Development of Promethazine Hydrochloride Mucoadhesive Patches for Buccal Delivery: In vitro, Ex vivo and In vivo Characterization

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Received; February 12, 2012; accepted April 30, 2012

ABSTRACT
Promethazine hydrochloride (PMZ HCl), an antiemetic, undergoes extensive first-pass metabolism (bioavailability 25%). The purpose of the present investigation was to develop mucoadhesive patches for transbuccal delivery of PMZ HCl using solvent casting technique with Hydroxy ethyl cellulose (Natrosol 250 E) and hydroxylpropyl methyl cellulose as mucoadhesive polymers and propylene glycol as the plasticizer and evaluate their physicochemical characteristics, in vitro drug release, moisture absorption, surface pH, mechanical properties, in vitro bioadhesion, in vivo residence time, and ex vivo drug permeation through porcine buccal membranes from optimized buccal patch and stability studies. The physicochemical interaction between PMZ HCl and polymers was investigated by Fourier Transform Infrared Spectroscopy. Ex vivo drug permeation through porcine buccal membrane was performed and 83.7% of the drug permeated in 6 hours with flux 0.19 mg h$^{-1}$ cm$^{-2}$. The optimized formulation AA4 showed maximum drug release (98%) in 6 hours in the Higuchi model release profile. Moisture absorption, surface pH, tensile strength, elongation at break, peak detachment force and work of adhesion values of the optimized formulation were found to be 68.1%, pH 6.7, 12.3 kg/mm$^2$, 69.2 % mm$^{-2}$, 7.5 N and 2.73 mJ respectively. Formulation AA4 showed 77.6% of the drug permeated through porcine buccal membrane in 6 hours and flux calculated to be 0.45 mg h$^{-1}$ cm$^{-2}$. FTIR studies showed no evidence of interaction between the drug and polymers. In vivo mucoadhesive behaviour of the optimized formulation was studied in healthy human volunteers and subjective parameters were evaluated. The stability of the optimized formulation was studied and no significant changes were detected in drug content, in vitro release and ex vivo permeation after 6 months.

KEYWORDS: Promethazine hydrochloride; buccal patches; bioadhesion; ex vivo permeation; in vivo residence time.

Introduction
The interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of those drugs that undergo first-pass effect. Drug delivery via the buccal route using bioadhesive dosage forms offers a novel route of drug administration. This route has been used successfully for the systemic delivery of a number of drug candidates (Anders and Merkle, 1989; Chen and Hwang, 1992). Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route (Nagai and Konishi, 1987; Harris and Robinson, 1992). Moreover, buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is an alternative route to administer drugs to patients who are unable to be dosed orally. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive patches (Guo, 1994), adhesive tablets (Dortunc et al., 1998), and adhesive gels (Ishida et al., 1983).

However, buccal films are preferable over adhesive tablets in terms of flexibility and comfort.

During the past decade, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery because of their ability to localize the dosage form in specific regions to enhance drug bioavailability (Gu et al., 1988). Bioadhesive polymers not only cause adhesion effects but also control the release rate of the drug release (Duchene et al., 1988). From a technological point of view, an ideal buccal dosage form must have 3 properties: (1) maintain its position in the mouth for a few hours; (2) release the drug in a controlled fashion, and (3) provide the drug release in a unidirectional way toward the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can also be achieved. The third objective can be fulfilled by preparing a system having uniform adhesiveness and an impermeable backing layer (Remunan-Lopez et al., 1998).