European Journal of Pharmaceutics and Biopharmaceutics xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Review article

Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview

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ARTICLE INFO

Article history:
Received 15 March 2013
Accepted in revised form 21 June 2013
Available online xxxx

Keywords:
Mucoadhesion
Mucoadhesive preparation
Texture Analyser
Oral mucosa
Oromucosal preparation
Polymer

ABSTRACT

Oral mucoadhesive preparations have gained increasing importance in the last decades, by reason of numerous advantages like easy application, discrete handling and no swallowing of the drug product. Pharmacopoeial methods to study mucoadhesion are not available so far, despite the new monograph for oromucosal preparations is valid since the European Pharmacopoeia 7.4 (2012) including a chapter on mucoadhesive preparations.

Several mucoadhesion test methods are reviewed concerning the applicability for various polymers, different drug dosage forms and comparability of experimental set-ups. Different test methods and experimental set-ups lead to huge differences regarding the results.

1. Introduction

Various mechanisms of mucoadhesion and modes to characterise the properties of mucoadhesive oral mucosal preparations have been published recently including diffusion [1], wetting [2], electronic [3], adsorption [4] and fracture mechanism [5].

The diffusion theory bases on the diffusion of a polymer into the mucin layer. It is dependent on the concentration gradient and the diffusion coefficient of the polymer [1,6].

The wetting theory describes the spreading of a material, mostly mucoadhesive liquids or low viscous formulations on the biological tissue. The degree of spreading can be calculated by an extension of the basic Young's equation [2].

The electronic theory bases on electron transfer between adhesive polymer and mucus by reason of differences in electronic charge. The mechanism includes the formation of a double layer due to interactions between the polymer and the mucus layer [6].

The adsorption theory describes the adhesion caused by primary and secondary bonds. Ionic, covalent and metallic bondings are classified as primary bonding, whereas van der Waals forces, hydrophobic interactions and hydrogen bonding are described as secondary bonding [4,6].

The fracture mechanism is concerned with the strength of the adhesive bond between mucoadhesive formulation and mucosa and the force which is needed to break this adhesive bond. Young's modulus of elasticity, fracture energy and critical crack length upon separation of two surfaces can be used to calculate the fracture strength [7].

Dependent on the dosage form and the kind of mucosa different mechanisms are discussed to be appropriate. A general definition of mucoadhesion is hardly feasible due to the multiple mechanisms of adhesion and dosage forms like, for example, gels or tablets. These facts have to be considered for the development of an applicable method to study mucoadhesion.

Comparability of the results is very difficult due to various parameters for the measurements. Until now, there is no standardised method available for studying mucoadhesion. This article gives an overview of published methods to characterise mucoadhesive polymers and preparations.

2. Mucoadhesive polymers

Mucoadhesive polymers can be divided into natural and synthetic polymers. Synthetic polymers contain cellulose derivatives, poly vinyl pyrrolidone, poly vinyl alcohol and poly hydroxyethyl methylacrylate, for example, whereas sodium alginate, guar gum, gelatin, and chitosan are counted among natural polymers [8].

Furthermore, polymers can be categorised regarding the mechanism of adhesion [9]. Park and Robinson classified polymers, which become sticky by getting in contact with water, polymers, that adhere to a mucosal tissue due to non-specific, non-covalent binding and those that bind to specific receptors on the mucosal surface.

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http://dx.doi.org/10.1016/j.ejpb.2013.06.023

Polymers for the use in mucoadhesive preparations can be anionic, cationic or nonionic. Anionic polymers have mucoadhesive properties due to hydrogen bonding with the mucus layer, whereas cationic polymers, e.g., chitosan form bonds with the negatively charged mucin chains. Free thiol groups can also be beneficial to support mucoadhesion due to disulphide bonds [8].

Park and Robinson pointed out that polyanions are preferred over polycations regarding adhesion as well as toxicity potential. Furthermore, carboxylated polyanions seemed to be favoured compared to sulphated polyanions taking bioadhesion and toxic potential into account [9].

Studies were performed using various polymers and dosage forms. Investigated polymers with mucoadhesive properties were, for example, carmellose (Na CMC) [10–13], carbomer [10,12,14,15], hypromellose (HPMC) [14,15], chitosan [15,16] and hyprolose (HPC) [15]. Some polymers, which are well known to own mucoadhesive properties, are listed in Table 1; additionally, the method for determining mucoadhesion is mentioned as well. Dosage forms comprise gels [10,11], thin films [15], solutions [16,17], microparticles [18] and tablets [14]. A suitable test should also cover other dosage forms like film strips or buccal films, which became part of the European Pharmacopoeia most recently.

From Table 1, it is evident that several combinations are feasible regarding the type of polymer, the type of test method and of course the dosage form. The most limiting factor by choosing an appropriate method to determine mucoadhesion is the choice of dosage form.

For example, for a tablet, some test methods like rheology or falling liquid film method cannot be used. The polymers are no limiting factor by choosing an adequate method, because most of the polymers can be used for the preparation of different dosage forms. In addition, most test methods are not dependent on the type of polymer.

3. Mucosa

The oral human mucosa consists of an epithelium, the lamina propria and the underlying submucosa. The epithelium of the buccal mucosa counts about 40–50 cell layers. The turnover time for the buccal epithelium cells is approximately about 5–6 days [19]. The buccal mucosa is completely covered with the mucus layer consisting of more than 95% water [20].

Thickness of the epithelium as well as keratinisation differs between human and animal mucosa. Thickness of buccal mucosa in humans, dogs and rabbits varies from 500 to 800 μm [19].

Some laboratory animals are not that appropriate for the use in mucoadhesion tests as others due to differences in keratinisation of the mucosal lining. Rats and hamsters, for example, have a fully keratinised surface layer [21]. Rabbits have para-keratinised tissue and are more suitable than other rodents [22]. Indeed, isolation of the non-keratinised part of rabbit mucosa is not easy due to a close contact to the keratinised tissue. Pigs, dogs and monkeys have a non-keratinised mucosal lining and are therefore more suitable to mimic human mucosa for mucoadhesion testing [21].

Table 1
Mucoadhesive polymers and the test method to determine adhesive properties of different formulations.

Polymer	Test method	Dosage form
Chitosan	Texture Analyser [15,23,52] Modified balance/surface tensiometer [26,28,30,53–56] Mucin particle method and BIACORE [43] Rheology [16] Ellipsometry [17]	Film [15,28,30,53–55] Gel [52] Tablet [23,26,53] Disc [56] Solution [16,17,43]
Cross-linked poly (acrylic acid)	Texture Analyser [10,52,57] Modified balance/surface tensiometer [20,58] Ellipsometry [17] Colloidal gold staining [46,59]	Gel [10,46,52] Caplet [57] Solution [17,20,58,59]
Gelatin	Modified balance/surface tensiometer [12,25,28] Rheology [16]	Polymer coated glass plates [12] Disc [25] Film [28] Solution [16]
Hydroxyethyl cellulose	Texture Analyser [11] Modified balance/surface tensiometer [30,56] Ellipsometry [17]	Gel [11] Solution [17] Film [30] Disc [56]
Hydroxypropyl methyl cellulose	Texture Analyser [15,60,61] Modified balance/surface tensiometer [12,27,53,55,62,63] Tensile apparatus [5,64] Mucin particle method and BIACORE [43]	Film [15,53,55,60,61] Polymer coated glass plates [12,62] Disc [27] Tablet [5,53,63,64] Solution [43]
Poly (acrylic acid)	Texture Analyser [10,15,52,60,61,65] Modified balance/surface tensiometer [12,27,53,56,66] Tensile apparatus [5,64,67] Rheology [16,65]	Gel [10,52,65] Film [15,53,60,61,67] Polymer coated glass plates [12] Disc [27] Tablet [5,53,64,66] Disc [56], Solution [9,16]
Sodium alginate	Tensile tester [68] Modified balance/surface tensiometer [12]	Polymer coated glass plates [12] Tablet [68]
(Sodium) carboxymethyl cellulose	Texture Analyser [10,11,52,60,61,69] Modified balance/surface tensiometer [12,56,62,66] Tensile apparatus [13] Ellipsometry [17]	Gel [10,11,52] Solution/gel [17,69] Film [60,61] Polymer coated glass plates [12,62] Disc [56] Tablet [66] Paste [13]
Sodium hyaluronate	Texture Analyser [10,52]	Gel [10,52]

Please cite this article in press as: C. Woertz et al., Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview, Eur. J. Pharm. Biopharm. (2013), http://dx.doi.org/10.1016/j.ejpb.2013.06.023