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Research Article

NOVEL PHARMACEUTICAL COCRYSTAL OF TELMISARTAN AND HYDROCHLOROTHIAZIDE

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ABSTRACT

Objective: Telmisartan (TEL), commonly used antihypertensive, is poorly soluble in water and has limited and variable bioavailability. Commercially, TEL is available as a single drug and in combination with hydrochlorothiazide (HYZ). Researchers have developed cocrystals of TEL with coformers, namely, oxalic acid, glutaric acid, and saccharin. An attempt was made to prepare the cocrystals of TEL with HYZ, an active pharmaceutical ingredient (API) itself so that both the APIs are available in a single tablet. The present study was aimed at enhancement in solubility of TEL by formation of its cocrystals.

Methods: The cocrystals of TEL with HYZ, in different stoichiometric ratios (1:0.5, 1:1, and 1:2), were prepared by solvent coevaporation and liquid-assisted grinding methods. The cocrystals, consisting of TEL:HYZ (in 1:0.5 ratio and 1:1 ratio), depicted maximum yield, drug content, saturation solubility, and flow properties. These cocrystals were characterized by X-ray analysis, infrared spectroscopy, and thermal analysis.

Results: The crystal structure of TEL-HYX revealed that it was a cocrystal, since no proton was transferred between the TEL and HYZ molecules. It was predicted that two molecules are associated through a hydrogen bond between an acidic group of TEL and sulfonamido group of HYZ. The cocrystallization improved the solubility of TEL 7 times. *In vitro* release rate of tablets of cocrystals was higher than that of marketed TEL tablets. HYZ has a potential to form the cocrystals of TEL.

Conclusion: The objective of improvement in the solubility of TEL was successfully achieved by the formation of cocrystals of TEL: HYZ.

Keywords: Telmisartan, Cocrystal, Hydrochlorothiazide, Hydrogen bond, Dissolution.

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INTRODUCTION

Pharmaceutical development aims at the synthesis of new active pharmaceutical ingredients (APIs) as well as improvement in the physicochemical properties of existing APIs. Many APIs are poorly water soluble and are absorbed poorly and variably. A cocrystal is defined as the crystal lattice arrangement consisting of two or more neutral molecules bonded together through the hydrogen bonding or non-covalent interactions [1]. Recently, many researchers are working on cocrystals as an attractive alternative for drug development since the physiochemical properties of cocrystals, namely, stability, dissolution rate, and bioavailability are improved (enhanced) than those of the parent molecule [2]. In addition, the pharmaceutical industries can file a patent for the cocrystal [3].

Telmisartan (TEL) is employed for the treatment of essential hypertension and acts by blocking angiotensin-II type-I receptors. TEL has a benzimidazole ring (pKa 4.7) and carboxyl group (pKa 6.7) and is weakly acidic, highly lipophilic (log p=7.2). It is reported to exhibit two polymorphs, namely, A and B, A is the stable form at room temperature [4]. TEL is poorly soluble under physiological conditions (pH 3–9) and leads to variable bioavailability (42–85%) [4-6]. For this reason, the commercially available free acid formulations of TEL are prepared by direct contact of TEL with a strong alkalizer such as sodium hydroxide. Such a production process is dangerous to human health. In addition, reproducibility of solubility may vary depending on a period of reaction time [7].

To overcome the disadvantages of the free acid of TEL, several salts of TEL have appeared in patents [8-12]. However, sodium salts of TEL may cause sodium ions retention and may increase blood pressure in the hypertensive patients [4]. Potassium, ammonium, magnesium, and calcium salts of TEL suffer from disadvantages such as high hygroscopicity and low thermal stability. TEL zinc salt [13] and TEL salts with meglumine and choline [11] are reported.

Previous studies, to improve the aqueous solubility of TEL, show the possibility of preparing solid dispersions [14-16], amorphous formulation [17], immediate release tablets [18], nanoparticles [19,20], and self-nanoemulsifying drug delivery systems [21,22]. However, the cocrystallization approach, for improving the aqueous solubility of TEL, has been investigated by Chadha *et al*. [23] and by Alatas *et al*. [24].

Hypertension is the major cause of morbidity and mortality in the world every year. In general, two or more anti-hypertensive medicines are prescribed for hypertensive patients to exert effective control over their blood pressure. The WHO has recommended fixed-dose dual or triple-combinations, consisting of more than one anti-hypertensive, in a single pharmaceutical formulation, for the treatment of hypertension. The results of the clinical trials have confirmed the benefits of the fixed- dose combinations, namely, ease of administration, greater patient compliance, therapeutic efficacy, and economy to a certain extent. Hence, the fixed-dose combination is preferred by the physicians and the patients as compared to a single drug to control the blood pressure [25].

TEL is available as Micardis® consisting of TEL alone and Micardisplus® consisting of TEL and hydrochlorothiazide (HYZ). The WHO has recommended telmisartan and HYZ combination since the combination is reported to provide better control over hypertension as compared to the individual drug [26]. HYZ, a Biopharmaceutics Classification System Class III drug, is reported to have high solubility and low permeability. It is used in the treatment of edema and hypertension.

The novelty of the work is to explore the ability of HYZ, an API itself, as a potential conformer and to enhance the solubility of TEL by the formation of TEL:HYZ cocrystals. Cocrystals are produced due to hydrogen bonding between drug and coformer. TEL has four hydrogen acceptor count and one hydrogen donor count. The hydrogen acceptor and hydrogen donor count of HYZ are 7 and 3, respectively. It is hypothesized that they can form suitable synthons which are a prerequisite for hydrogen bond formation.

METHODS

TEL IP and HYZ USP were kindly gifted by IPCA Pharmaceuticals Ltd Mumbai. Telismart 40 Tablets, manufactured by Helios Pharmaceuticals, Baddi, were purchased. Talc IP, magnesium stearate IP, and microcrystalline cellulose IP were purchased from New Neeta Chemicals, Pune. All other chemicals and solvents were of AR Grade.

Screening of cocrystals of TEL by solvent evaporation (SE) method and liquid assisted grinding (LAG) method

Cocrystals of TEL, varying in stoichiometric ratios of TEL:coformer, were prepared by SE and LAG method (Table 1).

Accurately weighed, TEL was dissolved in 5 ml of chloroform. HYZ, the coformer, was dissolved in 5 ml chloroform. The coformer solution was added to the TEL solution gradually with continuous stirring for 10 min at 1200 rpm at 28°C. The stirring was continued until complete dissolution. The container was left uncapped for 2 d for gradual evaporation of the solvent. White-colored cocrystals were obtained and triturated gently in the pestle mortar to a fine powder before analyses. Each formulation was prepared in three sets.

Accurately weighed TEL was mixed with HYZ in the pestle mortar (in the absence of solvent) for 20 min. Initial mixing was followed by dropwise addition of 2 ml chloroform with continuous trituration. The stirring was continued for 5 min. The container was left uncapped for gradual evaporation of the solvent at room temperature for 2 d. White colored cocrystals were obtained and triturated gently in the pestle mortar to a fine powder before analyses. Each formulation was prepared in three sets.

Evaluation of cocrystals

The % yield of cocrystal formulations was determined by the following equation.

$$\%\text{yield} = \frac{\text{weight of co} - \text{crystal formulation}}{\text{Weight of drug + co-former}} \times 100$$

Cocrystal formulation (equivalent to 40 mg of drug) was added to chloroform (10 ml) and was agitated on a magnetic stirrer at 100±10 rpm for half an hour at 37±0.5°C. Whatman filter paper no. 41 was employed for filtering the solution and the drug concentration was analyzed by ultraviolet (UV) spectrophotometric method. Drug content was calculated according to the following equation.

$$\%\text{drug content} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100$$

Excess amount of TEL and the cocrystal formulation was added to distilled water (10 ml) and the suspension was agitated on a magnetic stirrer at 100±10 rpm for 24 h at 37±0.5°C. Whatman filter paper no. 41 was employed for filtering the solution before UV spectrophotometric analysis at 296 nm.

The Hausner's ratio, compressibility index, and angle of repose of the cocrystals were determined. The cocrystal formulations A1 and C2, depicting highest solubility, drug content, % yield, and flow properties, were further characterized by Fourier-transform infrared spectroscopy, differential scanning calorimetry (DSC), and powder X-ray diffractometer (PXRD).

Formulation of tablets of cocrystals

Direct compression was employed to prepare the tablets consisting of TEL drug substance (tablet T1) and the cocrystal formulations A1 (tablet T2) and C2 (tablet T3). The excipients (microcrystalline cellulose, magnesium stearate, and talc) were sieved separately through # 60 sieve. The drug substance was mixed with the excipients (Table 2) and the mixture was compressed on a Rotary Tableting Machine (Mini Press - II "D" Rimek) using flat-faced punches (diameter 0.9 cm) for 3s. The tablets were prepared in triplicate.

Evaluation of tablets of cocrystals of TEL

The tablets T1, T2, and T3 and the marketed tablets were evaluated: Appearance, tablet dimensions [27], weight variation test [27], hardness test [28], friability test [28], and disintegration [27].

In vitro dissolution of tablets of cocrystals

In vitro drug release from T1, T2, and T3 tablets was performed by placing three tablets in USP Dissolution Apparatus 2. The dissolution medium was phosphate-buffered solution pH 7.5 (900 ml). The paddles were rotated at 75 rpm at 37±0.5°C. At predetermined time intervals, the samples were withdrawn, filtered, and subjected to UV spectrophotometric analysis. An equal volume of fresh dissolution medium was replaced to maintain the volume of the dissolution medium [27].

RESULTS AND DISCUSSION

Screening of cocrystals

Two screening methods, namely, SE and LAG, led to the formation of six solid forms containing TEL.

The hydrogen bond formation in the TEL:HYZ cocrystal is formed as follows.

TEL consists of two imidazole rings and an aromatic carboxylic acid. TEL offers four basic hydrogen bond acceptors, including aromatic nitrogen (N) in the imidazole rings and carbonyl group. The carboxylic acid of TEL donates hydrogen and can participate easily in hydrogen bonding [23,24].

The C=O- and OH- from the carboxylic acid functional group from TEL (-COOH) represent suitable synthons. The NH- and S=O of sulfonamido functional group ($-SO_2NH_2$) of HYZ represent suitable synthons. Fig. 1, drawn with ChemDraw software, shows the proposed hydrogen bonding between the guest and the host compounds. The O from C=O and H from –OH of TEL (-COOH) have a potential of hydrogen bonding with the H from $-NH_2$ and O from SO_2 ($-SO_2NH_2$) of HYZ. The ($-NH_2$) of HYZ acts as the proton donor. The O from the carboxylic acid of TEL acts as the proton acceptor. It interacts with the hydrogen atom and forms the hydrogen bonds N—H-----O and O—H-----O. It is proposed that the cocrystal will be formed by a heterosynthon.

Cambridge structural database describes hydrogen bond formation between imidazole ring and carboxylic acid. Caffeine and theophylline have an imidazole ring coupled with pyrimidinedione. Formation of cocrystals of caffeine with carboxylic acids, namely, oxalic acid [29], salicylic acid [30], and glutaric acid [31], is attributed to hydrogen bonding between imidazole ring and carboxylic acid. Cocrystals of theophylline with oxalic acid [32], benzoic acid [33], and salicylic

Table 1: Formulation of cocrystals of TEL

S. No.	Ingredients	Stoichiometric ratio of drug: coformer	Liquid-assisted grinding	Solvent evaporation
1	T+H	1:0.5	A1	C1
2	T+H	1:1	A2	C2
3	T+H	1:2	A3	C3

T – TEL; H – HYZ. TEL: Telmisartan, HYZ: Hydrochlorothiazide

Table 2: Formulation of tablets of cocrystals of TEL

S. No.	Ingredient	Purpose	Quantity/tabletT1 (mg)	Quantity/tabletT2 (mg)	Quantity/tabletT3 (mg)
1.	TEL	Drug substance	40	-	-
2.	Cocrystal formulation A1	Drug substance	-	172	-
3.	Cocrystal formulation C2	Drug substance	-	-	202
4.	Talc	Glidant	5	0.5	1
5.	Microcrystalline cellulose	Binder and Diluent	150	100	50
6.	Magnesium stearate	Lubricant/anti adherent	5	0.5	1
7.	Lactose	Filler	100	48	48

TEL: Telmisartan

Table 3: Characterization of cocrystals by the solvent evaporation method

S. No.	Formulation code	Ratio	Yield (%)	Drug content (%)	Solubility (µg/ml)
1.	A1	1:0.5	84.04±13.88	23.28±12.55	34.73±22.02
2.	A2	1:1	78.09±13.89	15.77±3.61	25.56±13.65
3.	A3	1:2	83.36±12.61	15.20±5.83	28.91±6.40

Each observation is mean±SD where sample size (n=3). SD: Standard deviation

Table 4: Characterization of cocrystals by liquid-assisted grinding method

S. No.	Formulation code	Ratio	Yield (%)	Drug content (%)	Solubility (µg/ml)
1.	C1	1:0.5	73.55±11.88	21.42±20.30	27.95±3.28
2.	C2	1:1	78.80±18.76	9.93±1.76	35.97±9.31
3.	C3	1:2	61.76±17.31	15.10±5.45	22.32±21.85

Each observation is (n=3)±SD. SD: Standard deviation

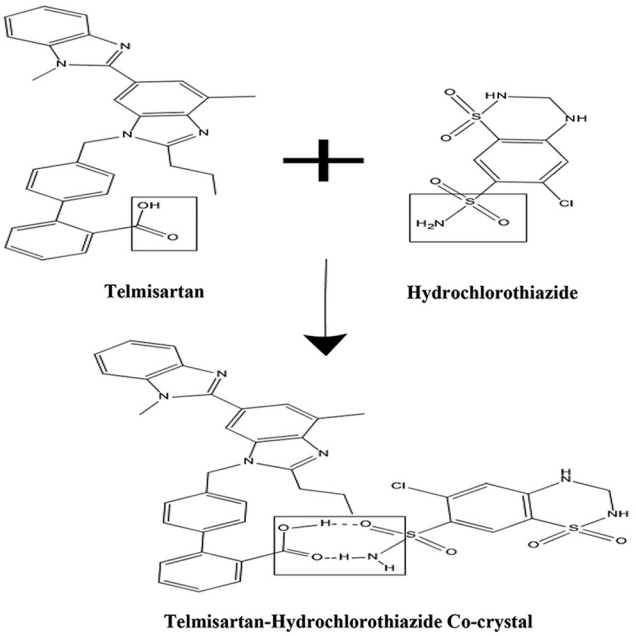

Fig. 1: Formation of hydrogen bond in cocrystals

acid [34] involve hydrogen bonding between imidazole ring and carboxylic acid. We propose the hydrogen bond formation between a carboxylic acid group of TEL and sulfonamido group of HYZ (Fig. 1).

It was predicted that the proposed solid-state was not the salt but it was the cocrystal since the difference between the pKa values of TEL (pKa=6.7) and of HYZ (pKa=7.9) was <2.

Evaluation of cocrystals

For cocrystals, the collected powders were white and fairly free-flowing. The percentage yield of cocrystals from LAG was high than from SE (Tables 3 and 4). The lower yield in the case of SE was attributed to the process loss.

The solubility of TEL in distilled water was 4.556 µg/ml. Both crystallization techniques improved the aqueous solubility of TEL approximately 7 times (Tables 3 and 4). The cocrystals A1 and C2 demonstrated higher drug solubility than other cocrystals. The inclusion of HYZ in solid dosage forms enhances the solubility of poorly water-soluble drug TEL. Enhancement in dissolution rate is produced by inhibition of crystallization of drugs. It was predicted that HYZ, when used in lower concentrations, was available for hydrogen bonding with TEL. Hence, the solubility of cocrystals of TEL was enhanced.

The % drug content of cocrystals, prepared by SE, was higher than the drug content of the cocrystals prepared by LAG (Tables 3 and 4). The drug content of cocrystals may be improved by optimization of the process parameters of LAG and SE.

The cocrystals, A1 and C2, revealed good flow properties. The compression properties of cocrystals were improved considerably than TEL (Table 5).

IR spectroscopy

The characteristic IR bands of the cocrystal A1 are listed in Table 6. The resulting spectra of the cocrystals A1 and C2 were different from the IR spectra of TEL and HYZ (Figs. 2 and 3, respectively). The broad bands, in the region of 2500–3500 cm^{-1}, indicated hydrogen bond formation in between TEL and HYZ. The cocrystals A1 and C2 revealed two characteristic bands, (1) at 1686.09 cm^{-1} for the C=O stretching and (2) at 1009.55 cm^{-1} for the C–N stretching of the aromatic ring. It indicated the presence of TEL in the solid phases of A5 and B8. In addition, the presence of HYZ was in the cocrystals A5 and B8 was confirmed from two characteristic bands, (1) at 1639, 1599 cm^{-1} for the NH bending and (2) 1194, 1138 cm^{-1} for SO_2.

The IR spectrum of the cocrystal A1 (Fig. 4) depicted changes in the frequency and bandwidth of interacting groups. It was attributed to the blending of TEL with HYZ and the subsequent formation of the hydrogen bonds between the two. The IR bands due to NH bending and SO_2 (in HYZ) were shifted to lower wavenumber. It indicates that both the groups are involved in some kind of interaction. The same was predicted by the ChemDraw software.

Table 5: Flow properties of cocrystals

S. No.	Component	Angle of repose (°)	Tap density	Bulk density	Carr's index (%)	Hausner's ratio
1.	TEL	31.21	0.35	0.21	51.38	2.05
2.	Cocrystal A1	35.56	0.36	0.29	20.46	1.26
3.	Cocrystal C2	32.18	0.19	0.16	15.85	1.19

Table 6: Relevant bands in IR spectra of cocrystal

S. No.	Functional groups	Observed value (cm^{-1}) for TEL/HYZ	Observed value (cm^{-1}) for cocrystal
1.	O-H stretching	3058.74	3059.51
2.	C=O stretching	1695.12	1686.09
3.	C-N stretching	1010.52	1009.55
4.	NH bending	1695, 1714, 1730	1639, 1599
5.	SO_2	1333	1194, 1138

TEL: Telmisartan, HYZ: Hydrochlorothiazide, IR: Infrared

Table 7: Characterization of tablets of TEL and cocrystals of TEL

Test	Tablet T1	Tablet T2	Tablet T3	Marketed tablet
Appearance	White	White	White	White
Weight** variation (g)	300±0.3269	320±0.3107	300±0.3418	300±0.0023
Hardness* (kg/cm^2)	4.5±0.62	4.6±0.23	4.6±0.51	4.87±0.25
Disintegration time (min)	1.5	7	8	7.0
Friability (% w/w)	1.1	0.6	0.61	0.79
Thickness* (mm)	48.33±0.57	48.33±0.57	47.66±0.57	0.3212±0.025
Diameter* (mm)	87.33±0.57	88±0.1	88.33±0.57	0.6324±0.001

Each observation* is mean±SD where sample size is 3, Each observation** is mean±SD where the sample size is (n=20). SD: Standard deviation, TEL: Telmisartan

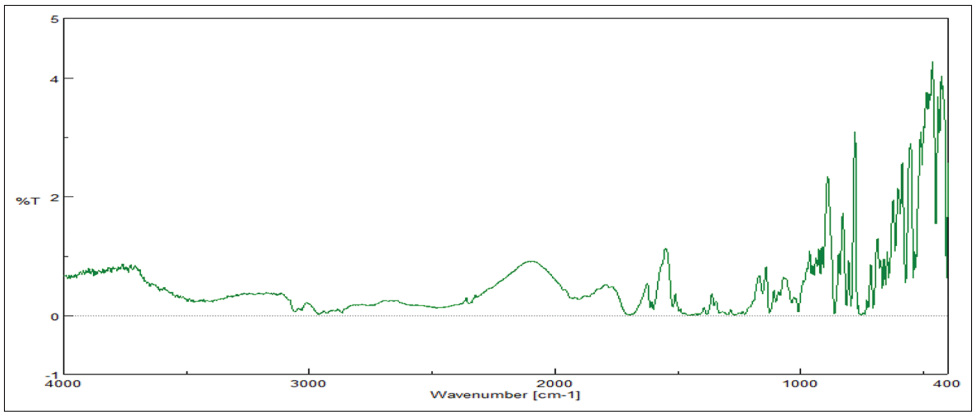

Fig. 2: Infrared spectrum of telmisartan

It indicated the formation of hydrogen bonds between C= O and N-H. It was inferred that the compound is a cocrystal rather than a salt. Besides, the difference between the pKa values of TEL (pKa=6.7) and of HYZ (pKa=7.9) is <2. It was inferred that the salt was not formed in between TEL and HYZ.

The IR spectrum of the cocrystal C2 depicted IR bands similar to the cocrystal A1.

DSC

The DSC thermogram of TEL revealed a sharp characteristic endothermic peak (T_{peak}=270.0°C) corresponding to its melting, indicating its crystalline nature. Single, sharp peak of TEL indicates that the drug sample is free from impurities. Phase transition started at 268.4°C and ended at 271.7°C (Fig. 5).

The DSC curve of HYZ depicted a peak at 270°C (Fig. 6).

The peaks in DSC curves of cocrystals A1 and C2 were different from those of TEL and HYZ. These peaks indicated the formation of H bonds and the possibility of crystal lattice arrangement between TEL and HYZ. A small endothermic peak around 53°C in DSC curves of cocrystals A1 and C2 (Figs. 7 and 8) may be attributed to a small mass loss from the cocrystal sample. The mass loss was attributed to the vaporization of moisture from the cocrystal. The DSC curve of A1 sample revealed two endothermic peaks at 208°C and 254°C immediately followed by an exothermic effect. This can be explained in two ways: (1) This thermal behavior is typical for a metastable form of a polymorphic drug substance that has a lower melting point than the stable form that recrystallizes into the stable form after melting. An endotherm at 208°C was attributed to the metastable form of TEL-HYZ cocrystal and an endotherm at 254°C was attributed to the stable form of TEL-HYZ cocrystal. A1 is a mixture of the metastable form (208°C) and the stable form (254°C). (2) Cocrystal A1 was obtained by SE of the chloroform-methanol mixture. The first endotherm at 208°C indicated it to be a solvate. The second endotherm at 254°C indicated the melting of A1. Cocrystal A1 was proposed either as a metastable form or as a solvate of the TEL–HYZ cocrystal. However, C2 obtained from the LAG method, depicted a single thermal event at 211°C, negating the presence of any solvation or transition. It indicated the formation of cocrystal since the

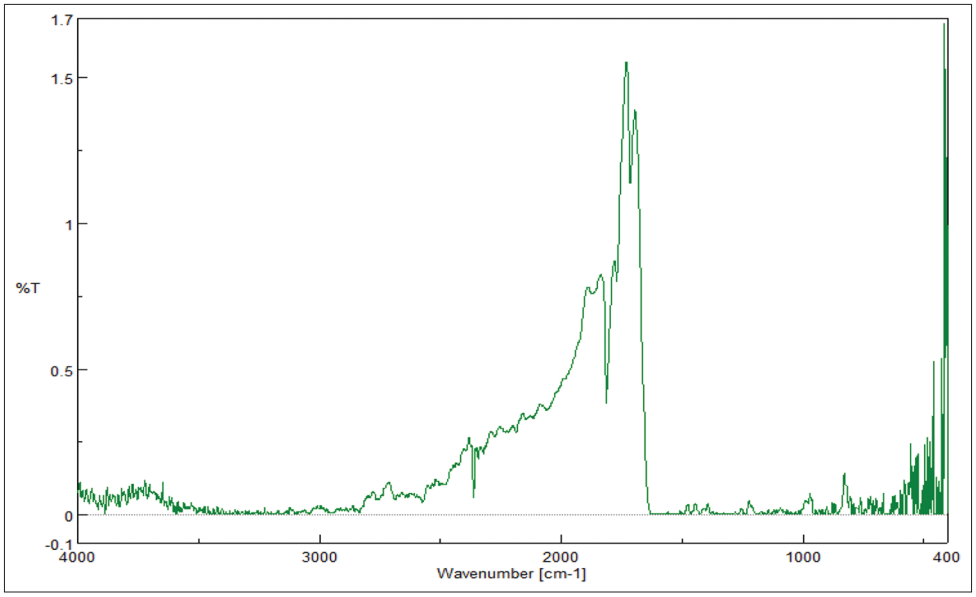

Fig. 3: Infrared spectrum of hydrochlorothiazide

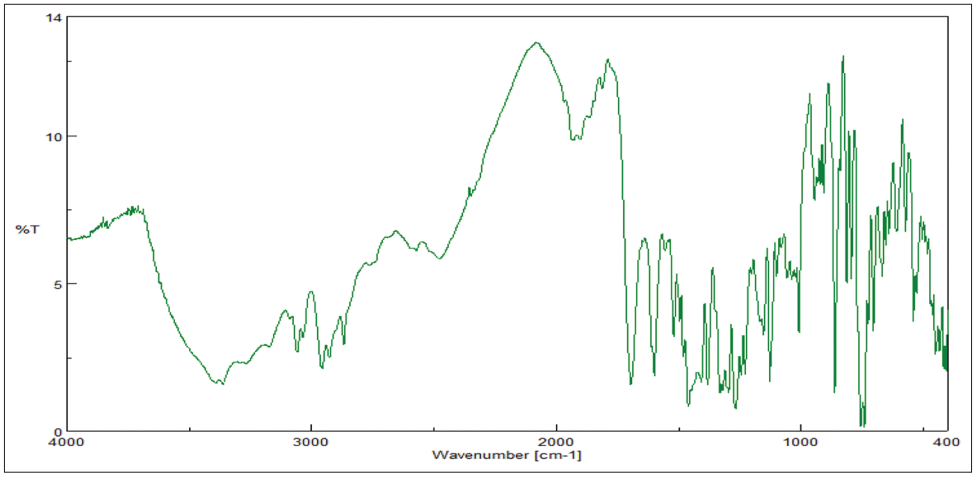

Fig. 4: Infrared spectrum of cocrystal A1

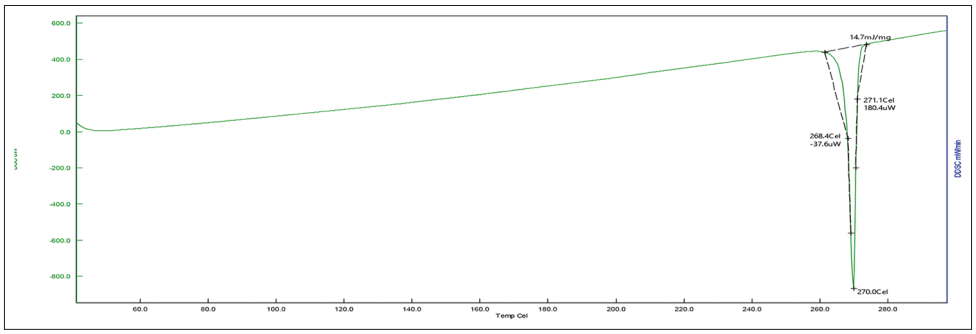

Fig. 5: Differential scanning calorimetry thermogram of telmisartan

melting temperature was different from the active and the conformer. As TGA data were not available, the formation of A1 as metastable polymorph or solvate could not be confirmed.

PXRD study

PXRD is the main instrument used to characterize the cocrystal formation. The new solid phase is formed if the resulting PXRD pattern of the solid product after grinding is different from the reactant solid compounds (the API and the coformer). The PXRD pattern of a crystalline sample is considered as the fingerprint of its crystal structure. Every new crystalline material exhibits unique peaks indicative of reflections from specific atomic planes (14). The X-ray diffraction pattern of TEL exhibited sharp, highly intense, and less diffused peaks at 2˚θ=6.86, 14.24, and 22.36 indicating the crystalline nature of the drug (Fig. 9).

The X-ray diffraction pattern of HYZ exhibited sharp, highly intense, and less diffused peaks at 2˚θ=16.52, 19.04, 20.82, 21.36, 24.50, and 28.76, indicating the crystalline nature of the drug (Fig. 10).

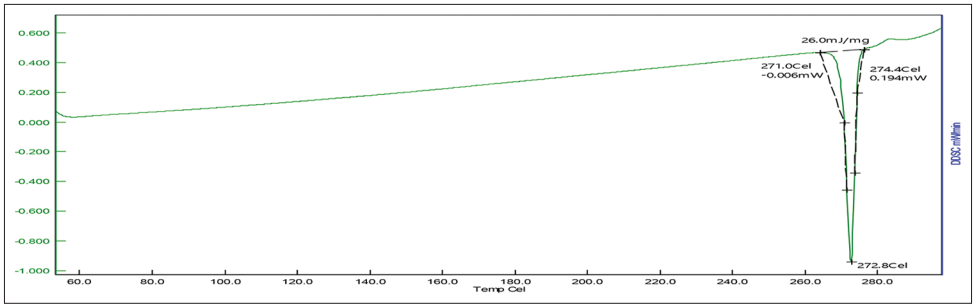

Fig. 6: Differential scanning calorimetry thermogram for hydrochlorothiazide

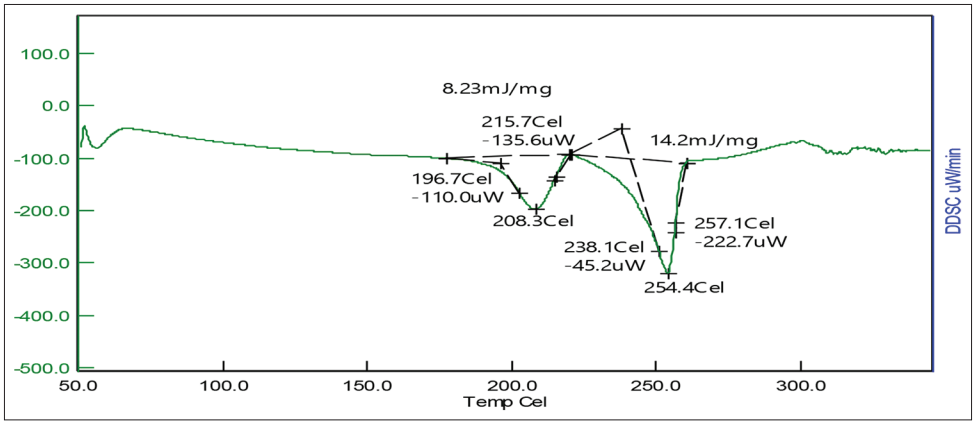

Fig. 7: Differential scanning calorimetry thermogram of cocrystal A1

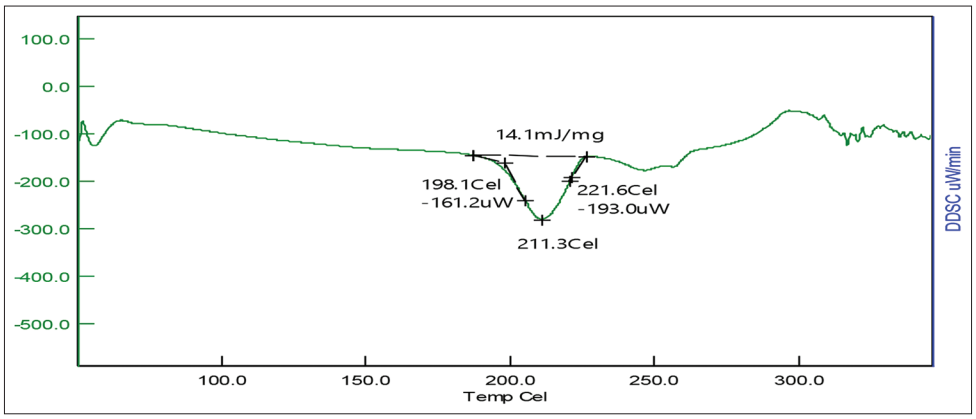

Fig. 8: Differential scanning calorimetry thermogram of cocrystal C2

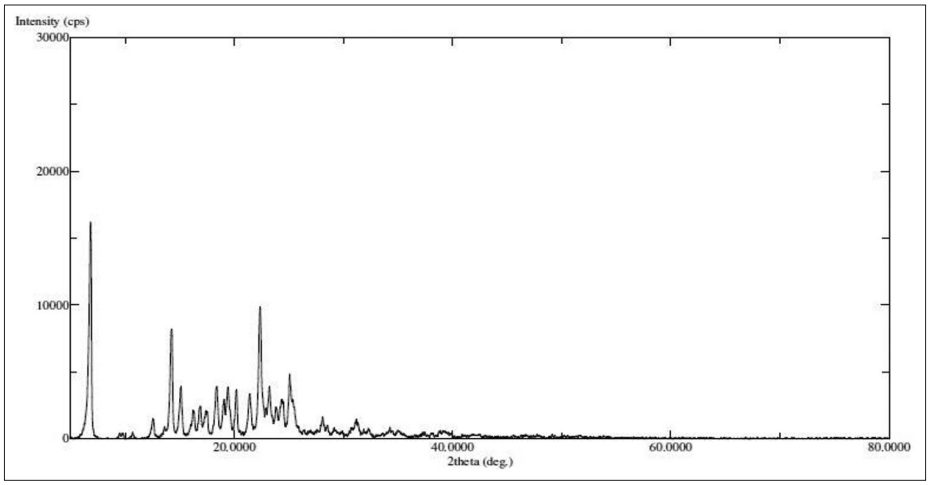

Fig. 9: Powder X-ray diffractometer pattern of telmisartan

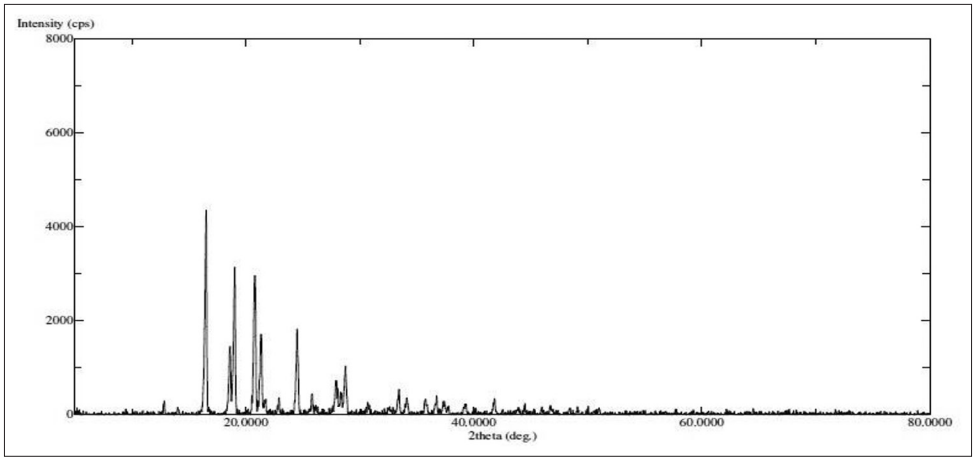

Fig. 10: Powder X-ray diffractometer pattern of hydrochlorothiazide

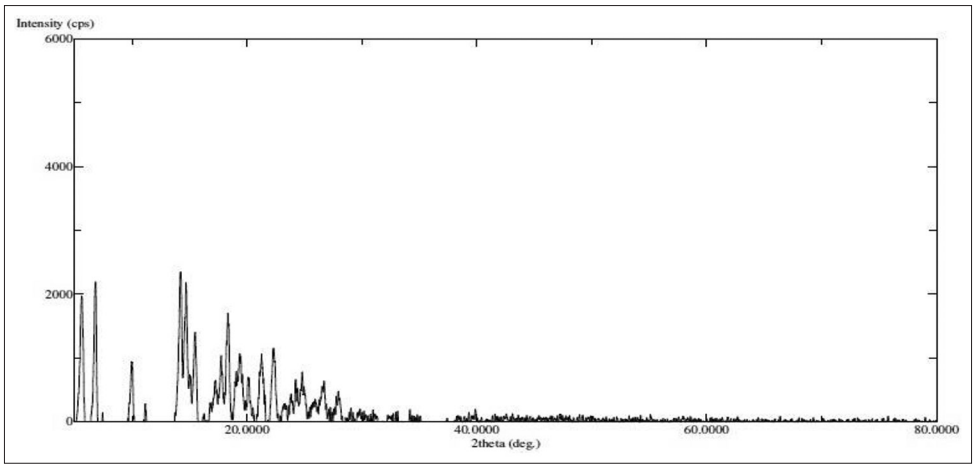

Fig. 11: Powder X-ray diffractometer pattern of cocrystal A1

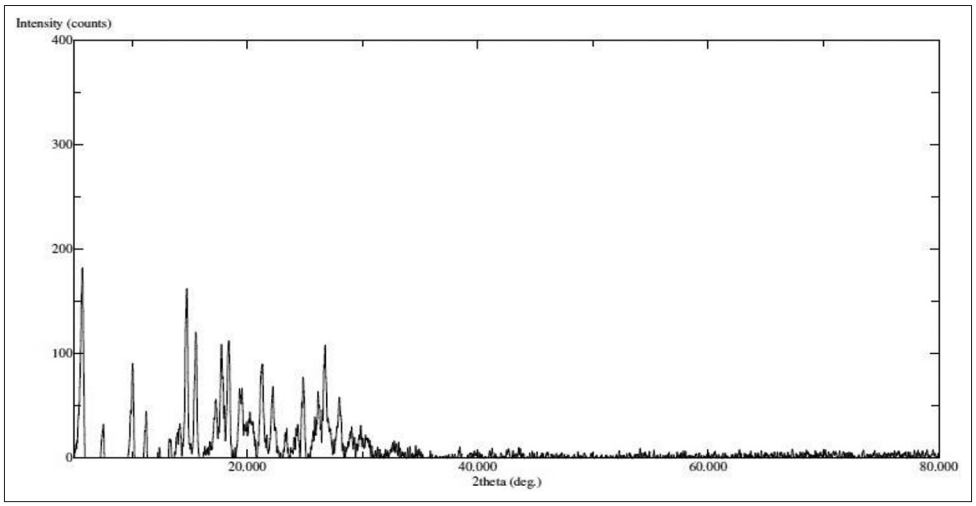

Fig. 12: Powder X-ray diffractometer of pattern cocrystal C2

The product solids were ascertained as new phases since there were noticeable differences in the peak positions of cocrystals A1 and C2 (Figs. 11 and 12) as compared to TEL and coformer diffraction lines. A prominent peak was observed in A1 and C2 at 2˚θ=10.00, 10.06, 10.10, and 11.24 with the appearance of numerous peaks. The peaks indicated the possibility of crystal lattice arrangement between TEL and the coformers to some extent. The inability of completion of crystal lattice rearrangement was attributed to inadequate drug: Coformer stoichiometric ratio or inadequate cocrystallization reaction conditions.

The IR spectroscopy, DSC, and the PXRD study confirmed the formation of crystal lattice arrangement between TEL and HYZ. Inclusion of HYZ in solid dosage forms enhances the solubility of poorly water-soluble drug TEL. Enhancement in dissolution rate is produced by inhibition of

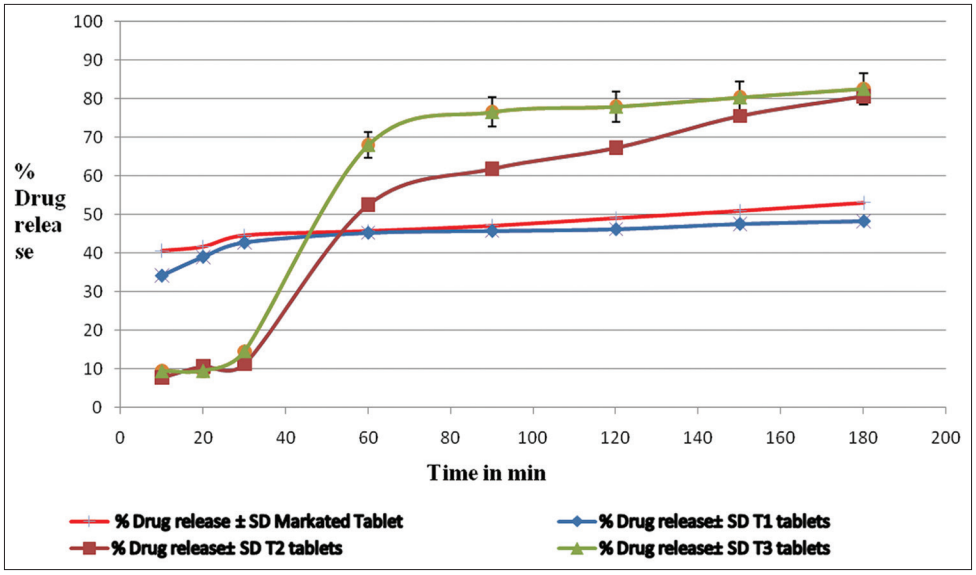

Fig. 13: Drug release profile for T1, T2, T3, and marketed tablets. Each observation is n=3±SD

crystallization of drugs. It was predicted that HYZ, when used in lower concentrations, was available for hydrogen bonding with TEL. Hence, the solubility of cocrystals of TEL was enhanced.

Evaluation of tablets of cocrystals

The tablets were round, white, smooth in appearance. Tablets T1, T2, and T3 complied with tablet thickness, diameter, weight variation, hardness, and friability (Table 7).

***In vitro* dissolution**

The dissolution profiles of pure TEL, TEL-HYZ cocrystal, and marketed tablets are shown in Fig. 12. The dissolution test showed that TEL- HYZ cocrystal has the percentage of TEL, dissolved after 60 min (dp 60 min), higher than TEL in house and marketed tablet. Dp 60 min, in phosphate buffer pH 7.5, for TEL alone, TEL-HYZ cocrystal A1 and C2 tablets and marketed tablet were 45.20%, 52.52%, 68.04%, and 45.7%, respectively, and at 180 min, 48.21%, 80.61%, 82.58%, and 53.12%, respectively (Fig. 13). A higher dissolution rate, observed for tablets of cocrystals, was attributed to improved aqueous solubility of TEL.

CONCLUSION

In the present study, it was demonstrated that TEL forms cocrystals with coformer HYZ. We have successfully improved the solubility of TEL by the formation of cocrystals of TEL:HYZ. Hence, the dissolution rate of TEL from the tablets was enhanced.

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AUTHORS' CONTRIBUTION

Dr. AlpanaKulkarnihas designed and supervised the experiments, also interpreted the results. Mr. Swapnil Shete has conducted the experiments and interpreted the results. Mr. Vishal Hol has participated in the interpretation of the results. Mr. RiteshBachhav has carried out the literature search related to the topic.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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