Results in Chemistry 4 (2022) 100315

Contents lists available at ScienceDirect

Results in Chemistry

journal homepage: www.sciencedirect.com/journal/results-in-chemistry

Differential scanning calorimetry: A screening tool for the development of diacerein eutectics

Rajeshri D. Patel [a,*], Mihir K. Raval [b]

[a] School of Pharmaceutical Sciences, Atmiya University, Rajkot 360 005, Gujarat, India
[b] Department of Pharmaceutical Sciences, Sardar Patel University, Vallabh Vidyanagar 388 120, Gujarat, India

ARTICLE INFO

Keywords:
Diacerein
Binary phase diagram
Eutectic
Kinetic solubility
Tamman's triangle

ABSTRACT

The application of DSC technique has been employed for better understanding the behavior of multi-component solid forms of poorly water-soluble drugs. Therefore, the purpose of the present work was to investigate the binary system of Diacerein (DIC) by preparing multi-component adducts using various coformers. DIC and different coformers were co-grounded with various solvents at 1:1, 2:1, and 1:2 M ratios. These solid forms were characterized using DSC, PXRD, FT-IR, and SEM. DSC analysis preliminary characterized that aliphatic and phenolic acid are competent enough to co-crystallize with DIC with lower melting endotherms via acetone assisted grinding method. The results of PXRD, FT-IR, and SEM confirmed the formation of two novel eutectics of DIC with fumaric acid (FUM) and 2, 4-dihydroxybenzoic (DIH) acid. Two eutectics, i.e., DIC-FUM (1:2) and DIC-DIH (1:3) with exact stoichiometry were further identified by using Tamman's triangle. The representative samples were subjected to kinetic solubility measurements. Both the produced eutectics showed superior solubility compared to DIC alone with their stable nature. Hence, a low melting depression eutectic could be resolved via DSC analysis applied as a diagnostic tool in designing the multi-component solid forms of the targeted drug molecule.

Introduction

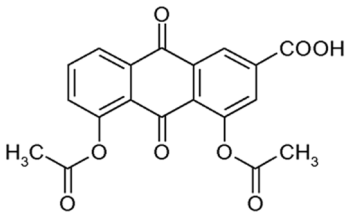
Diacerein (DIC; Fig. 1) is approved for the effective treatment ofosteoarthritis with mild anti-inflammatory, antipyretic, and analgesic activities [1]. DIC is a yellow crystalline powder with a molecular mass of 368.3 g mol^{-1} anda melting point 255.2 °C. Based on the aqueous solubility, it is classified as a Biopharmaceutical Classification System (BCS) II drug (≈ 3.197 mg mL^{-1}) that causes the issue in oral absorption (35–56%) [2–4]. Once DIC becomes bioavailable, it completely converts into its active metabolic form Rhein (Rh). The unabsorbed Rh irritates the intestinal mucosa and typically produces a weak laxative-like side effect [5–7]. Thus, to increase the bioavailability of DIC would allow less DIC to reach the colon, subsequently, leading to a reduction in the gastrointestinal side effects and dose. Various formulation approaches are adopted by scientists to overcome the bioavailability problem associated with DIC, which includes solid dispersion, complexation, nanofiber, Nano emulsion, nanoparticles, and many more.

In the present scenario, manipulating new solid forms employed in crystal engineering approach to diversify the multi-component forms particularly for active pharmaceutical ingredient (API). Ultimately, the resulted forms can lead to modifying the various pharmaceutically relevant parameters without compromising the efficacy of the drug [2,8–10]. The crystal engineering approach mainly involves the formation of novel eutectic, solid solution, polymorphs, solvate, hydrate, co-crystal, and co-amorphous systems. Among these, a eutectic mixture and a conglomerate of solid solution are non-covalent derivative that can efficiently improve the pharmaceutical properties of non-ionisable or poorly ionisable APIs with a counter molecule/coformer [11].

The thermal technique specifically differential scanning calorimetry (DSC) is extensively adopted for the examination of the solid-state functionality in pharmaceutical research. However, it is rarely used as a diagnostic tool to attain qualitative information about individual points. For instance, its utilisation could be restricted to a comparison of the melting behaviours of the participating compounds and their physical mixtures without the quantitative points of view [12–14]. As regards the multi-component forms, DSC has been anticipated as a screening tool for rapid identification of the multi-component system mainly co-crystal or eutectic [15,16]. The possible formation of the multi-component entity is presumed from the disappearance of the thermal events of the parent compounds and the appearance of new

* Corresponding author.
E-mail address: rajeshripatel.2504@gmail.com (R.D. Patel).

https://doi.org/10.1016/j.rechem.2022.100315
Received 20 October 2021; Accepted 25 February 2022
Available online 5 March 2022



Diacerein

Fig. 1. Chemical structure of Diacerein (DIC).

thermal events. This novel curve can be formed due to the generation of a new form. The majority of the studies are limited to the qualitative considerations by implementing DSC data. Here, we subjected materials to DSC, powder X-ray diffractometry (PXRD), Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR), Scanning electron microscopy (SEM), and kinetic behavior. The impacts of resulting materials were examined and compared for the screening of eutectic formation.

The aim of the present investigation was initiated with a comprehensive understanding of the DSC measurements and their applicability for qualitative and quantitative aspects. In this study, we have adopted the following development screening stages:

1) Application of Δp*K*a rule for the identification of the potential coformers.
2) Preparation of multi-component solids with selected coformers using various preparation methods.
3) Characterization of resulted mixtures using various characterization techniques.

This manuscript explains the screening and identification of appropriate coformers and assessment of the multi-component adducts of DIC in the early development stages. The systematic investigation was conducted by using a potential DSC tool for rapid selection and interpretation of novel solid forms with less trial.

Materials and methods

Materials

DIC (Pure drug) was generously provided by Ami Lifesciences Pvt. Ltd. (Baroda, India) and coformers used here are purchased from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India).Analytical grades of solvents, i.e. acetone, ethanol, methanol, acetonitrile, dimethyl sulphoxide and dimethyl formamide were procured from Merck Pvt. LTD. (Mumbai, India).

Preparation of multi-component solid forms by solvent assisted grinding (SAG) method

Multi-component solid forms of DIC (368.3 mg, 1 mmol) were produced with fumaric acid (FUM; 232.14 mg, 2 mmol) and 2, 4-dihydroxybenzoic acid (DIH; 462.4 mg, 3 mmol) via solvent assisted grinding (SAG) technique. The described amounts of both the coformers were co-ground separately with DIC for 20–30 min using agate mortar pestle by adding few drops (≈ 200 μL) of acetone to aid mixing between components. The obtained mass was scratched out and then dried in an oven (40 °C) for 2 h followed by gentle trituration before sieving through a 100 mesh (ASTM standard) before further analysis. The resultant products were stored in the glass vials inside desiccators [17,18].

Preparation of multi-component solid forms by reaction crystallization method (RCM)

Ssolution-based method i.e. reaction crystallization method (RCM) was used for the preparation of multi-component solid forms. Briefly, the mixtures of DIC and coformers (according to the molar ratios) were added to 50 mL solvent (acetone/methanol) containing flask. The resulting suspension was refluxed at 50 °C for 2 h while stirring. After refluxing, the mixture was cooled at room temperature overnight. The resulted solids were harvested, passed through ASTM sieve (#100), and placed in the desiccators for further study [19].

Solid-state characterization of multi-component solids

Differential scanning calorimetry (DSC)

DSC (DSC 60, Shimadzu, Japan) was used to perform the thermal analysis for DIC samples. Approximately 1–3 mg of powder was placed in hermetically sealed aluminum DSC pans. DSC pans were hermetically sealed with TA hermetic press and analyzed from 40 to 300 °C at a scanning rate of 5 °C min^{-1}. For all the experiments, a hermetically sealed aluminum empty crucible was used as a reference. An inert temperature was maintained by purging nitrogen gas at a flow rate of 100 mL min^{-1}.

Powder X-Ray diffraction (PXRD)

The PXRD patterns of powder samples were collected at room temperature with aPANanalytical diffractometer system (X'Pert pro Multi-Purpose Diffractometer, USA) equipped with an X'PertHighScore Plus detector. The X-ray radiation used was Cu-Kα (40 kV, 30 mA, and λ = 1.5418 Å). Measurements were determined over a 2θ range of 10–40° with a scan rate of 4° per min.

Attenuated total Reflectance Fourier Transform Infrared (ATR-FTIR)

A Cary-630 FTIR spectrometer (Agilent Technologies, USA) equipped with ATR (Diamond ATR crystal, Agilent) accessory was used for recording the IR spectra of the samples. Spectral data were acquired with Lab solution software. Each spectrum was collected for 4 scans at a spectral resolution of 2 cm^{-1}over the wavenumber region of 400–4,000 cm^{-1}.

Scanning electron microscopy (SEM)

The surface morphology and visual image analysis were performed by SEM analysis (JSM-6380, JEOL Ltd., Japan). The powder samples were placed on a double-sided tap, sputtered with gold. The coating process was operated at a voltage of 10 kV with an equipped image analyser. The sputter coater instrument was employed for making the sample electrically conductive. Several magnification ranges were used.

Kinetic solubility measurement

Before the solubility experiment, DIC and its representative samples (DIC-FUM and DIC-DIH) were sieved through 100-mesh sieves. Approx 50 mg of DIC powder (or corresponding to, for eutectics) were placed in 200 mL of different buffer solutions in triplicate, namely pH 1.2 (Hydrochloric acid buffer), pH 4.5 (Acetate buffer), and pH 6.8 (Phosphate buffer). The resultant suspension was kept in a shaker-incubator (Tempo Instruments and Equipments Pvt. Ltd., India) with rotation speed 150 rpm at 37 ± 0.5 °C. An aliquot of the dispersion was taken at 5, 10, 15, 30, 45, 60, 120, 180, 240, and 1440 min. The resulting samples were filtered through a 0.45 μm PVDF syringe filter (Millex-HV, Millipore) and the filtrate was suitably diluted and analyzed by RP-HPLC method [20].

Results

The purpose of the present study aimed to applied DSC technique as a screening tool for the formulation of multi-component solid forms. The following screening stages were employed for an in-depth understanding.

Screening stage 1: Application of ΔpKa rule for the identification of the potential coformers

Generally Regard as Safe (GRAS)-listed coformers with high potential functionalities have been selected to prepare multi-component solids (mainly targeting co-crystal/eutectic) via hydrogen bonding with DIC. The selection of coformers can be determined by understanding supramolecular chemistry, p*K*a difference, molecular mass, Hansen solubility parameter, and melting point [9]. Among these, a very simple and predominant approach i.e. p*K*a-based prediction has been employed to predict the formation of a multi-component system. It represents the Δp*K*a rule (Δp*K*a = p*K*a of protonated base (coformer/drug) - p*K*a of acid (drug/coformer). If Δp*K*a < -1, non-ionized complex (co-crystal/eutectic) may strongly recommend, whereas Δp*K*a > 3 may result in ionized complex (salt) formation. For Δp*K*a between $-1 < \Delta pKa < 3$, the resulting complex will be intermediate ionization or proton-sharing states that can be predicted as a salt/co-crystal/eutectic [21]. Various functional groups like –COOH, -C-O-C, and –COOC exhibiting in DIC have a significant role in the crystal engineering point of view. As a weakly acidic nature of DIC with p*K*a of 3.01, the coformers containing amine, carboxylic acid, amide, and carbonyl groups with higher p*K*a values have been chosen to facilitate any intermolecular interaction with DIC. On assessing the Δp*K*a rule, nicotinamide, 4-aminobenzoic acid, glutaric acid, nicotinic acid, oxalic acid, succinic acid, salicylic acid, DIH, urea, acetamide, aceclofenac, L-aspargine, FUM, aspartic acid, and p-amino salicylic acid were selected as a potential coformer to form intermolecular interaction with DIC.

Screening stage 2: Preparation of multi-component solids with selected coformers using various preparation methods

Multi-components adducts have been designed through different techniques such as solution-based co-crystallization (evaporation or slurry), fusion (co-melting), mechano-chemical (dry/solvent assisted grinding), ultrasound-assisted co-crystallization, co-extrusion (twin screw/hot-melt), spray drying, and supercritical fluid method [11,22–24]. All of these methods have their advantages and disadvantages, for example, scalability of the process, appropriate choice of solvent, sample size, reproducibility, maintaining the stability of new forms, impurity formations, and many more. Even though all the strategies might not be effective at producing a particular choice of multi-component solids, therefore it is useful, while screening for new solid forms, to utilize more than one technique.

At the first stage of screening, solvent assisted grinding (SAG) method with its advantages of efficient atomic reaction and reduced time over solid-state grinding was selected as a preliminary screening method [25]. Initially, a molar ratio of 1:1 of drug with various coformers was tried, but occasionally 2:1 or 1:2 ratios were applied for further verification. Depending upon the solubility of DIC, we also attempted a solution-based method like RCM for the preparation purpose. All resulted mixtures were subjected to various characterization techniques.

Screening stage 3: Characterization of resulted mixtures using various techniques

The solid-stage characterization was performed using various techniques like DSC, PXRD, FT-IR, and SEM analysis. Firstly, the prepared materials were verified by using the most preferred and rapid method, i.e., melting point determination and DSC. If the evidence of any intermolecular interaction was observed, the respective materials would qualify for further analysis. Only the qualified materials were confirmed by applying PXRD and FT-IR analysis.

Table 1
DSC responses of RCM and SAG experiments of DIC with various coformers..

Cofomer used	Methods	
	RCM	SAG
	Molar ratio*_Solvent	Molar ratio*_Solvent
Nicotinamide	-(1:2, 1:1, 2:1)_ET-(1:2, 1:1, 2:1) _ME	-(1:2, 1:1, 2:1)_AC-(1:2, 1:1, 2:1) _ET-(1:2, 1:1, 2:1) _ME-(1:2, 1:1, 2:1) _DMF-(1:2, 1:1, 2:1) _DMSO-(1:2, 1:1, 2:1) _ACN
4-Aminobenzoic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_ET-(1:2, 1:1) _ME-(1:2, 1:1) _AC-(1:2, 1:1) _DMF-(1:2, 1:1) _DMSO-(1:2, 1:1) _ACN
Glutaric acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
Nicotinic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
Oxalic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
Succinic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
Salicylic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
2,4-Dihydroxybenzoic acid	-(1:2, 1:1, 2:1)_ET-(1:2, 1:1, 2:1) _ME	-(2:1, 1:1),+**(1:2)_AC**-(2:1, 1:1, 1:2) _ACN-(2:1, 1:1, 1:2) _ET-(2:1, 1:1, 1:2) _ME -(1:1)_DMF -(1:1)_DMSO
Urea	-(1:1)_ET -(1:1)_ME	-(1:1)_AC -(1:1)_ET -(1:1)_ME
Acetamide	-(1:2, 1:1, 2:1)_ET-(1:2, 1:1, 2:1) _ME	-(1:2, 1:1, 2:1)_AC
Aceclofenac	-(1:2, 1:1, 2:1)_ET-(1:2, 1:1, 2:1) _ME	-(1:2, 1:1, 2:1)_AC
L-aspargine	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1, 2:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
Aspartic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
p-Aminosalicylic acid	-(1:2, 1:1)_ET-(1:2, 1:1) _ME	-(1:2, 1:1, 2:1)_AC-(1:2, 1:1) _ET-(1:2, 1:1) _ME
Fumaric acid	+**(1:2, 1:1, 2:1)**_ET +**(1:2, 1:1, 2:1)**_ME	+**(1:2, 1:1, 2:1)_ET** +**(1:2, 1:1, 2:1)_ME** +**(1:2, 1:1, 2:1)_AC** -(1:1)_DMF -(1:1)_DMSO -(1:1)_ACN

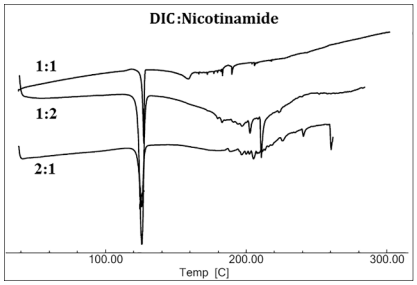
*Molar ratio represents the DIC:Coformer ratio.

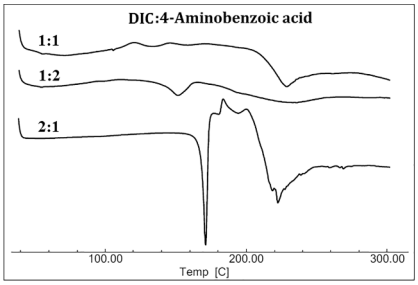
Interpretation by DSC analysis as a preliminary tool

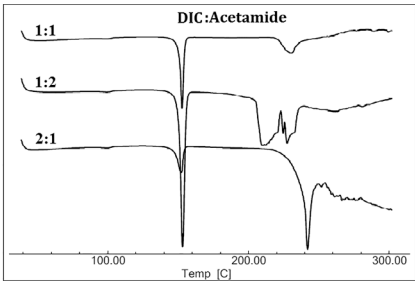
DSC is a thermo-analytical technique and is utilized for the quick probing of solid-state reactions with the advantage of less sample consumption and short analysis time. The results of the crystallization experiments using the aforementioned methods are represented in Table 1 in which positive sign (+) denoted the potential intermolecular

Table 2
DSC responses of coformers for co-crystallization with DIC using SAG method using different ratios..

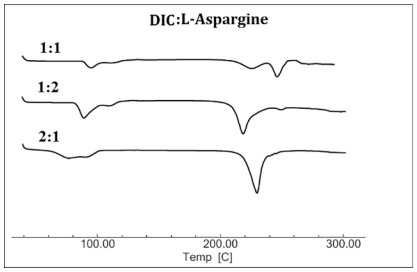
Drug/coformer (Molar ratio)	Melting Point From DSC (°C)		Observation	Inferences
	Coformer	SAG		
Diacerein (Pure Drug)	255.17	–	Decomposed after melting	–
Nicotinamide(1:1)	128.03	125.85, 211.23	Two distinct peaks and samples were decomposed	No evidence of multi-component adduct
Nicotinamide(1:2)		125.83, 210.69		
Nicotinamide(2:1)		130.85, 209.96		
4-Aminobenzoic acid (1:1)	188.23	171.25,222.37	Two distinct melting points were observed	-Do-
4-Aminobenzoic acid (1:2)		169.03,218.54		
4-Aminobenzoic acid (2:1)		175.53, 209.52		
Acetamide (1:1)	79–82	79.89, 244.98	Two separate fusion peaks	-Do-
Acetamide (1:2)		80.99, 148.64, 246.72	Three separate fusion peaks	
Acetamide (2:1)		79.30, 249.45	Two separate fusion peaks	

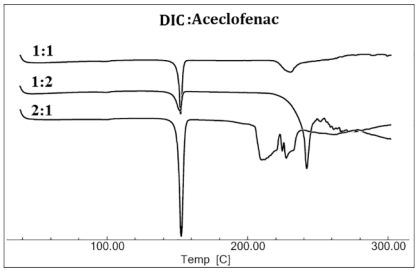


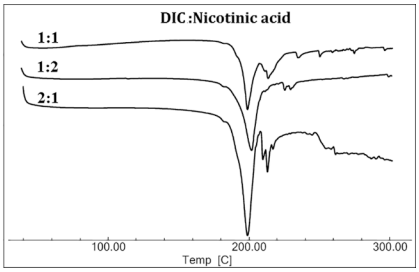




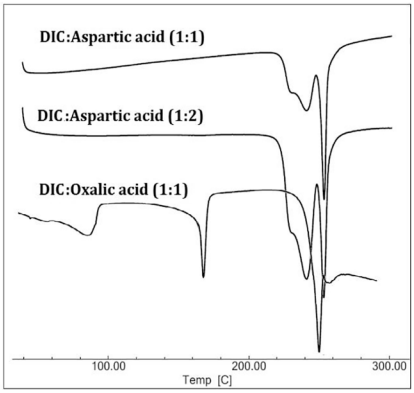
L-Aspargine(1:1)	101.52, 243.80	75.91, 230.31, 242.62	Two distinct fusion peaks with slightly lower melting endotherms	-Do-
L-Aspargine (1:2)		76.84, 229.78		
L-Aspargine (2:1)		75.23, 240.62		
Aceclofenac (1:1)	149–153	152.31, 230.34	Two distinct fusion peaks followed by decomposition	-Do-
Aceclofenac (1:2)		152.59, 230.34		
Aceclofenac (2:1)		151.98, 241.94		
Nicotinic acid (1:1)	234.42	202.43, 228.71	One single sharp fusion peak and second peak was very smallfollowed by decomposition	-Do-
Nicotinic acid (1:2)		202.28, 225.73		
Nicotinic acid (2:1)		201.87, 227.69		

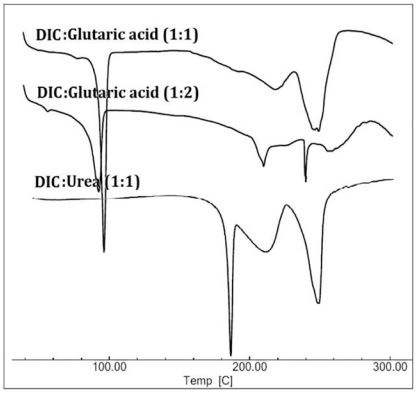


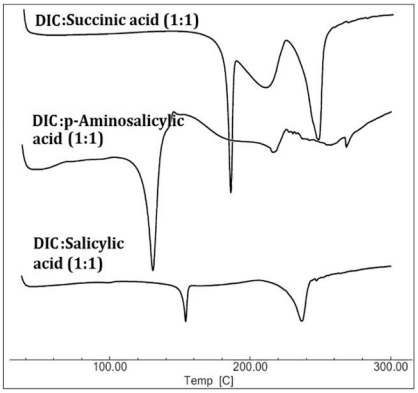




Aspartic acid (1:1)	270.24	241.00, 253.47	Two different fusion peaks	-Do-
Aspartic acid (1:2)		241.17, 253.20		
Oxalic acid (1:1)	180.35	172.18, 250.78	Melting behavior similar as starting materials	-Do-
Glutaric acid (1:1)	99.60	88.62, 218.38	Two separate fusion peaks	-Do-
Glutaric acid (1:2)		92.35, 209.87, 239.48	Three sharp fusion peaks	
Urea (1:1)	133–135	119.51, 235.04	Two different fusion peaks	-Do-
Succinic acid (1:1)	185.43	186.27, 248.73	Melting behavior similar as starting materials	-Do-
p-Aminosalicylic acid (1:1)	150.5	≈ 131.67, ≈ 217.56	One sharp endothermic peak followed by exotherm and then decomposition	-Do-
Salicylic acid (1:1)	157–158.6	155.48, 238.71	Two distinct fusion peaks followed by decomposition	-Do-



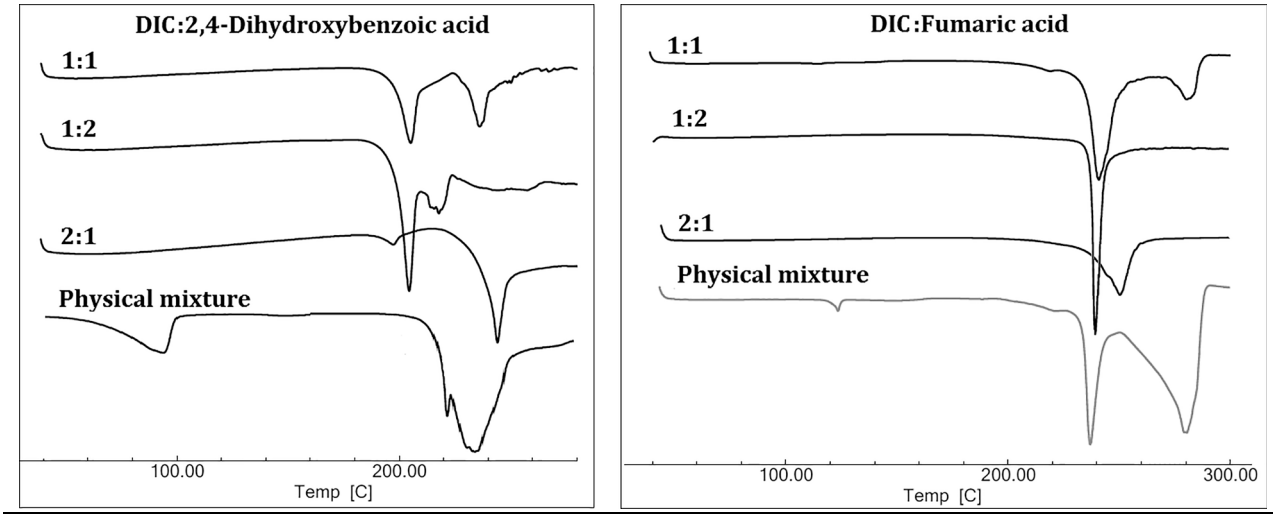




(*continued on next page*)

Table 2 (*continued*)

Drug/coformer (Molar ratio)	Melting Point From DSC (°C)		Observation	Inferences
	Coformer	SAG		
2,4-Dihydroxybenzoic acid* (1:1)	222.05	204.41,234.68	Both peaks were nearer to each other if change the ratio	Might be formedmulti-component adduct
2,4-Dihydroxybenzoic acid* (1:2)		202.35	Single peak having different melting fusion peak	
2,4-Dihydroxybenzoic acid* (2:1)		195.65,236.88	Both peaks were nearer to each other if change the ratio	
Fumaric acid* (1:1)	289.48	239.56	Sharp single fusion peak	Might be formedmulti-component adduct
Fumaric acid* (1:2)		240.29	Sharp single fusion peak	
Fumaric acid* (2:1)		237.09	Sharp single fusion peak	



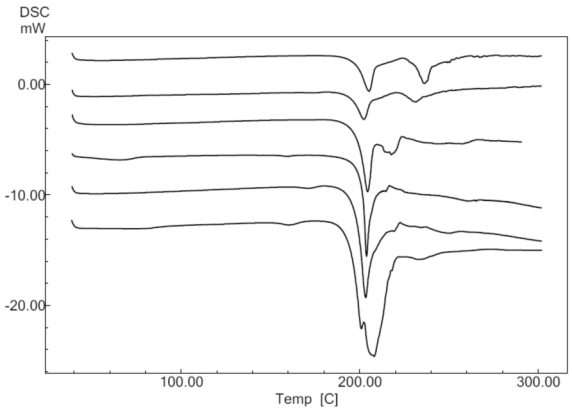


Fig. 2. Overlay of DSC scans of DIC-DIH system (A) and DIC-FUM system (B) at various molar ratios.

interaction. From the observations, a satisfactory outcome for the generation of the multi-component system via RCM method was not found. A possible reason for not obtaining novel solid forms could be the large differences in the solubility of DIC and corresponding coformers in the applied solvents (methanol and ethanol). It can be observed that DIC is inadequately soluble whereas coformers are well soluble in the applied solvents; DIC gets precipitated; if both DIC and coformer are well soluble, and no co-crystal/eutectic is formed. Such kind of co-crystallization is mainly influenced by concentration and various solvents used so that screening is very time and material consuming. Upon verification of the feasibility, the binary mixtures were generated using SAG experiment to avoid the solubility issues.

In SAG method, each sample was treated by adding a catalytic amount of various polarity organic solvents into the physical mixture of drug and coformer followed by trituration [17]. The choice of solvent was based on at least the partial solubility of drug and coformer in that particular solvent (Table 1). In the case of the solvents such as dimethyl sulfoxide, acetonitrile, and dimethyl formamide, crystallization of DIC with nicotinamide, 4-aminobenzoic acid, DIH, and FUM yielded totally waxy materials. Although DIC is more soluble in the above mentioned solvents, these solvents were precluded from further investigation. The possible mechanism for grinding of multiple components along with solvent facilitates diffusion of low molecular mass coformer into API crystal lattice thereby enhancing mobility and initiates the interaction quickly [26]. Finally, few drops (≈ 200 μL) of acetone were added to enhance the reaction possibility as it evaporated during the process without leaving any traces.

The DSC responses and melting endothermic events of the resulted materials prepared by acetone-assisted grinding technique are tabulated in Table 2. It has been seen that the DSC curve of DIC (Fig. 2) showed a single and sharp melting endotherm at 255.17 °C (ΔH_{fus} = 96.68 J g^{-1}) imparting its crystalline solid form [17]. Evidence of any multi-component solid forms is confirmed by comparing the DSC curves which were recorded. If DSC data reveal a single endothermic event that indicates a melting point lower or in between or greater than the melting points of the starting components then the resulting system is said to be co-crystal. In the case of eutectic mixture, the DSC curve exhibits a lower melting depression than the participating components. If heating of a binary mixture results from two endothermic events, each corresponding to the melting of the parent compounds, it indicates that the binary mixture remains as a physical mixture without evidence of intermolecular interactions [11,27].

The DSC scan of binary systems of DIC with 4-aminobenzoic acid, acetamide, aceclofenac, aspartic acid, oxalic acid, glutaric acid, urea, succinic acid, and salicylic acid showed two different endothermic peaks corresponding to their melting that indicated no evidence of the formation of multi-component adducts. On the other hand, few DSC scans for instant DIC with L-aspargine and nicotinamide exhibited slight depression in melting peaks at 232.78 °C and 225.73 °C which were

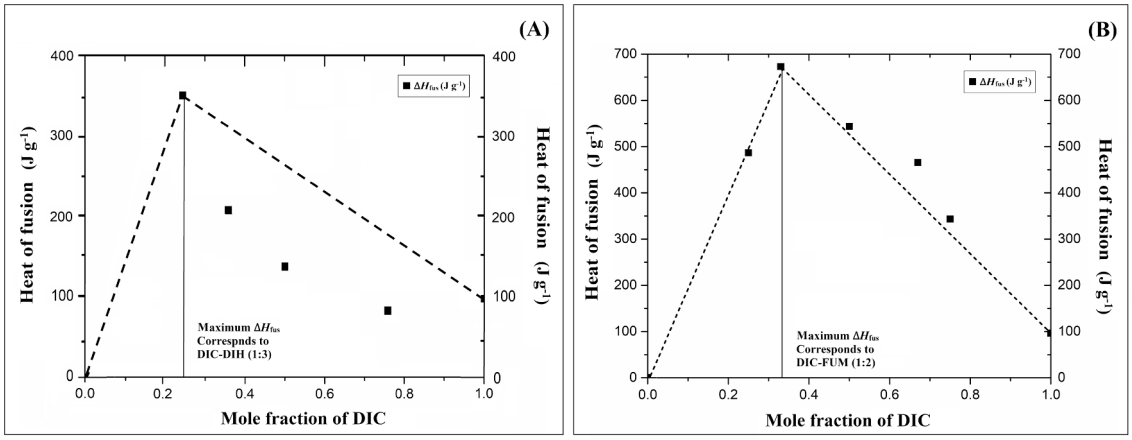


Fig. 3. Tamman's triangle construction of DIC-DIH system (A) and DIC-FUM system (B).

different from the melting of pure L-aspargine (243.80 °C) and pure nicotinamide (289.48 °C). This kind of melting behavior was observed due to the trituration in presence of solvent and resulted in the physical mixtures [28]. Other co-ground systems of DIC (with nicotinic acid and p-amino salicylic acid) showing the physical mixture followed by decomposition were also omitted for the next stage of material development.

Fortunately, the fruitful outcomes of DIC were successfully screened out with DIH and FUM by using SAG method. In the case of DIC-DIH system (1:1, 1:2 ratios) (Table 2) depicted endothermic events of drug and coformer in very close proximity. It might be an indication of positive interaction between the components towards the formation of multi-component adducts. Looking at such peak position, additional ratios 1:3 and 1:4 were produced and studied for their thermal behaviors (Fig. 2A). A single and sharp melting endotherm appeared for 1:3 ratio which was significantly different from melting of DIC (255.17 °C) and DIH (222.05 °C), pointing towards the formation of a novel and pure crystalline phase with no leftover of starting materials. While 1:4 ratio of DIC-DIH represented a single melting event with the presence of excess untreated DIC and DIH at the end of the DSC curve (Fig. 2A) which was attributed to the existence of the traces of parent components.

In contrast to this, a multi-component solid form of DIC-FUM (Fig. 2B) obtained by SAG method was also produced by RCM; however, all the ratios of DIC-FUM samples with various methods illustrated with the same melting behavior nearer to 233 °C for with or without trace amount of impurity.Among all the ratios of DIC:FUM samples, 1:2 ratio appeared a single and sharp melting peak without a trace amount of starting components indicating the formation of multi-component solids.The endothermic peak of DIC-FUM (1:2) and DIC-DIH (1:3) samples were located prior to the endothermic peak of both the starting components which indicates the formation of a new crystalline phase that could be co-crystal or eutectic. The described ratio for both the systems was further evaluated with help of Tamman's triangle. The values of enthalpy of fusion (ΔH_{fus}), determined by integration of various mass percentage peak area obtained from DSC scans were plotted against mole fraction of DIC (Fig. 3). The maximum ΔH value was found for DIC-DIH system (364.67 J g^{-1}) corresponding to 1:3 (Fig. 3A) and DIC-FUM system (672.93 J g^{-1}) corresponding to 1:2 ratio (Fig. 3B) which was in good accordance with DSC scans. This finding was further verified with the other characterization techniques.

Interpretation by PXRD characterization

PXRD characterization is a fingerprint and discriminative technique to analyze the solid-state structure via a distinct diffraction pattern of the participating components. The PXRD patterns of pure DIC and the qualified binary mixtures, and their physical mixtures are recorded in the range of 10-40° and revealed with characteristic sharp peaks at 2θ scattered angles as shown in Fig. 4. The obtained diffract organ of DIC depicted at 2θ of 10.5°, 17.4°, 21.9°, and 27.9° indicating the sign of crystalline nature [17]. The diffract organs of participating coformers and their forms revealed the characteristic patterns with sharp and intense peaks positions as displayed in Table 3. These peaks of coformers with a specific position and relative intensities are in good accordance with the published data for each [18,29]. It is noteworthy that the appearance of new, distinct, or shifted positions at 2θ scattered angles seen due to either of the participating components was an indication of the formation of a new crystalline phase i.e. co-crystal. As can be seen in DIC-DIH (1:3) and DIC-FUM (1:2) systems, all the characteristic peaks of pure drug and respective coformers were still preserved in the physical mixture as well as the co-crystallized samples also with the slight or insignificant change in the positions of the participating components. This observation with almost no evidence/deviation in the diffract organs with lower melting depression in all the cases confirmed the formation of eutectics and excluded the co-crystal formation [11].

Interpretation by ATR-FTIR analysis

FTIR analysis is the complementary tool to interpret any possible solid-state interaction. Fig. 5 illustrates FTIR spectra of pure DIC, the qualified binary mixtures. The IR spectrum of DIC showed a broad O–H stretching band of –COOH group at wavenumber 3069 cm^{-1}, two carbonyl stretching strong bands at 1785 cm^{-1} (ester groups), and 1679 cm^{-1} (ketone group). The characteristic absorption spectra of DIH revealed the wavenumber at 3490 cm^{-1}, 3560 cm^{-1}, 2900–3600 cm^{-1}, and 1791 cm^{-1} [17]. FTIR spectra of FUM described the wavenumber at 3084 cm^{-1} and 1657 cm^{-1}. FTIR spectra of DIC-DIH and DIC-FUM system described the addition of the characteristic vibrational bands corresponding to individual components without any considerable shifting reflecting the absence of significant chemical interaction [17,18]. Additionally, a melting point depression with no deviation in the diffraction peaks concluded the formation of eutectic rather the co-crystal.

Interpretation by SEM analysis

SEM study is employed for the morphological evaluation of pure components and their newly developed forms. Fig. 4 depicts pure DIC, DIH, FUM, and their multi-component solids. The morphology difference of the prepared eutectics with micrometer sizes was observed as a separate entity from the pure drug molecule which might be influenced by the physicochemical properties imparting the improved solid orals

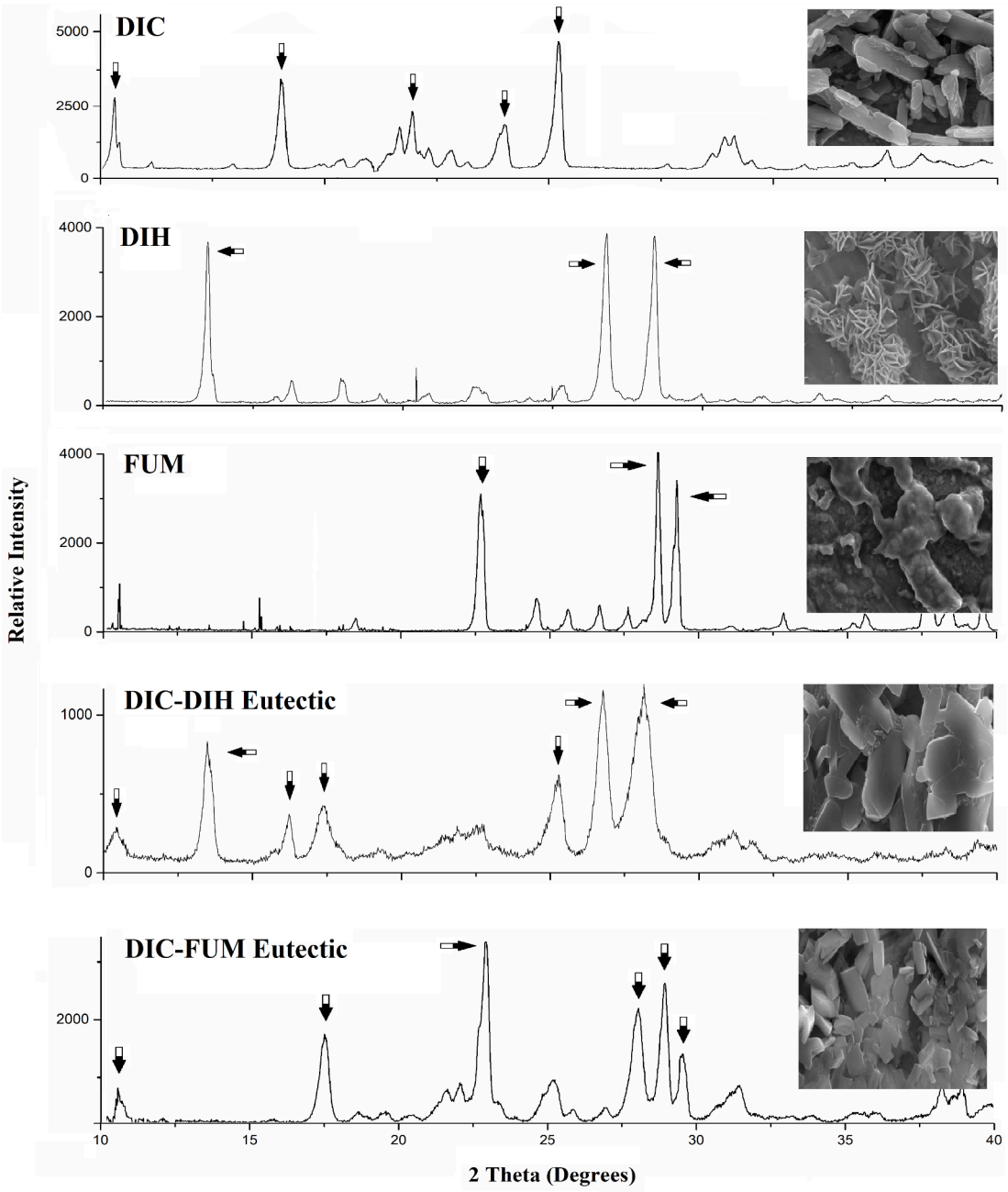


Fig. 4. Powder XRD patterns and SEM images of DIC; DIH; FUM; DIC-DIH Eutectic and DIC-FUM Eutectic.

Table 3
Characteristic diffraction peaks of raw materials and the qualified samples..

Samples	2 Theta (Degrees)
DIC	10.5, 17.4, 21.9, 27.9
DIH	13.5, 26.8, 28.4
FUM	22.8, 28.8, 29.4, 37.9
DIC-DIH Eutectic	13.6, 16.3, 17.4, 25.4, 26.9, 28.2
DIC-FUM Eutectic	22.79, 22.93, 27.93, 28.79, 29.40,

[30].

Kinetic solubility measurement

Fig. 6 represents the solubility measurement of pure DIC and co-crystallized eutectic samples in different buffer solutions. As can been seen, DIC has exhibited by the pH of the different solutions. In the case of DIC-DIH eutectic, the maximum solubility was observed in pH 6.8 at 4 h (345.76 μg mL^{-1}) while the solubility measurements in pH 1.2 and pH 4.5 were found to be 21.02 and 29.63 μg mL^{-1} respectively at 4 h. From 4 to 24 h, the apparent solubility of the prepared sample in pH 1.2, pH 4.5, and pH 6.8 solutions was increased 2.4, 1.9, and 1.5 times respectively, compared to the pure DIC. The results of solubility measurement of all the prepared eutectics also showed pH-dependent solubility. The same kind of behavior also was observed in case of DIC-FUM eutectic in various buffer solutions (Fig. 6) and the order of solubility from highest to lowest in the trend of DIC-DIH eutectic > DIC-FUM eutectic > Pure DIC.

Discussion

DIC is approved as an anti-osteoarthritis agent with poor water

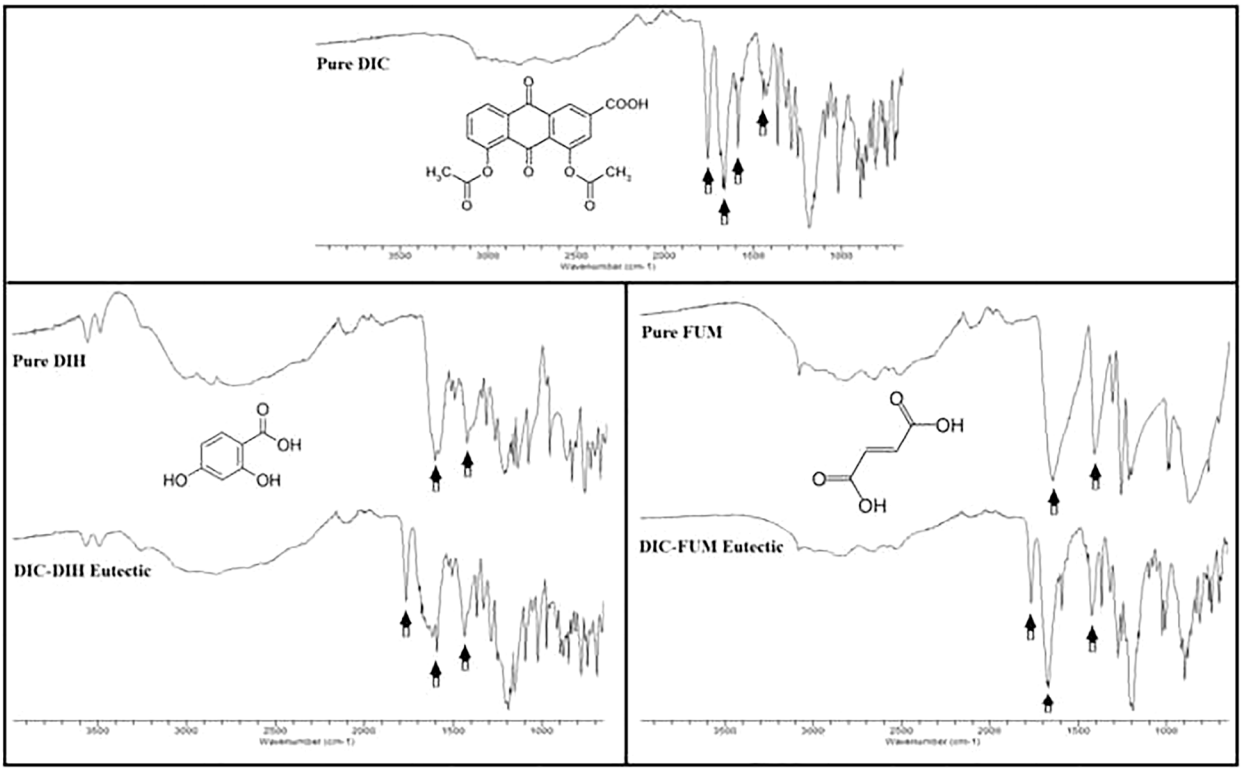


Fig. 5. ATR-FTIR spectra of DIC; DIH; FUM; DIC-DIH Eutectic and DIC-FUM Eutectic.

solubility. Design of new solid forms applying the concept of crystal engineering approach has been used to design the multi-component solid forms of DIC. Improving the functionality of a crystalline DIC by incorporating GRAS-listed coformers is a common approach in developing formulations of better bioavailability. In the present investigation, the simple screening strategies using DSC analysis have been applied for the interpretation of multi-component solids of DIC. Initially, the first screening stage included the Δp*K*a rule for the identification of potential coformers. The second screening stage consisted of the preparation (solid and solution-based) methods for the formation of multi-component solid forms. Binary mixtures of DIC with various coformers were generated by SAG and RCM techniques with various molar ratios. Our multi-component solid form screening has obtained a total of 15 coformers screened with various organic solvents, e.g., acetone, ethanol, methanol, acetonitrile, dimethyl sulfoxide, and dimethyl formamide. The third stage screening was performed with help of various characterization techniques. Upon verification of the preliminary characterization by DSC analysis, SAG method with acetone was utilized to screen the co-crystallization process (Table 1). Fortunately, DIH and FUM successfully showed positive evidence of a multi-component system with DIC (Table 2). Both the coformers have potential functional groups which could preferably form the hydrogen bond with DIC.

Out of all the ratios screened for DIC-DIH system, there was a true ratio i.e. 1:3 which showed a single and sharp melting point with maximum ΔH_{fus} value (Fig. 2A). While in the case of DIC-FUM system, all the ratios exhibited with single melting endotherms with or without leftover of the starting materials. Among these, the 1:2 ratio showed a sharp melting point without traces of participating components (Fig. 2B) [17]. The melting peaks of DIC-FUM and DIC-DIH samples were located prior to the endothermic events of the starting components which imparted the majority of the formation of eutectic. Furthermore, Tamman's triangle was applied for the verification of the molar ratio of the examined systems (Fig. 3). PXRD analysis revealed the absence of any new, distinct, or shifted positions in 2θ angles confirmed the formation of eutectic in the described system (Fig. 4 and Table 3). Unchanged vibrational spectra by FTIR analysis indicated the lack of significant chemical interactions between drug and coformer (Fig. 5). PXRD and FTIR data of the co-crystallized samples are in good agreement with the DSC outcomes, which excluded the existence of co-crystal and confirmed the eutectic formation [10,11]. Additionally, both the multi-component systems exhibited distinct morphological characteristics which provided the important tool to identify the new solid forms as a separate entity from their parent components (Fig. 4). The outcomes emphasis that the adhesive interactions (heteromeric; drug-coformer) are not strong enough to replace cohesive (homomeric; drug-drug/coformer-coformer) interaction between the components of each species. This can also be due to the size/shape that misfits between the interacting molecules and is ineffective in the transformation of the crystal packing of participating components. Therefore, the co-crystallized samples resulted in the eutectic binary system [10,11].

The eutectic formation with the advantage of a higher surface area and well dispersibility are preferred for better solubility and dissolution rate of poorly water-soluble drug. The unique property of the eutectic mixture for both systems was evaluated for the pH-dependent solubility behaviour. The results of solubility measurements of the DIC-DIH and DIC-FUM systems revealed superior solubility compared to pure DIC (Fig. 6). The possible mechanism behind this enhancement in solubility might be associated with poorly water-soluble API with more aqueous soluble coformer via non-covalent interaction. During the solubility experiment, DIH/FUM molecules diffused in the buffer solution faster than the pure DIC because the molecular mass is smaller than that of DIC as well as FUM/DIH exhibits a strong affinity towards the water molecules. Consequently, the less soluble DIC molecules become supersaturated in the solution as an amorphous phase which may result in the improvement in the kinetic solubility of prepared eutectic as compared to pure DIC [10–11,17].

Conclusion

We implemented the DSC technique as a diagnostic tool for

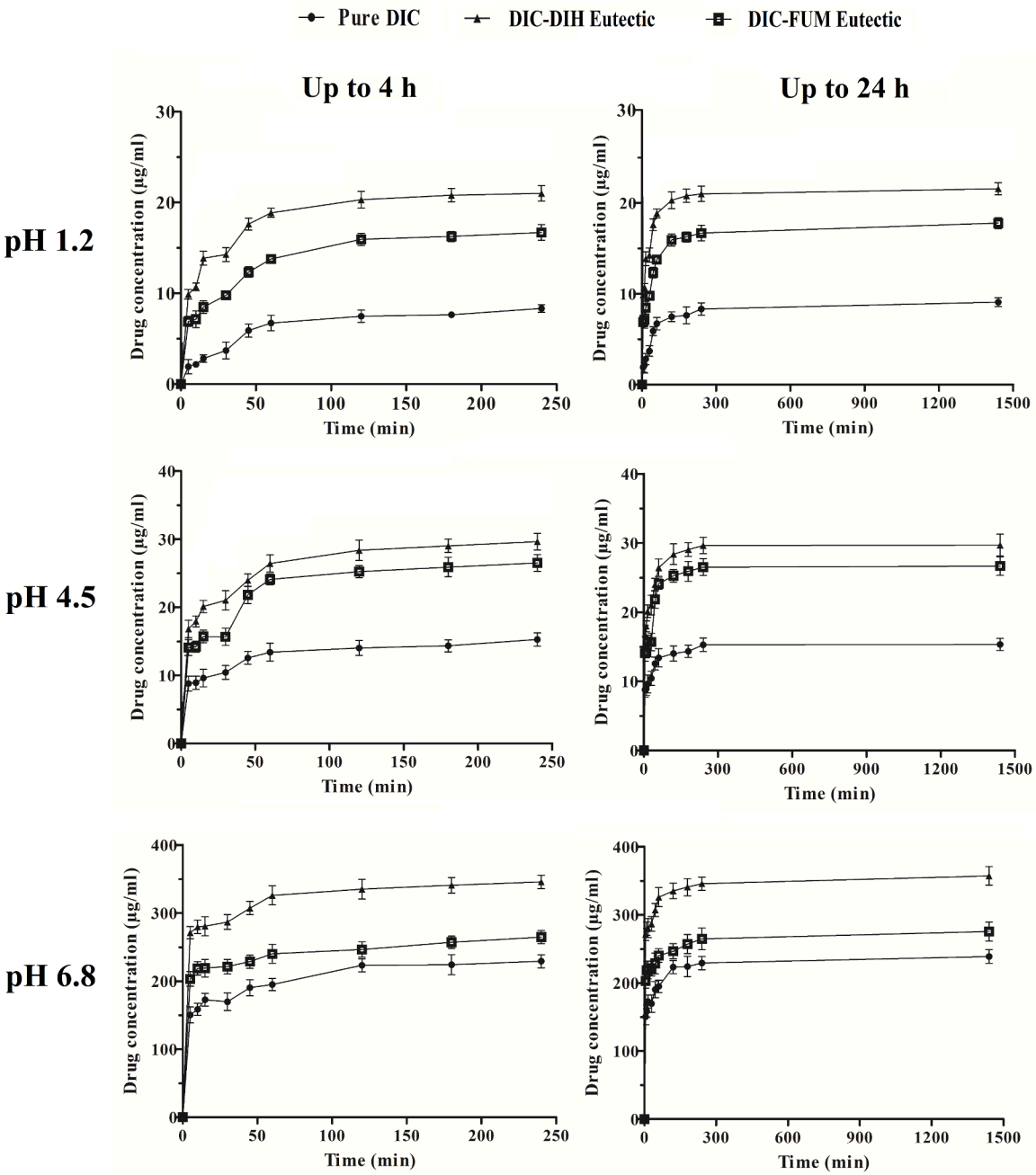


Fig. 6. Kinetic solubility measurements of DIC and the produced eutectics at pH 1.2, pH 4.5 and pH 6.8 during the first 4 h and throughout 24 h of the experiment.

expansively applicable in the pharma arena to investigate the binary system comprising of an active ingredient (DIC) and coformers (DIH and FUM) capable of the development of multi-component solids. We have observed that aliphatic and phenolic acids are competent enough to co-crystallized with DIC and also form eutectics via acetone assistant grinding method. Two novel eutectics have been developed and characterized using DSC, supporting the analysis of PXRD and FT-IR. The formation of eutectics with the different stoichiometry of DIH/FUM was observed. Moreover, the detailed pH-dependent solubility of the representative samples exhibited superior solubility of DIC with the formation of eutectics indicating the potential for further development in this field. In summary, the results revealed that the obscurity in designing a low melting depression eutectic can be resolved through DSC analysis, which is a versatile, cost-effective, and effortful tool in designing multi-component solid forms of the targeted drug molecule.

CRediT authorship contribution statement

Rajeshri D. Patel: Methodology, Validation, Investigation, Software, Writing – original draft, Visualization, Data curation. **Mihir K. Raval:** Supervision, Project administration, Resources, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

These works has received funding from the Department of Science and Technology, New Delhi, India providing DST-INSPIRE Fellowship under approved letter number DST/INSPIRE Fellowship/2013/1079.

References

[1] R. Chadha, S. Bhandari, Drug–excipient compatibility screening role of thermoanalytical and spectroscopic techniques, J. Pharm. Biomed. Anal. 87 (2014) 82–97.
[2] M.L. Cheney, N. Shan, E.R. Healey, M. Hanna, L. Wojtas, M.J. Zaworotko, V. Sava, S. Song, J.R. Sanchez-Ramos, Effects of crystal form on solubility and pharmacokinetics: a crystal engineering case study of lamotrigine, Cryst. Growth Des. 10 (2010) 394–405.
[3] S. Cherukuvada, T.N. Guru Row, Comprehending the formation of eutectics and cocrystals in terms of design and their structural interrelationships, Cryst. Growth Des. 14 (2014) 4187–4198.
[4] S. Cherukuvada, A. Nangia, Eutectics as improved pharmaceutical materials: design, properties and characterization, ChemComm. 50 (2014) 906–923.
[5] A.J. Cruz-Cabeza, Acid–base crystalline complexes and the pK a rule, CrystEngComm. 14 (2012) 6362–6365.
[6] G.R. Desiraju, Crystal engineering: from molecule to crystal, J. Am. Chem. Soc. 135 (2013) 9952–9967.
[7] R.S. Dhumal, A.L. Kelly, P. York, P.D. Coates, A. Paradkar, Cocrystalization and simultaneous agglomeration using hot melt extrusion, Pharm. Res. 27 (2010) 2725–2733.
[8] I. Elsayed, A.A. Abdelbary, A.H. Elshafeey, Nanosizing of a poorly soluble drug: technique optimization, factorial analysis, and pharmacokinetic study in healthy human volunteers, Int. J. Nanomedicine. 9 (2014) 2943–2953.
[9] T. Friscic, W. Jones, Recent advances in understanding the mechanism of cocrystal formation via grinding, Cryst. Growth Des. 9 (2009) 1621–1637.
[10] A.Y. Ibrahim, R.T. Forbes, N. Blagden, Spontaneous crystal growth of co-crystals: the contribution of particle size reduction and convection mixing of the coformers, CrystEngComm. 13 (2011) 1141–1152.
[11] W.J. Irwin, M. Iqbal, Solid-state stability: the effect of grinding solvated excipients, Int. J. Pharm. 75 (1991) 211–218.
[12] S. Karki, T. Friščić, W. Jones, W.S. Motherwell, Screening for pharmaceutical cocrystal hydrates via neat and liquid-assisted grinding, Mol. Pharm. 4 (2007) 347–354.
[13] R. Kaur, R. Gautam, S. Cherukuvada, T.N. Guru Row, Do carboximide–carboxylic acid combinations form co-crystals? The role of hydroxyl substitution on the formation of co-crystals and eutectics, IUCrJ. 2 (2015) 341–351.
[14] O. Magnard, K. Louchahi, M. Tod, O. Petitjean, P. Molinier, L. Berdah, G. Perret, Pharmacokinetics of diacerein in patients with liver cirrhosis, Biopharm. Drug Dispos. 14 (1993) 401–408.
[15] A.N. Manin, A.P. Voronin, K.V. Drozd, N.G. Manin, A. Bauer-Brandl, G.L. Perlovich, Cocrystal screening of hydroxybenzamides with benzoic acid derivatives: a comparative study of thermal and solution-based methods, Eur. J. Pharm. Sci. 65 (2014) 56–64.
[16] J. Martel-Pelletier, J.P. Pelletier, Effects of diacerein at the molecular level in the osteoarthritis disease process, Ther. Adv. Musculoskelet. Dis. 2 (2010) 95–104.
[17] P. Nicolas, M. Tod, C. Padoin, O. Petitjean, Clinical pharmacokinetics of Diacerein, Clin. Pharmacokinet. 35 (1998) 347–359.
[18] S. Pal, B.N. Roopa, K. Abu, S.G. Manjunath, S. Nambiar, Thermal studies of furosemide–caffeine binary system that forms a cocrystal, J. Therm. Anal. Calorim. 115 (2014) 2261–2268.
[19] R.D. Patel, M.K. Raval, A.A. Bagathariya, N.R. Sheth, Functionality improvement of Nimesulide by eutectic formation with nicotinamide: Exploration using temperature-composition phase diagram, Adv. Powder Technol. 30 (2019) 961–973.
[20] R.D. Patel, M.K. Raval, T.M. Pethani, N.R. Sheth, Influence of eutectic mixture as a multi-component system in the improvement of physicomechanical and pharmacokinetic properties of Diacerein, Adv. Powder Technol. 31 (2020) 1441–1456.
[21] R.D. Patel, M.K. Raval, T.M. Pethani, Application of a Validated RP-HPLC Method in Solubility and Dissolution Testing for Simultaneous Estimation of Diacerein and Its Active Metabolite Rhein in Presence of Coformers in the Eutectic Tablet Formulation, J. Chromatogr. Sci. 59 (2020) 697–705.
[22] R.D. Patel, M.K. Raval, N.R. Sheth, Formation of Diacerein−fumaric acid eutectic as a multi-component system for the functionality enhancement, J. Drug Deliv. Sci. Tec. 58 (2020).
[23] R.D. Patel, M.K. Raval, Formulation of Diacerein Cocrystal Using β-Resorcylic Acid for Improvement of Physicomechanical and Biopharmaceutical Properties, Org. Process Res. Dev. 25 (2021) 384–394.
[24] S.P. Patil, S.R. Modi, A.K. Bansal, Generation of 1: 1 carbamazepine: nicotinamide cocrystals by spray drying, Eur. J. Pharm. Sci. 62 (2014) 251–257.
[25] Z. Rahman, C. Agarabi, A.S. Zidan, S.R. Khan, M.A. Khan, Physico-mechanical and stability evaluation of carbamazepine cocrystal with nicotinamide, AAPS Pharmscitech. 12 (2011) 693–704.
[26] B.N. Roy, G.P. Singh, D. Srivastava, H.S. Jadhav, M.B. Saini, U.P. Aher, A novel method for large-scale synthesis of lamivudine through cocrystal formation of racemic lamivudine with (S)-(−)-1, 1′-Bi (2-naphthol)[(S)-(BINOL)], Org. Process Res. Dev. 13 (2009) 450–455.
[27] T. Tamura, N. Kosaka, J. Ishiwa, T. Sato, H. Nagase, A. Ito, Rhein, an active metabolite of diacerein, down-regulates the production of pro-matrix metalloproteinases-1,-3,-9 and-13 and up-regulates the production of tissue inhibitor of metalloproteinase-1 in cultured rabbit articular chondrocytes, Osteoarthr. Cartil. 9 (2001) 257–263.
[28] T. Tamura, K. Ohmori, Rhein, an active metabolite of diacerein, suppresses the interleukin-1α-induced proteoglycan degradation in cultured rabbit articular chondrocytes, Jpn. J. Pharmacol. 85 (2001) 101–104.
[29] J. Wang, Y. Cao, B. Sun, C. Wang, Characterisation of inclusion complex of trans-ferulic acid and hydroxypropyl-β-cyclodextrin, Food Chem. 124 (2011) 1069–1075.
[30] G. Zingone, F. Rubessa, Preformulation study of the inclusion complex warfarin-β-cyclodextrin, Int. J. Pharm. 291 (2005) 3–10.