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Research Article

Improved Bioavailability of Poorly Water-Soluble Drug Curcumin in Cellulose Acetate Solid Dispersion

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Abstract. Curcumin (Cur), one of the most widely used natural active constituents with a great variety of beneficial biological and pharmacological activities, is a practically water-insoluble substance with a short biologic half-life. The aim of this study was to develop a sustained-release solid dispersion by employing water-insoluble carrier cellulose acetate for solubility enhancement, release control, and oral bioavailability improvement of Cur. Solid dispersions were characterized by solubility, *in vitro* drug release, Fourier transform infrared spectroscopy, X-ray diffractometry, and differential scanning calorimetry studies. The *in vivo* performance was assessed by a pharmacokinetic study. Solid-state characterization techniques revealed the amorphous nature of Cur in solid dispersions. Solubility/dissolution of Cur was enhanced in the formulations in comparison with pure drug. Sustained-release profiles of Cur from the solid dispersions were ideally controlled *in vitro* up to 12 h. The optimized formulation provided an improved pharmacokinetic parameter (C_{max}=187.03 ng/ml, t_{max}=1.95 h) in rats as compared with pure drug (C_{max}=87.06 ng/ml, t_{max}=0.66 h). The information from this study suggests that the developed solid dispersions successfully enhanced the solubility and sustained release of poorly water-soluble drug Cur, thus improving its oral bioavailability effectively.

KEY WORDS: bioavailability; cellulose acetate; curcumin; solid dispersion; sustained release.

INTRODUCTION

According to the Biopharmaceutics Classification System, class II drugs are poorly water-soluble but highly permeable. Once these drugs are dissolved, they rapidly pass through biological membranes such as the gastrointestinal wall (1). Consequently, the solubility behavior of a class II drug is the key determinant of its oral bioavailability (2). To date, a considerable number of drugs need to be administered frequently a day because of their short half-life in the body, which results in a significant fluctuation in the plasma drug concentration and drug toxic side effects (3). Therefore, the development of a sustained-release oral dosage form instead of the conventional preparations for the side effect reduction and patient compliance improvement is desirable. The ideal formulation for enhancing the bioavailability of a class II drug with a short half-life *in vivo* would simultaneously increase its solubility and control its release.

Several approaches have been investigated to solve the aforementioned problems, including (a) combining solubilization technology, e.g., solid dispersion, with sustained-release techniques, e.g., a membrane-controlled tablet, and (b) polydisperse systems, e.g., self-microemulsion and nanoparticle (3,4). This method (a) would thus result in a more complex manufacturing process, and careful control of each step would be required to produce reproducible and reliable preparations (5). Although this method (b) can simultaneously modulate drug solubility and release, the low drug loading efficiency (often <5% for self-microemulsion and nanoparticle) will lead to a higher dosage and/or dosing frequency and reduced patient compliance (6,7).

One approach which can modify drug solubility and release in one step is the combination of solid dispersion and sustained-release technologies using pH-dependent or slow-dissolving carriers instead of conventional hydrophilic polymers (4). It has been reported that the dissolution and oral bioavailability of some drugs such as flurbiprofen and nitrendipine have been improved when this method was used (5,8). By using this technique, a drug can molecularly disperse in the polymeric carrier, and the release rate depends on the nature of the carrier (9). The advantages of this technology are as follows: cost reduction, convenience of preparation, and no problems with respect to drug loading capacity. However, there is still a risk of prompt release of the drug when the carrier is dissolved. Therefore, carrier selection is a critical factor. Incorporation of a sparingly water-soluble drug in an inert, hydrophobic carrier can possibly be used to achieve prolonged characteristics. The release of ibuprofen, indomethacin, and naproxen has been successfully sustained with the use of ethyl cellulose (10,11). Cellulose acetate (CA) is another water-insoluble cellulose derivate and widely used in oral sustained-release pharmaceutical formulations as a coating and film-forming agent (12). Compared with ethyl cellulose, it forms a more stable and flexible membrane (13),

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which avoids rupture of the coating film and controls the drug dissolution rate more efficiently during the initial period of release. Furthermore, better permeability of CA (almost ten times that of ethyl cellulose) (14) can promote complete release of the drug. Jiang *et al.* (15) have developed glipizide microspheres with CA which successfully controls drug release *in vitro*. Although CA is supposed to be a potentially suitable polymeric carrier, there are only a few reported studies on the sustained-release solid dispersions that employ CA as the rate-controlling matrix; the *in vivo* pharmacokinetic results of the system have not been reported yet.

The objective of the present study was to propose a sustained-release solid dispersion (SRSD) applying CA as the carrier with a release profile up to 12 h *in vitro*, evaluating the possible application of CA as a potential carrier for the solubility enhancement, release control, and oral bioavailability improvement of BCS II drugs with a short half-life *in vivo*. Curcumin (Cur), one of the most widely used natural active constituents with a great variety of beneficial biological and pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic, is a typical class II drug with a very short biologic half-life (6,7,16–18) and was used as the model drug. The formulations were investigated regarding their solubility/dissolution properties, solid state, oral absorption in rats, as well as the *in vitro–in vivo* correlation.

MATERIAL AND METHOD

Material

Cur was purchased from Tianjin GuangFu Fine Chemical Research Institute (Tianjin, China). CA (acetyl content, 40.1%) was purchased from Eastman Chemical Company (Tennessee, USA). Mannitol was purchased from Fengli Jingqiu Commerce and Trade Co., Ltd. (Beijing, China). Acetonitrile of high-performance liquid chromatography (HPLC) grade was purchased from SK Chemicals Agent Co., Ltd. (Ulsan, South Korea). HPLC grade water was used for the HPLC analysis. All other chemicals were of analytical grade.

Preparation of SRSD and Physical Mixture

Sustained-Release Solid Dispersion

To investigate the effect of CA content on the solubility/dissolution of Cur, four different ratios of drug/polymer, e.g., 1:1, 1:3, 1:5, 1:10 (*w/w*), were used. The SRSD was prepared by the solvent evaporation technique. Cur and CA were dissolved in acetone. Then, the solution was poured into a mortar and triturated lightly to evaporate acetone slowly. The obtained film was then dried under vacuum until constant weight was achieved, ground, and screened. Granules with sizes smaller than 150 μm were used for analysis, followed by storing in a desiccator under vacuum for at least 24 h.

Although CA is semi-permeable, pure CA films are still poorly permeable for the drug incorporated, which will result in a relatively low and inadequate cumulative release. For increasing the permeability of the CA membrane, mannitol was incorporated as the pore-forming agent to obtain the dispersions with weight ratios of 1:10:0.1, 1:10:0.5, and 1:10:1 (Cur/CA/mannitol). The homogenous mixture containing Cur and CA was dropped onto a certain amount of mannitol gently mixed by using a spatula and a mortar so that mannitol could disperse uniformly in the film. All other procedures were analogous to those described above.

Physical Mixture

The physical mixture (PM) of Cur, CA, and mannitol in the same ratios as SRSD was prepared by accurately weighing and thoroughly mixing in a mortar. The obtained mixtures of sizes smaller than 150 μm were stored in a desiccator under vacuum for at least 24 h before use followed by sieving with a sieve shaker. For convenience, all formulations were given a code name, which are listed in Table I.

HPLC Analysis

All HPLC assays were performed on a LabAlliance 201 system (Tianjin, China). A reversed-phase C_{18} column (Thermo, 250×4.6 mm, 5-μm particle size) linked with a uniphase C_{18} guard column was used. The mobile phase consisted of 1% (*v/v*) acetic acid solution and acetonitrile in the ratio of 45:55 (*v/v*). The flow rate of the mobile phase was 1 ml/min and the injection volume was 20 μl. The ultraviolet detector was set at a wavelength of 421 nm, and the temperature of the column was maintained at 30°C. The method employed for quantifying the concentration of Cur *in vitro* had a calibration range of 0.1–10 μg/ml with a limit of quantitation (LOQ) of 15 ng/ml, an accuracy of 98.20–100.21%, and intra- and inter-day precision values of relative standard deviations (RSD) of 0.62–1.00% (n=3). Meanwhile, the analytical method employed for the quantification of Cur *in vivo* had an LOQ of 25 ng/ml and operated in the concentration range of 25–500 ng/ml with a correlation coefficient of 0.9994, an accuracy of 97.35–104.00%, intra- and inter-day precision values with a %RSD in the range of 0.75–2.88%, and an extraction recovery of 80.4–88.0% (n=5). The assay was accurate and reproducible with coefficients of variation ranging from 1.3% to 3.4%.

Equilibrium Solubility Studies

An excess amount of Cur, SRSD, and PM were added slowly with stirring to 10 ml medium (15%, *v/v*, of ethanol, pH was adjusted to 2.0 by glacial acetic acid) in sealed glass vessels. All suspensions were protected from light and shaken in an air bath at 25±0.5°C for 72 h to achieve equilibrium solubility. After that, an aliquot was rapidly filtered through a 0.45-μm membrane and assayed by HPLC. Each experiment was performed in triplicate.

Dissolution Tests

The release characteristic of Cur was determined according to a USP dissolution II paddle method at a rotation speed of 100 rpm in 500 ml of the aforementioned testing medium at 37±0.5°C using a dissolution apparatus (RCZ-8A, Precise Apparatus of Tianjin University Co., Ltd, China). Samples of Cur, SRSD, and PM equivalent to 4 mg of Cur were placed in each vessel. The paddle was placed at 2.5 cm from the bottom of the vessel. Aliquots of 5 ml of the sample solution was withdrawn at specified time intervals, filtered through a 0.45-μm syringe filter, and analyzed for Cur with HPLC. The same

Table I. Formulation Composition and Equilibrium Solubility Studies of Cur (Mean±Standard Error) from PM and SRSD in Comparison with Pure Cur

Composition (*w*/*w*)					
Cur/CA	Mannitol (%)[a]	SRSD	Solubility (μg/ml)	PM	Solubility (μg/ml)
1:1	–	SD1	36.42±3.09*	PM1	15.70±1.37**
1:3	–	SD2	40.11±2.73*	PM2	15.78±0.89**
1:5	–	SD3	44.81±1.68*	PM3	16.17±1.81**
1:10	–	SD4	48.07±2.29*	PM4	16.67±1.23**
1:10	1	SD5	53.51±1.46*	PM5	16.60±0.60**
1:10	5	SD6	58.26±2.20*	PM6	17.59±0.53***
1:10	10	SD7	64.58±1.99*	PM7	18.85±1.91*
–	–	Cur	15.39±0.18	Cur	15.39±0.18

*$p<0.01$ (significant with respect to pure Cur)
**$p>0.05$ (not significant with respect to pure Cur)
***$p<0.05$ (significant with respect to pure Cur)
[a] Based on CA weight

volume of fresh medium was replaced after sampling. Each experiment was performed in triplicate.

Fourier Transform Infrared Spectroscopy

A Tensor 27 FTIR spectrometer (Bruker Optics, Germany) was used for Fourier transform infrared spectroscopy (FTIR) analysis. The samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400–4,000 cm^{-1}.

X-Ray Diffraction

X-ray diffraction was performed on a Rigaku D/max 2500v/pc X-ray powder diffractometer (Tokyo, Japan) using Ni-filtered CuK ∝ radiation. The samples were analyzed over a 2θ range of 3–60° with a scan step size of 0.02° and a scan step time of 1 s.

DSC Studies

Differential scanning calorimetry (DSC) measurements were performed on a Perkin-Elmer Diamond DSC differential scanning calorimeter (Perkin-Elmer, Waltham, MA). The accurately weighed sample was placed in an aluminum pan and an empty aluminum pan was used as a reference. The experiment was carried out under nitrogen atmosphere (flow rate, 20 ml/min) at a scanning rate of 10°C/min in the temperature range of 30–220°C.

In Vivo Study

Male Wistar rats weighting 250–300 g (SCXK (Jin) 20050001) were obtained from Radiation Medicine Institute for Laboratory Animal Research, Chinese Academy of Medical Sciences, Tianjin, China. All animal experiments complied with the requirements of the National Act of the People's Republic of China for the use of experimental animals. The study was approved by the Ethics Committee on Animal Research of Chinese Academy of Medical Sciences. Animals were acclimated for at least 5 days before the test and housed in cages at a constant temperature of 22±2°C with free access to standard laboratory diet and water. In the study, six rats were used. The oral bioavailability of Cur was determined at a dose of 50 mg/kg body weight according to a previous report (6). The drug was suspended in 1 ml of aqueous sodium carboxymethyl cellulose solution (1%, *w*/*v*) and given orally using an oral feeding sonde. A randomized crossover study design was employed. The animals were fasted but had free access to water 12 h before the experiments. A 1-week washout period was allowed between successive dosing. Then, the animals were treated with aqueous SRSD suspension at an equivalent dose.

Under ether anesthesia, blood samples (0.5 ml) were collected at fixed time intervals via the inner canthus of the rats. Plasma was separated by centrifuging the heparinized samples of blood at 3,500 rpm for 10 min. After each sampling, 500 μl of methanol was added to 100 μl of plasma and the mixture vortexed for 2 min. The organic layer was separated by centrifugation at 10,000 rpm for 15 min. The organic solvent was evaporated under nitrogen gas at ambient temperature; the residue was reconstituted in 100 μl of mobile phase and analyzed by HPLC.

RESULTS AND DISCUSSION

Equilibrium Solubility Studies

It has been reported in previous studies that Cur is hydrophobic and difficult to dissolve in water (6,18). Therefore, the choice of dissolution medium becomes a problem. For such a highly lipophilic compound, an aqueous solution containing ethanol even up to 50% (*v*/*v*) was used to enhance its solubility and provide sink conditions (7,17). In the present case, a medium containing less organic solvents than the previous one was used; additionally, its pH could simulate the gastric environment.

To determine the role of SRSD on the solubility of Cur, all formulations were examined. The results obtained from the equilibrium solubility studies were statistically validated by one-way analysis of variance with the pairwise comparison by Fisher's least significant difference procedure. The differences were considered statistically significant at $p<0.05$. It is clear from Table I that the solubility of Cur incorporated in the SRSD was further increased compared with that of the corresponding PM and the parent drug. The proportion of CA incorporated in SRSD had a significant influence on drug equilibrium solubility. When the drug/carrier ratio was increased from 1:1 to 1:10, the

solubility of the drug increased and followed the same order. However, this behavior was not observed for PM, the result being similar for PM1–PM4. Suitable drug/carrier ratio was optimized on the basis of equilibrium solubility studies. The best improvement was shown at a ratio of 1:10. Thus, for the formulations of SRSD with mannitol, the 1:10 ratio was chosen. The water insolubility of CA limited the release of Cur. To accelerate the release of the drug from CA-coated particles, the addition of water-soluble molecules to the particles was proposed. In this study, mannitol was added into SRSD as a pore-forming agent to promote the adequate release of the drug. After being exposed to the dissolution medium, mannitol was easily dissolved and aqueous channels were formed. When the weight fraction of mannitol was increased, the aqueous channels for drug release were increased, which led to the enhancement of the solubility of the drug. Moreover, the presence of mannitol was crucial, increasing drug solubility for PM6 and PM7, indicating the solubilization effect of mannitol.

The enhanced drug solubility from the SRSD can be attributed to the improved wettability based on the semi-permeability of CA, the pore-forming and solubilization effect of mannitol after being dissolved, and the transformation of Cur from the crystalline to the amorphous state applying solid dispersion technology (proven by FTIR, X-ray diffraction, and DSC studies).

Dissolution Testing

The dissolution behaviors of all formulations were studied in order to investigate the release profiles of the developed SRSD and shown in Fig. 1. The result proved that solid dispersion technology could enhance drug dissolution. It was evident that the rate of dissolution of pure drug was low; <15% of the drug was released within 1 h and only increased up to 50% within 12 h. In the case of SRSD, the dissolution of Cur was increased. It could be seen that the drug dissolution was dependent on the ratio of drug to polymeric carrier. As the proportion of CA increased, the dissolution of the drug increased correspondingly. The maximum cumulative drug release was found to be 77% with the formulation in the Cur/CA ratio of 1:10. During the testing, it was noted that the SRSD sinks immediately, whereas the pure drug kept floating on the surface for a longer time interval. These results indicated a CA-enhanced wettability of Cur and a carrier-controlled dissolution in the SRSD (19). The content of mannitol also affected drug dissolution from SRSD. When mannitol concentration increased, the dissolution of Cur increased correspondingly. Compared with pure drug, the dissolution rate of PM was enhanced: the dissolution percentage was 65% in 12 h due to the improved wettability of Cur by the semi-permeability of CA and the increased drug solubility by the solubilization effect of mannitol.

The developed SRSD with the use of a water-insoluble carrier, CA, successfully controlled the release of Cur. Compared with the release profiles of hydrophobic drugs with slow-dissolving carriers reported in the literature (almost 80% of flurbiprofen was released from PEO particles in 3 h) (8), sustained-release profiles of Cur were observed up to 12 h in our study. Although the pH-dependent system composed of three types of pH-sensitive carriers prepared by Yang *et al.* (5) could release drug within 7 h, a prompt drug release occurred within 30 min followed by the immediate collapse of each carrier under the corresponding pH conditions. Therefore, the SRSD stated in this study can enhance the solubility/dissolution and control the release of the hydrophobic drug Cur conveniently in one step.

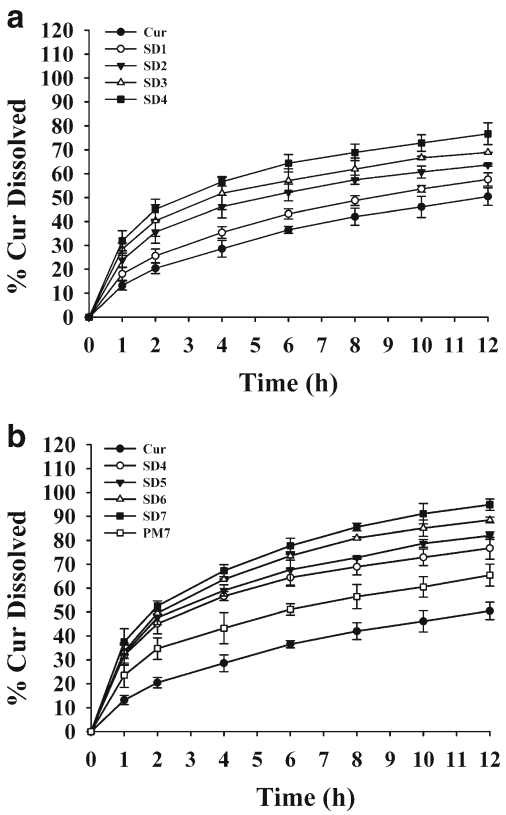

Fig. 1. Dissolution curves of Cur and from SRSD with various Cur/CA ratios (**a**) and SRSD with mannitol (**b**)

Solid-State Characterization

To investigate the mechanisms of solubility/dissolution enhancement of the SRSD, the following characterization studies were carried out for the most promising formulation, SD7 (SRSD of Cur/CA/mannitol=1:10:1, *w*/*w*/*w*).

FTIR Spectroscopy

The FTIR spectra were analyzed to characterize the potential interactions of the formulation. The FTIR spectra of CA, Cur, mannitol, SRSD, and the corresponding PM are shown in Fig. 2. The FTIR spectrum of CA in Fig. 2a shows peaks for the C=O functional groups at 1,752 cm^{-1}, the OH functional groups at 3,503 cm^{-1}, the CH_3 groups at 1,382/1,236 cm^{-1}, and the ether C–O–C functional groups at 1,032 cm^{-1}. The FTIR spectrum of Cur in Fig. 2b exhibited an absorption band at 3,504 cm^{-1}, attributed to the phenolic OH stretching vibration. Additionally, sharp absorption bands at 1,603 cm^{-1} (stretching vibrations of the benzene ring), 1,510 cm^{-1} (C=O and C=C vibration), 1,429 cm^{-1} (olefinic C–H bending vibration), 1,282 cm^{-1} (aromatic C–O stretching vibrations), and 1,028/857 cm^{-1} (C–O–C stretching vibrations) were noted. The mannitol spectrum in Fig. 2c was dominated firstly by the strong primary alcohol OH stretching vibration showing peaks at 3,399/3,289 cm^{-1}. These OH groups in mannitol were hydrogen-bonded to each other. At

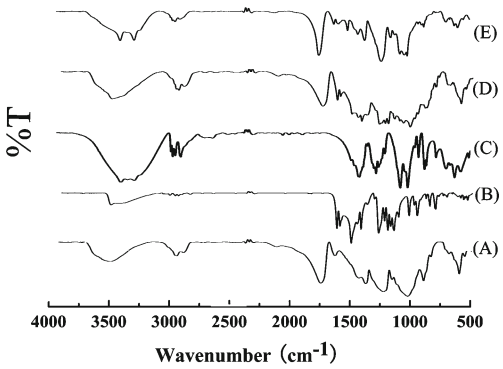

Fig. 2. FTIR spectroscopy of CA (*A*), Cur (*B*), mannitol (*C*), PM (*D*), and SRSD (*E*). SRSD: SD7, Cur/CA/mannitol=1:10:1 (*w*/*w*/*w*)

low frequencies, C–O stretching present in the primary and secondary alcohols, respectively, "R-CH_2-OH" and "R-CHOH-R," dominated and showed strong absorptions at 1,081 and 1,020 cm^{-1}. These tentative assignments agreed with the results of previous reports (18,20,21).

In FTIR technology, the presence of a peak at a specific wavenumber indicates the presence of a specific chemical bond. If specific interactions took place between the materials, the most obvious and significant difference would be the appearance of new peaks or a shift of existing peaks (20). The PM exhibited spectra corresponding to a superposition of their parent substances in Fig. 2d. There was no significant change in the spectrum. From this result, it was concluded that there were no significant interactions between the drug and the carrier, although some minor structural perturbations might have occurred. In the spectra of the SRSD shown in Fig. 2e, the spectra of the SRSD and the PM were quite superimposable, except the absorption band of OH for CA and Cur which was shifted toward the lower frequency of 3,403 cm^{-1}, indicating the formation of an intermolecular hydrogen bond which would result in the increased solubility/dissolution of drug (22). However, no additional peak was observed depicting the absence of any chemical interaction between the drug and the carrier.

X-Ray Diffraction

X-ray diffraction was performed in order to elucidate the physical structure of the drug in the SRSD. Figure 3 shows the powder X-ray diffraction patterns of CA, Cur, the SRSD, and the corresponding PM. The presence of numerous distinct peaks in the X-ray diffraction spectrum indicated that Cur was present as a crystalline material, whereas CA was amorphous. Various diffraction peaks of the drug crystals could be traced in the spectrum of the PM, e.g., at 2θ=14.37, 18.78, 20.78, 23.08, and 29.26, although with lower intensity. No new peaks were observed in the PM, suggesting the absence of a chemical interaction between the drug and the carrier (23), which was consistent with the results of FTIR. This revealed that the presence of CA in the formulation could shield a fraction of peaks of coexisting Cur due to its huge amount compared with that of Cur. A sample of SRSD showed a halo pattern with very slight reflections presented at 2θ values consistent with the PM. The result indicated the transformation of Cur from the crystalline to the amorphous state; however, a trace amount of the drug was still present in crystalline form, ruling out the possibility of a chemical interaction between Cur and CA.

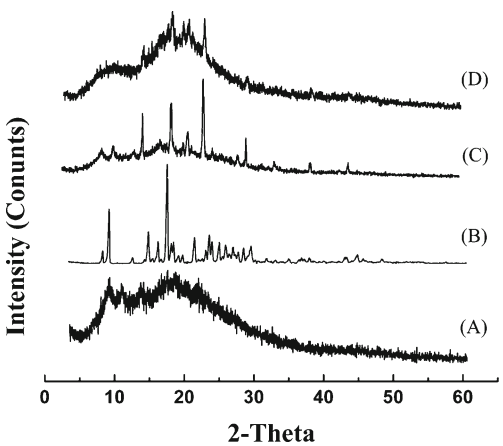

Fig. 3. X-ray diffraction of CA (*A*), Cur (*B*), PM (*C*), and SRSD (*D*). SRSD: SD7, Cur/CA/mannitol=1:10:1 (*w*/*w*/*w*)

DSC Studies

The DSC thermograms of CA, Cur, mannitol, SRSD, and the corresponding PM are represented in Fig. 4. The DSC curves of Cur (Fig. 4b) and mannitol (Fig. 4c) exhibited the corresponding single endothermic peaks at 187.72°C and 168.96°C, respectively, indicating their crystalline nature. During scanning, no peak was observed in the thermogram of CA (Fig. 4a). The thermogram of PM (Fig. 4d) showed an endothermic peak at 167.00°C corresponding to mannitol with a significantly reduced intensity. This could be attributed to the higher CA concentration and the uniform distribution of mannitol in the crust of the polymer, resulting in complete miscibility of molten mannitol in polymer (24). Moreover, the data also indicated the absence of interactions between mannitol and other components of the PM. Although the diffraction peaks of crystalline Cur were observed in PM by the X-ray diffraction, no endothermic peak was shown corresponding to Cur. It is possible that Cur might have been dissolved in the molten carrier during DSC measurement. In the case of SRSD (Fig. 4e), an almost identical thermal behavior as that of PM was observed, corroborating the absence of any drug–carrier chemical interaction. Analogous phenomena have also been reported by previous researches

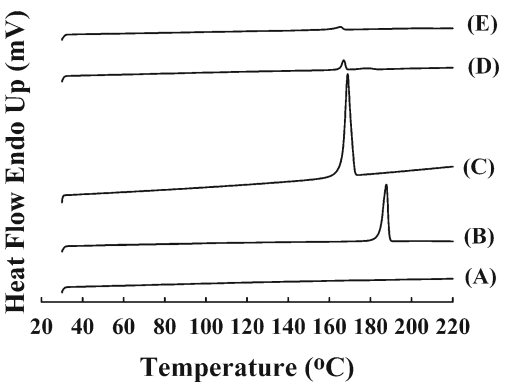

Fig. 4. DSC studies of CA (*A*), Cur (*B*), mannitol (*C*), PM (*D*), and SRSD (*E*). SRSD: SD7, Cur/CA/mannitol=1:10:1 (*w*/*w*/*w*)

(23,24). In accordance with the X-ray diffraction results, Cur might be in an amorphous state in the SRSD.

In Vivo Study

Cur-loaded SRSD was designed to improve the oral bioavailability of the drug. The profiles of the plasma concentrations of Cur *versus* time after oral administration of the pure drug and the SRSD (SD7, Cur/CA/mannitol=1:10:1, *w*/*w*/*w*) are depicted in Fig. 5. The pharmacokinetic data between Cur and SRSD were compared for statistical significance by Student's *t* test. A value of $p < 0.05$ was considered as significant. The plasma concentration of the SRSD at each time point (C_t) was compared with that of Cur. The pharmacokinetic analysis was computed using the Practical Pharmacokinetic Program, Version 97 (the Chinese Society of Mathematical Pharmacology, China). The parameters of Cur in the SRSD were compared with those of the parent drug and are summarized in Table II, e.g., the time to reach maximum plasma concentration (t_{max}), peak plasma concentration (C_{max}), absorption rate constant (k_a), elimination rate constant (k_{el}), half-life ($t_{1/2}$), and the area under the curve from 0 to t and 0 to ∞ (AUC_{0-t} and $AUC_{0-\infty}$). The relative bioavailability of SRSD compared with Cur was calculated by comparing those two AUC_{0-t}s.

The results showed that SRSD successfully sustained the absorption of Cur by achieving a prolonged t_{max} value compared with the plain drug. This suggested that the therapeutic period of Cur was extended after it was presented in the SRSD. Cur suspension upon oral administration resulted in a sharp C_{max} within 0.66 h and the plasma concentration of the drug decreased rapidly, indicating a rapid metabolism of Cur, which was proven by the obtained higher k_{el} and shorter $t_{1/2}$, whereas a relatively slow increase and sustained plasma concentration of Cur for a longer time was observed after the administration of the SRSD, with significantly delayed t_{max} and prolonged K_{el} and K_a, suggesting that an obvious sustained release of Cur from the formulation successfully resulted in the sustained absorption of Cur *in vivo* (7,25,26). Consequently, SRSD persisted for a longer period of time with a higher relative bioavailability of 701.64%.

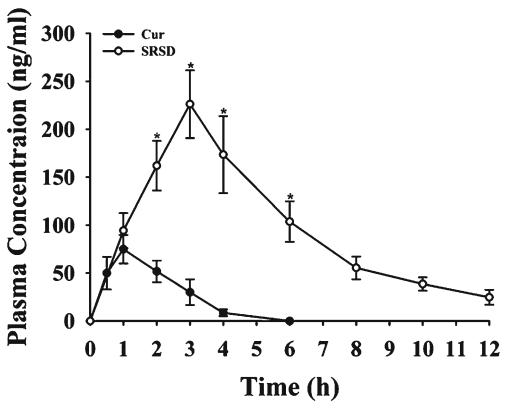

Fig. 5. Plasma concentration profile of Cur in rats following the administration of pure drug and SRSD. SRSD: SD7, Cur/CA/mannitol=1:10:1 (*w*/*w*/*w*). *$p<0.001$ (significant with respect to pure Cur)

Table II. Pharmacokinetic Parameters (Mean±Standard Error) for Drug and SRSD

Pharmacokinetic parameters	Cur	SRSD[a]
t_{max} (h)	0.66±0.06	1.95±0.17*
C_{max} (ng/ml)	87.06±24.02	187.03±34.59*
K_a (/h)	1.61±0.10	0.90±0.17*
K_{el} (/h)	1.43±0.20	0.26±0.03*
$t_{1/2}$ (h)	0.49±0.08	2.65±0.28*
$AUC_{0-\infty}$ (ng h/ml)	156.36±37.68	1,192.34±223.28*
AUC_{0-t} (ng h/ml)	156.03±37.68	1,094.79±195.02*
Comparative bioavailability (%)	100	701.64

*$p<0.001$ (significant with respect to pure Cur)
[a] SD7, Cur/CA/mannitol=1:10:1 (*w*/*w*/*w*)

According to previous studies, Cur is easily metabolized and the metabolic products are less active than Cur itself (16). Furthermore, the drug is sensitive to pH and tends to be inactive due to degradation at neutral to basic pH, e.g., intestinal fluid (7,17). The longer t_{max}, higher C_{max}, lower k_{el}, and larger AUC obtained by SRSD after oral administration suggested that the SRSD could sustain the absorption of Cur, prolong the drug transit time *in vivo*, prevent metabolism and degradation of the prototype molecules, and improve the bioavailability of the drug. Accordingly, the SRSD we proposed in this study could improve therapeutic efficacy and decrease the doses and side effects of the drug after oral administration. However, this needs further verification.

Cur is a typical class II drug with poor solubility and high permeability. The dissolution of the drug is the rate-limiting step for their absorption *in vivo*. In this study, the *in vitro* dissolution profile was compared with the *in vivo* cumulative absorption profile (F_a) obtained using the Wager–Nelson method (27,28) to investigate the *in vitro–in vivo* correlation (IVIVC) of the SRSD.

$$F_a = (C_t + K_{el}AUC_{0-t})/(K_{el}AUC_{0-\infty}) \times 100\%$$

The IVIVC was well characterized by a valuable relative linear model ($r=0.9940$, $p<0.001$) and is presented in Fig. 6. These results confirmed that the dissolution process was the rate-limiting step during the absorption of Cur in our animal model. The study of dissolution is one of the most useful methods for formulation screening in the early stage of

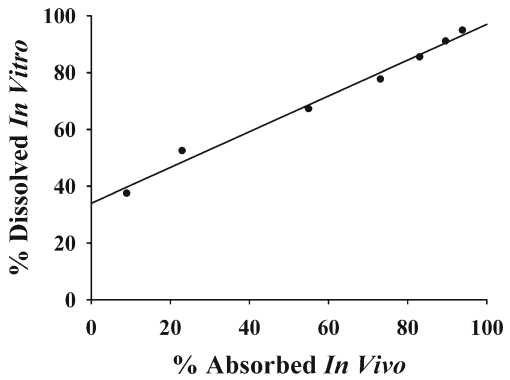

Fig. 6. IVIVC model linear regression plots of percent absorbed *versus* percent dissolved for SRSD. SRSD: SD7, Cur/CA/mannitol=1:10:1 (*w*/*w*/*w*)

formulation development. The IVIVC is a predictive mathematical model describing the relationship between an *in vitro* property and a relevant *in vivo* response. Therefore, a meaningful relation between the *in vivo* behavior of a dosage form and the *in vitro* performance of the same dosage form would allow *in vitro* data to be used as a surrogate for *in vivo* behavior (28).

It is difficult to choose a suitable release medium for Cur due to its practical low water solubility and extreme instability at neutral to basic pH. For such compounds, an aqueous solution containing ethanol even up to 50% (*v*/*v*) was used for its release. In the present study, the aqueous solution with 15% (*v*/*v*) of ethanol was employed. This dissolution medium contained fewer organic solvents than the previously used medium. The obtained good IVIVC proved the feasibility and rationality of the formulation regulation and evaluation under this dissolution condition. The *in vitro* dissolution data can be used to predict the rate and extent of oral drug absorption.

The SRSD with a water-insoluble carrier, CA, developed in this study could enhance the solubility/dissolution and sustain the release of the hydrophobic drug Cur in one step, which improved its *in vivo* transit time and oral bioavailability eventually.

CONCLUSION

To improve the oral bioavailability of poorly water-soluble drugs with short half-life *in vivo*, SRSD consisting of the water-insoluble carrier CA was developed for Cur. The solid dispersion technology ensured the transformation of Cur from the crystalline to the amorphous state and drug solubility increase; the water insolubility of the carrier effectively controlled the drug release. The proposed SRSD successfully prolonged the absorption of Cur and enhanced its bioavailability compared with the parent drug. Our studies proved that the developed SRSD is a promising and convenient method for improving oral absorption of drugs with poor aqueous solubility and short biologic half-life.

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