Acta Pharm. 57 (2007) 111–122
10.2478/v10007-007-0009-5

Short communication

Formulation of a self-emulsifying system for oral delivery of simvastatin: *In vitro* and *in vivo* evaluation

PRADEEP PATIL[1]
VANDANA PATIL[2]
ANANT PARADKAR[1*]

[1] *Department of Pharmaceutics*
Bharati Vidyapeeth Deemed University
Poona College of Pharmacy, Erandwane
Pune-411 038
Maharashtra State, India

[2] *Department of Environmental Sciences*
University of Pune
Ganeshkhind, Pune-411 007
Maharashtra State, India

The objective of the present work was to formulate a self-emulsifying drug delivery system (SEDDS) for simvastatin, which is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. Simvastatin SEDDS were formulated using a 1:1 (*V/V*) mixture of diesters of caprylic/capric acids and polyglycolyzed glycerides with varying concentrations of polyoxy castor oil and C8/C10 mono-/diglycerides. The developed SEDDS were evaluated for turbidimetry, droplet size analysis, drug content and *in vitro* diffusion profiles. *In vivo* performance of the optimized formulation was evaluated in rats using pharmacodynamic marker parameters like plasma total cholesterol (CH), triglycerides (TG) and high-density lipoprotein (HDL-CH) for 21 days. SEDDS containing 9.1% (*m/m*) simvastatin and 23.0% (*m/m*) of each excipient showed minimum mean droplet size (124 nm) and optimal drug diffusion. This test formulation showed significant reduction in plasma CH and TG (around 5-fold and 4-fold, respectively), while HDL-CH concentration was markedly higher (2-fold) compared a reference simvastatin suspension formulation after oral administration for 21 days of study. Test formulation has shown enhanced pharmacodynamic performance compared to reference formulation in rats. The study illustrated the potential of simvastatin SEDDS for oral administration and its biopharmaceutic performance.

Keywords: simvastatin, SEDDS, pharmacodynamics, oral administration, plasma lipids

Accepted November 2, 2006

For the therapeutic delivery of lipophilic active moieties (Class II drugs), lipid based formulations are inviting increasing attention. Amongst many such delivery options, like incorporation of drug in oils (1), surfactant dispersions (2), emulsions (3) and liposomes (4), one of the most popular approaches are the self-emulsifying drug delivery systems (SEDDS). SEDDS are mixtures of oils and surfactants, ideally isotropic, and sometimes containing cosolvents, which emulsify spontaneously to produce fine oil-in-water emul-

* Correspondence, e-mail: arparadkar@rediffmail.com

sions when introduced into aqueous phase under gentle agitation (5). Upon peroral administration, these systems form fine oil-in-water emulsions (or microemulsions) in the gastro-intestinal (GI) tract with mild agitation provided by gastric mobility. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for drug absorption (6, 7). Many researchers have reported various rational applications of SEDDS for delivering and targeting lipophilic drugs, *e.g.*, coenzyme Q10 (8), vitamin E (9), halofantrine (10) and cyclosporin A (11). Potential advantages of these systems include enhanced oral bioavailability (enabling dose reduction), more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut (12, 13). For selecting a suitable self-emulsifying vehicle, drug solubility in various components, identification of emulsifying regions and resultant droplet size distribution need careful monitoring, since these are drug-specific systems (8).

Simvastatin, a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract (14). It is a potent and specific inhibitor of 3-hydroxy--3-methyl-glutaryl coenzyme A (HMG CoA) reductase, which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in liver, and is hence widely used in the treatment of hypercholesterolemia and dyslipidemia, as an adjunct to diet. After oral administration, simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in liver, where it inhibits the rate-limiting step in cholesterol biosynthesis (15, 16). This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. There may also be some reduction in LDL production as a result of inhibition of hepatic synthesis of very low-density lipoprotein (VLDL), the precursor of LDL (17). Being a Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvements in its solubility and/or dissolution rate may lead to enhancement in bioavailability. Various attempts to enhance the dissolution rate and bioavailability of simvastatin have been reported (14, 18).

In the present study, SEDDS formulations containing simvastatin were developed using different proportions of oils and surfactant systems for oral administration. Isotropic systems were evaluated for the quality of emulsion produced, mean droplet size and *in vitro* drug diffusion. Optimized formulation was further evaluated for its *in vivo* performance in albino rats using pharmacodynamic markers such as plasma levels of total cholesterol (CH), high-density lipoprotein cholesterol (HDL-CH), triglycerides (TG), low--density lipoproteins (LDL) and very low-density lipoproteins (VLDL). Pharmacodynamic performance of the developed (test) formulation was compared against a reference formulation and was further analyzed statistically.

EXPERIMENTAL

Materials

Simvastatin was a generous gift from Ivax India Pvt. Ltd. (India). Diesters of caprylic/capric acids (Captex® 355) and C8/C10 mono-/diglycerides (Capmul® MCM) were generous gifts from Abitec Corp (USA). Polyglycolyzed glyceride (Lauroglycol® 90) was

a gift sample provided by Gattefosse (France). Polyoxyl 35 castor oil (Cremophore® EL, Cr-EL) was purchased from BASF (Germany). *In vitro* diagnostic kits (Cholesterol LS, HDL-CH and Triglycerides) were purchased from Ensure Biotech, India. Sigma® Dialysis Tubing (seamless cellulose tubing, MWCO 12000) was purchased from Sigma Chemical Co., USA. All other chemicals and reagents were of analytical grade and used as received.

Preliminary studies

Apparent solubilities of simvastatin were determined in different oils at ambient temperature. Based on these results, the oils selected were formulated in SEDDS using different surfactant systems (with varying ratios of surfactant to cosurfactant) by mixing the components in sealed glass vials. These systems were titrated with water and phase clarity and quality of emulsion produced were visually observed.

Formulation of SEDDS

Various formulations were prepared with a constant amount of simvastatin (9.09%, *m/m*) and varying ratios of surfactant to cosurfactant (Table I). In brief, simvastatin was dissolved in 1:1 (*V/V*) mixture of Captex and Lauroglycol (used as oil phase) in stoppered glass vials. Required amounts of Cr-EL and/or Capmul were added to the mixture and mixed well. These systems were warmed to 40 °C using a water bath for 30 min with intermittent shaking to ensure complete mixing. The prepared formulations were stored at ambient conditions until further use.

Turbidimetric evaluation

Self-emulsifying system (0.2 mL) was added to 0.1 mol L^{-1} hydrochloric acid (150 mL) under continuous stirring (50 rpm) on a magnetic plate (Ika-Werke, Germany) at ambient temperature, and the increase in turbidity was measured untill equilibrium was achieved using a turbidimeter (Type 131, Systronics, India). However, since the time required for complete emulsification was too short, it was not possible to monitor the rate of change of turbidity (rate of emulsification).

Table I. Compositions of SEDDS formulations

Composition	Formulation				
	A	B	C[a]	D	E
Simvastatin (mg)	200	200	200	200	200
Captex 355 (mL)	0.5	0.5	0.5	0.5	0.5
Lauroglycol 90 (mL)	0.5	0.5	0.5	0.5	0.5
Cremophor EL (mL)	1.0	0.75	0.5	0.25	–
Capmul MCM (mL)	–	0.25	0.5	0.75	1.0

[a] Test formulation

Droplet size analysis

Droplet size distribution of SEDDS diluted with water was determined using a photon correlation spectrometer (Zetasizer 3000 HAS, Malvern Ltd., UK) based on the laser light scattering phenomenon. Samples were diluted 200 times with purified water. Diluted samples were directly placed into the module and measurements were made in triplicate after 2-min stirring. Droplet size was calculated from the volume size distribution.

Drug content

Simvastatin from preweighed SEDDS was extracted by dissolving in 25 mL methanol. Simvastatin content in the methanolic extract was analyzed spectrophotometrically (Jasco V-530, Japan) at 238 nm, against the standard methanolic solution of simvastatin.

In vitro *drug diffusion studies*

In vitro diffusion studies were carried out for formulations A, B and C using the dialysis technique. One end of pretreated cellulose dialysis tubing (7 cm in length) was tied with thread and then 0.2 mL of self-emulsifying formulation (equivalent to 10 mg simvastatin) was placed in it along with 0.8 mL of dialyzing medium. The other end of tubing was also secured with thread and was allowed to rotate freely in the dissolution vessel of a USP 24 type II dissolution test apparatus (Electrolab TDT-06P, India) that contained 900 mL dialyzing medium (phosphate buffer pH 6.8) maintained at 37 ± 0.5 °C and stirred at 100 rpm. Placebo formulation (blank SEDDS, without drug) was also tested simultaneously under identical conditions so as to check interference, if any. Aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through Whatman filter paper (No. 41), were analyzed spectrophotometrically at 238 nm for simvastatin content. The data was analyzed using the PCP Disso v 3.0 software, India.

In vivo *study in rats*

The effect of formulation C (test formulation, TF) on plasma lipid profiles was determined by comparison with reference formulation (RF, *i.e.*, aqueous suspension containing 1.7 mg mL^{-1} simvastatin, mean particle size 23 μm) and 2% (*m/V*) gum acacia as a suspending agent) in healthy albino rats (Wistar strain) of either sex and weighing between 150–180 g. The study protocol was approved by the Institutional Animal Ethics Committee of Poona College of Pharmacy, Pune, India. Animals had free access to food and water. The animals were randomly divided into 4 treatment groups of 6 animals each, *viz.*, test treatment group (TTG), reference treatment group (RTG), placebo treatment group (PTG) and control treatment group (CTG). The treatment was given for 21 days. Each treatment group received daily 1.5 mL of coconut oil orally in the morning throughout 21 days. TTG, RTG and PTG additionally received formulation C (TF), aqueous suspensions of simvastatin (RF) and blank SEDDS, respectively. The administered oral dose of TF and RF was 1.7 mg per animal once a day (equivalent to 10 mg kg^{-1} per day). Blood samples were collected under light ether anesthesia by retro-orbital punc-

ture at predetermined time intervals, *viz.*, before treatment, and after 5, 10, 15 and 21 days in anticoagulated (EDTA-treated) glass vials. Plasma was separated by centrifugation at 3000 rpm for 25 min and stored frozen until further use.

Lipid profiling of plasma sample

Plasma samples were analyzed for total CH, HDL-CH and TG using *in vitro* diagnostic kits (Ensure Biotech, India). Briefly, fixed volumes of sample and standard were mixed with the working reagent separately, followed by incubation at 37 °C for 10 min. Absorbance of the developed color was read at 505 nm for CH and HDL-CH, and at 546 nm for TG determination. From the values of total CH, HDL-CH and TG, plasma very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) contents were determined from the above values (19).

Statistical analysis for the determination of differences in lipid profiles of treatment and control groups was done by the unpaired *t*-test and ANOVA (significance level $p < 0.05$). The results were confirmed by Bonferroni's multiple comparison as a post-hoc test.

RESULTS AND DISCUSSION

Out of different oils screened for simvastatin solubilization, Lauroglycol showed the highest solubility (around 90 mg mL^{-1}) while Captex accommodated approximately 60 mg mL^{-1} of simvastatin. However, the systems developed with the former oil yielded emulsions of moderate quality and the latter of very good quality, as observed visually. To obtain the balance between solubility and emulsion quality, both of these oils were mixed in a 1:1 (*V/V*) ratio and used as oil phase in further studies. Pseudo ternary phase diagrams were constructed to determine the region of emulsion formation (data not shown). Systems containing about 25–35% (*m/m*) Cr-EL yielded good quality emulsions. At higher amounts of Captex (more than 40%, *m/m*), although the region of emulsification increased, precipitation was observed in overnight storage under ambient conditions.

Compositions of different formulations prepared with varying Cr-EL to Capmul ratios are shown in Table I. All the prepared formulations were clear, isotropic solutions with no signs of precipitation or separation. After 500-times dilution with water, formulations A, B and C yielded good quality emulsions while D and E produced emulsions of moderate and poor quality, respectively. Lack of surfactant in formulation E resulted in a poor emulsion that readily broke, and was hence discarded. Turbidity of formulation C (which was a clear and transparent system of slightly bluish color) was below the limit of detection, probably due to very fine emulsion formed (Table II). Formulations A and B showed low turbidity values (14.21 NTU and 12.95 NTU, respectively) owing to the presence of adequate amounts of surfactant (Cremophor EL), wich primarily governs the resultant droplet size and its distribution. Oppositely, formulation D, with moderate quality emulsion formation because of inadequate surfactant, showed very high and variable turbidity (96.3 ± 15.2 NTU, mean ± SD, $n = 3$) due to coarser droplets, and hence it was discarded.

Table II. Evaluation of SEDDS formulations[a]

Evaluation parameter	Formulation			
	A	B	C	D
Turbidity (NTU)	14.21 ± 2.15	12.95 ± 2.06	BLD[b]	96.3 ± 15.24
Mean droplet size (nm)[d]	414.42 ± 35.24	258.43 ± 26.51	124.86 ± 17.83	ND[c]
Drug found (mg mL^{-1})	98.7 ± 10.3	102.1 ± 8.9	101.2 ± 9.7	ND[c]

[a] Mean ± SD, $n = 3$.
[b] BLD – below limit of detection.
[c] ND – not done.
[d] PI – polydispersity index was less than 0.35 in all experiments.

Droplet size analysis revealed the effect of varying amounts of Cr-EL and Capmul in the formulated SEDDS (Table II). Formulation C with a 1:1 (*V/V*) ratio of Cr-EL to Capmul showed the least mean droplet size, 124 nm (polydispersity index, 0.212). Changes in Cr-EL to Capmul ratios are most likely to alter the resultant HLB of the system and the properties of liquid crystal (LC) interfaces. This in turn governs the size of droplets formed (20). This is the appropriate choice of surfactant and cosurfactant together with their proper concentrations, which provides an optimum self-emulsifying formulation. The drug content varied for up to 3.9% between formulations A, B, and C, normaly, ranged between 98.7 and 102.1 mg mL^{-1} (shown in Table II).

Conventional dissolution testing of SEDDS has a limitation in mimicking its real-time *in vivo* dissolution and such a technique can only provide a measure of dispersibility of SEDDS in the dissolution medium. Alternatively, for evaluating the *in vitro* performance of SEDDS, drug diffusion studies using the dialysis technique are well documented in literature (14, 20, 21). In this study, diffusion profiles of all formulations did not show any significant differences during initial 1 h, which might be the lag period. However, at the end of 12 hours, formulation C showed about 82.2% diffusion against 69.3% and 48.9% from formulation B (simvastatin content 10.21 mg mL^{-1}) and A (simvastatin content 9.87 mg mL^{-1}), respectively (Table III). This clearly indicates the effect of mean droplet size on drug diffusion across dialyzing membrane. The amount of drug diffused at time t, Q_t, from the droplet to the aqueous environment can be given as:

$$Q_t = \mathrm{f}\ (1/r^2K)$$

Thus, Q_t is primarily a function of the radius of the droplet r and the partition coefficient K (which indicates polarity of the drug) (7). Accordingly, formulation C, with the least mean droplet size (124 nm) of all, offered very high surface area for drug partitioning, which eventually equilibrated with the dialyzing medium. Similar observations have been reported earlier (14). Based on these results, formulation C was chosen as a TF for further *in vivo* studies in rats.

Bioavailability enhancement of simvastatin has been demonstrated in dogs with the help of pharmacokinetic analysis (14). However, the primary site of action of simvastatin

Table III. Comparison of in vitro *diffusion profiles of SEDDS formulations*[a]

Time (h)	Drug diffused (%)		
	Formulation A	Formulation B	Formulation C
0	0	0	0
1	7.4 ± 1.2	8.0 ± 2.5	9.5 ± 2.7
2	10.6 ± 1.6	12.6 ± 2.2	17.6 ± 3.1
4	25.6 ± 2.0	36.9 ± 2.6	41.2 ± 2.6
6	37.6 ± 2.1	54.9 ± 3.6	64.2 ± 3.2
8	42.3 ± 3.1	63.9 ± 4.6	75.5 ± 4.1
10	46.6 ± 2.6	67.5 ± 4.6	79.5 ± 3.2
12	48.9 ± 3.8	69.3 ± 3.5	82.2 ± 2.9

[a] Mean ± SD, $n = 6$.

is liver and oral bioavailability is less than 5% (17). Due to high intra- and inter-population variations in liver metabolism patterns, plasma levels of simvastatin and its metabolite (simvastatin acid) fluctuate to a large extent. Hence, high degrees of variations in pharmacokinetic parameters of simvastatin and its active metabolite are often observed. Alternatively, *in vivo* performance of simvastatin can be also evaluated using its pharmacodynamic effects (17). Hypolipidemic activity of simvastatin causes reduction in elevated total CH, LDL-CH and TG levels in blood. At the same time, it causes elevation of plasma HDL-CH level, which promotes the removal of CH from peripheral cells and facilitate its delivery back to the liver. This pharmacodynamic effect is reported to be dose dependent (22), and hence was used as a basis for the comparison of *in vivo* performance of TF and RF. Administration of excess coconut oil, which is a rich source of saturated fatty acids, promotes biosynthesis of cholesterol in liver and leads to hypercholesterolemia (23). The serum lipid profiles of all the experimental groups at different time intervals are presented in Table IV. No significant differences were observed within or between four treatment groups for the three test parameters on day zero (initial) due to random sampling of animals. After 5 days, in case of PTG and CTG, significant increases (2 to 3-fold) in plasma CH, TG, VLDL and LDL levels were observed ($p < 0.01$); however, HDL-CH levels were fairly unchanged. After the same period, significant changes in plasma CH, TG, VLDL and LDL profiles were also observed for TTG and RTG ($p < 0.05$).

After 21 days of treatment with coconut oil (1.5 mL per day, orally), PTG and CTG showed a marked increase in total CH (3.8-fold and 3.5-fold, respectively) and TG (3.2--fold and 2.8-fold, respectively) ($p < 0.001$). Particularly, in the case of CTG, a significant increase in CH and TG, and VLDL and LDL levels ($p < 0.001$) and an insignificant increase in HDL-CH from day zero to day 21 of the treatment indicated the inducement of hypercholesterolemia due to administration of coconut oil. Similar findings were noted for PTG. Lack of significant differences in the tested parameters for CTG and PTG after the 21-day treatment inferred no appreciable effect of placebo components on the lipid

Table IV. Plasma CH, HDL-CH and TG levels at different time intervals[a]

Treatment group	Test parameter (mg%)	Time (days)				
		0	5	10	15	21
CTG	CH	54.7 ± 3.01[b]	93.4 ± 6.5[b]	145.1 ± 5.56	195.4 ± 6.54	258.9 ± 7.25[b,d]
	HDL-CH	18.5 ± 4.32	18.7 ± 3.65	20.4 ± 5.21	21.2 ± 3.54	20.4 ± 4.21[e]
	TG	64.2 ± 4.28[c]	103.4 ± 23.56[c]	166.5 ± 45.26	203.4 ± 54.26	243.7 ± 62.54[c,f]
PTG	CH	52.3 ± 3.98	102.9 ± 3.65	154.3 ± 4.56	205.2 ± 2.54	261.4 ± 5.62
	HDL-CH	21.5 ± 3.25	22.8 ± 2.54	21.6 ± 5.56	23.6 ± 4.56	24.9 ± 4.21
	TG	61.2 ± 3.87	115.8 ± 33.56	178.5 ± 55.68	223.4 ± 77.54	257.4 ± 62.54
TTG	CH	53.7 ± 3.54	58.6 ± 2.65	60.5 ± 3.68	62.0 ± 2.54	65.9 ± 3.24[d]
	HDL-CH	18.5 ± 3.17	25.7 ± 4.12	33.1 ± 4.21	40.1 ± 4.69	44.8 ± 4.21[e]
	TG	66.2 ± 5.64	71.6 ± 14.97	77.2 ± 15.26	81.5 ± 18.84	86.4 ± 14.54[f]
RTG	CH	56.8 ± 2.59	71.5 ± 3.01	85.9 ± 3.18	102.5 ± 3.54	119.0 ± 4.56[d]
	HDL-CH	20.8 ± 4.56	22.4 ± 3.54	26.8 ± 4.58	30.4 ± 5.65	35.6 ± 5.06[e]
	TG	67.9 ± 4.58	88.6 ± 12.56	109.6 ± 18.54	127.9 ± 18.14	143.8 ± 21.54[f]

CTG – control treatment group, PTG – placebo treatment group, TTG – test treatment group, RTG – reference treatment group
Some significant differences: [b] $p < 0.001$, [c] $p < 0.001$, [d] $p < 0.001$, [e] $p < 0.01$, [f] $p < 0.001$.
[a] Mean ± SD, $n = 6$.

profiles of experimental animals. On the contrary, as expected, in TTG, the increase in total CH and TG was much lower but significant ($p < 0.001$), while the RTG showed marginal increase (2.1-fold and 2.12-fold, respectively) ($p < 0.001$) in these parameters after the 21-day treatment. Moreover, the increase in plasma HDL-CH (approximately 1.4-fold for TTG and 0.7-fold for RTG) was remarkable ($p < 0.001$).

After the 21-day treatment, comparison of CTG against TTG and RTG revealed the lipid-lowering effect of simvastatin. Plasma CH and TG levels were significantly lower (0.25-fold and 0.35-fold, respectively) ($p < 0.001$) and HDL-CH levels were significantly higher (2.2-fold, $p < 0.001$) in TTG compared to CTG. Also, plasma CH and TG levels were significantly lower (0.46-fold and 0.59-fold, respectively) ($p < 0.001$) and HDL-CH levels were significantly higher (1.75-fold, $p < 0.001$) in the case of RTG compared to CTG.

Comparison of TTG against RTG, after the 21-day treatment, inferred the varying lipid-lowering effects of simvastatin from TF and RF. Plasma CH and TG levels were significantly lower (0.55-fold and 0.6-fold, respectively) ($p < 0.001$) and HDL-CH levels were significantly higher (1.23-fold, $p = 0.007$) in TTG compared to RTG. Also, it is apparent from Table IV that the changes in lipid levels from day zero to day 21 for TTG and RTG are different. Comparison of changes took place in plasma lipid levels of TTG and RTG groups after 21 days of study are shown in Table V. This clearly indicates the varying lipid-lowering effects of simvastatin obtained by administering TF and RF.

Table V. Comparison of TTG and RTG for pharmacodynamic parameters after 21 days of study[a]

Test parameter	Increase in plasma level (%)		Ratio (TTG/RTG)
	TTG[b]	RTG[c]	
CH	22.7 ± 2.5	105.6 ± 5.4	0.2
HDL-CH	142.5 ± 6.8	71.4 ± 4.6	2.0
TG	30.5 ± 2.6	115.0 ± 7.4	0.3
VLDL	29.9 ± 3.4	111.8 ± 4.6	0.3
LDL	–82.6 ± 4.4[d]	114.6 ± 6.6	–

[a] Mean ± SD, $n = 6$.
[b] TTG – test treatment group.
[c] RTG – reference treatment group.

Thus, TF showed a significantly better *in vivo* performance than RF in terms of pharmacodynamic parameters. This observation is in accord with earlier reports (14, 17). Enhanced pharmacodynamic performance of simvastatin formulated in SEDDS could be ascribed to the combined effect of different mechanisms, like the presentation of drug in solubilized form, large interfacial area made available for absorption, enhanced dissolution in the presence of surfactants, and increased cellular uptake of drug, probably due to inhibition of cellular efflux systems (5, 7, 24).

CONCLUSIONS

This study illustrated the potential of simvastatin SEDDS for oral administration. Further studies are required to establish a correlation between pharmacokinetics and pharmacodynamic responses of simvastatin when administered in the form of SEDDS.

Acknowledgements. – The authors acknowledge the generous support by Ivax India Pvt. Ltd., Abitec Corp., USA, and Colorcon Ltd. India (Gattefosse, France), for providing the gift samples of simvastatin, Captex and Capmul, and Lauroglycol, respectively. Pradeep Patil is thankful to the Council for Scientific and Industrial Research (CSIR), New Delhi, India, for financial assistance to this research work.

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S A Ž E T A K

Samoemulzirajući pripravci za peroralnu primjenu simvastatina: Ispitivanja *in vitro* i *in vivo*

PRADEEP PATIL, VANDANA PATIL i ANANT PARADKAR

Cilj rada bio je pripraviti samoemulzirajući sustav za isporuku lijeka (SEDDS) za simvastatin, hipolipemik koji se uz dijetu upotrebljava u terapiji hiperkolesterolemije i dislipidemije. Simvastatin SEDDS su pripravljene koristeći smjesu 1:1 (*V/V*) diestera kaprilne i kaprinske kiseline i poliglikoliziranih glicerida s različitim koncentracijama polioksil 35 kastorovog ulja i C8/C10 mono-/diglicerida. Pripravcima su ispitana turbidimetrijska svojstva, veličina čestica, udio lijeka i *in vitro* difuzijski profil. U pokusima *in vivo* na štakorima praćeni su parametri farmakodinamičkih markera kao što su ukupni

kolesterol u plazmi (CH), trigliceridi (TG) i lipoproteini velike gustoće (HDL-CH) tijekom 21 dana. Pripravci koji sadrže 9,1% (*m/m*) simvastatina i 23% (*m/m*) svake od pomoćnih tvari imaju najmanju prosječnu veličinu čestica (124 nm) i iz njih je difuzija lijeka optimalna. Ispitivani pripravci značajno snizuju CH i TG u plazmi (5, odnosno 4 puta), dok je koncentracija HDL-CH ostaje izrazito visoka, 2 puta viša u usporedbi s referentnom suspenzijom simvastatina poslije peroralne primjene tijekom 21 dan. Ispitivani pripravci imaju bolji farmakodinamički profil u odnosu na referentni pripravak pa imaju veliki potencijal za peroralnu primjenu simvastatina.

Ključne riječi: simvastatin, SEDDS, farmakodinamika, peroralna primjena, lipidi u plazmi, *in vivo* ispitivanja

Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy Erandwane, Pune-411 038, Maharashtra State, India

Department of Environmental Sciences, University of Pune, Ganeshkhind, Pune-411 007 Maharashtra State