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RESEARCH PAPER

Influence of Technological Variables on the Release of Theophylline from Hydrophilic Matrix Tablets

F. Veiga, T. Salsa, and M. E. Pina*

Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, 3000 Coimbra, Portugal

ABSTRACT

This study presents the results of in vitro dissolution of controlled-release theophylline tablets using hydroxypropylmethylcellulose as a rate-retarding polymer. The effects of the proportion of the polymer, the addition of diluents, and the surface area of matrix tablets on the theophylline release rate have been investigated. The results of the dissolution tests show that the drug was gradually released in all cases, and that the tablets had released 80% of their contents after 8 hr. The release rate decreased when the proportion of the polymer increased. The influence of adding diluents and effect of the surface area of matrix tablets were not observed in this study.

INTRODUCTION

The goal of any drug delivery system is to deliver a therapeutic amount of drug to the proper site in the body and maintain the desired drug concentration. An appropriately designed controlled-release drug delivery system can be a major advance toward these two goals (1).

The formulation of drugs in rigid gelatinous capsules or, much more often, in tablets using hydrophilic polymers with gelling capacities is of real interest in the field of controlled release. When these formulations meet water there is a rapid hydration of the macromolecules in the solid–liquid interface, followed by formation of a viscous layer. The matrix system produced as a result of this process can pass along the gastrointestinal tract without breaking up, releasing the drug progressively (2–7).

The use of theophylline as an antiasthmatic drug is based on the relaxation that it creates in the smooth musculature of the bronchi (8,9). This drug has a great variability in clearance (elimination half-lives 3–4 hr, adults 6–12 hr) and a narrow therapeutic range (7.5–20 μg/ml). Once or twice daily administration of controlled-

*To whom correspondence should be addressed.

release preparations in patients with chronic obstructive airway diseases is recommended and improves patient compliance (10).

During the past two decades, hydrophilic polymers, especially celluloses, have been extremely popular in controlling the release rate of soluble drugs from solid dosage forms. Their ease of compression, ability to accommodate large amounts of the drug, and the minimum influence exerted by the processing variables on the release rate are the main reasons for their popularity (6,11,12). In particular, hydroxypropylmethylcellulose (HPMC) has already been used by different researchers, with good results (13–17).

The work described here reports the effect of the technological variables—such as proportion of polymer, addition of diluents, and surface area of tablets—on the release of theophylline from matrices manufactured with hydroxypropylmethylcellulose.

MATERIALS AND METHODS

Materials

Theophylline anhydrous (Boehringer)
Hydroxypropylmethylcellulose (HPMC) (Methocel K 15M, Colorcon, Spain); the apparent viscosity of 2% (w/v) aqueous solution was 1500 cPs at 20°C
Lactose (Tablettose)
Tricalcium phosphate (Encompress)
Talc and magnesium stearate, reagent grade

Formulations

Previous dissolution studies were carried out in order to determine the necessary amount of polymer (HPMC). In all cases, drug content was maintained at 100 mg, and the total tablet mass was 200 mg. It was considered the next formulation:

Anydhrous theophylline	100 mg
HPMC	several %
Talc	4 mg
Magnesium stearate	2 mg
Diluent	200 mg

The proportions of polymer (HPMC) were 25%, 35%, and 45% of the total tablet weight (200 mg). For formulations with the proportion of polymer (25% and 45%), lactose and tricalcium phosphate were used as diluents. For formulations corresponding to the proportion of polymer (25% and 45%) and lactose as diluent, tableting was accomplished using flat- and concave-face punches. The compositions of individual tablets are shown in Table 1.

Preparation of Matrix Tablets

The drug, HPMC, and lactose were passed through a 100-mesh sieve and thoroughly mixed in a blender for 15 min. The lubricants (talc and magnesium stearate) were sieved by aperture diameter net of 500 mesh, added to the previous mix, and again blended for 5 min. The total weight of each batch was 400 g.

During the tableting, the mass variability of pressed tablets was determined and all that presented a variation higher than ±2.5% of theoretical mass were rejected.

Determination of Theophylline in the Matrix Tablets

Theophylline content of matrix tablets was determined by spectrophotometric analysis at 285 nm using a Schimadzu UV 160 spectrophotometer (18).

Table 1

Composition of Theophylline Matrix Tablets

		Ingredients (mg)					
Batch[a]	Formulation	Theophylline	HPMC, K15M	Lactose	Tricalcium Phosphate	Talc	Magnesium Stearate
A1	A	100	50	44		4	2
A2	A	100	50	44		4	2
B1	B	100	70	24		4	2
C1	C	100	90	4		4	2
C2	C	100	90	4		4	2
D1	D	100	50		44	4	2
E1	E	100	70		24	4	2

[a]1:flat-face punches; 2: Concave-face punches.

Average weight of the matrices was determined from 10 matrices that were pulverized; a aliquot theoretically corresponding to 20 mg of anhydrous theophylline was weighed and placed in a clean vial; 100 ml of distilled water were added and the vial was stirred on a mechanical agitation apparatus for 20 min at ambient temperature. Distilled water to bring the volume to 200 ml was added and the vial submitted to stirring. Subsequently, the solution was filtered and 50 ml were withdrawn and placed in a vial, and distilled water was added to make 100 ml. The vial was stirred.

A blank solution was prepared. It was not necessary to use a extraction method for drug, because interferences were not observed at 285 nm.

Disintegration Studies

As was mentioned, hydrophilic matrices should maintain their initial form during their action time (around 8 hr) in order to meet their goal. The disintegration test allows selection of tablets that satisfy that condition.

Six tablets were exposed for 2 hr at 37°C to gastric juice (USP XXII) using a disintegration apparatus (Erweka ZT3-2). After this time, the tablets were first rinsed with water and then immediately immersed in enteric juice (USP XXII) for 6 hr.

The tablets with hardness level between 5.5 and 6.0 kg (hardness level measured by the apparatus Erweka TBH 28) were selected because their form was maintained together with a good gelification.

In turn, the tablets with hardness level 3.5 and 4.0 kg were rejected because they presented some disintegration.

Hardness Level

The influence of compression force on release kinetics is not very important for hydrophilic matrices (19–21); however, this fact is only observed from compression force adequate to prevent the partial or total matrix disintegration.

The present work used a compression-force that made it possible to obtain tablets whose hardness level was between 3.5–4.0 kg and 5.5–6.0 kg. The value of hardness level was chosen in accordance with the results from the disintegration test.

Dissolution Studies

Dissolution studies were carried out according to the USP XXII paddle method. Determinations were performed with paddle agitation of 60 ± 1 rpm and the dissolution medium was 850 ml kept at 37 °C. A six-vessel dissolution apparatus (Hanson Research), in-line with a closed flow through the system using a peristaltic pump (Gilson) with eight channels and connected to a spectrophotometer (Schimadzu UV 160), was used for this purpose.

The dissolution media were buffer solution (0.05 M KH_2PO_4 and 0.05 M glacial acetic acid) and 0.01% Tween 20, adjusted to pH 1.3 with 37% HCl and to 5.3, 6.3, and 6.9 pH values by adding 4M NaOH (18,22,23).

While some researchers (13) assume that the dissolution medium composition does not influence the kinetics release of theophylline, the pH of the media used in this work was changed as a function of the time (Table 2). This methodology has been applied by other authors (18,24,25) because the solubility of theophylline presents variations with pH values.

In each study, four dosage forms were tested (corresponding to a four-cell spectrophotometer). However, a fifth station, a blank which contained only the dissolution medium, was used and submitted to identical variations of the remainder on its composition. The sink conditions were observed.

Progress of the dissolution was monitored by withdrawing filtered samples at predetermined intervals (at 15 min during the first 2 hr and at 30 min for the remainder) for 8 hr. The amount of theophylline in solution was determined by spectrophotometry (λ = 285 nm). Eight tablets from each batch were tested and their mean percentages of release calculated (18).

RESULTS AND DISCUSSION

Release profiles of theophylline from the tested formulations are shown in Figs. 1, 2, and 3. Considering the results obtained, it was found that only the proportion of polymer modified the release rate of the theophylline (Fig. 1). It is possible to verify that the release kinetics decreases when the amount of polymer is

Table 2

pH Values

Time (hr)	pH
0.0–0.5	1.3
0.5–1.0	5.0
1.0–4.0	6.3
4.0–8.0	6.9

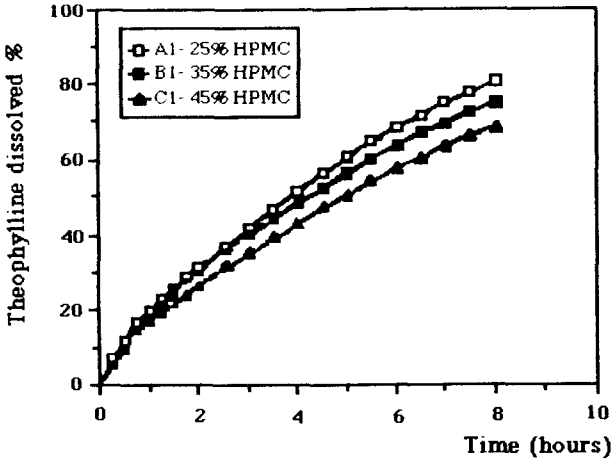

Figure 1. Influence of polymer percentage.

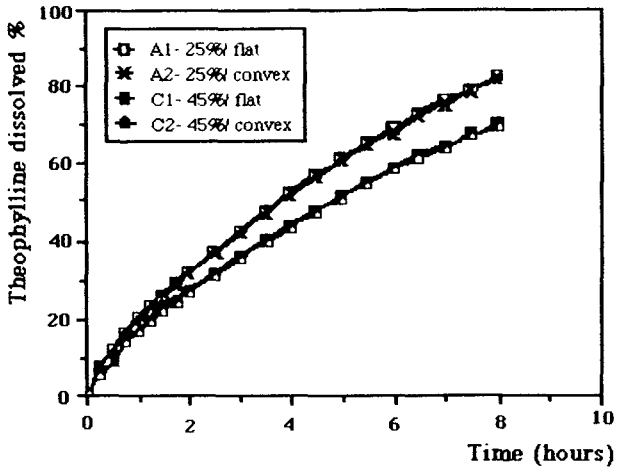

Figure 3. Influence of matrix tablet surface.

higher, which is in accordance with other authors (2,4,5,26–28).

In this study, the effect of adding diluents (soluble or insoluble) was not demonstrated (Fig. 2); although some authors had shown that those products, in large enough quantities, bring about marked differences in the release rate of active principles (6,29,30). So, it can be concluded that, in this work, the amount of diluent (11% or 22%) was not adequate to alter the release kinetics of theophylline.

Tablet shape does significantly affect the rate of release; the results of a study by Ford et al. (31), with prometazin tablets of equal weight and formulation, shows that the release rate, which follows the Higuchi kinetics, is inversely related to the surface area of the formulations/dissolution medium; this was also demonstrated by Costa et al. (32). For studying this technological parameter, flat- and concave-face punches were used in the compression of the same amount of the mixture, for obtaining different contact surfaces. However, the influence of this factor was not observed (Fig. 3), which is explained by the reduced weight of the tablets (200 mg) and mainly by the small difference in the surface area between flat and convex matrix tablets (1.978 and 1.884 cm^2).

The results of this investigation enable us to state that the hydrophilic matrices are an interesting way of formulating oral controlled-release theophylline tablets, using a fabrication process that is easy and does not require special production equipment.

However, it is possible to achieve a firmer basis for their use. Hence, the influence of different technological variables on release needs to be further studied. In addition, it is essential to consider the mechanisms implied in the release and the physicochemical properties of the active principles and polymers.

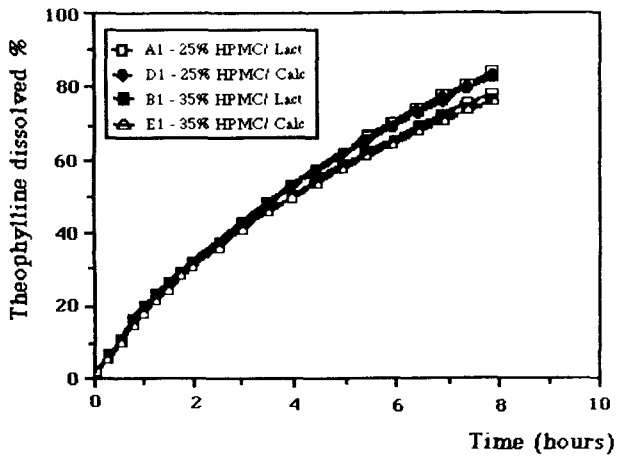

Figure 2. Influence of diluent nature.

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