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"ESTUDIO DEL COMPORTAMIENTO TECNOLÓGICO Y DE LIBERACIÓN DE SISTEMAS MATRICIALES ELABORADOS CON MEZCLAS DE DERIVADOS CELULÓSICOS COMERCIALES Y DE SÍNTESIS"

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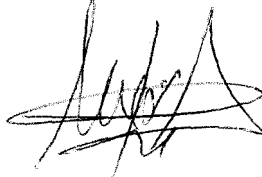
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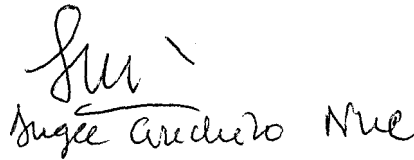Sevilla _29 de julio de 2009_

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CERTIFICAN:

Que la memoria que se presenta titulada **"ESTUDIO DEL COMPORTAMIENTO TECNOLÓGICO Y DE LIBERACIÓN DE SISTEMAS MATRICIALES ELABORADOS CON MEZCLAS DE DERIVADOS CELULÓSICOS COMERCIALES Y DE SÍNTESIS"** ha sido realizada bajo nuestra dirección y, reúne los requisitos necesarios para su defensa y calificación.

Para que conste a los efectos oportunos, expedimos y firmamos la presente certificación en Sevilla a doce de Julio de dos mil nueve.

Prof. Dra. Mª R. Jiménez-Castellanos   **Prof. Dra. C. Ferrero**

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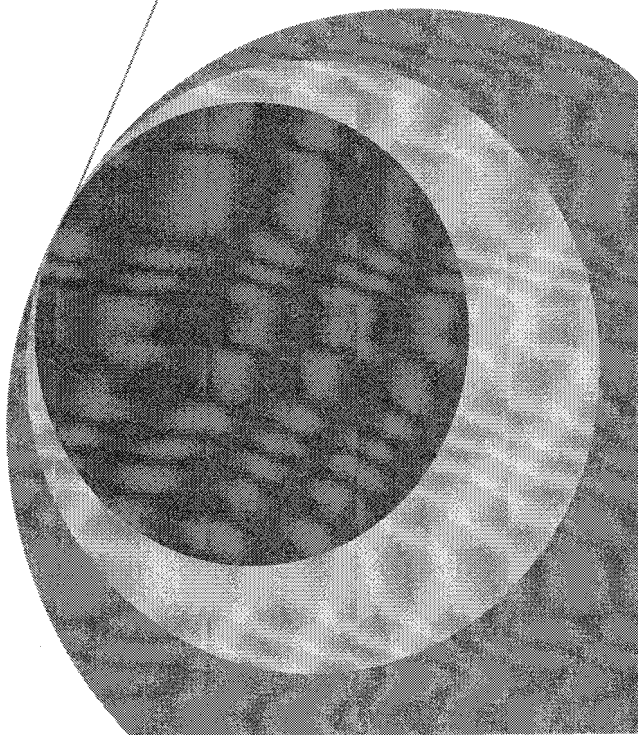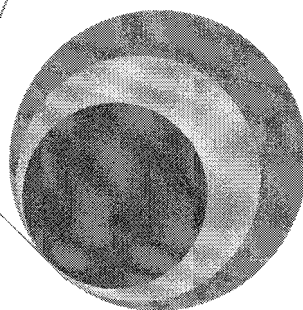
A mis hermanos, Carmen y Javier, de los que aprendo y ellos aprenden de mi.

ÍNDICE

INTRODUCCIÓN

La celulosa es uno de los materiales orgánicos más abundante de la naturaleza, al formar parte del tejido fibroso de las plantas. Desde un punto de vista químico, es un polisacárido obtenido a partir de las fibras de la madera o del algodón a las que se le elimina la lignina. La hidrólisis completa en medio ácido conduce a D-glucosa. En la molécula de celulosa, las aproximadamente 15000 unidades de D-glucosa están unidas por uniones 1-4 glucosídicas con una configuración beta, a diferencia del almidón, con configuración alfa. En la estructura de la Figura 1, n es el número de unidades de anhidroglucosa o grado de polimerización de la celulosa (Doelker, 1993). Cada unidad de anhidroglucosa contiene, a su vez, tres grupos hidroxilo (Wallace, 1990).
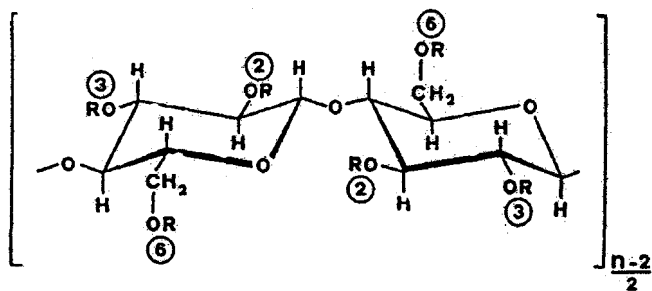
Figura 1.- Estructura de una sección de dos anhidroglucosas (Doelker, 1993).

El estado cristalino de la celulosa depende del tratamiento por el cual se haya obtenido (Levis y Deasy, 2001). Como todos los polímeros de elevado peso molecular, las fibras de celulosa presentan regiones fuertemente cristalizadas y ordenadas y regiones amorfas o desordenadas, cuya proporción puede afectar a ciertas propiedades como la compresibilidad, capacidad de absorción de agua y colorantes, capacidad de hinchamiento,

resistencia a la rotura, etc. (Doelker y col., 1987; Roberts y Rowe, 1987; Parker y col., 1988). Aunque es hidrófila, la celulosa, por ella misma, no es soluble en agua, debido a la gran cantidad de puentes de hidrógeno existentes entre los grupos hidroxilos de las cadenas macromoleculares. Por ello, las modificaciones químicas que sobre ella se realizan tienden, generalmente, a mejorar su comportamiento y más concretamente, obtener derivados que sean solubles en agua o en disolventes orgánicos. Así, cuando se considera un derivado de la celulosa, hay que tener presente:

1.- la naturaleza del grupo sustituyente,

2.- la proporción de grupos hidroxilo sustituidos,

3.- la uniformidad de la sustitución en la unidad repetida de anhidroglucosa y a lo largo de la cadena del polímero, y

4.- la longitud media y distribución de la masa molecular (viscosidad) (Doelker, 1993),

ya que todas estas características químicas pueden influir en sus propiedades.

Los derivados de la celulosa se suelen clasificar en función de la reacción química que tiene lugar sobre los grupos hidroxilos (Hebeisch y Guthrie, 1981). Atendiendo a nuestro estudio, es la reacción de eterificación del átomo de hidrógeno de los grupos hidroxilos la de mayor interés. En función del grado de sustitución o número medio de grupos hidroxilos sustituidos (máximo tres), se obtienen los distintos tipos de éteres de celulosa (Doelker, 1993).

Industrialmente, la eterificación de la celulosa es heterogénea debido al acceso restringido sobre alguna parte de las macromoléculas, por presentar uniones intra o intermoleculares. Todo ello conduce a una distribución no uniforme dentro de la

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unidad de anhidroglucosa y a lo largo de la cadena polimérica, resultando mezclas de moléculas de celulosa totalmente sustituidas, irregularmente sustituidas y no sustituidas. Desgraciadamente, el conocimiento de la distribución del sustituyente es complejo, ya que no sólo depende del reactivo sino también de dónde se adiciona (Doelker, 1993). No es extraño pues, encontrar éteres de celulosa de distintos proveedores que presentan características distintas (Landin y col., 1993). Por tanto, para obtener perfiles de liberación seguros y reproducibles de un fármaco, es necesario un profundo conocimiento de los factores responsables del distinto comportamiento de los diferentes tipos de sustituyentes de la celulosa y de la variabilidad interlote (Lucisano y col., 1989; Dahl y col., 1990; Mitchell y col., 1993). En este sentido se pronunci an Dahl y col. (1990), tras demostrar que las características de disolución de hidroxipropilmetilcelulosa (HPMC K4M) son dependientes de la composición química del polímero.

Los derivados de celulosa comercializados están disponibles en el mercado en forma de polvos o gránulos, con diferentes tamaños de partícula y grados de sustitución. De entre los derivados eterificados de la celulosa cabría destacar, por su mayor utilización como excipientes de liberación modificada, la metilcelulosa (MC), hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa (HPC).

La MC se obtiene por reacción de la celulosa purificada con cloruro de metilo en presencia de sosa caústica (Wallace, 1990). Con un contenido entre 50-1500 unidades de anhidroglucosa, aproximadamente, del 27 al 32% de los grupos hidroxilo están en

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forma de metiléter (Handbook of Pharmaceutical excipients, 2006). Si, además del cloruro de metilo para obtener la MC, se utiliza el óxido de propileno, se obtiene la HPMC, un derivado celulósico no iónico hidrofóbicamente modificado (Hu y col., 2004), que también se encuentra disponible en distintos grados en función de la viscosidad y extensión de la sustitución (Handbook of Pharmaceutical Excipients, 2006). Por su parte, la HPC se obtiene por reacción de la celulosa alcalina sólo con óxido de propileno.

A diferencia de muchos productos de la celulosa, estos derivados se disuelven en agua en todas proporciones, siendo limitada solamente su concentración por la viscosidad.

Los tres derivados de la celulosa anteriormente mencionados se usan ampliamente en formulaciones farmacéuticas orales y tópicas. Así, la MC de baja y media viscosidad se utiliza en formulaciones de comprimidos como aglutinante adicionado en polvo o en solución (Wan y Prasad, 1989; Funck y col., 1991; Itiola y Pilpel, 1991), mientras que los de alta viscosidad se pueden usar también como disgregantes (Esezobo, 1989). La HPMC y HPC se utilizan en formulaciones orales como aglutinantes de comprimidos y para recubrimiento (Delonca y col., 1977, 1978; Rowe, 1977, 1980; Stafford y col., 1978; Banker y col., 1981; Kitamori y Makino, 1982; Okhamafe y York, 1982; Johnson y col., 1993). Además, los tres derivados de la celulosa se utilizan en comprimidos de liberación prolongada, cuya velocidad puede ser modificada por variables tales como grado de viscosidad, tamaño de partícula, concentración de diluyente o fármaco, solubilidad del diluyente o adición de otros polímeros

hidrófilos (Ford y col., 1985a, b; Dahl y col., 1990; Shah y col., 1993; Kabanda y col., 1994; Xu y Sunada, 1995; Pérez-Marcos y col., 1996; Vázquez y col., 1996; Campos-Aldrete y Villafuerte-Robles, 1997; Salsa y col., 1997). Cuando estos polímeros se ponen en contacto con el agua, hidratan, formando una capa gelosa (Handy y col., 1982; Hogan, 1989; Sanghavi y col., 1989; Shah y col., 1989; Wilson y Cuff, 1989; Dahl y col., 1990; Johnson y col., 1993) que controla la liberación (Melia, 1991), como consecuencia de la transición vitreo-gelosa del polímero al penetrar el medio en la matriz (Velasco y col., 1999). La estructura de esta barrera es compleja, habiéndose demostrado que la movilidad del agua a través de la capa gelosa no es uniforme (Rajabi-Siahboomi y col., 1996). Así, McCrystal y col. (1996, 1997a, b) pusieron de manifiesto con estudios de calorimetria diferencial de barrido, la presencia de diversos eventos térmicos que confirman distintos estados del agua, los cuales se pueden ver afectados por factores como el peso molecular del polímero, tipo de sustituyente, concentración de polímero y naturaleza del fármaco. Además, diversos autores observan procesos de erosión en matrices de HPMC y HPC (Grabowski y col., 1985; Skoug y col., 1993; Bonferoni y col., 1995; Ju y col., 1995; Tahara y col., 1996; Katzhendler y col., 1997; Abrahamason y col., 1998). En este sentido, Tahara y col. (1995) señalan que, dependiendo de la solubilidad del fármaco, éste se libera bien por difusión a través de la capa gelosa o por erosión de la misma. Así, fármacos solubles en agua se liberan preferentemente por difusión del fármaco disuelto a través de la capa gelosa, mientras que principios activos poco solubles en

agua liberan predominantemente por un mecanismo de erosión (Alderman, 1984). La contribución de uno u otro mecanismo sobre el proceso de liberación total dependerá, pues, tanto de la solubilidad del fármaco como de las propiedades físicas y mecánicas de la capa gelosa que rodea al comprimido (Ford y col., 1987; Katzhendler y col., 2000).

Ferrero y col. (2000) ponen de manifiesto que, para estas matrices hinchables, tanto la hidrofilia como la higroscopicidad de los derivados sólo juegan un papel importante en las primeras etapas del proceso de hinchamiento y formación de la barrera gelosa. Además, matrices conteniendo un 20% de fenil-propanolamina y dichos derivados no mostraron una importante erosión de la misma. Mientras la difusión Fickian fue el mecanismo dominante en el caso de MC, un transporte anómalo caracterizó la cinética de liberación de los otros dos derivados celulósicos, coincidiendo con lo señalado por diversos autores (Ford y col., 1987; Catellani y col., 1988; Hogan, 1989; Ranga Rao y col., 1988, 1990; Colombo y col., 1990, 1992; Bettini y col., 1994; Peppas y Colombo, 1997). Krögel y Bodmeirt (1999) señalan que se puede obtener distintos perfiles de liberación dependiendo de la geometría del sistema matricial, ya que la liberación del fármaco se ve también influenciada por el área superficial del comprimido expuesta al medio de disolución.

Junto a la obtención de estos derivados de la celulosa, en los últimos años, se han realizado importantes esfuerzos para injertar la celulosa con polímeros sintéticos, que le confieran propiedades adecuadas. La longitud de estos injertos varía considerablemente dependiendo de las condiciones de copolimerización, siendo los

monómeros acrílicos y vinílicos los más ampliamente utilizados (Hebeisch y Guthrie, 1981).

En relación con esta línea de investigación, a principios de los años 90 comienza una colaboración entre el grupo "Biomateriales" de la Facultad de Química de la Universidad del País Vasco y el grupo "Optimización y Producción Farmacéutica" de la Universidad de Sevilla (Proyectos MAT1998-0488, MAT2001-3874-C02-01 y MAT2004-01599).

Así, el objetivo de la Tesis de la Dra. Castellano (1997) fue la combinación química de polímeros semisintéticos (derivados celulósicos -hidroxipropil y carboximetil celulosa, HC y CC- y de almidón de patata -hidroxipropil y carboximetil almidón, HA y CA-) con polímeros sintéticos (metacrilato de metilo -MMA-), sometiendo las sustancias obtenidas a dos procesos distintos de secado (estufa a vacío y liofilización). Además de realizarse una exhaustiva caracterización fisico-química de los mismos, se evidenciaron buenas perspectivas para el uso de estos materiales como agentes formadores de matrices. Como consecuencia de ello, la Tesis de la Dra. Ferrero (1999) se centró en una caracterización profunda del mecanismo de compactación de estos copolímeros, así como de los procesos subyacentes a la liberación del principio activo, que mostraron un comportamiento de estos sistemas como matrices inertes donde la liberación de la teofilina estaba controlada preferentemente por un proceso de difusión. Dado que la mayoría de las matrices no liberaron la totalidad del fármaco tras 14 horas de ensayo in vitro, la Dra. Miró (2002) abordó su Tesis Doctoral con el objetivo principal de determinar aquellas mezclas copolímero:excipiente de

compresión directa comercial que ofrecieran una adecuada velocidad de liberación, además de respetar la integridad de los sistemas matriciales. Paralelamente, la Dra. Bravo (2003) centró su Tesis Doctoral en el estudio de la influencia de la humedad sobre dichos copolímeros comparativamente con los carbohidratos de partida. Finalmente, la Dra. Ruiz (2005) evidenció que las formulaciones elaboradas con los copolímeros derivados del almidón de patata prolongan la liberación de teofilina "in vivo", utilizando perros beagle como animal de experimentación.

El uso de mezclas de polímeros representa otra alternativa para alcanzar propiedades de liberación adecuadas. Así, se han usado mezclas de distintos éteres de celulosa que, al proporcionar distinto grado de viscosidad, permiten modular la liberación del fármaco. La posibilidad de formar uniones de hidrógeno, más fuertes entre polímeros aniónicos y no iónicos, justifica que la fuerza de la interacción sea mayor que entre moléculas de la misma especie. Por eso, diversos autores (Baveja y Ranga Rao, 1986; Baveja y col., 1987; Ranga Rao y col., 1988) señalan el uso de mezclas de variedades poliméricas iónicas y no iónicas para obtener perfiles de liberación de orden cero para fármacos hidrosolubles. De acuerdo con Walker y Wells (1982), la adición de carboximetilcelulosa sódica (CMCNa) a HPMC proporciona un incremento de la viscosidad del 111% sobre la viscosidad calculada, siendo este sinergismo dependiente de la longitud de las cadenas (mayor para HPMC K4M que para HPMC E5, E15 y E50). Bonferoni y col. (1994) demuestran que los perfiles de liberación de salbutamol y de maleato de

clorfeniramina se pueden modificar por mezcla de λ-carragaen (polímero aniónico) y HPMC K4M, como consecuencia de la combinación de distintos mecanismos de liberación -erosión de la matriz y difusión, respectivamente- (Bonferoni y col., 1998). Chien (1982) señala que, mezclando distintas proporciones de polímeros con diferentes características de permeación, se puede alcanzar un amplio rango de velocidades de liberación para un principio activo por cambio de la difusividad del fármaco a través de la barrera polimérica. Así, Traconis y col. (1997) evalúan la integridad de unos comprimidos de metronidazol elaborados con una mezcla de HPMC (4000 cP) y CMCNa, siendo la difusión el factor más importante para el control de la liberación del principio activo a través del sistema.

Mezclas de resinas de intercambio iónico con HPMC permiten disminuir la velocidad de liberación del principio activo opuestamente cargado a las primeras, como consecuencia de su unión en el interior de las matrices del derivado celulósico (Feely y Davis, 1988). Shenouda y col. (1990) sugieren que la inclusión de un polímero erosionable (polietiloxazolina) en la matriz de HPMC puede modificar el comportamiento de la liberación mediante la combinación adecuada de los procesos de difusión y erosión. Pérez-Marcos y col. (1994) estudian la liberación del clorhidrato de propanolol a partir de matrices elaboradas con mezclas de HPMC K4M y Carbopol® 974 en distinta proporción, encontrando velocidades de disolución similares para los datos correspondientes al 5-35% del total de principio activo liberado a partir de matrices con el mismo peso de polímero. Sin embargo, observaron una liberación brusca para formulaciones conteniendo

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HPMC/Carbopol® 1:>3,una vez que el 35% de fármaco se había disuelto, debido a que la cantidad de agua embebida por este último polímero fue menor que para HPMC o la mezcla 1:1 de ambos polímeros.

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OBJETIVOS
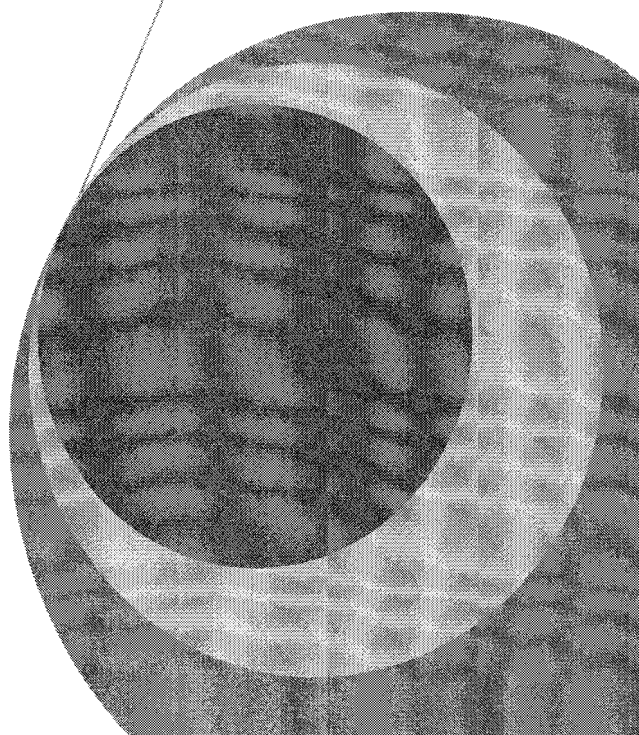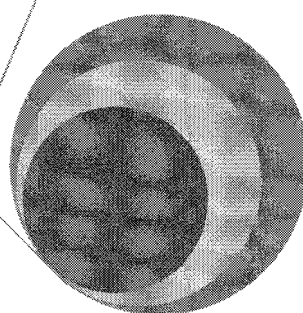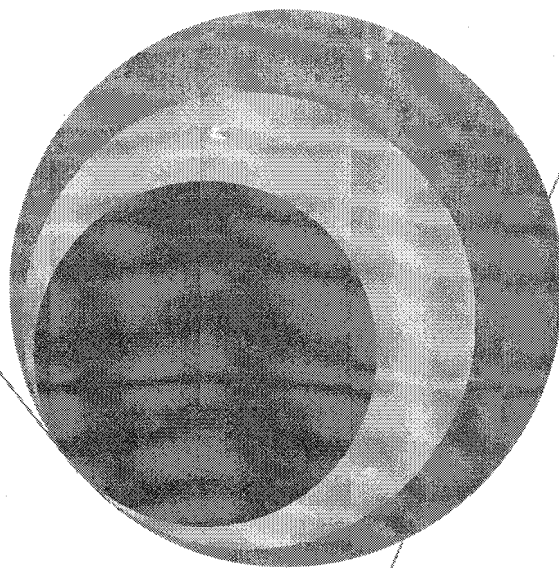
Siguiendo con esta línea de investigación, el objetivo de este trabajo se centra en evaluar la liberación de un fármaco modelo (teofilina) a partir de comprimidos matriciales elaborados con mezclas de polímeros celulósicos de distinto mecanismo de liberación. Para ello, se combinará nuestro copolímero de síntesis hidroxipropilcelulosa-metacrilato de metilo (HCMMA) con distintos tipos de polímeros celulósicos comerciales. El objetivo central se estructura en una serie de estudios:

CAPÍTULO I.- Influencia de la **viscosidad** de HPMC (HPMC K4M, HPMC K15M, HPMC K100M) sobre las características tecnológicas y de liberación a partir de comprimidos matriciales elaborados con mezclas HCMMA:HPMC en las proporciones 100:0, 75:25, 50:50, 25:75 y 0:100.

CAPÍTULO II.- Influencia del **grado de sustitución** de HPMC (HPMC K4M, HPMC E4M, HPMC F4M) sobre las características tecnológicas y de liberación a partir de comprimidos matriciales elaborados con mezclas HCMMA:HPMC en las proporciones 100:0, 75:25, 50:50, 25:75 y 0:100.

CAPÍTULO III.- Influencia del **tipo de sustituyente** de distintos derivados celulósicos (HPMC K4M, MC A4M y HPC H) de igual viscosidad (4000 cP) sobre las características tecnológicas y de liberación a partir de comprimidos matriciales elaborados con mezclas HCMMA:polimero comercial en las proporciones 100:0, 75:25, 50:50, 25:75 y 0:100.

CAPITULO I

Viscosidad

Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers: Effect of HPMC of different viscosity grades

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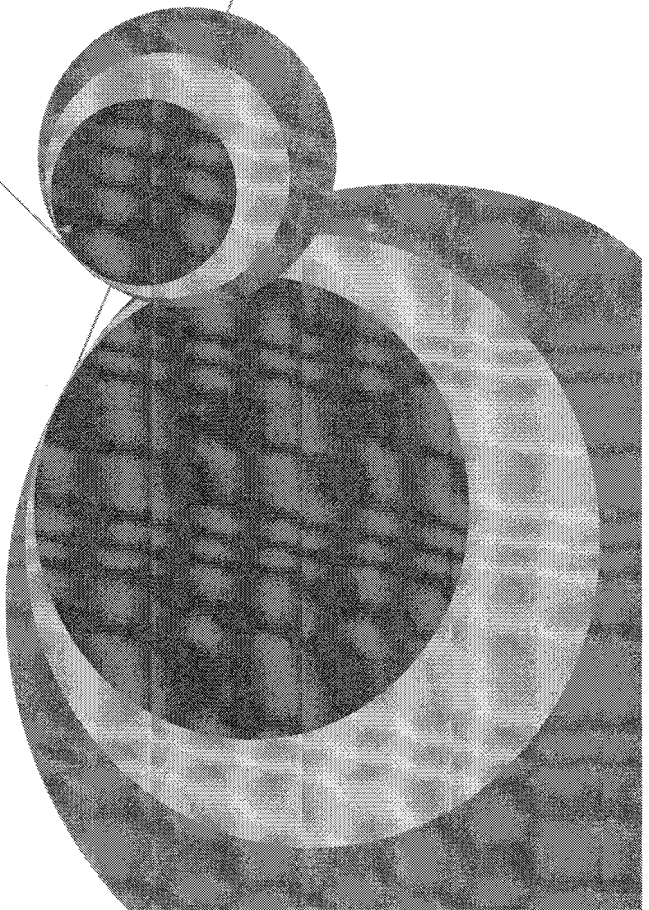
Abstract

The aim of this paper is the modification of the release behaviour of hydrophilic HPMC-based matrices of different viscosity grade by the introduction of a new inert polymeric excipient hydroxypropylcellulose-methyl methacrylate (HCMMA). The drug released could be control by both mechanisms, the swelling rate from the hydrophilic matrices, and the porosity, tortuosity and water uptake capacity from inert matrices. The effects of drying methods, presence or absence of viscosity (HCMMA in relation with HPMC), proportion of two polymers and different viscosity grade of HPMC were studied. It was observed that the mixtures with FD-HCMMA needed less pressure, presented higher plasticity and their tablets were easier to obtain compared with OD-HCMMA mixtures. Only FD-HCMMA:K100M mixtures did not show any differences in the percentage of theophylline released when FD-HCMMA proportion changed ($f2 >$ 95). All mixtures show double release mechanism, diffusion and erosion from the gel layer, but with higher contribution of the relaxation factor than on HPMC tablets. For the different mixtures HCMMA-HPMC, it is possible to see fronts movement profiles similar to swellable matrices. The results demonstrate that the use of high viscosity differences of HPMC or 50% HCMMA or above was required to produce modifications on theophylline monoaxial release modulation.

1. Introduction

In many therapies, it is necessary to adapt the release mechanism of the system to special biological characteristics. Monolithic devices or matrices represent a substantial part of the drug delivery systems. For oral administration, they are commonly manufactured as tablets by compaction of microparticulate powders. Generally, their release rate modulation is achieved using different types of polymers, distinguishing the most frequently, matrices containing swellable polymers or inert polymers. HPMC is the most commonly used hydrophilic polymer. The drug release mechanism of these hydrophilic systems occurs by water absorption, matrix swelling and, finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer (Colombo et al., 1996). In order to improve the control of drug release kinetics from hydrophilic matrices, many attempts to manipulate the relative influence of the two mechanisms of diffusion and relaxation have been made. Application of an impermeable coating that covers different surface portions of the hydrogel matrix (Colombo et al., 1987, 1990, 1992), graft the cellulose with synthetic polymers (Castellano et al., 1997), the use of ionic-exchange resin in the matrix (Feely and Davis, 1988), and the use of polymeric mixtures (Walker andWells, 1982; Bonferoni et al., 1994; Traconis et al., 1997) are some examples of the changing of drug diffusion or relaxation rates for the design of drug release from hydrophilic matrices.

Following these principles, the aim of this paper is to modify the release behaviour of these hydrophilic matrices by the introduction of a new inert polymeric excipient which possesses different release mechanism, combining the influence of swelling rate from hydrophilic matrices as well as the porosity, tortuosity and water uptake capacity from inert matrices.

Recently, a new generation of copolymers combining semi-synthetic (cellulose and starch derivatives) and synthetic (methacrylates) polymers (Castellano et al., 1997) have been introduced as excipients for oral controlled release matrices. Technological characteristics (Ferrero and Jiménez-Castellanos, 2002) and drug release kinetics (Ferrero et al., 2003) of these new polymers have been studied.

This paper evaluates the influence of different mixtures on technological characteristics and drug release from matrix tablets containing HPMC of different viscosity grades (HPMC K4M; HPMC K15M and HPMC K100M), as hydrophilic polymer, hydroxypropylcellulose-methyl methacrylate (HCMMA), as inert polymer and theophylline as model drug. The results will be focused in four points that will be compared and discussed: (a) effect of drying method (HCMMA was dried by two methods: vacuum oven and freeze dried); (b) effect of presence or absence of viscosity (inert polymers in relation with hydrophilic polymers); (c) effect of different proportion of two polymers in the matrix tablets; (d) effect of different viscosity grade of HPMC.

2. Materials and methods

2.1. Materials

Hydroxypropylmethylcellulose (Methocel® K4M -4000 cP-, K15M -15000 cP- and K100M -100000 cP-, Premium EP., Colorcon, England, batches KI10012N02, LA07012N01 and KJ07012N02, respectively) was selected as swellable polymer. The copolymer (batch SS02) synthesised by free radical copolymerisation of methyl methacrylate (MMA) and hydroxypropylcellulose (HC) was selected as inert polymer. The product (HCMMA) was dried either in a vacuum oven–OD copolymers–or freeze-dried–FD copolymers–(Castellano et al., 1997). The OD product was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

Anhydrous theophylline (Theophylline BP 80, Roig Farma, Barcelona, Spain, batch 0212030) was chosen as model drug.

Stearic acid (Estearina® L2SM, Pulcra, Barcelona, Spain, batch 0055003) was selected as lubricant.

Before use, the materials were stored at constant relative humidity (40%) and room temperature (20° C).

2.2. Methods

2.2.1. Mixtures preparation

Anhydrous theophylline (24%, w/w) and mixtures (75%, w/w) of inert and swellable polymers in different proportions (100:0,

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75:25, 50:50; 25:75 and 0:100 HCMMA:HPMC) were mixed for 15 min using a double cone mixer (Retsch, Haan, Germany) at 50 rpm. After addition of stearic acid (1%, w/w), the mixing procedure was continued for a further 5 min. A total of 23 mixtures were prepared. The nomenclature used for these HCMMA:HPMC mixtures was: the first two letters corresponding to the inert polymer, the following number is the proportion of inert polymer in the mixture, and the background is the variety of hydrophilic polymer.

2.2.2. Apparent particle density

The apparent particle densities of the mixtures were determined, in triplicate, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2004).

2.2.3. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz et al.,1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compaction characteristics of mixtures, a quantity of powder (500 mg) was preweighed and manually fed into the die (12 mm) and flat-faced compacts were prepared to have a constant breaking force of 70-80 N. Compaction data were collected from four tableting cycles.

Also, in order to produce a sufficient number of tablets for physical testing, the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70-80 N breaking force).

2.2.4. Standard physical test of tablets

The physical testing of tablets was performed after relaxation period of at least 24 h.

The tablet average weight, the standard deviation (S.D.) and the relative standard deviation (R.S.D.) were obtained from 20 individually weighed (Sartorius CP224S, Gottingen, Germany) tablets according to European Pharmacopoeia (2004).

The thickness of 10 tablets was measured individually placing them in and parallel to the face of an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The breaking force (European Pharmacopoeia, 2004) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability (European Pharmacopoeia, 2004) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 r.p.m. in an Erweka TA (Heusenstamm, Germany) friability tester.

2.2.5. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3

penetrometer. The volume of sample was roughly 20-90% of the penetrometer capacity. Working pressures covered the range 0.1-60000 p.s.i. and the mercury solid contact angle and surface tension were considered to be 130° and 485 erg/cm^3, respectively. Total porosity and pore size distribution were determined, in duplicate, for each tablet tested.

2.2.6. Drug release study

A special device (Bettini et al., 1994) was used in order to obtain rigorous radial release. The tablets were locked between two transparent Plexiglass$^®$ discs by means of four stainless steel screws. The upper disc was carved with concentric circles (from 8 to 20 mm of diameter), so that the tablet could be placed just in the centre. The assembled devices (three replicates) were introduced into the vessels of the dissolution apparatus 2 (Aidec, Barcelona, Spain) (European Pharmacopoeia, 2004) and tested for 24 h. Distilled water (900 ml) maintained at 37±0.5° C was used as dissolution medium and tablets were tested with a paddle rotation speed of 50 r.p.m. Filtered samples (2.8 ml) were withdrawn at specified time intervals via a peristaltic pump (Hewlett-Packard 8452a diode-array UV-vis spectrophotometer, Waldbronn, Germany). Theophylline release was monitored continuously at 272 nm on a Hewlett-Packard 8452a diode-array UV-vis spectrophotometer.

Drug release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963) (1), Korsmeyer et al. (1983) (2) and Peppas and Sahlin (1989) (3) equation:

$$M_t/M_\infty = k\ t^{1/2} \qquad (1)$$

$$M_t/M_\infty = k'\ t^n \qquad (2)$$

$$M_t/M_\infty = k_d\ t^m + k_r\ t^{2m} \qquad (3)$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k, k' are kinetic constants characteristic of the drug/polymer system, t is the release time, n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987), k_d, k_r are the diffusion and relaxation rate constants, respectively, m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 14.0 software. The determination coefficient (r^2) and the F-ratio probability were used to test the applicability of the release models.

Release profiles were compared using similarity factor, f_2, calculated by the following equation:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right]^{-0.5} \cdot 100 \right\}$$

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where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles (Losi et al., 2006).

2.2.7. Fronts movement study

Fronts movement measurements were effected as described elsewhere (Ferrero et al., 2000). Methylene blue (0.004%, w/v) was added to the dissolution medium (900 ml distilled water) in order to improve the visualisation of the different fronts. The experiment was carried out, in duplicate, in the same conditions as the radial release studies (37° C and 50 r.p.m.). At defined time intervals (0, 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720 min), the devices were removed from the dissolution apparatus and photographed by means of a camera (Sony® DSC-F717). Focal distance was kept constant during all measurements. The photographs analysed by computer using Corel Draw® X3 Software (Ferrero et al., 2003). The concentric circles carved on the top of the devices were taken as reference to adjust the photograph to the rulers. The initial diameter of the tablet, as well as the position of the different fronts, were obtained by placing tangent lines to these boundaries and seeing the corresponding values in the rulers. Four measurements at the two equatorial axes were made to allow precise measurement of fronts positions versus time. The interface between the matrix and the dissolution medium at the beginning of the experiment (initial diameter) was referred as position 0. The inward fronts movement was

represented by a negative value, while the outward movement was indicated by a positive one.

2.2.8. Statistical analysis

Density values and compaction data from the different mixtures were statistically analysed by one-way analysis of variance (ANOVA) using SPSS® 14.0 software. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted is significant when $p<0.05$.

3. Results and discussion

3.1. Apparent density

Table 1 shows the apparent densities of mixtures containing different proportions of HCMMA (OD or FD) and HPMC (K4M, K15M or K100M). Apparent particle density values were statistically higher ($p<0.05$) for FD than OD mixture (100:0) in agreement with Ferrero and Jiménez-Castellanos (2002), but lower ($p<0.05$) than HPMC mixtures at the same proportions (0:100).

The apparent density values of mixtures at different proportions and similar viscosity were between the values of mixtures with only one polymer, and these increase when decrease the proportion of HCMMA (OD or FD) in the mixture.

Finally, the viscosity factor do not affect statistically ($p<0.05$) the apparent density values, except in the case of OD75K15M and

FD75K15M, that present lower density values than the other mixtures at the same proportion. The differences in particle size distribution between HCMMA and HPMC, could explain this behaviour. To incorporate a small proportion (25%) of HPMC K15M (82µm) to HCMMA (OD 154 µm; FD 305 µm) could difficult helium penetration, that would lead to higher volumes and, hence, lower density values than the same mixtures with K4M (125 µm) and K100M (122µm). These differences decrease when increase HPMC proportions, as the final properties of the mixtures are determined by the main component.

Table 1.- Apparent density values from HCMMA:HPMC mixtures (100:0, 75:25, 50:50; 25:75, 0:100)

Mixture	Density (g/cm3)	Mixture	Density (g/cm3)	Mixture	Density (g/cm3)
OD-HCMMA	1.266 (0.002) CV=0.14%	OD75K4M	1.296 (0.002) CV=0.19%	FD75K4M	1.302 (0.003) CV=0.25%
FD-HCMMA	1.278 (0.004) CV=0.31%	OD75K15M	1.284 (0.002) CV=0.17%	FD75K15M	1.287 (0.004) CV=0.32%
HPMC K4M	1.365 (0.004) CV=0.26%	OD75K100M	1.293 (0.002) CV=0.17%	FD75K100M	1.300 (0.002) CV=0.12%
HPMC K15M	1.365 (0.002) CV=0.12%	OD50K4M	1.310 (0.003) CV=0.24%	FD50K4M	1.315 (0.002) CV=0.14%
HPMC K100M	1.360 (0.002) CV=0.13%	OD50K15M	1.306 (0.002) CV=0.12%	FD50K15M	1.313 (0.006) CV=0.44%
		OD50K100M	1.315 (0.003) CV=0.19%	FD50K100M	1.310 (0.001) CV=0.08%
		OD25K4M	1.339 (0.004) CV=0.27%	FD25K4M	1.341 (0.005) CV=0.37%
		OD25K15M	1.336 (0.004) CV=0.31%	FD25K15M	1.343 (0.003) CV=0.20%
		OD25K100M	1.340 (0.004) CV=0.30%	FD25K100M	1.338 (0.001) CV=0.09%

3.2. Preparation of tablets

Typical compaction parameters (Doelker, 1978; Järvinen and Juslin, 1981) are summarised in Table 2 and 3. The applied pressure (P) necessary to obtain tablets with a breaking force of 70-80N was significantly larger (p<0.05) for OD-HCMMA 100% than FD-HCMMA 100% matrices, according to Ferrero et al. (2003). The last mixture also presented higher plasticity (PI) and lower expansion work (We) and apparent net work (Wan) values. Apparent net work is defined by the equation:

$$Wan = Wsuperior - Wexpansion - Wfriction$$

Table 2.- Compaction parameters and physical tests from 100% matrices.

Mixture	Psup (MPa)	Wan (J)	We (J)	PI (%)	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD-HCMMA	369.42	18.833	5.111	78.67	499.2 (1.7)	4.092	80	1.47
	(5.26)	(0.188)	(0.373)	(1.18)	R.S.D.=0.35%	(0.013)	(3)	
FD-HCMMA	160.92	12.290	1.147	91.47	497.9 (1.4)	4.227	82	0.48
	(1.81)	(0.104)	(0.099)	(0.60)	R.S.D.=0.29%	(0.005)	(2)	
HPMC K4M	43.64	4.282	0.134	97.00	498.8 (1.6)	4.513	74	1.58
	(1.41)	(0.133)	(0.021)	(0.43)	R.S.D.=0.33%	(0.018)	(4)	
HPMC K15M	35.13	3.480	0.107	97.05	498.4 (2.1)	4.571	71	1.44
	(0.94)	(0.145)	(0.021)	(0.67)	R.S.D.=0.42%	(0.014)	(4)	
HPMC K100M	39.31	3.805	0.094	97.59	503.1 (1.9)	4.480	79	1.39
	(0.49)	(0.079)	(0.006)	(0.20)	R.S.D.=0.37%	(0.038)	(2)	

We, therefore, confirm that the drying process can modify the physico-mechanical characteristics of copolymers as has been

mentioned in previous studies (Ferrero and Jiménez-Castellanos, 2002).

Table 3.- Compaction parameters from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Psup (MPa)	Wan (J)	We (J)	PI (%)	Mixture	Psup (MPa)	Wan (J)	We (J)	PI (%)
OD75K4M	174.80	11.648	1.213	90.604	FD75K4M	109.40	9.292	0.655	93.417
	(5.59)	(0.411)	(0.194)	(1.108)		(0.52)	(0.075)	(0.034)	(0.302)
OD75K15M	200.45	12.039	1.434	89.363	FD75K15M	120.40	9.743	0.732	93.017
	(1.65)	(0.119)	(0.102)	(0.650)		(0.54)	(0.140)	(0.132)	(1.232)
OD75K100M	199.86	11.327	1.582	87.742	FD75K100M	109.30	8.960	0.596	93.760
	(3.13)	(0.212)	(0.085)	(0.604)		(1.51)	(0.176)	(0.062)	(0.679)
OD50K4M	99.65	7.726	0.459	94.411	FD50K4M	83.25	7.495	0.282	96.375
	(2.25)	(0.065)	(0.110)	(1.238)		(0.32)	(0.036)	(0.023)	(0.288)
OD50K15M	97.77	7.340	0.456	94.154	FD50K15M	79.48	6.968	0.290	96.010
	(2.10)	(0.149)	(0.036)	(0.356)		(1.62)	(0.146)	(0.046)	(0.582)
OD50K100M	104.13	7.938	0.350	95.778	FD50K100M	90.62	7.961	0.456	94.599
	(0.67)	(0.079)	(0.017)	(0.226)		(2.89)	(0.233)	(0.049)	(0.411)
OD25K4M	59.85	5.414	0.396	93.195	FD25K4M	48.93	4.771	0.141	97.046
	(1.36)	(0.099)	(0.044)	(0.671)		(0.66)	(0.091)	(0.028)	(0.354)
OD25K15M	53.44	4.849	0.262	94.886	FD25K15M	47.46	4.479	0.166	96.441
	(0.51)	(0.044)	(0.051)	(0.941)		(0.51)	(0.077)	(0.032)	(0.662)
OD25K100M	61.58	5.016	0.246	95.323	FD25K100M	57.55	5.230	0.187	96.290
	(2.91)	(0.235)	(0.014)	(0.352)		(1.25)	(0.152)	(0.017)	(0.479)

In relation with the applied pressure, HPMC 100% mixtures presented significant differences ($p < 0.05$) respect to HCMMA 100%. The first ones showed higher capacity to accept applied energy from the tablet machine (higher plasticity), lower elastic expansion during decompresion (We) and an easier tablet elaboration (lower Wan) than HCMMA.

The incorporation of two polymers into the mixtures reduced the necessary pressure to obtain the tablets and increased the

plasticity values compared to the HCMMA mixtures (100%). At similar viscosity grade, as HCMMA percentage decreases in the mixtures, the applied pressure, expansion work and apparent net work decreased. However, the plasticity parameters increase their values until 50:50 ratio, keeping then constant. We also observed that mixtures with FD-HCMMA needed less pressure, presented a higher facility to obtain the tablets, and higher plasticity than OD-HCMMA mixtures. These results agree with values showed for 100% formulations.

The viscosity factor has low influence in compaction parameter, and no tendency was possible to see.

We observed that the lubrication ratio values (data not showed) obtained from all formulations (0.881-0.746) did not fulfil the requirements (0.9) proposed by Bolhuis and Lerk (1973); in contrast with the values found for the ejection force (348-163 N) that were lower than 750 N (Bolhuis and Lerk, 1973).

3.3. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different mixtures are compiled in Tables 2 and 4.

All tablets fulfilled the guidelines specified in European Pharmacopoeia (2004) related to weight uniformity test.

The tablet thickness varied between 4 and 4.6 mm. In agreement with Ferrero et al. (2003), FD-HCMMA 100% obtained a higher value than OD-HCMMA 100%. This characteristic was fulfilled by all the mixtures. This might be related to a more porous structure in FD matrices.

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The breaking force test (European Pharmacopoeia, 2004) confirmed the values of 70-80 N for all tablets.

Table 4.- Physical tests from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)	Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD75K4M	500.0 (0.8) R.S.D.=0.17%	4.153 (0.012)	75 (2)	1.17	FD75K4M	498.0 (1.0) R.S.D.=0.20%	4.358 (0.009)	74 (2)	1.81
OD75K15M	500.6 (0.9) R.S.D.=0.19%	4.122 (0.025)	79 (2)	1.00	FD75K15M	499.7 (1.2) R.S.D.=0.23%	4.344 (0.007)	76 (2)	1.72
OD75K100M	499.5 (1.4) R.S.D.=0.29%	4.084 (0.014)	80 (1)	0.89	FD75K100M	498.6 (1.1) R.S.D.=0.23%	4.303 (0.013)	81 (1)	1.63
OD50K4M	500.6 (1.5) R.S.D.=0.29%	4.312 (0.011)	75 (2)	1.82	FD50K4M	500.7 (1.2) R.S.D.=0.24%	4.475 (0.007)	78 (2)	3.35
OD50K15M	499.6 (1.6) R.S.D.=0.33%	4.201 (0.014)	75 (2)	1.54	FD50K15M	499.6 (1.1) R.S.D.=0.23%	4.441 (0.014)	74 (2)	1.80
OD50K100M	499.2 (1.6) R.S.D.=0.32%	4.212 (0.002)	73 (3)	1.55	FD50K100M	499.4 (1.5) R.S.D.=0.30%	4.427 (0.012)	74 (2)	2.23
OD25K4M	502.2 (1.4) R.S.D.=0.28%	4.383 (0.011)	81 (3)	1.34	FD25K4M	499.0 (2.0) R.S.D.=0.40%	4.555 (0.012)	74 (3)	1.69
OD25K15M	501.9 (1.2) R.S.D.=0.26%	4.408 (0.010)	76 (3)	1.39	FD25K15M	500.4 (1.4) R.S.D.=0.28%	4.480 (0.013)	75 (5)	1.39
OD25K100M	499.0 (1.7) R.S.D.=0.34%	4.316 (0.009)	76 (2)	1.49	FD25K100M	501.4 (1.5) R.S.D.=0.30%	4.418 (0.016)	78 (3)	1.36

Only FD-HCMMA 100% and OD75K100M presented friability values lower than 1% (European Pharmacopoeia, 2004). Again, in accordance with Ferrero et al. (2003), FD-HCMMA 100% had lower friability values than OD-HCMMA 100%. However, with exception of FD25K15M and FD25K100M, the FD mixtures presented higher friability values than OD mixtures.

3.4. Mercury porosimetry measurements

In order to evaluate the microstructure of the matrices, the pore size distribution was measured by mercury intrusion-extrusion porosimetry. FD-HCMMA 100% presented higher porosity and higher small pores contribution (lower median pore

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diameter values), and lower average pore diameter than OD-HCMMA 100% (Table 5), in agreement with their larger and smaller thickness, respectively (Ferrero et al., 2003). HPMC 100% presented higher porosity, average pore diameter and median pore diameter than HCMMA, except HPMC K100M, whose porosity was similar to FD-HCMMA 100%. It also showed lower average pore diameter and higher small pores contribution than the other HPMCs.

When two polymers were incorporated to the mixture (Table 6), the porosity and average pore diameter values were higher than those corresponding to HCMMA 100%, except to FD75K100M that were similar. Comparing OD with FD mixtures, the first ones showed in general, lower porosity values, but higher average pore diameter, like happened in HCMMA 100% tablets.

Table 5.- Parameters characterising the porous structure of 100% matrices.

Mixture	Porosity (%)		Median pore diameter (Volume) (Å)		Average pore diameter (4V/A) (Å)	
OD-HCMMA	17.8	(1.4)	22650	(4916)	268.0	(19.8)
FD-HCMMA	23.6	(0.6)	9300	(1204)	241.5	(7.8)
HPMC K4M	31.4	(2.7)	41731	(1272)	601.0	(55.2)
HPMC K15M	33.6	(0.5)	35203	(1427)	639.0	(7.1)
HPMC K100M	23.3	(0.7)	21282	(1546)	434.5	(16.3)

According to HCMMA:HPMC ratio, at the same viscosity grade, as HCMMA percentage decrease, average pore diameter increased. On the other hand, as porosity values in OD mixtures increased but in FD mixtures, the higher porosity values were for 50:50 mixture. This higher porosity of 50:50 could affect the control release tendency attending to polymers ratio.

Besides, the viscosity grade showed, in general term, that higher viscosity entailed lower porosity values and average pore diameter. This tendency was not follow by both OD25K100M, with higher porosity and average pore diameter than OD25K15M, and FD75K15M, with similar porosity than FD75K4M. Small pores contribution did not present a clear tendency in viscosity grade factor and HCMMA:HPMC ratio.

Table 6.- Parameters characterising the porous structure of HCMMA:HPMC matrices.

Mixture	Porosity (%)		Median pore diameter (Volume) (Å)		Average pore diameter (4V/A) (Å)	
OD75K4M	22.0	(1.8)	29899	(3458)	338.5	(23.3)
OD75K15M	21.7	(0.1)	31646	(609)	335.0	(2.8)
OD75K100M	19.7	(0.8)	25473	(2229)	302.0	(9.9)
OD50K4M	27.2	(0.2)	36123	(588)	452.5	(2.1)
OD50K15M	25.0	(0.3)	26761	(1124)	402.0	(11.3)
OD50K100M	24.1	(1.9)	27560	(3677)	388.5	(29.0)
OD25K4M	28.5	(2.3)	37016	(1692)	510.0	(35.4)
OD25K15M	27.0	(3.6)	28124	(4599)	474.5	(61.5)
OD25K100M	28.0	(0.5)	30473	(1177)	482.5	(14.8)

Mixture	Porosity (%)		Median pore diameter (Volume) (Å)		Average pore diameter (4V/A) (Å)	
FD75K4M	26.2	(0.4)	18770	(1620)	299.5	(12.0)
FD75K15M	26.4	(0.1)	16748	(71)	283.0	(1.4)
FD75K100M	23.3	(2.0)	13334	(4962)	282.5	(21.9)
FD50K4M	34.0	(7.4)	27626	(797)	370.5	(6.4)
FD50K15M	28.4	(0.4)	22081	(1406)	353.5	(10.6)
FD50K100M	28.2	(0.2)	24203	(194)	354.0	(0.0)
FD25K4M	32.7	(0.1)	40703	(954)	504.0	(1.4)
FD25K15M	26.0	(2.0)	22913	(2695)	391.0	(24.0)
FD25K100M	25.8	(2.5)	24525	(1769)	385.5	(37.5)

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There was not a clear tendency between thickness and porosity data when we used two polymers into the mixture. It could be due to either physical interactions between the two polymers or/and some differences between the particle sizes and shapes of the two polymers.

According to IUPAC definitions, as the pore diameter values were accomplished between 20 and 500 Å, all mixtures possessed mesopores, except OD/FD25K4M, HPMC K4M and K15M 100%, that presented macropores (>500 Å).

3.5 Drug release study

Figure 1 illustrates the drug release profiles from HCMMA 100% and HPMC 100% matrices. Higher percentage of drug release was observed for HCMMA matrices, where OD tablets exhibited a faster release than FD tablets (f_2=60.3). HPMC K100M tablets displayed the lowest release, corresponding to higher viscosity grade. This is probably due to the degree of entanglement at high molecular weights, that reduced the effective molecular diffusion area (Colombo et al., 1995). Similar results were observed by Nellore et al. (1998) where the higher viscosity gel layers of Methocel® K100M matrices provided a more tortuous and resistant barrier to diffusion, resulting in slower release of metoprolol tartrate from these matrices.

No significant differences in release behaviour were observed for systems prepared with Methocel® K4M and K15M (f_2=99.5), in agreement with Colombo et al. (1995).

Figure 2 illustrates the release profiles from the matrices prepared from different mixtures of OD-HCMMA and FD-HCMMA with HPMC (K4M, K15M, K100M) in three defined proportions HCMMA:HPMC (75:25, 50:50, 25:75).
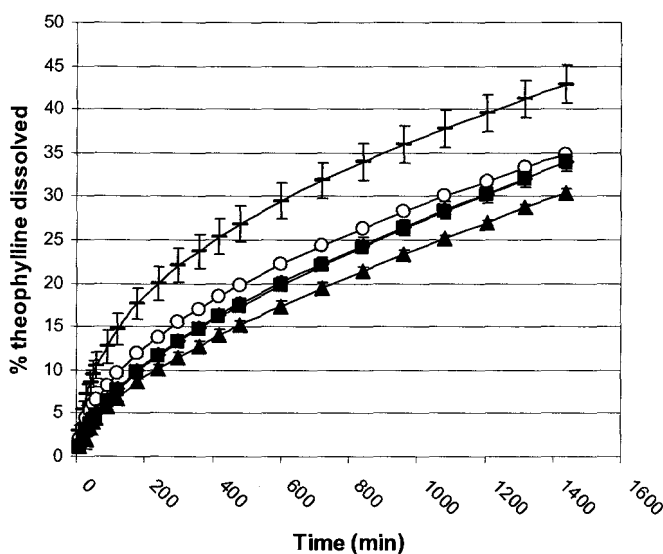
Fig. 1.- Release profiles of anhydrous theophylline (over 24 h) from tablets of OD-HCMMA (-), FD-HCMMA (○), and HPMC: K4M (♦), K15M (■), K100M (▲). The bars show the standard deviation.

The mixtures of HPMC with OD-HCMMA released less theophylline than the copolymer 100%, except for 75:25 OD-HCMMA-HPMC (K4M and K15M) that were similar. Likewise, the release of theophylline was lower when the viscosity grade increased (mixtures with K100M) mainly as a result of a slower diffusion and extensive swelling (Reynolds et al., 1998). Besides, the theophylline release could be increased at low percentage of HMPC (up to 50%). The f_2 values obtained comparing 75:25 and 50:50 proportions were $f_2 < 80$ and $f_2 > 97$ for 50:50 and 25:75.
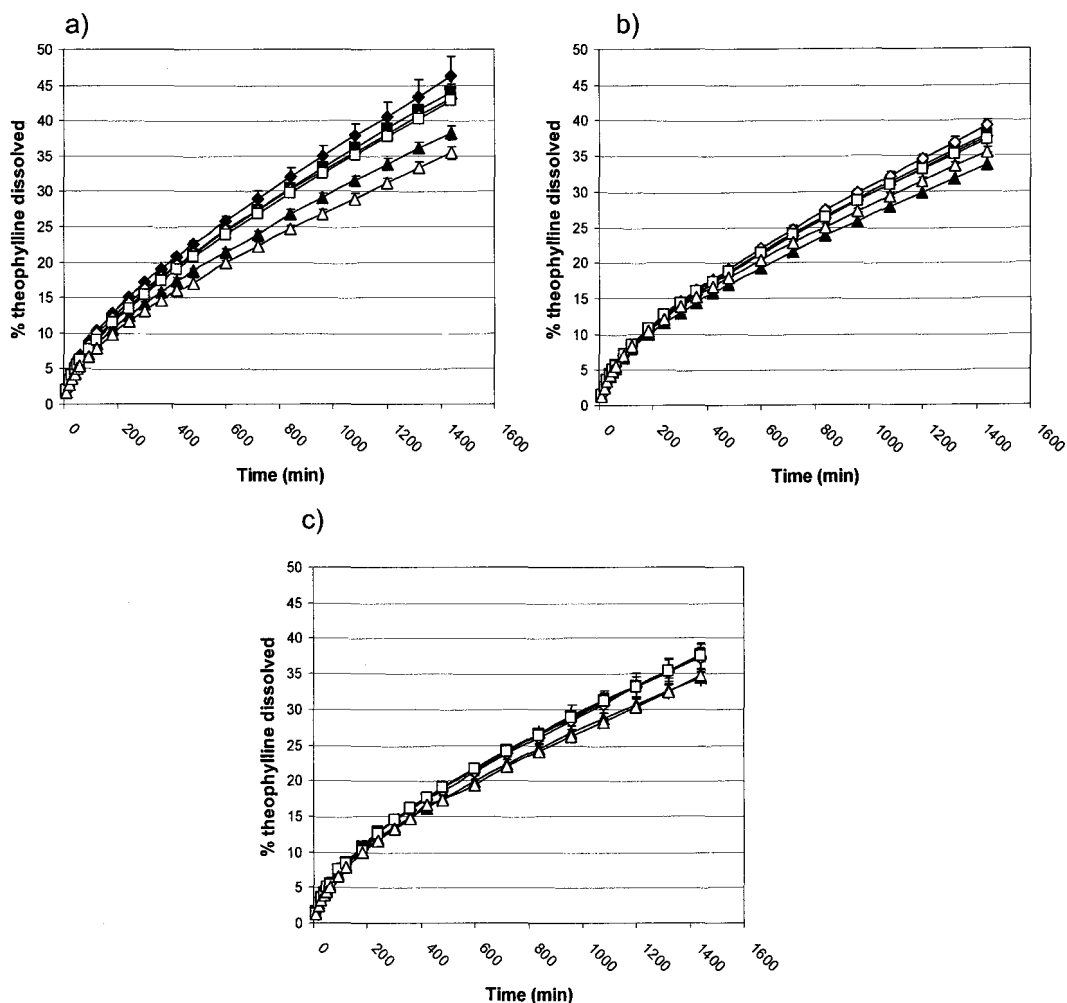
Fig.2.- Release profiles of anhydrous theophylline (over 24 h) from mixtures of HPMC with HCMMA: a) 75% HCMMA, b) 50% HCMMA, c) 25% HCMMA. The mixtures are represented in function of viscosity grade of HPMC: K4M (♦), K15M (■), K100M (▲), and drying method of HCMMA: OD mixtures are represented by closed symbols and FD mixtures by opened ones. The bars show the standard deviation.

As Takka et al. (2001) –HPMC K100M:Eudragit S- and Lotfipour et al. (2004) -HPMC K4M:Eudragit RSPO-, it is observed that the amount of HPMC played a dominant role, affecting the drug release in these mixtures. Kiortsis et al. (2005) showed that

the release rate of indomethacin (low solubility drug) decreased as the mass fraction of HPMC increased, replacing either drug or hydrophobic component. The profiles were more similar to HCMMA or HPMC 100% mixtures in function of predominant polymer. In this sense, Nellore et al. (1998) fit the polymer charge to 40%, changing the viscosity of the materials (Methocel K100LV, K4M, K15M, K100M). The mixtures showed a similar but less dramatic effect of the viscosity on metoprolol release than mixtures where polymer level was held to 10%, particularly at higher viscosity (K4M, K15M and K100M).

Only HPMC K100M mixtures had a slower or equal release than FD-HCMMA 100%. Related to viscosity grade and percentage of HPMC, the behaviour for FD-HCMMA:HPMC mixtures were similar to OD-HCMMA:HPMC ones, except FD-HCMMA:K100M blends. They did not show any differences in the percentage of theophylline released when FD-HCMMA ratio changed ($f_2 > 95$).

These results demonstrate that changes in the amount of HCMMA from 50% can be used to produce modifications on drug release rates in monoaxial delivery, because the presence of solid particles (theophylline and HCMMA) can reduce the entanglement HPMC chains, thus lowering gel resistance (Grassi et al., 2004).

Release data ($M_t/M_\infty < 0.6$) were analysed according to Higuchi (1963), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations. The main parameters are listed in Table 7 for 100% mixtures and in Tables 8 and 9 for mixtures of OD-HCMMA:HPMC and FD-HCMMA:HPMC, respectively. As the matrices under study presented an aspect ratio

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(diameter/thickness) around 3, the m value was 0.44 (Peppas and Sahlin, 1989). The determination coefficient (r^2) and de F-ratio probability were used to test the applicability of the release models.

In agreement with Ferrero et al. (2003), FD-HCMMA provided the best fit to the different models. Both, in OD and in FD matrices 100% (Table 7), the accurate fit to Higuchi equation, the n values from Korsmeyer equation and the prevalence of k_d over k_r in Peppas equation revealed a drug release mechanism controlled mainly by diffusion. Moreover, the different constants had lower values for FD matrices, which indicate a lower release of theophylline. Heng et al. (2001) reported that polymer powder of different size distribution, as these polymers (Ferrero and Jiménez-Castellanos, 2002), had influence on drug release rate but not on release mechanism.

Table 7.- Mathematical modelling and drug release kinetics from 100% matrices.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k	r^2	n	k'	r^2	k_d	k_r	r^2
	$(min^{-1/2})$			(min^{-n})		$(min^{-0.44})$	$(min^{-0.88})$	
OD-HCMMA	0.011	0.9950 (F=4011)	0.49	0.013	0.9869 (F=1500)	0.021	0.00011	0.9996 (F=24393)
FD-HCMMA	0.009	0.9999 (F=273578)	0.55	0.007	0.9957 (F=4614)	0.013	0.00008	0.99998 (F=457998)
HPMC K4M	0.009	0.9982 (F=10857)	0.61	0.004	0.9990 (F=20588)	0.010	0.00020	0.99997 (F=292743)
HPMC K15M	0.009	0.9980 (F=9821)	0.64	0.003	0.9962 (F=5205)	0.010	0.00020	0.99994 (F=158784)
HPMC K100M	0.008	0.9963 (F=5441)	0.65	0.003	0.9932 (F=2940)	0.008	0.00021	0.99958 (F=22657)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p=0.000).

The lower values of k and especially for k_d of K100M agreed with its lower release of theophylline. However, consistent with Salomen et al. (1979) and Ford et al. (1985), the matrices containing K4M, K15M and K100M grades of HPMC had similar Higuchi constants. This implies that viscosities of the hydrated matrices may be identical, despite the apparent differences in their viscosity grades (Ford et al., 1985). Campos-Aldrete and Villafuerte-Robles (1997) pointed out the necessity of a high concentration of HPMC (at least 20%) to disappear the effect of the viscosity grade on the Higuchi constant. Although HPMC 100% tablets had a good fit to Higuchi equation indicative of a diffusion mechanism, however, according to n values from Korsmeyer equation higher than 0.5, and the high values of k_r in Peppas and Sahlin equation reveals a drug release mechanism that combine diffusion through the gel layer and erosion of this gel layer, due to the relaxation component (Ford et al., 1991).

In all mixtures (Tables 8 and 9), the Higuchi constants were very similar, on the contrary to Vazquez et al. (1996), who indicated that the principal factor affecting the Higuchi constant, in mixtures with Methocel® K100LV and K100M, was the gelling agent composition. A drug release mechanism that combine diffusion and erosion is supported by the n values from Korsmeyer equation indicative of an anomalous drug release (Catellani et al., 1988), similar to obtain by Takka et al. (2001) in mixtures of Eudragit-HPMC K100M, and the higher values of k_r in Peppas equation for these mixtures in relation with only one polymer matrices. According to the same ratio, important differences were only displayed for K100M in k_r values for Peppas and Sahlin

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equation (Tables 8 and 9). Tahara et al. (1995) reported that the selection of the viscosity grade of HPMC is an important consideration in the formulation development, for a drug with poor aqueous solubility. This parameter (k_r) decreased when the HPMC proportions in the matrix tablets increased, being more important in the 75-50% HCMMA range. As HCMMA could destabilise the gel structure, with which a lower percentage of this copolymer or a higher viscosity of gel layer (HPMC K100M) could explain the lower drug release of theophylline in these matrices.

Table 8.- Mathematical modelling and drug release kinetics from OD HCMMA-HPMC mixtures.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k $(min^{-1/2})$	r^2	n	k' (min^{-n})	r^2	k_d $(min^{-0.44})$	k_r $(min^{-0.88})$	r^2
OD75K4M	0.012	0.9937 (F=3147)	0.60	0.006	0.9962 (F=5285)	0.010	0.00038	0.99965 (F=27002)
OD75K15M	0.012	0.9925 (F=2644)	0.62	0.005	0.9985 (F=13523)	0.008	0.00040	0.99987 (F=75013)
OD75K100M	0.010	0.994 (F=3272)	0.61	0.004	0.9982 (F=10967)	0.008	0.00032	0.99982 (F=53550)
OD50K4M	0.010	0.9948 (F=3834)	0.62	0.004	0.9979 (F=9185)	0.008	0.00030	0.99984 (F=59250)
OD50K15M	0.010	0.9953 (F=4240)	0.62	0.004	0.9968 (F=6285)	0.009	0.00029	0.99978 (F=44013)
OD50K100M	0.009	0.9963 (F=5320)	0.60	0.004	0.9971 (F=6901)	0.008	0.00023	0.99974 (F=35879)
OD25K4M	0.010	0.99624 (F=6305)	0.61	0.004	0.9984 (F=12454)	0.010	0.00025	0.9999 (F=97685)
OD25K15M	0.010	0.9973 (F=7284)	0.62	0.004	0.9989 (F=17677)	0.010	0.00024	0.9999 (F=177177)
OD25K100M	0.009	0.99707 (F=6807)	0.60	0.004	0.9981 (F=10435)	0.009	0.00022	0.99983 (F=56093)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p=0.000).

Table 9.- Mathematical modelling and drug release kinetics from FD HCMMA-HPMC mixtures.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k	r^2	n	k'	r^2	k_d	k_r	r^2
	$(min^{-1/2})$			(min^{-n})		$(min^{-0.44})$	$(min^{-0.88})$	
FD75K4M	0.012	0.9946 (F=3660)	0.60	0.005	0.9986 (F=14437)	0.0094	0.00034	0.99975 (F=37686)
FD75K15M	0.012	0.9926 (F=2697)	0.61	0.005	0.9989 (F=17681)	0.0081	0.00038	0.99993 (F=145695)
FD75K100M	0.009	0.9932 (F=2936)	0.59	0.005	0.9984 (F=12225)	0.0070	0.00030	0.9997 (F=31936)
FD50K4M	0.011	0.9950 (F=3956)	0.64	0.004	0.9971 (F=6786)	0.0088	0.00030	0.99983 (F=55770)
FD50K15M	0.010	0.9964 (F=5575)	0.61	0.004	0.9979 (F=9374)	0.0092	0.00026	0.99986 (F=68805)
FD50K100M	0.010	0.9968 (F=6313)	0.62	0.004	0.9945 (F=3627)	0.0092	0.00023	0.99971 (F=32563)
FD25K4M	0.010	0.99585 (F=4802)	0.61	0.004	0.999 (F=20669)	0.0090	0.00027	0.99971 (F=33262)
FD25K15M	0.010	0.99683 (F=6286)	0.63	0.004	0.9946 (F=3700)	0.0097	0.00025	0.99966 (F=28270)
FD25K100M	0.009	0.99622 (F=5277)	0.62	0.004	0.9968 (F=6302)	0.0087	0.00023	0.99939 (F=15553)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p=0.000).

3.6 Fronts movement study

With the purpose of obtaining useful information for a better understanding of the drug release mechanism from the different matrices, fronts movement kinetics were evaluated (Ferrero et al., 2003). According to Ferrero et al. (2003) for inert matrices (HCMMA 100%), three fronts could be clearly distinguished from the centre to the periphery of the matrix: water uptake front (between dry-partial wet polymer), complete wetting front (distinguishes a partial hydrated zone from a complete wet one) and erosion front (between the external surface of the matrix and the dissolution medium).

Fronts movement kinetics (over 12 h) depicted in Fig.3 for HCMMA 100% showed a nearly constant erosion front movement, which proved the absence of swelling in these matrices. As no swelling or erosion could be detected (the tablet diameter remained constant), it seems that copolymer tablets behave as matrices where the drug is released by diffusion through the porous structure. The fast initial water uptake observed might be due to the water penetration through capillaries and higher size pores.

Water uptake and complete wetting fronts seemed to move faster in FD-HCMMA 100% matrices, which is consistent with the highest initial porosity in these matrices (Table 5). However, this not explains the lower release of FD to OD HCMMA matrices 100%.
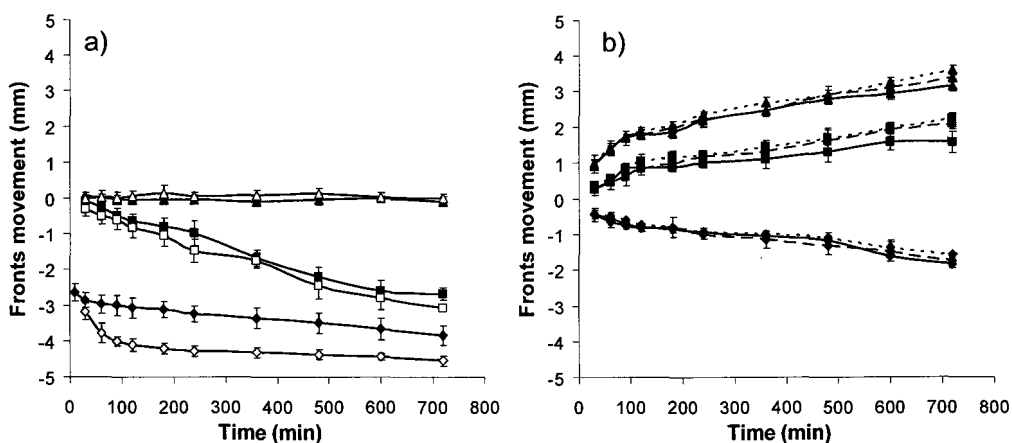

Fig 3.- Fronts movement (over 12 h) from 100% matrices. Swelling (water uptake for HCMMA) (♦), diffusion (complete wetting for HCMMA) (■) and erosion (▲) fronts from: a) OD-HCMMA (closed symbols), FD-HCMMA (open symbols). b) HPMC K4M (continuous line), K15M (uncontinuous line), K100M (points line).

Table 10 shows the approximate values for the apparent diffusion coefficient D', obtained from Higuchi rate constant. D' is expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusion coefficient of the drug in the dissolution medium.

Table 10.- Apparent diffusion coefficient (D') for all mixtures.

Mixture	D' (cm²/min)	Mixture	D' (cm²/min)	Mixture	D' (cm²/min)
OD-HCMMA	7.24×10^{-4}	OD75K4M	6.87×10^{-4}	FD75K4M	5.51×10^{-4}
FD-HCMMA	3.54×10^{-4}	OD75K15M	7.02×10^{-4}	FD75K15M	5.48×10^{-4}
HPMC K4M	2.50×10^{-4}	OD75K100M	5.42×10^{-4}	FD75K100M	3.53×10^{-4}
HPMC K15M	2.31×10^{-4}	OD50K4M	3.72×10^{-4}	FD50K4M	3.48×10^{-4}
HPMC K100M	2.68×10^{-4}	OD50K15M	4.16×10^{-4}	FD50K15M	3.46×10^{-4}
		OD50K100M	3.48×10^{-4}	FD50K100M	3.50×10^{-4}
		OD25K4M	3.50×10^{-4}	FD25K4M	2.94×10^{-4}
		OD25K15M	3.67×10^{-4}	FD25K15M	3.75×10^{-4}
		OD25K100M	2.93×10^{-4}	FD25K100M	3.10×10^{-4}

D' values were smaller for matrices obtained from FD mixtures 100%, which implies higher tortuosity values and an increment in the diffusional resistance for these tablets. These results explain the slower diffusion rate in these matrices in spite of their higher porosity (Table 5) and quicker water penetration.

In the opposite, for swellable matrix tablets, as HPMC 100%, Colombo et al. (1995) proposed these three fronts: swelling front (between dry-wet polymer able to swell), diffusion front (between wet polymer–clear gel) and erosion front (between clear gel–solvent). In Figure 3 not important differences can be seen for the three matrices compared with the different fronts. In agreement with Colombo et al. (1995), the rates of movement of the diffusion

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fronts were only slightly different for the three Methocel® grade formulations.

For the different mixtures HCMMA-HPMC, it is possible to see similar fronts movement profiles to swellable matrices (Figure 4), with no changes in swelling front respect to HPMC 100% matrices. Respect to viscosity grade (Methocel® K4M, K15M and K100M) the diffusion and erosion fronts increased with viscosity (K100M), being very similar for the other ones (K4M and K15M). The diffusion front dynamics indicate the transport of solid drug particles in the gel layer, as a consequence of polymer swelling (Bettini et al., 2001). If we consider that the penetration speed of water in all matrices are similar (similar swelling front), the K100M matrices will need more time to form the clear gel and become more viscous. According to Bettini et al. (2001), for poor water soluble drugs, the diffusion front moved very close to the erosion front and, therefore, the dissolved drug gel layer thickness, which represents the drug diffusive pathway, should be extremely thin, especially for K4M and K15M. Thus, a high probability existed for drug solid particles to escape from these matrices.

About the percentage of HPMC, erosion and diffusion fronts increased when decreased the proportion of HCMMA, so the fronts movement profiles resembled to HPMC 100% matrices, with the highest differences for 75% of HCMMA related to other ratios.

Lotfipour et al. (2004) explain the effect of the fillers on the release rate of atenolol because they reduced the tortuosity of the diffusion path of the drug.
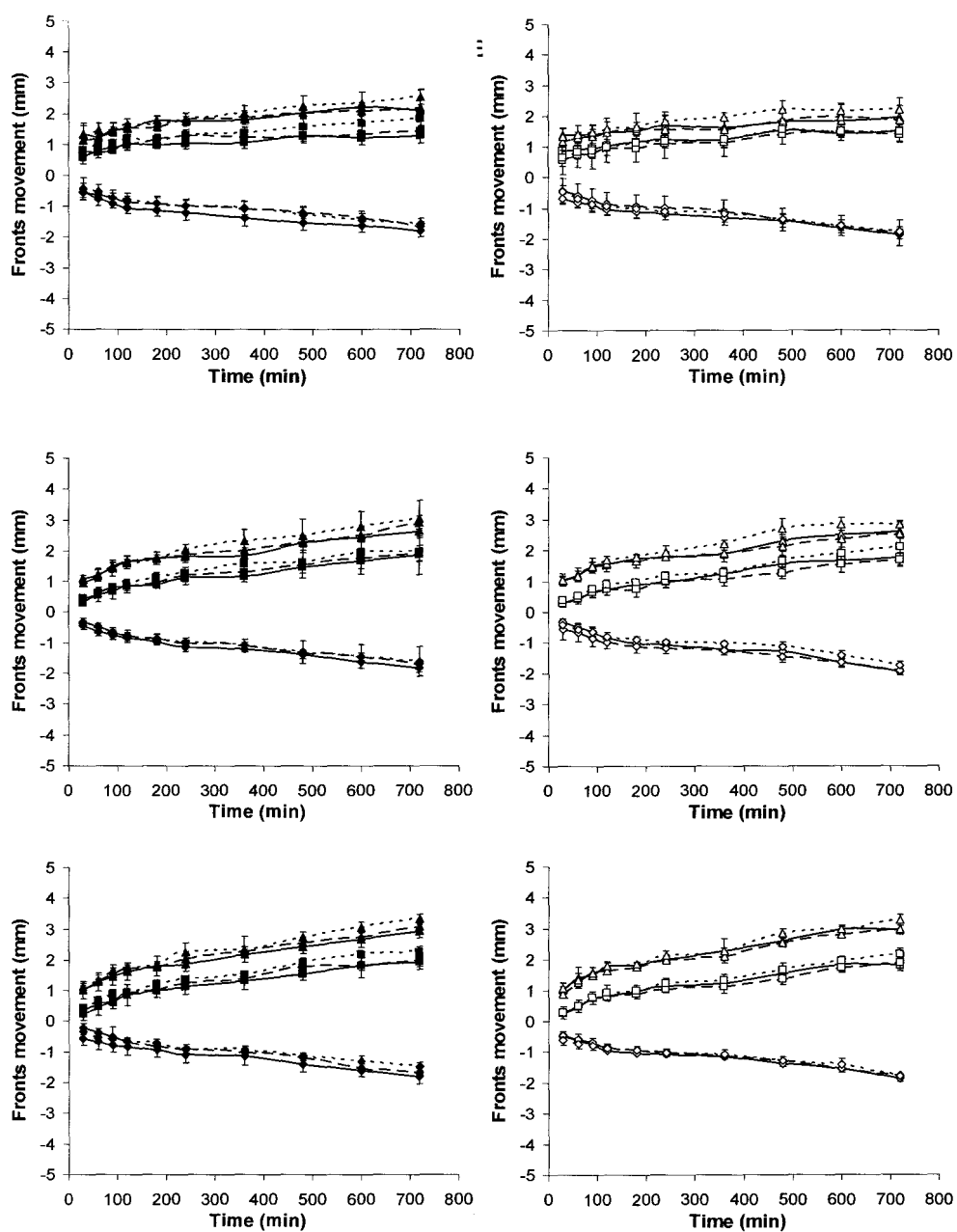
Fig 4.- Fronts movement (over 12 h) from HCMMA-HPMC mixtures: a) 75%-25%; b) 50%-50%; c) 25%-75%. Swelling (♦), diffusion (■) and erosion (▲) fronts from mixtures of: OD-HCMMA (closed symbols) or FD-HCMMA (open symbols) with HPMC K4M (continuous line), K15M (uncontinuous line) or K100M (points line).

Table 10 shows that when HCMMA decrease from 75% to 25%, the tortuosity of the diffusion path increases, being more important in the 75-50% intervals of HCMMA. This tortuosity was usually higher for K100M mixtures.

The relative movement of either the erosion and swelling fronts or erosion and diffusion fronts indicated the tendency to move in the same way. This phenomenon can be represented in terms of gel layer thickness (Colombo et al., 1995), which is defined as the difference between erosion and swelling front positions. As shown in Figure 5, the gel layer thickness was similar to Methocel K4M and K15M and higher to Methocel K100M. Besides, it raised when increased the proportion of HMPC in the mixtures, being very similar in 50:50 and 25:75 HCMMA:HPMC.
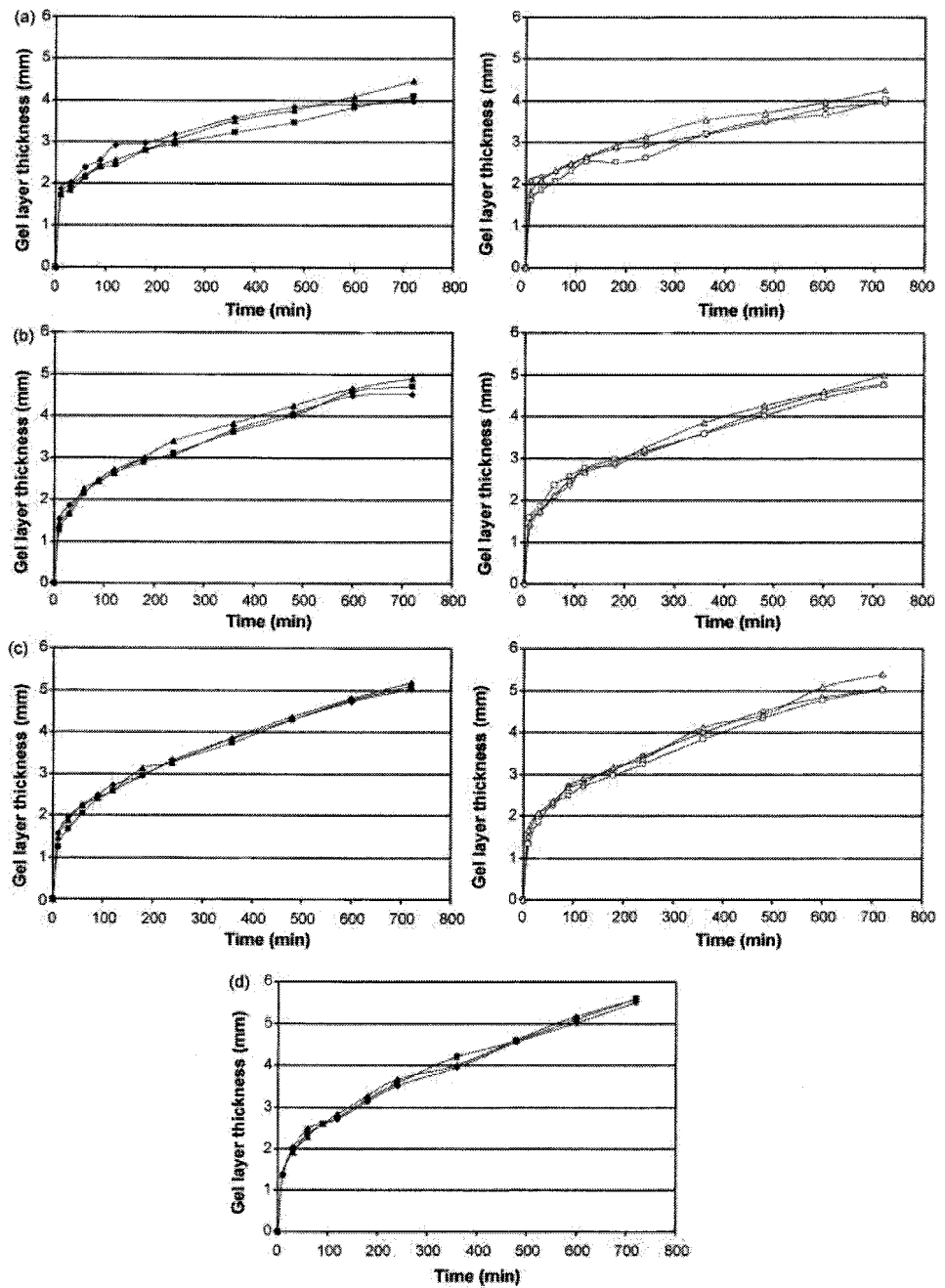
Fig 5.- Gel layer thickness from mixtures of HPMC with HCMMA: a) 75% HCMMA, b) 50% HCMMA, c) 25% HCMMA, d) 0% HCMMA. The mixtures are represented in function of viscosity grade of HPMC: K4M (♦), K15M (■), K100M (▲), and drying method of HCMMA: OD mixtures are represented by closed symbols and FD mixtures by opened ones

4. Conclusion

In conclusion, the results of this study confirm the possibility of modulation of theophylline release by mixing two polymers with different release mechanism. FD-HCMMA releases theophylline slower than OD-HCMMA, both by diffusion mechanism, but never below the control exerted by HPMC tablets. HPMC matrices show double release mechanism, diffusion and erosion of the gel layer, being predominant the diffusion pathway, affected by the viscosity grade. The different mixture of polymers studied also displayed this double mechanism, but in this case, with higher contribution of the relaxation factor. These mixtures need, for the modulation of theophylline monoaxial release, either above 50% of HCMMA or high viscosity differences of HPMC in the mixture.

5. Acknowledgements

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CAPÍTULO II

Grado de Substitución

Compaction Properties, Drug Release Kinetics and Fronts Movement Studies from Matrices Combining Mixtures of Swellable and Inert Polymers.II. Effect of HPMC with Different Degrees of Methoxy/Hydroxypropyl Substitution.

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Abstract

The aim of this paper is the modification of the release behaviour of hydrophilic HPMC-based matrices of different substitution degree (E4M, F4M, K4M) by the introduction of a new inert polymeric excipient hydroxypropylcellulose-methyl methacrylate (HCMMA) at different proportions (75:25, 50:50 and 25:75). The product (HCMMA) was dried either in a vacuum oven -OD copolymers- or freeze-dried -FD copolymers-. HPMC E4M formulations showed the worst compaction properties. All mixtures presented a percentage of theophylline release between 47% and 32% at 1440 minutes. The drying methods employed had only influence over the drug release in E4M and K4M formulations, at higher proportions of HCMMA, showing the highest release the mixtures containing OD-HCMMA. Combinations of diffusion and erosion release mechanisms were found to matrix tablets. All mixtures with F4M did not modify relaxation rate constant values of Peppas and Shalin equation (k_r) respect to F4M 100%. However, all mixtures with K4M showed the highest k_r values, which decreased when HCMMA proportion decreased. Only K4M mixtures showed a different diffusion front movement than the other mixtures. The modulation of theophylline monoaxial release was obtained using a high percentage of HCMMA, and HPMCs with a substantial difference of hydroxypropyl groups (F4M and K4M or E4M).

1. Introduction

Hydroxypropylmethylcellulose (HPMC) are celluloses ethers which are frequently used to provide a controlled release of drugs from matrix tablets (Melia, 1991). The interaction of these polymers with water is a major factor in formulation, processing and sustaining the drug release. Thus, the ability to hydrate rapidly when in contact with liquid water and thus to form a protective gel around the tablet matrix is an essential property for drug release (Carstensen and Li Wan Po, 1992). Application of an impermeable coating that covers different surface portions of the hydrogel matrix (Colombo et al., 1987, 1990, 1992), graft the cellulose with synthetic polymers (Castellano et al., 1997), the use of ion exchange resin in the matrix (Feely and Davis, 1988), the careful control of drug particle size (Ford et al., 1985a,b), drug/cellulose ether ratio (Ford et al., 1985a,b; 1987) or even matrix shape (Ford et al., 1987), and the use of polymeric mixtures (Walker and Wells, 1982; Bonferoni et al., 1994; Traconis et al., 1997) are some examples of the changing of drug diffusion or relaxation rates for the modulation of drug release from hydrophilic matrices.

Since diffusion plays such a prominent role in controlling drug release, the release kinetics are ever changing because of the changing diffusional path length. Indeed, the release kinetics follows the kinetics of swelling (Colombo et al., 1990). In a previous paper (Escudero et al., 2008), we demonstrate the possibility of modulation of theophylline release by mixing HPMC of different viscosity grades (hydrophilic matrices) and a new generation of copolymers (Castellano et al., 1997; Ferrero and

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Jiménez-Castellanos, 2002; Ferrero et al., 2003) introduced as excipient for oral controlled released matrices (inert matrices), combining the influence of swelling rate from hydrophilic matrices as well as the porosity, tortuosity and water uptake capacity from inert matrices.

Following these principles, and since there is evidence that varying the degree of substitution of HPMC used may also influence drug release characteristics (Alderman, 1984), the aim of this paper is to evaluate the influence of different mixtures on technological characteristics and drug release from matrix tablets containing HPMC of same viscosity grade but different substitution degree (HPMC K4M; HPMC E4M and HPMC F4M), as hydrophilic polymer, hydroxypropylcellulose-methyl methacrylate (HCMMA), as inert polymer and theophylline as model drug. Because in a previous paper (Escudero et al., 2008) we discuss the effect that drying method produced on the different technological characteristics and drug release from matrices tablets containing HCMMA, in this paper the results will be focused on the influence of: a) polymer type; b) ratio of two polymers in the matrix tablets; c) substitution degree of HPMC.

2. Materials and Methods

2.1. Materials

Inert polymer: the copolymer (batch SS02) synthesised by free radical copolymerisation of methyl methacrylate (MMA) and hydroxypropylcellulose (HC) was select as inert polymer. The

product (HCMMA) was dried either in a vacuum oven -OD copolymers- or freeze-dried -FD copolymers- (Castellano et al., 1997). The OD product was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

Commercial polymers: Hydroxypropylmethylcellulose (Methocel® K4M with 19-24% methoxyl groups and 7-12% hydroxypropyl groups, E4M with 28-30% methoxyl groups and 7-12% hydroxypropyl groups, F4M with 27-30% methoxyl groups and 4-7.5% hydroxypropyl groups, Premium EP., Colorcon, England, batches KI10012N02, LB24012N11 and KB21012N81, respectively) was selected as swellable polymer.

Others components: anhydrous theophylline (Theophylline BP 80, Roig Farma, Barcelona, Spain, batch 0212030) was chosen as model drug. Stearic acid (Estearina® L2SM, Pulcra, Barcelona, Spain, batch 0055003) was selected as lubricant.

Before use, the materials were stored at constant relative humidity (40%) and room temperature (20° C).

2.2. Methods

2.2.1. Mixtures preparation

Anhydrous theophylline (24%, w/w) and mixtures (75%, w/w) of inert and swellable polymers in different proportions (100:0, 75:25, 50:50, 25:75 and 0:100 HCMMA:HPMC) were mixed for 15 min using a double cone mixer (Retsch, Haan, Germany) at 50 r.p.m. After addition of stearic acid (1%, w/w), the mixing procedure was continued for a further 5 min. A total of 23 mixtures

were prepared. The nomenclature used for these HCMMA:HPMC mixtures was: the first two letters corresponding to the inert polymer (OD or FD), the following number is the proportion of inert polymer in the mixture (75, 50 or 25%), and the background is the variety of hydrophilic polymer (K4M, E4M or F4M).

2.2.2. Apparent particle density

The apparent particle densities of the mixtures were determined, in triplicate, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2007).

2.2.3. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz et al., 1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compaction characteristics of mixtures, a quantity of powder (500 mg) was preweighed and manually fed into the die (12 mm) and flat-faced compacts were prepared to have a constant breaking force of 70-80 N. Typical compaction parameters (maximum upper pressure -Psup-, apparent net work -Wan-, expansion work -We-, plasticity -Pl-) describe by Doelker (1978) and Järvinen and Juslin, (1981) were collected from four tableting cycles.

Also, in order to produce a sufficient number of tablets for physical testing, the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70-80 N breaking force).

The values obtained from the different mixtures were statistically analysed by one-way analysis of variance (ANOVA) using SPSS® 14.0 software. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted is significant when $p < 0.05$

2.2.4. Standard physical test of tablets

The physical testing of tablets was performed after relaxation period of at least 24 h.

The tablet average weight and the standard deviation were obtained from 20 individually weighed (Sartorius CP224S, Gottingen, Germany) tablets according to European Pharmacopoeia (2007). The thickness of 10 tablets was measured individually placing them in and parallel to the face of an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan). The breaking force (European Pharmacopoeia, 2007) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland). Tablet friability (European Pharmacopoeia, 2007) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 r.p.m. in an Erweka TA (Heusenstamm, Germany) friability tester.

2.2.5. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3 penetrometer. An adequate number of tablets per formulation tested was used according to obtain a stem volume between 20-90% of the penetrometer capacity. Working pressures covered the range 0.1-60000 p.s.i. and the mercury solid contact angle and surface tension were considered to be 130° and 485 nM.m-1, respectively. Total porosity was determined, in duplicate, for each tablet tested.

2.2.6. Drug release study

A special device (Bettini et al., 1994) was used in order to obtain rigorous radial release. The tablets were locked between two transparent Plexiglass® discs by means of four stainless steel screws. The upper disc was carved with concentric circles (from 8 to 20 mm of diameter), so that the tablet could be placed just in the centre. The assembled devices (three replicates) were introduced into the vessels of the dissolution apparatus 2 (Aidec, Barcelona, Spain) (European Pharmacopoeia, 2007) and tested for 24 h. Distilled water (900 ml) maintained at 37±0.5° C was used as dissolution medium and tablets were tested with a paddle rotation speed of 50 r.p.m. Filtered samples (2.8 ml) were withdrawn at specified time intervals via a peristaltic pump (Hewlett-Packard 8452a diode-array UV-vis spectrophotometer, Waldbronn, Germany). Theophylline release was monitored

continuously at 272 nm on a Hewlett-Packard 8452a diode-array UV-vis spectrophotometer.

Drug release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963) (Eq. 1), Korsmeyer et al. (1983) (Eq. 2) and Peppas and Sahlin (1989) (Eq. 3) equations:

$$M_t/M_\infty = k\ t^{1/2} \qquad (1)$$

$$M_t/M_\infty = k'\ t^n \qquad (2)$$

$$M_t/M_\infty = k_d\ t^m + k_r\ t^{2m} \qquad (3)$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k, k' are kinetic constants characteristic of the drug/polymer system, t is the release time, n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987), k_d, k_r are the diffusion and relaxation rate constants, respectively, m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

The optimum values for the present parameters in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 14.0 software. The determination coefficient (r^2) and the F-ratio probability were used to test the applicability of the release models.

Release profiles were compared using similarity factor, f_2, calculated by the following equation (Eq. 4):

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right]^{-0.5} \cdot 100 \right\}$$ (4)

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles (Losi et al., 2006).

2.2.7. Fronts movement study

Fronts movement measurements were effected as described elsewhere (Ferrero et al., 2000). Methylene blue (0.004%, w/v) was added to the dissolution medium (900 ml distilled water) in order to improve the visualisation of the different fronts. The experiment was carried out, in duplicate, in the same conditions as the radial release studies (37° C and 50 r.p.m.). At defined time intervals (0, 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720 min), the devices were removed from the dissolution apparatus and photographed by means of a camera (Sony® DSC-F717). Focal distance was kept constant during all measurements. The photographs analysed by computer using Corel Draw® X3 Software (Ferrero et al., 2003). The concentric circles carved on the top of the devices were taken as reference to adjust the photograph to the rulers. The initial diameter of the tablet, as well as the position of the different fronts, were obtained by placing tangent lines to these boundaries and seeing the corresponding values in the rulers. Four measurements at the two equatorial axes were made to allow precise measurement of fronts positions versus time. The interface between the matrix and the dissolution

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medium at the beginning of the experiment (initial diameter) was referred as position 0. The inward fronts movement was represented by a negative value, while the outward movement was indicated by a positive one.

3. Results and Discussion

3.1. Apparent particle density

Table 1 shows the apparent densities of mixtures containing different proportions of HCMMA (OD or FD) and HPMC (K4M, E4M and F4M). Apparent particle density values were statistically lower (p<0.05) for HCMMA than HPMC mixtures at the 100% proportions. The packing of the HPMC polymers is more effective than in case of the HCMMA materials, due to the markedly bigger size of the poly(methyl methacrylate) –PMMA- moiety compared to the methoxyl and hydroxypropyl groups.

Table 1.- Apparent density values (n=3) from HCMMA:HPMC mixtures (100:0, 75:25, 50:50; 25:75, 0:100)

Mixture	Density (g/cm³)	Mixture	Density (g/cm³)	Mixture	Density (g/cm³)
OD-HCMMA	1.266±0.002	OD75K4M	1.296±0.002	FD75K4M	1.302±0.003
FD-HCMMA	1.278±0.004	OD75E4M	1.284±0.004	FD75E4M	1.289±0.005
HPMC K4M	1.365±0.004	OD75F4M	1.289±0.003	FD75F4M	1.295±0.001
HPMC E4M	1.327±0.003	OD50K4M	1.310±0.003	FD50K4M	1.315±0.002
HPMC F4M	1.357±0.002	OD50E4M	1.306±0.005	FD50E4M	1.297±0.005
		OD50F4M	1.299±0.001	FD50F4M	1.297±0.001
		OD25K4M	1.339±0.004	FD25K4M	1.341±0.005
		OD25E4M	1.315±0.001	FD25E4M	1.316±0.001
		OD25F4M	1.333±0.004	FD25F4M	1.327±0.004

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

The apparent density values of mixtures at different proportions and same substitution degree were between the values of mixtures with only one polymer, and these increased with decreased proportions of HCMMA (OD or FD) in the mixture.

The substitution degree factor (same proportion) affects the apparent density values. In every case, the mixtures with E4M showed the lowest density values compared to K4M and F4M mixtures, according to 100% proportions (not statistical differences were found between OD/FD50E4M and OD/FD50F4M).

3.2. Preparation of tablets

In relation with the applied pressure (Table 2), HCMMA 100% presented significant differences ($p < 0.05$) respect to HPMC 100%. The last ones showed higher capacity to accept applied energy from the tablet machine (higher plasticity), lower elastic expansion during decompresion (We) and an easier tablet elaboration (lower Wan) than HCMMA.

Table 2.- Compaction parameters (n=4) and physical tests from 100% matrices.

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD-HCMMA	369.42±5.26	18.8±0.2	5.1±0.4	78.7±1.2	499.2±1.7	4.092±0.013	80±3	1.47
FD-HCMMA	160.92±1.81	12.3±0.1	1.1±0.1	91.5±0.6	497.9±1.4	4.227±0.005	82±2	0.48
HPMC K4M	43.64±1.41	4.3±0.1	0.1±0.0	97.0±0.4	498.8±1.6	4.513±0.018	74±4	1.58
HPMC E4M	66.95±0.93	5.4±0.1	0.2±0.0	95.2±0.3	498.0±1.5	4.289±0.013	69±1	2.05
HPMC F4M	41.07±0.86	3.9±0.1	0.1±0.0	96.8±0.4	501.4±1.7	4.545±0.011	76±4	1.86

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

The existence of two polymers into the mixtures reduced the necessary pressure to obtain the tablets (Table 3), and increased the plasticity values compared to the HCMMA 100% mixtures. At identical substitution degree but different percentage, when HCMMA percentage decreases in the mixtures, the applied pressure, expansion work and apparent net work decreased. In the mixtures with OD-HCMMA, the plasticity parameters increased their values from 75:25 until 50:50 ratio, keeping then constant. However, similar values were found for mixtures with FD-HCMMA, according with the more alike values found for FD-HCMMA and HPMC 100%. We also observed that mixtures with FD-HCMMA needed less pressure, presented lower expansion work, higher facility to obtain the tablets (not statistical differences were found between OD25F4M and FD25F4M), and higher plasticity than OD-HCMMA mixtures. These results agree with the parameters obtained for 100% formulations.

At same percentage in the formulations, HPMC E4M mixtures showed higher applied pressure (Psup) necessary to obtain tablets with a breaking force of 70-80N, higher elastic expansion during decompresion (We) and higher apparent net work (Wan) values than HPMC K4M and F4M, according to 100% mixtures (not statistical differences were found between OD75E4M and OD75F4M).

We observed that the lubrication ratio values (data not showed) obtained from all formulations (0.871-0.722) did not fulfil the requirements (0.9) proposed by Bolhuis and Lerk (1973) as direct compression excipients, in contrast with the values found for

the ejection force (378-168 N) that were lower than 750 N (Bolhuis and Lerk, 1973).

Table 3.- Compaction parameters (n=4) from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)
OD75K4M	174.80±5.59	11.6±0.4	1.2±0.2	90.6±1.1
OD75E4M	229.62±2.80	12.6±0.1	2.2±0.1	85.5±0.5
OD75F4M	236.07±2.19	13.4±0.1	2.3±0.1	85.4±0.5
OD50K4M	99.65±2.25	7.7±0.1	0.5±0.1	94.4±1.2
OD50E4M	191.58±3.02	11.5±0.1	1.2±0.1	90.4±0.9
OD50F4M	107.13±1.29	8.1±0.1	0.5±0.0	93.9±0.3
OD25K4M	59.85±1.36	5.4±0.1	0.4±0.0	93.2±0.7
OD25E4M	96.24±1.69	6.8±0.1	0.5±0.1	93.5±1.0
OD25F4M	59.22±1.67	5.1±0.1	0.3±0.0	94.8±0.3

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)
FD75K4M	109.40±0.52	9.3±0.1	0.7±0.0	93.4±0.3
FD75E4M	141.99±1.75	11.0±0.1	0.7±0.2	93.8±1.5
FD75F4M	114.29±2.37	9.8±0.5	0.7±0.0	93.0±0.5
FD50K4M	83.25±0.32	7.5±0.0	0.3±0.0	96.4±0.3
FD50E4M	125.11±1.33	9.4±0.1	0.8±0.1	92.2±1.0
FD50F4M	86.12±0.36	7.4±0.1	0.4±0.1	94.3±1.4
FD25K4M	48.93±0.66	4.8±0.1	0.1±0.0	97.0±0.4
FD25E4M	80.16±1.64	6.2±0.5	0.4±0.0	94.6±0.4
FD25F4M	57.74±0.34	5.4±0.1	0.2±0.0	96.7±0.4

*K4M mixtures were published in Escudero et al., 2008

3.3. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different mixtures are compiled in Tables 2 and 4.

Table 4.- Physical tests from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD75K4M	500.0±0.8	4.153±0.012	75±2	1.17
OD75E4M	500.4±0.5	4.006±0.004	77±2	1.28
OD75F4M	499.9±1.4	4.117±0.009	78±2	1.43
OD50K4M	500.6±1.5	4.312±0.011	75±2	1.82
OD50E4M	499.3±1.3	4.040±0.009	81±3	0.97
OD50F4M	499.4±1.3	4.212±0.002	79±3	1.62
OD25K4M	502.2±1.4	4.383±0.011	81±3	1.34
OD25E4M	500.2±1.4	4.141±0.008	78±4	1.60
OD25F4M	500.1±2.0	4.397±0.018	79±2	1.71

Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)
FD75K4M	498.0±1.0	4.358±0.009	74±2	1.81
FD75E4M	500.3±1.2	4.207±0.011	77±2	1.59
FD75F4M	499.6±1.0	4.350±0.006	79±1	1.67
FD50K4M	500.7±1.2	4.475±0.007	78±2	3.35
FD50E4M	498.6±1.0	4.232±0.006	77±3	1.72
FD50F4M	499.6±1.0	4.496±0.009	72±3	2.11
FD25K4M	499.0±2.0	4.555±0.012	74±3	1.69
FD25E4M	501.4±2.0	4.226±0.005	79±4	1.45
FD25F4M	500.5±1.2	4.513±0.007	72±3	1.66

*K4M mixtures were published in Escudero et al., 2008

All tablets fulfilled the guidelines specified in European Pharmacopoeia (2007) related to weight uniformity test. The tablet thickness varied between 4 and 4.6 mm. All FD-HCMMA mixtures obtained a higher value than OD-HCMMA mixtures. These results

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might be related to a more porous structure in FD matrices. The breaking force test (European Pharmacopoeia, 2007) confirmed the values of 70-80 N for all tablets. Only FD-HCMMA 100% and OD50E4M presented friability values lower than 1% (European Pharmacopoeia, 2007). The high values observed for this parameter make us think about the need of increase the breaking force in a future. With exception of FD25E4M and FD25F4M, the FD mixtures presented higher friability values than OD mixtures.

3.4. Mercury porosimetry measurements

In order to evaluate the microstructure of the matrices, the pore size distributions were measured by mercury intrusion-extrusion porosimetry. HCMMA 100% presented lower porosity than K4M and F4M 100%. However, HPMC E4M only showed lower porosity than FD-HCMMA (Table 5).

Table 5.- Porosity values (n=2) from HCMMA:HPMC mixtures (100:0, 75:25, 50:50; 25:75, 0:100).

Mixture	Porosity (%)	Mixture	Porosity (%)	Mixture	Porosity (%)
OD-HCMMA	17.8 ±1.4	OD75K4M	22.0 ±1.8	FD75K4M	26.2 ±0.4
FD-HCMMA	23.6 ±0.6	OD75E4M	25.3 ±0.3	FD75E4M	24.9 ±0.4
HPMC K4M	31.4 ±2.7	OD75F4M	18.1±1.0	FD75F4M	22.2 ±4.7
HPMC E4M	21.4 ±0.3	OD50K4M	27.2 ±0.2	FD50K4M	34.0 ±7.4
HPMC F4M	27.5 ±0.1	OD50E4M	24.7 ±0.1	FD50E4M	24.2 ±0.2
		OD50F4M	22.2 ±4.7	FD50F4M	29.1 ±0.1
		OD25K4M	28.5 ±2.3	FD25K4M	32.7 ±0.1
		OD25E4M	23.5 ±0.1	FD25E4M	25.9 ±0.1
		OD25F4M	27.6 ±0.4	FD25F4M	32.2 ±0.4

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

When two polymers were in the mixture (Table 5), the porosity values were higher than those corresponding to HCMMA 100% (not statistical differences were found between FD75F4M than FD-HCMMA 100%). If we compare OD with FD mixtures, in general, the formers showed lower porosity values, as happened in HCMMA 100% tablets.

When we compared HCMMA:HPMC ratios for the same substitution degree, the porosity only increased to K4M and F4M mixtures as HCMMA percentage decreased. To HPMC E4M mixtures, porosity values decreased when OD-HCMMA percentage decreased, keeping constant the porosity values with FD-HCMMA. The rough fibrous particles of F4M and K4M that constitute the compacts and the different particle size of E4M could explain the differences on porosity parameter.

Besides, respect to substitution degree (same HCMMA:HPMC ratio), the porosity did not present a clear tendency.

According to IUPAC definitions, as the pore diameter values were accomplished between 20 and 500 Å, all mixtures possessed mesopores, except to HPMC K4M 100%, OD/FD25K4M and OD/FD25F4M, that presented macropores (>500 Å).

3.5. Drug release study

Figure 1 illustrates the drug release profiles from HCMMA and HPMC 100% matrices.
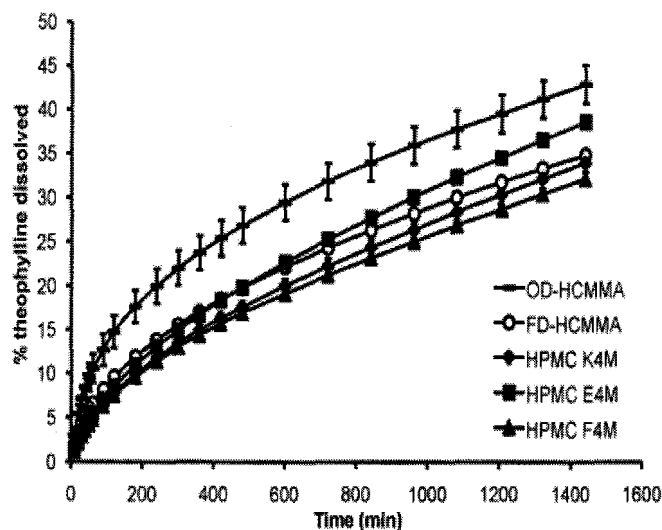
Figure 1. Release profiles of anhydrous theophylline (over 24 h) from 100% tablets. The bars show the standard deviation.

Higher percentages of drug release were observed for OD-HCMMA matrices than FD tablets (f_2=60.3). HPMC E4M showed a release profile between OD and FD-HCMMA, whereas HPMC K4M and HPMC F4M tablets displayed the lowest release (f_2=93.3).

Figure 2 illustrates the release profiles from the matrices prepared with different mixtures of OD-HCMMA and FD-HCMMA with HPMC (K4M, E4M, F4M) in three defined proportions HCMMA:HPMC (75:25, 50:50, 25:75). All mixtures presented a percentage of theophylline release between 47% and 32% at 1440 minutes. As the content of HCMMA in the mixtures was reduced, the ability to control drug release increased, mainly from 75:25 to 50:50 ratios, being the liberation profiles more similars to HPMC

100%. Mitchell et al. (1993) demonstrated that only low levels of cellulose ethers in a matrix showed interesting differences between different substitution degrees. The two grades of HPMC (E4M and K4M) behaved similarly and the major differences were with F4M, that always presented the lowest theophylline release, in agreement with its lowest hidrophylicity. We could observe that the drying methods employed have influence over the drug release in E4M and K4M. Thus, we found again important differences at higher proportions of HCMMA, showing the highest release OD-HCMMA with E4M and K4M. Not important differences were found to f_2 in the case of F4M related to either proportion or drying method used ($f_2>86$).

Release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963), Korsmeyer et al. (1983), and Peppas and Sahlin (1989) equations. The main parameters are listed in Table 6 for 100% mixtures, and in Tables 7 and 8 for mixtures of OD-HCMMA:HPMC and FD-HCMMA:HPMC, respectively. As the matrices studied presented an aspect ratio (diameter/thickness) around 3, the m value was 0.44 (Peppas and Sahlin, 1989). The determination coefficient (r^2) and the F-ratio probability were used to test the applicability of the release models.
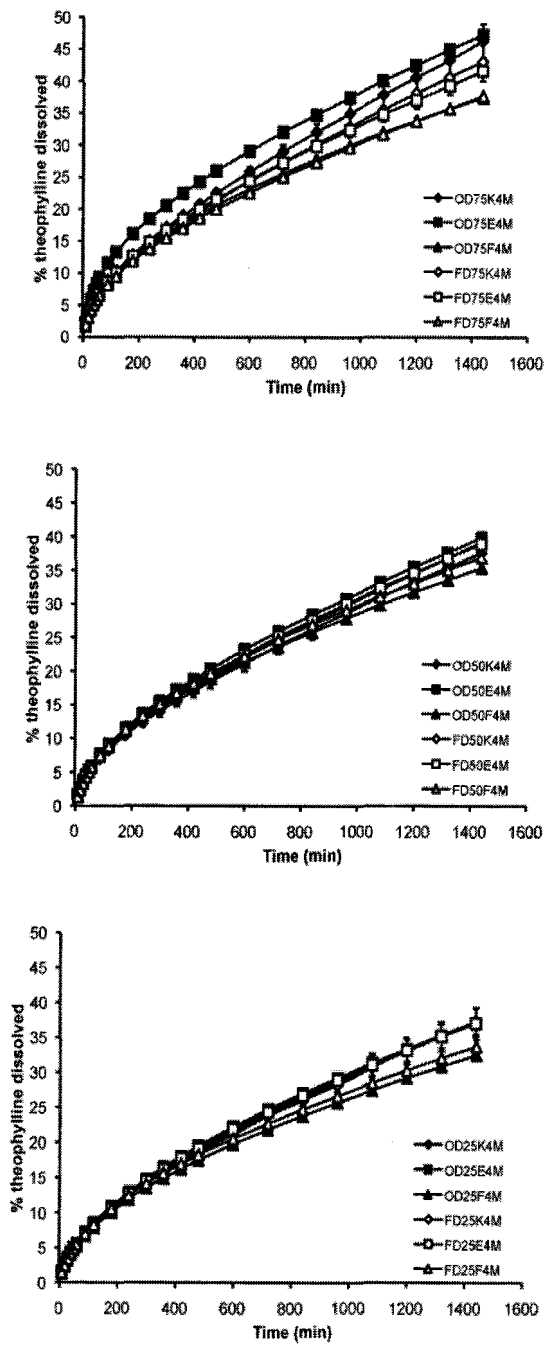
Figure 2. Release profiles of anhydrous theophylline (over 24 h) from mixtures of HPMC with HCMMA. The bars show the standard deviation.

Table 6.- Mathematical modelling and drug release kinetics from 100% matrices.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k $(min^{-1/2})$	r^2	n	k' (min^{-n})	r^2	k_d $(min^{-0.44})$	k_r $(min^{-0.88})$	r^2
OD-HCMMA	0.011	0.9950 (F=4011)	0.49	0.013	0.9869 (F=1500)	0.021	0.00011	1.0000 (F=24393)
FD-HCMMA	0.009	0.9999 (F=273578)	0.55	0.007	0.9957 (F=4614)	0.013	0.00008	1.0000 (F=457998)
HPMC K4M	0.009	0.9982 (F=10857)	0.61	0.004	0.9990 (F=20588)	0.010	0.00020	1.0000 (F=292743)
HPMC E4M	0.011	0.9979 (F=9495)	0.64	0.004	0.9986 (F=14334)	0.011	0.00023	1.0000 (F=323812)
HPMC F4M	0.009	0.9991 (F=21947)	0.63	0.003	0.9953 (F=4215)	0.010	0.00015	0.9999 (F=118900)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p=0.000).
*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

Although the matrices with two polymers (Tables 7 and 8) had a good fit to Higuchi equation, indicative of a diffusion mechanism, as the n values from Korsmeyer equation were higher than 0.50, and the values of k_r in Peppas and Sahlin equation were high, a combination of diffusion and erosion release mechanism were found. Their k_d values remained more or less similar to HPMC 100%, apart from OD75E4M and F4M mixtures, lightly increased k_d values. However, the most important changes were found in k_r values. In this sense, all mixtures with F4M did not modify this parameter respect to F4M 100%, in concordance with the lowest theophylline release. Likewise, all mixtures with E4M presented similar k_r values to E4M 100% proportion, except to OD75E4M, that showed the lowest k_r value, but in contrast, the highest k_d value that could justify its higher theophylline release. All mixtures with K4M showed the highest k_r values, which decreased when HCMMA proportion decreased, in concordance with the compression properties.

Table 7.- Mathematical modelling and drug release kinetics from OD HCMMA-HPMC mixtures.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k $(min^{-1/2})$	r^2	n (min^{-n})	k'	r^2	k_d $(min^{-0.44})$	k_r $(min^{-0.88})$	r^2
OD75K4M	0.012	0.9937 (F=3147)	0.60	0.006	0.9962 (F=5285)	0.010	0.00038	0.9997 (F=27002)
OD75E4M	0.012	0.9990 (F=19068)	0.56	0.009	0.9879 (F=1635)	0.016	0.00014	0.9993 (F=13249)
OD75F4M	0.010	0.9998 (F=92949)	0.59	0.006	0.9949 (F=3732)	0.013	0.00013	1.0000 (F=495932)
OD50K4M	0.010	0.9948 (F=3834)	0.62	0.004	0.9979 (F=9185)	0.008	0.00030	0.9998 (F=59250)
OD50E4M	0.011	0.9974 (F=7757)	0.62	0.004	0.9982 (F=11287)	0.011	0.00025	1.0000 (F=226444)
OD50F4M	0.010	0.9992 (F=24495)	0.59	0.005	0.9971 (F=6925)	0.011	0.00016	0.9999 (F=130262)
OD25K4M	0.010	0.9962 (F=6305)	0.61	0.004	0.9984 (F=12454)	0.010	0.00025	0.9999 (F=97685)
OD25E4M	0.010	0.9986 (F=14351)	0.61	0.004	0.9987 (F=14793)	0.011	0.00020	1.0000 (F=286940)
OD25F4M	0.009	0.9996 (F=45568)	0.61	0.004	0.9956 (F=4469)	0.011	0.00013	1.0000 (F=291821)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p=0.000).
*K4M mixtures were published in Escudero et al., 2008

Table 8.- Mathematical modelling and drug release kinetics from FD HCMMA-HPMC mixtures.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k $(min^{-1/2})$	r^2	n (min^{-n})	k'	r^2	k_d $(min^{-0.44})$	k_r $(min^{-0.88})$	r^2
FD75K4M	0.012	0.9946 (F=3660)	0.60	0.005	0.9986 (F=14437)	0.009	0.00034	0.9998 (F=37686)
FD75E4M	0.011	0.9981 (F=10556)	0.60	0.005	0.9968 (F=6235)	0.012	0.00023	0.9999 (F=65065)
FD75F4M	0.010	0.9986 (F=14430)	0.57	0.006	0.9971 (F=6875)	0.011	0.00019	0.9999 (F=73196)
FD50K4M	0.011	0.9950 (F=3956)	0.64	0.004	0.9971 (F=6786)	0.009	0.00030	0.9998 (F=55770)
FD50E4M	0.011	0.9968 (F=6313)	0.63	0.004	0.9968 (F=6190)	0.010	0.00026	0.9999 (F=143278)
FD50F4M	0.010	0.9995 (F=36444)	0.63	0.004	0.9934 (F=3020)	0.012	0.00015	0.9999 (F=146442)
FD25K4M	0.010	0.9959 (F=4802)	0.61	0.004	0.9990 (F=20669)	0.009	0.00027	0.9997 (F=33262)
FD25E4M	0.010	0.9985 (F=12968)	0.64	0.004	0.9965 (F=5710)	0.011	0.00021	1.0000 (F=632458)
FD25F4M	0.009	0.9996 (F=53599)	0.60	0.004	0.9961 (F=5105)	0.011	0.00013	0.9999 (F=172171)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p=0.000).
*K4M mixtures were published in Escudero et al., 2008

3.6. Fronts movement study

Fronts movement kinetics were evaluated (Ferrero et al., 2003) in order to obtain useful information for a better understanding of the drug release mechanism from different matrices. In a previous paper (Escudero et al., 2008) we explained more extensively the different behaviour of HCMMA matrices, according to the porosity and tortuosity values of the tablets. According to Ferrero et al. (2000) for inert matrices (HCMMA 100%), three fronts could be clearly distinguished from the centre to the periphery of the matrix: water uptake front (between dry-partial wet polymer), complete wetting front (distinguishes a partial hydrated zone from a complete wet one) and erosion front (between the external surface of the matrix and the dissolution medium).

For swellable matrix tablets, as HPMC 100%, Colombo et al. (1995) proposed three fronts: swelling front (between the still glassy polymer and its rubbery gel state), diffusion front (between the still undissolved (solid) drug and the dissolved drug in the gel layer) and erosion front (between the matrix and the dissolution medium). In Figure 3 no important differences can be seen in the erosion and swelling fronts for the three swellable matrices tested. Similarly, Ford (1999) did not found differences in water uptake of HPMC K4M, E4M and F4M. However, the diffusion front was different for HPMC K4M. This is due to the higher hydrophilic character of K4M that leads less available water to dissolve the theophylline.
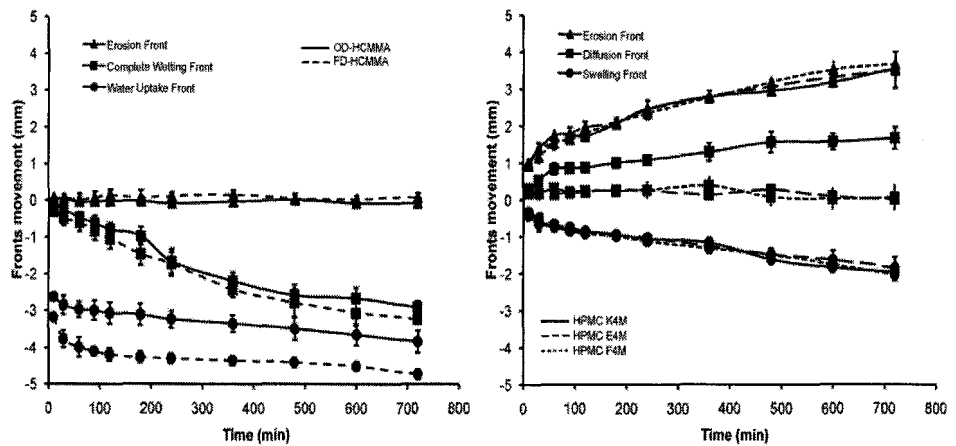
Figure 3. Fronts movement (over 12 h) from 100% matrices.

For the different mixtures HCMMA-HPMC, it is possible to see fronts movement profiles similar to swellable matrices (Figure 4), with no changes in swelling fronts compared to HPMC 100% matrices. On the other hand, erosion fronts increased for all mixtures when the proportion of HCMMA decreased. The highest differences were observed for the 75:25 proportion related to other ratios. About the substitution degree, the lowest advance of erosion front in E4M mixtures was in agreement with its highest release.

Again only K4M mixtures showed a diffusion front that moved outwards, whereas E4M and F4M diffusion front moved lightly inwards, that implies that the formation of clear gel was quicker in the latters than in K4M mixtures. In addition, it is possible to see small differences between OD and FD-K4M mixtures.
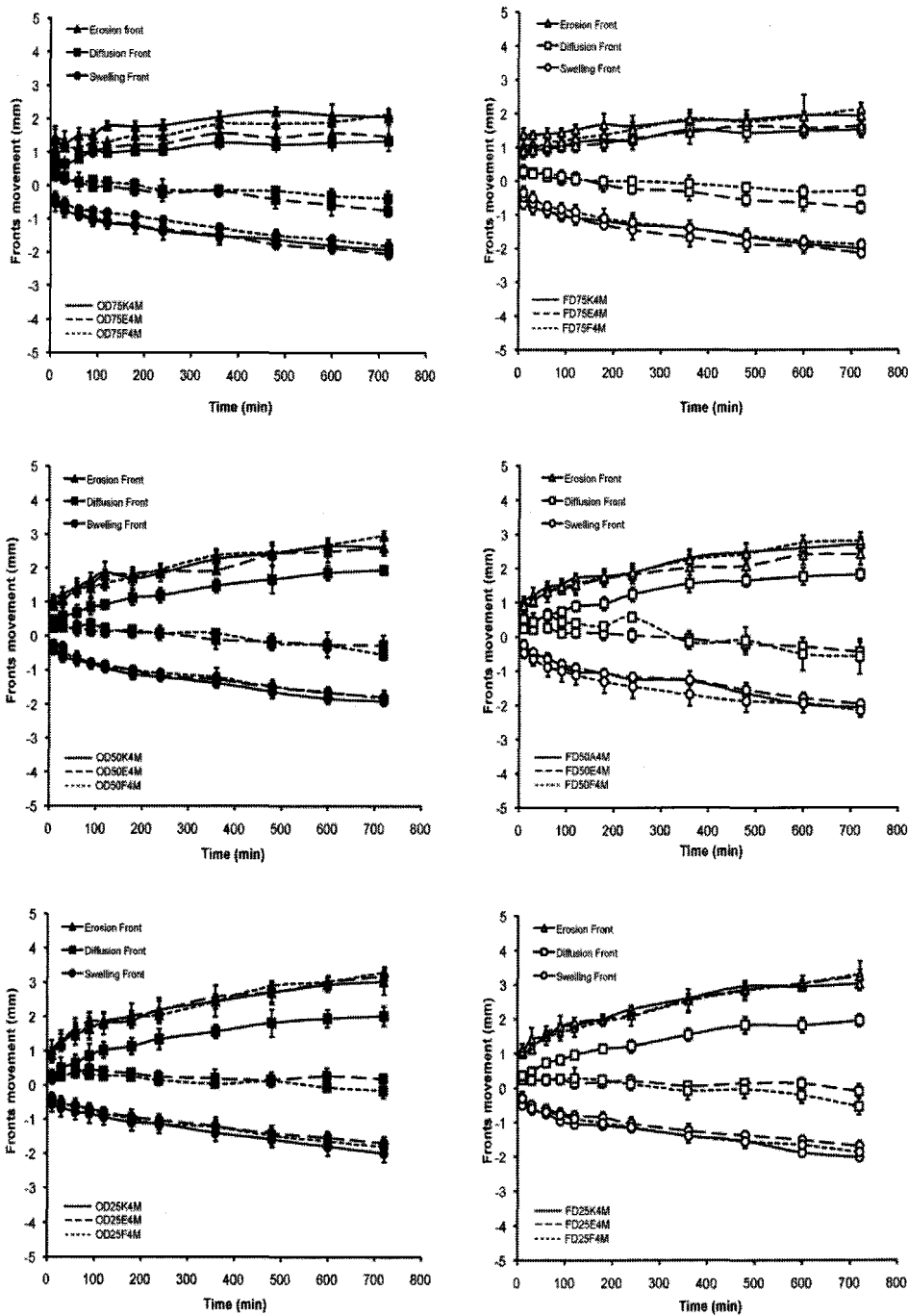
Figure 4. Fronts movement (over 12 h) from HCMMA-HPMC mixtures.

Lotfipour et al. (2004) explained the effect of the fillers on the release rate of atenolol, because they reduced the tortuosity of the diffusion path of the drug. We calculated the apparent diffusion coefficient (D') (Table 9), obtained from the Higuchi rate constant. D' is expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusion coefficient of the drug in the dissolution medium. In HCMMA:HPMC mixtures, when HPMC percentage decreased, tortuosity decreased, in agreement with Khurahashi et al. (1996). Although there was not a clear tendency in substitution degree, in general F4M mixtures had the higher tortuosity according with the lowest theophylline release.

Table 9.- Apparent diffusion coefficient (D') for all mixtures.

Mixture	D' (cm²/min)	Mixture	D' (cm²/min)	Mixture	D' (cm²/min)
OD-HCMMA	7.24×10^{-4}	OD75K4M	6.87×10^{-4}	FD75K4M	5.51×10^{-4}
FD-HCMMA	3.54×10^{-4}	OD75E4M	6.20×10^{-4}	FD75E4M	5.04×10^{-4}
HPMC K4M	2.50×10^{-4}	OD75F4M	5.85×10^{-4}	FD75F4M	4.52×10^{-4}
HPMC E4M	5.40×10^{-4}	OD50K4M	3.72×10^{-4}	FD50K4M	3.48×10^{-4}
HPMC F4M	2.87×10^{-4}	OD50E4M	5.29×10^{-4}	FD50E4M	5.16×10^{-4}
		OD50F4M	4.67×10^{-4}	FD50F4M	3.35×10^{-4}
		OD25K4M	3.50×10^{-4}	FD25K4M	2.94×10^{-4}
		OD25E4M	4.48×10^{-4}	FD25E4M	3.99×10^{-4}
		OD25F4M	2.92×10^{-4}	FD25F4M	2.44×10^{-4}

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

The gel layer thickness (Colombo et al., 1995) is defined as the difference between erosion and swelling front positions. The gel layer thickness was similar to K4M, F4M and E4M 100% mixtures. Besides, it rose when decreased the proportion of HCMMA in the mixtures. In all cases, E4M mixtures showed the lowest values. In addition, it is not possible to see differences between OD and FD mixtures.

4. Conclusions

Presence of HCMMA did not provide advantages in terms of compactions performance in the mixtures. However, mixtures with FD-HCMMA showed better compression properties than OD-HCMMA mixtures. The drying method used for HCMMA only affected the theophylline release at high concentration of these polymers in the mixtures. Diffusion and erosion mechanisms, joined to tortuosity on F4M mixtures leaded to a best control of theophylline release. The higher hydrophilicity of K4M explains the different diffusion front movement observed compared to the other HPMCs.

The modulation of theophylline monoaxial release combining swellable and inert polymers is only obtained with a mixture of HCMMA:HPMC 75:25, where HCMMA plays more important role than the viscosity (Escudero et al., 2008) or different degrees of methoxy/hydroxypropyl substitution of HPMC. It is true that similar theophylline release profiles are possible to see from mixtures HCMMA/HPMC of different viscosity grades (HPMC K4M, K15M and K100M) (Escudero et al., 2008) in relation with HCMMA/HPMC of different substitution type (HPMC K4M, E4M and F4M) justify by the experimental design. However, it is interesting to mention that only the mixture OD-HCMMA/HPMC E4M showed a high diffusion constant value (k_d) from Peppas equation to the proportion 75:25. Also, important differences are found in relation with relaxation rate constant values (k_r). So, the mixtures with E4M and F4M exhibited the lowest k_r values, which indicate that HCMMA destabilize less the gel structure of these

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two polymers than to K HPMC series (Escudero et al., 2008). Besides, the formation of a more clear gel in E4M and F4M mixtures was made evident by the fronts movement results. However, at 75:25 proportion and from a technological point of view, K HPMC series (Escudero et al., 2008) show better compression behavior than E4M and F4M. Therefore, a lower cost to obtain the modulation could be obtained using K HPMC series than HPMC E4M or F4M. Finally, it would be interesting to test another type of cellulose like HPC or MC which could modulate better the theophylline release with the new HCMMA copolymer.

5. Acknowledgements

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CAPITULO III

Tipo de Substituyente

Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers. III. Effect of polymer substitution type.

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Abstract

Theophylline monoaxial release from cellulose derivatives with different substitution type (HPMC K4M, HPC H, MC A4M) matrix tablets has been modulated by the introduction of a new inert polymeric excipient, hydroxypropylcellulose-methyl methacrylate (HCMMA), at different proportions (75, 50, 25%). HCMMA was dried either in a vacuum oven (OD-HCMMA) or freeze-dried (FD-HCMMA). MC A4M and its mixtures presented the best compaction properties, especially mixed with FD-HCMMA, according to 100% mixtures. Only high levels of HCMMA (75%) in the matrices showed interesting differences to drug release modulation. Also, at this proportion (75:25), the HPC H mixtures presented the highest differences in relation with OD or FD HCMMA respect to the others cellulose polymers. HPMC K4M and HPC H mixtures showed a combination of diffusion and erosion release mechanisms. However, MC A4M mixtures presented only diffusion mechanism, due to the absence of hydroxypropyl substituents, and according with its highest diffusion rate constant values. Only HPMC K4M mixtures presented a diffusion front that moves outwards while HPC H and MC A4M moves inwards. The modulation of theophylline monoaxial release was obtained using a high percentage of HCMMA, and the use of two cellulosic ethers, one of them with just one type of substituent (MC A4M or HPC H) and the other with two types of substituent (HPMC K4M), or changing the HCMMA copolymer (OD or FD) in the 75:25 mixture with HPC.

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1. Introduction

Cellulose derivatives are widely used to control the release of drugs from matrix formulations. However, according to the different characteristics of the polymer used, the drug delivery systems exhibit different release kinetics and swelling behaviour (Bettini et al., 1994). Also, the drug release from cellulose-tablets can be modified by the addition of other hydrophilic polymers. So Pérez-Marcos et al. (1994) indicated that combining propanolol hydrochloride with carpobol® 974 and HPMC K4M, these ingredients are capable of interacting to some extent with each other to control drug release; besides, changing the external environment further modifies the release processes it is possible to be obtained (Pérez-Marcos et al., 1996).

Bonferoni et al. (1994) demonstrated that salbutamol sulphate and chlorpheniramine maleate release profiles can be modified by the mixture of λ-carrageenan and HPMC K4M due to the combination of different release mechanism (Bonferoni et al., 1998). Nerurkar et al. (2005) indicated that lambda and iota carrageenan can be used in combination with cellulose ethers for the formulation of controlled-release ibuprofen tablets. Traconis et al. (1997) and Conti et al. (2007) studied the effect of addition of CMCNa to HPMC in the controlled release of metronidazole and diltiazem HCl, respectively. Juárez et al. (2001) related that the addition of CMC to HPMC matrices to get zero-order release kinetics could only be obtained by restricting the dissolution process. Also, the polymer's degree of substitution, position of the

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hydroxyl groups and viscosity grade contributes to the strength of interpolymer interactions non-ionic and ionic polymers.

The dissolution profiles obtained for atenolol tablets made with HPMC K100LV/K100M mixtures showed that the use of these polymers permits an efficient control of the release (Vázquez et al., 1996). It has been shown that the methacrylate acid polymer (Eudragit® L100-55) can significantly enhance the release of weakly basic drugs (papaverine HCl or propanolol HCl) from HPMC based hydrophilic matrices (Takka et al, 2001; Tatavarti and Hoag, 2006; Tatavarti et al, 2004).

Also, the drug release from HPMC matrix tablets has been modified for various purposes through the addition of anionic surfactants, ion-exchange resins (Feely and Davis, 1988; Sriwongjanya and Bodmeier, 1998; Takka et al, 2001), poly(ethyloxazoline) (Shenouda et al., 1990) and hydrogenated vegetable oil (Kiortsis et al., 2005).

Recently, Escudero et al. (2008, 2009) demonstrate the possibility of modulation of theophylline release by mixing HPMC of different viscosity grades or HPMC with different degrees of substitution (hydrophilic matrices) and a new generation of copolymers (Castellano et al., 1997; Ferrero et al., 2003; Ferrero and Jiménez-Castellanos, 2002), introduced as excipients for oral controlled released matrices (inert matrices), combining the influence of swelling rate from hydrophilic matrices as well as the porosity, tortuosity and water uptake capacity from inert matrices.

Following these principles, and since cellulose polymers of different substitution types possess different degrees of hydrophilic and hydrophobic substitution, and it is thought that

these substituents influence the way water attaches itself to the polymer (McCrystal et al., 1999) and, subsequently the formation of the barrier gel layer and water diffusion that determine the rate and mechanism of drug release (Rajabi-Siahboomi et al., 1996), the aim if this paper is to evaluate the influence of different mixtures on technological characteristics and drug release from matrix tablets containing different cellulose ether polymers (hydroxypropyl cellulose -HPC-, hydroxypropylmethyl cellulose -HPMC- and methylcellulose -MC-) of same viscosity grade, as hydrophilic polymer, hydroxypropylcellulose-methyl methacrylate (HCMMA), as inert polymer and theophylline as model drug. Because in a previous paper (Escudero et al, 2008) we discuss the effect that drying method produced on the different technological characteristics and drug release from matrices tablets containing HCMMA, in this paper the results will be focused on the influence of: a) polymer type; b) ratio of two polymers in the matrix tablets; c) substitution type on cellulose derivative.

2. Materials and methods

2.1. Materials

Inert polymer: the copolymer (batch SS02) synthesised by free radical copolymerisation of methyl methacrylate (MMA) and hydroxypropylcellulose (HC) was select as inert polymer. The product (HCMMA) was dried either in a vacuum oven -OD copolymers- or freeze-dried -FD copolymers- (Castellano et al.,

1997). The OD product was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

Commercial polymers: Hydroxypropylmethylcellulose (Methocel® K4M -4000 cP-, with 19-24 % methoxyl groups and 7-12 % hydroxypropyl groups, Premium EP., Colorcon, England, batch KI10012N02), Methyl cellulose (MC A4M -4000 cP- with 27.5-31.5 % methoxyl groups, Premium EP, Colorcon, England, batch OC11012 N02), and Hydroxypropylcellulose (HPC H-1000-4000 cP- with 53.4-77.5 % hydroxypropyl groups, Nisso®, Isiza, Spain, batch NAE-3601) were selected as swellable polymers.

Others components: anhydrous theophylline (Theophylline BP 80, Roig Farma, Barcelona, Spain, batch 0212030) was chosen as model drug. Stearic acid (Estearina® L2SM, Pulcra, Barcelona, Spain, batch 0055003) was selected as lubricant.

Before use, the materials were stored at constant relative humidity (40%) and room temperature (20° C).

2.2. Methods

2.2.1. Mixtures preparation

Anhydrous theophylline (24%, w/w) and mixtures (75%, w/w) of inert and swellable polymers in different proportions (100:0, 75:25, 50:50; 25:75 and 0:100 HCMMA:HPMC) were mixed for 15 min using a double cone mixer (Retsch, Haan, Germany) at 50 r.p.m. After addition of stearic acid (1%, w/w), the mixing procedure was continued for a further 5 min. A total of 23 mixtures were prepared. The nomenclature used for these

HCMMA:swelling polymer mixtures was: the first two letters corresponding to the inert polymer (OD or FD), the following number is the proportion of inert polymer in the mixture (75, 50, 25%), and the background is the variety of hydrophilic polymer (K4M, A4M, HPC).

2.2.2. Apparent particle density

The apparent particle densities of the mixtures were determined, in triplicate, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2007).

2.2.3. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz et al., 1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compaction characteristics of mixtures, a quantity of powder (500 mg) was preweighed and manually fed into the die (12 mm) and flat-faced compacts were prepared to have a constant breaking force of 70-80 N. Typical compaction parameters (maximum upper pressure –Psup-, apparent net work –Wan-, expansion work –We-, plasticity -Pl-) describe by Doelker (Doelker, 1978) and Järvinen and Juslin, (1981) were collected from four tableting cycles.

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Also, in order to produce a sufficient number of tablets for physical testing, the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70-80 N breaking force).

The values obtained from the different mixtures were statistically analysed by one-way analysis of variance (ANOVA) using SPSS® 14.0 software. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted is significant when $p < 0.05$.

2.2.4. Standard physical test of tablets

The physical testing of tablets was performed after relaxation period of at least 24 h.

The tablet average weight and the standard were obtained from 20 individually weighed (Sartorius CP224S, Gottingen, Germany) tablets according to European Pharmacopoeia (2007).

The thickness of 10 tablets was measured individually placing them in and parallel to the face of an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The breaking force (European Pharmacopoeia, 2007) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability (European Pharmacopoeia, 2007) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 r.p.m. in an Erweka TA (Heusenstamm, Germany) friability tester.

2.2.5. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3 penetrometer. An adequate number of tablets per formulation tested was used according to obtain a stem volume between 20-90% of the penetrometer capacity. Working pressures covered the range 0.1-60000 p.s.i. and the mercury solid contact angle and surface tension were considered to be 130° and 485 nM.m^{-1}, respectively. Total porosity was determined, in duplicate, for each tablet tested.

2.2.6. Drug release study

A special device (Bettini et al., 1994) was used in order to obtain rigorous radial release. The tablets were locked between two transparent Plexiglass® discs by means of four stainless steel screws. The upper disc was carved with concentric circles (from 8 to 20 mm of diameter), so that the tablet could be placed just in the centre. The assembled devices (three replicates) were introduced into the vessels of the dissolution apparatus 2 (Aidec, Barcelona, Spain) (European Pharmacopoeia, 2007) and tested for 24 h. Distilled water (900 ml) maintained at 37±0.5° C was used as dissolution medium and tablets were tested with a paddle rotation speed of 50 r.p.m. Filtered samples (2.8 ml) were withdrawn at specified time intervals via a peristaltic pump (Hewlett-Packard 8452a diode-array UV-vis spectrophotometer, Waldbronn, Germany). Theophylline release was monitored

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continuously at 272 nm on a Hewlett-Packard 8452a diode-array UV-vis spectrophotometer.

Drug release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963) (1), Korsmeyer et al. (1983) (2) and Peppas and Sahlin (1989) (3) equation:

$$M_t/M_\infty = k \, t^{1/2} \qquad (1)$$

$$M_t/M_\infty = k' \, t^n \qquad (2)$$

$$M_t/M_\infty = k_d \, t^m + k_r \, t^{2m} \qquad (3)$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k, k' are kinetic constants characteristic of the drug/polymer system, t is the release time, n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987), k_d, k_r are the diffusion and relaxation rate constants, respectively, m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 14.0 software. The corrected determination coefficient (r^2) was used to test the applicability of the release models.

Release profiles were compared using similarity factor, f_2, calculated by the following equation:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}$$

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles (Losi et al., 2006).

2.2.7. Fronts movement study

Fronts movement measurements were effected as described elsewhere (Ferrero et al., 2000). Methylene blue (0.004%, w/v) was added to the dissolution medium (900 ml distilled water) in order to improve the visualisation of the different fronts. The experiment was carried out, in duplicate, in the same conditions as the radial release studies (37° C and 50 r.p.m.). At defined time intervals (0, 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720 min), the devices were removed from the dissolution apparatus and photographed by means of a camera (Sony® DSC-F717). Focal distance was kept constant during all measurements. The photographs analysed by computer using Corel Draw® X3 Software (Ferrero et al., 2003). The concentric circles carved on the top of the devices were taken as reference to adjust the photograph to the rulers. The initial diameter of the tablet, as well as the position of the different fronts, were obtained by placing tangent lines to these boundaries and seeing the corresponding values in the rulers. Four measurements at the two equatorial axes were made to allow precise measurement of fronts positions versus time. The interface between the matrix and the dissolution medium at the beginning of the experiment (initial diameter) was referred as position 0. The inward fronts movement was

represented by a negative value, while the outward movement was indicated by a positive one.

3. Results and discussion

3.1. Apparent density

Table 1 shows the apparent densities of mixtures containing different proportions of HCMMA (OD or FD) and HPMC K4M, MC A4M or HPC H. Only OD-HCMMA did not show statistical differences with HPC ($p>0.05$) at 100% ratio, because of they showed similar particle size (154 μm and 168 μm, respectively).

The apparent density values of mixtures at different proportions and similar substitution type were comprised, in general, between the values encountered for 100% formulations (not statistical differences were found between OD-HCMMA 100%, OD25HPC and OD75HPC; FD-HCMMA 100% and FD75HPC). In general, the densities increase when the proportion of HCMMA (OD or FD) in the mixture decreased, except to the FD-HCMMA and HPC H mixtures (not statistical differences were found). Perhaps, a more similar particle size distribution (skewness coefficient 0.46 and 0.66 to FD-HCMMA and HPC H, respectively), and the lack of particle sizes lower than 54 μm for both polymers, could explain these results.

Table 1.- Apparent particle density values (n=3) from HCMMA:swelling polymer mixtures (100:0, 75:25, 50:50; 25:75, 0:100).

Mixture	Density (g/cm³)	Mixture	Density (g/cm³)	Mixture	Density (g/cm³)
OD-HCMMA	1.266±0.002	OD75K4M	1.296±0.002	FD75K4M	1.302±0.003
FD-HCMMA	1.278±0.004	OD75A4M	1.303±0.005	FD75A4M	1.302±0.002
HPMC K4M	1.365±0.004	OD75HPC	1.271±0.004	FD75HPC	1.281±0.001
MC A4M	1.360±0.002	OD50K4M	1.310±0.003	FD50K4M	1.315±0.002
HPC H	1.259±0.001	OD50A4M	1.306±0.002	FD50A4M	1.305±0.001
		OD50HPC	1.261±0.003	FD50HPC	1.268±0.001
		OD25K4M	1.339±0.004	FD25K4M	1.341±0.005
		OD25A4M	1.332±0.002	FD25A4M	1.336±0.001
		OD25HPC	1.271±0.004	FD25HPC	1.278±0.001

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

Finally, the substitution type factor affected statistically (p<0.05) the apparent density values between HPC H and HPMC K4M or MC A4M, displaying lower density values than the other mixtures at the same proportion, according to the 100% ratio.

3.2. Preparation of tablets

Typical compaction parameters are summarised in Table 2. In relation with the applied pressure, HCMMA 100% formulations presented significant differences (p<0.05) respect to all cellulose based. In agreement with others authors (Doelker, 1987; Nerurkar et al., 2005; Vueba et al., 2004), the last ones can be easily compressed to form sustained release swellable matrices. Also, theophylline is a plastic drug (Picker, 1999; Vachon and Chulia, 1999). So, these cellulose derivatives, showed higher capacity to accept applied energy from the tablet machine (higher plasticity), lower elastic expansion during decompresion (We) and hence, an easier tablet elaboration (lower Wan) than with HCMMA.

Table 2.- Compaction parameters (n=4) and physical tests from 100% matrices.

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD-HCMMA	369.42±5.26	18.8±0.2	5.1±0.4	78.7±1.2	499.2±1.7	4.092±0.013	80±3	1.47
FD-HCMMA	160.92±1.81	12.3±0.1	1.1±0.1	91.5±0.6	497.9±1.4	4.227±0.005	82±2	0.48
HPMC K4M	43.64±1.41	4.3±0.1	0.1±0.0	97.0±0.4	498.8±1.6	4.513±0.018	74±4	1.58
MC A4M	24.36±0.62	2.9±0.1	0.0±0.0	99.0±0.1	501.3± 1.8	4.815±0.012	80±2	1.23
HPC	37.00±0.73	3.6±0.1	0.0±0.0	98.7±0.2	499.2± 1.5	4.368±0.014	75±2	1.51

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

The presence of two polymers into the formulations reduced the necessary pressure to obtain the tablets (Table 3), and increased the plasticity values compared to the HCMMA 100% ratios. When HCMMA percentages decrease in the mixtures, the applied pressure, expansion work and apparent net work decreased, and the plasticity increased (not statistical differences were found between OD25K4M and OD50K4M). We also observed that mixtures with FD-HCMMA needed less pressure, exhibited lower expansion work (not statistical differences were found between OD25HPC and FD25HPC), and higher plasticity (not statistical differences were found between OD25HPC y FD25HPC) and hence, higher facility to obtain the tablets than OD-HCMMA mixtures (not statistical differences were found between OD50A4M and FD50A4M; OD25A4M and FD25A4M; OD25HPC and FD25HPC). These results agree with the parameters obtained for 100% formulations.

At same percentage in the formulations, MC A4M mixtures showed lower applied pressure (Psup) necessary to obtain tablets (breaking force = 70-80N), minor elastic expansion during

decompresion (not statistical differences were found between OD25A4M and OD25HPC; FD25A4M and FD25HPC) and lower apparent net work values (not statistical differences were found between OD25A4M and OD25HPC; FD50A4M and FD50HPC; FD25A4M and FD25HPC) than HPMC K4M and HPC H mixtures, according to 100% formulations.

Table 3.- Compaction parameters (n=4) from HCMMA:swellable polymer matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)
OD75K4M	174.80±5.59	11.6±0.4	1.2±0.2	90.6±1.1
OD75A4M	144.89±1.79	10.5±0.3	1.1±0.1	90.2±0.8
OD75HPC	210.63±3.33	11.9±0.3	1.8±0.1	86.4±1.1
OD50K4M	99.65±2.25	7.7±0.1	0.5±0.1	94.4±1.2
OD50A4M	66.67±1.62	5.9±0.2	0.3±0.0	94.9±0.5
OD50HPC	114.13±2.39	7.6±0.2	0.4±0.1	94.5±1.0
OD25K4M	59.85±1.36	5.4±0.1	0.4±0.0	93.2±0.7
OD25A4M	38.10±0.92	3.8±0.1	0.2±0.0	96.2±1.1
OD25HPC	49.25±1.78	3.8±0.1	0.1±0.0	98.0±0.3

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)
FD75K4M	109.40±0.52	9.3±0.1	0.7±0.0	93.4±0.3
FD75A4M	93.13±1.60	8.5±0.2	0.5±0.0	94.4±0.5
FD75HPC	112.73±1.07	10.4±0.1	0.8±0.1	93.3±1.1
FD50K4M	83.25±0.32	7.5±0.0	0.3±0.0	96.4±0.3
FD50A4M	64.54±0.68	6.2±0.1	0.2±0.0	96.8±0.6
FD50HPC	76.23±1.25	6.1±0.1	0.3±0.0	94.9±0.4
FD25K4M	48.93±0.66	4.8±0.1	0.1±0.0	97.0±0.4
FD25A4M	38.45±0.42	4.1±0.0	0.1±0.0	97.4±0.4
FD25HPC	47.49±1.62	3.8±0.1	0.1±0.0	97.4±0.5

*K4M mixtures were published in Escudero et al., 2008

We observed that the lubrication ratio values (data not shown) obtained from all formulations (0.8-0.6) did not fulfil the requirements (0.9) proposed by Bolhuis and Lerk (1973) as direct compression excipients, in contrast with the values found for the ejection force (436-132 N) that were lower than 750 N (Bolhuis and Lerk, 1973).

3.3. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different mixtures are compiled in Tables 2 and 4. All tablets fulfilled the guidelines specified in European Pharmacopoeia (2007) related to weight uniformity test.

The tablet thickness ranged between 4 and 4.8 mm. In general, FD-HCMMA mixtures gave tablets with higher thickness than OD-HCMMA mixtures (not statistical differences were found between OD50HPC and FD50HPC). These results might be related to a more porous structure in FD matrices.

The breaking force test (European Pharmacopoeia, 2007) confirmed the values of 70-80 N for all tablets.

Only FD-HCMMA 100%, OD75HPC, OD25HPC, FD50HPC and FD25HPC presented friability values lower than 1% (European Pharmacopoeia, 2007). The high values observed for this parameter make us think about the need of increase the breaking force in a future. With exception of FD50HPC, the FD mixtures showed higher friability values than OD mixtures.

Table 4.- Physical tests from HCMMA:swellable polymer matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD75K4M	500.0 ±0.8	4.153±0.012	75±2	1.17
OD75A4M	500.6 ±1.1	4.270±0.036	72±2	1.29
OD75HPC	501.1 ±1.3	4.092±0.011	79±2	0.99
OD50K4M	500.6 ±1.5	4.312±0.011	75±2	1.82
OD50A4M	499.3 ±1.3	4.452±0.003	73±3	1.44
OD50HPC	499.7 ±1.9	4.195±0.008	76±2	1.40
OD25K4M	502.2 ±1.4	4.383±0.011	81±3	1.34
OD25A4M	498.7 ±1.1	4.626±0.011	73±6	1.40
OD25HPC	502.6 ±1.5	4.248±0.023	80±2	0.87

Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)
FD75K4M	498.0 ±1.0	4.358±0.009	74±2	1.81
FD75A4M	499.3 ±1.1	4.432±0.012	75±2	1.69
FD75HPC	500.1 ±1.1	4.445±0.031	78±3	1.95
FD50K4M	500.7 ±1.2	4.475±0.007	78±2	3.35
FD50A4M	501.9 ±0.8	4.638±0.007	76±3	2.05
FD50HPC	500.1 ±1.3	4.117±0.013	79±4	0.98
FD25K4M	499.0 ±2.0	4.555±0.012	74±3	1.69
FD25A4M	500.7 ±1.2	4.754±0.009	76±2	1.46
FD25HPC	503.2 ±1.7	4.350±0.014	80±1	0.96

*K4M mixtures were published in Escudero et al., 2008

3.4. Mercury porosimetry measurements

In order to evaluate the microstructure of the matrices, the pore size distributions were measured by mercury intrusion-extrusion porosimetry (Table 5). HCMMA presented lower porosity

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than HPMC K4M, MC A4M and HPC H 100%, in agreement with the thickness presented by the matrices (Table 2).

When two polymers were incorporated to the formulation, the porosity was higher than those corresponding to HCMMA 100% (not statistical differences were found between FD50HPC and FD-HCMMA 100%). If we compare OD with FD mixtures, in general, the formers showed lower porosity values (not statistical differences were found between OD25HPC and FD25HPC), as encountered in HCMMA 100% tablets.

Table 5.- Porosity values (n=2) from HCMMA:swelling polymer mixtures (100:0, 75:25, 50:50; 25:75, 0:100).

Mixture	Porosity (%)	Mixture	Porosity (%)	Mixture	Porosity (%)
OD-HCMMA	17.8 ±1.4	OD75K4M	22.0±1.8	FD75K4M	26.2±0.4
FD-HCMMA	23.6 ±0.6	OD75A4M	25.5±0.8	FD75A4M	28.3±0.5
HPMC K4M	31.4 ±2.7	OD75HPC	19.8±1.2	FD75HPC	24.6±0.2
MC A4M	36.3±0.3	OD50K4M	27.2±0.2	FD50K4M	34.0±7.4
HPC	25.8±0.7	OD50A4M	26.7±0.6	FD50A4M	31.7±0.1
		OD50HPC	21.2±0.1	FD50HPC	23.4±0.3
		OD25K4M	28.5±2.3	FD25K4M	32.7±0.1
		OD25A4M	34.6±0.3	FD25A4M	35.6±0.3
		OD25HPC	23.0±0.1	FD25HPC	24.8±0.5

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

When we compared different HCMMA:swelling polymer ratios for the same substitution type, we found for the OD mixtures, that the porosity values increased, when decreased HCMMA in the mixtures, mainly due to the different porosity values of OD and the commercial polymers in 100% formulations. For the same reason, it is possible to see a similar behaviour in FD-MC A4M mixtures. In the case of FD-HPC mixtures, the porosity values do not change when the FD-HCMMA copolymer increased, due to the similar

porosity values presented for both polymers in 100% ratio. The great difference in particle size and particle size distribution along with the different porosity values of FD and HPMC K4M could explain that the 50:50 mixture reaches the porosity value of HPMC K4M 100%.

According to IUPAC definitions, as the pore diameter values were accomplished between 20 and 500 Å, all mixtures possessed mesopores, except to HPMC K4M 100%, MC A4M 100%, OD/FD25K4M and OD/FD25A4M, that displayed macropores (>500 Å).

3.5 Drug release study

Figure 1 illustrates the drug release profiles from HCMMA 100% and ethers of cellulose 100% matrices.
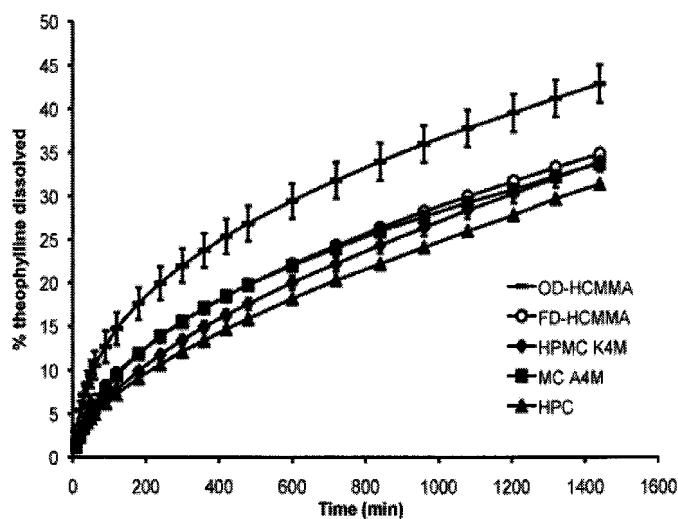

Figure 1. Release profiles of anhydrous theophylline (over 24 h) from 100% tablets. The bars show the standard deviation.

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Although it can be seen a faster release from the OD-HCMMA respect to FD-HCMMA, but not biopharmaceutically relevant difference were found (f_2=60.3). MC A4M and HPMC K4M showed similar release profiles than FD-HCMMA (f_2=96.3 and 85.2, respectively), whereas HPC H tablets displayed the lowest release, according to their lower porosity (Table 5) (f_2=74.4 and 51.6 respect to FD and OD-HCMMA).

Figure 2 illustrates the release profiles from the matrices prepared with different mixtures of OD-HCMMA or FD-HCMMA with HPMC K4M, MC A4M or HPC H in three defined proportions HCMMA:swelling polymer (75:25, 50:50, 25:75). All mixtures presented a percentage of theophylline release between 47% and 32% at 1440 minutes. Only high levels of HCMMA in the matrices showed interesting differences between them. So in 75:25 proportions, OD-HCMMA mixtures with HPMC K4M and HPC H behaved similarly and the major differences were encountered with MC A4M, which exhibited the lowest theophylline release, in agreement with its minor hidrophylicity (theophylline is a poor water soluble drug). However, both FD-HCMMA mixtures with MC A4M and HPC H showed similar behaviour and the main differences were observed with HPMC K4M, which presented the highest theophylline release. Therefore, the HPC H mixtures displayed the highest relative differences between OD or FD HCMMA compared to the others swelling cellulose polymers.

Not biopharmaceutically relevant differences were found in the others release profiles at 50:50 and 25:75 proportions (f_2>50).
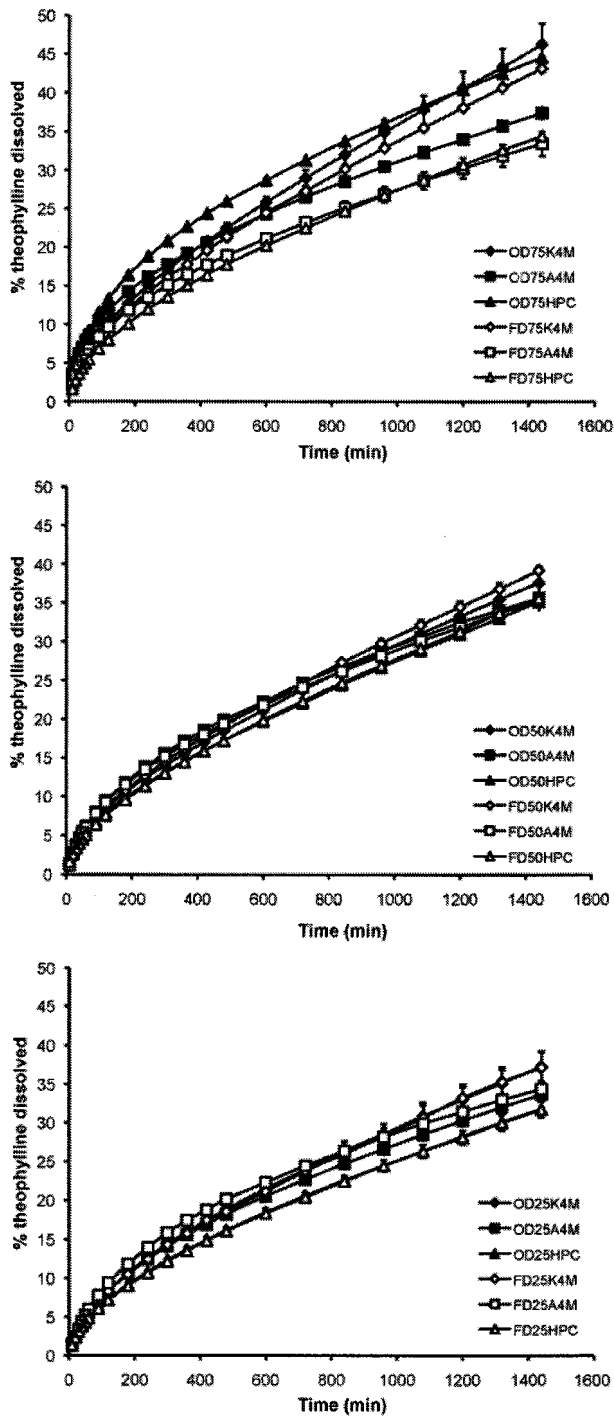
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Figure 2. Release profiles of anhydrous theophylline (over 24 h) from mixtures of swelling polymers with HCMMA. The bars show the standard deviation.

Release data (M_t/M_∞ < 0.6) were analysed according to Higuchi (1963), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations. The main parameters are listed in Table 6 for 100% mixtures, and in Tables 7 and 8 for mixtures of OD-HCMMA and FD-HCMMA:swelling derivative, respectively. As the matrices studied presented an aspect ratio (diameter/thickness) around 3, the m value was 0.44 (Peppas and Sahlin, 1989). The corrected determination coefficient (r^2) was used to test the applicability of the release models.

Table 6.- Mathematical modelling and drug release kinetics from 100% matrices.

Mixture	Higuchi ecuation		Korsmeyer equation			Peppas equation		
	k $(min^{-1/2})$	r^2	n	k' (min^{-n})	r^2	k_d $(min^{-0.44})$	k_r $(min^{-0.88})$	r^2
OD-HCMMA	0.011	0.9948	0.49	0.013	0.9862	0.021	0.00011	0.9996
FD-HCMMA	0.009	0.9999	0.55	0.007	0.9955	0.013	0.00008	0.9999
HPMC K4M	0.009	0.9981	0.61	0.004	0.9990	0.010	0.00020	0.9999
MC A4M	0.009	0.9982	0.63	0.004	0.9816	0.016	-0.00002	0.9999
HPC	0.008	0.9955	0.57	0.005	0.9996	0.007	0.00023	0.9999

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, corrected determination coefficient.
*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

When matrices with two polymers were studied (Tables 7 and 8), we found a combination of both released mechanisms, diffusion and erosion, but in all MC A4M mixtures, the erosion component is nearly negligible. The rate constant values from Higuchi equation ($min^{-1/2}$) were in good agreement with the 75:25 HCMMA:swelling polymer profiles (Figure 2). Also, when HCMMA percentage decreased, all the rate constant data from Higuchi

equation ($min^{-1/2}$) resemble the swelling polymer 100% tablets (Table 6).

Table 7.- Mathematical modelling and drug release kinetics from OD HCMMA: swellable polymer mixtures.

Mixture	Higuchi ecuation		Korsmeyer equation			Peppas equation		
	k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
OD75K4M	0.012	0.9934	0.60	0.006	0.9960	0.010	0.00038	0.9997
OD75A4M	0.010	0.9995	0.46	0.013	0.9993	0.014	0.00006	0.9994
OD75HPC	0.012	0.9985	0.55	0.009	0.9823	0.019	0.00032	0.9997
OD50K4M	0.010	0.9946	0.62	0.004	0.9977	0.008	0.00030	0.9999
OD50A4M	0.010	0.9999	0.61	0.005	0.9900	0.014	0.00008	0.9998
OD50HPC	0.009	0.9926	0.57	0.005	0.9986	0.007	0.00031	0.9998
OD25K4M	0.010	0.9967	0.61	0.004	0.9982	0.010	0.00025	0.9999
OD25A4M	0.009	0.9996	0.60	0.004	0.9959	0.011	0.00013	0.9999
OD25HPC	0.009	0.9961	0.58	0.004	0.9995	0.008	0.00022	0.9997

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r Peppas relaxation kinetic constant; r^2, corrected determination coefficient.
*K4M mixtures were published in Escudero et al., 2008

Table 8.- Mathematical modelling and drug release kinetics from FD HCMMA: swellable polymer mixtures.

Mixture	Higuchi ecuation		Korsmeyer equation			Peppas equation		
	k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
FD75K4M	0.012	0.9943	0.60	0.005	0.9986	0.009	0.00034	0.9997
FD75A4M	0.009	0.9996	0.53	0.007	0.9960	0.012	0.00008	0.9997
FD75HPC	0.009	0.9973	0.59	0.005	0.9998	0.009	0.00022	0.9999
FD50K4M	0.011	0.9947	0.64	0.004	0.9969	0.009	0.00030	0.9998
FD50A4M	0.010	0.9998	0.62	0.004	0.9854	0.013	0.00009	0.9999
FD50HPC	0.010	0.9927	0.61	0.004	0.9994	0.007	0.00031	0.9999
FD25K4M	0.010	0.9956	0.61	0.004	0.9990	0.009	0.00027	0.9997
FD25A4M	0.010	0.9986	0.63	0.004	0.9844	0.016	-0.00001	0.9999
FD25HPC	0.009	0.9963	0.61	0.004	0.9980	0.008	0.00022	0.9999

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r Peppas relaxation kinetic constant; r^2, corrected determination coefficient.
*K4M mixtures were published in Escudero et al., 2008

In the case of mixtures with the same ratio, the MC A4M formulations always showed higher diffusion rate constants (k_d) and lower relaxation rate constants (k_r) than the corresponding

constants for the others mixtures with HPMC K4M and HPC H. On the other side, HPC mixtures exhibited lower k_d values (except to OD75HPC) than HPMC K4M mixtures but similar k_r values, according to 100% matrices.

The exception of OD75HPC could be due to a problem of particle junctions in the matrix tablets. So, as FD-HCMMA has high particle size, the incorporation of a 25% of a swelling polymer (with lower particle size) helps the junction formations among particles. This hypothesis is supported by the lower pressure data obtained for 75:25 FD-HCMMA:swelling polymer mixtures (Table 3) than 100% FD-HCMMA (Escudero et al., 2008). Similar explanation could be proposed for OD75A4M. On the other hand, HPMC K4M and HPC H have similar particle size but with different particle distribution. So, while HPMC K4M has left-handed leptocurtic distribution (Staniforth, 2004), OD-HCMMA has the same distribution but to the right, showing HPC H the more symmetric leptocurtic distribution. Therefore, the possibility to form particle junctions is higher in the mixture OD75K4M than in the mixture OD75HPC. The pressure values obtained for both mixtures support this conclusion (Table 3).

3.6. Fronts movement study

Fronts movement kinetics were evaluated (Ferrero et al., 2003) in order to obtain useful information for a better understanding of the drug release mechanism from different matrices. In a previous paper (Escudero et al., 2008) we explained more extensively the different behaviour of HCMMA matrices,

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according to the porosity and tortuosity values of the tablets. According to Ferrero et al. (2000) for inert matrices (HCMMA 100%), three fronts could be clearly distinguished from the centre to the periphery of the matrix: water uptake front (between dry-partial wet polymer), complete wetting front (distinguishes a partial hydrated zone from a complete wet one) and erosion front (between the external surface of the matrix and the dissolution medium).

For swellable matrix tablets, as HPMC 100%, Colombo et al. (1995) proposed three fronts: swelling front (between the still glassy polymer and its rubbery gel state), diffusion front (between the still undissolved (solid) drug and the dissolved drug in the gel layer) and erosion front (between the matrix and the dissolution medium).
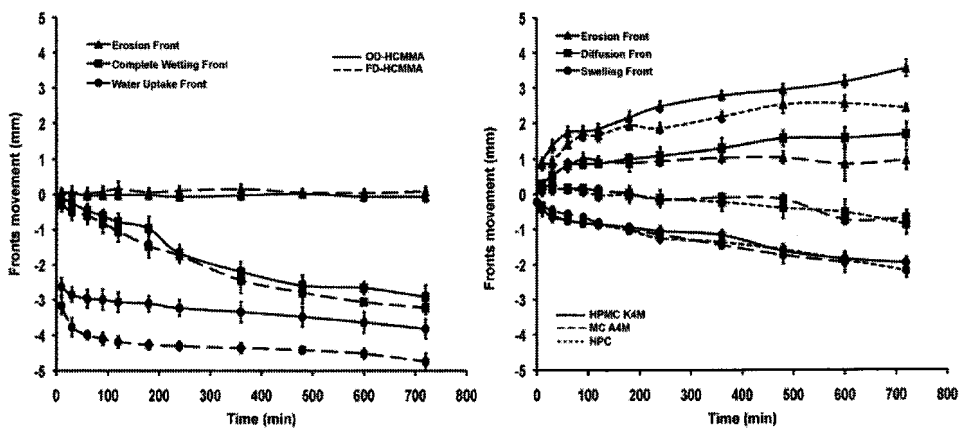

Figure 3. Fronts movement (over 12 h) from 100% matrices.

In figure 3, we cannot see remarkable differences in swelling front from the swelling matrices tested. Only HPMC K4M presented a diffusion front that move outwards while HPC H and

MC A4M moves inwards. This behaviour can be justified by the amount of bound water to these polymers. So, according to Mc Crystal et al. (1999), HPC H and MC A4M have similar bound water content but lower than HPMC K4M, what implies more free water available for dissolving the theophylline, and makes the diffusion front moves inwards.

The major differences in these matrices were found in erosion front. In decreasing order, the erosion front movement ranked as followed: HPMC K4M > HPC H > MC A4M, in agreement with their k_r values.

In HCMMA:swelling polymer mixtures (Figure 4), the swelling front presents no changes in comparison with 100% matrices. So, this front does not have dependency on the type of polymer and the ratio except to OD75HPC, which has the fastest swelling front movement, in agreement with it highest k_d value. In relation with diffusion and erosion fronts, the 75:25 ratio displayed the lowest differences between these two front movements. The erosion front movements were in agreement with the k_r values, due to the presence of inert polymer, that destabilizes the gel structure. Thus, when HCMMA fraction decreases, this front movement increases.

Lotfipour et al. (2004) proposed that the fillers reduced the tortuosity of the diffusion path of the drug on the release of atenolol. We calculated the apparent diffusion coefficient (D') (Table 9), obtained from the Higuchi rate constant. D' is expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusion coefficient of the drug in the dissolution medium. For

100% formulations, we observed higher D' values for HCMMA than commercial polymers 100% according to Fig. 1.
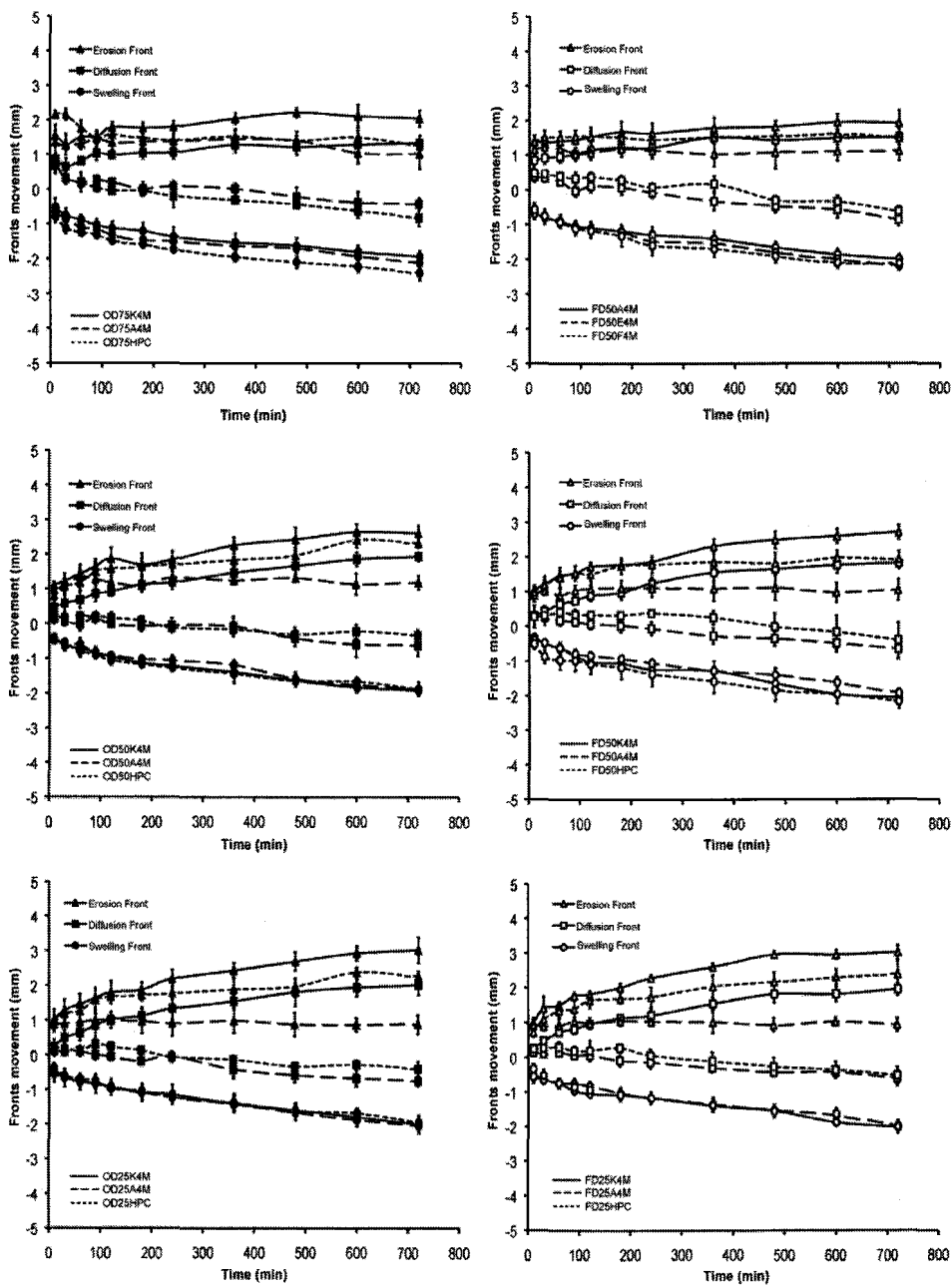

Figure 4. Fronts movement (over 12 h) from HCMMA:swelling polymer mixtures.

In the mixtures, FD HCMMA blends presented, in general, lower D' values than OD-HCMMA ones, in agreement with HCMMA 100% D' values. Attempting to the same substitution type and different ratios, in general, when HCMMA decreased, tortuosity increased (Table 9), because of the higher percentage of inert polymer, in agreement with the k_r values (Table 7, 8).

Table 9.- Apparent diffusion coefficient (D') for all mixtures.

Mixture	D' (cm²/min)	Mixture	D' (cm²/min)	Mixture	D' (cm²/min)
OD-HCMMA	7.24×10^{-4}	OD75K4M	6.87×10^{-4}	FD75K4M	5.51×10^{-4}
FD-HCMMA	3.54×10^{-4}	OD75A4M	4.01×10^{-4}	FD75A4M	2.82×10^{-4}
HPMC K4M	2.50×10^{-4}	OD75HPC	7.75×10^{-4}	FD75HPC	3.23×10^{-4}
MC A4M	2.03×10^{-4}	OD50K4M	3.72×10^{-4}	FD50K4M	3.48×10^{-4}
HPC	2.48×10^{-4}	OD50A4M	3.67×10^{-4}	FD50A4M	2.98×10^{-4}
		OD50HPC	3.97×10^{-4}	FD50HPC	4.53×10^{-4}
		OD25K4M	3.50×10^{-4}	FD25K4M	2.94×10^{-4}
		OD25A4M	2.22×10^{-4}	FD25A4M	2.59×10^{-4}
		OD25HPC	3.62×10^{-4}	FD25HPC	3.28×10^{-4}

*OD/FD-HCMMA and K4M mixtures were published in Escudero et al., 2008

When we studied the different substituents, the mixtures with MC A4M always showed the lowest D', related with the highest tortuosity; however, these mixtures presented, in general, the maximum k_d values. These results could be due to their highest porosity (Table 5). For the other mixtures, it was not displayed a clear trend for this parameter.

The gel layer thickness (Colombo et al, 1995) is defined as the difference between erosion and swelling front positions (Figure 5). OD and FD mixtures did not show remarkable differences in their behaviour in every formulation. When HCMMA ratio increased, the release control was governed by this copolymer and the gel

thickness differences were reducing. Initially, it is possible to see how OD75HPC presented a high gel layer thickness (Fig. 5). It is likely that this rapid growth provided a weak gel layer, that could release the drug rapidly by diffusion, in agreement with its highest k_d value.
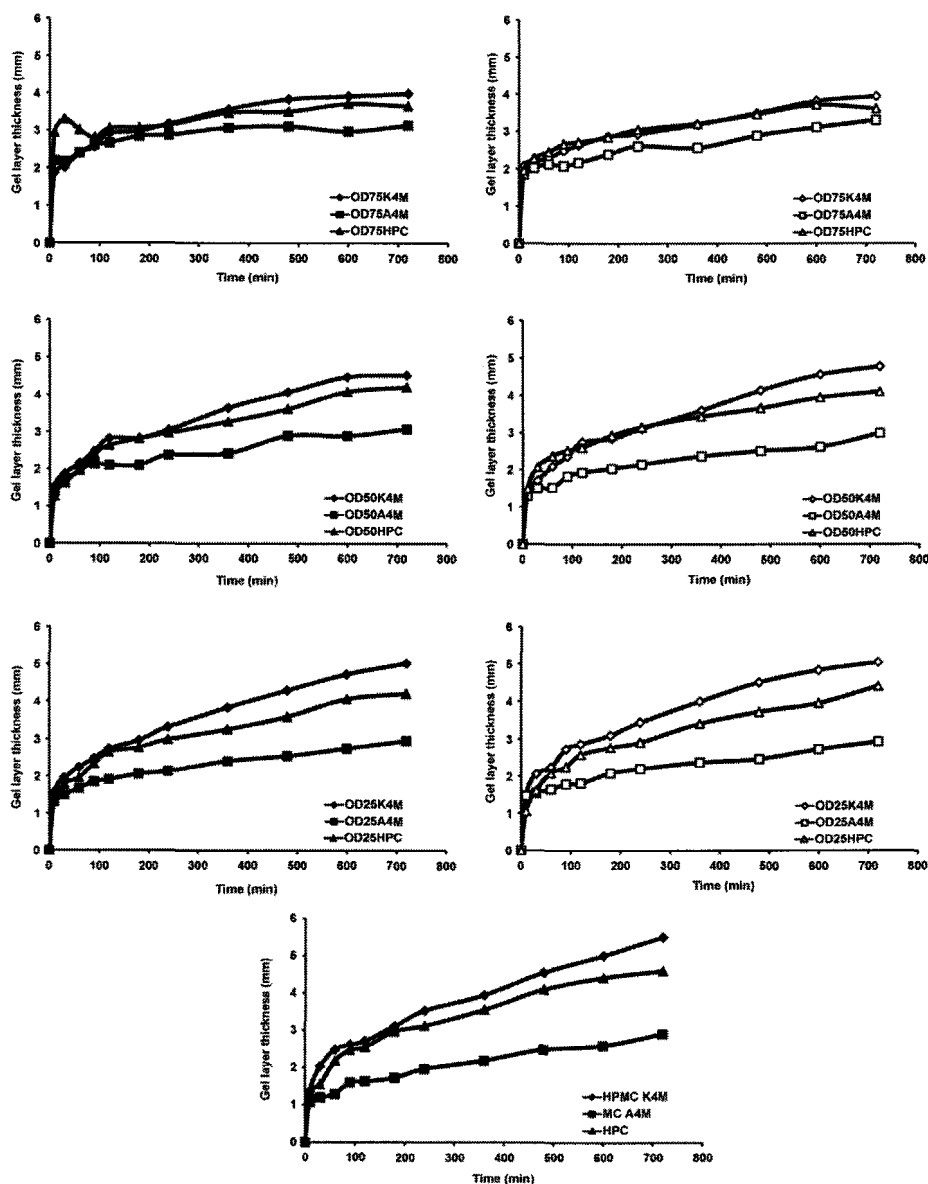

Figure 5. Gel layer thickness from mixtures of swelling polymers with HCMMA and swelling polymers 100%.

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4.- Conclusions

HPC H mixtures presented lower density values than the other mixtures at the same ratio; however, MC A4M mixtures showed the best compaction properties, especially with FD-HCMMA. In general, HPMC K4M mixtures displayed the fastest drug release at all proportions. Besides, only HPMC K4M mixtures presented a diffusion front that moved outwards while HPC H and MC A4M mixtures moved inwards. Therefore, the absence of hydrophobic or hydrophilic substituent in the cellulose ether polymers (MC A4M and HPC H), implies a lowest release profiles.

As in previous works (Escudero et al., 2008, 2009), the ratio 75:25 presented the most ample modulation of theophylline monoaxial release. However, in the present work, HCMMA played a more relevant role, because in mixtures with 25% of HPC, the modulation was obtained just changing our inert polymer (OD or FD). Besides, the matrices containing hydrophilic substituent in commercial polymers (HPC and HPMC K4M) showed diffusion and erosion release mechanisms, similar to mixtures with different viscosity grade (Escudero et al., 2008) or substitution degree (Escudero et al., 2009). However, the absence of hydrophilic substituent (MC A4M) revealed just a diffusion mechanism.

In conclusion, in order to modulate the theophylline monoaxial release it was necessary two mixtures containing: 75% of inert polymer in both cases (HCMMA) and 25% of two commercial polymers. Related to the commercial polymer there are some options: 1.- The use of two HPMCs with markedly different viscosity grades (HPMC K4M or K15M and K100M) (Escudero et al., 2008); or 2.- the use of HPMC F4M and another HPMC with a

different substitution degree (HPMC E4M or HPMC K4M) (Escudero et al., 2009); or 3.- the use of two cellulosic ethers, one of them with just one type of substituent (MC A4M or HPC H) and the other with two types of substituent (HPMC K4M).

Only in the case of HPC H, it is possible to modulate the theophylline monoaxial release using OD and FD HCMMA copolymer (75%) and this commercial polymer (25%).

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