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Original Article

PHARMACEUTICAL COCRYSTAL OF PRULIFLOXACIN WITH NICOTINAMIDE

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ABSTRACT

Objective: Cocrystals have been increasingly recognized as an attractive alternative for solid forms of drug products. In this work nicotinamide (NCT) was employed to form the cocrystal with the active pharmaceutical ingredient prulifloxacin (PF).

Methods: The PF-NCT cocrystal was prepared by employing slow evaporation and solution crystallization methodology from acetone as a solvent. The PF-NCT cocrystal was characterized by powder X-ray diffraction (PXRD), infrared (IR) spectroscopy, raman spectroscopy, ^{1}H NMR spectroscopy and differential scanning calorimetry (DSC). The PF-NCT cocrystal was then subsequently evaluated for pharmaceutical relevant properties such as aqueous solubility and hygroscopicity.

Results: Synthesis of cocrystal of prulifloxacin with nicotinamide were successfully carried out by solvent evaporation and solution crystallization methods using acetone solvent. The results from Powder X-ray diffraction, DSC, IR, Raman spectroscopic analysis revealed the formation of cocrystal of prulifloxacin and nicotinamide.

Conclusion: The PF-NCT cocrystal is moderately hygroscopic and exhibit enhanced solubility than the pure drug. This study confirms cocrystallization offers a valuable way to improve the physicochemical properties of the API.

Keywords: Cocrystallization, Prulifloxacin, Nicotinamide, Solvent evaporation method.

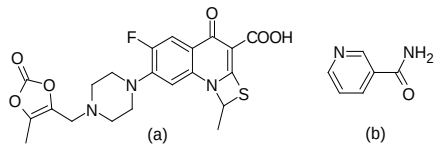
INTRODUCTION

Solubility of active pharmaceutical ingredients (APIs) is one of the highest concerns for oral commercial solid drugs [1,2]. The bioavailability of an oral medicine depends on its solubility in the gastrointestinal tract and its permeability across biological cell membranes [3,4]. Thus, enhancement of the solubility of an API is most important physicochemical property for pharmaceutical development [5]. Cocrystallization of APIs with coformers (e. g. other APIs or solubilizing agents) have shown improved physicochemical properties (solubility, bioavilability, melting point) [6-8].

A cocrystal is defined as a multiple component crystal that consists of two or more solid components in a definite stoichiometric ratio held together via non covalent interactions [9]. It has received increased attention in the pharmaceutical industry because of the potential to adjust the physiochemical and biological properties of original active pharmaceutical ingredients, such as melting point, solubility, bioavilability and chemical stability [10, 11]. Intermolecular interactions between different components provide opportunities for cocrystal preparation by design through the use of supermolecular synthons, such as pairs of carboxylic acid/carboxylic acid, carboxylic acid/aromatic nitrogen, carboxylic acid/amide and amide/aromatic nitrogen.

Cocrystal can be prepared through cogrinding of the components [12], cooling of a heteromeric solution [13], evaporation [14], sublimation [15] growth from the melt and slurry [16, 17]. Recently various cocrystals have been constructed by neat grinding of the two or more components together with a mortar and pestle or in a mixture mill, which has been termed solid state grinding [18,19]. A significant enhancement to solid-state grinding is popularly known as solvent-drop grinding or kneading [20] where the co crystalization kinetics may be notably enhanced by the addition of a few drops of solvent. Despite of its simplicity, a major draw back of the grinding method is that the product is usually too small in particle size and limited application at large scale.

Prulifloxacin (PF) is an API, chemically known as 6-Fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid, is one of the most important broad-spectrum antibacterial agents and a member of fourth generation fluoroquinoline family [21]. Fluoroquinolines inhibit enzyme DNA gyrase, which is responsible for the supercoiling of the DNA double helix, preventing the replication and repair of bacterial DNA and RNA [22]. This drug was first developed by Nippon Shinyaku and marketed with the trade name of Quisnon. PF exists in four polymorphic forms (Type-I, Type-II, Type-III and Form-A) [23, 24]. Marketed form is Type-III. Because of its low solubility and high permeability, this drug was classified as BCS class-II drug. The physical and chemical properties of prulifloxacin can be improved by cocrystalization with other small molecules. PF can form strong hydrogen bonds with coformers via O-H. O-H and O-H. N-H interactions. To the best our knowledge, only one reference involving the cocrystal of prulifloxacin with salicylic acid has been reported until now, in which the prulifloxacin-salicylic acid cocrystal was obtained by grinding method [25].



Scheme 1: Molecular structures of PF (a), NCT (b)

In this study the PF-NCT cocrystal prepared via slow evaporation and solvent crystallization methods. Nicotinamide (NCT) has been employed as a cocrystal former with prulifloxacin (PF). Nicotinamide was chosen as a cocrystal former with prulifloxacin as it is amide of niacin, one of the members of the vitamin B family (B_3), and has been used extensively as multi vitamin component and is largely considered to be safe[26].

Experimental section

The PF used was made in-house (>99% purity), and NCT (>99%) was purchased from Fisher Scientific. Analytical grade acetone was used for the experimentation.

Method 1: Prulifloxacin (1 mmol) was dissolved in 230 ml acetone by slight warming and filtered through micron filter. At room

temperature, 0.5 ml methanol solution containing 1 m mol of co former (NCT) was added into the PF solution. The solution was then slowly evaporated in a fume hood at room temperature. The product obtained was dried at 50 ^{0}C for 12 h to remove residual solvent.

Method 2: Pruli floxacin (1 m mol) was suspended in 65 ml of acetone. The mixture was heated to 55-60 ^{0}C which resulted in a clear solution. The hot solution was filtered through the micron filter. 0.5 ml methanol solution containing 1 m mol of coformer (NCT) was added in to the hot PF solution. The solution was evaporated to approximately 5 ml by heating at 55-60 ^{0}C. The hot solution was seeded with cocrystal (PF-NCT) and cooled to 30^{0}C. Stirred at room temperature over a period of 5h. The precipitate formed was filtered off and was dried at 50 ^{0}C for 12 h to remove residual solvent.

Characterization

Powder X-ray diffraction (PXRD) - The powder X-Ray diffraction pattern was measured on pan analytical X-ray diffractometer. The samples were scanned from 0 to 40° (2Θ). Infrared absorption spectrums (FTIR) were obtained using Perkin Elmer FTIR spectrophotometer. All the samples were compressed into disks with KBr and analyzed over the range of 400-4000 cm^{-1}. Raman spectroscopy were collected using a Raman RXN system. The ^{1}H NMR spectra were measured on a Bruker Avance 400 MHz FT magnetic resonance spectrometer. Differential scanning calorimetry (DSC) was conducted by using Mettler-Toledo DSc-821e differential scanning calorimeter.

Saturation solubility studies of PF and its cocrystal were carried out in water. An excess quantity of sample (50 mg) was added to 10 ml vials containing ultra pure water. The vials were then shaken in shaker water bath at a temperature of 35 ± 2^{0}C until the solution became saturated. After 24 h sample solution withdrawn and filtered through whatman's filter paper No. 1A. The concentration of the solution was determined spectroscopically using UV spectrometer (UV-1800, Shimadzu) at λ_{max} 280 nm. Stock solution for plotting the standard calibration curve was prepared by transferring accurately weighed quantity of PF/cocrystal into the volumetric flask. Required quantity of water was added to the above volumetric flask. The flask was shaken until the drug was completely soluble and flask was then makeup with remaining quantity of water. The absorbance of the solution measured at 280 nm using UV spectrometer.

RESULTS AND DISCUSSION

Fig 1 represents the PXRD pattern of the PF, NCT and PF-NCT cocrystal. PF shows its characteristic PXRD peaks at 7.6, 8.3, 13.9, 17.6, 18.2, 18.7, 21.54, 21.93, 26.2, 26.7 (highest) and 28.71º2Θ. The pattern of NCT is characterized by major peaks at 10.9 (highest), 17.24, 25.14, 25.29, 28.06, 28.72, 30.6º2Θ. The PF–NCT product shows its characteristic peaks at 7.1(highest), 14.89, 18.99, 25.83, 31.5 and 31.7º2Θ. Absence of characteristic peaks of PF and NCT clearly shows that PXRD of PF-NCT product clearly distinguishable from inputs which indicates the formation of a new solid phase.

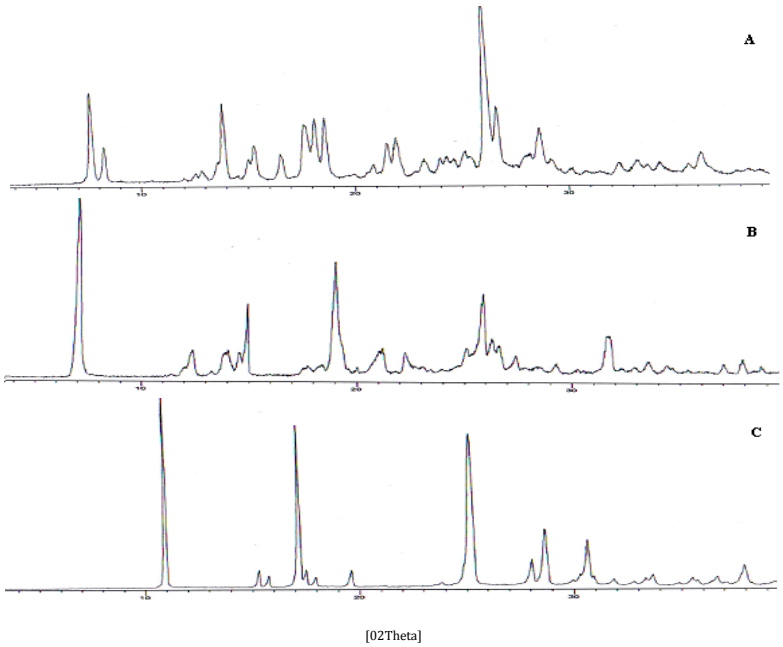


Fig. 1: PXRD pattern of PF (A), PF-NCT (B) and NCT (C)

Fig. 2 represents the ^{1}HNMR pattern of the PF-NCT cocrystal.^{1}HNMR shows small changes in the chemical shifts of cocrystal due to weak intermolecular hydrogen bonding between the two components. The ^{1}HNMR chemical shift assignments of PF–NCT are as follows. (CF_3COOD, 400 MHz): δ 9.8 (S, 1H), 9.28 (m), 9.14 (d, 1H, J=5.88 Hz), 8.36 (1H, m), 8.25 (d, 1H, J=12.7 Hz), 7.16 (d, 1H, J=6.68Hz), 6.6 (q, 1H, 6.44 Hz), 4.6 (s, 1H), 4.1-4.3 (m, 4H), 3.6–3.8 (m, 4H), 2.37 (m, 6H).

Intermolecular interactions

The FTIR spectra of PF and coformer and cocrystal are presented in the fig 3. The FTIR spectra of cocrystal shows obvious differences in the wave numbers and intensities for some major bands compared to their individual components. PF contains stretching vibration of (O-H) at 3430 cm^{-1}, (C=O) stretching vibration of ester at 1803 cm^{-1}, (C=O) stretching vibration of carboxylic acid at 1716 cm^{-1}, stretching vibration of (C=O) of ketone at 1629 cm^{-1}, stretching vibration of (C-H) at 2835 cm^{-1}, and bending vibration of (O-H) at 1397 cm^{-1} and stretching vibration of (C-O) at 1232 cm^{-1} and bending of (C-H) at 1469 cm^{-1}.

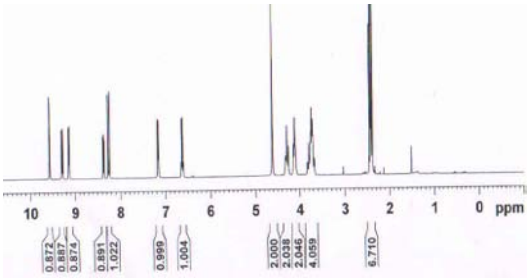
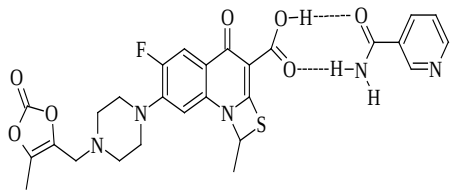


Fig. 2: ^{1}HNMR of PF-NCT Cocrystal

The integrals of the H signals marked in the figure 2 indicate the molar ratio of PF/NCT should be 1:1.



Scheme 2: Perspective view of Intermolecular hydrogen bonding between Prulifloxacin and nicotinamide

NCT contains asymmetric and symmetric stretching vibrations v(N-H)$_1$ and v(N-H)$_2$ of –NH2 at 3366 and 3160 cm^{-1}. Stretching vibration of (C=O) is at 1680 cm^{-1} and bending of (N-H) at 1618 cm^{-1}.

For PF – NCT cocrystal, the bands assigned to the asymmetric and symmetric vibrations of –NH_2 group are shifted to 3367 and 3180 cm^{-1} in the cocrystal. The (C=O) stretching vibration of NCT shifted to 1684 cm^{-1} in the cocrystal. (O-H) stretching vibration of PF shifted to 3591 cm^{-1} and (C=O) stretching vibration of ester in PF shifted to 1814 cm^{-1}. (C=O) stretching vibrations of carboxylic acid and ketone in PF are shifted to 1715 and 1627 cm^{-1} in the cocrystal. Bending vibration of (O-H) shifted to 1375 cm^{-1}. Bending vibration of (C-O) shifted to 1228 cm^{-1}. (C-H) band is replaced by a new band at 2947 cm^{-1} due to hydrogen bonding between -O-H (carboxylicacid) and –N-H (amide).

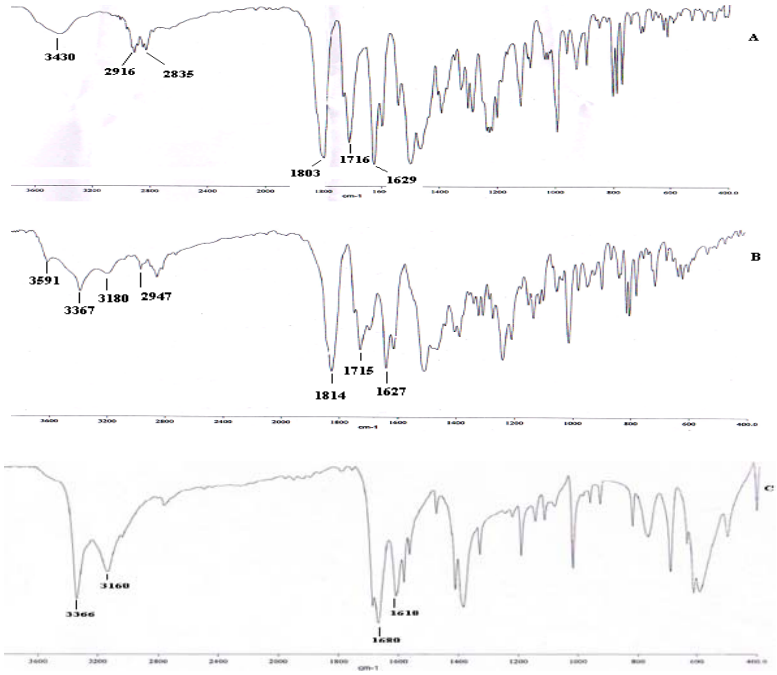
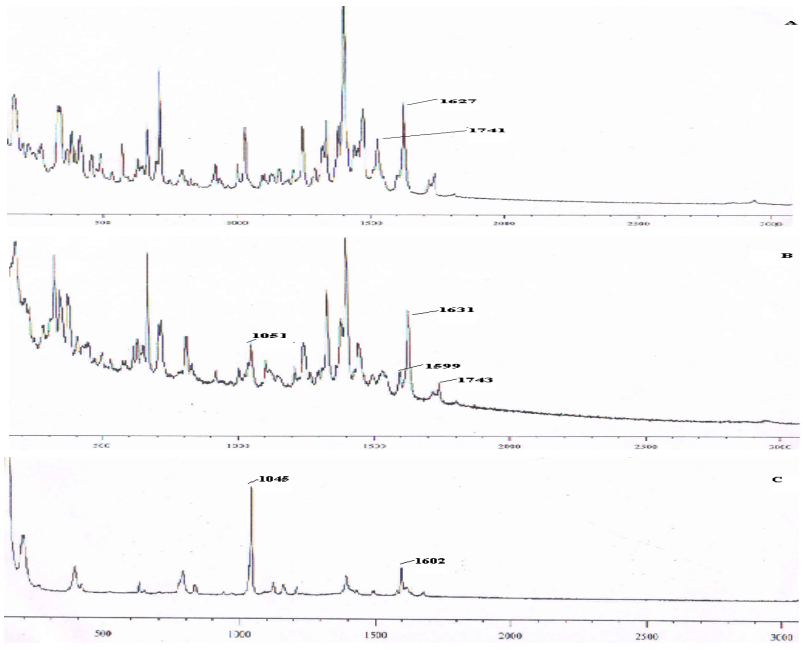


Fig. 3: FTIR of PF (A), PF-NCT cocrystal (B) and NCT (C)



Raman shift / cm-1

Fig. 4: Raman spectra of PF (A), PF-NCT (B) and NCT (C)

Themal properties

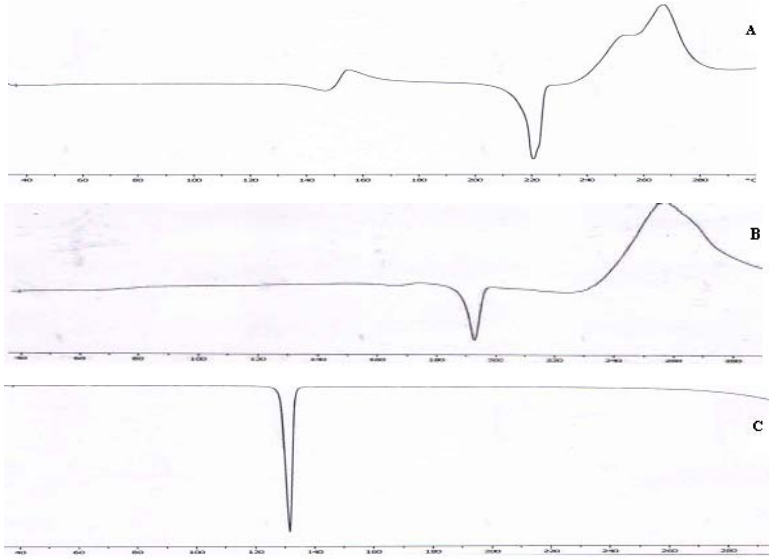


Fig. 5: DSC curves of PF (A), PF-NCT (B) and NCT (C)

Raman spectroscopic data were used to evaluate whether the complex is of a cocrystal or in the ionization state. Raman spectrums for nicotinamide, prulifloxacin and PF-NCT cocrystal are presented in fig 4. Raman spectroscopy for nicotinamide has bands at 1602 and 1045 cm^{-1}, corresponding to C=O stretching and NH_2 rocking.

Crystals of prulifloxacin exhibits Raman bands at 1741 and 1627 cm^{-1} (carbonyl groups). When a salt is formed with amine bases the carbonyl bands are shifted to lower frequencies by 30 to 40 cm^{-1}. In PF-NCT cocrystals frequencies of carbonyl groups are shifted, but the magnitude of shift is relatively small due to hydrogen bonding.

As shown in the figure 4 due to the formation of PF-NCT cocrystal the C=O bands of prulifloxacin are shifted to 1743 and 1631 cm^{-1}. The C=O and NH_2 bands of NCT are shifted to 1599 and 1050 cm^{-1}respectively. All these changes suggest the molecular complex of prulifloxacin and nicotinamide as cocrystal.

Thermo dynamic property of an API may be readily modified by cocrystal formation. The melting temperature of cocrystal is often between the API and coformer or below the both individual components. DSC experiments were conducted to study the thermal behavior of PF-NCT cocrystal and their individual components. The endothermic event of PF-NCT occurred at 193^0C between the melting point of PF (220 ^{0}C) and NCT (129 ^{0}C). This thermodynamic property of PF-NCT indicates that PF-NCT should be in one substance as a new solid form instead of a mixture. Fig 5 shows the thermograms of PF, PF-NCT complex and NCT.

Dissolution properties

The solubility of APIs can also be modified via cocrystal formation [27]. Initial saturated solubility studies were performed for PF-NCT cocrystal by using ultra pure water in shaker water bath at a temperature of 35 ± 2^0C. The results showed that PF-NCT cocrystal has more solubility that is 120 µg/ml than pure prulifloxacin 20 µg/ml in water. It shows pure prulifloxacin has moderate solubility which may have solubility problems. Such possible problems can be fixed by the use of cocrystals, which have a solubility classified as high. The 5-6 fold increase in solubility also offer potential choice to reduce the API dosage needed by the patient and, consequently, a high possibility to lower the cost of treatment.

Hygroscopicity

Sample of PF-NCT cocrystal was placed in a climate cabinet set at 25±2 ^{0}C and 80±2^0% relative humidity for 24 h in an open condition. The percentage of absorbed water by PF-NCT cocrystal increased by 3.2%. Which indicates PF-NCT cocrystal was moderately hygroscopic in nature. PXRD was used to examine any solid state transformation by stored samples at 35 ± 2 ^{0}C with 58 ± 2^0C RH for thirty days. Characteristic peaks at 7.1, 18.9, 25.8º2Θ indicates that 1:1 PF-NCT cocrystal is stable at 35 ± 2 ^{0}C with 58 ± 2^0C RH for the test period.

CONCLUSION

In this study prulifloxacin–nicotinamide cocrystal was obtained using slow evaporation and solution cocrystallization methods. Carboxylic acid-amide hydrogen bonds are the main intermolecular forces between PF and conformer. Compared to prulifloxacin PF-NCT cocrystal showed enhanced solubility. Excellent aqueous solubility and good stability characteristics are desirable for pharmaceutical formulations. This study confirms cocrystalization offers a valuable way to improve the physicochemical properties of the API.

CONFLICT OF INTERESTS

Declared None

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