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A Modified Drug Delivery System- Microspheres

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ABSTRACT

Microspheres are multiparticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. They are made from polymeric waxy or other protective materials such as natural, semi synthetic and synthetic polymers. Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 μm consisting of proteins or synthetic polymers. The range of techniques for the preparation of microspheres provides multiple options to control as drug administration aspects and to enhance the therapeutic efficacy of a given the drug. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. The present review highlights various types of microspheres, different methods of preparation, its applications and also various parameters to evaluate their efficiency. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, Radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction, Quassi emulsion solvent diffusion. Microspheres have wide range of applications because of controlled and sustained release.

Keywords: Microspheres, Bioadhesive, Controlled release, Patient Compliance

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INTRODUCTION

Microspheres are characteristically free flowing powders consisting of spherical particles of size less than 200 µm. Can be injects by 18 or 20 number needle. They consists proteins or synthetic polymers which are biodegradable in nature. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug[1]. Each particle is basically a mixture of drug, dispersed in a polymer form with release occurs by 1st order process. Drug release is controlled by dissolution/degradation of matrix. Because of their size and shape, Microspheres offer a ball-bearing effect.

Recent advances in polymer science and drug carrier technologies have promulgated the development of novel drug carriers such as bioadhesive microspheres that have boosted the use of "bioadhesion" in drug delivery.

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs[2] Magnetic microspheres use for target to tumors.

Microspheres used usually are polymers.

They are classified into two types:

Synthetic Polymers

1. Synthetic polymers are divided into two types.

(A) Non-biodegradable polymers[3]

For examples: Poly methyl methacrylate acrolein (PMMA), Glycidyl methacrylate, Epoxy polymers

(B) Biodegradable polymers

For example: Lactides and Glycolides and their copolymers, Poly alkyl cyano acrylates, Polyanhydrides and Poly-ε-caprolactone (PCL)

Natural polymers

Natural polymers are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates. (A) Proteins: Albumin, Gelatin4, and Collagen Carbohydrates: Agarose, Carrageenan, Chitosan, Starch Chemically modified carbohydrates: Poly dextran, Poly starch .

The microsphere in pharmaceutical industry has been considered since the 1960s for their following applications:

1. Masking of taste and odour.
2. Delay of volatilization.
3. Safe in case of toxic substances.
4. Flow of powder is Improve.
5. Sustained-release, controlled-release, targeted medication can produce.
6. Reduced dose dumping.

Ideal microparticulate carriers

The material utilized for the preparation of microparticulates should have the following properties

1. Longer duration of action.
2. Provide protection of drug.
3. Sterilizability.
4. Water solubility.
5. Toxicity.
6. Water dispersability .
7. Relative stability.
8. Bioresorbability.

METHODS OF PREPARATION

The choice of technique depends upon the nature of polymer as well nature of drug and the duration of therapy. The most important physical chemical factors that may be controlled in microsphere manufacture are:-

1. The particle size requirement.
2. Molecular weight of polymer
3. Polymer to drug ratio
4. No stability problem.
5. Final product should be non-toxic.
6. Total mass of drug and polymer.
7. Reproducibility.
8. Controlled particle size and dispersability in aqueous vehicles for injection.
9. Release of active reagent with a good control over a wide time scale.

Techniques for microsphere preparation

1. Single emulsion techniques
2. Double emulsion techniques
3. Polymerization
4. Phase separation coacervation technique
5. Spray drying
6. Solvent extraction
7. Wax coating Hot-melt method

Single emulsion technique

There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods , which is also shown in figure 1. as follows;

(1) Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for the Thermolabile drugs.

(2) Chemical cross linking agents: - by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by adding to Liquid paraffin containing a surfactant resulting formation of w/o emulsion[5]. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent[6].

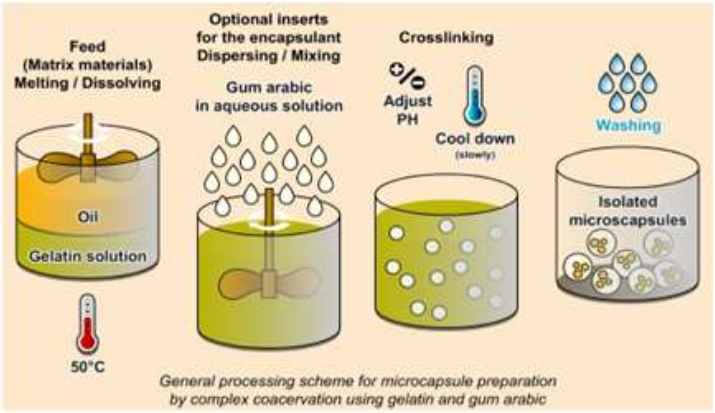
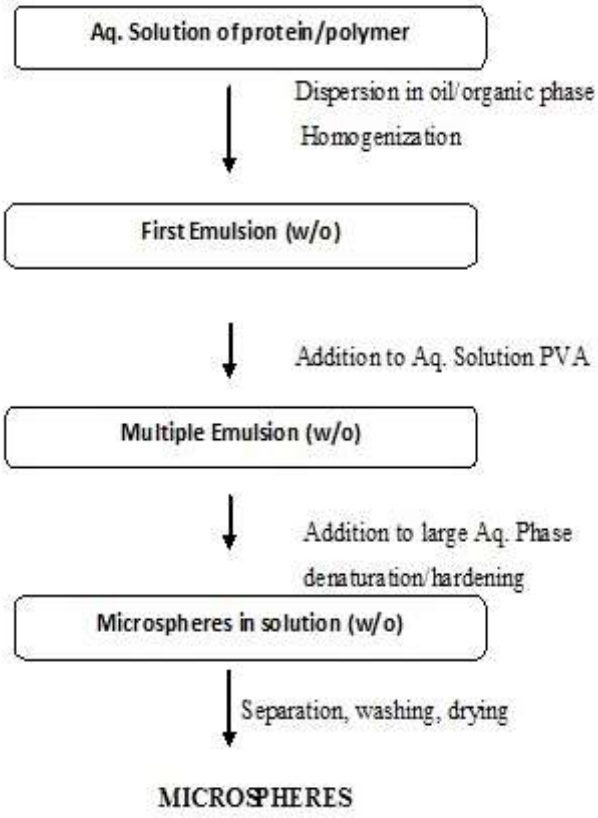


Figure 1: Formulation of microsphere by Single emulsion technique

Double emulsion technique

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect

Microcapsules by filtration and dry under vacuum[7]. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres1 genistein chitosan microsphere were prepared by the o/w/o multiple emulsion .



Double Emulsion Technique

Polymerization techniques

Mainly two techniques are using for the preparation of microsphere are classified as:

(a) Normal polymerization

In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres.

(b) Interfacial polymerization.

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet. Shown in table 3.

Polymers used in the microsphere preparation

➢**Synthetic Polymers**	➢**Natural Materials**
• **Non-biodegradable**	• **Proteins**
✓ Acrolein	✓Albumins
✓ PMMA	✓Gelatin
✓Glycidyl methacrylate	✓Collagen
✓Epoxy polymers	• **Carbohydrates**
• **Biodegradable**	✓Starch
✓Lactides and Glycolides copolymers	✓agarose
✓Polyalkyl cyanoacrylates	✓Carrageenan
✓Polyanhydrides	✓Chitosan
	• **Chemically modified carbohydrates**
	✓Poly (acryl) dextran
	✓DEAE cellulose
	✓Poly (acryl) starch

List of polymer used in microsphere

Phase separation coacervation technique

The process is based on the principle of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called coacervates. The coacervation can be brought about by addition of the third component to the system which results on the formation of the two phases, one rich in the polymer while the other one, i.e. supernatant, depleted of the

polymer. The methods are based on salt addition, non-solvent additi0on, addition of the incompatible polymer or change in pH.

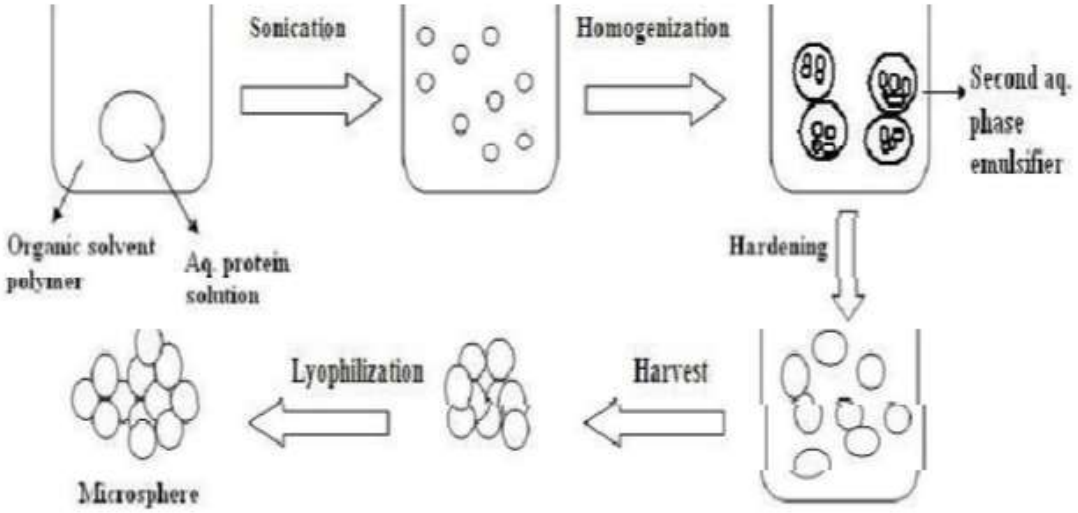


Figure 2: Formulation of microsphere by Phase separation coacervation technique

Spray drying and spray congealing techniques

Concept of spray drying technique depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray congealing. Evaporation is the basic mechanism in spray drying, whereas in spray congealing it is that of a phase inversion from a liquid to a solid. Both processes are similar, except for energy flow[8]. Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

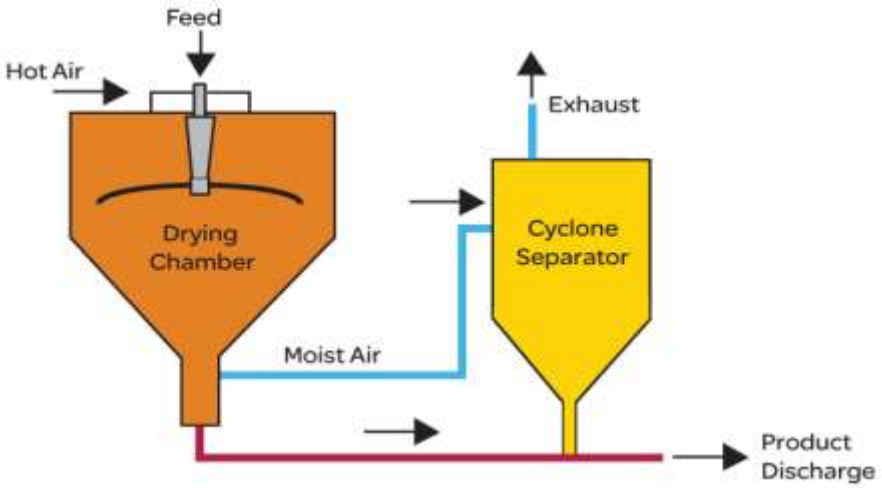


Figure 3: Formulation of microsphere by Spray drying and spray congealing technique

Three steps involved in spray drying :

a.) Atomization:

Atomization of a liquid feed change into fine droplets.

b.) Mixing:

It involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c.) Dry:

Dried powder is separated from the gas stream and collected.

In this technique 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.

Solvent extraction

In this method preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. Isopropanol can be use as water miscible organic solvents. By extraction with water, Organic phase is removed. Hardening time of microsphere can be decrease by this method. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

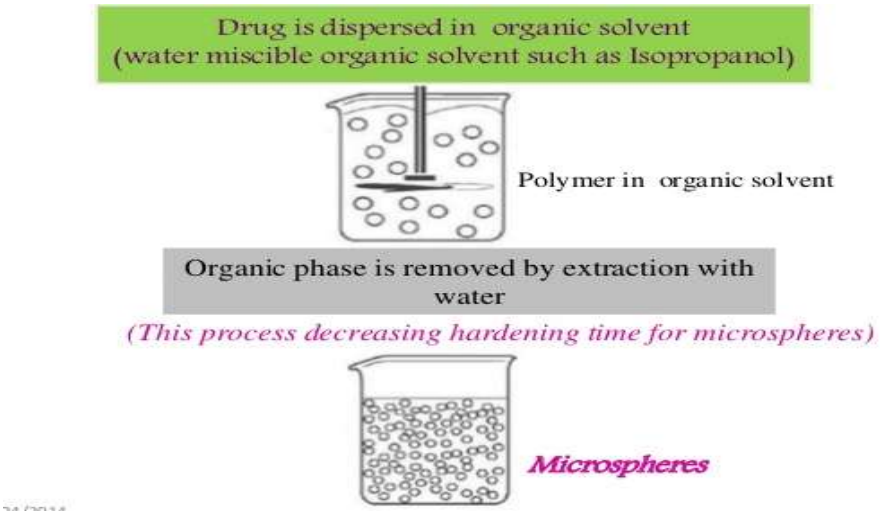
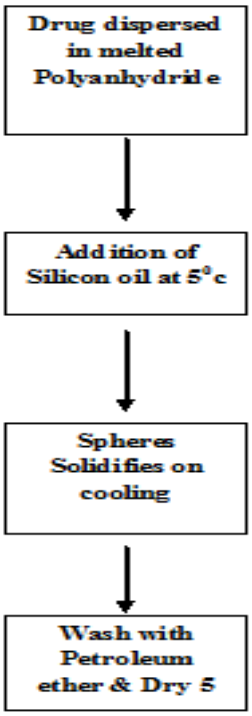


Figure 4: Formulation of microsphere by Solvent extraction

Wax Coating and Hot Melt

In this technique polymer is disperse in suitable dispersion medium and slowly cooled to form the microspheres. The polymers which having low melting point fabricated into microspheres by this technique easily[21]. For coating and coring of particle wax is use mostly. In which

encapsulate the drug by dispersion in the molted wax. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin. Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid. Mostly Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.



PHARMACEUTICAL APPLICATION OF MICROSPHERES

a. Vaccine delivery

b. Monoclonal antibodies

c. Imaging

d. Topical porous microsphere

e. Nasal drug delivery

f. Oral drug delivery

g. Targeting drug delivery

h. Gastro-retentive controlled delivery system

i. Bio-medical application

j. Pharmaceutical

Microspheres in vaccine delivery:

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, Safety and convenience in application and cost. In 2000 liminetal. prepared polymicro particle by using solvent evaporation method as a drug carrier for insulin.[9] The aspect of safety and minimization of adverse reaction is a complex issue[10]. The aspect of safety degree of the production of antibody responses is closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen

Lamprecht detail in 2000 prepared nanoparticle preparation of bovine serum albumin (BSA) by double emulsion method, found that on increase the protein concentration in the inner aqueous phase BSA encapsulationefficiency decreased while particle size was not influenced significantly. There is higher release rate with PLGA NP compared with PCL.

Monoclonal antibodies mediated Microspheres targeting

There are numbers of antibiotic drugs which are administrate in microsphere form, for improve the efficiency as well as compatibility with other salt. Such as amoxycilline, ampicillin, tetracilline, sulfadiazine, sulfathiazole, griseofulvine[11]. Monoclonal antibodies targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

1. Non specific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling via reagents

In 1999 Shan et al Prepared Amoxycillin and metronidazole loaded chitosan microspheres for stomach specific delivery were prepared for the treatment of Helicobacter pylori infection by

crosslinking in addition to precipitation with sodium tripolyphosphate. In vitro studies in simulated gastric fluid showed that the total amount of drug was released in 2 h due to the high porosity of the drug-loaded microspheres. However, amoxicillin showed 40% degradation in 10 h in simulated gastric fluid while metronidazole was stable for 24 h. This study showed the usefulness of porous metronidazole containing chitosan microspheres for eradication of the above infection[12]. Ampicillin microparticles by spraydrying technique a new derivative of chitosan, methylpyrrolidinone chitosan was used. Giunchedi et al., in1998) used Scanning electron microscopy, particle size analysis, differential scanning calorimetery and in vitro drug release studies were carried out to characterize the microparticles and microbiological assays were also performed using different bacterial strains. Results of the assay showed that ampicillin microspheres were able to maintain the antibacterial activity of the drug

Imaging

The particle size plays an important role in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labeled human serum albumin microspheres[13] Hejazi and Amiji (2003) Prepared microsphere by ionic crosslinking and precipitation method Studied the gastric residence time of tetracycline loaded chitosan microspheres. Following their oral administration in gerbils chitosan microsphere suspension in the nonacid-suppressed and acidsuppressed states. Animals were sacrificed at different time points, and the radioactivity in tissues and fluids was measured with a gamma counter[14].

Topical porous microspheres

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner[15].

Nasal Drug Delivery

Intranasal (IN) administration has many theoretical and practical advantages for the local and systemic delivery of a diverse therapeutic compound. IN delivery is needlefree, non-invasive, and essentially painless, does not require sterile preparation, and can be self-administered. The large surface area of the nasal mucosa originated from the presence of a large number of

microvilli, a porous endothelial membrane, and a highly vascularized epithelium serves a rapid onset of therapeutic effect. It is describes various systems, devices, formulations, and methods of delivery of drugs to the nose or nasal cavity . Depending on the therapeutic intent, intranasal drugs may be targeted for local treatment or systemic action. For treatment and prevention of nasal symptoms e.g. Rhinitis, Allergy, Decongestion and Local inflammation etc. Martinac and at el in 2004 prepared Loratadine-loaded microspheres by spray-drying of dispersions, emulsions and suspensions differing in polymeric composition and solvents used. And he delivered loratadine (lipophilic) drug through nasal drug delivery by making bioadhesive microsphere[16]. In nasal drug delivery, coupling of bioadhesive properties to microspheres is of great importance because of additional advantages: efficient absorption and enhanced bioavailability of the drug, a much more intimate contact with the mucus layer and reduction in frequency of drug administration due to the reduction in mucociliary clearance of drug delivery system adhering to nasal mucosa.

Oral drug delivery

Shefi angel timmy work on delivery of insulin by oral route by making microsphere with cyclodextrin making inclusion complex with drug molecule. In oral delivery of insulin for the treatment of diabetes mellitus. The main problem with insulin was degradation of drug due to enzyme in GI tract. Aliginate and enteric polymers, which protecting the insulin in acidic condition. Polk et al used chitosan alginate membranes for delayed release of protein.

Targeting drug delivery

Microspheres exhibit a prolonged residence time at site of application and thus contribute to better therapeutic performance of drugs. Microspheres have been developed for oral, buccal, ocular, rectal, nasal and vaginal routes for either systemic or local effects. This article presents introduction and the advanced pharmaceutical applications of bioadhesive microspheres. There are number of drugs which are given by different route of administration and having good targeting effect some of example are given in below table

Gastroretentive controlled delivery system

In which Floating systems are low-density systems that have float over the gastric contents and remain in the stomach for a prolonged period than conventional dosage forms. Gastric emptying of dosage form is extremely variable process and ability to control the emptying time is valuable asset for dosage forms, there are several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability. While the system floats over the

gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

Several polymers are use for gastroretentive controlled delivery system such are Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene oxide etc[17].

Target Drug Delivery of different drug by microsphere[13]

Drug	Route of administration	Polymer used
Acyclovir	Ocular	Chitosan
Insulin	Nasal	Degradable starch microspheres and lysophosphatidylcholine
Gentamicine	Nasal	Degradable starch microspheres and lysophosphatidylcholine
Furosemide	Gl	Polyglycerol esters of fatty acids
Insulin	Colonic	PGEF coated with Eudragit S100
Insulin	Vaginal	Hyaluronic acid esters

Tablets:

Ampicillin, Atenolol, Amoxycillin, Acetyl salicylic acid, Acetaminophen, Chlorpheniramine maleate, Ciprofloxacin, Captopril, Cinnarazine, Diltiazem, Fluoruracil, Isosorbide di nitrate, Riboflavin, Prednisolone, Theophilline.

Capsules:

Nicardepine, D8iazepam, Misoprostol, Propranolol, Verapamil. Microspheres/Floating beads: Aspirin, Verapamil, Ibuprofen, Ketoprofen, Amoxicillin,

Granules:

Riboflavin, Meloxicam, Nicardepine

Implantable devices

Microencapsulation has also been used medically for the encapsulation of live cells and vaccines. Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins, and hormones, which can prevent unwanted immunological reactions that would lead to inactivation or rejection. Microspheres are used for isolating materials until their activity is needed. The biotechnology industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of this product.

Pharmaceutical applications

A number of pharmaceutical microencapsulated products are currently on the market, such as aspirin, theophylline and its derivatives, vitamins, pancrelipase, antihypertensives, potassium chloride, progesterone, and contraceptive hormone combinations.68 Microencapsulated KCL

(Micro-K, R.H. Robins, Richmond, VA) is used to prevent gastrointestinal complications associated with potassium chloride. The dispersibility of the microcapsules and the controlled release of the ions minimize the possibility of local high salt concentrations, which could result in ulceration, hemorrhage, or perforation. Microspheres have also found potential applications as injection[18], or inhalation[19-20] products. The number of commercially available products does not reflect the amount of research that has been carried out in this area, nor the benefits that can be achieved using this technology. Most encapsulation processes are expensive and require significant capital investment for equipment. An exception is pan or sprays coating and spray drying, since the necessary equipment may already be available within the company. An additional expense is due to the fact that most microencapsulation processes are patent protected.

CONCLUSION

Microsphere promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The average particle size was found to be in the range of 224-361µm. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanning electron microscopy. Economic considerations have been a key factor in determining the number of pharmaceutical microencapsulated products.

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