International Journal of Pharmaceutics, 45 (1988) 145–152
Elsevier

IJP 01536

In vitro evaluation of modified starches as matrices for sustained release dosage forms

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(Received 20 July 1987)
(Modified version received 9 January 1988)
(Accepted 19 January 1988)

Key words: Hydrophilic matrix; Modified starch; Sustained release; Theophylline

Summary

A variety of modified starches were investigated as possible hydrophilic matrices for controlled drug release, using theophylline as the model drug. The type of starch modification, the influence of compression force, dissolution medium and other formulation variables on the drug release rate of theophylline have been investigated.

Introduction

Hydrophilic polymer matrices are still widely used in the formulation of sustained release dosage forms. The present communication is concerned with the in vitro evaluation of the potential use of modified starches as hydrophilic matrices for controlled drug release, using theophylline as the model drug. This study was undertaken as a screening test for the use of some physical and/or chemical modifications of starches such as: pregelatinisation by drum-drying or by extrusion, partial hydrolysis and cross-linking.

Several reports have been presented on the use of hydrophilic polymers, especially cellulose ethers, as delaying matrices. Huber et al. (1966, 1968) investigated the use of sodium carboxymethylcellulose and of hydroxypropylmethylcellulose as delaying agents, Lapidus and Lordi (1966, 1968) investigated the influence of temperature, diluents and polymer type on the release pattern and the applicability of Higuchi equations with respect to the drug availability from hydratable matrices.

Bamba et al. (1979) concluded that both the diffusion of water into the tablet and diffusion of dissolved drug are the rate-limiting steps in drug release from hydrophilic gum matrices. Salomon and co-authors (1979a and b) investigated both the influence of excipient viscosity, drug gum ratio, compression force, particle size, electrolyte concentration and tablet thickness on the release of a highly soluble salt from a hydroxypropylmethylcellulose (HPMC) matrix. Influence of anionic surfactants on the release of chlorpheniramine from HPMC tablets was studied by Daly et al. (1984). Ford et al. (1985a and b) examined the release of promethazine hydrochloride, propranolol hydrochloride and aminophylline from hydroxypropylmethylcellulose matrices.

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Materials and Methods

Materials

Microcrystalline theophylline was obtained from Riker (Belgium). Magnesium stearate, polyethyleneglycol 4000 and sodium benzoate were purchased from Pharmachemic (Antwerp, Belgium). Colloidal silicon dioxide (Aerosil 200) (Degussa, Frankfurt, F.R.G.) was used as a glidant. Lactose (ultra-fine grain), used as a water-soluble filler, was purchased from H.M.F. (Uitgeest, The Netherlands).

Table 1 summarizes the different types of modified starches evaluated in this study. All starches are from Amylum (Aalst, Belgium).

Tabletting

Tablets, containing theophylline in a modified starch matrix, were compressed at 250 MPa on an instrumented Courtoy single-punch compression machine equipped with flat-faced punches with a diameter of 11.2 mm. Drug release of theophylline from b-270 matrices was evaluated on tablets compacted by direct compression of 300 and 500 mg of drug–starch blends (1 : 1, 1 : 4, 1 : 9). Three drug–starch blends (Merigel R, Merigel XX and b-145) were compressed at 4 different pressure levels (50, 100, 250 and 400 MPa) in order to study the influence of densification on drug release. Powders were blend in a Turbula mixer (Type T2A, W.A. Bachofen AG, Switzerland) for 15 min at 60 rpm. The influence of hydrosoluble diluents on the release rate of theophylline from a b-270 matrix was studied on 500 mg tablets containing 250 mg theophylline and increasing amounts of lactose from 0% to 40% (w/w). The tablets were compressed at 250 MPa.

TABLE 1

Process characterization in the production of the starches used for the evaluation as hydrophilic matrices

Starch modification	Gelatinization by drum drying	Gelatinization by extrusion	Partial hydrolysis	Cross-linking with trimetaphosphate
Merigel R	+			
Merigel XX	+		+	
b-145		+		+
b-270		+		+ +
b-291		+		+ + +
b-294		+		+ + + +

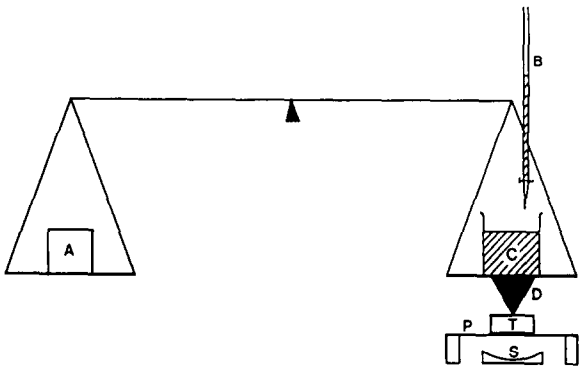

Fig. 1. Apparatus for the determination of gel strength of hydrated starch tablets. Key: C = beaker; B = burette; T = tablet; P = glass plate; S = mirror; D = cone-shaped pin.

Dissolution studies

The dissolution testing was performed using the paddle method (USP XXI) at a rotational speed of 60 rpm. The extinction was continuously measured using a spectrophotometer (Zeiss PM 6) set at 278 nm and a Philips Multipoint recorder. Dissolution experiments were performed on whole tablets in water, simulated gastric fluid (USP XXI) and simulated intestinal fluid (USP XXI). Each value is the mean of 3 determinations.

Liquid penetration

To evaluate the liquid penetration and subsequent swelling, tablets made of the different starches and compressed at 250 MPa were exposed to water at 37 °C for an 8-h period and the evolution of tablet diameter, thickness and weight was determined.

Determination of gel strength of hydrated starch tablets

Fig. 1 describes the apparatus used for the determination of the gel strength.

A beaker (C) is put on one plate of a two armed balance. This balance is equilibrated by adding water from burette (B) to the beaker. The swollen tablet (T) is fixed on a glass plate (P)

covering a mirror (S). At the underside of the plate a black cone-shaped pin is fixed (D). Because water is flowing at a constant rate from the burette into the beaker the pin exerts an increasing force on the tablet. The strength of the matrix is defined as the total amount of water (ml) necessary to perforate the tablet and was determined after complete hydration of the matrix (48 h).

Results and Discussion

Gel strength and swelling characteristics of the different modified starches

These experiments were used as a screening procedure for the selection of possible matrix candidates. Tablets made of native corn starch, partially depolymerized corn starch by acid hydrolysis and purely cross-linked corn starch disintegrate completely within 10 min and consequently cannot be used as matrices for sustained release. Partially hydrolysed but pregelatinised starches as Merigel XX do form a coherent gel structure. After a hydration period of 2.5 h this tablet split lengthwise into two halves. This phenomenon leads to a sudden increase of drug release as demonstrated by the dissolution experiments. Tablets made of pregelatinised (Merigel R, b-145) and increasingly cross-linked starches as b-270 and b-291 do form a strong and coherent gel. During these experiments it was noticed that the increase of tablet volume occurs axially for the b-145 tablets while the ones made of b-291, Merigel R and b-270 develop a radial volume increase. This phenomenon could be explained by differences in stress distribution in the tablet. As can be seen from Table 2, the maximal swelling occurs after 24 h and tablets made of b-270 and Merigel R matrices increase their weight about 7-fold, tablets made of b-145 and b-291 matrices about six times while tablets made of Merigel XX only increase their weight about 3 times.

TABLE 2

Swelling behaviour of different modified starch tablets in function of time

(1) = tablet diameter (mm); (2) = tablet thickness (mm); (3) = tablet weight (mg). All results are the mean of three experiments (± S.D.).

Time (h)		Merigel R	Merigel XX	b-145	b-270	b-291
0	(1)	11.28 ± 0	11.28 ± 0	11.28 ± 0	11.28 ± 0	11.28 ± 0
	(2)	2.73 ± 0.06	2.57 ± 0.03	2.42 ± 0.03	2.38 ± 0.03	2.38 ± 0.03
	(3)	300 ± 0	300 ± 0	300 ± 0	300 ± 0	300 ± 0
1	(1)	13.77 ± 0.15	13.38 ± 0.13	11.93 ± 0.06	13.57 ± 0.21	13.25 ± 0.13
	(2)	4.48 ± 0.11	4.04 ± 0.04	5.59 ± 0.47	4.45 ± 0.16	4.39 ± 0.08
	(3)	864 ± 4	787 ± 3	857 ± 11	850 ± 4	822 ± 2
2	(1)	14.45 ± 0.05	13.87 ± 0.16	12.60 ± 0.13	14.58 ± 0.13	13.95 ± 0.09
	(2)	4.57 ± 0.18	4.35 ± 0.08	5.94 ± 0.23	4.62 ± 0.06	4.53 ± 0.16
	(3)	1008 ± 4	866 ± 34	965 ± 6	993 ± 5	931 ± 4
4	(1)	15.55 ± 0.05	–	13.80 ± 0.05	16.03 ± 0.08	15.65 ± 0.10
	(2)	5.01 ± 0.06	–	6.30 ± 0.23	4.81 ± 0.12	4.57 ± 0.12
	(3)	1209 ± 9	–	1145 ± 9	1230 ± 10	1116 ± 4
8	(1)	17.22 ± 0.11	–	15.11 ± 0.26	18.28 ± 0.25	17.22 ± 0.24
	(2)	5.62 ± 0.16	–	7.08 ± 0.16	5.33 ± 0.10	5.51 ± 0.13
	(3)	1473 ± 9	–	1373 ± 21	1607 ± 12	1374 ± 8
24	(1)	19.62 ± 0.32	–	16.95 ± 0.15	20.78 ± 0.13	19.13 ± 0.10
	(2)	6.63 ± 0.11	–	7.61 ± 0.35	6.42 ± 0.03	5.52 ± 0.19
	(3)	2100 ± 14	–	1776 ± 30	2267 ± 21	1787 ± 16

Despite the pregelatinisation, b-291 disintegrates within 0.5 h which is to be attributed to its high cross-linking degree.

As reported by Bamba et al. (1979), some indications may be found on the evidence that besides the diffusion of dissolved drug out of the gelled mass, a limiting factor in the liberation of the drug from the tablet may be the diffusion of water into the tablet. As described by Pitkin and Carstensen (1975), the diffusion coefficient of water in tablets made of polysaccharides, can be calculated. The assumption was made that the tablet can be approximated by a sphere. The radius of a sphere with the same volume as the tablet cylinder was calculated. The volume of the swollen tablet was the average of the volumes at time zero and at 8 h. The diffusion coefficients calculated in this way are about 1.5×10^{-5} for b-291, 1.7×10^{-5} for b-270, 1.1×10^{-5} for b-145, 1.3×10^{-5} for Merigel R and 1.4×10^{-5} for Merigel XX. Because these values are in the range of usual diffusion coefficients one can assume that the diffusion of water into the tablet may be a rate-limiting process in the release of the drug.

The tablet gel strength, expressed as the amount of water necessary to perforate the matrix depends strongly on the material used. A b-291 matrix needs about 72.2 g of water, a b-145 and a b-270 matrix, respectively 52.3 and 43.6 g of water, and a Merigel R matrix only 13.9 g of water.

Release of theophylline from tablets made of modified starches theophylline blends

As could be expected from the data on matrix gel strengths, tablets made of native depolymerised or strongly cross-linked starches disintegrate within 10 min resulting in a rapid liberation of the active compound and therefore were not selected for further experiments.

Fig. 2 shows the dissolution profiles as the percent theophylline released in function of time for several starch modifications. All tablets are made of a starch–theophylline blend (9:1) and compressed at 250 MPa. The tablets made of pregelatinised starches present a prolonged drug release. Pregelatinisation by extrusion seems to induce a slower release in comparison to starches pregelatinised by the drum-drying process. Pre-

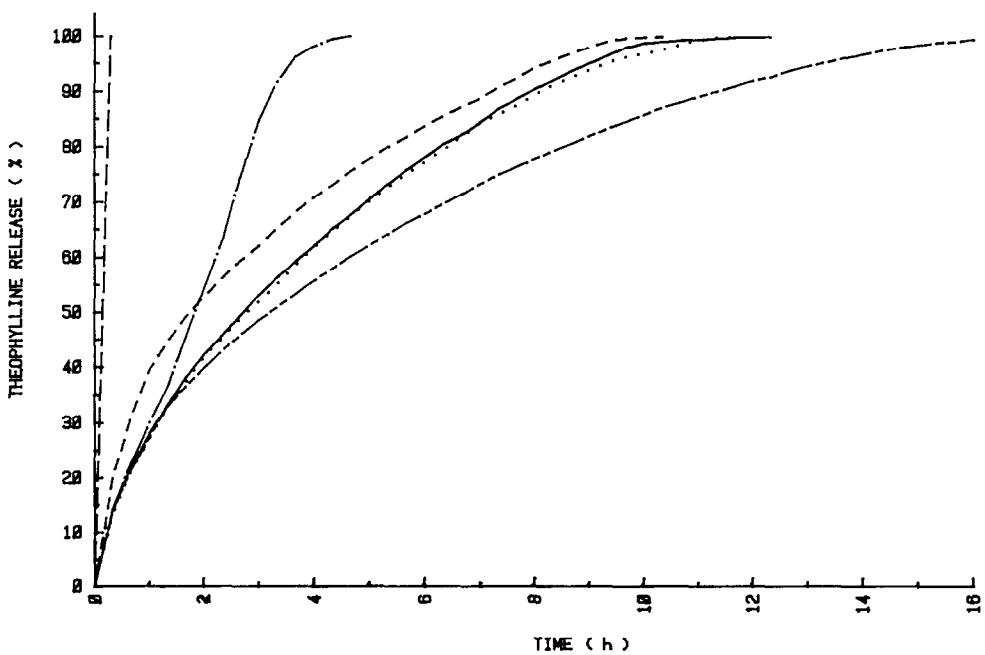

Fig. 2. The effect of the type of starch modification on the release of theophylline from 300 mg tablets containing 30 mg drug. Key: — — —, b-294; · – · – ·, Merigel XX; - - - - - -, b-291; ———, b-278; · · · · · ·, Merigel R; — - - —, b-145.

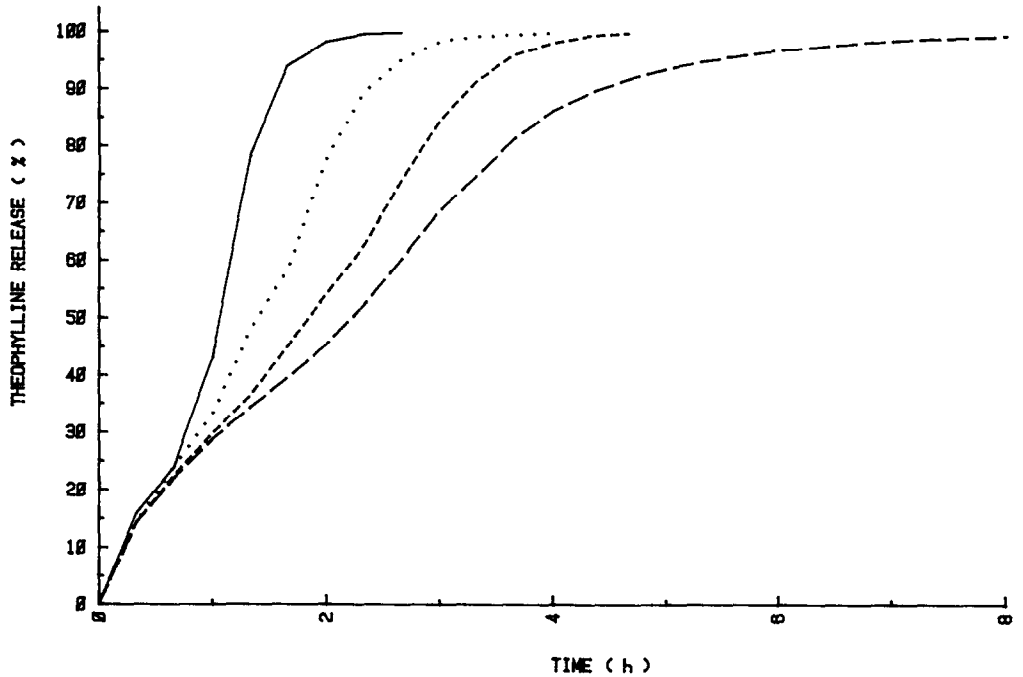

Fig. 3. The effect of compression force on the release of theophylline from 300 mg tablets (9:1 modified starch–drug ratio) containing Merigel XX as modified starch. Key: ———, 50 MPa; ·····, 100 MPa; - - - - - -, 250 MPa; — — —, 400 MPa.

gelatinisation coupled with an increasing cross-linking degree reduces the delay of drug release. As can be seen from Fig. 2, tablets made of Merigel XX compressed at 250 MPa show an abrupt capping, resulting in a sudden burst of drug release. This phenomenon is also seen with other starch modifications and the minimum pressure to avoid this effect is strongly material-dependent. In the case of Merigel XX, a pressure exceeding 400 MPa must be applied to keep the tablet together, while in the case of b-145 only 250 MPa is required (Fig. 3). On the contrary, matrices made of Merigel R and b-270 behave as pressure-independent systems during dissolution experiments.

The parameters analysed during the first series of experiments such as the drug release profile, the hardness of the gel structure and the influence of compression force on the drug release pattern, indicate that the b-270 matrix is a first choice material for further experiments on the starch matrices. Influence of tablet weight, starch–theophylline ratio and soluble diluents was studied on b-270 blends. As can be seen from Fig. 4 (dissolution data are plotted as the percent theophylline dissolved against the square-root of time), linearity is maintained when dissolution was studied on the whole tablet in case of 9:1, 4:1 and 1:1 starch–theophylline ratio. With an increasing starch–drug ratio, a decreased drug release rate is observed. This phenomenon can be explained as differences in the time required to swell increasing amounts of starch.

The small deviation of zero intercept in the case of the 1:1 and 9:1 ratio, can be explained by a failure of the system to obtain immediately the state of equilibrium as described by Higuchi (1963).

Influence of increasing the total tablet weight of a b-270 matrix tablet

Comparing the release rate of theophylline from 300 mg and 500 mg tablets, with two different starch–drug ratios (9:1 and 1:1) an increase in the amount of starch leads to a slower release rate (Fig. 5). This can be explained by an increase in total hydration time for the whole matrix tablet

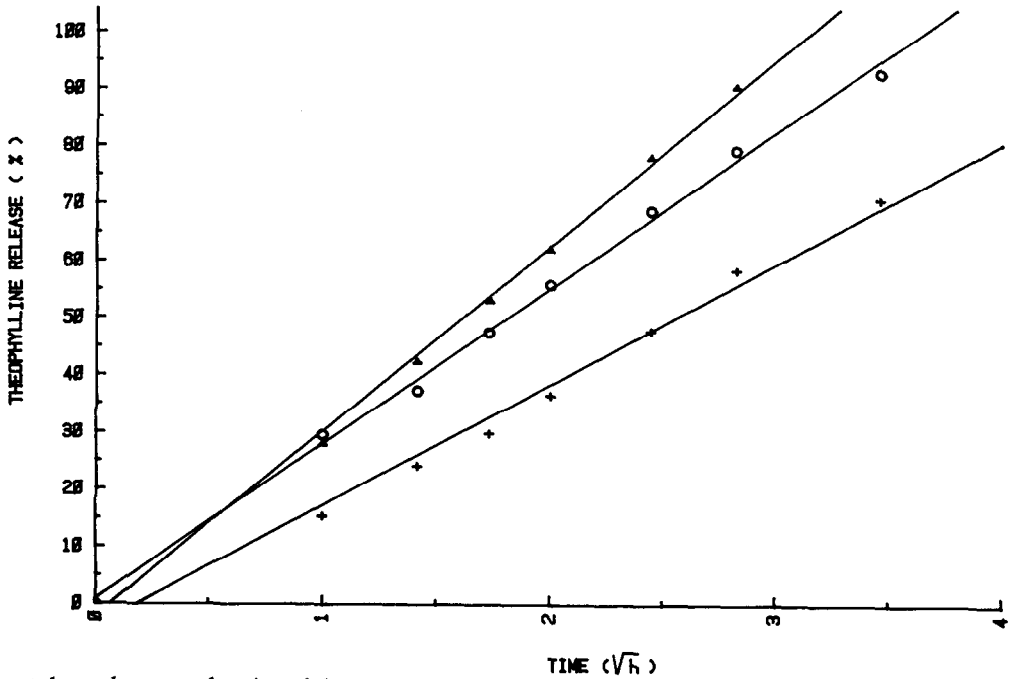

Fig. 4. Percent drug release as a function of the square-root of time from 300 mg tablets containing b-270 as modified starch for 3 different drug–starch ratios. Key: + ——— + (9 : 1); ○ ——— ○ (4 : 1); ▲ ——— ▲ (1 : 1).

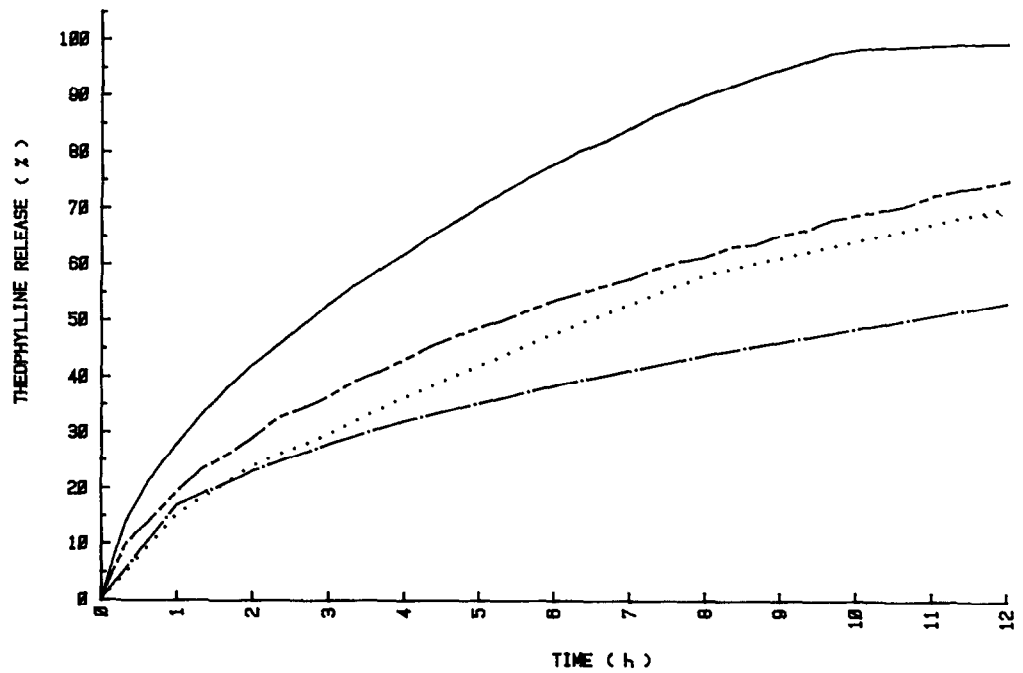

Fig. 5. Percent drug release from 300 mg and 500 mg tablets containing b-270 as modified starch with two different drug–starch ratios. Key: ·–·–·, 300 mg tablet – 9 : 1 ratio; — · · —, 300 mg tablet – 1 : 1 ratio; · · · · · ·, 500 mg tablet – 9 : 1 ratio; ———, 300 mg tablet – 1 : 1 ratio.

and confirms the previous statement that the release rate is a function of the total amount of starch in the formulation.

Influence of lactose as a soluble diluent on the release rate of theophylline from a b-270 matrix tablet

The effect of the addition of the water-soluble diluent, lactose, to tablets composed of 50% theophylline, b-270 and increasing amounts of lactose was studied. Fig. 6 shows the influence of the addition of increasing amounts of lactose on the release rate. As can be seen from Fig. 6, the addition of 10% lactose seems not to influence the release rate. On the contrary, increasing the amount of lactose from 10% to 20% and 30% (w/w) does change the release profile. During the first hour of release a burst effect releasing about 30% of the drug for a matrix with 20% lactose and about 40% of the drug for a matrix with 30% lactose was seen. This can be attributed to erosion of the tablet's outer layers and a delayed installation of an integer gel matrix. As the water-soluble diluent dissolves and diffuses, a decreased tortuosity and a higher drug release rate are expected. Although one can expect attrition occurring because of increasing amounts of lactose, no further positive deviation of drug release after one hour could be seen up to 30% (w/w) of lactose. Increasing the amount of lactose up to 40% makes it impossible to formulate a sustained release matrix. The drug is completely released within 30 min.

Influence of lubricants, silicium dioxide and dissolution medium on the drug release rate

The use of magnesium stearate and polyethylene glycol 4000 abolishes completely the slow release characteristics of the formulation. Only sodium benzoate does not alter the release pattern of theophylline from the b-270 matrix. The incorporation of silicium dioxide, in order to improve the flow characteristics of the powder, does not

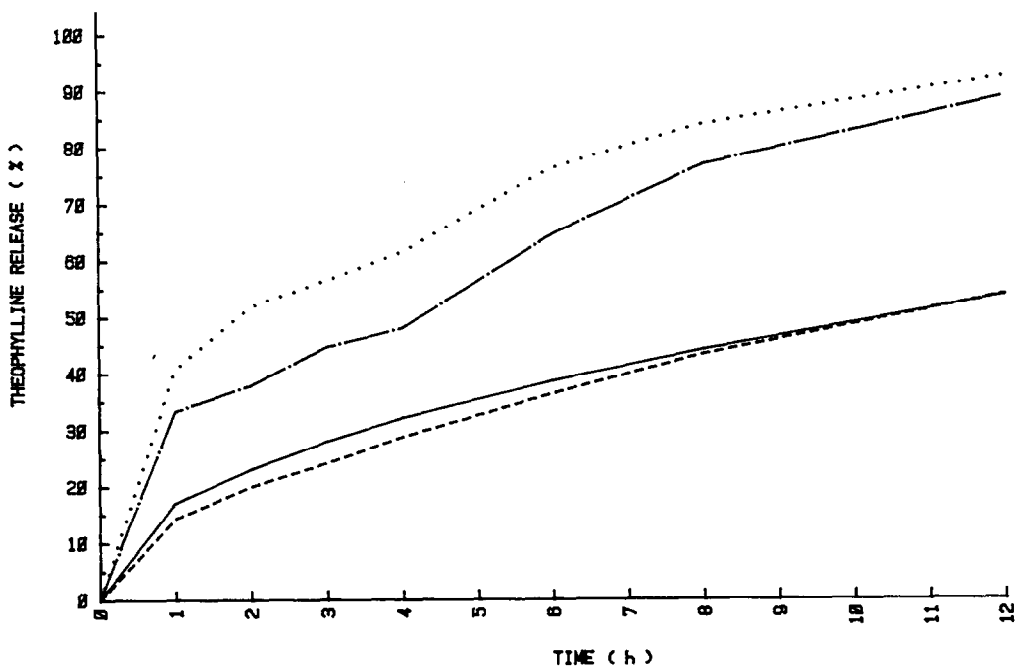

Fig. 6. Effect of the addition of lactose as tablet diluent on the release of theophylline from 300 mg tablets containing 30 mg theophylline, b-270 as modified starch and increasing amounts of lactose. Key: - - - - - -, 0% lactose; ———, 10% lactose; ·–·–·, 20% lactose; ·····, 30% lactose.

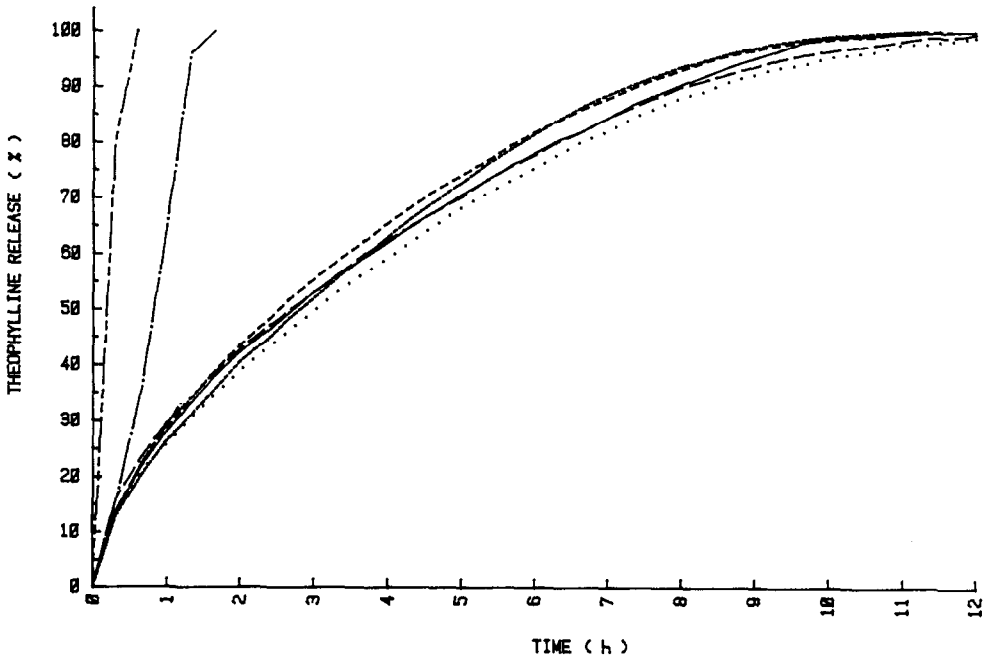

Fig. 7. Influence of the addition of magnesium stearate, polyethylene glycol 4000, sodium benzoate, silicium dioxide and composition of dissolution medium on the release of theophylline from 300 mg tablets containing 30 mg theophylline and b-270 as modified starch. Key: ·–·–·, magnesium stearate; — - - —, polyethylene glycol 4000; ·····, sodium benzoate; - - - - -, silicium dioxide; ———, water as dissolution medium; — — —, artificial gastric fluid; and · · · · · ·, artificial intestinal fluid as dissolution medium.

influence the matrix characteristics. Besides, the release rate is completely independent of the composition of the dissolution medium (Fig. 7).

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