Original Article

Solid SMEDDS: An Approach for Dissolution Rate Enhancement Using Telmisartan as Model Drug

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Abstract

Bioavailability improvement of poorly water-soluble drugs is a challenging task for many of the drug candidates. In recent years, an area that is ahead in popularity for different formulation expertise is the use of lipid-based careers to formulate self-emulsifying drug delivery systems (SEDDS) for enhancing the oral bioavailability of lipophilic drugs. The self-microemulsifying drug delivery systems (SMEDDS) are thermodynamically stable and isotropic solutions containing an oil, surfactant, co-surfactant (CoS; or solubilizer), and mixtures of drug which forms oil-in-water microemulsions when incorporated in water and stirred. Different techniques are available to convert liquid–self-microemulsifying drug delivery systems (L-SMEDDS) to solid among which an adsorption technique is economical and very simple. The solid–self-microemulsifying drug delivery systems (S-SMEDDS) of telmisartan (TEL) was developed in the present study which is a poorly water-soluble drug. Different formulations of L-SMEDDS were developed using Capmul PG 8 as oil, Cremophor RH 40 as a surfactant, and Transcutol P as a CoS and were later transformed to S-SMEDDS. The formulations were assessed for dilution study by visual observation, differential scanning calorimetry, analysis of solid S-SMEDDS morphologically, *in vitro* dissolution test, zeta potential measurement, etc. Significantly higher drug release was observed from S-SMEDDS as compared to plain TEL. Hence, it can be concluded that the adsorption technique is a promising approach for the formulation of S-SMEDDS with improved dissolution rate and concomitantly bioavailability.

Keywords: *SMEDDS, solubility, telmisartan, zeta potential*

Introduction

The most of new chemical entities under progress today are sparingly soluble and have poor bioavailability.[1] Different formulation approaches were reported to tackle these problems, which include the use of cyclodextrins, surfactants (S), solid dispersions, drug nanoparticles, lipids, permeation enhancers, and micronization.[2] The success of these approaches is limited because it requires longer processing time, specialized types of equipment, complicated manufacturing processes, and regulatory hurdles. In current years, an area that is having wide popularity with formulation development scientists is the use of lipid-based careers to formulate self-microemulsifying drug delivery systems (SMEDDS) to enhance the bioavailability by the oral route of several lipophilic drugs.[3,4]

SMEDDS are thermodynamically stable and isotropic solutions containing an oil, S, co-surfactant (CoS; or solubilizer), and mixtures of drugs which form oil-in-water microemulsions when incorporated with water and stirred. The drug in a dissolved form can be easily obtained because of the spontaneous formation of emulsion and the small droplet size produced provides a large interfacial surface area for absorption. Therefore, faster drug release from emulsion in a reproducible manner can be obtained with such a system.

Release characteristics of SMEDDS are independent of the fed/fasted state of the patient as well as gastrointestinal physiology. Microemulsion formation is independent of the dilution factor. SMEDDS also inhibits P-glycoprotein reflux, which will lead to an increase in the bioavailability of the drug. The system also promotes lymphatic transport of drugs and inhibits CYP-450 enzyme and thus will prevent high first-pass metabolism of telmisartan (TEL).

TEL is an angiotensin-II receptor antagonist. It is used alone or with thiazide diuretics to treat hypertension, chronic stable angina pectoris, and prinzmetal's variant angina.[5] TEL is practically insoluble in water (<8 mg/L

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at 37°C) with a partition coefficient (logP=7.7). It has high first-pass metabolism due to cytochrome P-450, cytochrome-3A4, and P-glycoprotein reflux; therefore, it has only 42% absolute bioavailability.[6] TEL also showed pH-dependent solubility and food effect on absorption. In the present study, an attempt was made to increase the solubility and *in vitro* dissolution of TEL by formulating it as SMEDDS for filling into hard gelatin capsules. The formulations using medium-chain triglycerides and polyglycolyzed glycerides as S were developed. The formulations were evaluated for their ability to form microemulsions based on the size of the droplet, dissolution characteristics, and zeta potential.

Materials and Methods

Materials

TEL was obtained as a genius sample from Glenmark Pharmaceuticals Ltd, India; Capmul PG 8, Capmul MCM, Captex-300, and Captex-355 were obtained from Abitech Corporation, WI. Oleic acid and sunflower oil were obtained from Fine Chemicals, Mumbai. Cremophor RH 40, Tween 80, Tween 20, and Span 20 were obtained from Colorcon Asia Pvt. Ltd, Singapore. Poly-ethyelene glycol (PEG 400), Transcutol P, and methanol were purchased from a local vendor.

Excipient screening—solubility studies

The shake flask method was used to determine the solubility of TEL in different oils, S, and CoS.[7] The extra quantity of TEL was added to each vial, having 2 mL of the particular vehicle i.e., oil, S, or CoS. The sonication was done for 10 min after sealing and heated for 40°C in a water bath to aid in the solubilization and proper mixing of TEL with the vehicles. These formulated mixtures were kept for 48 h in Orbital Shaking Incubator (REMI; DGS-2) for proper shaking maintained at room temperature. After 48 h, each vial was removed and kept for centrifugation at 3,000 rpm (revolution per minute) for 10 min using a centrifuge (REMI; Centrifuge-GBLC/71188). The drug which remains undissolved was separated by filtering the solution through 0.44 µ Whatman filter paper. Later methanol was used to dilute these aliquots of filtrates and the concentration of dissolved TEL was quantified by UV spectrophotometry at 294.80 nm.[8,9]

Selection of surfactant

A selection of best surfactant from a large pool of surfactant was carried out on the source of water uptake capacity,[10,11] emulsification study,[12,13] and % transmittance study. For the water uptake study selected oil and various S were mixed in the ratio of 1:4 and agitated to form a homogenous mixture using a magnetic stirrer (REMI; 2MIH). Oil-S mixture (1 mL) was placed in test tubes, and water was added dropwise till the system became turbid; then titration was stopped, and the volume of water uptake was noted.

The oil-S mixture (1 mL) was added in a dropwise manner into 400 mL distilled water for determination of % transmittance and was measured using UV-visible spectrophotometer at 680.2 nm. The oil and S were mixed in a 1:3 ratio for emulsification study and further heated at around 40–50°C and agitated to form a homogeneous mixture. The ratio given in literature was used (oil: S) for spontaneously emulsifying type III system. Oil and S mixture was incorporated in distilled water in 1:100 ratio and then visually assessed using the reference grading system as per Table 1.[14]

Selection of co-surfactant

A CoS was added to get a more efficient self-emulsification system. The results of water uptake capacity, emulsifying study, and % transmittance study were used (described above) to select the CoS.[15,16] The S was mixed with selected CoS in a 2:1 ratio to screen the CoS. The oily phase was incorporated into this mixture in a 1:3 ratio with gentle heating and agitated smoothly to form a homogeneous mixture.

Construction of pseudo-ternary phase diagram

The construction of a pseudo ternary phase diagram was done for oil, S/CoS (S_{mix}), and water using the water titration method.[17,18] Ternary mixtures were formulated by changing the composition of S, CoS, and oil. The S and CoS in varied ratios of (1:1, 2:1, 3:1, 1:3) were used and mixed. For the phase diagram of each, oil and specific S to CoS ratio were mixed methodically in varying ratios from 1:9 to 9:1 in separate conical Flask. Different nine combinations of oil and S_{mix} (i.e., 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) were formulated to cover extreme ratios for the study. The oil/S_{mix} was formed which is transparent and homogeneous by stirring for 5 min and obtained mixture was titrated with water and detected for flowability and phase clarity. When the system turns bluish or turbid, titration was stopped, and this point is used to determine the quantity of oil, S, and CoS. The results obtained were used to determine the boundaries of the microemulsion domain. The effect of drug incorporation on the microemulsion boundary was also determined. The Chemix school software version 3.5 was used to construct the phase diagram.

Formulation of SMEDDS batches

A series of A-J SMEDDS formulations specified in Table 2 were formulated using Capmul PG 8, Cremophor RH 40, and Transcutol P.[19] The proportion of oil, S, and CoS was

Table 1: Grading system for self-emulsification property of self-microemulsifying drug delivery systems

Sr.No.	Dispersibility and appearance	Time of self-emulsification (min)	Grade
1	Formulation spreads rapidly in water forming a clear and transparent microemulsion	<1	ME[a]
2	Formulation formed a transparent, gel-like intermediate structure before dispersing completely but could form a microemulsion	3–5	ME[b]
3	Formulation droplets spread in water to form a turbid emulsion	>5	E
4	Formulation exhibits poor emulsification with coalescence of oil droplets	NA	NE

Table 2: Developed formulation with their composition

Formulation	Ingredients (% w/w)				Surfactant/co-surfactant ratio
	Surfactant	Co-surfactant	Oil	Drug	
	Cremophor RH 40	Transcutol P	Capmul PG 8	Telmisartan	
A	59.40	29.70	9.90	1.00	2:1
B	52.80	26.40	19.80	1.00	2:1
C	46.20	23.10	29.70	1.00	2:1
D	39.60	19.80	39.60	1.00	2:1
E	33.00	16.50	49.50	1.00	2:1
F	58.80	29.40	9.80	2.00	2:1
G	52.28	26.14	19.60	2.00	2:1
H	45.75	22.87	29.41	2.00	2:1
I	39.21	19.60	39.21	2.00	2:1
J	32.67	16.33	49.01	2.00	2:1

determined by the pseudo ternary phase diagram. In the formulation batch A–E, the level of TEL was kept constant as (1%), and in formulation batch F–J, the level of TEL was kept constant as (2%). Briefly, in a glass vial, accurately weighed TEL was placed and oil, S, and CoS were also incorporated. The ingredients were further agitated by gentle stirring and were heated at 50°C until TEL was perfectly dissolved. This mixture was placed at room temperature until further use.[20]

Characterization of SMEDDS

Effect of dilution media pH in SMEDDS (Dilution Studies)

This study used to mimic conditions in of the gastrointestinal tract upon oral administration of pre-concentrate SMEDDS.[21] The effect of dilution on pre-concentrate SMEDDS was studied. In this study, particular formulations were imperiled to various dilutions (i.e., 1: 10, 1:50, and 1:100) by using 0.1N HCl and distilled water.

Percentage transmittance

The SMEDDS formulation (1 mL) was diluted with distilled water (100 mL). The spectrophotometric method was used to determine the percentage transmittance at 680 nm using distilled water as a blank.[15]

Self-emulsification and precipitation assessment

A visual assessment method was adopted to evaluate the self-emulsifying properties of SMEDDS formulations. The formulations were exposed to test the speed of emulsification, apparent stability, and clarity of the resultant emulsion and further categorized as per Table 1. Visual assessment was made by adding the SMEDDS pre-concentrate into distilled water (250 mL) or 0.1 N HCl in a dropwise manner. The glass beaker was used to carry out this test (at room temperature) and the contents were gently agitated magnetically at 100 rpm. The formulations were visually examined to find the *in vitro* performance using the grading system shown in Table 1. The visual inspection of the resultant emulsion was carried out after 24 h to check the precipitation. The formulations were then classified after 24 h as

- Clear (transparent with a bluish tinge or transparent)
- Nonclear (turbid)
- Stable (without precipitation at the end of 24 h)
- Unstable (presenting precipitation within 24 h)

Droplet size measurement

A SMEDDS formulation (1 mL) was diluted with 100 mL distilled water with constant stirring using a glass rod. The formulated emulsion was then exposed to particle size analysis. The droplet size distribution of the resultant microemulsion was determined by dynamic light scattering with particle size apparatus (Malvern Zetasizer, United Kingdom; Ver.5.03010). After equilibrium, the particle size was recorded. The formation of SMEDDS is taking place if droplet size reduction below 50 nm is carried out, which are isotropic, stable, and clear. This is an important factor in self-emulsification for the determination of the rate and extent of drug release including stability of the emulsion.

Drug content determination

A TEL SMEDDS (1000 mg) was solubilized in 100 mL of methanol in a volumetric flask separately. One milliliter of the stock solution was measured accurately and then transferred to a 10 mL volumetric flask to which 10 mL methanol was incorporated. Whatman filter paper is used to filter this solution. The above solutions were analyzed by UV Spectrophotometer at λ_{max} 294.80 nm. The amount of TEL present in the formulation was determined using the prepared standard calibration curves of TEL in methanol.

In Vitro dissolution studies of liquid–self-microemulsifying drug delivery systems

A quantitative *in vitro* release test was carried out in 900 mL of buffer pH 1.2 using US Pharmacopeia dissolution apparatus–I (basket). The basket was rotated at 100 rpm. The hard gelatin capsules (0 sizes) were used for the incorporation of liquid–self-microemulsifying drug delivery systems (L-SMEDDS) formulations and the in vitro drug release was studied. The plain drug and marketed formulation results were compared. In this study, a 5 mL sample of the medium was taken out from the flask and analyzed using UV spectrophotometrically at 291.4 nm. The removed volume was replaced each time with 5 mL of fresh medium. Dissolution studies were also performed in distilled water and phosphate buffer pH 7.4 to examine the effect of pH on drug release.

Viscosity determination

The structure and type of microemulsion system were characterized by rheological measurements. The viscosity of optimized microemulsion was evaluated by a viscometer (Brookfield LV DV-II + Pro) using a small sample adaptor 31 spindle at 5,10, 20, 50 rpm. Experiments were performed in triplicate for the sample.

Preparation of S-SMEDDS

In 100 mL distilled water, maltodextrin (10 g) was dissolved by the use of a magnetic stirrer.[22,23] Then the optimized formulation of L-SMEDDS (10 g) was then added with constant stirring, magnetically stirred to obtain a good o/w emulsion. The emulsion was spray-dried with a spray drier (Labultima; U-222) under the following conditions given in Table 3.

Evaluation of solid S-SMEDDS

Dilution study by visual observation

To study the effect of dilution on solid–self-microemulsifying drug delivery systems (S-SMEDDS), a dilution study was carried out.[22,23] In 100 mL of distilled water (in a glass beaker), S-SMEDDS (100 mg) were introduced that was retained at 37ºC and the contents were agitated slowly using a magnetic stirrer. When clear microemulsion is formed, it is qualitatively designated as "good," and when there was a turbid or milky white emulsion formed, it is termed as "bad" based on the emulsification ability of S-SMEDDS.

Differential scanning calorimetry

The compatibility of TEL with other excipients in the S-SMEDDS was studied using differential scanning calorimetry (DSC). The sample of about 2.5 mg was positioned in standard aluminum pans and dry nitrogen was used as effluent gas. The sample was scanned at a heating rate of 10°C/min between 40 and 300°C and 40 mL/min nitrogen flow. The differential scanning calorimetry gave an idea about the crystallinity of S-SMEDDS. It also allows us to study possible degradation pathways of the materials.

Morphological analysis of S-SMEDDS

The S-SMEDDS were studied for their macroscopic structure using Scanning Electron Microscope (SEM; FEI, the Netherlands) which is operating at 10 kV. The sample was placed on SEM stub and then coated with a thin layer of gold.

In vitro dissolution test of S-SMEDDS

A S-SMEDDS containing 10 mg of TEL were filled into a hard gelatin capsule (Capsule no. 00), and a dissolution test was carried out as described previously in distilled water, hydrochloric acid buffer pH 1.2, and phosphate buffer pH 7.4.[23]

Zeta potential and particle size measurement

Zeta potential and particle size were determined by Zetasizer, Malvern) was observed at 25°C at a scattering angle of 173°. The formulations were incorporated in water (diluted 100 times) and then positioned in an electrophoretic cell for measurement.[23,24]

Results and Discussion

Compatibility study

The thermogram of DSC of TEL, maltodextrin, TEL, and maltodextrin mixture are given in Figure 1. The thermograms of both TEL and the physical mixture of TEL and maltodextrin exhibited a sharp peak at 270.07°C and 269.70°C representing the melting point of TEL. The thermogram of polymer (maltodextrin) showed an endothermic peak at 222.53°C, which corresponds to the melting point of maltodextrin. The ratio for a drug:KBr (Potassium bromide), mixture:KBr, maltodextrin:KBr were maintained at (1:99). It is been shown [Figure 1] that the intensities of the thermograms are different. This is due to the weight of TEL in the mixture (TEL and maltodextrin in 1:1 ratio) which was less as compared to the thermogram of plain drug TEL. From the and DSC studies, it was concluded that the excipient and drug did not interact and are compatible.

Solubility studies

Solubility of TEL in CoS, S, and oils is shown in Figures 2, 3, and 4, respectively. Solubility studies were performed in triplicate and the result presented as mean with standard deviation. As shown in the figures, TEL exhibited good solubility in the Capmul PG 8 among the oils. Enhanced solubility of the drug is observed in medium-chain triglycerides (MCT) than low chain triglycerides because MCT possesses higher ester content per gram than long chain triglycerides (LCT); therefore, the drug has higher solubility in MCT than LCT. Thus for further studies, Capmul PG 8 as oil was selected. In the case of S, the drug exhibited good solubility in Cremophor RH 40, Tween 80, and in CoS Transcutol P, PEG 400 showed good solubility.

Selection of surfactant

The selection of S and CoS was ruled by their emulsification efficiency for the selected oily phase instead of their ability to solubilize the drug. Three nonionic S, namely Cremophor RH 40, Tween 20, Tween 80, were chosen for screening.

Table 3: Operating condition for spray drying process

Sr. No	Parameter	Value
1	Inlet temperature	80°C
2	Outlet temperature	70°C
3	Aspiration	85%
4	Feed rate	5 mL/min

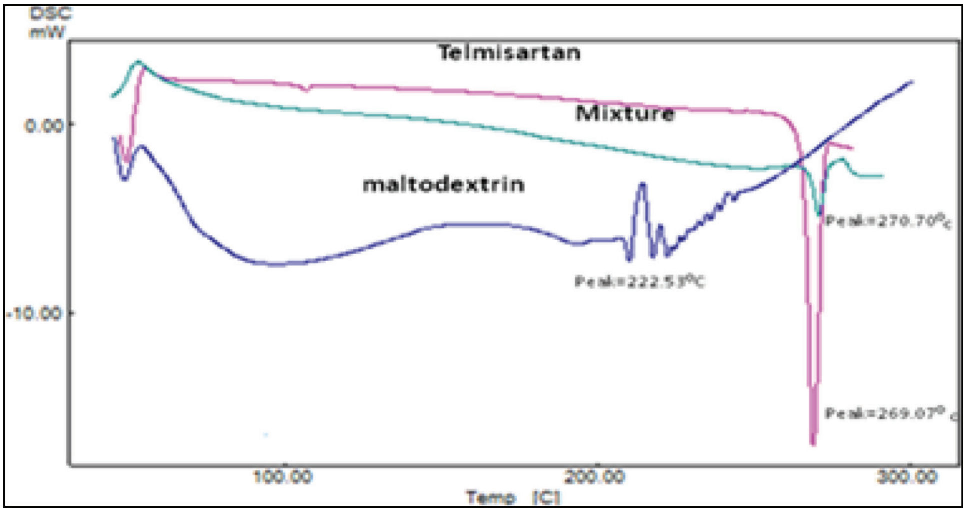

Figure 1: DSC thermogram of telmisartan, mixture, and maltodextrin. DSC = differential scanning calorimetry

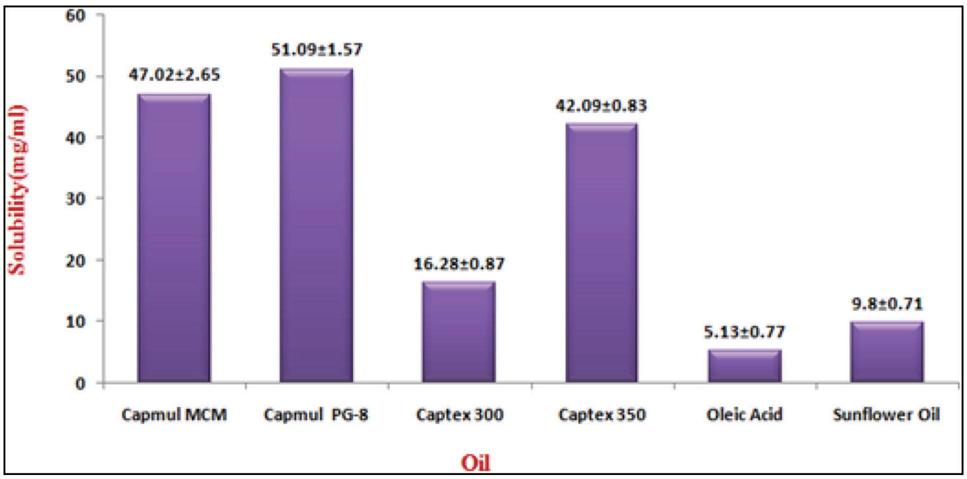

Figure 2: Solubility of telmisartan in various oils

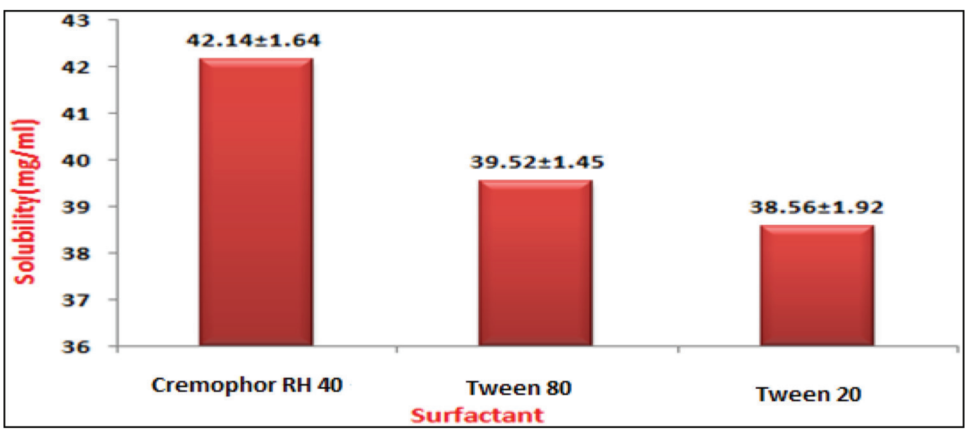

Figure 3: Solubility of telmisartan in various surfactants

S was selected collectively based on the emulsification study, % transmittance study, and water uptake study as shown in Tables 4 and 5, which distinguished the ability of S to emulsify selected oil phases. Tween 80 showed better ability to emulsify Capmul PG 8 whereas, Tween 80 and Tween 20 showed less water uptake capacity compared to the combination of them and shows poor emulsifier. Also, Cremophor RH 40 shows a better ability to emulsify Capmul PG 8 and a high-water uptake capacity. From this study, Capmul PG-8 as oil, RH40 as S was selected for further formulation and development.

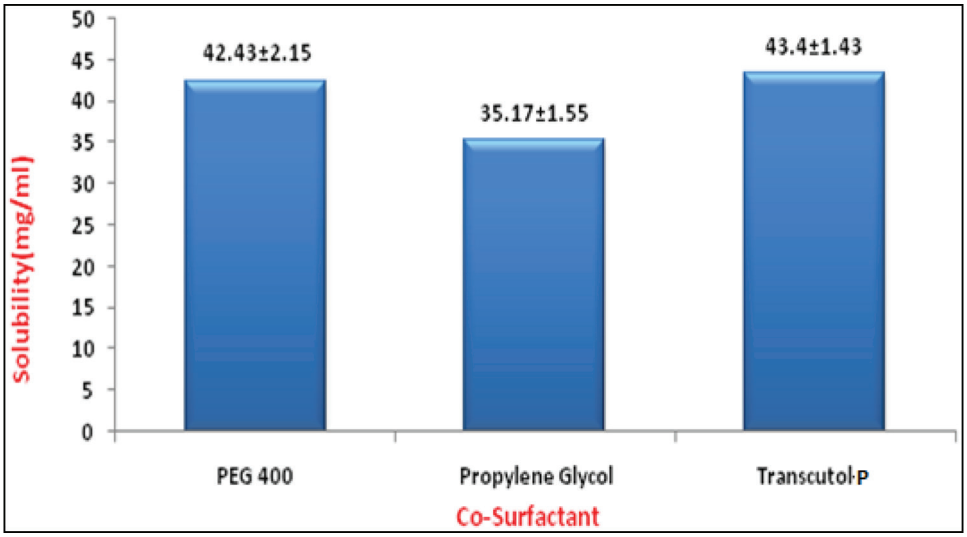

Figure 4: Solubility of telmisartan in various co-surfactants

Table 4: Selection of surfactants

Sr.No	Oil	Surfactant	Water uptake capacity (mL)	Emulsification study	% T	Remarks
1	Capmul PG 8	Tween 80	4 (H.V)	ME_a	93.59	Passed
2	Capmul PG8	Tween 20	3	ME_a	104.11	Passed
3	Captex300	Tween 80	1.5	E	58.22	Rejected
4	Captex 355	Tween 80	2 (oil globule set down)	NE	100.52	Rejected
5	Capmul MCM	Tween 80	2.3 (H.V)	NE	12.54	Rejected
6	Captex300	Tween 20	3.5	ME_b	78.37	Fair
7	Captex 355	Tween 20	1.4	E	1.59	Rejected
8	Oleic acid	Tween 20	1.2	E	2.16	Rejected
9	Capmul PG 8	Cremophor RH 40	5	ME_a	98.45	Passed

H.V = highly viscous

Table 5: Surfactant in ratio (oil: capmul PG 8)

Sr. No	Surfactant mixture	Water uptake capacity (mL)	Emulsification study	% Transmittance	Remarks
1	Tween 80 + Tween 20 (1:1)	1.8	ME_a	87.97	Fair
2	Tween80 + Tween 20 (2:1)	4.0	ME_a	89.16	Passed
3	Tween 80 + Tween 20 (1:2)	1.5	ME_b	82.48	Fair
4	Tween 80 + Tween 20 (1:3)	2.5	ME_a	87.47	Passed
5	Tween 80 + Tween 20 (3:1)	3.2	ME_a	99.42	Passed

Table 6: Selection of co-surfactants oil-capmul PG 8

Sr.No	Surfactant + co-surfactant	Water uptake capacity (mL)	Emulsification study	% Trasmittance	Remarks
1	Tween 80 + PEG 400	1	ME_a	74.47	Passed
2	Tween 80 + PEG 400	3	ME_a	76.46	Passed
3	Tween 80 +span 20	0.5	E	71.81	Rejected
4	Tween 80 + PEG 400	0.5	ME_b	91.92	Fair
5	Tween 80 + PG	4	ME_a	92.26	Passed
6	Tween 80 + span 20	0.2	E	18.22	Rejected
7	Tween 80 +Tween 20 + PEG 400	0.5	ME_b	76.73	Fair
8	Tween 80 + Tween 20 + PG	2	ME_a	70.05	Passed
9	Tween 80 +Tween 20 + span 20	0.6	E	69.75	Rejected
10	CRH 40 + TP (1:1)	6.2	ME_a	98.57	Passed
11	CRH 40 + TP (2:1)	7.1	ME_a	98.47	Passed
12	CRH 40 +TP (1:2)	6.5	ME_a	98.29	Passed
13	CRH 40 + TP (1:3)	6.3	ME_a	94.85	Passed
14	CRH 40 + TP (3:1)	6.8	ME_a	98.12	Passed

CRH = Cremophor, PEG = poly-ethyelene glycol, TP = Transcutol P

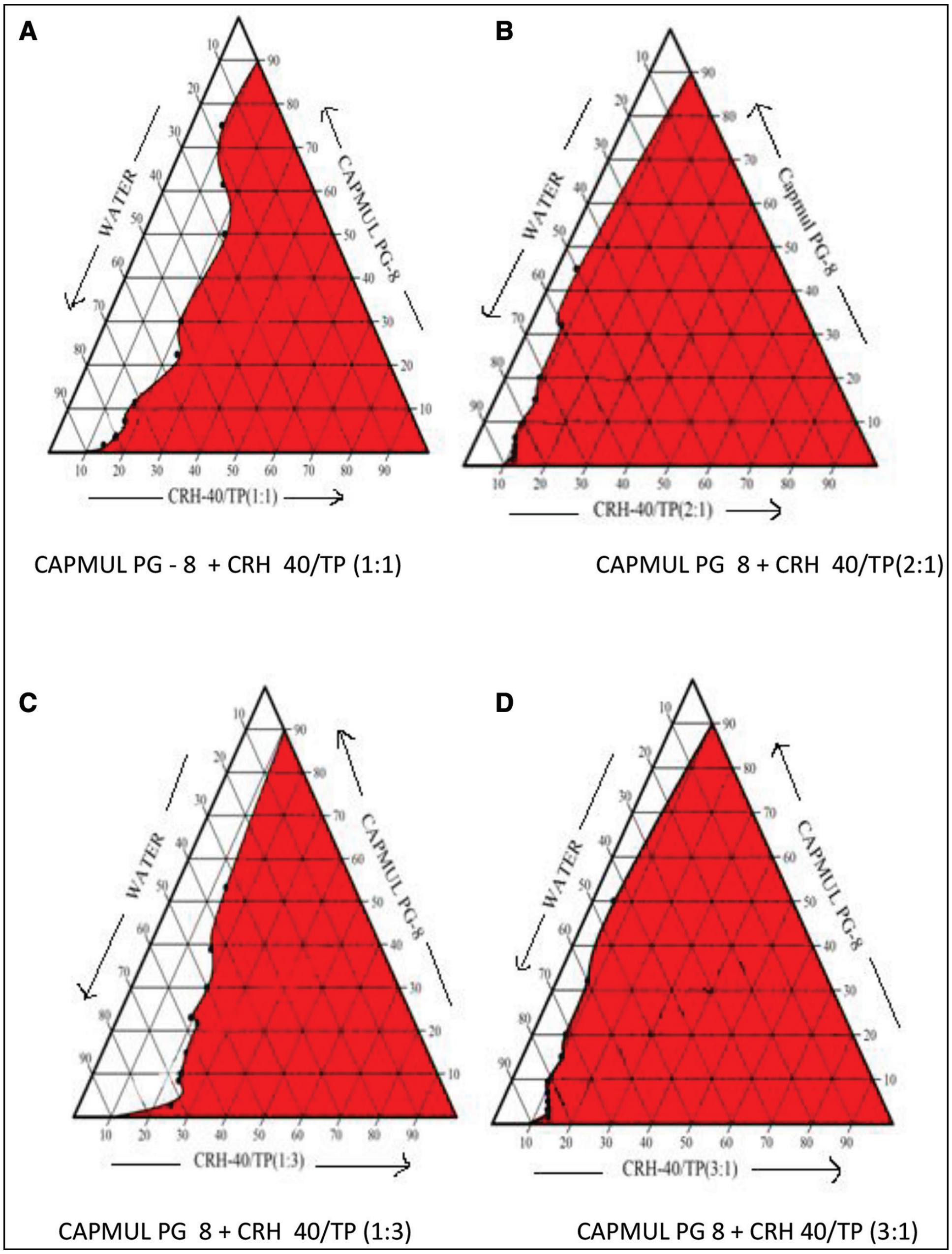

Figure 5: Capmul PG 8 + Cremophor (CRH) RH 40 + Transcutol P

Selection of co-surfactants

Table 6 shows the efficacy of CoS to enhance the emulsification of S. Propylene glycol cant form a clear solution with selected oil and mixed S and also has very less percentage of transmittance and water uptake capacity. PEG 400, Transcutol P, and hydrophilic CoS increased spontaneity of microemulsion formation and showed clear solution along with good water uptake capacity and, therefore, were selected for further studies. The proportion of S and CoS is the same throughout the study clearly shows the ability of CoS to improve the emulsification of S.

Construction of pseudo-ternary phase diagram

The pseudo ternary phase diagram was constructed to obtain concentration ranges of components for the formation of microemulsions. With only gentle agitation, self-micro emulsifying systems form fine o/w emulsions upon their addition into aqueous media. CoS and S are first adsorbed at the interface, decreased the interfacial energy, and also provided a mechanical barrier to coalescence.

The results of solubility studies and screening of S Capmul PG 8 were selected as the oil phase, Cremophor RH 40 as S, and Transcutol P as the CoS. For the construction of phase diagrams, purified water was used as an aqueous phase. Pseudo-ternary phase diagrams of S and CoS (S_{mix}), oil, and water but without drug incorporation were plotted. From pseudo-ternary phase diagram [Figure 5B] it is evident that Capmul PG 8 + Cremophor RH 40 + Transcutol P, system have larger micro emulsification region compared with Capmul PG 8 + Tween

80 + PEG 400, Capmul PG 8 + Cremophor RH 40 + PEG 400, and Capmul PG 8 + Cremophor RH 40 + Tween 80 systems.

Figure 6 showed phase diagrams in the presence of the drug, the incorporation of the drug, and large the microemulsion existence area if TEL (20 mg/g) was added into the formulation because the introduction of the drug in the lipid phase led to the growth of the lipid phase and consequently a need for a higher S/CoS ratio for stabilization.

Therefore, due to the larger micro emulsification area and greater capacity for oil incorporation indicates improve drug loading. From this pseudo-ternary phase diagram study, **Oil** (Capmul PG 8: 50–90%) and **S/CoS** (Cremophor RH 40/ Transcutol P: 10–50%) were selected for further formulation and development.

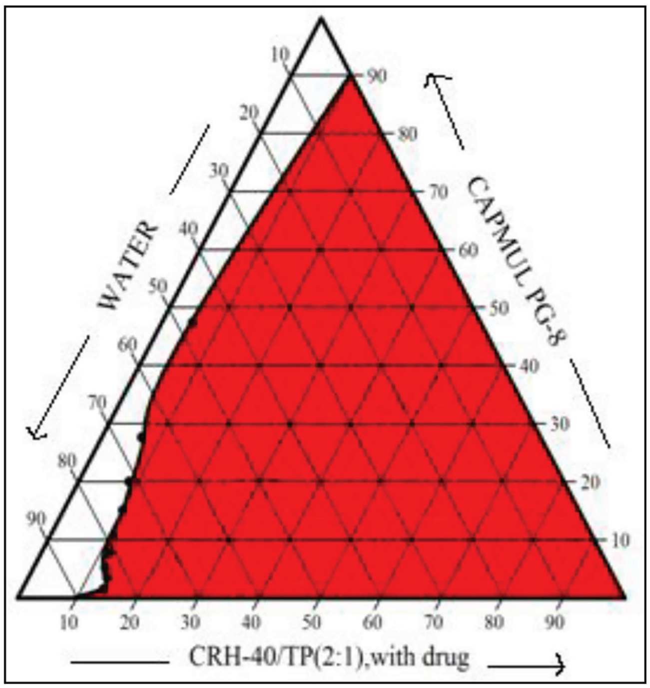

Figure 6: Capmul PG 8 + Cremophor (CRH) RH 40 + Transcutol P (with drug)

In conclusion, the study is very important to identify

Microemulsion formation area.
The ratio of S to CoS on it and maximum oil incorporation.
It also helped to determine a suitable ratio and concentration range of various components for the formation of SMEDD.

Based on the pseudo ternary phase diagram, ten different preliminary batches of SMEDDS were made using Capmul PG 8 as oil (10–50%), Cremophor RH 40 (30–60%), and Transcutol P (15–30%) and were selected for forwarding characterization through Self-emulsification and precipitation assessment, dilution study, % transmittance study, particle size analysis. First, all ten bathes were passes the test for dilution studies and % transmittance study. After that all batches were subjected to self-emulsification and precipitation assessment; from these batches, A–E passed the test, but batches F–J showed signs of precipitation when subjected to precipitation test for 24 h. Therefore, batches A–E were used for further formulation and development. Lastly, during optimization, selected formulation bathes were put through to particle size analysis; formulation batch A showed low particle size, which might be because of low oil concentration (10%) and due to Transcutol P which was more hydrophilic and easily penetrates the S layer and shows low particle size.

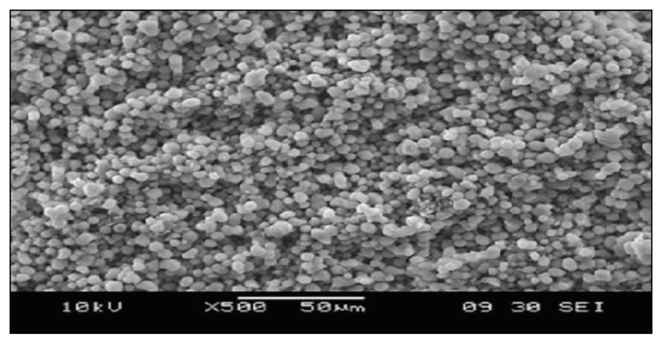

Figure 8: SEM images of S-SMEDDS (magnification ×500; scale = 50.0 µm). S-SMEDDS = solid–self-microemulsifying drug delivery systems

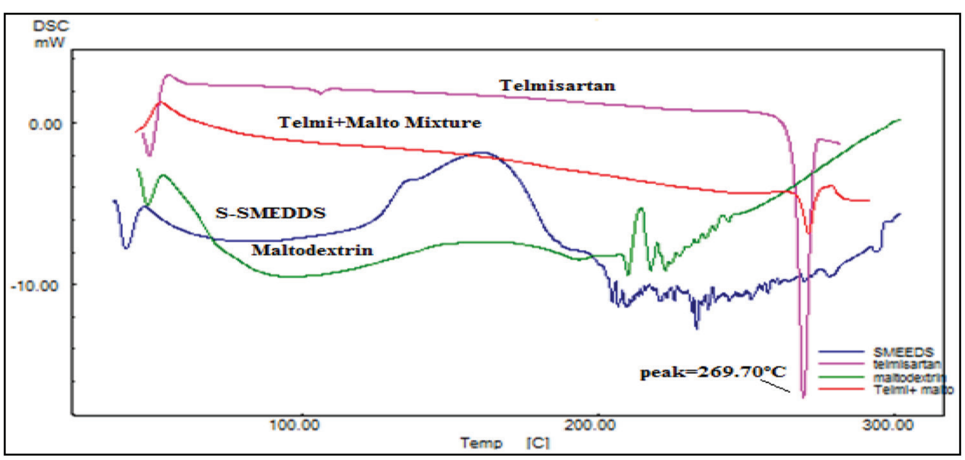

Figure 7: DSC thermogram of telmisartan, telmisartan + maltodextrin mixture, S-SMEDDS, maltodextrin. DSC = differential scanning calorimetry, s-SMEDSS = solid–self-microemulsifying drug delivery systems

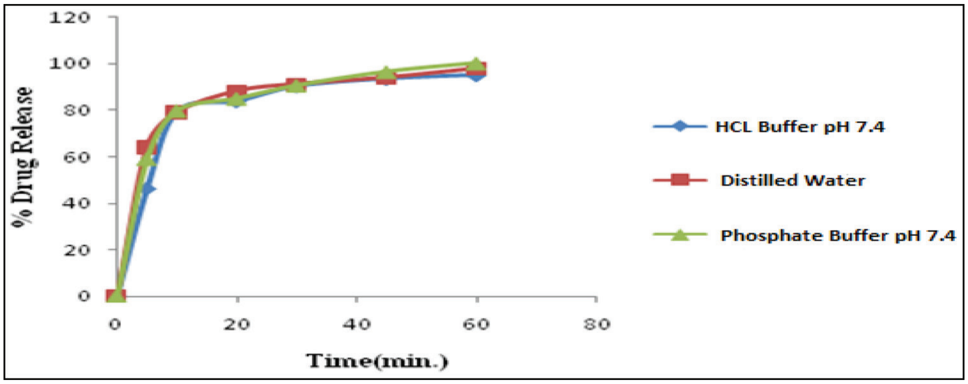

Figure 9: *In vitro* release study of S-SMEDDS. S-SMEDDS = solid–self-microemulsifying drug delivery systems

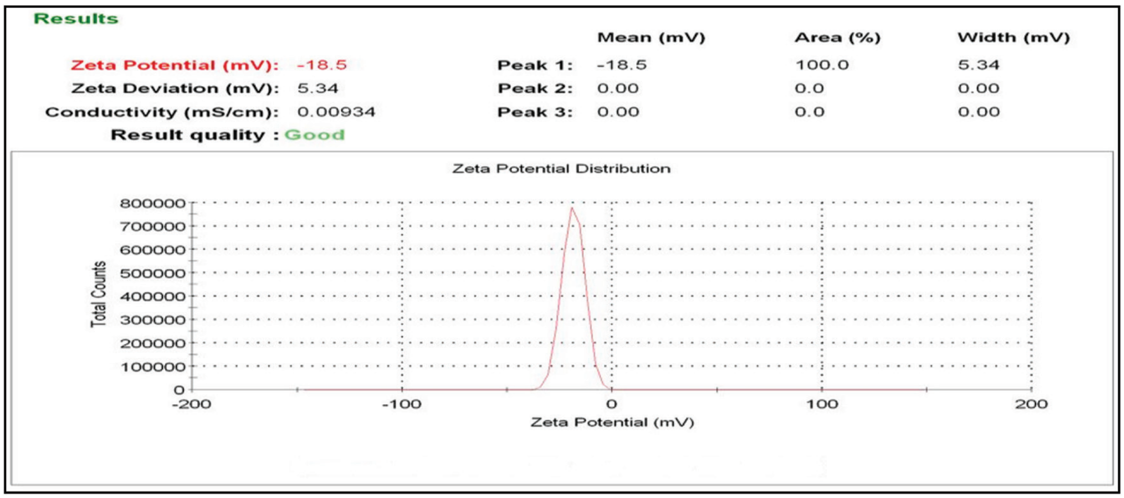

Figure 10: Zeta potential of optimize liquid SMEDDS formulation. SMEDDS = self-microemulsifying drug delivery systems

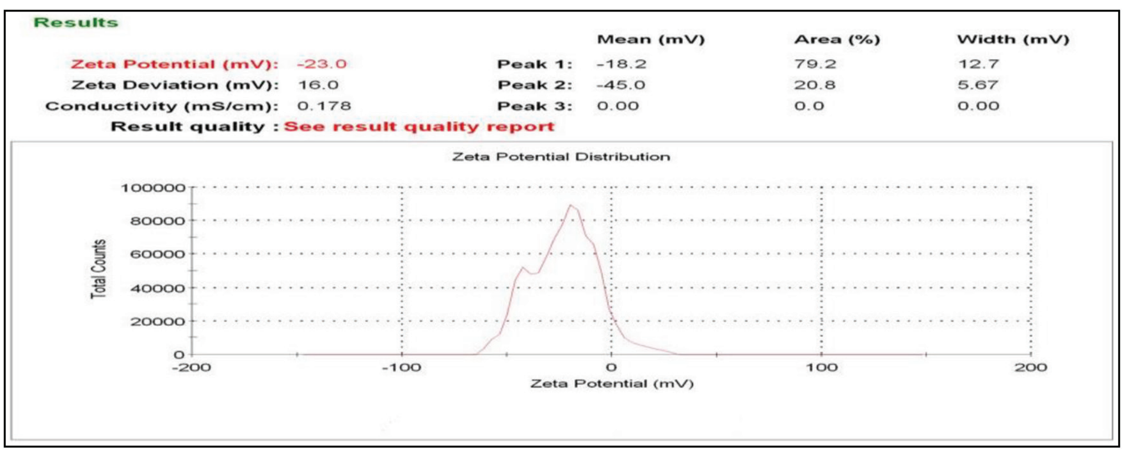

Figure 11: Zeta potential of S-SMEDDS formulation. S-SMEDDS = solid–self-microemulsifying drug delivery systems

Evaluation of S-SMEDDS

Dilution study by visual observation

To assess the self-emulsification of S-SMEDDS, a visual test was carried out in 100 mL distilled water at 37°C under gentle stirring. It is observed that S-SMEDDS showed spontaneous micro emulsification. Also, microemulsion was stable with no signs of phase inversion or phase separation even after 2 h.

Differential scanning calorimetry study

The compatibility of TEL with other excipients in the S-SMEDDS was studied using DSC. DSC curves of pure TEL, the physical mixture of TEL and maltodextrin (1:1), and the S-SMEDDS of TEL are depicted in Figure 7. Pure TEL showed a sharp endothermic peak at 269.07°C. The physical mixture exhibited small endothermic peaks for the drug. This effect could be attributed to dilution by maltodextrin.

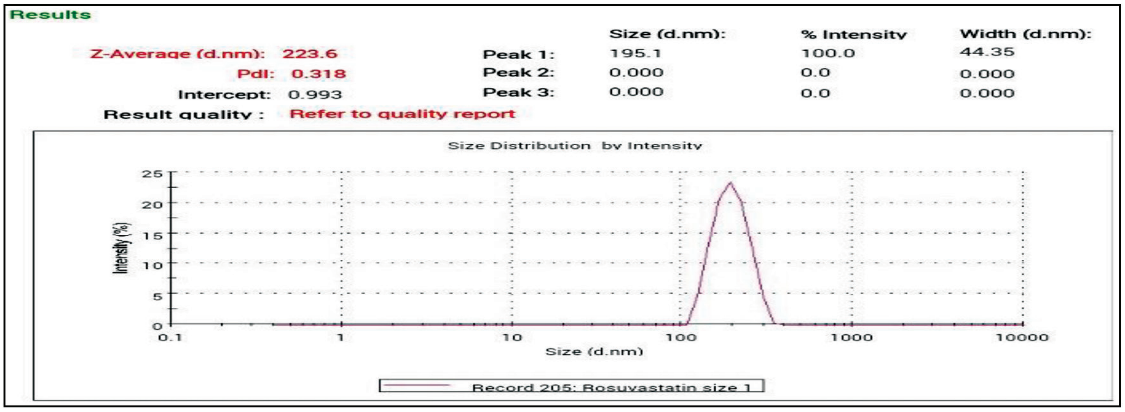

Figure 12: Particle size distribution of S- SMEDDS formulation. S-SMEDDS = solid–self-microemulsifying drug delivery systems

Maltodextrin did not show any peak over the entire range of the tested temperatures. No obvious peak of the drug was found in the S-SMEDDS of TEL showing that the drug must be present in a molecularly dissolved state in S-SMEDDS.

Morphological analysis of S-SMEDDS

Figure 8 showed that S-SMEDDS appeared as smooth-surfaced S-SMEDDS particles, indicating that the L-SMEDDS was adsorbed or coated inside the pores of maltodextrin and with a lesser amount of aggregation.

In vitro dissolution studies

In vitro dissolution study revealed [Figure 9] that S-SMEDDS also released more than 85% of the drug within 20 min and almost 95% up to 30 min irrespective of pH of dissolution media. This showed that drug releases from S-SMEDDS were found to be comparatively higher as compared to plain TEL.

Zeta potential and particle size measurement

The Zeta potential of the liquid systems is of considerable importance from the stability point of view. The systems having zeta potentials between +30 and −30 show good stability profiles. In this study, the zeta potentials of the formulations were −18.5 and −23.0 for L-SMEDDS and S-SMEDDS, respectively [Figures 10 and 11] which was less than −30 showing good stability. The particle size of S-SMEDDS was found to be 150 nm as shown in Figure 12.

Conclusion

The study concluded that S-SMEDDS of TEL formulated by adsorption process using maltodextrin represents good flow properties and drug content. The microemulsion with a micrometric range is formed after reconstitution. The *in vitro* drug release was comparatively higher than that of plain TEL. Hence adsorption process using maltodextrin as a solid carrier may efficiently formulate S-SMEDDS which enhance dissolution rate and intestinal permeability and concomitantly bioavailability.

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Nil.

Conflicts of interests

There are no conflicts of interest.

References

1. Ewart TC, Dominique C, Hassan B. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Adv Drug Delivery Rev. 2008; 60:747-56.
2. Dahan A, Hoffman A. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. J Control Release 2008;129:1-10.
3. Porter CJ, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv Drug Deliv Rev 2008;60:673-91.
4. Morozowich W, Gao P. Developing solid oral dosage forms: Pharmaceutical theories and practice. Elsevier 2005;1:443-68.
5. Rang HP, Dale MM, Ritter JM, More PK. Pharmacology. 5th ed. Churchil Edinburgh: Churchill Livingstone; 2003.
6. Anthony CM, Osselton MD, Widdor B. Clarke's analysis of drug and poisons in pharmaceuticals, body fluids and postmorten material. Pharmaceutical Press 2004;3:1601-2.
7. Jing C, Bo Y, Yu Z, Weiwei Z, Houli L, Hongxiang L, Guangxi Z. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. Pharmaceutical Nanotechnology. Int J Pharm 2009;371:148-55.
8. Preeti KS, Sharma S. Formulation and In-vitro charecterization of self-nanoemulsifying drug delivery system of cinnarizine. Int J Comprehensive Pharmacy 2011;9:1-6.
9. Jesper L. Method for measurement of solubility and dissolution rate of sparingly soluble drugs. Examensarbate Institution for Kemitknik. Masters work in Chemical Engineering 2010:1-24.
10. Yu Z, Weiwei Z, Houli L, Hongxiang L, Guangxi Z. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. Pharmaceutical Nanotechnology. Int J Pharm 2009;371:161-5.
11. Xi J, Chang Q, Chan CK, Meng ZY, Wang GN, Sun JB, *et al*. Formulation development and bioavailability evaluation of a self-nanoemulsified drug delivery system of oleanolic acid. AAPS Pharmscitech 2009;10:172-82.
12. Date AA, Nagarsenker MS. Design and evaluation of microemulsions for improved parenteral delivery of propofol. AAPS Pharmscitech 2008;9:138-45.
13. Date AA, Nagarsenker MS. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm 2007;329:166-72.

14. Borhade V, Nair H, Hegde D. Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS Pharmscitech 2008;9:13-21.
15. Azeem A, Rizwan M, Ahmad FJ, Iqbal Z, Khar RK, Aqil M, *et al*. Nanoemulsion components screening and selection: A technical note. AAPS Pharmscitech 2009;10:69-76.
16. Patel AR, Vavia PR. Preparation and in-vivo evaluation of SMEDDS (Self-Microemulsifying Drug Delivery System) containing fenofibrate. AAPS PharmSciTech 2007;9:E344-52.
17. Enas AM, Ehab RB, Magdy IM. Preparation and evaluation of self-nanoemulsifying tablets of carvedilol. AAPS PharmSciTech 2009;10:183-91.
18. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, *et al*. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 2004;274:65-73.
19. Singh AK, Chaurasiya A, Singh M, Upadhyay SC, Mukherjee R, Khar RK. Exemestane loaded self-microemulsifying drug delivery system (SMEDDS): Development and optimization. AAPS Pharmscitech 2008;9:628-34.
20. Dixit AR, Rajput SJ, Patel SG. Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS Pharmscitech 2010;11:314-21.
21. Singh SS, Sarkar B, Dhanwan RK. Microemulsion drug delivery system:for bioavailability enhancement of ampelopsin. ISRN Pharmaceutics 2012;108164:1-4.
22. Sander C, Holm P. Porous magnesium aluminometasilicate tablets as carrier of a cyclosporine self-emulsifying formulation. AAPS Pharmscitech 2009;10:1388-95.
23. Sharma S, Preeti KS. Formulation, In-vitro characterization and stability studies of self microemulsifying drug delivery systems of domperidone. Int J Innovative Pharm Research 2010;1: 66-73.
24. Warangkana W, Alison B, Lawrence MJ. Light-scattering investigations on dilute nonionic oil-in-water microemulsions. AAPS PharmsciTech 2000;2:1-11.