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Original Article

FORMULATION AND EVALUATION OF COCRYSTALS OF A BCS CLASS II DRUG USING GLYCINE AS COFORMER

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ABSTRACT

Objective: Development of pharmaceutical co-crystals is an interesting area of research as co-crystals are unique because they have the advantages of maintaining drug's intrinsic properties along with improvement in its physicochemical attributes. Objective of this research was to improvise solubility of a Biopharmaceutics Classification System (BCS) class II drug (Ezetimibe) along with better dissolution profile using cocrystallization technique.

Methods: In the present study, pharmaceutical cocrystals of a BCS class II drug, Ezetimibe, were prepared using glycine as coformer using neat grinding method. Prepared cocrystals were characterized using Hot Stage Microscopy (HSM), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) and Powder X-Ray Diffract meter (PXRD). In addition, solubility and dissolution studies were also performed.

Results: HSM study and DSC study represented melting at Ezetimibe (166 °C), Glycine (233 °C) and cocrystals (174 °C), respectively. Melting point of cocrystal is between API and coformer, indicating towards interaction. During XRD studies, a new peak was observed at 14.7193 and 23.3211 at position 2θ in comparison to parent peaks of Ezetimibe (18.5537, 19.2737 and 21.6487) and Glycine (19.0631, 21.8418, 25.3521, 35.4189, 39.0489 and 39.1631). PXRD pattern of cocrystals represented several newer peaks (-OH group in API shifted from 3241.42 cm^{-1} to 3202.61 $cm^{-1}$and-NH_2 in Glycine shifted from 1601.86 cm^{-1} to 1690.18 cm^{-1}). This indicated towards possible interaction between these two-group leading to cocrystal formation. Improvement in dissolution profile of cocrystals (89.59%) was observed over the pure drug (32.41%) in 90 min.

Conclusion: Pharmaceutical cocrystals of Ezetimibe with glycine as coformer represented a promising approach in tailoring the physicochemical properties.

Keywords: Cocrystals, Solubility, Bioavailability, Ezetimibe, Coformer, Glycine

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INTRODUCTION

Pharmaceutical research field focuses mainly on either development of newer drug delivery systems or newer solid dosage forms for selected active pharmaceutical ingredient. Many problems faced during pharmaceutical product development are mainly due to the drug's physicochemical properties. Drug effectiveness depends on its properties such as solubility, stability, dissolution rate and hygroscopicity etc. Cocrystal technique is an emerging technique to improvise the solubility and dissolution rate profile of poorly soluble APIs, which can improve bioavailability without any covalent bond modification of active pharmaceutical ingredient (API) along with maintaining a stable crystalline form. Using cocrystallization technique, desired physical and chemical properties of an API can be obtained in comparison to the parent API or its salt [1, 2]. Cocrystals are also advantageous as they are comparatively stable and have lesser probability to phase transformations. Cocrystals are solid crystalline compounds which contain either two or more components in crystal lattice with a definite stochiometric ratio involving certain intermolecular interactions resulting in unique physicochemical properties of cocrystals [3]. During cocrystal formation, API or its salt interacts with a coformer and a new solid-state (cocrystal) with certain new physicochemical properties is obtained. Selection of coformer is based on its inertness in terms of pharmacology and its safety. Cocrystals have been useful in order to modify physical properties such as solubility, dissolution, bioavailability and thermal stability behaviour etc. along with mechanical properties of API's [4]. For example, cocrystals of indomethacin, piroxicam, hydrochlorothiazide, Mefenamic acid etc. with different coformers have been reported in literature to improve solubility and physicochemical properties of APIs [5–9]. Human gastrointestinal tract has a variable pH throughout, therefore after oral administration of a drug, due to different solubility in different pH of gastrointestinal fluids, nonlinearity and variability in absorption and thus safety and efficacy of drugs cannot be evaluated properly. Therefore, major challenge remains the solubility improvement of poorly soluble drugs [10–12].

The primary objective of this work was to use crystal engineering for improvising the solubility and dissolution rate of a BCS class II drug Ezetimibe (EZE). It is a hypocholesterolemic agent and works by inhibiting cholesterol absorption. It mainly works by decreasing low-density lipoprotein (LDL) for certain primary and secondary cholesterol health events. EZE selectively inhibits the absorption of cholesterol and related phytosterols from the intestine resulting in reduced cholesterol levels in the blood [13-15]. It is usually administered in conjunction with healthy diet to lower down cholesterol profile in hyperlipidemic patients.

EZE is lipophilic molecule which has log P (octanol/water) value of 4.5. Due to its hydrophobicity, it exhibits lesser bioavailability of around 35–65%. EZE contains ionizable groups (pKa ~9.48) with weakly acidic nature. It is practically insoluble in water (0.08 mg/ml) with good intestinal permeability. It comes under BCS class II drug category [16, 17]. This property is a common problem during drug development which can be solved by converting API's into cocrystals/salts/solid dispersions to obtain desired Physico-chemical properties. Certain literature has also been reported where solubility of EZE has been improved via cocrystallization. Cocrystals of Ezetimibe are reported in literature with certain coformers such as L-proline, Methylparaben, Imidazole, Benzoic and Salicylic acid [18–20].

MATERIALS AND METHODS

Materials

EZE was received as a gift sample from Sun Pharma Industries Private Limited, Gurugram, India. Glycine, Adipic Acid, Maleic acid, Mannitol and Malonic acid were procured from LobaChemie Pvt. Ltd. Mumbai, India. Solvents used for cocrystal preparation were of HPLC grade and were procured from Thermo Fisher Scientific India Pvt. Ltd. All the materials were used as received.

Initial screening

A CSD analysis was carried out using ref. code COTYOA in Mercury 3.10.3 (Build 205818) to study previously published cocrystals as

well as to identify the possibility of newer supramolecular synthons. Few coformers were selected from CSD data are Glycine, Adipic acid, Malonic acid, Maleic acid and Mannitol.

EZE molecule is beta lactam which is 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone. From previously published studies it was observed that the EZE molecule contains the C=O group and-OH groups (n=2) which can form OH---O, OH---N, O---NH backed supramolecular synthons. Thus, the hydroxy group presents excellent possibilities to construct supramolecular synthons with a wide range of amide and carboxylic group containing coformers. EZE is weakly basic based on its pKa (pKa=9.75). Taking this as a lead the EZE molecule was screened with several amide and carboxylic acid containing coformers using the molecular complementarity tool of Mercury 3.10.3 (Build 205818).

Neat grinding method

Accurately weighed EZE (molecular weight: 409.4 mg) and Glycine (GLY) (molecular weight: 75.07 mg) in 1:1 and 1:2 molar ratios were mixed and grinded well with help of pestle-mortar. Little amount of Ethanol was also added to help in mixing during trituration. The mixture of drug and coformer was grinded approximately for 30 min. The resulting powder was obtained and collected in a container. Container was sealed well and kept away from light and moisture till further use (EZE-GLY). Similarly, combination of EZE was prepared with Mannitol (182.17 mg) in 1:1 and 1:2 molar ratios using methanol in neat grinding method [19].

Solution crystallization method

Accurately weighed EZE (molecular weight: 409.4 mg) was mixed with Malonic acid (molecular weight: 104.06) in different stoichiometric ratios (1:1 and 1:2). It was properly dissolved in Ethanol (10 ml) and left for evaporation of solvent. The fine needle shaped crystals were obtained after 5 d. These were collected into a container and stored properly away from light and moisture till further use. Similar combination of EZE with Adipic acid (146.14 mg) and Maleic acid (116.1 mg) was made in different stoichiometric ratios (1:1 and 1:2) using solution crystallization method with methanol as solvent [19].

Physical mixture preparation method

Drug and coformer was mixed in defined stochiometric ratio. This mixture was taken and stored properly, away from light and moisture.

Solubility studies

Solubility studies of EZE and different combinations were done to check solubility pH 4.5 acetate buffer+0.45%SLS. Each combination (n=3) was added in excess quantity in 30 ml of media and gently agitated on a magnetic stirrer for 48 h at 37 °C±0.5 °C and filtered using 0.45 µm syringe filter. UV absorption of solubility samples was taken at 233 nm using UV-visible spectrophotometer after suitable dilution. The mean results of triplicate measurements were calculated [5].

Hot stage microscopy (HSM)

HSM analysis of the samples were carried on an Olympus microscope using Linkam hot stage (THMS600, UK). The data generated was visualized using LINK software with linksys32 patch for the hot stage control. HSM analysis was performed at 10X scale.

Differential scanning calorimetry (DSC)

DSC measurements were carried out in DSC Q10 V9.9 (TA instruments, USA). This was calibrated for heat and temperature with standard of indium. Sample (approx. 2 mg) was placed in sealed non-hermetic aluminium pans and scanned from 30-300 °C at 10 °C rate/min under atmosphere of dry nitrogen (60 ml min^{-1}). The resulting data was analyzed with Universal Analysis 2000 Software (TA instruments).

Powder X-ray diffraction (PXRD)

PXRD patterns of the samples were collected on X'Pert PRO diffractometer system (PANalytical, Almelo, Netherlands) with a Cu Kα radiation (1.54060 Å). The tube current and voltage and current were set at 40 mA and 45 kV, respectively. Each sample was further placed in a sample holder made up of aluminium and measured using continuous scan between 3.5°-50° in 2θ with a step size (0.017°) and step time (25 s/step).

Fourier transformation infrared spectroscopy (FTIR)

FTIR spectra of the samples were recorded using Alpha Bruker 120602880 (Bruker, Germany). The IR spectra was measured over 4000-400 cm^{-1} range. KBr pellet method was used. The obtained data was analyzed using OPUS software v.7.2.139.1294 spectrometer (Bruker, Germany).

Dissolution studies

The dissolution studies were performed in 500 ml of pH 4.5 acetate buffer with 0.45% sodium lauryl sulphate in USP type II dissolution apparatus (LabIndia DS8000, LabIndia Analytical, Maharashtra, India) with paddle speed at 50 rpm. Pure API (10 mg), physical mixture (10 mg of API equivalent amount), cocrystals (10 mg of API equivalent amount) and marketed product (Ezentia Tablets 10 mg) were studied for dissolution studies (n=6). Samples were added into dissolution medium. Samples were collected at specified time points (15, 30, 45, 60, 90 min). Each sample was filtered with 0.45-micron filter for analysis at 232 nm using UV Spectrophotometer (Shimadzu UV-1800) [19].

Stability profile of optimized cocrystals

The stability profile of optimized cocrystals includes the change in the stored cocrystals for accelerated stability study testing as per ICH guidelines. Optimized cocrystals were filled separately in empty hard gelatin capsules and sealed. 30 capsules were packed in HDPE bottles. These bottles were placed at accelerated stability conditions for 6 mo. Samples were withdrawn after 1M/3M/6M and evaluated for stability parameters such as description, assay and dissolution [5].

RESULTS

Initial screening

EZE molecule is azetidinone derivative which offers donor (two H-bond) and acceptor (five H-bond) functionalities. Hence the possible supramolecular outcomes may be O–H···N, O–H···O and N–H···O. Considering previous reports on the cocrystallization behaviour of EZE, the hydroxyl (-OH) group of EZE and NH_2 of carboxylic acid of GLY were targeted to form supramolecular synthon between the EZE and the coformers. EZE and Glycine cocrystallization was done using neat grinding method. API and malonic acid combination were prepared with solvent crystallization method to prepare cocrystals. Based on CSD data, Malonic Acid was opted as coformer which theoretically will not form cocrystals with EZE. This was further confirmed during screening and characterization studies. Screening studies confirmed that interaction was observed in EZE–GLY combination in 1:1 combination. No interaction was observed with Adipic acid, Malonic acid, Maleic Acid and Mannitol (table 1).

Solubility studies

Screening studies along with solubility studies confirmed that interaction was observed in EZE–GLY combination. Slight improvement in solubility studies was observed with Malonic Acid in 1:1 ratio. No interaction and no significant on solubility improvement was observed with Adipic acid, Maleic Acid and Mannitol (table 1).

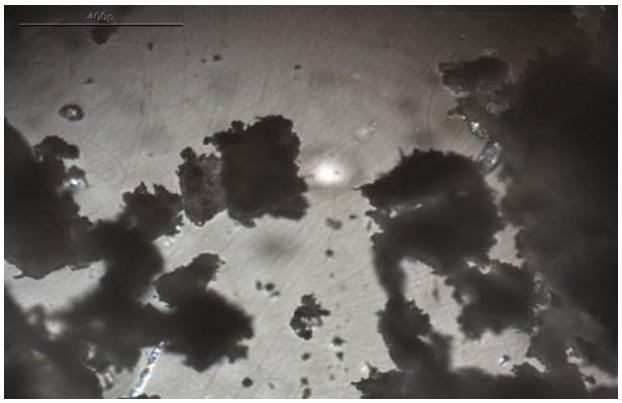
Hot stage microscopy (HSM)

HSM studies were performed with two coformers: Malonic Acid and Glycine. Malonic Acid represented a melting point at 136 °C, whereas API melting point was observed at 163-165 °C. It shows that no interaction has happened between malonic acid and API as individual melting points were observed during HSM studies (fig. 1). If interaction had happened, then melting point of cocrystal would have appeared in some where middle of melting points of API and coformer.

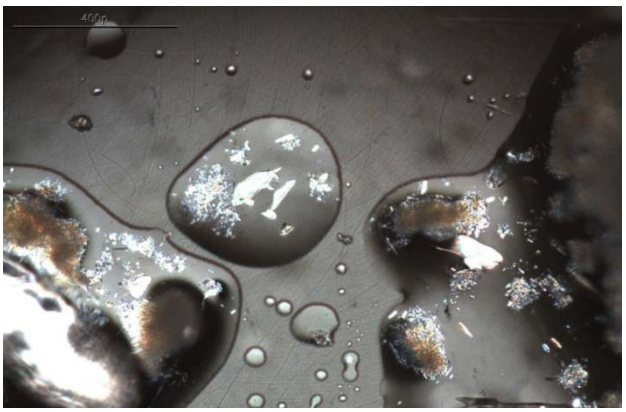
Table 1: Screening of API with different coformers

Coformer	Solvent	M. Pt. of coformer (°C)	M. Pt. of combination (°C)	Method	Solubility*
Ezetimibe			166.5		120.20±2.3
Mannitol (1:1)	Methanol	165	165.9	Neat Grinding	122.30±3.5
Mannitol (1:2)			163.7		116.30±2.8
Malonic Acid (1:1)	Methanol	136	163	Neat Grinding	142.30±4.5
Malonic Acid (1:2)			163.5		144.12±3.8
Adipic Acid (1:1)	Methanol	152.1	163.1	Solution crystallization	135.44±3.7
Adipic Acid (1:2)			165.5		141.15±2.9
Maleic Acid (1:1)	Methanol	202.5	203	Solution crystallization	131.05±2.9
Maleic Acid (1:2)			204.6		137.22±3.4
Glycine (1:1)	Ethanol	233	174.2	Neat Grinding	306.44±3.1
Glycine (1:2)			178.6		304.14±2.9

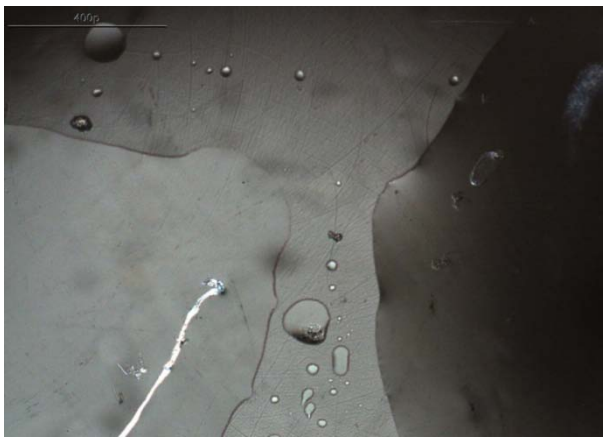
*Results expressed in mean±SD (n=3)



(A) Initial Melting at 95 °C (Magnification: 10X)



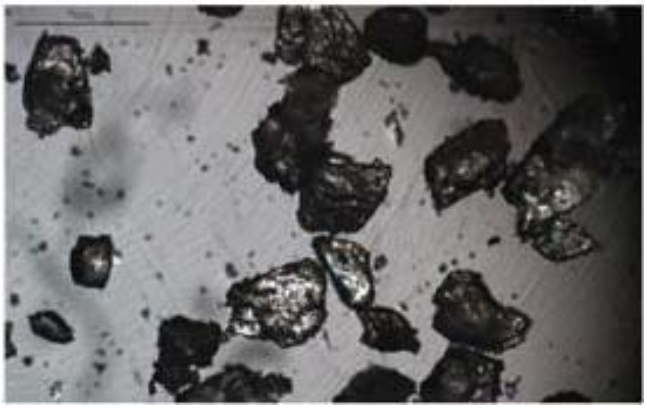
(B) Melting at 136 °C (Magnification: 10X)



(C) Initial Melting at 165 °C (Magnification: 10X)

Fig. 1: HSM micrographs depicting the thermal behaviour of EZE-Malonic acid combination

HSM studies were also performed for API and GLY. HSM images of melting of API and GLY were taken at different temperature as represented in fig. 2. Cocrystal melted in between melting point of API and GLY. This indicates towards interaction among API and coformer resulting in change in melting point of cocrystal. This was further confirmed during the experimentation using other screening techniques. Despite the structural similarities between the coformers, EZE only formed cocrystals with GLY. Therefore, further investigation into the cocrystallization mechanism was made. EZE-GLY cocrystals complete melting was observed at 174 °C.



A) Melting at 110 °C (Magnification: 10X)

B) Melting at 174 °C (Magnification: 10X)

Fig. 2: HSM micrographs depicting the thermal behaviour of EZE-GLY combination

DSC studies

DSC was used for the thermal study of pure drug, coformer and cocrystals. DSC profile of EZE, Malonic acid and their combination were evaluated. Malonic Acid represented a melting point at 136 °C, whereas API melting point was observed at 163-165 °C. It shows that no interaction has happened between malonic acid and API as individual melting points were observed (fig. 3).

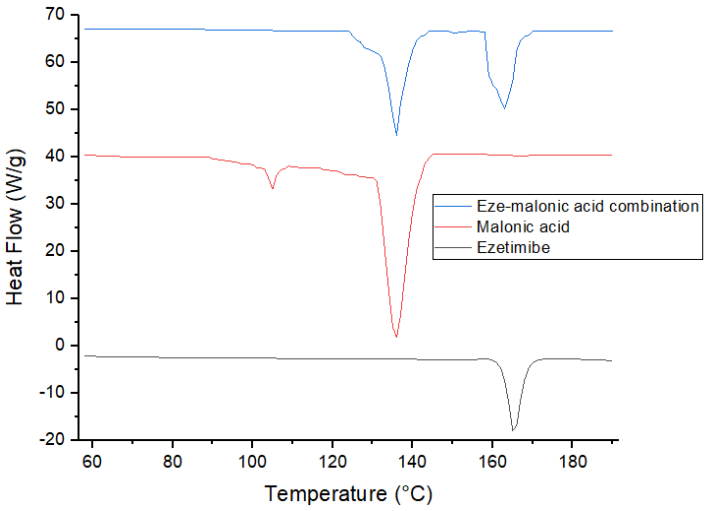


Fig. 3: DSC thermogram of EZE, Malonic acid and EZE-Malonic acid combination

EZE and coformer GLY represented melting endotherm at 166 °C and 233 °C respectively. The prepared cocrystals EZE-GLY shows single melting sharp endotherm at 174 °C which lies in between that of the individual compounds. DSC peak of physical mixture is not sharp and appears close to cocrystals. It may happen due to minor interaction between coformer and API, therefore a peak of weaker intensity of physical mixture appears near to cocrystals. It seems that some minor interaction got initiated but was not complete. Due to this, a peak of weaker intensity appeared in physical mixture. Appearance of sharp peak in the cocrystals DSC curve confirms the formation of new solid phase. Sugandha *et al.*, 2014 reported Ezetimibe cocrystals with methyl paraben in 1:1 stoichiometric ratio. Melting point of cocrystal was reported different than melting point of Ezetimibe and coformers used in the study. After analysis of an elaborative study of 50 cocrystalline compounds they reported that 51% cocrystals had melting points between the API and coformer, 39% were lower than either the API or coformer, 6% were higher, and 4% had the same melting point as either the API or conformer [19]. In another report, Sevukarajan *et al.*, 2011, obtained from the cocrystals of Aceclofenac having a lesser melting point when compared with pure drug and conformers [21]. These observations clearly indicated the formation of stable interaction between ezetimibe and the coformer. This confirms the presence of new crystalline solid form (fig. 4).

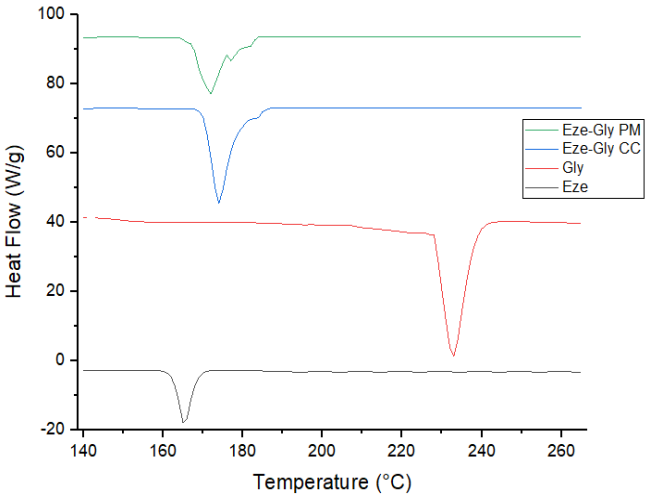


Fig. 4: DSC thermogram of EZE, GLY, PM and cocrystals

PXRD studies

Every compound exhibits distinct peaks in the PXRD pattern and thus the PXRD patterns of API, coformer can be easily differentiated from that of the cocrystals [21–24]. Prominent peaks of GLY were observed at position of 2θ were 19.0631, 21.8418, 25.3521, 35.4189, 39.0489 and 39.1631 with peak intensity observed was 42.53, 52.65, 100, 29.64, 45.04 and 44.13%. These prominent peaks of GLY in PXRD pattern confirmed the crystalline nature of compound. Prominent peaks of EZE were observed at position 2θ were 18.5537, 19.2737 and 21.6487 with peak intensity observed was 50.8, 100 and 28.57%. These prominent peaks of GLY in PXRD pattern confirmed the crystalline nature of compound. In the analysis of PXRD of physical mixture, there was observance of slight shift in prominent peaks of both components. This slight shift in position 2θ might be due to instrumental analysis. In cocrystal of EZE and GLY, new peak was observed at 14.7193 and 23.3211 at position 2θ with intensity of 37.17 and 25.45%. Slight shift in parent peak of EZE were observed at position 2θ were 18.5855, 19.3163 and 21.7163 with decrease in intensity at 21.7163. Similarly, at position 2θ 25.2876 slight shift in GLY peak was observed (fig. 5). These shift in prominent peaks might be due to occurrence of bonding between EZE and GLY.

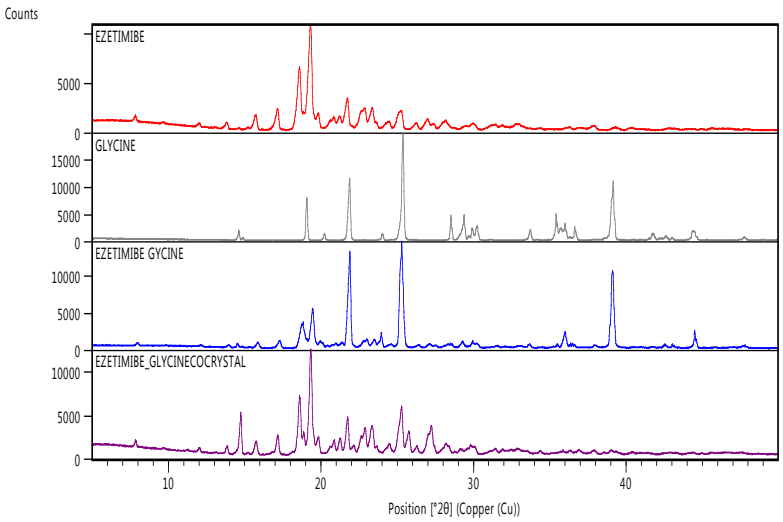


Fig. 5: PXRD pattern of EZE, GLY, physical mixture and cocrystal

FTIR studies

PXRD and DSC studies of EZE-GLY combination, points towards the formation of a new crystalline phase. To study further about molecular interactions, FTIR study was employed. The FTIR spectra for pure EZE (fig. 6), has band at 3241.42 cm^{-1} corresponding to O-H stretch. GLY FTIR spectra is presented in fig. 7. In case of cocrystals (fig. 8), band corresponding to O-H stretching has shifted to 3202.61 cm^{-1} which is broad corresponding to-OH group stretching. Shift in these peaks strongly indicated about certain weak interactions and formation of hydrogen bond between EZE and GLY. C=O group in EZE (1271.71) and GLY (1227.2) also did not show any interaction and remain unchanged in Cocrystal (1221.08 cm^{-1}). Pure EZE spectrum has strong bands at 1714.83 cm^{-1} which corresponds to carbonyl (C=O) stretching of lactam. The peak in GLY spectrum appeared due to N-H bending mode in primary amine at 1601.86 cm^{-1} got shifted towards 1690.18 cm^{-1} in the cocrystal.

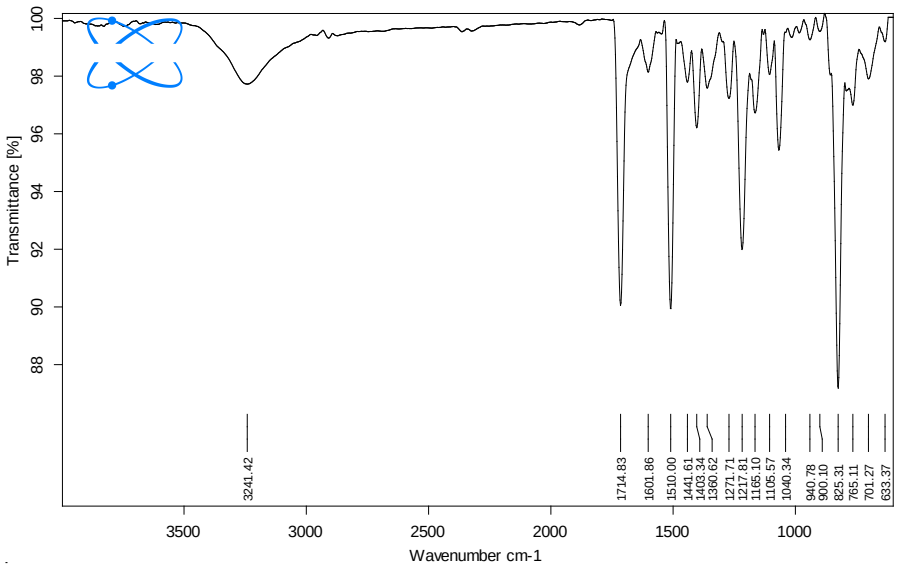


Fig. 6: FTIR spectrum of ezetimibe

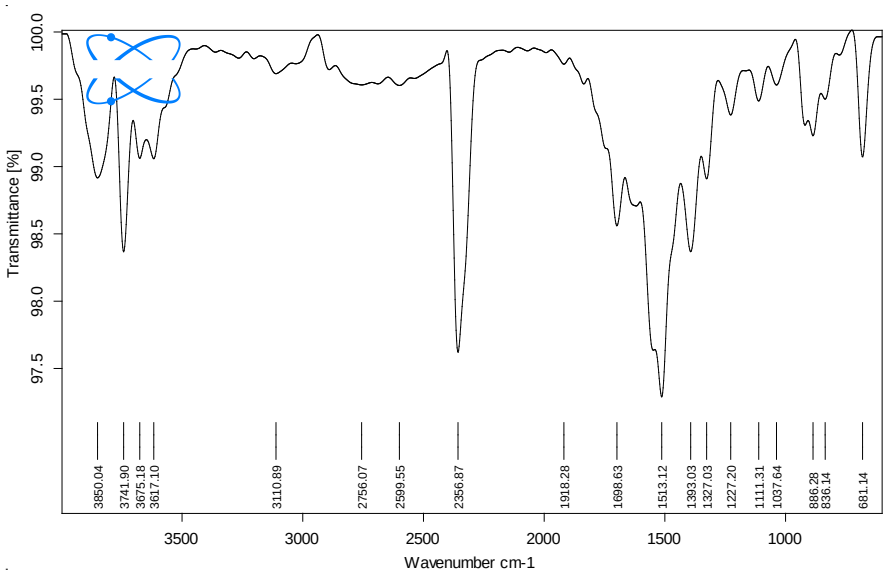


Fig. 7: FTIR spectrum of glycine

Table 2: % Cumulative drug release data

Sample	% Cumulative drug release				
	15 min	30 min	45 min	60 min	90 min
Ezetimibe	23.50±1.21	27.20±2.10	27.46±1.76	28.52±0.88	32.41±1.22
Physical Mixture	25.67±1.55	27.99±1.52	32.35±1.28	35.33±1.08	38.34±0.98
Cocrystal	63.38±0.91	80.20±0.81	86.59±0.96	86.19±1.96	89.59±1.06
Market sample	74.61±1.62	86.51±0.92	91.01±2.40	97.72±1.28	99.09±1.36

Results expressed in mean±SD (n=6)

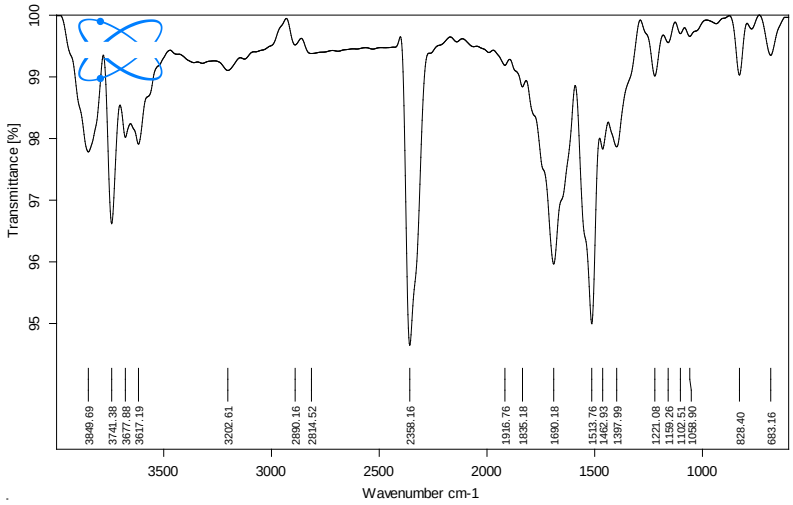


Fig. 8: FTIR spectrum of EZE-GLY cocrystals

Dissolution studies

Drug release profile (n=6) was performed in pH 4.5 Acetate Buffer+0.5%SLS (table 2). The cocrystals exhibited enhanced solubility over pure drug in dissolution media (f2=68; f1=5) (fig. 9). Significant improvement in % Cumulative Drug Release in dissolution profile of cocrystals was observed in comparison to pure drug.

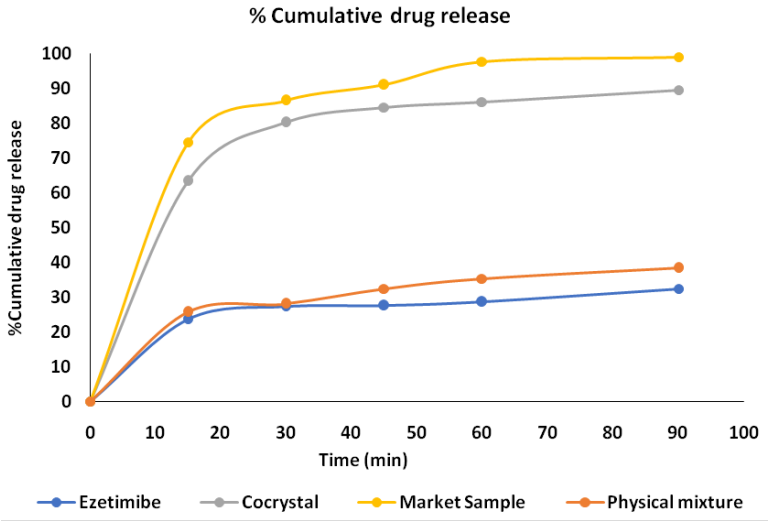


Fig. 9: Graphical representation of % cumulative drug release

Table 3: Stability studies data

S. No.	Sample	Test name	Initial*	40 °C/75%RH			30 °C/65%RH		
				1M*	3M*	6M*	1M*	3M*	6M*
1	Ezetimibe	Description	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder
		Assay	99.60±1.21	98.12±1.68	98.01±1.25	97.25±2.02	99.12±2.00	98.57±1.44	98.11±1.06
		Disso							
		30 min	27.20±2.01	25.89±1.89	25.42±2.10	24.89±1.77	25.99±1.03	25.65±1.22	24.96±1.21
		60 min	28.52±1.05	28.55±2.05	28.01±0.98	26.41±1.33	28.77±0.98	28.45±0.87	27.48±1.02
		90 min	32.41±2.16	34.22±1.34	33.11±1.28	30.15±0.99	34.49±1.02	33.88±1.35	32.19±0.97
3	Cocrystals	Description	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder	Off white colored powder
		Assay	99.70±1.55	98.44±1.67	97.22±1.27	95.99±1.33	99.12±1.44	98.69±1.55	98.45±1.31
		Disso							
		30 min	81.51±1.44	81.22±1.57	81.01±1.53	80.20±1.28	81.11±1.26	80.89±1.33	80.11±1.99
		60 min	90.21±1.22	89.22±1.49	88.39±1.39	86.26±1.05	89.99±2.09	89.11±1.48	88.16±1.28
		90 min	94.25±1.78	94.17±1.34	92.57±1.28	91.28±1.37	93.45±2.01	93.18±1.32	92.45±1.55

*Results expressed in mean±SD (n=3)

Stability studies

No significant change in the physicochemical parameters of cocrystal formulation was observed during stability in comparison to initial parameters. Stability Study results are tabulated in table 3.

DISCUSSION

EZE is a BCS Class II drug with low solubility. Objective of this study was to improvise solubility of poorly water-soluble drug BCS class II drug (Ezetimibe) using cocrystal approach. Cocrystal techinque is employed as an effort to improve physicochemical properties of Ezetimibe [25]. In this regard, an attempt was made to prepare crystal engineered multicomponent form of EZE with the primary motive of enhancing its aqueous solubility. Solubility was improved using EZE-GLY combination during initial screening. Based on preliminary screening and solubility studies, two coformers–Glycine and Malonic acid were selected. HSM (fig. 1) and DSC studies (fig. 3) confirms possibility of cocrystals formation between EZE and Malonic Acid. HSM study (fig. 2) and DSC study (fig. 4) represented melting at EZE (166 °C), GLY (233 °C) and cocrystals (174 °C) respectively. Melting point of cocrystal is between API and coformer indicating towards interaction. Similar results were reported by Sanphui *et al.*, 2015 for cocrystals of Hydrochlorothiazide where melting point of coformer is between API and conformer [8]. During PXRD studies, new peak was observed at 14.7193 and 23.3211 at position 2θ in comparison to parent peaks of EZE (18.5537, 19.2737 and 21.6487) and GLY (19.0631, 21.8418, 25.3521, 35.4189, 39.0489 and 39.1631) (fig. 5). PXRD pattern of cocrystals represented several newer peaks and absence of the characteristic prominent peaks of drug and coformer confirmed the formation of a new crystalline phase. During FTIR studies, peaks of hydroxyl group in API-3241.42 cm^{-1} (fig. 6) has shifted to 3202.61 cm^{-1} in cocrystals (fig. 8). Primary amine group in GLY at 1601.86 cm^{-1} (fig. 7) got shifted to 1690.18 cm^{-1} in cocrystal (fig. 8). This indicated towards possible interaction between these two-group leading to cocrystal formation between EZE and GLY. Sugandha *et al.*, 2014, reported similar shifts in FTIR spectra of the cocrystal of ezetimibe and methyl paraben prepared by the reaction crystallization process. Cocrystal showed the maximum number of significant changes in FTIR spectrum. Broader peak due to hydroxyl group shifted to a less broad peak indicating that hydroxyl group participated in interaction. The carbonyl group (lactam) of ezetimibe and coformer shifted to higher wavenumber indicating towards electrostatic repulsion between the lone pair of electrons present in carbonyl group of both the drug and conformer [19]. Cocrystals exhibited faster dissolution (fig. 9) which might be due to altered crystallization pattern, shape, crystal habit and size of the cocrystal. Cocrystallization must have led to improvement in solubility profile of cocrystals into the official dissolution media resulting in faster dissolution. These results are in accordance with studies by Mulye *et al.*, which reported improvement in physicochemical properties of Ezetimibe using cocrystallization [17]. Improvement in solubility, dissolution and tablettability has also been reported by Hiendrawan *et al.*, 2016 for Paracetamol and dipicolonic acid cocrystals [26]. Adahalli *et al.* reported improvement in tablet compression properties and improved dissolution for antihyperlipidemic drug using co-amorphous technique [27]. Anand *et al.* reported improvement in solubility, dissolution and pharmacokinetic profile of Ezetimibe drug using co-crystallization using 3-pyridine carboxylic acid as coformer using solution crystallization method [28]. Several other authors also reported improvement in solubility and dissolution profile of drugs like carbamazepine, artesunate using cocrystallization method [29, 30].

CONCLUSION

The present study was aimed to improvise aqueous solubility of BCS class II drug, Ezetimibe. Cocrystallization approach was used to prepare and improve the solubility of the API. The present study illustrated preparation and characterization of cocrystals of Ezetimibe with Glycine as coformer employing liquid assisted grinding technique. DSC results show different melting point in cocrystals indicated towards formation of a new solid phase. From FTIR studies, it was revealed that new solid form resulted from weak interactions between API and coformer. XRD studies indicated towards modification of crystal habits of API and coformer. Dissolution study of cocrystals revealed improvement in drug release from cocrystals. Stability of the cocrystals was confirmed from stability studies. From above results, it was clear that cocrystals can be a useful approach for improving solubility of BCS Class II drug, Ezetimibe.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

All the authors confirm that there is no conflict of interest.

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