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Physicochemical characterization and mechanisms of release of theophylline from melt-extruded dosage forms based on a methacrylic acid copolymer

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Abstract

The purpose of the current study was to investigate the physicochemical properties of melt-extruded dosage forms based on Acryl-EZE® and to determine the influence of gelling agents on the mechanisms and kinetics of drug release from thermally processed matrices. Acryl-EZE® is a pre-mixed excipient blend based on a methacrylic acid copolymer that is optimized for film-coating applications. Powder blends containing theophylline, Acryl-EZE®, triethyl citrate and an optional gelling agent, Methocel® K4M Premium (hydroxypropyl methylcellulose, HPMC, hypromellose 2208) or Carbopol® 974P (carbomer), were thermally processed using a Randcastle single-screw extruder. The physical and chemical stability of materials during processing was determined using thermal gravimetric analysis and HPLC. The mechanism of drug release was determined using the Korsmeyer–Peppas model and the hydration and erosion of tablets during the dissolution studies were investigated. The excipient blends were physically and chemically stable during processing, and the resulting dosage forms exhibited pH-dependent dissolution properties. Extrusion of blends containing HPMC or carbomer changed the mechanism and kinetics of drug release from the thermally processed dosage forms. At concentrations of 5% or below, carbomer was more effective than HPMC at extending the duration of theophylline release from matrix tablets. Furthermore, carbomer containing tablets were stable upon storage for 3 months at 40 °C/75% RH. Thus, hot-melt extrusion was an effective process for the preparation of controlled release matrix systems based on Acryl-EZE®.

Keywords: Melt-extrusion; Methacrylic acid copolymer; Eudragit® L 100-55; Acryl-EZE®; Carbomer; Hydroxypropyl methylcellulose

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1. Introduction

Controlled delivery of bioactive agents is a major focus of pharmaceutical research since multiple dosing regimens often present problems with patient compliance, toxicity and therapeutic index (Sood and Panchagnula, 2003). Polymeric drug carrier systems have been widely studied to sustain, modify or target drug delivery. Hot-melt extrusion (HME) of thermoplastic polymers is one method that has been used to produce a variety of controlled release dosage forms, including pellets, granules, tablets, suppositories, transdermal systems and ophthalmic inserts (Breitenbach, 2002; Zhu et al., 2002; McGinity and Zhang, 2003).

Young et al. investigated the pH-dependent drug release properties of melt-extruded bead matrices containing the acrylic copolymer Eudragit® Preparation 4135 F (Young et al., 2003). These systems controlled drug release in media where the polymer was insoluble, however, the influence of excipients on drug release was not investigated. Acryl-EZE® is a pre-mixed excipient blend optimized for enteric film-coating that is based on methacrylic acid copolymer type C (Eudragit® L 100-55). The polymer is insoluble in acidic media and dissolves step-wise at pH values greater than 5.5. Furthermore, Acryl-EZE® is an excellent candidate for thermal processing since the polymer is pre-plasticized with triethyl citrate.

Mixtures of polymers, particularly cellulose ethers, are useful in regulating the drug release properties of dosage forms (Pose-Vilarnovo et al., 2004). In matrix tablets, polymer mixtures modify drug release rate by producing gel barriers of varying consistency (Sung et al., 1996; Vazquez et al., 1996). This effect is often due to interactions between the excipients that modify the matrix viscosity and/or polarity as well as the internal structure of the tablet through which the drug must diffuse (Alvarez-Lorenzo et al., 1999, 2001).

Matrix systems containing hydrophilic polymers have been widely studied since drug release from these matrices is controlled by a combination of polymer swelling, erosion and diffusion through the hydrated gel (Di Colo et al., 2001). Hydroxypropylmethyl cellulose (hypromellose) polymers are linear non-ionic cellulose ethers and have been extensively studied regarding both mechanistic and technological factors involved in drug release (Ford et al., 1991; Mahaguna et al., 2003; Shah et al., 1993). In contrast, the carbomers are anionic, high molecular weight polymers of acrylic acid and have been used in tablet formulations to produce zero-order or near zero-order drug release kinetics (Capan et al., 1989; Perez-Marcos et al., 1991).

The purpose of the current study was to investigate the physicochemical properties of melt-extruded cylindrical rods, tablets and pellets containing an enteric coating system based on methacrylic acid copolymer type C and to determine the influence hydroxypropyl methylcellulose (HPMC, hypromellose 2208, Methocel® K4M Premium) and carbomer (Carbopol® 974P) in these extrudates on the mechanisms and kinetics of theophylline release. The physical and chemical stability of materials was studied using thermal gravimetric analysis and HPLC. The mechanism and kinetics of drug release were investigated using model fitting and matrix hydration and erosion studies.

2. Materials and methods

2.1. Materials

Acryl-EZE® was donated by Colorcon (West Point, PA). Anhydrous theophylline, anhydrous citric acid and glacial acetic acid were purchased from Spectrum Chemical (Gardenia, CA). Carbopol® 974P (carbomer) and Methocel® K4M Premium (hydroxypropyl methylcellulose, HPMC) were provided by Noveon (Cleveland, OH) and Dow Chemical (Midland, MI), respectively. Triethyl citrate (TEC) was donated by Morflex (Greensboro, NC). Acetonitrile was purchased from EM Science (Gibbstown, NJ). All powdered materials were passed through a 30 mesh screen prior to processing.

2.2. Thermal analysis of materials

Thermal gravimetric analysis (TGA) was performed using a Perkin-Elmer (Norwalk, CT) 7-Series Thermogravimetrical Analyzer. The temperature ramp speed was set at 10 °C/min, and the percentage weight loss of the samples was monitored from 25 to 600 °C. Volatiles were removed from samples by storing powders under vacuum with desiccants at 25 °C for 72 h prior to thermal studies.