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Research Article

DESIGN AND EVALUATION OF EXTENDED RELEASE RANOLAZINE LIQUISOLOID TABLETS USING PLACKETT–BURMAN SCREENING DESIGN

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ABSTRACT

Objective: The short biological half-life of Ranolazine (RAN) and consequently the difficulties in maintaining the desired concentrations in the blood, determined the need for the development of an extended release formulation which can achieved by developing a matrix tablet using Eudragit L100-55. Furthermore, including some materials like polyvinylpyrrolidone to liquid medication (microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of the drug. The aim of the present study was to develop RAN liquisolid tablets using Plackett–Burman (PB) design to screen the effect of five formulation and process factors on the formulation.

Methods: RAN liquisolid tablets were prepared by liquisolid technique using PB design to screen the effect of five formulation and process factors. The RAN liquisolid formulations were characterized by pre and post compression parameters, differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy, and *in-vitro* drug release.

Results: Parameters such as Neusilin US2, Aerosil 200, polyethylene glycol grades (PEG) 400, polyvinyl pyrrolidone (PVP) K30, and Eudragit L100-55 showed an influential effect on the selected responses angle of repose, thickness, and hardness as observed in Pareto charts of PB design. Hence, liquisolid technique was selected to develop the extended release liquisolid tablets of RAN.

Conclusion: PB design was proved to be appropriate tool to study effect of Neusilin US2, Aerosil 200, PEG 400, PVP K30, and Eudragit L100-55 on the response variables and to recognize the most influencing factor by using liquisolid technique.

Keywords: Ranolazine, Liquisolid technique, Eudragit L100 55, Plackett–Burman.

INTRODUCTION

The oral route of administration is strongly preferred because it is convenience, relatively low production cost, and the high level of patient safety. However, there are some problems associated with the oral drug delivery like poor bioavailability, high first pass metabolism, frequent drug administration, etc. Extended-release systems allow the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled release dosage forms [1,2].

Ranolazine (RAN) is indicated for the treatment of chronic angina in patients who have not achieved an adequate response with other antianginal drugs. Its novel mechanism of action increases oxygen supply to the myocardium without compromising hemodynamic status. RAN is extensively metabolized in gut and liver and its absorption is highly variable. The apparent terminal half-life of poorly soluble RAN is 2.5+0.5 hrs [3,4].

The short biological half-life of RAN and consequently the difficulties in maintaining the desired concentrations in the blood, determined the need for the development of an extended release formulation. The desired extended-release characteristics are achieved by developing a matrix tablet, where a pH-dependent polymer (methacrylic acid ethyl acrylate copolymer 1:1) is used that is insoluble in low pH and begins to dissolve at about pH >5. In this way, the polymer restricts the high solubility of RAN in acidic mediums (e.g., gastric environment) and achieves an extended-release by dissolving in a basic environment, where drug is less soluble and thus more time is needed for its release [5-10].

A most preferred copolymer is a methacrylic acid copolymer, type C, USP (which is a copolymer of methacrylic acid and ethyl acrylate having between 46.0% and 50.6% methacrylic acid units). Such a copolymer is commercially available as Eudragit L100-55 (as a powder). Sustained-release formulation of Eudragit L100-55 can be an alternative for the administration of such drugs [11].

As RAN belongs to BCS Class II, solubility enhancement is necessary so that the drug is released and gets solubilized immediately at the site of action to produce its therapeutic effect. Liquisolid technology was used to prepare the extended release tablet of RAN to obtain the sustained effect with the increased solubility. The dose of RAN is above 100 mg, and it is difficult to formulate liquisolid formulation of the high-dose drug. However, by including some materials like polyvinyl pyrrolidone (PVP) to liquid medication (microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of the drug. By adding such materials to the liquid medication, low amount of carrier is required to obtain a dry powder with free flowability and good compactibility [12]. Therefore, the basic objective of the study was to design and *in vitro* evaluation of sustained-release tablets of RAN for effective treatment of angina-pectoris using the liquisolid technique.

METHODS

Materials

RAN was obtained from Macleods Pharmaceuticals Ltd., India. Polyethylene glycol grades (PEG 200, 400, 600) were obtained from Research lab Fine Chem Industries, Mumbai; Microcrystalline cellulose (Flocel PH102, Flocel PH 101, Flocel PH 112) were obtained from Gujarat Microwax Pvt Ltd, Neusilin US2, Fujicalin (Gangwal Chemicals pvt ltd, Maharashtra), Aerosil 200, Ca-bo-sil were obtained from Akhil Healthcare (P) Ltd, Eudragit L100 55 was a gift sample from Evonik (Mumbai, India), PVP K30 obtained from Research lab Fine Chem Industries, Mumbai.

Solubility studies

Solubility study of RAN was performed in various solvents such as propylene glycol, polyethylene glycol 200, polyethylene glycol 400, polyethylene glycol 600; glycerine and distilled water; to select suitable non-volatile solvent for the preparation of liquisolid formulation by "shake flask method." Excess amount of drug was added to each of vial containing 1 ml of solvents as mention above. The solutions were placed on vortexer followed by shaking on rotary shaker for 72 hrs at 37°C. The drug concentration in each supernatant was analyzed by UV-spectrophotometer [13,14].

Angle of slide measurement (θ)

Angle of slide is used as a measure of flow properties of powders. Determination of angle of the slide is done by weighing the required quantity of carrier material and placing it at one end of the metal plate having a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as the angle of slide. Angle of 33° is considered as optimum [15].

Flowable liquid retention potential determination (φ)

Increasing amount of selected solvent was added and mixed well with the 10 g of each of material (carrier and coating, respectively). The corresponding Phi-value was calculated from the following equation after every addition of the non-volatile liquid.

The Phi-value corresponding to an angle of slide of 33° was recorded as the flowable liquid retention potential of carrier and coating material. The Phi-values for carrier and coating material have been abbreviated as φ_{CA} and φ_{CQ}, respectively. The carrier and coating material with maximum liquid retention potential have been selected as optimum [16].

Calculation of loading factor (Lf), amount of carrier (Q), and coating material (q) [13]

On the basis of Phi-value of the optimized carrier and coating material; the liquid load factor (L_f) and quantities of carrier and coating materials were calculated by using following formula.

$$L_f = \varphi_{CA} + \varphi_{CQ}(1/R)$$
$$L_f = W/Q$$
$$R = Q/q$$

Where, L_f=Liquid load factor; φ_{CA} = Flowable retention potential for carrier material; φ_{CQ} = Flowable retention potential for coating material; R = Excipient ratio (Q/q); W = Weight of liquid vehicle; Q = Weight of carrier material; q = Weight of coating material.

Drug excipient compatibility study

Drug and excipient were mixed in the specific quantity and placed in sealed vials for 4 weeks at 40°C/75% RH as per ICH guidelines. Initials were prepared for comparing the test vials for physical observation.

Plackett–Burman (PB) screening design [17-21]

A set of experiments using the PB screening design was adopted to prepare liquisolid formulation of RAN. This design investigates every input factor and arranges them on the Pareto chart based on the magnitude of its influence with positive or negative sign, respectively. PB design screens large number of input factors and at the same time reduces the number of runs. The t-statistic is determined by estimating the standard effect of each input factor. The factors with a bar extending beyond the vertical line on the Pareto chart shows significant influence at 95% confidence level. The factors show positive or negative sign on the Pareto chart reflecting increased or decreased effect respectively when moving from lowest to the highest level for the specific factor. The ANOVA results are used to determine the most influencing effect. Total twelve experimental trials involving five independent and three dummy variables were generated using STATGRAPHICS XVI. Four factors that may affect the experimental responses and four dummy factors were selected as independent variables at two levels for the study (Table 1). The amount of PEG 400 (A), Neusilin US2 (B), Aerosil 200 (C), PVP K30 (D), Eudragit L100 55 were selected as independent variables and Dummy 1 (E), Dummy 2 (F), Dummy 3 (G) and Dummy 4 (H) were selected as dummy variables and the angle of repose, thickness and hardness were set as response variables. The variables were correlated using the following polynomial equation with PB design.

$$Y = A0 + A1X1 + A2X2 + A3X3 + A4X4 + \ldots\ldots\ldots + AnXn$$

Where, Y is the response, A0 is the constant, and A1 is the coefficients of the response.

Preparation of liquisolid tablets

Liquisolid formulation of RAN denoted as F1-F13 (Table 2) were prepared and compressed into tablets each containing 375 mg drug, using the single punch tablet press. PEG 400 was used as the liquid vehicle, and different drug concentrations were prepared as 10% and 20%. PVP K30 was added in the mixture. Then Neusilin US2 as the carrier powder and silica (Aerosil 200) as the coating material at different powder excipient ratio (R) were added. Finally, Eudragit L100 55 was used as per the concentrations in all systems and mixed. The mixture was blended for a period 10 minutes. The blend was compressed into tablets using the single punch tablet press.

Evaluation of pre compression parameters

Angle of repose [22]

Accurately weighed 5 g of blend samples were passed separately in a glass funnel of 25 ml capacity with diameter 0.5 cm. The funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample was allowed to flow from the funnel, so the height of the pile *h* just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters.

Angle of repose was calculated by formula:

$\theta = \tan -1 (h/r)$

Hausner's ratio (HR)

HR was obtained by using formula:

HR = TD/BD

Carr's index (CI) [23]

CI, which is calculated as follows:

$$CI(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Evaluation of post compression parameters

Thickness

The thickness was measured using Vernier caliper. Five tablets from each batch were used and average values were calculated.

Hardness

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Six tablets from each formulation were tested for hardness.

Table 1: The independent variables and levels of PB design

Independent variables	Low (−1)	High (+1)	Units
PEG 400 (A)	41.667	66.176	mg
Neusilin US2 (B)	308.30	430.44	mg
Aerosil 200 (C)	71.74	102.77	mg
PVP K30 (D)	18	20	mg
Eudragit L100 55 (E)	55	60	mg

PB: Plackett-Burman, PEG: Polyethylene glycol grades

Table 2: Composition of RAN liquisolid formulations

Batches	Drug	Drug conc. (%)	R value	Lf	PEG 400 (mg)	Neusilin US2 (mg)	Aerosil 200 (mg)	PVP K30 (mg)	Eudragit L100 55 (mg)	Total (mg)
F1	375	85	6	1.025	66.176	430.44	71.74	20	60	1031.231
F2	375	85	3	1.431	66.176	308.3	102.77	18	55	930.527
F3	375	85	6	1.025	66.176	430.44	102.77	18	60	1060.261
F4	375	90	6	0.969	41.667	430.44	102.77	20	55	1032.746
F5	375	90	6	0.969	41.667	430.44	102.77	18	60	1035.746
F6	375	90	3	1.351	41.667	308.3	71.74	18	55	874.958
F7	375	85	3	1.431	66.176	308.3	102.77	20	55	932.527
F8	375	90	3	1.351	41.667	308.3	102.77	20	60	912.988
F9	375	85	6	1.025	66.176	430.44	71.74	20	55	1026.231
F10	375	90	3	1.351	41.667	308.3	71.74	20	60	881.958
F11	375	90	6	0.969	41.667	430.44	71.74	18	55	999.716
F12	375	85	3	1.431	66.176	308.3	71.74	18	60	904.497

R: Carrier: coating ratio, Lf: Liquid load factor, PVP: Polyvinyl pyrrolidone, RAN: Ranolazine, PEG: polyethylene glycol grades

Friability

The test was performed using Roche friabilator (Electrolab).

Drug content

The RAN content in different liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 375 mg of RAN was dissolved in 100 mL methanol. 1 mL of this solution was diluted to 10 mL with methanol and measured spectrophotometrically at λmax of 272 nm [24].

In vitro drug release

The *in vitro* drug release of RAN from the optimized liquisolid tablets was performed using USP dissolution a Type II apparatus (LABINDIA DS 8000). Liquisolid tablets were put into each of 900 mL 0.1 HCl, at 37±0.5°C with a 100 rpm rotating speed. Samples (10 ml) were withdrawn at regular time intervals (1, 4, 8 and 12 hrs) and filtered using a 0.45 µm filter. An equal volume of the dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method at 272 nm [25].

Differential scanning calorimetry (DSC)

The thermal behavior of RAN and its liquisolid formulation were examined by DSC (Mettler Toledo India Pvt. Ltd, DSC Star 1). The system was calibrated with a high purity sample of Indium. Scanning was done at the heating rate of 10°C/minute over a temperature range of 0-200°C.

Powder X-ray diffraction (PXRD)

PXRD patterns were recorded by X-ray diffractometer (x-Pert, Philips, UK) using Cu-Ka radiation (1.542 A) with a voltage of 40 kV and a current of 35 mA. Samples were scanned from 2° to 50° 2θ.

Scanning electron microscopy (SEM)

The external morphology was determined by SEM (Oxford Instruments, INCA X-Sight, UK) Samples were mounted on double-faced adhesive tape and coated with a thin gold - palladium layer by sputter-coated unit and surface topography was analyzed [17].

Stability studies [23]

Stability studies were carried out for 45 days for the optimized batch of RAN liquisolid tablets at a temperature 40±2°C/RH 75±5%. The physical observation and drug content were checked at regular intervals of 15 days.

RESULTS

Solubility studies

Angle of slide measurement (θ) and flowable liquid retention potential determination (φ)

Table 3 shows the angle of slide measurements and flowable liquid retention potentials for carrier and coating materials by which the best suitable carrier and coating material was selected.

Drug excipient compatibility study

Drug and excipient were mixed in specific quantity and placed in sealed vials for 4 weeks at 40°C/75% RH as per ICH guidelines. Initials were prepared for comparing the test vials for physical observation

PB screening design

In PB screening design, five factors that may affect the experimental responses and three dummy factors were selected as independent variables at two levels for the study. The outline and observed responses of PB formulation (PBF) on two levels were considered (Table 4).

Effect of independent factors on

Angle of repose

The Pareto chart (Fig. 1) indicates that the factors Aerosil 200, Neusilin US2 and Eudragit L100 55 concentration possess a significant influence on the angle of repose. Neusilin US2 and Aerosil 200 had showed negative effect as confirmed by least p=0.0032 and 0.0017, respectively (Table 5). This indicates that as the concentration of Neusilin US2 and Aerosil 200 increases the angle of repose decreases, which affects the flow properties of liquisolid formulation by giving the good to excellent flow to the liquisolid powder. Eudragit L100 55 had showed negative effect as confirmed by least p=0.0282 (Table 5). The ANOVA results confirm that Aerosil 200, Neusilin US2 and Eudragit L100 55 exhibit p<0.05 indicating that the factors are significantly different from zero at 95.0% confidence level. The regression coefficient for the angle of repose indicates 98.67% of variability around the mean.

Correlation between study factors on the response is shown by following equation;

Angle of repose = 66.1219 – 0.000136004*A – 0.0276732*B – 0.133742*C + 0.248333*D – 0.308667*E + 0.46*Factor_F – 0.191667*Factor_G + 0.493333*Factor_H.

Effect on thickness

The Pareto chart (Fig. 2) indicates that the factors Neusilin US2 and PEG 400 concentration possess a significant influence on the thickness of liquisolid tablet. Neusilin US2 and PEG 400 had showed positive effect as confirmed by least p=0.0099 and 0.0308 respectively (Table 5). This indicates that as the concentration of Neusilin US2 and PEG 400 changes thickness varies. The ANOVA results confirm that Neusilin US2 and PEG 400 exhibit p<0.05 indicating that the factors are significantly different from zero at 95.0% confidence level. The regression coefficient for angle of repose indicates 95.69% of variability around the mean.

Correlation between study factors on the response is shown by following equation;

Table 3: θ and Φ values of carrier and coating materials

	Excipients	θ	φ
Carrier material	MCC 112	30.15	0.419
	Flocel 101	30.98	0.289
	Flocel 102	31.43	0.038
	Neusilin US2	33.07	0.582
	Fujicalin	33.59	0.251
Coating material	Aerosil 200	33.12	1.24
	Cabosil	33.78	0.581

Table 4: Outline and observed responses of formulations F1 to F12

Batches	A	B	C	D	E	F	G	H	Angle of repose	Thickness (mm)	Hardness (kg/cm²)
F1	+	+	-	+	+	-	+	-	29.42	6.2	7.9
F2	+	-	+	-	-	-	+	+	31.25	6	7.6
F3	+	+	+	-	+	+	-	+	27.12	6.4	7.78
F4	-	+	+	+	-	+	+	-	28.36	6.1	8.7
F5	-	+	+	-	+	-	-	-	26.08	6.3	8.6
F6	-	-	-	-	-	-	-	-	34.29	5.8	8.2
F7	+	-	+	+	-	+	-	-	31.85	5.9	7.75
F8	-	-	+	+	+	-	+	+	30.05	5.7	8.4
F9	+	+	-	+	-	-	-	+	33.31	6.2	8.2
F10	-	-	-	+	+	+	-	+	35.66	5.6	8.3
F11	-	+	-	-	-	+	+	+	32.73	5.75	8.25
F12	+	-	-	-	+	+	+	-	34.20	5.9	7.6

Table 5: Summary of analysis of variance

Independent variables	Angle of repose		Thickness		Hardness	
	F-ratio	p-value	F-ratio	p-value	F-ratio	p-value
A	0.00	0.9937	14.88	0.0308	46.19	0.0065
B	76.30	0.0032	34.31	0.0099	8.80	0.0592
C	115.03	0.0017	7.37	0.0729	0.51	0.5271
D	1.65	0.2895	1.65	0.2888	5.25	0.1059
E	15.91	0.0282	1.00	0.3910	0.05	0.8362

Thickness = 4.05567 + 0.0091803*A + 0.00279734*B + 0.00510259*C-0.0375*D + 0.0116667*E – 0.0458333*Factor_F-0.0458333*Factor_G-0.0458333*Factor_H

Effect on hardness

Hardness was found to be in the range of 7.6 - 8.7 kg/cm² depending on the excipient concentration as shown in Table 4. The Pareto chart (Fig. 3) indicates that the factors Neusilin US2, PVP K30 and PEG 400 concentration possess a significant influence on the Hardness. PEG 400 showed negative effect confirmed by least p=0.0065 (Table 5). Neusilin US2 and PVP K30 had showed positive insignificant effect as compared to Aerosil 200 and Eudragit L100 55 which confirmed by least p=0.0592 and 0.1059 respectively (Table 5). The ANOVA results confirm that PEG 400 exhibit p<0.05 indicating that the factors are significantly different from zero at 95.0% confidence level. The regression coefficient for the angle of repose indicates 95.41% of variability around the mean.

Correlation between study factors on the response is shown by following equation;

Hardness = 6.75792 - 0.0246168*A + 0.002156*B + 0.00204104*C + 0.101667*D – 0.004*E – 0.0433333*Factor_F – 0.0316667*Factor_G – 0.0183333*Factor_H

Evaluation of precompression parameters

The angle of repose was found to be in the range of 27.12 - 35.66° which indicated good flow for all the batches. CI was found to be <20, which indicated good flowability for all the batches. HR was between 1.07 and 1.18 showed good flow ability (Table 6).

Evaluation of post compression parameters

Hardness and thickness of liquisolid tablet were found to be in the range of 7.6-8.6 kg/cm² and 5.6-6.4 mm respectively. Friability of tablets was found to be acceptable, i.e. below 1%. The drug content of all liquisolid tablets were found to be in between acceptable range (Table 7).

***In vitro* drug release**

The percent release of RAN from liquisolid tablet containing varying amounts of Eudragit L100 55 from F1 to F12 was found to be above 90.00% at 12 hrs (Figs. 4 and 5). The batch F8 showed the extension of drug release 95.18% at 12 hr when compared to all other batches (Tables 8 and 9) and was considered to include the optimum quantity of all excipients.

DSC

It was reported that RAN has a melting point of 120°C. DSC graph shows a sharp characteristic endothermic peak at 120.48°C (onset at 118.49°C and endset at 122.05°C) (Fig. 6).

DSC thermogram of liquisolid formulation showed that there is no change in the peak of drug. The peak at 45.57°C was found due to the presence of excipients (Fig. 7).

PXRD

The diffraction pattern of RAN revealed several sharp high-intensity peaks suggesting that the drug existed as crystalline material. PXRD pattern of RAN and liquisolid formulation were compared (Figs. 8 and 9). It was observed that there is a reduction in the peak intensity in PXRD pattern of liquisolid formulation.

SEM

SEM analysis of RAN showed irregular shapes and sizes. SEM analysis of the batch F8 liquisolid formulation showed spherical granules, which are observed due to the presence of Neuslin US2 and coating by Aerosil 200 on the liquisolid powder (Fig. 10).

Stability studies

Stability studies for the F8 batch were carried out at a temperature of 40±2°C/RH 75±5% for a period of 45 days. Tablets were evaluated for physical appearance and drug content. There was no any significant change in physical appearance and drug content during stability studies.

DISCUSSION

In the liquisolid formulation non-volatile liquid solvent is optimized for the high drug solubility in solvent. Solubility of RAN was found to be higher in PEG 400 in comparison with other solvents (Table 10). Thus, PEG 400 was selected to be the suitable solvent for preparing liquisolid formulation.

The angle of slide for carrier and coating materials was used to determine flowable liquid retention potentials, which are needed for calculation of the liquid load factor. From the obtained θ and φ values of carrier material, Neusilin US2 and Aerosil 200 was selected as the suitable carrier material coating material respectively for the preparation of liquisolid formulation of RAN because higher the φ value at angle of slide θ = 33° is considered as better carrier material and coating material (Table 3, Figs. 11 and 12).

The compatibility was observed between drug and excipients by the physical observations. (Table 11).

PB design was applied as a screening method for identifying the most influencing significant factors. The main effect of formulation and process parameters on the responses is the main requirement in the development of RAN liquisolid formulation is to be predicted. Five factors affecting the experimental responses and three dummy factors were selected as independent variables at two levels (−1 and +1) as shown in (Table 1**)**. Levels of each independent variable were selected on the basis of drug concentration, L_f and R-value. The outline and

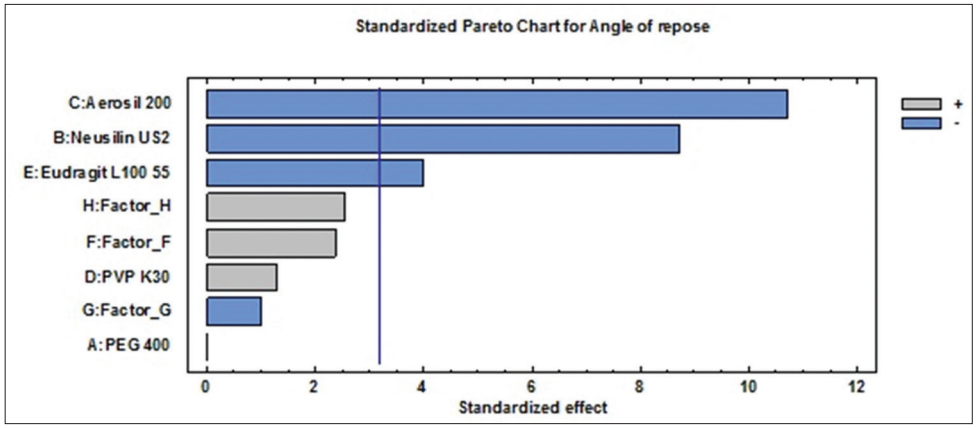

Fig. 1: Pareto chart of the standardized effects of independent factors on angle of repose

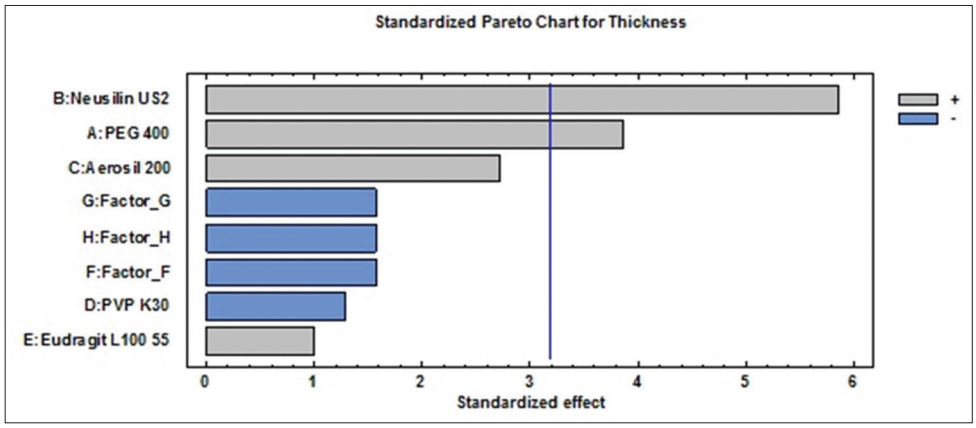

Fig. 2: Pareto chart of the standardized effects of independent factors on thickness

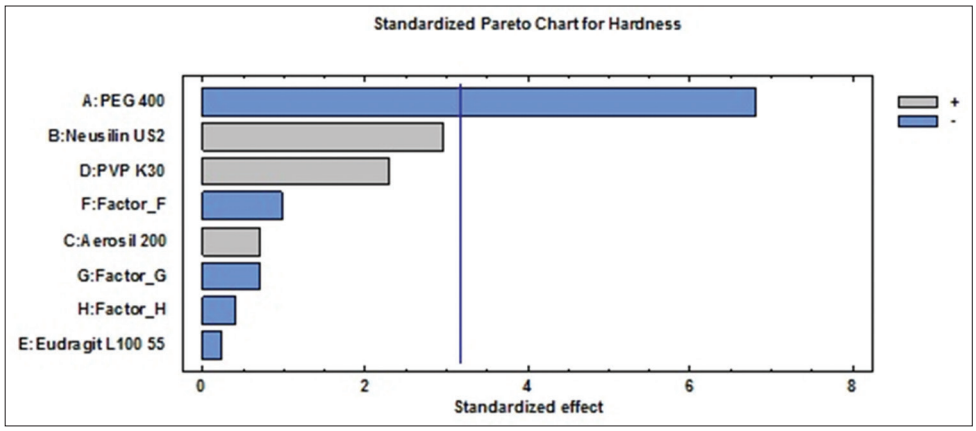

Fig. 3: Pareto chart of the standardized effects of independent factors on hardness

observed responses of PBF on two levels were considered (Table 4). Polynomial equations for individual response reflect the relationship between dependent and independent factors.

The angle of repose was found to be in the range of 27.12-35.66° depending on the excipient concentration (Table 4). The Pareto chart (Fig. 1) depicts that Aerosil 200, Neusilin US2, and Eudragit L100 55 concentration possess a significant influence on the angle of repose. Neusilin US2 has amorphous nature, possesses very large specific surface area and has high oil and water adsorption capacity. Neusilin US2 provides dry nature to drug and PEG 400 complex that cause the free flowing nature to the liquisolid granules. The flowability of powders depends on the forces between individual powder particles. A number of different forces determine the mechanism of adhesion: Van-der-Waals forces, electrostatic forces, liquid bridges and entanglement. Smaller the solid particles are, the more pronounced these effects are, and consequently the more cohesive the powder (i.e., poor powder flow properties). Aerosil 200 helps to improve the flow of powders by acting to counteract these different mechanisms. Van-der-Waals forces and electrostatic attraction decrease with increasing distance between the particles. Small Aerosil 200 aggregates adhere to the surface of the larger powder particles. Thus increase the distance, and reduce the attractive forces between them. The hydrophilic nature of Aerosil 200 allows it to attract and preferentially bind moisture,

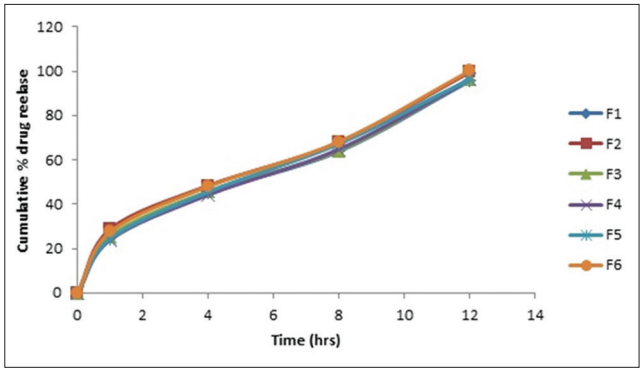

Fig. 4: Dissolution profile of formulations F1 to F6

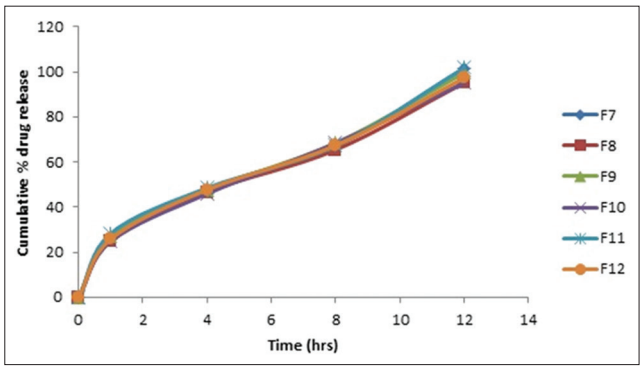

Fig. 5: Dissolution profile of formulations F1 to F6

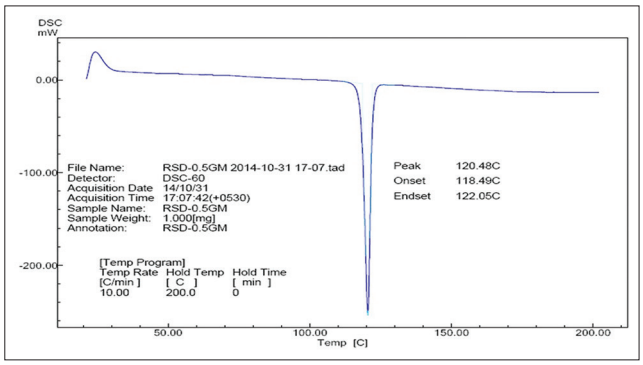

Fig. 6: Differential scanning calorimetry thermogram of ranolazine

helping to eliminate liquid bridges between solid particles that hinder powder flow. In addition, aggregates of Aerosil 200 also fill in voids and irregularities on the particle surface, decreasing entanglement between the larger particles. Thus, there is an improvement in the flow property of liquisolid formulation powder. Neusilin US2 and Aerosil 200 had showed negative effect which confirms that as the concentration of Neusilin US2 and Aerosil 200 increases angle of repose decreases which affects the flow properties of liquisolid formulation by giving the good to excellent flow to the liquisolid powder. Eudragit L100 55 was added externally and provided an external coating to the liquisolid powder that give proper flow to the granules. Eudragit L100 55 had showed negative effect indicated the same effect as that of Neusilin US2 and Aerosil 200. Based on the above findings the input factors Aerosil 200, Neusilin US2 and Eudragit L100 55 should be fixed at appropriate values for further optimization studies.

Thickness was found to be in the range of 5.6-6.4 mm depending on the excipient concentration (Table 4). The Pareto chart (Fig. 2) depicts that Neusilin US2 and PEG 400 concentration possess a significant influence

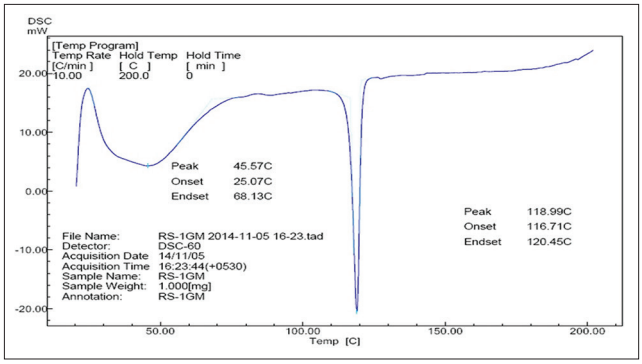

Fig. 7: Differential scanning calorimetry thermogram of liquisolid formulation F8

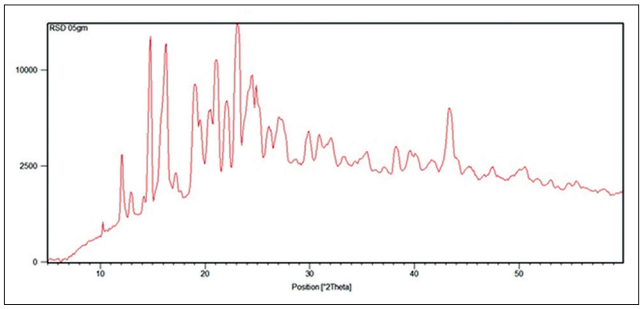

Fig. 8: Powder X-ray diffraction of ranolazine

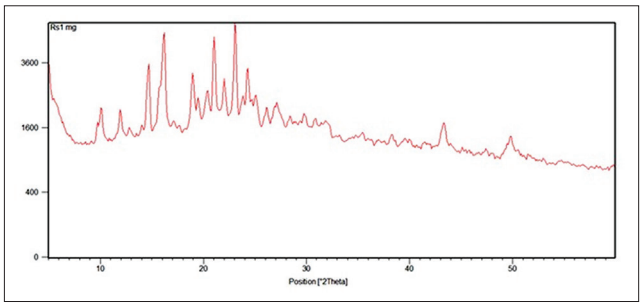

Fig. 9: Powder X-ray diffraction of liquisolid formulation F8

Table 6: Angle of repose, CI and HR of formulations F1 to F12

Batches	Angle of repose	CI	HR
F1	29.42	11.94	1.13
F2	31.25	12.36	1.14
F3	27.12	11.78	1.12
F4	28.36	12.05	1.13
F5	26.08	11.32	1.12
F6	34.29	14.68	1.15
F7	31.85	12.62	1.13
F8	30.05	11.54	1.12
F9	33.31	13.47	1.14
F10	35.66	15.11	1.17
F11	32.73	13.08	1.14
F12	34.20	15.03	1.17

CI: Carr's index, HR: Hausner's ratio

on the thickness of liquisolid tablet. The change in the concentration of Neusilin US2 and PEG 400 varies the thickness of liquisolid tablet. Neusilin US2 has large surface area and porous nature, adsorbs high loads of oils or water and can be mechanically compacted into high-quality tablets. Due to the presence of higher concentration of Neusilin US2 thickness does not decrease. This is due to coating of Neusilin US2 particles to drug and PEG 400 complex and avoids the squeezing out of

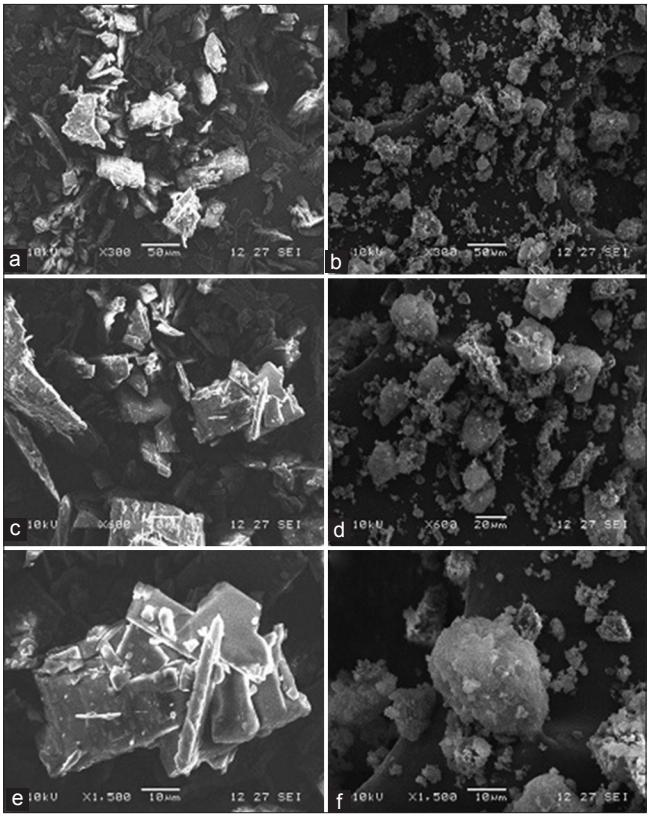

Fig. 10: (a,c,e) Scanning electron microscopy image of OLM and (b,d,f) Scanning electron microscopy image of liquisolid formulation

Table 7: Hardness, friability, thickness, and drug content of formulations F1 to F12

Batches	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)
F1	7.9	0.19	6.2	98.35
F2	7.6	0.17	6	98.47
F3	7.78	0.18	6.4	101.23
F4	8.7	0.29	6.1	97.67
F5	8.6	0.23	6.3	98.26
F6	8.2	0.26	5.8	99.59
F7	7.75	0.16	5.9	97.88
F8	8.4	0.24	5.7	98.69
F9	8.2	0.21	6.2	99.75
F10	8.3	0.24	5.6	97.91
F11	8.25	0.22	5.75	99.25
F12	7.6	0.17	5.9	97.43

Table 8: *In vitro* drug release of formulations F1 to F6

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	24.59	28.75	25.61	23.95	24.43	27.57
4	45.16	48.40	45.84	44.25	45.58	48.04
8	63.86	67.91	64.20	64.83	67.27	68.19
12	95.64	99.56	96.32	96.22	96.41	100.20

PEG 400 as it adsorbs on the drug and PEG 400 complex. As the PEG 400 concentration increases the thickness of liquisolid tablet decreases, which results into squeezing out of PEG 400 during compression. Thus, there is combined positive effect of Neusilin US2 and PEG 400 on the liquisolid tablet thickness. There is also a positive insignificant effect of Aerosil 200 on the thickness as compared to the effect of PVP K30

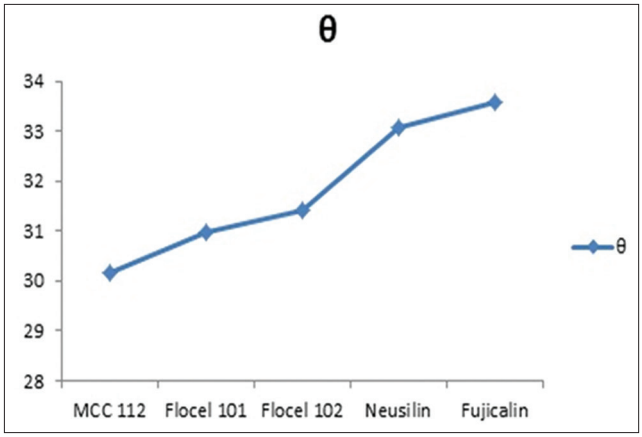

Fig. 11: θ of carrier material

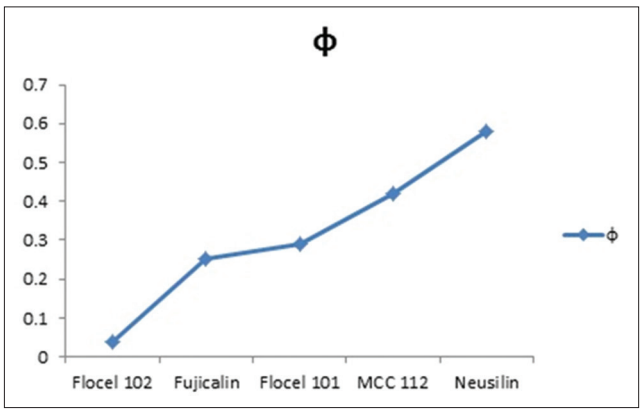

Fig. 12: Φ of carrier material

Table 9: *In vitro* drug release of formulations F7 to F12

Time (hr)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	26.29	24.92	27.23	24.83	28.32	25.85
4	47.08	46.70	47.65	45.95	48.54	47.80
8	66.93	65.39	68.42	68.39	67.21	67.38
12	101.63	95.18	99.56	95.25	101.76	97.35

Table 10: Solubility studies of RAN

Serial No.	Solvents	Solubility (mg/ml)
1	Propylene glycol	4.46
2	PEG 200	3.91
3	PEG 300	4.06
4	PEG 400	7.02
5	PEG 600	4.17
6	Glycerine	1.80
7	Distilled water	0.39

RAN: Ranolazine, PEG: Polyethylene glycol grades

and Eudragit L100 55. Based on the above findings the input factors Neusilin US2 and PEG 400 should be fixed at appropriate values for further optimization studies.

The Pareto chart (Fig. 3) depicts Neusilin US2, PVP K30, and PEG 400 concentration possess a significant influence on the angle of repose. As PEG 400 increases the hardness of tablet decreases as it exhibit the more porosity to the liquisolid formulation. Neusilin US2 and PVP K30 had showed positive insignificant effect. Neusilin US2 is superior in compressibility. Neusilin US2 makes hard tablets at low compression

Table 11: Drug excipient compatibility study

Drug: Excipient	Ratio	Physical observation				
		Condition: 40°C/75% RH				
		Initial	1 week	2 weeks	3 weeks	4 weeks
Drug+Neusilin US2	1:1	White to off crystalline powder	No change	No change	No change	No change
Drug+Aerosil 200	1:1	White to off crystalline powder	No change	No change	No change	No change
Drug+Eudragit L100 55	1:1	White to off crystalline powder	No change	No change	No change	No change
Drug+PVP K30	1:1	White to off crystalline powder	No change	No change	No change	No change
Drug+PEG 400	1:1	White to off crystalline powder	No change	No change	No change	No change

force and, in addition, improves the hardness of other filler and binder excipients. Hence, Neusilin US2 was used in less concentration. PVP K30 in less concentration gives the proper binding and thus hardness to the liquisolid tablet. This indicates that as the concentration of Neusilin US2 and PVP K30 increases the hardness of liquisolid tablet increases as an insignificant effect. Based on the above findings the input factors PEG 400, Neusilin US2 and PVP K30 should be fixed at appropriate values for further optimization studies.

The angle of repose, CI and HR were found to be within the acceptable range indicated good flow properties of the liquisolid blends (Table 6). Hardness and thickness varied depending on the change in the concentration of excipients. Friability and drug content of all batches were found to be in the limit (Table 7).

The percent release of RAN from liquisolid tablet with varying quantity of Eudragit L100 55 of all batches was found to be above 90.00% at 12 hrs (Figs. 4 and 5). This indicates the Eudragit L100 55 controls the drug release according to change in concentration observed from drug release of tablets. F8 batch shows low % drug release as the Eudragit L100 55 concentration is at high level. The results of *in vitro* drug release showed a relationship between the carrier to coating material ratio and the *in vitro* release of RAN from liquisolid tablets. A decrease in the R-value results in retardation of release rate as there is the presence of Neusilin US2, and Aerosil 200 are used as carrier and coating materials, respectively. Liquisolid formulation with low R-values contains low quantity of Neusilin US2, high quantities of Aerosil 200, and high liquid/powder ratios. If high amounts of Aerosil 200 are used, which means that the R-value is low, the liquisolid formulation is overloaded with liquid formulation due to a high liquid load factor. In this case, the drug releases from the liquisolid tablet slowers down. PVP K30 in high concentration also showed the better binding property and thus retarded the drug release. Therefore, liquisolid formulation F8 batch of RAN contains low quantity of Neusilin US2, high quantity Aerosil 200, low R-value and high drug concentration which gives us the extension to the release of drug.

DSC thermogram depicted that the drug remains stable in the liquisolid formulation. PXRD studies showed diminished peak suggests conversion of the crystalline drug into amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rates by liquisolid formulation. SEM analysis concluded the absence of irregular morphology of drug after formulation resulting into the spherical nature of powder particles in liquisolid blend. The powder was observed in the dispersed state which gives the idea of free flowing nature. Liquisolid formulation F8 was found to be stable by performing stability studies.

CONCLUSION

The liquisolid technique was selected to develop the liquisolid tablets of high dose RAN, to obtain retardation of drug release using Eudragit L100 55 as a release retardant polymer. Thus, the disadvantage that high dose water insoluble drug cannot be formulated by liquisolid technique can be overcome by use of PVP K30. Liquisolid tablets of RAN were successfully prepared by using Neusilin US2 as a carrier material, Aerosil 200 as a coating material and PEG-400 as a non-volatile solvent with two different ratios of R-values and drug: solvent ratios. Formulation and process variables were screened by PB ObD approach to study the effect of factors affecting the responses of RAN liquisolid formulation. Factors like Neusilin US2, Aerosil 200, PEG 400, PVP K30 and Eudragit L100 55 were found to have significant effect on responses like angle of repose, thickness, and hardness as per their concentration. The dissolution of RAN of batch F8 was found to be the proper sustained effect to drug release due to the presence of high quantity of Eudragit L100 55 and PVP K30 respectively, low quantity of Neusilin US2, high quantity Aerosil 200, low R-value and high drug concentration. PB design was proved to be an appropriate tool to study the effect of parameters on the response variables and to recognize the most influencing factor.

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