IJPSR (2018), Volume 9, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 August, 2017; received in revised form, 15 October, 2017; accepted, 20 October, 2017; published 01 May, 2018

MICROSPHERES AS CONTROLLED DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

Shweta Saini [1], Sandeep Kumar [1], Manjusha Choudhary [2], Nitesh [3] and Vikaas Budhwar [*1]

Department of Pharmaceutical Sciences [1], Maharshi Dayanand University, Rohtak - 124001, Haryana, India.
Institute of Pharmaceutical Sciences [2], Kurukshetra University, Kurukshetra - 136118, Haryana, India.
Faculty of Pharmacy [3], RPIIT, Bastara, Karnal - 132001, Haryana, India.

Keywords:

Microspheres, Types of microspheres, Controlled release, Applications and advancements of microspheres, Polymers

Correspondence to Author:
Dr. Vikaas Budhwar

Assistant Professor,
Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak -124001, Haryana, India.

E-mail: vikaasbudhwar@yahoo.com

ABSTRACT: Oral modified or controlled dosage forms have always proven to be more effective alternative to conventional or immediate release dosage forms. Controlled or modified drug delivery systems offer numerous advantages of delivering a drug to the body in a précised manner with an aim to minimize its unwanted side effects and maximize its benefits. Targeted drug delivery systems target a particular site in the body to maximize the drug concentration in a specified tissue or organ of the body which improves therapeutic efficacy of the drug, decrease toxicity and with better patient compliance and convenience. In past few decades, microspheres have promised targeted or controlled delivery of drugs in the body which has proved to be better than the conventional drug delivery. Recently microspheres have been used to deliver drugs, vaccines, antibiotics and hormones in a controlled manner. The present study aims to review different aspects of the microparticulate drug delivery system along with types of microspheres, methods of preparation and different applications as targeted or controlled drug delivery system.

INTRODUCTION: One of the most challenging areas of research in pharmaceuticals is the development of novel delivery systems for the controlled release of drugs and their delivery at the targeted site in the body to minimize the side effects and enhance the therapeutic efficacy of drugs [1 - 3]. The basic principle behind the controlled drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamics properties of drug in such a way that its efficacy is maximized by reducing side effects, dose frequency and cure the disease in short time by using low amount of drug administered with the most suitable route [4].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.9(5).1760-68

Article can be accessed online on:
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(5).1760-68

Microsphere, as carrier for drug is one of the various approaches of drug delivery which maximizes the drug concentration at the target site [5]. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles. It can also be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level with particle size range of 1-100 µm [6 - 7]. There are various Marketed microsphere products available in market that is listed in **Table 1**.

In 1997, first time microspheres were prepared for the sustained action of the drug [8]. Since then, microparticles have proved to be good candidates for sustained and controlled release of drug and become an alternative of conventional or immediate release formulations. These particles are also a beneficial to deliver the active pharmaceutical ingredients which are pharmacologically active but are difficult to deliver due to limited solubility in water. In such type drugs, the attainment of required therapeutic concentrations of drug in the blood is problematic enabling to attain higher C_{max}, T_{max} and area under curve [9]. Microsphere - based formulations can release a constant amount of drug in the blood or to target drugs to specific site in the body [10, 11].

While establishing the drug delivery system, some of the major key points which have to be kept in mind are the type of carrier used, the route of administration, the target of drug delivery and the strategy designed to enhance therapeutic efficacy of drug. These are the factors which can reduce the undesirable effects of the active pharmaceutical entity [12].

TABLE 1: LIST OF MARKETED MICROSPHERES DRUG PRODUCTS [3]

Drug	Commercial name	Technology
Risperidone	Risperdal^R, Consta^R	Double emulsion (o/w)
Naltrexon	Vivitrol^R	Double emulsion (o/w)
Leuprolide	Leupron Depot^R	Double emulsion (o/w/o)
Octreotide	Sandostatin^R LAR	Phase separation
Somatropin	Nutropin^R	Spray drying
Triptorelin	Trelstar Depot, Decapeptyl^R SR	Phase separation
Lanreotide	Somatuline^R LA	Phase separation
Bromocriptine	Parlodel LAR^{TM}	Spray drying
Minocycline	Arestin^R	N/A

Types of Microspheres:

Bioadhesive Microspheres: These microspheres adhere to the site of application for prolonged period of time and produce desirable therapeutic drug concentration in the sustained manner [13 - 15].

Magnetic Microspheres: Due to their smaller size (<4μm) these ferromagnetic microspheres are captured in micro vessels and dragged into the adjacent tissues by magnetic field [13, 16, 17]. Therefore they are suitable for targeted delivery of APIs.

Therapeutic Magnetic Microspheres: These microspheres have been tried for delivery of anticancer drugs into the carcinogenic cells like liver tumor. Some other drugs such as proteins and peptides have also been tried to target the tissue through this system.

Radioactive Microspheres: Radioactive microspheres are designed to target the diseased areas without harming the normal surrounding tissues. Different radioactive microspheres such as α, β and γ-emitters are injected through the arteries that lead to target tumor where these deliver the high radiation dose [13, 18].

Floating Microspheres: They are retained in the gastric fluid for prolonged period of time due to their low-density which provide buoyancy to float over gastric fluids and release the drug slowly to sustained the action [19 - 20].

Diagnostic Microspheres: Supramagnetic microspheres of iron oxide can be used to diagnose the liver metastases and also used to differentiate bowel loops from abdominal structures [21].

Advantages of Controlled Drug Delivery System: Controlled drug delivery system offers the following properties which make them favourable for application in different fields [22].

1. Constant therapeutic concentration for prolonged period of time.
2. Improved patience compliance due to reduction in dosing frequency.
3. Ability to be injected into the body because of their spherical shape and smaller size.
4. Improved bioavailability and reduce side effects.
5. Controllable variability in degradation and drug release.

Polymers used for Microspheres Preparation: A variety of substances such as biodegradable and non-biodegradable have been used by researchers for the preparation of microspheres. Polymers from different origin (such as natural, synthetic and modified natural) are commonly used for the preparation of microspheres. To select the polymer being used for the preparations, few parameters must be consider like nontoxicity, biocompatibility, easy availability and biodegradability of polymers used. These polymers increase the residence time of drug in the body and lead to better bioavailability of drug than the conventional drug delivery methods [23]. Some synthetic polymers which are commonly used for carrier preparations listed in **Table 2**.

TABLE 2: TYPES OF SYNTHETIC POLYMERS [24]

Biodegradable	Non-biodegradable
Lactides and glycolides and their copolymers	Polymethyl methacrylate, glycidyl methacrylate
Polyanhydrides	Acrolein
Polycynoacrylates	Epoxy polymer

Natural Polymers: Chitosan, Albumin, Sodium alginate, Gelatin, Cellulose ether, Xantham gum, Scleroglucan, Gum Arabica, Tamarind seed polysaccharide, Locust bean gum (**Table 3**).

TABLE 3: APPLICATIONS OF NATURAL POLYMERS

Chitosan [25]	To treat obesity, anemia, insomnia, crohn's disease, skin problems, absorption enhancer, suitable for controlled drug release
Gelatin [26]	For treating osteoarthritis, rheumatoid arthritis, weight loss, to strengthen fingernails, joints and bones, used in food, cosmetics and medicines, film- forming material
Cellulose [27]	Used as diluent/ binder, film coating agent for drugs, ointment base
Alginate [28]	Used to prepare mucoadhesive drug delivery systems, thickening agent, stabilizer, texture- improver, emulsifier, gelling agent

Methods of Preparation: Different techniques have been tried for the formulation of microspheres using different polymers. Some of these are discussed below:

1. Single Emulsion Solvent Evaporation Technique: This method involves the dissolution of polymers in an organic solvent followed by emulsification in an aqueous phase containing emulsifying agent. The o/w emulsion thus formed is stirred for several hours under ambient conditions to allow evaporation of solvent, which is then filtered, rinsed and dried in desiccators [29].

Phutane *et al.*, (2010) designed and formulated the microspheres of glipizide with polymers ethyl cellulose and Eudragit by emulsion solvent diffusion-evaporation technique and evaluated to sustain the release of drug for long time [30]. Yuksel *et al.,* (1997) prepared polymeric microspheres containing Nicardipine hydrochloride with Eudragit-RS and Eudragit-RL by using solvent evaporation method [31].

2. Double Emulsification Technique: Double emulsion technique involves the preparation of double emulsion either w/o/w or o/w/o. The aqueous drug solution is dispersed in a lipophilic organic continuous phase. The continuous phase that consists of polymer solution eventually encapsulates drug contained in dispersed aqueous phase to form primary emulsion. The pre-formed emulsion is subjected to homogenization or sonication before addition to aqueous solution of polyvinyl alcohol (PVA) to form primary emulsion. Das *et al.*, (2007) prepared Zidovudine-ethylcellulose microspheres by double emulsification method and the drug release pattern from microsphere was best fitted in Higuchi model, indicating diffusion-controlled principle [32].

Jelvehgari *et al.*, (2010) evaluated controlled release microspheres of tolmetin sodium using ethyl cellulose as retardant material, span 80 as droplet stabilizer and n-hexane as hardening agent using w/o/w double-emulsion solvent diffusion method. The drug loaded microspheres extended the drug release up to 24 hours and was found to be diffusion and erosion controlled [33].

3. Spray Drying Method: Both drug and polymers are dissolved in suitable solvent to form solution which is subjected to spray through nozzle in a spray drier under different experimental conditions. Pavanetto *et al.*, (1993) prepared Vitamin-D3 microspheres using five different polymers of lactide class by spray drying and evaluated that different release profiles were obtained from microspheres depending on type of polymer [34].

4. Spray Congealing: Drug is dissolved into melt of lipophilic polymer material to form hot mixture and allowed to atomize with pneumatic nozzle into a vessel that is stored in a carbon dioxide ice bath. Fabricated microparticles are dried under vacuum at room temperature for many hours [35]. Gao *et al.,* (2011) prepared lipid-polymer composite microspheres (LP-MS) of 10- hydroxy camptothecin for colon-specific drug delivery using pH-sensitive polymer Eudragit S100 and non-polar lipid compritol 888 ATO by an ultrasonic spray freeze-drying technique. Drug release studies indicated that about 15 % drug released below pH 6.8 whereas more than 30 % was released at pH 7.4 which concluded that microparticles could be a promising tool for colon targeted drug delivery [36].

5. Melt Dispersion Technique: Hot mixture of drug and polymer is emulsified into an aqueous surfactant solution that has been heated above polymer melting point to form emulsion which is finally allowed to cool in an ice bath. Ghaly *et al.,* (1996) formulated microspheres of Ibuprofen by melt dispersion technique and concluded that melt dispersion technique was successful method for preparation of sustained release ibuprofen microspheres [37 - 38].

6. Coacervation Phase Separation Method: Coacervation is the separation of macromolecular solution into two immiscible liquid phases out of which one is dense coacervate phase while another is dilute equilibrium phase. Arunachalam *et al.,* (2010) prepared gelatin microspheres containing ofloxacin using glutaraldehyde as cross-linker by co-acervation phase separation method and found that prepared microspheres could sustain drug release over a period of 8 hrs [39].

7. Chemical and Thermal Cross - linking Method: Aqueous solution of natural polymer containing drug to be incorporated is dispersed in organic phase to form w/o emulsion followed by solidification either by thermal cross linking or addition of chemical cross linking agent such as glutaraldehyde [40]. Joseph *et al.,* (2014) developed biocompatible microspheres of diclofenac sodium to reduce dosing frequency, gastro intestinal side effects and improve patient compliance and results showed that drug release from microspheres was prolonged to provide sustained release pattern [41]. Samad *et al*., (2009) formulated oral controlled release microspheres of rifampicin with gelatin B, (biodegradable and biocompatible polymer) and natural cross linker sucrose by thermal cross linking method [40].

8. Ionic Gelation Method: In this method, a hydrophilic polymer is complexed with a multivalent cationic (*e.g*. calcium chloride) or polyanionic (*e.g*. sodium tripolyphosphate) to form highly viscous gel particles. An opalescent suspension is obtained. Then the suspension is centrifuged to obtain microspheres. Microspheres are freeze dried followed by lyophilization for 24 hours. The resulting microspheres are formed due to electrostatic interactions between positively charged group and negatively charged anion. Selveraj *et al.,* (2011) prepared chitosan loaded microspheres of acyclovir by using this method, to release the drug in a controlled manner for treatment of ocular viral infections. The release of drug from microspheres followed the first order kinetics with non-fickian diffusion mechanism [42].

Applications of Microparticles in Drug Delivery Systems: Microparticulate delivery system advances various applications for drugs that have poor bioavailability. Many pharmaceutical encapsulated products are capturing the market, like aspirin, theophylline and its derivatives, Vitamins, anti-hypertensive, potassium chloride, progesterone and contraceptive hormone combinations. Microcapsules are used in pharmaceutical and biotechnology products, beauty products, diagnosis, biological filtration devices, animal treatment and zoo's technical products, eatables and food preservatives, flavors, fragrances, detergents, paints, pesticides, binders, industrial chemicals, daily use products, packaging, textiles, photographic and graphic arts materials.

In Vaccine Delivery: For an ideal vaccine, it must have capability, convenience and safety in application and its cost must be reasonable. Traditional vaccine's weakness can be overcome by biodegradable delivery systems for vaccines supplied by parenteral route. The prerequisite of vaccine is protection against microorganism or its toxic product. Lee *et al*., (2012) carried *in-vivo* studied of a vaccine delivery system based on thiolated Eudragit microsphere for its ability to elicit mucosal immunity against enterotoxigenic *Esherichia coli* (ETEC). The results suggested that thiolated Eudragit microsphere would be a promising candidate for an oral vaccine delivery system to elicit systemic and mucosal immunity [43]. Many antigens are being investigated as shown in the **Table 4** below for their efficient delivery through microspheres.

TABLE 4: ANTIGENS UNDER INVESTIGATION FOR THEIR DELIVERY THROUGH MICROSPHERES

Name of Antigen	Polymer	Technique	Reference
Staphylococcus enterotoxin B	dl-PLGA	Solvent evaporation	44, 45
Diphtheria toxoid	dl-PLA	w/o/w emulsion	46
Hepatitis B surface antigen	PGA	Phase separation suspension	47
Tetanus toxoid	PLA,PLGA	Emulsion method	48, 49

In Oral Drug Delivery: To administer any drug in the body, oral drug delivery system is the utmost preferable and the most suitable route. Therefore, there are large numbers of controlled or sustained release methods for oral administration of drug. Orally administered drugs generally depend on its solubility and absorption. These drugs which exhibits poor aqueous solubility and low bioavailability microsizing of such drugs leads to increase the oral absorption and bioavailability. Microparticles are having in achieving quick onset of action for drugs that are completely but slowly absorbs and this system is used by many researchers for sustained the release of drug in the stomach or upper GIT [50].

Cheng *et al.*, (2015) formulated the floating microparticles of diltiazem by using cellulose acetate and Eudragit R5100. Drug release from the microparticulate was found to be 77.62 ± 2.12 - 97.50 ± 1.04 at the end of 12 hrs, the research concluded that microparticulate floating oral drug delivery system of diltiazem would be an effective alternative to conventional oral tablets for cardiac delivery [51]. Cetin *et al.*, (2014) improved the bioavailability and decreased the ulcerogenic potential of diclofenac sodium by formulation and evaluation of Eudragit RS100/RL100 loaded microspheres by solvent evaporation technique [52].

Ocular Drug Delivery System: For opthalmic application, microspheres are very good drug carriers. The ocular bioavailability of many drugs is increased considerably as compared to traditional aqueous eye drop formulations. Conventionally, drugs having small particle size are more desirable in acceptance by the patients than large particle size drugs. Due to this, microspheres are commonly used for long lasting ocular drug delivery systems, while microparticles having large particle size exhibit slower elimination kinetics from the precorneal compartment. Duarte *et al.*, (2007) prepared ophthalmic drug delivery systems of acetazolamide using Eudragit RS 100 and RL 100 by compressed anti-solvent technology. The prepared microparticles exhibited slower release than single drug [53].

Intranasal Delivery: The intranasal route is exploited for delivery of peptides and proteins. The conventional dosage forms are rapidly cleared from nasal mucosa. The bioadhesive microspheres providing greater control over surface character and release pattern is better alternative to gel dosage formulations. Yadav *et al*., (2008) prepared domperidone microspheres for intranasal administration by emulsification cross-linking technique using starch and epichlorhydrine as cross-linking agent and showed good mucoadhesive property and swelling behaviour [54].

Buccal and Sublinguial Drug Delivery: The buccal mucosa may have potential for delivering peptide drugs low molecular weight, high potency and long biological half-life [55]. Nerker *et al*., (1997) developed mucoadhesive microspheres of venlafaxine using linseed mucilage as a muco-adhesive agent by spray-drying technique for buccal delivery with an intention to avoid hepatic first-pass metabolism, by enhancing residence time in the buccal cavity [56].

Gene Delivery: Even though viral vectors are proven to be advantageous for gene delivery owing to their high efficiency and ability to target wide range of cells, their use is limited due to immunogenic response of subjects. Microspheres have substituted viral vectors in gene delivery on a large extent. Non viral delivery system has various compensations over viral vectors like low immune response, ease of preparation, site targeting, large scale production and unrestricted plasmid size.

For gene delivery, polymer has been used as a carrier of DNA. Also, polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. MacLaughlin *et al.*, (1998) showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered *in-vivo* by chitosan and depolymerized chitosan oligomers to express a luciferase gene in the intestinal tract [57]. Leong and co-workers (1998) developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatin & plasmid DNA [58].

Colon Specific Drug Delivery: The colon specific drug delivery system should be capable of protecting the drug route to colon drug release and absorption should not take place in stomach and small intestine. The bioactive agent should not be degraded, released or absorbed till the system reaches colon [59]. Deore *et al*., (2013) formulated colon targeted tinidazole microspheres by emulsion solvent evaporation method using Eudragit polymer and concluded that Eudragit microspheres would be a promising carrier for colon targeted delivery of tinidazole [60].

Enhance Bioavailability: Microparticles increase the bioavailability of poorly soluble drugs. Several research studies shows that microparticulate drug delivery systems enhance the bioavailability of drugs by increasing the residence time at the absorption site or targeting the drug at the acting site [61 - 62]. Zhang *et al.,* (2015) described the use of carboxylated mesoporous carbon microparticles (cMCMs) to enhance the oral bioavailability of carvediol [63]. Khonsari *et al.,* (2014) prepared gastric mucoadhesive disk microparticles of metformin by emulsification solvent evaporation using different ratios of carbomer 934P and ethyl cellulose. Drug release was observed 82.22 % at 8 hrs and it showed that the use of microparticles as a drug delivery system enhanced oral bioavailability of drug molecules [64].

Microparticles in Cancer Therapy: Cancer is an abnormal and uncontrolled division of cells, known as cancer cells that invade and destroy the surrounding tissues. Microsphere technique in cancer therapy is the most convenient method now a day. The traditional technique of delivery system aims both normal and abnormal cells. Microparticle drug delivery system is unable to focus only on abnormal cells. Microsphere technique is possibly the single method that can show its therapeutic effect only at specific sites, deprived of any remarkable adverse effects on normal cells [65].

Breast Cancer: In breast cancer, cytotoxin laden microspheres are administered *via* a catheter, inserted surgically exactly into both the subclavian artery or to the part of the subclavian artery. Though, the additional discriminating insertion into the first part of subclavian artery (thyrocervical trunk) can be attained by replacing the angiographic catheters immediately inside the arteria mammaria interna.

Intra-arterial administration of these microspheres, are carried by blood circulation to the capillary area where they deliver the therapeutic agent to the desired site and cause embolization [66]. As shown in animal studies, adriamycin-loaded albumin microspheres (1994) are highly effective apart from free drug in suppressing multiplication of cancer causing cells when they are administered radiologically in arteria mammaria interna by using a catheter [67].

Brain Tumor: A microsphere delivery system has been established to administer the diagnostic agent to the brain tumor cells. Controlled release microspheres of 5-fluorouracil were formulated by using polymethylidene malonate as polymer. The degradation rate of polymer was much deliberated, therefore they delivered the therapeutic agent for a longer duration and hence provided a sustained release drug delivery system [68].

Lung Cancer: Microspheres are also favorable in treatment of carcinoma cells of lungs. According to Chao *et al.*, (2013) camptothecin loaded polyethylene glycolated (PEGylated) microparticles extended the release of Camptothecin and results from *in-vitro* and *in-vivo* studies demonstrated a significant increase in anti-cancer activity [69].

CONCLUSION: Microspheres drug delivery system is the most popular drug delivery system among researchers and scientists, because of their advantages of controlled and sustained release action, reduced the dose frequency, and improved the stability, bioavailability and dissolution rate.

Controlled or targeted microspheres facilitate the accurate delivery of drug to the target site and enhance the dissolution rate of drugs because of larger surface area, and this drug delivery system acts as a potential system to increase the bioavailability of the drugs. Sometimes, microspheres also have some disadvantages such as dose dumping, low entrapment and loading efficiency, polymer toxicity, higher cost, few marketed formulations because of difficulties in the scale up techniques from lab scale to industrial scale. Besides this, microspheres drug delivery system is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for noninvasive delivery of potent peptide and perhaps protein drug molecules. In future, with the discovery of newer polymers and better techniques of formulation and by combining various other strategies, microspheres will find the central place in novel drug delivery.

ACKNOWLEDGEMENT: The authors are grateful to Department of Pharmaceutical Sciences, M. D. University, Rohtak, Haryana for its constant support and encouragement.

CONFLICT OF INTEREST: The authors have no conflict of interest.

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How to cite this article:
Saini S, Kumar S, Choudhary M, Nitesh and Budhwar V: Microspheres as controlled drug delivery system: An updated review. Int J Pharm Sci Res 2018; 9(5): 1760-68.doi: 10.13040/IJPSR.0975-8232.9(5).1760-68.