.
- Solvent removal rate.
- Dispersed and continues phase ratio.
- Nature of drug hydrophilic/hydrophobic[9].

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VIII. CLASSIFICATION OF MICROCAPSULES.

On the basis of morphology; microcapsules are classified into 3-types viz. monocore, polycore and matrix.

Monocore microcapsules consist of only one core enclosed in the shell, while polycore capsules have many cores enclosed within the shell. On the other hand, in matrix encapsulation, the core material is distributed homogeneously into the shell material. In addition to these three basic morphologies, microcapsules can also be mononuclear with multiple shells[10].

IX. ROLE OF POLYMERS :

- Polymers are substances of high molecular weight made up by repeating monomer units.
- Polymer molecules may be linear or branched, and separate linear or branched chains may be joined by crosslinks.
- Polymers are used widely in pharmaceutical systems as adjuvants, coating materials and, a components of controlled and site- specific drug delivery systems[11].

X. IDEAL CHARACTERISTICS OF MICROSPHERES :

- 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.
- Susceptibility to chemical modification[12].

XI. TECHNIQUES TO MANUFACTURE MICROCAPSULES:

Drug microencapsulation can be achieved by using different microencapsulation techniques.

i) Chemical microencapsulation processes :

A. Interfacial polymerization : Interfacial polymerization refers to the formation of a polymer at the interface between two liquid phases. The wall of microcapsules is formed at or on the surface of a droplet or particle by the reactive monomer polymerization. A multi-functional monomer is dissolved in the liquid form of core materials, and the mixture is dispersed to a desired drop size in an aqueous phase involving a dispersing agent and a multi-functional amine. The rapid reaction of polymerization then generates the wall shell of microcapsules[13].

B. Free Radical Polymerization : Free radical polymerization involves an initiator and a monomer. The initiator molecules are firstly converted to free radicals by heating, photolysis or electrolysis. The free radicals then become highly active to obtain electrons from the molecules of the monomers. The microparticles are formed through the growth of polymer chains as a result of electron transfer between the reactive monomers. Drug loaded microparticles are produced by imbibing the dried microparticles in the drug solution[14].

ii) Physicochemical Microencapsulation Processes :

A. Air suspension: Microencapsulation by air suspension method consists of the dispersing of solids, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particulate core materials are suspended on an upward moving air stream. The chamber design and its operating parameters influence a recirculating flow of the particles through the coating-zone portion of the coating-chamber, where a coating material is sprayed to the moving particles. During each pass through the coating-zone, 3 the core material receives a coat and this cyclic process is repeated depending on the purpose of microencapsulation. The supporting air stream also serves to dry the product while it is being encapsulated. The drying rate is directly related to the temperature of the supporting air stream used[15].

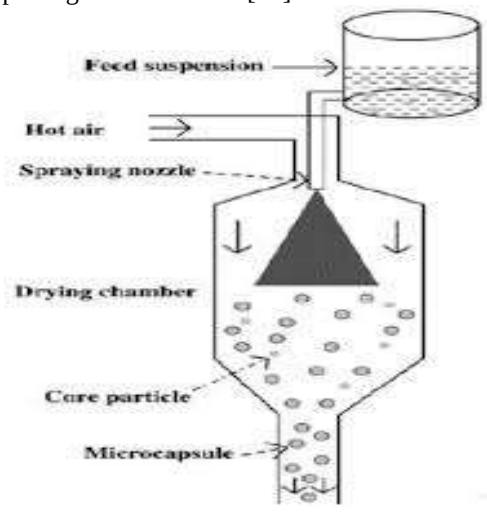

Fig.1 Air suspension method for microencapsulation

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B. Coacervation (Phase Separation) : The electrostatic interaction between oppositely charged biopolymers results into the formation of soluble complexes, which further aggregate to decrease the free energy of the system until their size and surface properties render them insoluble. Subsequently, a liquid–liquid phase separation occurs which is known as complex coacervation. Complex coacervation is a liquid–liquid phase separation phenomenon that occurs when electrostatically opposite charged biopolymers (protein/polysaccharides) are brought together under certain specific conditions[16].

Fig. 2 Coacervation Method (PhaseSeparation).

C. Ionotropic gelation : Ionotropic gelation depends on the ability of polyelectrolytes to crosslink in the existence of counter ions to produce the spherical crosslinked hydrogel beads. The hydrophilic beads are generated by an addition of drug loaded anionic polymeric drops into an aqueous solution of polyvalent cations. The diffusion of cations into the polymeric drops leads to a three-dimensional lattice of ionically crosslinked moiety. The mechanical strength and permeability of the beads can be enhanced by an input of polycations or polyelectrolytes to the bead surface[17].

iii) Mechanical Microencapsulation Processes :
A. Fluid Bed Coating : Fluid bed coating refers to a process that solid drug particles are suspended on a jet of air followed by spraying a liquid coating on the drug particles, and the coated wall is solidified through solvent evaporation or cooling procedures. Wurster in 1953 developed the coating technique by using a coating chamber with a cylindrical nozzle and a perforated bottomplate for spraying the coating material on the core particles[18].

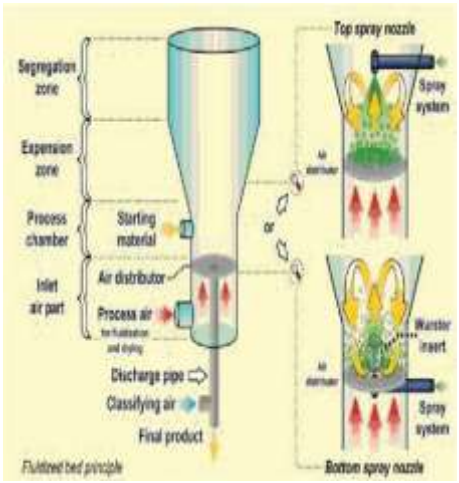

Fig. 3 Fluid Bed Coating.

B. Solvent Evaporation / Extraction : Dissolving or dispersing the core drug in the coating polymer solution, followed by the dispersion of core-wall solution in a liquid vehicle with agitation. The coating material then shrinks around the core drug to produce the microcapsules by 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 is miscible with both water and solvent) .Water insoluble polymers are used as encapsulation matrix using this technique. Biodegradable polymer PLGA (poly(lactic-co-glycolic acid)) is frequently used as encapsulation material. Different kinds of drugs have been successfully encapsulation: for example hydrophobic drugs such as cisplatin, lidocaine, naltrexone and progesterone; and hydrophilic drugs such as insulin, proteins, peptide and vaccine[19].
C. Spray Drying : Spray drying is a relatively low cost technology, rapid, reproducible, allowing easy scale-up, when compared with other microencapsulation techniques, justifying the preference in industrial terms. Spray-drying method was industrially employed since 1927. The core particles are firstly dispersed in a wall polymer solution and then sprayed into a hot chamber. The wall material solidifies onto the core particles because the input solvent evaporates and therefore the microcapsules can be formed in a poly nuclear or matrix type. Spray-drying is normally used for encapsulating labile drugs due to its short contact time in the drier. Spraying drying can be applied with the use of supercritical carbon dioxide for the entrapment of sensitive drugs such as proteins[20].

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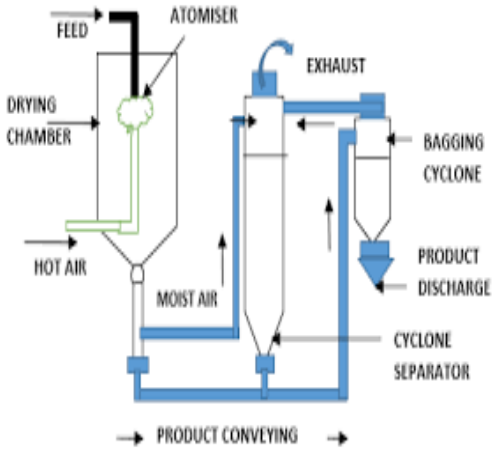

Fig. 4. Spray Drying Method for Microencapsulation.

D. Pan Coating : The microencapsulation of relatively large particles by pan methods has become wide spread in the pharmaceutical industry. With respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating and there process has been extensively employed for the reparation of controlled release beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds and the coated with protective lagers of various polymers. In practice, the coating is applied as a solution or as an atomized spray to the desired solid core material in the coating pan. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans. In some cases, final solvent removal is accomplished in drying oven[21].

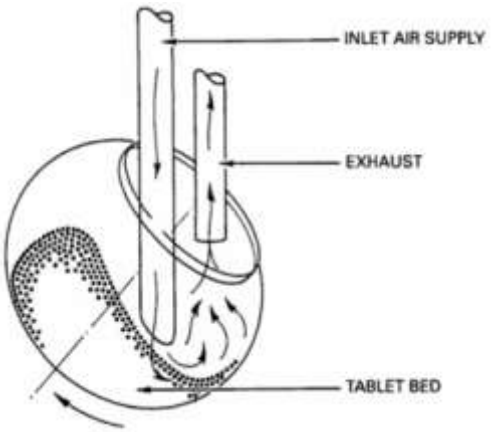

Fig. 5. Pan Coating Method for Microencapsulation.

XII. RELEASE MECHANISMS:

Mechanisms of drug release from microcapsules are

1. Osmosis: The polymer coat of microcapsule acts as semi permeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat[22].
2. Diffusion: Diffusion is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores. Thus, the overall release depends on, (a) the rate at which dissolution fluid penetrates the wall of microcapsules, (b) the rate at which drug dissolves in the dissolution fluid, and (c) the rate at which the dissolved drug leak out and disperse from the surface. The kinetics of such drug release obeys Higuchi's equation as below,

$$Q = [D/J\,(2A - \varepsilon\, CS)\, CS\, t]^{1/2}$$

Where, Q is the amount of drug released per unit area of exposed surface in time t;

D is the diffusion coefficient of the solute in the solution;

A is the total amount of drug per unit volume;

CS is the solubility of drug in permeating dissolution fluid;

ε is the porosity of the wall of microcapsule;

J is the tortuosity of the capillary system in the wall.

The above equation can be simplified to Q = vt where, v is the apparent release rate[23].

3. 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[24].
4. 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[25].
5. 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[26].

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XIII. APPLICATIONS OF MICROENCAPSULATION:

Applications of microencapsulation can be described in detail as given below:

1. Agricultural Applications[27,28].
- Reduce insect populations by disrupting their mating process.
- Protects the pheromone from oxidation and light during storage and release.

2. Catalysis.
- Safe handling, easy recovery, reuse and disposal at an acceptable economic cost[29].
- Metal species such as palladium (II) acetate and osmium tetroxide have been encapsulated in polyurea microcapsules and used successfully as recoverable and reusable catalysts without significant leaching and loss of activity[30].

3. Food Industry
- Adding ingredients to food products to improve nutritional value can compromise their taste, colour, texture and aroma[31].
- Sometimes they slowly degrade and lose their activity, or become hazardous by oxidation reactions[32].
- Ingredients can also react with components present in the food system, which may limit bioavailability[33].

4. Pharmaceutical Applications.
- Potential applications of this drug delivery system are replacement of therapeutic agents (not taken orally today like insulin), gene therapy and in use of vaccines for treating AIDS, tumors, cancer and diabetes[34].
- The delivery of corrective gene sequences in the form of plasmid DNA could provide convenient therapy for a number of genetic diseases such as cystic fibrosis and hemophilia[35].
- Lupin has already launched in the market worlds first Cephalexin (Ceff-ER) and Cefadroxil (Odoxil OD) antibiotic tablets for treatment of bacterial infections[36].
- Aspirin controlled release version ZORprin CR tablets are used for relieving arthritis symptoms.
- Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythms.
- Niaspan CR tablet is used for improving cholesterol levels and thus reducing the risk for a heart attack[37].
- Some of the applications of microencapsulation can be described in detail as given below:

1. Prolonged release dosage forms.
2. Prepare enteric-coated dosage forms selectively absorbed in the intestine rather than the stomach.
3. It can be used to mask the taste of bitter drugs.
4. To reduce gastric irritation.
5. Used to aid in the addition of oily medicines to tableted dosage forms. To overcome problems inherent in producing tablets from otherwise tacky granulations. This was accomplished through improved flow properties. eg. The non-flowable multicomponent solid mixture of niacin, riboflavin, and thiamine hydrochloride and iron phosphate may be encapsulated and made directly into tablets.
6. To protect drugs from environmental hazards such as humidity, light, oxygen or heat. eg. vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation.
7. The separations of incompatible substances, eg. pharmaceutical eutectics. The stability enhancement of incompatible aspirin chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing[38].

XIV. CONCLUSION:

The research in the area of microencapsulation has huge potential to give raw material advantageous traits resulting in superior products. The very much popular microencapsulation technique is the most convenient way of protection and masking, reduce dissolution rate, facilitation of handling, and spatial targeting of active ingredient. This article reveals the need of microencapsulation technique which delivers the drugs at a controlled rate for a desired period of time. It is a promising technique for wide range of diseases.

A variety of microencapsulation methods are currently available and novel techniques are continuously being discovered and developed. Although several microencapsulated products are commercially available, there still exists a wide gap between the practical applications and full potential of this technology. Bridging this gap depends on a deeper understanding of the mechanisms involved in microencapsulation processes as well as better assessment of drug and polymer specific properties. Major issues that need to be addressed include how to control drug release to achieve desired release profile, how to maintain the stability and activity of the encapsulated drug (especially bio macromolecules), and how to effectively direct microparticles to target pathological site. Additionally more emphasis should be put on the transfer of bench-scale processes to manufacturing scale. Overcoming these challenges will advance

microencapsulation technology to a new level that will allow increasingly more sophisticated pharmaceutical drug systems to be realized.

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