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QUALITY BY DESIGN (QbD) APPROACH FOR THE MODIFICATION OF POORLY SOLUBLE DRUGS

Mehta Dhirendra Kumar*[1], Kachawa Vijay Singh[2], Sharma Ranu[3], Garg Ayush, [4]Kumar Dileep[5] and Dr. Dwivedi Jayesh[6]

[1]Reasearch Scholar, Department of Quality Assurance, Pacific College of Pharmacy, Udaipur, Rajasthan, India.
[2]Assistant Professor, Department of Quality Assurance, Pacific College of Pharmacy, Udaipur, Rajasthan, India.
[3]Associate Professor, Department of Pharmaceutical Chemistry, Pacific College of Pharmacy, Udaipur, Rajasthan, India.
[4]Associate Professor, Department of Pharmaceutics, Pacific College of Pharmacy, Udaipur, Rajasthan, India.
[5]Assistant Professor, Department of Pharmacology, Pacific College of Pharmacy, Udaipur, Rajasthan, India.
[6]Professor, Department of Pharmaceutics, Pacific College of Pharmacy, Udaipur, Rajasthan, India.

***Corresponding Author: Mehta Dhirendra Kumar**

Reasearch Scholar, Department of Quality Assurance, Pacific College of Pharmacy, Udaipur, Rajasthan, India.

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ABSTRACT

The current work aims to modification of poor soluble drugs by QBD approach. Quality by design (QbD) encourages the pharmaceutical industry to use risk management and science-based manufacturing principles to gain process and product understanding and thus assures quality of the product. Physiochemical properties and 3^2factor are analysis in this study. FTIR, DSC thermogram etc are also done. Ranolazine and olmesartanmedoxomil with different polymers are used.

KEYWORDS: Physiochemical properties, poorly soluble drug, QbD approach.

1. INTRODUCTION

1.1 Physicochemical properties of drug substance

Prior to the development of major dosage forms, it is essential that certainfundamental physical and chemical properties of the drug molecule and otherdivided properties of the drug powder are determined. This information decidesmany of the subsequent events and approaches in formulation development. Thisfirst learning phase is known as pre-formulation. The overall object of thepre-formulation is to generate useful information to the formulator to design anoptimum drug delivery system. Pre-formulation studies on a new drug moleculeprovides useful information for subsequent formulation of a physicochemicalstable and bio-pharmaceutically suitable dosage form. During processdevelopment physicochemical properties of the solid form such as crystallinity, polymorphism, particle size, powder flow property, solubility, hygroscopicity, ionization constant, partition coefficient, surface characteristics etc. are likely tochange.[1,2,3]

1.2 Biopharmaceutical Classification System

The Biopharmaceutical Classification System (BCS) is an experimental modelthat measures permeability and solubility under prescribed conditions. Theoriginal purpose of the system was to aid in the regulation of post-approvalchanges and generics, providing approvals based solely on *in vitro* data whenappropriate. Importantly, the system was designed around oral drug delivery sincethe majority of drugs are and remains orally dosed. Waivers, permission to skip *invivo* bioequivalence studies, are reserved for drug products that meet certainrequirements around solubility and permeability and that are also rapidly dissolving. However, the industry is using the BCS as a tool in drug product development. Asa simple example, BCS can be used to flag drugs that should not be testedclinically unless appropriate formulation strategies are employed.[4,5,6]

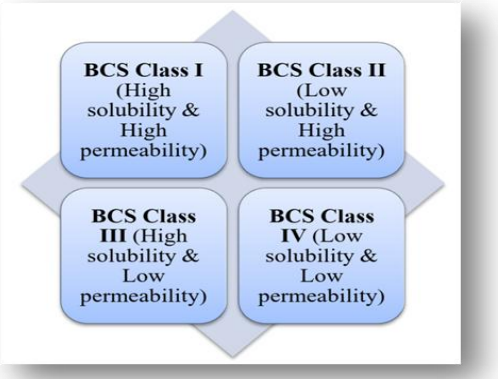

Figure 1: Biopharmaceutical classification system.

Quality by Design (QbD)

Product quality is ensured by raw material testing, drug substancemanufacturing, a fixed drug product manufacturing process, in- processmaterial testing, and end product testing. The quality of raw materialsincluding drug substance and excipients is monitored by testing. If they meetthe manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Because of uncertainty as to whether.

Ifpharmaceutical companies fulfill all requirements of FDA approvedspecifications or other standards such as USP for drug substance or excipients,they can be used for the manufacturing of the products. Finished drug productsare tested for quality by assessing whether they meet.

QbD means designing and developing formulations and manufacturingprocesses to ensure predefined product quality. According to ICH Q8 definesquality as "The suitability of either a drug substance or drug product for itsintended use. This term includes such attributes as the identity, strength, andpurity." The recent approach is QbD where if drug substance and excipientsmeet the specification the next step of unit operation is carried out such as Mixing, blending, drying, compression, coating etc. with fixed processparameters Quality in pharmaceuticals is very much important since it directlydeals with patient's health and so Food and Drug Administration (FDA) has setstringent law for drug approval**.** QbD is overarching philosophy articulated inboth the cGMP regulations and in robust modern quality system.[7,8,9]

2. MATERIAL AND METHODS

Olmesartan medoxomil and Ranolazine are purchase from Macleods pharmaceutical ltd and all the excipients are pharmaceutical grade.

2.1 Pre-formulation of OLM and RAN

2.1.1 Characterization of drugs

a. General description

The appearance, colour and odor of drugs were observed and noted.

b. Melting Point determination

Melting points of drugs were determined by Capillary Method. Fine powder ofdrug was filled in the capillary tube. Thecapillary tube inserted in the sample holder of melting point apparatus and athermometer is also placed in the apparatus. The temperature at which powdermelted was noted.

c. Calibration curve

Stock solution: An accurately weighed amount (10 mg) of OLM wasdissolved in 100 ml of distilled water, 0.1N HCl and pH 6.8 PBS respectively, with constant shaking till its complete dissolution followed by volume makeup to 100 ml with respective media.

i. Calibration curve in distilled water

0.1, 0.15, 0.2, 0.25, 0.3, 0.35 and0.4 ml stocksolution of distilled water were diluted to 10 ml with distilledwater to obtain concentration of 1 µg/ml, 1.5 µg/ml, 2 µg/ml, 2.5 µg/ml, 3µg/ml, 3.5 µg/ml and 4 µg/ml respectively.

ii. Calibration curve in 0.1N HCl

0.1, 0.15, 0.2, 0.25, 0.3, 0.35 and 0.4-mlstock solution of 0.1N HCL were diluted to 10 ml with 0.1N HCL toobtain concentration of 1 µg/ml, 1.5µg/ml, 2 µg/ml, 2.5 µg/ml, 3 µg/ml,3.5 µg/ml and 4 µg/ml respectively.

iii. Calibration curve in pH 6.8 phosphate buffer system (PBS): 0.5, 1, 1.5,2-, 2.5 and 3-ml stock solution of pH 6.8 buffer were diluted to 10 ml withpH 6.8 buffer to obtain concentration of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20µg/ml, 25 µg/ml and 30 µg/ml respectively.The absorbance of these dilutions were measured at 257nm (λ_{max}) withrespective media as blank.

d. Fourier-Transform Infrared Spectrometry (FTIR)

The FTIR spectrums of drug samples were recorded on a Shimadzu FTIR-8400. The spectra were recorded after appropriate background subtractionusing FTIR spectrometer equipped with a diffuse reflectance accessory and a data station. About 2-3 mg of the sample was mixed with 100 mg of dry potassium bromide and the sampleswere scanned from 4000-400 cm^{-1}wave numbers at a resolution of 2 cm^{-1}. Thecharacteristic peaks were recorded.

e. Differential Scanning Calorimetry (DSC)

The thermal behaviour of drug samples was examined by DSC. The system was calibrated with a highpurity sample of Indium. Scanning was done at the heating rate of 10ºC/minover a temperature range of 0 to 200 ºC. Melting endotherms of the drug andoptimized formulation were determined in the same way.

f. Scanning Electron Microscopy (SEM)

The external morphology of drugs was determined by scanning electronmicroscopy. Samples were mountedon doublefaced adhesive tape and coated with a thin gold–palladium layer by sputter-coated unit and surface topography was analysed.

h. Determination of particle size

The mean particle size was determined by laser diffraction technique usingMalvern 2000 SM. Analysis was carriedout at room temperature keeping angle of detection 90º. The mean particle sizewas expressed in terms of D (0.9), that is, size of the 90% of the particle.

i. Bulk density (BD) and Tapped density (TD)

Accurately weighed sample was taken in a 25 ml measuring cylinder. Volumeof packing was measured and tapped 100 times using Tap density testerand tapped

volume of packingrecorded.BD and TD were calculated using following formula;

$$\mathbf{BD} = \frac{Weight\ of\ the\ Powder}{Volume\ of\ the\ packing}$$

$$\mathbf{TD} = \frac{Weight\ of\ the\ Powder}{Tapped\ Volume\ of\ the\ packing}$$

j. Angle of repose

Accurately weighed samples were passed separately in a glass funnel of 25mlcapacity with diameter 0.5cm. Funnel was adjusted in such a way that the stemof the funnel lies 2.5cm above the horizontal surface. The sample was allowedto flow from the funnel, so the height of the pile h just touched the tip of thefunnel. The diameter of the pile was determined by drawing a boundary alongthe circumference of the pile and taking the average of three diameters Angle of repose was calculated by formula:

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

k. Hausners ratio (HR)

HR was obtained by using formula;

HR = TD/BD

l. Carr's index

Carr's index (CI) which is calculated as follows:

$$CL\% = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

2.2 Liquisolid Parameters for Liquisolid formulations of OLM and RAN

a. Angle of slide measurement (θ)

Angle of slide is used as a measure of flow properties of powders.Determination of angle of slide is done by weighing the required quantity ofcarrier material and placing it at one end of the metal plate having a polishedsurface. The end is gradually raised till the plate becomes angular to thehorizontal at which powder is about to slide. This angle is known as the angleof slide. Angle of 33^0 is considered as optimum.

b. Flowable liquid retention potential determination (φ)

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

Φ–value = Wt. of liquid/Wt. of solid

The Phi-value corresponding to an angle of slide of 33° was recorded as theflowable liquid retention potential of carrier and coating material. The Phivalues for carrier and coatingmaterial have been abbreviated as $\varphi_{CA}$and φCOrespectively. The carrier and coating material with maximum liquid retentionpotential have been selected as optimum.

2.3 Drug excipient compatibility study for Liquisolid formulations of OLM and RAN

Drug and excipient were mixed in 1:1 ratio and placed in sealed vials for 4weeks at 40°C/75% RH as per ICH guidelines.

2.4 3^2Factorial Design for Liquisolid tablets (QbD approach)

Further to determine the optimum values of the most influencing factors chosenfrom PB screening design, 3^2factorial design was applied and a response surfaceequation was derived in order to investigate the interaction between the factors. Inthis design 2 factors were evaluated, each at 3 levels,and experimental trials were performed at all 13 possible combinations. The two independent variables wereselected as X1 and X2. A statistical model incorporating interactive andpolynomial terms was utilized to evaluate the response.

$Y = b0+ b1X1+ b2X2+ b12X1X2+ b11X12+ b22X22$ (2)

Where, Y is the dependent variable, b0 is the arithmetic mean response of the 13 runs, and b1 is the estimated coefficient for the factor X1. The main effects(X1and X2) represent the average result of changing one factor at a time from itslow to high value. The interaction terms (X1 X2) show how the response changeswhen 2 factors are changed simultaneously.

2.5 Formulation of Liquisolid tablets of OLM and RAN

For OLM

Liquisolid tablets of OLM were prepared each containing 20 mg drug, usingthe single punch tablet press. OLM was dispersed in PEG 400. Neusilin USand Aerosil 200 were added to the above mixture under continuous mixing ina mortar. Finally, Primojel as superdisintegrant and Lactose as filler weremixed and mixture was blended for a period 10 minutes. The blendwascompressed into tablets using the single punch tablet press.

For RAN

Liquisolid tablets of RAN were prepared each containing 375 mg drug, usingthe single punch tablet press. RAN was dispersed in PEG 400. PVP K30 wasadded in the mixture. Neusilin US2 and Aerosil 200 were added to the abovemixture under continuous mixing in amortar. Finally, Eudragit L100 55 was mixed and mixture was blended for a period 10minutes. The blend wascompressed into tablets using the single punch tablet press.

2.6 Evaluation of Liquisolid tablets of OLM and RAN

a. Post compression parameters

i. Thickness

The thickness was measured using verniercaliper. Five tablets from eachbatch were used and average values were calculated.

ii. Hardness

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Six tablets from each formulation were tested for hardness.

iii. Friability

The test was performed using Roche friabilator. Twenty tablets were weighed and placed in the drum of the friabilator. The tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted and re-weighed.

The % friability was then calculated using formula,

$$\% \text{ Friability} = \frac{\text{Weight of tablets before test} - \text{weight of tablets after test}}{\text{Weight of tablets after test}} \times 100$$

iv. Disintegration time

The disintegration time of the tablets was measured in distilled water (37 ± 2°C) using disintegration test apparatus with disk. Five tablets from each formulation were tested for the disintegration time.

v. Drug content

The OLM content in different liquisolid tablet formulations wasdetermined by accurately weighing 20 tablets of each formula individually.Each tablet was then crushed and a quantity of powder equivalent to 10 mgof OLM was dissolved in 100 mL methanol. 1 mL of this solution wasdiluted to 10 mL with methanol and measured spectrophotometrically at λmax of 257nm.

For RAN

The *in vitro* drug release study of the RAN tablets was performed usingUSP Type II dissolution apparatus Liquisolidtablets were put into each of 900 mL 0.1 HCl, at 37±0.5°C with a 100-rpmrotating speed. Samples (10 ml) were withdrawn at regular time intervals (1, 4, 8 and 12 hr) and filtered using a 0.45 m filter. An equal volume ofthe dissolution medium was added to maintain the volume constant. Thedrug content of the samples was assayed using UV visiblespectrophotometric method at 272 nm. All measurements were done in triplicate.

b. Polynomial fitting, ANOVA and Optimization

Design Expert trial version 8.0.7.1 was used for polynomial fitting and ANOVA results. Appropriate modelswere selected by comparing lack of fit, p values and R2 values. Graphs wereplotted for statistically significant models with insignificant lack of fit atdesired confidence levels. The formulations were optimized using desirabilityapproach to select optimum combination of formulation variables (X1 and X2).

2.7 Stability studies of Liquisolid tablets of OLM and RAN

Stability studies were carried out for 6 months for the optimized batches of OLMand RAN liquisolid tablets at a temperature 40±2°C/ RH 75±5%. The physicalobservation and drug content were checked at 1st, 3rd and 6thmonth.

3. RESULT AND DISCUSSIONS

3.1 Pre-formulation

3.1.1 Characterization

a. General description

OLM was observed as a white to light yellowish-white, crystalline, odourlesspowder.

b. Melting Point

Melting point of OLM and RAN was measured and found to be in range 181-183°Cwhich was in accordance with compliance reported melting point, 175-180°C.

c. Calibration curve

i. In distilled water

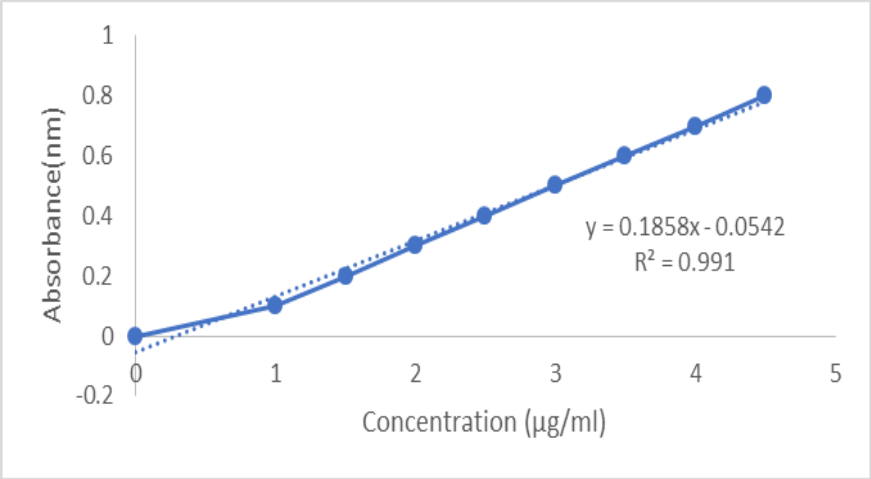

Figure 2: Calibration curve in distilled water.

ii. In 0.1N HCl

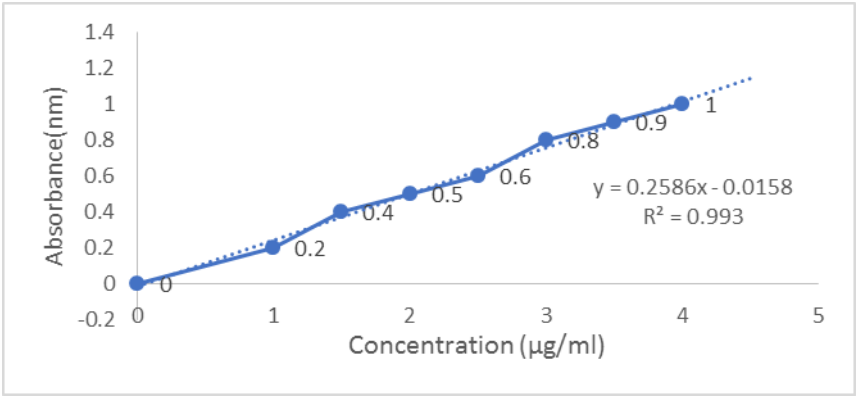

Figure 3: Calibration curve in 0.1N HCl.

iii. In pH 6.8 PBS

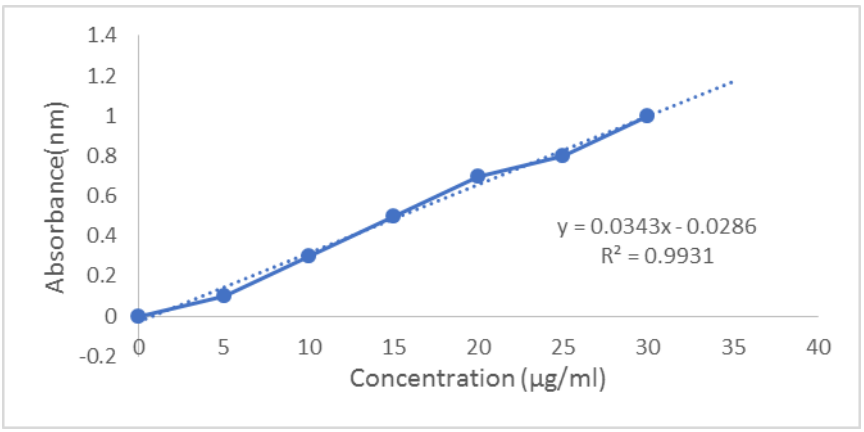

Figure 4: Calibration curve in pH 6.8 PBS.

d. Fourier-Transform Infrared Spectrometry (FTIR)

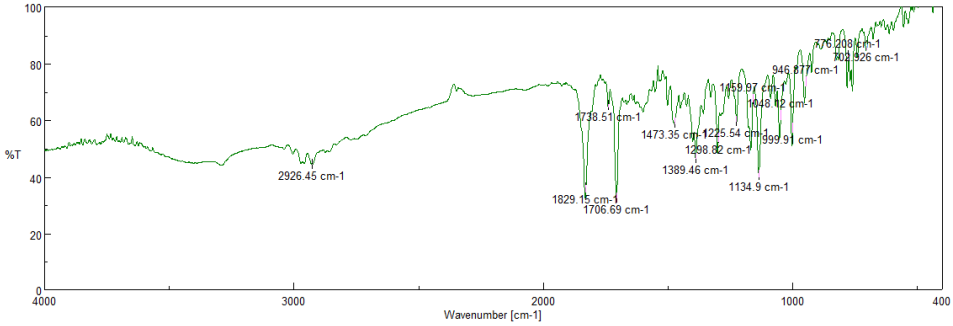

Figure 5: FTIR spectrum.

Table 1: Peaks in FTIR spectrum.

Functional group	Peaks obtained in the drug
C-H, str, Sp2	2960-2850 cm^{-1}
C-H, str, Sp3	2960-2850 cm^{-1}
C=O str	1706.69 cm^{-1}, 1829.15cm^{-1}
N-H, str	3300–3100 cm^{-1}
C-O str	1350-1050 cm^{-1}

e. Differential Scanning Calorimetry (DSC)

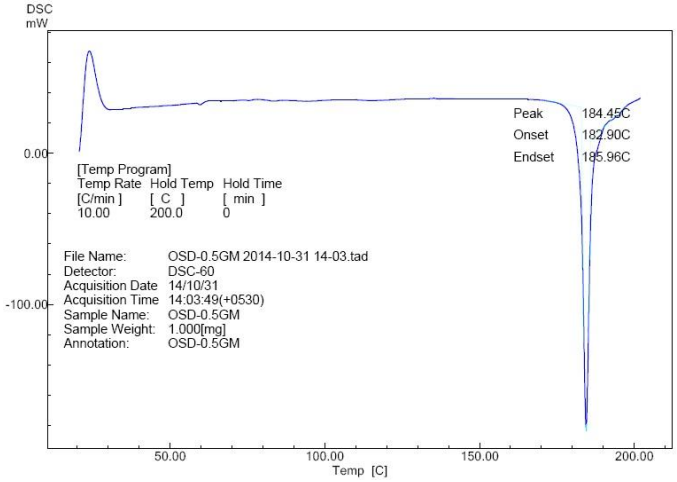

Figure 6: DSC thermogram of OLM.

f. Scanning Electron Microscopy (SEM)

SEM analysis of crystalline OLM and RAN was carried out under 3000X, 9000X and30000X whichshowed irregular shapes and sizes.

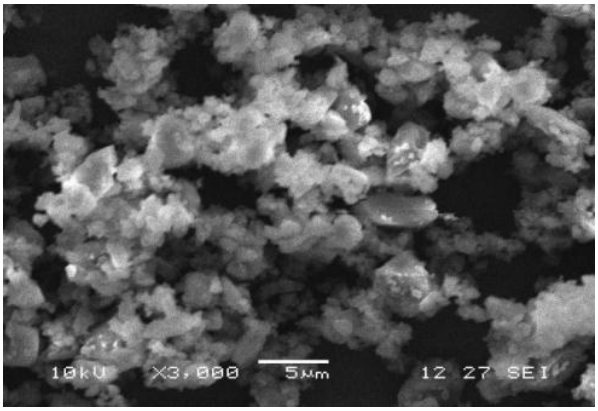

Figure 7: SEM image of OLM under 3000X.

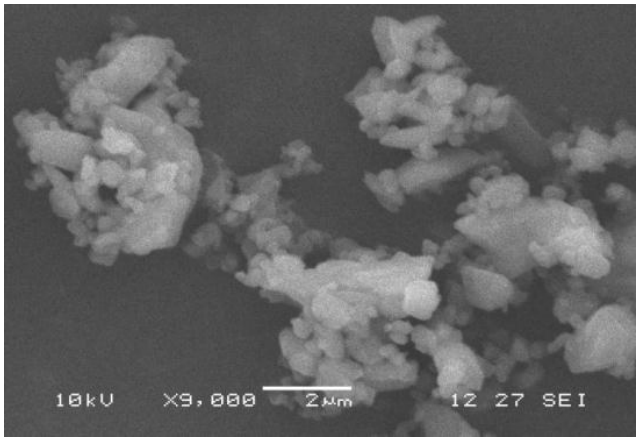

Figure 8: SEM image of OLM under 9000X.

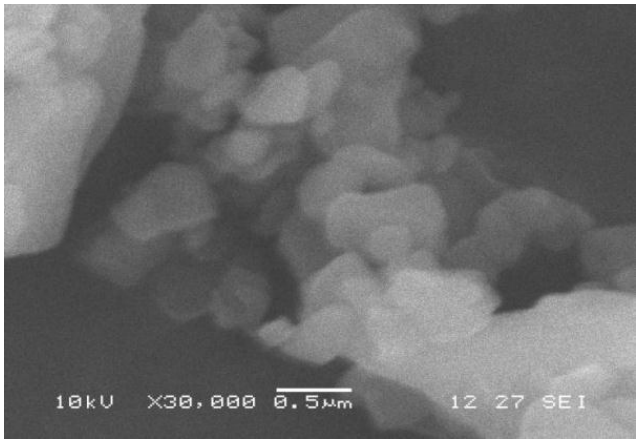

Figure 9: SEM image of OLM under 30000X.

g. Determination of particle size

The mean particle size of OLM and RAN in terms of D (0.9), that is, size of the 90% ofthe particle was found to be 1478.373 µm.

h. Bulk density (BD) and Tapped density (TD)

The BD and TD of OLM and RAN was found to be 0.466 gm/ml and 0.5981 gm/mlrespectively.

i. Angle of repose

Angle of repose of OLM and RAN was found to be 38.43° that indicates 'fair' flow.

j. Carr's index

Carr's index of OLM and RAN was found to be 20.28 that indicates 'fair' flow.

k. Hausners ratio

Hausners ratio of OLM and RAN was found to be 1.28 that indicates 'passable' flow.

5.1.2. Solubility studies

In the liquisolid formulation non-volatile liquid solvent is optimized for thehigh drug solubility in solvent. The solubility in various non-volatile solvent. The table shows that solubility of OLM and RAN in PEG 400 ishigher in comparison with other solvent. PEG 400 undergoes morehydrophobic interactions and cause the drug to solubilize. Thus PEG 400 wasselected to be the suitable solvent for preparing liquisolid formulation ofOLM and RAN.

3.2 Liquisolid Parameters for Liquisolid formulations of OLM

a. Angle of slide measurement (θ)

Angle of slide for carrier and coating materials was used to determineflowable liquid retention potentials, which are needed for calculation of theliquid load factor (Lf). From the obtained θ and φ values of carrier material. Neusilin US2 and Aerosil 200 wasselected as the suitable carrier material and coating material respectively forthe preparation of liquisolid formulation of OLM because higher the φ value atangle of slide θ = 33° is considered as better carrier material and coatingmaterial.

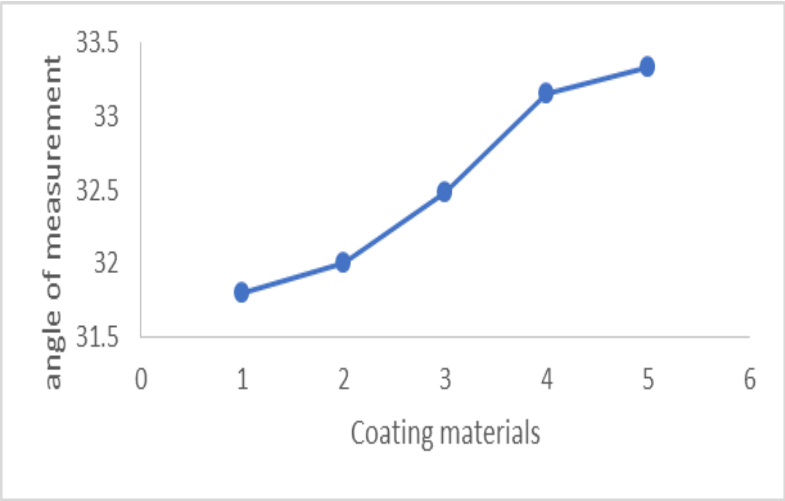

Figure 10: Ɵ of Carrier Materials.

b. Flowable liquid retention potential determination (φ)

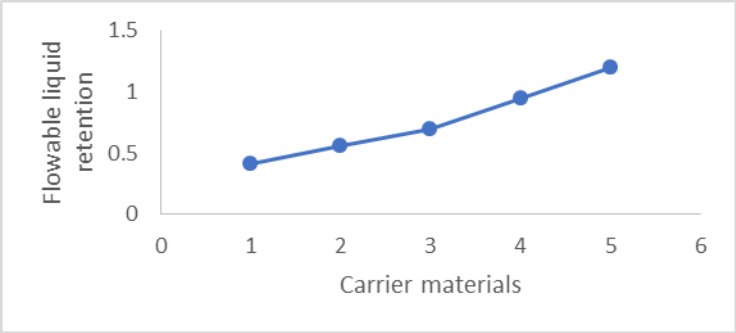

Figure 11: Φ of Carrier Materials.

3.3 Drug excipient compatibility study for Liquisolid formulations of OLM

From the above study, the excipients selected for drug excipient compatibilitystudy were PEG 400, Neusilin US2, Aerosil 200, Lactose, Primojel (sodiumstarch glycolate).

a. Physical Observation

No change was observed in physical observationsof vials during comparison and found to be compatible for 4 weeks at40°C/75% RH.

Table 2: Drug excipient compatibility study.

S. no.	Drug: excipient	Ratio	Physical observation				
			Condition: 40˚ C/ 75% RH				
			Initial	1 week	2 weeks	3 weeks	4 weeks
1.	**Drug + Neusilin US2**	1:1	White to off crystalline powder	No change	No change	No change	No change
2.	**Drug + Aerosil 200**	1:1	White to off crystalline powder	No change	No change	No change	No change
3.	**Drug + Lactose**	1:1	White to off crystalline powder	No change	No change	No change	No change
4.	**Drug + Primojel**	1:1	White to off crystalline powder	No change	No change	No change	No change
5.	**Drug + PEG 400**	1:1	White to off crystalline powder	No change	No change	No change	No change

b. FTIR

i. OLM and RAN

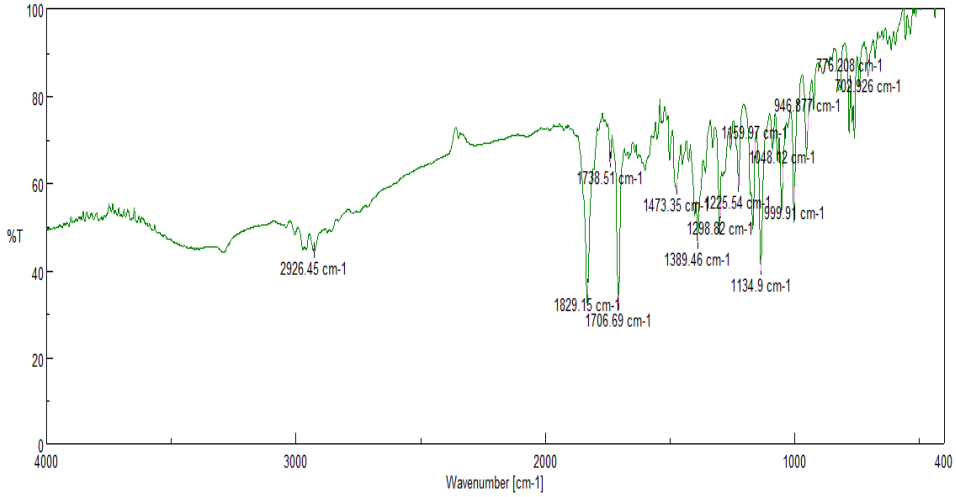

Figure 12: FTIR spectrum of OLM.

ii. OLM + Neusilin US

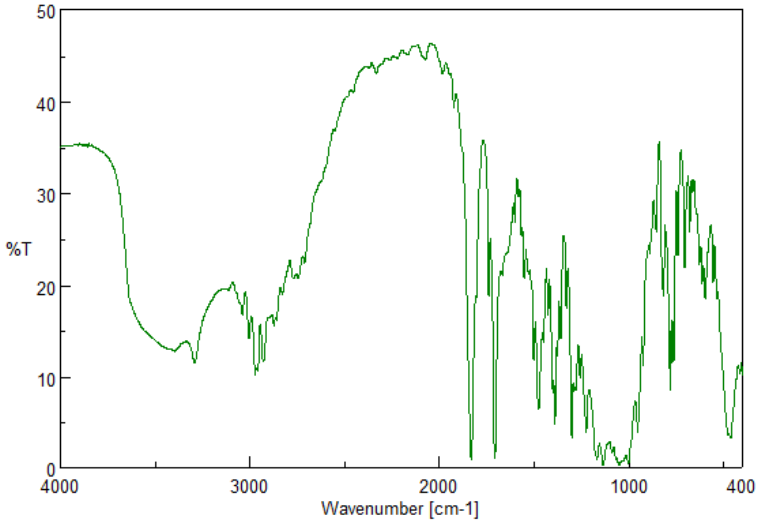

Figure 13: FTIR spectrum of OLM + Neusilin US

iii. OLM + Aerosil 200

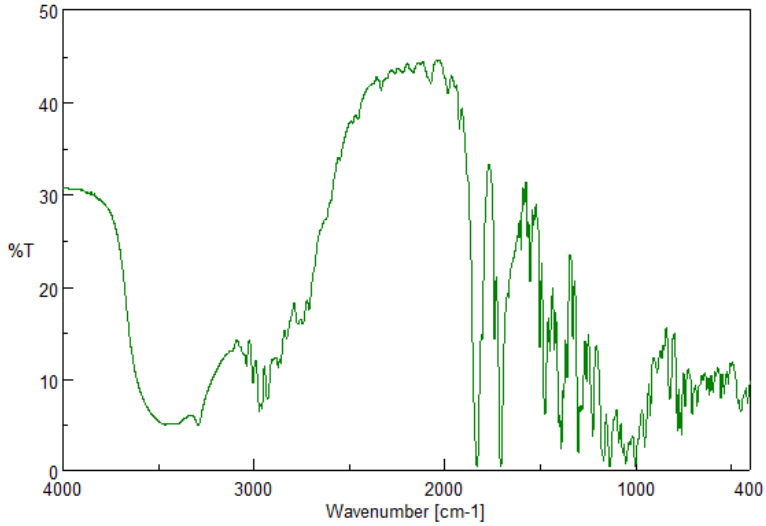

Figure 14: FTIR spectrum of OLM + Aerosil 200

iv. OLM + Primojel

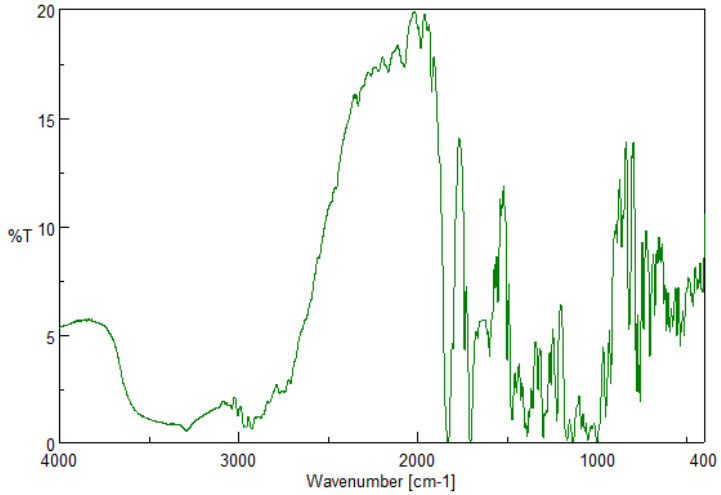

Figure 15: FTIR spectrum of OLM + Primojel.

v. OLM + Lactose

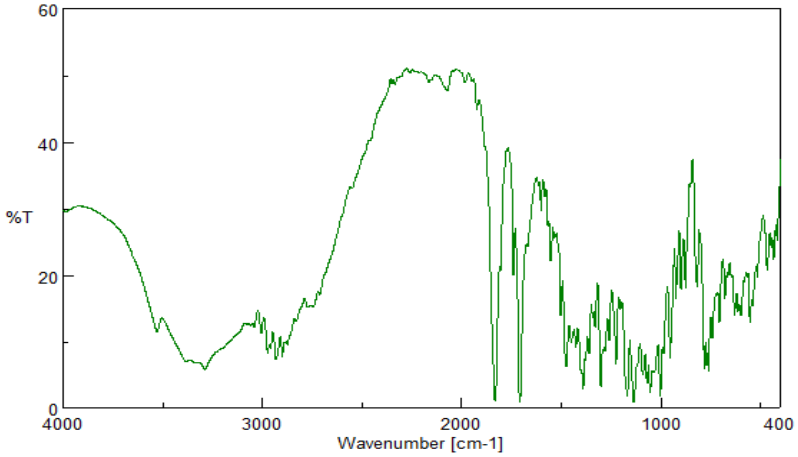

Figure 16: FTIR spectrum of OLM + Lactose.

3.4 3^2Factorial Design for Liquisolid tablets of OLM

A 3^2factorial design was applied to optimize the two factors that were chosenfrom the first PB screening design. As amount of Neusilin US2 (X1) and amountof Aerosil 200 (X2) showed the significant influenced effect on the responsesthese factors were used as independent variables. In this design, by keeping thedrug dose and quantity of other excipients same as that of batch F2 from PBscreening design, 2 factors Neusilin US2 (X1) and Aerosil 200 (X2); wereevaluated, each at 3 levels and experimental trials were performed atall 13 possible combinations. The hardness and % drug releaseat 2 min were selected as dependent variables (responses).

3.4.1 Formulation of Liquisolid tablets

Liquisolid tablets of OLM and RAN were successfully prepared and were used forfurther evaluation studies.

3.4.2 Evaluation of Liquisolid tablets

a. Post compression parameters

Table 3: Evaluation of post compression parameters.

Batches	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Disintegration Time (min)	Drug content (%)
OL1	4.73	5.11	0.19	1.11	97.45
OL2	4.75	5.11	0.16	1.13	99.16
OL3	4.81	5.12	0.18	1.01	98.98
OL4	4.78	5.13	0.17	1.25	96.12
OL5	4.72	5.11	0.21	1.13	102.01
OL6	4.83	5.14	0.14	1.15	101.01
OL7	4.68	5.06	0.27	1.25	100.02
OL8	4.73	5.09	0.16	1.17	99.12
OL9	4.74	5.12	0.18	1.10	97.14
OL10	4.71	5.07	0.25	1.19	98.52

3.5 *In vitro* drug release

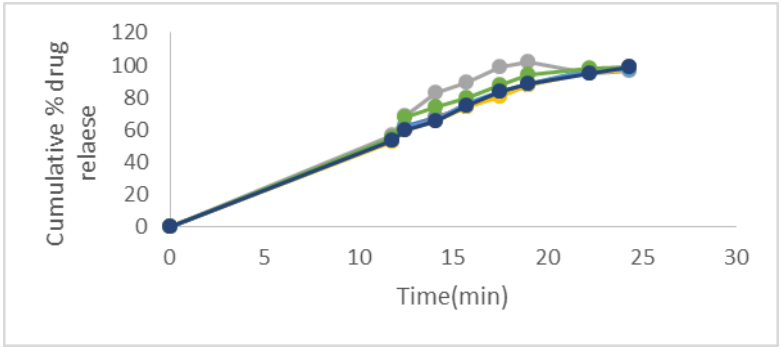

Figure 17: Dissolution profile of pure drug and FormulationsOL1 to OL7.

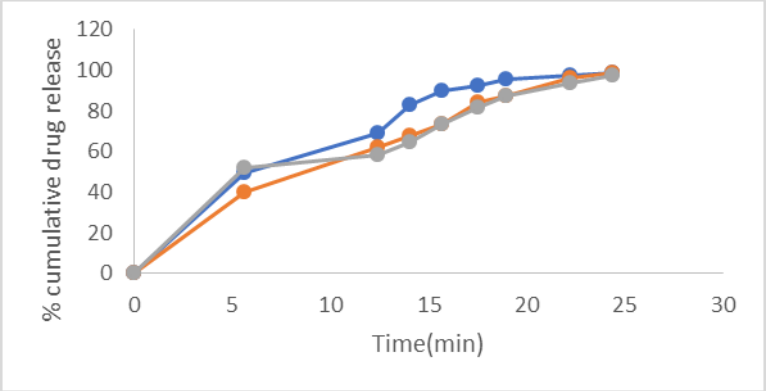

Figure 18: Dissolution profile of pure drug and Formulations (OL8 to OL10).

b. Polynomial fitting, ANOVA and Optimization

i. Polynomial Fittings

a) Effect on Hardness

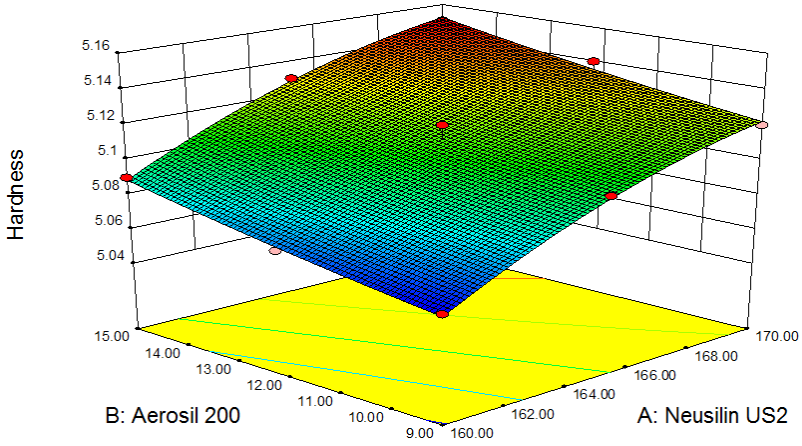

Figure 19: Response surface plot showing effect of formulation variables on Hardness.

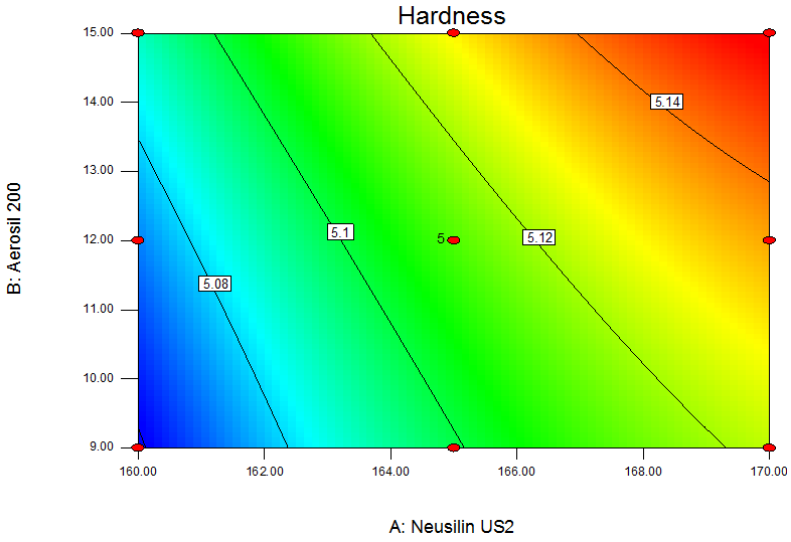

Figure 20: Contour plot showing effect of formulation variables on Hardness

b) Effect on % drug release at 2 min

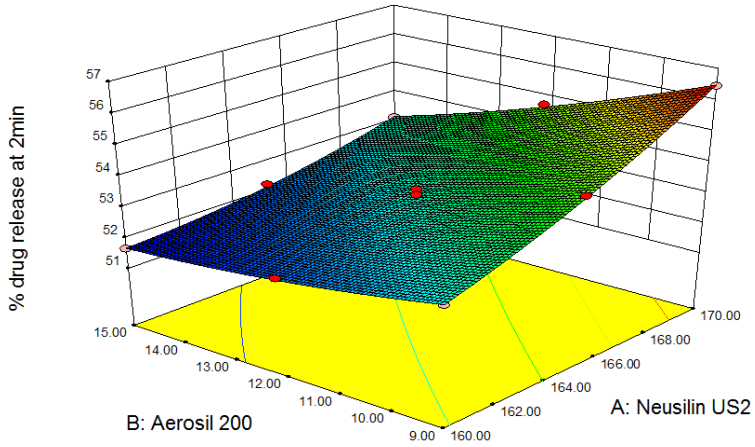

Figure 21: Response surface plot showing effect of formulation variables on % drug release at $t_2$min.

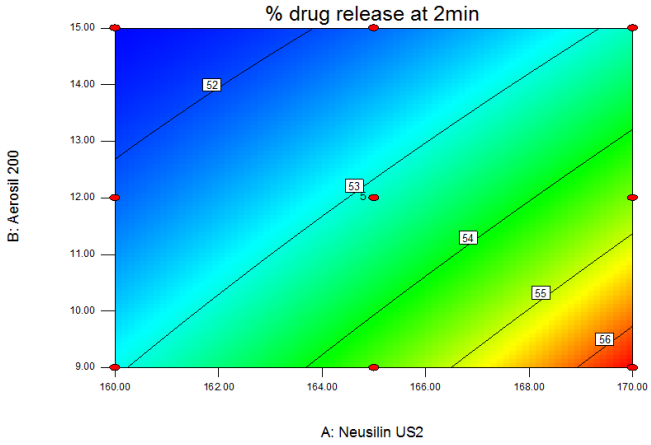

Figure 22: Contour plot showing effect of formulation variables on % drug release at $t_2$min.

ii. ANOVA

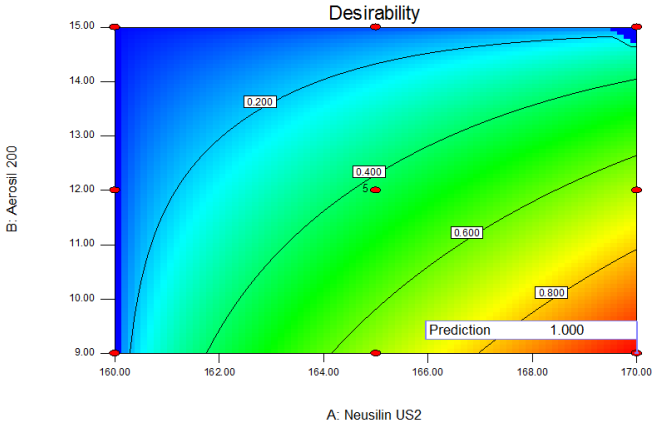

Figure 23: Desirability forliquisolid tablets.

iii. Optimization

Table 4: Criteria for optimization ofliquisolid tablets.

		Lower	Upper
Name	**Goal**	**Limit**	**Limit**
Neusilin US2	Maximize	142	152
Aerosil 200	Minimize	8	12
Hardness	In range	5.06	5.15
%Drug release at 2min	Maximize	51.66	56.45

3.6 Stability studies of Liquisolid tablets

Stability studies for the optimized tablets were carried out at a temperature of40±2°C/ RH 75±5% for a period of 6 months. Tablets were evaluated for physicalappearance and drug content. There was no any significant change in physicalappearance and drug content at 1st, 3rd and 6th month.

Table 5: Stability studies.

Months	Physical appearance	Drug content
1st month	No change	97.51 %
3rd month	No change	98.36 %
6th month	No change	97.17 %

4. SUMMARY & CONCLUSION

Summary

The present research work describes the formulation and evaluation of Liquisolidtablets of OLM and RAN. Liquisolid technology is a promising method used forenhancing solubilityof the poorly soluble drugs.

OLM Liquisolid tablets

Liquisolid powder was successfully prepared to enhance the solubility ofOLM and RAN. Solubility study depicted that OLM and RAN has maximum solubility in the non-volatilesolvent, PEG 400.Since, Φ values of Neusilin US2 and Aerosil 200 were found to be higher at θ= 33°C, they were selected as carrier and coating material for liquisolidformulation when compared to other carrier and coating materials. Drug excipients compatibility study showed no significant change and werefound to be compatible for 4 weeks at 40°C/75% RH.Angle of repose was found tobe in the range 25.86 – 37.09°; Carr's index was found to be in range of 8.78 – 16.66 %; Hausners ratio was found to be in range of 1.02 – 1.19.Solubility of liquisolid powder showed increase by 9.24 folds in distilledwater, by 5.32 folds in 0.1 N HCl and by 7.56 folds in pH 6.8 buffer.A 3^2 factorial design was applied to optimize the two factors Neusilin US(X1) and Aerosil 200 (X2) that were chosen from the first PB screeningdesign. Experimental trials were performed at all 13 possible combinations.The hardness and % drug release at 2 min were selected as dependentvariables (responses). *In vitro* dissolution studies revealed, that batch showed the highest drugrelease (101.58% at 15 min) which can be attributed due to the initial burstrelease of the drug from the tablet in 2 min.OL3 was selected as optimized batch based on statistical results. ANOVAsuggested that model chosen for response hardness and % drug release at 2min had an insignificant lack of fit with maximum desirability. The value ofcorrelation coefficient (R^2) also indicated the appropriateness of the selectedmodel.

CONCLUSION

Liquisolid technique was successfully used to design and develop the solid oral dosage form of poorly soluble drugs, OLM and RAN. Rapid release tablets of OLMand extended release of RAN were screened, optimized and evaluated using QbDapproach. Physicochemicalproperties like powder flow properties, particle size, solubility and dissolution ofOLM and RAN were effectively modified with improved stability. Liquisolid tablets of OLM were successfully prepared by using Neusilin US as acarrier material, Aerosil 200 as a coating material, Primojel as a disintegrant, PEG400 as a non-volatile solvent with two different ratios of R values and drugconcentration. The dissolution of liquisolid tablet of OLM was found to be rapid dueto the presence of high quantity of Neusilin US2, low quantity Aerosil 200, high Rvalue and low drug concentration.Liquisolid tablets of RAN were successfully prepared by using Neusilin US as acarrier material, Aerosil 200 as a coating material and PEG-400 as a non-volatilesolvent with two different ratios of R values and drug: solvent ratios. 3^2Factorial designs describedthe individual and interactive effect of Neusilin US2 and Aerosil 200 resulting intothe optimization. PB design and 3^2Factorial design, as a QbD approach, proved to beappropriate tools to study effect of parameters on the response variables, to recognizethe most influencing factor and to carry out the optimization studies.

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