Original Article

ENHANCING THE SOLUBILITY OF DIPYRIDAMOLE BY LIQUISOLID COMPACTS BASED ON A FACTORIAL DESIGN APPROACH

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Abstract

Dipyridamole is a phosphodiesterase inhibitor used to prevent postoperative thromboembolic events. It is a poorly water-soluble drug with absolute bioavailability of 37-66 %. Water-insoluble drugs still have a poor dissolution rate, one of the biggest problems facing the pharmaceutical industry. To improve the dissolution rate of Dipyridamole, liquisolid compacts were developed in the present study. Liquidsolid formulations were prepared using Peceol, Avicel PH 112, and Aerosil, in different ratios, as a non-volatile solvent, carrier material and coating material respectively. Excipients and drug interactions were characterized through FT-IR. These studies showed no interaction between excipients and drug. 32 factorial design approach was implemented. The formulations were optimized using Design Expert version 13.00 (StatEase Inc., Minneapolis, MN, USA). An optimal formulation exhibited an angle of repose of 25.12°, a hardness of 3.1 kg/cm2 and a percentage cumulative drug release of 99.22 % after 10 minutes. The observed values were found to be similar to the predicted values. Based on these observations, DPY–O can be considered to be the optimum formulation.

Keywords: Dipyridamole, Liquisolid, Design Expert, FT-IR.

INTRODUCTION

Research in the field of formulation science remains most vibrant in the field of solubility or dissolution enhancement techniques. This is one of the most discussed but still unresolved issues. Dissolution and solubility are fundamental concepts in the physical and chemical sciences, including biopharmaceutical and pharmacokinetic considerations. It is the solubility/dissolution behaviour of a drug that drives its oral bioavailability, with the gastrointestinal tract becoming the rate-limiting step for its absorption. Because of these nonoptimal biopharmaceutical properties, more than 40% of new drug candidates fail to enter drug development pipelines. [1].

The dissolution profile and, consequently, the absorption efficiency and bioavailability of water-insoluble drugs and/or liquid lipophilic medications have been enhanced over the years [2]. It has been demonstrated by several researchers that liquisolids are the most promising method for promoting drug dissolution [3–5]. Without further modifications, liquid lipophilic drugs can be converted into liquisolids. The choice of non-volatile solvent is important when formulating a solid water-insoluble drug. It should be initially dissolved or suspended in the non-volatile solvent system that will produce the desired concentration of the drug solution or drug suspension. For liquid vehicles, it is recommended to use inert, water-mixable organic solvents with a high boiling point. Examples include propylene glycol, liquid polyethylene glycols, polysorbates, fixed oils, or glycerine [5].

Dipyridamole is a nucleoside transport inhibitor and a PDE3 inhibitor medication that inhibits blood clot formation [6]. when given chronically and causes blood vessel dilation when given at high doses over a short time. Dipyridamole inhibits the phosphodiesterase enzymes that normally break down cAMP (increasing cellular cAMP levels and blocking the platelet aggregation, response to ADP) and/or cGMP. Dipyridamole inhibits the cellular reuptake of adenosine into platelets, red blood cells, and endothelial cells, leading to increased extracellular concentrations of adenosine. [7]

Hence, the objective of the present work was to formulate the liquisolid compacts for Dipyridamole to improve the solubility and dissolution rate using 23 Factorial Design approach, which can increase clinical efficacy or reduce the oral dosage required to achieve the same effect.

MATERIALS AND METHODS

Materials

Dipyridamole was obtained as a gift sample from Hetero Drugs (Pvt. Ltd), Hyderabad., India. Maisine CC, Peceol & Lubrafac were purchased from Gattefosse, Mumbai, Maharashtra., India. Microcrystalline Cellulose, Aerosil, Talc, Dicalcium Phosphate were purchased from S.D. Fine Chem. Ltd. Mumbai., India. All additional chemicals, reagents, and solvents used were of analytical grade.

Solubility Studies

Solubility studies for Dipyridamole were performed by using various solvents. Excess amount of Dipyridamole was added in 10 ml of selected non-volatile liquid solvents to form a supersaturated solution in a glass vial. The mixtures were vortexed for 15 minutes to facilitate the mixing of drug and non-volatile solvent. The mixtures were kept in a shaker incubator at 25°C for 48 h to achieve equilibrium. The samples were centrifuged at 5000 rpm for 30 min to sediment insolubilized drugs. Filtered solution was appropriately diluted with methanol, and UV absorbances were measured at 283 nm wavelength. Concentration of dissolved drug was determined using standard equation.

Measuring Angle of Slide (θ)

Angle of slide is used as a measure of flow properties of powders. Determination of angle of slide is done by weighing the required quantity of carrier material and placing it at one end of the metal plate having a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as the angle of slide.

Measuring Flowable liquid retention potential (φ):

Increasing amount of selected solvent was added and mixed well with 10 gm of each of material (carrier and coating respectively) and angle of slide was determined using the above mentioned procedure. The angle of slide value of around 33º represents the optimal flowable property of the excipient with respect to the solvent. The corresponding Phi-value was calculated from the following equation. [8]

Φ–value = Wt. of liquid/Wt. of solid

Measuring Liquid Load Factor (Lf)

On the basis of Phi-value of optimized carrier and coating material the liquid load factor (Lf) and quantities of carrier and coating materials were calculated using following formula.

$Lf = \varphi CA + \varphi CQ\ (1/R)$

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy helps to determine any chemical interaction between drug and excipients used in formulation. The FTIR spectra for Dipyridamole and optimized powder mixture for liquisolid preparations were obtained using Bruker II Alpha spectrophotometer in the range of 4000–400 cm−1 pressure.

Preparation of Powder for Liquisolid Tablets

Initial trials of Liquisolid tablets were done with the calculated values of Avicel 112 and Aerosil 200. PVP K 30 was selected as the binder and Sodium starch glycolate was used as a disintegrant, DCP was used a diluent and the tablets were compressed using 8 mm punches to an average weight of 250 mg. Based on the observations of these initial trials, it was concluded that of all the excipients used, Avicel 112 and Aerosil 200 were found to be the main factors influencing tablet properties like flow, hardness, and friability. Hence, these two factors were selected for the design.

32 Factorial Design for Liquisolid Tablets

Design Expert trial version 13.00 (StatEase Inc., Minneapolis, MN, USA) was used to optimize the formulations. To determine the optimum values of the most influencing factors, 32 factorial design was applied, and a response surface equation was derived in order to investigate the interaction between the factors. In this design 2 factors were evaluated, each at 3 levels as shown in Table 1, and experimental trials were performed at all 9 possible combinations as shown in Table 2. The two independent variables were selected as X1 and X2. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X12 + b22X22$$

Where, Y is the dependent variable, b0 is the arithmetic mean response of the 9 runs and b1 is the estimated coefficient for the factor X1. The main effects (X1and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1 X2) show how the response changes when 2 factors are changed simultaneously.

Table 1: Levels of variables in coded and actual form for Dipyridamole Liquisolid Tablets

Levels (coded)	**Variables**	
	X1 – Avicel 112 (mg) (Actual)	**X2 - Aerosil 200 (mg) (Actual)**
-1	70	3.5
0	This value is set by software	
+1	130	9.5

The angle of repose, hardness and % drug release at 10 minutes were selected as dependent variables (responses).

In this design, by keeping the drug dose and quantity of other excipients same, 2 factors Avicel 112 (X1) and Aerosil 200 (X2); were evaluated, each at 3 levels (Table 2) and experimental trials were performed at all 9 possible combinations shown in Table 3 . Angle of repose, Hardness and % drug release at 10 minutes were selected as the responses to evaluate the effect of factors X1 and X2.

Table 2: Factorial Batches of Liquisolid Tablets of Dipyridamole

Factorial Batch Code	**Coded**		**Actual**	
	X1 – Avicel 112 (mg)	**X2 – Aerosil 200 (mg)**	**X1 – Avicel 112 (mg)**	**X2 – Aerosil 200 (mg)**
DPY1	0	-1	100	3.5
DPY2	+1	+1	130	9.5
DPY3	-1	+1	70	9.5

DPY4	-1	0	70	6.5
DPY5	-1	-1	70	3.5
DPY6	0	+1	100	9.5
DPY7	+1	0	130	6.5
DPY8	+1	-1	130	3.5
DPY9	0	0	100	6.5

Table 3: Formulation of Liquisolid Tablets of Dipyridamole:

Ingredients (mg)	**DPY1**	**DPY2**	**DPY3**	**DPY4**	**DPY5**	**DPY6**	**DPY7**	**DPY8**	**DPY9**
Dipyridamole	50	50	50	50	50	50	50	50	50
Peceol	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Avicel 112	100	130	70	70	70	100	130	130	100
Aerosil 200	3.5	9.5	9.5	6.5	3.5	9.5	6.5	3.5	6.5
Sodium starch glycolate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K- 30	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Dicalcium phosphate	66.44	30.44	90.44	93.44	96.5	60.44	33.44	36.44	63.44
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250	250	250	250

Liquisolid tablets of DPY were prepared each containing 50 mg of drug. DPY was dispersed in Peceol. Avicel 112 and Aerosil 200 were added to the above mixture under continuous mixing in a mortar. Finally, Sodium starch glycolate as superdisintegrant, PVP K- 30 as binder and Dicalcium phosphate as filler were mixed and the mixture was blended for a period of 10 minutes.

Pre Compression Parameters:

The blends of all formulations were evaluated for angle of repose which is indicative of flow properties.

Compression:

To the above blend, Magnesium stearate and Talc were added and the blend was compressed using 8 mm round flat punches in a single punch tablet press. Liquisolid tablets of DPY were successfully prepared and were used for further evaluation studies.

Evaluation of Compressed Tablets of Dipyridamole

Thickness:

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

Hardness:

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

Friability:

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

Disintegration Time:

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

Drug Content:

The DPY content in different liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 10 mg of DPY was dissolved in 100 ml methanol. 1 ml of this solution was diluted to 10 ml with methanol and measured spectrophotometrically at λmax of 283 nm.

In Vitro Drug Release:

The in vitro drug release study of the DPY tablets was performed using USP Type II dissolution apparatus (LABINDIA DS 8000). Liquisolid tablets and pure drug (50 mg) separately, were put into each of 900 ml 0.1 N HCl, at 37±0.5°C with a 50 RPM rotating speed. Samples (10 ml) were withdrawn at regular time intervals (5, 10, 15, 20, 30 and 45min) and filtered using a 0.45μm filter. An equal volume of the dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method at 283 nm. All measurements were done in triplicate.

Evaluation of Responses:

Design Expert trial version 13.00 (StatEase Inc., Minneapolis, MN, USA) was used to optimize the formulations. was used for polynomial fitting and ANOVA results. Appropriate models were selected by comparing lack of fit, p values and R2 values. Graphs were plotted for statistically significant models with insignificant lack of fit at desired confidence levels.

Stability Studies

The stability study is an indicative method for determination of durability of quality and quantity of therapeutic agents with the passes of time under the influence of various atmospheric conditions such as temperature, humidity, light and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions at 40°C ± 2°C/75% RH ± 5% RH. Stability studies were conducted towards 3 batches of optimized for 3 months using Newtronic Stability Chamber-NLWH327SI. Samples were withdrawn after 3rd month and were analysed, and results are tabulated.

Differential Scanning Colorimetry (DSC):

Thermal analysis of Optimized Formulation was performed using thermal analyzer (Shimadzu DSC-60) Temperature axis and cell constant were calibrated by utilizing indium (In) (Auda S.H et al., 2014).

RESULTS & DISCUSSION

In the liquisolid formulation non-volatile liquid solvent is optimized for the high drug solubility in solvent. The solubility in various non-volatile solvents is given in Table 4. The table shows that solubility of DPY in Peceol is highest in comparison with other solvents. Peceol undergoes more hydrophobic interactions and cause the drug to solubilize. Thus, Peceol was selected to be the suitable solvent for preparing liquisolid formulation of Dipyridamole.

Table 4: Solubility data in different Non-Volatile liquid solvents

Name of solvent	Solubility (mg/ml)
Water	0.81
0.1 N HCl	35.45
Labrafac	24
Peceol	46
Maisine CC	18
Tween 80	10.7
Span 80	16.4
PEG 400	8.2

Angle of Slide & Flowable Liquid Retention Potential

Table 5: θ and φ values of Carrier and Coating materials

	Excipients	θ	φ
Carrier material	Avicel 102	32.51	0.351
	Avicel 112	33.13	0.609
	Lactose monohydrate	31.6	0.272
Coating material	Aerosil 200	33.02	1.60
	Cab-O-Sil	34.99	0.655

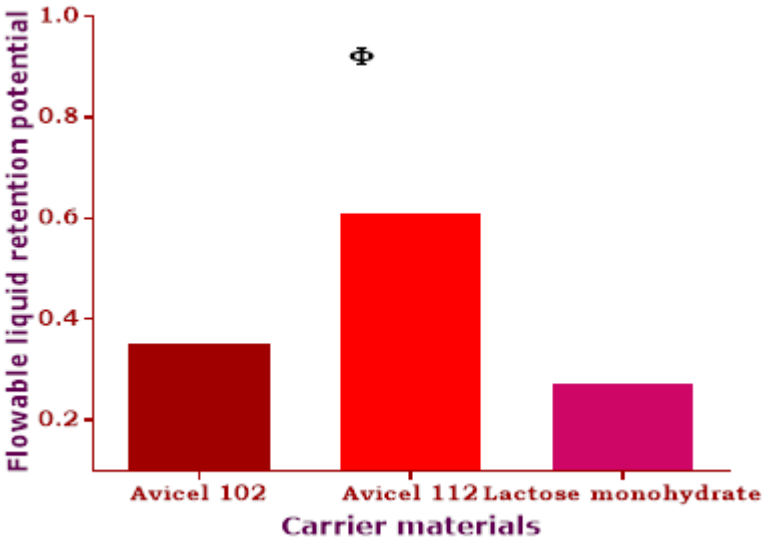

Figure 1: φ of Carrier Material

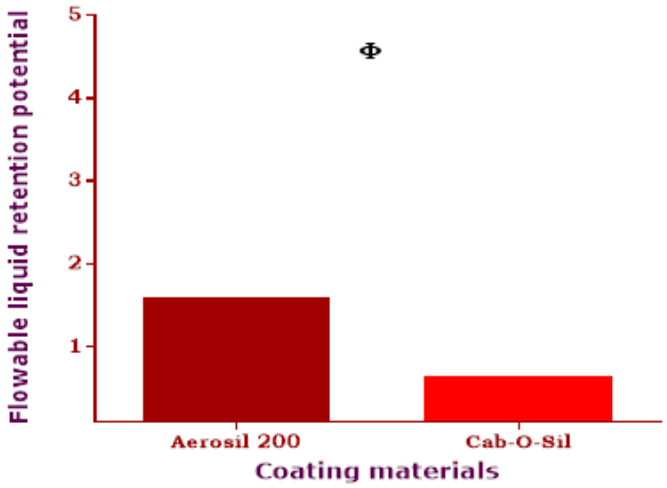

Figure 2: φ of Coating Materials (Y axis is corrected)

The Phi-value corresponding to an angle of slide of 33° was recorded as the flowable liquid retention potential of carrier and coating material. The Phi- values for carrier and coating material have been abbreviated as φCA and φCO respectively. The carrier and coating material with maximum liquid retention potential have been selected as optimum.

Higher the φ value at angle of slide 33° is considered as better carrier material and coating material. θ and φ values of various carrier material and coating materials are shown in Table 5 and Figure 1 & 2. Avicel 112 and Aerosil 200 were found to have highest phi value i.e. 0.609 and 1.60 respectively. Hence Avicel 112 and Aerosil 200 were selected as an optimum carrier and coating materials respectively for the DPY liquisolid formulation.

3.3 Measuring Liquid Load Factor (Lf)

On the basis of Phi-value of optimized carrier and coating material the liquid load factor (Lf) and quantities of carrier and coating materials were calculated using following formula.

Lf = φCA + φCQ (1/R)

= 0.609 + 1.6 * 1/15

= 0.715

FTIR

IR spectrum of quetiapine fumarate (Refer to Figure 3) shows a broad peak at 3383.13 cm-1 may be due to O-H stretching, 2921.45 cm-1 C-H stretching, 1536.24 cm-1 may be due to N-H bending, 760.39 cm-1 may be due to C-C stretching. The IR spectrum of the drug along with individual excipients and mixtures, it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the formulation derived during the present investigation as shown in Figures 3&4. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the excipients used.

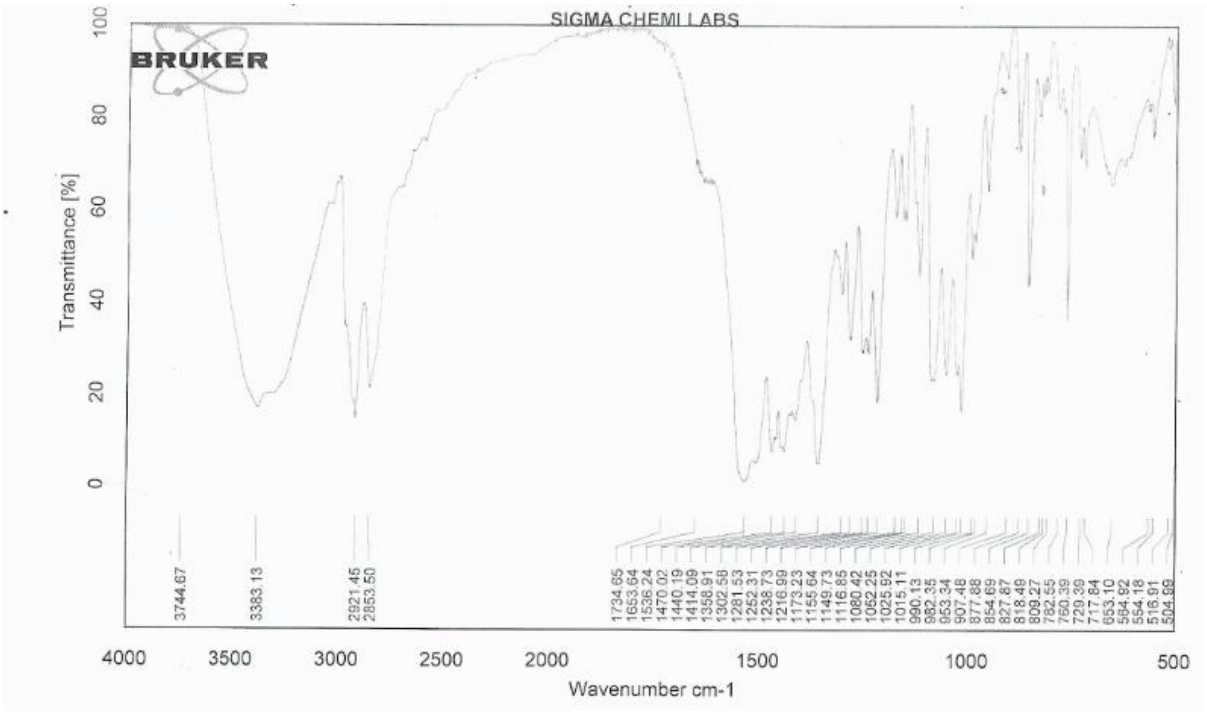

Figure 3: FTIR Spectra of Pure Drug Dipyridamole

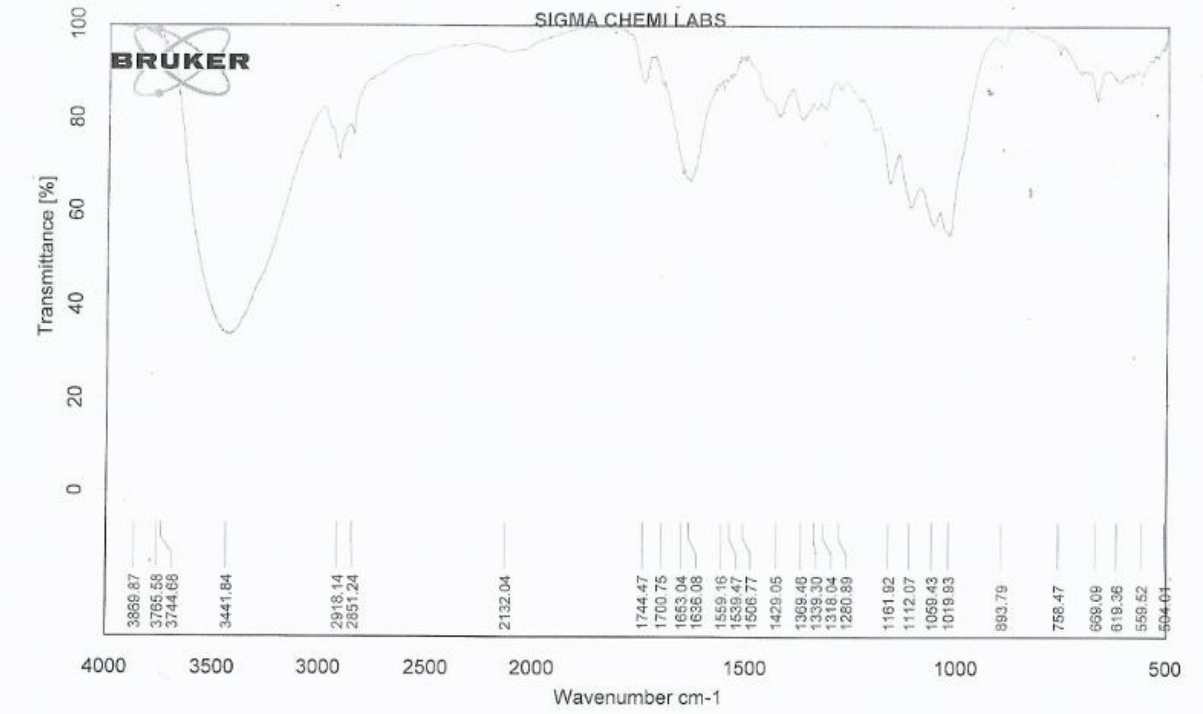

Figure 4: FTIR Spectra of Dipyridamole Formulation Mixture

Pre & Post Compression Parameters of Dipyridamole Tablets

Table 6: Results for Pre & Post Compression Parameters

Batches	Angle of repose (º)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)	Drug content (%)
DPY1	27	4.22	2.1	0.18	51	98.54
DPY2	24	3.16	3.4	0.15	15	99.07
DPY3	28	4.08	2.8	0.17	67	98.24
DPY4	31	4.03	2.6	0.16	46	97.22
DPY5	32	3.56	2.1	0.19	21	101.73
DPY6	26	3.49	2.3	0.13	14	100.01
DPY7	25	4.08	2.2	0.21	92	101.12
DPY8	28	4.37	3.5	0.15	40	98.42
DPY9	29	4.62	2.5	0.17	31	98.94

As shown in Table 6, Angle of repose of the formulations varied from 24° to 32° & thickness of liquisolid tablet was found to be in the range of 3.16 to 4.62 mm. It was observed that as the concentration of Avicel 112 and Aerosil 200 changes thickness varies. Avicel 112 has large surface area and porous nature, adsorbs high loads of oils or water and can be mechanically compacted into high quality tablets. Hardness of liquisolid tablet was found to be in the range of 2.1 to 3.5 kg/cm2 respectively. Avicel 112 is superior in compressibility. Avicel 112 makes hard tablets at low compression force and in addition, improves

the hardness of other filler and binder excipients. Avicel 112 with combination of Primojel and Dicalcium phosphate here improves the hardness and increases the bulk of tablet. But concentration of Dicalcium phosphate is same in all trials so there is no individual effect of Dicalcium Phosphate here on hardness. Increase in hardness and compression pressure did not affect the disintegration time and as well as friability. This indicates that as the concentration of Avicel 112 increases hardness of liquisolid tablet increases. Friability of tablets was found to be below 1% which is acceptable. Disintegration time of liquisolid tablets were in the range of 15- 92 secs. Drug content of all liquisolid tablets were found to be in between acceptable range.

In Vitro drug release:

Table 7: In Vitro Drug Release of Dipyridamole Tablet Formulations DPY1 to DPY9

Time (minutes)	Pure Drug	DPY 1	DPY 2	DPY 3	DPY 4	DPY 5	DPY 6	DPY 7	DPY 8	DPY 9
0	0	0	0	0	0	0	0	0	0	0
5	12.81	56.44	49.73	47.05	48.15	53.01	48.28	56.42	62.36	50.21
10	27.45	92.77	84.49	80.73	83.52	85.87	81.87	88.11	98.95	84.68
15	38.08	94.62	94.27	92.13	91.87	92.10	92.58	94.58	99.85	92.02
20	42.71	99.73	99.06	97.28	98.48	98.98	97.58	99.13	99.98	98.85
30	47.52	---	99.47	97.79	99.17	99.38	98.22	99.52	---	99.31

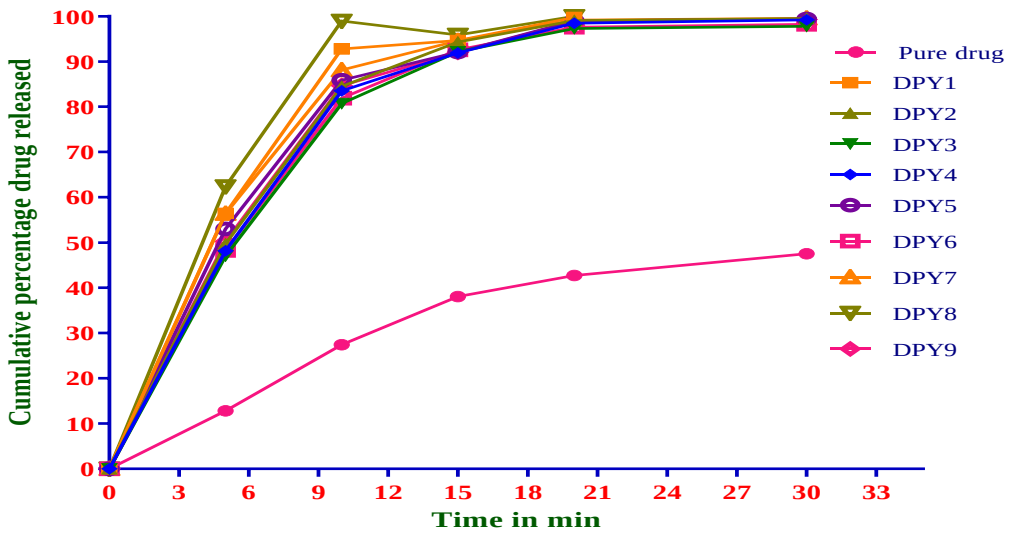

Figure 5: Dissolution Profile Comparison of Pure Drug & Formulations DPY1-DPY9

The percent drug release from DPY liquisolid tablet of batches DPY1 to DPY9 is shown in Figure 5 & Table 7. The pure drug showed a release of 27.45 % after 10 minutes and 47.52 % after 30 minutes. The % drug release after 10 minutes from all the batches was found to be in the range of 80.73 to 98.95. The batch DPY8 showed the highest drug release 99.98% at 20 minutes when compared to all other batches and pure drug. The obtained results of in vitro drug release showed a relationship between the carrier to coating material ratio and the in vitro release of DPY from liquisolid tablets. An increase in the R- value results in an enhanced release rate as there is higher quantity of Avicel 112 and low quantity of Aerosil 200. This is associated with enhanced wicking, disintegration and thus, enhanced drug release showed by batch DPY8. If high amounts of Aerosil 200 are used, which means that the R-value is low, the liquisolid formulation is overloaded with liquid formulation due to a high liquid

load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus slows down release rates. Of all the formulations, the highest % drug release was from DPY8 which was 98.95 % at 10 minutes whereas % drug release of pure drug at 10 minutes was 27.45 %. This suggests that liquisolid technology has enhanced the solubility and dissolution of DPY.

Evaluation of responses:

Response 1: Angle of repose

Table 8: Fit Summary

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0048		0.7747	0.6544	Suggested
2FI	1.0000				
Quadratic	0.6592		0.6587	-0.3229	
Cubic	0.6250		0.6000	-8.1125	Aliased

Table 9: ANOVA for Linear model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	46.17	2	23.08	14.75	0.0048	significant
A-Avicel 112	32.67	1	32.67	20.88	0.0038	
B-Aerosil 200	13.50	1	13.50	8.63	0.0260	
Residual	9.39	6	1.56			
Cor Total	55.56	8				

The Model F-value of 14.75 implies the model is significant. There is only a 0.48% chance that an F-value this large could occur due to noise.

P-values 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.

Final Equation in Terms of Coded Factors

Angle of repose = + 27.89 - 2.33 A - 1.50 B + 0.0000 AB + 0.6667 A^2 - 0.8333 B^2

Final equation in terms of Actual Factors

Angle of repose = + 42.41 – 0.225 A + 0.703 B – 2.708 AB + 0.0007 A^2 - 0.092 B^2

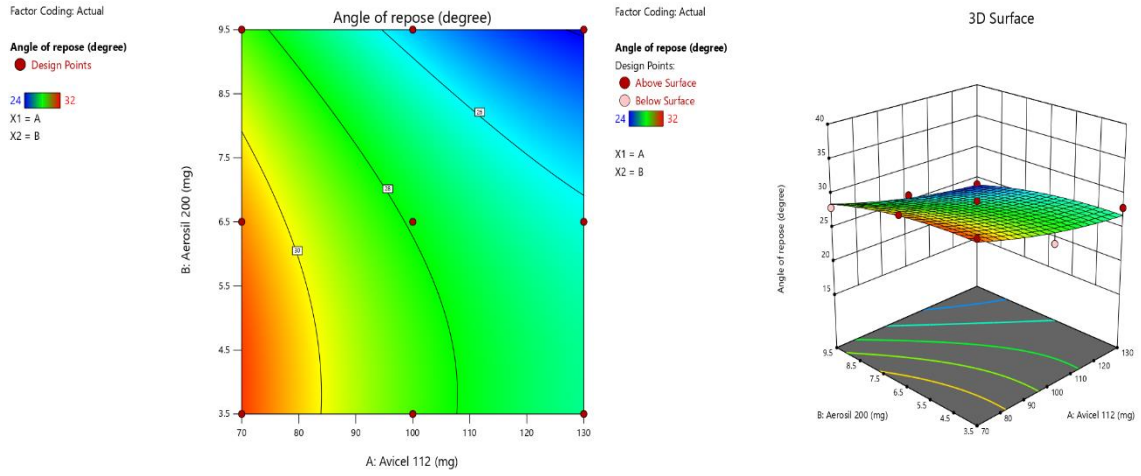

Figure 6: Response Surface Plots for Angle of Repose

The response angle of repose was analysed using the design expert software. The fit summary indicates the suitability of linear model (R2 = 0.8310). In the ANOVA table, the model F value of 14.75 implies the model is significant. There is only a 0.48 % chance that an F value this large could occur due to noise. P values less than 0.05 indicates the model terms are significant. In this case, A and B are significant model terms. The fit statistics indicates the predicted R2 of 0.6544 is in reasonable agreement with the adjusted R2 value of 0.7747 i. e., the difference is less than 0.2.

The one factor graph of Avicel 112 vs Angle of repose indicates that as the quantity of Avicel 112 was increased, the angle of repose was found to decrease significantly. The one factor graph of Aerosil 200 vs Angle of repose indicates that as the quantity of Aerosil 200 was increased, the angle of repose was found to decrease moderately.

Response 2: Hardness

Table 10: Fit Summary

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0044		0.8171	0.7520	Suggested
2FI	1.5054				
Quadratic	0.4983		0.6497	-0.6220	
Cubic	0.5731		0.4900	-6.0229	Aliased

Final equation in terms of coded values

Hardness = + 2.61 +0.2667 A + 0.1333 B – 0.2000 AB

Final equation in terms of actual values

Hardness = - 0.011111 + 0.023333 Avicel 112 + 0.266667 Aerosil 200 – 0.002222 Avicel 112 * Aerosil 200

Table 11: ANOVA for Linear model

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	45.16	2	22.58	13.68	0.005708	**Significant**
A-Avicel 112	31.42	1	31.42	19.78	0.0029	

B-Aerosil 200	12.10	1	12.10	8.34	0.0358	
Residual	8.27	6	1.38			
Cor Total	51.79	8				

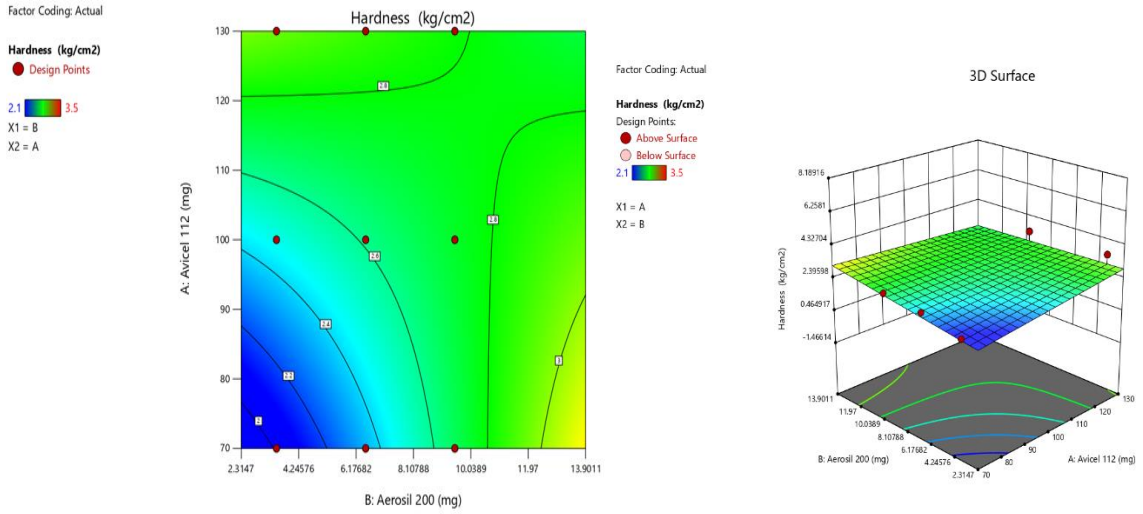

Figure 7: Response Surface Plot for Hardness

The fit summary for hardness indicates the suitability of linear model (R2 = 0.8372). In the ANOVA table, the model F value of 13.68 implies the model is significant. There is only a 0.57 % chance that an F value this large could occur due to noise. P values less than 0.05 indicates the model terms are significant. In this case, A and B are significant model terms. The fit statistics indicates the predicted R2 of 0.6435 is in reasonable agreement with the adjusted R2 value of 0.7853 i. e., the difference is less than 0.2.

The one factor graph of Avicel 112 vs Hardness indicates that as the quantity of Avicel 112 was increased, the hardness was found to increase moderately. However in the one factor graph of Aerosil 200 vs Hardness, it was observed that increase in the amount of Aerosil 200 had very slight increase in the hardness.

Response 3: Percentage Drug Release

Table 12: Fit Summary

Source	**Sequential p-value**	**Lack of Fit p-value**	**Adjusted R^2**	**Predicted R^2**	
Linear	0.0024		0.8206	0.6261	
2FI	0.0400		0.9146	0.7797	Suggested
Quadratic	0.2515		0.9433	0.7478	
Cubic	0.2641		0.9881	0.7297	Aliased

Final Equation in Terms of Coded Factors

% Drug Release = + 86.78 + 3.57 A – 5.08 B – 2.33 AB

Final Equation in Terms of Actual Factors

% Drug Release = + 69.05722 + 0.287333 Avicel 112 + 0.894444 Aerosil 200 – 0.025889 Avicel 112* Aerosil 200

Table 13: ANOVA for Linear Model

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	253.30	3	84.43	29.56	0.0013	significant
A-Avicel 112	76.54	1	76.54	26.80	0.0035	
B-Aerosil 200	155.04	1	155.04	54.29	0.0007	
AB	21.72	1	21.72	7.60	0.0400	
Residual	14.28	5	2.86			
Cor Total	267.58	8				

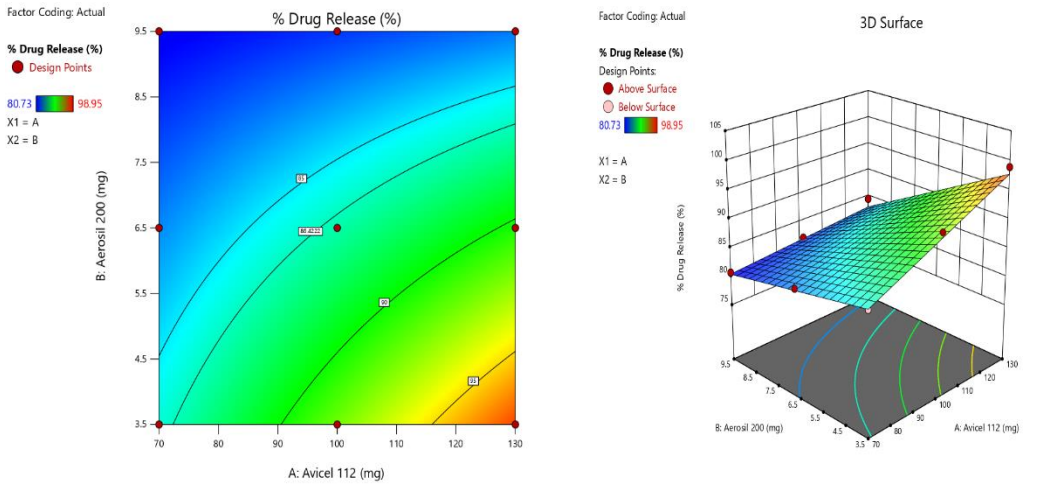

Figure 8: Response Surface Plot for % Drug Release

The fit summary for the response % Drug Release (10 minutes) indicates the suitability of 2F1 model (R2 = 0.9466). In the ANOVA table, the model F value of 29.56 implies the model is significant. There is only a 0.13 % chance that an F value this large could occur due to noise. P values less than 0.05 indicates the model terms are significant. In this case, A and B are significant model terms. The fit statistics indicates the predicted R2 of 0.7797 is in reasonable agreement with the adjusted R2 value of 0.9146 i. e., the difference is less than 0.2.

The one factor graph of Avicel 112 vs % Drug Release (10 minutes) indicates that as the quantity of Avicel 112 was increased, the % Drug Release (10 minutes) was found to increase significantly. In contrast, the one factor graph of Aerosil 200 vs % Drug Release (10 minutes) indicated that as the Aerosil 200 was increased, % Drug Release (10 minutes) was found to decrease.

Optimisation of Dipyridamole Liquisolid Tablets

Table 14: Criteria for Optimization of Dipyridamole Liquisolid Tablets

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:Avicel 112	is in range	100	150	1	1	3
B:Aerosil 200	is in range	3.5	9.5	1	1	3
Angle of repose	is target = 25	24	26	1	1	3
Hardness	maximize	2.1	3.5	1	1	3
% Drug Release	maximize	90	98.95	1	1	3

Table 15: Optimization of Dipyridamole Liquisolid Tablets

Number	Avicel 112	Aerosil 200	Angle of repose	Hardness	% Drug Release	Desirability	
1	150.000	4.278	25.000	3.204	99.372	0.924	Selected
2	150.000	4.101	25.088	3.215	99.899	0.899	
3	150.000	4.485	24.896	3.190	98.752	0.880	
4	149.586	4.342	25.000	2.611	99.106	0.715	
5	149.390	4.373	25.000	. 2.611	98.982	0.715	
6	149.790	4.310	25.000	2.611	. 99.237	0.715	

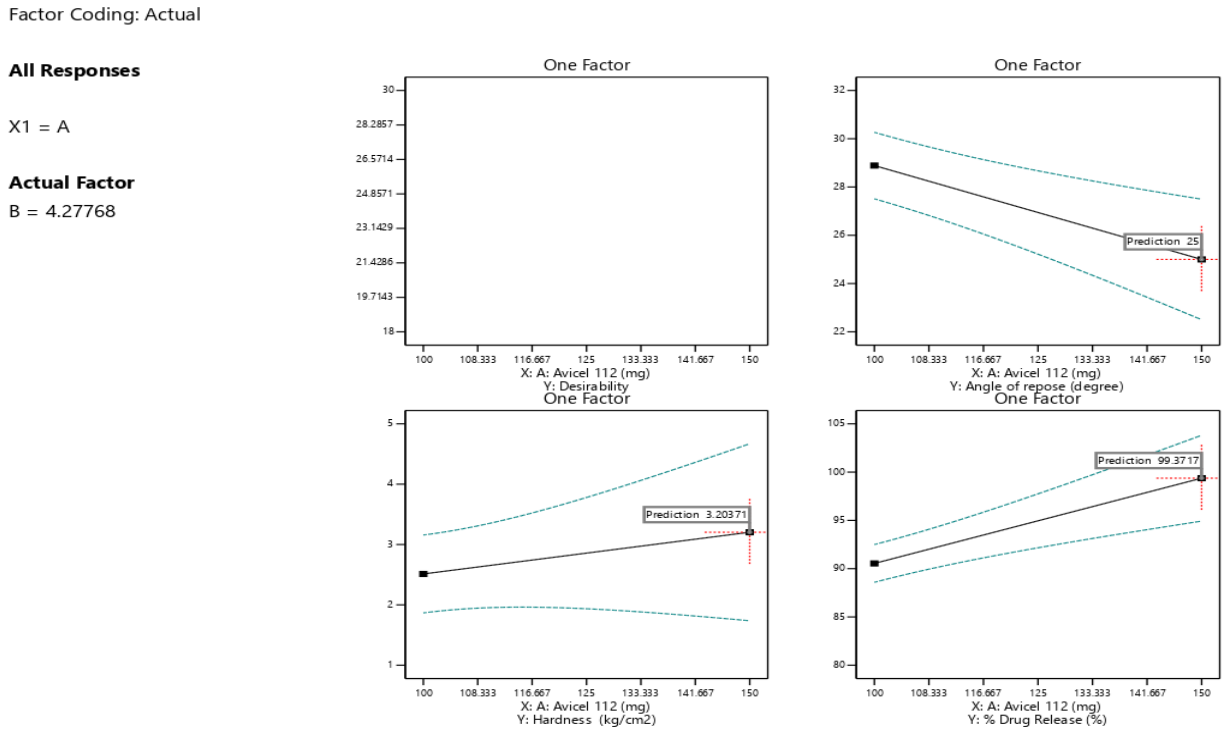

Figure 9: Response Surface Plot for Optimization of Dipyridamole Liquisolid Tablets

For optimization, criteria were set for the variables and responses as per the requirement shown in Table 14. Solutions for the same were obtained and shown in Table 15, which depicted that first solution i.e. Avicel 112 = 150.00 mg and Aerosil 200 = 4.278 mg were selected to get hardness 3.204 kg/cm2 and % drug release at 10 min = 99.372 with the desirability 0.924. So as per the above discussion, first solution was selected as optimized batch and was further used for evaluation.

Table 16: Formulation Table for Optimised Dipyridamole Liquisolid Formulation

Ingredients	Quantity in mg
Dipyridamole	50
Peceol	0.06
Avicel 112	150
Aerosol 200	4.278
Sodium starch glycolate	12.5
PVP K- 30	12.5

Dicalcium phosphate	15.662
Magnesium stearate	2.5
Talc	2.5
Total weight	250

Table 17: Pre & Post Compression Parameters of Optimized Formulation

Parameters	Observed Values
Angle of repose (°)	25.12
Thickness (mm)	4.31
Hardness (kg/cm^2)	3.1
Friability (%)	0.11
Disintegration Time (sec)	38
Drug content (%)	99.65

Table 18: In Vitro Drug Release Studies of Optimized Dipyridamole Formulation

Time (minutes)	Percentage Cumulative Drug Release
0	0
5	71.36
10	99.22
15	99.81
20	---
30	---

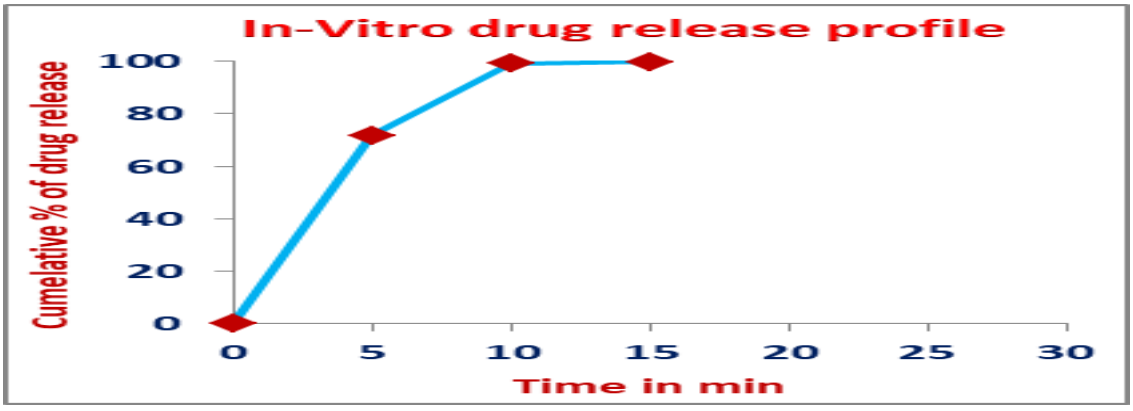

Figure 10: In Vitro drug release profile of Optimised Dipyridamole Formulation

The optimum formulation was found to exhibit angle of repose of 25.12 o, hardness of 3.1 kg/cm2 and drug release of 99.22 % at 10 mins. The observed values were found to be similar to the predicted values. Based on these observations, DPY–O can be considered to be the optimum formulation.

Stability Studies for Optimised Dipyridamole Liquisolid Formulation (DPY- O):

The formulations were loaded for stability as per ICH guidelines into stability chambers which were maintained at 40°C ± 2°C/75% RH ± 5% RH. Stability studies were conducted for 3 months. Samples were withdrawn at 1 month, 2 months and 3 months. Third month samples were analysed for optimized formulation and results are tabulated.

Table 19: Stability studies for Dipyridamole Liquisolid Optimized Formulation

	Dipyridamole at 40°C ± 2°C/75% RH ± 5% RH	
Formulation	**Optimized Trial**	
	Initial	**After 3 months**
Dissolution Time (minutes)	**% Cumulative Drug Release**	
0	0	0
5	71.36	71.27
10	99.22	99.21
15	99.81	99.73
20	---	---
30	---	---
Average Hardness (kg/cm^2)	3.1	3.0
Average Friability %	0.11	0.14
Average Drug Content %	99.65	97.17

Differential Scanning Colorimetry (DSC):

This technique allows a rapid assessment of possible interaction by disclosing transition in exhibition, dissipation of endothermic or exothermic peaks, and transition in the pertinent enthalpy standards in thermal curves of drug-excipients combinations given in the figures 10 and 11. DSC – spectrum of optimised formulation before and after stability studies showed that there was no possible interaction and degradation found in the samples analysed.

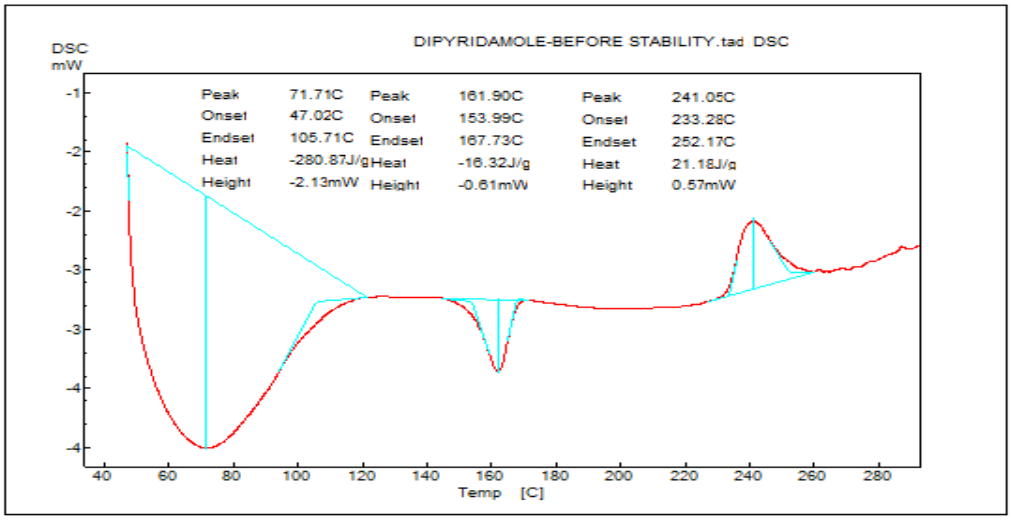

Figure 11: DSC studies for the Optimized Dipyridamole Formulation before Stability

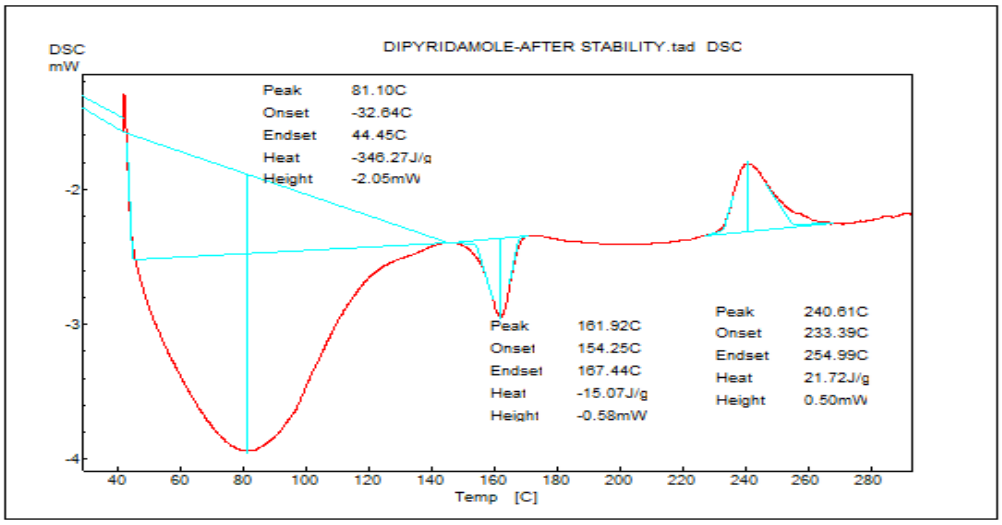

Figure 12: DSC studies for the Optimized Dipyridamole Formulation after Stability

CONCLUSION

The use of peceol in the formulation of liquisolid preparations has proven promising. The dissolution properties of dipyridamole liquisolid tablets fabricated from Peceol were found to be superior to those of other liquisolid formulations. Design Expert version 13.00 (StatEase Inc., Minneapolis, MN, USA) was used to optimize the formulations. The optimum formulation was found to exhibit angle of repose of 25.12 o, hardness of 3.1 kg/cm2 and drug release of 99.22 % at 10 mins. The observed values were found to be similar to the predicted values. Based on these observations, DPY –O can be considered to be the optimum formulation.

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REFERENCES

1. R. A. Prentis, Y. Lis, and S. R. Walker, "Pharmaceutical innovation by the seven UK-owned pharmaceutical companies (1964–1985)," British Journal of Clinical Pharmacology, vol. 25, no. 3, pp. 387–396, 1988.
2. S. G. Kapsi and J. W. Ayres, "Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability," International Journal of Pharmaceutics, vol. 229, no. 1-2, pp. 193–203, 2001.
3. Y. Javadzadeh, B. Jafari-Navimipour, and A. Nokhodchi, "Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine)," International Journal of Pharmaceutics, vol. 341, no. 1-2, pp. 26–34, 2007.
4. A. Nokhodchi, Y. Javadzadeh, M. R. Siahi-Shadbad, and M. Barzegar-Jalali, "The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts," Journal of Pharmacy and Pharmaceutical Sciences, vol. 8, no. 1, pp. 18–25, 2005.
5. S. Spireas, S. Sadu, and R. Grover, "In vitro evaluation of hydrocortisone liquisolid tablets," Journal of Pharmaceutical Sciences, vol. 87, no. 7, pp. 867–872, 1998.
6. "Dipyridamole" at Dorland's Medical Dictionary
7. Brown DG, Wilkerson EC, Love WE (March 2015). "A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons". Journal of the American Academy of Dermatology. 72 (3): 524–34.
8. A. A. Elkordy, E. A. Essa, S. Dhuppad, and P. Jammigumpula, "Liquisolid technique to enhance and to sustain griseofulvin dissolution: effect of choice of non-volatile liquid vehicles," International Journal of Pharmaceutics, vol. 434, no. 1-2, pp. 112–132, 2012.