

Review Article

ROLE OF MICROSPHERES IN NOVEL DRUG DELIVERY SYSTEMS: PREPARATION METHODS AND APPLICATIONS

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ABSTRACT

Microsphere based drug delivery system has gained substantial attention in the modern era. Microspheres are normally free-flowing powders that can be made with both natural and synthetic polymers. The sizes of the microspheres ranges from 1 to 1000 μm . Microspheres are matrix systems in which the drug is uniformly dispersed, dissolved or suspended. Microspheres contain solid or liquid drug dissolved or dispersed in a matrix system. The current review provides an inclusive outline of up to date and novel developments on formations of microspheres which have been reported to increase bioavailability, improves stability, enhances biological half-life and reduces the toxicity of the drug. Microsphere provides efficient delivery of various proteins and peptide molecules. There are different types of microspheres such as bio adhesive microsphere, magnetic microsphere, floating microsphere, and polymeric microspheres. Diverse kinds of methods are used in the formulation of microsphere e. g. Simple emulsion-based method, Double emulsion-based method, Interfacial deposition technique, Interfacial polymerization technique, Phase separation method, and Spray drying. Microspheres deliver the drug in a controlled manner through different routes like oral, topical, naso-pulmonary and gene therapy. The Polymeric based microspheres are model carriers for numerous controlled delivery applications owing to their capacity to encapsulate a diversity of drugs, bio-compatibility, high bio-availability and continuous drug release character. Therefore, by developing newer techniques, it can give more therapeutic effects and improves the safety of drugs. The formation of microspheres has been reported to increase bioavailability, improves stability, enhances biological half-life and reduces the toxicity of the drug.

Keywords: Microspheres, Drug delivery, Polymeric, Improved stability

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INTRODUCTION

A drug proposed for clinical use must have an optimal therapeutic index (ratio of minimum effective to the maximum safe concentration of drug). Many chemotherapeutic agents have a narrow therapeutic window leads to restricted clinical use and increased toxic side effects. So, these kinds of drugs are incorporated in a polymer system, which ensures the controlled release of drugs to provide optimum drug levels at the target site [1]. Numerous targeted drug delivery systems have come up with different techniques to attain controlled and targeted drug delivery. Microsphere based targeted drug delivery system is gaining substantial importance in the modern era [2].

The size of microspheres ranges from 1 to 1000 μm . Microspheres are matrix systems containing active ingredient uniformly dispersed, dissolved or suspended. Microspheres contain solid or liquid drug dissolved or dispersed in a matrix system [3]. Microspheres of size less than 800 μm pass through the pyloric sphincter without any effect of gastric emptying, thereby excluding the inter-individual variations. Microsphere particles of size above 100 nm remain at the administering site till phagocytic clearance. Microspheres uptake by the lymphatic system were notably between the size ranges from 10–80 nm [4]. The surface charge plays a significant role in the aggregation of particles. Aggregation of particles leads to a decrease in the uniformity of dose and disturbs the normal flow of blood [5, 6].

Advantages of microspheres

Microspheres suggests several advantages over conventional methods of drug delivery, as well as couture of medicine release rates, safeguard of delicate drugs and augmented patient ease and acquiescence. Also, Enhances solubility of the lipophilic drugs, constant plasma drug concentration is achieved, reduced dose size, dosing frequency and side effects, polymer coating prevents the drug from enzymatic degradation, bioavailability of the drug is improved, improves stability of drug, enhance biological half-life of

drug, reducing toxicity, and protects the GIT from the drugs which produce gastric irritation [6].

Disadvantages of microspheres

Some of the disadvantages of microsphere-based drug delivery can be that once injected, it is hard to remove from the body if the drug produces some adverse toxic effects. Also, Dosage form containing microspheres should be handled with care, not to be crushed or chewed. The Release rate might differ from one dose to another. Gastric contents and GI transits might modify the release of drug [2].

Drug release mechanism through microspheres

The drug diffusion occurs throughout the integral polymer system or the pores filled with aqueous fluid. Hydrophilic drugs may get dissolved in the pores containing aqueous fluid. Uptake of aqueous fluid causes polymer network to swell, indicates the building of new pores and osmotic pressure. Swelled polymer increases the volume; therefore, helpful diffusion coefficient of the drug is also improved, and more drug molecules go into the aqueous phase. The polymer matrix may also get eroded from the bulk or surface of microspheres [7, 8].

Types of microspheres

Mucoadhesive/Bioadhesive microspheres

Adhesion of microspheres on any mucosal membrane (e. g. ocular, vaginal, oral, buccal, rectal, and nasal) is termed as Bioadhesion/Mucoadhesion. Adhesion of microspheres at the target site will increase the duration of action of a drug and thus improves the bioavailability. Natural or synthetic polymers used to produce adhesion to the biological membrane. Mucoadhesive polymers improve the contact time of the microspheres with the mucous membranes; absorption of the drug takes place through mucosa [9, 10]. Mucin turnover is likely to restrict the residence time of the bioadhesive microspheres on the mucus membrane and it does not depend upon the strength of the mucoadhesive polymers [11].

Fluoxetine is an antipsychotic drug that considerably undergoes first-pass hepatic metabolism. Therefore mucoadhesive microspheres were formed to improve bioavailability and sustain the drug release by increasing the residence time of the drug in the gastrointestinal tract [12, 13].

Magnetic microspheres

Magnetic microspheres are tiny particles which freely move through blood vessels without producing any obstruction, they are susceptible to be arrested in any vessel and extravasate into tissues by magnetic field of 0.5-0.8 tesla. In response to the external magnetic field magnetic microspheres reaches the target site and releases the drug [14]. In this system, drug can be either encapsulated in the polymer (silica or hydroxyl apatite) or attached to the microsphere surface. Magnetic core of the microspheres consists of magnetite, magnetic ferrites (cobalt ferrite or manganese ferrite). Magnetic microspheres are used in targeting of anticancer drugs (paclitaxel, mithotrixate doxorubicin, cisplatin). Magnetic microspheres are used for extraction of stem cells and also used in isolation of DNA, cell organelles, cells or proteins [14]. The content of magnetic material and the extent of magnetic field applied govern the retention of microspheres at the targeted site [15].

Floating microspheres

These microspheres are kind of gastro retentive systems which prolongs the drug residence time in stomach having size of less than 200 micrometer [16]. The drugs used may produce local action in the stomach (antacids, antibiotics for ulcers caused by *H. Pylori* bacteria) or likely to be absorbed through stomach (albuterol, amoxicillin). These are hollow microspheres or microballons designed to float on the gastric fluid with the density of less than one. Various polymers used in the formulation of floating microspheres are chitosan, polyvinyl acetate, eudragit, agar, acrylic resins, polyacrylates. These polymers in the presence of gastric juices swells to form a colloidal gel barrier from which drug is released in controlled manner, air gets trapped in the swollen polymer which reduces the density of the system and impart buoyancy to the microspheres [17]. Bhadouriya *et al.* (2014) developed and evaluated a floating drug delivery system containing clopidogrel bisulphate to increase bioavailability and to reduce the side effects caused by the drug like development of drug resistance and gastric bleeding [18, 19].

Radioactive microspheres

These are radiolabeled microspheres used for targeting the drugs to tumors in cancer treatment. Radiolabeled microspheres are very stable and have proven efficacy in the field of primary and secondary cancers without any effect of radiation over the normal tissues. Radioactive microspheres are injected in the blood capillaries near to the tumor [20]. They contain one or more radionuclides, radioactivity in contrast to drugs never released from the microspheres but acts from within a typical radioisotope distance. Radio microspheres are of different kinds containing alpha emitters, beta emitters and gamma emitters [21]. The type of materials used for making radio microsphere are glass (aluminosilicate, Lithium silicate), albumin (human or bovine serum albumin), resins (aminex A-27, aminex A-5), polymers (polylactic acid, polyglycolic acid) [20, 22]. Yttrium-90 (beta emitter) microspheres may help to treat the liver cancer by destroying the tumor cells through radiations [23].

Polymeric microspheres

It mainly consist of polymer and drug, also contain a block co-polymer which prevent the opsonization (linking of opsonin with the microsphere to facilitate its phagocytosis) of drug delivery system. Polymeric microspheres are coated with recognition molecules such as an antigen, nucleic acid probes, and antibodies can be loaded with lipophilic dyes and other compounds. Different kinds of polymers can be used to direct the release of drugs to a particular organ [24].

Classification of polymeric microspheres

Biodegradable polymeric microspheres

Natural polymer like starch has biodegradable, biocompatible, and bio adhesive properties. Concentration of the polymer used may

affect the bioavailability of drug. Its disadvantage is, in clinical use loading efficiency of drug in biodegradable micro-spheres is complicated and the drug release is hard to be controlled [25].

Synthetic polymeric microspheres

They are used clinically and are also used as bulking agent (used to treat stress urinary incontinence), soft tissue fillers (used in correcting lips, wrinkles and scars), embolic particles (used in the treatment of cancer), and drug delivery vehicles. Disadvantage of synthetic polymeric microspheres is, they likely to move away from site of injection and may cause embolism and organ damage [26].

Natural polymers

Obtained from different sources like carbohydrates (E. g. Agarose, Chitosan, Carrageenan, Starch), Proteins (E. g. Albumin, Collagen, Gelatin, Silk fibroin) and chemically modified Carbohydrates (E. g. Poly acryl dextran, Poly acryl starch, DEAE cellulose) [27, 80, 81].

Synthetic polymers

They are divided into two types. Biodegradable polymers (E. g. Lactides, Glycolides and their co-polymers, Poly anhydrides, Polyalkyl cyano acrylates, another is Non-biodegradable polymers (E. g. Poly methyl methacrylate (PMMA), Glycidyl methacrylate, Epoxy polymers, Acrolein) [28].

Methods to formulate microspheres

Simple emulsion-based method

Several carbohydrates and proteins are prepared by this method. In this natural polymers are solubilized in aqueous medium and then dispersed in organic solvent. Next step is cross-linking of polymer which is carried out by following methods-

Heat cross-linking

In this, dispersion is added into previously heated non-aqueous phase; therefore it is unsuitable for the Thermo labile drugs.

Cross-linking by chemical agents

Formaldehyde, di-acid chloride, glutaraldehyde are used for cross linking of polymers. The problem of using these agents during preparation is that microspheres must be properly centrifuged and then washed to remove chemical residues. Solution of chitosan in acetic acid is poured into previously heated Liquid paraffin containing a surfactant resulting formation of w/o emulsion [29]. Metformin HCL microspheres were prepared by using 25% glutaraldehyde solution [30].

Double emulsion-based method

This method helps forming w/o/w type emulsion by adding the primary w/o emulsion into polyvinyl alcohol solution and stirred for half an hour. Now slowly add the water into the emulsion over a period of half an hour. Microspheres were then collected, filtered and vacuum dried [31]. This method is best for hydrophilic drugs, peptides, vaccines and proteins. Both natural and synthetic polymers are used in the formation of microspheres by this method [32].

Polymerization technique

The two techniques used to prepare microspheres are classified as:

Normal polymerization

This method includes heating of a single monomer or mixture of monomers along with the initiator or catalyst to initiate polymerization. Polymer so obtained may be mounded into microspheres. Drug is added during the process of polymerization. Heat of reaction is difficult to dissipate, which may affect the pharmacological activity of thermolabile drugs. Lower temperature conditions are involved in suspension polymerization in which the monomer mixture is heated with active drug as droplets dispersion in the continuous aqueous phase. Microspheres of size less than 100 μm are obtained by suspension techniques. Emulsion polymerization contains initiator in aqueous phase and it is also carried out at low temperature as suspension polymerization.

External phase is normally used as water so that heat can easily dissipate. Polymers might form at higher rate by these techniques but polymer can get associated with the unreacted monomer or other additives [32].

Interfacial polymerization

In this technique, polymerization occurs at the interface between the two immiscible liquid phases to form a film of polymer that effectively encapsulates the dispersed phase. Two reacting monomers are used; one was dissolved in continuous phase while other was dispersed in a continuous phase throughout which the second monomer is emulsified. Two conditions were raised depending upon solubility of the formed polymer in the emulsion droplet that is if formulation formed is of the monolithic type the polymer was soluble in droplet and capsular type if the polymer was insoluble in droplet [30, 32].

Spray drying and congealing method

Spray drying is an extensively used industrial process involving the formation of microspheres. In this method, polymer solution, drug and solvent is atomized into a fine spray with help of atomizer. Hot stream of gas is passed through the sprayed droplets, which results in evaporation of liquid and forming dried microsphere particles. In spray drying the finished product must fulfill some specific quality standards regarding particle size, net moisture content, bulk density, and shape of microspheres.

In spray congealing method, drug is dissolved or suspended in melted excipients and atomized into cold nitrogen leading to solidification of droplets and microsphere formation. Spray congealing is a solvent-free process [33-35].

Wax coating and hot melt

In this, the polymer is dispersed in appropriate medium and gradually cooled to prepare microspheres. The polymers used should have low melting point [36]. Wax is used to form core and coat of the particle and the drug is dispersed in the molten wax. The wax suspension is dispersed into cold solution, for example, liquid paraffin with high speed mixing. Agitation is continued for one hour and then continuous phase was decanted and microspheres were collected. Microspheres were then air-dried. It is not an expensive method as a comparison to other methods and the release of drug is more rapid. Carnauba wax and beeswax can be used as the coating materials and their mixture can be used in order to achieve desired characteristics [37].

Ionotropic gelation method

In this method, sodium alginate and eudragit are the polymers used. To prepare microspheres polymers and drug is dispersed in sodium alginate solution and added dropwise in calcium chloride solution with continuous stirring. These microspheres help providing sustained release of drugs and increase the dosing interval [38].

Solvent evaporation method

Degradation of proteins and peptides can be prevented by encapsulating them in microspheres through this technique [39]. Microspheres are formed by dissolving eudragit polymer in organic solvent (for e. g. chloroform) to form a uniform polymer solution. Required amount drug can be added to this polymer solution and mixed thoroughly; this mixture was then added to aqueous mucilage of sodium carboxymethyl cellulose containing tween 80 and stirred at 1000 rpm. Organic solvent was removed by evaporation with continuous stirring at room temperature. Sodium carboxymethyl cellulose acts as a microencapsulating agent and tween 80 as a surfactant [40].

Coacervation phase separation method

Researchers have been investigated the use of cellulose acetate phthalate and cellulose acetate as polymers [41-43] using organic solvents [44-46] in microencapsulation of a drug-using this method. To form microspheres the drug is added to liquid paraffin previously containing polysorbate. Polymer solution is made by dissolving polymer in organic solvent and added to the drug mixture with

continuous stirring until solvent gets evaporated at room temperature.

Applications of microspheres

Microspheres used for vaccine delivery

Vaccine provides protection by developing resistance against infectious diseases. Some examples of vaccines encapsulated in microspheres are tetanus vaccine, diphtheria vaccine, cholera vaccine [47]. Microspheres containing vaccines improve immunologic response by prolonging the antigen release for weeks to even months [48, 49]. Degradation of vaccine is prevented by encapsulating it in a suitable carrier until it gets released. The controlled delivery of vaccine may diminish systemic side effects and can encapsulate multiple antigenic epitopes or both antigen and adjuvant in a single carrier. Biodegradable polymers are used for the sustained release of encapsulated antigen and which degrade in the body to nontoxic, low-molecular-weight products that can be easily eliminated [50]. Chitosan microspheres are capable to encapsulate a wide range of antigens. Synthetic biodegradable polymers such as poly lactic-co-glycolic acid is the best option and mostly used for antigen encapsulating single-shot vaccines [51].

Microspheres containing monoclonal antibodies

(Mabs)-Monoclonal antibodies have high specificity for antigen molecules present at the target site [52]. Specificity of monoclonal antibodies is used for targeting microspheres carrying pharmacologically active molecules to target sites. Covalent coupling, nonspecific adsorption, coupling via reagents, specific adsorption are methods used to attach monoclonal antibodies with microspheres. The free carboxyl group, aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies [53]. Microspheres carrying anti-vascular endothelial factor formulation (containing monoclonal antibodies) showed release up to six months [54].

Microspheres in gene delivery

For delivery of genes, mostly recombinant adenoviruses are used because of their high efficiency and have an extensive range of cell targets, though when used in vivo they generate immune responses and oncogenicity. Also, repeated gene therapy is required when viral vectors are used. In non-viral gene delivery microspheres are used to encapsulate genes, provides sustained gene delivery [55]. Microspheres are stable, easy to prepare, target the cells/tissue, generate low immune responses, and large-scale reproducible production is also possible.

Ophthalmic drug delivery through microspheres

Polymers used for ophthalmic drug delivery imparts bio adhesion, and permeability-enhancing properties. Polymer hydrogels are more effective due to their elasticity as compare to other formulations for ophthalmic drug delivery such as ointments or suspensions. A Chitosan gel improves adhesion to the mucin membrane, spreads over the conjunctiva and the corneal surface of the eye and precorneal drug residence times is increased by preventing the elimination of drug through lachrymal flow. Drug loaded microspheres can be suspended in a polymer hydrogel system to achieve sustained or controlled delivery of drug in eye [53, 56].

Nasal drug delivery through microspheres

The nasal mucosa is an ideal site for bioadhesive drug delivery systems. Microspheres are created to have good bioadhesive properties and swell easily in contact with the nasal mucosa improving the bioavailability and residence time of the drugs in the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride. Nasal administration of chitosan microspheres containing diphtheria toxoid produces a defensive local and systemic immune response against the toxoid by enhancing the production of IgG antibodies [57]. Microspheres absorb the moisture present in mucosa results in shrinking of the nasal cells cause short term separation of tight junction through which absorption of drug is increased [58]. Dextran and starch microspheres are considered to be safe for nasal drug

delivery [59]. Alginate Microspheres containing ondansetron prepared by Ionic-gelation method used to sustain the drug release for extended time period though nasal mucosa [60].

Microspheres for delivery of protein and peptides

Microspheres made up of biodegradable polymers were studied for their controlled release of proteins and peptides. Microspheres help to maintain steady-state plasma concentration of protein or peptide for long periods of time [61]. Bio-degradable polylactic acid and polylactic-co-glycolic acid and chitosan microspheres are applicable in microsphere formulation of protein/peptide drugs [62]. Marketed peptide drugs like, triptorelin, lanreotide, buserelin, and abarelix use the microsphere-based delivery system [63].

Microspheres used in cancer treatment

Radioactive microspheres containing β -emitter (e. g. yttrium-90) used for targeting tumors present in liver.

Suspension of radioactive microspheres is injected into the hepatic artery, microspheres having a diameter of 30 micron gets into the tumor vessels. Tumor cells get destroyed after getting exposed to radiations without destroying neighboring normal cells [64]. Polymeric microspheres containing 5-fluorouracil drug can be used to treat colon cancer. These polymeric microspheres protect the drug from getting degraded in the gastric environment.

Marketed formulations of microspheres

Various marketed formulations of microsphere are as given in (table 1), with their active agents and for use in disease condition [9, 65-67].

Some of the patents on microsphere formulations

Various patents on Microsphere Formulations are available based on the type of formulation used in drug delivery, which is given in (table 2).

Table 1: Marketed formulations of microspheres

Dosage form	Active ingredient	Disease condition	Marketed products
Injectable suspension (i. m.)	Naltrexone	Alcoholism, opioid dependency	Vivitrol®
Injectable suspension (i. m.)	Respiridone	Schizophrenia	Risperdal®consta®
Powder for injection (s. c.)	Somatropin	Growth hormone deficiency	Nutropin® Depot
Powder for Injection (i. m)	Bromocriptine	Parkinson's disease, Acromegaly	Parlodel® LAR
Powder for suspension for injection (s. c, i. m)	Triptorelin	Advanced prostate cancer	Decapeptyl®
Injection (s. c)	Buserelin	Prostate cancer	Suprecur® MP
Extended-release injectable Suspension (s. c.)	Exenatide	Type-2 Diabetes mellitus	Bydureon®
Injectable suspension (i. m.)	Lanreotide	Acromegaly, Gastroenteropancreatic Neuroendocrine tumors, Thyrotropic adenomas	Somatuline® LA
Implant or Injectable suspension (s. c.)	Goserelin acetate	Prostatic carcinoma, Endometriosis	Zoladex®
Injectable suspension (Intragluteal inj.)	Ocetreotide	Acromegaly, carcinoid tumor, vasoactive intestinal peptide tumors	Sandostatin LAR®
Powder form	Minocycline	Periodontitis	Arestin®
Suspension depot injection	Leuprolide acetate	Endometriosis	Lupron® depot

Table 2: Various patents on microsphere formulations

Patent title	Patent number	Year	References
Microspheres for controlled-or sustained-release delivery of therapeutics	US 9,381,159 B2	2016	[68]
Microspheres for Treatment of Brain Tumors	US 8,691,791 B2	2014	[69]
Programmable buoyant delivery technology	US2010/0015224A1	2010	[70]
Magnetic Microspheres for Use in Fluorescence-Based Applications.	US 7,718,262 B2	2010	[71]
Gastroretentive controlled-release microspheres for improved drug delivery	US006207197B1	2001	[72]
Metal-Coated Polyaldehyde Microspheres	4,624,923	1986	[73]
Porous wall hollow glass microspheres as carriers for biomolecules	US2012/0201892A1	2012	[74]
Bioadhesive Microspheres and their Use as Drug Delivery and Imaging Systems	US 6,235,313 B1	2001	[75]
Polymeric Microspheres	US 6,720,007 B2	2004	[76]
Process for Preparing Microspheres for Prolonged Release of the LHRH Hormone and its Analogues, Microspheres and Formulations Obtained	5,540,937	1996	[77]
Production of Microspheres	US 7,374,782 B2	2008	[78]
Compositions and methods for treating intracellular infections	US 6,264,991 B1	2001	[79]

CONCLUSION

Microspheres have revealed immense promise for the delivery of remedial agents owing to their biocompatibility, easiness of administration and potential for lasting sustained release. Additionally, microspheres are valuable for delivering numerous types of compounds, as well as small molecule drugs, vaccines, gene therapy agents and protein therapeutics. For past several years of studies, it has been exhilarating development in methods of production, managing of drug release rates and particularly stabilization of the encapsulated materials. In the coming decade, the development in macro-molecular pharmaceuticals will compel more advances in particle fabrication and drug encapsulation techniques, in addition to common methods of stabilizing protein and gene therapeutics. Improvements in developed technologies, novel strategy for stabilization of delicate therapeutics and progress

of novel approaches for site-specific particle targeting will ensure that microspheres play a significant job in the drug delivery field in the coming decade, too.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise.

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