

Review on Microspheres

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Abstract:

Microspheres can be employed to deliver medication in a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix¹. The current review provides an in-depth discussion of therapeutic aspects of microsphere drug delivery including consideration of the prerequisite area for micro particulate, types of polymers used, method of preparation, method of release & kinetics, type of microspheres in brief, characterization & targeting of microspheres & practical aspects of microspheres

Keywords: *Microspheres, Targeting, Microspheres polymer, Types of Microspheres*

Introduction

The drug should be delivered to specific target sites at a rate and concentration that permit optimal therapeutic efficacy while reducing side effect to minimum and patient compliance during therapy. Site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bioerodible polymer, implants monoclonal antibodies and various particulate carriers (Ex. nanoparticles and microspheres etc) the micro particulate delivery system if modified then maintains the desired concentration at the site of interest without side effect.

The term microcapsule is defined as a spherical particle with size varying from 50nm to 2µm containing a core substance. Alternate terminology for the microsphere is microbeads and -beads are used alternatively.

History: between 1940s and 1960s, the concept of chemical microencapsulation technology began as an alternative means of delivering drugs. In continued quest for the more refined systems' in 1980s polymer/Membrane technology came to be known at forefront.²

Prerequisite areas for ideal micro particulate carrier system

The polymers and other material utilized for the preparation of microsphere should give following characteristics:

Target ability, Polyvalent, Biocompatibility, Longer duration of action, Sterilizability, Relative stability, Water solubility, Control of content release, Bioresorbability, Water solubility and dispensability, Reduction of toxicity, Protection of drug²

Types of polymer used in preparation of microspheres²

Classification:

1] Synthetic polymer

A] Non biodegradable:

- Acrolein
- Glycidyl methacrylate
- Epoxy polymer
- PMMA

B] Biodegradable:

- Polyanhydrides
- Lactides and glycolides and their copolymer.
- Polyalkyl cyano acrylates

2] Natural Materials

A) Proteins

- Albumins
- Gelatins
- Collagens

B) Carbohydrates

- Chitosan
- Carrageenan
- Starch
- Agaose

C) Chemically modified carbohydrate

- Poly (acryl) dextran
- Poly (acryl) starch
- DEAE cellulose

Table 1: Polymer with their bio adhesive property

Polymer	Qualitative bioadhesive property
Carboxymethyl cellulose	Excellent
Carbopol	Excellent
Polycarbophil	Excellent
Tragacanth	Excellent
Sodium /alginate	Excellent
HPMC	Excellent
Gelatin	Fair
Pectin	Poor
Acacia	Poor
Providone	Poor

Method of preparation

1) Single emulsion technique: In single emulsion technique of preparation of microsphere the aqueous solution or solution of polymer is disperse in organic phase of oil or chloroform with constant stirring and sonication.

2) Double emulsion technique: this involves formation double emulsions or multiple emulsion of type w/o/w and is best situated for water soluble drugs, protein peptides and vaccines the aqueous protein solution is dispersed in lipophilic organic continuous phase. The continuous phase is generally of polymer solution that eventually encapsulation of the protein content in disperse aqueous phase. The primary emulsion is then subjected to homogenization or sonication before addition to aqueous solution of polyvinyl alcohol this result in formation of double emulsion. The emulsion

is then subjected to solvent removal either by solvent evaporation or by solvent extraction process. The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring emulsions so that the organic phase evaporate out. The solid microspheres are subsequently obtained by filtering and washing.³

3) Other Important methods of preparations

Polymerization technique including normal & interfacial polymerization, phase separation coacervation technique, Spray drying and spray congealing technique, Solvent extraction technique²

Entrapment of Drug in Microspheres

The active component can be loaded by means of the physical entrapment, chemical linkage and surface absorption the entrapment largely depends on the method of preparation and nature of the drug or polymer. The loading is carried out in pre-formed microspheres by incubating them with high concentration of the drug in a suitable solvent

Drug Release Kinetics from Microspheres

Release of the active constituent is an important consideration in case of microspheres. Many theoretically possible mechanisms may be considered for the release of drug from the micro particulates.

1. Liberation due to polymer erosion or degradation,
2. Self diffusion through the pore,
3. Release from the surface of the polymer,
4. Pulsed delivery initiated by the application of an oscillating or sonic field.

The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microsphere(s) is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself. The drugs could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second pore diffusion mechanism and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuses into the core through biodegradable or non-

biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors the macromolecule/ polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. The pore diffusion method is named so because as penetrating water front continues to diffuse towards the core. The dispersed protein/drug dissolves creating a water filled pore network through which the active principle diffuses out in a controlled manner. In case of the biodegradable polymers, the release is controlled by both the erosion as well as diffusion process⁴. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the Monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix. This plasticization of the matrix finally leads to the cleavage of the hydrolytic bonds. The cleavage of the bond is also facilitated by the presence of the enzyme (lysozymes) in the surroundings. The erosion of the polymer may be either surficial or it may be bulk leading to the rapid release of the drug active components. The rate and extent of water uptake therefore determines release profile of the system and depends on type of the polymer, porosity of the polymer matrix, protein drug loading, etc.

Factors affecting the release:

Controlled release is an attainable and desirable characteristic for drug delivery systems. The factors affecting the drug release rate revolve around the structure of the matrix where the drug is contained and the chemical properties associated with both the polymer and the drug. Conventional oral delivery is not rate controlled. A drug encapsulated in a slowly degrading matrix provides the opportunity for slower release effects, but polymer degradation is not the only mechanism for the release of a drug. The drug release is also diffusion controlled as the drug can travel through the pores formed during sphere hardening. In some cases, drugs containing nucleophilic groups can cause increased chain scission of the polymer matrix, which also increases the rate of drug expulsion. Polymer molecular weight, drug distribution, polymer blending, crystallinity, and other factors are important in manipulating release profiles⁵.

Factors affecting the release from the particulate system :

- Drug

Position in microspheres Molecular weight
physicochemical properties Concentration
Interaction with matrix

- Microspheres

Type and amount of the matrix polymer Size and density of the microspheres Extent of cross linking, Denaturation or -polymerization
Adjuvant

- Environment

- PH
- Polarity
- Presence of enzyme

Suitable Drug Candidates for Microspheres drug delivery:

Various drugs have their greatest therapeutic effect when released at the targeted area of body particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the other part of the body, which is where absorption occurs and contact time is limited appropriate candidate for microsphere drug delivery system is the drug possesses Narrow absorption window in GI tract, e.g., riboflavin and levodopa Drugs that act locally in the stomach, e.g., antacids and misoprostol. Drug having Poor bioavailability, potent drug so as to incorporate the small amount into the microsphere, and drug should not affect the local area for which is intended to act.

Release type of Microspheres:

A) Reservoir Type System:

Release from the reservoir type system with rate controlling membrane proceeds by first penetration of the water through the membrane followed by dissolution of the drug in the penetrating dissolution fluid. The dissolved drug after partitioning through the membrane diffuses across the stagnant diffusion layer. The release is

essentially governed by the Fick's first law of diffusion

B] Matrix System:

Release profile of the drug from the matrix type of the device critically depends on the state of drug whether it is dissolved or dispersed in the polymer matrix. In the case of the drug dissolved in the polymeric matrix, amount of drug, and the nature of the polymer (whether hydrophobic or hydrophilic) affect the release profile²

Types of Microspheres

Albumin Microspheres: Much of earlier use of serum albumin microspheres was limited to the diagnostic purpose as the microsphere of different size range locates themselves differentially at selected sites to facilitate the imaging. Because of selected uptake of protein carrier by tumour cells, the microspheres of albumin are being widely used for the targeted drug delivery to the tumour cells⁵.

Gelatin Microspheres: Gelatin microspheres are mostly studied because they are prone to strong opsonization. Gelatin microspheres is prepared by cross linking gelatin in water in oil emulsion with glutaraldehyde. Opsonic gelatin microsphere are also prepared by similar method by dispersing gelatin in oil followed by cross-linking with glutaraldehyde⁶.

Starch Microspheres:

Starch is one of the most abundant biodegradable polymers that belong to carbohydrate class. It consists of the principle glucopyranose unit, which undergoes hydrolysis to yield D-glucose. Starch being a polysaccharide, consists of larger number of the free hydroxyl groups. By means of these free hydroxyl groups a large number of the active narcotic antagonist and anticancer agents such as cisplatin, cyclophosphamide and doxorubicin⁸

Polyanhydride Microspheres:

Polyanhydride are biodegradable and biocompatible polymers. They were first prepared using aromatic monomers. The Polyanhydride can be manufactured with desired features such as crystallinity, controlled degradation rate, degree cross-linking, water uptake, etc. Polyanhydride microspheres can be prepared by solvent evaporation, solvent extraction, hot melt technique and spray drying techniques. For the hot melt encapsulation procedure

ingredients can be incorporated within as well as active on surface of microspheres. The starch microspheres when introduced into the body cavity undergo potential swelling, leading to the development of mucoadhesive character⁷. Therefore, they are not cleared rapidly from the body cavity. Intra nasally administered insulin starch microspheres are cleared slowly and offer a delivery mode for protein and small molecules¹²

Dextran Microspheres:

Dextran, a carbohydrate is used to prepare hydrogel type of biodegradable and biocompatible systems. It can be chemically modified that provide higher percentage of drug or proteins incorporation. Simple method of incorporating aldehydes group to dextran is by oxidation using sodium iodate. Protein loaded dextran microspheres are prepared by water in water emulsion technique. In this method an aqueous solution of the methacrylated dextran is emulsified in aqueous solution of polyethylene glycol (PEG). The dispersed methacrylated phase is then cross-linked by using radical polymerization of the dextran bound methacrylate groups. This leads to the formation of the dextran microspheres with hydrogel character.

Poly Lactide and poly Glycolide Microspheres:

Poly (lactic acid) (PLA), poly (glycolic acid) (PGA) and their copolymer poly (lactide co glycolide) (PLGA) represent the group of synthetic biodegradable polymers. They were used earlier as absorbable sutures, implant material and recently as the carrier for the drug. L poly (lactic acid) has been reported as a suitable carrier for sustained release.

Chitosan microsphere: The effect of Chitosan has been considered mainly because of its positive charge; however, the adsorption process could also be the result of other forces might exist between molecules, such as hydrogen bonding or Vander Waal's forces. These interactions might have a strong impact on the absorption and bioavailability of pharmaceutical. Due to attractive properties and wider applications of Chitosan-based microcapsules and microspheres they are used as a carrier for the applications in controlled drug release^{9,10}

Polyphosphazene Microspheres:

Polyphosphazene polyacids are potent immune stimulating compounds. Polyphosphazene polymers have a long chain backbone of alternating nitrogen and phosphorus atom with two side group attached to each phosphorus atom. Polyphosphazene polymers form highly swollen ionotropic gel in the presence of the multivalent ions in aqueous media, such as calcium. Because of this property the polyphosphazene microspheres can be prepared under very mild conditions of low temperature and in absence of the organic solvent the microspheres are prepared by using a droplet apparatus, which produces spherical gel particle of size range 0.5-1.5 μm . In this method a 2.5% w/v phosphazene solution is added in the form of the droplets to a 7.5% w/v aqueous solution of calcium chloride.⁸

Other Important types of microspheres:

Polysaccharides or Lipid Cross linked Chitosan Microspheres¹⁰, Alginate microsphere, Carrageenan polysaccharide or lipid cross linked chitosan microsphere¹⁰, Poly alkyl cyanoacrylate microsphere, and Poly Acrolein microspheres

Targeting Using Micro particulate Carriers (Applications):

Floating Microspheres:

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core⁴. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer¹¹.

Microspheres in Vaccine Delivery:

Microsphere played vital role in vaccine delivery for protection against the microorganism or their toxic product. Biodegradable delivery system for vaccines is given by parenteral route. The interest in parenteral carrier lies since they offer specific advantages including improved antigenicity by adjuvant action, Modulation of antigen release and Stabilization of antigen.

Magnetic Microspheres:

Magnetic monitoring has the advantage of being efficient in allowing high local concentration of therapeutic agents. A variety of magnetically

responsive carriers have been proposed for chemo-therapeutic agents. These include magnetite containing matrices (microspheres or nanoparticles of the starch, albumin, ethyl cellulose, etc.), ethylolate based emulsion and natural cells such as erythrocyte ghosts. Magnetic targeting is one of the most efficient methods developed for targeting of active agents. Magnetic microspheres are prepared by mixing water soluble drugs and 10 nm magnetite Fe_3O_4 particles in an aqueous solvent of matrix material. This mixture is then emulsified in the oil. Ultrasonication or shearing is done to produce particle of suitable size range.

Magnetic microspheres are administered via intra-arterial or intravenous injection. Intra-arterial injection is given to achieve high systemic targeting while intravenous administration helps in achieving high pulmonary targeting^{12,13}.

Monoclonal Antibodies Mediated Microspheres (Immunomicrospheres):

Monoclonal antibodies mediated targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. And can be utilized to target microspheres loaded bioactive molecules to selected sites⁷. The Monoclonal Antibodies can be attached to the microspheres by any of the following methods:

1. Non specific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling via reagents³

Chemoembolization:

Chemoembolization is an endovascular therapy, which involves the selective arterial Embolization of a tumour together with simultaneous or subsequent local delivery of the chemotherapeutic agent. Chemoembolization is an extension of traditional percutaneous Embolization techniques. With Chemoembolization, investigators embolize tumours with micro particles soaked with chemotherapeutic agents. The theoretical advantage is that such embolizations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of tumour².

Topical porous microspheres (Micro sponges):

Micro sponges are porous microspheres possess 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, sunscreens and anti-infectives, etc these porous microspheres with active ingredients can be incorporated in to 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. The Micro sponge system can reduce significantly the irritation of effective drugs without reducing their efficacy¹⁵

Route targeting:

Oral

The controlled release systems have been developed for oral administration¹⁴. Oral route is also suggested for the delivery of the soluble antigens this as viable alternative can be considered due to the ability of the particles of definite size range. The risk of dose dumping is minimized with this formulation the smaller size of particles and high drug loaded particles show faster release and oral route is also suggested for the delivery of the soluble antigens.

Intranasal

In this type of targeting the microspheres is given at the surface of nasal mucosa by considering the mucociliary clearance²⁰. The particle size range of microspheres for targeting the respiratory tract is given table no.

Table .2 particle size of the microspheres for targeting of specific area

Respiratory part	Required Particle size (μm)
Nose	25-30
Throat	20-28
Pharynx	20-24
Larynx	15-20
Trachea	10-15
Bronchi	8-12
Bronchioles	8-10
Alveolar duct	5-8
Alveoli	4-8

Ocular

The eye and the cornea are easily accessible targets. The washout effect, however, presents difficulties in retention of micro particulate drug carrier in the corneal sac. The rapid conversion of the particulate suspension to gel form reportedly leads to their longer retention in the eye⁵.

Encapsulation of microspheres its techniques and polymers used:

Table: 3 Microspheres entrapped drugs along with techniques and polymers used of intended formulation

Drug	Micro encapsulation technique	Polymer	Intended formulation
Ibuprofen	Solvent Evaporation	Eudragit (R) RS 100, Polystyrene,	Modified Release
	Solvent Evaporation	Ethyl cellulose. Polystyrene	Prolonged Release
	Coacervation Phase separation using Sodium sulphate	Hydroxypropyl methylcellulose phthalate	Increased Rate of Release
	Coacervation Phase separation	Sodium alginate	Modified Release
Diclofenac	Multiple Emulsion Technique with acacia as stabilizer	Poly(δ -valerolactone)	Prolonged Release

	A Non- Aqueous Emulsion Method	Ethylcellulose, oloxamer 188, HPMC phthalate	Sustained Release
	Congealable Disperse Phase Method	Glycerol monostearate Tween 80	Sustained Release
Ketoprofen	Modified W/O/W Complex Emulsion Technique	Cellulose acetate butyrate. Polystyrene	Controlled Release
	Spray- Drying	Eudragit S and L, Cellulose acetate Phthalate, Cellulose acetate Trimellitate, HPMC phthalate	Gastro resistant micro capsules with slow release
	Spray- Drying	Cellulose Acetate, Trimellitate, Ethylcellulose	Slow release
	Emulsion/Solvent Evaporation	Eudragit RS	Sustained release
Indomethacin	Phase Separation-Coacervation	Benzalkonium chloride	Increase Release
	Phase Separation-Coacervation	Albumin, Chitosan	Slow re lease
	Phase Separation-Coacervation	Ethylcellulose	Increase Release
	Spray Drying Technique	Hydroxypropyl methyl cellulose Polyvinyl Alcohol, Hydroxypropyl Cellulose	Fast Dissolution
Ketorolac	Coacervation Phase Separation	Eudragit s100	Sustained Release
	Emulsion solvent evaporation	Albumin	Controlled release/IM admnstration
Asprin	Solvent Evaporation	Ethylcellulose	Modified Release/ Tablets
	Oil -In- Water Emulsification/ Solvent Evaporation	Ethylcellulose	Modified Release
	Spray -Congealed	Hydrogenated soybean oil	Controlled Release
Naproxen	Emulsion cross linking	Albumin	Intra articular
	Emulsion solvent evaporation	PLGA	Intra articular
	Co-Precipitation Technique	EudragitL100-55	Extended Release/Tablets
Meclofenamate	An Emulsion-Solvent Evaporation Method	Cellulose propionate	Sustained-Release

Characterization parameters & methods:

Microspheres are characterized in the following given parameters:

Table 4: Parameters & method for microspheres characterization

Sr. no.	Characterizations Parameters	Method
1	Particle size and shape	Light microscopy & SEM
2	Chemical analysis	Electron Spectroscopy
3	Degradation of polymer	FTIR
4	Density Determination	Pycnometer
5	isoelectric Point	Micro electrophoresis
6	Surface Carboxylic Acid Residue	Radioactive glycine
7	Surface amino acid residue	Radioactive 14c-acetic acid conjugate.
8	Capture efficiency	UV spectroscopy
9	Release study	USP paddle apparatus
10	Flow property	Angle of contact

Practical aspects of Microspheres for Drug delivery

1) Applications:

Microspheres designed for oral treatment target the gastrointestinal (GI) tract, and encapsulation can enhance GI treatments. Toxic drugs, which can cause side effects when administered in large quantities, or insoluble drugs, which may require large doses to promote absorption, can be administered with a lower frequency and smaller

quantity The adhesion properties of biospheres can be exploited so that they stick to the adhesive tissues thus prolonging absorption time at lower doses

2) Commercialization of Microspheres:

Drug delivery is a primary topic in the biopharmaceuticals industry and microspheres do overcome many of the shortcomings of conventional drug delivery routes. To date a

limited number of companies provide commercially available microspheres and/or have active product development programs in the field. For market applications, microspheres systems are expected to undergo phase and clinical testing just as non-encapsulated drug systems. Patents mentioning polymer microspheres systems are also seen which shows their potential commercial importance

3) In vivo administration of Microspheres

The use of microspheres in mammals is not a theoretical issue but an applied reality. It shows how it was possible to obtain reasonable accordance between in vitro and in vivo In examples representative of animal testing Recently, made microspheres from poly (ortho-ester) for the delivery of DNA vaccines and tested them in mice. The polymer can prevent the DNA from degradation and the release takes place inside the cell where the weakly acidic environment degrades the polymer without compromising the biological activity of the DNA¹³

Conclusion

Overall conclusion is microspheres are good carrier for the drug in case of targeting delivery of the drug, microspheres drug delivery is safe and effective and utilized in various areas like floating, drug targeting, and vaccine delivery etc. procedure for preparation & evaluation for microspheres formulations are widely available with effective reproducibility. Microspheres drug delivery covers large area of drug targeting hence required consistence performance study to correlate the invivo performance.

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