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MUCOADHESIVE DRUG DELIVERY SYSTEM

[1]G.Sindhu Sravanthi,[2]Nandam. Hemalatha*,[3]Katteboina. Venkata Sai Padmini, [4]Shaik. Allavuddin, [5]J.N.Suresh Kumar.

Department of Pharmaceutics, Narasaraopeta Institute Of Pharmaceutical Sciences, Narasaraopet, Kotappakonda Road, Guntur district.

ABSTRACT

Mucoadhesive drug system interact with the mucus layer covering the mucosal epithelial surface, mucin molecular and increase the residence time of the dosage form at the site of absorption. Mucosal adhesion is backed by several theories which include electronic, absorption, wetting, diffusion, fracture and mechanical. Stages of mucoadhesion include contact stage and consolidation stage. Mucoadhesion while considering drug delivery is having several merits, because of the ideal physiochemical characters of the mucosal membrane by ionic bonds, covalent bonds, van-der-waal bonds and hydrogen bond. Various sites for mucoadhesive drug delivery system are ocular, nasal, buccal cavity; GIT, vaginal, rectal and several specific dosage forms have been reported. Factors affecting mucoadhesion are molecular weight, flexibility of polymerchain,P^H, presence of carboxylate group and density. several synthetic and natural polymers are identified assuitable candidates for mucoadhesive formulation. EX-vivo/in-vitro studies utilizing gut sac of rate provides indepth knowledge about the adhesive property of the dosage form as well as polymers.

Keywords: Bioadhesion, mucoadhesion, van-der-waal force, consolidation stage.

Introduction:-

Bioadhesion:-

Bioadhesion is defined as an ability of a material to adhere to a biological tissue for an extended period of time. In case of polymer, it attach to the mucin layer of mucosal tissue, the term mucoadhesion is used. Adhesion may be defined simply as a process of fixing of two surface to one another.

Mucus composition

Mucus is translucent and viscid secretion which forms thin continuous gel blanket, secreted by goblet cell.

Water – 95%

Glycoprotein and lipids - 0.5 – 5%

Mineral salts – 1%

Free proteins – 0.5- 1%

Mucus glycoproteins are the high molecules proteins that contain attached oligo-polysaccharide units. The mucus contains following oligosaccharide unit.

L-fructose

D-galactose

N-acetyl-D-glucosamine

N-acetyl-D-galactose amine

Sialic acid

Function of mucosa:-

Protective barrier

Adhesion

Lubrication

Principles of bioadhesive:-

The mucoadhesive must spread over the substrate to initiate close contact for promoting the diffusion of the drug with in the mucous.

Thus, the mechanism of mucoadhesion is generally divided into two steps

A. Contact stage

B. Consolidation stage

A. Contact stage:-

1. The contact between the mucoadhesive and the mucous membrane.

2. Spreading and swelling of the formulation.

3. Initiating its deep contact with the mucus layer. In some case, the delivery system is mechanically attached over the membrane such as for ocular (or) vaginal formulations.

Absorption theory:-

After an initial contact between two surfaces the material adheses because of surface force acting between the two atoms in the two surfaces. Two types of chemical bond resulting from this force.

1. Primary chemical bond of covalent nature, which are undesirable in bioadhesion because their high strength result in permanent bond.
2. Secondary chemical bond having many different forces of attraction, including electrostatic forces, vander walls forces and hydrogen bond and hydrophobic bonds.

Wetting theory:-

It essentially measures the spreadability of the bioadhesive polymer on the mucus. Essential characteristics for the bioadhesive materials include zero(or) nearly zero contact angle. Relatively low viscosity and an intimate contact that excludes air entrapment. Therefore the interfacial energies are responsible for the contact of two surfaces and for the adhesive strength.

Diffusion theory:-

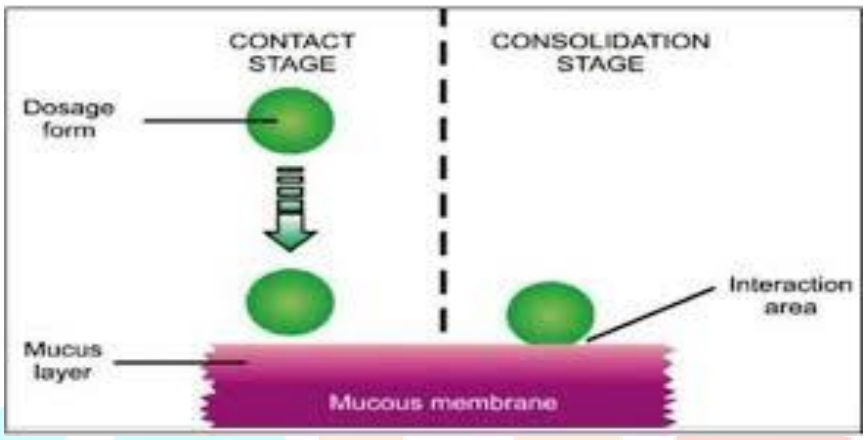
According to this, the polymer chains and mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depths on the diffusion coefficient and time of contact. The diffusion coefficient depends on the value of molecular weight between cross links and decrease significantly as the cross linking density increase.

B. The consolidation stage:-

In this step, various physicochemical interaction occur to consolidate and strengthen the adhesive joint, resulting in a prolonged adhesion, a second consolidation stage is required.

There are 2 theories explaining this process

1. First theory based on the intra molecular interaction proposes that the mucoadhesive molecule interpenetrate and bond by 2° interaction with mucus glycoprotein
2. Second theory is the dehydration theory, which proposes that when a material capable of rapid gelation in an aqueous environment is brought into contant with second gel water movement occurring between gels until equilibrium reached.



Theories of bioadhesion:-

1. Electronic theory:-

Electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This result in the formation of an electronic double layer at the interface .adhesion occurs due to attractive forces across the double layer.

2. Fracture theory:-

The theory relates the difficulty of separation of two surfacesafter adhesion.

Fracture theory equivalent to adhesive strength is given by

$$G = (E\sum/L)1/2$$

Where,

E = Youngs modulus of elasticity

$\sum$ = Fracture energy

L = critical crock length

Factors affecting mucoadhesion:-

1. Polymer related factors :-
    i. Molecular weight
    ii. Concentration of active polymers
    iii. Flexibility of polymer chains
    iv. Spatial conformation
    v. Swelling
2. Environment related factors :-
    i. P^H of polymers – substance interface
    ii. Applied strength
    iii. Initial contact time
3. Physiologicalfactors :-
    i. Mucin turn over
    ii. Disease state

Molecular weight:-

The mucoadhesive strength of a polymer increases which molecular weight about 100000. Direct correlation between the mucoadhesive strength of Polyoxyethylene polymers and their molecular weight lies in the range of 2, 00,000 – 7, 00,000.

Flexibility of polymer chain:-

It is important for interpretation as water soluble polymer becomes cross linked, the mobility of the individual polymer chain decrease, as the cross linking density increases , the effective length of chain which can penetrate into mucus layer decreases even further and mucoadhesive strength is reduced .

Cross linking density:-

The average pore size, the number and average molecular weight of the cross- linked polymer and the density of cross-linked polymer are three important and inter-related structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking diffusion of water into the polymer network at lower rate which in turn causes an insufficient swelling of the polymer.

Spatial conformation:-

Besides molecular weight or chain length , spatial confirmation is also important despite a high molecule weight of 19,500,000 for dextrans they have similar adhesive strength to that of poly ethylene glycolith a molecular weight of 2,00,000 .

Concentration of active polymer:-

This is an optimum concentration of polymer corresponding to the best bioadhesive. In highly concentrated system, the adhesive strength decreasesignifieantly.

Environment related factors:-

a) P^H:-

P^HWas found to have a significant effect on mucoadhesionP^H influences the change on the surface of both mucus and polymers mucus will have a different change density depending on P^H because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids.

b) Applied strength:-

To place a solid mucoadhesive system, it is necessary to apply a defined strength, depending on the type of polymer poly (acrylic acid\divinyl benzene) or carbopol, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. If high pressure is applied for a long period of time, polymers become mucoadhesive even through they do not have attractive interactive with mucin.

c) Initial contact time:-

Initial contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpretation of the mucoadhesive polymer chains. More adhesive strength increases as the initial contact time increases.

Physiological factors

Mucin turnover:-

The natural turnover of mucin molecules from the mucus layer is important for at least two reasons. Firstly the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. Secondly,mucin turnover result in substantial amounts of soluble mucin,molecules. These molecules interact with mucoadhesive before they have chance to interact with mucuslayer. The gas mucosa accumulates secreted mucin on the luminal surface of the tissue during early stage 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 mucus layer to be determined.

Disease state:-

The physiochemical properties of the mucus are know to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of female reproductive tract and inflammatory conditions of the eye.

If mucoadhesive are to be used in the disease states, the mucoadhesive property needs to be evaluated under the same conditions.

Permeability coefficient:-

To compare the permeation of various drug, a standard and equation calculating the permeability coefficient can be used, one of the equation is

$$p = \frac{\%\, permeated \times V_d}{\mathrm{A} \times \mathrm{t} \times 100}$$

Where

P = permeability coefficient (cm\s)

A = surface area for permeation

V_d = volume of donor compartment

t= time

This equation assumes that the concentration gradient of the drug passing through the membrane remains constant with time.

Penetration enhance:-

To increase the absorption of poorly soluble drug especially large hydrophilic molecules, permeation enhance have becomes of increasing interest in recent years.

Properties of penetration enhance:-

1. Safe and effective
2. Pharmacologically inactive

3. Chemically inert
4. Reversible effect

Permeation enhance have surfactant like properties and those that are water soluble polymer seems to be most active at concentration about CMC.

Mechanism of absorption enhancement:-

1. Increasing the fluidity of the cell membrane
2. Extracting inter and intracellular lipids
3. Disrupting lipids structure e.g., solubilization by formation of micelles to create aqueous channels
4. Altering cellular proteins
5. Increasing the thermodynamic activity of the drug
6. Overcoming enzymatic barriers, particularly too peptide and protein drug.
7. Altering surface mucin rheology.

Advantages:-

1. Prolongs the residence time of the dosage form at the site of absorption.
2. To avoid the first pass metabolism
3. Due to increasing residence time it enhance absorption and hence the therapeutic efficacy of the drug
4. Excellent accessibility
5. Rapid absorption because of enormous blood supply and good blood flow rate.
6. Increasing in drug bioavailability due to first pass metabolism avoidance.
7. Drug is protected from degradation in the acidic environment in the GIT.
8. Improved patient compliance and ease of drug administration.

Disadvantages:-

1. Medication administered orally dose not enter the blood stream immediately after passage through the buccal mucosa.
2. Certain drug when ingested undergo drug destruction
3. Oral ingestion results in more exposure of drug to GI tract
4. The absorption of mucoadhesive drug is adversely affected by the presence of food. Tetracycline particular complicate the administration of this class of antibodies vio oral route.

Ideal characteristic of bioadhesive polymer:-

1. Polymer should form a strong non covalent bond with the mucin-epithelial surface.
2. Polymer should quick adhere to most tissues and should passers some specificity to desired site.
3. Polymer should allow for the easy incorporation of the drug as well as its release at desired time.
4. Polymer should not be irritation to the mucus membrane.
5. Polymer should be immunogenic.
6. Polymer and their degradation should not be absorbed from the GST.
7. The polymer should possess cohesiveness to provide strength inside the inner layer.

S.NO	POLYMER	BIOADHESIVE PROPERTIES
1	Carboxy methyl cellulose (CMC)	+++
2	Carbopol 934	+++
3	Tragacanth	+++
4	Sodium alginate	+++
5	Gelatin	++
6	Acasia	+
7	Polyethylene glycol (PEG)	+
8	Hydroxyl propyl cellulose (HPC)	+

Where

+++ = excellent

++ = Fail

+ = poor

Evaluation of bioadhesive tablets:-

Weight variation:-

Twenty tablets will be weighed individually and then collective, average weight of the tablets calculates, then weight variation calculates.

Hardness:-

The hardness of the tablets will determine using Monsanto hardness testes.

Friability test:-

The tablets will test for friability testing using roche friabilator. For this test, six tablets weigh and subject to combine abrasion and shock in the plastic chamber of friabilator evolving at 25rmp for 4 min and the tablets reweigh.

Content uniformity:-

The tablets will be accurately weigh and power crush is glass pestle mortar. An accurately weigh amount equivalent to 5 mg of pure drug take and assay. Perform using U.V visible spectrophotometrically at 228 nm in triplicates.

SurfaceP^H:-

It is determine in order to investigate the possibility of any irritation in the oral cavity. The tablet will keep in contact with simulated saliva solution for 2h and P^H note by bringing the electrode in contact with surface formation.

Swelling studies:-

The tablets(n =3) will be weigh individually and placed separately in petridish containing 5 ml of isotonic phosphate buffer P^H(6.5) solution. At regular intervals (0.5,1,2,3,4,5,and 6n), the tablets remove from the petridishes and surface water remove carefully using the filter paper, reweigh (W2) and swelling index can be calculate by

$$SI= w_2 - w_1/w_1$$

CONCLUSION

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the adhesion of the drug are important factors in the oral bioavailability of many drugs. The factors which are determinant in overall success of the mucoadhesive drug delivery are the polymer physicochemical properties and the in-vivo factors such as the mucin turnover rate, mucin flow. A number of both in-vitro and in-vivo techniques have been developed for the evaluation of the mucoadhesive drug delivery system. Mucoadhesive dosage forms extand form the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery system. The most widely studied and accepted polymers for mucoadhesion have been the hydrophilic, high molecular weight, anionic molecular like carbomers. Recently the focus have been on the novel second generation polymers like the thiolated polymers, lectins and lecithins.

Despite the huge amount of work been done on this drug dekivery platform, the focus has been primarily on the formulation of gastrorentive dosage forms,

Hence, work must be done to exploit this drug delivery system for various other approaches like drug targeting and site specific drug delivery system.

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