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Modified starches as hydrophilic matrices for controlled oral delivery. II. In vitro drug release evaluation of thermally modified starches

J. Herman and J.P. Remon

Laboratory of Pharmaceutical Technology, State University of Ghent, Ghent (Belgium)

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Summary

Because of their cold water swellability, non-toxicity and low cost, thermally modified starches might be interesting excipients for sustained release tablets. The formation of an obstructive gel layer is required to ensure a sustained drug release. Only fully pregelatinized starches containing a low amount of amylose produced such gel layers in water. Tabletting additives as silicium dioxide did not influence the drug release rate while lubricants such as magnesium stearate and polyethyleneglycol 6000 increased the drug release rate dramatically. Only sodium benzoate seemed a useful lubricant which even prolonged the drug release. The gel strength of the hydrated tablets seemed proportional to the degree of amylose in the formulated starch. For starches containing 25% amylose, at a low compression force a splitting of the tablet was seen after a few hours of dissolution. This phenomenon, called "mussel effect", caused a burst in the drug release which was increased by a large starch particle size. A compression force of at least 200 MPa could prevent this mussel effect. The drug release rate from tablets containing amylose-free starches was not influenced by the compression force, nor by the starch particle size. Thermally modified starches containing a low amount of amylose (25% and lower) revealed promising properties as directly compressible tabletting excipients for sustained release purposes.

Introduction

During the last decade many controlled-release tablet formulations based on hydrogel matrices have been developed. Cellulose derivatives have been the most successful choice for this purpose (Buri and Doelker, 1980). Some authors have mentioned the possible use of thermally modified starches for prolonged release purposes (Rak et al., 1983; Van Aerde and Remon, 1988). Mohile (1986) reported the formulation of an acetyl salicylic acid-sustained release tablet based on modified starches. The non-toxicity and the low production costs of the thermally modified starches make them of great interest for the formulation of controlled release tablets. A fundamental study on the production and characterization of these products was reported recently (Herman et al., 1989). That study pointed out that both the chemical composition of the starch and the modification techniques have a considerable influence on the physical properties of the modified starches.

Correspondence: J.P. Remon, Laboratory of Pharmaceutical Technology, State University of Ghent, B-9000 Ghent, Belgium.

This paper presents the in vitro evaluation of several thermally modified starches as controlled-release agents. The influence of the chemical composition, the degree of pregelatinization, the modification technique and the particle size of the starches on the drug release was evaluated. Gel strengths of the fully hydrated tablets were measured as a prediction for the resistance against tablet erosion in vivo. The influence of pH and ionic strength on the drug release was evaluated using different dissolution media. As it is the intention to formulate a directly compressible drug-starch powder mix, the influence of different tablet additives on drug release and the influence of the compression force were reported.

Based on these results some tablet formulations are selected for further in vivo drug absorption evaluations.

Materials and Methods

Influence of tabletting excipients on the in vitro drug release

Tablet formulations were composed of anhydrous theophylline (≤ 500 μm, Flandria, Ghent, Belgium) which was chosen as a model drug, starch (spray-dried/pregelatinized, drum-dried and extruded starches), silicium dioxide (Aerosil 200, ≤ 180 μm, Pharmachemic, Antwerpen, Belgium) and a lubricant as indicated in Table 1. The powders were mixed for 10 min in a Turbula mixer (Type T2A, Pleuger, Basel, Switzerland). A 100 mg powder mix was compressed on an eccentric instrumented press (Korsch, type EKO, Frankfurt, F.R.G.) equipped with 7 mm flat punches at a pressure of 100 MPa. The release experiments of theophylline from the different tablets were performed in water at 37 °C using the paddle dissolution system (USP XXI), rotating at 50 r.p.m. The drug concentration was monitored continuously using a Zeiss PM 6 spectrophotometer (Zeiss, Oberkochen, F.R.G.).

The comparison in drug dissolution between formulae I and II (Table 1) allowed us to examine the influence of 0.5% silicium dioxide. The comparison in drug dissolution between formula III and IV, V and VI (Table 1) revealed information about the influence of magnesium stearate (≤ 180 μm, Flandria, Ghent, Belgium), sodium benzoate (≤ 180 μm, Flandria, Ghent, Belgium) and polyethyleneglycol 6000 (≤ 180 μm, Pharmachemic, Antwerpen, Belgium) on the drug release rate.

Influence of chemical composition, modification technique and degree of pregelatinization on the in vitro drug release

Three native starches containing different amounts of amylose were used to evaluate the influence of the chemical composition of the starches on the drug release: 0% amylose (Meriwax), 25% amylose (Meritena), both from Amylum (Aalst, Belgium) and 70% amylose (Hylon VII, National Starch, Bridgewater, NJ, U.S.A.). Drum-drying and extrusion of native starches were performed by Cerestar (Vilvoorde, Belgium). Modification of the native starches by spray-drying, preceded or not by partial or full pregelatinization was performed as described in a previous paper (Herman et al., 1989).

TABLE 1

Composition of the tablets used to investigate the influence of the type of modified starch, glidant and lubricants on the theophylline release rate (mg per tablet)

	I	II	III	IV	V	VI
Starch	60	59.70	59.88	59.58	58.68	58.68
Theoph. anh.	40	39.80	39.92	39.72	39.12	39.12
Silic. diox.	–	0.50	0.20	0.20	0.20	0.20
Magn. stear.	–	–	–	0.50	–	–
Sodium. benz.	–	–	–	–	2.0	–
PEG 6000	–	–	–	–	–	2.00

Formula V is referred to as "standard formula".

All these starches were formulated according to formula V (Table 1), indicated as "standard formula". The drug dissolution tests were performed as described in the previous section.

Influence of compression force on the in vitro drug release

250 mg of the standard formula were compressed at 50, 200 and 300 MPa on a computerized high-sensitive eccentric press (Courtoy, Halle, Belgium) equipped with 13 mm flat punches. These tablets were subjected to dissolution experiments according to the method described in the first section.

Influence of starch particle size on the in vitro drug release

Three different sieve fractions of the starches were used: below 40 μm, between 40 μm and 90 μm, and above 90 μm. These fractionated starches were formulated in the standard formula (250 mg tablet weight) and compressed at 200 MPa using an eccentric press equipped with 13 mm flat punches. The tablets were subjected to the previously described dissolution experiments.

Gel strength of the fully hydrated tablets

All pregelatinized amylose-free starches and pregelatinized starches containing 25% amylose were formulated according to the standard formula and compressed at 200 MPa as described in the previous section. The tablets were subjected to a complete drug release in water. The gel strength of the remaining gels was measured over a penetration depth of 2 mm using an Instron Universal testing machine (Type 1026, Instron Ltd., U.K.) fitted with a 9 mm plunger. The hardness was calculated as described by Herman et al. (1989) and expressed in N.

Influence of the dissolution media on the in vitro drug release

Dissolution tests on 13 mm tablets made of standard powder mixes and compressed at 200 MPa, were performed at 37 °C in 3 different dissolution media: water, simulated gastric fluid and simulated intestinal fluid (U.S.P. XXI).

Results and Discussion

Influence of tablet excipients on the in vitro drug release

No difference in dissolution could be observed between formulae I and II indicating that silicium dioxide does not affect the drug release (Table 1).

The drug release from tablets containing 0.5% magnesium stearate or 2.0% polyethylene glycol 6000 (formulae IV and VI) is much faster than from non-lubricated tablets (formula III). In contrast, sodium benzoate (formula V) does not increase the drug release rate. These results confirm the data published by Van Aerde and Remon (1988). In several cases, it even decreases the dissolution rate (Table 2). Silicium dioxide and sodium benzoate are suitable tabletting excipients for hydrogel matrices based on thermally modified starches.

Influence of degree of pregelatinization on the in vitro drug release

Due to the disintegration of the tablets a fast drug release (< 5 min) is seen for tablets containing native and non-pregelatinized spray-dried starches independent of the origin. The disintegration of the tablets is due to a limited swelling of the starch grains in water (Ingram and Lowenthal, 1966). The drug release from tablets containing spray-dried partially pregelatinized starches is decreased (< 20 min) compared to tablets containing native starches, but is still fast. This can be explained by an abstention or a limited gel formation because starch grains are not able to swell in

TABLE 2

Influence of different lubricants on the drug release rate from tablets of different modified starches containing 25% amylose

	Pregelatinizing process		
	Spray drying	Extrusion	Drum drying
− Lubricant	70 ± 18	440 ± 28	420 ± 26
+ Magn. stear.	14 ± 6	174 ± 42	54 ± 13
+ PEG 6000	10 ± 3	84 ± 26	48 ± 2
+ Sod. benz.	180 ± 13	498 ± 12	567 ± 28

The time (min; ± S.D.) of 80% release is indicated ($n = 3$).

TABLE 3

Influence of amylose concentration and pregelatinization process on the drug release rate from tablets containing different starches

Amylose content (%)	Pregelatinization process		
	Spray drying	Extrusion	Drum drying
0	630 ± 40	170 ± 11	640 ± 13
25	70 ± 13	440 ± 12	420 ± 28
70	38 ± 17	4 ± 1	*

Time (min; ± S.D.) of 80% release is indicated ($n = 3$).
* Native Hylon VII starch cannot be fully pregelatinized by drum-drying (Herman et al., 1989).

cold water as long as the starch slurry has not reached the gelatinization temperature during the thermal modification process (Leach et al., 1959). Based on these results only fully pregelatinized starches were selected for further investigation on their possible use as slow-release agents.

Influence of the starch composition and modification technique on the in vitro drug release

Table 3 indicates the influence of the native starch composition and the modification technique on the in vitro drug release. Starches containing 70% amylose do not form an obstructive gel layer at the surface of the tablet, but swell progressively with the formation of a porous spongy layer. This layer erodes quickly resulting in a fast drug release.

Extrusion and drum-drying seem useful modification techniques for starches containing 25% amylose. Less than 80% drug was released after 7 h. Amylose-free starches, modified by spray drying and drum drying, show the slowest drug release. Less than 80% drug was released after 10 h. However, one should emphasize that the swollen gel layer of the amylose free starches seems very weak. In vivo the erosion of such a gel layer may accelerate the drug release.

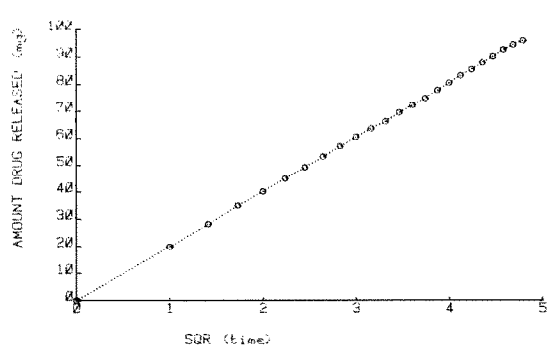

Fig. 1. Amount of drug released vs square root of time for an amylose free drum dried starch tablet in water at 37 °C.

For all tablet formulations containing pregelatinized amylose free starches, a Fickian drug release mechanism was observed. An example for drum-dried corn starch is shown in Fig. 1. The individual points of the plot had a correlation coefficient of 0.999949 calculated using the least-squares method. As hydrogels which swell in cold water generally do not follow a Fickian diffusion mechanism, the observed Fickian drug release mechanism may be due to a combination of polymer swelling and erosion (Lee, 1985).

Influence of compression force on the in vitro drug release

In the production of slow release tablets, it is advisable to develop a matrix system which ensures a pressure independent drug release rate. Fig. 2 shows the drug release rate for modified starches containing 25% amylose which is inversely related to the compression force. In an initial phase of the dissolution profiles, the release from amylose-free starches and starches containing 25% amylose are similar. After a few hours the tablet containing starches with 25% amylose

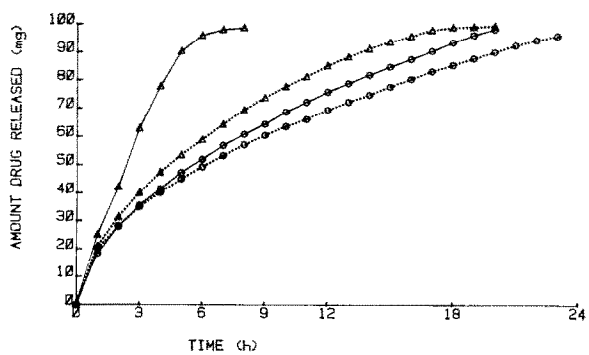

Fig. 2. Influence of compression force on drug release from hydrophilic matrices containing drum-dried starches; (△———△), 25% amylose, 50 MPa; (△·····△), 25% amylose, 200 MPa; (○———○), 0% amylose, 50 MPa; (○·····○), 0% amylose, 200 MPa.

splits into two parts resulting in a burst of drug release because of an increase in free surface area. This phenomenon is called "mussel effect". A compression force of 200 MPa seems sufficient to prevent this mussel effect. These results confirm the data published by Van Aerde and Remon (1988). Above this pressure no pressure dependency is observed for all tablets containing amylose-free starches.

Influence of the starch particle size on the in vitro drug release

During pregelatinization the starch particle size increases. For the spray-dried starches, the particle size is doubled compared to the native starches. The particle size of drum-dried and extruded starches depends on the final grinding step (Herman et al., 1989).

The drug release from tablets containing amylose-free starches was not influenced by the particle size of the starch. For starches containing 25%, amylose, a high particle size (> 90 μm) induced the mussel effect, resulting in a fast drug release (Table 4). Keeping the particle size below 90 μm seems efficient to overcome the mussel effect, ensuring a pressure-independent slow drug release.

Gel strength of the hydrated tablets

The gel strength of the fully hydrated tablets is introduced as a possible indication of resistance against gastro-intestinal abrasion. A large difference was observed between tablets containing 0% and 25% amylose (Table 5). For starches containing 25% amylose, spray-dried starches reveal a higher gel strength than the drum-dried and extruded ones, respectively. Nevertheless, drug release rate values are in conflict with the gel strength data. These observations can be explained as follows: starches containing 25% amylose produce a gel with a relatively low cohesiveness during the drug release process. The layer from which the drug has dissolved separates slowly from the tablet as small flakes. This phenomenon is much more pronounced for spray-dried starches than from drum-dried and extruded starches. A tablet containing amylose-free starches forms a cohesive glassy and non-separating gel in the region where the drug has been released. The gel strength and the fast separation of the drug free layer from the tablet will influence the drug release in vivo. It is not possible yet to predict which property will dominate the drug release in vivo.

TABLE 4

Influence of the particle size of extruded starches on the drug release rate

Particle size	starch type	
	0% Amylose	25% Amylose
> 90 μm	132± 8	350±28
40–90 μm	132± 6	720± 6
≤ 40 μm	127±13	890± 6

Time (min; ±S.D.) of 80% release is indicated ($n = 3$).

TABLE 5

Gel strength of the hydrated tablets (expressed in N; ± S.D.) ($n = 3$)

Modification technique	starch type	
	0% amylose	25% amylose
Spray drying	0.22±0.07	7.76±0.04
Drum drying	0.03±0.01	5.80±0.80
Extrusion	*	3.21±0.86

* The tablet dissolved before all drug was released.

Influence of the dissolution media on the in vitro drug release

Only for starches containing 25% amylose and compressed at a very low pressure (50 MPa), a remarkable increase of the drug release rate is observed in simulated gastric fluid compared to the drug release rate in simulated intestinal fluid and water (Table 6).

This increase in drug dissolution rate is in correlation with the low viscosities of corresponding starch pastes in acidic medium (Herman et al., 1989). The fact that the highest change in release rate is observed for tablets compressed at a low compression force is due to the low compaction of the tablet. Due to this low degree of compaction, the dissolution medium substance which is able to hydrolyse the starch molecules, has penetrated

TABLE 6

Influence of dissolution media on drug release from hydrogel matrices containing drum-dried starches compressed at 50 MPa and 200 MPa

Amylose	50 MPa			200 MPa		
	SGF	SIF	water	SGF	SIF	water
0%	711	804	842	780	960	870
25%	55	420	257	514	669	677

Time (min) of 80% drug release is indicated ($n = 3$; $S.D._{max} = 13$).

into the tablet before the obstructive gel layer is formed.

The increase in drug release rate in acidic medium was negligible for tablets containing amylose-free starches.

The addition of amylase to the simulated intestinal fluid does not influence the drug release rate. So, from a moderate compression force, the dissolution media do not influence the drug dissolution rate considerably.

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