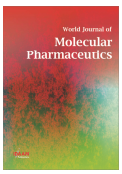

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REVIEW ARTICLE

Review on mucoadhesive microspheres

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ABSTRACT

With progress in biotechnology, combinational chemistry and genomics, a broad variation of new, potent and specific therapeutics being formulated. But because of common problems like poor stability, high potency and low solubility of drugs the drug delivery can affect the efficacy and potency for commercialization. Thus there is a need to develop more effective, safe methods and devices for drug delivery. Among the various methods and devices that have been utilized for controlled delivery, microspheres are one of the most important and common type of drug delivery system. Microspheres represent a most important part of novel drug delivery system by integrity of their desired carrier capacity and small size. Because of their short residence time, bioadhesive properties can be linked to microspheres to produce mucoadhesive microspheres. Bioadhesion is a condition in which two materials, at least one of which is biological in nature and are carry together for extended period of time by means of interfacial forces. It is a carrier linked drug delivery system in which particle size if microspheres range from 1-1000 µm in diameter they having a core of drug and outer layers are completely of polymers as coating materials. Mucoadhesive microspheres show merits like improved bioavailability of drug because of more surface to volume ratio, efficient absorption, also they increase the intimate contact of drug with the mucus membrane, targets the drug at the specific absorption site as well as sustained and controlled delivery of drug from dosage form. The aim of the present study is to provide an overview of several features and aspects of mucoadhesive microspheres based on different methods of preparation, use of various polymers, methods of evaluation of mucoadhesive microspheres and their approaches in drug delivery.

INTRODUCTION

Drug action can be enhanced by making a new drug delivery system, such as mucoadhesive microspheres drug delivery system. These systems stay closely connected to absorption tissues, mucus membrane and delivering the drug at the target site which leads to increasing bioavailability and both systemic as well as local effects [1]. Oral route of drug administration is established the most appropriate and desire route for drug delivery. Microspheres play most important part in particulate drug delivery system due to desired carrier capacity and small size. In this multiparticulate drug delivery system particle size varies from 1-1000 µm in diameter, although the progress of these microspheres is limited, because of their small residence time at the absorption site [2]. Therefore it would be convenient for providing an close or intimate contact of drug with absorbing medium and this can be accomplish by incorporating mucoadhesive properties to microspheres and developing mucoadhesive microspheres [3-5].

Mucoadhesion and Bioadhesion:

The term bioadhesion is a state in which two materials and at least one of which is biological in nature and these are held together by interfacial forces for longer period of time [6]. For drug delivery intension, the term bioadhesion incorporates attachment of drug to a specific biological site. The biological site can be a mucus layer on the surface of a tissue or epithelial tissue. If there is attachment between drug carrier and mucus layer, the situation is called as

mucoadhesion [7]. Bioadhesion should not be baffled mucoadhesion; in bioadhesion the substrate is attached to biological membrane and if substrate is attached to mucus cote or membrane then it is mucoadhesion [8].

Merits of Mucoadhesive Microspheres:

- Formulation stays longer at targeted site due to adhesion and intimate contact of drug with mucus layer and enhances bioavailability of drug by using less concentration of API for disease treatment.
- Reduce dosing frequency because of increased residence time together with controlled drug release.
- Provide an outstanding route, for systemic delivery of drugs with high level of first pass metabolism there by leads to improved bioavailability [1, 9].
- Additionally, dose related toxic effects may be minimized and cost reduction may be accomplished due to drug targeting at the disease site [10].
- Greater patient compliance and more convenience due to minimum dosing frequency of drug administration.
- Extended and sustained release of drug carrier.
- Wide and consistent distribution of drug all over the gastrointestinal tract which increases the drug absorption.
- Improving processability like flowability, dispersibility and solubility.
- Depletion in variation or fluctuation in steady state levels so therefore greater control of disease condition and minimum intensity of systemic and local toxic effects [1, 11].
- Drug medicament which are unsteady in the acidic environment are demolish by alkaline and enzymatic environment of intestine can be administered by this route e.g. sublingual, buccal, vaginal, oral [1].

Various Polymers Used In the Development of Mucoadhesive Microspheres:

Mucoadhesive polymers are soluble in water or water insoluble in which having swell-able network and connected together by cross linking agents [12]. Mucoadhesive properties of dosage form is generally reached by the use of water-soluble polymers in the formulations, which leads to better ability of dosage form to adhere to mucosal membrane [13].

A good polymer for mucoadhesive microspheres should have following properties [14, 15]:

- It should be non-irritant to the mucus layer.
- The degradation products of the polymers should be non-irritant and non-toxic.
- It should ideally form a strong non-covalent bond with mucosal call surface.
- It should stick very quickly to most of the tissue and should possess some target specificity.
- The cost of the polymer should not be to high so that the formulated dosage form remains competitive i.e. it should be economical.
- During storage of dosage form the polymer should not decompose.

Classification of Mucoadhesive Polymers:

There are several mucoadhesive polymers of synthetic as well as natural origin, which are classified in Table 1.

Table 1: List of mucoadhesive polymers

Synthetic polymers [16]	**Natural polymers** [17]
Hydroxy propyl methyl cellulose (HPMC)	Chitosan
Methyl cellulose	Pectin
Ethyl cellulose	Sodium alginate
Hydroxy propyl cellulose (HPC)	Locust bean gum
Hydroxy ethyl cellulose (HEC)	Xanthan gum
Sodium carboxy methyl cellulose (SCMC)	Guar gum
Poly ethylene oxide	Karaya gum
Poly hydroxyethylmethylacrylate	Tragacanth
Poly vinyl alcohol (PVA)	Gelatin
Poly vinyl pyrrolidone (PVP)	Lecithin
Poly(acrylic acid) polymers	Soluble starch

Methods of Development of Mucoadhesive Microspheres:

Mucoadhesive microspheres can be formulated by using various techniques like [16]:

1. Double emulsion method
2. Single emulsion method
3. Solvent removal method
4. Hot melt microencapsulation
5. Phase separation coacervation
6. Inotropic gelation
7. Spray drying
8. Solvent extraction method

1. Double Emulsion Method:
This method is first of all introduced by Ogawa Y *et al.* in year 1988 and this is most convenient and widely used method of preparation [18]. In double emulsion method aqueous solution of polymer and drug is added to the organic phase continuous stirring to get water in oil emulsion. This emulsion then transferred to huge volume of water which contains an emulsifying agent like PVA or PVP with constant stirring to get multiple emulsions (W/O/W) continue the stirring for evaporation of organic solvent which leads to solid microspheres. After that microsphere are washed and dried [19, 20].

2. Single Emulsion Method:
The microspheres prepared by natural polymers i.e. from carbohydrates and proteins are basically formulated by using single emulsion method [21].

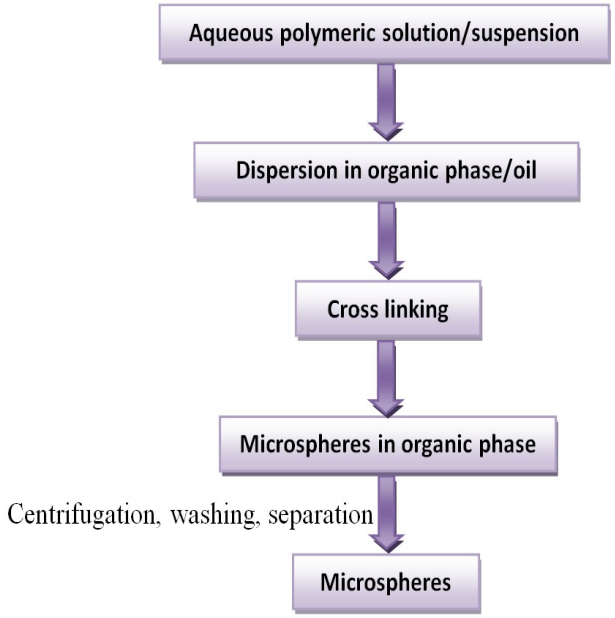

Figure 1: Schematic representation if single emulsion method.

3. Solvent Removal Method:
This method is desirable for those polymers which are water labile such as polyanhydrides. In solvent removal method of microencapsulation, the dosage form is dissolved and dispersed in a solution of chosen polymer in an organic solvent like methylene chloride. This mixture is then poured to oil phase containing emulsifying agent like Span 85 and organic solvent. Then petroleum ether is added into oil phase and stirred until solvent is extracted. Then formed microspheres dried in vacuum [20, 22].

4. Hot Melt Microencapsulation:
This method is also mostly comfortable for those polymers which are unstable in water. In this method initially polymer is melted and then with continues mixing solid drug particles are added. The formed mixture is then suspended in a immiscible solvent with continues stirring and heating. The temperature for heating is more than the melting point of the polymers so that to get stable emulsion. The resulting emulsion is chilled to solidify and dry polymer particles after that filter and wash the microspheres with petroleum ether [23].

5. Phase Separation Coacervation Method:
In this method aqueous or organic solution or drug is dispersed or dissolved in polymer solution that results into polymer rich droplets followed by washing and drying to form microspheres [23].

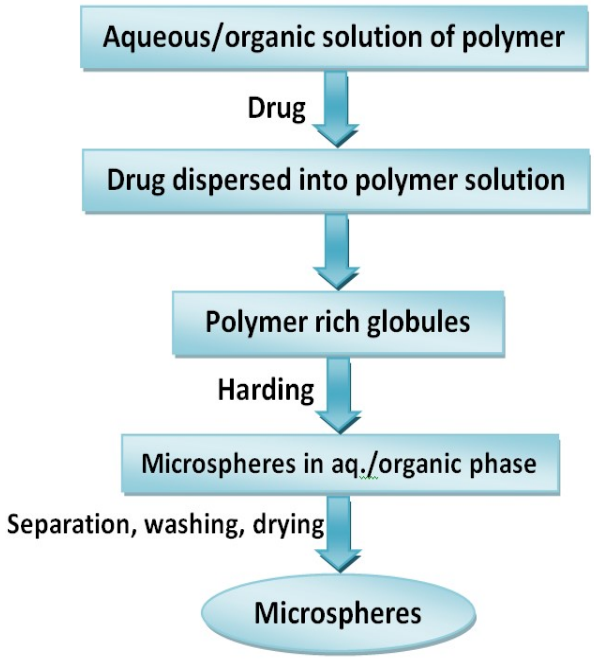

Figure 2: Phase separation method

6. Inotropic Gelation:
Inotropic gelation method was firstly developed by Lim F and Moss RD. In this method gel type of polymers like alginates are dissolved in aqueous solution which is then followed by addition of active ingredient in the mixture and eject the solution through needle to manufacture mini droplets which is then fall into calcium chloride solution with continuous stirring at minimum speed. Gelled microspheres are produced because of divalent calcium ion available in hardening solution which cross-links the polymers [5, 24].

7. Spray Drying:
In spray drying method first of all the whole polymer are dispersed or dissolved in a appropriate volatile organic solvent like acetone, dichloromethane etc. after that drug is dispersed in polymeric solution with maximum speed homonigezation [25]. The dispersion is then form very fine droplets in hot air and evaporates solvent instantaneously which leads to production of microspheres in the range of 1-100µm. Separation of microparticles from hot air is achieved by using cyclone separator while the solvent is evaporated by vacuum drying [26, 27].

8. Solvent Extraction Method:
In this method drug and polymer should be dispersible in organic solvent which leads to formation of an aqueous solution this aq. solution is extracted with water-miscible organic solvent to form microspheres in aq. solution [20, 21].

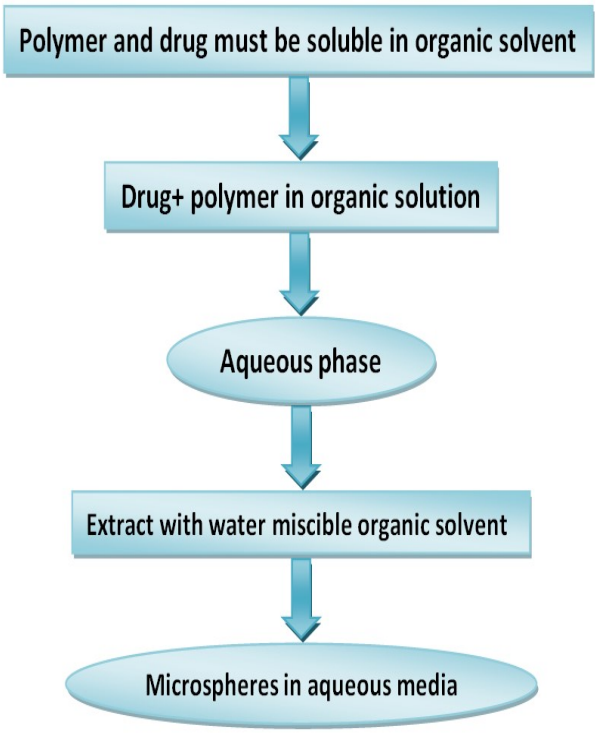

Figure 3: Solvent extraction method

Characterization of Mucoadhesive Microspheres:
1. Inter Activity Study by FTIR/TLC.
IR Spectroscopic Studies:
The IR spectra of microspheres and drug are performed. The similar peak analogous to the functional groups characteristics confirms that polymers and method of preparation doesn't affect drug stability.

Thin Layer Chromatographic Study:
TLC method plays important role in determination of drug stability in formulated microspheres. The Rf value of developed microspheres can be side by side compared with the Rf value of pure drug. The value shows the drug stability.

UV-FTIR:
The polymer drug connection and degradation of drug during microencapsulation can be determined by FTIR. The pellets of drug and potassium bromide are make ready by pressing together or compressed the powders at 20 psi all around 10 min on KBr-press and spectra are examined in the wave number range 4000-600 cm^{-1}. This study is determined on formulations, physical mixture, drug and empty microspheres [1, 21, 28].

2. Particle Size Determination of Formulated Microspheres:
Optical Microscopy:
Optical microscope is used to determine and calculate particle size. The measurement is concluded under 45^x objective and 10^x eye piece and about 100 particles are calculated.

3. Surface Morphology by (SEM) Scanning Electron Microscopy:
SEM plays very important role in determination of surface morphology of multiparticulate drug delivery system. In SEM method microspheres are directly mounted on slab of SEM sample with the help of two-sided gluing tape and coated with gold film at minimum pressure. Then scanning electron photomicrographs of drug loaded microparticles are taken. A very small quantity of microspheres is dispersed on gold stub this stab contains sample which is placed in SEM. At acceleration voltage of 20KV and assembly pressure of 0.6 mm Hg a scanning electron photomicrograph is taken [29-31].

4. Particle Size Analysis:
Dynamic light scattering technology is used to determine particle size distribution and particle size. In this method 100mL of water is taken, microspheres are dispersed in water and sonicated for 1min, to eliminate agglomerations. The mean volume diameter is noted and polydispersity is found out by the SPAN factor. A high-level value of SPAN shows a high polydispersity and wide distribution in size [32-34].

5. Swelling Index:

This method is employed for evaluation of sodium alginate microspheres. Various solutions are taken like distilled water, buffer solution of pH (1.2, 4.5, 7.4) and alginate microspheres (100mg) are put in a wire basket and place on above solution and swelling is permitted at 37°C and alteration in weight variation between weight due to swelling and starting weight of microspheres is measured by taking weight at regular intervals.

The swelling index of microparticles is calculated by using formula:

Swelling index = (mass of swollen microspheres – mass of dry microspheres/ mass of dried microspheres) 100 [35, 36].

6. Entrapment Efficiency [37, 38]:

The % encapsulation efficiency is calculated by using following equation:

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

7. Stability Studies:

Microspheres are placed into screw capped glass vessel and stored them at following circumstances:

- Room temperature (27+/-2°C)
- Oven temperature (40+/-2°C)
- Ambient humid condition
- Refrigerator (5°C-80°C) [39].

CONCLUSION

Mucoadhesive microspheres DDS have been acquiring a lot of importance of different researchers and scholars due to their benefits of sustained and controlled release action, and adaptability as a drug carrier. Mucoadhesive microspheres make sure that the continuation of effective plasma concentration over extended period of time by prolonging the drug release. This drug delivery system also expands the gastric residence time of drug in the GIT. Mucoadhesive drug delivery system is a assuring area for systemic delivery for orally ineffective drugs and attractive substituent for non-invasive delivery of potent peptide as well as perhaps protein drug molecules.

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