Mebeverine-Loaded Electrospun Nanofibers: Physicochemical Characterization and Dissolution Studies

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ABSTRACT: Both fast dissolving and sustained release drug delivery systems (DDSs) comprising mebeverine hydrochloride (MB-HCl) embedded in either povidone (PVP) K60 or Eudragit® L 100-55 nanofibers have been prepared by electrospinning. The fibers are found to have cylindrical morphologies with smooth surfaces, except at high drug loadings that appear to induce surface roughness (PVP) or fragmentation (Eudragit). There is a general increase in fiber diameter with drug loading. Differential scanning calorimetry and X-ray diffraction demonstrate that the drug exists in an amorphous state in the fibers. Infrared spectroscopy data indicate that the drug has good compatibility with the polymer, whereas nuclear magnetic resonance spectroscopy and high-performance liquid chromatography analyses confirmed that the MB-HCl was not degraded during the spinning process. *In vitro* dissolution tests of the PVP fiber mats show them to dissolve within 10 s, an improved dissolution profile over the pure drug. The Eudragit fibers show pH-dependent drug release profiles, with only very limited release at pH 2.0 but sustained release over approximately 8 h at pH 6.8. The Eudragit nanofibers have the potential to be developed as oral DDSs for localized drug release in the intestinal tract, whereas the PVP materials may find the application as buccal delivery systems or suppositories. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:283–292, 2014

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INTRODUCTION

Electrospinning is a simple and versatile process by which nanoscale fibers can be produced using an electrostatically driven jet of a polymer solution or polymer melt.[1–5] Electrospun nanofibers show great promise for developing many types of novel drug delivery systems (DDSs) owing to their high surface area, high porosity, and ability to encapsulate high drug loadings.[3,6,7]

Mebeverine hydrochloride (CAS 2753-45-9; MB-HCl; see Fig. 1) is an antispasmodic agent used in the treatment of irritable bowel syndrome and mucous colitis among other conditions.[8,9] It is classified as a cholinergic muscarinic antagonist, and acts directly on the smooth muscle of the intestine. MB-HCl has poor oral bioavailability; it suffers extensive first pass metabolism through the action of esterases in the blood plasma, and has a short half-life *in vivo*.[10] As a result of its method of action and *in vivo* degradation, traditional MB-HCl formulations do not provide immediate relief of symptoms and typically show activity 2 h, but not 4 h, after administration.[11] The development of DDSs able to provide very rapid or long-lasting relief of symptoms is hence desirable. To achieve the latter, modified release formulations such as Colofec MR® have been developed. Researchers have also investigated MB-HCl containing suppositories to deliver the drug very rapidly and provide immediate relief of symptoms.[12–15] Variation of the excipients used to prepare suppositories yielded very different drug release profiles, and can result in treatments requiring significantly lower dosages than are necessary with traditional oral administration.[13,14]

In addition to its primary role as an antispasmodic agent, MB-HCl has found application as a local anesthetic for dental treatments[16–18]; the development of mucoadhesive MB-HCl oral films is thus also much sought after.

One way in which the targeted delivery of MB-HCl may be achieved is by encapsulation in a polymer matrix: a number of researchers have explored this avenue,[9,18,19] but to date no electrospun MB-HCl formulations have been reported. In this work, we sought to prepare both mucoadhesive fast-dissolving and sustained-release formulations for MB-HCl via the electrospinning technique.

The preparation of electrospun materials, especially with very hydrophilic polymers, has proven effective in the generation of rapidly dissolving DDSs through the formation of solid solutions in which the drug–drug intermolecular forces are much reduced.[20–23] Electrospun sustained-release formulations may also be prepared through the selection of appropriate polymers and offer a separate set of benefits, releasing the embedded drug slowly over a prolonged period of time.[24,25]

In this study, povidone (PVP) K60 and Eudragit® L100-55 were selected for investigation. Both are synthetic biocompatible polymers used in US FDA approved drug products.[26] The application of such synthetic polymers in DDSs is attractive as they have relatively well defined molecular weights and physicochemical characteristics.[27] PVP is a hydrophilic polymer frequently used in pharmaceutical formulations as a wet

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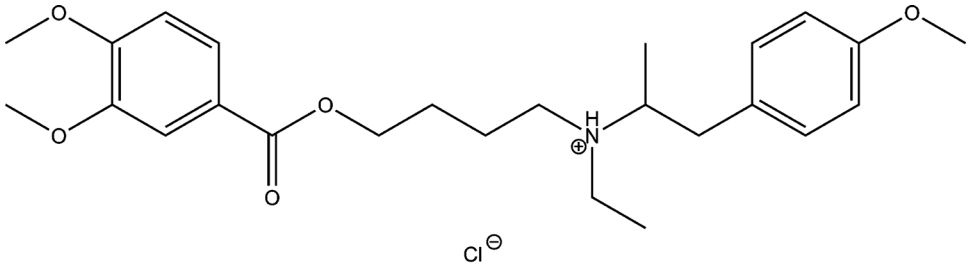

Figure 1. The chemical structure of MB-HCl.

granulation binder. It also finds utility as a bioadhesive[28] and to prepare solid dispersions for improving the dissolution rates of poorly water soluble drugs.[21,29,30] Rectal suppositories utilizing the mucoadhesive properties of PVP are already established,[31] and the application of electrospun nanofibers in rectal treatments has also been demonstrated.[32] Therefore, it was envisaged that a combination of these approaches could lead to an enhanced DDS for MB-HCl suitable for rectal or buccal administration.

Eudragit® L 100-55 is one of a family of polymeric methacrylic esters developed by Rohm Pharma, and now owned by Evonik Industries. Eudragit polymers have been widely used for the formulation of oral dosage forms including as tablet coatings, tablet matrices, and to prepare microspheres and nanoparticles for controlled drug delivery in the gastrointestinal (GI) tract.[24,33,34] These applications arise primarily because of the pH-sensitive solubility of the polymers. Eudragit® L 100-55 is soluble in solutions of pH 5.5 or greater, and has been utilized to develop DDSs able to protect the active pharmaceutical ingredient (API) in the stomach and release it only in the intestinal tract.[19] The incorporation of MB-HCl into such a formulation could hence deliver the drug to the GI tract in a sustained manner, allowing it to act on the smooth muscle therein over a prolonged period of time.

In this investigation, MB-HCl-loaded fibers were prepared with the polymers PVP K60 and Eudragit® L100-55 using the electrospinning technique. A range of fibers was prepared with MB-HCl concentrations varying from 5% to 55% (w/w). By choosing polymers that provided both very rapid (PVP) and sustained pH-sensitive (Eudragit® L100-55) release, formulations were generated that can effectively deliver MB-HCl by oral, buccal, or rectal application.

MATERIALS AND METHODS

Materials

Mebeverine hydrochloride and PVP (MW 360,000, PVP K60) were purchased from Sigma–Aldrich (Gillingham, UK). Eudragit® L 100-55 was a gift from Evonik GmbH (Darmstadt, Germany). All other chemicals used were of analytical grade and used as provided.

Sample Preparation

PVP *Fibers*

A 10% (w/v) PVP K60 solution was prepared by dissolving the appropriate amount of PVP in ethanol and stirring overnight. The required amount of MB-HCl was predissolved in 2 mL of ethanol and added to 5 mL of the polymer solution. Mechanical stirring was applied for at least 20 min at room temperature to obtain homogeneous solutions prior to electrospinning. The spinning solutions were then carefully loaded into a 5-mL syringe to avoid any air bubbles. The positive electrode of a high-voltage power DC supply (HCP 35-65000; Fug Elektronik, Rosenheim, Germany) was connected to a metal needle tip (0.3 mm inner diameter). The grounded electrode was connected to a metal collector (17×17 cm^2) wrapped with aluminum foil. Electrospinning was carried out under ambient conditions ($22 \pm 1^\circ$C and relative humidity $35 \pm 3\%$). An electrical potential of 15 kV was applied across a fixed distance of 12 cm between the tip and the collector. The feed rate was maintained at 1.25 mL/h using a syringe pump. A series of fibers with drug loadings of 0%, 5%, 15%, 30%, and 55% (w/w) were prepared (see Table S1 in the Supporting Information for details of spinning solution compositions); these are denoted P0, P1, P2, P3, and P4, respectively. After fabrication, the fibers were stored over silica gel beads in a desiccator to facilitate the removal of residual organic solvents and moisture.

Eudragit Fibers

A 20% (w/v) Eudragit® L 100-55 solution was prepared by dissolving the polymer in a solvent mixture comprising ethanol and dimethylacetamide (5:1, v/v) with stirring overnight. The required amount of MB-HCl was predissolved in 2 mL of ethanol and 5 mL of the polymer solution added. Electrospinning was performed using similar procedures to those detailed above (15 kV applied voltage, 0.6 mL/h flow rate, and 12 cm spinneret to collector distance). A series of fibers with drug loadings of 0%, 5%, 15%, 30%, and 55% were prepared (see Table S2 for details of spinning solution compositions), and are denoted E0, E1, E2, E3, and E4. As for the PVP materials, the fibers were stored in a desiccator after preparation.

Controls

Physical mixtures (PMs) were prepared by manually mixing MB-HCl with each polymer. The PM of PVP K60 (PPM) was prepared by mixing the drug and polymer at a 55:45 (%, w/w) ratio, whereas the Eudragit PM (EPM) was formed by mixing the drug and polymer in an approximately 30:70 (%, w/w) ratio. These formulations were selected to mirror the fibers with highest loading used for release in each case.

Characterization

Scanning Electron Microscopy

The fiber morphologies were assessed using a JEOL JSM-5600LV scanning electron microscope (JEOL, Tokyo, Japan).