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REVIEW ARTICLE

MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. In this regard, this review covers the areas of mechanisms and theories of mucoadhesion, mucoadhesive polymers and also various mucoadhesive dosage forms.

Key words: Mucoadhesive, Gastrointestinal tract (GIT), Bioadhesion

INTRODUCTION:

Over the last two decades mucoadhesion has become of interest for its potential to optimizelocalized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the nasal cavity). The need to deliver "challenging" molecules such as biopharmaceuticals (proteins and oligonucleotides) has increased interest in this area. Mucoadhesives materials could also be used as therapeutic agents in their own right, to coat and protect damaged tissues (gastric ulcers or lesions of the oral mucosa) or to act as lubricating agents (in the oral cavity, eye and vagina).[7]

Mucoadhesion and 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, while the term cytoadhesive implies adhesion to cells. Mucoadhesive drug delivery systems are type of gastro retentive drug delivery systems. [2, 6]

In the formulation of oral controlled-release dosage forms, considerable benefits may ensue from the use of mucoadhesive polymers providing relatively short-term adhesion between the drug delivery system and the mucus or epithelial cell surface of the gastrointestinal tract. The binding between polymer and mucous membrane will therefore involve secondary forces, such as hydrogen bonds or Vander Waals forces. Mucoadhesives may, therefore, be regarded as a specific class of bioadhesives.[4]

Mucoadhesive/ biodhesive drug delivery systems includes the following sytem[6],

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Advantages of mucoadhesive drug delivery system:[3, 11]

Mucoadhesive delivery system offers several advantages over other oral controlled release systems which are as follows-

- Prolongation of residence time of drug in gastrointestinal tract (GIT).
- Targeting and localization of the dosage form at a specific site.
- Also, the mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in high drug flux at the absorbing tissue

The ability to localize a drug delivery system in a selected region of the GI tract could conceivably lead to improved bioavailability, especially for drugs exhibiting narrow windows of absorption or instability in certain sectors of the tract[4].

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Mucous membranes:

Mucous membrane (mucosa) is the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. It consists of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made up moist by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/stratified (e.g. in the esophagus, vagina and cornea). The single layered epithelia contain goblet cells which secrete mucus directly onto the epithelial surfaces, the multilayered/stratified layer contain specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of its weight, making it a highly hydrated system. The mucin glycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies on different mucosal surfaces, from 50 to 450 µm in the stomach to less than 1 µm in the oral cavity. The major functions of mucus are that of protection and lubrication.[4, 7]

Theories of mucoadhesion:

A number of theories are present that explain the mechanisms with which mucoadhesives adhere to the mucus layer. There are six main theories that describe the possible mechanisms of mucoadhesion: the electronic, the adsorption, the wetting, the diffusion theory, the fracture theory, and the mechanical theory[10, 11, 13].

1. The electronic theory assumes that transfer of electrons occurs between the mucus and the mucoadhesive due to differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive leads to the formation of a double layer of electrical charges at the interface of the mucus and the mucoadhesive. This results in attraction forces inside the double layer.[8, 9]

2. Fracture theory[11] is the most widely used theory in studies on the mechanical measurement of mucoadhesion. It determines the force required to separate two surfaces after adhesion is established. This force S_m is frequently calculated in tests of resistance to rupture by theratio of the maximal detachment force, F_m, and the total surface area, A_o, involved in the adhesive interaction.

$$Sm \equiv \frac{Fm}{Ao}$$

Since this theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. It is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer.

3. Adsorption theory according to this theory the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions[12, 24].

4. Wetting theory applies to liquid systems which are present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity. The contact angle should be equal or close to zero to provide adequate spreadability[5, 13].

5. Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. It is assumes 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 polymers are reached when the depth of penetration is approximately equivalent to the polymer chain size. For the diffusion, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better the mucoadhesive bond[13, 5].

6. Mechanical theory considers that adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process[5, 13].

Mechanisms of Mucoadhesion:

The mechanism of mucoadhesion is generally divided into two steps:

- Contact stage and,
- Consolidation stage.

The contact stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the second step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system,

allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds[11, 24].

Polymers used for mucoadhesive drug delivery system:

The properties of the mucoadhesive drug delivery system, e.g. their surface characteristics, force of mucoadhesion, releasepattern of the drug, and clearance, are influenced by the typeof polymers used to prepare them. Suitable polymers that canbe used to form mucoadhesive dosage forms include solubleand insoluble, non-biodegradable and biodegradable polymers.These can be hydrogels or thermoplastics, homopolymeres,copolymers or blends, natural or synthetic polymers.[14]

Polymer candidates need to be nontoxic and nonabsorbable, adhere rapidly to wet tissues, and release the incorporated drug in a controlled manner[4].

Classification of polymers:

Table 1: First generation polymers

Polymer	Example
a. Hydrophilic Polymers[15, 17]**-** water-soluble polymers that swell indefinitely in contact with water, undergo complete dissolution	Methylcellulose, hydroxyethyl cellulose, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, carbomers, chitosan and plant gums
b. Hydrogels[25, 17]**-** water swellable polymers	poly(acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate, guar gum and modified guar gum
c. Thermoplastic Polymers[14,15,19]	**Synthetic polymers-** polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters and halides, polymethacrylic acid, polymethylmethacrylic acid. **Biodegradable polymers-** poly(lactides), poly(glycolides), poly(lactide- co-glycolides), polycaprolactones, polyalkyl cyanoacrylates, Poly(orthoesters), poly(phosphoesters), polyanhydrides, polyphosphazenes.

2. Specific site directed bioadhesives—the next generation:[14, 19]

The first generation mucoadhesive polymers lack specificity and can bind to any mucosal surface. This disadvantage limits their use for fabrication of mucoadhesive drug delivery system for a particular tissue. The development of polymers and microspheres grafted with mucus or cell-specific ligands have increased therapeutic benefit and made site-specific drug delivery possible. Any ligand with a high binding affinity for mucin can be covalently linked to the microspheres and be expected to influence the binding of microspheres. Targeting of the drugs can be achieved by using the following ligands.

(a) Lectins: Lectins are the proteins of non-immune origin that bind to carbohydrates specifically and non covalently. Lectins can increase the adherence of microparticules to the intestinal epithelium and enhance penetration of drugs. Lectins have been identified as potential carriers for peptides in an oral mucoadhesive system. [3]

Lactins may be used to target therapeutic agents for different gut components or even for different cells (e.g. complex-specific lectins for parietal cells or fucose-specificlectins for M cells). The bioinvasive mechanism has been described for the activity of lectins as targeting moieties. After binding to specific cells, lectins undergo cellular uptake and subsequently can also exhibit strong binding to nuclear pore membranes. The polystyrene microparticules coated with tomato lectin were shown to be specifically adhesive to enterocytes. Tomato lectin is a potential targeting moiety due to its low toxicity and high specificity, but its inactivation due to cross-reactivity with mucus limits its usefulness. The potential of tamato lectin can, however, be tapped by exploiting its cellular uptake for drug delivery.The other useful lectin ligands include lectins isolated from: *Abrus precatroius, Agaricus bisporus, Anguilla anguilla, Arachishypogaea, Pandeiraea simplicifolia, and Bauhinia purpurea*[14].

The drug delivery which uses lactins forms a promising approach for the peroral, specific mucoadhesive formulations. The use of lectins for targeting drugs to tumor tissue is currently under intensive investigation as

the human carcinoma cell lines exhibit higher lectin binding capacity than the normal human colonocytes[14].

(b) Bacterial Adhesions: Bacteria are able to adhere to epithelial surfaces of the enterocytes with the help of fimbriae. Fimbriae are long, lectin like proteins found on the surface of many bacterial strains. Their presence correlated with pathogencity, e.g. adherence of Escherichia coli to the brush border of epithelial cells mediated by K99 fimbriae is aprerequisite for subsequent production and cellular uptake of E. coli enterotoxin. Thus, the drug delivery system based on bacterial adhesion factors could be an efficient mechanism to increase adhesion of mucoadhesive microspheres to epithelial surfaces. Another study envisaging the importance of bacterial adhesion has been carried out using "invasion," which is a membrane protein from Yersinia pseudotuberculosis. Cellular uptake of polymeric nanospheres functionalized with invasion has been observed using confocal laser scanning microscopy[14,19].

(b) Amino Acid Sequences: Some amino acid sequences have complementary parts on the cell and mucosal surfaces and when attached to microparticles can promote binding to specific cell surface glycoproteins. The cell surface glycoproteins are altered in the presence of disease conditions and these altered protein sequences can be targeted by complementary amino acid sequences attached to the drug delivery device, e.g. amino acid sequences such as Arg-Gly-Asp and others, if attached to the matrix, could promote adhesion by binding with specific cell surface glycoprotein[14].

(c) Thiomers: these presumptive new generations of mucoadhesive polymers are thiolated polymers-designated thiomers. In contrast to well-established mucoadhesive polymers these novel polymers are capable of forming covalent bonds. The bridging structure most commonly encountered in biological systems–the disulfide bond–has thereby been discovered for the covalent adhesion of polymers to the mucus gel layer of the mucosa. Thiomers are mucoadhesivebasis polymers, which display thiol bearing side chains[26].

(d) Antibodies: The antibodies produced against selected molecules present on mucosal surfaces. Due to their high specificity, antibody can be a rational choice as a polymeric ligand for designing site-specific mucoadhesives. This approach is useful for targeting drugs to tumor tissues, e.g. the hyaluronic acid esters (HYAFF) bioadhesive microspheres in the presence of a mucosal adjuvant-LTK 63 administered intranasally are reported to induce a significantly enhanced serum IgG antibody response in comparision to intramuscular immunization with haemagglutinin obtained from influenza A virus. Polyphosphazene microspheres with adsorbed influenza antigen and tetanus toxiod can be administered intranasally to have increased immune responses.[14]

Sites for mucoadhesive drug delivery systems:

The common sites of application where mucoadhesive drug delivery systems have the ability to delivery pharmacologically active agents include eye conjunctiva, oral cavity, vagina, nasal cavity and gastrointestinal tract. The following are the site for mucoadhesive drug delivery system[15].

1. Mucoadhesive drug delivery systems for buccal cavity:

The buccal cavity has limited surface area of around 50 cm^2 but the easy access to the site makes it a preferred location for delivering active agents. The buccal cavity provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is somewhat more permeable than the buccal mucosa (because the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery.[15]

Many buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the buccal route, albeit with relatively low bioavailability (0.1–5%) owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa. Buccal mucoadhesive dosage forms include tablets, patches, films, and semisolids (gels and ointments). Although numerous buccal mucoadhesive dosag forms have been investigated, only a few products are commercially available. Striant™ a testosterone buccal system (tablet-like gum patch) is recently approved by the United States Food and Drug Administration (FDA). It is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Although numerous buccal mucoadhesive dosage forms have been investigated, only a few products are commercially available.[21]

Miconazole buccal tablets (MBT), are unique because of adherence to buccal mucosa, allowing once daily

administration, are currently available and have been recently approved by the US FDA for the treatment of oropharyngeal candidiasis in adults[23]

2. Mucoadhesive drug delivery systems for nasal cavity:

Like buccal cavity, nasal cavity also provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The mucosal layer of nasal cavity has a surface area of around 150-200 cm^2. The residence time of a particulate matter in the nasal mucosa varies between 15 and 30 min, which have been attributed to the increased activity of the mucociliary layer in the presence of foreign particulate matter.[15, 22]

Mucoadhesion in nasal cavity increases drug residence time and possibly enhances drug absorption, this mechanism may not work for all compounds, especially large molecules such as proteins. Some polymers interact with the mucus and/or the epithelium in such a way as to increase epithelial permeability. Controlled release can be achieved also after nasal administration. [20]

2. Mucoadhesive drug delivery systems for eye:

Ophthalmic mucoadhesives drug delivery system also is another area of interest. Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches.[15]

Particulate systems coated with flexible, mucoadhesivepolymer chains could be entrapped and/orbound in the mucus layer of the tear film or retainedin the conjunctival sac, thus withstanding drainage. Mucoadhesiveminitablets or inserts are promising ocular drug deliverysystems to treat external and intraocular eye infections. [19]

3. Mucoadhesive drug delivery systems for vaginal and rectal cavity:

For the delivery of the active agents, the vaginal and the rectal lumen have also been explored both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location. [15]

Mucoadhesive polymers are very promising candidates for systemic and local vaginal drug delivery.There is still ongoing research dealing with muco(bio) adhesive vaginal formulations that are capableof delivering the active agent for an extended periodat a predictable rate. To date most of the existingdosage forms are based on the synthetic poly(acrylates)but in the near future natural compounds suchas chitosan or carrageenan and new derivatives willgain more significance.[18]

4. Mucoadhesive drug delivery systems for gastrointestinal tract

Gastrointestinal tract is also a potential site which has been explored since long for the development of mucoadhesive based formulations. The modulation of the transit time of the delivery systems in a particular location of the gastrointestinal system by using mucoadhesive polymers has generated much interest among researchers around the world.[15]

The oral administration of colloidal suspensions of polymeric particles (nanoparticles or microspheres in the micron-range and made from non-swellable polymers) leads to the mucoadhesion of a significant fraction of the particles. Clearly, the particles are captured by the mucous gel layer while the remainder of the particles undergoes unmodified transit.[16]

By using bioadhesive magnetic granules, targeting to esophageal mucosa and other regions of GI tract can be achieved. The various parameters that influence targeting to a specific site using bioadhesive granules include the composition of formulation, the amount of magnetic material in granule, the magnitude of magnetic field. This approach can be used to treat the cancer of alimentary canal. [1]

Techniques for the Determination of Mucoadhesion:

Numerous methods have been developed for studying mucoadhesion. Since no standard apparatus is available for testing bioadhesive strength, an inevitable lack of uniformity between test methods has arisen. Nevertheless, three main testing modes are recognized – tensile test, shear strength, and peel strength[34].

The peel test is based on the calculation of energy required to detach the patch from the substrate. The peel test is of limited use in most bioadhesive systems. However, it is of value when the bioadhesive system is formulated as a patch[34].

Wash-off test is used to determine the mucoadhesive property of delivery systems. In the test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the delivery system is put on the surface of the tissue (exposed mucosal surface) with the subsequent vertical attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 37oC. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time

for the complete detachment of the delivery system from the mucosal layer is determined[33].

Recently mucoadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves immobilization of the polymer (powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface. The polymer-mucin interaction is measured by an optical phenomenon called Surface Plasmon Resonance (SPR), which measures the change in the refractive index when mucin binds on the polymer surface[33].

Recent advances in mucoadhesive drug delivery system:

1. Enhancement in transport of drug: The combination of the surfactantCremophor, as an absorption enhancer, and hyaluronicacid, as a viscosifying and bioadhesive polymer, could significantly increase the nose-to-brain transport of the test molecule, especially in the olfactory bulb and frontal cortex regions. Sodiumhyaluronate as a mucoadhesive component in nasal formulationenhances delivery of molecules to brain tissue[27].

2. Mucoadhesive multiparticulate patch for the intrabuccal controlled delivery of lidocaine: Cavallariet. al., prepared Mucoadhesivebuccal patches, containing 8 mg/cm2 lidocaine base, and developed by solvent casting method technique, using a number of different bio-adhesive and film-formingsemi-synthetic and synthetic polymers (Carbopol, Poloxamer, different type Methocel) and plasticizers (PEG 400, triethyl citrate); the patches were evaluated for bioadhesion, in vitro drug release and permeation using a modified Franz diffusion cell. A lidocaine/Compritol solid dispersion in the form ofmicrospheres, embedded inside the patch, alone or together with free lidocaine, was also examined to prolong the drug release[28].

3. Inclusion complex, between water-soluble β-cyclodextrin-grafted chitosan derivatives and eugenol was investigated as a new type of mucoadhesive drug carrier[29].

4. Mucoadhesive 4-carboxybenzenesulfonamide-chitosan with antibacterial properties:

The mucoadhesive 4-carboxybenzensulfonamide (4-CBS)-chitosan can be successfully synthesized via a coupling reaction using various (w/w) ratios of 4-CBS to chitosan (0.05:1–1:1) in the presence of 1-ethyl- 3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC) as a coupling reagent. The mucoadhesive property of chitosan, especially in an acidic (<pH 6.0) environment, was increased by conjugating an aromatic sulfonamide group at the C_2-N position of chitosan. Four different feeding ratios of 4-CBS to chitosan in the presence of EDAC were investigated. The 0.2:1 (w/w) ratio 4-CBS:chitosan revealed a 20-fold stronger mucoadhesion to mucin type II than the native chitosan in the simulated gastric fluid (SGF; pH 1.2), and a swelling ratio after 1 h in water, SGF and simulated intestinal fluid (pH 7.4) of about 2.9-, 3.0- and 3.4-fold higher than that of chitosan, respectively[30].

In tissue culture, the 4-CBS-chitosan, like chitosan, were showed potential antibacterial activity against Escherichia coli and Staphlyococcusaureus as model Gram-negative and Gram-positive bacteria, respectively[30].

5. Nanocarrier-aided mucosal vaccination: In the scope of nasal/oral vaccination, it is particularly interestingto favor the uptake of antigen-loaded nanocarriers by microfold (M) cells. Following nanoparticle uptake, the M-cells transportthe antigen-loaded nanoparticles to the nasal/gut associatedlymphoid tissue by transcytosis for subsequent uptakeand processing by dendritic cells and initiation of immune responses. Following nasal/oral administration of particulate antigens,both cellular and humoral immune responses against pathogens can beinduced. The cellular immune response of the adaptive immune systemis comprised of both T helper (Th) lymphocytes (CD4+) and cytolytic Tlymphocytes (CTL), also known as killer T lymphocytes (CD8+). CD4+T cells are responsible for orchestrating and directing an immune response, whereas CD8+ T cells traffic to the sites of infection and lyseinfected cells. The use of nanocarriers as delivery vehicles for mucosal vaccinationhas has been the subject of a great number of experimental studies[31].

However, only recently nanocarrier-based mucosal (e.g., nasal) vaccinationformulations have reached clinical trials[31].

6. Polymeric hybrid gel (HG) system: the development of a polymeric hybrid gel (HG) system with two biopolymers, alginate and chitosan simultaneously functioning as cisplatin (cis-diaminedichloroplatinum (II), CDDP) carrier and mucoadhesive reservoir. This system may locally deliver CDDP to the per-itoneal cavity, but also be suitable for other parts of the femalereproductive tract. The localized application of aCDDP-alginate–chitosan HG poses a promising approach to successfully enhance drug accumulation at targeted disease sites whilereducing nonspecific systemic toxicities. This maximizes drugeffects during a considerably shorter period of time. Furthermore, utilizing this gel for local adhesion to all mucosal surfaces enablesits simultaneous use for various different areas of the female reproductive tract. This approach may especially hold advantages for theuse within the peritoneal cavity treating ovarian cancer[32]

CONCLUSION:

This review about the mucoadhesive drug delivery systems might be a useful tool for the efficient design of novel mucoadhesive drug delivery systems. Mucoadhesive drug delivery systems have applications from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. Recent advancement in mucoadhesive drug delivery system explores the importance of the system. With the influx of a large number of new drug molecules due to drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules.

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