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RESEARCH PAPER

Excipient-Excipient Interaction in the Design of Sustained-Release Theophylline Tablets: In Vitro and In Vivo Evaluation

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ABSTRACT

Sustained-release (SR) theophylline (TPH) tablets were prepared by applying the moisture-activated dry granulation method. The interaction between the excipients sodium alginate (SAL) and calcium gluconate (CG) was the base for the formation of a cross-linked matrix that may regulate TPH release from the formulated tablets. The prepared granules showed good physical characteristics concerning the flow properties and compressibility, with the angles of repose in the range 29–31, and the compressibility indices ranged between 15% and 25%. The granules had low friability values (3.0%–4.2%), depending on SAL:CG ratios. The corresponding tablets showed good physical properties, with a lower rate of drug release compared with the commercial TPH tablets (Quibron®). The release of TPH from the prepared tablets was not markedly affected by either the concentration of added dry binder (carbopol 934) or the tablet hardness, indicating that the rate-determining step in drug release was the diffusion through the produced calcium alginate matrix. Tablets formulated with equal ratios of CG and SAL that showed good physical properties and slow TPH release were chosen for bioavailability studies in beagle dogs, and results were compared with those for Quibron. The in vivo data showed a comparable plasma concentration profile for both tablet formulations, with prolonged appearance of drug in the plasma in detectable amounts for up to 24 h. The formulated tablets showed 104.65% bioavailability relative to that of the commercial tablets. The rate and extent of absorption of TPH showed no significant differences

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from that of the commercial tablets. Moreover, no significant differences were found in the pharmacokinetic parameters related to the rate and extent of TPH absorption from the prepared and commercial tablets.

INTRODUCTION

Tablet excipients are substances that, mixed with drugs to act as vehicles or to modify physical, physicochemical, and physicomedical properties of the pharmaceutical product, may lead to changes in biopharmaceutical performance (1). The choice of the proper excipient is essential to minimize problems associated with formulation design. Controlled-release products require that the excipients used in the delivery systems should exhibit well-controlled physicochemical characteristics to provide reproducible in vitro performance (2). Studies of the possible interaction between tablet ingredients in the solid dosage forms are necessary because these interactions can affect the bioavailability and rate of drug release (3,4). The addition of inert fillers in tablets of dicumarol resulted in significant therapeutic variations (5). Indomethacin release from hydroxypropylmethylcellulose and lactose tablets depended on the type of binding solvent added (6).

Theophylline (TPH) is a drug still used in the management of asthma. It has a relatively short half-life and narrow therapeutic index, with 5–20 μg/ml serum concentrations (7). Thus, sustained-release (SR) formulations that can produce more uniform serum concentrations with less fluctuation in peak-trough levels (8) are useful for the oral delivery of TPH. In addition, sustained-release TPH formulations can ensure good patient compliance since it is difficult for a patient to take oral medication repeatedly during an acute asthma attack. TPH was previously chosen for preparation in oral sustained-release formulations (9).

Although several methods have been used to incorporate drugs into matrices to control drug release, most of them may not be suitable for large-scale manufacture. However, matrices prepared using common tableting procedures are preferable as a simple method for the preparation of sustained-release tablets (10,11). In addition, the cost of formulation development, raw materials, and manufacture are among the significant factors in sustained-release delivery system formulation for oral dosing.

Sodium alginate (SAL) is a purified substance of natural polysaccharide that is very safe (12,13) and low cost; it has been widely used as a stabilizing, thickening, dispersing, and gelating agent for food (14). SAL has the ability to react with divalent ions to give water-insoluble cross-linked matrices utilized in the preparation of sustained-release diclofenac sodium and ambroxol hydrochloride beads (15,16).

The purpose of this study was to prepare sustained-release TPH tablets by applying the moisture-activated dry granulation method (17,18) using SAL and calcium gluconate (CG) as excipients that could interact during tablet preparation to form a cross-linked matrix that may regulate drug release. The tablets produced were evaluated in vitro and in vivo and compared with one of the commercially available sustained-release tablets.

EXPERIMENTAL

Materials

Theophylline and β-hydroxy-ethyl theophylline (Sigma Chemicals, St. Louis, MO); sodium alginate (BDH Co., Poole, England); calcium gluconate (Hopkin & Williams Ltd., Essex, England); and carbopol 934 (Serva, Heidelberg, Germany) were used as received. Solvents used for chromatographic determinations were high-performance liquid chromatography (HPLC) grade; all other reagents and solvents were analytical grade.

Preparation of Granules

The calculated amounts of TPH, SAL, and CG were mixed while being ground together using a mortar and pestle to obtain different CG:SAL ratios. The powder blends, except for the directly compressed tablets, were moistened with the least amount of demineralized water (about 3%) possible. The moistened friable mass was then passed through a 10-mesh sieve and placed on Teflon-coated foil. The granules produced were then dried in an air oven for 4 h at 40°C.

Moisture Content of the Granules

The moisture content of the granules for each batch was determined using a moisture balance (Mettler PM

480, Switzerland) fitted with an infrared heating unit (Mettler LP 16).

Flow Properties and Compressibility of the Granules

Flow properties of the granules were evaluated by determining the angle of repose and compressibility index. Static angle of repose was measured according to the fixed-funnel and free-standing cone method (19). A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip 2 cm high H above graph paper placed on a flat, horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. The mean diameter $2R$ for the base of the powder cone was determined, and the tangent of the angle of repose was given by

$$\tan \theta = H/R$$

where θ is the repose angle.

Compressibility index I values of the different formulations were determined by measuring the initial volume V_0 and final volume V of granules after subjecting to 100 taps in a graduated measuring cylinder using the following equation (20):

$$I = (1 - V/V_0) \times 100$$

Determination of the Mean Particle Diameter

Sieve analysis was carried out using 25 g of the tested granules and a series of U.S. standard sieves, ranging in size from 315 to 900 μm. The granules were placed on the top sieve and mechanically shaken for 10 min on a shaker (Erweka Co., Frankfort, Germany). The fraction retained on each screen was determined, and the geometric mean diameters of the granules were calculated from the sieve analysis data (21).

Friability of the Granules

The friability of the granules was determined by testing a certain size fraction of the granules using a Roche friability tester (TA3R, Erweka, Apparatebau, Germany). The size fraction of the granules that passed through the 800-μm sieve and were retained on the 600-μm one was used in this test. The drum of the friabilator was charged with 20 g of the granules being tested, and the tester was run for 8 min at 25 rpm. The sample was then shaken through a 600-μm sieve for 2 min, with the help of the shaker, and the weight of the retained granules was assessed. The friability of the granules was calculated as a percentage according to the following equation:

$$(\text{Initial weight} - \text{Final weight})/\text{Initial weight} \times 100$$

Preparation of Tablets

Carbopol 934 at different concentrations (2.5%, 5%, 7.5%, or 10% w/w) and 2% magnesium stearate were mixed with the prepared granules for 10 min using a Turbula mixer (Erweka). The compositions of different tablet formulations are shown in Table 1. TPH tablets were prepared by compressing the treated granules or powder blend (in the case of direct compression) using a flat-faced 9-mm punch tableting machine (Korsch, type EKO, Frankfort, Germany). Tablet weight was adjusted to contain approximately 100 mg TPH. Tablets with hardness values of 6.5, 11, 15, and 30 Kp were prepared by applying suitable compression forces.

Table 1

Composition of Formulated Tablets

Formula	TPH (mg)	CG (mg)	SAL (mg)	Carbopol 934 (% w/w)	Mg Stearate (% w/w)	Nature
A	100	150	200	5.0	2.0	Granules
B	100	200	200	5.0	2.0	Granules
C	100	250	200	5.0	2.0	Granules
D	100	200	200	2.5	2.0	Granules
E	100	200	200	7.5	2.0	Granules
F	100	200	200	10.0	2.0	Granules
G	100	200	200	0.0	2.0	Granules
H	100	200	200	5.0	2.0	Physical mixture

Evaluation of Tablets

The prepared tablets were evaluated for the uniformity of thickness, hardness (Erweka TBH 28, Frankfort, Germany), friability (Erweka friabilator, model A3R, Frankfort, Germany), and disintegration time (Erweka, model ZT4, Heusenstamm, Germany) according to USP 22 tests. The diametral compression test devised by Fell and Newton (22) was used to determine the tensile strength T, using the formula

$$T = 2P/\pi Dt$$

where P is the applied stress, D is the diameter of the tablet, and t is the tablet thickness. Three tablets from each batch were subjected to tensile strength determination.

In Vitro Dissolution Studies

Drug release determination from different formulated tablets, as well as from commercially available sustained-release tablets, was performed using USP 22 dissolution apparatus 2 at 50 rpm and an automated monitoring system (PU 9605/60 tablet dissolution system software, Philips IBM computer connected to PU 8620 spectrophotometer cell programmer, and Watson Marlow prestatic pump, Cambridge, England). Dissolution medium was 750 ml of distilled water at 37°C ± 0.5°C. Drug release was monitored at 272 nm as a function of time. The data shown are the mean of three tablets.

Animal Experiments

Five male beagle dogs weighing 10.2 ± 1.3 kg were used in this study in a crossover design. After fasting overnight, during which water was allowed freely, each dog was placed in an upright position in a restrainer stand. The dog's legs were shaven and cannulated through the cephalic vein using an 18-gauge cannula. A washout period of a week was allowed between successive dosing.

Dosing and Sampling

Doses of 200 mg of theophylline in the form of the prepared sustained-release tablets (two 100-mg tablets) or as sustained-release commercial tablets (Quibron®) were given by oral intubation on two different occasions to dogs starved for 18 h prior to the experiment. Blood samples (3 ml) were collected just prior to tablet administration and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, and 24.0 h postadministration into heparinized tubes. The samples were immediately centrifuged at 4000 rpm for 7 min, and the plasma was separated and frozen at −20°C pending analysis.

Analysis of Plasma Samples

Plasma concentrations of TPH were assayed using a modified HPLC method for TPH assay that was described by Al-Angary et al. (23). The method involved the use of 300-µl aliquots of β-hydroxyethyltheophylline solution as the internal standard (5 µg/ml in 70% acetonitrile in water) to be added to 200-µl plasma samples in small plastic centrifuge tubes. The tubes were vortexed for 30 s and then centrifuged at 5000 rpm for 5 min. An aliquot of 25 µl of the supernatant solution for each sample was injected into the HPLC system (Waters Assoc., Milford, MA). The HPLC separation was achieved with a µ-Bondapak C_{18} cartridge column (Waters Assoc.; 10 µm, 10 cm × 8 mm id) using a mobile phase consisting of acetonitrile : acetate (0.01 M) buffer (7 : 93) adjusted at pH 4.2 with a flow rate of 3 ml/min. The effluent was monitored at 270 nm (Waters Assoc. M-481 variable-wavelength ultraviolet [UV] detector). The concentration of TPH was determined using a constructed calibration curve prepared on the day of sample assay.

Pharmacokinetic Analysis

The maximum plasma concentration C_{max} and the time to reach that maximum T_{max} were obtained directly from the plasma concentration-time data of each dog. The area under the plasma concentration-time curve AUC_{0-24} was determined for each dog by the linear trapezoidal rule for the period of plasma sampling. The area of the tail was calculated using the plasma concentration at the last time point and the elimination rate constant K_{el}. The values of K_{el}, and accordingly $t_{1/2}$ were estimated from the least-square regression analysis of the elimination segment of the curve. All results were expressed as mean ± standard deviation (mean ± SD).

Statistical Analysis

The significance of the difference between the formulated tablets and the commercial sustained-release tablets was evaluated using analysis of variance (ANOVA) at a significance level of $p \leq .05$.

RESULTS AND DISCUSSION

The moisture-activated dry granulation method was chosen for preparation of tablets to facilitate the cross-linking reaction between SAL and CG in the presence of water; the efficiency of dry blending and the advantages of wet granulation are combined. The dry granules produced had low moisture content, which was as low as 1.0%–1.5% for all batches. Although the granules were irregular with rough surfaces at all CG:SAL excipient ratios studied, the granules showed acceptable flow characteristics, with angles of repose that ranged between 35° and 37° (24), compared with poor flowability of powder blends, with angles of repose equal to 49°–55°.

Particle size analysis of the granules showed that the greater the CG content in the excipient mixture, the larger was the mean particle diameter, and an increase in the amount of CG ensured complete reaction, resulting in large and hard granules. At a CG:SAL ratio of 5:4, the particle size of the granules was 640 ± 12 μm, while at lower ratios of 1:1 and 3:4, the mean particle diameters decreased to 623 ± 9 and 617 ± 8, respectively.

The granules produced were hard, as indicated by the friability tests at all CG:SAL ratios; this could indicate a successful cross-linking reaction. The friabilities of the granules were 4.2%, 3.3%, and 3.0% for 3:4, 1:1, and 5:4 CG:SAL ratios, respectively. Generally, the low friability values could be attributed to the high mechanical strength of the granules (i.e., good ability to withstand handling during the subsequent processing into tablets).

The flowability of the granules was even improved with the addition of the binder, carbopol 943, and the lubricant magnesium stearate, which was mixed with the granules before tableting; the angles of repose were 29°–31°. This could be attributed to the smoothing effect of these materials on the outer surfaces of the granules; it has been reported that increases in surface irregularity contribute significantly to increased porosity and changes in the packing arrangement of particles (25).

The results also show that values of the compressibility index of the different batches of granules ranged between 15% and 25%, indicating the suitability of the granules for direct compression.

The physical characteristics of the TPH tablets prepared with the moisture-activated dry granulation method are shown in Tables 2 and 3. Table 2 shows that a change of CG:SAL ratios can affect the physical properties of the tablets. At nearly the same hardness (about 11.0 Kp), different tensile strengths were obtained at different CG:SAL ratios. In the presence of 5% carbopol, tablets with an equal amount of CG and SAL (1:1 ratio) showed the highest tensile strength with least tablet thickness compared with other ratios, while no measurable differences in tablet friability was obtained. Table 2 also shows that increasing carbopol concentration from 2.5% to 10% was accompanied by increased tablet thickness and decreased tensile strength. Cross-linked polyacrylic acid polymers are known for their adhesive properties, which may account for the strength of the tablets at a low polymer

Table 3

Effect of Hardness on Tablet Characteristics

Formula	Hardness (Kp)	Tensile Strength (Kp/cm^2)	Thickness (mm)	Friability (%)
B	6.5	15.85	2.90	1.40
B	11.0	27.16	2.86	1.10
B	15.0	39.47	2.69	1.15
B	30.0	82.19	2.60	1.00

Calcium gluconate/sodium alginate (CG/SAL) ratio was 1/1 for all batches.
Carpobol 934 concentration was 5% for all batches.

Table 2

Effect of Calcium Gluconate/Sodium Alginate (CG/SAL) Ratios and Concentration of Carbopol 934 on Tablet Characteristics

Formula	CG/SAL Ratio	Carbopol 934 (%)	Tensile Strength (Kp/cm^2)	Thickness (mm)	Friability (%)
A	3/4	5.0	27.85	2.79	1.15
B	1/1	5.0	29.73	2.63	1.15
C	5/4	5.0	27.16	2.86	1.13
D	1/1	2.5	32.35	2.40	1.15
E	1/1	7.5	28.89	2.72	1.20
F	1/1	10.0	27.98	2.78	1.35

Tablet hardness was 11.0 Kp for all batches.

concentration (25). At high concentrations of fine powdered carbopol, the thickness of the tablets increased, and the tensile strength of the tablets decreased. This was also supported by the results of friability tests, in which friabilities increased from 1.15% to 1.35% by increasing the carbopol concentration from 2.5% to 10%.

Table 3 shows that a change of tablet hardness was accompanied by an obvious change in tablet tensile strength. Changing the tablet hardness from 6.5 to 30 greatly increased the tensile strength, from 15.85 to 82.19, in the presence of 5% carbopol, and there was an expected decrease in tablet friability.

Figures 1–4 show the release of TPH from different tablet formulations. In all cases, tablets remained intact during the dissolution time course. Figure 1 shows the release profile of TPH from the tablets prepared from the moisture-activated dry granulations or by the direct compression of the physical mixture. Comparing the dissolution profiles shows that tablets prepared from granules retarded the drug release. This indicates that a calcium alginate matrix was formed and serves as a reservoir for controlling TPH release. Because the calcium alginate matrix is hydrophobic and insoluble, the dissolution of TPH is probably limited by poor hydration of the matrix and subsequent slow diffusion of TPH. This was confirmed by observing drug release from tablets prepared by direct compression of the physical mixture, which showed fast drug release, with the release of TPH complete in about 1.5 h. Figure 1 also shows that tablets prepared from the formula containing the low CG:SAL ratio (3:4) offered faster drug release than that from tablets containing higher ratios (1:1 and 5:4). This could indicate that the 3:4 ratio was not enough for complete reaction between CG and SAL.

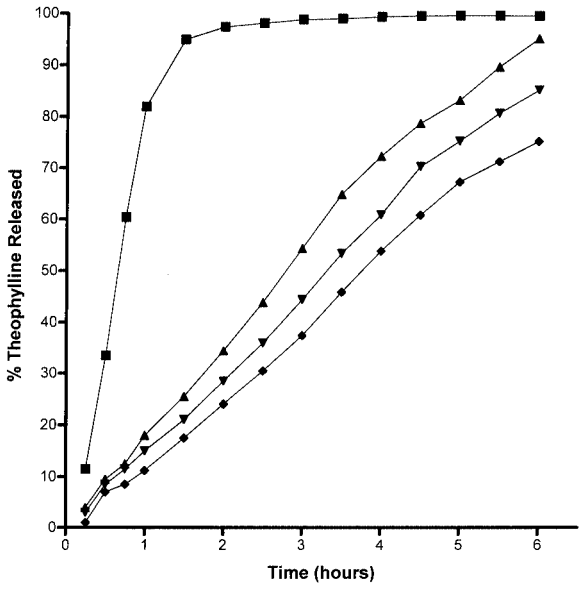

Figure 1. Effect of calcium gluconate:sodium alginate (CG:SAL) weight ratios on theophylline release from formulated tablets compared with tableted 1:1 physical mixture of CG:SAL: △, 3:4; ♦, 1:1; ▼, 5:4; ■, physical mixture. Tablet hardness 11.0 Kp; carbopol 934 content 5%.

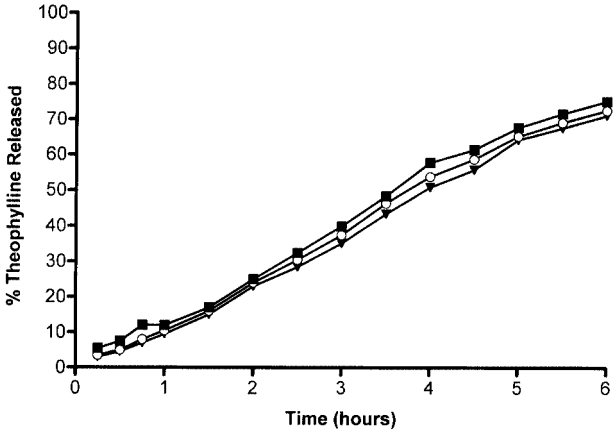

Figure 2. Effect of tablet hardness on theophylline release from formulated tablets: ■, 6.5 Kp; ○, 11.0 Kp; ▼, 15 Kp. CG:SAL 1:1; carbopol 934 content 5%.

The effect of different tablet hardnesses (6.5, 11.0, and 15.0 Kp) and different concentrations of carbopol 934 (2.5%, 5.0%, 7.5%, and 10% w/w) on TPH release are also shown in Figs. 2 and 3, respectively. The results revealed that no clear differences in drug release could be obtained by increasing the amount of carbopol above

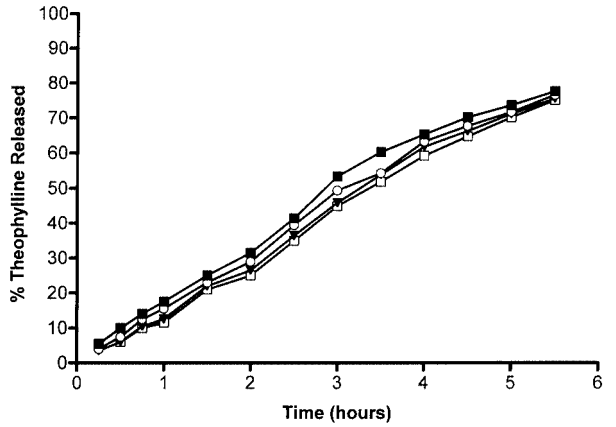

Figure 3. Effect of carbopol 934 concentration on theophylline release from formulated tablets: ■, 2.5%; ○, 5%; ▼, 7.5%; □, 10%. CG:SAL = 1:1; tablet hardness 11.0 Kp.

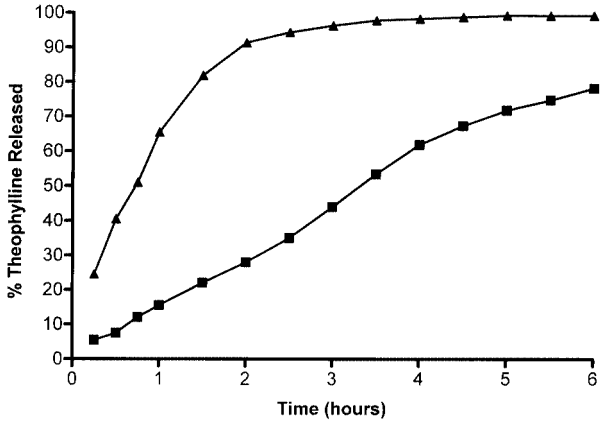

Figure 4. Theophylline release from formulated tablets (formula B) and commercial tablets (Quibron): ■, formulated tablets; △, Quibron.

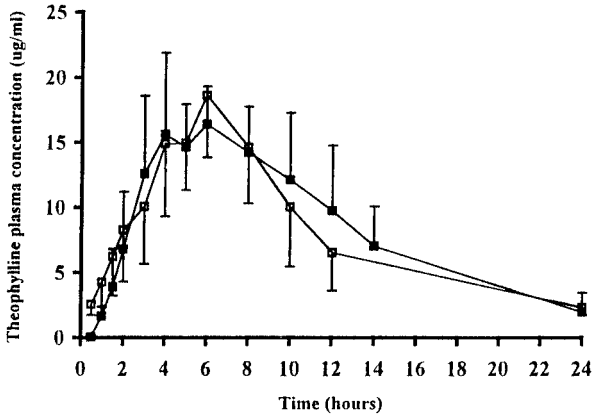

Figure 5. Mean (±SD) plasma concentration of theophylline following oral administration of ■ formulated and □ Quibron sustained-release tablets to five beagle dogs.

2.5%; the drug release is controlled by diffusion through the calcium alginate matrix independent of the binder concentration. Figure 2 shows that no change in TPH release was obtained by increasing tablet hardness, which confirms that the rate-determining step in drug release is diffusion through the cross-linked alginate matrix produced.

Based on the results obtained, it can be concluded that the release rate of TPH varies depending on CG:SAL ratios and the method used in tableting, while the increase in tablet hardness and amount of binder had no appreciable effect on drug release, although they may affect the physical properties of the tablets.

The above results show that formulation B had acceptable physical characteristics and produced continuous TPH release for a long time. Figure 4 shows the in vitro TPH release from the chosen formulated tablets (formula B) compared with one of the commercially available sustained-release tablets (Quibron). The formulated tablets showed much slower drug release than that of Quibron, and about 75% of TPH was released from the formulated tablets within 6 h compared with 100% drug release in about 3 h from Quibron.

Thus, it was necessary to conduct an in vivo study for formula B and compare it with that of Quibron. The two types of tablets were administered orally in two separate studies to beagle dogs. The mean (±SD) plasma concentration time profiles for the two tablet formulations are shown in Fig. 5. The results showed comparable plasma concentration profiles with prolonged appearance of drug in plasma in amounts detectable for up to 24 h. The mean pharmacokinetic parameters of TPH following oral administration of the formulated and commercial tablets are shown in Table 4.

The maximum plasma concentration C_{max} and the time to reach this maximum concentration T_{max} obtained from the mean of the individual plasma concentration time data for each dog were 19.57 ± 2.92 μg/ml and 5.4 ± 2.79 h, respectively, for the proposed tablet formulation, while they were 19.36 ± 5.6 μg/ml and 5.2 ± 1.09 h, respectively, for the commercial Quibron tablets.

The above results could indicate comparable absorption of TPH from both formulations with no significant differences in C_{max} and T_{max} for the two formulations ($p > .05$). This was also supported with the determined absorption rate defined as $C_{max}/AUC_{0-\alpha}$, which was 0.0935 ± 0.0215 and 0.0977 ± 0.018 h^{-1} for formulated and com-

Table 4

Pharmacokinetic Parameters (Mean ± SD) of Theophylline After Oral Administration of Formulated Sustained-Release (SR) and Commercial SR Tablets to Dogs (N = 5)

Phamacokinetic Parameters	Formulated SR Theophylline Tablets	Commercial SR Theophylline Tablets
C_{max} (μg/ml)	19.57 ± 2.92	19.36 ± 5.60
T_{max} (h)	5.4 ± 2.79	5.2 ± 1.09
C_{max}/AUC (h^{-1})	0.0935 ± 0.022	0.0977 ± 0.018
K_e (h^{-1})	0.148 ± .081	0.1513 ± 0.079
$t_{1/2}$ (h)	5.45 ± 2.25	5.53 ± 2.04
AUC_{0-t} (μg · h/ml)	197.66 ± 34.84	187.57 ± 65.78
$AUC_{0-\alpha}$ (μg · h/ml)	216.14 ± 44.77	206.57 ± 71.56
Relative bioavailability	104.43%	—

mercial tablets, respectively, with no significant differences ($p > .05$). This ratio was considered a good parameter for evaluation of the absorption of prolonged-release formulations (26,27). The area produced under the plasma concentration-time curve was 197.66 ± 34.84 μg · h/ml in 24 h and 216.14 ± 44.77 μg · h/ml up to infinite time for formulated tablets compared with 187.57 ± 65.78 and 206.57 ± 71.56 μg · h/ml, respectively, for the commercial tablets. No statistically significant differences ($p > .05$) were found, and the relative bioavailability was 104.63%. Table 4 also shows that the half-life of TPH was 5.45 ± 2.25 h for formulated tablets and 5.53 ± 2.04 h for commercial tablets, with no statistically significant differences ($p > .05$). Generally, no significant differences were found in the pharmacokinetic parameters related to the rate and extent of TPH absorption from the prepared and commercial tablets (i.e., C_{max}, T_{max}, and AUC values).

It could be concluded that sustained-release TPH tablets could be prepared from a calcium alginate matrix using a simple granulation technique and depending on excipient-excipient interaction. The tablets showed slow dissolution in vitro with sustained-release property. In vivo results demonstrate prolonged absorption of TPH from the formulated tablets.

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