International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 6 Issue 2, January-February 2022 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Mucoadhesive Drug Delivery System

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ABSTRACT

The term bioadhesive describes materials that bind to biological substrates, such as mucosal membranes and in bioadhesive drug delivery systems, the term bioadhesion is used to describe the bonding or adhesion between a synthetic or natural polymer and soft tissues such as epithelial cells. The bioadhesive drug delivery formulation highlights the fact that readily accessible sites are utilized with the eye, oral cavity and vegina being targeted. The GI tract and the nasal cavity have also been extensively examined as a site for bioadhesive drug delivery The prospect of writing this review article is to present comprehensive information related to mucoadhesion and mucoadhesive drug delivery systems. The article has highlighted all the aspects of mucoadhesive drug delivery systems which will be helpful for researches and academics. The article includes detailed information about mucosa- the anatomy and physiology, the mechanisms and theories related to mucoadhesion, evaluation parameters of mucoadhesive dosage forms, mucoadhesive polymers and novel approaches related to mucoadhesive drug delivery system. The potential merits and demerits of mucoadhesive drug delivery as well as that of the polymers are also discussed.

KEYWORDS: *bioadhesion, factors, mucosa, mucoadhesion, parameters, polymers*

How to cite this paper: Vanitha G B | Mrs. S. Shyamla | Mr. S. Jeevanandham "Mucoadhesive Drug Delivery System" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-6 | Issue-2, February 2022, pp.963-977, URL: www.ijtsrd.com/papers/ijtsrd49267.pdf

IJTSRD49267

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the system circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutics advantages, such as, ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half–life are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained –controlled release formulations in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systematic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so the drug could be supplied continuously to its absorption sites in the GIT.

These drug delivery system suffer from mainly two adversities i.e. the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET),which can result in incomplete drug release from the dosage form in the adsorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolonged gatric retention time improves bioavailability, increases the duration of drug releases, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment .Also prolonged GRT in the stomach could be advantageous for local action in the upper part of the small intestine, e.g, treatment of peptic ulcer etc.,

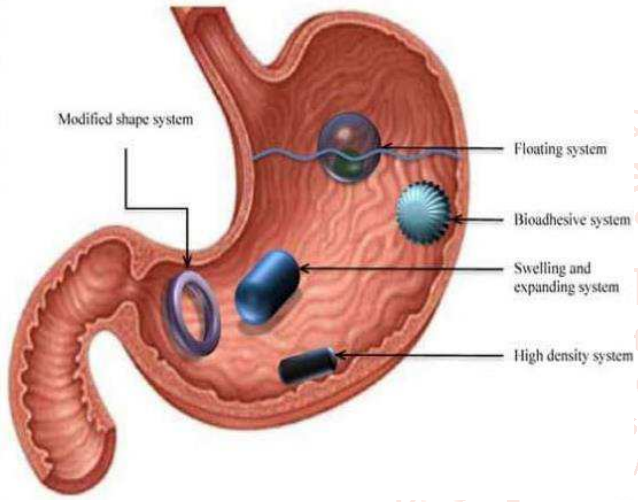
DEFINITION:

Gastro retentive drug delivery systems are the novel formulation systems which are designed to prolong the gastric retention time and to have target-specific drug release in the upper part of stomach for local or systemic therapeutic effects.

Their gastric retention is prolonged either by retaining them in stomach for longer periods or by floating the drug in gastric fluid for a period of time to increase the disintegration time.

APPROACHES:

- High density (sinking) system that is retained in the bottom of stomach,
- Low density (floating) system that causes buoyancy in gastric fluid,
- Mucodhesive systems that causes bioadhesion to stomach mucosa.
- Swellable system which limits emptying of the dosage form through the pyloric sphincter of stomach,
- Super porous hydrogel systems,
- Magnetic system etc.



ADVANTAGES:

- Improved drug absorption because of increased GRT.
- Enhanced bioavailability.
- Controlld drug delivery.
- Reduced dosing frequency.
- Ease of administration.
- Better patient compliance.
- Targeted therapy for local aliments in the upper GIT.
- Reduced fluctuations of drug concentration.

Delivery of drugs with narrow absorption window in small intestine region.

DISADVANTAGES:

- Retention in stomach is not desirable for drugs that cause gastric lesions/irritations. e.g. NSAIDS.
- Drugs degraded in the acidic environment of stomach .e.g. Insulin.
- Drugs undergo significant first-pass metabolism. e.g. Nifedipine
- Drugs have limited acid solubility. e.g. Phenytion.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- These systems do not offer significant over the conventional dosage forms for drugs, which are absorbed throughout GIT.

FACTORS AFFECTING GRDDS:

The important factors controlling the gastric retention time are as follows;

1. Density of dosage form
2. Shape and size of dosage form
3. Nature of food taken
4. Effect of gender, posture and age

1. DENSITY OF DOSAGE FORM:

The density of dosage form has great influence in case of gastric retentive dosage forms as it determines the location of the dosage form and its therapeutics effect. Formulation with a density higher than gastric juice sinks and that with a lesser density floats on the gastric fluid. A density of <1.0 g/cm^3 is required to exhibit floating property of the formulation.

2. SHAPE AND SIZE OF DOSAGE FORM:

The size and shape of dosage form has important influence on retention time. The retention time for larger dosage form is greater than smaller ones because larger size will not allow it pass quickly through the pyloric antrum into intestine. Generally a diameter range of 7.5 -9.9 mm is preferred than other forms. Ring and tetrahedron shaped formulations have better residence time than other shapes.

3. NATURE OF FOOD TAKEN:

Food intake, the nature of the food, caloric content and frequency of feeding have a profound effect on the gastric retention dosage forms. The presence and absence of food in the stomach influences the GRT of the dosage forms. Usually, the presence of food increases drug absorption by allowing it to stay at the absorption site for longer time.

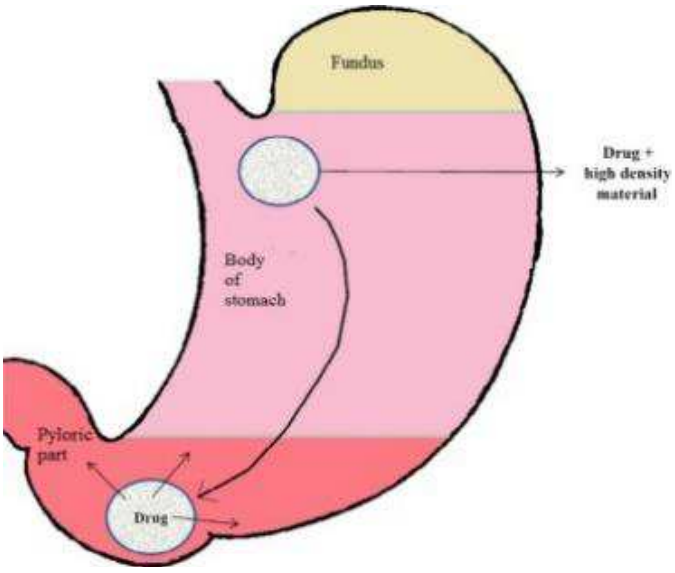
4. EFFECT OF GENDER,POSTURE AND AGE:

Generally females have slower gastric emptying rate than males. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying s slowed down.

APPROACHES FOR GRDDS:

HIGH DENSITY SYSTEM:

This approach involves formulation of dosage forms with density that must exceed density of normal stomach content (1.004g/ml). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert material such as iron powder, titanium dioxide, barium sulphate. The resultant pellets can be coated with diffusion controlled membrane.

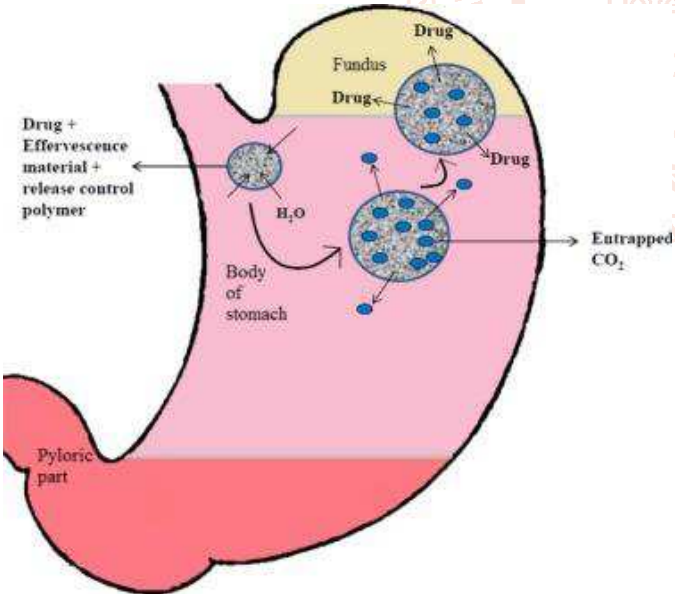


LOW DENSITY (FLOATING) SYSTEM:

By virtue of their low densities, FDDS remain afloat above the gastric contents for prolonged periods of time and provide continuous release of the drug. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT. Their dominance over the other types of GRRDS is also evident from the large number of floating dosage forms being commercialized and marketed world-wide.

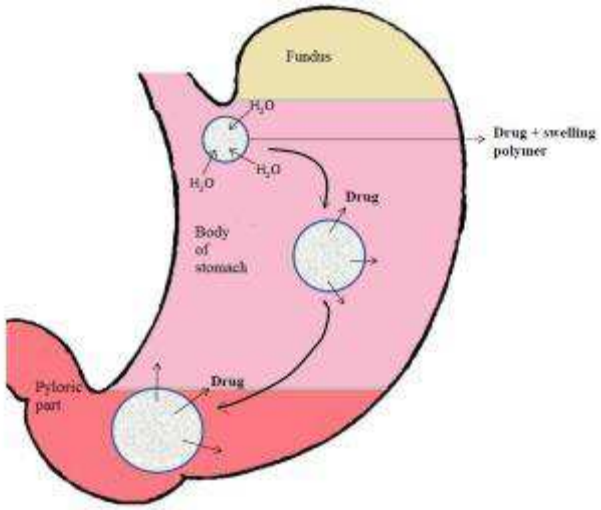
CLASSIFICATION OF FLOATING SYSTEM:

- Effervescent system
- Non effervescent system



SWELLING SYSTEM:

These are the dosage forms, which after swallowing swells to such an extent that their exit from the pylorus is prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. These systems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter. The formulations are designed for gastric retention and controlled delivery of drugs in the gastric cavity, such formulations remain in the gastric cavities for several hours even in the fed state. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release. On coming in contact with gastric fluid the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical chemical cross links in the hydrophilic polymer network. These cross links prevents the dissolution of the polymer and hence maintain the physical integrity of the dosage form. An optimum cross-linking, which maintains a balance between the swelling and the dissolution, should be maintained. Agyilirah developed a polymeric coating system that formed an outer membrane on the conventional tablets. In the dissolution media the membrane detached from the core and sweeled to form a balloon that kept the unit floating. the size of the units increased by three to six folds, thus the floating ability as well as the increased dimension offered the system gastro retentive property.



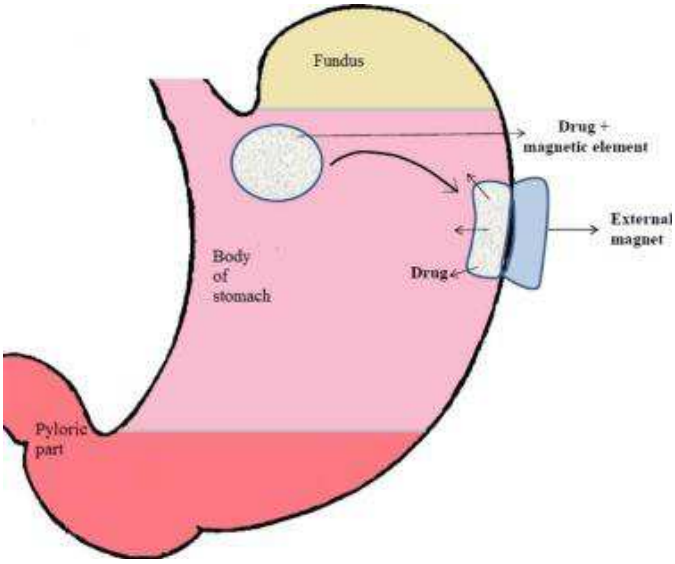
SUPERPOROUS HYDROGELS:

Superporous hydrogels are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states during which the premature evacuation of the dosage form may occur. Superporous hydrogel have a pore size >100µm which swell to equilibrium size within a minutes, due to rapid intake of waterby capillary wetting through inter connected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure by gastric contraction. This is achieved by co- formulation of a hydrophilic particulate material.

MAGNETIC SYSTEM:

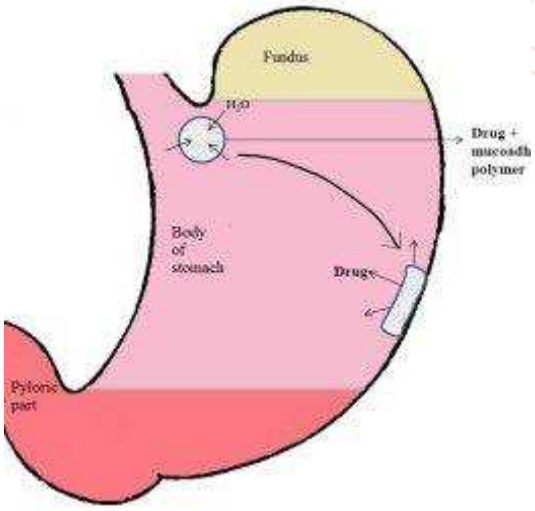
This system is based on the simple idea that the dosage form contains a small internal magnet, and a

magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time.



MUCOADHESIVE/BIOADHESIVE SYSTEM:

Mucoadhesive drug delivery system contain,a mucoadhesive polymers that adhere to the gastric mucosal surface and prolong its gastric retention in the GIT.The capability to adhere to the mucus gel layer makes mucoadhesive polymers very useful excipients in the GRDDS.These polymers can be natural such as sodium alginate, gelatin, guar gum etc.,semisynthetic polymers such as HPMC,carbopol,sodium carboxy methyl cellulose. The adhesion of polymer with mucous membrane may be mediated by hydration, bonding, or receptor mediated.



APPLICATIONS OF GRDDS:

- Enhanced bioavailability
- Sustained drug delivery
- Site of specific drug delivery
- Absorption enhancement
- Minimized adverse activity at the colon
- Reduced fluctuation of drug concentration

REVIEW OF LITERATURE:

Hemal Thakorbhai Tandel et al., 2017 they reported a comprehensive information related to mucoadhesion and mucoadhesive drug delivery systems. It has highlighted all the aspects of mucoadhesive drug delivery systems which will be helpful for researches and academics. These include detailed information about mucosa- the anatomy and physiology, the mechanisms and theories related to mucoadhesion, evaluation parameters of mucoadhesive dosage forms, mucoadhesive polymers and novel approaches related to that drug delivery system. The potential merits and demerits of that drug delivery as well as that of the polymers are also discussed.

Sandesh Asati et al.,2019 have formulated the highlighted fact of bioadhesive that readily accessible sites are utilized with the eye, oral cavity and vagina being targeted. The GI tract and the nasal cavity have also been extensively examined as a site for bioadhesive drug delivery. The mucoadhesion formulation attaches with the mucus membrane. Mucoadhesion is a useful strategy for drug delivery systems, such as tablets, patches, gels, liposomes, micro/nanoparticles, nanosuspensions, microemulsions and colloidal dispersions. The mucoadhesion bypasses the first pass metabolism and used for localized delivery of biomolecules such as peptides, proteins and oligonucleotides. These drug delivery system engages much attention due to their benefits such as prolong retention time, fast uptake and increased bioavailability of active substance. Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass metabolism. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. These aims to provide an overview of the various aspects of mucoadhesion, theories of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, mucoadhesive polymers and herbal drugs.

Devkant Sharma et al., 2014 Oral delivery of drugs is by far the most preferable route of drug delivery. These route has high patient acceptability, primarily due to ease of administration. Effective oral drug delivery depend upon the factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form, and site of absorption of drug.. Henceforth a wide spectrum of dosage form have been developed for the drugs which have narrow absorption window,

unstable at intestinal pH, soluble in acidic pH and have site of action specific to stomach. The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. These includes floating system, swelling and expanding system, bio/mucoadhesive system, high density system and other delayed gastric emptying devices. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits, demerits and applications of gastro retentive drug delivery systems.

Krishan kumar et al.,2013 have focused on the investigations of the interfacial phenomena of mucoadhesion with the mucus. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for an extended period of time by the help of interfacial forces. A number of polymers have shown characteristics of bioadhesion and have been used in the formulation of various conventional and novel drug delivery systems. Studies demonstrated that these carriers not only increase the local therapeutic activity, but also increase the systemic availability of the drugs by increasing the residence time at the site of application. The current review is an attempt to throw some light on the basics of the mucoadhesion: the mechanism of bioadhesion and the polymers that are used in the design of the bioadhesive delivery system with their properties that affect the bioadhesion.

MUCOADHESIVE DRUG DELIVERY SYSTEM:

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface & increase the residence time of dosage form at the site of absorption.

Mucoadhesive drug delivery system is a part of controlled delivery system.

INTRODUCTION

Since the early 1980, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology.

Combine mucoadhesive with enzyme inhibitory & penetration enhancer properties & improve the patient compliance.

It has been developed for buccal, nasal, rectal, vaginal routes for both synthetic and local effects.

Hydrophilic high molecular weight such as peptides that cannot be administered & poor absorption, then MDDS is the best choice.

MUCO	+	ADHESIVE
-inner layers called mucosa -inner epithelial cell lining -covered with viscoelastic fluid -secreated by goblet cells -composed of water and mucin -other components include proteins, lipids and mucopolysaccharides, electrolytes -main role is protective and lubricates.		-tendency substances to remain adhere to surface -if the substances adhere to biological mucosal layers is called mucoadhesion

MUCUS:

Mucoadhesive inner layers is called mucosa inner epithelial cell lining is covered with viscoelastic fluid.

Thickness varies from 40µm to 300 µm.

COMPOSITION OF MUCUS:

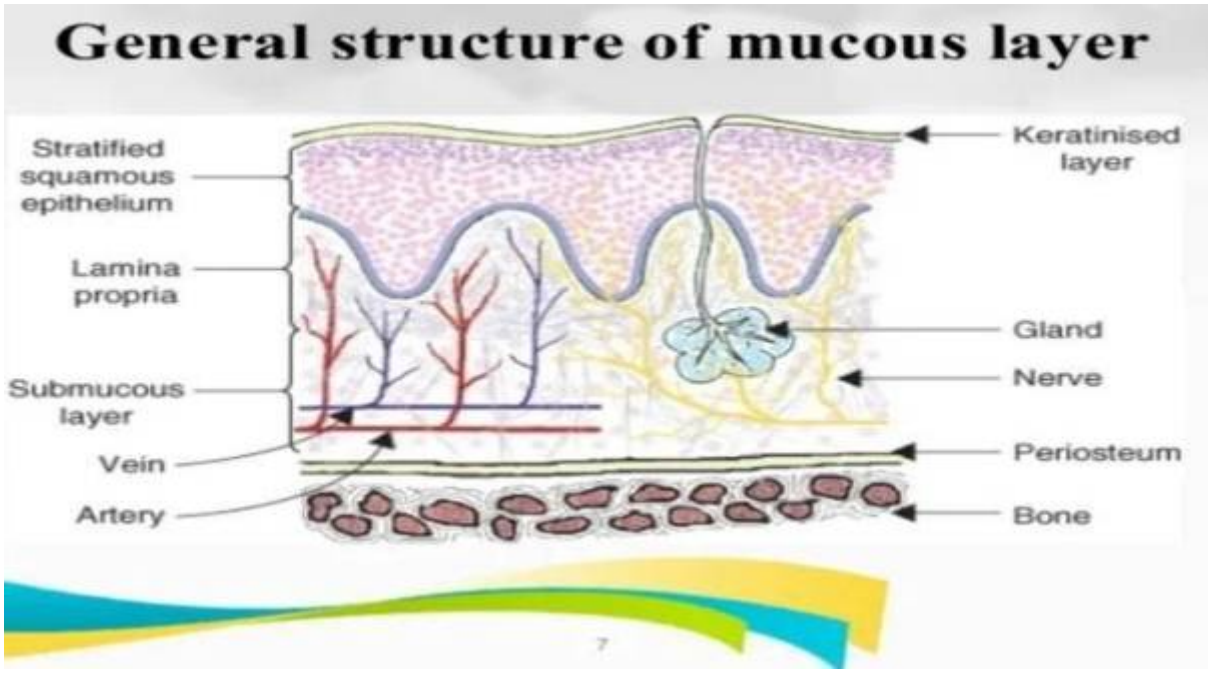
Water ……95%

Glycoproteins and lipids ……...0.5-5%

Mineral salts ……..1%

Free proteins ……..0.5-1%

GENERAL STRUCTURE OF MUCOUS LAYER



FUNCTION OF MUCUS

- **PROTECTIVE:** particularly from its hydrophobicity.
- **BARRIER:** in tissue absorption of the drugs and influence the bioavailaibility.
- **ADHESION:** mucus has strong cohesion properties.
- **LUBRICATION:** keep mucosal membrane moist.

MECHANISM OF MUCOADHESION:

The mechanism responsible in the formation of mucoadhesive bond.

Step-1: Wetting and swelling of the polymer (contact stage).

Step-2: Interpenetration between the polymer chains and the mucosal membranes.

Step-3: Formation of bonds between the entangled chains (both known as *consolidation stage*)

STEP-1

- Wetting and swelling step occurs when polymer spreads over the surface of mucosal membrane to develop intimate contact.
- Swelling of polymer occur because the components of polymer have an affinity for water.

STEP-2

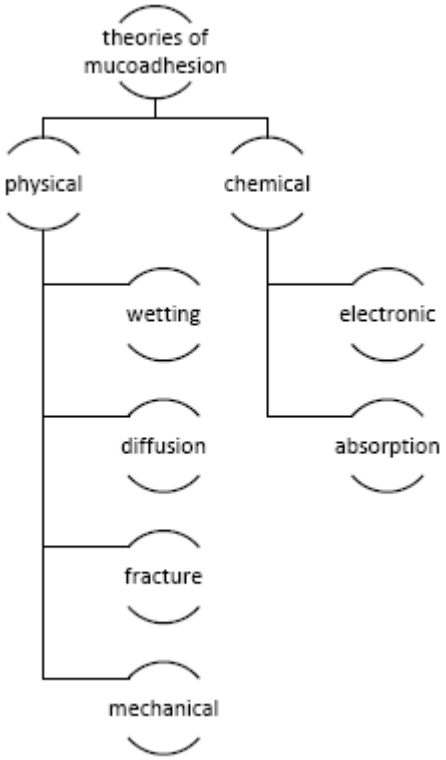
- In this step the mucoadhesive polymer chain and the mucosal polymer chains intermingle and entangles to form adhesive bonds.
- Strength of bonds depends upon the degree of penetration of two polymer groups.

STEP-3

- This step involves formation of weak chemical bonds between the entangled polymer chains.
- Bonds includes primary bonds such as covalent bonds and secondary interactions such as vanderwalls and hydrogen bonds.

THEORIES OF MUCOADHESION:

There are six traditional theories which have resulted from studies on the performance of variety of materials and polymer- polymer adherence. The classification of these theories are shown below. The contact angle and time of contact plays a significant role in mucoadhesion.



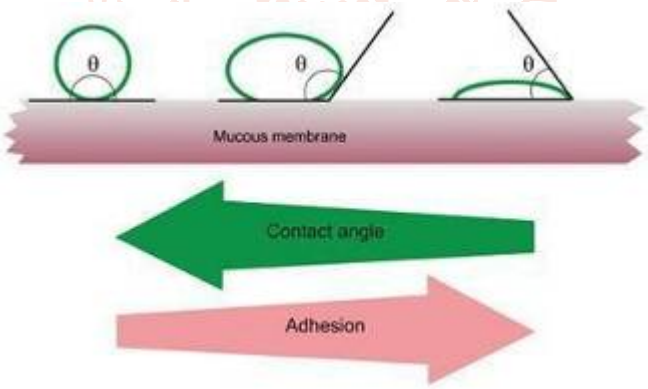
Wetting theory:

The affinity between the liquid systems and the mucus membrane is obtained by ascertaining the contact angle. As a basic concept, as the contact angle decreases, the affinity increases. The contact angle must be near to zero to provide sufficient spread ability. It is an illustrative diagram showing effect of contact angle between the dosage form and mucous membrane.

The spread ability coefficient, SAB, is measured from the difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in equation: SAB=γB-γA-γAB

Higher the individual surface energy of mucus and device in relation to the interfacial energy, more is the work of adhesion, WA.

WA= γA + γB – γAB

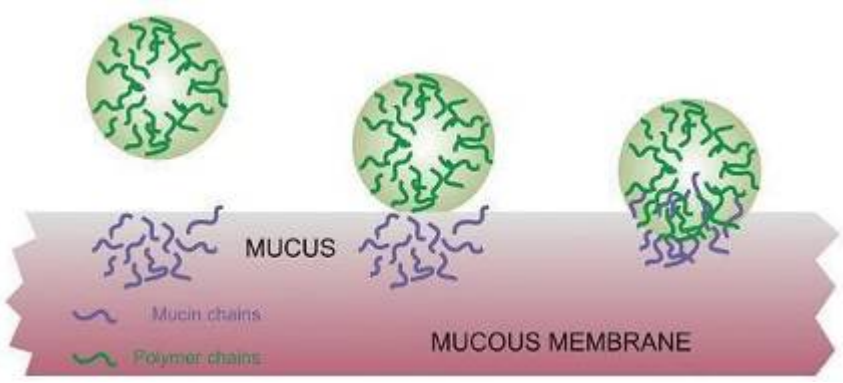


Diffusion theory

The diffusion theory explains the phenomenon of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains. As the bond strength enhances, the degree of the penetration increases. The secondary interactions due to inter-diffusion can be seen in Fig. Diffusion coefficient, polymer chain flexibility, nature of mucoadhesive chains, mobility and contact time of polymer chains are the factors on which the degree of penetration depends. The depth of interpenetration required to produce a firm bio adhesive bond lies in the range 0.2–0.5 μm. This depth of interpenetration of polymer and mucin chains can be found out by the following equation: The interpenetration depth, I= (tDb)1/2

Where t = contact time and Db = diffusion coefficient of the mucoadhesive material in the mucus.

For diffusion to ensue, it is crucial that the systems involved have good mutual solubility, that is, both the bio adhesive and the mucus should have identical chemical structures.

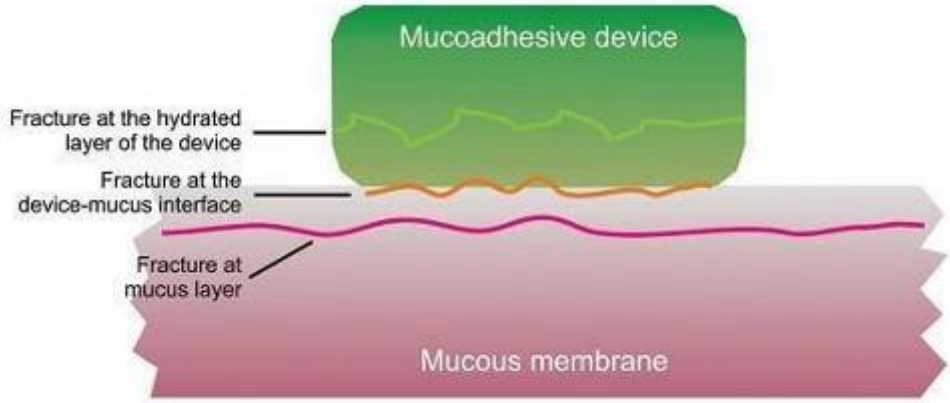


Fracture theory

This theory examines the force needed to dissociate two surfaces after adhesion is established. The work of fracture has been found to rise when the polymer network fibres are longer or if the degree of cross-linking within such a system is decreased. This concept aids in the measurement of fracture strength (σ) after the separation of two surfaces via its relationship to the Young's modulus of elasticity (E), the fracture energy (ε) and the critical crack length (L) through the following equation: $\sigma=(E*\varepsilon/L)1/2$

The force, Sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A0, involved in the adhesive interaction:
$Sm= Fm/Ao$

The regions of mucoadhesive bond rupture can be seen in figure.



Mechanical theory

Mechanical theory proposes that the adhesion is because of the filling of the imperfections of a rough surface by a mucoadhesive liquid. The irregularities enhances the interfacial area available for interactions thus enhancing energy dissipation. The mechanisms ruling mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied. Intrinsic factors of the polymer are related to its molecular weight, concentration and chain flexibility. For linear polymers, mucoadhesion is directly proportional to molecular weight, but the same does not hold for non-linear polymers.

Electronic theory

The electronic theory relies on the hypothesis that the bioadhesive material and the target mucous membrane have diverse attributes of electronic surface. Based on this, when the surfaces come in contact with each other, there is an electron transfer to balance the Fermi levels, arising due to the formation of electrical double layer at the interface of the bioadhesive and the mucous membrane. The bioadhesive force is assumed to be present due to the attractive forces over this double layer.

Adsorption theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak Vander Waals forces and hydrogen bond formation. Various mucoadhesive interactions are: Ionic bonding, Covalent bonding, Hydrogen bonding, Vander Waals bonding, Hydrophobic bonding. For example, hydrogen bonds are the dominant interfacial forces in polymers having carboxyl groups. These forces are very important in the adhesive interaction phenomena because they might be individually weak, a great number of interactions can result in a strong global adhesion.

FACTORS AFFECTING MUCOADHESION:

I. POLYMER RELATED FACTORS:

- Molecular weight
- Concentration of active polymer
- Flexibility of polymer chain
- Spatial conformation
- Swelling and cross linking
- Hydrophilicity

II. ENVIRONMENT RELATED FACTORS:

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

III. PHYSIOLOGICAL FACTORS:

- Mucin turn over
- Disease state
- Renewal rate of mucosal cells

Molecular weight:

The interpenetration of polymer molecules is favoured by low molecular-weight polymers, whereas entanglements are favored at higher molecular weights. The optimum molecular for the maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer upto 100,000.

Concentration of active polymer:

Optimum concentration of active polymer is required. In remarkably concentrated system, beyond a certain optimum level, the adhesive strength declines drastically because the coiled molecules become separated from the medium so the length of chain available for permeation become limited. When the concentration of polymer is very less, the number of penetrating polymer chains per unit volume of the mucous is small and the interaction between polymers and mucous becomes erratic.

Flexibility of polymer chain:

As water soluble polymer becomes cross linked, the individual polymer chain mobility drops and thus the effective chain length that can penetrate into the mucus layer reduces which decreases the mucoadhesive strength. Flexibility depends on the viscosity and diffusion coefficient. Higher polymer flexibility causes greater diffusion into mucus network.

Spatial conformation:

The spatial conformation of the polymer (the shape the molecule preferentially occupies in a certain medium) is also extremely important. An example of the importance of spatial conformation to bioadhesion can be seen when comparing the molecular weight of dextran(19,500,000) to that of polyethylene glycol (PEG) (200,000).Although the molecular weight of dextran is much higher, both polymers have a similar adhesive strength. This phenomenon is due to the helical conformation of dextran that may shield many adhesively active groups, unlike PEG, which have a linear conformation.

Swelling and cross linking:

Cross-linking density is inversely proportional to the degree of swelling. The lower the cross-link density, the higher the flexibility and hydration rate, the larger the surface area of the polymer, the better the mucoadhesion .To achieve a high degree of swelling, a lightly cross-linked polymer is favoured. The mucoadhesion of cross-linked polymers can be enhanced by the inclusion in the formulation of adhesion promoters, such as free polymer chains and polymers grafted onto the performed network.

Hydrophilicity:

A hydrophilic molecule is one that has the tendency to interect or be dissolved by water and other polar substances. Bioadhesive polymers possess numerous hydrophilic functional groups. These hydrophilic functional groups (i.e., hydroxyl and carboxyl groups) allow hydrogen bonding with the substrate and swelling in aqueous media.

pH of the polymer:
pH has an effect on the surface charge of both mucus and polymers. The charge density of mucus will differ depending on pH, because of variation in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which might influence adhesion.

Applied strength:
The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. Polymers become mucoadhesive even though they do not have attractive interactions with mucin if high pressure is applied for the sufficiently long period of time.

Initial contact time:
Bioadhesive strength is directly proportional to the initial contact time. It also determines the extent of swelling and interpenetration of polymers. It is not controllable for gastric systems.

Moistening:
Moistening allows the mucoadhesive polymer to spread over the surface and create a macromolecular network of sufficient size for the penetration of polymer and mucin molecules to increase the mobility of polymer chains.

Presence of metal ions:
Combining with charged groups of polymer and/or mucous can reduce the number of interaction sites and the strength of mucoadhesive bonding

Mucin turnover:
High mucin turnover which occurs many times is not beneficial Because

A. The high mucin turnover limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though the polymer has a good bioadhesive property.
B. High mucin turn over may produce soluble mucin molecule, thus molecule interact with the polymer, before they interact with mucin layer. Hence there will not be sufficient mucoadhesion.

Disease state:
The physicochemical property of mucus may alter during some diseased state, such as common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc.

Renewal rate of mucosal cells:
Renewal rate of mucosal cells differs considerably on the basis of types of mucosa.

It limits the endurance of bioadhesive systems on mucosalsurfaces.

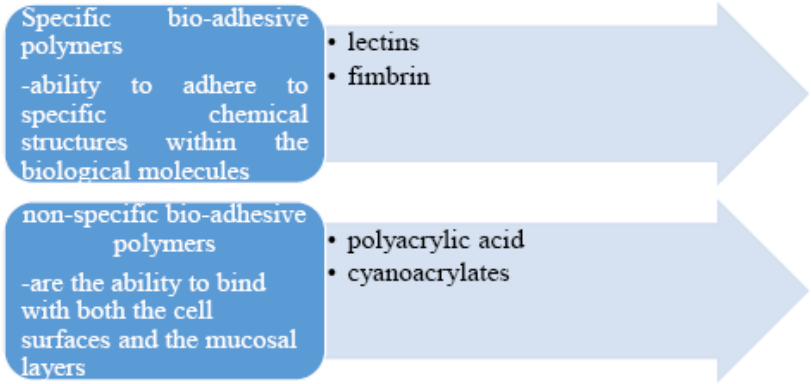
MUCOADHESIVE POLYMERS:
Mucoadhesive polymers are either water soluble or insoluble, which are swellable networks, connected by cross linking agents.

POLYMER CLASSIFICATION:

A. ACCORDING TO THEIR SOURCE

natural and semisynthetic	synthetic
• chitosan • agarose • gelatin • pectin • CMC,HPMC	• Carbopol • PVA,PVP • Metha acrylic acid • polycarbophil

B. BASED ON SPECIFICITY



chitosan:

Chitosan is a biodegradable, nontoxic polymer obtained by deacetylation of the N-acetyl glucosamine units of chitin, generally by hydrolysis under alkali conditions at high temperature. It is a biocompatible, pH-dependent cationic polymer, which is soluble in water up to pH 6.2. Due to its positive charge it shows ionicinteraction with the negative charge of the sialic acid residues of mucus thus possessing very good bioadhesive properties.

Derivatives of chitosan with improved mucoadhesion

- Thiolated polymers
- Quaternized chitosan
- Fatty acid derivatives
- Copolymers of chitosan.

Sodium carboxymethyl cellulose (Na CMC)

It is a low-cost, commercial, soluble and polyanionic polysaccharide derivative of cellulose. High and medium viscosity solutions of Na CMC possess thixotropic behavior. The bioadhesive properties of the Na CMC are remarkable and it has been used in the development of various bioadhesive formulations such as matrix tablets, microspheres, buccal patches and nanoparticles.

Mucoadhesive buccal patch containing metoprolol succinate was prepared by using Na CMC showed drug release of 81.9% for 6 hrs.

Carbopol

Carbopol or carbomer are high molecular weight polymers of acrylic acid cross-linked with either allyl sucrose or allyl ethers of pentaerythritol. These contain 56% and 68% of carboxylic acid groups calculated on the dry bases. These are used as suspending agent or viscosity increasing agent, dry and wet binder, as well as rate controlling agent in tablets, enzyme inhibitor of intestinal protease in peptide containing dosage form, etc. Carbomer is a pH-dependent polymer which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties in comparison with other polymers (e.g., cellulose derivatives and polyvinyl alcohol). Different mucoadhesive formulations containing carbopol have been developed and it was found that these demonstrated excellent mucoadhesive property and release the drug in controlled manner for a longer period of time.

Hydroxypropyl methyl cellulose

HPMC, a semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, emulsifier, suspending agent, thickening agent and controlled-delivery component in oral medicaments, is found in a variety of commercial products. Also known as hypermellose, it is a thermosenstive polymer whose aqueous solution sets into gel when heated up to critical temperature. It also shows good bioadhesive property due to its ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer. Various films, tablets and gels formulations have been formulated using HPMC as mucoadhesive polymer. The formulation shows very good mucoadhesion and provided sustained release.

Gelatin

Gelatin is a natural water soluble protein which is normally obtained by denaturation of collagen. It has good biodegradability, biocompatibility, and low antigenicity.]It is used as support material for gene delivery, cell culture, and more novel is use in tissue engineering. Gelatin-based systems can give zero order release of biologically active agents such as drugs, peptides and proteins. It is possible to entrap bioactive compounds into pegylated liposome-gelatin gel.

Lectins

Lectins are natural proteins useful for bio-recognition of cells and proteins. They are structurally varying proteins and glycoprotein which reversibly bind to specific residues of carbohydrates. After binding to the cell, these might stay on the surface of cell or may be face endocytosis. Thus provide site specific and controlled drug release. The disadvantage is that they are immunogenic.

CHARACTERISTICS OF MUCOADHESIVE POLYMERS:

An ideal muco adhesive polymer has the following characteristics,

1. It must be loaded substantially by the active compound.
2. It must swell in the aqueous biological environment of the site of absorption.
3. It must interact with mucus or its components for adequate adhesion.
4. It must allow controlled release of the active compound when swelled.
5. It must be excreted unaltered or biologically degraded to inactive, nontoxic oligomers.
6. It must possess sufficient quantities of hydrogen bonding chemical groups.
7. It must possess high molecular weight.
8. It must possess high chain flexibility.
9. It must have the surface tension that may induce spreading into mucous layer.

EFFECT OF POLYMER PROPERTIES ON MUCOADHESION

Properties	Effects
Functional group	COOH, OH, NH2 , SO4 H groups favor mucoadhesion
Molecular weight	More is molecular weight (above 100,000) more is the bioadhesion
Flexibility	Higher is the flexibility of the polymer more is the diff usion and hence more mucoadhesion
Chain length	With decrease in chain length interpenetration increases
Degree of hydration	Excessive hydration leads to decreased mucoadhesion
Degree of cross-linking	Increased mucoadhesion cross-linking decreased
Polymer concentration	For semisolid: increase in concentration decrease mucoadhesion. For solid dosage form: increase in concentration increase mucoadhesion
Charge	Nonionic polymers posses less mucoadhesion than ionic and cationic polymers exhibits more mucoadhesion than anionic

BIOADHESIVE PROPERTY OF DIFFERENT POLYMER

polymer	Bioadhesive property
CMC sodium	Excellent
Carbopol	Excellent
Polycarbophil	Excellent
Tragacanth	Excellent
Sodium alginate	Excellent
HPMC	Excellent
Gum karaya	Very good
Gelatin	Very good
Guar gum	Very good
Pectin	Good
Acacia	Good
Chitosan	Good
Hydroxypropyl cellulose	Good

DELIVERY SYSTEM:

1. Oral mucoadhesive delivery systems
2. Nasal mucoadhesive delivery systems
3. Ocular mucoadhesive delivery systems
4. Vaginal mucoadhesive delivery systems
5. Rectal mucoadhesive delivery systems
6. Cervical mucoadhesive delivery systems
7. Gastrointestinal mucoadhesive delivery system

Oral mucoadhesive delivery system:

The most commonly used routes are the buccal and sublingual. The nonkeratinized epithelium in the oral cavity, that is, the soft palate, the mouth floor, the ventral side of the tongue, and the buccal mucosa offer a relatively permeable barrier for drug transport .Oral mucosae are comprised of multiple layers of cells, which show various patterns of differentiation. Blood supply to the oral cavity tissue is provided by the external carotid artery. This artery branches to the maxillary lingual and facial artery. The oral mucosa do not contain mucus secreting goblet cells, however, mucins are found in human saliva. Saliva consists of 99% water and the mucins dissolved within it form a gel of 20–100 μm thickness. Paracellular transport is generally followed by hydrophilic compounds and large or highly polar molecules whereas lipophilic drugs follow transcellular transport through the lipid bilayer. Advantages of the oral route over others include the bypassing of the hepatic first pass metabolism, improvement in drug bioavailability, improved patient compliance, excellent accessibility, unidirectional drug flux, and improved barrier permeability that intact skin. The application of mucoadhesive delivery systems to the oral cavity allows both local and systemic delivery. Local therapy is used to treat conditions such as aphthous ulceration gingivitis, periodontal disease, and xerostoma. Common dosage forms include adhesive gels, tablets, films, patches, ointments, mouthwashes, and pastes. The most frequently used dosage form for buccal drug delivery up to now has been adhesive tablets. Tablets can be applied to many regions of the oral cavity, such as cheeks, lips, gums, and the palate. Such tablets allow the drinking eating and speaking without any major discomfort. Advantages of this novel delivery system include rapid absorption, a user-friendly administration technique, precise dosing control, and bolus delivery.

Nasal mucoadhesive delivery system

The human nasal mucosa is a highly dense vasculature network and is a relatively permeable membrane structure. The area of the nasal mucosa is normally approximately 150 cm2. The nasal epithelium exhibits high permeability as only two cell layers separate the nasal lumen from the dense blood vessel network in the lamina propria. The main lining of the nasal cavity is the respiratory epithelium. It allows the clearance of mucus by the mucociliary system and is composed of ciliated and non-ciliated columnar cells, goblet cells, and basal cells. The respiratory epithelium is covered by a mucus layer which can be divided into the periciliary layer and a gel-like upper layer. The periciliary layer is less viscous than the gel-like layer. Mucociliary clearance allows the removal of foreign substances and particles from the nasal cavity, therefore preventing them from reaching the upper airways. This process is facilitated by the cilia that propel the mucous layer towards the nasopharynx. Advantages of the nasal route of delivery include rapid uptake and the avoidance of first pass hepatic metabolism. Disadvantages include local toxicity and irritation, mucociliary clearance of 5 minutes, the presence of proteolytic enzymes and the possible influence of pathological conditions (cold and allergies). The application of bioadhesive delivery systems such as liquids, semisolids, and solids may significantly increase retention time.

Ocular Mucoadhesive Delivery Systems

The ocular route is mainly used for local treatment of eye pathologies. Conventional delivery methods to the eye are generally unsuccessful due to the inherent protective mechanisms of the eye (tear production, tear flow, and blinking), the limited area of absorption and the lipophilic character of the corneal epithelium. The precorneal tear film is the first structure encountered by an ocular dosage form. It consists of three distinct layers. The outer layer is of oily and lipid nature and it prevents tear evaporation. The middle layer contains an aqueous salt solution and the inner layer is a mucus layer that is secreted by the conjunctiva goblet cells and lacrymal gland. This layer maintains moisture in the corneal and conjunctival epithelia. The ocular membranes comprise the cornea, which is non-vascularized and the conjunctiva, which is vascularized. The major pathway for ocular drug penetration is considered to be the corneal epithelium. It consists of five or six layers of non-keratinized squamous cells. Solutions and suspensions are swiftly washed from the cornea and ointments can alter the tear refractive index and blur the vision. Therefore, prolonging the residence time by mucoadhesion may provide the required conditions of successful ocular delivery.

Vaginal mucoadhesive delivery systems:

The vagina is a fibro vascular tube connecting the uterus to the outer surface of the body. The vaginal epithelium consists of a stratified epithelium and lamina propia. The vagina offers a substantial area for drug absorption because numerous folds in the epithelium increase in total surface area. A rich vascular network surrounds the vagina, whereas the vaginal epithelium is covered by a film of moisture consisting mainly of cervical mucus and fluid secreted from the vaginal wall. The dosage forms that are usually used for the vaginal route are solutions, gels, suspensions, suppositories, creams, and tablets. They all have a short residence time [95–97]. Bioadhesives

may control drug release and extend the residence time of such formulations. They may contain drug or act in conjunction with moisturizing agents.

Rectal Mucoadhesive Delivery Systems

The rectum is a part of the colon. It is 10 cm in length and has a surface area of 300 cm2. The main function of the rectum is the removal of water. The rectum has a relatively small surface area for drug absorption. The absorption of drugs through the rectum is generally achieved by a simple diffusion process through the lipid membrane. Advantages of the rectal route of delivery include the avoidance of first pass metabolism. The use of bioadhesive delivery systems in the rectum can also decrease the drug migration distance.

Cervical and Vulval Delivery Systems

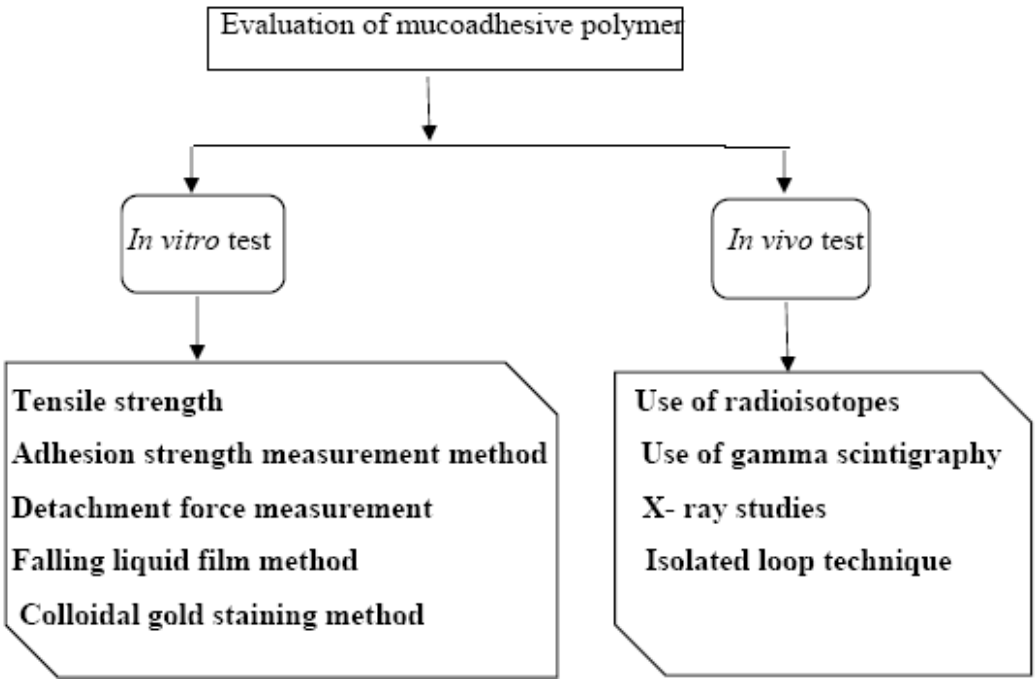
A number of recent studies have been carried out to investigate application of mucoadhesive delivery systems to the cervix and vulva due to the increasing prevalence of human papilloma virus associated neopasias. A novel bioadhesive cervical patch containing 5-fluorouracil for the treatment of cervical intraepithelial neoplasia (CIN) was developed by Woolfson *et al*. The patch was a drug-loaded bioadhesive patch prepared from a gel containing 2% w/w plasticized with 1% w/w glycerine. The casting solvent used was ethanol:water 30:70. The film was bonded directly to a backing layer formed from thermally cured poly(vinyl chloride) emulsion. Substantial drug release through human cervical tissue samples was observed over approximately 20 hours.

Gastrointestinal Mucoadhesive Delivery Systems

The oral route is undoubtedly the most favored route of administration. It represents the most convenient route of drug administration, being characterized by high patient compliance. The mucosal epithelium along the gastrointestinal tract varies. In the stomach, the surface epithelium consists of a single layer of columnar cells whose apical membrane is covered by a conspicuous glycocalyx. A thick layer of mucus covers the surface to protect against aggressive luminal content. The small intestine in characterized by an enormous surface area available for the absorption of nutrients and drugs. The intestinal epithelium consists of a single layer of three types of columnar cells: enterocytes, goblet cells, and enteroendocrine cells. The large intestine (colon) has the same cell populations as the small intestine, and its main function is the absorption of water and electrolytes. The role of mucus in the intestine is to facilitate the passage of food along the intestinal tract and to protect the gut from bacterial infections [106]. Problems associated with the oral route include hepatic first pass metabolism, degradation of drug during absorption, mucus covering GI epithelia, and high turnover of mucus covering GI epithelia and the high turnover of mucus. Recently, the gastrointestinal tract (GIT) delivery has emerged as a very important route of administration. Bioadhesive retentive system involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the GIT. The use of bioadhesive systems would increase GI transit time and increase bioavailability.

EVALUATION:

Mucoadhesive drug delivery systems can be evaluated by testing their adhesion strength. Various *in vitro* and *in vivo* tests are available to determine the adhesion strength of the mucoadhesive polymers.



CONCLUSION:

Mucoadhesion have great pharmaceutical application and the phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. It is a growth area whose goal is the development of new devices and more intelligent polymers, as well as the creation of new methodologies. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. In the future, the choice of the polymer for oral mucosa with appropriate technology and delivery technique be utilized for the treatment of many diseases both mucosal and systemic and the catalogue of drugs which can be delivered via the mucosa could be greatly increased. The advancement in muco-buccal adhesive technology and sustained local drug release also have the potential for reducing the systemic side effects from ingested or injected therapies, where an oral mucosal disease is the target of therapy.

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