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Pharmaceutical Development and Technology

ISSN: 1083-7450 (Print) 1097-9867 (Online) Journal homepage: https://www.tandfonline.com/loi/iphd20

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To cite this article: Amresh Kumar, Pradeep Kumar Naik, Deepak Pradhan, Goutam Ghosh & Goutam Rath (2020): Mucoadhesive Formulations: Innovations, Merits, Drawbacks and Future Outlook, Pharmaceutical Development and Technology, DOI: 10.1080/10837450.2020.1753771

To link to this article: https://doi.org/10.1080/10837450.2020.1753771

Mucoadhesive Formulations: Innovations, Merits, Drawbacks and Future Outlook

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Abstract

Mucosa has now been recognized as a potential site for both local and systemic delivery of therapeutics. Mucoadhesive drug delivery systems with customizable release profiles have recently gained considerable interest among formulation scientists to improve clinical outcomes of drugs. This review summarizes the current development in the processing methods and polymers involved in mucoadhesive drug delivery systems. Mucoadhesive drug delivery systems are suitable for drugs that have a localized effect, undergo extensive pre-systemic metabolism, narrow absorption window and narrow therapeutic index. Polymer characteristics like surface charge, hydrophilic surface groups, wettability, molecular weight, chain flexibility, molecular conformations etc. are critical for assessing the extent of mucoadhesiveness and treatment response. The current review focuses on valuable principles, merits, drawbacks and future outlooks of different mucoadhesive drug delivery systems.

Keywords: Mucoadhesion; Buccal; Sublingual; Ocular; Nasal; Vaginal

1 Introduction

In recent years, mucosal drug delivery has received significant attention for both local and systemic delivery of therapeutics. Mucoadhesive drug delivery systems are associated with better compliance rates because of painless administration, low enzymatic activity, easy accessibility and ability to target local disorders. Unlike oral administration, which presents a harsh environment for therapeutic proteins and peptides, mucosal route offer a relatively mild and safe environment for the absorption of drugs. Further, highly vascularised, and thin epithelium of mucosa, allows therapeutic substances with molecular weight up to 5,000 Da, to enter directly into systemic circulation. However, it is important to understand the structures and functions of underlying tissue for developing successful drug products for better patient compliance (Laffleur 2016). Anatomical factors (thickness of the mucosal membrane, membrane integrity, microbiome of mucosal sites and keratinisation of mucosal surface), physiological factors (mucus turnover, muscular activity of surrounding tissues, mucus pH, cells and enzyme secretion,) and pathological factors (level of inflammation, infection at the mucosal site, cellular differentiation)must be considered for the selection of mucoadhesive dosage form. Mucosal epithelium of the cornea, anal canal, vagina, and oral cavity consisting of non-keratinized stratified squamous epithelium, while the surface layer of the masticatory mucosa containing keratinized epithelium. Keratinized and non-keratinized mucosal tissues differ in their composition and properties, affecting mucosal permeability of drugs. Keratinized mucosal epithelium has small amounts of neutral lipids like ceramides, while the non- keratinized epithelium contains amphiphilic lipids like cholesterol and glucosylceramides. Non- keratinized epithelium exhibits relatively higher permeability than keratinized epithelium for both polar and non-polar drugs. Permeability of the buccal mucosa is approximately 4-4000 times higher than that of the skin. Pre-systemic drug metabolism remains an important issue faced by pharmaceutical scientists to ensure consistent clinical performance. Unlike oral route, low expression of drug-metabolizing enzymes at the mucosal site, reduces pre-systemic metabolism of drugs, facilitating drug bioavailability.

Further, mucosal sites associated with professional antigen-presenting cells like mucosa-associated lymphoid tissue (MALT), gut-associated lymphoid tissue (GALT) and nasopharyngeal-associated lymphoid tissue (NALT) make it an attractive site for non-invasive delivery of vaccine (Creighton & Woodrow 2019).Besides peptide antigens, the mucosal route has been successfully applied for the delivery of several therapeutic proteins and peptides, including insulin, growth hormone, thyrotropin-releasing hormone, leuprolide,

and oxytocin. Moreover, mucosal site offers many advantages to treat various local mucosal diseases. Patients treated with clonidine mucoadhesive buccal tablets shows comparable pharmacokinetic profiles and fewer adverse events compared to the oral dose of plain clonidine (Vasseur et al. 2017). In recent years, mucoadhesive based vaginal preparations have shown promising results in the treatment of vaginal infections. Miconazole nitrate infused solid lipid microparticles in a topical gel formulation of polycarbophil exhibit desired biophysical properties for vaginal application. *In-vivo* results show excellent antifungal activity (86%), compared to marketed formulation, Daktar (75%) with no sign of tissue toxicity. Mucosal sites are easily accessible for the delivery of therapeutics and provide an easy means to terminate drug therapy, improving medication adherence in unconscious, paediatric and geriatric patients. Omeprazole loaded mucoadhesive film stabilized with maltose, cyclodextrins, polyethylene glycol, and l-arginine displayed desired pharmaceutical attributes for buccal application for paediatric patients. However, anatomical and physiological aspects of specific mucosal site need to consider for achieving desired therapeutic endpoints. Table 1 provides important information about anatomical and physiological processes of principal mucosal sites, helpful towards the rational designing of an appropriate mucoadhesive drug delivery system(Pandey et al. 2017).

Table 1.

Moreover, drug carriers should be inert, non-toxic, biocompatible, biodegradable and release the therapeutics at a controlled rate for improved efficacy. Several approaches such as creams, gels, pellets, tablets, capsules, pessaries, foams, and films have been extensively studied for mucosal drug delivery. Table 2 lists the major components of a few reported mucoadhesive drug delivery systems along with the route of administration.

Table 2.

Physiochemical properties of drugs and polymers play an important role in determining optimal clinical efficacy (Peppas et al. 2009). Drug candidate with a molecular weight of less than 500D, aqueous solubility more than 1mg/mL, log P value in-between 1-2 and the dose should not exceed 10 mg daily, are ideally suited for mucoadhesive delivery systems. Nanotechnology-based mucoadhesive formulations helps to overcome the issues related with conventional dosage forms like erratic drug absorption, premature drug release, in-adequate target residence time, and poor control over drug release kinetics. Micro or nano-carriers because of their high surface area and structural flexibility offer immense opportunity to

regulate surface wettability, drug solubility, swelling efficacy and programme drug release to maximise the therapeutic outcomes. Drug target residence time is an important factor in determining the clinical efficacy of mucoadhesive dosage form. Several theories, such as electronics, adsorption, wettability, diffusion, fracture, and mechanical theories have been proposed to explain mucoadhesion (Fig 1). The mechanism involved in mucoadhesion largely depends on the physicochemical properties of polymers. Polymer properties like chemical structure, surface charge, molecular weight, rate of hydration etc. affect the extent of mucoadhesion, greatly facilitate drug utilization (Singh et al. 2017).The mechanism of the mucoadhesion triggered by the two conjugative steps: contact stage and consolidation stage. In the contact stage, the mucoadhesive polymer starts spreading and swelling; facilitate deep contact of polymer component with the mucus layer. In the consolidation stage, the mucoadhesive polymer gets activated in the presence of moisture and get attachedto the mucous linings through various chemical bonds such as covalent, hydrogen, vanderWallbonds, etc. (Anil & Sudheer 2018). Cationic polymers of high molecular weight shows better mucoadhesion. Literature strongly suggests that high molecular weight chitosan shows better interactions with the mucus layer resulted in the enhancement of mucoadhesive strength. Polymers solubility play an important role in tailoring mucoadhesiveness. Chemical modifications of polymers improve their solubility and swelling capacity for higher mucoadhesiveness (Casettari et al. 2012). Cationic polymers with $-NH_2$ have greater water solubility at acidic pH than neutral pH, whereas anionic polymers with -COOH group have greater aqueous solubility at alkaline pH than acidic pH. Cationic polymers like chitosan and aminoalkyl methacrylate copolymer (Eudragit E) have improved solubility, expanded conformation structure and higher mucoadhesiveness at acidic medium (pH below 5). Similarly, anionic polymers like poly(methacrylic acid-co-methyl methacrylate), hydroxypropyl methylcellulose phthalate (HPMC-P) and HPMC acetate succinate require an alkaline environment for optimum adhesive performance (Kweinor Tetteh &Rathilal 2019). Further, solubility is a dynamic parameter that can be alter by appropriate surface modification or by addition of substituent groups like ester, methoxyl, hydroxypropyl, acetyl and succinyl groups into the polymer skeleton. For example, carboxylic / ester ratio of 1:1 in Eudragit L is soluble in pH 6 whereas 1:2 molar ratio of carboxylic / ester in Eudragit S is soluble in pH 7 (Hauptstein et al. 2014; Kocak et al. 2017). Mucoadhesive properties of chitosan increases by about 200-fold with the addition of aromatic rings or thiol groups in ligand molecules. In a comparative analysis on the adhesive strength of different polymers including chitosan, polyacrylic acid (PAA), carbopol and their

thiolated derivatives showed following rank order of adhesion time: chitosan > thiolatedpolycarbophil > thiolated PAA > Carbopol 980 > polycarbophil (Grabovac et al. 2005). It is assumed that the mucoadhesive force increases with increasing polymer chain length and ionizable groups in the polymer structure. Apart from this, the adhesive force also depends on the diffusion coefficient, ability to form a hydrogen bond, degree of hydration, chain flexibility, contact time and chemical nature of the polymers. According toa recent report, adhesive bond lies within the range of 0.2–0.5μmcould be adequate for achieving better mucoadhesive strength.

Further, mucus turnover and its physiochemical properties like viscoelasticity, pH, ionic strength and surface charge, adversely affect the rate and extent of drug absorption. Minor changes in the mucosal composition have a significant impact on the mucoadhesive performance of the formulation. Each mucosal site has its own merits and limitations to regulate residence time of the dosage form. Buccal and sublingual sites are suitable for drugs that undergo extensive first-pass metabolism, but these sites are not suitable for bitter and unpleasant drugs. Rectal and vaginal routes are considered being ideal to treat localized diseases but are inconvenient for long-term therapy. Similarly, nasal and ophthalmic sites are consider suitable to treat localized disease but have limitations like mucociliary drainage and local irritation. However, there are some important concerns like mucus turnover, limited surface area, and local toxicity must have taken into account for the design of an efficient mucoadhesive formulation.. New insight in bio-adhesive polymers helps to overcome the above restrictions, concomitantly improved the therapeutic performance. The section below focuses on methods and compositions of promising mucoadhesive drug delivery systems delivered via the mucosal route.

Fig 1.

2 Mucoadhesive drug delivery systems

Over the past few decades, mucoadhesive drug delivery systems have researched extensively for both local and systemic delivery of therapeutics through various mucosal routes.

2.1 Buccal drug delivery

Buccal drug delivery involves the administration of therapeutics via buccal mucosa of the oral cavity. Buccal epithelium has an easy accessibility and high compliance rates compared to other mucosal sites for drug delivery. Apart from this, buccal route offers a promising alternative for systemic drug therapy due to the direct access of drugs to the blood without presystemic metabolism. Further non-keratinized epithelia, rich blood supply and low level of proteolytic enzymes increases the systemic bioavailability of drugs following buccal administration. However, the major drawbacks associated with buccal drug delivery includes high saliva turnover, unpalatable taste, mastication, buccal microbiome, and limited contact area. Recently, there are several mucoadhesive delivery systems available in the market including buccal tablets, films, nanofibers, nanoparticles, wafers, gels, can treat a wide range of pathological conditions. The buccal drug delivery systems are usually preferred to target diseases occurring at mucosal sites. However, bi-directional drug release patterns significantly influence drug availability at the target site. Dosage form design, with desired mucoadhesive property and a good insight on mucoadhesive polymers offer an effective means to circumvent above issues. Polymers such as hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, methacrylic acid copolymers, or ethylcellulose could exhibits favourable physiochemical and mucoadhesive properties for the delivery of therapeutics through the buccal mucosa (Roy et al. 2013), (Kathe & Kathpalia 2017). Figure 2 illustrates the interplaying roles of polymer profile and particle size on the mucoadhesive strength (Fonseca-Santos & Chorilli 2018).

Fig 2.

Govindasamy et al. have preparaed a buccal patch of carbamazepine containing different proportions of polymers like methylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol and ethylcellulose using solvent casting method (Govindasamy et al. 2013). The results of all the formulations revealed good adhesive properties with unidirectional drug release behaviour and estimates the maximum drug release within the specified mucoadhesion period. Drugs

with a bitter taste and which irritate the mucosa are not suitable for buccal administration. Sweetening agents amalgamated with suitable polymer masking the local taste receptors has got much attention to develop buccal mucoadhesive dosage form. Yuan et al. successfully used mucoadhesive ion exchange fiber for taste masking of propranolol hydrochloride. *In-vitro* and *in-vivo* studies demonstrated slow and steady drug release over 30 days without the perception of taste. (Yuan et al. 2014). Penetration enhancers such as dimethyl sulfoxide, linoleic acid, isopropyl myristate, and oleic acid are often co-administered to improve drug absorption across the keratinized section of buccal mucosa (Shaikh et al. 2012). Prasanth et al. studied permeation enhancing ability of different enhancers like dimethyl sulfoxide, linoleic acid, isopropyl myristate, and oleic acid on salbutamol sulphate. Among different selected enhancers, oleic acid found to be an efficient permeation enhancer due to its inherent ability to increase the intracellular Ca^{+2}level(Prasanth et al. 2014).

Selection of an appropriate polymer plays a major role in defining the therapeutic objectives, as it will affect drug loading efficacy, drug release kinetic, mucoadhesiveness and formulation stability. According to the source of origin, mucoadhesive polymers can divide into two categories, i.e., natural and synthetic. Natural and synthetic polymers have their own pros and cons. Polymer parameters like biocompatibility, long-term stability and immunogenicity must taken into account. Further, swelling behaviour and diffusional characteristics of polymers in different physiological pH are critical to relate the release characteristics, mucoadhesiveness and overall therapeutic performance. According to kind of interaction with mucin, polymers are broadly classified into two groups: specific and nonspecific. The specific mucoadhesive polymers (e.g lectin) can attach to a particular component of the mucosa, while the nonspecific polymers may adhere to both surface structures of cells and mucosal layer e.g polyacrylic acid. Polymers are further categorized into cationic, anionic and neutral depending upon their surface charges. Among different polymers, cationic polymer exhibits higher adhesive property because of its greater affinity for poly-anionic mucins. Besides having mucoadhesive properties, cationic polymers also exhibit excellent antimicrobial activity against several pathogens. However, the antimicrobial potency depends on the size and charge density of the polymers. Similarly, the adhesion strength of a polymer depends on the number of factors including chain length, molecular weight, chain flexibility, spatial arrangements of functional groups, reactive groups density, etc. Therefore, polymers should be carefully selected based on their physical, chemical,

biophysical and physio-chemical characteristics to achieve optimal mucoadhesiveness. Fig 3 enlists examples of selected polymers in each category (Boateng et al. 2015).

Fig 3.

Chen et al. planed a gastro-retentive floating bead containing emodin to treat stomach cancer (Chen et al. 2019). The results demonstrated that all preparations have prolonged retention up to 8hr, sustained drug release profile and good mucoadhesive properties. Recently, a phase II study, designed to compare the pharmacokinetics and safety profiles of clonidine mucoadhesive oral tablets following a single rising dose administration (50 and 100µg) in 36 healthy human volunteers. Results revealed that mucoadhesive formulation shows high and prolonged drug concentration in saliva (C_{max} of 209.24 and 387.09 ng/ml for 50 and 100 µg, respectively) compared to tablet formulation (2.65 ng/ml for 100 µg HCl tablet) with no significant change in safety profile (Vasseur et al. 2017). Susan and co-workers invented a controlled release mucoadhesive formulations for chemoprevention of oral cancer and precancerous lesions. In a preferred embodiment, mucoadhesive formulation comprises a biodegradable polymer, anti-interleukin, vitamin A analogue, and estradiol metabolite (Regina & Paul 2017). Immuno-histochemical assessment of cytokeratin and vimentin showed effective levels of therapeutic agents at the target site. Mucoadhesive films due to their flexibility and comfort are useful in the treatment of the local pathological condition of gums, inner lips, inner cheeks, or tongue. US Pat. No. 8529939 disclosed a bioadhesive composition for ulcerative conditions in the oral cavity like cancer sores, fever blisters, and hemorrhoids, etc. This composition encased with a blend of sodium carboxymethyl cellulose and xanthan gum for site specific delivery of encapsulated therapeutics.(Masters & Berg 2013). In a recent trial, multi-laminated mucoadhesive film containing ornidazole and dexamethasone sodium phosphate display significant mucosal wound repair and reduced ulcer inflammation characterized by high C_{max} of ornidazole (37.04 µg/ml) and dexamethasone (9.737 µg/ml)in saliva (Zhang et al. 2019). Molecular weight and surface properties of polymers have played a key role in governing mucoadhesion. Buccal films containing clindamycin phosphate was fabricated by solvent casting method using low and medium molecular weight deacetylated chitosan and sodium alginate for treatment of periodontitis. According to the results, the films got from low molecular weight deacetylated chitosan showed a better mucoadhesive performance (2.601N) when compared with medium molecular weight films (1.131N). The low molecular weight deacetylated chitosan films due to higher hydrophilicity and improved mucosal transfection ability resulting a longer

retention time and a better utilization of loaded drug. On the contrary, formulation with high mucoadhesive functionality shows faster *in-vitro* drug release compared to those with low mucoadhesiveness (Kilicarslan et al. 2018).

Strong mucoadhesiveness is highly desirable to deal with frictional forces that involved in reducing cohesion like mastication, speaking, saliva secretion and swallowing. Thiolated polymers or addition of thiol groups reported enhancing mucoadhesiveness through disulphide bonds with cysteine-rich subdomains of mucosal glycoprotein. Further, thiolated polymers revealed an increase in drug permeation through a different mechanism including efflux inhibition or enhance influx and controlled drug release characteristics. The stability of thiolated derivatives remains a major concern persistently reduces long-term interest. Pellets prepared from thiolated flaxseed mucilage shows increase mucoadhesiveness compared to unmodified ones. This is attributed to the formation of inter and intra disulphide bond between cysteine rich domain of mucus and thiolated mucilage (Devi & Bhatia 2019). Similarly, Laffleur et al. tested stability, safety, mucoadhesiveness and permeability of thio-hyaluronic acid ethyl ester (HA-SH) as an advanced excipient for buccal drug delivery. Results show a 3.4-fold higher mucoadhesion and 4.4-fold higher permeation than unmodified polymer (Laffleur et al. 2017). Laffleur and Rotteges have evaluated the potential of chitosan mercaptonicotinic acid (MNA) composite as a mucoadhesive material. The results obtained suggested preactivated chitosan-mercaptonicotinic acid revealed a 18.8 fold enhanced stability and12.56 fold higher adhesive properties compared to unmodified chitosan (Laffleur & Röttges 2019). The oxidation of free thiol groups, seems to reduce the mucoadhesive potential of certain thiomers. Pre-activation and coupling reactions have been extensively studied to improve the stability and adhesive performance of thiomers. Pre-activation of chitosan–thiobutylamidine with mercaptonicotinamide demonstrated 1.8-fold higher stability and 1.6-fold higher mucoadhesive properties compared to the unmodified chitosan (Laffleur et al. 2013). Similarly, preactivated carboxymethylcellulose displayed superior mucoadhesion performance with a 3.0-fold increase in mucoadhesive time and 8.8-fold enhancement in mucoadhesiveness (Laffleur et al. 2016). Polymeric nanoparticles are extensively investigated for buccal drug delivery. Besides, higher mucoadhesive features, nanoparticles also exhibit enhanced drug diffusion across the buccal mucosa, suitable for high molecular weight drugs for systemic effects. Williams and co-workers established the perspective of metal/metal oxide nanoparticle-embedded polymer films for the buccal delivery of protein and peptide including insulin, oxytocin, corticotrophin-releasing hormone,

follicle-stimulating hormone, growth hormone, inhibin, gastrin, leptin, renin, etc(Williams et al. 2012). Medication administered via a buccal route gets diluted by the saliva. Further, swallowing of saliva can also potentially resulting in lower efficiency. Unidirectional buccal formulations reported improving the therapeutic performance of many drugs. Sanvordeker et al. disclosed trilaminate film comprising of hydratable mucoadhesive base layer, a non-adhesive reservoir layer and a water-impermeable carrier film facilitates unidirectional release of encapsulated therapeutics and avoid drug from swallowing (Sanvordeker & Leung 1990). Irrespective of significant opportunity, buccal drug delivery presents some challenges like small absorptive surface, not preferred for systemic delivery, not suitable for drugs with unpleasant taste, high therapeutic dose or unstable at buccal environment.

2.2 Sublingual drug delivery

The sublingual route provides an attractive opportunity for transmucosal drug delivery owing to its distinct anatomy and physiology. Sublingual administration is useful for rapid onset of action because of thin non-keratinized stratified epithelium and rich vascular network (Khan et al. 2017). Cardiovascular drugs preferred as the sublingual vein drain the blood into the brachiocephalic vein and further, it goes to the superior vena cava and reaches to the cardiac system. Therefore, it is useful for life-saving drugs or drugs used in a medical emergency like cardiovascular drugs such asperindopril, captopril, nitrendipine, propranolol and amlodipine besylate (Schwarz & Weisspapir 2015). Sublingual administration of atorvastatin calcium and trimetazidine hydrochloride combination considered being a promising dosage form for the treatment of coronary heart diseases with instant action and improved patient compliances(Atia et al. 2019). Over the years, sublingual route extensively investigated for drugs that undergo extensive pre-systemic metabolism (Sattar et al. 2014). Further, sufficient amount of saliva in the oral cavity enhances the dissolution rate of the drugs, and hence useful for class II and IV drugs (Mansuri et al. 2016). Schwarz et al. described a mucoadhesive composition for enhanced systemic absorption of pharmaceuticals such as sildenafil, insulin, and leptin following sublingual administration. This composition is encased with mucoadhesive polymer such as chitosan, carboxymethylcellulose for improving mucoadhesion. Further the preferred embodiment consists of sweetening agent to enhance the palatability of the composition and a plasticizer to improve flexibility and durability of the product. However, too much saliva and tongue movement makes it not appropriate for long term treatment. Polymers play an integral role in the determining the performance by increasing the residence time of the therapeutics at the application site. An ideal polymer

component must be biocompatible and nontoxic. Further polymer must adhere instantly to mucosal tissues; and allows controlled local drug delivery at the site of treatment. Polymers which are commonly used includes polyacrylic acid derivatives, cellulose and its derivatives (e.g. methylcellulose, hydroxypropyl methylcellulose), natural gums (e.g. carrageenan, xanthan gum), lectin-mediated polymers (e.g. thiolated polymer) and chitosan (Chen et al. 2015). Babaian et al. disclosed a bioadhesive film for sublingual administration of anti-anginal drug. The film consisting of 70% by weight of vinylpyrrolidone and 1 to 30%by weight of acrylate as bioadhesive polymers and a therapeutic active substance having anti-anginal action preferably 3.0-30.0% by weight of formulation. The film was prepared by using the conventional film casting method. The invention offers distinct advantage of quick bioadhesion within 1-2 seconds and almost fully absorbed after 38 minutes. Analysis of the clinical data revealed, the drug from the prepared film was absorbed about 8 times more rapidly than the conventional dosage form, and the doses of drug is 8 times lower compared to conventional dose. Aerosol delivery may be considered as a good alternative to overcome issue related to smaller absorptive surface area of the sublingual site (26 cm^2) (Babaian et al. 1989). Cutler et al. described the sol-gel composition of sublingual spray comprising of dihydroergotamine (DHE) as the active ingredient, cyclodextrin as a solubilizer, dextran as a mucoadhesive component and sugar alcohols as a plasticizer for the treatment of migraine. The developed aerosol dissolved quickly in the sublingual cavity allowing rapid absorption of the DHE through the sublingual mucosa to the systemic circulation; thereby provide quick relief against migraine. Oral administration of DHE requires a large dose of about 20-30 mg due to erratic oral absorption and extensive pre-systemic metabolism. These elevated doses can cause nausea and vomiting, as an adverse effect. Similarly, substantial constraints are impeded by intranasal DHE administration. The intranasal dose of a DHE (2 mg)as 4 intranasal sprays results in low drug level in plasma compared to oral administration(Cutler 2003).

Nanotechnology offers several means to improve drug transportation, helps to overcome the absorption barrier for improved efficacy. Frank et al. described the technique for preparing amphiphilic nanoparticles for their controlled adhesion to sublingual mucosa without compromising the stability of the particles. Nanofibers owing to their unique structural features like large surface area, surface topology, and porosity greatly improve residence time at the site of application. Furthermore, polymeric nanofibers are widely investigated to improve the drug's bioavailability with a narrow absorption window. Josef et al. disclosed a

nanofiber-based mucoadhesive formulation consisting of a multi-layered structure with a thickness ranging from 0.1 to 1000 µm for unidirectional transmucosal delivery of encapsulating drug in the form of the dispersed nanocrystal. The disclosed carrier was useful for the localized delivery of therapeutically active ingredient over an extended period. Results of permeability studies showed that the nanoparticles concentration is not a limiting factor up to an experimented value of 15-60 mg/mL, and serve as a promising carrier for transmucosal drug delivery via the sublingual route(Chou et al. 2013).

The sublingual route is usually preferred for potent drugs for the restricted absorptive surface area, washing out of drug by saliva and low permeability. The presence of a buccal microbiome also acts as a barrier for the absorption of therapeutic protein and peptides. Further, patient-related factors such as variation in genetic makeup and other clinical conditions must be critically analysed for optimizing the therapeutic performance of mucoadhesive sublingual formulations.

2.3 Ocular drug delivery

Topical drug delivery demonstrates poor corneal bioavailability (<2%) due to several factors including limited surface area, poor retention, reflex blinking, decreased corneal permeability, lower cul-de-sac volume and lacrimal secretions. Mucoadhesive drug delivery systemsplay an important role in increasing the precorneal residence time for improved ocular bioavailability. However, ocular irritation has received a great deal of attention associated with a mucoadhesive polymer like chitin. The extent of eye irritation can be directly proportional to the polymer's molecular weight. Thiolation and deacetylation are useful approaches to reduce the molecular weight of the chitin-based polymer without compromising mucoadhesiveness. Chitosan's mucoadhesive properties are well documented and are likely to be associated with many mechanisms, forming hydrogen bond with mucin and electrostatic interactions between the positively charged amines and the negative sialic acid residue of mucin. Molecular conformation and hydrophobic effects of chitosan also affects its mucoadhesive properties. The higher molecular weight chitosan (approximately >1400KDa) shows better penetrability as compared to lower molecular weight chitosan (500-800KDa). Further, chitosan has the inherent ability to improve the healing process of corneal infections. The healing process may be mediated through a rapid migration of keratocyte that provokes the production of collagen at the infection site leading to fasten the recovery process (Khare et al. 2014). Limited solubility of chitosan in physiological conditions is a

major drawback for its successful translation into clinical practices. Chitosan's chemical reactivity is harnessed to overcome this inconvenience. The primary amine and secondary hydroxyl group present in chitosan may be chemically modified to modulate their solubility (Khare et al. 2014; Morrison & Khutoryanskiy 2014; Preethi & Narendra 2015).Several approaches such as acylation, quaternization, thiolation, phosphorylation, carboxyalkylation, and sulfationhave been employed to improve chitosan solubility in aqueous media (Menchicchi et al. 2014). Thiolated chitosan has several advantages and favourable features over native chitosan, such as enhancing solubility at low substitution, improved mucoadhesive strength and higher cellular permeation (Chatterjee et al. 2017).Further, chemical modification of chitosan leads to the formation of some internal and external bisulfide bonds in the polymeric structure, provides a strong cohesive features. Ganet al. developed a new two-step method for synthesizing thiolated low molecular chitosan with a high degree of replacement(Gan et al. 2009). Ocular delivery of cyclosporine A using chitosan nanoparticles demonstrated improve drug distribution in both anterior and posterior segment of eye.(M Ways et al. 2018). Topical eye drop is a non-invasive and the most common way to treat eye infections. Topical route is effective for the treatment of diseases in the anterior segment of the eye. However, drug delivery to posterior segment of the eye diseases, including glaucoma, age-related macular degeneration (AMD) and diabetic macular edema remains a significant challenge for formulation developers (Tsai et al. 2018). De Silva et al. prepared daptomycin (a natural lipopeptide antibiotic) loaded chitosan nanoparticles for the treatment of intraocular infections such as endophthalmitis, and characterized for both *in-vitro* and *in-vivo* antimicrobial efficacy. The experimental findings shows higher antimicrobial activities compared to the nude drug (da Silva et al. 2015). Experimental endpoints showed that nanocarriers due to its unique ability to penetrate ocular barriers, adapted successfully for posterior eye drug delivery. Further, permeability enhancers such as calcium chelators (EDTA), surfactants (palmitoyl carnitine, sodium caprate, and sodium dodecyl sulphte) are often considered to increase drug permeability for enhanced therapeutic outcomes in posterior ocular diseases(Rodrigues et al. 2018).

Polysaccharide- based hydrocolloids provides enough lubrication for easy ocular drug administration without any vision disturbances (Fangueiro et al. 2016). Gu et al. described a mucoadhesive ocular drug delivery system of cyclosporine A with improved corneal retention. The disclose relates to a novel composition consisting of dextran as the bioadhesive material, polylactide as a hydrophobic material and sodium citrate as a buffering agent,to overcome issues related to posterior segment drug delivery for improved therapeutic

activity on target tissues(Gu et al. 2018).Similarly, Hosseini et al. prepared controlled release mucoadhesive formulations comprises of 0.1 to 6.5% by weight of the aqueous solution of polycarbophil and therapeutically active agents (dexamethasone and azithromycin) in a concentration of 0.025% to 0.25% by weight of the composition. Results showed no significant change in intraocular pressure following topical administration twice daily over two weeks compared with a marketed formulation, DuraSite®. Results concluded that the composition can be selected after ocular surgery (Hosseini & Bowman 2017).Thermo-responsive *in-situ* gel offers several advantages over conventional dosage forms including ease of administration, extended-release of the drug, good stability, enhanced bioavailability and biocompatibility. Fedorchak et al. disclosed a thermo-responsive *in-situ* mucoadhesive ocular gel to overcome the obstacle of current treatment practices. The liquid thermo-responsive hydrogel comprising of drug-loaded polymer microparticles with an average diameter of 1 to 10µm, provides sustained release of encapsulated therapeutics over an extended period in the lower fornix of the eye (Fedorchak et al. 2014). The mucoadhesive hydrogel containing 2.5 – 5 % w/w of cellulose, dextran, chitosan, or a combination thereof. Clinical outcomes indicated that *in situ* gel comprising of poloxamer/chitosan 16:1 represents 4-fold increment in the retention time compared to conventional solution. Results further suggested that mucoadhesiveness and mechanical properties of the gel depends on the concentration of selected polymers and their molecular weight (Gratieri et al. 2010). Further, a thermoresponsive hydrogel made of modified hydroxypropyl methylcellulose and α-cyclodextrin showed a significant enhancement in the ocular absorption of diclofenac sodium when compared to hydrophobically unmodified polymer(Iohara et al. 2017).

However, drug release remains a major challenge due to low tear turnover. Therefore, it is logical to consider the physio-chemical properties of both polymers and drugs, such as molecular weight, concentration, and the surface charge for enhanced therapeutic intervention in eye disease.

2.4 Nasal drug delivery

The nasal route provides a promising non-invasive alternative for achieving both local and systemic delivery of drugs. Unlike the buccal mucosa, nasal mucosa consisting of non-keratinized monolayer stratum corneum associated with microvilli with a surface area of approximately 160 cm^2. Further nasal mucosa is highly vascularized that support rapid absorption of the therapeutic agents (Rohrer et al. 2018). Recently, intranasal drug delivery

system has come out as a well-grounded approach to deliver a wide range of therapeutics to the central nervous system (CNS). Ongoing examinations have featured the requirement for clinically feasible strategies , where optimal CNS penetration is accomplished through the right parity of penetrability, a low potential for dynamic efflux, and the suitable physicochemical properties (Dong 2018). Nasal mucoadhesive drug delivery system may provide a unique pathway for the treatment of various neurological diseases, such as neuroinfections, Parkinson's disease, Alzheimer's disease, multiple sclerosis and chronic age-related neurodegenerative diseases, as this route allows direct transport of therapeutics from nose to brain (Erdő et al. 2018). There are three known mechanisms by which the drug enters the brain from nasal cavity: (i) the olfactory pathway (direct paracellular or transcellular transport via the olfactory neurons or olfactory epithelial cells); (ii) the trigeminal pathway (transport via trigeminal nerves); and (iii) the systemic pathway (drug transport into the brain through the systemic blood circulation) (Gänger&Schindowski 2018). Gholizadeh et al. developed a smart thermosensitive chitosan-based ibuprofen nasal spray formulation for the treatment of neurologic disorders. Chitosan due to its polycationic nature interact with negatively charge sialic acid of nasal mucosa, ensure increased retention time of the drug near olfactory epithelium for higher brain uptake. Further, it has been observed that the bioadhesive strength of a polymer increases with a molecular weight above 100KD (Chonkar et al. 2015). *In-vitro* experiments shows the rapid gelation of the formulation approx. 2.9 times faster than the mucociliary clearance rate (20 min), leading to increase drug transport from nose to brain (Gholizadeh et al. 2019). Although the nasal mucoadhesive drug delivery system has many significant advantages but, it is highly compromised in conditions associated with running nose. Controlled and sustained drug delivery strategy with a novel polymeric formulation like *in situ* gelling system may provide a tangible solution to overcome such issue. Gel formulation will increase the residence time on the mucosal surface and will release the drug in a controlled manner. Galgatte et al. developed a mucoadhesive *in-situ* gel to improve the bioavailability of the sumatriptan succinate. The experimental result supports the *in-situ* gel for the administration of sumatriptan succinate through the nasal route (Galgatte et al. 2014). Sherafudeen and Vasantha developed*in situ* nasal gels of loratadine by using polymers HPMCK-100 and xanthan gum. Viscosity of the gel was found to be increased with an increasing concentration of HPMCK-100. The viscosity of the developed *in situ* gels shows an immediate increase in viscosity when comes in contact with nasal pH (6.4), comply the requirement of sol-gel phase transition, concurrently improve drug retention in the nasal cavity. Cellulose derivatives because of their desirable mucoadhesive property

significantly extend the residence time of the drugs in the nasal cavity. Cellulose derivatives are also found to be effective in enhancing the intranasal drug absorption of both hydrophobic and hydrophilic macromolecular drugs. A combination of cellulose with other absorption enhancers such as aminoglycoside antibiotics and bisphosphonates show an increased drug bioavailability when compared to polymer alone. Polymers blend often gives desired properties to meet specific product needs compared to individual polymer (Sherafudeen& Vasantha 2015).

Pridgen and co-workers disclosed a mucoadhesive composition containing sodium alginate and chitosan of about 0.15 to about 15% by weight of the composition and an active therapeutic agent, triamcinolone/ acyclovir is about 0.01-5% by weight of the composition with a suitable plasticizer. According to the invention, the mucoadhesive composition provides a controlled release formulation intended for the treatment of localized conditions like pharyngitis, aphthous stomatitis, bacterial infections, radiation-induced mucositis, fibromyalgia,etc. Continuous swelling of the polymers in presence of the nasal secretion, allows gradual release of encapsulated therapeutics in 120 min. The disclosed composition avoids first-pass metabolism, leads to improved bioavailability with better patient compliance(William L. Pridgen 2019). Slusher and Raisetal. described a mucoadhesive nasal composition for the treatment and diagnosis of neurological diseases containing glutamate carboxypeptidase II as diagnostic and mucoadhesive agents for imaging of the brain or peripheral nervous system(Slusher & Rais 2018).

Recently, *in-situ* gel based system has been extensively investigated for sustained nasal delivery of therapeutics. Abou-Taleb and co-workers investigated the bioavailability of nefopam hydrochloride using a niosomal-based *in-situ* gel nasal formulation. Results shows niosome with size ranges from 550-600nm exhibited entrapment efficiency of 80%and zeta potential ranging from -16.8±0.13 to -29.7±0.15mV. Pharmacokinetics studies showed a significant increase in drug bioavailability of approximately 4.77-fold when compared to oral solution of the drug (Abou-Taleb et al. 2018). Similarly, Nayar described aqueous nasal spray composition of corticosteroids with increased mucoadhesion and viscoelasticity for alleviating or treating corticosteroid-responsive conditions or diseases. The formulation composed of a mixture of non-steroidal anti-inflammatory drugs and polymers such as chitosan and/or polycarbophil. The said nasal spray compositions offered the unique benefit of mucoadhesiveness and film-forming properties for sustained release of medicaments for improved therapeutic outcomes (Nayar 2016).

Besides the aforementioned advantages, nasal delivery is associated with risk of local toxicity, nasociliary reflex, rapid removal of the therapeutic agents. Further conditions like cold and allergies may significantly alter the nasal bioavailability of the therapeutic agents. The other challenging issue of intranasal drug delivery is its low dose volume (25-200µL) which may not be suitable for low water-soluble drugs or those which require a high dose of drug (Djupesland 2013).Further, the limited surface area of nasal mucosa demands for controlled administration of potent, non-allergenic agents with desired physicochemical properties.

2.5 Vaginal drug delivery

Vaginal route offers a promising alternative to drug administration to treat both local (vaginitis caused by various pathogens like bacteria, fungi or virus) and systemic conditions (hormone replacement therapy, cervical cancer, ovulation-inducing activity, and diabetic mellitus, etc). Vaginal administration allows self-administration with minimal professional interference. Further, intra-vaginal drug delivery ensures site specific drug delivery, greatly improves the therapeutic efficacy of drugs. Apart from these advantages, vaginal delivery also offers a promising alternative for systemic drug bioavailability by avoiding first-pass metabolism. Furthermore, a low level of protease activity, high permeability and thin epithelium (200-300µm) make it a promising alternative for the systemic delivery of low molecular weight drugs(Agarwal & Aggarwal 2015).Ideally, the selection of intravaginal administration relies on the applicability of the intended response. However, several factors can influence drug absorption via intravaginal application. These includes the amount of vaginal secretion, vaginal pH, vaginal flora, formulation factors, vaginal pathophysiology, and menstrual cycle. *In-situ* gel, hydrogel, film, suppositories, creams, nanofibers, multi-particulate carriers, and vaginal rings are usually designed for vaginal drug administration. Vaginal mucoadhesive drug delivery may be considered to be an ideal dosage regimen for the prevention of HIV transmission and other sexually transmitted pathogens. Shegokar and Singh designed a vaginal microbicide gel of antiretroviral drug, tenofovir. Developed formulation demonstrate potent inhibition of HIV transmission in phase I clinical trials (Shegokar& Singh 2014). Similar results were observed by Mahalingam et al. for vaginal microbicide gel containing IQP-0528, a pyrimidinedione analogue against HIV. The major findings of this experiment suggest complete protection against HIV transmission with no sign of toxicity orirritationt o vaginal tissue (Mahalingam et al. 2011). Vaginal mucoadhesive drug delivery offers a favourable alternative for the treatment of urinary tract

infections (UTI). Literatures evidence suggests that women are more prone to develop UTI than men because of the shorter urethra, which shortens the distance for the pathogens like bacteria, fungus, etc. to reach the bladder. Oral administration of drugs like trimethoprim/sulfamethoxazole, fosfomycin, nitrofurantoin, cephalexin, ceftriaxone are usually recommended for the treatment for UTI(Tan & Chlebicki 2016).Chang et al. recently reported a mucoadhesive thermo-sensitive gel for localized delivery of clotrimazole at the site of infection .The results indicate higher and prolonged antifungal activity compared to conventional PEG based formulation (Chang et al. 2017). It is observed that the incidence of UTI increases many folds after the menopause due to high pH (> 4.5) of genitourinary tract(Ahmad et al. 2008). To counteract this pathological condition, a pH modifier as an active ingredient in the vaginal mucoadhesive formulation may have a beneficial impact. Amphora is one of such mucoadherant non-cytotoxic vaginal formulation comprising of 88 mg (1.76%) L-lactic acid, 50 mg (1%) citric acid, 20 mg (0.4%) potassium bitartrate in a 5 mg dose (equivalent to 5 mL) which maintain the acidic pH of the vagina. It is currently in phase III clinical trial as a single therapeutic dose (Nelson 2018). Further, vaginal site also offers a potential route for contraceptive therapeutics. Hormonal contraception may alter hormone levels, and possibly increase the risk of cervical and breast cancer. Therefore, non-hormonal contraceptive such as ferrous gluconate dihydrate has been employed as an alternative contraception method with fewer side effects. Jalalvandi and Shavandi produced an *in-situ* formulation and pH-responsive hydrogel for vaginal delivery of therapeutic agents. Two sets of injectable hydrogels, such as aldehyde-functionalized chitosan (AL-CS) and N-succinyl chitosan(NS-CS) have been prepared through schiff-base connections. The matrices were packed with Iron (II) gluconate dehydrate, doxycycline and a non-hormonal contraceptive. It is found that the rapid release of spermicide and the sustained release of doxycycline from prepared hydrogel makes it a promising candidate for vaginal contraceptive (Jalalvandi & Shavandi 2018). The patent disclosed a suppository and tablet composition for intra-vaginal delivery of progesterone. A vaginal tablet comprising of active therapeutic agents of about 13-20%, lactose (65-85%) and starch paste as disintegrant of about 2-5% by weight of the composition. The said composition forms a milky suspension approximately 6-8 hours after administration into the vagina. Results indicated that the formulation releases encapsulated drug within the therapeutic range over a period of 48 hours. The composition helps to overcome the limitations of conventional vaginal suppositories including erratic drug release, poor stability and quick throughout from the vagina(Greco & McGinity 1992). In another patent, Park et al. suggested mucoadhesive composition of the poly-ionic complex of

cationic chitosan and anionic polyacrylic acid for sustained release of active substance against vaginal infection. Anionic to cationic polymers were used in the ratio of 1:2.5 to 1:15for an optimum therapeutic effect. The said formulation due to excellent mucoadhesiveness and pH-dependent drug release behaviour, deemed suitable for the treatment of localized vaginal infections. Supplementation of estrogen is useful in controlling and preventing menopausal symptoms, including vaginal dryness, vaginal odour, vaginal or vulvar irritation, etc. Accordingly, a soft gel mucoadhesive composition for intra-vaginal administration of estradiol is used in the treatment of vulvovaginal atrophy and other conditions. The soft gel composition of the invention, offers advantages of having localized delivery, ease administration, improved safety and minimizing vaginal discharge following intra-vaginal administration(Mirkin et al. 2019). Liposome anchored with thiolated cationic polymers offer a promising approach for vaginal delivery of therapeutic peptides. The molecular mechanism involved in such enhancement may be due to polycation induced leakage from cells. Further, the presence of the primary amino functional group in the parent moiety of the polymer gets protonated in the acidic medium, makes the encapsulated peptides more hydrophilic, facilitate their permeation through paracellular opening. Accordingly, Bazzill and co-workers disclosed a hybrid composition comprising of liposomal particles consisting of peptide molecules dispersed in one or more cationic lipids (DOTAP and/or DOPE) and thiolated hyaluronic acid (HA) as a mucoadhesive polymer. The composition offers several advantages like high drug pay load, controlled release, higher stability, enhanced permeation and site specific drug delivery (Bazzill et al. 2016). Recent reports indicated that abnormal vaginal micro- flora is associated with increased sexually transmitted diseases, fungal infections, and urinary tract infections. Accordingly,Nivoliez disclosed a mucoadhesive sustained-release composition comprising of mucoadhesive components, and sulphur and hydrogen peroxide producing vaginal microbiome(5x 10^{10} CFU of *lactobacilli*) for the treatment of candidiasis and recurrent candidiasis (Nivoliez 2017). Vaginal formulations are interesting options for the administration of drugs like contraceptives, microbicides, and anti-infectives.

Irrespective of potential advantages, post-menopausal physiology, and sexual responses are highly contextual to attain the desired clinical responses. The table below summarizes a comprehensive review of the patents related to mucoadhesive carriers through various mucosal routes.

Table 3.

Conclusion

Mucoadhesive drug delivery systems offer an attractive non-invasive alternative for rapid, controlled drug delivery for both local and systemic applications. Further mucosal sites such as buccal, sublingual, nasal, ocular and vaginal mucosa offered easy accessibility with low enzymatic activity, allows easy removal of the carriers, thereby improve patient adherence. However, physiochemical properties of the drug, polymer, carriers and pathophysiology of disease play an important role in realizing the therapeutic goal. New generation mucoadhesive polymers including thiolated and pre-activated polymers show improved mucoadhesiveness compared to unmodified polymers. Nevertheless, several patent applications describe the importance and usefulness of mucoadhesive formulations for both local and systemic drug delivery. Degree of keratinization, mucosal thickness, low absorptive surface area, mucosal microbiome, and mucosal secretion are the key challenges must be addressed for determining the acceptability of a mucosal site for optimum therapeutic response.

Current andFuture Development

Mucosal sites due to their easy accessibility, the low enzymatic activity allows easy removal of the carriers, thereby offering an attractive non-invasive alternative for rapid, controlled drug delivery for both local and systemic applications. However, selection of an appropriate therapeutic agent, polymer and carrier system according to the pathophysiological state of the mucosa is important for optimum treatment outcomes. An ideal drug candidate for mucoadhesive delivery systems should have a molecular weight of less than 400-500D, aqueous solubility is more than 1mg/mL, log P value in-between 1-2 and the daily dose should not be greater than 10 mg. High mucoadhesiveness is highly desirable to deal with forces involves in reducing mucosal cohesion like mastication, saliva secretion, swallowing, microbiome, sexual and menstrual cycle-related intervention. Therefore, chemical structure, surface charge, surface tension, molecular weight, rate of hydration and concentration of polymers play crucial role in governing the retention time of drug delivery systems at the site of application. Recently cationic, thiolated and pre-activated thiomers polymers are widely investigated in mucosal drug delivery applications. In addition to the suitable polymer, an appropriate carrier system with high pay load, controllable physicochemical properties, proper drug localization, minimum premature release, and controlled release behaviour is highly desirable to circumvent the issues related with

conventional mucoadhesive drug delivery systems. Recent insights in the use of carriers for the mucosal delivery indicated nanocarriers enable higher retention at the mucosal site, tuneable drug release behaviour and enhanced permeability for higher therapeutic outcomes. Nanofibers due to 'unique structural and functional properties appear to be a potential carrier for mucosal drug delivery(Yang et al. 2017). In addition to superior biophysical properties, nanofibers have the ability to increase drug solubility, thus emerging as a potential alternative to improve the bioavailability of poorly soluble drugs(Wang et al. 2017). Further electrospinning and electrospraying appear to be a versatile and simple electrostatic spinning technique capable to impart the nanofiber matrices with many desirable properties suitable for mucoadhesive systems(Liu et al. 2018).Nevertheless, degree of keratinization, mucosal thickness, low absorptive surface area, mucosal microbiome and mucosal secretion are the key challenges must be addressed for determining the acceptability of a mucosal site for optimum therapeutic response.

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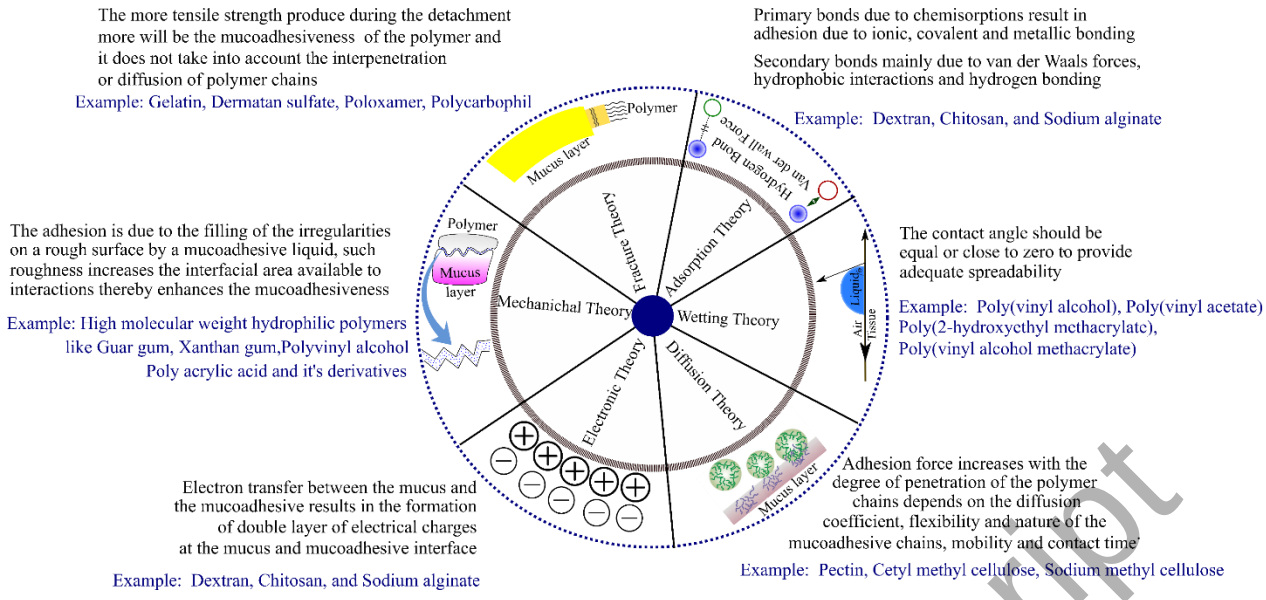

Fig 1: Illustration of different mechanisms involved in mucoadhesion and key factors influencing retention

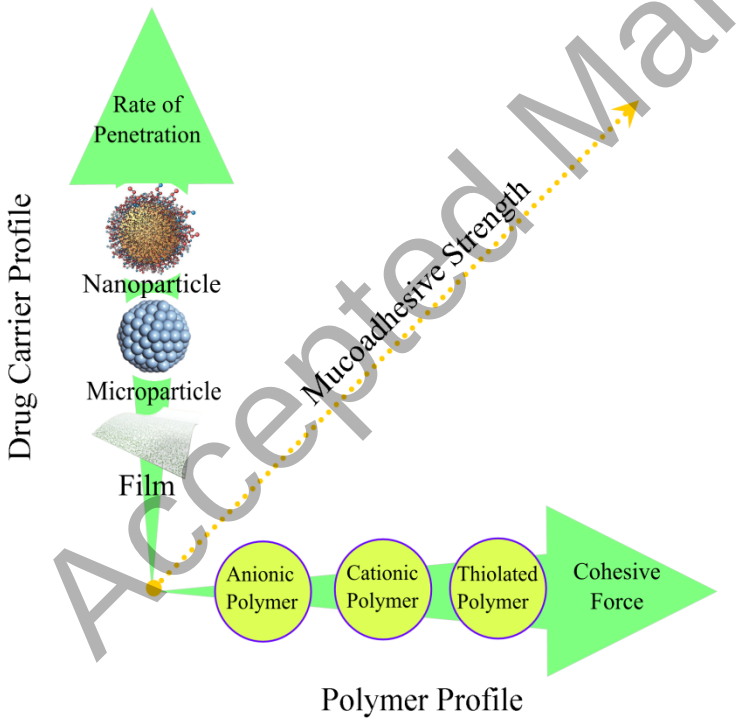

Fig 2: Polymers properties and their use in designing different types of mucoadhesive drug delivery systems

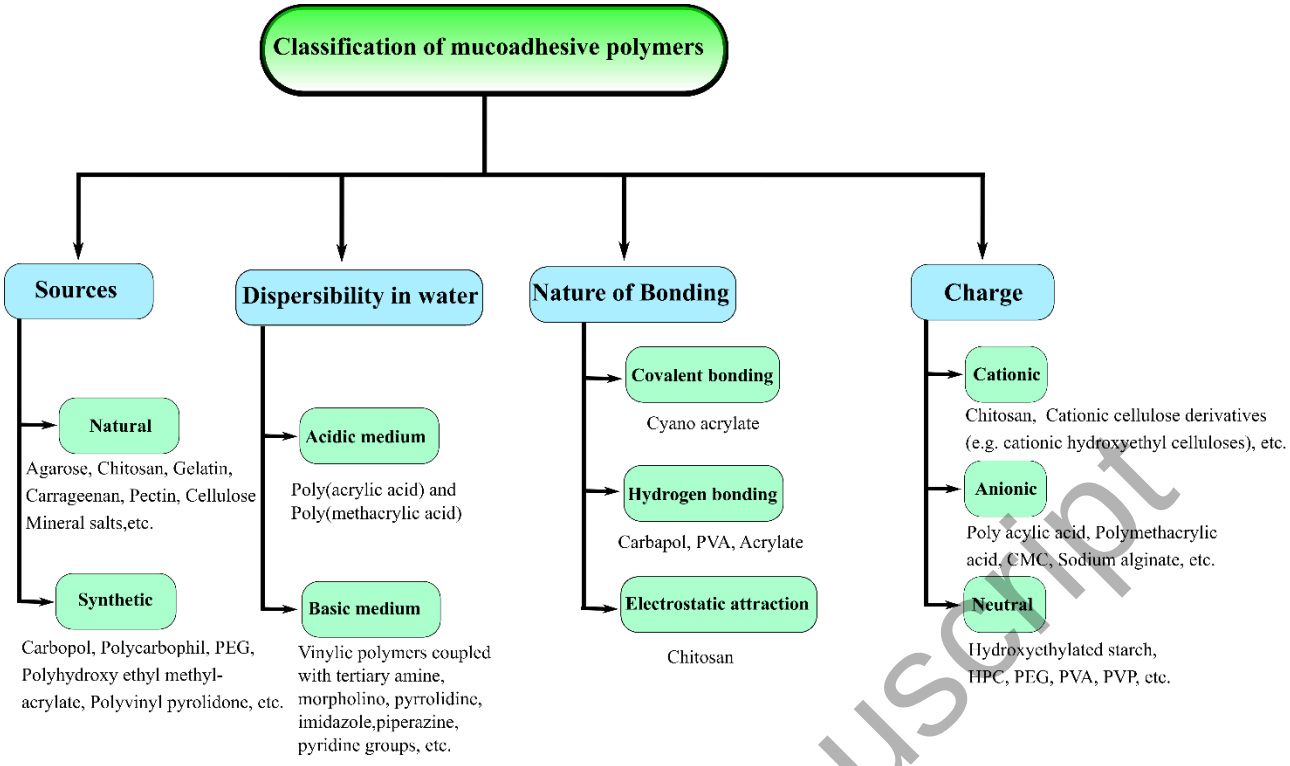

Fig 3: An overview of mucoadhesive polymers classified based on different ways i.e. source, solubility in water, nature of bonding, and charge

Table 1: Key aspects in the design and development of appropriate mucoadhesive drug delivery system

Aspects	Buccal	Sublingual	Ocular	Nasal	Vaginal	Comments
Surface area	214 ± 4.2 cm^2 (Collins & Dawes 1987)	26.5 ± 4.2 cm^2 (Collins & Dawes 1987)	125±15 mm^2 (Sotoyama et al. 1995)	150±16cm^2 (Harkema et al. 2006)	65.73 -107.07 cm^2 (Pendergrass et al. 2003)	Highly potent drugs for localized disease are desirable for optimal effects
Mucus secretion	0.5-2 litres (Collins & Dawes 1987)	0.8 to 1.5 *litres* (Collins & Dawes 1987)	0.1–0.4 g/*L and* 2L of tear per day (M S Norn 1965)	0.2 to 2 litre/*day*(Marom et al. 1984)	1-4mL/day (Weed & Carrera 1970)	Mucoadhesive, unidirectional and controlled drug release pattern is necessary to overcome challenges of mucosal secretion
pH	6.78 ±0.5 (Baliga et al. 2013)	6.78 ±0.5 (Baliga et al. 2013)	7.0±0.3 (Avetisov et al. 2014)	6.0±0.5 (England et al. 1999)	4.0±0.5 (Kim et al. 2018)	Drug should have maximum solubility at mucosal pH
Membrane thickness and properties	30-40 cells (500-600 µm) Both keratinized and non-keratinized stratified squamous epithelium(Teelavath & Patnaik 2019)	8–12 cells (0.1–0.2 mm) Stratified squamous, non-keratinized (Teelavath & Patnaik 2019)	5–7 cell layers 5µm keratinized and stratified (Gipson 2016)	5-6 cell layers 0.3–5 mm stratified squamous non-keratinized (Harkema et al. 2006)	8–10 cell layer (4-6 mm), Non-keratinized stratified squamous epithelium (Patyka et al. 2015)	Keratinized epithelium provides an additional barrier for drug absorption and thin epithelium support systemic delivery and vice versa
Blood supply	15-22 mL/min (Gilhotra et al. 2014)	26-35mL/min (Gilhotra et al. 2014)	1-2ml/min (Grudzińska & Modrzejewska 2018)	0.5-8mL/min (Dubois et al. 1998)	5-10mL/min(Wagner & Ottesen 1980)	Increased blood flow helps improve systemic absorption and helps in specific targeting of tissue supplied with rich blood vessels
Microbiome	10^8 - 10^{10}cells/mL (*Bifidobacterium*, *Lactobacillus* genera) (Dassi et al. 2018)	10^8 - 10^{10}cells/mL (*Bifidobacterium*, *Lactobacillus* genera) (Dassi et al. 2018)	10^8 -10^9cells/mL (*Staphylococcus*, *Haemophilus* genera) (Bharathi et al. 2010)	10^8 - 10^{10}cells/mL (*Pseudomonas and Acinetobacter* genera) (Escapa et al. 2018)	10^8 - 10^{10}cells/mL (*Lactobacillus* genera) (Valenti et al. 2018)	Microbiome provides additional barrier and helps to maintain local pH and in biodegradation of polymers
Site intervention	Taste receptors, speaking, chewing or swallowing	Taste receptors, speaking, chewing or swallowing	Highly sensitive, reflex blinking and tear production	Nasolacrimal and ciliary expulsion	Sexual and menstrual cycle-related intervention	Appropriate mucoadhesive technology is essential to overcome challenges associated with the concerned mucosal site
Target diseases	*Buccal ulceration*, *periodontal disease* and buccal cancer (Piemonte et al. 2018)	Infection and inflammation of *sublingual* gland and coronary heart disease (Alkurt & Peker 2009)	Conjunctivitis, dry *eyes*, cataracts, and glaucoma	Nasal obstruction, nasal allergies, *chronic sinus infections*, nasal polyps and neurological *diseases* (Bachert et al. 2014)	Vaginitis, contraceptives, STD, UTI, etc. (Madden et al. 2012)	Mucoadhesive based topical and local controlled drug delivery systems have shown enhanced bioavailability and therapeutic outcomes
Drug properties	MW (≤500Da), Log P (1-2), Solubility (>1mg/mL), Dose (≤10mg), Melting point (≤ 200) and Non-toxic (Wolk et al. 2014)	MW (≤500Da), Log P (1-2), Solubility (>1mg/mL), Dose (≤10mg), Melting point (≤ 200) and Non-toxic (Wolk et al. 2014)	MW (≤500Da), Log P (1-2), Solubility (>1mg/mL), Dose (≤10mg), Melting point (≤ 200) and Non-toxic (Patel et al. 2013)	MW (≤400Da), Log P (1-2), Solubility (>1mg/mL), Dose (≤10mg), Melting point (≤ 200) and Non-toxic (Gänger & Schindowski 2018)	MW (≤500Da), Log P (1-2), Solubility (>1mg/mL), Dose (≤10mg), Melting point (≤ 200) and Non-toxic (Ham & Buckheit 2015)	Physiochemical properties of drug and drug pharmacological and toxicological information are critical aspects to derive clinical response

Polymers	MW (≥100KD), Branched, Polyionic, Hydrocolloids, Biodegradable, Controlled drug release, and Non-toxic (Bagan et al. 2012)	MW (≥100KD), Branched, Polyionic, thiolated, Hydrocolloids, Biodegradable, Controlled drug release, and Non-toxic (Tangri & Madhav 2011)	MW (≥100KD), Branched, Polyionic, Hydrocolloids, Biodegradable, Controlled drug release, and Non-toxic (Asane et al. 2008)	MW (≥100KD), Branched, Polyionic, Hydrocolloids, Biodegradable, Controlled drug release, and Non-toxic (Asane et al. 2008)	MW (≥100KD), Branched, Polyionic, Hydrocolloids, Biodegradable, Controlled drug release, and Non-toxic (Acartürk 2009)	Macromolecules, degree of polymerization, properties of polymers and biodegradability plays a key role to achieve desired barrier pr operties

Table 2: Compositions of selected mucoadhesive drug delivery systems reported for different mucosal sites

Sl. No	Types of drugs	Indication	Dosage form	Polymer
Buccal Drug Delivery				
1.	**NSAIDs** Diclofenac sodium, Piroxicam,	Treatment of pain and inflammatory diseases	Tablet (Sonawane et al. 2017), (Modi et al. 2017)	Cashew nut tree gum, HPMCK4M, Carbopol, Chitosan, Sodium CMC
2.	**Antihypertensive** Diltiazem hydrochloride, Lisinopril, Metoprolol tartrate, Losartan potassium, Propranolol hydrochloride, Timolol maleate	Treatment of high blood pressure, heart failure, and after heart attacks		Carbopol-934P, Sodium CMC, HPMCK4M, Sodium alginate, guar-gum, HEC, Xanthan gum
3.	**Antiemetic** Domperidone, Granisetron hydrochloride	Treatment of nausea and vomiting		Carbopol 934P, Metocel K4M, Chitoan, Sodium alginate, HPMC 50cps
4.	**Antidiabetic** Repaglinide	Treatment of type 2 diabetes mellitus		Carbopol 934P, HPMC, Sodium CMC, HEC
5.	**Bronchodilator** Salbutamol sulfate	Treatment of asthma		Carbopol 934P, HPMC K4M,Chitosan
6.	**Vasoconstrictor** Sumatriptan	Migraine headaches and cluster headaches		Chitosan, HPMC K4M, Sodium alginate
7.	**Antiviral** Acyclovir	Treatment of herpes simplex virus infections, chickenpox, and shingles		Carbopol 943P, HPMC K100M
8.	**Anti-inflammatory** Benzydamine	Anti-inflammatory treatment of inflammatory conditions of the mouth and throat	Gel(Verma et al. 2011)	Sodium carboxymethyl cellulose, Hydroxyethylcellulose
9.	**Antifungal** Miconazole	Treatment of ringworm, pityriasis Versicolor, and yeast infections	Patch (Shaikh et al. 2011)	Acylates, polyisobutylene adhesive polysiloxane adhesives
10.	**Opioid analgesic** Fentanyl	Pain medication and together with other medications for anaesthesia	Film (Taghizadeh et al. 2009)	Pressure Sensitive Adhesive silicon (Si-PSA)

Sublingual Drug Delivery				
11.	**Anti-cholinergic agent** Scopolamine	Motion sickness	Spray (Sanghai et al. 2016), (Al-Ghananeem et al. 2007)	Chitosan
12.	**Anti-cholinergic agent** Physostigmine	Alzheimer's diseases, Glaucoma	Tablet (Saurí et al. 2017), (Preethi & Shabaraya 2017), (Varshosaz et al. 2015)	Starch 1500
13.	**ACE inhibitor** Captopril	Hypertension, Congestive heart failure, Renal problems associated with diabetes		Sodium starch glycolate
14.	**Calcium channel blocker** Nifedipine	Hypertension and Angina		Croscarmellose, Sodium aspartame, Alcoholic solution of PVP
15.	**Antacid** Rabeprazole sodium	Ulcerative GERD		Crospovidone, Croscarmellose sodium
16.	**Calcium channel blocker** Amlodipine besylate	Hypertension Coronary Artery Disease		Crospovidone, Avicel PH-102, Tulsion671
17.	**Opioid analgesic** Fentanyl citrate	Used as a pain medication		Croscarmellose, Silicified microcrystalline cellulose
18.	**Anti-anxiety** Lorazepam	Used for anxiety and to relieve muscle spasms		Microcrystalline cellulose, Polacrilin potassium
19.	**Hypnotic** Zolpidem tartrate	Treatment of insomnia.		Colloidal silicon dioxide, Silicified microcrystalline cellulose, Croscarmellose
Ocular Drug Delivery				
20.	**Antibiotic** Gatifloxacin	Treatment for bacterial infection	Gel(Irimia et al. 2018), (Prabhu & Koland 2019), (Jagdale et al. 2016), (Kalam et al. 2008)	Alginate and HPMC
21.	**Quinolone antibiotic** Ofloxacin	Treatment for bacterial infection		Carbopol 940 and HPMC
22.	**Beta-blockers** Timolol maleate	Treatment of high pressure inside the eye due to glaucoma		Poly(N-isopropyl acrylamide)-Chitosan, Pluronic F-127 and Chitosan
23.	**Cholinergic parasympathomimetic agent** Pilocarpine	Treatment of ocular hypertension		Alginate and Pluronic-based *in situ* gelling, Xyloglucan
24.	**NSAIDs** Indomethacin	Inflammatory eye diseases		Gelrite (gellan gum)
Nasal Drug Delivery				
25.	**Dopaminergic agonist** Apomorphine	Parkinson's disease	Powder (Alhalaweh et al. 2011), (Tas et al. 2009)	Carboxymethyl cellulose, Carbopol971P, Degradable starch microspheres
26.	**NSAIDs** Ketorolac acid	Management of moderate to severe pain	Spray(Quadir et al. 2000)	Microcrystalline cellulose
27.	**Gonadotropin-releasing hormone (GnRH) agonist** Leuprolide	Treatment of anaemia	Powder (Alhalaweh et al. 2011), (Tas et al. 2009)	Microcrystalline cellulose / Hydroxypropyl cellulose

28.	**Neurotransmitter** Dopamine	Treatment of very low blood pressure	Liquid (Chaturvedi et al. 2011)	Hydroxypropyl cellulose
29.	**Prokinetic agents** Metoclopramide	Treatment of the symptoms of slow stomach emptying (gastroparesis) in patients with diabetes	Gel(Mahajan & Gattani 2010) Powder(Alhalaweh et al. 2011), (Tas et al. 2009)]	Hydroxypropyl cellulose, Chitosan, Carbopol981P/, Carbopol934/ Hydroxypropyl cellulose
30.	**Contraceptive** Levonorgestrel	Birth control	Liquid (Chaturvedi et al. 2011)	Carbopol934P, Chitosan
31.	**Aminoglycoside antibiotics** Gentamicin	Treatment of bacterial infections	Powder(Alhalaweh et al. 2011), (Tas et al. 2009)	Degradable starch microspheres / Sodium tauro-24,25-dihydro fusidate
32.	**Peptide hormone** Insulin	Treatment of Diabetes mellitus	Liquid (Chaturvedi et al. 2011)	Chitosan
Vaginal Drugs Delivery				
33.	**Hormone analog** Progesterone	Infertility, secondary amenorrhea	Gel (Mahajan & Gattani 2010)	Polycarbophil and Carbopol® 974P
34.	**Non-ionic surfactants** Nonoxynol-9	Contraception (As a spermicide)	Gel (Mahajan & Gattani 2010)	Sodium carboxymethylcellulose
35.	**Prostaglandin E2 (PGE2)** Dinoprostone	Induction of labor	Suppository (Kurian et al. 2016)	Colloidal silicon dioxide
36.	**Imidazole antifungal** Butoconazole	Fungal infection	Cream (Martin Lopez 2015)	Hydroxypropyl methylcellulose (Methocel K4M)
37.	**Antiprotozoal** Metronidazole	Bacterial vaginosis	Gel (Mahajan & Gattani 2010)	Carbopol® 974P
38.	**Steroid hormone** Estradiol	Atrophic vaginitis	Vaginal tablet (Hiorth et al. 2014)	-
39.	**Polyol compound** Glycerin	Vaginal dryness symptoms	Moisturizer (Cunha et al. 2014)	Polycarbophil and Carbopol® 974P
40.	**Acid-buffering** Monosodium citrate	Restoration and maintenance of vaginal acidity	Gel (Ahmad et al. 2008)	Tragacanth, Acacia gum

Table 3: Summary of patents on mucoadhesive composition used for drug delivery applications.

S.N.	Patent No	Patent title	Active Pharmaceutical Ingredients (APIs)	Dosage forms/Carriers	Compositions/Outcomes
Oral route					
1	US4755386A	Buccal formulation	Estradiol	Tablet	Buccal tablet formulation comprises of 2 to about 10% w/w of carbomer 934 P; about 3 - about 6% w/w of Crospovidone, sugar and about 50 micrograms to 2 mg of Estradiol, which is prepared using a compression force of approx 1000 PSI, which is disintegrate in about 10-15 minutes (Hsiao & Cacace 1988)..
2	US6242004B1	Bioadhesive tablet	Piroxicam	Tablet	Bioadhesive tablet contained a bioadhesive layer comprising of 5 100% w/w of Methocel K15M, Methocel K100M as the bioadhesive materials and Melatonin as therapeutics of about 5 % w/w. The tablet shows a controlled drug release for 8 hours without disintegrating (Rault 2001)
3	US10536800	Solid mucoadhesive composition	*Sambucus nigra, Centella asiatica*	Tablet	Mucoadhesive tablet comprises ingredients of Sambucus nigra, Centellaasiatica and Echinacea purpurea. It contains excipients Carbopol 974P (10-20% w/w), Polyvinyl pyrrolidone (10-20% w/w) and Lactose. Mucoadhesive sublingual film exhibits a retention time of more than5 hours at the site of application (Levine & Satter 2011).
4	US20060068004A1	Buccal delivery of sea cucumber tablets	*Actinopyga echinites*	Tablet	Formulation comprising of sea cucumber extract is approximately 5% - 35% by weight of tablet formulation with other excipients like sugar, Maltose, Starch hydrolysate, and Xylitol. Comparatively, low pressure was used for compression. The dosage units dissolved quickly and

					allow rapid absorption of the sea cucumber tablets via the buccal mucus membrane into the systemic circulation(Shah 2006).
5	US6197346B1	Bioadhesive microspheres and their use as drug delivery and imaging systems	Sulfasalazine	Micro-sphere	Mucoadhesive polymeric microspheres consisting of 1-5% w/w of mucoadhesive polymers, Sulfasalazine and Betamethasone and Barium sulphate as a contrast medium. In the treatment of bowel disease, bioadhesive were recommended for oral administration of ample drugs (Mathiowitz et al. 2001)
6	US7604795B1	Nanoparticles for protein drug delivery	Peptide drug	Nano-particle	Mucoadhesive nanoparticles contain Chitosan, Polyglutamic acid, and a peptide drug or bioactive agent for release by the use of oral or nasal route with improved permeability (Sung et al. 2009).
7	US11574407	Mucoadhesive Oral Formulations of High Permeability, High Solubility Drugs	Metformin Ranitidine	Nano-particle	Mucoadhesive formulation consisting of Poly (Adipic) anhydride, Poly (Fumaric-co-sebacic) anhydride and therapeutic agents such as Valacyclovir, Gabapentin, metformin, and ranitidine HCl, etc. The insertion of mucoadhesives in the solid oral dosage form brings the dosage form into close immediacy with the target epithelium and enhances diffusion of the drug into intestinal tissue (Jacob et al. 2007).
8	US13695113	**Pharmaceutical powder compositions**	Benzodiazepine	Powder	Pharmaceutical dosage form consisting of mucoadhesive agents like Hydroxyethylcellulose and dispersing agents such as Ethylene oxide, Propylene oxide copolymers gives good absorption of drug delivery in the bloodstream via the oral route (Coghill & Armstrong 2013)
9	US9326981	Sublingual apomorphine	Apomorphine	Film	The sublingual film compose of Apomorphine for the treatment of Parkinson's disease (Giovinazzo et al. 2016)
Topical route					

10	US20050214230	Novel Stomatological gel	Chlorhexidine gluconate, Diclofenac	Gel	Mucoadhesive gel of Diclofenac sodium and Chlorhexidine gluconate were competent in delivering the active ingredient to the affected area and having good retention quality and were helpful for the treatment of pain-related to different dental diseases (Mehta et al. 2005).
11	US11525837	Mucoadhesive thermoresponsive medicament-carrier composition	5-Aminolevulinic acid	Gel	The gel formulation comprising of Carbopol 941P, 5-Aminolevulinic acid was particularly helpful for topical delivery of biologically active compounds and used in the photodynamic diagnosis or therapy with advantages of improved efficacy and few side effects (Tsui-Min Tsai 2007).
12	US13277130	Mucoadhesive xyloglucan-containing formulations useful in medical devices and in pharmaceutical formulations	Diclofenac sodium	Aqueous solution	Mucoadhesive and controlled release formulation consisting of 0.05% to 5% by weight of a natural polymer with Xyloglucan structure, 10% to 70% by weight of Glycerol and a therapeutically active agent such as Diclofenac sodium was helpful in application to the nasal, oral, and vaginal mucous membranes like moisturizing and softening agents or as pharmaceutical release system with enhanced bio-adhesiveness (Bottoni et al. 2012).
13	US5876744A	Highly bioadhesive and mucoadhesive compositions containing polyvinyl alcohol, polycarbophil and biopolymer for the treatment of skin conditions and as vehicles for active ingredients	-	Aqueous Solution	Compositions having high bio-adhesion, mucoadhesion and viscoelasticity, containing mixtures of synthetic polymers, such as Polyvinyl alcohol and Polycarbophil, and of biopolymers, such as alginic acid, hyaluronic acid and dermatan sulfate, useful in the treatment of skin and mucosal tissues dryness and dehydration, and suitable as vehicles for active ingredients in percutaneous absorption (Valle et al. 1999).

Ocular route					
14	US9878000B2	Mucoadhesive nanoparticle composition comprising immunosuppressant and methods of use thereof	Cyclosporine	Nano-particle	Mucoadhesive nanoparticle consisting of a hydrophobic block comprising polylactide and a hydrophilic block Dextran that contains an immunosuppressant administration of the immunosuppressive drug to a mucosal site(Gu et al. 2018).
15	US6696426B2	Preservative-free ophthalmic oxazolidinone antibiotic drug delivery systems	Oxazolidinone	Solution	The ophthalmic formulation consists of Oxazolidinone antimicrobial drug, in a physiologically compatible buffer. The composition is particularly beneficial for the treatment of eye infections caused by gram-positive bacteria (Singh et al. 2004)
16	US7893040B2	Cyclodextrin nanotechnology for ophthalmic drug delivery	Cyclodextrin	Solution	Ophthalmic composition made of 0.1% - 90% drug/Cyclodextrin complex in physiological buffer. Cyclodextrin formulations helps to deliver therapeutically effective drug amounts to the posterior section of the eye. (Loftsson & Stefánsson 2011)
17	US6489335B2	Treatment of Ocular diseases	Tacrolimus	Aqueous based cream	Composition discloses a drop, spray or implant of Tacrolimus in an inert carrier like microspheres or liposomes to provide a controlled release of encapsulated drug. Cyclosporin A has good penetration into the cornea but not into the anterior chamber, and does not increase intraocular pressure or cause cataracts (Peyman 2002)
Nasal route					
18	US5935604A	Nasal drug delivery composition containing nicotine	Nicotine	Micro-spheres	Nasal drug delivery contains Nicotine for rapid absorption and a controlled release phase can be achieved by providing an ion-exchange material (polymeric material like Polysaccharide or bioadhesive ion-exchange microspheres) which will

					form a complex with the Nicotine (Illum 1999)
19	US7604795B1	Nanoparticles for protein drug delivery	Polyglutamic acid	Nano-particle	Chitosan and Polyglutamic acid with bioactive agents in delivery nasal absorption enhance permeability. Chitosan and its derivatives are effective and safe absorption enhancers to improve mucosal (nasal, peroral) delivery of hydrophilic macromolecules such as Protein and Peptide drugs (Sung et al. 2009)
20	US5578588	Controlled release nasal testosterone gels, methods and pre-filled multi-dose applicator systems for prenasal administration	Testosterone	Gel	The composition discloses a lipophilic matrix consisting of mineral oil, Paraffin, Isopropyl myristate, Isopropyl palmitate and therapeutically active compound like Testosterone. Intranasal Testosterone gels offer many advantages that include rapid adsorption due to abundant capillary vessels, fast onset of action, avoidance of hepatic first-pass metabolism, a utility for chronic medication and ease of administration. (Mattern & Hacker 1996).
Vaginal route					
21	US6982091B2	Vaginal delivery of chemotherapeutic agents and inhibitors of membrane efflux systems for cancer therapy	Verapamil	Solution	The invention is for a mucosal and trans-mucosal delivery system comprising of a triglyceride of fatty acids and Polyethylene glycol contain chemotherapeutic agent and/or inhibitor of membrane efflux systems to the vagina for topical vaginal and/or systemic cancer therapy using a mucoadhesive composition. (Pauletti et al. 2006)
22	US20170014458A1	Mucoadhesive sustained-release	A probiotic strain of a genus Lactobacillus	Vaginal tablet	The vaginal tablet consists of a probiotic strain of a genus Lactobacillus

		vaginal tablet			compressed with a suitable excipient for sustain release of therapeutic agents for vaginal infections (Throl et al. 2015).
23	US20190290582	Vaginal hydrogel for delivery of therapeutics	Glycosaminoglycan	Vaginal hydrogel	The vaginal hydrogel composes of glycosaminoglycan. The composition mainly consists of a mucoadhesive agent as well as a therapeutic agent. The composition delivers the therapeutic at a pH that is optimal for the vaginal environment, 3.5 and 5 (Gerton & Mann 2018).
24	US8178123B2	Method for augmentation of intraepithelial and systemic exposure of therapeutic agents having substrate activity for cytochrome P450 enzymes and membrane efflux systems following vaginal and oral cavity administration	Cytochrome P-450 enzymes	vaginal or buccal mucoadhesive film, vaginal suppository or buccal pellet	Vaginal or buccal delivery of therapeutic agents having a substrate affinity for metabolic Cytochrome P-450 enzymes and membrane efflux transporter systems. A method for aug mentation of systemic exposure to the therapeutic agents having a substrate affinity for Cytochrome P-450 enzymes and membrane efflux transporter systems, by delivering said agents to the systemic circulation through the vaginal or buccal mucosa. (Pauletti et al. 2012)
25	US10600849	Intravaginal mucosal or transmucosal delivery of antimigraine and antinausea drugs	Zolmitriptan dexamethasone	Intravaginal Device	Intravaginal device comprising of a mucoadhesive agent, penetration enhancer and hydrophilic or lipophilic carries for the local and systemic delivery of the antimigraine and/or antinausea (Pauletti et al. 2004).