IJPSR (2020), Volume 11, Issue 7 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 October 2019; received in revised form, 18 March 2020; accepted, 21 March 2020; published 01 July 2020

MICROPHARMACEUTICAL'S - A REVIEW ON MICROSPHERRICAL APPLICATIONS AND RECENT ADVANCES

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Keywords:

Micronization, Bioadhesion, Microspheres, Biodegradable Polymer

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ABSTRACT: Microspheres are small spherical free-flowing particles, with diameters 1 µm to 1000 µm consisting of proteins or synthetic polymers which are biodegradable in nature. They are prepared to obtain prolonged or controlled drug delivery to improve, bioavailability, stability and to target the drug to a specific site at a predetermined rate. Microspheres are of various types and are prepared by different techniques as spray drying technique, solvent evaporation technique, single-emulsion technique, double-emulsion technique, *etc*. Microspheres do not receive much attention not only for prolonged-release but also for targeting of anticancer drugs. Microspheres can be applied in different fields as in cosmetics, oral drug delivery, target drug delivery, ophthalmic drug delivery, gene delivery, and others discussed in the review. In the future, with various other techniques microspheres will find a place in novel drug delivery, specifically in diseased cell sorting, diagnostics, genetic materials, safe, targeted & effective *in-vivo* delivery. The present review highlights various types of microspheres, different methods of preparation, its applications, and recent advances in microspherical drug delivery systems.

INTRODUCTION: Microspheres are small spherical free-flowing particles, with diameters 1 µm to 1000 µm consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres;

- Microcapsules
- Micrometric

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DOI: 10.13040/IJPSR.0975-8232.11(7).3101-08

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(7).3101-08

In microcapsules, an entrapped substance is distinctly surrounded by a distinct capsule wall whereas, in micrometric, the entrapped substance is dispersed throughout the matrix. Microspheres can be manufactured from various natural and synthetic materials.

Microsphere plays a very efficient role in improving the bioavailability of conventional drug delivery system. Clinically acceptable shelf life, uniform particle size, and controlled dispersibility in aqueous vehicles for injection can be easily achieved with the help of a microparticle drug delivery system. Changes in temperature, pH, solvent addition, and evaporation/agitation may affect the stability of microparticles to be

encapsulated is the major drawback of microspheres [1, 2]. The different types of microspheres are as follows:

Mucoadhesive Microspheres: Adhesion of drug to the mucosal membrane such as buccal, ocular, rectal, nasal, *etc*. can be termed as bio adhesion. Mucoadhesive microspheres exhibit a prolonged residence time on the site of application and cause intimate contact with the absorption site and produce better therapeutic action [2, 3].

Magnetic Microspheres: Magnetic microspheres localizes the drug to the disease site. They have magnetic carriers that receive magnetic responses and transmitted to the magnetic field from incorporated materials. The polymers used for magnetic microspheres are chitosan, dextran, *etc*. The advantage of the magnetic microsphere is that a large amount of freely circulating drugs can be replaced by a smaller amount of magnetically targeted drug [4].

Floating Microspheres: The drug is released slowly at the desired rate and floating on gastric content, which increases gastric residence timing of drug, which increases fluctuation in plasma concentration resultant reduces the chances of dose dumping [5].

Method of Preparation:

Spray Drying: In the spray drying method the polymer is first dissolved in a suitable solvent such as dichloromethane, acetone, *etc*. The drug in the solid form is then dispersed in the polymer solution with high-speed 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 and leads the formation of the microspheres in a size range of 1-100 μm. Microparticles are separated from the hot air by cyclone separator whereas the trace of solvent is removed by vacuum drying6.

Solvent Evaporation: Solvent evaporation involves the formation of an emulsion between polymeric solution and an immiscible continuous phase, whether aqueous (o/w) or non-aqueous.

The whole process takes place in a liquid manufacturing vehicle phase. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dispersed in the coating polymer solution. Core materials may be either water-soluble or water-insoluble materials. With agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is dispersed in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules will form [7].

Single Emulsion Technique: The natural polymers are dispersed in an aqueous medium followed by dispersion in a non-aqueous medium like oil. Then, the cross-linking of the dispersed globule is carried out either by means of heat or by using the chemical cross-linkers. The chemical cross-linking agents used are glutaraldehyde, formaldehyde, acid chloride, *etc*. Heat denaturation is not suitable for thermolabile substances. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release and bio performance of the final multi particulate product. Excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation is the main demerit for chemical cross-linking [7, 8].

Double Emulsion Technique: In this method, the formation of the double emulsion of type w/o/w preparations can be formulated, and a double emulsion technique is suitable for water-soluble drugs, peptides, proteins, and the vaccines. In this method, both natural and synthetic polymers can be used. In this method, the aqueous protein solution is dispersed in a lipophilic organic continuous phase with the active constituent. The continuous phase generally consists of the polymer solution that eventually encapsulates the protein contained in the 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.

Then after the formation of double emulsion, the excess solvent can be removed either by a solvent evaporation method or by the solvent extraction method. A number of hydrophilic drugs like Luteinizing Hormone-Releasing Hormone (LH-RH) agonist, vaccines, proteins/peptides, and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction [8].

Phase Separation Coacervation Technique: Coacervates are defined as a method or a technique that decreases the solubility of the polymer in the organic phase which leads to the formation of a polymer rich phase called the coacervates. This technique is based upon the formation of coacervates in which the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes the first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of a polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size, and agglomeration of the formed particles [9]. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins, the formed polymerizes 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 [10].

Spray Drying and Spray Congealing: The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. 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 of 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 the feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillin. Thiamine mononitrate and sulpha ethyl thiadiazole are encapsulated in a mixture of mono and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however, leads to the formation of porous microparticles [11, 12].

Solvent Extraction: Solvent extraction method is used for the manufacturing of microparticles, which involves removal of the organic phase by extraction of the non-aqueous solvent. This method involves water-miscible organic solvents as isopropanol. The organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of the water, a ratio of emulsion volume to the water and the solubility profile of polymer [13].

Quassi Emulsion Solvent Diffusion: Controlled release microspheres of drugs with acrylic polymers can be manufactured by Quassi emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of drug, ethanol and polymer. The concentration of polymer is in order to enhance plasticity. At first, the internal phase is manufactured at 60 ℃ and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for two hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40 ℃ for a day [13, 14].

Applications of Microparticles in Drug Delivery System:

Ophthalmic Drug Delivery: Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydrogels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or

ointments, ophthalmic chitosan gel improves adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has a more targeted effect and allows lower doses of the drugs. In contrast, the polymer-based colloidal system was found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nano-particulate containing cyclosporine). The microparticulate drug carrier (microspheres) seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan [14].

Gene Delivery: Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. The non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production [15]. The polymer has been used as a carrier of DNA for gene delivery applications. Also, the polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Mac Laughlin *et al.* showed that plasmid DNA containing cytomegalovirus 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 [16].

Intratumoral and Local Drug Delivery: Intratumoral and local drug delivery strategies have gained momentum recently as a promising modality in cancer therapy. In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films were fabricated [17]. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. Polymer films containing paclitaxel were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study [18].

Oral Drug Delivery: The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of the polymer to form films may permit its use in the formulation of film dosage forms as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications [16, 17].

Nasal Drug Delivery: The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer-based drug delivery systems, such as microspheres, liposomes, and gels, have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to 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 diphtheria Toxoid incorporated into chitosan microparticles results in a protective systemic and local immune response against Diphteria Toxoid with enhanced IgG production. Nasal formulations have induced significant serum IgG responses similar to secretory IgA levels, which are superior to parenteral administration of the vaccine. Nasal absorption of insulin after administration into polymer powder was found to be the most effective formulation for nasal drug delivery of insulin in sheep compared to chitosan nanoparticles and chitosan solution [19].

Buccal Drug Delivery: Polymer is an excellent polymer to be used for buccal delivery because it has muco / bioadhesive properties and can act as an absorption enhancer. Buccal tablets based on chitosan microspheres containing chlorhexidine diacetate gives a prolonged release of the drug in the buccal cavity improving the antimicrobial

activity of the drug [20]. Polymer microparticles with no drug incorporated have antimicrobial activity due to the polymer. The buccal bilayered devices (bilaminated films, palavered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic crosslinking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity [21, 22].

Gastrointestinal Drug Delivery: Polymer granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone [19, 23]. Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery system. The release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 h *e.g.,* Metoclopramide and glipizide loaded chitosan microspheres [18].

Peroral Drug Delivery: As polymer and most of its derivatives have a mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many perorally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs. A protective effect for polymer embedded peptides towards degradation by intestinal peptidases can be achieved by the immobilization of enzyme inhibitors on the polymer. The mucoadhesive property of polymer gel can be enhanced by threefold to sevenfold by admixing chitosanglyceryl mono-oleate. Drug release from the gel followed a matrix diffusion controlled mechanism. Nifedipine embedded in a chitosan matrix in the form of beads have prolonged release of drug compared to granules [24].

Vaginal Drug Delivery: Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly improved, and this is found to increase the residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controller drug release in the treatment of mycotic infections. Vaginal tablets of polymer containing metronidazole and acriflavine have shown adequate release and good adhesion properties [22].

Transdermal Drug Delivery: Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems, and wound dressings. Polymer gel beads are a promising biocompatible and biodegradable vehicle for treatment of local inflammation for drugs like prednisolone, which showed sustained release action improving therapeutic efficacy. The rate of drug release was found to be dependent on the type of membrane used. A combination of chitosan membrane and chitosan hydrogel containing lidocaine hydrochloride, a local anesthetic, is a good transparent system for controlled drug delivery and release kinetics [25].

Colonic Drug Delivery: Polymer has been used for the specific delivery of insulin to the colon. The chitosan capsules were coated with an enteric coating (Hydroxypropyl methylcellulose phthalate) and contained, apart from insulin, various additional absorption enhancers and enzyme inhibitor. It was found that capsules specifically disintegrated in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence of a bacterial enzyme, which can degrade the polymer [26].

Multi Particulate Delivery System: H. Steckel and F. Mindermann-Nogly have prepared chitosan pellets using the extrusion/spheronization technology. Microcrystalline cellulose was used as an additive in concentrations ranging from 0-70%. The powder mixture was extruded using water and dilutes acetic acid in different powder to liquid ratios. The study showed that chitosan pellets with a maximum of 50% (m/m) could be produced with demineralized water as granulating fluid. The mass

fraction of chitosan within the pallets could be increased to 100% by using dilute acetic acid for the granulation step. Other potential applications include: Conversion of oil and other liquids to solids for ease of handling, taste and odor masking, to delay the volatilization, Safe handling of toxic substances [26, 27].

Recent Advancement in Microsphere:

Important Utilizations of Chitosan Polymer Cholesterol-Lowering Effects: Chitosan and cellulose were used as examples of fibers with high, intermediate, and low bile acid-binding capacities, respectively. These rum cholesterol levels in a control group of mice fed a high fat/high cholesterol diet for 3 weeks increased about 2-fold to 4.3 mM, and inclusion of any of these fibers at 7.5% of the diet prevented this increase from occurring. In addition, the amount of cholesterol accumulated in hepatic stores due to the HFHC diet was reduced by treatment with these fibers. The three kinds of fibers showed similar hypo-cholesterolaemic activity; however, cholesterol depletion of liver tissue was greatest with cholestyramine. The mechanisms underlying the cholesterol-lowering effect of cholestyramine were: Decreased cholesterol (food) intake, decreased cholesterol absorption efficiency and increased faecal bile acid and cholesterol excretion. The latter effects can be attributed to the high bile acid-binding capacity of cholestyramine. In contrast, incorporation of chitosan or cellulose in the diet reduced cholesterol (food) intake but did not affect either intestinal cholesterol absorption or faecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterol-lowering [28, 29].

Increase Stability of Drug: Chitosan polymer is used to increase the stability of the drug in which the drug is complexed with chitosan and make a slurry and kneading for 45 min until dough mass. This dough mass is passed through sieve no. 16 and make a granule is completely stable at different condition [28].

Orthopedic Patients: Chitosan is a biopolymer that exhibits osteoconductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive coating to improve Osseointegration of orthopedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration [30].

Cosmetics Industry: Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantial, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. *e.g.*; Hair setting lotion, Oxidation Hair-coloring Com-position, Hair toning Composition, Skin Cream, Hair treatment Composition, Gel-form [30, 31].

Dental Medicine: Chitosan has been recognized to accelerate wound healing to attain an aesthetically valid skin surface, and to prevent excess scar formation. In dental medicine, chitosan is also applied as a dressing for oral mucous wound and a tampon following the radical treatment of maxillary sinusitis. Furthermore, it is being investigated as an absorbing membrane for periodontal surgery. Chitosan has a variety of biological activities and advertised as a healthy food that is effective for improvement and/or cares of various disorders, arthritis, cancer, diabetes, hepatitis, *etc.* [31, 32]

Chitosan as Permeation Enhancer: It has been reported that chitosan, due to its cationic nature is capable of opening tight junctions in a cell membrane. This property has led to a number of studies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides. Because the absorption enhancement is caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability [28, 31].

Chitosan as Mucoadhesive Excipient: Bio-adhesivity is often used as an approach to enhance the residence time of a drug in the GI tract, thereby increasing the oral bioavailability. A comparison between chitosan and other commonly used polymeric excipients indicates that the cationic polymer has higher bioadhesive compared to other natural polymers, such as cellulose, Xantham gum and starch [31, 32].

Effect of Chitosan:

Citric Acid Ratio on Drug Release: It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmotic agents for the release of the water-insoluble drug. Due to its high molecular weight and a linear unbranched structure, chitosan is completely biodegradable, toxicologically harmless and low cost and exhibits an excellent gelation characteristic. Hence, the potential for chitosan to be used as a polymeric osmotic agent in the osmotic pump is obvious. The hydration and gel formation of chitosan is very much dependent on the pH of the surroundings. It is insoluble at an alkaline and neutral pH but soluble at the acid condition. Upon dissolution, amine groups of the polymer become protonated, forming a resultant viscous and soluble polysaccharide. Inclusion of citric acid as a pH-regulating excipient in the developed formulations was expected to decrease the micro-environmental pH of the core to a suitable level at which chitosan could form appropriate viscous gelling solution and hence, to enhance the osmotic pressure of core tablets [33].

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CONCLUSION: We have concluded from this review that in the microspherical drug delivery system the microspheres can be prepared by different techniques along with its pharmaceutical application for delivering the definite amount of drug at a controlled and predetermined rate. Micro spherical drug delivery system includes targeted, oral, topical, sustained and naso-pulmonary therapy, *etc*. Microspheres can give much more therapeutic and commercial benefits by improving safety and reducing the toxicity of potent medication. Currently, pharmaceutical companies are introducing new products related to micro spherical drug delivery systems in the market which may produce a better therapeutic response than conventional drug delivery. The development of drug delivery technologies can be applied for solving problems regarding pharmaceutical, biopharmaceutical, and pharmacokinetic aspects thus, the delivery systems are growing and accepting worldwide for its better utilization.

ACKNOWLEDGEMENT: I would like to acknowledge Dr. Pallavi Rai for her valuable and altruistic guidance and support.

CONFLICTS OF INTEREST: There are no conflicts of interest.

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How to cite this article:
Rastogi H, Pandey AK and Purkyustha HD: Micropharmaceutical's - a review on microspherrical applications and recent advances. Int J Pharm Sci & Res 2020; 11(7): 3101-08. doi: 10.13040/IJPSR.0975-8232.11(7).3101-08.