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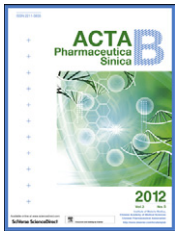

ORIGINAL ARTICLE

Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release

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Gastroretentive dosage form;
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Carbopol

Abstract The aim of the present study was to develop and characterize a gastroretentive dosage form suitable for controlled drug release. It consists of a drug loaded polymeric film made up of a bilayer of immediate (IR) and controlled release (CR) layers folded into a hard gelatin capsule. Gastroretention results from unfolding and swelling of the film and its bioadhesion to the gastric mucosa. Furosemide, a drug with a narrow absorption window, was selected as the model drug. Inclusion of hydroxypropyl β-cyclodextrin in both layers and Carbopol® 971P NF in the CR layer of the bilayer film resulted in optimum drug release, bioadhesion and mechanical properties. The film with zig-zag folding in the capsule was shown to unfold and swell under acidic conditions and provide IR of drug over 1 h and CR for up to 12 h in acidic medium. X-ray diffraction, differential scanning calorimetry and scanning electron microscopy revealed uniform dispersion of furosemide in the polymeric matrices. The results indicate the dosage form is gastroretentive and can provide controlled release of drugs with narrow therapeutic windows.

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1. Introduction

The development of controlled release formulations has had a tremendous impact on the drug delivery field particularly for drugs with a narrow absorption window. However, typical controlled release formulations are limited by insufficient retention in the stomach. To extend the residence time of dosage forms in the stomach, a number of strategies have been developed[1–4], including (a) reducing the density to promote floating in the gastric contents, (b) increasing the density to promote retention in the lower part of the stomach, (c) introducing mucoadhesive properties and (d) producing a formulation that swells or unfolds in the stomach to hinder its escape through the pyloric sphincter. Each of these approaches has its advantages and disadvantages.

An alternative strategy is to combine bioadhesion with the ability to expand by unfolding and swelling. This paper describes the design of a formulation incorporating a drug loaded polymeric film folded in a hard gelatin capsule. After ingestion, the capsule dissolves and releases the film which then unfolds in the stomach and swells to a larger dimension resulting in its increased retention. The concept of a gastroretentive drug loaded polymeric films has been previously reported and the effects of shape, folding pattern and polymer characteristics on performance of gastroretention has been studied[1].

Although this type of dosage form has various advantages such as the convenience of a hard gelatin capsule and the ability to modify drug release through using a multilayer design, there remain a number of issues. These include the difficulty in formulating a drug loaded polymeric film and the selection of a polymer with the desired ability to unfold and expand in the stomach. This paper focuses on practical aspects of designing such a dosage form and the difficulties encountered in its development.

Furosemide (4-chloro-2-furfurylamino-5-sulphamoyl benzoic acid) is a loop diuretic widely used in the treatment of congestive heart failure and edema. It works by inhibiting the $Na^+/K^+/2Cl^-$ transporter in the ascending limb of the loop of Henle[5]. Furosemide is a Biopharmaceutical Classification System (BCS) class IV drug with poor aqueous solubility and permeability. It is mainly absorbed in the upper gastrointestinal tract and has a short half life of less than 2 h. The conventional dosage form shows erratic absorption which results in poor bioavailability (30–60%) and the requirement for dosing 3–4 times/day[6]. In addition, the peak diuretic effect results in significant adverse effects in some geriatric patients. On this basis, a controlled release formulation of furosemide is very desirable.

Generally, a controlled release formulation is designed to provide immediate release (IR) to achieve the therapeutic drug concentration in a short period of time and controlled release (CR) to maintain the concentration for the desired period of time. The dose of furosemide to be incorporated in the developed formulation was decided on the basis of the *in vitro* release pattern of the marketed formulation, Lasix Retard® 60 mg. It was found that the marketed formulation showed the desired controlled release in pH 6.8 buffer but slower release at lower pH (Supplementary Fig. 1). At pH 6.8, about 30% of the drug was released in the first hour followed by release of the remaining drug over the subsequent 12 h. By considering biopharmaceutical parameters including oral bioavailability, half life and plasma steady state concentration[7], it was decided to design a formulation incorporating 30% of the total furosemide dose in a polymeric film for IR and the remainder in a mucoadhesive film folded and inserted in a capsule for CR. The aim was to design a dosage form providing optimal drug release for maximum absorption.

2. Materials and methods

2.1. Materials

Furosemide was obtained from Ipca Labs (Mumbai, India). Polyvinyl alcohol (Gohnesol®), hydroxypropyl methylcellulose (Methocel® E4M, HPMC E4M), poly(ethyl acrylate-*co*-methyl methacrylate-*co*-trimethylammonioethyl methacrylate chloride) (Eudragit® RLPO) and acrylic acid polymer (Carbopol® 971P NF) for preparation of polymer films were provided by Nippon Gohsei (Japan), Colorcon (India), Degussa-Evonik (Germany) and Noveon (India) respectively. Polyethylene glycol 400 (PEG 400, Lutrol® E400) from Merck (India) was used as a plasticizer. PEG-40 hydrogenated castor oil (Cremophore® RH 40), 2-pyrrolidinone (Soluphor® P) and hydroxypropyl β-cyclodextrin (HPBCD, Kleptose® HP) for use as solubilizers were supplied by BASF Ltd. (Germany), Colorcon (India) and Signet Chemical Corporation (India) respectively. All other reagents and chemicals were of analytical reagent grade and used as received.

2.2. Preparation of films

Films with single and double layers were prepared by the solvent casting method on a Mathis lab dryer and lab coater (Mathis AG, Switzerland) using a knife over the roll assembly. Preparation of the solutions used to make single films and the method of making the bilayer film are as follows.

2.2.1. Solution A (controlled release (CR) layer)

A polymeric dispersion was prepared by dissolving HPMC E4M, Eudragit® RLPO, Carbopol® 971P NF (5:0.95:0.05) in isopropanol:water (3:1). A furosemide solution was prepared containing furosemide:Soluphor® P:Cremophore® RH 40 in the ratio 1:1.75:1.75. The furosemide solution was mixed with the polymeric dispersion (1:1) followed by addition of HPBCD (1.5 M) with vigorous stirring to give solution A.

2.2.2. Solution B (immediate release (IR) layer)

Polyvinyl alcohol (15% *w*/*w*) was dissolved in distilled water to which PEG 400 (5%, *w*/*w*) was added as plasticizer. Furosemide was dissolved in 0.05 M NaOH solution and the solution mixed with the polymer solution (1:1) followed by addition of HPBCD (1.5 M) with vigorous stirring to give solution B.

2.2.3. Bilayer film

First solution A was cast on the release liner and allowed to dry at 40 °C for at least 90 min. Then solution B was cast over the formed controlled release layer and allowed to dry for 60 min at 40 °C followed by 30 min at 60 °C. On removal for the release liner, the films were checked for possible imperfections before being cut into 4 cm × 2 cm rectangles and used to fill hard gelatin size 00 capsules by zigzag folding.