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RESEARCH ARTICLE

Pharmaceutical Cocrystallization of Naproxen and Paracetamol: A Rational Design Approach toward Enhanced Solubility, Stability, and Formulation Efficiency

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Abstract: Fixed Dose Combination (FDCs) Therapy was widely used due to the limitations of monotherapy in the complex disease condition such as cardiovascular disease, Cancer, Diabetics, Infectious disease etc. Therefore Drug-Drug Cocrystals of Naproxen and Paracetamol was synthesized by using solvent grinding and Solvent crystallization Techniques. The Naproxen, a BCS Class II drug act as API and Paracetamol slightly soluble drug act as conformer. The Naproxen and Paracetamol in the molar ratio 1:1.230 mg of Naproxen (1 mMole) and 151 mg Paracetamol (1 mMole) were used in the formation of Cocrystals. The Naproxen- Paracetamol Cocrytsals were characterized by FTIR, DSC, XRD and SEM analysis. The melting point, solubility, in vitro dissolution and stability studies were conducted for the cocrystals. The formation of Naproxen-ParacetamolCocrystals were supported and confirmed based on the data of the FTIR, DSC and XRD. The SEM also showed change in the habit of Cocrystals compared to pure drugs. The Naproxen- Paracetamol Cocrytsals showed 11-fold increase in the solubluity in water compared to Naproxen. The dissolution rate Naproxen- Paracetamol Cocrytsals were also dramatically improved compared to pure drugs. The pharmacokinetic study of Naproxen-ParacetamolCocrystals showed increased in the bioavailability of fixed dose combination.

Keywords: Cocrystals, Solubility, Physico-chemical properties, SEM, XRD.

INTRODUCTION

Improving the physicochemical characteristics of drug molecules, as well as their solubility and dissolution rate, is a crucial aspect in the formulation of oral dosage forms, ultimately leading to enhanced oral bioavailability. (Yellela *et al* 2010, Vemulla *et al* 2010) Number of ways is used to improve oral bioavailability of API such as Nanoparticles (Muller *et al* 2000) , Liposome (Fong *et al* 2015), polymer micelle (Gaucher et al 2010), microemulsion (Rui Xue Guo *et al* 2016). Other techniques are also available for the improvements of solubility and dissolution rate such as solid dispersion (Gorajana *et al* 2015), micelle formation (Hsu CH et al 2008), complexation (Parikh RK *et al* 2005), hydrotrophy (Roy BK *et al* 2002), size reduction (Muller *et al* 1998). Numerous formulations face difficulties during development owing to complex procedures, with some additionally exhibiting issues related to solubility and stability. (Fasinu P et al 2011). Crystal engineering is one of the way by which we can improve all these properties. Cocrystals represent a class of solid crystalline materials that are gaining prominence in the pharmaceutical field for improving key physicochemical characteristics of APIs, such as solubility, stability, and bioavailability. (G. Kuminek *et al* 2019; K. *Suresh et al* 2013; B.B. Eedara *et al* 2019; M.L. Cheney *et al* 2011; D.X. Li *et al* 2019; C.V.G. Narendra *et al* 2011). Co-crystal is defined as a crystalline material consisting of two or more compound, at least two of which are held together by weak interaction, and at least one of which is a co-crystal former. According to the present invention, naproxen solvates that do not contain a co-crystal former are not co-crystal.Theco-crystals may however, includes one or more solvate molecules in the crystalline lattice (R. R. Thenge *et al* 2012). The aim of this research was to prepare and characterize cocrystals of naproxen-paracetamol to improve the physical properties of the drug.

MATERIALS AND METHODS

Materials

Paracetamol and Naproxane were obtained as a gift sample from Glenmark Generics, limited, Goa, India. The solvents were purchased from SD Fine Chemical Mumbai. All the solvents used are of analytical grade.

Formulation of co-crystals by Solvent-drop Grinding Method

A pharmaceutical co-crystal of Naproxen and Paracetamol was prepared using the solvent grinding method. Equimolar amounts of Naproxen (0.230 g) and Paracetamol (0.151 g) were ground together in a mortar and pestle for 90 minutes. During the grinding process, a few drops of ethanol—approximately 10% of the total weight—were added as a solvent. The resulting solid powder was carefully collected from the mortar walls

and stored in a suitable container for further analysis. (R. R. Thenge *et al* 2020).

Formulation of co-crystals by Solvent Evaporation Method:

A pharmaceutical co-crystal of Naproxen and Paracetamol was prepared using the solvent evaporation method. Equimolar amounts of Naproxen (0.230 g) and Paracetamol (0.151 g) were mixed, and 5 mL of ethanol was added to the mixture under continuous stirring. The solution was then refluxed for 5 minutes, after which the solvent was reduced to one-fourth of its original volume using a water bath. The remaining solvent was allowed to evaporate at room temperature, and the resulting solid product was dried and stored in a container for further studies. (R. R. Thenge *et al* 2020).

Preparation of physical mixture

Naproxen and Paracetamol were accurately weighed and physically mixed in a 1:1 molar ratio. Manual mixing was carried out carefully to avoid any potential reaction between the components. The resulting physical mixture served as a reference standard to confirm the presence of hydrogen bonding interactions between the two drugs in the co-crystal form.

Fourier transform infrared (FT-IR) spectrophotometry:

FT-IR spectroscopy was conducted using an FTIR instrument (Thermo, India) to analyze Naproxen, Paracetamol, their physical mixture, and co-crystals prepared via both solvent drop grinding and solvent evaporation methods. Each sample was finely ground and uniformly mixed with potassium bromide (KBr) at a ratio of 1% w/w. The mixture was then compressed into a disc and placed in the sample holder. Spectral scanning was carried out over a wavenumber range of 4000 to 400 cm^{-1}. (R. R. Thenge *et al* 2020).

Differential scanning calorimetry (DSC):

Differential Scanning Calorimetry (DSC) analysis was performed to evaluate differences in the melting points of Naproxen, Paracetamol, and co-crystals prepared via solvent drop grinding and solvent evaporation methods. Samples weighing between 5 to 7 mg were placed in aluminum pans, hermetically sealed, and analyzed using a DSC instrument (Mettler Toledo, India). The thermal analysis was carried out over a temperature range of 20–400 °C at a constant heating rate of 10 °C/min. (R. R. Thenge *et al* 2020).

Powder x-ray diffractometry (PXRD):

Powder X-ray Diffraction (PXRD) analysis was carried out for Naproxen, Paracetamol, and the co-crystals obtained via solvent drop grinding and solvent evaporation methods. The analysis was performed using a Bruker D2 Phaser (2nd generation, Germany) equipped with CuKα radiation. Each sample was carefully filled into a glass sample holder and leveled with a glass plate to ensure a uniform surface. PXRD measurements were conducted at room temperature over a 2θ range of 5° to 40°, with an operating voltage of 40 kV and a current of 40 mA.

Scanning electronmicroscopy (SEM):

Photographic images of Naproxen, Cocrystals of solvent drop grinding method and Cocrystals of solvent evaporation method were captured using Carl Zeiss Supra55, Germany. Each sample was mounted on a sample holder and coated with a 10 nm layer of gold-aluminum to enhance conductivity. Morphological analysis was performed using Scanning Electron Microscopy (SEM) at appropriate magnifications, operated at an accelerating voltage of 20 kV and a current of 12 mA. (R. R. Thenge *et al* 2020).

Solubility studies:

The solubility of Naproxen, Paracetamol, and their co-crystal was evaluated in phosphate buffer (pH 6.8). An excess amount of the co-crystal (100 mg) was added to a glass-stoppered flask containing 50 mL of the buffer medium and maintained at 37 ± 0.5 °C. The mixture was stirred continuously on a magnetic stirrer at 150 rpm for 24 hours to reach equilibrium. After equilibration, the suspension was filtered using Whatman filter paper No. 1. The filtrate was appropriately diluted, and the concentration of the drug was determined spectrophotometrically at 235 nm. (R. R. Thenge *et al* 2020).

Dissolution studies:

Micromeritic Properties of the Co-crystal

Angle of Repose:

The angle of repose was measured using the fixed funnel method. A precisely weighed amount of the drug (5 g) was placed in a funnel. The funnel's height was adjusted so that its tip was just in contact with the peak of the powder heap. The sample was then allowed to flow freely onto a flat surface. The base diameter of the resulting cone was measured, and the angle of repose was calculated using the following equation (ND Deshmukh et al., 2012):

$\tan\theta = r/h$

where θ represents the angle of repose, h is the cone's height, and r is the radius of its base.

Bulk Density:

Bulk density was determined by transferring an accurately weighed sample (5 g) of the drug into a graduated cylinder. The cylinder was dropped onto a hardwood surface from a height of 1 inch, three times at 2-second intervals. Bulk density was then calculated using the formula (ND Deshmukh et al., 2012):

Bulk density=Bulk volume/Weight of the powder

Tapped Density:

Tapped density was measured by placing a 5 g sample of the drug into a graduated cylinder, which was then

dropped from a height of 1 inch onto a hard surface 100 times at 2-second intervals. The final volume occupied by the sample was recorded, and tapped density was calculated using the equation (ND Deshmukh et al., 2012)

Tapped density=Final volume/Weight of the blend

Compressibility Index:
The compressibility index, also known as Carr's index, indicates the ability of a powder to undergo compression. (R. R. Thenge*et al* 2020).

Carr's compressibility index = [(tapped density- bulk density / tapped density)] × 100

Hausner ratio
The Hausner ratio was determined as described by Tekade*et al*. (2010) using the equation:

Hausner ratio=Df/Dt

Where *Df* is the tapped density and *Dt* is the bulk density.

In-Vivo Pharmacokinetic Study
The pharmacokinetic study protocol for candesartan cocrystals received approval from the Institutional Animal Ethical Committee (1136/AC/10/CPCSEA). In vivo kinetic evaluations were carried out by orally administering both the pure drug and its cocrystals to rats, followed by collection of blood samples at predetermined intervals to determine plasma drug concentrations. Male Wistar rats, weighing between 250–280 g, were used for the in vivo pharmacokinetic investigations. The animals were fasted for 12–16 hours prior to dosing, provided water during the first hour of sampling, and given feed thereafter. For the experiment, the rats were divided into five groups (n = 6), comprising a standard drug group and cocrystal groups. Animals in the standard drug group received an oral dose of naproxen suspended in 1% HPMC at 12 mg/kg body weight. Similarly, the cocrystal groups were administered their respective formulations at doses equivalent to 12 mg/kg naproxen. Following oral dosing, blood samples (0.4 mL) were withdrawn from the retro-orbital vein at intervals up to 24 hours, specifically at 0.25, 0.5, 1, 2, 4, 6, and 8 hours. Samples were collected in tubes pretreated with 5% EDTA solution, then centrifuged at 4 °C for 15 minutes at 10,000 rpm to separate plasma. The clear plasma was stored at −80 °C until analysis. The obtained plasma concentration values were plotted against time to determine pharmacokinetic parameters.

RESULTS AND DISCUSSION

Crystalline pure Naproxen–Paracetamol was obtained from the supplier and used directly for co-crystal synthesis. The drug displayed good solubility in ethanol but was practically insoluble in distilled water, chloroform, ethyl acetate, and acetone. Ethanol was therefore selected as the preferred solvent owing to its availability, low cost, and ability to dissolve the co-former. Co-crystals were prepared via solvent grinding and solvent evaporation methods. Alternative techniques, including solution co-crystallization, slurry conversion, and anti-solvent addition, were not feasible due to solubility constraints.

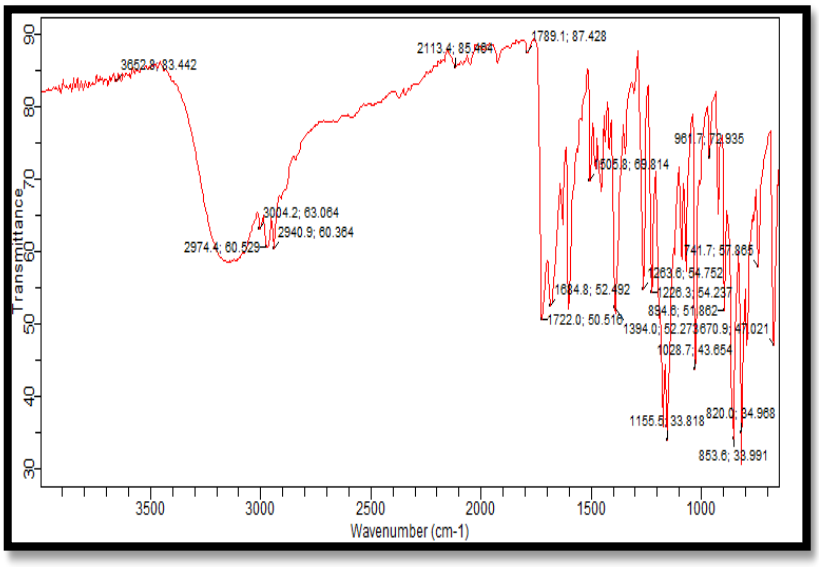
In both methods, Naproxen was used as the primary drug and Paracetamol as the co-former in a 1:1 molar ratio. Paracetamol was selected for its high aqueous solubility and functional groups capable of both hydrogen bond donation and acceptance. The prepared co-crystals, along with pure Naproxen, were subjected to characterization and evaluation, including solubility and dissolution studies.

FTIR Spectroscopystudies
Naproxen-Paracetamol cocrystals were studied by Infrared spectroscopy with distinct shifts in the inherent bands Naproxen which could be seen in Naproxen alone. Different frequency wavenumbers were noted in addition to absorptions of C=O or C=C and -NH group vibrational bands that shift to lower wavenumbers. This is very indicative of a new cocrystalline compound formation (Figure 1(a-e)). In the naproxen drug spectrum, bands were observed at 1729 cm-1 and 3324 cm-1 showing vibration wavenumbers for –C=C- and - C=O, -NH band of Naoroxen drugs alone was found to be around 3324 cm-1. However, the same frequency wavenumbers Naoroxen drug alone was found to be around 3324 cm but band around 1729 cm-1 found in Naproxen powder was absent in the cocrystal hip spectrum. The band at 1729 cm-1 was found to be absent in the cocrystal hip spectrum. The absorptions for physical mixtures showed all the characteristic absorptions of naproxen drug showing constant absorption wavelength and no appearance of absorption peaks or bands at wavenumbers of 1502-1729 cm-1 & 2832-3423 cm-1 thus indecent of any binding or physiochemical interactions between both anti-inflammatory and analgesic drugs.

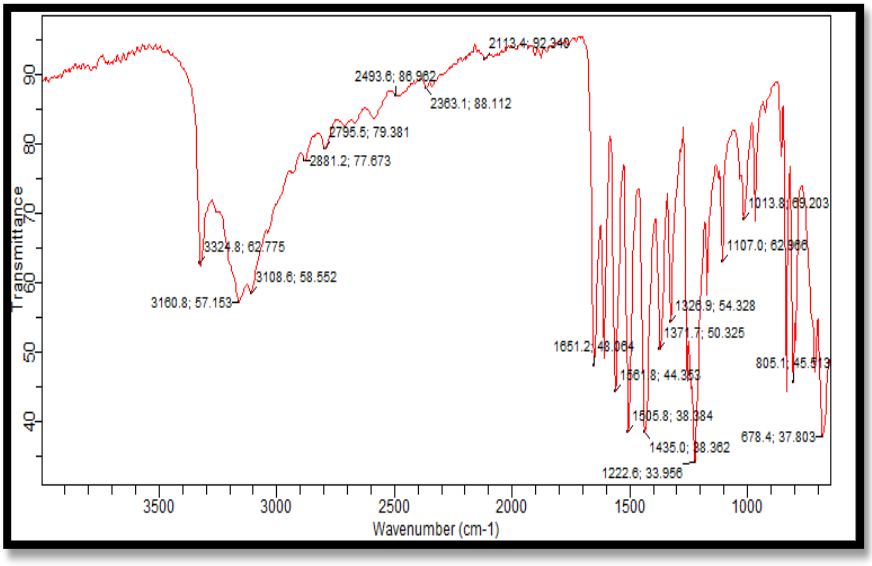
Table No-1: FTIR data of pure drug & co-crystal of Naproxen- Paracetamol

Sr. no	Crystal codes	C=C stretching	C=O stretching	C-O-C stretching	O-H stretching	N-H Stretching	N-C=O stretching
1	Naproxen	1505.8	1722	1155.5	3004.2	-	-
2	Paracetamol	1561.8	-	1107.0	3160.8	3324.8	1651.2

3	Physical mixture	1561.8	1725.8	1174.1	3160.8	-	1654.9
4	Cocrystal of N-P by SGM	1505.8	1729.5	1269.8	3160.8	-	1654.9
5	Cocrystal of N-P by SEM	1502.1	-	1222.6	3104.9	3317.3	1651.2

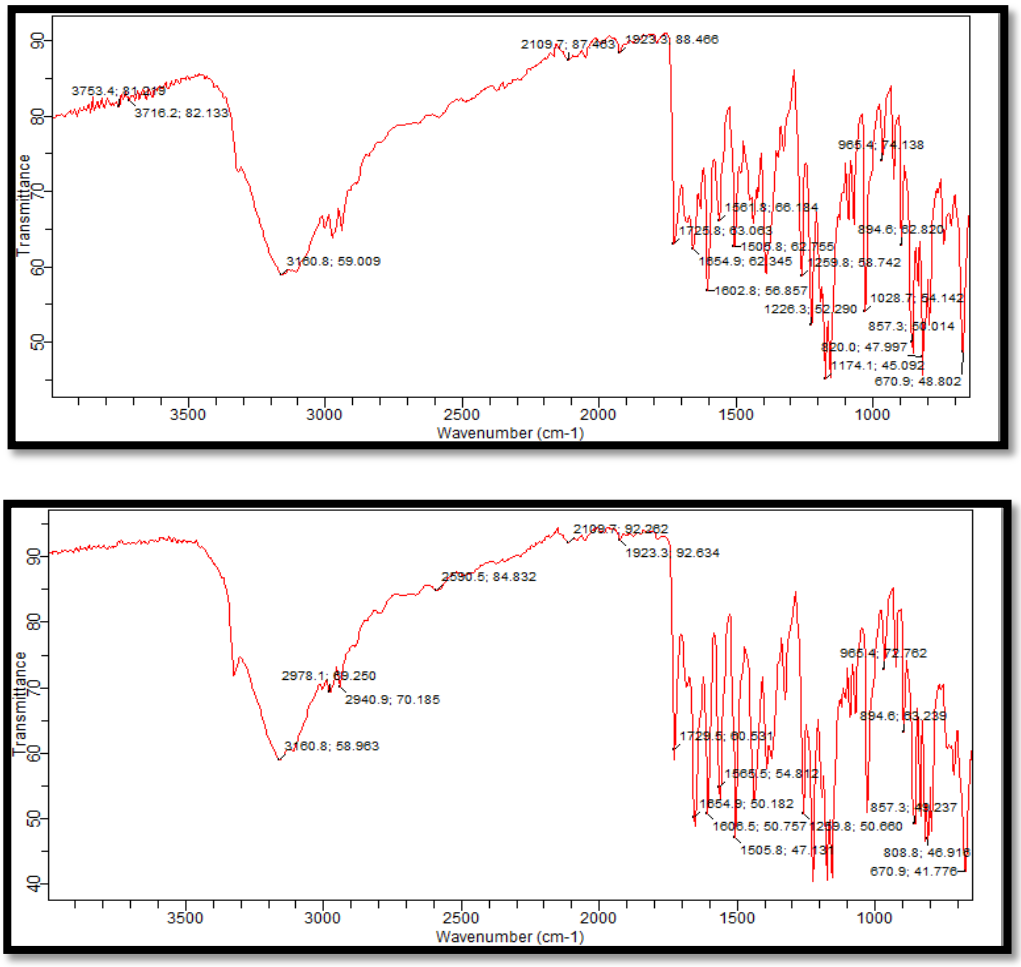


FigNo-1. a: FTIR spectra of Naproxen



FigNo-1. b: FTIR spectra of Paracetamol

FigNo-1.c: FTIR spectra of Physical mixture of Naproxen-Paracetamol



FigNo-1.d:FTIR spectra of Cocrystal of Naproxen-Paracetamol by Solvent Grinding Method

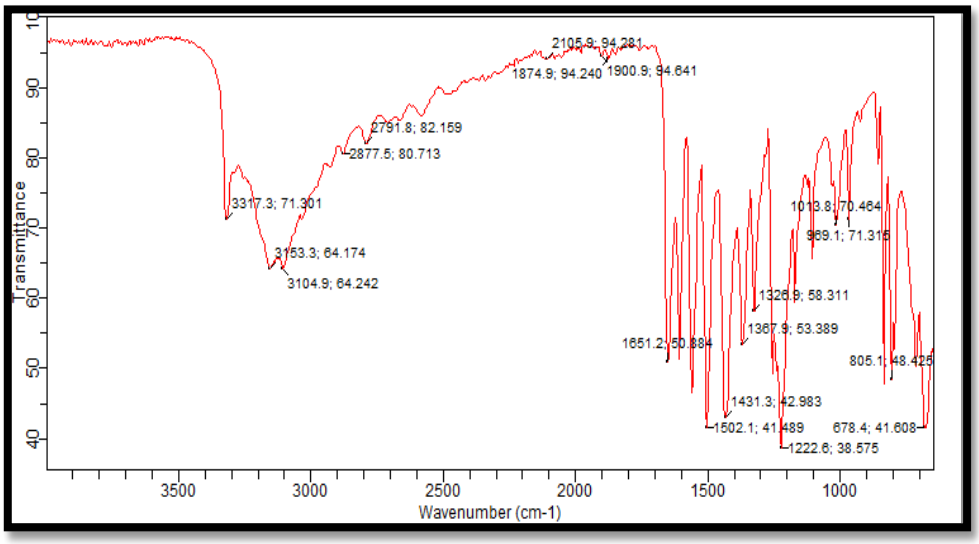
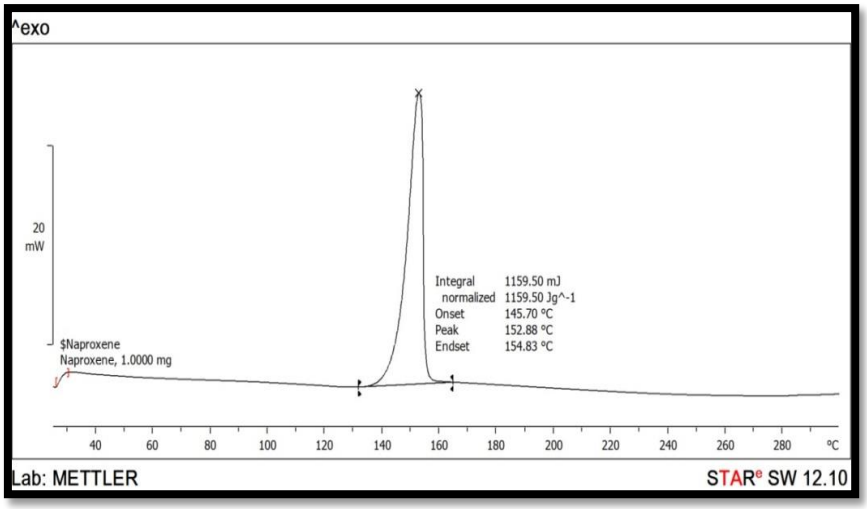


Fig No-1.e: FTIR spectra of Cocrystal of Naproxen- Paracetamol by Solvent Evaporation Method

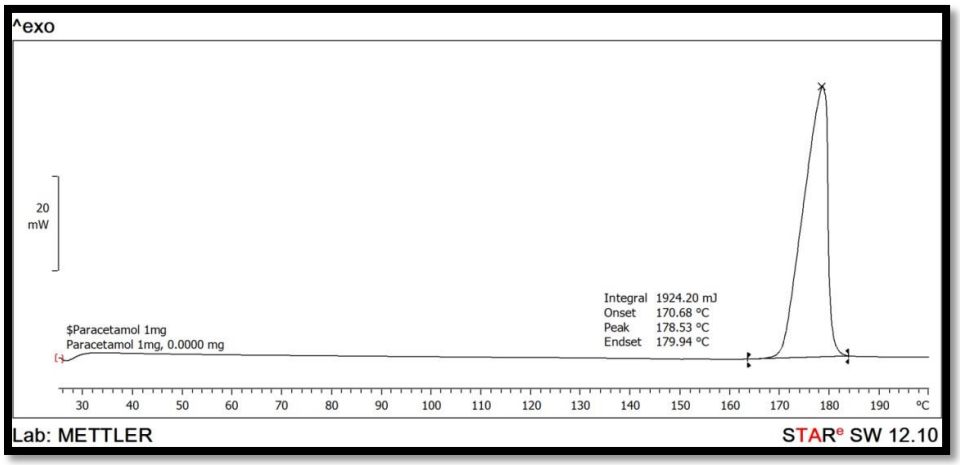
Differential scanning calorimetry

All co-crystals prepared via solvent grinding and solvent evaporation methods displayed the characteristic exothermic peak of Naproxen–Paracetamol co-crystals. Differential scanning calorimetry (DSC) is commonly used to analyze the composition of pharmaceutical co-crystals, particularly when they exhibit distinct melting points. The thermal behavior of the pure drug and co-crystals is presented below. The DSC curve for Naproxen–Paracetamolshowed sharp exothermic peaks at approximately 145.70 °C and 170.68 °C, corresponding to their melting points. Co-crystals obtained by the solvent grinding method exhibited an exothermic peak, whereas those prepared via solvent evaporation displayed a shift in the

endothermic peak toward lower temperatures. Specifically, shifts of the endothermic and exothermic peaks to 163.47 °C and 166.57 °C, respectively, indicate a reduction in the melting point of the drug in the co-crystals. This reduction in melting point is associated with the enhanced solubility of the drug.

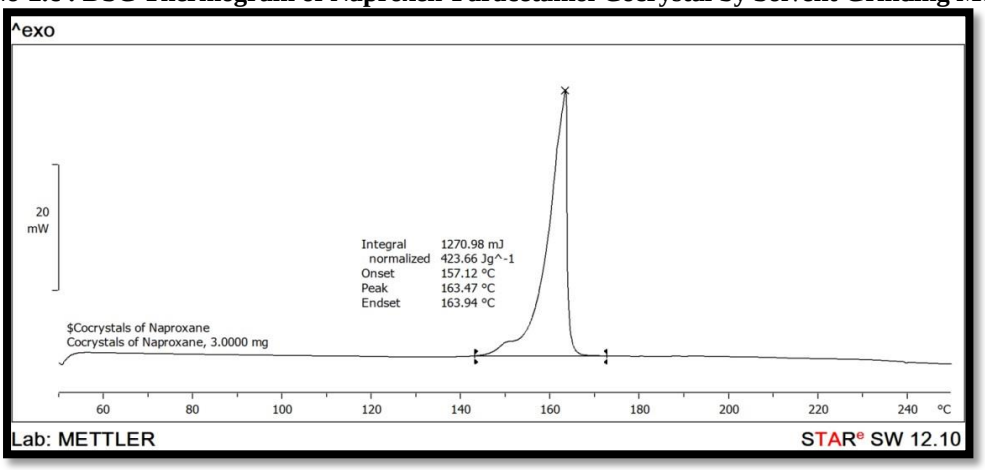


FigNo-2.a:DSC Thermogram of pure drug Naproxen



FigNo-2.b: DSC Thermogram of pure drug Paracetamol

Fig No-2.c : DSC Thermogram of Naproxen-Paracetamol Cocrystal by Solvent Grinding Method



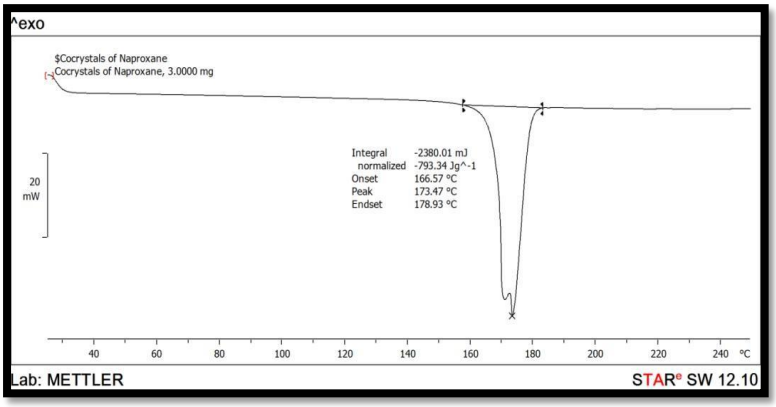
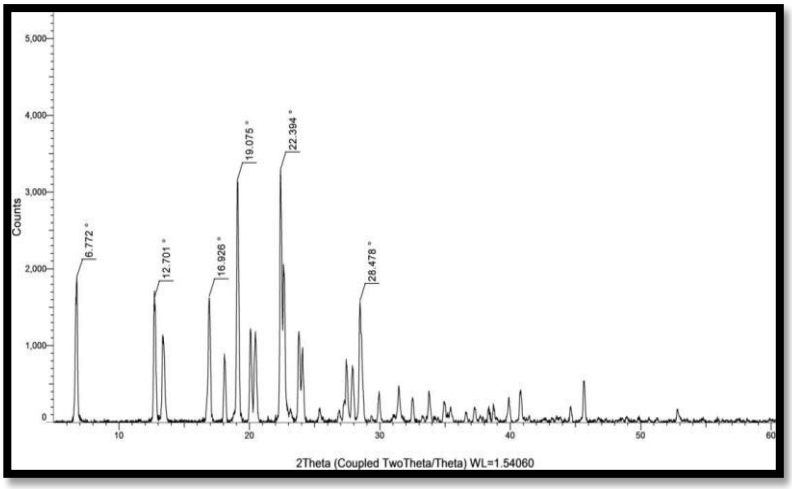


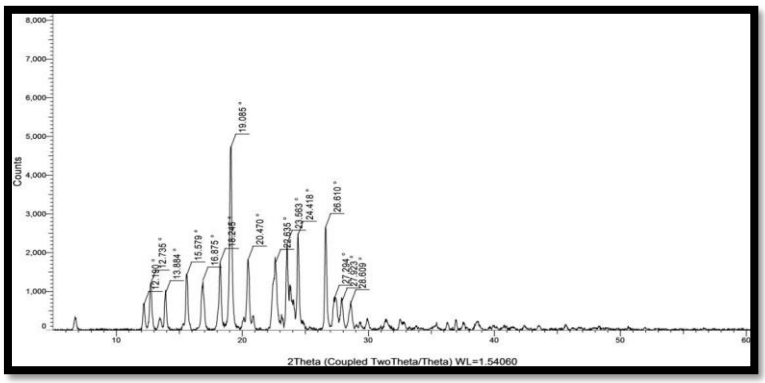
Fig No-2.d : DSC Thermogram of Naproxen- Paracetamol Cocrystal by Solvent Evaporation Method

PowderX-raydiffraction

The X-ray diffraction (XRD) patterns of the various co-crystals were analyzed using an X-ray diffractometer. Compared to the co-crystals, the pure drug exhibited a greater number of peaks. The XRD spectra of Naproxen–Paracetamol co-crystals showed a reduced number of peaks but an increase in peak intensity for both preparation methods. In particular, the co-crystals prepared by the solvent evaporation method displayed a marked increase in peak intensity. The XRD patterns of the pure drug and the co-crystals formed in the presence of a co-former exhibited essentially similar diffraction patterns (2θ values), indicating that crystallization by the solvent evaporation method did not result in structural modification. However, variations in relative peak intensities may be attributed to differences in crystal size and habit, which could be influenced by the differing solubility of the drug in the medium.



FigNo-3.a:XRD Spectra of pure drug Naproxen



FigNo-3.b: XRD Spectra of Naproxen- Paracetamol cocrystal by Solvent Grinding Method

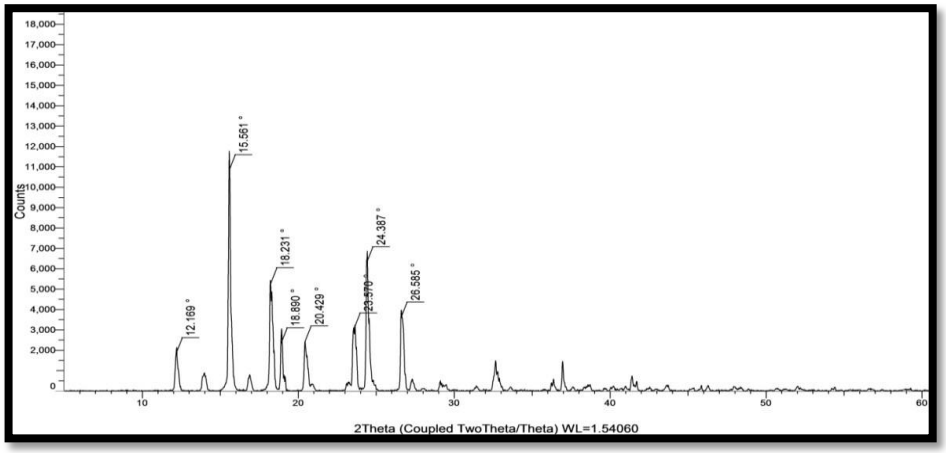
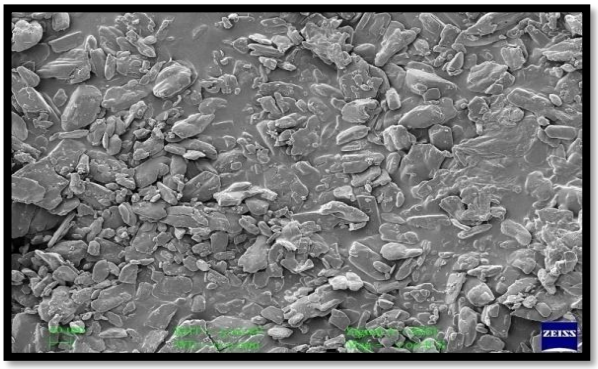


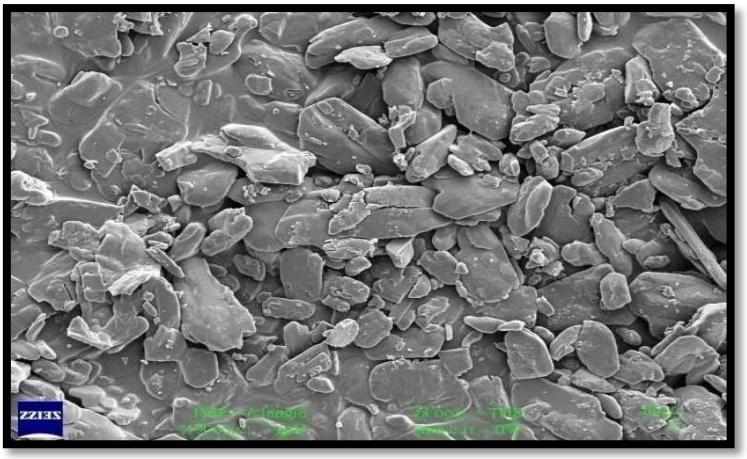
Fig No-3.c : XRD Spectra of Naproxen-Paracetamol cocrystal by Solvent Evaporation Method

Scanning Electron Microscopy

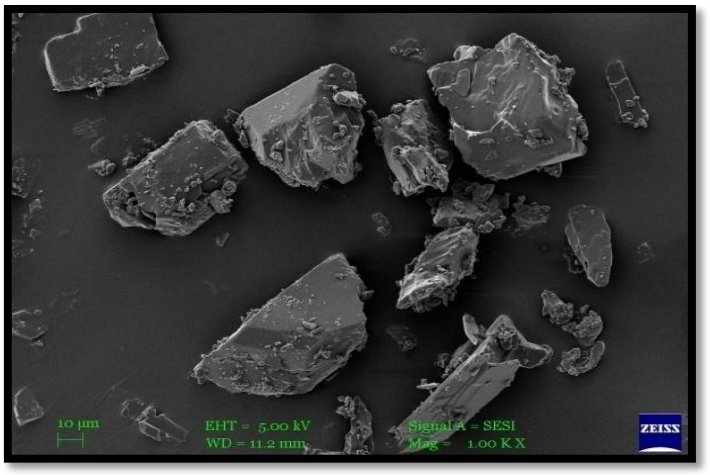
The morphology of naproxen, paracetamol, and their co-crystals was examined using scanning electron microscopy. Photomicrographs of naproxen and paracetamol revealed irregularly sized particles with an amorphous structure, whereas the co-crystals exhibited well-defined size, shape, and crystalline form with clump formation. These observations indicate notable changes in the crystal size and shape between the pure drugs and their co-crystals.



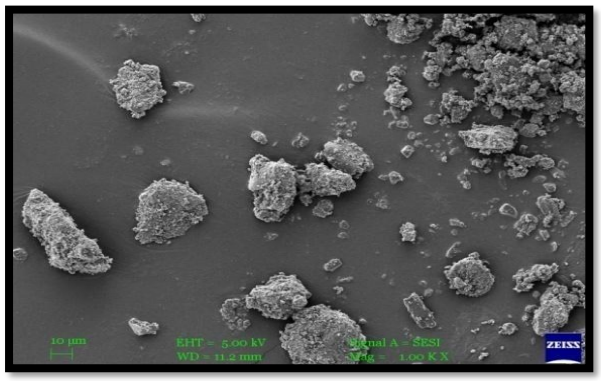
FigNo-4.a:SEM of Naproxen



FigNo-4.b:SEM of Naproxen drug



FigNo-4.c:SEM of cocrystal by solvent grinding method



FigNo-4.e:SEM of cocrystal by solvent evaporation method

Solubility studies

Solubility studies revealed that pure naproxen exhibited the lowest solubility (2.625 µg/ml). Co-crystals prepared with paracetamol as a co-former via the solvent grinding method demonstrated a solubility of 21.0 µg/ml, representing an eightfold increase. Co-crystals produced by the solvent evaporation method showed a solubility of 13.125 µg/ml, corresponding to a fivefold increase. The enhanced solubility of Naproxen–Paracetamol co-crystals is attributed to the melting of the co-former associated with the co-crystal structure, compared to pure naproxen.

Table No-2: Solubility data of various co-crystal forms.

Sr. no.	Co-Crystal	Solubility (µg/ml)
1	Naproxen	2.625
2	N/P cocrystal by solvent grinding method	21.0
3	N/P cocrystal by solvent evaporation method	13.125

Dissolution studies

The dissolution profile of Naproxen–Paracetamol co-crystals exhibited variations in dissolution rate that corresponded to their relative crystallinity and solubility. The dissolution study results are presented graphically as percent drug release versus time. Among the tested samples, the highest dissolution rate was observed for the co-crystal prepared via the solvent grinding method, compared to the one obtained by solvent evaporation. The presence of paracetamol as a co-former in the co-crystals contributed to a marked improvement in the dissolution rate.

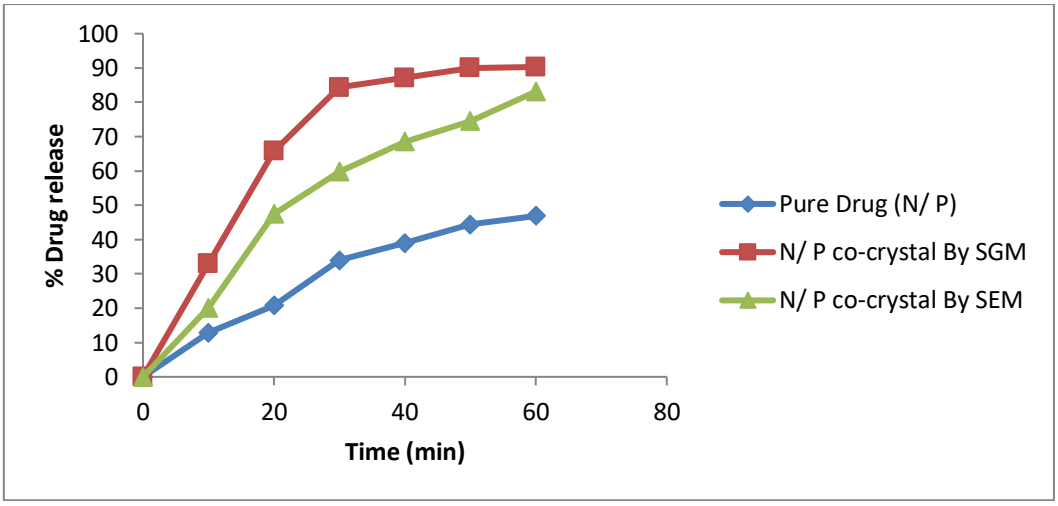


Fig No-5: Dissolution study of Naproxen- Paracetamol Cocrystal

Micromeritic properties of co-crystal

The micromeritic properties of the co-crystal were assessed by determining bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose, with the results presented in Table 3.

The angle of repose serves as an indicator of powder flowability. In powders with poor flow properties, particles tend to adhere to one another, impeding movement through a funnel of fixed height onto a flat surface. This results in the formation of a cone with a small base radius and a large angle of repose, and the opposite occurs in powders with good flowability. Apart from flowability, powder compressibility can be assessed by determining the percentage difference between tapped and bulk densities, expressed as Carr's index, or by calculating the ratio of tapped to bulk densities, known as Hausner's ratio.

Paracetamol is characterized by poor flowability and compressibility. Its angle of repose typically exceeds 40, indicating a passable powder that may cause blockages. In this study, the measured angle of repose for pure paracetamol was 44.073°, while Carr's index and Hausner's ratio were 25.068% and 1.33, respectively.

Naproxen is also recognized for its poor flowability. The high cohesiveness of naproxen particles results in low inter-particulate friction, necessitating agitation during handling. The measured angle of repose for naproxen was approximately 47°, with Carr's index and Hausner's ratio recorded at 27.058% and 1.373, respectively. In contrast, all prepared co-crystals exhibited excellent flow properties, with angles of repose of 29° and 30°, respectively, as presented in Table 3. The compressibility, expressed as Carr's index, was excellent for formulations N1 and N2, measuring 7.7% and 7.9%, respectively. Hausner's ratio, which aligns with Carr's index as an indicator of flowability, also confirmed these findings. Both co-crystals demonstrated superior flowability compared to the "good" range, and overall, all prepared co-crystals showed significant improvement in both flowability and compressibility relative to pure paracetamol and pure naproxen, both of which displayed poor performance in these parameters.The volume of untapped powder provides an indication of its flowability. Powders with good flow properties occupy minimal volume, as their particles rapidly arrange with minimal inter-particulate spaces. In contrast, poorly flowing powders occupy a larger apparent volume due to numerous voids between particles. A small difference between tapped and bulk densities reflects good flowability and compactibility, enabling particles to pass quickly through a cylinder and form a compact cake with minimal inter-particle spaces even before tapping—this behavior was observed in the co-crystals.
For the two co-crystals studied, the difference between tapped and bulk densities was approximately 0.018, signifying excellent flowability compared to their parent drugs, paracetamol and naproxen, which exhibited differences of 0.109 and 0.115, respectively. The enhancement in the poor micromeritic properties of paracetamol and naproxen upon co-crystallization is attributed to increased bonding surface area, introducing an active flat slip plane with lower interlayer interaction energy. This facilitates plastic deformation, improving compressibility. Additionally, the improved flowability of the co-crystals may be related to their crystal habit, which is influenced by the external shape of the crystals.

Table No-3: Micromeritic properties of co-crystal

Formulation	Angle of Repose	Bulk density	Tapped density	Carr's index	Hausner's ratio	Melting Point
Naproxen	47.192±0.476 poor	0.306±0.017	0.421±0.04	27.058±3.177 poor	1.373±0.058 good	153^{O}C

Paracetamol	44.073±0.594 Poor\	0.324±0.008	0.433±0.019	25.068±1.419 poor	1.33±0.025 passable	169 ° C
N-P co-crystal by solvent grinding	29.421±0.289 good	0.208±0.007	0.225±0.006	7.732±0.704 excellent	1.084±0.008 excellent	150^{0}C
N-P co-crystal by solvent evaporation	24.284±0.202 good	0.26±10.006	0.283±0.004	7.91±0.033 excellent	1.083±0.039 excellent	165^{0}C

In-Vivo Pharmacokinetic Study

The *in vivo* pharmacokinetic parameters of Naproxane and Cocrystals were studied in Wistar rats. The measured mean Naproxane and Cocrystalsl plasma concentrations versus time after single oral administration in male Wistar rats using 0.5% oral Solution. The pharmacokinetic parameters calculated from the non-compartment model using linear trapezoidal. The pharmacokinetic parameters of Naproxane obtained from non-compartmental analysis using a linear trapezoidal method after a single oral dose of 10 mg/kg of Naproxane to Wistar rats. The t1/2, Tmax and Cmax of the drug was found to be about 2.80±0.6 hr, 1.0±0.0hr, and 480±25.6 ng/ml respectively along with AUC0-t of 2219±243.1 ng/mL*h. In contrast, Cocrystals demonstrated higher Cmax and AUC0-t as compared to pure Naproxane (Cmax= 625± 28.4ng/ml, AUC0-t = 3024±352.5). Conversely, the Tmax of the Cocrystals was same as compared to the pure Naproxane. The relative bioavailability of Naproxane and CocrystalsCocrystals formulation was found to be about 2.4 folds higher, which may be due to conversion of drug into its new solid phase which is having high internal energy that promotes quick dissolution and hence higher bioavailability was observed.

CONCLUSION

FTIR analysis confirmed that no chemical interaction occurred between the drug and the cocrystals produced by either solvent grinding or solvent evaporation. Complementary DSC and XRD data revealed no evidence of polymorphic transitions, yet demonstrated pronounced modifications in crystal size and habit attributable to the presence of the coformer. SEM imaging further substantiated these findings, highlighting marked differences in particle size and morphology between the pure drugs and their cocrystals. Collectively, these results establish cocrystallization as a robust and versatile strategy for optimizing the physicochemical profile of the fixed-dose combination, offering significant potential for enhanced formulation performance and therapeutic efficacy.

REFERENCES

1. Cheney, M. L., Weyna, D. R., Shan, N., Hanna, M., Wojtas, L., &Zaworotko, M. J. (2011).Coformer selection in pharmaceutical cocrystal development: A case study of a meloxicam–aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics. *Journal of Pharmaceutical Sciences, 100*(6), 2172–2181.
2. Deshmukh, N. D., Thenge, R. R., & Mahajan, N. M. (2012). Formulation and evaluation of bisoprolol fumarate fast-dissolving tablet by direct compression techniques. *International Journal of Pharmaceutical Research and Bio-Science, 1*(5), 364–378.
3. Eedara, B. B., Tucker, I. G., Zujovic, Z. D., Rades, T., Price, J. R., & Das, S. C. (2019). Crystalline adduct of moxifloxacin with trans-cinnamic acid to reduce the aqueous solubility and dissolution rate for improved residence time in the lungs. *European Journal of Pharmaceutical Sciences, 136*, 1–11.
4. Tiwari R, Patil A, Verma R, Deva V, Suman Rudrangi SR, Bhise MR, Vinukonda A. Biofunctionalized polymeric nanoparticles for the enhanced delivery of erlotinib in cancer therapy. *J Biomater Sci Polym Ed.* 2025 May; 36(7):817-842. doi: 10.1080/09205063.2024.2429328. Epub 2024 Nov 23. PMID: 39579362.
5. Fong, S. Y., Brandl, M., & Bauer-Brandl, A. (2015). Phospholipid-based solid drug formulations for oral bioavailability enhancement: A meta-analysis. *European Journal of Pharmaceutical Sciences, 80*, 89–110. https://doi.org/10.1016/j.ejps.2015.08.005
6. Gaucher, G., Satturwar, P., Jones, M.-C., Furtos, A., &Leroux, J.-C.(2010). Polymeric micelles for oral drug delivery.*European Journal of Pharmaceutics and Biopharmaceutics, 76*(2), 147–158.
7. Gorajana, A., Rajendran, A., Yew, L. M., &Dua, K. (2015).Preparation and characterization of cefuroxime axetil solid dispersions using hydrophilic carriers.*International Journal of Pharmaceutical Investigation, 5*(3), 171–178.
8. Guo, R. X., Fu, X., Chen, J., Zhou, L., & Chen, G. (2016).Preparation and characterization of microemulsions of myricetin for improving its

antiproliferative and antioxidative activities and oral bioavailability.*Journal of Agricultural and Food Chemistry*, *64*(32), 6286–6294.

9. Hsu, C. H., Cui, Z., Mumper, R. J., & Jay, M. (2008).Micellarsolubilization of some poorly soluble antidiabetic drugs.*AAPS PharmSciTech*, *9*(2), 939–943.
10. Kuminek, G., Cavanagh, K. L., da Piedade, M. F. M., & Rodríguez-Hornedo, N. (2019).Posaconazolecocrystal with superior solubility and dissolution behavior.*Crystal Growth & Design*, *19*(11), 6592–6602.
11. Li, D. X., Li, J., Deng, Z. W., & Zhang, H. L. (2019).Piroxicam–clonixin drug–drug cocrystal solvates with enhanced hydration stability.*CrystEngComm*, *21*(28), 4145–4149.
12. Müller, R. H., Jacobs, C., &Kayser, O. (2000).Nanosuspensions for the formulation of poorly soluble drugs.In F. Nielloud& G. Marti-Mestres (Eds.), *Pharmaceutical Emulsion and Suspension* (pp. 383–407). Marcel Dekker.
13. Müller, R. H., & Peters, K. (1998).Nanosuspensions for the formulation of poorly soluble drugs: I. Preparation by a size-reduction technique. *International Journal of Pharmaceutics*, *160*(2), 229–237.
14. Narendra, C. V. G., Adityanath, P., Somesh, S., &Sheetal, C. (2011). Co-crystallization of aceclofenac and paracetamol and their characterization. *International Journal of Pharmaceutical Life Sciences*, *2*(8), 1020–1028.
15. Parikh, R. K., Mansuri, N. S., Gohel, M. C., &Soniwala, M. M. (2005).Dissolution enhancement of nimesulide using complexation and salt formation techniques. *Indian Drugs*, *42*(3), 149–154.
16. Roy, B. K., &Moulik, S. P. (2002).Functions of hydrotropes (sodium salicylate, proline, pyrogallol, resorcinol and urea) in solution with special reference to amphiphilebehaviors.*Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *203*(1–3), 155–166.
17. Suresh, K., Goud, N. R., &Nangia, A. (2013).Andrographolide: Solving chemical instability and poor solubility by means of cocrystals. *Chemistry – An Asian Journal*, *8*(12), 3032–3041.
18. Tekade, N. P., Bhajipale, N. S., Ganesan, V., Thenge, R. R., &Dewade, D. R. (2010). Orodispersible tablets of lansoprazole: Formulation, characterization and *in vitro* evaluation. *International Journal of ChemTech Research*, *2*(1), 400–405.
19. Thenge, R., Patel, R., Kayande, N., &Mahajan, N. (2020). Co-crystals of carvedilol: Preparation, characterization and evaluation. *International Journal of Applied Pharmaceutics*, *12*(1), 42–44.
20. Thenge, R. R. (2012). Crystal modification of aceclofenac by spherical crystallization to improve solubility, dissolution rate and micromeritic properties.*Journal of Pharmacy Research*, *5*(2), 974–977.
21. Vemula, V. R., Lagishetty, V., &Lingala, S. (2010).Solubility enhancement techniques.*International Journal of Pharmaceutical Sciences Review and Research*, *5*(1), 41–51.
22. Yellela, S. R. K. (2010). Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs.*Journal of Bioequivalence & Bioavailability*, *2*(2), 28–36.