Journal of Controlled Release 153 (2011) 106–116

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Advances in oral transmucosal drug delivery

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ARTICLE INFO

Article history:
Received 27 September 2010
Accepted 24 January 2011
Available online 4 February 2011

Keywords:
Transmucosal
Permeation pathways
Buccal absorption
Mucoadhesive
Dosage forms

ABSTRACT

The successful delivery of drugs across the oral mucosa represents a continuing challenge, as well as a great opportunity. Oral transmucosal delivery, especially buccal and sublingual delivery, has progressed far beyond the use of traditional dosage forms with novel approaches emerging continuously. This review highlights the physiological challenges as well as the advances and opportunities for buccal/sublingual drug delivery. Particular attention is given to new approaches which can extend dosage form retention time or can be engineered to deliver complex molecules such as proteins and peptides. The review will also discuss the physiology and local environment of the oral cavity *in vivo* and how this relates to the performance of transmucosal delivery systems.

Contents

1. Introduction

The cost involved both in terms of money and time in the development of a single new chemical entity has made it mandatory for pharmaceutical companies to reconsider delivery strategies to improve the efficacy of drugs that have already been approved. However, despite the tremendous advances in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents due to low cost, ease of administration and high level of patient compliance. However, significant barriers are imposed on the per oral administration of drugs, such as hepatic first pass metabolism and drug degradation within the gastrointestinal (GI) tract prohibiting the oral administration of certain classes of drugs especially biologics e.g. peptides and proteins. Consequently, other absorptive mucosae are being considered as potential sites for drug administration including the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. These transmucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery such as the possible bypass of the first pass effect and avoidance of presystemic elimination

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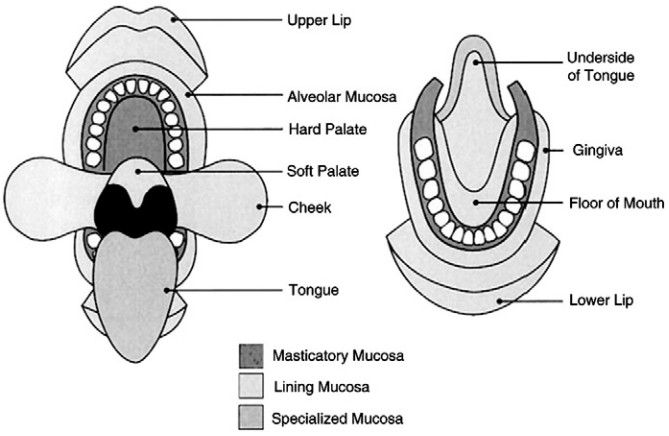
within the GI tract [1]. Amongst these, delivery of drugs to the oral cavity has attracted particular attention due to its potential for high patient compliance and unique physiological features. Within the oral mucosal cavity, the delivery of drugs is classified into two categories: (i) local delivery and (ii) systemic delivery either via the buccal or sublingual mucosa. This review examines the physiological considerations of the oral cavity in light of systemic drug delivery and provides an insight into the advances in oral transmucosal delivery systems.

2. Overview of the oral mucosa

The anatomical and physiological properties of the oral mucosa have been extensively reviewed by several authors [1–3]. The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Fig. 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells (Fig. 2). The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss [4]. Beneath the epithelium are the basement membrane, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue.

Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums) [5]. The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propia and a submucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces; which are both keratinized and some non-keratinized [6].



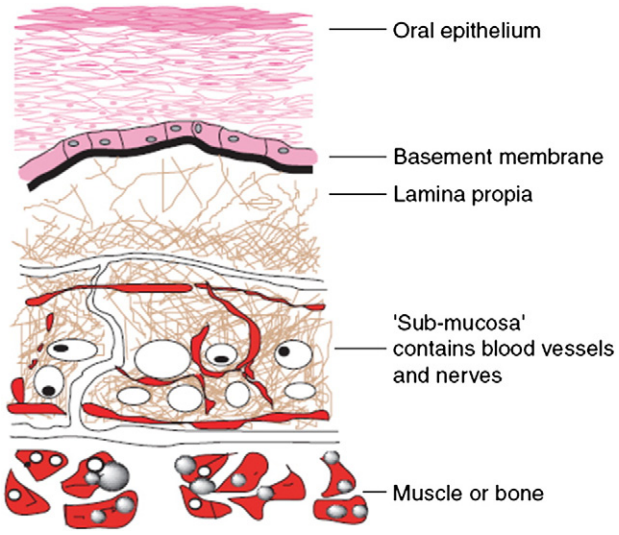


Fig. 2. Schematic diagram of buccal mucosa [8].

3. Physiological barriers for oral transmucosal drug delivery

The environment of the oral cavity presents some significant challenges for systemic drug delivery. The drug needs to be released from the formulation to the delivery site (e.g. buccal or sublingual area) and pass through the mucosal layers to enter the systemic circulation. Certain physiological aspects of the oral cavity play significant roles in this process, including pH, fluid volume, enzyme activity and the permeability of oral mucosa. For drug delivery systems designed for extended release in the oral cavity (e.g. mucodhesive systems), the structure and turnover of the mucosal surface is also a determinant of performance. Table 1 provides a comparison of the physiological characteristics of the buccal mucosa with the mucosa of the GI tract.

The principle physiological environment of the oral cavity, in terms of pH, fluid volume and composition, is shaped by the secretion of saliva. Saliva is secreted by three major salivary glands (parotid, submaxillary and sublingual) and minor salivary or buccal glands situated in or immediately below the mucosa. The parotid and submaxillary glands produce watery secretion, whereas the sublingual glands produce mainly viscous saliva with limited enzymatic activity. The main functions of saliva are to lubricate the oral cavity, facilitate swallowing and to prevent demineralization of the teeth. It also allows carbohydrate digestion and regulates oral microbial flora by maintaining the oral pH and enzyme activity [13,14]. The daily total salivary secretion volume is between 0.5 and 2.0 l. However, the volume of saliva constantly present in the mouth is around 1.1 ml, thus providing a relatively low fluid volume available for drug release from delivery systems compared to the GI tract. Compared to the GI fluid, saliva is relatively less viscous containing 1% organic and inorganic materials. In addition, saliva is a weak buffer with a pH around 5.5–7.0. Ultimately the pH and salivary compositions are dependent on the flow rate of saliva which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation [15]. For example, at high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH.

Saliva provides a water rich environment of the oral cavity which can be favorable for drug release from delivery systems especially those based on hydrophilic polymers. However, saliva flow decides the time span of the released drug at the delivery site. This flow can lead to premature swallowing of the drug before effective absorption occurs through the oral mucosa and is a well accepted concept known as "saliva wash out". However, there is little research on to what

Table 1
Comparison of different mucosa [9–12].

Absorptive site	Estimated Surface area	Percent total surface area	Local pH	Mean fluid volume (ml)	Relative enzyme activity	Relative drug absorption capacity
Oral cavity	100 cm^2 (0.01 m^2)	0.01	5.8–7.6	0.9	Moderate	Moderate
Stomach	0.1–0.2 m^2	0.20	1.0–3.0	118	High	Moderate
Small intestine	100 m^2	98.76	5.0–7.0	212	High	High
Large intestine	0.5–1.0 m^2	0.99	6.0–7.4	187	Moderate	Low
Rectum	200–400 cm^2 (0.04 m^2)	0.04	7.0–7.4	–	Low	Low

delivery from different drug delivery systems and thus further research needs to be conducted to better understand this effect.

Drug permeability through the oral (e.g. buccal/sublingual) mucosa represents another major physiological barrier for oral transmucosal drug delivery. The oral mucosal thickness varies depending on the site as does the composition of the epithelium. The characteristics of the different regions of interest in the oral cavity are shown in Table 2. The mucosa of areas subject to mechanical stress (the gingiva and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, sublingual, and buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides [16]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia [17,18].

Within the oral mucosa, the main penetration barrier exists in the outermost quarter to one third of the epithelium [23,24]. The relative impermeability of the oral mucosa is predominantly due to intercellular materials derived from the so-called membrane coating granules Q (MCGs) [2]. MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia [25]. They are found near the upper, distal, or superficial border of the cells, although a few occur near the opposite border [25]. Several hypotheses have been suggested to describe the functions of MCGs, including membrane thickening, cell adhesion, production of a cell surface coat, cell desquamation and as a permeability barrier. Hayward [25] summarized that the MCGs discharge their contents into the intercellular space to ensure epithelial cohesion in the superficial layers, and this discharge forms a barrier to the permeability of various compounds. Cultured oral epithelium devoid of MCGs has been shown to be permeable to compounds that do not typically penetrate the oral epithelium [26]. In addition, permeation studies conducted using tracers of different sizes have demonstrated that these tracer molecules did not penetrate any further than the top 1–3 cell layers. When the same tracer molecules were introduced sub-epithelially, they penetrated through the intercellular spaces. This limit of penetration coincides with the level where MCGs are observed. This same pattern is observed in both keratinized and non-keratinized epithelia [3], which indicates that MCGs play a more significant role as a barrier to permeation compared to the keratinization of the epithelia [27].

The cells of the oral epithelia are surrounded by an intercellular ground substance called mucus, the principle components of which are complexes made up of proteins and carbohydrates; its thickness ranges from 40 to 300 μm [28]. In the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Although most of the mucus is water (≈95–99% by weight) the key macromolecular components are a class of glycoprotein known as mucins (1–5%). Mucins are large molecules with molecular masses ranging from 0.5 to over 20 MDa and contain large amounts of carbohydrate. Mucins are made up of basic units (≈400–500 kDa) linked together into linear arrays. These big molecules are able to join together to form an extended three-dimensional network [29] which acts as a lubricant allowing cells to move relative to one another, and may also contribute to cell–cell adhesion [14]. At physiological pH, the mucus network carries a negative charge due to the sialic acid and sulfate residues and forms a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer [30–32]. This gel layer is believed to play a role in mucoadhesion for drug delivery systems which work on the principle of adhesion to the mucosal membrane and thus extend the dosage form retention time at the delivery site.

Another factor of the buccal epithelium that can affect the mucoadhesion of drug delivery systems is the turnover time. The turnover time for the buccal epithelium has been estimated to be 3–8 days compared to about 30 days for the skin [2].

4. Physiological opportunities for oral transmucosal drug delivery

Despite the challenges, the oral mucosa, due to its unique structural and physiological properties, offers several opportunities for systemic drug delivery. As the mucosa is highly vascularized any drug diffusing across the oral mucosa membranes has direct access to the systemic circulation via capillaries and venous drainage and will bypass hepatic metabolism. The rate of blood flow through the oral mucosa is substantial, and is generally not considered to be the rate-limiting factor in the absorption of drugs by this route (Table 2).

For oral delivery through the GI tract, the drug undergoes a rather hostile environment before absorption. This includes a drastic change in GI pH (from pH 1–2 in the stomach to 7–7.4 in the distal intestine), unpredictable GI transit, the presence of numerous digestive enzymes and intestinal flora [33,34]. In contrast to this harsh environment of the GI tract, the oral cavity offers relatively consistent and friendly physiological conditions for drug delivery which are maintained by the continuous secretion of saliva. Compared to secretions of the GI tract, saliva is a relatively mobile fluid with less mucin, limited enzymatic activity and virtually no proteases [35].

Enzyme degradation in the GI tract is a major concern for oral drug delivery. In comparison, the buccal and sublingual regions have less enzymes and lower enzyme activity, which is especially favorable to protein and peptide delivery. The enzymes that are present in buccal mucosa are believed to include aminopeptidases, carboxypeptidases,

Table 2
Characteristics of oral mucosa.

Tissue	Structure	Thickness (μm) [20]	Turnover time (days) [22]	Surface area ($cm^2 \pm$ SD) [6]	Permeability [19]	Residence time [19]	Blood flow* [21]
Buccal	NK	500–600	5–7	50.2 ± 2.9	Intermediate	Intermediate	20.3
Sublingual	NK	100–200	20	26.5 ± 4.2	Very good	Poor	12.2
Gingival	K	200	–	–	Poor	Intermediate	19.5
Palatal	K	250	24	20.1 ± 1.9	Poor	Very good	7.0

Table 3
Permeabilities of water for human skin and oral mucosa regions (Adapted from Squier and co-workers [38]).

Region[a]	*Kp* ($\times 10^{-7} \pm$SEM cm/min)
Skin	44 ± 4[b]
Oral mucosa	
Hard palate	470 ± 27
Buccal mucosa	579 ± 16
Lateral border of tongue	772 ± 23
Floor of mouth	973 ± 33

[a] Human (n = 58).
[b] Permeability constant (Kp) significantly different compared to oral mucosa at $p<0.05$.

Table 4
Regional difference in permeability expressed in terms of a uniform permeability barrier (Adapted from Squier and Hall [39]).

Tissue region	Thickness (μm ± SEM)		Mean Kp expressed in terms of a uniform barrier of 100 μm thick ($\pm$SEM $\times 10^{-7}$)	
	Total epithelium	Permeability barrier	Water	Horseradish peroxidise
Skin	69 ± 4	16 ± 1	21.1 ± 4.3	9.4 ± 1.8
Gingiva	208 ± 9	35 ± 4	98.3 ± 16.0	79.5 ± 11.4
Buccal mucosa	772 ± 20	282 ± 17	173.2 ± 24.6	99.1 ± 10.6
Floor of mouth	192 ± 7	23 ± 1	1271.3 ± 203.1	331.6 ± 51.9

dehydrogenases and esterases. Aminopeptidases may represent a major metabolic barrier to the buccal delivery of peptide drugs. Proteolytic activity has been identified in buccal tissue homogenates from various species and a number of peptides have been shown to undergo degradation [36]. Bernkop-Schnurch and co-workers [37] studied the peptidase activity on the surface of porcine buccal mucosa and found that no carboxypeptidase or dipeptidyl peptidase IV activity was detected on the buccal mucosa, while aminopeptidase N activity was detected using Leu-*p*-nitroanilide. However, this study represents only the surface of procine mucosa and hence more research will be required to fully characterize the levels and type of different enzymes presents especially in human buccal mucosa.

The buccal and sublingual routes are the focus for drug delivery via the oral mucosa because of the higher overall permeability compared to the other mucosa of the mouth. The effective permeability coefficient values reported in the literature across the buccal mucosa for different molecules, range from a lower limit of 2.2×10^{9} cm/s for dextran 4000 across rabbit buccal membrane to an upper limit of 1.5×10^{5} cm/s for both benzylamine and amphetamine across rabbit and dog buccal mucosa, respectively [2]. The oral mucosa is believed to be 4–4000 times more permeable than that of skin [24]. Squier and co-workers [38] revealed that the permeability of water through the buccal mucosa was approximately 10 times higher, whilst in floor of the mouth the permeability was approximately 20 times higher than skin (Table 3). In another study by Squier and Hall [39], the permeability constant was calculated for water and Horseradish peroxidase across skin and oral mucosal surface (Table 4).

Drugs can be transported across epithelial membranes by passive diffusion, carrier-mediated active transport or other specialized mechanisms. Most studies of buccal absorption indicate that the predominant mechanism is passive diffusion across lipid membranes via either the paracellular or transcellular pathways (Fig. 3) [40–44]; although these may actually be the same pathway. The hydrophilic nature of the paracellular spaces and cytoplasm provides a permeability barrier to lipophilic drugs but can be favorable for hydrophilic drugs. In contrast, the transcellular pathway involves drugs penetrating through one cell and the next until entering the systemic circulation. The lipophilic cell membrane offers a preferable route for lipophilic drugs compared to hydrophilic compounds [1]. Drugs can transverse both pathways simultaneously although one route could be predominant depending on the physicochemical properties of the drug [31].

Although passive diffusion is the predominant mechanism of absorption from the oral mucosa, specialized transport mechanisms have also been reported for a few drugs and nutrients. A study by Kurosaki and co-workers [45] reported that the rate of absorption of D-glucose from the dorsal and ventral surface of the tongue was significantly greater than that of L-glucose, which indicated the occurrence of some specialized transport mechanism. In addition, the existence of sodium-dependant D-glucose transport system was reported across stratified cell layer of human oral mucosal cells [46]. Table 5 provides examples of several drugs transported via different

5. Oral transmucosal drug delivery technologies

Continuous research into the improvement of the oral transmucosal delivery of drugs has resulted in the development of several conventional and novel dosage forms like solutions, tablets/lozenges, chewing gums, sprays, patches and films, hydrogels, hollow fibers and microspheres. These dosage forms can be broadly classified into liquid, semi-solid, solid or spray formulations [54]. Oral transmucosal systems for systemic drug delivery are usually designed to deliver the drug for either i) rapid drug release for immediate and quick action, ii) pulsatile release with rapid appearance of drug into systemic circulation and subsequent maintenance of drug concentration within therapeutic profile or iii) controlled release for extended period of time (as depicted in Fig. 4).

Several companies are currently engaged in development and commercialization of drug delivery technologies based on oral transmucosal systems. Table 6 shows a list of products commercially approved for oral transmucosal administration. A list of companies currently engaged in developing technology platforms for oral transmucosal drug delivery system is shown in Table 7. The majority of the commercially available formulations are solid dosage forms such as tablets and lozenges. A few companies have had successes in developing technology platforms for films or patches with most aimed at achieving rapid drug release and clinical response. The limitations associated with such type of dosage forms include uncontrolled swallowing of released drug into GI tract and difficulties in holding the dosage form at the site of absorption. These are the areas where more research focus is required, especially using mucoadhesive systems.

5.1. Mucoadhesive systems

Other than the low surface area available for drug absorption in the buccal cavity, the retention of the dosage form at the site of absorption is another factor which determines the success or failure of buccal drug delivery system. The utilization of mucoadhesive systems is essential to maintain an intimate and prolonged contact of the formulation with the oral mucosa allowing a longer duration for absorption. Some adhesive systems deliver the drug towards the mucosa only with an impermeable product surface exposed to the oral cavity which prevents the drug

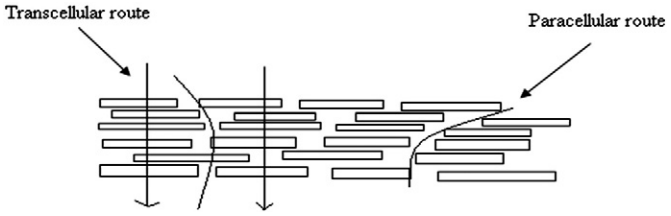


Table 5
Examples of drugs transported via different mechanisms through buccal mucosa.

Name of Drug	Transport mechanism	Path way	Tissue	References
5-Aza-2′-deoxycytidine	Passive	Not defined	Buccal mucosa	[40]
2′, 3′-dideoxycytidine	Passive	Not defined	Buccal mucosa	[41]
Flecainide	Passive	Paracellular	Buccal mucosa	[42]
Sotalol	Passive	Paracellular	Buccal mucosa	[42]
Nicotine	Passive	Paracellular, Transcellular	TR146 Cell culture and buccal mucosa	[43]
Lamotrigine	Passive	Transcellular	Buccal mucosa	[44]
Galantamine	Passive	Not defined	Human oral epithelium and buccal mucosa	[47]
Naltrexone	Passive	Not defined	Buccal mucosa	[48]
Buspirone	Passive	Transcellular	Buccal mucosa	[49]
Ondansatron HCl	Passive	Not defined	Buccal mucosa	[50]
Monocarboxylic acids	Carrier mediated	Carrier mediated	Primary cultured epithelial cells	[51,52]
Glucose	Carrier mediated	Carrier mediated	Buccal, oral mucosal cells and dorsum of tongue	[53]

release into oral cavity [76]. For example, Lopez and co-workers [77] designed bilaminated films to provide unidirectional release of drug and avoid buccal leakage. They contained a bioadhesive layer made up of chitosan, polycarbophil, sodium alginate and gellan gum while backing layer made up of ethyl cellulose.

5.1.1. Theories of mucoadhesion

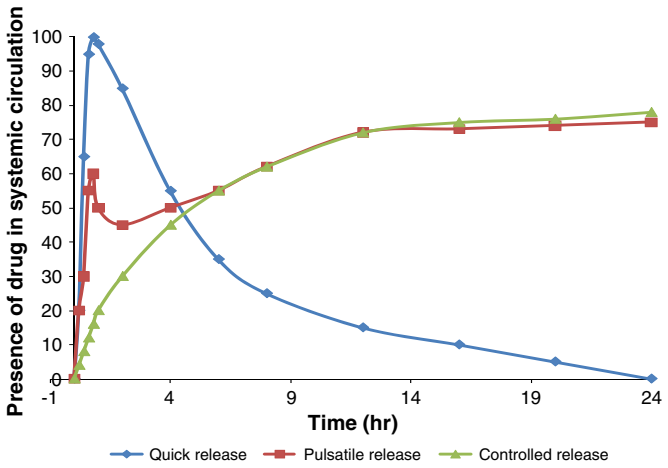
The most widely investigated group of mucoadhesives used in buccal drug delivery systems are hydrophilic macromolecules containing numerous hydrogen bond-forming groups [78]. The presence of hydroxyl, carboxyl or amine groups on the molecules favors adhesion. They are called 'wet' adhesives as they are activated by moistening and will adhere non-specifically to many surfaces. Unless water uptake is restricted, they may over hydrate to form slippery mucilage. For dry or partially hydrated dosage forms two basic steps in mucoadhesion have been identified [79]. Step one is the 'contact stage' where intimate contact is formed between the mucoadhesive and mucous membrane. Within the buccal cavity the formulation can usually be readily placed into contact with the required mucosa and held in place to allow adhesion to occur. Step two is the 'consolidation' stage where various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanisms involved. These theories include mechanical-interlocking, electrostatic, diffusion–interpenetration, adsorption and fracture processes [80], whilst undoubtedly the most widely accepted theories are founded upon surface energy thermodynamics and interpenetration/diffusion [81]. The wettability theory is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the spreadability of the drug delivery system across the biological substrate [82]. The electronic theory describes that adhesion occurs by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer [83]. According to fracture theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This "fracture theory" relates the force for polymer detachment from the mucus to the strength of their adhesive polymer network strands are longer or if the degree of cross-linking within such a system is reduced [84]. According to the adhesion theory, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency [85]. The diffusion–interlocking theory proposes the time-dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer. This is a two-way diffusion process with penetration rate being dependent upon the diffusion coefficients of both interacting polymers [78].

5.1.2. Polymers for mucoadhesive systems

The polymeric attributes that are pertinent to high levels of retention at applied and targeted sites via mucoadhesive bonds include hydrophilicity, negative charge potential and the presence of hydrogen bond forming groups. Additionally, the surface free energy of the polymer should be adequate so that 'wetting' with the mucosal surface can be achieved. The polymer should also possess sufficient flexibility to penetrate the mucus network, be biocompatible, non-toxic and economically favorable [86]. According to the literature mucoadhesive polymers are divided into first generation mucoadhesive polymers and second generation novel mucoadhesive polymers. The first generation polymers are divided into three major groups according to their surface charges which include anionic, cationic and non-ionic polymers. The anionic and cationic polymers exhibit stronger mucoadhesion [87].

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulations due to their high mucoadhesive functionality and low toxicity. Such polymers are characterized by the presence of carboxyl and sulfate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Typical examples include polyacrylic acid (PAA) and its weakly cross-linked derivatives and sodium carboxymethyl cellulose (Na CMC). PAA and Na CMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin [88]. Among the cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature [89]. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose [89]. Chitosan is a popular polymer to use due to its biocompatibility, biodegradability and favorable toxicological properties [90]. Chitosan has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus [91]. The major benefit of using chitosan within pharmaceutical applications has been the ease with which



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