Application of optimization tools for preparation of nebivolol liquid solid composite compressed tablet

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\textbf{ABSTRACT}

The purpose of this study is to make Nebivolol more efficient by converting it into a liquid solid composite compressed tablet. Blending cum sonication process was used to create the liquid solid composite. By altering the independent variables such as vehicle, carrier, and superdisintegrants, nearly 12 compositions were created in a 23 factorial design with four centre points. The influence on response, such as disintegration time in seconds and wetting time in seconds, was then determined. In addition, the liquid solid composite was compacted into a tablet and its percent invitro drug release was assessed. Based on disintegration time and wetting time, the optimal solid liquid compacts sustained release tablet formulation was identified to be LSC6, which may be ideal candidates for boosting the solubility and dissolution rate of less soluble medications like Nebivolol.

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INTRODUCTION

The “Liquid-solid” technique is a novel and capable addition towards such an aims for solubility enhancement and dissolution improvement, thereby it increases the bioavailability (Patel and Shah, 2016). It contains liquid medications in powdered form. This technique is an efficient method for formulating water insoluble and water soluble drugs. The mixing of drug-loaded solutions with appropriate carrier and coating materials is the basis for this approach (Anil et al., 2018). The use of a non-volatile solvent improves wettability and guarantees that the medication is dispersed molecularly in the formulation, resulting in increased solubility (Dalvi and Ingale, 2014). This method can be used to modulate medication release (sustained release) by utilizing hydrophobic carriers (non-volatile solvents) (Spireas and Bolton, 1999). Solubility and dissolution rate can be enhanced with this method, and long-term drug delivery systems for water-soluble substances can be produced (Javadzadeh et al., 2007).

Nebivolol binds to 98 percent of proteins and is processed mostly in the liver (CYP2D6-mediated) with an elimination half-life of about 10 hours (Reiter, 2004). Nebivolol is excreted extensively in the kidneys and faeces. In CYP2D6 extensive metabolizers, the half-life of nebivolol was found to be 12 hours, whereas in poor metabolizers, it was found to be 19 hours. The bioavailability of Nebivolol is quite high (96%) in CYP2D6 metabolizers with low metabolism; however, it is only about 12% in extensive metabolizers (Offermanns and Rosenthal, 2008).

To improve solubility, dissolution, and bioavailability while bypassing first-pass metabolism, the drug
must be delivered quickly into systemic circulation. As a result, it is necessary to construct Nebivolol as a liquid solid composite compressed tablet, which may improve its solubility and dissolution.

**MATERIALS AND METHODS**

Aurobindo Pharma Pvt. Ltd. provided a complimentary sample of nebivolol. Propylene glycol, Avicel, Aerosil, and Crosspovidone are all sourced from Himedia Labs Ltd in Chennai and are utilized in the manufacture of the dosage form.

**Formulation of liquisolid compacts compressed tablet**

To obtain a uniform mixture, a weighed quantity of nebivolol and a liquid vehicle (propylene glycol) are blended together using a sonication technique. The resulting liquid combination is placed into a specified amount of carrier material (Avicel) and homogenized at 100 RPM to ensure that the liquid medication is evenly distributed throughout the carrier (Jain et al., 2014). After that, the needed amount of coating substance (Aerosil) is weighed and homogeneously combined. To enable complete absorption of drug medication into the interior structure of carrier and coating materials, the prepared powder combination is spread as a homogeneous layer on the surface of a mortar and let to stand for 5 minutes (Jassim, 2017). To make a final liquisolid system combination, add the needed amount of disintegrants (Crosspovidone) to the aforesaid combination. Using an 8mm tablet punch in a tablet compression machine, the obtained liquisolid system is further compressed into a tablet (Kawabata et al., 2011). It should be noted that the mixing speed, mixing duration, and standing time can all be adjusted based on the circumstances (Kapsi and Ayres, 2001). Tables 1 and 2 shows the formulation and optimization strategy for the Nebivolol liquisolid system.

**Drug polymer interaction studies**

**FTIR study**

The research was carried out to identify the molecular structure, which served as an analysis made to assess the molecule’s purity. Using KBr pellets, an FTIR spectrophotometer (Horiba, Japan) was used to get IR spectroscopy. The sampling frequency was 4400 to 400 cm⁻¹, with a 1 minute scan interval. Figure 3 (A) and Figure 3 (B) show the spectra of the pure drug and the mixture. There is no alteration in peak shape or shift, indicating that the medication and excipients are compatible (Hussain et al., 2014).

**Evaluation of Pre-compression parameter of solid liquid composite granules**

**Angle of repose**

Angle of repose is used to calculate the frictional forces involved in a granule combination. It can be estimated by setting the funnel to a specific height and passing the blend through it under the effect of gravity, which will form a pile. After establishing a sharp edge on the pile, the height and surface of the pile, and the angle of repose can be computed using the Equation (1).

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]  

\( \theta = \) angle of repose; \( h = \) height of pile; \( r = \) radius of pile

**Bulk and Tapped Density**

Weigh the granules or pellets (W) precisely and pour into a graduated cylinder. The volume of the cylinder \( V_0 \) was calculated for bulk density, and then the cylinder was tapped for 100 times on a wooden panel and the volume of the cylinder \( V_f \) was recorded for tap density. The following Equation (2) are used to calculate bulk and tapped density,

\[ \text{Bulk density} = \frac{W}{V_o} \]

\[ \text{Tap density} = \frac{W}{V_f} \]

\( W = \) Weight of the pellets or granules; \( V_o = \) Initial volume; \( V_f = \) Final volume

**Hausner’s ratio**

The ratio of tapped density to bulk density is known as Hausner’s ratio. The better the flow property, the lower the value of Hausner’s ratio. The following Equation (3) is used to compute the ratio. It assesses the powder’s ability to be compressed.

\[ \text{Hausner’s ratio} = \frac{\rho_{\text{tapped density}}}{\rho_{\text{bulk density}}} \]

**Carr’s index**

The percentage compressibility (Carr’s index) was determined by multiplying the difference between tapped density and bulk density by 100. It assesses the interparticulate interaction between particles (Karmarkar et al., 2010). All the pre-compression parameter and its limits are shown in Table 3. Equation (4) follows,

\[ \text{Carr’s index (\%)} = \frac{\rho_{\text{tapped density}} - \rho_{\text{bulk density}}}{\rho_{\text{tapped density}}} \times 100 \]
Evaluation of Post-compression parameter of solid liquid composite compressed tablet

Weight variation
Weigh each of the 20 tablets. The Equation (5) must be used to calculate the average weight and the % weight variance. Individual tablets were then weighed and correlated to an average weight. The weight variation test is passed if the comparative variation is within the I.P limits as shown in Table 4. (Haritha, 2017).

\[
\text{Percentage weight variation} = \frac{W_1 - W_2}{W_2} \times 100
\]

\(W_1 = \text{Individual weight of capsule or tablet; } W_2 = \text{Average weight of capsule or tablet.}\)

**Figure 1: Calibration curve of Nebivolol in pH6.8**

**Figure 2: Solubility Studies of Nebivolol in various solvents**

Thickness & diameter
To measure the thickness randomly measure 20 tablets from each batch with vernier callipers, and the average thickness is derived from mean standard deviations.

Friability
20 tablets (W1) are weighed separately, then placed on the Roche friabilator and spun for 100 revolutions at 25RPM. For the % friability from the Equation (6), the tablets are reweighed (W2). According to the IP limit, the percentage of friability should not exceed 1%. (Uddin et al., 2016).

\[
\text{%Percentage friability} = \frac{W_2 - W_1}{W_1} \times 100
\]

\(W_1 = \text{Initial weight of pellets; } W_2 = \text{Final weight of pellets}\)

Hardness
Crushing strength is determined by subjecting the produced tablets to the force required to break them. The test is carried out in a Pfizer hardness tester. The IP limit must be in the level of 4-6kg/cm².

Wetting time
It is determined by the tablet’s internal structure and the excipients’ hydrophilicity. It’s wetting time. In a petri plate (internal diameter 6.5 cm) holding 6ml of water, a piece of double-folded tissue paper was inserted. The tablet was placed on the paper, and the time it took for the tablet to completely wet was recorded in seconds. The procedure was somewhat altered by keeping the water at 37 degrees Celsius (Fahmy and Kassem, 2008).

Disintegration time
6 tablets should be placed in the disintegration apparatus’s tube. The tube is submerged in phosphate saline buffer (pH6.8), and the time it takes for the tablet to dissolve must be recorded. Uncoated tablets take 30 minutes to dissolve (Yadav et al., 2010; Sanjayamitra and Ganesh, 2018; Savjani et al., 2012).

Invitro Drug release studies
Under typical settings at room temperature, tablets are placed in a six station USP Type II dissolution test device with 900ml of phosphate buffer saline (pH6.8). At a 5 minute interval, aliquots are removed and a new volume of buffer is added. In a UV visible spectrophotometer, the absorbances of aliquots were evaluated at 280nm. Samples are withdrawn at various time intervals to determine the percent of drug release in each time interval by measuring absorbance, and the same amount of buffer is supplied to maintain sink conditions. Time in hours on the x-axis and cumulative percent drug
## Table 1: Absolute values of levels of independent variables employed in $2^3$ factorial design

| S. No. | Independent Variables                                                                 | Coded | Levels |
|--------|---------------------------------------------------------------------------------------|-------|--------|
| 1      | Drug Concentration (Nebivolol) in the liquid vehicle (Propylene glycol) (% w/w)      | X1    | -1     |
|        |                                                                                      |       | +1     |
| 2      | Concentration of Carrier (Avicel) the formulation (% w/w)                             | X2    | -1     |
|        |                                                                                      |       | +1     |
| 3      | Concentration of super disintegrants [Crosspovidone] in the formulation (% w/w) in mg| X3    | -1     |
|        |                                                                                      |       | +1     |

Response Constraint

Y1  Disintegration Time in sec  Minimum

Y2  Wetting Time in sec  Minimum

## Table 2: Optimization of Nebivolol liquid solid composite compressed tablet

| Batch No | Nebivolol conc. in vehicle (%w/w) | Conc. of carrier (Avicel) (mg) | Conc. of Disintegrants (Crosspovidone) (mg) | Conc. of coating material (Aerosil) (mg) | Liquid vehicle (propylene glycol) (mg) | Unit dose (mg) |
|----------|-----------------------------------|-------------------------------|--------------------------------------------|----------------------------------------|--------------------------------------|----------------|
| LSC 1    | -1 / 10                           | -1 / 87.5                     | -1 / 17.5                                  | 5.125                                  | 90                                   | 205            |
| LSC 2    | 1 / 20                            | 1 / 175                       | 1 / 35                                     | 7.75                                   | 80                                   | 310            |
| LSC 3    | 1 / 20                            | -1 / 87.5                     | 1 / 35                                     | 5.5625                                 | 80                                   | 222.5          |
| LSC 4    | 1 / 20                            | 1 / 175                       | -1 / 17.5                                  | 7.3125                                 | 80                                   | 292.5          |
| LSC 5    | 1 / 20                            | 1 / 175                       | -1 / 17.5                                  | 7.3125                                 | 80                                   | 292.5          |
| LSC 6    | 1 / 20                            | -1 / 87.5                     | 1 / 35                                     | 5.5625                                 | 80                                   | 222.5          |
| LSC 7    | -1 / 10                           | 1 / 175                       | 1 / 35                                     | 7.75                                   | 90                                   | 310            |
| LSC 8    | -1 / 10                           | -1 / 87.5                     | -1 / 17.5                                  | 5.125                                  | 90                                   | 205            |
| LSC 9    | 1 / 20                            | -1 / 87.5                     | -1 / 17.5                                  | 5.125                                  | 80                                   | 205            |
| LSC10    | -1 / 10                           | 1 / 175                       | -1 / 17.5                                  | 7.3125                                 | 90                                   | 292.5          |
| LSC11    | -1 / 10                           | -1 / 87.5                     | 1 / 35                                     | 5.5625                                 | 90                                   | 222.5          |
| LSC12    | -1 / 10                           | 1 / 175                       | 1 / 35                                     | 7.75                                   | 90                                   | 310            |

## Table 3: Post compression evaluation parameter with limits for flow character

| SL.No: | Flow character | Angle of repose | Hausner’s ratio | Carr’s index |
|--------|----------------|-----------------|-----------------|--------------|
| 1.     | Excellent      | <20             | 1.00-1.11       | ≤10          |
| 2.     | Good           | 20-30           | 1.12-1.18       | 11-15        |
| 3.     | Fair           | —               | 1.19-1.25       | 16-20        |
| 4.     | Passable       | 30-34           | 1.26-1.34       | 21-25        |
| 5.     | Poor           | —               | 1.35-1.45       | 26-31        |
| 6.     | Very poor      | >35             | 1.46-1.59       | 32-37        |
| 7.     | Very poor      | —               | >1.6            | >38          |
Table 4: Weight variation percentage deviation of tablets and capsules

| Sl.no | Average weight of Tablet (mg) | Percentage deviation |
|-------|-----------------------------|----------------------|
| 1.    | 130 or less                 | 10%                  |
| 2.    | 130-324                     | 7.5%                 |
| 3.    | More than 324               | 5%                   |

Table 5: Evaluation of pre-compression parameters of solid liquid compacts

| Batch No | Bulk Density (g/ml) | Tapped Density (g/ml) | Angle of Repose (θ) | Carr’s Index | Hausner’s ratio |
|----------|---------------------|-----------------------|---------------------|--------------|-----------------|
| LSC 1    | 0.61±0.028          | 0.79±0.039            | 38.25±0.25          | 22.50±0.37   | 1.2±0.01        |
| LSC 2    | 0.59±0.019          | 0.74±0.045            | 35.89±0.16          | 20.00±0.44   | 1.2±0.01        |
| LSC 3    | 0.57±0.037          | 0.70±0.052            | 33.20±0.15          | 19.02±0.34   | 1.2±0.02        |
| LSC 4    | 0.60±0.053          | 0.76±0.043            | 37.59±0.19          | 21.24±0.12   | 1.2±0.01        |
| LSC 5    | 0.63±0.068          | 0.78±0.052            | 34.25±0.25          | 19.34±0.52   | 1.2±0.02        |
| LSC 6    | 0.53±0.065          | 0.64±0.045            | 29.62±0.92          | 14.96±0.34   | 1.1±0.02        |
| LSC 7    | 0.57±0.056          | 0.70±0.023            | 32.50±0.55          | 18.18±0.25   | 1.2±0.01        |
| LSC 8    | 0.54±0.045          | 0.66±0.036            | 31.85±0.53          | 17.14±0.32   | 1.2±0.01        |
| LSC 9    | 0.65±0.065          | 0.80±0.26             | 31.49±0.32          | 18.75±0.49   | 1.2±0.01        |
| LSC10    | 0.55±0.04           | 0.66±0.06             | 31.98±0.04          | 16.98±0.06   | 1.2±0.02        |
| LSC11    | 0.54±0.065          | 0.64±0.042            | 30.54±0.41          | 15.37±0.35   | 1.1±0.02        |
| LSC12    | 0.51±0.063          | 0.59±0.055            | 28.27±0.45          | 14.22±0.33   | 1.1±0.01        |

Table 6: Optimization of Nebivolol Liquid compacts for Tablet formulation 2^3 factorial design and effect of independent variable on dependent variable

| Run   | Independent variable (Level Codes and its concentration) | Dependent variable |
|-------|--------------------------------------------------------|--------------------|
|       | X1 | X2 | X3 | Disintegration time (Sec) | Wetting time (Sec) |
|       | Y1 | Y2 |     | Y1 | Y2 |
| LSC1  | -1 | -1 | -1 | 150 ± 2.66 | 46 ± 2.16 |
| LSC2  | 1  | 1  | 1  | 65 ± 2.16  | 22 ± 2.12 |
| LSC3  | 1  | -1 | 1  | 74 ± 2.24  | 24 ± 2.06 |
| LSC4  | 1  | 1  | -1 | 95 ± 2.68  | 34 ± 2.08 |
| LSC5  | 1  | 1  | -1 | 130 ± 2.72 | 45 ± 2.12 |
| LSC6  | 1  | -1 | 1  | 70 ± 2.88  | 20 ± 2.32 |
| LSC7  | -1 | 1  | 1  | 90 ± 2.42  | 32 ± 2.36 |
| LSC8  | -1 | -1 | 1  | 170 ± 2.34 | 54 ± 2.34 |
| LSC9  | 1  | -1 | -1 | 165 ± 2.30 | 52 ± 2.40 |
| LSC10 | -1 | 1  | -1 | 155 ± 2.24 | 48 ± 2.62 |
| LSC11 | -1 | -1 | 1  | 90 ± 2.32  | 35 ± 2.24 |
| LSC12 | -1 | 1  | 1  | 80 ± 2.42  | 32 ± 2.22 |

Table 7: Effect Summary on independent variable on dependent variable

| Source                        | LogWorth | P Value   |
|-------------------------------|----------|-----------|
| Disintegrants                 | 4.084    | 0.00008   |
| Drug concentration in the liquid | 1.474    | 0.03357   |
| Carrier                       | 0.980    | 0.10471   |
### Table 8: Analysis of variance on effect of independent variable on Disintegration time

| Source      | DF  | Sum of Squares | Mean Square | F Ratio | Prob > F |
|-------------|-----|----------------|-------------|---------|----------|
| Model       | 3   | 15800.000      | 5266.67     | 21.1548 |          |
| Error       | 8   | 1991.667       | 248.96      |         | Prob > F |
| C. Total    | 11  | 17791.667      |             | 0.0004* |          |

### Table 9: Parameter Estimates of independent variable on Disintegration time

| Term                         | Estimate  | Std Error | t Ratio | Prob>|t| |
|------------------------------|-----------|-----------|---------|------|------|
| Intercept                    | 110.83333 | 4.554836  | 24.33   | <.0001* |
| Disintegrants                | -33.33333 | 4.554836  | -7.32   | <.0001* |
| Carrier                      | -8.333333 | 4.554836  | -1.83   | 0.1047 |
| Drug concentration in the liquid | -11.66667 | 4.554836  | -2.56   | 0.0336* |

### Table 10: Effect Test of independent variable on Disintegration time

| Source                               | Nparm | DF  | Sum of Squares | F Ratio | Prob > F |
|--------------------------------------|-------|-----|----------------|---------|----------|
| Disintegrants                        | 1     | 1   | 13333.333      | 53.5565 | <.0001* |
| Carrier                              | 1     | 1   | 833.333        | 3.3473  | 0.1047   |
| Drug Concentration In The Liquid     | 1     | 1   | 1633.333       | 6.5607  | 0.0336*  |

### Table 11: Effect Summary independent variable on dependent variable

| Source             | LogWorth | P Value |
|--------------------|----------|---------|
| Disintegrants      | 3.802    | 0.00016 |
| Drug concentration in the liquid | 1.651    | 0.02236 |
| Carrier            | 0.615    | 0.24258 |

### Table 12: Analysis of variance on effect of independent variable on wetting time

| Source      | DF  | Sum of Squares | Mean Square | F Ratio | Prob > F |
|-------------|-----|----------------|-------------|---------|----------|
| Model       | 3   | 1247.5833      | 415.861     | 18.0156 |          |
| Error       | 8   | 184.6667       | 23.083      |         | Prob > F |
| C. Total    | 11  | 1432.2500      |             | 0.0006* |          |

### Table 13: Parameter Estimates of independent variable on wetting time

| Term                         | Estimate  | Std Error | t Ratio | Prob>|t| |
|------------------------------|-----------|-----------|---------|------|------|
| Intercept                    | 37.25     | 1.386943  | 26.86   | <.0001* |
| Disintegrants                | -9.25     | 1.386943  | -6.67   | 0.0002* |
| Carrier                      | -1.75     | 1.386943  | -1.26   | 0.2426 |
| Drug concentration in the liquid | -3.91667 | 1.386943  | -2.82   | 0.0224* |

### Table 14: Effect Test of independent variable on wetting time

| Source                               | Nparm | DF  | Sum of Squares | F Ratio | Prob > F |
|--------------------------------------|-------|-----|----------------|---------|----------|
| Disintegrants                        | 1     | 1   | 1026.7500      | 44.4801 | 0.0002*  |
| Carrier                              | 1     | 1   | 36.7500        | 1.5921  | 0.2426   |
| Drug concentration in the liquid     | 1     | 1   | 184.0833       | 7.9747  | 0.0224*  |
RESULTS AND DISCUSSION

Preformulation studies

Preparation of Calibration Curves Nebivolol

Nebivolol absolute wavelength (max) was determined to be 280 nm. The calibration curve for Nebivolol was drawn between concentration in g/ml on the x axis and absorbance in nm on the y axis utilizing solvent such as pH 6.8 phosphate buffer. Within the concentration range, it shows a significant association and linearity from 5 to 30 g/ml, with an $R^2$ value of 0.995 in phosphate buffer pH 6.8. As a result, Nebivolol is in compliance with the Beers Rule. The findings are depicted in Figure 1.
Solubility studies

The following are the solubility descriptions of the drug in various solvents based on the data provided in Figure 2. The Shake flask method is used to perform solubility experiments in isothermal circumstances. The solubility test for Nebivolol was carried out and the results estimated using various solvents. Nebivolol has a modest solubility in water (2.515±2.21 mg/ml) but is highly soluble in propylene glycol (16.142±2.31mg/ml), methanol (26.151±1.21mg/ml), castor oil (20.321±1.34mg/ml), Capmul MCM (20.415±1.52mg/ml). Nebivolol was found to be moderately soluble like polyethylene glycol (12.079±1.51mg/ml), and Tween 80 (10.24±1.56mg/ml). The highly soluble solvents were chosen as the optimal solvent for the solid liquid composite based on the results of these solubility tests.

Drug and Excipients compatibility studies

FT-IR Studies

The FTIR spectrum as follows,

The main functional groups with their wave numbers are –OH stretching of 3302.92cm⁻¹ in Nebivolol and 3305.96cm⁻¹ in Physical mixture; 1494.05 cm⁻¹ for N-H bending vibration in Nebivolol and 1494.25cm⁻¹ and 1494.25cm⁻¹ in physical mixture, 1433.89 for C-H bending vibration and 1434.07cm⁻¹ in Physical mixture; 1215.36cm⁻¹ for O-H bending is shown in Nebivolol and 1215.61cm⁻¹ are shown as O-H bending in Physical mixture; 1075.89cm⁻¹ for C-N stretching vibrations(amines) is shown in Nebivolol and 1075.59cm⁻¹ are shown in Physical mixture, 812.71 cm⁻¹ was shown as C-H bending in Nebivolol and 812.92cm⁻¹ in Physical mixture. Physical mixtures such as Nebivolol with additives and Nebivolol pure medication, have the same functional groups. Figure 3 (A) and Figure 3 (B) show the results.

Measuring of pre-compression parameters of liquid solid compacts prepared for tablet

Table 5 lists the pre-compression parameters for liquid compacts LSC1 to LSC12. According to the data, the Angle of repose, Carr’s index, and Hausner’s ration data determined to be good flow properties for LSC6, LSC12, and it is less than 35°. The flow properties are excellent when blended with excipients. The granules’ bulk density suggests that they are packed well. The flow property is excellent when blended with excipients. The granules’ bulk density shows that they have an excellent packaging quality. For LSC6 and LSC12, the Carr’s index was determined to be less than 15% for all formulations, indicating satisfactory flow characteristics. The Hausner’s ratio was less than 2% for all of the granules. Because the angle of repose and compressibility index measurements demonstrate that granules flow well, direct compression is used for tablet formation.

Response of Response independent variables on Disintegration Time in Optimization of Nebivolol Liquid compacts for Tablet formulation

The 2³ factorial optimization design and its result are shown in Tables 6, 7, 8, 9, 10, 11, 12, 13 and 14 and Figure 4 revealed about the effect of independent variables like Drug Concentration (Nebivolol) in the liquid vehicle (Propylene glycol) (% w/w); Concentration of Carrier (Avicel) the formulation (% w/w); Concentration of Super disintegrants [Crosspovidone] in the formulation (% w/w) in mg on dependent variables like disintegration time and wetting time in sec during the preparation of Nebivolol solid liquid composite compressed tablet. According to the results, there was a substantial relationship between disintegration time and disintegrating agent, as well as carrier substance. It was demonstrated by the surface response graph in Figure 4 that on increasing the disintegrating agent, it shows a reduction in disintegration time of the solid liquid composite tablet. With ANOVA, the ‘P’ value for executing the disintegrants vs. disintegrating time in sec was determined to be 0.05, indicating a significant difference in disintegration time when the concentration of Super disintegrants like crosspovidone is increased. At high +1 level disintegrating agent (i.e. 10% of crosspovidone), LSC6 formulation showed desired disintegration time of around 70 ± 2.88 sec when compared to other formulations. Increased vehicle concentration in the manufacture of solid liquid compacts resulted in a decrease in the wetting time of the solid liquid compact tablet, confirming the tablet’s shows rapid disintegration. The ‘p’ value was found to be 0.05 by establishing it in ANOVA as indicated in Table 8, confirming that raising the concentration of vehicle caused a significant change in wetting time. At high +1 levels of vehicle and disintegrants concentration, with low levels of carrier substance, LSC6 formulation demonstrated a quick wetting property of tablet of about 20 ± 2.32 sec. LCS2, LCS3, LSC6, LCS7, and LCS12 formulations were discovered to be the optimal solid liquid compacts compressed tablet formulations, which may be ideal candidates for further evaluation parameter like in-vitro drug release studies, based on the optimization data. The polynomial Equations (7) and (8) were created using the coeffi-
cient values from optimization design, which were generated by changes in the independent variable depending on the dependent variables,

\[
Di\text{sinintegration time (DT)} = 110.83 - 11.66 X1 - 8.33 X2 - 33.33 X3
\]
\[
Wetting\text{ time (WT)} = 37.25 - 3.96 X1 - 1.75 X2 - 9.25 X3
\]

Response of independent variables on Wetting Time in Optimization of Nebivolol Liquid compacts for Tablet formulation

The selected LCS2, LCS3, LCS6, LCS7, and LCS12 liquid solid compacts compressed tablet was performed to invitro drug release tests in 6.8pH phosphate buffer based on optimization parameters. When comparing the percent cumulative quantity of drug release are shown in Figure 5, it was established that the LSC 6 formulation has the highest amount of drug release in a sustained manner (99.82 2.54% in 12 hr time interval). As a result, formulation containing 10% cross povidone and 25% avicel carrier exhibit a sustained and maximal level of drug release over a 12-hour period.

CONCLUSIONS

The liquid solid composite was formulated by blending cum sonication technique. The optimization of liquid solid composite was done by varying the independent variable like concentration of vehicle, concentration of carrier and concentration of superdisintegrants and determined their effect on response variables like Disintegration time and Wetting time. Further the liquid solid composite compressed tablet was evaluated for % in-vitro drug release. From the optimization results it was confirmed that LSC6 solid liquid composite compresses tablet was found to be the optimized formulation, based on disintegration time, wetting time and % amount of drug release, which may be the good candidates for enhancing the solubility and dissolution rate of less soluble drugs like Nebivolol.

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Conflict of Interest

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