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"OVERVIEW: FORMULATION ASPECT OF MUCOADHESIVE MICROSPHERE AND ITS PHARMACEUTICAL APPLICATION"

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ABSTRACT

The small size and high drug carrier capacity, microspheres are an important component of novel drug delivery systems. The polymer's bioadhesive feature can be exploited make microsphere mucoadhesive microspheres. Bioadhesion is the state in which two materials, at least one of which is biological in nature, are held together by interfacial forces for an extended period of time. Microspheres have a drug core and an outer layer of polymer as a coating material, with diameters ranging from 1-1000µm. Mucoadhesive microspheres have advantages such as efficient absorption, increased bioavailability, and increased drug residence time at the site of administration, as well as producing sustained drug release from dosage forms and specific drug targeting to the absorption site. The recent study is undertaken to for mechanism of mucoadhesion, theories of mucoahesion, method of preparation, method of evaluation, and application of mucoadhesive microsphere in drug administration as well as pharmaceuticals.

KEYWORDS: Mucoadhesive microsphere, Method of preparation, Evaluation.

INTRODUCTION

The significant therapeutic benefits, oral controlled release dosage forms have been developed throughout the past three decades. However, this strategy hasn't worked for a number of critical medications with a restricted absorption window in the upper gastrointestinal tract, such as the stomach and small intestine. This is because the dosage form has a short transit time in these anatomical segments.[1] The development of new drug delivery systems, such as the mucoadhesive microsphere drug delivery system, can improve drug action. These systems stay in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site, resulting in an increase in bioavailability and local and systemic effects.[2] Microspheres as drug carriers are one of the most innovative approaches for sustaining and regulating pharmacological action at a specific spot (e.g tissue). They are spherical free-flowing powders made up of proteins or synthetic polymers that are either biodegradable or non-biodegradable in nature, with a particle size ideally spanning from 1 to 1000micrometer. Microspheres are divided into two categories: Microcapsules and micromatrices are described as follows: microcapsules are those in which the entrapped substance is distinctly surrounded by distinct capsule wall, whereas micromatrices are those in which the entrapped substance is dispersed or dissolved through the particle matrix, with the potential for controlled drug release.[3]

MUCOADHESIVE DRUG DELIVERY SYSTEM[4]

Mucoadhesive drug delivery methods make use of the bioadhesion of certain polymers, which become adhesive when hydrated and can thus be utilised to target a medicine to a specific area of the body for long periods of time. Bioadhesion is an interfacial phenomena in which two materials are held together by interfacial forces, at least one of which is biological. Adhesion between a polymer and a biological membrane is an example of an artificial material adhering to a biological substrate. The word "mucoadhesion" is used to describe the attachment of a polymer to the mucin layer of a mucosal tissue. Various approaches can be used to deliver mucoadhesive drug delivery systems:-

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

MUCOADHESIVE MICROSPHERE

Microparticles and microcapsules with a diameter of 1—1000 µm and made wholly of a mucoadhesive polymer or with an exterior coating of it are called mucoadhesive microspheres.[5] Microspheres, in general, have the potential to be used for targeted and controlled drug delivery; however, coupling bio-adhesive properties to microspheres has additional advantages, including

efficient drug absorption and bioavailability due to a high surface to volume ratio, a much more intimate contact with the mucous layer, and specific drug targeting to the absorption site.

MECHANISM OF MUCOADHESION[6,7,8]

Mucoadhesion is defined as the attachment of a medication and an appropriate carrier to the mucosal layer. Mucoadhesion is a complicated phenomena involving polymer chain wetting, adsorption, and interpenetration. The following are the mechanism of mucoadhesion:

1) Close proximity of a mucoadhesive delivery method to the mucosal membrane (wetting or swelling phenomenon) The delivery system is mechanically attached in certain situations, such as for ocular or vaginal formulations, while in others, such as for the nasal route, the deposition is facilitated by the organ's aerodynamics to the membrane, and the system is supplied.
2) Penetration of the mucoadhesive delivery method into tissue or the mucous membrane's surface (interpenetration)

MUCOADHESION THEORIES[9]

Mucoadhesion is a complicated process, and several ideas have been presented to explain how it works. Mechanical interlocking, electrostatic, diffusion interpenetration, adsorption, and fracture processes are among these hypotheses.

1. Wetting theory[9]

The wetting theory is used to describe liquid systems that have an attraction for a surface and spread over it. This affinican be found by using contact angle measurement is an example of a technique The basic rule is that the larger the affinity, the lower the contact angle. To ensure proper spreadability, the contact angle should be equal to or close to zero. The difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB} can be used to compute the spreadability coefficient, S_{AB}, as shown in the equation below. To produce a good degree of mucoadhesion, this theory highlights the relevance of contact angle and the lowering of surface and interfacial energy.

$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$

2. Diffusion theory[9]

The interpenetration of both polymer and mucin chains to a sufficient depth to establish a semi-permanent adhesive connection is described by diffusion theory. The adhesion force is thought to increase with the degree of penetration of the polymer chains. The diffusion coefficient, the flexibility and composition of the mucoadhesive chains, motility, and contact time all influence the penetration rate. According to the literature, the needed depth of interpenetration for a successful bioadhesive connection is between 0.2 and 0.5 m. The following equation can be used to calculate the interpenetration depth of polymer and mucin chains:

$l = (tDb)½$

where t is the contact time and Db is the diffusion coefficient.

3. Fracture theory[9]

This is likely the most widely used theory in research of mucoadhesion mechanical measurement. It looks at how much force is needed to separate two surfaces once adhesion has been created. In tests of resistance to rupture, this force, s_m, is typically estimated as the ratio of the maximal detachment force, F_m, and the entire surface area, A_0, engaged in the adhesive interaction.

$S_m=F_m/A_0$

The fracture theory ignores the interpenetration and diffusion of polymer chains since it only considers the force required to separate the components. As a result, it's suitable for computations involving rigid or semi-rigid bioadhesive materials with polymer chains that don't penetrate the mucus layer.

4. Electronic theory[10]

The electronic hypothesis is based on the notion that the electronic surface characteristics of the bioadhesive material and the target biological material are different. According to this, when two surfaces come into contact, electron transfer happens in an attempt to balance the Fermi levels, resulting in the creation of a double layer of electrical charge at the bioadhesive and biologic surface interface. The attractive forces across this second layer are thought to be responsible for the bioadhesive force.

5. Adsorption theory[10]

The bioadhesive bond created between an adhesive substrate and tissue, according to this idea, is owing to weak van der waals forces and hydrogen bond formation. It's one of the most widely recognised bioadhesion ideas.

ADVANTAGES OF MUCOADHESIVE MICROSPHERE[11,8]

1) A smaller size adds to a larger surface area, which can boost the efficacy of a poorly soluble substance.
2) Maintaining a consistent supply of drugs in the body to increase patient compliance.
3) Improved drug use will increase bioavailability and decrease the occurrence or severity of side effects.
4) A significant cost reduction and a reduction in dose-related adverse effects may be obtained.
5) The use of specialised bioadhesive molecules allows for the prospective targeting of specific areas or tissues, such as the GI system.
6) Lower administration frequency may result from increased residence duration combined with restricted API release.
7) Provides an effective route for systemic distribution of medicines with a high first-pass metabolism, increasing bioavailability.
8) Patient compliance and convenience are improved due to fewer drug administrations.

9) The medicine is distributed uniformly and widely throughout the gastrointestinal tract, which enhances drug absorption.
10) Drug release that is prolonged and consistent.
11) Maintaining therapeutic medication concentrations in the plasma.
12) Increased processing efficiency (improving solubility, dispersibility, flowability).
13) Improved plasma level management increases the safety margin of high-potency medicines.
14) Less variation in steady state levels, resulting in better disease control and a reduction in the severity of local or systemic adverse effects.
15) Drugs that are unstable in an acidic environment and are destroyed by enzymatic or alkaline intestinal environments can be taken through this route, such as buccal, sublingual, or vaginal.

DISADVANTAGES OF MUCOADHESIVE MICROSPHERE[2]

1) The formulas' release could be altered.
2) Food and the rate of transit through the gut, as well as mucin turnover rate, can affect the rate of release.
3) There are differences in the release rate from one dose to the next.
4) Any deterioration in the dosage form's release pattern could result in toxicity.
5) These dose forms are not crushable or chewable.

MUCOADHESIVE POLYMER[12,13]

The following are the optimal features of mucoadhesive polymers:[14]

1) Sticky polymers that owe their bioadhesion to their stickiness when introduced in watery environments.
2) Polymers that stick together due to non-specific, non-covalent interactions that are largely electrostatic (although hydrogen and hydrophobic bonding may be significant).
3) Polymers that connect to specific cell surface receptor locations.

Table 1: Classification of Mucoadhesive Polymer.

Sr. No.	Types Of Polymer	Examples
1.	**Based on Origin** a) Synthetic mucoadhesive polymer	Cellulose derivative, Poly(acrylic acids), Poly(hydroxyethyl methylacrylate), Poly(ethylene xide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol) etc.
	b) Natural Mucoadhesive polymer	Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, soluble starch, Gelatin, Pectin, Chitosan etc.
2.	**Based on Nature** a)Hydrophilic polymer	Poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, Poly (Vinyl alcohol), Poly vinyl Pyrrolidone) etc.
	b) Polysaccharides and derivatives	Chitosan methyl cellulose, Xanthan gum, gellan gum, Carrageenan etc.
3.	**Novel Mucoadhesive Polymer** a) Lectins	Merolectins, Hololectins, Chimerolectins
	b) Thiolated Polymers	Chitosan-iminothiolane, Poly (acrylic acid)-cysteine, Chitosan-thioglycolic acid, alginate cysteine, sodium carboxymethylcellulose-cysteine etc.

RECENT ADVANCEMENT IN MUCOADHESIVE DRUG DELIVERY SYSTEM[4]

Mucoadhesive Polymers

A variety of polymers have been studied for their potential application as mucoadhesives. Polyacrilic acid (PAA) is thought to be a good mucoadhesive. PAA stands for copolymerized with polyethylene glycol (PEG) or polypropylene glycol (PPG) PVP (Vinyl Pyrrolidone) (Vinyl Pyrrolidone) (Vinyl Pyrrolidone) (Vinyl Pyrroli) properties.

Devices

To accomplish long-term medication release, several laminating devices have been created. It is possible to classify it

- Diffusion of drug from the drug/polymer matrix regulates the total rate of drug release from the device in monolithic (or matrix) systems where the drug is dissolved or dispersed in the polymer system.
- Diffusional barrier over a polymeric membrane regulates the overall drug release rate in reservoir (or membrane) systems.

METHOD OF PREPARATION OF MUCOADHESIVE MICROSPHERE

1. Emulsion cross linking method[2]

The researcher Thanoo and his associates described this method. The reactive functional group of the polymer is used to crosslink with the aldehyde group of the cross linking agent in this approach. Emulsifying the polymer aqueous solution in the oily phase produced a water-in-oil (w/o) emulsion in this approach. A appropriate surfactant, such as span 80 or dioctyl sodium

sulphosuccinate, was used to stabilise aqueous droplets. To harden the droplets, an appropriate cross-linker, such as gluteraldehyde, was used to cross link the stable emulsion. To remove residues of oils, microspheres were filtered and washed repeatedly with hexane or petroleum ether. Finally, they were rinsed in water to remove crosslinkers before being dried at room temperature for 24 hours.

2. Polymerization technique[3]

The polymerization processes utilised to make the microspheres are categorised as follows:

• Normal polymerization
• Interfacial polymerization

Normal polymerization

1. Bulk polymerization- To start the polymerization and complete the process, a monomer or a mixture of monomers and the initiator is commonly heated. To facilitate or accelerate the rate of the reaction, the catalyst or initiator is introduced to the reaction mixture. The resulting polymer can be shaped or split into microspheres. Adsorptive drug loading or drug addition during the polymerization process are two options for drug loading.
2. Suspension polymerization-Suspension polymerization is performed by heating a monomer or a mixture of monomers with active principles (drugs) in a continuous aqueous phase as droplets dispersion. An initiator and other chemicals may also be present in the droplets.
3. Emulsion polymerization- However, it differs from suspension polymerization since the initiator is present in the aqueous phase, where it diffuses to the surface of the micelles or emulsion globules later.

Interfacial polymerization

Two reactive monomers are used in the interfacial polymerization process, one of which is dissolved in the continuous phase while the other is disseminated in the continuous phase. The second monomer is emulsified in the continuous phase, which is usually aqueous in nature. At the interface, the monomers present in either phase diffuse and polymerize quickly. Depending on the solubility of the produced polymer in the emulsion droplet, two circumstances emerge. If the polymer is soluble in the droplet, the carrier will form in a monolithic form on the hand. The generated carrier is of the capsular (reservoir) kind if the polymer is insoluble in the monomer droplet. The reactivity of the monomer chosen, their concentration, and the composition of the vehicle of either phase, as well as the temperature of the system, can all influence the degree of polymerization. The particle size can be controlled by controlling the size of the dispersed phase's droplets or globules. The polymerization reaction can be regulated by keeping the monomer concentration constant, which can be accomplished by adding an excess of the continuous phase.

3. Ionotropic gelation technique[15]

The ability of polyelectrolytes to cross link in the presence of counter ions to create hydrogel beads, also known as gelispheres, is the basis of ionotropic gelation. Gelispheres are spherical crosslinked hydrophilic polymeric entities that can gel and swell extensively in simulated biological fluids, with medication release controlled by polymer relaxation. The hydrogel beads are made by dropping a drug-loaded polymeric solution into a polyvalent cation aqueous solution. The cations diffuse into the polymeric droplets containing the medication, generating a three-dimensional lattice of ionically crosslinked moieties.

4. Spray drying method[11,16]

Microencapsulation is a rapidly gaining popularity technology that is a unique way to encapsulate materials in the form of micro and nanospheres/particles. It is defined as a procedure that entangles one substance (active agent) within another substance (coating material). Because the solvent evaporates quickly from the droplets, the spray drying method has been widely employed to dry thermally labile materials/substances.18 This was utilised to make polymer microspheres that were drug-charged. This entails putting the raw material into a liquefied coating liquid, then spraying the combination into the air for quick surface solidification and solvent evaporation. In precise laboratory circumstances, organic solvent and polymer solution are synthesised and sprayed in varied weight ratios and drug to produce microspheres packed with pharmaceuticals. This is quick, although the rapid drying may cause crystallinity loss.

5. Single emulsion technique[17]

This technique is used to prepare a variety of proteins and carbohydrates. Natural polymers are dissolved in aqueous medium and then dispersed in an oil phase, which is a non-aqueous medium. That is the first stage in the process. Cross linking is done in the next step using two different methods.

1. Heat-induced crosslinking: by dispersing the dispersion in heated oil, although this method is not suitable for the Thermolabile medicines.
2. Chemical cross linking agents: -by using agents such as formaldehyde, di acid chloride, glutaraldehyde, and so on. However, if added at the time of preparation and then centrifuged, washed, and separated, it has the disadvantage of exposing the active ingredient to chemicals excessively. By mixing chitosan solution (in acetic acid) with liquid paraffin containing a surfactant, a w/o emulsion is formed. Metformin hydrochloride microsphere are prepare by using gluteraldehyde 25 percent solution as a cross linking agent.

6. Double emulsion technique[17]

It is the creation of multiple emulsions, i.e. W/O/W, by pouring the primary w/o emulsion into aqueous poly vinyl alcohol solution. This w/o/w emulsion required 30

minutes of constant stirring. Over the course of 30 minutes, gradually add some water to the emulsion. Microcapsules are collected via filtering and dried under vacuum 2. Water soluble medicines, peptides, proteins, and vaccinations are the best candidates. This approach can be used with both natural and synthetic polymers. A lipophilic organic continuous phase disperses the aqueous protein solution. The active components may be present in this protein solution. 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 microsphere collection.

7. Phase separation coacervation technique[18]

This method works by lowering the polymer's solubility in the organic phase, causing the creation of a polymer-rich phase known as coacervates. The drug particles are disseminated in a polymer solution, and an incompatible polymer is added to the system, causing the first polymer to phase separate and swallow the drug particles. The addition of a non-solvent causes the polymer to solidify. This approach used butadiene as an incompatible polymer to create poly lactic acid (PLA) microspheres. The rate of achieving coacervates impacts the dispersion of the polymer film, particle size, and agglomeration of the produced particles, hence process variables are crucial. Because the formation of microspheres begins, the formed polymerize globules start to stick together and form agglomerates, agglomeration must be avoided by stirring the suspension with a suitable speed stirrer. Because there is no defined state of equilibrium attainment, the process variables are crucial because they govern the kinetics of the produced particles.

8. Hot melt microencapsulation[19]

The polymer is melted first, then mixed with solid medicine particles that have been sieved to fewer than 50 microns. The mixture is suspended in a non-miscible solvent (such as silicone oil), agitated constantly, and heated to 5°C above the polymer's melting point. After stabilising the emulsion, it is chilled until the polymer particles solidify. Decantation with petroleum ether is used to wash the resultant microspheres. The fundamental goal of this technology is to create a microencapsulation process that is suited for water labile polymers, such as poly anhydrides. It is possible to make microspheres with a diameter of 11000 m, and the size distribution can be easily regulated by changing the stirring rate. The sole disadvantage of this procedure is that the medicine is exposed to a moderate temperature.

9. Solvent evaporation[19]

In a liquid manufacturing vehicle, the procedures are carried out. The microcapsule coating is disseminated in a volatile solvent that is incompatible with the liquid production vehicle phase of the process. In the coating polymer solution, a core material to be microencapsulated is dissolved or distributed. To obtain the proper size microcapsule, the core material combination is distributed in the liquid production vehicle phase by agitation. When the solvent for the polymer of the core material is dispersed in the polymer solution and the polymer shrinks around the core, the mixture is heated if necessary to evaporate the solvent. Matrix-type microcapsules are generated when the core material is dissolved in the coated polymer solution. Water soluble or water in soluble materials can be used as the core components. The formation of an emulsion between a polymer solution and an immiscible continuous phase, whether aqueous (o/w) or non-aqueous, occurs during solvent evaporation. Microcapsules of hyaluronic acid and gelating prepared by complex coacervation were compared to mucoadhesive hyaluronic acid microspheres, Chitosan glutamate, and a combination of the two prepared by solvent evaporation.

Table 2: Some examples of Mucoadhesive Microsphere prepared by different methods.

Sr. No.	Drug	Polymer used in preparation of mucoadhesive microsphere	Method of preparation of mucoadhesive microsphere
1	Metronidazole[32]	Sodium alginate, HPMC, Carbopol	Ionic gelation method
2	Betahistine dihydrichloride[33]	Chitosan	Single emulsion/solvent evaporation
3	Ciprofloxacin[34]	Ethylcellulose, HPMC, Carbomer940	Emulsion solvent diffusion evaporation method
4	Captopril[35]	Sodium alginate	Emulsification method
5	Glicazide[36]	Isabgol	Emulsification cross linking technique
6	Metronidazole[37]	Eudragit L-100, Carbopol 940, Sodium alginate, guar gum	Ionic gelation method
7	Ramipril[38]	Carbopol Ethylcellulose	Solvent evaporation method
8	Mesalamine[39]	Eudragit S-100, Sodium alginate	Modified emulsification method
9	Metoclopramide HCl[40]	Sodium alginate, Chitosan HCl	Spray drying method
11	Simvastatin[41]	Sodium alginate, Carbopol 940, HPMC(K100M), Sodium CMC, Ethyl cellulose, PMC, Guar gum,	Ionic gelation method

		Methyl cellulose, Xanthan gum	
12	Ranitidine[42]	Sodium alginate, SCMC, HPMC K100, Carbopol 940, Eudragit RS 100	Ionic gelation method
13	Ondansetron[43]	Carbopol 940, HPMC K15M, Ethyl cellulose	Solvent evaporation technique

EVALUATION OF MUCOADHESIVE MICROSPHERE

1) Particle size shape and morphology[8]

Using an optical microscope equipped with an ocular micrometre and a stage micrometre, all of the microspheres are measured for size and shape. The optical microscope was used to measure the particle sizes of over 100 microspheres at random. Photomicrographs of drug-loaded microspheres were acquired using a scanning electron microscope. On a gold stub, a small amount of microspheres was distributed. Following that, the stub containing the sample was inserted in a microsphere Scanning electron microscopy (SEM).

2) Micromeritics[20]

a) **Angle of repose**- Each batch's angle of repose was determined using the glass funnel method. The formula was used to calculate the angle of repose:

$\text{Tan}^{-1} h/r = \theta$

b) **Bulk density:** Bulk density in a graduated measuring cylinder of a known mass of microspheres. The bulk density was estimated by dividing the weight of microspheres in grammes by their bulk volume in cm3.

c) **Tapped density**: Tapped density refers to the volume of powder calculated by tapping a measuring cylinder containing a pre-weighed sample amount. The ratio of the weight of microspheres in gramme to the volume of microspheres after tapping in cm3 was used to compute the tapped density of microspheres.

d) **Carr's compressibility index**

Carr's compressibility index= (Tapped density-Bulk density)/Tapped density x100

3. UV-FTIR (Fourier Trasforms Infrared Spectroscopy)[22]

The FTIR can be used to evaluate drug polymer interaction as well as drug degradation during microencapsulation processing. The powders are compressed at 20 pressure for 10 minutes on a KBrpress to make drug and potassium bromide pellets, and the spectra are scanned in the wave number range of 4000 600 cm1. FTIR study is carried on pure drug, physical mixture, formulations and empty microspheres.

4. Swelling Index[7,21,30]

The ability of mucoadhesive microspheres to swell at the absorbing surface by absorbing fluids available at the absorption site, which is a basic prerequisite for mucoadhesion beginning, is depicted by the swelling index. The following equation can be used to calculate the percent swelling value.

% swelling = DT - D0 / D0 × 10

Where, D0 = weight of dried microspheres
DT = weight of swelled microspheres

5. Present production yield[23]

The weight yield of various batches of microspheres was estimated by comparing the weight of the end product after drying to the total weight of the medication and polymers at the start.

Weight yield = (practical weight of microspheres/ theoretical weight of microspheres) × 100

6. Drug entrapment efficiency[24,30]

The real loading and entrapment (encapsulation) efficiency can be used to determine the success of drug loading: The real medication loading procedure is as follows:

DL (%) =drug (mg) /(drug + polymer) (mg) ×100

The general formula for calculating the entrapment efficiency value is:

EE (%) =entrapped drug content (mg)/ theoretical drug content (mg)/ ×100

Various factors, such as the kind and circumstances of the process, influence the optimum entrapment efficiency (100%).

7. In-vitro wash off test[25]

The microspheres' mucoadhesive characteristics were assessed using an in vitro wash-off test. Thread was used to bind a 4cm x 4cm piece of goat intestinal mucosa to a glass slide. The prepared slide was hung on one of the groves of a USP pill dissolving test device, and microspheres were dispersed(100) onto the wet, washed tissue specimen. The tissue specimen was moved up and down regularly in the beakers containing the simulated gastric fluid USP (pH1.2) and the pH 7.0 Phosphate buffer by the disintegration test device. The amount of microspheres remaining adhering to the tissue was counted after 30 minutes, 1 hour, and hourly intervals up to 8 hours.

Mucoadhesion property = No. of microsphere adhere/No. of microsphere applied x 100

8. In-vitro dissolution study[25]

The USP dissolution apparatus –II (Paddle method) was assembled with 900mL of dissolution media in the dissolution vessel. The medium was allowed to reach a temperature of 37°C + 0.5°C after equilibration. Microspheres were deposited in the dissolution vessel, which was then covered, and the equipment was run at 50 rpm for 8 hours. At predetermined intervals, 5mL of

the dissolution fluid was withdrawn, filtered, and replaced with a 5mL blank sample. The dissolving fluid was diluted appropriately, and the samples were spectrophotometrically examined using a UV spectrophotometer.

9. In-vitro mucoadhesive strength measurement[7,26]

The mucoadhesive strength was determined using a modified balance method. The cellophane membrane was cut into pieces and treated with 0.1 N NaOH before being used. Separately, two pieces of cellophane membrane were tied to two wooden pieces, one of which was fixed to the sieve and the other to the balance on the right hand side. By putting extra weight on the left hand wooden, the right and left woodens were balanced. Extra weight from the left pan was removed to sandwich the two pieces of cellophane membrane and some pressure was applied to remove the presence of air. 100 mg of microsphere was placed between these wooden pieces containing cellophane membrane, and extra weight from the left pan was removed to sandwich the two pieces of cellophane membrane and some pressure was applied to remove the presence of air. For 5 minutes, the balance was held in this position. The left–hand pan was steadily filled with water at a rate of 1ml/min until the microsphere separated from the egg membrane surface. The amount of water (ml) needed to separate the microsphere from the cellophane membrane surface was used to determine mucoadhesive strength. The following formulae were used to compute the mucoadhesive strength:

Force of adhesion(N)= Mucoadhesion strength(gm) x 9.81/1000

Bond strength = Force of adhesion /disk surface area

10. Differencial scanning colorimetry (DSC) stydy[27,28]

The DSC thermograms of drug and drug-excipient mixes were weighed directly in the punctured DSC aluminium pan and scanned in the temperature range of 20–300°C under a dry nitrogen environment. The temperature was raised at a rate of 100 degrees Celsius per minute, and thermograms were taken to look for any interactions.

11. Drug content estimation[30,31]

The method of extraction of drug contained in microspheres was used to determine the drug content of the manufactured microspheres. Powdered drug-loaded microspheres (100 mg) were extracted for 24 hours in 100 ml Phosphate buffer 6.8 PH. The resulting microsphere dispersion was then sonicated for 30 minutes to ensure thorough mixing before being filtered through Whatman filter paper. Using 6.8 PH phosphate buffer as a blank, the concentration of drug contained in the filtrate was measured spectrophotometrically at 206.3 nm. Each determination was made in three different ways. The drug content of the prepared microsphere was determined using the formula below:

Drug Content= Calculated Drug Content / Total amount of Microspheres x 100

12. In vivo method[29]

The techniques that use the biological response of the organism locally or systemically, as well as those that involve direct local detection of penetrant absorption or accumulation at the surface, are used to evaluate the permeability of intact mucosa. The systemic pharmacological effects of medicines following application to the oral mucosa were used in some of the first and most basic studies of mucosal permeability. In vivo investigations using animal models, buccal absorption assays, and perfusion chambers for evaluating drug permeability are the most extensively utilised methodologies.

Animal model

Animal models are mostly used to screen a set of compounds, investigate the mechanisms and utility of permeation enhancers, or assess a set of formulations. There have been a lot of animal models documented in the literature, but just a handful in vivo (animal). Dogs, rats, rabbits, cats, hamsters, pigs, and sheep have all been used as animal models. In general, the method begins with the animal being anaesthetized before the dose form is administered. The oesophagus is ligated in rats to restrict absorption by routes other than the oral mucosa. The blood is extracted and examined at various times.

APPLICATION OF MUCOADHESIVE MICROSPHERE[13,22]

1. Controlled and sustained release dosage forms.
2. 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.
3. It has been used to protect drugs from factors such as humidity, light, oxygen, and heat. Although the microsphere does not yet provide a perfect barrier for materials that degrade when exposed to oxygen, moisture, or heat, it can provide a high level of protection against these elements. Microspheres, for example, have been shown to protect vitamin A and K from moisture and oxygen.
4. Encapsulation has been used to achieve separations of incompatible compounds, such as medicinal eutectics. This is a situation where two materials come into direct touch and form a liquid. Microencapsulating both aspirin and chlorpheniramine maleate before combining improves the stability of the incompatible mixture.
5. The usage of microspheres can help to reduce volatility. A volatile chemical that has been encapsulated can be held for prolonged periods of time without evaporation.
6. Microspheres have also been employed to reduce the risk of dangerous or noxious chemicals being handled. After microencapsulation, the toxicity caused by fumigants, herbicides, insecticides, and pesticides has been reduced to an advantage.
7. Microspheres can lower the hygroscopic characteristics of various core materials.

8. To decrease stomach discomfort, many medications have been microencapsulated.
9. A microsphere approach for producing intrauterine contraceptive devices has also been developed.
10. Chemotherapeutic agents are delivered to liver tumours using therapeutic magnetic microspheres. This technique can also target drugs such as proteins and peptides. Mucoadhesive microspheres have a longer residence period at the application site, resulting in more intimate contact with the absorption site and better therapeutic activity.
11. Radioactive microspheres are utilised to image the liver, spleen, bone marrow, and lung, among other organs, and can even be used to image thrombus in deep vein thrombosis.

CONCLUSION

The mucoadhesion is the property that allows microparticles to cling to mucosal membranes in the nose, mouth, and gastrointestinal tract. The use of a mucoadhesive microsphere to deliver the medicine to the target region is a promising method. It prolongs drug residence time, improves drug bioavailability, protects the drug, and raises plasma drug concentration. The primary goal of a mucoadhesive microsphere is to provide controlled medication release. As a result, it was established that mucoadhesive microspheres provide regulated medication release and boost drug bioavailability.

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