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SUPERINTENDENCIA DE INDUSTRIA Y
DIVISION DE NUEVAS CREACION
E. S. D.

Re: Expediente No. **06.010.699**
Solicitud de patente a nombre de **GRÜNENTHAL GMBH.**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **GRÜNENTHAL GMBH**, domiciliada en Aachen, Alemania, solicitante de la patente de la referencia, en respuesta al oficio No. 869 notificado por fijación en lista el 29 de enero de 2010, relacionado con el concepto técnico de fondo No. 04239, me permito presentar ante ese despacho los siguientes documentos que fueron requeridos con fundamento en el artículo 46 de la Decisión 486.

1. L. Maggi et al, "High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms". *Int. J. Pharm.* 195. (2000), pp. 229-238.

2. C. J. Kim, "Effects of drug solubility, drug loading and polymer molecular weight on drug release from Polyox® tablets". *Drug. Dev. Ind. Pharm.* 24 (1998), pp. 645-651.

3. Zhang et al, "Properties of Sustained-Release Tablets Prepared by hot-melt Extrusion". *Pharm. Dev. Tech.* 1999, 4 (2), 241-250

Sobre este particular, me permito manifestar que con la presentación de estos tres documentos queda totalmente atendido el requerimiento de ese despacho fundamentado en el artículo 46 de la Decisión 486.

Señor Superintendente,

DILIA MARIA RODRIGUEZ D'ALEMAN
CC. 41.654.882
TP 20824 CSJ
NRA

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High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms

L. Maggi, R. Bruni, U. Conte *

Department of Pharmaceutical Chemistry, University of Pavia, Viale Taramelli 12, I-27100 Pavia, Italy

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Abstract

High molecular weight polyethylene oxides (PEOs) have recently been proposed as an alternative to hydroxypropylmethylcellulose (HPMC) in controlled release matrix tablets. In this study, we compared the performance of PEO and HPMC polymers when employed in the Geomatrix® [1] technology, a versatile, well-known method to achieve extended release of drugs at a constant rate. Four core formulations were prepared, containing a soluble drug (diltiazem) and, alternatively, PEO or HPMC of two different viscosity grades. These formulations have the same composition except for the polymer employed. Similarly, four barrier formulations were also prepared, which only differ in the kind of polymer employed. Three-layer Geomatrix® systems were then prepared using these core and barrier formulations. The release profiles of the different three-layer systems obtained were compared, to verify if PEO could efficiently replace HPMC in this type of dosage form. The results show that slower release rates can be obtained from the plain matrices containing HPMC compared to PEO, moreover HPMC, used in the barrier formulations, is generally more efficient in controlling drug release rate in three-layer Geomatrix systems. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Polyethylene oxides; Hydroxypropylmethylcellulose; Hydrophilic matrix; Three-layer system; Controlled release

1. Introduction

Among the various hydrophilic polymers employed for drug release control, hydroxypropylmethylcellulose (HPMC) is the most commonly used polymer in matrices for extended release of drugs, due to its versatility, compatibility with many drugs and safety (Alderman, 1984). Nevertheless, high molecular weight polyethylene oxides (PEOs) have recently been proposed as an alternative to HPMC for controlled drug delivery (Royce, 1993; Kim, 1995, 1998). Apicella et al. prepared extended release hydrophilic matrices, which contain high molecular weight PEOs as the hydrophilic polymer, and demonstrated that this kind of delivery system shows a non constant release rate (Apicella et al., 1993). Yet, drug release at a constant rate is often desirable, to

* Corresponding author. Tel.: +39-382-507374; fax: +39-382-507382.

E-mail address: cupa@chifar.unipv.it (U. Conte)

[1] Geomatrix® is a registered trademark of Skye Pharma AG, Muttenz, CH.

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maintain the plasmatic levels of the drug in the therapeutic range, thereby avoiding the peak and valley profile characteristics of conventional dosage forms in a multidose regimen.

Table 1
Percent composition of different core formulations

Core	CY_1	CM_1	CY_2	CM_2
PEO (Polyox WSR N60K)	38.2			
HPMC (Methocel K4M)		38.2		
PEO (Polyox WSR 303 NF)			38.2	
HPMC (Methocel K100M)				38.2
Diltiazem hydrochloride	49.3			
Lactose	11.0			
Magnesium stearate	1.0			
Colloidal silicon dioxide	0.5			

Table 2
Percent composition of different barrier formulations

Barrier	bY_1	bM_1	bY_2	bM_2
PEO (Polyox WSR N60K)	45.0			
HPMC (Methocel K4M)		45.0		
PEO (Polyox WSR 303 NF)			45.0	
HPMC (Methocel K100M)				45.0
Lactose	45.0			
Hydrogenated castor oil	8.5			
Magnesium stearate	1.0			
Colloidal silicon dioxide	0.5			

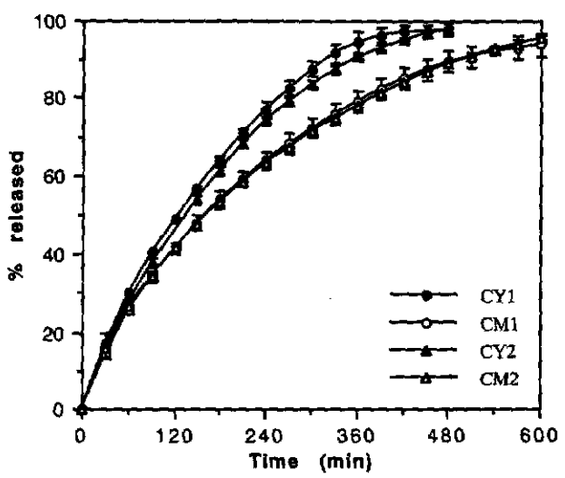

Fig. 1. Release profiles of the core formulations CY_1, CM_1, CY_2 and CM_2.

Geomatrix® technology is widely employed to obtain constant drug release (Conte and Maggi, 1998). This drug delivery system consists of two or three-layer tablets in which the outer layers are drug-free modulating barriers, while the active ingredient is contained in the central layer (or core). All the layers contain a hydrophilic polymer, usually HPMC (Conte et al., 1994). The multi-layer design and the use of polymeric barriers allow the drug release profile to be modulated in a wide range. The barrier layers reduce the surface of the core exposed to the outer environment and, by controlling water penetration in the matrix, they modulate the drug release rate (Conte et al., 1993).

In this study, high molecular weight PEOs were used as the hydrophilic polymer in the core and/or in the barrier layers of Geomatrix systems, in particular, Polyox® WSR N60K (molecular weight 2×10^6) and Polyox® WSR 303 (molecular weight 7×10^6), which are believed to be comparable to Methocel® K4M and Methocel® K100M (Union Carbide bulletin, 1993). These four polymers were used to prepare two PEO and two HPMC plain matrices (cores of the Geomatrix systems), which have the same composition except for the kind of polymer contained. As a model drug, a well-known soluble drug (diltiazem hydrochloride) was employed. The dissolution behaviour of these formulations in the form of plain matrices without barrier layers was compared. Three-layer Geomatrix tablets were then prepared, employing the previously detailed core formulations and four different types of barriers containing PEO or HPMC. The release profiles of the different three-layer systems were compared to verify if PEO could efficiently replace HPMC in this type of drug delivery system. The influence of polymer type and viscosity grade on drug release rate and kinetics was evaluated.

2. Experimental

2.1. Materials

Diltiazem hydrochloride was supplied by Profarmaco S.p.A. (Milan, Italy). HPMCs (Methocel

Table 3
Times (min) at which 75% of the drug is released (t_{d75}) from different core and three-layer systems (mean value, $n = 3$)

Formulation	Plain matrix no barriers	Geomatrix three-layer systems			
		bY_1	bM_1	bY_2	bM_2
CY_1	222	505	616	624	792
CY_2	246	559	687	657	946
CM_1	324	651	724	715	1013
CM_2	357	629	782	761	1199

K4M and Methocel K100M) were supplied by Colorcon (Orpington, UK) while PEOs (Polyox WSR 303 and Polyox WSR N60K) were supplied by Union Carbide Corp. (Danbury, CT, USA).

Polyox WSR N60K (molecular weight 2×10^6) is characterised by a viscosity grade comparable to Methocel K4M. A 2% (p/v) water solution of Polyox WSR N60K has a viscosity range of 2000 and 4000 cP (Brookfield viscometer, with a No 3 spindle at 10 rpm, 25°C, Union Carbide bulletin, 1993), and a 2% (p/v) water solution of Methocel K4M has a viscosity of 4000 cP (Ubbelohde tube, 20°C, Colorcon bulletin, 1992). Polyox WSR 303 (molecular weight 7×10^6) is believed to be comparable (Union Carbide bulletin, 1993) to Methocel K100M.

The other excipients were lactose and magnesium stearate (C. Erba, Milan, Italy), hydrogenated castor oil (Cutina HR, Henkel Chimica, Milan, Italy) and colloidal silicon oxide (Syloid 244, Grace GmbH, Worms, Germany).

2.2. Methods

The four cores and the four barrier formulations were prepared by mixing the drug (only in the case of core formulations), the hydrophilic polymer and the excipients for 30 min (Turbula, Bachofen, Basel, CH Switzerland). The compositions of the various mixtures are reported in Tables 1 and 2.

The core matrices were prepared by direct compression of the powder mixtures. A single punch reciprocating tablet machine (Korsh EK0, Berlin, Germany), equipped with convex punches of 10 mm in diameter was used. The tablets weighed 244 mg $\pm$ 1% and the thickness is 3.63 mm $\pm$ 1%. The PEO tablets (CY_1 and CY_2) showed a crushing strength of 98.3 $\pm$ 2.9 N, while this parameter was 172 $\pm$ 5.2 and 195 $\pm$ 7.1 N for the core matrices containing Methocel K4M or K100M, respectively. To prepare three-layer Geomatrix tablets, the die was accurately and progressively filled with weighed amounts of the different mixtures (barrier, drug formulation and barrier again). The powders were manually layered and the compression cycle was activated. The resulting tablets weighed 504 mg $\pm$ 1% and the tablet thickness was 6.30 mm $\pm$ 2%. The crushing strength was 177 $\pm$ 14 N for Geomatrix tablets with PEO cores and the four different barriers and 289 $\pm$ 15 N for those with HPMC cores and the four different barriers, respectively.

All systems contain 120 mg of diltiazem hydrochloride as active.

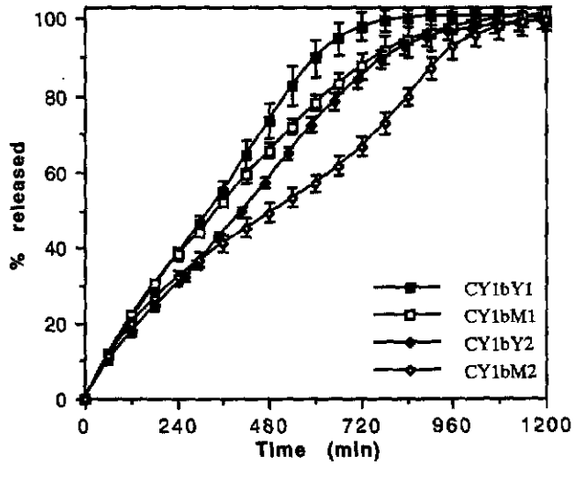

Fig. 2. Release profiles of Geomatrix three-layer systems with CY_1 cores and the four different barrier formulations.

Table 4
Prevailing release kinetics (correlation coefficients, R^2) of the different three-layer Geomatrix systems

Formulation	bY_1	bM_1	bY_2	bM_2
CY_1	Anomalous (0.994)	Anomalous (0.997)	Anomalous (0.999)	Anomalous (0.996)
CM_1	Anomalous (0.999)	Anomalous (0.999)	Anomalous (0.994)	Anomalous (0.998)
CY_2	Linear (0.997)	Linear (0.999)	Linear (0.999)	Higuchi (0.998)
CM_2	Linear (0.998)	Linear (0.999)	Linear (0.999)	Linear (0.998)

In vitro dissolution tests were performed in 1 l of distilled water at 37°C, with the USP apparatus 2 (paddle), at 100 rpm (three replicates). The amount of drug released was assessed by UV detection at 236 nm (Spectracomp 602, Advanced Products, Milan, Italy).

The release data were fitted using the well-known empirical equation proposed by Korsmeyer and Peppas (1983)

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ is the fractional drug release, t the release time, k is a kinetics constant and n the diffusion exponent, characteristic of the release mechanism. For a cylindrical matrix that can swell, $0.89 < n < 1.0$ indicates a zero order release, while $0.45 < n < 0.89$ shows anomalous release kinetics (Ritger and Peppas, 1987; Peppas and Sahlin, 1989).

A linear regression analysis of the logarithmic form of Eq. (1) was carried out, and a correlation coefficient (R^2) > 0.99 was obtained in all cases.

The significance of the differences between the various formulations in terms of time at which 75% of the drug is released (t_{d75}) was evaluated (Student's t test).

It is known that polyethers can undergo chain cleavage through autooxidation (Union Carbide bulletin, 1993). This degradation causes a reduction of the molecular weight of the polymer and, as a consequence, may influence the controlled release efficiency of the matrix. For this reason, the dissolution profiles of all the systems considered were evaluated after the tablets had been stored for 1 year in polyethylene bottles at room temperature.

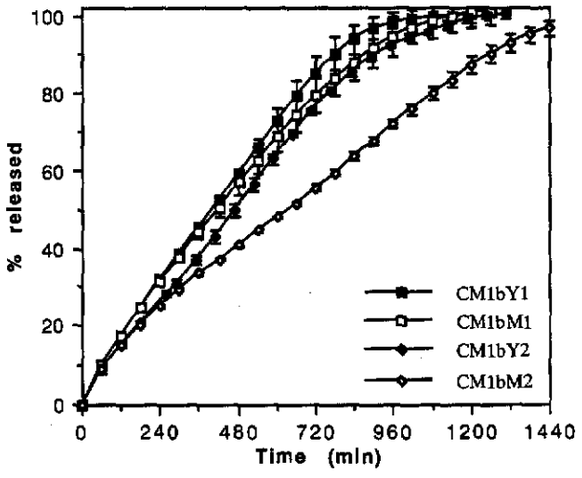

Fig. 3. Release profiles of Geomatrix three-layer systems with CM_1 cores and the four different barrier formulations.

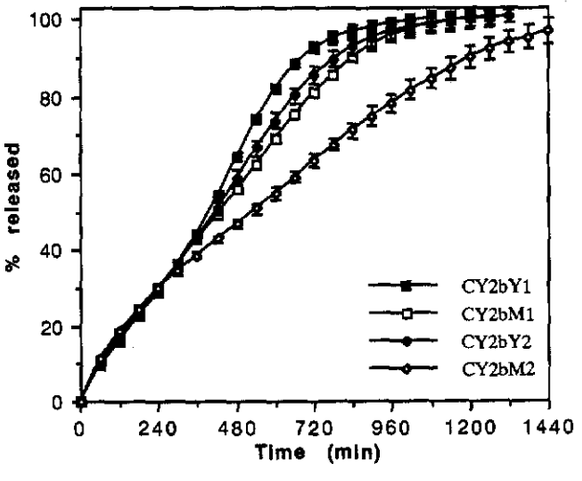

Fig. 4. Release profiles of Geomatrix three-layer systems with CY_2 cores and the four different barrier formulations.

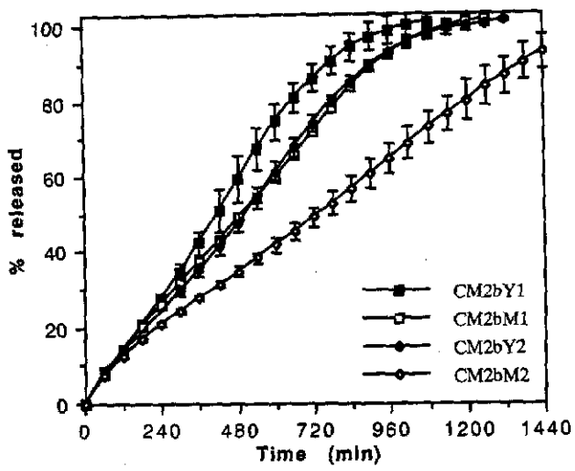

Fig. 5. Release profiles of Geomatrix three-layer systems with CM_2 cores and the four different barrier formulations.

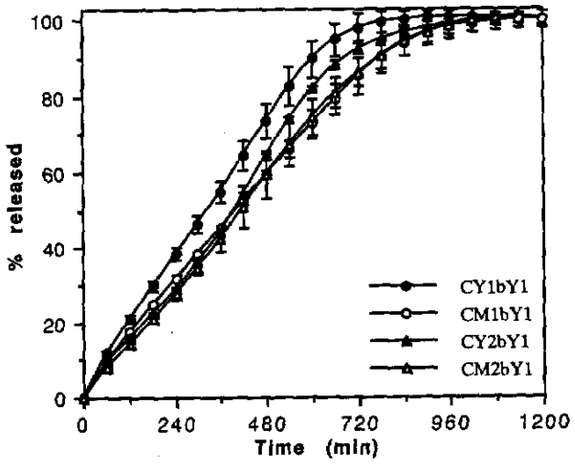

Fig. 6. Release profiles of Geomatrix three-layer systems with bY_1 barrier and the four different core formulations.

To study the morphological behaviour of the different type of polymeric material during the dissolution test, some plain tablets, made of pure polymers, were also prepared. These tablets were placed in dissolution in the same conditions as previously detailed, sampled after different time intervals and sectioned. The photomicrographs of these pure polymeric tablets were evaluated according to a method previously described (Conte and Maggi, 1996), using a video microscope and an image analyser (CV9000, FKV SRL, Sorisole, BG, Italy). From the images the height and diameter of the tablets can be measured to evaluate the volume increase during dissolution test.

3. Results and discussion

The results of the dissolution tests performed on the four different core formulations showed that the diltiazem release rate from the two matrices containing HPMC is slower compared to

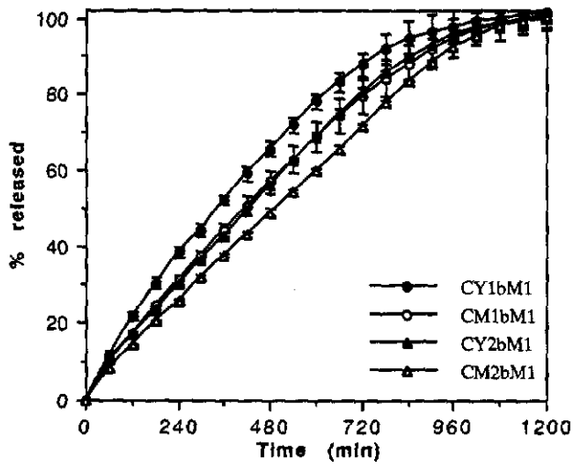

Fig. 7. Release profiles of Geomatrix three-layer systems with bM_1 barrier and the four different core formulations.

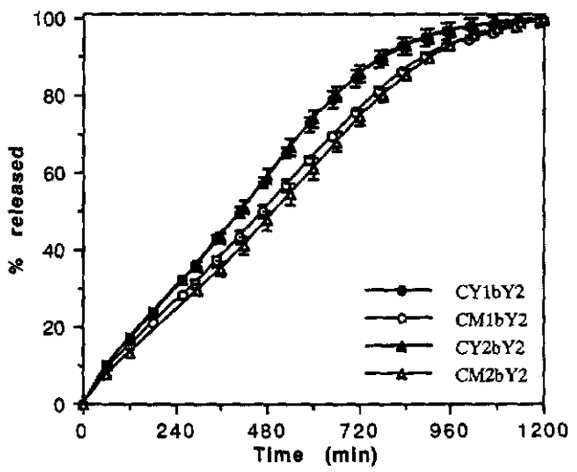

Fig. 8. Release profiles of Geomatrix three-layer systems with bY_2 barrier and the four different core formulations.

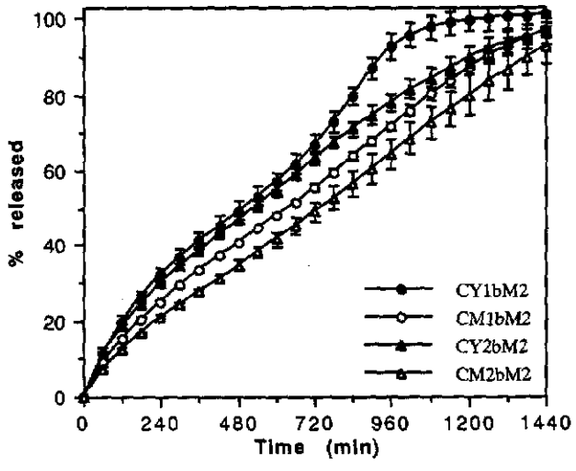

Fig. 9. Release profiles of Geomatrix three-layer systems with bM_2 barrier and the four different core formulations.

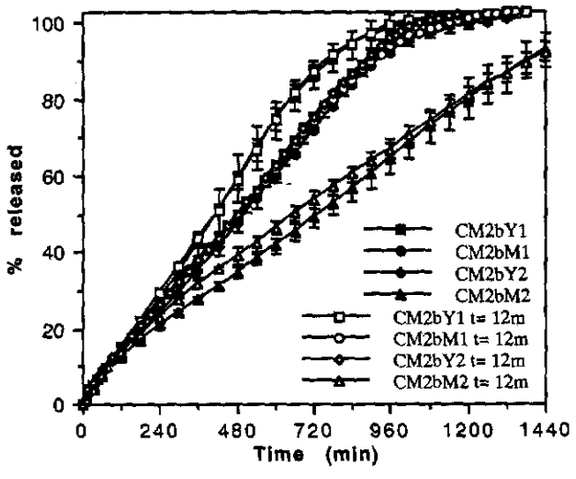

Fig. 10. Release profiles of Geomatrix three-layer systems with CM_2 cores and the four different barriers at time zero and after 1 year of storage at room temperature.

the release rate of PEO matrices (Fig. 1). The t tests showed significant differences in t_{d75} between CY_1 and CM_1 and between CY_2 and CM_2 formulations ($P < 0.01$, Table 3). On the other hand, by comparing the dissolution behaviour of the core formulation containing Methocel K4M to that of the core composition containing Methocel K100M, no significant difference between the dissolution profiles of these formulations can be evidenced. Similar considerations can be made in the case of CY_1 and CY_2 cores. Thus, the viscosity grade of the polymer contained in these matrices seems to have slight influence on the release profile of the core formulations. For all the core tablets, the kinetics which best fits the release data is the Higuchi ($R^2 \geq 0.999$). This means that the drug is mainly released by Fickian diffusion.

The application of the different barrier layers causes a strong reduction in the drug release rate in all the core formulations (Table 3). In particular, the application of bM_1 barriers to the different cores, doubles the t_{d75} of the plain matrices, while the t_{d75} of Geomatrix systems with bM_2 barriers are three-fold compared to that of the core tablets. On the other hand, the barriers made of PEO of comparable viscosity are less efficient in reducing drug release rate.

The release profiles of the three-layer tablets with CY_1 as core layer and with the four different barrier formulations are compared in Fig. 2. As expected, barriers containing polymers of higher viscosity (bY_2 and bM_2 barriers) are more efficient in controlling drug release rate compared to those containing polymers of lower viscosity (bY_1 and bM_1, $P < 0.01$). Moreover, diltiazem release from the devices with CY_1 cores and HPMC barriers is slower than the release from systems with CY_1 core and PEO barriers of comparable viscosity. This trend is more evident for the barriers containing polymers of higher viscosity ($P < 0.05$ between bY_2 and bM_2 barriers, while $0.05 < P < 0.1$ between bY_1 and bM_1 barriers).

The above mentioned systems show anomalous release kinetics as shown in Table 4, and also the Geomatrix systems with CM_1 cores and the four different barriers show anomalous release kinetics (Table 4). The dissolution profiles of three-layer matrices with CM_1 cores and bY_1, bM_1 or bY_2 barriers are very similar (Fig. 3). On the contrary, the application of the barrier layers containing HPMC of higher viscosity (bM_2), causes a stronger reduction in drug release rate compared to the other CM_1 three-layer tablets ($P < 0.05$). Similar behaviour was shown by the three-layer systems containing CY_2 cores and the four different barrier formulations (Fig. 4). CY_2bY_1, CY_2bM_1 and CY_2bY_2 dissolution patterns are very similar, while bM_2 barrier seems to be more efficient in controlling drug delivery rate in this

Table 5
Times (min) at which 75% of the drug is released (t_{d75}) from different core and three-layer systems stored for 1 year at room temperature (mean value, $n = 3$)

Formulation	Plain matrix no barriers	Geomatrix three-layer systems			
		bY_1	bM_1	bY_2	bM_2
CY_1	223	528	586	632	835
CY_2	278	560	708	667	951
CM_1	309	616	703	765	1089
CM_2	357	632	759	792	1186

core formulation. On the contrary, the release profiles of three-layer matrices with CM_2 cores and the four different barriers compared to CM_1 and CY_2 three-layer devices are more differentiated (Fig. 5).

The three-layer devices containing in the core the polymers of higher viscosity, release the drug at a lower rate compared to the systems containing the polymers of lower viscosity (Table 3; Figs. 4 and 5). For all cases, the best fit was determined to be linear (Table 4) except for CY_2bM_2 which best fit is the Higuchi type.

The barriers made of HPMC seem more efficient in reducing drug delivery than PEO barriers, and their efficiency in drug release modulation depends on the viscosity grade of the polymer (Table 3).

By comparing the dissolution behaviour of the Geomatrix three-layer systems with the same barrier but with cores containing the four different polymers, very similar dissolution patterns were obtained (Figs. 6–8). This means that the core composition has less influence on the drug delivery modulation in this kind of device, while the barriers play the leading role in controlling drug release from the Geomatrix three-layer systems. Only in the case of the barrier containing HPMC of higher molecular weight a rank order can be evidenced as a function of the viscosity grade of the polymer contained in the core (Fig. 9).

The stability test does not evidence any problem related to possible oxidation of the PEO chain. The dissolution profiles of all the systems considered at time zero and after 1 year of storage at room temperature, are completely superimposable (three-layer systems with CM_2 cores and the four different barriers are reported in Fig. 10 as example). No significant difference could be evidenced in t_{d75} (Table 5).

The results of the swelling studies performed on the plain tablets made of pure polymer evidence quite different morphological behaviour of HPMCs and PEOs during hydration. In fact, HPMCs tablets showed a slow and continuous volume increase, up to four-fold (Methocel K4M) or six-fold (Methocel K100M) the volume of the dry tablet, after 20 h in distilled water (Fig. 11). On the other hand, tablets made of pure PEOs swell rapidly (up to six-fold or two-fold in the case of Polyox WSR 303 or Polyox NF-60K tablets, respectively, after 8 h), but these polymers form a weaker gel, tend to be eroded much more quickly and the tablet volume decreases progressively (Fig. 11).

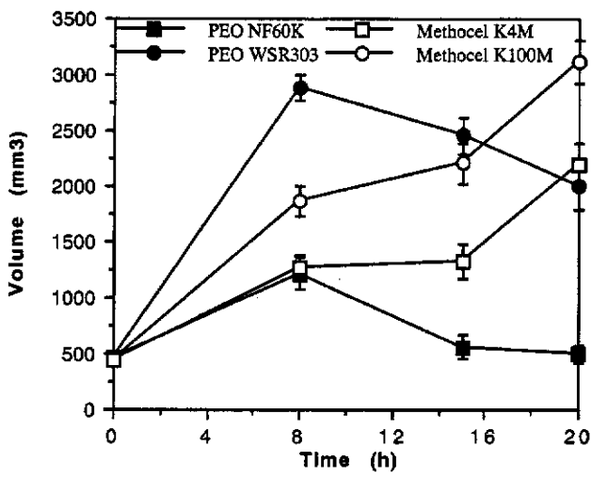

Fig. 11. Swelling study, volume increase of the tablets made of pure polymer.

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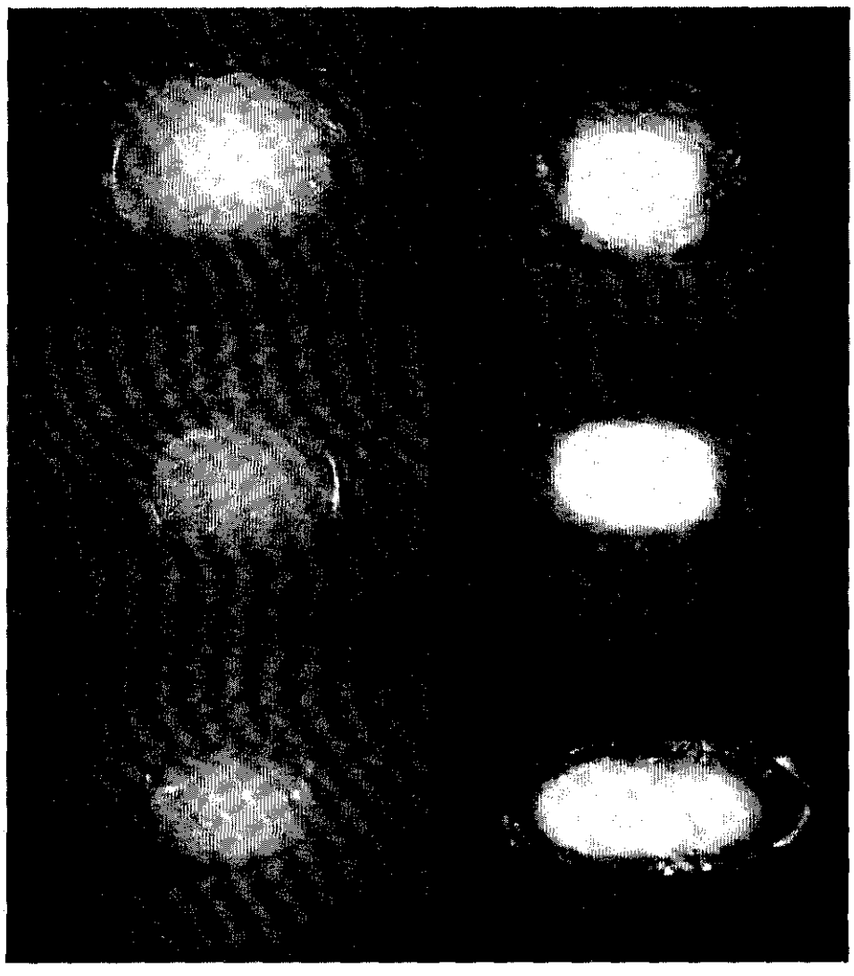

Fig. 12. Photographs of the tablets made of pure polymer during dissolution. Left column, Polyox WSR N60K; Right column, Methocel K4M. From top to bottom, after 8, 15 and 20 h.

Moreover, the photomicrographs of the tablets made of pure HPMCs evidenced a slow hydration rate: after 20 h a bulky glassy core could still be evidenced in both Methocel K4M (Fig. 12) and Methocel K100M tablets (Fig. 13). Methocel K100M showed a stronger resistance to erosion compared to Methocel K4M, as evidenced by the presence of a gel layer characterized by a considerable thickness at the tablet surface (Fig. 13).

On the other hand, PEOs showed a faster hydration rate: after 15 h in water only a small portion of the tablet made of Polyox WSR 303 was still in the glassy state (Fig. 13), and the Polyox NF-60K tablet was completely gelled (Fig. 12). After 20 h both polymers were fully gelled, but Polyox WSR 303 was eroded at a slower rate because it seems to form a stronger gel compared to Polyox NF-60K. The volume of the Polyox WSR 303 tablet was about five-fold compared to that of the tablet made of PEO of lower viscosity after 20 h in water (Fig. 11).

As expected, HPMC and PEO of higher viscosity grade are characterised by a slower hydration rate and by a stronger resistance to erosion compared to the corresponding polymers of lower viscosity.

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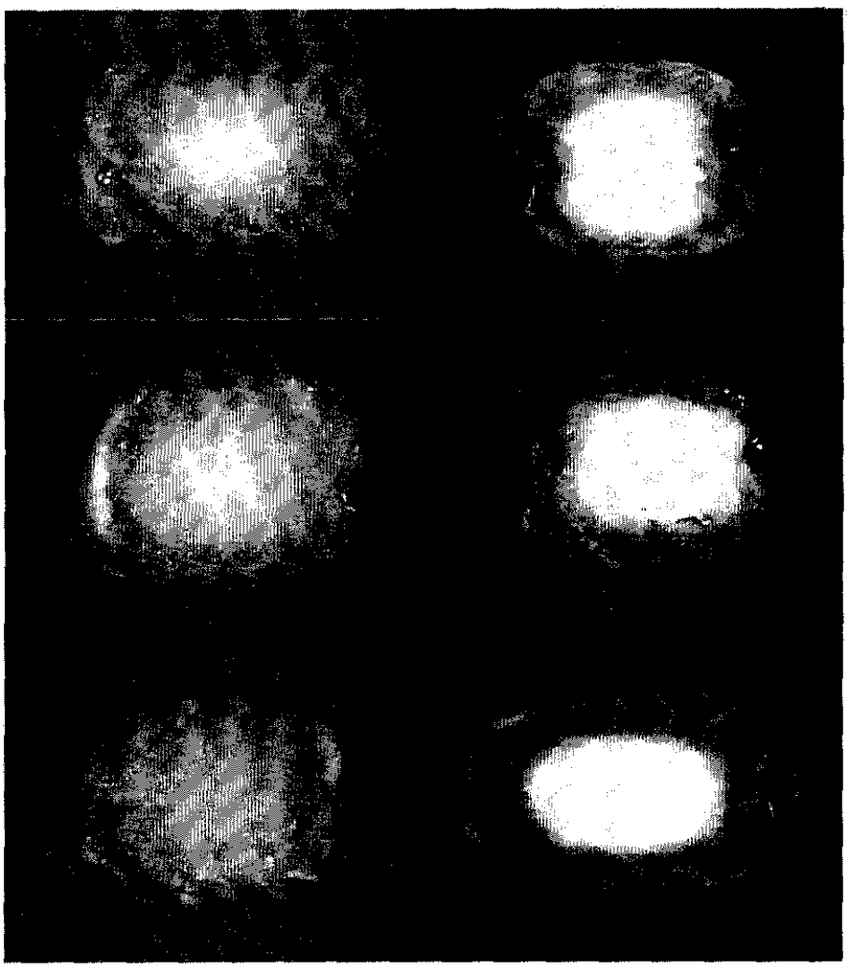

Fig. 13. Photographs of the tablets made of pure polymer during dissolution. Left column, Polyox WSR 303NF; Right column, Methocel K100M. From top to bottom, after 8, 15 and 20 h.

4. Conclusions

PEOs appear to be less efficient when compared to HPMCs in reducing the delivery rate of a soluble drug as diltiazem hydrochloride, probably because they form a weaker gel layer than HPMCs of comparable viscosity. A softer gel can be more rapidly removed by the dissolution medium, and therefore, the matrix system more easily susceptible to an erosion process.

However, the active core and barrier layer design of the Geomatrix technology allows a stronger control of the release kinetics and an optimal modulation of the dissolution profiles can be easily achieved whether PEOs or HPMCs are used. The storage at room temperature has little, if any, influence on the controlled release efficiency of all the systems considered.

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RESEARCH ARTICLE

Effects of Drug Solubility, Drug Loading, and Polymer Molecular Weight on Drug Release from Polyox® Tablets

Cherng-ju Kim

School of Pharmacy, Temple University, 3307 North Broad Street, Philadelphia, Pennsylvania 19140

ABSTRACT

This study investigated the effects of polymer molecular weight, drug solubility, addition of a water-soluble excipient, and drug loading on zero-order release kinetics and elucidated the release mechanism of a drug from directly compressed tablets. Directly compressed tablets consisting of polyethylene oxides (PEO) (MW = 0.9, 2.0 and 4.0 × 10^6) and drugs (solubility ranging from 290 to 25,000 mg/l) were formulated with or without a water-soluble excipient (lactose). For PEO tablets (MW = 0.9 × 10^6), drug release is primarily swelling/erosion controlled for drugs for which solubility is below 1%, resulting in zero-order release kinetics. For PEO tablets (MW = 4.0 × 10^6), drug release is controlled at a zero-order rate by the dissolution rate of the drug at high loading (39%). At low loading (20%), drug diffusion through the swollen gel layer becomes the governing release mechanism. For a highly water-soluble drug (e.g., diclofenac Na), drug diffusion is the controlling mechanism regardless of the molecular weight of the PEOs. Zero-order release kinetics can be achieved with PEO tablets (MW = 0.9 × 10^6) for drugs for which solubility is below 1%. PEO tablets (MW = 2.0 × 10^6) provided zero-order release for poorly water-soluble drugs (below 0.2%) at 39% drug loading. It is possible to attain zero-order release kinetics with PEO tablets (MW = 4.0 × 10^6) using a drug which has a solubility of less than 0.1%.

INTRODUCTION

Extended release of biologically active drugs is highly desirable for drugs that have characteristically short half-lives. There are a number of approaches for preparation of extended-release dosage forms (1,2). Although monolithic systems, composed of hydrophobic polymers and excipients, are commonly used for extended-release dosage forms because they are not costly or difficult to produce, they provide a square-root of time (sqrt) kinetics. There are several ways to improve the release kinetics of these extended-release dosage forms ranging from non-Fickian to zero-order release. Incorporation of hydrophilic polymers into monolithic matrices modifies sqrt kinetics to anomalous kinetics attributable to the swelling and erosion of the hydrophilic polymers. In particular, monolithic matrix systems governed by the swelling and erosion processes of the polymers provide a zero-order rate resulting from the synchronization of the swelling and erosion which causes boundaries to move (3,4). However, it is rare to find hydrophilic and pharmaceutically applicable polymers that furnish the synchronization of the two processes (swelling and erosion).

Recently, Apicella et al. (5) and Kim (6) have demonstrated that a polyethylene oxide (PEO) matrix can generate balanced rates of swelling and erosion. In PEOs of 0.6, 0.9, and 2.0×10^6, synchronization of the swelling and erosion processes was observed. In contrast, PEOs possessing a molecular weight of 4.0×10^6 did not furnish the balanced processes of swelling and erosion; rather it was observed that the swollen gel layer kept increasing until the entire polymer was hydrated, followed by a decrease in size because of the erosion of the swollen gel (5,6). Because of the synchronization of the swelling and erosion of the polymers having a molecular weight of less than 2.0×10^6, zero-order release profiles have been observed from theophylline and acetophylline, whereas anomalous release kinetics were reported for the polymers of MW = 4.0×10^6 (5,6). Apicella et al. (5) and Kim (6) used laminated film tablets and smaller compressed tablets, respectively. Furthermore, Kim (7) developed donut-shaped tablets to achieve zero-order release kinetics from the polymers of MW = 4.0×10^6.

In this study, we investigated the effect of polymer molecular weight, drug solubility, addition of a water-soluble excipient, and drug loading on the zero-order release kinetics of PEO tablets, and elucidated the release mechanisms of drugs from directly compressed tablets.

MATERIALS AND METHODS

Materials

Polyox®-WSR NF (PEO) of average molecular weights 0.9, 2.0, and 4.0×10^6 was supplied by Union Carbide (Danbury, CT). Theophylline anhydrous USP, salicylic acid USP, sulfapyridine, and lactose USP were purchased from Amend Co. (Irving, NJ), and magnesium stearate USP was obtained from Mallinckrodt Chemical (Jersey City, NJ). Diclofenac Na and sulfathiazole were purchased from Sigma Chemical Co. (St. Louis, MO). Ethanol (200% proof) was obtained from Pharmaco Co. (Bayonne, NJ). All materials were used as received.

Preparation of Tablets

The ingredients (PEO, drug, and magnesium stearate) were blended and then compressed using a Carver press machine (model C, Wabash, IN). All tablets contained 1 wt% magnesium stearate as a lubricant. Tablet punches with flat surfaces were used to prepare all of the tablets with an 11.1 mm diameter and a weight of 550 mg, except for the sulfathiazole tablets (400 mg and 9.5 mm diameter), in order to finish the experiments within a reasonable time frame. All tablets were charged with formulation, and a compression of 4000 lb was exerted by hand.

Testing of Tablets

In vitro release of drugs from the PEO tablets was carried out in distilled/deionized water by using the USP basket procedure at a stirring rate of 100 rpm at 37°C. Theophylline, diclofenac Na, salicylic acid, sulfapyridine, and sulfathiazole were chosen as model drugs. The release of diclofenac Na, theophylline, salicylic acid, sulfathiazole, and sulfapyridine was assayed by an HP8252A diode-array spectrophotometer (Hewlett Packard) at 250, 244, 298, 268, 288, and 296 nm, respectively. Because of the low solubility of the drugs (sulfathiazole and sulfapyridine), the dissolution medium was replaced a few times to maintain sink conditions during the in vitro dissolution test.

The release kinetic data (up to 60% release) were treated by the following phenomenological equation (8):

$$\ln \frac{M_t}{M_\infty} = \ln k + n \ln t \qquad (1)$$

where M_t, M_∞, k, and n are the amounts of drug released at time t, the total amount of drug in the tablet, the constant, and the exponent for the release kinetics, respectively. Zero-order and anomalous release kinetics are represented by $0.89 < n < 1.0$ and $0.45 < n < 0.89$, respectively, for a swellable cylindrical matrix (8). A linear regression analysis was performed and a correlation coefficient (r^2) ≥ 0.99 was obtained. Duplicate or triplicate experiments were carried out for each formulation, but only a representative experiment is shown in this study for the clarity of figures because data were found to be very close (or superimposed) to each other.

RESULTS AND DISCUSSION

Preliminary reports show that high molecular weight PEOs are good candidates for oral extended-release dosage forms (6). PEOs of MW = 0.9 and 2.0×10^6 provide a constant release of drugs from compressed tablets. However, those tablets were of smaller size (≈ 180 mg), resulting in difficulties in identifying the fundamental release mechanisms of drugs from the PEO tablet matrices. In this study, PEO tablets of 550 mg and dimensions of 3.5 × 11.1 mm were used. The release profiles of drugs from PEO tablets of MW = 4.0×10^6 (PEO4) are shown in Fig. 1. Apicella et al. (5) and Kim (6) reported that the synchronization of the swelling and erosion of the polymer (PEO4) was not observed under a stereomicroscope. Drug release from PEO4 tablets is controlled by the swelling of the polymer at the early stage of release followed by the erosion of the polymer at the later stage of release. Drug release takes place through the swollen gel layer for almost half of the release time so that the release kinetics are anomalous because of the high swelling of PEO4. It was shown (9,10) that the high swelling of the polymer furnishes an increase in drug diffusivity, resulting in the deviation from the Fickian release kinetics toward zero-order kinetics. While PEO4 is fully swollen, drug release is carried out by diffusion through the gel and erosion of the swollen gel. The surface area of the swollen gel that accommodates drug release diminishes with time. Figure 1 illustrates the effect of drug solubility on the drug release from PEO4 tablets (39% loading). As drug solubility decreases, the duration of drug release increases. The release of diclofenac Na (2.5% solubility in water) is characterized as non-Fickian kinetics where $n = 0.72$ up to 70% release followed by a long tailing at the later stage of release. In this case, drug diffusion through the swollen gel matrix

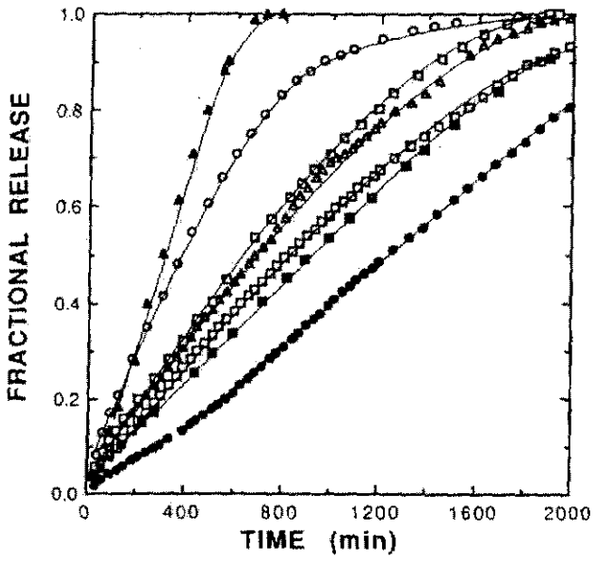

Figure 1. Effect of drug solubility on the release of drugs from PEO4 tablets (39% loading): (○) diclofenac Na; (□, △) theophylline; (□, ■) salicylic acid; (●) sulfathiazole; (▲) sulfapyridine.

is the governing step for the drug release, and the swelling of the polymer causes the release kinetics to shift to anomalous transport. As drug solubility decreases below 1% (theophylline and salicylic acid), drug release slows because of the longer dissolution time of the drug in the matrix. Because of this slow dissolution of the drug, the contribution of drug diffusion on the drug release from the PEO4 tablets with 39% loading becomes smaller, and the swelling of the polymer and the dissolution of the drug are comparable to control the release kinetics of theophylline and salycilic acid. Drug release takes place by the dissolution of the drug followed by drug diffusion. This results in further linear non-Fickian kinetics in which $n = 0.79$ and $n = 0.81$ for theophylline and salicylic acid, respectively. Linear release kinetics of theophylline can also be obtained from highly swellable/nonerodible tablets (11).

As drug solubility decreases further below 1000 mg/l, the dissolution of the drug becomes a dominant process in controlling the drug release from PEO4 tablets. This accounts for a constant release with $n = 0.96$ and $n = 1.10$ for sulfathiazole and sulfapyridine up to 85–90% release, respectively. Upon contact with water, the PEO4 polymer goes through a transition, and swollen polymer is formed. The swelling front penetrates inwardly to the core of the matrix, leaving the suspended drug behind.

It takes about 10–12 hr to complete the hydration process (swelling) of the entire PEO tablet. The solid/dissolved drug is suspended in the swollen gel and is released through the erosion of the hydrated polymer during the hydration process. This erosion is then followed by the dissolution of the drug in large volumes of the dissolution medium along with the diffusion of the dissolved drug, which is a smaller portion. Because of the low solubility of sulfathiazole (590 mg/l, the drug release shows a slightly sigmoidal profile, and for much lower solubility drugs a time lag was observed (not shown in Fig. 1) (12). Smaller tablets (9.5 mm diameter) were used for the release of sulfathiazole in order to finish the release test within a reasonable time frame. However, it is justifiable to draw a conclusion from release data based on the smaller tablets and extend it to the regular size tablets (11.0 mm diameter) because the ratio of diameter to thickness of the smaller tablets is less than that of the larger tablets. Unexpectedly, a much shorter release time was observed for sulfapyridine. We postulate that PEOs may form an associate complex with sulfapyridine, evidenced by the lower swelling of the polymer.

A constant release of drug from an inert matrix was reportedly obtained for these systems controlled by the dissolution of the drug (13,14). A mathematical model describing dissolution controlled systems can be expressed by

$$\frac{\partial c}{\partial t} = \frac{1}{x^n}\left(\frac{\partial}{\partial x} Dx^n \frac{\partial c}{\partial x}\right) - k_d\,(c_s - c) \qquad (2)$$

where c is the dissolved drug concentration in the matrix, t is the time, D is the diffusion coefficient, c_s is the drug solubility, k_d is the dissolution rate constant, x is the diffusional distance, and $n = 0$, 1, and 2 for a slab, cylinder, and sphere, respectively. If the dissolution rate constant is very small, the second term on the right side of Eq. (2) is the rate-limiting process for overall release behavior.

When the drug diffusion coefficient is time dependent and/or position dependent, drug release is zero-order along with a drug dissolution contribution (14). Even if the dissolution front advances further toward the core of the matrix, the increasing time of drug diffusion from the drug dissolution front to the dissolution medium is faster than the rate of drug dissolution. The increase in the drug diffusion coefficient can be accounted for by the swelling of the polymer in this study. Also, the erosion of swollen polymer shortens the travel distance of the dissolved drug from the dissolution front to the surrounding medium. It has been reported that the higher the polymer swells, the more linear the release kinetics (10,11). In the extreme case, zero-order release kinetics can be obtained purely by the polymer swelling (9). However, in this study the drug in the polymer matrix is suspended until the swollen polymer erodes at the gel/dissolution medium interface. As the molecular weight of the PEO decreases, however, the release mechanism shifts to the swelling/erosion-controlling processes of polymer. The synchronization gel layer of PEO of MW = 0.9×10^6 (PEO0.9) and PEO of MW = 2.0×10^6 (PEO2) was reportedly established between the rate of swelling and the rate of erosion of the swollen polymer (6). A mathematical expression for this process is given by (3,15)

$$\frac{M_t}{M_\infty} = \alpha\sqrt{t} + \beta t \qquad (3)$$

where α and β are constants. Eq. (3) describes that drug release takes place by a combination of drug diffusion (the first term on the right side) and polymer erosion (the second term on the right side). However, polymer relaxation does not take place at the swelling front because PEOs are not glassy polymers (glass transition temperature, T_g, below zero) in the dry state. When synchronization of the two fronts is obtained, the second term on the right side dominates, resulting in linear release kinetics via polymer erosion. Except for diclofenac Na, the release profiles of theophylline, salicylic acid, and sulfathiazole from PEO0.9 and PEO2 tablets yield zero-order kinetics (75–85% release), as illustrated in Figs. 2 and 3. The influx of water into the polymer matrix is enhanced by the presence of highly water-soluble drugs, such as diclofenac Na. Water penetration becomes much faster than the rate of swelling, leading to the rapid diffusion of the drug even through the unswollen polymer matrix. As a result, anomalous kinetics prevail over zero-order kinetics. However, the release kinetics of diclofenac Na from PEO0.9 and PEO2 tend to favor a linear release changing from $n = 0.72$ for PEO4 tablets to $n = 0.85$ and 0.91 for PEO2 and PEO0.9 tablets, respectively. The values of the release exponent n for PEO2 tablets are 0.83, 0.86, and 1.12 for theophylline, salicylic acid, and sulfathiazole, respectively, whereas those for PEO0.9 tablets are 1.01, 0.97, and 1.17 for theophylline, salicylic acid, and sulfathiazole, respectively. This results from the greater contribution of the swelling/erosion (synchronization) processes of the polymer in comparison to drug diffusion in the swollen gel.

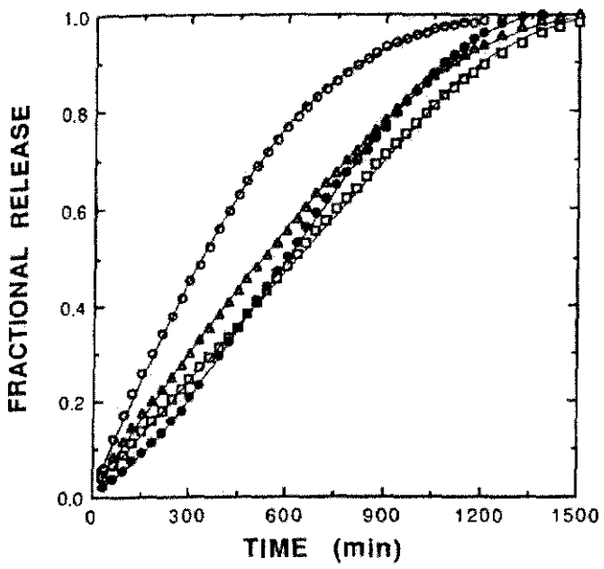

Figure 2. Effect of drug solubility on the release of drugs from PEO2 tablets (39% loading): (○) diclofenac Na; (△) theophylline; (□) slicylic acid; (●) sulfathiazole.

The effect of drug loading on the kinetics from the PEO4 tablets is illustrated in Fig. 4, which shows that the effect of drug loading is dependent upon drug solubility. As drug loading increases from 20 to 39%, the release of diclofenac Na from the PEO4 tablets becomes

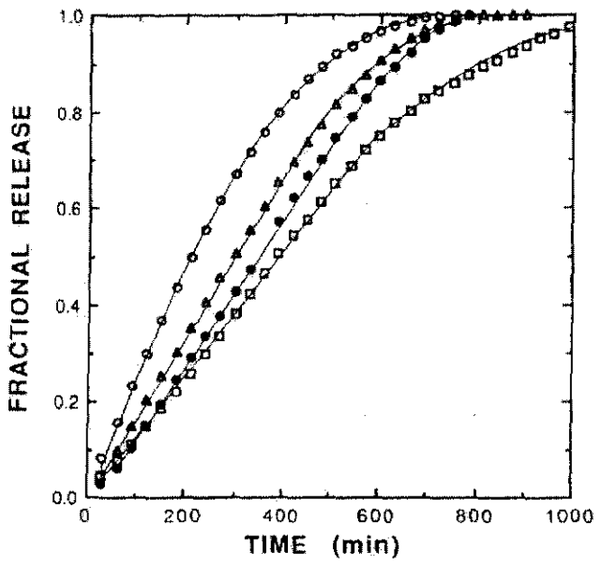

Figure 3. Effect of drug solubility on the release of drugs from PEO0.9 tablets (39% loading): (○) diclofenac Na; (△) theophylline; (□) salicylic acid; (●) sulfathiazole.

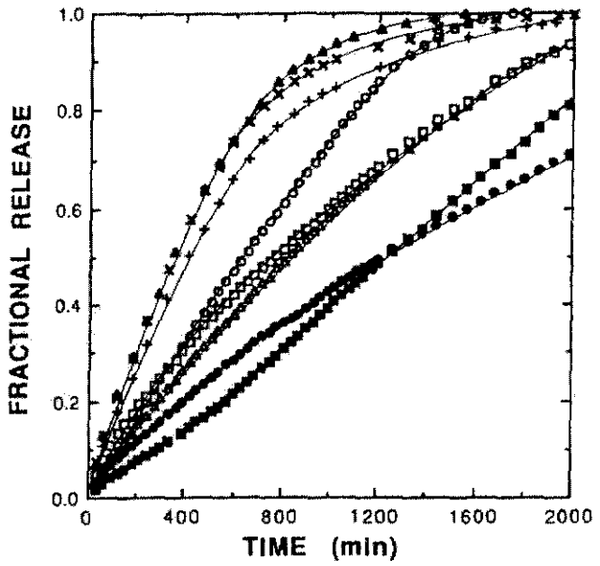

Figure 4. Effects of drug loading and a water-soluble additive on the release of drugs from PEO4 tablets: (▲) diclofenac Na (39% drug, 0% lactose); (x) diclofenac Na (20% drug, 19% lactose); (+) diclofenac Na (20% drug, 0% lactose); (○) salicylic acid (39% drug, 19% lactose); (□) salicylic acid (20% drug); (△) salicylic acid (39% drug); (●) sulfathiazole (20% drug); (■) salfathiazole (39% drug).

faster because when the loading becomes higher, drug diffusion controls the release kinetics. In other words, the properties of the polymer, such as swelling and erosion, become lesser contributing factors in the release kinetics. However, as drug loading increases for salicylic acid and sulfathiazole, drug release slows, resulting in more favorable release kinetics, exhibiting $n = 0.81$ and $n = 0.94$ for salicylic acid and sulfathiazole, respectively. For the 20% drug-loading PEO4 tablets, the release kinetics exponent n is 0.72 and 0.78 for salicylic acid and sulfathiazole, respectively. This observation was also found for PEO2 and PEO0.9 tablets. This indicates that drug diffusion plays a more important role in the release kinetics at the 20% loading level where the majority of drug in the matrix is in the dissolved state, whereas at the 39% loading level a smaller portion of drug is suspended in the matrix. Therefore, as long as a high drug loading is maintained for poorly water-soluble drugs (i.e., salicylic acid), the addition of a water-soluble excipient to the matrix does not influence the release kinetics other than to cause shortened release time as shown in Fig. 4. Figure 5 summarizes the effects of drug loading, drug solubility, and polymer molecular weight on release kinetics. For sulfathiazole, the release profiles

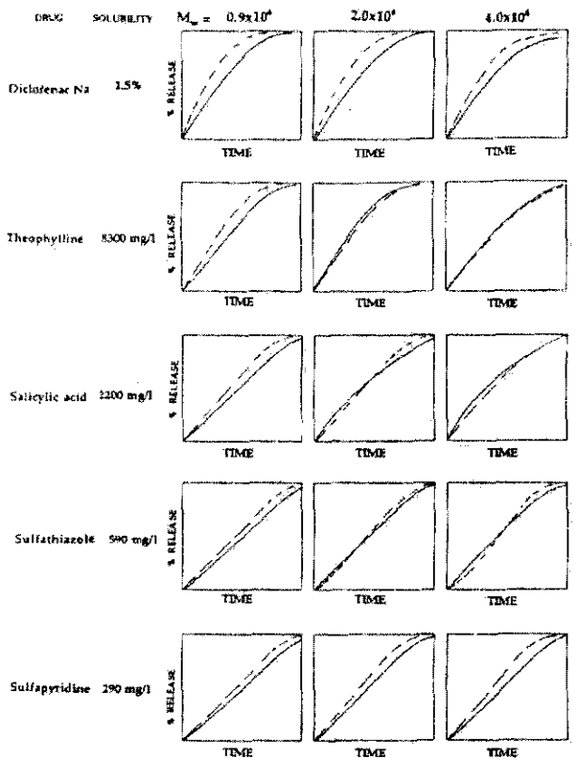

Figure 5. Summary of effects of drug solubility, PEO molecular weight, and drug loading on the release of drugs from PEO tablets: (—) 20% loading; (---) 39% loading.

from the 20 and 39% loaded PEO4 tablets cross over each other at the middle of the release profile. It seems that the rate of drug diffusion is faster than the rate of drug dissolution. In this case, the diffusion of the dissolved drug (a large portion) in the 20% loaded PEO4 tablets is more rapid at the early stage of release than that (a small portion) of the 39% loaded PEO4 tablets. The crossover of two release profiles from PEO2 tablets occurs at a slightly higher drug solubility (salicylic acid).

However, when drug solubility is about 290 mg/l, drug release kinetics become zero-order regardless of the drug loading (20 and 39%), and the drug release rate becomes faster at the higher loading. This is attributable to the release mechanism for a drug with very low water solubility, for which the drug release occurs by the erosion of the polymer followed by the dissolution of the drug in the dissolution medium. As a result, the higher loading in the matrix and the smaller fractions of polymers in the matrix give rise to the faster erosion rate of the polymer. For PEO0.9 tablets, drug release is governed by the swelling/erosion processes of the polymer, giving rise to the faster dissolution of the polymer with zero-order kinetics as the drug loading increases. For the release of diclofenac Na from the PEO0.9 tablets, drug diffusion is a controlling factor for the release kinetics, so that at the lower drug loading a linear release (n = 0.93) results.

Like capsules that produce dosage forms that can release different doses with the same release kinetics, tablets should be designed with a different formulation to achieve the same release profiles. This can be achieved by adding a water-soluble excipient in a tablet (low dose). Figure 4 also presents the effect of a water-soluble component on the drug release kinetics. An additional water-soluble component in the matrix reduces the polymer content and enhances the hydration of the polymer matrix by osmotic pressure. The release of diclofenac Na from PEO4 tablets, displaying that drug release is enhanced by the higher drug loading, is increased by the addition of a water-soluble excipient (lactose). As a result, the release of diclofenac Na from a PEO4 tablet containing 39% loading is superimposable, except in the final stage of release, with that from a PEO4 tablet containing 20% drug/19% lactose, provided each tablet has the same total weight.

In conclusion, the controlling mechanism of drug release from PEO tablets is dependent upon the drug solubility, drug loading, the addition of a water-soluble excipient, and the molecular weight of PEOs. For a highly water-soluble drug (e.g., diclofenac Na), drug diffusion is the rate-controlling step for the PEOs investigated in this study. This leads to anomalous transport behavior with aid from the swelling of the polymer, whereas for poorly water-soluble drugs the swelling/erosion process of the polymers is the dominating mechanism for PEOs of MW = 0.9 and 2.0 × 10^6, resulting in zero-order kinetics. For a PEO of MW = 4 × 10^6, drug release is governed by drug dissolution for poorly water-soluble drugs (salicylic acid and sulfathiazole) with aid from the swelling of the polymer for which the diffusion coefficient is enhanced by the swelling of polymers. For low loading levels (20%) of poorly water-soluble drugs, the effect of dissolution of the drug on the linear release kinetics diminishes, resulting in anomalous transport behavior.

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RESEARCH ARTICLE

Properties of Sustained-Release Tablets Prepared by Hot-Melt Extrusion

Feng Zhang and James W. McGinity

College of Pharmacy, The University of Texas at Austin, Austin, Texas 78712

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ABSTRACT

The objectives of the present study were to investigate the properties of polyethylene oxide (PEO) as a drug carrier and to study the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets prepared by hot-melt extrusion. During the hot-melt extrusion process, a dry powder blend of drug, polymer, and other adjuvants was fed into the extruder and melted inside the barrel of the machine. The molten mass was extruded through a rod-shaped die and then cut manually into 400-mg tablets. CPM and PEO were shown to be stable under the processing conditions. The molecular weight of the PEO, the drug loading percentage, and the inclusion of polyethylene glycol as a processing aid, were all found to influence the processing conditions and the drug release properties of the extruded tablets. Faster release of CPM from the matrix tablets was observed in acidic medium than in purified water and phosphate buffer (pH 7.4). Drug release from the matrix tablet was controlled by erosion of the PEO matrix and the diffusion of the drug through the swollen gel layer at the surface of the tablets. CPM was dispersed at the molecular level in the PEO matrix at low drug loading level and recrystallization of CPM was observed at high drug loading levels. Hot-melt extrusion was demonstrated to be a viable novel method to prepare sustained-release tablets. PEO was shown to be a suitable polymeric carrier for this process.

KEY WORDS: *Chlorpheniramine maleate; Hot-melt extrusion; Polyethylene oxide; Sustained-release tablets.*

INTRODUCTION

During the past 30 years, extensive research has been pursued with modified- and sustained-release drug delivery systems. The advantages of such systems over traditional dosage forms include improved patient compliance and more constant blood levels of drug, which can significantly increase the efficacy and reduce the side effects (1). The use of slowly eroding matrix tablets has been one of the most common approaches for preparing sustained-release dosage forms. Water-swellable polymers or polysaccharides have been used as binders and retardants. The most widely used processes to manufacture rapid and sustained-release tablets include the wet granulation and direct compression techniques. The wet granulation process is a labor- and equipment-intensive technique involving several steps. Excipients such as binders, lubricants, and glidants are required to facilitate processing.

Address correspondence to Feng Zhang. Fax: (512) 471-7474. E-mail: second@mail.utexas.edu

The direct compression and dry granulation techniques are subject to content uniformity and segregation problems during the tableting process. Poor compressibility of the tablet excipients or the drugs may introduce additional problems into the compaction process.

Hot-melt extrusion technology is one of the most important processing techniques in the plastic industry. During the process, polymer and excipients are transferred by a rotating screw through a heated barrel of the extruder. The polymer melts at the elevated temperature and the molten mass is continuously pumped through the die attached at the end of barrel. The molten polymer rapidly solidifies when the extrudate exits the machine through the die. When the shape of die is changed, the final product may take the form of a film, pipe, tube, or granule (2). To produce granules or tablets via hot-melt extrusion, a pharmaceutical-grade polymer must be selected that can be processed at a relatively low temperature because of the thermal sensitivity of most drugs. All components must be thermally stable at the processing temperature during the short duration of the heating process.

Several researchers have successfully used the hot-melt extrusion technique. Follonier et al. (3) extruded diltiazem hydrochloride pellets with poly(ethylene-*co*-vinyl acetate), polymethacrylate, and cellulose derivatives without significant degradation of the drug. Aitken-Nichol et al. (2) successfully applied the hot-melt extrusion process to fabricate a solvent-free lidocaine hydrochloride film based on the Eudragit® E 100 resin.

The objectives of the present study were to investigate the properties of polyethylene oxide (PEO) as a drug carrier and to study the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets prepared by hot-melt extrusion. Polyethylene glycol 3350 (PEG 3350) was included as a plasticizer in this system to facilitate the processing. The influence of PEG 3350 on the drug release properties of the tablet and the stability of PEO were also investigated. Wide-angle x-ray diffraction (WAXD), differential scanning calorimetry (DSC), and IR spectroscopy were used to characterize the crystalline and thermal properties of the extruded tablets.

MATERIALS AND METHODS

Materials

PEO resins of molecular weights 1,000,000 and 7,000,000 were provided by the Union Carbide Corp. (Danbury, CT) under the trade name Polyox® WSR. CPM and PEG 3350 were purchased from Spectrum Chemical Manufacturing Corp. (Gardena, CA).

Processing Method

The types of extruders currently available for hot-melt extrusion include the single- and twin-screw extruders. Depending on the geometric design and function, the screw is generally composed of three different sections: feeding section, melting section, and the metering section. The function of the feeding section is to transfer the solid material forward into the melting section. The polymer gradually melts as it enters the melting section. Initially, melting results from the heat transferred to the barrel from the heating devices. As additional polymer melt is formed in the barrel, the heat dissipation induced by the constant shearing of the polymer melt becomes an additional source of heat. Inside the metering section, materials primarily exist in the molten state. The molten mass is continuously pumped through the metering section and passed through the die in a variety of shapes. The geometric design of the metering section is an important factor in determining output rate of the extruder.

In the present study, the dry blend of drug and polymer was processed using a single-screw extruder (C. W. Brabender Instrument Inc., S. Hackensack, NJ). The extruder was driven by a plasti-*corder*® (model EPL-V5501) electronic torque rheometer unit. The length-to-diameter ratio (*L*/*D*) of the barrel with two heating zones was 15:1. A single flight screw of uniform pitch was used in the present study. A rod-shaped die was attached to the end of the barrel. All of the excipients were dried in an oven at 40°C for 24 hr prior to processing to minimize any degradation that might occur as a result of absorbed moisture. All components were mixed homogeneously in a twin-shell blender for 20 min. These materials were then transferred into the feeding hopper of the extruder. The temperature setting for the different heating zones and the extrusion torque during processing were recorded. The dwell time of the polymer inside the barrel was approximately 2–3 min. The extrudate was cooled to 50–60°C and then manually cut into tablets (10 mm in diameter and 4.5 mm in thickness).

In Vitro Release Properties

Dissolution studies were performed according to Method II of the USP 23. The analysis of the CPM was conducted on a Waters® (Millford, MA) high-pressure liquid chromatography (HPLC) system with a Waters 486 ultraviolet (UV) detector, together with a Waters pump (model 501). The data were collected with Millennium software. The HPLC column was a Nucleosil® C-18 (5 μm), 250 mm × 4.6 mm inner diameter (i.d.) from All-

tech Associates, Inc. (Deerfield, IL). The mobile phase consisted of 30% acetonitrile with 70% pH 2.0 buffer solution (50 mM potassium phosphate monobasic) at a flow rate of 1.5 ml/min. The retention time of the CPM was 3 min. The content uniformity studies were performed on six tablets using HPLC analysis.

Physical Characterization

DSC was used to characterize the thermal properties of the drug and polymers, the physical mixtures, and the extrudate. The differential scanning calorimeter used in the present study was a DSC model 2920 (TA Instruments, New Castle, DE). Ultrahigh pure nitrogen was used as the purge gas at a flow rate of 150 ml/min. Approximately 10–20 mg of sample was weighed and sealed in a nonhermetic aluminum pan. The temperature ramp speed was set at 10°C/min for all studies.

WAXD was performed to characterize the crystalline properties of the excipients and the extrudate. A vertical scanning diffractometer (type 42273, Philips Electronic Instruments, Mount Vernon, NY) was used in the present experiments. The x-ray source was CuKα radiation under 35 kV and 20 mA. The angle of the scan ranged from 10° to 40° in increments of 0.05°/sec.

IR spectroscopy was used to study the possible complexation between the CPM and the polyethylene oxide. A potassium bromide disk of the sample was prepared and the IR scan was conducted on a Magna-IR Spectrometer (model 550, Nicolet Instrument Inc., Madison, WI).

Gel permeation chromatography was used to study the stability of the polymer under the current processing conditions. The molecular weight was determined using a Waters system, which included a WISP model 710B autosampler, model 510 solvent delivery system, Ultrahydrogel® 1000 and 2000 columns connected in series, and a model 410 differential refractometer as the detector. The PEO standards were used in the analysis. Double-distilled water containing 0.1 M sodium nitrate was used as the mobile phase at the flow rate of 1 ml/min.

RESULTS AND DISCUSSION

PEO resins are non-ionic, water soluble, high molecular weight homo-polymers manufactured by the heterogeneous catalytic polymerization of ethylene oxide. The resin meets all the specifications of the official compendia and is available in a broad range of molecular weights, i.e., as low as 100,000 and up to 7,000,000. Resins with molecular weights of 1,000,000 and 7,000,000 were investigated in the present study. PEO is a thermal plastic polymer and depending on the molecular weight, the melting point of the polymer ranges from 60 to 75°C. Above the melting point, the polymer can be extruded or molded by conventional thermoplastic processing techniques. The extrudate swelled diametrically, a phenomenon known as die swelling, when extruded through the die. In the present study, the extrudate had a diameter of 10 mm, whereas the diameter of the die was 6 mm. The screw imposed shear stress to the polymer melt during the extrusion process. Because of the elastic property of the polymer melt, the extrudate swelled upon leaving the die to recover this deformation. The extent of swelling depends on the processing conditions and the nature of the material (4).

PEO has been used to prepare sustained-release tablets of theophylline via direct compression. Theophylline has been widely used as a model drug in previous research concerned with sustained-release matrix tablets (5). Theophylline is a high-dose drug and possesses good compaction properties (6–8). Generally, the drug is released from the water-soluble polymer matrix tablets by diffusion through the polymer as well as by the erosion and dissolution of the polymer. Both mechanisms depend on the hydrophilicity and the molecular weight of the polymer or retardant.

CPM is a low-dose crystalline drug. Such low-dose drugs may present content uniformity problems in matrix tablets prepared by direct compression. Both PEG and PEO are manufactured via the polymerization of the ethylene oxide monomer. Because of the linear and regular structure, they exist as semicrystalline polymers under room temperature. The solid structure consists of an intimate mixture of ordered crystals and randomly structured amorphous region. The DSC scans, shown in Fig. 1, demonstrate the profiles for PEG 3350, PEO (1 m), and CPM with melting points at 64.04, 72.97, and 136.90°C, respectively. The melting peaks of CPM and PEO were both observed for the physical mixtures at all drug-loading levels. The multitude of peaks observed in the x-ray diffraction pattern of PEO and CPM powder also verified their crystalline properties (Fig. 2). The most intensive peaks for PEO and CPM were found at 2θ angles equal to 23.30° and 20.20°, respectively. The x-ray diffraction profile of the PEO was actually the superimposed sharp diffraction lines of the ordered crystals and the diffusion lines of amorphous regions of the material. The x-ray diffraction peaks of PEO were much broader than the peaks of CPM, which is a crystalline material.

PEO has been reported to be susceptible to oxidation either in bulk or in solution during long-term storage (9).

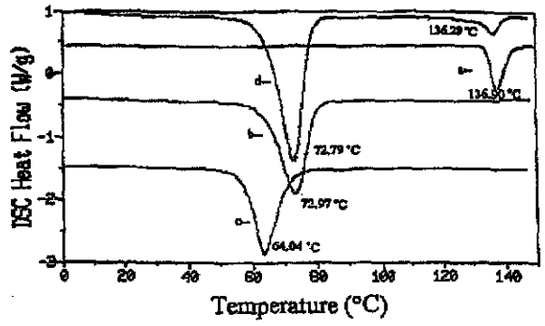

Figure 1. DSC profiles of CPM, PEG, PEO and physical mixture of CPM and PEO. (a) CPM; (b) PEO (1.0 m); (c) PEG (3350); (d) physical mixture of CPM and PEO (1.0 m).

In the hot-melt extrusion processing, the polymer was subjected to both thermal and shearing stresses. High temperature could contribute to the depolymerization of the polymer chain, whereas shearing effects from the screw could result in polymer chain scission. Matrix tablets containing only CPM and PEO and processed by hot-melt extrusion at 115°C, displayed a slight yellow color compared to the unprocessed PEO powder. DSC profiles of the extruded tablets demonstrated a decrease of approximately 4°C in the melting point of PEO after extrusion, which was probably due to a decrease in the molecular weight of the polymer during the processing. With the addition of PEG 3350, the extrusion process can proceed at a lower temperature and torque, as shown in Table 1. No change in color of the extruded tablets was observed after the addition of PEG 3350. The results from gel permeation chromatography are shown in Table 2. There was no significant difference in the weight average molecular weight of PEO following the processing, when the 40% PEG 3350 was included as a processing aid. Without the addition of PEG, a 15% decrease in the molecular weight of PEO and slightly longer retention times were detected.

During the extrusion process, the minimum rotation speed of the screw was set at 25 rpm. The maximum torque capacity of the extruder was 50 Newton-Meter (N · m). For each formulation, a minimum zone temperature was required for the material to be processed. The processing conditions for the hot-melt extruded CPM formulations are shown in Table 1. The polymer melt viscosity was primarily influenced by the molecular weight of polymer and the temperature of the melt. As the molecular weight of the polymer was increased, the interchain friction and entanglement also increased. Friction and entanglements functioned to restrict the flow and movement of the polymer chains with respect to each other. Once beyond a critical molecular weight, the chains were long enough to be entangled, making flow more difficult. This critical molecular weight of PEO was reported to be 10,000 by Porter and Johnson (10). Below the critical molecular weight, the polymer melt viscosity was approximately proportional to the weight average molecular weight. Above the critical molecular weight, the viscosity of the polymer melt at low shear rate has been reported to depend on the weight average molecular weight up to a power of 3.5 (11).

High viscosity will contribute to an increase in the extrusion torque and more rapid polymer chain scission degradation because of the mechanical strength imposed by the screw. When PEO with a molecular weight of 7 million (Table 1, formulation G) was substituted for PEO with a molecular weight of 1 million (Table 1, formulation C), the torque exceeded the capacity of the extruder. The high torque associated with formulation G made the processing under the same zone temperature settings as formulation C nonfeasible. The zone temperatures were increased to decrease the melt viscosity in order for the polymer to be processed (formulation H). An increase in the zone temperature by approximately 20°C significantly lowered the extrusion torque (formulation H). Increasing the temperature is the most common practice to facilitate a polymer extrusion process in the plastic industry. The melt viscosity decreases exponentially with respect to the increase in the temperature and has been reported to follow the Arrhenius equation (11):

$$\eta_i = K \times e^{E/RT} \quad (1)$$

In this equation, K is a constant that depends on the structure and the molecular weight of the polymer, E is the activation energy of the polymer for the flow process and it is a constant for the same type of polymer, R is the gas constant and T is the temperature in degrees Kelvin. The activation energy for the PEO was reported by Costagliola et al. to be 6.4 kcal/mol (12).

PEG 3350 was used as a processing aid in the present study. PEG is composed of the same structural unit as PEO, but has a lower molecular weight than PEO. Because PEO and PEG have the same repeating unit, they were completely miscible in the solid state, as demonstrated by a single melting point when PEG and PEO were both present in the extrudate [Fig. 3(a)]. Because the molecular weight of PEG 3350 is much lower than the reported critical molecular weight of polyethylene oxide,

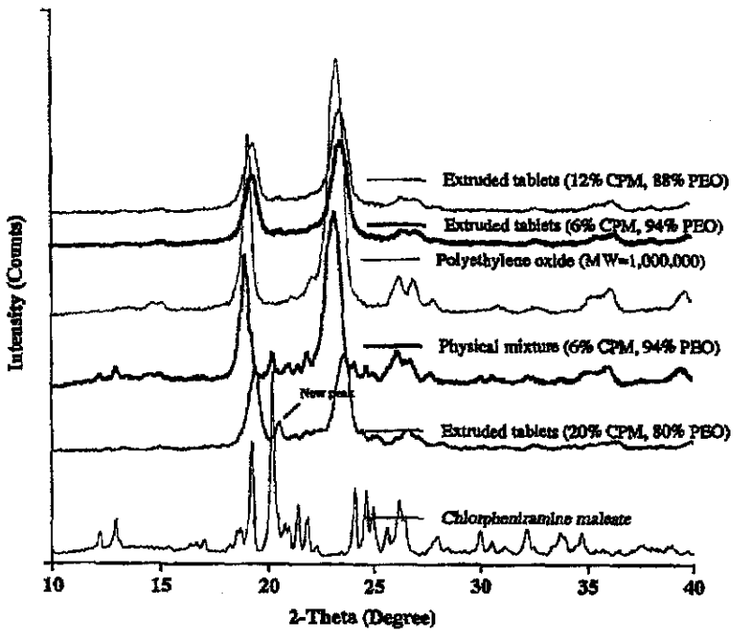

Figure 2. Wide angle x-ray diffraction profiles of CPM, PEO, physical mixture, and the extruded tablets.

Table I

Processing Conditions for Hot-Melt Extruded Tablets Containing CPM

	Formulation (%)				Zone Temperature (°C)			Screw Speed (rpm)	Torque N · m
	CPM[a]	PEO-7[b]	PEO-1[c]	PEG[d]	T_1	T_2	T_3		
A	6	—	94	0	110	115	130	25	34
B	6	—	88	6	100	115	130	25	29
C	6	—	74	20	70	70	85	40	23
D	6	—	54	40	70	75	85	40	10
E	12	—	88	—	100	115	120	25	40
F	20	—	80	—	100	115	120	25	21
G	6	74	—	20	70	75	85	25	Overload
H	6	74	—	20	90	90	100	40	21

[a] Chlorpheniramine maleate.
[b] Polyethylene oxide (7,000,000).
[c] Polyethylene oxide (1,000,000).
[d] Polyethylene glycol (3350).

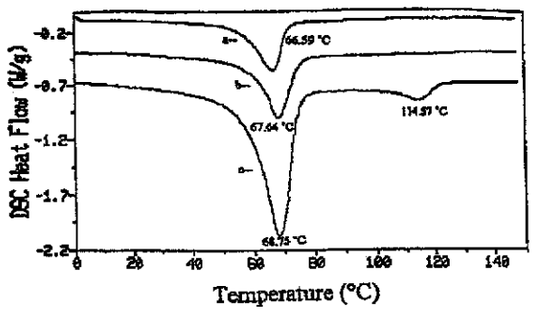

Figure 3. DSC profiles of extruded tablets. (a) 6% CPM, 20% PEG, and 74% PEO (1.0 m); (b) 6% CPM and 94% PEO (1.0 m); (c) 20% CPM and 80% PEO (1.0 m).

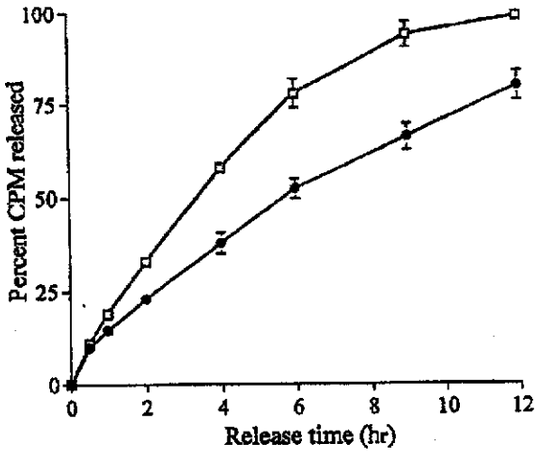

Figure 4. Influence of molecular weight of PEO on the release of CPM from matrix tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water. ●: 6% CPM, 20% PEG (3350), and PEO (7.0 m); □: 6% CPM, 20% PEG (3350), and PEO (1.0 m).

which is 10,000, the presence of PEG molecules between the PEO chains was able to dilute and weaken the cohesive interactions between the PEO chains and reduce friction and entanglement by increasing the interchain space between the PEO molecules.

The melt viscosity was significantly decreased via the addition of PEG. As shown in Table 1, formulations B, C, and D could be processed at a much lower temperature and torque settings when the PEG 3350 was present. PEG has a much higher thermal conductivity and lower melting point than PEO. The melting of physical mixtures of these formulations occurred faster in the process. When 40% PEG was included in the formulation (Table 1, formulation D), the hot-melt extrusion process could function at 75°C. Most drugs are stable at this temperature during the 2–3 min extrusion process.

Drug release properties of CPM from the matrix tablets were investigated using the USP Method II apparatus. Samples were assayed by an HPLC method. CPM was found to be stable under the current extrusion conditions and there was no change in the retention time before and after the extrusion process. Complete recovery of the drug in the dissolution media was found after a 24-hr study. The profiles in Fig. 4 demonstrate that drug release was significantly reduced when the PEO (7 m) was used in the polymeric matrix.

The release rates of CPM from the PEO extruded tablet were influenced by the presence of the PEG (Fig. 5). The PEG 3350 hydrated and dissolved faster than the

Table 2

Stability of PEO as a Function of Processing Temperature

	Formulation (%)			Zone Temperature (°C)			Weight Average MW ($\times 10^5$)	Peak Retention Time
	CPM[a]	PEO-1[b]	PEG[c]	T_1	T_2	T_3		
A	6	94	0	110	115	130	0.71 ± 0.05	14.7
D	6	54	40	70	75	85	0.90 ± 0.10	14.4
I		100		Without being processed			0.92 ± 0.08	14.3

[a] Chlorpheniramine maleate.
[b] Polyethylene oxide (1,000,000).
[c] Polyethylene glycol (3350).

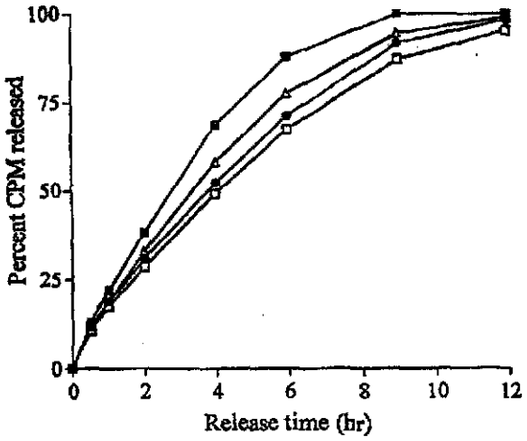

Figure 5. Influence of PEG (3350) on the release of CPM from matrix tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water. □: 6% CPM, 0% PEG (3350), and 94% PEO (1.0 m); ●: 6% CPM, 6% PEG (3350), and 88% PEO (1.0 m); ▲: 6% CPM, 20% PEG (3350), and 74% PEO (1.0 m); ■: 6% CPM, 40% PEG (3350), and 54% PEO (1.0 m).

PEO. The hydration and dissolution rate of the entire matrix system were thus accelerated because of the presence of the PEG. The presence of PEG also decreased the viscosity of the hydrated layer, which facilitated the diffusion of CPM from the swollen gel layer surrounding the tablets. The release of CPM from the matrix tablet as a function of the dissolution media is shown in Fig. 6. Faster drug release from the tablets was seen in acidic medium (0.1 N HCl) compared to purified water or phosphate buffer (pH 7.4, 50 mM). The solubility of CPM at 37°C in all three media exceeds 1 g/ml. The difference in the dissolution profiles could be the result of an interaction between PEO and the hydrogen ions in the acidic medium. The ether oxygen atom of PEO has two spare pairs of electrons, and it is able to form a hydrogen bond with the abundantly presented hydrogen ions in the acidic media. The interaction with the hydrogen ions would result in the strong electrostatic repulsion between the polymer chains. This thermodynamically favored process increases the solubility and dissolution rate of PEO in the acidic media, resulting in the faster drug release rate. Bailey et al. (13) also found that the PEO was more rapidly soluble in acidic medium and observed that the upper critical temperature of an aqueous PEO solution was significantly raised in acidic media by a strong hydrogen bonding effect.

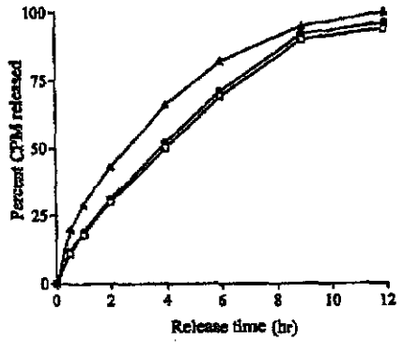

Figure 6. Influence of dissolution medium on the release of CPM from matrix tablets (6% CPM, 6% PEG, and PEO 1.0 m) using USP Method II at 37°C and 100 rpm in 900 ml dissolution medium. ▲: 0.1 N HCl without enzyme; □: simulated intestinal fluid (pH 7.4) without enzyme; ●: purified water.

The profiles in Fig. 7 demonstrate the influence of drug loading on the release of CPM from the PEO tablets in purified water. The reproducibility of the dissolution data in Figs. 5–7 was quite good, with standard deviations in the 4% range. When the drug content was increased from 6 to 12%, no change in the percentage of

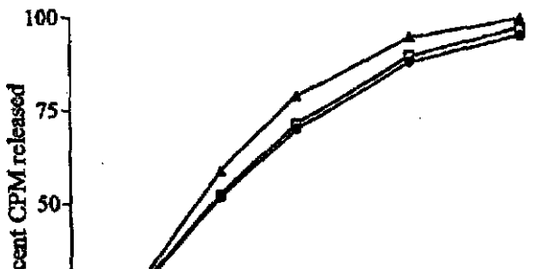

Figure 7. Influence of drug loading on the release of CPM from matrix tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water. ●: 6% CPM and 94% PEO (1.0 m); □: 12% CPM and 88% PEO (1.0 m); ▲: 20% CPM and 80% PEO (1.0 m).

drug release with respect to time was observed. There was only a slight increase when the drug loading reached 20%. Drug loading levels greater than 20% were not investigated because a solid cylindrical extrudate could not be obtained.

The melting peak of CPM was not present in the DSC scan of the extrudate at the 6 and 12% drug loading levels [Fig. 3(b)]. This indicated that CPM was dispersed at the molecular level and formed a solid solution within the PEO matrix. The hot-melt extrusion process was conducted at approximately 80°C. The drug and polymer were subjected to this condition for approximately 2–3 min and under these conditions, the CPM was able to dissolve in the polymer matrix. During the cooling process, the CPM molecules were locked in between the polymer chains at the molecular level because of the high viscosity of the polymer melt. In the crystalline state, per fiber identity period of PEO polymer chains exists as two helical structures containing seven CH_2CH_2O units (14). It is expected that a significant amount of drug was trapped in this particular helical interstitial space of the PEG or PEO crystal when the molten polymer–drug composites were solidified. At the 20% drug loading level, a new melting point was detected at 114°C [Fig. 3(c)]. Because no degradation products were observed from HPLC analysis and no shift in the peak or change in the shape of the UV scan was observed, the new peak could not be attributed to a degradation product of CPM.

PEO has been found to form crystalline complexes with barbiturates, guanidine hydrochloride, and urea (14). Our results demonstrated that complex formation did not occur. If the complex had been formed, an expected exothermic peak because of the complexation between drug and polymer should have been observed in the DSC scan of the physical mixture [Fig. 1(d)]. DSC results demonstrated that the drug was able to recrystallize during the cooling step from the molten mass containing 20% drug. Some polymer chains were incorporated into the crystal lattice of CPM and formed a solid solution containing CPM and PEO. The melting point was thus depressed from 136.9 to 114.6°C, as shown in Fig. 3. Similar phenomena have been observed in solid solutions of chloramphenicol (15) and griseofulvin (16).

The results of the x-ray diffraction analysis (Fig. 2) were in good agreement with the DSC data. For the physical mixtures, characteristic peaks of both substances were present in the x-ray diffraction profiles at all drug loading levels. The most intensive peak for CPM was absent at 6 and 12% drug loading levels in the extruded tablets. This confirmed the conclusion from the DSC profiles that the CPM was present at the molecular level in the extruded tablets. However, at 20% drug loading level, a new peak appeared at 2θ equal to 20.55° in the extruded tablets, whereas the characteristic peak of CPM at 20.20° was absent. The peak shift was due to the presence of PEO in the CPM crystal structure.

IR spectroscopy also showed that no chemical interaction occurred between the drug and the polymer. No shift was observed in the IR absorption peaks of CPM after the drug was physically blended with the PEO. The potassium bromide disk of the physical mixture of CPM and PEO was stored at 85°C for 10 min to simulate the extrusion process. No change in the spectrum was seen in the sample that was subjected to the thermal treatment.

Drug is normally released from hydrophilic colloidal matrices via diffusion through a swollen gel layer and erosion of the gel layer (7,17). To account for both release mechanisms, drug release can be generally expressed as follows (18):

$$Q = K \times t^n \quad (2)$$

where n is the diffusional exponent for drug release, which gives an indication of the release mechanism. For a highly water-soluble drug and relatively high-viscosity grade of water-soluble polymer matrix, drug release is generally controlled by the diffusion and is described by the Higuchi model (19). The amount of drug released is found to be dependent on the square root of the time in the Higuchi model. However, drug release from low-viscosity polymers often shows a deviation from the square root of time kinetics. In this case, drug is released to a significant extent by erosion of the swollen gel layer, in addition to diffusion. At the beginning of the dissolution process, because the swelling is much faster than the dissolution of the polymer, the thickness of the gel layer increases as a function of time. At some later point, these two processes could proceed at the same rate, thus leading to a constant gel layer thickness. This "front synchronization process" has been proposed to account for the observed zero-order drug release mechanism from matrices containing hydrophilic polymers (20,21). A linear relationship ($n = 1$) was demonstrated to exist for the percent drug released as a function of time, during the initial stages of the dissolution studies. In the present study, an approximate linear relationship was observed between the percentage of drug released and the dissolution time during the first 6 hr (Fig. 8). The deviation from linearity after 6 hr was due to depletion of the polymer reservoir from the swelling process. The incorporation of PEG in the extrudate facilitated the penetration of the water mol-

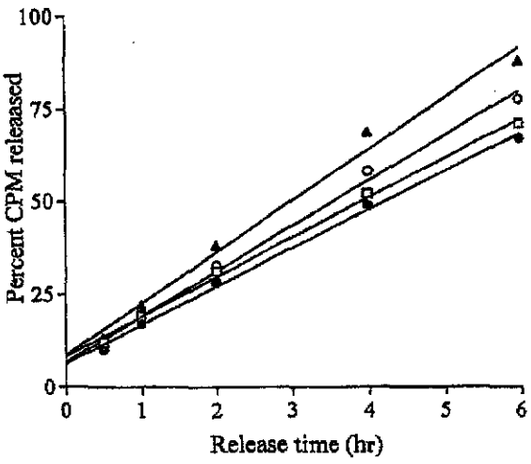

Figure 8. Linear fitting of release data of CPM from PEO matrix tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water during the first 6 hr. ●: 6% CPM, 0% PEG (3350), and 94% PEO (1.0 m), $y = 10.303x + 6.382$, $r^2 = 0.997$; □: 6% CPM, 6% PEG (3350), and 88% PEO (1.0 m), $y = 10.649x + 8.248$, $r^2 = 0.997$; ○: 6% CPM, 20% PEG (3350), and 74% PEO (1.0 m), $y = 12.158x + 6.777$, $r^2 = 0.994$; ▲: 6% CPM, 40% PEG (3350), and 54% PEO (1.0 m), $y = 13.819x + 8.571$, $r^2 = 0.989$.

ecules and the swelling process, resulting in drug release at a faster rate.

In summary, the hot-melt extrusion technique was demonstrated to be a viable method for the preparation of sustained-release tablets, without the use of a tablet press. It offers many advantages over traditional techniques. Solvents and water are not used in this process. Fewer processing steps are needed and time-consuming drying steps are eliminated. There are no requirements on the compressibility of the active ingredient and the entire procedure is simple, continuous, and efficient. The drug, polymer, and other ingredients must be stable at the elevated processing temperature during the 2–3 min that the powder blend is processed through the equipment. PEO was demonstrated to be an excellent thermoplastic polymer for this process. Because additional mixing of the components occurred in the barrel of the machine, the content uniformity of the extruded tablets was within 99.0–101.0% of the theoretical content. Modified releases profiles were achieved as a function of the molecular weight of the PEO. When incorporated as a processing aid, PEG significantly decreased the processing temperature as well as the torque exerted on the PEO/CPM blend during the extrusion process.

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