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REVIEW ARTICLE

Mucoadhesive Drug Delivery Systems for Pediatric and Geriatric Patients

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Mucoadhesive drug delivery systems for pediatric and geriatric patients

SUMMARY

A mucoadhesive drug delivery system (MDDS) has been an intelligent approach to the delivery of drugs at the target site. In MDDS, mucus membrane and type of polymer play a vital role in the mucoadhesion phenomenon. In order to explain the mechanism behind mucoadhesion, various theories have been proposed, such as electronic, adsorption, wetting, diffusion, and fracture theory. MDDS has been beneficial to some particular patients, preferably pediatric and geriatric. Several challenges, such as taste masking, dose determination, dosage form spitting, target delivery, the bioavailability of the drug, adverse drug reaction, toxicity, etc., are faced while developing any delivery system for these special patient populations. Keeping these challenges in mind several researchers have attempted to design and formulate MDDS. The current review focuses on a basic overview of mucoadhesion, various theories of mucoadhesion, and mucoadhesive polymers. The later part of the review focuses on the MDDS for pediatric and geriatric patients with their significance. Different patented formulations and active clinical trials for geriatric and pediatric populations have also been discussed.

Key Words: *Mucoadhesive; pediatric; geriatric; disease; patents; clinical study.*

Pediatri ve Geriatri Hastaları için Mukoadezif İlaç Taşıyıcı Sistemler

ÖZ

Mukoadezif ilaç taşıyıcı sistemler (MDDS) ilaçların hedef bölgeye taşınması için akıllıca bir yaklaşım olmuştur. MDDS'de mukus membran ve polimer tipi mukoadezyon olgusunda önemli rol oynamaktadır. Mukoadezyonun arkasındaki meknaizmayı açıklamak için elektronik, adsorpsiyon, ıslanma, difüzyon ve parçalanma theorisi gibi çeşitli teoriler ileri sürülmüştür. MDDS, tercihen pediatrik ve geriatrik olmak üzere bazı özel hastalar için faydalı olmuştur. Bu özel hasta popülasyonu için bir taşıyıcı system geliştirilirken tat maskeleme, doz tayini, dosage form spitting, hedefleme, ilacın biyoyararlanımı, sadvers ilaç reaksiyonu, toksisite gibi çeşitli zorluklarla karşılaşılmaktadır. Bu zorlukları akılda tutarak birçok araştırmacı, MDDS'yi kendilerine uygun şekilde tasarlamaya ve formüle etmeye çalışmıştır. Mevcut derleme, mukoadezyon hakkında temel bir genel bakışa, çeşitli mukoadezyon teorilerine ve mukoadezif polimerlere odaklanmaktadır. İncelemenin sonraki kısmı, pediatrik ve geriatrik hastalar için MDDS'ye ve önemine odaklanmaktadır. Bu popülasyonlar için devam eden çeşitli patentli formülasyonlar ve klinik denemeler de tartışılmıştır.

Anahtar Kelimeler: *Mukoadezif; pediatrik, geriatrik; hastalık; hastalar; klinik çalışma.*

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INTRODUCTION

The phenomenon in which two materials, at least one of which is biological, are held together by interfacial forces for a prolonged period is known as bioadhesion. When the adhesive polymer comes in contact with the mucous membrane, the phenomenon is referred to as mucoadhesion, and the delivery system associated with it is called a mucoadhesive drug delivery system (MDDS). MDDS is an approach to drug delivery that aims to exploit the natural adhesion between soft tissues, such as the gastrointestinal mucosa and specific polymers, for the delivery of drugs and other molecules which would otherwise be unable to cross the mucosal barrier and access the bloodstream. MDDS provides local (e.g., through oral delivery) and systemic drug delivery (e.g., through pulmonary mucosa). Furthermore, MDDS provides drug delivery passage through different routes, such as oral, buccal, nasal, pulmonary, gastrointestinal, vaginal, and rectal routes. It has advantages over other formulations due to the wide variety in the delivery passage, such as the administration of unstable and difficult-to-administer bioactives and proteins with higher molecular weight. Avoidance of first-pass metabolism, increased bioavailability, ease of administration, and increased residence time, which results in enhanced therapeutic activity, are some merits of MDDS (Boddupalli et al., 2010; Alawdi & Solanki, 2021; Kumar et al., 2020).

MUCUS MEMBRANE

The moist lining walls of various body cavities, such as the gastrointestinal and respiratory systems, are known as mucous membranes (mucosae). The mucous membrane is made of a connective tissue layer (lamina propria) and a layer of epithelial cells covered with a mucus layer; the cellular structure of the gastrointestinal tract is shown in Figure 1. The layers of epithelial cells vary according to the site; for instance, epithelial cells at the buccal site are about 40 – 50 cell layers thick, while at the sublingual site, the epithelial cell layer is fewer in number. Mucus, the gelatinous fluid secreted by mucous cells or goblet cells that covers the tissue layers in the respiratory, digestive, reproductive, and urinary tracts, is composed of 95% water, and the It has advantages over other formulations due to the wide variety in the delivery passage, such as the administration of unstable and difficult-to-administer bioactive and proteins with higher molecular weight. It has advantages over other formulations due to the wide variety in the delivery passage, such as the administration of unstable and difficult-to-administer bioactives and proteins with higher molecular weight. remaining are lipids, inorganic salts, phospholipids, and mucin. Mucin, the most significant structural component of mucus, is a mixture of glycoproteins and glycolipids. The glycoprotein molecules range from 0.5 – 20 MDa. Mucin is present in two forms, secreted mucin and membrane-bound mucin, both are composed of subunits linked with peptide linkage and intramolecular disulfide bridges of cysteine. The subunit is a combination of the oligosaccharide side chain and protein backbone. The protein backbone comprises of three amino acids, threonine, serine, and proline. The oligosaccharide chain is constituted of N-acetylglucosamine, N-acetylgalactosamine, sialic acid (N-acetylneuraminic acid), galactose, and fucose. Due to the presence of sialic acid (carboxylate group) and ester sulfate at the terminal ends of the oligosaccharide units, mucin has a negative charge in terms of electrical charges. The main functions of mucin are to provide protection, lubrication, and to maintain the mucus layer's structural integrity. Mucus also contains lysosomal enzymes that help to break down large molecules and clear cellular debris (Smart, 2005; Khutoryanskiy, 2011).

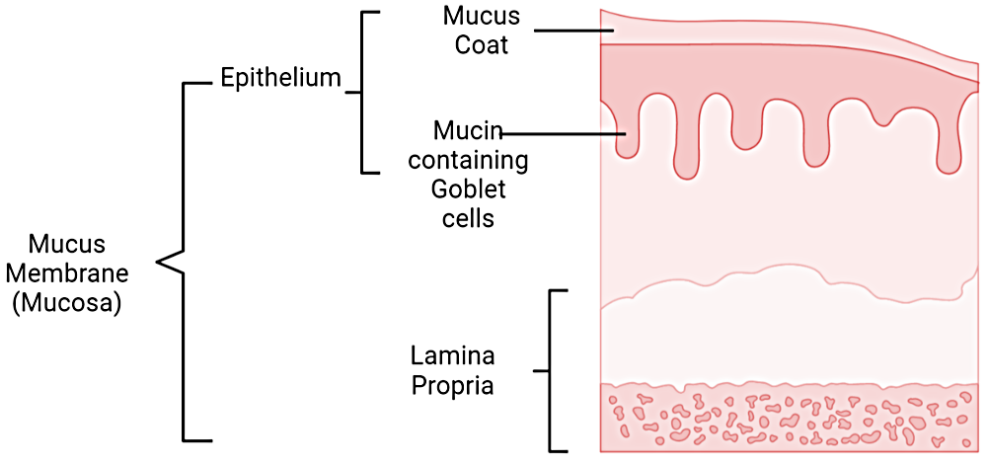

Figure 1. The cellular structure of gastrointestinal mucosa.

The mucoadhesion phenomenon has not been figured out completely yet but a proposed theoretical consideration to understand the mechanism is discussed here. The mechanism has been bifurcated into two stages: the contact stage, and the consolidation stage. In the contact stage, contact is established between the mucoadhesive polymer and mucous membrane. Wetting of the mucoadhesive polymer occurs and both surfaces come in contact to establish a bond between them. In the consolidation stage, interactions, and bond formation take place between the two surfaces. The physiological bonds formed between the mucous membrane and mucoadhesive polymer are of different strengths, such as weaker bonds (hydrogen and van der Waals bond) and stronger bonds (covalent bond). The fundamental mechanism of adhesion is explained in various perspectives named theories of adhesion (Bansil & Turner, 2006).

THEORIES OF ADHESION

Mucoadhesion is a complex phenomenon and different theories have been proposed to explain the mechanism. These theories, summarized in Table 1, are useful for understanding the adhesion of mucoadhesive polymer with biological membranes.

Among various theories, adsorption theory has been widely explored, as it explains the chemical bonding between mucoadhesive polymer and mucin. On the other hand, electron theory delineates the role of charge in adhesion. Though one may anticipate that each of these theories would be applied separately, instead all theories are involved throughout the mucoadhesion process (Chatterjee et al., 2017).

Table 1. Theories of mucoadhesion.

Theory	Comments	Ref.
Diffusion Theory	– It describes the diffusion of polymer toward the adhesive surface – The diffusion process is governed by its concentration gradient at the applied surface – The penetration of the mucoadhesive polymer depends on the diffusion coefficient	(Chatterjee et al., 2017; Bassi da Silva et al., 2017)
Electronic Theory	– It describes the transfer of electrons across the applied surface – Adhesion occurs due to differences in electronic distribution and attractive forces result in the formation of an electric double layer at the interface	(Leite et al., 2012; Dodou et al., 2005)
Adsorption Theory	– It suggests that forces (van der Waals forces, hydrogen bond, ionic bond, and covalent bond) at the surface are responsible for the adhesive contact developed between a mucoadhesive polymer and the mucosa	(Shaikh et al., 2011; Zhu et al., 2018)
Wetting Theory	– This applies to liquid systems – It explains the ability of the liquid system to spread on the applied surface	(Zhu et al., 2018; Peykova et al., 2012)
Fracture Theory	– Describes the force required to separate the two layers after adhesion is completed – Used to measure the adhesion between rigid or semi-rigid mucoadhesive system	(Singh et al., 2017; Kumar et al., 2014)

MUCOADHESIVE POLYMERS

The mucoadhesive property of a dosage form is achieved by the polymers used in the dosage form. The polymers that have hydrophilic properties have the potential to adhere to the mucous membrane and are the most suitable ones for the preparation of mucoadhesive formulations. The structural properties of mucoadhesive polymers significantly affect mucoadhesion. The presence of hydrophilic groups such as hydroxyl, amino, sulfate, and carboxyl groups favors mucoadhesion, but excessive hydration decreases mucoadhesion. For maximum mucoadhesion, the polymer should have intense cationic or anionic charges, high molecular weight should, possess long-chain flexibility, and should have good spreadability onto mucus (Mansuri et al., 2016).

Characteristics of an ideal mucoadhesive polymer (Mansuri et al., 2016; Khutoryanskiy et al., 2011)

i. The mucoadhesive polymer should adhere to the desired surface and preferably have some site-specificity.

ii. It should be compatible with the drug and have no interference with the release of the drug.

iii. It must be non-irritant to the mucus membrane.

iv. Its by-products must be non-toxic and easily absorbed through the mucosal membrane.

It must be in a stable state during storage and for the duration of the product's shelf-life.

Mucoadhesive polymers can be classified according to their origin, chemical nature, and mechanism of adhesion, which are mentioned in Table 2. As demonstrated in Figure 2, most polymers have carboxylic acid, which tends to form H-bonds with the mucin structure. Some polymers, when coming in contact with biological fluid, get ionized due to changes in pH. A negative charge in both polymer and mucin creates repulsion, and this repulsive force uncoils the polymer. The uncoiling leads to entanglement and interaction of the polymer with the mucin complex structure. Examples of such H-bonding polymers are polycarbophil and carbomer from acrylate derivatives, carboxymethylcellulose (CMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) from cellulose derivatives. Alginate, pectin, and hyaluronic acid also form H-bonding with hydroxyl groups of mucin. Thiolated polymer derivatives such as thiolated polycarbophil and thiolated chitosan form disulfide bonds with cysteine moiety present in mucin structure. Chitosan, a cationic polymer, establishes electrostatic interaction with mucin. The positively charged amines of chitosan interact with negatively charged sialic acid of mucin and form adhesion. The extent of adhesion depends on the availability of sialic acid (Pathak & Malviya, 2020; Chatterjee et al., 2017).

Table 2. Classification of mucoadhesive polymers.

Class of Polymer	Polymer	Description	Mechanism of adhesion	Ref.
Natural Polymer	Chitosan	It is a naturally occurring polysaccharide derived from chitin. It is widely used in MDDS for its mucoadhesive properties.	The cationic charge over chitosan forms strong electrostatic interaction with negatively charged mucus components along with epithelial surfaces.	(Sogias et al.2008)
	Alginate	It is obtained from brown seaweed. It acts by forming a gel-like matrix with mucosa. Moreover, it provides sustained drug release.	Alginate provides better mucoadhesion due to its lower surface tension than mucin, resulting in better adhesion.	(Kesavan et al.2010)
	Hyaluronic Acid (HA)	It is a glycosaminoglycan found in the body and offers biocompatibility and good mucoadhesive properties.	Thiolation of HA provides excellent mucoadhesion by the disulfide bonds between the sulfhydryl moieties of the polymer and cysteine-rich residues of the mucus.	(Griesser et al.2018)
Synthetic Polymers	Polyacrylic acid (PAA)	PAA is the common synthetic polymer MDDS uses for its bioadhesion properties and pH responsiveness behavior.	The pendant carboxylic acid of PAA forms a hydrogen bond with the mucosal tissue and offers better mucoadhesion.	(Vakili et al.2021)
	Polyethylene glycol (PEG)	It is used as a hydrophilic polymer for enhancing the mucoadhesive property of other polymers. It also increases the residence time and drug diffusion in mucosal tissues.	PEG can strongly act as a mucoadhesive polymer by interpenetrating polymer effects between the PEG chain and the mucus mesh or via H-bonding between ether oxygen atom in PEG and sugars on glycosylated mucins.	(Wang et al.2008)
	Polyvinyl alcohol (PVA)	PVA is a synthetic polymer, modified to exhibit mucoadhesive properties.	PVA is a non-ionic polymer that binds to mucus via hydrogen bonds and chain enlargement.	(Ikeuchi-Takahashi et al.2017)
Semi-synthetic polymers	Hydroxypropyl methylcellulose (HPMC)	HPMC is a cellulose derivate used for its mucoadhesive properties and offers controlled drug release.	The presence of large number of hydroxyl groups on the molecular structure of HMPC results in water absorption and swelling because of the hydrophilic nature that results in h-bonding between the polymer chain and glycoprotein of mucin.	(Zhang et al.2000)
	Carbomer	Carbomers are the polymers that form a gel in an aqueous environment. And offers good mucoadhesive properties and is used in topical drug delivery systems.	The mucoadhesion is due to the formation of hydrogen bonds between the carbomer and glycoprotein of mucus.	(Singla et al.2000)
Thiolated polymers	Thiolated chitosan	The thiolation of chitosan (addition of -SH group) results in better mucoadhesive properties than simple chitosan.	Addition of thiol (-SH) group into chitosan forms thiolated chitosan, which exhibits better mucoadhesion by thiol-disulfide exchange reactions with mucus components	(Wibel et al., 2021)

Some polysaccharide-based polymers, such as xyloglucan, xanthan gum, gellan gum, carrageenan, guar gum, polygalacturonic acid, and pullulan, also have mucoadhesive properties. With mucin, these polymers form H-bonds due to the presence of hydroxy groups. In addition to this, xanthan gum's intricate structure gets physically entangled with the mucin to offer better mucoadhesion (Ludwig, 2005).

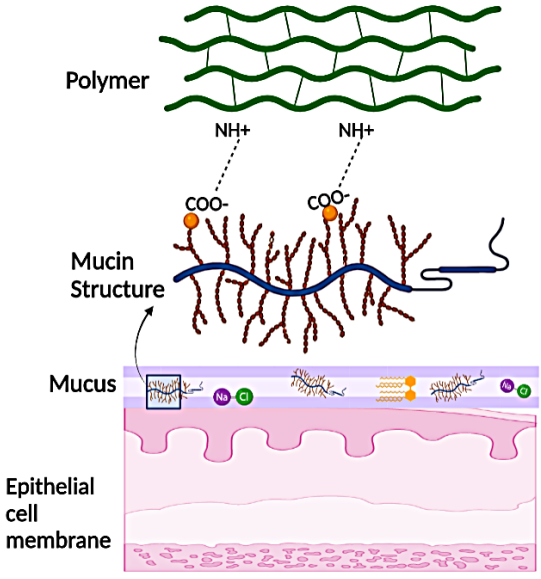

Figure 2. Mucoadhesive polymeric interaction with mucin structure.

MUCOADHESIVE DRUG DELIVERY SYSTEM FOR PEDIATRIC PATIENTS

The pediatric population includes individuals from infants (after birth) to adolescents (16 years old). As per FDA 1998 guidelines, the pediatric population is divided into sub-populations according to their developments which include physical, cognitive, and psychosocial factors. The sub-populations are neonates, infants, developing children, and adolescents.

The neonate (birth to 1 month) is not a uniformly distributed population of patients. They again differ in terms of the gestation period and weight. Their hepatic and renal clearance systems are immature and rapidly evolving, while the blood-brain barrier is not yet entirely formed. As a result, there is a risk of toxicity (e.g., chloramphenicol - grey baby syndrome), therefore doses may need to be modified throughout the first few weeks of life.

Infants include the pediatric population from 1 month to 2 years. At this stage, CNS starts maturing, the immune system is developing, the entire body is growing, and the hepatic and renal clearance routes are rapidly maturing. The reliability of oral absorption also improves.

The developing children population includes children from ages 2 to 12 years. This stage is vital for the development of the psychomotor system. Skeletal development, weight increase, school attendance, and academic success are all things that doctors may take into account when prescribing drugs. Girls experience puberty at an earlier age, with some cases seeing atypical beginning as early as nine years old.

Adolescents (12 to 16-18 years) is the time of accelerated development and continuing neurocognitive expansion in children. Medicinal items may interrupt the functions of estrogen and testosterone (sex hormones) and obstruct development during this era of sexual maturation. The pubertal growth spurt can be severely affected by drugs and conditions that slow or speed up puberty, altering the advancement pattern and potentially changing eventual height. Increasing cognitive and emotional changes may have an impact on clinical trial results (Freeks et al., 2019).

Pharmacokinetics

The majority of medications provided to pediatric patients are ingested orally. Drug physiochemical and physiological properties, digestive fluid content and volume, transit time, gut microbiota, drug-metabolizing enzymes, and drug transporters, are some of the factors that collectively affect the absorption of food, drug, and drug formulations (Nicolas et al., 2017). The pH of the stomach is nearly neutral during birth and drops to approximately within 48 hours of birth, which then returns to neutral again during the next 24 hours and remains

neutral for the next 10 days. Later, the gastric pH gradually drops until it reaches adult levels around the age of two (Debotton & Dahan, 2014). This higher pH in neonates may preserve acid-labile medicines and may explain the greater bioavailability of beta-lactam antibiotics at least in part (Huang & High, 1953). Gastric emptying and intestinal motility also impact the rate and volume of intestinal drug absorption. Below the age of 8 months, stomach emptying is delayed due to underdeveloped motility neuro regulation (Wollmer, 2021). From birth to older children, the volume of distribution is reduced, and clearance increases exponentially (Anderson, Woollard & Holford, 2000).

Drug clearance is significantly faster in children than adults and adolescents, while neonates have a lower clearance rate (Lundeberg & Roelofse, 2011). However, clearance rate can vary according to the conditions and the type of drug. Obsessive-compulsive disorder (OCD) and depressive disorders have been identified as prevalent psychiatric diseases in adolescents. Serotonin reuptake inhibitors appear to be safe and helpful in treating of depression and OCD in children and adolescents. Fluoxetine is one of the most widely investigated serotonin reuptake inhibitors in juvenile and adult populations. Because fluoxetine inhibits CYP2D6, clearance reduces, half-life increases, and serum concentrations are higher after successive doses than after a single dose (Wilens et al., 2002).

Drug metabolism is another crucial factor in determining drug exposure. In general, drug metabolism that is underdeveloped at birth gradually improves over the first year of life and then reaches adult levels. Drug-drug interactions can occur when drug-metabolizing enzymes are inhibited or activated, leading to higher or lower drug levels (Hines, 2013).

Challenges

A pediatric population is a diverse group of people, with a wide range of sizes and ages. Variability in determining doses for drugs with a narrow therapeutic index is especially concerning when it comes to young patients. A prescribed drug for oral administration might cause gastrointestinal drug degradation. In contrast, oral transmucosal drug delivery will avoid enterohepatic circulation, rapid acid degradation, and partial first-pass effects of hepatic metabolism. Various drug delivery challenges for pediatrics are represented in Figure 3 (Venkateswarlu, Naik & Chandrasekhar, 2016).

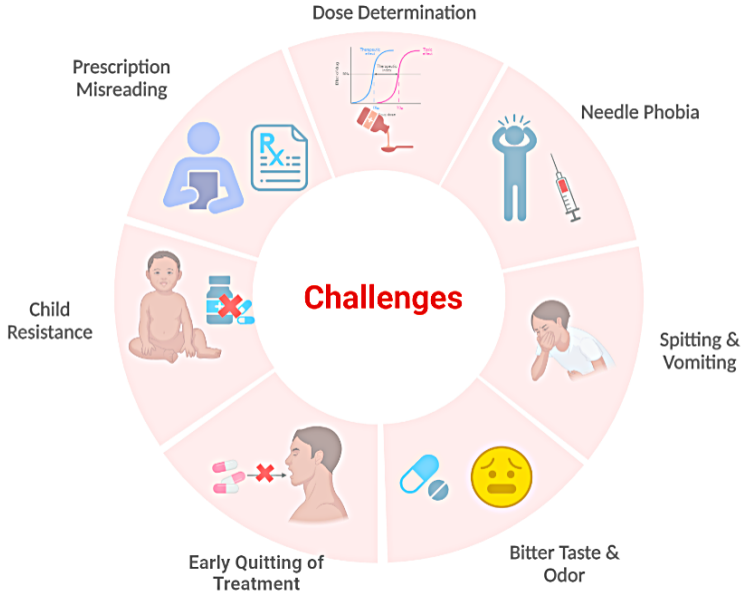

Figure 3. Dealing with pediatric patients for drug administration encounters several challenges.

Bitter taste, fear of injection and associated pain, and odor of some active substances lead to considerable patient non-compliance. A bitter taste and an unpleasant odour during dispensing can cause spitting and vomiting, making it difficult to administer the required dose. Forgetting, quitting treatment because symptoms have resolved, misinterpretation of instructions, child resistance, and apparent ineffectiveness or harmful effects of the drugs have all been reported as reasons for not being able to deliver medication as prescribed (Matsui, 2007; Malkawi et al., 2022; Singh et al., 2021).

MDDS Formulation Approaches

MDDS formulation approaches can play an important role in obtaining the required therapeutic activity. Polymers possess a crucial part in the entrapment of drugs and interaction with mucus constituents such as mucin. The complex structure of polymers makes them a suitable candidate that reduces the release rate of drugs to attain sustained release. The effect of the complex structure of polymers has been encountered by some authors while studying the stability characteristics of buccal films (Khan & Boateng, 2018). Combining different polymers can sometimes result in a synergistic effect in the mucoadhesion process and a change in the drug release profile. This improved polymer function is obtained by the interaction of charged ions within the polymers and with mucin structure (Trastullo, 2016; Sneha, Hari & Devi, 2018).

Administration of drugs through the buccal route possesses several advantages for pediatric populations as the drug bypasses first-pass metabolism and gets absorbed directly into the systemic circulation. Additionally, the films have a patient compliance factor, which increases their acceptability (Boateng, 2017). Fast-dissolving films, developed in the 1970s, are a better alternative to conventional dosage forms for pediatric and geriatric patients as they offer various advantages such as fast disintegration, rapid release, direct drug delivery to the systemic circulation, and rapid onset of action (Panda, Dey & Rao, 2012).

Several attempts have been made to formulate buccal films for conditions such as oral diseases, gastric problems, cancer, HIV, etc. In one of the research projects cetylpyridinium chloride, buccal films were developed for oral-related problems (gingivitis, periodontitis, aphthous ulcers, and dental caries) (Abouhussein et al., 2020), whereas in another study propranolol bioadhesive films were developed for cardiovascular disorders (Mohamad et al., 2020). Furthermore, drugs such as omeprazole (Khan & Boateng, 2018), lidocaine (Leopold et al., 2002), cinnamon (Gandhi et al., 2020), ondansetron (Trastullo et al., 2016), and lamivudine (Sneha, Hari & Devi, 2018) were also employed for formulating mucoadhesive films/ patch which provides local as well as direct systemic delivery. A summary of these formulations has been presented in Table 3.

Table 3. Examples of pediatric mucoadhesive formulations.

Drug	Disease	Formulation	Inference	Ref.
Cetylpyridinium chloride	Gingivitis, Periodontitis, Aphthous ulcers, and Dental caries	Buccal films	Chitosan blended with Polyvinyl alcohol (PVA) films showed good antibacterial activity and high average tensile strength compared to homo-polymeric films.	(Abouhussein et al., 2020)
Propranolol hydrochloride	Heart-related diseases such as arrhythmias, high blood pressure, Infantile haemangioma, etc.	Buccoadhesive films	The presence of glycerine accelerates the mucoadhesion process, as it possesses a hydroxyl group for H-bond formation. The carpool-based film showed increased bioavailability by 1.9 times as compared to the commercialized oral tablet.	(Mohamad et al., 2020)
Omeprazole	Ulcer and GERD	Buccal films	A combination of metolose and β-cyclodextrins (CD) has an excess of hydroxyl group, which reduces its interaction with a mucus membrane.	(Khan & Boateng, 2018)
Lidocaine	Mild topical anesthesia	Mucoadhesive patch	Lidocaine-containing DentiPatch has mucoadhesive strength that lasts up to 45 minutes. The patch can be preferred over gel as it lasts longer and is safer for pediatric use.	(Leopold et al., 2002)
Cinnamon	Dental caries	Mucoadhesive patch	Regarding anti-*Streptococcus* mutant action, both cinnamon and probiotic patches were equivalent in terms of inhibition and responsible for the sustained release of the drug.	(Gandhi et al., 2020)
Ondansetron hydrochloride	Nausea and vomiting caused by cytotoxic chemotherapy or radiotherapy and postoperatively.	Buccal films	Adding chitosan and gelatin polymer in the buccal film increases drug permeation. HPMC with sodium hyaluronate leads to high viscous gelled state film, resulting in sustained release of ondansetron.	(Trastullo et al., 2016)
Lamivudine	Chronic HIV	Buccal film	Polymer combination (Sodium carboxymethylcellulose and PVP) establishes sustained release profile, and reduces the rapid dissolution of hydrophilic lamivudine, leading to an increase in its bioavailability.	(Sneha, Hari & Devi, 2018)

MUCOADHESIVE DRUG DELIVERY SYSTEM FOR GERIATRIC PATIENTS

The geriatric population includes elderly individuals aged 65 years and above. They are more susceptible to disease syndromes and accidents because they have lower regeneration capacities than younger ones. Gerontologists have established subgroups to emphasize the variability of old age (Schwartz et al., 2019). The division includes the youngest old people (65 to 74 years), middle-aged people (75 to 84 years), and oldest-old people (over 85 years).

Aging causes significant modifications in organ functionality, especially in the liver and kidney. According to research, the youngest old people face a 24 to 47% drop in liver blood flow, whereas in aged people, this drop is linked to a considerable decrease in systemic clearance of drugs with a high extraction ratio, such as imipramine, lidocaine, and verapamil (Zizza, Ellison & Wernette, 2009; Hayes, Langman & Short, 1975). In middle-aged people, glomeruli and kidney mass drop by 20-30%, and although renal function does not diminish in about

one-third of patients, fewer groups demonstrate an age-related rise in creatinine clearance (Klotz, 2009). But it is not always necessary that all older patients have compromised organ function. A study claimed that physically weak older persons do not necessarily have reduced drug clearance and that adults over 85 can still metabolize CYP3A4 substrates (McLachlan, 2018).

Pharmacokinetics

As people grow older, the drug pharmacokinetics in their bodies alters. Older individuals are more susceptible to a drug's adverse effects and face trouble swallowing solid dosage forms. Some physiological changes have been reported in the gastrointestinal (GI) tract and liver function and these changes in geriatric patients are the differentiating factors from normal individuals.

The apparent volume of distribution (V_d) of polar drugs (e.g., lithium, digoxin) decreases with an increase in body fat. A decrease in total body water concentration leads to an increase in the concentration of lipophilic drugs (e.g., diazepam), which further alters the plasma protein binding and limits therapeutic activity. It has been observed in some individuals that the concentration of serum albumin often decreases with aging (Mian et al., 2018; Krnieli, 2013).

Most drug metabolism occurs in the liver. Despite no remarkable changes in the liver function of geriatrics, in some individuals, it has been observed that the activity of a liver enzyme involved in drug metabolism is lowered. This results in the extended half-life of some drugs. Moreover, the aging-related parenchymal cell loss and decreased hepatic blood flow impact liver's capacity to metabolize drugs. These elements worsen elderly patients' ability to eliminate drugs from the body and lead to an increase in undesirable side effects. The kidney is the primary organ involved in drug elimination; aging-related changes in pharmacokinetics are mostly caused by decreased renal function, which is the most important factor in the emergence of harmful drug responses in older people (Mangoni & Jackson, 2004).

Challenges

Geriatric patients usually have a long and complicated medical history. Healthcare providers must become familiar with general age-related changes and the specific clinical characteristics that can make diagnosis more difficult. When dealing with patients who have a complex medical history, some challenges include polypharmacy, delirium, dementia, and depression, as well as a higher risk of pathologies and chronic illnesses (Maher, 2021), represented in Figure 4. Difficulty in swallowing in geriatrics poses a dilemma for medication management (Laroche, 2021). Even if it has been swallowed, other complications such as dosage form administration error, absence of consent to administer, therapy ineffectiveness, side effects, fear of adverse effects, and cross contamination can be encountered and challenging to treat the geriatric patient (Shariff, 2020).

Approaches

Many drug delivery systems are delivered by oral route, which has numerous advantages over traditional ones. These advantages include enhanced bioavailability due to bypassing the primary metabolism and avoidance of enzymatic or acid-related degradation in the gastrointestinal tract, faster onset of action, and considerably improved patient compliance. Oral transmucosal formulations of several pharmacological categories of drugs, such as analgesics (e.g., fentanyl), cardiovascular drugs (e.g., captopril and nitroglycerin), and sedatives, have been developed for geriatric patients (Ahmad et al., 2014).

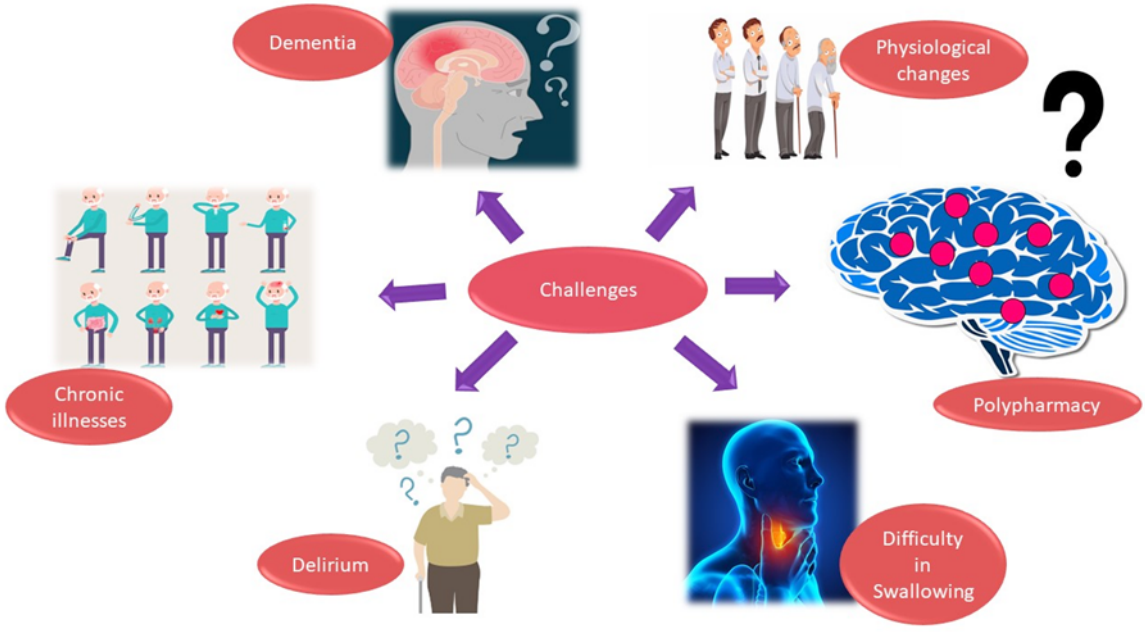

Figure 4. Challenges faced by geriatric patients while drug administration

Because of the increased blood flow rate and permeability of the buccal mucosa, oral thin films provide rapid absorption and bioavailability and are suitable for treating elderly patients. Several mucoadhesive delivery systems have been formulated using these approaches for geriatric patients (Alaei& Omidian, 2021; Yir-Erong et al., 2019; Boeteng, 2017). Controlled and sustained-release formulations are recommended to reduce the dosing frequency in geriatric patients.

As discussed above for, pediatric patients' formulations such as buccal films and fast-dissolving films loaded with drugs or nanoparticles are beneficial for geriatric patients. As both the categories need special care, the formulation approach is similar but differs in a few aspects such as disease conditions (Yir-Erong et al., 2019). In a study, a propranolol mucoadhesive buccal film was prepared and indicated for cardiac-related diseases such as hypertension, arrhythmias, and angina pectoris (Jovanović et al., 2021). In another study, aripiprazole nanocrystals were incorporated into the buccal film, which was further examined for indication in schizophrenic patients (Al-Dhubiab et al., 2017). Furthermore, drugs such as loratadine (Kumria, Nair & Al-Dhubiab, 2014), ondansetron (Kumria et al., 2013), meloxicam (Gardouh et al., 2013), azilsartan medoxomil (Khodke, Yadav, & Sawale, 2018), selegiline (Sridhar et al., 2018), nifedipine (Alshaya et al., 2022), and digoxin (Rodrigues et al., 2021) were used to formulate mucoadhesive films/ gel for various disease condition. A summary of these formulations has been mentioned in Table 4.

Table 4. Examples of geriatric mucoadhesive formulations.

Drug	Disease	Formulation	Interference	Ref.
Propranolol hydrochloride	Cardiovascular diseases such as hypertension, arrhythmias, angina pectoris	Mucoadhesive Gelatin Buccal film	Type B gelatin has good mucoadhesive properties and the film showed better solubility and bioavailability.	(Jovanović et al., 2021)
Aripiprazole	Schizophrenia	Nanocrystal-suffused buccoadhesive film	Aripiprazole nanocrystal incorporated in buccal films. The film is non-tacky, smooth, non-irritant, and has good mucoadhesion while exhibiting high drug release and increased permeation.	(Al-Dhubiab et al., 2017)
Loratidine	Allergic rhinitis	Mucoadhesive film	Mucoadhesive properties of films were significantly improved with an increase in HPMC and Eudragit. The film is non-irritant, nontoxic, and gives prolonged protection to people allergic to seasonal allergens.	(Kumria, Nair & Al-Dhubiab, 2014)
Ondansetron hydrochloride	Nausea and vomiting	Buccoadhesive film	Film formed using HPMC and Eudragit polymer exhibited better mucoadhesion, drug release rate, and increased bioavailability.	(Kumria et al., 2013)
Meloxicam	Joint disorder	Buccal film	Meloxicam buccal films formulated using polyvinyl alcohol and propylene glycol increase the mucoadhesive properties; the film showed optimum drug content drug release.	(Gardouh et al., 2013)
Azilsartan medoxomil	Stroke, Heart attack	Fast-dissolving oral strip	Azilsartan Medoxomil oral films displayed 98.5% drug release from the film within 3.4 minutes.	(Khodke, Yadav, & Sawale, 2018)
Selegiline hydrochloride	Anti-Parkinson's agent	Mucoadhesive thermosensitive nasal gel	The Selegiline thermosensitive nasal (SNT)-gel made with a combination of poloxamer and Chitosan combination shows great mucoadhesion. The comparative study showed SNT-gel has a better brain targeting profile than conventional in Parkinson's disease.	(Sridhar et al., 2018)
Nifedipine and Atorvastatin	Hypertension and hyperlipidemia	Nanofibers loaded in buccal drug delivery system.	Nifedipine and atorvastatin calcium loaded in nanofibers were developed using an electrospun nanofiber system and showed significant mucoadhesion, improved bioavailability, and provides a prolonged drug release rate. The complete drug release was achieved after 2 hours.	(Alshaya et al., 2022)
Digoxin	Heart Failure	Oromucosal Alginate film fused With Zain Nanoparticle	Digoxin zein nanoparticles incorporated in sodium alginate buccal film show a great mucoadhesive property. The formulation has appropriated tensile strength and is compatible with buccal mucosa.	(Rodrigues et al., 2021)

PATENTS

Giovinazzo *et al.* featured an apomorphine sublingual film for the treatment of Parkinson's disease. The film is placed in the sublingual region for immediate drug release and rapid action (Giovinazzo et al., 2016). Cyclosporine nanoparticle for the treatment of excessive immunological activity has been formulated using amphiphilic copolymer, composed of hydrophilic (dextran) and hydrophobic (polylactide) parts (Hsing-Wen Sung et al., 2009).

Giuseppe Bottoni et al. featured a mucoadhesive controlled-release aqueous solution containing glycerol and a naturally pure polymer with a xyloglucan structure. The formulation was applied to mucous membranes such as the nasal, oral, and vaginal mucous membranes as moisturizing and softening agents (Hsiao & Cacace, 1988).

Another study has reported the formulation of a drug-carrier composition that consists of a mucoadhesive polymer and a thermoresponsive polymer for use in delivering pharmaceutical ingredients or biologically active substances. This formulation is used in the topical administration of biologically active substances and is helpful in photodynamic diagnosis or therapy (Tsui-Min, 2007). Some other examples of mucoadhesive formulations that have been patented are presented in Table 5.

Table 5. List of some patented mucoadhesive drug delivery systems.

Sr. No.	Patent no.	Patent title	Dosage forms/ Carriers	Active Pharmaceutical Ingredient	Remark	Ref.
1.	US 9326981 B2	Sublingual Apomorphine	Sublingual Film	Apomorphine	Apomorphine sublingual film for the treating Parkinson's disease, sexual dysfunction, and depressive disorders.	(Giovinazzo et al., 2016)
2.	US 7604795 B1	Nanoparticles for protein drug delivery	Nanoparticle	Polyglutamic acid	Developed a nanoparticle system and method for protein/peptide drug preparation using polyglutamic acid and chitosan. The nanoparticle system improved permeability and transport across tight junction cells.	(Hsing-Wen Sung et al., 2009)
3.	US 4755386 A	Buccal formulation	Tablet	Estradiol	Establish different compositions for the buccal formulation of poorly bioavailable drugs. A buccal tablet formulation having specified excipient concentration, which includes 2 to 10% w/w of carbomer 934 P (as polymeric adhesive), 3 to 6% w/w of crospovidone (as disintegrants), 2 to 50 mg of estradiol (as an active pharmaceutical ingredient), and other useful ingredients.	(Hsiao & Cacace, 1988)
4.	US 6197346 B1	Bioadhesive microspheres and their use as drug delivery systems	Micro-sphere	Sulfasalazine	Mucoadhesive microspheres were formulated using different mucoadhesive polymers. To enhance the bioadhesive force, various polymers of different classes were combined and evaluated. Betamethasone, barium sulfate, and sulfasalazine are used as active ingredients. For the oral delivery of several medications in the treatment of intestinal problems, these bioadhesives were suggested.	(Mathiowitz, Chickering, & Jacob, 2001)
5.	US 20060228427 A1	Solid mucoadhesive composition	Tablet	*Sambucus nigra, Centella asiatica*	The mucoadhesive tablets consist of *Sambucus nigra, Echinacea purpurea,* and *Centella asiatica* (as an active ingredient) for treating mucosal lesions. The formulation composition also includes carbopol 974P as an adhesive polymer (10–20% w/w), polyvinyl pyrrolidone (10–20% w/w), and lactose as bulking agents.	(Levine & Satter, 2006)
6.	US 13695113	Pharmaceutical powder compositions	Powder	Benzodiazepine	The composition of the mucoadhesive characteristic powder was established. It contains polyethylene glycol as a solubilizing agent (0.1 to 20% w/w), polyplasdone XL 10 as disintegrants (0.1 to 10% w/w), and other ingredients. The powder was used in central nervous system drug delivery to treat or prevent anxiety, epilepsy, insomnia, alcohol dependence, muscular disorders, and mania.	(Coghill & Armstrong, 2013)
7.	US 9878000 B2	Mucoadhesive nanoparticle composition comprising immunosuppress-ant and methods of use thereof	Nanoparticle	Cyclosporine	A mucoadhesive nanoparticle delivery system for the treatment of inflammatory disease made of amphiphilic copolymer (consisting of a hydrophobic polylactide part and a hydrophilic dextran part) that was used to deliver the immunosuppressive drug. The nanoparticle enhanced retention time and target delivery.	(XiaofeiGu, Liu & Jones, 2018)
8.	US 20120088726 A1	Mucoadhesive xyloglucan-containing formulations useful in medical devices and pharmaceutical formulations	Aqueous solution	Diclofenac sodium	A mucoadhesive controlled drug release formulation comprised of a natural polymer with a Xyloglucan structure, Glycerol, and a therapeutically active agent such as Diclofenac was formulated. The mucoadhesive solution was effective when applied to the oral, nasal, and vaginal mucous membranes as a moisturizing and softening agent.	Bottoni et al., 2012)

9.	US 20070281007 A1	Mucoadhesive oral formulations of high permeability, high solubility drugs	Nano-particle	Metformin, Ranitidine (BCS I)	A mucoadhesive polymeric coating material was developed for oral formulations to increase permeation of BCS class 1 drugs (gabapentin, valacyclovir, ranitidine, and metformin). The mucoadhesive polymers used were Poly (Adipic) and Poly (Fumaricco-sebacic) anhydride. The formulations had enhanced permeation due to facilitative diffusion, showed target delivery, and increased bioavailability.	(Jacob et al., 2007)
10.	US 20070231352 A1	Mucoadhesive thermos-responsive medicament carrier composition	Gel	5-Amino-levulinic acid	A thermoresponsive mucoadhesive drug carrier was prepared using carbopol 941P and 5-aminolevulinic acid, for topical application. The formulation had increased adherence, yet it is convenient to remove after a certain period. The gel is employed in photodynamic diagnosis since it has better effectiveness and fewer adverse effects.	(Tsui-Min, 2007)
11.	WO 2018/113916 Al	A mucoadhesive oromucosal formulation comprising a nicotine complex	Oromuco-sal formu-lation	Nicotine	A nicotine complex oromucoadhesive solution system comprising of nicotine ionic complex with one mucoadhesive water-soluble anionic polymer. It increased residence and bioavailability of drug after oral administration. They minimized side effects such as irritation and cavities in the throat and oral region.	(Nielsen, 2018)

CLINICAL STUDIES

To prevent and treat oral mucositis, dos Santos Filho EX et al. conducted a randomized phase I clinical trial on a mucoadhesive formulation including curcuminoids (Zingiberaceae) and *Bidens pilosa* Linn (Asteraceae) extract. The safety of using the mucoadhesive formulation for the prevention and treatment of chemoradiotherapy-induced oral mucositis (OM) was established (dos et al., 2018).

A comparison of the efficacy of a commercial brand and mucoadhesive formulations containing 0.1% xylometazoline was conducted by Tzachev et al. The clinical study design was a cross-over double-blinded study, performed on twenty subjects possessing perennial allergic rhinitis; all the side effects and therapeutic effects were monitored carefully. The results showed that using test mucosal solution exerts fewer side effects than the commercial product (Tzachev et al., 2002).

A study was conducted by Iacovelli et al. on the efficacy of a new product named Aqualief® containing carnosine and karkadé as main ingredients against xerostomia occurring in patients dealing with neck and head cancer. The randomized double-blinded crossover study conducted on thirty patient subjects who required the treatment for xerostomia for over eight days revealed that patients taking Aqualief® showed a pH drop in gastric fluid with no serious adverse effects. Although, there is a need to investigate more adverse effects with a more significant number of patients (Iacovelli et al., 2021).

Francois et al. formulated a cyclodextrin-based vaginal cream of itraconazole, and a clinical trial was performed on eight healthy volunteers with 2% itraconazole vaginal cream. Five grams of cream administered to the volunteer demonstrated the tolerability of the cyclodextrin-based vaginal cream. Furthermore, the efficacy of the vaginal creams in the phase III clinical trial, with 170 patients, showed that the formulation is non-toxic and well tolerated (Francois et al., 2003).

In various studies, it has been found that cinnamon bark oil is effective as an antimicrobial agent. A comparative study was conducted between two different mucoadhesive patches, one containing cinnamon bark oil and the other with probiotic blend [*Lactobacillus rhamnosus* (TSP-Lrh1) and *Lactobacillus plantarum* (TSP-Lp1)] against salivary

Streptococcus mutans in active children. The double-blinded placebo-controlled study of 60 patients divided into three groups: cinnamon oil group, probiotic blend group, and controlled (placebo) group, each containing 20 patients, revealed that both cinnamon oil and probiotic blend containing mucoadhesive patches were effective in curing the patients (Gandhi et al., 2020).

In another study, six male patients participated in testing the potential of lyophilized nasal insert used in delivering large molecular weight insulin compared with conventional nasal spray. It was found that the prepared nasal formulation does not have any role in enhancing the absorption of insulin rather, it extends the residence time (McInnes et al., 2007).

Oral mucositis is extensively observed among patients who are undergoing chemoradiation for the treatment of head and neck cancer. Several attempts have been made to at least reduce the adverse effects of chemotherapy. Giralt and his team have made an attempt to address oral mucositis through a randomized phase two trial of mucoadhesive gel containing clonidine. Patients undergoing radiation for head and neck cancer were given mucoadhesive buccal tablets that were either clonidine-containing or a placebo. A total of 183 patients were evaluated, and it was found that there was no significant difference between the clonidine-containing and placebo groups. Despite this, the researchers suggested that clonidine may have some effect on oral mucositis patients and recommended further investigation (Giralt et al., 2020). Another attempt has been made by Lozano and co-workers with melatonin-containing mucoadhesive oral gel to prevent of oral mucositis. A total of 84 patients were taken to perform a double-blinded randomized phase 2 trial with a placebo as a control. The study concluded that in comparison with the placebo treatment, the 3% melatonin mucoadhesive gel group had a significant reduction in oral mucositis and shortened the duration of oral mucositis (Lozano et al., 2021).

Tyring et al. conducted a phase three double-blinded randomized multi-center trial, placebo-controlled study on the mucoadhesive tablet of acyclovir for treating of recurrent herpes labialis. A total of 775 patients were taken, from which 378 were given acyclovir buccal tablets and 397 were given a placebo. The results showed that the recurrence of herpes labialis was reduced and delayed after only a single administration of the acyclovir tablet (Tyring et al., 2014).

MUCOADHESIVE FORMULATION

The mucoadhesive drug delivery system involves various dosage forms that provide localized and sustained drug release at mucosal surfaces. The most common drug delivery systems used in mucoadhesive drug delivery are discussed hereunder in Table 6.

Table 6. Various mucoadhesive drug delivery dosage forms.

Sr. No.	Dosage form	Characteristics	Advantages	Disadvantages
1	Films and strips	Mucoadhesive films and strips are applied to the mucosal surfaces and adhere to them. They deliver drugs directly to the target site, such as buccal or sublingual mucosa. Flims and strips are easy to apply and offer controlled rug release.	• Easy application and removal • Discreet and comfortable to wear • Improved drug absorption due to large surface area	• Limited drug loading capacity • Variable drug release due to changes in environmental conditions • Formulation is challenging
2	Gels and pastes	Mucoadhesive gel and pastes are viscous formulations topically applied to mucosal surfaces.	• Ease of application and spreading over mucosal surface • High drug loading capacity • Offer sustained drug release	• Limited residence time • Capable of leaking from the application site • Can cause discomfort or localized irritation
3	Inserts and Suppositories	Inserts and suppositories are solid or semisolid dosage forms that are inserted inside the body cavity such as the vagina or rectum and adhere to the mucosal surfaces for prolonged drug release.	• Prolonged drug release • Most suitable for localized treatment • Offer sustained therapeutic levels at the target site	• Limited drug retention • Limited drug loading capacity • Insertion may be uncomfortable.
4	Microspheres and Nanoparticles	These are the tiny particles designed to adhere to mucosal surfaces.	• Increased drug residence time at the mucosal surface • Improved drug stability • Offers controlled and sustained drug release	• Challenging to obtain uniform particle size distribution • Potential of particle aggregation and sedimentation • Complex formulation and manufacturing
5	Sprays and Aerosols	Mucoadhesive sprays and aerosols are formulations that can be applied as mist or sprays to mucosal surfaces.	• Easy application and patient compliance • Uniform and controlled drug delivery to the target site • Large surface covered in a single application	• Challenges in obtaining optimal and uniform spray pattern • Limited drug loading capacity • Potential drug loss due to deposition at the non-target site
6	Patches	Mucoadhesive patches are adhesives that are applied to the skin or mucosal surfaces for transdermal and buccal drug delivery.	• Prolonged drug release • Sustained therapeutic levels • Controlled and predictable drug delivery system • Convenient and non-invasive application	• Limited drug loading capacity • The adhesive may be irritant to the skin • Challenge in, maintaining adhesion for extended periods
7	Implants	Mucoadhesive implants are solid devices placed inside the body cavity for sustained drug release. They adhere to the mucosal surface and release the drug gradually.	• Extended drug release for a long time • Localized and targeted drug action • Potential for tunable release rate and tailored therapy	• Risk of infection • Limited flexibility in adjusting drug release once implanted • Invasive implantation procedure

The use of mucoadhesive formulations is not only limited to laboratories but it has been commercialized in the market. Table 7 presents some marketed preparation of mucoadhesive formulations.

Table 7. Marketed products of mucoadhesive formulation.

Sr. No.	Marketed product	Dosage form	Bioadhesive agent	Active ingredient/ Therapeutic class
1.	DentiPatch®	Patch	Xanthum gum	Lidocaine[Analgesic]
2.	Aci-Jel	Gel	Tragacanth (Acacia)	Glacial acetic acid Oxyquinoline sulfate
3.	Advantage 24	Vaginal film	Carbomer	Nonoxynol- 9 [Contraceptive]
4.	Buccastem®	Buccal tablet	Xanthum gum	Prochlorperazine maleate [Antipsychotics]
5.	Bonjela®	Gel	Hypromellose	Cetalkonium chloride, Choline salicylate [Antiulcer]
6.	Corsodyl gel®	Oral paste	HPMC	Chlorhexidine Digluconate [Antimicrobial]
7.	Crinone	Vaginal gel	Carbomer	Progesterone [Hormone]
8.	Gynol-II	Vaginal film	carboxymethylcellulose Polyvinyl pyrrolidone	Nonoxynol- 9[Contraceptive]
9.	Coreg	Buccal patch	HPMC	Carvedilol [Hypertension]

CONCLUSION AND FUTURE PROSPECT

Mucoadhesive drug delivery systems are promising for enhancing the local availability, permeability, and bioavailability of pharmaceutically active ingredients. An ideal mucoadhesive dosage form must be small, flexible, have high drug loading capacity, prolonged retention, and control, and sustained drug release at the site of action. Pharmaceutical scientists work to develop sustainable, economical, multifunctional, compatible, nontoxic, matrix-forming, polymers with an enhanced mucoadhesive polymer having significant mechanical properties for developing customized mucoadhesive drug delivery systems. Absorption, distribution, metabolism, excretion, and toxicology are important pharmacokinetic and pharmacodynamic challenges required to be addressed for developing a mucoadhesive drug delivery system. The establishment of standard-derived methods for determining *in-vitro, in-vivo*, and *ex-vivo* mucoadhesive properties is also important in the formulation and development of MDDS. Clinical trial evidence supports the efficacy and safety of MDDS and must also be accounted for in managing the regulatory approval track of these systems. In recent years tremendous efforts have been placed by regulation, industry, and academia to develop patient-centric pharmaceutical product regulation in the noticeable availability of age-appropriate formulations in the market. The selection of appropriate excipient and formulation design is important for developing a pharmaceutical product to address the manufacturability, patient safety, economy, and end-user requirements. In addition, advancements in drug delivery technology could propose a possible solution to the common challenges associated with pediatric and geriatric patients (e.g., palatability, ease of use, swallowing, respected administration, therapeutic efficacy, etc.) for better patient compliance and therapy. An appropriate balance must be ensured for implementing innovations for developing cost-effective age-appropriate pharmaceutical products addressing the challenges associated with the Pediatric and geriatric patients of therapeutically effective medication.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Conceptualization, Methodology, Investigation, Writing - Original Draft (AR, SSR); Formal Analysis, Data Curation (RR, DR); Writing - Review & Editing, Supervision, Visualization, Project Administration (OAR, IS)

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