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Research Article

COCRYSTAL FORMATION OF PARACETAMOL WITH INDOMETHACIN AND MEFENAMIC ACID: AN EFFICIENT APPROACH TO ENHANCE SOLUBILITY

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ABSTRACT

Objective: Drug molecules with limited aqueous solubility are rather challenging in formulation development and may pose the risk of insufficient exposure and thus poor efficacy in patients upon oral administration. Co-crystallization is the process to enhance the physical properties of the molecule, especially the solubility. Mefenamic acid and indomethacin belong to nonsteroidal anti-inflammatory agents (NSAIDs) and are often combined with paracetamol in various formulations. Co-crystallization technique was used to combine two drugs in a single solid phase and thus to achieve a newer approach for combination therapy. Using the newer approach co-crystals of mefenamic acid and indomethacin with paracetamol were prepared.

Method: Co-crystallization of two drugs was carried out in different solvent systems using different methods like solvent evaporation, grinding, antisolvent addition and ultrasound assisted techniques. COOH---N and COOH---O heterosynthons were used as an element in the co-crystal design strategy. Differential Scanning Calorimetry (DSC) and X-ray Powder Diffraction (XRPD) techniques were employed to support the formation of co-crystals and to find out the optimized ratio of components of co-crystals.

Results and Conclusion: Synthesis of co-crystals of mefenamic acid and indomethacin with paracetamol was successfully carried out by different methods from which solvent evaporation method was found to be the best amongst all methods for the selected APIs. Ethanol proved to be the best solvent for the formation of co-crystals among the selected solvent system. The results from DSC and X-ray Powder Diffraction analysis revealed the formation of co-crystals of indomethacin and mefenamic acid with paracetamol.

Keywords: Co-crystallization, Paracetamol, Indomethacin, Mefenamic acid, Solvent evaporation method.

INTRODUCTION

Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. Currently number of techniques addresses the problem of poor solubility and dissolution rate of poorly soluble drugs [1]. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients [2]. Frequently, however, the Active Pharmaceutical Ingredients crystallize into one or more crystal forms that possess undesirable physical properties and hence there is a need for the development of crystalline form of APIs with desired physicochemical properties. Various options are available including single component and multiple-component modifications of an API, including polymorphs, salts, solvates, and hydrates. In addition to these established crystalline API modifications, pharmaceutical co-crystals, or crystalline molecular complexes involving an API, have recently attracted interest as an alternative approach [3].

Crystal engineering comprises rational design and tailored fabrication of (functional) crystal structures and hence offers manifold prospects to selectively enhance the physicochemical properties of drugs on the basis of knowledge of crystallization processes and molecular properties of APIs [3, 4].

The concept of co-crystallization constitutes a selective route to the concerted design of pharmaceutical compounds with desired pharmacokinetic and physical properties. The term "co-crystals" is not easily defined but is most commonly used in order to describe a crystal containing two or more components that form a uniform phase. A more refined definition describes a co-crystal as a "multi-component crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is a neutral API and the co-crystal former is a pharmaceutically acceptable ion or molecule. [5, 6].

Co-crystals often contain self-assembly units based on supramolecular synthons that are derived from motifs that are commonly found in crystal structures. Generally in the case of pharmaceutical co-crystals, at least one of the components must be an API, while the additional co-crystal former(s) should be pharmaceutically acceptable entity such as frequently used food additives and excipients [7].

In early studies, Etter and co-workers proposed several "hydrogen-bond rules," including the observations that all good proton donors and acceptors are used in hydrogen bonding, and the best donor typically pairs with the best acceptor in a given crystal structure. The combined use of the hydrogen-bond rules with a geometric analysis assisted Etter and co-workers in implementing rational design of co-crystals in the synthesis of many new supramolecular structures.

Allen et al. demonstrated a quantification of the "robustness" of a certain class of intermolecular arrangements (commonly called motifs, or synthons) involving strong hydrogen-bonded bimolecular ring motifs. Their analysis involved examining trends within the Cambridge Structural Database (CSD), a searchable repository containing more than 300,000 small-molecule crystal structures. They assessed the robustness of a motif in terms of its "formation probability," that is, the observed frequency of motif formation among all structures containing the necessary functional group components. A higher number of hydrogen bond formation probability suggested a greater utility in a co-crystal design scheme.

By relying on robust intermolecular interactions with demonstrated solid-state reproducibility, synthon-based co-crystals design has become increasingly important to the synthesis of new co-crystal materials. In the future, automated searches for formation probabilities pertaining to the molecular structure of an API of interest will be an important step towards rational pharmaceutical co-crystal design [8, 9].

The design of co-crystals seems to be straight forward because donor and acceptor functionalities can be brought together more easily than with single component systems since the partners are more accessible to arrange themselves into an optimal geometry, leading to favorable intermolecular interactions.

The success of this supramolecular synthesis is governed by the problem that arises if one component prefers to crystallize as a neat compound instead of the formation of a molecular complex.

Using O-H···N interactions and also N-H···O, one can produce numerous co-crystals from di- acids and nitrogen containing aromatic ring and some other compounds as shown in Figure 2.

In the absence of strong hydrogen bridges, also, much weaker intermolecular interactions such as C-H···X (X=O, N) can also be used alone to form molecular complexes [10, 11].

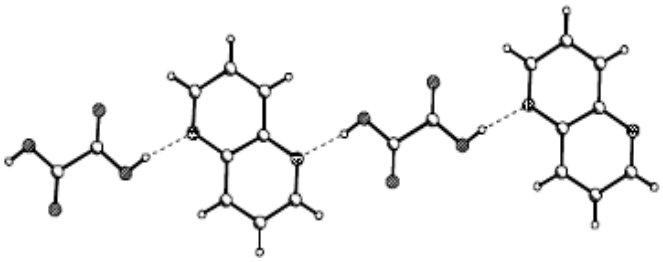

Fig. 1: Basic diagrammatic representation of co-crystals

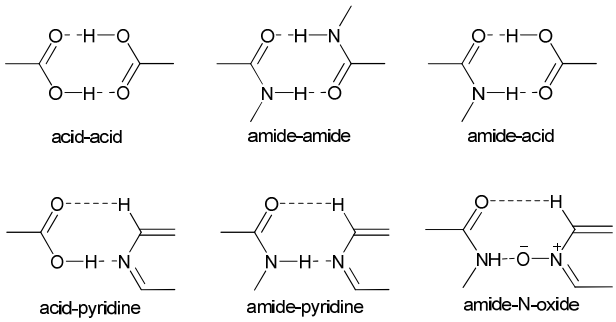

Fig. 2: Some common strong hydrogen-bond homosynthons and heterosynthons

MATERIALS AND METHODS

Paracetamol (acetaminophen), N-(4-Hydroxyphenyl)-acetamide (Figure 3C) is a widely used analgesic and antipyretic agent for the relief of fever, headaches, minor pains, etc. It is a major ingredient in numerous cold and flu remedies. In combination with other non-steroidal anti-inflammatory drugs and opioid analgesics, Paracetamol is also used in the management of severe pain (such as post operative pain) [12].

Mefenamic acid is an anti-inflammatory drug belonging to the class of nonsteroidal anti-inflammatory agents (NSAIDs) used to treat period pain and other pains. The combination of mefenamic acid and paracetamol is marketed through several formulations for example Spamic plus (500 mg mefenamic acid + 500mg paracetamol) by Intra Labs India Pvt Ltd, Spasmonil Forte (450 mg mefenamic acid + 500 mg paracetamol) by Cipla Limited etc. for several indications. The combination is also effective to treat migraine.

Indomethacin also belongs to the class of NSAIDs and is used to treat gout or certain types of bursitis and tendonitis. Combination of indomethacin and paracetamol is available as capsules – 25 mg indomethacin + 300 mg paracetamol and 25 mg indomethacin + 500 mg paracetamol, marketed by Mercator Pharmaceuticals.

For the experimental purpose drugs - mefenamic acid and indomethacin were obtained from **Zydus-Cadila** as a gift samples and were used as obtained.

Co-crystallization technique can be used for the formation of co-crystals of mefenamic acid and indomethacin with paracetamol. The enhancement in the physicochemical property can be the add-on advantage to the newer combinational approach.

Table 1: Physical characterization of selected Active Pharmaceutical Ingredients

Drug	Molecular weight (g/mol)	Melting point (˚C)	Solubility in water	Solubility in alcohol
Mefenamic acid	241.28	230-231	Insoluble	Sparingly
Indomethacin	357.78	155-160	Partially	Sparingly
Paracetamol	151.17	169-172	Partially	Sparingly

In the Figures 3A to 3C, all atoms marked with rounds show hydrogen bond acceptor property and all with squares show hydrogen bond donor property. Considering the structure, prediction of the formation of co-crystal becomes achievable.

Paracetamol molecule (Figure 3C) contains two hydrogen bond donors; the phenolic O–H and the amidic N–H groups and one acceptor; the amidic oxygen atom. There is reasonable expectation for the strongest hydrogen bond formation between the best donor and best acceptor. During co-crystal formation the hydrogen bond donors and acceptor of paracetamol are in competition with those of the mefenamic acid and indomethacin. Hence during the formation of co-crystal the structure adopted is that which optimizes the donor–acceptor interactions in the co-crystal. Mefenamic acid

molecule possesses two hydrogen bond donors; the carboxylic O-H and amine N-H group and one hydrogen acceptor; the Oxygen atom of carboxylic C=O group. Indomethacin molecule contains one hydrogen donor; the carboxylic O-H and three hydrogen bond acceptors; namely, oxygen atom of amidic group, carboxylic group (C=O) and methoxy group.

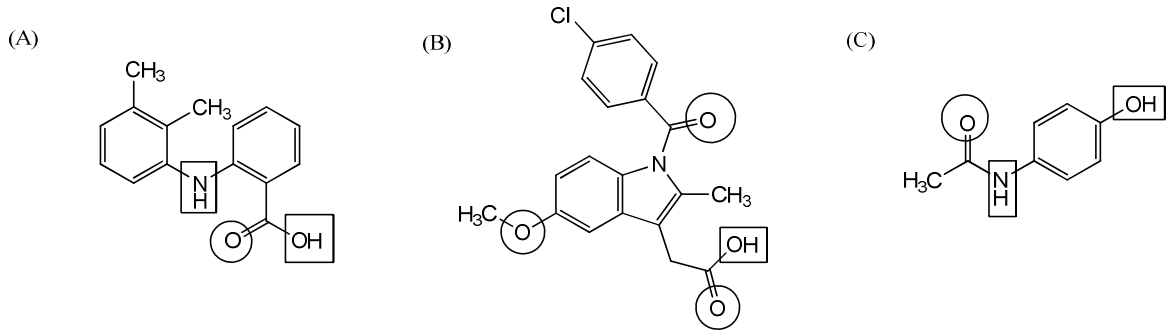

Fig. 3: Hydrogen bond donor and acceptor sites of (A) mefenamic acid, (B) indomethacin and (C) Paracetamol

Synthesis of co-crystals

Various methods like grinding, ultrasound assisted co-crystallization and solvent evaporation were employed for the preparation of co-crystals of mefenamic acid and indomethacin with paracetamol. Solvent evaporation method was found to be the best for the preparation of co-crystals in the present study.

Methods of synthesis

Solvent Evaporation method

Co-crystals of Mefenamic acid with Paracetamol

To a mixture of 0.001 mol of mefenamic acid and 0.001 mol of paracetamol, 5 mL of ethanol was added with continuous stirring. Mixture was refluxed for 5 minutes and additional solvent was evaporated to a quarter of its volume on water bath. Product obtained was dried under room temperature and was investigated by microscopy, melting point, XRPD and DSC. The experiments were performed with five different solvents like ethanol, chloroform, acetone, tetrahydrofuran and n-propanol, representing a wide range of dielectric constants (4.8–37.5) and containing at least one representative from each of the polar protic, polar aprotic, and nonpolar solvent categories.

Co-crystals of Indomethacin with Paracetamol

0.001 mol of indomethacin and 0.001 mol of paracetamol were ground together with mortar and pestle followed by addition of 5 mL of ethanol with continuous stirring. Mixture was refluxed for 5 minutes and additional solvent was evaporated to a quarter of its volume on water bath. Product obtained was dried under room temperature and was investigated by microscopy, melting point, XRPD and DSC. The experiments were performed with five different solvents like ethanol, chloroform, acetone, tetrahydrofuran, and n-propanol, representing a wide range of dielectric constants (4.8–37.5) and containing at least one representative from each of the polar protic, polar aprotic, and nonpolar solvent categories.

Table 2: Melting point of synthesized co-crystals

Co-crystals Code	Components	Ratio of components	Melting point (˚C)
CM1	Mefenamic acid + Paracetamol	1:1	160-165
CI1	Indomethacin + Paracetamol	1:1	130-135

Table 3: Characterization of formation of co-crystals by using different solvents

S. No.	Co-crystal components	Solvent investigated	Observations from XRPD Pattern
1	Mefenamic acid and Paracetamol	Acetonitrile	Similar to that of paracetamol
		Ethyl acetate	Physical mixture only
		Isopropyl alcohol	Non-uniform crystals
		Methanol	XRPD pattern indicates physical mixture only
		Ethanol	Different pattern compared to selected APIs
2	Indomethacin and Paracetamol	Acetonitrile	Pattern similar to that of paracetamol
		Ethyl acetate	Physical mixture only
		Isopropyl alcohol	Problem in synthesis of co-crystals
		Methanol	XRPD pattern indicates physical mixture only
		Ethanol	Different pattern compared to selected APIs

Characterization

The obtained co-crystals were investigated by different techniques and analysis which include:

1. Melting Point (Scientific MP1)

2. Microscopic evaluation (LYNX XSP-35)

3. Differential Scanning Calorimetry (DSC) (DSC-60)

4. X-ray Powder Diffraction (XRPD) (PW3064)

Microscopic Evaluation

Microscopic evaluation was used as a primary investigation tool to confirm the formation of co-crystals visually and to observe the crystal habit of the synthesized co-crystals. The shape of co-crystals was compared with the pure drugs. Crystallization of the pure drug was also carried out in the same solvent which was used for the preparation of co-crystals to investigate differences in crystal habit of co-crystals with that of pure drugs.

Differential Scanning Calorimetric (DSC) Analysis

DSC analysis is a thermoanalytical tequnique used to identify the difference in the amount of heat required to increase the temperature of a sample and reference as a function of temperature. The samples were analyzed by Differential Scanning Calorimeter (model DSC-60) over the range of 50-300°C at the rate of 20°C per minute.

DSC, thermoanalysis gave characteristic and comparable results for the APIs and the synthesized co-crystals as shown in Figures 4 and 5. The DSC data of the co-crystals revealed single sharp endotherms at 164.71, and 134.76 °C for products CM1 (co-crystals of mefenamic acid with paracetamol) and CI1 (co-crystals of indomethacin with paracetamol) respectively. These endotherms, which correspond to the melting point of the solids, occur at significantly different temperatures to those of paracetamol (169–172 °C) or mefenamic acid (230-231 °C) and indomethacin (155-160 °C), indicating the formation of co-crystals and not simple physical mixtures. The co-crystals described here showed reduced melting temperatures from that of paracetamol, suggesting that the cohesive energy of co-crystals CM1 and CI1 is decreased from that of pure paracetamol form.

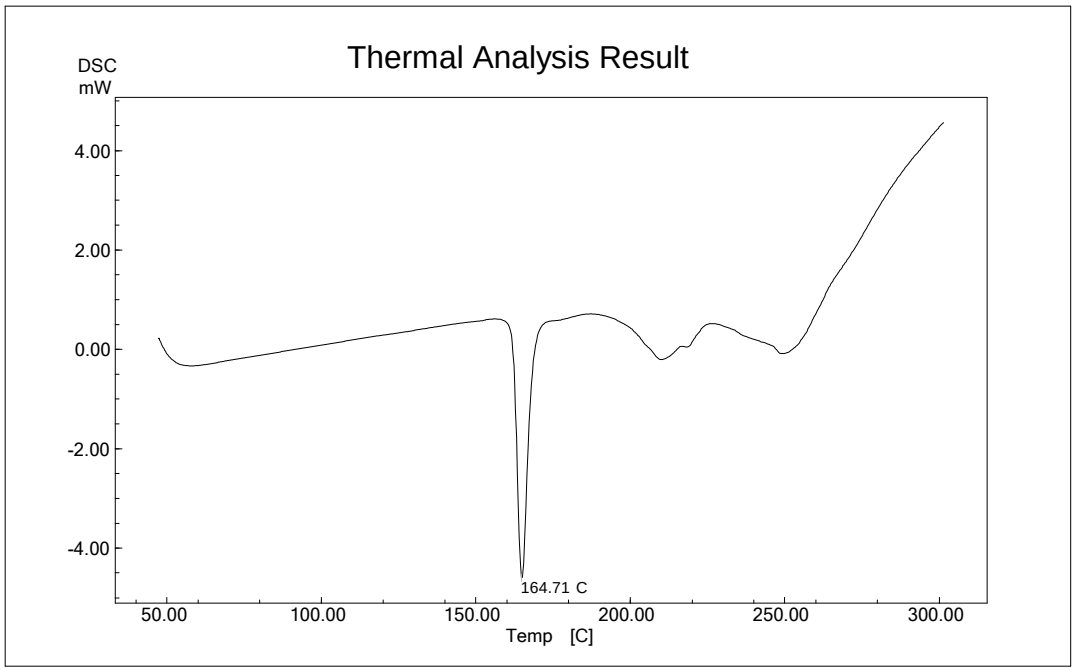

Fig. 4: Differential Scanning Calorimetric analysis of CM1 (Co-crystals of mefenamic acid with paracetamol)

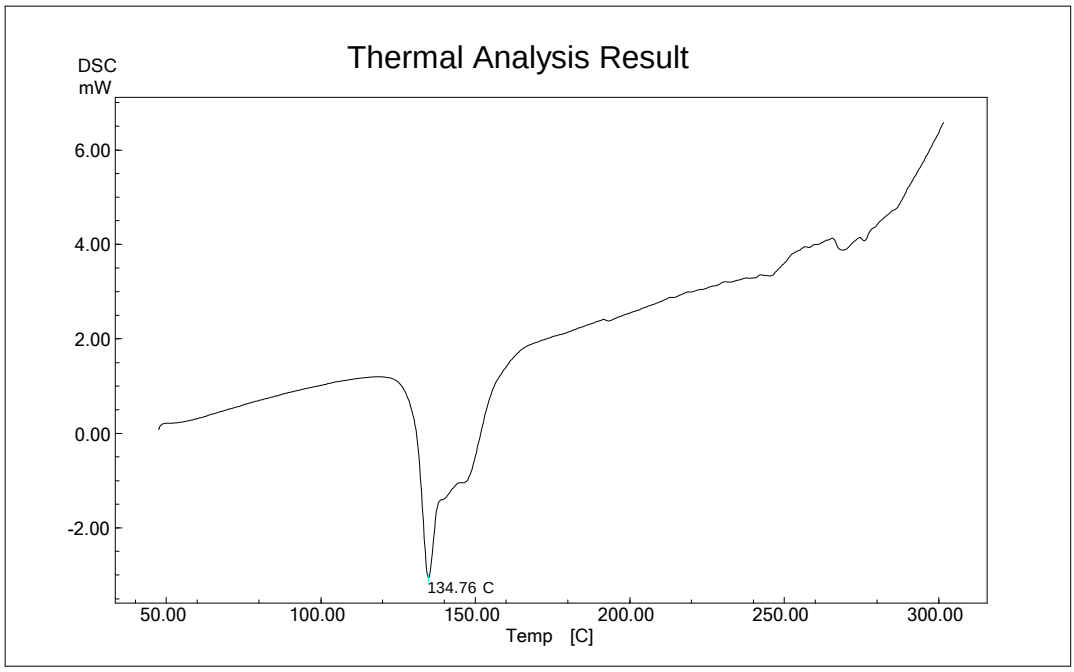

Fig. 5: Differential Scanning Calorimetric analysis of CI1 (Co-crystals of indomethacin with paracetamol)

X-ray Powder Diffraction (XRPD)

X-ray powder diffraction was done for the synthesized co-crystals. It reveals the information about the crystal structure, chemical composition, and physical properties of the material and also helps in structural characterization. XRPD spectra were taken on a sample stage Spinner PW3064 at the minimum step size 2Theta:0.001 and minimum step size Omega:0.001. The XRPD pattern results for co-crystals of mefenamic acid and indomethacin with paracetamol are completely different from those of the pure drugs (mefenamic acid, indomethacin and paracetamol). The results of XRPD analysis suggest complete formation of co-crystals.

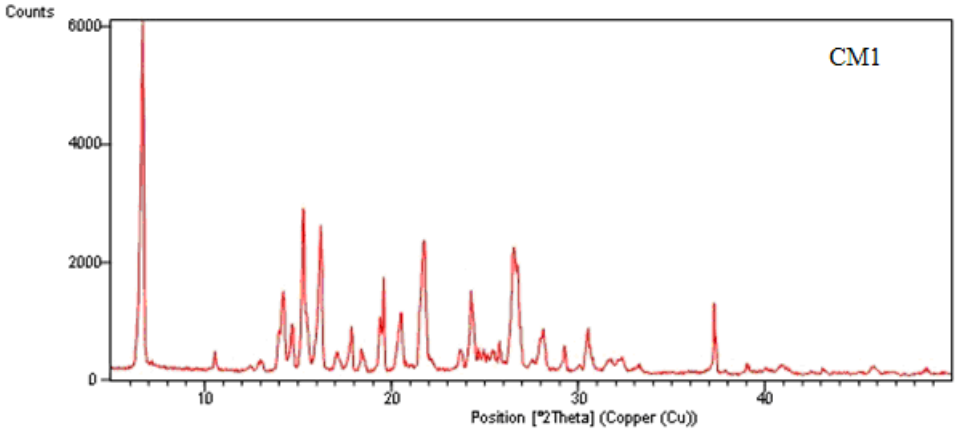

Fig. 6: XRPD spectra of co-crystals of mefenamic acid with paracetamol (CM1)

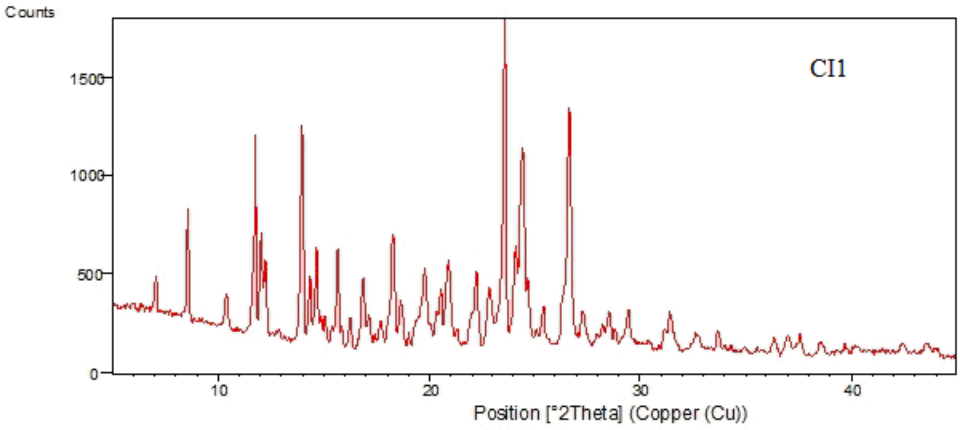

Fig. 7: XRPD spectra of co-crystals of indomethacin with paracetamol (CI1)

RESULTS AND DISCUSSION

Synthesis of co-crystals of mefenamic acid and indomethacin with paracetamol was carried out by different methods from which solvent evaporation method was found to be the best amongst all methods for the selected APIs. Various solvents were employed for the synthesis of co-crystals but ethanol was proved to be the best as shown in Table 3. Other solvents suffered from drawbacks like mutual solubility of mefenamic acid or indomethacin with paracetamol.

Primary analysis was done by checking melting point range and inspecting visually the crystal pattern of co-crystals and comparing them with crystals of pure drugs using microscopy. Microscopy analysis of synthesized co-crystals revealed visual difference between the co-crystals and pure drugs. Both the synthesized co-crystals CM1 (mefenamic acid with paracetamol) and CI1 (indomethacin with paracetamol) showed narrow range of melting point which confirms the formation of stable co-crystals.

Differential Scanning Calorimetry (DSC) of CM1 (co-crystals of mefenamic acid with paracetamol) shows the single prominent endothermic peak at 164.7°C (Figure 4), which is neither the melting point of mefenamic acid nor of paracetamol. This supports the formation of co-crystals of mefenamic acid with paracetamol. Similarly, DSC result of CI1 shows the prominent endothermic peak at 134.7°C as shown in Figure 5, which is substantially different from the melting point of indomethacin and paracetamol. These results suggested the complete formation of co-crystals of indomethacin with paracetamol.

Analysis of the X-ray Powder Diffraction data of the polycrystalline materials arising from solvent evaporation experiments revealed that for critical co-crystal formation of paracetamol with mefenamic acid or indomethacin, reflections arising from the starting materials are absent, indicating the presence of new phase when they were taken in 1:1 proportion. XRPD analysis supports the formation of co-crystals of mefenamic acid and indomethacin with paracetamol as showing different patterns in diffractogram with that of pure mefenamic acid and indomethacin (Figures 6 and 7 respectively). The synthesis method was optimized by using different solvents by taking equimolar ratio of mefenamic acid:paracetamol and indomethacin:paracetamol. Utilizing ethanol as a solvent for co-crystallization was found to be the best as compared to the selected solvents. Further there is a scope for optimization of ratio of two drugs for co-crystal formation after performing pharmacokinetic studies for desired dosage regime.

CONCLUSION

Combinations of Mefenamic acid and indomethacin with paracetamol are available in different formulations (tablets, capsules etc.) in the market. Formation of co-crystals of two different drugs prescribed in combination can be employed as a newer approach with improved physicochemical properties. The approach utilized for co-crystal formation has dual advantage like improvement in the physicochemical properties of APIs as well as incorporation of two different drugs in a single solid phase.

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