Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2019; 9(1); 21-26
doi: 10.25258/ijddt.9.1.4

ISSN: 0975 4415

Research Article

Glibenclamide-Nicotinamide Cocrystals Synthesized by The Solvent Evaporation Method to Enhance Solubility and Dissolution Rate of Glibenclamide

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Received: 13th Nov, 18; Revised: 6th Jan, 19, Accepted: 12th Feb, 19; Available Online: 25th Mar, 2019

ABSTRACT
Purpose: To develop glibenclamide-nicotinamide cocrystals with the solvent evaporation method and evaluate their solubility and dissolution properties. Methods: Cocrystals of glibenclamide-nicotinamide (1:2) were prepared with the solvent evaporation method. The prediction of interactive cocrystals was observed using *in silico* method. The solubility and dissolution were performed as evaluation of cocrystals. The cocrystals also were characterized by differential scanning calorimetry (DSC), infrared spectrophotometry, and powder X-ray diffraction (PXRD). Result: The solubility and dissolution profile of glibenclamide-nicotinamide cocrystal (1:2) increased significantly compared to pure glibenclamide as well as its physical mixture. Characterization of cocrystal glibenclamide-nicotinamide (1:2) including infrared Fourier transform, DSC, and PXRD, indicated the formation of a new solid crystal phase differing from glibenclamide and nicotinamide. Conclusion: The confirmation of cocrystal glibenclamide-nicotinamide (1:2) indicated the formation of new solid crystalline phases that differ from pure glibenclamide and its physical mixture.

Keywords: Cocrystal, Glibenclamide, Nicotimanide, Solvent Evaporation.

INTRODUCTION

Solubility, dissolution, and gastrointestinal permeability are important parameters that affect the rate of absorption and bioavailability of the drug[1]. The solubility of a drug in water plays an important role in the absorption of the drug after oral administration. Thus, the bioavailability of a drug depends not only on water solubility and drug permeability, but also on dissolution rate and first-pass metabolism of a drug. However, water solubility and permeability of a drug are important parameters for the bioavailability of the oral dosage form[2,3]. In the discovery of this drug, almost 70% of new active pharmaceutical ingredients (API) show poor solubility in water and lead it into poor dissolution in the GI fluids. This is the main parameter in the bioavailability of drugs after oral administration[3]. Therefore, increasing the dissolution rate of poor water soluble drugs is important in enhancing their bioavailability.

Glibenclamide (5-chloro-N-[2-[4-(cyclohexylcarbamoylsulfamoyl) phenyl] ethyl]-2-methoxybenzamide) is one such API with poor solubility in water. It is a type 2 antidiabetic drug used for controlling glycemia[4]. Based on biopharmaceutical classification system (BCS), glibenclamide is belong to class II, which means it is highly permeable and low soluble. Several methods for increasing the solubility of glibenclamide have been studied, such as solid dispersion[5], surface solid dispersion, nanoparticles[6], and nanoemulsions[7]. But the disadvantage of those methods is that they are less stable when made in a solid preparation.

The use of cocrystals is a method to improve the solubility of an active pharmaceutical ingredient (API). It also improves dissolution rate and bioavailability of the drug. Structurally, components that contain crystalline material present in a definite stoichiometric amount[8]. Cocrystal is the crystalline complexes of two or more neutral molecular constituents bonded together in the crystal lattice through hydrogen bonding[9]. Complex crystal formation consists of a drug and a coformer with a defined stoichiometric ratio, connected by a synthon. The *synthon* in pharmaceutical crystals engineering is "a noncovalent interaction involving hydrogen bonds, Van der Waals, and π-π electrons"[10]. The key in designing cocrystals is choosing a synthon that is likely to form a crystallization process[9]. The *in silico* method can predict the interaction of synthon, API, and the coformer.

In the present work, cocrystals of glibenclamide-nicotinamide was synthesized by solvent evaporation to improve API's solubility, similar to previous studies. Glibenclamide has potential hydrogen acceptors and donor functional groups like chlorine, secondary amides, and sulphonamide that increase the formation of noncovalent interactions with various cocrystal coformers, such as nicotinamide[11]. The solvent evaporation (SE) methods

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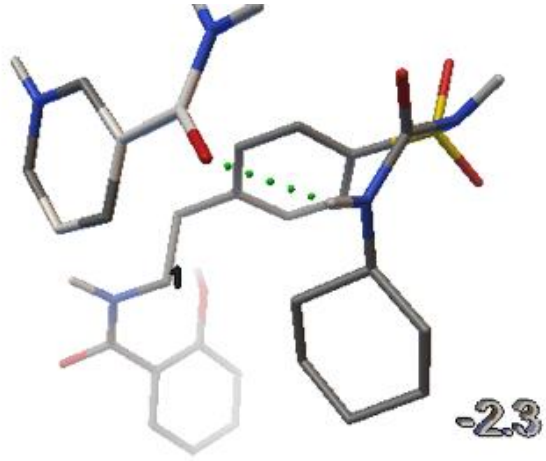

Figure 1: *In silico* molecule, modeling the simulation of glibenclamide and nicotinamide.

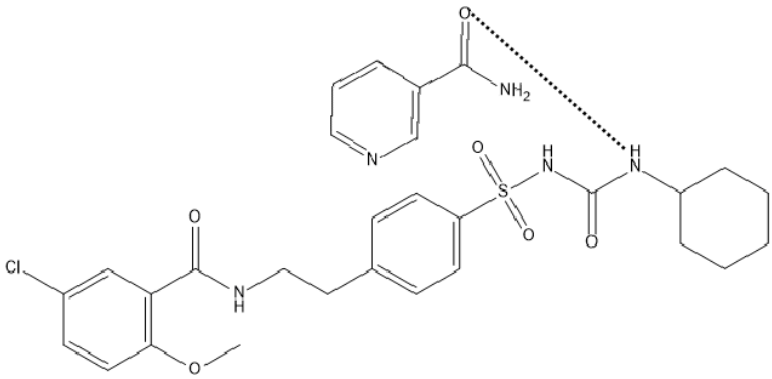

Figure 2: Prediction of interaction between glibenclamide and nicotinamide.

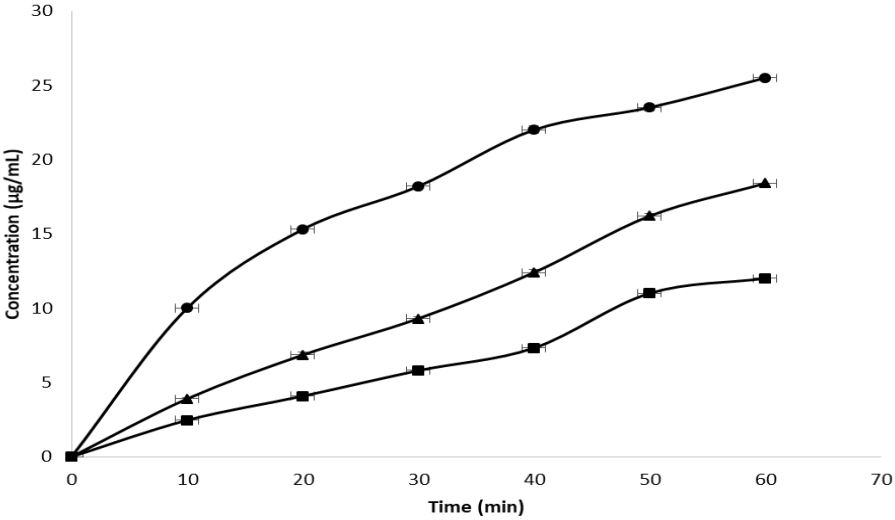

Figure 3: Dissolution of (■) pure glibenclamide, (▲) a physical mixture of glibenclamide-nicotinamide (1:2), and (●) cocrystal of glibenclamide-nicotinamide (1:2); values are mean ± standard deviation (n = 3).

used for synthesizing cocrystals might be more effective for refinement; in addition, the SE method is commonly used in the pharmaceutical industry[10]. Nicotinamide was used as a coformer because it has been successfully employed as a cocrystal former[12]. The aim of this study is to develop glibenclamide-nicotinamide cocrystals with the solvent evaporation method and evaluate their solubility and dissolution properties.

EXPERIMENTAL

Materials

Glibenclamide was obtained from Indofarma (Solan, HP, India) with a purity of > 99%, methanol ProAnalysis obtained from Merck (Darmstadt, Germany), nicotinamide ProAnalysis from Merck, and potassium dihydrogen phosphate ProAnalysis from Merck.

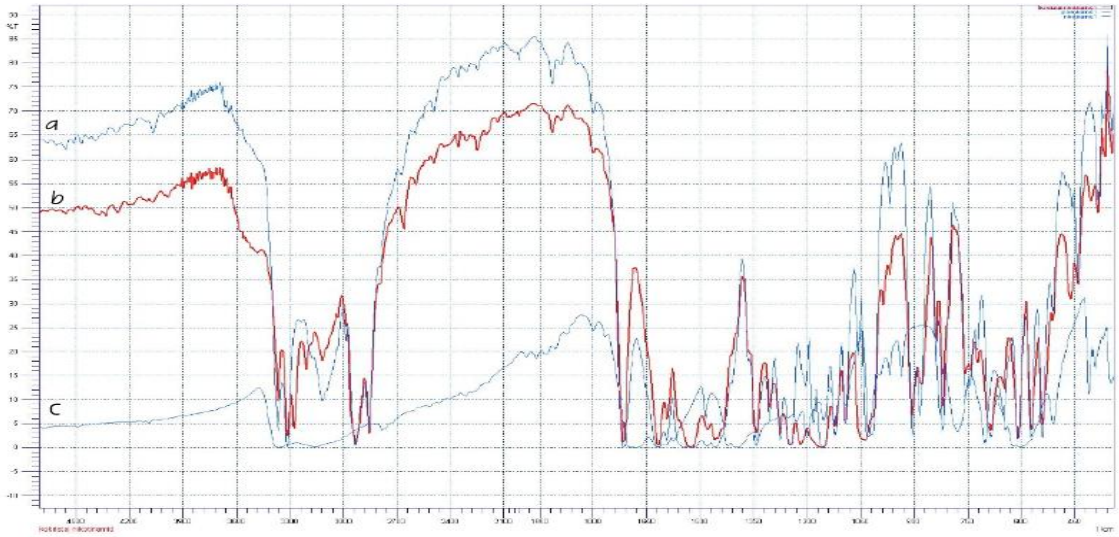

Figure 4: Infrared spectrum of pure glibenclamide (a), cocrystal of glibenclamide-nicotinamide (b), and nicotinamide (c).

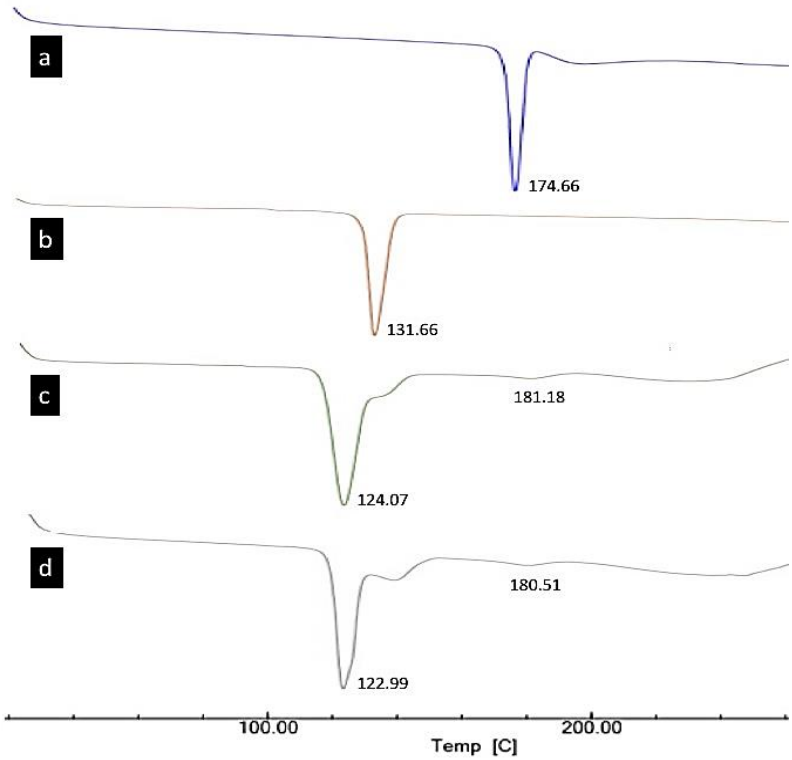

Figure 5: Thermograms of (a) pure glibenclamide, (b) nicotinamide, (c) physical mixture of glibenclamide and nicotinamide (1:2), and (d) co-precipitate of glibenclamide-nicotinamide (1:2)

Methods

In silico molecular docking

2D structures of glibenclamide (ChemSpider ID: 54809) and its coformers in .mol format were downloaded from www.chemspider.com. All of the .mol files of the molecules were converted into .pdb files by employing OpenBabelGUI 2.2.3 then it opened in AutoDock 4.2.3 and converted into .pdbq files by adding polar hydrogen and Kollman charges. The.pdbq files were converted into .pdbqt files by calculating their torsion angles, and were ready to be used for docking. Docking was repeated five times for each coformer. Parameters observed were both the type and energy (Ei) of interactions[13,14].

Preparation of cocrystal using a solvent evaporation method

Glibenclamide and nicotinamide (equimolar) were carefully weighed at 0.5 grams and 0.24 grams, respectively. Each compound was dissolved in methanol separately. The two solutions were mixed and stirred for a few min. An equimolar solution of both components was evaporated using a water bath at 40°C for 48 h. The obtained product was dried at room temperature overnight

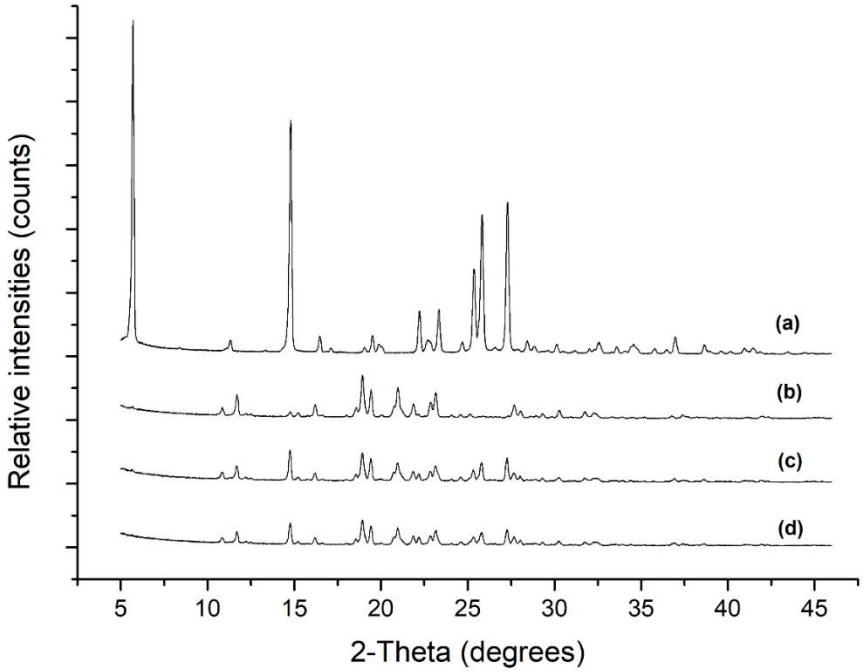

Figure 6: The PXRD result of nicotinamide (a), pure glibenclamide (b), physical mixture glibenclamide-nicotinamide (1:2) (c), and the solvent evaporation product of glibenclamide-nicotinamide (1:2) (d).

Table 1: Solubility of glibenclamide and cocrystals.

Sample	Mean ± SD
Pure glibenclamide	10.79 ± 0.12
PM (1:2)	13.58 ± 0.18
Glibenclamide-nicotinamide (1:2)	18.63 ± 0.21

and further analyzed for its unique characteristics[15]. The cocrystals of glibenclamide-nicotinamide was further mentioned as glibenclamide-nicotinamide in this article.

Determination of solubility

Solubility determination was performed for cocrystal of glibenclamide-nicotinamide, physical mixture of glibenclamide-nicotinamide (PM), and glibenclamide. In total, 50 mg of each sample was placed in an Erlenmeyer flask containing aquadest and agitated in a mechanical shaker for 24 h at room temperature. The saturated solutions were filtered through a 0.45 µm membrane filter, and the dissolved drug was analyzed spectrophotometrically at 266 nm[1].

Dissolution test

The intrinsic release behaviors of glibenclamide and its cocrystals were determined with a dissolution test (USP type 2 apparatus). The glibenclamide sample and its cocrystals were put into 900 ml of a buffered phosphate with a pH of 8 and stirred at 75 rpm. Dissolution samples were filtered through a syringe filter of 0.45 µm pore size and were measured periodically (at 0, 10, 15, 30, 45, and 60 min) and analysed by UV spectrophotometer at 266 nm[16].

Characterization of cocrystals

Fourier Transform infrared spectroscopy (FT-IR) analysis

Samples powders were mixed with potassium bromide crystals and crushed until homogeneous, and then compressed to a pressure of 20 psi. The infrared spectrum was obtained with an infrared spectrophotometer (Shimadzu, Japan) in a range of wave numbers 400-4000 cm^{-1} using FT-IR[1,9,10].

Powder X-ray diffraction (XRPD) studies

Powder X-ray diffraction (Phillips *PW1835*® diffractometer, Amsterdam, The Netherlands) analysis was performed at room temperature. The condition of measurement was set using Cu Ka radiation (l = 1.54 Å), a tube stage of 40 kV, and a tube current of 40 mA. Data were collected in the range of 2 theta of 5–40° and at a scan rate of 1–2°/min[9,10].

Differential scanning calorimetry (DSC)

Thermal analyses of the drug, coformer, and solvent evaporation products were performed on a DSC. The thermograph was recorded under a gas flow of 50 mL/min. Samples were analyzed from 30 to 200°C with a heating rate of 10°C/min[17].

Statistical analysis

Solubility and dissolution test was performed triplicate, and its data were presented as mean ± standard deviation (SD), then the differences among the groups were analyzed using the one-way analysis of variance (ANOVA)[18].

RESULTS

In silico simulation

The results of the *in silico* method between glibenclamide and nicotinamide are shown in Fig. 1, while the interaction between glibenclamide and nicotinamide is shown in Fig. 2.

Solubility

The result of the solubility test showed that cocrystallization can increase the solubility of glibenclamide in water. Solubility of PM (1:2) and

glibenclamide-nicotinamide increased 25.11% and 73.03%, respectively, compared with pure glibenclamide.

DISSOLUTION

Based on Fig. 3, glibenclamide-nicotinamide has better dissolution results than pure glibenclamide and PM. Statistically, increase of glibenclamide-nicotinamide dissolution rate was significant than pure glibenclamide, but increase of PM dissolution rate was not significant.

Characteristics of cocrystals

The FTIR spectra of glibenclamide showed a characteristic peak with high intensity at 3313.17 cm^{-1} of N-H, 3116.97 cm^{-1} of O-H, 2931.8 cm^{-1} of C-H, 1712.79 cm^{-1} of C=O, and 1612.49 cm^{-1} of C=C. The nicotinamide spectrum was exhibited at 3363.86 cm^{-1} of N-H, 1905.67 cm^{-1} of C=N, and 1678.07 cm^{-1} of C=O. The solvent evaporation product of glibenclamide-nicotinamide (1:2) exhibited its spectrum at 3313.71 cm^{-1} of N-H, 3116.97 cm^{-1} of O-H, 2657.91 cm^{-1} of C-H, and 1593.20 cm^{-1} of C=O.

DISCUSSION

Based on the *in silico* study, the Gibbs-free energy of the molecular conformation between glibenclamide and nicotinamide was -2.3 kcal/mole. The negative value indicates the possibility of glibenclamide and nicotinamide interaction spontaneously[19]. This interaction, resulted from hydrogen bond formation between glibenclamide and nicotinamide, showed in green line in Fig. 1. The hydrogen bond affects the hydrophilicity of APIs thus increase their solubility in water and dissolution rate[14]. But the hydrogen bond did not form in PM because glibenclamide and nicotinamide were not equimolar, therefore increase of its solubility and dissolution rate were not significant. In addition, the increase in the dissolution rate of glibenclamide correlates with solubility, the diffusion constant, boundary-layer thickness, and function of the surface area. The solvent evaporation method can also modify the diffusion of a molecule of glibenclamide by affecting its hydrodynamic properties and influencing its release behavior. The presence of a solvent in a liquid phase of the solvent evaporation (SE) method can improve the rate of cocrystal formation[10].

The FTIR results (Fig. 4) showed that all samples presented the same spectrum pattern in the fingerprint region. The widening peak at 3300 cm^{-1} was related to the possibility of the hydrogen bond formation in the solvent evaporation product of glibenclamide-nicotinamide (1:2)[9,10]. This indicated that there was not a chemical reaction, and that no new functional groups were formed in the cocrystals of glibenclamide-nicotinamide[20].

The thermal behavior of glibenclamide was identified by differential scanning calorimetry. The melting point transition from each samples suggests the formation of cocrystals[21]. As shown in Fig. 5, the new endothermic peak of glibenclamide-nicotinamide (1:2) presented at 122.9°C was lower than pure glibenclamide, nicotinamide, and its physical mixture. Decline of the melting point and heat content of the cocrystal directly correlates with enhancement of glibenclamide solubility[21]. The average endothermic energy represented degree of crystallinity, therefore glibenclamide-nicotinamide (1:2) cristallinity was higher than its PM[9]. The observation of thermogram demonstrated that (1) the new crystal phase formed i.e. glibenclamide-nicotinamide, (2) glibenclamide-nicotinamide was stable below its melting point, and (3) glibenclamide-nicotinamide did not have residual solvent, because methanol evaporation was not observed in the thermogram[22].

The PXRD pattern is one of the characterization tools to confirm the formation of the new solid phase with a fingerprint of the crystal structure[11]. All crystal forms of a compound can produce an X-ray diffraction pattern according to their characteristics[10]. Based on diffractogram (Fig. 6), glibenclamide-nicotinamide pattern was different from pure glibenclamide indicate the formation of a new solid crystalline phase, either change in the crystal form, or the addition of a crystal lattice from glibenclamide[1,17].

CONCLUSION

Preparation of cocrystals glibenclamide-nicotinamide (1:2) used the solvent evaporation method. The solubility and dissolution test of glibenclamide-nicotinamide cocrystal (1:2) increased significantly compared to pure glibenclamide and its physical mixture. The confirmation of cocrystal glibenclamide-nicotinamide (1:2) indicated the formation of new solid crystalline phases that differ from pure glibenclamide and its physical mixture.

ACKNOWLEDGEMENT

The authors thanks Universitas Padjadjaran for financial support for this research under Riset Fundamental Unpad 2018 Scheme.

CONFLICT OF INTERESTS

No conflict of interest is associated with this work.

AUTHORS' CONTRIBUTIONS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All the authors contributed equally to this work.

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