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Review Article

Mucoadhesive Microcapsules: A Review

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Abstract

Now a days trends in development of mucoadhesive drug delivery system (MDDS) is particularly appropriate than oral control release, for getting local systematic delivery of drugs in gastro intestinal tract (GIT) for an extended interval of time at a predetermined rate. The mucoadhesive system have a significant impact that draws further attention to potential benefits like improved bioavailability of therapeutic agents, extensive drug residence time at the site of administration and a comparatively faster drug uptake into the systemic circulation. The drug release from mucoadhesive multiparticulates is contingent on several types of factors comprising carrier need to produce the multiparticles and quantity of medication drug contained in them. Mucoadhesion is characterized by selected theories and mechanisms. Various strategies emergent in mucoadhesive multiparticulate drug delivery system (MMDDS) by *in-vitro* as well as ex-vivo description and characterization are also critically discussed. Apart from these, the primary focus during this review is to highlight current patents, clinical status, and regulatory policy for enhancement of mucoadhesive multi-particulate drug delivery system in the present scenario.

Keywords: Mucoadhesive Drug Delivery System; Therapeutic Agents; Mucoadhesion

Introduction

Mucoadhesion [1] is defined as the state in which two materials are adhered together, which implies attachment of a drug carrier system to a specific biological location. Adherence of the two materials is attained by contact between a pressure-sensitive adhesive and a surface (mucus membrane). These two surfaces are held together during the treatment period governed by different forces [2] which are later explained in theories of mucoadhesion section. For obtaining the best possible therapy, mucoadhesive multiparticulate system (MMS) is in capable of implementing a remedy at a pharmacologically better curative efficient rate to an enviable location for the essential stage. During MMS development, several strategies have been employed for site-specific mucoadhesion so as to provide improved and reproducible pharmacokinetics behavior [3]. Unlike conventional formulations, they are less dependent on the gastric emptying, resulting in less inter and intra-subject variability in GI (gastrointestinal) transit time. They are also better distributed and less likely to cause local irritation [4]. MMS does not allow dose dumping and possess uncompromising drug safety than the conventional dosage forms. Definitely, it implies to release the whole dosage into the stomach by such phenomenon that leading to pain and ulcer as well as condensed efficacy, because of an enteric-coated tablet having its film coating layer is completely altered and destroyed. On the other hand, in mucoadhesive delivery system, every particulate (single subunit) is made-up with the release characteristics [5] and any smash up only relates to the release behavior of subunit that has been concerned, which ultimately shows a tiny fraction of whole dose.

Mechanism of mucoadhesion [6]

The overall mechanism basically includes creation of mucoadhesive bond.

Step I (Contact stage): It involves the wetting and consequently swelling of the bioadhesive or polymer which takes place when a polymer is placed on the mucous membrane and results in to a deep contact. Here polymer swelling arises since the substances of polymer have an attraction for water.

Step II (Polymer chains and mucosal membrane Interpenetration): Just like that in the second phase, the polymer chains of mucoadhesive and the mucosal layer can interact and entangles by formation of adhesive bonds. Later on the contact has been recognized and perforation of the bioadhesive into the crevices of tissue exterior portion. Afterwards a correlation exists and bioadhesive chains impregnate with those of mucus. This phenomenon also had been occurred by force of bonds which rely on extent of perforation among two polymer groups.

Step III (Bonds creation among the entwined chains): Here both collectively recognized as consolidation stage. In this case, the weak chemical bonds can resolve at that time.

Factors affecting mucoadhesion [7]

- **Polymer related factors:** Several properties or characteristics of the active polymer play a vital role in mucoadhesion. Among them, polymer molecular weight, concentration, swelling, of polymer chains flexibility, and particular confirmation which may affect the mucoadhesion.
- **Environment associated factors:** pH of the polymer-substrate interface, functional strength and first contact time is able to influence the mucoadhesion.
- **Physiological factors:** Disease state and mucin turn over are the important physiological factors, which can also affect mucoadhesion.

Mucoadhesion theories [8]

Mucoadhesion will be able to outline and it is concerned with molecular interactions. The appropriate occurrence of mucoadhesion, these diverse forces of interactions is entirely narrated by the subsequent theories.

Electronic theory: Electronic hypothesis concerned to the principle that jointly mucoadhesive and biological materials acquire divergent electrical charges, thus when both resources make contact with, each other, then they swap over electrons foremost to construct a twofold electronic layer at the boundary, where the striking forces within this electronic twofold layer, found out the mucoadhesive potency.

Adsorption theory: As stated by the adsorption theory, the mucoadhesive machine coheres to the mucus by means of secondary chemical interactions, for example in Vander Waals forces and electrostatic attraction hydrogen bonds, or by means of hydrophobic interactions.

Wetting theory: The wetting theory implies to liquid systems which related to the current affinity to the surface in order to broadcast over it. Contact angle which is considered as one of the prime measurement tools for the creation of such kind of affinities. The universal rule indicates that the greater affinity correlates to lower the contact angle. The contact angle is supposed to be the identical or close up to zero in order to afford sufficient spreadability.

Diffusion theory: Diffusion theory narrated to the inter-perforation together of mucin as well as chains of polymer up to an adequate depth in order to build up a semi-permanent adhesive bond. Such a penetration rate absolutely be contingent on the several parameters such as nature of the mucoadhesive chains, diffusion coefficient, flexibility, motility in association with contact time.

Fracture theory: This is probably one of prime well-known theory in studies, associated to the mucoadhesion measurement by mechanical processes. Once complete formation of adhesion, it totally examine the force required to take apart both the surfaces.

Mechanical theory: By proper packing of the irregularities upon a mucoadhesive liquid coarse surface that finally taken as one of the important factor which leads to consideration of adhesion phenomenon by mechanical concepts. In addition to this, such coarseness or roughness steadily grows the interfacial area that's obtainable for interactions by the subsequent addition of squandering energy and it will be take into account of most significant observable fact of the procedure.

Mucosal docked vesicle theory: This theory implies about at specific mucosal epithelium vital absorption merely takes place. It may probable that the globules simply can interrelate with the mucous as well as mucosal basal membrane exclusively. Pharmacologically active drugs secluded, in the vesicle that may be liable to spread transversely to the basal membrane of mucosal layer and come into the blood stream for effective distribution at the time of occurrence of docking or releasing.

Mucoadhesive polymers [9-12]

To overcome the relatively short gastrointestinal (GI) time and improve localization for oral controlled or sustained release drug

delivery systems, bioadhesive polymers that adhere to the mucin/epithelial surface are effective and lead to significant improvement in oral drug delivery. Improvements are also anticipated for other mucus-covered sites of drug administration. Bioadhesive polymers find application in the eye, nose, and vaginal cavity as well as in the GI tract, including the buccal cavity and rectum. A mucoadhesion promoting agent or the polymer is added to the formulation which helps in promoting the adhesion of the active pharmaceutical ingredient to the oral mucosa. The polymer should be carefully selected on the basis of the following properties:

- **High molecular weight**: The polymer must have a high molecular weight to promote adhesion between the polymer and the mucus.
- **Optimum polymer chain length**: Polymer chain length must be optimum. It should be long enough to promote the interpenetration and short enough to facilitate diffusion.
- **High viscosity:** Mucoadhesive polymers should have properties which make them viscous upon application over the site.
- **Degree of cross linking:** It influences chain mobility and resistance to dissolution. Highly cross linked polymers swell in the presence of water and retain their structure. Swelling favours controlled release of the drug and increases the polymer/mucus interpenetration. Butas the cross linking increases, the chain mobility decreases which reduces the mucoadhesive strength.
- **Spatial conformation:** High molecular weight dextran molecules (19,500,000) have adhesive strength similar to that of polyethylene glycol (PEG) (200,000) as the helical conformation of dextrans shields lots of adhesive groups, particularly responsible for adhesion, distinct to PEG polymers having a linear conformation.
- **Flexibility of polymer chain:** This promotes the interpenetration of the polymer within the mucus network.
- **Concentration of polymer:** An optimum concentration is required to promote the mucoadhesive strength. It depends on dosage form, for example in the case of solid dosage form the adhesive strength increases with increase in the polymer concentration, whereas in the case of semi-solid dosage forms an optimum concentration of polymer is required beyond which the adhesive strength decreases.
- **Charge and degree of ionization:** The effect of polymer charge on mucoadhesion was determined after attaching few different chemical entities to chitosan and then mucoadhesive strength was evaluated. The hydrochloride salt of chitosan showed marked adhesiveness in comparison to plain chitosan. The attachment of ethylenediaminetetraacetic acid (EDTA) as an anionic group significantly increased the mucoadhesive strength. The complex of diethylenetriamine pentaacetic acid (DTPA) with chitosan exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low charge. Hence the mucoadhesive strength can be ordered as anion N cation N nonionic on the basis of surface charge.
- **Optimum hydration:** Excessive hydration leads to decreased mucoadhesive strength due to the formation of a slippery mucilage.
- **Optimum pH:** Mucoadhesion is optimum at low pH conditions but at higher pH values a change in conformation may occur, like a rod like structure can make polymer more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces.

Microcapsules

Microencapsulation is the process [13] of enclosing a substance inside a miniature called capsule. Microcapsules are a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core/internal phase, whereas the wall is sometimes called a shell/coating. The microcapsule size range from 1µ - 7 mm. All the 3 states i.e. solid, liquid and gases may be encapsulated which may affect the size and shape of capsules.

Methods of encapsulation [14-20]

Preparation of microcapsules as prolonged action dosage form can be achieved by various techniques under following headings.

- Coacervation phase separation
  - By temperature change
  - By incompatible polymer addition
  - By non-solvent addition
  - By salt addition
  - By polymer-polymer interaction
  - By solvent evaporation
- Multi orifice centrifugal process.
- Pan coating
- Air suspension coating

- Spray drying and spray congealing
- Polymerization
- Melt dispersion technique

Coacervation phase separation

Microencapsulation by coacervation phase separation is generally attributed to the national cash register (NCR) corporation and the patents of Green et.al. The general outline of the processes consists of three steps carried out under continuous agitation.

- Formation of three immiscible chemical phases.
- Disposition of the coating and
- Rigidization of the coating

By thermal change

Phase separation of the dissolved polymer occurs in the form of immiscible liquid droplets and if a core material is present in the system, under proper polymer concentration, temperature and agitation conditions, the liquid polymer droplets coalesce around the dispersed core material particles, thus forming the embryonic microcapsules. As the temperature decreases, one phase becomes polymer-poor (the microencapsulation vehicle phase) and the second phase. (the coating material phase) becomes polymer-rich.

By incompatible polymer addition

It involves liquid phase separation of a polymers coating material and microencapsulation can be accomplished by utilizing the incompatibility of dissimilar polymers existing in a common solvent.

By non-solvent addition

A liquid that is a non-solvent for a given polymer can be added to a solution of the polymer to induce phase separation. The resulting immiscible liquid polymer can be utilized to effect microencapsulation of an immiscible core material.

By salt addition

There are two types of coacervation: simple and complex. Simple coacervation involves the use of only one colloid, e.g. gelatin in water and involves removal of the associated water from around the dispersed colloid by agents with a greater affinity for water, such as various alcohols and salts. The dehydrated molecules of polymer tend to aggregate with surrounding molecules to form the coacervate. Complex coacervation involves the use of more than one colloid. Gelatin and acacia in water are most frequently used and the coacervation is accomplished mainly by charge neutralization of the colloids carrying opposite charges rather than by dehydration.

By polymer-polymer interaction

The interaction of oppositely charged poly electrolytes can result in the formation of a complex having such reduce solubility that phase separation occurs.

By solvent evaporation

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent, which is dispersed in volatile solvents, 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. In the case in which the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The solvent evaporation technique to product microcapsules is applicable to a wide variety of core materials. The core materials may be either water soluble or water insoluble materials.

Multiorifice - centrifugal process

The South-West research institute (SWRI) has developed a mechanical process for producing microcapsules that utilizes centrifugal forces to hurl, a core material particle through an enveloping microencapsulation membrane therapy effecting mechanical microencapsulation. Processing variables include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity of the coating material and the viscosity and surface tension of the core material. This method is capable of microencapsulating liquids and solids of varied size ranges, with diverse coating materials.

Pan coatings

The microcapsulation of relatively large particles by pan coating method has become wide spread in the pharmaceutical industry and solid particles greater than 600 μg in size are generally considered essential for effective coating. The coating is applied as a solution or as an automized spray to the desired solid core passed over the coated materials during coatings is being applied in the coating pans.

Air suspension coating

The process consists of the dispersing of solid particulate core materials in a supporting air stream and the spray coating of the air suspended particles. Within coating chambers, particles are suspended on an upward moving air stream. The design of the chamber and its operating parameters effect a recirculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution is spray-applied to the moving particles.

Spray drying and spray congealing

Spray drying and spray congealing processes are similar in that both involve dispersing the core material in liquified coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby relatively rapid solidification of the coating is affected. The principle difference between the two methods is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of solvent in which the coating material is dissolved. Coating solidification in spray congealing method, however, is accomplished by thermally congealing a molten coating material or by solidifying the dissolved coating by introducing the coating core material mixture into a nonsolvent. Removal of the nonsolvent or solvent from the coated product is then accomplished by sorption extraction or evaporation techniques.

Polymerization

The method involve the reaction of monomeric unit located at the interface existing between a core material and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a liquid or gas and therefore the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid or solid-gas interface e.g. microcapsules containing protein solutions by incorporating the protein in the aqueous diamine phase.

Melt-Dispersion Technique

In this technique the coating material is melted by heating upto 80°C. The drug is suspended in it and then emulsified in water containing emulsifying agent at 80°C under stirring. Microcapsules are formed as the temperature of the system reaches to room temperature.

Characterization of mucoadhesive microcapsules [21-23]

The parameters that are generally evaluated for characterization of microcapsules are:

- **Particle size and shape:** The most widely used procedure to visualize microcapsule are conventional light microscopy and Scanning electron microscopy (SEM). Both techniques can be used to determine the shape and outer structure of microcapsule. SEM provides higher resolution in contrast to the light microscopy. It allows investigation of the microsphere surfaces and after particles are cross sectioned, it can also be used for the investigation of double walled systems. Confocal laser scanning microscopy (CLSM) is applied as a nondestructive visualization technique, which allows characterization of structures not only on surface, but also inside particle.
- **Fourier transform - infrared spectroscopy: (FTIR**): FTIR is used to determine the degradation of the polymeric matrix of the carrier system, and also interaction between drug and polymer system if present.
- **Density determination:** The density of the microcapsule can be measured by using a multi volumepychnometer. Accurately weighed sample in a cup is placed in pychnometer, helium is introduced at a constant pressure in chamber and allowed to expand. The expansion results in a decrease in pressure within the chamber. From two pressure readings the volume and hence density of microcapsule can be determined.
- **Isoelectric point:** The micro electrophoresis is an apparatus used to measure electrophoretic mobility of microsphere from which the isoelectric point can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behavior or ion absorption nature of microsphere.
- **Capture efficiency:** The capture efficiency of microcapsule or the percent drug entrapment can be determined by allowing washed microcapsule to lyse. The lysate is then subjected to determination of active constituents as per monograph. The percent encapsulation efficiency is calculated using following equation
- **Contact angle:** The angle of contact is measured to determine the wetting property of microcapsule. It determines the nature of microsphere in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water surface by placing a droplet in circular cell mounted above the objective of inverted microscope. Contact angle is measured at 20°C within a minute of decomposition of microsphere.

Tensile strength test

Tensile force could be applied and maximum force required in detaching next to fracture and adhesion work can be determined via force displacement curve. Tensile strength is the strength re-

quired to detach the mucoadhesive cups perpendicularly from freshly excised bovine buccal mucosa. In this test stress is uniformly distributed all over the mucoadhesive joint. In a study, the large intestine mucus membrane of pig was attached to upper movable disc. Polymers were used in different concentrations. After determining the maximum force and work to detach, it was concluded that the tensile strength was dependent on the concentration as well as the type of polymer used.

Shear strength test

The shear strength of the adhesive cups and the force necessary for parallel detachment from freshly excised bovine buccal mucosa were determined by Metia and Bandyopadhyay using particularly designed apparatus. The mucoadhesive cup was fixed to a movable plastic strip by synthetic polymer. The other side of the cup was pressed over excised bovine buccal mucosa for 30 s applying constant pressure. After 5 min, the weight required to detach the adhesive cup from the mucosa was recorded.

Peel strength test

Peel strength is the amount of force or energy required for tangential detachment of mucoadhesive formulation (cups) from freshly excised bovine buccal mucosa. The stress in this test is mainly focused at the edge of adhesive system. The tensile strength and shear strength tests have been used to determine mechanical property of the developed mucoadhesive formulations, while peel strength test determines resistance towards the peeling force. From the literature it is clear that the most commonly used mucoadhesive evaluation method is the tensile strength test.

In vitro retention time

The *in vitro* retention time is one of the most important physical parameters for the evaluation of amucoadhesive cup. Amucoadhesive cup was pressed over the excised bovine buccal mucosa for 30s after previously being secured on a glass slab and was immersed in a beaker containing 500 ml of isotonic phosphate buffer (pH 6.6) at 37 ± 0.2°C. A stirrer was fitted at a distance of 5 cm from the assembly and rotated at 25 rpm and the time for complete erosion or detachment of the formulation from the mucosa was recorded.

Ex vivo mucoadhesion time

A mucoadhesive patch was used to study mucoadhesive time. Phosphate buffer pH 6.6 (800 ml) was used as disintegration medium maintained at 37°C. Porcine check mucosa, 3 cm long, was attached to the surface of a glass slab which was vertically attached to the apparatus. The patch was then hydrated from one surface using 15 µl phosphate buffer and then it was brought into contact with the mucosal membrane. The apparatus was allowed to move up and down to immerse the patch completely in the buffer solution. The time required for complete detachment of the patch from the mucosal surface was recorded.

Mucoadhesive force determination

A tensile tester (Rheometric Scientific Inc., UK) was used to measure the mucoadhesive force of the adhesive polymeric systems using a plastic (PVC) plate. Polymeric films and plastic plates were cut with the predetermined area (1 cm^2, thickness of 0.8 mm) and the film was wetted with water and positioned over the surface of the plastic plate. It was kept in contact with the plate under the force of finger tip for 2 minutes before the measurement. The peak force required to detach the film from the plastic plate was measured.

In vivo mucoadhesion study

The *in vivo* performance of a mucoadhesive formulation not only depends on the mechanisms taking place at the interface, but also on the properties of the whole mucoadhesive composite such as the dosage form, the mucosa and the interface linking them. Wistar rats were used for *in vivo* study.

Rheological methods

They have been performed viscosimetric assays to analyse the formulation-mucin interaction macroscopically. From this experiment, the viscosimetric changes of the system were monitored ensuing the mucoadhesion force determination constituted by the polymer chosen and mucin. This interaction force energy of the physical and chemical bonds of the mucin–polymer then transformed into mechanical energy or work which causes the change in viscosity.

Kinetics of drug release

Release of the active constituent is an important consideration in case of microcapsules. Many theoretically possible mechanisms may be considered for the release of the drug from the micro particulates.

Conclusion

Mucoadhesive systems might take part in an increasing role in the development of new pharmaceuticals. This review was aimed to study different mucoadhesive systems. The polymers used in for-

mulation of these systems are of great variety and has different specific properties for mucoadhesive characteristics to be presented. Mechanistic approach followed by different polymeric systems to adhere with the mucus membrane has shown in better way to choose it for novel formulation to be formulated and evaluated. Different mucoadhesion evaluation techniques described has been found useful for the systematic *in vitro* study of numerous mucoadhesive formulations. Further the selection of best mucoadhesive agent depends on the therapeutic challenge which is to be solved and accordingly a suitable mucoadhesive polymer or its derivative could be selected to develop a promising delivery system.

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