WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review on Mucoadhesive Drug Delivery System

[1]Darshan Anil Sonawane, [2]Bharti D. Aher, [3]Akshada Sanjay More, [4]Gautam Sanjay Pawar, [5]Jaydip Gopal Kapdnis, [6]Lalit Bhausaheb Aher, [7]Tejas Jagannath Bhadane

[1,3,4,5,6,7]Student, NDDS, Swami Institute of Pharmacy

[2]Assistant Professor, NDDS, Swami Institute of Pharmacy

Abstract:

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucous molecules and increase the residence time of the dosage form at the site of absorption. This paper describes some aspects of bioadhesion such as mucus layer, mucoadhesion, and theories of bioadhesion and the adhesion mechanism. The methods used to study bioadhesion, factors affecting mucoadhesive and bioadhesive polymers are described. The methods that evaluate the mucoadhesive dosage forms and finally the bioadhesive drug delivery systems designed for several therapeutic purposes are presented. The term mucoadhesive derived from two words mucous plus adhesion it means the adhesive polymer containing drugs which adhere on mucous surface to blood stream is called mucoadhesive. Mucoadhesive system utilised the bioadhesive property of polymer and polymer stick on mucous layer and released into blood stream.

Keywords: Mucoadhesion, theories, stages of mucoadhesion, bioadhesive polymer, evaluation of mucoadhesive propertires, factors affecting mucoadhesive.

Introduction:

The creation of innovative release systems has made it possible to increase a drug's effect. Mucoadhesive systems have the potential to be used as drug carriers because they can increase contact with the epithelial barrier by extending their stay at the absorption site. The mucous membrane is the primary administration site for bioadhesive systems, however when sustained cutaneous action is sought, a need for innovative bioadhesive formulations for dermal administration has also been noted. It is unusual that a longer effect will be felt after applying creams, solutions, and lotions to the skin because these preparations might be quickly washed away by moisture, temperature, and physical activity.Human mucous membranes are comparatively porous and facilitate quick medication absorption. They are distinguished by an epithelial layer with mucus on its surface. Glycoproteins, lipids, inorganic salts, and 95% of its mass is water, making mucus a highly hydrated system. The most significant mucus glycoprotein, mucin, is in charge of the mucus's morphology. Mucus has a variety of extra purposes depending on the epithelium it covers, but its primary purposes are to protect and lubricate the epithelium. In the stomach, mucus can range in thickness from 50-450 micrometres to less than 1 micrometre in the oral cavity.Although the names are interchangeable, mucoadhesive is usually used to describe bioadhesive systems that are applied to mucosal membranes. The name "bioadhesive" is derived from the phrases "bio + adhesion" and refers to a crucial feature of the polymer utilised in mucoadhesive drug delivery systems. The terms "bio" and "adhesion" both refer to adhering or sticking. In other words, bioadhesion refers to any feature that makes a polymer stick to a biological surface. The most recommended method of medicine delivery is via the oral route. The following categories of drug administration through oral cavity membranes are possible:

- Sublingual delivery: This is the systemic administration of medication via the mucosal lining of the oral cavity.
- Buccal delivery: This is the administration of medication through the cheeks' mucosal membranes (buccal mucosa).
- Local delivery: Oral drug administration using this method. The buccal area of the oral mucosal cavity provides a desirable route of administration for regulated systemic medication delivery. The delivery of medications through the mucosal lining of the cheeks is known as buccal administration. Although the buccal mucosa is favoured for systemic transmucosal medication administration, the sublingual mucosa is known to be more permeable. This is because the buccal mucosa is a more favourable area for retentive systems due to its expanse of smooth muscle and relatively immobile mucosa. Therefore, the buccal mucosa is more suited for sustained medication administration. [1]

ADVANTAGES OF ORAL MUCOADHESIVEDRUG DELIVERY SYSTEMS:

- Increases the bioavailability by extending the dosage form's period in residence at the absorption site.
- Great accessibility and quick start-up.

- Quick absorption due to an abundant blood supply and healthy blood flow rates.Improved patient compliance; drug is preserved from deterioration in the git's acidic environment.[2]

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:

- The development of local ulcers as a result of prolonged contact with a substance with ulcerogenic properties.
- The lack of an appropriate model for in vitro screening to discover medications suitable for such administration is one of the key obstacles to the development of oral mucosal delivery.
- Taste and irritability acceptance by the patient.Eating and drinking are not permitted.[2]

Mucous membrane:

- The mucous membrane is the membrane that lines the body's cavities and canals, primarily the gastrointestinal, urinary, and respiratory systems. The mucous membrane is found lining various bodily passages and organs, including the ureters, urethra, and urine bladder as well as the mouth, nose, eyelids, trachea, lungs, stomach, and intestine.Meaning of mucous membrane: The mucous membrane is an epithelial tissue that lines many tubular organs and body cavities, including the gastrointestinal tract and respiratory tubes.[3]

Mucous Membrane Function:

- The mucous membrane's and mucus' primary job is to maintain the tissue's moisture (for example in the respiratory tract, including the mouth and nose).
- Mucous membranes also shield the body from potentially dangerous substances. For example, the stomach mucosa shields against stomach acid, and the bladder mucosa lining shields the underlying tissue from urine.
- Mucous membranes also shield the body from potentially hazardous substances. For example, the stomach's mucosa shields against stomach acid, and the bladder's mucosa lining shields the underlying tissue from urine.
- The endometrium, the uterus' mucous membrane, swells each month and is expelled during menstruation. [3]

Examples of the Mucous Membrane :

- -Vocal fold lining and bronchial mucosa
- -endometrium: uterine mucosa oesophageal mucosa
- -stomach mucosa
- -Abdominal mucosa
- -Nasal lining
- -The nasal mucosa
- -Mouth mucosa
- -Genital mucosa
- -Vulvar mucosa
- -Tongue's frenulum tongue's anal canal
- -Conjunctiva of the palm[3]

Layer of mucous membrane:

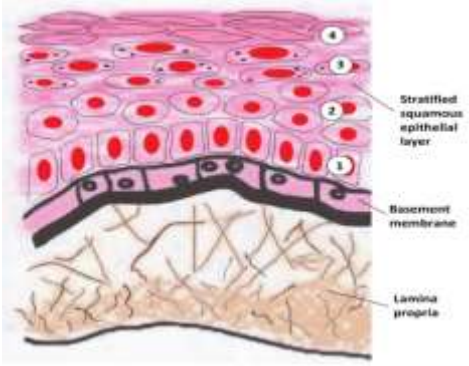

Fig:1 Layer of mucous membrane

A mucous membrane, also known as mucosa, is a type of membrane that lines internal organ surfaces and other spaces in an organism's body. It is made up of a layer of loose connective tissue on top of one or more layers of epithelial cells. At body openings like the eyes, eyelids, ears, inside the nose, inside the mouth, lips, the genital areas, the urethral entrance, and the anus, it is continuous with the skin and primarily of endodermal origin. Some mucous membranes release mucus, a viscous fluid that acts as a barrier. The membrane's job is to keep dirt and germs out of the body while also preventing dehydration of human components. [4,5]

Composition of Mucous Layer:

In humans, the mean thickness of this layer, which is produced by the globet cells lining the epithelia, ranges from around 50 to 450 m. Mucus is a transparent and viscous secretion that forms a thin, problematic gel. Its general composition is as follows.

- - Water -95%
- - Lipids and glycoproteins: 0.5% to 3%
- -Salts with minerals: 1%
- - 0.5% to 1.0% of free proteins[2]

Mucous Membranes:

The wet surfaces (mucosa) lining the walls of several body compartments, such as the gastrointestinal and respiratory systems, are known as mucus membranes. They are made up of a connective tissue layer called the lamina propria, which is followed by an epithelial layer whose surface is typically kept moist by a mucus layer. The stomach, small and large intestines, and bronchi are examples of epithelia that are either single layered or multilayered/stratified (e.g. in the esophagus, vagina and cornea). The latter contain, or are close to tissues containing, specialised glands such salivary glands that produce mucus onto the epithelial surface. The former contain goblet cells, which directly secrete mucus onto the epithelial surfaces.Either a gel layer of mucus that is adhering to the mucosal surface or a luminal soluble or suspended type of mucus is present. Mucin glycoproteins, lipids, inorganic salts, and water are the main ingredients of all mucus gels; the latter makes up more than 95% of their weight, making them a highly hydrated system. Mucus has two main purposes: lubrication and protection. [4]

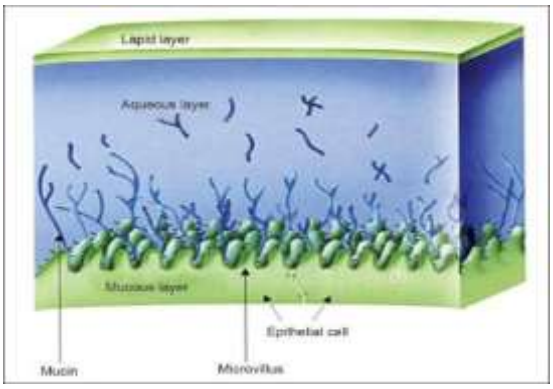

Fig:2 Mucous membrane

THEORIES OF MUCOADHESION:

The examination of mucoadhesion has been adopted from six general hypotheses of adhesion: -

Electronic theory:

According to the electronic theory, because adherin surfaces' electrical structures differ, electron transfer happens when they come into touch. According to the theory, this would cause an electrical double layer to form at the interface, followed by adhesion brought on by attraction forces. According to this idea, adhesion forms when electrons from the mucus and the mucoadhesive system transfer to one another due to variations in their electrical structures. At the mucus and mucoadhesive contact, a double layer of electrical charges is created as a result of the electron transfer between the two materials. The creation of attractive forces within this double layer is the end result of this process. [2,4,6]

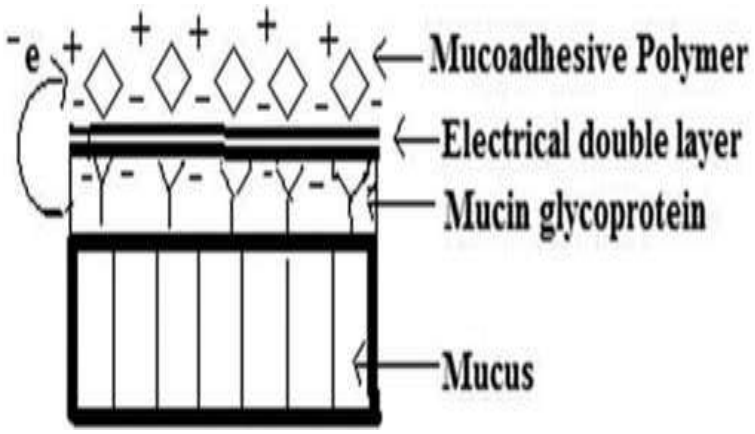

Fig:3 Electronic theory

The wetting theory:

The wetting theory takes surface and interfacial energy into account and is mostly used to liquid systems. In order for adhesion to form, a liquid must have the capacity to spread spontaneously onto a surface. It is possible to determine a liquid's affinity for a surface using methods like contact angle goniometry, which measures the liquid's contact angle with the surface. In general, the lower the contact angle, the higher the liquid's affinity to the solid.[20]

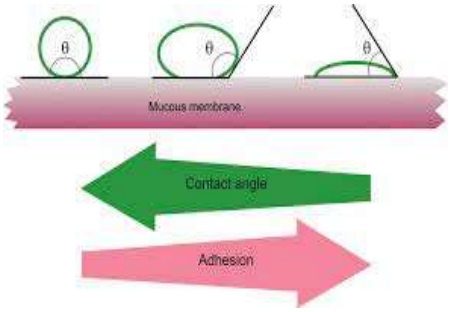

Fig:4 The wetting theory

Diffusion theory:

According to diffusion theory, both mucin and polymer chains must interpenetrate deeply enough to form an adhesive bond that is semi-permanent. According to popular belief, the degree of polymer chain penetration has an impact on how strong the adhesion is. This penetration rate is influenced by the mucoadhesive chains' flexibility, nature, mobility, and contact time. It also depends on the diffusion coefficient. The literature states that a bioadhesive bond must form at a depth of interpenetration between 0.2 and 0.5 m in order to be effective. The following equation can be used to predict the interpenetration depth of polymer and mucin chains:

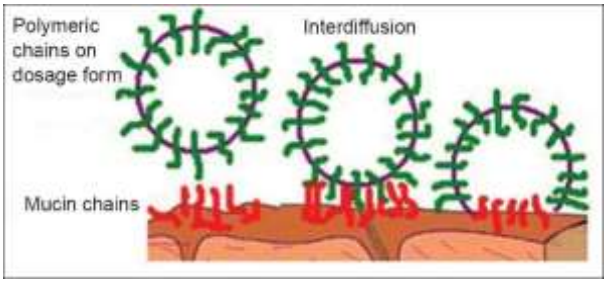

Fig:5 Diffusion theory

l = (tDb)½……..(1)

where t is the contact period and Db is the mucoadhesive material's mucus-specific diffusion coefficient. When the depth of penetration is almost equal to the polymer chain size, the adhesion strength of the polymer is obtained. When it comes to mutual solubility, meaning that the mucus and the bioadhesive have identical chemical structures, it is crucial for diffusion to take place. The mucoadhesive bond is stronger the more structurally similar the two molecules are. [2,4,7]

Adsorption theory:

According to the vander Waals and hydrogen bonding forces and the adsorption hypothesis, adhesives attach to surfaces. These forces are thought to be the primary causes of the sticky contact. The chemisorptions hypothesis, a branch of this, postulates that an interaction across the interface happens as a result of strong covalent bonding. [2,8]

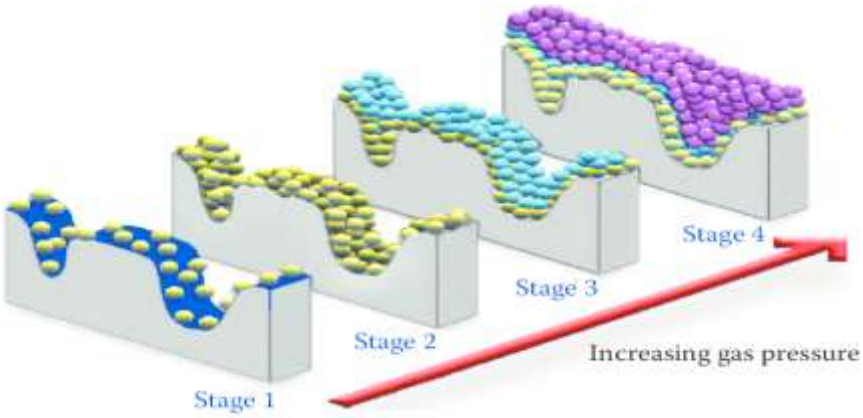

Fig:6 - Adsorption theory

Mechanical theory:

According to the mechanical theory, adhesion results from a liquid adhesive's interlocking (after it sets) into surface imperfections. Though it is believed that a viscoelastic and plastic effect, rather than a mechanical one, plays a more significant role in the adhesion process, rough surfaces also offer an increased surface area that is available for interaction and an enhanced viscoelastic and plastic dissipation of energy during joint failure. [2,9,20]

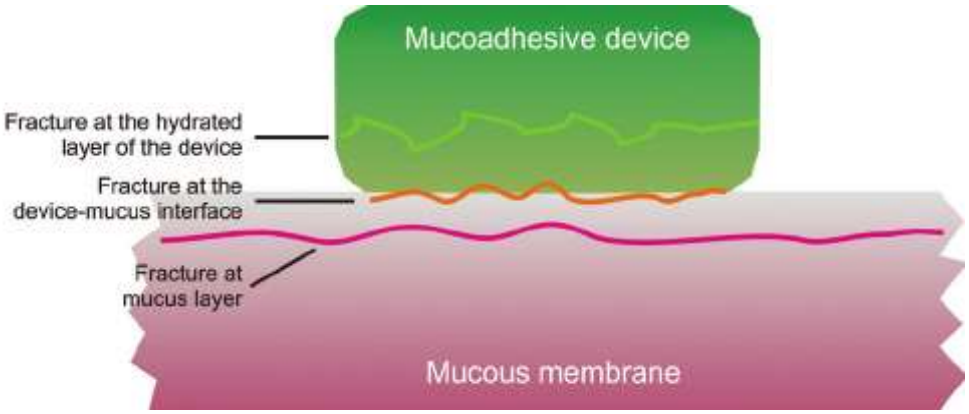

Fig:7 - Mechanical theory

MECHANISM OF MUCOADHESION:

The attachment of the medicine and an appropriate carrier to the mucous membrane is known as mucoadhesion. Wetting, adsorption, and interpenetration of polymer chains are all important aspects of the complicated phenomena known as mucoadhesion. The following are the mechanisms of mucoadhesion:

1. Close proximity of a bioadhesive to a membrane (wetting or swelling phenomenon)
2. Bioadhesive entrapment within the tissue or on the mucous membrane surface (interpenetration)[10,21]

Bioadhesives are classified into three types:

Type I

Bioadhesion is defined as adhesion between biological items that doesn't use synthetic materials. cell aggregation and cell fusion.

Type II

Cell adherence to culture dishes or adhesion to other materials, such as metals, woods, and other synthetic materials, are two examples of Type II bioadhesion.

Type III

Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues. The goal of the development of bioadhesive is to duplicate, mimic or improve biological adhesives which are both durable where required and degradable where necessary and not toxic at all (Grinnel, 1978) Muco-adhesive drug delivery systems utilize the property of bioadhesion of certain water-soluble polymers which become adhesive on hydration (Nagai & Machida, 1985) and hence can be used for targeting a drug to a particular region of the body for extended periods of time.The mucosal layer lines a number of regions of the body including the GI tract, the urogenital tract the airways, the ear, nose and eye. These represent potential sites for attachment of any bioadhesive system and hence, the mucoadhesive drug delivery systems may include the following:

1. Buccal delivery system
2. Sublingual delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system
7. Gastrointestinal delivery systems.[10]

Evaluation of Mucoadhesive Properties:

Various in vivo and in vitro methods are used for testing the efficacy of the mucoadhesive nature of a polymer matrix. The commonly used in vitro/ex vivo methods include tensile strength measurement, shear strength measurement and chip-based systems, whereas various imaging techniques are used for the evaluation of the delivery systems under in vivo conditions. This section will describe various methods.[12,16]

Used to study the mucoadhesive properties:

By soaking filter paper in 8% mucin dispersion, in vitro tensile strength is measured. The maximal force needed to separate the filter paper and polymer surfaces after the mucoadhesive bonding is then measured after the mucin-coated filter paper has been in contact with the hydrated polymeric samples (in physiological solutions) for a predetermined amount of time. Ex vivo experiments are carried out similarly, with the exception that excised mucosal tissues (such as buccal mucosa, intestinal mucosa, and vaginal mucosa) are used in place of the mucin-coated filter paper.Additionally, the maximum detachment force necessary to separate the surfaces of the polymer matrix and mucin solution after adhesion can be evaluated by incubating the hydrated polymer matrix surface remained in contact with a viscoelastic 30% (w/w) mucin solution in water. The wash-off test can also be used to assess a delivery system's mucoadhesiveness. Using double-sided cyanoacrylate tape, mucosal tissue is affixed to a glass slide for the test. Davis developed a method to estimate the mucoadhesive polymers' transit times. By tagging the polymer with a gamma emitting nucleotide and using gamma scintigraphy to estimate the transit time, the transit time might be visualised.[1,22]

Polymers in Mucosal Drug Delivery:

In order to localise the active agents to a specific region or site, mucoadhesive delivery techniques are being investigated. In order to extend the active agent's residence period at the intended area, polymers have been crucial in the creation of such systems. Natural or artificial polymers may be used in mucosal delivery systems. We will briefly go over a few of the most popular kinds of mucoadhesive polymers in this section.[23]

1. Hydrophilic Polymers:

These types of polymers can dissolve in water. When these polymers are used to create matrices, the matrices expand in an aqueous medium and then dissolve. When compared to neutral polymers, the mucoadhesive characteristics of the polyelectrolytes are stronger. Due to their capacity to form a potent hydrogen bond with the mucin found in the mucosal layer, anionic polyelectrolytes, such as poly(acrylic acid) and carboxymethyl cellulose, have been widely used to build mucoadhesive delivery systems. Due to its outstanding biocompatibility and biodegradability, chitosan serves as an excellent example of a cationic polyelectrolyte that has been widely employed for producing mucoadhesive polymer.Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property . To create a drug-delivery matrix with mucoadhesive properties, the ionic polymers may be combined with the counter-ionic drug molecules to form an ionic complex. In a recent experiment, the powerful cardiac -blocker levobetaxolol hydrochloride caused a poly(acrylic acid) compound to partially neutralise. The release of the integrated medication made the delivery mechanism more prone to dissolving over time. The same principle can be used to create mucoadhesive microcapsules utilising the orifice-ionic gelation technique. Using sodium alginate, sodium carboxymethyl cellulose, carbopol 934P, and hydroxy propylmethyl cellulose, this technology was used to develop a gliclazide delivery system, an anti-diabetic medication. Due to the mucoadhesive qualities of gliclazide, the delivery method demonstrated a prolonged release of the drug. Non-ionic polymers have also been employed for mucoadhesive characteristics, such as poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly(vinyl alcohol), and poly(vinyl pyrrolidone). In order to boost the bioavailability of the active ingredients by lessening the drainage of the supplied formulations, the hydrophilic polymers can also be utilised as viscosity modifying/enhancing agents in the creation of liquid ocular administration systems. In the presence of medications, these polymers can be immediately squeezed to provide a mucoadhesive delivery system.Ocular mucoadhesive delivery systems use a variety of polysaccharides and their derivatives, including chitosan, methyl cellulose, hyaluronic acid, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan gum, gellan gum, guar gum, and carrageenan. In addition to their capacity to form films, cellulose and its derivatives have been found to exhibit surface active properties. Because they cause less eye irritation, cellulose derivatives with lesser surface acting properties are typically favoured in ocular administration methods. Sodium carboxymethyl cellulose has been discovered to have exceptional ocular mucoadhesive properties among the many cellulose derivates. In order to create sustained delivery systems, several anionic polymers have been combined with cationic cellulose derivatives, such as cationic hydroxyethyl celluloses.[17 , 18, 19]

2) Hydrogels:

Three-dimensionally cross-linked polymer chains that have the capacity to store water within their porous structure are known as hydrogels. The hydrophilic functional groups like hydroxyl, amino, and carboxyl groups are primarily responsible for the hydrogels' ability to hold water. The mucoadhesive property of hydrogels created by the condensation reaction of poly(acrylic acid) and sucrose increased with the cross-linking density, which was explained by the increase in poly(acrylic acid) chain density per unit area. Acrylates were employed to create mucoadhesive delivery systems that can transfer peptide bioactive agents to the upper small intestine region without affecting the peptides' bioactivity.In an example experiment, Wood and Peppas created a system in which wheat germ agglutinin was used to functionalize ethylene glycol chains that had been grafted onto methacrylic acid hydrogels. By tying up with certain carbohydrate moieties found in the intestinal mucosa, wheat germ agglutinin aided in extending the delivery system's intestinal residence time. Mucoadhesive hydrogel-based formulations for increasing the bioavailability of the poorly water-soluble drug are used in addition to drug targeting. Buparvaquone, a medication with a low water solubility, was made into a nanosuspension by Muller and Jacobs by integrating it into hydrogels made of carbopol and chitosan. When compared to nanosuspension, the mucoadhesive delivery systems showed enhanced drug bioavailability. This was explained by the delivery system's longer retention period within the gastrointestinal tract.[12,23]

3) Thiolated polymers:

In order to improve the mucoadhesive properties of the polymers (such as poly (acrylic acid) and chitosan) as well as the paracellular uptake of the bioactive agents, the presence of free thiol groups in the polymeric skeleton facilitates the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin. Chitosan-iminothiolane, poly (acrylic acid)-cysteine, poly (acrylicacid) - homocysteine, thioglycolicacid, thioethylamidine, alginate-cysteine, poly (methacrylic acid) -cysteine, and sodium carboxymethylcellulose-cysteine are a few examples of thiolated polymers.[12]

4) Lectic based polymer:

Lectins are proteins that can reversibly bind with particular sugar or carbohydrate residues. They are present in both the animal and plant kingdoms as well as different microbes. Numerous lectins have been proven to be immunogenic and poisonous, and when exposed repeatedly to vulnerable people, they can cause systemic anaphylaxis. The specific cyto-adhesive properties of lectins are being investigated in order to create tailored delivery systems

due to their specific affinity for sugar or carbohydrate residues. Numerous targeted delivery strategies have been investigated using lectins derived from legumes. [12]

Factors affecting mucoadhesive:

Hydrophilicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer are a few of the variables that may have an impact on mucoadhesion.

Hydrophilicity:

Numerous hydrophilic functional groups, including hydroxyl and carboxyl, are present in bioadhesive polymers. These groups enable the formation of hydrogen bonds with the substrate, which causes swelling in aqueous conditions and maximises the exposure of possible anchor sites. Additionally, swollen polymers have the greatest space between their chains, increasing chain flexibility and facilitating effective substrate penetration.[15]

Molecular weight:

The interpenetration of polymer molecules is favored by low-molecular-weight polymers, whereas entanglements are favored at higher molecular weights. The optimum molecular weight for the maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer up to 100,000. Beyond this level, there is no further gain.[15]

Cross-linking and swelling:

The amount of swelling is negatively correlated with cross-link density. More flexibility and hydration occur with higher cross-link densities, and mucoadhesion is improved by polymers with bigger surface areas. It is preferred to use a lightly cross-linked polymer to produce a high degree of swelling. However, a slippy mucilage forms and can be readily dislodged from the substrate if there is too much moisture present and the degree of swelling is too extreme. By using adhesion promoters in the formulation, such as free polymer chains and polymers grafted onto the premade network, cross-linked polymers' mucoadhesion can be improved.[22]

Special conformation:

In addition to molecular weight and chain length, a polymer's spatial conformation is crucial. Dextrans have an extremely high molecular weight (19,500,000), although their adhesive strength is comparable to that of polyethylene glycol (PEG), which has a molecular weight of 200,000. In contrast to PEG polymers, which have a linear conformation, dextran has a helical conformation that may conceal multiple adhesively active groups, which are principally in charge of adherence.[22]

pH:

The adherence of bioadhesives with ionsizable groups might be affected by the pH at the bioadhesive to substrate contact. Many bioadhesives that are employed in medication delivery are polyanions with functionalities for carboxylic acids. It will be primarily ionised if the local pH is above the polymer's pK; if the pH is below the polymer's pK, it will be primarily unionised. The pKa of the polymers in the poly(acrylic acid) family ranges between 4 and 5. Around pH 4-5, these polymers' highest adhesive strength is seen, and it gradually declines above pH 6. [12,13]

Concentration of active polymer:

Beyond the optimal concentration, the adhesive strength in highly concentrated solutions substantially decreases. The coiled molecules become solvent-poor and there are fewer chains available for interpenetration in concentrated solutions. Only formulations that are more or less liquid mucoadhesive seem to find attention in this result. Duchêne demonstrated that the stronger the mucoadhesion is for solid dosage forms like tablets, the higher the polymer content.[12,13]

Drug excipient concentration:

The concentration of the drug and excipients may affect mucoadhesion. Propranolol hydrochloride's impact on Carbopol® hydrogel adhesion, a poly(acrylic acid) polymer with a light crosslinking, was investigated by BlancoFuente. Due to an increase in elasticity brought on by the complex formation between the medication and the polymer, the author exhibited greater adhesion when water was limited in the system. Large amounts of water caused the complex to precipitate out, which slightly lessened its sticky properties. Mucoadhesion to porcine cheek tissue was greatly improved by increasing the toluidine blue O (TBO) content in mucoadhesive patches made of Gantrez® (poly(methylvinylether/maleic acid). Due to electrostatic interactions between the cationic medication and anionic copolymer, there was an increase in internal cohesion inside the patches, which was the cause of this. [13]

Reference:

1) https://www.scielo.br/j/bjps/a/R4HQjrQQqdrwCLCb6TkGPmw/?format=pdf&lang=eneference

2) https://www.researchgate.net/publication/285926200_Mucoadhesive_Drug_Delivery_System_A_Review

3) https://www.vedantu.com/biology/mucous-membrane

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3255397/

5) https://www.google.com/search?q=layer+of+mucous+membrane+diagram

6) https://www.researchgate.net/figure/Fig-1-Diagrammatic-representation-of-electronic-theory_fig1_235989970

7) https://www.google.com/search?q=wetting+theory+of+mucoadhesion&source

8) https://www.researchgate.net/figure/Illustration-of-nitrogen-adsorption-theory

9) https://www.google.com/search?q=mechanical+theory+of+mdds+diagram&source

10) https://d1wqtxts1xzle7.cloudfront.net/58760642/Mucoadhesive_drug_delivery_system__An_overview.pdf_

11) https://d1wqtxts1xzle7.cloudfront.net/58760642/Mucoadhesive_drug_delivery_system__An_overview.pdf_suraj.pdf2.pdf?1554101495=&response-content-disposition=inline%3B+filename%3DInter

12) https://www.tandfonline.com/doi/epdf/10.1163/138577209X12478283327236?needAccess=true&role=button

13) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3053525/

14) Nirali publication

15) Tiwari D, Goldman D, Sause R, Madan PL. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. AAPS Pharm Sci 1999;1:13-21.

16) . M. C. Bonferoni, P. Chetoni, P. Giunchedi and S. Rossi, Eur. J. Pharm. Biopharm. 57, 465 (2004).

17) A. Ludwig, Adv. Drug Deliv. Rev. 57, 1595 (2005).

18) S. Rossi, M. C. Bonferoni, F. Ferrari and C. Caramella, Pharm. Dev. Technol. 4, 55 (1999).

19) G. P. Andrew, T. P. Laverty and D. S. Jones, Eur. J. Pharm. Biopharm. 71, 505 (2009).

20) Smart J.D. (2005), The basics and underlying mechanisms of mucoadhesion, Adv.DrugDeliv. Rev., 57:1556-1568.

21) Akhtar M.H., Gupta J., Mohuddin M., Faisal M.D. (2012), A comprehensive Review on Buccal Drug Delivery System, Int. J. Of Pharm. Res. and Dev., 3(11):59-77.

22) Gu JM, Robinson JR, Leung SH. Binding of acrylic polymers to mucin/epithelial surfaces: Structure–property relationships. Crit Rev Ther Drug Carrier Syst 1998;5:21-67.

23) F. Thielmann, M. Naderi, V. Khutoryanskiy and O. Khutoryanskaya, available at: http://www. aapsj.org/abstracts/NBC_2007/NBC07-000679.PDF