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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

J.J. Escudero, C. Ferrero, M.R. Jiménez-Castellanos *

Dpto. Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, C/Profesor García González n 2, 41012 Sevilla, Spain

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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 min. 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 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

* Corresponding author. Tel.: +34 954556836; fax: +34 954556085.
E-mail addresses: mrosa@us.es, gamarusoj@hotmail.com (M.R. Jiménez-Castellanos).

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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

2.1.1. 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.

2.1.2. 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.

2.1.3. 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 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 (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 rpm 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% and 90% of the penetrometer capacity. Working pressures covered the range of 0.1–60000 psi 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 rpm. 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:

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

$$\frac{M_t}{M_\infty} = k'\,t^{n} \quad (2)$$

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