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Formulation and Evaluation of Liquisolid Compacts of Olanzapine

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ABSTRACT

The Main objective of the present study was to enhance the dissolution rate of olanzapine by liquisolid compact method. Olanzapine is practically insoluble in water. Solubility of olanzapine was estimated in different nonvolatile solvents. The study was designed to evaluate the effect of various formulation parameters like Drug concentration and Excipient ratio on angle of repose and % drug release using 3^2 full factorial design. Quality control tests were done to evaluate each batch of tablets. Liquisolid compact powder was subjected to angle of repose, Carr's index, and hausner's ratio to determine flow property. Hardness, friability, disintegration time, drug content, dissolution rate are determined. Fourier transforms infrared analysis, x-ray diffraction studies also performed. All the formulations showed acceptable flow property and better drug release. The optimized batch was subjected to stability studies for 30 days. The dissolution profile of optimized batch was compared with direct compressed tablet and with marketed preparation. Fourier transform infrared spectroscopy conformed that drug does not interact with excipients which are added in the formulation. X-ray diffraction study proved that olanzapine (crystalline form) converted into amorphous form. From this study it was concluded that liquisolid compact technique improves dissolution rate of olanzapine.

Keywords: Liquisolid compact, Solubility enhancement, Olanzapine, Nonvolatile solvent, Neusilin, Aerosil 200

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INTRODUCTION:

The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its dissolution and oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The poor dissolution rate of such water-insoluble drug is a major impediment to the development of pharmaceutical dosage forms. A number of new chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution[1] For drugs belonging to Bio-pharmaceutical classification system (BCS) class II (poor water solubility and high permeability) dissolution rate is often the rate determining step and, which determines the rate and degree of absorption. The oral route remains the most preferred route of drug administration due to its convenience, good patient compliance and low production costs. The oral absorption of drugs is often controlled by dissolution in the gastrointestinal tract.[2]

Olanzapine chemically is (2 – methyl 1- 4 - (4 - methyl -1-piperazinyl)-10H-thieno-[2, 3b], [1, 5] benzodiazepine), a thieno benzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics which was approved by the Food and Drug Administration. Olanzapine belong to BCS class II category i.e., it is inherently highly permeable through biological membranes, but exhibits low aqueous solubility. The pharmacokinetics of Olanzapine is linear and dose proportional within the approved dosage range from 1 mg up to 20 mg. The absolute bioavailability is only approximately 31.5% due to extensive hepatic metabolism. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate. Olanzapine is a yellow crystalline solid drug, with higher solubility observed in 0.1N HCl.[3-5]

Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, like solubilization, pH adjustment, cosolvents, microemulsion, self-emulsification, drug complexation, and particle size reduction etc. Amongst these the most promising method for promoting dissolution is the use of the liquisolid system. [6]

This technique of liquisolid preparation is used to formulate a drug solution in solid dosage forms. Drug solution is generally, prepared by dissolving the drug in non-volatile water-miscible solvent. The prepared tablet of liquisolid

formulation contains the drug held in solution. The main advantages of this technique are Enhanced bioavailability can be obtained as compared to conventional tablets, Production cost is low compared to soft gelatin capsules. The drug is formulated in a tablet form or encapsulated dosage form and is held in the solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles. [7]

The aim of present work is to increase the solubility and in-vitro dissolution of practically insoluble drug Olanzapine, by formulating into liquisolid tablet consist of Neusilin, Aerosil 200 as carrier and coating material and PEG 400 as liquid vehicle and also to study the influence of various formulation parameters on dissolution rate enhancement of liquisolid compacts of olanzapine. The in-vitro release of such preparations were assessed and in-vitro release of optimized batch was compared to that of conventional tablet using a USP dissolution apparatus II (paddle) in 900 ml 0.1N HCl pH 1.2 for 60 minutes.

MATERIAL AND METHODS

The following gift samples were received: Olanzapine (Cadila Healthcare Limited., Ahmedabad); Neusilin (Fuji Chemicals Ltd., Japan) and Aerosil 200 (Cadila Healthcare Ltd., Ahmedabad). Cross povidone and Polyethylene glycol 400 (PEG400) is obtained from S.D. Fine Chem Ltd., Mumbai. Magnesium stearate and Talc is obtained from Loba Chemie Pvt.Ltd., Mumbai. All reagents used were of analytical grade.

Experimental Methodology

Preparation of olanzapine standard graph in pH 1.2 standard buffer [8]:

Accurately weighed 10 mg of olanzapine was dissolved in 100 ml volumetric flask containing 10mL of methanol and freshly prepared dissolution medium. The obtained solution of olanzapine was used as stock solution (100 µg/ mL). From the stock solution 0.1,0.2,0.4,0.5,0.6,0.8 and 1 ml were withdrawn and diluted to 10 ml with pH 1.2 standard buffer to yield concentration of 1,2,4,5,6,8 and 10 µg/mL respectively. Absorbance of each solution was measured at λmax 259 nm against a reagent blank using Shimadzu 1700 UV Spectrophotometer and plotting the graph of absorbance versus concentration (µg/mL).

Preparation of olanzapine standard curve in Methanol:

Accurately weighed 10 mg of olanzapine was dissolved in 100 mL volumetric flask containing methanol. The obtained solution of olanzapine was used as stock solution (100 µg/ mL). From the stock solution 0.1,0.2,0.4,0.5,0.6,0.8,1 and 1.2 ml were withdrawn and diluted to 10 mL with Methanol to yield concentration of 1,2,4,5,6,8,10 and 12 µg/mL respectively. Absorbance of each solution was measured at λmax 270 nm against a reagent blank using Shimadzu 1700 UV Spectrophotometer. Samples were analyzed in triplicate, and the average values were used for plotting the graph of absorbance versus concentration (µg/mL).

Solubility studies [10]

The solubility of Olanzapine in Distilled water, Glycerine, 0.1 N HCl, Propylene glycol, PEG 400, Tween 80, SPAN 80 and Oleic acid were carried out to evaluate the suitability of the non-volatile liquid vehicles as solvent for Olanzapine. Saturated solutions were prepared by adding excess amount of Olanzapine into 10 ml of each liquid vehicle. The resulting solutions were kept in shaker for 48 hr. After this period, the solutions were sonicating on the bath sonicator for 1 hour and centrifuged. The drug concentration in each supernatant was determined using UV spectrophotometer at 270 nm after dilution in methanol as appropriate. The concentration of Olanzapine in each liquid vehicle was calculated based on the calibration curve of Olanzapine in methanol. From these results, the solubility of Olanzapine in the respective liquid vehicle was calculated.

Infrared Spectra Analysis [9,11]

Drug excipient interaction study was carried out by FTIR analysis. IR spectra of the Liquisolid system were recorded by the KBr pellet method. The spectrum of pure Olanzapine and Physical mixture of liquisolid compacts was obtained.

X-Ray Powder Diffraction (XRPD)

X-ray diffractograms of pure Olanzapine and Liquisolid formulation were studied using Philips Analytical XRD instrument. The scanning range was from 5 to 80 at 2 theta scale

Optimal flowable liquid retention potential determination for selection of carrier and coating material [12]

The optimal flowable liquid-retention potential (Φ-value) of each powder excipient (Neusilin US2, Flocel 101,Methyl cellulose, Ethyl Cellulose, Xanthan gum and Aerosil 200) in liquid vehicles (PEG 400) were calculated based on the angle of slide measurement. Each powder excipient was mixed with increasing amounts of liquid vehicle, and the resulting liquid/powder admixture was placed on one end of a polished metal plate which was tilted gradually until the liquid/powder admixture starts to slide. The angle of the plate formed with the plane surface during the slide is defined as the angle of slide. The Φ-value of excipient in different concentrations of liquid vehicles was calculated based on equation given below.

$$\Phi \text{ value} = \frac{\text{Weight of Non-Volatile Liquid Vehicle}}{\text{Weight of Solid}}$$

Calculation of Liquid Load Factor (Lf) Required Quantities of Carrier (Q) and Coating (q) Materials

The formulation design was done by using mathematical model described by spires et al

In this study PEG 400, Neusilin US2, Aerosil 200 was used as vehicle, carrier, coating material. The concentration of the drug solution were taken as 10%, 15%, 20% w/w, and carrier coating ratios were taken as 10:1, 15:1, 20:1.

Ratio of carrier and coating material was calculated by

$R = Q/q$

Where Q is amount of carrier, q is amount of coating material.

Loading factor was determined by adding carrier material to drug solution until it produce good flow property and compressibility.

$Lf = W/Q$

Where W is weight of liquid medication, Q is weight of carrier material.

Loading factor was also calculated by using Φ-values of carrier, coating material and by using R value.

$Lf = \Phi + \Phi\,(1/R)$

Once, liquid loading factor was obtained, the appropriate quantities of carrier (Q) and coating (q) material required were calculated using following equations,

$Q = W/Lf$

q = Q/R

Method of preparation of liquisolid systems

- The drug was initially dispersed in nonvolatile system (PEG 400) termed as liquid vehicle at different concentration.
- To this liquid medication, the calculated amount of the carrier was added by continuous mixing in the mortar and kept for 5-10minutes for complete absorption of liquid on carrier material.
- Then, coating material was added and mixed until mortar contents start to look like dry powder. To the above binary mixture crosspovidone as disintegrant and Magnesium Stearate and Talc were added and mixed in mortar.
- The resultant liquisolid powder is evaluated for flow property i.e Angle of repose, Carr's index and Hausner's ratio.
- All liquisolid preparations were compacted into tablets using a Rotary press tablet machine having flat-faced punch with a compression force that provide acceptable tablet hardness.
- The resultant liquisolid tablets were evaluated for Thickness, Diameter, Hardness, Friability, Drug content, Disintegration and *In vitro* dissolution.

Precompression Evaluation Parameters[13]

Bulk Density [14]

An accurately weighed quantity of powder, which was previously passed through sieve # 40 and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measured was called as the bulk volume. The bulk density was calculated using the formula

Db =M/Vb

Where, M is the mass of powder and Vb is bulk volume of powder

Tapped Density

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula

Dt = M/Vt

Where, M is the mass of powder and Vt is tapped volume of powder

Angle of Repose:

It is defined as the angle between the free surfaces of a pile of powder to the horizontal plane. The relationship between angle of repose and type of flow is shown below.

Tanθ= h/r

Where, θ is the angle of repose, h is the height in cms and r is the radius in cms

Table 1: Relation between Angle of Repose and Type of Flow

Angle of repose(ɵ)	Flow property
25-30	Excellent
31-35	Good
36-40	Fair-aid not needed
41-45	Passable-may hang up
46-55	Poor-must agitate vibrate
56-65	Very poor
>65	Very, very poor

Hausner's Ratio:

The prepared liquisolid formulations were weighed and poured into a 100 ml cylinder. The poured bulk volume (Vb) and the tapped volume (Vt) after 300 taps, was recorded to a constant volume, or a tap density tester was used to calculate the poured bulk density (Pb) and the tapped density (Pt) in g/mL. From the values of bulk density and tapped density, Hausner ratio was calculated using the following formula.

Hausner's Ratio=Tapped density / Bulk density

Table 2: Relationship between Hausner's Ratio and Flow Property

Hausner ratio	Flow property
1.10-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Percentage Compressibility (Carr's Index):

Percentage Carr's Index (% compressibility) was calculated as 100 times the ratio of the difference between the tapped density and bulk density to the tapped density. Carr's index (CI) is calculated as follows:

CI (%) = [(Tapped density – Bulk density) / Tapped density] x100

Table 3: Relation between Carr's Index and Type of Flow

Compressibility index (%)	Flow property
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

Post compression evaluation parameters

a) Weight Variation Test: To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively using an electronic balance Shimadzu, model AX2000, Japan. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100 and the test was performed according to the USP official method.

b) Crushing Strength

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Tablet dimension (diameter and thickness), and crushing strength of 5 randomly selected tablets were determined using Dr. Schleuniger tablet hardness tester (Pharmatron 8, Germany).

c) Disintegrating time Apparatus: Electrolab ED-2L Disintegration test apparatus

Media: Distilled water **Procedure:** The assembly was suspended in the specified liquid medium in a 1000 ml beaker. The volume of liquid was taken such that when the assembly was in highest position the wire mesh was at least 25 mm below the surface of the liquid and when the assembly was in lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the tube of the assembly and disk was added to each tube. The apparatus was operated for specified time and temperature at 37±2⁰C. Time for complete disintegration of tablet was noted down.

d) Friability test Apparatus: Electrolab Friability tester, Model EF 2 **Procedure:** A sample of 10 tablets was taken and was carefully dedusted prior to testing. The tablets were accurately weighed and placed in the drum of the Roche Friabilator. The drum was rotated for 100 times at 25 rpm and the tablets were removed, dedusted and accurately weighed. % Friability calculated by following formula:

% Friability = [(W1 – W2) / W1] × 100

Where W1 = Initial weight of 10 tablets; W2 = Weight of the 10 tablets after testing

Acceptance criteria: Friability of tablets should be less than 0.5-1% as per USP.

e) In vitro Dissolution [15] Drug release studies were carried out using paddle type II dissolution test apparatus (900 ml, 50 rpm, 37°C ± 0.5°C) in standard buffer pH 1.2. At the end of the each sampling time period 5ml of the samples were taken and analyzed for drug content. A 5ml volume of fresh and filtered dissolution medium was added to make the volume after each sample withdrawal. After withdrawing, samples were filtered and analyzed after appropriate dilution by using Double beam UV-spectrophotometer. The concentration was calculated using standard calibration curve.

Optimization of Liquisolid Tablet Using 3^2 Full Factorial Designs and Preparation And Evaluation Of Check Point Batch[16]

In order to investigate the effect of formulation variables on the response variables, and to predict an optimized formulation, a 3^2 factorial design was adopted. Nine batches were prepared as per the design layout shown in table 4. One optimized check-point batch was prepared on the basis of generated overlay plot of responses to validate the model generated. Checkpoint Batch was evaluated and results are shown in table 12

Table 4: List of Different Dependent & Independent Variables

Independent Variables						Dependent Variables		
X1			X2			Y1	Y2	Y3
Excipient ratio (R value)			Concentration of Drug in nonvolatile solvents %w/w			Angle of repose	Percentage Drug Release at 15 minutes in standard buffer pH 1.2	Percentage Drug Release at 30 minutes in standard buffer pH 1.2
-1	0	+1	-1	0	+1			
10	15	20	10	15	20			

Comparison of check point batch with directly compressible tablet (DCT) and Marketed product

Formulated liquisolid compact of olanzapine was compared with DCT and marketed product. Olanzapine tablet is available in the market from different companies. Marketed product Olexa Tab 10 mg was taken for comparison.

Stability study of check point batch

The tablets were stored at 25°C and 75% relative humidity condition for 1 month. The stored tablets were evaluated using dissolution test. The dissolution data of aged tablets were compared with those of freshly prepared tablets. Stability study was carried out for one month at 25°Cand 75 % RH in desiccators. The tablets from the optimized batch were placed at 25°C and 75 % RH for 30 days. At the end of 30 days, the dissolution studies of tablets were carried out. Student t-test was applied for dissolution study at initial stage and after 30 days of storage, the dosage form did not show any significant difference (tcal< ttab.) as shown in **table 14**.

RESULTS AND DISCUSSIONS:

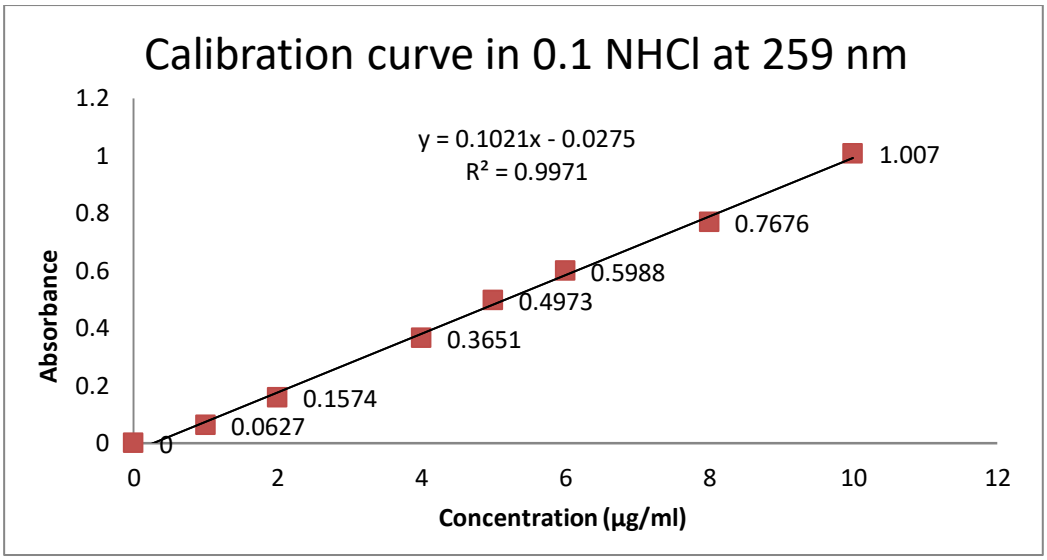

Figure 1: Calibration Curve of Olanzapine in 0.1NHCl

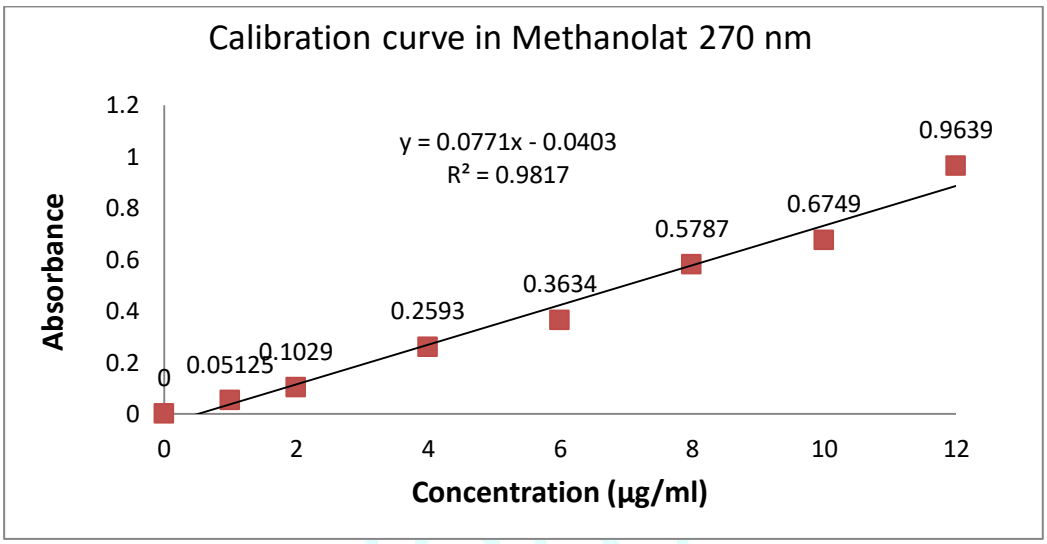

Figure 2: Calibration Curve of Olanzapine in Methanol

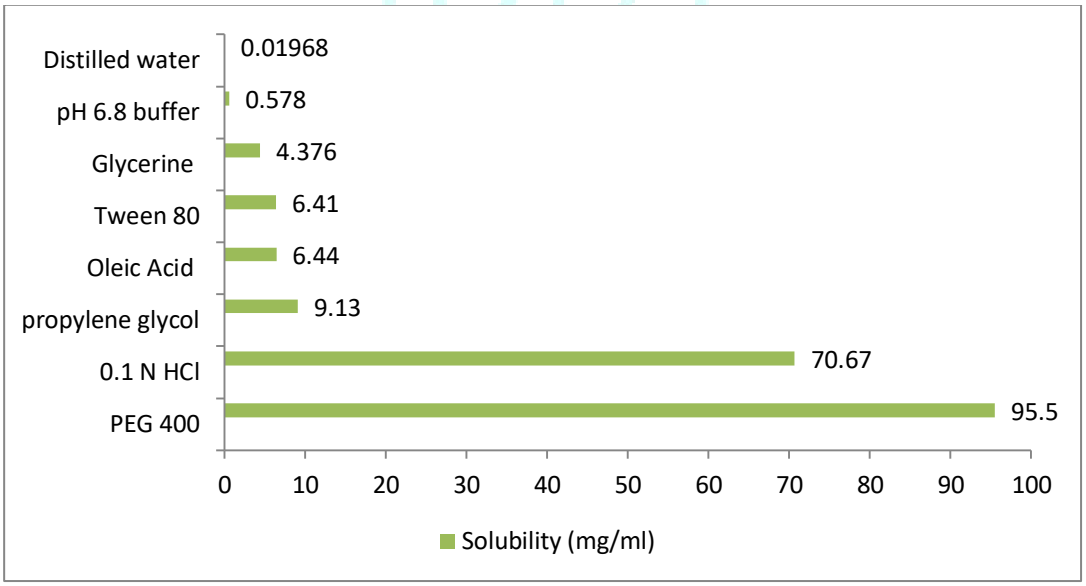

Figure 3: Solubility of Olanzapine in different Nonvolatile solvents

As shown in figure 3 solubility of Olanzapine is found more in PEG 400 as compared to other solvents.

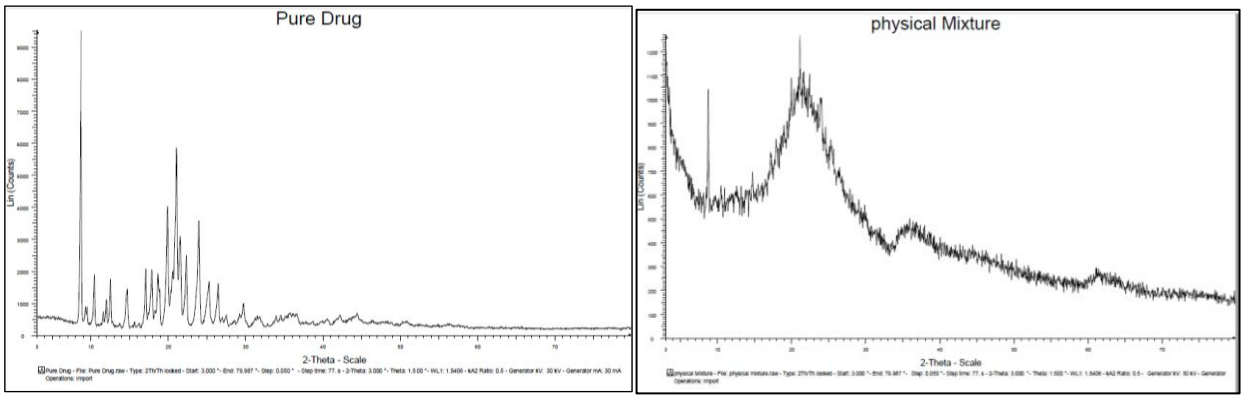

Figure 4: XRD crystallogram of Olanzapine and **Physical mixture**

Figure 4 shows the X-ray diffractograms of pure olanzapine and pure mixture of excipients and liquisolid formulation. The XRD analysis of olanzapine shows a characteristic high intensity peaks at 2θ value of 8.5,10, 14, 15.5,20, 22.5, and 25. Thus, it is confirmed that the drug is in the crystalline state. The liquidsolid formulation shows peaks with reduced intensity at similar values of 2θ. This confirms that there is solublization of the drug present in the formulation.

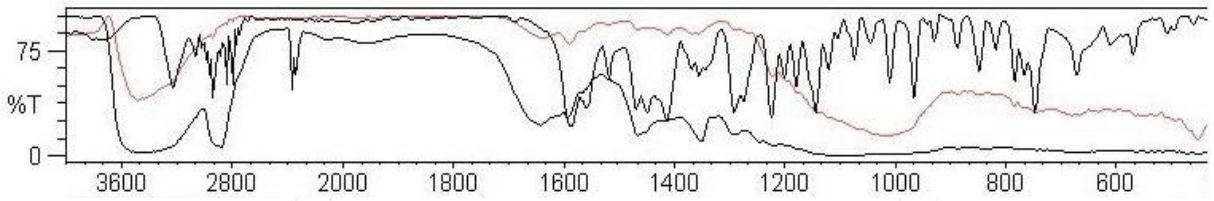

Figure 5: overlay FT-IR spectra of Olanzapine, Physical mixture and Liquisolid system of drug

From the Figure 5, one can see that there is no introduction of any new peak in the functional group region and there isn't removal of any peak in the spectra of Liquisolid formulation. This concludes that no functional group present in the drug or excipients is degraded and there is no formation of any new functional group.

Table 5: Formulations as per 3^2 Full Factorial Design.

Batch	Conc. Of OLZ %w/w[a]	R[b]	W (Weight of liquid)	Lf	Neusilin US2 Q=W/Lf (mg)	Aerosil 200 q=Q/R (mg)	Cross povidone 3%	Total unit weight (mg)[c]
LSC1	10	10	100	0.977	102.35	10.24	6.67	229.26
LSC2	10	15	100	0.954	104.82	6.98	6.65	228.45
LSC3	10	20	100	0.943	106.04	5.30	6.64	227.98
LSC4	15	10	66.66	0.977	68.23	6.82	4.70	161.41
LSC5	15	15	66.66	0.954	69.87	4.66	4.69	160.88
LSC6	15	20	66.66	0.943	70.69	3.53	4.68	160.56
LSC7	20	10	50	0.977	51.17	5.12	3.79	130.08
LSC8	20	15	50	0.954	52.41	3.49	3.78	129.68
LSC9	20	20	50	0.943	53.02	2.65	3.77	129.44

a: Each tablet contains 10mg equivalent Olanzapine dissolved in PEG 400
b: R = Carrier : Coating ratio; R = Q/q
c: Each tablet contains Magnesium stearate 1% and Talc 2%

Table 6: Pre compression evaluation parameters of Liquisolid system of LSC 1 to LSC 9

Batch	Bulk density (gm/cm^3) Mean±SD	Tapped density (gm/cm^3) Mean±SD	Angle of repose (θ) Mean±SD	Hausner's ratio Mean±SD	Carr's index (%) Mean±SD
LSC1	0.20 ±0.02	0.25±0.08	28.78±2.92	1.25±0.24	20±1.72
LSC2	0.23±0.03	0.27±0.07	25.17±1.88	1.17±0.18	14.8±2.74
LSC3	0.18±0.01	0.22±0.06	25.05±2.99	1.22±0.26	18.18±2.03
LSC4	0.18±0.02	0.23±0.09	30.96±1.32	1.27±0.32	18.52±1.73
LSC5	0.20±0.01	0.22±0.03	28.37±0.61	1.10±0.25	9.09±1.06
LSC6	0.27±0.03	0.33±0.04	28.86±1.91	1.22±0.01	18.18±1.05
LSC7	0.30±0.04	0.41±0.11	30.17±0.69	1.37±0.12	26.83±2.18
LSC8	0.27±0.02	0.37±0.07	29.58±3.75	1.37±0.39	27.03±1.64
LSC9	0.21±0.03	0.27±0.08	32.62±3.78	1.29±0.17	22.22±3.94

Hausner ratio and Carr's index were calculated from the density values. The results revealed that batch LSC 2 and 5 have Carr's index between 9 to 15 indicates excellent and good flowability. The rest of the batches had fair, passable and poor flowability as Carr's index was above 16. The batches LSC 2 and 5 had Hausner ratio between 1.10 to 1.18 which indicate good flowability and rest of the batches had fair, passable and poor flowability as hausner's ratio was between 1.19 to 1.37. From the results of angle of repose batch LSC 1,2,3,4,5,6,7,8 which were between 25 to 30 and this indicates excellent flowability while LSC 9 had good flowability.

Table 7: Post compression evaluation parameters of Liquisolid system of LSC 1 to LSC 9

Batch	Weight variation (mg)	Thickness (mm)	Hardness (N)	% Friability	Disintegration time (sec)	% Drug content
LSC1	226±1.23	2.2	57.4±1.7	0.767	180±2.7	98.53
LSC2	224±1.33	2.2	56±1.5	0.763	175±2.4	97.12
LSC3	224±1.45	2.2	54.2±1.32	0.760	115±3.21	96.98
LSC4	150±1.27	1.2	59.1±1.56	0.762	179±2.55	98.95
LSC5	150±2.56	1.2	58±2.7	0.750	165±2.9	98.62
LSC6	150±2.15	1.2	57.9±1.45	0.749	104±3.05	98.55
LSC7	113±1.89	1.1	58.2±1.27	0.711	118±3.65	99.95
LSC8	100±2.98	1.1	58.6±1.3	0.620	98±2.15	99.78
LSC9	112±2.19	1.1	57.4±1.37	0.623	99±2.69	98.56

Liquisolid compacts with high R-values contain high amounts of Neusilin, low quantities of Aerosil 200. This is associated with enhanced wicking, disintegration. Disintegration time of LSC 3, 6, 8 and 9 was found to be lesser as compared to LSC 1, 2,4,5,7 in which higher amount of Aerosil 200 was present. Similarly, for Hardness and Friability also.

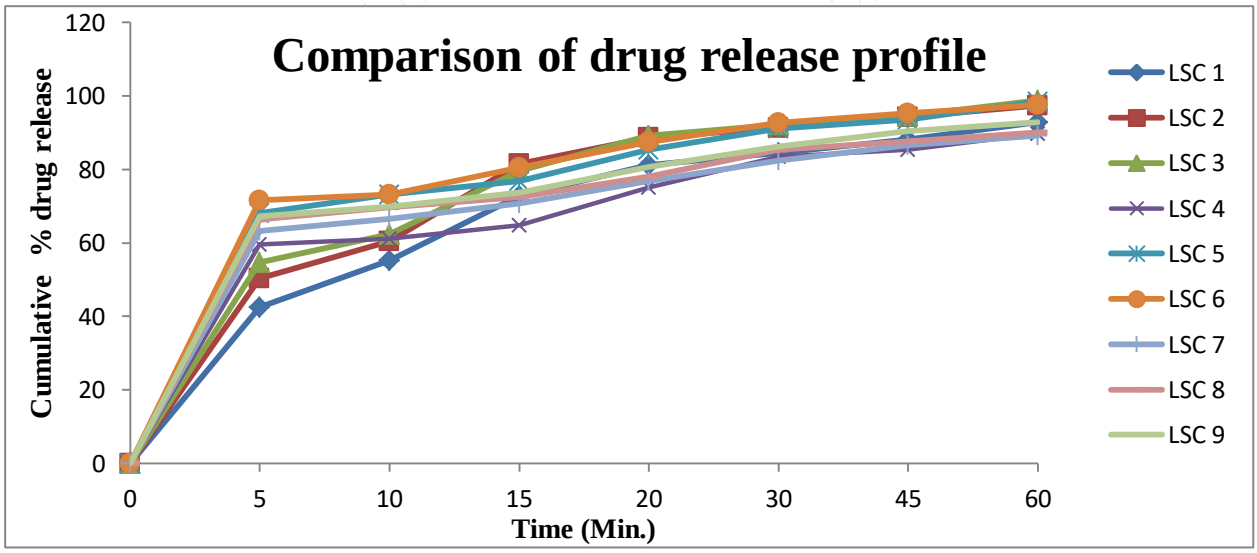

Figure 6: In Vitro Dissolution Profile of Batch LSC 1 to LSC 9 in standard buffer pH 1.2

Table 8 shows the design layout of full factorial design with response variables. The results were subjected to multiple regression analysis and equations were evolved.

Table 8: Data Transformation of 3^2 Full Factorial Design.

Batch	Actual value		Coded value		Response		
	Excipient ratio R	Drug concentration %w/w	X1	X2	Angle of Repose (Y1)	%Drug release in 15 minutes (Y2)	%Drug release in 30 minutes (Y3)
LSC 1	10	10	-1	-1	28.78	79.63	94.89
LSC 2	10	15	0	-1	25.17	81.51	95.71
LSC 3	10	20	1	-1	25.05	85.30	96.87
LSC 4	15	10	-1	0	30.96	86.42	98.39
LSC 5	15	15	0	0	28.37	91.23	99.41
LSC 6	15	20	1	0	28.86	92.20	99.50
LSC 7	20	10	-1	1	30.17	83.42	90.16
LSC 8	20	15	0	1	29.58	86.31	91.21
LSC 9	20	20	1	1	32.62	87.27	93.89

Discussions and Summary output of regression analysis

Response surface methodology was used to generate a highly significant mathematical model, which can adequately describe or predict the optimization of Liquisolid tablets. Angle of repose, % drug release in 15 minutes and % drug release in 30 minutes for the nine batches (LSC 1 to LSC 9) showed a wide variation, i.e. 32.62 to 25.05, 79.63 to 92.20 and 90.16 to 99.50 respectively. The data clearly indicate that Angle of repose and % drug release values were strongly dependent on the selected independent variables. The fitted equations relating the responses are shown in the table 6,7 and 8 respectively. ANOVA and multiple regression analysis were performed using the Design Expert 8.0.7.1 trial software and Microsoft excels 2007. $Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X12 + b22X22$

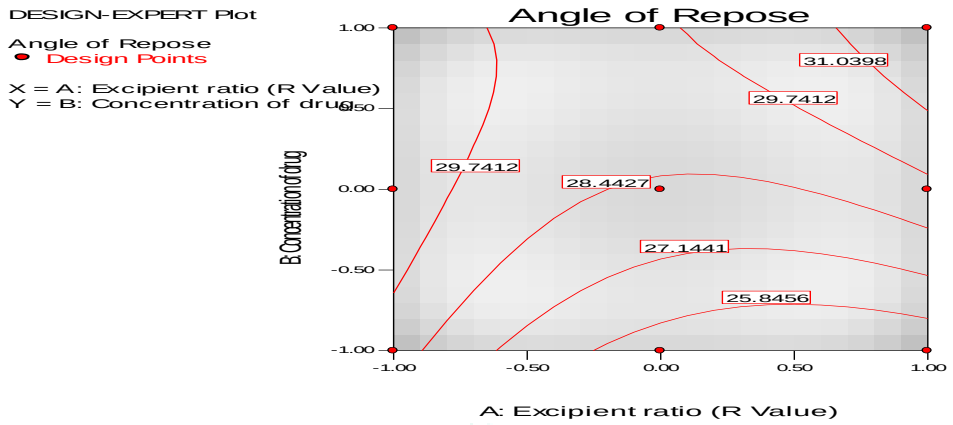

Figure 7: Two-Dimensional Contour Curve for Angle of repose (Y1).

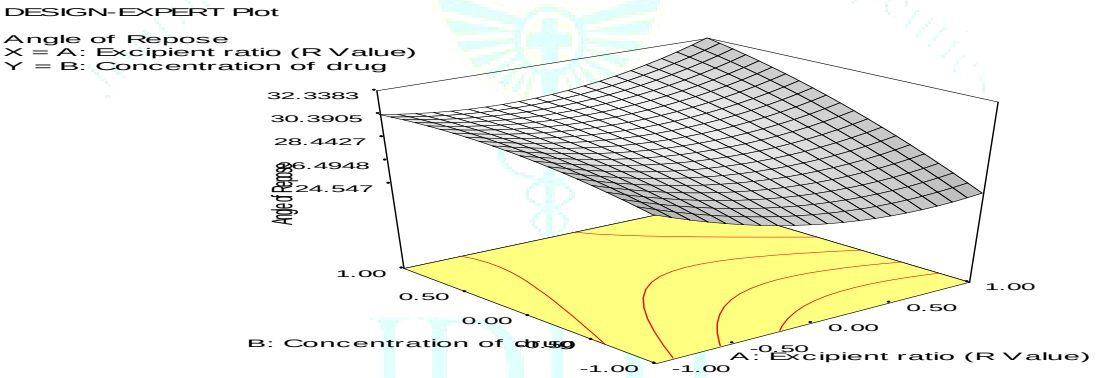

Figure 8: 3D Response Surface Curve for Angle of repose (Y1).

Table 9: Summary output of regression analysis for effect of X1 and X2 on Y1

Multiple R	0.9924
R Square	0.9850
Adjusted R Square	0.9600
Standard Error	0.4959
Observations	9

Coefficient	**Coefficient value**	**P-value**	**Level of significance**
b0	28.26	4.93E-06	**---**
b1	-0.56	0.068845	Non-significant
b2	2.23	0.001606	Significant
b12	1.55	0.008335	Significant
b11	1.70	0.016748	Significant
b22	-0.83	0.097509	Non-significant
Equation			
Full Quadratic Model	$28.26-0.56X1+2.23X2+1.70X1^2-0.83X2^2+1.55X1X2$		
Reduced Linear Model	28.84-0.56X1+2.23X2		
Equation in terms of Actual factors			
Reduced Linear Model	23.84-0.11*R value+0.45*concentration of drug		

Effect of X1 and X2 on Y1

The significance level of coefficients b1 and b22 were found to be greater than P = 0.05 and hence they were omitted from the full model. For response Y1 reduced mathematical model was evolved omitting the insignificant terms (p>0.05) by adopting multiple regression analysis. The coefficients b2, b11 and b12 were found to be significant at P < 0.05 and hence they were retained. The results of the multiple linear regression analysis revealed that Increase in the excipient ratio (R value) there is decrease in angle of repose which may be shown by coefficient b1 bears a negative sign. Increase in the drug concentration there is increase in angle of repose which may be shown by coefficient b2 bears a positive sign.

R^2 value is 0.9850 which explains that about 98.50 % of variability is expresses by this model. Reduced model suggest that effect of factor on response is linear so, this is linear model which is shown in figure 7 and 8.

Table 10: Summary output of regression analysis for effect of X1 and X2 on Y2

Multiple R	0.9881
R Square	0.9763
Adjusted R Square	0.9369
Standard Error	1.033
Observations	9

Coefficient	**Coefficient value**	**P-value**	**Level of significance**
b0	90.38	1.37E-06	---
b1	2.55	0.009089	Significant
b2	1.76	0.025094	Significant
b12	-0.46	0.44349	Non-significant
b11	-0.64	0.443575	Non-significant
b22	-6.04	0.003705	Significant
Equation			
Full Quadratic Model	$90.38+2.55X1+1.76X2-0.64X1^2-6.04X2^2-0.46X1X2$		
Reduced Linear Model	$85.92+2.55X1+1.76X2$		
Equation in terms of Actual factors			
Reduced Linear Model	72.99+0.51*R value+0.35*concentration of drug		

Effect of X1 and X2 on Y2

The significance level of coefficients b11 and b12 were found to be greater than *P* = 0.05 and hence they were omitted from the full model. For response Y2 reduced mathematical model was evolved omitting the insignificant terms (p>0.05) by adopting multiple regression analysis.

The coefficients b1, b2 and b22 were found to be significant at *P* < 0.05 and hence they were retained. Therefore, it was concluded that the interaction term do not contribute significantly to the prediction of % Drug release. The results of the multiple linear regression analysis revealed that Increase in the excipient ratio (R value) there is increase in drug release at 15 minutes which may be shown by coefficient b1 bears a positive sign. This may be explained by increase in R value there is decrease in concentration of Aerosil which contributes to hydrophobicity and so there is increased and rapid wetting of particles at higher R values, so there is increase in dissolution rate of drug. R^2 value is 0.9763 which shows that 97.63% of variability on response can be expressed by this model. Reduced model suggest that effect of factor on response is linear so, this is a linear model which is confirmed figure 9 and 10.

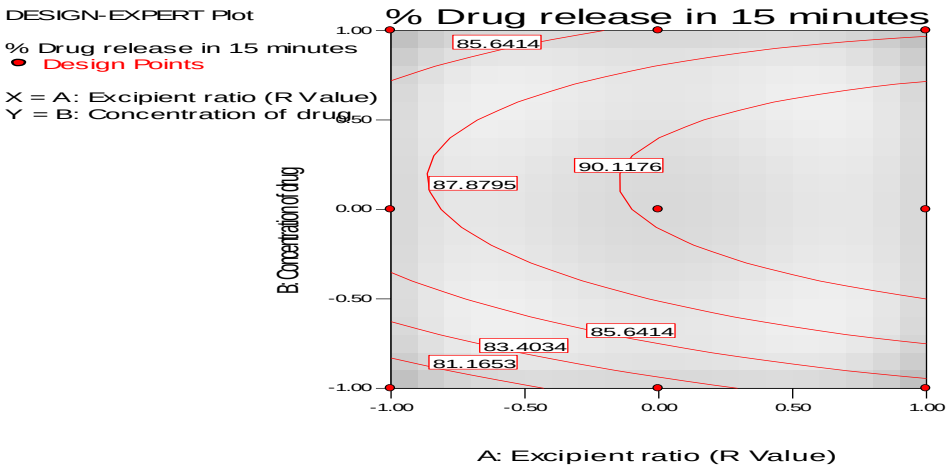

Figure 9: Two-Dimensional Contour Curve for % Drug release in 15 minutes (Y2).

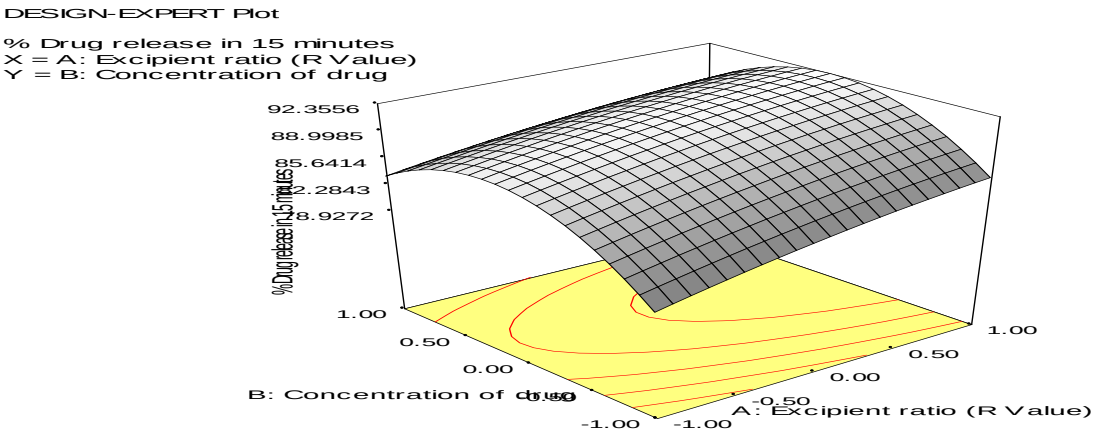

Figure 10: 3D Response Surface Curve for % Drug release in 15 minutes (Y2).

Table 11: Summary output of regression analysis for effect of X1 and X2 on Y3

Multiple R	0.9914
R Square	0.9829
Adjusted R Square	0.9545
Standard Error	0.7214
Observations	9

Coefficient	**Coefficient value**	**P-value**	**Level of significance**
b0	98.98	3.53428E-07	---
b1	1.14	0.030740352	Significant
b2	-2.04	0.006211909	Significant
b12	0.44	0.311943527	Non-significant
b11	0.17	0.756400131	Non-significant
b22	-5.31	0.001890105	Significant
Equation			
Full Quadratic Model	$98.98+1.14X1-2.04X2+0.17X1^2-5.31X2^2-0.44X1X2$		
Reduced Linear Model	95.56+1.14X1-2.04X2		
Equation in terms of Actual factors			
Reduced Linear Model	98.25+0.23*R value-0.41*concentration of drug		

Effect of X1 and X2 on Y3

The significance level of coefficients b11 and b12 were found to be greater than $P = 0.05$ and hence they were omitted from the full model. For response Y2 reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis.

The coefficients b1, b2 and b22 were found to be significant at $P < 0.05$ and hence they were retained. Therefore, it was concluded that the interaction term do not contribute significantly to the prediction of % Drug release. R^2 value is 0.9829 which shows that 98.29% of variability on response can be expressed by this model. Reduced model suggest that effect of factor on response is linear so, this is a linear model which is confirmed by figure 11 and 12.

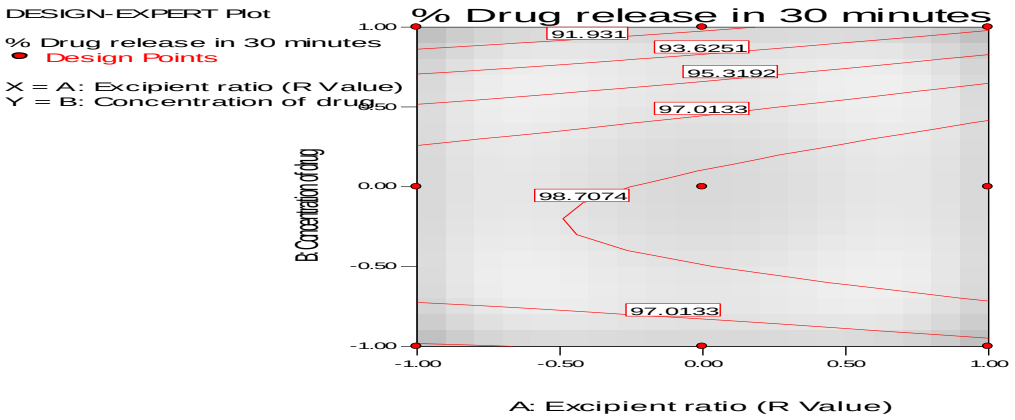

Figure 11: Two-Dimensional Contour Curve for % drug release in 30 minutes (Y3)

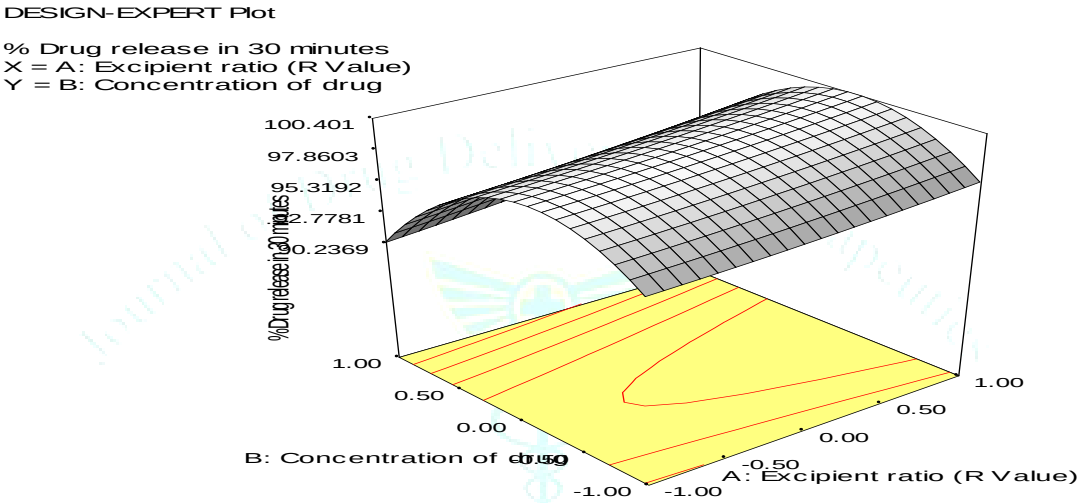

Figure 12: 3D Response Surface Curve for % Drug release in 30 minutes (Y3).

Mathematical model validation by checkpoint batch and Optimization of the formulation

The optimization was performed by superimposing the contour plots of the response Y1, Y2 and Y3 locating the region of optimal surface common as shown in Figure 13.

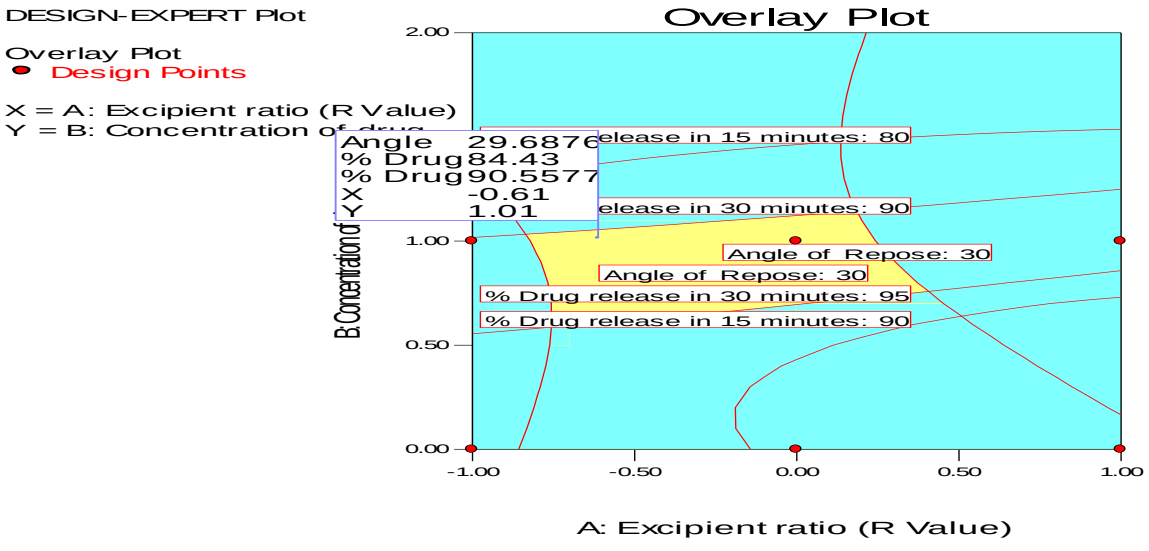

Figure 13: Overlay plot of response variables

The overlay of the responses generated an optimized area, as per the desired criteria. The angle of repose was set in range 25-30. The percentage drug release at 15 Min. (Y1) was set in range 80-90 % and % drug release at 30 min. was set in the range 90 -95%. These specifications satisfy the requirements for the good flow properties and for the immediate release from the dosage form. It can be concluded that by adopting a systemic formulation approach, one can reach to an optimum point in the shortest time with minimum efforts.

Table 12: Preparation of Check Point Batch LSC 10

Batch	Conc. Of OLZ %w/w[a]	R[b]	W (Weight of liquid)	Lf	Neusilin US2 Q=W/L_f (mg)	Aerosil 200 q=Q/R (mg)	Cross povidone 3%	Total unit weight (mg)[c]
LSC10	19.93	10.98	50.19	0.971	51.67	4.71	3.79	130.27

Table 13: Comparison between the observed and predicted values

Response	Chek point batch LSC 10	
	Predicted	Observed
Angle of repose	29.97	30.17
% drug release in 15 minutes	84.13	82.15
% drug release in 30 minutes	90.66	91.23

Observed value was found to be similar to the predicted values. Thus, it was confirmed that factors like concentration of drug and carrier to coating ratio are significant for the angle of repose and drug release from the formulation. Model generated is thus, validated.

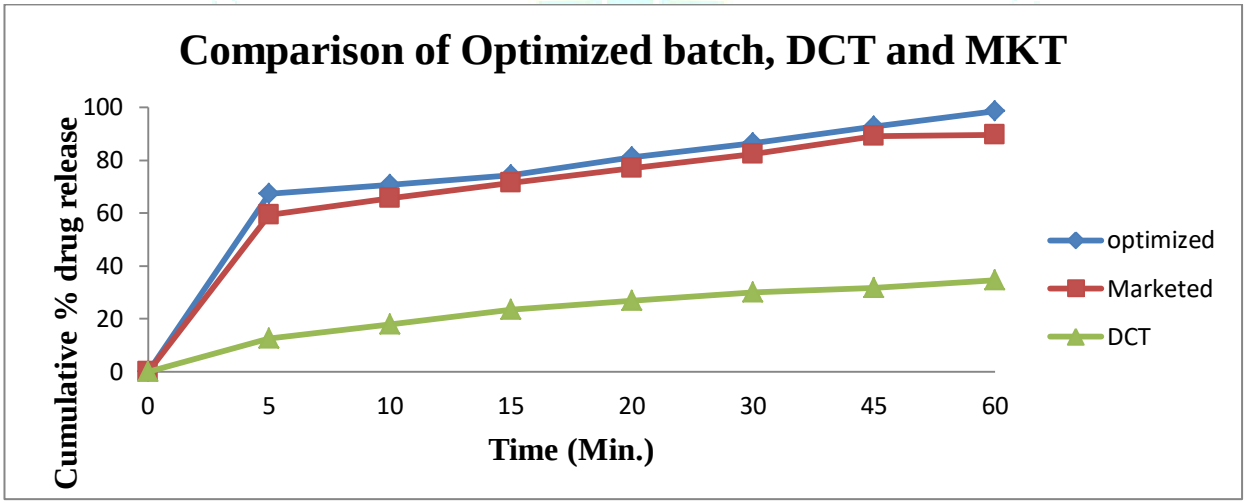

Figure 14: Dissolution Profile Comparison in Standard buffer pH 1.2

Stability study of optimized batch LSC 10:

The tablets were stored at 25°C and 75% relative humidity condition for 1 month. The stored tablets were evaluated using dissolution test. The dissolution data of aged tablets were compared with those of freshly prepared tablets. At the end of 30 days, the dissolution studies of tablets were carried out. Student t-test was applied for dissolution study at initial stage and after 30 days of storage, the dosage form did not show any significant difference (tcal< ttab.) as shown in table 14.

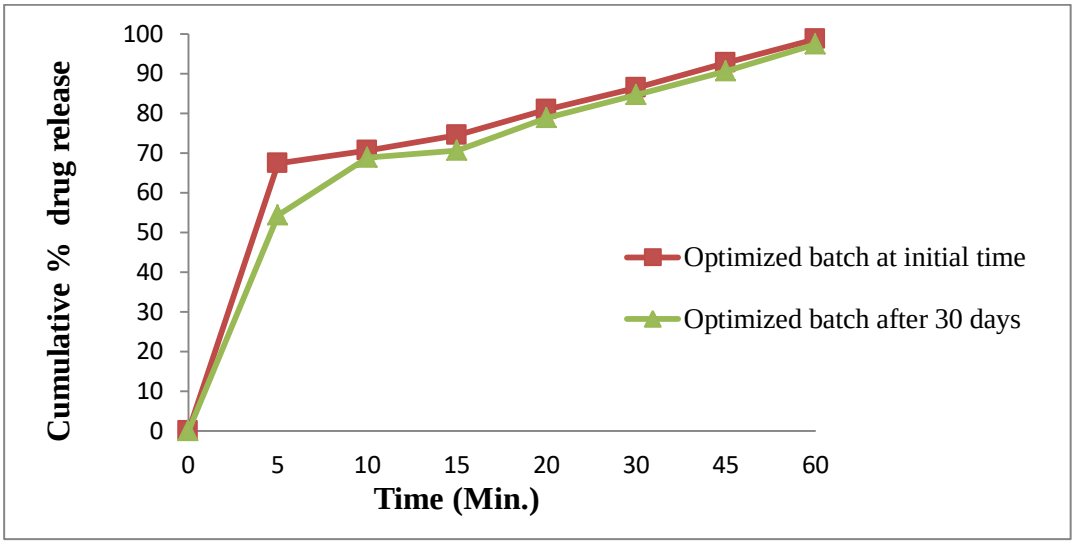

FIGURE 15: Comparison of in- Vitro Release Profile of Batch LSC 10 Tablet Initial and after (30day) Stability Study

Table 14: Student t- Test between Initial and After 30 Days of Batch LSC 10

t-Test: Paired Two Sample for Means		
	Variable 1	*Variable 2*
Mean	75.18034	72.53222
Variance	917.3598	938.3531
Observations	9	9
Pearson Correlation	0.991225	
Hypothesized Mean Difference	0	
df	8	
t Stat	1.961664	
P(T<=t) one-tail	0.042719	
t Critical one-tail	1.859548	
P(T<=t) two-tail	0.085438	
t Critical two-tail	2.306004	

Student t – test between before and after 30 days of storage showed insignificant difference (tcal< ttab.). It conforms that the formulation is stable for the time being. The developed dosage form passes stability study carried out for 30 days at 25˚C and 75 % RH.

CONCLUSION:

The aim of the present investigation was to study the influence of various formulation parameters on dissolution rate enhancement of liquisolid compacts of olanzapine. Drug identification by X-ray crystallography showed it was pure and crystalline in nature. PEG 400 was chosen for solubilization of drug. Neusilin® and Aerosil 200 were chosen as carrier and coating material respectively. FT-IR studies show the drug compatible with excipients. 3^2 factorial design was applied for optimization of formulation. The liquisolid tablets were formulated with three different drug concentrations, 10, 15, 20 %w/w, and three different carrier to coating ratio, 10, 15, 20. The check point batch was formulated and evaluated; all results were found to be in specified limit. The check point batch was subjected to stability studies for 30days and there was no remarkable difference was found in dissolution studies. Optimized batch, DCT and MKT were compared for the dissolution rate. There was increase drug release in Optimized batch compared to DCT and MKT. The improvement in dissolution contributes to the presence of nonvolatile solvents in the formulation which improves solubility and wetting properties of drug.

From present investigation it was concluded that PEG 400 proved to be promising liquid vehicle for formulation of liquisolid compacts for improvement in the dissolution of poorly water soluble drug. Further, it was found that tablet weight was considerably reduced with Neusilin®. Liquisolid technique is one of the promising approach for improvement in dissolution rate of poorly soluble drugs.

REFERENCES:

1. Mohiuddin MZ, Puligilla S, Chukka S, Devadasu V, Penta J, Formulation and Evaluation of Glyburide Liquisolid Compacts, International Journal of Pharma Research & Review, Feb 2014; 3(2):36-46
2. Charman SA, Charman WN. Oral modified release delivery systems, Modified Release Drug Delivery Technology, New York,2003, 1-9
3. Available from: http://www.rxlist.com[Last accessed on 2019 June 8]
4. Available from: http://www.drugbank.com [Last accessed on 2019 June 8]
5. Available from: http://www.druglib.com [Last accessed on 2019 June 8]
6. Karmarkar AB, Gonjari ID, Liquisolid Technology for Dissolution rate Enhancement or Sustained Release, Expert Opinion Drug Delivery, 2010; 7, 1227-1234
7. Kishor G, Dr. Sayyad FJ, Liquisolid compact a review, International Journal of Pharmaceutical and Biological Research, Apr-May 2013; 4 (2):26-31.
8. Kale CA, Kulkarni GS, Chopade VV, Chaudhari SY and Chaudhari PD, Development And Validation Of A Stability Indicating UV-Vis Spectrophotometric Assay Method Of Olanzapine By Using Different Stress Degradation Conditions, World Journal Of Pharmacy And Pharmaceutical Sciences, 2014;3(8):589-599.
9. Available from http://www.usppf.com/pf/pub/index.html [Last accessed on 2016, 26th March]
10. Gavali SM, Pacharane SS, Sankpal SV, Jadhav KR, Liquisolid compact: A new technique for enhancement of drug dissolution, International Journal of Research in Pharmacy and Chemistry, 2011; 1(3):705-713.
11. United State Pharmacopoeia, Rockville, USA. Olanzapine Summary Validation Report, 30th edition, December 1, 2015
12. Spireas S, Bolton SM, Liquisolid systems and methods for preparing same, U. S. Patent 5. 968 550, **1999**
13. Banker GS and Anderson NL, Lachman L, Liberman HA, Kanig JL, Tablets In Theory and Practice of Industrial Pharmacy, Varghese Publishing House, The Bombay India,3rd edition, 1987:293-345.
14. U. S. Pharmacopoeia and National formulary, Bulk density and tapped density. (USP29-NF24). 2011: 2638.
15. Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), August-2012
16. Kothawade J, Nerkar P, Mahajan H, Ige P, Formulation and In Vitro Evaluation of Liquisolid Compacts of Cefuroxime Axetil for Dissolution Rate Improvement. Indian Journal of Novel Drug delivery, Jul-Sep, 2015; 7(3):116-125