

## SOLID DOSAGE FORM DEVELOPMENT OF GLIBENCLAMIDE WITH INCREASING THE SOLUBILITY AND DISSOLUTION RATE USING COCRYSTALLIZATION

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### ABSTRACT

**Objective:** The aim of this study was to develop a solid dosage form of glibenclamide with increasing the solubility properties of glibenclamide with cocrystallization method.

**Methods:** Virtual screening was performed to investigate the interaction between glibenclamide and a co-former. Saccharin, the selected co-former, then co-crystallized with glibenclamide with equimolar ratios of 1:1 and 1:2 using the solvent evaporation method. Further characterization was performed using an infra-red (IR) spectrophotometer, differential scanning calorimetry (DSC), and powder x-ray diffraction (PXRD).

**Results:** Co-crystals of 1:2 equimolar ratio were more highly soluble compared to pure glibenclamide (30-fold for 12 h and 24-fold for 24 h). The dissolution rate had also increased from 46.838% of pure glibenclamide to 77.655% of glibenclamide co-crystal in 60 min. There was no chemical reaction observed during the co-crystallization process based on the IR spectrum. However, there was a new peak in the X-Ray diffractogram and a reduction of melting point in the DSC curve, indicating the formation of co-crystals.

**Conclusion:** The optimal co-crystal ratio of glibenclamide-saccharin was found to be 1:2, which was successful in improving the solubility of glibenclamide.

**Keywords:** Glibenclamide, Co-crystal, Saccharin, Dissolution

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### INTRODUCTION

Oral preparation is the easiest and most widely used drug delivery route because it has several advantages, namely ease of administration, high level of patient compliance, cost-effective, and tends to be flexible in terms of dosage formulations. However, the biggest challenge in designing oral dosage form is low bioavailability property. Bioavailability is influenced by several factors, including water solubility, drug permeability, dissolution rate, first-pass metabolism, and pre-systemic metabolism. The most common causes of low bioavailability are low solubility and permeability [1, 2].

Today, nearly 40% of pharmaceutical preparations on the market have low solubility based on the biopharmaceutical classification system (BCS). It is estimated that 90% of drugs that currently being developed are classified to poor-soluble drugs [3]. In the past, the industry consensus thought that those candidates was highly risk in drug development. However, because of the large number of them, the industry consensus also changed the point of view of the drugs from avoidance to acceptance as the dedication of the research provided to solve the challenges regarding the solubility [4, 5].

In dealing with this problem, the pharmaceutical industry has developed several methods to improve drug solubility. These methods include salt formation [6], co-crystal [7], self-emulsifying drug delivery systems (SEEDS) [8], cyclodextrin [9], pH-micro-environmental modifiers [10], solid lipid nanoparticles [11], micelles [12], high energy polymorphs [13], soft gelatin capsules [14], and liposomes [15]. Co-crystallization method and salt formation have several advantages in physicochemical properties and are able to improve the parent drug without changing therapeutic efficiency [7]. Traditionally, the formation of salt is more widely used by researchers in the medicinal and synthetic chemistry field by using bases or weak acids [6]. However, only 20-30% of the new molecules can form salt spontaneously, so that 70-80% of the remaining molecules must be given via different routes to increase solubility [16]. Another simple method to improve solubility is co-crystallization. Co-crystallization method is a method of co-crystal formation by adding co-former into active pharmaceutical

ingredients in order to increase solubility without affecting its pharmacological activity [17]. Formation of co-crystal is better in reducing unintended property of the parent substance [18].

The previous study showed that co-crystallization method can increase the solubility of simvastatin 2-fold from pure simvastatin with malic acid as the co-former [19]. Benzoic acid and aspartam also could be used as co-former in improving atorvastatin solubility by the co-crystallization method, from 22.08 ppm to 28.91 ppm and 30.20 ppm, respectively [20]. In this study, the co-crystal of glibenclamide-saccharin were prepared with the equimolar ratio is 1:1 and 1:2. Saccharin is the excipient that easily accessible and has an affordable price. As a co-former, saccharin could increase ketoprofen solubility up to 30% [21].

### MATERIALS AND METHODS

#### Materials

Glibenclamide was obtained from PT. Indofarma Tbk, Bekasi, Indonesia. Saccharin, methanol, potassium dihydrogen phosphate, and potassium hydrogen phosphate were purchased from Merck, Germany. All reagents used were analytical grade.

#### Methods

##### Virtual screening

The virtual screening method was used to predict the bond formed between glibenclamide and its co-former. The expected bonds were hydrogen, van der Waals, and  $\pi$ - $\pi$  bonds. The 2D structure of the active pharmaceutical ingredients and co-former was prepared using ChemBioDraw Ultra 12.0 (trial version) and converted into cdx format. The 2D structure was converted into a 3D structure using ChemBio3D Ultra 12.0 (trial version) by the mechanical method (Hartree-Fock, set 321G), and the file was saved as a .pdb format. Molecular docking of active pharmaceutical ingredients was performed using PyRx-Virtual Screening Tools (trial version) with AutoDock Vina as the engine. The molecular docking results were analyzed based on binding affinity value, type, and the position of

bonds formed between glibenclamide and the co-former using AutoDock Tools-1.5.6rc3 (trial version) [22].

#### Preparation of glibenclamide co-crystal using solvent evaporation method

Glibenclamide and saccharin were weighed in accordance with equimolar ratios of 1:1 and 1:2. Each mixture was dissolved in methanol homogeneously and evaporated in a water bath at 45 °C for 24 h or until the methanol completely evaporated. The co-crystal obtained was stored in a desiccator and further analyzed for characterization and evaluation [22].

#### Optimization of pH of glibenclamide dissolution medium

Buffer phosphate solution (BPS) was used as the dissolution medium and prepared with various pH (6.4; 7.6; 8.0) for 900 ml. Dissolution test of standard glibenclamide was performed using type 2 apparatus (paddle) at 75 rpm for 60 min (37 ±0.2 °C). At predetermined interval times (5; 10; 15; 30; 45; 60 min), 5 ml of sample was taken and then replaced by fresh medium. The aliquot sample was analyzed using a UV Spectrophotometer (analytical Jena, specord 200®) to quantify the amount of dissolved glibenclamide concentration and the optimum pH of the medium [23].

#### Determination of solubility

Each co-crystal of glibenclamide was weighed equivalently to 20 mg glibenclamide then put into 20 ml distilled water and shaken for 12 and 24 h using a mechanical agitator (IKA HS 260 basic®) at 120 rpm at room temperature. After shaking, the solution was filtered and diluted into 100 ppm using methanol. Each sample was analyzed using a UV-Vis Spectrophotometer (analytical Jena, specord 200®) [24].

#### Dissolution test

Dissolution test of glibenclamide was performed using type 2 apparatus (paddle) at 75 rpm for 60 min (37 ±0.2 °C). The medium was BPS (pH 8.0) 900 ml. At predetermined interval times (5; 10; 15; 30; 45; 60 min), 5 ml of sample was taken and then equally replaced by fresh medium. The aliquot sample was analyzed using a

UV Spectrophotometer (analytical Jena, specord 200®) to quantify the amount of dissolved glibenclamide concentration [23].

#### Characterization

##### Infrared spectrophotometry

1 mg of Co-crystal of glibenclamide was carefully weighed and homogeneously mixed with 250 mg of KBr. The mixture was compressed at 80 Psi to obtain a pellet. The pellet was analyzed using an infrared spectrophotometer (Shimadzu®) at room temperature in a range of wavenumbers from 400-4000 cm<sup>-1</sup>. The KBr pellet was used as a blank [25].

##### Powder X-ray diffraction (PXRD)

PXRD measurements were conducted using Phillip PW 1835 under the following conditions: target, Cu; voltage, 40 kV; and current, 40mA. The scans were performed with a detector step size of 0.02 ° over an angular range of 2θ = 2-50 ° [26].

##### Differential scanning calorimetry (DSC)

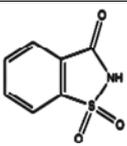
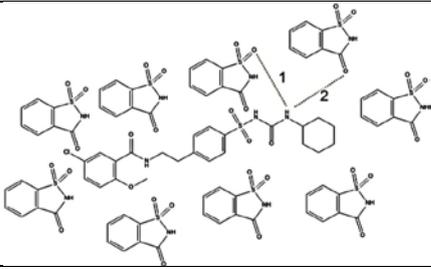
DSC analysis was performed using Linseis DSC PT1000, which was periodically calibrated using indium. Approximately 4 mg of the powder sample was placed in an aluminum pan with a pinhole for the measurement. Dry nitrogen was used as the inert gas at a flow rate of 30 ml/min, and the measurements were carried out at 50-300 °C at a heating rate of 10 °C/min [26].

## RESULTS AND DISCUSSION

### Virtual screening of glibenclamide co-crystal

Virtual screening was performed using molecular modelling and the molecular docking program to predict the bonds formed when combining glibenclamide and the co-former structure. Virtual screening was used to determine which co-former should be used in later steps [27]. Molecular docking was used to determine that the selected parameter of the co-former had a high number of hydrogen bonds and a small value of energy of interaction (E<sub>i</sub>); the smaller the E<sub>i</sub>, the stronger the bond [20].

Table 1: The result of the virtual screening of glibenclamide-saccharin

Co-former	2D-structure	Interaction	E <sub>i</sub> (kca/mol)
Saccharin			1.-4.467 2.-3.951

The virtual screening results showed that two interactions were observed. Hydrogen bonds were formed from hydrogen atoms of the amide groups of glibenclamide and oxygen atoms of sulfonyl of saccharin (table 1). In addition, π-π and van der Waals bonds could also be used as a selection parameter of the co-former. However, π-π bonds have lower electronegativity than hydrogen bonds, and van der Waals bonds are weaker than hydrogen bonds [28, 21]. Covalent bonds are undesirable because they are immensely strong, will bind irreversibly to the body, and may cause toxicity [29].

#### Preparation of glibenclamide co-crystal

Slow solvent evaporation and grinding are widely used co-crystallization methods, thus the common principles in the co-crystallization process were solvent-based and grinding. Therefore, the co-crystallization process of glibenclamide-saccharin was performed using the basic solvent evaporation method, as the objective was to attain solubilization and slow evaporation. While the solvent evaporated, the molecules in the solution reacted and

formed hydrogen bonds. Thus, an advantage of this method was that the optimal co-crystal obtained might improve the solubility of the active pharmaceutical ingredient [30]. Co-crystallization using the equimolar ratio of each component was appropriate in the solvent evaporation method because, with the stoichiometry ratio, the possibility of generating intermolecular bonds is high [31].

#### Determination of solubility

In this study, the determination of solubility of the glibenclamide co-crystal was performed based on the Higuchi and Connor method, which consists of five steps to determining the solubility of a compound: sample preparation, equilibration, separation, sample analysis, and data analysis [24].

The solubility of glibenclamide-saccharin (1:2) was higher than the solubility of its pure form and glibenclamide-saccharin (1:1) (fig. 1). The higher content of the co-former led to the improvement of solubility because the co-former can reduce barriers of the

compound, thus making the solubilization process easier [32]. In this study, saccharin as a co-former was capable of reducing the

barrier because it was highly soluble in water and then ionized; thus, the drug was solubilized easier [33].

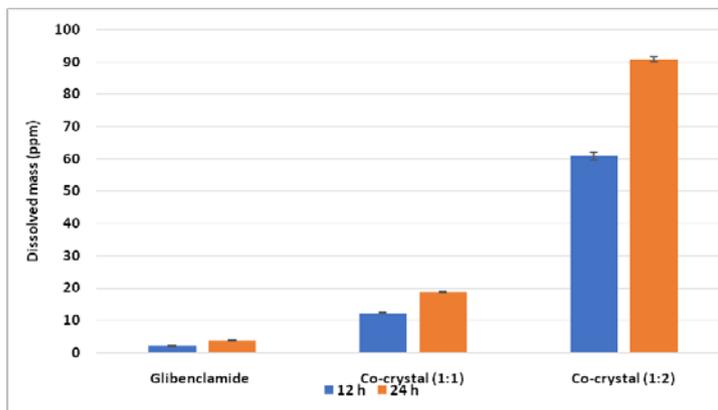


Fig. 1: Solubility of glibenclamide co-crystal for 12 and 24 h (All the values were calculated as mean±standard deviation; n=3)

**Dissolution test**

The dissolution test was performed on the co-crystal with the best equimolar ratio based on the solubility test i.e., glibenclamide-saccharin 1:2 compared with pure glibenclamide. Optimization of

pH of dissolution medium was performed at pH 6.4, 7.6, and 8.0. In table 4, the concentration of standard glibenclamide 60 min was 9.91, 16.43, and 45.31 ppm for pH 6.4, 7.6, and 8.0, respectively. Based on the results, 8.0 was the optimum pH for the dissolution test of glibenclamide.

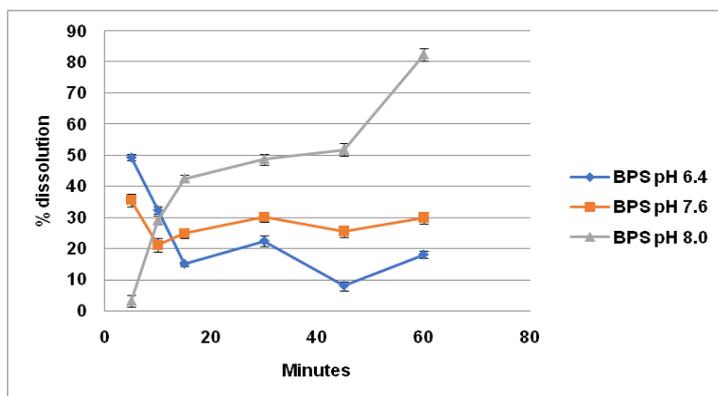


Fig. 2: Optimization of pH of dissolution medium (All the values were calculated as mean±standard deviation; n=3)

In fig. 2, the dissolution rate of co-crystal of glibenclamide-saccharin was higher than its pure form. As stated in the literature, glibenclamide only dissolved 45% in 60 min. In this study, pure

glibenclamide dissolved 46.83% in 60 min [34]. However, the co-crystal of glibenclamide-saccharin (1:2) dissolved 77.65% in 60 min.

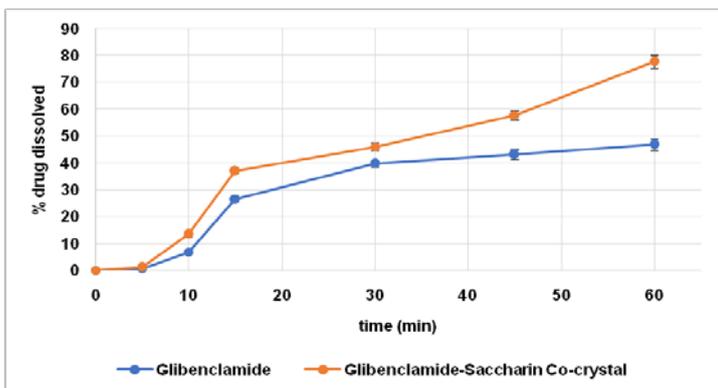


Fig. 3: Result of dissolution test of pure glibenclamide (blue line) and glibenclamide-saccharin (red line) (All the values were calculated as mean±standard deviation; n=3)

### Characterization

Characterization of the co-crystal was performed on glibenclamide-saccharin (1:2) and its pure form. The aim of characterization was to determine the characteristics of the co-crystal and compare it with pure glibenclamide.

### Infrared spectrophotometry

In fig. 3, the peaks of pure glibenclamide were 33367.71  $\text{cm}^{-1}$  and 3313.71  $\text{cm}^{-1}$  (N-H Stretch), 3116.97  $\text{cm}^{-1}$  (O-H Stretch), 2931.80  $\text{cm}^{-1}$ , and 2854.65  $\text{cm}^{-1}$  (C-H Stretch), 1716.65  $\text{cm}^{-1}$  (C=O Stretch) and 1616.35  $\text{cm}^{-1}$  (C=C Stretch). The peaks of pure saccharin were 3398.57  $\text{cm}^{-1}$  (N-H Stretch), 3093.82  $\text{cm}^{-1}$  (O-H Stretch), 2974.23  $\text{cm}^{-1}$  (C-H Stretch) and

1724.3665  $\text{cm}^{-1}$  (C=O Stretch). The peaks of the co-crystal of glibenclamide-saccharin were 3367.71  $\text{cm}^{-1}$  and 3313.71  $\text{cm}^{-1}$  (N-H Stretch), 3093.82  $\text{cm}^{-1}$  (O-H Stretch), 2931.80  $\text{cm}^{-1}$  and 2854.65  $\text{cm}^{-1}$  (C-H Stretch), 1616.35  $\text{cm}^{-1}$  (C=C Stretch) and 1720.50  $\text{cm}^{-1}$  (C=O Stretch). The C=O peak was weakened from 1716.65  $\text{cm}^{-1}$  to 1720.50  $\text{cm}^{-1}$ , indicating that there was a formation of hydrogen bonds marked by a bond on the extended of C=O group, which reduced the bond strength. Compared to the functional group of glibenclamide-saccharin and its components (glibenclamide and saccharin), no new peaks were observed, indicating that no additional functional group was formed and no chemical reaction occurred during co-crystal preparation. However, the peaks of 2009.83  $\text{cm}^{-1}$ , 1975.11  $\text{cm}^{-1}$ , and 1863.24  $\text{cm}^{-1}$  in the glibenclamide-saccharin spectrum were from the saccharin peaks.

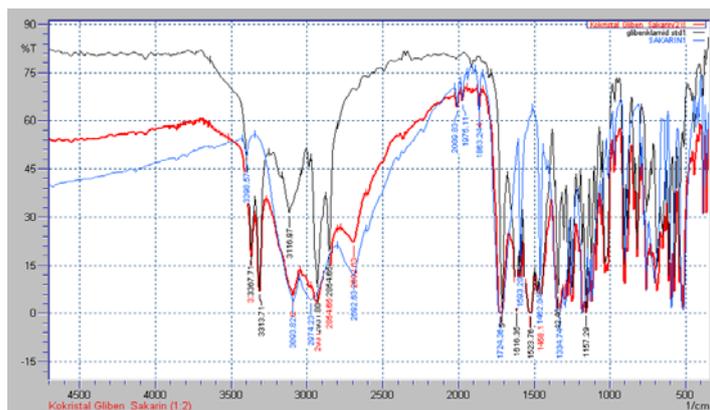


Fig. 4: Infrared spectrum of pure glibenclamide (black line), saccharin (blue line), and glibenclamide-saccharin (red line)

### Powder X-ray diffraction (PXRD)

In fig. 4, the intensity of the glibenclamide-saccharin (1:2) diffractogram was higher than glibenclamide and saccharin. Pure glibenclamide was semi-crystalline, but both saccharin and glibenclamide-saccharin were crystalline. The highest intensity of

glibenclamide-saccharin (1:2) was 100% at  $2\theta$  of 15.79°. Peak amounts of pure glibenclamide and glibenclamide-saccharin were different, at 40 and 44 peaks, respectively.

These differences indicate that there was a difference in the structure due to the co-crystal formation [35, 36].

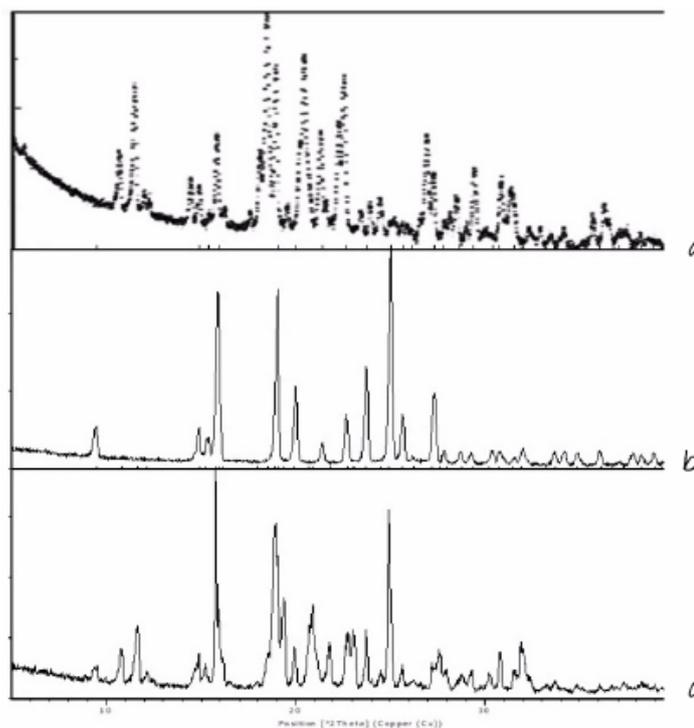


Fig. 5: Diffraction of glibenclamide (a), saccharin (b), and glibenclamide-saccharin (1:2) (c)

Table 2: The result of PXRD

2θ (°)	Intensity		
	Glibenclamide	Saccharin	Glibenclamide-saccharin (1:2)
15.79	11.30	10.68	100
24.93	10	44	83.02

### Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is an analytical instrument used in characterization to determine the solid-state interaction of two compounds or more by giving heat energy to the co-crystals to evaluate thermodynamic changes (endothermic or exothermic peaks) [37]. Changes were noted in the thermodynamic aspects of the solid as well as in the shape of the solid crystalline structure due to the physical interaction by the thermal analysis of two compounds or more [25].

The thermogram of glibenclamide, saccharin, and glibenclamide-saccharin can be seen in fig. 5 and table 6. In the thermogram, there was an endotherm peak of pure glibenclamide at 174.66 °C,

indicating the melting point of glibenclamide, and 259.89 °C, indicating the decomposition of glibenclamide. The endotherm peak of saccharin was at 229.06 °C, indicating that saccharin did not have a melting point but started to degrade after reaching said temperature. The glibenclamide-saccharin melting point was lower than those of glibenclamide and saccharin alone, at 157.87 °C. Compared to solubility properties, it is reasonable to conclude that glibenclamide-saccharin has a higher solubility than pure glibenclamide. According to the literature, the co-crystallization process results in a change of the melting point of the compound compared to its components, as a co-crystal melting point is typically lower than those of its components [22, 37].

Table 5: The result of DSC analysis

Sample	Melting point (°C)		
	Onset	Peak	Endset
Glibenclamide	171.96	174.66	178.33
Saccharin	225.65	229.06	233.61
Glibenclamide-saccharin	145.60	157.87	170.69

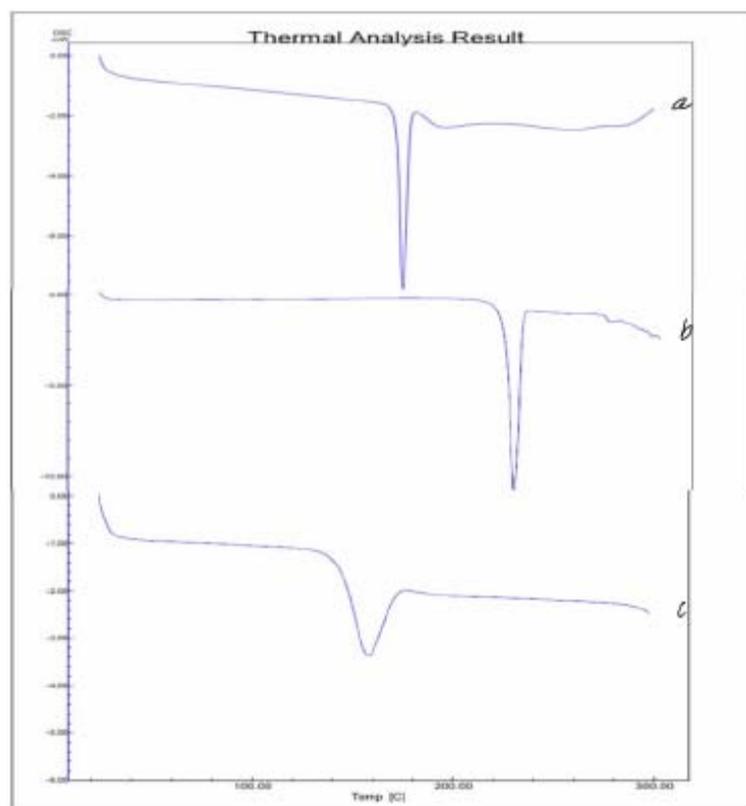


Fig. 6: DSC thermogram of (a) glibenclamide, (b) saccharin, and (c) glibenclamide-saccharin (1:2)

### CONCLUSION

The co-crystallization method was successful in improving the solubility of glibenclamide using saccharin as the co-former with an optimal equimolar ratio of 1:2. The dissolution rate also increased from 46.838% of pure glibenclamide to 77.655% of glibenclamide co-crystal in 60 min. There was no chemical interaction observed

based on the infrared spectrum, but the co-crystal was successfully formed based on the diffractogram and thermogram.

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**CONFLICTS OF INTERESTS**

All authors have none to declare

**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally

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