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FORMULATION AND OPTIMIZATION OF LIQUISOLID TABLETS OF OLMESARTAN MEDOXOMIL USING 3² FACTORIAL DESIGN

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ABSTRACT: Olmesartan medoxomil, a BCS class II drug, is an angiotensin-II receptor antagonist used for the treatment of hypertension. A liquisolid tablet of Olmesartan medoxomil was developed to improve its dissolution and flow properties. The commonly used carrier Avicel was compared with Neusilin. Because of higher liquid load factor, Neusilin was selected as a carrier for further optimization study using 3² Factorial design. Two independent factors, % drug concentration in a liquid vehicle (X1) and carrier coating ratio (X2) were studied, each with three levels and the systems was assessed for two dependent variables; % drug dissolution and angle of repose. Mathematical equations and response surface plots were used to relate the dependent and independent variables. All prepared liquisolid formulations were characterized for pre-and post- compression parameters. The optimized formulation F7 (15% drug concentration and 30 carrier coating ratio) was tested for X-ray powder diffractometry and FTIR. Results showed that maximum drug dissolution was exhibited by systems with minimum drug concentration in liquid vehicle and optimum carrier to coating ratio. Optimized formulation displayed significantly enhanced dissolution profiles than that of marketed formulation. In conclusion, avicel could be replaced by neusilin for the formulation of low weight liquisolid tablets along with increased dissolution.

INTRODUCTION: Over past few years, various formulation techniques have been developed, to improve the solubility and dissolution of poorly soluble substances, with different degrees of success. There are multiple methods which have been used for past many years, to enhance the dissolution characteristics of water-insoluble drugs which include micronization, lyophilisation, soliddispersion. Out of which the recent research focus on "liquisolid compact technique" is one of the successful tools to achieve the goal [1].

Several researchers have shown that the liquisolid technique is one of the most promising methods for enhancing the dissolution rate of poorly water-soluble drugs. Liquisolid systems are considered as acceptably flowing and compressible powdered forms of liquid medications that imply oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable non-volatile solvent systems.

Various grades of cellulose, starch, lactose, *etc.*, may be used as the carriers, whereas very fine particle size silica powders may be used as the coating (or covering) materials. A new formulation-mathematical model is provided by Spireas S. *et al.,* to calculate the optimum quantities of carrier and coating materials required to yield acceptably flowing and compressible liquid / powder admixtures.

This model was based upon the theory that the carrier and coating materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties [2-4]. Liquisolid Compacts of poorly soluble drugs containing a drug molecularly dispersed in a solubilizing vehicle show enhanced drug dissolution due to an increased surface area of drug, an increased aqueous solubility of the drug, and an improved wettability of the drug particle. Accordingly, this improved drug dissolution may result in higher drug absorption and thus, an improved oral bioavailability [5, 6].

Olmesartan medoxomil is chemically 2, 3-dihydroxy-2-butenyl 4-[1-hydroxy-1-methylethy]-2-propyl- 1- [p(o- 1H- tetrazol- 5-ylphenyl) benzyl] imidazole-5-carboxylate, cyclic 2,3-carbonate [7]. Clinical studies have suggested that Olmesartan medoxomil exerts a beneficial effect on the treatment of hypertension. It is an Angiotensin II receptor blocker. It is a white crystalline powder and has limited solubility [8]. Olmesartan medoxomil has poor flow properties and undesirable dissolution properties.

In this study, formulation and optimization of liquisolid tablets were done using Olmesartan medoxomil as a model drug. The formulation of a high dose, poorly soluble drug is one of the limitations of the liquisolid technique. As the release rate of drug is proportional to fraction of dispersed drug in liquid vehicle, higher dose requires higher liquid amount. Also, to maintain acceptable flowability and compressibility, high levels of carrier and coating materials are needed. However, this results in an increase in tablet weight and sizes which are difficult to swallow [9]. To overcome this, the commonly used carrier Avicel PH102 was compared and replaced with highly adsorptive carrier Neusilin US2. The drug dissolution study of all batches was assessed, and optimized batch obtained from experimental design was compared with the marketed formulation.

MATERIALS AND METHODS:
Materials: Olmesartan medoxomil API was kindly gifted by Glenmark Pharmaceuticals, Mumbai. Propylene glycol, Tween 20, Tween 80, PEG 400, PEG 200 and Glycerine were obtained from Research Lab Fine Chem Industries, Mumbai. Neusilin US2 was obtained from Gangwal

Chemicals Pvt. Ltd. Mumbai (Fuji Chemical Industry, Japan). Microcrystalline cellulose (Avicel PH-102) was purchased from Reliance Cellulose Products Ltd. Mumbai. Aerosil was purchased from Degussa Evonik, Mumbai. Croscarmellose sodium was obtained from Navketan pharma, Aurangabad. All other reagents and solvents used were of the analytical or pharmacological grade.

Solubility Study: To select the best non-volatile solvent for the liquisolid formulation, solubility study of Olmesartan medoxomil was done in various solvents like propylene glycol, polyethylene glycol 200, polyethylene glycol 400, glycerine, Tween 20 and Tween 80 by shake flask method. An excess amount of drug was added to each vial containing 1ml of solvent mentioned above. The solutions were placed on a rotary shaker for 48 hr at room temperature. The drug concentration in each supernatant was analyzed by UV spectrophotometer at 257 nm [10].

Angle of Slide Measurement (θ): The angle of slide is used as a measure of flow properties of powders. Two grams of powder excipients were weighed accurately and placed at one end of an aluminummetal plate with a polished surface. This end was raised gradually until the plate made an angle θ with the horizontal at which the powder was about to slide. This angle θ represented the angle of slide. The angle of slide corresponding to 33° considered as optimal flow properties [11-13].

Flowable Liquid Retention Potential Determination (Φ- value) [13]: The liquid vehicle with increasing amounts was added and mixed well with 10gm of each material (carrier and coating). At each concentration of liquid vehicle added, the angle of slide was re-determined as stated above. The corresponding Φ-value calculated from equation,

$$\Phi-\text{value} = \text{weight of liquid} / \text{weight of solid}$$

The Φ-values were plotted graphically against the corresponding angles of slide θ. The Φ-value corresponding to an angle of slide of 33° represented the flowable liquid retention potential (Φ–value) of that material. The Phi value for carrier and coating material has been abbreviated as Φ_{CA} and Φ_{CO} respectively [14, 15].

Calculation of Loading Factor (L_f), amount of Carrier Material (Q) and Coating Material (q) [14, 16]: By using Phi value of carrier and coating material, the liquid load factor (L_f) and quantities of carrier and coating materials were calculated by using following formula:

$$L_f = \Phi_{CA} + \Phi_{CO}. (1/R)$$
$$L_f = W/Q$$
$$R = Q/q$$

Where, L_f- Loading factor.
Φ_{CA}- Flowable liquid retention potential of the carrier material.
Φ_{CO} - Flowable liquid retention potential of coating material.
R- Ratio of Carrier and Coating material (Q/q)
W- Weight of Liquid vehicle.

Formulation of Comparative Batches of Liquisolid Tablets Using Avicel and Neusilin as a Carrier: To select the best carrier for the further optimization study, liquisolid powder systems were prepared using carriers (Avicel PH102) and (Neusilin US2) separately. The desired quantity of the previously weighed solid drug (Olmesartan medoxomil) was dissolved in liquid vehicle (Tween 20). Next, the calculated weights (W) of the resulting liquid medications (equivalent to 20mg drug) were incorporated into the calculated quantities of the carrier material Avicel (Q) and mixed thoroughly. The resulting wet mixture was blended with the calculated amount of the coating material (Aerosil 200) (q) using a standard mixing process to form a simple admixture [17, 18].

Several factors were varied like the concentration of the drug in liquid vehicle Tween 20 *i.e.* 15%, 25%, 35% w/w and carrier: coat ratios (different R values) ranging from 10 to 30. Finally, 5% w/w of croscarmellose sodium as a disintegrant was mixed with the above mixture for 10 min. The same procedure was repeated for the formulation of liquisolid systems using Neusilin as a carrier material and (Aerosil 200) as a coating material. The composition of the tablets is shown in **Table 1.**

TABLE 1: COMPOSITION OLMESARTAN MEDOXOMIL LIQUISOLID TABLETS USING AVICEL (LS-A) AND NEUSILIN (LS-N) AS CARRIER

Batch no.	% Drug Conc.	R (Q/q)	W	L_f	Q (W/L_f) Avicel / neusilin (mg)	Q Aerosil	CCS (mg)	Total wt. (mg)
LS-A1	15	10	133.33	0.292	456.61	45.66	31.78	667.38
LS-A2	25	10	80	0.292	273.97	27.40	19.06	400.43
LS-A3	25	20	80	0.160	500.00	25.00	30.25	635.25
LS-A4	35	10	57.14	0.292	195.68	19.57	13.62	286.01
LS-A5	35	20	57.14	0.160	357.13	17.86	21.60	453.73
LS-A6	35	30	57.14	0.116	492.59	16.42	28.30	594.45
LS-N1	15	10	133.33	1.584	84.17	8.41	11.29	237.2
LS-N2	25	10	80	1.584	50.50	5.05	6.77	142.32
LS-N3	25	20	80	1.452	55.09	2.75	6.89	144.73
LS-N4	35	10	57.14	1.584	36.07	3.60	4.84	101.65
LS-N5	35	20	57.14	1.452	39.35	1.96	4.92	103.37
LS-N6	35	30	57.14	1.408	40.58	1.35	4.95	104.02

W-weight of liquid medication (drug + liquid vehicle); L_f-liquid load factor; Q-weight of carrier material; q-weight of coating material; R-carrier: coating ratio; CCS-Croscarmellose sodium; LSA1-LSA6: Formulations using avicel; LSN1-LSN6: Formulations using neusilin.

Pre-compression Study: The flow properties of the liquisolid systems were estimated by determining the angle of repose, Carr's index, and Hausner's ratio. The angle of repose was measured by the fixed funnel and free standing cone method. The bulk density and tap densities were determined for the calculation of Hausner's ratio and Carr's Index [19].

Tablet Preparation: The final powdered mixture of liquisolid powder system was compressed into tablets of desired weight of 20mg strength each using 10 stations rotary tablet press (FLUIDPACK-GMP Model) flat faced punch and die, size of 8mm were used. Weight adjustment knob, pre-compression force knob, and the thickness knob were adjusted to obtain tablets with good integrity

and strength. All the tablets were evaluated as follows.

Tablet Hardness, Friability Test and Disintegration Test: The hardness of the liquisolid tablets was evaluated by using Pfizer hardness tester. Friability test was performed by using Roche friabilator. Disintegration test of all formulation was carried out in distilled water by using Disintegration test apparatus [19, 20].

Drug Content Uniformity: Ten tablets from each batch were powdered individually, and a quantity equivalent to 20mg of Olmesartan medoxomil was accurately weighed and extracted with a suitable volume of methanol. Each extract was suitably diluted and analyzed spectrophotometrically at 257 nm using UV-visible spectrophotometer [21].

***In vitro* Drug Dissolution Study:** The *in vitro* drug dissolution study was performed by using USP dissolution type II apparatus (Lab India Disso-2000) at 37 ± 0.5 °C using phosphate buffer pH 6.8 (900ml) as dissolution medium and 50rpm. The required amount of aliquots were withdrawn at a suitable time interval (5, 10, 15, 20, 30, 45 and 60 min.) and filtered through 0.45µm filter paper and diluted as per need with phosphate buffer pH 6.8. The samples were then analyzed at λ_{max} of 257 nm by UV-visible spectrophotometer [21].

Optimization of Process Variables by Applying 3^2 Factorial Design: From the comparative study of carriers, avicel and neusilin, neusilin was selected for further optimization study. Three level two factors, 3^2 factorial design was employed for the preparation of the liquisolid tablets using neusilin as a carrier. Two independent factors were studied, each at three levels and experimental trials were performed at nine possible combinations. The percent drug concentration in liquid vehicle and excipient ratio (neusilin aerosil ratio) were selected as independent variables. The percent drug dissolution and angle of repose were selected as dependent variables. The coded and the actual values of the experimental design are given in **Table 2.** Various computations for the current optimization study were performed using Design Expert software (Design Expert trial version 8.0.7.1; State-Ease Inc., Minneapolis, MN, USA) [22]. The composition of the tablets is shown in **Table 3.**

TABLE 2: TRANSLATION OF CODED LEVELS TO ACTUAL VALUES

Coded values	Actual values	
	X1	X2
-1	10	15
0	20	25
+1	30	35

X1 = Neusilin: Aerosil (Carrier: coating ratio R)
X2 = % Drug concentration in liquid vehicle.

TABLE 3: COMPOSITION OF OLMESARTAN MEDOXOMIL LIQUISOLID SYSTEMS BY FACTORIAL DESIGN

Batch no.	% Drug Conc.	R (Q/q)	W	L_f	Q (W/L_f) Neusilin (mg)	Q Aerosil (mg)	CCS (mg)	Total wt. (mg)
F-1	15	10	133.33	1.584	84.17	8.41	11.29	237.2
F-2	25	10	80	1.452	50.50	5.05	6.77	142.32
F-3	35	10	57.14	1.408	36.07	3.60	4.84	101.65
F-4	15	20	133.33	1.584	91.82	4.59	11.48	241.22
F-5	25	20	80	1.452	55.09	2.75	6.89	144.73
F-6	35	20	57.14	1.408	39.35	1.96	4.92	103.37
F-7	15	30	133.33	1.584	94.69	3.15	11.55	242.72
F-8	25	30	80	1.452	56.81	1.89	6.93	145.63
F-9	35	30	57.14	1.408	40.58	1.35	4.95	104.02

An appropriate amount of liquid medication containing 20mg of drug was incorporated in each tablet.

Evaluation Study: Pre-compression and post compression evaluation of formulations was done as discussed earlier for the comparative trial batches.

Characterization of Optimized Batch: The optimized batch was subjected to following characterization studies.

***In vitro* Drug Dissolution Study:** The dissolution profile of optimized batch of liquisolid tablets was compared with the conventional marketed tablets of Olmesartan medoxomil (Olmesar) by using USP dissolution type II apparatus (Lab India Disso-2000) at 37 ± 0.5 °C using phosphate buffer pH 6.8 (900ml) as dissolution medium and 50rpm. Appropriate aliquots were withdrawn at a suitable

time interval (5, 10, 15, 20, 30, 45 and 60 min.) and filtered through 0.45µm filter paper and diluted as per need with phosphate buffer pH 6.8. Samples were analyzed at λ_{max} of 257 nm by UV-visible spectrophotometer [21].

X-RAY Powder Diffractometry (XRPD): For characterization of crystalline state, the X-ray powder diffraction studies of the optimized batch were carried out by using, X-Ray diffractometer (Model: D2 PHASER Germany), with a copper target, at a voltage of 30 kV and current of 10 mA. The scanning angle ranged from −3 to 160°.

Fourier-transform Infrared Spectroscopy (FTIR): FTIR spectra of Olmesartan medoxomil and optimized formulation were recorded on FTIR spectrophotometer (JASCO FTIR-410), using KBr pellet method.

Stability Study: The optimized Liquisolid formulation (F-7) packed in aluminum foil was placed in a glass container and then subjected to a stability study at 40 °C/75 % RH for 45 days. Samples were withdrawn at 15-day time intervals and evaluated for physical properties, drug content and drug dissolution.

RESULT AND DISCUSSION:

Solubility Study: The **Table 4** shows solubility data of Olmesartan medoxomil in various non-volatile solvents. It showed more solubility in Tween 20 as compare to others. Thus, to minimize the required amount of liquid, Tween 20 was chosen as the non-volatile liquid vehicle for the formulation of liquisolid tablets.

TABLE 4: SOLUBILITY OF OLMESARTAN MEDOXOMIL

Solvent	Solubility[*] (mg/ml)
Propylene glycol	3.06 ± 0.056
PEG- 200	13.62 ± 0.22
PEG- 400	13.97 ± 0.09
Glycerin	0.396 ± 0.05
Tween 20	18.83 ± 0.18
Tween 80	17.69 ± 0.14

[*]mean ± S.D. n = 3

TABLE 5: LIQUID LOAD FACTOR OF EXCIPIENTS

R	L_f (Neusilin and Aerosil)	L_f (Avicel and Aerosil)
10	1.584	0.292
20	1.452	0.160
30	1.408	0.116

Flowable Liquid Retention Potential (Φ- value) and Liquid Load Factor Determination: The angle of slide of both carrier and coating material was determined for the determination of flowable liquid retention potential which is required for calculation of Liquid load factor. **Fig. 1**, Illustrates the relation between the angle of slide and flowable liquid retention potential. It shows that the Flowable Liquid Retention Potential (Φ -value) for Neusilin corresponding to an angle of slide of 33° was approximately equal to1.32, for Avicel PH 102 it was 0.0275 and for Aerosil 200 it was 2.64. Readings for Liquid load factor are shown in **Table 5**. From the table, it shows that liquid load factor of Neusilin is more than that of Avicel. Despite such a high liquid load factor, the formulation fulfilled the required flow ability and tablet hardness. The high liquid loading capacity may be explained by its extremely high specific surface area [23].
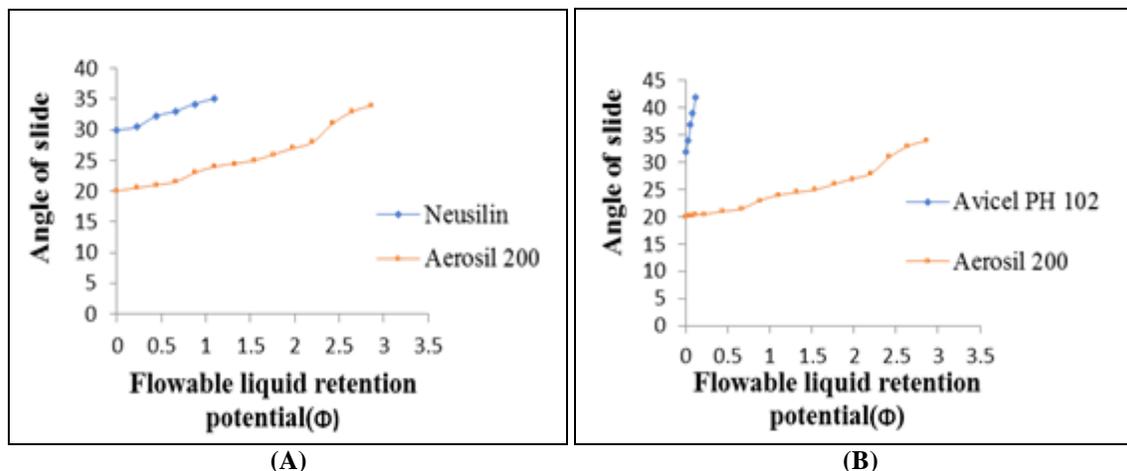

(A)   (B)

FIG. 1: (A) RELATION BETWEEN FLOWABLE LIQUID POTENTIAL OF NEUSILIN AND AEROSIL 200 (B) RELATIONS BETWEEN FLOWABLE LIQUID POTENTIAL OF AVICEL PH-102 AND AEROSIL 200

Pre-compression Study of Liquisolid Tablets Using Avicel and Neusilin as a Carrier: The liquisolid powder systems were subjected to flow property evaluation.

Flow Properties Evaluation: The angle of repose of Liquisolid powder systems containing avicel and aerosil was found to be in the range of 27.9° to 30.97° and other containing neusilin, and aerosil was found in the range of 25.32° to 28.78° indicating acceptable flow properties, and this was further supported by lower Carr's index value. Values of carr's index for the avicel liquisolid system was found to be 17.14 to 22.11, and for the neusilin liquisolid system, it was found to be 16.66 to 22.00 which showed that powder flow was fair to pass limit. Hausner's ratio was found to be in a range of 1.22 to 1.51 for the avicel liquisolid system and 1.20-1.31 for the neusilin liquisolid system.

Post Compression Evaluation of Tablets: After evaluation of powder characteristics, liquisolid powder systems of both avicel and neusilin were compacted into tablets which then subjected to evaluation.

Thickness, Hardness, Friability, Drug Content

and Disintegration Time Determination: The results of this evaluation study are shown in **Table 6**. The thickness of tablet was increased by an increase in the weight of the tablet and was in the range that patient could swallow tablet easily. The hardness of all the tablets was observed in the range of 4-5 kg/cm^2 depending on excipient concentration. The type of carrier has affected the hardness of tablets. The larger surface area associated with neusilin than avicel may cause an increase in contact points between particles and consequently increasing binding and crushing strength [23]. Uniform drug content was observed for all these formulations as per the IP specification (90-110%). The friability of the tablets was within the limit, and slight variation in friability was because of the difference in compression force applied and total weight. All liquisolid tablets were disintegrated within 15 min as per specifications given for the uncoated tablets in the IP. It was shown that avicel exhibited fast aqueous penetration into compacts, so act as a disintegrant. The disintegration time of tablets containing neusilin was slightly more than tablets containing avicel may be because of more hardness of former and poor disintegration property of silicate [23].

TABLE 6: EVALUATION DATA OF LIQUISOLID TABLETS USING AVICEL (LSA1-A6) AND NEUSILIN (LSN1-LSN6)

Batch. no.	Thickness* (mm)	Hardnes* (Kg/cm^2)	Weight Variation* (mg)	% Drug Content*	% Friability*	Disintegration time* (min)
LS-A1	3.5±0.12	4.5±0.05	667.48±0.76	99.23±0.36	0.51±0.05	2.94±0.28
LS-A2	2.8±0.09	4.4±0.06	400.72±0.89	98.89±0.21	0.57±0.03	5.32±0.91
LS-A3	3.0±0.06	4.6±0.08	635.3±0.68	100.09±0.23	0.52±0.02	4.28±0.39
LS-A4	2.0±0.1	4.1±0.07	286.45±0.65	99.01±0.27	0.58±0.04	7.21±0.42
LS-A5	2.5±0.07	4.3±0.01	453.52±0.60	98.70±0.50	0.55±0.01	6.91±0.36
LS-A6	2.8±0.06	4. 2±0.02	594.32±0.69	99.58±0.34	0.54±0.02	6.37±0.58
LS-N1	4.16±0.05	4.7±0.02	238.56±0.82	99.18±0.33	0.59 ± 0.02	3.21±0.34
LS-N2	3.14±0.08	4.5±0.05	143.24±0.87	98.12±0.49	0.56 ± 0.06	5.92±0.76
LS-N3	3.2±0.06	4.6±0.03	145.08±0.74	99.71±0.21	0.53 ± 0.12	5.39±0.49
LS-N4	2.7±0.1	4.2±0.07	102.41±0.66	100.08±0.6	0.55± 0.05	8.42±0.37
LS-N5	3.0±0.11	4.6±0.08	104.49±0.85	98.67±0.94	0.54± 0.14	7.63±0.24
LS-N6	3.24±0.4	4.9±0.1	105.22±0.69	99.38±0.58	0.52± 0.15	7.11±0.63

*mean ± S.D. n = 3

***In-vitro* Drug Dissolution:** As per dissolution study, the concentration of drug in the liquid vehicle has been shown to affect the dissolution rate. As per data presented in **Table 7**, faster dissolution rate obtained at lower drug concentration (15%) in both cases may be because the drug is dissolved in a large amount of liquid vehicle. However, the amount of liquid vehicle depends on the solubility of the drug in the liquid vehicle and required drug dose. Also, to adsorb higher amount of liquid vehicle, quantities of excipients should also be increased which in turn increases the weight of the tablet. It was observed that initial % drug dissolution from tablets

containing neusilin is somewhat less as compare to tablets containing avicel may be because of more hardness of tablets containing neusilin. But final drug dissolution is more from neusilin liquisolid tablets because of more amount of liquid vehicle held by neusilin. The neusilin with its high surface area and high liquid load factor can be used for the formulation of tablets with lower weights than

avicel. For 15% drug concentration, the weight of tablet containing neusilin is 237.2mg while for the same drug concentration weight of tablet containing avicel is 667.38mg. Thus, from a comparative study of these two carriers, neusilin was selected as a carrier for further optimization study using Factorial design.

TABLE 7: DISSOLUTION DATA OF LIQUISOLID TABLETS USING AVICEL (LSA1-A6) AND NEUSILIN (LSN1-LSN6)

Sr. no	Time (min)	% Drug Dissolution										
		LS-A1	LS-A2	LS-A3	LS-A4	LS-A5	LS-A6	LS-N1	LS-N2	LS-N3	LS-N4	LS-N5
1	5	39.67	36.3	37.62	35.39	36.39	35.77	35.92	34.26	34.14	33.12	33.12
2	15	62.30	61.16	61.35	58.47	58.58	60.31	61.13	60.65	59.24	56.68	56.68
3	30	79.39	78.19	79.09	75.86	76.59	80.78	83.78	78.68	79.52	75.91	75.91
4	45	86.18	85.16	86.27	83.49	84.06	86.13	89.14	85.16	86.89	84.72	84.72
5	60	89.77	87.35	86.15	82.66	84.22	85.72	94.92	91.12	93.12	86.91	88.19

Formulation of Liquisolid Tablets Using Neusilin as Carrier by using experimental design: Liquisolid powder systems of Olmesartan medoxomil were prepared as per 3^2 factorial design. From previous experimental work, neusilin

was used as a carrier for the optimization study using an experimental design. These powder systems were then subjected to evaluation of flow properties and their results are presented in **Table 8.**

TABLE 8: FLOW PROPERTIES OF LIQUISOLID POWDER SYSTEMS OF FACTORIAL DESIGN BATCHES

Formulation	Angle of repose[*] (°)	Carr's compressibility index[*]	Hausner's ratio[*]
F-1	27.43 ± 0.12	19.56 ± 0.50	1.23 ± 0.015
F-2	28.11 ± 0.09	20.65 ± 0.83	1.25 ± 0.02
F-3	31.96 ± 0.41	21.94 ± 0.80	1.27 ± 0.025
F-4	27.02 ± 0.39	16.84 ± 0.86	1.19 ± 0.016
F-5	28.73 ± 0.63	19.1 ± 0.79	1.23 ± 0.03
F-6	30.58 ± 0.19	20.43 ± 0.88	1.25 ± 0.015
F-7	26.14 ± 0.26	15.38 ± 0.59	1.17 ± 0.005
F-8	30.12 ± 0.52	20.43 ± 0.78	1.25 ± 0.015
F-9	29.82 ± 0.61	19.13 ± 0.75	1.24 ± 0.035

*mean ± S.D. n = 3

Flow Properties of the Powdered Liquisolid Systems: The angle of repose was found to be in the range of 26.14 ± 0.26 to 31.96 ± 0.41 indicating acceptable flow properties, and this was further supported by lower compressibility index values. The Carr's compressibility index for all formulations lies within the range of 15.38 ± 0.59 to 21.94 ± 0.80. Hausner's ratio was in a range of 1.17 ± 0.005 to 1.27 ± 0.025.

Evaluation Data of Liquisolid Tablets of Factorial Design Batches: Prepared liquisolid systems were compacted into tablets and subjected to various evaluation tests.

Thickness, Hardness, Friability, Drug Content and Disintegration Time Determination: The

results of evaluation study are shown in the following **Table 9**. The thickness of all formulations F-1 to F-9 was in the range of 2.63 ± 0.04 to 4.37 ± 0.06mm. The hardness of all the tablets was observed in the range of 4-5 kg/cm². It was observed that, as the amount of neusilin goes on increasing, hardness also increases. With the decrease in R values, hardness was decreased. This low hardness could be attributed to the less amount of added neusilin and poor compressibility of aerosil. Uniform drug content was observed for all the formulations as per the IP specification (90-110%). The friability of the tablet was within the limit and slight variation in friability because of the variation in compression force applied and total weight. The disintegration test revealed that the all

the liquisolid tablet were disintegrated within 15 min, which is as per specifications given for the

uncoated tablets in the IP.

TABLE 9: EVALUATION DATA OF LIQUISOLID TABLETS OF FACTORIAL DESIGN BATCHES

Formulation	Thickness* (mm)	Hardness* (Kg/cm^2)	% Friability*	Disintegration time* (min)	% Drug Content*
F-1	4.15 ± 0.05	4.21 ± 0.12	0.58 ± 0.01	2.18 ± 0.98	99.16 ± 0.32
F-2	3.12 ± 0.02	4.03 ± 0.09	0.55 ± 0.03	2.53 ± 0.76	98.78 ± 0.68
F-3	2.63 ± 0.04	4.11 ± 0.11	0.55 ± 0.02	3.12 ± 0.81	100.12 ± 0.22
F-4	4.21 ± 0.02	4.35 ± 0.16	0.54 ± 0.04	4.72 ± 0.36	98.94 ± 0.80
F-5	3.21 ± 0.03	4.11 ± 0.19	0.53 ± 0.01	5.17 ± 0.48	100.06 ± 0.15
F-6	2.9 ± 0.15	4.2 ± 0.13	0.53 ± 0.06	5.67 ± 0.27	98.87 ± 0.38
F-7	4.37 ± 0.06	4.55 ± 0.05	0.49 ± 0.04	5.48 ± 0.72	99.24 ± 0.55
F-8	3.45 ± 0.05	4.2 ± 0.14	0.52 ± 0.07	6.10 ± 0.63	99.48 ± 0.32
F-9	3.1 ± 0.13	4.4 ± 0.17	0.52 ± 0.08	6.71 ± 0.98	99.84 ± 0.27

*mean ± S.D. n = 3

***In-vitro* Drug Dissolution Study:** As per dissolution study data showed in **Table 10**, the concentration of drug in the liquid vehicle has been shown to affect the dissolution rate. The formulations with lower drug concentration showed the more dissolution might be because the drug is dissolved in more amount of liquid vehicle. But the drug concentration can be decreased to a certain

limit because of limited liquid loading capacity of the excipients. On the other hand, the increase in carrier coating ratio showed an increase in drug dissolution rate, might be because of the presence of more amount of neusilin in those formulations. The effect of these two variables was further explained by surface response plots.

TABLE 10: DATA FOR DRUG DISSOLUTION STUDY OF FACTORIAL DESIGN BATCHES

Time (min)	% Drug Dissolved*								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
5	36.20±1.21	35.22±1.35	34.60±0.73	35.23±0.79	34.14±1.22	33.32±0.92	33.72±0.86	32.90±0.97	32.27±1.09
15	60.63±0.87	60.64±1.18	57.67±0.68	60.34±0.88	59.01±1.12	58.94±0.63	59.43±0.74	58.62±1.64	57.18±0.93
30	82.78±1.11	79.35±1.31	76.12±0.79	80.59±0.72	79.15±0.98	78.69±1.17	81.73±0.93	80.69±1.21	77.77±0.86
45	89.67±1.32	86.72±0.76	80.01±0.96	88.86±1.09	86.88±1.33	81.16±0.58	90.63±1.08	87.92±1.42	84.68±1.1
60	93.35±1.24	89.02±1.3	84.12±0.83	95.89±0.95	90.83±0.76	86.01±0.81	97.05±0.65	92.81±1.23	88.72±1.02

*mean ± S.D. n = 3

Factorial Design with Surface Plot and Optimization of Process Variables: The responses (dependent variables) % drug dissolution (Y1) and angle of repose (Y2) of F-1 to F-9 batches were found to be 97.05% -84.12% and 31.96°-26.14°. The maximum drug dissolution and excellent angle of repose were observed in batch F7, having % drug concentration 15% and neusilin:aerosil ratio 30. An interactive statistical model equation was generated to evaluate the selected response which is as follows:

$$Y = b_0 + b_1 X1 + b_2 X2$$

Where Y is the predicted response, b_0 is the arithmetic mean response of 9 runs, and b_1 is the estimated coefficient for the factor X1. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low value to

its high value. (STAT-EASE, design expert trial, 8.0.7.1).

Final Equations in Terms of Actual Factors:

(Y1) % Drug dissolution = +97.40056 - 0.20567 X1 + 0.08650 X2 ………............ 1

(Y2) Angle of Repose = +26.84472 + 0.14817 X1 – 0.082833 X2 …………........2

From equations and 3D surface plots, it is evident that the independent variable (X1) % drug concentration was found to have a negative effect on drug dissolution and positive effect on the angle of repose and the (X2) neusilin aerosil ratio was found to have a positive effect on drug dissolution and negative effect on the angle of repose. That is, as % drug concentration increases, % drug dissolution from tablets decreases, may be because

of a decrease in the quantity of solvent and angle of repose increases, may be because of a decrease in the quantity of carrier and coating material which is responsible for the improvement of flow property. As the neusilin aerosil ratio increases from 10 to 30, it facilitates drug dissolution, and a decrease in angle of repose may be due to increase in neusilin

quantity. Thus, both the variable selected showed the significant impact on % drug dissolution and angle of repose of the formulation, but % drug concentration has more impact than neusilin aerosil ratio on both the responses. The 3D Surface plot for the effect of selected variables on % Drug dissolution and Angle of repose is shown in **Fig. 2.**
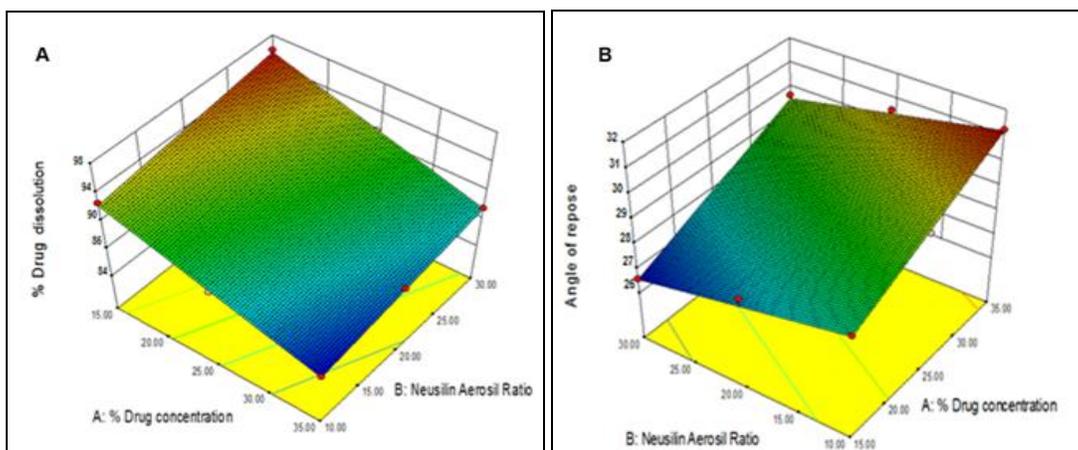
FIG. 2: 3D SURFACE PLOT FOR THE EFFECT OF SELECTED VARIABLES ON (A) % DRUG DISSOLUTION AND ON (B) ANGLE OF REPOSE

TABLE 11: ANALYSIS OF VARIANCE

Source	Response 1 (Y1): % Drug release				
	Sum of Squares	D_f	Mean Square	F-Value	p-value Prob > F
Model	29.87	2	14.93	748.76	0.0001
A- % Drug Conc.	25.38	1	25.38	1272.44	0.0001
B- Excipient ratio	4.49	1	4.49	2225.08	0.0001
Residual	0.12	6	0.020	-	-
Cor total	29.99	8	-	-	-
Source	Response 2 (Y2): % Angle of repose				
	Sum of Squares	Df	Mean Square	F-Value	p-value Prob > F
Model	17.29	2	8.64	196.22	0.0001
A- % Drug Conc.	13.17	1	13.17	299.00	0.0001
B- Excipient ratio	4.12	1	4.12	93.45	0.0001
Residual	0.26	6	0.044	-	-
Cor total	17.55	8	-	-	-

Analysis of Variance: As per ANOVA and Regression analysis data, for both the responses best fit model is linear model. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The value of correlation coefficient was found to be 0.9960, and the "Pred-R squared" of 0.9906 is in reasonable agreement with the "Adj R-Squared" of 0.9947 in case of % drug dissolution while the value of correlation coefficient was found to be 0.9849 and the "Pred-R squared" of 0.9716 is in reasonable agreement with the "Adj R-Squared" of 0.9799 in

case of Angle of Repose. The results clearly indicate that the % drug dissolution and angle of repose both are strongly affected by the variables selected for the study.

TABLE 12: SUMMARY OF REGRESSION ANALYSIS FOR RESPONSES Y1 AND Y2

Linear model	Formulations (F1-F9)		
	R^2	Adjusted -R^2	Predicted -R^2
Response Y1	0.9960	0.9947	0.9906
Response Y2	0.9849	0.9799	0.9716

Y1- % drug release, Y2- angle of repose.

Characterization of the Optimized Batch: From the different solutions obtained from Design Expert software, the F-7 batch was selected as optimized

batch having % drug concentration 15% and neusilin:aerosil ratio 30. The dissolution profile of optimized batch of liquisolid tablets was compared with the conventional marketed tablets of Olmesartan medoxomil (Olmesar). The % dissolution of the pure drug (Olmesartan medoxomil) after one hr is 38.63%, of marketed tablet it was 78.62 %, and an optimized batch of liquisolid tablet showed 97.49 % drug dissolution. According to "diffusion layer model" for dissolution, the dissolution rate is in proportion to concentration gradient in stagnant diffusion layer. Drug dissolution is directly proportional to the surface area available for dissolution.

As all the dissolution tests were conducted at a constant speed (50 rpm) and in same dissolution medium, the thickness of stagnant diffusion layer and diffusion coefficient for drug dissolution may be almost identical. Hence surface area can be considered as a major factor responsible for enhancing dissolution rate [24].

The prepared liquisolid tablets contain a drug dissolved in Tween 20 in the form of a molecular dispersion hence, the surface area of drug available for dissolution is highly increased. Thus, molecularly dispersed drug in liquisolid tablets may be responsible for greater dissolution rates compared to marketed formulations. The graph of dissolution profile comparison of the optimized batch with the marketed formulation is shown in **Fig. 3**.
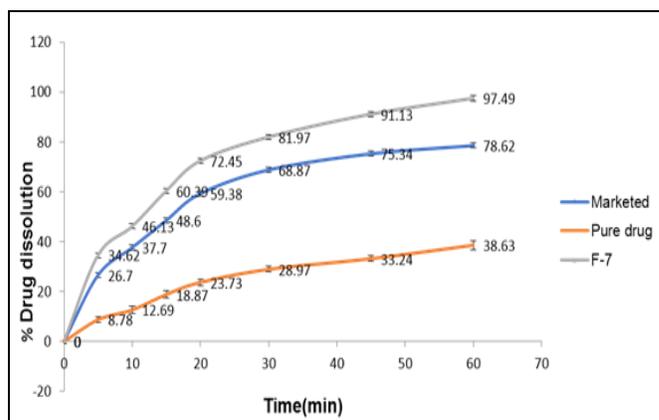

FIG. 3: DISSOLUTION PROFILE COMPARISON OF THE OPTIMIZED BATCH (F-7) WITH THE MARKETED FORMULATION

X-Ray Powdered Diffraction Study of the Optimized Batch: The powdered X-ray diffraction patterns of pure drug, excipients, and formulation are depicted in **Fig. 4**. Olmesartan medoxomil is present in a crystalline form; neusilin and aerosil are present in an amorphous form. X-ray diffraction patterns of the liquisolid formulations containing neusilin as carrier and aerosil as a coating material (F-7) showed the complete disappearance of the characteristic peaks of the drug, and this may be due to solubilisation of the drug in the liquid vehicle. The absence of crystallinity was due to solubilisation of the drug that is either absorbed or adsorbed by the carrier or coating material So, X-ray diffraction analysis was unable to differentiate the physical state of the drug in the liquisolid formulations which evidenced complete solubilisation of the drug in a liquid vehicle [25].
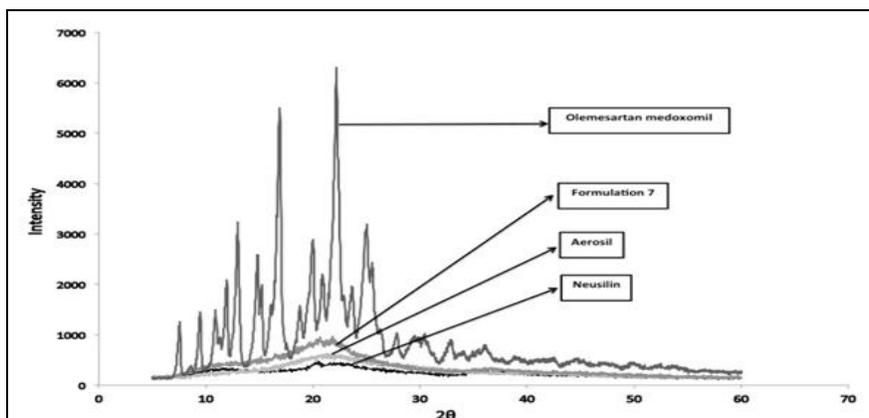

FIG. 4: X-RAY DIFFRACTION PATTERNS OF PURE DRUG (OLMESARTAN MEDOXOMIL), EXCIPIENTS AND FORMULATION (F-7)

FTIR Study of the Optimized Batch: IR spectrum of pure Olmesartan medoxomil (A) and optimized liquisolid system (B) is shown in **Fig. 5.**

The IR spectra of Olmesartan medoxomil exhibited characteristic peaks at 3429cm^{-1} due to aromatic amine stretching, 3039cm^{-1} (aromatic C-H

stretching) 1832cm^{-1} (C=O stretching of the carboxyl ion, 1476cm^{-1} because of C-N aromatic stretching and at 1053cm^{-1} (aromatic C-O-C stretching) [26]. The FTIR spectra of the optimized liquisolid system (F-7) displayed same characteristic peaks eliminating the possibility of any chemical interaction between Olmesartan medoxomil and excipients used in the formulation.
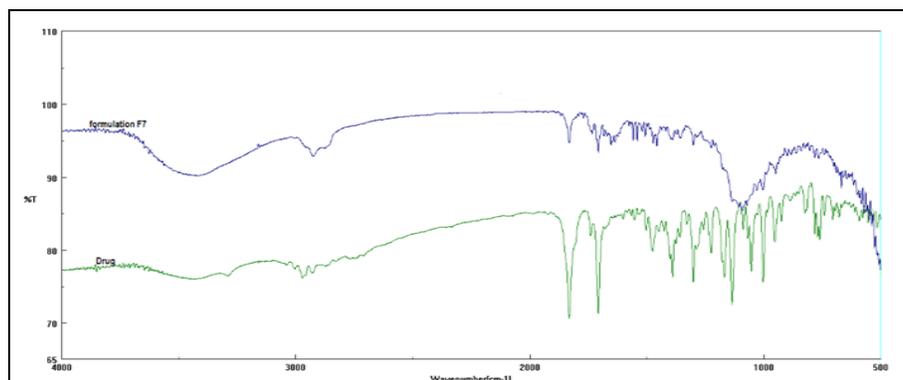

FIG. 5: IR SPECTRUM OF PURE DRUG (OLMESARTAN MEDOXOMIL) AND OPTIMIZED FORMULATION (F-7)

Stability Study: The optimized formulation (F-7) was subjected to stability studies at 40 °C / 75% RH for 45 days. Samples were withdrawn at 15-day time intervals and evaluated for physical properties, drug content and drug dissolution. Results showed that physical appearance, drug content and drug dissolution of the formulation remained unchanged.

CONCLUSION: The present study conclusively evidenced the use of 3^2 factorial design is valid for predicting the effect of percent drug concentration and excipient ratio in the optimization of liquisolid formulations. It could be shown that neusilin with its higher liquid adsorption capacity than the commonly used carrier avicel allows the production of liquisolid formulations with lower tablet weight. The application of liquisolid systems improved the solubility, dissolution and flow properties of Olmesartan medoxomil as the model drug.

CONFLICT OF INTEREST: Authors declare no conflict of interest.

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