Sys Rev Pharm 2020; 11(3): 261 – 268
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Formulation and *In-Vitro* Characterization of Solidified Nebivolol Self-Nanoemulsion using Liquisolid Technique

Lubna A. Sabri[1*], Ahmed A. Hussien[1]
[1]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Iraq.
E-mail: lubnasabri14@gmail.com

Article History: *Submitted: 10.01.2020* *Revised: 02.02.2020* *Accepted: 12.03.2020*

ABSTRACT
Recently, supersaturable self-nanoemulsion (Su-SNE) is an advanced approach that can address low oral bioavailability issues. The antihypertensive drug, nebivolol (NBH), has low bioavailability, about 12%, due to its poor solubility and extensive pre-systematic metabolism. This work aimed to convert liquid nebivolol Su-SNE to powder using a liquisolid technique for exploiting the privileges of both Su-SNE and liquisolid approaches. Liquid NBH-loaded Su-SNE composed of imwitor 988, cremophor EL, propylene glycol and soluplus was adsorbed onto avicel PH101 and aerosil 200 admixture. The powder flow properties and *in-vitro* dissolution tests were carried out. Furthermore, the solid-state of optimized formula was characterized by SEM, DSC, X-ray diffraction, FT-IR analysis, and mean droplets size after redispersion in 0.1N HCl. The optimum liquisolid formula (SL-F8) revealed good flowability and significant dissolution improvement with 98.8% ± 0.99 drug dissolved compared to 23.1% ± 1.5 of pure NBH at 60 min. The solid-state characterization study of formula (SL-F8) showed an amorphous state of NBH within the solidified nanosystem without any interactions with the excipient used. Also, it gave nanoemulsion with mean droplets size about 47.77nm ±1.58 and PDI 0.289± 0.03, which was close to liquid Su-SNE with 55.27nm ± 1.22 droplets size and PDI 0.294± 0.01. Consequently, the liquisolid technique is a promising strategy for solidification of a liquid self-emulsifying system with improving dissolution rate and maintaining nanoemulsion properties.

Keywords: Avicel PH101, dissolution efficiency, liquisolid powder, supersaturable self-nanoemulsion

Correspondence:
Lubna A. Sabri
Department of Pharmaceutics, College of Pharacy
University of Baghdad
Iraq
E-mail: lubnasabri14@gmail.com

DOI: 10.5530/srp.2020.3.29

INTRODUCTION

For chronic disease management, the oral route for drug delivery is still the most preferred, owing to easily self-administrated, lower cost, and convenient for the patient. [1]

Nebivolol (NBH) is a third-generation cardioselective beta-blocker with vasodilation activity. Moreover, it has strong antioxidant properties and anti-inflammatory. [2] NBH can be proposed according to BCS as a class II drug. The oral bioavailability of NBH is about 12% due to poor solubility and extensive pre-systematic metabolism and hence, limited its clinical efficacy. [3]

Over the last few decades, lipid-based nanotechnology has been exploited to address poor oral bioavailability by developing various types of effective nanocarrier. [4, 5] Supersaturable self-nanoemulsion (Su-SNE) is one of the lipid nanocarriers, which refers to a preconcentrate or anhydrous mixture. It is typically composed of the drug candidate dissolved in a homogenous, transparent mixture of natural or synthetic oil(s), surfactant(s), co-surfactant(s) with precipitation inhibitor. Upon contacting with gastrointestinal fluids, Su-SNE can rapidly form *in-situ* a stable o/w nanoemulsion with peristalsis aids. The resulted nano-size dispersion provides a larger surface area for the drug-releasing with high concentration gradient for absorption. [6] Additionally, most of the components utilized in SNE as drug vehicles are permeability bioenhancer and promoter for intestinal lymphatic absorption that results in bioavailability improvement. [5]

Traditionally for oral delivery, the liquid self-nanoemulsion (L-SNE) formulation has fabricated as soft or hard capsules such as Neoral® (cyclosporine), Agenerase® (amprenavir), and Aptivus® (Tipranavir). [7] However, there are significant several practical drawbacks for broad marketing of L-SNE include high production costs, incompatibilities with capsules material during storage, and drug leakage with improper sealing.[8]

Plethora review articles have discussed various industrial techniques, which can be exploited for the conversion of L-SNE to solid powder either directly in one-step or indirectly in several steps. [8-10]

In this study, the adsorption technique was chosen as the most simple, lowest production cost and most accessible of process control with high stability among other solidification techniques. [11] Liquisolid technique is a promising approach for converting L-SNE into a dry, non-adherent flowable powder suitable for encapsulation or tabletting. [12] By this technique, liquid vehicle, which may be a drug solution, drug suspension or liquid medication firstly absorbs into the porous carrier and then added coating material to improve the flowability. [13] Liquisolid preparations can act as a tool for dissolution enhancement of poorly soluble drugs. [14]

So this study aimed to prepare solid supersaturable self-nanoemulsion as lipid nanocarrier for nebivolol using the liquisolid technique. The prepared liquisolid powders were evaluated to select the optimum formula, which was subjected to solid-state characterisation and redispersion property to indicate the feasibility of the solidification method.

EXPERIMENTAL

Chemicals

The following materials were used for preparation solid Su-SNE: imwitor® 988 (IOI Oleochemical, GmbH, Germany). Avicel PH101 and aerosil 200 (Safa Pharmaceutical Industries Co., Iraq). Nebivolol hydrochloride (Baoji Guokang Bio-Technology Co., China). cremophor®EL (International Laboratory, USA),

propylene glycol (Evans Medical Ltd, Liverpool, England), soluplus (BASF, Germany).

Preparation of nebivolol supersaturable self-nanoemulsion liquisolid powder

Liquid supersaturated self-nanoemulsion (L-SuSNE) of nebivolol was prepared and optimized in the preliminary study. The L-SuSNE was prepared by dissolving nebivolol (2%w/w) in 262.5 mg mixture of 9.5% imwitor 988, 42.9 % cremophor EL, 42.9 % propylene glycol and 4.7% w/w soluplus as oil, surfactant, co-surfactant, and precipitation inhibitor, respectively. After that, the mixture was vortexed and sonicated (Power sonic 410, Hwashin, Korea) until a clear liquid was obtained.

Then, a combination of Avicel PH101 and aerosil 200 were selected as carrier and coating materials, respectively for solidification of prepared L-SuSNE. Three different carrier: L-SNE ratio (1.5:1, 2:1 and 2.5:1) and carrier: coating materials ratio (R= 10, 15 and 20) were tried for the preparation of liquisolid powder, as shown in table 1.

The steps involved in the development of solid powder include; the L-SuSNE was loaded and mixed with calculated quantities of the carrier material. After that, the resulting wet mixture was blended with the pre-calculated quantities of coating material to obtain a uniform dry powder. Then, it was sieved through sieve number-60 and left at ambient temperature for 48 hours. [15] After that, the prepared powder was tested for its flow properties to optimize the carrier: L-SuSNE ratio and then packed into capsules.

Table 1: Composition of solidified nebivolol supersaturable self-nanoemulsion prepared by adsorption method

Formula * code	R **	Carrier: L-SuSNE ratio	Avicel PH101 (mg)	Aerosil 200 (mg)	Unit dose weight(mg)
SL-F1	10	1.5:1	402	40	710
SL-F2		2:1	536	53.5	857.5
SL-F3		2.5:1	670	67	1005
SL-F4	15	1.5:1	402	27	697
SL-F5		2:1	536	36	840
SL-F6		2.5:1	670	45	983
SL-F7	20	1.5:1	402	20	690
SL-F8		2:1	536	27	831
SL-F9		2.5:1	670	33.5	971.5

*Each formula contained 268 mg of L-SuSNE, R**= Avicel PH101: aerosil 200 ratio.

Evaluation of flow properties of liquisolid powder

The conventional laboratory methods for the assessment of flow properties are as following: The fixed funnel method was used to calculate the angle of repose (θ). Bulk and tapped density were measured to calculate Carr's index (CI) and Hausner ratio (HR), as described previously. [12] The obtained values were compared to the flowability range stated in the United States Pharmacopeia. [16] The powder mixture showed good flowability was filled into hard gelatin capsules and further investigated.

In-vitro dissolution of nebivolol from solid self-nanoemulsion capsules

The release profile of NBH from solid self-nanoemulsion capsules was obtained using USP type II (PharmaTest, Germany) dissolution apparatus. The dissolution medium was 500 ml of 0.1N HCl with the paddle rotation speed of 100 rpm. At predetermined time intervals, a sample of 5 ml was withdrawn and replaced with an equal volume of fresh dissolution medium. The filter syringe of 0.22 µm was used to filter withdrawn samples. The concentration of NBH in the filtrate was analyzed using UV-spectrophotometer (UV1100 model, EMC-LAB, Germany) at 281 nm. The dissolution of pure powder was also done.

For comparing in a single value, the model-independent approach was applied to evaluate the dissolution profiles of prepared liquisolid and pure NBH powder. The percent dissolution efficiency (% $DE_{60\ min}$), the mean dissolution time ($MDT_{60\ min}$), and the similarity factor (*f2*) were computed. [17] The dissolution data were analyzed using a DDSolver software program.

According to the data collected from the flow parameters evaluation and in-vitro dissolution tests, the selection of the best NBH-loaded solid Su-SNE formula was made for further investigation.

Morphological analysis by field emission-scan electron microscopy (Fe-SEM)

The Fe-SEM (MIRA3 Tescan, ARYA Electron Optic, Brno, Czech Republic) for the high-resolution image was used to investigate the external particle shape and surface morphology. It was conducted for pure NBH and optimized nebivolol solid Su-SNE (formula SL-F8). Each powder sample was sprinkling onto specimen stub with the aid of double-sided adhesive tape. At room temperature, each sample was coated by 20 µm gold layer for electrical conduction.

Thermal analysis by differential scanning calorimetry (DSC)

Thermal behaviour of NBH, physical mixture of an equal amount (NBH, Avicel PH 101, and aerosil 200), as well as, optimized formula (SL-F8), was assessed using DSC (DSC-60 plus Shimadzu, Japan). An approximate weight (15 mg)

of each sample was placed in a standard aluminium pan. The samples were scanned at a heating rate of 10 °C/ minute starting from 25°C up to 300 ° C under argon gas flow.

X-ray diffraction analysis

The X-ray diffraction pattern was conducted for pure NBH powder, physical mixture of NBH with solid blend at 1:1 ratio, and the optimum formula (SL-F8). The diffractometer (XRD-6000 Shimadzu, Japan) was operated to scan over a (2θ) range of 2 –80° using the copper-target X-ray tube. The measurement was done at a voltage of 40 kV, current of 30 mA and scan speed of 8 degrees/ min.

Fourier Transform Infrared Spectroscopy (FTIR)

Any incompatibility or interaction of the drug with the solid formulation excipients was determined by comparing FTIR spectra of the selected optimum formula with a pure drug, L-SuSNE, and solid (SL-F8) formulae. The spectrum was analyzed using (FTIR, Shimadzu, Japan, with Specac® Quest ATR- diamond type, UK). The tested samples were placed directly onto the crystal area and scanned over the range between 4000 - 400 cm^{-1}.

Reconstitution properties of the optimum nebivolol solid self-nanoemulsion capsule

The optimum formula (SL-F8) was reconstituted by dispersing and stirring on a magnetic stirrer for 30 min. Then, it allowed settling for supernatant droplets size analysis. The average droplet size and PDI of 100 fold dilution of liquisolid powder with 0.1 N HCl were assessed and compared to L-SuSNE using particle size analyzer (Brookhaven Corp 90 Plus, NY, USA).

Statistical analysis

The experiments result represented as a mean of triplicate samples ± standard deviation (SD). By employing the one-way analysis of variance (ANOVA) to detect the significant differences between the data of interest. The result was significantly considered different when the probability value (p) was less than 0.05 using Microsoft Excel 2010.

RESULTS AND DISCUSSION

Preparation of nebivolol self-nanoemulsion liquisolid powder

From preliminary study, we could prepare successful nebivolol Su-SNE that emulsified rapidly upon dilution within 36 ±1.2 sec. Dilution provided o/w emulsion with nano-size droplets (55.28 nm ± 1.22) and a polydispersity index (PDI) 0.294 ± 0.005. Moreover, the formula gave high apparent nebivolol concentration more than 90% over 240 min and enhanced nebivolol intestinal permeability by 3.2 folds compared to pure powder.

From our preformulation study, we found that Avicel, which is a commonly used diluent, had a lower adsorbing capacity for prepared Su-SNE about 0.54 g ± 0.1 /1g of Avicel compared to 1.46 g± 0.15/ 1g of aerosil 200 adsorbents. However, Avicel allowed complete desorption of SNE components compared to the possible strong interaction of a drug with silica-based adsorbents. Besides that, aerosil 200 is fumed silica with a low density, high bulk volume, as well as gel-forming property. [18] Intriguingly, Gumaste and Serajuddin also observed that silica with small pore size adversely impacted the releasing rate of drug-loaded SNE. [19] Therefore, a mixture of Avicel PH101 (as a diluent carrier) and aerosil 200 (as coating adsorbent), were selected in an attempt to enhance dissolution and reduce the total bulk volume of the prepared liquisolid powder. [14]

Adsorbing of L-SuSNE onto a solid mixture produced a powder with a greasy pale yellow appearance at carrier: L-SuSNE ratio (1.5:1). Contrariwise, dry white powders resulted in a higher ratio (2:1 and 2.5:1) used. Thus, suggesting good adsorption of L-SuSNE onto solid blend.

Evaluation of flow properties of liquisolid powder

Inadequate powder flow has negatively impacted on the blending uniformity, and hence, causing inaccurate filling dose, and finally defective end-products.

Flowability data were illustrated in table 2. A high liquid loading (i.e., carrier: L-SuSNE 1.5:1) exhibited poor flowability. Such finding might be due to excess oily nature components that resulted in sticky agglomerates and impaired the flow.

In contrary to 2:1 and 2.5:1 carrier: L-SNE ratio, they showed an acceptable flow with (θ^o) ranged between (30.27^o ± 0.49 – 35.03^o ± 1.5). The values of CI% and HR were varied from (9.31 ±1.48 to 15.56 ±0.57) and (1.09 ±0.02 to 1.19 ±0.01), respectively.

Statistically at different carrier: coating ratio (R), a non-significant difference in flowability (θ^o) was getting for the same carrier:L- SuSNE ratio.

Table 2: The flowability parameters of liquisolid self-nanoemulsion formulations

Formulation Code	Angle of repose (degree)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Flow type
SLF1 (1.5:1)	41.1 ±1.1	0.39±0.01	0.47±0.01	17.98±0.88	1.22 ±0.01	poor
SLF2 (2:1)	34.54 ±0.77	0.37±0.015	0.44±0.025	14.92±1.58	1.18 ±0.02	good
SLF3 (2.5:1)	35.03 ±1.49	0.35±0.014	0.41±0.014	15.56±0.57	1.19 ±0.01	good
SLF4 (1.5:1)	42.17 ±1.72	0.38±0.03	0.46±0.00	17.67±0.49	1.22 ±0.01	poor
SLF5 (2:1)	30.27±0.49	0.30±0.01	0.33±0.02	9.4±1.84	1.11 ±0.02	excellent
SLF6 (2.5:1)	33.37 ±0.67	0.35±0.01	0.39±0.01	9.31±1.48	1.09 ±0.02	good
SLF7 (1.5:1)	42.57±1.12	0.37±0.03	0.47 ± 0.05	21.29±1.2	1.27± 0.02	poor

SLF8 (2:1)	32.5 ±0.81	0.33±0.01	0.37±0.013	10.4±0.76	1.15 ±0.01	good
SLF9 (2.5:1)	33.89 ±1.59	0.33±0.02	0.38±0.02	12.1±0.29	1.14±0.03	good

In-vitro dissolution of nebivolol from solid self-nanoemulsion capsules

The release profiles of NBH-loaded solid SuSNE capsules that revealed good flow properties (SL-F2, SL-F3, SL-F5, SL-F6, SL-F8 and SL-F9) and plain NBH powder were evaluated in 0.1N HCl. As observed from Figures 1, at constant carrier: L-SuSNE ratio (2:1), the percent drug dissolved from the prepared capsule was 81.01%± 1.26, 89.2%± 2.12 and 94.9%± 0.71 of formulas SL-F2, SL-F5 and SL-F8, respectively, at 20 min. Similar findings observed from figure 2 for formulas SL-F3, SL-F6 and SL-F9, with dug dissolving percents were 87.8 %± 1.41, 89.15 %± 0.78 and 94.45 % ± 3.32, respectively. Results suggested that percent dissolving drug was directly proportional with excipients ratio (R-value). In general, all solid SuSNE formulations significantly ($p < 0.05$) enhanced dissolution compared to pure NBH powder, which showed only 10.3% ± 1.48 drug dissolved at 20 min.

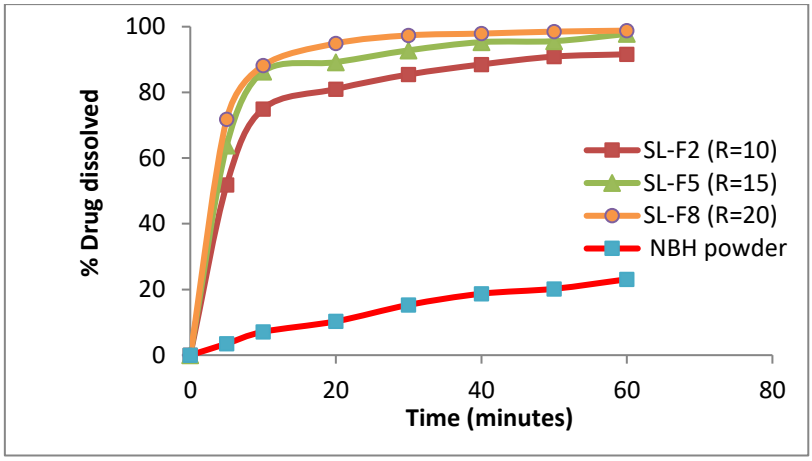

Figure 1: Comparative dissolution profile of nebivolol-loaded solid self-nanoemulsion at different (R= carrier: coating) and constant carrier: L-SuSNE (2:1) with Pure nebivolol in 0.1N HCl

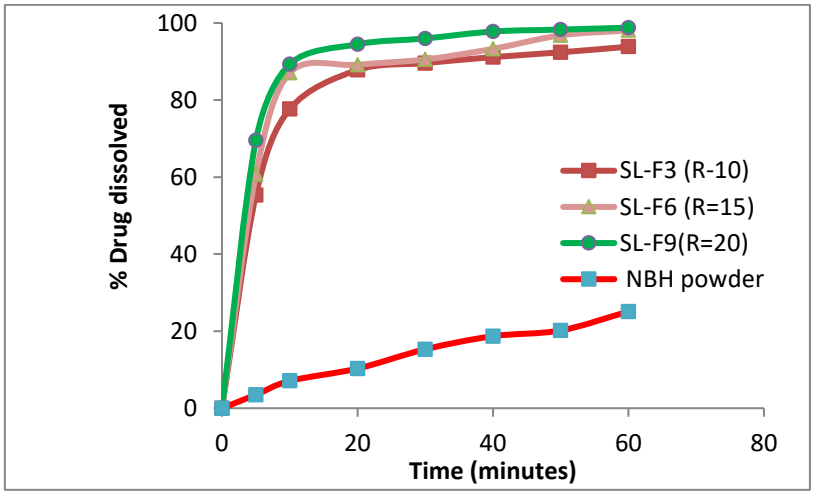

Figure 2: Comparative dissolution profile of nebivolol-loaded solid self-nanoemulsion at different (R=carrier: coating) and constant solid adsorbent: L-SNE (2.5:1) with pure nebivolol in 0.1N HCl

In this essence, as soon as the capsule shell disintegrated, the solid adsorbent particles, that contained NBH in a soluble state in Su-SNE, would finely suspend in the dissolution medium. Avicel can absorb water rapidly and improve particles wettability. Thereby, it enables fast desorption of Su-SNE components leading to spontaneous nanoemulsion formation. Consequently, it provided polar nanosize droplets with a large surface area for nebivolol releasing. [20] On the other hand, the pure powder was merely exposing of NBH hydrophobic crystalline particles to the dissolution medium.

Table 3 compared the calculated dissolution parameters for the prepared formulations with plain drug powder. It was clear that all prepared liquisolid powder had *f2* values (similarity factor) below 50, which mean they were not similar. Furthermore, % drug dissolved at 10 min and MDT_{60min} data could conclude that formula (SL-F8) that contained Avicel: aerosil at R=20 gave the best release in 10

minutes with the highest dissolution efficiency in comparison with other formulas. It showed a maximum percentage drug release of nearly 100% within 30 min. So the formula (SL-F8) was considered as the selected formula for further investigation of the solid-state.

Table 3: Dissolution Parameters of Solidified L-SNE Formulations compared to nebivolol powder

Formula code	% dissolved in 10 min ($\%Q_{10min}$)	Dissolution efficiency (DE%)	Mean dissolution time ($MDT_{60\ min}$)	Similarity factor (*f2*)
SL-F2	74.98 ± 0.67	78.91 ± 0.01	8.30 ± 0.13	10.14
SL-F3	77.6 ± 1.27	82.28 ± 0.03	7.39 ± 0.36	9.08
SL-F5	86.25 ± 1.48	86.40 ± 0.06	7.02 ± 0.12	7.72
SL-F6	87.05 ± 1.91	85.65 ± 0.07	7.07 ± 0.89	7.91
SL-F8	94.8 ± 0.71	89.91± 0.04	5.34 ± 0.81	6.67
SL-F9	89.25 ± 1.5	89.59 ±0.13	5.52 ± 0.23	6.79
Plain NBH powder	7.1 ± 1.26	26.15± 0.02	----	----

Evaluation of the optimum nebivolol self-nanoemulsion liquisolid capsule

Morphological analysis by field emission-scan electron microscopy (Fe-SEM)

The NBH photomicrograph showed smooth surface rectangular shape crystals of different sizes, as shown in figure 3, indicating crystalline nature which would be further confirmed by the DSC and XRD. On the other hand, the optimized formula (SL-F8) showed the complete absence of NBH rectangular crystals. At a higher magnification power, the optimum liquisolid formula revealed surface of Avicel with overspread of coating, which referred to the success of the adsorption method for L-SuSNE.

A.

B.

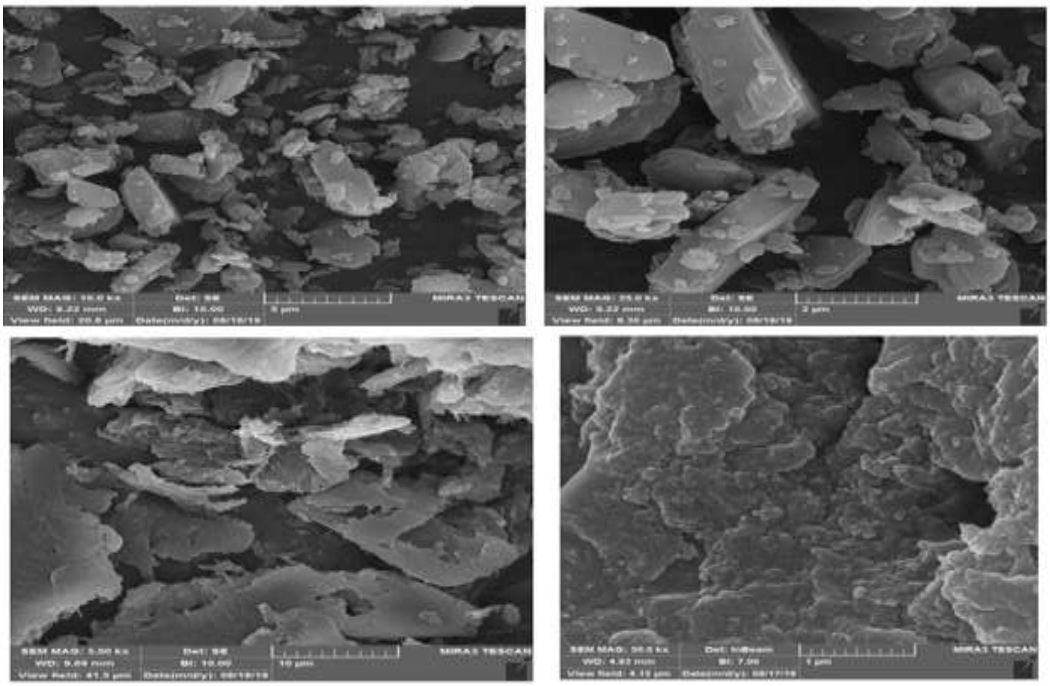

Figure 3: The photomicrographs of A) NBH pure powder and B) the optimum solidified Su-SNE formula (SL-F8), respectively at two magnification power of Fe-SEM

Thermal analysis by differential scanning calorimetry (DSC)

The DSC thermogram of pure NBH powder showed a single sharp endothermic peak at about 228.47°C, as depicted by figure 4. The peak was corresponding to its melting point with high purity, similar to previously published data.[21] The physical mixture thermogram also exhibited NBH endothermic peak at 225.3°C, suggested that there was good compatibility between NBH and solid adsorbents. In other words, the drug was still in the crystalline form that not affected by mixing with Avicel and aerosil 200. Meanwhile, the absence of NBH

characteristic endothermic peak from solidified Su-SNE formula (SL-F8) thermogram was noticed. That suggested the conversion of crystalline NBH to the amorphous state and/or complete solvation of NBH in the SNE components. The appearance of a board peak at 138 °C might represent the whole system melting behaviour, as suggested by Ali and Hussein.[22]

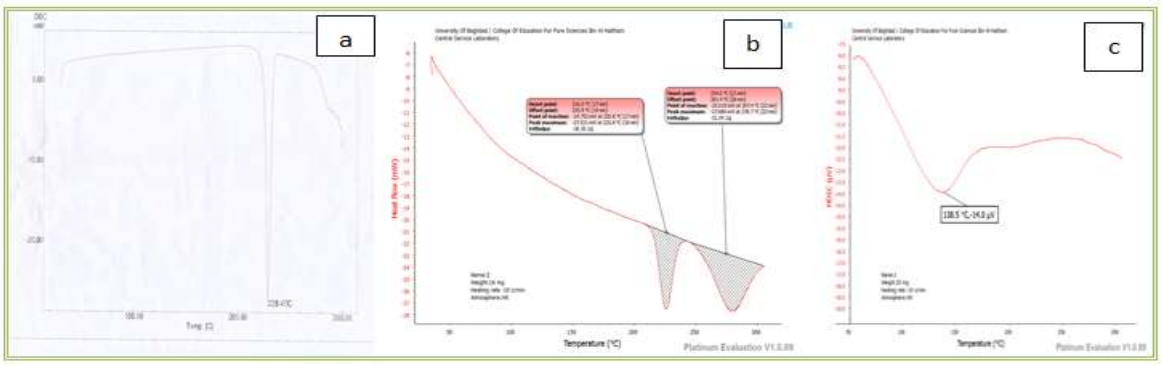

Figure 4: The DSC thermograph of (a) NBH, (b) physical mixture, and (c) solid Su-SNE formula SL-F8.

X-Ray Diffraction Analysis

Figure 5 illustrated the X-ray pattern of pure NBH, physical mixture of NBH with solid adsorbents, and the optimized solid formula (SL-F8). As observed from the diffractogram, NBH had distinct sharp peaks at 2θ values of 5.9, 11.63, 13.23, 16.118, 18.32, 18.97, 20.24, 21.22, 21.89, 24.81° and most intense characteristic peak at 25.48°. This pattern indicated NBH crystalline state and agreed with that reported in the literature. [23] On the other hand, the x-ray diffraction pattern of the physical mixture exhibited all NBH characteristic peaks, but they appeared at a lower intensity. Whereas, NBH characteristic crystalline peaks completely disappeared in the diffraction pattern of formula (SL-F8) and only showed a diffused peak pattern at 2θ angle of 15.23, 19.32 and 22.52° which related to Avicel pH101.[24]

It was evident that the results obtained from X-ray diffraction pattern and DSC supported the transformation of NBH from the crystalline to the amorphous state. This fact indicates that even though the drug is in solid dosage form, it was incorporated within the powder substrate in solubilized form. Almost, it represents a molecularly dispersed state, which contributes to enhancing a drug dissolution rate. Such results were in agreement with previous studies. [25,26]

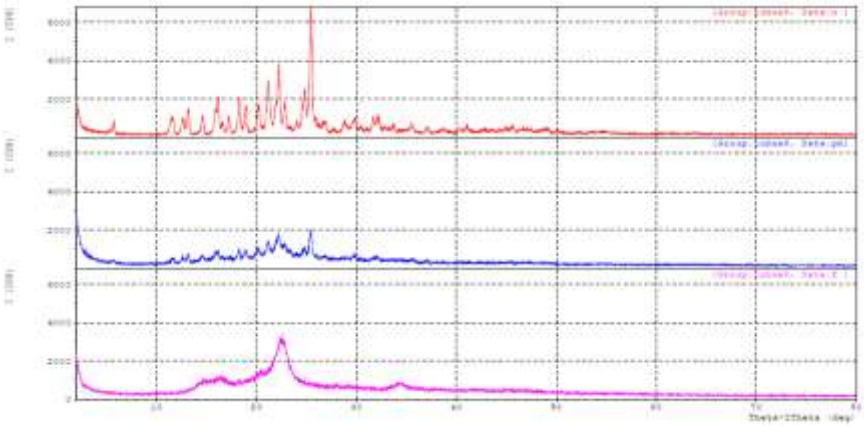

Figure 5: The X-ray diffractograms of (1) pure NBH powder, (2) physical mixture of nebivolol: Avicel: aerosil 200 at ratio 1:1:1 and (3) the optimum solid self-nanoemulsion formula (SL-F8).

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum of the solidified SNE (SL-F8) formula was investigated and compared with the FTIR spectrum of pure NBH and L-SuSNE, as shown in figure 6. Thereby could certifying chemical stability or any possible change in the drug structure that may occur during solidification steps due to interaction with excipients used.

The FTIR spectrum of L-SuSNE and SL-F8 formulas showed fewer peaks of the drug with peaks overlapping in the fingerprint region, which indicated a greater degree of trapping of NBH inside the SNE components. Moreover, there was a broad peak of O-H at wavenumber ranges (3600–3200 cm^{-1}), which hidden NBH characteristic peaks at 3390 and 3190.26 cm^{-1}due to O-H and N-H stretching vibration.[27] That can be ascribed by hydrogen bond formation between NBH and excipients used so that there was an enhancement of NBH solubilisation and dissolution.

Also, the principal peaks of NBH at 1624.06 and 1543 cm^{-1} for aromatic C=C, as well as, 1211.3 cm^{-1} were maintained

in spectra of L-SuSNE and SL-F8 formulas at their known position with a slight shift of N-H bending peak to 1492.9 cm^{-1}. Moreover, no new peaks were noticed in figure 6 other than that related to excipients used, indicating that no chemical interaction occurred among the components and NBH. In other words, NBH chemical integrity and the molecular structure were not changed even after the formulation.

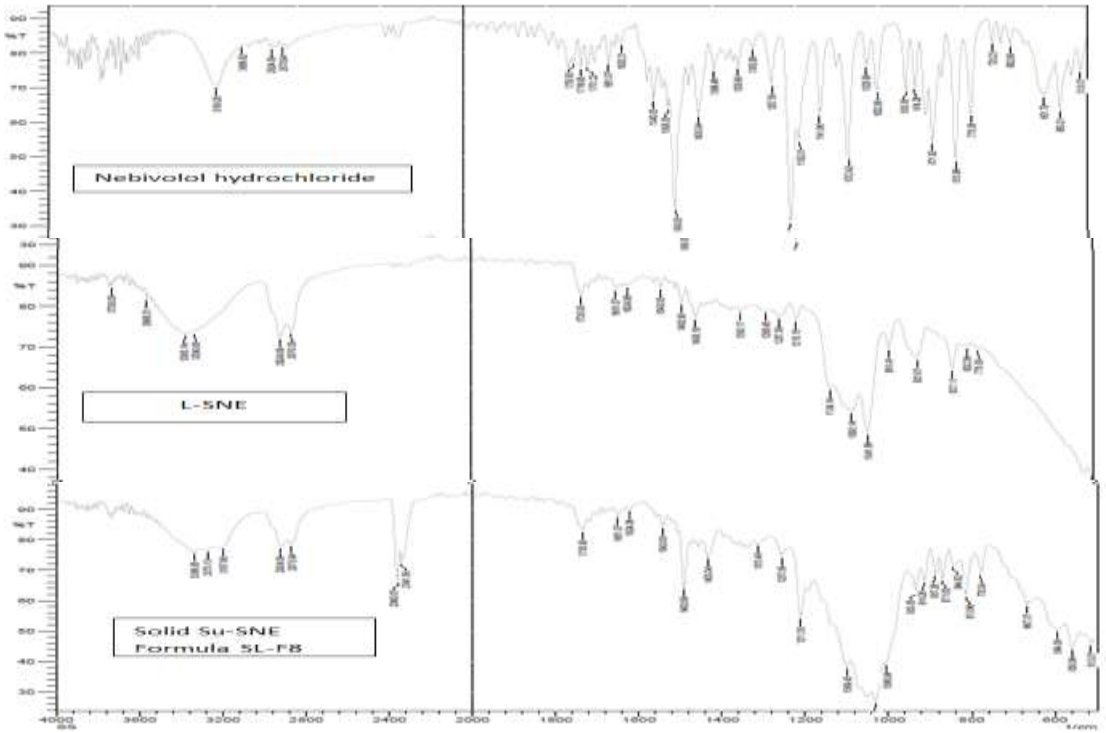

Figure 6: The FTIR spectrum of the nebivolol liquid supersaturable self-nanoemulsion (L-SNE) and solidified self-nanoemulsion powder (SL-F8) formulas compared to pure nebivolol.

Reconstitution properties of the optimum nebivolol self-nanoemulsion liquisolid capsule

For the successful transformation of L-SNE into solid dosage forms, should preserve its self-nanoemulsifying properties. In other words, the solidified SuSNE is expected to rapidly form nanoemulsion upon contact with aqueous medium and agitation in GIT, which is similar to L-SuSNE performance. In other words, the globule size was not affected by methods and/or carriers used for the solidification.

The capsule formula (SL-F8) showed mean droplets size about 47.77 nm ±1.58 with PDI 0.289± 0.03, which was close to L-SNE, which had 55.27 nm ± 1.22 droplets size with PDI 0.294± 0.005. It indicated that adsorption of L-SNE onto the solid carrier was not significantly affected emulsification capacity of SNE components but also capable of maintaining the system properties and quality.

CONCLUSION

Adsorption technique based on liquisolid concept, as a cost-effective method, could successfully be applied for solidification of nebivolol Su-SNE and maintained the nanosize scale of the droplets upon dispersion. The resulted liquisolid powder revealed good flowability and significant improvement of dissolution rate as compared to pure drug. liquisolid technique is a promising strategy for solidification of a liquid self-emulsifying system and suitable for large scale capsules production or may compress into tablets.

REFERENCES

1. Homayun B, Lin X, Choi H-J. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics 2019;11(3):1-29.
2. Fongemie J, Felix-Getzik E. A Review of nebivolol pharmacology and clinical evidence. Drugs 2015; 75: 1349–1371.
3. Sipos E, Szabo ZI, Redai E, Szabo P, Sebe I, Zelko R.. Preparation and characterization of nanofibrous sheets for enhanced oral dissolution of nebivolol hydrochloride. J Pharm Biomed Anal 2016; 129: 224-228.
4. Nabi B, Rehman S, Baboota S, Ali J. Insights on oral drug delivery of lipid nanocarriers: a win-win solution for augmenting bioavailability of antiretroviral drugs. AAPS PharmSciTech 2019; 20:1-11.
5. Cherniakov I, Domb AJ, Hoffman A. Self-nanoemulsifying drug delivery systems: an update of the biopharmaceutical aspects. Expert Opin Drug Del 2015 Jul; 12(7): 1121-1133.
6. Lee DR, Ho MJ, Jung HJ, Cho HR, Park JS, Yoon SH, *et al*. Enhanced dissolution and oral absorption of tacrolimus by supersaturable self-emulsifying drug delivery system. Int J Nanomedicine. 2016 Mar 18; 11:1109-17.

7. Kovvasu SP, Kunamaneni P, Joshi R, Betageri GV. Self-emulsifying drug delivery systems and their marketed products: A review. Asian J Pharm 2019; 13 (2):73-84.
8. Midha K, Nagpal M, Singh G, Aggarwalt G. Prospectives of solid self-microemulsifying systems in novel drug delivery. Cur Drug Del. 2017;14:1078-96.
9. Singh B, Beg S, Khurana RK, Sandhu PS, Kaur R, Katare OP. Recent advances in self-emulsifying drug delivery systems (SEDDS). Critical reviews in therapeutic drug carrier systems. 2014;31(2):121-85.
10. Mandic J, Zvonar Pobirk A, Vrecer F, Gasperlin M. Overview of solidification techniques for self-emulsifying drug delivery systems from industrial perspective. Int J Pharm. 2017;533(2):335-45.
11. Alwadei M, Kazi M, Alanazi FK. Novel oral dosage regimen based on self-nanoemulsifying drug delivery systems for codelivery of phytochemicals –Curcumin and thymoquinone. Saudi Pharmaceutical Journal 2019;27(6):866-76.
12. Elkadi S, Elsamaligy S, Al-Suwayeh S, Mahmoud H. The development of self-nanoemulsifying liquisolid tablets to improve the dissolution of simvastatin. AAPS PharmSciTech 2017; 18(7): 2586-25972.
13. Lu M, Xing H, Jiang J, Chen X, Yang T, Wang D, Ding P. Liquisolid technique and its applications in pharmaceutics. Asian J Pharm Sci 2017; 12: 115–123.
14. Khames A. Investigation of the effect of solubility increase at the main absorption site on bioavailability of BCS class II drug (risperidone) using liquisolid technique. Drug Delv 2017; 24(1): 328-338.
15. Spireas S, Bolton M. Liquisolid Systems and Methods of Preparing Same. U.S. Patent1999; 5:968,550.
16. Pharmacopeia, U. United States Pharmacopeia and National Formulary (USP 30–NF 25); US Pharmacopeia: Rockville, MD, USA, 2006.
17. Simionato LD, Petrone L, Baldut M, Bonafede SL, Segall AI. Comparison between the dissolution profiles of nine meloxicam tablet brands commercially available in Buenos Aires, Argentina. Saudi Pharm J. 2018;26(4):578-584.
18. Yeom DW, Chae BR, Kim JH, Chae JS, Shin DJ, Kim CH, et al. Solid formulation of a supersaturable self-microemulsifying drug delivery system for valsartan with improved dissolution and bioavailability. Oncotarget. 2017;8(55):94297-316.
19. Gumaste SG, Serajuddin ATM. Development of solid SEDDS, VII: Effect of pore size of silica on drug release from adsorbed self-emulsifying lipid-based formulations. Euro J Pharm Sci. 2017;110:134-47.
20. Abo Enin HA, Abdel-Bar HM. Solid super saturated self-nanoemulsifying drug delivery system (sat-SNEDDS) as a promising alternative to conventional SNEDDS for improvement rosuvastatin calcium oral bioavailability. Expert Opinion Drug Deliv. 2016;13(11):1513-21.
21. Vijayanand P, Patil JS, Reddy MV. Formulation and comparative pharmacokinetic evaluation of orodispersible tablets and films of nebivolol hydrochloride. J Pharm Invest 2015;45:237-47.
22. Ali HH, Hussein AA. Oral solid self-nano-emulsifying drug delivery systems of candesartan citexetil: formulation, characterization and in vitro drug release studies. AAPS Open 2017;3:6 (1-17).
23. Elfahl O, Essa E, El Maghraby G. Solid dispersion induced co-crystallization for enhanced dissolution rate of nebivolol hydrochloride: development of rapidly disintegrating tablets. Eur J Biomed Pharm Sci. 2019;6(2):5-17.
24. Azubuike CP, Okhamafe AO. Physicochemical, spectroscopic and thermal properties of microcrystalline cellulose derived from corn cobs. Int J Recycl Organic Waste Agriculture. 2012;1(1):67-73.
25. Khames A. Formulation and characterization of eplerenone nanoemulsion liquisolids, an oral delivery system with higher release rate and improved bioavailability. Pharmaceutics. 2019 Jan 18;11(1):1-18.
26. Motawea A, Borg T, Tarshoby M, Abd El-Gawad AE. Nanoemulsifying drug delivery system to improve the bioavailability of piroxicam. Pharm Dev Technol. 2017;22(3):445-456.
27. Silverstein RM, Bassler G C, Morril TC. Spectrometric identification of organic compounds. Fourth edition. USA: John Wiley & Son; 1981:106-129.
28. Dai, J. Preface to the fourth issue of Journal of Cardiovascular Disease Research (2010) Journal of Cardiovascular Disease Research, 1 (4), pp. 163-164. DOI: 10.4103/0975-3583.74257