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Preparation and characterization of simvastatin/DMβCD complex and its pharmacokinetics in rats

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Simvastatin is poorly bioavailable because it is practically insoluble in water and shows dissolution rate-limited absorption. Solubilizing effects of several β-cyclodextrin (βCD) derivatives such as HPβCD, SBEβCD and DMβCD on simvastatin in aqueous solution were investigated using the phase solubility technique. The solubility diagram of simvastatin with each βCD derivative could be classified as AL-type, indicating soluble complex formation of 1:1 stoichiometry. Among the above βCD derivatives DMβCD was found to be the ideal complexing agent for improving drug solubility. The simvastatin complex with DMβCD was prepared using the co-evaporation method and was then characterized by differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FT-IR) and *in vitro* dissolution. Dissolution and pharmacokinetic studies indicated that the simvastatin/DMβCD complex exhibited an increased dissolution rate, rapid absorption, and improved bioavailability in rats compared to free drug. Maximum plasma concentration (c_{max}) and the time to reach it (t_{max}) were 21.86 μg mL^{-1} and 1.4 h for the drug complex, 8.25 μg mL^{-1} and 3.0 h for free drug, respectively. Main pharmacokinetic parameters such as t_{max}, c_{max} were significantly different ($p < 0.01$) between the simvastatin complex and free drug. Bioavailability of the simvastatin complex relative to free drug was up to 167.0 %.

Keywords: simvastatin, DMβCD, complex, solubility, dissolution rate, pharmacokinetics

Simvastatin is a cholesterol lowering agent, which is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase belonging to the class of statins. It is an inactive prodrug that undergoes enzymatic and chemical conversion in the intestine, plasma, and liver to the hydroxy acid form of the drug (SVA), the main pharmacologically active metabolite. After conversion, SVA acts by decreasing cholesterol synthesis and increasing low density lipoprotein catabolism leading to the reduction of cholesterol levels and subsequent

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prevention of coronary heart diseases; simvastatin is therefore widely used to treat hypercholesterolemia (1). As the drug is practically insoluble in water, it is poorly absorbed from the gastrointestinal (GI) tract after oral administration, which results in low bioavailability and also poor clinical efficacy (2, 3). Many methods or techniques such as micronization, solid dispersion, cyclodextrin complexation, microemulsion, liposomes, nanoparticles, phospholipid complex, and self-microemulsifying drug delivery system (SMEDDS), *etc*. have been tried to improve the solubility, dissolution rate and thus oral bioavailability of the drug (4–12).

Cyclodextrins (CDs) are well known molecular entities used as pharmaceutical excipients mainly to modulate the physicochemical and pharmaceutical properties of some drugs, such as increased solubility and dissolution rate, improved chemical stability and bioavailability, reduced toxicity and irritation and controlled rate release (13). In recent years, several important derivatives of βCD, such as hydroxypropyl-β-cyclodextrin (HPβCD), sulfobutylether-β-cyclodextrin (SBEβCD) and dimethyl-β-CD (DMβCD), have gained considerable attention owing to their greater aqueous solubility, higher safety and better complexation ability (14–16). Thus, simvastatin complexation with the above water-soluble βCD derivatives may be an ideal method to solve the problems of poor solubility, dissolution rate and thus low oral bioavailability of the drug.

So far, CDs such as αCD, βCD, γCD, randomly methylated-βCD (RMβCD) and HPβCD have been reported to be able to form inclusion complexes with simvastatin (17, 18). Further, it has been found that the drug/HPβCD complex orally administered to rats displayed higher hypolipidemic activity in terms of total cholesterol serum levels compared to free simvastatin (19). However, optimal CD complexing excipients for improving the solubility and dissolution rate of the drug are unknown and the exact bioavailability of the drug/CD complex following oral dosing has not been reported in the literature. Hence, the objective of this study was to investigate and compare the solubilizing effects of several derivatives of βCD on aqueous solubility of simvastatin. The optimal complexing agent DMβCD was then chosen to prepare a simvastatin complex. DSC, FT-IR and dissolution rate studies were used to characterize the properties of the drug/DMβCD complex. Pharmacokinetics and relative bioavailability of the simvastatin/ DMβCD complex was also evaluated in rats.

EXPERIMENTAL

Materials

Simvastatin of 98.2 % purity was purchased from Jinxin Pharmaceutical Industry Co. (China). βCD of 100.0 % purity, HPβCD of 99.0 % purity (degree of substitution 4.9 and average molecular weight 1419 Da) and SBEβCD of 99.5 % purity (degree of substitution 6.2 and average molecular weight 2115 Da) were all purchased from Shandong Xinda Biotechnology Co., Ltd. (China). DMβCD of 99.6 % purity (degree of substitution 13.0 and average molecular weight 1317 Da) was a gift from Binzhou Zhiyuan Biotechnology Co., Ltd. (China). The HPLC grade acetonitrile was obtained from Beijing Mreda Technology Co., Ltd. (China). All other chemicals and solvents were of analytical reagent grade and used as received without further purification. Deionized double-distilled water was used throughout.

Determination of simvastatin content

Simvastatin content was determined by the reversed-phase high-performance liquid chromatography (RP-HPLC) method with minor modifications (20). The HPLC system consisted of a LC-20AT pump equipped with a SIL-20A autosampler, a SPD-20A ultraviolet-visible detector from Shimadzu (Japan). The analysis was performed at room temperature on a C18 column (250×4.6 mm i.d., 5.0 μm, Japan). The mobile phase was a mixture of 0.025 mol L^{-1} phosphate buffer (pH 4.5) and acetonitrile at a volume ratio of 20/80 (*V*/*V*) and was pumped at a flow rate of 1.0 mL min^{-1}. The injection volume was 20 μL and the detection wavelength was fixed at 238 nm. Quantification was carried out according to the correlation relationship between the chromatographic peak area of the drug (*A*) and its mass concentration (*c*). The obtained calibration equation ($A = 57725c - 12919$, $n = 7$) showed good linearity over the concentration range of 0.22–21.7 μg mL^{-1} with the correlation coefficient of over 0.9995. The lowest limit of quantification (LLOQ) for drug determination was 0.22 μg mL^{-1}. Within-day and between-day precisions of the analytical method were both lower than 2.0 %. The accuracy of drug determination was found to be 99.43 ± 0.75 % ($n = 9$).

Phase solubility studies

To investigate and compare the solubilizing effect of several βCD derivatives, such as HPβCD, SBEβCD and DMβCD, on simvastatin, phase solubility studies were performed according to the method reported by Higuchi and Connors (21). An excess amount of simvastatin was added to 10 mL of aqueous solutions containing increasing concentrations of several of the above β-CD derivatives (each from 0 to 10 mmol L^{-1}) and then shaken in screw capped glass vials at 37.5 °C for 48 h, the time considered sufficient to reach the equilibrium. All the suspensions were withdrawn, filtered through a 0.45 μm syringe filter and properly diluted with water and then analyzed for drug content by the RP-HPLC method, as reported above. The phase solubility diagram was constructed by plotting the drug concentration against the CD concentration. The apparent complexation constant (K_c) of the simvastatin complex with each CD was calculated from the linear graph obtained by plotting the concentration (mmol L^{-1}) of the drug in the solution *versus* CD concentration (mmol L^{-1}) according to the equation: K_c = Slope/[Intercept(1 – Slope)].

*Preparation of simvastatin/DM*β*CD complex*

According to the results of the above phase solubility studies, DMβCD was found to be the optimal complexing excipient for solubilizing simvastatin among all the investigated CDs. Thus, the drug complex with DMβCD at a 1:1 stoichiometric ratio was prepared by the co-evaporation method (22). Accurately weighed simvastatin was dissolved in a minimum volume of acetone, while DMβCD was dissolved in a suitable volume of water. After that, the drug solution was added dropwise and fully mixed with the DMβCD solution in a mortar. The resultant mixture was evaporated at 60 °C to dryness in a vacuum oven. The obtained solid was passed through a 100 mesh sieve for further use. A physical mixture of the drug with DMβCD in the same molar ratio was prepared by simply mixing the two components.

*Confirmation of simvastatin/DM*β*CD complex*

Differential Scanning Calorimetry (DSC) analyses of simvastatin, DMβCD, simvastatin /DMβCD physical mixture (PM) and simvastatin /DMβCD complex were carried out

on a simultaneous thermal analyzer STA 449 F3 Jupiter® (Netzsch-Gerätebau GmbH, Germany). Samples weighing between 5 and 10 mg were loaded into open aluminum pans and placed into the DSC cell. The cell had a nitrogen purge flowing at approximately 20 mL min^{-1}. The DSC was used to analyze the samples from 40–200 °C at a 10 °C/min heating rate. An indium pan served as reference, and all scans were performed in triplicate. The instrument was calibrated before sample analysis using an indium standard.

Fourier-transform infrared (FT-IR) analyses of the samples were performed using a Perkin-Elmer Spectrum Two spectrometer (PerkinElmer Corporation, USA). Simvastatin, DM*β*CD, simvastatin /DM*β*CD PM and simvastatin /DM*β*CD complex was mixed separately with IR grade KBr in the weight ratio of 100:1 for tablet preparation. Final spectra were performed in a range of 400–4000 cm^{-1} with 2 cm^{-1} resolution. All samples were analyzed in triplicate.

Solubility of simvastatin/DMβCD complex

Solubilities of simvastatin and its DM*β*CD complex were determined using water or pH 7.0 phosphate buffer containing 0.5 % (*m*/*V*) SLS as solvents to examine the effect of pH and surfactant on drug solubility. An excess amount of samples was added to 5 mL of water or the pH 7.0 phosphate buffer in glass test tubes sealed with stoppers. The tubes were kept in a thermostatic water bath and shaken at 50 ± 0.5 °C and 50 rpm until reaching equilibrium for a period of 48 h. A portion of solution was withdrawn and then filtered through a 0.45-μm syringe filter and suitably diluted with the mobile phase. Finally, the drug concentration was also analyzed using the above RP-HPLC method.

Dissolution of simvastatin/DMβCD complex

Dissolution studies were conducted using a ZRS-8 intelligence dissolution tester (Tianjin, China) based on the 2015 edition of Chinese Pharmacopoeia, apparatus 2 method. Powders of simvastatin and its DM*β*CD complex equivalent to 10 mg of the drug were placed in 900 mL of pH 7.0 phosphate buffer thermostatically maintained at 37 ± 0.5 °C, using a paddle stirring speed of 100 rpm. At specific time intervals, 5 mL of samples were withdrawn and immediately filtered through a 0.45 μm syringe filter. Meanwhile, an equal volume of the dissolution medium maintained at 37 ± 0.5 °C was added to keep the dissolution medium volume constant. The filtrates were appropriately diluted and subjected to drug analysis using the above HPLC method. The results are reported as the cumulative percent drug dissolved in three replicates.

Animal experiments

Pharmacokinetics and bioavailability of the simvastatin/DM*β*CD complex were performed in comparison with free drug in male Wistar rats (Inner Mongolia University Experimental Animal Center, Hohhot, China), weighing 200–220 g. The study was approved by the Institutional Animal Ethics Committee of Affiliated Hospital, Inner Mongolia Medical University. Throughout the experiment, the animals were housed in plastic cages on corn-cob bedding at room temperature (25 °C) with a 12 h light/dark cycle. The animals were kept in these facilities for at least 1 week before the experiment and fasted for 12 h prior to experiments with free access to water. Twelve rats were randomly divided into two

groups of six animals each. The test and reference groups were given orally 1 mL 100 g^{-1} b.m. of 0.5 % *m*/*V*) CMC aqueous suspension containing free simvastatin or its DMβCD complex at a dose of 50 mg kg^{-1} b.m. *via* gastric gavage needles, respectively. Blood samples of 0.5 mL each were withdrawn into 1.5-mL heparinized PE tubes at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 and 10.0 h following oral dosing by retro-orbital puncture. At the same time, an equal volume of 0.9 % normal saline was given intraperitoneally to rats immediately after each blood sampling. All plasma samples were obtained by centrifuging blood samples at 4,000 rpm for 10 min and were stored at –20 °C until HPLC analysis.

Analysis of simvastatin in plasma

Simvastatin in rat plasma was quantified by the HPLC-UV method according to the reported method with some modifications (23, 24). Briefly, aliquots of 200 μL plasma were pipetted into 5-mL centrifuge tubes, 100 μL of methanol and 20 μL of internal standard (5 μg mL^{-1} lovastatin solution prepared with methanol) were added and vortexed for 2 min. Then, 800 μL of cyclohexane was added, vortexed for 30 s and then centrifuged for 10 min at 4000 rpm. The organic layer was transferred to clean centrifuge tubes and then evaporated under a gentle nitrogen flow at 45 °C until dryness. The residue was reconstituted with 400 μL of methanol, vortexed for 60 s and then centrifuged for 10 min at 4000 rpm. Finally, 20 μL of the supernatant was injected into the HPLC system using an autosampler. Bioanalysis of simvastatin was performed on a Wondasil C18 column (250×4.6 mm, i.d., 5 μm, Japan) with a guard column SuperSustain C18 (10×4.0 mm, i.d., 5 μm, Japan). The mobile phase consisted of acetonitrile, water and acetic acid at a volume ratio of 70/30/0.1 (*V*/*V*) and was set at a flow rate of 1.0 mL min^{-1}. The detection wavelength was fixed at 238 nm. All assays were performed at the column temperature of 30 °C. Quantification was performed according to the peak area ratio of the drug to internal standard ($Y = A_{drug}/A_{IS}$). The obtained calibration equation ($Y = 0.0339c - 0.0123$, $n = 7$) showed good linearity over the concentration range of 0.18–36.7 μg mL^{-1} with the correlation coefficient of over 0.9994. The lowest limit of quantification (*LLOQ*) for drug determination in rat plasma was 0.367 μg mL^{-1}. Accuracy of simvastatin determination in rat plasma was found to be 102.4 ± 4.38 % ($n = 9$). Within-day and between-day precisions of the analytical method were both lower than 10.0 %. Mean extraction recovery of simvastatin in rat plasma was over 90.0 %.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed by means of a model-independent method using the 3P97 pharmacokinetic program issued by the Chinese State Food and Drug Administration. The elimination rate constant (K_{el}) was obtained as the slope of the linear regression of the log-transformed plasma concentration values *versus* time data in the terminal phase. The elimination half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$. Peak concentration (c_{max}) of the drug in plasma as well as the time to reach it (t_{max}) were observed as raw data. The area under the curve to the last measurable concentration ($AUC_{0\text{-}t}$) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0\text{-}\infty}$) was calculated as $AUC_{0\text{-}t}+c_t/K_{el}$, where c_t is the last measurable concentration. Analysis and comparison of the pharmacokinetic parameters of free simvastatin and its DMβCD complex were performed using the SPSS statistical software (version 22.0, SPSS Inc.). $p < 0.05$ was taken as statistically significant.

RESULTS AND DISCUSSION

Phase solubility studies

As shown in Fig.1, the solubility of simvastatin increased linearly as a function of CD concentration. The phase solubility diagram of simvastatin for each CD follows an AL-type according to the Higuchi and Connors classification, suggesting the soluble complex formation of 1:1 stoichiometry over the concentration range (0–10 mmol L^{-1}) investigated. These results are in close agreement with previous reports (19, 25). The apparent complexation constant (K_c) values calculated from the phase solubility diagram were 91895, 53530, 23564 and 4702 L mol^{-1} for DM*β*CD, SBE*β*CD, HP*β*CD and *β*CD complex, respectively. In other words, the host-guest molecular interaction forces between simvastatin and CDs were in the order: DM*β*CD > SBE*β*CD > HP*β*CD > *β*-CD, suggesting that the effect of steric hindrance of the sulfobutylether group in SBE*β*CD or the hydropropyl group in HP*β*CD was greater than that of the methyl group in DM*β*CD (26). Moreover, the solubilizing effect of the above CDs on the drug was also in the order: DM*β*CD > SBE*β*CD > HP*β*CD > *β*-CD. When the concentration of each CD was reached at 10 mmol L^{-1}, the drug solubility showed approximately a 900-fold increase for DM*β*CD, 530-fold increase for SBE*β*CD, 230-fold increase for HP*β*CD and 80-fold increase for *β*CD compared to free simvastatin. Thus, DM*β*CD seems to be the ideal complexing agent for solubilizing the drug.

Confirmation of simvastatin/ DMβCD complex

The DSC thermograms of simvastatin, DM*β*CD, simvastatin/DM*β*CD (PM), simvastatin /DM*β*CD complex are given in Fig. 2. Simvastatin was characterized by a sharp melting endothermic peak at 140.5 °C during DSC analysis and the thermogram of DM*β*CD exhibited a very broad endothermic effect in the temperature range 45–120 °C, which at-

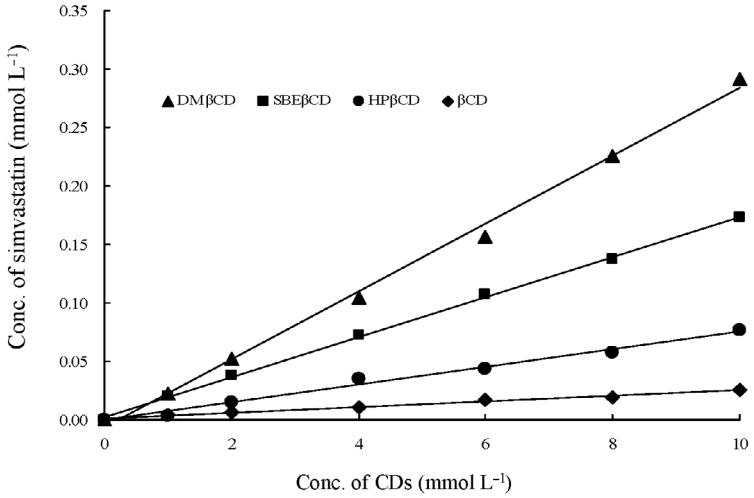

Fig. 1. Phase solubility diagram of simvastatin as a function of CD concentration at 37.5 °C.

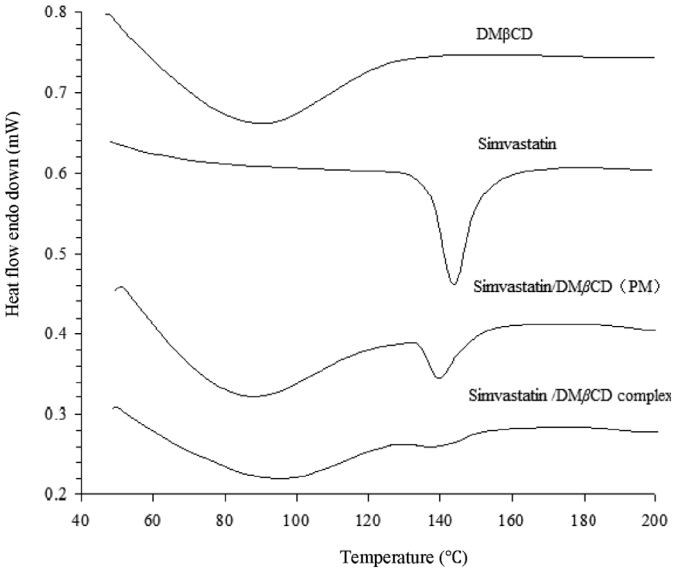

Fig. 2. DSC thermograms of simvastatin, DM*β*CD, simvastatin/DM*β*CD (PM) and simvastatin/DM*β*CD complex.

tained a maximum about 90 °C due to the release of water molecules. The DSC curve of simvastatin/DM*β*CD (PM) shows two peaks: a broad endotherm around 90 °C corresponding to the water loss of DM*β*CD and an endothermal melting peak at 139.5 °C characteristic of the drug. For the simvastatin/DM*β*CD complex, however, the endothermic peak corresponding to the drug almost disappeared and, furthermore, the melting temperature of the drug changed to less than 138 °C, probably revealing conversion of simvastatin crystalline to amorphous form after complexation by DM*β*CD.

The FT-IR spectra of simvastatin, DM*β*CD, simvastatin/DM*β*CD (PM) and simvastatin/DM*β*CD complex are shown in Fig. 3. The characteristic absorption peaks of simvastatin were found at 3545 cm^{-1} (free O–H stretching vibration), 2970 cm^{-1} (methyl C–H stretching vibration), 1723 and 1696 cm^{-1} (stretching vibration of C=O for ester and lactone), 1285 cm^{-1} (lactone –C–O–C stretching vibration) and the FT-IR spectra of DM*β*CD showed prominent absorption bands at 3415 cm^{-1} (O–H stretching vibration) and 2940 cm^{-1} (C–H stretching vibration) and 1175 cm^{-1}, 1010 cm^{-1} (C-H, O–H stretching vibration). In addition, the FT-IR spectra of simvastatin/DM*β*CD (PM) showed no obvious differences from the separate spectra of simvastatin and DM*β*CD, especially as the obvious stretching vibration peak of the carbonyl group for the drug still existed. For the FT-IR spectra of the simvastatin/DM*β*CD complex, however, the characteristic absorption peaks of the carbonyl group of the drug in the range of 1600–1800 cm^{-1} almost disappeared. This can be probably attributed to the complexation of the drug into the DM*β*CD hydrophobic cavity. The above results also indicate that the carbonyl group of lactone ring of simvastatin might be involved in the complexation process (27).

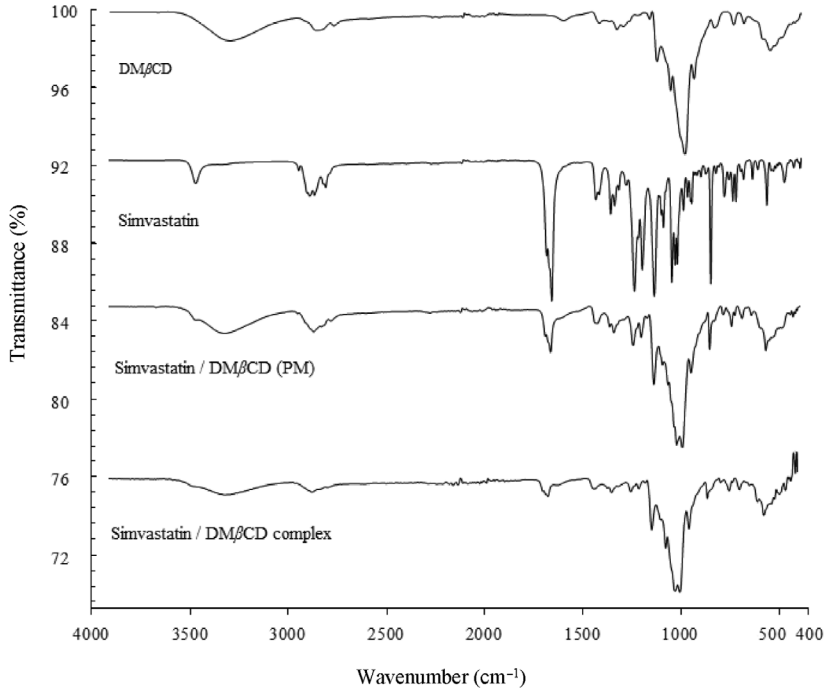

Fig. 3. FT-IR spectra of simvastatin, DM*β*CD, simvastatin/DM*β*CD (PM) and simvastatin/DM*β*CD complex.

Solubility of simvastatin/DMβCD complex

The observed solubilities of free simvastatin and its DM*β*CD complex in distilled water or pH 7.0 phosphate buffer containing 0.5 % SLS are shown in Table I. The solubility of the drug/DM*β*CD complex exhibited a 250-fold increase in water, 2.65-fold increase in pH 7.0 phosphate buffer containing 0.5 % SLS at 50 ± 0.5 °C compared to free drug. The results were very similar to those reported by Aushuman *et al*. (2). According to the chemical

Table I. Solubility of free simvastatin and its DMβCD complex in water and pH 7.0 phosphate buffer containing 0.5 % SLS at 50 ± 0.5 °C

Formulations	Solubility (μg mL^{-1})	
	Water	pH 7.0 phosphate buffer containing 0.5 % SLS
Simvastatin	0.23 ± 0.03	242.5 ± 38.9
Simvastatin/DM*β*CD complex	57.5 ± 19.3[a]	641.8 ± 51.5[a]

Data are represented as mean ± SD (n = 3). [a] $p < 0.01$, compared to free drug.

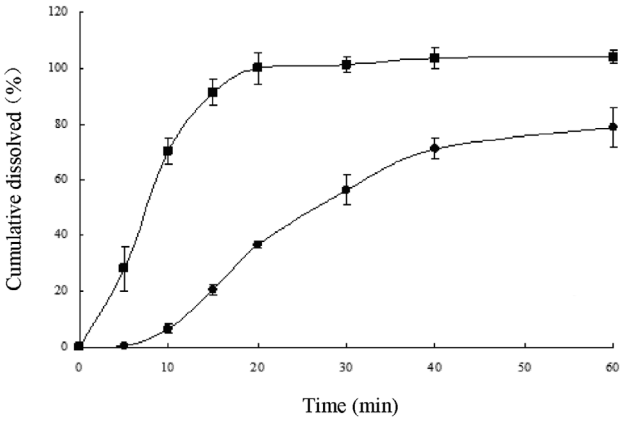

Fig. 4. Dissolution profiles of simvastatin (circles) and its DM*β*CD complex (squares) in pH 7.0 phosphate buffer. Data are represented as mean ± SD (n = 3).

structure of simvastatin, it seems impossible for the drug to convert to salt forms in water or pH 7.0 phosphate buffer. Thus, the obviously increased solubility of free simvastatin in pH 7.0 phosphate buffer containing 0.5 % SLS could be primarily attributed to the solubilizing effect of the surfactant SLS rather than to the effect of medium pH. Since the solubility of simvastatin in water was quite low and the solubilizing effect of SLS on the drug, however, was very significant, the increase in solubility of the simvastatin/DM*β*CD complex was more remarkable in water than in pH 7.0 phosphate buffer containing 0.5 % SLS. In other words, the solubilizing effect on the drug of SLS alone seemed to be more prominent than that of DM*β*CD alone.

Dissolution of simvastatin/DMβCD complex

Fig. 4 shows the dissolution profiles of simvastatin and its DM*β*CD complex. The nearly complete dissolution of simvastatin from the drug/DM*β*CD complex could be reached in 20 min; however, the cumulative dissolution for free drug was less than 40 % at the same time, and lower than 80 % in 60 min. Based on the results of our research, the notably improved dissolution rate of simvastatin might be attributed to the amorphous state, increased wettability of the drug and complex formation with DM*β*CD in aqueous solution (28).

Pharmacokinetic studies

The mean plasma concentration-time profiles after intra-gastric administration of the simvastatin/DM*β*CD complex suspension as well as free drug suspension are illustrated in Fig. 5, while the main pharmacokinetic parameters of the drug are summarized in Table II. From the plasma time profile, very rapid absorption of the drug from the DM*β*CD complex was observed in rats and t_{max} was only approximately 1.4 h. In contrast, the maximum plasma concentration (c_{max}) was achieved in about 3.0 h when free drug was given to rats

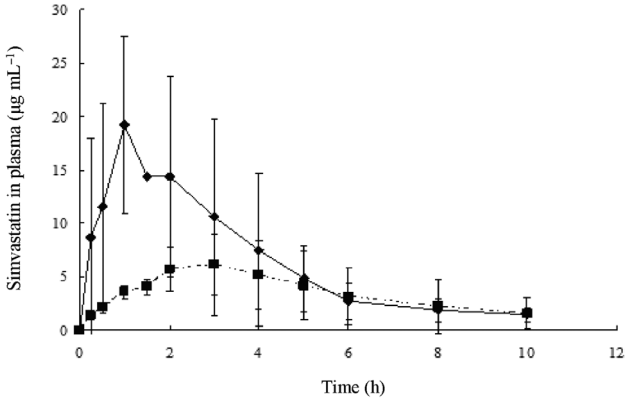

Fig. 5. Mean plasma concentration-time profiles after oral administration of simvastatin/DMβCD complex (diamonds) as well as free drug (squares) at the dose of 50 mg kg^{-1} to rats. Data are represented as mean ± SD (n = 6).

orally. The above results suggested that simvastatin was more easily dissolved and thus absorbed from the drug/DMβCD complex in rats. Furthermore, the obtained c_{max} for the drug complex was found to be approximately 2.5 times higher than that for free drug at a dose of 30 mg kg^{-1}. Moreover, the $AUC_{0-\infty}$values were 72.96 ± 39.94 and 43.68 ± 27.14 μg h mL^{-1} for the drug complex and free drug, respectively. The bioavailability of the drug/DMβCD complex relative to free drug was calculated to be up to 167.0 %, suggesting that complexation of simvastatin by DMβCD resulted in about 1.7-fold higher extent of drug absorption than that of free drug. The faster absorption and increased bioavailability of the drug/DMβCD complex in rats could be probably attributed to the significantly improved aque-

Table II. Pharmacokinetic parameters of simvastatin/ DMβCD complex in rats using free drug as a control

Parameters	Free drug	Simvastatin/DMβCD complex
t_{max} (h)	3.0 ± 0.63	1.42 ± 0.49[a]
c_{max} (μg mL^{-1})	8.25 ± 2.66	21.86 ± 4.89[a]
$t_{1/2}$ (h)	3.22 ± 0.96	3.24 ± 1.35[b]
K_{el} (h^{-1})	0.23 ± 0.07	0.25 ± 0.11[b]
AUC_{0-t} (μg h mL^{-1})	35.27 ± 16.81	66.20 ± 38.50[a]
$AUC_{0-\infty}$ (μg h mL^{-1})	43.68 ± 27.14	72.96 ± 39.94[a]
F_r (%)	167.0 %	

Data are represented as mean ± SD (n = 6). Dose 50 mg kg^{-1}.

[a] $p < 0.01$ or 0.05, [b] $p < 0.05$, compared to the control.

AUC_{0-t} – area under the plasma concentration-time curve from time zero to the time of last measured concentration, $AUC_{0-\infty}$ – area under the plasma concentration-time curve from time zero to infinite, c_{max} – peak concentration; t_{max} – time to reach peak concentration; $t_{1/2}$ – elimination half-life; K_{el} – elimination rate constant.

ous solubility and rapid dissolution rate of simvastatin due to complexation with DMβCD. The results of pharmacokinetic studies were in agreement with those of the pharmacodynamic studies previously reported by Jun *et al*. (19), which proved that the simvastatin/ HPβCD complex showed better reduction of total cholesterol and TG levels than free drug in rats.

CONCLUSIONS

Phase solubility studies demonstrated that the water-insoluble drug simvastatin with several water-soluble βCD derivatives, such as HPβCD, SBEβCD and DMβCD, could be able to form a 1:1 stoichiometric complex in water. Among the above CDs, DMβCD was found to be the ideal complexing agent for improving the drug solubility and it also exhibited the largest complexation ability with the drug. The co-evaporation method was applied to prepare the drug complex with DMβCD. DSC and FT-IR suggested conversion of the simvastatin crystalline nature to amorphous one and the presence of intermolecular hydrogen bonds between the drug and DMβCD. Solubility and dissolution studies indicated that the aqueous solubility and dissolution rate of the drug were obviously enhanced compared to free drug. Furthermore, the pharmacokinetic and bioavailability studies confirmed that the simvastatin/ DMβCD complex showed faster absorption and higher bioavailability than free drug in rats. This could be mainly attributed to the enhanced solubility and increased dissolution due to complexation of the drug with DMβCD. Thus, DMβCD will have a potential to be used for enhancement of solubility and dissolution rate, and thereby bioavailability of the water-insoluble simvastatin.

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