International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 2, 2022

Original Article

# DESIGN AND EVALUATION OF LIQUISOLID COMPACTS OF NEBIVOLOL HYDROCHLORIDE

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*Received: 20 Nov 2021, Revised and Accepted: 24 Jan 2022*

**ABSTRACT**

**Objective:** The aim of this study was to investigate the potential of a liquisolid system to improve the dissolution rate and the bioavailability of nebivolol hydrochloride.

**Methods:** Solubility of nebivolol was determined in different nonvolatile solvents to finalize the best nonvolatile vehicle having maximum solubility. The liquisolid compacts were prepared using Fujicalin as a carrier material, Aerosil 200 as a coating material, Polyethylene glycol 400 as a liquid vehicle, and Croscarmellose sodium as a super disintegrating agent. $2^3$ full factorial design was used to optimize the formulation in which the drug concentration, PVP K 30, Excipient ratio (R), and nebivolol containing nonvolatile solvent liquid level were selected as independent variables by using design expert software. The eight liquisolid compact formulations were prepared. Nebivolol liquisolid compacts were evaluated for drug content, tablet hardness, Friability, disintegration, and dissolution. An *in vivo* study was carried out in male Wistar rats.

**Results:** The solubility of nebivolol hydrochloride in polyethylene glycol 400 was found to be greater than the other nonvolatile solvents. The liquisolid system of nebivolol was formulated successfully using Fujicalin, Aerosil 200, and polyethylene glycol 400. *In vitro* evaluation parameters for the liquisolid compact were within the prescribed limits. It was found that optimized liquisolid tablet formulation showed higher dissolution than the marketed tablet, with 88.33±0.94 % drug release within 120 min and the drug release was more than 75 % in 30 min for nebivolol LS-3N, which is optimized. LS-3N liquisolid compacts follow the Peppas model and exhibited first-order release.

**Conclusion:** The liquisolid compacts can be a promising alternative for the formulation of water-insoluble drug nebivolol hydrochloride with improved dissolution and bioavailability.

**Keywords:** Liquisolid compacts, Nebivolol hydrochloride, Fujicalin


DOI: https://dx.doi.org/10.22159/ijap.2022v14i2.43657. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

## INTRODUCTION

The most convenient and commonly employed route of drug delivery is oral ingestion. The oral route remains the preferred route of drug administration due to its convenience, better patient compliance, and low production costs [1, 2]. According to the biopharmaceutical classification system (BCS), drug candidates featuring poor solubility and high membrane permeability are categorized as BCS class 2, for which the oral absorption is often limited by the dissolution rate in the gastrointestinal tract. It is well established that the poor solubility and dissolution property of water-insoluble drugs are one of the main reasons for poor or erratic bioavailability [3, 4]. As pharmaceutical approaches are critical factors in improving the bioavailability of BCS class 2 drugs, various formulation strategies have been attempted for this purpose, such as particle size reduction [5], solid dispersion [6–8], complexation [9], self-emulsification [10], the inclusion of drug solution or suspension into soft gelatin [11] and liquisolid technology [12]. One of the most promising strategies for release enhancement is the liquisolidcompacts (LSC) [13]. Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. "Liquisolid technology"is also referred to as "powder solution technology" [14]. The term "liquisolidmedication" implies oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials [15]. Particles that possess porous surfaces with high absorption properties may be used as the carrier material. The increasing moisture content of carriers results in decreased powder flowability. The coating material must cover the surface and maintain powder flowability [16]. The liquisolid tablets that contain water-insoluble drugs are expected to enhance drug dissolution because of the increased wetting properties of the drug particles and the large surface area available for dissolution. The liquisolid tablets are suitable to formulate low-dose water-insoluble drugs [17].

Nebivolol is a third-generation lipophilic beta blocker used to treat hypertension [18-20]. In clinical studies, preliminary evidence showed promising efficacy and tolerability and suggested a potential for reduced mortality in patients with heart failure [21]. It has less bioavailability (12 %) due to low water solubility (0.091 g/100 ml) and dissolution rate [22, 23]. It is included in Class 2 of the Biopharmaceutical Drug Classification System. Nebivolol drug has extensive first-pass metabolism, low dose (5 mg) as well as low solubility. It could be a promising candidate for liquisolid dosage forms [24].

## MATERIALS AND METHODS

### Materials

Nebivolol hydrochloride was a gift sample from Cadila Pharmaceuticals Ltd, Ankleshwar. Fujicalin was kindly supplied by Gangwal Chemicals Pvt. Ltd. Croscarmellose sodium, Span 20, and Span 80 were purchased from Merck Limited, Mumbai. Aerosil 200, Brij 35, Hydrochloric acid, Lactose, Magnesium stearate, PEG 200, PEG 400, Potassium dihydrogen orthophosphate, Propylene glycol, PVP K-30, Tween 20, Tween 80 were purchased from SD. Fine-Chem., Mumbai. PEG 600 were purchased from Finar chemicals, Mumbai. All other analytical grade chemicals were used.

### Methods

#### Saturation solubility studies

For the selection of the best nonvolatile solvents, solubility studies were performed. In this procedure, pure drug (nebivolol hydrochloride) was dissolved in four different nonvolatile solvents (PEG 200, propylene glycol, PEG 400, PEG 600, Tween 20, Tween 80, Span 20, Span 80, and Brij 35). An excess amount of pure nebivolol

was added to the above solvents, and these solutions were shaken on the rotary shaker for 72 h at 25 °C under constant vibration. After 72 h period, the saturated solutions were filtered using Whattman filter paper, and the filtrate was collected [25, 26] and analyzed by UV spectrophotometer at 282 nm.

**Application of mathematical model for designing nebivolol hydrochloride liquisolid formulations**

To achieve good flow behavior and compressibility of liquisolid systems, a mathematical model designed by Spireas *et al.* was used as a formulation design model for the liquisolid tablets. The formulation design of liquisolid compacts involves the determination of the following parameters [27, 28].

**Angle of slide**

To determine the angle of slide, the required amount of carrier is weighed and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. The angle is known as the angle of slide. It was used as a measure of the flow properties of powders.

**Liquisolid flowability test**

A test method, called the liquisolid flowability test, was developed and employed to determine the flowable liquid retention potential (Φ-value) of several powder excipients likely to be included in liquisolid compacts.

Powder admixtures containing carrier: coating (Fujicalin: Aerosil 200) ratio (R) values of 25, 20 were selected.

To a specified quantity of powder admixture corresponding to a specific R-value, increasing amounts of best nonvolatile solvent were added. The resulting powder admixture was assessed for acceptable flowability by determining its angle of slide. The flowable liquid load factor ($\Phi L_f$) of the admixture was determined at an angle of slide 33°.

$$\Phi L_f = W/Q$$

Where W= weight of nonvolatile solvent

Q= weight of powder admixture

After the determination of flowable liquid load factor ($\Phi L_f$) for all the different R-values.

The liquid loading factor for the production of a liquisolid system with acceptable flowability can be determined by:

$$\emptyset Lf = \emptyset + \emptyset\Psi/R$$

Where Φ and Ψ values correspond to the flowable liquid retention potential of the carrier and coating material, respectively.

As soon as the optimum liquid load factor is determined, the appropriate quantities of the carrier ($Q_0$) and coating ($q_0$) material required to convert a given amount of liquid formulation (W) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Q° = W/L°$$

$$q° = Q°/R$$

$$R = Q°/q0°$$

R represents the ratio between the weights of the carrier ($Q_0$) and the coating ($q_0$) materials are required to convert liquid formulation (W) into acceptably flowing and directly compressible powder.

**Experimental design for designing liquisolid powder compacts**

A $2^3$ factorial design consists of three independent variables at two levels. According to this design, eight runs were conducted [29]. The independent variables selected for this study were X1, PVP K 30; X2, Excipient ratio (carrier: coating (Fujicalin: Aerosil 200) ratio (R)); X3, % Nonvolatile vehicle containing nebivolol (Polyethylene glycol 400). The dependent variables were Y1, Angle of repose; and disintegration time (YDT); Y3 % Drug release. The levels of independent variables are listed in table 1. A statistical model incorporating interactive and polynomial terms evaluated the response.

$$Y = b0 + b1X1 + b2X2 + b3X3 + b12\,X1X2 + b13\,X1X3 + b23\,X2X3 + b123\,X1X2X3$$

Where Y is the dependent variable, $b_0$ is the arithmetic mean of the eight trials, and $b_i$ is the estimated coefficient for the factor $X_i$. The $X_1$, $X_2$, $X_3$ are the coded value of the concentration of PVP-K30 in the formulation, the Fujicalin: Aerosil 200 ratio, nonvolatile vehicle containing nebivolol. The interaction terms ($X_1X_2$) show how the response changes when two factors simultaneously vary.

**Table 1: Absolute values of variables employed in factorial design in nebivolol liquisolid formulations**

| S. No. | Variables | | Levels | |
|---|---|---|---|---|
| | Absolute | Coded | -1 | +1 |
| 1 | Concentration of PVP-K30 in the formulation (% w/w) | $X_1$ | 2 | 4 |
| 2 | Excipient ratio (Fujicalin–Aerosil 200) | $X_2$ | 20 | 25 |
| 3 | Nonvolatile vehicle containing nebivolol (%w/w) | $X_3$ | 30 | 50 |

**Preparation of liquisolid powder compacts**

Liquisolid compacts were formulated according to the $2^3$ factorial design (table 1). The weighed amount of drug substance was dispersed in the calculated amount of nonvolatile solvent (polyethylene glycol PEG 400), the liquid vehicle. The mixing procedure was conducted in three stages as described by Spireas *et al.* [30]. Firstly, the weighed quantity of carrier material (Fujicalin) was blended with liquid medication in order to distribute the liquid medication into the powder evenly. Then, the calculated amount of coating material (Aerosil 200) was added to the system under continuous triturating in a mortar. Finally, to the above binary mixture super disintegrating agent, i.e., croscarmellose sodium was added and mixed for 10 to 20 min producing the final liquisolid powder, which was compressed using a multi-station rotary tablet compression machine (Lab press limited, India).

**Micromeritic properties of prepared pre-compressed liquisolid powder systems**

A fixed funnel method was used to study the angle of repose (θ). A weighed quantity of samples was transferred into a graduated cylinder from each batch to determine the bulk and tap density using USP-I tapped density tester (TD 1025, Labindia Instruments, Mumbai, India). The experiments were performed in triplicate. The parameters selected to study flow properties were determined using Equations [31, 32].

$$\text{Tan}\,\theta = h/r$$

$$\text{Bulk density } (\sigma b) = \frac{\text{Mass}}{\text{Poured volume}}$$

$$\text{Tapped density } (\sigma t) = \frac{\text{Mass}}{\text{Poured volume}}$$

$$\text{Carr}'\text{s index } (\%) = \frac{(\sigma t - \sigma b)}{\sigma t} \times 100$$

$$\text{Hausner}'\text{s ratio} = \frac{\sigma t}{\sigma b}$$

**Post compression studies of the nebivolol liquisolid powder compacts**

The prepared liquisolid compacts further evaluated for drug content (n = 6), hardness (n = 20), friability (n = 20) and weight variation (n

= 20). The drug content in each batch was determined by triturating 6 tablets in a mortar with the help of a pestle. The amount equivalent to one average tablet was weighed and dissolved in 0.1 N hydrochloric acid. The flask was placed in an orbital shaking instrument (Remi, Electrotechnik Ltd., Vasai, India). Temperature and rpm were adjusted to room temperature and 150, respectively. Later was filtered through a 0.45 µm Millipore membrane filter paper. The few ml of initial filtrate was discarded, and the sufficient volume of filtrate was collected. The amount of the drug was estimated by UV visible spectrophotometer. The hardness of the liquisolid compacts was evaluated using Monsanto hardness tester (MHT-20, Kshitij International, Ambala, India), the mean hardness of each formula was determined. The friability of prepared formulations was determined using Roche Friabilator (FT 1020, Labindia, Mumbai, India). The disintegration time of the liquisolid compacts was measured using a disintegration tester (DT 1000, Labindia, Mumbai, India). Weight variation test was performed according to the official method (USP) using an electronic balance [31, 32] (ATX224, Shimadzu, Japan).

### *In vitro* drug release

*In vitro* drug release of the samples was carried out using USP-type II dissolution apparatus (paddle type-(DS 8000, Labindia, Mumbai, India)) at 50 rpm in 900 ml of 0.1 N hydrochloric acid at 37±0.5 °C. At different time intervals, 5 ml of sample is withdrawn and filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were analyzed at $\lambda_{max}$ of drug [33] (282 nm). The percentage cumulative drug release (% CDR) was calculated.

### Release kinetics

The drug release kinetics of the various formulations were determined to understand the order of the drug release and the mechanism of drug release. The drug release kinetics of the formulations was determined in 0.1 N hydrochloric acid solution.

### Zero-order

This model represented an ideal release profile to achieve the prolonged action. In zero kinetics, the release of the drug is independent of the concentration of the drug present in the dosage form. The zero-order is expressed in the equation as

$$\%\ \text{Drug release} = k.\text{Time}$$

A plot of the amount of drug released versus time will be linear if the release kinetics follows zero-order. The linearity is decided by the regression coefficient ($R^2$). The $R^2$ values lie in the range of 0 to 1. The higher the value of $R^2$, the better the correlations [34].

### First-order

This model applied to the study of hydrolysis kinetics and to study the release profiles of dosage forms, such as those containing water-soluble drugs in porous matrices. The dissolution of the drug often follows first-order in immediate release (conventional) dosage forms and sustained-release products. The release of a drug depends on the concentration of the drug present in the dosage form. The first order is expressed in the equation as

$$\text{Log (fraction unreleased)} = (k/2.303) * \text{time}$$

A plot of log amount of drug unreleased versus time will be linear if the release kinetics follows the first order [34].

### Higuchi equation (diffusion rate controlled)

A few sustained and controlled release drug delivery systems release the drug by diffusion. This model was applied to the uniform swellable polymer matrix, as in the case of matrix tablets with water-soluble a drug. In the matrix tablet, the outside layer of the drug is exposed to the bathing solution in which it is dissolved first. Then the drug diffuses out of the matrix. The process continues until all the drug diffuses. When the initial drug loading was below the solubility limit, the release was achieved by simple diffusion through the polymer. For this purpose, data treatment is done using the Higuchi equation may be expressed as follows [34].

$$M = kt1/2$$

Where, M = percentage of drug released

t = time

k = proportionality constant

### Hixson-Crowell equation (dissolution rate controlled)

Tablets and capsules disintegrate into granules and small particles. Then the drug dissolves slowly from the surface of the particles and goes into the dissolution medium. The drug's dissolution rate from these particles can be derived, which is the cube root of the weight. For the analysis of data, Hixson Crowell root law is used.

When the initial drug loading was above the solubility limit, the dissolution of the drug in the polymer and drug release became the dissolution rate limited. Hixson Crowell equation is expressed in equation

$$M01/3 - Mt1/3 = kt$$

Where $M_0$= mass of the drug particles initially, t=0

$M_t$= mass of the drug particles at a time, t

k= proportionality constant

t= time

Hixson Crowell cube root law is used for verifying the drug release pattern from dosage forms and powders. If a linear plot is obtained, when time and (fraction of drug unreleased)$^{1/3}$ are taken on the x-axis and y-axis, respectively, then the drug release is dissolution rate controlled. The slope of the line gives the k value [35].

### Korsmeyer-peppas equation

This model was widely used; when the release mechanism was not well known or when more than one type of release phenomena could be involved [36-38].

$$\text{Log}(\%\ \text{Released}) = \log(k) + n.\log(\text{Time})$$

### Compatibility study by FTIR

Chemical interaction between the drug and excipients was studied by the FTIR technique. FTIR spectra of the drug and optimized liquisolid compacts were recorded on FTIR spectroscopy (Shimadzu 8400, Japan) using the potassium bromide (KBr) pellet method [39]. The scanning range was 4000-400 $cm^{-1}$ at a resolution of 1 $cm^{-1}$.

### Differential scanning calorimetry (DSC)

The physical state of nebivololin liquisolid compacts was characterized by differential scanning calorimetry (DSC-60, Shimadzu, Japan). Samples (3–5 mg accurately weighed to 0.005 mg) were placed in aluminum pans, and the lids were crimped using a Shimadzu crimper. The thermal behavior of the samples was investigated at a scanning rate of 10 °C $min^{-1}$, covering a temperature range of 40-300 °C. The instrument was calibrated with an indium standard [40].

### X-ray powder diffractometry (XRD)

To determine the powder characteristics, X-ray powder diffraction studies of pure drug and optimized were performed. X-ray powder diffraction patterns were recorded on XRD Maxima 7000 Shimadzu, Japan. The scanning rate employed was 6 ° $min^{-1}$ over the 10 to 50 ° diffraction angle (2θ) range [41].

### Stability studies of optimized liquisolid compacts

The optimized liquisolid formulation was subjected to accelerated stability study and carried out at 40±2 °C/75±5 % RH., as per ICH guidelines Q1A (R2) 2003. The formulation was kept in air-tight glass vials and assayed periodically, at the time points of 0,1, 2, 3 mo means on 1$^{st}$, 30$^{th}$, 60$^{th,}$ and 90$^{th}$ day, for drug content dissolution performance [27, 41].

### *In vivo* studies

The research project animal experimentation was taken approval

from the Committee for the Purpose of Control And Supervision of Experiments on Animals (CPCSEA) by the Institutional Ethical Committee (IAEC) Approval No: CPCSEA/IAEC/JLS/13/08/20/20 in Jeeva Life Sciences (CPCSEA Reg No: 1757/PO/RcBiBt/S/14/CPCSEA), Hyderabad. To conduct *in vivo* experiments and have been executed following the regulatory standards. Male Wistar rats, weighing approximately 160-180 g, were purchased from Sainath Agencies, Musheerabad, Hyderabad, India, and were fasted for 12 h before drug administration but permitted liberated admittance for water. Doses were calculated according to the conversion factor [42, 43]. Pharmacokinetic data were analyzed using PK solver add-in [44] in MS-Excel 2007.

Male Wistar rats were divided into three groups (six animals each), and each animal received one of the following preparations: nebivolol pure drug, liquisolid compacts optimized formulation (LS-3N), marketed formulation (Nebistar-5 mg) suspension in sodium alginate solution (0.5 %) containing drug equivalent to 0.513 mg/Kg of body weight through dose conversion. The formulations were administered by oral route by oral gavage/feeding needle/gastric catheter, blood samples (2 ml) were withdrawn at time intervals of 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 18 and 24 h through retro-orbital plexus, centrifuged at 5000 rpm for 10 min [45, 46] and plasma samples were analyzed by RP-HPLC.

## RESULTS AND DISCUSSION

### Solubility studies

Efforts were made to select the nonvolatile solvent having higher solubility of nebivolol. The solubility of nebivolol in different nonvolatile solvents like PEG 200, PEG 400, PEG 600, Propylene glycol, Tween 20, Tween 80, Span 20, Span 80, Brij 35 at 25 °C was studied, and the obtained solubility data were represented in fig. 1. In liquisolid formulations, the drug solubility in the nonvolatile solvents is essential. Higher the solubility, the more the drug particles dissolved in the liquid vehicle prior to the adsorption onto the carrier materials. The selection of nonvolatile solvent with a high solubilizing capacity for the drug leads to an increased fraction of molecularly dispersed nebivolol which in turn leads to enhanced drug release [47].

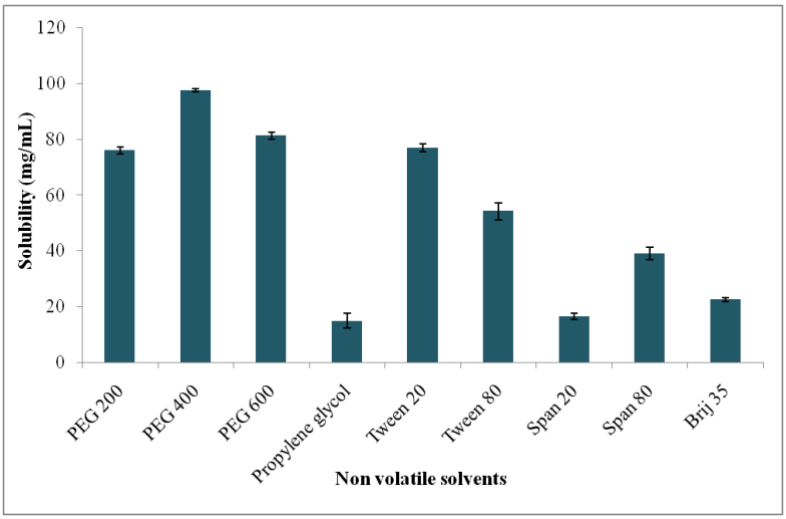


**Fig. 1: Solubility of nebivolol in different nonvolatile solvents (mean±SD, n=3)**

### Application of mathematical model for designing nebivolol hydrochloride liquisolid formulations

### Angle of slide

The angle of slide test was performed to assess the flow properties of liquid/powder admixtures (mixture of carrier and coating material) of various excipients employed in the formulation of liquisolid compacts of nebivolol. An angle of slide of 33° was considered as optimum value [48]. The angle of slide values of several powder admixtures for different excipients ratios was enumerated in tables 2 to 3.

When increasing amounts of nonvolatile solvent (PEG 400) were added to the powder admixture of Fujicalin-Aerosil 200 with an excipients ratio of R=20, an angle of slide value of 33° was obtained using 1.4 g of PEG 400 and 5.0 gm of powder admixture. This value was taken for the determination of liquid load factor ($\Phi L_f$).

Upon addition of increasing amounts of nonvolatile solvent (PEG 400) to the powder admixture of Fujicalin-Aerosil 200 (5.0 g) with an excipient ratio of R=25, an angle of slide value of 33° was obtained when 1.2 g of PEG 400 was added. This value was taken for the determination of liquid load factor ($\Phi L_f$).

### The liquid load factor

$$\Phi L_f = \Phi + \Psi/R$$

$\Phi$ Value–flowable liquid retention potential of the carrier

$\Psi$ Value-flowable liquid retention potential of the coating material

**Table 2: Liquid load factor values for Fujicalin-Aerosil 200 admixture with R=25, 1/R value=0.04**

| S. No. | Weight of admixture(g) | Weight of nonvolatile solvent (mL) | Angle of slide n=3 (AM*±SD) | Φ Value-carrier | Ψ Value-coating | ΦLf |
|---|---|---|---|---|---|---|
| 1 | 5 | 0 | 37.00±2.00 | 0 | 0 | 0 |
| 2 | 5 | 1.2 | 33.66±1.15 | 0.249 | 6.24 | 0.499 |
| 3 | 5 | 1.4 | 30.00±1.00 | 0.291 | 7.28 | 0.582 |
| 4 | 5 | 1.6 | 28.00±1.00 | 0.332 | 8.32 | 0.665 |
| 5 | 5 | 1.8 | 26.33±0.57 | 0.374 | 9.36 | 0.748 |
| 6 | 5 | 2 | 23.66±1.52 | 0.416 | 10.40 | 0.832 |
| **7** | 5 | 2.2 | 20.66±0.57 | 0.457 | 11.44 | 0.915 |

**Table 3: Liquid load factor values for Fujicalin–Aerosil 200 admixture with R= 20, 1/R value= 0.05**

| S. No. | Weight of admixture (g) | Weight of nonvolatile solvent (mL) | Angle of slide n=3 (AM*±SD) | Φ Value-carrier | Ψ Value-coating | $\Phi L_f$ |
|---|---|---|---|---|---|---|
| 1 | 5 | 0 | 37.66±1.52 | 0 | 0 | 0 |
| 2 | 5 | 1.2 | 35.33±0.57 | 0.252 | 5.04 | 0.504 |
| 3 | 5 | 1.4 | 33.00±1.00 | 0.294 | 5.88 | 0.588 |
| 4 | 5 | 1.6 | 28.66±1.52 | 0.336 | 6.72 | 0.672 |
| **5** | 5 | 1.8 | 26.33±2.08 | 0.378 | 7.56 | 0.756 |
| 6 | 5 | 2.0 | 24.66±0.57 | 0.420 | 8.40 | 0.840 |
| **7** | 5 | 2.2 | 23.00±1.00 | 0.462 | 9.24 | 0.924 |

**Flowable liquid retention potential (*Φ* value)**

The procedure for determining Flowable liquid retention potential (*Φ*- value) was explained in the materials and methods chapter. Flowable liquid load factor values Vs. 1/R for Fujicalin–Aerosil 200 admixture

**Table 4: Flowable liquid load factor ($\Phi L_f$) for various R values**

| R | 1/R | Flowable liquid load factor ($\Phi L_f$) * |
|---|---|---|
| *Fujicalin and Aerosil 200 admixture* | | |
| 25 | 0.04 | 0.499 |
| 20 | 0.05 | 0.588 |

*Values are obtained by using the equation, $\Phi L_f$= W/Q, Where W= weight of nonvolatile solvent, Q= weight of powder admixture

It was found that the carrier to coating ratio, i.e., R-value, affected the $L_f$ and consequently the hardness, disintegration time, and dissolution behaviors of nebivolol liquisolid systems. The $L_f$ decreased 0.588, 0.499 with the increase of R-value for 20, 25 respectively for Fujicalin: Aerosil liquisolid formulations. Fujicalin, a calcium hydrogen phosphate powder with a high specific surface area of 40 $m^2$/g, improves the liquisolid approach [49]. Fujicalin can load the maximum amount of liquid and maintain good flow properties if a decrease in the excipients ratio (R-value) increases the load factor.

**Formulation development**

From the above studies, various formulations of liquisolid compacts of nebivolol were developed. The developed formulations were subjected to different evaluation tests. The dissolution profiles of the optimized formulation were compared with the marketed product (Nebistar-5 mg) and pure nebivolol.

**Formulation composition**

The formulation compositions of LS-1N to LS-8N using Fujicalin (as a carrier) and Aerosil 200 (as coating material) are reported in table 5. The formulations were prepared with pharmaceutically approved excipients to get the required properties for tablets. The lubricant was added to improve the flow property of powder during compression. The formulations were compressed with 6 mm round standard concave punches.

**Table 5: Formulation composition of LS-1N to LS-8N with Fujicalin as a carrier and Aerosil 200 as a coating material**

| Ingredients (mg) | LS-1N | LS-2N | LS-3N | LS-4N | LS-5N | LS-6N | LS-7N | LS-8N |
|---|---|---|---|---|---|---|---|---|
| PEG 400 (% w/w) | 30 | 30 | 30 | 30 | 50 | 50 | 50 | 50 |
| Fujicalin: Aerosil 200 ratio (R) | 20 | 20 | 25 | 25 | 20 | 20 | 25 | 25 |
| Loading factor | 0.588 | 0.588 | 0.499 | 0.499 | 0.588 | 0.588 | 0.499 | 0.499 |
| **Quantity (mg/tablet)** | | | | | | | | |
| Nebivolol | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| PVP K-30 | 2 | 4 | 2 | 4 | 2 | 4 | 2 | 4 |
| Fujicalin | 33 | 33 | 33 | 33 | 19.8 | 19.8 | 20.03 | 20.03 |
| Aerosil 200 | 1.6 | 1.6 | 1.3 | 1.3 | 0.99 | 0.99 | 0.8 | 0.8 |
| Croscarmellose sodium (5 %) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate (1 %) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Lactose | 52.27 | 50.279 | 52.279 | 50.279 | 66.167 | 64.167 | 66.167 | 64.167 |
| Total weight | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

In these formulations, PEG 400 was used as a nonvolatile vehicle to make the solution nebivolol, Fujicalin was used as carrier material, and Aerosil 200 used as coating material, PVP K-30 was used as crystal inhibitor and binder, lactose was used as a diluent, croscarmellose sodium (CCS) as a superdisintegrant, and magnesium stearate as lubricant. Direct compression technology has been employed for preparing of tablets.

**Precompression studies**

Precompression parameters for the formulation blends of LS-1N to LS-8N were studied to verify the improvement in flow properties, and the results were presented in table 6. From the pre-compression studies of the formulations, it has been observed that the flow properties of the formulation blends were good to excellent.

**Table 6: Precompression parameters of various blends (Formulations with Fujicalin)**

| Formulation code | Angle of slide* (°) | Angle of repose* (°) | Bulk density* ($g/cm^2$) | Tapped density* ($g/cm^2$) | Compressibility index* (CI) (%) | Hausner's ratio* (%) |
|---|---|---|---|---|---|---|
| Pure nebivolol | 47.00±0.77 | 43.38±2.60 | 1.04±0.044 | 1.35±0.047 | 22.77±2.10 | 1.29±0.035 |
| LS-1N | 33.83±2.36 | 32.32±0.50 | 0.479±0.002 | 0.563±0.008 | 14.90±1.41 | 1.17±0.019 |
| LS-2N | 33.50±1.32 | 34.51±0.93 | 0.488±0.012 | 0.575±0.013 | 15.06±3.88 | 1.17±0.055 |
| LS-3N | 33.33±0.52 | 27.77±0.49 | 0.462±0.007 | 0.532±0.020 | 13.07±3.27 | 1.15±0.043 |
| LS-4N | 33.16±0.28 | 25.43±0.26 | 0.449±0.025 | 0.526±0.024 | 14.56±2.91 | 1.17±0.039 |
| LS-5N | 33.83±1.60 | 34.44±0.62 | 0.496±0.003 | 0.580±0.018 | 14.37±2.15 | 1.16±0.029 |
| LS-6N | 33.66±2.08 | 38.10±0.51 | 0.507±0.003 | 0.594±0.005 | 14.63±1.10 | 1.17±0.015 |
| LS-7N | 33.66±3.51 | 28.22±0.25 | 0.492±0.007 | 0.570±0.008 | 13.76±2.44 | 1.16±0.033 |
| LS-8N | 33.00±1.00 | 27.49±0.98 | 0.499±0.002 | 0.584±0.004 | 14.53±0.94 | 1.17±0.012 |

*Each value represents the mean±SD, n=3, The angle of repose for formulation blends of LS-1N to LS-8N was found to be in the range of 25.43° to 38.10° indicates acceptable flow.

The bulk density and tapped density of all the formulation blends of LS-1N to LS-8N varied from 0.449-0.507 g/cm²and 0.526-0.594 g/cm², respectively. The values obtained lie within the acceptable range, and no significant differences were found between bulk density and tapped bulk density. These results help in calculating the % compressibility of the powder.

The percentage compressibility for all the formulation blends of LS-1N to LS-8N lies in the range of 13.07 to 15.06 %, respectively.

Hausner's ratio of powder mix was determined by the data of bulk density and tapped bulk density. Hausner's ratio for all the formulation blends of LS-1N to LS 8N lie from 1.15 to 1.17, respectively, indicating excellent flow properties of the blend.

**Post compression studies**

**Weight variation test**

The average weight with a percentage deviation of twenty tablets of each batch is depicted in table 7. As per the USP limits, the percentage deviation for an uncoated tablet of weight between 130-324 mg is 7.5 % [50]. The weight variation of liquisolid compacts was found to be 99.98 to 100.60 mg for liquisolid formulations. The percentage deviation of all tablet formulations was found within the specification limits, and hence all the liquisolid batches passed the weight variation test as per USP.

**% Friability**

The friability of the liquisolid tablet was measured using a Roche friability tester at a rotation speed of 25 rpm. The drum was rotated for 4 min (100 rotations). Any loose dust from the tablet was removed and was weighed accurately [51]. Percentage friability was calculated, and the data obtained was given in table 7, and the Friability for all the formulations of nebivolol liquisolid compacts of Fujicalin was found to be less than 0.35 %.

**Hardness**

The hardness of the formulations LS-1N to LS-8N was found to be in the range of 3.10-4.99 kg/cm²and was reported in table 7. All formulations were found to have good mechanical strength.

**Disintegration time**

The important parameter in the formulation of liquisolid compacts is the disintegration time. Once the tablet disintegrates, then the tablet dissolution will be faster. This will increase the effective surface area of the particles available for dissolution [52]. In the present investigation, the tablet disintegration time ranged from 19.00-24.50 sec for LS-1N to LS-8N formulations, respectively, and was enlisted in table 7. The disintegration time was found to be within the acceptable range.

**Content uniformity**

Content uniformity for tablets of all the formulations ranges from 98.99-100.02 % (table 7). The results indicate that the contents for tablets of all the formulations were uniform and containeda therapeutic dose of nebivolol.

***In vitro* dissolution studies**

*In vitro* dissolution studies of all the liquisolid formulations of nebivolol using Fujicalin (LS-1N to LS-8N) and pure drug were studied in 0.1 N hydrochloric acid. The comparative *in vitro* dissolution profiles are given in fig. 2.

**Table 7: Post-compression parameters of liquisolid tablets**

| Formulation code | Weight (mg) AM±SD, n=20 | Weight variation | Friability (%) | Hardness (kg/cm²)*, n=20 | Disintegration time (sec)* | Drug content uniformity (%)* |
|---|---|---|---|---|---|---|
| LS-1N | 100.50±0.50 | Pass | 0.25 | 3.17±0.55 | 29.66±0.50 | 99.98±0.02 |
| LS-2N | 100.00±1.00 | Pass | 0.14 | 3.30±0.26 | 49.00±3.21 | 99.46±0.50 |
| LS-3N | 100.17±0.16 | Pass | 0.22 | 4.38±0.43 | 11.33±1.26 | 99.11±0.86 |
| LS-4N | 100.60±0.45 | Pass | 0.15 | 4.99±0.88 | 32.66±0.76 | 98.99±1.00 |
| LS-5N | 100.13±0.32 | Pass | 0.32 | 3.28±0.67 | 39.33±1.20 | 100.02±0.15 |
| LS-6N | 100.33±1.52 | Pass | 0.25 | 3.10±0.78 | 40.33±2.00 | 100.00±1.00 |
| LS-7N | 100.33±0.38 | Pass | 0.18 | 4.00±1.00 | 25.66±2.29 | 99.51±0.46 |
| LS-8N | 99.98±0.02 | Pass | 0.29 | 4.12±0.54 | 28.33±1.52 | 99.33±0.54 |

*Each value represents the mean±SD, n=6

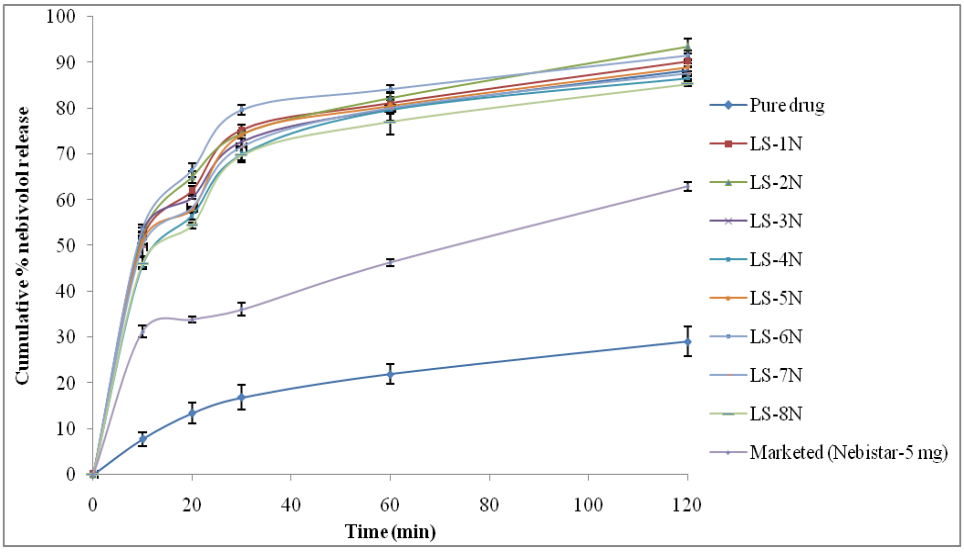


**Fig. 2: Comparative *in vitro* dissolution profile of the nebivolol liquisolid compact formulations LS-1N to LS-8N (mean±SD, n=3)**

From fig. 2, it was evident that the drug release was more than 50 % in 20 min for all the nebivolol LS formulations. LS-1N to LS-8N prepared with Fujicalin. Further, the formulation LS-3N showed complete release in 30 min. From fig. 2, it was clearly evident that the drug release was more than 75 % in 30 min for nebivolol LS-3N, which is optimized. The formulation LS-3N showed complete release in 120 min (fig. 2).

The *in vitro* drug release profiles of all the liquisolid formulations demonstrated higher drug release when compared to pure drug and marketed products (Nebistar-5 mg). As the Concentration of disintegrant and PVP K-30 increased, an increase in drug release was observed. Amongst all the formulations, LS-3N formulation showed the highest drug release, i.e., 77.84 % within 30 min. Beyond 30 min, no significant increase in dissolution was observed. Hence it was selected as an optimized formulation based on design expert software.

The comparative release trend for formulation formulations along with pure drug and marketed product (Nebistar-5 mg) are depicted in fig. 2.

However, the drug release from the marketed product (Nebistar-5 mg) was limited to drug release of 16.90 % respectively in 30 min and shown in fig. 2. Thus, the *in vitro* dissolution studies indicated the importance of liquisolid compacts to enhance the solubility and dissolution rates.

**Application of experimental design for designing liquisolid tablets**

The $2^3$ factorial design was selected to study the effect of independent variables PVP K 30 ($X_1$), Fujicalin: Aerosil 200 ratio ($X_2$), and nonvolatile liquid (PEG 400) ($X_3$) on dependent variables angle of repose, disintegration time, and drug release. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses [53].

The responses of the formulations prepared by $2^3$ factorial design batches are shown in table 8. The data clearly indicates that the angle of repose, disintegration time, and percent drug release values strongly depend on the selected independent variables. The fitted regression equations relating the responses, angle of repose, disintegration time, and percent drug release are shown in the equations, respectively. The equation conveyed the basis to study the effects of variables. The regression coefficient values are the estimates of the model fitting [54]. The polynomial equations can also be used to conclude the magnitude of co-efficient and the mathematical sign it carries, i.e., positive or negative [55]. The negative coefficient of variables indicates an increase in variable level decreases the particularresponse, and a decrease invariable increases the response. On the otherhand, the positive coefficient of variables indicates an increase invariable level increases the response, and a reduction in level decreases the response.

The model obtained from the regression analysis was used to build 3-D graphs, in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots. The response surface plots were generated using Design-Expert® Software (Stat-Ease Inc., Minneapolis, USA) to observe the effects of independent variables on the response studied, such as angle of repose, disintegration time, and drug release. Graphical presentation of the data helped show the relationship between the response and the independent variables. The information given by the graph was similar to that of mathematical equations obtained from statistical analysis.

**Table 8: Observed responses from $2^3$ factorial design**

| S. No. | Formula code | Independent variables | | | Dependent variables | | |
|---|---|---|---|---|---|---|---|
| | | Concentration of PVP K 30 in the formulation ($X_1$) (% w/w) | Excipient ratio ($X_2$) | Amount of liquid vehicle ($X_3$) (% w/w) | Angle of repose* | Disintegration time* | Nebivolol release in 30 min* |
| 1 | LS-1N | -1 | -1 | -1 | 32.32±0.50 | 29.66±0.50 | 70.34±1.11 |
| 2 | LS-2N | +1 | -1 | -1 | 34.51±0.93 | 49.00±3.21 | 72.58±0.55 |
| 3 | LS-3N | -1 | +1 | -1 | 27.77±0.49 | 11.33±1.26 | 77.84±1.20 |
| 4 | LS-4N | +1 | +1 | -1 | 25.43±0.26 | 32.66±0.76 | 69.98±1.42 |
| 5 | LS-5N | -1 | -1 | +1 | 34.44±0.62 | 39.33±1.20 | 73.23±0.75 |
| 6 | LS-6N | +1 | -1 | +1 | 38.10±0.51 | 40.33±2.00 | 74.72±1.02 |
| 7 | LS-7N | -1 | +1 | +1 | 28.22±0.25 | 25.66±2.29 | 71.59±2.85 |
| 8 | LS-8N | +1 | +1 | +1 | 27.49±0.98 | 28.33±1.52 | 69.81±1.60 |

*Each value represents the mean±SD (n=3)

**Effect of formulation variables on angle of repose**

The *in vitro* performance of nebivolol loaded liquisolid compacts showed an angle of repose depending upon the formulation variables, i.e., PVP K 30 ($X_1$), Fujicalin: Aerosil 200 ($X_2$), and liquid nonvolatile solvent level ($X_3$). The results showed that the optimized angle of repose was 27.77 ° when compared with that of pure drug. The effect of formulation variables on the angle of repose is given in Eq.

$$\text{Angle of repose} = 31.03 + 0.3475\,X1 - 3.81\,X2 + 1.03\,X3 - 1.11\,(X1\,X2) + 0.3850\,(X1\,X3) - 0.400\,(X2\,X3)$$

In the above equation, $b_1$ and $b_3$ bear positive signs indicating an increase in the angle of repose in PVP K30 ($X_1$), and liquid nonvolatile solvent ($X_3$) increased. $b_{12}$, $b_{23}$ bears negative sign in the same equation indicating the interaction effect of $X_1X_2$, $X_2X_3$ decreased the angle of repose, $b_{13}$ bear positive sign, which indicates that the interaction effect of $X_1X_3$ increased the angle of repose.

The relationship between dependent and independent variables was further elucidated using contour plots and RSM 3D plots. The effects of $X_1$, $X_2$, and $X_3$ and their interaction on the angle of repose are given in fig. 3-4.

**Effect of formulation variables on disintegration time**

The *in vitro* performance of nebivolol loaded liquisolid compacts showed disintegration time depending upon the formulation variables, i.e., PVP K 30 ($X_1$), Excipient ratio ($X_2$), and nebivolol containing liquid nonvolatile solvent level ($X_3$). The results showed that the optimized formulation disintegration time of nebivolol-loaded liquisolid compacts demonstrated 11.33 sec. The effect of formulation variables on the disintegration time is given in Eq.

$$\text{Disintegration time} = 32.04 + 5.54\,X1 - 7.54\,X2 + 1.37\,X3 + 0.4575\,(X1X2) - 4.63\,(X1X3) + 1.13(X2X3)$$

In the above equation, $b_1$ and $b_3$ bear positive signs indicating an increase in disintegration time in PVP K30 ($X_1$), Fujicalin: Aerosil 200 ($X_2$), and liquid nonvolatile solvent level ($X_3$) increased $b_2$ bear negative sign indicating an decrease in disintegration time in Fujicalin: Aerosil 200($x_2$) increased, $b_{12}$, $b_{23}$ bears positive sign in the same equation indicating the interaction effect of $X_1X_2$, $X_2X_3$ increased the disintegration time, $b_{13}$ bear negative sign which

indicates that the interaction effect of $X_1X_3$ decreased the disintegration time.

The relationship between dependent and independent variables was further elucidated using contour plots and RSM 3D plots. The effects of $X_1$, $X_2$, and $X_3$ and their interaction on disintegration time are given in fig. 5-6.

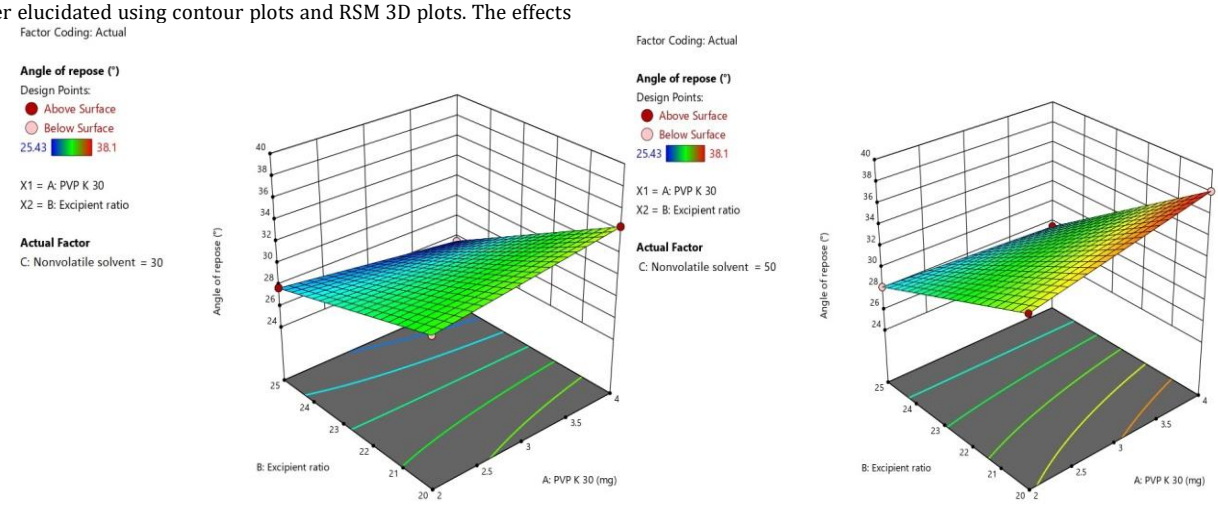


**Fig. 3: Response surface plots for the study of the effect of variables on angle of repose at nonvolatile liquid-30 %, 50 % ($R^2$=1.00 from ANOVA table)**

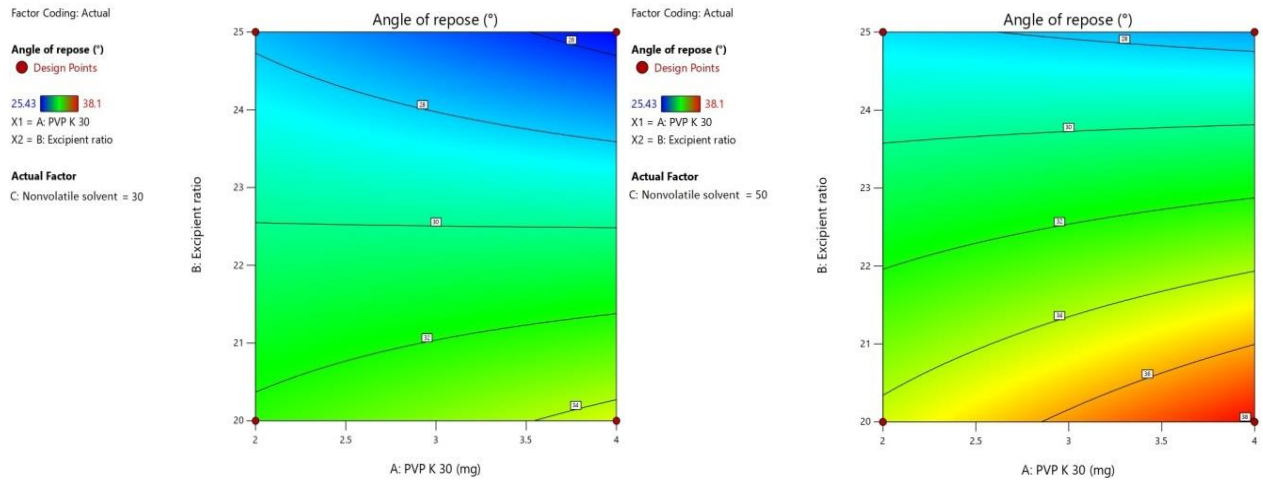


**Fig. 4: Contour plots for the study of the effect of variables on angle of repose at nebivolol concentration-30 %, 50 %**

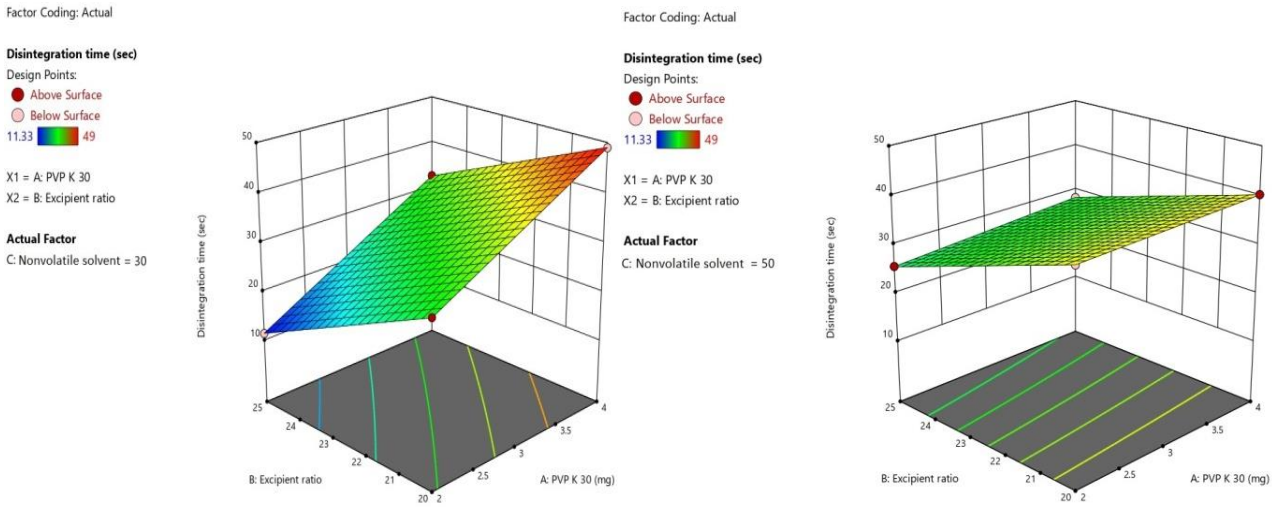

**Fig. 5: Response surface plots for the study of the effect of variables on disintegration time at (nonvolatile liquid-30 %, 50 %) ($R^2$=1.00 from ANOVA table)**

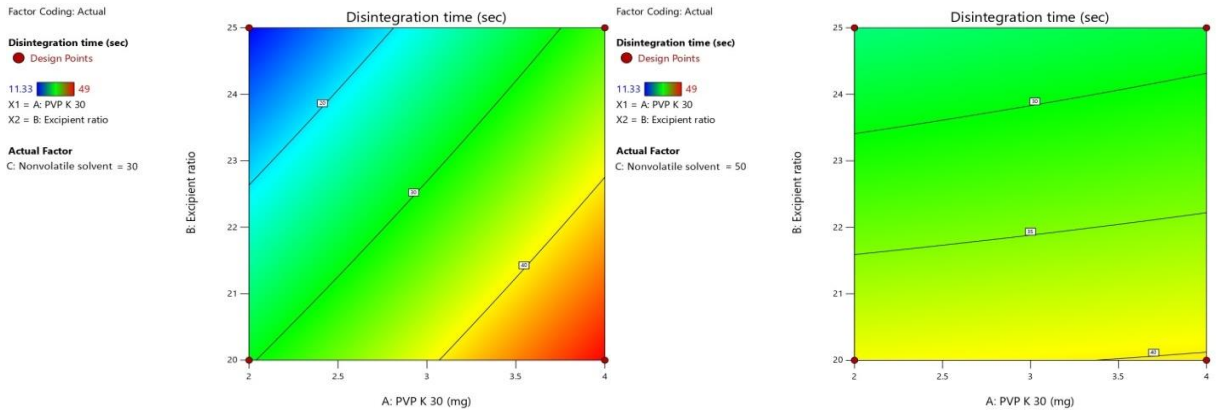


**Fig. 6: Contour plots for the study of the effect of variables on disintegration time at nonvolatile liquid-30 %, 50 %**

### Effect of formulation variables on nebivolol release

The *in vitro* performance of nebivolol loaded liquisolid compacts showed % drug release depending upon the formulation variables, i.e., PVP K 30 ($X_1$), Excipient ratio ($X_2$), and nonvolatile liquid ($X_3$). The results showed that the optimized drug release of nebivolol-loaded liquisolid compacts demonstrated 77.84 % in 30 min. The effect of formulation variables on the disintegration time is given in Eq.

$$\% \text{ Nebivolol drug release} = 78.07 + 0.2187\,X1 - 2.07\,X2 - 0.6388\,X3 - 1.22\,(X1X2) - 0.1587\,(X1X3) + 0.1663\,(X2X3)$$

In the above equation, $b_1$ bear positive sign indicating an increase in % drug release in PVP K 30 ($X_1$), increased the % drug release. In the above equation, $b_2$ and $b_3$ bear negative signs indicating an increase in % drug release in excipient ratio ($X_2$), and amount of liquid vehicle ($X_3$) decreased, $b_{12}$, $b_{13}$ bears negative sign in the same equation indicating the interaction effect of $X_1X_2$, $X_1X_3$ decreased the % drug release, $b_{23}$ bear positive sign which indicates that the interaction effect of $X_2X_3$ increased the drug release.

The relationship between dependent and independent variables was further elucidated using contour plots and RSM 3D plots. The effects of $X_1$, $X_2$, and $X_3$ and their interaction on % nebivolol drug release are given in fig. 7-8.

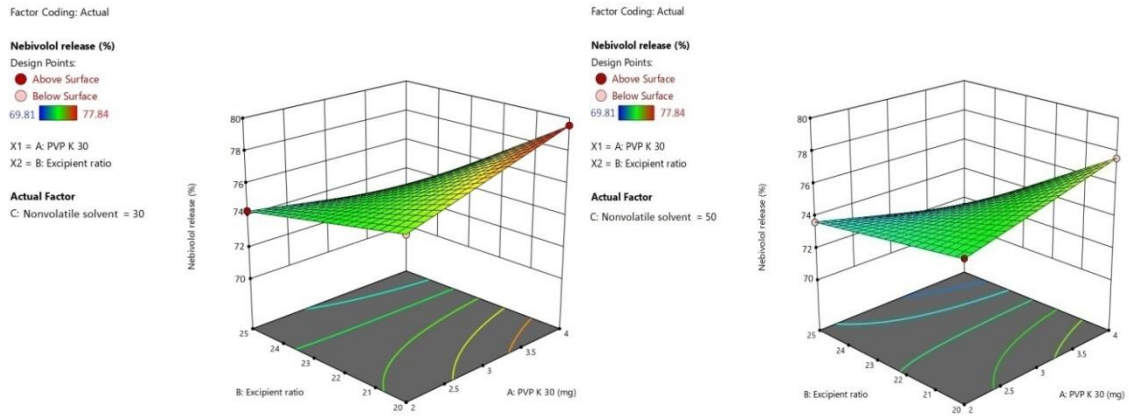


**Fig. 7: Response surface plots for the study of the effect of variables on nebivolol release at nonvolatile liquid-30 %, 50 % ($R^2$=0.9999 from ANOVA table)**

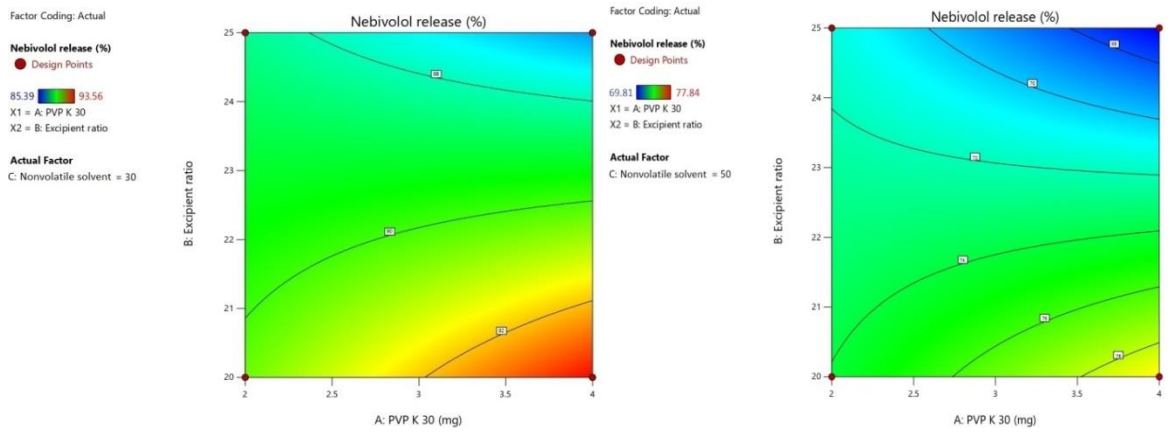


**Fig. 8: Contour plots for the study of the effect of variables on nebivolol release at nonvolatile liquid-30 %, 50 % ($R^2$=0.9999 from ANOVA table)**

**Selection of the optimized batch based on desirability function**

The desirability function of design expert® 12 trial version (Stat-Ease. Inc. Minneapolis, USA) was used to select the optimized batch. The optimized batch was selected based on the following criteria: angle of repose-minimum, disintegration time-minimum, and % drug release-maximum. The overlay plot and desirability plot generated for the selection of an optimized batch is given in fig. 9. The transformed value for various independent variables in the optimized formulation was as follows: PVP K 30 ($X_1$)=2 mg, Excipient ratio R ($X_2$) =25 and PEG 400 ($X_3$) =30 % w/w. % relative error between the practically observed value and the predicted value was less than 10 % which proved the validity [56] of the model (table 9). The analysis yielded significant results.

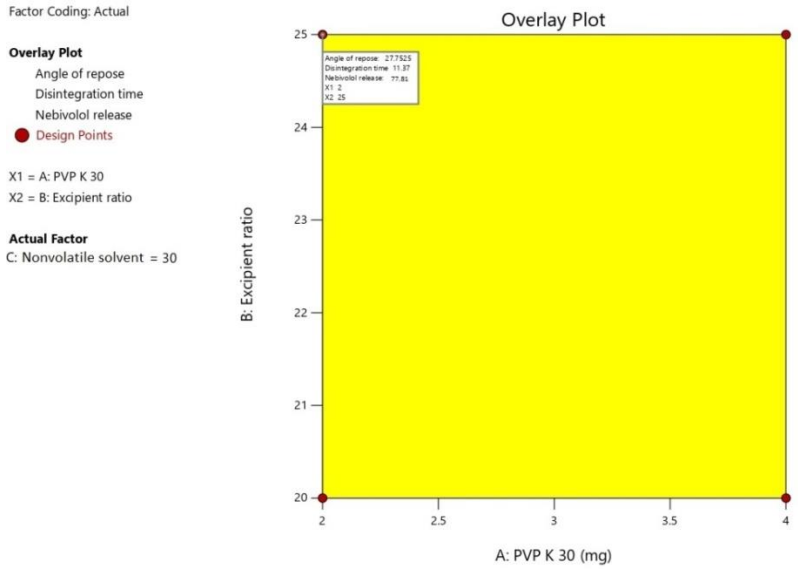


**Fig. 9: Overlay plot for optimized batch**

**Table 9: Results for checkpoint batch (LS-3N)**

| Dependent factor | Predictedvalue | Experimental value | Relative error (%) |
|---|---|---|---|
| Angle of repose ( °) | 27.7525 | 27.77 | -0.063 |
| Disintegration time (sec) | 11.370 | 11.33 | 0.351 |
| Nebivolol release (%) at 30 min | 77.8188 | 77.84 | -0.028 |

**Comparison of optimized liquisolid (LS-3N) with other products**

The results of dissolution studies of formulations are presented in fig. 10. According to the findings, LS-3N was the better formulation producing the best drug release profile.

The comparative release trend for formulation LS-3N along with pure drug and marketed product (Nebistar-5 mg) are depicted in fig. 10. The *in vitro* drug release profile of liquisolid (LS-3N) demonstrated higher drug release compared to pure drug and marketed product (Nebistar-5 mg). Hence, it was selected that it is the optimized formulation (Design expert software). However, the drug release from the marketed product (Nebistar-5 mg) was limited to drug release of 36.13 %, in 30 min (fig. 10). Thus, the *in vitro* dissolution studies indicated the usefulness of nebivolol liquisolid compacts to enhance the solubility and dissolution rates.

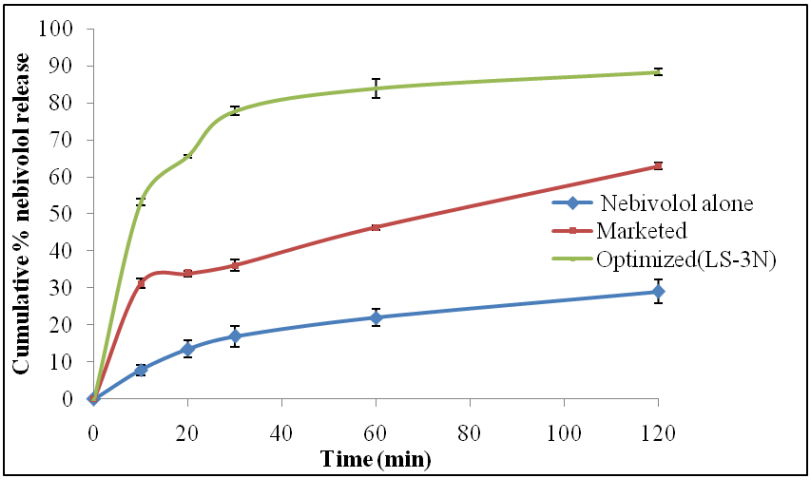


**Fig. 10: Comparative *in vitro* dissolution profiles of the optimized formulation LS-3N, pure drug, marketed product (Nebistar-5 mg)**

**Release kinetics**

The *in vitro* dissolution data for all the liquisolid formulations was subjected to the release kinetics to identify the order of release and mechanism of release. Different model-dependent approaches (zero order, first order, Higuchi, Korsemayer-Peppas plots) were performed for dissolution profile comparison of all liquisolid compacts [57]. The regression coefficient ($R^2$) values obtained from the dissolution data were tabulated in table 10 (LS–1N to LS-8N) along with the pure drug and the marketed product (Nebistar-5 mg). The results of these models indicate LS-3N liquisolid compacts follow the Peppas model and exhibited first-order release.

**Table 10: Estimation of release kinetics and mechanism of nebivolol all liquisolid formulations, pure drug, and marketed formulation (Nebistar-5 mg)**

| Formulation code | Zero-order | First-order | Higuchi's diffusion | Hixson crowell cube root law | Korsmeyer's peppas | |
|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ | n |
| Pure drug | 0.844 | 0.882 | 0.987 | 0.998 | 0.966 | 0.512 |
| LS-1N | 0.544 | 0.851 | 0.833 | 0.948 | 0.941 | 0.224 |
| LS-2N | 0.449 | 0.779 | 0.756 | 0.940 | 0.895 | 0.170 |
| **LS-3N** | **0.536** | **0.830** | **0.826** | **0.954** | **0.958** | **0.209** |
| LS-4N | 0.585 | 0.838 | 0.865 | 0.960 | 0.941 | 0.263 |
| LS-5N | 0.558 | 0.843 | 0.842 | 0.952 | 0.929 | 0.233 |
| LS-6N | 0.505 | 0.817 | 0.803 | 0.947 | 0.907 | 0.210 |
| LS-7N | 0.561 | 0.837 | 0.847 | 0.956 | 0.950 | 0.234 |
| LS-8N | 0.583 | 0.831 | 0.861 | 0.963 | 0.936 | 0.254 |
| Marketed product | 0.754 | 0.887 | 0.943 | 0.984 | 0.932 | 0.285 |

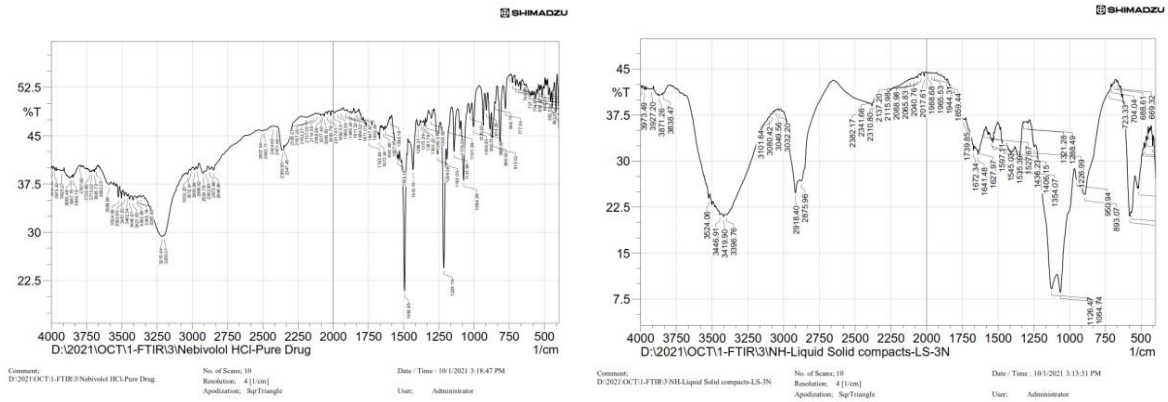


**Fig. 11: FTIR spectra of pure nebivolol drug, optimized formulation (LS-3N)**

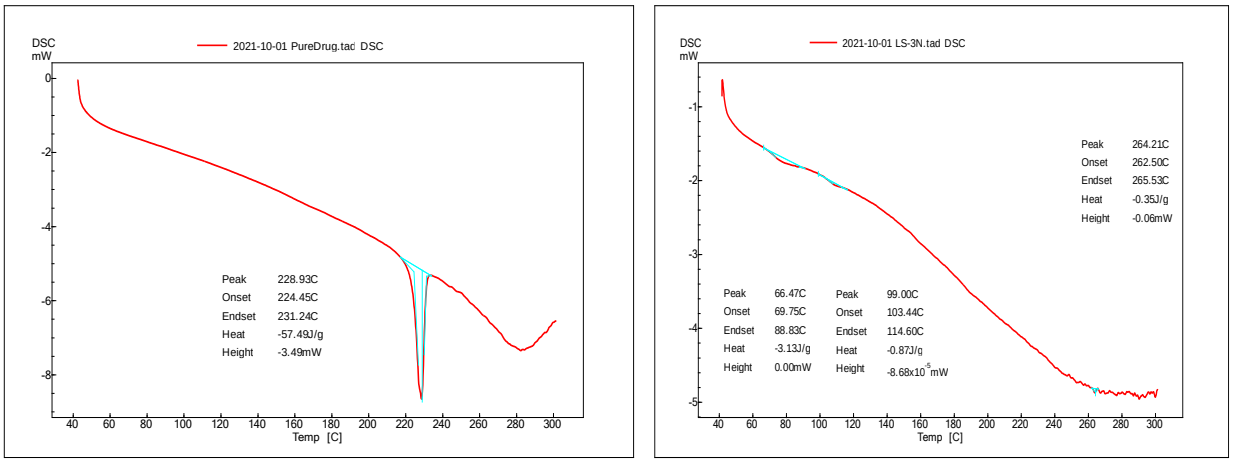


**Fig. 12: DSC thermograms of pure nebivolol, optimized formulation (LS-3N)**

### FTIR compatibility studies

Fourier transform infrared spectroscopy (FTIR) techniques have been used to study the physical and chemical interaction between drugs and excipients. In the spectra of optimized nebivolol loaded formulation of liquisolid compacts (fig. 11), the peak characteristics of the excipients were present at almost the same positions. In contrast, nebivolol peaks were also present but at a reduced absorption intensity, indicating the trapping of nebivolol inside the carrier matrix. None of the spectra showed any peaks other than those assigned to nebivolol and excipients, which indicates that there is no difference between the IR patterns of the optimized formulation of nebivolol and pure drug.

### Differential scanning calorimetry (DSC) studies

Differential scanning calorimetry (DSC) curve for nebivolol showed a sharp endothermic (melting) peak at 228 °C (fig. 12). The nebivolol peak was absent in the DSC curve of optimized formulation of nebivolol liquisolid powder compacts, indicating that the drug in final formulation was less crystalline (more amorphous). Conversion of a crystalline form of drug to an amorphous form exhibits enhanced solubility, which led to improved dissolution release profile of the drug by formulation of liquisolid compacts.

### X-ray powder diffractometry (XRD)

X-ray powder diffraction (XRD) analysis was used to assess the degree of crystallinity of the liquisolid compacts constituents. Nebivolol showed major peaks at 2θ values of 25.33°, 22.06°, 21.08° (fig. 13 A). Analysis of XRD patterns of the nebivolol loaded optimized formulation (fig. 13 B) indicated that all the significant peaks corresponding to nebivolol disappeared, which shows conversion of a crystalline form of drug to amorphous form due to the addition of the excipients to the formulation.

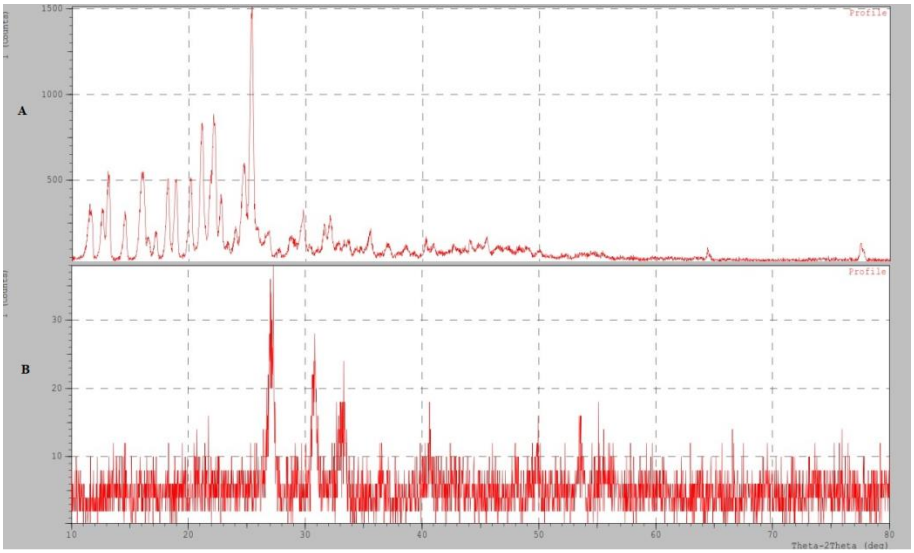


**Fig. 13: XRD patterns of A) pure nebivolol B) Optimized nebivolol loaded liquisolid compacts (LS-3N)**

**Table 11: Stability data of nebivolol liquisolid compacts (LS-3N)**

| Time (day) | Liquisolid compacts (LS-3N) stored at 40 °C and 75 % RH, AM±SD, n=3 | |
|---|---|---|
| | % Cumulative nebivolol release (in 30 min) | % Nebivolol content |
| 1st day | 77.84±1.20 | 99.11±0.86 |
| 30th day | 77.72±0.98 | 99.05±0.77 |
| 60th day | 77.48±0.74 | 98.12±0.72 |

| | | |
|---|---|---|
| 90thday | 77.36±0.81 | 98.11±0.66 |

**Accelerated stability studies of nebivolol liquisolid compacts (LS-3N)**

The stability profile of liquisolid compacts (LS-3N) was evaluated for drug content nebivolol release (table 11). Minor changes are noticed in drug content and nebivolol release during three months of storage at 40±2 °C/75±5 % RH. This confirms that the optimized formulation (LS-3N) is stable.

***In vivo* studies**

The pharmacokinetic behaviors of nebivolol API and nebivolol loaded liquisolid compacts (LS-3N) were investigated with a drug equivalent to 0.513 mg/kg of body weight in Wistar rats. The amounts of nebivolol in the plasma were determined by HPLC method established in this work. Plasma nebivolol concentration-time levels were measured and plotted against time (fig. 14). The PK parameters are listed in table 12. The following are the observations.

- The results showed that $C_{max}$ of nebivolol liquisolid compacts were approximately 1.96 folds higher than that of pure nebivolol.
- Additionally, $t_{max}$ of, liquisolid compacts were lower than that of pure nebivolol, suggesting that liquisolid compacts could improve drug release and absorption in GIT.
- The increase in AUC of liquisolid LS-3N is 1.31 fold higher than nebivolol alone and nearer to marketed product.

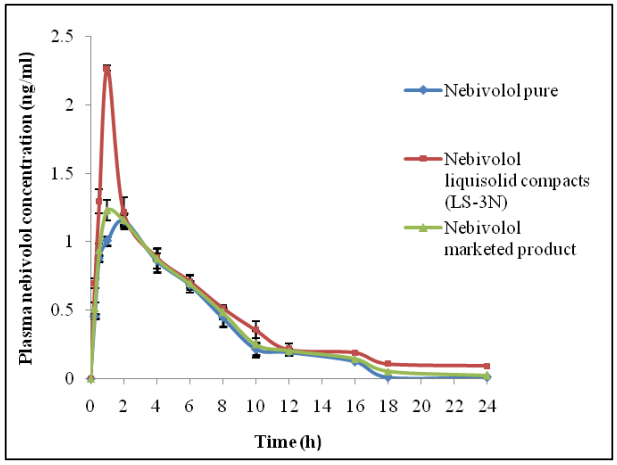


**Fig. 14: Plasma drug concentrations-time profiles of nebivolol API, liquisolid compacts (LS-3N) and marketed product in Wistar rats (AM±SD, n=6)**

**Table 12: Pharmacokinetic parameters of nebivolol drug, marketed formulation and liquisolid compacts (LS-3N)-noncompartmental analysis**

| PK parameter | Nebivolol suspension alone | Liquisolid compacts (LS-3N) | Marketed formulation | Folds increase (liquisolid) over pure sample | Folds increase over marketed product |
|---|---|---|---|---|---|
| $C_{max}$ (ng/ml) | 1.152±0.055 | 2.269±0.035 | 1.229±0.021 | 1.96 | 1.84 |
| $t_{max}$ (h) | 2±0 | 1±0 | 1±0 | | |
| $AUC_t$ (ng-h/ml) | 8.345±0.686 | 11.007±0.688 | 9.045±0.612 | 1.31 | 1.21 |
| $AUMC_t$ (ng-h/ml) | 33.286±3.496 | 67.334±4.721 | 52.004±3.526 | 2.02 | 1.29 |
| $AUC_i$ (ng-h/ml) | 8.383±0.738 | 12.126±0.894 | 9.148±0.615 | 1.44 | 1.32 |
| $AUMC_i$ (ng-h/ml) | 47.184±5.954 | 108.285±1.830 | 54.980±0.718 | 2.29 | 1.96 |
| $MRT_{0-24}$ (h) | 5.386±0.123 | 6.117±0.047 | 5.749±0.061 | 1.13 | 1.06 |
| Clearance (CL) (ml/min) | 0.597±0.049 | 0.412±0.021 | 0.546±0.033 | | |
| $V_d$ (ml) | 2.630±0.080 | 5.186±0.589 | 2.575±0.107 | | |

Each value represents the mean±SD (n=6)

Even in drug dissolution studies, the nebivolol dissolution is very rapid and optimized formulation established more than 75 % cumulative % nebivolol release in 30 min. The dissolution of liquisolid is faster than the marketed product. A corresponding higher $C_{max}$ levels are observed over marketed product (table 12). It indicated that the absorption of nebivolol was evidently improved after it was dispersed in liquisolid compacts (fig. 14). In summary, the prepared liquisolid compacts could effectively improve the oral bioavailability of nebivolol.

**CONCLUSION**

The results showed that the liquisolid technique could be adopted as a new tool to produce promising nebivolol compacts containing Fujicalin. It was shown that a desirable release profile and flow properties are achievable in liquisolid compacts. Liquisolid compacts could be prepared using Fujicalin as a carrier and Aerosil 200 as a coating material. The liquisolid tablets formulated with PEG 400 nonvolatile vehicle at a level of 30 % w/w is the best formulation among the eight batches of liquisolid tablets prepared, in terms of faster disintegration time, acceptable dissolution profile, and superior flow properties. The FTIR studies revealed that excipients were compatible with the drug. DSC and XRD studies showed that there is a decrease in crystallinity of the nebivolol in liquisolid compact formulation. A fall in crystallinity means improved dissolution release profile. The optimized formulation (LS-3N) showed a higher dissolution rate when compared with that of pure nebivolol drug, marketed formulation.

In conclusion, it can be stated that the objective of the study was achieved in improving the solubility of the nebivolol using liquisolid technology.

**ACKNOWLEDGEMENT**

The Authors are thankful to Dean and Principal, Department of Pharmacy, University College of Technology, Osmania University, for extending the support to carry out the research work. Finally, the authors express their gratitude to the Sura Labs, Dilsukhnagar, Hyderabad, for providing research equipment and facilities.

**FUNDING**

Nil

**AUTHORS CONTRIBUTIONS**

Ramya Sri Sura has generated the research plan, completed the practical work, prepared and revised the manuscript. Subrahmanyam CVS and Shyam Sunder Rachamalla have given guidance and supervision to carry out this study.

**CONFLICT OF INTERESTS**

None

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