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REVIEW ARTICLE

Gastrointestinal mucoadhesive drug delivery system: an overview

Rajesh Asija[1]*, Sangeeta Asija[1], Pankaj Vyas[1], Raj Singh Chauhan[1], Nitin Nama[1]

[1]Maharishi Arvind Institute of Pharmacy, Jaipur-302020, Rajasthan, India

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ABSTRACT

The current article has been focused on the mucoadhesive drug delivery system. Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiological characters of both the dosage form and the mucosal lining. Gastrointestinal mucoadhesive dosage form may be designed to enable prolonged retention time at the site of absorption as well as providing a controlled rate of drug release for improved therapeutic outcome. Various sites for mucoadhesive drug delivery system are bucal cavity, nasal cavity, ocular, gastrointestinal tract, vaginal, rectal. This review article aims to provide an overview of the various aspects of mucoadhesion like mechanism and theories involved in mucoadhesion as well as to describe the most used methodologies and polymers in mucoadhesive drug delivery system.

Key words: Mucoadhesive drug delivery system, Bioavailability, Mucoadhesion, Gastrointestinal tract

INTRODUCTION:

Since the early 1980s, the concept of Bioadhesion has gained considerable interest in pharmaceutical technology. Bioadhesion may be defined as the state in which two materials, at least one of them is biological in nature, are held together for an extended period of time by interfacial forces, which may consist of valence forces, interlocking action, weak van der waals and hydrogen bonds.[1] Mucoadhesion is the relatively new and emerging concept in drug delivery so mucoadhesion can be defined as the ability of synthetic or biological macromolecule to adhere to mucosal tissue. The concept of mucoadhesion is one that has the potential to prolong the residence time of the dosage form at the site of absorption. It makes easier the contact of the dosage form with the underline absorption surface and thus contribute to improved or better therapeutic performance of the drug.[3]

The mucoadhesive drug delivery system may include the following:

1. Buccal delivery system
2. Sublingual delivery system
3. Nasal delivery system
4. Ocular delivery system
5. Vaginal delivery system
6. Rectal delivery system
7. Gastrointestinal delivery system[4]

Mechanisms of mucoadhesion:

The mechanism of mucoadhesion is divided into two steps:

(1) Contact stage and (2) Consolidation stage.

Contact stage is characterized by the contact between the mucoadhesive and the mucous membrane. Formulation intiating it's deep contact with mucous membrane by spreading and swelling. In the consolidation step, the mucoadhesive are activated in the presence of moisture. Moisture plasticizes the system, and breaks the molecules of mucoadhesive and allows them to link up by weak vander waals and hydrogen bonds.[6]

Theories of mucoadhesion:

Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories of mucoadhesion adapted from studies on the performance of several materials and polymer adhesion which explain the phenomenon.

Electronic theory: It is based on the premise that both mucoadhesive and biological materials acquire opposite electrical charges. Thus, when both materials mucoadhesive and biological layer come into contact with each other, they transfer electrons between them leading to the building of a double electronic layer at the interface.

Adsorption theory: According to the adsorption theory, the mucoadhesive material adheres to the mucus layer

*Corresponding author: Dr. Rajesh Asija || E-mail: rjchauhan0888@gmail.com

by secondary chemical interactions, such as electrostatic attraction or hydrophobic interactions ,van der Waals bonds and hydrogen bonds.

Wetting theory: The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be originated by using measuring techniques such as the contact angle. The general rule states that the contact angle is inversely proportional to the affinity. The contact angle should be equal or close to zero to provide adequate spreadability.

Diffusion theory: Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. It is supposed that the adhesion force increases with the degree of penetration of the polymer chains. The penetration rate is depends on the nature of the mucoadhesive chains, flexibility and, mobility, diffusion coefficient and contact time

Fracture theory: This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It determines the force required to separate two surfaces after adhesion is established.

Mechanical theory: Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.[8]

Mucoadhesive polymers:

Mucoadhesive drug delivery systems are based on the adhesion of a drug/ carrier to the mucous membrane. To promote this adherence a suitable carrier is required.

Various mucoadhesive polymers can broadly categorized as follow in table 1:

Table 1: mucoadhesive polymers

Polymers	Examples
Synthetic polymers[11]	Cellulose derivatives (Ethyl cellulose, Methylcellulose, Hydroxyl ethylcellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose), Poly acrylic acid polymers (Carbomers, Polycarbophil)
Natural polymers[11]	Tragacanth, Chitosan, Sodium alginate, Gelatin, Guar gum, Xanthum gum, soluble starch.

Mucoadhesive polymers can also classify into subsequent categories:

Traditional non-specific first-generation mucoadhesive polymers:

First-generation mucoadhesive polymers may be divided into two major categories, namely:

1) Anionic polymers,
2) Cationic polymers,

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Typical examples include Poly acrylic acid (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin.

In the cationic polymer systems, definitely chitosan is the most extensively used polymer. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose.[12]

Novel second-generation mucoadhesive:

Lectins: The most widely investigated of such systems in this respect are lectins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues.

Thiolated polymers: The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present inmucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly acrylic acid and chitosan).Various thiolated polymers include chitosan–iminothiolane, poly acrylic acid–cysteine, poly acrylic acid–homocysteine, chitosan–thioglycolic acid etc.[3]

Factors affecting mucoadhesion:

1. Polymer-Related Factors:

i) Molecular weight:

The optimum molecular weight for maximum bio-adhesion depends upon type of mucoadhesive polymer at concern. The threshold molecular weight required for successful bio-adhesion is at least 100,000. For example, polyethylene glycol (PEG), with a molecular weight of 20,000 has less adhesive character, but PEG with 200,000 molecular weight has improved, and PEG with 400,000 has superior adhesive properties.

ii) Concentration of active polymer:

An optimum concentration for a mucoadhesive polymer to produce maximum bioadhesion is to be

determined. In highly concentrated system, adhesive strength drops significantly beyond the optimum level.

iii) Flexibility of polymer chains:

Chain flexibility is important for interpenetration and entanglement. The mobility of an individual polymer chain decreases when water soluble polymers become cross linked. As the cross linking density increases, the effective length of the chain which penetrate into the mucus layer decreases, which results in reduction in mucoadhesive strength.

iv) Spatial conformation:

Spatial conformation of a molecule is also important, besides molecular weight or chain length, despite a high molecular weight of dextrans that is 19,500,000, have similar adhesive strength to that of PEG, having a molecular weight of 200,000. Dextran have the helical conformation which shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.

v) Swelling:

Swelling characteristics are related to the mucoadhesive itself and its environment. Swelling depends on polymer concentration, ionic strength, and presence of water during the process of bioadhesion.[14]

2. Environment-Related Factors:

i) pH of polymer - substrate interface:

pH can influence the formal charge on the surface of the mucus as well as certain ionizable mucoadhesive polymers. Mucus has a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone

ii) Applied strength:

To place a solid mucoadhesive system, it is essential to apply a defined strength. The adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The initial pressure applied to the mucoadhesive tissue at the contact site, can influence the depth of interpenetration.

iii) Initial contact time:

Initial contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. As the initial contact time increases mucoadhesive strength is also increases.

3. Physiological Factors:

i) Mucin turns over

The natural turnover of mucin molecules from the mucus layer is important because the mucin turnover is expected to limit the residence time of the mucoadhesives on the mucus layer. Despite how high the mucoadhesive strength, they are separated from the surface due to mucin turnover.[15-18]

Approaches to mucoadhesive drug delivery system:

1) Gastroretentive drug delivery systems:

These are the systems which can remain in gastric region for several hours and significantly prolongs the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It releases the drug there in a controlled & extended manner, so that the drug could be supplied continuously to absorption site in GIT.

Mucoadhesive tablets

Mucoadhesive tablet have potential to be used for controlled release drug delivery but coupling of mucoadhesive properties to tablet has additional advantages. Mucoadhesive tablet can be tailored to adhere to any mucosal tissue found in GIT, thus offering the possibilities of localized as well as systemic controlled release of drug.[19]

Mucoadhesive micro and/or nanoparticles

Despite the limited loading capacity of drug, bioadhesive micro-and /or nanoparticles have been widely investigated for three major features

1. Immobilization of particles on the mucosal surface by adhesion after modification of surface properties via bioadhesive polymers.
2. Very large specific surface between the dosage forms and the oral mucosa.
3. Sustained release of entrapped drug, leading to higher absorption

2) Intestinal drug delivery system:

These are the systems which can remain in intestinal region for several hours and prolongs the intestinal transit time. Prolonged transit improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has also used for local drug delivery to proximal small intestines.

Mucoadhesive patch

One of the proposed approaches for inducing greater levels of absorption and stability at the intestinal epithelium is the use of a multilayered patch system. Patches consist of layers of thin, flexible membranes, an impermeable backing, a drug reservoir, a rate-controlling membrane; and an adhesive. When the patch is applied, the drug flows through the skin into the bloodstream at a rate regulated by the membrane that is preprogrammed to keep the drug at an effective level from a technological standpoint, these protective, rate-controlling and adhesive properties are also ideal for oral dosage forms intended for delivery to the intestinal mucosa.[26]

Evaluation parameters of mucoadhesion:

Mucoadhesive Strength:

Mucoadhesive strength of the tablet is measured on the modified physical balance. The appratus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height is fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This is kept in beaker filled with buffer media 0.1N HCl pH 1.2, which is then placed below right side of the balance.

Goat or rat stomach mucosa is to be used as a model membrane and buffer media 0.1N HCl pH 1.2 is used as moistening fluid. The underlying mucous membrane is separated by surgical blade and wash thoroughly with buffer media 0.1N HCl pH 1.2. It is then tied over the protrusion in the Teflon block using a thread. The block is then kept in glass beaker. The beaker is filled with phosphate buffer media 0.1N HCl pH 1.2 up to the upper surface of the goat stomach mucosa to maintain mucosa viability during the experiment. The one side of the tablet is attached to the glass slide of the right arm of the balance and then the beaker is raised slowly until contact between goat mucosa and mucoadhesive tablet is established. A preload of 10 mg is placed on the slide for 5 min (preload time) to established adhesion bonding between mucoadesive tablet and goat or rat stomach mucosa. The preload and preload time should be kept constant for all formulations. After the completion of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water stopped when mucoadhesive tablet is detached from the goat or rat stomach mucosa. The weight of water required to separate mucoadhesive tablet from stomach mucosa is to be noted as mucoadhesive strength in grams. Following parameters are calculated with the help of mucoadheshive strength [35-37]

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area of tablet (m2)}}$$

Swelling index:

Swelling of tablet excipients particles involves the absorption of a liquid which increases weight and volume of tablet. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. When liquid enters into the particles through pores and bind to large molecule which results breaking the hydrogen bond and causes the swelling of particle. Swelling can be measured in terms of % weight gain by the tablet.

For each formulation batch, single tablet is to be weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet is put out from the beaker and weighed again up to 8 hours. Following formula is used for calculating swelling index.[37-39]

$$\text{Swelling Index (S.I.)} = \frac{(Wt - Wo)}{Wo}$$

Where, S.I. = Swelling index

Wo= Weight of tablet before placing in the beaker

Wt = Weight of tablet at time t

Determination the Residence Time

The residence time of mucoadhesives at the application site provide quantitative information on their mucoadhesive properties. The transit time of GI of mucoadhesive preparations have been examined using radioisotopes and the fluorescent labeling techniques.

GI Transit using Radio-Opaque Tablets:

It is a simple procedure involves the use of radio-opaque markers, e.g. $baso_4$, used in the mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time. **Gamma Scintigraphy Technique:**

Distribution and retention time of the mucoadhesive tablets can be studied using the gamma scintigraphy technique. Study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled HYAFF tablets.[37,40]

CONCLUSION:

This overview about the gastrointestinal Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. These system remains in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to an increase in bioavailability and both local and systemic effects. There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (lectins, thiomers, etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides for future technological advancement.

REFERENCES:

1. Ahuja A., Khar RK, Ali J., Mucoadhesive drug delivery system. Drug Dev. Ind. Pharm. 23(5); 1997:489-515.
2. Bindu M. Boddupalli, Zulkar N.K. Mohammed, Ravinder A. Nath, David Banji, Mucoadhesive drug

delivery system: an overview, J. Adv. Pharma. Tech. & Res. 1(4); 2010:381-387.

3. Tangri P., Khurana S., Madhvan N.V.S., Mucoadhesive drug delivery: mechanism and methods of evaluation, Int. J. Pharma and Bio Sci. 2(1); 2011:458-467.
4. Alexander A., Ajazuddin, Tripathi D.K., Verma T., Swarna, Maurya J., Patel S., Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system: a review, Int. J. App. Bio.and Pharma. Tech. 2(1); 2011:434-445.
5. Dhutwalia P., Kanwar K., Anju, Amrit and Ankush, A review on mucoadhesive drug delivery systems: a novel approach, Int. J. Pharm., Chem. and Bio. Sci. 4(2); 2014:277-290.
6. Hogerstrom H, Edsman K, Strwmme M., Low-frequency dielectric spectroscopy as a tool for studying the compatibility between pharmaceutical gels and mucus tissue., J. Pharm. Sci. 92(9); 2003:1869-81.
7. Mythri G., Kavitha K., Rupesh Kumar M., Singh J., Novel mucoadhesive polymers –a review, J. Appl. Pharm. Sci. 1(8); 2011:37-42.
8. Callens C, Ceulemans J, Ludwig A, Foreman P. and Remon JP. Rheological study on mucoadhesivity of some nasal powder formulations. Eur. J. Pharm. and Biopharma. 55(3); 2003:323-328.
9. Helliwell M, The use of bioadhesive in targeted drug delivery within the gastrointestinal tract. Adv. Drug Deliv. Rev.11; 1993: 221-251.
10. Andrews G.P., Laverty T.P., Jones D.S, Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharma. and Biopharma. 71(3); 2009:505-518.
11. Rathee P., Jain M., Garg A., Nanda A., Hooda A., Gastrointestinal mucoadhesive drug delivery system: A review, J. Pharm. Res. 4(5); 2011:1448-1453.
12. Gavin P., Laverty T., David S., mucoadhesive polymeric platforms for controlled drug delivery, Eur. J. Pharma. and Biopharm. 7(1); 2009:505-518.
13. Mahajan P., Kaur A., Aggarwal G., Harikumar S.L., Mucoadhesive drug delivery system: a review, Int. J. Drug Dev. & Res. 5(1); 2013:11-20.
14. Madsen F., Eberth K., Smart J, A rheological assessment of the nature of interactions between mucoadhesive polymers and a homogenised mucus gel, Biomaterials 19(11-12); 1998:1083-1092.
15. Jamzad S., Tutunji L., Fassihi R., Analysis of macromolecular changes and drug release from hydrophilic matrix systems, Int. J. Pharm. 292(1-2); 2005:75–85.
16. Lueben H.L.V, Mucoadhesive polymers in peroral peptide drug delivery. V. Effect of poly (acrylates) on the enzymatic degradation of peptide drugs by intestinal brush border membrane vesicles. Int. J. Pharm. 141(1); 1996:39–52.
17. Apicella A., Cappello B., Del Nobile M.A., La Rotonda M.I., Mensitieri G., Nicolais L, Polyethylene oxide (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials 14(2); 1993:83-90.
18. Singh B, Chakkal S.K, Ahuja N, Formulation and optimization of controlled release mucoadhesive tablets of Atenolol using response surface methodology. AAPS Pharm. Sci. Tech. 7(1); 2006:34-41.
19. Deshpande A.A., Rhodes C.T., Shah N.H., Malick, A.W, Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev. Ind. Pharm. 22(6); 1996:531-539.
20. Bardonnet P.L., Faivre V., Punj W.J., Piffaretti J.C., Falson F, Gastroretentive dosage forms: overview and special case of H. pylori. J. Contr. Rel. 111(1-2); 2006:1-18.
21. Sonar S.G., Jain K.D., More M.D, Preparation and in vitro evaluation of bilayer and floating bioadhesive tablets of rosiglitazone maleate, Asian J. pharma. sci. 2(4); 2007:161-169.
22. Madgulkar A., Kadam S., Pokharkar V, Development of trilayered mucoadhesive tablet of itraconazole with zero order release, Asian J. Pharm. 2(1); 2008:57-60.
23. Wang J, Tauchi Y, Deguchi Y, Morimoto K, Tabata Y, Ikada Y, Positively charged gelatin microspheres as gastric mucoadhesive drug delivery system for eradication of H. Pylori., Drug Delivery. 7(4); 2000:237-243.
24. Umamaheshwari R.B., Ramteke S., Jain N.K, Anti–Helicobacter pylori effect of mucoadhesive nanoparticles bearing Amoxicillin in experimental gerbils model. AAPS Pharm.Sci.Tech. 5(2); 2004:60-68.
25. Patel J.K., Patel M.M, Stomach specific Anti-Helicobacter pylori therapy: Preparation and evaluation of Amoxicillin-loaded chitosan mucoadhesive microspheres. Curr. Drug Deli. 4; 2007:41-50.
26. Rajnikanth P.S., Karunagaran L.N., Balasubramaniam J., Mishra B, Formulation and evaluation of Clarithromycin Microspheres for eradication of Helicobacter Pylori. Chem. Pharm. Bull. 56(12); 2008:1658-1664.
27. Davaran S., Rashidi M., Khandaghi R., Hashemi M, Development of a novel prolonged-release nicotine

transdermal patch. Pharmacol. Res. 51(3); 2005:233–237.

28. Burkman R.T, The transdermal contraceptive system, Am. J. Obstet. Gynecol. 190(4); 2004:S49–S53.

29. Thomas B.J., Finnin B.C, The transdermal revolution. Drug Discov. Today 9(16); 2004:697–703.

30. Nagai, T., Machida, Y, Buccal delivery systems using hydrogels. Adv. Drug Deli. Rev. 11(1-2); 1993:179–191.

31. Eaimtrakarn S., Itoh Y., Kishimoto J.I., Yoshikawa Y., Shibata N., Takada K, Rentention and transit of intestinal mucoadhesive films in the rat small intestine. Int. J. Pharma. 224(1-2); 2001:61–67.

32. Shen, Z., Mitragotri, S, Intestinal patches for oral drug delivery. Pharm. Res. 19(4); 2002:391–395.

33. Kathryn W., Zancong S., Samir M, Oral delivery of macromolecules using intestinal patches: application for insulin delivery. J. Contl. Rel. 98(1); 2004:37-45.

34. Gupta A, Garg S, and Khar R, Measurement of bioadhesive strength of mucoadhesive buccal tablets:design of in vitro assembly .Indian Drug. 30(1); 1992:152-155.

35. Patel V.M., Prajapati G., Patel M.,Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS Pharma. Sci. tech. 8(3); 2007:234-242.

36. C Margeta, BS Sachin. B Debjit, B Bhowmik, B Jayakar. Formulation and evaluation of controlled release mucoadhesive oral tablet of Clarithromycine. Der pharmacia Lettre. 1(1); 2009:83-91.

37. Rajput G., Majmudar F., Patel J., Thakor R., Rajgor N.B., Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. Sys. Rev. Pharm. 1(1); 2010:36-44.

38. Carvalho F.C., Bruschi M.L., Evengelista R.C., Gremiao M.P.D., Mucoadhesive drug delivery systems, Braz. J. Pharma. Scien. 46(1); 2010:1-21.

39. Chowdary K.P.R. and Srinivas L., Mucoadhesive drug delivery systems: a review of Current Status, Indian drugs. 37(9);2000:400-406

40. Krishnaiah Y.S.R, Kondala Rao B., Rama Prasad Y.V., Satyanarayana S. Gamma scintigraphy : an imaging technique for noninvasive in vivo evaluation of oral dosage forms. Indian Drugs. 35(7); 1988:387-398.

