



Microspheres as a platform for drug delivery

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ABSTRACT

Microspheres are promising drug delivery system with a particle size ranging from 1- 1000 micrometer. Microspheres have relatively small particle size and efficient drug loading capacity. They have many advantages as a drug carrier especially extended drug effect and selective targeting of anticancer drugs for tumor cells. Microspheres have different types and can be formulated via several techniques allowing variety in their application as a drug delivery platform. Microspheres can be loaded with different types of drugs, they are biocompatible and can be prepared from biodegradable particles. Microspheres have been implemented for different routes of administration including buccal, oral, ocular and transdermal showing enhanced therapeutic effects. This review aims to highlight the advantages of microspheres, types of microspheres including (bioadhesive, floating, magnetic, radioactive and polymeric), different methods of preparation including (Single emulsion technique, Double emulsion method, Coacervation method, Spray drying technique, Polymerization techniques and Freeze Drying) and their pharmaceutical applications.

Keywords: [polymers, bioadhesive, floating, spray drying]

1. Introduction

Microspheres are spherical particles with very small diameter in the micron or nanometer range, consists of a biodegradable plastic polymer carrying drug or antibody for release when the shell is degraded.

Microspheres have many advantages as prolonged and constant therapeutic action, lower the dose frequency , lower GIT irritation, lower dose dumping effect, protection of drug against environment, extending biological half-life, Masking un acceptable taste and odor and enhancing bioavailability

Beside advantages, microspheres suffer from high expenses, Low reproducibility due to variations in the release rate from one dose to another, Parental delivery of microspheres which can lead to interaction with the blood component and unavailability of being crushed or chewed..

Types of microspheres

- Bioadhesive
- Floating
- Magnetic
- Radioactive
- Polymeric

Bio-adhesive microspheres

Bioadhesive microspheres are formulated utilizing polymers which on hydration inside body can adhere to the targeted area for sufficient time delivering the drug to it. (Gurunath Dhadde Indrayani D Rault, Hanmant Mali et al., 2021)

Floating microspheres

Floating microspheres are hollow microspheres depend in their action on keeping bulk density of the drugs loaded in them lower than that of the gastric. This give them the advantage on extending the drug release for long periods as they can float on the gastric liquids surface(Najmuddin et al., 2010)

Magnetic microspheres

Magnetic microspheres depends in their action on targeting the drug formulated with very small magnetic particle to the targeted areas using an external magnetic source. They can move across capillaries without causing an esophageal occlusion due to their very small size. They are potential in treating magnetic hyperthermia in tumors (Joshi et al., 2010).

Radioactive microspheres

Radioactive microspheres are α emitters, β emitters, γ emitters from one or more radio-nuclides. They are injected in the veins that are linked to the targeted organ so, they are used for targeting radiation to a specific area without affecting the surrounding areas (Yadav et al.,2008) .

Polymeric microspheres

polymeric microspheres are classified based on the polymer type whether it is natural or synthetic polymer.

Natural polymeric microspheres

They are formulated using natural polymers as starch, agarose and poly dextran. They are characterized by being biodegradable, biocompatible, bioadhesive and also prolonged residence time due to its ability of swelling upon contact with aqueous medium resulting in gel formation. In spite of that, the drug loading is a complex technique and the drug release rates are difficult to be controlled (Saralidze et al., 2010).

Synthetic polymeric microspheres They are safe and biocompatible polymers and are commonly used in many clinical application. But they have disadvantages in migration possibility away from injection site which can result in embolism and organ damage.11. they can be biodegradable as Lactides or non biodegradable as Poly methyl methacrylate (PMMA) (Trivedi et al., 2008).

2. Method**2.1 Methods of preparation of microspheres****2.1.1. Single emulsion technique**

This method suits natural polymeric microspheres where aqueous solution or suspension of the natural polymers are added to the non-aqueous medium. Then, cross-linking of the dispersed globules can be achieved thermally or chemically using formaldehyde (Vyas and Khar, 2010; Trivedi et al., 2008).

2.1.2. Double emulsion method

This method is most commonly used for oral controlled release water soluble drugs. Firstly, the drug is dissolved in the aqueous phase of the primary (o/w) emulsion then, homogenization followed by addition of the external aqueous phase which is PVA solution.

2.1.3. Coacervation method or phase separation method

This method can be used for both hydrophilic and hydrophobic drugs producing reservoir type in which the drug is encapsulated inside polymer shell and matrix-type the drug is soluble within the polymer phase subsequently. Coacervation is brought via subjecting the biphasic system to conditions (Salt addition, Temp. Change, Incompatible polymer addition) which decrease the solubility of the polymer in the organic phase to produce coalescence of the polymer (Li et al., 1998) .

2.1.4. Spray drying technique

In this method microspheres are produced by dispersing the drug in volatile organic solution containing the polymer followed by direct exposure to hot air for atomization of the dispersion and solvent evaporation. The formed microspheres can be separated lately from hot air by using cyclone separator and dried using vacuum dryer (Mathew et al.,2008)

2.1.5. Polymerization techniques:

Polymerization can be either normal or interfacial

2.1.5.1. *Normal polymerization: • It depends on heating monomers with the initiator or catalyst. If these monomers are directly heated along with the initiator it is called bulk polymerization. If the monomers are dispersed as droplets in a continuous aqueous phase and the droplets contain an initiator this is called suspension polymerization. If the initiator is maintained in the aqueous phase it is called emulsion polymerization.*

2.1.5.2 *Interfacial polymerization: It in this type of polymerization, different monomers at the boundary between the two immiscible liquid interacts and produce polymeric film encapsulates the dispersed phase.*

2.1.6. Freeze Drying

This method depends on sublimation of the emulsion where the continuous organic phase of the emulsion is frozen and removed at low temperature and pressure so, the polymer and drug particles are separated.

2.2. Mechanism of drug release from microspheres

Drug release from the microsphere can happen through any of the following mechanisms or combination of more than one including diffusion, polymer degradation, hydrolysis or erosion.

2.3. Characterization of microspheres

2.3.1. *Particle size analysis: the morphological characters of microspheres are mostly determined by conventional light microscopy (LM), scanning electron microscopy (SEM) and transmission electron microscope(TEM). scanning electron microscopy and transmission electron microscope are better than light microscopy as they provide higher resolution power giving more details of the microspherical surface.*

2.3.2. *The flow properties :The flow properties can be examined via determining the carr's compressibility index , and resting angle of repose.*

2.3.3. *Thermal analysis Thermal analysis techniques employ organized changes in temperature and analyze changes in heat and enthalpy.*

2.3.4. Drug Entrapment Efficiency

The total entrapment of drugs in the microspheres can be calculated through the following equation,

$$\% \text{ Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100$$

2.3.5. Density Determination:

multi-volume cyclometer is used for density measurements.

2.3.6. Isoelectric Point

Isoelectric point can be concluded from electrophoretic mobility of microspheres recorded by micro electrophoresis.

2.3.7. In-vitro Methods:

Release patterns of microspheres in dissolution media are recorded via using Dissolution apparatus.

2.3.8. Solubility determination

Solubility of microspheres can be determined by adding excess amount of drug loaded microspheres in ml water in screw capped glass vials and use mechanical shakers for shaking the mixture for two hours. Then, filter the mixture and determine the

Applications

1. Buccal Drug Delivery

Polymeric microspheres are superior for buccal delivery because they have mucoadhesive properties improving drug absorption. microparticles of diclofenac sodium prepared by double-emulsion method showed better retention of diclofenac in mucosa (Jelvehgari et al., 2014).

2. Transdermal Drug Delivery

sodium alginate microspheres prepared by emulsification method and incorporated into transdermal patch exhibited controlled release of Flurbiprofen with non- fickian diffusion as release mechanism (pola et al., 2010). sinapine thiocyanate transdermal delivery from gelatin microspheres and hyaluronic acid microneedles for treatment of allergic asthma in guinea pigs was more efficient when compared with traditional subcutaneous application (Feng et al., 2022)

3. Microspheres used in cancer treatment

Microspheres are very potential in cancer treatment due to their selectivity for tumor cells so avoiding side effects on normal cells. Aclitaxel-loaded PLGA microspheres showed significant inhibition of lung tumor (Zhan et al., 2019). 5-fluorouracil microspheres with a mean size of 45 μm implanted by stereotaxy showed sustained release and effective treatment in Malignant gliomas brain tumors (Menei et al., 1999) .

4. ophthalmic drug delivery

Polymeric microspheres adhere well to corneal surface of the eye prolonging the precorneal drug residence time. lactide-co-glycolide microspheres enhanced the ocular bioavailability of Ofloxacin by 11.7-fold relative to the market eye drops (Sayed et al., 2015). chitosan microspheres prepared by emulsification technique prolonged release of acyclovir increasing its ocular bioavailability (Genta et al., 1997)

5. Oral Drug Delivery

Alginate-chitosan microspheres have been recorded to enhance oral delivery of protein drugs (Zhang et al., 2011). Ethyl cellulose-Carbopol microspheres enhanced the oral bioavailability of acyclovir and increased mean residence time in plasma compared to that of acyclovir suspension (Tao et al., 2009).

6. Colonic drug delivery

canagliflozin-loaded chitosan hyaluronic acid microspheres prepared by coacervation technique showed enhanced coloprotective effects (Nasr et al., 2022).

Conclusion

Microspheres as a platform for drug delivery are very promising due to high loading capacity, extended drug effect and targeting selectivity. They have been applied in variant delivery systems and targeted to different organs showing enhanced results relative to other delivery systems

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