International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1171-1187 www.ijprajournal.com ISSN: 2249-7781

Bioadhesive Drug Delivery System system

Manisha Sanjay Dapke
1) Mr.LD.Hingane. (M Pharm PhD Scholar) 2) Mr.Bagwan.L.R
College :- Aditya Pharmacy College ,Beed
Address :- Nalwandinaka,Beed, Maharashtra.Pincode. :- 431122

Date Of Submission: 01-03-2021 Date Of Acceptance: 10-03-2021

ABSTRACT: The term bioadhesioncommonly defined as adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesivedrug delivery system, bioadhesionoften refers to the adhesion between the excipients and biologicaltissue.
When adhesion is restricted to mucous layer lining of the mucosal surface layer known asMucoadhesion.For the purpose of drug delivery, the term bioadhesion is defined as the ability ofthedrugcarrier system or the material to adhere to a biological tissue for extended period of time, leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivereddrugs.
In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface (e.g. mouth ulcer) to reduce the overall required and minimize side effect that may be caused by systemic administration ofdrugs.Now, due to bioadhesion, the immobilization of drug carrying particles at themucosalsurface would result in,
A prolonged residence time at a site of absorption oraction
A localization of the drug delivery system (DDS) at a given targetsite.
Increase in the drug concentration gradient due to the intestine contact of the particles with mucosalsurface.
Possible by pass of first passeffect
Avoidance of presystemic elimination withinGIT.
Depending on the particular drug, a better enzymatic flora for drugabsorption.
Inclusion of penetration enhancers such as sodium glycocholate, sodium taurocholateand protease inhibitors in dosage form results in better absorption of peptides andproteins.

Keywords –Bioadhesion , Mucoadhesion , Polypeptides , Applied strength , Lozenges ,Susceptible **,**

I. INTRODUCTION

The process involved in the formation of bioadhesivebonds has been described in three steps:

Wetting and swelling of polymer to permit intimate contact with biologicaltissue.Interpenetration of bioadhesivepolymer chain and entanglement of polymer and mucinchains.Formation of weak chemical bonds between entangledchain.

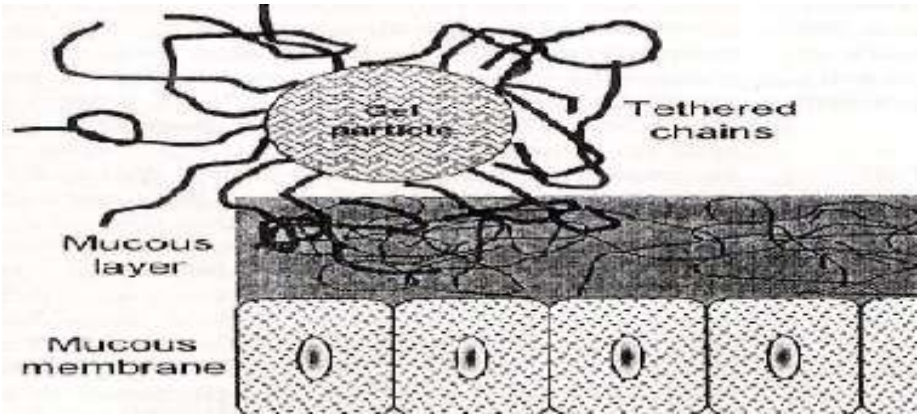

Fig 1: Biological membrane

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BIOLOGICAL MEMBRANE :

Membranes of internal tracts of the body are covered with a thick gel like structure known as mucinandmucinis synthesized by goblet cells and special exocrine glands with mucous cellacini.

This bioadhesivemucinconsists of highly hydrated, cross-linked, linear, flexible and random coil glycoprotein molecules with net negativecharge.

The cell surface membrane also possesses a net negative charge due to the presence of charged groups. Thus the binding of mucin to cell surfaces, which is a result of interaction between the two surfaces with same net charge, indicates that adhesive forces dominate the electrostatic repulsive forces between the twosurfaces.

Composition and characteristic of mucous

Mucinsare synthesized by the gobletcellsand special exocrineglands

Mucin is of glycoprotein family, having mol.wt.1-40 dalton

Mucin network is negative because of Presence of sialic acid which has pKa of 2.6 Presence of chargedgroups.

Two basic steps have been identified for mucoadhesion :

(1) Contactstage :- An intimate contact is formedbetweenthemucoadhesiveandmucousmembrane.

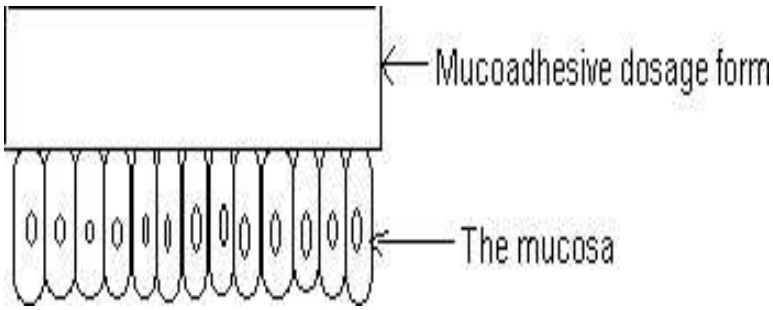

Fig 2 : Contact stage

(2) **Consolidation stage :-**

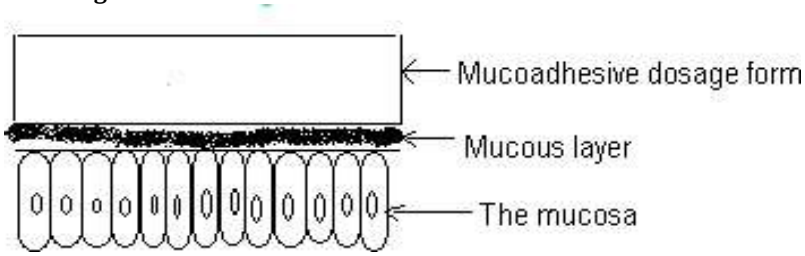

Fig 3 : **Consolidation stage**

It has been proposed that if strong or prolonged adhesion is required, with larger formulations exposed to stresses such as blinking or mouth movements, then a second " consolidation " stage is required. The mucoadhesive, the mucosa, and the interfacial region, consisting of mucous.

Adhesive joint failure may occur at weakest components of the joint. The strength of the adhesive joint will depend on the cohesive nature of the weakestregion.

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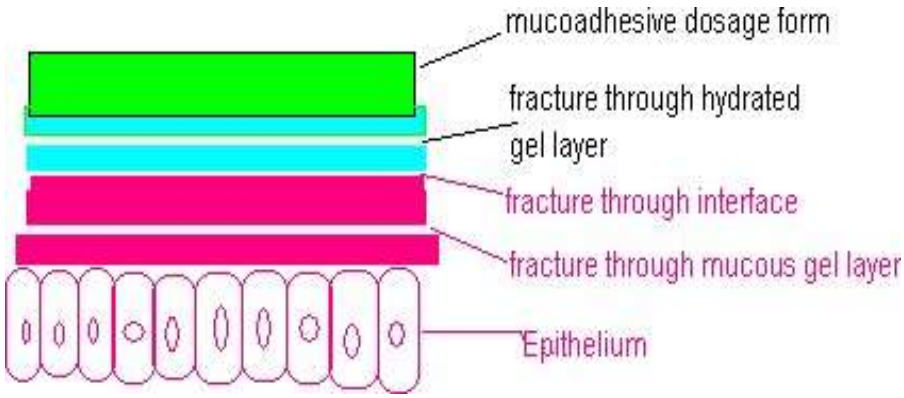

Fig 4 : Possibilities in mucoadhesion failure

To understand the above problem there are two theories of how this gel strengthening occurs.

(1) Macromolecular interpenetrationeffect

(2) Rheological synergy study:-

The rheological synergy study suggests that as soon as mucus and mucoadhsiveinterpenetrate, they are likely to interact and form a surface gel layer that will substantially inhibit any furtherinterpenetration.

The theory proposed that consolidation arises from the ability of dry or partially hydrated mucoadhesive materials to swell and hydrate mucous gel, and it is water movement rather macromolecularinterpenetration.

Mechanism Of Hydrogel Hydration:-

Swelling is an affinity consequence of the affinity of polymeric components for water. Polymers swell because of an imbalance between the chemical potential of solvent within the polymer and that in the surrounding medium. Thus solvent moves as a result of polymeric "osmotic pressure "until equilibrium is achieved and the internal and external chemical potentials areequivalent.

For low- molecular weight hydrophilic polymers the equilibrium state is a solution; for high molecular weight crossed linked polymers it can be a water swollengel.

The extent and rate of swelling are affected by the degree of crsslinking and chain length If the surrounding medium contains solute, the rate of swelling decreases, particularly if the solute is large and cannot enter the hydrogelsnetwork.

THEORIES OF BIOADHESION

1.**Electronic theory: -** According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucous glycoprotein due to differencein their electronic structure. This results in formation of electrical double layer at the interface.

2.Adsorption theory: - After an initial contact between two surfaces, thematerialadheres because of surface forces acting between the atoms in the two surfaces.

3.Wetting theory: - Predominantly applicable to liquid bioadhesive systems. The thermodynamic work of adhesion is a function of surface tension of the surface in contact as well as interfacial tension. The interfacial energy is responsible for the contact between the two surfaces and adhesivestrength.

4.Fracture theory: - It attempts to relate the difficulty of separation of two surfaces afteradhesion.

5. Diffusion theory: - The polymer chains and mucus mix to a sufficient depthto create a semipermant adhesive bond.

FACTORS AFFECTING MUCOADHESION

(1)POLYMER RELATED FACTORS:-

1)Molecularweight:-

There is certain molecular weight at which bioadhesion is at amaximum.

The interpenetration of polymer molecules is favorable for low molecular weight polymers, whereas entanglements are favored for high molecular weightpolymers.

It seems hat the bioadhesive forces increases with the molecular weight of the bioadhesivepolymer up to 100000, and that beyond this level there is not much affect.

2)Concentration of activepolymer

Bremeckerrelates that there is an optimum concentration of polymer corresponding to the bestbioadhesion.

In highly concentrated systems, the adhesive strength drops significantly.

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In fact, in concentrated solutions, the coiled molecules become solventpoor, and the chains available for interpenetration are notnumerous.
This result seems to be of interest only for more or less liquidbioadhesiveforms

3)Degree of hydration
Depending on the degree of hydration adhesive properties are different. It is maximum at a certain degree ofhydration.
When the degree of hydration is high, adhesiveness is lost probably due to formation of slippery, non-adhesive mucilage in an environment of large amount of water at or near theinterface.

4)Charge on polymer
Mucosal surface is negatively charged. So positively charged polymer might facilitate the mucoadhesive process. Perhaps the initial step of mucoadhesionof a positively charged polymer to the biologic surface is through electrostatic attraction, followed by mechanical interlinking of polymer chains, vanderwaalforces, H bonds andotherforces. Chitosan have bioadhesion due to electrostatic attraction between positively charged D- glucosamine residue of chitosan and negatively charged sialic acid residues.

5) Flexibility of polymerchain
6) Spatialconfirmation
7) Swelling

8)Presence of functional group
Non-invasive delivery of hydrophilic macromolecular drugs such as peptides, nucleic acids & polysaccharides is one of the major challenges in modern pharmaceutical technologies. Thiomersarethiolatedpolymers.
Due to immobilization of thiol groups on well established polymers like chitosan &polyacrylicacid their permeation enhancement, enzyme inhibitory &mucoadhesivepropertiesareimproved.
The immobilization of thiol groups on microparticlesimprovesmucoadhesiveproperties.

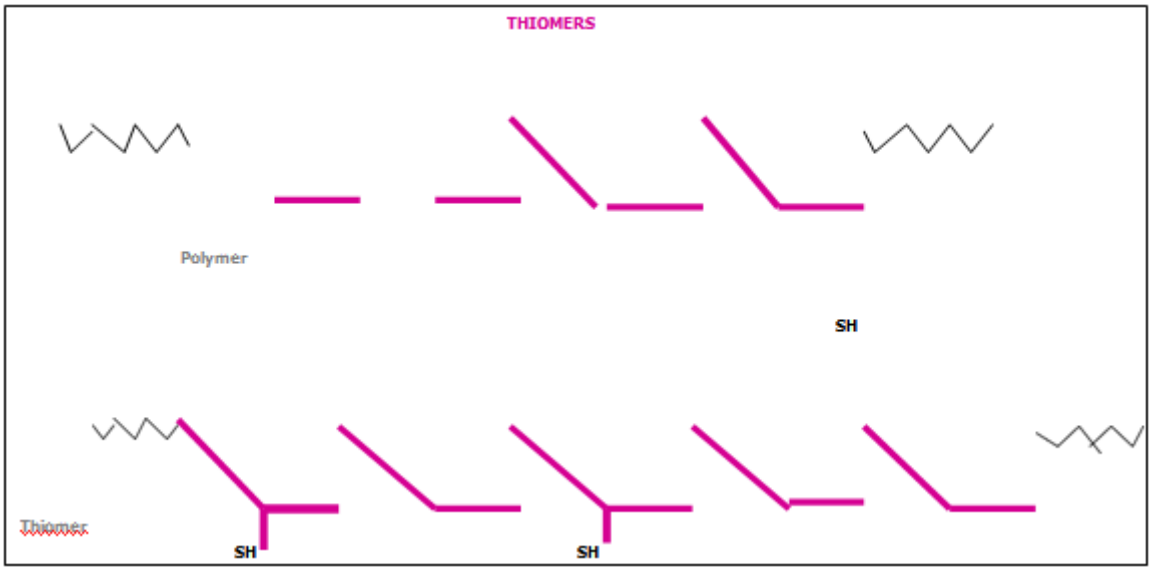

Fig 5: Thiomers

(2)ENVIRONMENT RELATEDFACTORS:-
(1)pH pH was found to have a significant effectonmucoadhesion.
pH influences the charge on the surface of both mucus and the polymers.
Mucus will have a different charge density depending on the pH because of the difference in the dissociation of the functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone. Robinson et al. Observed that the pH of the medium is critical for the degree of hydration of highly cross linked polyacrylicacid polymers, increasing between pH 4 to pH 5, continuing to increase slightly at pH 6- pH 7, and decreasing at more alkaline levels. This behavior was attributed to difference in the charge density at the different pHlevels.

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(2)Appliedstrength

To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesion strength increases with the applied strength or with the duration of its application, up to an optimum level.

(3)Initial contacttime

The initial contact time between the mucoadhesives and the mucus layer determines the extent of swelling and the interpenetration of the polymer chains. The mucoadhesive strength increases as the initial contact timeincreases.

(4) Swelling

Interpenetration of chains is easier when polymer chains are disentangled and free of interactions. When swelling is too great, a decrease in the bioadhesion occurs, such a phenomena must not occur too early, in order to lead to a sufficient time for action of the bioadhesivesystem.

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(3)PHYSIOLOGICAL FACTORS:-

(1)Mucinturnover

The natural turnover of the mucinmolecules from the mucus layer is important for at least two reasons-

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The mucinturn over is expected to limit the residence time of mucoadhesive dosage form on the mucuslayer.

Mucinturnover results in substantial amount of soluble mucinmolecules. These mucinmolecules interact with mucoadhesivebefore they have a chance to interact with the mucuslayer.

(2)Diseasestates

The physiological properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers etc. The exact structural changes taking place in mucus under these conditions are notyet clearly understood.

There are some other factors that influence the chemical or physical characteristics of mucinormucoadhesive layer and will have an effect on the extent of interaction and strength ofmucoadhesion.

BIOADHESIVE POLYMERS

They are water soluble and water insoluble polymers which are swellablenetworks jointed by crosslinkingagents.

Characteristics of an ideal polymer :

Degradation products should be non toxic and non absorbable fromg.i.t Non irritant to mucousmembrane.

Form a strong non covalent bond with mucinepithelial cell surfaces.

Should adhere quickly to moist tissue and should possess sitespecificity.

Allow easy incorporation of the drug and offer no hindrance to itsrelease.

Polymer must not decompose on storage or during shelf life of dosageform.

Cost effective.

POLYMER	BIOADHESIVE PROPERTY
Carboxy methyl cellulose	+++
Carbopol 934	+++
Polycarbophil	+++
Tragacanth	+++
Poly (acrylic acid / divenyl benzene)	+++
Sodium alginate	+++
Hydroxy ethyl cellulose	+++
Gum karaya	++
Gelatin	++
Guar gum	++

International Journal of Pharmaceutical Research and Applications
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POLYMER	BIOADHESIVE PROPERTY
Thermally modified starch	+
Pectin	+
PVP	+
Acacia	+
PEG	+
Psyllium	+
Amberlite – 200 resin	+
HPC	+
Chitosan	+
Hydroxy ethyl methacrylate	+

Summary of work on Mucoadhesive dosage Forms:-

(1). Anti hypertensive, Antianginal, and related drugs:

Drug	Route/ Purpose	Dosage form	Polymer
Captopril	Oral, SR	Tablet	Carbopol 934
Chlorthiazid e	Orar, SR	Beads	POlycarbop hil
Nifedipine	Buccal, SR Nasal SR	Patch Gel	Sodium alginate, PEG6000 PEG 6000, carbopol
IsosorbideDinitrate	Buccal SR	Tablet	PVP, Polyacrylic acid
Verapamil HCl	Buccal SR	Tablet	HPC-M, arbopol 934
DeltiazemH Cl	Buccal SR	Tablet	Carbopol 934, PVP
Propranolol	Buccal SR Nasal SR	Patc h Gel	Sodium CMC -
Nitroglyceri ne	Buccal SR	Tablet	-
Hydralazine	Buccal SR	Tablet	Carbopol 934, CMC
Vasopressin	Nasal SR	Solutio n	Sodium hyaluronate.
Dopamine	Nasal SR	Solutio n	HPC

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(2)Analgesic and anti-inflammatorydrugs

Morphine Sulphate	Oral SR	Tablet	Protein Prosobet L85, HPMC
Buprenorphi ne	Buccal SR	Patch	Polyisobutylene, Polyisoprene, Carbopol 934 P
Ketorolac Tromethami ne	Buccal SR	Tablet	-
Lignocaine HCl	Gingival SR	Film	-
Triamcinolon e Acetonide	Buccal SR	Tablet	HPC, Carbopol 934
Prednisolone	Buccal SR	Ointment	Carbopol, white petrolatum
Antipyrine	Rectal SR	Gel	Hydroxy ethyl methacrylate

(3)Anti asthmaticdrugs

Salbutamol sulphate	BuccalSR BuccalSR	Film Tablet	- -
Terbutalinesulphate	Buccal SR	Film	-
Beclomethaso ne Dipropionate	Nasal SR	Powdr e	HP C
Di- isoproterenol	Oral CR	Tablet	HP C

(4) Anti infectivedrugs

Metronidazole	Oral SR Buccal SR Oral, vaginalSR	Tablet	Carbopol 934, HPMC HPMC, polyacrylic acid HPC, Carbopol 934 P
Miconazole	Buccal SR	Tablet	Drum dried starch, Polyacrylic acid
Cetylpyridiniu m Chloride	Buccal SR	Tablet	-
Clotrimazole	Buccal SR	Tablet	-
Gentamycin	Nasal SR	Microsphe re	Starch

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(5) **Anti neoplastic drugs**

Bleomycin	Vaginal SR	Disk	HPC, Carbopol 934
5-Fluorouracil	Vaginal SR	Stick	HPC, Carbopol 934
Interferon B	Nasal SR	Powder	Avicel, Human serum albumin

(6) **Hormonal Drugs**

Insulin	Oral	Tablet	HPC, Carbopol934
Insulin	Nasal	Gel Powder	Polyacrylic acid Carbopol 934
Testosterone	Buccal	Tablet	-
Calcitonin	Nasal	Gel	Polyacrylic acid

(7) **Ophthalmic drugs**

Progesterone	Occular	-	-
Pilocarpine	Occular SR	Gel	Hyaluronic acid
Tropicamide	Occular SR	Gel	Hyaluronic acid

Mucosal Permeation Enhancers :

1. 23-laurylether
2. Aprotinin
3. Azone
4. Benzalkoniumchloride
5. Cetylpyridiniumchloride
6. Cetyltrimethylammoniumbromide
7. Cyclodextrin
8. Dextransulfate
9. Lauricacid

POTENTIAL SITES FOR BIOADHESIVE DRUG DELIVERY

The mucosal layer lines number of regions of the body including the GI tract, urogenital tract the airways, the ear, nose, eye etc. These represent the potential sites for the attachment of many bioadhesive systems and hence mucoadhesive drug delivery system include the following-

1.Buccal Drug Deliverysystem
2.Sublingual Drug Deliverysystem
3.Oral Drug Deliverysystem
4.Nasal Drug Deliverysystem
5.Ocular Drug Deliverysystem
6.Vaginal Drug Deliverysystem
7. Rectal Drug Deliverysystem

Other classification of bioadhesive dosage form:-

Solid bioadhesive formulations

Tablets
BioadhesivemicroparticlesBioadhesive inserts
Bioadhesive wafers
Lozenges

Semisolid bioadhesive Formulations

Gels
Films

Liquid bioadhesive formulations

Suspensions
Gel forming liquids

BUCCAL BIOADHESIVE DRUG DELIVERY: -

Oral cavity has rich blood supply and direct access to systemic circulation. The oral route is suitable for drugs which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in theliver.

In oral cavity, buccal and gingival areas are associated with a smaller flow of saliva as compared to the sublingual region, thus the duration of adhesion of the delivery system would be longer at these areas than at the sublingual region

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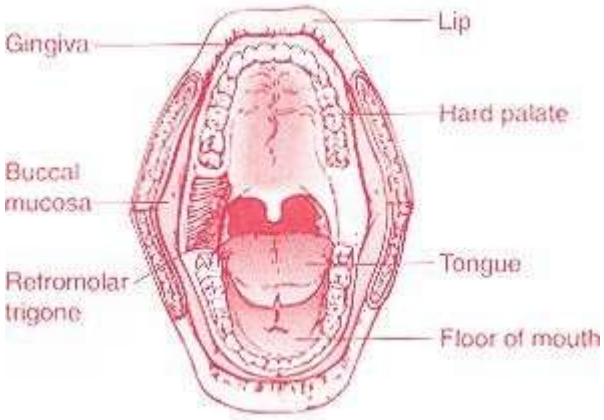

Fig 6 : Oral cavity

Buccal absorption of drug

To penetrate the mucosa to a significant degree a drug should have relatively low molecular weight and exhibit biphasic solubility patterns, that is, be soluble in both the aqueous salivary fluid and lipid membrane barrier to show penetration. High molecular weight muccopolysachrides such as heaperin and proteins such as insulin are not well absorbed. A significant amount of drug should be un- ionized at salivary pH and the drug should also not bind strongly to the oral mucosa.

Oral mucosa as site for drug delivery

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

1. Sublingual delivery:-

Which is systemic delivery of drugs through the mucosal membranes lining the floor of themouth.Sublingual mucosa is relatively permeable due to the thin membrane and large veins, hence allow rapid absorption and acceptable bioavailability of manydrugs.Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatin capsules filled with liquid drug.Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa.

2. Buccal delivery:-

Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa) Buccal mucosa is significantly less permeable than sublingual mucosa, which makes it more suitable for sustained drug delivery and is generally not able to provide the rapid absorption and good bioavailabilitiesseen with sublingualadministration.The buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems used for oral transmucosaldrugdelivery.Thusthe buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptidedrugs.Get higher patient compliance due to accessibility of the cheek lining and lack of invasive measures.

3. Local delivery:-

Which is drug delivery into the oral cavity.

TYPES OF BUCCAL BIOADHESIVE DOSAGE FORM

BIOADHESIVE BUCCAL TABLETS

Bioadhesive tablets are immobilized drug delivery systems.

They can be formulated into monolithic partially coated or multilayered matrices.

Drug can be co-incorporated with an absorption enhancer, if required. Partial coating of a monolithic tablet affords the protection of every face of the tablet, which is not in contact with themucosa.Incase of bi-layered tablets, drug can be incorporated in the adhesive layer, which comes in contact with the mucosalsurface.Following are the possible designs for buccal bioadhesive drug delivery-

The limitations of bioadhesive tablets are: -

The small surface of contact with themucosa.

Their lack of physicalflexibility.

It is difficult to get high release rates, which is required for somedrugs. The extent and frequency

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of contact may cause irritation following chronic application on the buccal and sublingualmucosa.
e.g. of buccoadhesive tablets:-

a. Sublingual mucosal delivery of nitroglycerin - Susadrin®
b. Buccal mucosal delivery of prochlorperazine- Buccastem® chewing gum buccal mucosal delivery of Nicotine –Nicorette

BUCCAL PATCHES

Adhesive patches can be designed either for unidirectional release or multidirectional release.

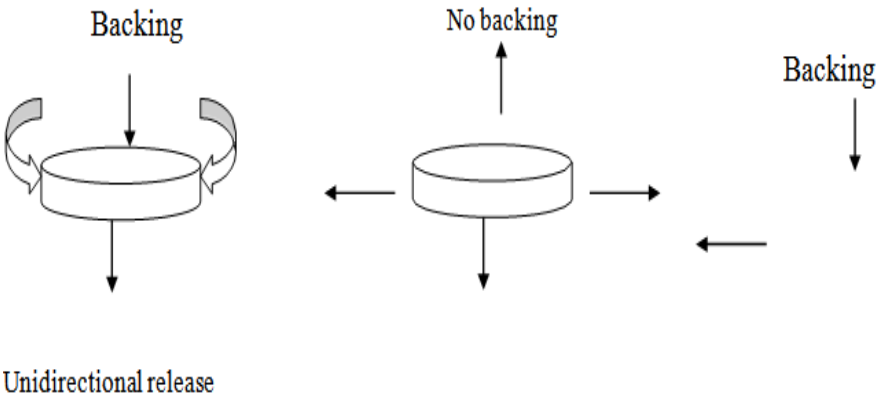

Fig 7 : Buccal patches

The adhesive part of the system can be used as drug carrier or as an adhesive for the retention of a drug loaded non-adhesivelayer.
The use of as an impermeable backing layer will maximize the drugconcentration gradient and prolong adhesion because the system is protected from saliva.
Polyacrylicacid based patches have been used successfully for the delivery of opoidanalgesics

Application aids

Depending on the therapeutic aim of a buccal patch, it may be necessary to consider a design with an application aid. A good application aid should help a patient handle a thin and small patch in such a way that the patch itself does not have to be held with the f ingers. As it may be difficult to put two fingers holding a patch deep into the mouth to reach an administration site deep into the distal region of the buccal cavity. An example of this is shown in thefigure-

Advantages Of Buccoadhesive Drug DELIVERY SYSTEMS Good patientcompliance.
Administration and termination of therapy iseasy.
Due to lack of langerhanscells it is tolerant to potentialallergens.
This route can administer drugs that are unstable in the acidic environment of this stomach or are destroyed at the enzymatic or alkaline environment of theintestine.
Permits localization of the drug to the oral cavity for prolonged period oftime.
Offers an excellent route for systemic delivery of drugs having drawbacks of first pass metabolism, convenient for drugs that show poorbioavailability.
Significant dose reduction can beachieved.
The presence of saliva ensures relatively large amounts of water for drug dissolution unlike the rectal and transdermalroutes.
Offers a passive system for drug absorption and does not require anyactivation.
Consist of non-keratinised epithelium resulting in somewhat more permeable tissue than theskin.

LIMITATION OF BUCCOADHESIVE DRUG DELIVERY SYSTEM

One of the major limitations with buccal drug delivery is the low flux, which results in low drugbioavailability.

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Drugs which irritate the mucosa or have bitter or unpleasant taste or anobnoxiousodor or unstable at buccal pH cannot be administered by this route.
Only drugs with small dose requirements and drugs that are absorbed by passive diffusion can be administered by thisroute.
There is a possibility of patient swallowing the dosageform.
Eating and drinking may become restricted..

Gastrointestinal Bio/Muco Adhesive Drug Delivery

GIT as a target for drug delivery

The target sites for bioadhesion in GIT are- The mucosaltissue.
The mucosal gellayer.
The thickness of the mucingel layer varies regionally through out theGIT. There is a continuous renewal of the mucosal layer by a turnover process, which limits the duration ofmucoadhesion**.**
The micro particles are attached to the mucosal layer through specific or nonspecific interactions.

NON – SPECIFIC BIOADHESION

Non-specific bioadhesionwith the intestinal membrane occurs through physiochemical interactions.Inthe GIT, particles are directly mixed with liquid materials in the stomach, whichislikely to strongly decrease the adhesiveness of such polymers because of the premature hydration of the polymer, which takes place before the contact with mucosal surface.Sothe various approaches of GI bioadhesionof colloidal particles are based on the use of non-swellable, hydrophobicpolymers.Inthis case, adhesion is mainly due to inherent tendency of these small particles to develop intimate contacts with large mucosalsurfaces.

Non-specific bioadhesion suffers from two major drawbacks-

Only a fraction of the dosage form administered is absorbed while remaining part is subjected to direct fecal elimination.Duetounspecificityof the interactions, targeting to a specialized area of the mucosa with unmodified particles isunrealistic.

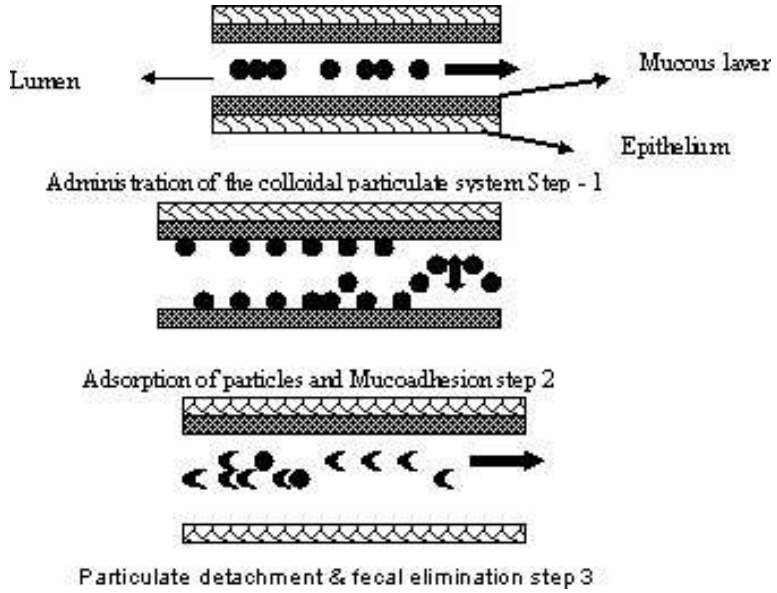

Fig 8: non specific bio adhesion

SPECIFIC BIOADHESION

Specific adhesion is adhesion directly to surface of the cells of the mucosa and this involves specific ligand receptor interactions between complementarystructures. Ideally, the adhesion takes place when the dosage form reaches the desiredsite.

Different targets within GIT can be identified depending on the pharmaceutical applications. The targetsare, Mucosal glycoprotein, M-cells Epithelial cells, Payer's patches or gut-associated lymphoid tissue etc.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1171-1187 www.ijprajournal.com ISSN: 2249-7781

Limitation of specific bioadhesion strategy-

Specific bioadhesion strategy is likely to be limited in vivo by the limited capacity of the particles to diffuse through the mucous layer before reaching cellsurfaces.

The search of ligands exhibiting a sufficient specificity and lack of toxicity at the same time may be crucialtask.

A possible alteration or a blockage of the cell membrane functions and the immunogenicity of the ligand should beconsidered

Lectin conjugates (cytoadhesion)

The concept is specifically based on certain materials that can reversibly bind to cell surfaces in theGIT.

This next generation of mucoadhesivesfunctions with greater specificitybecause they are based on receptor-ligand-like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself.One such class of compounds that has these unique requirements is called lectins.

Lectins have been used extensively for oral delivery in recent years because of their inherent property to provide specific binding to biological surfaces bearing sugar residues located at the surface of epithelial cells and they are resistant to acidic pH and enzymaticdegradation.

The binding of lectins is only possible if corresponding sugar moieties are available on the mucosalsurface.

Lectin-based drug delivery systems have applicability in targeting epithelialcells, intestinal M cells, and enterocytes.

Lectins favor binding at neutral pH; it is more likely that they will be suited to small intestinalapplications.

Toxicity is an important factorto bear in mind, as some lectins can be toxicat certain levels.

Colonic Bioadhesive Drug Delivery

Kakoulides et al., synthesized azo-crosslinkedpoly (acrylic acid) for colonic delivery as well as for adhesionspecificity.They evaluated in vitro degradation and ex vivo bioadhesionof the synthesizedpolymer.Azo- networks based on acrylic backbone croslinked with 4,4'- divenyl benzene. The study indicates that there is optimum crosslinking density to allow non-adhesive particles to reach thecolon. In colonic environment, the azo-network degrades to produce a structure capable of developing subsequent mucoadhesive interaction with colonicmucosa.

Suspensions

Sucralfate suspensions adhere directly to mucosal surfaces within the GIT. This adhesion is not due to bioadhesivepolymer but due to the acidification of the insoluble powder leading to the formation of an adhesive paste. Incorporation of a bioadhesive agent, however, has demonstrated enhanced invitroadhesion of sucralfateformulation within theoesophagus.

Bioadhesiveliquids

Gastric reflux of acidic materials from the stomach into the oesophagus leads to damage of the oesophagal tissue, bioadhesive liquids that coat the oesophagus after oral administration may be used to protect this mucosal surface from gastric reflux. These adhesive liquids that coat the oesophagus may be used to deliver drugs for the treatment of local disorders including motility dysfunction, fungal infections and oesophagal cancer.

In situ gelling system

Rectal insitu gelling and mucoadhesiveMeberevineHCl solution for rectal administration by using poloxamer407 and poloxamer188 which are having thermogelling property. MeberevineHClundergo first pass metabolism. It is used in the irritable bowlsyndrome.

INTRA-PERIODONTAL POCKET BIOADHESIVE DRUG DELIVERY

FIBERS- Commercially available delivery system (AcitsiteO) is based on a monolithic ethylene vinyl acetate fiber that deliverstetracycline

FILMS - It can reach to the base of the pocket to be treated. The physical properties of the film with its sufficient adhesiveness keeps it sufficiently submerged without any noticeable interference with patients eating and oral hygienehabits.

DEGRADABLE DEVICES- Resorbablehydroxy propyl cellulose based devices for delivery of tetracycline and chloerhexidine as well as ofloxacin have been tested clinically (in vivo retention was seen even after 24 hrs).

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Volume 6, Issue 1 Jan-Feb 2021, pp: 1171-1187 www.ijprajournal.com ISSN: 2249-7781

PERIOCHIP –is a film made up of degradable matrix of crosslinkedhydrolyzed gelatin. It is a subgingival delivery method.

Fig 9 : Periochip

PRIODONTAL BIOADHESIVE GEL: - Made with bioadhesive polymers like CMC, methyl cellulose, PVP, carbopol. This has been formulated for metronidazole.

NASAL BIOADHESIVE DRUG DELIVERY SYSTEMS

The key parameters in case of nasal drug deliveryare– 1 . Dispersionpatterns.
2. Bioadhesion.

The nasal mucosa allows effective absorption of a variety of lipophilic drug and hydrophilic drugs such as peptides andproteins.The major difficulty in administering these drugs intra-nasally is their lowbioavailabilitydue to enzymatic degradation, mucociliary clearance and poor mucosal membrane permeability. This problems can be overcome by co-administering penetration enhancers or/and mucoadhesivesubstance.

Chitosans are biodegradable high molecular weight cationic polysaccharide having mechanism of transport enhancement by transient opening of tight junction innasalmembrane and the property of bioadhesion , enhance the nasal absorption in human volunteers of polypeptides and other polar drugs.

1.Liquid BioadhesiveTechnology

A range of studies has been performed with liquid bioadhesiveformulations of variableviscosity.

Pennigtonet al. has shown that an increase in viscosity of a solution by means of the bioadhesive material hydroxypropylmethylcellulose results in a prolonged clearance time from the nasal cavity. Concentrations of 0.6, 0.9, and 1.25% HPMC resulted in clearance half-life of 0.47, 1.7, and 2.2 hrsrespectively inhuman.

2.Self- Gelling BioadhesiveSystem

A problem may be encountered in therapeutic use with application of the bioadhesive liquid gel system in the nasal cavity, especially if a high concentration of the polymer is used. The formulations are not likely to be readily delivered using a normal nasal spray device but rather will have to be applied with the means of atube.

To overcome this problem, bioadhesive formulation that gel upon interaction with the nasal mucosa (due to either increase in temperature, increase in ionic strength, or presence of calcium ions), so- **called environmentally responsive polymers** have been exploited for nasal drug delivery. For e.g. thermogellingpolymer PluronicF127 is a poyoxyethylene polyoxy propylene block copolymer that is liquid at a concentration of more than 25% in buffer at 4ºC, whereas room temperature or at higher temperature it forms a clear viscousgel.

3.Bioadhesive Powder System

Nagai and co-workers investigated the use of bioadhesivepowder dosage form for the administration of peptides such as insulin to the nasalcavity.

The bioadhesive agents studied in combination with the freeze-dried insulin includes crystalline cellulose, hydroxypropyl cellulose and Corbopol934. All formulations tested gave significant decrease in the plasma glucose levels when administered nasally to dog and rabbitmodels**.**

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 1 Jan-Feb 2021, pp: 1171-1187 www.ijprajournal.com ISSN: 2249-7781

4.Bioadhesive Microsphere System

Illum et al first suggested the use of the bioadhesive microspheres. These microspheres swell when they comein contact with the nasal mucosa to form a gel and control the rate of clearance from the nasal cavity, thereby giving poorly absorbed drugs sufficient time to absorb from the nasalmucosa.

OCULAR BIOADHESIVE DRUG DELIVERY SYSTEMS

1.Hydrogels

Hydrogels-sodium hyaluronateandcarbomerare the two hydrogels, providing considerable bioadhesivenature. Artificial tears for the treatment of dry eye (e.g. Viscotear®, Novartis) are the carbomersolutions that adhere on the surface of the eye providing a lubricatedsurfaceocular drug delivery because it has similar features to mucin.
E.g. negative charge, expanded nature etc.

2.SolidFormulations

Solid ophthalmic delivery devices are thin disks or small cylinders made with appropriate polymeric materials and fitting into the lower or upper conjuctivalsac. Some inserts like now classical occusertcan release the drug at a slow constant rate for one week. So, mucoadhesivepolymers can be profitably used as constituents of inserts to achieve prolonged contact with the conjunctival sac and to alleviate the risk of expulsion fromcul-de-sac.

3.Particulate Drug Delivery systems

Liposomes, microspheres and nanoparticles – are manufactured with bioadhesive polymers to show controlled drug release properties.

Evaluation Of Bioadhesive Drug Delivery System:-

1. IN VITRO / EX VIVOMETHODS

a. Methods based on measurement of tensilestrength.
b. Methods based on measurement of shearstrength.

OTHER IN VITRO METHODS

c. Adhesion weightmethod
d. Fluorescent probemethod
e. Flow channelmethod
f. Falling liquid filmmethod
g. Colloidal gold stainingmethod
h. Mechanical spectroscopicmethod
i. Thumbtest
j. Viscometricmethod
k. Adhesionnumber
l. Electricalconductance

2. IN VIVOMETHODS

a. Use of radioisotopes
b. Use of gammascintigraphy

Measurement of residence time / retention time

Measured at site ofapplication.Provides quantitative information on mucoadhesive properties. Carbopol is considered superior for sustained drug delivery in case of The GI transit time of many mucoadhesives have been examined usingradioisotopes e.g. ^{51}Cr and the time dependent distribution of the radioactivity in the GIT is measured.
As same, redionuclidessuch as ^{99m}Tc, ^{113m}In or ^{123}I are used and their transit through the GIT is measured by γscintigraphy.

If we want to test the esophageal bioadhesiveretention, then Longitudinal sections of ex vivo porcine oesophageal tissue is used and sections are equilibrated to 37°C in a humidity chamber immediately prior to use. The tissue is washed at a rate of 1ml/min to simulate salivaflow.1.5 mL of formulation was mixed with ~0.2 MBqTc99m as a radioactive label and it is spread evenly over the mounted tissue surface and washing initiated. Eluate was collected into tubes at regular intervals up to 30 minutes. The radioactivity in each tube was measured to determine the percentage of the dose washed off at each timepoint

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Measurement of adhesive strength

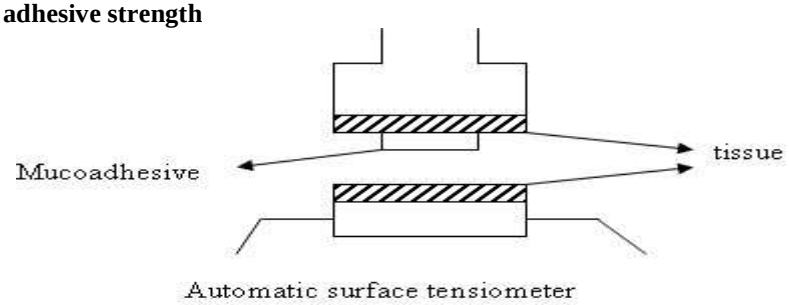

Fig 10: Mesurement of adhesive system

Three different types of stress, tensile, shear and peel stress aremeasured.

For simulation of actual application conditions, the ideal substrate would be the tissue to which the mucoadhesive system will be applied and the force required to separate mucoadhesives from mucosal tissue is measured using modified automatic surfacetensiometer.The results from measuring tensile strength provides information regardingtheeffects of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure onbioadhesion.

The shear stress measures the force that causes mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact.The shear mucoadhesive strength is measured by flow channel method where force necessary for the detachment of a particle placed on the mucingel was determined by passing humid air through the flowcell.The peel test involves the application of stress over a fine line at the edge rather than over the entire area of contactsites.

Thumb test

Here, the adhesiveness is qualitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contacttime. It provides useful information on mucoadhesivepotential.

Adhesion Number

With a mucoadhesive in the form of small particles, the adhesion number can be used as a parameter forMucoadhesion.

The adhesion number (Na)is,

Na = (N/No)*100

Where,

No = total no. of applied particles

N = no. of particles attached to the substrate.

It is assumed that as the adhesion strength increases, the adhesion number also increases.

Falling liquid film method

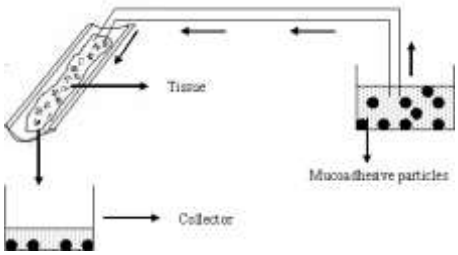

Fig 11 : Falling liquid film method

Small intestinal segments from rats were placed at an inclination on a tygon tube. The adhesion of particles to this surface is measured by passing the particle suspension over the surface and by comparing the fraction of particles adhered to the tissue; the adhesion strength of different polymers can bedetermined.

Membrane viscosity

The interaction between polymers and cell membranes was examined by labeling the cell membranes with fluorescentprobes.The lipid bilayer and proteins of cell membranes were labeled with pyrene and fluorescein isothiocyanate.The fluorescence spectrum of pyreneand the fluorescence depolarization of fluorescein isothiocyanatewere used to examine the change in membrane viscosity after interaction withpolymer.

In vivo evaluation methods

In vivo methods used for evaluation methods are based on administration of polymers to a laboratory animal and tracking their transit through the GI system. Administration methods include forced oral gavage, surgical stomach implantation and infusion through a loop placed in situ in the small intestine. Tracking generally followed with the help of X-ray studies, radio opaque markers and radioactive elements etc. For

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e.g. X- ray studies for monitoring GI transit time for bioadhesive tablet made of $BaSO_4$ and radiolabelledmicrospheres and nanoparticles is carriedout.

Mucoadhesive strength measurement.

Here first tissue novel bioadhesive system (NBAS) is placed or adhered to the rabbit or porcine buccal mucosa. Whole assembly paced in the krebssolution . Then NBAS is clamped. On other side, from the burette liquid is poured and amount of liquid required to detach the NBAS from tissue is measured. An thus bioadhesivestrength measured.

Dissolutin of Buccal tablet:-

Mumtaz and Chang model for the dissolution of the buccal tablet as shown in figure.From the inlet dissolution medium is poured and from outlet it is collected. And assayed.

II. CONCLUSION

Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. The various sites where mucoadhesive polymers have played an important role include buccal cavity, nasal cavity, rectal lumen, vaginal lumen and gastrointestinal tract. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents.

Mucoadhesive dosage forms have a high potential of being useful means of delivering drugs to the body, perhaps particularly for topical or local administration where the mechanical trauma experienced by the dosage form may be minimized. This overview about the mucoadhesive dosage forms might be a useful tool for the efficient design of novel mucoadhesive drug delivery systems. Mucoadhesive drug delivery systems have applications from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. With the influx of a large number of new drug molecules due to drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules.

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