



MICROSPHERES - A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Microencapsulation is the process of enclosing micron sized particles of solids or droplets of liquids or gasses in an inert shell, which isolates and protects the particle from the external environment as well as control the drug release profile. Microencapsulated particle is having diameter between 1- 1000µm which differ them from other technologies such as nanotechnology and macroparticle. This review paper discusses the background of microencapsulation technology, commonly used microencapsulation methods with its advantages and disadvantages and its applications in pharmaceutical field. This paper will also discuss about the other factors affecting microencapsulation and its limitation.

KEYWORDS: Microcapsule.

INTRODUCTION

Microencapsulation is one of the most interesting fields in the area of pharmaceutical technology in which very tiny droplets or particles of liquid or solid material are coated with a continuous film of polymeric material^[1,2]

Controlled drug delivery, using biodegradable polymer has gained a lot of attention in last two decades. Microencapsulation is a process by which solid, liquid or even gaseous particles are coated with a continuous film which is composed of polymeric material. These particles are in the size range of 1-1000µm and are widely used as a drug carrier for controlled release. Bungen burg de Jong and Kan first published the first research leading to the development of microencapsulation procedures for the pharmaceuticals in 1931 and dealt with the preparation of gelatin spheres and the use of gelatin using coacervation process.^[3] Usually the drug substances are encapsulated or coated in a polymer-forming particle with a diameter in range of 1 to 1000 µm and are widely used as a drug carrier.^[4]

Microencapsulation enables protection of the drug from the environment, stabilization of sensitive drug, elimination of incompatibilities, or masking of unpleasant taste, conversion of liquid drugs in a free flowing powders, prevention of vaporization of many volatile drugs, etc.^[1,4] Microcapsules helps to maintain constant drug concentration in blood thereby increasing patent compliance, decreasing dosing frequency and toxicity. Other reasons for microencapsulation may be - liquid drugs can be converted into free flowing powder,

incompatibility among the drugs can be prevented, the site of absorption can be altered. Bakes and Anderson reported that the stability of Vitamin A palmitate can be enhanced by formulating it in the form of microspheres.

Microcapsules provide constant drug concentration in blood thereby increasing patent compliance, decreasing dosing frequency and toxicity. Thus, microencapsulation technology is gaining continuous interest in controlled release-based delivery systems. The latter include sustained release from each individual microcapsule and offer greater uniformity and reproducibility.^[5] They also protect drug from enzymatic and photolytic cleavage hence considered to be best for drug delivery of proteins.^[6,7]

Microspheres are defined as "Monolithic sphere or therapeutic agents which are distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters within micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin whereas the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and

stabilities, process safety and economic considerations^[8]. Microspheres for oral use are used to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. However microparticulate delivery systems get distributed more uniformly in the gastrointestinal tract. The outcome is more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.^[9] Microencapsulation is used to modify and retard drug release. Due to its small particle size, they are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.^[10]

ADVANTAGES.^[13]

- 1) Microspheres provide constant and prolonged therapeutic effect.
- 2) Reduces the dosing frequency and thereby improve the patient compliance.
- 3) They could be injected into the body due to the spherical shape and smaller size.
- 4) Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- 5) Microsphere morphology all owes a controllable variability in degradation and drug release.

LIMITATION^[13]

Some of the disadvantages were found to be as follows:

- 1) The modified release from the formulations.
- 2) The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- 3) Differences in the release rate from one dose to another.
- 4) Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- 5) Dosage forms of this kind should not be crushed or chewed.

CRITERIA FOR MICROSPHERE PREPARATION

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique.^[14] The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, coprecipitation etc.^[15] Preparation of microspheres should satisfy certain criteria^[23]:

- 1) The ability to incorporate reasonably high concentrations of the drug.
- 2) Stability of the preparation after synthesis with a clinically acceptable shelf life.

3) Controlled particle size and dispersability in aqueous vehicles for injection.

4) Release of active reagent with a good control over a wide time scale.

5) Biocompatibility with a controlled biodegradability and

6) Susceptibility to chemical modification.

MECHANISM AND KINETICS OF DRUG RELEASE

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion.^[17,18,19]

1. Diffusion is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels. Thus, the overall release depends on,

- (1) The rate at which dissolution fluid penetrates the wall of microcapsules,
 - (2) The rate at which drug dissolves in the dissolution fluid and
 - (3) The rate at which the dissolved drug leak out and disperse from the surface.
- (26) The kinetics of such drug release obeys Higuchi's equation^[20] as below: $Q = [D/J(2A - a C S) C S t]^{1/2}$.

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;

C is the solubility of drug in permeating dissolution fluid; a 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.

2. DISSOLUTION

Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid. Thickness of coat and its solubility in the dissolution fluid influence the release rate.^[21]

3. 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.^[21]

4. EROSION

Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release^[22] with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol.

METHODS FOR MICROENCAPSULATION

1. Spray Drying

2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction
8. Quassi emulsion solvent diffusion:

1. Spray Drying

In Spray Drying technique, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution with high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μ m. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.^[23]

2. Solvent Evaporation

This process is carried out in a liquid manufacturing vehicle phase. The microcapsule coating is dispersed 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 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 of the core material is dispersed in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.^[23,24]

3. Single emulsion technique

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. In the next step, the cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation. The nature of the surfactants used to

stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bio performance of the final microencapsulated product.^[25]

4. Phase separation coacervation technique

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetics of the formed particles since there is no defined state of equilibrium attainment.^[26]

5. Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction.^[27]

6. Spray drying and spray congealing

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μ m. Microparticles are separated from the hot air by means of

the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulphathiazole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however, leads to the formation of porous microparticles.^[25,26]

7. Solvent extraction

Solvent extraction method is used for manufacturing of microparticles, involves removal of the organic phase by extraction of the or non aqueous solvent. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer.^[28]

8. Quasi emulsion solvent diffusion

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microspheres can be manufactured by a quasi emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol and polymer. The concentration of polymer is in order to enhance plasticity. At first, the internal phase is manufactured at 60°C and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microspheres. The product is then washed and dried by vacuum oven at 40°C for a day.^[29]

However solvent evaporation techniques have become more useful method as compared to other methods. In this method of microencapsulation, controlled particle sizes in the nano- to microsphere range can be achieved by high encapsulation materials and various conditions in order to achieve high encapsulation efficiency and a low residual solvent content. However, several process variables had been identified by researcher, which could affect the formulation of microsphere by solvent evaporation method, such as, type of solvent, drug to polymer ratio, rate of solvent removal, effect of internal aqueous phase volume in case of solvent evaporation followed by multiple emulsion, effect of addition of buffer or salts to the internal or external phase, which can affect the size of microcapsules and also the release pattern of drug from microcapsules.^[30-33]

Solvent evaporation technique to formulate microcapsules of pharmaceuticals

Solvent evaporation technique for microencapsulation of pharmaceuticals involves four major steps, like (a) incorporation of pharmaceuticals, (b) droplet formation, (c) solvent removal, and (d) drying.

(a) Incorporation of pharmaceuticals

The polymer is dissolved in a suitable water immiscible solvent, and the pharmaceutical agent is directly added into the solution of polymeric-matrix materials by dissolution/dispersion in suitable solvents, or emulsification of aqueous solution of the pharmaceutical agents immiscible with the matrix-material solution. For the preparation of solution or dispersion of pharmaceutical agents, impeller or static mixing, high speed-stator mixing or microfluidization techniques are generally used.

(b) Droplet formation

This step determines the size of resulting microcapsules. The size of microcapsules affects the drug encapsulation efficiency and the rate of drug release. The following procedures are used in droplet formation, namely:

- **Stirring**

The external phase is filled into a vessel and agitated by an impeller. The drug/matrix dispersion is then added, drop wise or all at once, under agitation at a speed sufficient to reach the desired droplet size.^[34]

- **Static mixing**

Static mixer consists of baffles or other flow obstacles installed in a tube. The baffle arrangement repeatedly splits and recombines the stream of fluid passing through the tube.

- **Extrusion**

It involves feeding of drug/matrix dispersion through single or multichannel pathways directly into the continuous phase. When drug/ matrix dispersion leaves the pathways discrete droplets are formed within the slow flowing continuous phase. In extrusion, flow is laminar, the droplets are formed at the site of introduction of drug/matrix dispersion into continuous phase, due to which there is no effect on size of droplets formed thereafter. Whereas in static mixing, turbulent flow occurs which constantly acts on the dispersed phase and thus, there is a continuous change in the size of droplets.

- **Dripping**

Microcapsules have been prepared by dripping 10 % and 15 % (w/w) solution of poly (ethylene-co-acetate) in dichloromethane, containing dispersed protein particles from a needle into an electric field. The droplet formed was detached from the needle by electrostatic forces.

(c) Solvent removal

Solvent removal can be achieved either by evaporation or by extraction. In both processes, the drug/matrix

dispersion should be slightly soluble in the continuous phase, so that, partitioning into continuous phase can occur that leads to precipitation of the matrix material. The two ways of solvent removal can be performed, namely:

- **Solvent evaporation**

In this method, the capacity of the continuous phase is insufficient to dissolve the entire volume of dispersed phase solvent. Thus, solvent evaporates from the surface of the dispersion to obtain hardened microcapsules.

- **Solvent extraction**

This is a two-step process. Firstly, the drug/matrix dispersion is mixed with a small quantity of continuous phase to yield desired size of droplets. Then secondly, further more continuous phase and/or additional extraction agents are added at an amount sufficient to absorb the entire solvent leaching from droplets of drug/matrix. This results into formation of solid microcapsules.

- **Drying**

Solidified microparticles from the continuous phase are by either filtration or centrifugation. Then the particles are rinsed with suitable liquids to remove adhering substance such as dispersion stabilizers or non-encapsulated drug. Finally, these microparticles are dried at elevated temperature or under reduced pressure to yield free flowing powder.

Various solvent evaporation techniques of microencapsulation

Solvent evaporation techniques are carried out in a liquid manufacturing vehicle (emulsion), which is prepared by agitation of two immiscible liquids. The process involves dissolving microcapsule coating (polymer) in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. Several methods can be used to achieve dispersion of the oil phase in the continuous phase. These are as follows:

(a) Oil/water emulsion followed by solvent evaporation

The drug substance is either dispersed or dissolved in the polymer-solvent system. Then, it is added to the aqueous phase by continuous agitation. The system is agitated until the solvent separates into the aqueous phase and is removed by evaporation. This process results in hardened microsphere, which contains drugs or agents to be encapsulated.^[35-39] Usually, high shear is used to prepare emulsion; the resultant product has a much smaller particle size than the emulsion produced by conventional agitation. Other methods to prepare emulsion include the use of a microfluidizer and sonication. A major problem related with this technique is poor encapsulation efficiency of moderately water-soluble and water-soluble compounds, which partitioned out from the organic dispersed phase into the aqueous continuous phase. Successful entrapment of drug within

microcapsules is thus highly dependent on its solubility in the aqueous phase.

(b) Water-oil-water multiple emulsion followed by solvent evaporation system

This method for preparation of microsphere was reported to overcome the problem of low encapsulation efficiency of water-soluble drugs prepared by conventional w/o emulsion solvent evaporation method.^[40,41] In this technique, polymer is dissolved in a suitable organic phase. In this organic phase, aqueous drug solution is emulsified using high-speed homogenizer operating around 15000-20000 rpm for about 30 seconds to prepare w/o primary emulsion. This primary emulsion is added to external aqueous phase containing surfactant at homogenizer speed around 8000 rpm for 30 seconds and then stirred at 300 rpm for 3 hours at room temperature for permitting evaporation of organic solvent or it can be also performed under vacuum. The microcapsules obtained is collected by ultracentrifugation, filtration and then, lyophilized. Among them, lyophilisation decreases the burst effect. However, it may be change from drug to drug to obtain acceptable microcapsule size and drug release.

(c) Water/oil/oil or water/oil/oil/oil multiple emulsion followed by solvent evaporation

Iwata and McGinity developed a multiple emulsion of the W/O/O/O type.^[41] Multiphase microcapsules of PLGA containing water-in oil (W/O) emulsions were prepared by a multiple emulsion solvent evaporation techniques. Acetonitrile was used as the solvent for the polymer, and light mineral oil comprised the continuous phase for the encapsulation procedure in this investigation. Drug loading efficiencies of model water-soluble compounds was found 80 to 100 %. Scanning electron microscopy of transverse cross sections of the multiphase microsphere of W/O/O/O type belonged to the class of reservoir-type drug delivery devices. Utilization of this type of multiple emulsion system allows the encapsulation of the primary water in oil emulsion within a polymeric microsphere. The oil in the primary emulsion prevents contact between the internalized protein and the polymer/solvent system prevents possible denaturation of the protein by the polymer or the solvent. Likewise, the possibility of polymeric degradation due to reactive proteins or drug compounds is also limited.^[42,43]

(d) Modified water-in-oil-in-water (W₁/O/W₁) double emulsion followed by solvent evaporation

In an investigation, Kim *et al.*,^[44] has developed gas foamed open porous biodegradable polymeric microsphere. Highly open porous biodegradable polymeric microsphere. Highly open porous biodegradable polymeric microspheres were fabricated for use as injectable scaffold micro carriers for cell delivery. They modified water-in-oil-in-water (W/O/W) double emulsion solvent evaporation method for producing the microspheres. The incorporation of an

effervescent salt, ammonium bicarbonate, in the primary W droplets spontaneously produced carbon dioxide and ammonia gas bubbles during the solvent evaporation process, which not only stabilized the primary emulsion, but also created well interconnected pores in the resultant microspheres. The porous microspheres fabricated under various gas foaming conditions were characterized. The surface pores became as large as 20 μm in diameter with increasing the concentration of ammonium bicarbonate, being sufficient for cell infiltration and seeding. These porous scaffold microspheres could be potentially utilized for cultivating cells in a suspension manner and for delivering the seeded cells to the tissue defect site in an injectable manner. In another investigation, Yang *et al.*,^[45] have developed and characterized PLGA microspheres containing protein fabricated by double-emulsion solvent evaporation method. Sahoo *et al.*^[46], have developed ethyl cellulose microspheres of stavudine using double emulsion followed by solvent evaporation technique.

Effect of factors influencing microencapsulation by solvent evaporation technique

(a) Effect of polymer

Various polymers have their inherent quality. Therefore, the quality of the microencapsulation varies depending upon the polymer used. In pharmaceutical industry, biodegradable polymers are used for microencapsulation. The molecular weight of polymers used in microencapsulation using solvent evaporation technique is also another important factor. Fu *et al.*, have developed a long acting injectable Huperzine A-PLGA microsphere for the chronic therapy of Alzheimer's disease. These microspheres were prepared by solvent evaporation method. It was observed that the PLGA 15000 microspheres possessed a smooth and regular particle size of around 50 μm . The drug encapsulation percentage of microsphere prepared from PLGA 15000, 20,000 and 30,000 were 62.75 %, 27.52 % and 16.63 %, respectively.^[47] The drug encapsulation efficiency of these microspheres was found increased with the increment in molecular weight of polymer (here, PLGA) due to stronger barrier characteristics of high molecular weight polymers. In this study, they have also found an increment of drug encapsulation efficiency in these microspheres as the polymer concentration was increased in oily phase, and poly vinyl alcohol (PVA) concentration decreased in aqueous phase. In another investigation, Uchida *et al.*, have used different PLGA and they have experienced the same as previous investigation stated above. They found highest obalbumin loading in PLGA (85:15) than other PLGA grades.^[48]

(b) Effect of organic solvents

Bodmeier and McGinity have performed an investigation on preparation of quinidine sulphate microsphere using o/w emulsion-solvent evaporation technique to understand the effect of solvent, volume of solvent on drug loading. They have observed that the successful

entrapment of drug within microsphere is associated with a fast rate of precipitation of the polymer from the organic solvent phase; a low water solubility of the drug in the aqueous phase; and a high concentration of the polymer in the organic phase.^[49] It was initially expected that favorable solubility of the drug in the organic solvent would enhance the drug content in the microsphere. The solubility of quinidine sulphate in methylene chloride and chloroform were determined to be 9.16 and 97.57 g/l, respectively. Although, the solubility of quinidine sulphate in chloroform was found to be 10 times higher than methylene chloride and the drug content was found to be higher in microspheres prepared with methylene chloride as compared that with chloroform. This showed that the solubility of drug in solvent as an important factor, which was affecting entrapment of the drug content in the microcapsules.

(d) Effect of drug to polymer ratio

The drug to polymer ratio can influence the quality of the microcapsules prepared by solvent evaporation technique. An investigation reported significant increase in drug entrapment efficiency (%) of ethyl cellulose microparticles containing metformin HCl prepared by solvent-evaporation technique ($P < 0.05$) was observed with the decreasing drug-polymer ratio (increasing polymer content), when stirring speed and surfactant concentration were constant.^[57] The increasing amount of polymer facilitated better coating onto the drug particles. Decreasing the drug-polymer ratio from 1 : 2 to 1 : 6 (increasing the ethyl cellulose content) in the preparation of these ethyl cellulose microparticles resulted in the formation of comparatively larger microparticles (145.89 ± 18.95 to $373.60 \pm 23.52\mu\text{m}$). Again, we have found the retardation of the drug release rate depends on the drug-polymer ratio. As the ethyl cellulose content in the microparticles increased, the drug release rate from these microparticles was decreased due to increased thickness of the polymeric matrix. In an investigation on the poly (methyl methacrylate) (PMMA) microspheres loaded with bovine serum albumin (BSA), a ratio of less than 1:10 was suggested to yield protein loadings of $> 80\%$.^[51]

(e) Effect of drug solubility in continuous phase

Drug loss may occur to continuous phase while the dispersed phase remains in a transitional, semi-solid state. If the solubility of drug in the continuous phase is higher than in the dispersed phase, then the drug may easily diffuse into the continuous phase during this stage. It was observed that the encapsulation efficiency of quinidine sulphate was 40 times higher in alkaline (pH-12) continuous phase than in the neutral (pH-7) continuous phase because quinidine sulphate is insoluble in alkaline pH whereas very soluble in neutral pH.^[52]

(f) Rate of solvent removal

The rate of solvent removal from microsphere prepared by the solvent evaporation technique has a great impact on the physiochemical properties of the

microsphere.^[53,54] In an investigation, Izumikawa *et al.*^[53] have observed a significant difference in physical property and drug release profile between progesterone loaded PLA microsphere prepared by either reduced pressure solvent evaporation or a solvent evaporation method under atmospheric conditions. Encapsulation efficiency was greater for microsphere prepared by the reduced pressure solvent extraction method (RSE) than for those prepared by the atmospheric solvent evaporation (ASE).

(g) Effect of buffer or added salt

The buffer and salt added in the system can change the quality of the microencapsulation. In an investigation, Herrmann and Bodmeier have prepared somatostatin acetate-containing polylactide microspheres and evaluated these prepared microspheres for drug encapsulation efficiency, drug release, and morphological properties.^[55] They have found that the addition of buffers and salts to the internal aqueous phase resulted in the formation of a dense and homogenous polymer matrix. The drug release profile of these somatostatin acetate-containing polylactide microspheres consisted of a rapid drug release phase followed by a slow release phase. Addition of buffer salts to the internal aqueous phase might be promoting an influx of water from the external phase due to a difference in osmotic pressure. This resulted in a more porous microsphere structure, faster drug release, and lower drug encapsulation efficiency.

(h) Effect of interaction between drug and polymer

The interaction between drug encapsulated and polymer can change in drug encapsulation efficiency. The interaction between drug and polymer may be hydrophilic or hydrophobic interaction. In case of hydrophilic or ionic interaction, the drug is best encapsulated in polymers containing free carboxylic end groups. In case of hydrophobic interaction, relatively hydrophobic end capped polymers are more effective in increasing encapsulation efficiency.^[56] On the other side, such interaction between drug and polymer may limit the protein release from the microsphere^[57]. In certain cases, co-encapsulated excipients can mediate interaction between protein and polymer. Encapsulation efficiency of tetanus toxoid in PLGA increased, when gamma hydroxylpropylcyclodextrin (g-HPCD) were incorporated. It is supposed that the g-HPCD increased the interaction by involving amino acid side group of the toxoid into its cavity and simultaneously interacting with PLGA through Vander Waal and hydrogen bonding forces.^[58]

(i) Effect of drug solubility in continuous phase

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Advancement in Microsphere

1. Floating microsphere: Floating microsphere have bulk density less than gastric fluids, thus they remain floating in the stomach without affecting the gastric emptying rate. Therefore gastric retention time is increased and fluctuation in plasma drug concentration is reduced or controlled by floating microsphere. In addition it reduces dumping of dose, dosing frequency, increases therapeutic efficacy, solubility and dispersability.^[59] Floating microsphere is of two types

a) Effervescent type- Swellable polymers e.g. methylcellulose, chitosan and various effervescent compound e.g. sodium bicarbonate, citric acid, tartaric acid are used for the preparation of effervescent dosage form. Floating microsphere of effervescent type liberates carbon-dioxide gas due to which the density of the system is reduced and remains in floating condition in stomach for a prolonged period of time, this result in release of drug slowly at a desired rate.

b) Non-effervescent type- Highly swellable cellulose type hydrocolloids, polysaccharide and matrix forming polymer such as polycarbonate, polyacrylate are used to form non effervescent system. This is prepared by thoroughly mixing the drug and gel forming hydrocolloids. On administration, it swells up when comes in contact with gastric fluid and attain a bulk density i.e. less than 1 g/ml.^[60]

2. Radioactive microsphere

Radioactive microsphere is used in the same way as nonradioactive microsphere. Delivery of high concentration of drug to the target site does not damage normal surrounding tissue. As compare to drugs, radioactivity substance is not released from the microsphere but proceed from inside a radioactive typical distance. The α emitters, β emitters and γ emitters are used as radioactive microsphere. Radioactive microsphere is used for diagnostic and therapeutic purpose.^[61,62]

3. Hollow Microsphere

Hollow microspheres also called as microballoons is filled up with the drug in their outer polymer shells and are prepared by emulsion-solvent diffusion technique. The ethyl alcohol: dichloromethane solution of the drug and polymer (enteric acrylic) is transfer into a stirring aqueous solution of PVA which is thermally controlled at 400°C. Gas is generated by dispersing the polymer droplet by evaporation of dichloromethane which leads to formation of an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for a period of more than 12 hours in-vitro.

Different drugs can be prepared by hollow microsphere by using various materials e.g. polycarbante, calcium alginate, Eudragit S 100 etc.^[63,64]

4. Magnetic Microsphere

In magnetic microsphere small amount of magnetically targeted drug is delivering to the target site in place of high amount of free circulating drug. Those materials which response to magnetic field are used in the preparation of magnetic microsphere are chitosan, dextran etc.^[65] Magnetic microsphere is used for diagnostic and therapeutic purpose. Supermagnetic iron oxides radiolabelled is used as therapeutic magnetic microsphere for imaging of liver metastasis, distinguish loop of bowel from other abdominal structure, whereas iron carbon particles radiolabelled with isotope 188Re, 90y etc are used as diagnostic microsphere for liver tumours.^[62]

5. Mucoadhesive Microsphere

Mucoadhesive microsphere adhere to mucus layer and release drug at desired rate. In mucoadhesive microsphere the intimate contact time with the mucus surface is increased. This results in an increased drug retention time as well as drug concentration at the targeted site.^[66,67] Mucoadhesive formulation can be administered through various routes such as nasal, gastrointestinal, buccal, Ocular etc.^[68] Therapeutic efficacy is improved as well as absorption; bioavailability of normally poorly absorbed drug is improved.^[69]

CONCLUSION

The microencapsulation technology which started as a way for encapsulating dyes and flavours has now become one of the most interesting fields in the field of controlled drug delivery systems. The encapsulation technology has advanced to such a level that not only small molecular weight molecules but also macromolecules such as proteins and genes can be delivered by microparticulate carrier. But although technological advances has led to commercialization of several microparticulate products but many technical problems are yet to be overcome. Some of such technical problems which are faced are-maintaining stability of encapsulated drugs till lifetime, manipulating release rates according to application etc. Still the microencapsulation technology will remain as one of the most important areas in drug delivery and various other applications.

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