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A promising nanomatrix system of simvastatin for oral delivery: Evaluation *in vitro* and *in vivo*

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Abstract: Because of the low solubility, the oral bioavailability of simvastatin (SV) was poor, which restricted the application in clinic. In order to increase the dissolution and the oral absorption of simvastatin, we prepared a novel solid nanomatrix of SV with pharmaceutical acceptable nano-sized silica and Eudragit®. The nanomatrix was prepared using solvent evaporate method and the formulation was optimized. The X-ray diffraction (XRD) and differential scanning calorimetry (DSC) were used to analyze the physicochemical characterization of the SV nanomatrix. The results indicated that the SV existed in the nanomatrix was in a state of molecule or amorphous form. The optimal formulation, consisted of SV, Eudragit® L100-55 and Sylysia 350 (1:5:5, w/w/w), significantly enhanced the dissolution of SV compared with Zocor. And the relative bioavailability was 272% to Zocor. The oral absorption of simvastatin was enhanced markedly. The SV nanomatrix after storage for 1 year displayed similar performance *in vitro* and *in vivo* with the freshly prepared nanomatrix. The stability of SV nanomatrix achieved the desired objectives. In conclusion, the nanomatrix system described here had superior performance *in vitro* and *in vivo* and was expected to have a promising future as an alternative oral drug delivery system for SV.

Keywords: Simvastatin, nanomatrix, stability, dissolution *in vitro,* bioavailability.

INTRODUCTION

Simvastatin (SV), a pro-drug of simvastatin acid, is suitable for hyper-cholesterolemia and cardiovascular diseases in clinic (Affandi *et al.*, 2017). Because of the poor solubility of simvastatin (about 1.5μg/mL) and the extensive first pass effect, the oral bioavailability of simvastatin was unsatisfactory (<5%) (Elkadi *et al*., 2017). Therefore the clinical application of simvastatin was restricted. Recent studies show that simvastatin has additional pharmacological properties such as endothelial protection, antioxidant, anti-inflammatory effects, antitumor and the anabolic effect on bone (Nath *et al*., 2013). Therefore, in order to obtain a superior application, several alternative delivery systems of simvastatin have been investigated, including solid dispersion (Lu *et al*., 2014), transdermal film (Parhi and Suresh, 2016), self-micro emulsifying drug delivery system (Karim *et al.,* 2015), lipid nanoparticles and nanostructured lipid carrier (Tiwari and Pathak, 2011), micro spheres (Nath *et al*., 2013) and inclusion compound (Ungaro *et al*., 2011).

The problem on the dissolution of simvastatin was partially solved by the previous explorations. However, some challenges, such as long-term stability, drug loading capacity, the safety of the ingredients, industrial scale production, still existed. Therefore, it is crucial to develop a suitable system for oral delivery of simvastatin.

It is well known that for the poor water-soluble drugs, the dissolution within the gastrointestinal (GI) tract was inefficient and then lead to a low absorption. Researchers have paid more and more attentions to resolve the problems. Fortunately, the nanotechnology based formulations possessed various advantages. The nanotechnology involves two strategies: (1) preparing the drug itself as nano-sized particles (Liu *et al*., 2015; Bonhoeffer *et al*., 2017; Yu *et al*., 2017) and (2) nanocarrier materials utilized to form nanoparticle (Zhang *et al*., 2015; Biswas, 2016).

The (2) method with nanocarriers was appropriate to a wide range of drugs (Jia *et al*., 2011; Dai *et al*., 2015; Alexander *et al*. 2016). And more and more pharmaceutical materials with nano-structures such as colloidal silicon dioxide (Sylysia or Aerosil) (Khanfar and Al-Nimry, 2017), calcium silicate (Florite) (Kim *et al*., 2017), magnesium aluminum silicate (Lai *et al*., 2017), MCM-41 (Bukara *et al*., 2016) and SBA-15 (Wang *et al*., 2012) were investigated as drug delivery system to increase the drug dissolution and bioavailability. Therefore, we intended to prepare a new formulation of simvastatin with nanocarriers to improve the dissolution *in vitro* and oral bioavailibility.

In the paper, we prepared a novel nanomatrix delivery system of simvastatin. The safe and acceptable excipients in pharmacy were selected to construct the solid nanomatrix. The formulation optimization, physic-cochemical properties, *in vitro* dissolution and the oral bioavailibility were studied to evaluate the SV nanomatrix system.

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Table 1: Simvastatin nanomatrix prepared for the formulation optimization

No.	SV (mg)	A200 (mg)	A300 (mg)	S350 (mg)	EL100-55 (mg)	Formulations
1	100		100		300	SV:A300:EL100-55 = 1:1:3
2	100		300		300	SV:A300:EL100-55 = 1:3:3
3	100		500		300	SV:A300:EL100-55 = 1:5:3
4	100		300		100	SV:A300:EL100-55 = 1:3:1
5	100		300		300	SV:A300:EL100-55 = 1:3:3
6	100		300		500	SV:A300:EL100-55 = 1:3:5
7	100	500			500	SV:A200:EL100-55 = 1:5:5
8	100		500		500	SV:A300:EL100-55 = 1:5:5
9	100			500	500	SV:S350:EL100-55 = 1:5:5

Table 2: Pharmacokinetic parameters of simvastatin acid after oral administration of nanomatrix or Zocor at a dose of 20 mg/Kg in rats (n=5)

Formulation	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-10} (μg·h/mL)
Nanomatrix-1	3.72 ± 0.49 **	1.78 ± 0.54 *	12.46 ± 1.51**
Nanomatrix-2	3.77 ± 0.65 **	1.72 ± 0.46 *	12.81 ± 1.38 **
Nanomatrix-3	2.69 ± 0.51 *	1.66 ± 0.51 *	9.43 ± 1.05 *
Zocor	1.41 ± 0.35	2.39 ± 0.33	4.71 ± 0.84

Nanomatrix-1: the formulation containing S350 storaged for 1 year (SV:S350:EL100-55=1:5:5),
Nanomatrix -2: the formulation containing S350 newly prepared (SV:S350:EL100-55=1:5:5),
Nanomatrix -3: the formulation containing A300 (SV:A300:EL100-55=1:5:5),
* $p < 0.05$ versus Zocor group; ** $p < 0.01$ versus Zocor group.

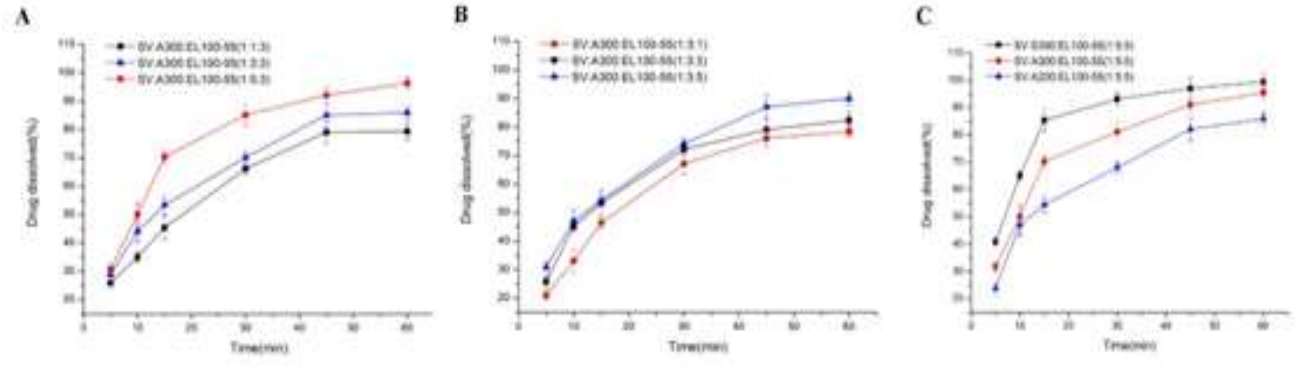

Fig. 1: Dissolution profiles of simvastatin from different formulations. (A) containing different content of A300; (B) containing different content of EL100-55; (C) containing different kinds of colloid silica. Data are expressed as means ± SD. (n=3)

MATERIALS AND METHODS

Materials and animals

Simvastatin and simvastatin acid was purchased from Hubei Prosperity Galaxy Chemical Co., LTD, (Hubei, China). Eudragit L100-55 (EL100-55), Eudragit L100 (EL100), Eudragit S100 (ES100), Aerosil 200 (A200) and Aerosil 300 (A300) were donated by Evonik Corporation (Germany). Sylysia 350 (S350) was supplied by Fuji Silysia Co., Ltd (Japan). HPLC-grade methanol was purchased from tjconcord Co., Ltd. (Tianjin, China). All other chemicals were of analytical grade.

Male Sprague-Dawley (SD) rats (190±10g), were provided by Laboratory Animal Center of Henan university of science and technology. All care and handling of animals were performed with the approval of Ethics Committee of Henan University of Science and Technology.

HPLC analysis of simvastatin in vitro

The concentrations of simvastatin were detected by a HPLC system (LC 2000, Techcomp, Shanghai, China) with a ultraviolet detector (LC2030, Techcomp, Shanghai, China). The mobile phase was a mix system of methanol and deionized water (90:10, *v/v*). And a reversed phase column (Diamosil C18, 200×4.6mm, 5.0μm) was used to separate simvastatin at 30°C. The flow rate, sample volume and the detection wavelength were 1.0mL/min, 20μL and 235nm, respectively. The analytical method was fully validated (data not shown).

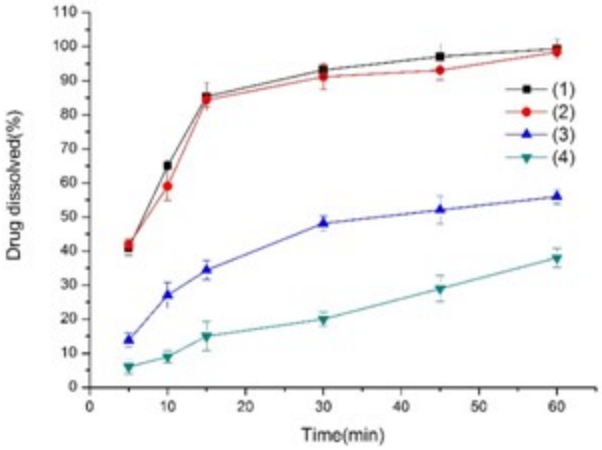

Fig. 2: Dissolution curves of simvastatin from different formulations. (1) nanomatrix newly prepared; (2) Nanomatrix after 1 year of storage; (3) Zocor; (4) crude simvastatin powder. Data are expressed as means ± SD. (n=3)

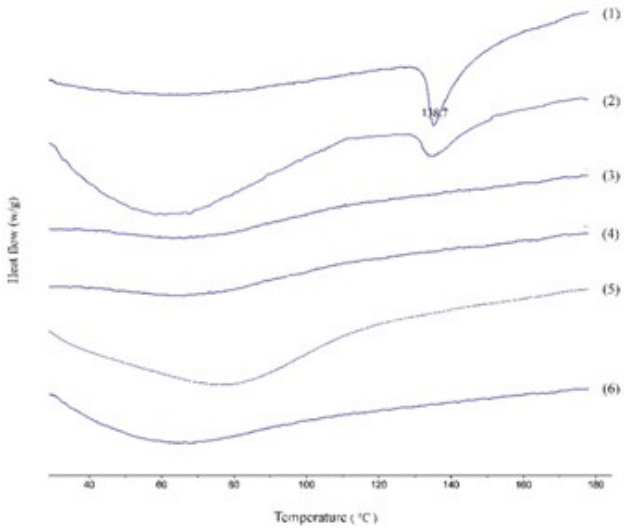

Fig. 3: DSC patterns of (1) simvastatin; (2) physical mixture of SV, EL100-55 and S350 (1:5:5); (3) Nanomatrix containing SV, EL100-55 and S350 (1:5:5); (4) Nanomatrix after 1 year storage; (5) EL100-55; (6) S350.

Preparation of simvastatin nanomatrix

The nanomatrix of simvastatin containing Eudragit® and the nanocarrier colloidal silica was simply prepared by the rotary evaporation method. In brief, 100mg of simvastatin was dissolved in 30mL absolute ethanol. Then Eudragit® (EL100-55, EL100 or ES100) according to the formulation was slowly added to the simvastatin solution and stirred until dissolved. And then the silica (A200, A300 or S350) was suspended into the above solution and mixed under the condition of stirring (1,000 rpm, 10 min) and ultra-sonication (100W, 30 min). Finally, the solvent ethanol was removed thoroughly by a rotary evaporator under reduced pressure at 40°C to form the solid powder, which was further pulverized and then passed through a 100-mesh sieve to obtain simvastatin nanomatrix.

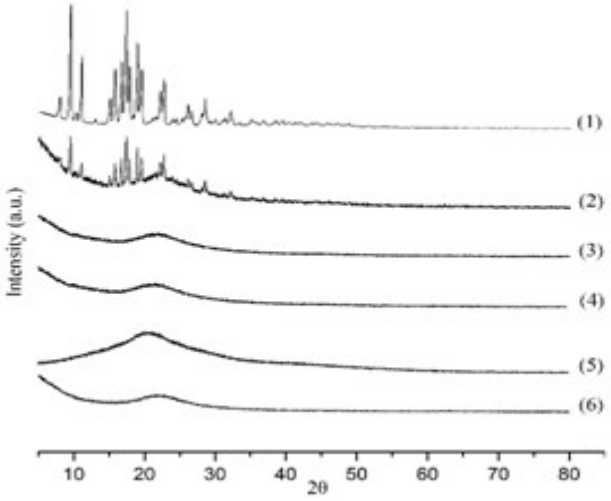

Fig. 4: X-ray diffraction patterns of (1) simvastatin; (2) physical mixture of SV, EL100-55 and S350 (1:5:5); (3) Nanomatrix containing SV, EL100-55 and S350 (1:5:5); (4) Nanomatrix after 1 year storage; (5) EL100-55; (6) S350.

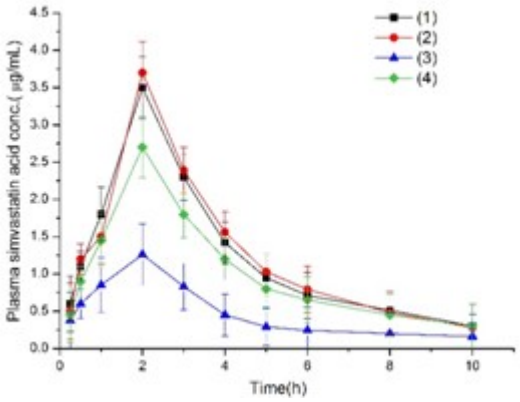

Fig. 5: Average plasma drug concentration-time profiles of simvastatin acid after oral administration of nanomatrix or Zocor at a dose of 20mg/Kg in rats. (1): nanomatrix containing S350 storaged for 1 year (SV:S350:EL100-55=1:5:5), (2): nanomatrix containing S350 newly prepared (SV:S350:EL100-55=1:5:5), (3): Zocor, (4): nanomatrix containing A300 (SV:A300:EL100-55=1:5:5). Data are presented as means ± SD. (n = 5)

In vitro dissolution study

The dissolution tests were carried out using a paddle dissolution apparatus (ZRS-8G, Tianjin Tianda Tianfa Technology Co. Ltd Co., China) as reported in the literature with a little modification (Jia *et al*., 2011). The simvastatin nanomatrix (equivalent to 40mg simvastatin) was suspended in 900mL dissolution medium (phosphate buffer solution containing 0.3% sodium dodecyl sulphate, pH 7.0) at 37°C and 100 rpm. At the specified time points (5, 10, 15, 30, 45 and 60min), 5mL dissolution medium

was take out and replaced by the equal volume of fresh dissolution medium. The samples obtained were filtered using a 0.45μm membrane and analyzed according to the HPLC method described above. The experiment was performed in triplicate.

Differential scanning calorimetry (DSC)

The thermal analysis of simvastatin, S350, EL100-55, physical mixture and simvastatin nanomatrix were performed using a Q100 DSC thermal analysis system (Thermal Analysis Co., USA). Samples were sealed in aluminum pans and then heated from 30°C to 180°C at a scanning rate of 5°C/min under a dry nitrogen flow (20 mL/min).

X-ray diffraction (XRD)

The X-ray diffracto gram of each sample was scanned with a D8 ADVANCE X-ray diffractometer (Bruker Co., Germany), which was equipped with the Cu-alpha radiation source filtered by a nickel foil. The tube was run at a power of 40kV voltage and 40 mA current. The range of diffraction angle was 5°-80° and the increasing step was 0.02°.

Bioavailability and pharmacokinetics study

Animals and Dosing Protocol

Male SD rats were randomly divided into 3 groups (5 rats per group). After fasted for 12h with free access to water, the rats were administered with different simvastatin nanomatrixs by gavage, Zocor as a reference. The single dose of simvastatin for all the groups was 20mg/Kg. At specified time points, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, and 10 h after administration, 0.5mL blood samples were taken out from the orbital venous plexus and placed into heparinized tubes. The plasma was immediately separated by centrifugation (5,000 rpm, 10 min) and stored at -20°C until analysis.

Plasma Processing and Analysis

Plasma processing in the study was performed according to the literature and made a little modification (Karim *et al*., 2015). And simvastatin in each sample was detected by HPLC method. Briefly, 100μL plasma was mixed with 400μL acetonitrile, 50μL internal standard solution (lovastatin, 1μg/mL), and 50μL phosphoricacid solution (pH6.0), and then vortexed for 2 min. After centrifugation (10,000 rpm, 10 min), the supernatant was removed and dried under nitrogen at 40°C. The residue was restructured with 50μL of mobile phase to detect the simvastatin acid with the HPLC system. The HPLC system described above was employed here, except that the separation was carried out using a Diamosil C18 column (200×4.6mm, 5.0μm) with a C18 guard column (12.5×4.6mm, Phenomenex). The mix system of acetonitrile and 5mM ammonium acetate (90:10, v/v) was used as the mobile phase. For the method validation, 380μL acetonitrile and 20μL simvastatin acid solution instead of 400μL acetonitrile were added to the blank plasma. The limit of detection (LOD) and the limit of quantitation (LOQ) were 0.01 and 0.05μg/mL, respectively. The standard curve was linear in the range of 0.1-4.0μg/mL (r=0.9995). The intra- and inter-day relative standard deviation was below 5% and the recovery values of 95-105 % verified the accuracy of the method.

Pharmacokinetic parameters

According to the standard non-compartment model, DAS software (ver. 2.1.1, Mathematical Pharmacology Professional Committee of China) was used to calculate the pharmacokinetic parameters, including time of maximum concentration (t_{max}), maximum plasma concentration (C_{max}), and area under the concentration-time curve (AUC_{0-10}).

Stability study

The simvastatin nanomatrix prepared according to the optimized formulation was stored in sealed EP tube at room temperature. After 1 year, the DSC, XRD, drug dissolution *in vitro* and bioavailibility studies were carried out.

STATISTICAL ANALYSIS

Quantitative data were presented as mean ± standard deviation (SD). Statistical comparison between test and control group was evaluated by the two-tailed Student's *t* test or a two way analysis of variance (ANOVA) with SPSS 20.0. A *p* value less than 0.05 was regarded as significance, while less than 0.01 was high significance.

RESULTS

The preparation of simvastatin nanomatrix

Different simvastatin nanomatrixs were prepared according to the formulations listed in table 1. In the study, we aimed to prepare a SV nanomatrix with fast dissolution rather than enteric behavior. So drug dissolution behavior was used as the evaluate index to optimize the formulation. EL100-55 could maintain the supersaturated status of poor soluble drugs and was benefit for the drug dissolution. Therefore, EL100-55 was added in the nanomatrix. The effects of the ratios (silica to SV and Eudragit® to SV) and different kinds of silica (A200, A300, S350) on the drug dissolution behavior were investigated. And the dissolution curves were shown in fig. 1. From the results shown in fig. 1, we could see that the drug dissolution increased as the ratio of A300 to SV increased (fig.1A). The similar phenomenon was observed for EL100-55 (fig.1B). For the different silica, the formulation contained S350 displayed the best dissolution behavior (fig.1C). The results above indicated that when the ratios of silica to SV and Eudragit to SV were up to 5:1, the drug dissolution in the system reached the best state. So, SV: S350: EL100-55 = 1: 5: 5 as the optimal formulation was used for the further study.

In vitro dissolution test

In order to investigate the dissolution enhancement of the SV nanomatrix system, *in vitro* dissolution studies were carried out in the study fig. 2 illustrated the dissolution behaviour of simvastatin from different formulations in PBS solution. It indicated that the dissolution of SV with poor solubility was greatly increased. In terms of the dissolution rate, the sequence for different formulation was as follow: crude simvastatin powder <Zocor <nanomatrix and nanomatrix stored for 1 year. The result suggested that crude simvastatin powder displayed the poorest dissolution, and the commercial product possessed superior dissolution behavior. When the drug was prepared into nanomatrix, the dissolution increased further, which was the same as expected. After 1 year of storage, the SV nanomatrix kept almost same dissolution behavior, which confirmed the physical stability of SV nanomatrix system.

Differential scanning calorimetry (DSC)

The DSC thermograms of simvastatin, S350, EL100-55, physical mixture and simvastatin nanomatrix were shown in fig. 3. A sharp negative peak at about 140°C appeared in the thermogram of simvastatin, which was consistent with the melting point of simvastatin. The excipients (S350 and EL100-55) showed no characteristic endothermic peak because of their amorphous states. A similar but gentle peak appeared at the same position in the thermograms of the physical mixture. The result suggested that simvastatin crystal existed in the sample. Because A300 and EL100-55 was included in the physical mixture, simvastatinn was diluted to less than 10% of the mixture, which lead to the weak peak intensity. In the thermograms of simvastatin nanomatrix, both of the samples of newly prepared and stored for one year, the melting peaks were absent. The results suggested that simvastatin in the nanomatrix was in a molecular or amorphous state and the state of simvastatin did not change during the storage. That is to say, the simvastatin nanomatrix possessed good physical stability.

X-ray diffraction (XRD)

Fig. 4 displayed the X-Ray diffractograms of different samples. As shown in fig. 4, several intensive diffraction peaks exhibited in the diffractograms of simvastatin due to the unique crystalline structure. Because of the amorphous state of EL100-55 and S350, no diffraction peak appeared in their diffractograms. What's more, we could see that the characteristic diffraction peak of simvastatin also evidently appeared in the diffractiongram of the physical mixture. It could be regarded as simple superposition of pure drug, EL100-55 and S350. However, the characteristic diffraction peaks of simvastatin in the nanomatrix thoroughly disappeared. The result suggested that simvastatin was highly dispersed in the nanomatrix in the form of noncrystalline state. No diffraction peak appeared in nanomatrix after 1 year storage, which proved here that EL100-55 and S350 in the formulation could inhibit the change of simvastatin from noncrystalline to the crystalline state and then maintained enough physical stability (Gao *et al.*, 2016).

Oral bioavailability and pharmacokinetics study

The oral absorption of SV nanomatrix were evaluated compared with Zocor. Simvastatin acid metabolized from simvastatin *in vivo* was detected. The plasma drug concentration-time profiles of simvastatin acid in different groups were shown in fig. 5. And the related pharmacokinetic parameters were displayed in table 2. The oral administration of SV nanomatrix according to the optimal formulation resulted in fastest absorption (t_{max} =1.72h), highest C_{max} (3.77μg/mL) and AUC_{0-10} (12.81 μg/mL·h). In contrast, the commercial product, Zocor showed slowest absorption, lowest C_{max} and AUC_{0-10}. The relative bioavailability was up to 272% in comparison with Zocor. The oral bioavailability of SV in nanomatrix was markedly increased. That is to say, the difference of bioavailability between the nanomatrix and Zocor was highly significant (p<0.01). It was worth noting that, when S350 was replaced by A300, the C_{max}, T_{max} and AUC_{0-10} decreased, respectively and the relative bioavailability was 136% between the two formulations. The results suggested that the nanomatrix including S350 was superior to that of A300, which was consistent with the dissolution study above and the previous studies (Dai *et al.*, 2015). In conclusion, the SV nanomatrix prepared according to the optimized formulation exhibited superior performance *in vivo*.

It is worthy of note that the SV nanomatrix after 1 year of storage displayed the similar behavior *in vivo* and pharmacokinetic parameters with the nanomatrix freshly prepared. And the relative bioavailability was 103%. The results suggested that the stability of SV nanomatrix was satisfactory and was also in accordance with the results of dissolution *in vitro*.

DISCUSSION

It was well known that the silica and polymers could make drugs highly dispersed in the system and increased the dissolution (Alexander *et al.,* 2016). Different kinds of Eudragit (EL100-55, EL100, ES100) could maintain the supersaturated status of poor soluble drugs and the enteric dissolution behavior was not needed. What's more, the effect of the three kinds of Eudragit on the drug dissolution was similar reported by the literature (Jia *et al.,* 2011). Therefore, EL100-55 was selected in the experiments. The prepare of SV nanomatrix was simple, however we found that if the polymer, Eudragit, absented in the formulation, only silica and simvastatin, the materials were apt to gather and then prevented the preparation. While, if only the polymer and simvastatin included, the sample was too sticky to handle. So, the

ratios were set as 1:1, 1:3, 1:5, respectively, to investigate the effect of the ratios on the drug dissolution.

Both XRD and DSC analysis confirmed the molecular or amorphous state of SV in the nanomatrix system. This might be attributed to the excipients in the nanomatrix which had the adsorption effect and the high dispersion effect and inhibited the crystallization of simvastatin (Miura *et al*., 2011). And the results also explained the superior dissolution behavior of simvastatin nanomatrix.

From the dissolution test and bioavailability study, we could see that SV nanomatrix prepared according to the optimal formulation exhibited superior performance *in vitro* and *in vivo*. It could be explained from several aspects. Firstly, SV highly dispered in the nanomatrix in a molecule or amorphous state, which mainly attributed to the huge internal and external surface area of S350. Secondly, the bioadhesive EL100-55 could maintain the supersaturation of the drug and prolong the time of the nanomatrix staying on the small intestinal mucosa (Di Nunzio *et al*., 2008; Miller *et al.*, 2008; Jia *et al*., 2011; Ikram *et al*., 2015; Kenechukwu and Momoh, 2016). Thirdly, the potential first pass metabolism could be effectively decreased by the pH-sensitive character of EL100-55 (Elzayat *et al.*, 2016; Hasan *et al*., 2016). And the colloidal silica and Eudragit played the role of protection for drugs (Palanikumar *et al*., 2015), which was the primary cause for the superior stability of the nanomatrix system.

CONCLUSION

In the study, we prepared a novel simvastatin nanomatrix for oral delivery using mesoporous materials as carriers. The optimal formulation was obtained as follow: SV: S350: EL100-55 =1: 5: 5. The mesoporous materials S350 and EL100-55 containing in the formulation were accepted in pharmaceutical field. These made the nanomatrix apt to be industrialized. In the nanomatrix, SV was highly dispersed in a molecule or amorphous state. The optimal SV nanomatrix proved a superior dissolution and absorption performance compared with the commercial product. And the stability was also satisfactory. In conclusion, the nanomatrix can be expected as an ideal delivery system of SV for oral administration and has a promising future.

REFERENCES

Affandi MM, Tripathy M and Majeed A (2017). Arginine complexes with simvastatin: Apparent solubility, *in vitro* dissolution and solid state characterization. *Curr Drug Deliv.*, **15**(1): 77-86.

Alexander GC, Vines JB, Hwang P, Kim T, Kim JA, Brott BC, Yoon YS and Jun HW (2016). Novel multifunctional nanomatrix reduces inflammation in dynamic conditions *in vitro* and dilates arteries *ex vivo*. *ACS Appl. Mater Inter*, **8**(8): 5178-5187.

Biswas N (2016). Modified mesoporous silica nanoparticles for enhancing oral bioavailability and antihypertensive activity of poorly water soluble valsartan. *Eur. J. Pharm. Sci.*, **99**: 152-160.

Bonhoeffer B, Kwade A and Juhnke M (2017). Impact of formulation properties and process parameters on the dispensing and depositioning of drug nanosuspensions using micro-valve technology. *J. Pharm. Sci-US*., **106**(4): 1102-1110.

Bukara K, Schueller L, Rosier J, Daems T, Verheyden L, Eelen S, Martens JA, Van den Mooter G, Bugarski B and Kiekens F (2016). *In vivo* performance of fenofibrate formulated with ordered mesoporous silica versus 2-marketed formulations: A comparative bioavailability study in beagle dogs. *J. Pharm. Sci*., **105**(8): 2381-2385.

C DiNunzio J, A Miller D, Yang W, W McGinity J and Williams R (2008). Amorphous compositions using concentration enhancing polymers for improved bioavailability of itraconazole. *Mol. Pharm*., **5**(6): 968-980.

Dai W, Guo Y, Zhang H, Wang X and Zhang Q (2015). Sylysia 350/Eudragit S100 solid nanomatrix as a promising system for oral delivery of cyclosporine A. *Int. J. Pharm*., **478**(2): 718-725.

Elkadi S, Elsamaligy S, Al-Suwayeh S and Mahmoud H (2017). The development of self-nanoemulsifying liquisolid tablets to improve the dissolution of simvastatin. *AAPS Pharm. Sci. Tech*., **18**(7): 1-12

Elzayat EM, Abdel-Rahman AA, Ahmed SM, Alanazi FK, Habib WA and Sakr A (2016). Multiple response optimization of processing and formulation parameters of Eudragit RL/RS-based matrix tablets for sustained delivery of diclofenac. *Pharm. Dev. Technol*., **1**:1-11.

Gao Y, Xie Y, Sun H, Zhao Q, Zheng X, Wang S and Jiang T (2016). Effect of pore size of three-dimensionally ordered macroporous chitosan-silica matrix on solubility, drug release and oral bioavailability of loaded-nimodipine. *Drug Dev. Ind. Pharm*., **42**(3): 464-472.

Hasan AA, Sabry SA, Abdallah MH and El-Damasy DA (2016). Formulation and in vitro characterization of poly(dl-lactide-co-glycolide)/Eudragit RLPO or RS30D nanoparticles as an oral carrier of levofloxacin hemihydrate. *Pharm. Dev. Technol*., **21**(6): 655-663.

Ikram M, Gilhotra N and Gilhotra RM (2015). Formulation and optimization of mucoadhesive buccal patches of losartan potassium by using response surface methodology. *Adv. Biomed. Res*., **4**(3): 239.

Jia Z, Lin P, Xiang Y, Wang X, Wang J, Zhang X and Zhang Q (2011). A novel nanomatrix system consisted of colloidal silica and pH-sensitive polymethylacrylate improves the oral bioavailability of fenofibrate. *Eur. J. Pharm. Biopharm*., **79**(1): 126-134.

Karim FT, Kalam A, Anwar R, Miah MM, Rahman MS

and Islam SM (2015). Preparation and evaluation of SEDDS of simvastatin by *in vivo, in vitro* and ex vivo technique. *Drug Dev. Ind. Pharm*., **41**(8): 1338-1342.

Kenechukwu FC and Momoh MA (2016). Formulation, characterization and evaluation of the effect of polymer concentration on the release behavior of insulin-loaded Eudragit((R))-entrapped mucoadhesive microspheres. *Int. J. Pharm. Investig*., **6**(2): 69-77.

Khanfar M and Al-Nimry S (2017). Stabilization and amorphization of lovastatin using different types of silica. *AAPS Pharm. Sci. Tech*., 1**8**(6): 2358-2367.

Kim KS, Yang ES, Kim DS, Kim DW, Yoo HH, Yong CS, Youn YS, Oh KT, Jee JP, Kim JO, Jin SG and Choi HG (2017). A novel solid self-nanoemulsifying drug delivery system (S-SNEDDS) for improved stability and oral bioavailability of an oily drug, 1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol. *Drug Deliv*., **24**(1): 1018-1025.

Lai J, Lin W, Scholes P and Li M (2017). Investigating the effects of loading factors on the in vitro pharmaceutical performance of mesoporous materials as drug carriers for ibuprofen. *Materials*, **10**(2): 150.

Liu D, Pan H, He F, Wang X, Li J, Yang X and Pan W (2015). Effect of particle size on oral absorption of carvedilol nanosuspensions: *In vitro* and *in vivo* evaluation. *Int. J. Nanomed*, **10**: 6425-6434.

Lu Y, Tang N, Lian R, Qi J and Wu W (2014). Understanding the relationship between wettability and dissolution of solid dispersion. *Int. J. Pharm*., **465**(1-2): 25-31.

Miller DA, DiNunzio JC, Yang W, McGinity JW and Williams RO (2008). Targeted intestinal delivery of supersaturated itraconazole for improved oral absorption. *Pharm Res-DORDR*, **25**(6): 1450-1459.

Miura H, Kanebako M, Shirai H, Nakao H, Inagi T and Terada K (2011). Stability of amorphous drug, 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H- pyridazin-3-one, in silica mesopores and measurement of its molecular mobility by solid-state (13)C NMR spectroscopy. *Int. J. Pharm*., **410** (1-2): 61-67.

Nath SD, Son S, Sadiasa A, Min YK and Lee BT (2013). Preparation and characterization of PLGA microspheres by the electrospraying method for delivering simvastatin for bone regeneration. *Int. J. Pharm*., **443**(1-2): 87-94.

Palanikumar L, Kim HY, Oh JY, Thomas AP, Choi ES, Jeena MT, Joo SH and Ryu JH (2015). Noncovalent surface locking of mesoporous silica nanoparticles for exceptionally high hydrophobic drug loading and enhanced colloidal stability. *Biomacromolecules*, **16**(9): 2701-2714.

Parhi R and Suresh P (2016). Formulation optimization and characterization of transdermal film of simvastatin by response surface methodology. *Mater Sci. Eng. C-Mater*, **58**(C-7): 331-341.

Tiwari R and Pathak K (2011). Nanostructured lipid carrier versus solid lipid nanoparticles of simvastatin: Comparative analysis of characteristics, pharma-cokinetics and tissue uptake. *Int. J. Pharm*., **415**(1-2): 232-243.

Ungaro F, Giovino C, Catanzano O, Miro A, Mele A, Quaglia F and La Rotonda MI (2011). Use of cyclodextrins as solubilizing agents for simvastatin: Effect of hydroxypropyl-β-cyclodextrin on lactone/ hydroxyacid aqueous equilibrium. *Int. J. Pharm*., **404**(1-2): 49-56.

Wang Z, Chen B, Quan G, Li F, Wu Q, Dian L, Dong Y, Li G and Wu C (2012). Increasing the oral bioavailability of poorly water-soluble carbamazepine using immediate-release pellets supported on SBA-15 mesoporous silica. *Int. J. Nanomed*, **7**: 5807-5818.

Yu P, Lu S, Zhang S, Zhang W, Li Y and Liu J (2017). Enhanced oral bioavailability and diminished food effect of lurasidone hydrochloride nanosuspensions prepared by facile nanoprecipitation based on dilution. *Powder Technol*., **312**: 11-20.

Zhang Z, Quan G, Wu Q, Zhou C, Li F, Bai X, Li G, Pan and Wu C (2015). Loading amorphous Asarone in mesoporous silica SBA-15 through supercritical carbon dioxide technology to enhance dissolution and bioavailability. *Eur. J. Pharm. Biopharm*., **92**: 28-31.