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RESEARCH ARTICLE

Virtual screening of coformers and solubility test for glibenclamide cocrystallization

Arif Budiman, Sandra Megantara, Ayu Apriliani

Department of Pharmaceutical Sciences and Pharmaceutics, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor Sumedang, Indonesia

Correspondence to: Arif Budiman, E-mail: arifbudimanapt@gmail.com

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ABSTRACT

Background: The therapeutic effectiveness of active pharmaceutical ingredients (API) depends on their solubility. API, which has poorly soluble drugs, can cause low bioavailability. According to the biopharmaceutical classification system (BCS), glibenclamide is classified under BCS Class II drugs), which has low solubility and high permeability. Cocrystallization is one method to enhance the physical properties of drugs, especially the solubility. **Aims and Objectives:** In this study, we apply the approach to the solid state to estimate the probability of cocrystal formation using virtual screening, and then, study the solubility and dissolution test of one of the best coformers. **Materials and Methods:** We used virtual screening of coformers for glibenclamide by employing the molecular docking method. AutoDock was used for docking, and the type and energy (Ei) of interaction were observed. The work was continued by the cocrystallization process using dry grinding. Solubility and dissolution tests have referred to the Higuchi and Connor methods using the ultraviolet spectrophotometer. **Results:** Based on molecular docking, the best of three from coformers were oxalic acid (Ei = −1.6 kcal/mol), benzoic acid (Ei = −2.6 kcal/mol), and ascorbic acid (Ei = −2.1 kcal/mol). The result of the solubility test showed that glibenclamide oxalic acid increases by 81.6% compared to pure glibenclamide at 24 h. The result of the dissolution test showed that glibenclamide oxalic acid has a better curve (77.3% in 60 min) that pures glibenclamide (44.52% in 60 min). **Conclusion:** This study indicated that oxalic acid as a coformer can increase the dissolution profile of glibenclamide by the approach cocrystalization method.

KEY WORDS: Cocrystal; Molecular Docking; Glibenclamide; Dry Grinding

INTRODUCTION

The therapeutic effectiveness of active pharmaceutical ingredients (API) depends on their solubility. API, which has poorly soluble drugs, can cause low bioavailability.[1,2] This study previously shows that crystal engineering can improve the solubility and dissolution rate, which impacts bioavailability. The API crystal forms possess undesirable physical properties, and hence, there is a need for the development of a crystalline form of APIs with desired physicochemical properties.[3]

Glibenclamide, one of the APIs, has poor solubility in water. This property can lead to poor dissolution rate and subsequent decrease of its gastrointestinal absorption. In the biopharmaceutical classification system, glibenclamide, included in Class II, has a high permeability but a low solubility, because of that, the absorption of glibenclamide was limited, according to its dissolution rate.[4] Several methods have been studied to increase the solubility of glibenclamide, such as the solid dispersion method,[5] surface solid dispersion, nanoparticles,[6] and nanoemulsion.[7] The disadvantage of these methods is less stable when made in a solid preparation, so the dissolution rate of glibenclamide is incompatible with its bioavailability.[8]

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One method that can improve the solubility is cocrystal. Cocrystal cocrystallization is a one method to improve the physical property that structurally crystalline material containing component presents in a definite stoichiometric amount 1,4. To predict the ability of API, a coformer can be formed into a cocrystal, and it can be used for experimental screening. We can also use virtual screening. One approach is to analyze the structures of crystalline solids based on the pairing of H-bond donors and acceptors.[9] The study shows that molecular electrostatic potential surfaces can be used to rank the relative H-bond donor/acceptor strengths of different functional groups, and this approach has been used to predict the formation of ternary cocrystals.[10]

In this paper, we apply this approach to the solid state to estimate the probability of cocrystal formation using virtual screening, and then, to study the solubility and dissolution test of one of the best coformers.

MATERIALS AND METHODS

Hardware and Programs

Personal computers equipped with Intel Core i5 2.30 GHz processor DRAM 4 GB was used in this work. Programs were SPORES, Open Babel GUI 2.2.3, PLANTS1.2, and MGLTools1.5.6 shell script for the initial preparation of the ligands and Auto Dock 4.2.3 for docking process.[11,12]

Molecular Docking

2D structures of glibenclamide (Chem Spider ID: 54809) and its coformers in. *mol* format were downloaded from www.chemspider.com.All. *mol* files of the molecules were converted into. *pdb* files by employing OpenBabelGUI 2.2.3. The files were then 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* by calculating their torsion angles and were ready to be used for docking. Docking was repeated 5 times for each coformer. Parameters observed were the type and energy (Ei) of interactions.[11,12]

Preparation of the Glibenclamide Cocrystal

The glibenclamide cocrystal was prepared by the dry grinding method and taking component 1:1 and molar ratio (glibenclamide BM 494: Oxalic acid BM 126).

Determination of Solubility

Around 50 mg of glibenclamide was placed in Erlenmeyer containing Aquadest. These were 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 amount of the drug dissolved were analyzed spectrophotometrically at 266 nm.[1]

The Dissolution Test

In vitro dissolution studies of pure glibenclamide and glibenclamide-oxalic acid were conducted with the USP Type II apparatus (paddle type). The studies used 900 ml of a buffer phosphate with a pH of 8 and USP apparatus 2 with an agitation rate of 75 rpm. Samples of each preparation equivalent to 50 mg of drug were added into the dissolution medium. The sample was measured periodically (0, 10, 15, 30, 45, and 60 min) and was analyzed spectrophotometrically at 266 nm.[13,14]

RESULTS

The structure of glibenclamide can be seen in Figure 1. The result of virtual screening of coformer for glibenclamide can be seen in Table 1.

The prediction of cocrystal formation of glibenclamide oxalic acid can be seen in Figure 2.

Interaction between glibenclamide and oxalic acid using 2D docking method can be seen in Figure 3.

The result solubility studies of glibenclamide cocrystal using oxalic acid can be seen in Table 2.

The result of dissolution test from glibenclamide cocrystal can be seen in Table 3 and Figure 4.

DISCUSSION

The molecule of glibenclamide contains two aromatic, 1 hydrogen bond acceptors and 2 hydrogen bond donors (HBDs) (HBDs, and hence, it is possible to form cocrystals with certain coformers. The coformers chosen in this work were ten coformers including fumaric acid, citric acid,

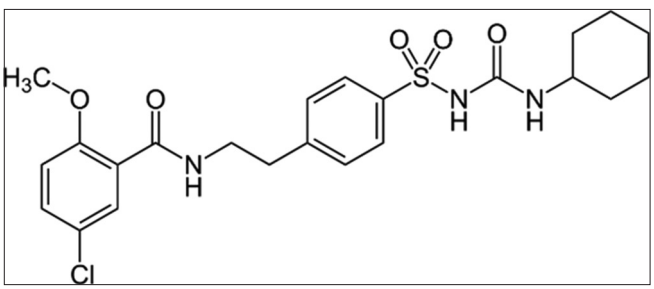


Figure 1: Structure of glibenclamide

Table 1: Virtual screening of coformers for glibenclamide

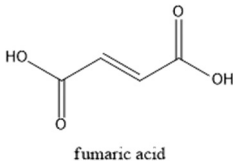
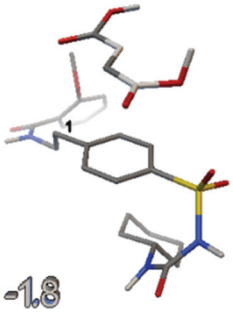
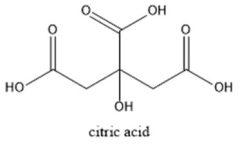
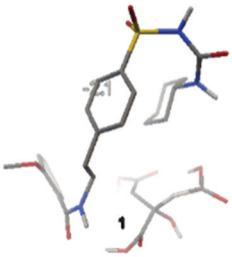
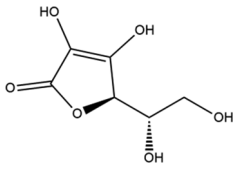
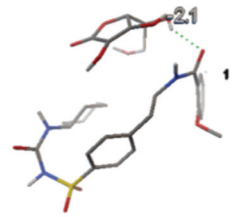
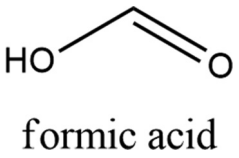
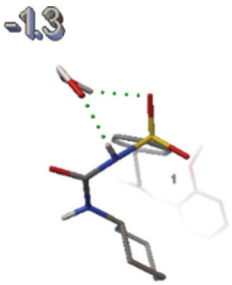
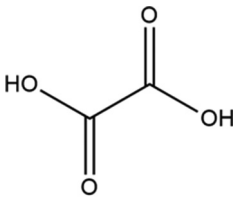
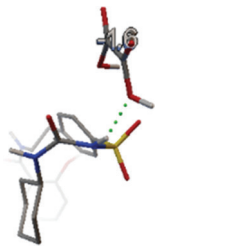
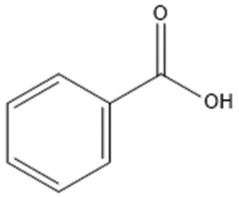
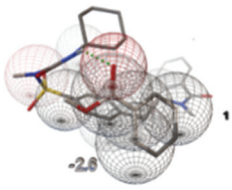
Coformer	Structure 2D	Interaction	Ei (kcal/mol)
Fumaric acid	 fumaric acid		−1.8 no interaction
Citric acid	 citric acid		−2.1 no interaction
Ascorbic acid	 ascorbic acid		−2.1 1 hydrogen bond
Formic acid	 formic acid		−1.3 2 hydrogen bond
Oxalic acid	 oxalic acid		−1.6 1 hydrogen bond
Benzoic acid	 benzoic acid		−2.6 1 hydrogen bond

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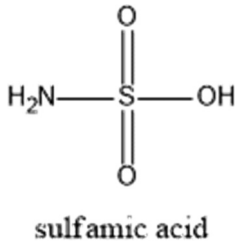
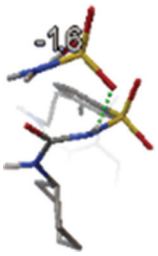
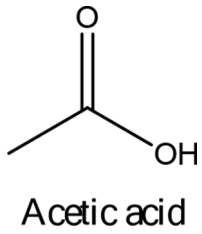
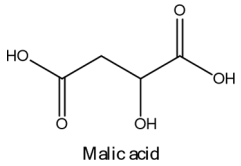
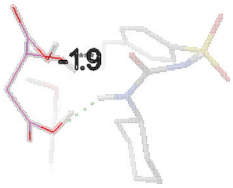
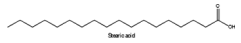
Table 1: (*Continued*)

Coformer	Structure 2D	Interaction	Ei (kcal/mol)
Sulfamic acid			−1.6 1 hydrogen bond
Acetic acid			−1,5 1 hydrogen bond
Malic acid			−1,9 1 hydrogen bond
Stearic acid			−2,1 no interaction

ascorbic acid, formic acid, oxalic acid, benzoic acid, sulfamic acid, acetic acid, malic acid, and stearic acid.

For the solubility and dissolution test, oxalic acid was used as coformer because oxalic acid can interact through one hydrogen bond (Ei = −1,6 kcal/mol) with glibenclamide. The prediction of interaction between glibenclamide and oxalic acid can be seen in Figure 2.

The selection of cocrystal method used dry grinding method. This is a preliminary study so that no organic solvent is used in manufacturing glibenclamide cocrystal. The result showed that glibenclamide oxalic acid increases the solubility compared to pure glibenclamide. In Table 2, glibenclamide oxalic acid increases 94.8% after 12 h and 81.6% after 24 h compared to pure glibenclamide. The increased solubility of glibenclamide occurs due to the formation of hydrogen bonds between glibenclamide and oxalic acid.[15]

Table 3 showed that glibenclamide has better curve (47.12% in 10 min, 75.05% in 30 min, and 77.3% in 60 min) than pure glibenclamide (27.82% in 10 min, 31.72% in 30 min, and 44.52% in 60 min). This indicates that solubility data are complementary of dissolution, if cocrystal solubility

Table 2: Solubility studies of glibenclamide cocrystal

Formula	Concentration of glibenclamide (%) at 12 h	Concentration of glibenclamide (%) at 24 h
Pure glibenclamide	3.32	4.53
Glibenclamide-oxalic acid	6.47	8.23

Table 3: Dissolution test of glibenclamide cocrystal

Times (minutes)	Pure glibenclamide (%)	Glibenclamide-oxalic acid (%)
0	0	0
5	19.87	18.24
10	27.82	47.12
15	27.9	61.94
30	31.72	75.06
45	36.7	75.76
60	44.52	77.3

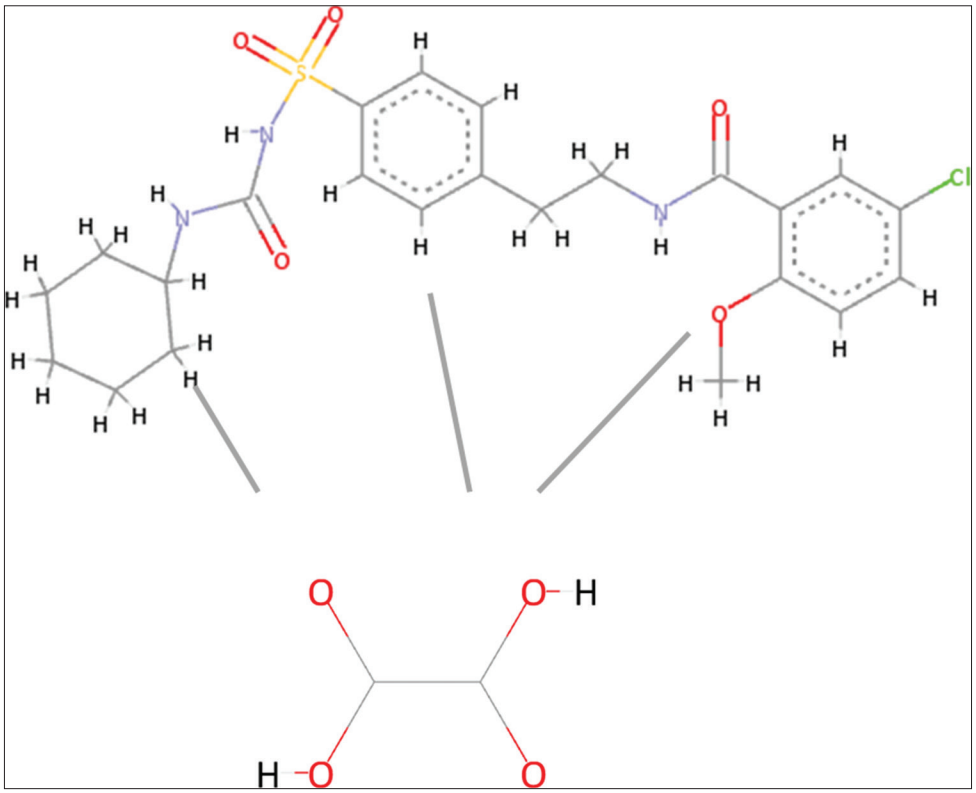


Figure 2: The prediction of cocrystal formation of glibenclamide oxalic acid

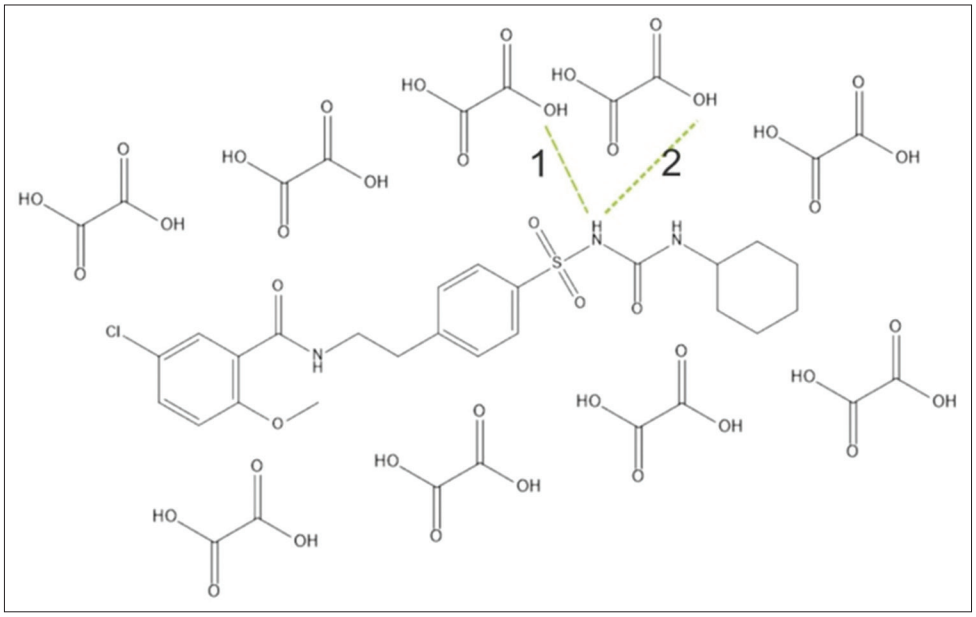


Figure 3: Interaction between glibenclamide and oxalic acid using two-dimensional docking method

is increased in comparison to pure or standard; intrinsic dissolution is also improved for cocrystals in comparison with pure or standard.[16]

CONCLUSION

Based on molecular docking, the best of three coformers were oxalic acid (Ei = −1,6 kcal/mol), benzoic acid (Ei = −2,6 kcal/mol), and ascorbic acid (Ei = −2,1 kcal/mol). The result of the solubility test showed that glibenclamide oxalic acid increases 181.7% compared to pure glibenclamide at 24 h. The result of the dissolution test showed that glibenclamide oxalic acid has a better curve (77.3% in 60 min) than pure glibenclamide (44.52% in 60 min). This indicated that a coformer can increase the dissolution profile of glibenclamide by the approach cocrystalization method.

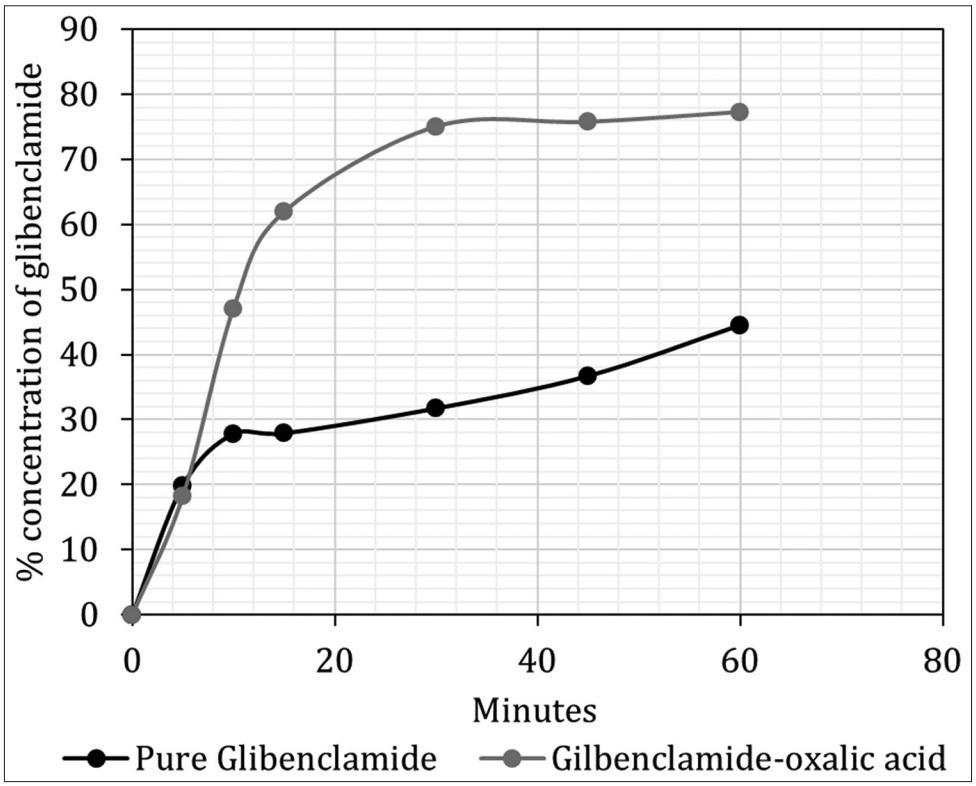


Figure 4: Dissolution profile of glibenclamide (blue) and the glibenclamide-oxalic acid (orange)

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