WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 11, Issue 5, 2093-2102 Research Article ISSN 2278 – 4357

COCRYSTALLIZATION OF KETOPROFEN AND BENZOIC ACID BY USING SOLVENT- DROP GRINDING METHOD

Jayashree Gaja*, K. Jesindha Beyatricks and S. Tharani

Hillside College of Pharmacy and Research Centre, 9, Kanakapura Rd, Raghuvanahalli, Bangalore City Municipal Corporation Layout, Bengaluru, Karnataka 560062.

Article Received on
19 March 2022,

Revised on 09 April 2022,
Accepted on 29 April 2022

DOI: 10.20959/wjpps20225-22069

***Corresponding Author**
Prof. Jayashree Gaja
Hillside College of Pharmacy and Research Centre, 9, Kanakapura Rd, Raghuvanahalli, Bangalore City Municipal Corporation Layout, Bengaluru, Karnataka 560062.

ABSTRACT

The purpose of this work was to prepare ketoprofen-benzoic acid cocrystal by solvent drop grinding method to improve solubility of the drug Ketoprofen. Ketoprofen and conformer benzoic acid in molar ratio 1:1 was used to formulate molecular complex using methanol as solvent. Characterization of cocrystal was done by Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy. The formed cocrystal of Ketoprofen exhibits different physicochemical characteristics compared to the constituent materials. The prepared cocrystal showed an improvement in solubility with respect to the pure drug.

KEYWORDS: Co-crystals, Co-formers, Solvent drop technique, Ketoprofen, Solubility.

INTRODUCTION

A co-crystal is a multicomponent crystalline material formed by two or more molecules held together by weak interaction in the same lattice.[1] Co-crystallization is one of the techniques generally implemented by researchers to fix the physicochemical properties of an active pharmaceutical ingredient (API).[2] Co-crystallization of API is the most frequently selected technique to optimize physiochemical properties while retaining its molecular structure. The physiochemical properties apparently proven to be fixed through co-crystallization are solubility, dissolution rate, moisture uptake, stability, and bioavailability.[3,4] The co-crystals are held, by supramolecular heterosynthons that occur between the functional groups like carboxylic acid–aromatic nitrogen, carboxylic acid–amide and alcohol–pyridine, with non-covalent forces, often including hydrogen bonding.[5,6]

At present, several methods and techniques are available for the solubility enhancement of which solid dispersion, salt formation, cryogenic techniques, crystal engineering, supercritical fluid process, nanosuspensions, etc. are the most prominent one. A pharmaceutical cocrystal is a novel approach to improve the physicochemical properties such as solubility of compounds.[7, 8]

Pharmaceutical co-crystals could be prepared by different methods like solvent evaporation, anti-solvent addition, crystallization from the melt, solid state grinding, etc.[9]

Grinding method in co-crystallization is divided into two technique: dry and solvent drop grinding. Dry grinding is aimed at modifying crystalline phase formation through two mechanism: molecular diffusion due to displacement and cleavage planes formation in each cell unit. Solvent drop grinding is performed by adding a small amount of specific solvent to grinding process, an amount that can affect the process of cocrystal formation. Solvent drop grinding method posses several advantage over dry grinding, including shorter time of cocrystal phase formation and possibility of obtaining pure cocrystal.[10,11]

Ketoprofen is a derivative of propionic acid with non-steroidal anti-inflammatory activity (NSAID). The antipyretic effect is due to a resetting of hypothalamic thermoregulatory center, whereas the anti-inflammatory and analgesic effects are due to inhibition of prostaglandin synthesis.[12] Ketoprofen is a BCS class II drug having low solubility and high permeability. It exhibits lowaqueous solubility and dissolution properties.These properties cause Kp to have slow absorption and low bioavailability.[13,14,15]

The purpose of this work is to improve the solubility poorly water-soluble Ketoprofen by cocrystal formation using solvent drop grinding method with benzoic acid as co-former.

MATERIALS AND METHODS

Materials: Ketoprofen (KP) was purchased from yarrow chemicals Pvt Ltd (Mumbai, India). Benzoic acid and methanol was obtained from future lab (Bangalore, India).

Methods:

a. **Pre formulation studies of drug:** The drug was observed visually to study its color odor, appearance, melting point etc.
b. **Formulation of cocrystals:** The co-crystals of Ketoprofen were prepared by using a solvent drop grinding method. Co-former benzoic acid was taken with the Ketoprofen in a

equimolar ratio of 1:1 in a mortar and neatly grounded with the pestle in for 2 hr duration in presence of a solvent (methanol).

c. Evaluation/ Characterization of cocrystals

- **Physical appearance:** Cocsrystals were observed visually to study its texture, color odour, taste etc.

- **Determination melting point:** For determination of melting point drug was filled in to capillary tube sealed at one end. The capillary containing the drug was inserted into a slot of melting point apparatus and temperature at which drug melts was noted.

- **Solubility study:** To determine the aqueous solubility of pure drug Ketoprofen and cocrystals of Ketoprofen and drug, solubility study was carried out using distilled water. Ketoprofen pure drug and Ketoprofen -Benzoic acid co-crystal formulation containing Ketoprofen equivalent to 20mg was added to 50 ml water and was shaken vigorously using mechanical agitator for 24h 120 rpm. The mixture was filtered and passed through milipore membrane of 25 µm. Filtrate was measured at 260nm using uv-vis spectroscopy.[16]

- Fourier Transform Infrared Spectroscopy (FTIR): FTIR study of ketoprofen, benzoic acid and cocrystals was per-formed by employing KBr disc technique. The spectrum was recorded over the range of 4000–400 cm^{-1}. The graph obtained was interpreted for the peaks obtained.[17]

- Differential Scanning Calorimetry (DSC): Thermal analysis was done to know the interaction of coformer with the ketoprofen. DSC of Ketoprofen, benzoic acid and cocrystal was per-formed by using DSC Q10 V9.9 Build 303, US instrument. About two milligrams of the sample taken in a closed aluminium pan and heated at the rate of 10 °C /min, covering a temrature range from 20 to 300 °C in an atmosphere of nitrogen gas. An empty aluminium pan was taken as the reference pan.[18]

RESULTS AND DISCUSSION

Pre formulation studies of drug: Organoleptic properties: white or off-white, odorless, nonhygroscopic, fine to granular powder, melting at about 97°C.

Melting point of cocrystals: Melting point of cocrystals was found to be in the range of 68-72 ^{0}C.

Solubility studies: Considering the ketoprofens poor water solubility, this study attempted to modify its physicochemical properties using cocrystals to improve its hydrophilicity. The pure ketoprofen has a maximum solubility of 117.18µg/mL in water, whereas ketoprofen benzoic acid cocrystal, the solubility was effectively increased to 144.89 µg/mL.

Fourier Transform Infrared Spectra (FTIR): The result shows that there was no incompatibility seen in between drug Ketoprofen and benzoic acid used, as there was no significant change in the pattern of peaks of the pure drug with microspheres (fig 4,5,6).

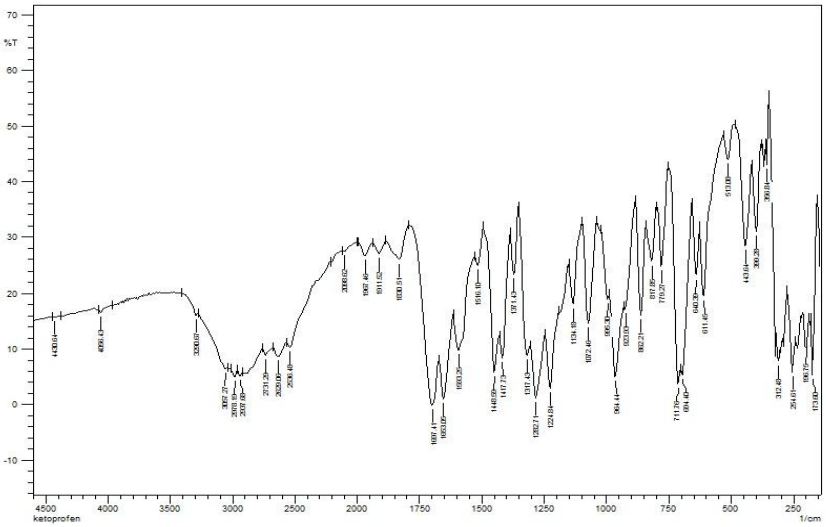

Fig. 4: FTIR Spectra of Ketoprofen.

FTIR spectra of Ketoprofen have 2 characteristic absorption peaks of carbonyl peak at 1695 and 1655 cm^{-1} .I t was ascribed to C=O stretching of carboxylic acid and C=O stretching of ketone, respectively[19] (Fig. 4).

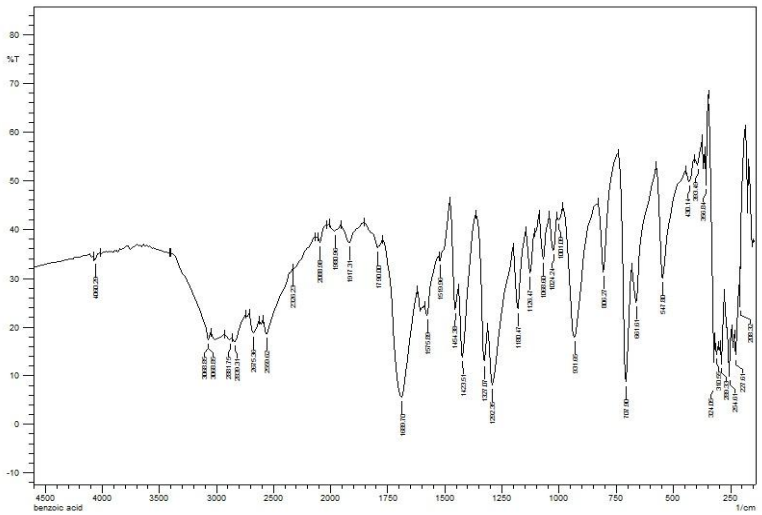

Fig. 5: FTIR Spectra of Benzoic Acid.

From the FTIR spectral analysis all the principal peaks observed in pure drug were present in the FTIR spectra with some additional peaks were observed with cocrystals, which could be due to the presence of coformer. No drug-coformer interaction was observed in the FTIR spectra of the cocrystals since the absorption peaks of the drug still could be detected in the mixture.

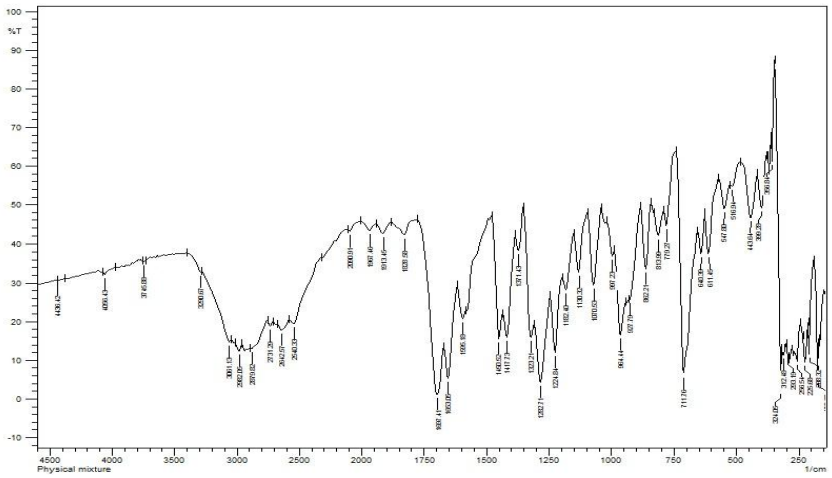

Fig. 6: FTIR Spectra of Ketoprofen-Benzoic acid Cocrystal.

Differential Scanning Calorimetry (DSC): Its necessary to have an idea about the physical properties of the newly formed sample, which can be observed using thermoanalytical techniques, like differential scanning calorimetry (DSC) and thermogravimetric analysis, which are characterization techniques to determine the thermal properties of cocrystals. DSC thermograms play an important role in showing the melting endotherm maximum of a sample. This information about melting endotherms maxima may give an idea about a new complex phase.[21] DSC also presents the novel behavior of a crystallized mixture during heating and cooling. The change in heat of fusion and heat of crystallization with a change in concentration can be observed during the DSC technique.[22,23]

The DSC thermograms obtained from the analysis of ketoprofen, benzoic acid, and cocrystals is shown in fig.1, 2 and 3 respectively. The obtained thermograms showed the endothermic peaks.

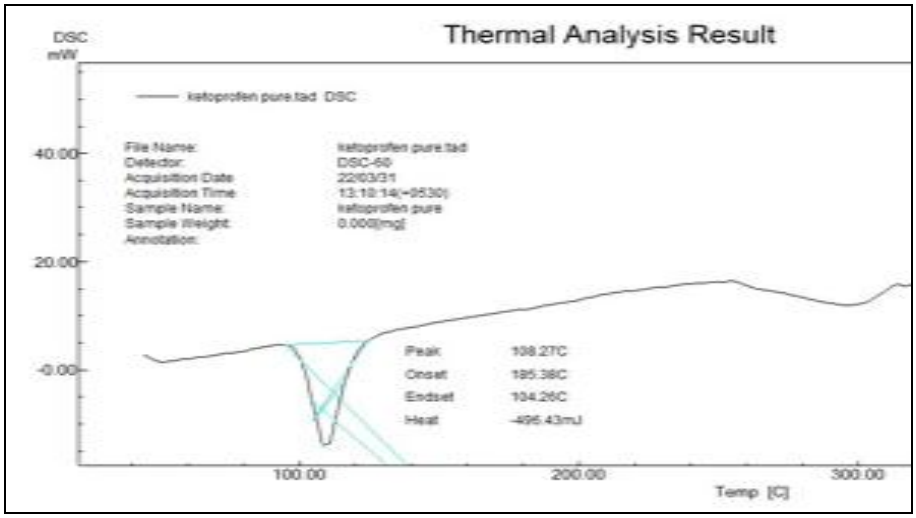

Fig. 1: DSC thermogram of ketoprofen.

The drug ketoprofen shows sharp endothermic peak at 102.27 ^{0}C representing its melting point whereas benzoic acid shows endothermic peak at 140.7 ^{0}C representing its melting point.

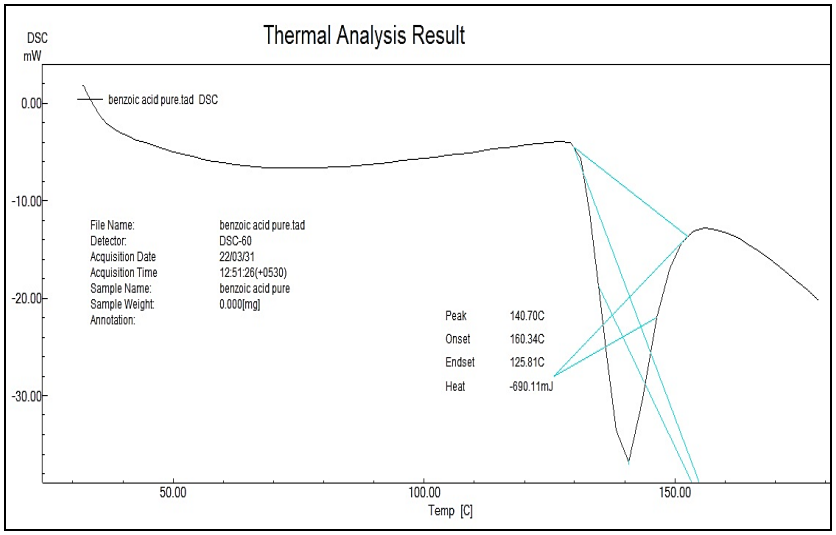

Fig. 2: DSC thermogram of benzoic acid.

In Figure 3 thermographs showed changed position of peaks that confirmed the formation of cocrystals. DSC data of the prepared cocrystals (figure 3) showed a noticeable reduction in melting point displaying sharp endothermic peak 86.4 ^{0}C and also the absence of corresponding peaks of ketoprofen and benzoic acid. Formation of cocrystal was evidenced by the appearance of a single endothermic peak attributed to melting of cocrystal phase. No other peak appeared in this thermogram which shows that the drug has been completely cocrystallized.[24]

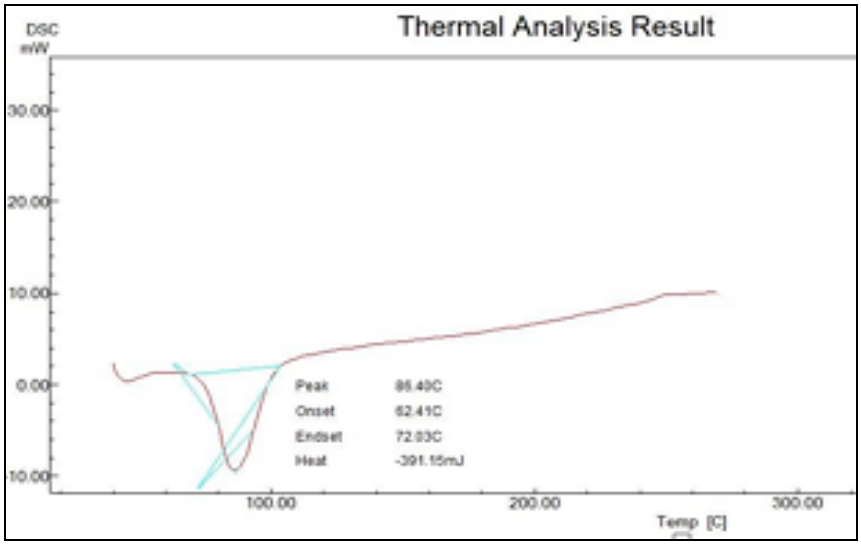

Fig. 3: DSC Thermogram of Ketoprofen-Benzoic Acid Cocrystal.

CONCLUSION

Herein, ketoprofen and benzoic acid cocrystal have been synthesized successfully in a fixed molar ratio (1:1) by using solvent drop grinding method. The interaction of drug and conformer was found to be via hydrogen bonding between carboxylic acid of both components. Thus, the cocrystallization of ketoprofen provides another approach to development of products having better physicochemical properties compared to parent molecules.

REFERENCES

1. Raheem TA, Juturu T, Nayak S, Kamath S. Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications. Adv Pharm Bull, 2020; 10(2): 203-212.
2. Wang JR, Yu X, Zhou C, et al. Improving the dissolution and bioavailability of 6-mercaptopurine via co-crystallization with isonicotinamide. Bioorg Med Chem Lett., 2015; 25(5): 1036-1039.
3. Maeno Y, Fukami T, Kawahata M, et al. Novel pharmaceutical cocrystal consisting of paracetamol and trimethylglycine, a new promising cocrystal former. Int J Pharm, 2014; 473(1-2): 179-186.
4. The co-crystals are held, by supramolecular heterosynthons that occur between the functional groups like carboxylic acid–aromatic nitrogen, carboxylic acid–amide and alcohol–pyridine, with non-covalent forces, often including hydrogen bonding

5. Douroumis D, Ross SA, Nokhodchi A. Advanced methodologies for cocrystal synthesis. Adv Drug Deliv Rev, 2017; 117: 178–95.
6. Savjani JK, Pathak C. Improvement of physicochemical parameters of acyclovir using cocrystallization approach. Braz J Pharm Sci, 2016; 52 (4): 727–4.
7. Kumar S, Nanda A Pharmaceutical cocrystals: an overview. Indian J Pharm Sci, 2017; 79(6): 858–871.
8. Zaini E, Sumirtapura YC, Soewandhi SN, Halim A, Uekusa H, Fujii K. Cocrystalline phase transformation of binary mixture of trimethoprim and sulfamethoxazole by slurry technique. Asian J Pharm Clin Res, 2010; 3(4): 26–9.
9. Ghadi R, Ghuge A, Ghumre S, Waghmare N, Kadam VJ. Co-crystals: emerging approach in pharmaceutical design. Indo Am J Pharm Res, 2014; 4(7): 3881–93.
10. Trask, AV, Jones W. Crystal Engineering of Organic Cocrystals by the Solid-State Grinding Approach. In: Toda, F. (eds) Organic Solid State Reactions. Topics in Current Chemistry, vol 254. Springer, Berlin, Heidelberg, 41–70.
11. Friščić T, Fabian L, Burley JC, Jones W, Motherwell WDS. Exploring cocrystal-cocrystal reactivity via liquid-assisted grinding: the assembling of racemic and dismantling of enantiomeric cocrystals. Chemical Communications, 2006; 9, (48): 5009.
12. Kumar R, Singh A, Garg N, Siril PF. Solid lipid nanoparticles for the controlled delivery of poorly water soluble non-steroidal anti-inflammatory drugs. Ultrason Sonochem, 2018; 40(Pt A): 686-696.
13. Kantor TG. Ketoprofen: a review of its pharmacologic and clinical properties. Pharmacotherapy, 1986; 6(3): 93-103.
14. Shohin IE, Kulinich JI, Ramenskaya GV, et al. Biowaiver monographs for immediate-release solid oral dosage forms: ketoprofen. J Pharm Sci, 2012; 101(10): 3593-3603.
15. Yadav PS, Kumar V, Singh UP, Bhat HR, Mazumder B. Physicochemical characterization and in vitro dissolution studies of solid dispersions of ketoprofen with PVP K30 and d-mannitol. Saudi Pharm J., 2013; 21(1): 77–84.
16. Rachmaniar R, Tristiyanti D, Hamdani S, Afifah. Solubility and dissolution improvement of ketoprofen by emulsification ionic gelation. InAIP Conference Proceedings AIP Publishing LLC. 2018; 9, 1927, 1: 030024.
17. Marzia Cirri, Francesca Maestrelli, Natascia Mennini, Paola Mura, Physical–chemical characterization of binary and ternary systems of ketoprofen with cyclodextrins and phospholipids, J. Pharm. Biomed. Anal, 2009; 50(5): 683-689.

18. Mahajan NM, Zode GH, Mahapatra DK, Thakre S, Dumore N, Gangane PS. Formulation development and evaluation of transdermal patch of piroxicam for treating ysmenorrhea. J Appl Pharm Sci, 2018; 8(11): 35-41.
19. Hosny KM., Rambo SM., Al-Zahrani MM., Al-Subhi SM., Fahmy UA. Ketoprofen emulgel: preparation, characterization, and pharmacodynamic evaluation. Int Pharm Sci Rev Res, 2013; 20(2): 306- 310.
20. Patel JR., Carlton RA., Needham TE., Chichester CO., & Vogt FG. Preparation, structural analysis, and properties of tenoxicam cocrystals. Int. J. Pharm, 2012; 436(1-2): 685–706.
21. Elbagerma, MA., Edwards HG. M, Munshi, T, Hargreaves MD., Matousek P., and Scowen IJ. Characterization of New Cocrystals by Raman Spectroscopy, Powder X-ray Diffraction, Differential Scanning Calorimetry, and Transmission Raman Spectroscopy. Cryst. Growth Des, 2010; 10: 2360–2371.
22. Dai XL., Wu C, Li JH, Liu LC, He X., Lu TB., & Chen JM. Modulating the solubility and pharmacokinetic properties of 5-fluorouracil via cocrystallization. Cryst Eng Comm, 2020; 22(21): 3670-3682.
23. Qiao Y, Qiao R., He Y, Shi C, Liu Y, Hao H. ... & Zhong, J. Instrumental analytical techniques for the characterization of crystals in pharmaceutics and foods. Cryt. Growth Des, 2017; 17(11): 6138-6148.
24. Saganowska P., & Wesolowski M. DSC as a screening tool for rapid co-crystal detection in binary mixtures of benzodiazepines with co-formers. Therm. Anal. Calorim, 2018; 133(1): 785–795.