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Analytical Study of Mucoadhesion Buccal Drug Delivery Systems

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Abstract - The current article focuses on the principles of mucoadhesive drug delivery systems based on adhesion to biological surfaces that are covered by mucus. An overview of the last decade's discoveries on mucoadhesion and applications of mucoadhesive hydrogels as drug carriers is given. Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Over the past few decades, mucosal drug delivery has received a great deal of attention. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. 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. This review article aims to provide an overview of the various aspects of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, and finally various mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal).

Keywords: ***Mucoadhesion, Mucoadhesive drug delivery systems, Mucoadhesive materials***

I. Introduction

In the last two decades, mucoadhesion has shown renewed interest for prolonging the residence time of mucoadhesive dosage forms through various mucosal routes in drug delivery applications. Mucoadhesive-based topical and local systems have shown enhanced bioavailability. Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow. Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes. Thus mucosal drug delivery system could be of value in delivering a growing number of high-molecular-weight sensitive molecules such as peptide and oligonucleotides. In this review, the aim is to provide detailed understanding of mucoadhesion, bioadhesion of polymer, and techniques for the determination of mucoadhesion; finally most common routes of mucoadhesive administration will be presented along with examples of formulation studied.

II. Review of Literature

- Ganesh P, et.al., have displayed the Buccal medication conveyance framework as the successful medication conveyance framework, which kills the issues of hepatic first pass digestion system and medication corruption in the gastro-intestinal tract. This paper likewise examines the assessment of buccal medication conveyance by the appraisal of swelling list and bioadhesion study.

- Patel K.V. et.al., presents Buccal organization of medications gives a helpful course of organization for both systemic and nearby medication activities. Key preferences and confinements identified with the buccal medication conveyance framework has likewise been talked about in the inspected. In the advancement of these buccal medication conveyance frameworks, mucoadhesion of the gadget is a key component. Mucoadhesive polymers have been used in various measurements structures in endeavors to accomplish systemic conveyance of medications through the buccal mucosa. Late advancements in the dose structure advancement and in vivo and in vitro mucoadhesion testing routines has additionally been centered.

- Navneet Verma, et.al., exhibited on the speculations of mucoadhesion for the buccal medication conveyance framework. Among the different transmucosal courses, buccal mucosa has superb openness, a spread of smooth muscle and moderately stationary mucosa, thus suitable for organization of retentive dose structure. Direct access to the systemic dissemination through the inner jugular vein detours drugs from the hepatic first pass digestion system prompting high bioavailability. Moreover, movies have enhanced patient consistence because of their little size and lessen thickness, analyzed for instance tablets. Likewise displayed the perfect PROPERTIES of polymers and the readiness systems for movies.

- Ganesh G.N.K, et.al., Prepared buccal tablets were relatively assessed for their physicochemical parameters like weight variety, hardness, thickness and friability test. The surface pH, swelling record, bio-glue quality, in-vivo living arrangement time are additionally done which has been critical. In vitro medication discharge rate has been examined.

- Asha S.John, et.al, have examined on the bilayered mucoadhesive tablets and assessed the physcochemical properties for the buccal medication conveyance like medication substance, swelling study, lattice disintegration, surface PH study and so on, bioadhsion time and so on.,

- Rahamatullah Shaikh, et.al., displayed on Mucoadhesion, which is usually characterized as the bond between two materials, no less than one of which is a mucosal surface. Over the recent decades, mucosal medication conveyance has gotten a lot of consideration. Mucoadhesive measurements structures may be intended to empower delayed maintenance at the site of utilization, giving a controlled rate of medication discharge for enhanced remedial result. Utilization of measurements structures to mucosal surfaces may be of profit to medication atoms not amiable to the oral course, for example, those that experience corrosive corruption or broad first-pass digestion system. The mucoadhesive capacity of a measurement structure is needy upon a mixture of variables, including the way of the mucosal tissue and the physicochemical properties of the polymeric plan. This paper plans to give a diagram of the different parts of mucoadhesion, mucoadhesive materials, variables influencing mucoadhesion, assessing strategies.

- John D.Smart, presents the paper on the instrument of medication conveyance by means of the oral mucosa. The life structures of oral mucosa likewise has been introduced. The buccal course has been utilized for a long time to convey medications, for example, certain steroids that are subjected to first-pass digestion system. Further late enthusiasm for this course has

been created with respect to the non-parenteral conveyance of new peptide and protein medications delivered as a consequence of advances in the biotechnology.

- Hitesh patel, prented a paper on the buccal medication conveyance incorporates the components influencing the medication conveyance by means of the oral mucaosa, in the same way as atomic weight, adaptability, hydrogen-holding limit, cross-connecting thickness, charge, fixation, hydration (swelling), and certain natural elements. This paper likewise includes a note the buccal mucoadhesive measurement structures like buccal movies, buccal tablets, buccal gels and treatments, and buccal patches.

- Puratchikody, et.al., presents the future difficulties and opportunities in the buccal medication conveyance framework. The late developments and applications are decently clarified in this paper. The economically accessible buccal mucoadhesive measurement structures are recorded in this paper. The definition outline likewise has been clarified. The pharmaceutical, physiological, and the pharmacological contemplations for the detailing configuration are decently clarified.

- Pranshu Tangri, et,al., exhibited a paper on the on the standards of mucoadhesive medication conveyance frameworks taking into account attachment to organic surfaces that are secured by bodily fluid. An outline of the most recent decade's disclosures on mucoadhesion and uses of mucoadhesive hydrogels as medication transporters is given. Systems that are often used to study the attachment strengths and physicochemical connections between hydrogel, bodily fluid, and the basic mucosa are evaluated. Mucoadhesive medication conveyance frameworks is a standout amongst the most imperative novel medication conveyance frameworks with its different preferences and it has a considerable measure of potential in forming measurement structures for different constant illnesses.

1. Bioadhesion and Mucoadhesion

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. In biological systems, bioadhesion can be classified into 3 types:

- Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.

- Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.

- Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

For medication conveyance purposes, the term bioadhesion suggests connection of a medication transporter framework to an indicated organic area. The organic surface can be epithelial tissue or the bodily fluid cover on the surface of a tissue. In the event that glue connection is to a bodily fluid cover, the marvel is alluded to as mucoadhesion. Leung and Robinson portrayed mucoadhesion as the connection between a mucin surface and a manufactured or common polymer. Mucoadhesion ought not be mistaken for bioadhesion; in bioadhesion, the polymer is joined to the organic film and if the substrate is bodily fluid layer the term mucoadhesion is utilized.

1.1 Factors Affecting Drug Delivery via Buccal Route

The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability

decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules.

1.2 Toxicity and Irritancy Associated With Buccal Drug Delivery

Formulations that produce local damage at the site of application, such as ulceration of the mucosa, would preclude their widespread usage as a result of the associated pain and discomfort. This is articularly important in buccal drug delivery where the formulation is in contact with the mucosa for extended periods. Toxic effects can arise from the drug itself, the bioadhesive or from other components of the formulation

1.3 Methods to Increase Drug Delivery via Buccal Route

Absorption enhancers :-Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates.

Limitations of Buccal Drug

DELIVERY

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows.

- For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
- The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
- For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.
- Once placed at the absorption site the patch should not be disturbed.
- Eating and drinking are restricted until complete absorption has taken place.

Advantages of Buccal Drug Delivery

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract

2. Improved patient compliance due to the elimination of associated pain with injections;

3. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.

4. Increased ease of drug administration

5. Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.

6. In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration.

MUCOADHESION

The term bioadhesion can be characterized as the state in which two materials, no less than one natural in nature, are held together for a developed time of time by interfacial powers (Good, 1983). In natural frameworks, bioadhesion can be arranged into 3 sorts:

• Type 1, grip between two organic stages, for instance, platelet conglomeration and wound mending.

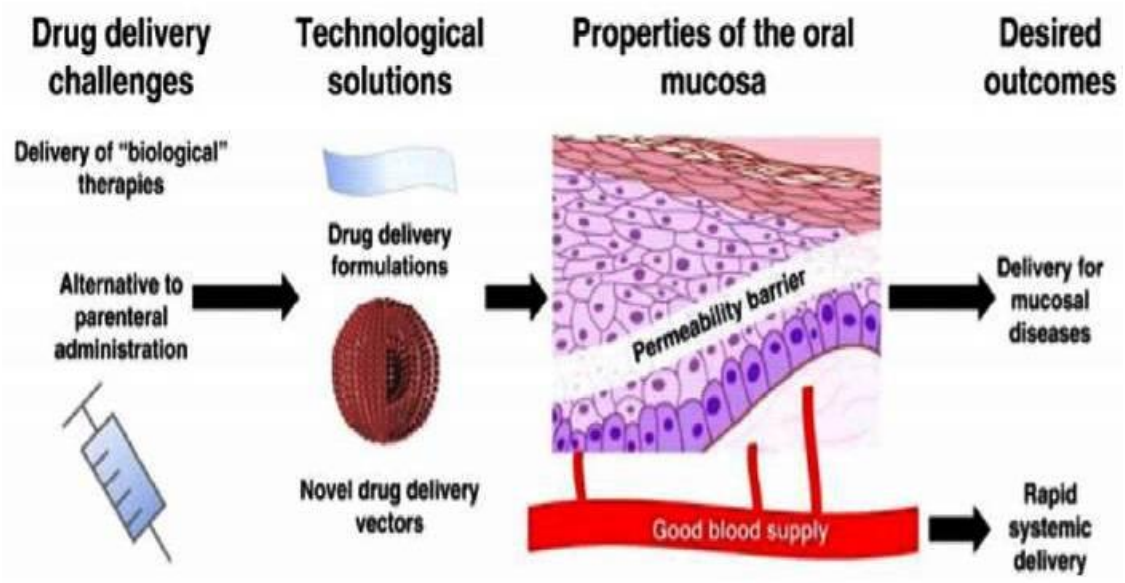
• Type 2, grip of an organic stage to a simulated substrate, for instance, cell bond to society dishes and bio-film arrangement on prosthetic gadgets and additions.

• Type 3, grip of a fake material to an organic substrate, for instance, bond of manufactured hydro gels to delicate tissues (Henriksen et al., 1996) and attachment of sealants to dental polish.

For drug conveyance purposes, the term bioadhesion infers connection of a medication bearer framework to a pointed out natural area. The organic surface can be epithelial tissue or the bodily fluid cover on the surface of a tissue. In the event that cement connection is to a bodily fluid layer, the sensation is alluded to as mucoadhesion. Leung and Robinson (Leung and Robinson, 1988) depicted mucoadhesion as the association between a mucin surface and a manufactured or regular polymer.

Mucoadhesion ought to not be mistaken for bioadhesion; in bioadhesion, the polymer is connected to the organic layer and if the substrate will be bodily fluid film the term mucoadhesion is utilized. Hydrocolloids will be accepted to stick to mucosa upon hydration, as the manufactured polymer particles get to be all the more openly portable and have the capacity to orientate cement locales positively with those of the substrate. As the level of hydration increments, glue quality was discovered to reduction, since mucoadhesive bonds get to be overextended. It is recommended that the hydrogen bond-shaping limit of the polymer is vital in this impact, and might underline the welldocumented mucoadhesive properties of polymers having various carboxyl gatherings, for example, carbopol and polycarbophil. In any case, the more noteworthy swelling properties of the polymer expanded ionization may prompt a lessening in mechanical quality and accompanying decrease in mucoadhesive properties. Built in light of the mucoadhesion speculations, it might be reasoned that the most proficient mucoadhesive polymers have physiochemical properties that are nearly identified with those of the bodily fluid substrate.

Figure1. Representation of Approaches to oral Mucoadhesive Drug Delivery System



ADVANTAGES

• Prolongs the residence time of the dosage form at the site of absorption
• To avoid the first pass metabolism
• Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug
• Excellent accessibility
• Rapid absorption because of enormous blood supply and good blood flow rates
• Increase in drug bioavailability due to first pass metabolism avoidance
• Drug is protected from degradation in the acidic environment in the GIT
• Improved patient compliance & ease of drug administration
• Faster onset of action is achieved due to mucosal surface

III. MECHANISM OF MUCOADHESION

The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must be dominated. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be absorbed by the substrate because of the attraction by the surface water (Lee et al., 2000). Due to its relative complexity, it is likely that the process of mucoadhesion cannot be described by just one of these theories. Lee, Park, Robinson, 2000 had described the mechanism of mucoadhesion in four different approaches. These include

• Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity)

• Fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many Mucoadhesive that have hydrated in the luminal contents on delivery to the

lower gastrointestinal tract) Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina)

• Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered into the esophagus or eye) It is unlikely that the mucoadhesive process will be the same in each case (Chowdary and Srinivas, 2000). In the study of adhesion, generally, two stages in the adhesive process supports the mechanism of interaction between mucoadhesive materials and a mucous membrane Thus, the mechanism of mucoadhesion is generally divided in two stages, the contact stage and the consolidation stage.

Experimental Methodology For Buccal Permeation Studies

Before a buccal drug delivery system can be formulated; buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

A. In vitro Methods

At the present time, most of the in vitro studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the in vitro permeation experiments

B. In vivo Methods

In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volu me is then determined in order to assess the amount of drug absorbed. Various modifications of the buccal absorption test have been carried out correcting for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization.

C. Experimental Animal Species

Aside from the specific methodology employed to study buccal drug absorption/permeation characteristics, special attention is warranted to the choice of experimental animal species for such experiments. For in vivo investigations, many researchers have used small animals including rats and hamsters) or permeability studies.

Buccal Drug Delivery System

Other than the low flux associated with buccal mucosal delivery, a major limitation of the buccal route of administration is the lack of dosage form retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems. Bioadhesive polymers are defined as polymers that can adhere onto a biological substrate. The term mucoadhesion is applied when the substrate is mucosal tissue. Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. Diverse classes of polymers have been investigated for their potential use as mucoadhesives. These include synthetic polymers such as monomeric a cyanoacrylate, polyacrylic acid, hydroxypropyl methylcellulose , and poly methacrylate derivatives as well as naturally occurring polymers such as hyaluronic acid and

chitosan. Other synthetic polymers such as polyurethanes, epoxy resins, polystyrene, and natural-product cement have also been extensively investigated.

In general, dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by the patient. These requirements can be met by using hydrogels. Hydrogels are hydrophilic matrices that are capable of swelling when placed in aqueous media (87). Normally, hydrogels are crosslinked so that they would not dissolve in the medium and would only absorb water. When drugs are loaded into these hydrogels, as water is absorbed into the matrix, chain relaxation occurs and drug molecules are released through the spaces or channels within the hydrogel network. In a more broad meaning of the term, hydrogels would also include water-soluble matrices that are capable of swelling in aqueous media, these include natural gums and cellulose derivatives. These 'pseudo-hydrogels' swell infinitely and the component molecules dissolve from the surface of the matrix. Drug release would then occur through the spaces or channels within the network as well as through the dissolution and/or the disintegration of the matrix. The use of hydrogels as adhesive preparations for transmucosal drug delivery has acquired considerable attention in recent years. Table1 summarizes the related research on mucoadhesive polymers and delivery systems.

Table 1. Related research on Mucoadhesive polymers and delivery systems

Bioadhesive Polymer(s) Studied	**Investigation Objectives**
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 HPC-CP 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
Poly(acrylic acid-co- butylacrylate)	Relationships between structure and adhesion for mucoadhesive polymers
HEMA copolymerized with Polymeg®(polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine
Cydot® by 3M (bioadhesive polymeric blend of CP and PIB)	Patch system for buccal mucoadhesive drug delivery
Formulation consisting of PVP, CP, and cetylpyridinium chloride (as stabilizer)	Device for oramucosal delivery of LHRH - device containing a fast release and a slow release layer
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
HPMC and Polycarbophil (PC)	Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion
PVP, Poly(acrylic acid)	Transmucosal controlled delivery of isosorbide dinitrate
Poly(acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and poly ethyleneglycol monomethylether monomethacryalte	To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery
Poly acrylic acid and poly ethylene glycol	To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization

Drum dried waxy maize starch (DDWM), Carbopol 974P, and sodium stearylfumarate	Bioadhesive erodible buccal tablet for progesterone delivery

Abbreviations: **CP** = Carbopol 934P, **HPC** = Hydroxy propyl cellulose, **PVP** = Poly(vinyl pyrrolidone), **CMC** = Sodium carboxymethyl cellulose, **HPMC** = Hydroxy propyl methyl cellulose, **HEC** = Hydroxy ethyl cellulose, **PVA** = Poly(vinyl alcohol), **PIB** = Poly(isobutylene), **PIP** = Poly(isoprene).

IV. Conclusion

The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility. The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first -pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. Now researchers are looking beyond traditional polymers, in particular next-generation mucoadhesive polymers (lectins, thiols, etc.); these polymers offer greater attachment and retention of dosage forms. However, these novel mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases.

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