Mucoadhesive Buccal Tablets Based on Chitosan/Gelatin Microparticles for Delivery of Propranolol Hydrochloride

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ABSTRACT: Propranolol administration through buccal route offers some distinct advantages thanks to the easy access to the oral mucosa, fast onset of action, and avoidance of hepatic and intestinal degradation mechanisms. To overcome the effective removal existing in the buccal cavity, mucoadhesive delivery systems are considered a promising approach as they facilitate a close contact with the buccal mucosa. The aim of this study was to prepare mucoadhesive tablets based on chitosan/gelatin microparticles for buccal delivery of propranolol hydrochloride. Spray-dried microparticles were prepared with different chitosan–gelatin weight ratios and characterized in terms of yield and morphology. Microparticles were subsequently compressed with the drug to obtain loaded buccal tablets. *In vitro* water uptake, mucoadhesion, release, and permeation tests were performed to investigate tablet ability to hydrate, to adhere to the mucosa, and to deliver drug through buccal mucosa. Microparticles showed a different morphology based on the different chitosan–gelatin weight ratios. Moreover, buccal tablets based on the prepared microparticles showed different technological and functional characteristics in virtue of their composition. In particular, tablets with an excess of chitosan showed the best mucoadhesive properties, allowed the permeation of the greatest drug amount among all formulations, and could be promising for buccal administration of propranolol hydrochloride. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4365–4372, 2015
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INTRODUCTION

Propranolol hydrochloride is a nonselective β1 and β2-adrenergic antagonist, clinically used for hypertension, angina, atrial fibrillation, postinfarction, sinus tachycardia, arrhythmias, and obstructive cardiomyopathy. When it is administered through oral route, it is almost completely absorbed, but the considerable first-pass hepatic and the short half-life (from 3 to 5 h) lead to a low drug bioavailability (15%–23%).[1] For this reason, propranolol oral administration requires a frequent dosing and consequently causes a poor patience compliance. Problems such as the high first-pass metabolism can be circumvented by administering the drug via the buccal route that ensure drug absorption through the buccal epithelium and its direct passage into the systemic circulation.[2,3] Furthermore, buccal mucosa is easily accessible and suitable for dosage form administration and removal in cases of toxicity. Despite these advantages, buccal drug administration is characterized by the rapid clearance of the drug from the mucosal surfaces, because of the movement of the tongue and jaws, the continuous dilution of the released drug by saliva, and the chewing followed by swallowing.[4,5] This may compromise the residence time of drug in buccal cavity and provide a low bioavailability. For this reason, drug inclusion into a mucoadhesive formulation is desirable to achieve prolonged mucosal contact and higher drug concentration on the mucosal surface.[6,7]

In the last years, among the different mucoadhesive buccal delivery systems, gels,[8] films,[9–11] tablets,[12,13] and microparticles[14] have gained a great deal of interest. In particular, buccal tablets can be easily prepared by direct compression, they could be intended to dissolve or erode slowly, and they are simple to use. They are the less comfortable among the several buccal formulations (especially with respect to film and gels), but they possess some distinct advantages. In fact, they allowed to incorporate a higher amount of drug if they are compared with film; furthermore, they can ensure a more accurate and measured drug dosing if they are compared with semisolid formulations, which can be easily washed away by saliva.[15]

In this study, we investigated the possibility to formulate mucoadhesive buccal tablets based on chitosan and gelatin microparticles for propranolol hydrochloride delivery. Chitosan is a N-deacetylated product of the polysaccharide chitin and is widely employed for the preparation of different delivery systems[16] thanks to its biocompatibility, nontoxicity, biodegradability, and mucoadhesivity.[17–19] In the last years, among the different type of drug delivery systems, several chitosan-based microparticles were formulated by many authors.[20–25] Another important property of chitosan is its ability to form ionically cross-linked hydrogels,[26–29] thanks to the presence of amino groups, which at pH lower than its p*K*a (6.3), are ionized and can interact with anionic polymers or proteins, such as gelatin.

In the first step of this study, we evaluated the feasibility to produce microparticles with different chitosan and gelatin weight ratios by studying the parameter conditions (such as the polymeric concentrations of nebulized dispersions) able to allow microparticle production. The obtained microparticles were characterized in terms of yield and morphology and subsequently compressed with the drug in order to obtain loaded tablets. The influence of the different microparticle compositions on the technological and functional properties of buccal tablets was investigated through several tests. In particular,

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in vitro mucoadhesion, water uptake, release, and permeation tests were performed in order to investigate the mucoadhesion properties and the ability of tablets to hydrate and to deliver drug through buccal mucosa.

EXPERIMENTAL

Materials

Type B gelatin from bovine skin (~225 Bloom, isoelectric point in the range of pH 4.5–5.5) was obtained commercially from Sigma–Aldrich (Milan, Italy); chitosan (Mw = 150 kDa, deacetylation degree 84%, p*K*a 6.3) and propranolol hydrochloride were purchased commercially from Fluka (Milan, Italy). All other chemicals and solvents were of analytical grade and purchased from Carlo Erba (Milan, Italy). Water uptake, mucoadhesion, release, and permeation studies were carried out in aqueous buffers with the following compositions: 7.4 mM $Na_2HPO_4{\cdot}10H_2O$, 1.1 mM KH_2PO_4, 136 mM NaCl for buffer solution pH 7.4; 26 mM KH_2PO_4, 51 mM $Na_2HPO_4{\cdot}12H_2O$ adjusted with hydrochloric acid to pH 6.8.

Preparation of Chitosan/Gelatin Microparticles

For microparticle preparation, chitosan (0.5%–2%, w/v) was dissolved in acetic acid (at the same concentration of chitosan) and stirring for a minimum of 12 h at room temperature. Gelatin solutions (0.5%–2%, w/v) were prepared by dissolving the protein in distilled water and stirring for 1 h at 50°C until complete solubilization. Then, different volumes of chitosan and gelatin solutions were mixed obtaining final polymeric dispersions with different chitosan–gelatin weight ratios (10:0, 8:2, 6:4, 4:6, 2:8, 0:10). The obtained dispersions (500 mL) were nebulized under continuous magnetic agitation, through a nozzle (diameter 0.7 mm) using a spray-dryer (Büchi Mini Spray Dryer, B-191; Switzerland). The drying conditions were as follows: inlet temperature, 125°C; outlet temperature, 60°C; air flow rate, 600 NL/h, feed rate of 20%, vacuum in the system at −85 mm water column, aspirator level at 35%. The obtained microparticles were weighted for the determination of solid complex yield. Percentage process yield was calculated as follows:

$$\text{Yield}\,(\%) = [(A/B) \times 100]$$

where A is the recovered amount of microparticles and B is the theoretical solid amount in the formulation.

Fourier Transformed Infrared Spectroscopy

Infrared spectra of chitosan and gelatin raw materials and microparticles were recorded with a Jasco FT-IR (Fourier transformed infrared) 4100 spectrophotometer (Jasco, Lecco, Italy) in order to study interactions between chitosan and gelatin. Samples were gently triturated with KBr powder in a weight ratio of 1:10 and then pressed using a hydraulic press at a pressure of 100 tons for 5 min to prepare KBr discs. These discs were placed in the sample holder and scanned between 4000 and 450 cm^{-1}.

Scanning Electron Microscopy

The morphological structure of chitosan/gelatin microparticles was studied by scanning electron microscopy (SEM) analysis. Microparticles were fixed on supports and coated with gold palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Samples were then observed with LEO 420 (LEO Electron Microscopy Ltd., Cambridge, UK) using secondary electron imaging at 15 kV in order to examine the structure of microparticles.

Preparation of Tablet, Weight, and Content Uniformity

Tablets were prepared by direct compression of 100 mg of microparticles (compaction force: 18 kN) with a single punch press (type Korsch, Korsch Maschinenfabrik No. 1.0038.86, Berlin, Germany). The drug-loaded tablets were prepared compressing physical mixture of microparticles and propranolol hydrochloride (drug concentration of 5%, w/w). The average diameter and height were measured through a Mitutoyo pocket thickness gauge (Mitutoyo Manufacturing Company Ltd., Tokyo, Japan).

Tablets were weighted in order to evaluate the weight uniformity. For the determination of propranolol hydrochloride content, five tablets for each formulation were dissolved in 10 mL of phosphate buffer (pH 7.4) containing 2 mL of HCl 0.1 M solution. The amount of drug was determined as described in Abruzzo et al.[10] Briefly, the chromatographic system was composed of a Shimadzu (Milan, Italy) LC-10ATVP chromatographic pump and a Shimadzu SPD-10AVP UV–Vis detector set at 254 nm. Separation was obtained on a Phenomenex (Torrance, California) Sinergy Fusion-RP 80A (150 × 4.6 mm^2 i.d., 5 μm) coupled to a Phenomenex SecurityGuard C18 guard cartridge (4 × 3.0 mm^2 i.d., 5 μm). The mobile phase was composed of a mixture of acetonitrile–pH 3.0 solution of triethylamine (0.5%) 30:70 (v/v). The flow rate was 0.4 mL/min and manual injections were made using a Rheodyne 7125 injector with a 20-μL sample loop. Data processing was handled by means of a CromatoPlus computerized integration system (Shimadzu Italia, Milan, Italy).

Friability Studies and Hardness Test

Friability tests were conducted by subjecting at least 10 tablets to repeat revolutions (25 rpm for 4 min) using a friability tester. After dusting, tablets were weighted before and after the testing, and percentage friability was measured as a percentage of weight lost during a standardized abrasion. The hardness of the tablets was determined using Monsanto hardness tester and it is expressed in kg/cm^2.

In Vitro Water Uptake

For the *in vitro* water uptake evaluation, each type of tablet was immersed in a Becker containing phosphate buffer at pH 6.8 at 37°C (20 mL) simulating human saliva. At regular intervals (after each hour for 5 h), the tablets were taken and excess surface water was carefully removed. Tablets were weighted and the water uptake was determined according to the following equation:

$$\text{Water uptake}\,(\%) = [(W_h - W_d) \times 100]/W_d$$

where W_h is the weight of the hydrated tablets and W_d is the initial weight of the dry tablets.

In Vitro Mucoadhesion Studies

For these studies, porcine buccal mucosa was used as biological membrane because of the similarity to the human buccal