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Research Paper

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Advantages of introducing an effective crystalline inhibitor in curcumin amorphous solid dispersions formulated by Eudragit E100

Na Fan,[2] Jingyang Li[1,] and Jing Li[1,*]

[1]School of Pharmacy, Shenyang Medical College, Shenyang, PR China
[2]Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang, PR China

*Correspondence: Jing Li, School of Pharmacy, Shenyang Medical College, No. 146 Huanghe North Street, Shenyang, PR China; Email: dddefghijklmn@163.com

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Abstract

Objectives This paper was to elucidate the advantages of using an effective crystalline inhibitor, which was hydroxypropyl methylcellulose E5 (HPMC), in inhibiting crystallisation for curcumin amorphous solid dispersion (Cur ASDs) formulated by Eudragit E100 (E100).

Methods Physical characterisation such as differential scanning calorimetry and powder X-ray diffraction revealed the solid state during the formation of dispersion and clarified the compatibility between Cur and excipient.

Key findings The liquidity of excipient and the change of T_g in Cur ASDs demonstrated that the addition of HPMC can reduce molecule motion of the whole system, improve T_g of Cur ASDs and inhibit crystallisation of Cur ASDs. The water uptake experiment and molecular dynamic modelling further confirmed the effective solution and matrix crystallisation inhibition role of HPMC.

Conclusions The elucidation of HPMC as auxiliary excipient on inhibiting crystallisation for Cur ASDs will bring huge value in designing Cur ASDs in the future.

Keywords: curcumin amorphous solid dispersions; physical characterisation; crystallisation inhibition

Introduction

Oral administration has been the most common and popular way of administration due to its safety and patient compliance. After the formulation enters the gastrointestinal tract orally, the active pharmaceutical ingredient (API) releases from the formulation, dissolves in the gastrointestinal fluid and plays a curative effect on the target site. If the drug is water-insoluble, poor dissolution makes it difficult to obtain good bioavailability.[1–3] Therefore, it is important to improve dissolution and inhibit crystallisation during the development of water-insoluble drugs. At present, many approaches such as micronisation, salt formation, amorphous solid dispersions (ASDs), eutectic, nanocrystalline have been employed to improve drug dissolution and bioavailability. Among all these strategies, ASDs is an effective method to increase the solubility and oral bioavailability of water-insoluble drugs.[4–6] ASDs are defined as API (amorphous or molecular state of high energy) dispersed in the hydrophilic carriers. When ASDs dissolved in the gastrointestinal fluids, supersaturation often occurs, which drives rapid and sustained absorption.[7, 8] In previous studies, ASDs can be prepared with single polymer or binary polymers by solvent evaporation, freeze drying, spray drying, hot melt extrusion and antisolvent precipitation to achieve specific goals.[9, 10] For instance, polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) were applied for preparing tanshinone IIA ASDs;[11] the typical case of binary polymers used as ASDs excipient was indomethacin ASDs formulated with polyacrylic acid and hydroxypropylmethyl cellulose.[12] Herein, polyacrylic acid was applied for increasing the dissolution rate of the drug, while cellulose derivatives were added to maintain supersaturation of the drug by effectively inhibiting crystallisation.

Curcumin (Cur), which exhibits keto–enol tautomerism, is a hydrophobic polyphenol derived from the rhizome of turmeric (Curcuma longa).[13] In the current stage, the diverse pharmacological and biological properties of Cur such as anti-oxidant, anticancer and anti-inflammatory effects and the good safety have received great attention.[14–16] Phase I clinical trials show that Cur can be safely administered to 12 g daily and there is no toxicity after administering orally daily at 8 g for 3 months to the human body.[17, 18] However, the poor dissolution and oral bioavailability of Cur originated from poor aqueous solubility and its rapid hydrolysis under alkaline conditions limits its usage.[19] Therefore, various formulation approaches have been made to increase the solubility and stability of Cur, including nanoparticles, ASDs,[17] cyclodextrin complexation[20] and so on. Cur ASDs is one of the most promising strategies due to the high melting point (180°C) and the moderate hydrophobicity (log P 2.5) of Cur.[17] Single or binary hydrophilic polymers, such as polyoxyethylene pyrrolidone K30 (PVP), Eudragit E100, polyethylene glycol (PEG) and hydroxypropylmethyl cellulose E5 (HPMC) have been employed for enhancing solubility and dissolution of Cur.[14, 21] It should be noted that the binary polymers of E100 and HPMC are used as excipients for Cur ASDs. The E100 is a cationic polyelectrolyte that belongs to the family of (meth) acrylate copolymers.[22] It consists of dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate with the molar ratio of 2:1:1.[23] Ionic interactions can be formed between E100 and Cur, thus enhancing the dissolution of Cur.[24] It has also been reported that cellulose derivatives appear to be great candidates as crystalline inhibitors, including HPMC, hydroxypropylmethyl cellulose acetate succinate (HPMCAS) and so on.

In this study, Cur ASDs were prepared by binary polymers of E100 and HPMC due to the dissolution enhancement of E100 and the crystallisation inhibition of HPMC. Herein, the solid state of Cur in Cur ASDs was studied by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). The addition of HPMC in excipient was able to increase the viscosity of the system and improved T_g value of Cur ASDs thereby inhibiting crystallisation of Cur ASDs. Furthermore, the impact of HPMC on inhibiting crystallisation in Cur ASDs was mainly studied by water uptake measurement and molecular dynamic modelling. At last, the anti-oxidant assay was used to demonstrate the free radical scavenging activity of Cur and Cur ASDs.

Materials and Methods

Materials

Cur with purity of more than 99.8 % was purchased from meilunbio Co., Ltd (Dalian, China). Eudragit E100 (E100) was kindly provided by Evonik Co., Ltd (Germany). Hydroxypro-pylmethyl cellulose E5 (HPMC) was obtained from Anhui Shanhe Pharmaceutical Excipients Co., Ltd (Huainan, China). Other chemical agents were provided by Tianjin Bodi Chemical Holding Co., Ltd (Tianjin, China).

Preparation of Cur ASDs

Cur and Eudragit E100 (E100) or binary polymers (E100/HPMC with weight ratio of 1:1, 3:1, 6:1, 9:1, respectively) were dissolved in a suitable amount of ethanol. The weight ratio between drug and excipient focused on 1:6. The solvent ethanol was completely removed by rotary evaporation (Rongya, China) at 40°C. Afterwards, the Cur ASDs were dried in vacuum oven (60°C) overnight to remove any residual solvent. The Cur ASDs were ground using a mortar and pestle and then sieved (60 mesh) to obtain uniform particles that named as Cur-E100, Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 6:1 and Cur-E100/HPMC 9:1.

Solid state of Cur and Cur ASDs

Powder X-ray diffraction

The samples (Cur, E100, E100/HPMC mixture, Cur-E100, Cur-E100/HPMC mixture) were analysed using a Shimadzu XRD-6000 diffractometer (Shimadzu Corporation, Kyoto, Japan) equipped with a Cu-Ka source and set in Bragg-Brentano geometry, scanning between 5 and 40°C 2θ at 8°C/min with a 0.04°step size.

Differential scanning calorimetry

A DSC (METTLER, Switzerland) was used to obtain the thermograms. Approximately 4 mg was accurately weighed and sealed in aluminium pans with perforated lids. The samples were heated from 30 to 250°C rate at 10°C/min, while purging with nitrogen at a flow rate of 40 ml/min.

Effect of HPMC on Cur ASDs

Effect of HPMC on liquidity of excipient

A smooth glass plate with a length of 52 mm was taken and the tilt angle of the smooth glass plate was set at 30°. Later the gliding time of 500 μg/ml pH 1.0 HCl solution of E100 and E100/HPMC mixture on the glass plate was determined.

Effect of HPMC on T_g of Cur ASDs

Heating curves of Cur-E100, Cur-E100/HPMC 1:1 and Cur-E100/HPMC 6:1 were obtained using modulated DSC (Model Q2000, TA Instruments, New Castle, Delaware) equipped with a refrigerated

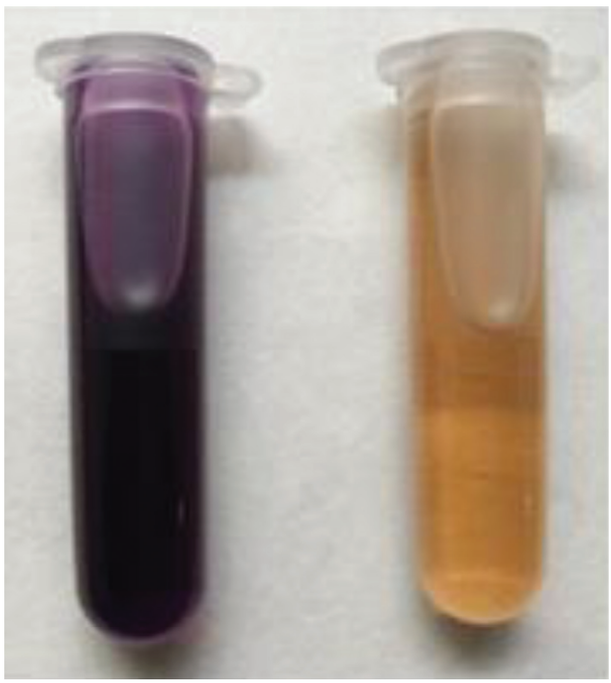

Figure 1 The colour of DPPH before or after exposer to an anti-oxidant.

cooling accessory. Nitrogen, 50 ml/min, served as the purge gas. A 2–5 mg sample was weighed into aluminum T-zero sample pans with pin holes (TA instruments) and sealed. Samples were heated from 0 to 120°C at 10°C/min, quickly cooled to 0°C at the maximum instrument cooling rate (15°C/min), then heated from 0 to 200°C at 10°C/min; transitions are reported from this second heating scan.

Effect of HPMC on crystallisation inhibition of Cur ASD

Water uptake experiment

Cur and Cur ASDs were stored in a desiccator with potassium nitrate (RH 92.5%) for up to 10 days at room temperature (25–28°C). Afterwards, in-vitro dissolution experiments of these hygroscopic samples were carried out. The hygroscopic samples of Cur and Cur ASDs (containing 4 mg Cur) were dissolved in 250 ml pH 1.0 hydrochloric acid using the small cup method (50 rpm, 37°C) with a RC806D dissolution tester (Tianjin, China). Aliquots (5 ml) were withdrawn at predetermined time intervals and replaced with equivalent amount of fresh dissolution medium after each sampling to maintain constant volume. The sample medium was analysed using UV-1120 (Shimadzu, Japan) at the wavelength of 425 nm after going through 0.45 μm microporous membrane.

Molecular dynamic modelling

A box containing 4 molecules of Cur, 60 molecules of H_2O and 4 molecules of corresponding excipient (E100, E100/HPMC 1:1, E100/HPMC 3:1, E100/HPMC 6:1 and E100/HPMC 9:1) was built. The initial density was set to 1 g/cm^3. Geometry optimisation was performed with the force field of COMPASSII. Dynamic optimisation was carried out and parameters were as follows: (1) Force field: COMPASSII; (2) Ensemble: NPT; (3) Temperature: 310 K; (4) Time step: 1fs; (5) Total simulation time: 200 ps. Other parameters were maintained at the default value. The diagrams of temperature, energy and kinetic density were obtained after the dynamic optimisation.

Anti-oxidant assay

In general, anti-oxidant potential of Cur ASDs was determined by scavenging activity of stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical.[25, 26] DPPH was a stable free radical and produced a violet colour in methanol. When the free radical was exposed to an anti-oxidant, its free radical property was lost and its colour changed to light yellow. Extent of colour change of Cur and Cur ASDs was monitored by UV absorption at its maximum absorption in methanol of 517 nm (Figure 1). The scavenging reaction between (DPPH) and an anti-oxidant (H-A) can be represented as:

$$\underset{\text{(Violet)}}{\text{DPPH}} + (\text{H}-\text{A}) \rightarrow \underset{\text{(Yellow)}}{\text{DPPH}-\text{H}} + \text{A}$$

When anti-oxidants reacted with DPPH, the DPPH was reduced to the DPPH-H, thus the absorbance was decreased. The degree of

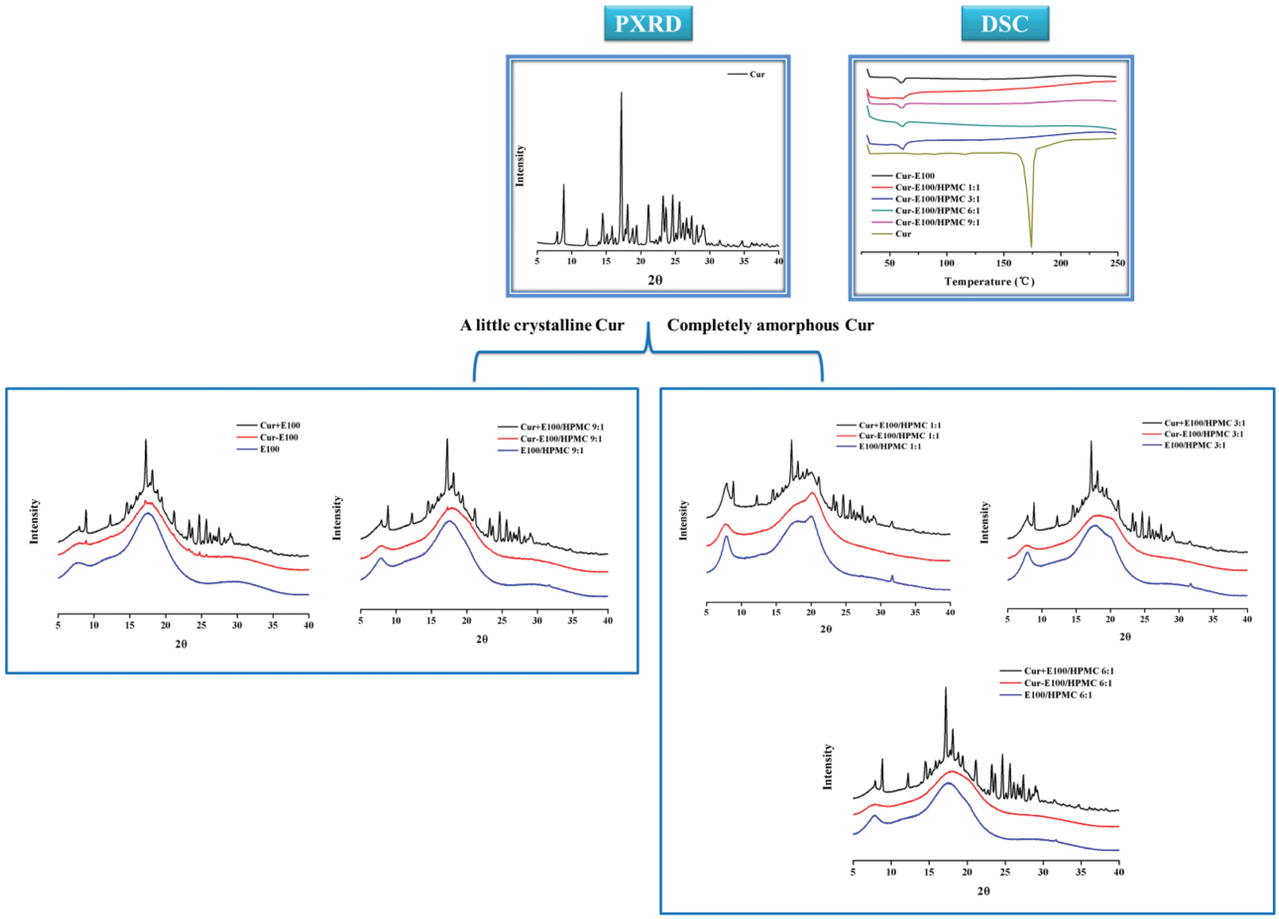

Figure 2 Powder X-ray diffractograms of curcumin, excipient, physical mixtures (Cur+E100 or Cur+E100/HPMC mixture) and Cur ASDs (Cur-E100 or Cur-E100/HPMC mixture) and DSC thermograms of Cur and Cur ASDs.

discolouration indicated the scavenging potential of the anti-oxidant compounds due to the hydrogen donating ability. The solution samples were prepared with various concentrations (1, 3, 5, 8, 10 μg/ml) of Cur ASDs. Three millilitres of Cur ASDs was mixed with 1.0 ml of DPPH (0.2 mm). The obtained solution was shaken vigorously and allowed to stand in the dark at room temperature for 30 min. All measurements were performed in triplicate. The percent anti-oxidant inhibition (ability to scavenge DPPH radical) was calculated using the equation:

$$\text{Inhibition } (\%) = (A_{\text{blank}} A_{\text{sample}})/A_{\text{blank}} \times 100$$

where A_{blank} is the absorbance of 0.2 mm DPPH and A_{sample} is the absorbance of Cur or Cur ASDs. The percentage of DPPH radical scavenging activity was plotted against the sample concentration.

Statistical analysis

Experimental results are expressed as the mean ± standard deviation. Statistical differences of was analysed using Kruskal–Wallis test or Student's test.

Results and Discussion

Solid state of Cur and Cur ASDs

The PXRD patterns of the Cur, excipient, physical mixtures and Cur ASDs are shown in Figure 2. The characteristic peaks of crystalline Cur were at 7.89°, 8.82°, 12.22°, 14.45°, 17.15°, 21.13°, 24.65° and 29.09° 2θ. According to the literature,[27] there are three kinds of Cur polymorphs. The Cur polymorph in our study was Form 1 according to PXRD results. The PXRD patterns of all physical mixtures showed the characteristic peaks that were similar to crystalline Cur, indicating the presence of crystalline Cur in the physical mixtures. The intensity levels of characteristic peak at 17.15° for Cur, Cur+E100, Cur+E100/HPMC 1:1, Cur+E100/HPMC 3:1, Cur+E100/HPMC 6:1 and Cur+E100/HPMC 9:1 were 1.5×10^6, 1.1×10^5, 8.0×10^4, 1.0×10^5, 1.2×10^5, 1.1×10^5, respectively. It was obvious that the intensity of this characteristic peak (17.15°) for Cur was much stronger than physical mixtures. This result illustrated that the excipient embedded the crystalline Cur and a relatively large proportion of HPMC in excipient can embed more crystalline Cur (such as Cur+E100/HPMC 1:1, the intensity of characteristic peak

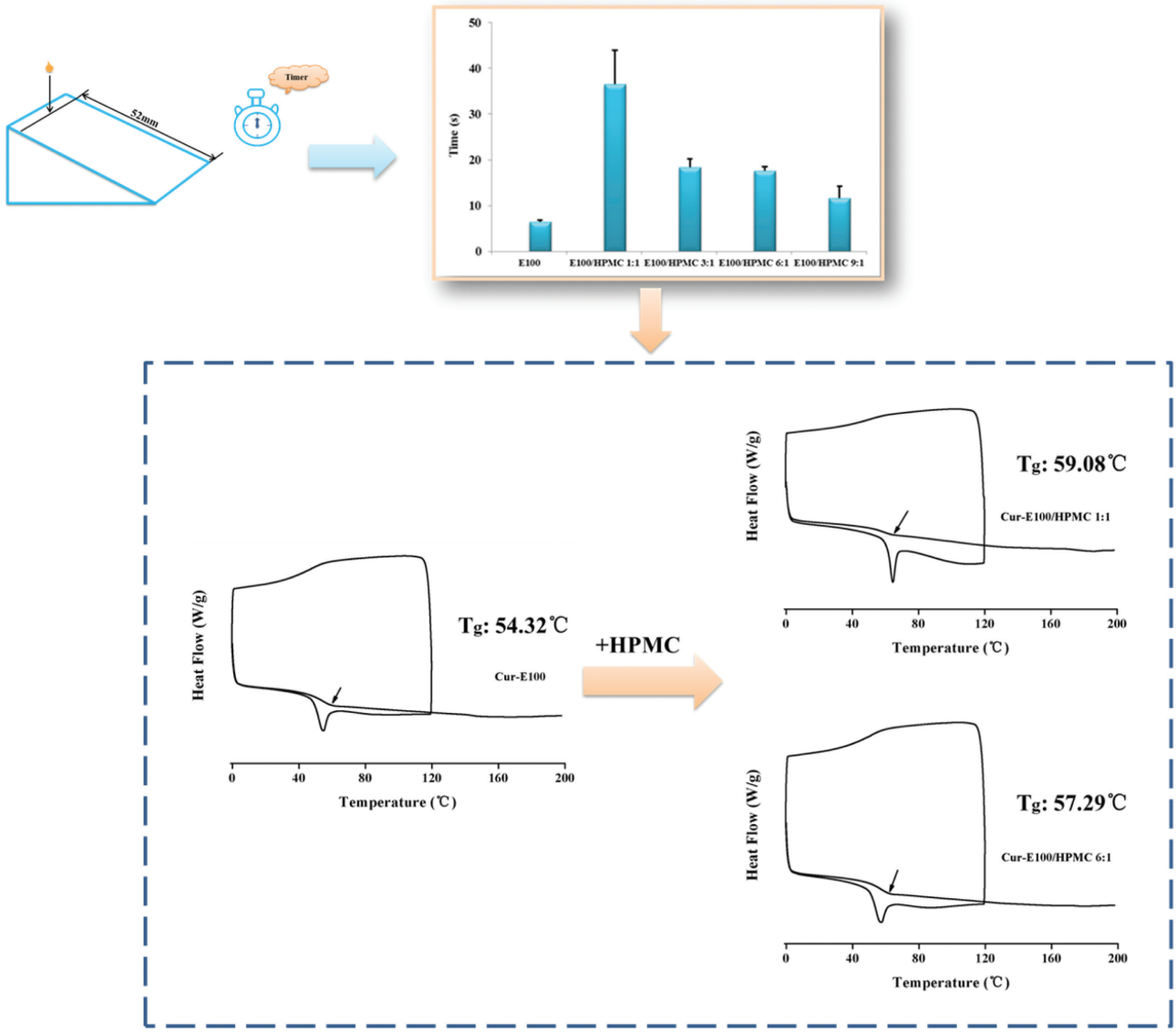

Figure 3 The gliding time of 500 μg/ml pH 1.0 polymer solution on the glass plate and the T_g of Cur ASDs.

at 17.15° was 8.0 × 10^4). As seen in Figure 2, Cur-E100 and Cur-E100/HPMC 9:1 had a part of characteristic peaks that were similar to crystalline Cur; however, other Cur ASDs (Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1 and Cur-E100/HPMC 6:1) showed no characteristic peaks that were similar to crystalline Cur. These results demonstrated that there was a little crystalline Cur in Cur-E100 and Cur-E100/HPMC 9:1 and there was completely amorphous Cur in Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1 and Cur-E100/HPMC 6:1. This phenomenon showed that addition of HPMC in Cur ASDs had a significant ability in inhibiting crystallisation of Cur. In Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1 and Cur-E100/HPMC 6:1, a considerable proportion of HPMC can form hydrogen bonding with Cur so that HPMC can inhibit crystallisation of Cur and maintain the amorphous state. On the contrary, some crystalline Cur can be seen in Cur-E100 and Cur-E100/HPMC 9:1 because no or a little hydrogen bonding can be formed between HPMC and Cur. Figure 2 also shows the DSC thermograms of Cur ASDs (Cur-E100, Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 6:1 and Cur-E100/HPMC 9:1), the thermogram of pure Cur exhibited an endothermic peak at 175°C, corresponding to its melting point. However, there was no endothermic peak at 175°C in Cur ASDs, suggesting that the drug was in an amorphous state. Based on the results of PXRD and DSC, the Cur mostly changed from crystalline state to amorphous state when Cur formulated with E100 and HPMC.

Effect of HPMC on Cur ASDs

Effect of HPMC on liquidity of excipient and T_g of Cur ASDs

The viscosity of the solution can be easily and quickly obtained by the convenient method. The gliding time of 500 μg/ml pH 1.0 polymer solution on the glass plate is shown in Figure 3. The gliding time of E100 was very short while the addition of HPMC prolonged the gliding time because viscosity of HPMC (40–60 mPa/s) was much higher than E100 (15 mPa/s). Therefore, the gliding time prolonged as increasing the proportion of HPMC in E100/HPMC mixture. That was because HPMC increased the viscosity of E100/HPMC mixture.

Glass transition referred to a process that the amorphous molecules changed from glassy state into a high-elastic or viscous fluid state. The temperature that amorphous molecules converted from glassy state to a high-elastic state or a viscous fluid state was named glass transition temperature (T_g). Thus, T_g can be used as a sign of the speed of molecular motion.[28] Moreover, the speed of molecular motion can be depicted by the relaxation time.[29] The physical stability of amorphous drugs was closely related to molecular motion. The addition of polymers can significantly increase the relaxation time and slow the crystallisation rate. In other words, when T_g showed a high value, the molecules of system moved slowly, thus prolonging the relaxation time and reducing the crystallisation rate. As seen in Figure 3, the addition of HPMC improved T_g of Cur-E100/HPMC 1:1 and Cur-E100/HPMC 6:1 compared to Cur-E100. And the T_g of Cur-E100/HPMC 1:1 was higher than Cur-E100/HPMC 6:1 due to a larger proportion of HPMC in Cur-E100/HPMC 1:1. These results were ascribed to following two main reasons: (1) The addition of HPMC in excipient increased the viscosity of the whole system, thus reducing the molecular motion. Therefore, the T_g of Cur ASDs increased with the increase of HPMC. (2) When hydrogen bonding was formed between drug and polymer, the relaxation time of drug significantly increased, thus improving the physical stability of the system.[30] In our study, the greater the proportion of HPMC in the excipient, the more hydrogen bonding formed between HPMC and Cur, resulting in higher T_g of the system and stronger stability of Cur ASDs. Furthermore, HPMC containing both donor and acceptor groups formed hydrogen bonding with both Cur donors and acceptor moieties, thus disrupting self-associations of Cur, which was important to crystal formation. Therefore, the addition of HPMC in Cur ASDs can inhibit crystallisation effectively.

Crystallisation inhibition of HPMC on Cur ASDs

Water uptake experiment

As seen in Figure 4, the overall trend of drug release for hygroscopic samples was similar to that of non-hygroscopic samples. During the dissolution process, only the cumulative drug release of Cur-E100 reduced, the cumulative drug release of other Cur ASDs containing HPMC did not decrease, reflecting the crystallisation inhibition ability of HPMC. Polymers were used to inhibit crystallisation by the means of reducing the drug molecular mobility, increasing the glass transition temperature (T_g) of the system or forming hydrogen bonds with the drug for good physical stability in ASDs during processing and storage of ASDs.[31–33] Herein, HPMC not only improved the viscosity of the whole system, reduced Cur molecular mobility and increased T_g in Cur ASDs, but also formed hydrogen bond between HPMC and Cur, thus inhibiting crystalliation and improving physical stability in Cur ASDs.[34, 35]

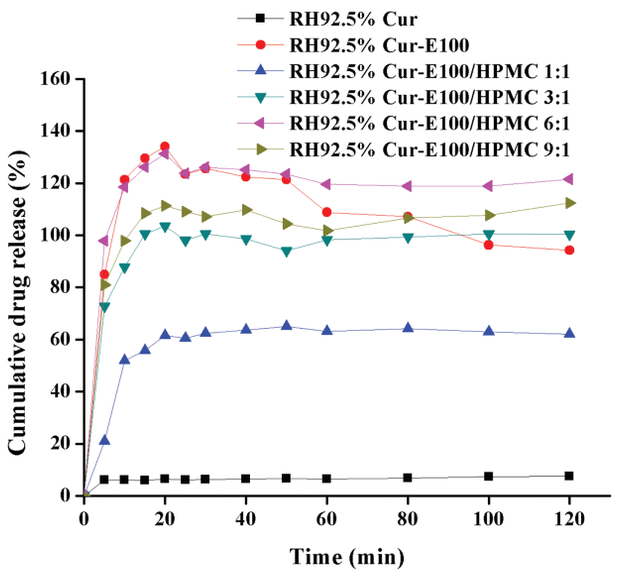

Figure 4 In-vitro dissolution of hygroscopic sample of Cur ASDs.

Table 1 Molecular dynamics results of final total energy and density. Data of significant differences between mixture without HPMC and with HPMC were calculated using Student's test. The significant difference symbol was put in the top right corner of the data

Samples	Final total energy (Kcal/mol)	Final density (g/cm^3)
Cur-E100	6000	0.98
Cur-E100/HPMC 1:1	3200*	1.13
Cur-E100/HPMC 3:1	3000*	1.08
Cur-E100/HPMC 6:1	3800*	1.08
Cur-E100/HPMC 9:1	3750*	1.06

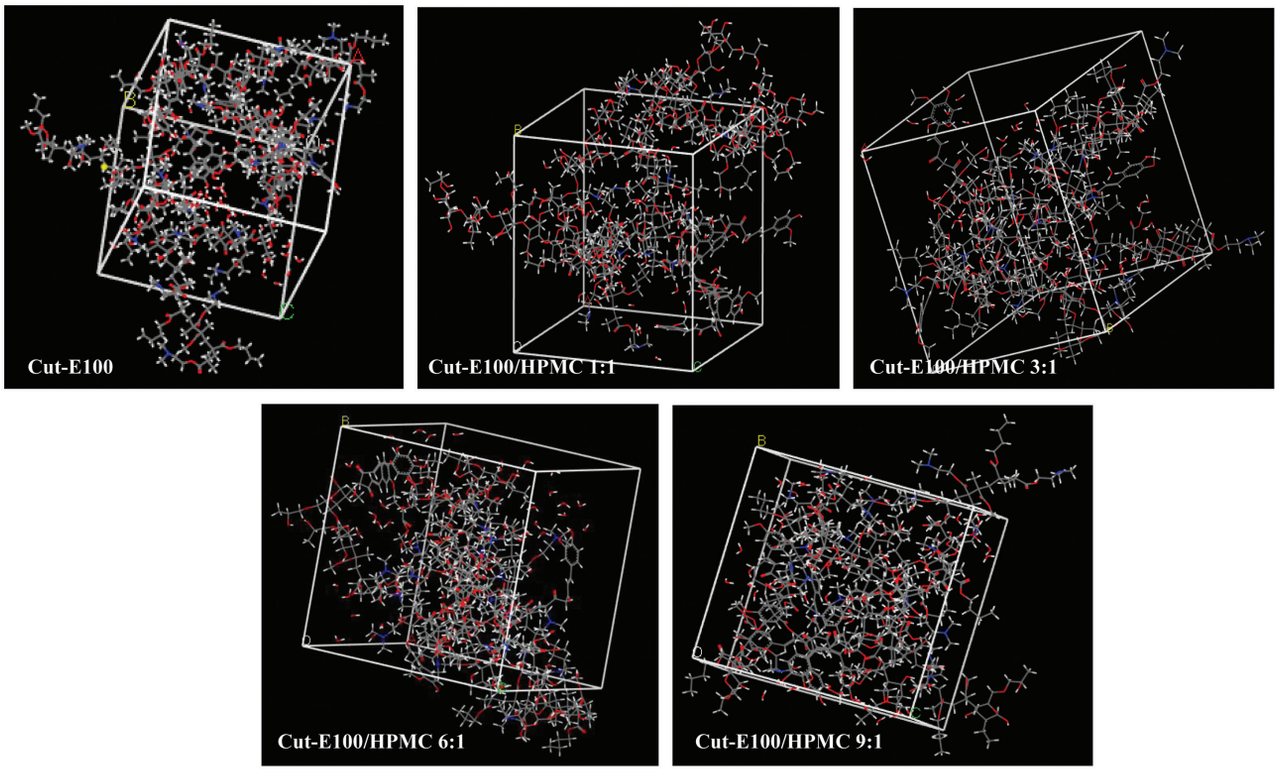

Figure 5 Molecular dynamics of crystalline Cur in excipient solutions.

Molecular dynamic modelling

The intermolecular interactions between drug and polymers made polymers firmly attached into the surface of hydrophobic drug, which avoided the direct exposure of Cur molecules in the aqueous media. The polymers were crucial for inhibiting drug crystallisation. Molecular dynamic modelling was conducted to simulate the attachment of polymers on the drug particle surface in the aqueous media and to provide a molecule-level description of polymers behaviour in the ternary system (drug–polymer–water). Herein, five molecular modelling boxes containing the same amount of water, different excipients (E100, E100/HPMC 1:1, E100/HPMC 3:1, E100/HPMC 6:1 and E100/HPMC 9:1) and Cur molecules were operated for the same period of time. The first key point should focus on the final total energy and density of Cur ASDs, which were shown in Table 1. It can be seen that the addition of HPMC significantly decreased the final total energy while increasing the final density when comparing Cur-E100/HPMC mixture with Cur-E100. It was because HPMC in Cur ASDs significantly improved the viscosity of the whole system, thus reducing Cur molecular mobility and resulting in the low total energy and high density. Therefore, the addition of HPMC had significant effect on inhibiting crystallisation and improving physical stability. A greater proportion of HPMC in E100/HPMC mixture had stronger influence on inhibiting crystallisation and improving physical stability. The second key point in consideration should be the aggregation degree of Cur molecules since the aggregation degree of Cur molecules showed the growing rate of crystal drug molecules. When the crystal Cur grew up, the aggregation degree increased. As seen in Figure 5, after running the box for the same period of time, crystalline Cur molecules in E100 medium trended to aggregate much more than E100/HPMC 1:1, E100/HPMC 3:1, E100/HPMC 6:1 and E100/HPMC 9:1 medium. The results demonstrated that HPMC can exert outstanding advantages in inhibiting solution crystallisation as auxiliary excipient.

Anti-oxidant assay

The free radical scavenging activity of Cur ASDs, which was evaluated through the change of absorbance produced by the reduction of DPPH, is shown in Figure 6 (specific values are shown in Table 2). When anti-oxidants reacted with DPPH through donation of hydrogen (H^+), the absorbance of DPPH radical decreased and the inhibition of anti-oxidants increased. The colour change from violet to yellow can also be observed visually. Priyadarsini *et al.*[36] proposed that phenolic hydroxyl groups of Cur were necessary for the scavenging of DPPH free radical. On this basis, the methoxy group of Cur that belonged to the strengthening relationship with phenolic hydroxyl groups of Cur increased its anti-oxidant activity. As we can see from Figure 6, Cur ASDs exhibited a significant free radical scavenging activity at various concentrations (1, 3, 5, 8, 10 μg/ml), demonstrating that the intermolecular interactions between Cur and excipient did not affect the anti-oxidant activity of Cur. The inhibition profiles of Cur ASDs belonged to binomial function and with increasing concentration of Cur ASDs, the inhibition of Cur ASDs was stronger. Moreover, the anti-oxidant activity of Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 6:1 and Cur-E100/HPMC 9:1 was stronger than Cur-E100 because the inhibition values of Cur-E100/HPMC 1:1, Cur-E100/HPMC 3:1, Cur-E100/HPMC 6:1 and Cur-E100/HPMC 9:1 was higher than Cur-E100 (Table 2). These results demonstrated that the addition of HPMC weakened the intermolecular interactions between C=O of E100 and phenolic hydroxyl groups of Cur. Among Cur ASDs with HPMC, the inhibition values of Cur-E100/HPMC 6:1 were the highest at

Table 2 Inhibition of anti-oxidant activity of DPPH by Cur ASDs. Data of significant differences between samples were calculated using Kruskal–Wallis test.

Samples	Inhibition (%)									
	1 μg/ml	SD	3 μg/ml	SD	5 μg/ml	SD	8 μg/ml	SD	10 μg/ml	SD
Cur-E100	78.07	0.12	83.07	0.06	86.81	0.05	90.62	0.11	90.07	0.05
Cur-E100/HPMC 1:1	78.88	0.05	83.40	0.05	87.43	0.03	91.22	0.05	93.31	0.03
Cur-E100/HPMC 3:1	78.85	0.03	83.46	0.00	87.64	0.03	91.29	0.21	93.31	0.03
Cur-E100/HPMC 6:1	78.51	0.00	83.88	0.00	87.75	0.06	91.54	0.17	93.39	0.03
Cur-E100/HPMC 9:1	78.19	0.00	83.78	0.08	86.38	0.05	90.87	0.03	92.25	0.03

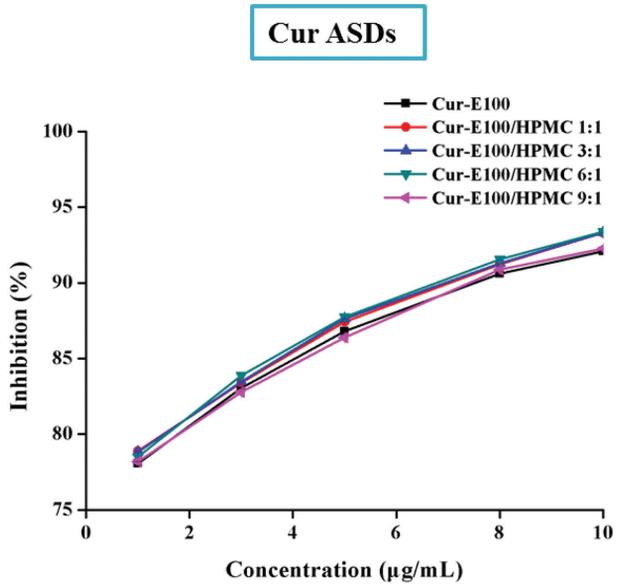

Figure 6 Inhibition of anti-oxidant activity of DPPH by Cur ASDs.

the concentrations of 3, 5, 8, 10 μg/ml, which was consistent with our previous study.[37] In conclusion, the intermolecular interactions between Cur and excipient did not affect the anti-oxidant activity of Cur, the phenolic hydroxyl groups of Cur can react with DPPH free radical, thus scavenging DPPH free radical and further enhancing the anti-oxidant of Cur ASDs.

Conclusions

Herein, we prepared Cur ASDs with binary polymers of E100 and HPMC. The crucial advantages of E100 in inhibiting drug crystallisation were studied. According to the results of DSC and PXRD, crystal Cur converted to amorphous Cur when crystal Cur formulated with E100 and HPMC by solid dispersions. The addition of HPMC can reduce molecule motion of the whole system and improve T_g of Cur ASDs, thus inhibiting crystallisation of Cur ASDs. The water uptake experiment and the molecular dynamic modelling further confirmed that HPMC had the ability to inhibit crystallisation. The elucidation of HPMC as auxiliary excipient on inhibiting crystallisation for Cur ASDs will bring huge value in designing Cur ASDs in the future.

Conflict of Interest

There is no conflict of interest in this paper.

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