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A focus on mucoadhesive polymers and their application in buccal dosage forms

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ABSTRACT

Mucosa of the buccal cavity is considered a convenient and easily accessible site for the administration of drugs intended for both local and systemic delivery. Aiming to optimize the pharmacokinetic, buccal mucoadhesive drug delivery systems are proposed. Mucoadhesion is a complex process involving chemical interactions between mucin and polymers. The success and degree of mucoadhesion bonding is based on various polymer-based features. The evolution of such systems has moved from first-generation hydrophilic polymers, able to form unspecific interactions, to more specific second-generation systems based on lectins, or on novel materials obtained by modification of polymers with various functional groups such as thiol groups. A wide range of formulations has been proposed for the delivery of small molecules, but comparatively few have found their way onto the market. The article reviews the information regarding the most promising mucoadhesive polymers and their application in the design and development of buccal mucoadhesive dosage forms.

1. Introduction

Oromucosal preparations are widely used to administrate drugs to the oral cavity or to the throat to obtain both a local and systemic effect. Indeed, the oral mucosa is easily accessible and highly vascularized by a relative fast blood flow (2.4 mL/min/cm^2), allowing a direct access to the systemic circulation by-passing the liver first-pass effect with consequent high bioavailability and acceptability by the patient [1]. Moreover, as being characterized by a rapid cellular turnover (5–6 days), the oral mucosa is less susceptible to damage or irritation potentially related to drugs or excipients used to design the dosage forms [2]. On the other hand, the main disadvantages are related to the low permeability of the mucosal membrane and short permanence time of conventional dosage forms due to mechanical stresses and swallowing. To overcome these limitations, mucoadhesive dosage forms have gained interest [3]. According to the European Pharmacopoeia, mucoadhesive preparations "are intended to be retained in the oral cavity by adhesion to the mucosal epithelium and may modify systemic drug absorption at the site of application" and "they may be supplied as mucoadhesive buccal tablets, buccal films or other mucoadhesive solid or semisolid preparations". These preparations include a hydrophilic polymer which, on wetting with saliva, swells and adheres to the mucosal surface by interacting with the mucus substrate [4]. Mucus is a complex viscous adherent secretion mostly produced by the mucus secreting cells belonging to the sublingual and minor salivary glands and lining the epithelial surfaces of the oral cavity [5]. Mucus is mainly composed of water and mucins forming a viscoelastic mixture of proteins, immunoglobulins, enzymes, lipids, nucleic acids, cellular debris and various ionic species. Mucins are hydrophilic high molecular weight glycoproteins composed by a single chain protein-based backbone (formed by amino-acids as serine, threonine and proline), from which branch off many large oligosaccharide-based chains (composed by N-acetylgalactosamine, N-acetylglucosamine, galactose, fucose and N-acetylneuramic acid or sialic acid). In particular, MG1, one of the major mucins produced by human salivary glands, plays a role in maintaining hydration, providing lubrication and limiting the attachment of microorganisms [6]. As in the oral cavity, the pH oscillates from 6.2 to 7.4, the presence of sulfate groups associated to carboxylate groups (i.e. sialic acid residuals) at the terminus of some sugar units causes mucins to be negatively charged and to

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behave as anionic polyelectrolytes [7].

Mucoadhesion is the result of multiple steps of interaction between a mucoadhesive polymer and mucins. Even though several theories were developed to comprehensively explain this phenomenon [8,9], it is preferable to divide the process of mucoadhesive bond formation in two main events [7]. In the first phase, the mucoadhesive dosage form gets wet, swells and expands into the mucus network irregularities, contributing to the formation of a double layer of mechanical interpenetration between the polymer and the mucus layer. The second phase is the result of chemical interactions, i.e. covalent and ionic bonds, hydrogen bonds, electrostatic interactions and van der Waals forces, between the two substrates.

The mucins/polymer interactions are strongly influenced by polymer-related factors (e.g. average molecular weight, chain flexibility, hydration, hydrogen bonding capacity and charge) and buccal environmental factors (e.g. pH, ionic strength and mucins), both of which can modulate the degree of adhesion and the residence time of the mucoadhesive dosage form [7].

Considering the complexity of the mucoadhesion process, the current review aims to discuss the main features of mucoadhesive polymers and their possible use in the development of buccoadhesive dosage forms.

2. Mucoadhesive polymers

Mucoadhesive polymers should present some characteristics which facilitate the interactions with mucins. First, polymers should present suitable chain flexibility at the pH and ionic strength of the mucus. Within a homogeneous class of polymers, the increase of chain flexibility is expected to favor interpenetration and, therefore, mucoadhesion. At the same time, an optimum molecular weight is likely to exist for mucoadhesion [10]. Indeed, the polymer chains have to be small enough to easily interpenetrate the mucus layer, but also large enough to form entanglements with mucins (Fig. 1) [11]. As an example, the mucoadhesive properties of high molecular weight hyaluronan are lower than those of medium molecular weight hyaluronan [12]. Finally, the degree and rate of polymer swelling become relevant in the case of solid dosage forms since mucoadhesion reaches a maximum at an optimal water content and the over-hydration reduces adhesion [13].

Since no compendial assays are described to evaluate the mucoadhesive properties and a huge number of very different experimental protocols are reported in literature, a ranking cannot be established. Among the most studied polymers, univocal evidences of mucoadhesive properties are available for polyacrylates, hyaluronan, chitosan, cellulose derivatives, alginate, pectin and gelatin [14]. Polyvinylpyrrolidone (PVP), which has been mainly used in combination with other mucoadhesive materials [15], exhibits poor or absent mucoadhesive properties, independently of the testing method or the substrate used [16,17]. On the other hand, both the chemical manipulation of an existing mucoadhesive polymer or the design of a composite material are the most exploited approaches to improve mucoadhesion. Therefore, the possibility for a simple classification of polymers based on the net charge or the source, fails to succeed.

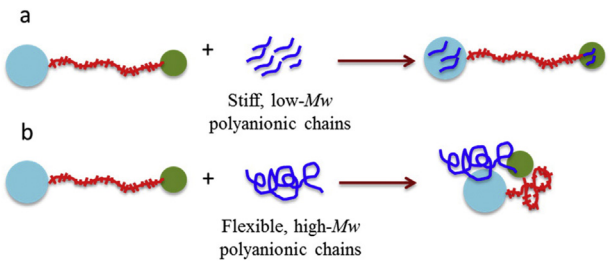

Fig. 1. Model for the interaction between a polyanion and the double-globular comb structure of mucin as a function of polymer molecular weight and chain flexibility. "Reprinted with permission from Menchicchi B., Fuenzalida J.P., Hensel A., Swamy M.J., David L., Rochas C., Goycoolea F.M. – Biophysical analysis of the molecular interactions between polysaccharides and mucin. – Biomarcomolecules, 16, 924–935, 2015". Copyright© 2015, American Chemical Society.

The effect of polymer charge density on the mucoadhesive process is not completely clarified, even if it has been suggested that polyanions are preferred to polycations and carboxyl-containing polymers are better than sulfated ones [18,19]. In the same way, the classification based on sources presents some limitations. Indeed, even though it is clear when the polymer is completely synthetized, the borderline between natural and semisynthetic polymers is sometimes questionable. On the basis of these considerations, we analyzed mucoadhesive polymers merely on their main chemical structures, distinguishing between them and the composite materials.

2.1. Polyacrylates

They are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinylglycol. Poly(acrylic acid) (PAA) possesses excellent mucoadhesive characteristics due to the ability of the carboxylic groups to form strong hydrogen bonds with the oligosaccharide chains of mucin. The physical entanglement between the polymer and mucus layers also plays an important role in promoting mucoadhesion. Therefore, in this case, mucoadhesion results from a series of physico-chemical processes, such as hydrophobic interactions, hydrogen and van der Waals bonds, which are controlled by pH and ionic composition.

Polyacrylates are available in a wide range of molecular weights, form transparent, easily modified gel networks, are non-toxic and are considered safe (GRAS status) for oral use by the FDA. Among PAA derivatives, polycarbophil (Noveon®) and carbomer (Carbopol®) have been extensively studied as mucoadhesive platforms for drug delivery [20]. One clear distinction between carbomer and polycarbophil is the level of cross-linking and the cross-linking agent itself. Carbomers are cross-linked with allyl sucrose or allylpentaerythritol, whereas polycarbophil is cross-linked with divinylglycol. Both compounds have the same acrylic backbone, but vary in their cross-link density. Carbomer grades with no residual benzene content, like Carbopol® 934P, 971P and 974P, may be used as mucoadhesive polymers in oral preparations, suspensions and tablets [21]. Polycarbophil is insoluble in aqueous media, but has a high swelling capacity starting from pH 4 [22], permitting high levels of entanglement within the mucus layer. Additionally, the non-ionized carboxylic acid groups bind to the mucosal surfaces via hydrogen bonding interactions.

Carbopol® has many advantages in the design of sustained-release delivery systems, such as good gel-forming ability and mucoadhesive properties. This may be a result of its ionic nature and high sensitivity to the pH of the medium. Carbopol® carboxyl groups do not dissociate at pH 1.2, resulting in a tightly enclosed matrix. However, almost all Carbopol® carboxyl groups dissociate at pH 6.8, resulting in the formation of a swollen gel [23]. Therefore, Carbopol® can be expected to exhibit both pH-sensitive and mucoadhesive features.

Even if PAAs have excellent mucoadhesive properties, these polymers swell upon hydration, with potential problems in patient compliance. To solve this drawback, poly(sodium methacrylate, methylmethacrylate)s (PMM) have been proposed since, upon hydration, they do not show an evident swelling layer and their dissolution is governed by erosion [24]. Their intrinsic dissolution