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Cocrystals of Modafinil-Nicotinic acid:A Novel Cocrystal for Enhanced Bioavailability

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Abstract: In this work, we are the first to identify and report pharmaceutically effective cocrystals of poorly soluble drug Modafinil (MOD) using crystal engineering approach. A multi-component system of MOD with nicotinic acid (NIC) as coformer at 1:1 molar ratio was prepared tosimultaneously improve solubility, dissolution and bioavailability by applying liquid assistantgrinding technique. Nicotinic acid as a potential coformer for cocrystal preparation was predicted using a novel approach of Hansen Solubility Parameter (HSP) group contribution method. Various evaluation parameters pertaining to confirm cocrystal formation like Fourier Transformer Infrared spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Field Emission Scanning Electron Microscopy (FESEM) were carried out. Further effect of precipitation inhibitors (HPMC) onin-vivobioavailability enhancement was also studied. MOD-NIC cocrystals formation was confirmed by integrating results of instrumental techniques. Aqueous solubility andin-vivopharmacokinetic study proved 5.96 and 1.88 times higher bioavailability respectively in case of prepared cocrystals compared to MOD alone whereas bioavailability further increased by 2.72 times when these cocrystals were administered in presence of precipitation inhibitor. Hence, solid state manipulation was successful for preparing modafinil cocrystals as a potential method for illustrating several properties. The concept of cocrystals coupled with precipitation inhibitors significantly enhanced the bioavailability of modafinil.

Keywords: Modafinil, nicotinic acid, cocrystals, bioavailability

Introductio

Cocrystal are neutral crystalline solid materials composed of two or more compounds generally in a stoichiometric proportion. One of the compounds is drug and the remaining being excipients selected from generally recognized as safe (GRAS) list. Cocrystals possess superior physicochemical properties especially solubility than the parent compound. Cocrystals are employed to prepare specialized preparations called supersaturable formulationsusing HPMC as a precipitation inhibitor(PPI). They generate supersaturable drug solution after oral administration. Further this prevents the drug getting precipitated making the solution form available for drug absorption for prolonged periods. This approach significantly enhances bioavailability of poorly soluble drugs like modafinil. In this study, an attempt was made to prepare and characterize modafinil cocrystals which thereafter were tested for the effect of supersaturable formulations for the enhanced bioavailability.

Methods

Preparation of Modafinil Cocrystals: Modafinil cocrystals were prepared using nicotinic acid as a coformer. Nicotinic acid was selected based on the Hansen solubility parameter (HSP). Here HSP for modafinil was calculated using group contribution methods such as Fedors(26.27H), Hoy's(23.13H), and Van Krevelan (23.15H) methods. Similarly the HSP for nicotinic acid was Fedors (27.11H), Hoy's (25.71H), and Van Krevelan (23.95H) methods. It was reported that if the difference in the HSP of drug and coformer is less than 7MPa1/2as suggested by Greenhalgh, then cocrystals may be formed.1This combination of drug and coformer obeys this rule. Liquid assisted grinding method was employed to prepare the cocrystals.2Modafinil and nicotinic acid were taken in equal ratio and were subjected to grinding using ethanol for 45 min. The surface solvent was removed by storing the samples in desiccators, containing calcium chloride in the well till further use.

Characterization of Modafinil Cocrystals: Modafinil cocrystals were subjected to characterization for the properties such as melting point (DBK melting point apparatus), aqueous solubility(Reciprocating shaker water bath, Research & Test Equipments), dissolution(TDT 08LElectrolab). They were also analysed using several instrumental techniques like particle size analysis (using Zetasizer, Malvern Instruments Ltd), infrared spectroscopy (Shimadzu, Kyoto, Japan), differential scanning calorimetry (Shimadzu 60, Kyoto, Japan available at Manipal), X-Ray diffraction studies (XPERT-PRO).

Bioavailability studies of modafinil-nicotinic acid cocrystals: The three groups of healthy albino rabbits (2.5 kg average weight) were subjected to in vivostudies. The first was administered with modafinil API (4.0 mg/kg), second group was administered with Modafinil-nicotinic acid cocrystals (6.0 mg/kg), and third group was administered with Modafinil-nicotinic acid cocrystals with HPMC (7.5 mg/kg). After drug administration, blood was withdrawn at regular time intervals (0, 0.5, 1, 2, 4, 8, 12, 24, and 48 hours). The withdrawn blood was centrifuged at 4500 rpm for 20 min at 4 oC. The supernatant was collected and injected into HPLC system. Prior permission from IAEC was taken to carry out the animal studies (Letter no. BEA.BPh/183/2018-19, dated 10/11/2**018).**

Results and Discussion

Remarkable changes were noticed in the physicochemical properties of modafinil-nicotinic acid cocrystals. Melting point of the cocrystals was found to be 100 ℃ which is different from the melting point of either the drug or coformer. The solubility of the modafinil was increased from 0.52 + 0.01 mg/ml of API to 3.10 + 0.02 mg/ml of cocrystals. Thirty percent of the drug was released from modafinil API within 60 min where as 100% the drug was released in 30 min from the cocrystals.

Vibrational shifts were observed when the spectra of modafinil and nicotinic acid were compared with the spectrum of the cocrystals. The overlay of the thermograms of modafinil, nicotinic acid, and the cocrystals is shown in the Figure 1. The perusal to the figure reveals that the cocrystals were formed. The overlay of the diffraction patterns of modafinil, nicotinic acid, and the cocrystals is shown in the Figure 2. From the figure, the formation of the cocrystals was confirmed.

Mean modafinil-plasma concentration time profile is shown in the Figure 3. The mean plasma concentration was increased to 719.26 μg/ml from 521.54 μg/ml. This increase is attributed to the increased solubility of modafinil due to cocrystal formation. Further addition of HPMC delayed the precipitation of modafinil and maintained the concentration of modafinil over a prolonged period of time which improved the AUC to 901.59 μg/ml. The study signifies predominance of the non-covalent derivative.

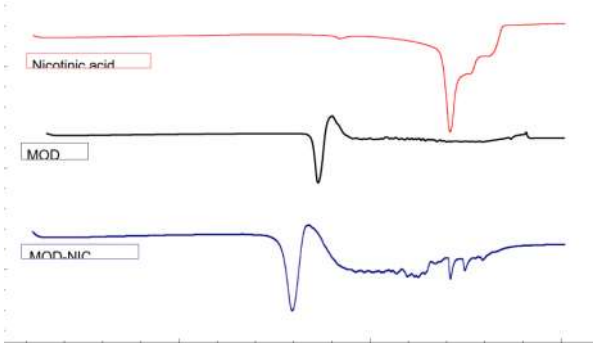

Figure 1. Overlay of DSC of modafinil, nicotinic acid, and modafinil-nicotinic acid cocrystals.

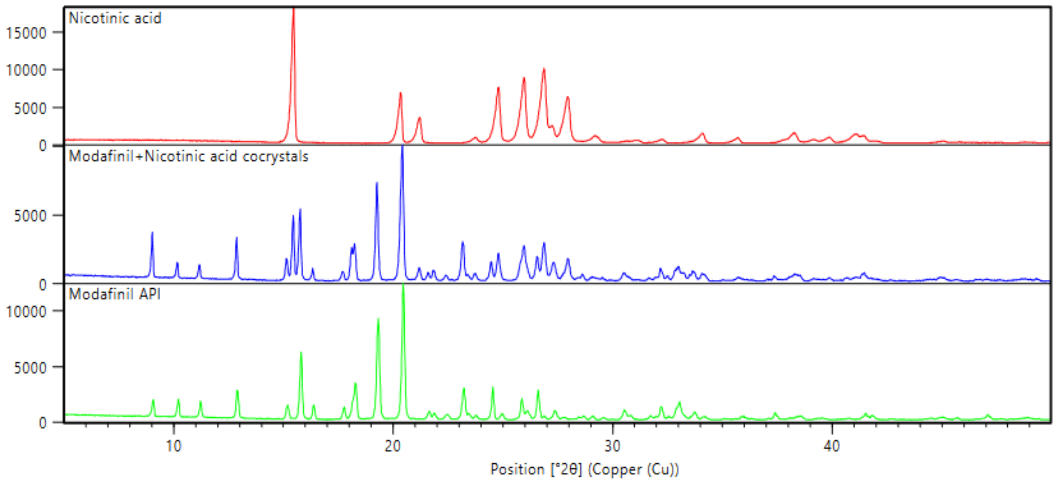

Figure 2. Overlay of XRD of modafinil, nicotinic acid, and modafinil-nicotinic acid cocrystals.

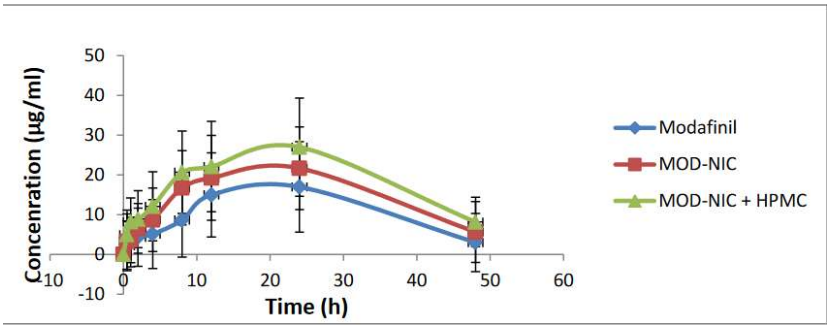

Figure 3. Mean modafinil-plasma concentration time profile.

Conclusions

In summary, solubility parameter can be used as a tool to select suitable coformers to prepare cocrystals. Liquid assisted grinding technique was proved as a useful method for the preparation of cocrystals. The work emphasizes the application of cocrystals to improve physicochemical properties of the drug. Further it illustrates the use of HPMC as a PPI to maintain the supersaturated solution state of the drug in vivo. Suitable formulation of modafinil with calculated quantities of the excipients including PPI can increase the bioavailability of modafinil.

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