Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 301 (2005) 112–120
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

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

Christopher R. Young [a,*], Caroline Dietzsch [a], Matteo Cerea [b], Thomas Farrell [c], Kurt A. Fegely [c], Ali Rajabi-Siahboomi [c], James W. McGinity [a]

[a] *Drug Dynamics Institute, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA*
[b] *Istituto di Chimica Farmaceutica e Tossicologica, Università degli Studi di Milano, Viale Abruzzi 42, I-20131, Milano, Italy*
[c] *Colorcon, 415 Moyer Boulevard, P.O. Box 24, West Point, PA 19486, USA*

Received 21 December 2004; received in revised form 5 May 2005; accepted 11 May 2005

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

* Corresponding author. Tel.: +1 617 444 6376; fax: +1 617 444 6344.
E-mail address: cryoung76@rcn.com (C.R. Young).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.05.025

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.

2.3. Melt-extrusion of dosage forms

The hot-melt extruded formulations consisted of theophylline, Acryl-EZE®, TEC and an optional gelling agent, HPMC or carbomer. The powders were blended for 5 min in a V-shell blender and then mixed with TEC using a ceramic mortar and pestle. The blends (250 g) were then extruded using a Randcastle Microtruder® RCP-0750 (Cedar Grove, NJ) single-screw extruder. The extruder was equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections). The temperature of the extruder barrel zones and die were set as follows using external temperature controllers: Zone 1 = 90 °C, Zone 2 = 95 °C, Zone 3 = 110 °C and Die = 115 °C. A 6 mm cylindrical die and a screw speed of 20 rpm were employed for tablet production. The cylindrical extrudates were manually cut into tablets weighing approximately 250 mg.

For pellet productions, a 1.2 mm cylindrical die and a screw speed of 10 rpm were employed. After exiting the die, the polymeric strand was fed into a Randcastle Pelletizer RCP-2.0 and uniformly cut into cylindrical pellets. A 75 g sample of pellets was then transferred into a Caleva Model 120 Spheronizer (Dorset, UK) that was maintained at 60–70 °C using a Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun. A detailed description of the hot-melt extrusion and spheronization process was reported earlier (Young et al., 2002). The pellets were spheronized for approximately 15 min.

2.4. In vitro drug release studies

Dissolution studies were performed according to Apparatus 2 guidelines (paddle method) of USP 27 in a Van Kel VK7000 Dissolution Tester equipped with an auto sampler (Model VK 8000). The medium (900 mL) was maintained at 37 °C and agitated at a speed of 50 rpm. Complete drug release was determined after mixing the vessel contents with a homogenizer for 5 min. The enteric dissolution properties of tablets were studied using dissolution testing for 2 h in 0.1N HCl followed by testing in pH 6.8 phosphate buffered solution (PBS, 50 mM).

Samples were analyzed for drug content using a Waters HPLC system equipped with a photodiode array detector (Model 996) extracting at 281 nm. Samples were pre-filtered through a 0.2 μm membrane (Gelman Laboratory, GHP Acrodisc) to remove insoluble excipients. An auto sampler (Model 717 plus) was used to inject 10 μL samples, and the data were collected and integrated using Empower® Version 5.0 software. The column was an Alltech Inertsil™ ODS-3 3 μm, 150 mm × 4.6 mm, and the mobile phase contained a mixture of water:acetonitrile:glacial acetic acid in volume ratios of 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The retention time of the theophylline was approximately 3.6 min. Linearity was demonstrated from 1 to 100 mg/mL ($r^2 \geq 0.998$) and the relative standard deviation of six injections was less than 1%.

2.5. Analysis of dissolution data

The mechanism of drug release from cylindrical rods (6 mm × 6 cm, 2.5 g) during dissolution investigations in 0.1N HCl or pH 6.8 PBS was determined using Eq. (1), the Korsmeyer–Peppas model:

$$\frac{M_t}{M_\infty} = at^n \tag{1}$$

where M_t corresponds to the amount of drug released in time t, M_∞ the total amount of drug released at infinite time, a a constant incorporating structural and geometric characteristics of the drug dosage form, and n is the release exponent. Drug release data where $M_t/M_\infty \leq 0.6$ were employed for determination of the release exponent.

2.6. Hydration/erosion studies

The hydration and erosion of melt-extruded tablets (250 mg) were studied in either 0.1N HCl or pH 6.8 PBS under conditions identical to those described above for dissolution testing. Tablets were carefully removed from the dissolution vessel at predetermined time-points, and the wet weight was measured. The dosage forms were then dried at 55 °C in a vacuum with desiccants for 7 days, and the remaining dry weight was determined gravimetrically. The percent hydration and mass remaining of tablets were calculated according to the following equations:

$$\%\text{hydration} = 100\left(\frac{W_2 - W_3}{W_3}\right) \tag{2}$$

$$\%\text{mass remaining} = 100\left(\frac{W_3}{W_1}\right) \quad (3)$$

where W_1 is the initial dry weight of the tablet, W_2 the wet weight, and W_3 is the remaining dry weight after dissolution testing. Three tablets were used for each time-point.

3. Results and discussion

Matrix tablet formulations based on Acryl-EZE® were prepared by hot-melt extrusion using the ingredients listed in Table 1. All formulations contained 20% theophylline based on the total formulation weight and 25% TEC based on the weight of Acryl-EZE®. Although Acryl-EZE® contains TEC, additional plasticizer facilitated melt processing by decreasing torque, processing time and pressure at the die. The concentrations of the gelling agents studied were 2.5, 5 and 10%. The formulations containing HPMC required more drive amps and created higher pressures at the die when compared to the other blends. Furthermore, the mixture containing 10% HPMC could not be extruded using the processing temperatures and plasticizer levels employed in the current study.

3.1. Thermal stability of materials

The thermal stability of materials was studied using TGA and HPLC. TGA is useful for determining the maximum processing temperatures since this method indicates thermal stability by measuring weight loss due to decomposition as a function of temperature. As seen in Fig. 1, formulation components did not demonstrate weight loss at the processing temperatures used in the extrusion experiments which ranged from 90 to 115 °C. Acryl-EZE® exhibited a transition in the thermogram at approximately 170 °C. A blend of Eudragit® L 100-55 and TEC also exhibited a weight loss at this temperature, whereas the weight of Eudragit® L 100-55 alone remained constant at temperatures below 200 °C. Thus, the transition in the thermogram of Acryl-EZE® at 170 °C was due to the loss of TEC. Although TGA provides a working temperature range, additional techniques are required to fully characterize the chemical stability of materials. The chemical stability of theophylline after HME was verified using a USP reversed-phase HPLC method.

Table 1
Percent compositions of formulations for melt-extrusion

Component	Formulation					
	1	2	3	4	5	6
Theophylline	20	20	20	20	20	20
Acryl-EZE	64	62	60	62	60	56
Triethyl Citrate	16	15.5	15	15.5	15	14
Methocel K4M Premium	–	2.5	5	–	–	–
Carbopol 974P	–	–	–	2.5	5	10

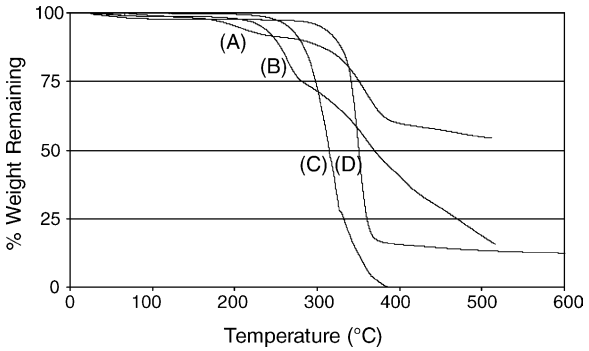

Fig. 1. Thermal gravimetric analysis of formulation components. Key: (A) Acryl-EZE®; (B) Carbopol 974P; (C) Theophylline; (D) Methocel® K4M Premium.

3.2. Drug release studies

Melt-extruded matrix tablets based on Acryl-EZE® exhibited pH-dependent theophylline release. As seen in Fig. 2, the melt-extruded tablets released approximately 10% drug after 2 h in 0.1N HCl. Approximately 75% drug was released after 4 h, which included 2 h in the acidic media and 2 h in pH 6.8 PBS. The rapid drug release rate observed in the pH 6.8 medium was due to the pH-dependent solubility properties of the matrix polymer, Eudragit® L 100-55, which is an essential component of Acryl-EZE®. The anionic methacrylic acid copolymer is widely employed for pH-dependent drug delivery applications since it solubilizes in aqueous media above pH 5.5.

It can also be seen in Fig. 2 that the addition of HPMC to the melt-extruded matrix tablet increased theophylline release in 0.1N HCl. Since Eudragit®

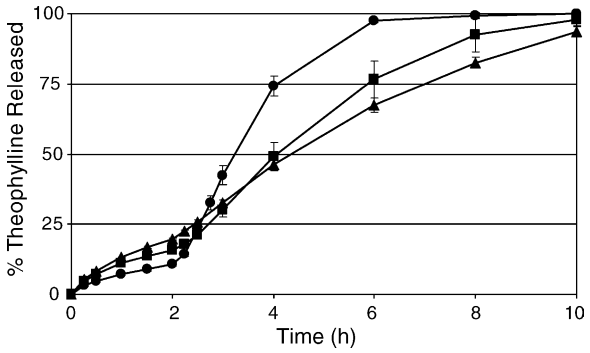

Fig. 2. Influence of Methocel® K4M Premium on the theophylline release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1N HCl followed by 8 h in pH 6.8 PBS, 900 mL, 37 °C, 50 rpm, $n = 6$). Key: (●) 0%; (■) 2.5%; (▲) 5%.

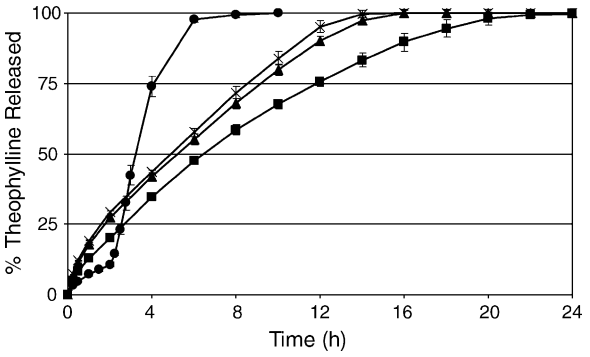

Fig. 3. Influence of Carbopol 974P on the theophylline release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1N HCl followed by 22 h in pH 6.8 PBS, 900 mL, 37 °C, 50 rpm, $n = 6$). Key: (●) 0%; (■) 2.5%; (▲) 5%; (×) 10%.

L 100-55 is insoluble in this acidic medium, the hydrophilic polymer changed the drug release rate by increasing drug diffusivity in the matrix. The amount of drug released during the first 2 h of dissolution testing increased with increasing HPMC concentration. Pollock and Balwinski (2000) observed that HPMC accelerated drug release from a delivery system containing an insoluble polymer by swelling and opening channels through which dissolution medium could enter the core.

Although HPMC was a porosity modifier in 0.1N HCl, the high molecular weight polymer decreased the rate of theophylline release in the pH 6.8 medium. At pH 6.8, where Eudragit® L 100-55 is soluble, the hydration of the HPMC present in the matrix further decreased the rate of theophylline release due to the formation of an entangled gel network that reduced the erosion rate of the tablet (Gao et al., 1996; Nellore et al., 1998; Maggi et al., 1999).

The influence of carbomer on the theophylline release rate is illustrated in Fig. 3. Like HPMC, carbomer increased drug release in the acidic medium by increasing matrix permeability due to polymer swelling and erosion from the tablet. However, carbomer significantly reduced the rate of theophylline release in the pH 6.8 medium when compared to HPMC due to an increase in the magnitude and rate of swelling of individual polymer hydrogels at pH 6.8. The increased swelling decreases the size of channels between the polymer hydrogels and reduces drug diffusivity in the matrix. Additionally, the gel network formed by HPMC is due to entanglement of linear polymer chains, and the gel layer erodes as the chains of the hydrophilic polymer dissolve. Carbopol hydrogels does not erode in the same manner as HPMC hydrogels since the former is water insoluble due to chemical crosslinking.

The theophylline release profiles of carbomer containing tablets did not appear to be influenced by changes in the medium pH during enteric dissolution investigations. However, dissolution studies at pH 1.0 or 6.8 without media changes revealed that the matrix tablets exhibited pH-dependent drug release properties. The formulation containing 2.5% carbomer released approximately $68 \pm 1.4\%$ theophylline after 10 h of enteric dissolution testing. In pH 1.0 and 6.8 media, the level of drug released after 10 h was 52 ± 1.0 and $83 \pm 5.3\%$, respectively (ANOVA, $n = 6$, $p < 0.05$). The higher percentage of theophylline released at pH 6.8 was due to the more rapid hydration and neutralization of the carboxy vinyl polymer that occurs at pH 6.8.

The dissolution profiles of the tablets containing 5 or 10% carbomer, which exhibited complete drug release after approximately 14 h, were not significantly different as illustrated in Fig. 3 ($f_1 = 5$, $f_2 = 81$). Generally, dissolution curves are considered equivalent when difference values (f_1) are less than 15 and similarity values (f_2) are greater than 50 (Center for Drug Evaluation and Research, 1997). However, the matrices containing 2.5% carbomer significantly extended the duration of drug release. Complete theophylline release was not obtained until approximately 20 h of dissolution testing.

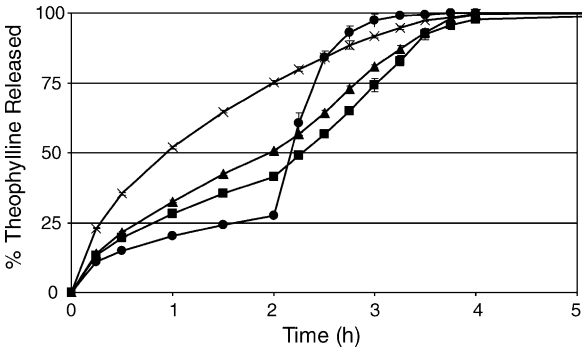

Fig. 4. Influence of Carbopol 974P on the theophylline release properties of melt-extruded Acryl-EZE® beads (paddle method, 2 h in 0.1N HCl followed by 3 h in pH 6.8 PBS, 900 mL, 37 °C, 50 rpm, $n = 6$). Key: (●) 0%; (■) 2.5%; (▲) 5%; (×) 10%.

Unlike the results of HPMC containing tablets, increasing the concentration of carbomer did not extend the duration of drug release. This finding is likely due to the differences in the swelling properties and the ionic nature of the polymeric additives. The swelling of HPMC is not influenced by medium pH, whereas the swelling of carbomer hydrogels increases with pH, reaching a plateau in the pH range of 5–10. Carbomer polymers swell significantly due to ionization of carboxylate groups (pK_a 6.0 ± 0.5) on the polymer backbone (Bulletin 17, 2002).

As illustrated in Fig. 4, Carbopol 974P also significantly influenced the drug release properties of melt-extruded beads. Drug release rate increased in the pH 1.0 medium and decreased in the pH 6.8 medium upon addition of the polymer. However, unlike the findings of dissolution investigations of matrix tablets, carbomer only extended theophylline release for approximately 1 h longer than the melt-extruded beads without the polymeric additive. Furthermore, the beads containing 2.5% carbomer did not exhibit a significantly extended dissolution profile when compared to the beads containing 5 or 10% of the polymer. The rapid release of theophylline was due to the high surface area to volume ratio of beads. Other researchers have noted that matrix geometry significantly influences drug release rates from systems containing swellable polymers (Katzhendler et al., 1997; Siepmann et al., 2000). Matrix tablets were employed for model fitting and hydration/erosion studies since they exhibited a longer duration of drug release.

3.3. Mechanisms and kinetics of drug release

The mechanism of drug release from matrices containing swellable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms (Siepmann and Peppas, 2001). The Korsmeyer–Peppas model is used to analyze drug release from pharmaceutical dosage forms when the release mechanism is not well known or when more than one type of release phenomena is involved (Korsmeyer et al., 1983). The exponent, termed the release exponent or n value, was studied by Peppas and coworkers (1985) to characterize different drug release mechanisms from thin films. They noted that profiles with $n = 0.5$ exhibited a drug release mechanism controlled by Fickian diffusion, while drug release rate was independent of time and controlled by a swelling mechanism when $n = 1$. A zero-order release mechanism is also known among polymer scientists as case-II transport. Values of n between 0.5 and 1.0 were regarded as an indicator for the superposition of both phenomena, and the drug release mechanism was termed anomalous (non-Fickian) transport.

The values of n for cylindrical systems were later determined (Ritger and Peppas, 1987): $n = 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous transport) and $n = 0.89$ (case-II transport). Furthermore, when determining the n exponent, only the portions of the release curve where $M_t/M_\infty \leq 0.6$ should be used. Another commonly overlooked requirement is that drug release occurs in a one-dimensional way, thus the length to width ratio of the device must be at least 10 (Costa and Lobo, 2001).

Drug release data from the dissolution investigations of cylindrical rods (0.6 cm × 6.0 cm) in either pH 1.0 or 6.8 medium were used for model fitting. As illustrated in Table 2, dissolution data fit the model well as a correlation coefficient (r^2) greater than 0.99 was obtained in all cases. The systems without a swelling agent approached a release mechanism described by Fickian diffusion in 0.1N HCl and exhibited primarily case-II transport (zero-order release) in pH 6.8 PBS. The difference in release mechanism as a function of medium pH was a result of the pH-dependent solubility properties of Eudragit® L 100-55 in Acryl-EZE®.

Table 2
Korsmeyer–Peppas model fitting of dissolution data from cylindrical melt-extrudates (dimensions: 6 mm × 6 cm, paddle method, 900 mL, 37 °C, 50 rpm, $n = 6$)

Percent additive	0.1N HCl		pH 6.8 PBS	
	r^2	n	r^2	n
0	0.9995	0.47	0.9987	0.84
Methocel K4M				
2.5	0.9987	0.49	0.9997	0.80
5	0.9997	0.55	0.9993	0.72
Carbopol 974P				
2.5	0.9985	0.51	0.9992	0.60
5	0.9970	0.53	0.9996	0.61
10	0.9973	0.54	0.9994	0.64

The tablets containing 2.5% HPMC or carbomer also exhibited near Fickian diffusion controlled release in 0.1N HCl, but an anomalous (non-Fickian) diffusional mechanism became apparent as the concentration of the gelling polymers increased. The additives resulted in an anomalous mechanism of drug release by increasing drug diffusivity in the matrix in the medium where Eudragit® L 100-55 was insoluble. The release exponent ranged from 0.64 to 0.80 in pH 6.8 PBS for all HPMC and carbomer containing extrudates. Thus, theophylline release from these matrices was controlled by a combination of matrix erosion and diffusion of the drug in the hydrated polymer matrix.

Although the mechanism of theophylline release was pH-dependent, the overall kinetics of drug release from melt-extruded tablets containing 2.5, 5 or 10% carbomer were near zero-order ($r^2 = 0.9844$, 0.9884 and 0.9917, respectively) during enteric dissolution testing. Zero-order release kin nets would not be expected since Acryl-EZE® contains met acrylic acid copolymer type C. The HPMC containing tablets exhibited a biphasic drug release profile during enteric dissolution testing.

3.4. Hydration/erosion studies

The hydration and erosion of matrix tablets during dissolution investigations were studied to determine the influence of gelling agents on the mechanism of drug release from melt-extruded tablets. The results of these studies supported the findings of fitting to the Korsmeyer–Peppas model. Fig. 5 illustrates the

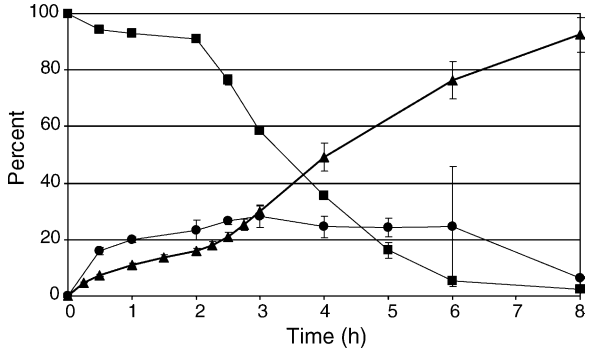

Fig. 5. Influence of 2.5% Methocel® K4M Premium on the hydration, erosion and drug release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1N HCl followed by 6 h in pH 6.8 PBS, 900 mL, 37 °C, 50 rpm, hydration/erosion: $n = 3$, drug release: $n = 6$). Key: (●) hydration; (■) mass remaining; (▲) theophylline released.

hydration, mass remaining and drug release profiles for tablets containing 2.5% HPMC. The results indicate that drug release was primarily diffusion controlled in 0.1N HCl as there was minimal hydration or erosion of the matrix. When the medium was changed to pH 6.8 PBS, the diffusional exponent (n) increased to 0.80 as a result of significant tablet erosion. The low concentration of HPMC formed a gel with insufficient strength to maintain the matrix structure upon dissolution of Eudragit® L 100-55.

As illustrated in Fig. 6, extrude matrix tablets containing 2.5% carbomer exhibited less hydration in the 0.1N HCl when compared to the pH 6.8 medium.

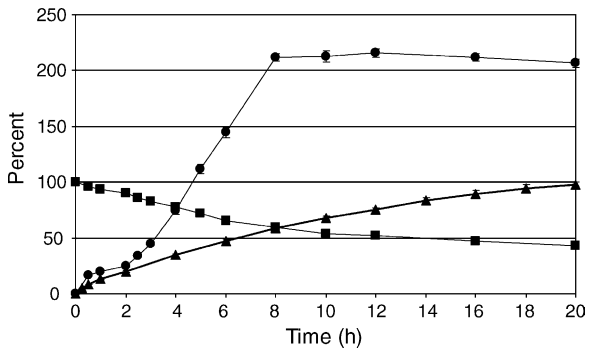

Fig. 6. Influence of 2.5% Carbopol 974P on the hydration, erosion and drug release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1N HCl followed by 18 h in pH 6.8 PBS, 900 mL, 37 °C, 50 rpm, hydration/erosion: $n = 3$, drug release: $n = 6$). Key: (●) hydration; (■) mass remaining; (▲) theophylline released.

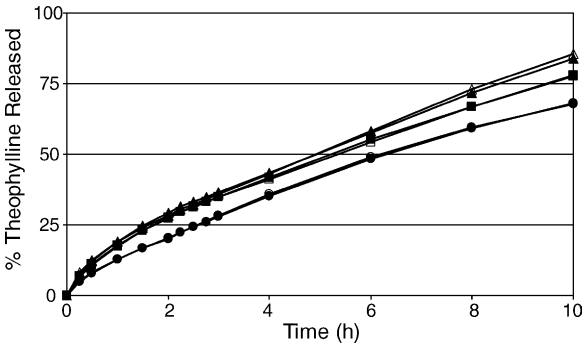

Fig. 7. Stability of theophylline release rate from melt-extruded Acryl-EZE® tablets containing Carbopol 974P upon storage for 3 months at 40 °C/75% RH in induction sealed HDPE containers with silica desiccant (paddle method, 2 h in 0.1N HCl followed by 8 h in pH 6.8 PBS, 900 mL, 37 °C, 50 rpm, $n = 6$). Key: (●) 2.5%, initial; (◯) 2.5%, stored; (■) 5%, initial; (□) 5%, stored; (▲) 10%, initial; (△) 10%, stored.

Formation of a hydrogel in pH 6.8 PBS prevented significant matrix erosion and an apparent increase in the drug release rate. This phenomenon also resulted in an anomalous (non-Fickian) drug release mechanism. The tablets absorbed approximately 1.5 times their weight in water after 4 h in pH 6.8 PBS. The percent water uptake and mass loss of these tablets was stable between the 8 and 20 h time points. Previous investigators have also noted that carbomer forms mechanically strong matrices at low concentrations due to the chemically crosslinked structure of the polymer that swells, but does not dissolve, in water (Perez-Marcos et al., 1991).

3.5. Stability of drug release

Matrix tablets containing Acryl-EZE® and 2.5% carbomer were stored at 40 °C/75% RH in induction sealed HDPE containers containing silica desiccants. The drug release rates from hydrophobic polymeric matrices have been reported to decrease upon storage due to changes in the dimensional structure of the matrix (Omelczuk and McGinity, 1993; Zhang et al., 2001). As seen in Fig. 7, the dissolution profiles of matrix tablets containing 2.5, 5 or 10% carbomer were stable upon storage for 3 months at accelerated conditions. These results are in agreement with the findings of previous researchers who have noted that melt-extruded matrix dosage forms do not exhibit changes in matrix structure upon storage since compression and intense mixing of molten materials during processing results in a product with low free volume (Kidokoro and McGinity, 2001).

4. Conclusions

The current study demonstrated the applicability of Acryl-EZE® (a pre-mixed excipient blend optimized for enteric film-coating) to be used in melt-extrusion processes to prepare controlled release systems. The blend was stable during thermal processing and resulted in dosage forms with pH-dependent dissolution properties.

Results also illustrated the influence of the physicochemical properties of gelling agents on the mechanism and kinetics of drug release from melt-extruded dosage forms. At low concentrations, Carbopol® 974P was more effective than Methocel® K4M Premium at controlling theophylline delivery in a medium where methacrylic acid copolymers exhibited solubility. These findings were attributed to chemical crosslinking nature of the polymeric additive, which created a gel network that resulted in slow erosion of the dosage form during dissolution studies in pH 6.8 PBS.

References

Alvarez-Lorenzo, C., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C., Concheiro, A., 1999. Microviscosity of hydroxypropylcellulose gels as a basis for prediction of drug diffusion rates. Int. J. Pharm. 180, 91–103.

Alvarez-Lorenzo, C., Duro, R., Gómez-Amoza, J.L., Martinez-Pacheco, R., Souto, C., Concheiro, A., 2001. Influence of polymer structure on the rheological behavior of hydroxypropylmethylcellulose-sodium carboxymethylcellulose dispersions. Colloid Polym. Sci. 579 (11), 1045–1057.

Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. Eur. J. Pharm. Biopharm. 54, 107–117.

Capan, Y., Senel, S., Calis, S.T., Hincal, A.A., 1989. Formulation and in-vivo evaluations on sustained release acetylsalicylic acid tablets. Pharm. Ind. 51, 443–448.

CDER Center for Drug Evaluation and research, 1997. Dissolution Testing of Immediate Release Solid Dosage Forms, BP1, http://www.fda.gov/cder/guidance/1713bp1.pdf.

Costa, P., Lobo, J.M.S., 2001. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.

Di Colo, G., Burgalassi, S., Chetoni, P., Fiaschi, M.P, Zambito, Y., Saettone, M.F., 2001. Gel-forming erodible inserts for ocular controlled delivery of ofloxacin. Int. J. Pharm. 215, 101–111.

Ford, J.L., Mitchell, K., Rowe, P., Armstron g, D.J., Elliott, P.N.C., Rostron, C., Hogan, J.E., 1991. Mathematical modeling of drug release from hydroxypropylmethylcellulose matrices: effect of temperature. Int. J. Pharm. 71 (1–2), 95–104.

Gao, P., Skoug, J.W., Nixon, P.R., Ju, T.R., Stemm, N.L., Sung, K.C., 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Int. J. Pharm. 85, 732–740.

Katzhendler, I., Hoffman, A., Goldberger, A., Friedman, M., 1997. Modeling drug release from erodible tablets. J. Pharm. Sci. 86, 10–115.

Kidokoro, M., McGinity, J.W., 2001. Properties of tablets containing granulations of ibuprofen and acrylic copolymer prepared by thermal processes. Pharm. Dev. Technol. 6, 263–275.

Korsmeyer, R.W., Gurny, R., Doelker, E.M., Buri, P., Peppas, N.A., 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Maggi, L., Evelyn, O.M., Torre, M.L., Conte, U., 1999. Formulation of biphasic release tablets containing slightly soluble drugs. Eur. J. Pharm. Biopharm. 48, 37–42.

Mahaguna, V., Talbert, R.L., Peters, J.I., Adams, S., Reynolds, T.D., Lam, F.Y.W., Williams III, R.O., 2003. Influence of hydroxypropyl methylcellulose polymer on in vitro and in vivo performance of controlled release tablets containing alprazolam. Eur. J. Pharm. Biopharm. 56, 101–108.

McGinity, J.W., Zhang, F., 2003. Melt-extruded controlled-release dosage forms. In: Ghebre-Sellassie, I., Martin, C. (Eds.), Pharmaceutical Extrusion Technology, vol. 133. Marcel Dekker, New York, pp. 183–208.

Nellore, R.V., Gurvinder, S.R., Hussain, A.S., Tillman, L.G., Augsburger, L.L., 1998. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. J. Contr. Rel. 50 (1–3), 247–256.

Noveon Inc., 2002. Bulletin 17: Controlled release tablets and capsules.

Omelczuk, M.O., McGinity, J.W., 1993. The influence of thermal treatment on the physical-mechanical and dissolution properties of tablets containing poly(DL-lactic acid). Pharm. Res. 10, 542–548.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Perez-Marcos, B., Gutierrez, C., Gomez-Amoza, J.L., Rartinez-Pacheco, R., Souto, C., Concherio, A., 1991. Usefulness of certain varieties of carbomer in the formulation of hydrophilic furosemide matrices. Int. J. Pharm. 67, 113–121.

Pollock, D.K., Balwinski, K.M., 2000. The utility of hypromellose as a porosity modifier in an ethylcellulose compression coating. In: Proceedings of the 27th International Symposium on Controlled Release of Bioactive Materials, Paris, France.

Pose-Vilarnovo, B., Rodríguez-Tenreiro, C., Santos, J.F., Vázquez-Doval, J., Concheiro, A., Alvarez-Lorenzo, C., Torres-Labandeira, J.L., 2004. Modulating drug release with cyclodextrins in hydroxypropyl methylcellulose gels and tablets. J. Contr. Rel. 94, 351–363.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J. Contr. Rel. 5, 37–42.

Shah, N., Zhang, G., Apelian, V., Zheng, F., Infield, M.H., Mallick, A.W., 1993. Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: effect of polymer concentration. Pharm. Res. 10 (11), 1693–1695.

Siepmann, J., Kranz, H., Peppas, N.A., Bodmeier, R., 2000. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. Int. J. Pharm. 201, 151–164.

Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Del. Rev. 48, 139–157.

Sood, A., Panchagnula, R., 2003. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. Int. J. Pharm. 261 (1–2), 27–41.

Sung, K.C., Nixon, P.R., Skoug, J.W., Ju, T.R., Gau, P., Topp, E.M., Patel, M.V., 1996. Effect of formulation variables on drug and polymer release form HPMC-based matrix tablets. Int. J. Pharm. 142, 53–60.

Vazquez, M.J., Casalderrey, M., Duro, R., Gomez-Amoza, J.L., Martinez-Pacheco, R., Souto, C., Concheiro, A., 1996. Atenolol release from hydrophilic matrix tablets with hydroxypropylmethyl cellulose (HPMC) mixtures as gelling agent: effects of the viscosity of the HPMC mixture. Eur. J. Pharm. Sci. 4, 39–48.

Young, C.R., Koleng, J.J., McGinity, J.W., 2002. Production of spherical pellets by a hot-melt extrusion and spheronization process. Int. J. Pharm. 242, 87–92.

Young, C.R., Koleng, J.J., McGinity, J.W., 2003. Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process. J. Microencapsul. 20, 613–625.

Zhang, Y.E., Tchao, R., Schwartz, J.B., 2001. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. Pharm. Dev. Technol. 6, 131–144.

Zhu, Y., Shah, N.H., Malick, A.W., Infeld, M.H., McGinity, J.W., 2002. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int. J. Pharm. 241, 301–310.