Superior solubility and dissolution of zaltoprofen via pharmaceutical cocrystal

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Abstract

Objective: Pharmaceutical cocrystal is a promising tool to enhance solubility and dissolution of poorly soluble drugs. Zaltoprofen (ZFN) is nonsteroidal anti-inflammatory drug with prevalent solubility problem. The present study was undertaken to enhance the solubility and dissolution of zaltoprofen through pharmaceutical cocrystal by screening various coformers.

Materials and Methods: Cocrystals of zaltoprofen were prepared in 1:1 and 1:2 ratio of drug:coformer by dry grinding method. The melting point and solubility of crystalline phase was determined. The potential cocrystals were characterized by differential scanning calorimetry (DSC), infrared spectroscopy (IR) and powder X-ray diffraction (PXRD). Corystals were subjected to dissolution rate and stability study.

Results: Zaltoprofen-nicotinamide (ZFN-NIC) Cocrystals demonstrated deviation in melting point and solubility. The cocrystals were obtained in both 1:1 and 1:2 ratio with nicotinamide. The analysis of Infrared noticeably indicated the shifting of characteristic bands of zaltoprofen. Crystallinity of cocrystals was evident from the XRPD pattern and notable difference in 2θ value of intense peaks. DSC spectra of cocrystals exhibited altered endotherms analogous to melting point. Cocrystals showed faster dissolution rate and 55% increase in the extent of dissolution compared to pure drug. The cocrystals were found stable at room temperature and accelerated conditions.

Conclusion: The prepared cocrystals exhibited greater solubility and dissolution as compared to pure drug and found stable at room temperature and accelerated conditions.

Key words: Pharmaceutical cocrystal; zaltoprofen; solubility; dissolution.

INTRODUCTION

After oral administration solubility and dissolution rate of drug is crucial factor for sufficient bioavailability of drug. This factor offers main challenge to the formulation scientist for the development and formulation of effective drug. More than 40% of drugs in the development suffers from bioavailability problems owing to poor solubility. Alternative strategies have been introduced to enhance solubility, dissolution rate and bioavailability. These involves salt formation, solid dispersion, cyclodextrin complexation, microemulsification, solubilization, micronization etc.[1-4]

Recently pharmaceutical cocrystals attracted massive attention of formulation experts busy in the formulation development. Due to inherent thermodynamic stability of crystalline active pharmaceutical ingredients (API), these are preferred in pharmaceutical industry. Pharmaceutical cocrystals have emerged as effective tool to tailor the physical properties of API like solubility and dissolution along with stability. The principal advantage of this technique is pharmacological effect of drug remain unchanged.[5-7] Cocrystals are defined as stoichiometric multi-component system united by non-covalent interactions in which two diverse components are solid under ambient conditions. Documented advantages of cocrystals are improved stability against humidity, chemical stability, improved dissolution and bioavaialability and tabletability. Various methods were studied to enhance solubility like hydrotropy, solid dispersion etc. Probably pharmaceutical cocrystals of ZFN have not been reported till date.[8-14]

Zaltoprofen is a nonsteroidal anti-inflammatory propionic acid class drug.It is used in the treatment of acute and chronic inflammation and in the treatment of rheumatoid arthritis. It is practically insoluble in water and associated with side effects like ulcerogenicity, bellyache and indigestion. Moreover, ZFN is weakly ionisable so salt formation is impossible to enhance the solubility of drug. Rapid onset and improved

bioavailability are enviable for analgesics. Hence there is strong scientific and clinical need to prepare novel forms of ZFN possessing modified solubility and dissolution rate which can be formulated for oral administration. Accordingly the present study was aimed to prepare novel pharmaceutical cocrystals of ZFN with improved solubility and dissolution.[15,16]

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 throughout the research.

Preparation of cocrystal

Dry grinding method was adopted for the preparation of ZFN cocrystals. Drug and coformers were mixed in different molar ratio (1:1 and 1:2) in mortar and pestle for 45 min to form cocrystals. This was dried an overnight at ambient temperature and stored in tight containers.[17] 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.

Evaluation of corystals

Drug content

The cocrystal powder equivalent to 10 mg of drug was accurately weighed and dissolved in 10 ml volumetric flask and volume was adjusted with phosphate buffer pH 6.8. The resulting solution was filtered, suitably diluted and absorbance of the solution was measured at 243 nm.[18] (Shimadzu UV 1800)

Determination of melting point

Melting point of the compounds were determined using digital melting point apparatus (Labtronics Ltd).

Saturation solubility

Excess amount of pure drug and cocrystals were dissolved in the 10 ml vials containing drug to estimate solubility. The vials were agitated on rotary shaker and allowed to stand for equilibration for 24 hrs. The samples were filtered after 24 hrs, suitably diluted with distilled water and analyzed by UV Spectrophotometer at 243 nm.

IR spectroscopy

IR spectroscopy was employed to determine the possible interaction between drug and coformers. Samples were mixed with potassium bromide and compressed into discs before scanning between 4000-400 cm-1 with resolution of 4 cm-1 by shimadzu IR Spectrophotometer.

Differential scanning calorimetry

The thermal behavior of drug alone 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 utilized 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.

In vitro dissolution study

Pure ZFN and its cocrystals were subjected to dissolution study by USP type II apparatus (Electrolab, Mumbai, India). Dissolution study was performed in 900 ml of pH 6.8 phosphate buffer at 37±0.5°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.[19]

Stability study

The selected cocrystals were subjected to stability study at room temperature and 400C ± 20C with 75% ± 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 attributes were studied to

assess the stability viz. drug content, melting point, solubility, in vitro drug release etc.

RESULTS AND DISCUSSION

The 25 coformers were screened to prepare cocrystal with ZFN by dry grinding method. The coformers were selected based on the literature survey and to increase the chances of formation of number of new cocrystals. Among various coformers studied nicotinamide successfully interacted with ZFN, giving novel cocrystal forms. The obtained ZFN cocrystals were subjected to evaluation and stability study.

Drug content

Drug content of ZFN-NIC 1:1 and 1:2 cocrystals was determined in the phosphate buffer pH 6.8 and obtained 95.87±0.98% and 95.88±1.10% respectively.

Melting point and saturation solubility

Melting points of pure drug, coformers and cocrystals were estimated and reported in Table 1. In addition saturation solubility of pure drug and cocrystals was also determined and reported in Table 1. These parameters were used as preliminary screen for cocrystal. Melting points of the ZFN-NIC cocrystals were lower than the pure drug. This may be attributed to multicomponent system and probable formation of cocrystals. The altered melting points might be due to interaction between zaltoprofen and nicotinamide, modified crystallinity of molecules or distinct packing arrangement. This interaction results in altered molecular arrangement which lead to novel crystal forms with distinct physical properties.[20, 21]

Solubility of few cocrystals was improved but ZFN-NIC cocrystals exhibited remarkable increase in solubility indicating successful interaction of drug and coformer. However greater solubility was obtained with ZFN-NIC 1:2 cocrystals (1.516±0.467 mg/ml) than 1:1 (0.926±0.134 mg/ml). The ZFN-NIC 1:1 and 1:2 cocrystals showed 42 folds and 66 folds increase in solubility in comparison to pure drug. The results were compared by Dunnet test and indicates statistically significant differences in solubility ($P<0.05$) between pure drug and cocrystals. This indicates interaction between ZFN and nicotinamide leading to formation of cocrystal. The interaction between oxygen atom of the drug and primary amide hydrogen of the nicotinamide might have formed the cocrystal. The similar studies were reported for cocrystals of meloxicam, lornoxicam, aceclofenac etc.[22,23]

On the basis of results ZFN-NIC 1:1 and 1:2 cocrystals were further characterized and confirmed.

Table 1: Melting point and solubility of cocrystals

Drug/Potential cocrystal	Melting point of coformer(°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	133.5	0.452±0.078	135	0.445±0.095
ZFN-Nicotinamide	122-124	128	0.926±0.134	121	1.516±0.467
ZFN-Glutaric acid	96	119.5	0.0136±0.0089	120.5	0.0819±0.023
ZFN-Malonic acid	130	113.5	0.0083±0.093	116.5	0.0077±0.001
ZFN-Benzoic acid	122	103	0.416±0.098	100	0.721±0.278
ZFN-Tartaric acid	164-167	146.5	0.0218±0.013	146.5	0.0103±0.008
ZFN-Oxalic acid	99	117	0.0147±0.017	115.5	0.0261±0.009
ZFN-Citric acid	148-150	135.5	0.0098±0.00097	134.5	0.0080±0.002
ZFN- Urea	131	129.5	0.367±0.067	128.5	0.228±0.090
ZFN-Succinic acid	184	152	0.0287±0.008	153	0.0210±0.007
ZFN-Sodium saccharine	226-230	126.5	0.154±0.069	181	0.207±0.067

ZFN-Pluronic 68 AR	53-54	65.5	0.152±0.089	62.5	0.139±0.083
ZFN-Magnesium stearate	88.5	91.5	0.761±0.284	126.5	0.536±0.132
ZFN-Crotonic acid	74-75	124	0.064±0.016	95	0.0714±0.021
ZFN-Phydroxy benzoic acid	208	160	0.820±0.349	164.5	0.980±0.230
ZFN-Caffeine	238	175.5	0.354±0.078	152	0.435±0.098
ZFN-3,5 dihydroxy benzoic acid	236-238	184.5	0.256±0.086	187.5	0.372±0.068
ZFN-Piperazine citrate	183-187 °C	197	0.160±0.067	199.5	0.179±0.043
ZFN- Cinnamic acid	132-134	113	0.339±0.129	117.5	0.440±0.065
ZFN-Adipic acid	151-154	141	0.0282±0.009	143	0.0202±0.009
ZFN-Hydroquinone	172.3	123.5	0.109±0.008	124.5	0.0597±0.006
ZFN-Isonicotinic acid	310	284	0.0950±0.021	292	0.103±0.089
ZFN-Acetamide	79-81	98.5	0.0246±0.026	92	0.0232±0.007
ZFN- Maleic acid	135	124.5	0.0700±0.039	130.5	0.0785±0.013
ZFN- Ascorbic acid	190	158	0.0593±0.009	160	0.0525±0.013

*Average of three determinations Mean±SD

IR spectroscopy

The IR spectrum for pure drug, coformer and ZFN cocrystals was recorded and shown in Figure 1 and 2. The principle bands were identified and related changes were recorded. The IR spectrum of pure ZFN shows the presence of the characteristic peaks which were recorded at 1699 cm-1 and 1668 for stretching of carboxylic group, –C-S-C- aromatic streching peaks observed at 939.39 cm-1, OH stretching in carboxylic group at 2950 cm-1 and CH3 stretching at 1330 cm-1. The IR

spectrum of nicotinamide revealed an absorption band at 3145 cm-1 for NH2 stretching of primary amide, 3342 cm-1 for pyridine ring region, NH bending is observed at 1593cm-1 and aromatic C=C peaks observed at 1614 cm-1. These spectra are in good agreement with the published data. The IR bands were significantly changed in the cocrystal in comparison to pure drug and coformer indicating interaction between drug and coformer. [24]

In case of 1:1 cocrystal changes were observed in the peaks corresponding to carboxylic group stretching which was observed at 1634 cm-1, OH stretching at 3000 cm-1 in comparison to drug and NH2 stretch and NH bending at 3450 and 1583 cm-1as compared to nicotinmaide whereas 1654 cm-1, 3000 cm-1, 3300 cm-1 and 1583 cm-1 for 1:2 cocrystal respectively.

The new peak at 3450 cm-1 and 3400 cm-1 was observed indicating formation of hydrogen bond between drug and coformer in the ZFN-nicotinamide 1:1 and 1:2 cocrystal prepared by neat grinding method respectively.[25]

Similar changes in the IR spectrum of other drugs like piroxicam, hydrochlorothiazide were reported and taken as sign of the cocrystal formation.[26-27] Hence the changes recorded in the study can be taken as a indicator of the cocrystal formation between the drug and coformer.

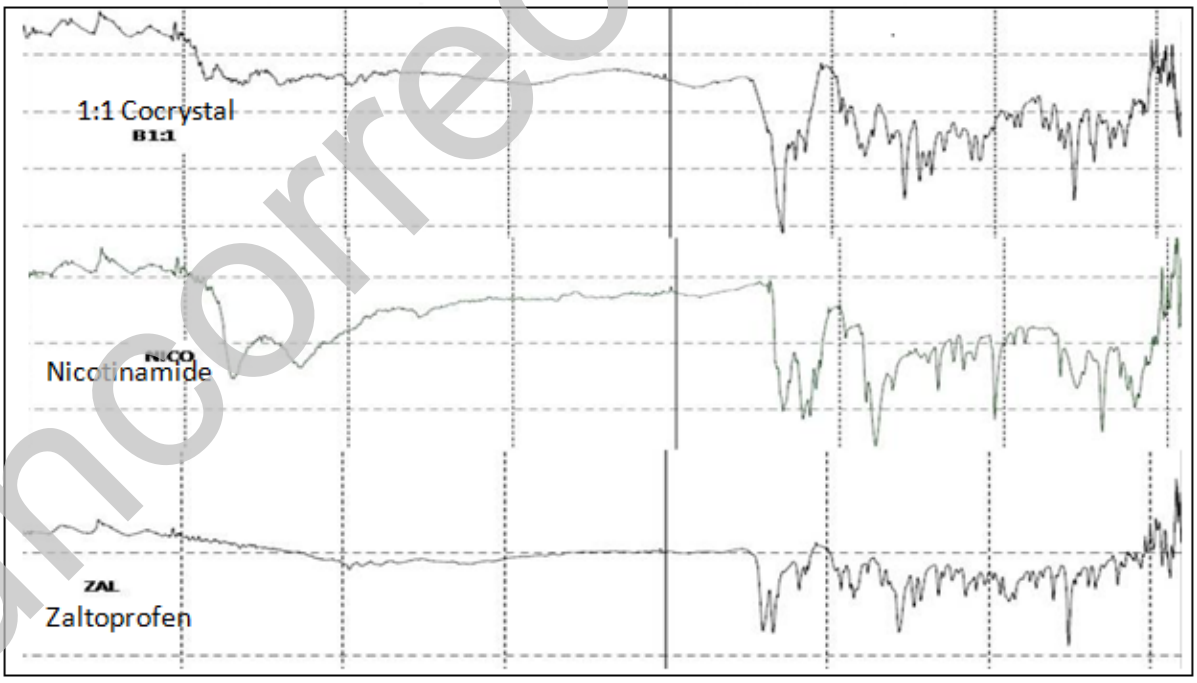

Figure 1: Overlay IR spectra of 1:1 cocrystal

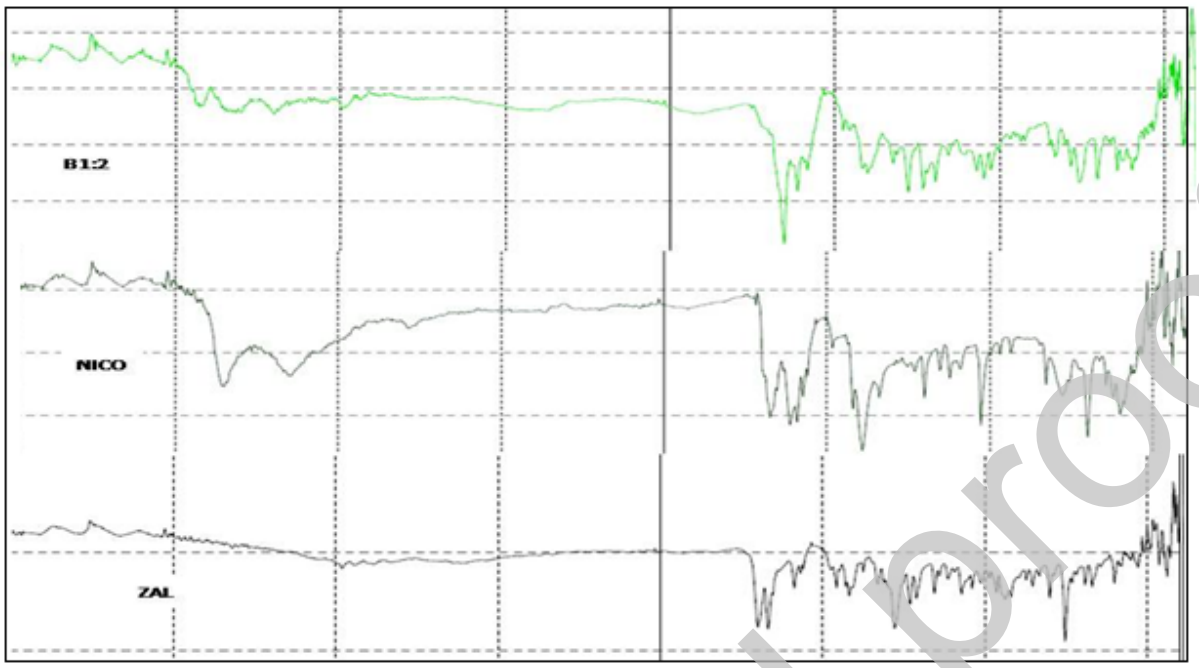

Figure 2: Overlay IR spectra of 1:2 cocrystal

Differential scanning calorimetry

ZFN, nicotinamide and ZFN-NIC cocrystals were characterized by DSC. The pure drug and nicotinamide showed characteristic endothermic peak at 137.69 °C and 129.67 °C respectively corresponding to their melting point. Similar thermal behavior was reported for the drug and coformer.[28]

ZFN-NIC (1:1 and 1:2) cocrystals exhibited melting point at 109.20°C and 123.50°C respectively which is significantly different from the pure drug. Moreover, the peak onset for pure drug was obtained at 131.52°C whereas 102.40°C and 120.02°C for 1:1 and 1:2 cocrystals respectively.

The changes in the thermal properties were reported as evidence for the formation of cocrystal.[29] Hence the present investigation indicates the formation of cocrystal. (Figure 3)

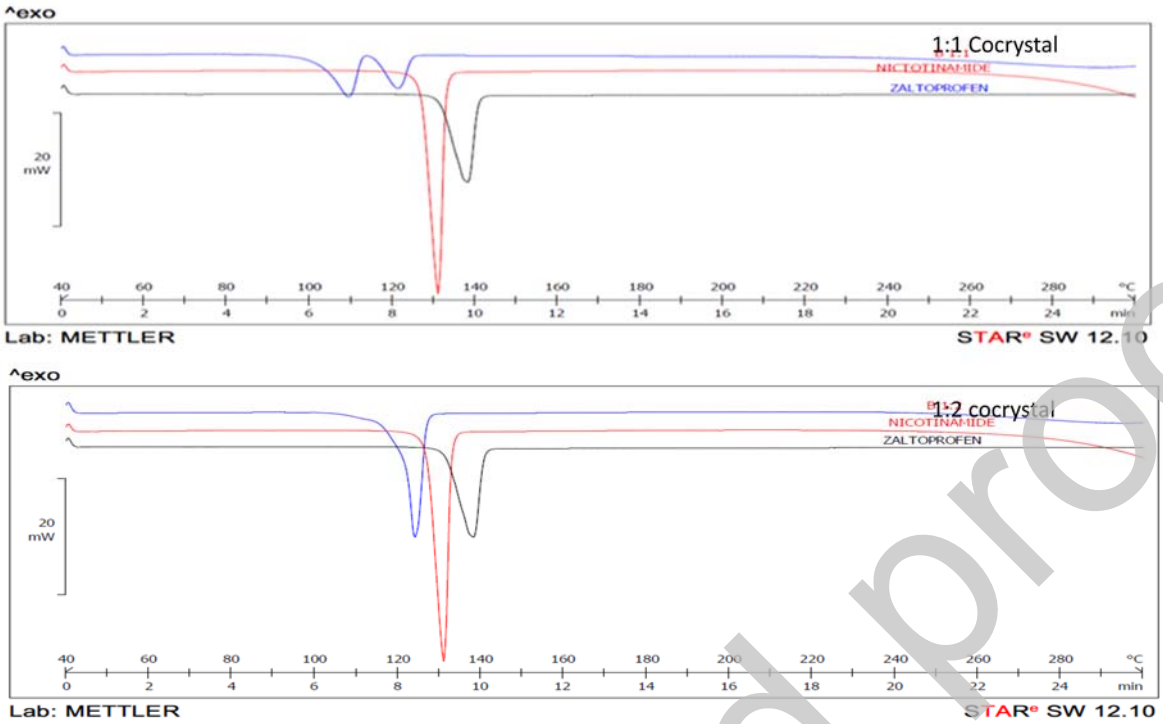

Figure 3: Overlay DSC thermogram of 1:1 and 1:2 cocrystals

Powder X-ray diffraction

The PXRD patterns for ZFN, nicotinamide and ZFN-NIC cocrystals are shown in Figure 4 and 5. The materials in the powder state give different peaks of varying intensities at certain positions. The diffractogram of the ZFN showed characteristic numerous sharp, intense diffraction peaks at different 2θ values (15, 17.5, 19, 31, 32.5, 42) indicating the crystalline nature. In addition diffraction peaks obtained for nicotinamide were 25, 30, 34.5, 37, 47.5, 50.5 2θ values. Similar diffraction pattern was reported in the previous investigations. The PXRD pattern of the cocrystal was distinguishable from its components and some additional diffraction peaks were appeared which did not exist in the pure drug or coformer. The additional diffraction peaks for 1:1 and 1:2 cocrystals were obtained at 2θ values 16, 17, 18, 19, 20, 30.5, 37.5 and 17.5, 18.5, 26.5, 34.5, 37.5, 40.5, 50.5 respectively. The appearance of new diffraction peaks in the diffractogram of cocrystal shows formation of new crystalline phase (cocrystal). The formation of cocrystals based on the PXRD pattern were reported which showed new peaks that differ from the peaks corresponding to its input components.[30,31]

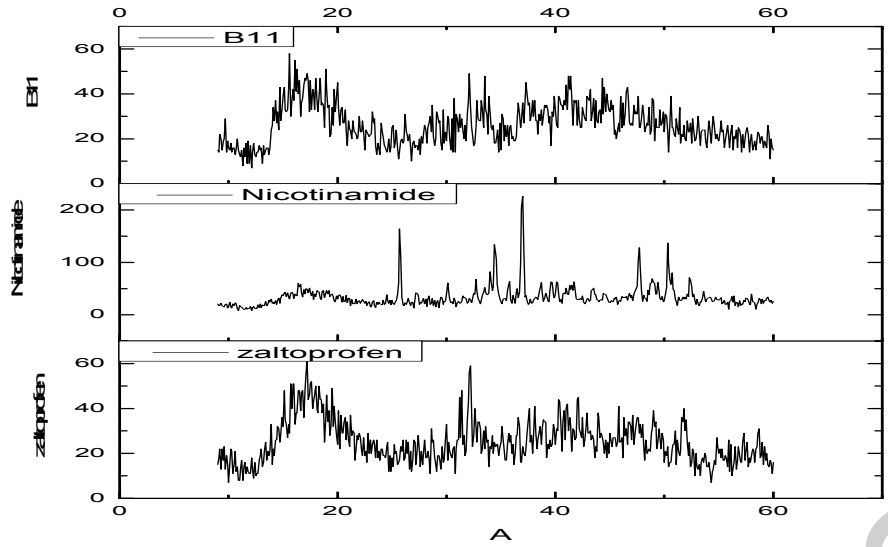

Figure 4: Overlay PXRD pattern for 1:1 cocrystal

B11 (1:1 cocrystal)

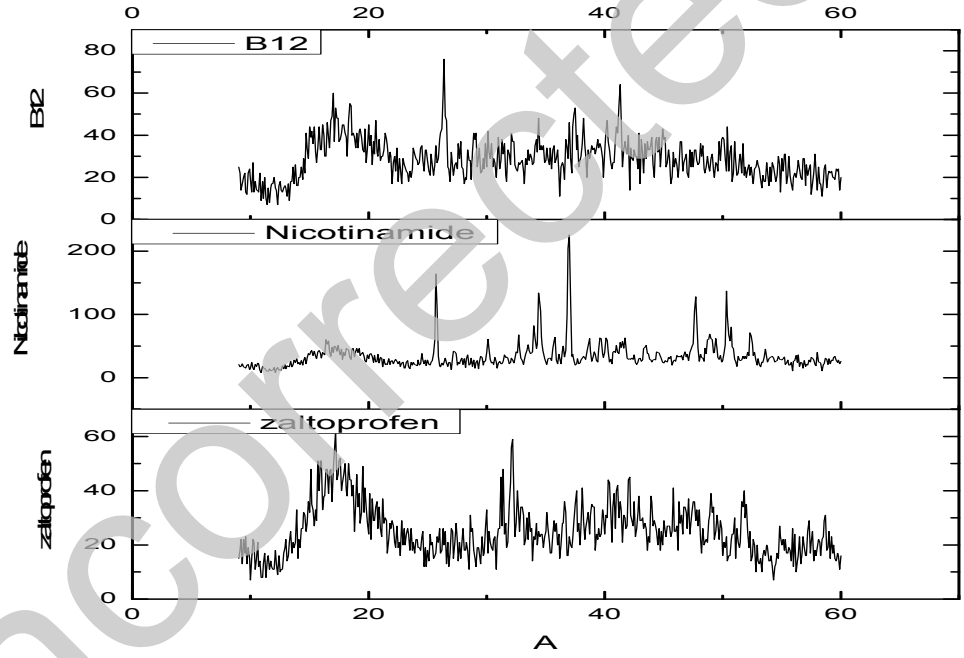

Figure 5: Overlay PXRD pattern for 1:2 cocrystal

B12 (1:2 cocrystal)

In vitro dissolution study

The dissolution rate plays crucial role in the bioavailability of drugs with poor solubility. The dissolution experiment was conducted on the pure drug and

cocrystals. The dissolution profile of the pure drug and the prepared cocrystals is shown in Figure 6. The dissolution profile of pure drug indicates slow dissolution rate with only 27.17±0.89% of the drug being dissolved in the first 10 min. The total amount of drug dissolved in 60 min was 43.82±1.06% and calculated dissolution efficiency was only 27.4%. However cocrystals of the ZFN resulted in substantial increase in the dissolution rate. The amount of drug dissolved in first 10 min was 50.66±0.32% and 46.67±0.65% for 1:1 and 1:2 cocrystals respectively. The maximum amount of drug dissolved was 98.89±0.48% for 1:2 cocrystal with dissolution efficiency of 86.71% whereas 94.14±0.91% for 1:1 cocrystal having dissolution efficiency of 81.78%. This can indicate the weaker crystalline structure of the formed cocrystal as evident from higher dissolution rate. Moreover greater dissolution of ZFN from cocrystal can be attributed to enhanced solubility of cocrystal in the dissolution media. Cocrystallization had been well documented as a competent technique for dissolution enhancement.[32] The similarity factor test denotes the dissolution of pure drug was dissimilar to the prepared cocrystals (F2 value 20% and 22% for 1:1 and 1:2 cocrystal).

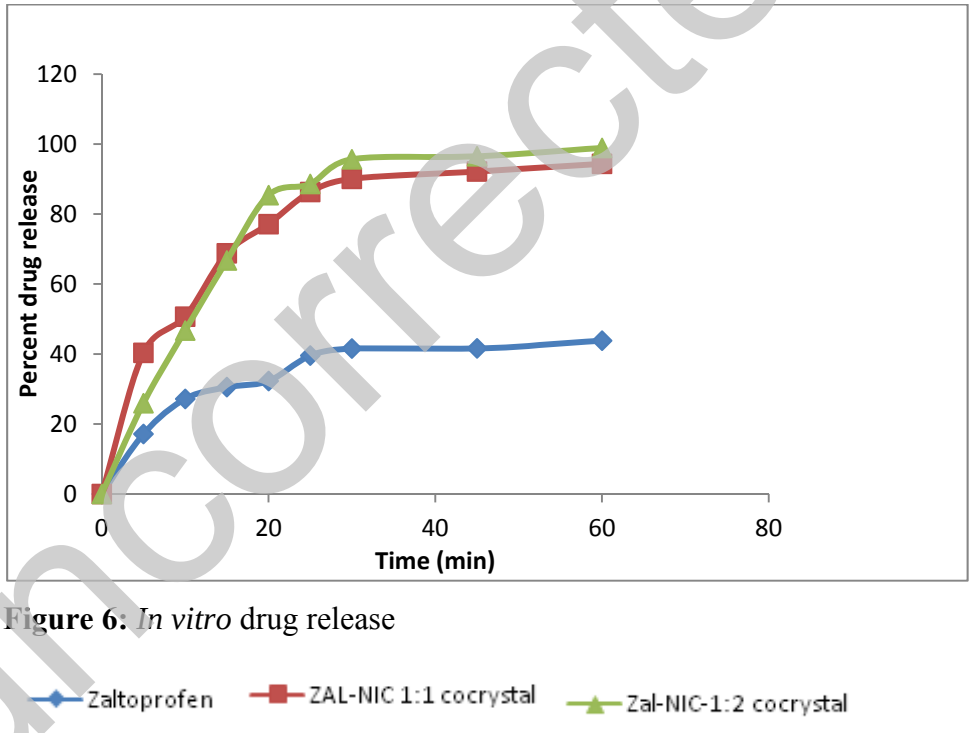

Figure 6: *In vitro* drug release

Stability study

Drug and cocrystals were subjected to stability study at room temperature and accelerated conditions for three months to assess the stability of cocrystals. All the

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 except ZFN:NIC 1:2 cocrystal solubility at accelerated conditions. However pure drug exhibited changes in the solubility and percent dissolution during stability period indicating instability. Hence the cocrystals stability was enhanced in comparison to pure drug. This demonstrates the potential of cocrystals to improve the stability of drug. Similar studies have been reported for theophylline.[33] The results are given in Table 2.

Table 2: Stability study of cocrystals

Parameters	**Sampling**	**Zaltoprofen (Accelerated)**	**Zaltoprofen (Room temperature)**	**Cocrystal Neat grinding (Accelerated)**		**Cocrystal Neat grinding (Room temperature)**	
				1:1	**1:2**	**1:1**	**1:2**
Melting point (^{0}C)	Initial	133-134	133-134	111-114	120-121	111-114	120-121
	1 month	133-134	133-135	114-115	115-117	116-117	124-126
	2 month	132-133	131-133	115-118	117	116-118	115-117
	3 month	132-134	131-134	114-116	116	115-116	116-118
Solubility (mg/ml)	Initial	0.01513	0.0151	0.926	1.516	0.9261	1.516
	1 month	0.01518	0.0131	1.016	1.202	1.077	1.159
	2 month	0.01464	0.0136	1.126	1.268	1.126	1.308
	3 month	0.01445	0.0131	0.913	1.070	1.020	1.149
In-vitro dissolution (%)	Initial	52.01	52.01	98.32	98.89	98.32	98.89
	1 month	64.76	65.49	98.78	94.51	99.26	99.45
	2 month	64.81	64.81	98.74	98.39	98.74	98.39
	3 month	64.06	63.63	99.53	99.74	98.69	98.81
Drug content	Initial	-	-	95.87	95.88	95.87	95.88
	1 month	-	-	95.70	95.3	95.74	95.57

	2 month	-	-	95.2	94.96	95.47	95.90
	3 month	-	-	95.00	95.05	95.08	95.59

CONCLUSION

Dry grinding of ZFN with nicotinamide resulted in the formation of cocrystal. The formation of cocrystals was ascertained by melting point transformations, DSC changes, shifts in Infra red bands, changes in 2θ values in XRPD which mutually supported each other. The newly prepared cocrystals exhibited greater solubility and dissolution as compared to pure drug and found stable at room temperature and accelerated conditions. The study endorsed the high potential of the technique for future applications with other drugs.

Conflict of interest: No conflict of interest declared by authors.

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