RESEARCH ARTICLE

Synthesis of Glibenclamide-Oxalic Acid Cocrystal using ThermalSolvent-Free Method

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ABSTRACT

Solubility is an important parameter affecting the bioavailability of drugs. The solubility of an active pharmaceutical ingredient (API) could be improved through the formation of cocrystal, which is a crystalline complex composed of two or more different molecules. Glibenclamide (GCM) is an API with poor solubility in water, which belongs to class II, characterized as highly permeable with low solubility. Therefore, this study aimed to synthesize and characterize the cocrystal of GCM-oxalic acid (OA) using the melting method. The interaction between GCM-OA complexes was predicted using the *in silico* method. Also, the cocrystal complexes were characterized by differential scanning calorimetry (DSC), infrared (IR) spectrophotometry, and powder X-ray diffraction (PXRD), as well as, through solubility and dissolution tests. The result showed that GCM and OA have the potential of forming cocrystal through the *in silico* method. Also, the cocrystal of GCM-OA with a molar ratio 1:2, significantly improved the solubility and dissolution profile of GCM. In addition, the spectrum IR of cocrystal exhibited a shifting peak at 1,700 cm^{-1} indicating the presence of intermolecular interaction between GCM and OA. Furthermore, the DSC and PXRD analyses showed a new single endothermic peak and new diffraction peak pattern, respectively, indicating the formation of a new crystalline component.

Keywords: Cocrystal, Glibenclamide, Melting method, Oxalic acid.

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INTRODUCTION

Solubility is one of the main factors influencing the therapeutic effect of active pharmaceutical ingredients (APIs).[1] According to Tagaki *et al*., 40% of API used as drugs are poorly water-soluble.[2] However, there is a need for the APIs to be soluble, especially for an oral drug, which is in solution form, thus, making it to be adsorbed as needed in oral bioavailability to achieve a target product profile. Also, modifying the solubility of APIs is very important as it improves its bioavailability, hence, affecting the therapeutic effect.[3]

GCM (5-chloro-N-[2-[4-(cyclohexyl carbamoyl sulfamoyl) phenyl] ethyl]-2-methoxybenzamide) is one of the most prescribed oral anti-hyperglycemic agents.[4] Based on the biopharmaceutical classification system (BCS), it is classified as a class II drug due to its high permeability and poor water solubility.[5] Several methods have been applied to increase the solubility and dissolution properties of GCM, such as, formulation of solid and liquid SMEDDS,[6,7] nanoparticles,[8] nanoemulsion,[9] and formation of solid dispersions with the use of cyclodextrins and polymers.[10]

Cocrystallization is an alternative method used in improving the physical and mechanical properties of APIs without affecting the pharmacological activities.[11,12] Cocrystal is a crystalline complex composed of two or more different molecules bonded in the crystal lattice through hydrogen bonds.[13] Also, a large number of non-toxic compounds with hydrogen bonding functionalities could act as coformers generally regarded as safe (GRAS).[14] The complex crystal formed is usually made up of a drug and a coformer connected by a synthon with a defined stoichiometric ratio. The synthon is a non-covalent interaction involving π-π electrons bonds, van der Waals, and hydrogen bonds, commonly used in pharmaceutical crystals engineering, thus, choosing a synthon is the key for designing cocrystal.[15]

Therefore, this study was aimed at synthesizing and characterizing cocrystal from GCM-OA through the melting

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method. This is similar to a previous article, where GCM was used as APIs due to its possession of hydrogen acceptors and donor functional groups, such as, chlorine, secondary amides, and sulphonamide.[16] The melting method has the advantage of synthesizing more efficient cocrystal with no organic solvent compared with the wet method.[17]

MATERIAL AND METHODS

Chemicals

GCM was purchased from Indofarma (Solan, HP, India) with a purity of over 99%, methanol and OA were purchased from Merck (Darmstadt, Germany). The chemical structures of GCM and OA are shown in Figure 1.

In silico Molecular Docking

The 2D structures of GCM and OA were obtained from www.chemspider.com. These were converted into .pdb files, then opened in AutoDock 4.2.3, and further converted into .pdbq files by Kollman charges and adding polar hydrogen. The .pdbq were also converted into .pdbqt by calculating their torsion angles and then, used for docking. The parameters observed from the sample were the type and energy (Ei) of interactions.

Preparation of Cocrystal through Melting Method

Various molar ratio mixture of GCM and OA were weighed and shaken to get a physical mixture of both components. The mixture was then heated at 190ºC for 10 minutes, and the product was cooled at room temperature. This was grinded into powder form with the use of mortar and pestle, and further analyzed for its characteristics.

Cocrystals Characterization

Fourier Transform Infrared Spectroscopy (FTIR) Analysis

Samples of cocrystal were mixed with KBr crystals, grinded till a homogeneous form was obtained, and then compressed through the pressure of 20 psi. Furthermore, it was subjected to an infrared spectrophotometer (Shimadzu, Japan) to obtain its spectra over a range of 4,000 to 400 cm^{-1}.

Powder X-ray Diffraction (XRPD) Studies

The XRPD pattern was obtained using the Phillips PW1835® diffractometer (Amsterdam, Netherlands). The measurement was through Cu Ka radiation (l = 1.54 Å), with a fixed tube current of 40 mA and a voltage of 40 kV. The data were obtained through a fixed time step scanning method in the range of 5 to 40° (2Ø).

Differential Scanning Calorimetry (DSC)

The thermal analyses of the samples were conducted using Shimadzu DT-40 thermal analyzer calorimeter by weighing 5 mg of the sample in its aluminum pan. This was then heated from 30 to 200ºC at a heating rate of 10ºC/min under nitrogen flow.

Determination of Supersaturation Solubility

The samples were accurately weighed and dispersed in an Erlenmeyer flask containing 10 mL aquadest. This was then shaken with a mechanical shaker for 24 hours at room temperature. The samples were filtered through a 0.45 µm membrane filter, diluted, and then analyzed spectrophotometrically at 266 nm.

Dissolution Test

The dissolution test of GCM and its cocrystals were performed with a USP type 2 apparatus. Both substances were dispersed into 900 mL buffered phosphate with a pH of 8, and stirred at 75 rpm. Then, 5 mL aliquots sample were withdrawn at 0, 10, 15, 30, 45, and 60 minutes. These were filtered through a 0.45 µm membrane filter, diluted, and analyzed spectrophotometrically at 266 nm.

Statistical Analysis

The solubility and dissolution tests of the samples were performed in triplicate and data expressed as mean ± standard deviation (SD). Statistical analysis was performed using the one-way analysis of variance (ANOVA) and statistical differences were considered significant at $p < 0.05$.

RESULT AND DISCUSSION

Virtual screening was performed to predict the bonds between GCM and OA using molecular docking and modeling. Also, molecular docking was used to determine the number of hydrogen bonds and Ei of cocrystal.[18] The result of the molecular docking between GCM and OA, as shown in Figure 2, indicates the presence of hydrogen bonds between the two substances.

The thermal method was used for synthesizing the cocrystal in this study. The advantages of this method include the rapid formation of cocrystal, only need a small sample, and the organic solvent is not used in the process. The melting method, on the other hand, cannot be used as a general approach as some drugs are thermally unstable or volatile, hence, cannot withstand melting without degradation.[3] In addition, other physical transformations, such as, polymorphic

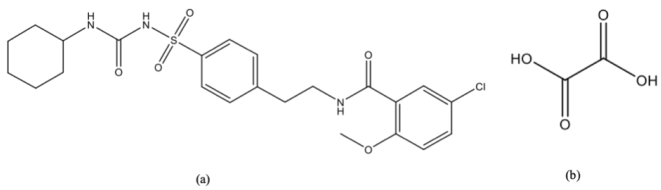

Figure 1: Chemical structures of **(a)** GCM and **(b)** OA

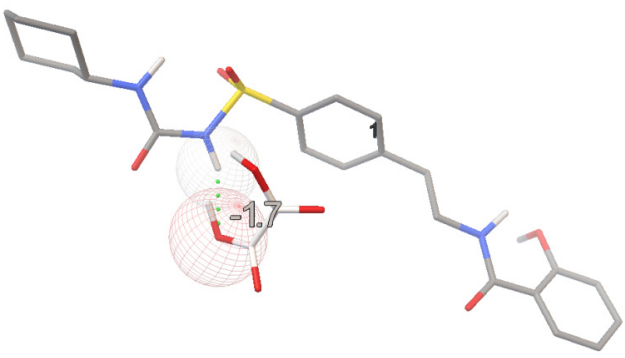

Figure 2: Virtual screening result of GCM-OA cocrystal

transition or dehydration in the temperature range of interest could complicate the thermal behavior of these components.[19]

In the pharmaceutical industry, the solubility of a drug is important as it affects its bioavailability. Furthermore, the solubility of cocrystal, as depicted in Figure 3, shows that the solubility of GCM-OA with the molar ratio of 1:2, is higher than GCM intact. Based on this finding, the formation of cocrystal could significantly improve the solubility of GCM. This could be as a result of the intermolecular hydrogen bonding interactions between these two components.[20]

The dissolution profile of GCM in the cocrystal system, is shown in Figure 4. Based on the result, the cocrystal of GCM-OA improved the dissolution profile of GCM. In addition, the cocrystal significantly increased the dissolution profile of GCM to about two-fold compared with GCM intact. The result also showed that the GCM-OA cocrystal has a faster dissolution rate than GCM. This could probably be as a result of the intermolecular hydrogen bonds between GCM and OA. Additionally, the cosolvency phenomenon could result in the dissolution improvement, as OA, which is very soluble in water could act as a solubilization agent for GCM.[21]

In this study, the PXRD was used to confirm the crystalline state of GM-OA cocrystal. The pattern of GCM, OA, and cocrystal of GCM-OA obtained, are shown in Figure 5. The result shows a significant difference in the pattern of GCM-OA cocrystal compared with GCM and OA individually, indicating the formation of a new crystalline component.

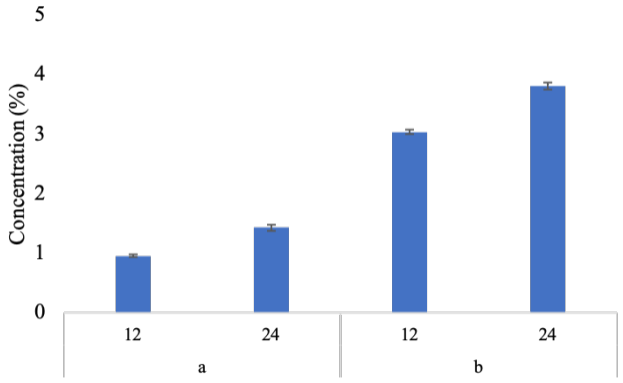

Figure 3: Saturation solubilities of **(a)** GCM and **(b)** cocrystal of GCM-OA (mean ± standard deviation, n = 3)

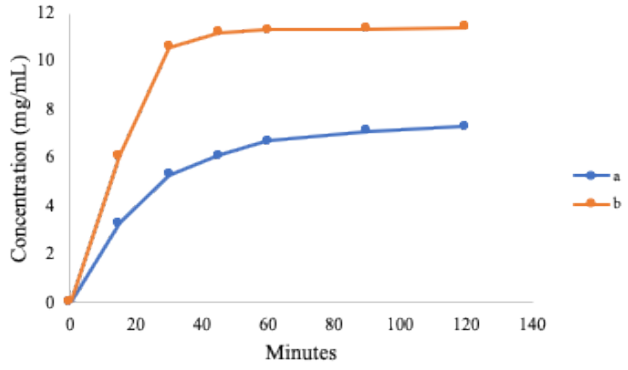

Figure 4: Dissolution profile of **(a)** GCM and **(b)** cocrystal of GCM-OA (mean ± standard deviation, n = 3)

Furthermore, the FTIR measurements were conducted to characterize the interactions between GCM and OA. The spectrum of GCM, OA, and GCM-OA cocrystal are shown in Figure 6. The peaks in the region of 3,300 to 3,400 cm^{-1} and 1,712.48 cm^{-1} are shown in the crystalline GCM due to the N-H stretching of secondary amide and C=O (carbonyl stretch), respectively. Also, the GCM-OA cocrystal showed a shift in the carbonyl stretch (C=O) from 1,712.48 to 1,704.76 cm^{-1}, indicating the possibility of C=O and O-H group participating in the intermolecular H-bonding. This observation is an indication of the possible interaction of hydrogen bonds between GCM and OA.

Differential Scanning Calorimetry (DSC)

Cocrystal could modify the thermal property of API. Also, the characterization of the thermal behavior of the samples was conducted using the DSC. It helped to analyze the interaction between GCM and OA through the appearance, disappearance, or shifts of exothermal or endothermal effects.[22] The thermogram of GCM, OA, and cocrystal of GCM-OA

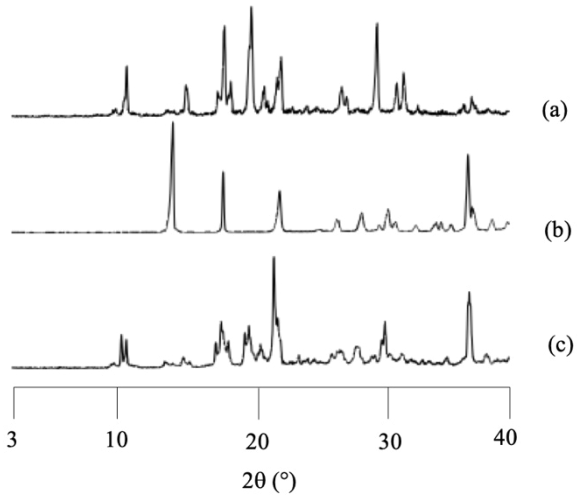

Figure 5: PXRD pattern of (a) GCM, (b) OA and (c) cocrystal of GCM-OA.

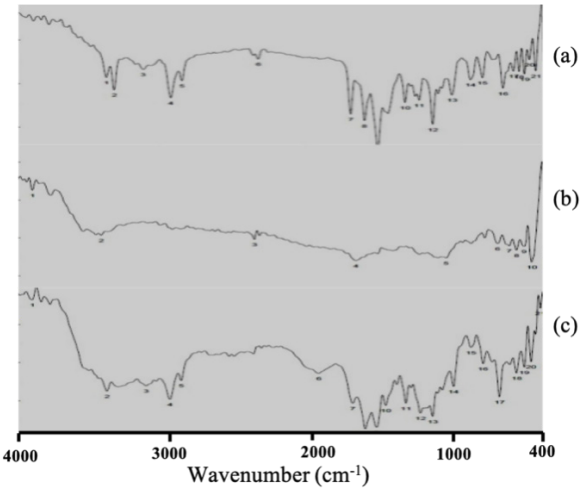

Figure 6: Spectrum IR of **(a)** GCM, **(b)** OA, and **(c)** cocrystal of GCM-OA

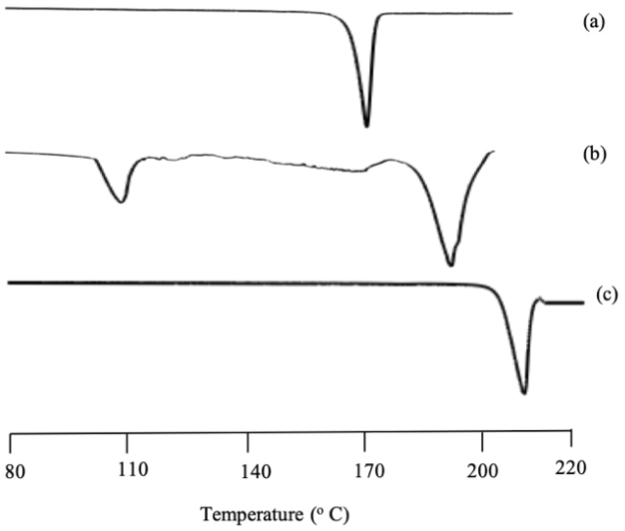

Figure 7: Spectrum IR of **(a)** GCM, **(b)** OA, and **(c)** cocrystal of GCM-OA

are shown in Figure 7. GCM showed a single endothermic peak at 174.66ºC, while OA showed endothermic peaks at 104.2 and 193.4ºC. Also, GCM-OA cocrystal showed a single endothermic peak at 212.4ºC, indicating the formation of a new crystalline component.[23]

CONCLUSION

This study showed the cocrystallization of GCM with OA using the melting method. Basically, this method was used in order to avoid the use of organic solvent. The *in silico* method was also used to predict the possible interaction between GCM and OA in the resultant cocrystal. Then, the samples were further characterized using DSC, PXRD, and IR. Based on the results, the interaction between GCM-OA showed the possible formation of a new crystalline component with a better solubility and dissolution profile.

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