UNIVERSITI TEKNOLOGI MARA

INVESTIGATION OF NICOTINAMIDE:CINNAMIC ACID AND NICOTINAMIDE:*p*-COUMARIC ACID COCRYSTALS

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ABSTRACT

A pharmaceutical cocrystal is defined as a solid compound that contains two or more different molecular components, which able to modify the physicochemical properties of drugs. In this work, cinnamic acid (CIN), and *p*-coumaric acid (COU) were employed as the coformers for the cocrystal formation with nicotinamide (NIC) as the active pharmaceutical ingredient (API). The cocrystals formations were studied using various feed molar ratios (1:1, 1:2, and 2:1) of API and coformer using different solvent (methanol, ethanol, and acetonitrile). The cocrystals formations were investigated through different solid state methods namely neat grinding, liquid-assisted grinding, and fast evaporation. The solid state samples were characterized using DSC, PXRD, and FTIR. Crystal structures of the cocrystals were determined by a single crystal X-ray diffraction (SCD) and supported with ^{1}H-NMR data. Both cocrystals of NIC:CIN (1:1) and NIC:COU (1:1) resolved from SCD were packed in the monoclinic with the space group $P2_1/c$, and $Z=4$. An amide-carboxylic acid heterosynthon was detected in both molecular packing of the cocrystals, with intermolecular hydrogen bonds of O-H···N and N-H···O. Molecular modelling technique was used to assess the molecular interactions using both empirical atom-atom and *ab initio* quantum mechanical methods to predict the morphology of the cocrystals. The simulated cocrystals morphologies were in a good agreement with the morphology observed experimentally. The hydrogen bonding interaction simulated by this method was also in agreement with the SCD result. The formation of NIC:CIN (1:1) cocrystal has significantly improved the solubility, which differ to NIC:COU (1:1) that experienced receded solubility in ethanol as compared to NIC. The antioxidant properties of the cocrystals determined using the DPPH radical scavenging assay showed remarkable improvement in the radical scavenging activity of NIC:CIN (1:1) cocrystal with 43.46 % , and the NIC:COU (1:1) cocrystal with 77.06 % compared to NIC individually, at 1000 μM, and 31.3 μM respectively.

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CHAPTER ONE
INTRODUCTION

1.1 Research Background

The common challenge faced by a pharmaceutical scientist is to effectively deliver the active pharmaceutical ingredients (APIs) in solid form due to poor aqueous solubility (Shewale, Shete, Doijad, Kadam, Patil, & Yadav, 2015), which lead to only about 10% of the active compounds in their solid forms are marketable (Variankaval, Cote, Doherty, 2008). A number of approaches have been pursued to improve the solubility of the APIs such as micronization, use of salt forms, and the use of cosolvents and micellar solutions (Raghuram, Sarwar Alam, Prasad, & Has, 2014). Although these techniques can effectively overcome the problem, there is still a need to optimize its physicochemical properties without tampering the molecular structure itself.

Previous works suggested that cocrystallization approach is able to enhance the solubility of the APIs without modifying the chemical structure, which have attracted most attention due to their unique properties such as enhancement of solubility/dissolution, physical/chemical stability and mechanical properties (Aakeröy, Forbes, & Desper, 2009; Huang, Zhang, Gao, Zhang, & Shi, 2014; Keramatnia, Shayanfar, & Jouyban, 2015; Kitak, Dumicic, Planinsek, Sibanc, & Srcic, 2015; Mittapalli, Mannava, Khandavilli, Allu, & Nangia, 2015; Song, Chen, & Lu, 2015; Stavropoulos, Johnston, Zhang, Rao, Hurrey, Topp, & Kadiyala, 2015; Baghel, Cathcart, & O'Reilly, 2016; Thipparaboina, Mittapalli, Thatikonda, Nangia, Naidu, & Shastri, 2016; Gadade, Pekamwar, Lahoti, Patni, & Sarode, 2017; Lee, Kim, Park, Rhee, Park, & Park, 2017; Sopyan, Fudholi, Muchtaridi, & Sari, 2017; Cadden, Klooster, Koles, & Aitipamula, 2019; Park, Yoon, Yun, Ban, Yun, & Kim, 2019; Ren, Liu, Hong, Li, Sun, Wang, Zhang, & Xie, 2019; Samipillai & Rohani, 2019; Weng, Wong, Xu, Xuan, Wang, Chen, Sun, Lakerveld, Kwok, & Chow, 2019).

Almarsson and Zaworotko (2004) coined the term cocrystal as being a subset of a broader group of multicomponent crystal. Cocrystals that is also known as crystalline molecular complexes are defined as multicomponent crystalline solids