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Review Article

Novel review on mucoadhesive drug delivery system

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ABSTRACT

Mucoadhesive drug delivery systems bind to the mucus layer covering the mucosal epithelial surface and enhance the residence time of the dosage form at the place of absorption. The process of mucoadhesion is a complex incident which contains wetting, adsorption and interpenetration of polymer chains among the other delivery systems. The mucoadhesive capability of a dosage form depends on a variety of factors such as nature of the mucosal membrane and physicochemical properties of formulation. The ideal character of a mucoadhesive polymer includes without any change in the physical property of the delivery matrix, minimum interference to release the active agent and inhibit the enzymes present at the delivery site and enhance the penetration of the active agent. Mucoadhesive polymers have been used to enhance the contact time for a wide variety of drugs and routes of administration has shown dramatic enhancement in both specific therapies and more general patient compliance. This article mainly reviews about the advantages, composition and functions of mucus, mechanism and various theories of mucoadhesion and different types of mucoadhesive polymers. It also emphasizes about the different mucoadhesive drug delivery systems (oral, nasal, ocular, gastro, vaginal and rectal), existing mucoadhesive formulations and finally evaluation parameters of mucoadhesive systems.

Keywords: Mucoadhesion; bioadhesion; consolidation stage; mucoadhesive polymers; mucoadhesive drug delivery systems

INTRODUCTION

Mucoadhesion concept came into existence in the year 1980's and gained considerable interest in pharmaceutical technology (Chickering DE III. et al., 1999). The molecular force of attraction among two unlike bodies which makes to hold together is called as Adhesion (Avenel Q. 1989). The adhesive phenomenon related to ability of some synthetic, biological macromolecules and hydrocolloids to attach to biological tissues for therapeutic purpose in medicine was described by using the term Bioadhesion (Kaelbe DH. et al., 1977). The term mucoadhesion is used when the biological substrate is a mucosal surface (Robinson JR. et al., 1990). The targeting of various absorptive mucosal layers of the body parts includes the ear, nose, eye, gastrointestinal tract, urogenital tract with the help of mucoadhesive polymer which will get attached on to the related tissue. This system of drug delivery is called as Mucoadhesive drug delivery system. Various types of polymers have been incorporated within the matrix of drug delivery system to keep the active ingredients and to induce sustained release characteristics (Jasti Drs B. et al., 2003). The mucoadhesive systems as drug carriers has been used for maintenance of the residence time and the absorption site, showing its intensified contact with the epithelial barrier (Hägerström H. et al., 2003). The development of controlled drug delivery system using bioadhesive molecules includes a reduction in dose frequency and an increase in patient compliance (Woodley J. et al., 2001). In medical applications, the bioadhesive systems have been broadly used for many years other than different drug delivery in the fields like density for denture adhesives (Wright P. et al., 1981), stoma adhesives such as Karaya gum in stomahesive (or) synthetic polyprotective (Winkler R. et al., 1974) and for surgical applications cyanoacrylates are used as Surgical Glue (Ray CD).

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Advantages

Mucoadhesive Drug Delivery Systems shows many advantages over other controlled drug delivery systems by virtue of its targeting and by increasing its residence time.

1. Increases the residence time of the formulation at the delivery site enhancing API bioavailability using lower API concentration.

2. Use of definite bioadhesive molecules allows for targeting of particular sites or tissues, for example the gastrointestinal tract.
3. Improved residence time lead to the enhanced absorption and achieving greater efficacy of drug.
4. Avoiding first pass metabolism.
5. The acidic environment present in gastrointestinal tract were the drug can be protected from degrading.
6. Dose related side effects may be reduced.

Mucus

Mucus is a viscous, slippery gel that cover most of the mucosal surfaces throughout the GIT (Allen A. 1981). Mucous membrane of human organisms are relatively permeable and allow faster drug absorption. It is synthesized by specialized goblet cells in the columnar epithelium which lines all of the organs that exposed to the external environment .The thickness of mucus may vary from 50 to 450µm in the stomach to less than 1µm in oral cavity (Smart JD. 2005).

Composition of Mucous Membrane

Mucus is a consistent mixture composed of approximately 95% water, 0.5 to 5% of glycoproteins and lipids, 0.5 to 1% of mineral salts, 1% of free proteins, inorganic salts, immunoglobulin's, cellular and serum macromolecules and trefoil peptides (Allen A. 1983). The major component that is liable for viscous and elastic gel like properties is the glycoproteins and mucins. Mucins are large molecules with molecular weight differing from 0.5×10^6 to over 4×10^6 g/mol. The gastrointestinal mucins consists of 70% to 80% carbhohydrates, 12% to 25% of proteins and approximately 5% of ester sulphate. Multiples of basic units with ranging molecular weight of 40,000 to 500,000 are present in undergraded mucins which is linked together to give linear arrays (Silberberg A, et al., 1982).

Secretion and Function of Mucus

Mucus is secreted in GIT by specialized cells as a polymer of high molecular weight .Not like other gastrointestinal secretions, it adhere to the mucosal epithelial surfaces as a water insoluble gel (Allen A. 1981). By chemically analyzing the mucus, it showed the presence of small amounts of lipids, proteins, bacteria, sloughed off epithelial cells and in some cases nucleic acids. Relevant to the concept of mucoadhesion, two kinds of mucus can be distinguished of which one kind showing the water insoluble mucus gel lining the GIT which form the target substrate and has a variable thickness of 50 to 450µm in man and on half that in Second kind of soluble, often viscous mucus present in the luminal contents.

The basic unit recieved from a single chain polypeptide backbone has two distinct regions. A glycosylated polypeptide chain rich in serine, proline and threonine to which a large number of carbohydrate chains are bound. The other followed by one (or) two terminal peptide segments that bear very little or no carbohydrate side chains which are referred to as "naked protein sections".

Five different monosaccharide's which may be present on carbohydrate chains are D-galactose, L-fucose, N-acetyl galactosamine, N-glucosamine and silica acid. Oligosaccharides are covalently attached via O-glycosidic linkage from N–acetyl galactosamine to serine and threonine residues of protein core. The silica acid located on terminal position on the carbohydrate chain and the presence of ester sulphate residue on internal position. For example, the presence of N-acetylglucosamine-6-sulphate in pig gastric mucus. The presence of silica acid and ester sulphate shows negative charges which is thought to be important for interactions with polycationic materials (Lehr CM. et al., 1991).

MECHANISM OF MUCOADHESION

The contact between mucoadhesive and mucous membrane, with spreading and swelling of the formulation initiating its deep contact with the mucus layer was seen in first stage i.e., the contact angle (See Figure 1).

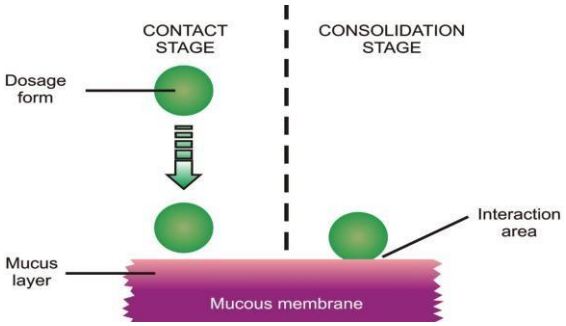

Figure 1: The two steps of the mucoadhesion process

In consolidation stage, in the presence of moisture the mucoadhesive materials are activated. The system is plasticized by moisture, permitting the mucoadhesive molecules to divide and to link up by Vander Waals force and hydrogen bond (Hogerstrom H. et al., 2003).

THEORIES OF MUCOADHESION

Numerous theories (Madsn F. et al., 1998) have been presented to clarify the mechanism involved in mucoadhesion. The theories include electrostatic, mechanical-interlocking, diffusion-interpenetration, adsorption and fracture process. The most broadly accepted theories include the surface energy thermodynamics and interpenetration/diffusion.

The wettability theory

It is mainly suitable to liquid or low viscosity mucoadhesive systems. The theory is essentially used to evaluate the spread capability of API across the biological substrate. The theory states that the adhesive agent

penetrate into surface irregularities of the substrate which become hardened and get anchored itself to the surface. Using wettability and spread ability, the adhesive performance of such elastoviscous liquids may be clear. Free movement of the adhesive upon the surface of the substrate means that it should overcome any surface tension effects present at the surface (McBain JW. et al., 1925). Therefore the contact angle (θ), which can be easily determined experimentally, is connected to interfacial tension (γ), of both components using

$$\gamma SG = \gamma SL + \gamma LG \cos \theta \quad (1)$$

$$S = \gamma SG - (\gamma SL - \gamma LG) \quad (2)$$

Where,

γLG is liquid gas surface tension

γSL is solid liquid surface tension and

γSG is solid gas surface tension.

The mucoadhesive polymers exhibiting same structure and functional groups to the mucus layer will show the increased miscibility which results in a greater degree of polymer spread capacity across the mucosal surface. Polymer contact angles of such systems will facilitate the hydration of the polymer chains and hence promoting the intimate contact between polymeric delivery platforms and the mucus substrates.

The electronic theory

This theory (Dodou D. et al., 2005) describes about the adhesion occurring between mucus and mucoadhesive system by means of electron transfer. The transfer of electrons between mucus and mucoadhesive systems resulted in the creation of a double layer of electrical charges at the mucus and mucoadhesive interfaces. The total result of such process resulted in the formation of attractive forces within this double layer.

The adsorption theory

The mucoadhesive device adheres to the mucus by the way of secondary chemical interactions (Kinloch AJ. Et al., 1980) such as Vanderwaals force, hydrogen bonds, electrostatic attraction or hydrophobic interactions. Primary Bonds owed to chemisorptions result in adhesion due to covalent, ionic and metallic bonding, which is generally unattractive due to their permeancy.

The fracture theory

This theory describe the force required to separate the two surfaces after adhesion. The "fracture theory" relates the force necessary for polymers disconnection from the mucus to the strength of their adhesive bond. The work fracture is greater when the polymer network strands are longer or if the degree of cross-linking within such system is reduced (Ahagon A. et al., 1975) with the help of the following equation, the theory allows the purpose of fracture strength (σ) following separation of two surfaces via its relationship to Young's module of elasticity (E), the fracture energy (f) and the critical crack length (L).

$$\sigma = (E \times €/L)^{1/2} \quad (3)$$

The diffusion interlocking theory

The time dependent diffusion of mucoadhesive polymers chains keen on the glycoprotein chain network of the mucus layer was explained by this theory. This is a two way diffusion process where the penetration rate being reliant upon the diffusion coefficient of both acting polymers. The factors responsible for such processes are molecular weight, cross-linking, chain mobility/flexibility, temperature and expansion capacity of both networks (Lee JW. et al., 2000). The longer polymer chains may diffuse, interpenetrate and ultimately entrap to a greater extent with surface mucus. It is recognized that a critical chain length of at least 100,000 Daltons is necessary to attain interpenetration and molecular entanglement. The polymer mobility is decreased when excessive cross linking is occurred (Ludwig A. 2005). When the solubility parameters of the bioadhesive polymer and the mucus glycoprotein are same, then the highest diffusion and bioadhesive strength may be achieved (Vasir J. et al., 2003). The maximum adhesion which occurs between two substrates throughout interpenetration has been supported by experimental evidence in recent studies using AFT-FTIR and rheological technique which may be determined by means of the depth of interpenetration (I), and the diffusion coefficient (D_b).

$$t = I^2 / D_b \quad (4)$$

FACTORS AFFECTING MUCOADHESION

There are many factors (Jimenez-Castellanos MR. et al., 1993) affecting mucus adhesion such as molecular weight, pH, swelling, hydrophilicity, flexibility, charge, concentration of the active polymer.

Molecular Weight

The optimum molecular weight for the increase of mucoadhesion rely on the type of polymer. Molecular weights of up to 100,000 favors mucoadhesion beyond this not much effect is obtained (Gurny R. et al., 1984). The bio adhesiveness improves with rising molecular weight for linear polymers, which suggests that interpenetration is more critical for low molecular weight polymers and entanglement is significant for high molecular weight polymers.

Flexibility

The differed polymer chains contain a substantial degree of flexibility in order to accomplish the desired entanglement and interpenetration with the mucus (Huang Y. et al., 2000). Increase in interpenetration of polymer chain resulted to the increase in structural flexibility of the polymer upon incorporation of polyethylene glycol. Flexibility and mobility of polymers are correlated to viscosities and diffusion coefficient (Gu

JM. Et al., 1998), as higher flexibility of polymer causes greater distribution into the mucus network.

Cross Linking Density

As the Cross linking density (McCarron PA. et al., 2004) is inversely proportional to the degree of swelling. The decline in cross link density, increases in the hydration rate and flexibility. A lightly cross linked polymer response to obtain a high degrees of swelling. If excessive moisture is present and the degree of swelling is too high, a slippy mucilage results and this can be easily detached from the substrate.

Spatial Conformation

Dextrans with a molecular weight (Jimenez-Castellanos MR. et al., 1993) of 19,500,000 and 200,000 shows similar bioadhesive strength which may be explained in terms of the helical conformation. Many adhesive groups may be bounded by dextran helical conformation which is responsible for adhesion rather than PEG polymers which have a linear conformation.

Concentration of Active Polymer

Most favorable concentration of a polymer (Peppas NA. et al., 1985) is responsible for better mucoadhesion. Beyond the optimum concentration, in highly concentrated systems, the adhesion strength gradually decreases. In concentrated solutions, the molecules which are coiled, shows poor solubility and the chains present for interpretation are not numerous. For solid dosage forms such as tablets, having higher the polymer concentration, stronger the mucoadhesion.

Hydration

It is required for the expansion of mucoadhesive polymer to increase and create a proper macromolecular attachment of sufficient size and also to stimulate mobility in the polymer chains so that the interpenetration between polymers and mucin is increased. Optimum swelling and mucoadhesion (Peppas NA. et al., 1985) occurs when certain degree of hydration is present.

Charge

Non ionic polymers shows smaller degree of adhesion (Park H. et al., 1989) compared to anionic polymers. For mucoadhesion to occur, strong anionic charge on the polymer is necessary. In neutral, slightly alkaline medium, cationic polymers shows superior mucoadhesion properties.

pH

The charge on the surface of mucus is influenced through the hydrogen ion concentration. Due to the variation in dissociation of functional groups on the carbohydrate moiety and amino acid of polypeptide backbone charge density depending on pH (Park H. et al., 1985). The mechanism of mucoadhesion clearly exhibited that the protonated carboxyl groups rather than the ionized carboxyl groups react with mucin molecules by forming several hydrogen bonds.

MUCOADHESIVE POLYMERS

A very long molecule consisting of structural and repeating units, connected by covalent chemical bonds is called polymer. Mucoadhesive polymers (Peppas NA. et al., 1996) are synthetic or natural macromolecules which are capable of attaching to mucosal surfaces. More than 40 years ago, the concept of mucoadhesive polymers has been introduced into the pharmaceutical literature and it has been accepted as a potential strategy to prolong the residence time and to progress the specific localization. By using different *in-vitro* methods and techniques, mucoadhesive properties of broad range of polymeric materials have been performed

Ideal characteristics of mucoadhesive polymer

- Should adhere to the site of attachment for a few hours
- Should release the drug in a controlled fashion
- Should provide drug release in an unidirectional way towards the mucosa
- Should facilitate the rate and extent of drug absorption
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

CLASSIFICATION OF MUCOADHESIVE POLYMERS

Based on origin

Synthetic mucoadhesive polymers

Cellulose derivatives, poly (acrylic acid) polymers, poly (hydroxyl ethyl methyl methacrylate), poly vinyl pyrrolidine, poly vinyl alcohol and carbopol.

Natural Mucoadhesive Polymers

Tragacanth, sodium alginate, karaya gum, xanthan gum, guar gum, lectin, soluble starch , gelatin, Pectin and chitosan are the natural mucoadhesive polymers.

Based on Nature

Hydrophilic polymers

The hydrophilic polymers when comes in contact with water they tend to swell indefinitely and eventually undergo complete dissolution. The greater mucoadhesive property is extended by polyelectrolytes.

Examples:- Poloxamer, methyl cellulose, hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose, sodium carboxyl methyl cellulose, carbomers, chitosan, poly vinyl alcohol and poly acrylic acid.

Hydrogels

Hydrogels are three dimension cross-linked polymers which have the affinity to hold water within its porous structure. They are also said to be wet adhesives as they need moisture to exhibit the adhesion property.

Examples:- Carrageenan, Sodium alginate, Guar gum.

Based on charge and generation

First generation non-specific mucoadhesive polymers

First generation mucoadhesive polymers are divided into three main subsets namely

1) Anionic polymers
2) Cationic polymers
3) Non –ionic polymers

The anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength (Ludwig A. 2005). Classification of mucoadhesive polymers based on their bioadhesive nature are shown in Table 1.

Table 1: Mucoadhesive Polymers and their Bioadhesive Property

POLYMER	BIOADHESIVE PROPERTY
CMC Sodium	+++
Carbopol 934	+++
Polycarbophil	+++
Tragacanth	+++
Sodium alginate	+++
Hydroxy ethyl cellulose	+++
Hydroxy propyl methyl cellulose(HPMC)	+++
Gelatin	++
Guar gum	++
Gum karaya	++
Thermally modified starch	+
Pectin	+
PVP	+
Acacia	+
Psyllium	+
Amberlite -200 resin	+
Hydroxy Propoxy Cellulose	+
Chitosan	+

+++ =Excellent, ++ =Fair, + =poor

Anionic Polymers

Due to their high mucoadhesive functionality and low toxicity, the anionic polymers are the most widely employed mucoadhesive polymers. They are distinguished by the presence of carboxyl and sulphate functional groups which exhibit negative charge at pH values exceeding the plea of the polymer.

Example:- Poly (acrylic acid), Polycarbophil, Carbopol

Poly acrylic acid extensively studied as mucoadhesive platforms for drug delivery to GI tract (Singla AK. et al., 2000). Polycarbophil has increased swelling capacity under neutral pH environment but it is insoluble in aqueous media. Polycarbophil is exhibited to increase its mass 100 times in aqueous media at neutral pH (Robinson J. et al., 1995). Polyacrylic polymers (Ugwoke M. et al., 1999) are existing with a wide range of molecular weight, which posses simply gel forming network, non irritant, non toxic and are considered safe for oral use by the FDA.

Cationic Polymers

Cationic polymer shows negative charge at physiological pH which tends to interact with the mucus surface. Chitosan (Portero A. et al., 2007) is most widely investigated for its mucoadhesiveness which occurs due to the electrostatic interaction of amino groups with the sialic groups of mucin in the mucus layer. Chitosan a cationic polysaccharide, produced by the deacetylation of chitin. Among presently investigated mucoadhesive polymers, chitosan has given superior importance as it is showing good biocompatibility, biodegradability and due to their approving toxicological properties.

Novel Second Generation Polymers

Second generation polymers are less prone to mucus turnover rates, with some species binding specifically to mucosal surfaces with more precision which are termed as cytoadhesives. As surface carbohydrates and protein composition differs regionally at target sites, drug delivery may be achieved accurately.

Examples:- Lectins, Bacterial adhesion, Thiomers

Lectins

Lectins exhibit significant benefits in relation to site targeting, many are toxic or immunogenic and effects of repeated lectin exposure are largely unidentified. Lectins are naturally occurring proteins that play a key role in biological recognition phenomenon involving cells and proteins. Lectins belong to a group of structurally different proteins and glycoproteins that can attach reversely to a exact carbohydrate residues (Clark MA. et al., 2000). After initial mucosal cell adhesion, lectins can either remain on the cell surface or in the case of receptors mediated adhesion which became internalized during a process of endocytosis[44]. Such systems could offer duality of functions in that lectin based platforms could not just allow targeted specific attachment but additionally offer a method of controlled drug delivery of macromolecular pharmaceuticals passing through active cell mediated drug uptake (Lehr C. 2000). Based on the molecular structure, three groups of lectins can be differed.

1. Merolectins: Having only one carbohydrate recognizing domain
2. Hololectins: Attaining two or more carbohydrate recognizing domain

3. Chimerolectins: Having additional unrelated domain

Bacterial adhesion

Target specific drug delivery can be achieved where the pathogenic bacteria readily adhere to mucosal membranes in the gastrointestinal tract. K_{99}-Fimbriae, an attachment protein derived from *E.coli* has been covalently attached to polyacrylic acid derivatives (Bernkop-Schnürch A. et al., 1995).The drug delivery system based on bacterial adhesion can be an efficient mechanism to enhance the adhesion of bioadhesive microspheres to epithelial surfaces.

Thiolated polymers

A new generation of mucoadhesive polymers is thiolated polymers or designated thiomers. They are derived from hydrophilic polymers such as polyacrylates, chitosan and deacetylated gellan gum (Leitner V. et al., 2003). The presence of gellan groups allows the formation of covalent bonds with cysteine rich sub domains of the mucus gel layer, leading to increased residence time and improved bioavailability (Albrecht K. et al., 2006). Thiomers (Dekker J et al., 2002) are mimic, the natural mechanism of secreted mucus layer by the creation of disulfide bond. The covalent bonding mechanisms lead to interaction that are less prone to changes in ionic strength or pH.

Common sites of application for mucoadhesive drug delivery

The mucoadhesive formulations have been broadly used for their targeted and controlled release delivery to various mucosal membranes which are lined on the body parts such as oral cavity, eye conjunctiva, GI tract, nasal cavity and vagina.

Oral mucoadhesive drug delivery system

Oral ingestion is the most preffered and predominant for drug delivery. The buccal and sublingual routes are considered as the most usually used routes. The non keratinized epithelium (Leung SHS. Et al., 1992) in the oral cavity, such as the soft palate, the mouth floor, the ventral side of the tongue and the buccal mucosa, provides a relatively permeable difficulty for drug transport.

The buccal mucosa has excellent convenience, an expanse of smooth muscle and relatively inert mucosa which has shown the prolonged presence of dosage forms. Through internal jugular vein it directly enters in to the systemic circulation the drugs are bypassed from the hepatic first pass metabolism leading to high bioavailability. Buccal drug delivery (Patel VM. et al., 2007) can be removed in cases of toxicity during the removal of dosage form thereby presenting a safe and easy method of drug utilization.

Other advantage include quick onset of action due to highly vascular buccal mucosa, low enzymatic activity, painless administration, versatile for designing both as a unidirectional or multidirectional release systems for local or systemic actions .

Due to the occurrence of large number of smooth muscles and immobile mucosa, sublingual mucosa has shown more permeability than the buccal mucosa. The release of drug in sublingual route is more rapid were as in buccal mucosa, the release of drug is achieved in a controlled manner.

Nasal mucoadhesive drug delivery system

The nasal delivery mucosa (Grezeskowiak E. et al., 1998) provides a vital route for systemic drug delivery. The nasal epithelium exhibit a relatively high permeability where the presence of highly dense vascular network. The advantage of intranasal drug delivery is to the nasal cavity provides a large highly vascularized surface area during which first pass metabolism can be avoided, when the blood drained from the nose to systemic circulation.

The disadvantage of this route is the fast clearance from the nasal cavity thus preventing extended periods for drug release. The most interesting areas of research in the field have been the use of intranasal drug delivery for the induction of antibody responses in serum as well as local and distal mucosal secretions, owing to the absorption through the nasal associated lymphoid tissue.

Ocular drug delivery system

The delivery of drug (Saettone M. et al., 1995) to the eye is a challenging task because there are several activities such as tear production, tear flow and blinking of eyes which defend the eye from external environmental factors. The types of dosage forms which may be induced into eye include drops, gels, ointments and solid ocular inserts (Carlfors J. et al., 1998). The major concern over the use of mucoadhesive polymers within the eye is the non-specificity of first generation platforms. Due to the continuous blinking of eye lids, there is a rapid removal of drug from the ocular cavity which results in poor bioavailability. This can be overcome by delivering the drug in the form of ocular inserts or patches. Ocular inserts may present improved control of drug release rate and prolonged residence times.

Gastrointestinal mucoadhesive drug delivery system

Gastrointestinal tract delivery has emerged as a most vital route of administration. Mucoadhesive retentive dosage forms involve the use of mucoadhesive polymers which can hold on to the epithelial surfaces in the GIT which results in the increased residence time and increased bioavailability. Targeted drug delivery systems in this respect have been focused on mucoadhesive patches and micro particles using first generation polymers. The large mucoadhesive dosage forms such as tablets shows reduced adherence to mucosal surfaces due to large dosage mass shared with the vigor-

ous movement of the GI tract. The use of mucoadhesive delivery systems have resulted in changed pharmacokinetic profiles where there is limited evidence to suggest to such a phenomenon is directly related to increased adhesion within the gastrointestinal tract (Davis SS. 2005). Some of the factors limiting their success are the high mucus turnover and encasement of delivery vehicle within mucus shell which be significant.

Rectal mucoadhesive drug delivery system

Drugs that are proposed to undergo extensive first pass metabolism can be bypassed by delivering through the rectal route.

Vaginal drug delivery system

Since ancient times, it has been known that the vagina as a route of drug delivery which had been offering many advantages like averting of first pass metabolism, severity of gastrointestinal side effects, avoidance of pain, tissue damage and permitting low molecular weight drugs. Several drawbacks include cultural sensitivity, gender specificity, personal hygiene, local irritation and influence of sexual intercourse to be noticed while designing vaginal formulation (Davis SS. et al., 2005). Vagina is a fibro muscular tube connecting the uterus to the outer surface of the body. The surface area is improved by numerous folds in the epithelium and the micro ridges covering epithelial cell surface (Vermani K. et al., 2000). Changes in the thickness of vaginal epithelium (Ishida M. 1983) lead to the considerable change in the rate and extent of absorption of vaginally administered drugs.

Existing formulations used

Tablets

Mucoadhesive tablets have the prospective to be used for controlled release drug delivery. They adhere to the mucosa increasing the retention time. The mucoadhesive tablets under studies had shown to deliver therapeutic doses of Flurbiprofen near the saliva for 12hr. The tablet coupled with mucoadhesive properties had shown efficient absorption and increased bioavailability of the drugs due to a high surface to volume ratio and provides a much more contact with the mucus layer. The daily dosage requirement was decreased as the drug release was sustained within the oral cavity. Staraint™ is available as a commercial mucoadhesive tablet for testosterone replacement therapy (Saettone M. et al., 1995) and Nitrogard is a different mucoadhesive tablet which delivers nitroglycerin for angina relief and prevention.

Sprays

Across the sublingual mucosa, glyceryl trinitrate has been rapidly delivered for angina relief using a spray. The RapidMist™ spray developed by Generex Biotechnology corporation is capable to deliver large molecular, such as insulin across oral mucosa (Vazquez JA. et al., 2010). The new applications of the RapidMiSt™ system in development include vaccination against influenza and cancers, pain management and weight loss.

Films/Wafers

In terms of flexibility and comfort, the mucoadhesive films may be opted rather than adhesive tablet. The mucoadhesive films consists of polymeric films which are capable of loading upto 20mg of drug which gets dissolved on the tongue in less than 30sec. They directly deliver the drug to the systemic circulation by crossing permeability (Intel Genx Corp. et al., 2006) barrier where rapid treatment of conditions is necessary such as migraines, motion sickness, pain relief, impotence and nausea.

Patches

Patches are intended to deliver the drugs in a controlled way which adhere to the oral mucosa. There are functionally three different types of Oro-adhesive patches. Patches with a dissolvable matrix which delivers the drug to the oral cavity. These are longer acting than tablets and lozenges and produce sustained drug release. Non-dissolvable backing patches systems used for systemic drug delivery. They deliver a controlled dose into the oral mucosa for 10-15hr. The main disadvantage is that the patch can deliver a limited dose of drug and the patch has to be removed after the dose is delivered.

Gels

Since 1980's, gels have been investigated as a means of controlled drug delivery system. The bioadhesive gels are prepared to provide localized drug delivery inside the body to enhance the drug absorption process in a site specific approach. The advantage of gel is easy dispersion throughout the oral mucosa. By using mucoadhesive formulation, retention time of gels have been increased providing adequate drug penetration. The medicinal agents used for treating periodontitis is delivered at local site using adhesive gels.

Methods of evaluation

For testing the effectiveness of the mucoadhesive capability of a polymer matrix various *in-vitro* and *in-vivo* methods are performed. The various methods used to know the mucoadhesive properties are

Method of determining mucoadhesive strength

Method used to assess the mucoadhesiveness of the system is through the determination of adhesive strength between polymer and the attached substrate. The adhesive strength at the bonding interface can be calculated by measuring the force required to detach from one entity to other through the application of external force. Application of either tensile, shearing or peeling force lead to the destruction of adhesive bond. To conclude the mucoadhesion of various polymers,

the modified edition of Wilhelmy Plate is used which consists of a glass plate suspended from a microbalance and immersed in a model of mucus under controlled temperature which is depicted in Figure 2. Under constant experimental conditions, the force required to dettach the plate out of the sample is measured (Smart JD. et al., 1984).

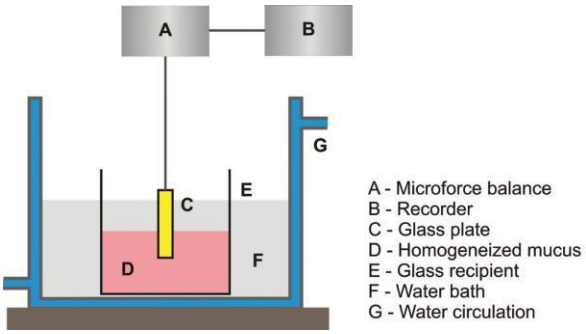

Figure 2: Apparatus to determine mucoadhesion using Wilhelmy's technique

***In-vitro* permeation test**

The most common methods used for determining the mucoadhesive properties are done by performing *in-vitro* tests. These tests are vital in the development of controlled release mucoadhesive systems as they help in determining the permeation release kinetics, compatibility and physical stability.

Wash off/mucoadhesion test

The equipment used to measure the rupture tensile strength is the texture analyzer or a universal testing machine.

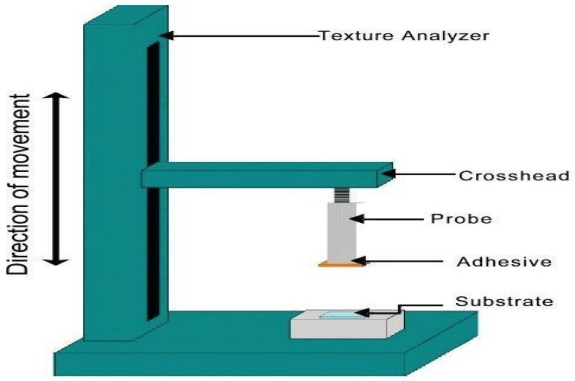

Figure 3: Texture profile analyzer in bio-adhesion test mode

In this test, a piece of animal mucous membrane has been taken and tested for the force required to take away the formulation from a model membrane which consists of disc composed of mucin. The extensively used commercial apparatus [depicted in Figure 3] which operates in bioadhesive test mode.

Adhesive weight method

To assess the specific adhesion force of microparticles, Wilhelmy plate technique or microforce balance technique can be used. It involves the application of microforce balance and microtensiometer which is more specific in yielding the contact angle and surface tension. By controlling the pH and physiological temperature, the mucous membrane is located in a small mobile chambers. A distinctive microsphere is inserted by a thread to a stationary microbalance. The mucous membrane present in the chamber is lifted up until it comes in contact with the microsphere and after contact, time is lowered back to initial position. Microsphere having size smaller than 300µm are not indicated by microforce balance but has the advantage of providing results at a more microscopic lenses, rather being more reproducible and sensitive.

Rheological measurement of mucoadhesion

In predicting the mucoadhesive capability of a polymer formulation the flow and deformation study can be useful. The rheological profiling of polymer mucus mixture can provide an suitable *in-vitro* model representatives of true *in-vivo* behavior of mucoadhesive polymers (Riley R. et al., 2001). The rheological move towards polymer systems was first suggested by Hassan and Gallo. In this method, the rheological interaction between a polymer gel and mucin was determined. The results showed that the mucoadhesive polymers/mucin mixture exhibited rheological profiles, the causes of which are attributed to bond formation between polymer and mucus pertaining in an increase in total system structure.

***In-vitro* tensile strength**

It is done to determine the maximum force required to remove the filter paper and polymer surfaces after the mucoadhesive bonding. It is carried out by dipping a filter paper in 8% mucin dispersion. The filter paper coated with mucin is located in contact with the hydrated polymeric samples for a definite period of time to determine the tensile strength.

***In-vitro* drug release**

Using modified dissolution apparatus, the i*n-vitro* release was assessed in phosphate buffer solution with different pH values at 37^0c. The apparatus consists of 250ml beaker as a receptor compartment along with a glass rod attached to a grounded glass disk as a donor tube. The mucoadhesive release buccal tablet was fixed with the glass disk with instant adhesive. The donor tube was then immersed into receptor compartment and specific conditions were maintained. The solution was drawn and was filtered by using 0.2µ filter and the amount of pH released was determined by measuring the absorbance at 290nm using UV spectrophotometer. The cumulative quantity of drug release was calculated by plotting on the graph.

Falling liquid film method

Rango Rao and Buri (1989) proposed a method which was used by Nielsen, Schubert and Hansen (1998) where the mucus membrane was placed on to stainless

steel cylindrical tube which has been longitudinally cut. In a cylindrical cell the support is placed inclined with a temperature maintained at 37^{0}c. Through the mucous membrane, the isotonic solution was pumped and collected in a beaker (Fig.4).

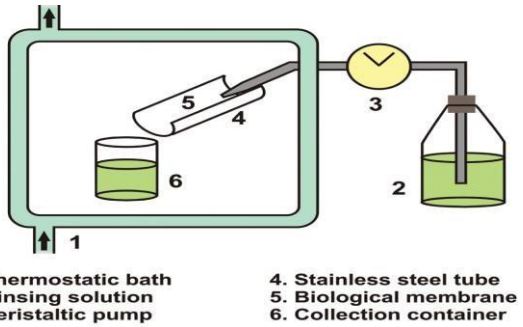

Figure 4: Schematic representation of in-vitro model used by Nielsen, Schubert and Hansen (1998)

The amount present on the mucous membrane can be counted by using coulter counter. For semi solid systems, by using high performance liquid chromatography, the non-adhered mucoadhesiveness can be quantified. The validation of this method showed that the type of mucus used does not rely on the results obtained. The method allows the observation of formation of liquid crystalline mesophase on the mucus membrane after the flowing of the fluids and through analyst by means of polarized light microscopy.

Fluorescent probe method

The extension of adhesion exhibited by the polymers can be assessed by using this method. The method requires the labeling of membranes and phospholipids with fluorescein isothiocyanate. The components are then combineed with the bioadhesive material and any changes in the fluorescent spectra can be determined.

Biacore method

It is an another method used for evaluating the adhesivity of adhesive polymers to mucin. It is based on the principle underlying an optical phenomenon called Surface Plasmon Resonance (SPR) (Myszka DG. et al., 1998). In Biacore method, the mucoadhesive property of polymers was found where each polymer was immobilized on the surface of the sensor chip and the mucin suspension was passed through the sensor chip. When the mucin particle binds with the polymer on the sensor chip surface, the solute concentration and the refractive index on that surface alters by increasing resonance unit responses. The analyte can be removed from the polymer by means of a regenerating reagent. The major advantage of Biacore method is its label free detection of binding and the ability to observe the change in response to real time.

CONCLUSION

The procedure of mucoadhesion can permit for the target-controlled delivery of wide range of therapeutic molecules. Mucoadhesive drug delivery system is a capable technology with vital applications in the development of drug delivery systems. It shows a promising future in enhancing the bioavailability and particular requirements by using the physico-chemical factors of both the dosage form and mucosal lining. Among all polymer properties, the charge, hydrophilicity and molecular weight can affect the efficacy and success of adhesive bond. Moreover, environmental factors like tonicity and mucus turnover rate must also be considered before formulating mucoadhesive systems. Taking such kind of considerations into account, polymers can be structured chemically and engineered for the purpose of particular pharmaceutical application. A promising research in this area is still needed to develop more efficient mucoadhesive polymers and carriers and to develop a platform technology for delivery of different categories of drugs like peptides, enzymes and biotechnology products by various routes of administration.

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