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Dinesh Kumar
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, India.

Surender Verma
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, India.

Kamal
Assistant Professor, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, Haryana, India.

Correspondence
Kamal
Assistant Professor, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, Haryana, India.

Microspheres: Different approaches in the utilization of microparticulate system- A review

Dinesh Kumar, Surender Verma and Kamal

Abstract
Microspheres are the colloidal drug delivery system. Microspheres are characteristically free-flowing powders consisting of proteins/synthetic polymers that are biodegradable in nature and ideally having a particle size less than 200mm. Biodegradable microspheres can be utilized to direct drugs to certain organs through capillary blockade. Its success depends on the size of the microspheres used and on the mode of administration (intravenous/intra-arterial). The microspheres can also be used for targeting anticancer drugs to the tumor. This review represents the various dimensions and prospective for different areas where microspheres can be used to function as a great drug delivery system. The major categories and types of micro particulate system that can be utilized ranging from radioactive microspheres to floating microspheres for site targeted or sustained release, are being discussed in this review.

Keywords: Microspheres, different approaches, review

Introduction
Microspheres or microcapsules are multi-particulate systems, preferred over the conventional dosage forms like tablet and capsule because of their increased surface area, thus increasing the absorption of the drug, reducing the dosing frequency, and improving the patient compliance. Irritation commonly associated with topical therapies is one of the most significant factors contributing to lack of adherence and therefore therapeutic withdrawal [1]. The local application-site reactions may be linked to components of the formulation and/or to the active drug itself. Microspheres are formed through a quasi-emulsion solvent diffusion method. Conventionally, an organic internal phase consisting of drug, ethyl alcohol, polymer, and triethyl citrate (TEC)/trichloromethane is introduced to an external phase of distilled water and polyvinyl alcohol (PVA) that is allowed to emulsify and then is continuously stirred for two hours. This mixture is then filtered to obtain the microspheres. Another way of synthesizing microspheres is free radical suspension polymerization, solvent evaporation, ion gelation techniques [2].

Particle size, pore structure, diameter, volume, and release characteristics of the microspheres will determine the functional parameters. Particle size itself may influence the release rate of the active drug from the microsphere. The larger the particle size, the faster the release rate. In addition to enhanced tolerability, microsphere formulations provide the benefit of improved drug stability [3, 4]. With the advancement in drug delivery techniques, there was also a hike in the prospective of utilization of micro-particulate system in various drug delivery processes. Some of the important types of microspheres are discussed below:

1. Biodegradable microspheres
2. Colored microspheres
3. Cosmetics microspheres
4. Lipid microspheres
5. Magnetic microspheres
6. Mucoadhesive microspheres
7. Floating microspheres
8. Ocular microspheres
9. starch microspheres
10. Structural microspheres

Biodegradable Microspheres

For delivery of drugs that are highly toxic with low therapeutic index, microspheres are prepared by using some biodegradable polymers like bovine serum albumin. Such microparticles help to deliver highly toxic drugs such as Methotrexate (MTX) that causes toxicities like stomatitis, gingivitis, glossitis, ulceration, and bleeding of the mucous membrane when given orally and hematological effects like leucopenia, thrombocytopenia, anemia, hemorrhage from various sites in single-dose intravenous administrations, and also some hepatic toxicities by administering as conventional dosage forms [5]. Sustained and targeted delivery of MTX will reduce these toxicities considerably by maintaining a low and constant level of drug in the blood. Microspheres are reported to possess high specificity toward tumor sites and good controlled release properties were exhibited by using biodegradable polymers [7, 8]. Hence, it was envisaged to prepare microspheres of MTX using biodegradable carrier albumin and evaluate them for sustained release where a biphasic release pattern was observed with all the batches, which is a slow first phase followed by a rapid release from biodegradable polymer. The future prospective for such an approach would be the incorporation of maximum amount of drug in the microspheres followed by a sustained drug release.

Coloured Microspheres

In 1967, plastic radioactively labeled microspheres (RM) were introduced for the measurement of regional perfusion [8]. One year later, Makowski *et al*. introduced the reference blood withdrawal technique for the quantification of regional blood flow [9]. In 1969, Domenech *et al.* [10] first validated the use of RM for the measurement of regional myocardial blood flow (RMBF). Thereafter, this method has become the standard technique for the measurement of RMBF in various experimental settings. However, because of the precautionary measures needed to minimize radiation exposure, use of RM is restricted to specially licensed laboratories. Storage of microspheres, as well as disposal of radioactive waste, is expensive and an environmental hazard. To avoid some of these limitations inherent in the RM method, Hale *et al*. [11] proposed a method for measuring RMBF with nonradioactive, colored microspheres (CM). According to this technique, samples are digested by a combination of enzymatic and chemical methods. Aliquots of the microspheres trapped within a given sample are then counted in a hemocytometer by an investigator using light microscopy. Polystyrene microspheres are dyed with one of five different colors: white (Blankophor MAR), yellow (Resolin-Brillant-Gelb 1OGN 200%), violet (Resolin-Rot-Violett FBL 200%), and blue (Resolin-Brillant-Blau BGLN 200%) obtained from Bayer AG, Leverkusen, FRG; and red (Terasil Rot E-BST) obtained from CIBAGEIGY AG, Wehr, FRG. To test the stability of dye attachment to the microspheres in vitro, 5 x 105 CM of each coloured microsphere were suspended in 2 ml saline and stored each for 2 months [12]. This study demonstrates that RMBF can be accurately measured with a cost-effective, nonradioactive technique that currently allows up to five measurements in a single experimental preparation. This technique avoids all problems related to radioactivity and is cost effective. To avoid radioactivity, more time for dyeing of microspheres and for tissue and blood sample processing is required, that is, about 8 hours for preparing a batch of 100x 106 CM and about 20 hours for processing of 100 samples. Potentially, this time can be reduced by the future use of an autosampler in conjunction with the spectrophotometer. An extension for use of more colors is also conceivable. This technique enables laboratories without access to RM to measure RMBF and enables others to perform more sequential measurements.

Cosmetics Microspheres

Cosmetic Microspheres (CM) are semi-transparent, white, micron-sized spherical ceramic particles used as fillers/ texture enhancers in a variety of cosmetics formulations, including lipsticks, pressed and loose powders, mascara, hand lotions and more. Their spherical shape can give cosmetic formulations a silky-soft, luxurious feel, while helping to provide more consistent processing – and at a lower cost-in-use, compared to conventional premium fillers, such as boron nitride, PMMA, spherical silica and nylon microspheres [13]. The ceramic composition of cosmetic microspheres makes them non-absorbent, to maintain spread ability and help prevent formulations from drying out. It also allows higher pigment loading in products such as cream powders. Cosmetic microspheres offer an excellent balance of total and scattered Light Transmission properties, compared to conventional fillers such as PMMAs and silica, for creating a “soft focus” effect that can help optically blur skin lines and wrinkles, without creating a mask-like appearance. The spherical shape creates a low friction with a ball bearing effect that adds a silky feel and texture to cosmetic formulations. Easy dispersibility and rapid wetting enhances the production efficiency. These are inert and non porous with high loading potential that helps in a greater formulation flexibility. Moreover, they can improve cosmetic performance without adding any cost.

Lipid Microspheres

Targeting delivery of drugs to the diseased lesions is one of the most important aspects of Drug Delivery System (DDS). To convey a sufficient dose of drugs to the lesion, suitable carriers of drugs are needed. Lipid microspheres (lipid emulsion) have been developed, mainly in Japan, as excellent carriers of drugs. With advances in medicine and pharmaceutical science, many potent biologically active substances have been introduced into clinical practice. These substances include prostaglandins, cytokines and other biologically active polypeptides [14]. In contrast with hormones, these potent biological substances are often produced locally when needed and act locally in the body. Once they enter the systemic circulation, however, they are rapidly metabolized, to avoid adverse effects at distant sites. Prostaglandins are a good example of this. When prostaglandins are administered systemically, their pharmacological actions affect the whole body, and as a result, various adverse reactions develop. To transport a large amount of drugs, suitable carriers are needed. Liposomes are excellent drug carrier vehicles for DDS [15-17]. However, liposomes are relatively unstable and are not easily mass-produced. Lipid microspheres, with an average diameter of 0.2 pm, and consisting of soybean oil and lecithin (Fig. l), however, are widely used in clinical medicine for parenteral nutrition.

Lipid microspheres themselves are very stable and can be stored for up to two years at room temperature. They have no particular adverse effects, even at dose levels of 500 ml. regarding their distribution in the body, lipid microspheres, like liposomes accumulate in inflamed tissues and other lesions [18, 19]. Liposteroid has been marketed in Japan as well as in other countries. Lipo-flurbiprofen has also been marketed in Japan.

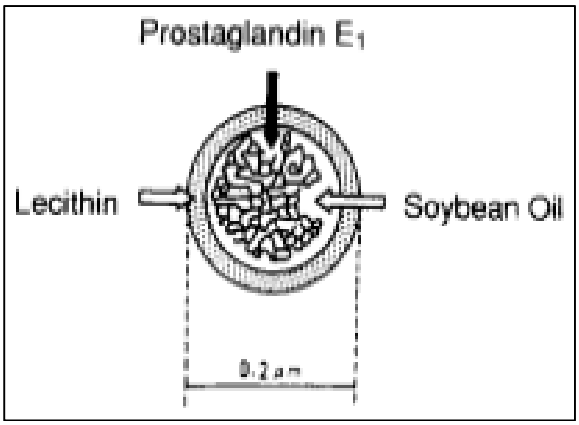

Fig 1

Magnetic Microspheres

In the recent years, due to requirements of clinical therapy, the development of appropriate carriers for controlled drug delivery is a challenge for researchers. Some of the proteins, peptides, drugs and oligonucleotides are unstable compounds that need to be protected from degradation in the biological environment. Magnetically controlled drug targeting is one of the various possibilities of drug targeting. This technology is based on binding targeted drugs with magnetic microparticles which concentrate the drug in the area of interest. One such approach was accomplished using cationic chitosan coating a negatively charged Fe_3O_4 microparticle by electrostatic adsorption and subsequent polymerization of acrylic acid onto CS coated Fe_3O_4 cores. The superparamagnetic property of polymer magnetic microspheres is critical for their application in biomedical and bioengineering fields which prevents polymer magnetic microspheres from aggregation and enables them to redisperse rapidly when the magnetic field is removed [20].

Mucoadhesive Microspheres

The success of microspheres is limited owing to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes [21]. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site [22-24]. Carbopol and sodium alginate as a polymer in the preparation of mucoadhesive microspheres represent good mucoadhesive and biodegradable properties.

Floating Microspheres

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal [25, 26].

Polymers that are used in the preparation of floating microspheres are basically gas generating agents such as Sodium bicarbonate, citric acid and tartaric acid, viscolysing agent such as Sodium Alginate, Carbopol 934 or swelling agents such as Hydroxypropylmethylcellulose.

Ocular Microspheres

Conventional drug delivery systems; which include solutions, suspensions, gels, ointments and inserts, suffer with the problems such as poor drainage of instilled solutions, tear turnover, poor corneal permeability, nasolacrimal drainage, systemic absorption and blurred vision. Nanocarrier based approaches seem to be most attracting and are extensively investigated presently. it has been reported that particulate delivery system such as microspheres and nanoparticles; vesicular carriers like liposomes, niosomes, pharmacosomes and discomes improved the pharmacokinetic and pharmacodynamic properties of various types of drug molecules [27].

The maximum size limit for microparticles for ophthalmic administration is about 5-10 mm above which a scratching feeling in the eye can result upon ocular instillation. That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application. Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs [28-29]. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan. Similarly Poly butyl cyanoacrylate nanoparticles, containing pilocarpine into collagen shields, showed greater retention and activity characteristics with respect to the controls. Nanospheres made up of poly lactic acid (PLA) coated with Poly Ethylene Glycol (PEG) shown better efficacy compared to conventional dosage form of Acyclovir for the treatment of ocular viral infections [30]. Microspheres of poly lacto glycolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/ spray-drying technique maximum size limit for microparticles for ophthalmic administration is about 5-10 mm above which a scratching feeling in the eye can result upon ocular instillation. That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application. Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan. Similarly Poly butyl cyanoacrylate nanoparticles, The entrapment of immunologically isolated cells with hollow fibres or microcapsules before their administration into the eye is called Encapsulated Cell Technology (ECT) which enables the controlled, continuous, and long-term delivery of therapeutic proteins directly to the posterior regions of the eye. The polymer implant containing genetically modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patients' eyes. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis [31].

Starch Microspheres

The ability of polysaccharides to form a network structure (gel), even at very low concentrations, constitutes one of their

most important functional properties. The formation of a 3D network structure (gelation) offers an effective means of increasing the chemical stability and mechanical properties of the system [32-34]. A wide range of modification mechanisms that can be applied to starches is known. These include self-association (induced by changes in pH, ionic strength or physical and thermal means), complexation with salts and covalent crosslinking as used in the present study. Furthermore, starch is appealing to the area of drug delivery as it allows producing systems of a low toxicity that are biodegradable and very stable. Therefore, the cost-effectiveness of starch based products is another important attractive for the use of starch in drug delivery and other biomedical applications. In particular, starch microspheres have been widely investigated for different drug delivery applications. For instances, Illum *et al*. [35] reported on bioadhesive microspheres that could not be cleared easily from the nasal cavity. The half-life of clearance for starch microspheres was in the order of 240 min as compared to 15 min for the control formulations. If gentamycin was administrated in combination with starch microspheres, a significant increase in bioavailability was obtained. [36] Another example is the magnetic starch microspheres developed by Fahlvik *et al*. [37] for parenteral administration of magnetic iron oxide to enhance contrast in magnetic resonance imaging. This could be an interesting processing route to be used in the future to try to develop magnetic-responsive controlled systems for delivery of biological active substances.

Structural Microspheres

In recent years, the silica composite microspheres are widely used in many fields of colloid and material science because they exhibit special properties that are substantially different from those of bulk material. According to the distribution of silica in the composite microspheres, there are core-shell composite microspheres, scatter composite microspheres, and hollow microspheres, respectively. [38] The composite microsphere with core-shell structure is attracting a great deal of interest because of the diverse applicability of this material. Scha¨rtl focally reviewed the application of cross-linked core-shell particles especially as an optical tracer [39]. Hotta *et al*. synthesized the ordered macroporous silica by centrifuging silica-coated polystyrene spheres and then calcining the close-packed spheres [40]. Yang and Zhang prepared silica-coated polystyrene microspheres encapsulating quantum dots so that silica coatings provided a suitable surface for further conjugation of biomolecules [41]. Rolf *et al*. prepared highly charged inorganic/organic colloidal core-shell particles which not only are monodisperse and perfectly dispersed but also are easily modified and have a low refractive index [42].

Conclusion

Although topical drug therapy is associated with benefits, such as reduced risk of systemic side effects, certain drugs have a tendency to induce local irritation. Novel formulations have attempted to improve tolerability through various means, including the avoidance of irritating excipients, the incorporation of moisturizing ingredients into the vehicle base, and the use of controlled-release microsphere delivery. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body. Microsphere drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. The Microsphere offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action. In future by combining various other approaches, Microsphere technique will find the vital place in novel drug delivery system.

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