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Preparation and evaluation of a chitosan salt–poloxamer 407 based matrix for buccal drug delivery

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Abstract

The aim of this work was to prepare and evaluate a matrix for buccal drug delivery composed of a chitosan salt and poloxamer 407. Different chitosan salts were formed by reacting chitosan with acetic, citric, and lactic acid. Various proportions of poloxamer 407 were added to the aqueous solution of chitosan salt, and the residue obtained by lyophilisation was compressed into discs, using a 30 kN compression force. An experimental design (3^2) was used to study the influence of the type of chitosan salt and of the relative amount of poloxamer on drug release capacity, swelling, erosion, and mucoadhesiveness of matrices.

The results showed that matrix properties depended significantly on both relative amount of poloxamer and chitosan salt type. The rank orders of chitosan salts for the four processes evaluated were as follows: drug release: chitosan acetate>chitosan citrate>chitosan lactate; swelling: chitosan lactate>chitosan acetate=chitosan citrate; erosion: chitosan citrate>chitosan lactate>chitosan acetate; mucoadhesion: chitosan lactate>chitosan acetate=chitosan citrate. Mucoadhesion was particularly favoured when poloxamer 407 was present at about 30% (w/w). The matrix composed of chitosan lactate and poloxamer 407 showed the best characteristics for buccal administration.

Keywords: Buccal delivery; Chitosan; Poloxamer 407; Mucoadhesion; Controlled release

1. Introduction

The buccal route presents several advantages compared to traditional methods of systemic drug administration [1,2]. The direct entry of the drug into the systemic circulation obviates the first pass hepatic metabolism; in addition, the drug can be easily administered and, if necessary, removed from the site of application which is easily accessible for self-medication. By contrast, some drawbacks must be taken into account when a dosage form is proposed for buccal administration. Among these is the need for the device to maintain its position for many hours against buccal motion and salivary flow, the latter also

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being responsible for dissolving a possible relevant part of the drug, thus reducing the mucosal absorption. Consequently, the dosage form must have good adhesive properties and show an efficient control of drug delivery. This can be accomplished by using excipients with adequate characteristics. Numerous bioadhesive polymers have been investigated for purposes of buccal administration, namely, sodium carboxymethylcellulose, hydroxypropylcellulose, Carbopol, and polycarbophil [3,4]. Another interesting polymer, chitosan, mixed with sodium alginate, was studied as a vehicle in buccal tablets [5], while chitosan glutamate, interacted with polycarbophil and other anionic polymers, was proposed for bilaminated films and bilayered tablets. It has been shown that drug release is influenced by swelling and erosion of the matrix, whereas matrix adhesiveness can be modulated using different mixtures of polymers, both adhesive and not [6].

In this paper, we propose a matrix for buccal drug delivery, composed of a chitosan salt and poloxamer 407 (P407). Chitosan is the *N*-deacetylated product of chitin, a polysaccharide very abundant in nature. Chitosan is gaining increasing importance in the pharmaceutical field due to its favourable properties such as biocompatibility, non-toxicity, and biodegradability.

It has been shown that this polymer has good mucoadhesiveness and a significant enhancing effect on the permeation of drugs across the buccal mucosa [7,8]. P407, also known as pluronic F127, is a polyoxyethylene–polyoxypropylene–polyoxyethylene type block copolymer consisting of 70% polyoxyethylene units. It has the ability to form a clear gel in aqueous media at a concentration of approximately 20% (w/w) or more and exhibits the unique property of reversible thermal gelation; this latter is achieved at a higher temperature (e.g., body temperature) and is reversible upon cooling (e.g., at refrigerator temperature) thereby yielding a low viscosity solution. In addition, P407 has low toxicity, high solubilizing capacity, and excellent drug-release characteristics, all of which have been exploited in the polymer's use as a drug delivery vehicle for a variety of therapeutic agents [9–11].

The combination of chitosan acetate with P407 has been adopted for a mucosal vaccine delivery system, in which the two components showed a synergistic effect on the immune response [12]. P407 was also used in association with Carbopol to obtain mucoadhesive gels [13]. Taking into account the fact that chitosan salts have different physical properties and can have different effects on mucosa permeability [14–16], the aim of this work was to study the behaviour of a matrix composed of a chitosan salt and P407, investigating the effect of the type of chitosan salt and of the proportions of the components on matrix swelling, release capacity, and adhesion. It was expected that P407 could play an important role, based on its capacity of gelling during matrix hydration and the possibility of interaction with chitosan through hydrogen bonding.

Propranolol hydrochloride, a water-soluble compound and a widely used β-blocker, was selected as a model drug, as it is among those drugs whose systemic bioavailability might be strongly improved by buccal delivery.

2. Material and methods

2.1. Materials

P407 (Lutrol F 127®), was a kind gift from BASF, Milan, Italy. Medium molecular weight chitosan [molecular weight about 400 000, viscosity 286 mPa s at *C*=1% (w/w) in 1% (w/w) acetic acid, deacetylation grade 81%], lactic acid aqueous solution [85% (w/w)], and propranolol hydrochloride were all purchased from Sigma Aldrich (Milwaukee, USA). All the other chemicals were of reagent grade. Water was purified using the Milli-Q Plus system (Millipore, USA).

2.2. Methods

2.2.1. Experimental design

In order to verify the influence of the type of chitosan salt (qualitative variable) and of the relative amount of poloxamer (quantitative variable) on the drug release capacity, swelling, erosion, and mucoadhesiveness of the compressed matrices under study, an experimental design was planned. A full factorial design at two factors and three levels (3^2), with a replicate at the central level of the quantitative variable for each value of the qualitative variable, was chosen.