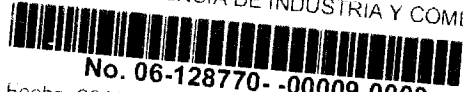


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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-128770- -00009-0000

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Doctora

Alix Carmenza CÉSPEDES DE VERGEL

Jefe División de Nuevas Creaciones

Superintendencia de Industria y Comercio

E. S. D.

REF: Expediente No.

06-128770

Patente de Invención:

**“FORMAS FARMACEUTICAS
ORALES, PROTEGIDAS FRENTE AL
ABUSO QUE CONTIENEN (1R,2R)-3-
(3-DIMETILAMINO-1-ETIL-2-METIL-
PROPIL)-FENOL”**

Solicitud Internacional No. **PCT/EP2005/006990**

Titular:

GRUNENTHAL GMBH

RESPUESTA A REQUERIMIENTO ARTÍCULO 46 OFICIO No 1433 Y CONCEPTO TECNICO No. 285

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17'192.062 de Bogotá, abogado graduado portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de Apoderado de **GRUNENTHAL GMBH**, domiciliado en Zieglerstrasse 6, 52078 Aachen, Alemania; encontrándome dentro de la debida oportunidad procesal para dar respuesta al auto proferido por su Despacho, mediante Oficio No.1433 y Concepto Técnico No. 0285, notificado por fijación en lista de 5 de febrero de 2010, me permito manifestar y anexar:

1. - Manifiesto y Anexo:

Para dar cumplimiento con lo solicitado por su Despacho y conforme a lo

HUMBERTO RUBIO & CIA.

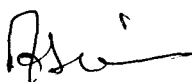
ABOGADOS
Expediente No. 06-128770
Pagina 2 de 2

establecido en el Artículo 46 de la Decisión 486, estamos adjuntando publicaciones de los documentos:

- 1.1- 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.
- 1.2- 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
- 1.3- Zhang et al, Pharm. Dev. Tech, 1999, 4. 241-250

Por separado estamos dando respuesta al Oficio No **1432** notificado por estado de 5 de febrero de 2010, como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, solicitando a su Despacho continuar con el tramite de rigor.

Atentamente,



HUMBERTO RUBIO CAMACHO

C.C. 17'192.062 de Bogotá

**T.P. 50.007 Consejo Superior
de la Judicatura**

COD. 4134



Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study

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Abstract

Hydrophilic matrix tablets containing polyethylene oxides as the retarding polymer have been successfully employed in the controlled release of drugs. To evaluate the relative influence of drug diffusion and polymer erosion mechanisms in the drug delivery process, we studied the hydration behaviour of matrix tablets containing a water-soluble drug and PEOs of two different molecular weights: Polyox WSRN 1105 ($M_w = 0.9 \times 10^6$) and Polyox WSRN 301 ($M_w = 4 \times 10^5$). The hydration rate, the extent of swelling, and the erosion rate of matrices containing the polymer, the drug and tableting excipients were evaluated in comparison to tablets made of pure polymer. The results of these studies on function of the release behaviour were then discussed.

The results show that the higher molecular weight PEO swells to a greater extent and tends to form, upon hydration, a stronger gel, which is therefore less liable to erosion, if compared to the lower molecular weight PEO. This difference in the erosion behaviour can explain the different efficiencies of the two polymeric products in modulating the delivery rate of the water-soluble drug. Moreover, the presence of other soluble components (drug and excipients) in the dosage form enhances the erosion trend of the tablets with a consequent reduction of the efficiency of the polymer in drug release control. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Polyethylene oxides; Swelling/erosion characteristics; Dissolution behaviour; Morphological modifications

1. Introduction

High molecular weight polyethylene oxides (PEOs) have been successfully employed in controlled release swellable matrices [1–3]. The use of oral controlled release matrices made of hydrophilic polymers that swell and form a gel layer upon contact with water, and then erode slowly, thus modulating the drug delivery rate, has been extensively investigated [4]. The polymers employed are hydrophilic, linear, uncrosslinked molecules; when matrices containing these types of polymer come into contact with water, forces of attraction (chiefly hydrogen bonding) start acting between polymer and water. Due to the high water-affinity of the polymer, these forces are likely to be preferred over polymer–polymer interactions; the forces holding the polymer

segments together are therefore reduced and the polymer chains can swell [5]. Water diffuses into the matrix and when its concentration reaches a threshold value, the polymer swells and a gel layer is formed at the matrix surface. In the gel phase, polymer chains slowly begin to unfold and gradually become solvated; however, the presence of physical entanglements between neighbouring chains hinder polymer dissolution [6]. At the outermost surface, the polymer is diluted to the point where the chains disentangle, the polymer has no longer structural integrity and dissolves as single molecules or as discrete agglomerates, i.e. erosion [7,8]. This complex gelatinous layer forms a diffusional barrier that retards further water uptake but can also modulate drug release rate. Water-soluble drugs are mainly released by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble drugs are more likely released through erosion of the gel [9]. The contribution of these two phenomena to the overall drug release process is influenced not only by drug solubility,

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but also by the physical and mechanical properties of the gel layer that forms around the tablet. When the release mechanism involves the synchronisation of swelling and erosion rates, the matrix may provide zero-order release kinetics [10,11].

Previous works have demonstrated that laminated films [12] or small tablets [2] containing a drug and polyethylene oxide (PEO) characterised by molecular weight (in the range 0.6×10^6 – 2×10^6) can generate comparable swelling and erosion rates. In contrast, matrices containing higher molecular weight PEOs did not show any synchronisation of swelling and erosion, and drug release seems to be related more to swelling rather than to erosion rate [13].

In this work, the dissolution behaviour of matrix tablets containing PEOs of two different molecular weights was studied; the aim is to evaluate the efficiency of PEOs in modulating drug release rate, its morphological behaviour, and to study the prevailing release mechanisms. The swelling and erosion characteristics of the two different polymers were evaluated on tablets made of pure polymer while, to verify the effects of soluble components on the behaviour of the polymers under study and the swelling/erosion characteristics of matrices containing the polymer, a soluble model drug (diltiazem hydrochloride), and tableting excipients were studied. The morphological behaviour during dissolution of such dosage forms was compared to the drug release profiles and evaluated in terms of drug release modulation efficiency.

Finally, the influence of the compression force applied to the tablets on the overall dissolution behaviour of these delivery devices was evaluated and discussed.

2. Experimental

2.1. Materials

Diltiazem hydrochloride was supplied by Profarmaco S.p.A. (Milan, Italy). PEOs (Polyox WSRN 1105, $M_w = 0.9 \times 10^6$, and Polyox WSRN 301, $M_w = 4 \times 10^6$) were kindly donated by Union Carbide Corp. (Danbury, CT, USA). The other excipients were lactose, magnesium stearate (C. Erba, Milan, Italy), and colloidal silicon oxide (Syloid 244, Grace GmbH, Worms, Germany).

2.2. Methods

Two different formulations (coded A1 and B1) were prepared by mixing the drug, the hydrophilic polymer and the excipients for 30 min (Turbula T2A, Bachofen, Basel, CH). The compositions of the two different mixtures are reported in Table 1.

Table 1
Percent composition of the two hydrophilic matrix formulations

Formulation	A1	B1
PEO M_w : 0.9×10^6 (Polyox WSRN 1105)	38.2	/
PEO M_w : 4×10^6 (Polyox WSRN 301)	/	38.2
Diltiazem hydrochloride	49.3	49.3
Lactose	11.0	11.0
Magnesium stearate	1.0	1.0
Colloidal silicon dioxide	0.5	0.5

The true density of the two pure polymers and of the two formulations was measured (AccuPyc 1330, Micro-metric, Norcross, GA).

The tablets were prepared by direct compression of the two formulations or of the two pure polymers using a single-punch tableting machine (Kilian, Cohn, D) instrumented with piezoelectric load washers (Kistler, Winterthur, CH) for compression force measurements [14] and equipped with flat punches diameter 9.5 mm. 366 mg of powder, accurately weighed, was introduced into the die and the automatic compression cycle was activated. The compression force was adjusted at two different levels: 10 and 30 kN.

All the tablets weighed $366 \text{ mg} \pm 1\%$; A1 and B1 matrices contain 180 mg of diltiazem hydrochloride as active agent. The thickness and diameter of the tablets produced were measured. The porosity was calculated through tablet volume and true density of the different powders.

To verify the effects of the application of a certain compression force level on the solid state of the polymer (crystalline or amorphous), DSC thermographs of the pure polymers before and after compression at the two different forces were recorded (DSC 821E, Mettler Toledo GmbH, Schwerzenbach, CH). The samples were heated from 30°C to 130°C ; heating rate $10^\circ\text{C}/\text{min}$.

The crushing strength of the tablets was measured with a suitable apparatus equipped with a high sensitive load washer (Kistler, Winterthur, CH) [14].

In vitro dissolution tests were performed in 1 l of distilled water at 37°C , with the USP apparatus 2 (paddle), at 100 rpm (six replicates). The amount of diltiazem released was measured by UV detection at 236 nm (Spectracomp 602, Advanced Products, Milan, Italy). The release data were fitted using the familiar empirical equation proposed by Korsmeyer and Peppas [15],

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

where M_t/M_∞ is the fractional drug released, t the release time, k is a kinetic constant and n the diffusion exponent characteristic of the release mechanism. For a cylindrical matrix, $0.89 < n < 1.0$ indicates a zero order release, while $0.45 < n < 0.89$ shows anomalous release

kinetics [16]. A linear regression analysis of the logarithmic form of Eq. (1) was carried out, and a correlation coefficient (R) > 0.99 was obtained in all cases.

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

The swelling/erosion characteristics of the various tablets were studied using an image analyser that enables measuring the dimensions of the whole tablet and of the solid or gelled phases during dissolution [17]. Tablets withdrawn from the dissolution vessels at different time intervals were sectioned and their photographs recorded using a digital microscope camera (SV Micro™, Sound Vision Inc., Taunton, MA, USA), equipped with a 50 mm C-mount lens. From the images, the dimensions of the whole tablet, of the solid phase and the thickness of the gel layer formed at the tablet surface can be easily measured using the software provided for the image analysis (CV9000 Ver. 4.0, FKV S.r.l., Sorisole, BG, Italy). In fact, in the images, the different morphological phases appear as well-defined areas of contrast. These tests were performed on the tablets made of polymer, drug and soluble filler and also on tablets made of pure polymer, to evaluate the effects of the presence of the water-soluble components on the hydration characteristics of the matrices.

3. Results and discussion

Both pure polymers and the formulations containing the drug also showed favourable compaction properties. Increasing the compression force from 10 to 30 kN does not cause remarkable variations either in the dimension of the tablets made of pure polymer (thickness and volume), or in tablet porosity (Table 2). The tablets made of the two different pure polymers showed similar crushing strength if compressed at 10 kN. If the compression force is increased to 30 kN, tablets made

of pure PEO of higher molecular weight (B) seem to be less hard compared to A tablets (Table 2). Increasing the compression force from 10 to 30 kN causes an increase in tablet hardness only in the case of PEO of lower molecular weight, while it does not increase, significantly, the hardness of tablets made of PEO of $M_n = 4 \times 10^5$.

However, the tablets made of pure polymer always looked much harder compared to the formulations containing the drug and other excipients, while maintaining slightly higher porosity.

The results of the DSC tests evidenced similar melting behaviour for the bulk polymer powder and the same polymer compressed at the two different force levels, for both PEOs. In the case of PEO 900,000, the heat of fusion of the bulk powder was statistically different compared to the tablets compressed at 30 kN, while it is comparable to 10 kN tablets; peak temperatures were not statistically different. In the case of PEO 4,000,000 the heat of fusion of the powder is different compared to compressed tablets, but it is comparable at the two different compression levels. The melting temperatures were not statistically different (Fig. 1). The degree of crystallinity seems slightly affected by the compression process, and the application of increasing force levels does not cause a remarkable reduction of this parameter.

Moreover, the compression force seems to have no influence on the dissolution behaviour of the matrices under study. The dissolution profiles of the matrices containing PEO of lower molecular weight (A1), obtained at 10 or 30 kN are quite superimposable (Fig. 2). No significant difference can be evidenced between t_{d75} ($224 \text{ min} \pm 7$ and $213 \text{ min} \pm 9$ for tablets compressed at 10 or 30 kN, respectively; $p > 0.01$).

Similar considerations can be made in the case of B1 tablets ($353 \text{ min} \pm 10$ and $344 \text{ min} \pm 10$ for tablets compressed at 10 or 30 kN respectively; $p > 0.01$). On the other hand, diltiazem release rate from the matrices containing PEO of higher molecular weight (B1) is much

Table 2
Characteristics of the tablets made of pure polymers or of drug formulations as a function of the compression force applied (mean values $\pm$ SD)

Tablet	Compression force (kN)	Thickness (mm)	Volume (mm ³)	Porosity (%)	Crushing strength (N)
A	10	4.45 $\pm$ 0.05	335.6 $\pm$ 3.6	12.2 $\pm$ 1.1	215 $\pm$ 9
	30	4.40 $\pm$ 0.08	334.0 $\pm$ 4.9	11.9 $\pm$ 1.3	255 $\pm$ 1
B	10	4.37 $\pm$ 0.06	330.6 $\pm$ 4.3	10.9 $\pm$ 1.2	203 $\pm$ 6
	30	4.38 $\pm$ 0.06	328.4 $\pm$ 5.0	10.4 $\pm$ 1.6	214 $\pm$ 4
A1	10	4.11 $\pm$ 0.03	314.0 $\pm$ 2.4	11.6 $\pm$ 0.7	102 $\pm$ 3
	30	4.03 $\pm$ 0.05	306.1 $\pm$ 2.6	9.1 $\pm$ 0.8	145 $\pm$ 16
B1	10	4.11 $\pm$ 0.04	314.0 $\pm$ 3.3	11.9 $\pm$ 1.0	103 $\pm$ 2
	30	4.06 $\pm$ 0.04	309.5 $\pm$ 2.6	10.8 $\pm$ 0.8	107 $\pm$ 5

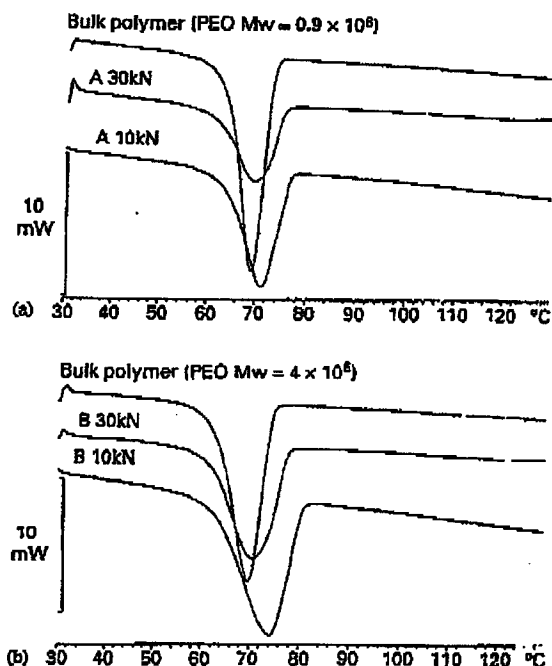


Fig. 1. DSC heating curve of: (a) PEO $M_w = 0.9 \times 10^6$ and (b) PEO $M_w = 4 \times 10^6$. The bulk pure polymer is compared to powder obtained after compression at 10 or 30 kN.

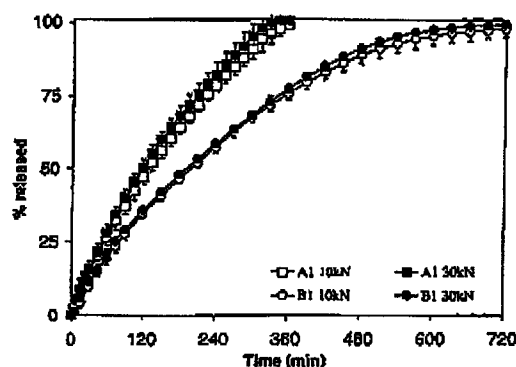


Fig. 2. Release profiles of the two drug formulations A1 and B1 containing PEO of M_w of 0.9×10^6 or 4×10^6 , respectively, compressed at two different compression forces of 10 and 30 kN (mean values $\pm$ SD, $n = 6$).

slower compared to the release rate of A1 matrices. While the release kinetics is similar, the diffusion exponent (n) ranges from 0.80 to 0.98 (Table 3). The photomicrographs of the matrices obtained from the two drug formulations, containing PEO of different molecular weights, evidence quite different morphological behaviour during hydration (Fig. 3). In the images the solid/dry phase appears as a white opaque area, while the gel phase is more transparent.

A1 tablets (containing PEO of $M_w = 0.9 \times 10^6$) hydrate quickly but the gel layer is thinner at the tablet surface. The dimensions of the matrices increase slightly at the beginning of the hydration process and very soon start decreasing considerably. On the other hand, B1 matrices (containing PEO of $M_w = 4 \times 10^6$) show a remarkable and prolonged increase in dimensions while the gel layer appears thicker if compared to A1 tablets (Fig. 3). In both cases, a glassy core can be evidenced until the fourth hour, and then the matrix is completely gelled. By measuring the dimensional modifications of the tablets during hydration, it is possible to evaluate the



Fig. 3. Left column: photographs of the tablets made of the drug formulation A1 (PEO $M_w = 0.9 \times 10^6$) during dissolution. From top to bottom: after 1, 2 and 3 h. Right column—matrices made of the drug formulation B1 (PEO $M_w = 4 \times 10^6$). From top to bottom: after 1, 2 and 4 h.

Table 3

Prevailing release kinetics (correlation coefficients, R) and diffusion exponents of the two formulations considered

Formulation	Compression force (kN)	Release kinetics (R)	Diffusion exponent (n)
A1	10	Zero order (0.997)	0.91
A1	30	Zero order (0.997)	0.98
B1	10	Anomalous (0.994)	0.89
B1	30	Anomalous (0.999)	0.80

swelling process and the erosion rate of the matrices, while the hydration rate of the system can be related to the persistence and extension of the dry core.

All the matrices tend to increase more in height than in diameter (Figs. 4 and 5). In the case of matrices containing the lower molecular weight polymer, the test is stopped after 3 h, because the matrix is difficult to handle.

The A1 matrices upon contact with the dissolution medium, swell up to about 150% their initial height (Fig. 4) and 110% their initial diameter (Fig. 5) while a thin gel layer of less than 2 mm is formed at the tablet surface (Fig. 6). Then, swelling and erosion tend to synchronise; the gel thickness is constant while tablet dimensions slowly decrease during dissolution. This means that probably, after the initial rapid swelling, this

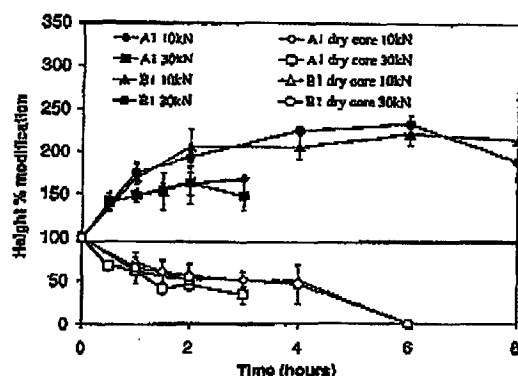


Fig. 4. Percent height modification of matrices made of the two drug formulations containing PEO of $M_w = 0.9 \times 10^6$ (A1) or PEO of $M_w = 4 \times 10^6$ (B1), during dissolution; whole tablet (black symbols) and glassy core (white symbols). Mean values $\pm$ SD, $n = 3$.

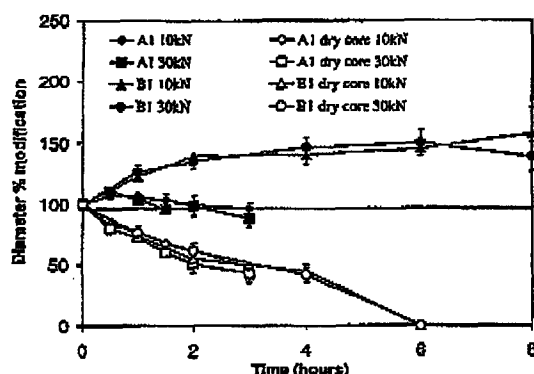


Fig. 5. Percent diameter modification of matrices made of the two drug formulations containing PEO of $M_w = 0.9 \times 10^6$ (A1) or PEO of $M_w = 4 \times 10^6$ (B1), during dissolution; whole tablet (black symbols) and glassy core (white symbols). Mean values $\pm$ S.D., $n = 3$.

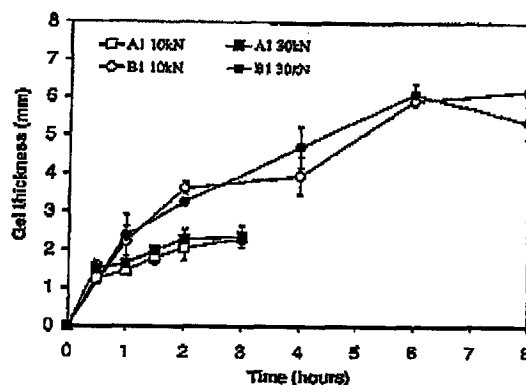


Fig. 6. Gel layer thickness during dissolution of tablets made of the two drug formulations A1 and B1 containing PEO of M_w of 0.9×10^6 or 4×10^6 , respectively (mean values $\pm$ SD, $n = 3$).

matrix forms a weak gel that is eroded at the same rate at which it is formed.

This behaviour suggests that swelling and erosion rates are comparable and that the two mechanisms are both effective in the control of drug release process.

On the contrary, in the case of B1 formulation, the tablet dimensions increase until the sixth hour of dissolution (Figs. 4 and 5). Also the gel thickness increases progressively during dissolution from 2 mm after 1 h up to 6 mm after 6 h (Fig. 6). It is only after 6–8 h, when the matrix is completely hydrated and gelled, that the erosion process begins to prevail and, as a consequence, the tablet dimensions and the gel layer thickness tend to decrease. These results suggest that the presence of PEO of higher molecular weight causes the formation of a stronger gel, which is less liable to erosion, than PEO of lower molecular weight. In this case, the erosion rate is slower and cannot counter-balance the swelling rate; as a consequence, the gel thickness increases progressively. Otherwise, both formulations containing PEOs of different molecular weight show quite comparable hydration rates (the dimensions of the dry cores decrease consistently). Thus, in B1 matrices swelling plays the leading role in drug release modulation.

These coincide with the kinetics study; in fact, the systems containing PEO of $M_w = 4 \times 10^6$ (B1) showed an anomalous best fit, which is consistent with a release mechanism involving polymer relaxation in combination with drug diffusion.

The compression force applied does not seem to influence the morphological behaviour of any of the systems during dissolution.

The swelling behaviour of tablets made of pure polymer confirms the influence of the polymer molecular

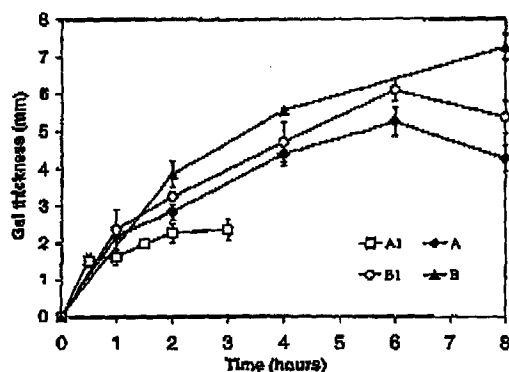


Fig. 7. Gel layer thickness during dissolution of tablets made of pure PEOs (A and B), compared to the drug formulations containing 38% of the same polymers, A1 and B1 (mean values $\pm$ SD, $n = 3$).

weight on the overall release process and enables to evidence the effect of soluble components (drug and excipients) which enhance matrix hydration, swelling and dissolution, and thus gel erosion.

The thickness of the gel layer of matrices obtained from the A1 formulation does not increase markedly during the test, while the pure polymer forms a stronger gel, the thickness of which increases progressively and only after 6 h begins to decrease (Fig. 7). This trend is less evident in the case of the polymer of higher molecular weight. Tablets containing PEO of $M_w = 4 \times 10^6$ show always thicker gel layers compared to tablets containing the lower molecular weight polymer, which increase until the sixth hour in dissolution, for both pure polymer (B) and formulated tablets (B1). However, B tablets show a slightly higher gel layer thickness than B1 matrices. After the sixth hour, the gel layer at B tablet surface still increases, while in the case of B1 tablets the erosion process begins to prevail and the gel layer thickness begins to decrease.

The images of the tablets made of pure polymer (Fig. 8) show clearly that the two different polymers are characterised by similar hydration rates, but completely different erosion rates. The dimensional reduction of the glassy core in terms of height (Fig. 9) and diameter (Fig. 10) evidenced that the extension of the portion of the tablet that was still dry, decreases during dissolution at similar rate for all the systems considered.

Otherwise, the pure polymer of higher molecular weight swells to a greater extent compared to its lower molecular weight counterpart. Tablets made of pure PEO of $M_w = 4 \times 10^6$ swell up to 250% of their initial height and up to 180% of their initial diameter after 8 h, then the erosion process prevails on swelling and tablets' dimensions decrease. Tablets made of pure PEO of $M_w = 0.9 \times 10^6$ show a different swelling behaviour: their height increases rapidly up to 170% after 1 h, is

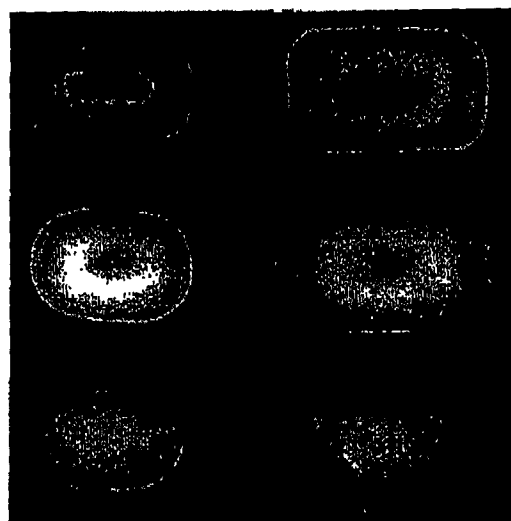


Fig. 8. Photographs of the tablets made of pure polymer during dissolution: from top to bottom after 2, 4 and 8 h. Left column, PEO $M_w = 0.9 \times 10^6$, right column, PEO $M_w = 4 \times 10^6$.

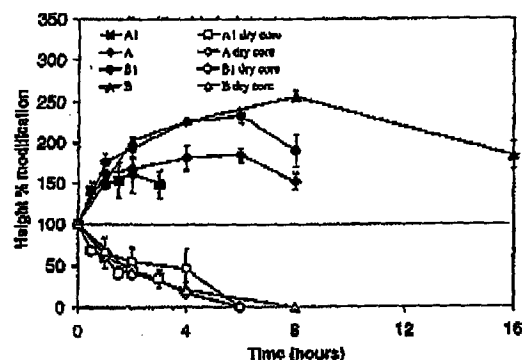


Fig. 9. Percent height modification of the tablets made of pure PEOs (A and B), compared to the drug formulations containing 38% of the same polymers, whole tablet (black symbols) and glassy core (white symbols). Mean values $\pm$ SD, $n = 3$.

more or less constant until the sixth hour and then begins to decrease. Similar considerations can be made in the case of diameter variations. These results confirm that this polymer, due to its lower molecular weight and viscosity, forms a softer gel that is more liable to erosion. As a consequence, the presence of water-soluble components has a greater effect on tablets containing PEO of lower molecular weight than on tablets containing PEO of $M_w = 4 \times 10^6$. The dimensions of tablets containing 38% of PEO $M_w = 0.9 \times 10^6$ are about half when compared to pure polymer tablets, while the dimensions of matrices containing 38% of PEO of $M_w = 4 \times 10^6$ appear less affected by the presence of water soluble materials.

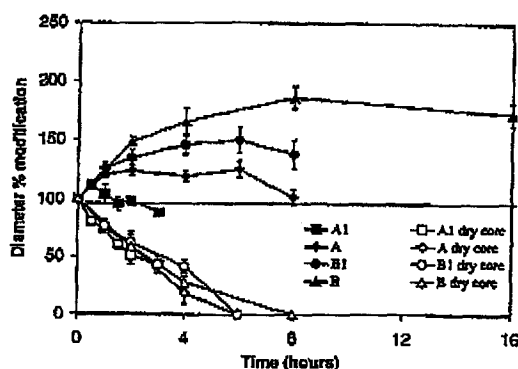


Fig. 10. Percent diameter changes of the tablets made of pure PEOs ($M_w = 0.9 \times 10^6$ and 4×10^6), compared to the drug formulations containing 36% of the same polymers, whole tablet (black symbols) and glassy core (white symbols). Mean values $\pm$ SD, $n = 3$.

4. Conclusions

Tablets made of pure PEO of molecular weight 0.9×10^6 or 4×10^6 showed similar hydration rates but very different swelling/erosion behaviour. B swells to a greater extent, and forms a stronger gel, which lasts on the tablet surface for a longer period, if compared to A.

The presence of soluble components causes the formation of a more diluted gel, which is more liable to erosion, and the matrices dissolve in a shorter time, but this effect is less evident when the higher molecular weight PEO is used.

The differences in swelling/erosion behaviour of the two polymers can explain the differences in drug release profiles from A1 and B1 matrices. Matrices containing higher molecular weight PEO, seem to drive the release mechanism toward a combination of swelling and diffusion, while polymer erosion seems to play a minor role in controlling drug delivery from this kind of devices. On the contrary, in the case of matrices containing PEO of lower molecular weight, the drug delivery mechanism seems to involve only swelling and erosion; the synchronisation of swelling and erosion rates may lead to constant release kinetics.

Finally, the dissolution behaviour of the formulation considered is not affected by the compression force applied during the manufacturing process.

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Drug Release from Compressed Hydrophilic POLYOX-WSR Tablets

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Abstract □ Drug release from compressed tablets manufactured with a powder mixture of poly(ethylene oxide) (PEO), a drug, and magnesium stearate is presented. Several factors such as molecular weight, drug loading, drug solubility, the pH of the dissolution medium, and stirring rate are investigated. The drug release from the high molecular weight PEO tablets ($MW = 2 \times 10^6$ and 4×10^6) is governed by the swelling of the polymer rather than by the erosion of the polymer, leading to anomalous release kinetics. However, the drug release from the low molecular weight PEO ($MW = 0.9 \times 10^6$) is controlled primarily by the swelling/erosion of the polymer, resulting in front synchronization and a constant release rate. It is observed that drug loading and drug solubility do not influence the release of drugs from low molecular weight PEO tablets. The pH of the dissolution medium and the stirring rate do not affect the drug release regardless of the molecular weight of the PEO.

Hydrophilic polymers have been investigated for controlled drug release to achieve non-Fickian release kinetics. The hydrophilic polymers such as (hydroxypropyl)methyl cellulose (HPMC) and polyvinyl alcohol (PVA), which form gels upon contact with water and erode slowly, have been utilized for oral drug delivery systems.¹⁻⁶ During the release of drugs from these hydrophilic matrices, two mechanistic phenomena take place: the swelling and the erosion of the polymer.^{4,5} The release kinetics are dependent upon the relative magnitude of the rate of polymer swelling at the moving rubbery/glassy front and the rate of polymer erosion at the swollen polymer/dissolution medium front. It has been shown that it is necessary to attain the synchronization of the velocities of the swelling front and the erosion front in order to achieve zero-order release kinetics from hydrophilic polymer matrices.^{7,8}

The establishment of front synchronization is not commonly observed in pharmaceutical dosage forms because poorly water soluble polymers are employed.⁹ In this case, it has been demonstrated that the swelling process of the polymer was the foremost process controlling the drug release from HPMC compared to the erosion of swollen polymer, resulting in anomalous Fickian kinetics.^{10,11} However, it has been shown that a constant gel thickness is observed with linear release kinetics for PVA matrices.^{5,6} It has been reported that moving front synchronization at the glassy/rubbery interface and at the swollen gel/dissolution medium interface is not a prerequisite for zero-order release from hydrophilic polymer tablets (HPMC and PVA).⁶ This results from the release data of preswollen and dry tablets. As a result, the release of drugs from the hydrophilic matrices is governed by the erosion of the polymer. In this case, the surface area of the matrix providing for the diffusion of drugs is a more important variable. It has been reported that the rate of drug release from hydrophilic matrices may be independent of drug solubility.³⁻⁶ The hydrodynamic condition (i.e. stirring) determines the gel thickness between the two fronts. In an extreme case, the two fronts are superimposed and the swelling rate of the polymer plays a central role in the rate of drug release.³

Cross-linked poly(ethylene oxide) (PEO) has been investigated for controlled drug delivery.¹² However, it has been shown recently that drug release from un-cross-linked low molecular weight PEO of $MW = 0.6 \times 10^6$ (laminated films) ensures a constant release rate by achieving synchronized gel thickness.¹³ On the other hand, the drug release from the high molecular weight PEO of $MW = 4 \times 10^6$ is predominantly controlled by the swelling of the polymer rather than by the erosion of the polymer. This results in a nonconstant release induced by the diffusion of drugs through the swollen gel layer.¹³

In this study, some factors affecting the release of drugs from compressed PEO tablets are presented: molecular weight, stirring rate, drug solubility, and drug loading.

Experimental Section

Materials—POLYOX-WSR NFs of average molecular weight of 0.9×10^6 , 2×10^6 , and 4×10^6 were supplied by Union Carbide Corp. (Danbury, CT). Theophylline anhydrous U.S.P. and magnesium stearate U.S.P. were purchased from Amend Co. (Irving, NJ) and Mallinckrodt Chemical (Jersey City, NJ), respectively. Diltiazem hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO). The materials were used as received.

Preparation of Tablets—The ingredients (PEO, drug, and magnesium stearate) were mixed and then tableted using a single punch tablet machine (Stokes Model F, Philadelphia, PA). A set of tablet punches with flat surfaces were used to prepare tablets with an 8.1 mm diameter. They were charged with the formulation, and the compression was executed by turning over the machine by hand. The hardness of the resulting tablets was 5.5–7.0 Kp (Schleuniger Model 2E/106, Switzerland). The resulting tablets weighed about 160 mg.

Testing of Tablets—In vitro release of drugs from the different formulation tablets was carried out by using the USP basket procedure in distilled/deionized water at a stirring rate of 100 rpm and 37 °C, if not otherwise stated. Theophylline and diltiazem hydrochloride were chosen as model drugs. The release of theophylline and diltiazem hydrochloride was assayed by a HP8252A diode-array spectrophotometer at 244 and 266 nm, respectively. The release kinetic data (up to 60% release) were treated by the following equation:¹⁴

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

where M_t , M_∞ , k , and n are the amount of drug released at time t , the total amount of drug in the tablet, a constant, and the exponent for the release kinetics, respectively. According to the criteria for release kinetics from a swellable matrix (cylindrical shape), zero-order and anomalous transport kinetics are represented by $0.89 < n < 1.0$ and $0.45 < n < 0.89$, respectively. A linear regression analysis (Microsoft Excell 5.0) of the logarithmic form of eq 1 was carried out with $R^2 \geq 0.99$. A 95% confidence level is indicated in parenthesis beside the exponent.

Gel Layer Thickness Measurement—Both circular faces of the cylindrical tablet were covered with two transparent Mylar sheets, fixed onto the bases via an epoxy glue.¹¹ The covered tablet was withdrawn periodically from the dissolution medium, and the moving boundaries both at the glassy/rubbery interface and at the matrix/dissolution medium interface were measured via a stereo microscope (Olympus SZ60) with a measuring device attachment. Later, the tablet was returned to the bath.

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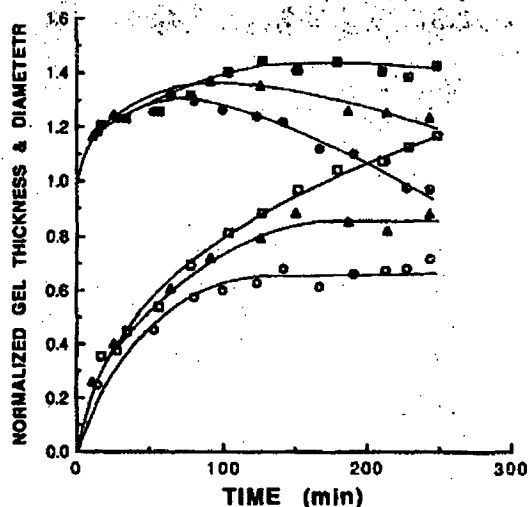


Figure 1—Time course of swelling and erosion front movement of drug-free PEO tablets versus gel thickness [(O) MW = 0.9×10^6 , (Δ) 2×10^6 , ($\square$) 4×10^6] and diameter [(●) MW = 0.9×10^6 , ($\blacktriangle$) 2×10^6 , ($\blacksquare$) 4×10^6].

Results and Discussion

Drug release from PEO tablets is governed by swelling/drug diffusion or swelling/polymer erosion depending upon the characteristics of the different molecular weights of the PEOs. In order to distinguish between the two mechanisms, swelling experiments involving drug-free tablets of MWs = 0.9×10^6 , 2×10^6 , and 4×10^6 were carried out. Attempts were made in vain to observe the clear moving fronts of drug-loaded tablets due to the diffusive reflection of light. The swollen gel thickness and outer diameter of a drug-free PEO tablet are presented in Figure 1. As the front approaches the core of the tablet, the distinctive boundary observed at the early time of swelling becomes ill-defined. Figure 1 demonstrates that the constant gel thickness is obtainable with the PEO tablets of MWs = 0.9×10^6 and 2×10^6 , whereas the swollen gel thickness from the PEO tablet of 4×10^6 keeps increasing with time. Early in the swelling/erosion process, the overall size of the tablet along with the gel layer increases rapidly due to the immediate swelling of the PEO tablet. The swelling rate of the polymer equals the dissolution rate of the swollen polymer gel, resulting in the synchronization of the gel layer thickness. Figure 1 exhibits that the synchronization of the gel layer thickness has taken place earlier with the low molecular weight PEO. We would like to point out that the constant gel layer thickness occurs shortly after the outer diameter starts becoming smaller. The higher the molecular weight, the later the synchronization takes place. However, for a higher molecular weight PEO tablet (4×10^6) the synchronized gel layer is not observed and the gel layer thickness keeps increasing, as observed from HPMC matrices.^{4,10} This observation is in good agreement with results obtained by others.¹³ It was observed that the swollen PEO gel, even after the front meets at the core of tablets, lasts a much longer time, 2 to 4 h depending upon the PEO molecular weight, compared to other swellable/erodible polymers such as PMMA/MAA and PVA.^{5,16} As a result, it is expected that the release kinetics are governed by the erosion/drug diffusion process after the swelling front meets at the core of the tablet.

Figure 2 shows the effect of PEO molecular weight on drug release of theophylline from the tablets. The rate of dissolution (erosion) of hydrophilic polymers decreases with increasing molecular weight.^{16,17} This results in a decreasing release rate of theophylline from PEO tablets with the release exponent n of $0.99(\pm 0.024)$, $0.80(\pm 0.004)$, and $0.83(\pm 0.019)$

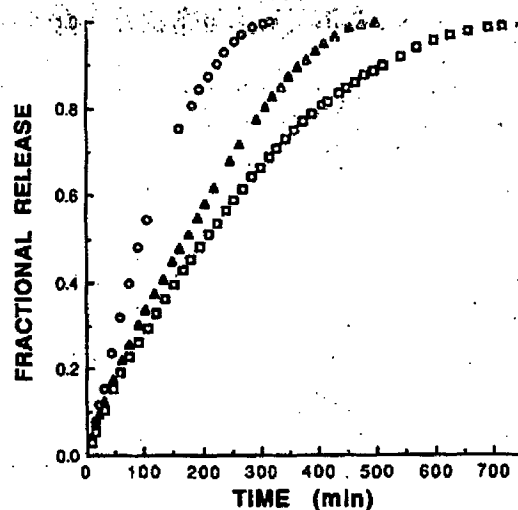


Figure 2—Effect of molecular weight on the release of theophylline from PEO tablets: (O) MW = 0.9×10^6 , (Δ) 2×10^6 , ($\square$) 4×10^6 .

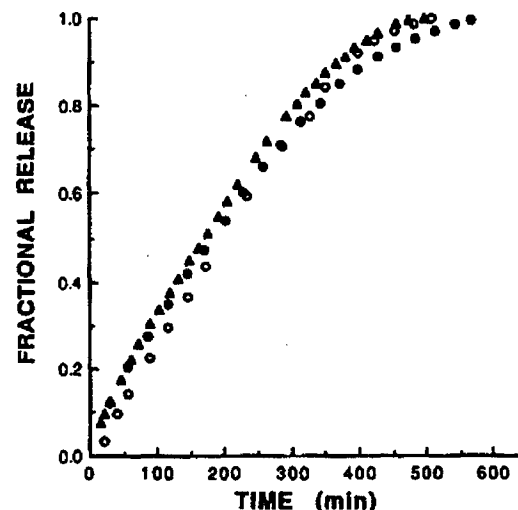


Figure 3—Effect of the pH of the dissolution medium on the release of theophylline from PEO tablets (MW = 2×10^6): (O) pH 1.5, ($\bullet$) pH 7.4, (Δ) distilled/deionized water.

with the increasing molecular weight of PEOs of 0.9×10^6 , 2×10^6 , and 4×10^6 , respectively. The lower molecular weight PEO (MW = 0.9×10^6) tablet exhibits a constant release rate, whereas PEO tablets having molecular weights of 2×10^6 and 4×10^6 exhibit anomalous release kinetics. This demonstrates that the synchronized gel thickness plays an important role in the release kinetics early in drug release. For a high molecular weight PEO tablet, the erosion rate of the swollen gel layer slows down significantly, resulting in an increase in the thickness of the swollen layer. As the molecular weight of the polymer increases, the dissolution rate of the polymer decreases compared to the swelling rate of the polymer, so drug diffusion through the swollen gel layer becomes the foremost process controlling the release mechanism. Others observed similar release kinetics with PEO¹³ and HPMC.^{24,10} Both PEO and HPMC polymers make a transition from glassy state to rubbery state with a lowering of the glass transition temperature upon contact with water. With high molecular weight (or high viscosity grade) polymers of PEO and HPMC, the swelling of the polymer is the dominant step in controlling release kinetics over the erosion of the swollen polymer. With low molecular weight polymers of PEO and HPMC, the erosion

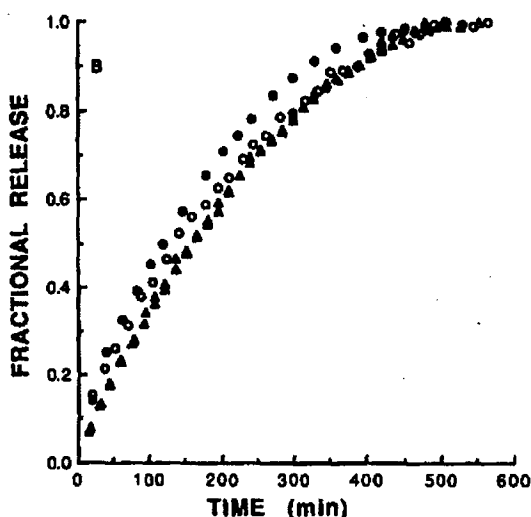
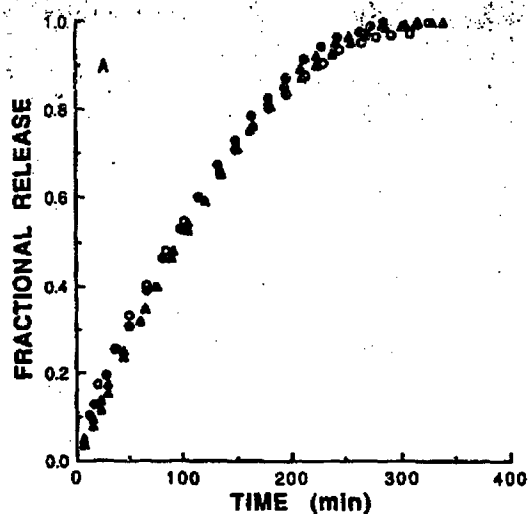


Figure 4—Effect of drug loading and drug solubility on the release of theophylline and diltiazem hydrochloride PEO tablets: A (MW = 0.9×10^6), diltiazem hydrochloride [(○) 39%, (●) 20%], theophylline [(△) 39%, (▲) 20%]; B (MW = 2×10^6), diltiazem hydrochloride [(●) 39%, (○) 20%], theophylline [(▲) 39%, (△) 20%].

The polymer is the rate-determining step for the release kinetics. However, the degree of swelling of PEO is higher than HPMC, therefore drug release from PEO matrices provides more favorable kinetics with $n \approx 0.8$ compared to $n \approx 0.66$ for HPMC.¹⁸

The release of theophylline from PEO tablets is not significantly influenced by the pH variation of the dissolution medium, as presented in Figure 3. This suggests that PEO material, like HPMC,¹⁹ may be a good candidate for oral drug delivery systems because oral dosage forms travel along the gastrointestinal tract in which the pH changes from an acidic environment (pH < 2) in the stomach to a weak base (pH ≈ 8) in the intestines.

The effect of drug loading on the release of theophylline is shown in Figure 4A,B. No significant difference in release rate can be observed with the different drug loadings of theophylline in PEO tablets. The release kinetics of PEO tablets of MW = 0.9×10^6 remain unchanged, with the exponent n ranging from $0.90(\pm 0.016)$ to $0.99(\pm 0.024)$ even though the drug loading is increased. Even for PEO tablets of MW = 2×10^6 , the release profiles of theophylline from 20% and 39% loaded tablets are superimposed with the

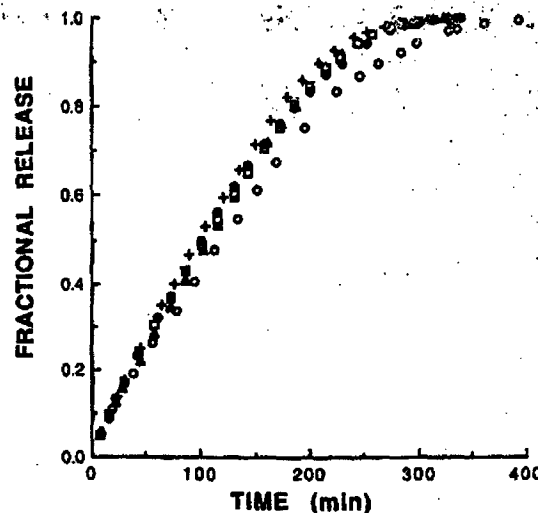


Figure 5—Effect of stirring rate on the release of theophylline from PEO tablets (MW = 0.9×10^6): (○) 50 rpm, (△) 100 rpm, (□) 150 rpm, (●) 200 rpm, (▲) magnetic stirring.

exponent n ranging from $0.80(\pm 0.004)$ to $0.82(\pm 0.007)$. In these cases, the diffusion of theophylline (<1.0% solubility in water) through the swollen gel layer does not play an important role in the release mechanism in PEO tablets. The diffusion of water into the matrices is not greatly facilitated by the water uptake of drugs but rather by the water uptake of the hydrophilic polymer. This implies that the swelling/erosion of the polymer is the controlling variable rather than the diffusion of drugs through the swollen gel layer. However, this observation may not be true when a highly water-soluble drug (diltiazem hydrochloride, solubility > 50%) is employed. Figure 4A,B show the effect of drug solubility on the release of drugs from PEO tablets. With a low molecular weight PEO, the solubility of the drug does not markedly affect the release of drugs from PEO tablets as reported with other hydrophilic polymers.²⁻⁶ A mathematical model (eq 2) presented by Harland et al.⁵ can predict that the drug release kinetics is independent of the drug solubility for the systems having front synchronization:

$$\frac{M_t}{M_\infty} = \alpha\sqrt{t} + \beta t \quad (2)$$

where α and β are constants. Equation 2 indicates that drug release can be described by a combination of drug diffusion (the first term on the right-hand side) and polymer relaxation (the second term on the right-hand side). As drug release time progresses, the second term on the right-hand side is dominant from systems exhibiting front synchronization, resulting in a linear relationship with time (zero-order). The constant β is independent of drug solubility but is dependent upon the drug and polymer volume fractions at moving boundaries.⁵ In the case of a low molecular weight PEO, even if water penetration into the matrices is boosted by increasing the amount of highly water-soluble drugs (diltiazem hydrochloride) incorporated in dosage form, the swelling/erosion process of the polymer precedes the diffusion process of drugs through the gel layer. This suggests that the polymer mainly controls the drug release kinetics.⁹ On the other hand, drug release data from the 20% and 39% loading tablets (diltiazem hydrochloride) are not superimposed as found for the theophylline tablets, when the molecular weight of PEO is 2×10^6 . As the drug loading level is increased, the water influx rate is enhanced by the water-soluble drug (diltiazem hydro-

chloride). Then the diffusion of drugs through the swollen gel layer precedes the swelling/erosion of the polymer (2.0×10^6).

The dissolution rate of the swollen polymer increases with increasing hydrodynamics of the dissolution testing so that the release of drugs from the matrix would be hastened. The effect of the stirring rate on the release of theophylline from PEO tablets (0.9×10^6) is shown in Figure 5. As the stirring rate is increased from 50 to 100 rpm, the release of theophylline becomes faster. However, drug release from PEO tablets is indistinguishable by further increasing the stirring rate beyond 100 rpm. The same observation is made with the higher molecular weight PEO tablets (not shown here). The insensitivity of PEO tablets to the stirring rate, which was not found in other erodible polymer systems,^{5,6} is another characteristic that makes PEO a good candidate for oral dosage forms.

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RESEARCH ARTICLE

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

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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.

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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 CuK α 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).

PEG 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 2 θ 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).

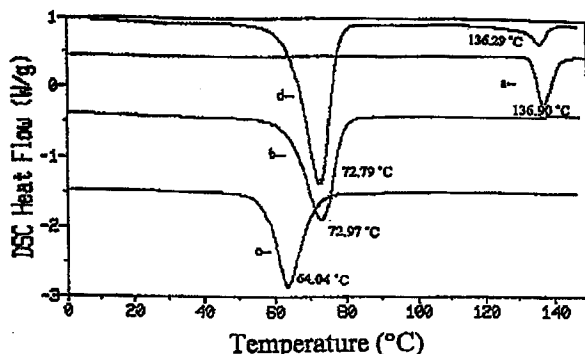


Figure 1. DSC profiles of CPM, PEG, PEO and physical mixture of CPM and PEO. (a) CPM; (b) PEO (1.0 m); (c) PEG (3350); (d) physical mixture of CPM and PEO (1.0 m).

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 molec-

ular 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):

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

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,

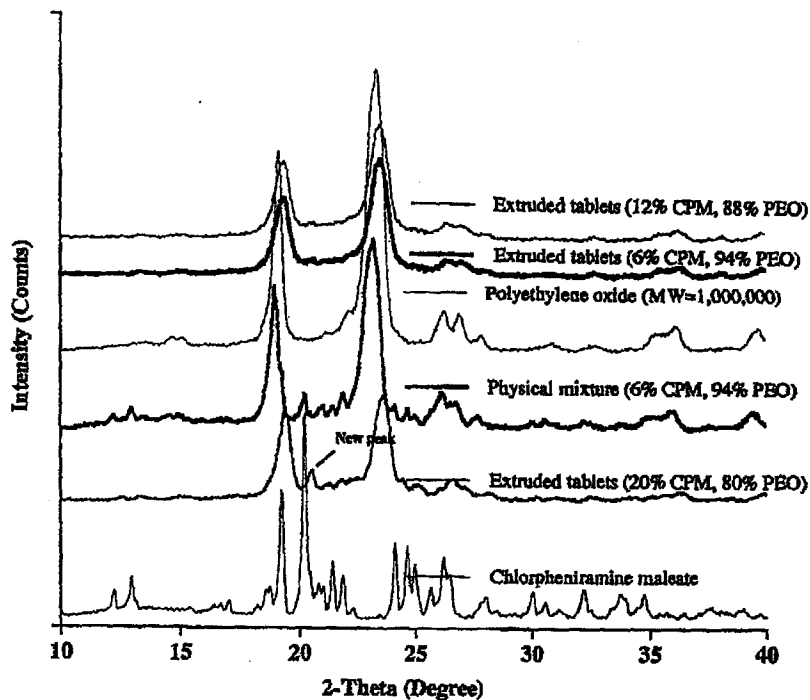


Figure 2. Wide angle x-ray diffraction profiles of CPM, PEO, physical mixture, and the extruded tablets.

Table 1

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).

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(54) Title: DOSAGE FORM THAT IS SAFEGUARDED FROM ABUSE

(54) Bezeichnung: GEGEN MISSBRAUCH GESICHERTE DARREICHUNGSFORM

(57) Abstract: The invention relates to a dosage form that is safeguarded from abuse. In addition to one or more active substances, that could be subject to abuse, said form comprises two or more of the following constituents (a)-(d): (a) at least one substance that irritates the nasal and/or pharyngeal region; (b) at least one agent that increases viscosity, which forms a gel in an extract that is obtained from the dosage form with the addition of an additional quantity of an aqueous liquid, whereby the gel can still be introduced into the body; (c) at least one antagonist for the active substance or substances that could be subject to abuse; (d) at least one emetic.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft eine gegen Missbrauch gesicherte Darreichungsform, die neben einem oder mehreren Wirkstoffen mit Missbrauchspotential zwei oder mehr der nachfolgenden Komponenten a)-d) aufweist: (a) wenigstens einen den Nasen- und/oder Rachenraum reizenden Stoff; (b) wenigstens ein viskositätserhöhendes Mittel, das in einem mit Hilfe einer notwendigen Mindestmenge an einer wässrigen Flüssigkeit aus der Darreichungsform gewonnenen Extrakt ein Gel bildet, welches beim Einbringen in eine weitere Menge einer wässrigen Flüssigkeit visuell unterscheidbar bleibt; (c) wenigstens einen Antagonisten für den Wirkstoff bzw. die Wirkstoffe mit Missbrauchspotential; (d) wenigstens ein Emetikum.

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DOSAGE FORM THAT IS SAFEGUARDED FROM ABUSE

The present invention relates to an abuse-proofed dosage form which, apart from one or more active ingredients with potential for abuse, comprises two or more of the following components a)-d):

- 10 (a) at least one substance which irritates the nasal passages and/or pharynx,
- (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which
15 gel remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
- (c) at least one antagonist for the active ingredient
20 or active ingredients with potential for abuse,
- (d) at least one emetic.

Many pharmaceutical active ingredients, in addition to
25 having excellent activity in their appropriate application, also have potential for abuse, i.e. they can be used by an abuser to bring about effects other than the medical ones intended.

Opiates, for example, which are highly active in combating
30 severe to very severe pain, are frequently used by abusers to achieve a state of narcosis or euphoria.

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- (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
- (c) at least one antagonist for the active ingredient or active ingredients with potential for abuse,
- (d) at least one emetic.

Components (a) to (d) are additionally each individually suitable for abuse-proofing the dosage form according to the invention. Component (a) is accordingly preferably suitable for countering nasal and/or parenteral abuse, component (b) is preferably suitable for countering parenteral abuse, component (c) is preferably suitable for countering nasal and/or parenteral abuse and component (d) is preferably suitable for countering parenteral and/or oral and/or nasal abuse. The combination according to the invention of at least two of these above-stated components makes it possible to protect the dosage form according to the invention still more effectively from abuse.

In one embodiment, the dosage form according to the invention comprises three of components (a)-(d) in the abuse combination, preferably (a), (b) and (c) or (a), (b) and (d).

In a further embodiment, the dosage form according to the invention comprises all of components (a)-(d).