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Research Article

Fabrication and Dissolution Studies of Self-micro Emulsifying Drug Delivery System Containing Simvastatin

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ABSTRACT

The majority of active pharmaceuticals, which are in the parlance, do suffer from hindrances of poor aqueous solubility. The scientific fraternity across the globe has explored numerous approaches to address the low bioavailability of the drugs. One amongst such strategies is delivering the actives via lipid-based carrier systems. The present investigation was undertaken to enhance the solubility of simvastatin (a cholesterol-lowering medicine), employing several oils and a blend of surfactants and co-surfactants. The ratios were optimized based on a phase diagram. There was a formulation of 11 batches of SMEDDS formulations having different compositions. The preparations were subjected to dissolution studies. The maximum solubility of the drug was determined as 143 ± 5.3 mg in Lauroglycol 90. The average drug release was in the range of 88 ± 1.6-101 ± 2.5 %. The addition of a stabilizer (Transcutol) does not significantly affect the drug release. It could be suggested at this juncture that simvastatin may be more bioavailable in case confined within a lipid-based delivery system.

Introduction

The oral delivery of drugs has been challenging for drug development scientists, as about 40% of the new chemical entities have low aqueous solubility, and therefore, oral delivery is often linked with repercussions of poor bioavailability. Several strategies have been fastidiously attempted to enhance the oral bioavailability of these drugs embracing particle size reduction (micronization or nanosizing), complexation with cyclodextrins, salt formation, solubilization using cosolvents, surfactants, nanoemulsion, and self-micro emulsifying drug delivery system (SMEDDS).[1] Alteration of the physicochemical features, like salt formation and particle size reduction, could increase the dissolution rate of the drug; nevertheless, such tactics are not every time used; for instance, salt formation of neutral substances is not possible.[2,3]

SMEDDS is an isotropic mix comprising of oil, surfactant, co-surfactant, and the active pharmaceutical ingredient, which may produce nano-sized oil-in-water microemulsion having droplet size below 100 nm in aqueous phases via mild agitation.[4] These systems have been demonstrated to improve poor bioavailability of confined drugs such as Phillygenin,[5] tectorigenin,[6] nifedipine,[7] loratadine,[8] methotrexate,[9] telmisartan,[10] etc.

Simvastatin (SVS) is a cholesterol-lowering drug known for its ability to thwart cardiovascular diseases because it corrects hypercholesterolemia and may defer the course of atherosclerosis. It acts via reversible as well as competitive blockade of 3-hydroxy-3-methylglutaryl coenzyme A reductase, an enzyme responsible for the biosynthesis of cholesterol inside the liver.[11] Besides, simvastatin yields numerous pleiotropic (non-lipid-lowering) vasculoprotective activities predominantly accountable for its anti-ischemic

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and anti-anginal actions necessitate systemic availability to some extent.[12] This drug, highly promising in lipid-lowering, suffers from poor bioavailability and goes for extensive gut-wall metabolism while administered as an immediate-release tablet. In view of this, several approaches have been attempted, including SMEDDS by scientists across the globe. The findings from the research have suggested SMEDDS to be a potential system to address the poor bioavailability concern of the SVS.[13-16] The several lipids have been used to formulate the SMEDDS, which are observed to be effective as well innocuous as far as safety and stability of the carrier is concerned.

The present investigation is also an endeavor to characterize the active pharmaceutical ingredient (API) for solubility characteristics. After that, design and evaluate the SMEDDS using the excipients that are biocompatible and provide the formulation development team an alternative set of lipidic carriers for the delivery of SVS.

Materials and Methods

Materials

The drug simvastatin was a gratis supply from Sun Pharma Limited (erstwhile Ranbaxy Laboratories) Gurugram, India. The oils/surfactants Maisine 35-1, Labrafil M 2125 CS, Labrasol, Plurol Oleique CC 497, Luroglycol 90, and Transcutol, were purchased from Gatte fosse, France. All other chemicals used were of analytical grade.

Methods

Solubility Studies

The solubility of the drug into diverse oils (Maisine 35-1, Labrafil M 2125 CS, Labrasol, Plurol-oleiovecc 497, Luroglycol 90 and Transcutol) was determined using a modified method as reported elsewhere.[17] Briefly, an excess of the drug was added to the 15 mL vials containing about 1 to 2 grams of vehicle, and this blend was then heated to dissolve the drug, thereafter allowed to cool to room temperature. In case the solution is clear more of the drug is added to it, and the procedure is repeated. The endpoint is indicated by the appearance of turbidity upon addition of the drug despite heating the mixture. The amount of drug added before this stage is taken as solubility of drug per unit of the vehicle (expressed as w/w).

Preparation of Calibration Curve

A standard plot of UV absorbance of SVS at various concentrations in phosphate buffer (pH 7) was obtained. Since the drug has poor aqueous solubility, the surfactant sodium lauryl sulfate (SLS) was added at a strength of 0.5% w/v. The graded concentrations were chosen within the range (0–15 µg/mL) in which Beer-Lambert's law of UV absorption spectroscopy would be valid. The analysis was performed at a wavelength of 239 nm. All studies were done in triplicate.

Preparation of Self-microemulsifying Drug Delivery System (SMEDDS)

The drug and excipients were weighed accurately, then surfactant and drug were dissolved by sonication. Following this, co-surfactant was mixed with this solution and eventually added the oily phase so as to form a transparent formulation. The pre-concentrate was filled manually into hard gelatin capsules at the required quantity, still in a fluid condition. Size 'O' capsule was used in all trials.

Construction of Phase Diagram

The use of this diagram permits one to determine the areas of microemulsions. Microemulsions being quaternary systems, their graphic representation requires a space representation. These in order to simplify things, a pseudo-ternary diagram is used. The microemulsions are assumed to be a three pseudo- components mixture a) water phase b) oil phase and c) S /Co-S mixture. The mixture of those four components is defined and can be plotted on the pseudo- ternary diagram.

Determination of the Microemulsion Area

Starting with a defined mixture of one of the two phases and the S, Co-S mixture, add little by little the remaining phase and observe the behavior of the formula. A visual test to assess the self-micro emulsifying properties was conducted as follows, 0.2 mL of the various formulation was introduced into 300 mL of water in a glass beaker at 37°C and contents were mixed gently with the stirrer. The tendency to form emulsion spontaneously and also the progress of emulsion droplets were observed.

Dissolution Studies

The dissolution study was conducted for 30 minutes in USP type II apparatus (Paddle) at 50 rpm in 900 mL of phosphate buffer (pH 7). The temperature was maintained at 37.5 ± 0.5 °C.

Results and Discussion

Solubility Studies

The self-micro emulsifying formulation consists of one or more surfactants and drugs dissolved in oil. The mixture should be clear monophasic liquid at ambient temperature and have suitable solvent properly for the drug. The solubility data of SVS in various surfactants and oils is presented in Table 1. Ostensibly, the drug being lipophilic in nature, is more soluble in nearly all the oils selected while having a maximum of 143 ± 5.3 mg/gm in Lauroglycol 90.

Preparation of Calibration Curve

The SVS was observed to follow linearity in the selected concentration range, which is evident with a coefficient of correlation approaching 1 (r^2-0.9986). The line of

Table 1: Drug solubility in vehicles used for SMEDDS formulations

Vehicle	*Chemical description*	*Applications*	*Solubility (mg/gm ± SD)*
Maisine 35.1	Glycery monolinoleate	Oily carrier with solubilizing properties for liquid and soft gelatin capsule formulation	84 ± 2.1
Labrofil M 1944 CS	Oleoy/Macrogol-6 Glycerides	Bioavailability enhancer for liquid or soft gelation capsule formulation	50 ± 1.7
Labrasol	Caprylocaroy/Macrogol-8 Glycerides	Solubilizer and absorption enhancer for liquid or soft gelatin capsule formulation	56 ± 1.5
Lauroglycol 90	Propylene glycol monolaurate	Solubilizer and absorption enhancer for liquid or soft gelatin capsule formulation	143 ± 5.3
Transcutol P	Diethylene glycol monoethyl/ether	Powerful solubilizer of both water and oil-soluble	87 ± 6.4

Table 2: Composition of SEDDS

Formulation No.	*Batch/ Drug amount*	*Lipid*	*Surfactant*	*Co-Surfactant*	*Solubilizer*	*Fill weight per capsule (mg)*
I	*Simvastatin*	*Maisine 35-1*	*Labrasol*	*Plurol Oleique CC 497*	*Transcutol*	
	(A) 40 mg	(19mg)	(400 mg)	(67mg)		526 mg
	(B) 40 mg	28 mg	400 mg	67 mg		535 mg
	(C) 40 mg	38 mg	400 mg	67 mg		544 mg
	(D) 40 mg	56 mg	400 mg	67 mg		563 mg
II	*Simvastatin*	*Labrafil M 2125 CS*	*Labrasol*	*Lauroglycol 90*		
	(E) 40 mg	19 mg	400 mg	67 mg		526 mg
	(F) 40 mg	28 mg	400 mg	67 mg		535 mg
	(G) 40 mg	38 mg	400 mg	67 mg		544 mg
	(H) 40 mg	56 mg	400 mg	67 mg		563 mg
III	*Simvastatin*	*Maisine 35-1*	*Labrasol*	*Lauroglycol 90*	*Transcutol*	
	(I) 40 mg	19 mg	400 mg	67 mg	40 mg	566 mg
	(J) 40 mg	28 mg	400 mg	67 mg	80 mg	605 mg
	(K) 40 mg	38 mg	400 mg	67 mg	160 mg	685 mg
IV	*Simvastatin*	*Maisine 35-1*	*Labrasol*	*Lauroglycol 90*		
	(L) 40 mg	19 mg	400 mg	67 mg		526 mg
	(M) 40 mg	28 mg	400 mg	67 mg		535 mg
	(N) 40 mg	38 mg	400 mg	67 mg		544 mg
	(O) 40 mg	56 mg	400 mg	67 mg		563 mg

the equation from this plot is used for calculation of concentrations while performing the analysis (Fig. 1).

Preparation of Self-microemulsifying Drug Delivery System (SMEDDS)

Simvastatin is marketed in tablets 20, 40, and 80 mg dose strength. For the purpose of this study, the 40 mg strength was selected for trails, as lower drug levels in the formulation may yield better characteristics – A series of self microemulsifying systems were prepared in each of the four formulae with varying concentration of oil (4–12%), surfactant (88–96%) and co-surfactant (10–16%), in all the formulations, the level of drug was constant. Table 2 represents composition of different formulations.

Construction of Phase Diagram

The varying oils, surfactant-co-surfactant ratios were analyzed for preparation of the phase diagram, the

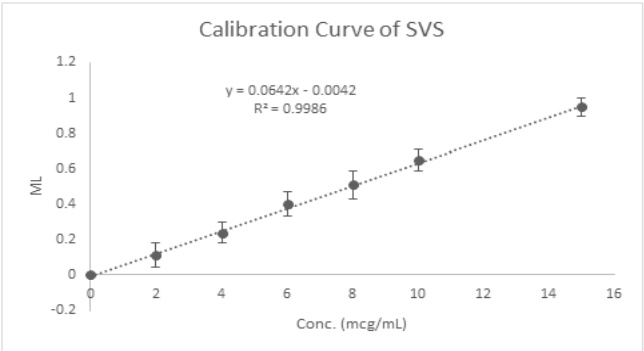

Fig.1: Calibration curve of SVS in Phosphate buffer (pH7) with 0.5% SLS

microemulsion area was marked by drop-wise addition of water to the system. The formulation was hazy at the beginning and turned clear upon the addition of water to it. Nevertheless, the microemulsion turned hazy again in case the addition of water was continued.

The first such phase diagram was formulated using Maisine 35- 1 (oil), Labrasol (surfactant), and Luroglycol 90 (co-surfactant), where surfactant to oil ratios were 88:12; 92:8, and 96:4, respectively (Fig.2).

In other system a stabilizer (Transcutol) in a concentration of half of Labrasol was added while keeping the remainder of the composition similar as in preceding system (Fig.3).

Dissolution Studies

In the case of formulation I-Batch (A) maisine was used as oil phase, Labrasol as surfactant and plurol-oleique as co-surfactant. *In vitro* dissolution of Batch A was carried out for 30 minutes. The dissolution of drug was quite good and complete. In next Batch B, we increased the oil phase concentration from 4% (in Batch A) to 6% (in Batch B), and the concentration of surfactant + Co - surfactant used was the same. *In vitro* dissolution of Batch B was similar to Batch A. It was concluded that there was not much difference *in vitro* drug release on changing the concentration of oil phase. In Batch C, the oil phase concentration was increased to 8% and the *in vitro* drug release of Batch C was lowered on increasing the oil concentration from 6 to 8%. In Batch D again the concentration of oil Phase was increased to 12%. Then vitro drug release of Batch D was also lowered on further increasing the concentration of oil phase from 8 to 12%. As compared to Batch A and B, the concentration of oil phase used was 4 and 6% respectively. From the above observations, it was concluded that on increasing the concentration of oil Phase above a particular limit, the *in Vitro* drug release can become lower (Fig. 4).

In the above four Batches E, F, G, H, we have used Labrafil M -2125 as oil phase, labrasol as surfactant and Luroglycol 90 as co-surfactant (Fig. 5). In these four Batches, the concentration of oil was the only change, rest all remained the same. In Batch E, the concentration of oil phase used was 4%. The *in vitro* dissolution of batch E was carried out for 30 min. and the *in vitro* drug release was found to be good and complete. On further increasing the concentration of oil phase in batch F, from 4 to 6%, there was no difference in an *in vitro* drug release. Also, on further increasing oil concentration to 8% in Batch G,

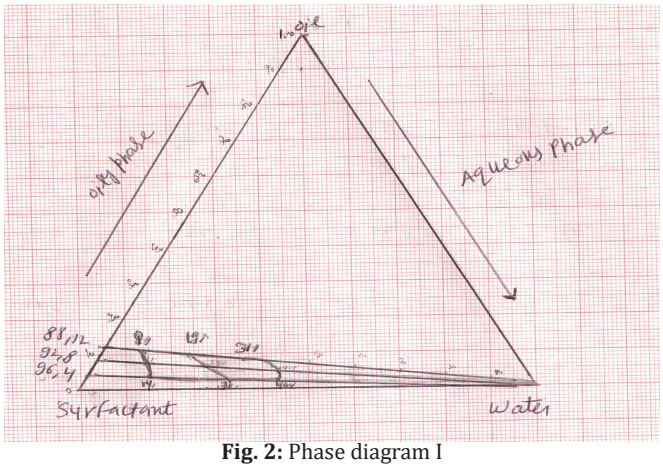

Fig. 2: Phase diagram I

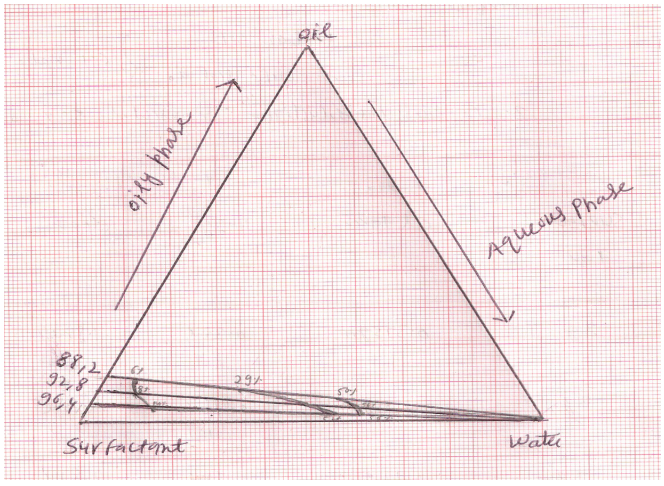

Fig. 3: Phase diagram II

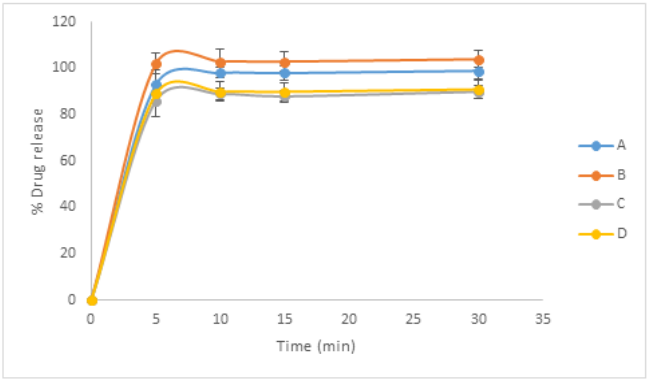

Fig. 4: Percentage drug release different oil concentration of formulation-I

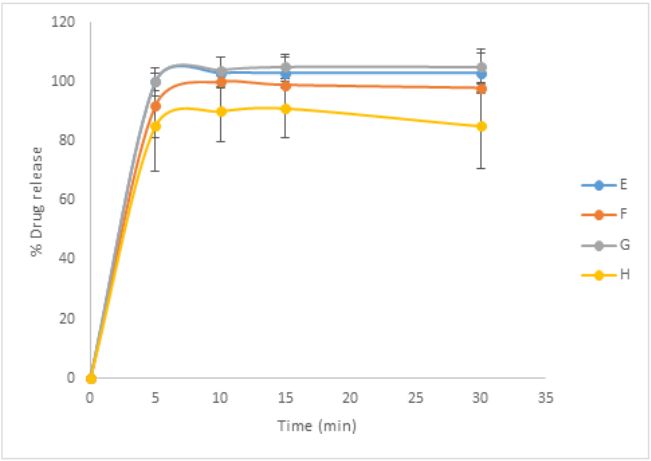

Fig. 5: Percentage drug release different oil concentration of formulation-II

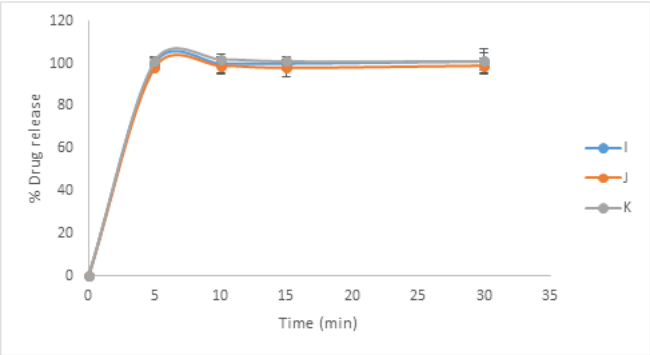

Fig. 6: Percentage drug release different oil concentration of formulation-III

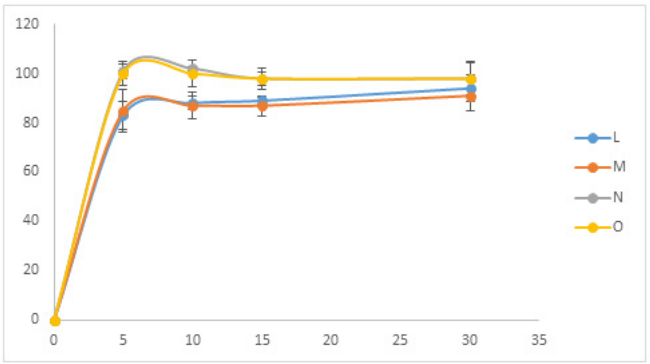

Fig. 7: Percentage drug release different oil concentration of formulation-IV

the *in vitro* drug release was the same as in batch E and F. But on further increasing the concentration of the oil phase from 8 to 12 %, the *in vitro* drug release became on the lower side, i.e., around 90%. It was concluded from the above observations, on using the oil phase concentration up to 8%, the *in vitro* drug release was similar, but on further increasing the oil concentration, i.e., 12%, the *in vitro* drug release become on lower side.

In the above three batches (I, J, K) the oil used was maisine. Surfactant used was Labrasol, and the co-surfactant used was Luroglycol-90. In the above 3 batches, solubilizer, transcutol was also added. The concentration of solubilizer transcutol used was 10% in Batch I, 20% in Batch J and 40% in Batch K. Then vitro drug dissolution of all three batches were carried out. Still, the *in vitro* drug release of all three batches was similar form the above results, in was concluded that changing the concentration of solubilizer from 10 to 40 % there was no effect on *in vitro* drug release (Fig. 6). In the above 3 batches, solubilizer, transcutol was also added. The concentration of solubilizer transcutol used was 10% in Batch I, 20% in Batch J and 40% in Batch K. Then vitro drug dissolution of all three batches were carried out. Still, the *in vitro* drug release of all three batches were similar form the above results, in was concluded that changing the concentration of solibilizer from 10 to 40 % there was no effect on *in vitro* drug release.

In Batch L, the concentration of oil phase used was 4%. The *in vitro* dissolution of batch L was carried out for 30 minutes and the *in vitro* drug release was found to be good and complete. On further increasing the concentration of oil phase in batch M, from 4 to 6%, there was no difference in an *in vitro* drug release. Also, on further increasing oil concentration to 8% in Batch N, the *in vitro* drug release was higher as in batch L and M. But on further increasing the concentration of oil phase from 8 to 12 %, the *in vitro* drug release became on the higher side, i.e., around 98%. It was concluded from the above observations, on using the oil phase concentration up to 6%, the *in vitro* drug release was similar, but on further increasing the oil concentration, i.e., 12%, the *in vitro* drug release become on the higher side (Fig. 7).

Conclusion

Lipid-based formulations, including SMEDDS offer the potential for enhancing the absorption of poorly water-soluble and/or poorly permeable drugs. A few commercial examples of these formulations include cyclosporine, Ritonavir, Sequinavir, and amprenavir. However, a few limitations exist with these formulations, including stability, manufacturing method, interaction of content with gelatin shells, and limited solubility of some drugs in lipid solvents. Simvastatin, being amphiphobic drug is neither soluble in oil nor in water. Solubility studies using various lipids, surfactants and co-surfactants showed higher solubility in maisine 35-1 and co-surfactant Luroglycol-90. Formulations of Simvastatin comprising maisine 35-1 oil and surfactant Labrasol gave optimal self-micro emulsifying property upon inclusion of a co-surfactant Plurol-oleique, Luroglycol-90. The addition of additional co-surfactant increased the lipophilicity of droplets. Thus, being amphiphobic in nature, the drug did not show any reverse equilibrium towards lipophilic side. The drug in the solution remained constant even for a longer time. Thereafter, inferences drawn from the formulation of SEMDDS and dissolution studies suggest an improvement in the solubility profile of a selected drug. Therefore, the inclusion of a drug in the lipophilic system may be considered an alternative approach for improving the simvastatin's poor bioavailability.

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References

1. Wu L, Qiao Y, Wang L, Guo J, Wang G, He W, et al. A Self-microemulsifying Drug Delivery System (SMEDDS) for a Novel Medicative Compound against Depression: a Preparation and Bioavailability Study in Rats. AAPS PharmSciTech. 2015; 16(5):1051-1058.

2. Talegaonkar S, Azeem A, Ahmad FJ, Khar RK, Pathan SA, Khan ZI.Microemulsions: A Novel Approach to Enhanced Drug Delivery. Recent Pat Drug Deliv Formul. 2008; 2:238-257.
3. Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS)-challenges and road ahead. Drug Deliv. 2015;22(6):675-690.
4. Yi T, Zhang J. Effects of Hydrophilic Carriers on Structural Transitions and *In Vitro* Properties of Solid Self-Microemulsifying Drug Delivery Systems. Pharmaceutics. 2019; 11 (6):267.
5. Wang L, Yan W, Tian Y, Xue H, Tang J, Zhang L. Self-Microemulsifying Drug Delivery System of Phillygenin: Formulation Development, Characterization and Pharmacokinetic Evaluation. Pharmaceutics. 2020;12(2):130.
6. Zhang Y, He L, Yue S, Huang Q, Yang J. Characterization and evaluation of a self-microemulsifying drug delivery system containing tectorigenin, an isoflavone with low aqueous solubility and poor permeability. Drug Deliv. 2017; 24(1):632-640.
7. Khansili A, Bajpai M. Formulation, Evaluation and Characterization of Solid Self-Micro Emulsifying Drug Delivery System (Solid SMEDDS) containing Nifedipine. Research J. Pharm. and Tech.2013; 6(3):278-284.
8. Desai P, Thakkar A, Ann D, Wang J, Prabhu S. Loratadine self-microemulsifying drug delivery systems (SMEDDS) in combination with sulforaphane for the synergistic chemoprevention of pancreatic cancer. Drug Deliv Transl Res. 2019;9(3):641-651.
9. Kim DS, Cho JH, Park JH, Kim JS, Song ES, Kwon J, et al. Self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate. Int J Nanomedicine. 2019; 14:4949-60.
10. Jaiswal P, Aggarwal G, Harikumar SL, Singh K. Development of self-microemulsifying drug delivery system and solid-self-microemulsifying drug delivery system of telmisartan. Int J Pharm Investig. 2014; 4(4):195-206.
11. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005; 19: 117-125.
12. Tiwari R, Pathak K. Statins therapy: a review on conventional and novel formulation approaches. J Pharm Pharmacol. 2011; 63: 983-998.
13. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm. 2004; 274(1-2):65-73
14. Ćetković Z, Cvijić S, Vasiljević D. *In vitro*/in silico approach in the development of simvastatin-loaded self-microemulsifying drug delivery systems. Drug Dev Ind Pharm. 2018; 44(5):849-60.
15. Kumar A, Nanda A. Design and optimization of simvastatin self-microemulsifying drug delivery system for enhanced therapeutic potential. Asian J Pharm. 2018; 12: S159-S165.
16. Karim FT, Kalam A, Anwar R, Miah MM, Rahman MS, Islam SM. Preparation and evaluation of SEDDS of simvastatin by in vivo, *in vitro* and ex vivo technique. Drug Dev Ind Pharm. 2015; 41(8):1338-1342.
17. Bhalekar M, Upadhaya P, Madgulkar A. Formulation and characterization of solid lipid nanoparticles for an anti-retroviral drug darunavir. Appl Nanosci. 2017; 7:47-57.

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