In Vitro and in Vivo Evaluation in Dogs and Pigs of a Hydrophilic Matrix Containing Propylthiouracil

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A hydrophilic matrix tablet containing 300 mg of propylthiouracil was formulated with several types of hydroxypropylmethylcellulose. The influence of polymer and drug granule particle size, polymer concentration, crystallinity and geometry of the polymer particles, the polymer incorporation outside or inside the granule, addition of a filler and tablet hardness were studied. Polymer concentration, polymer particle size and geometry, filler addition and type of the filler used had a major influence on in vitro drug dissolution profiles. The bioavailability of propylthiouracil in dogs from the hydrophilic matrices investigated was low, because of the short gastro-intestinal transit times of the matrix tablets in the dogs. The matrix tablets reached the colon in fasted dogs within 2–3 hours after administration. The results indicated the poor predictability of bioavailability experiments in dogs with hydrophilic matrices. Although the bioavailability data in pigs seemed promising, a transit time study revealed a long stomach residence time of the matrix tablets in pigs. These data suggested that pigs are an inappropriate animal model for bioavailability studies of erodible matrix tablets.

KEY WORDS: hydroxypropylmethylcellulose; propylthiouracil; sustained release; in vitro release; bioavailability in dogs and pigs.

INTRODUCTION

Propylthiouracil (PTU) is a member of the thiocarbamide group of drugs used to treat hyperthyroidism. Conventional tablets are mainly commercialised as 50 mg tablets. Given its chronic use and its pharmacokinetic properties, PTU is a potentially good candidate for prolonged release preparations (1). Because of the lipophilic characteristics of PTU and the incomplete recovery from inert and lipophilic matrices, a hydroxypropylmethylcellulose (HPMC) matrix was chosen to formulate a sustained release tablet. HPMC's are cellulose ether derivatives frequently used for the formulation of sustained release matrix tablets. Several papers reported on various factors affecting the drug release rate from HPMC matrices (2–4). Some data are available on the formulation of sustained release hydrophilic matrices containing water insoluble drugs (5,6). The purpose of this study was to evaluate the influence of HPMC type, source, particle characterisation, addition of fillers and tablet manufacturing parameters on the in vitro release of PTU and to evaluate the bioavailability of PTU from the matrix tablets in dogs and pigs.

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MATERIALS AND METHODS

Materials

PTU has an aqueous solubility of 1g/900 ml (20°C). The solubility is pH independent between pH 1 and 8. The drug shows a needle type crystal morphology. Two different suppliers of HPMC's were used: Methocel (Colorcon, Orpington, UK) and Metolose (Seppic, Paris, France). Table I reviews the different HPMC's used.

Unless specified the HPMC was passed through a 125μm sieve before use. The influence of fillers was studied using lactose (Tablettose, Meggle, Wasserbourg, Germany), dicalcium phosphate dihydrate (Encompress, C.N.Schmidt b.v., Amsterdam, The Netherlands) and microcrystalline cellulose (Avicel PH102, FMC International, Wallingstone, Irland). For the PTU determination the following products were used: PTU (USP reference standard, Rockville, MD, USA), PTU and methylthiouracil (MTU) (Sigma, St. Louis, MO, USA). Heparin Novo 5000 U.I/ml (S.A. Novo Nordisk Pharma N.V., Brussels, Belgium) was used as anticoagulant agent in blood samples. All other chemicals used were analytical grade or reagent grade.

Methods

Manufacture of Tablets

The drug (300 g) was granulated with 180 ml of a 5% (w/v) alcoholic P.V.P. solution (PVP-K30, BASF, Brussels, Belgium) in a planetary mixer for 5 min. at 60 rpm (Hobart K45 SS, Troy, Oh, USA). The wet mass was passed through a 1 mm screen and next the granules were dried at 30°C for 3 hours. Hydroxypropylmethylcellulose (and the adjuvants) was added in the dry form after granulation (procedure A) and blended for 10 min. in a Turbula mixer (Type TA2, W.A.Bachofen, Basel, Switzerland) or HPMC was granulated with the drug (procedure B). Finally, 0.2% magnesium stearate (<125μm) (Flandria, Gent, Belgium) was added and additionally blended for 5 min. in the Turbula mixer (Type TA2, W.A.Bachofen, Basel, Switzerland). The blend was then compressed on an excentric compression machine (Erweka Type Eko, Frankfurt, Germany) fitted with 12 mm flat punches. Each tablet contained 300 mg drug. Unless specified the tablet hardness was 118 (±10N) (Heberlein & Co.AG, Wattwil, Switzerland).

In Vitro Dissolution

The USP XXII Paddle Method II was used at a rotational speed of 120 rpm testing three tablets in each case. The dissolution medium consisted of 900 ml simulated intestinal fluid without enzymes (pH 7.5) and was maintained at 37°C (±1°C). The extinction was continuously monitored using a Beckman spectrophotometer (DU-65 Spectrophotometer, CA, USA) set a 325 nm. When the influence of tablet hardness was studied the tablet was glued to a plexiglass support that was put into the dissolution vessels. The surface

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Table I. Characteristics of Hydroxypropylmethylcelluloses Used

Type	a	b	c	d
60SH4000[x]	3770	28.7	9.7	2.96
E4M[xx]	4445	28.8	9.0	3.20
F4M[xx]	4776	28.7	6.5	4.41
K100LV[xx]	100	23.2	9.3	2.49
K4M[xx]	5100	21.7	8.2	2.65
K15M[xx]	15000	22.8	8.9	2.56
K100M[xx]	100000	21.7	10.4	2.09

(a) viscosity (mPa.s.) USP method, (b) % methoxyl groups, (c) % hydroxypropoxyl groups and (d) methoxyl/hydroxypropoxyl substitution ratio

[x] Metolose (Seppic, Paris, France)

[xx] Methocel (Colorcon, Orpington, UK)

glued to the support was maximally 3% of the total tablet surface. This modification was done as the tablets made at low hardness floated in the dissolution medium.

X-ray diffractometry was performed on Methocel E4M and Metolose 60SH4000 using a Phillips, Type PW 105 CuK_α (40kV, 20mA), Eindhoven, The Netherlands.

Electron microscopy pictures were taken using a Jeol JXA-50A, SEM (JEOL, Japan).

Animals, Drug Administration and Blood Sampling

Bioavailability of conventional and sustained-release matrix tablets in dogs and pigs. Six healthy dogs weighing 25–35 kg and six healthy cross-bred pigs weighing 21–30 kg were used. Conventional tablets (Propylthiouracile 50 mg, Exel Pharma S.A./N.V., Brussels, Belgium) and sustained-release matrix tablets containing besides the drug, 30% K4M and 30% K15M were administered orally to the animals respectively. Additionally, sustained-release matrix tablets containing besides the drug 30% K4M:K15M (50/50) were administered orally to the dogs. All matrix tablets contained 300 mg PTU and were prepared according to procedure A. When conventional tablets were administered six tablets were given at once. From 20 h. before the experiment until 8 h. after tablet administration the animals were fasting. They had free access to water, except during one hour before drug administration. The tablets were given with 200 ml of water. Blood samples (4 ml) were withdrawn in glass tube containing heparin solution (60 µl) from the vena saphena in dogs at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24 and from the left ear in pigs at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 24 and 32 h. following drug administration.

Absorption of PTU from different locations within the intestinal tract in dogs. This study was performed in two normal dogs weighing 25 and 29 kg, respectively. The studies were performed under general anaesthesia. The dogs were premedicated with a combination (Thalamonal, Janssen Pharmaceutica NV, Beerse, Belgium) of droperidol (0.25 mg/kg) and fentanyl (0.005 mg/kg). Anaesthesia was induced with thiopental (8 mg/kg) and maintained on N_2O/O_2/Fluothane (49.25/49.25/1.5 v/v). After clipping, the abdomen was prepared for aseptic surgery. A ventral midline laparotomy was performed from the level of about three centimetres caudal of the xiphoid cartilage to a point midway between the umbilicus and pubis to expose the abdominal viscera. After opening the linea alba and peritoneum, the duodenum was exteriorised in one dog and the ileum in the other dog. In the first dog, the test suspension containing 300 mg PTU/15 ml was injected into the duodenum by direct needle puncture at a point two centimetres caudal to the pylorus. In the other dog the suspension was injected into the ileum at a point two centimetres proximal to the ileocolic orifice. After the procedure the viscera were returned to the abdomen and the abdominal incision was closed with interrupted absorbable sutures, followed by routine closure of subcutaneous tissue and skin. Blood samples (4 ml) were withdrawn from the vena saphena at 0, 0.5, 1.5, 2, 4 and 6 h. following drug administration. Two weeks after the first procedure the abdomen was reopened in the same manner and the procedure was repeated in a cross-over design. During two days after surgery the dogs were treated with antibiotics (Peni-Strepto 20 + 20, 1 ml/15 kg I.M., Psyphac, Brussels, Belgium).

Influence of p-[dipropylsulfamoyl]-benzoic acid (probenecid) administration on the bioavailability of PTU from a sustained-release matrix tablet. Four healthy dogs with a body weight ranging from 25–35 kg were given 250 mg of probenecid orally at 8 AM and 8 PM for four days. Probenecid was formulated in hard gelatine capsules (n°00) and administered with 50 ml of water. On the fourth day a 30% K15M matrix tablet containing 300 mg of PTU was administered 30 min. after the probenecid administration at 8 AM. The dogs were fasted as described above. Blood samples were obtained at the same time intervals as described above.

Transit of matrix tablets in the gastro-intestinal (GI) tract of dogs and pigs. Two healthy dogs weighing 26 and 29 kg and five healthy cross-bred pigs weighing 21 to 30 kg were given four tablets each with an interval of 2 h. Dog one (26 kg), pigs one and two received 30% K4M matrix tablets, while, the second dog (29 kg), pigs 3, 4 and 5 received 30% K15M matrix tablets. All tablets contained 300 mg of PTU. The tablets were coloured differently in order to be traced in the GI tract post mortem. Eight hours after the first tablet administration, the animals were sacrificed and the tablets were localised in the GI tract, recovered and the remaining amount of drug determined.

Analytical Procedure

Plasma samples were analyzed using a validated HPLC method (7). Coefficient of variation for repeatability was lower than 7%, for reproducibility lower than 8% and the accuracy was lower than 6%. The limit of detection was 5 ng/ml in plasma.

Data Analysis

Area under the plasma concentration time curve was calculated using Absplots program (8). AUC values were calculated from 0 to 6h. for the resorption study from different locations within the intestinal tract in dogs, from 0 to 24h. and 32h. for the bioavailability studies in dogs and pigs, respectively. The relative bioavailability in dogs and pigs was calculated as ($AUC_{0\text{-}24/32}$ sustained release tablet/$AUC_{0\text{-}24/32}$ conventional tablet) × 100. Values are given as means ± S.D. For statistical analysis non parametric statics were used and a p value of <0.05 was considered significant (9).

RESULTS AND DISCUSSION

Influence of Type and Origin of HPMC Used on the in Vitro Drug Dissolution

The drug investigated is poorly water soluble and highly dosed. A hydrophilic matrix tablet was chosen as the use of inert and lipophilic matrices led to an incomplete recovery of the drug from those matrices during dissolution. Fig. 1 shows the influence of polymer concentration on the drug release profile for different HPMC types. The tablets were produced following procedure A. Except for the Methocel F4M and K100LV where the dissolution rate remained high even at a 80% HPMC level, all other types showed a decrease in dissolution rate for an increase in HPMC:drug ratio. Because of limitations in the geometry of matrix tablet especially concerning the swallowing ability, it was decided to use matrices containing 30% of HPMC (30% calculated on the amount of drug-PVP granules; HPMC:drug ratio 3:10).

Influence of Polymer Particle Size

Fig. 2 shows the influence of polymer particle size for two polymers Metolose 60SH4000 and Methocel E4M both used in a concentration of 30% and considered to be equivalent. Tablets made with Metolose 60SH4000 (manufacturing procedure A) and the sieve fraction above 125μm showed a marked increase in dissolution rate. When Methocel E4M (manufacturing procedure A) was used, the sieve fraction above 125μm was unable to form a controlled release tablet formulation as 100% drug was released within 1 hour. Also, there was a pronounced difference between the micronized polymer and the polymer sieve fraction below 125μm as 40% and 60% of the drug was released after 8 h., respectively. When the polymers were micronized, Methocel E4M showed a 40% drug release after 8 h. in comparison to 55% drug released for the Metolose 60SH4000. These results suggested that besides molecular weight, degree of substitution and particle size distribution other factors play a role in the formation of a rapidly swelling layer and in the erosion process. X-ray analysis did not reveal any difference in crystallinity between Methocel E4M and Metolose 60SH4000. Hence, the suggestion that differences in synthetic and recrystallization procedures could account for differences observed between similar HPMC's was not confirmed (10). Electron microscopy pictures (Fig. 3) revealed a difference in particle shape for both polymers. The Methocel E4M particles (Fig. 3a) looked oval in comparison to the fiber like Metolose 60SH4000 particles (Fig. 3b). The behaviour of the Metolose 60SH4000 matrix tablets in function of particle size could be explained by the fiber content and the problems encountered in sieving fiber like materials. The Methocel E4M used did not reveal a significant fraction of fiber like material. Differences in the amount of fiber shaped material might affect the matrix forming behaviour of the polymer, and for some polymers this difference could be batch dependent.

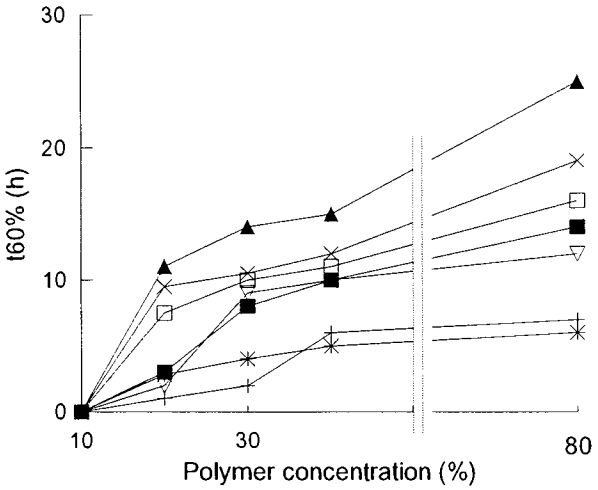


FIGURE 1. Influence of polymer concentration on the 60% drug release time for matrix tablets containing 300mg drug and different concentrations of polymers (<125μm). (n = 3, SD was less than 1h). E4M (■), F4M (+), K100LV (*), K4M (□), K15M (×), K100M (▲) and 60SH4000 (▽).

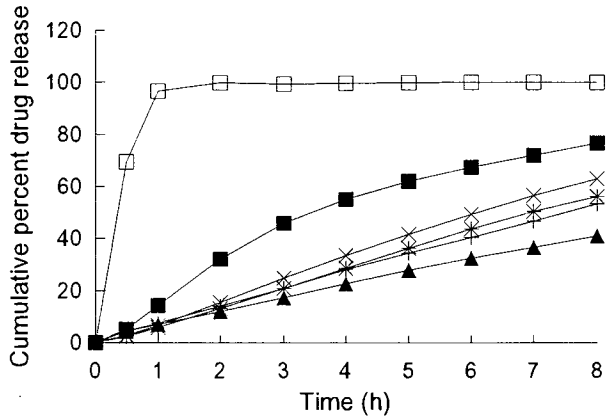


FIGURE 2. Influence of polymer particle size on the amount of drug released in function of time for a matrix tablet containing 300mg drug and 30% polymer (n = 3, SD < 7%). 60SH4000 (>125μm) (■), 60SH4000 (<125μm) (+), 60SH4000 (micronized) (*), E4M (>125μm) (□), E4M (<125μm) (×) and E4M (micronized) (▲).

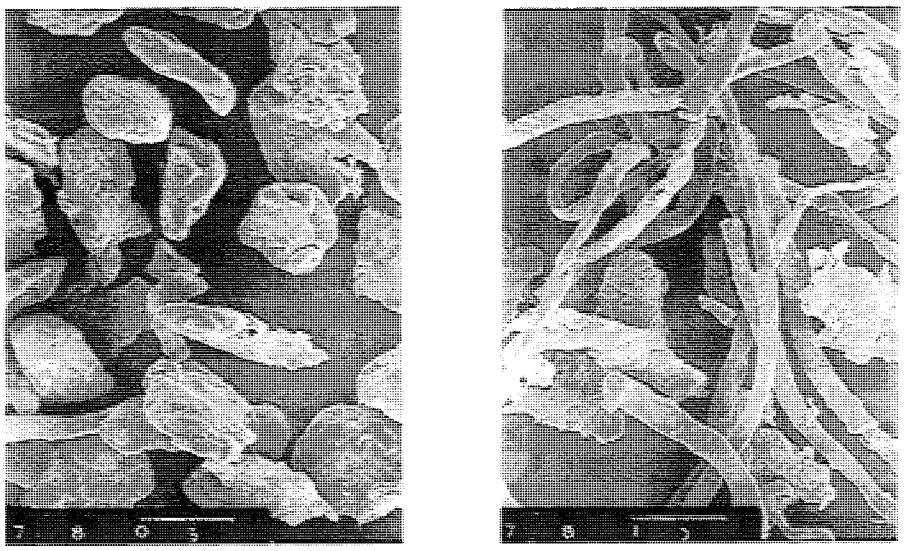
Influence of Granulation Procedure, Tablet Hardness and Granule Size

Tablet manufacturing was performed via two different granulation procedures. HPMC was incorporated into the granules or added to the drug granules. The incorporation inside or outside the granules did not affect the drug release rate even not in the initial phase.

The influence of tablet hardness was performed on the 30% Methocel E4M, K4M and Metolose 60SH4000 tablets, compressed up to a hardness of 44, 69, 132, and 157 (±10N) (Heberlein & Co.AG, Wattwil, Switzerland), respectively. Tablet hardness influenced the initial drug release phase. Tablets made at a hardness of 44 N with Methocel K4M showed an initial burst effect due to a partial initial disintegration. Once the polymer was swollen the dissolution profiles remained similar to the ones of tablets compressed to a higher hardness. When other HPMC's were used, a similar observation was noticed but the effect was less pronounced for polymers of higher molecular weight.

No difference in release profile was observed for a drug

Electron microscopy pictures of sieved (90-125 μm) polymers (150X)



E4M (3a) 60SH4000 (3b)

FIGURE 3. Electron microscopy pictures of sieved (90–125 μm) E4M (3a) and sieved (90–125 μm) 60SH4000 (3b).

granule size fraction between 250 and 1000μm. As in the case of tablet hardness, mainly the initial drug release was influenced by a drug granule size below 250μm.

Influence of Fillers

The influence of a swellable non-soluble diluent (microcrystalline cellulose Avicel PH102), a non-swellable non-soluble diluent (dicalcium phosphate dihydrate) and a non-swellable soluble diluent (α-lactose monohydrate) was studied on matrix tablets made of Methocel E4M, K4M and Metolose 60SH4000. The three diluents were tested in a concentration range between 0 to 70% of the total formula. The addition of an adjuvant did not allow the adjustment of the dissolution rate due to the high initial erosion of the matrix. As the addition of fillers did not allow for the adjustment of the in vitro drug release profiles and because of the limits in tablets geometry it was decided to formulate matrix tablets containing 30% of polymer for the in vivo experiments.

Bioavailability in Dogs

Three types of matrix tablets, formulated with 30% of K4M, K15M and K4M:K15M (50:50), respectively and six conventional tablets were administered. As $t_{60\%}$ (Fig. 1) was similar for both K4M and K15M tablets, these polymers were chosen in order to compare their in vivo behaviour as erosion is probably the main mechanism of drug release in vivo. Fig. 4 shows the average plasma levels of PTU after administration of the conventional tablets and the three matrix tablets. After administration of the matrix tablets the plasma levels remained low and the relative bioavailability values were 31% (±15), 26% (±24) and 27% (±6) respectively for K4M, K15M and K4M:K15M (50:50) tablets (n = 6). These values are not statistically different (Friedman test; p = 0.05).

Because of the low bioavailability from the matrices, the question was raised if the resorption of PTU might preferentially occur in the upper part of the GI tract. No data are available on the resorption of PTU from different parts of the GI tract in the dog. Fig. 5 shows the concentration time profiles of PTU after local administration (300 mg/15 ml). The AUC_{0-6} values were 41 (dog 1), 49 (dog 2) and 36 (dog 1), 31 (dog 2) μg/ml.h in the upper and low part of GI tract, respectively. Although the fact that up to 30% reduction of the resorption of PTU in the lower part of the intestine might

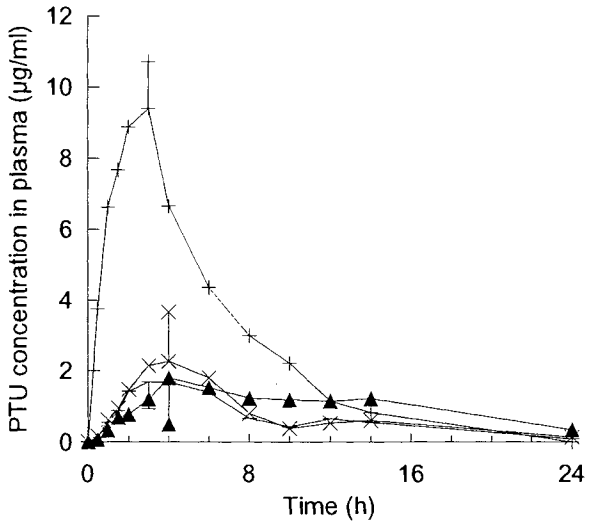


FIGURE 4. Mean concentration-time profiles following oral administration of 300 mg of PTU in dogs. For clarity, the SD is only shown for the peak concentration (n = 6). (+) conventional tablets, (×) K4M matrix tablet, (▲) K15M matrix tablet and (−) K4M:K15M 50/50 matrix tablet.

lead to a reduction in the overall extent of the drug resorption from a sustained release dosage form, it can not be made responsible for the very low plasma levels observed after administration of the different hydrophilic matrix tablet formulations.

Kampmann J.P. and Skovested L., (11) suggested that a high first-pass effect could be the cause for a lower PTU oral bioavailability in man. In animal experiments it has been demonstrated that a major part of the drug is excreted as propylthiouracil-glucuronide (12). Probenecid, an inhibitor of renal tubular secretion of organic acids, has been shown to block the formation of acyl and ether glucuronidation of some drugs (13,14) and was administered in order to evaluate the influence of glucuronidation on PTU bioavailability. The AUC_{0-24} values for a 30% K15M, 300 mg PTU tablet were 18 (±5) and 12 (±8) μg/ml.h respectively with and without probenecid administration (n = 4). The AUC_{0-24} was not significantly increased by probenecid administration (Wilcoxon test; p = 0.05) indicating that a first-pass glucuronidation in the liver was not responsible for the observed low plasma levels.

It has been suggested that the transit time of solid dosage forms in dogs is rapid in comparison to man and that the dog might not be a good model to evaluate oral sustained release preparations (15). The difference in the length of the small intestine correlates well with the reported average transit time in dogs and humans: 2 h. versus 4 h., respectively and this appears to be true for dosage forms as well. Besides, the difference in mixing patterns in the colon and the shortness of the large bowel may also reduce the absorption of some drugs relative to humans. Examples of a poor predictability of the availability of sustained release formulation and short transit times in dogs were reported in literature (16–20). In our study, the consecutive administration of matrix tablets with a two hours period interval showed that tablets are already found in the colon of the dog two hours after administration (Table II). It can be concluded that

Table II. Dog GI Tract Length, Tablet Matrix Localisation and Percent of Drug Found (Post Mortem) in GI Tract after Consecutive Administration of Matrix Tablets

		Dog 1	Dog 2
Type of matrix administered		K4M (30%)	K15M (30%)
Weight (kg)		26	29
Total length of small intestine (cm)		339	241
Length of colon (cm)		53	34
Number of tablets recovered in colon (post mortem)		3	4
Percent of drug found in tablet after an administration time of (in hours)	8	tablet not found	74
	6	56	83
	4	51	84
	2	79	87

the dog is not a good experimental model for testing large eroding matrix tablets due to the short transit time. In an attempt to find an appropriate model for a comparative evaluation of large erodible tablets, a comparative bioavailability study was performed in pigs. Fig. 6 shows the average plasma levels of PTU after administration of the conventional tablets and two matrix tablets based on K4M and K15M respectively. The relative bioavailability values calculated over a 32 h. sampling period were 133% (±57) and 119% (±40) for the K4M and K15M matrix tablets, respectively, and were not significantly different (Wilcoxon test; p = 0.05; n = 6). The initial release rate from the K4M matrix tablet seemed faster in comparison to the K15M matrix tablet and was probably due to a lower initial swelling rate of the K15M matrix. After consecutive administration of matrix tablets with a two hours period interval, most tablets were found in the stomach even 8 h. after administration (Table III). These data support the findings of Hossain et al. (21) who stated that nondisintegrating dosage forms were retained for a long time in the stomach of pigs. Although the

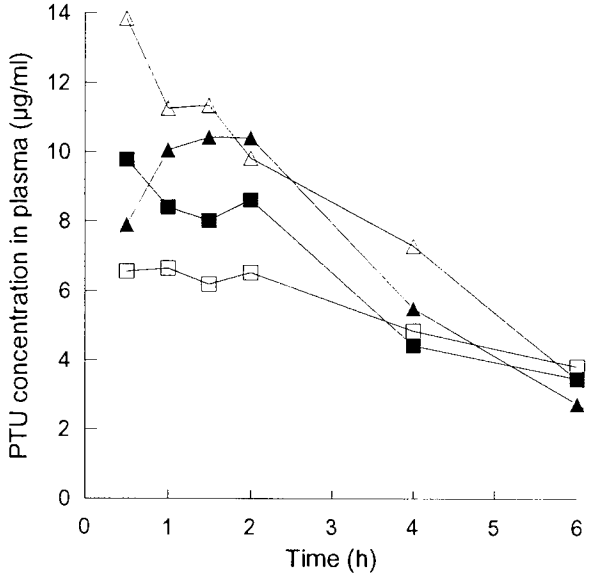


FIGURE 5. Concentration-time profiles following local administration of 300 mg PTU in GI tract of two dogs. (▲) duodenum dog 1, (■) ileum dog 1, (△) duodenum dog 2 and (□) ileum dog 2.

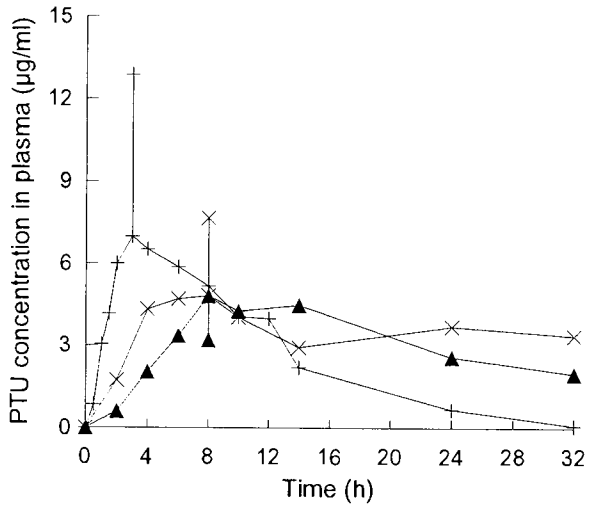


FIGURE 6. Mean concentration-time profiles following oral administration of 300 mg of PTU in pigs. For clarity, the SD is only shown for peak concentration (n = 6). (+) conventional tablets, (×) K4M matrix tablet and (▲) K15M matrix tablet.

Table III. Pig GI Tract Length, Tablets Matrix Localisation and Percent of Drug Found (Post Mortem) in GI Tract after Consecutive Adminsitration of Matrix Tablets

Type of matrix administered		K4M (30%)				K15M (30%)					
Pig n°		1		2		3		4		5	
Total length of small intestine (m)		10.7		10.5		12.8		15.0		12.8	
Length of caecum and colon (m)		3.0		2.6		4.2		2.5		2.6	
Tablet localisation and percent of drug found in tablet after an administration time of (in hours)	8	S	*	S	*	S	*	C	*	S	*
			55		12		31		27		35
	6	S	65	SI	20	S	42	C	27	SI	41
	4	S	75	S	42	S	54	SI	56	S	50
	2	S	80	S	69	S	75	S	66	SI	73

S (stomach), SI (small intestine) and C (caecum).
* (percent of drug found in tablet).

plasma concentration time profiles obtained in pigs were promising, the gastric retention time is too long for pigs to be a good model for bioavailability studies for large erodible matrix tablets.

In conclusion our findings indicated that a PTU hydrophilic matrix tablet can be formulated and that dogs and pigs are not appropriate model animals for the bioavailability studies of large erodible matrix tablets.

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