Am J Transl Res 2022;14(3):1495-1506
www.ajtr.org /ISSN:1943-8141/AJTR0135338

Original Article

Inclusion complex of lurasidone hydrochloride with Sulfobutylether-β-cyclodextrin has enhanced oral bioavailability and no food effect

Jin Wang[1], Binbin Huang[1], Jie Dai[1], Guoguang Chen[1], Lili Ren[1,2]

[1]*School of Pharmacy, Nanjing Tech University, 5th Mofan Road, Nanjing 210009, Jiangsu, China;* [2]*Department of Microbiology and Immunology, Stanford University, Stanford, CA 94305, USA*

Received May 17, 2021; Accepted February 14, 2022; Epub March 15, 2022; Published March 30, 2022

Abstract: Objectives: This study aimed to improve the solubility in water and bioavailability *in vivo* of lurasidone hydrochloride (LUR). Methods: The saturated aqueous solution method was used to prepare an inclusion complex of LUR with sulfobutylether-β-cyclodextrin, or SBE-β-CD (LUR-SBE-β-CD). A single-factor test was used for the preliminary screening of important preparing conditions including the ethanol concentration, the SBE-β-CD concentration, temperature, and pH. Then central composite design response surface methodology (CCD) was adopted for the optimum craft. Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and powder X-ray diffraction (PXRD) were used to confirm the formation of LUR-SBE-β-CD. The *in vitro* release profiles of LUR-SBE-β-CD were determined at different pHs and in simulated gastrointestinal fluid. Results: The dissolution studies revealed that the dissolution of LUR in LUR-SBE-β-CD was much improved in the four media and simulated gastrointestinal fluid. Similar profiles of LUR-SBE-β-CD were obtained in pharmacokinetic studies whether beagle dogs took food or not. Conclusions: The bioavailability of LUR can be improved and the food effect can be eliminated by LUR-SBE-β-CD.

Keywords: Lurasidone hydrochloride, sulfobutylether-β-cyclodextrin, inclusion complex, bioavailability, food effect

Introduction

Solubility studies of drugs have shown that 40% of agents are found to be poorly soluble in water. This percentage has even reached 80~90% in various therapeutic areas [1, 2]. This is according to the Biopharmaceutics Classification System (BCS), in which BCS II drugs, which have high permeability but poor aqueous solubility, have poor oral bioavailability [3, 4].

Lurasidone hydrochloride (LUR), an antagonist of dopamine (D_2) and serotonin ($5\text{-}HT_{2A}$), is a novel benzisothiazole, second-generation and orally antipsychotic agent (Latuda®) [5, 6], which has been used in the treatments of adult schizophrenia [7, 8]. LUR, a drug that belongs to BCS II drug category, is poorly soluble in water (only 0.224 mg/ml in plain water), which leads to low bioavailability (estimated to be about 9 to 19%). Taking the drug in the fed state may influence the dissolution and absorption of LUR in the gastrointestinal tract (GI) [9]. Previous research showed that lurasidone absorption was affected by food consumption. Compared with a fasted state, the absorption of lurasidone increased by two-fold when administered with food, as well as the maximum concentration (C_{max}) increased by three-fold. Moreover, the T_{max} was prolonged by 0.5~1.5 h in the fed state. Because food can affect the LUR bioavailability significantly, a minimum of 350 calories of food is recommended before the taking of the drug [10, 11]. Therefore, enhancing the solubility and dissolution properties of LUR might improve its absorption in the GI, as well as the bioavailability of LUR. To sum up, improving oral bioavailability without food effect should be taken into account.

A good amount of research has been conducted on improving the solubility and oral bioavail-

ability of LUR. *Miao* [12] found that a self-nanoemulsifying technology can improve the bioavailability of LUR and diminished food interference. Kumar and Burgess [13] adopted the Nano suspensions system of LUR to increase the dissolution. However, shortcomings are existent; for example, the low drug loading and poor stability of these drug delivery systems limit their development.

Cyclodextrin is a cyclic oligosaccharide [14] in which the inner central cavity is hydrophobic and the outer surface is hydrophilic. Those molecules can partly or all enter the interior cavity of cyclodextrin [15-17]. The physicochemical characteristics of molecules encapsulated may be affected, such as their dissolution, solubility, and bioavailability. But the low aqueous solubility restricts the practical application of the natural form. So, modified cyclodextrins that possess better physical and chemical properties emerged as required, including carboxymethyl-β-cyclodextrin (CM-β-CD), methyl-β-cyclodextrin (M-β-CD), sulfobutylether-β-cyclodextrin (SBE-β-CD). SBE-β-CD [18] (its trade name is Captisol®), a biocompatible and non-toxic CD derivative, exhibits complexing abilities and better solubility than the parent β-CD [19, 20]. It has been widely applied to the field of pharmacy. Compared with other CD derivatives, the outer hydrophilic and inner hydrophobic residues are more obvious due to the repulsion of the end group's negative charge coupled with the four-carbon butyl chain of SBE-β-CD [21, 22]. Hence, inclusion complexes with cyclodextrin should be an effective method to solve the problems above.

A saturated aqueous solution method was utilized to prepare LUR-SBE-β-CD. Single-factor test and CCD are used for the optimization of important preparing conditions of LUR-SBE-β-CD.

In the research, the saturated aqueous solution method was used. Single-factor test and CCD are used for the optimization of important preparing conditions of LUR-SBE-β-CD. The phase solubility was studied and PXRD, DSC, SEM, and FTIR were used to characterize LUR-SBE-β-CD. Also, the dissolution studies of LUR-SBE-β-CD were evaluated. In the end, the pharmacokinetics and bioavailability of LUR-SBE-β-CD were evaluated in beagle dogs by oral medication.

Materials and methods

Materials

SBE-β-CD (DS = 7; Mw = 2241) was obtained from Yuanzhu Technology Co. Ltd (Taizhou, China). LUR was presented by Nhwa Pharmaceutical Co. Ltd (Xuzhou, China). Latuda® (40 mg, tablet) was purchased from Sumitomo Dainippon Pharma. Co. Ltd (Japan).

Phase solubility studies

The effect of SBE-β-CD on the solubility of LUR was evaluated in this experiment. Briefly, A series concentration (5, 10, 20, 30, and 40 m/v) of SBE-β-CD solutions with excess LUR were prepared for this experiment. Samples were vibrated at 25°C for 24 h with an oven-controlled oscillator. LUR concentration was measured by the validated method based on HPLC analysis. The chromatographic system (Shimadzu, Japan) was purchased from Japan. 20 μL volume of samples was injected into a Baseline® C18 Column (4.6 × 250 mm, 5 μm) and the detection wavelength was 230 nm. The flow rate was 1.0 ml/min with a 50:50 (v/v) mixture of acetonitrile and 10 mM of phosphate buffer (pH 3.0) at 30°C. The following equation was used to calculate the complex formation constant (Ks):

$$K_s = \frac{slope}{S_0(1 - slope)} \quad (1)$$

Where *slope* represents the and slope of linear equation and S_0 represent the solubility of LUR with SBE-β-CD.

Method of preparing LUR-SBE-β-CD

LUR-SBE-β-CD was prepared with a saturated water solution. First, the pH of the SBE-β-CD aqueous solution was adjusted with 0.1 M NaOH or HCl. Next, LUR was dissolved in ethanol and dropped into SBE-β-CD aqueous solution slowly. After that, the mixed suspension was dried for the soft paste at 50°C and it was washed three times by methylene chloride to further separate the uncomplexed LUR. Finally, the inclusion complex was harvested by drying in a vacuum drying oven at 35°C for 4 h and sieving through a 50-mesh sieve (the aperture of which is 300 μm).

Table 1. Three factors and five levels of central composite design

Variables	Scopes and levels				
	-1.682	-1	0	1	1.682
Concentration of ethanol (A, %)	3.18	10	20	30	36.82
pH (B)	2.32	3	4	5	5.68
Concentration of SBE-β-CD (C, %)	8.18	15	25	35	41.82

Table 2. Dosage regimen of LUR-SBE-β-CD inclusion complex and Latuda® in beagle dogs (n = 2)

Group	Period 1	Period 2	Period 3	Period 4
1	A	D	B	C
2	B	A	C	D
3	C	B	D	A
4	D	C	A	B

A: Commercial product (fasted). B: Commercial product (fed). C: LUR-SBE-β-CD (fasted). D: LUR-SBE-β-CD (fed).

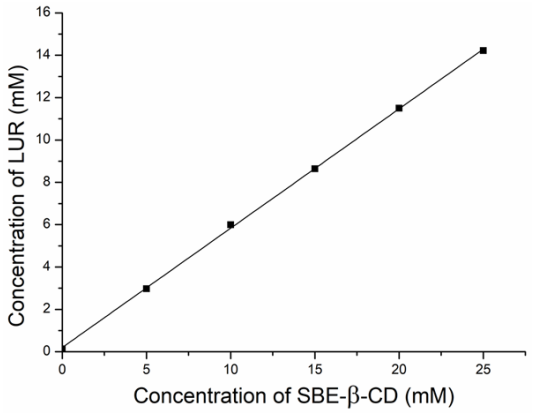

Figure 1. Phase solubility diagram plotted with concentration of LUR against increasing concentration of SBE-β-CD in water.

Evaluation index

Typically, encapsulation efficiency (EE) and drug loading efficiency (DE) are determined to evaluate the inclusion efficiency. In this study, samples were obtained by dissolving LUR-SBE-β-CD in ethanol through ultrasound. LUR content in the inclusion complex was detected by HPLC. The following equations were used for the calculation of EE and DE.

$$Encapsulation\ efficiency = \frac{LUR\ content\ in\ inclusion\ complex}{LUR\ feeding\ amount} \times 100\% \quad (2)$$

$$Drug\ loading\ efficiency = \frac{LUR\ content\ in\ inclusion\ complex}{amount\ of\ inclusion\ complex} \times 100\% \quad (3)$$

Single-factor test

The EE and DE of LUR-SBE-β-CD were affected by ethanol concentration, temperature, the amount of SBE-β-CD and pH. The initial conditions were 40°C, 20% ethanol, 20% SBE-β-CD and pH 4 for the single-factor experiment. When one of these factors varied, the other values of factors were fixed. All preparation processes are described above in *Method of preparing LUR-SBE-β-CD*.

Central composite design response surface methodology (CCD)

Factors that significantly affect DE and EE of LUR-SBE-β-CD were optimized by CCD with Design-Expert 8.0.6 software. The CCD with three factors and five levels was designed. The values of pH, concentration of ethanol, and SBE-β-CD were selected. The interrelated CCD are presented in **Table 1**.

Characterization and solubility studies

FTIR studies: FTIR spectrometer (Shimadzu Corporation, Japan) was used in this experiment. Before the experiment, KBr mixed with samples was finely ground. Infrared transparent matrices were obtained with a hydrostatic press and spectra must be collected from 400~4000 cm^{-1}, and the resolution was 4 cm^{-1}.

DSC studies: LUR, SBE-β-CD, physical mixtures and LUR-SBE-β-CD were characterized using Phoenix DSC-204 thermal instrument (Phoenix Corporation, Selb, Germany). Samples were added in pans and heated from 40°C to 400°C with a rate of 10°C/min.

PXRD studies: Crystal forms of LUR, SBE-β-CD, physical mixture, and LUR-SBE-β-CD were characterized by PXRD analysis. This study was performed employing a Philips FW 1700 X-ray diffractometer with a voltage of 40 kV. Samples were scanned from 5° to 50° with a speed of 0.02°/s.

SEM studies: LUR, SBE-β-CD, physical mixture, and LUR-SBE-β-CD were studied by SEM (JSM-5800, JOEL, Tokyo, Japan) at 15 kV for the surface morphology. Before SEM observation, samples coating with platinum were fixed on a brass stub in the vacuum.

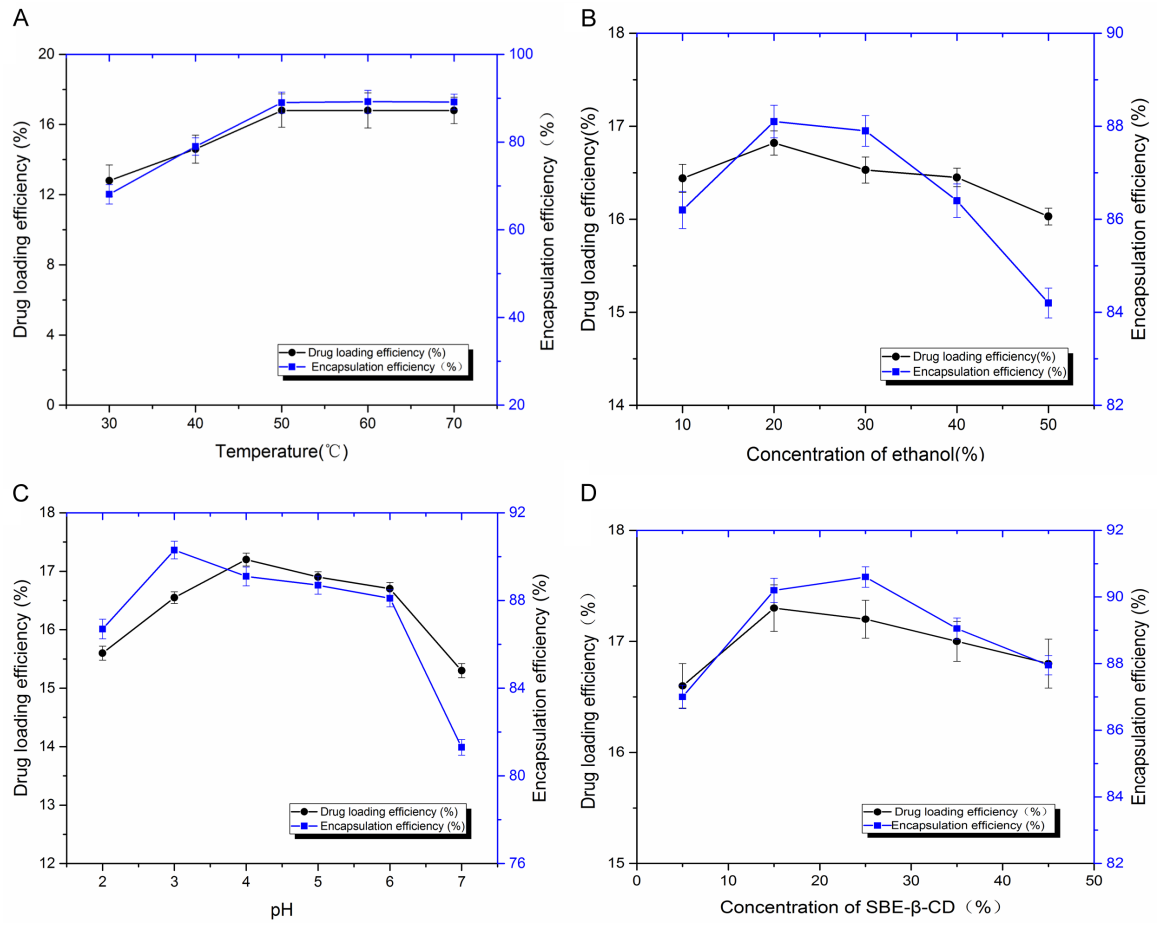

Figure 2. Effect of temperature (A), concentration of ethanol (B), pH (C) and concentration of SBE-β-CD (D) on loading efficiency and encapsulation efficiency (n = 3).

Saturation solubility: Solubility studies of samples were determined by the excess amount of LUR API and LUR-SBE-β-CD in four dissolution media: hydrochloric acid (pH 1.2), acetum (pH 4.5), phosphate buffer (pH 6.8) and water (pH 7.0). Vibrating the solutions was done for 48 h, with the temperature stable at 37°C, then, filtering the solutions was done and the HPLC method was used as mentioned above to determine solubility. The experiments were repeated three times.

In vitro dissolution studies

Dissolution studies of LUR-SBE-β-CD and Latuda® were conducted in the paddle method by using a six-vessel dissolution tester (Shanghai Huanghai Instrument Co. China). Four dissolution mediums with different pH were added with the temperature of 37°C and stirred at 50 rpm. At 5, 10, 15, 20, 30, 45, 60 and 90 mins, 5 mL of the sample was taken and the equivalent volume of temperature equilibrated medium was added in 15 s. The samples were filtered and determined by HPLC.

The similarity factor f_2 was determined to estimate the similarity degree of dissolution curves of LUR-SBE-β-CD and Latuda® in different media. The following equation was used for the calculation of f_2 [23].

$$f_2 = 50\log\left[\frac{100}{\sqrt{1+\frac{\sum_{i=1}^{n}(R_t - T_t)^2}{n}}}\right] \quad (4)$$

In the equation, n is the number of the time points, R_t represents the accumulated release rate of Latuda® and T_t is the accumulated release rate of LUR-SBE-β-CD.

For two profiles, the value of f_2 was between 0~100. The larger f_2 is, the higher the similarity

Table 3. The central composite design and response value of each factor level

Run	Critical factor			Response	
	Concentration of ethanol (%)	pH	Concentration of SBE-β-CD (%)	Drug loading efficiency (%)	Encapsulation efficiency (%)
1	10.00	3.00	15.00	15.90	82.59
2	36.82	4.00	25.00	14.50	78.38
3	10.00	3.00	35.00	15.88	83.56
4	20.00	4.00	25.00	17.90	89.32
5	20.00	4.00	25.00	18.00	90.30
6	20.00	4.00	8.18	16.09	84.32
7	30.00	5.00	35.00	15.02	82.97
8	20.00	4.00	25.00	17.81	91.25
9	20.00	4.00	41.82	16.81	85.78
10	30.00	3.00	35.00	15.06	82.98
11	20.00	2.23	25.00	16.03	84.01
12	30.00	5.00	15.00	15.99	83.66
13	20.00	5.68	25.00	16.56	85.00
14	20.00	4.00	25.00	17.97	90.56
15	20.00	4.00	25.00	17.88	91.38
16	30.00	3.00	15.00	15.98	83.75
17	3.18	4.00	25.00	14.83	78.22
18	10.00	5.00	35.00	15.38	82.99
19	10.00	5.00	15.00	15.83	82.09
20	20.00	4.00	25.00	17.79	89.88

between the two dissolution curves. The value of f_2 from 50 to 100 means that the release profiles have a similarity. On the contrary, the value of f_2 from 0 to 50 means that the two release profiles have no similarities.

Pharmacokinetics studies in dogs

Given relevant research [19], 8 healthy beagle dogs (female and male each half, 2~3 years old), weighing 14.85±1.37 kg, were used in our experiments (The experiment was approved by the Nanjing Medical University Institutional Animal Care and Use Committee (No. 2014-10113). All experimental operations adhered to the "Principles of Laboratory Animal Care"). In a light-controlled room, every standard cage only had one beagle dog. The temperature of the room was 20°C.

The pharmacokinetic study of LUR-SBE-β-CD (6.98 mg/kg, 103.7 mg) and reference formulation of Latuda® (1.25 mg/kg, 18.56 mg) were tested in beagle dogs with the 4 × 4 crossover experiment. Beagle dogs were tested in two states: fasted and fed conditions (washout period is 7 days). Before the experiment, the total of 8 beagle dogs were randomly divided into 4 groups (half male and half female) and the specific experimental design was shown in **Table 2**. In fasted studies, beagle dogs had fasted for 12 h, and the dogs were free to drink water. After 24 h of experimental study, dogs could be free to eat dry dog food. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h, 4 ml blood samples were collected from the forelimb of dogs with sodium heparin tubes. Before analysis, the samples were centrifuged at 4000 rpm for plasma.

Then, 1 mL plasma was mixed with 40 μL Ziprasidone (2 μg/mL, internal standard) and then mixed with 5.0 mL ethyl acetate. The supernatant was collected and dried with N_2. Finally, the samples were analyzed with the HPLC method above. Pharmacokinetic parameters were calculated according to the non-compartment model.

Statistical analysis

All statistical values in this experiment were analyzed with Origin 8.6. and shown as the M ± SD. All statistical comparisons were performed using one-way ANOVA, and *P*-value <0.05 was considered significant.

Results and discussion

Phase solubility studies

Results of the phase solubility equilibrium diagram from **Figure 1** indicated that the concentration of LUR and SBE-β-CD have a linear relationship between 0~25 mM. The complexation between LUR and SBE-β-CD was extrapolated to be an AL-type based on Higuchi and Connors by linear fitting ($y = 0.568x + 0.138$) with a correlation coefficient of 0.999. The type of plot showed a stoichiometric rate of 1:1 molecular complexation between SBE-β-CD and LUR. The complex formation constant, *K*s, was 9527.6

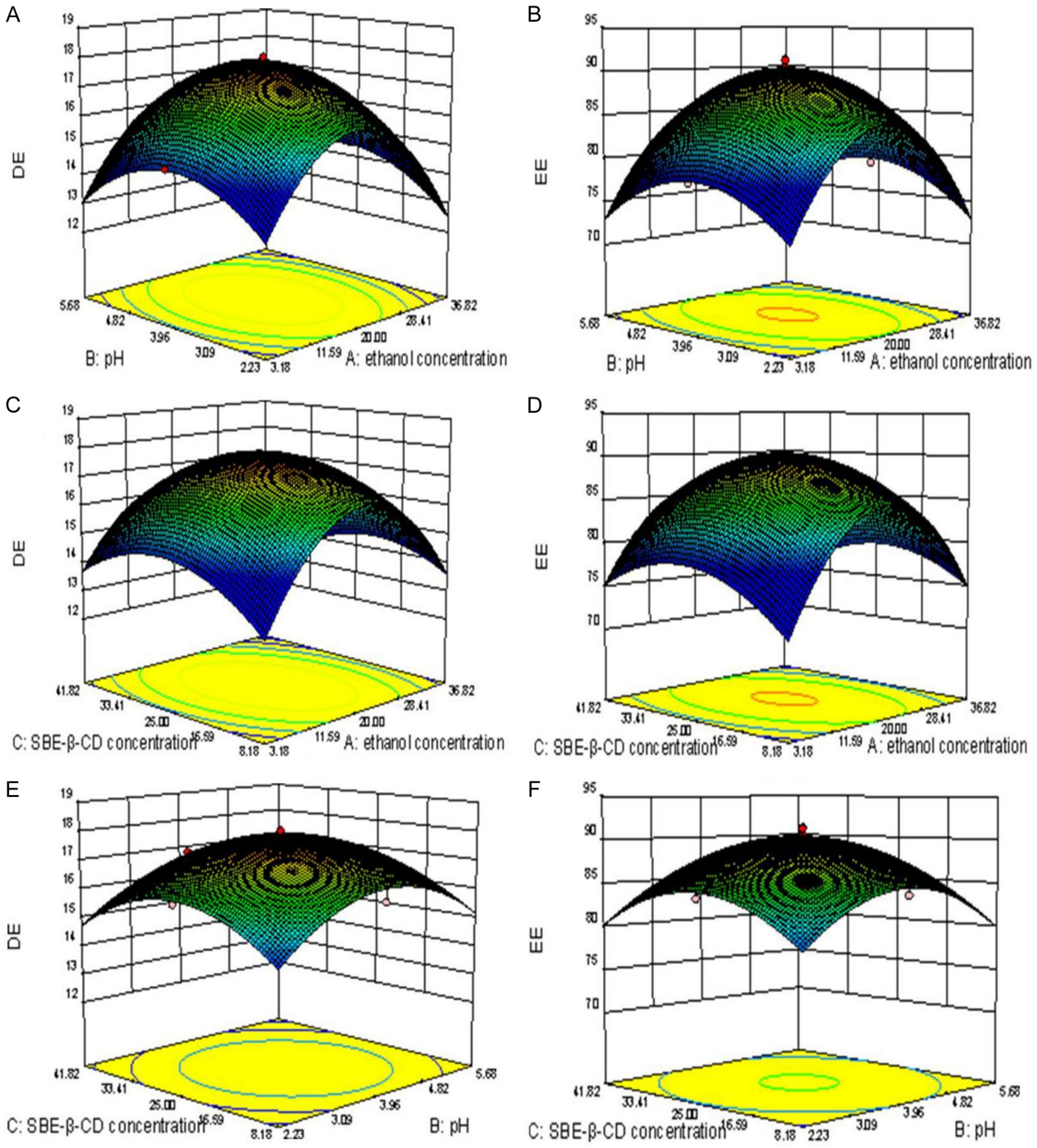

Figure 3. Response surface plots showing the effects of concentration of ethanol (A and B), concentration of SBE-β-CD (C and D) and pH (E and F) on drug loading efficiency and encapsulation efficiency.

M^{-1}, indicating that the stability of LUR-SBE-β-CD was good.

Experimental design

Single-factor test: To obtain the desired EE and DE, preparing conditions were filtered through the single-factor test. As shown in **Figure 2A**, the EE and DE acquired a rapid growth as the temperature was rising in the initial of reaction, and obtained a maximum value at about 50°C. There was no obvious trend in growth when the temperature was over 50°C. According to **Figure 2B**, the concentration of ethanol was one of the most significant factors. As depicted in **Figure 2C**, pH was also a vital factor. The curve showed a characteristic of a downtrend when pH was below 3 or over 5, which indicated that the optimum pH range was 3~5, corresponding to the pKa (4.65) of LUR. **Figure 2D** shows that encapsulation efficiency and drug

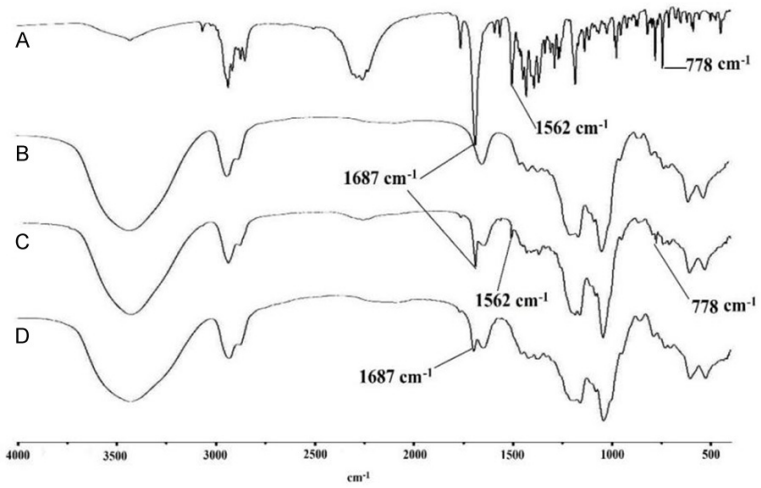

Figure 4. Infrared spectrogram of LUR (A); SBE-β-CD (B); physical mixture of LUR and SBE-β-CD (C) and LUR-SBE-β-CD inclusion complex (D).

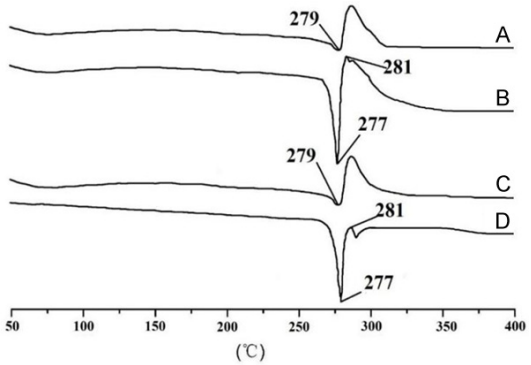

Figure 5. DSC of SBE-β-CD (A); LUR (B); LUR-SBE-β-CD inclusion complex (C); physical mixture of LUR and SBE-β-CD (D).

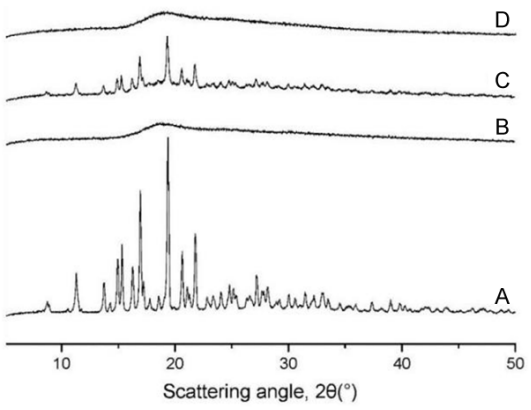

Figure 6. Powder X-ray diffraction patterns of LUR (A), SBE-β-CD (B), physical mixture (C) and LUR-SBE-β-CD inclusion complex (D).

loading efficiency increased with the concentration of SBE-β-CD.

The concentrations of SBE-β-CD, ethanol, and pH were found to be the most important factors while the temperature was the least important factor in this study. The single-factor test was an impactful test that underlay the further optimization.

Central composite design and statistical analysis: 20 experiments investigated the influence of the preparing conditions on the EE and DE. Times of experiments were produced by software and the relevant data of 20 experiments are shown in **Table 3**. Experimental data and the two polynomial equations under the coding factor were analyzed by Design-expert 8.0.6 software.

$$DE = 17.89 - 0.11 \times A + 0.021 \times B - 0.084 \times C + 0.068 \times A \times B - 0.018 \times A \times C - 0.06 \times BC - 1.15 \times A^2 - 0.57 \times B^2 - 0.52 \times C^2$$

$$EE = 90.42 - 0.18 \times A + 0.036 \times B + 0.21 \times C + 0.12 \times A \times B - 0.42 \times A \times C + 0.0012 \times BC - 4.1 \times A^2 - 1.9 \times B^2 - 1.71 \times C^2$$

Where the concentration of ethanol, pH, and the concentration of SBE-β-CD are represented by A, B and C. The variation of samples in DE and EE was attributable to the experimental factors because the correlation coefficient (R^2) were 0.9984 and 0.9806. From **Figure 3A** and **3B**, DE and EE showed an initial increase and then decrease slightly with the increase of ethanol concentration. As shown in **Figure 3C** and **3D**, DE and EE increased slowly as the SBE-β-CD grew. **Figure 3E** and **3F** implied that DE and EE decreased with the decrease of pH value. The best formulation conditions for preparing LUR-SBE-β-CD could be predicted by the equation and the response surface. The optimized conditions that were determined were: concentration of ethanol 19.88% (v/v), pH 4.01, concentration of SBE-β-CD 24.88% (w/v) and the predicted DE and EE was 17.9% and 90.4%. According to the optimum conditions, the DE and EE of LUR-SBE-β-CD prepared were 17.65% and 89.2%, which is close to the predicted values. Finally, the conditions above were selected as the best process for preparing LUR-SBE-β-CD.

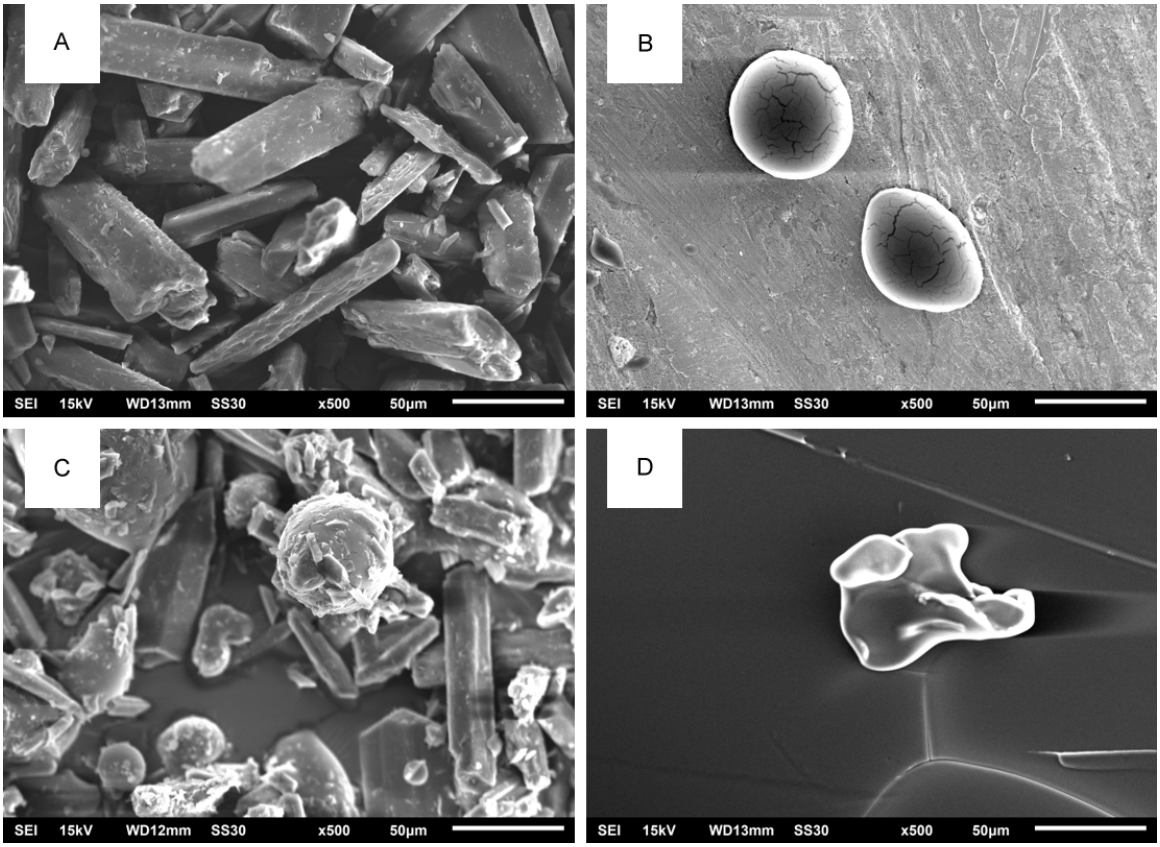

Figure 7. Scanning electron micrographs of LUR (A); SBE-β-CD (B); Physical mixture of LUR and SBE-β-CD (C); Inclusion complex of LUR and SBE-β-CD (D).

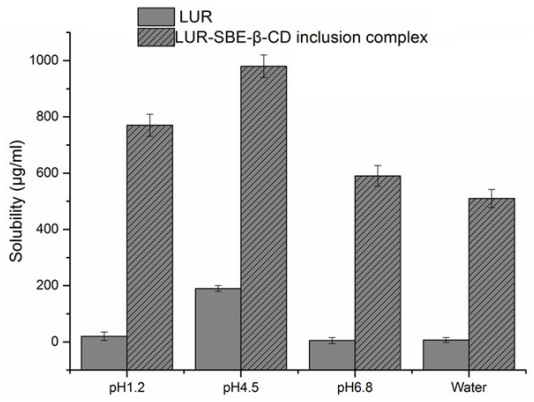

Figure 8. Saturation solubility of LUR and LUR-SBE-β-CD in pH 1.2, 4.5, 6.8 and water (pH 7). All values were shown as mean ± SD (n = 3).

Characterization and solubility studies

FTIR studies: As shown in **Figure 4**, LUR-associated peaks of LUR and physical mixture were nearly identical. The characteristic peak of LUR in LUR-SBE-β-CD at 1687 cm^{-1} was markedly reduced. The diagnostic peaks of LUR in inclusion complexes located at 1562 cm^{-1} and 778 cm^{-1} also disappeared, suggesting LUR-SBE-β-CD was successfully prepared and LUR entered the cavity of SBE-β-CD. In addition, no new chemical bonds were found in LUR-SBE-β-CD, which indicated that there were no chemical reactions in the process.

DSC studies: DSC thermogram of LUR, SBE-β-CD, physical mixture, and LUR-SBE-β-CD are presented in **Figure 5**. LUR has one endothermic peak at 277°C and one exothermic peak at 281°C, while SBE-β-CD has one endothermic peak at 279°C. The DSC curve of the physical mixture was more like an overlap of endothermic peaks from LUR and SBE-β-CD. The curve of LUR-SBE-β-CD revealed the complexation of LUR in SBE-β-CD, indicating that no chemical reactions occurred during the preparation of LUR-SBE-β-CD.

PXRD studies: As can be seen from **Figure 6**, LUR was crystalline as demonstrated by numerous distinct peaks, while no obvious diffraction peaks in SBE-β-CD. The physical mixture of LUR and SBE-β-CD showed multiple diffraction

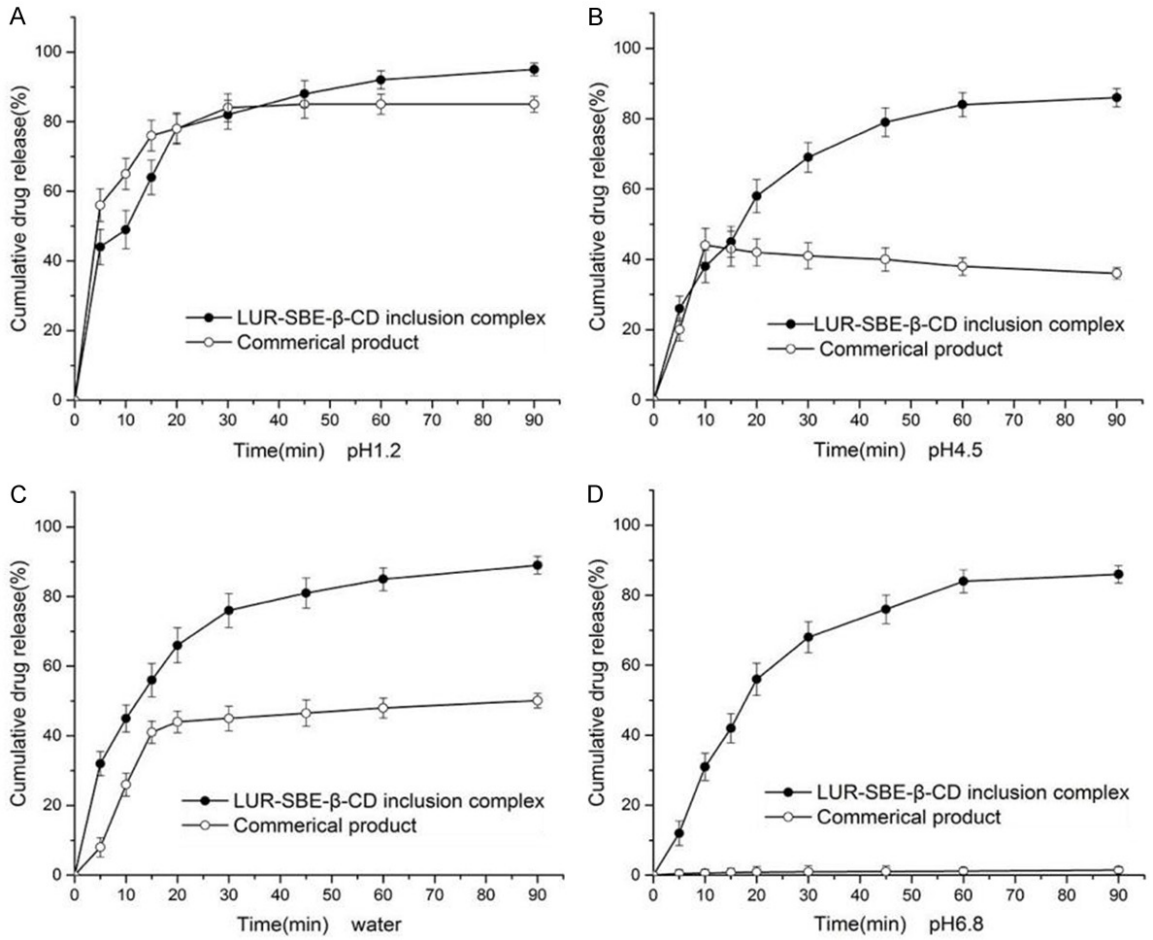

Figure 9. Dissolution profiles of LUR-SBE-β-CD inclusion complex and commercial product in pH 1.2 (A), pH 4.5 (B), water (pH 7) (C) and pH 6.8 (D).

peaks, which could be regarded as the superposition of the diffraction peaks of two substances. On the other hand, the crystalline of the drug in the inclusion complex was reduced or a change was induced in the crystal orientation, illustrating LUR and SBE-β-CD can strongly affect each other.

SEM studies: Morphology of SBE-β-CD exhibited a round and smooth state while obvious crystallite structure was provided with LUR API (**Figure 7A**). The physical mixture (**Figure 7C**) contained individual LUR and SBE-β-CD particles with irregular morphology. No crystallites associated with LUR or heterogeneous phases were observed in LUR-SBE-β-CD (**Figure 7D**), demonstrating the complete entrapment of LUR into the cavities of SBE-β-CD.

Solubility studies: LUR-SBE-β-CD and LUR API were tested in four dissolution mediums (pH 1.2, pH 4.5, pH 6.8 and pH 7) and shown in **Figure 8**. Compared with LUR API, the solubility of LUR in inclusion complex was dramatically enhanced, over 29.8, 5.4, 39.3 and 37 times higher in the different media, which indicated that LUR-SBE-β-CD was a successful formulation to solubilize LUR.

In vitro dissolution studies

Dissolution profiles of LUR-SBE-β-CD and Latuda® in different dissolution mediums were given in **Figure 9**. From the figures, Latuda® acquired the highest cumulative dissolution in pH 1.2 (>85%) and the lowest dissolution in pH 6.8 (<3%). The precipitation would occur when commercial product in pH 4.5 solution. In contrast, LUR-SBE-β-CD showed a higher release characteristic of more than 85% in the four solutions. This revealed that the inclusion complex might diminish the effect of pH variability

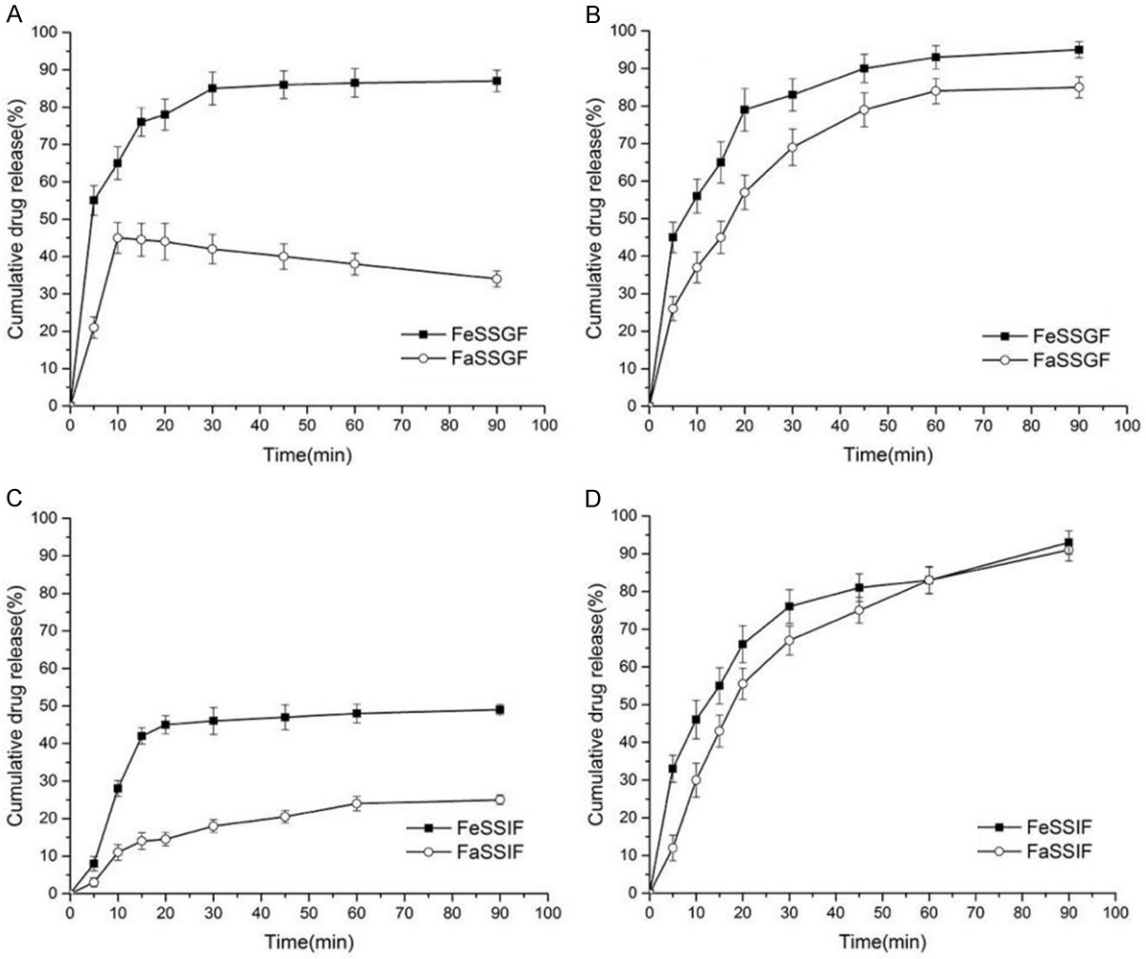

Figure 10. Drug release profiles of commercial product (A: Latuda® in simulated gastric fluid; C: Latuda® in simulated intestinal fluid) and LUR-SBE-β-CD (B: LUR-SBE-β-CD in simulated gastric fluid; D: LUR-SBE-β-CD in simulated intestinal fluid).

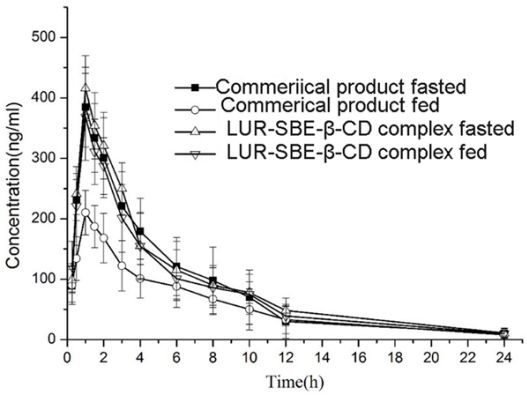

Figure 11. Mean dose-normalized lurasidone concentration-versus-time profiles after administration of LUR-SBE-β-CD complex and commercial product (tablet, Latuda®) in fasted and fed dogs (n = 8).

on LUR. As the results showed, the cumulative dissolution of LUR was increasing when LUR-SBE-β-CD was formed and almost not affected by pH. **Figure 10** describes the *in vitro* dissolution curves of LUR-SBE-β-CD and Latuda®. From **Figure 10A**, the cumulative dissolution of the commercial product was 35% in Fasted State Simulating Gastric Fluid (FaSSGF) and 87% in Fed State Simulating Gastric Fluid (FeSSGF) at 90 min. The precipitation phenomenon appeared and the dissolution rate decreased in the later period. Notably, the commercial products showed an incomplete dissolution and no similarity in FaSSGF and FeSSGF. From **Figure 10B**, the cumulative dissolution of LUR in LUR-SBE-β-CD was 86% in FaSSGF and 96% in FeSSGF. From **Figure 10C**, in FaSSIF/FeSSIF, the cumulative dissolutions of commercial tablets was 25% and 49%, respectively. The release profile of the two drugs *in vitro* was not alike because the value of f_2 value was 30. As **Figure 10D** shows, the cumulative dissolu-

Table 4. Pharmacokinetic values of LUR in beagle dogs after oral administration of LUR-SBE-β-CD complex and commercial product (Latuda®) (n = 8)

	Commercial product (fed)	Commercial product (fasted)	LUR-SBE-β-CD (fed)	LUR-SBE-β-CD (fasted)
C_{max} (ng/ml)	384.9±78.1	210.0±64.5#	415.7±83.9*	368.7±69.9*
T_{max} (h)	1.0±0.5	0.9±0.4	1.0±0.3	0.9±0.6
$AUC_{(0-t)}$ (ng/ml h)	2128±142	1414±91#	2272±154*	2085±133*
$AUC_{(0-\infty)}$ (ng/ml h)	2180±166	1505±101#	2376±155*	2155±120*
Relative bioavailability (%)	100	69.0	109.0	98.8

#P<0.05 compared with Commercial product (fed). *P>0.05 compared with Commercial product (fed).

tion of LUR in the inclusion complex was up to 90%. The similarity factor f_2 of release profiles was 57. Generally, the higher the value of f_2, the more similar the two release profiles. This revealed that the dissolution curves of LUR-SBE-β-CD were similar in FaSSIF/FeSSIF, which diminished the effect of gastrointestinal tract environments and preliminarily proved that food had no influence on LUR-SBE-β-CD. The food effect on LUR could not be completely explained by this study, thus the explanation of potential food interactions was further studied *in vivo* by pharmacokinetics studies in beagle dogs.

Pharmacokinetics studies in dogs

The pharmacokinetic curves of LUR-SBE-β-CD and Latuda® in beagle dogs with food or not are given in **Figure 11** and the pharmacokinetic parameters are presented in **Table 4**. LUR was absorbed rapidly after oral administration. The values of T_{max} of commercial products in fasted and fed states were 1.0±0.5 h and 0.9±0.4 h. Similarly, the values of T_{max} of inclusion complex in fasted and fed state observed from **Table 4** were 1.0±0.3 h and 0.9±0.6 h, respectively. The bioavailability of Latuda® in the fed state was taken as the reference (100%). The relative bioavailability of commercial products in the fasted state was only 69.0%, indicating that absorption of the commercial products was affected by food. In contrast, the relative bioavailability of LUR-SBE-β-CD was the same in fasted (98.8%) and fed (109.0%) states. Statistical analysis reveals that value of C_{max}, AUC (0-t) and AUC (0-∞) of the commercial product was different (P<0.05) in fasted and fed state. However, these parameters were almost the same in the inclusion complex in the two states (P>0.05). This shows that the LUR-SBE-β-CD inclusion complex had successfully improved the oral bioavailability of LUR without taking food; as a result, it was rarely affected by food.

Conclusions

In this research, LUR was poorly soluble in water but was successfully developed to be a novel oral formulation with diminished food effect. The mole ratio of LUR and SBE-β-CD was determined by phase solubility studies. The preparing conditions of the saturated water solution method were successfully optimized by the single-factor test and CCD. Characterization studies proved the formation of LUR-SBE-β-CD. The dissolution test revealed that variational gastroenteric environments and different release mediums almost did not affect the release behaviors of the LUR-SBE-β-CD inclusion complex in comparison with the commercial product. Compared with the commercial product, the bioavailability of inclusion complex exhibited an important enhancement and the food effect on drug absorption could be ignored. Therefore LUR-SBE-β-CD was a developed formulation that could improve the bioavailability of the water-insoluble drugs in the fasted state.

Acknowledgements

This work was supported by the National Science and Technology Major Project (No: 2019zx09301057).

Disclosure of conflict of interest

None.

Address correspondence to: Guoguang Chen and Lili Ren, School of Pharmacy, Nanjing Tech University, 5th Mofan Road, Nanjing 210009, Jiangsu, China. Tel: +86-13701403207; E-mail: guoguangchen@163.com (GGC); Tel: +86-13912979060; E-mail: renlili@njtech.edu.cn (LLR)

References

[1] Abu Hashim II, Ghazy NF and El-Shabouri MH. Potential use of phospholipids in combination with hydrophilic carriers for enhancement of the dissolution and oral bioavailability of imidazole antifungal class II drugs. Pharmazie 2015; 70: 706-715.

[2] Basalious EB and Ahmed MA. Phospholipid based self-nanoemulsifying self-nanosuspension (p-SNESNS) as a dual solubilization approach for development of formulation with diminished food effect: fast/fed in vivo pharmacokinetics study in human. Eur J Pharm Sci 2017; 109: 244-252.

[3] Brewster ME and Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev 2007; 59: 645-666.

[4] Dondapati D, Srimathkandala MH, Sanka K and Bakshi V. Improved solubility and dissolution release profile of lurasidone by solid self-nanoemulsifying drug delivery system. Anal Chem Let 2016; 6: 86-97.

[5] Loftsson T and Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. J Pharm Pharmacol 2010; 62: 1607-1621.

[6] Loftsson T and Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J Pharm Sci 1996; 85: 1017-1025.

[7] Luna EA, Bornancini ER, Tait RJ, Thompson DO, Stobaugh JF, Rajewski RA and Stella VJ. Evaluation of the utility of capillary electrophoresis for the analysis of sulfobutyl ether beta-cyclodextrin mixtures. J Pharm Biomed Anal 1996; 15: 63-71.

[8] Lu S, Yu PP, He JH, Zhang SS, Xia YL, Zhang WL and Liu JP. Enhanced dissolution and oral bioavailability of lurasidone hydrochloride nanosuspensions prepared by antisolvent precipitation-ultrasonication method. Rsc Advances 2016; 6: 49052-49059.

[9] Kumar S, Xu X, Gokhale R and Burgess DJ. Formulation parameters of crystalline nanosuspensions on spray drying processing: a DoE approach. Int J Pharm 2014; 464: 34-45.

[10] Miao Y, Chen G, Ren L and Ouyang P. Controlled release of ziprasidone solid dispersion systems from osmotic pump tablets with enhanced bioavailability in the fasted state. Drug Dev Ind Pharm 2015; 41: 1353-1362.

[11] Madan JR, Pawar KT and Dua K. Solubility enhancement studies on lurasidone hydrochloride using mixed hydrotropy. Int J Pharm Investig 2015; 5: 114-120.

[12] Miao Y, Sun J, Chen G, Lili R and Ouyang P. Enhanced oral bioavailability of lurasidone by self-nanoemulsifying drug delivery system in fasted state. Drug Dev Ind Pharm 2016; 42: 1234-1240.

[13] Martini A, Torricelli C, Muggetti L and Deponti R. Use of dehydrated beta-cyclodextrin as pharmaceutical excipient. Drug Dev Ind Pharm 1994; 20: 2381-2393.

[14] Ogasa M, Kimura T, Nakamura M and Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology (Berl) 2013; 225: 519-530.

[15] Osborne IJ, Mace S and Taylor D. A prospective year-long follow-up of lurasidone use in clinical practice: factors predicting treatment persistence. Ther Adv Psychopharmacol 2018; 8: 117-125.

[16] Rinaki E, Dokoumetzidis A and Macheras P. The mean dissolution time depends on the dose/solubility ratio. Pharm Res 2003; 20: 406-408.

[17] Lurasidone. Aust Prescr 2016; 39: 25-6.

[18] Szejtli J. Medicinal applications of cyclodextrins. Med Res Rev 1994; 14: 353-386.

[19] Sotthivirat S, Haslam JL and Stella VJ. Evaluation of various properties of alternative salt forms of sulfobutylether-beta-cyclodextrin, (SBE)(7M)-beta-CD. Int J Pharm 2007; 330: 73-81.

[20] Sotthivirat S, Haslam JL and Stella VJ. Controlled porosity-osmotic pump pellets of a poorly water-soluble drug using sulfobutyl ether-beta-cyclodextrin, (SBE)(7M)-beta-CD, as a solubilizing and osmotic agent. J Pharm Sci 2007; 96: 2364-2374.

[21] Shono Y, Jantratid E, Janssen N, Kesisoglou F, Mao Y, Vertzoni M, Reppas C and Dressman JB. Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. Eur J Pharm Biopharm 2009; 73: 107-114.

[22] Uehata K, Anno T, Hayashida K, Motoyama K, Hirayama F, Ono N, Pipkin JD, Uekama K and Arima H. Effect of sulfobutyl ether-beta-cyclodextrin on bioavailability of insulin glargine and blood glucose level after subcutaneous injection to rats. Int J Pharm 2011; 419: 71-76.

[23] Wang SM, Han C, Lee SJ, Patkar AA, Masand PS and Pae CU. Asenapine, blonanserin, iloperidone, lurasidone, and sertindole: distinctive clinical characteristics of 5 novel atypical antipsychotics. Clin Neuropharmacol 2013; 36: 223-238.