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Modified starches as hydrophilic matrices for controlled oral delivery
III. Evaluation of sustained-release theophylline formulations based on thermal modified starch matrices in dogs

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Summary

The sustained-release of theophylline from several thermal modified starch matrices was evaluated in dogs in comparison to the commercial formulation Theodur 300. Matrices formulated with starches containing 70% amylose revealed a minor shift in t_{max} in comparison with a conventional tablet. The matrices containing amylose free starches showed t_{max} values of ± 4 h. Starch matrices containing 25% amylose demonstrated a good sustained-release performance, comparable to Theodur 300. The influence of the drug/starch ratio was investigated on two types of starches containing 25% amylose: drum dried corn starch and extruded corn starch. A starch/drug ratio between 50/50 and 70/30 showed no significant influence on the biopharmaceutical parameters investigated.

Introduction

In the formulation of controlled release tablets based on hydrophilic matrices, hydroxypropylmethylcellulose is the most widely used polymer. The use of thermal modified starches as hydrophilic matrices was suggested by Rak et al. (1983) and by Van Aerde and Remon (1988). Mohile (1986) reported on the development of an acetylsalicylic acid sustained release tablet based on a thermal modified starch, but the starch modification was not specified. In two previous papers, Herman et al. (1989) and Herman and Remon (1989) reported on the physical and chemical characterisation of a large variety of thermal modified starches and on the in vitro drug release from thermal modified starch matrices. This study reports on the ability of different thermal modified starches to sustain theophylline plasma levels in dogs in comparison to a commercial sustained release formulation and a conventional tablet formulation. The influence of drug/starch ratio on the plasma concentration time profile was also investigated.

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Materials and Methods

Tablet formulations

The following modified starches were used: extruded high amylose (EHA FC 0034), extruded corn starch (ECS, FC 830034), extruded waxy

maize (EWM, FC 001A4), drum dried corn starch (DDCS, SF 127014) and drum dried waxy maize (DDWM, SF 124104), all from Cerestar (Vilvoorde, Belgium). The starches were mixed with anhydrous theophylline (< 250 μm) in a ratio of 60 : 40 (w : w), Aerosil 200 (Pharmachemic, Antwerp, Belgium) 0.2% (w/w) and sodium benzoate (Flandria, Ghent, Belgium) 2.0% (w/w) for 10 min in a Turbula mixer (Type T2A, Basel, Switzerland).

All tablets contained 300 mg anhydrous theophylline and were compressed at 300 MPa using 13 mm flat punches with bevelled edges on a Korsch eccentric press (type EKO, Frankfurt, F.R.G.).

A conventional tablet formulation was prepared containing 459.2 mg Avicel PH 102 (FMC, Philadelphia, USA), 300 mg anhydrous theophylline and 7.8 mg Primojel (E. Mendell, New York, USA). This conventional preparation was characterised by 90% drug dissolution in 10 min using the paddle method (USP XXI).

Theodur 300 (Astra-Nobelpharma, Brussels, Belgium) was used as the commercial sustained release formulation.

Drug administration

Six female dogs weighing 25–29 kg were used for the comparative experiments with the different starch matrices and for the study on the influence of drug/starch ratio on plasma concentration-time profiles. An intra- and intervariability study was performed on DDCS matrices and Theodur utilizing three male and three female dogs weighing 24–26 kg. The dogs were starved 12 h before and 8 h after drug administration. They received water ad libitum. Drugs were administered using a randomized block design. The tablets were given with 200 ml water. Between two experiments in each dog there was an interval of 1 week. Blood samples (1 ml) were withdrawn from the cephalic vein at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24 and 30 h following drug administration. The samples were collected in heparinized glass tubes. Plasma was separated by centrifugation for 10 min at 3000 rpm and frozen at -20°C pending analysis.

Analytical procedure

The HPLC method described by Lauff (1987) was modified in order to obtain an optimal separation of the interacting metabolites. All chemicals were of analytical or HPLC grade; 100 μl of an internal standard solution (15 μg ml^{-1} 3-methylxanthine in water), 100 μl of a saturated solution of sodium bicarbonate, and 100 μl of a saturated ammonium sulfate solution were added to 100 μl plasma. The solution was vortexed for 5 s and extracted with 3 ml of a chloroform-isopropanol mixture (9 : 1, v/v). The solution was centrifuged for 5 min at 3000 rpm. After separation and evaporation of the organic layer under a nitrogen stream (35°C), the residue was redissolved in 100 μl of the mobile phase and 20 μl were injected into the chromatograph. The HPLC equipment consisted of a solvent pump set at a constant flow rate of 1 ml min^{-1} (L 6000 pump, Hitachi, Tokyo, Japan), a variable-wavelength detector (L 4000 UV detector, Hitachi, Tokyo, Japan) set at 273 nm, a reversed-phase column (Lichospher 100 RP-18, 5 μm, Merck, Darmstadt, F.R.G.) and an automatic integrating system (D 2000 chromato-integrats, Hitachi, Tokyo, Japan). The eluent solution consisted of 1.6 g Tris buffer, 824 ml acetonitrile, 125 ml methanol, 1.0 ml hexylamine and 824 ml deionized water. The pH of this solution was adjusted to 7.5 with hydrochloric acid.

Statistics

In vivo data were assessed by the Friedman analysis of variance test. Statistical difference was accepted for $p < 0.05$.

Results and Discussion

Hussein et al. (1987) showed that the dog is a good animal model for the evaluation of sustained release formulations of theophylline and for the prediction of their performance in humans. Theodur 300 has been described as an excellent theophylline prolonged release tablet formulation and was chosen as a reference preparation (Shangraw, 1988). A comparative dose of 300 mg theophylline was selected for all other formulations. The mean

TABLE 1

Plasma peak concentration, t_{max} and area under the curve after administration of 300 mg theophylline as a conventional tablet, Theodur 300 and several tablets made of thermal modified starch matrices (means ± S.D. are shown)

	C_{max} [a] ($\mu g\ ml^{-1}$)	t_{max} (h)	AUC [a] ($\mu g\ h\ ml^{-1}$)
Conventional tablet	14.7 (±1.7)	1.3 (±0.4)	113.3 (±16.1)
Theodur 300	11.5 (±3.1)	6.2 (±2.7)	131.0 (±20.3)
Starch matrix			
EHA	12.8 (±1.5)	2.7 (±2.4)	110.9 (±23.3)
DDCS	11.4 (±4.2)	8.0 (±4.0)	129.9 (±37.8)
ECS	9.1 (±1.8)	4.2 (±2.1)	95.3 (±26.0)
DDWM	13.2 (±4.0)	3.8 (±1.9)	104.9 (±36.3)
EWM	13.9 (±3.4)	3.8 (±1.3)	119.8 (±14.0)

[a] N.S. (Friedman test).

plasma theophylline concentration-time profiles after administration of 300 mg theophylline as a conventional tablet, as Theodur 300 or as tablet matrices made of some thermal modified starches (starch-drug ratio: 60/40) are shown in Fig. 1. C_{max}, t_{max} and AUC values are listed in Table 1. C_{max} and AUC were not significantly different (Friedman test; $p = 0.05$) for the conventional tablet, Theodur 300 and hydrophilic starch matrices made of DDCS, DDWM, EWM and ECS. The t_{max} of the conventional formulation was short (1.3 ± 0.4 h), while it was clearly prolonged in the case of Theodur 300 (6.2 ± 2.7 h) and the DDCS matrix (8.0 ± 4.0 h). The E.H.A. matrix showed a t_{max} of (2.7 ± 2.4 h) while intermediate values were observed for the ECS (4.2 ± 2.1 h), DDWM (3.8 ± 1.9 h) and EWM (3.8 ± 1.3 h) matrices.

Earlier communications (Herman et al., 1989) showed a correlation between the amylose content of the starches and the in vitro drug release rate; starches containing 70% amylose produced matrices with a high in vitro drug release rate. It was also noted that the gels formed by some amylose free starches showed a pronounced slow release but were weak and might erode quickly in

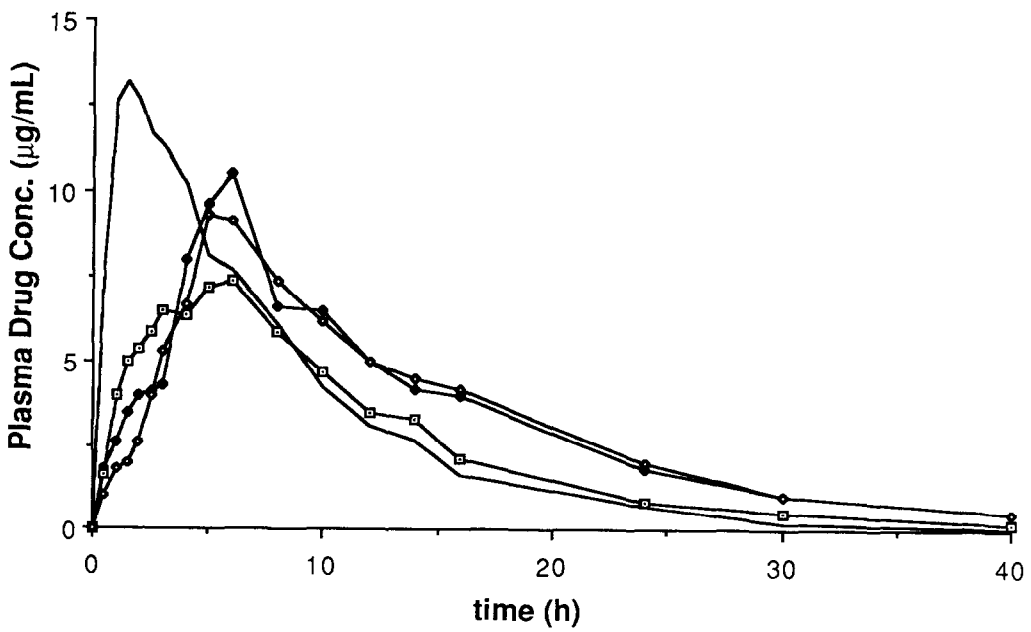

Fig. 1. Mean plasma concentrations of theophylline obtained after intake of 300 mg of a conventional preparation (———), Theodur (◆———◆) and hydrophilic matrices made of drum dried corn starch (◆———◆) and extruded corn starch (⊡———⊡) ($n = 6$).

TABLE 2

Plasma peak concentration, t_{max} and area under the curve after administration of 300 mg theophylline as drum dried corn starch and extruded corn starch matrices (starch-drug ratios: 50/50, 60/40 and 70/30; means ± S.D. are shown)

	C_{max} [a] (mg ml^{-1})	t_{max} (h)	AUC [a] (μg h ml^{-1})
Starch matrix			
DDCS 50/50	8.0 (±3.0)	8.2 (±4.6)	120.1 (±18.9)
DDCS 60/40	11.4 (±4.2)	8.0 (±4.0)	129.9 (±27.8)
DDCS 70/30	9.9 (±3.5)	7.3 (±1.9)	151.4 (±57.1)
ECS 50/50	12.3 (±2.1)	5.3 (±2.4)	129.9 (±32.1)
ECS 60/40	9.1 (±1.8)	4.2 (±2.1)	95.3 (±26.0)
ECS 70/30	10.8 (±2.8)	3.8 (±1.3)	117.4 (±39.0)

[a] N.S. (Friedman test).

the gastrointestinal tract. The in vivo data obtained in this study are in good agreement with these observations. A low average t_{max} value was seen for the extruded high amylose matrix (2.7 h) while higher t_{max} values were observed for the drum dried and extruded corn starch matrices containing 25% amylose (8 and 4.2 h, respectively). An average t_{max} value of about 4 h was obtained for both the drum dried and extruded waxy maize starch matrices, probably due to a high erosion rate of the weak gels.

As DDCS and ECS starch matrices showed the most promising plasma concentration time profiles (Fig. 1) the influence of the starch-drug ratio was investigated for both these matrices. Matrices presenting a starch-drug ratio of 50/50, 60/40 and 70/30 were prepared. C_{max}, t_{max} and AUC are shown in Table 2. C_{max} and AUC were not significantly different (Friedman test; $p = 0.05$) for the different starch/drug ratios investigated in the case of the DDCS and ECS matrices. The average t_{max} values were 7.8 and 4.5 h for the DDCS and the ECS matrices, respectively.

As drum dried corn starch matrices showed sustained plasma concentration profiles similar to Theodur, the inter- and intraindividual variability

TABLE 3

Peak plasma concentration, t_{max} and area under the curve after administration of 300 mg theophylline as Theodur 300 and drum dried corn starch matrices (starch / drug ratio: 60 / 40) (both formulations were administered to six dogs and each formulation was administered twice)

Dog number	C_{max} [a] (μg ml^{-1})		t_{max} (h)		AUC [a] (μg h ml^{-1}) (0 → 24 h)	
	Theodur	DDCS	Theodur	DDCS	Theodur	DDCS
A_1	11.5	8.5	6	4	98.5	88.9
A_2	18.2	8.7	5	4	149.6	94.3
B_1	13.7	13.0	3.5	8	100.8	133.3
B_2	14.3	13.2	6	4	157.4	96.8
C_1	12.3	7.8	3	3	130.8	55.4
C_2	7.8	18.8	8	6	132.8	162.8
D_1	15.3	9.0	8	8	120.0	104.1
D_2	13.7	9.7	8	4	135.4	98.7
E_1	13.3	3.7	12	12	145.7	50.9
E_2	11.3	12.8	10	12	118.2	138.9
F_1	9.7	9.5	5	12	110.4	92.3
F_2	7.2	12.0	10	6	79.4	92.7
Mean value (±S.D.)	12.4 (±3.0)	10.6 (±3.7)	7.0 (±2.6)	6.9 (±3.4)	123.2 (±22.1)	100.8 (±32.0)
Mean intra-variability difference (±S.D.)	3.0 (±2.0)	3.6 (±3.9)	2.6 (±1.9)	2.8 (±2.2)	30.5 (±19.1)	40.5 (±40.2)

[a] N.S. (Friedman test).

was studied for both formulations. A 60/40 starch/drug ratio was selected for this experiment.

Table 3 indicates the results of the inter- and intravariability experiments on Theodur 300 and the DDCS matrix (60/40). C_{max}, t_{max} and AUC were not significantly different (Friedman test; $p = 0.05$) for both preparations. The intravariability for the bioavailability parameters was acceptable and similar for both formulations. As inter- and intravariability in bioavailability are low, investigations on the evaluation of DDCS matrices in comparison to Theodur 300 will be performed in humans.

This study showed that drum dried corn starch matrices performed as well as sustained release formulations in the dog. A starch-drug ratio between 50/50 and 70/30 did not influence C_{max}, t_{max} or AUC significantly. The most important factor influencing the plasma concentration time profiles was the chemical composition of the starches. Starches with an amylose content of 25% showed a sustained release performance comparable to Theodur 300. The thermal treatment technique of the starches seemed of minor influence.

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