

# Design and Preparation of Zaltoprofen-Nicotinamide Pharmaceutical Cocrystals via Liquid Assisted Grinding Method

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## ABSTRACT

**Introduction:** Pharmaceutical cocrystal is an endowed approach to augment solubility and dissolution of drugs with limited aqueous solubility. Zaltoprofen is a nonsteroidal anti-inflammatory drug with prevailing solubility problem. The present study deciphers preparation of cocrystals of lipophilic drug zaltoprofen to improve the solubility and dissolution by screening various cofomers. **Methods:** Cocrystals of zaltoprofen were prepared in 1:1 and 1:2 molar ratio of drug: cofomer by liquid assisted grinding method. The crystalline phase was subjected to evaluation by melting point and solubility. The potential cocrystals were characterized by differential scanning calorimetry (DSC), infrared spectroscopy (IR), powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM). Dissolution rate and stability of cocrystals was also investigated. **Results:** Zaltoprofen-nicotinamide (ZFN-nicotinamide) cocrystals revealed variation in melting point and solubility. Two cocrystals were obtained in 1:1 and 1:2 ratios with nicotinamide. IR spectrum distinctly showed the shifting of typical absorption bands of zaltoprofen. Crystallinity of cocrystals was clear from the PXRD pattern and noteworthy difference in  $2\theta$  value of intense peaks. DSC spectra of cocrystals revealed altered endotherms analogous to melting point. Cocrystals exhibited rapid dissolution rate and 56% increase in the extent of dissolution compared to pure drug. The cocrystals were found stable at stability conditions. SEM revealed difference in the crystal morphology. **Conclusion:** Hence, it can be concluded that ZFN-nicotinamide cocrystal could present an improved drug design approach to surmount dissolution and bioavailability related challenges linked with lipophilic drug zaltoprofen.

**Key words:** Cocrystal, Zaltoprofen, Liquid assisted grinding, Solubility, Dissolution.

## INTRODUCTION

The crucial task in the development of drug product is searching appropriate solid form of an Active Pharmaceutical Ingredient (API) with desired physicochemical properties. The rational approach is a use of solid forms with greater solubility to improve dissolution and bioavailability.<sup>1-5</sup> Amorphous solids, hydrates/solvates, polymorphs and salts have been used conventionally to improve solubility and dissolution. However, amorphous solids or metastable polymorphs of an API possess greater solubility but are thermodynamically unstable in solid

state. Hence, erratic product quality and therapeutic performance may be observed. Therefore, conventional solid forms may not fulfill the need for development of successful product.<sup>6-11</sup>

Pharmaceutical cocrystals have emerged as a way of modifying solubility, dissolution, bioavailability and other physicochemical and pharmacokinetic properties of drug substances, keeping their molecular structure intact. Cocrystal is a stoichiometric multi-component system connected by non-covalent interactions containing two

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distinct components which are solid under ambient conditions. A pharmaceutical cocrystal constitutes an API and benign food or drug grade excipient called as coformer.<sup>12-15</sup>

In the past, various attempts have been made to improve the solubility and dissolution rate of ZFN. The different methods *viz.* nanosuspension, mixed solvency, spherical crystallization were investigated to enhance the solubility of zaltoprofen. In our previous research, pharmaceutical cocrystals of zaltoprofen by neat grinding method were prepared, characterized and reported with improved solubility, dissolution rate and stability profile.<sup>16,17</sup>

Zaltoprofen is a nonsteroidal anti-inflammatory drug belongs to propionic acid class. It is used in the treatment of acute and chronic inflammation and rheumatoid arthritis. Practically, ZFN is insoluble in water and coupled with side effects like ulcerogenicity, belly-ache and indigestion.<sup>18-20</sup> Moreover, it is not possible to enhance the solubility of ZFN via salt formation due to its weakly ionisable nature. Improved bioavailability and fast onset are advantageous for analgesics. Hence there is need to prepare novel solid state forms of ZFN having modified solubility and dissolution rate. Bio-availability of ZFN a BCS class II drug is dissolution rate limited, owing to low solubility and high permeability.<sup>21,22</sup>

Formation of cocrystals appears to be a beneficial strategy in terms of innovation of newer drugs and ease of processing as compared to other approaches to tailor solid state of a crystal.

In the present investigation, cocrystals of ZFN were prepared and characterized with the objective to enhance the solubility and dissolution rate with improved stability profile.

## MATERIALS AND METHODS

### Materials

Zaltoprofen was received as gift sample from ICPA laboratory Ltd. Mumbai (India). All other chemicals were purchased from the SD Fine Chemicals Mumbai (India). Double distilled water was used for the study.

### Preparation of cocrystal

Liquid assisted grinding method was employed to prepare ZFN cocrystals. Drug and coformers were mixed in distinct molar ratio (1:1 and 1:2) in mortar and pestle for 45 min to develop cocrystals. Methanol was added drop wise in very small quantity to moisten the mixture of drug and coformer during grinding. The resultant cocrystals were dried overnight at ambient temperature,

passed through 60 mesh sieve and stored in air tight container until use. The 25 coformers were screened for the preparation of cocrystals *viz.* salicylic acid, nicotinamide, glutaric acid, malonic acid, benzoic acid, tartaric acid, oxalic acid, citric acid, urea, succinic acid, saccharine sodium, Pluronic 68 AR, Magnesium stearate, crotonic acid, P-hydroxy benzoic acid, Caffeine, 3,5 dihydroxy benzoic acid, Piperazine citrate, Cinnamic acid, Adipic acid, Hydroquinone, Isonicotinic acid, Acetamide, Maleic acid, Ascorbic acid.<sup>23,24</sup>

## Evaluation of cocrystals

### Drug content

An accurately weighed quantity of cocrystal equivalent to 10 mg of drug was dissolved in 10 ml volumetric flask in phosphate buffer pH 6.8. The solution was filtered through whatmann filter paper (grade 41), diluted suitably and absorbance of the solution was recorded at 243 nm. (Shimadzu UV 1800).

### Determination of melting point

Digital melting point apparatus (Labtronics Ltd) was used to determine melting point of the compounds.

### Saturation solubility

Solubility was determined by adding excess quantity of pure drug and cocrystals in the 10 ml vials containing distilled water. The vials were agitated on rotary shaker and allowed to stand for equilibration for 24 hr. After 24 hr, samples were filtered, diluted and analyzed at 243 nm by UV Spectrophotometer.<sup>25</sup>

### IR spectroscopy

IR spectroscopy was adopted to find the probable interaction between drug and coformers. Samples were mixed with potassium bromide and compressed into discs before scanning between 4000-400  $\text{cm}^{-1}$  with resolution of 4  $\text{cm}^{-1}$  by shimadzu IR Spectrophotometer.

### Differential scanning calorimetry

The thermal behavior of ZFN and cocrystal was determined on Mettler Toledo DSC 822e Module. Weighed samples were loaded into aluminum pan before crimping and heated at a rate of 5°C/min, covering 0 to 300°C temperature range, under a nitrogen stream. The instrument was calibrated using indium and empty aluminum pan was used as a reference.

### Powder X-ray diffraction

The silicon sample holders were used to get diffraction patterns of pure ZFN and cocrystal (Bruker D8 Advance Diffractometer). The instrument was equipped with a fine focus X-ray tube and each sample was placed

on to a goniometer head that was motorized to permit spinning of the sample during data acquisition.

### Scanning electron microscopy

Particle size and surface morphology of zaltoprofen and Cocrystal was studied using a general scanning electron microscope (JEOL JSM 6360A). Powder samples were sprinkled onto double sided adhesive carbon tape on an aluminium stub. A thin coating of platinum was applied to the sample using an JSC 1600 coater prior to microscopy.

### In vitro dissolution study

ZFN and its cocrystals were subjected to dissolution study by USP type II apparatus (Electrolab, Mumbai, India). Dissolution study was executed in 900 ml of pH 6.8 phosphate buffer at  $37 \pm 0.5^\circ\text{C}$  and 50 rpm for 60 min. The pure drug and cocrystal equivalent to 80 mg of drug was used for the study. The 5 ml of samples were withdrawn after specified time interval and analyzed by UV spectrophotometer at 243 nm.<sup>26,27</sup>

The dissolution profiles of ZFN and cocrystals were compared by similarity factor according to following equation

$$f_2 = 50 \text{ Log} \left\{ \left[ 1 + \frac{1}{n} \sum_{n=1}^n (R_t - T_t)^2 \right]^{-0.5} * 100 \right\}$$

Where  $f_2$  is similarity factor, n is the number of observations,  $R_t$  is the average percentage drug dissolved from reference formulation and  $T_t$  is the average percentage drug dissolved from test formulation. An  $f_2$  value above 50 indicates similarity in two profiles. It lies between 0 and 100.

In addition, the dissolution profiles were statistically analyzed by Dunnet test. Results were considered significant at  $P < 0.05$ .

### Micromeritic studies

Flow properties of an API may be influenced by particle size, shape, size distribution, surface texture, moisture content and other properties. Hence, parameters such as tapped density, bulk density, angle of repose, Carr's index and Hausner's ratio that could give information regarding flow of prepared cocrystals were evaluated.<sup>28</sup>

### Stability study

Stability study of selected cocrystals was performed at room temperature and  $40^\circ\text{C} \pm 20^\circ\text{C}$  with  $75\% \pm 5\%$  RH for 3 months. The sample of 1 gm was placed in epindron tube in stability chamber throughout the stability duration and analyzed after 30 days, 60 days and 90 days interval. The different traits were examined to assess the

stability viz. drug content, melting point, solubility, *in vitro* drug release etc.<sup>29</sup>

## RESULTS AND DISCUSSION

Among various coformers studied, nicotinamide effectively interacted with ZFN to give cocrystals. All the potential cocrystals were preliminary evaluated in terms of melting point and solubility. ZFN-nicotinamide cocrystals were selected for further studies as they demonstrated promising results.

### Drug content

Drug content of ZFN-nicotinamide (1:1 and 1:2) cocrystals was determined in phosphate buffer pH 6.8. Drug content for 1:1 and 1:2 cocrystal was obtained  $99.33 \pm 1.12\%$  and  $95.87 \pm 0.96\%$  respectively. Result indicates drug content was within acceptable limits.

### Melting point and saturation solubility

Melting point and saturation solubility of various potential cocrystals was determined and presented in Table 1. Variable changes in the melting point with different coformers were observed. Melting point of ZFN-nicotinamide cocrystal was reduced which might be due to interaction between ZFN and nicotinamide or formation of new cocrystalline phase with altered physical properties. The drop in the melting point unveiled multicomponent system and designated formation of new cocrystalline phase.

ZFN-nicotinamide cocrystals exhibited notable increase in the solubility as compared to pure drug showing effective interaction between drug and coformer. However, ZFN-nicotinamide 1:1 cocrystal indicated higher solubility ( $3.28 \pm 0.336$  mg/ml) than 1:2 cocrystal ( $1.372 \pm 0.875$  mg/ml). About 149 folds and 63 folds increase in the solubility of ZFN was observed in case of ZFN-nicotinamide 1:1 and 1:2 cocrystals respectively. The improved solubility of cocrystals could be due to formation of cocrystalline phase with altered physical properties viz. solubility. It can be hypothesized that, interaction between oxygen atom of the drug and primary amide hydrogen of the nicotinamide might have formed the cocrystal. Similar studies were reported for cocrystals of glipizide, aceclofenac etc.<sup>26,30</sup>

Based on the results, ZFN:nicotinamide cocrystals were further subjected to evaluation and validated.

### Infrared analysis

IR spectra of zaltoprofen (Figure 1) shows the presence of the characteristic peaks which were recorded at  $1699 \text{ cm}^{-1}$  and  $1668$  for stretching of carboxylic group, -C-S-

**Table 1: Melting point and saturation solubility of cocrystals.**

Drug/Potential cocrystal	Melting point of conformer (°C)	Cocrystal melting point (1:1) (°C)	*Cocrystal solubility (mg/ml) (1:1)	Cocrystal melting point (1:2) (°C)	*Cocrystal solubility (mg/ml) (1:2)
Zaltoprofen	133-135		0.022±0.005		
ZFN-Salicylic acid	158-159	134	0.045±0.013	139.5	0.512±0.098
ZFN-Nicotinamide	122-124	118.5	3.28±0.336	112.5	1.372±0.875
ZFN-Glutaric acid	96	117.5	0.045±0.005	114	0.036±0.013
ZFN-Malonic acid	130	114	0.012±0.003	111	0.0091±0.002
ZFN-Benzoic acid	122	107.5	0.310±0.132	101	0.414±0.099
ZFN-Tartaric acid	164-167	137	0.202±0.082	151	0.0091±0.067
ZFN-Oxalic acid	99	116	0.024±0.002	120.5	0.025±0.013
ZFN-Citric acid	148-150	140.5	0.0098±0.005	138	0.010±0.087
ZFN- Urea	131	132	0.112±0.072	130.5	0.219±0.068
ZFN-Succinic acid	184	158.5	0.010±0.009	155	0.011±0.008
ZFN-Sodium saccharine	226-230	143.5	0.247±0.087	137	0.227±0.090
ZFN-Pluronic 68 AR	53-54	-	0.075±0.001	64.5	0.096±0.031
ZFN-Magnesium stearate	88.5	97	0.477±0.099	94	0.426±0.110
ZFN-Crotonic acid	74-75	105	1.834±0.512	94.5	0.079±0.028
ZFN-P-hydroxy benzoic acid	208	156	0.692±0.068	172	1.041±0.473
ZFN-Caffeine	238	154.5	0.678±0.078	172	0.546±0.120
ZFN-3,5-dihydroxy benzoic acid	236-238	183	0.339±0.054	186	0.297±0.098
ZFN-Piperazine citrate	183-187 °C	198	0.224±0.045	199.5	0.184±0.065
ZFN- Cinnamic acid	132-134	110	0.430±0.055	118.5	0.660±0.192
ZFN-Adipic acid	151-154	132	0.022±0.008	141	0.015±0.008
ZFN- Hydroquinone	172.3	128.5	0.091±0.009	139	0.111±0.067
ZFN-Isonicotinic acid	310	268	0.103±0.067	271	0.237±0.079
ZFN-Acetamide	79-81	70	0.025±0.004	106	0.016±0.008
ZFN- Maleic acid	135	134	0.058±0.008	124.5	0.088±0.029
ZFN- Ascorbic acid	190	163	0.017±0.003	154	0.067±0.012

\*Results are expressed as mean±standard deviation (n=3)

C- aromatic stretching peaks observed at 939.39 cm<sup>-1</sup>, OH stretching in carboxylic group at 2950 cm<sup>-1</sup> and CH<sub>3</sub> stretching at 1330 cm<sup>-1</sup>. The IR spectrum of nicotinamide revealed an absorption band at 3145 cm<sup>-1</sup> for NH<sub>2</sub> stretching of primary amide, 3342 cm<sup>-1</sup> for pyridine ring region, NH bending is observed at 1593cm<sup>-1</sup> and aromatic C=C peaks observed at 1614 cm<sup>-1</sup>. These spectra are in good agreement with the published data.

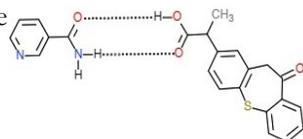
The IR bands were significantly shifted in the cocrystal in comparison to pure drug and coformer indicating interaction between drug and coformer. (Table 2)

The new peak was observed in the both cocrystal spectra at 3450 cm<sup>-1</sup> supporting the formation of cocrystal. The peak at 3450 cm<sup>-1</sup> may be due to formation of intermolecular hydrogen bond between hydrogen of

**Table 2: Vibrational peaks of drug, coformer and cocrystal.**

Sample	IR peaks
Zaltoprofen	COOH stretching-1699 and 1668 cm <sup>-1</sup> OH stretching – 2950 cm <sup>-1</sup>
Nicotinamide	NH <sub>2</sub> stretching primary amide 3145 cm <sup>-1</sup> NH bending 1593cm <sup>-1</sup>
ZFN-nicotinamide 1:1 cocrystal	COOH stretching-1623 cm <sup>-1</sup> OH stretching – 2900 cm <sup>-1</sup> NH <sub>2</sub> stretching primary amide 3200 cm <sup>-1</sup> NH bending 1583cm <sup>-1</sup>
ZFN-nicotinamide 1:2 cocrystal	COOH stretching-1653 cm <sup>-1</sup> OH stretching – 3000 cm <sup>-1</sup> NH <sub>2</sub> stretching primary amide 3300 cm <sup>-1</sup> NH bending 1593cm <sup>-1</sup>

primary amide N-H and oxygen atom in the drug. Possible structure



Similar changes in the IR spectrum of other drug like meloxicam, hydrochlorothiazide were reported and taken as signal of the cocrystal formation.<sup>31,32</sup> Changes in the IR peaks of fenofibrate were used to signal the formation of cocrystal of fenofibrate with nicotinamide. The changes were attributed to possible hydrogen bonding interaction between drug and coformer. Formation of cocrystal was also authenticated in case of nevirapine cocrystal by changes in IR peak intensities.<sup>33,34</sup>

### Differential scanning calorimetry

Thermal behavior of ZFN, nicotinamide and ZFN-nicotinamide cocrystals was studied by DSC. (Figure 2) The observed melting endotherm for ZFN was obtained at 137.69°C whereas 129.67°C for nicotinamide. Similar thermal results were reported for ZFN and nicotinamide. In case of ZFN-nicotinamide (1:1 and 1:2) cocrystals melting point of ZFN has shifted lower and observed at 109.59°C and 122.66°C respectively. Moreover, the peak onset for ZFN was obtained at 131.52°C whereas ZFN-nicotinamide cocrystals (1:1 and 1:2) exhibited peak onset at 103.28°C and 110.61°C which indicates possibility of formation of the cocrystal. Hence, the present study shows formation of cocrystal as evident from the altered thermal properties which was reported as sign for cocrystal formation. Initial regions of thermogram did not contain any desolvation peak indicating no possibility of formation of solvates or hydrate.<sup>35</sup> Cocrystals of irbesartan with chitosan were confirmed by DSC and reported. Results of DSC indicated the cocrystals were present in crystalline state and supported the formation of cocrystal.<sup>36</sup>

### Powder X-ray diffraction

The fingerprint method to evaluate solid forms is PXRD. The diffractogram of ZFN and nicotinamide exhibited characteristic intense diffraction peaks at various 2θ values showing the crystalline nature. (Table 3) The cocrystals showed different extent of crystallinity. The PXRD pattern of the cocrystals was different from the ZFN or nicotinamide and some additional diffraction peaks were appeared which were not present in the drug or coformer (Figure 3). Hence, appearance of new diffraction peaks signals the formation of new crystalline phase. Cocrystal formation based on the PXRD

pattern is well established.<sup>37</sup> Drug-drug cocrystals of apremilast an antipsoriasis drug with nicotinamide, caffeine and salicylic acid coformers were reported. The PXRD pattern of cocrystal was different from the pure drug and used to validate formation of new cocrystal.<sup>38</sup>

### Scanning electron microscopy

Surface morphology of ZFN, nicotinamide and cocrystals was studied by SEM and presented in Figure 4. ZFN showed irregular shaped crystals whereas nicotinamide exhibited rod like structure. Thread like structure of cocrystals was observed indicating the crystallinity. The substantial enhancement in crystallinity supports the formation of cocrystal.<sup>24</sup>

### In vitro dissolution study

The dissolution profile of the ZFN and the prepared cocrystals is reported in Figure 5. The dissolution profile of ZFN indicates slow dissolution rate and total amount of drug dissolved in 60 min was 43.82%. The calculated dissolution efficiency was only 27.4%. However, cocrystals of the ZFN resulted in substantial increase in the dissolution rate. All the cocrystals exhibited complete drug release within 60 min. The maximum amount dissolved was 99.47% for 1:1 cocrystal with dissolution efficiency of 86.71%. Formation of cocrystal has been well established as an efficient technique for dissolution enhancement. The similarity factor test denotes the dissolution of ZFN was dissimilar to the prepared cocrystals ( $f_2$  value 15 and 20 for 1:1 and 1:2 cocrystals respectively).<sup>39</sup>

The result was compared by Dunnet test and statistically significant difference in the dissolution of cocrystals and ZFN was obtained ( $P < 0.05$ ).

### Micromeritic characterization

It was evident from the results that, flow properties of cocrystals were better as compared to pure ZFN. The

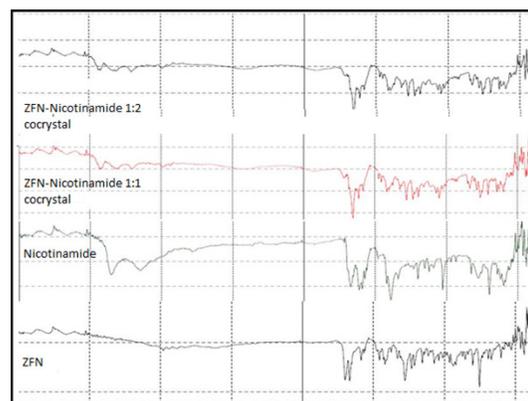


Figure 1: Overlay IR spectra of ZFN, nicotinamide and cocrystals.

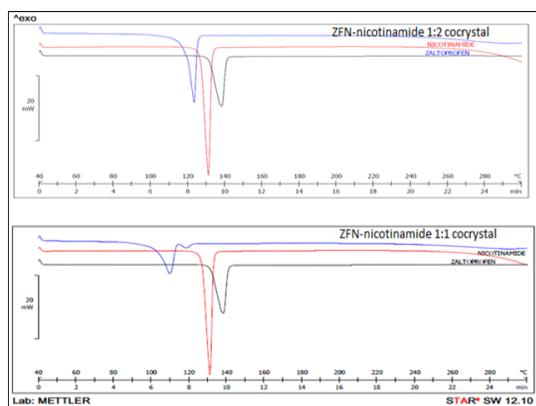


Figure 2: DSC thermograms of zaltopfen, nicotinamide and cocrystals.

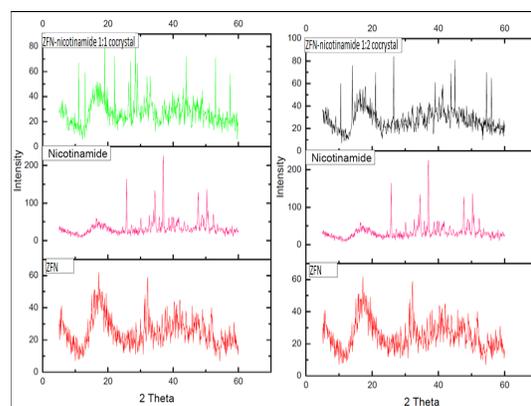


Figure 3: PXRD pattern of zaltopfen, nicotinamide and cocrystals.

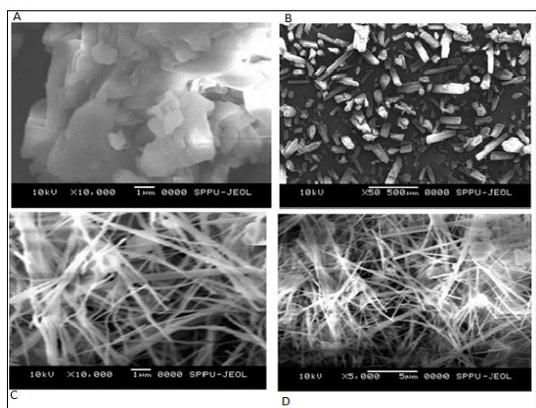


Figure 4: SEM images of Zaltopfen (A), Nicotinamide (B), ZFN-nicotinamide 1:1 cocrystal (C) and ZFN-nicotinamide 1:2 cocrystal (D).

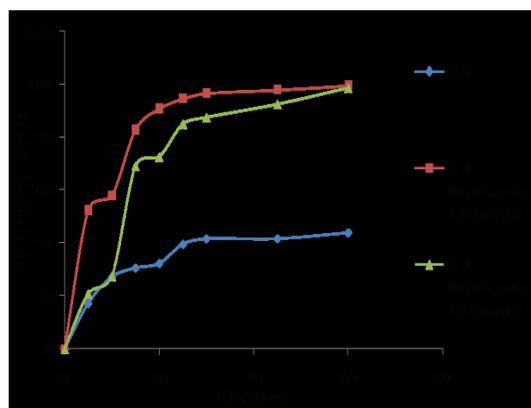


Figure 5: Dissolution study of drug and cocrystal.

Table 3: PXRD diffraction peaks.	
Drug/coformer/Cocrystal	2θ values
Zaltopfen	15, 17.5, 19, 31, 32.5, 42
Nicotinamide	25, 30, 34.5, 37, 47.5, 50.5
ZFN-nicotinamide 1:1 Cocrystal	11, 13, 19, 22, 27, 28.5, 29, 44, 53, 57.5
ZFN-nicotinamide 1:2 Cocrystal	10.5, 14, 18, 21, 26.5, 39, 43.8, 45, 54.5, 56

values of angle of repose, Carr’s index and Hausner’s ratio were greater for ZFN indicating the poor flow. However, the values of these parameters were lowered for cocrystals showing improved flow properties in comparison to pure ZFN (Table 4). This showed the potential of cocrystals to tailor the flow properties.<sup>40</sup>

**Stability study**

During storage, solubility and dissolution of cocrystals may be altered owing to change in crystallinity. Hence, stable cocrystals with greater dissolution rate are desirable. Accordingly, drug and cocrystals were subjected to stability study at room temperature and accelerated conditions for three months to assess the stability of

cocrystals. Cocrystals were found stable at both storage conditions and no substantial change in the estimated parameters like melting point, solubility, *in vitro* drug release and drug content was obtained.<sup>41</sup> (Table 5)

**CONCLUSION**

Pharmaceutical cocrystals of ZFN were prepared with nicotinamide by liquid assisted grinding method. Cocrystal formation was validated by DSC, IR and PXRD which jointly supported each other. SEM also revealed crystallinity supporting the formation of cocrystals. The newly prepared cocrystals exhibited higher solubility and dissolution as compared to ZFN and found stable. Cocrystals also showed potential to enhance the micromeritic characteristics. Hence, cocrystals could provide alternative drug design strategy to conquer dissolution and bioavailability pertaining problems linked with poorly soluble ZFN. However, further correlation with *in vivo* studies will be required.

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Table 4: Micromeritic properties.

Sample	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
Pure drug	0.35±0.17	0.47±0.09	30.72±0.49	27.84±0.88	1.38±0.15
ZFN-nicotinamide 1:1 cocrystal	0.48±0.19	0.57±0.23	22.24±0.75	14.72±0.67	1.17±0.35
ZFN-nicotinamide 1:2 cocrystal	0.50±0.29	0.62±0.43	24.28±0.45	15.12±0.62	1.21±0.55

Results are expressed as mean±standard deviation (n=3)

Table 5: Stability study.

Parameters	Zaltoprofen (RT)*	Zaltoprofen (AT)*	Cocrystal (RT)*		Cocrystal (AT)*	
			1:1	1:2	1:1	1:2
Melting point (°C)	131-134	132-134	117-118	110-114	116-117	113-117
Solubility (mg/ml)	0.0131	0.01445	2.162	1.296	2.148	1.149
In vitro dissolution (%)	63.63	64.06	99.47	98.04	99.48	99.79
Drug content	-	-	99.96	95.15	99.99	95.02

\*RT – Room temperature, AT- Accelerated temperature

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## ABBREVIATIONS

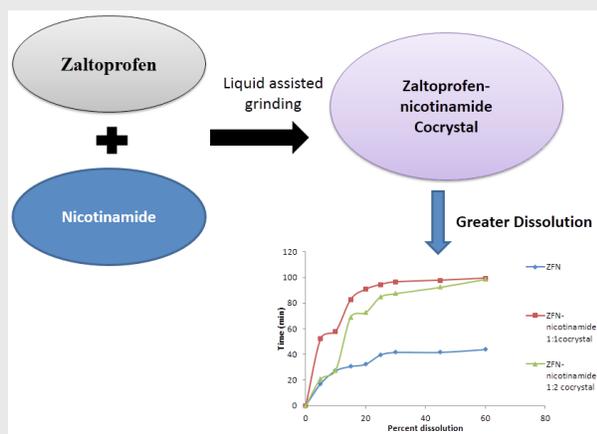
**ZFN:** Zaltoprofen, **IR:** Infrared spectroscopy, **DSC:** Differential scanning calorimetry, **SEM:** Scanning electron microscopy; **PXRD:** Powder x-ray diffraction.

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## PICTORIAL ABSTRACT



## SUMMARY

Pharmaceutical cocrysal of zaltopfen were successfully prepared with nicotinamide cofomer in 1:1 and 1:2 ratio using liquid assisted grinding method. The changes in melting point and solubility provided initial clue regarding cocrysal formation. The formation of cocrysal was further validated by alteration in IR, DSC, PXRD and SEM. The ZFN-nicotinamide cocrysal exhibited improved solubility and dissolution as compared to pure drug.

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