



Teaser Mucoadhesive polymers are able to provide protection or even mucus substitution for leaky mucus barriers associated with a dry eye, dry mouth, and dry vagina, collectively named 'dry X syndrome'.



Mucoadhesive polymers in the treatment of dry X syndrome

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Mucoadhesive polymers are an essential tool in the treatment of diseases where dry mucosal surfaces are involved. In this review, we focus on the application of mucoadhesive polymers in the context of dry eye, dry mouth, and dry vagina syndrome, collectively named 'dry X syndrome'. With a prolonged residence time on mucosal membranes, mucoadhesive materials are as targeted treatment option, with the mucosa as an intended site of action. Thus, mucoadhesive polymers are able to ease local irritation or itching, alleviate chewing difficulties, improve tear-film break-up time, and help to restore physiological conditions. Here, we discuss the different classes of mucoadhesive material and their performance in the treatment of dry X syndrome.

Introduction

Patients with dry X syndrome frequently encounter secondary ailments, such as blurred vision, dental caries, deteriorated sense of taste, inflammation and an impaired quality of life. The major cause of such symptoms is a leaky mucus layer, which is not able to provide a sufficient barrier. This mucosal barrier can be restored with mucoadhesive polymers because of positive interactions, noncovalent bonding, or even covalent crosslinking on mucosal membranes (Fig. 1). With a prolonged residence time, mucoadhesive polymers provide protection or even act as a mucus substitute, easing local irritation or itching, alleviating chewing difficulties, or improving tear-film break-up time. Thus, mucoadhesive polymers help to restore physiological conditions and quality of life for patients with dry X syndrome and can be regarded as the first treatment of choice because of their soothing effects.

The eye, mouth, or vaginal tissues are those that are most likely to be affected by dry X syndrome. Keratoconjunctivitis sicca, commonly referred to as dry eye, has a prevalence of approximately 14% [1], although the age-specific incidence of dry eye can range from 5% to 35% [2]. Tear replacement or supplementation by topical artificial tears and lubricants are first-line therapies.

Tear volume supplementation, tear film stabilization, and protection of the ocular surface by reducing friction between the eyelids and the cornea are examples of tear lubricant mechanisms [3]. Artificial tears smooth the corneal surface in patients with dry eye, an effect that might also

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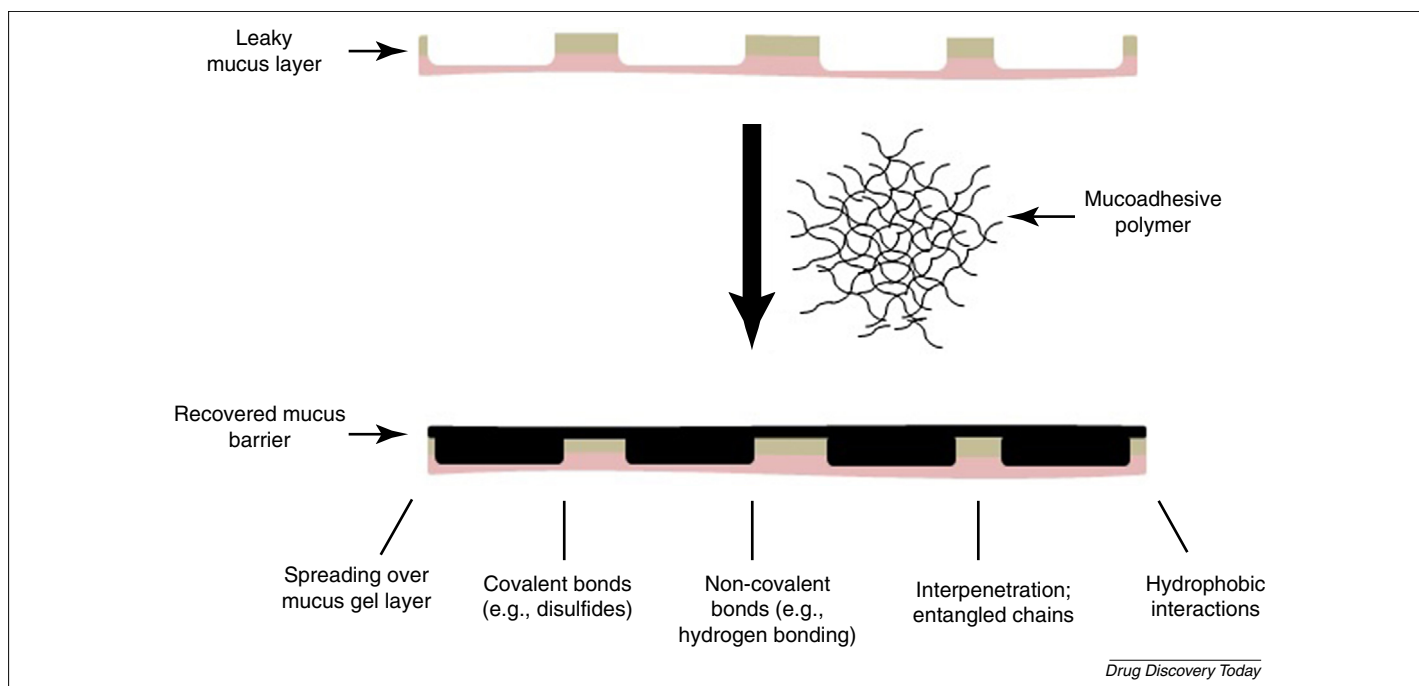


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**FIGURE 1**

Basic concept of an attractive interaction between a leaky mucosal surface associated with dry X syndrome and a mucoadhesive polymer resulting in a mucus barrier restoration.

contribute to improved vision [4]. However, artificial tears are delivered intermittently in contrast to continuously produced natural tears and their effects can be limited because the rapid elimination by tear turnover. To approach physiological conditions, a variety of mucoadhesive polymers are added to enhance the contact time with the ocular surface. These are intended to adhere to, and simulate, the mucous layer of the tear film [5].

Dry mouth syndrome or xerostomia is a potent application field for mucoadhesive polymers. Dry mouth can be caused by multiple factors, such as drug adverse effects [6], local radiation [7], or diseases of the salivary glands [8]. It also has a high prevalence, of approximately 25% [9]. Apart from an acidifying oral environment, oral infections, difficulties talking, or dental caries can also occur. Patients with dry mouth syndrome generally have an impaired or even lacking oral mucus layer. As a consequence, saliva substitutes and lubricants containing mucoadhesives are the agents of choice to soothe dry mouth symptoms. For patients with severe xerostomia, high-viscosity products, such as gels, might be preferable to liquid dosage forms with lower viscosity because of the longer duration of xerostomia relief. Lubrication is one of the major functions of human saliva and is defined as the ability of a substance to reduce friction between two moving surfaces [10]. Saliva substitutes are intended to improve deranged lubrication and hydration of oral tissues, maintaining oral health function [11]. The aim is to alleviate the patient's oral discomfort as well as to reduce the need to frequently sip water.

The third disease covered by this review is dry vagina, which is reported by one quarter to one-half of postmenopausal women as a result of decreasing estrogen levels [12]. This physiological hormone is essential for keeping the tissues of the vagina lubricated and healthy. A lack of estrogen can cause thinning or shrinking of the vaginal tissue and, as a consequence, dryness and

inflammation [13]. Mucoadhesive vaginal drug delivery is also used for the delivery of estrogens to the vaginal mucosa because these polymers adhere to the mucus membrane, preventing leakage of the formulation and aiding long-term retention [14]. Given that hormone replacement therapy (HRT) has various disadvantages, such as an increased risk of cancer, mucoadhesive formulations can be regarded as valid treatment alternatives.

In this review, we discuss the use of mucoadhesive polymers for the treatment of dry X syndrome in terms of the different classes of mucoadhesive material used, including synthetic, semisynthetic, and natural as well as thiolated polymers. We also highlight the application and performance of mucoadhesive agents in the treatment of dry X syndrome, with an overview of currently available formulations.

A refresher on mucoadhesion and postulated mechanisms of action

Mucoadhesive dosage forms are able to interact with the mucus gel layer, which covers the epithelial surfaces of the major absorptive areas in the human body. Mucoadhesion in general can be defined as an attractive interaction between a mucoadhesive material and the respective mucosal surface. The concept of mucoadhesion can be divided into two stages, the contact or wetting stage and the consolidation stage, which can be regarded as the establishment of adhesive interactions [15]. The relative importance of each stage depends on the individual application. The subsequent intermolecular cohesion follows from covalent or noncovalent bonds or attractions. Examples of such chemical interactions include ionic or disulfide bonds as well as electrostatic dipole–dipole forces, hydrogen bonding, or hydrophobic forces [16]. Mechanistic explanations for the chemical interactions include the electronic theory and the adsorption theory, whereas theories based on physical

phenomena include the wetting theory, the interpenetration or diffusion theory, and the fracture theory [17–19].

The electronic theory describes adhesion in terms of different electronic structures of the components involved, whereby adhesion occurs as a result of attractive forces. The adsorption theory focuses on materials attaching to mucus as a result of secondary forces, such as van der Waals, hydrogen bonding, or hydrophobic interactions. The so-called ‘wetting theory’ highlights the ability of a mucoadhesive agent to spread over the mucus gel layer resulting in intimate contact with the mucosal surface. In this context, the diffusion theory suggests that mucoadhesion is based on entangled chains between the mucoadhesive polymer and the target site. In this case, a semipermanent bond is formed as a result of profound interpenetration. Finally, the fraction theory analyzes the forces required for the separation of two surfaces after adhesion. It is suitable for calculating the strength of adhesive bonds. However, mucoadhesion is likely to be a complex combination of all these theories.

Mucoadhesive agents generally increase the viscosity of the formulation and, thus, result in prolonged adhesion at the intended site of action, such as the oral cavity, vaginal mucosa, or ocular surface. In addition to an increased residence time on mucosal surfaces, an ideal mucoadhesive minimizes the loss of a formulation because of the strong inner cohesiveness within the material. If the cohesive properties of the polymer are not sufficiently high, the adhesive bond will fail within the mucoadhesive polymer itself rather than between the mucus gel layer and the polymer. Further benefits of mucoadhesive polymers as potential delivery systems are a reduced administration frequency, helping patient’s compliance, and the possibility to target specific (mucosal) areas in the human body.

Common mucoadhesive representatives: innovation from one generation to the next

Classification according to binding mechanisms

Mucoadhesive polymers can be classified in several ways, based on, for example, their binding mechanism or chemical structure. In principle, the carboxylic moiety (–COOH) of anionic polymers, such as polyacrylic acid (PAA), is predominantly responsible for hydrogen bond formation [20,21]. Mucoadhesion of cationic polymers, such as chitosan, results from electrostatic interactions between the polymer and anionic substructures, such as negatively charged mucins within the mucus gel layer [22]. However, for chitosan, hydrogen bonding and hydrophobic effects also act as driving forces for mucoadhesion [23]. Non-ionic polymers, such as polyethylene glycols (PEG), are thought to be responsible for hydrogen bonding and the subsequent entanglement of polymer chains [24]; thus, neutral polymers can be generally regarded as less adhesive. Therefore, the above-mentioned, rather conventional, polymers tend to form noncovalent bonds with mucus substructures.

An innovative class of functionalized mucoadhesives that are able to form covalent disulfide bonds on mucosal surfaces are thiolated polymers [25]. These designated thiomers are equipped with thiol moieties on the polymeric backbone and, therefore, are able to interact via thiol–disulfide exchange reactions with mucus. In this way, disulfides can be formed because the mucus gel layer contains mucins with cysteine-rich substructures [26]. By virtue of

the covalent disulfide bonding inter- and intramolecularly, benefits of both enhanced cohesion and strong mucoadhesion are achieved with designated thiomers.

Classification according to the origin of the polymer

Mucoadhesive polymers are versatile not only in their mechanisms of attachment, but also their origin. Here, we provide an overview of different mucoadhesive polymers with a focus on the relevance for the treatment of dry X syndrome; we also provide a comparison of their mucoadhesive and cohesive properties (Table 1).

Natural mucoadhesive polymers

Natural polymers, such as polysaccharides, can be distinguished: for example, guar gum, also called guaran, is a galactomannan and, thus, has a mannose backbone and galactose side groups. It is made from guar beans and is listed as a generally recognized as safe (GRAS) product by the US Food and Drug Administration (FDA) [27]. It is a valuable mucoadhesive agent [28], and guar derivatives, such as hydroxypropyl guar, also show enhanced attachment to mucosal surfaces [29]. Xanthan gum is a complex high-molecular-weight polysaccharide with viscosity-enhancing properties [30]. This polysaccharide is produced by a bacterium and presents a negative charge because of the presence of carboxylic acid groups. Based on its profound gel-forming capacity, ophthalmic compositions containing xanthan gum have already been patented [31]. Another polysaccharide in the natural polymers group is starch, which comprises glucose molecules with amylose as linear and amylopectin as branched subunits. Magnetic resonance scans revealed a residence time of up to 24 h following vaginal administration (Fig. 2) [32]. Tailor-made starch derivatives have also been suggested for vaginal and buccal delivery because of their profound adhesion capacity [33]. A mucoadhesive potential for ocular delivery has also been proposed for amylopectin-based starch combined with PAA [34,35], with a constant fluorescein concentration in the ocular cavity for up to 8 h. In addition, as an anionic natural polysaccharide, pectin is commonly used in pharmaceutical formulations because of its gelling and thickening properties [36]. It has a complex structure with homogalacturonan as a basic unit and can be produced from plant cell walls. An enhanced residence time of up to 5 h has been determined for pectin on buccal mucosa [37]. In addition to hydrogen bonding, the mucoadhesion of pectin might also result from uncoiling of the polymer chains as a consequence of electrostatic repulsion and subsequent mucin entanglement [38]. Gellan gum is another anionic polysaccharide with mucoadhesive features, and carboxymethyl gellan gum has shown a 2.7-fold higher mucoadhesive strength compared with non-modified gellan gum [39]. Gelrite[®], a low-acetyl commercial derivative of gellan gum, gels in the presence of mono- or divalent cations, which are present in lacrimal fluid. It has been used successfully in ocular antibiotic delivery with a prolonged therapeutic efficiency [40]. Last but not least, carrageenans are a family of linear sulfated polysaccharides that are extracted from edible seaweeds. They are not only used for various commercial applications as gelling or thickening agents [41], but are also known for their mucoadhesive potential [42].

In addition to polysaccharides, some glycosaminoglycans are also naturally occurring mucoadhesives. Hyaluronic acid (HA), which is an unbranched anionic glycosaminoglycan comprising

TABLE 1

Mucoad- and cohesive ranking of polymers as well as commercially available formulations relevant for the treatment of dry X syndrome.

Polymer	Origin	Mucoadhesive ranking ^a	Cohesive ranking ^b	Commercial products ^c
Guar gum	Natural	+(+)	++	DES: Systane [®]
Xanthan gum	Natural	+(+)	++(+)	DMS: Biotène Oralbalance [®] ; MedActive [®] DVS: Summer's Eve [®]
Starch	Natural	+(+)	+(+)	
Pectin	Natural	+(+)	++	DVS: Summer's Eve [®]
Gellan gum	Natural	+(+)	++(+)	DES: Timoptic XE [®]
Carrageenan	Natural	+(+)	+(+)	DMS: GC Dry mouth gel [®]
HA	Natural	++(+)	++	DES: Hyloforte [®] ; Hylocomod [®] ; Artelac [®] DVS: Gynomunal [®] ; Santes [®]
Gelatine	Natural	++	++	DVS: K-Y Liquibeads [®]
Chitosan	Semisynthetic	++(+)	++(+)	
Derivatized cellulose (MC, HEC, HPC, HPMC, CMC)	Semisynthetic	++	++	DES: Lacrisert [®] ; Systane [®] ; Celluvisc [®] ; Lacrisic [®] DMS: Biotène Oralbalance [®] ; Salix [®] ; Oramoist [®] ; BioXtra [®] ; Oralube [®] ; Xylimelts [®] ; GC Dry mouth gel [®] ; MedActive [®] DVS: K-Y Jelly [®] ; Astroglide [®] ; Summer's Eve [®]
PEG	Synthetic	+	+	DVS: Fem Glide [®]
PVA	Synthetic	+	+	DES: Liquifilm o.k. [®]
PAA	Synthetic	++(+)	++(+)	DES: Artelac [®] ; Vidisic [®] DMS: Biotène Oralbalance [®] ; Oramoist [®] DVS: Replens [®] ; Fem Glide [®]
PVP	Synthetic	+	+	DES: Protagent [®] ; Lacrisic [®] ; Liquifilm o.k. [®] DMS: Oramoist [®]
Thiolated polymers	Semisynthetic/synthetic	+++	+++	DES: Lacrimera [®]
Preactivated thiolated polymers	Semisynthetic/synthetic	+++	+(+)	

^a Mucoadhesive ranking: +++, strong; ++, medium; +, low.^b Cohesive ranking: +++, strong; ++, medium; +, low.^c Commercial product: DES: dry eye syndrome; DMS: dry mouth syndrome; DVS: dry vagina syndrome.

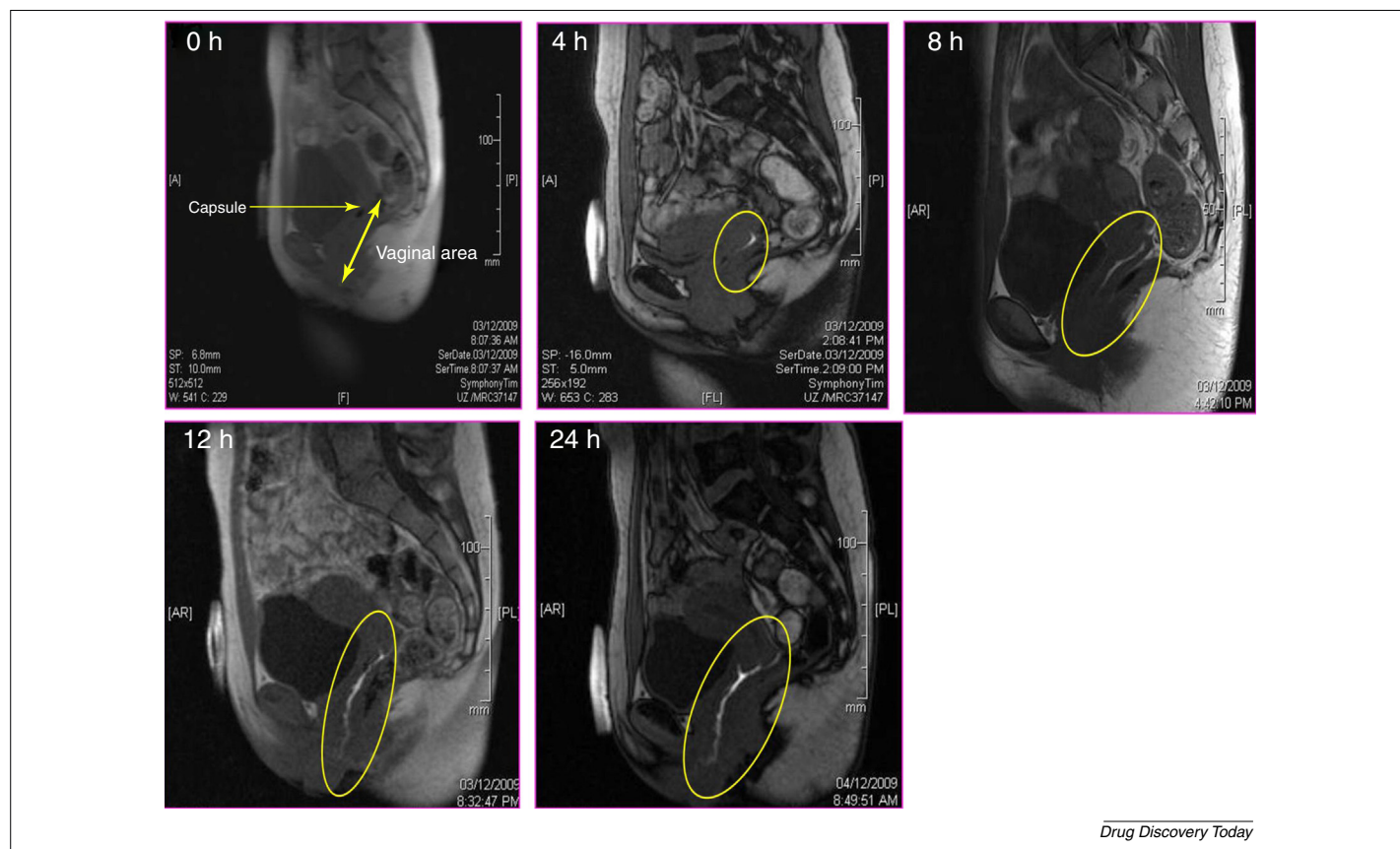
disaccharide units of glucuronic acid and *N*-acetyl-d-glucosamine, is a mucoadhesive polymer with great potential [43]. It is produced by fermentation and differs from other glycosaminoglycans in that it lacks sulfate moieties. HA is a vital component of the extracellular matrix and synovial fluids of mammals, making it biocompatible and biodegradable by hyaluronidases [44]. Sodium hyaluronate solutions have been advocated in the management of a variety of dry-eye states, and its residence time on the ocular surface is significantly longer than that for buffered saline; beneficial changes in tear-film thickness have also been demonstrated [45,46]. HA as natural polymer showed a mean half-life on the ocular surface of 321 s, significantly longer than semisynthetic hydroxypropylmethylcellulose (HPMC) with 44 s and polyvinyl alcohol (PVA) with 39 s [47].

Natural polypeptides, such as the water-soluble and linear gelatine, also act as mucoadhesives. Gelatine is derived from collagen and serves many pharmaceutical needs, including the manufacture of pharmaceutical capsules, ointments, cosmetics, or tablet coatings [48]. Its derivatives, such as positively charged aminated gelatine, are also tools for mucoadhesive delivery systems [49].

Semisynthetic mucoadhesive polymers

An important member of the semisynthetic mucoadhesive polymer group is chitosan. When the degree of deacetylation of chitin reaches approximately 50%, it becomes soluble in aqueous acidic media and is called chitosan. This poly-D-glucosamine is the only pseudonatural cationic polymer and is equipped with film-forming properties [50]. Chitosan has been reported to show excellent

mucoadhesion on ocular [51], buccal [37], and vaginal [52] mucosa, which makes it a promising candidate for the treatment of dry X syndrome. For example, a precorneal clearance half-life of up to 10 min was achieved for an ocular gel containing chitosan compared with only 1.5 min for the control without chitosan [53]. Furthermore, on buccal mucosa, a residence time of more than 24 h was determined for chitosan [37]. The same extended residence time of 24 h has been shown via near-infrared imaging for different molecular-weight chitosans [54]. Another important member of the semisynthetic mucoadhesive polymer group is derivatized cellulose. Cellulose is the most abundant biopolymer in nature, comprising a linear chain of D-glucose units, although a variety of semisynthetic ether and ester derivatives are also available. For the treatment of dry X syndrome, cellulose ethers, including methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), and carboxymethylcellulose (CMC) salts (calcium or sodium CMC), take center stage. In general, commonly used cellulose ethers and esters for topical and mucosal drug delivery are considered to be nontoxic and nonirritating materials, and some are GRAS listed. Given that there are many alterations possible to partially synthetic polymers, such as varying the degree of substitution and molecular weight, it is almost impossible to make a universally valid statement about their mucoadhesive rankings (for a review on each derivative, see [55]). However, for CMC, viscosity-dependent enhanced mucoadhesion on the ocular surface for up to 43 min has been reported (J.R. Paugh, PhD

**FIGURE 2**

Sagittal 3D gradient echo magnetic resonance scans obtained 0, 4, 8, 12, and 24 h after administration of starch pellets. Circles identify the vaginal area with a high contrast between starch pellets (from a disintegrated capsule) and pelvic structures as a result of the incorporation of gadolinium. After 12 and 24 h, pellets were spread throughout the vagina.

Source: Adapted from [32].

thesis, University of New South Wales, 1997). For HPMC, HPC, and HEC, a longer ocular residence time compared with phosphate buffer was proven via fluorescence decay curves in humans (Fig. 3a) [56]. Furthermore, both CMC and HPMC have shown a retention time of up to 8 h on buccal mucosa [37,57] (Fig. 4).

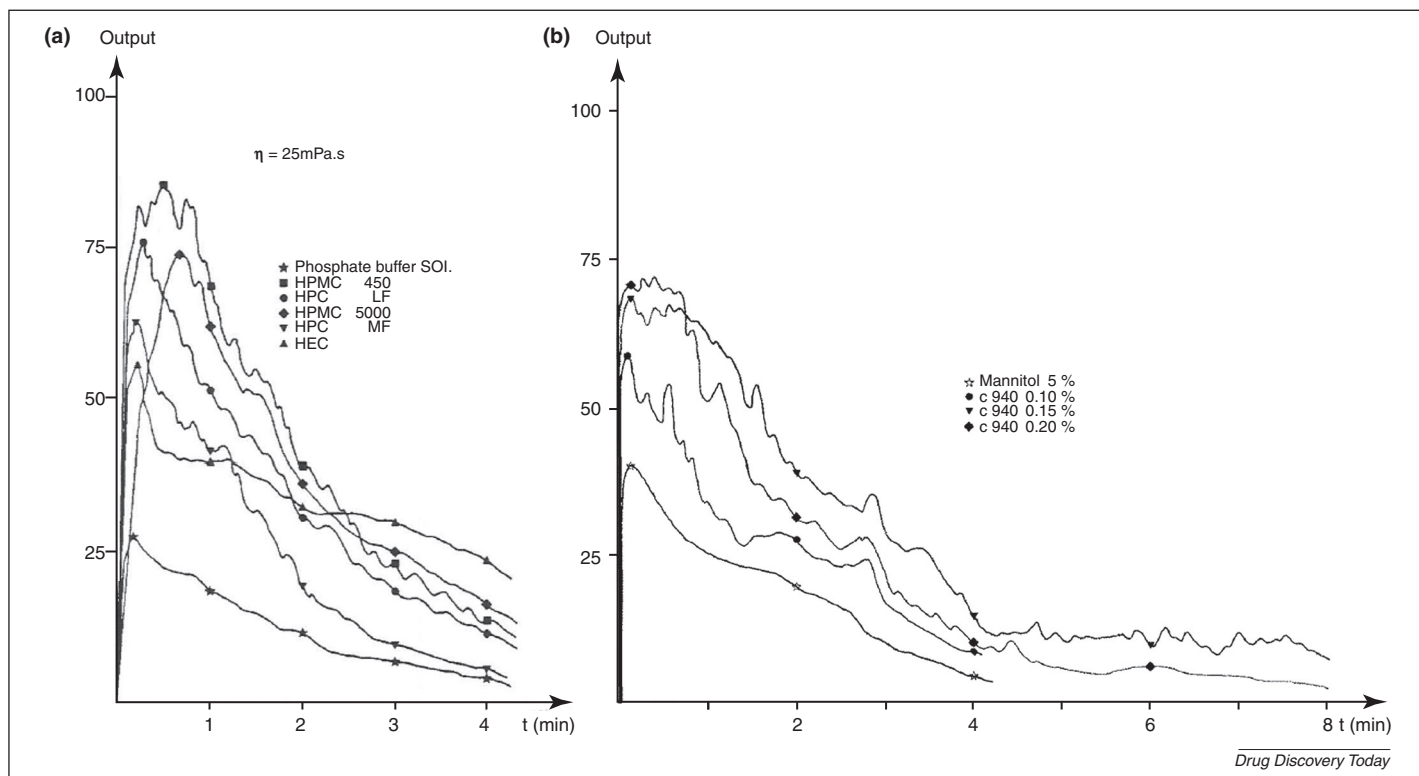
Synthetic mucoadhesive polymers

The third class of mucoadhesive polymers are synthetic materials. PEG is a polyether compound, also known as polyethylene oxide (PEO). The mucoadhesive properties of PEG are debatable because there are no functional groups, such as carboxylic acid or thiol moieties, that can specifically interact with components of mucin. Nevertheless, PEG is thought to be an 'adhesion promotor' because it facilitates mucoadhesion via interpenetration [58]. Surprisingly, a superior ocular residence time of 36.3 min for PEG eye drops has been determined compared with approximately 18 min for saline alone [59]. For PVA, weak mucoadhesion occurs, although purifying freeze-thaw cycles have been reported to increase its adhesive capacity [60]. PAA, also known as carbomer, is an anionic polymer of acrylic acid that has profound mucoadhesive properties. It has numerous applications in oral mucoadhesive drug delivery because of its ability to interact with mucus glycoproteins and to remain localized to a specific site. The ocular contact time of carbomers has been recorded to be concentration dependent, with approximately 2.5 h for a 2% gel [61] (Fig. 3b) [56]. There is also a good correlation between human ocular contact time and the

elastic properties of carbomer gels [61]. In addition, combinations with other mucoadhesives appear to be beneficial because films containing PAA, HPMC, and PEG remained on vaginal tissues for up to 6 h [63]. Crosslinked carbomer derivatives, such as commercially available Noveon[®] AA-1 Polycarbophil, are also synthetic mucoadhesives [64]. Tablets comprising PAA derivatives showed the highest mucoadhesion force compared with other common mucoadhesives, such as HPMC or pectin, with a residence time of more than 24 h on buccal mucosa [37]. Polyvinyl pyrrolidone (PVP), usually referred to as povidone, is a non-ionic linear polymer comprising 1-vinyl-2-pyrrolidinone and, thus, is another synthetic polymer. Its mucoadhesive potential is somewhat controversial and has been reviewed elsewhere [65]. However, its readiness to form films has been evaluated as being beneficial when combined with other mucoadhesives [66].

Next-generation mucoadhesive polymers

Mucoadhesive polymers of the next generation, such as thiomers, differ from the aforementioned polymers because they are able to form covalent bonds. Thiolated polymers have improved mucoadhesive features and a wide choice of thiomers is available. Enhanced affinities for mucosal surfaces have been reported for thiolated polymers compared with their nonthiolated counterparts; for example, a retention time of up to 50 h has been reported for thiolated chitosan [67]. In addition, adhesion periods 26 times longer on vaginal mucosa than the corresponding unmodified

**FIGURE 3**

Fluorescence decay curves of cellulose solutions (a) and Carbopol 940 (b) after ocular application in humans.

Source: Adapted from [57] (a) and [64] (b).

**FIGURE 4**

In vivo mucoadhesion behavior of the selected carboxymethylcellulose (CMC)/hydroxypropylmethylcellulose (HPMC) buccal disc immediately after application (a) and after 4 h (b).

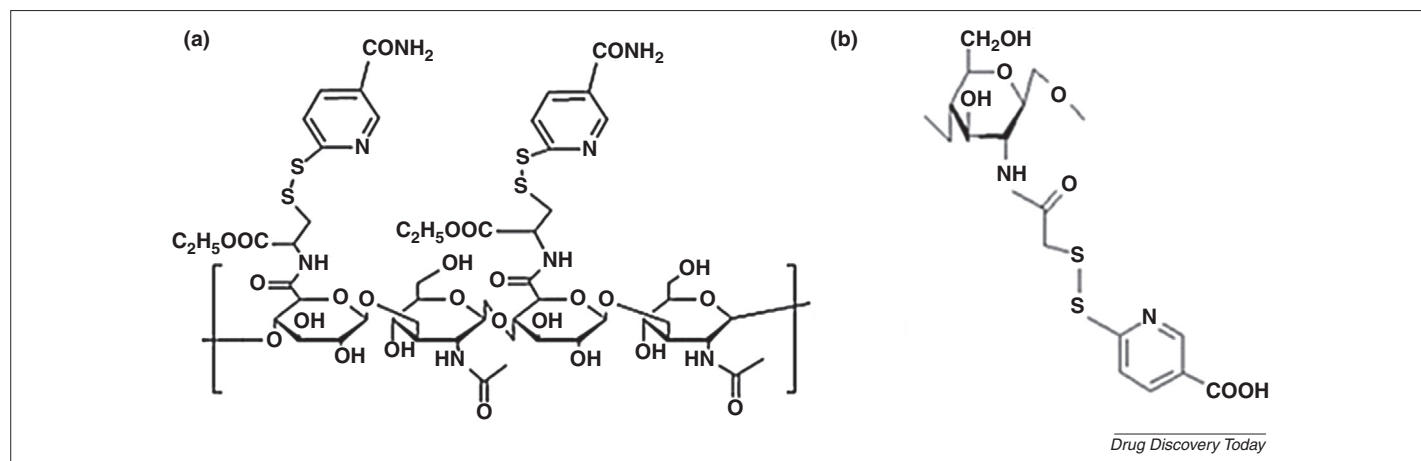
Source: Adapted from [58].

polymer have been reported for thiolated chitosan [68]. Thiolated PAA also appears to be a promising mucoadhesive tool given that an up to 2.3-fold increase in mucoadhesive strength on vaginal mucosa was reported for this thiomers compared with nonthiolated PAA [69]. Recently, thiolated carrageenan [70], xanthan gum [71], and gelatin [72] have been designed and show promising mucoadhesive potential for versatile applications. The mechanism of disulfide exchange reactions with mucosal surfaces is also valid for so-called 'preactivated' thiomers. Free thiol moieties are protected via covalent disulfide attachment of an aromatic thiol donator, such as mercaptanpicotinic acid. In addition to their unique mucoadhesive properties, such thiomers are more stable against oxidation compared with their corresponding thiolated counterparts. Preactivated HA [73] or chitosan [74] have recently been developed and are illustrated in Fig. 5.

The treatment of dry X syndrome

Mucoadhesive polymers associated with dry eye syndrome

Mucoadhesive polymers are often able to form hydrogels, retain water, and enhance the viscosity of a formulation, which makes them ideal as a major component of artificial tears. Different artificial tears have been investigated with regard to their precorneal residence time, whereby higher viscosity formulations showed around twice the ocular contact time compared with saline alone [59]. In addition to an enhanced ocular residence time, higher viscosities can also be associated with lower ocular drainage rates [75]. Some commercially available products for the treatment of dry eye and the respective mucoad- and cohesive rankings are provided in Table 1.

**FIGURE 5**

Structure of preactivated thiolated hyaluronic acid (HA) (a) and preactivated thiolated chitosan (b).

Source: Adapted from [75] (a) and [76] (b).

Cellulose derivatives, such as HPMC [76], are ‘old hands’ as tear supplementation for the treatment of dry eye. Nevertheless, a CMC solution was recently reported to improve tear-film stability for patients with dry eye after phacoemulsification in the context of age-related cataracts [77]. In addition, a treatment with HPMC-containing ocular lubricants compared with other formulations containing PAA, PVP, and a combination of HPMC and PVP revealed the highest corneal density in patients with dry eye [78]. One example of a product containing cellulose derivatives is Systane[®], which is a lubricant eye drop containing HPMC in combination with hydroxypropyl-guar. This product shows pH-sensitive viscosity enhancement, which is beneficial because pH tends to be higher in dry eyes [79]. Thus, Systane is thought to cross-link after instillation in the dry eye, creating an elastic matrix with increased effect duration.

Mucoadhesive glycosaminoglycans, such as HA and chitosan, have been proposed as valuable ingredients for dry eye treatment. A novel eye drop formulation containing HA and trehalose as active ingredients (Thealoz Duo[®]) has been clinically evaluated to be as effective as Systane [80]. The idea behind such combinations is to achieve a synergistic effect of a mucoadhesive polymer (HA) in combination with trehalose to prevent ocular damage [32]. Another example of such a ‘joint venture’ is HyloDual[®], which contains HA in combination with ectoine. Ectoine is a low-molecular-weight zwitterionic solute with strong water-binding capacity, which might lead to the fluidization of sebaceous lipid films, improving dry eye symptoms [81].

Furthermore, improved results for HA treatment compared with cellulose derivatives have been published in relation to corneal epithelial cell protection [82,83]: the results of these studies indicated that HA had a significantly longer residence time, higher water retention, and protective effect compared with CMC- and HPMC-based lubricants. A combination of CMC and HA was recently elucidated to improve ocular dry eye symptoms in humans [84]. Another dual-polymer eye drop formulation comprising HA and hydroxypropyl-guar was recently evaluated in models of the human corneal epithelium [85]. The formulation provided effective hydration and lubrication with a prolonged

retention of effect and, therefore, might promote desiccation protection and retention on the ocular surface. An additional positive effect in the treatment of dry eye with HA was shown in a clinical trial of Rejena[™], as compared with vehicle lacking HA [86]. HA-containing eye drops have also been evaluated to be more effective compared with carbomer-based gels in terms of their effects on improving ocular surface health and discomfort [87].

As a member of the mucoadhesive glycosaminoglycan group, chitosan has been proposed for use in artificial tear formulations because it remained on the precorneal surface as long as commonly used artificial tears, such as Protagent-SE[®], with an ocular elimination half-life of 6–8 min [88]. In addition to spreading over the entire precorneal area, an antibacterial effect of chitosan has also been reported. This is an advantage in cases of dry eye because secondary infections can occur. In addition, the physiological ocular mucus contains chitinous material [89] and, thus, chitosan might be beneficial in restoring an impaired ocular mucus barrier.

In terms of polysaccharides with mucoadhesive features, arabinogalactan, tamarind seed, and xanthan gum show beneficial effects for the treatment of dry eye. Arabinogalactan solutions with pronounced mucoadhesive properties on the ocular surface have been suggested as potential therapeutics for dry eye protection and the treatment of corneal wounds [90]. Beneficial protective activity in a dry eye model in rabbit [91] as well as relief of dry eye symptoms equivalent to a HA formulation (Hyalistil[™]) [92] have also been reported for tamarind seed. In addition, an interaction for mucin with an ophthalmic liquid dosage form containing xanthan gum has also been unraveled [93].

Synthetic polyanionic polymers, such as PAA, have been proposed as long-lasting artificial tears for the relief of dry eye syndrome. The use of these high-molecular-weight polymers is based on their inherent mucus-like and lubricating properties, as well as good retention on the ocular surface [5]. Thus, PAA-based gels have been reported to show a longer precorneal residence time and a more effective soothing of dry eye symptoms compared with CMC-based artificial tears [94] and a PVA eye gel [95]. Synergistic mucoadhesive effects of PAA in combination with PVP compared with standard PAA-based ocular gels (Vidisc[®] and Thilo Tears[®])

have been recorded [5]. PVP alone also has positive effects on dry eyes because a PVP-containing formulation was shown to be safe and effective in treating mild to moderate dry eyes, resulting in the improvement of tear-film stability, ocular surface lubrication, and patients' symptomatology [96] (for review on clinical trials on artificial tears, see [97]).

In terms of solid-dosage forms, ophthalmic inserts comprising HPC (product on the market: Lacrisert[®]) have shown improved symptoms in patients with moderate to severe dry eye syndrome [98,99] and autoimmune dry eye [100]. In addition, a lyophilisate with HPMC as an active ingredient has been developed, although its clinical efficacy in the treatment of dry eye remains to be demonstrated [101].

Although there is a plethora of products for the treatment of dry eye, no statistically significant differences among product types have been found in terms of an improvement of the exposed ocular surface [102]. This indicates that noncovalent mucoadhesion has similar effects on the ocular surface, independent of the polymer class.

Nevertheless, thiomers as innovative mucoadhesive agents are able to form covalent bonds with mucus glycoproteins and have been used for the treatment of dry eye. For example, chitosan-*N*-acetylcysteine (C-NAC) remained on the ocular surface for up to 22 h [103,104]. After administration of 0.1% (w/w) C-NAC (Fig. 6), different pharmacokinetic effects compared with control and

nonthiolated chitosan were clearly detectable after 24 and 48 h of ocular instillation (study sponsored by Croma Pharma GmbH and performed at the AIT Austrian Institute of Technology GmbH, Health & Environment Department, Biomedical Systems, 2444 Seibersdorf, Austria, unpublished results 2016). These currently unpublished results support the initial stabilization of the tear film as a result of the electrostatic attraction of the positively charged chitosan backbone and negatively charged domains of mucins. In addition, covalent interactions of free thiol moieties originating from C-NAC and disulfides from mucosal glycoproteins are responsible for the enhanced stability of the polymer-mucin network (Fig. 6). C-NAC also showed a potential protective effect on the ocular surface in a dry eye model as a result of decreased inflammatory cytokine expression [105]. The first thiomers product for the treatment of dry eye will be commercially available soon in the form of Lacrimera[®], which contains C-NAC as thiolated chitosan. A crosslinked hydrogel-based formulation containing thiolated HA increased tear break-up time in rabbits and significantly reduced symptoms of dry eye in dogs while only being applied twice daily [106]. This thiomers formulation was also compared with a standard HA-containing tear supplement in a clinical study in dogs with dry eye [107]. Thiolated HA was found to be superior in improving ocular surface health and was preferred subjectively by dog owners. Thiolated PAA was also reported to prolong the tear film break-up time and fluorescein concentration

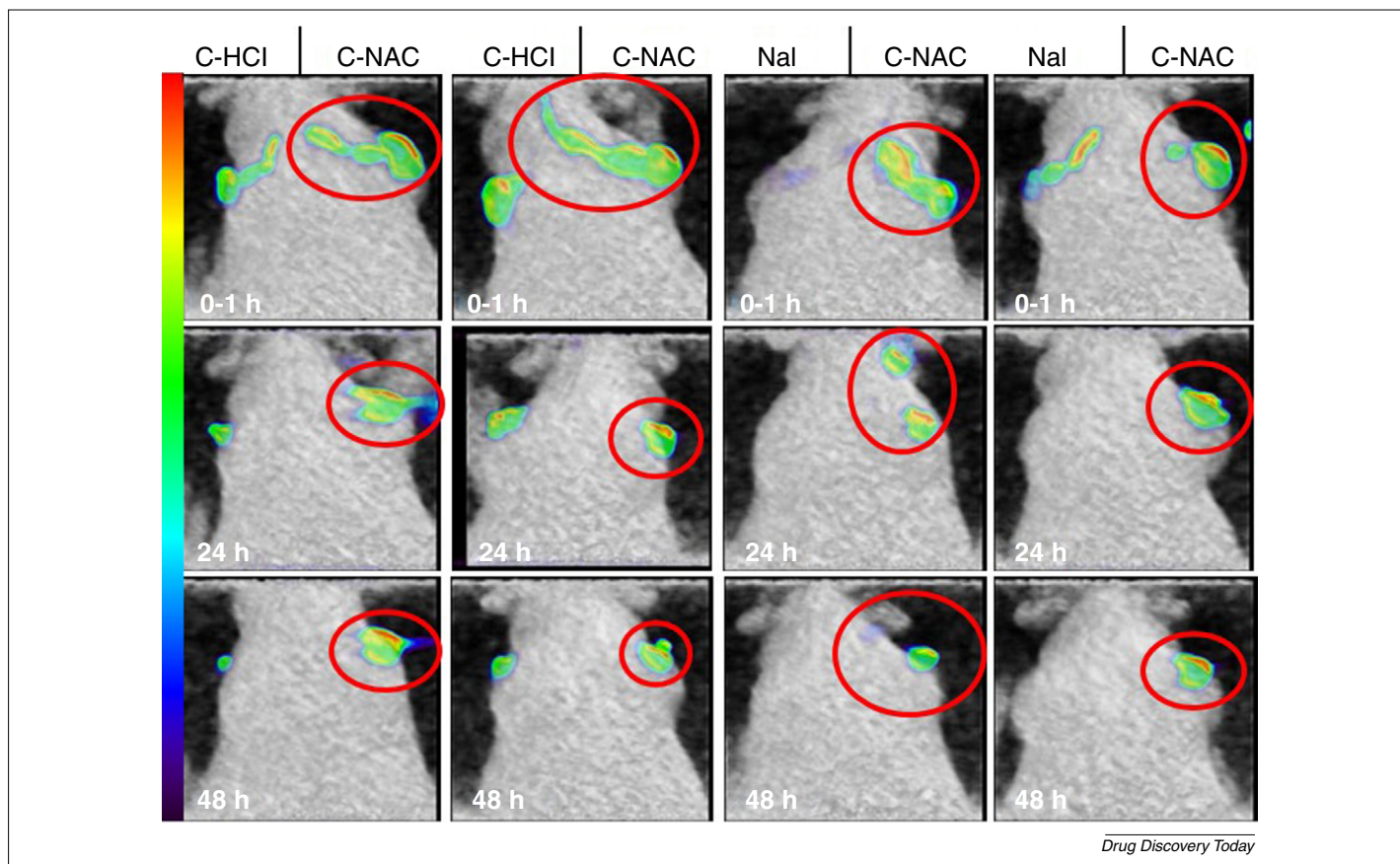


FIGURE 6

Projection images from test subjects after instillation (0–1 h) and up to 48 h after administration of ¹²⁴I-chitosan-*N*-acetylcysteine (C-NAC, red circles) into each right eye and ¹²⁴I-chitosan-hydrochloride (C-HCl) or Na¹²⁴I (NaI) into the left eye, respectively. Radioactivity concentration is expressed as the percentage applied dose per gram tissue (% AD/g) and the radiation scale is set from 0 to 8% AD/g (study sponsored by Croma Pharma GmbH and performed at the AIT Austrian Institute of Technology GmbH, Health & Environment Department, Biomedical Systems, 2444 Seibersdorf, Austria, unpublished results 2016).

on the ocular surface for more than 8 h during an *in vivo* study with humans (M. Hornof, PhD thesis, University of Vienna, 2003) [108]. By contrast, the fluorescein concentration rapidly decreased after application of aqueous eye drops or inserts based on nonthiolated PAA [108]. A relation between oxidative stress and the etiology of corneal epithelial alterations in dry eyes has been indicated [109]. This might be one reason why antioxidative thiomers appear to be of advantage in the treatment of dry eye. In addition, the high water-binding capacity of gel-forming polymers might lead to a less toxic decreased tear osmolarity and dilution of inflammatory cytokines in the tear film. Another benefit is the outstanding mucoadhesion resulting from disulfide crosslinking with ocular mucins. The prolonged residence time could offer a protective effect on the ocular surface and tear-film stabilization. Thiomers mimic the physiological conjunction of mucin oligomers via disulfide bonds and, therefore, might be beneficial for the recovery of impaired mucus layers associated with dry mucosae.

Mucoadhesive polymers associated with dry mouth syndrome

Mucoadhesive agents are primary ingredients of saliva substitutes with cellulose derivatives (i.e., CMC and HEC) as the main ingredients. With saliva substitutes containing mucoadhesive polymers, it is possible to approximate physiological saliva [110], which is a major benefit for saliva supplementation or substitution. Apart from this saliva-mimicking effect, the resaturation of an impaired mucus layer is likely to be the main reason why mucoadhesive polymers are beneficial in the treatment of dry mouth. Table 1 lists some of the commercially available formulations for the treatment of dry mouth, and the respective mucoadhesive agent. Animal mucin has also been evaluated in the treatment of xerostomia. However, many of the mucin-based products of bovine origin have been discontinued, mainly as a result of concerns regarding their efficacy and transmissible spongiform encephalopathy [111], with Saliva Orthana[®] as the only current representative on the market.

Commercially available oral lubricants contain mucoadhesive agents, which generally increase the viscosity of the formulation, and CMC is one of the most common representatives [112]. For example, GC Dry Mouth Gel[®] utilizes a CMC base and has been shown to be effective in patients following radiation treatment [113]. Another CMC-based artificial saliva significantly improved symptoms associated with severe cases of xerostomia [114]. As another cellulose derivative, HEC is also represented on the market: HEC-based Biotène[®] products showed an improvement in intraoral dryness, ability to eat normal, and superior palliative effects compared with placebo in patients with postradiation xerostomia [115,116]. Furthermore, for Biotène Oral Balance Gel[®], a significant reduction in dryness-related complaints in patients with severe xerostomia was reported [117]. An intraoral device intended for the slow release of Biotène Oral Balance Gel was not evaluated as being beneficial in reducing xerostomia symptoms compared with the gel alone [118]. This might be because the formulation already contains mucoadhesive agents, which ensure a prolonged residence time within the oral cavity. Thus, the positive effect on oral dryness seems to be independent of the slow release or bolus application of the gel. However, mucoadhesive tablets containing PAA, HPC, and PVP were compared with Biotène products and found to be superior in terms of

the sensation of mouth dryness [119]. Therefore, a combination of mucoadhesive polymers might result in synergistic mucoadhesive effects, as outlined above for the treatment of dry eye. Another HEC product, BioXtra[®], significantly reduced symptoms in patients with radiation-induced xerostomia in a clinical study [120]. Furthermore, the assumption that higher viscosity is beneficial for mucoadhesion is supported because the more viscous BioXtra system had a longer lasting moisturizing effect in the oral cavity compared with Biotène products, although both products are based on HEC [121].

Given the different dosage forms available, subjects rated a HEC gel to be significantly better than a CMC spray, a HEC citric acid spray, or liquid margarine [122]. As far as solid-dosage forms are concerned, CMC-based systems, such as saliva-stimulating lozenges containing CMC (Salix[®]) or self-adhering intraoral discs (XyliMelts[®]), have been proposed for the efficient treatment of dry mouth [123,124].

In addition to cellulose derivatives, synthetic polymers, such as PAA, are potential active ingredients in the treatment of dry mouth [111]. A combination of mucoadhesive polymers containing poloxamer, CMC, and xanthan gum as the mucoadhesive composition (MedActive[®]) was described to alleviate symptoms of dry mouth [125]. A combination of xanthan gum and egg white (Novasial[®]) has been evaluated as a suitable saliva equivalent for the treatment of xerostomia [126]. Last but not least, preactivated chitosan thiomers as a novel class of biomaterials have also been outlined as a potential treatment modality for dry mouth syndrome because of their lubrication properties and outstanding mucoadhesiveness [73].

The treatment of xerostomia appears to be very individual [127], which is why patients have to try different saliva substitutes to find the most suitable one for them. However, given that the number of clinical studies comparing different oral lubricants or saliva substitutes is limited, further studies on the clinical performance of such products are required.

Mucoadhesive polymers associated with dry vagina syndrome

In terms of vaginal formulations, gels are beneficial because they feel comfortable and are easily spread to provide intimate contact with the vaginal mucosa. Their high water content and rheological properties contribute to their hydrating and lubricating features, which are favorable in the treatment of vaginal dryness. Generally, vaginal moisturizers are gels or creams used regularly to maintain hydration of the vaginal epithelium for long-term relief of vaginal dryness. By contrast, vaginal lubricants provide short-term relief, such as for intercourse-related vaginal dryness [128].

Table 1 illustrates some commercially available vaginal formulations, including the relevant mucoadhesive agent and its mucoid and cohesive capacities. A study comparing a PAA-based nonhormonal drug-free mucoadhesive vaginal moisturizer (Replens[®]) and local estrogen therapy in the treatment of vaginal dryness showed Replens to be a safe and effective alternative to estrogen vaginal cream [129]. Both therapies increased vaginal moisture, vaginal fluid volume, and vaginal elasticity with a return to the premenopausal pH state. Although another study reported that vaginal moisturizers, such as Replens, are less effective than estrogen, it is still claimed that drug-free formulations reverse the symptoms of vaginal atrophy and decrease discomfort during

intercourse [130]. Concerning the vaginal residence time, contrasting results have been reported for Replens. A study on postmenopausal women reported that the formulation was retained in the vaginal cavity for 3–4 days [131]. However, in another *in vivo* study, significant retention of the same-formulation gel was not reported in five out of the six volunteers studied [132]. Thus, the residence time of this mucoadhesive formulation seems to be strongly dependent on interindividual differences. A comparison of the vaginal deposition and moisturization of Summer's Eve[®], based on pectin, and Replens, based on polycarbophil, revealed that the latter had a significantly higher vaginal residue. Nevertheless, both formulations showed an almost equal relief of vaginal dryness [133]. Thus, both mucoadhesive formulations improve vaginal dryness independent of the respective total amount of remaining product in the vagina.

Apart from a prolonged residence time, mucoadhesive polymers are also able to easily cover mucosal surfaces in the vagina. For PAA-based (Replens) as well as MC/CMC-based products (K-Y Jelly[®]), spread over almost three-quarters of the maximum possible vaginal area has been reported [134].

Recently, a HA-based vaginal gel (Hyalofemme[®]) was recently suggested as an alternative to estrogen-based treatments in relieving the symptoms of vaginal dryness [135,136]. Similarly, a solid-dosage form containing HA (Santes[®] ovuli) has also been highlighted as a safe and effective alternative for the treatment

of vaginal atrophy symptoms in postmenopausal women, especially when HRT is not recommended [137]. Another vaginal gel comprising HA (Gynomunal[®]) has also been proposed to be a valid treatment modality for the short- and long-term relief of vaginal dryness [138,139].

Concluding remarks

Mucoadhesive polymers are the tools of choice in formulating remedies for the treatment of dry mucosal surfaces. Although the postulated mechanisms of action vary between the classes of mucoadhesive polymer, the outcomes are more similar. A targeted delivery option for dry X syndrome is provided, with the relevant mucosal surfaces as the site of intended action. Given their prolonged residence time, impaired mucus gel layers and physiological functions can be restored. This also leads to beneficial outcomes in view of secondary ailments associated with dry X syndrome. According to the location of the mucosa and patient-specific preferences, a suitable delivery system (liquid, semi-solid, or solid formulation) can be chosen. All classes of mucoadhesive polymer have been evaluated in the treatment of dry X syndrome and are currently strongly represented on the market.

Conflict of interest statement

Prof. Bernkop-Schnürch has nothing to disclose.

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