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PLACKETT-BURMAN SCREENING OF OLMESARTAN MEDOXOMIL LIQUISOLID TABLETS: QUALITY BY DESIGN APPROACH

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ABSTRACT: Solubility is considered as the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Olmesartan medoxomil (OLM) is poorly soluble belongs to BCS class II. The drug is rapidly absorbed following oral administration, with a bioavailability approximately 26%. Liquisolid technique was used to enhance the aqueous solubility and dissolution rate to obtain faster on set of action, minimize the variability in absorption, and improve its oral bioavailability. The aim of the present study was to develop Olmesartan medoxomil liquisolid tablets using Quality by Design (QbD) approach to screen the effect of four formulation and process factors on the formulation. OLM liquisolid tablets were prepared by Liquisolid technique. Plackett-Burman (PB) design was used to screen the effect of four formulation and process factors to improve solubility and bioavailability. The liquisolid formulation were characterized by pre and post compression parameters, DSC, XRD, SEM, and *in-vitro* drug release. Excipients like Neusilin US2, Aerosil 200, PEG 400 and Primojel 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 liquisolid compacts of Olmesartan medoxomil, to obtain fast dissolving effect which enhances the solubility and bioavailability. PB design was proved to be appropriate tool to study effect of Neusilin US2, Aerosil 200, PEG 400 and Primojel on the response variables and to recognize the most influencing factor by using Liquisolid technique.

INTRODUCTION: A major challenge for pharmaceutical science is the poor dissolution characteristics of water insoluble drugs. There are many solubility enhancement techniques such as drug solid dispersions, micronization, co-precipitation, lyophilization, micro–encapsulation, use of pro-drug and drug derivatization processes, inclusion of drug solutions into soft gelatin capsules etc [1].

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Solubility is considered as the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response [2]. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.

Bio-Pharmaceutical classification class II drugs i.e. low solubility and high permeability, the rate of oral absorption is often controlled by the rate in the GIT. Thus rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption. Therefore solubility profile and dissolution rate profiles of drugs are major key factors for its oral bio-availability [3]. Olmesartan medoxomil (OLM) is an anti-hypertensive prodrug

ester that is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. It is a selective ATl subtype angiotensin II receptor antagonist and blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. OLM is indicated for the treatment of hypertension [4]. OLM is poorly soluble belongs to BCS class II. The drug is rapidly absorbed following oral administration, with a bioavailability approximately 26%. Peak plasma concentrations of OLM occur 1 to 2 h after an oral dose and are highly bound to plasma proteins (99%) [5]. Rapid onset of action is desirable to provide fast relief in the treatment of heart failure. Hence, it is necessary to enhance the aqueous solubility and dissolution rate of OLM to obtain faster on set of action, minimize the variability in absorption, and improve its overall oral bioavailability [6].

Therefore, a technique named "powdered solution technology", has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. Powdered solutions are designed to contain liquid medications in powdered form. The concept of powdered solutions convert a liquid drug or poorly water-soluble solid drug dissolved in a suitable non -volatile solvent into a dry, non-adherent, free flowing and readily compressible powder by its simple admixture with selected carrier and coating materials and this method does not involve drying or evaporation [7]. Hence, the objective of the present work was to formulate the liquisolid compacts for OLM to improve the solubility and dissolution rate by Quality by design approach.

MATERIALS AND METHODS:

Materials:

Olmesartan medoxomil was obtained from Emcure Pharamaceuticals Ltd. Pune. Polethylene glycol grades (PEG 200, 400, 600) and lactose 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, Primojel was obtained from Shreeji Pharma International. All materials were of either pharmacological grade or analytical grade.

Solubility studies [8, 9]:

Solubility study of OLM was performed in various solvents like Propylene glycol, Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600, Glycerine, Tween 20, Tween 80, Span 20, Span 80, Liquid paraffin, 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 hours at 37^{o}C. The drug concentration in each supernatant was analyed by UV-spectrophotometer.

Angle of slide measurement (θ) [10]:

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 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^{0} is considered as optimum.

Flowable liquid retention potential determination (φ) [11]:

Increasing amount of selected solvent was added and mixed well with the 10 gm 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 has been abbreviated as φ_{CA} and φ_{CO} respectively. The carrier and coating material with maximum liquid retention potential have been selected as optimum ().

Calculation of loading factor (Lf), amount of carrier (Q) and coating material (q) [8]:

On the basis of Phi-value of 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 excipients were mixed in specific quantity and placed in sealed vials for 4 weeks at 40°C/75% RH and 60°C as per ICH guidelines. Initials were prepared for comparing the test vials for physical observation.

Plackett Burman (PB) screening design [12-16]:

A set of experiments using the PB screening design was adopted to prepare liquisolid compacts of OLM. 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. 't' statistic is determined by estimating the standard effect of each input factor. The factors with bar extending beyond the vertical line on the pare to chart shows significant influence at 95% confidence level. The factors show positive or negative sign on the pare to 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 four independent and four dummy variables were generated using Stat graphics XVI. Four factors that may affect the experimental responses and four dummy factors were selected as independent variables at two levels for the study as shown in **Table 1**. The amount of PEG 400 (A), Neusilin US2 (B), Aerosil 200 (C), Primojel (D) 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 thickness, hardness and angle of repose were set as response variables. The variables were correlated using the following polynomial equation with PB design.

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

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

TABLE 1: INDEPENDENT VARIABLES AND LEVELS OF PB DESIGN

Independent variables	Low	High	Units
PEG 400 (A)	80	180	mg
Neusilin US2 (B)	141.39	155.64	mg
Aerosil 200 (C)	7.78	14.39	mg
Primojel (D)	20.77	21.17	mg

Preparation of liquisolid tablets:

From **Table 2** liquisolid systems of OLM (denoted as F1 to F13) were prepared and compressed into tablets each containing 10 mg drug, using the single punch tablet press.

TABLE 2: COMPOSITION OF OLM LIQUISOLID FORMULATIONS

Batches	Drug (mg)	Drug conc.	R	Lf	PEG 400 (mg)	Neusilin US2 (mg)	Aerosil 200 (mg)	Primojel (mg)	Lactose (mg)	Total (mg)
F1	20	10%	10	1.273	180	141.39	14.39	20.77	60	416.55
F2	20	10%	20	1.156	180	155.64	7.78	21.17	60	424.59
F3	20	20%	20	1.156	80	155.64	7.78	20.77	60	324.19
F4	20	20%	20	0.566	80	141.39	7.78	21.17	60	310.34
F5	20	10%	20	1.156	180	155.64	7.78	21.17	60	424.59
F6	20	20%	20	1.156	80	155.64	14.39	20.77	60	330.8
F7	20	20%	10	0.566	80	141.39	7.78	20.77	60	309.94
F8	20	10%	20	1.156	180	155.64	14.39	20.77	60	430.8
F9	20	10%	10	1.273	180	141.39	7.78	20.77	60	409.94
F10	20	10%	20	1.273	180	141.39	14.39	21.17	60	416.95
F11	20	20%	10	0.566	80	141.39	14.39	21.17	60	316.95
F12	20	20%	10	0.514	80	155.64	14.39	21.17	60	331.2

R: Carrier: coating ratio, Lf: Liquid load factor

All liquisolid formulations contained Neusilin US2 as the carrier powder and Aerosil 200 as the coating material at different powder excipient ratio (R). PEG 400 was used as the liquid vehicle and different drug concentrations were prepared as 10% and 20%. Liquisolid tablets were prepared as follows; OLM was dispersed in PEG 400 and the mixture of Neusilin US2- Aerosil 200 and were added to the mixture under continuous mixing in a mortar. Finally, Primojel as superdisintegrant and Lactose as filler were mixed and 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 [17]:

Accurately weighed blend samples were passed separately in a glass funnel of 25ml capacity with diameter 0.5cm. Funnel was adjusted in such a way that the stem of the funnel lies 2.5cm 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:

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

Hausners ratio (HR):

HR was obtained by using formula;
HR = TD/BD

Carr's index[18]:

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

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

Evaluation of post compression parameters:

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.

Thickness:

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

Friability: The test was performed using Roche friabilator (Electrolab)

Disintegration time [19]: The disintegration time of the tablets was measured in distilled water (37 ± 2°C) using disintegration test apparatus (Electrolab, India) with disk. Five tablets from each formulation were tested for the disintegration time.

Drug content [20]: The OLM 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 10 mg of OLM was dissolved in 100 mL methanol. 1 mL of this solution was diluted to 10 mL with methanol and measured spectrophotometrically at λmax of 257nm.

***In vitro* drug release[19]:** The *in vitro* drug release of OLM from the optimized liquisolid tablets was performed using USP dissolution a Type II apparatus (LABINDIA DS 8000). Liquisolid tablets and pure drug (20 mg) separately, were put into each of 900 mL phosphate buffer pH 6.8, at 37±0.5°C with a 50 rpm rotating speed. Samples (10 ml) were withdrawn at regular time intervals (2, 4, 6, 8, 10, 15, 20 and 25min) and filtered using a 0.45μm 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. All measurements were done in triplicate.

Differential Scanning Calorimetry (DSC): The thermal behaviour of OLM and liquisolid formulation was 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 10ºC/min over a temperature range of 0 to 200 ºC.

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

Scanning electron microscopy (SEM)[12]: The external morphology was determined by scanning electron microscopy (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 morphology was analyzed.

Stability studies[18]:
Stability studies were carried out for 45 days for the optimized batch of OLM 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 AND DISCUSSION:

Solubility studies:

In the liquisolid formulation non-volatile liquid solvent is optimized for the high drug solubility in solvent. The solubility in various non-volatile solvent is given in **Table 3**. The table shows that solubility of drug in PEG 400 is higher in comparison with other solvent. Thus PEG 400 was selected to be the suitable solvent for preparing liquisolid formulation of OLM.

TABLE 3: SOLUBILITY OF OLMESARTAN MEDOXOMIL

Sr no	Solvents	Solubility (mg/ml)
1	Propylene glycol	15.2
2	PEG-200	7.4
3	PEG-400	23.6
4	PEG-600	11.3
5	Glycerin	6.8
6	Tween 20	17.3
7	Tween 80	11.6
8	Span 80	3.2
9	Span 20	13.7
10	Liq.paraffin	0.85
11	Distilled water	4.6

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

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 (Lf). From the obtained θ and φ values of carrier material as shown in **Table 4** and **Fig.1** and **2**, Neusilin US2 and Aerosil 200 was selected as the suitable carrier material coating material respectively for the preparation of liquisolid formulation of OLM because higher the φ value at angle of slide θ = 33° is considered as better carrier material and coating material.

TABLE 4: Θ AND Φ VALUES OF CARRIER AND COATING MATERIALS

	Excipients	θ	Φ
Carrier material	MCC 112	31.8	0.412
	Flocel 101	31.87	0.294
	Flocel 102	32.48	0.036
	Neusilin US2	33.16	0.576
	Fujicalin	33.34	0.259
Coating material	Aerosil 200	32.39	1.04
	Cabosil	34.58	0.563

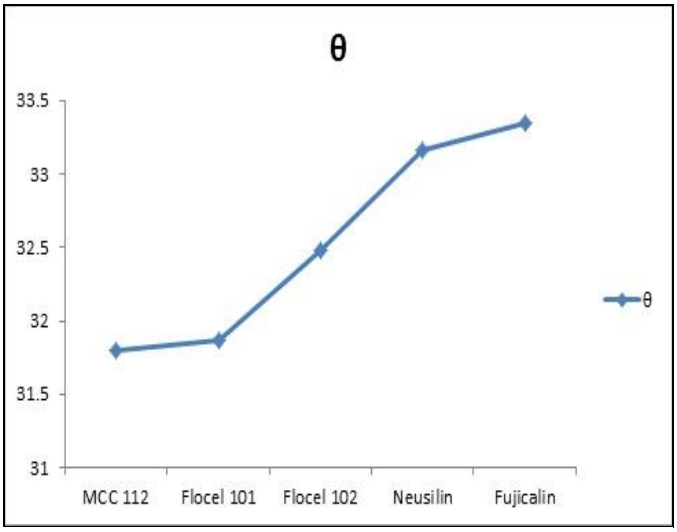

FIG.1: Θ OF CARRIER MATERIAL

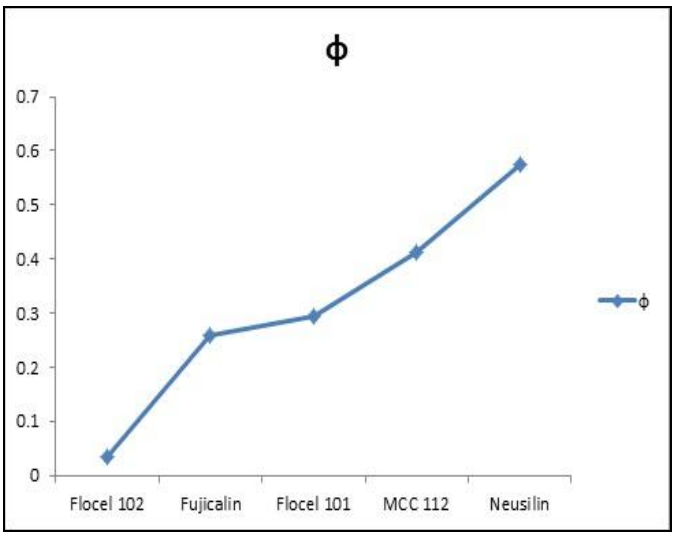

FIG.2: Φ OF CARRIER MATERIAL

Drug excipient compatibility study:

As shown in the **Table 5**, no change was observed in physical observations of vials during comparison and found to be compatible for 4 weeks at 40°C/75% RH ICH guidelines.

TABLE 5: 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 + Lactose	1:1	White to off crystalline powder	No change	No change	No change	No change
Drug + SSG	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

Plackett Burman (PB) screening design:

PB design was applied as a screening method for identifying the most influencing significant factors. Prediction of the main effect of formulation and process parameters on the responses is a crucial requirement in the development of OLM liquisolid formulation. Four factors that may affect the experimental responses and four dummy factors were selected as independent variables at two levels for the study. Levels of each independent variable were selected on the basis of Drug concentration, Lf and R value. **Table 6** shows the outline and observed responses of PB formulation (PBF) on two levels. Polynomial equations for individual response reflect the relationship between dependent and independent factors.

TABLE 6: 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/cm^2)
F1	+	-	+	-	+	+	+	-	35.11	4.67	4.2
F2	+	+	-	+	-	+	+	-	31.29	4.80	4.4
F3	-	+	-	-	+	-	-	-	32.36	4.23	4.9
F4	-	-	-	+	-	-	-	-	34.88	4.20	5.2
F5	+	+	-	+	-	-	+	+	31.11	4.9	5.2
F6	-	+	+	-	+	+	-	+	26.15	4.42	4.8
F7	-	-	-	-	-	+	-	-	35.02	4.27	4.6
F8	+	+	+	-	+	+	-	+	27.37	4.78	5.18
F9	+	-	-	-	+	-	+	-	37.09	4.47	4.13
F10	+	-	+	+	+	-	+	+	33.1	4.40	4.79
F11	-	-	+	+	-	+	+	+	33.58	4.20	4.5
F12	-	+	+	+	-	-	-	+	25.86	4.15	4.66

TABLE 7: 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	5.31	0.1045	238.19	0.0006	44.20	0.0069
B	122.32	0.0016	41.94	0.0075	226.41	0.0006
C	43.17	0.0072	2.29	0.2275	6.89	0.0787
D	1.10	0.3719	1.32	0.3335	67.62	0.0038

Effect of independent factors on:

Angle of repose:

Angle of repose was found to be in range of 25.86 – 37.09 depending on the excipient concentration shown in **Table 6**. The Pareto chart **Fig. 3** indicates that the factors Neusilin US2 and Aerosil 200 concentration possess significant influence on the angle of repose. Neusilin US2 is amorphous, possesses very large specific surface area and has high oil and water adsorption capacity. Neusilin US2 gives dry nature to drug and PEG 400 complex which cause the free flowing nature to the liquisolid granules. The flowability of powders is governed by 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. Typically the 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.

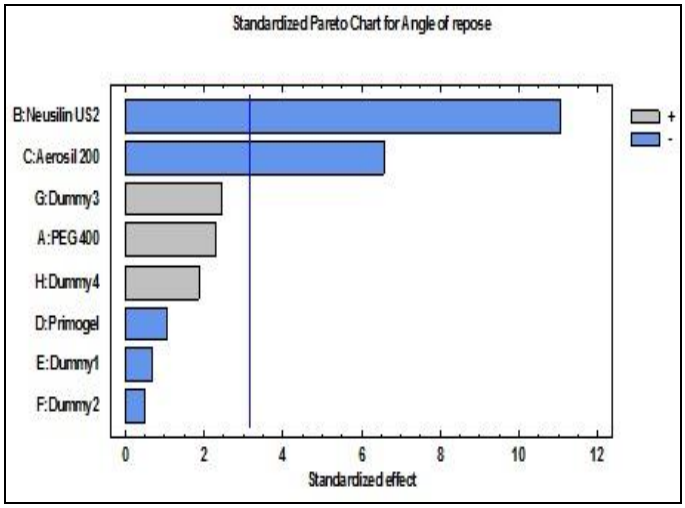

FIG.3: PARETO CHART OF THE STANDARDIZED EFFECTS OF INDEPENDENT FACTORS ON ANGLE OF REPOSE

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, thereby increasing the distance, and reducing the attractive forces between them. The hydrophilic nature of Aerosil 200 allows it to attract and preferentially bind moisture, 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 improvement in the flow property of liquisolid formulation powder. Neusilin US2 and Aerosil 200 had showed negative effect as confirmed by least p value 0.0016 and 0.0072 respectively denoted in **Table 7.**

This indicates 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. The ANOVA results confirm that Neusilin US2 and Aerosil 200 exhibit p-values less than 0.05 indicating that the factors are significantly different from zero at 95.0% confidence level. The regression coefficient for angle of repose indicates 98.38% of variability around the mean.

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

Angle of repose = 124.927 + 0.0120333*A - 0.405146*B - 0.518911*C - 1.36667*D - 0.183333*Dummy1 - 0.133333*Dummy2 + 0.638333*Dummy3 + 0.491667*Dummy4

Based on the above findings the input factors Neusilin US2 and Aerosil 200 should be fixed at appropriate values for further optimization studies.

Effect on Thickness:

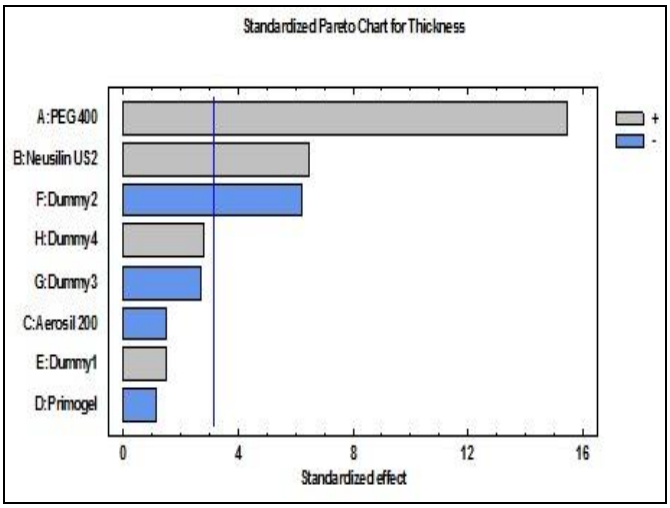

FIG.4: PARETO CHART OF THE STANDARDIZED EFFECTS OF INDEPENDENT FACTORS ON THICKNESS

Thickness was found to be in range of 4.15 – 4.9 mm depending on the excipient concentration shown in **Table 6**. The Pareto chart **Fig. 4** indicates that the factors PEG 400 and Neusilin US2 concentration possess significant influence on the thickness of liquisolid tablet. PEG 400 and Neusilin US2 had showed positive effect as confirmed by least p value 0.0006 and 0.0075 respectively denoted in **Table 7**.

This indicates that as the concentration of PEG 400 and Neusilin US2 changes thickness varies. As the PEG 400 concentration increases the thickness of liquisolid tablet decreases which results into squeezing out of PEG 400 during compression. 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 decreases. This is due to coating of Neusilin US2 particles to drug and PEG 400 complex and avoids the squeezing out of PEG 400 as it adsorbs on the drug and PEG 400 complex. Thus there is combined positive effect of PEG 400 and Neusilin US2 on the liquisolid tablet thickness. The ANOVA results confirm that Neusilin US2 and Aerosil 200 exhibit p-values less than 0.05 indicating that the factors are significantly different from zero at 95.0% confidence level. The regression coefficient for angle of repose indicates 99.13% of variability around the mean.

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

Thickness = 3.77639 + 0.00425*A + 0.0125146*B - 0.00630358*C - 0.0791667*D + 0.0208333*Dummy1 - 0.0858333*Dummy2 - 0.0375*Dummy3 + 0.0391667*Dummy4

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

Effect on Hardness:

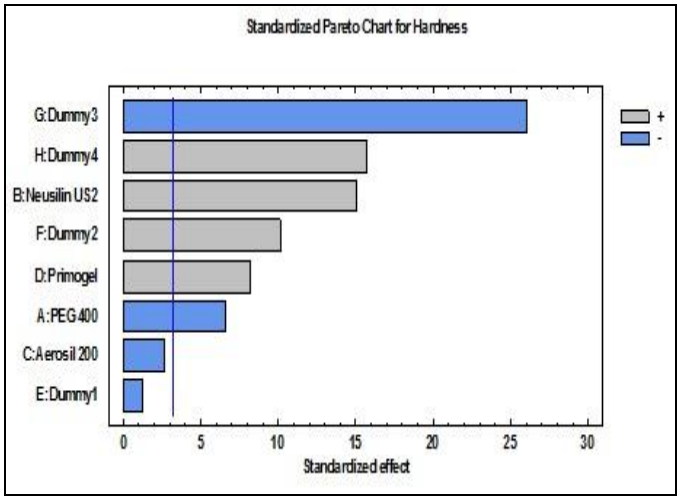

FIG. 5: PARETO CHART OF THE STANDARDIZED EFFECTS OF INDEPENDENT FACTORS ON HARDNESS

Hardness was found to be in range of 4.13 – 5.2 kg/cm^2 depending on the excipient concentration shown in **Table 6**. The Pareto chart **Fig. 5** indicates that the factors Neusilin US2, Primojel and PEG 400 concentration possess significant influence on the angle of repose. Neusilin US2 and Primojel had showed positive effect as confirmed by least p value 0.0069 and 0.0006 respectively denoted in **Table 7**. Neusilin US2 is superior in compressibility. Neusilin US2 makes hard tablets at low compression force and in addition, improves the hardness of other filler and binder excipients. Neusilin US2 with combination of Primojel and lactose here improves the hardness and increases the bulk of tablet. But concentration of lactose is same in all trials so there is no individual effect of lactose here on hardness. Increase in hardness and compression pressure did not affect the disintegration time and as well as friability.

This indicates that as the concentration of Neusilin US2 and Primojel increases hardness of liquisolid tablet increases. PEG 400 showed negative effect confirmed by least p value 0.0038 as shown in **Table 7**. As PEG 400 increases the hardness of tablet decreases as it exhibit the more porosity to liquisolid formulation. The ANOVA results confirm that Neusilin US2, Primojel and PEG 400 exhibit p-values less than 0.05 indicating that the factors are significantly different from zero at 95.0% confidence level. The regression coefficient for angle of repose indicates 99.78% of variability around the mean.

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

Hardness = -6.23907 - 0.00126667*A + 0.020117*B - 0.0075643*C + 0.391667*D - 0.0116667*Dummy1 + 0.0966667*Dummy2 - 0.248333*Dummy3 + 0.15*Dummy4

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

Evaluation of pre compression parameters:

From **Table 8,** Angle of repose was found to be in the range of 26.15 – 37.09° which indicated good flow for all the batches, Carr's index was found to be less than 20 which indicated good flowability for all the batches and Hausner's ratio were found to be in between 1.07 to 1.18 showed good flow ability.

TABLE 8: ANGLE OF REPOSE, HAUSNER'S RATIO AND CARR'S INDEX OF FORMULATIONS F1 TO F12

Batches	Angle of repose	Hausner's ratio	Carr's index
F1	35.11	1.18	15.42
F2	31.29	1.16	12.34
F3	32.36	1.16	12.78
F4	34.88	1.13	14.56
F5	31.11	1.11	11.46
F6	26.15	1.14	14.22
F7	35.02	1.17	15.66
F8	27.37	1.12	11.42
F9	37.09	1.07	15.76
F10	33.1	1.17	13.52
F11	33.58	1.17	13.76
F12	25.86	1.12	11.29

Evaluation of post compression parameters:

As shown in **Table 9,** Hardness and thickness of liquisolid tablet was found to be in the range of 4.13 to 5.2 kg/cm^2 and 4.15 to 4.9 mm respectively. Friability of tablets was found to be below 1% which is acceptable. Disintegration time of liquisolid tablets were in the range of 1-2 minutes. Drug content of all liquisolid tablet were found to be in between acceptable range.

TABLE 9: EVALUATION OF POST COMPRESSION PARAMETERS OF FORMULATIONS F1 TO F12

Batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (min)	Drug content (%)
F1	4.2	4.67	0.18	1.13	98.98
F2	4.4	4.80	0.28	1.20	99.16
F3	4.9	4.23	0.29	1.17	97.45
F4	5.2	4.20	0.13	1.25	96.12
F5	5.2	4.9	0.23	1.09	102.01
F6	4.8	4.42	0.26	1.20	101.01
F7	4.6	4.27	0.14	1.22	100.02
F8	5.18	4.78	0.10	1.18	99.12
F9	4.13	4.47	0.24	1.25	97.14
F10	4.79	4.40	0.19	1.23	98.52
F11	4.5	4.20	0.15	1.18	98.71
F12	4.66	4.15	0.20	1.16	97.34

***In vitro* drug release:**

TABLE 10: *IN VITRO* DRUG RELEASE OF FORMULATIONS F1 TO F6

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	51.14	54.16	50.14	53.38	56.42	53.56
4	70.13	67.35	64.84	61.23	68.31	68.24
6	85.01	81.25	76.25	68.57	79.15	74.35
8	89.08	88.58	84.37	78.25	86.21	78.87
10	92.13	98.25	94.27	85.86	94.32	87.36
15	94.08	99.14	96.28	90.24	97.36	96.28
20	96.13	-	97.63	94.11	99.41	97.21
25	97.20	-	100.28	97.43	-	101.22

The percent release of OLM from liquisolid tablet containing varying amounts of Neusilin US2 (carrier material) and Aerosil 200 (coating material) from F1 to F12 was found to be approximate 100.00% up to 30 min as shown in **Fig.6 and 7**. This indicates the fast release of drug is observed from above formulations. The batch F2 showed the highest drug release 99.14% at 15 min

when compared to all other batches. The %drug release of all the formulations was showed in **Table 10** and **11**. The obtained results of *in vitro* drug release showed a relationship between the carrier to coating material ratio and the *in vitro* release of OLM from liquisolid tablets. An increase in the R-value results in an enhanced release rate as there is presence of Neusilin US2 and Aerosil 200 are used as carrier and coating materials, respectively.

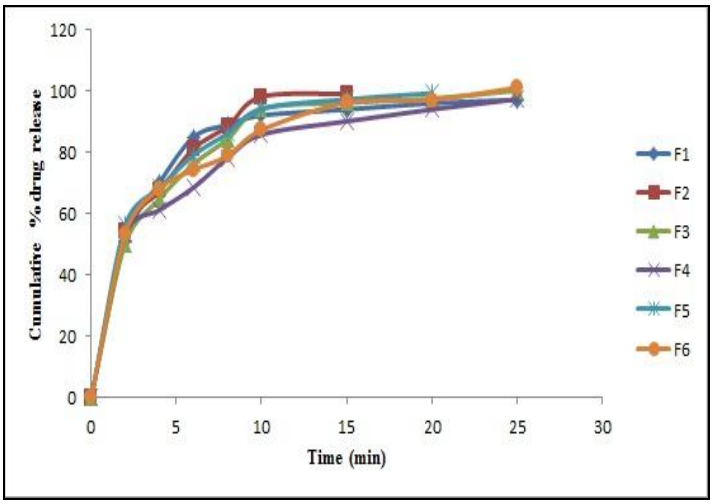

FIG.6: DISSOLUTION PROFILE OF FORMULATIONS F1 TO F6

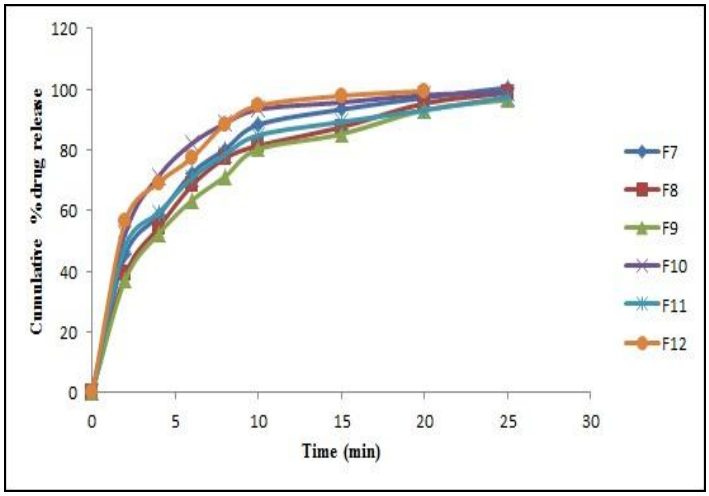

FIG.7: DISSOLUTION PROFILE OF FORMULATIONS F7 TO F12

Neusilin US2 in combination with the superdisintegrant Primojel cause the faster disintegration of liquisolid tablet and shows higher drug release in less time.Liquisolid formulation with high R-values contains high quantity of Neusilin US2, low quantities of Aerosil 200, and low liquid/powder ratios.

This is associated with enhanced wicking, disintegration and thus, enhanced drug release showed by batch F2. 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 such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus slowers down release rates 15, 5.

Therefore, Spireas *et al*, recommend a minimum R-value of 20 which is considered in batch F2.Therefore, liquisolid formulation F2 batch of OLM contains high quantity of Neusilin US2, low quantity Aerosil 200, high R value and low drug concentration which gives us the enhanced solubility and hence fast dissolution.

TABLE 11: *IN VITRO* DRUG RELEASE OF FORMULATIONS F7 TO F12

Time (min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
2	45.49	39.12	37.27	52.41	48.43	56.74
4	58.34	54.46	52.32	71.31	59.32	69.17
6	72.34	68.24	63.36	82.10	70.75	77.35
8	80.21	77.26	71.24	88.72	78.52	88.47
10	88.32	81.38	80.24	93.36	84.86	94.58
15	93.36	87.52	85.2	95.68	89.24	97.82
20	97.21	95.34	93.18	98.11	93.11	99.36
25	100.53	98.82	96.52	98.91	97.43	-

DSC:

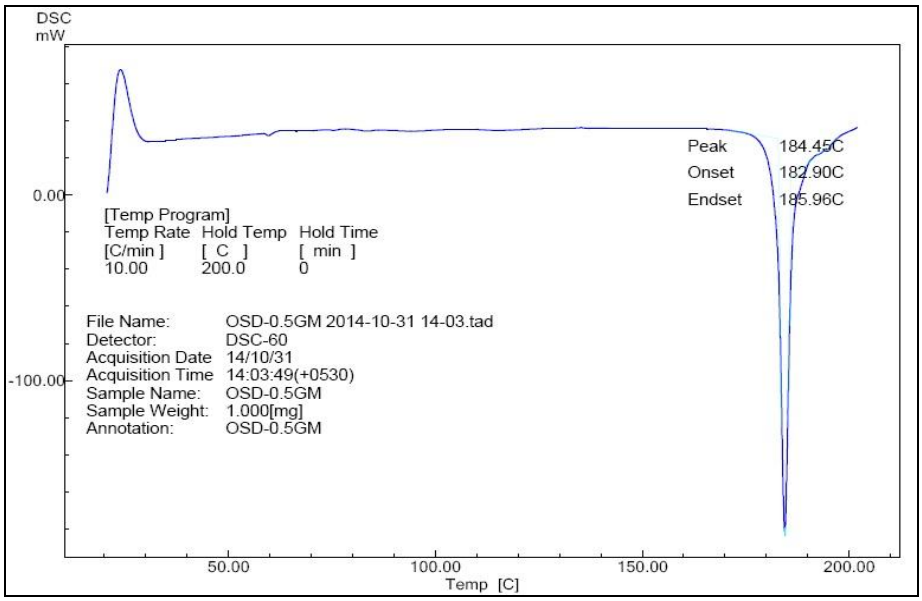

FIG.8: DSC THERMOGRAM OF OLM

It was reported that OLM has melting point of 175-180 ºC. DSC thermogram of OLM **Fig.8** shows a sharp characteristic endothermic peak at 184.45ºC corresponding to its melting (onset at 182.90ºC and endset at 185.96ºC) indicating its crystalline nature

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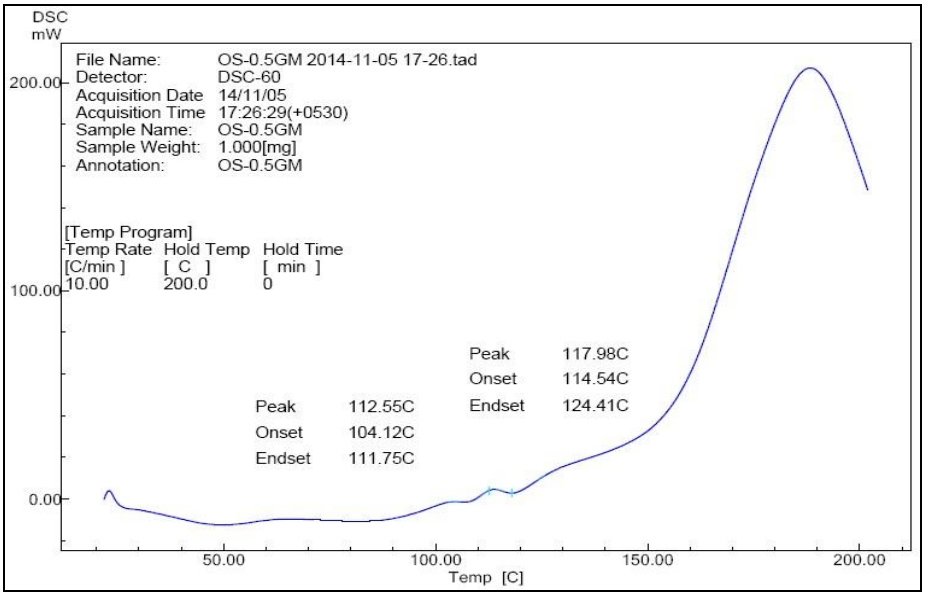

FIG.9: DSC THERMOGRAM OF LIQUISOLID FORMULATION

In the DSC thermogram of liquisolid formulation **Fig. 9** there is disappearance of sharp peak and two small indistinct endothermic peaks were observed. Thus there is no melting in the mixture which indicates the conversion of crystalline to amorphous nature by the liquisolid technique.

PXRD:

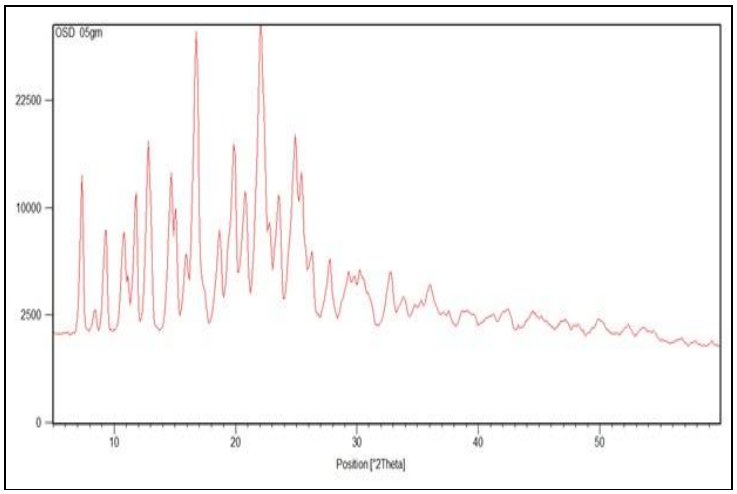

FIG.10: PXRD OF OLM

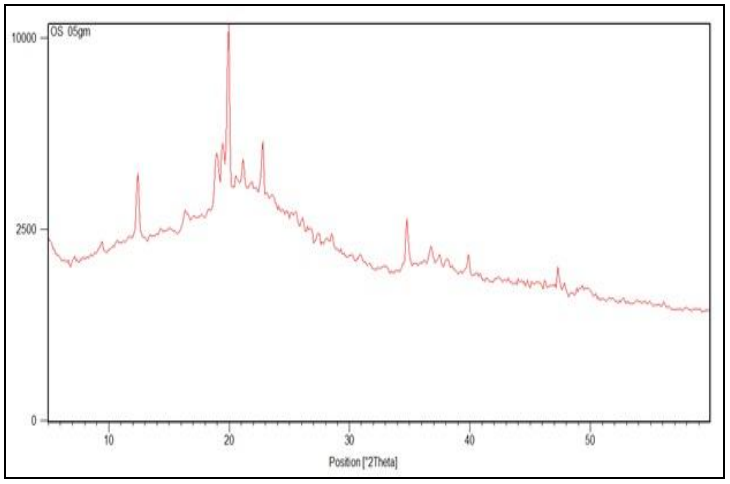

FIG.11: PXRD OF LIQUISOLID FORMULATION

The diffraction pattern of OLM **Fig.10** revealed several sharp high intensity peaks suggesting that the drug existed as crystalline material. The XRD patterns of OLM and liquisolid formulation were compared. It was observed that there is reduction in the peak intensity in XRD pattern of liquisolid formulation **Fig.11**. This diminished peak suggests conversion of drug into amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rates by liquisolid formulation. As shown in **Fig.12 a), c)** and **e),** SEM analysis indicated OLM of irregular shapes and sizes. SEM analysis in **Fig.12 b), d)** and **f),** of the batch F2 liquisolid formulation showed spherical granules which are observed due to the presence of Neuslin US2 and coating by Aerosil 200 on the liquisolid powder. Powder was observed in the dispersed state which gives the idea of free flowing nature.

Stability studies:

Stability studies for the optimized tablets 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. Hence, it was concluded that the F2 batch tablets have good stability during their shelf life.

SEM:

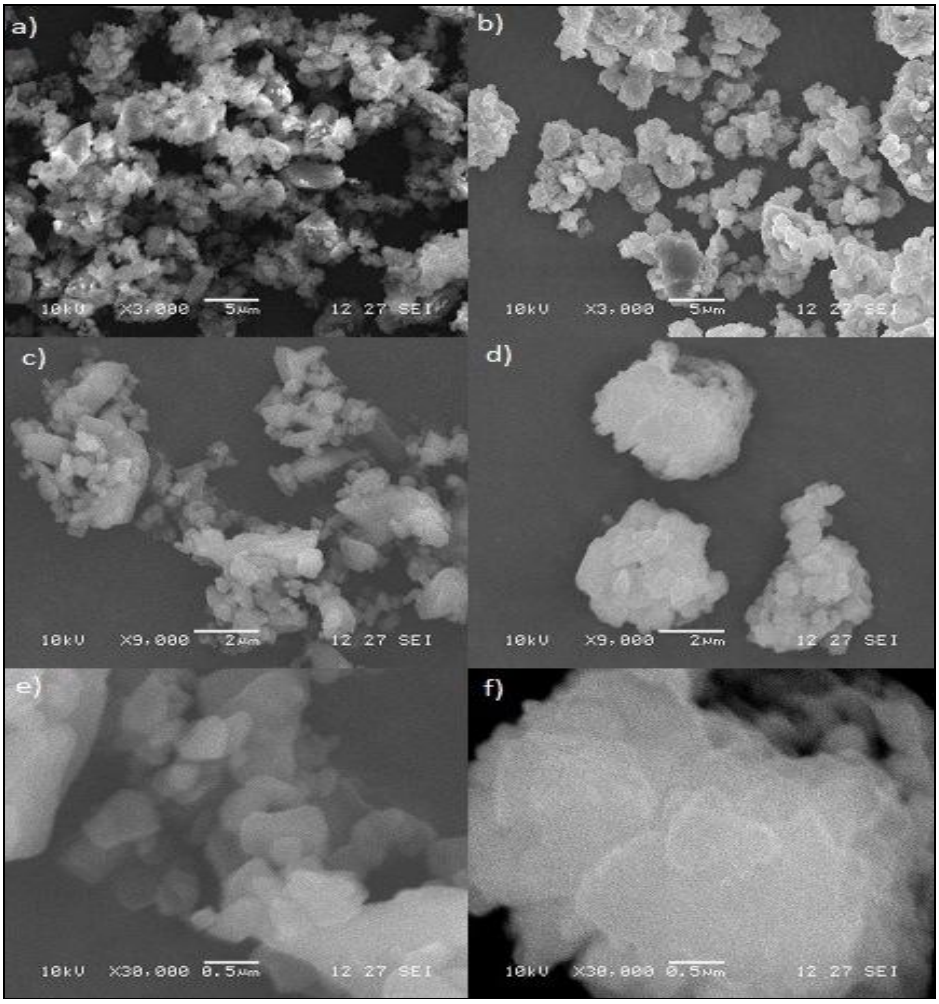

FIG.12: A), C), E) SEM IMAGE OF OLM AND B), D), F) SEM IMAGE OF LIQUISOLID FORMULATION

CONCLUSION: OLM has low solubility and low bioavailability. Hence Liquisolid technique was selected to develop the liquisolid compacts of OLM, to obtain fast dissolving effect which enhances the bioavailability. Liquisolid tablets of OLM 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 Plackett Burman ObD approach to study the effect of factors affecting the responses of OLM liquisolid formulation. Factors like Neusilin US2, Aerosil 200, PEG 400 and Primojel were found to have significant effect on responses like angle of repose, thickness and hardness. The dissolution of OLM of batch F2 was enhanced due to the presence of high quantity of Neusilin US2, low quantity Aerosil 200, high R value, low drug concentration and high quantity of Primojel. PB design was proved to be appropriate tool to study effect of parameters on the response variables and to recognize the most influencing factor. It was concluded that OLM liquisolid compacts showed significant increase in dissolution as compared to marketed tablets using PB design.

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