Controlled Release of Paracetamol from Amylodextrin Tablets: *In Vitro* and *in Vivo* Results

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Amylodextrin is a suitable excipient for the design of solid controlled-release systems. The release of paracetamol from tablets containing 30% drug and 70% amylodextrin was studied *in vitro* and *in vivo*. *In vitro* dissolution profiles showed almost-constant drug release rates during 8 hr, when measured in 0.05 *M* buffer, pH 6.8. Peroral administration of the tablets to man showed almost-constant paracetamol plasma levels up to 14 hr, as compared to fast absorption and fast elimination of a reference paracetamol solution. The plasma profiles of eight volunteers demonstrated a small intersubject variability during the first day after tablet administration. Increasing variability and decreasing plasma levels during the second day were caused by excretion of tablets from the bodies. Cumulative input as a function of time showed near-zero-order drug release during the first day. The *in vivo* results indicate that amylodextrin tablets are not hydrolyzed by α-amylase, present in the gastrointestinal tract.

KEY WORDS: amylodextrin; paracetamol; controlled release; tablet; *in vitro;* absorption profile.

INTRODUCTION

Amylodextrin is a linear dextrin, with an average of 35 glucose units per molecule (1). It can be obtained from waxy maize by enzymatic hydrolysis of the α-1,6 glycosidic bonds of amylopectin by pullulanase. An initial study indicated that powder mixtures of theophylline monohydrate, and amylodextrin can be easily compacted in tablets, demonstrating controlled drug release. Tablets of 300 mg, containing 70% amylodextrin and 30% theophylline monohydrate, having a diameter of 9 mm, and compacted at 10 or 15 kN, showed almost-constant drug release rates. Up to 75% of theophylline monohydrate could be incorporated in the amylodextrin tablets, without impairing the nearly constant drug release kinetics. The present study was performed to verify the *in vivo* behavior of the controlled-release amylodextrin system by peroral administration to man. Paracetamol, a widely used nonnarcotic analgesic, was chosen as the model drug. Both the *in vitro* and the *in vivo* release profiles obtained for amylodextrin tablets with a drug load of 30% were evaluated.

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MATERIALS AND METHODS

Chemicals

Amylodextrin was produced as described by Te Wierik *et al.* (1). Paracetamol pulv. pH Eur. (Genfarma, NL-Maarssen) was used as the model drug. Amylodextrin and paracetamol were stored at 20 ± 1°C and 45 ± 5% relative humidity. All other chemicals used were of analytical grade.

Preparation of Tablets

Amounts of 70% amylodextrin (<180 μm) and 30% paracetamol (<180 μm) were mixed in a Turbula mixer during 30 min. Tablets of 333 mg were compacted on an instrumented hydraulic press (ESH Testing, Brierley Hill, UK) in a die with a diameter of 9 mm having flat-faced punches. The compaction force was 10 kN, with a load rate of 2 kN/sec. The forces were applied during 0.1 sec.

In Vitro Drug Release

In vitro dissolution testing was performed in a paddle apparatus (Prolabo, Rhône-Poulenc, F-Paris) under conditions specified in the USP XXII. The dissolution medium 1 L of 0.05 *M* phosphate buffer, pH 6.8, was deaerated and maintained at 37 ± 1°C. The rotation speed of the paddle was 100 rpm. The samples were analyzed for drug content at $\lambda_{243\ nm}$, using a Biochrom spectrophotometer (LKB, GB-Cambridge). The experiment was carried out four times.

In Vivo Study Design

The protocol was approved by the Ethical Committee of the University Hospital in Groningen.

Two preparations were administered orally to each volunteer:

(i) three paracetamol-containing amylodextrin tablets, corresponding to a total of 300 mg of paracetamol; and

(ii) a neutral solution containing 300 mg of paracetamol in 200 mL of water, used as a reference.

Eight healthy male volunteers (age, 24–29 years; weight, 70–82 kg) participated in the study. The paracetamol preparations were given to the volunteers in a crossover design. The solid dosage forms were administered with 200 mL of water. The study was carried out with a washout period of about 1 week after each administration.

The subjects were asked to take no drugs 2 weeks before and during the entire study. They were asked to refrain from alcoholic beverages and caffeine- or theobromine-containing beverages or food for 12 hr before and on the day of blood sampling.

All volunteers fasted for 12 hr prior to dosing. Breakfast was served about 40 min after dosing. A light meal was taken 4 hr after dosing. Dinner was served 11 hr after drug administration.

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Predose blood samples (±7 mL) were obtained immediately before dosing by venipuncture (Venojects) in a forearm vein. After dosing of the reference solution blood samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hr. After administration of the amylodextrin tablets blood samples were taken at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 28, and 32 hr. Plasma samples (separated from the whole blood by centrifugation) were stored at −18°C until analyses.

Assay Procedure

To 1 mL of plasma 200 μL of trichloroacetic acid solution (20%) was added. The mixture was vortexed for 15 sec and centrifuged at 1800*g*, 500 μL of the clear supernatant was transferred to a reaction tube, and 4.5 mL of 0.05 *M* phosphate buffer pH 7.4 was added. After mixing, the solution was transferred to a sample bottle of the autoinjector and 100 μL of the solution was injected on the column. A calibration line was prepared by adding, respectively, 0, 5, 10, 15, 20, 40, 60, and 80 μL standard solution (100 mg paracetamol/L aqua dest.) to 1.0 mL blank plasma. These samples were analyzed as described.

The analytical column was a ChromSpher C_{18} column (Chrompack; mean particle size, 5 μm; 250 mm × 4.6-mm I.D.) used with a Guard-pak holder ("yo-yo") + μBondapak C_{18} Guard-pak insert. The mobile phase used was water:acetonitrile:methanol:acetic acid (86:7:7:0.02) and the flow rate was 1.0 mL/min. The column effluents were monitored at $\lambda_{245\ nm}$.

Pharmacokinetic Analysis

The absorption profiles of paracetamol were calculated from the plasma data using numerical deconvolution (2). The plasma concentrations obtained from the orally administered reference solution were used to calculate the cumulative input from the tablets.

RESULTS AND DISCUSSION

The *in vitro* release profiles of paracetamol from amylodextrin tablets with a drug load of 30% are depicted in Fig. 1. The release was measured in 0.05 *M* phosphate buffer, pH 6.8, during 8 hr. After an initial slight burst effect the release profiles, performed fourfold, all show constant release rates.

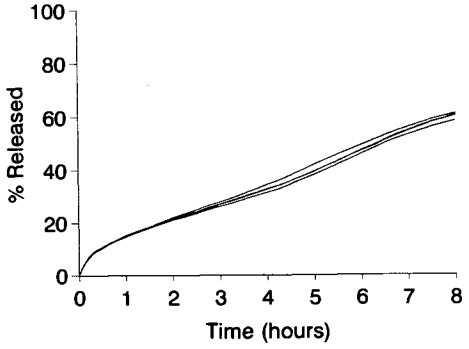

Fig. 1. Drug release profiles from amylodextrin tablets containing 30% paracetamol, measured in 0.05 *M* buffer, pH 6.8 (n = 4).

The very small variation between the separate release patterns demonstrates the high reproducibility of the programmed release system. Within 8 hr 60% of the incorporated drug was released. Considering *in vivo* drug release from programmed release tablets, the pH in the gastrointestinal tract may influence the drug release rate. In healthy subjects the stomach has an acidic environment, with pH's ranging from approximately 1 to 5, whereas the pH in the small intestine and colon ranges from approximately 5 to 8 (3). In a previous study (4) amylodextrin tablets containing 30% paracetamol showed almost-identical release profiles during 20 hr when measured in acidic (0.1 *M* HCl) or neutral (0.05 *M* buffer, pH 6.8) medium. Paracetamol is a weakly acidic drug (pK_a = 9.5) which is largely nonionized in the gastrointestinal tract (5). It was therefore expected that the changing acidity over the gastrointestinal tract would not affect the *in vivo* release of paracetamol from amylodextrin tablets.

Figure 2 reflects the results obtained from the *in vivo* experiments. The plasma levels both after peroral administration of amylodextrin–paracetamol tablets and after peroral administration of a paracetamol reference solution are depicted. Mean values of eight subjects are given together with their standard deviations. Both preparations, containing 300 mg of paracetamol, were administered to the volunteers on an empty stomach. This allows the preparations to be transported rapidly to the small intestine, where absorption starts (6). Some plasma pharmacokinetic parameters of paracetamol from both preparations are shown in Table I. Regarding the reference solution, it is clear that absorption is very fast, followed by fast elimination. Table I reflects an average T_{max} of 28 ± 17 min for the reference solution, corresponding to an average C_{max} of 3.67 ± 0.50 mg/L. The

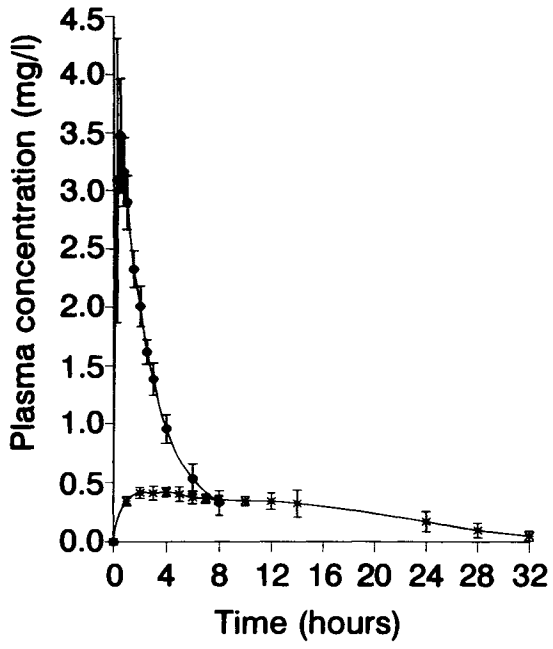

Fig. 2. Plasma levels of paracetamol after administration of amylodextrin tablets (*) and a reference solution (●), respectively. Mean ± SD (n = 8).

Table I. Plasma Pharmacokinetic Parameters of Paracetamol

	Reference solution		Tablets				
					Cumulative input		
Subject no.	C_{max} (mg/L)	t_{max} (min)	C_{max} (mg/L)	t_{max} (hr)	8 hr	14 hr	32 hr
1	3.25	45	0.48	14.00	0.40	0.64	0.98
2	3.47	30	0.51	5.00	0.37	0.51	0.68
3	3.48	15	0.39	5.00	0.37	0.53	0.85
4	3.78	30	0.48	3.00	0.39	0.53	0.72
5	3.85	15	0.46	4.00	0.36	0.44	0.46
6	2.90	60	0.39	2.00	0.35	0.51	0.59
7	4.43	15	0.45	2.00	0.34	0.51	0.73
8	4.22	15	0.45	2.00	0.31	0.47	0.57
Average	3.67	28	0.45	4.63	0.36	0.52	0.70
SD	0.50	17	0.04	4.00	0.03	0.06	0.16

elimination half-life of paracetamol varies from 1 to 3 hr in normal subjects (7). Administration of the paracetamol-containing amylodextrin tablets resulted in sustained release profiles. The fast increase in the paracetamol plasma concentration (Fig. 2) within the first hour is attributed to the small burst effect from the tablets as observed in the *in vitro* study (Fig. 1). Constant paracetamol plasma levels of approximately 0.4 mg/L were achieved over a period of almost 14 hr. This result demonstrates balanced absorption and elimination of paracetamol. The reproducibility of drug release from the amylodextrin tablets is demonstrated by the small intersubject variability. Table I reflects an average C_{max} of 0.45 ± 0.04 mg/L and an average t_{max} of 4.63 ± 4.00 hr. Evidently the mean plasma levels decreased at the end of the first and during the second day of the experiment because of excretion of tablets by increasing numbers of the volunteers.

The cumulative input of paracetamol from the amylodextrin tablets is reflected in Fig. 3 and was calculated using the paracetamol solution as the reference. The regression line for the cumulative input was calculated for the time values ranging from 2 to 14 hr, to avoid both the influence of the burst effect and excretion of the tablets from the bodies. The regression line was calculated to be cumulative input = $0.03t + 0.12$, with $r = 0.9987$. Regarding this fairly linear relationship for the calculated time interval, it is therefore concluded that zero-order release kinetics from amylodextrin tablets are maintained mainly under *in vivo* conditions. In Table I the cumulative input data are given for three time values. At 8, 14, and 32 hr a cumulative input of 0.36 ± 0.03, 0.52 ± 0.06, and 0.70 ± 0.16, respectively, was obtained.

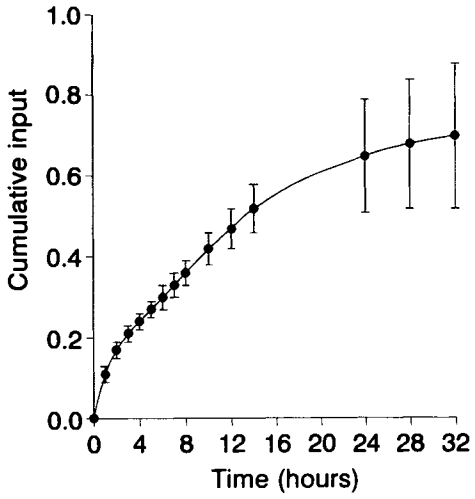

Fig. 3. Absorption profile of paracetamol from amylodextrin tablets, calculated using numerical deconvolution. The cumulative input (fraction of the dose absorbed) is plotted against time and was calculated using the paracetamol solution as the reference. Mean ± SD (n = 8).

Comparison of the *in vitro* and the *in vivo* release profiles shows, in both cases, an initial small burst effect, followed by an almost-constant drug release rate and cumulative input, respectively, from the tablets during 8 hr. However, the *in vitro* profiles reflect a total drug release of 60% within 8 hr (Fig. 1), compared to a cumulative input of only 36% paracetamol within 8 hr from the *in vivo* data (Table I). Probably the different hydrodynamic conditions during the *in vitro* and *in vivo* experiments are responsible for this difference.

Finally, no effect of degradation of the tablets by α-amylase was noted. Amylodextrin powder is hydrolyzed by α-amylase, an enzyme which is present in the gastrointestinal tract (8). The *in vivo* results presented support the assumed inaccessibility of the enzyme to the amylodextrin tablets, because of the nearly constant drug plasma concentrations up to 14 hr, with small intersubject variability.

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