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Zero-order release three-layered tablet with an acemetacin solid dispersion core and a hydroxypropyl methylcellulose capped matrix

Xiaole Qi, Yujie Jiang, Xiangbo Li, Ziwei Zhang, Zhenghong Wu
Key Laboratory of Modern Chinese Medicines, China Pharmaceutical University, Nanjing 210009, People's Republic of China
Correspondence to: Z. Wu (E-mail: zhenghongwu66@cpu.edu.cn)

ABSTRACT: The purpose of this study was to prepare a three-layered tablet with hydroxypropyl methylcellulose (HPMC) polymers as a capped matrix to achieve a zero-order release for acemetacin. As the middle active core, a solid dispersion in poly(vinyl pyrrolidone)–K30 polymers was manufactured via a solvent method to improve the solubility of acemetacin. A Box–Behnken design was used to optimize the formula, when the amounts of HPMC in the middle layer, HPMC in the external layer, and mannitol in the middle layer were chosen as the influencing factors. The dissolution profiles of the optimized formula exhibited superior fitting to the zero-order release in 24 h. A bioavailability experiment was carried out by the administration of those three-layered tablets to rabbits and their comparison with market Gaoshunsong controlled release capsules. The delayed time to reach the maximum plasma concentration, decreased the maximum plasma concentration, area under the plasma concentration-time curve (0–48 h) AUC_{0-48}, and area under the plasma concentration-time curve (0–∞) $AUC_{0-\infty}$ were 9.33 ± 2.51 h, 8.59 ± 0.94 μg/mL, 200.81 ± 11.36 μg h/mL, and 212.902 ± 31.66 μg h/mL, respectively. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42059.

KEYWORDS: applications; drug-delivery systems; hydrophilic polymers

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INTRODUCTION

Oral controlled release systems exhibit a number of advantages, such as an improvement in patient compliance, therapeutic efficacy and safety, greater selectivity of pharmacological activity, and decreased side effects and dosing frequency. Various methods have been used to achieve controlled release, including film coating,[1–3] multilayering,[4,5] and osmotic pump controlled release systems.[6,7] In addition, multilayer tablets have gained much focus, mainly because of their low price, ease of manufacturing, and effectiveness. Among them, three-layered matrix tablets are of great interest among researchers to design a zero-order-release drug-delivery system. The release of drugs from three-layered tablets follows these steps.[8] In the initial stage, the top and bottom layers are applied to obstruct the release of the middle layer through the limiting of the solvent penetration and the reduction of the surface area available for drug release. Throughout the dissolution, the top and bottom hydrophilic barrier layers swell and erode where the surface area available for drug release increases. Hence, the decrease in the release rate because of the reduction of the drug concentration gradient is compensated by the simultaneous increase in the available area for drug diffusion release; this results in nearly linear release profiles.[9] On the basis of this theory, the Rhone-Poulenc Rorer developed a device for the 24-h extent release of diltiazem hydrochloride, which was launched in 1992 in the United States. In recent years, with the development of hydrophilic and hydrophobic polymers, three-layered tablets with different kinds of polymer materials, such as guar gum,[10–12] poly(ethylene oxide),[13,14] hydroxypropyl methylcellulose (HPMC),[15] chitosan, and xanthan gum,[16] have been investigated to achieve desirable objectives. Additionally, the tensile strength of tablets, adhesion strength of layers, and other factors influencing the quality criteria of tablets have also been studied.

Typically, the majority of model drugs in three-layered tablets are highly water-soluble drugs.[8,9,11,12,17] There have been few studies focused on poorly water-soluble drugs[17] because of their low bioavailability. Hong and Oh[13] chose poorly water-soluble nifedipine as a model drug to prepare three-layered tablets. However, in their results, the release data was fitted to the power law equation,[18] and the reaction orders of the equation *n* values were between 0.52 and 0.6. This indicated that the release profile of nifedipine was not a zero-order release.

In this study, we prepared three-layered tablets with HPMC as the matrix material to obtain a zero-order release system. Acemetacin, a nonsteroidal anti-inflammatory drug for the treatment of rheumarthritis and rheumatoid arthritis, was chosen as a model drug, and a solid dispersion was prepared to improve their solubility. Compared to indometacin, acemetacin significantly reduced the gastrointestinal side effects. Various factors,

including the molecular weight and amounts of the polymers, could affect the release of drug from three-layered matrix tablets; thus, Box–Behnken design (BBD) was used to optimize the formula. BBD is widely used to control pharmaceutical processes, including optimizing granulation,[19] formulation of extended-release matrix tablets,[20] or transdermal delivery systems design.[21]

The aims of this study were to prepare and evaluate a three-layered tablet with HPMC polymers as a capped matrix to achieve a zero-order controlled release of acemetacin, a poorly water-soluble drug. A solid dispersion was prepared to improve the solubility of acemetacin, and differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were carried out to confirm the solubilizing effect. The influencing factors of the amounts of HPMC and mannitol were optimized by BBD. In addition, the optimized formula was fitted to the zero-order equation, first-order equation, and Higuchi equation, whereas R^2 was calculated to estimate the release mechanism. Finally, an *in vivo* pharmacokinetic study was carried out in rabbits and a comparison was done to market Gaoshunsong controlled release capsules.

EXPERIMENTAL

Materials

The following chemicals were obtained from commercial suppliers and used as received: acemetacin (Hubei Jianyuan Chemical Co., Ltd., Hubei Province, China), HPMC (Shin-Etsu, Tokyo, Japan, Metolose 90 SH-4000 SR), Mannitol (Roquette, France, Pearitol 100 SD), poly(vinyl pyrrolidone) (PVP)–K30 (BASF, Germany), and magnesium stearate (Anhui Shanhe Pharmaceutical Excipients Co., Ltd., Anhui Province, China). All other materials were reagent grade and were used as received.

Preparation of the Solid Dispersion of Acemetacin

The solid dispersion was prepared by conventional solvent evaporation methods[22] to improve the solubility and bioavailability of acemetacin. According to the results of the preliminary experiments,[22] PVP–K30 was chosen as the carrier material for its better reproduction. Different molar ratios of the drug to PVP–K30 (1 : 1, 1 : 2, 1 : 3, 1 : 5, 1 : 7, and 1 : 9) were dissolved in ethyl alcohol and transferred to a rotary evaporator (BILON RE-5205, Bilang Apparatus, Co., Ltd., Zhengzhou, China) to remove the solvent in a gradually increasing temperature range of 20–80°C. Then, a round-bottomed flask containing the solid dispersion adhering to its wall was placed into a vacuum desiccator (FZG-8, Shenwei Pharmaceutical Equipment Co., Ltd., Nanjing, China) for 24 h in 40°C at −0.1 MPa. Finally, the solid dispersion was scratched from the wall, pulverized by a mortar and pestle, sieved by an 80-mesh sieve and stored in the desiccator (I0234-029, Junguan Equipment Co., Ltd., Shanghai, China) at room temperature until use.

The dissolution profiles were performed with a United States Pharmacopoeia 32 apparatus II (paddle) with 900 mL of distilled water at 37 ± 0.5°C, and the paddle speed was 50 rpm. After they were filtered by a 0.45-μm filter, the concentrations of acemetacin in the samples were determined at 319 nm by high-performance liquid chromatography (HPLC) with a reverse-phase column (Inertsil ODS-3, 4.6 × 250 mm, *i.d.* = 5 μm, GL Sciences, Japan). A 0.05*M* sodium acetate solution (pH 6.0, adjusted with acetic acid) with methanol (30 : 70) was used as the mobile phase at a flow rate of 1.0 mL/min. Methodological studies, such as studies of the linearity, specificity, and precision within and between days, were done to satisfy the requirements of the methodology.

Table I. Composition and Accumulative Release Values of the Three-Layered Tablets of Acemetacin

Formulation (mg/tablet)	
Solid dispersion[a]	180
HPMC[b]	155
Mannitol	165
Magnesium stearate	3
Accumulative release value (%)	
2 h	3.82 ± 0.23
12 h	49.33 ± 3.51

Average tablet weight = 503 mg ± 5%.
[a] There was 90 mg of acemetacin per 180 mg of solid dispersion.
[b] The top layer was 60 mg, the middle layer was 35 mg, and the bottom layer was 60 mg.

The solubility of the pure acemetacin and acemetacin solid dispersion were determined by the addition of an excess amount of drug in vials with 10 mL of pH 6.8 phosphate buffer and shaking in a 37 ± 0.5°C incubator (YBP 6, Tianjin Pharmacopeia Standard Instrument Co., Tianjin). After 48 h of incubation, the samples were centrifuged (Sigma 3K30, Harz, Germany) at 3000*g* for 15 min to remove the undissolved acemetacin. The supernatant was taken and diluted to quantify the acemetacin by HPLC, as mentioned previously.

The change of acemetacin's crystalline domain in the solid dispersion was explored with DSC (Q 200, TA Instruments) and XRD (X'Pert PRO, PANalytical, The Netherlands). The drug (acemetacin), the carrier (PVP–K30), and solid dispersion were subjected to DSC study with a differential scanning calorimeter at a scanning speed of 10°C/min in the temperature range 40–200°C under a nitrogen gas flow. The same samples used for DSC were tested for their XRD patterns, with a diffractometer under ambient conditions in the 2θ range of 3–40°.

Preparation of Three-Layered Matrix Tablets

The formula of the three-layered tablets is shown in Table I. Solid dispersion particles containing 90 mg of acemetacin in the middle layer were mixed with other excipients thoroughly in a mortar for 5 min. We prepared the three-layered tablets by first filling the bottom layer in the die cavity, adding the middle layer on the precompressed bottom layer, and then filling the top layer on top. The tablets were prepared by direct compression with a single-punch tablet press (TDP, Tianxiang Jiantai Co., Ltd., Shanghai, China) with an 11-mm diameter flat face to a crush strength of 10–12 kg, as measured by a hardness tester (YPD-200C, Huanghai Medicine and Drug Test Instruments, Shanghai, China).

Optimization of the Three-Layered Tablets with BBD

BBD was used to optimize the formula of the three-layered tablets with a design-expert program. In this design, three factors

Table II. Factors and Levels of Response Measured with Surface Method Design (BBD) to Optimize the Formulation

	Levels used		
	−1	0	1
A	30	40	50
B	40	50	60
C	70	80	90
Response	Constraints		
Y_1	$0.05 < Y_1 < 0.12$		
Y_2	$0.44 < Y_2 < 0.96$		

were evaluated, each at three levels, and experimental trials were performed at all 17 possible combinations. The amount of HPMC in the middle layer (*A*), the amount of HPMC in the external layer (*B*), and the amount of mannitol in the middle layer (*C*) were selected as independent variables (Table II). The cumulative release percentage (*Y*) of the drug at 2 and 12 h were selected as responses. The proposed response for *Y* is given as follows:

$$Y=\beta_0+\beta_1\times A+\beta_2\times B+\beta_3\times C+\beta_4\times A_2+\beta_5\times B_2 +\beta_6\times C_2+\beta_7\times A\times B+\beta_8\times B\times C+\beta_9\times A\times C \quad (1)$$

where β_0 is the intercept and β_1–β_9 are the coefficients for the factors *A*, *B*, and *C* and their interaction terms.

In Vitro Release Characteristics of Three-Layered Tablets of Acemetacin

The release characteristics of all of the formulas were determined with a United States Pharmacopoeia 32 Apparatus I (basket) at a rotation speed of 100 rpm in 1000 mL of the dissolution medium at 37°C with a dissolution tester (ZRS-8G, Tianda Tianfa Technology Co., Ltd., Tianjin, China). The dissolution medium of pH 6.8 phosphate buffer used was prepared as follows: we added distilled water to a mixture of 250 mL of 2.0*M* potassium dihydrogen phosphate and 112 mL of 2.0*M* sodium hydroxide until the volume was 1000 mL. After the dissolution samples (10 mL) were selected at predetermined time intervals, a similar volume of fresh dissolution medium was added to keep the volume in the vessel constant. The collected samples were filtered through a 0.45-μm Millipore filter. The concentrations of acemetacin in samples were determined by HPLC, as mentioned previously. *Y* of drug from the tablets was calculated and plotted as a function of time.

The *in vitro* release data was fitted to different kinetic models (zero-order, first-order, and Higuchi) to evaluate the release pattern of the drug. The largest value of the correlation coefficient (*R*) indicated a superiority of the release-profile fitting to the mathematical equation.

In Vivo Study in Rabbits

Six healthy male rabbits (weighing 2.0–2.5 kg) were supplied by the Qinglong Mountain Animal Centre. All of the animals were allowed free access to food and water, and all studies were conducted in accordance with the principles of Laboratory Animal Care and were approved by the Department of Laboratory Animal Research at China Pharmaceutical University (SYXK 2007-0025). The use of animals was allowed by the China Pharmaceutical University Animal Management and Ethics Committee.

The rabbits were divided into equal groups (groups I and II), and a crossover study was carried out. Group I rabbits ($n = 3$) were administered the three-layered, optimized matrix tablets, and the reference market capsules were given to group II ($n = 3$). After a washout period of 2 weeks, the administrations of the group I and II were exchanged. Both the tablets and capsules were orally administrated after a 12-h overnight fast. Food and drink were withheld for at least 2 h after dosing. The blood samples were collected from the ear veins of the rabbits at predetermined time intervals (0, 1, 2, 4, 6, 8, 9, 10, 12, 24, and 48 h). The blood samples were centrifuged at 2600*g* for 5 min in an Nr.12154 rotor (Sigma 3K30), and the plasma was separated and stored at −20°C until it was analyzed by HPLC.

The concentration of acemetacin in the rabbit plasma was determined by a reverse-phase HPLC with an LC-10AT liquid chromatograph with a mixture of methanol (70% v/v) and pH 6.0 phosphate buffer (30% v/v) as the mobile phase. A volume of 0.5 mL of plasma was accurately measured into a 2.5-mL centrifuge tube; this was followed by the addition of 20 μL of ibuprofen solution (internal standard, 100 μg/mL). The mixture was mixed by a vortex mixer and centrifuged at 12,000 rpm for 10 min. The supernatant liquid was injected directly into the column (Wonda-Sil C18-WR, 4.6 × 250 mm). Methodological studies, such as studies of linearity, specificity, and precision within and between days, were done to satisfy the requirements of the methodology.

Pharmacokinetic Parameters and Statistical Analysis

Pharmacokinetics parameters were determined from the plasma concentration–time data by means of a model-independent method with a computer program, DAS. The overall elimination rate constant (*K*; h^{-1}) was calculated from the slope of linear regression of the log-transformed plasma concentration–time data in the terminal phase. The half life $t_{1/2}$ was calculated as 0.693/K. The maximum plasma concentration (C_{max}; μg/mL) and the time to reach the maximum plasma concentration (T_{max}; h) were obtained from the individual plasma concentration–time curves. The area under the plasma concentration-time curve (0–48 h) AUC_{0-48} and area under the plasma concentration-time curve (0–∞) $AUC_{0-\infty}$ (μg h/mL) were determined by means of the trapezoidal rule.

The pharmacokinetic parameters, including C_{max}, T_{max}, AUC_{0-48} and $AUC_{0-\infty}$, were calculated with analysis of variance with the style of mean plus or minus standard deviation (SD). Additionally, the 90% confidence interval of the ratio of test/reference with log-transformed data was computed. The inclusion of the confidence interval within 0.8–1.25 was considered as bioequivalence.[23] In all cases, a value of $p < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Preparation and Solubility of Solid Dispersion

The selection of appropriate materials is important because they play important roles in the preparation of solid dispersions. The most frequently used materials are poly(ethylene glycol) 4000, poly(ethylene glycol) 6000, PVP, mannitol, and cyclodextrin. We

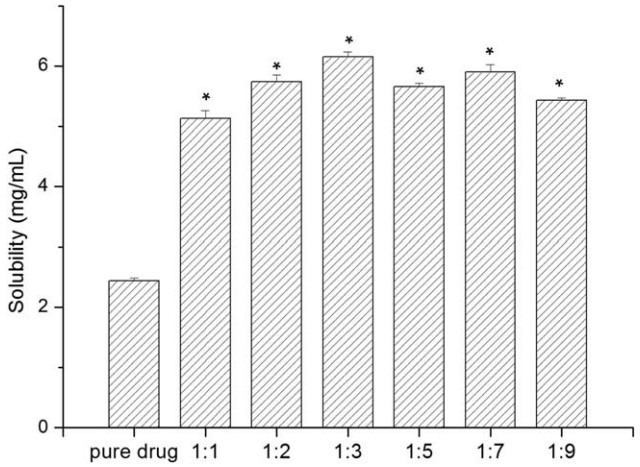

Figure 1. Solubility of acemetacin and acemetacin solid dispersions with different molar ratios of the drug and PVP–K30 (1 : 1, 1 : 2, 1 : 3, 1 : 5, 1 : 7, and 1 : 9) in a pH 6.8 phosphate buffer at 37 ± 0.5°C (mean ± SD, $n = 6$).

used PVP–K30[24] as a carrier because of to its high melting point, heat stability, and solubility. The solid dispersion was prepared by the solvent method and compared to pure acemetacin with regard to its solubility and dissolution rate. After the preparation of the solid dispersion, the solubility of acemetacin in pH 6.8 phosphate-buffered saline was significantly increased ($p < 0.05$) from 2.44 mg/mL of the pure drug to 5.74 mg/mL of the solid dispersion when the molar ratios of drug to PVP–K30 was fixed at 1 : 1 (Figure 1). The release profile (Figure 2) of the acemetacin solid dispersion showed that the dissolution of acemetacin in distilled water significantly increased with increasing proportion of PVP–K30.

The change in the drug crystallinity was investigated with DSC and XRD. The DSC thermograms and XRD diffractograms of the acemetacin, PVP–K30, physical mixture of acemetacin and PVP–K30, and solid dispersion are shown in Figures 3 and 4. The DSC thermograms of the drug gave characteristic endothermic peaks at 150.8°C, which corresponded to the melting points.

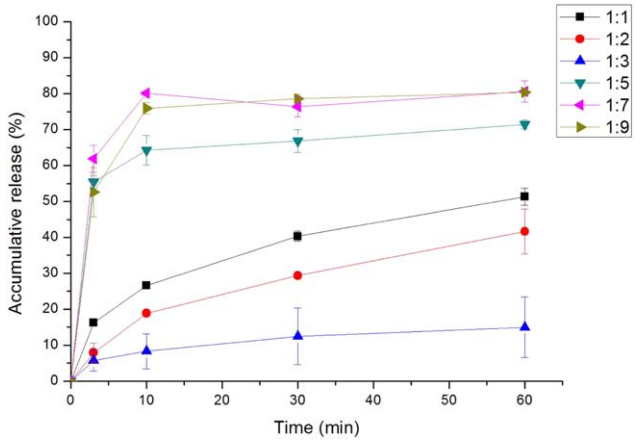

Figure 2. Dissolution profiles of acemetacin from solid dispersions with different molar ratios of the drug and PVP–K30 (1 : 1, 1 : 2, 1 : 3, 1 : 5, 1 : 7, and 1 : 9) in distilled water at 37 ± 0.5°C (mean ± SD, $n = 6$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

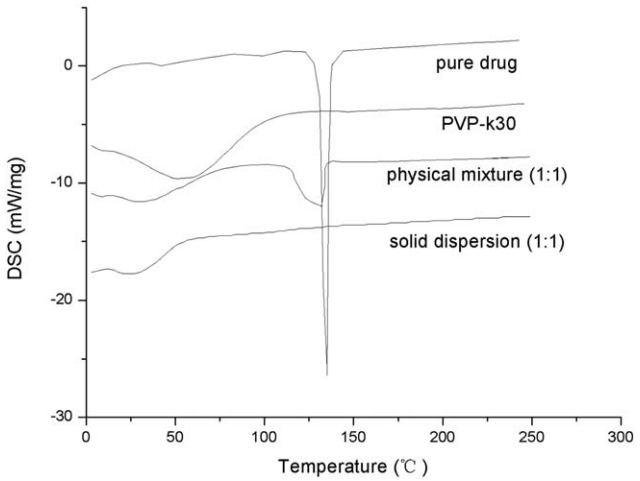

Figure 3. DSC curves of the pure drug, PVP–K30, a physical mixture (1 : 1 w/w), and solid dispersion (1 : 1 w/w).

The DSC thermogram of the physical mixture exhibited two distinctive endothermic peaks of acemetacin and PVP–K30. As shown in Figure 3, there were slightly peak shifts of both endothermic peaks; this could be explained by the interaction between acemetacin and PVP–K30 in the physical mixture. In contrast, no characteristic endothermic peak associated with the crystalline drug was observed in the thermogram of the acemetacin solid dispersion. This demonstrated that the state of acemetacin was amorphous, and this could explain the dissolution results.

The solid dispersion of acemetacin in PVP–K30 was successfully prepared by a solvent method with the improved solubility and dissolution of acemetacin. Acemetacin, a water-insoluble drug, was solubilized by the manufacture of a solid dispersion. The increased solubility was due to the change in the crystallinity of the drug from crystalline form to amorphous state; this led to a decrease in the crystal size and an improved wettability of drug when it was in contact with the dissolution medium. These studies indicated that different solubility between the pure drug and solid dispersion was due to their distinct crystallinity. An

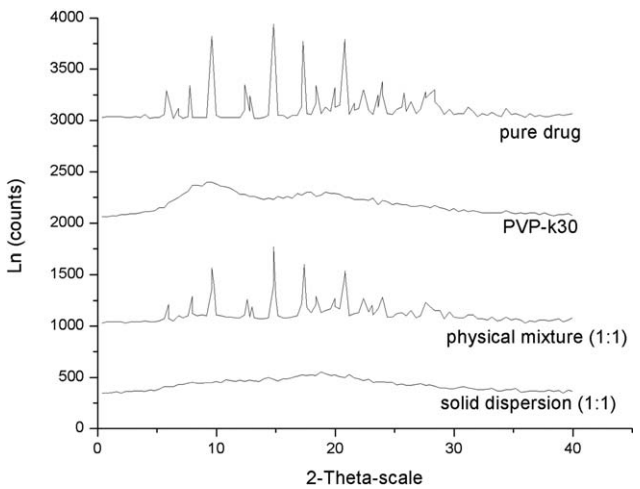

Figure 4. X-ray powder diffraction patterns of the pure drug, PVP–K30, a physical mixture (1 : 1 w/w), and a solid dispersion (1 : 1 w/w).

Table III. Significance of the Regression Equation Coefficients for Y Values

	Y_1		Y_2	
Term	F	p	F	p
A	28.64	0.0011	66.18	<0.0001
B	3.35	0.1101	258.15	<0.0001
C	6.38	0.0394	8.05	0.0251
$A \times B$	0.70	0.4307	10.90	0.0131
$A \times C$	1.43	0.2702	0.85	0.3863
$B \times C$	0.41	0.5403	2.09	0.1917
A^2	4.68	0.0673	6.04	0.0437
B^2	0.74	0.4177	0.89	0.3761
C^2	4.11	0.0802	0.096	0.7659

obvious difference between the acemetacin and the solid dispersion in the XRD diffractograms indicated the formation of the acemetacin solid dispersion.

Statistical Analysis of BBD and Optimization

The regression equations representing the relationship between Y and the independent variables were as follows:

$$Y_1 = 0.069 - 0.016 \times A - 5.375 \times 10^{-3} \times B + 7.425 \times 10^{-3} \times C + 3.475 \times 10^{-3} \times A \times B - 4.975 \times 10^{-3} \times A \times C + 2.675 \times 10^{-3} \times B \times C + 8.763 \times 10^{-3} \times A^2 - 3.488 \times 10^{-3} \times B^2 + 8.213 \times 10^{-3} \times C^2 \quad (2)$$

$$Y_2 = 0.062 - 0.08 \times A - 0.16 \times B + 0.28 \times C + 0.046 \times A \times B - 0.013 \times A \times C + 0.020 \times B \times C + 0.033 \times A^2 + 0.013 \times B^2 + 4.213 \times 10^{-3} \times C^2 \quad (3)$$

where Y_1 is the cumulative percentage drug released at 2 h, Y_2 is the cumulative percentage drug released at 12 h, and Y is a coded fitting equation. When the p value is less than 0.05, it shows that this term is significant, and when the p value is less than 0.001, it shows that the term is highly significant and has a greater influence than other variables. The F value and p values, which determine the significance of each term, are presented in Table III. The corresponding variables will be more significant if the absolute F value becomes larger and the p value becomes smaller. It was obvious that the A and C terms had a significant influence on the drug Y at 2 h. This result demonstrates that at the early stages, the drug-release behaviors of the three-layered tablets were mainly determined by the composition of the middle layer, including the amounts of HPMC and mannitol. However, many terms, such as A, B, C, $A \times B$, and A^2, were related to the drug-release values at 12 h. Among them, A and B seemed to be of high significance through the analysis of the F and p values. It could be explained that along with the release process, the rule of B seemed to be crucial. In other words, the HPMC capped matrix in the top and bottom layers were applied to control the drug release. The optimized levels of A, B, and C were 37.45, 59.71, and 84.61 mg, respectively. The observed responses (Y_1 and Y_2) of the optimized formula were 0.0827 and 0.5489, respectively, compared to 0.0829 and 0.5375 predicted by BBD; this indicated that the release profile from the optimized formula was close to the predicted values. The dissolution profile of the optimized formula was fitted to zero-order, first-order, and Higuchi equations. The R^2 values shown in Table IV indicate that the zero-order equation was a superior to fit to the release data. The optimized three-layered tablets formula obtained from BBD was certified to fit to a zero-order equation.

Table IV. R^2 Values of the Optimized Formulation Fitted to Zero-Order, First-Order, and Higuchi Equations

Equation	R^2
Zero-order equation	0.993
First-order equation	0.990
Higuchi equation	0.948

In Vitro Release of the Three-Layered Tablets

The *in vitro* drug-release profiles of the three-layered tablets and controlled market capsules are shown in Figure 5. Compared to the market capsules, the three-layered tablets displayed a better linearity, which indicated a zero-order controlled release peculiarity. As shown in Table I, the accumulative drug release values of the three-layered tablets were 3.82 ± 0.23 at 2 h and 49.33 ± 3.51 at 12 h, respectively; this demonstrated a fine controlled release of acemetacin. In the initial stage (0–2 h), the HPMC capped matrix in the top and bottom layers were applied to postpone the drug-release form the middle layer through the limiting of the solvent penetration into the middle layer and the reduction of the surface area available for dissolution. We envisaged that the drug was mainly diffused from the lateral side of the middle layer, and the release behaviors were determined by A. However, both barrier layers were prone to swelling and erosion during dissolution, and this led to an improvement in the surface area available for drug release. This was considered to be a valid compensation to the decreased

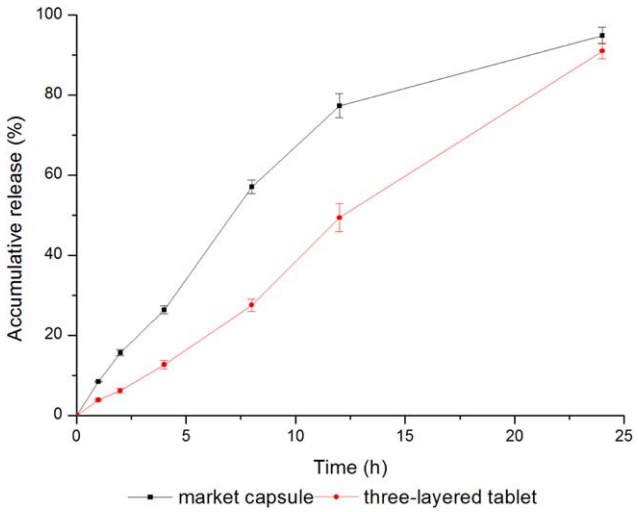

Figure 5. Comparison of the release profiles of one-layered tablets and three-layered tablets at 37°C in pH 6.8 phosphate-buffered saline (mean ± SD, $n = 6$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

release rate caused by the reduction of the drug concentration gradient. An increase in the percentage of hydrophilic polymer in these layers led to the deduction of the release rate, and the addition of the amount of mannitol to form pores and channels increased the diffusion of drug because of its high solubility in water.[25] Compared to that in the controlled market capsules, the *in vitro* release of the drug from the three-layered tablets displayed a good controlled released profile; this indicated that in the initial stage, the two barrier layers had no effect on the release rate, whereas the HPMC and mannitol in middle layer played very important roles. With the swelling and eroding of barrier layers, the interaction between the core layer and external layer increased gradually.

In Vivo Pharmacokinetics Study

The mean plasma concentration versus time profiles of the optimized formula of the three-layered matrix tablets and reference market capsules are shown in Figure 6. The mean pharmacokinetic parameters are summarized in Table V. The bioequivalence test was constructed as follows. The 90% confidence intervals for the test/reference ratio of the log-transformed data of AUC_{0-48} and $AUC_{0-\infty}$ were within 1.003–1.23 and 0.72–1.978, respectively. The 90% confidence intervals for AUC_{0-48} and $AUC_{0-\infty}$ were within 0.8–1.25; this satisfied the bioequivalence criteria. The parameters of AUC_{0-48} and $AUC_{0-\infty}$ indicated that the three-layered tablets developed in this study were slightly better than the market capsules (reference). The mean C_{max} of the optimized three-layered matrix tablets was smaller than that of the reference market capsules, and the 90% confidence interval (0.418–1.636) failed to satisfy the bioequivalence criteria. The smaller C_{max} and delayed T_{max} indicated that the barrier layers retarded the drug release effectively. In general, the *in vivo* pharmacokinetics study revealed that acemetacin three-layered tablets improved the bioavailability of acemetacin with a distinct delay in T_{max}. The prolonged absorption and elimination of acemetacin could be explained by the function of the top and bottom barriers layers; this could postpone the drug release from the middle drug-containing layer. This was in accordance with the sustained drug release *in vitro*.

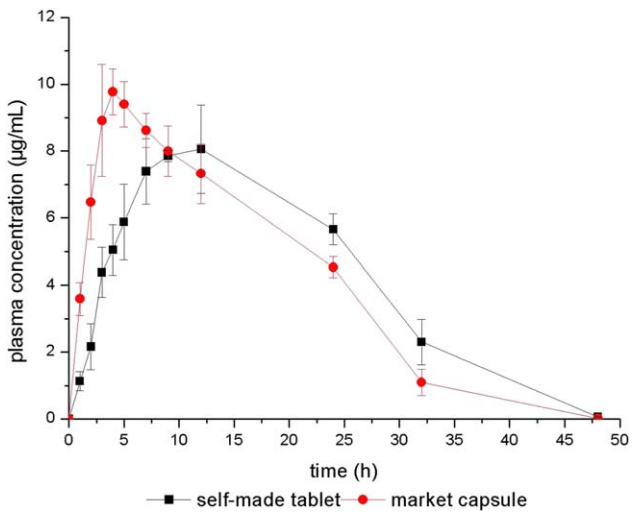

Figure 6. Plasma concentration versus time profiles (mean ± SD, $n = 3$) obtained after the oral administration of 90 mg of acemetacin in optimized three-layered matrix tablets and market capsules (reference) in rabbits. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table V. Pharmacokinetic Parameters (Mean ± SD) Obtained After the Oral Administration of Optimized Three-Layered Tablets and Market Capsules to Rabbits ($n = 3$)

Parameter	Optimized three-layered tablets	Reference market capsules	Statistical test (p)
C_{max} (μg/mL)	8.59 ± 0.94	10.34 ± 0.38	[a]
T_{max} (h)	9.33 ± 2.51	3.67 ± 0.58	[b]
AUC_{0-48} (μg h/mL)	200.81 ± 11.36	193.65 ± 5.97	
$AUC_{0-\infty}$ (μg h/mL)	212.902 ± 31.66	196.18 ± 1.83	[a]
$t_{1/2}$ (h)	8.37 ± 6.84	5.83 ± 3.71	

[a] $p < 0.05$.
[b] $p < 0.01$.

CONCLUSIONS

The development of a controlled release system with poorly water-soluble drugs is a universal problem. On the basis of this study, we can claim that a promising once-daily controlled release three-layered matrix tablet for a poorly water-soluble drug, acemetacin, has been successfully designed, developed, and evaluated. DSC and XRD diffraction demonstrated that an amorphous drug formed in the solid dispersion, and the formula optimized by BBD optimization exhibited a desirable dissolution profile that approached a zero-order release. Moreover, the *in vivo* pharmaceutical study indicated that the optimized three-layered tablets gave higher oral bioavailability than the market release capsules. In general, these studies suggested the designed three-layered tablets may be a promising strategy for oral controlled release systems for poorly water-soluble drugs.

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