Exploration of critical formulation parameters for enhancing dissolution rate by liquisolid compacts through experimental design.

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ABSTRACT:

Domperidone is a dopamine receptor blocker at both chemoreceptor trigger zone showing antiemetic activity. It is administered orally having oral bioavailability of only 13-17% due to poor aqueous solubility. The aim of the present investigation was to study the influence of various formulation parameters on dissolution rate enhancement of liquisolid compacts of Domperidone. Combination of non-volatile system Acrysol EL135: Tween 80 in ratio 0.9:0.1 was chosen for solubilisation of Domperidone. Neusilin® and Aerosil 200 were chosen as carrier and coating material respectively. 3^2 factorial design was applied for optimization of formulation having different drug concentrations and different carrier to coating ratio as independent variables. The check point batch was formulated and evaluated, all results were found to be in specified limit. There was increase drug release in Optimized batch compared marketed product. The improvement in dissolution contributes to the presence of non-volatile solvents in the formulation which improves solubility and wetting properties of drug. Liquisolid technique is one of the promising approach for improvement in dissolution rate of poorly soluble drugs.

KEYWORDS: Domperidone, Acrysol EL135, liquisolid compacts, Neusilin®, 3^2 factorial design.

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INTRODUCTION :

Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously.(SB 2009) The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists.(Ratnakar 2016) The term liquisolid compacts as described as immediate or sustained release tablets or capsules that are prepared using the technique of “liquisolid systems” combined with inclusion of appropriate adjuvants required for tabletting or encapsulation such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively.(Spireas, Sadu et al. 1998) Liquisolid compacts prepared by using different solvents which dissolves the poorly soluble drug and gives better bioavailability.(Gubbi and Jarag 2009, Gubbi and Jarag 2010)

With the liquisolid technology as described by Spireas a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. (Spireas, Sadu et al. 1998, Spireas, Jarowski et al. 1992) Domperidone, benzimidazole derivative with a molecular weight of 425.91gm/mol, is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution problem thus it has poor bioavailability (15%). When given as immediate release tablet, onset of action is half an hour and the drug effect lasts for 4-7h. The elimination half-life is 5-7 hr and protein binding of Domperidone is

91- 93%. Although, Domperidone is a weak base with good solubility in acidic pH but in alkaline pH, its solubility is significantly reduced. It has poor aqueous solubility (0.986mg/L) and the oral bioavailability of Domperidone has been reported at the range of 13-17%.(Sangnim, Zandu et al. 2022) The poor aqueous solubility may be one possible reason for its low bioavailability.(Ismail, Kerdpol et al. 2021) In order to increase the bioavailability of Domperidone, liquisolid compact system approach has been tried.

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties.(El-Hammadi and Awad 2012, Javadzadeh, Siahi et al. 2007) To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed.(Spireas, Sadu et al. 1998, Spireas, Jarowski et al. 1992) Different constants are introduced such as flowable (Φ-value) and compressible (Ψ-number) liquid retention potential for each powder-liquid combination.(Jafar, Mhg et al. 2010, Verheyen, Blaton et al. 2002) The Φ-value of a powder is defined as the maximum amount of a given non-volatile liquid that can retained inside powder bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-number of a powder is defined as the maximum amount of liquid that can retain inside powder bulk [w/w] while maintaining acceptable compactability so that resulting in compacts having sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the so-called “pactisity”, which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms “acceptable flow and compression properties” imply the desired and thus preselected flow and compaction properties, which must be met by the final liquisolid formulation. Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed as “liquid load factor Lf” [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

Loading Factor was calculated by equation:

Loading factor $Lf = \Phi ca + \Phi co * 1/R$; $Lf = W/Q$; $R = Q/q$

Where, Φca = liquid retention potential for carrier material (such as Neusilin® US2); Φco = liquid retention potential for coating material (Aerosil 200); R = ratio of carrier to coating material; W = weight of liquid medication; Q = amount of carrier material; q = amount of coating material.(Spireas, Sadu et al. 1998)

MATERIALS AND METHODS:

Materials

Domperidone USP was obtained as gift sample from Cadila Pharmaceuticals Ltd, Mumbai, Fujicalin® and Neusilin® was obtained as a gift sample from Fuji Chemicals Ltd., Japan. Acrysol EL-135, Acrysol K-150 were procured from Corel Pharma Chem, Ahmedabad, India and Tween 80 IP is purchased from S. D. Fine Chem. Ltd., Mumbai.

Methodology for preparation of liquisolid compacts

The drug was initially dispersed in non-volatile systems termed as liquid vehicles 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 sodium starch glycolate as disintegrant and lubricants were added and mixed in mortar. The resultant liquisolid powder is evaluated for flow properties such as 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 and in-vitro dissolution.(Nokhodchi, Hentzschel et al. 2011)

Solubility study for selection of liquid vehicle

The solubility of Domperidone in standard buffer having pH 1.2, Glycerine, Propylene glycol, PEG 400, Tween 80, Oleic acid, Acrysol EL-135, Acrysol K-150 were carried out to evaluate the suitability of the non-volatile liquid vehicles as solvent for Domperidone. Saturated solutions were prepared by adding excess amount of Domperidone into 1 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 287 nm after dilution in methanol as appropriate. The concentration of Domperidone in each liquid vehicle was calculated based on the calibration curve of Domperidone in methanol. From these results, the solubility of Domperidone in the respective liquid vehicle was calculated. X-ray diffractograms of pure Domperidone and pure mixture of excipients and liquisolid formulation were done for confirmation of solubility.(Bose, De et al. 2022, Jafar, Mhg et al. 2010)

Selection of Carrier and Coating Material

Selection of carrier and coating material is based on Optimal flowable liquid-retention potential (Φ-value). The optimal flowable liquid-retention potential (Φ-value) of each powder excipient (Flocel PH101, Flocel PH 102, Neusilin®, Fujicalin®, and Aerosil 200) in liquid vehicles (Acrysol EL-135: tween 80 in ratio 0.9:0.1) were calculated based on the angle of slide measurement (Table 1). 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.(Hentzschel, Alnaief et al. 2012) The angle of the plate formed with the plane surface during the slide is defined as the angle of slide (Figure 1). The Φ-value of excipient in different concentrations of liquid vehicles were calculated based on equation given below.(Shah, Patel et al. 2012)

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

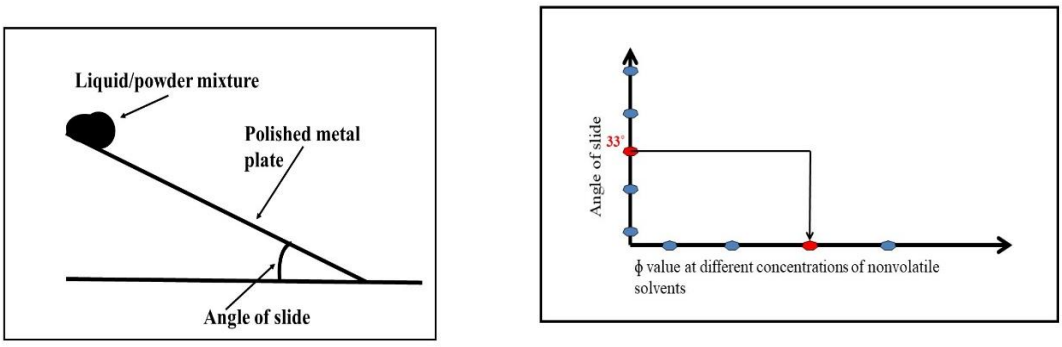

Figure 1. Angle of slide and Graphical representation of Φ value at angle of slide 33°

Table 1. Composition of Different Carriers to calculate acceptable Flowable Liquid-Retention Potential

Name of carrier/coating material	Weight of liquid	Weight of solid
Flocel 101	0	1
	0.1	1
	0.2	1
	0.3	1
	0.4	1
	0.5	1
	0.6	1
	0.7	1
Flocel102	0	1
	0.1	1
	0.2	1
	0.3	1
	0.4	1
	0.5	1
Neusilin® US2	0	0.5
	0.1	0.5
	0.2	0.5
	0.3	0.5
	0.4	0.5
	0.5	0.5
Fujicalin®	0	0.5
	0.1	0.5
	0.2	0.5
	0.3	0.5
	0.4	0.5
	0.5	0.5
Aerosil 200	0	0.5
	0.1	0.5
	0.2	0.5
	0.3	0.5

Drug Excipient Compatibility Studies

FT-IR study was carried out to analyse the compatibility study of the drug with excipients. Change in characteristic peak specific for a functional group of drug was the evaluation parameter for this type of compatibility test.(Ismail, Kerdpol et al. 2021)

Evaluation of Liquisolid compact tablet

The flow property of material ready to compress was evaluated by measuring angle of repose, Hausner ratio, and Carr's index as a precompression evaluation parameters. Weight Variation Test, Crushing Strength, Disintegration time, Friability test, Content Uniformity Test were evaluated for tablets as post compression evaluation parameters. (Awandekar, Tekade et al. 2022, Ratnakar and Gohel 2018)

In vitro drug dissolution test

Drug release studies were carried out using paddle type II dissolution test apparatus (900 ml, 75 rpm, 37°C) in standard buffer having pH 1.2. At the end of each sampling time period, 5ml of the samples were taken and analysed for drug content. A 5ml volume of fresh and filtered dissolution medium was added to make the volume after each sample withdrawal. Sample is analysed at 284 nm in UV Visible spectrophotometer.(Molavi, Hamishehkar et al. 2020, Ratnakar, Patel et al. 2012)

Optimization of formulation:

There were various formulation variables, which affect the preparation and properties of liquisolid tablet, which were identified and studied in preliminary studies. Two factors which mainly affect the dissolution rate

were drug concentration in liquid vehicle and carrier to coating ratio (Excipient ratio) (Table 2). These parameters were considered as independent variables. 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 3. Dependent variables selected were angle of repose and percentage drug release at 15 minutes in Standard buffer pH 1.2 (Table 2).

Table 2. List of Different Dependent & Independent Variables

Independent Variables						Dependent Variables	
X_1			X_2			Y_1	Y_2
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
-1	0	1	-1	0	+1		
15	20	25	10	15	20		

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

Batch	Domperidone Conc. %w/wa	Rb	W	Lf	Neusilin® US2 Q=W/Lf (mg)	Aerosil200 q=Q/R (mg)	Sodium starch glycolate 5%	Total unit weight (mg)c
LST1	10	15	100	0.946	105.70	7.04	10.63	226.04
LST2	10	20	100	0.9395	106.43	5.32	10.58	224.95
LST3	10	25	100	0.9356	106.88	4.27	10.55	224.29
LST4	15	15	66.67	0.946	70.47	4.69	7.09	150.70
LST5	15	20	66.67	0.9395	70.95	3.54	7.05	149.97
LST6	15	25	66.67	0.9356	71.25	2.85	7.03	149.53
LST7	20	15	50	0.946	52.85	3.52	5.31	113.03
LST8	20	20	50	0.9395	53.21	2.66	5.29	112.48
LST9	20	25	50	0.9356	53.44	2.13	5.27	112.15

a: Each tablet contains 10mg equivalent domperidone dissolved in Acrysol EL-135 and tween 80 in ratio 0.9:0.1

b: R = Carrier: Coating ratio; R = Q/q

c: Each tablet contains magnesium stearate 1% and talc 2%

Comparison of optimized formula with Marketed tablet formulation (MKT)

Formulated liquisolid compact of Domperidone was compared with marketed product. Domperidone tablet is available in the market from different companies. Marketed product DOMSTAL Tab 10 mg was taken for comparison**.** Comparison is done using in vitro dissolution study and model independent parameters like dissolution efficiency, mean dissolution time and similarity and dissimilarity factor (f1&f2) were calculated.(Kumar, Murthy et al. 2021)

RESULT:

Solubility Studies for selection of non-volatile vehicle.

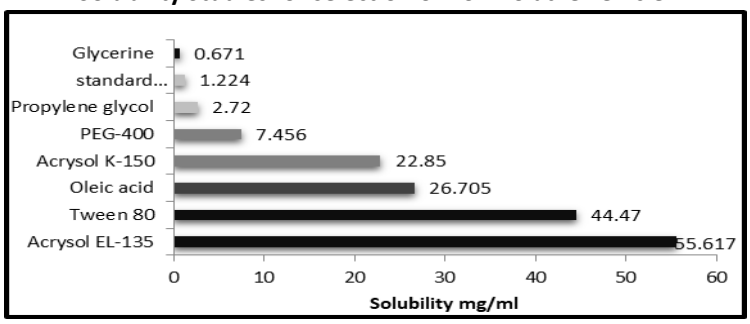

Figure 2. Solubility of Domperidone in various liquid vehicles

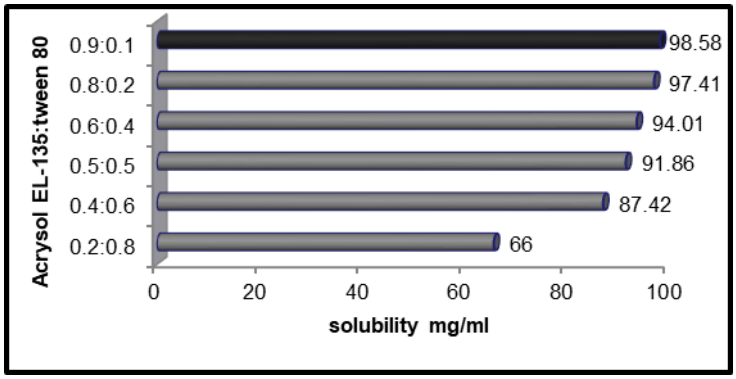

Figure 3. Solubility of Domperidone in combination of Acrysol EL-135: Tween80

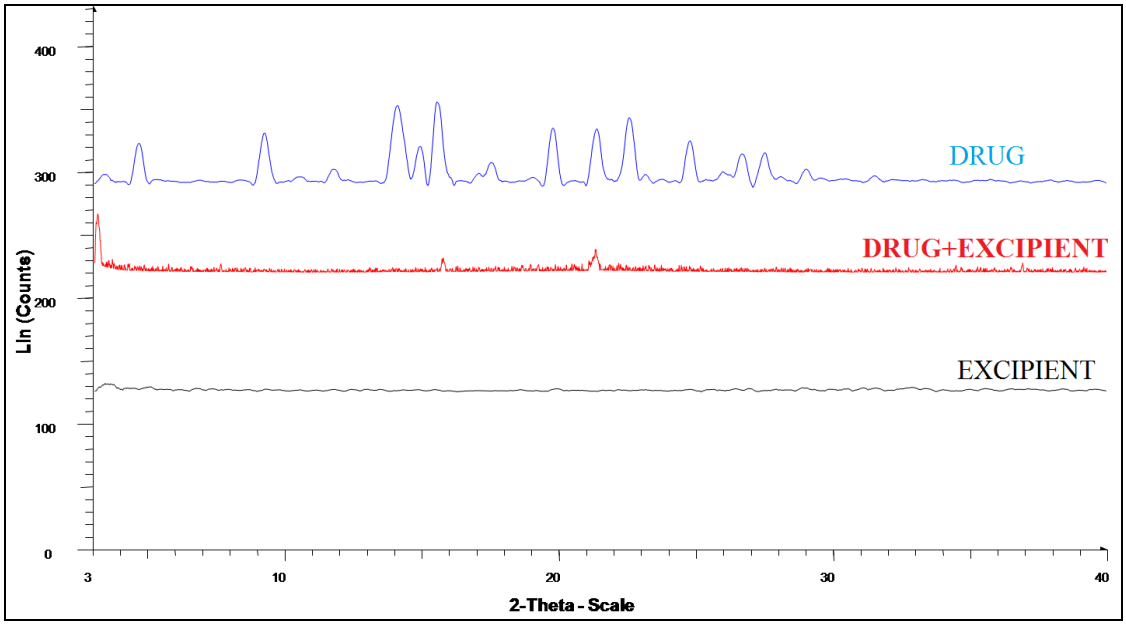

Figure 4. Overlay X-ray Diffractograms of Pure Drug, Excipient Mixture and Liquisolid Formulation

According to the data as seen in figure 2, the solubility of Domperidone was found more in non-volatile solvent as compared to Standard buffer pH 1.2. This is beneficial to enhance the dissolution rate of Domperidone. According to data, there was improvement in solubility when combination of two non-volatile solvents Acrysol EL-135 and tween 80, in different ratios were tried. Ratio 0.9:0.1 showed highest solubility. Solubility of Acrysol EL-135: tween 80 in ratio 0.9:0.1 was found to be 98.58 mg/mL as per figure 3. It is highest compared to other combinations and non-volatile solvents too. Confirmation of solubility of drug in solvents incorporated in liquisolid system shown by disappearance of sharp peaks of drug during X-ray diffractograms. (Figure 4).

Selection of carrier and coating material:

Angle of slide measurement is an effective way for determination of the flowable liquid-retention potential (Φ-value) of fine powders with particle diameter below 150 µm, and this technique had been successfully used in the design of various liquisolid formulations.(Spireas, Sadu et al. 1998). Since Flocel PH 101, Flocel PH 102, Neusilin®, Fujicalin® and Aerosil 200 have particle sizes of approximately 50 µm, 100 µm 44-177µm,115µm and 0.2-0.3 µm (from manufacturer COA), respectively, hence angle of slide measurement would be an appropriate method to determine the flow properties of these powder excipients in the relevant liquid vehicles. The Φca-value and Φco-value will decide the amount of carrier and coating materials required to produce dry free flowing powder.(Spireas, Sadu et al. 1998)

The calculated Φ-value was plotted against the corresponding angle of slide and the Φ-value at 33˚ represents the optimal flowable liquid retention potential (Φ-value) of the powder excipient in the corresponding liquid vehicle (Table 4).

The weight of liquid per unit weight of powder that is corresponding to 33˚ was used to determine the loading factor (Lf) at each R value. The liquid retention potential is a property that depends on both the excipient used and the liquid absorbed or adsorbed by that excipients(Shah, Patel et al. 2012) (Table 4). Neusilin® has shown higher liquid retention potentials in both liquid vehicles compared to other excipients. This is can be attributed to higher specific surface area of Neusilin® particles (300 m^2/g) that allows the adsorption of larger amount of liquids on its surface compared with those of Flocel PH 102 (1.21–1.30 m^2/g), Fujicalin® (36.9 m^2/g) and Aerosil (200 m^2/g). So, Neusilin® and Aerosil 200 were selected as carrier and coating material respectively.

Table 4. Optimum Flowable Liquid Retention Potential Φ value at 33˚ angle

Name of carrier/coating material	Weight of liquid	Weight of solid	Φ value	Angle of slide	Optimum Flowable Liquid Retention Potential Φ value at 33˚ angle
Flocel 101	0	1	0	40	0.04
	0.1	1	0.1	21	
	0.2	1	0.2	26	
	0.3	1	0.3	30	
	0.4	1	0.4	25	
	0.5	1	0.5	26	
	0.6	1	0.6	24	
	0.7	1	0.7	29	
Flocel102	0	1	0	36	0.24
	0.1	1	0.1	42	
	0.2	1	0.2	35	
	0.3	1	0.3	28	
	0.4	1	0.4	21	
	0.5	1	0.5	33	
Neusilin® US2	0	0.5	0	17	0.92
	0.1	0.5	0.2	25	
	0.2	0.5	0.4	29	
	0.3	0.5	0.6	30	
	0.4	0.5	0.8	31	
	0.5	0.5	1	35	
Fujicalin®	0	0.5	0	25	0.72
	0.1	0.5	0.2	39	
	0.2	0.5	0.4	36	
	0.3	0.5	0.6	35	
	0.4	0.5	0.8	32	
	0.5	0.5	1	30	
Aerosil 200	0	0.5	0	25	0.39
	0.1	0.5	0.2	24	
	0.2	0.5	0.4	34	
	0.3	0.5	0.6	45	

Evaluation of Liquisolid tablet

The results from precompression parameters (Table 5) revealed that batch LST3, LST9, LST6 have Carr's index between 11 to 15 indicates good flowability. The rest of the batches had fair and passable flowability as Carr's

index was above 16. The batches LST6, LST9 had Hausner ratio between 1.12 to 1.18 which indicate good flowability and rest of the batches had fair flowability as hausner's ratio was between 1.19 to 1.25. From the results of angle of repose batch LST2, LST3, LST4, LST5, LST6, LST7, LST8, LST9 which were between 25 to 30 and this indicates excellent flowability while LST1 had good flowability. From the pre compression evaluation parameters it is concluded that LST3, LST6, LST9 had value of angle of repose, Carr's index and Hausner ratio in range of good flow properties.

The results from post compression parameters are shown in Table 5. 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 LST3, LST6, LST9 was found to be lesser as compared to LST1, LST4, LST7 in which higher amount of Aerosil 200 was present. This was also similar in harness and friability.

Drug content in LST3, LST6, LST9 was lesser compared to other batches due to presence of higher excipient ratio. All results of evaluated tablets were found to be in specified limit. Disintegration time is dependent on the carrier to coating ratio (R). As the value of R increases the disintegration time decreases. The dissolution profiles of LST 1 to LST 9 in standard buffer pH 1.2 is shown in figure. 5.

Table 5. Pre compression evaluation parameters of Liquisolid system of LST 1 to LST 9

Pre compression evaluation parameters						
Batch	Angle of repose (ɵ)		Carr's index (%)		Hausner's ratio	
LST1	32.56		21.56		1.25	
LST2	28.78		15.83		1.23	
LST3	28.86		14.23		1.19	
LST4	29.13		19.97		1.23	
LST5	27.74		16.24		1.22	
LST6	25.69		14.41		1.18	
LST7	27.59		15.98		1.22	
LST8	26.20		15.08		1.21	
LST9	25.05		14.58		1.18	
Post compression evaluation parameters						
Batch	Weight variation (mg)	Thickness (mm)	Hardness (N)	% Friability	Dis-integration time (sec)	% Drug content
LST1	226±1.23	2.2	57.4±1.7	0.767	180±2.7	98.53
LST2	224±1.33	2.2	56±1.5	0.763	175±2.4	97.12
LST3	224±1.45	2.2	54.2±1.32	0.760	115±3.21	96.98
LST4	150±1.27	1.2	59.1±1.56	0.762	179±2.55	98.95
LST5	150±2.56	1.2	58±2.7	0.750	165±2.9	98.62
LST6	150±2.15	1.2	57.9±1.45	0.749	104±3.05	98.55
LST7	113±1.89	1.1	58.2±1.27	0.711	118±3.65	99.95
LST8	100±2.98	1.1	58.6±1.3	0.620	98±2.15	99.78
LST9	112±2.19	1.1	57.4±1.37	0.623	99±2.69	98.56

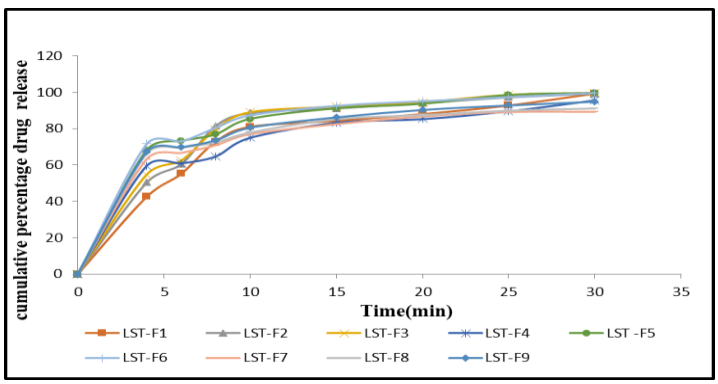

Figure 5. Comparison of in vitro Release Profile of Batch LST 1 To LST 9 in standard buffer pH 1.2

Effect of Excipient ratio (R value) (X_1) and concentration of drug (X_2) on Y_1 (Angle of repose) and Y_2 (Percentage drug release at 15 minutes)

Table 6 displays the effects of the independent factors on the dependent variables, which are the drug concentration and excipient ratios' effects on the angle of repose and release of drug at 15 minutes.

Table 6. Data Transformation of 3^2 Full Factorial Design.

Batch	Actual value		Coded value		Responses	
	Excipient ratio R	Drug concentration %w/w	X_1	X_2	Angle of Repose (Y_1)	Percentage drug release in 15 minutes (Y_2)
LST 1	15	10	-1	-1	32.56	84.42
LST 2	20	10	0	-1	28.78	91.23
LST 3	25	10	1	-1	28.86	92.20
LST 4	15	15	-1	0	29.13	83.35
LST 5	20	15	0	0	27.74	91.15
LST 6	25	15	1	0	25.69	92.73
LST 7	15	20	-1	1	27.59	82.41
LST 8	20	20	0	1	26.20	85.30
LST 9	25	20	1	1	25.05	86.26

For response Y_1, reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis (Table 7). The coefficients b1 and b2 was found to be significant at $P < 0.05$ and hence they were retained. Therefore, it was concluded that the interaction term and polynomial terms do not contribute significantly to the prediction of Angle of repose. Increase in the excipient ratio (R value), there was decrease in angle of repose which may be shown by coefficient b_1 bears a negative sign. This may be explained by increase in R value there is increase in concentration of Neusilin® which contributes to good flow properties of liquisolid systems. Increase in the drug concentration there is decrease in angle of repose which may be shown by coefficient b_2 bears a negative sign. This may be explained by increase in drug concentration there is decrease in amount of non-volatile liquids to be added to the liquisolid systems which contributes to improvement in flow property on decrease of drug concentration. R^2 value is 0.9525 which explains that about 95.25 % 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 confirmed by 3D response surface plots and contour plot as per figure 6.

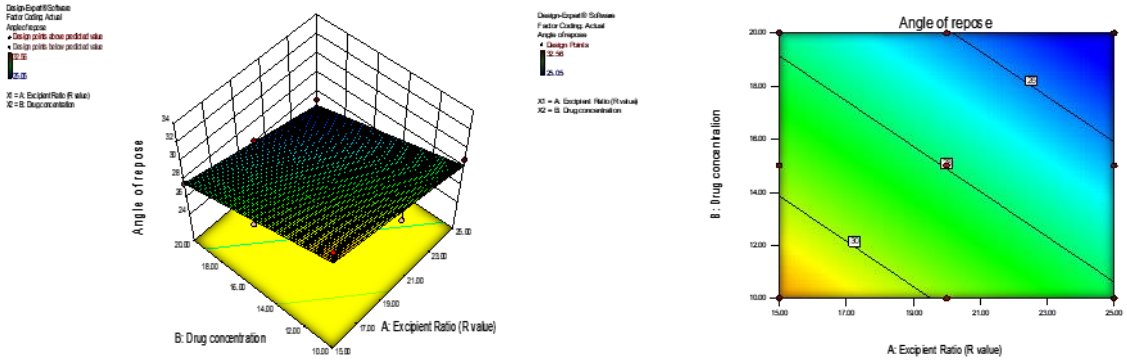

Figure. 6. 3D Response Surface Curve and Two-Dimensional Contour Curve for Angle of repose (Y_1).

Table 7. Summary output of regression analysis for effect of Excipient ratio (R value) (X_1) and concentration of drug (X_2) on Y_1 (Angle of repose) and Y_2 (percentage drug release at 15 minutes)

Summary output of regression analysis for effect of Excipient ratio (R value) (X_1) and concentration of drug (X_2) on Y_1 (Angle of repose)			
Coefficient	Coefficient value	P-value	Level of significance
b_0	27.13778	2.38E-05	---
b_1	-1.61333	0.016163	Significant
b_2	-1.89333	0.010379	Significant
b_{12}	0.573333	0.387824	Non-significant
b_{11}	0.653333	0.334094	Non-significant
b_{22}	0.29	0.523097	Non-significant
Equation			
Full Quadratic Model	$27.13-1.61X_1-1.89X_2+0.57X_1X_2+0.65X_1^2+0.29X_2^2$		
Reduced Linear Model	$27.13-1.61X_1-1.89X_2$		
Summary output of regression analysis for effect of Excipient ratio (R value) (X_1) and concentration of drug (X_2) on Y_2 (percentage drug release at 15 minutes)			
Coefficient	Coefficient value	P-value	Level of significance
b_0	90.63111	3.57E-06	---
b_1	3.501667	0.009242	Significant
b_2	-2.31333	0.028592	Significant
b_{12}	-2.33167	0.104087	Non-significant
b_{11}	-2.10667	0.128198	Non-significant
b_{22}	-0.9825	0.262494	Nonsignificant
Equation in terms of coded factors			
Full Quadratic Model	$90.63+3.50X_1-2.31X_2-2.33X_1X_2-2.10X_1^2-0.98X_2^2$		
Reduced Linear Model	$90.63+3.50X_1-2.31X_2$		

For response Y_2 reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis (Table 7). The coefficients b1 and b2 was found to be significant at $P < 0.05$ and hence they were retained. Therefore, it was concluded that the interaction term and polynomial terms 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 was increase in drug release at 15 minutes which may be shown by coefficient b_1 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 was increase in dissolution rate of drug. Increase in the drug concentration there was decrease in drug release at 15 minutes which may be shown by coefficient b_2 bears a negative sign. This may be explained by increase in drug concentration there is decrease in amount of non-volatile liquids to be added to the liquisolid systems, so there is less wetting of drug and less improvement in solubility due to lack of sufficient non-volatile liquid to solubilise the drug. R^2 value is 0.95483 which shows that 95.48% 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 3D response surface plots and contour plots as per figure 7

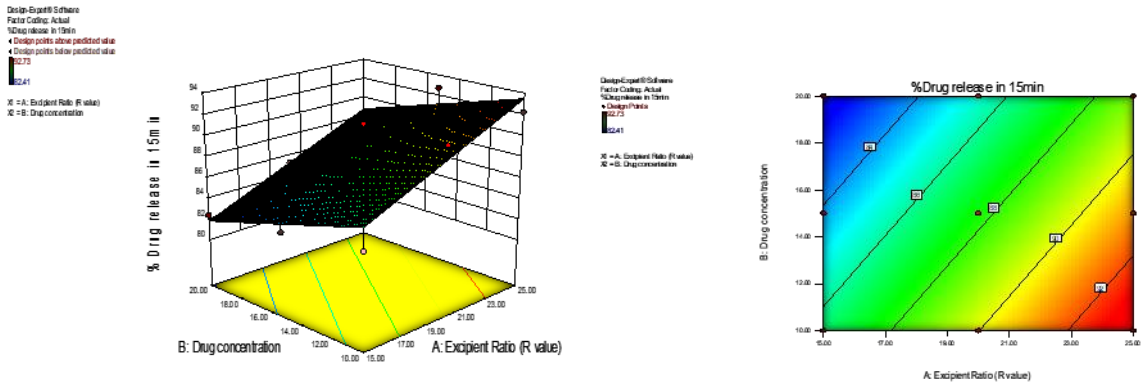

Figure 7. 3D Response Surface Curve and Two-Dimensional Contour Curve for % Drug Release in 15 minutes (Y_2).

The overlay of the responses (Figure 8) generated an optimized area, as per the desired criteria. The angle of repose was set in range 25-28. The percentage drug release at 15 Min. was set in range 85-90 %. One optimized check-point batch (Table 8) was prepared on the basis of generated overlay plot of responses to validate the model generated. Checkpoint Batch was evaluated for pre compression and post compression parameter and results are shown in Table 9. All results of evaluated tablets were found to be in specified limit.

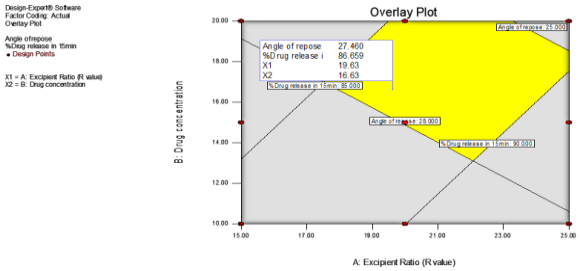

Figure 8. Overlay Plot of Response Variables

Table 8. Formulation of checkpoint batch LST 10

Batch	Domperidone Conc. %w/wa	Rb	W	Lf	Neusilin® US2 Q=W/Lf (mg)	Aerosil 200 q=Q/R (mg)	Sodium starch glycolate 5%	Total unit weight (mg)c
LST 10	16.63	19.63	60.13	0.94	63.98	3.26	6.37	135.32

a: Each tablet contains 10mg equivalent domperidone dissolved in Acrysol EL-135 and tween 80 in ratio 0.9:0.1

b: R = Carrier : Coating ratio; R = Q/q

c: Each tablet contains magnesium stearate 1% and talc 2%

Table 9. Pre compression and post compression evaluation parameters of LST 10

Batch	Angle of repose (ɵ) Mean ± SD	Carr's index (%) Mean ± SD	Hausner's ratio Mean ± SD
LST 10	27.627±0.14	15.17±0.53	1.22±0.009

Weight variation (mg)	Thickness (mm)	Hardness (N)	% Friability	Dis-integration time (sec)	Percentage Drug content
135±1.36	1.2	58.45±2.6	0.785	160±1.2	98.91

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.

Similarity factor f_1 and dissimilarity factor f_2 was found between percentage drug release up to 30 minutes of optimized batch and MKT. f_1 value was found to be 10.907 and f_2 value was found to be 53.597. From the data it infers that both dissolution profile is dissimilar according to f_1 and similar according to f_2 but to very less extent because percentage drug release is rapid within 15 minutes in Optimized batch as compared to MKT. As per figure 9, there was increase drug release in optimized batch compared to MKT. The improvement in dissolution contributes to the presence of non-volatile solvents in the formulation which improves solubility and wetting properties of drug.

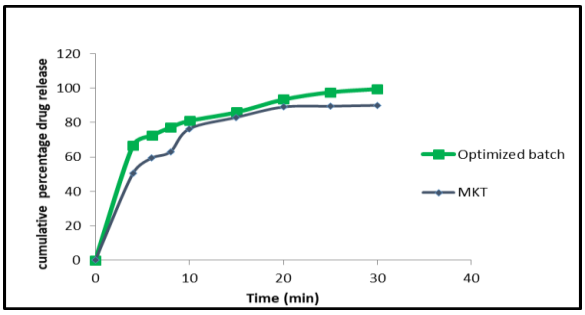

Figure 9. Dissolution Profile Comparison of Optimized batch tablet and Marketed tablet (DOMSTAL 10mg) in Standard buffer pH 1.2

CONCLUSION:

From present investigation it was concluded that Acrysol EL 135 and Tween 80 proved to be promising liquid vehicle for formulation of liquisolid compacts for improvement in the dissolution of poorly water soluble drug. It was also concluded that Neusilin® was found to be having better carrier and adsorbent properties. 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.

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CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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None

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