



## RESEARCH ARTICLE

# Formulation, Optimization and Evaluation of Self Emulsifying Immediate Release Tablet of Nebivolol HCl using 3<sup>2</sup> Factorial Design

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**Abstract**

Nebivolol Hydrochloride (NEB) is a lipophilic molecule with low solubility in GI fluid, and high metabolism which leads to its low oral bio availability 12%. The aim of the present investigation was to develop immediate release self emulsifying tablet (IR-SET) as solid SMEDDS to enhance the solubility and permeability of the drug. Solubility study, pseudo-ternary phase diagrams and 3<sup>2</sup> factorial design were used to select the components of the system and optimize the composition of liquid SMEDDS. Optimal L-SMEDDS contains Kollisolv GTA, Tween 80 and Propylene glycol as oil, surfactant and co-surfactant, respectively in the ratio of 20:26.66:53.34 % w/w, formulates L-SMEDDS with droplet size (55.98 nm), PDI (0.37), emulsification time (16±1.52 sec) and drug content (97.43±0.30 %). The liquid SMEDDS were adsorbed onto Neusilin US2 by adsorption technique to form S-SMEDDS. DSC and SEM studies suggested that NEB in the S-SMEDDS may be present in the molecular dispersed state and was sufficiently adsorbed onto solid carrier, respectively. S-SMEDDS was compressed into IR-SET by direct compression method and composition of IR-SET was optimized using 3<sup>2</sup> factorial design. Optimal IR-SET showed disintegration time (92 + 0.57 sec), droplet size (68.57 nm), PDI (0.34) and drug content (96.33±0.15 %). In vitro dissolution studies and ex vivo diffusion studies in rat stomach suggested that SMEDDS played an important role in solubility and permeability enhancing effect. Accelerated stability studies indicated that formulation were stable. Our results illustrated the increase in solubility and permeability of drug from IR-SET.

**Keywords:** Self micro emulsifying drug delivery system (SMEDDS); Solid self micro emulsifying drug delivery system (S-SMEDDS); immediate release self emulsifying tablet (IR-SET); Nebivolol Hydrochloride (NEB); 3<sup>2</sup> factorial design

## Introduction

Poorly water soluble compounds represent an estimated 40% of compounds in development and many major marketed drugs, and this figure is only likely to increase and creating huge problems in pharmaceutical product development process [1]. Drug insolubility poses significant challenges during drug development owing to its impact on the extent and rate of drug absorption into

the body and hence on bioavailability. It can prevent the absorption of therapeutic level of drug, delay a drug's onset of action and decrease its therapeutic benefit. These problems can result in patients being given higher and more frequent drug doses, which can result in increased therapy costs, greater likelihood of side effects and complicated dosing regimens. The problem of efficiently delivering these drugs has long challenged scientists to develop innovative delivery systems that increase their bioavailability. So as a part of novel drug delivery system, self micro emulsifying drug delivery systems (SMEDDS) are also gaining the interests. SMEDDS are isotropic mixtures of oil, hydrophilic surfactant and/or a co-surfactant, and a solubilised

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Received: 06 Feb 2018, Accepted: 12 Jun 2018



drug. When the SMEDDS comes in the contact with the sufficient water, the system forms self-emulsion and the droplet size reduces to nano size there by increases the solubility and permeability of the drug molecules. This technique is very much useful for the drug candidates which are poorly soluble and have high log P values [2, 3]. Conventionally, SMEDDS is prepared as liquid dosage forms that can be encapsulated in hard or soft gelatin capsules, but liquid formulation present drug precipitation and packing challenges mainly due to solvent evaporation. Moreover, non-solid formulations are more prone to chemical instability and capsule shell incompatibility leading to the possibility of leakage upon storage and even during handling [4].

The Solid SMEDDS are new approach to overcome above mention problems. In this formulation the liquid self emulsifying ingredients are incorporated into powder and processed to make solid dosage form such as tablets, capsules, pellet, etc. by using different techniques such as adsorption, spray drying, etc. Nowadays, more focus is given on new dosage forms containing the advantages of SMEDDS [5, 6].

Recently scientists have more focus on self emulsifying immediate release tablet (IR-SETS) [7]. These tablets possess following advantages- they are convenient and easy to handle and more robust, stable dosage; better compliance for patients having allergy to capsules shells or who do not prefer to take capsules. Also, these tablets have capacity to release drug faster as compared to its capsule SMEDDS [4, 8].

Nebivolol Hydrochloride is a third generation, highly selective  $\beta$  adrenoceptor antagonist indicated for treatment of essential hypertension. Nebivolol HCl is a lipophilic molecule. It has low solubility in GI fluid, and high metabolism which leads to its low absolute oral bioavailability 12%. Suitable log P (octanol/water) of 4.03, an oral dose of a 5 mg and being a BCS class II drug strongly provide a rationale to develop its SMEDDS [9]. The utility of self emulsifying system in improving the dissolution of NEB has been reported [10]. However, in the present study an attempt was made toward the use of different oils, surfactants and co-surfactants for the preparation of L-SMEDDS and use of different adsorbents for preparing solid dosage form i.e., IR-SET.

## Materials and Methods

### Materials

Nebivolol Hydrochloride was provided as gift sample by Emcure Pharmaceutical Ltd. (Pune, India). Kollisolv GTA and Kollidon CL were provided as gift sample by BASF (Mumbai, India). Neusilin US2 was provided as gift sample by Gangwal chemicals pvt. Ltd., (Mumbai, India). Tween 80, Propylene gly-

col and Magnesium stearate were purchased from Loba chemie Pvt. Ltd., Mumbai, MCC PH102 was purchased from S. D. fine chem. Ltd., Mumbai, PVP K 30 was purchased from Sisco research laboratory Pvt. Ltd., Mumbai.

### Methods

#### *Drug- Excipient compatibility studies*

FTIR spectrum of NEB with the excipients i) Kollisolv GTA, Tween 80 and Propylene glycol (L-SMEDDS) ii) SMEDDS loaded Neusilin US2, MCC PH102, PVP K30, Kollidon CL (IR-SET) were recorded on FTIR spectroscopy. To check for compatibility, the spectrums of pure NEB and NEB with excipients were matched for appearance or disappearance of any peak [11].

#### *Preparation of L-SMEDDS*

Selection of excipients and formulation of L-SMEDDS involves following step:

- 1 Solubility studies to selected excipients showing maximum drug solubility [12].
- 2 Emulsification efficiency of surfactants and co-surfactants to check their ability to emulsify selected oil [11].
- 3 Pseudo-ternary phase diagram were constructed to obtain the concentration range of components for the existing region of micro emulsions [13].
- 4 Optimization and Evaluation of NEB loaded L-SMEDDS by  $3^2$  factorial design to observe the combined effect of the concentration of oil as well as the concentration of Smix (surfactant: co-surfactant) on the droplet size, emulsification time and percent transmittance for obtaining the optimized liquid SMEDDS [14–16].

#### *Preparation of S-SMEDDS*

To prepare IR-SET, the first step is to convert L-SMEDDS into free flowing powder and to evaluate for efficient adsorption of L-SMEDDS on adsorbent.

S-SMEDDS was prepared by mixing L-SMEDDS containing NEB with different adsorbent (Neusilin US2, Aerosil 200, Microcrystalline cellulose PH102 and Lactose) and the angle of repose and quantity of adsorbent required was observed as a response. In brief L-SMEDDS was added drop wise over adsorbent contained in small mortar. After each addition, mixture was homogenized using pestle to ensure uniform distribution of formulation. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and stored until further use [17].

#### *Scanning electron microscopy*

The surface morphology of Nebivolol HCl, Neusilin US2 and S-SMEDDS were studied by using scanning electron microscope, the micrographs at different magnifications were recorded by working at an excitation voltage of 10 kV [17, 18].

#### *Differential scanning calorimetry*

DSC thermograph of NEB with the excipients i) Kollisolv GTA, Tween 80 and Propylene glycol (L-SMEDDS) ii) SMEDDS loaded Neusilin US2, Avicel PH102, PVP K30, Kollidon CL (IR-SET) were recorded on differential scanning calorimeter. The thermograms of pure NEB and NEB with excipients were matched for appearance or disappearance of any peak and enthalpy height [17, 18].

#### *Optimization of IR-SET by factorial design*

The objective of the present investigation was to observe the combined effect of PVP K30 (binder) as well as Kollidon CL (super disintegrant) on the disintegration time and friability (dependent responses). Factorial design with 3 levels to estimate curvature in response (i.e.  $3^2$  factorial with total no. of experiments = 9) was used [19, 20].

#### *Preparation of self emulsifying immediate release tablets (IR-SETS)*

IR-SETS of NEB were prepared by direct compression technique. For this NEB containing S-SMEDDS and all other excipients according to the formula were weighed accurately. All excipients were passed through sieve # 22 and mixed for 15 minutes. Magnesium stearate previously passed through sieve # 60 was then mixed with above blend for 5 minutes. The mixture was then compressed into tablets using 10 station rotary tablet compression machine with 10.0 mm flat round punches with tablet weight equivalent to 450 mg [20].

#### *Evaluation of self emulsifying immediate release tablets (IR-SETS)*

##### *i] Friability test*

The test was performed using Roche Friabilator. The device was rotated at 25 rpm for 100 revolutions [21].

##### *ii] Hardness*

Hardness indicates the ability of tablet to withstand mechanical shocks while handling. The hardness of tablets was determined using Monsanto hardness tester. It is expressed in  $\text{kg}/\text{cm}^2$  [21].

##### *iii] Disintegration test*

The test was carried out using USP disintegration apparatus in acid buffer pH 1.2 as a disintegration media maintained at  $37 \pm 2^\circ\text{C}$  [21].

##### *iv] Droplet size analysis and polydispersity index*

The droplet size of the prepared formulation was determined by photon correlation spectroscopy using NANOPHOX (NX0088). Prepared formulation IR-SET was diluted to 100 ml with double distilled water and the mean droplet size and polydispersity index were determined [22].

##### *v] Zeta potential determination*

The zeta potential of the prepared formulation was determined by Malvern Zetasizer 3000HS. Prepared IR-SET was diluted to 100 ml with double distilled water and the zeta potential was determined [23].

##### *vi] Drug content*

The drug content of prepared formulation was determined by placing IR-SET in 10 ml volumetric flask and diluted with methanol. The flask was subjected to sonication for 30 minutes. The solution was filtered through whatman filter paper and analysed using UV-Visible double beam spectrophotometer [24].

##### *vii] In-vitro drug release*

NEB loaded L-SMEDDS was filled in size '0' hard gelatin capsules. In-vitro release profile of L-SMEDDS and IR-SET were studied using USP apparatus II at  $37 \pm 0.5^\circ\text{C}$  with a rotating speed of 50 rpm in dissolution media acid buffer pH 1.2, 900 ml. During the study, 10 ml of the aliquots were removed at predetermined time intervals (10, 20, 30, 40, 50, and 60 minutes) from the dissolution medium and replaced with fresh medium. The amount of NEB released in the dissolution medium was determined using UV-Visible double beam spectrophotometer [11].

##### *viii] Ex-vivo release profile*

For ex-vivo drug release study, stomach of previously sacrificed Male Sprague-Dawley rat was isolated and thoroughly washed with phosphate saline buffer pH 7.4 to remove the mucous and lumen contents. NEB L-SMEDDS and IR-SET were diluted separately with acid buffer pH 1.2 and were filled in the stomach. Both the ends of the tissues were tied properly to avoid any leakage and were placed into beaker containing 50 ml of phosphate saline buffer pH 7.4 as the acceptor phase with the continuous aeration supply under gentle stirring at  $37 \pm 2^\circ\text{C}$ . Samples were withdrawn from the acceptor phase at periodic time intervals and subjected to spectrophotometric analysis [25].

**Table 1** Translation of experimental conditions into physical unit for IR-SET

Coded Values	Actual Values (%)		Response	
	X <sub>1</sub> PVP K30 as binder (%)	X <sub>2</sub> Kollidon CL as super disintegrant (%)	Y <sub>1</sub> (sec)	Y <sub>2</sub> (%)
-1	2	2	Disintegration time	Friability
0	3.5	3.5		
+1	5	5		

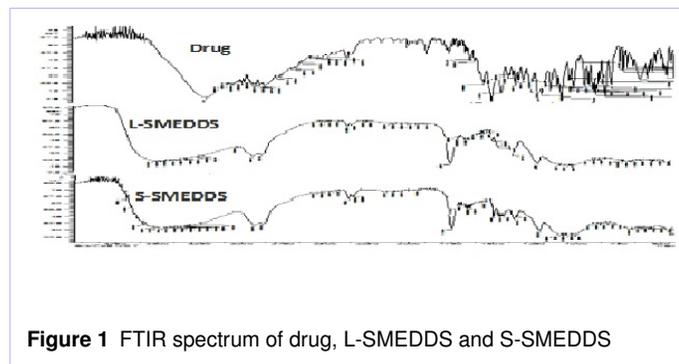
### ix] Accelerated stability study

Optimized IR-SETS were packed in aluminum foil and placed in stability chambers at 40°C /75% RH. Formulations were removed at each time point (0 day, 1 month and 2 months) and evaluated for drug content and % drug release in 10 minutes [26].

## Results & Discussion

### Drug-Excipient compatibility studies

FTIR spectrum of drug, L-SMEDDS and S-SMEDDS are given in figure 1. The principal IR absorption peaks of NEB were all observed in the L-SMEDDS and IR-SET. These spectral observations thus indicated no interaction between the NEB and the excipients.

**Figure 1** FTIR spectrum of drug, L-SMEDDS and S-SMEDDS

### Preparation of L-SMEDDS

Based on solubility studies, emulsification efficiency test and pseudo-ternary phase diagram Kollisolv GTA, Tween 80 and Propylene glycol were selected as oil, surfactant and co-surfactant, respectively. Composition of NEB loaded L-SMEDDS was optimized using 3<sup>2</sup>factorial design. The different formulations were prepared by applying factorial design using concentration of oil and Smix (surfactant and co-surfactant) in different concentrations. Optimal L-SMEDDS contains Kollisolv GTA, Tween 80 and Propylene glycol in the ratio of 20:26.66:53.34 % w/w, formulates L-SMEDDS with lower droplet size (55.98 nm), PDI (0.37), emulsification

time (16±1.52 sec), zeta potential (-26.8 mV) and drug content (97.43±0.30 %).

### Preparation of S-SMEDDS

Among the different adsorbent, Neusilin US2 has shown good flow property (32.72±2.4) and required in 1:0.5 ratio, whereas Aerosil 200 was also required in same ratio but shown passable flow property (41.81±1.18) and therefore Neusilin US2 was selected as adsorbent.

**Table 2** Selection of adsorbent for S-SMEDDS

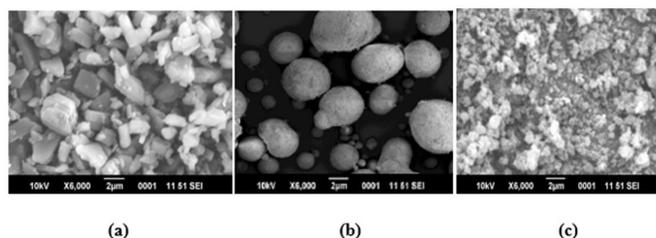
Adsorbent	Quantity of adsorbent required	Angle of Repose
Aerosil 200	1:0.5	41.81±1.18 (passable)
Neusilin US2	1:0.5	32.72±2.4(good)
MCC	1:2	43.15± 1.55 (passable)
PH102	1:1.5	37.32± 2.17 (fair)

### Scanning electron microscopy

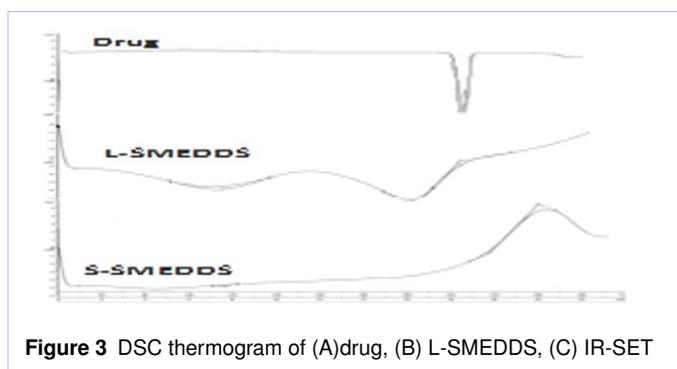
Scanning electron microscopy reveals the morphology of solid SMEDDS. From the Figure 2 (a) Nebivolol HCl appeared to be made of smooth rectangular crystalline structures, and from Figure 2 (b) Neusilin US2 appeared to be spherical porous particles. Micrographs of solid SMEDDS Figure 2 (c) shows liquid SMEDDS adsorbed onto the surface of Neusilin US2 particles. Crystalline structures characteristic of solid Nebivolol HCl was not seen in solid SMEDDS micrographs suggesting that the drug must be present in a completely dissolved state in the solid SMEDDS.

### Differential scanning calorimetry

Plain drug shows sharp endothermic peak at 233.3°C, figure 3 (A). The sharp endothermic peak of Nebivolol HCl was replaced with diffused peak indicating that the drug must be present in molecularly dissolved state in L-SMEDDS, figure 3 (B). Optimized IR-SET showed the disappearance of endothermic peak of the drug which indicates the presence of drug in molecularly dissolved state, figure 3 (C).



**Figure 2** SEM images of (a) NebivololHCl (b) Neusilin US2 (c) Solid SMEDDS



**Figure 3** DSC thermogram of (A) drug, (B) L-SMEDDS, (C) IR-SET

### Optimization of IR-SET by factorial design

The objective of the present investigation was to optimize the conc. of PVP K30 and Kollidon CL mixture for preparation of IR-SET. The results are given in Table 3.

The responses of the formulations prepared by  $3^2$  factorial design batches are shown in Table 3. All the data were computed by design expert software (Version 8.0.7.1). The model, which shown a lesser P value ( $\leq 0.05$ ) and greater F value (Table 4) was identified as the fitting model and shown that disintegration time and friability fitted to linear model.

The fitted regression equations relating the responses like disintegration time and friability are shown in the following equations, respectively. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries (i.e. either positive or negative). The positive sign indicated direct effect whereas negative sign indicated inverse effect.

$$\text{Disintegration time} = 128.56 - 0.67 (X_1) - 30.17 (X_2) \dots\dots\dots(1)$$

$$\text{Friability} = 0.59 - 0.15 (X_1) - 9.167E - 003 (X_2) \dots\dots\dots(2)$$

Graphical presentation of the data helps to show the relationship between the responses and the independent variables. The information obtained from the graphs was similar to that ob-

tained from mathematical equations by statistical analysis. (Figure 4).

### Optimization (Model validation)

The solutions for numerical optimization of IR-SET were given by design expert software. The formulation B9 was considered for model validation. The values of responses predicted from the obtained model by software and the results obtained by experimentation are shown in Table 5. The close resemblance between observed and predicted response values indicates the validity of the generated model. Table 6 shows the quantity of ingredients in optimized batch.

### Evaluation of self emulsifying immediate release tablets (IR-SETS)

#### i] Friability test

The optimized IR-SETS showed  $0.424 \pm 0.03\%$  friability. The friability is less than 1%, which indicates that the tablets can handle the mechanical stress.

#### ii] Hardness

The optimized IR-SETS showed  $2.8 \pm 0.29 \text{ kg/cm}^2$  hardness. This indicates that the tablets can handle the mechanical stress.

#### iii] Disintegration test

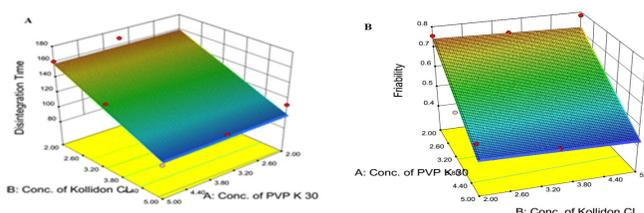
The optimized IR-SETS showed  $92 \pm 0.57 \text{ sec}$ . This indicates that the tablet can disintegrate and release the self emulsifying system immediately.

#### iv] Droplet size analysis and polydispersity index

The optimized IR-SET showed  $68.57 \text{ nm}$  droplet size and  $0.34$  polydispersity index, respectively. The smaller droplet size of the micro emulsion droplets indicates more rapid absorption and improves the bioavailability of drug. Figure 5 shows the droplet size distribution of optimized formula.

**Table 3** Results of B1-B9 batches

Batch	X <sub>1</sub> Conc. of PVP K30 (%)	X <sub>2</sub> Conc. of Kollidon CL (%)	Y <sub>1</sub> Disintegration Time (sec)	Y <sub>2</sub> Friability (%)
B1	2.00	5.00	112±1.52	0.783±0.05
B2	2.00	2.00	156±2.08	0.756±0.03
B3	2.00	3.50	125±0.57	0.735±0.04
B4	3.50	5.00	101±1.15	0.532±0.07
B5	3.50	3.50	105±0.57	0.558±0.05
B6	3.50	2.00	169±1.15	0.515±0.05
B7	5.00	2.00	161±0.57	0.523±0.03
B8	5.00	3.50	136±1.52	0.443±0.04
B9	5.00	5.00	92±0.57	0.424±0.03

**Figure 4** Responsesurface plot for (A) disintegration time and (B) friability**Table 4** ANOVA results of the measured responses (Y)

	Coefficient	Y <sub>1</sub>	Y <sub>2</sub>
ANOVA	P Value	0.0034	0.0019
	F Value	16.87	21.13

**Table 5** Comparison of predicted and experimental values.

Responses	Design expert	B9
	Predicted	Experimental
Disintegration time (sec)	97.7222	92.00
Friability (%)	0.428944	0.424

**Table 6** Optimized formula of IR-SET

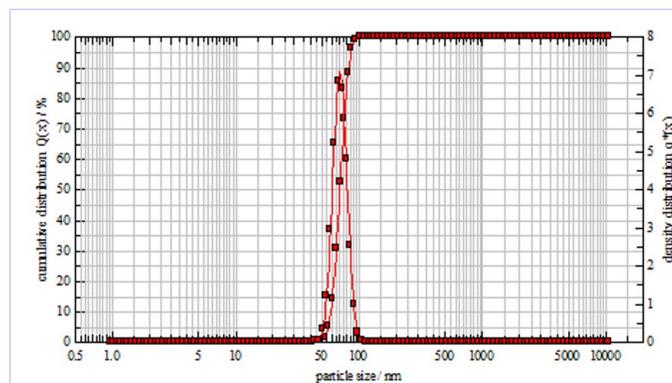
Components	% w/w
L-SMEDDS loaded Neusilin US2	Equivalent to 5 mg of NEB
PVP K30	5%
Kollidon CL	5%
Magnesium Stearate	1%
MCC PH102	q.s.

#### v] Zeta potential determination

Zeta potential of the optimized IR-SET was found to be -25.3 mV, indicating the stable micro emulsion.

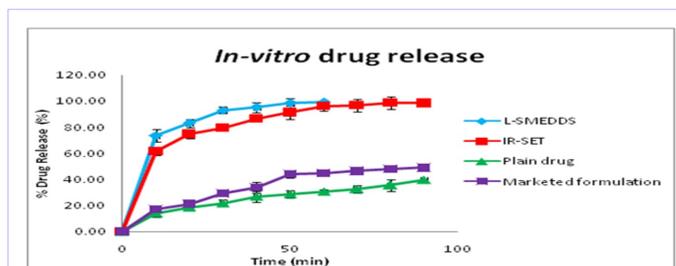
#### vi] Drug content

Drug content of IR-SETS was found to be 4.81 + 0.03 mg/ml, respectively. So, drug content in percentage was calculated and the optimized formula had 96.33±0.15 % of drug, respectively.

**Figure 5** Dropletsize distribution of optimized IR-SET

#### vii] In-vitro drug release

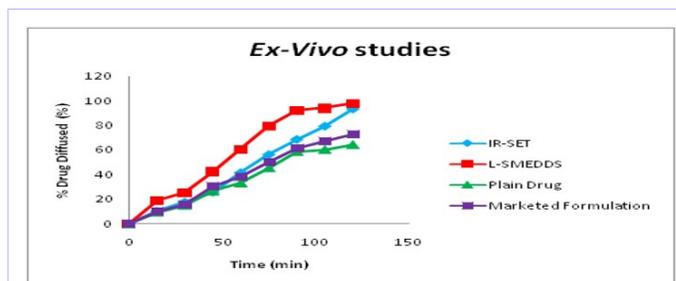
The *in-vitro* dissolution studies were performed in order to ensure the quick release of the drug in the dissolution medium. For L-SMEDDS and IR-SET formulations, it was observed that 73.44 % and 61.28 % of the drug released within first ten minutes of the dissolution time, respectively. This indicates that conversion of L-SMEDDS to IR-SET does not affect the drug release. Whereas, Plain drug and Marketed formulation, showed only 13.79 % and 17.10 % of the drug release, respectively. This clearly demonstrated the superior dissolution behaviour of the developed SMEDDS as compared to Plain drug and Marketed formulation.



**Figure 6** In-vitro drug release profile of the L-SMEDDS, S-SMEDDS, Plain drug and Marketed formulation

#### viii] Ex-vivo release profile

After 2 hours of diffusion, 97.56 % of the drug was diffused from L-SMEDDS and 93.24% of the drug was diffused from IR-SET, while from Plain drug suspension and Marketed formulation the diffusion was found to be 64.28 % and 72.73 %, respectively. Thus, the amount of the drug diffused through the biological membrane was more when it was given in the form of SMEDDS formulations. The enhancement in diffusion is due to formation of small droplets in nanometer range and improved permeation of the NEB because of the presence of surfactant, which reduces the interfacial tension of formulation.



**Figure 7** Ex-vivo diffusion studies

#### ix] Accelerated stability study

The accelerated stability study was performed at 40°C/ 75% RH for IR-SETS. The observations clearly prove that after the stability study, formulation doesn't show significant difference, indicating stability of formulations.

## Conclusions

The self micro emulsifying drug delivery system was developed as a novel technique to efficiently deliver water insoluble drug candidates with objective of enhanced solubility and hence bioavailability. Nebivolol HCl was chosen as model drug which has limited water solubility, low bioavailability, and high

partition coefficient and was best candidate for this system. L-SMEDDS was efficiently optimised using 3<sup>2</sup> factorial design. S-SMEDDS was efficiently prepared using Neusilin US2 by adsorption technique. DSC and SEM studies suggested that NEB in the S-SMEDDS may be present in the molecular dispersed state and was sufficiently adsorbed onto solid carrier, respectively. Composition of IR-SET was optimized using factorial design. The different formulations were prepared by applying by 3<sup>2</sup> factorial design using PVP K30 and Kollidon CL in different concentrations with disintegration time and friability as response. The results of ANOVA indicated that all models were significant. The close resemblance between observed and predicted response values indicated the validity of the generated model. Optimal IR-SET contains L-SMEDDS loaded Neusilin US2, MCC PH 102 as diluent, PVP K30 as binder, Kollidon CL as super disintegrant and showed disintegration time (92 + 0.57 sec), friability (0.424+0.03%), hardness (2.8+0.29 kg/cm<sup>2</sup>), droplet size (68.57 nm), PDI (0.34), zeta potential (-25.3 mV) and drug content (96.33±0.15 %). in vitro dissolution performance was almost similar for L-SMEDDS and IR-SET showed 73.44% and 61.28% drug release in 10 minutes, respectively which was significantly higher than the Marketed formulation and Plain drug. The results of ex vivo diffusion of NEB in rat stomach suggested that SMEDDS played an important role in absorption enhancing effect. Our results illustrated the potential use of IR-SET to dispense poorly water soluble drug by oral route.

## References

- [1] Sikarra D, Shukla V, Kharia AA, Chatterjee DP. Techniques for Solubility Enhancement of Poorly Soluble Drugs: An Overview. *Journal of Medical Pharmaceutical and Allied Sciences*. 2012;1:18–38.
- [2] Deokate UA, Shinde N, Bhingare U. Novel Approaches for Development and Characterization of SMEDDS: Review. *International Journal of Current Pharmaceutical Research*. 2013;5:7–8.
- [3] Kamble V, Jagdale DM, Kadam VJ. Self Micro Emulsifying Drug Delivery System. *International Journal of Pharma and Bio Sciences*. 2010;1:1–9.
- [4] Qureshi M, Mallikarjun C, Kian W. Enhancement of Solubility and Therapeutic Potential of Poorly Soluble Lovastatin by SMEDDS Formulation Adsorbed on Directly Compressed Spray Dried Magnesium Aluminometasilicate Liquid Loadable Tablets: A Study in Diet Induced hyperlipidemic Rabbits. *Asian Journal of Pharmaceutical Sciences*. 2014;p. 1–17.
- [5] Shah S, Shah M, Agrawal Y. Self-Micro Emulsifying Drug Delivery System: A Novel Approach for Enhancement of

- Oral Bioavailability of Poorly Soluble Drugs. *American Journal of PharmTech Research*. 2012;2:204–215.
- [6] Koushik Y, Preethi S, Satish P, Shankar M, Thakur R. Development of Solid Self Micro Emulsifying Drug Delivery Systems. *International Journal of Pharmaceutical Sciences and Nanotechnology*. 2013;6(2):2014–2021.
- [7] Kang J. Immediate Release of Ibuprofen from Fujicalin based fast dissolving self emulsifying tablets. *Pharmaceutical Technical Newsletters*. 2011;p. 1–3.
- [8] Zhenghong W, Xiaole Q, Jiayi Q. Self-Micro Emulsifying Dispersible Tablets of Celastrol: Formulation Development, Characterization and Bioavailability Evaluation. *International Journal of Pharmaceutics*. 2014;p. 40–47.
- [9] ;. Available from: [www.drugbank.com](http://www.drugbank.com).
- [10] Narkhede R, Gujar K, Gambhire V. Design and Evaluation of Solid Self-Nanoemulsifying Drug Delivery Systems (S-SNEDDS) for Nebivolol Hydrochloride. *International Journal of Institutional Pharmacy and Life Sciences*. 2014;4(2):224–237.
- [11] Prajapati S, Dumaniya S, Patel C. Formulation and Evaluation of Self-Nanoemulsifying Powder of Ezetimibe. *Journal of Pharmaceutical Science and Drug Designing*. 2014;1(1):1–8.
- [12] Gangineni R, Dontha P, Konda S. Formulation, Characterization and Evaluation of Self Emulsifying Drug Delivery System. *JPR:BioMedRx: An International Journal*. 2013;1(7):665–672.
- [13] Patel K, Patel B. Enhancement of Oral Bioavailability of Valsartan by using Solid Self Emulsifying Drug Delivery System. *International Journal of Universal Pharmacy and Bio Sciences*. 2013;3(3):141–155.
- [14] Pimple S, Yeole S, Chaudhari P. Formulation and Evaluation of Self Micro Emulsifying Drug Delivery System for Poorly Water Soluble Drug Risperidone. *International Journal of Pharmaceutical Sciences Review and Research*. 2013;23(1):155–162.
- [15] Khan F, Islam M, Roni M. Systematic Development of Self-Emulsifying Drug Delivery Systems of Atorvastatin with Improved Bioavailability Potential, *Scientia Pharmaceutica*. *Scientia Pharmaceutica*. 2012;80:1027–1043.
- [16] Ansari D, Parmar S, Bhadra S. Optimization of Self Micro Emulsifying Delivery System of Clofazimine using Box-Behnken Experimental Design, *Pharmagene*. *Pharmagene*. 2013;1(3):53–61.
- [17] D B, D'Souza J. Formulation and Evaluation of Solid Self Micro Emulsifying Drug Delivery System using Aerosil 200 as Solid Carrier. *International Current Pharmaceutical Journal*. 2012;1(12):414–419.
- [18] Patil S, V P, Shete A, Doijad R. Design, Development and In Vitro Characterization of Self Emulsifying Drug Delivery System for Irbesartan. *Iranian Journal of Pharmaceutical Sciences*. 2013;9(2):67–80.
- [19] Panner S, Kulkarni P. Preparation and statistical optimization of self nanoemulsifying tablets of Efavirenz using 23 factorial designs. *International Journal of Drug Delivery*. 2014;6:50–57.
- [20] Lokesh P, Abdul A, Sailaja P. Design, Development and Formulation of Orodispersible Tablets of a Model Drug Using Response Surface Methodology. *Pharmaceutica Analytica Acta*. 2012;3(9):1–15.
- [21] Paul Y, Tyagi S, Singh B. Formulation and Evaluation of Oral Dispersible Tablets of Zidovudine with different Superdisintegrants. *International Journal of Current Pharmaceutical Review and Research*. 2011;2(2):81–91.
- [22] Amrutkar C, Salunkhe K, Chaudari S. Study on Self Nano Emulsifying Drug Delivery System of Poorly Water Soluble Drug Rosuvastatin Calcium. *World Journal of Pharmaceutical Research*. 2014;3(4):2137–2151.
- [23] Puttachari S, Kalyane N, Gupta S. Design and Evaluation of Self-Micro Emulsifying Drug Delivery Systems of Acyclovir. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2014;6(4):677–681.
- [24] Reddy A, Babu N, Debnath S. Design Development and Evaluation of Novel Nanoemulsion of Simvastatin. *International Journal of Advanced Pharmaceutics*. 2013;3(2):94–101.
- [25] Prajapati S, Joshi H, Patel C. Preparation and Characterization of Self-Microemulsifying Drug Delivery System of Olmesartan Medoxomil for Bioavailability Improvement. *Journal of Pharmaceutics*. 2013;p. 1–8.
- [26] Mohd AB, Sanka K, Bandi S, Diwan P, Shastri N. Solid self-nanoemulsifying drug delivery system (S-SNEDDS) for oral delivery of glimepiride. *Drug delivery*. 2015;22(4):499–508.