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Review Article

MUCOADHESIVE MICROSPHERES FOR CONTROLLED DELIVERY OF DRUGS

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ABSTRACT

Microspheres constitute an important part of the novel drug delivery system by virtue of their small size and efficient carrying capacity. Due to their long residence time, bioadhesive characteristics mucoadhesion can be coupled to microspheres to develop mucoadhesive microspheres. Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces. Microspheres are the carrier linked drug delivery system in which particle size is ranges from 1 to 1000 μm range in diameter having a core of drug and entirely outer layers of polymer as a coating material. Mucoadhesive microspheres have advantages like efficient absorption and improved bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, controlled and sustained release of drug from dosage form and exact targeting of drugs to the absorption site. The present study aims to provide an overview of various aspects of mucoadhesive microspheres, methodology of preparation of mucoadhesive microspheres, method of evaluation, and their applications in drug delivery.

Keywords: Mucoadhesion, Mucoadhesive microsphere, Controlled release.

INTRODUCTION

In contrast to the drug delivery system, the word novel is searching something new out of necessity. There are various approaches in delivering a therapeutic substance to the target site in a sustained and controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are defined as small, insoluble, free-flowing spherical particles consisting of a polymer matrix and drug and their sizes from about 50 nm to about 2 mm. Free-flowing powders and granulates are needed for a variety of industrial processes. These, however, do not always meet the exact standards which modern manufacturing demands of them, due to their varying grain, size, distribution, and odd shapes. These properties are detrimental to efficient processing and lead to agglomeration, inexact dosage, abrading with loss of material, or low reproducibility of castings. Pharmaceutical applications require highly reproducible dosage. These microspheres are free-flowing and roll with practically no friction that means there is no abrasion guaranteeing a dust-free environment. Administration of drugs in the form of microspheres usually improves the treatment by providing the localization of the active substances at the site of action and by prolonging the release of drugs [1].

Types of microspheres

Mucoadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, biodegradable polymeric microspheres, and synthetic polymeric microspheres [2].

Problems with other dosage form

- Powders and granules, do not always meet the exact standards varying grain size distribution and odd shapes
- These properties are detrimental to efficient processing and lead to agglomeration, inexact dosage, abrading with loss of material, or low reproducibility of castings
- Pharmaceutical applications require highly reproducible dosage and the controlled release of active agents, which cannot be achieved with conventional powders and granulates.

Mucoadhesion

Mucoadhesion is a topic of current concern in the design of current interest in the design of the drug delivery system. Mucoadhesive microspheres exhibit a prolonged residence time at the site of absorption and facilitates an intimate contact with the underlying absorption surface and thus improves or the therapeutic performance of drugs. Hence, uptake and bioavailability of the drug is increased. The frequency of dosing is reduced and patient compliance is increased [3,4].

Limitation of mucoadhesive microspheres [5]

Some of the disadvantages were found to be as follows:

- The difference in the release rate can be found from one dose to another
- The release rate may vary from a variety of factors like the rate of transit, food through gut, etc.
- Any loss of integrity in release pattern of the dosage form may lead to potential toxicity
- These types of dosage forms cannot be crushed or chewed
- The release from the formulations may get modified.

Mucous membranes [6]

Mucus membranes are the moist surfaces lining walls of various body cavities such as the gastrointestinal (GI) and respiratory tracts. Mucus is secreted by the goblet cells. Mucus is present either as a gel layer adherent to the mucosal surface or in suspended form or as a luminal soluble. The main components of all mucus gels are mucin glycoprotein, water, lipids, and inorganic salts. The mucus serves as a protective barrier and a lubricant also (Fig. 1).

Mechanism of mucoadhesion [8]

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucosal layer. Mucoadhesion is a complex phenomenon, which involves wetting, adsorption, and interpenetration of polymer chains. Mucoadhesion has the following mechanism:

- Intimate contact between a mucoadhesive delivery system and mucosal membrane (wetting or swelling phenomenon)
- Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (interpenetration, Fig. 2 shows the mechanism of mucoadhesion).

Characteristics of an ideal mucoadhesive polymer

1. The polymer and its degradation products should be non-toxic and should be non-absorbable from the GI tract
2. It should be non-irritant to the mucus membrane

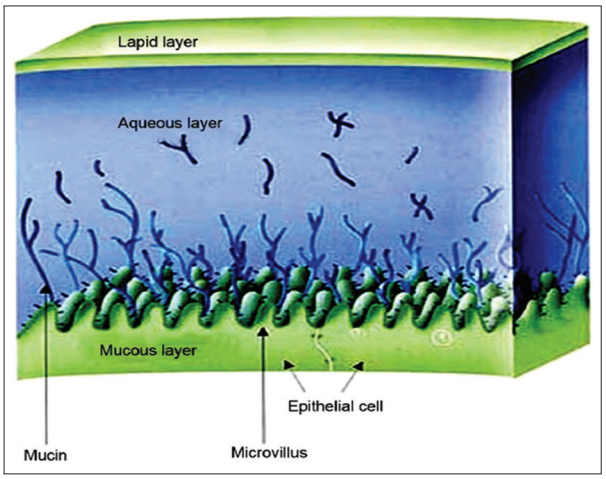

Fig. 1: Structure of mucous membrane [7]

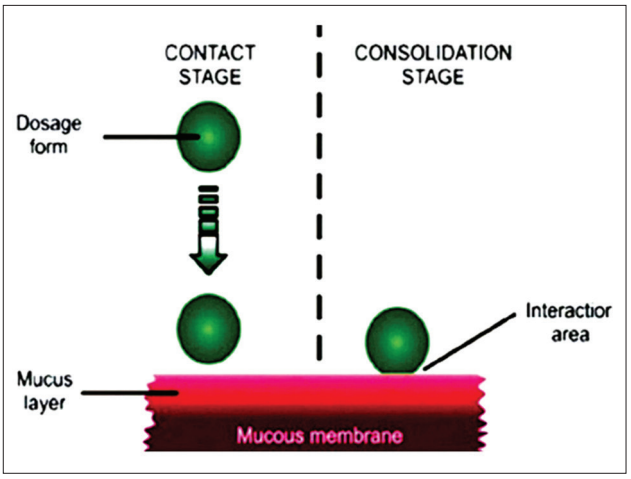

Fig. 2: Mechanism of mucoadhesion [7]

3. It should adhere quickly to most tissue and should possess some site specificity
4. It should allow easy incorporation of the drug and should offer no hindrance to its release
5. The polymers must not decompose on storage or during the shelf life of the dosage form
6. The cost of the polymer should not be high so that the prepared dosage form remains competitive (Table 1) [9].

Advantages of mucoadhesive microspheres [5,11]

- Controlled release for longer period of time
- Frequency is reduced and hence patient compliance is increased
- Constant release and hence no peaks and troughs in concentration of drug
- Low dose and hence toxic effect is less
- Targeting the tissue is possible
- Other organ toxicity is less.

Applications of microspheres

Some of the applications of microspheres are described in detail as following:

- Microsphere can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach
- It has been used to protect drugs from environmental hazards such as humidity, light, oxygen, or heat
- The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation
- Controlled and sustained release dosage forms
- Microsphere can be used to decrease the volatility
- Microsphere has also been used to decrease potential danger of handling of toxic or noxious substances
- The hygroscopic properties of many core materials may be reduced by microsphere
- Many drugs have been microencapsulated to reduce gastric irritation [12]
- Microsphere method has also been proposed to prepare intrauterine contraceptive device
- Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action
- Radioactive microspheres are used for imaging of liver, spleen, bone marrow, lung, etc., and even imaging of thrombus in deep vein thrombosis can be done [13].

Table 1: A short list of mucoadhesive polymers [10]

Synthetic polymers	Natural polymer
HPMC	Chitosan
Poly (acrylic acid) polymers (carbomers, polycarbophil)	Sodium alginate
PVP	Pectin
PVA	Locust bean gum
Poly hydroxyethyl methacrylate	Guar gum
Polyethylene oxide	Xanthan gum
Na CMC	Karaya gum
HEC	Gelatin
HPC	Tragacanth
EC	Soluble starch

HPMC: Hydroxy propyl methyl cellulose, PVP: Polyvinyl pyrrolidone, Na CMC: Sodium carboxymethyl cellulose, HEC: Hydroxyl ethyl cellulose, HPC: Hydroxypropyl cellulose, EC: Ethyl cellulose, PVA: Polyvinyl alcohol

METHODS OF PREPARATION

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by microencapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross-linking, drug of cross-linking, evaporation time, co-precipitation, etc. The various methods of preparations are:

Phase separation coacervation technique

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and a mismatched polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of 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. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize 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 [12].

Emulsion cross-linking method

In this method, the drug is dissolved in aqueous gelatin solution which is previously heated for 1 hr at 40°C. The solution is added dropwise to liquid paraffin while stirring the mixture at 1500 rpm for 10 minutes

at 35°C, results in w/o emulsion then further stirring is done for 10 minutes at 15°C The produced microspheres are washed respectively 3 times with acetone and isopropyl alcohol which then air dried and dispersed in 5 ml of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross-linking and then treated with 100 ml of 10 mm glycine solution containing 0.1%w/v of tween 80 at 37°C for 10 minutes to block unreacted glutaraldehyde. Examples for this technique is gelatin A microspheres.

Solvent evaporation

The processes are carried out in a liquid manufacturing vehicle. 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 dissolved or dispersed in the coating polymer solution. 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 disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix - type microcapsules are formed. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous (Fig. 3) [14,15].

Spray drying

In spray drying, 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

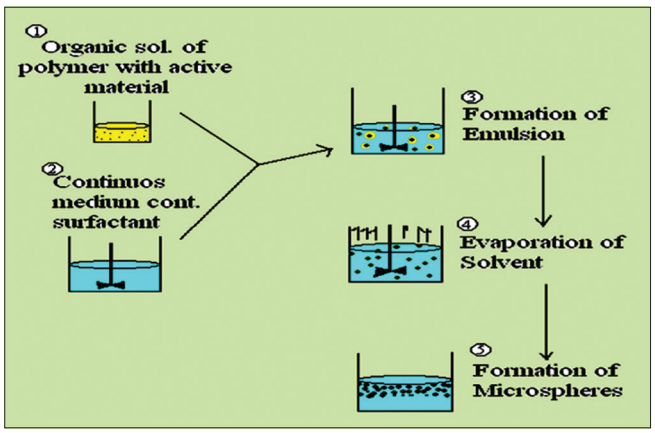

Fig. 3: Solvent evaporation method

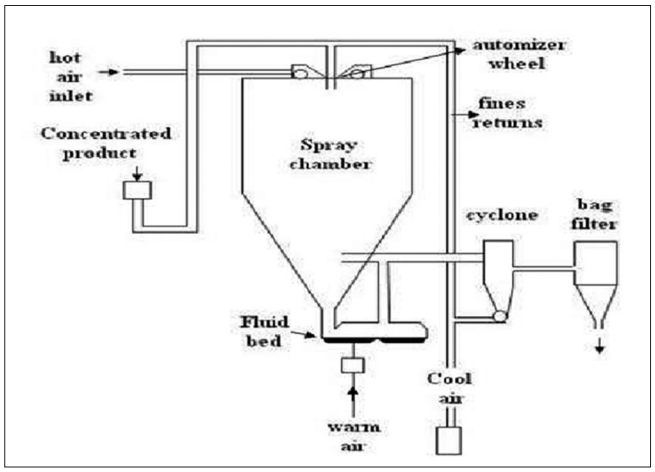

Fig. 4: Spray drying method [16]

leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 µm. Microparticles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid, and this leads to the formation of porous microparticles (Fig. 4).

Ionotropic gelation

This method was developed by Lim and Moss [17]. Using this method, microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce microdroplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres.

EVALUATION PARAMETERS

Particle size

It will be determined by optical microscopy [8].

Shape and surface morphology

It will be determined by scanning electron microscopy (SEM). It is a technique which gives surface morphology information. Data from the SEM, scanning tunneling microscopy, and the electron microscopy provides insight to the surface morphology of microspheres and the morphological changes produced through degradation of the polymer. Changes in the surface morphology occurring through degradation of the polymer can be studied by incubating the microspheres in the phosphate buffer saline at different intervals of time. It was found that microspheres with the coarser surface improve the adhesion through stronger mechanical interactions, while smooth surface of the microspheres leads to weak mucoadhesive properties [18,19].

Drug entrapment or capture efficiency

The entrapment efficiency of the microspheres or the percent entrapment can be determined by keeping the microspheres into the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected for determination of active constituents as per monograph requirement. The percent entrapment efficiency is calculated using following equation [8].

$$\text{Entrapment efficiency} = \frac{\%\,\text{Drug loading}}{\%\,\text{Theoritical loading}} \times 100$$

Where,

$$\%\,\text{Drug loading} = \frac{\text{Weight of drug in microsphere}}{\text{Weight of microsphere}}$$

Percentage yield

Percentage yield will be calculated to know about the efficiency of any method. Thus, it helps in selection of appropriate method of production [20].

$$\%\,\text{Yield} = \frac{\text{Total weight of microparticle}}{\text{Total weight of polymer}} \times 100$$

Degree of swelling

Degree of swelling illustrates the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption, which is a primary requirement for initiation of mucoadhesion [21]. Degree of swelling can be calculated by change of polymer volume (Wg–Wi).

$$\text{Degree of swelling} = \frac{W_g - W_i}{W_g} \times 100$$

Where,

W_i - Initial weight of microspheres,

W_g - Final weight of microspheres.

Mucoadhesion test

The mucoadhesive properties of the microspheres are evaluated by *in-vitro* wash-off test. A 1 cm by 1 cm piece of rat stomach mucosa was tied onto a glass slide (3 inch by 1 inch) using thread. Microspheres are spread onto the wet rinsed tissue specimen, and the prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the simulated gastric fluid USP (pH 1.2). At the end of 30 minutes, 1 hr, and at hourly intervals up to 10 hrs, the number of microspheres still adhering onto the tissue was counted [22].

Compatibility study

Differential scanning calorimetry (DSC)

It is a thermoanalytical technique in which the amount of heat required to increase the temperature of sample and reference is measured as a function of temperature. DSC thermograms of the microspheres will be recorded with DSC. Accurately weigh samples of the drug are taken in the pans. An empty aluminum pan can be used as a reference pan. The system will be purged with nitrogen gas. Heating will be done at a fix rate.

Fourier transform infrared (FTIR) spectroscopy

IR spectra of the microsphere will be recorded using FTIR spectrophotometer between the ranges by making a pellet of the samples with KBr. The resultant spectra will then compared with a standard reference and observe for any type of deviation from the standard.

Drug release studies

In general, standard IP/BP/USP dissolution apparatus is used to study *in-vitro* release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using rotating basket or paddle type dissolution apparatus [23]. The formulation will be taken in the baskets. The dissolution media (900 ml) will be taken in the beaker. The apparatus will be set at selected rpm. Sampling will be done at different time intervals. Drug release study will be performed for 12 hrs. Drug content will be determined using ultraviolet spectrometer [14,15,24].

CONCLUSION

Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. Mucoadhesive microspheres have been proved as a promising tool in delivery of drugs to a particular site in controlled manner, as they deliver the drug to a particular site for longer duration, the absorption of drug increased and hence, the bioavailability of the drug get increased. Therefore, it can be say that in future also mucoadhesive microspheres will play an important role in the development of new pharmaceuticals employing more advanced techniques and materials.

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