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SOLUBILITY IMPROVEMENT OF TELMISARTAN BY COCRYSTALLIZATION WITH CITRIC ACID

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ABSTRACT: Crystal engineering of cocrystals promises a new approach for the development of suitable solid phase when the solubility of API is compromised. Cocrystals are an emerging solid-state form to change physicochemical and biopharmaceutical drug properties. A cocrystal is defined as a stoichiometric hydrogen-bonded complex in the solid state between the active drug species and a suitable coformer molecule that is safe for human consumption. In the present work, cocrystal of telmisartan has been prepared with citric acid. The TEL-CA cocrystal prepared by fast evaporation technique was initially characterized using DSC and FTIR studies. The PXRD pattern of the cocrystal was completely different from that of drug and coformer. The crystal structure determined using Material Studio software (Accelrys) showed triclinic symmetry with P1 space group. TEL-CA cocrystal forms a hetersynthon involving the amine group of telmisartan and carboxylic acid group of citric acid. The equilibrium solubility and intrinsic dissolution rate of cocrystal showed improvement in solubility as compared to pure drug. The pharmacokinetic parameters also showed a two fold increase in bioavailability of drug in cocrystal.

INTRODUCTION: An important goal of solid-state pharmaceutical development is to increase drug solubility while maintaining a stable form[1-3]. Cocrystals are an emerging solid-state form to change physicochemical and biopharmaceutical drug properties [4 - 6]. A pharmaceutical cocrystal is defined as a multicomponent molecular complex comprising of a solid API and a coformer (which is safe for human consumption) that interact through noncovalent interactions in a definite stoichiometric ratio without compromising the structural integrity but improving the solubility [7, 8].

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Pharmaceutical cocrystals brought attraction to the pharmaceutical industry because they offer multiple opportunities to modify the chemical and/or physical properties of an API without making or breaking covalent bonds [9 - 12]. Formation of pharmaceutical co-crystal offers scope to transform an amorphous or hard-to-crystallise API into a readily handled, stable crystalline solid. Therefore, co-crystallization would be better alternative to replace other solid forms (metastable polymorphs, amorphous form, salts etc.) and thus offer greater stability and other desirable properties suitable for processing [13, 14].

Besides this, pharmaceutical cocrystals are considered as new chemical entities that impart many unique and useful properties to the parent compound and are subjected to intellectual property issue [15, 16]. In this context, cocrystallization of an antihypertensive drug telmisartan, which has poor

aqueous solubility [17, 18], has been performed with citric acid to improve its pharmaceutical properties.

MATERIALS AND METHODS:

Materials: The anhydrous telmisartan was obtained from Unichem Piramal Healthcare, India. The investigated counter molecule, citric acid was purchased from Himedia labs, India. All other solvents and chemicals were of analytical grade.

Method: The initial step for the formation of cocrystal involved screening of various coformers[19]. The coformers for screening were selected on the basis of complementary functional group present in the drug and conformer [20, 21]. During the process of preparation of cocrystals, no cocrystals were produced by neat grinding of components or by liquid assistant grinding. To produce cocrystals, telmisartan and citric acid were dissolved in ethanol and chloroform (1:1) in stoichiometric ratio and subjected to fast evaporation in rota evaporator.

Telmisartan - Citric acid (TEL-CA) cocrystal: TEL (514mg) and CA (192mg) were dissolved in 10ml of chloroform: ethanol (1:1). The mixture was stirred for half an hour and evaporated by using rota evaporator at 40 ℃. The precipitates were removed from the RBF and kept in cool and dry place.

Characterization of Cocrystals:

Differential scanning calorimetry (DSC): DSC thermogram of TEL, coformer CA and its cocrystal TEL-CA were obtained using DSC, Q20 TA-Instruments Waters (LLC, USA). The instrument was calibrated for temperature and heat flow accuracy using the melting of pure indium. 3-5mg of samples were loaded in sealed non-hermetic aluminum pans and were run with temperature range of 20-300 ºC with heating rate of 10 ºC per minute under nitrogen atmosphere (flow rate 50 cc/min). The data were managed by TA Q series advantage software (Universal Analysis 2000).

Fourier transform infrared spectroscopy (FTIR): A spectrum RX I FT-IR spectrometer (PerkinElmer, UK) was employed in the KBr diffuse-reflectance mode (sample concentration 2 mg in 20mg of KBr) for collecting the IR spectra of the samples. The spectra were measured over the range of 4000-400 cm^{-1}. The data was analyzed using Spectrum software.

Powder X-ray diffraction (PXRD): PXRD of powder samples were recorded on X`Pert PRO diffractometer system (PANalytical) with Cu Kα radiation (1.54060 Å). The tube voltage and current were set at 45 kV and 40 mA respectively. The divergence slit and anti scattering slit setting were setting at 0.48 ºC for the diffraction experiment on 10 mm sample size.

Crystal structure determination from PXRD: The cocrystal structure was determined from powder diffraction data using the Reflex Plus module of Material Studio. The overall prediction process was carried out in four steps: indexing, Pawley fitting, structure solution and Rietveld refinement. In the indexing step, the crystal class and the approximate lattice parameters were derived from the peak positions in the experimental powder diffraction pattern using X-cell. A table was generated from the results of X-cell the arranged the proposed unit cell according to their figure of merit. The unit cell with the highest figure of merit was selected and an empty cell was generated. The accurate lattice constants and the cell parameter were determined by Pawley fitting/refinement. The R_{wp} (weighted Rietveld parameter) value obtained after the refinement was used to establish the arrangement between the calculated and the experimental powder patterns and hence confirm the accuracy of the crystal class and the lattice parameters. The space group that showed the highest figure of merit was selected and the Pawley refinement was repeated with the selected space group to obtain another $R_{wp.}$

The optimized structure of the drug molecules was imported into the refined unit cell and the motion groups were defined. The structure was obtained using the reflex powder solve module that involved the Monte Carlo/ simulated annealing procedure. 10 cycle of simulated annealing were selected with each cycle involving 2 140 100 steps. The similarity between the experimental and the calculated diffraction patterns was confirmed by the R_{wp} values. Furthermore, Rietveld refinement of the structure was performed to obtain a final structure solution and a final R_{wp} values.

Solubility studies: The solubility study of TEL, and its cocrystal was performed using water bath shaker. An excess amount of sample (about 50 mg) in phosphate buffer of pH 6.8 and 0.1N HCl of pH 1.2 in conical flasks. The flasks were sealed properly and shaken at 200 rpm at 37 ºC for 24 h in water bath shaker (MSW-275 Macro scientific works, Delhi) and filtered through 0.22 µm membrane filter and analyzed for the drug HPLC method consisting of mobile phase *i.e.* acetonitrile and methanol in 60:10 ratio and UV detector set to absorbance of 295 nm was used to determine the concentration of TEL in cocrystals.

Intrinsic dissolution studies: Intrinsic dissolution study of TEL, its cocrystal was performed on dissolution test apparatus, DS 8000 (Lab India Analyticals) in phosphate buffer pH 6.8 at 37 ºC and 0.1N HCl pH 1.2. For intrinsic dissolution, pellet of sample was formed with the help of die and punch and then compressed by tablet press. The die with pellet was attached to dissolution holder and immersed in dissolution media. 5ml of phosphate buffer pH 6.8 with replacement was withdrawn at 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90 minutes and filtered through membrane filter (0.22 µm). The concentration of telmisartan in cocrystal was determined by measuring absorbance at 295 nm using method established in HPLC and the average values were calculated. Intrinsic dissolution rate were determined by plotting a graph between respective concentrations vs. time and compared with that of pure drug.

High performance liquid chromatography: HPLC analysis was performed using a Waters Alliance system, which includes a Water 2695 separation module, a Water 2996 Photodiode Array Detector and a Sun Fir^{tm} C18 5-µm column (4.6mm × 150mm).

Stock standards of telmisartan for solubility and dissolution studies prepared by dissolving TEL in methanol and diluted with mobile phase. Mobile phase consisting of a mixture of ammonium acetate: acetonitrile: methanol (30:60:10) was used to prepare various concentrations of calibration standards on a range of 1-10 µg/ml. The sample of solubility experiments were diluted with the mobile phase and injected (20µL) into the column in triplicate. The mobile phase was prepared at a flow rate of 0.8 ml/min through the column at a temperature of 30 °C. TEL was detected at 295 nm.

***In vivo* pharmacokinetic studies:** For *in vivo* pharmacokinetic study, 4-5 weeks old female Wistar rats (180-270g) were procured and kept in animal house for adaptation of environment. The animals were provided with standard pellet diet and water. Experiments were performed as per guidelines of committee for the purpose of control and supervision on experiments on animals (CPC-SEA). The experimental protocol was approved by institutional animal ethics committee (I.A.E.C.).

The animals were divided into five groups of six animals each. Group 1 was control, group 2 was given pure drug (TEL) while group 3 received cocrystal TEL-CA. A single dose of all the preparations were suspended in 0.5 % (w/v) sodium carboxymethyl cellulose (CMC) and administrated by oral gavage. Each animal was treated with a TEL dose equivalent to 1 mg kg^{-1} BW. The dose volume of all administration was maintained at 5 ml BW.

Group 1: The rats were vehicle treated. 0.5% (w/v) of sodium carboxymethyl cellulose (CMC) suspension was administered by oral gavage. It is treated as control group.

Group 2: The single dose of telmisartan 1 mg in 5 ml of CMC was administered to animal.

Group 3 A single dose of TEL-CA cocrystal 1.37 mg in 5 ml of CMC was administered to animal.

Serial blood samples were collected from the retro-orbital venous plexus of the rat at 0.5 min, 2h, 4h, 8h, 18h, 24h and 28h into heparinized plastic tubes, the blood samples were treated with caprin and centrifuged at 10000 rpm for 10 min treated with acetonitrile and again centrifuged. The plasma was separated and stored at -20 °C until drug analysis carried out by the HPLC method. Pharmacokinetic parameters such as $C_{max,}$ AUC_{o-t} and relative bioavailability of the pure drug and the developed cocrystal was calculated by using non-compartmental analysis.

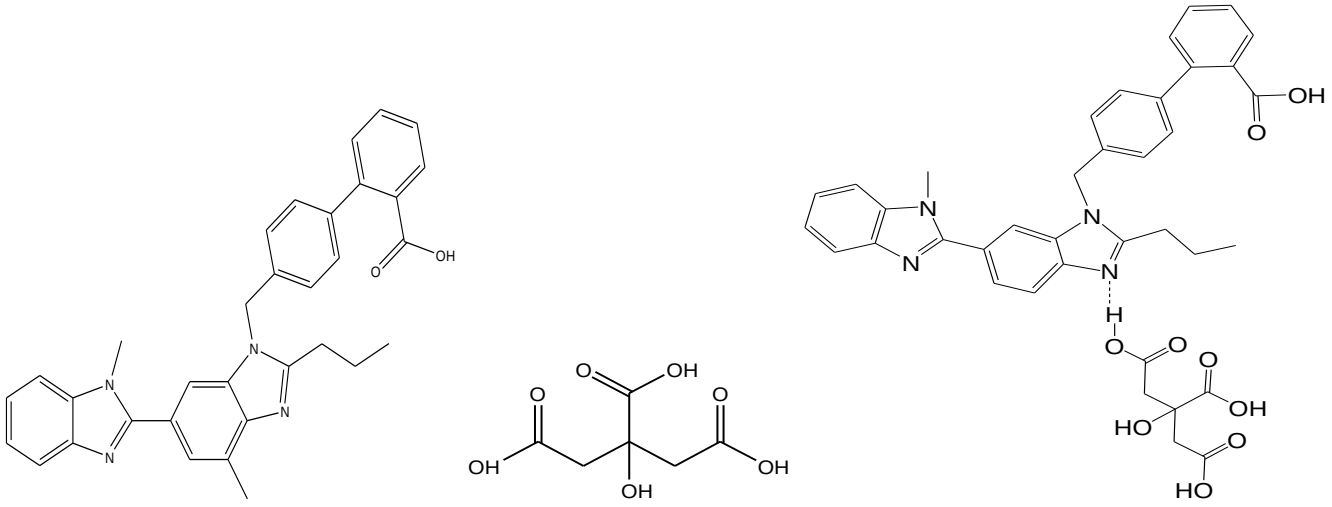
RESULTS AND DISSCUSSION:

Design of Multicomponent Forms: The design of cocrystals is based on the complementary

functional groups present in the API and coformers. The "synthon approach" is used to construct a supermolecule by utilizing specific molecular fragments to establish "supramolecular synthon" for successful cocrystallization. A key step in the design of such assemblies is the identification of complementary functional groups. Supramolecular synthons are the templates for possible complementary functional group types, supramolecular synthons can be divided into homosynthons formed by self-complementary functional groups and heterosynthons formed by different but complementary functional groups.

The drug molecules selected in the present study, telmisartan, has both amine and carboxylic acid groups available for the interaction with coformer molecules. This suggests that the cocrystallization experiment can result in either in homosynthon or a heterosynthon between drug and coformers.

$\triangle pK_a$ as well as the stereo-hindrance are also considered during the design of pharmaceutical cocrystals. This step in a multi-component molecular crystal characterization determines if the new compound is a multi-component crystal (an unionized species) or a salt (ionized species). TEL is highly lipophillic (log *P*= 7.2) and has two pK_a values, 4.7 (benzimidazole) and 6.7 (carboxylic) (Chadha *et al*., 2014). CA exhibits a pK_a of 3.13, 4.67 and 5.40 for the three carboxylic acid groups present in the molecule. The difference between the pK_a of TEL and counter ions suggest the possibility of cocrystal formation.



(a) (b) (c)

FIG. 1: STRUCTURE OF (A) TEL, (B) CA AND (C) SYNTHON OF TEL WITH CA

Characterization of Telmisartan: Co-crystals of TEL were developed with citric acid (CA) as described in experimental section. Solid state characterization was performed using various analytical tools and results are discussed below.

Differential scanning calorimetry: The thermal behavior of TEL, coformers and its cocrystal is shown in **Fig. 2**. The melting of telmisartan appeared at 268 ºC and CA was observed at 157.02 ºC while the corresponding cocrystal showed melting at 187.12 ºC which is in between the melting of two components of adduct. Thus appearance of melting peaks in between the melting of two components indicates formation of cocrystal. The existence of different solid forms leading to cocrystal in TEL is further confirmed by FT-IR, PXRD.

TABLE 1: THERMAL BEHAVIOR OF DRUG AND COCRYSTAL IN DSC THERMOGRAM

S.no	Sample	Melting Peak (°C)
1.	TEL	268.14
2.	CA	157.02
3.	TEL-CA	187.12

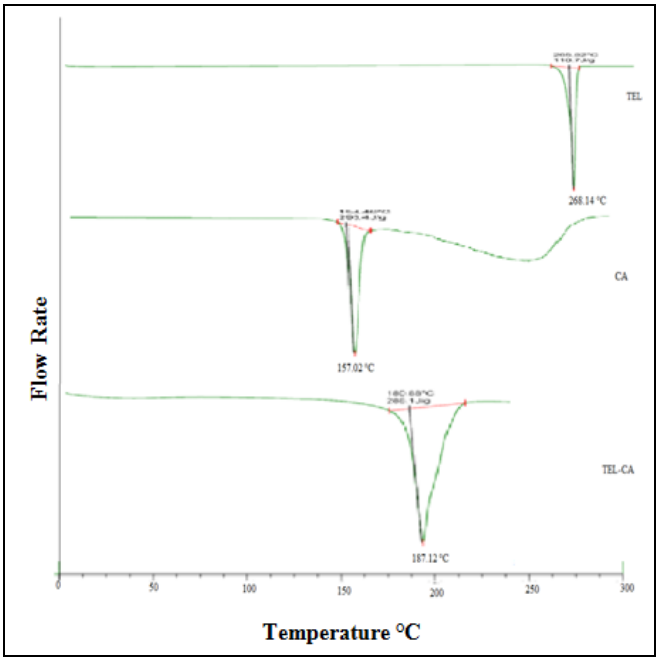


FIG. 2: DSC CURVE OF DRUG, CITIRIC ACID AND THEIR COCRYSTAL

Fourier Transform Infrared Spectroscopy (FTIR): The FT-IR spectra of TEL and its cocrystal were obtained in order to evaluate the possible interactions between telmisartan and coformers. The IR spectra of TEL and their respective coformers are depicted in **Fig. 3** and the characteristic stretching vibrations are shown in **Table 2**. The changes in carbonyl, hydroxyl and amine functional groups were used to investigate the molecular interaction between two components in cocrystal studies.

IR spectra of TEL showed characteristic stretching vibrations of carbonyl at 1697 cm^{-1}, amine (stretch) at 3057 cm^{-1}, amine (bend) 1602 cm^{-1} and vibration band of O-H stretch appeared 3395 cm^{-1}.

FT-IR spectrum of TEL-CA showed vibration band of O-H stretch shifted to 3497 cm^{-1}, carbonyl shifted to 1706 cm^{-1} and 1747 cm^{-1} and amine stretch was shifted to 3294 cm^{-1}. This suggests that -OH group and amine group between drug and coformer results in formation of cocrystal. The above results reveal that both carboxylic acid moiety as well as amine moiety of benzimidazole ring are involved in the cocrystal formation. These changes suggest that these peaks are involved in H-bond leading to cocrystal generation. Further, studies are required to clarify which part of drug molecule interacts with the carboxylic acid of coformers.

TABLE 2: CHARACTERISTIC VIBRATION PEAKS IN IR SPECTRUM OF TEL, CITRIC ACID AND THEIR COCRYSTAL

Compound	O-H stretch (in acids) (cm^{-1})	N-H stretch (cm^{-1})	C-H Alkane Stretch (cm^{-1})	C=O (cm^{-1})	C-N (cm^{-1})	C-O (cm^{-1})	N-H bend (cm^{-1})
TEL	3395	3057	2958	-	1455	1267	1602
CA	3497	3294	2770	1747, 1706	1427	-	-
TEL-CA	3522	3059	2664	1742, 1699, 1604	1456	1229	-

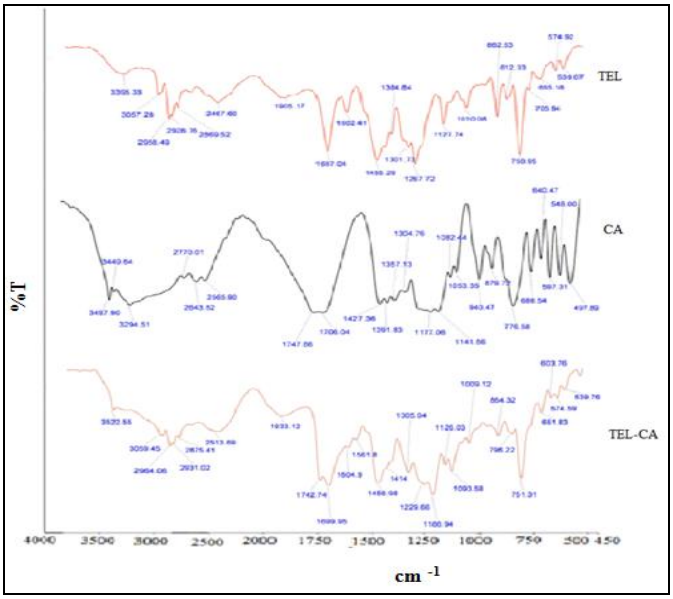


FIG. 3: FTIR SPECTRA OF TEL, CITRIC ACID AND THEIR COCRYSTAL

Powder X-ray Differaction (PXRD): PXRD is important tool for identification of new solid multicomponent form. The PXRD pattern of the crystalline structure is considered as fingerprint of its crystal structure. Every new crystalline material exihibits unique peaks indicative of reflections from specific atomatic planes. The PXRD patterns of TEL, CA and TEL-CA are summarized in **Table 3.** The PXRD patten of telmisartan showed characteristic peaks at 2θ 10.64, 12.48, 14.25, 15.06, 16.81, 17.27, 18.29, 19.02, 20.15, 21.37, 22.29, 23.82, 24.88. The PXRD pattern of TEL-CA cocrystal prepared by solvent evaporation technique showed unique crystalline peaks observed at 2θ values are 3.709,7.330, 8.846, 11.025, 13.43, 19.97, 22.22, 22.58, 23.30, 25.12 and 27.47 which were absent both in drug and

coformer. The peaks at 14.25, 15.06 and 23.13 present in drug dissapeared in cocrystal. The unique PXRD patterns of the new cocrystals were found to be completely different from the pure raw materials indicating formation of a new solid phase (**Fig. 4**).

TABLE 3: CHARACTERISTIC PEAKS OF TEL AND ITS COCRYSTAL AS OBSERVED IN PXRD PATTERNS

	2θ
TEL	6.790, 9.440, 10.64, 12.48, 14.25, 15.06, 16.20,16.81, 17.27,18.29, 19.02, 19.35, 20.15, 21.37, 22.29, 23.82, 24.88
CA	14.387, 15.099, 16.846, 18.030, 18.331, 19.774, 22.401, 24.130, 26.267,29.102, 30.186, 31.584, 37.878
TEL-CA	3.709, 6.167, 8.846, 9.924, 12.136, 13.435, 14.728, 15.526, 16.018, 17.452, 19.382, 19.972, 22.222, 22.580, 25.128, 27.478

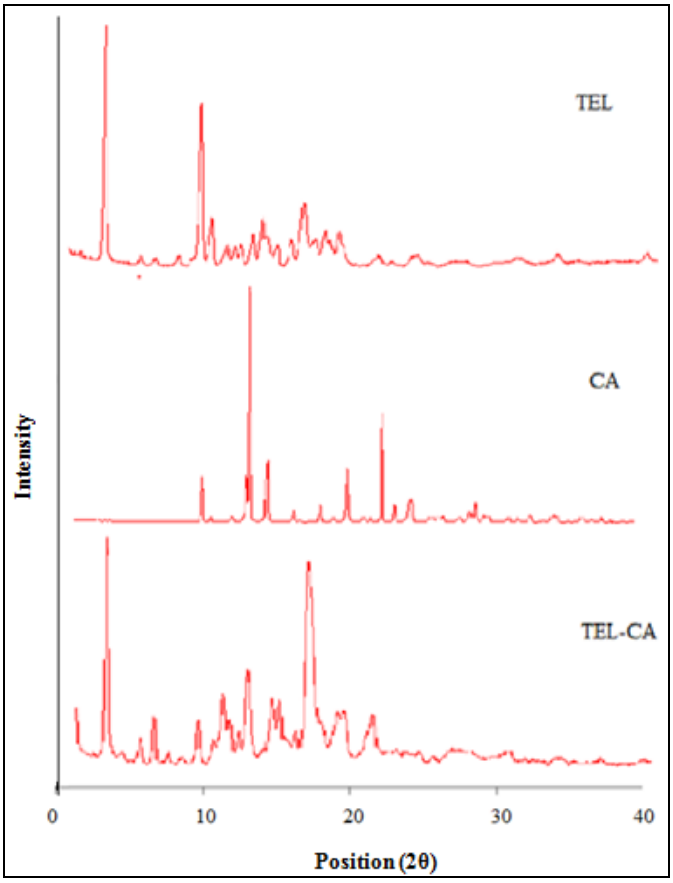


FIG 4: PXRD SPECTRA OF TEL, CITRIC ACID AND THEIR COCRYSTAL

Crystal structure determination by PXRD: The crystal structure of TEL-CA was also determined from powder X-ray diffraction as discussed in experimental section. The powder XRD pattern was also indexed using the program X-CELL giving a unit cell with triclinic symmetry (a=14.5183, b=9.9805, c=6.7943, α=6.7943, β=102.387, γ=90.2320) with space group P1 (Table 4).The asymmetric unit consist of one molecule of TEL and one molecule of citric acid. A reasonable crystal structure with R_{wp}= 20.25 % was obtained after 2,00,000 simulated annealing step shown in **Fig. 5**. The packing arrangement of TEL-CA is shown in **Fig. 6** which shows that here also a heterosynthon involving imidazole groups of TEL and carboxylic acid group CA is formed in the cocrystal.

TABLE 4: CRYSTALLOGRAPHIC DATA OF TEL-CA

Space group	P1(Triclinic)
Cell lengths	a=14.5183, b=9.9805, c=6.7943
Cell angles	α=6.7943, β=102.387, γ=90.2320
Cell volume	941.221

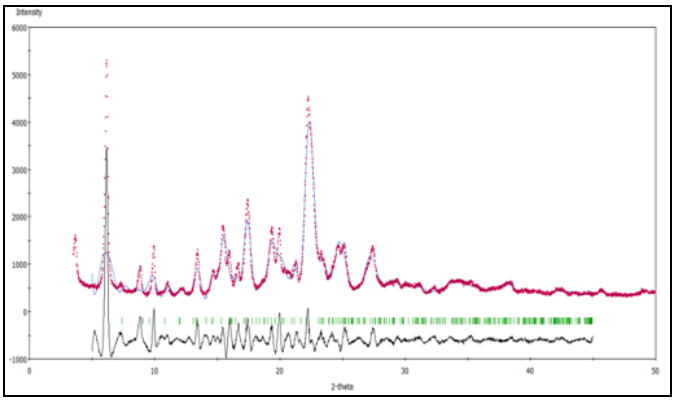


FIG 5: X-RAY INTENSITY AS A FUNCTION OF 2θ. OBSERVED (EXPERIMENTAL) PATTERN, CALCULATED (BEST RIESTVELD FIT PROFILE) PATTERNS OF TEL-CA COCRYSTAL

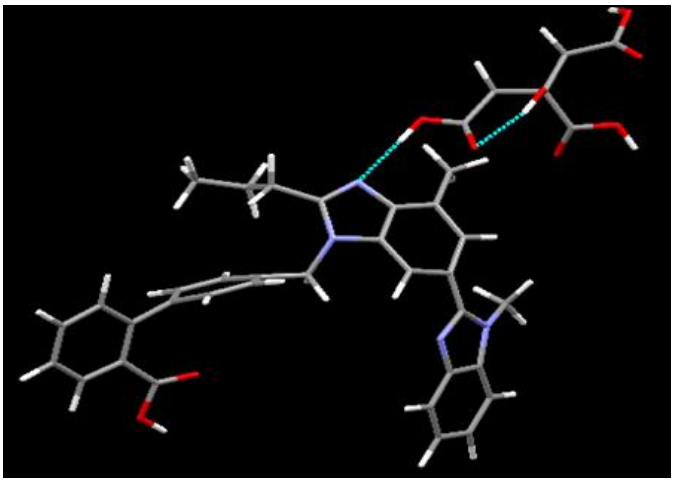


FIG. 6: PACKING DIAGRAM OF TEL-CA COCRYSTAL

Equilibrium solubility study: Solubility of drug and its cocrystal was performed in phosphate buffer pH 6.8 and 0.1N HCl pH 1.2 at 37 °C for 24 h are shown in table 5. The concentration of pure drug multicomponent forms determined by HPLC method using mobile phase (10 mM ammonium acetate buffer pH 4.5: ACN: MeOH, 30:60:10 %v/v). The solubility studies showed that these new solid forms exhibit a comparatively higher solubility as compared to the pure drug.

TABLE 5: EQUILIBRIUM SOLUBILITY (mg/ml) OF MULTICOMPONENT FORMS IN PHOSPHATE BUFFER (pH 6.8)

S.no.	Compounds	Phosphate buffer (pH 6.8)	Fold increase	0.1N HCl (pH 1.2)	Fold increase
1.	TEL	0.07	-	0.14	-
2.	TEL-CA	0.08	1.1	0.34	2.4

Intrinsic dissolution study: Intrinsic dissolution study of TEL and its multicomponent form was performed in pure water at 37 °C. Intrinsic dissolution profile of TEL and its cocrystal at various time intervals are shown in **Fig. 7**. Cocrystals showed good IDR as compared to pure drug. A maximum of ~1.6 fold increase in the dissolution rate was observed for cocrystals in comparison to pure drug (**Table 6**).

TABLE 6: INTRINSIC DISSOLUTION PARAMETER OF TEL AND ITS COCRYSTAL

Compounds	Intrinsic dissolution rate (IDR) (mg/cm^2/min)	Improvement in IDR (folds)
TEL	0.03	-
TEL-CA	0.05	1.6

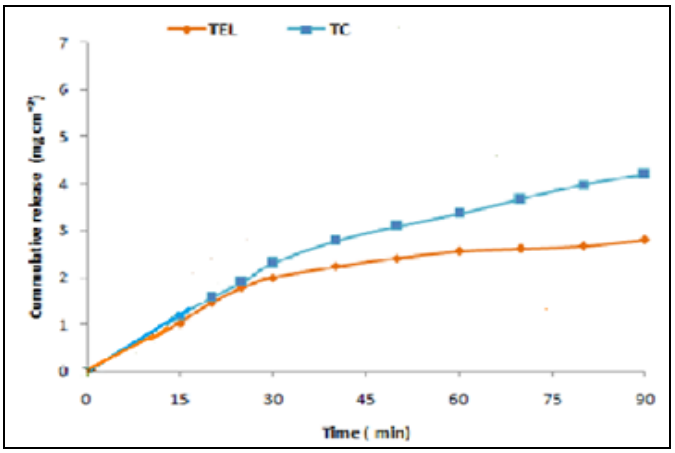


FIG. 7: INTRINSIC DISSOLUTION PROFILE OF TEL AND THEIR COCRYSTAL

Pharmacokinetics Study: Pharmacokinetic parameters of TEL and its cocrystal were determined by non-compartmental method. Telmisartan plasma concentration was assessed by the sensitive HPLC method. The pharmacokinetic parameters for pure drug TEL and TEL-CA were calculated by trapezoidal rule using kinetica software, shown in **Table 7**. The data shows that AUC_{0-28} of cocrystals was found to be 2-fold increase in bioavailability than telmisartan (**Fig. 8**).

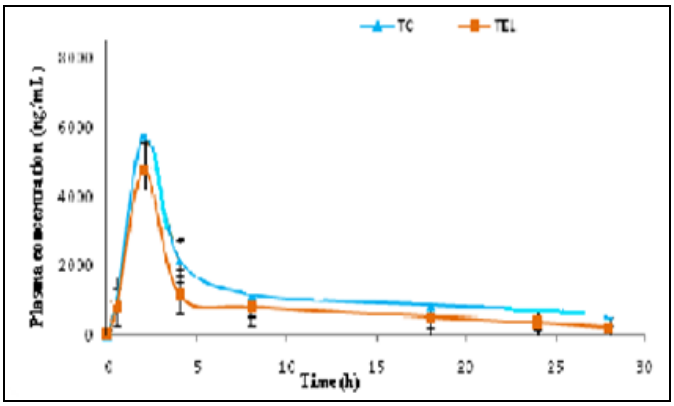


FIG. 8: THE PLASMA CONCENTRATION–TIME PROFILE AFTER ORAL ADMINISTRATION OF TEL AND TEL-CA

TABLE 7: RELATIVE PHARMACOKINETIC PARAMETER FOR TELMISARTAN AND ITS COCRYSTAL

Drug/c-crystal	C_{max} (ng ml^{-1})	AUC_{0-28} (ng h ml^{-1})	Relative Bioavailability %
TEL	4745.81	22989.12	2
TEL-CA	5750.57	36406.4	2

CONCLUSION: Cocrystallization with coformers was evaluated as a pharmaceutical development methodology to control solubility/dissolution parameters of TEL. The TEL-CA come under the category of pharmaceutical cocrystals because of generally recognized as safe status of coformer.

The main evidence for formation of cocrystal was obtained from DSC and PXRD data. The melting peak of cocrystal was in between melting points of the two components suggesting cocrystal formation. The PXRD for cocrystal contained new peaks showing a new crystalline phase. The orientation of drug molecule and coformer in a crystal lattice of the cocrystal were determined by

simulation studies. The high R_{wp} value indicated good correlation between experimental and simulated PXRD data of cocrystals.

The solubility parameters of TEL were increased as a function of cocrystals, indicating the solubility of TEL can be improved via cocrystallization. Also, this cocrystal showed ~1.6 times increased in dissolution behavior as compared to pure drug. As the solubility and dissolution are often related, we believe that bioavailability of TEL may also increased after the formation of cocrystals, which has been proved by studying the pharmacokinetic parameters of the cocrystal. Higher plasma concentration of cocrystal justified its better solubility and enhanced *in vivo* absorption of drug.

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CONFLICTS OF INTEREST: The authors have no conflicts of interest.

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