Pharmacokinetics of Indomethacin, a Metabolite of Acemetacin, Following a Single dose and Multiple doses Administered as Acemetacin Sustained-Release Tablets in Healthy Male Volunteers

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The objective of this study was to estimate the pharmacokinetics of the newly developed once-daily acemetacin sustained-release tablets compared with those of the commercial acemetacin sustained-release capsules. Ten male healthy Chinese volunteers were included in the study. The administration schedule was a randomized crossover design. Each volunteer received 90 mg of the tablet or the capsule in the single-dose study, and each received 90 mg of the tablet or the capsule once daily for 6 consecutive days in the multiple-dose study. The areas under the concentration-time curve ($AUC_{0-24\ hr}$), maximal concentrations of indomethacin (C_{max}), time to reach peak concentration (T_{max}), and elimination half-life ($T_{1/2}$) values of indomethacin (an active metabolite of acemetacin) were 6.72 ± 0.99 μg.hr/ml, 0.82 ± 0.08 μg/ml, 4.2 ± 0.6, and 10.1 ± 4.2 hr, respectively. The steady-state $AUC_{120-144\ hr}$ and steady-state maximal concentration of the tablets increased to 10.33 ± 1.06 μg.hr/ml and 1.14 ± 0.10 μg/ml, respectively. The pharmackinetic parameters ($AUC_{0-24\ hr}$, C_{max}, $T_{1/2}$, and mean residence time) for two formulations were not significantly different but the average T_{max} of the tablets was delayed by 1 hr compared with that of the capsules (4.2 ± 0.6 *vs.* 3.2 ± 0.6 hr, $p < 0.05$). The mean relative bioavailability of the tablets was 97.9 ± 14.8% compared with that of the capsules. It could be concluded that the pharmacokinetic parameters of the newly developed sustained-release tablets are similar to those of the sustained-release capsules, excluding the T_{max} value. A significant correlation was obtained between the *in vivo* mean absorption rate and the *in vitro* mean dissolution rate for the newly developed sustained tablets.

Key words —— acemetacin, dissolution, indomethacin, pharmacokinetics, sustained-release capsule, sustained-release tablet

INTRODUCTION

Acemetacin was first made available commercially in Germany in 1980. It is a well-tolerated nonsteroidal drug (NSAID) with antiinflammatory, analgesic, and antipyretic properties[1,2] and an inhibitor of the cyclooxygenase enzyme that is involved in the synthesis of prostaglandins, which are an important part of the inflammatory chain. Indications for acemetacin include: chronic articular rheumatism;[3] psoriatic arthritis;[4] acute inflammatory events in degenerative arthropathies, in particular arthropathies of large joints and the spinal column; ankylosing spondylitis;[5] gout attacks; inflammatory events of joints, muscles, and tendons; and tenosynovitis, bursitis, and lumbago-sciatic pain.

The molecular structure of acemetacin is shown in Fig. 1. In humans, 50–90% of the acemetacin absorbed is converted into indomethacin and other inactive metabolites and a potently inhibits prostaglandin synthesis with indomethacin *via* the same mechanism.

NSAIDs have commonly been associated with upper gastrointestinal (GI) tract side effects, including a high incidence of gastric and duodenal ulceration.[6] Modified or sustained-release dosage forms

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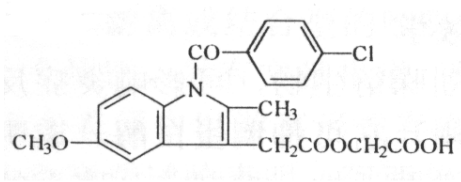

Fig. 1. Structure of Acemetacin

of NSAIDs have been developed for reducing the administration times, lowering the peak-to-trough fluctuation of drug concentrations, and decreasing the severity of upper GI side effects. The incidences of GI side effects of acemetacin were lower than those of indomethacin in Chinese patients on the mainland [18.6% for acemetacin *vs.* 37.9% for indomethacin in RA patients, 8.9% for acemetacin *vs.* 13.6% for indomethacin in osteoarthritis (OA) patients],[7] and in Taiwan.[8] However, the side effects of acemetacin were still evident with stomachache and nausea following oral administration of acemetacin regular-release capsules (Shijiazhuang First Pharmaceutical Factory, Shijiazhuang, China) for 1 month (90 patients) and 4 months (25 patients).[9]

The Rantudil Retard capsules (containing acemetacin 90 mg) are the acemetacin sustained-release capsules developed by Bayer Pharmaceutical Company (Germany) for more convenient administration (once daily for sustained-release capsules *vs.* t.i.d. for acemetacin regular capsules). The upper GI tract tolerance of Rantudil Retard capsules is unknown. Rantudil Retard capsules reach maximal plasma concentrations in approximately 4 hr, after 6 and 10 hr later, the blood concentration of retard acemetacin is higher than that of nonretard acemetacin, as indicated on the Bayer website (http://www.bayer.com.tr/pharma/english/rantudilretard.html), suggesting that the sustained-release capsules are able to decrease the peak-to-trough fluctuation. The sustained-release capsules are marketed in many countries, excluding China. Investigations of acemetacin sustained-release tablets have not been published, and the pharmacokinetic data on the sustained-release capsules are not available in Chinese.

Acemetacin sustained-release tablets were developed by our laboratory to reduce administration times compared with the regular capsules, as were the Rantudil Retard capsules, and the preclinical results of the tablets met the requirements for a new drug application of the State Food and Drug Administration of China. The objective of this study was to estimate the pharmacokinetics of the newly developed acemetacin sustained-release tablets compared with the marketed sustained-release capsules in male healthy Chinese volunteers.

MATERIALS AND METHODS

Preparation and Dissolution Rates —— The sustained-release tablets were prepared according to the wet granulation method. Briefly, acemetacin and hydroxylpropylmethyl cellulose (HPMC K4M, Colorcon Shanghai Branch, China) were homogeneously mixed, and a suitable amount of 1% HPMC K4M solution (dissolved in 50% ethanol) as a binder was added to the mixture for granulation (20 mesh/2.54 cm). The wet granules were dried at 50°C. Magnesium stearate was added to the dried granules as a lubricant and mixed well. The mixed granules were then sieved (18 mesh/2.54 cm) and pressed into tablets. Each tablet contained 90 mg of acemetacin, 10 mg of HPMC K4M, and 1.0 mg of magnesium stearate. The sustained-release tablets met the standards of the Chinese Pharmacopoeia (2000, part II) for the tablets.

The dissolution rates of acemetacin sustained-release tablets were tested using the rotating basket method in the Chinese Pharmacopoeia (2000, part II). The dissolution test apparatus was a ZRS-8 tester (Electronic Equipment Plant of Tianjin University, Tianjin, China). Six tablets (each tablet containing 90 mg of acemetacin) were placed in six baskets, respectively, and then rotated in 900 ml of potassium dihydrogen phosphate buffer, pH 6.8, consisting of 0.02 mol/l potassium dihydrogen phosphate, 0.2 mol/l sodium hydroxide and distilled water (250 : 118 : 632, v/v/v). Temperature was set at 37 ± 0.5°C and the rotation rate was 100 revolutions per min. Release solution (10 ml) was separately sampled from each flask at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 hr and filtered using micropore filters (0.8 μm). After sampling, 10 ml of fresh buffer medium was immediately added to the flasks. The filtrates of samples were determined at a wavelength of 318 nm using a 752-type ultraviolet spectrophotometer (Shanghai Analysis Equipment Factory, Shanghai, China). An appropriate amount of standard acemetacin (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China) was weighed after drying at 105°C, dissolved in the potassium dihydrogen phosphate buffer as a control for determination, and assayed at a wave-

length of 318 nm. Dissolution rates were calculated at each time point.

Dissolution rates of the sustained-release capsules (lot No. ACWX1, Bayer AG, Germany) containing 90 mg of acemetacin in each capsule were determined using the same conditions as for the sustained-release tablets. Dissolution rates of acemetacin regular capsules containing 30 mg of acemetacin in each capsule (commercially available from Shijiazhuang First Pharmaceutical Factory) were also measured for comparison with the dissolution rates of sustained-release tablets or sustained-release capsules.

Analytical Procedures —— The HPLC-UV method was modified according to reports by Notarianni and Collins,[10] Jones *et al*.,[11] and Hu (1999), *et al*.[12] Briefly, the Jasco HPLC system consisted of a Jasco PU-980 isocratic pump with a Rheodyne 7725i sampler, a Jasco UV-975 detector set at 254 nm, and a chemostation (Jasco Inc., Japan). The mobile phase used was 0.02 mol/l potassium dihydrogen phosphate-methanol (29 : 71, v/v) solution adjusted to pH 4.2 using phosphoric acid. Operating conditions were: column, 150 × 4.6 mm Techspere octadecylsilica (ODS) with 12 × 4.6 mm ODS safeguard column; flow rate, 1.0 ml/min; room temperature; and injection volume, 20 μl. Standard acemetacin, indomethacin, and naproxen (as an internal standard) used for plasma analysis were purchased from the National Institute for the Control of Pharmaceutical and Biological Products. Appropriate amounts of acemetacin and indomethacin were weighed, and dissolved in methanol, and serial standard solutions consisting of 0, 0.1, 0.4, 0.6, 0.8, 1.0, 1.2, and 1.5 μg/ml of acetametacin or indomethacin were prepared, respectively. Aliquots of acemetacin 50 μl, indomethacin 50 μl and internal standard solution 50 μl were added to human blank plasma 0.4 ml in a 10 ml tube, and then mobile phase solution 0.2 ml was added. The mixed solution was mixed for 30 sec using a vertex mixer. 1,2 Dichloroethane 5 ml was added to the tube, the tube was vibrated for 10 min using a vibrator, and then centrifuged (8000 revolution per min) for 20 min. The organic layer in the tube was transferred to another tube and evaporated in a 60°C water bath in the fume hood. The residue evaporated was reconstituted using mobile phase solution 100 μl and injected into HPLC system.

The lower limits of quantification (LOQ) of the assay were 0.01 μg/ml for acemetacin and for indomethacin when the signal-to-noise ratios were set at 3, respectively. Linearity was obtained for acemetacin concentrations between 0.10 and 1.50 μg/ml ($r^2 = 0.9995$) or for indomethacin concentrations between 0.10 and 1.50 μg/ml ($r^2 = 0.9985$). The coefficient of variation of the interday and intraday precision of the quality control ranged from 2.4 to 6.3% for acemetacin, and from 2.7 to 8.5% for indomethacin, respectively. Mean acemetacin recoveries from human plasma were from 97.7 ± 2.1 to 100.3 ± 3.3%, and mean indomethacin recoveries were from 95.7 ± 2.9 to 99.8 ± 2.2%.

Volunteers —— The study was carried out according to the principles of the Declaration of Helsinki, and approved by the Local Ethics Committee of the Peking University Health Science Center (Beijing, China), and written, informed consent was obtained from each volunteer. Ten male healthy Chinese volunteers were included in the study. Inclusion criteria were: males aged between 20 and 30 years, and body weight ranging from 53 to 75 kg. Blood count, renal function, liver function tests, and serum lipids were within the normal range. The volunteers were required to abstain from any medicine including herbal medicine, alcohol, caffeine-containing beverages, and grapefruit during the experimental period. Exclusion criteria included severe concomitant disease, past history of deep-vein thrombosis, or rheumatoid-related disorders. Treatment with any drug 1 week before or during the entry into the study was regarded as an exclusion criterion.

Single-dose Administration —— The randomized and crossover design for oral administration were performed, and the 10 volunteers were divided into two equal groups. The experiment was completed in four stages and the interval between stages was 1 week.

In the first stage, each volunteer in group I ($n = 5$) received a 90-mg acemetacin sustained-release tablet (1 tablet) at 08:00, followed by drinking 200 ml of warm water. Volunteers in group II ($n = 5$) received 90 mg of the sustained-release capsule (1 capsule, lot no. ACWX1, Bayer AG) at 08:00. Blood samples (2 ml each) were collected from vein vessels in the antebrachium at 0 (before dosing), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 16.0 and 24.0 hr after the start of oral administration. Blood samples were placed in heparinized tubes and then centrifuged at 3000 revolutions per min. The plasma was separated and stored in a freezer at –20°C until subsequent analysis.

In the second stage, each volunteer in group I ($n = 5$) received a 90-mg sustained-release capsule,

and those in group II (n = 5) received a 90-mg sustained-release tablet. Sampling time points and blood sample treatments were the same as those in the first stage.

Multiple-dose Administration —— In the third stage, each volunteer in group I (n = 5) received a 90-mg sustained-release tablet every day at 08:00 for 6 days, and those in group II (n = 5) received a 90-mg sustained-release capsule every day at 08:00 for 6 days. Two hours after oral administration, breakfast was served. Lunch and dinner were served at 12:00 and 17:30, respectively. Blood samples (2 ml each) were collected at 72, 96, 120, 121, 121.5, 122, 123, 124, 125, 126, 128, 130, 132, 136, and 144 hr after oral administration, and processed using the same procedures as above.

In the fourth stage, each volunteer in group I (n = 5) received a 90-mg sustained-release capsule every day at 08:00 for 6 days, and those in group II (n = 5) received a 90-mg sustained-release tablet every day at 08:00 for 6 days. Blood samples were collected and processed the same as in the third stage.

Pharmacokinetics and Statistic Analyses —— The pharmacokinetic parameters were calculated using the 3P97 Practical Pharmacokinetic Program (Mathematic Pharmacological Association of China, China) operated in MS-DOS (Microsoft, U.S.A.). Briefly, the areas under the concentration-time curve ($AUC_{0-24\ hr}$) were calculated according to the trapezoidal rule. $AUC_{0-\infty}$ was estimated from $AUC_{0-24\ hr} + C_{24\ hr}/K$, where $C_{24\ hr}$ is the indomethacin concentration at 24 hr, and K is the elimination rate constant of indomethacin that was estimated from the one-compartmental model. Maximal concentration (C_{max}), time to reach peak concentration (T_{max}), and elimination half-life ($T_{1/2}$) were all estimated from the one-compartmental model. Mean residence time (MRT) was calculated using a noncompartmental model. Similarly, $AUC_{120-144\ hr}$ and $AUC_{120-\infty}$ were obtained according to the trapezoidal rule. Steady-state peak concentration (C^{ss}_{max}) and trough concentration (C^{ss}_{min}) were estimated with inclusion of the multiple-dose function in the exponential expression in the one-compartment model. Mean steady-state concentration (C_{ss}) was calculated using $AUC_{120-144\ hr}/\tau$. The relative bioavailability of acemetacin sustained-release tablets was the ratio of $AUC_{120-144\ hr}$ of the sustained-release tablet to $AUC_{120-144\ hr}$ of sustained-release capsules. The *in vivo* mean drug absorption rate (%) was estimated using the Wagner-Nelson equation, and the correlation between the *in vitro* dissolution (%) and *in vivo* absorption rates (%) of the sustained-release tablet was performed using the 3P97 software with linear regression.

Data expressed are as the mean ± standard deviation (S.D.), and the statistical analyses for logarithmically transformed parameters (AUC, C_{max}, C^{ss}_{max}, C^{ss}_{min}, and C_{ss}) between the two formulations were based on the two-sided t-test. In addition, the comparisons of the T_{max}, $T_{1/2}$, MRT, and plasma concentrations of the two formulations at the same time points were based on analysis of variance (ANOVA). The correlation between the *in vitro* release rate and *in vivo* absorption rate was based on the correlation coefficient t-test.

RESULTS

Dissolution Rates

The dissolution profiles of the sustained-release tablets, sustained-release capsules, and regular capsules are illustrated in Fig. 2. Dissolution rates of the sustained-release tablets approximately showed a zero-order kinetic process, and the equation was $D_1 = 13.57 \times T$, $r^2 = 0.9222$, where D_1 represents the dissolution rate (%) of acemetacin sustained-release tablets, and T the dissolution time (hr). Dissolution

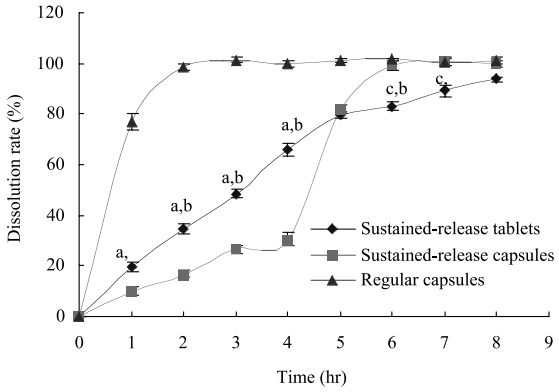

Fig. 2. *In Vitro* Dissolution Rate Profiles of Acemetacin Sustained-Release Tablets, Sustained-Release Capsules (Consisting of 30 mg of Fast-Release and 60 mg of Delayed-Release Acemetacin, Bayer AG), and Acemetacin Regular-Release Capsules (Shijiazhuang First Pharmaceutical Factory)

The dissolution medium was potassium dihydrogen phosphate buffer, pH 6.8, consisting of 0.02 mol/l potassium dihydrogen phosphate, 0.2 mol/l of sodium hydroxide, and distilled water (250 : 118 : 632, v/v/v); temperature was set at 37 ± 0.5°C and the basket rotating rate was 100 revolutions per min. Notes: a, significantly higher, $p < 0.01$, *vs*. sustained-release capsules at the same time point; b, significantly lower, $p < 0.01$, *vs*. regular capsules at the same time point; c, significantly lower, $p < 0.01$, *vs*. sustained-release capsules at the same time point.

rates of sustained-release capsules (n = 6) showed a zero-order kinetic process at the initial phase from 0 to 4 hr followed by first-order kinetics from 4 to 7 hr. The equations were $D_{21} = 8.12 \times T$, $r^2 = 0.9793$, and $D_{22} = 9.30 \times T + 38.01$, $r^2 = 0.9793$, where D_{21} and D_{22} represent the dissolution rate (%) of sustained-release capsules at the initial and the second release phase, respectively.

In view of the measured results, the dissolution rates of the sustained-release tablets (%, n = 18) were significantly higher ($p < 0.01$) in the initial 4 hr, similar at 5 hr, but markedly lower ($p < 0.01$) from 6 to 8 hr compared with those of the sustained-release capsules (%, n = 18) at the same time points, respectively. However, the dissolution rates of the sustained-release tablets were significantly lower ($p < 0.01$) than those of the regular capsules at the same time points until acemetacin was nearly fully released from the tablet matrix at 8 hr. The acemetacin of regular capsules dissolved completely within 2 hr, while the dissolution time for the sustained-release capsules was up to 6 hr.

As for the estimated results, the *in vitro* dissolution rate of the sustained-release tablets showed that the simulated acemetacin release rate was approximately 13.57% per hour using the formula $D_1 = 13.57 \times T$, the release time anticipated was closed to 8 hr (100% dissolution rate is at 7.36 hr according to the D_1 formula). The release of acemetacin from the sustained-release capsules in the first 4 hr was estimated to be 8.12% per hour using the formula $D_{21} = 8.12 \times T$, and 47.31% per hour in the following hours using $D_{22} = 9.30 \times T + 38.01$. The release time estimated was about 5.5 hr using the two formulae.

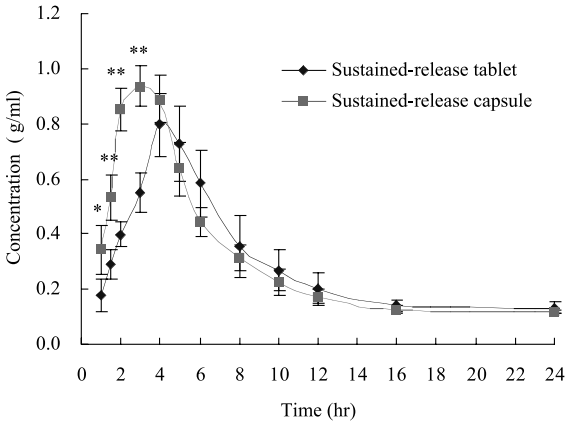

Fig. 3. Active Metabolite Indomethacin Concentrations *vs*. Time Profiles following a Single dose 90 mg of Acetamecin Administered Orally as a Sustained-Release Tablet or Sustained-Release Capsule

*$p < 0.05$, **$p < 0.01$, tablets *vs*. capsules at the same time point.

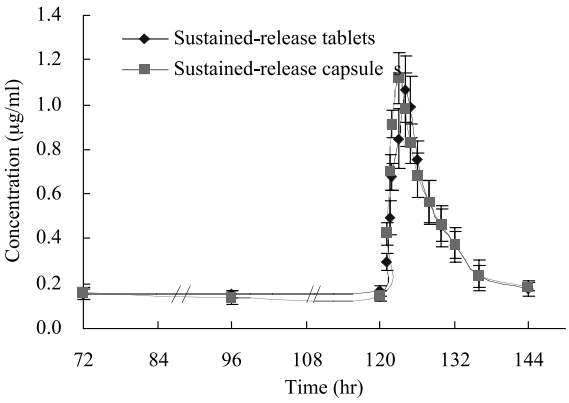

Fig. 4. Active Metabolite Indomethacin Concentration-Time Profiles following Multiple doses of 90 mg of Acetamecin Once Daily Administered Orally as Sustained-Release Tablets or Sustained-Release Capsules for 6 Consecutive Days

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Indomethacin Plasma Concentrations

The mean indomethacin plasma concentrations in the first and second stages following a single-dose (90 mg) administration of the sustained-release tablets were 0.18 ± 0.06 μg/ml at 1 hr, 0.80 ± 0.11 μg/ml at 4 hr (maximal concentration), and 0.13 ± 0.02 μg/ml at 24 hr. Those for the sustained-release capsules were 0.34 ± 0.09 μg/ml at 1 hr, 0.94 ± 0.07 μg/ml at 3 hr (maximal concentration), and 0.12 ± 0.01 μg/ml at 24 hr. In comparison, the time to reach maximal concentration of the sustained-release tablets was delayed for 1 hr, as shown in Fig. 3. Before reaching the maximal concentration, the indomethacin concentrations of the sustained-release capsules at 1, 1.5, 2, and 3 hr were significantly higher than those for the sustained-release tablets at the corresponding time points ($p < 0.05$ or $p < 0.01$), respectively.

The mean maximal indomethacin concentrations in the third and fourth stages following multiple doses (90 mg once daily) administered as the sustained-release tablets or the sustained-release capsules were 1.07 ± 0.15 μg/ml at 124 hr, and 1.12 ± 0.11 μg/ml at 123 hr, respectively. Compared with single-dose administration, the maximal indomethacin concentrations for both formulations were slightly increased after multiple-dose administration, as depicted in Fig. 4. In addition, trough indometha-

Table 1. Pharmacokinetic Parameters of Indomethacin, an Active Metabolite of Acetamecin following a Single dose 90 mg of Acetamecin Orally Administered as the Sustained-Release Tablet or Sustained-Release Capsule

Parameter	Sustained-release tablets	Rantudil Retard capsules
$AUC_{0-24\ hr}$ (μg.hr/ml)	6.72 ± 0.99	7.11 ± 0.50
$AUC_{0-\infty}$ (μg.hr/ml)	8.56 ± 0.95	8.73 ± 0.91
C_{max} (μg/ml)	0.82 ± 0.08	0.97 ± 0.07
T_{max} (hr)	4.2 ± 0.6*	3.2 ± 0.6
$T_{1/2}$ (hr)	10.1 ± 4.2	9.6 ± 3.4
MRT (hr)	15.5 ± 3.5	13.4 ± 3.6

*$p < 0.05$, sustained-release tablets *vs.* sustained-release capsules.

Table 2. Pharmacokinetic Parameters of Indomethacin following Multiple dose 90 mg Once Daily of Aacetamecin Administered Orally as Sustained-Release Tablets or Sustained-Release Capsules

Parameter	Sustained-release tablets	Rantudil Retard capsules
$AUC_{120-144\ hr}$ (μg.hr/ml)	10.33 ± 1.06	10.65 ± 1.12
$AUC_{120\ hr-\infty}$ (μg.hr/ml)	12.86 ± 1.56	13.19 ± 1.66
C^{ss}_{max} (μg/ml)	1.14 ± 0.10	1.18 ± 0.08
C^{ss}_{min} (μg/ml)	0.17 ± 0.03	0.16 ± 0.02
C_{ss} (μg/ml)	0.43 ± 1.21	0.42 ± 1.15
T^{ss}_{max} (hr)	4.1 ± 0.7*	3.4 ± 0.5
$T_{1/2}$ (hr)	9.3 ± 1.9	9.3 ± 1.9
MRT (hr)	14.5 ± 1.7	14.2 ± 1.9

*$p < 0.05$, sustained-release tablets *vs.* sustained-release capsules.

cin concentrations at 120 hr following multiple doses of the sustained-release tablets or sustained-release capsules were 0.17 ± 0.03 and 0.16 ± 0.02 μg/ml, respectively.

Pharmacokinetics

After modeling using 3P97 software, $AUC_{0-24\ hr}$ of indomethacin following a single 90-mg dose of acetamecin administered as sustained-release tablet or as sustained-release capsule were 6.72 ± 0.99 and 7.11 ± 0.50 μg.hr/ml, respectively. C_{max} were 0.82 ± 0.08 and 0.97 ± 0.07 μg/ml, T_{max} were 4.2 ± 0.6 and 3.2 ± 0.6 hr, and $T_{1/2}$ were 10.1 ± 4.2 and 9.6 ± 3.4 hr, respectively, as shown in Table 1. The pharmackinetic parameters ($AUC_{0-24\ hr}$, C_{max}, $T_{1/2}$, and MRT) of the two formulations were not significantly different ($p > 0.05$, not indicated in Table 1), excluding the T_{max} value ($p < 0.05$).

After multiple doses, the estimated average $AUC_{120-144\ hr}$ of indomethacin for acetamecin sustained-release tablets and for sustained-release capsules were 10.33 ± 1.06 and 10.65 ± 1.12 μg.hr/ml, respectively. Mean C^{ss}_{max} were 1.14 ± 0.10 and 1.18 ± 0.08 μg/ml, times to reach peak concentrations at steady-state (T^{ss}_{max}) were 4.1 ± 0.7 and 3.4 ± 0.5 hr, and $T_{1/2}$ were 9.3 ± 1.9 and 9.3 ± 1.9 hr, respectively, as shown in Table 2. The estimated mean C_{ss} were 0.43 ± 1.21 μg/ml for the tablets and 0.42 ± 1.15 μg/ml for the capsules. The pharmackinetic parameters (C^{ss}_{max}, T^{ss}_{max}, C_{ss}, $T_{1/2}$, and MRT) for the two formulations after multiple doses were not significantly different ($p > 0.05$, not indicated in the Table 2), excluding the T^{ss}_{max} value ($p < 0.05$). The relative bioavailability of acemetacin sustained-release tablets was 97.9 ± 14.8%.

In Vitro and *in Vivo* Correlation

The *in vivo* mean drug absorption rates of the sustained-release tablets were 19.01 ± 2.43 at 1 hr, 36.41 ± 3.12 at 2 hr, 59.08 ± 1.56 at 3 hr, 80.77 ± 3.12 at 4 hr, and 96.38 ± 3.90 at 6 hr. It was shown that a significant correlation was obtained between the *in vivo* average absorption rate and the *in vitro* average dissolution rate (coefficient square: $r^2 = 0.9928$, $p < 0.01$), as shown in Fig. 5.

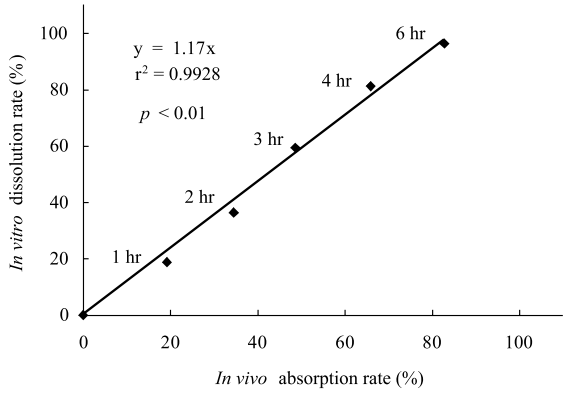

Fig. 5. Linear Correlation between the *in Vitro* Dissolution Rate of Acetamecin from the Sustained-Release Tablet and *in Vivo* Absorption Rate of Indomethacin following a Single dose 90 mg of Acemetacin Administered Orally as a Sustained-Release Tablet

DISCUSSION

HPMC is commonly used in hydrophilic matrix drug delivery. In the present study, HPMC K4M was used because it formed a strong viscous gel on contact. The sustained-release effect of acematacin came from the hydrophilic gel matrix formed by HPMC K4M. During the dissolution process, moisture penetrated into the matrix network, and the matrix was a gradually eroded until it completely dissolved at 8 hr.

Considering the purpose of the once-daily administration of the sustained-release tablet, controlling the release rate is necessary. Otherwise, the total amount of acemetacin would be released in a short time when the tablet is administered once daily. It, therefore, would lead to more fluctuating concentrations compared with the regular capsule administered t.i.d. because the amount of acemetacin in the sustained-release tablet is equivalent to an entire daily dose (30 mg × 3 administration times per day for regular capsules). The dissolution of the sustained-release tablets that showed a zero-order process and finished at 8 hr would be ideal because drugs or food remains in the GI tract up to 8–10 hr, and the upper GI tract (from stomach to small intestine) is probably the main absorption site of drugs or food. Furthermore, sustained release may also palliate the irritation by acemetacin of the GI tract, although this assumption needs to be confirmed in the further clinical trials.

In the control group, dissolution of sustained-release capsules showed a two-phase profile that had an S-type curve. This may be caused by the capsule components: the rapidly dissolving part (containing acemetacin 30 mg) and delayed-release part (containing acemetacin 60 mg). In contrast, the dissolution of the regular capsules showed an immediate-release profile and reached nearly 100% within 2 hr, demonstrating that the dissolution rates of both the sustained-release tablets and the sustained-release capsules were well controlled although the dissolution profiles were different.

The concentration-time profile of the sustained-release tablets showed that the T_{max} was delayed to 4 hr, indicating that the *in vivo* release rate of acemetacin was also well controlled by the hydrophilic gel matrix. However, the T_{max} of the sustained-release capsules was 3 hr though the dissolution rate of the capsules in the initial 4 hr was slower than that of the tablets. This may suggest that the *in vivo* drug absorption rate of the sustained-release tablets could be more correlated with the *in vitro* dissolution rate, thus further indicating that the *in vitro* dissolution rate could be an indicator for the quality control of the sustained-release tablets. A significant correlation ($r^2 = 0.9928$, $p < 0.01$) between the *in vitro* dissolution rate % and *in vivo* absorption rate, supported this assumption. In addition, the sustained-release tablets appeared to be more beneficial in alleviating the upper GI tract side effects such as gastric and duodenal ulceration due to the longer T_{max} (4 hr for the sustained-release tablets *vs*. 3 hr for the sustained-release capsules).

The mean drug absorption rate in the present study was calculated using the single-dose concentration-time data of indomethacin instead of those of acemetacin because the complete concentration-time profiles for acemetacin were not be available from present study although it was reported that the blood level ratios of acemetacin and indomethacin are equal after single and after multiple administration of acemetacin.[13] The possible reason may be due to the fact that the most of the acemetacin absorbed was converted into indomethacin and other inactive metabolites. During the process, the absorption may show mixed rate orders, *i.e.*, first and multiple rate orders. These may be because the acemetacin may be degraded by esterolytic cleavage to indomethacin in GI tract before and during the absorption process or after being absorbed. The final absorption process may be complicated. Nevertheless, the Wagner-Nelson method could estimate the absorption process of acemetacin in human subjects because the method need not be first order, as indicated in the website (http://www.boomer.org/c/

p3/c18/c1803.html).

In comparing the single-dose profile with the multiple-dose profile, the pharmacokinetic analysis of the sustained-release tablets showed that the single-dose and multiple-dose profiles at a dose interval (24 hr) were similar in shape. However, the C^{ss}_{max} value after multiple-dose administrations was slightly increased compared with C_{max} after a single-dose administration. This is derived from the additional effects following multiple doses. The T_{max}, $T_{1/2}$, and MRT values estimated from the single dose were close to T^{ss}_{max}, $T_{1/2}$, and MRT from multiple doses, respectively.

The pharmacokinetic parameters of the sustained-release tablets were similar to those of the sustained-release capsules, excluding the T_{max} value ($p < 0.05$). It was interesting that the *in vitro* dissolution rates of sustained-release capsules were lower than those of the sustained-release tablets in the initial 3 hr, but the statistical analysis showed that the concentrations of sustained-release capsules at 1, 1.5, 2, and 3 hr were significantly higher than the concentrations of the sustained-release tablets at the corresponding time points. This may suggest that the *in vivo* absorption rates of the capsules may not be consistent with their *in vitro* dissolution rates. This difference may be derived from the different controlled-release materials, and the different release environments *in vitro* and *in vivo*. The sustained-release capsule was dissolved more slowly in the first phase *in vitro*, however, it was released faster *in vivo* because of more intense eroding by peristalsis in the GI tract. Although the sustained-release tablet was in the same release environment, the tablet appeared to be more solid or massive to resist such erosion.

Most pharmacokinetic parameters obtained from the present study were similar to those reported. Nevertheless, the $T_{1/2}$ value of indomethacin after oral administration of acemetacin was 7.1 hr in the young healthy volunteers ($n = 10$) or 7.2 hr in elderly patients with osteoarthritis ($n = 10$).[11] When acemetacin was administered orally to patients with rheumatic disease and concomitant liver disease (fatty liver, cirrhosis), the mean $T_{1/2}$ of indomethacin was about 4 hr.[14] The plasma half-life ($T_{1/2}$) of indomethacin in premature infants was reported to range from 11 to 20 hr[15,16] and correlated with gestational age. The absorption of orally administered indomethacin appeared to be incomplete and plasma clearance much longer than in the adult. Our results showed the half-life of indomethacin was around 10 hr. The variations in $T_{1/2}$ may be derived from age, pathology, and ethnic differences.

It can be concluded that the main pharmacokinetic parameters of the newly developed sustained-release tablets are similar to those of sustained-release capsules, excluding the T_{max} value. A significant correlation was obtained between the *in vivo* mean absorption rate and the *in vitro* average dissolution rate of the newly developed sustained tablets.

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