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RESEARCH ARTICLE

Preparation and pharmacokinetics in beagle dogs of once-a-day tetramethylpyrazine phosphate sustained-release pellets

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Abstract

In this study, once-a-day tetramethylpyrazine phosphate (TMPP) sustained-release pellets were successfully prepared. The pellets cores were carried out in extrusion-spheronization machine and then coated in fluidized-bed. To optimize cumulative release profile, two different coating systems with the same the TMPP pellets cores were employed. The first coating system consisted of surlease, containing HPMC E5 (0.1% w/w), i.e., P1. The second coating system only consisted of surlease, i.e., P2. The two kinds of coating systems were both given coating levels in terms of weight gain of 10%. The resulted once-a-day TMPP sustained-release pellets (OTSP), the mixture of P1 and P2 with the weight proportion of 1:1, were filled in a capsule (150 mg TMPP/capsule). The relative bioavailability of OTSP was studied in six beagle dogs after oral administration using a commercial TMPP tablets as a reference. The C_{max} and T_{max} for OTSP and TMPP tablets were 213.06 ng/mL, 2.50 h and 3402.13 ng/mL, 0.33 h, respectively and the relative bioavailability of P3 was 97.18% compared with TMPP tablets. Based on the results, it was indicated that TMPP sustained-release pellets and TMPP conventional tablets were bioequivalent.

Keywords: Tetramethylpyrazine phosphate, once-a-day sustained-release pellets, extrusion-spheronization, fluidized-bed, pharmacokinetics, beagle dogs

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Introduction

Tetramethylpyrazine phosphate (TMPP) (Figure 1) has been widely used in China for the treatment of cardiovascular and cerebrovascular disorders[1–3]. It was found to be a new type of block calcium channels, reduce the bioactivity of platelets and platelet aggregation, inhibit free radicals, increase cerebral blood flow[4–6] and improve blood viscosity[7]. However, after oral administration, TMPP has a short biological half-life of 0.5–2 h[8]. At present, there are TMPP tablets and TMPP capsules on sale for oral administration. The two kinds of dosage forms are given orally, 150 mg three times daily, then a sustained-release, once-a-day TMPP dosage form may reduce the dosing frequency and improve patient compliance. In our preliminary study, we have known that solubility of TMPP in distilled water, 0.1 M HCl and pH 6.8 phosphate buffer saline (pH 6.8 PBS) at 37°C is 65.21, 150.62 and 80.43 mg/mL, respectively. The result about the absorption mechanism of intestines showed TMPP could be absorbed at all of the four intestinal segments with increasing absorption amount per units as follows: colon > duodenum > jejunum > ileum, but without saturation[9]. Therefore, once-a-day TMPP sustained-release dosage form is feasible.

Multiple-unit sustained-release dosage forms, such as pellets, are considered to have many therapeutic advantages in comparison with large single-unit dosage forms. They can disperse in the gastrointestinal tract (GI tract) homogeneously thus maximize drug absorption, reduce peak plasma fluctuations, minimize the risk of local GI tract irritation and dose dumping, decrease dosing frequency, increase patient compliance, improve the safety and efficacy of the active ingredient.

The purpose of this study was to develop once-a-day TMPP sustained-release pellets (OTSP) and evaluate its pharmacokinetics in beagle dogs.

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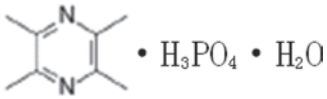

Figure 1. The chemical structure of TMPP.

Materials and methods

Materials

Tetramethylpyrazine phosphate (TMPP, 101.0% purity) and tetramethylpyrazine phosphate tablets were both purchased from Beijing Yanjing Pharmaceutical Factory (Beijing, China). Lactose, mannitol, sucrose, glucose (Shanghai Hong Guang factory, Shanghai, China), Microcrystalline cellulose (MCC, Avicel PH101; FMC, USA), Surelease (E-07-19010; Colorcon, USA) and Methocel E5 (HPMC E5; Colorcon, USA) were used. The other chemical reagents were of analytical grade or better.

Animals

Six male beagle dogs, similar in age (2 years) and weight (10.0 ± 0.5 kg), were obtained from the Animal Center of China Pharmaceutical University (Nanjing, China). They were housed in individual cages and received a standard diet and water ad libitum. All the animals were clinically healthy and haematologically and biochemically normal throughout the experimental period. Food, but not water, was withheld for 24 h before and after drug administration.

Methods

Preparation of OTSP

Preparation of the pellets cores In this study, a laboratory-scale extrusion-spheronization machine (Shenyang Pharmaceutical University, Shenyang, China) was used for preparing the TMPP pellets cores. After preliminary experiments, the optimum formulation of pellets cores was obtained. The composition of the pellets cores consisted of MCC (30%, w/w), TMPP (50%, w/w), lactose (15%, w/w) and magnesium stearate (5%, w/w). Briefly, TMPP (150 mg/capsule) with MCC, lactose and magnesium stearate was mixed intimately for 5 min in a planetary mixer, then the appropriate quantity of distilled water was added slowly and mixed for a further 5 min. Approximately 100 g of this wet mass was packed into the barrel of a ram extruder with a 0.8 mm screen. A piston was inserted into the barrel and the system attached to a mechanical press, which was activated to extrude at a ram speed of 200 mm/min. The extrudates were spheronized in 100 g quantities for 5 min at 1000 rpm on a 24.0 cm diameter crosshatched plate of a spheronizer. After spheronization, the resultant pellets were dried for 24 h at 30°C in a fan-assisted hot air oven (Chongqin yinhe Co., Chongqin, China).

The prepared and dried pellets pores were sieved with a set of China Standard Sieves to provide sieve fractions. The pellets pores produced approximately 85% of the pellets pores in the size fraction 0.50–0.85 mm. The value of the two-dimensional shape factor e_R^{10} was 0.89 ± 0.08.

Fluid bed coating For obtaining optimized cumulative release profile, two different coating systems with the same TMPP pellets cores were employed. The first coating system consisted of surlease containing HPMC E5 (0.1% w/w). HPMC E5 (4%, w/w) solution was prepared and kept overnight. Surlease was diluted with water to 8% w/w. Then 4% HPMC E5 solution was added to the diluted surlease to produce the required HPMC E5 contents and stirred throughout the coating process. This kind of pellets was called P1. The second coating system only consisted of surlease. Surlease was diluted with water to 8% w/w, then stirred throughout the coating processes. This kind of pellets was called P2. The resulted OTSP, the mixture of P1 and P2 with the weight proportion of 1:1 was filled in a capsule (150 mg TMPP/capsule).

For coating, 50 g quantities of the TMPP pellets cores were used and coated in the fluidized-bed (mini-Glatt, Glatt, Germany). For the two kinds of coating systems, the condition of coating was the same. The inlet and the outlet air temperatures were 55 and 37°C, respectively. The nozzle outlet was 0.5 mm in diameter with the atomizing air pressure in a range between 0.6 and 0.7 bar and the solution was sprayed at a pumping rate of 1.0 g/min. The coating process was continued for sufficient time to give coating levels in terms of weight gain of 10% both for the first coating system and for the second coating system.

Determination of the content of TMPP in pellets

The quantity of TMPP was assayed by ultraviolet spectroscopic method at the wavelength of maximum absorbance at 295 nm. From each batch of the coated pellets, a certain amount (1 g) was taken and ground to fine powder using a mortar and pestle. Then about 100 mg of powders were accurately weighed and added to a 100 mL volumetric flask containing 70 mL of distilled water. After a 10 min of ultrasonic extraction, the solution was diluted with distilled water to 100 mL and then filtered through a 0.45 μm membrane. Precisely 1 mL of the filtrates was diluted 100-fold with distilled water to get the sample solution. The absorption of sample solution was measured at a wavelength of 295 nm. The intra-day accuracy of the method for TMPP ranged from 98.5 to 101.8%, while the intra-day precision ranged from 0.6–2.2%. The inter-day accuracy ranged from 97.6100.8%, while the inter-day precision ranged from 1.83.9%. The precision and accuracy of the method were both well consistent with analysis requirement and no absorption of the physical mixture of the excipients existed at 295 nm. The content of TMPP in the P1, P2 and OTSP was 36.73, 34.19 and 35.46% (w/w), respectively.

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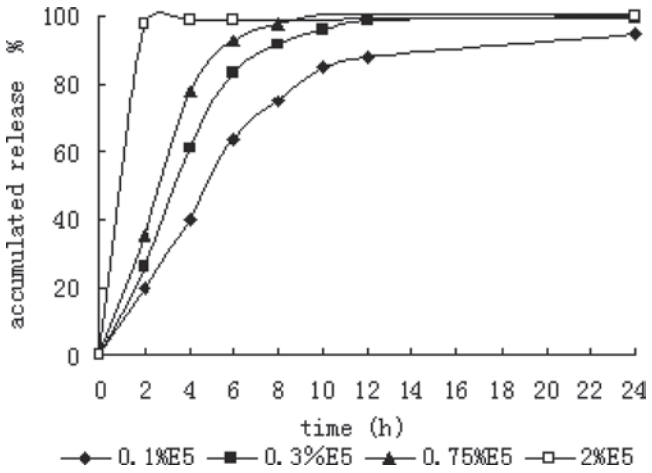

Figure 2. Effects of the amounts of HPMC E5 in surlease on the drug *in vitro* release under the condition of giving a constant 10% coating amount in distilled water.

Dissolution studies

The release of TMPP from P1, P2 and OTSP was performed according to a dissolution test apparatus of China pharmacopoeia (2005 edition, rotating basket method). In this study, 900 mL of dissolution medium was kept at 37 ± 0.5°C and the rotating speed was 100 rpm. Distilled water, 0.1 M HCl solution and pH 6.8 PBS were used as different kinds of dissolution media, respectively. One capsule containing P1, P2 or OTSP, equivalent to 150 mg TMPP, was used in all dissolution studies. 10 mL of samples were withdrawn and filtrated using 0.8 μm cellulose nitrate membrane, and replaced with an equal volume of the same fresh medium at 2, 4, 6, 8, 10, 12, 14 and 24 h. The filtrates were diluted and assayed by ultraviolet spectroscopic method at 295 nm. Dissolution tests were performed in triplicate.

Pharmacokinetics study of OTSP in beagle dogs

Chromatography

The concentrations of TMPP in plasma were determined by HPLC. The stationary phase and μBondapak C_{18} column (250 mm × 4.6 mm, 5 μm), were kept at 35°C. The mobile phase was a mixture of methanol: double distilled water (50:50, v:v). The flow rate was 1.0 mL/min. The detection wavelength was 295 nm.

Assay method

The plasma sample (100 μL) and phosphate buffer saline (pH 8.0, 10 μL) were transferred to a 1.5 mL polyethylene centrifuge tube, vortexed for 30 s and then mixed with acetonitrile (200 μL) for 1 min. The precipitate of denatured proteins was separated by centrifugation at 12,000 rpm for 10 min. An aliquot (20 μL) of supernatant was directly injected for HPLC analysis.

The method was validated by adding various quantities of TMPP to blank beagle dog plasmas. The resulting concentrations of TMPP were 0.02, 0.1, 1, 3, 8, 12, 25 and 40 μg/mL. These calibrations were subjected to the entire analytical procedure, as well as to validate the linearity, precision and accuracy of the method.

Pharmacokinetics study of OTSP in beagle dogs

The study was conducted according to a single-dose, randomized and own control crossover design and washout period was one week between the treatments of the study. In this design, six adult male beagle dogs divided into two groups were fasted for 24 h, but allowed to access to water freely. One 1-sized gelatin capsule containing OTSP equivalent to 150 mg TMPP was orally administered to a group of beagle dogs. The three commercial TMPP tablets equivalent to 150 mg TMPP were orally administered to another group of dogs. After oral administration of OTSP, 1 mL of blood samples were collected from the jugular vein at 0.5, 1, 1.5, 2, 3, 6, 8, 12, 16 and 24 h. However, after oral administration of the tablets, 1 mL of blood samples were collected from the jugular vein at 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 6 and 8 h. The plasma obtained after centrifugation at 4000 rpm for 10 min was immediately stored at –20°C until HPLC analysis. After washout period of one week, the two groups of beagle dogs were administered exchangedly.

Data analysis

The peak concentration (C_{max}) and the time of peak concentration (T_{max}) were obtained directly from the experimental points. The other pharmacokinetic parameters were computed by software program 3p97. The relative bioavailability (F) was calculated by: $F = (AUC_p / AUC_t) \times 100\%$, where AUC_p and AUC_t are the area under the curve after oral administration of OTSP and TMPP tablets, respectively.

Results and discussions

Preparation of pellets cores

Pellets cores could be prepared by many methods including extrusion-spheronization, centrifugal granulation, blank pores sprayed drugs solution and so on[11,12]. Since the oral amount of TMPP in one day (150 mg/day) was great and the solubility of TMPP in distilled water at 25°C was 27.21 mg/mL, the method of blank pores sprayed drug solutions was infeasible. Based on our laboratory condition, the method of extrusion-spheronization to prepare TMPP pellets cores was chosen.

There were many important influencing factors on the shape and size of TMPP pellets cores during the process of extrusion-spheronization, such as the amount of MCC, the amount and kind of sugar, the amount of distilled water, the speed of spheronization and so on. During the process of extrusion-spheronization, either the more amount of MCC or the little amount of sugar brought out the regular core of pellets in shape and size. Compared with mannitol, sucrose and glucose, lactose made the core of pellets more regular in shape and size. The amount of distilled water was determined by trial and error, as judged by the quality of the pellets, in terms of narrow size distribution and spherical dorm. Too little distilled water resulted in the pellets core columnar and there were many powders during the process of

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spheronization, while too much distilled water caused the pellets core agglomerate. The higher rotating rate could make the core of pellets more regular in shape and size and the speed of extrusion had little effect.

Influencing factors of coating formulations on *in vitro* release

Only varying the proportion of HPMC E5 in surlease and the coating amount of surlease containing HPMC E5, or only changing the coating amount of surlease could not get excellent sustained-release effect *in vitro* and the higher bioavailability *in vivo*. The dissolution rate of TMPP from sustained-release pellets was either too quick or too slow, which was not in accordance with the ideal sustained-release profiles. Through many trials, we found that it was necessary for getting an excellent sustained-release effect to blend the P1 and P2. During the process of coating, the effect of the formulation of coating on *in vitro* release was estimated.

Some comparative studies were conducted to investigate whether there was a significant difference on the proportion of HPMC E5 in surlease and the different coat loading of pellets cores on *in vitro* release. The influence of the amounts of HPMC E5 in surlease on *in vitro* release was shown in Figure 2. Obviously, under the condition of giving a constant 10% coating amount, as the amounts of HPMC E5 in surlease increased, the release rate of drug from pellets increased. When at a proportion of 2% HPMC E5 in surlease, the release of TMPP from pellets in distilled water was almost complete at about 2 h, which was resulted from HPMC E5 in the film of surlease used as pore-forming agent. The drug release was enhanced with the increasing amount of HPMC E5. However, at 0.1% HPMC E5 in surlease, the percentage of drug released decreased significantly, when the coating amount increased, which was presented in Figure 3.

A series of different amounts of surlease were applied and the cumulative release profiles are shown in Figure 4. As the coat loading of surlease increased, the drug release decreased obviously. As shown in Figures 3 and 4, irrespective of whether the sustained-release film contained the pore-forming agent, when the coating amount increased, the drug release decreased and the amounts of drug released from P1 and P2 were incomplete. Thus, a suitable coating amount was essential to simultaneously obtain excellent sustained-release effect *in vitro* and the higher bioavailability *in vivo*. At last, we chose the formulation of P1, i.e., the pellets coated with 10% surlease containing 0.1% HPMC E5, and the formulation of P2, i.e., the pellets coated with 10% surlease. After blending P1 and P2 with the weight proportion of 1:1, the mixture named OTSP was filled in a capsule (150 mg TMPP/capsule).

Dissolution studies

The profiles of TMPP released from P1 and P2 in three dissolution media are shown in Figure 5 and Figure 6, respectively. When comparisons were made between the two formulations, it was found that there were some

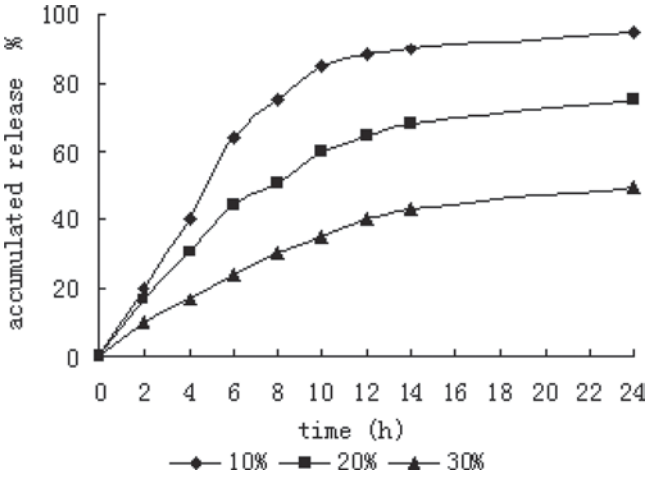

Figure 3. Effects of coating amounts of surlease containing 0.1% HPMC E5 on the drug *in vitro* release in distilled water.

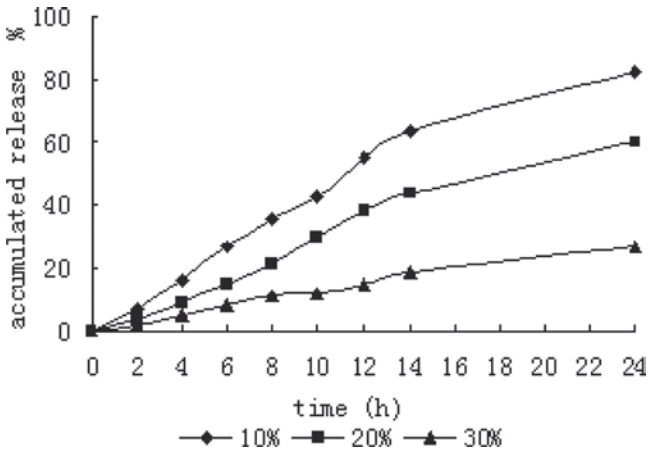

Figure 4. Effects of coating amounts of surlease on the drug *in vitro* release in distilled water.

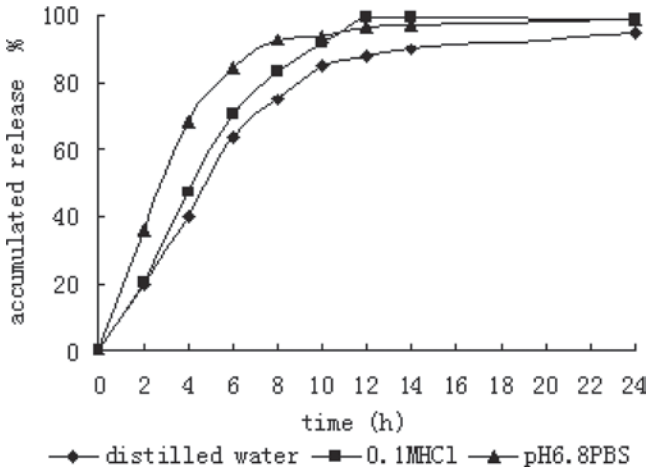

Figure 5. Effects of the pH of the dissolution media on the *in vitro* dissolution profile from P1.

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differences in the release of TMPP. As far as P1 was concerned, due to surlease containing HPMC E5, the release rate of TMPP from P1 was quicker than that from P2. For example, in 0.1 M HCl, the accumulated release percentages of TMPP from P1 and P2 were 70.51 and 30.04% by 6 h, 98.87 and 56.96% after 12 h, respectively. In distilled water, the accumulated release percentages of TMPP from P1 and P2 were 64.51 and 26.13% by 6 h, 88.24 and 54.56% after 12 h, respectively. In pH 6.8 PBS, the accumulated release percentages of TMPP from P1 and P2 were 84.3 and 28.79% by 6 h, 96.62 and 57.64% after 12 h, respectively.

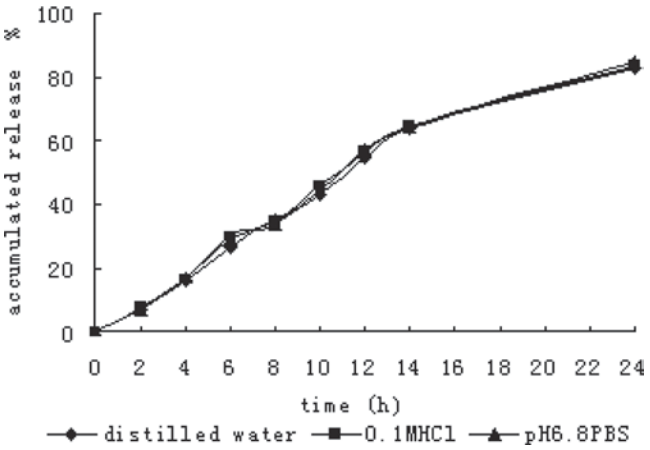

Figure 6. Effects of the pH of the dissolution media on the *in vitro* dissolution profile from P2.

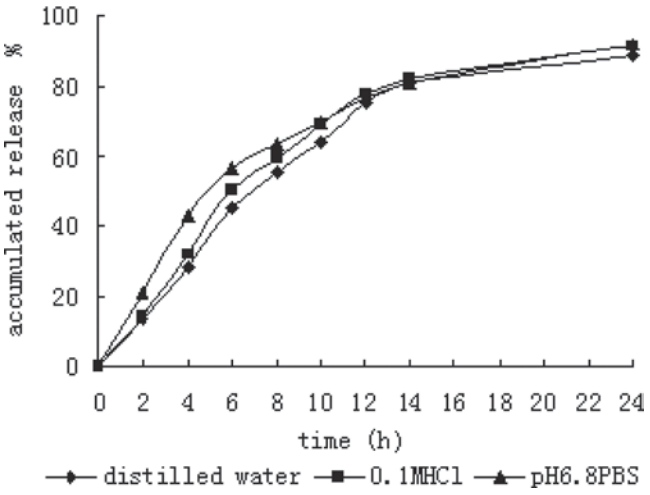

Figure 7. Effects of the pH of the dissolution media on the *in vitro* dissolution profile from once-a-day TMPP sustained-release pellets.

From Figure 5, it is indicated that the release rate of TMPP from P1 was significantly influenced by the pH of the dissolution media. The release rate of drug in pH 6.8 PBS was quicker than that in 0.1 M HCl and distilled water. It was considered that the release rate of drug had some relationship with the solubility of TMPP in the three media. Nevertheless, the release rate of drug from P2 was not influenced by the pH of the dissolution media (Figure 6). The profiles of TMPP released from P3 in three dissolution media are shown in Figure 7.

Bioavailability

Under the chromatographic conditions described above, optimized separation and detection conditions were achieved in plasma. The retention time of TMPP is shown in Figure 8 at about 7.6 min. The detection limit for TMPP at a signal-to-noise ration of 3:1 was 10 ng/mL in plasma.

The calibration curve of TMPP was linear in the range of 0.0240 μg/mL plasma. Using the linear least squares regression, the calibration line of TMPP was $y = 0.0021 \times (\mu g/mL) + 0.013$ with $r^2 = 0.9952$ in plasma. The mean relative recoveries of TMPP at high, middle, low concentrations were ranged from 96.45 to 99.13% in plasma. Both intra- and inter-day precision (expressed as percent relative standard deviation, RSD%) of TMPP were within 15.0% in plasma. The intra-and inter-day day accuracy (expressed as percent of nominal values) ranged from 93.13 to 100.52% in plasma. Therefore, it was found that recoveries, intra- and inter-day RSD of TMPP in dog plasma were satisfying.

The pharmacokinetics of OTSP was investigated. Figure 9 shows the mean plasma concentration-time curves of TMPP in beagle dogs after oral administration of the OTSP and TMPP tablets. Their bioavailability parameters are listed in Table 1.

The plasma level in beagle dogs after oral administration of TMPP tablets rose quickly and the average maximum concentration (4.40 μg/mL) reached at 0.33 h. There

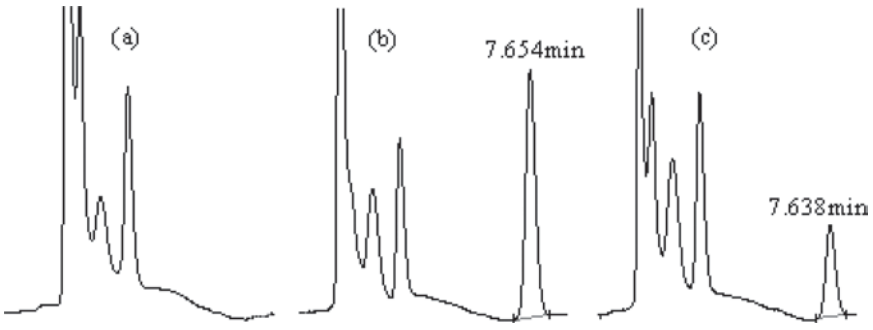

Figure 8. Typical HPLC chromatograms of blank beagle dogs plasma (A), blank beagle dogs plasma spiked with TMPP (B) and plasma sample after oral administration of once-a-day TMPP sustained-release pellets (C).

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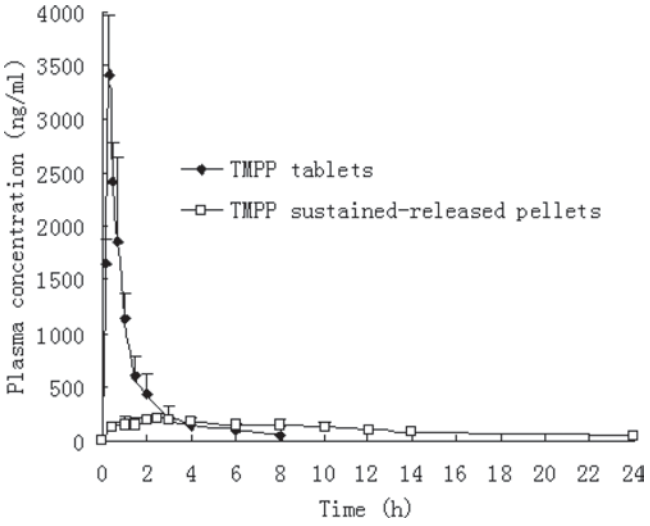

Figure 9. Mean plasma concentration-time profiles of TMPP in beagle dogs after oral administration of TMPP tablets and once-a-day TMPP sustained-release pellets (equivalent to 150 mg of TMPP) ($n = 6$).

was a marked fall in drug plasma concentration between 0.33 and 4 h. At 8 h, the average concentration was below detectable plasma levels in our studies. For OTSP, the average maximum concentration (0.42 μg/mL) reached at 2 h after oral administration, while the fall in drug concentration occurred at a lower rate than that of TMPP tablets. Even at 24 h after oral administration, the drug concentration was 85 ng/mL. Compared with TMPP tablets, the relative bioavailability of OTSP judged from $AUC_{0-24\,h}$ was found to be 97.18%, which showed that the availability of the two dosages in beagle dogs was bioequivalent.

The pharmacokinetic data were simulated by non-linear least squares. The results showed that open two-compartment model and first-order absorption were fitted to TMPP tablets plasma concentration-time curves in beagle dogs, however, open one-compartment model and first-order absorption were more fitted to OTSP plasma concentration-time curves in beagle dogs. From the results, it is supposed that, the sustained-release dosage form can change the behavior of TMPP *in vivo* in beagle dogs.

Conclusion

OTSP were produced successfully. Since the use of surlease is convenient and simple, it is considered as the sustained-release material. By trial and error, we know it is impossible by using one kind of film to simultaneously obtain excellent sustained-release effect *in vitro* and the higher bioavailability *in vivo* under the condition of only using surlease. Finally, the two kinds of films containing surlease with and without HMPC E5 are chosen to be used together. During experiments, the TMPP pellets cores exhibit adequate size and shape using extrusion-spheronization technique. The coating amount of surlease and the amount of HPMC E5 in surlease have a significant effect on drug *in vitro* release. From the dissolution studies, it is indicated that the optimum sustained-release profile of TMPP from OTSP is obtained. After oral administration of OTSP, the better properties of sustained-release are also obtained in beagle dogs.

Table 1. Pharmacokinetic parameters of TMPP after oral administration of TMPP tablets and TMPP sustained-release pellets in beagle dogs.

Parameter	TMPP tablets	TMPP sustained-release pellets
C_{max}/ng·mL^{-1}	3402.13 ± 584.97	213.06 ± 32.44*
T_{max}/h	0.33 ± 0.09	2.50 ± 0.29*
$AUC_{0-24\,h}$/(ng·mL^{-1})*h	2801.24 ± 560.17	2722.25 ± 369.42
$AUC_{0-\infty}$/(ng·mL^{-1})*h	3064.32 ± 421.38	3548.32 ± 248.92
MRT/h	1.52 ± 0.35	9.43 ± 1.05*
$F_{0-24\,h}$/%		97.18 ± 9.76

x ± s, n = 6.
*P < 0.05 vs. TMPP tablets.

Declaration of interest

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