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Mucoadhesive: As Oral Controlled Gastroretentive Drug Delivery System

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ABSTRACT:

Mucoadhesion is a field of current interest in the design of drug delivery systems. Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects. In this paper main prominence on gastrointestinal dosage forms along with concepts, mechanism of mucoadhesion, factors affecting mucoadhesion, permeation enhancers and evaluation methods and also some review regarding research work already been carried. An overview of the last decade's discoveries on mucoadhesion and applications of mucoadhesive as drug carriers is given. Mucoadhesive drug delivery systems with its various advantages have a lot of potential in formulating dosage forms for various chronic diseases.

KEY WORDS: Mucoadhesion, buccal route, therapeutic performance, permeation enhancers.

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1. INTRODUCTION:

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic 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-lives 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 is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic 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 that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT)[1]. These drug delivery systems suffer from mainly two adversities: 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 absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose[2]. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment[3]. Also prolonged gastric retention time (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.

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[4], low density (floating) systems that causes buoyancy in gastric fluid[5, 6, 7], mucoadhesive systems that causes bioadhesion to stomach mucosa [8], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9, 10] superporous hydrogel systems, magnetic systems [11]etc.

1.1 Suitable Drug Candidates For Gastroretention:

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of theGIT:

- Narrow absorption window in GI tract,

e.g., riboflavin and levodopa

- Primarily absorbed from stomach and upper part of GI tract,

e.g., calcium supplements, chlordiazepoxide and cinnarazine

- Drugs that act locally in the stomach,

e.g., antacids and misoprostol

- Drugs that degrade in the colon,

e.g., ranitidine HCl and metronidazole

- Drugs that disturb normal colonic bacteria,

e.g., amoxicillin trihydrate

1.2 Factors Controlling Gastric Retention of Dosage Forms:

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

1.3 Approaches To Achieve Gastric Retention:

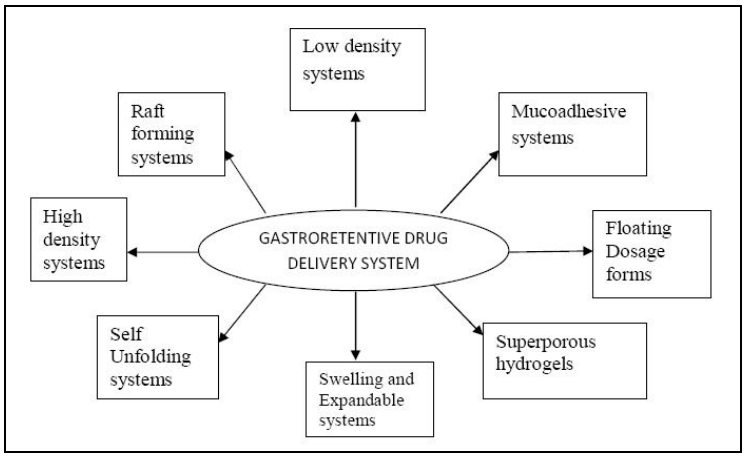

Fig.no.1. Approaches to achieve gastric retention

2. BIOADHESION/MUCOADHESION:

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces. Generally speaking, bioadhesion is a term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface.

The mucoadhesive drug delivery system may include the following [12]:

- Gastrointestinal delivery system.
- Sublingual delivery system.
- Vaginal delivery system.
- Nasal delivery system.

- Ocular delivery system.
- Rectal delivery system.
- Buccal delivery system.

2.1 Concepts:

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface.In biological systems, four types of bioadhesion could be distinguished

- Adhesion of a normal cell on another normal cell.
- Adhesion of a cell with a foreign substance.
- Adhesion of a normal cell to a pathological cell.
- 4. .Adhesion of an adhesive to a biological substance.

For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Bioadhesion can be modeled after a bacterial attachment to tissue surfaces, and mucoadhesion can be modeled after the adherance of mucus on epithelial tissue.

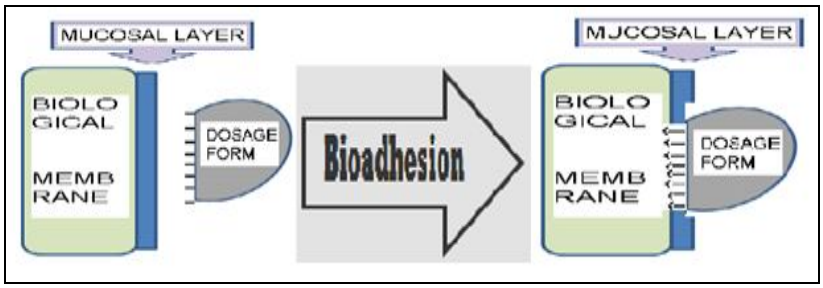

Fig.no.2. Concept of bioadhesion

2.2 Mechanism of Bioadhesion:

For Bioadhesion to occur, three stages are involved.

Stage-1: An intimate contact between a Bioadhesive and a membrane either from a good wetting of the Bioadhesive and a membrane or from the swelling of bioadhesive.

Stage-2: Penetration of the bio-adhesive into the service of the tissue takes place.

Stage-3: Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bounds can then settle.

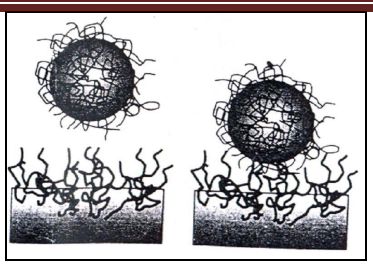

Fig.no.3. Interpenetration of Bioadhesive and mucous polymer chain

The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electro static interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

3. RATIONALE FOR USING BIOADHESIVE/MUCOADHESIVE SYSTEMS:

The GI tract is the most preferred and commonly used route for the delivery of drugs. Physiological properties of the GI tract which supported absorption are relative large volume of fluid, peristaltic movement of stomach and intestines, large mucosal area throughout the lumen and extensive blood flow through the mesenteric circulation. For oral drug delivery, the drug absorption is limited by the GI transit time of dosage forms. Since many drugs are absorbed only from upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption. Bioadhesion may be able to delay the gastric emptying time and intestinal transit of pharmaceutical dosage forms via interaction with either mucus lining or mucosa of the GI tract. The idea of using bioadhesive materials in the development of pharmaceutical formulations appeared in the early 1980s. The aim was to develop drug delivery systems those would increase the absorption of a drug, for both local and systemic effects, as a result of intimate and prolonged contact at the site of absorption.

Mucoadhesive drug delivery systems have three distinct advantages when compared to conventional dosage forms. Firstly, the mucoadhesive systems, which are readily localized in the region applied to, can improve and enhance the bioavailability of drugs, for example, a greater bioavailability of amoxicillin, clarithromycin, griseofulvin, calcitonin , insulin , testosterone was observed from mucoadhesive dosage systems. Secondly, these dosage forms can facilitate the intimate contact with underlying absorption surface resulting in a better absorption. Lastly, they can prolong residence time at the site of application to permit once or twice a day dosing.

4. PHARMACOKINETIC ASPECTS[13-18]

4.1. Absorption window-validation that the drug is within the category of narrows absorption window agents:

Currently various experimental techniques are available that permit us to verify the absorption properties of the tested molecule, to determine the mechanism of intestinal absorption and to elucidate the permeability at different regions of the GI tract. In general, appropriate candidates for CR-GRDD are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of the transport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non CR mode of administration.

4.2. Enhanced bioavailability:

Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgical means. On the other hand, the bioavailability of riboflavin and levodopa CR-GRDD is significantly enhanced in comparison to administration of non-GRDD CR polymeric formulations. It may be concluded that several different processes, related to absorption and transit of the drug in the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption. Therefore, in vivo studies are necessary to determine the release profile of the drug from the dosage form that will provide enhanced bioavailability.

4.3. Enhanced first pass biotransformation:

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

4.4. Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum:

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, CR-GRDD may elevate absorption compared to the immediate and CR dosage forms.

4.5. Reduced frequency of dosing:

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDD may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

4.6. Targeted therapy for local ailments in the upper GI tract:

The prolonged and sustained administration of the drug from the GRDD to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

5. PHARMACODYNAMIC ASPECTS[19]

5.1. Reduced fluctuations of drug concentration:

Continuous input of the drug following CR-GRDD administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

5.2. Improved selectivity in receptor activation:

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

5.3. Reduced counter-activity of the body:

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

5.4. Extended time over critical (effective) concentration:

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

5.5. Minimized adverse activity at the colon:

Retention of the drug in the GRDD at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDD formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to development of microorganism's resistance. In most cases, due complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CR-GRDD compared to the other dosage forms.

6. ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS[20]

- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates
- Drug is protected from degradation in the acidic environment in the GIT.
- Improved patient compliance

7. DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.

8. ORAL GASTROINTESTINAL BIOADHESIVE DOSAGE FORM APPLICATIONS:

Several dosage forms for oral use have been reported.

8.1 Tablets:

Multilayer tablet allows a variety of geometrical arrangement. Such systems that consist of acrylic polymers or cellulose provide immediate and high adhesion strength at a certain site for prolonged period of time.

8.2 Micro and/or Nanoparticles:

Despite the limited loading capacity of drug, bioadhesive micro-and /or nano-particles have been widely investigated for three major features:

1. Immobilization of particles on the mucosal surface by adhesion after modification of surface properties via bioadhesive polymers.
2. Very large specific surface between the dosage forms and the oral mucosa.
3. Sustained release of entrapped drug, leading to higher absorption.

8.3 Capsules

Capsules, usually gelatin capsules, containing a suspension or liquid, include bioadhesive polymers such polycarbophil or carbopol. Gelatin interacts with bioadhesive polymer during or following dissolution, and thus bioadhesiveness of the polymer is lost before the bioadhesive polymer has a chance to interact with the mucus layer.

9. THEORIES OF BIOADHESION/ MUCOADHESION:

The process of bioadhesion can be broadly classified into two categories, namely chemical (electronic and adsorption theories) and physical (wetting, diffusion and cohesive theory) methods .[21-22]

9.1. Wetting:

Concept of contact angle and reduction of surface interfacial energy to get maximum strength of mucoadhesion was studied by this theory. It determines thermodynamic work and contact angles of adhesion. It applies to liquid systems which present affinity to the surface in order to spread over it. It limited to concept of liquid. It postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. Highly hydrophilic polymer have low contact angle than mucosal surface, thus intimate contact due to high interfacial surface free energy and lower contact angle greater the incidence of affinity. It is advisable and recommend to keep contact angle should be close to zero or equal to get favorable condition for adequate spreadability.

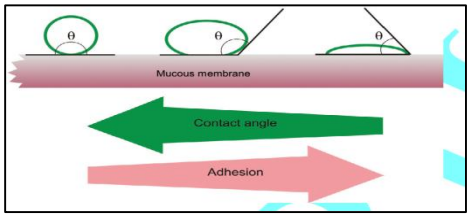

Fig.no.4. Influence of contact angle on mucoadhesion.

Above diagram showing influence of contact angle between device and mucous membrane on bioadhesion.

9.2. Diffusion theory:

It explains alignment of polymeric chains into mucin and in-depth of mucus turn, it exists for concentration gradient. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size . It is believed that the range of 0.2-0.5 m of interpenetration is required to produce an effective bioadhesive bond. Longer the polymer chains diffuse entangle to give favorable effects with surface mucin and critical chain length of at least 100.000 Da is compulsory to attain interpenetration[23] .The greater the structural similarity between bioadhesive and mucin, the better the mucoadhesive bond. Due to the Concentration gradient, the bioadhesive polymer chains penetrate at rates that are dependent on the diffusion coefficient of a macromolecule through a cross-linked network and the chemical potential gradient. The pharmaceutical scientists are engaged in bringing out design predictable, controlled delivery of bio active agents and ATR-FTIR analysis to distinguish effect of interpenetration miscibility of both system with one another [24] .The excipients incorporated to formulate have good mutual solubility. The rate of the drug release from matrix product depends on the initial drug concentration and relaxation of the polymer chains, which overall displays a sustained release characteristic. Properties like orientation of functional groups molecular weight, cross-linking density, chain mobility [25],temperature, charge polymer network pH, and status of tissue (hard or soft).

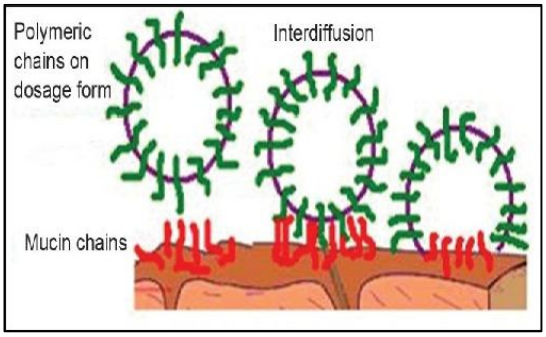

Fig.No.5. Secondary interaction between mucoadhesive device and of mucus.

9.3. Electrostatic theory:

Formation of electrical double layer at interface and serves of attractive forces which only responsible for maintain contact between two layers, transfer of elections between mucin and mucoadhesion interface promote formation of double layer [26] of electric charge. The bioadhesive force is believed to be due to attraction forces across this electrical double layer. The complete migration of electron exchange between mucoadhesive system and mucus helps to initiation of adhesion due to electron gradient atmosphere in both sides.

9.4. Mechanical theory:

The intensity of adhesion onto smooth and rough surface varied and interlocking of adhesive liquid between above said surfaces explains adhesion capacity and its concept. Roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process. The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion

9.5. Fracture:

It nothing but explains about determination of tensile strength. And as name itself explains about the force required for separation of two surfaces after subjecting adhesion. The sequence in event during fracture theory shown Figure 6. It analyses the force required to separate two surfaces after adhesion is established. The resistance to cause rupture is explained by ratio of maximal detachment of force and total surface area in adhesive interaction but not take role in diffusion and interpenetration of polymer chains. The complete orientation of mucin with glycoprotein network interaction is picturized in Figure 7. Over all it acts as tool to evaluate [27-28] and distinguish between rigid and semi-rigid bioadhesive material of its functional activity. Fracture theory of adhesion is related to separation of two surfaces after adhesion.

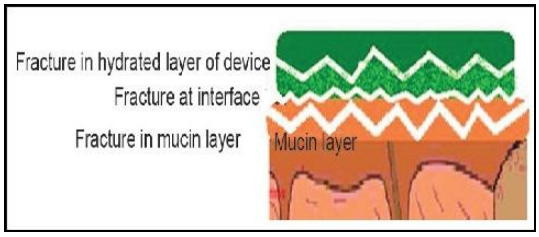

Fig.No.6. Fractures occurring for mucoadhesion.

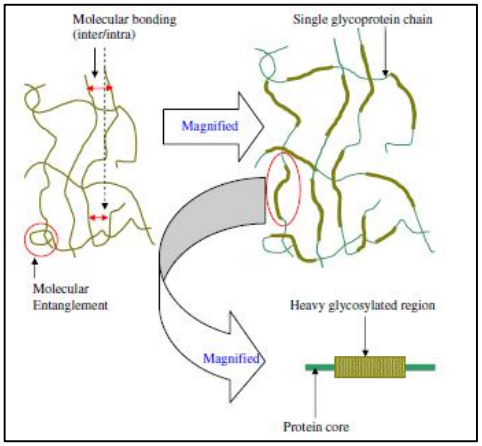

Fig.No.7. The composition and interaction of glycoprotein within mucosa.

9.6. Adsorption theory:

If Adhesion is particularly strong then it favors chemisorptions process imparts adherence to tissue because of importance of primary or secondary forces or bonds(hydrophobic and hydrogen bonding and vander Waals forces) surface force responsible to results in chemical bonding which depends on orientation of chemical structure at interface maintains adherence between two surfaces. When polymers containing carboxyl groups it denotes that supports towards dominance in hydrogen bonds only. The examples of technique used to study the adsorption between mucoadhesive polymers and mucin in mucus are perfusion wash technique, everted sac technique and the techniques that measure the mucin remained after interaction.

10. MUCOADHESIVE POLYMER:

There are two broad classes of mucoadhesive polymers hydrophilic polymer and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties, poly vinyl pyrrolidone (PVP) , Methyl cellulose (MC), Sodium carboxy methylcellulose (SCMC) Hydroxy propyl cellulose (HPC) and other cellulose derivative. Hyrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

- Anionic group- Carbopol, Polyacrylates and their crosslinked modifications
- Cationic group- Chitosan and its derivatives
- Neutral group- Eudragit- NE30D etc.

10.1 Characteristics of an Ideal Mucoadhesive Polymer:

1. The polymer and its degradation products should be nontoxic and should be no absorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong no covalent bond with the mucin–epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

Table No. 1. Examples of some Mucoadhesive polymers

Natural	Synthetic	Biocompatible	Biodegradable
Na alginate Pectin Tragacanth Gelatin Carrageenan	Polyvinyl alcohol, Polyamides, polycarbonates, Polyalkylene glycols, Polyvinyl ethers, Esters and halides, Polymethacrylic acid, Polymethyl methacrylic acid, Methylcellulose, Ethylcellulose, Hydroxypropyl cellulose, Hydroxypropyl Methylcellulose, Sod. Carboxymethylcellulose	Esters of haluronic acid, Polyvinyl acetate, Ethylene glycol	Poly (lactides), Poly(glycolides), Poly(lactide-co-glycolides), Polycaprolactones, Polyalkyl cyanoacrylates. Polyorthoesters, Polyphosphoesters, Polyanhydrides, Polyphosphazenes Chitosan Poly ethylene oxide

Robinson and his group using the fluorescence technique concluded that:

1. Cationic and anionic polymers bind more effectively than neutral polymers.
2. Polyanions are better than polycations in terms of binding/ potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water soluble polymers.
3. Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
4. Degree of binding is proportional to the charge density on the polymer.

5. Highly binding polymers include carboxy methyl cellulose, gelatine, hyaluronic acid, carbopol, and polycarbophyl.

11. FACTORS AFFECTING MUCOADHESION

11.1 Polymer related factors:

i) Molecular weight

ii) Concentration of active polymer

iii) Flexibility of polymer chains

iv) Special confirmation

v) Swelling

11.2. Environment related factors:

i) pH of polymer - substrate interface

ii) Applied strength

iii) Initial contact time

11.3. Physiological factors:

i) Mucin turns over

ii) Disease state

12. NOVEL MUCOADHESIVE POLYMERS UNDER DEVELOPMENT:

For optimal buccal mucoadhesion, Shojaei and Li have designed, synthesised and characterised a copolymer of PAA and PEG monoethylether monomethacrylate (PAA-co-PEG) (PEGMM) [29]. By adding PEG to these polymers, many of the shortcomings of PAA for mucoadhesion, outlined earlier, were eliminated. Hydration studies, glass transition temperature, mucoadhesive force, surface energy analysis and effect of chain length and molecular weight on mucoadhesive force were studied. The resulting polymer has a lower glass transition temperature than PAA and exists as a rubbery polymer at room temperature. Copolymers of 12 and 16-mole %PEGMM showed higher mucoadhesion than PAA. The effects of hydration on mucoadhesion seen by the copolymers revealed that film containing lower PEGMM content, which had higher hydration levels, had lower mucoadhesive strengths. The 16-mole %PEGMM had the most favourable thermodynamic profile and the highest mucoadhesive forces. Polymers investigated in this study also showed that the molecular weight and chain length had little or no effect on the mucoadhesive force.

Novel polymers of PAA complexed with PEGylated drug conjugate were investigated by Lele, et al.[30] Only a carboxyl group containing drugs such as indomethacin could be loaded into the devices made from these polymers. An increase in the molecular weight of PEG in these copolymers resulted in a decrease in the release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG.

A new class of hydrophilic pressure-sensitive adhesives (PSAs) that share the properties of both hydrophobic PSAs and bioadhesives has been developed by Corium Technologies[31] . These Corplex™ adhesive hydrogels have been prepared by non-covalent (hydrogen bond) cross-linking of a film-forming hydrophilic polymer (for example PVP) with a short-chain plasticizer (typically PEG) bearing complementary reactive hydroxyl groups at its chain ends. Owing to the appreciable length and flexibility of PEG chains, a relatively large space can be provided for a stoichiometric complex and a 'carcass-like' structure. The specific balance between enhanced cohesive strength and large free volume in PVP–PEG miscible blends influences their PSA behaviour. Properties of these hydrophilic PSA hydrogels prepared by the carcass-like cross-linking method can be modified using a polymer with complementary reactive groups to form 'ladder-like' cross-links with PVP. Thus, these Corplex™ PSA hydrogels have a broad range of unique adhesive/cohesive properties that enable topical and drug delivery systems to be applied to either skin or mucosa.

Table No. 2. The different bioadhesive polymers with their adhesion time.

Polymer	Adhesion time in hours; means ± SD (*n* = 3–5)
Thiolated Chitosan	161.2 ± 7.2
Thiolated Polycarbophil	26.0 ± 0.9
Thiolated Poly(Acrylic Acid)	19.4 ± 0.8
Hydroxypropylcellulose	15.2 ± 0.4
Carbopol 980	12.5 ± 0.9
Carbopol 974	10.3 ± 0.9
Polycarbophil	10.2 ± 0.8
Carbopol 980	9.8 ± 0.2

An AB block copolymer of oligo(methyl methacrylate) and PAA has been synthesised for prolonged mucosal drug delivery of hydrophobic drugs [32]. These block copolymers form micelles in an aqueous medium, which was confirmed by a fluorescence probe technique using pyrene. A model drug, doxorubicin hydrochloride, when incorporated into these micelles, results in its release being prolonged at a slower rate.

Table No. 3. List of compounds used as oral mucosal permeation enhancers

23-lauryl ether
Aprotinin
Azone
Benzalkonium chloride
Cetylpyridinium chloride
Cetyltrimethylammonium bromide
Cyclodextrin
Dextran sulfate
Lauric acid
Lauric acid/Propylene glycol
Lysophosphatidylcholine
Menthol
Methoxysalicylate
Methyloleate
Oleic acid
Phosphatidylcholine
Polyoxyethylene
Polysorbate 80
Sodium EDTA
Sodium salicylate
Sodium taurodeoxycholate
Sulfoxides

Polymers with thiol groups were also investigated as a new generation of mucoadhesive polymers. A study conducted by Bernkop-Schnurch, et al. demonstrated that introduction of a sulphahydryl group increased the adhesive properties of mucoadhesive polymers [33]. In this study, cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator, forming amide bonds between the primary amino group of the amino acid and the carboxylic acid moieties of the polymer. The results showed that there was considerable improvement in the overall behaviour of adhesion and adhesive properties when tested on porcine intestinal mucosa at a pH level above five.

In addition, mucoadhesive microspheres were studied recently by Bogataj, et al. for application in the urinary bladder [34]. The microspheres were prepared by a solvent evaporation method using Eudragit RL or hydroxypropylcellulose as matrix polymers. In another study, microspheres with a Eudragit RS matrix polymer and different mucoadhesive polymers, i.e. chitosan hydrogen chloride, sodium salt of carboxymethyl cellulose and polycarbophil were prepared and found to be useful as platforms for oral peptide delivery, with a high capacity of binding to bivalent cations, which are essential cofactors for intestinal proteolytic enzymes [35].

Mucoadhesive range of various polymers and their range mentioned in following order and intensity of bioadhesion with respect to different polymers summarized in Table 2.

Carbopol>Tragacanth>Sodium Alginate>HMC>Gelatin>MC>Arabic Gum

Table No. 4. Related research on mucoadhesive polymers and delivery systems

HPC and CP	Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination
HPC and CP	Measured Bioadhesive property using mouse peritoneal membrane
CP, HPC, PVP, CMC	Studied inter polymer complexation and its effects on bioadhesive strength
CP and HPMC	Formulation and evaluation of buccoadhesive controlled release delivery systems
HPC, HEC, PVP, and PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer
HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPCCP freeze dried mixture as core base
CP, PIP, and PIB	Used a two roll milling method to prepare a new bioadhesive patch formulation
Xanthum gum and Locust bean gum	Hydrogel formation by combination of natural gums
Chitosan, HPC, CMC, Pectin, Xantham gum, and Polycarbophil	Evaluate mucoadhesive properties by routinely measuring the detachment force form pig intestinal mucosa
Hyaluronic acid benzyl esters, Polycarbophil, and HPMC	Evaluate mucoadhesive properties
Hydroxyethylcellulose	Design and synthesis of a bilayer patch (polytef-disk) for thyroid gland diagnosis
Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide Drugs
Poly(acrylic acid) and Poly(methacrylic acid)	Synthesized and evaluated crosslinked polymers differing in charge densities and

	Hydrophobicity
Number of Polymers including HPC, HPMC, CP, CMC.	Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion
Poly(acrylic acid-co-acrylamide)	Adhesion strength to the gastric mucus layer as a function of crosslinking agent, degree of swelling, and carboxyl group density
Poly(acrylic acid)	Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics
Poly(acrylic acid-co-methyl methacrylate)	Effects of polymer structural features on mucoadhesion
HEMA copolymerized with Polymeg® (polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine
Poly(acrylic acid-co-butylacrylate	Relationships between structure and adhesion for mucoadhesive polymers
CMC, Carbopol 974P, Carbopol EX- 55, Pectin (low viscosity), Chitosan chloride,	Mucoadhesive gels for intraoral delivery
CMC, CP, Polyethylene oxide, Polymethylvinylether/Maleic anhydride (PME/MA), and Tragacanth	Buccal mucoadhesive device for controlled release anticandidal device – CMC tablets yielded the highest adhesive force

13. EVALUATION OF MUCOADHESIVE DOSAGE FORMS:

13.1 In vitro tests / ex vivo [36]

- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Falling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
- Swelling properties
- In vitro drug release studies
- Mucoretentability studies

13.2 In vivo methods [37]

- Use of radioisotopes
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of electron paramagnetic resonance (EPR) oximetry
- X ray studies
- Isolated loop technique

13.1 In vitro method:

A. Methods determining tensile strength:

Review of the literature confirmed that the most common technique used for the measurement of bioadhesion test is tensile strength method. McCarron *et al*. and Donnelly have reported extensively on the use of a commercial apparatus, in the form of a texture profile analyzer [Figure 8] operating in bioadhesive test mode, to measure the force required to remove bioadhesive films from excised tissue *in vitro*.

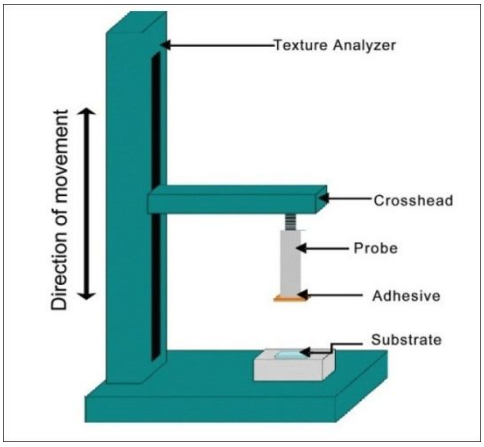

Fig.No.8. Texture profile analyzer in bioadhesion test mode

The texture analyzer, operating in tensile test mode and coupled with a sliding lower platform, was also used to determine peel strength of similar formulations [Figure 9]

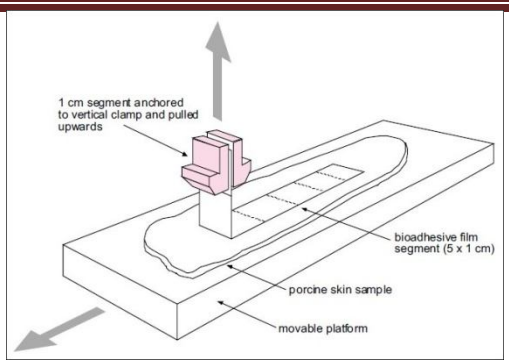

Fig.No.9. Simplified representation of a typical test set-up used to determine peel strength of bioadhesive films

B. Falling Liquid Film method:

A new method is proposed by Rango Rao and Buri in which the chosen mucous membrane is placed in a stainless steel cylindrical tube, which has been longitudinally cut. This support is placed inclined in a cylindrical cell with a temperature controlled at 37 ºC. An isotonic solution is pumped through the mucous membrane and collected in a beaker. Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter. For semi-solid systems, the non adhered mucoadhesive can be quantified by high performance liquid chromatography .This methodology allows the visualization of formation of liquid-crystalline mesophase on the mucous membrane after the flowing of the fluids and through analysis by means of polarized light microscopy [38,39,40]

C. Swelling index [41,42,43,44]

The extent of swelling can be measured in terms of % weight gain by the dosage form. The swelling index is calculated using following formula.

Swelling Index (S.I.) = (Wt-Wo) / Wo

Where, S.I. = Swelling index

Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker

D. Mucoadhesive Strength [45]

Mucoadhesive strength of the dosage form can be measured on the modified physical balance. The design used for measuring the mucoadhesive strength is shown in Figure 10. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide

with copper wire and additional weight, to make the right side weight equal with left side pan. A teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This is kept in beaker filled with buffer media 0.1N HCl pH 1.2, which is then placed below right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer media 0.1N HCl pH 1.2 can be used as moistening fluid. The one side of the dosage form is attached to the glass slide of the right arm of the balance and then the beaker is raised slowly until contact between goat mucosa and mucoadhesive dosage form is established. A preload of 10 mg is placed on the slide for 5 min (preload time) to established adhesion bonding between mucoadhesive dosage form and goat or rat stomach mucosa. The preload and preload time are kept constant. After the completion of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.81}{1000}$$

Bond strength (N/m2) = Force of adhesion (N)/ Surface area of tablet (m2)

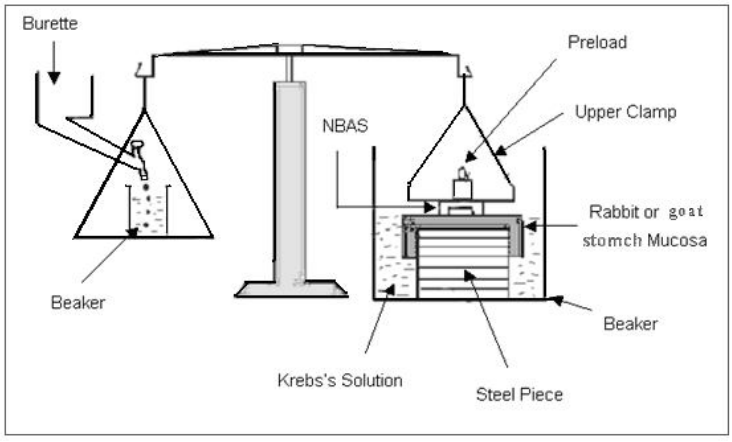

Fig.no.10. Muco adhesion Test Assembly

E. Stability Studies:

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

13.2 Measurement of the Residence Time/In Vivo Techniques

Measurements of the residence time of mucoadhesive at the application site provide quantitative information on their mucoadhesive properties. The GI transit times of many mucoadhesive preparations have been examined using radioisotopes and the fluorescent labeling techniques.

A. GI Transit using Radio-Opaque Tablets

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time. Feces collection (using an automated feces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesives labeled with Cr-51, Tc- 99m, In-113m, or I-123 has been used to study the transit of the tablets in the GI tract.

B. Gamma Scintigraphy Technique

Distribution and retention time of the mucoadhesive tablets can be studied using the gamma scintigraphy technique. A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled HYAFF tablets. Dimensions of the stomach part of the sheep can be outlined and imaged using labeled gellan gum, and the data collected are subsequently used to compare the distribution of radio labeled HYAFF formulations. The retention of mucoadhesive-radio labeled tablets based on HYAFF polymer was found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to stomach epithelium. The combination of the sheep model and the gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomach mucoadhesive tablets.

14. CONCLUSION:

In conclusion, the concept of mucoadhesive drug delivery is to scope the property of mucoadhesion of certain polymers with the sustained release delivery systems in order to circumvent the problem of inability of oral formulations to restrain and localize at the site of absorption in gastrointestinal tract. They offer advantage of enhanced bioavailability of drugs entrapped in, and to localize them at absorption window for longer period of time.

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin. Drug Deliv. 2006; 3(2): 217- 33.
2. Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. Int J Pharm 1998; 174: 47-54.
3. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J. Pharm. Res. 2008; 7(3): 1055-66.
4. Rouge N, Allemann E, Gex-Fabry M, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multipleunit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm Acta. Helbetiae 1998; 73: 81
5. Streubel A, Siepmann J, Bodmeier R. Multiple unit Gastroretentive drug delivery: a new preparation method for low density microparticles. J. Microencapsul 2003; 20: 329-47.
6. Goole J, Vanderbist F, Aruighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J. Pharm. 2007; 334: 35-41.
7. Sharma S, Pawar A. Low density multiparticulate systemfor pulsatile release of meloxicam. Int. J .Pharm. 2006; 313:150-58.
8. Santus G, Lazzarini G, Bottoni G, Sandefer EP, Page RC, Doll WJ, Ryo UY, Digenis GA. An in vitro- in vivo investigation of oral bioadhesive controlled release furosemide formulations. Eur. J. Pharm. Biopharm. 1997; 44:39-52.
9. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J. Cont. Release 2003; 90: 143-62.
10. Deshpande A A, Shah N, Rhodes CT, Malik W. Development of a novel controlled-release system for gastric retention. Pharm. Res .1997; 14: 815-19.

11. Fujimori J, Machida Y, Nagai T. Preparation of a magnetically-responsive tablet and configuration of its gastric residence in beagle dogs. STP Pharma Sci 1994; 4: 425-30.

12. Jain NK, Controlled release and Novel Drug Delivery. 1st edition.CBS publishers and Distributors New Delhi.1997; 353-370.

13. Tao S, and Desai T. Gastrointestinal patch systems for oral drug delivery DDT, 2005; 10(13)

14. Nasa P, Mahant S, Sharma D. Floating systems:A novel approach towards gastroretentive drug delivery systems. Int. J. Pharm. Pharm.Sci. 2010; 2: 0975-1491.

15. Surana A. and Kotecha R. An overview on various approaches to oral controlled drug delivery system via gastroretention. 2010; 2(2):

16. Sheu M, Chen R, Ho.Hsiu, Yu C. Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. European Journal of Pharmaceutical Sciences 2010; 39:82–89.

17. K Vinod, Vasa Santhosh, S Anbuazaghan, Banji David, et al. Approaches for gastrotentive drug delivery systems International Journal of Applied Biology and Pharmaceutical Technology 2010; I(2):589-601.

18. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. International Journal of Pharmaceutics 2006; 316:86–92.

19. Hoffman A, Stepensky D, Lavy E, Klausner S, Michael Friedman. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int. J. Pharma. 2004; 277:141–153.

20. G.S. Asane. mucoadhesive gastro intestinal drug delivery system : an overview, 2007; 5 (6) http// www.pharmainfo.net. Accessed on 06/07/2010.

21. Hubbell J A. Biomaterials in tissue engineering. Biotechnology, 1995; 13: 565-576.

22. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Ind. J. Pharm. Sci .2008;70:43-8.

23. Smart JD. The basics and underlying mechanism of mucoadhesion Adv. Drug. Deliv. Rev. 2005; 57:1556-68.

24. Clochard M, Dinand E, Rankin S, Simic S,Brocchini S. New strategies for polymer development in pharmaceutical science-a shortreview, J.Pharm. Pharmacol. 2001;53(9):1175-1184.

25. Kathryn E. Uhrich ,Scott M. Cannizzaro ,Robert S. Langer. Polymeric Systems for Controlled Drug Release, Chem. Rev.1999; 99:3181-3198.

26. Dodoud,Breedveld P,Mucoadhesive in the Gastrointestinal tract :Revisiting Literature for novel application . Eur. J. Pharm. Biopharm. 2005; 60:1-16.

27. Hager stroom H,Edsman K. Low freequency dielectric spectroscopy as a tool for studying the compatibility between Pharmaceutical gels and Mucus tissue. Pharm. Sci. 2003;92:1869-81.

28. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm .1997;23:489-515.

29. Shojaei AM and X Li, "Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monoethylether monomethacrylate", J. Control. Rel., 1997;47:151–161.

30. Lele BS and Hoffman AS. Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride-drug linkages. J. Control. Rel., 2000; 69:237–248.

31. Cleary G W, Feldstein M M, Singh P and Platé N A. A New Polymer Blend Adhesive With Combined Properties to Adhere to Either Skin or Mucosa for Drug Delivery. Podium Abstract, 30th Annual Meeting and Exposition of the Controlled Release Society, Glagsow, Scotland, 2003;19–23.

32. Inoue T, Chen G, Nakamae K and Hoffman A S. An AB copolymer of oligo (methyl methacrylate) and poly(acrylic acid) for micellar delivery of hydrophobic drugs. J. Control. Rel., 1998: 51 (2–3) 221–229.

33. Bernkop-Schnurch A, Schwarch V and Steininger S. Polymers with thiol groups: A new generation of mucoadhesive polymers. Pharm. Research, 1999;16 (6) :876–881.

34. Botagataj M, Mrhar A and Korosec L, "Influence of physiochemical and biological parameters on drug release from microspheres adhered on vesical and intestinal mucosa, Int. J. Pharm., 1999; 177:211–220.

35. Chen H and Langer R. Oral particulate delivery: status and future trends. Adv. Drug Delivery Rev., 1998; **196 (**34**):**339–350.

36. Botagataj, M., Mrhar, A. and Korosec, L. Influence of Physicochemical and Biological Parameters on Drug Release from Microspheres Adhered on Vesicular and Intesitnal Mucosa, Int. J. Pharm., 177, 1999, 211-20.

37. Sam AP, Van Dan Heuij JT, Tukker J. Mucoadhesion of both film- forming and non film forming polymeric materials as evaluated with the Wilhelmy plate method. Int J Pharm, 53, 1989, 97-105.

38. Nielsen LS.; Schubert L. Hansen J. Bioadhesive drug delivery systems. I. Characterization of mucoadhesive properties of systems based on glyceryl mono-oleate and glyceryl monolinoleate. Eur. J. Pharm. Sci., v.6, n.3, p.231- 239, 1998.

39. Rango Rao KV, Buri PA. Novel in situ method to test polymers and coated microparticles for bioadhesion. Int. J. Pharm., v.52, n.3, p.265-270, 1989.

40. Chowdary, C P R., Rao Y S. Mucoadhesive microspheres for controlled drug delivery. Biol. Pharm. Bull., 2004; 27(11):1717-1724.

41. Patel VM , Prajapati G, Patel M. Mucoadhesive Bilayer tablets of Propranolol Hydrochloride. AAPS Pharmasci tech, 2007, 8, 234- 242.

42. Margeta, C, Sachin. BS, Debjit B, Bhowmik B, Jayakar B. Formulation and evaluation of Controlled release mucoadhesive oral tablet of Clarithromycine. Der pharmacia Lettre; 2009; 1: 83-91.

43. Richardson JL, Armstrong TI, Vaginal delivery of calcitonin by hyaluronic acid formulations. In: Mathiowitz E, Chickering DE, Lehr CM, editors. Mucoadhesive Drug Delivery Systems—Fundamentals, Novel Approaches and Development '98. New York: Marcel Dekker; 1999; 563–99.

44. Rajput G, Majmudar F, Patel J, et al. Stomach-specific mucoadhesive microsphere as a controlled drug delivery system. Sys. Rev. Pharm, 2010;1: 36-44.

45. Sonani N G., Hiremath S P, Dasankoppa F S. et al. Design and evaluation of gastroretentive mucoadhesive Cephalexin tablets. Pharmaceutical development and technology. July 2009; on line.