Review Article

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THEORIES AND FACTORS AFFECTING MUCOADHESIVE DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT
Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. When the associated biological system is mucous, it is called mucoadhesion. This property of certain polymeric systems have got place in the drug delivery research in order to prolong contact time in the various mucosal route of drug administration, as the ability to maintain a delivery system at a particular location for an extended period of time has a great appeal for both local action as well as systemic drug bioavailability. A complete and comprehensive theory that can predict adhesion based on the chemical and/or physical nature of a polymer is not yet available. Several theories have been proposed to explain the fundamental mechanisms of adhesion such as glues, adhesives, and paints, have been adopted to study the mucoadhesion. Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanisms involved. These theories include mechanical-interlocking, electrostatic, diffusion–interpenetration, adsorption and fracture processes. They are Electronic theory, Adsorption theory, Wetting theory, Diffusion theory, Fracture theory. The objective of the study is to explain the different mechanisms involved in mucoadhesion and various factors affecting mucoadhesion.
Key Words: Drug delivery, Polymer, Adsorption & Bioadhesion.

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INTRODUCTION

Bioadhesives are natural polymeric materials that act as adhesives. The term is sometimes used more loosely to describe a glue formed synthetically from biological monomers such as sugars, or to mean a synthetic material designed to adhere to biological tissue[1]. The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface[2]. It may be defined as attachment of synthetic biological macromolecules to a biological tissue[3]. A more specific term than bioadhesion is mucoadhesion. Mucoadhesion in drug delivery systems has recently gained interest among pharmaceutical scientists of promoting dosage form residence time as well as improving intimacy of contact with various absorptive membranes of the biological system[4].

The mucoadhesive drug delivery system may include the following[5, 6, 7, 8].

- Buccal delivery system
- Sublingual Delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system
- Gastro Intestinal delivery system

THEORIES OF BIOADHESION

Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanism involved. The theories include electronic theory, adsorption theory, wetting theory, diffusion theory, fracture theory.

There are five classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon[9]. These theories include mechanical-interlocking,

electrostatic, diffusion-interpenetration, adsorption and fracture processes. These numerous theories should be considered as supplementary processes involved in the different stages of mucus substrate interaction[10]. These theories were originally developed to explain the performance of such diverse materials such as glues, adhesives; paints have been adopted to study the mucoadhesion[11, 12, 13].

ELECTRONIC THEORY

According to electronic theory, attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material[14,15]. Because of different electronic properties of the mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occur[16]. Electron transfer occurs between the two forming double layer of electric charges at the interface[15]. This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structure. Thus it results in the formation of double layer of electric charges at the mucus and the mucoadhesive interface with subsequent adhesion due to attractive forces[17].

ADSORPTION THEORY

According to the adsorption theory, bioadhesive bond is due to van der Waals interactions, hydrogen bonds, electrostatic attractions or hydrophobic interactions[16,17,18]. It has been proposed that these forces are main contributors to the adhesive interaction[17]. Adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate[10].

Strong Polymer Forces: Covalent bonds

Weak Secondary Forces: Ionic bond, Hydrogen bond, van der Waals forces[14, 15].

Primary bonds are due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding.

Secondary bond arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding[10].

WETTING THEORY

The wetting theory postulates that the adhesive component penetrates the surface irregularities, hardness and anchors itself to the surface[16]. The wettability theory is mainly applicable to liquid or low viscosity mucoadhesive system and is essentially a measure of the spreadability of active pharmaceutical ingredient delivery system across the biological substrate[10]. Wetting theory is the ability of bioadhesive to spread and develop intimate contact with the mucus membrane. Spreading coefficient of polymers must be positive in order to adhere to a biological membrane, and contact angle between the polymer and cells must be near to zero[14]. The wetting theory emphasizes the intimate contact between the mucoadhesive polymer and the mucous, primarily in liquid systems. It uses interfacial tension to predict spreading and subsequent adhesion[17,18]. The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by use of measuring techniques such as the contact angle[19]. It is predominantly applicable to liquid bioadhesive systems. It analyses adhesive and contact behaviour in terms of the ability of a liquid or paste to spread over a biological systems[4]. The adhesive performance of viscous liquids may be defined, using wettability and spreadability; critical parameters are determined from solid surface contact angle measurements[17] (**Fig 1, 2)**

DIFFUSION THEORY

The diffusion theory states that interpenetration and entanglement of both polymer and mucin chains are responsible for mucoadhesion. The more structurally similar a mucoadhesive to the mucosa, the greater is the mucoadhesion[17]. It is believed that an interpenetration layer of 0.2-0.5 micrometer is required to produce an effective bond. This process is driven by concentration gradient and is affected by the molecular chain lengths and their motilities[18]. This theory describes the physical entanglement and interpenetration of mucin strand into the porous structure of the polymer substrate[15]. The interpenetration is governed by diffusion coefficients and contact time which in turn are dependent on the molecular weight and flexibility of the chains[14] probable penetration depth {L} can be estimated by formula:-

L = (t*Db)^1/2

t=time of contact

Db=diffusion coefficient of the bioadhesive material in mucus[20]

This is a two-way diffusion process with penetration rate being dependent upon the effective coefficient of both interacting polymers. [16] Sufficient polymer chain flexibility, adequate exposure for the surface contact of polymers, similar chemical structures and the diffusion coefficients of the bioadhesive polymer are among the factors which influence the inter-diffusion of the macromolecule network[21]. **(Fig 3)**

FRACTURE THEORY

The fracture theory analyses the force that is required for the separation of two surfaces after adhesion[1,14,17]. The maximum tensile strength produced during detachment can be determined by dividing the maximum force of detachment {Fm} by the total surface area {Ao}, involved in the adhesion interactions[14].

Sm = Fm/Ao

The fracture theory analyzes the force required to separate two surfaces after adhesion. This assumes that the failure of the adhesive bond occurs at the interface. However, failure normally occurs at the weakest component, which is typically a cohesive failure within one of the adhering surfaces[17]. **(Fig 4)**

Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains[8].

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process. It is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables. [8, 15]

Factors Affecting Mucoadhesion[22,23,24,25,26]

Polymer related factors

- Molecular weight
- Concentration of active polymer
- Flexibility of polymer chains
- Spatial confirmation
- Swelling {Hydration}
- Hydrogen bonding capacity
- Cross linking density
- Charge

Environment related factors

- pH of polymer - substrate interface
- Applied strength
- Initial contact time
- Moistening
- Presence of metal ions

Physiological factors

- Mucin turnover
- Disease state
- Rate of renewal of mucosal cells
- Concomitant diseases
- Tissue movement

POLYMER RELATED FACTORS

Molecular Weight

The optimum molecular weight for maximum bioadhesion depends upon type of mucoadhesive polymer used. For example, polyethylene glycol (PEG), with a molecular weight of 20 000, has little adhesive character, whereas PEG with 200 000 molecular weight has better, and PEG with 400 000 has superior adhesive properties[15,27,28]. The optimum molecular weight for maximum mucoadhesion depends upon the type of mucoadhesive polymer and tissue. The interpenetration of polymer molecules is favourable for low molecular weight polymers whereas entanglements are favours for high molecular weight polymers[14]. Low-molecular-weight polymers penetrate the mucus layer better. High molecular weight promotes physical entangling. Polymers with higher molecular weights will not moisten quickly to expose free groups for interaction with the substrate, while polymers with low molecular weights will form loose gels or will dissolve quickly[11].

Concentration of Active Polymer

There is an optimum concentration for a mucoadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chain available for interpenetration becomes limited[8,25]. It affects the availability of long polymer chains for penetration into the mucus layer. Thus it is important mainly for liquid and viscous drug delivery system[13]. The importance of this factor lies in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer is also small[29].

Flexibility of Polymer Chains

Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become cross-linked, the mobility of an individual polymer chain decreases and thus the effective length of the chain that can penetrate into the mucous layer decreases, which reduces mucoadhesive strength[25,30,31]. It is required for diffusion of chains and their entanglement with mucin. For polymers with high levels of linkage, the mobilities of the individual polymer chains decrease, leading to decrease in mucoadhesion strength. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucous. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients. Higher flexibility of a polymer causes greater diffusion into the mucous network[16,32]. The increased chain interpenetration can be attributed to the increased structural flexibility of the polymer upon incorporation of poly ethylene glycol[15,33].

Spatial Confirmation

Besides molecular weight or chain length, spatial confirmation of a molecule is also important. Despite having a high molecular weight of 19 500 000, dextrans have adhesive strength similar to that of PEG, with a molecular weight of 200 000. The helical confirmation of electrons may shield many adhesively active groups, primarily responsible for adhesion unlike PEG polymers that have a linear confirmation[14,25,34]. Also the effect of polymer concentration is dependable on the physical state (solid / liquid) of the bioadhesive drug delivery systems; more is the polymer concentration results in higher bioadhesive strength[35].

Swelling (Hydration)

Hydration is required for a mucoadhesive polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. [16] Swelling characteristics are related to the mucoadhesive itself and its environment. Swelling depends on the polymer concentration, the ionic strength, and the presence of water. During the dynamic process of bioadhesion, maximum in-vitro bioadhesion occurs with optimum water content. Over hydration results in the formation of a wet slippery mucilage without adhesion[8,25]. Swelling depends both on polymer concentration and on water present. When swelling is too high, decrease in bioadhesion occurs. Such phenomena must not occur too early, in order to exhibit a sufficient action of the bioadhesive system[30,31]. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network[16,32]. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs[36,37].

Hydrogen Bonding Capacity

Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds[16]. Ability to form hydrogen bonds is due to the presence of functional (COOH, OH, etc.). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate, and poly methacrylicacid, as well as all their copolymers are polymers with good hydrogen bonding capacity[36,38].

Cross Linking Density

The average pore size, the number average molecular weight of the cross-linked polymers and the density of cross-linking are three important and interrelated structural parameters of a polymer network[16,39]. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin[32]. It was reported that, this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer[40].

Charge

Charge sign of polymer is an important element for bioadhesion[28,41] The non-ionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Strong anionic charge on the polymer is one of the required characteristics for mucoadhesion[36]. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium[42]. Additionally, some cationic high-molecular-weight polymers such as chitosan have shown to possess good adhesive properties[43]. The strength of mucoadhesion of polymers with carboxyl groups was much stronger than that of those with neutral groups[44].

ENVIRONMENT RELATED FACTORS

pH of Polymer-Substrate Interface

pH can influence the formal charge on the surface of the mucous as well as certain ionizable mucoadhesive polymers[15]. Mucus will have 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[25, 30]. Changes in pH lead to differences in the extent of dissociation of functional groups in carbohydrate sequences or polypeptide amino acid sequences, as well as in the polymer[10]. pH of the medium is important for the degree of hydration of cross-linked polycyclic acid, showing consistently increased hydration from pH 4 to pH 7, and then a decrease as alkalinity or ionic strength increases. For example polycarbophil does not show a strong mucoadhesive property above pH 5, because it is uncharged rather than ionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However, at higher pH, the chain is fully extended due to electrostatic repulsion of the carboxyl ate anions[8,15,31,45].

Applied Strength

For placing a solid mucoadhesive system, it is necessary to apply a defined strength. Whatever may be the polymer, poly acrylic acid/ divinyl benzene or carbopol 934, the adhesion strength increases with the applied

strength or with the duration of its application up to an optimum[8,25]. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration[46]. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin. Pressure applied to the system for attachment affects the depth of diffusion of chains and it cannot be controlled for systems used in the GIT[14].

Initial Contact Time

The initial contact time between the mucoadhesive and mucous layer determines the extent .of swelling and interpenetration of the mucoadhesive polymer chains. Mucoadhesive strength increases as the initial contact time increases[15,47]. Although with the initial pressure the initial contact time can dramatically affect the performance of a system[32]. Duration of initial contact time determines the extent of swelling and diffusion of polymer chains and it cannot be controlled for systems used in the GIT.

Moistening

Moistening is required to allow the mucoadhesive polymer to spread over the surface and create a "macromolecular network" of sufficient size for the interpenetration of polymer and mucin molecules and to increase the mobility of polymer chains. However, there is a critical level of hydration for mucoadhesive polymers characterized by optimum swelling and bioadhesion.

Presence of Metal Ions

Interaction with charged groups of polymers and/or mucous can decrease the number of interaction sites and the tightness of mucoadhesive bonding[10].

PHYSIOLOGICAL FACTORS

Mucin Turnover

Mucin is large molecule with molecular masses ranging from 0.5 to over 20 MDa[48]. The natural turnover of mucin molecules from the mucous layer is important for at least two reasons.

Firstly, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucous layer. No matter how high the mucoadhesive strength is. Mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesives[49].

Secondly, mucin turnover results in substantial amounts of soluble mucin molecules[8,14,25]. These molecules interact with mucoadhesives before they have chance to interact with the mucous layer[49,50,51].

Surface fouling is unfavourable for mucoadhesion to the tissue surface[8,25]. Mucin turnover may depend on the other factors such as the presence of food. The gastric mucosa accumulates secreted mucin on the luminal surface of the tissue during the early stages of fasting. The accumulated mucin is subsequently released by freshly secreted acid or simply by the passage of ingested food; the exact turnover rate of the mucous layer remains to be determined.

Disease State

The physiochemical properties of the mucous are known to change during disease conditions such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial, and fungal infections of female reproductive tract, and inflammatory conditions of the eye. If mucoadhesives are to be used in the diseased state, the mucoadhesive property needs to be evaluated. [14, 52]

Rate of Renewal of Mucoadhesive Cells

Rate of renewal of mucoadhesive cells varies extensively for different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

Concomitant Diseases

Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo- and hypersecretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation.

Tissue Movement

Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms[10]. **(Table: 1)**

CONCLUSION

Mucoadhesion has been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form the absorption surface to improve and enhance the bioavailability of drugs. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to an increase in bioavailability and both local and systemic effects. Mucoadhesive drug delivery system prolong the absorption of drugs and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug. There are various factors which contribute to the absorption of drugs from the mucoadhesive dosage forms.

REFERENCES

1. Smith AM, Callow JA, Biological Adhesives, Wikipedia, 2006:1
2. Bhatt JH, Designing and Evaluation of Mucoadhesive Microspheres of Metronidazole for oral Controlled Drug Delivery, Pharmainfo.net, 2009.
3. Abnawe, Sumit Anand, Mucoahesive Drug Delivery System, Pharmainfo.net, 2009.
4. Das Bibin K, P Deepa, Mucoadhesive Agents, Project and review articles, 2009.

5. Asane GS, Mucoadhesive Gastro Intestinal Drug Delivery System, Pharmainfo.net, 2007;5.
6. Patil SB et. al., Mucoadhesive polymers: Means of improving drug delivery, Pharma Times, 2006; 38: 25-27.
7. Ganga S, Mucosal Drug Delivery, Pharmainfo.net, 2007; 5.
8. Rajput GC et al., Stomach Specific Mucoadhesive Tablets as Controlled Drug Delivery System, International Journal on Pharmaceutical and Biological Research, 2010;1 : 30-41.
9. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B, Polymers in Mucoadhesive Drug Delivery System, Critical Reviews in therapeutic drug carrier systems,:1-13.
10. Punitha S, Girish Y, Polymers in mucoadhesive buccal drug delivery system, International Journal of Research and Pharmaceutical Sciences, 2010;1:170-186.
11. Duchene D, Touchard F, Peppas NA, Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Development and Industrial Pharmacy, 1988; 14: 283-318.
12. ChickeringIII DE, Mathiowitz E, Fundamentals of bioadhesion In Bioadhesive drug delivery systems-Fundamentals, 1999: 1-85.
13. Hagerstorm H, Polymer gels as pharmaceutical dosage forms, Uppasala University, Sweden, 2003.
14. Sachan Nikhil, K Bhattacharya, A Basics and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems, International Journal of Pharmaceutical and Clinical Research, 2009;1:10-14.
15. Roy Saroj Kumar, Prabhakar Bala, Bioadhesive Polymeric Platforms for Transmucosal Drug Delivery Systems, Tropical Journal of Pharmaceutical Research, 2010; 9 : 91-104.
16. Bhalodia Ravi, Basu Biswajit, Garala Kevin, Joshi Bhavik, Mehta Kuldeep, Buccoadheive Drug Delivery Systems, International Journal of Pharma and Bio Sciences, 2010;1 : 1-32.
17. Hameed Amel Yasseen, Development and Evaluation of Liposomal Mucoadhesive Gel for Nasal Delivery of Acyclovir, International Journal on Pharmaceutical and Biological Research, 2010;1 :30-41
18. Hagerstrom, Helene; Polymer gels as Pharmaceutical Dosage Forms, Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy 293.
19. Carvalho Flavia et.al. Mucoadhesive drug delivery systems, Brazilian Journal of Pharmaceutical Sciences, 2010; 46.
20. Jasti Drs B, Li X, Cleary G, Recent advances in mucoadhesive drug delivery systems. Pharmtech, 2003;1: 194-197.
21. Lee JW, Park JH, Robinson JR, Bioadhesive-based dosage forms: the next generation, J Pharm Sci, 2000; 89:850-66.
22. Chen JL, Cyr GN, Composition producing adhesion through hydration in mainly Adhesion in biological system. New York, Academic Press: 163-181.
23. Ch'ng HS, Park H, Kelly P, Robinson JR, Bioadhesive polymers as platform for oral controlled drug delivery , J. Pharm. Sci,. 1985;74: 399-405.
24. Bhatt JH, Designing and Evaluation of Mucoadhesive Microspheres of Metronidazole for Oral Controlled Drug Delivery, Pharmainfo.net, 2009, Power Point Presentation.
25. Rajput GCet.al., Stomach Specific Mucoadhesive microsphere as a controlled drug delivery system, International Journal on Pharmaceutical and Biological Research 2010;1:30-41.
26. Miller Nazila Salamat, Chittchang Montakarn, Johnston Thomas P, The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery Reviews, Elsevier, 2005; 57 : 1666 – 1691.
27. Hoffman A, Pharmacodynamic aspects of sustained release preparations. Adv Drug Del Rev 1998; 33: 185-99.
28. Tiwari D, Goldman D, Sause R, Madan PL. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations, AAPS Pharm Sci, 1999; 1: E13.
29. Solomonidou D, Cremer K, Krumme M, Kreuter J. Effect of carbomer concentration and degree of neutralization on the mucoadhesive properties of polymer films, J Biomater Sci, 2001; 12: 1191-1205.
30. Kamath KR, Park K, Mucosal adhesive preparations, In Encyclopedia of Pharmaceutical Technology, 1995;12: 132-162.
31. Chowdhary KPR, Shrinivas Rao Y, Mucoadhesive drug delivery systems, A review of current status, Indian Drugs 2000; 37: 400-406.
32. Robinson JR, Leung SHS, Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships, Crit Rev Ther Drug Carr Syst 1998;5: 21-67.
33. Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco and bioadhesion: tethered structures and site-specific surfaces, J Control Release, 2000;65: 63-71.
34. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems, Drug Dev Ind Pharm, 1997;23:489–515.
35. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as controlled drug delivery systems, International Journal of Pharmaceutics 2003;255:13-32.
36. Peppas NA, Buri PA, Surface interfacial and molecular aspects of polymer bioadhesion on soft tissues, J Control Release 1985;2:257-75.
37. Miller NS, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery, Adv Drug Del Rev, 2005; 57:1666–1691.
38. Park K, Robinson JR. Mechanisms of mucoadhesion of poly (acrylic acid) hydrogels, Pharm Res, 1987;4:457-464.
39. Flory PJ. Principle of Polymer Chemistry, Cornell University Press, Ithaca, New York: 1995:541-556.
40. Flory PJ, Principle of polymer chemistry, Cornell University Press, New York, 1953: 541.
41. Park K, Chang HS, Robinson JR. Alternative approaches to oral-controlled drug delivery: bioadhesive and in situ systems, Recent advances in Drug Delivery System, Plenum Press, 1984:163.
42. Park H, Amiji M, Park K, Mucoadhesive hydrogels effective at neutral pH, Proc Int Symp Control Release Bioact Mater 1989;16:217-18.
43. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE, In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers, Int J Pharm, 1992;78:43-48.
44. Chang HS, Park K, Kelly P and Robinson JR, Bioadhesive polymers as platform for oral controlled drug delivery, J Pharm Sci, 1985;74:399-404.
45. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Rao YR, Polymers for Mucoadhesive Drug Delivery System: A Current Status, Drug Dev Ind Pharm, 2008; 34:1246–1266.
46. Ponchel G, Irache Jaun-M, Specific and non-specific bioadhesive particulate systems for oral delivery to gastrointestinal tract, Advanced Drug Delivery Reviews 1998;34:191-219.
47. Kamath KR, Park K, Mucosal adhesive preparations, Encyclopaedia of pharmaceutical technology, New York, 1994:133-138.
48. Harding SE, Mucoadhesive interactions, Biochemical Society Transactions, 2003;31: 1036-1040.
49. Lehr CM, Poelma FGJ, Junginger HE, Tukker JJ. An estimate of turnover time of intestinal mucus gel layer in the rat in situ loop, International Journal of Pharmaceutics 1991; 70: 235-240.
50. Lehr CM. From sticky stuff to sweet receptors-achievements, limits and novel approaches to bioadhesion, European Journal of Drug Metabolism Pharmacokinetics 1996;21:139-148.

51. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE, In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers, International journal of Pharmaceutics 1992; 78: 43-48.
52. Allen A, Pain RH, Robson TR, Model for the structure of the gastric mucous gel nature 1976;264:88-89.
53. Aidoo Sheila, Bioadhesive Polymers, ppt., Slide No. 1-50, available at: userweb.port.ac.uk/ roldom/Mucoadhesives/Bioadhesives.ppt.

Table 1: Type of bioadhesive formulations

Types	Form	Example	Route	Used as / for	Ref
Solid	Tablet	Buccastem®	Buccal mucosa	Nausea Vomiting Vertigo	[10, 53]
	Inserts	Pilogel®	Eye	Glaucoma	
	Lozenges	_	Mouth	Antibiotics Local Anesthetics	
Semisolid	Gels	_	Eye Vagina Oral cavity	-	
	Films	Zilactin®	Mucosa	Cold sores Mouth ulcers	
Liquid	Viscous	Artificial tears	Mucosa	Dry eyes	
	Gel forming	-	Eye	-	

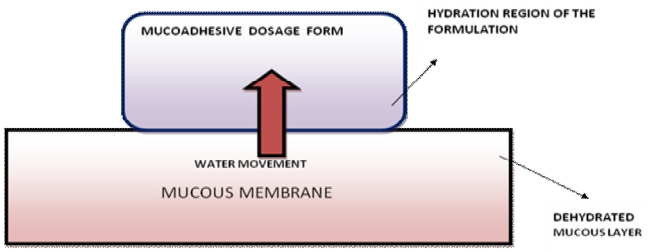

Fig.1 Mucoadhesion Wetting Theory

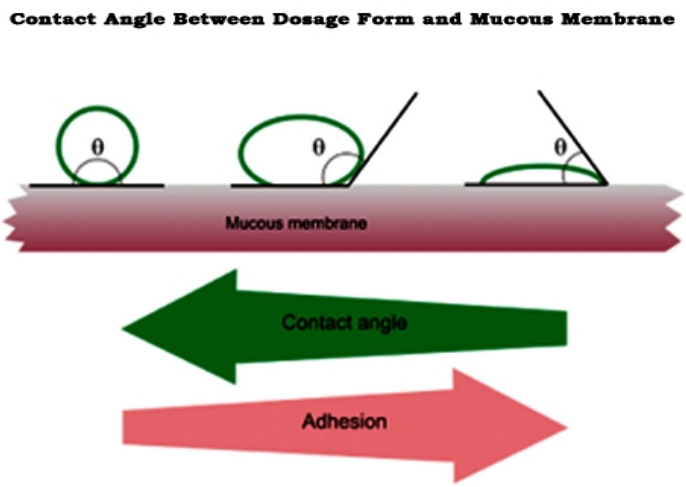

Fig. 2 Contact Angle between Dosage Form and Mucous Membrane

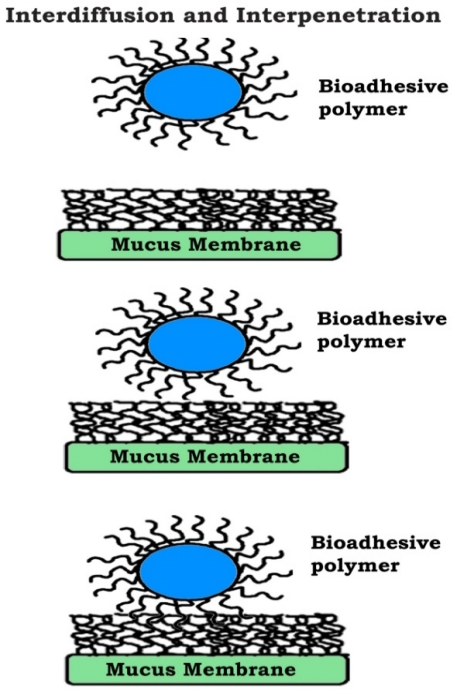

Fig. 3 Inter-diffusion and Interpenetration of Polymer and Mucous Membrane

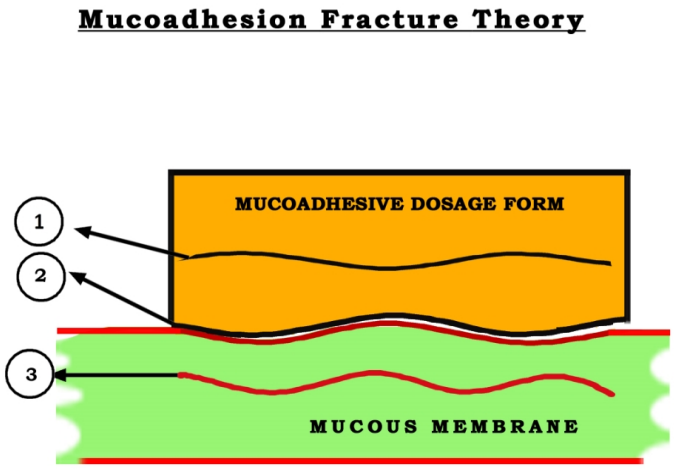

Fig 4 Mucoadhesion Fracture Theory