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Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum

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Abstract

The aim of this study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets containing chitosan and xanthan gum prepared by a hot-melt extrusion process. Drug release from hot-melt extruded (HME) tablets containing either chitosan or xanthan gum was pH and buffer species dependent and the release mechanisms were controlled by the solubility and ionic properties of the polymers. All directly compressed (DC) tablets prepared in this study also exhibited pH and buffer species dependent release. In contrast, the HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release. When placed in 0.1N HCl, the HME tablets formed a hydrogel that functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained high ionic strength, whereas tablets without chitosan did not form a hydrogel to retard drug release in 0.1N HCl. The HME tablets containing both chitosan and xanthan gum showed no significant change in drug release rate when stored at 40 °C for 1 month, 40 °C and 75% relative humidity (40 °C/75% RH) for 1 month, and 60 °C for 15 days.

Keywords: Chitosan; Xanthan gum; Hot-melt extrusion; Sustained release; Hydrogel; pH independent release; Buffer species independent release

1. Introduction

The pH of the gastrointestinal tract (GI tract) varies from pH 1 to 3 in the stomach and increases to approximately pH 7–8 in the colon. Furthermore, the pH of the stomach can fluctuate with food intake, as well as with the age and health of the patient (Ogata et al., 1984; Dressman et al., 1990; Russell et al., 1993; Charman et al., 1997).

Sustained release dosage forms extend the duration time of drug therapy, reduce side-effects and increase safety and patient compliance by reducing the frequency of dosing. Multiple daily administration of an immediate release dosage form results in patient non-compliance. To control and modulate drug release properties of tablets, retardant polymers including hydrophilic polymers such as hydroxypropyl methyl cellulose (HPMC) (Siepmann et al., 1999a, 1999b, 2000; Roshdy et al., 2001; McConville et al., 2004; Sangalli et al., 2004), hydroxypropyl cellulose (HPC) (Roshdy et al., 2001), sodium alginate (Rubio and Ghaly, 1994; Kulkarni et al., 1999) and polyvinyl alcohol (PVA) (Peppas and Wright, 1998; Morita et al., 2000; Peppas and Simmons, 2004); as well as the ammonio methacrylate copolymers such as Eudragit® RL and RS (Eshra et al., 1994; Kidokoro et al., 2001; Zhu et al., 2002); or methacrylic acid copolymers like Eudragit® L and S (Palmieri et al., 2000; Bruce et al., 2003, 2005) have been utilized in solid dosage forms. For these retardants, hydrophilic polymers control drug release from tablets by hydrogelation (Lu et al., 1991; Dhopeshwarkar and Zatz, 1993; Peppas et al., 2000; El-Gazayerly, 2003; Peppas, 2004). The retardation mechanism is based on the intra-molecular hydrogelation of a hydrophilic polymer during dissolution and has been reported to be affected by the ionic strength of the dissolution medium (Talukdar and Plaizier-Vercammen, 1993; El-Gazayerly, 2003). Due to differences in ionic strength of gastric and intestinal fluids, as well as wide variations and fluctuations in its pH of the GI tract, the in vitro and in vivo data for sustained release dosage forms may not always correlate.

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The aim of our study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets containing hydrophilic retardant polymers prepared by a hot-melt extrusion process. Chitosan and xanthan gum were investigated as the model hydrophilic retardant polymer.

Chitosan is a linear hydrophilic polysaccharide polymer of D-glucosamine. It is a non-toxic natural polycationic polymer that is degraded by the microflora in the colon. Chitosan is produced by the alkaline deacetylation of chitin. It is an abundant polymer in nature and is present in the exoskeleton of crustaceans such as crabs or shrimp. Chitosan has been widely researched for its potential use as a pharmaceutical ingredient. The characteristics of crosslinked chitosan with an anionic polymer (Takahashi et al., 1990), applications of chitosan in controlled release dosage forms (Chandy and Sharma, 1993; Tapia et al., 1993; Gupta and Ravi Kumar, 2000; Mitrevej et al., 2001; Agnihotri and Aminabhavi, 2004; Berger et al., 2004), evaluations of matrix tablets containing microcrystalline chitosan (Säkkinen et al., 2002) and applications of chitosan in thermo-sensitive chitosan-based hydrogels (Ruel-Gariépy et al., 2004) have been reported. In addition, the ability of chitosan to retard drug release depends on its molecular weight. High molecular weight chitosans function as matrix tablet retardants, whereas low molecular weight chitosans can function as drug release enhancers for poorly water-soluble drugs due to an improvement in wettability resulting from the solubility of low molecular weight chitosans in water (less than 10,000) (Shiraishi et al., 1990; Imai et al., 1991).

Xanthan gum is a polysaccharide consisting of a cellulose backbone and trisaccharide side chains containing glucuronic acids that give this polymer a negative charge. Although primarily used as a suspending agent, xanthan gum has been reported to function as a matrix retardant in solid dosage forms (Dhopeshwarkar and Zatz, 1993; Talukdar and Plaizier-Vercammen, 1993; El-Gazayerly, 2003; Mu et al., 2003; Rowe et al., 2003).

2. Materials and methods

2.1. Materials

Chitosan (deacetylation degree: 89.4%, powder) and chlorpheniramine maleate (CPM) were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Daichitosan® M (deacetylation degree: 87.4%, 75 μm pass powder) and Daichitosan® H (deacetylation degree: 84.8%, 150 μm pass powder) were donated by Dainichiseika Color and Chemicals Mfg. Co. Ltd. (Tokyo, Japan). PEO (SENTRY™ POLYOX™ WSR N80-LEO NF GRADE, Mw = 200,000) was purchased from Dow Chemical Co. (Midland, MI). Glyceryl monostearate (GMS) was purchased from Sasol Germany GmbH (Witten, Germany). Xanthan gum (XANTURAL® 180) was donated by CP Kelco U.S. Inc. (Chicago, IL). Microcrystalline cellulose (Avicel® PH-101) was supplied by FMC Corporation (Newark, DE). CPM was passed through a 250 μm screen prior to further processing.

2.2. Viscosity

The viscosity of 0.5% (w/v) chitosan solution in 0.5% (v/v) acetic acid solution was measured in triplicate with a Brookfield digital viscometer (LVDV-I+, Brookfield Engineering Laboratories Inc., Middleboro, MA) at 25 ± 1 °C after 1 min of rotation using a spindle #2. The rotation speed was 20 rpm.

2.3. Preparation of directly compressed (DC) tablets

A 200 g sample of powder containing 10% CPM as the model drug, functional polymers and excipients was blended using a mortar and pestle for 2 min. A 300 mg sample of the blended materials was then compressed using a hydraulic compactor (Fred S. Carver Inc., Menomonee Falls, WI) at the pressure of 2000 kg. The hardness of a DC tablet was measured in six replicates using a tablet hardness tester (WTP-3, Heberlein & Co. AG, Wattwil, Switzerland).

2.4. Preparation of hot-melt extruded (HME) tablets

The formulations used in this study are shown in Table 1. A 200 g sample of powder containing 10% CPM, functional polymers and excipients was first blended in a mortar and pestle for 2 min. The blended materials were then fed into the hopper of a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ). The processing temperatures were 90 °C (zone 1), 95 °C (zone 2), 105 °C (zone 3) and 110 °C (die). The screw speed was 15 rpm and the processing time for the powders

Table 1
Tablet formulations used in the present study

	Composition (%)				
	Formulation #1	Formulation #2	Formulation #3	Formulation #4	Formulation #5
Chlorpheniramine maleate	10	10	10	10	10
Daichitosan® H	43	–	43	–	–
Daichitosan® M	–	–	–	43	–
Chitosan (spectrum)	–	–	–	–	43
Microcrystalline cellulose	17	43	–	–	–
Xanthan gum	–	17	17	17	17
PEO	27	27	27	27	27
GMS	3	3	3	3	3
Total	100	100	100	100	100