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RESEARCH ARTICLE

Dipyridamole Cocrystal Tablets with Enhanced Solubility and Dissolution at Intestinal pH

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SUMMARY

Aim of the study was to prepare dipyridamole (DPM) cocrystals to alter its physicochemical properties as it is poorly soluble in water, 6.8 pH buffer and belongs to BCS class II. Cocrystals were prepared using neat grinding method. Initial screening of cocrystals was done with melting point determination indicating formation of nine cocrystals. Based upon interference studies nine cocrystals were finalized for solubility and dissolution studies. DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid and DPM-oxalic acid cocrystals showed the significant enhancement in solubility and dissolution in 6.8 pH buffer. Further confirmation was done by Differential Scanning Calorimetry (DSC) and Powder X-ray diffraction (PXRD) studies. DPM-hippuric acid cocrystals have shown promising results for formation of cocrystals and considered for tablet formulation. DPM-hippuric acid cocrystal tablets were prepared by using various levels of carboxymethyl cellulose and microcrystalline cellulose. These tablets showed acceptable physical characteristics with subsequent rapid dissolution.

Key Words: *Dipyridamole (DPM), Cocrystals, Neat grinding, DSC, Solubility, Dissolution.*

Bağırsak pH'sında Geliştirilmiş Çözünürlük ve Çözünme Özelliğine Sahip Dipiridamol Kokristal Tabletler

ÖZ

Çalışmanın amacı, suda ve 6,8 pH tamponunda az çözünen ve BCS sınıf II'ye ait olan dipiridamol'ün (DPM) fizikokimyasal özelliklerini değiştirmek üzere ko-kristallerinin hazırlanmasıdır. Ko-kristaller düzenli öğütme metodu kullanılarak hazırlanmıştır. Ko-kristallerin ilk taraması, dokuz ko-kristalin oluşumunu gösteren erime noktası tayini ile gerçekleştirilmiştir. Girişim çalışmalarına dayanarak, çözünürlük ve çözünme çalışmaları için dokuz ko-kristal seçilmiştir. DPM-sitrik asit, DPM-hippurik asit, DPM-tartarik asit ve DPM-oksalik asit ko-kristalleri, 6.8 pH tamponunda çözünürlük ve çözünmede anlamlı bir artış göstermiştir. İleri doğrulama, Diferansiyel Taramalı Kalorimetre (DSC) ve Toz X-Ray Difraksiyonu (PXRD) çalışmaları yapılmıştır. DPM-hippurik asit ko-kristalleri, ko-kristallerin oluşumu için umut verici sonuçlar vermiş ve tablet formülasyonu için düşünülmüştür. DPM-hippurik asit ko-kristal tabletleri, çeşitli seviyelerde karboksimetil selüloz ve mikrokristalin selüloz kullanılarak hazırlanmıştır. Bu tabletler, daha sonra hızlı çözünme ile kabul edilebilir fiziksel özellikler göstermiştir.

Anahtar Kelimeler: *Dipiridamol (DPM), Ko-kristaller, Düzenli öğütme, DSC, Çözünürlük, Çözünme Hızı.*

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INTRODUCTION

Cocrystals are multicomponent system consisting of API and GRAS listed coformers that are held together by nonionic interaction such as hydrogen bonding or Vanderwall forces (Qiao et al., 2011; Thimmasetty et al., 2021). The coformer selected can be a drug, excipient or nutraceuticals having functional groups like amine, alcohol, amide, and carboxylic acid that form hydrogen bonding with the API (Stahl et al., 2002; Gadade et al., 2016; Thipparaboina et al., 2016). Crystal engineering approach can alter physicochemical behavior such as solubility, dissolution, and stability of an API for improvement in bioavailability of poorly soluble drug (Blagden et al., 2007; Izutsu et al., 2016). In the market, cocrystals of caffeine-citric acid/citrate, valproic acid/ Na-valproate, and escitalopram-oxalic acid/oxalate are available though many more under investigation (Kumar et al., 2014).

Dipyridamole (DPM) is BCS class II drug having pH dependent solubility and is primarily absorbed in the stomach. DPM has low oral bioavailability (37-66%) because of its insolubility at alkaline pH (Paul et al., 2018). Solid dispersion, self emulsifying drug delivery system, micronization, cyclodextrin complexation are reported techniques in the literature to alter the dissolution behavior of DPM (Guo et al., 2011; Savjani et al., 2012). Cocrystals are suitable alternative approach to improve physicochemical properties of DPM to overcome the problem of poor bioavailability (Yadav et al., 2009; Gawade et al., 2021). Since there is only one literature support for the formation of co-crystals of DPM with tartaric acid, there is a scope for obtaining the DPM co-crystals with acidic coformers to enhance its solubility and absorption (Kojo et al., 2017). An attempt was made to formulate DPM cocrystal tablets to enhance solubility and dissolution rate.

MATERIALS AND METHODS

Materials

DPM was procured as a gift sample from Aurobindo Laboratories, Hyderabad. All other chemicals and excipients used in this research were obtained from S D Fine-Chem Limited, Mumbai.

Methods

Preparation of DPM-cocrystals

Neat grinding method was opted for DPM cocrystal preparation. DPM and coformers were grinded in (1:1 molar ratio) in mortor and pestle for 30 minutes at room temperature. Products were stored in desiccators for further use (Thimmasetty et al., 2021). List of coformers used in this study was represented in **Table 1.**

Characterization of DPM cocrystals

Melting point

Initial screening of cocrystals was done based on melting point. Fifteen coformers were selected given in **Table 1**. Melting point of DPM and cocrystals was determined by open capillary tube method using melting point apparatus (Biotech, India) (Schultheiss et al., 2009). The procedure was repeated in triplicate (n=3).

Saturation solubility studies of DPM-cocrystals

Solubility of DPM and its cocrystals was carried out in 0.1N hydrochloric acid, 6.8 phosphate buffer and distilled water. The DPM and cocrystals were added in excess quantity separately in volumetric flasks containing different media to form supersaturated solutions and rotated in orbital shaker (Kemi industries, Kerala) at room temperature (25°C), with a 50 rpm, for 24 h. After attainment of equilibrium, samples were withdrawn, filtered using 0.45µm whattmann filter paper, diluted and analyzed by UV spectrophotometer. Procedure was repeated in triplicate (Dai et al., 2018; Nijhawan et al., 2014).

Dissolution studies of DPM-cocrystals

DPM dissolution studies were carried out at acidic (0.1N HCl) and alkaline basic pH (6.8)for 1 hr using USP dissolution test apparatus II (Electrolab, Dissolution tester, TDT-08L) by paddle method in 900 mL of pH 1.2 and 6.8 phosphate buffer at 50 rpm maintained at 37±0.5°C. DPM and its cocrystals containing the drug equivalent to 25 mg were filled in hard gelatin capsule. 5 ml of sample was withdrawn at 10 minutes interval for a period of 1 hr and analyzed spectrophotometrically (Panzade et al., 2017).

Differential Scanning Calorimetry (DSC) of DPM-cocrystals

A differential calorimetry scanning (DSC7020 thermal analysis system HITACHI) was used for thermal analysis of DPM and DPM cocrystal samples. Powder samples of approximately 2.0 mg were placed in aluminum open crucibles and heated at a rate of 10°C/min up to 400°C (Cheney et al., 2011; Saganowska et al., 2018).

Powder X-ray diffraction (PXRD) of DPM-cocrystals

The cocrystals of dipyridamole and pure drug were characterized at 25 °C using XPERT-PRO diffractometer with Cu-Kα (λ = 1.54060 Å) at 45 kV and 40 mA (Bevill et al., 2014; Nijhawan et al., 2022).

Preparation of DPM-hippuric acid cocrystal tablets

Based on dissolution results, DPM-hippuric acid cocrystals were selected for tablet compression as per formulae given in Table 1. DPM-hippuric acid cocrystals were geometrically mixed for 15 min with other additives (CMC, MCC, mannitol, magnesium stearate) and compressed by Rimek 12 station rotary mini tablet compression machine at sufficient compression force to obtain hardness in the range of 3-4 kg/cm^2 using 4 mm round punch with flat surface.

Table1: Formulation of DPM-hippuric acid cocrystal tablets.

S.No	Drug and other excipients (mg)	Formulations (200 mg)			
		DPMF1	DPMF2	DPMF3	DPMF4
1	DPM-hippuric acid cocrystals	26	26	26	26
2	Carboxy methyl cellulose (CMC)	8	4	4	8
3	Microcrystalline cellulose (MCC)	60	64	60	64
4	Mannitol	102	102	106	98
5	Magnesium stearate	4	4	4	4

Characterization of DPM-hippuric acid tablets

For evaluation of DPM-hippuric acid tablets post compression parameters such as hardness, thickness, friability, weight variation, disintegration studies, drug content, and dissolution studies were carried out. The thickness of tablets was determined by using Vernier calipers. Friability was determined using tablet friability tester (FT 1020, LABINDIA), the device that subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving and dropping the tablet at a height of 6 inches in each revolution. The tablets were subjected to 100 revolutions and dedusted by muslin cloth and reweighed. The percent loss in weight (F) was calculated as shown by Eq. 1. For Uniformity of weight, twenty tablets from each batch were randomly selected, weighed together and individually to check the average weight. Percent weight variation calculated (Eq. 2) (Indian Pharmacopoeia, 2018).

$$F = \frac{intial\ weight - final\ weight}{intial\ weight} x100 \quad (1)$$

$$\%weightvariation = \frac{individual\ weight - final\ weight}{individual\ weight} x100 \quad (2)$$

In vitro disintegration test of tablets was performed in tablet disintegration test apparatus (DT

1000, LABINDIA) containing six cylindrical tubes with #10 (aperture size 2±0.2 mm) sieve. Randomly chosen six tablets were added to tubes containing pH 6.8 phosphate buffer as the medium maintained at 37°±2°C and disintegration time was recorded.

RESULTS AND DISCUSSION

Melting point determination

Melting point of the prepared cocrystals was determined up to four weeks. All the observed values are compared with reported values (Marydele et al., 2006; Raymond CR et al., 2009; Cheney et al., 2010). From Table 2 it can be observed that nine cocrystals are formed based on the principle of lowering of melting point.

DPM-citric acid cocrystals showed melting point of 80-110 °C which is neither nearer to DPM (165 °C) nor to the coformer (citric acid-153°C), similar is the case of DPM-hippuric acid, DPM-tartaric acid, DPM-malonic acid, DPM-succinic acid, DPM-fumaric acid, DPM-adipic acid, DPM-oxalic acid, and DPM-cinnamic acid cocrystals. These observations indicated that the cocrystals might have formed with the respective coformer. Cocrystals with salicylic acid, benzoic acid aspirin, maleic acid, glutamic acid and glutaric acid showed melting within the 7 days of preparation of cocrystals hence rejected for further evaluation. DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid, DPM-malonic acid, DPM-succinic acid, DPM-fumaric acid, DPM-adipic acid, DPM-benzoic acid, DPM-cinnamic acid cocrystal preparations were selected for further analysis.

Table 2: Melting point values of DPM, coformers and cocrystals

S. No.	Name	MP (^{0}C) (Reported Values)	MP (^{0}C) (Obs. values)	Inference
	DPM	164-167 (drug)	165	-
1	DPM - citric acid anhydrous	153 (coformer)	80-110	Cocrystals might have formed
2	DPM - hippuric acid	187-188 (coformer)	110-130	Cocrystals might have formed
3	DPM - tartaric acid	168-170 (coformer)	110-120	Cocrystals might have formed
4	DPM - malonic acid	135-137 (coformer)	150-160	Cocrystals might have formed
5	DPM - Succinic acid	184-190 (coformer)	110-120	Cocrystals might have formed
6	DPM- fumaric acid	287 (coformer)	120-140	Cocrystals might have formed
7	DPM - adipic acid	152.1 (coformer)	110-120	Cocrystals might have formed
8	DPM - oxalic acid	101-102 (coformer)	90-100	Cocrystals might have formed
9	DPM - cinnamic acid	133 (coformer)	80-90	Cocrystals might have formed
10	DPM - salicylic acid	158.6 (coformer)	converted into liquid within 7days of preparation	Cocrystals might not have formed
11	DPM - benzoic acid	122 (coformer)	converted into liquid within 7days	Cocrystals might not have formed
12	DPM – Aspirin	136 (coformer)	converted into liquid within 7days	Cocrystals might not have formed
13	DPM - maleic acid	135 (coformer)	converted into liquid within 7days of preparation	Cocrystals might not have formed
14	DPM - glutamic acid	213-224 (coformer)	converted into liquid within 7days	Cocrystals might not have formed
15	DPM - glutaric acid	115 (coformer)	converted into liquid after 7days	Cocrystals might not have formed

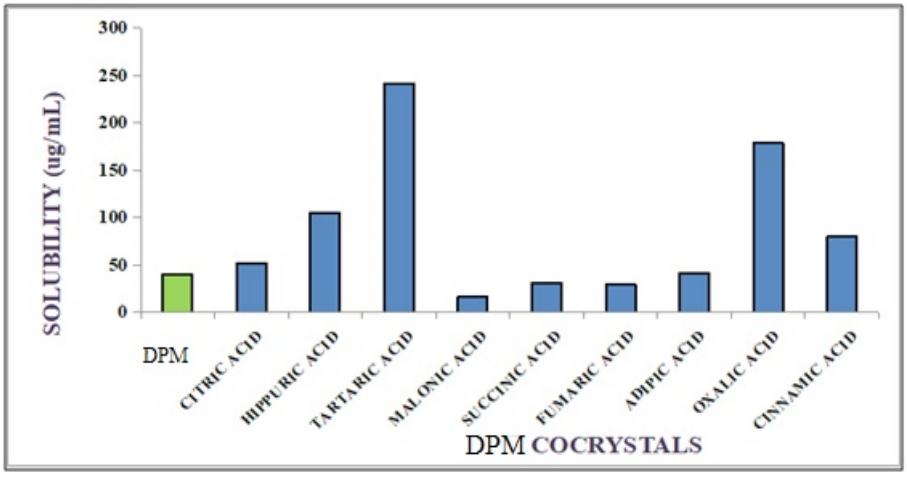


Figure 1: Solubility profile of DPM co-crystals in pH 1.2 at 25 °C

Physicochemical Properties of DPM-cocrystals

Saturation solubility studies of DPM-cocrystals

The data of solubility studies was recorded and the solubility profile of DPM-cocrystals is graphically represented in Figure 1-3.

Among nine cocrystals, six: DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid, DPM-adipic acid, DPM-oxalic acid and DPM-cinnamic acid showed higher solubility in the 1.2 pH buffer than DPM (40.18 mg/mL). The order of the solubility of the cocrystals in 1.2 pH buffer was found to be tartaric acid > oxalic acid > hippuric acid > cinnamic acid >citric acid > adipic acid >DPM.

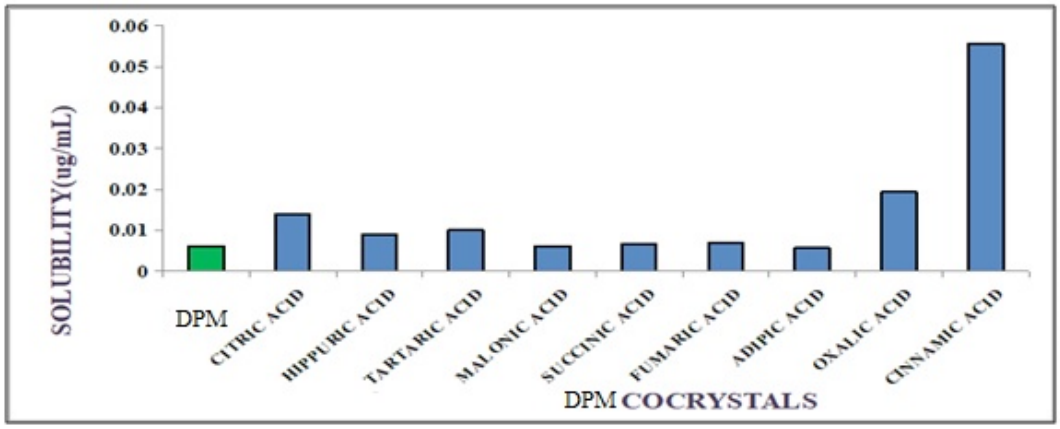


Figure 2: Solubility profile of DPM co-crystals in pH 6.8 phosphate buffer at 25 °C

Among nine cocrystals, DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid, DPM-succinic acid, DPM-fumaric acid, DPM-oxalic acid and DPM-cinnamic acid showed higher solubility in 6.8 pH buffer than DPM (0.0062 mg/mL). The order of the solubility of the co-crystals in 6.8 pH buffer was found to be cinnamic acid > oxalic acid > citric acid > tartaric acid > hippuric acid > fumaric acid > succinic acid >DPM.

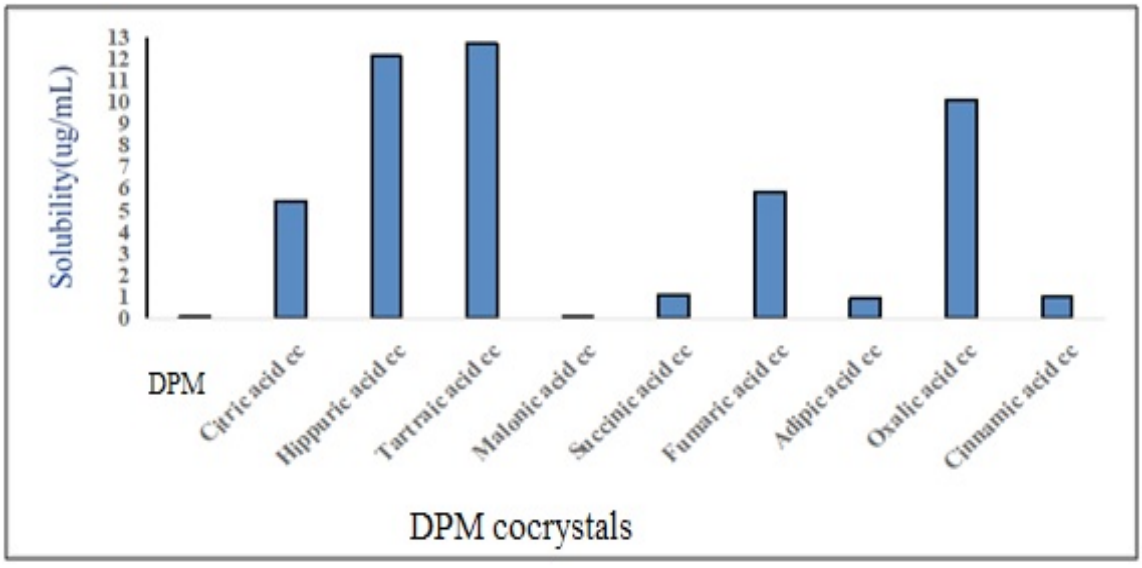


Figure 3: Solubility profile of DPM co-crystals in distilled water at 25 °C

Among nine cocrystals, all nine: DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid, DPM-malonic acid, DPM-succinic acid, DPM-fumaric acid, DPM-adipic acid, DPM-oxalic acid and DPM-cinnamic acid showed higher solubility in distilled water than DPM (0.01096 mg/mL). The order of the solubility of the co-crystals in distilled water was found to be tartaric acid > hippuric acid > oxalic acid > fumaric acid > citric acid > succinic acid > cinnamic acid > adipic acid > malonic acid >DPM.

Based upon the melting points and solubility studies, six cocrystals, DPM-citric acid cocrystals, DPM-hippuric acid cocrystals, DPM-tartaric acid cocrystals, DPM-succinic acid cocrystals, DPM-oxalic acid cocrystals and DPM-cinnamic acid cocrystals were selected for the further studies.

Dissolution studies of DPM cocrystals

The dissolution-time profile of DPM-cocrystals in pH 6.8 and 1.2 buffers was recorded in Figure 4 and 5.

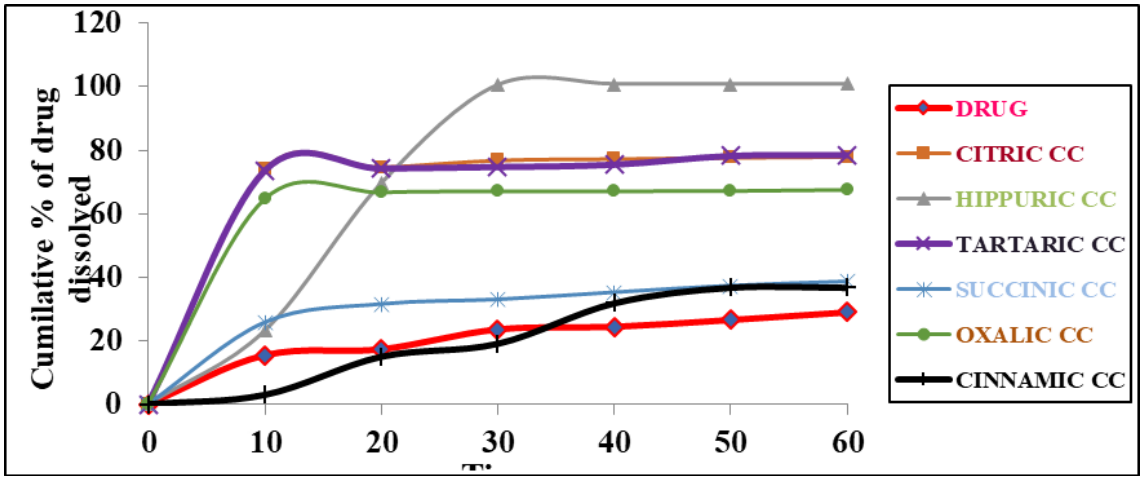


Figure 4: Dissolution profiles of DPM and its cocrystals in 6.8 phosphate buffer

The dissolution–time profiles of DPM and cocrystals in pH 6.8 buffer showed the following order: hippuric acid > tartaric acid > citric acid > oxalic acid > succinic acid > cinnamic acid > DPM. 100% drug release was observed for DPM-hippuric acid cocrystals within 60 min while, the DPM showed only 28.98% in 60 min. The rate and extent of dissolution was found to be maximum for DPM-hippuric acid cocrystals.

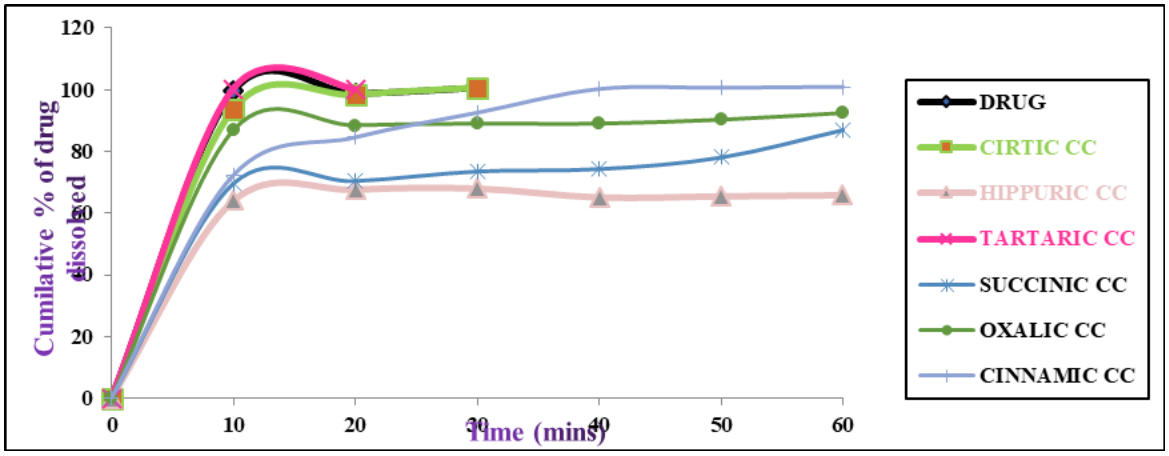


Figure 5: Dissolution profiles of DPM and its cocrystals in 0.1N HCl

In pH 1.2 buffer dissolution rate of DPM was 100% within 30 min, citric acid and tartaric acid cocrystals also showed 100% dissolution profile whereas, DPM-hippuric acid cocrystals, DPM-succinic acid cocrystals, DPM-oxalic acid cocrystals and DPM-cinnamic acid cocrystals showed 68.14%, 73.67%, 88.9% and 92.51% of dissolution rates respectively within 30 min.

The cocrystals showed marked increase in the dissolution in the 6.8 pH buffer as compared to 1.2 pH buffers. Based upon the dissolution studies in 6.8 pH buffer DPM-citric acid cocrystals, DPM-hippuric acid cocrystals, DPM-tartaric acid cocrystals and DPM-oxalic acid cocrystals were selected for further characterization by DSC.

DSC of DPM-Cocrystals

The DSC thermogram of DPM was recorded and the melting point was observed to be 166.27 °C indicating the purity of DPM. Thermograms of drug cocrystals were shown in Figure 6. In DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid and DPM-oxalic acid preparations endothermic peaks were observed at 127°C, 122°C, (118°C,134°C) and 90°C respectively. Literature value for melting of citric acid, hippuric acid, tartaric acid and oxalic acid are reported as 153°C, 188°C, 169°C and 101°C respectively (Marydele et al., 2006; Raymond CR et al., 2009; Cheney et al., 2010). The endothermic peak of co-crystal was found to be different than drug and co-crystal former, thus confirming the formation of new phase. In DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid and DPM-oxalic acid preparations endothermic peaks were observed, which were neither near to the melting point of drug nor the coformer. This inferred absence of physical mixture and the formation of cocrystals. Single sharp endothermic peak was observed incase of DPM-hippuric acid cocrystal which was neither near to the DPM nor to the hippuric acid. Hence DPM-hippuric cocrystals were further selected for PXRD studies and preparation of tablet dosage formulation.

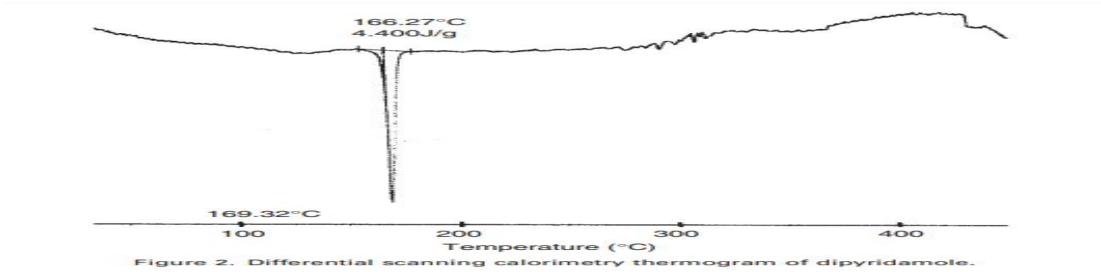
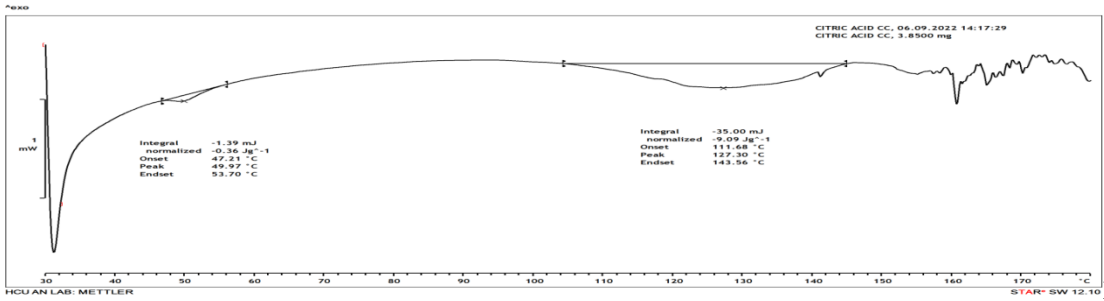


Figure 2. Differential scanning calorimetry thermogram of dipyridamole.

A



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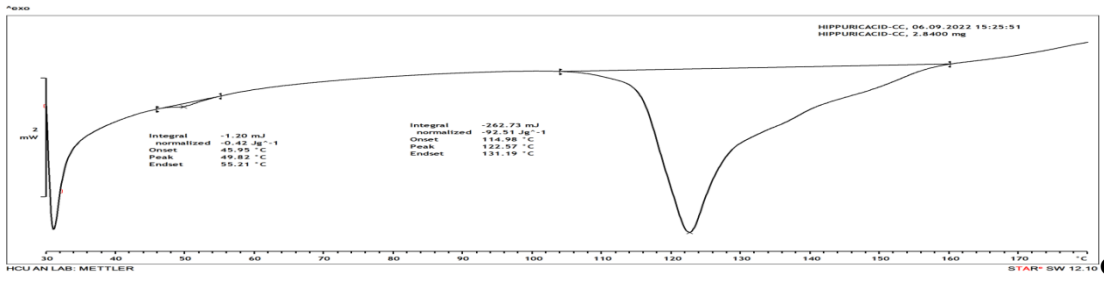

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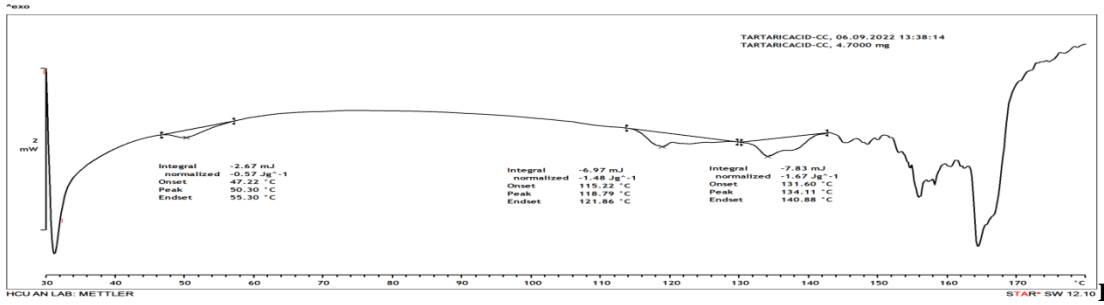

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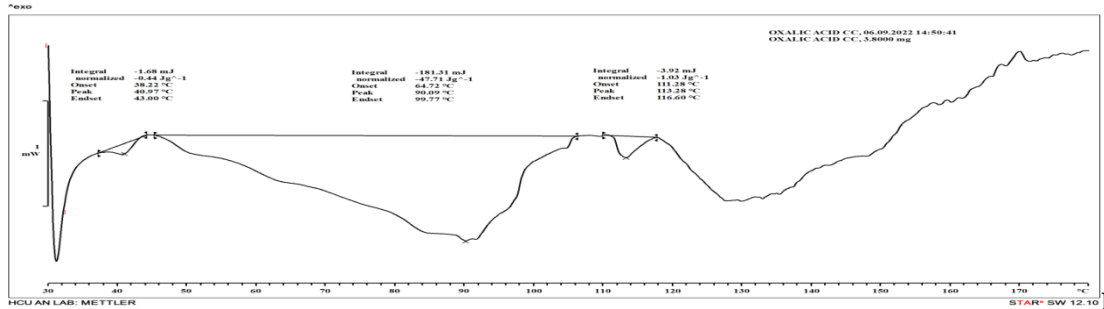

E

Figure 6: DSC thermogram of (A) DPM, (B) DPM-citric acid, (C) DPM-hippuric acid, (D) DPM-tartaric acid, and (E)DPM-oxalic acid cocrystals.

Powder X-Ray Diffraction of DPM-Cocrystals

PXRD provides a distinctive fingerprint diffraction pattern characteristic of a particular crystal structure. The 2θ value for 100% intensity of DPM was found at 20.4 and intense peaks of crystallinity were observed, indicating its crystalline nature. Overlay of PXRD of DPM, cocrystals and coformers were shown in Figure 7. The 2θ value for 100 % intensity of hippuric acid was observed at 18.4.

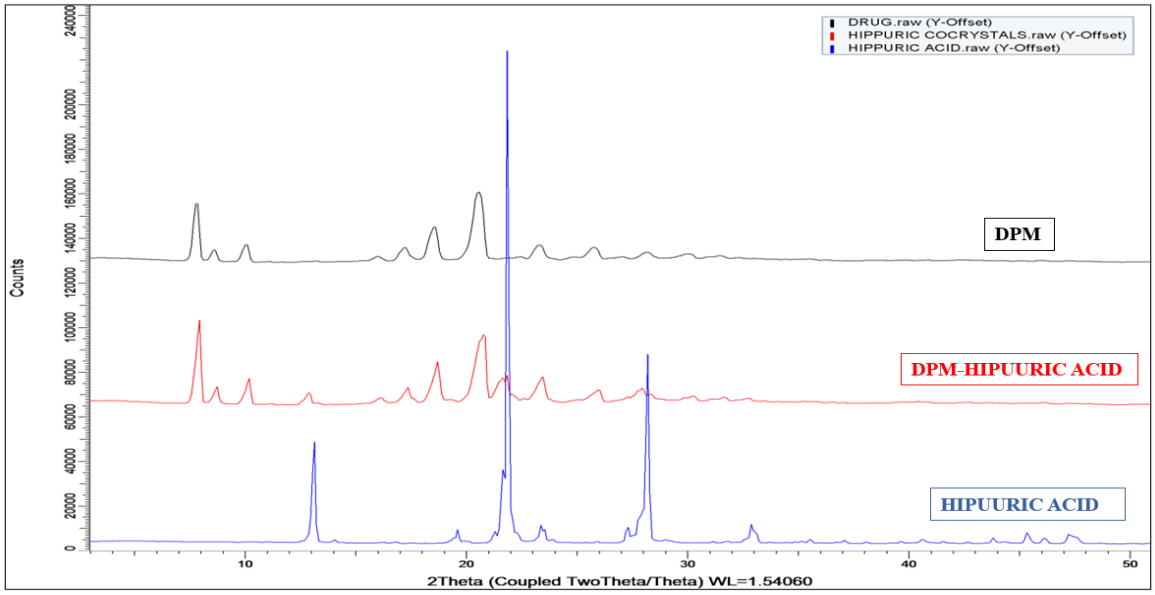

Figure 7. Overlay PXRD pattern of DPM-hippuric acid co-crystal with its individual components.

PXRD pattern of above prepared DPM cocrystals showed the presence of new peaks, alteration in peak intensities that infers different crystal habits and arrangement of molecules indicating generation of distinct crystalline forms.

DPM-hippuric acid cocrystals tablets were formulated with various levels of MCC (super disintegrating agent) and carboxy methyl cellulose as a binder.

Characterization of DPM-Hippuric Acid Tablets

Disintegration time, hardness, thickness, friability, drug content & % weight variation for $DPMF_1$, $DPMF_2$, $DPMF_3$and $DPMF_4$ formulations were reported in Table 3. All parameters were found to be satisfactory. Hardness of tablets was found to be in the range of 3-4 kg/cm^2 that confirms the resistance of tablets to shipping or breakage under conditions of storage and transportation. Friability results indicated good mechanical strength of tablets as the percentage of friability is less than 1% confirming to the compendial limits. Percentage deviation of weight was less than ±7.5%, complying with Pharmacopeial specifications confirming uniformity of weight. Drug content was found to be within the specified limits of 90 to 110% of the stated amount. Disintegration time of all the prepared tablets was within the range of 54-61 seconds that comply with the disintegration time for uncoated tablets as per IP (<15 minutes) (Indian Pharmacopoeia, 2018)

Table 3. Characterization of DPM-hippuric acid tablet formulations

	$DPMF_1$	$DPMF_2$	$DPMF_3$	$DPMF_4$
Disintegration time(sec)*	54±0.81	60±0.81	56±0.47	55±0.81
Hardness(kg/cm²)*	4±0.81	3±0.4	3±0.47	4±0.8
Thickness(cm*10⁻²m)*	0.36	0.36	0.36	0.36
Friability(%)	0.847±0.002	0.826±0.003	0.833±0.001	0.819±0.002
Drug content(AM±SD)*	96±0.53	95±0.81	95±0.81	95.33±0.54
% Weight variation	0	1	0.5	1

*Mean of three determinations (n=3)

Dissolution studies of DPM-hippuric acid cocrystal tablets

Dissolution studies of DPM-hippuric acid cocrystal tablets were performed in pH 6.8 buffer and reported in (Figure 8).

The order of dissolution profiles of DPM-hippuric acid formulations ($DPMF_1$, $DPMF_2$, $DPMF_3$, $DPMF_4$) in pH 6.8 phosphate buffer resulted as F1>F2>F3>F4.

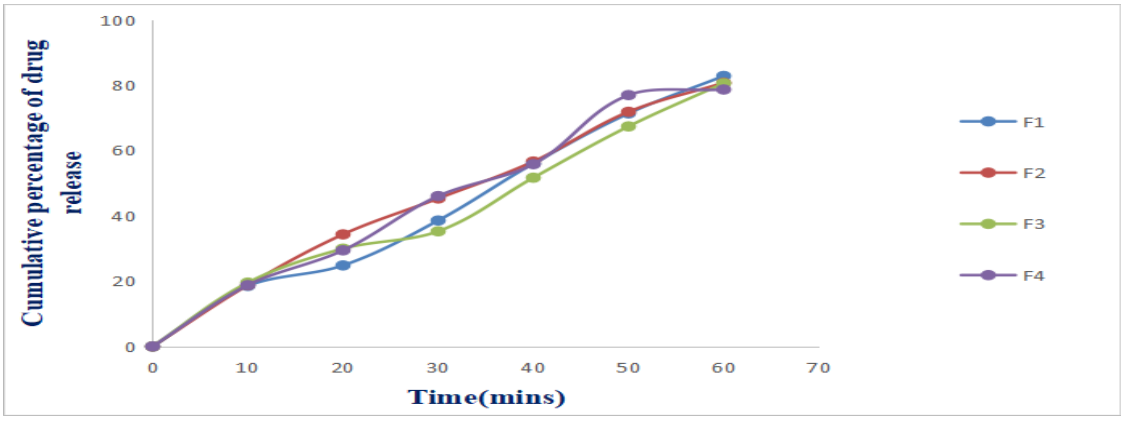

Figure 8. Dissolution profiles of DPM-hippuric acid formulations in pH 6.8 phosphate buffer.

Optimization of formulation of DPM-hippuric acid tablets

Factorial design analysis of DPM release at 60 min

The 60 min cumulative % DPM release data was analysed and recorded in the Table 4 and 5. The coefficients were recorded in the standard format and equation (3) was obtained. From the software analysis, the following polynomial equation was obtained at 10mins.

$$Y = 82.78 - 4.43X_1 - 4.5X_2 + 1.94X_1X_2 \quad \text{.....(3)}$$

Table 4: DPM release data at 60 min

S. No.	Treatments	Cumulative DPM Release (%)
1	1	82.78
2	CMC, X_1	80.7
3	MCC, X_2	80.58
4	Interaction term, X_1X_2	78.65

Table 5. 2^2 Factorial analysis of DPM at 60 min.

S. No.	Combination	Coefficient	significance	SS ratio
1	b0	82.7875	---	----
2	b1	-4.4375	---	44.9957%
3	b2	-4.5075	----	46.4265%
4	b12	1.9375	-----	8.5778%

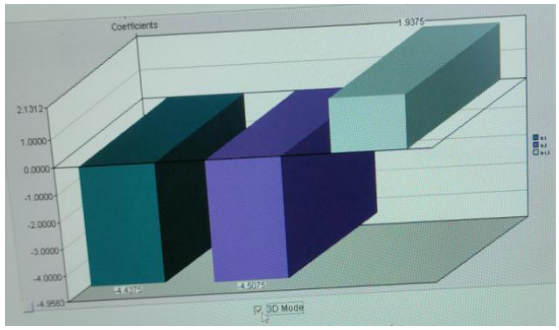

Figure 9: Graph identifying the influence of factors on DPM release at 60mins.

The MCC, (X_2) was highest (SS ratio = 46.426 %). The coefficient has negative sign, i.e., the higher the amount of X_2, less will be the DPM release. The CMC, (X_1) is the second main factor (SS ratio = 44.99 %). The coefficient has negative sign, i.e., the higher the amount of X_1, less will be the DPM release. The interaction term, (X_1X_2) was negligible (SS ratio = 8.577 %). The coefficient has a positive sign, i.e., the higher the amount of X_1X_2, greater will be the DPM release.

Further, analysis is attempted by observing the simulation and search method. The main factors, say X_1 andX_2 *are* larger (nearly 50%) compared to the effects of their interactions (X_1X_2) and hence, the curvature effect was insignificant. The steepest ascent method was used for the simulation and optimization of the conditions or theoretical formulation.

Method of calculation – Simulation: Steepest ascent method was systematic simulation that is made with MCC jump by 2 mg, The CMC and other concentrations are automatically fixed. Then, responses are calculated using equations. The data are given in Table 6.

Table 6: Random simulation for steepest ascent method for 60 min release analysis

S.No	CMC	MCC	Estimated response
1	4	60	82.78
2	8	64	

The decision is taken regarding the ingredient concentrations. The concentrations finalized are: CMC (8 mg) and MCC (60 mg) for the desired cumulative % drug release of 82.78.

CONCLUSIONS

The melting point of DPM-cocrystals indicated a decrease in the melting point as compared to DPM (166.27 ^{0}C), suggesting the possibility of cocrystals formation. Melting point data suggested formation of eleven cocrystals. Solubility studies were conducted for the 9 cocrystals. Among those, 6 cocrystals: DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid, DPM-succinic acid, DPM-oxalic acid and DPM-cinnamic acid cocrystals showed increased solubility in pH 1.2, 6.8 buffers and distilled water. Dissolution studies of 6 cocrystals resulted in improved dissolution

rate in pH 6.8 buffer compared to the DPM. The 100% drug release was observed for DPM-hippuric acid cocrystals within 60 min while the DPM showed only 28.98% in 60 min. DPM-citric acid, DPM-hippuric acid, DPM-tartaric acid and DPM-oxalic acid preparation showed endothermic peaks, which were neither near to the melting point of DPM nor the coformer that inferred absence of physical mixture and the formation of cocrystals. PXRD pattern of cocrystals showed distinct diffraction pattern. DPM-hippuric acid tablets were prepared and among four formulations (F_1, F_2, F_3, F_4), F_1 formulation resulted as the optimised formula with the highest dissolution rate with accordance to the theoretical response. As anticipated in the objectives of the present work, the attempts were met. DPM-cocrystals with improved physicochemical properties were obtained.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

AUTHOR CONTRIBUTION STATEMENT

Author contributions: Concept -Monika Nijhawan; Design - Monika Nijhawan, Gunnam Sailaja; Supervision- Monika Nijhawan ; Data Collection and/or Processing -Sadhna Dhyagala; Analysis and/or Interpretation – Monika Nijhawan; Literature Search Rajeswari Aleti; Critical Reviews -Monika Nijhawan,Trapti Saxena, Gunnam Sailaja

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