

Tailoring the Dissolution Rate of Candesartan through Cocrystal Formation

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Abstract

Context: Cocrystal technique is a novel approach for altering the physicochemical properties of an active pharmaceutical ingredient (API). Pharmaceutical cocrystals are formed by non-covalent interactions between an API and a coformer chosen from the generally recognized as safe (GRAS) substance list. Many examples exist in the literature where the cocrystal formations have led to the improvement in the dissolution of several APIs. **Aims:** Candesartan is a poorly water-soluble drug having an antihypertensive effect. The objective of the research work is to enhance the dissolution rate of candesartan through cocrystallization technique. **Materials and Methods:** Coformers were selected from the GRAS list after identifying the hydrogen bonding groups in the drug and the coformers. The coformers employed were nicotinic acid, succinic acid, nicotinamide, and benzoic acid. Cocrystals were prepared using solution crystallization method. The differential scanning calorimetry obtained data showed the cocrystal formation with the coformer benzoic acid only. Further characterization was carried out by thermogravimetric analysis, Fourier-transform infrared, Raman spectroscopy, and powder X-ray diffraction studies. Thereafter, the cocrystal was subjected to solubility and dissolution studies. Statistical Analysis Used: The dissolution studies were subjected to *t*-test using SPSS 16. **Results:** The analytical data confirmed the formation of cocrystal. There was 1.78-fold enhancement in the solubility and its dissolution profile also improved. **Conclusions:** The solubility and *in vitro* dissolution studies clearly demonstrated that cocrystallization of candesartan with benzoic acid may be a potential approach for improving its aqueous solubility.

Key words: Candesartan, cocrystal, dissolution, solubility

INTRODUCTION

Aqueous solubility is an important parameter for an active pharmaceutical ingredient (API) to be considered for its successful clinical development. The enhanced solubility has a significant impact on the pharmacokinetic profile of the orally delivered APIs as it facilitates better gastrointestinal absorption and reduces the dosage level required.^[1] Different approaches such as micronization, solid dispersions, use of surfactants, formation of self-emulsifying systems, polymorphs, and formation of complexes with cyclodextrin have been utilized for enhancing the solubility of API.^[2-7]

Nowadays, cocrystal approach for solubility enhancement has attracted tremendous interest. Cocrystal can be defined as a crystalline complex of two or more neutral molecular constituents (solid at ambient conditions) bond together in a crystal lattice through non-covalent interactions

in a definite stoichiometric ratio.^[8-10] Cocrystallization involves a wide range of intermolecular interactions such as Van der Waals contact forces, π - π stacking interactions, ion-ion, ion-dipole, and dipole-dipole interactions, coordinate bonding (metal-ligand), hydrogen bonding, and halogen bonding.^[11,12] A pharmaceutical cocrystal^[13,14] is an amalgamation of an active (API) and a coformer selected from the generally recognized as safe (GRAS) list of USFDA.^[15]

The designing of cocrystals extensively embodies the concept of supramolecular synthon. The possible supramolecular

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synthons mostly employed in pharmaceutical cocrystals are the ones that are formed due to the formation of hydrogen bonds between carboxylic homodimer, amide homodimer, and heterodimers of carboxylic acid-pyridine, carboxylic-amide, and alcohol-ether [Figure 1].

The literature reports the formation of pharmaceutical cocrystals of carbamazepine,^[18-20] ibuprofen,^[21] paracetamol,^[22] fluoxetine hydrochloride,^[23] itraconazole,^[24] indomethacin,^[25] niclosamide,^[26] lornoxicam,^[27] mefloquine hydrochloride,^[28] and ezetimibe^[29] which have been made to enhance the aqueous solubility.

The present study attempts to improve the solubility and dissolution of candesartan using cocrystal approach. Candesartan is a non-peptide angiotensin II, type I antagonist mainly used in the treatment of hypertension or heart failure having an oral bioavailability of <5%.^[30,31] The prodrug of candesartan, candesartan cilexetil, has been synthesized by esterification of a carboxylic acid group which facilitates rapid and complete conversion to active candesartan during GI absorption. Even after its conversion to its prodrug form, the oral bioavailability still remains poor because of its low aqueous solubility.^[31] Several research groups have tried to enhance the solubility of candesartan cilexetil using methods such as solid dispersions,^[32] inclusion complexes,^[33] liquisolid compacts,^[34] nano emulsions,^[35] and nanoparticles,^[36] but for pure candesartan, only the research group of Yingnan^[37] has tried to enhance the solubility through the salt formation. This prompted us to explore the cocrystal approach for enhancing the candesartan aqueous solubility.

The study has been undertaken to explore the potential of carboxylic acid group and the acidic nitrogen of the tetrazole ring present in candesartan for the formation of hydrogen bonds between the drug and the suitable cofomers chosen from the GRAS list. Solution crystallization method has been used for the preparation of cocrystal as it is one of the most suitable methods to prepare cocrystals for air stable samples. After preparation of the cocrystal, it has been characterized using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR), Raman spectroscopy, and powder X-ray diffraction (PXRD). The solubility and dissolution studies have been carried to observe the enhancement in the solubility of the prepared cocrystal.

MATERIALS AND METHODS

Candesartan was received as a gift sample from Jubilant Life sciences. All cofomers were purchased from SD fine chemicals limited, Mumbai. Solvents used for crystallization were of HPLC grade (Rankem, India). Analytical chemicals such as sodium hydroxide and potassium dihydrogen orthophosphate were purchased from Fischer Scientific, India.

Preparation of cocrystal

The cofomers selected for cocrystal formation included nicotinic acid, nicotinamide, benzoic acid, and succinic acid. The cocrystals were prepared by solution crystallization method by taking the drug and the cofomer in a molar ratio of 1:1.^[38,39] They were then dissolved in appropriate solvents as given in Table 1. The resultant solutions were then slowly evaporated at 20°C in a Rotavapor set at 10 rpm. Finally, the reduced volume was left for air drying. The cocrystal obtained was further characterized [Figure 2].

DSC

DSC of the samples was conducted using DSC Q10 (TA Instruments, USA) which was calibrated for temperature and enthalpy using indium. Samples were placed in aluminum pans and scanned from 25–200°C at a heating rate 10°C/min under purging gas nitrogen at a flow rate of 50 mL/min). Data were managed by TA Explorer software.

TGA

TGA was performed using a Perkin Elmer DTG-6000 analyzer. The samples were heated from 20°C to 350°C at a rate of 10°C/min under nitrogen gas environment.

FTIR spectroscopy

The infrared absorption spectra of drug, cofomer, and the cocrystal were obtained using FTIR spectrophotometer (IR

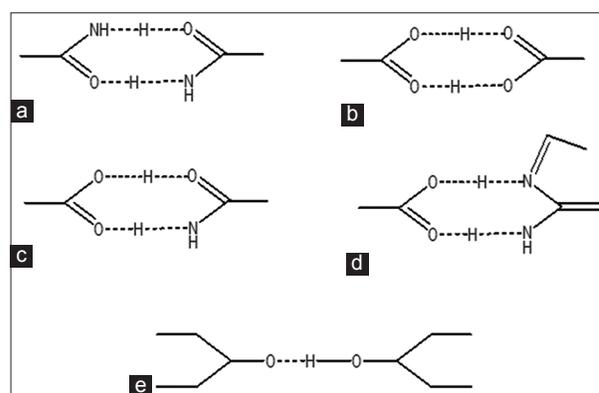


Figure 1: Synthons in pharmaceutical cocrystals^[16,17]

Table 1: Preparation of cocrystals

Cofomer	Quantity of drug and cofomer	Solvent used
Nicotinic acid	1 mmol each	15 mL of acetone
Nicotinamide	1 mmol each	15 mL of tetrahydrofuran
Succinic acid	1 mmol each	15 mL of acetone
Benzoic acid	1 mmol each	15 mL of acetone

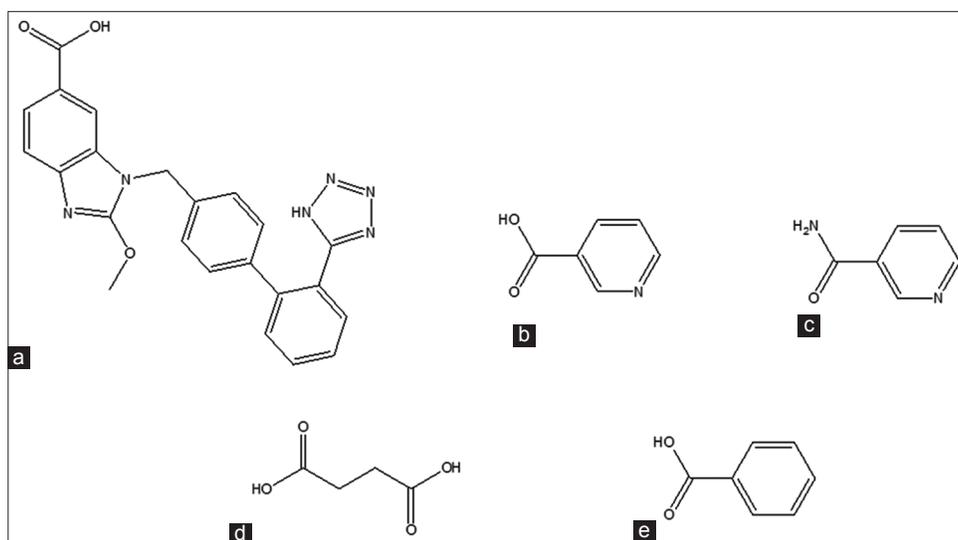


Figure 2: Structure of candesartan and coformers (2a) candesartan, (2b) nicotinic acid, (2c) nicotinamide, (2d) succinic acid, (2e) benzoic acid

sPrestige-21, Shimadzu) over a measurement range of 4000–600 cm^{-1} . Pellet was prepared by mixing 5 mg of sample with 10 times of its weight of potassium bromide. Data were analyzed using IR solution software.

Raman spectroscopy

An alpha 300 RA AFM-Raman spectrophotometer (WITec GmbH, Ulm, Germany) was used to obtain the Raman spectra. A laser (532 nm DPSS laser with a maximum power after single mode fiber of 70 mW) was coupled into the microscope using a single mode optical fiber coupling, and the Raman signal was collected into a multimode optical fiber which was connected to the UHTS 300 spectrograph.

PXRD studies

PXRD of candesartan, coformer, and cocrystal was recorded on Bruker AXS D8 advance diffractometer system with a Cu $K\alpha$ radiation (1.5406 Angstrom) at 40 kV and 35mA. Diffraction patterns were collected over 2θ range of 3–80° with a step size of 0.020° and step time 31.2 s. The experimental PXRD patterns were refined using Diffrac plus software.

Scanning electron microscope (SEM)

The surface morphology of the cocrystal was evaluated by SEM (JSM-6390LV, Jeol, Japan).

Solubility studies

Solubility studies were undertaken on the pure drug and its cocrystals in a 50:50 (v/v) ethanol-water mixture using shake flask method. In this study, an excess amount of candesartan

and cocrystal was added in separate vials containing 5 mL of the ethanol and water mixture. The vials were then kept in an orbital shaker at $37^\circ\text{C}\pm 0.5^\circ$ for 48 h. The solutions were then filtered through a 0.45- μm syringe filter. The amount of drug dissolved was analyzed spectrophotometrically at 256 nm (UV 18000, Shimadzu).

Dissolution studies

The dissolution studies were carried out in 900 mL of phosphate buffer pH 7.4 with 0.7% w/w of Tween 20 as dissolution media at 50 rpm and at a temperature of $37\pm 0.5^\circ\text{C}$ in a USP Type II dissolution apparatus. 16 mg drug or its equivalent amount of cocrystal was added to the dissolution medium. Appropriate aliquots were withdrawn at suitable time interval till 7 h. The volume of dissolution medium was adjusted to 900 mL by replacing it with fresh medium. The samples withdrawn were filtered through a 0.45 μm syringe filter, suitably diluted, and analyzed spectrophotometrically at 258 nm.

RESULTS AND DISCUSSIONS

Thermal analysis (DSC and TGA)

The development of any new solid phase is primarily determined by DSC and TGA studies. Only the DSC thermograms of pure candesartan and benzoic acid indicated a sharp single endothermic peak with melting points (T_m) at 171.9°C and 122.2°C, respectively. The cocrystal (candesartan with benzoic acid) showed an intense endothermic peak with a melting point (T_m) at 131.6°C. This is in corroboration with the reported literature data which suggest that melting point of cocrystals often lies between that of API and the conformer.^[40]

The DSC thermograms of candesartan with other coformers did not show any single sharp endothermic peaks and hence were not considered for further analysis.

The TGA curve of pure benzoic acid showed a negligible weight loss of 2.58% in the range of 30–140°C followed by a loss of 97.35% which was due to degradation of benzoic acid. Candesartan showed a loss of 38.87% in the range of 235–400°C. The TGA of cocrystal showed a negligible weight loss of 0.228% in the temperature range of 62–85°C corresponding to the weight loss due to solvent. The mass loss in cocrystal occurred in two stages. The first mass loss in the range of 140°C–235°C was 20.58% which was similar to that of the benzoic acid. The second mass loss of 32.21% in the range of 235–400°C was similar to the mass loss pattern of candesartan [Figures 3 and 4].

FTIR studies

It is one of the important analytical tools for the characterization of cocrystals. A comparison of spectra indicates that band shifting has occurred between the starting compounds and cocrystal. The FTIR of candesartan shows major bands at 2939 cm^{-1} $\nu(\text{O-H})$, 1755 cm^{-1} $\nu(\text{C=O})$, 1246 cm^{-1} $\nu(\text{C-O})$ ether stretch, and 1550 cm^{-1} $\nu(\text{N=N})$ corresponding to respective functionalities. The major bands of benzoic acid are 3008 cm^{-1} $\nu(\text{O-H})$, 1689 cm^{-1} $\nu(\text{C=O})$, and 2831 cm^{-1} $\nu(\text{C=C})$ indicating the presence of respective functional groups. In the cocrystal, the (C=O) peak of the candesartan has shifted to 1705 cm^{-1} while that of benzoic acid has moved to 1608 cm^{-1} . A peak broadening has been observed around the wave number 3100 cm^{-1} which suggests the formation of an intermolecular hydrogen bond between the carboxylic groups of both candesartan and benzoic acid [Figure 5].

Raman spectroscopy

It provides valuable information about vibrational modes of a molecule that often results from changes in the physical state of the drug. The changes also may occur because of differences in hydrogen bonding and molecular conformations.^[41] In Raman spectra of pure candesartan, bands appear at 1711.95 cm^{-1} $\nu(\text{C=O})$, 1299.21 cm^{-1} $\nu(\text{C-N})$, 1437.78 cm^{-1} $\nu(\text{N=N})$ aromatic, 1615 cm^{-1} $\nu(\text{C=N})$, 1711.95 cm^{-1} $\nu(\text{C=O})$, 1157.71 cm^{-1} $\nu(\text{C-O-C})$ asymmetric ester, and 3071.27 cm^{-1} $\nu(\text{O-H})$. During cocrystallization of candesartan with benzoic acid, the shifts of band seems to appear at 1722.37 cm^{-1} $\nu(\text{C=O})$, 1293.75 cm^{-1} $\nu(\text{C-N})$, 1437.56 cm^{-1} $\nu(\text{N=N})$ aromatic, 1608.87 cm^{-1} $\nu(\text{C=N})$, 1722.37 cm^{-1} $\nu(\text{C=O})$, 1161.70 cm^{-1} $\nu(\text{C-O-C})$ asymmetric ester, and 3068.36 cm^{-1} $\nu(\text{O-H})$. The band for (O-H) of carboxylic group of the pure drug has shifted to a lower wavenumber by 3 cm^{-1} , thus indicating that the carboxylic group might have participated in the hydrogen bond formation [Figure 6].

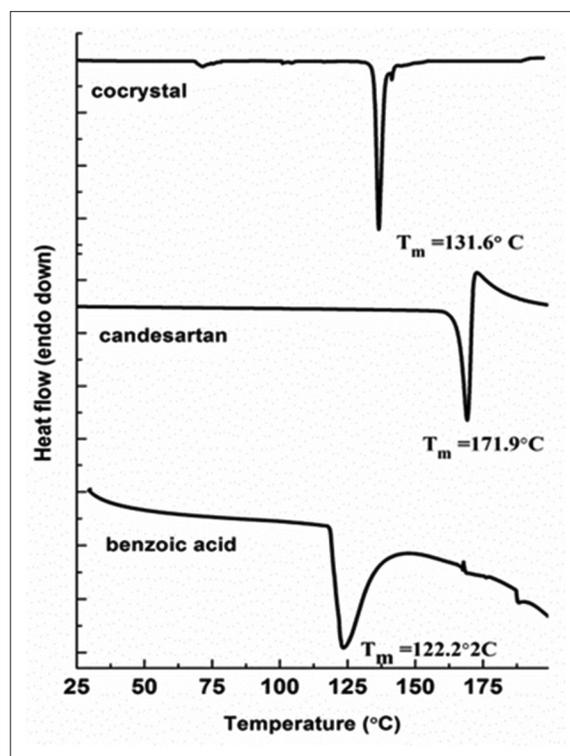


Figure 3: Differential scanning calorimetry scans of candesartan, benzoic acid, and cocrystal

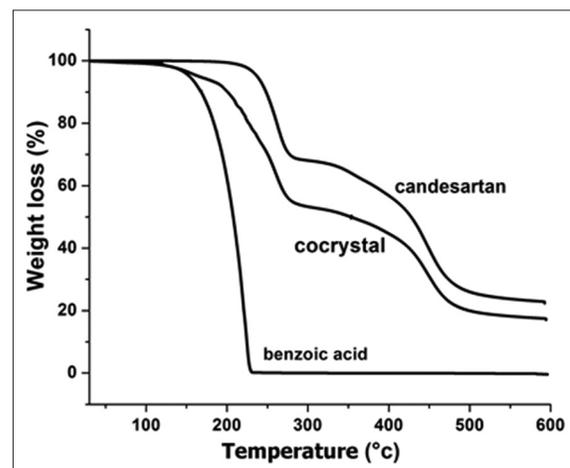


Figure 4: Thermogravimetric analysis curve of candesartan, benzoic acid, and cocrystal

PXRD

PXRD gives an insight into the formation of a new solid phase. The formation of a new solid phase can be concluded if any distinct difference occurs between the PXRD diffractogram of the cocrystallized product and the reactants. The PXRD diffractogram of candesartan exhibited characteristic reflections at 2θ 9.865°, 10.151°, 16.969°, 17.196°, 18.619°, 19.073°, 20.277°, 23.234°, 22.884°, and 25.082°. Similarly, for benzoic acid, the PXRD diffractogram exhibited characteristic reflections at 2θ 8.176°, 16.198°,

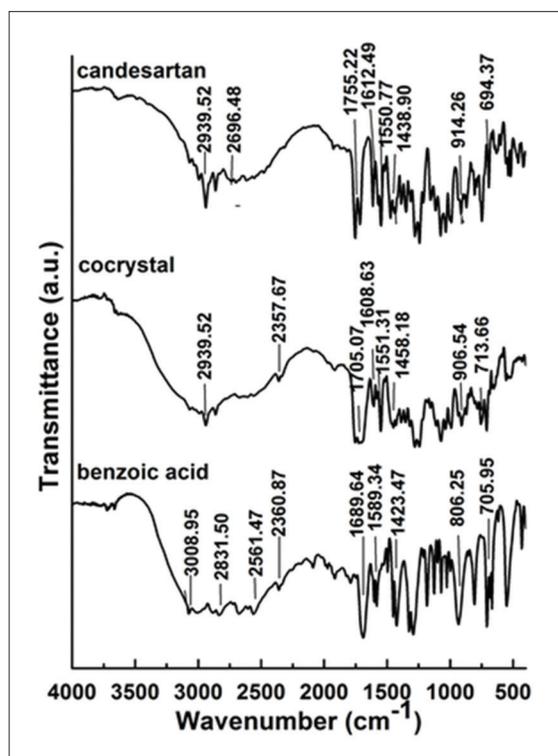


Figure 5: Fourier-transform infrared spectra obtained for candesartan, benzoic acid, and cocrystal

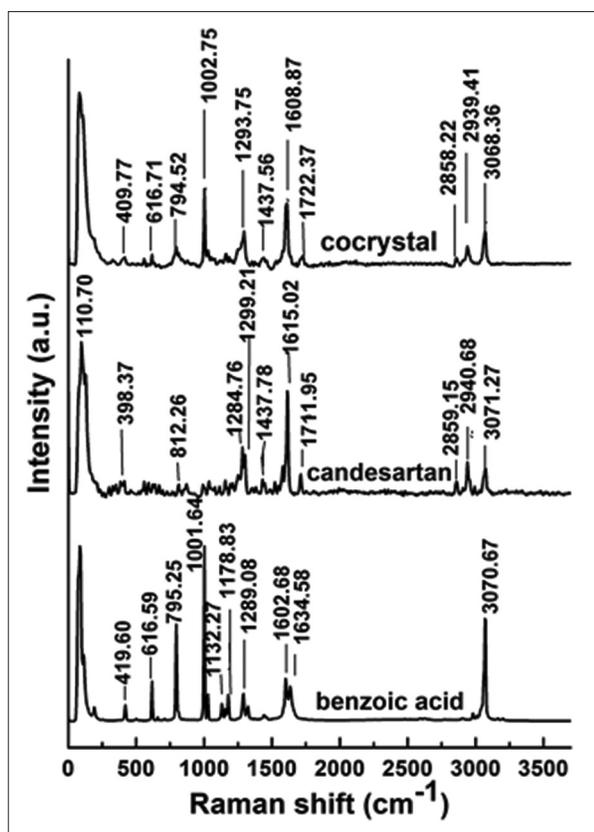


Figure 6: Raman spectra obtained for candesartan, benzoic acid, and cocrystal

17.146°, 19.034°, 23.661°, 25.691°, 25.983°, 27.655°, 27.86°, 30.01°, and 30.273°. The major peak with 100% intensity had reflections at 2θ 9.865° and 17.146° for candesartan and benzoic acid, respectively. The diffractogram of prepared cocrystal exhibited major reflections at 2θ 8.096°, 17.133°, and 23.708°. The most intense peak was observed at 2θ 23.70°. The characteristics reflections of pure drug and cofomer were absent in the diffractogram of the cocrystal. It seems that not only the characteristic peaks obtained in the diffractogram of cocrystal were different as compared to pure drug and cofomer but also the relative intensities of all the peaks were drastically reduced; further, the relative intensities of all the peaks were also drastically reduced. The intensity might have decreased due to different crystal habit and arrangement of molecules which happens when new crystals forms are formed. Henceforth, it can be inferred that the solid product obtained is pure and homogenous [Figure 7].

SEM

The SEM overview of pure drug, benzoic acid, and cocrystal is depicted in Figure 8. The particles of cocrystal appear to be needle-shaped.

Solubility studies

Candesartan is a poorly aqueous water-soluble drug, so the solubility of the pure drug and cocrystal was carried out in a 50:50 (v/v) ethanol-water mixture. The pure drug candesartan exhibited a solubility of 2.032 ± 0.050 mg/mL, whereas the solubility of cocrystal was found out to be 3.606 ± 0.074 mg/mL. The results suggested that there has been an enhancement of 1.78 fold in the solubility of candesartan after cocrystallization.

Dissolution studies

The solubility studies clearly showed that cocrystals of candesartan had a higher solubility than pure candesartan. The dissolution studies were thereafter carried out to ascertain whether the increase in solubility is correlated with the increase in the *in vitro* drug release. The *in vitro* release study of candesartan and the cocrystal was carried out in phosphate buffer pH 7.4 (0.7% w/w tween 20). At the end of 7 h, candesartan showed the drug release of 18.42%, whereas the drug release for the cocrystal was found to be 85.22%. The results have been graphically depicted in form of dissolution curves in Figure 9.

The release data and dissolution efficiency (DE %) at a different sampling time of drug and cocrystal is shown in Table 1. The results were analyzed by t-test at a significance level of 95%. The results clearly showed that significant difference exists between the release rate and DE % of pure drug and cocrystal ($P < 0.05$). The faster dissolution of candesartan from cocrystal may be attributed to changed crystallinity pattern, size, shape, and its crystal habit [Table 2].

Table 2: Dissolution data and dissolution efficiency percent (DE %) of pure candesartan and cocrystal in phosphate buffer 7.4, (0.7% w/w tween 20) at 37±0.5°C

Sample	%DR ₄₅ ^a ±SD	%DR ₆₀ ^a ±SD	%DR ₁₂₀ ^a ±SD	DE _{60%}	DE _{120%}
Candesartan	01.63±1.25	06.04±0.95	11.83±1.50	3.15	27.08
Cocrystal	37.25±2.35	53.09±3.15	68.35±1.73	5.23	32.35

^aIndicates±SD., (n=3); SD: Standard deviation, %DR₄₅, %DR₆₀, and %DR₁₂₀: Percentage drug release in 45 min, 60 min, and 120 min; DE_{60%} and DE_{120%}: Dissolution efficiency percentage at 60 min and 120 min

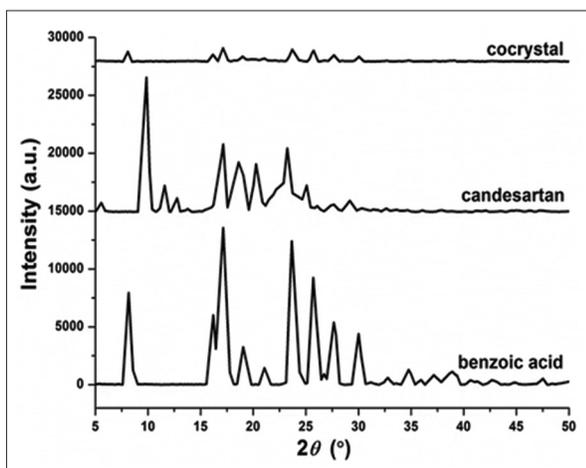


Figure 7: Powder X-ray diffraction pattern of candesartan, benzoic acid, and cocrystal

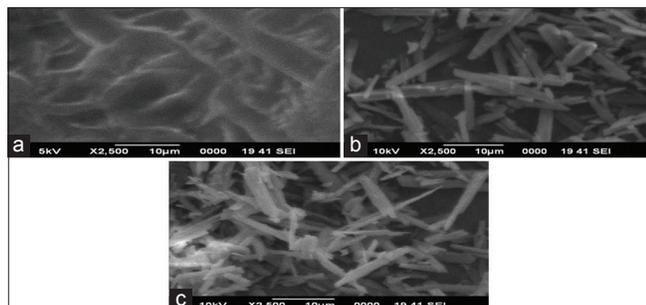


Figure 8: (a) Scanning electron microscopy (SEM) images of benzoic acid at ×2500, (b) SEM images of candesartan at ×2500, (c) SEM images of cocrystal at ×2500

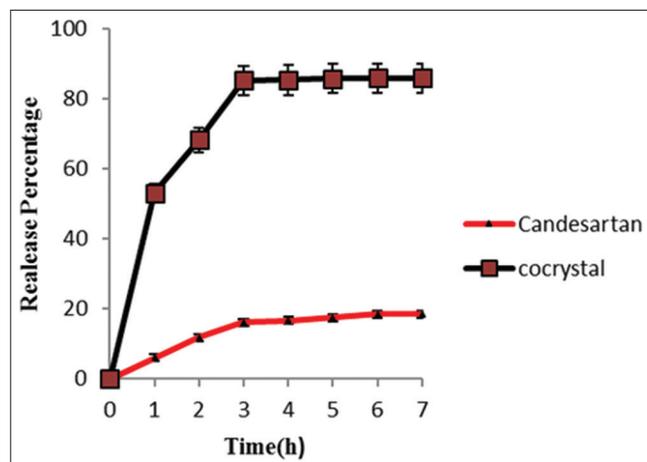


Figure 9: Dissolution curves of candesartan and cocrystal

CONCLUSION

Tailoring the physicochemical properties through cocrystal approach is gaining momentum as it is a novel approach for enhancing the aqueous solubility of poorly water-soluble drugs. The present study illustrates the formation and characterization of a cocrystal of candesartan using benzoic acid as a coformer by solution crystallization method. The analytical tools such as DSC, TGA, FTIR, Raman, and PXRD confirmed the formation of the cocrystal. The cocrystal formed showed a remarkable improvement in the drug release profile as compared with the pure drug.

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REFERENCES

1. Van Arnum P. Solubilizing the insoluble. *Pharm Technol* 2010;34:50-6.
2. Chaumeil J. Micronization: A method of improving the bioavailability of poorly soluble drugs. *Methods Find Exp Clin Pharmacol* 1998;20:211-6.
3. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm* 2000;50:47-60.
4. Kawakami K, Oda N, Miyoshi K, Funaki T, Ida Y. Solubilization behavior of a poorly soluble drug under combined use of surfactants and cosolvents. *Eur J Pharm Sci* 2006;28:7-14.
5. Abdalla A, Mäder K. Preparation and characterization of a self-emulsifying pellet formulation. *Eur J Pharm Biopharm* 2007;66:220-6.
6. Singhal D, Curatolo W. Drug polymorphism and dosage form design: A practical perspective. *Adv Drug Deliv Rev* 2004;56:335-47.
7. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. *Chem Rev* 1998;98:2045-76.
8. Aakeroy CB, Salmon DJ. Building co-crystals with molecular sense and supramolecular sensibility. *Cryst Eng Comm* 2005;7:439-48.

9. Bhogala BR, Basavoju S, Nangia A. Tape and layer structures in cocrystals of some di- and tricarboxylic acids with 4,4 [prime or minute]-bipyridines and isonicotinamide. From binary to ternary cocrystals. *Cryst Eng Comm* 2005;7:551-62.
10. Jones W, Motherwell WD, Trask AV. Pharmaceutical cocrystals: An emerging approach to physical property enhancement. *MRS Bull* 2006;31:875-9.
11. Maitland GC, Smith EB, Wakeham W. Intermolecular Forces: Their Origin and Determination. Oxford: Oxford University Press; 1981.
12. Cinčić D, Friščić T, Jones W. Isostructural materials achieved by using structurally equivalent donors and acceptors in halogen-bonded cocrystals. *Chem Eur J* 2008;14:747-53.
13. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. *J Pharm Sci*. 2006;95:499-516.
14. Sanphui P, Goud NR, Khandavilli UB, Nangia A. Fast dissolving curcumin cocrystals. *Cryst Growth Des* 2011;11:4135-45.
15. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: Three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001;26:331-42.
16. Bruni G, Berbenni V, Maggi L, Mustarelli P, Friuli V, Ferrara C, *et al.* Multicomponent crystals of gliclazide and tromethamine: Preparation, physico-chemical, and pharmaceutical characterization. *Drug Dev Ind Pharm* 2018;44:243-50.
17. Basavoju S, Bostrom D, Velaga SP. Indomethacin-saccharin cocrystal: Design, synthesis and preliminary pharmaceutical characterization. *Pharm Res* 2008;25:530-41.
18. Walsh RD, Bradner MW, Fleischman S, Morales LA, Moulton B, Rodriguez-Hornedo N, *et al.* Crystal engineering of the composition of pharmaceutical phases. *Chem Commun* 2003;2:186-7.
19. Fleischman SG, Kuduva SS, McMahon JA, Moulton B, Walsh RD, Rodríguez-Hornedo N, *et al.* Crystal engineering of the composition of pharmaceutical phases: Multiple-component crystalline solids Involving carbamazepine. *Cryst Growth Des* 2003;3:909-19.
20. Ullah M, Hussain I, Sun CC. The development of carbamazepine-succinic acid cocrystal tablet formulations with improved *in vitro* and *in vivo* performance. *Drug Dev Ind Pharm* 2016;42:969-76.
21. Jennifer AM, Joanna AB, Vishweshwar P, Tanise RS, Olga LM, Michael JZ. Crystal engineering of the composition of pharmaceutical phases. 3¹ Primary amide supramolecular heterosynthons and their role in the design of pharmaceutical co-crystals. *Z Kristallogr* 2005;220:340.
22. Vishweshwar P, McMahon JA, Peterson ML, Hickey MB, Shattock TR, Zaworotko MJ. Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. *Chem Commun* 2005;36:4601-3.
23. Childs SL, Chyall LJ, Dunlap JT, Smolenskaya VN, Stahly BC, Stahly GP. Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic Acids. Molecular complexes of fluoxetine hydrochloride with benzoic, succinic, and fumaric Acids. *J Am Chem Soc* 2004;126:13335-42.
24. Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee JM, Guzmán HR, *et al.* Crystal engineering of novel cocrystals of a triazole drug with 1, 4-dicarboxylic acids. *J Am Chem Soc* 2003;125:8456-7.
25. Alhalaweh A, Sokolowski A, Rodríguez-Hornedo N, Velaga SP. Solubility behavior and solution chemistry of Indomethacin cocrystals in organic solvents. *Cryst Growth Des* 2011;11:3923-9.
26. Sanphui P, Kumar SS, Nangia A. Pharmaceutical cocrystals of niclosamide. *Cryst Growth Des* 2012;12:4588-99.
27. Nijhawan M, Santhosh A, Babu PR, Subrahmanyam CV. Solid state manipulation of lornoxicam for cocrystals–physicochemical characterization. *Drug Dev Ind Pharm* 2014;40:1163-72.
28. Yadav AV, Dabke AP, Shete AS. Crystal engineering to improve physicochemical properties of mefloquine hydrochloride. *Drug Dev Ind Pharm* 2010;36:1036-45.
29. Sugandha K, Kaity S, Mukherjee S, Isaac J, Ghosh A. Solubility enhancement of ezetimibe by a cocrystal engineering technique. *Cryst Growth Des* 2014;14:4475-86.
30. Unger T. Pharmacological aspects of candesartan, an effective AT1-receptor blocker. *Eur Heart J Suppl* 2004;6:h11-h6.
31. Shibouta Y, Inada Y, Ojima M, Wada T, Noda M, Sanada T, *et al.* Pharmacological profile of a highly potent and long-acting angiotensin II receptor antagonist, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylic acid (CV-11974), and its prodrug, (+/-)-1-(cyclohexyloxycarbonyloxy)-ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylate (TCV-116). *J Pharmacol Exp Ther* 1993;266:114-20.
32. Gurunath S, Nanjwade BK, Patila PA. Enhanced solubility and intestinal absorption of candesartan cilexetil solid dispersions using everted rat intestinal sacs. *Saudi Pharm J* 2014;22:246-57.
33. Shaikh SM, Avachat AM. Enhancement of solubility and permeability of candesartan cilexetil by using different pharmaceutical interventions. *Curr Drug Deliv* 2011;8:346-53.
34. Sayyad FJ, Tulsankar SL, Kolap UB. Design and development of liquisolid compact of candesartan cilexetil to enhance dissolution. *J Pharm Res* 2013;7:381-8.
35. Gao F, Zhang Z, Bu H, Huang Y, Gao Z, Shen J, *et al.* Nanoemulsion improves the oral absorption of candesartan cilexetil in rats: Performance and mechanism. *J Controlled Release* 2011;149:168-74.

36. Nekkanti V, Pillai R, Venkateshwarlu V, Harisudhan T. Development and characterization of solid oral dosage form incorporating candesartan nanoparticles. *Pharm Dev Technol* 2009;14:290-8.
37. Chi Y, Xu W, Yang Y, Yang Z, Lv H, Yang S, *et al.* Three candesartan salts with enhanced oral bioavailability. *Cryst Growth Des* 2015;15:3707-14.
38. Zhang GG, Henry RF, Borchardt TB, Lou X. Efficient cocrystal screening using solution-mediated phase transformation. *J Pharm Sci* 2007;96:990-5.
39. Childs SL, Rodriguez-Hornedo N, Reddy LS, Jayasankar A, Maheshwari C, McCausland L, *et al.* Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. *Cryst Eng Comm* 2008;10:856-64.
40. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst Growth Des* 2009;9:2950-67.
41. Elbagerma MA, Edwards HG, Munshi T, Hargreaves MD, Matousek P, Scowen IJ. Characterization of new cocrystals by raman spectroscopy, powder X-ray diffraction, differential scanning calorimetry, and transmission raman spectroscopy. *Cryst Growth Des* 2010;10:2360-71.

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