

# Cocrystals of Modafinil-Nicotinic Acid: A Novel Cocrystal for Enhanced Bioavailability <sup>†</sup>

Tanmoy Ghosh <sup>1,\*</sup>, Thimmasetty Juturu <sup>2</sup>, Shashank Nayak Nagar <sup>2</sup> and Shwetha Kamath <sup>2</sup>

<sup>1</sup> Department of Pharmaceutics, Faculty of Pharmacy, Ramaiah University of Applied Sciences, Bangalore 560054, India

<sup>2</sup> Department of Pharmaceutics, Bapuji Pharmacy College, Davangere and Rajiv Gandhi University of Health Sciences, Davangere 577004, India; thimmasetty@yahoo.com (T.J.); shashanknayak87@gmail.com (S.N.N.); shwetha26pharma@gmail.com (S.K.)

\* Correspondence: tanmoysakti@gmail.com

<sup>†</sup> Presented at the 2nd International Electronic Conference on Crystals, 10–20 November 2020; Available online: [https://iocc\\_2020.sciforum.net/](https://iocc_2020.sciforum.net/).

Published: 13 January 2021

**Abstract:** In this work, we are the first to identify and report pharmaceutically effective cocrystals of the poorly soluble drug Modafinil (MOD) using a crystal engineering approach. A multi-component system of MOD with nicotinic acid (NIC) as the coformer at a 1:1 molar ratio was prepared to simultaneously improve the solubility, dissolution and bioavailability by applying a liquid assistant grinding technique. Nicotinic acid as a potential coformer for cocrystal preparation was predicted using a novel approach of the Hansen Solubility Parameter (HSP) group contribution method. Various evaluation parameters pertaining to confirm cocrystal formation, such as 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 effects of precipitation inhibitor Hydroxypropyl methyl cellulose (HPMC) on in-vivo bioavailability enhancement were also studied. MOD-NIC cocrystals formation was confirmed by integrating the results of instrumental techniques. Aqueous solubility and in-vivo pharmacokinetic study proved 5.96 and 1.88 times higher bioavailability, respectively, in the case of prepared cocrystals compared to MOD alone, whereas bioavailability further increased by 2.72 times when these cocrystals were administered in the 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

---

## 1. Introduction

Cocrystal are neutral crystalline solid materials composed of two or more compounds generally in a stoichiometric proportion. One of the compounds is a drug and the other one is usually an excipient selected from generally recognized as safe (GRAS) list of USFDA. Cocrystals possess superior physicochemical properties—especially solubility—compared to the parent compound. Cocrystals are employed to prepare specialized preparations called supersaturable formulations using HPMC as a precipitation inhibitor (PPI). They generate a supersaturable drug solution after oral administration. Further, this prevents the drug from precipitating making the solution form available for drug absorption for prolonged periods. This approach significantly enhances the 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 enhanced bioavailability.

## 2. 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 (26.27 H), Hoy's (23.13 H), and Van Krevelan (23.15 H) methods. Similarly, the HSP for nicotinic acid was Fedors (27.11 H), Hoy's (25.71 H), and Van Krevelan (23.95 H) methods. It was reported that if the difference in the HSP of drug and coformer is less than 7 MPa<sup>1/2</sup> as suggested by Greenhalgh, then cocrystals may be formed. [1] This combination of drug and coformer obeys this rule. The liquid assisted grinding method was employed to prepare the cocrystals. [2] Modafinil and nicotinic acid were taken in an 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 and test equipment), dissolution (TDT 08LElectrolab). They were also analyzed using several instrumental techniques such as particle size analysis (using Zetasizer, Malvern Instruments Ltd, UK.), infrared spectroscopy (Shimadzu, Kyoto, Japan), differential scanning calorimetry (Shimadzu 60, Kyoto, Japan available at Manipal), X-ray diffraction studies (XPERT-PRO).

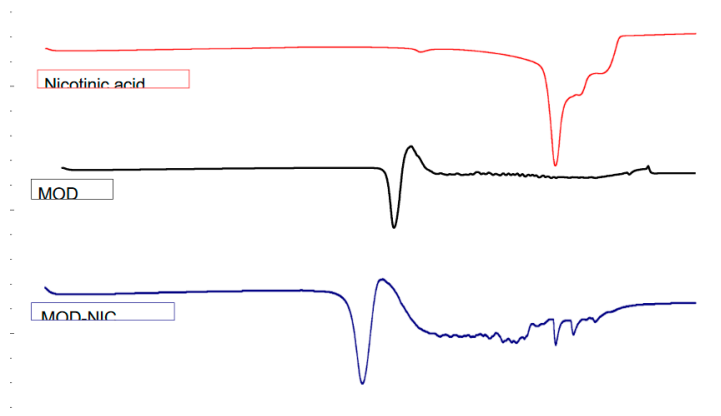
**Bioavailability studies of modafinil-nicotinic acid cocrystals:** the three groups of healthy albino rabbits (2.5 kg average weight) were subjected to in vivo studies. The first was administered with modafinil API (4.0 mg/kg), second group was administered with modafinil–nicotinic acid cocrystals (6.0 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 h). The withdrawn blood was centrifuged at 4500 rpm for 20 min at 4 °C. The supernatant was collected and injected into HPLC system. Prior permission from IAEC was obtained to carry out the animal studies (Letter no. BEA.BPh/183/2018-19, dated 10 November 2018).

## 3. Results and Discussion

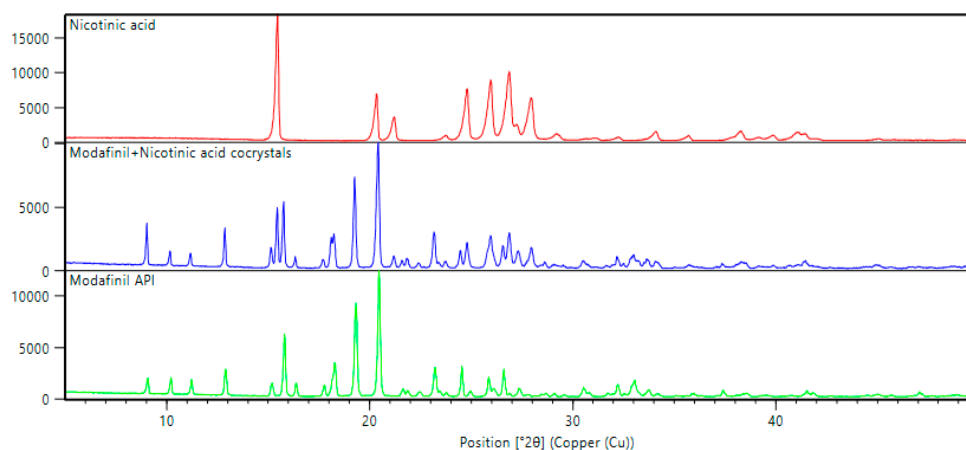
Remarkable changes were noticed in the physicochemical properties of modafinil–nicotinic acid cocrystals. Melting point of the cocrystals was found to be 100 °C which is different from the melting point of either the drug or coformer. The solubility of the modafinil was increased from 0.52 + 0.01 mg/mL of API to 3.10 + 0.02 mg/mL of cocrystals. Thirty percent of the drug was released from modafinil API within 60 min, whereas 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 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 Figure 2. From the figure, the formation of the cocrystals was confirmed.

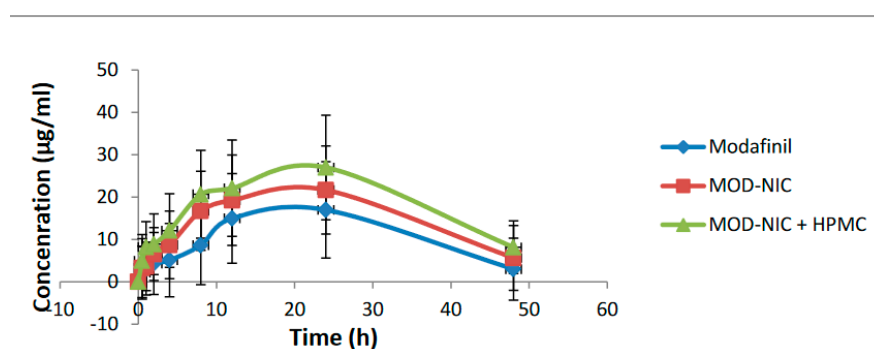
Mean modafinil–plasma concentration time profile is shown in Figure 3. The mean plasma concentration was increased to 719.26 µg/mL from 521.54 µg/mL. This increase is attributed to the increased solubility of modafinil due to cocrystal formation. Further addition of HPMC delayed the precipitation of 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 differential scanning calorimetry (DSC) of modafinil, nicotinic acid, and modafinil-nicotinic acid cocrystals.



**Figure 2.** Overlay of X-ray diffraction (XRD) of modafinil, nicotinic acid, and modafinil-nicotinic acid cocrystals.



**Figure 3.** Mean modafinil-plasma concentration time profile.

#### 4. Conclusions

In summary, the solubility parameter can be used as a tool to select suitable coformers to prepare cocrystals. The liquid assisted grinding technique was proven 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.

**Acknowledgments:** The authors acknowledge Rajiv Gandhi University of Health Sciences, Karnataka for funding this project (Project Code: P036) and Bapuji Pharmacy College, Davangere, Karnataka for providing the necessary facilities.

## References

1. Mohammed, M.A.; Alhalaweh, A.; Velaga, S.P. Hansen solubility parameter as a tool to predict cocrystal formation. *Int. J. Pharm.* **2011**, *407*, 63–71.
2. Arijit, M.; Robin, D.R.; Myerson, A.S. Cocrystal formation by ionic liquid assisted grinding; case study with cocrystals of caffeine. *CrystEngComm* **2018**, *20*, 3817–3821.

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



© 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).