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MICROSPHERES AS DRUG DELIVERY SYSTEM – A REVIEW

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ABSTRACT

Microspheres are the free flowing powders of proteins or synthetic polymers which are biodegradable in nature and having a particle size less than 200 µm. The therapeutic efficacy of microspheres containing drug is depend upon their characteristics which can be altered in required terms by alter the materials, methods, polymers or techniques used. The method of the preparation of microspheres providing multiple options to control as drug administration aspects and to enhance the therapeutic efficacy of a given the drug. Microspheres drug delivery systems offer various advantages compared to conventional dosage forms, which include improved efficacy, improved patient compliance, reduced toxicity and convenience. The aim of this review is to study various aspects of the microparticulate drug delivery system including method of prepration, evaluation, application & characterization microsphere.

KEYWORDS: Microspheres, novel drug delivery, therapeutic efficacy, Controlled release.

INTRODUCTION[1,2,3]

Microspheres are used as carriers of drug and used to the controlled release of drug, vaccines, antibiotics, and hormones. Microspheres is an "therapeutic agent which are distributed throughout the matrix either as a molecular dispersion of particle. There haveing small spherical free flowing particle with a diameter in a range of 1 µm to 1000 µm. Microspheres are manufactured by using natural and synthetic materials polymer and waxes. Solubility, Stability, and drug release depend upon the type of polymer used for the preparation of microspheres.

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release. This approach is using microspheres as carriers for drugs. It is

the reliable means to deliver the drug to target the specific site. If modified and to maintain the desired concentration at the site of interest without untoward effects. Microspheres not only for prolonged release, but also for targeting of anticancer drugs to the tumor. In future microsphere combining various other strategies, microspheres can be central place in novel drug delivery, particularly in diseased cell sorting, gene, diagnostics & genetic materials, safe, and effective in vivo delivery and supplements of disease organ and tissues in the body.

Advantages of microspheres[4]

1. Particle size reduction for enhance solubility of the poorly soluble drug.
2. Provide constant and prolonged therapeutic effect.
3. Provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery.
6. Avoid first pass metabolism.
7. Improved protein & peptide drug delivery system.
8. Ability to bind & release a high concentration of a drug.
9. Method of preparation is simple,
10. Masking of taste.
11. Enhance biological half-life.
12. Improve physical stability and gastric enzymatic stability.

DISADVANTAGES[5]

1. Poor in vitro-in vivo correlation.
2. Higher cost of formulation.
3. drug is difficult in case of toxicity, poisoning.

TYPES OF MICROSHERES

Sr.No	Type of microspheres	Description
1.	Bio adhesive microspheres[6]	Adhesion can be defined as sticking of drug to the membrane by using the sticking property of water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, nasal, ocular, rectal, etc. can be termed as bio adhesion. These types of microspheres exhibiting it a prolonged residence time at the site of application and causes intimate contact with absorption site and it produces better therapeutic action.
2.	Magnetic microspheres[7]	Magnetic microspheres which localize the drug to the disease site. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's bloodstream and then stopped with a powerful magnetic field in the target. In this larger amount of freely circulating drug can be replaced by the smaller amount of magnetically targeted drug to locally diseased sites, reaching effectively up to several folds increased localized drug levels. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials which is used for magnetic microspheres are Dextrans, chitosan etc. Depending on the type of particular drug.
3.	Floating microspheres[8]	In this types of microsphere the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The release of drug is slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. it also minimise chances of striking and dose dumping. another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.
4.	Radioactive microspheres.[9]	In the release rate from Radio immobilization therapy are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the release rate of the controlled release dosage form .may vary from a various factors like food and the rate of transit through gut.

Materials Used[10,11]

Microspheres used usually are polymers. They are classified into two types.

Sr.No	polymers.	Example
1.	**Synthetic Polymers** a. Non-biodegradable polymers. b. Biodegradable polymers	E.g. Polymethylmethacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers. E.g. Lactides, Glycolides & their copolymers, Poly alkyl cyanoacrylates, Poly anhydrides
2.	**Natural polymers Proteins:** **Carbohydrates:** **Chemically modified carbohydrates:**	E.g. Albumin, Gelatin, and Collagen. E.g. Agarose, Carrageenan, Chitosan, Starch. E.g. Poly dextran, Poly search.

Methods of Preparation[12,13]

Preparation of microspheres should satisfy certain criteria:

Sr.No	Technique	Description
1.	Single emulsion technique:	In micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepare by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium follow by dispersion in non- aqueous medium like oil. then cross linking of the dispersed globule is carried out. The cross linking can occur by heat or by using the chemical cross linkers. In chemical cross linking agents used are, formaldehyde, glutaraldehyde, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking having disadvantage is excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, separation, washing.
2.	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 to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The solution of aqueous protein is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. In this continuous phase is generally consisting of the polymer solution that eventually encapsulates of the protein containeing 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. the number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, proteins/peptides, vaccines, and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation.

3.	Polymerization techniques: 1) Normal polymerization. 2) Interfacial polymerization. Both are carried out in liquid phase.	In this techniques it carried out using different techniques as bulk, precipitation suspension, , emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers. 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.
4.	Phase separation coacervation technique:	In this process is based on the main principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In phase sepration method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system. which is makes first polymer to phase separate and engulf the drug particles. In Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important because the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration can be avoided by stirring the suspension using a suitable speed stirrer hence, 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 kinetic of the formed particles since there is no defined state of equilibrium attainment.
5.	Spray drying and spray congealing:	Spray drying methods is based on the drying of the polymer and drug in air. the removal of the solvent or cooling of the solution, so two processes are name spray drying and spray congealing respectively. The polymer are firstly dissolve in a suitable solvent such as volatile organic, dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under highspeed 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 µm.
		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.
6.	Solvent extraction:	Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. In this method involves water miscible organic solvents such as isopropanol. as Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. 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.

PHARMACEUTICAL APPLICATION OF MICROSPHERES[14,15]

Sr.No	Applications	Description
1.	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, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue.
2.	Targeting using microparticulate carriers	The concept of targeting, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system. Placement of the particles indiscrete anatomical compartment leads to their retention either because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.
3.	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 microspheres9 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
4	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

Microspheres for drug delivery

Sr.No	Drug	Polymer used	Result
1.	Desmopressin[16]	Starch	Addition of LPC causes a five folds increase in Cmax and two folds increase in bioavailability
2.	Gentamicin[17]	Degradable starch microspheres and lysophosphatidylcholine	Increased nasal absorption
3.	Insulin[17]	Degradable starch microspheres and lysophosphatidylcholine	Efficient delivery of insulin into the systemic circulation via nasal route
4.	Amoxicillin[18]	Ethyl cellulose-Carbopol-934P	Greater anti H. pylori activity
5.	Furosemide[19]	Polyglycerol esters of fatty acids (PGEFs)	Increased bioavailability Higher AUC effective absorption from the absorption window.
6.	Vancomycin[20]	PGEF(polyglycerol esters of fatty acids coated) with Eudragit S 100	Well absorbed even without absorption enhancers.
7.	Glipizide[21]	Chitosan-alginate	Prolonged blood glucose reduction
8.	Delapril HCL[22]	Polyglycerol esters of fatty acids (PGEFs)	MRT of drug is increased
9.	Glipizide[23]	Chitosan	Prolonged blood glucose reduction Glipizide
10.	Fluorouracil[24]	Glutaraldehyde, Chitosan	Slow down of release of drug
11.	Aceclofenac[25]	Eudragit	Controlled release and minimize local side effect
12.	Cisplatin[26]	Chitosan, Chitin	Reduce release rate
13.	Amoxicillin[27]	Sodium tripolyphosphate	Slow release rate
14.	Gentamicin[28]	PLGA and PCL	Controlled release
15.	Mitoxantrone[29]	Glutaraldehyde – saturated toluene	Glutaraldehyde – saturated toluene
16.	Oxantrazol[30]	Chitosan	Enhance the delivery of drug in brain 100 times
17.	Dilitazam[31]	Casein, chitosan	Retard drug release
18.	Progesterone[32]	Glutaraldehyde, chitosan	Maintain plasma drug

			concentration
19.	Insulin[33]	Chitosan	Improve systemic absorption
20.	Furosemide[34]	Chitosan	Reduse affect of external variables
21.	Indomethacin[35]	Chitosan	Decrease in the release rate
22.	Ketoprofen[35]	Chitosan	modulate drug release

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