

BIOPHARMACEUTICAL EVALUATION OF NEW SLOW RELEASE TABLETS OBTAINED BY HOT TABLETING OF COATED PELLETS WITH TRAMADOL HYDROCHLORIDE

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Abstract: This study was aimed at a biopharmaceutical evaluation of a new oral dosage form of tramadol hydrochloride (TH) – slow release tablets obtained by hot tableting of coated pellets, 100 mg (TP), compared to the conventional slow release tablets, Tramal Retard[®], 100 mg (TR). Both TP and TR formulations showed a similar release profile of TH (f_2 was 71) in *in vitro* release studies. The *in vivo* study was a two-treatment, two-period, two-sequence, single-oral dose 100 mg, crossover design using rabbit model with the phases separated by a washout period of 14 days. It was shown that the amount of TH absorbed into the systemic circulation is similar for TP and TR (the 90% confidence intervals for the AUC_{0-4h} , $AUC_{0-\infty}$ and ratios were 85–122 and 92–107%, respectively). However, after administration of slow release tablets obtained by hot tableting of coated pellets, a prolonged absorption and elimination processes and a smoother and more extended plasma profile of TH were observed. It can be assumed that the use of a new oral dosage form of TH in patients affects the extension of analgesia after single administration of the drug, with its gradual absorption into the systemic circulation.

Keywords: tramadol, hot tableting, pellets, rabbits

Tramadol hydrochloride (TH) is well established in the treatment of acute and chronic pain. As it is effective and well-tolerated, the use of TH has increased substantially in a wide range of pain conditions (1, 2). Its usual dosage regimen is 50–100 mg every 4–6 h up to 400 mg, the mean absolute bioavailability is about 70% and the elimination half-life is 5.5 h (3–6).

Successful long-term treatment of patients with painful conditions requires an appropriate dosage form, optimal dosing, and patient compliance. Sustained-release formulations (SR) are very helpful in achieving treatment objectives. Stable serum levels without marked peak-to-trough fluctuations and reduced frequency of dosing improve patient compliance, patient satisfaction, and, ultimately, quality of life (7, 8). SR formulations are recommended in chronic pain treatment, especially in patients who require around-the-clock treatment of pain for an

extended period of time (9–11). Many oral SR formulations of TH, including pellets, have been shown to improve patient compliance and chronic pain control (1, 10–20).

In our previous work, a newly developed method of hot tableting of pellets with TH was presented (21). Pellets were coated with an Aquacoat ECD aqueous dispersion. In the proposed hot tableting method, granulates containing PEG 3000 provide the tableted pellets sufficient protection from being destroyed. An evidence of such protection is confirmed by the fact that TH's slow release profile from the tableted pellets is comparable to that of uncompressed pellets (21). It is known that differences between oral formulations might represent the most important factor responsible for the differences in both rate and extent of absorption of the drug, reflected in the pharmacokinetic parameters (7, 22). Thus, our study was aimed at a biopharmaceutical

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evaluation of those newly developed tableted pellets with TH.

MATERIALS AND METHODS

Preparation of coating pellets with TH

Pellet cores were obtained by wet granulation of a powder mixture, and the extruded mass was spheronized afterwards. The initial experiments allowed us to establish the following composition of pellet cores: TH 60.0%, microcrystalline cellulose (MCC), PH101 35.0% and glyceryl behenate 5.0%. All substances were granulated with water (30 g/100 g of the powder mixture) in a high-shear mixer (Glatt VG 5, Dresden, Germany). The wet granulate was extruded in an extruder (Caleva model 25, Dorset, UK) through a 1.0 mm diameter sieve. The extrudate (about 30 g) was spheronized for 5 min in a 120 mm spheronizer (Caleva model 120, Dorset, UK) fitted with a cross-hatch plate rotating at 1800 rpm. The resulting pellet cores were dried at 45°C in a tray oven for 16 h. Pellet cores of 0.6–1.0 mm in diameter comprised the largest fraction (about 65%) in the given conditions of extrusion and spheronization.

Pellets cores were coated in a fluidized bed coater using the Würster bottom column with ethanol solution of ethylcellulose (EC/EtOH). The ethanol solution of ethylcellulose was plasticized with triethyl citrate 25%, w/w, based on the mass of the polymer. The coating conditions were as follows: inlet air temperature (45°C), outlet air temperature (35°C), atomization air pressure 2.0 bar, fluidizing air flow (180 m³/h) and coating rate 10–13 g/min. The film coating resulted 27 µm thickness was sprayed onto drug-loaded pellets to achieve drug release over 8 h.

Hot TH pellets tableting

Tablet formulation was composed of a mixture of TH pellets (0.6–1.0 mm) in the ratio of 50.0% pellets and 50.0% granulate, which was obtained during wet granulation process conducted in a high-shear mixer using water as a binder (30 g/100 g of powder): PEG 3000 (24.3%) and microcrystalline cellulose (24.3%). Granulate was separately dried in a blow dryer (Venticell BMT, Brno, Czech Republic) at 45°C for 16 h. The dried granulates were then passed through a sieve with a mesh size of 1.0 mm. Then the pellets (100 mg pellets containing 45.8 mg TH), croscarmellose sodium (2.4%) and sodium stearyl fumarate (0.4 %) were added, and the mixture was mixed for 5 min. Croscarmellose sodium was added as a disintegrating substance to

ensure disintegration of tablets into pellets. Sodium stearyl fumarate was used as a lubricant to prevent hot granulate from sticking to the punches.

A ratio of 50.0% pellets and 50.0% granulate ensured that the tablet formulation has adequate flow, which could otherwise be adversely affected by tackiness of heated tablet formulation.

The resulting tablet formulation was spread evenly on a paper tray and heated in a blow dryer to a temperature not greater than 56°C. A tablet press granulate feeder was heated in another blow dryer. The feeder was then immediately mounted onto a rotary tablet press (Korsch XL 100, Berlin, Germany) filled with the heated tablet formulation. The tableting parameters were as follows: spherical punches of 10.0 mm in diameter, curve radius – 9 mm, main compression force – 1.0 kN, precompression force – 0.1 kN, single tablet mass – 370.0 mg.

In vitro release studies

Dissolution test was performed in 1000 mL of water at 37°C (± 0.5°C). An automated Hansson Research Sr8+ basket apparatus dissolution tester (Hansson Research, Chatsworth, CA, USA) with an on-line UV/Vis spectrophotometer (Agilent 8453, Wilmington, USA) was used. At different time intervals (1, 2, 3, 4, 5, 6, 7 and 8 h) the concentration of TH in the samples was analyzed spectrophotometrically at 272 nm. Single tablet mass was 370.0 mg and contained 98.7 mg TH. The dissolution results were calculated with reference to SR tablets (Tramal Retard[®], 100 mg) batch no AN043 (Grünenthal GmbH, Aachen, Germany). All dissolution profiles are the mean of 12 dissolution tests performed under sink conditions.

Similarity of dissolution profile of the tablets was compared using model-independent method by linear regression at specified time points, and calculating a similarity factor f_2 . An f_2 value between 50 and 100 suggests that two dissolution profiles are similar.

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

In this equation, f_2 is the similarity factor, n is the number of time points, R_i is the mean percent drug dissolved of e.g., a reference product, and T_i is the mean percent drug dissolved of e.g., a test product (23).

In vivo studies

Ten adult healthy New Zealand White rabbits (mean weight ± SD, 3.45 ± 0.20 kg) were used in this study. Before the study, animals were housed individually in standard cages. Food was withheld from all animals for 12 h prior to and 12 h following

drug administration. Throughout the study, the rabbits had an unlimited access to water. The studies were carried out in accordance with the consent of the Local Ethics Committee at the University of Life Sciences in Poznan (No. 15/2008) and the "Guide for the Care and Use of Laboratory animals" (24).

A two-treatment, two-period, two-sequence, single-oral dose, randomized, crossover design was used with the phases separated by a washout period of 14 days.

SR formulations (a slow release tablets obtained by hot tableting of coated pellets, 100 mg) prepared in the Department of Pharmaceutical Technology, Medical University of Gdańsk, Gdańsk, Poland, and SR tablets (Tramal Retard® 100 mg tablets, batch no 292L01; Grünenthal, Aachen, Germany), were used for oral administration.

All animals received *per os* (*p.o.*) one tablet (100 mg of TH) of each formulation. Immediately after administration of TH, 20 mL of fresh water were given to the rabbits to ensure that the tablet was swallowed and entered the stomach.

Two weeks after oral administration, all animals were given TH intravenously (*i.v.*) at a dose 10 mg/kg (Poltram 100 mg/2 mL, batch No. 510804; Polpharma, Poland) with a view to calculating absolute bioavailability (F) and mean absorption time (MAT) of TH.

TH was always administered between 8 a.m. and 9 a.m. All blood samples (1.5 mL) were drawn from the catheter remaining in the marginal ear vein.

Blood samples were collected before administration of TH (sample 0) and then at 5, 15, 30, 45, 60, 120 min, and 4, 8, 24, 30 h after *p.o.* administration, or 1, 5, 10, 15, 30, 45, 60, 120 min, and 4, 6, 8 h following *i.v.* administration. Blood samples were transferred into labelled, heparinized test tubes and immediately centrifuged at $2880 \times g$ for 10 min. Plasma samples were stored at -30°C until analysis.

Drug analysis

Chemicals and reagents

Tramadol hydrochloride, $\text{C}_{16}\text{H}_{25}\text{O}_2\text{N}\cdot\text{HCl}$, CAS: 27203-92-5; internal standard – phenacetin, CAS: 62-44-2 and triethylamine (HPLC grade) were purchased from Sigma-Aldrich (Steinheim, Germany). Acetonitrile, n-hexane, methanol, ethyl acetate (HPLC grade) were from Merck (Darmstadt, Germany). Sodium hydroxide, monopotassium phosphate, anhydrous potassium hydrogen phosphate (analytical grade) were from POCH (Gliwice, Poland).

Chromatographic system

Plasma concentrations of TH were analyzed by high-performance liquid chromatography with diode-array UV detection (isocratic analysis using HPLC Waters 2695 Separations Module with autosampler, Waters 2487 Dual λ Absorbance Detector, the wavelength 218 nm, an analytical column LiChrosorb RP-18, 250 mm \times 4.6 mm, 5 μm from Waters; temperature of column 30°C , mobile phase: acetonitrile (300 mL) – 0.01 M phosphate buffer (700 mL) with addition of 0.05% triethylamine (0.5 mL) to achieve pH of mobile phase 3.0, flow rate of mobile phase 1.0 mL/min, volume of each injection 100 μL , retention time of TH and phenacetin, respectively, 5.64 and 8.19 min, total analysis time 12.0 min, according to methods developed by Gan et al. (25) and Szkutnik-Fiedler et al. (26). Data collection and processing were carried out using Empower Pro software, v. 1154. HPLC method was validated in accordance with the published EMA guideline (27).

Method validation

The HPLC-UV method was specific and selective. There were no interfering peaks in blank plasma at the retention times of TH and internal standard. The calibration for TH was linear in the range of 10–1000 ng/mL ($n = 9$, $r = 0.9996 \pm 0.0002$, RSD 0.02%).

The recovery of TH was greater than 90% for all tested concentrations. Intra-day and inter-day precision of TH in rabbit plasma were less than 7%, and accuracy was less than 10%. The LLOQ of TH was 10 ng/mL, and LOD was 2.11 ng/mL. CV values of short-term stability of plasma samples were 4.39 and 6.64% for TH concentrations of 50 and 200 ng/mL, respectively. The recovery of TH in long-term freezer stability after storage at -30°C for 30 days was more than 88% for both tested concentrations.

Pharmacokinetic and statistical analysis

The pharmacokinetics of TH after oral and intravenous administration was determined by use of the noncompartmental approach based on the statistical moment theory. All parameters were calculated using WinNonlin® 5.3 Professional (Pharsight). The maximum drug plasma concentration (C_{max}) and the time at which C_{max} was achieved (t_{max}) after *p.o.* administration were determined directly from the concentration vs. time curve. The elimination rate constant (k_{el}) was calculated by a linear least squares regression analysis, using the last three plasma ln concentrations vs. time points.

Elimination half-life ($t_{1/2kel}$) was calculated according to equation $t_{1/2kel} = \ln 2/k_{el}$. The mean residence time (MRT) was equal to $AUMC_{0-\infty} / AUC_{0-\infty}$. Area under the plasma curve from zero to the last measurable concentration (AUC_{0-t}) was calculated using

the linear trapezoidal method. Area under the plasma curve from zero to infinity ($AUC_{0-\infty}$) and area under the first moment curve from zero to infinity ($AUMC_{0-\infty}$) were calculated by the linear trapezoidal method with extrapolation to infinity. The extrapo-

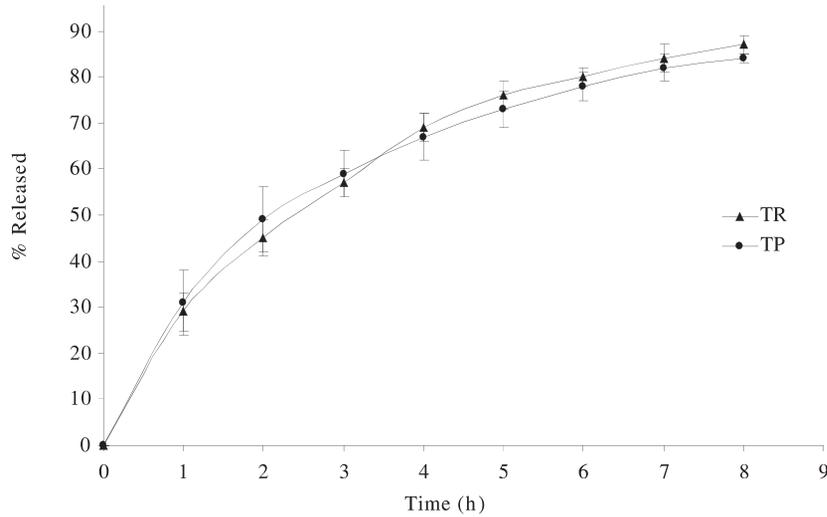


Figure 1. *In vitro* tramadol hydrochloride release (mean \pm RSD) from slow release tablets obtained by hot tableting of coated pellets, 100 mg (TP) compared to Tramal Retard[®] tablets, 100 mg (TR), n = 12

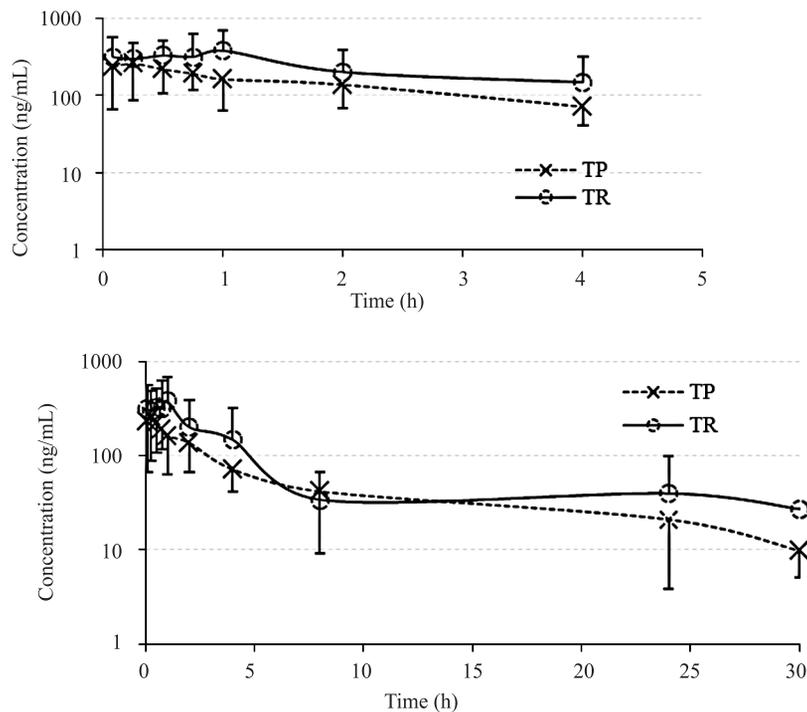


Figure 2. Plasma concentration-time profiles (mean \pm SD) of tramadol hydrochloride after oral administration of slow release tablets obtained by hot tableting of coated pellets, 100 mg (TP) and Tramal Retard[®] tablets, 100 mg (TR) in rabbits (n = 10). One hour after administration of tramadol hydrochloride a statistically significant difference was observed (p = 0.0276)

lated area was estimated by equations: $AUC_{last-\infty} = C_{last} / k_{el}$, $AUMC_{last-\infty} = (t_{last} \times C_{last} / k_{el} + C_{last} / k_{el}^2)$, in which C_{last} is the last measured concentration and t is the time of C_{last} . $AUMC_{0-\infty}$ and $AUC_{0-\infty}$ values were dose normalized. The absolute bioavailability $F(\%)$ of TH was calculated using equation:

$$F(\%) = [AUC_{0-\infty p.o.} \times D_{i.v.} / AUC_{0-\infty i.v.} \times D_{p.o.}] \times 100$$

The relative bioavailability (RB (%)) = $AUC_{0-\infty TP} / AUC_{0-\infty TR}$, mean absorption time ($MAT = MRT_{p.o.} - MRT_{i.v.}$), absorption rate constant ($k_a = 1/MAT$) and absorption half-life ($t_{1/2ka} = \ln 2 \times MAT$) were also determined.

Coefficients of variation (CV), defined as the ratio of the SD to the mean ($CV = (SD/mean) \times 100\%$) for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ and TH plasma concentrations at all evaluated time points after administration of TP and TR, were also calculated.

All statistical analyses were performed using Statistica PL 10 software (StatSoft, Inc.).

Shapiro-Wilk test was used to check if analyzed data follow normal distribution. Paired t -test or Wilcoxon test (in case data did not follow normal distribution, i.e., for plasma concentrations at time points: 30, 45, 60 min and 24 h and t_{max}) were used to compare plasma concentrations and pharmacokinetic parameters of TH. The arithmetic mean, standard deviation, median, range (minimum and maximum value) and geometric mean for pharmacokinetic parameters of TH are presented. The TP and TR bioequivalence was evaluated by means of statistical analysis of variance (ANOVA) and calculating the standard 90% confidence intervals (90%

CI) of the geometric mean ratios (TP/TR) with logarithm (ln)-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} . The bioequivalence was considered when the ratio of averages of log-transformed data for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} was within 80–125%. All tests were considered statistically significant at p value less than 0.05.

RESULTS

In vitro release studies

Dissolution profiles of TP and TR proved to be similar (similarity factor f_2 for the TH release profiles was 71) (Fig. 1).

In vivo studies

Mean plasma concentration-time profiles of TH are shown in Figure 2. Statistical evaluation of plasma concentration-time profiles of TH after oral administration of TP and TR showed no significant differences between these two formulations at all evaluated times, except after 1 h (170.6 ± 101.5 ng/mL vs. 423.1 ± 315.4 ng/mL for TP and TR, respectively, $p = 0.0276$). CV values for TH plasma concentrations at all time points ranged from 43.0 to 72.2% and from 59.1 to 92.6% (after administration of TP and TR, respectively). CV values for TH plasma concentrations in the first two hours (time points: 5, 15, 30, 45, 60 and 120 min) were generally lower after TP administration (72.2, 61.5, 53.6, 43.0, 59.5 and 55.7%) compared with TR (66.1, 91.4, 59.1, 99.7, 74.5 and 99.0%). Pharmacokinetic

Table 1. Comparison of the bioavailability of tramadol hydrochloride (one-way analysis of variance ANOVA) after oral administration of a new slow release tablets obtained by hot tableting of coated pellets, 100 mg (TP) and Tramal Retard® tablets, 100 mg (TR) in rabbits.

| | AUC_{0-t} (ng × h/mL) | | $AUC_{0-\infty}$ (ng × h/mL) | | C_{max} (ng/mL) | |
|---------------------------------------|-------------------------|---------|------------------------------|---------|-------------------|--------|
| | TP | TR | TP | TR | TP | TR |
| Mean | 962.22 | 1100.08 | 1060.93 | 1119.14 | 279.67 | 446.96 |
| SD | 309.30 | 673.51 | 548.14 | 656.68 | 109.47 | 151.60 |
| Median | 906.13 | 939.45 | 962.89 | 984.63 | 285.40 | 458.70 |
| Min | 452.26 | 424.99 | 464.69 | 457.23 | 146.10 | 220.90 |
| Max | 1403.20 | 2501.06 | 2299.14 | 2520.20 | 502.50 | 653.50 |
| %CV | 32.14 | 61.22 | 51.66 | 58.68 | 39.14 | 33.92 |
| Geometric mean ratio TP/TR and 90% CI | 98.42 (85 – 122) | | 98.47 (92 – 107) | | 61.98 (56 – 70) | |

($n = 10$).

TH – tramadol hydrochloride, C_{max} – maximum plasma concentration, AUC_{0-t} – area under the plasma curve from zero to the last measurable concentration, $AUC_{0-\infty}$ – area under the plasma curve from zero to infinity, Mean – arithmetic mean, SD – standard deviation, Min – minimum value, Max – maximum value, 90% CI – 90% confidence interval of the geometric mean ratio (TP/TR), CV – coefficient of variation defined as the ratio of the SD to the mean: $CV = (SD/mean) \times 100\%$.

Table 2. Descriptive statistics of the pharmacokinetic parameters of tramadol hydrochloride after oral administration of a new slow release tablets obtained by hot tableting of coated pellets, 100 mg (TP) and Tramadol Retard® tablets, 100 mg (TR) in rabbits (n = 10).

| | k_{el} (h ⁻¹) | | $AUC_{0-\infty}$ (ng × h/mL) | | MRT (h) | | $t_{1/2el}$ (h) | | t_{max} (h) | | MAT (h) | | k_e (h ⁻¹) | | $t_{1/2ka}$ (h) | |
|---------|-----------------------------|------|---------------------------------|----------|------------|-------|-----------------|-------|---------------|------|------------|------|--------------------------|------|-----------------|------|
| | TP | TR | TP | TR | TP | TR | TP | TR | TP | TR | TP | TR | TP | TR | TP | TR |
| Mean | 0.18 | 0.32 | 5994.64 | 12113.57 | 5.91 | 5.01 | 4.40 | 3.89 | 0.34 | 1.05 | 3.14 | 2.09 | 0.42 | 0.51 | 2.17 | 1.45 |
| SD | 0.16 | 0.24 | 3842.13 | 20797.35 | 4.14 | 3.47 | 2.88 | 2.65 | 0.25 | 1.29 | 1.52 | 0.49 | 0.26 | 0.13 | 1.06 | 0.35 |
| Median | 0.11 | 0.30 | 4799.50 | 4530.45 | 5.01 | 3.60 | 4.22 | 3.05 | 0.25 | 0.63 | 2.91 | 2.10 | 0.34 | 0.48 | 2.01 | 1.46 |
| Min | 0.03 | 0.06 | 678.38 | 720.40 | 1.46 | 1.60 | 1.01 | 1.10 | 0.08 | 0.08 | 0.96 | 1.26 | 0.19 | 0.36 | 0.67 | 0.87 |
| Max | 0.61 | 0.74 | 14626.90 | 78552.20 | 17.06 | 14.40 | 11.82 | 10.00 | 1.00 | 4.00 | 5.06 | 2.80 | 1.04 | 0.79 | 3.51 | 1.94 |
| G mean | 0.13 | 0.23 | 4703.36 | 5097.65 | 4.77 | 4.14 | 3.56 | 3.16 | 0.26 | 0.56 | 2.75 | 2.03 | 0.36 | 0.49 | 1.91 | 1.41 |
| p value | p = 0.0303 | | p = 0.1559 | | p = 0.2769 | | p = 0.3129 | | p* = 0.0249 | | p = 0.0177 | | p = 0.1525 | | p = 0.0177 | |

* Wilcoxon test

Statistical analysis of the data was performed using the paired t-test and Wilcoxon test (t_{max}). All tests were considered statistically significant at $p < 0.05$. TH – tramadol hydrochloride, k_{el} – elimination rate constant, $AUC_{0-\infty}$ – area under the first moment curve from zero to infinity, MRT – mean residence time, $t_{1/2el}$ – elimination half-life, t_{max} – time to reach maximum plasma concentration, MAT – mean absorption time, k_e – absorption rate constant, $t_{1/2ka}$ – absorption half-life, Mean – arithmetic mean, SD – standard deviation, Min – minimum value, Max – maximum value, G mean – geometric mean

parameters of TH and their statistical evaluation are summarized in Table 1 and Table 2. The mean C_{max} values (mean ± SD) of the TP and TR were: 279.67 ± 109.47 and 446.96 ± 151.60 ng/mL, respectively (statistically significant differences: $p = 0.0003$, t -test). The medians (range) of t_{max} values were also statistically different for TP and TR (Wilcoxon test, $p = 0.0249$) and were 0.25 (0.08–1.00) and 0.63 (0.08–4.0) hours, respectively.

However, comparison of the extent of the drug absorption (AUC_{0-t} and $AUC_{0-\infty}$ values) revealed no statistically significant differences. Moreover, 90% confidence intervals (CIs) for the ratios of geometric means for AUC_{0-t} and $AUC_{0-\infty}$ were within the range 80 to 125% proposed by EMA (23) and were 85 to 122%, and 92 to 107%, respectively. Ninety percent CIs for C_{max} (56 to 70%) were not included in this range (Table 1). Comparison of %CV for AUC_{0-t} and $AUC_{0-\infty}$ has shown generally lower values after TP administration (Table 1).

After administration of TP, higher values of: MAT (by 33.1%, $p = 0.0177$, t -test), MRT (by 15.2%, $p > 0.05$, t -test), $t_{1/2ka}$ (by 33.8%, $p = 0.0177$, t -test), $t_{1/2el}$ (by 11.6%, $p > 0.05$, t -test) and lower values of: k_a (by 21.4%, $p > 0.05$, t -test) and k_{el} (by 77.8%, $p = 0.0303$, t -test) for TH were observed. It may indicate a prolonged absorption and elimination processes of TH (Table 2).

The absolute bioavailability $F(\%)$ of TH was $32.8 \pm 7.4\%$ and $45.8 \pm 12.9\%$ after TP and TR administration. The relative bioavailability of TH was 83.97%.

DISCUSSION

A new oral dosage form of TH – slow release tablets obtained by hot tableting of coated pellets, 100 mg (TP), was compared in our study to the conventional slow release tablets – Tramadol Retard®, 100 mg (TR). It is known that pellets constitute multiple-unit dosage forms, which have many advantages as compared to the traditional tablets (21). They are more evenly distributed in the stomach, which leads to a lower risk of high local concentration and of adverse effects. Any disturbances at the administration stage, for example crushing with teeth, or otherwise changed release rate of absorption may not apply to all pellets. Moreover, these forms are

characterized by a high reproducibility of release due to a relatively large surface and the short diffusion way of the drug (21, 28). Results of many animal studies (29–33) could indicate that different oral formulations of TH have a variable systemic availability and, consequently, could cause an unpredictable clinical response; this is why pharmacokinetic study of each new formulation of the drug is so important.

In our study, no statistically significant differences between these two formulations were observed when comparing the extent of the drug absorption (90% CIs values for AUC_{0-t} and $AUC_{0-\infty}$ were within the range of 80–125%) and concentration-time profiles (except TH concentrations 1h after administration, $p = 0.0276$). However, a comparison of TP's and TR's pharmacokinetics may indicate prolonged absorption and elimination processes of TH after TP administration (higher values of MAT, MRT, $t_{1/2ka}$ and $t_{1/2kel}$ and lower values of k_a and k_{el}). TP exhibited a significantly lower C_{max} and a shorter t_{max} of TH compared with TR. The C_{max} of TH, both after TP and TR administration, was higher than that reported e.g., in dogs (mean \pm SD, 40 ± 110 ng/mL; SR tablet, dose of 4–6 mg/kg) (29), horses (mean \pm SEM, 57 ± 0.07 ng/mL; SR tablet, dose of 5 mg/kg) (30), but lower than in cats (mean \pm SEM, 914 ± 232 ng/mL; IR tablet dose of 5.2 mg/kg) (31) and dogs (mean \pm SD, 1402.75 ± 695.52 ng/mL; IR tablet, dose of 100 mg, mean dose of 11.2 mg/kg) (32).

Values of plasma concentrations and hence pharmacokinetic parameters of TH after TP and TR administration were considerably variable among rabbits. Although all of the rabbits had similar body weight and fasted 12 h prior to drug administration and 12 h afterwards to minimize the variability caused by food, differences in bioavailability, gastrointestinal transit time, disintegration of the oral dose form, and rate of absorption can affect plasma concentrations of TH. However, TP formulation produced a smaller inter-subject variability in AUC_{0-t} and $AUC_{0-\infty}$ and plasma concentrations of TH at all evaluated time points. Inter-animal variability (related to differences in absorption rate or gastrointestinal transit time, etc.) was also described by e.g., Pypendop and Ilkiw (31) or Cox et al. (22) in most of the pharmacokinetic parameters and plasma concentrations of TH after oral administration.

The mean absolute bioavailability of TH after TP and TR administration was relatively low (about 40%). This may be related to the poor absorption and strong metabolism of TH in rabbits. It is known

that administration of controlled release drugs does not always entail increased bioavailability (28). Generally, biological availability of TH in animals after administration of SR tablets is usually lower than after IR tablets (29, 30, 33).

CONCLUSIONS

After administration of slow release tablets obtained by hot tableting of coated pellets, a prolonged absorption and elimination processes and a smoother and more extended plasma profile of TH in rabbits were observed. Using animal model, both TP and TR tablets have a similar *in vitro* release profile and similar values. It can be expected that the use of a new oral dosage form of TH in patients affects the extension of analgesia after single administration of the drug, with its gradual absorption into the systemic circulation.

Conflict of interest

The authors state no conflict of interest.

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