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Formulation and in-vitro Evaluation of Supersaturable Dry Micro-emulsion for the Enhancement of Dissolution

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ABSTRACT

The present study deals with formulation of Supersaturable solid self-microemulsifying drug delivery system of poorly water soluble drug.SMEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug that form a fine oil-in-water emulsion when introduced into aqueous phase under gentle agitation.

The present research work describes a Supersaturable solid self-microemulsifying drug delivery system of Nebivolol using Castor oil, Tween 80 and PEG 400. Nebivolol is a cardioselective β-adrenergic receptor antagonist with limited water solubility which accounts for low oral bioavailability (12%).

Hence, the main objective of study was to formulate Supersaturable S-SMEDDS of Nebivolol in order to achieve a better dissolution rate which would further help in enhancing oral bioavailability using HPMC as PPI.Pseudo-ternary phase diagrams were plotted to check for the micro-emulsification range and to evaluate the effect of Nebivolol on the emulsification behavior of the phases. Prepared SMEDDS formulations were tested for microemulsifying properties and microemulsions were evaluated for robustness to dilution, assessment of efficiency of self emulsication, emulsification time, viscosity, drug content and in-vitro dissolution. The optimized SMEDDS formulation further evaluated for centrifugation studies, freeze thaw cycling, particle size distribution, DSC, SEM and zeta potential were carried out to confirm the stability of the formed SMEDDS. The liquid formulation was solidified by using spray dryer, using Aerosil 200 as solid carrier. Thus Supersaturable S-SMEDDS of Nebivolol may provide the useful solid dosage form for oral poorly water soluble drugs.

Key words: Nebivolol, Self micro emulsifying drug delivery system, Dissolution, Solid-carrier, Castor oil, Tween 80, PEG 400.

INTRODUCTION

The low solubility of many new drug candidates is a substantial challenge facing by the pharmaceutical industry[1]. Self-microemulsifying drug delivery system (SMEDDS) can be defined as an isotropic multi-component drug delivery system composed of surfactant, co-surfactant and oil which spontaneously form microemulsion in the presence of water[2-3]. Conventional self-microemulsifying drug

delivery systems (SMEDDS) are widely used in enhancing the oral absorption of poorly-soluble drugs[4-7]. When SMEDDS formulations introduced into gastrointestinal area (GI), drug precipitation may be occurred and lead to failure of improvement of intestinal absorption. On the other hand, high surfactant level typically present in SMEDDS formulations can cause GI side-effects. The supersaturatable self-microemulsifying drug delivery system (S-SMEDDS) represents a new thermodynamically stable formulation approach wherein it is designed to contain a reduced amount of surfactant and water-soluble polymer (precipitation inhibitor or supersaturated promoter) to prevent precipitation of the drug by generating and maintaining a supersaturated state *in-vivo*. The S-SMEDDS formulations can result in enhanced oral absorption as compared with the related self-emulsifying drug delivery systems (SMEDDS) formulation and the reduced surfactant levels may minimize gastrointestinal surfactant side effects[8-11].

Various viscosity grades of hydroxypropyl methylcellulose (HPMC) are well-recognized for their ability to inhibit crystallization and thereby, generate and maintain their supersaturated state for extended time periods[12].*In vitro* dilution of the S-SEDDS formulation results in the formation of a microemulsion, followed by slow crystallization of the drug on standing indicate that the supersaturated state of the system is prolonged by HPMC in the formulations.

Nebivolol is a cardioselective β-adrenergic receptor antagonist and highly lipophilic compound with having log P=2.44 and belongs to BCS class II group with having low oral bioavailability (12%), which stems from poor solubility of Nebivolol in water.

Aim of the present work is to develop and evaluate orally administrable capsule by the technique called supersaturable solid self-microemulsifying emulsion of an antihypertensive agent Nebivolol by using suitable surfactant, co-surfactant and oil having greater release compared to available formulation in the market.

Materials and Methods

Materials

Nebivolol is obtained as gift sample from Watson Pharma Ltd (Hyderabad, India).Tween 80,PEG-400,Castor oil obtained as gift sample from Nulife Pharmaceuticals,Pimpri(Pune,M.S).

Aerosil-200 obtained as gift sample from Solanki chemicals, Bhosari, Pune (M.S.). Methanol HPLC grade was purchased from Loba chem.

Methods

Solubility Studies [13-15]

The solubility of drug was determined by adding excess amount of the drug in small vials containing 2 ml of selected oil, surfactants and co-surfactants separately. The drug was mixed in respective oil and surfactant manually with glass rod for 30 minutes then the vials were kept for sonication about two hours. The vials were tightly stopper and were continuously stirred for 72 hrs in orbital shaking incubator (REMI; RIS 24 BL) at 25^0C. Oils were centrifuged (REMI; C- 24BL) at 3500 rpm for 20 min. The supernatant was separated and dissolved in methanol and solubility was quantified by UV-Spectrophotometer (SHIMADZU UV-1700; 06103) at 281 nm after appropriate dilution with methanol.

Pseudo ternary phase diagram [16,17]

For constructing pseudo-ternary phase diagram, Castor oil was selected as oil. Tween 80 as a surfactant and PEG-400 as a cosurfactant shows better emulsifying properties with Castor oil. Microemulsion formation area was found to be S/Cos highest at S/Cos=1:1 and 2:1 (ratio of concentration of surfactant to cosurfactant). At S/Cos= 1:1 system had capacity to solubilize as much as 50% (w/w) of oily phase. A larger microemulsion region allows to the higher microemulsifying potential of the combination. Thus one can find regions having better microemulsifying ability at lower proportion of surfacatnt and having higher drug loading potential.

Selection of formulations from phase diagrams [21,22]

From phase diagram (Figure 1) nine formulations were selected containing 50% - 20%(w/w) of oil phase which are mention in a Table 1. Formulations containing higher % of S/Cos have the tendency to precipitate drug in vivo as also retard the release of drug both of which are undesirable features.Hence the objective was to select a formulation having lower % of S/Cos. Supersaturable SMEDDS has been designed to reduce the amount of surfactant by incorporating a water soluble polymeric precipitation inhibitor (PPI).

Thermodynamic stability study [24,25]

SMEDDS are thermodynamically stable systems comprising of isotropic mixtures of oil, surfactant and cosurfactant with no phase sepration,creaming and cracking.Selected formulation were subjected to thermodynamic stability stress study such as heating and cooling cycles at each temperature 4° C and 45° C for not less than 48 h and freeze thaw cycle comprising six cycles between -20°C and 25° C with storage at each temperature for not less than 48 h. This was followed by centrifugation at 3500 rpm for 30 min.The optimized NEB S-SMEDDS was stored at 40° C/75% RH (Newtronics chamber) for 03 month and evaluated for % transmission, Drug content and Globule size.

Self-emulsification time [18]

Visual evaluation is the primary means of self-emulsification assessment. Each formulation (1 ml) was introduced into 500 ml of distilled water in a glass flask at room temperature and stirred gently using magnetic stirrer.

Preparation of NEB SMEDDS [23]

From solubility study and comparison of the constructed ternary phase diagrams, SMEDDS component were selected for drug incorporation and further optimization a series of SMEDDS formulations were prepared using Tween-80 and Polyethylene glycol-400 as the S/Cos combination and Castor oil as the oil. NEB SMEDDS were prepared by dissolving drug(5 mg) into S/Cos in glass vials and oil were accurately weighed in to glass vial. Components were mixed and heated (40–50 °C) to form a homogenous mixture and stored at room temperature until used. Compositions of liquid SMEDDS formulations are shown in Table 1.

Table 1: Composition of liquid SMEDDS of Nebivolol

S/CoS Ratio	Nebivolol (mg)	Formulation Code**	Castor oil* (%)	Tween 80 (%)	PEG 400 (%)
2:1	5	F1	50	30.83	14.16
	5	F2	45	34.16	15.83
	5	F3	40	37.5	17.5
	5	F4	35	40.83	19.16
	5	F5	30	44.16	21.83
	5	F6	20	50.83	24.16
1:1	5	F7	40	27.5	27.5
	5	F8	30	32.5	32.5
	5	F9	20	37.5	37.5

Note: *: oil enriched with the drug
**: HPMC is added 5% in each formulation to avoid in-vivo precipitation

Evaluation of Drug loaded SMEDDS

Selected formulations were evaluated for percentage transmittance, cloud point, viscosity, globule size, Drug content**,** *in vitro* dissolution study.

Percentage transmittance study [26]

1ml of each formulation was diluted 100, 1000 fold with water, 0.1N HCl, phosphate buffer pH 7.4 and percentage transmittance was determined using UV-Vis spectrophotometer [Shimadzu] at 281 nm using respective solvent/reagent as blank.

Viscosity measurement [13]

Viscosity was determined using Brookfield DV II RV cone and plate rheometer (Brook field Engineering Laboratories, Inc, Middleboro, MA) with spindle # CPE40 was used for the determination of viscosity of the formulations.

Globule size analysis [27,28]

The globule size was measured with Malvern zetasizer nano zs (Nano ZS, Malvern Instruments, Worcestershire, UK)[19] able to measure sizes between 10 to 5000 nm. Helium-neon gas laser having intensity of 4 mW was the light source. The instrument is based on the principle of dynamic light scattering (DLS).

Drug content [29]

The percent drug content of NEB in SMEDDS was estimated by dissolving appropriate quantity of individual SMEDDS equivalent to 100 mg in 0.2 M HCl. The samples were mixed thoroughly to dissolve the drug in 0.2 M HCl. The sample was sonicated using ultrasonicator for 15 min and analyzed using UV spectrophotometer and absorbance was recorded.

In-vitro Dissolution Test [30-32]

Formulation F2, F3, F7 and F8 (dose equivalent to 5 mg) was filled in size '0' hard HPMC capsule and it is compared with plain drug NEBIVOLOL tablet 5mg. In-vitro release profiles of SMEDDS and plain drug of NEB were studied using USP XXIII apparatus II (Electrolab India, Mumbai, India) at 37± 0.5°C with a rotating speed of 75 rpm in 0.1N HCl as the dissolution media (500 mL). During the study, 5 ml of aliquots were removed at predetermined time intervals (5, 10, 15, 20, 25, 35, 45, 55 and 60 min) and replaced with fresh media. The amount of NEB released in the dissolution medium was determined by UV-VIS spectroscopic method.

Method of preparation of Nebivolol S-SMEDDS [33]

For the preparation of solid SMEDDS, SMEDDS was mixed with various solid carriers namely anhydrous Anhydrous Lactose, Aerosil 200, and MCC (Microcrystalline cellulose) in various ratios (1:1, 1:2 and 1:3). Briefly, the SMEDDS was added dropwise over the solid adsorbent contained in a broad bottom beaker. After each addition, the mixture was homogenized using glass rod to ensure uniform distribution of the droplet.

Evaluation parameters of the S-SMEDDS containing Nebivolol [20]

Reconstitution properties of S-SEDDS [34]

A visual test was carried out to assess self-emulsification of S-SMEDDS in 100 ml double distilled water at 37°C under gentle agitation. S-SMEDDS showed spontaneous micro emulsification and there was no sign of phase separation or phase inversion of micro emulsion even after storage for 2 h.

Powder properties for solid SMEDDS [34,35]

Selected formulations were evaluated for Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of repose.

DSC [36]

The DSC thermogram of NEB S-SMEDDS was recorded using Differential scanning calorimeter. Approximately 5 mg of sample was heated in a closed pierced aluminum pan from 30 °C to 500 °C at a heating rate of 10°C/min under a stream of nitrogen at a flow rate of 40 ml/min.

IR [37]

The NEB S-SMEDDS was examined by infrared absorption spectral analysis and was compared with the reference standard IR spectrum of adsorbent (Aerosil 200). The spectrum was obtained in range of 400-4000cm-1.

Scanning Electron Microscopy (SEM) [38]

The surface morphology of samples was determined using analytical scanning electron microscope. The samples were lightly sprinkled on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Afterwards, the stub containing the coated samples was placed in the scanning electron microscope chamber.

Drug content determination [29]

100 mg samples were dissolved in 10ml water and stirred by vortex mixing. The solutions were filtered using 0.45 µm membrane filters. The content was estimated by Spectroscopic method.

Globule size determination [27,28]

The formulations were diluted with distilled water to ensure that the light scattering intensity was within the instrument's sensitivity range. Double distilled water was filtered through 0.45 µm membrane filters. The globule size was measured with Malvern Zetasizer nano zs able to measure sizes between 10 to 5000 nm. The measurement conditions were: He-Ne Red laser, 4.0 mW, 633 nm; temperature, 25 °C; refractive index, 1.333; or with adjustment if needed. The instrument is based on the principle of dynamic light scattering (DLS).The samples were measured at 37 °C after addition of 1 g of SMEDDS mixture in 250 ml water.

In vitro release [30-32]

For in vitro release study, solid SMEDDS equivalent to 5 mg of NEB was filled in '0' HPMC capsule. The dissolution studies were performed using USP dissolution apparatus-II at a rate of 75 rpm. All dissolution studies were performed by using 500 ml of 0.1 N HCl. The temperature was set at 37 °C±0.5 °C. Samples of 5 ml of the media were collected and replaced with equal volume of fresh media. The samples were analyzed using Spectroscopic method.

Stability study [39]

The optimized NEB S-SMEDDS was stored at 40° C/75% RH (Newtronics chamber) for 03 month and evaluated for % transmission, Drug content and Globule size.

Result and discussion

Nebivolol showed highest solubility in castor oil (Oil), TWEEN 80 (Surfactant) and PEG 400 (Surfactant) than other oils and surfactants (Figure 1). Hence these excipients were selected to formulate the SMEDDS of Nebivolol (Table 2).

Table 2: Solubility Study of Drug in Oil, Surfactant and Co surfactant

Vehicle	Solubility(mg/ml) Mean ±SD	Vehicle	Solubility(mg/ml) Mean ±SD
Water	0.00403	Ethanol	81.53 ± 1.06
Tween 80	87.3 ± 1.74	Castor oil	124.45 ± 1.34
Tween 20	38 ± 0.23	Olive oil	65.6 ± 0.96
Tween 40	43.83 ± 1.25	Oleic acid	83.4 ± 1.23

Cremophor–RH 40	56.06 ± 1.11	Olive oil + Castor oil	79.86 ± 0.76
PEG-400	114.31 ± 0.08	Olive oil + Oleic acid	60.74 ± 1.73
PG	80.41 ± 0.14		

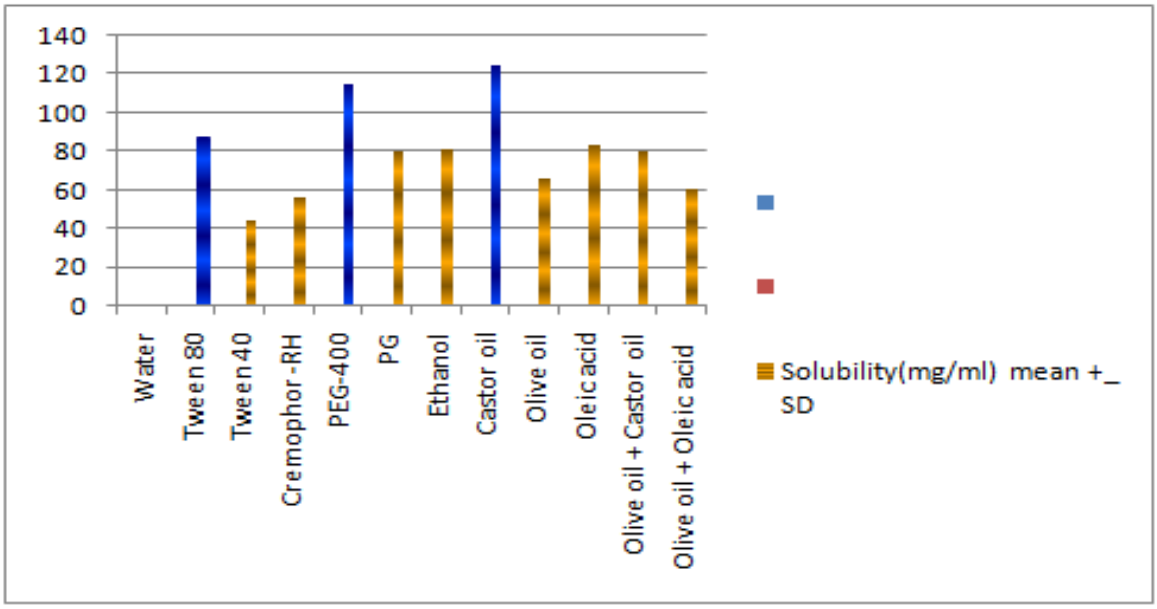


Figure :1 Bar diagram showing solubility of Nebivolol in Oils, Surfactant and co surfactant

Construction of PseudoTernary Phase Diagrams

For constructing pseudo-ternary phase diagram, Castor oil was selected as oil. Tween 80 as a surfactant and PEG-400 as a cosurfactant shows better emulsifying properties with Castor oil. Microemulsion formation area was found to be S/Cos highest at S/Cos=1:1 and 2:1 (ratio of concentration of surfactant to cosurfactant). At S/Cos= 1:1 system had capacity to solubilize as much as 50% (w/w) of oily phase. (Figure 2)

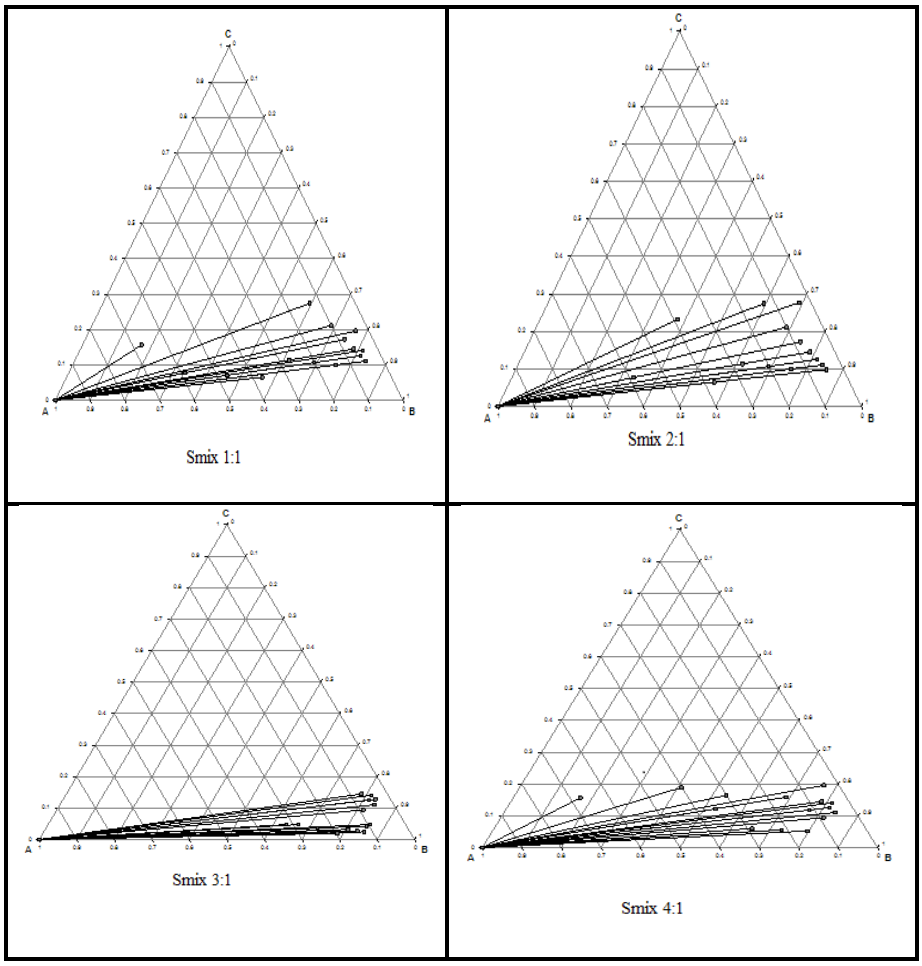


Figure 2 : Pseudo ternary phase diagram of system containing components : Castor oil (A) as a oil, Smix i.e. Tween 80 as surfactant and PEG-400 as co-surfactant (B) and Water (C). Ratio of surfactant to cosurfactant (v/v) in (A) is 1:1, in (B) is 2:1, in (C) is 3:1 and in (D) is 4:1. The dark area indicates the microemulsion region.

Thermodynamic stability study

Thermodynamic stability study of formulations were carried out to avoid selection of metastable formulation and to discriminate between microemulsion and emulsion. Among all formulation, those formulations which show phase separation during freeze - thaw cycle and centrifugation respectively were discarded. The formulations which passed thermodynamic stability test were subjected to self emulsification test. It was observed that formulation F6 and F9 did not pass the thermodynamic stress test and therefore thus were dropped for further study. The results are as shown in Table 3.

Table 3: Thermodynamic stability study and emulsification study

Formulation Code	Heating cooling cycles $45^0C/4^0C$	Centrifugation	Freeze thaw cycle	Inference
F1	Y	Y	Y	Passes
F2	Y	Y	Y	Passes
F3	Y	Y	Y	Passes
F4	Y	Y	Y	Passes

F5	Y	Y	Y	Passes
F6	Y	N	_	Fails
F7	Y	Y	Y	Passes
F8	Y	Y	Y	Passes
F9	Y	N	_	Fails
Note: Y: Maintenance of homogeneity of prepared microemulsion, N: Separation of component of microemulsion concentrate. Where, H/C-Heating cooling cycle, cent.-centrifugation test, Freeze Thaw.-Freeze thaw cycle and Disperse.-Dispersibility test				

Viscosity measurement

Viscosities of all seven formulations are mentioned in the Table 4. F3 and F8 shows less viscosity (26 and 28 cp respectively) as compared to other formulations. In general, the selected microemulsion formulations had a very low viscosity. Low viscosity of the formulations is important from point of view of large scale handling as also providing lesser resistance to the diffusion of drug molecules to the external environment.

Table 4: Physical properties of F1, F2, F3, F4, F5, F7 and F8 formulation

Percentage Transmission* (%)	**F1**	**F2**	**F3**	**F4**	**F5**	**F7**	**F8**
Water 100 fold	88.36±0.91	88±1.00	87±1.00	81.45±0.85	84±1.00	88.36±0.54	87.23±0.97
Water 1000 fold	97.63±1.52	97.43±1.15	98.84±0.16	92.26±0.97	92.28±0.01	98.87±0.11	97.69±1.05
0.1 N HCl 1000 fold	99.05±0.23	98.55±1.15	98.69±0.57	95.56±1.04	96.78±0.05	98.94±1.09	97.89±1.12
pH 7.4 Buffer 1000 fold	97.49±0.44	96.12±0.57	98±1.0	90.99±1.03	95.03±0.01	97.88±1.23	98.04±0.03
Cloud Point(°C)	81	79	83	75	78	80	82
Viscosity(cp)	33	30	26	29	35	32	28
Note: *=Percentage Transmission expressed as a mean (n=3)							

Particle size distribution (PSD) and ζ potential analysis

The droplet size of the emulsion is a crucial factor self-emulsification performance because it determines the rate and extent of drug release as well as drug absorption. Also, it has been reported that the smaller particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. Table 5 shows the particle size of F8 formulation which shows minimum globule size 112.7 nm with PDI 0.169.

Table 5: The particle size, Polydispersity Index and Zeta potential of optimized formulations

Sr No.	**Formulation Code**	**Globule size analysis (nm)**	**Polydispersity Index**	**Zeta Potentioal**
1	F1	169.00	0.214	-0.76
2	F2	135.51	0.568	-3.9
3	F3	124.12	0.342	-2.68
4	F4	179.86	0.215	-10.54
5	F5	168.46	0.367	-7.89
6	F7	143.07	0.856	0.38
7	F8	112.7	0.169	-5.56

Drug Content (%)

The drug content in solid SMEDDS of NEB was almost identical with those obtained in liquid SMEDDS so there is no change of percentage drug content after conversion of liquid to solid SEDDS (Table 6). Drug content of the optimized SEDDS formulation batch (F8) for ratio 1:1 was found to be highest i.e. 94.85 %. So, it was considered as optimized batch. (Table 7)

Table 6: Drug Content (%) in Liquid SMEDDS

Formulation Code	F1	F2	F3	F4	F5	F7	F8
Drug content (%)	95.23	96.31	95.51	95.28	93.89	96.55	95.76

Table 7: Drug content determination in NEB S-SMEDDS

Self-emulsification study

As dilution of formulation progresses, the micellar system passes through swollen w/o reverse micelles systems, to bicontinuous phase and finally to o/w microemulsion system. Thus in the latter transition there is a possibility of migration of surfactant from interface .Thus due to disruption of interfacial barrier film leaching of drug from core of micelle to external environmental leading to precipitation may take place According to the grading system, Grade A and Grade B are acceptable formulations for further study.

Reconstitution properties of S-SMEDDS

The prepared Nebivolol S-SMEDDS were evaluated for the micromeritic properties such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. (Table 8) The Carr's index, Hausner's ratio and angle of repose all are passable range. The bulk density and tapped density of mixture of Aerosil 200 and Nebivolol S-SMEDDS is 0.4318 g/ml and 0.475 g/ml indicated that the prepared Nebivolol S-SMEDDS has higher bulk volume.

Table 8: Micromeritic properties of mixture of MCC and Aerosil-200 with F8 SMEDDS

Sr.No	Micromeritic Properties	Lactose	MCC	Aerosil 200
1	Bulk Density (g/ml)	0.7333	0.504	0.4318
2	Tapped Density(g/ml)	0.788	0.550	0.475
3	Angle of Repose(°)	31.55	34.56	29.65
4	Carr's Index (%)	13.97	13.36	10.094
5	Hausner ratio	1.16	1.12	1.10

DSC

The DSC thermogram of Nebivolol shows a sharp endothermic peak at 229.6°C (Figure 3), indicated the melting point of Nebivolol. For the NEB S-SMEDDS, the small endothermic peak may be due to solubilisation of Nebivolol in the solid SMEDDS.

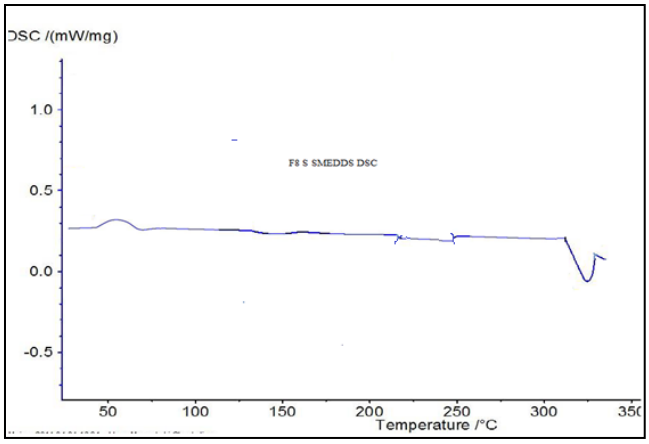
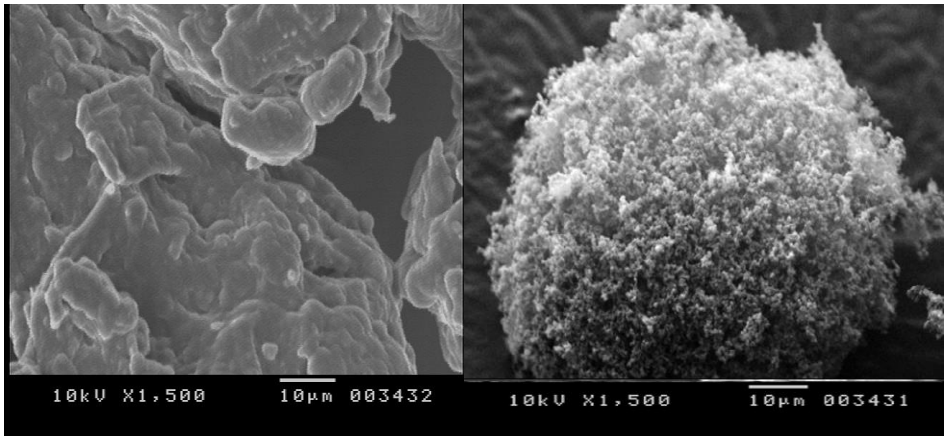


Figure 3: DSC Thermogram of NEB S-SMEDDS

SEM

The scanning electron micrographs of Aerosil 200 and Nebivolol S-SMEDDS are shown in Figure 4. Aerosil 200 appeared with a rough surface with pores. However, the Nebivolol S-SMEDDS appeared as smooth-surfaced, indicating that the liquid SMEDDS is absorbed or coated inside the pores of Aerosil 200.



(a) (b)

Figure 4: SEM of (A) NEB-SMEDDS and (B) Aerosil 200

Globule size determination

The mean droplet size and polydispersity index of the reconstituted NEB S-SMEDDS and F8 liquid SMEDDS microemulsions are presented in Table 9. As shown below, the average droplet sizes of both microemulsions were less than 150 nm. The droplet size of the microemulsion from the NEB S-SMEDDS was slightly increased as compared to the F8 liquid SMEDDS.

Table 9: Globule size of NEB S-SMEDDS and F8 liquid SMEDDS

Code	Globule size (nm)	PDI
F8 Liquid SMEDDS	112.07	0.215
NEB S-SMEDDS	116.56	0.282

***In vitro* release**

In vitro drug release study is generally done as an quality control tool, during the production of dosage form to check either the drug release is according to predetermined specifications or not. In vitro drug release studies were performed for NEB S-SMEDDS and marketed tablet (Nebider), shown in Figure 5. The drug release from the NEB S-SMEDDS in 20 min was more than 85% and the drug release from the Nebider showed less than 10 % which was significantly less as compared to NEB S-SMEDDS. However, there was no significant difference in drug release between NEB S-SMEDDS and F8 liquid SMEDDS. (Table 10)

Table 10: In vitro release of F8 liquid SMEDDS Nebivolol, NEB S-SMEDDS and Nebider (Marketed tablet)

Time	Reference	F8 (L)	F8 (S)
0	0.00	0.00	0.00
5	7.02	69.34	62.56
10	7.75	80.68	76.97
15	9.43	87.56	82.24
20	9.87	90.15	85.58
25	11.07	92.76	88.46
30	12.28	94.95	91.12
35	12.87	96.78	92.87
40	13.35	97.53	94.35
45	13.86	98.45	96.25
50	14.42	99.68	97.78
55	15.02	99.87	98.67
60	15.64	99.99	99.54

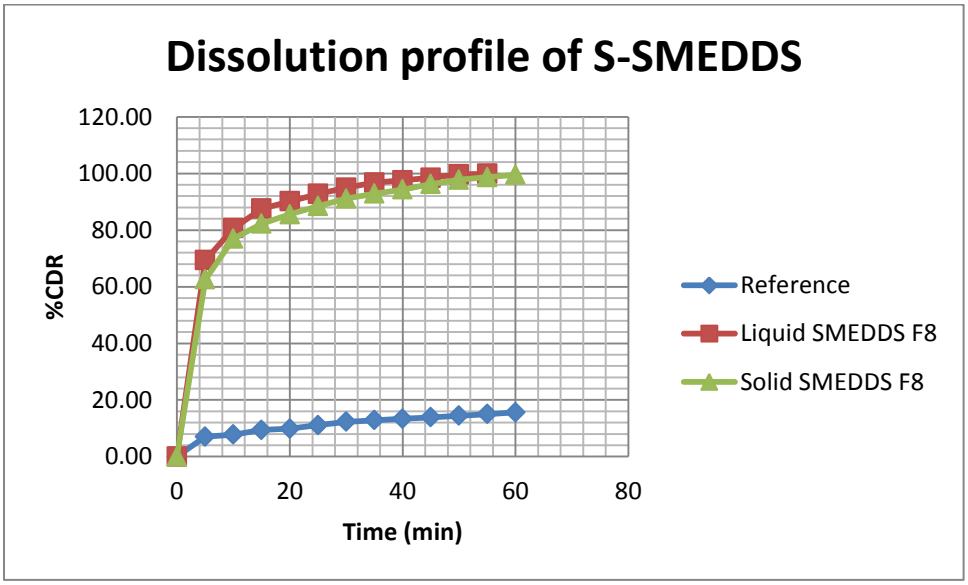


Figure 5: Dissolution profile of F8 liquid SMEDDS Nebivolol, NEB S-SMEDDS and Nebider (Marketed tablet)

Stability study

The Nebivolol S-SMEDDS formulation subjected to stability studies was evaluated in terms of % transmission and it was found to be 85.24% and 96.12% after 3 month (Table 11). There was no change in drug content in 3 month shows that drugs are chemically stable in S-SMEDDS. The globule size was found to be 120.12 nm.

Table 11: Stability Study of F8 S-SMEDDS at 40±2 °C/75±5% RH

Time (days)	Percent Transmission		Drug content (%)	Globule size (nm)
	100 fold dilution with DM water.	1000 fold dilution with DM water.		
0	86.45	97.34	94.85	116.56
15	85.56	96.89	94.59	117.89
30	85.23	96.78	94.27	118.67
45	85.18	96.	94.05	118.75
60	85.12	96.29	93.86	118.78
90	85.24	96.12	93.79s	120.12

Conclusion

Supersaturable SMEDDS of Nebivolol was successfully formulated to achieve higher release as well as bioavailability of NEB in F8 formulation of SMEDDS in comparison to plain drug suspension. Stability of the formulation was confirmed by thermodynamic stability study and long term stability study. The release and bioavailability from F8 SMEDDS was increased due to presence of drugs in lipidic micro form as well as in dissolved state. Additionally increased gastric stability of NEB contributes increased bioavailability of NEB.S-SMEDDS of NEB was prepared by adsorption method, using Aerosil-200 as adsorbent. The solid SMEDDS consisted of well-separated particles with smooth surface and preserved the self-emulsification performance of the liquid SMEDDS. The DSC study shows that NEB S-SMEDDS may be in the dissolved state. In-vitro dissolution test showed that the solid SMEDDS had a faster in vitro release rate than the plain drug suspension NEB.

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