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Mucoadhesive Property: A Better Approach in Designing and Development of Dosage Form [A Review]

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Abstract: Mucoadhesion can be defined as the adherence of two components together with each other for longer period of time due to the influence of interfacial force of attraction. In mucoadhesion, the one component must have biological origin and other component may be synthetic or biological origin. In the phenomenon of mucoadhesion wetting, adsorption and interpenetration is occurs. Mucoadhesion can be used as drug delivery system due to various advantages like longer residence time, avoiding hepatic first pass metabolism. In the current review emphasis has been given on the various routes for administration of drug using mucoadhesion as property, mechanism and different theories related to mucoadhesion and classification of mucoadhesive materials. The present study also focuses on various patents for the delivery of drug using mucoadhesive properties.

Key words: Mucoadhesion · Adsorption · Drug Delivery · Mucoadhesive Materials Etc

INTRODUCTION

Now a day there is various drug delivery systems are used for administration of drugs through different routes. In early 1980's, a new property for delivered of drugs *i.e.* mucoadhesion was introduced [1, 2]. Mucoadhesion and bioadhesion are common terms used in the dosage form. These two terms have some difference like in bioadhesion, the adhesion of two biological surfaces or one biological and other synthetic surface via any of bond occurs while in mucoadhesion, the mucus coat acts as the adhesive attachment. The primary requirement for bioadhesion is that one surface should be biological in nature [3, 4]. Epithelial tissue is one of the best examples of the biological surface. Mucoadhesion increases the contact period between the mucus membrane and the drug delivery system which results in the increased residence time of particular dosage form at the mucous membrane. The invention of mucoadhesive property make a new era in development of dosage form and become a point of attraction for researchers to find the alternative approach for administration of drug by different types of dosage form. The phenomenon of the mucoadhesion can be used by various routes like Buccal, Vaginal, Nasal, Ocular, Sublingual, Gastro intestinal etc for administration of drugs.

Advantages of Mucoadhesive Property [2-5]: Muchoadhesive property for the drug delivery system has several advantages as followings:

- Targeting of drug is possible.
- Increased residence time, thus led to the more therapeutic effect of the drug.
- Mucosa and dosage form are in closed contact so as to produce better effect.
- Local disorders can be targeted.
- Minimum side effect.
- Overall dose of drug can be reduced.
- Due to presence of large number of blood capillaries and high blood flow at the mucoadhesive site, the rate of absorption becomes higher.
- Avoid hepatic first pass metabolism.
- In comparison with the acidic environment of the gastro intestinal tract, the drug is protected from the degradation.

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Mechanism of Mucoadhesion [6, 7]: Almost every mucosal route has low residence time (Less than one hour) which cause incomplete absorption of drug from its dosage form at the site. To overcome such kind of problems some polymers containing mucoadhesive property are generally used in designing and development of dosage form. The mucoadhesive polymers increase the adhesion of dosage form to the mucous membrane or increases the residence time of the drug delivery system.

The mechanism of adhesion of certain macromolecule is not much clear but it is assumed that the mucoadhesion is occurs by following three steps.

- First of all the wetting and swelling of polymer takes place.
- Secondary interpenetration of polymer takes place and
- At last, the formation of weak bonds like vandervaals and electrostatic bonds takes place.

Factors That Effect Mucoadhesion [8, 9]:

I. Factor Based upon Polymers: Polymer's molecular weight, concentration of the used polymer, swelling of the polymer.
II. Physical Factors: pH of the surface to which the preparation adheres, contact time and temperature of the mucin.
III. Physiological Factors: Diseased state and rate of the mucin generated.

Various Theories Related to Mucoadhesion [10, 11]:

a. Electronic Theory:This theory states that the attractive forces between the mucin and bioadhesive material are responsible for the adhesion.
b. Adsorption Theory: According to this theory the forces on the surface results in the formation of chemical bond.
c. Wetting Theory: This theory states that it is the capability of the bioadhesive polymer to spread over the mucin surface and develop the immediate contact with the mucus membrane leads to the formation of mucoadhesion.
d. Diffusion Theory: According to this theory the physical arrangement of the mucus strands with the polymer chains is responsible for the mucoadhesion.

Various Routes Drug Delivery Systems

Buccal Route: The outer most layer of oral route is made up of the stratified squamous epithelium, under which lies the basement layer, lamina propria and the innermost layer is submucosa. The buccal mucosa epithelium is 40-50 cell layer thick, the estimated turnover of the buccal epithelium is 5-6 days. The buccal mucosa is 500-800 µm in measurement.in comparison to the skin the permeability of buccal mucosa is 4-4000 times greater. The buccal drug delivery have many advantages for the application of drug delivery like easy accessibility and lower enzymatic activity, also the termination of the therapy is easy in case of any contradiction which makes it safer to use for the drug application [12]. Through this route the polymers like sodium carboxymethylcellulose, hydroxypropylcellulose and polycarbophil are administered for the peptide, proteins and polysaccharide [13-15]. Patient compliance is very high through this route. Many mucoadhesive systems such as buccal patches, film, gel, tablet etc. are used for the administration of the drug [16, 17].

Ophthalmic Route: Eye is spherical in shape the eye wall comprising of three layers the outermost is sclera, the middle one is choroid layer and the inner most is the retina. The epithelium of the eye is squamous stratified with the thickness 50-100µm with the turn over one cell layer a day. Different mucoadhesive delivery systems are used for the achievement of the therapeutic effect through this route like *in situ* gel, inserts, ointment, eye drops etc. they can be formulated through both biodegradable and non biodegradable materials [18, 19]. This route shows lower bioavailability for the *in vivo* administration of the carbomer and polycarbophil [20]. Viscocity and the pH are the two important factors which are kept in mind while designing a delivery system for the ophthalmic route alteration in them because the irritation to the patient, finally leads to the termination of the therapy [21].

Vaginal Route: The human vagina is 6-10cm long. The vaginal wall is categorized in three layers the outer most is epithelial layer, middle layer is muscular coat and the inner most layer is tunica adventia. Vagina lacks of any gland but it secretes large amount of fluids. Lactic acid in vagina acts as the buffer and maintains the pH between 3.8-4.2. Variousmucoadhesive delivery systems like pessaries, tablets, gels etc. are used through this rote for the therapeutic effect. This route have many advantages like drug delivery system administered through this route avoids the hepatic first pass

metabolism, large surface area, high vascular blood supply but the frequent cleansing mechanism and mensuration cycle of the vagina is this limitation of this route. Bioadhesive polymers such as polycarbophil, hydroxypropylcellulose and polyacrylic acid are used in the preparation of major vaginal preparations [22-28].

Nasal Route: The gross surface area of nasal cavity is about 150 cm^2 and the gross volume is about 15ml. Nasal septum divides the nasal cavity into two halves. The individual volume of each cavity is approx. 7.5ml and surface is about 75 cm^2. The nasal cavity has three main regions vesitibular, respiratory and olfactory region. The major advantages of this route are that the drug deliver through this system avoids hepatic first pass metabolism and highly vascularised surface provide large surface area for drug absorption. Many mucoadhesive drug delivery systems like nasal gel, powders, *in situ* gel etc. are used for drug delivery. One of the major limitations of this route is mucocilliary clearance. Majorly sympathomimetic vasoconstrictors, alpha adrenergic stimulators are administered through this route, drug targeting can also be done through this route [29, 30].

Various Mucoadehsive Materials: Mucoadhesive material were used to form the adhesive tablets for the treatment of the stomatis additionally it was also found that the insulin shows greater bioavailability in the form of mucoadhesive powder as compared to the tablet, when it was administered through the nasal route [31, 32]. The mucoadhesive materials were categorized into two generation that is first generation mucoadhesive materials and second generation mucoadhesive materials.

Generation First Mucoadhesive Materials: Basically materials of this generation are natural or may be synthetic hydrophilic molecules which contain many functional groups. Which leads to the generation of the hydrogen bonds like carboxyl, hydroxyl and amino groups does not adhere to a specific surface. The mucoadhesives were used as denture mixers and common examples of these are carbomers, chitosan, alignates and derivatives of cellulose. These compounds can be used in the different solid formulations like tablets, transdermal, micro particles etc. and in semisolid preparations like gels, suppositories, pesseries, paste and ointments [33]. The first generation mucoadhesive polymers are categorized into three catogries, these are cationic, anionic and non ionic. The cationic molecule interacts with the mucus membrane at the physiological pH which is negatively charged. Due to the electrostatic interaction of the amino group of the polymer with the sialic group of mucin. This type of mucoadhesion occurs in the polymer like chotosan. Chitosan is extracted from the deacetylation of chitin. It is a semi-synthetic polymer. It is used as mucoadhesive polymer in various mucoadhesive drug delivery systems [34]. Many studies on chitosan show that it can enhance the absorption of hydrophilic molecule [35]. It was also found in the various studies that the mucoadhesion property of chitosan is higher than the carboxy methylcellulose and poly carbophil.

The polymers which are derived from polyacrylic acid are anionic and mucoadhesive. The phenomenon lies in the mucoadhesion of these polymers is physical chemical process like hydrophobic interactions, hydrogen and van der waals bonds, pH and ionic composition controlled these systems [34]. Polyacrylic acid hydrogels are mostly studied mucoadhesive systems. In partially hydrated state the structural chain of these hydrogels are very flexible and having non abrasive characteristics, this nature of polymer reduces the tissue damage which is caused due to friction when they come in contact with each other [36]. Mostly the poly acrylic acid derivatives like polycarbophil are insoluble in water but on hydration they form viscous gel [34]. Carboxy methyl cellulose and alignates are other example of anion polymers.

Non ionic polymers are the third category of the first generation mucoadhesive material. It basically includes hydroxypropylmethylcellulose, hydroxyl ethylcellulose, methylcellulose etc. [37]. It is the newly discovered class of the bioadhesive material. this class include the esters groups of fatty acid like glycerylmonooleate and glycerylmonolinoelate, these have cabability to form liquid crystal which helps in formation of controlled drug delivery system. Lyotropic liquid crystalline meophases of these fatty acids were occurred at the body temperature [38]. Some of the hydrogels do not form crystals, but they have capability of forming gel. When they are exposed to the external stimuli. These type of systems are dependent on the environmental stimulus like temperature and pH.Poloxamers and carbomers are the thermosensitive polymers and polymers polyacrylic acid is an example of pH sensitive polymer [39, 40]. The rheological property of both environmental dependent polymer and liquid crystals are determine the phenomenon of mucoadhesion for the gel [39-41].

Generation Second Mucoadhesive Materials: These have several advantages over the first generation like site specificity, drug targeting and they do not alter with production rate of the mucus. Many multifunctional materials are used to study the novel mucoadhesive systems. But the polymer which have capability of incorporating the both hydrophilic and lipophillic drug, which also shows the mucoadhesion characteristics in both liquid and solid state, also it should have the ability to prevent the drug from enzymatic degradation and should have to increase the absorption of the drug to a particular site of action like on tissue or a cell. These are the some of the ideal features of the polymer and these polymers are called as the second generation polymers [7]. These are used instead of non specificbioadhesive [33]. Due to the reason that they are structure specific so as to adhere the specific chemical structure of a cell or tissue or a mucus surface. Lectins, invasins, fimbrial proteins, antibodies and the compounds which are obtained from the addition of thiol group to several known molecules are the some of the best examples [34, 42, 43].

Lectins come under the category of the immunogenic vegetal glycoproteins and also have a property to recognize sugar molecule. They also have the cabadilityof binding non covalently to the glycolated components of the cell membrane. But they does not bind with the mucus. This type of adhesion is called cytoadhesion.

Commonly the isolation of pectinsare done from *Abrusprecatroius, Agaricusbisporus, Anguilla anguilla, Arachishypogaea, Pandeiraeasimplicifolia and Bauhinia purpurea* [42].

*Yersinia pseudotuberculosis*is an example of bacteria in which phagocytosis is stimulated at cell membrane via integrin receptor. Adherence to the epithelial surface of erythrocytes is an ability of bacterial fimbrial proteins. It occurs due to the adherence property of bacteria is an efficient mechanism for enhancing the adhesion strength of the mucoadhesive materials.

Due to the site specificity of the antibodies, they can be used against variety of the molecules which are existing on the mucus surface. The site specificity of the antibodies makes them a rational choice for developing site-specific mucoadhesives. Antibodies can also being used for the targeting of the drug.

Various Patents on Different Mucoadhesive Formulation:-

S.NO	APPLICANT	PATENT ON	PATENT NO.	YEAR
1	BettiniRuggero *et al.*	Relation of aqueous compostions of hyaluronic acid in addition with its salt comprising of mucoadhesive and thermosensitive property.	TW201429478(A)	2014 [45].
2	Nordsiek Michael and BalajiKodumudi	Aqueous based gel formulation of metronidazole having mucoadhesive property used for several purposes.	MX2014000066(A)	2014 [46].
3	Masters David and Berg Eric	Method of Prepration and use of mucoadhesive drug delivery devices	US2014107227(A1)	2014 [47].
4	Sant-Lu Nathalie *et al.*	Mucoadhesive formulation for curing pathological reaction of immune system by inducing tolerance to an antigen.	US2014079795	2014 [48].
5	Johannes Leierer	Improved property of polymer compounds by the covalent binding of the thiol group.	CN103709289(A)	2014 [49].
6	Hubinette Fredrick	Method of Formulation of nicotine mucoadhesive film.	CA2868445 (A1)	2013 [50].
7	Choy Young and Park Chun Gwon	The nanostructure mucoadhesive particle used as drug delivery system having long retention time on mucus surface and showing less irritation to it.	KR20130127934(A)	2013 [51].
8	Attali Pierre *et al.*	Mucoadhesive buccal tablets are used for the prevention of herpes simplex virus disease.	US2013210841(A1)	2013 [52].
9	DekinaSvitlana Serhivna *et al.*	Various formulation recipes of mucoadhesive film.	UA99889(C2)	2012 [53].
10	Popov T *et al*	Method for preparing a pharmaceutical composition with enhanced mucoadhesion	GB2423711 (A)	2006 [54].

Addition of the conjugated sulfidryl groups formed the thiolated polymer. Thiolated chitosan is an example of thiolated polymer. It shows greater mucoadhesion because of the formation of the disulfide bridge glycoproteins present in the mucus. These products also enhance the mucus permeation. The enhancement in the mucus permeation occurs by the mechanism of glutathione regeneration so they offer antiprotease activity because of the binding capability with the divalent cations. These features of thiolated chitosan make it an ideal polymer for the delivery of proteins and peptides in the mucus membrane. Tiolatedpolycarbophil also greater mucoadhesion [44].

CONCLUSION

Mucoadhesion as an drug delivery system attracts attention of various researchers now a days due to many of advantages like avoidance of first pass metabolism, increased retention time, patient compliance, improved bioavailability and greater surface absorption of drug. The adherence time of the dosage form with the mucus membrane is greater which in turn increases the effectiveness of a drug delivery system. This review include many factors which makes mucoadhesion as an ideal drug delivery system and various routes through which administration of mucoadhesive formulations are possible.

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