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MELT GRANULATION AND LIQUISOLID TECHNIQUE APPROACH FOR THE ENHANCEMENT OF SOLUBILITY OF DIPYRIDAMOLE

K. Rajesh Kumar,
Research Scholar, Bhagwant University, Ajmer, Rajasthan, INDIA-305004

Dr. Mohd. Javed Naim
Faculty of Pharmacy, Bhagwant University, Ajmer, Rajasthan, INDIA-305004
Corresponding Author E-mail: kumpati.rajeshkumar@gmail.com

ABSTRACT:

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products. The aim of the present study was to increase the solubility of a poorly water soluble BCS class II drug, dipyridamole. Liquisolid Systems of Dipyridamole were prepared using Maisine CC, Avicel pH 102, Aerosil and Tween 80. And were prepared by hot melt granulation technique with Gelucire 48/16 and Polyox WSR N-80 which involved preparation of a homogenous dispersion. The formulations were evaluated for drug excipient interactions, change in crystallinity of drug, flow properties, and general quality control tests of tablets using Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), The lower ratio of Drug: Liquid are showing good flow at a particular excipient ratio. This might be due to lower amount of liquid in the formulation due to which cohesive forces might be less. Polyox WSR N-80 showed better angle of repose values when compared to Gelucire. As Gelucire is a lipid-based excipient its granulation properties are less. All the formulations prepared by liquid solid compact showed almost entire drug release within 15 min. because of the drug being in solubilized state.where as in Melt granulation technique Polyox is a water swellable polymer due to this drug diffusion is lower whereas Gelucire is a water-soluble excipient. Based on the drug release MGF3 formulation showed better results.

Keywords: Dipyridamole, Liquisolid Systems, hot melt granulation technique,Gelucire 48/16,Polyox WSR N-80, Maisine CC, Avicel pH 102.

1. INTRODUCTION:

Success of the oral dosage forms depends on the adequate dissolution and absorption of the drug substance from the gastrointestinal region (Lu M et al., 2017). Water insoluble drugs suffer the disadvantage of poor absorption and dissolution are major challenges being faced by pharmaceutical industry. A high number of potent drugs are not reaching the commercial stage owing to their poor bioavailability. This has made formulation scientists to research on alternatives for enhancement of drug solubility and bioavailability. Co-grinding, particle size reduction, formation of inclusion complex/salts, solid dispersions, nanoparticles are some of the approaches being followed to overcome this hurdle (Dias RJ et al., 2017). In recent years, liquisolid compact approach has come into light as a promising technique for improvement of drug dissolution rate.

The liquisolid compact technique was first introduced by Spireas et al. which they applied to water insoluble drugs that were converted to solid dosage form with rapid release and defined the approach as a way to convert a liquid drug into a free flowing, dry, compressible powder achieved by physical blending with appropriate excipients

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named as carrier and coating materials(Lu M et al., 2017, Spireas S and Sadu S,1998). An increase in wetting properties and surface area of the drug accessible for dissolution is observed. The process involves absorption of liquid drug (as a solution, suspension) onto a carrier's interior framework till saturation point resulting in formation of a thin liquid layer on surface of carrier that is then subjected to absorption of a fine coating material (Lu M et al., 2017).

Dipyridamole, a phosphodiesterase inhibitor employed as antithrombotic is prescribed in management of postoperative thromboembolic complications following angina. The drug is a weakly basic drug exhibiting pH dependent solubility showing high solubility in acidic pH and low solubility in high pH that means incomplete absorption in intestinal region (Jiang H et al.,2015).

In present work, dipyridamole has been formulated by liquisolid system and melt granulation method for solubility enhancement.

2.MATERIALS AND METHODS:

2.1.Materials:

Dipyridamolewas purchased fromAurobindo Pharma Pvt Ltd,Hyderabad.Maisine CC and Brig 35 were obtained as a gift sample fromDr. Reddy'slaboratories Pvt. Ltd. Avicel pH 102 and Aerosil were purchased from Sigma-Aldrich, Germany. Tween 80was purchased from Sigma Aldrich Bangalore, India. PEG 400, PEG 600 and Span 80 were obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai.

2.2.Methodology:

2.2.1. Preparation of Standard Graph of Dipyridamole:

50mg of Dipyridamole was dissolved in 50ml of 0.1N HCL in volumetric flask to obtain 1000 µg/ml. From stock solution-I, 10 ml solution was transferred in 100ml volumetric flask and volume was made up to 100ml with 0.1N HCL to obtain 100 µg/ml. From stock solution-II aliquots of 1, 2, 3, 4 and 5ml were taken and volume was made adjusted to 50ml with 0.1N HCL to get 2, 4, 6, 8, 10µg/ml solution. The absorbances of solutions were determined against blank. A standard graph showing the absorbance vs. different concentrations was plotted and correlation coefficient (R^2) was also calculated.

2.2.2. Solubility Studies:

The solubility of Dipyridamole in non-volatile liquid vehicles, which are being used to prepare the liquisolid systems, were studied by preparing saturated solutions of the drug in these solvents and analyzing their drug content spectrophotometrically. Specially, Dipyridamole was mixed in 7ml screw capped vials with such amounts of each of the above solvents in order to produce systems containing an excess of drug. The mixtures were shaken on an automatic test tube shaking machine for 24 hours and then settled for another 2 hours. The screw capped vials were centrifuged at 2500 Rpm for further settling of undissolved crystalline material and thereby obtaining a clear

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supernatant. After centrifugation, accurately measured quantities of the filtered supernatant solutions were further diluted with methanol and analyzed spectrophotometrically at 283 nm for their drug content (Kisan R Jadhav et al., 2011).

2.2.3. Flowable Liquid Retention Potential:

The success of liquisolid system with an acceptable flow rate and compressibility depends on liquid load factor (Lf) and excipient ratio (R). The liquid load factor (Lf) is a characteristic of amount of vehicle used in the formulation that is defined as the weight ratio of the liquid medication (W) and carrier. The excipient ratio (R) of a powder is defined as the ratio between the weights of carrier (Q) and coating material (q) present in the formulation (Spireas S and Bolton SM,1999). Hence, the powder excipients ratio and liquid load factor of the formulations are related as follows:

Lf = **ΦCA +** Φ**Co**(1/R)

where **ΦCA** and Φ**Co** are flowable liquid-retention potential of carrier and coat material, respectively.

2.2.4. Compatibility study of drug and polymer using FTIR:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker Alpha II. The potassium bromide pellet method was used for solid samples and for liquids, samples were transferred to Liquid cell followed by recording the spectra over the wave number of 4000 to 500cm^{-11} (Ali Nasr et al.,2016).

2.2.5. Liquisolid Compacts Preparation Technique for Dipyridamole:

Procedure: Drug and Solvents were taken in suitable quantities and transferred into motor and dispersed and calculated amount of carrier and coating material was added to the dispersion and blended in mortar. The mixing was done in three stages: first, the system was mixed slowly to allow uniform distribution of liquid medication; second, the mixture was spread as a uniform layer on the surface of the mortar and left standing for a few minutes. In the third stage, the powder was scraped off the mortar surfaces by means of spatula. To this blend Sodium starch glycollate was added and blended to obtain a uniform mixture and this is made in to plugs and filled in capsules shown in Table 1.

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Table 1: Formulation of Liquisolid Systems of Dipyridamole

Formulations	LSF1	LSF2	LSF3	LSF4	LSF5	LSF6	LSF7	LSF8
Drug: Liquid	1:2	1:4	1:2	1:4	1:2	1:4	1:2	1:4
Ca: Co (R)	20	20	40	40	20	20	40	40
Lf	0.24	0.24	0.165	0.165	0.2928	0.2928	0.2178	0.2178
Drug (mg)	25	25	25	25	25	25	25	25
MaisineCC(mg)	50	100	50	100	-	-	-	-
Tween 80 (mg)	-	-	-	-	50	100	50	100
Avicel pH 102 (mg) Q	312.5	520.8	454.4	757.4	256.14	426.8	344.34	573.92
Aerosil (mg) q	15.624	26.04	11.362	18.938	12.806	21.34	8.608	14.348
SSG (mg) 5%	20.14	33.592	27.038	45.06	17.196	28.64	21.38	35.662
Capsule size '0'	163	163	163	163	163	163	163	163
Unit weight of blend (mg)	**423.264**	**705.432**	**567.8**	**946.398**	**361.142**	**601.78**	**449.328**	**748.93**
Total weight of filled capsule (mg)	**586.264**	**868.432**	**730.8**	**1109.398**	**524.142**	**764.78**	**612.328**	**911.93**

R = Carrier:Coating (Q:q)-[Microcrystalline Cellulose: Aerosil Liquid

load Factor: Lf = W (Weight of Liquid medication)/Q (Carrier material) LV: Liquid Vehicle (Maisine CC & Tween 80)

2.2.7. Melt Granulation Technique for Dipyridamole:

Procedure: The polymer was weighed and transferred into porcelain dish and thid was placed on hot and heated (55ºC for Gelucire 48/16 pellets and 65ºC for Polyox WSR N-80) until the polymer was melted. Porcelain dish was removed from the hot plate and to it weighed quantity of drug was added and stirred to get a uniform mixture. After solidification of this mixture, it was broken into pieces and passed through #40 mesh. To this Avicel pH 102 and SSG was passed through #40 and were added and blended. Aerosil and Magnesium stearate was passed through #60 and blended. Finally, this blend was filled into capsules given in Table 2.

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Table 2: Formulation of Dipyridamole by Melt Granulation Technique

Formulations	MGF1	MGF2	MGF3	MGF4	MGF5	MGF6	MGF7	MGF8
Drug: Polymer	1:0.25	1:0.5	1:1	1:2	1:0.25	1:0.5	1:1	1:2
Drug (mg)	25	25	25	25	25	25	25	25
Gelucire 48/16 pellets(mg)	6.25	12.5	25	50	-	-	-	-
Polyox WSR N-80 (mg)	-	-	-	-	6.25	12.5	25	50
Avicel pH 102 (mg)	15.5	9.25	43.5	18.5	15.5	9.25	43.5	18.5
SSG (mg) 5%	2.5	2.5	5	5	2.5	2.5	5	5
Aerosil (mg) 0.5%	0.25	0.25	0.5	0.5	0.25	0.25	0.5	0.5
Magnesium stearate (mg) 1%	0.5	0.5	1	1	0.5	0.5	1	1
Capsule size	Size 4	Size 4	Size 3	Size 4	Size 4	Size 4	Size 2	Size 2
Capsule weight (mg)	39	39	50	39	39	39	63	63
Weight of blend (mg)	50	50	100	100	50	50	100	100
Total weight of filled capsule (mg)	89	89	150	139	89	89	163	163

3.Evaluation:Determination of Flow Properties& Disintegration Time

3.1. Angle of repose: The angle of repose of powder blend was determined by the funnel method. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation:

$\theta = \tan^{-1} h/r$

Where, h and r are the height and radius of the powder cone

3.2. Determination of bulk density & tapped density: An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (Vf) was measured and continued operation till the two consecutive

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readings were equal (Lachman et al., 1987). The bulk density and the tapped density were calculated using the following formulae:

Bulk density = W/V_0 Tapped density = W/V_f

Where, W= Weight of the powder

V_0 = Initial volume V_f= final volume.

3.3. Compressibility Index (Carr's index): Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. The less compressible material is the more flowable. (Lachman et al., 1987).

CI = (TD-BD) x 100/TD

Where, TD is the tapped density and BD is the bulk density.

3.4. Hausner's Ratio: It is the ratio of tapped density and bulk density. Generally, a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index (S. D Mankar and M.S.Bho,2019)

3.5. In vitro disintegration time: The disintegration time was measured using Disintegration test apparatus in water(37± 2°C). The time in seconds taken for the complete disintegration of the tablet/capsule with no palpable mass in the apparatus was measured in seconds.

3.6.In vitro dissolution profile: Dissolution studies were carried out by USP paddle method Type II apparatus at 37± 0.50 ° c, taking 900 ml of 0.1N HCl as a dissolution medium. Speed of rotation of paddle was set at 50 rpm. Absorbance of sample was measured at 283 nm by using UV spectrophotometer (Shinde Anilkumar J et al., 2010).

3.7. DSC Studies:DSC thermogram of pure drug and mixture were recorded using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan). The measurement was performed between 30 and 350^{o}C at heating rate 10^{o}C/min. The obtained DSC graphs were interpreted and compared for any presence of interactions (J. L. Ford and T. E. Mann, 2012).

3.8. Stability Studies: The formulations were loaded for stability as per ICH guidelines into stability chambers which were maintained at 40°C and 75% RH. Stability studies were conducted for 3 months. Samples were withdrawn at 1 month, 2 months and 3 months. Third month samples were analyzed and results are tabulated (Skelly, P. J. and Tighe, B. J,1979)

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4. RESULTS and DISCUSSION:

Standard graph of Dipyridamole was constructed using concentration 2, 4, 6, 8, 10 (µg/ml) in 0.1N HCL. It is evident from the figure 1&2 that the graph is linear with regression coefficient value of R2 = 0.9999 and slope = 0.05797 at λ max of 283nm.

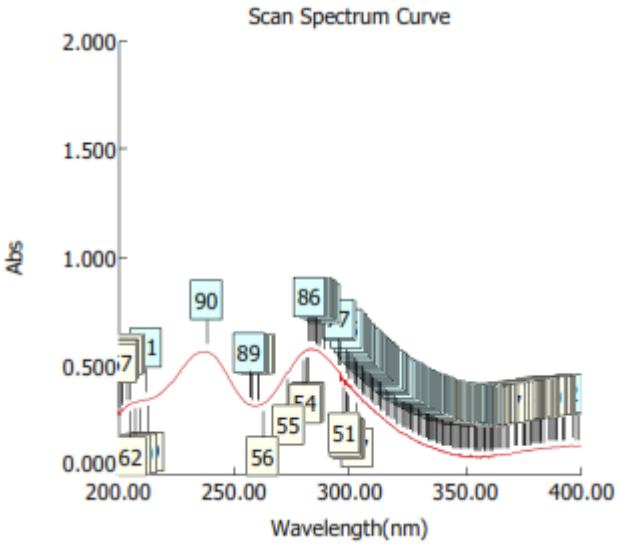
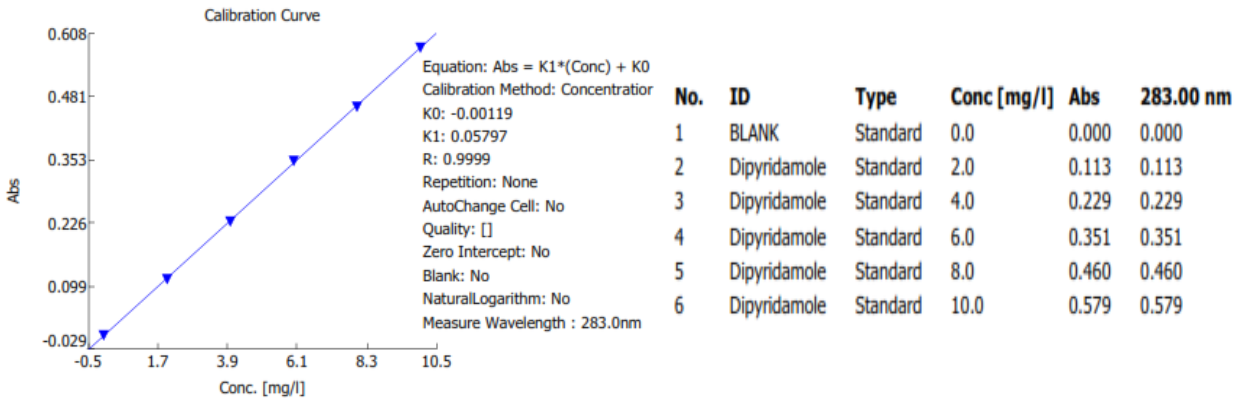


Figure 1: Spectrum Scan of Dipyridamole (µg/ml)



No.	ID	Type	Conc [mg/l]	Abs	283.00 nm
1	BLANK	Standard	0.0	0.000	0.000
2	Dipyridamole	Standard	2.0	0.113	0.113
3	Dipyridamole	Standard	4.0	0.229	0.229
4	Dipyridamole	Standard	6.0	0.351	0.351
5	Dipyridamole	Standard	8.0	0.460	0.460
6	Dipyridamole	Standard	10.0	0.579	0.579

Figure 2. Calibration Curve for Dipyridamole

4.1. Solubility Studies:

Solubility studies of Dipyridamole in non-volatile liquid vehicles were studied and the results were extrapolated to determine the percent mg/ml of Dipyridamole in its saturated solution with the solvents under investigation. Results are shown in Table 3.

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Table 3: Solubility Studies

S.No	Non-Volatile Liquid Vehicles	Absorbance at 283.00 nm	Solubility (µg/mL) at 283.00 nm
1	PEG 400	0.117	202.0725
2	PEG 600	0.065	112.2625
4	MAISINE CC	0.243	419.6891
6	BRIG 35	0.058	100.1727
7	TWEEN 80	0.172	297.0639
8	SPAN 80	0.120	207.2539

Observation: From the above data obtained, Maisine CC (419.6891µg/mL) & Tween 80 (297.0639 µg/mL) were found to have good solubility with Dipyridamole.

4.2. Flowable Liquid Retention Potential:

The flowable liquid-retention potential of carrier and coat material results are depicted in the table 4

Table4: Flowable Liquid Retention Potential

Material	Maisine CC	Tween 80
Avicel pH 102	0.090	0.1428
Aerosil	3	3

4.3. FTIR Studies:

The FT-IR spectrophotometer was used to identify as well as determine the possibilities of any interaction between the formulation components at the optimized composition. As showed in the Fig. 4, there was no substantial differentiation in the FT-IR spectra of the drug when compared to the spectra of the physical mixture of drug and polymers. The FT-IR spectra of the drug and polymer showed that there was no shift in the major peaks. This further revealed that there was no variation in the properties of the drug and polymers in the formulation. Hence, the drug and polymers were compatible with each other.

IR spectrum of Dipyridamole shows a broad peak at 3397.87 cm^{-1} may be due to O-H stretching, 2922.08 cm^{-1} C-H stretching, 1535.90 cm^{-1} may be due to N-H bending, 759.99 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

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formulation derived during the present investigation as shown and Figures 3 and 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 polymers used.

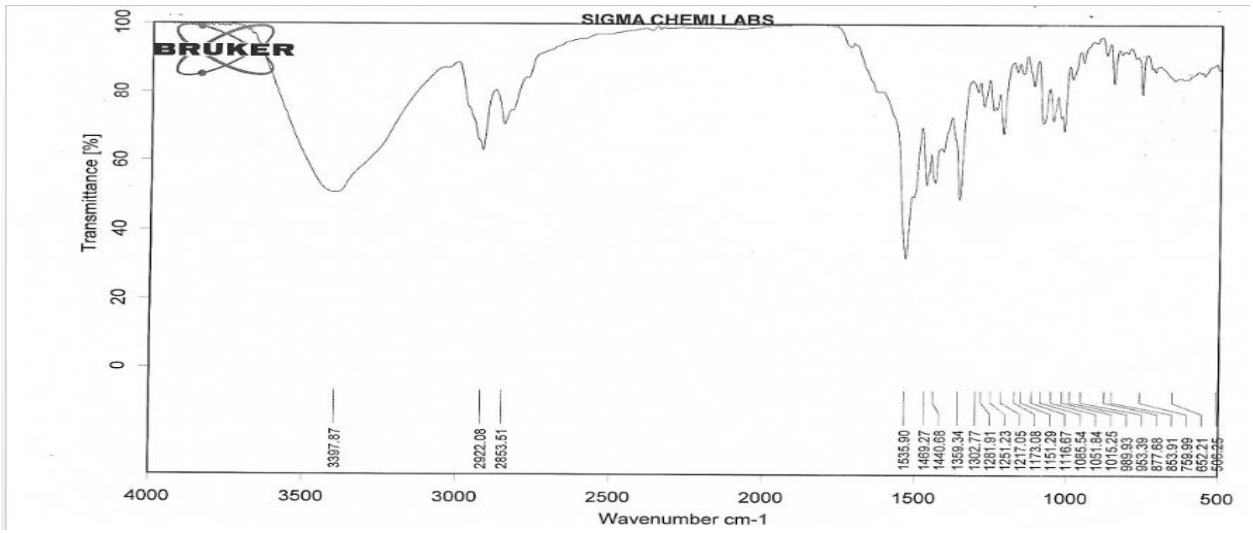

Figure 3: FTIR Spectra of Pure Drug Dipyridamole

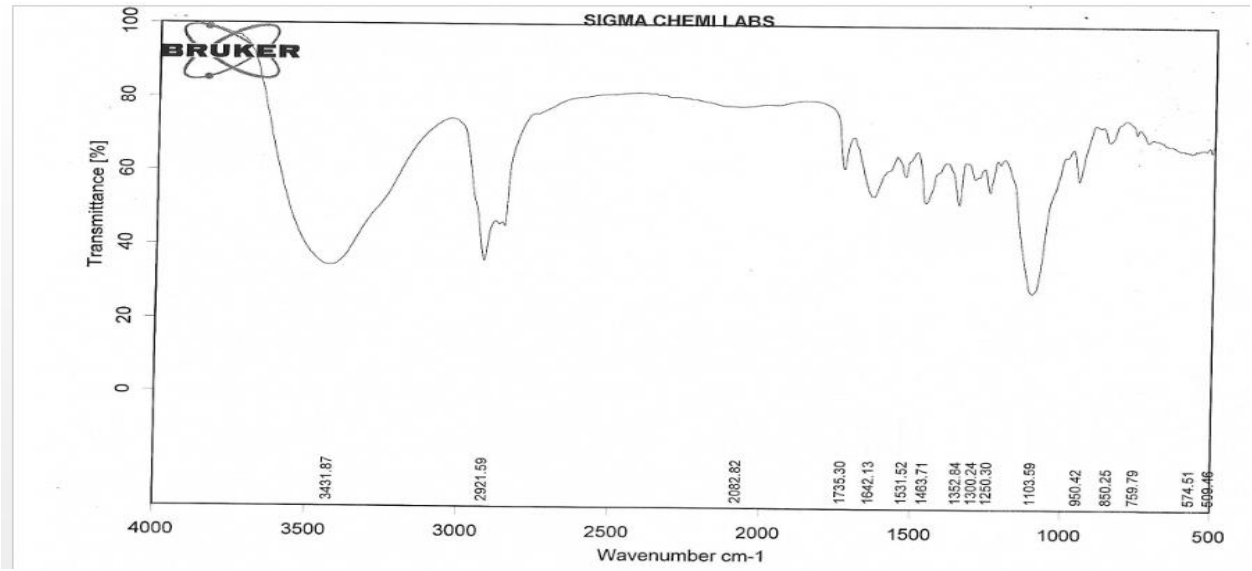

Figure 4: FTIR Spectra of Formulation Mixture

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4.4.Evaluation:

As the angle of repose (Φ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. The angle of repose values of all the formulations are ≤ 35 implying all are having good flow. The lower ratio of Drug: Liquid are showing good flow at a particular excipient ratio. This might be due to lower amount of liquid in the formulation due to which cohesive forces might be less.

Powders showing Carr's index (Ci) up to 25 are considered of acceptable flow properties. In addition to Carr's index, Hausner ratio found that the ratio was related to the inter particle friction, so that powders with low interparticle friction, had ratios of approximately 1.25 indicating good flow.

The CI values of all the formulation are between 18.7 – 28.95 and Hausner ratio values are between 1.231 – 1.407 indication fair to passable flow. The CI and Hausner value of LSF5 is lowest which might be due to the lower are ratio of Drug: Liquid and excipient ratio of 20. Disintegration of all the capsules occurred within 72 sec values given in Table 5.

Table 5: Flow Properties of Formulations LSF1-LSF8 (Liquisolid Compacts Technique for Dipyridamole)

Formulations	**LSF1**	**LSF2**	**LSF3**	**LSF4**	**LSF5**	**LSF6**	**LSF7**	**LSF8**
Angle of repose	33	30	34.5	35.5	27.5	34	31	35
Bulk density	0.292	0.257	0.221	0.225	0.260	0.223	0.224	0.223
Tapped density	0.375	0.357	0.287	0.306	0.320	0.314	0.312	0.303
CI	21.95	27.91	22.86	26.47	18.75	28.95	28.21	26.32
Hausners ratio	1.281	1.387	1.296	1.360	1.231	1.407	1.393	1.357
DT (min: sec)	1:08	1:02	0:58	1:03	1:10	1:12	1:05	0:59

4.5. In Vitro Drug Release:

The drug particles in liquisolid formulations were dispersed in selected hydrophilic liquid vehicle, which means the wetting properties of the drug particles were increased; hence, the surface area of drug particles available for dissolution increased tremendously. After liquisolid capsule was disintegrated, the primary particles of liquisolid suspended in the dissolution medium contained drug particles in a state of molecular dispersion. This is indicated by higher dissolution values within 5 minutes values given in Table 6 and Figure 5.

For conventional tablet, the surface exposed for dissolution is very limited, due to the hydrophobicity of the drug particles. Accordingly, the higher dissolution rates observed in liquisolid formulations may be attributed to significantly larger surface area of the molecularly dispersed drug particles and small amount of liquid vehicle might be

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sufficient to improve the solubility of drug particles by acting as a cosolvent. As a consequence, concentration gradient of the drug will be increased between the surface of drug particle and dissolution media, and hence, the drug dissolution rate increased. All the formulations showed almost entire drug release within 15 min. because of the drug being in solubilized state. LSF3, LSF4 and LSF8 showed higher release immediately which might be due to the higher excipient ratio since more coating of liquid medicament is possible.

Table 6 : Percentage Cumulative Drug Release for the Formulations LSF1-LSF8

	% Cumulative drug release							
Time (in min.)	**LSF1**	**LSF2**	**LSF3**	**LSF4**	**LSF5**	**LSF6**	**LSF7**	**LSF8**
0	0	0	0	0	0	0	0	0
5	88.66	93.07	97.13	101.45	86.57	88.03	94.74	98.45
10	90.76	98.10	101.00	102.06	94.53	98.72	96.84	101.97
15	95.79	98.72	103.59	102.56	98.52	100.50	99.35	101.51
20	97.83	99.51	103.56	102.48	101.03	101.27	101.77	102.34
30	99.83	99.61	103.62	102.50	100.89	101.43	101.59	101.96
45	99.85	99.58	103.58	102.52	100.96	101.38	101.55	101.84

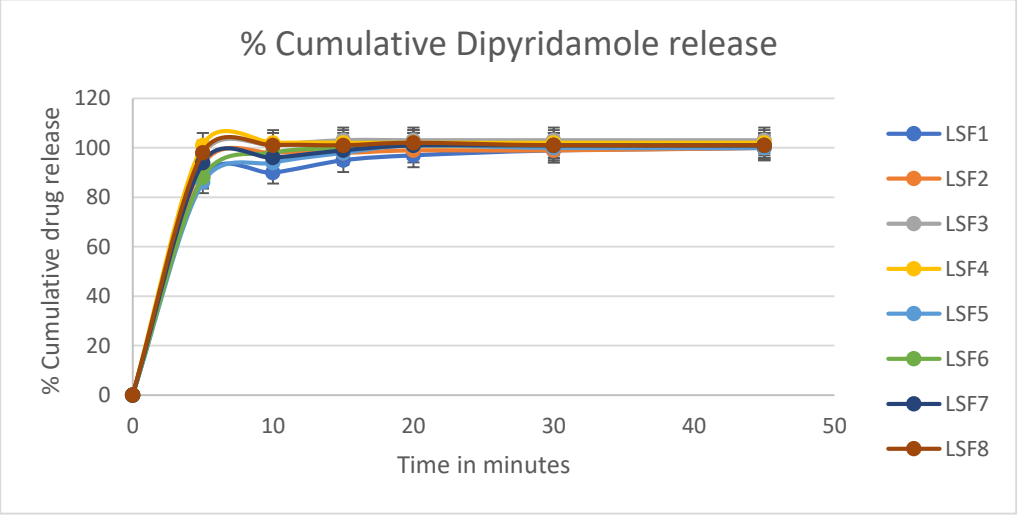

Figure 5: Percentage Cumulative Drug Release for the Formulations LSF1-LSF8

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4.6. Evaluation:

Determination of Flow Properties & Disintegration Time

Table 7: Flow Properties of Formulations MGF1-MGF8 (Dipyridamole by Melt Granulation Technique)

Formulations	MGF1	MGF2	MGF3	MGF4	MGF5	MGF6	MGF7	MGF8
Angle of repose	29	27	22.5	19	21.5	21	18	16.5
Bulk density	0.427	0.422	0.438	0.478	0.341	0.303	0.290	0.312
Tapped density	0.518	0.478	0.543	0.558	0.461	0.446	0.421	0.444
CI	17.65	11.76	19.23	14.29	26.09	32.14	30.95	29.63
Hausner ratio	1.214	1.133	1.238	1.167	1.353	1.474	1.448	1.421
DT (in minutes)	1:03	0:59	1:12	1:04	1:05	1:08	1:15	1:18

Angle of repose values indicate excellent to good flow ranging from 18 - 29.Formulations containing Polyox WSR N-80 showed better angle of repose values when compared to Gelucire. This might be because of better granulation of polyox WSR.As Gelucire is a lipid-based excipient its granulation properties are less.

Difference between bulk density and tapped density is less for Gelucire formulations indicating good flow. The CI and Hausner values are less for Gelucire formulation this is again in correlation with the properties of the polymer used for melt granulation. As Gelucire is a lipid-based excipient the inter particle frictions are less due to which CI and Hausner Ratio values are less.Disintegration of all the capsules occurred within 80 sec.

4.7.In Vitro Drug Release:

Dissolution of all the formulations showed entire drug release. And as polymer concentration is increased dissolution has increased but at higher concentration of polymer, harder granules are formed due to which initial release of drug is less is less for MGF4 and MGF8.Polyox formulations showed lower initial drug release compared to Gelucire formulation. Polyox is a water swellable polymer due to this drug diffusion is lower where asGelucire is a water-soluble excipient.Based on the drug release MGF3 formulation showed better results.

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Table 8: Percentage Cumulative Drug Release for the Formulations MGF1-MGF8

	% Cumulative Drug Release							
Time (in minutes)	**MGF1**	**MGF2**	**MGF3**	**MGF4**	**MGF5**	**MGF6**	**MGF7**	**MGF8**
0	0	0	0	0	0	0	0	0
5	90.34	94.95	100.27	49.89	30.60	37.94	70.85	65.83
10	99.98	99.14	101.57	80.07	61.62	63.93	92.44	89.35
15	103.13	100.58	101.69	100.62	70.64	79.44	99.14	99.64
20	103.01	100.37	101.23	101.52	83.63	90.34	100.95	100.81
30	101.61	100.67	101.13	102.52	96.00	101.45	100.64	101.20
45	102.50	100.88	101.08	102.48	99.98	103.55	101.04	101.32

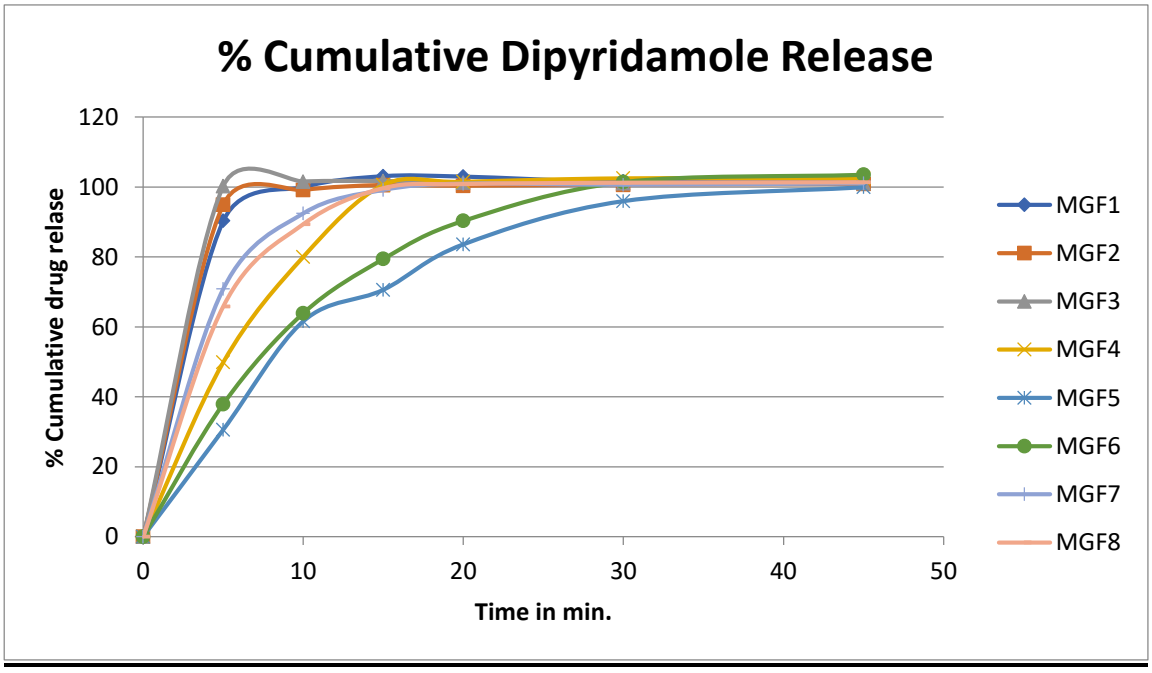

Figure 6: Percentage Cumulative Drug Release for the Formulations MGF1-MGF8

4.8.Stability data of Dipyridamole:

DSC Studies: DSC is conducted, before and after stability for both Liquisolid compacts and melt granulation technique formulation mixture as showing the Figure 7 to 10, and they exhibited both exothermic and endothermic peaks and there is no much significant changes observed.

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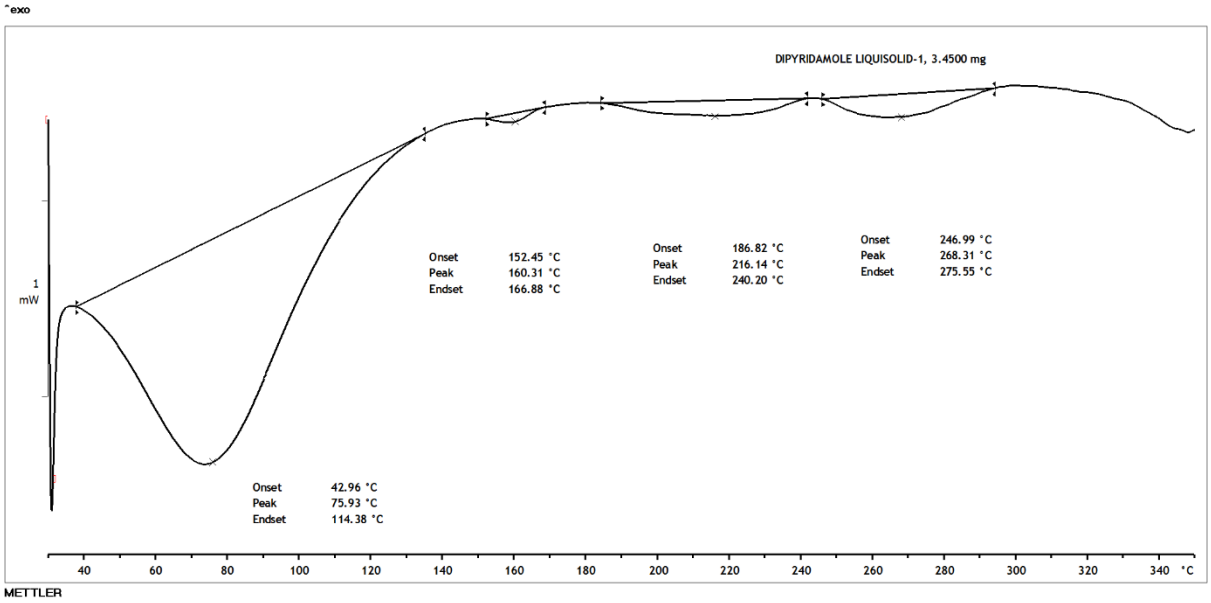

Figure 7: DSC Spectra of Optimized Formulation before stability: Liquisolid Technique

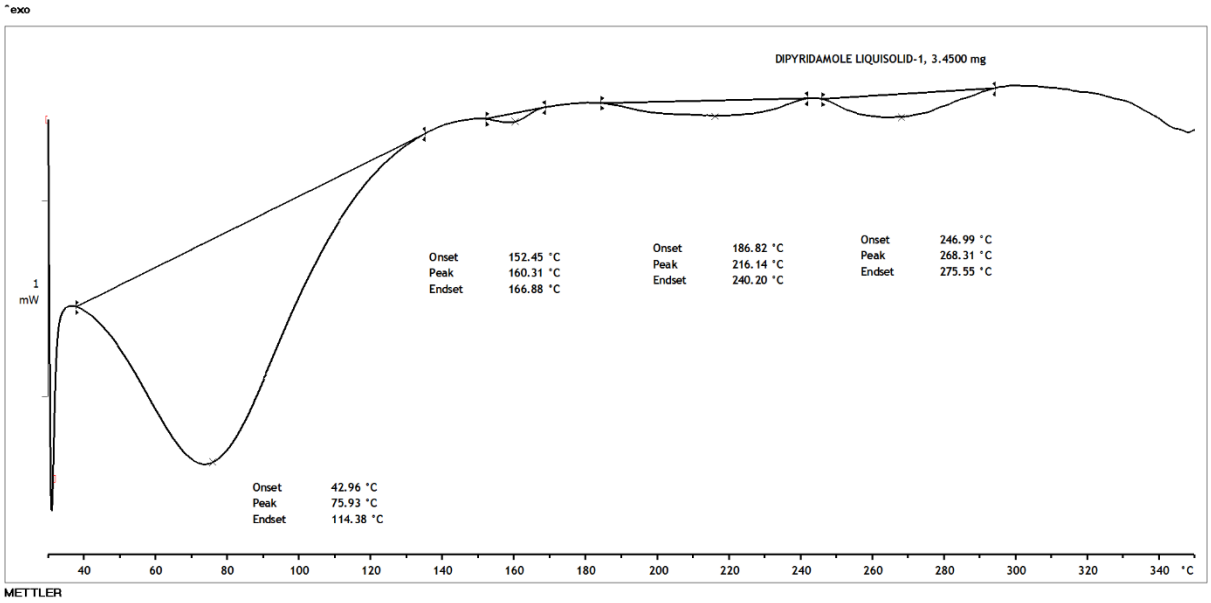

Figure 8: DSC Spectra of Optimized Formulation after stability: Liquisolid Technique

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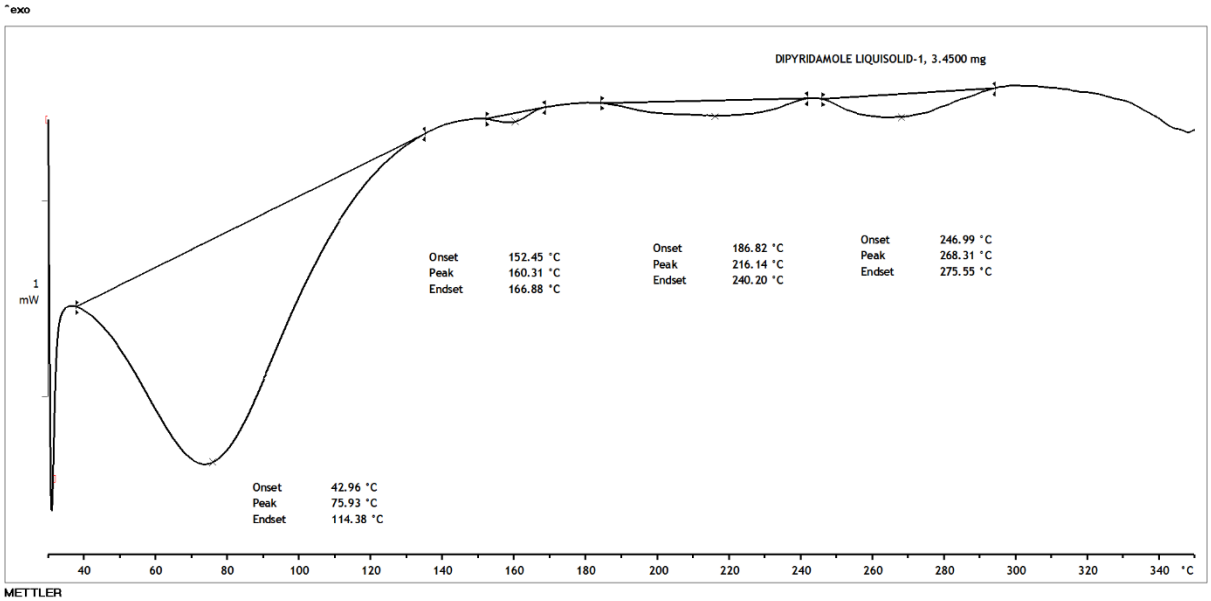

Figure 9: DSC Spectra of Optimized Formulation before stability: Melt Granulation Technique

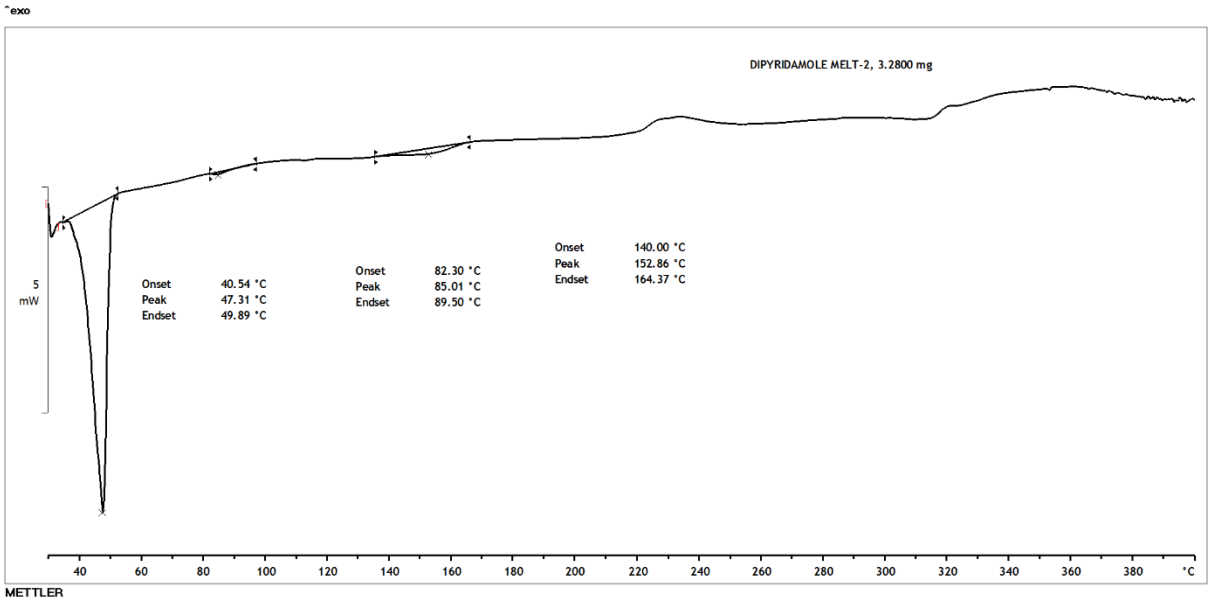

Figure 10: DSC Spectra of Optimized Formulation before stability: Melt Granulation Technique

The optimized formulation was subjected to stability studies at 40ºC ± 2ºC/ 75%±5 RH for 3 months.Optimized formulations prepared with Liquisolid Technique and Melt Granulation were evaluated for In Vitro Drug release and reported in table 9.

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Table 9: Stability data of Dipyridamole

		Initial	After 3 months
Formulation	**% Drug Release at 5 Minutes**		
Liquisolid Systems	**LSF4**	**101.45**	**102.03**
Melt-Granulation Technique	**MGF3**	**100.27**	**100.15**

5.Conclusion:

The present study concludes that the liquisolid compaction and melt granulation was found to be a promising technique for improving the dissolution of poorly soluble drug like Dipyridamole. The formulations were evaluated for flow properties, compatibility studies like FTIR and DSC. The dissolution data treatment using different parameters further confirmed the improvement in dissolution. LSF4 and MGF3 were selected as optimized formulations.

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