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A Concised Review on Microspheres as Novel Drug Delivery System

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ABSTRACT

Microspheres are characteristically spherical and free flowing powders having particle size ranging from 1-1000 μm consisting of proteins or synthetic polymers. Microspheres are free flowing solid particle made up of biodegradable and non-biodegradable components Microspheric drug delivery system has wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. Microspheres form an essential part of novel drug delivery systems. Microspheres reduce the dosing frequency and improve patient compliance by designing and evaluating Sustained Release microspheres for effective control of many chronic diseases. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. A Microsphere has its drug dispersed throughout the particle i.e. the internal structure is a matrix of drug and polymeric excipients. The objective of this article is to emphasize on the principles underlying the development and evaluation of microspheres as a controlled and targeted drug delivery system.

Keywords: Microspheres, Microcapsules, Cross linking agents, Polymeric matrix, Dispersion medium

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INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (1µm to1000 µm)[1]. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix[3]. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release[2].

Advantages

- Masking of odour or bitter taste.
- Improve physical stability and gastric enzyme stability.
- Better process ability (improved flowability, dispersability).
- Reduced dose size.
- Improve bioavailability.
- Microsphere provides increased therapeutic efficacy and prolonged duration of action.
- Microsphere provides controlled, sustained and targeted drug delivery.
- Microsphere can be injected into body because of small size and spherical shape[4,5].

Limitation

- Rate of controlled release dosage form may vary due to certain factors like intrinsic and extrinsic factors.
- There is difference in the rate of release of drug from one dosage from to another dosage form.
- Low drug loading (maximum of 50%) for controlled release parental
- Dumping of dose result in failure of therapy.
- Once injected it is difficult to remove the carrier completely from the body in case of
- Toxic effect or adverse effect.
- Parental delivery of microsphere may interact or form complexes with the blood component[6].

Materials used

Different polymers are used in microspheres. They are classified into two types: Synthetic polymers are divided into two types. Non-biodegradable and biodegradable polymers.

Synthetic Polymers: divided into two types;

1. Non-biodegradable

4,5- Acrolein, Glycidyl methacrylate, Epoxy polymers, etc.

2. Biodegradable

(6)-Polyanhydrides, Polyalkyl cyano acryalates Lactides and glycolides and their copolymers[7,8].

Natural materials: obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

i) Proteins (albumin, gelatin, collagen)

ii) Carbohydrate (starch, agarose, carrageenan)

iii) Chemically modified carbohydrates [poly (acryl dextran), Poly (acryl starch)][9,10]

Polymeric microsphere

The various types of polymers are used for preparation of microspheress e.g.

- Albumin microspheres
- Gelatin microspheres
- Starch microspheres
- Dextran microspheres
- Poly lactide and poly glycolide microspheres
- Polyanhydride microspheress and polyphosphazene microspheres
- Chitosan microspheres
- Polysaccharides or lipid cross linked chitosan microspheres
- Carrageenan microspheres
- Alginate microspheres
- Poly (alkyl cyanoacrylate) microspheres[11].

Method of preparation [12]

- Single emulsion technique
- Double emulsion technique
- Polymerization technique
- Normal polymerization
- Interfacial polymerization

- Phase separation coacervation technique
- Spray drying and spray congealing
- Solvent extraction
- Quassi emulsion solvent diffusion
- Wax coating & hot melt

Single emulsion technique There are several Proteins and carbohydrates, which are prepared by this technique. In which the natural polymers are dissolved in aqueous medium and the followed by dispersion in oil phase i.e. non-aqueous medium. That is the first step in Next step cross linking is carried out by two methods.

Cross linking by heat: by adding the dispersion into heated oil, but it is unsuitable for the thermo labile drugs.

Chemical cross linking agents: by using agents i.e. formaldehyde, di acid chloride, glutaraldehyde etc. but it is having a disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) is added to Liquid paraffin containing a surfactant resulting formation of w/o emulsion. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25% solution as a cross linking agent.

Double emulsion technique

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase homogenization/vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres1 genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method[13].

Polymerization techniques Mainly two techniques are using for the preparation of microsphere are classified as:

Normal polymerization

In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients.

Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolve in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet[14].

Phase separation coacervation technique

It is the simple separation of a micro molecular solution into two immiscible liquid phases. In this process, the polymer is solubilized to form a solution. This process is designed for preparing the reservoir type system e.g. encapsulate water soluble drugs i.e. peptides, proteins etc. The principle of coacervation is decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, formation of dispersion of drug particles in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Matrix types preparations can also be prepared by this process for hydrophilic drug e.g. steroids, addition of non-solvent results in the solidification of polymer.

Spray drying and congealing

Spray drying and spray congealing methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or the cooling of the solution, the two processes are named spray drying and spray congealing respectively. 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 lead to the formation of small droplets or the fine mist from which the solvent evaporates leading to the formation of

microspheres in a size range 1-100µm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying[15].

Solvent extraction

Solvent evaporation method is used for manufacturing of micro particles, involves removal of the organic phase by extraction or non-aqueous solvent. This method involves water miscible organic solvents as isopropanol. 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. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer[15].

Quassi emulsion solvent diffusion

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the micro sponges[15].

Wax Coating and Hot Melt

In this technique polymer is disperse in suitable dispersion medium and slowly cooled to form the microspheres. The polymers which having low melting point fabricated into microspheres by this technique easily. For coating and coring of particle wax is use mostly. In which encapsulate the drug by dispersion in the molted wax. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin. Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid. Mostly Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics [15].

Physicochemical Evaluation Characterization

Particle size and shape

The most widely used procedures to visualize microspheres are conventional light microscopy (LM) and scanning electron microscopy (SEM). Light microscopy (LM) provides a control over

coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically**.** SEM provides higher resolution in contrast to the LM[16].

Fourier Transfom-Infrared Spectroscopy

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATR- FTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions[17].

Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (27+/-2 0C)
3. Oven temperature (40+/-2 0C)
4. Refrigerator (5 0C -80C).

It was carried out of a 60 days and the drug content of the microsphere was analysed[18].

Entrapment efficiency

Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water With the help of ultrasonic stirrer for 3 hr., and was filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.

$$\% \text{ Entrapment} = \text{Actual content/Theoretical content} \times 100$$ [19]

Angle of contact

The angle of contact is measured to determine the wetting property of a micron particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface. The angle of contact is measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres[20].

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using both rotating elements, paddle and basket. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance.

REFERENCES

1. Li, S.P., Kowalski C.R., Feld K.M., Recent Advances in Microencapsulation Technology and Equipment, Drug Dev Ind Pharm.1988; 14: 353-376.
2. Kataria Sahil, Middha Akanksha, Sandhu Premjeet, Ajay Bilandi and Bhawana Kapoor Microsphere: A Review ,International Journal Of Research In Pharmacy And Chemistry 2011; 1(4) ,1184-1198.
3. S.P.Vyas and R.K.khar "Targeted and Controlled Drug Delivery: Novel Carrier System 1st edition. CBS publication and distributors, New Delhi 2002;81-121.
4. Sahil Kataria, Middha Akansha, Sandhu Premjeet . Microsphere: A Review. International Journal of Research in Pharmacy and Chemistry 2011; 1(4):1184-1197.
5. Meena Kedar Prasad, Dangi J.S., Samal P.K. Recent Advances in Microspheres Manufacturing Technology. International Journal Of Pharmacy and Technology March 2011; 3:854-893.
6. Bansal Harsh, Kaur Simar Preet,Gupta A.K. et al. Microsphere : Methods Of Preparation And Applications, A Comparative Study. International Journal of Pharmaceutical Sciences Review and Research 2011; 10:69-78.
7. Kreuter J., Nefzger M., Liehl E., Czok R. And Voges. International Journal of Pharmaceutical Development & Technology R. J. Pharm sci.1984;72:11-46.
8. Margel S. and Wiesel E. MICROSPHERES: A NOVEL DRUG DELIVERY SYSTEM AN OVERVIEW J.polym.sci.1983; 22:145-149.
9. Sugibayashi K., Akimoto M., Moromoto Y., Nadai T. and Kato Y. Microspheres as a novel drug delivery system- a review International journal of chem tech research. 2009; 1(3):526-534.
10. Yoshioka T., Hashida M., Muranishi S. and Sezaki H.Specific delivery of mitomycin C to the liver, spleen and lung:nano and microspherical carriers of gelatin Int. J. pharm. 1981;8:131-141.
11. Khar, R.K., Vyas, S.P. Targeted and Controlled Drug Delivery- Novel Carrier Systems., 1st edition, CBS Publications and Distributors, New Delhi, 2002;417-418.

12. Alagusundaram M, Madh sudana C, Umashankar K. A Review on Microsphere Int J Chemtech Research 2009; 1(3): 526-534.
13. Nirav P, Dhagash P, Praful B, Vikaram P and Dharshan N. Microsphere as a novel drug delivery .Intr J Pharma Life Sci 2011; 2(8): 992-997.
14. Harsh B, Simar K, Atul G. Application and advancement of microsphere as controlled
15. delivery system: A review .Int J Pharma Sci Review and Research 2011; 10(1): 69-78.
16. Amol C, Jadhav KR, Kadam VJ. Int J Pharma Sci Review and Research A Review on Microsphere. 2010; 5(1), 8-17.
17. Kannan.K., Karar.K.P., Manavalan.R., Formulation and Evaluation of Sustained Release Microspheres of Acetazolamide by Solvent Evaporation Technique, J.Pharm.Sci & Res. 2009; 1 (1):36-39.
18. Kawashia Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyamas. Characterization of polymorphs of tranilast anhydrate and tranilast monohydrate when crystallized by two solvent change spherical crystallization techniques. J Pharma Sci., 1991; 81: 472–478.
19. Tamizharsi S., Rathi C.J., Rathi., Formulation and Evaluation of Pentoxyfylline-Loaded Poly (ε-caprolactone) Microspheres, Indian Journal of pharmaceutical Sciences. 2008; 70(3):333-337
20. Chowdary K.P.R., Suri B.J., Permeability of Ethylene Vinyl Acetate Copolymer Microcapsules: Effect of Solvents, Indian Journal of pharmaceutical Sciences. 2003; 65(1):62-65.