Enhancing Dissolution Rates of Gliclazide via Co-crystallization with Nicotinamide

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ABSTRACT— ***Gliclazide is a drug with poor water solubility and high permeability (BCS II), The absorption rate of this drug, when taken orally is controlled by dissolution rate in the gastrointestinal tracts. Co-crystallization method is widely used to improve the dissolution rate of this type of drug. This study aims to improve the dissolution rate of gliclazide by Co-crystallization method with nicotinamide as a coformer. Co-crystallization were prepared by solvent evaporation methods using methanol. Pure gliclazide, co-crystal gliclazide-nicotinamide in molar ratio 1:0,5, 1:1, 1:2, 1:2,5, 1:3, 1:3,5, 1:4, 1:5, and 1:7 and physical mixtures were characterized by DSC, FTIR, XRD and dissolution testing. Characterization by DSC and XRD in ratio 1:0,5, 1:1, and 1:2 showed a lower endothermic peak of gliclazide, and decrease in the intensity of the diffraction pattern by XRD. Characterization by FTIR virtually showed no shift of absorption peaks of gliclazide in ratio 1:0,5, 1:1, and 1:2. FTIR spectrum of cocrystal in ratio 1:7 showed a shift of absorption peaks for C=O and N-H. Results of dissolution testing for cocrystal in ratio 1:0,5, 1:3, 1:7, and physical mixture in ratio 1:7 showed higher dissolution rate than pure gliclazide. The highest of dissolution rate is cocrystal gliclazide-nicotinamide in ratio 1:7. Similarity analysis (f_2) showed no similarity of dissolution rate for pure gliclazide, cocrystal gliclazide-nicotinamide in ratio 1:0,5, 1:3, 1:7 and physical mixture in ratio 1:7.***

Keywords— gliclazide, nicotinamide, co-crystallization, dissolution rate

1. INTRODUCTION

The attempt to increase the solubility of poorly soluble drugs can be made in various ways including the solid dispersion, prodrug formation, the formation of inclusion complexes of active substances with the carrier, Co-Crystal formation and modification of compounds to form salts and solvates [1]. Co-Crystallization is the formation of solid material consisting of two or more molecules of solids which form different crystal lattice and connected by intermolecular bonds such as hydrogen bonding [2]. Co-Crystal comprises of an active agent and the Co-Crystal built agent, for example, nicotinamide, oxalic acid, succinic acid, malonic acid etc. Co-Crystallization method can be used to modify the physical properties of the active substance such as its solubility and stability without changing its active substance composition. Pharmaceutical Co-Crystal active substance will have different behavior than the pure active substance such as differences melting point, solubility, dissolution, bioavailability, moisture, chemical stability, etc. [3].

The series of a drug in the body include the pharmaceutical and pharmacokinetic phase. Biopharmaceutical phase begins with the release of the drug and then the drug will dilute and absorb through the cell membrane to blood circulation. This process will determine the slowest speed of the drug to reach blood circulation. for drugs with poor solubility in water, the absorption stage will be resolved by dissolution process in the gastrointestinal tract [4]. Dissolution is the suspension process of a substance in a specific solvent. Drugs dissolution process in the gastrointestinal tract will affect the amount of drug absorbed by the body [1].

Based on Biopharmaceutics Classification System (BCS) drugs are grouped into four groups; the one with high solubility and high permeability (BCS I), drugs with low solubility and high permeability (BCS II), a drug with high solubility and low permeability (BCS III), and drugs with low solubility and permeability (BCS IV) (5). Drugs that belong to class II and IV BCS will have less bioavailability due to dissolved drug particles will be absorbed in a low rate or will not be absorbed entirely. Improvement of dissolution rate of less soluble drugs will increase drug levels in the blood [5].

In this study, Gliclazide is used as an active substance poorly soluble model and nicotinamide as a forming crystal. Gliclazide is an oral compound antihyperglycemic second generation sulfonylurea class which is used for type II diabetes mellitus (NIDDM or Non-Insulin Dependent Diabetes Mellitus) treatment [6, 7]. Gliclazide belongs to a group of Class II BCS with high permeability and low solubility compound [5]. Gliclazide is practically insoluble in water, soluble both

in methylene chloride or dichloromethane, partially soluble in acetone, and slightly soluble in ethanol 96% [8]. Nicotinamide (vitamin B3)is used to form Co-Crystal (co-crystal former) which are inert and has a low toxicity. Nicotinamide has two bonding sites which can be formed non-covalently with another compound, such as pyridine and amine group [9].

2. MATERIALS AND METHODS

Materials
Gliclazide (PT. Kalbe Farma Tbk), Nicotinamide, filter dissolution, hydrochloric acid (HCl) 37% pro analysis (Merck), methanol, distilled water and other reagents related to the research

Co-Crystal and Physical Mixture Preparation
Co-Crystal for this study were made by solvent method, as follows: number of gliclazide and nicotinamide in a molar ratio of 1: 0.5 (C-GN 0.5), 1: 1 (C-GN 1), 1: 2 (C-GN 2), 1: 2.5 (C-GN 2.5), 1: 3 (C-GN 3), 1: 3.5 (C-GN 3.5), 1: 4 (C-GN 4), 1: 5 (C-GN 5) and 1: 7 (C-GN 7) diluted in methanol. The solution was evaporated to obtain a dry mass and stored for 48 hours. The physical mixture (PM) was made by mixing gliclazide and the carrier in a mortar without crushing.

Dissolution test
The dissolution test conducted on the active ingredient gliclazide, gliclazide Co-Crystal - nicotinamide and physical mixture gliclazide - nicotinamide. The dissolution test carried out in acidic media 0,1N HCl pH 1.2 with 900 mL of type II dissolution apparatus with a rotation speed of 100 rpm and a temperature of 37 ± 0.5 ^{0}C. The sample used was equivalent to 80 mg gliclazide. The sampling was done in minutes: 5, 10, 15, 30, and 60 then measuring the absorbance using a UV-Vis spectrophotometer at a wavelength of 228 nm.

Characterization of Co-Crystal
Co-crystal were characterized by differential scanning calorimeter (DSC), the FTIR spectra, and X-Ray Diffraction of pure drug and their co-crystal. DSC curves of co-crystal were obtained by Differential Scanning Calorimetry (Perkin Elmer). The FTIR spectra of pure drug and their co-crystal were obtained on a Perkin –Elmer types one by using KBr disc method [10]. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4cm-1. X-Ray Diffraction testing was obtained by Shimadzu X-Ray Diffractometer. Testing with X-Ray diffraction was conducted at room temperature, with Cu as an anode and a monochromatic graphite. Tests performed on 40kV voltage, current 25 mA. The samples were analyzed at an angle 2θ in the range 5-700 and process parameters set at 0.020 scans stage (2θ) and sweep speed coupe / 0.5 seconds [10].

Data Analysis
The similarities between the results of dissolution testing of co-crystal with pure gliclazide were carried out using the formula as follows:

$$f2 = 50 \times log\left\{\left[1 + (1 \div n)\sum_{t=1} n\,(R_t - T_t)^2\right]^{-0.5} x\ 100\right\}$$

with:
n = number of sampling points
Rt = percent on average solute at time t for formula 1
Tt = percent on average solute at time t for formula 2

3. RESULTS AND DISCUSSION

Characterization of DSC results in an endothermic peak of gliclazide on 172, 27 ^{0}C (melting point) with ΔHf105, 59 J / g. pointed peak of gliclazide shows the high crystalline nature of gliclazide (Fig.1). On nicotinamide was obtained sharp enough endothermic peak at 133,100C and ΔHf275, 97 J / g, it also shows a fairly high crystalline nature of nicotinamide. In the DSC thermogram for Co-Crystal gliclazide-nicotinamide on three ratios (1: 0.5, 1: 1 and 1: 2) all showed two peaks indicating high peak for gliclazide and nicotinamide, however, showed a decrease in the endothermic peak for gliclazide and nicotinamide. There was no new peak on the Co-Crystal thermogram. It means there was no new compound from Co-Crystallization of gliclazide and nicotinamide (Fig. 2).

Sample : Gliclazide (G)
Purge gas : Nitrogen (20 cc/min)
Scan rate : 10/min
Weight : 8.6 mg

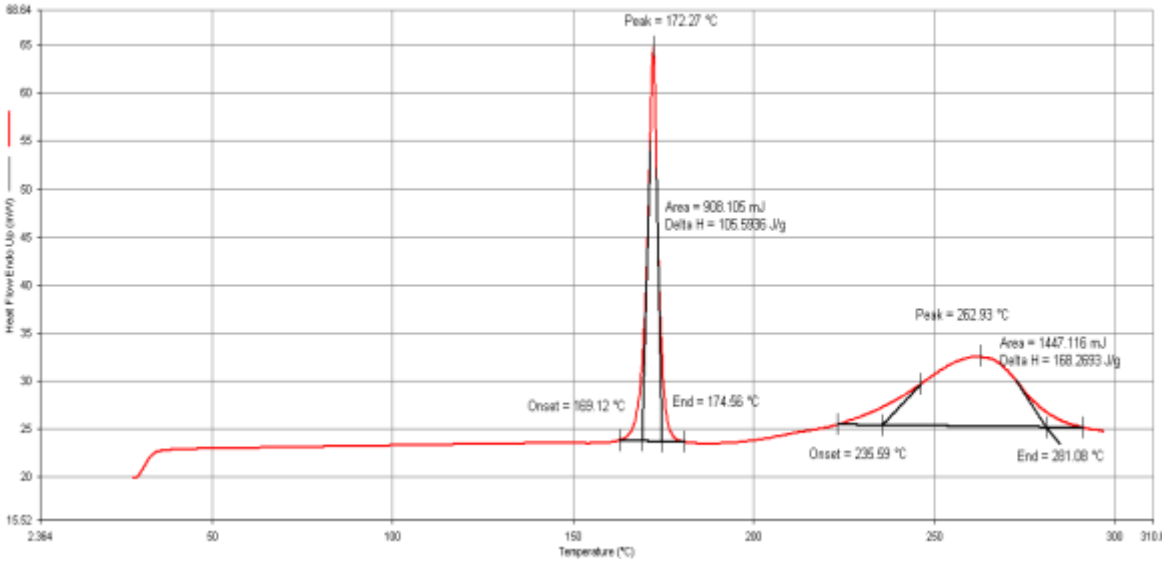

Fig. 1: Pure gliclazide DSC Thermogram

Sample : co-crystal gliclazide-nicotinamide 1: 2 (C–GN 2)
Purge gas : Nitrogen (20 cc/min)
Scan rate : 10/min
Weight : 6.5 mg

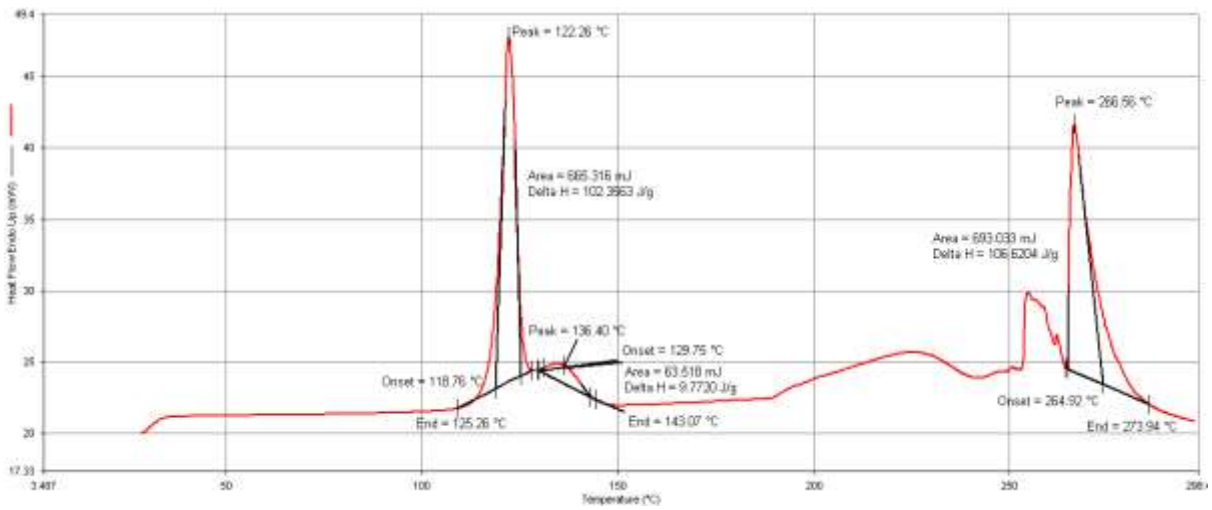

Fig. 2: Co-crystal gliclazide-nicotinamide 1: 2 (C-GN 2) DSC thermogram

From X-ray diffraction pattern for Co-Crystal and general physical mixtures, there is a decline in the intensity of the Co-Crystal gliclazide or physical mixture pattern, compared to the pure gliclazide and nicotinamide. It showed a decrease in the crystalline degree from gliclazide and nicotinamide (Fig. 3).

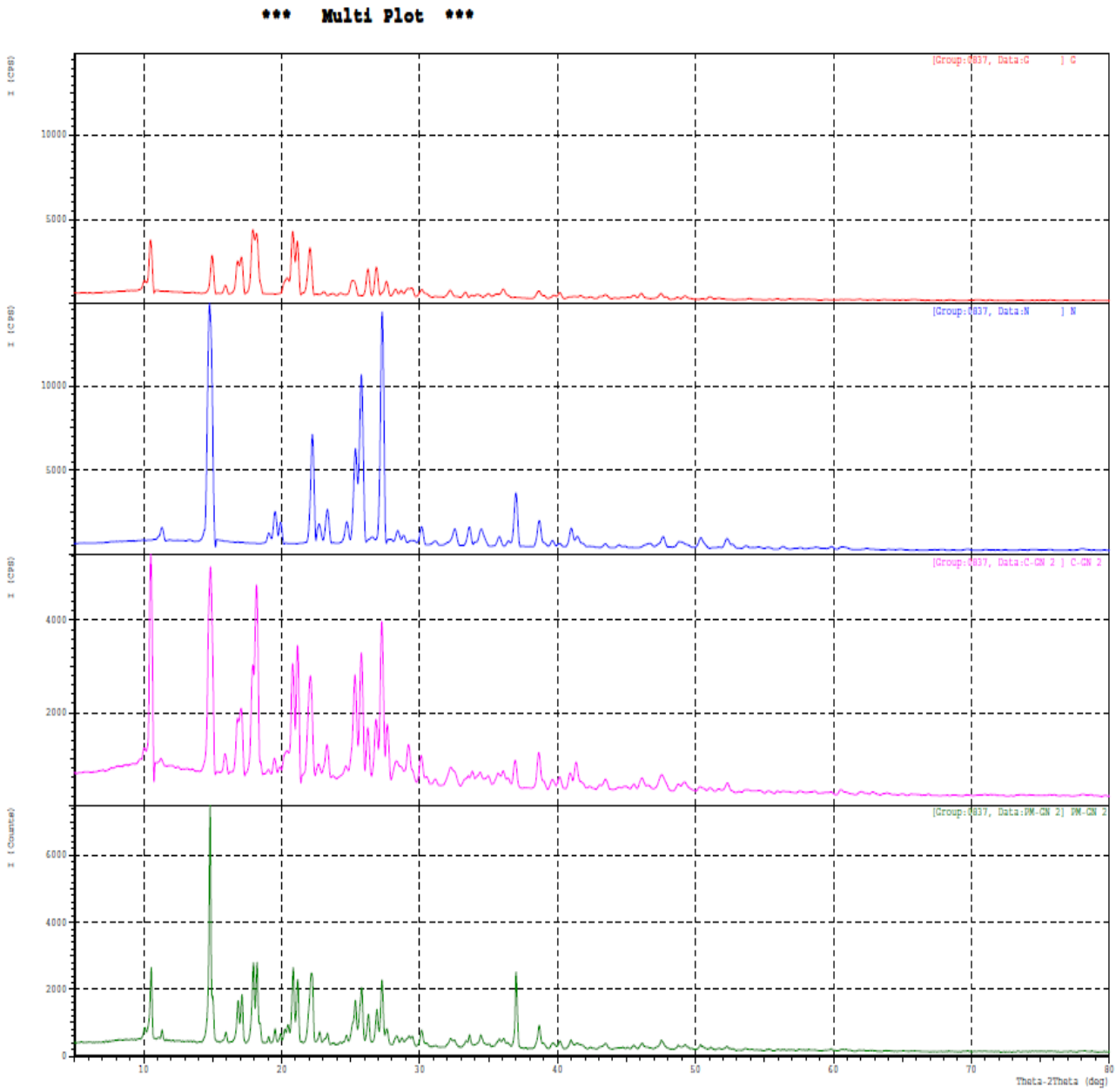

Fig. 3: X-ray diffraction pattern of **gliclazide**, **nicotinamide**, **Co-crystal gliclazide-**nicotinamide **1**: **2 (C-GN 2) and physical mixture gliclazide-**nicotinamide **(PM-GN 2) from top to bottom**

FTIR spectra obtained peak characteristics at 3274 cm-1, 1711 cm-1, 1353 cm-1 and 1164 cm-1 for gliclazide. Absorption band at 3274 cm-1 illustrates the amine group (NH), a sharp peak at 1711 cm-1 for carbonyl group (C = O), and the peaks at 1353 and 1164 cm-1 for sulfonyl group (S = O) (Fig. 4).

Comparing the FITR spectrum for gliclazide with the FTIR spectrum for Co-Crystal gliclazide-nicotinamide and physical mixture at a molar ratio of 1: 0.5, 1: 1 and 1: 2, we observed that the peak characteristics are almost unaffected. So it is assumed that there is no interaction between the active substances with coformer. Furthermore, we manufactured Co-Crystal gliclazide-nicotinamide in six different molar ratios is 1: 2.5, 1: 3, 1: 3.5, 1: 4, 1: 5 and 1: 7 made by the solvent method. A dry mass formed were characterized by FTIR to determine the chemical interaction. From the Characterization by FTIR for the gliclazide-nicotinamide molar ratio of 1: 5 and 1: 7, there is the unobserved peak for C=O on gliclazide (in the ratio of 1: 5) and the peak for C=O and NH on gliclazide (in the ratio of 1: 7) (Fig.5). This equally typical spectrum shifting indicated possible interactions between inter-molecule hydrogen connection for gliclazide and gliclazide – nicotinamide. especially on 1: 7 nicotinamide ratio because the shift occurs in the spectrum C=O and NH wavelength.

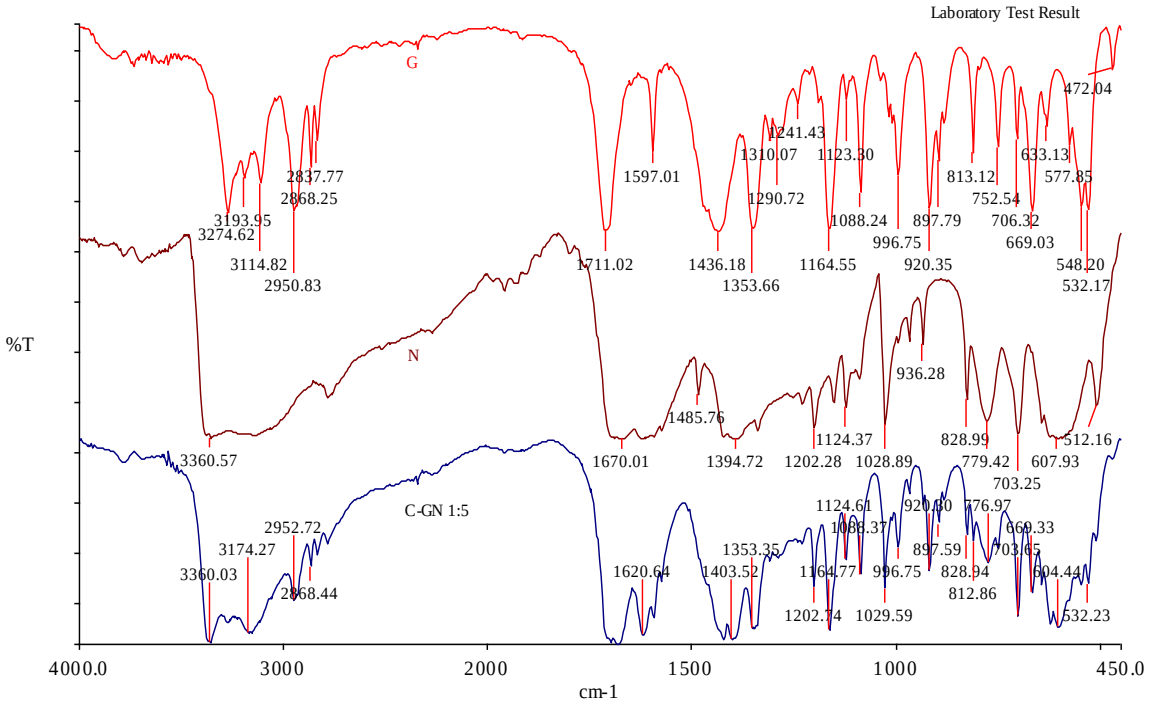

Fig. 4: FTIR spectra of gliclazide, nicotinamide, and nicotinamide Co-crystal gliclazide-1:5 (C-GN 5)

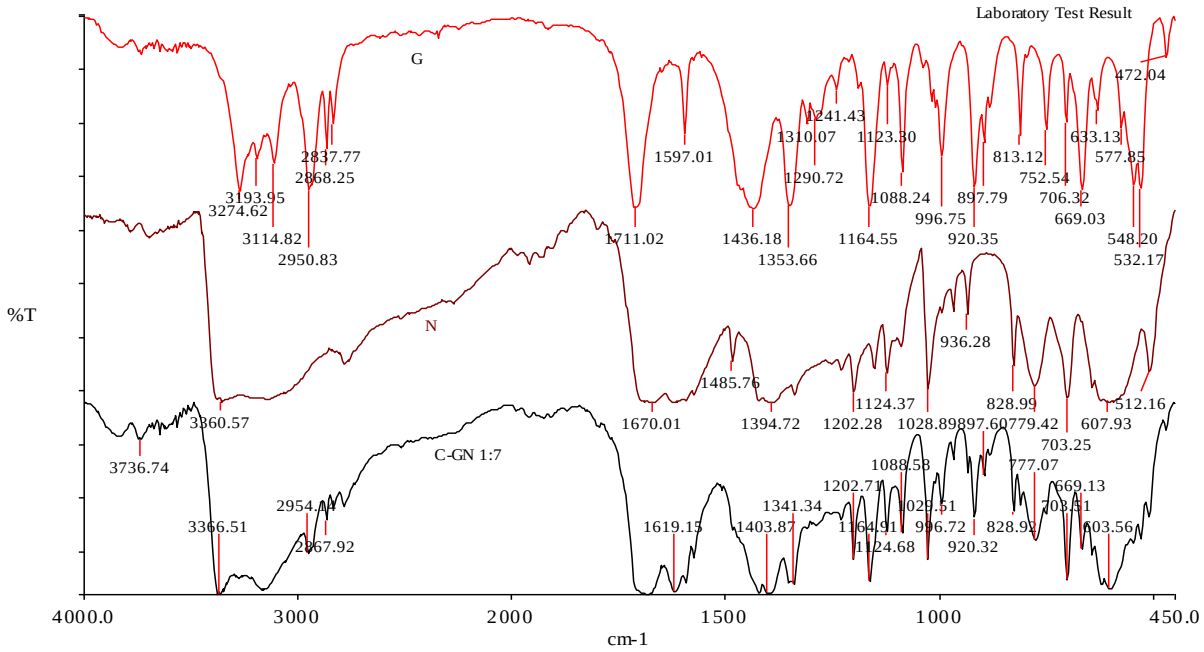

Fig. 5: FTIR spectra of gliclazide, nicotinamide, and nicotinamide gliclazide Co-crystal 1: 7 (C-GN 7)

From The dissolution test result (Fig.6) we could see that the treatment of gliclazide with nicotinamide by dissolution in various comparisons showed an increase in dissolution rate when compared with pure gliclazide. The fastest dissolution rate was obtained from C-GN 7 wherein the 15th minute already achieved levels of dissolved > 90%. Improved solubility of gliclazide resulting in a higher dissolution rate than pure gliclazide was caused by several things, among others, changes in the crystal properties of gliclazide shown by the lower melting point of gliclazide with DSC, which indicates _ a decrease in the degree of crystalline. A decrease in the degree of crystalline was also indicated by the results of the spectrum of X-ray diffraction. FTIR spectra results indicated the possibility of molecular interactions of gliclazide-nicotinamide at a ratio of 1: 7 which would increase the solubility of gliclazide. an increase in the rate of dissolution was also apparent in the physical mixture of gliclazide-nicotinamide 1:7 that looked higher than the rate of dissolution of pure gliclazide and gliclazide-nicotinamide treatment 1: 0.5 and 1: 3. It is also possible that nicotinamide's water-solublility affected the solubility of gliclazide.

Statistical f2 analysis for gliclazide, C-GN 0.5, C-GN 3, C-GN 7, and PM-GN 7 all resulted in the value of f2 <50 so there was no similar dissolution rate [11].

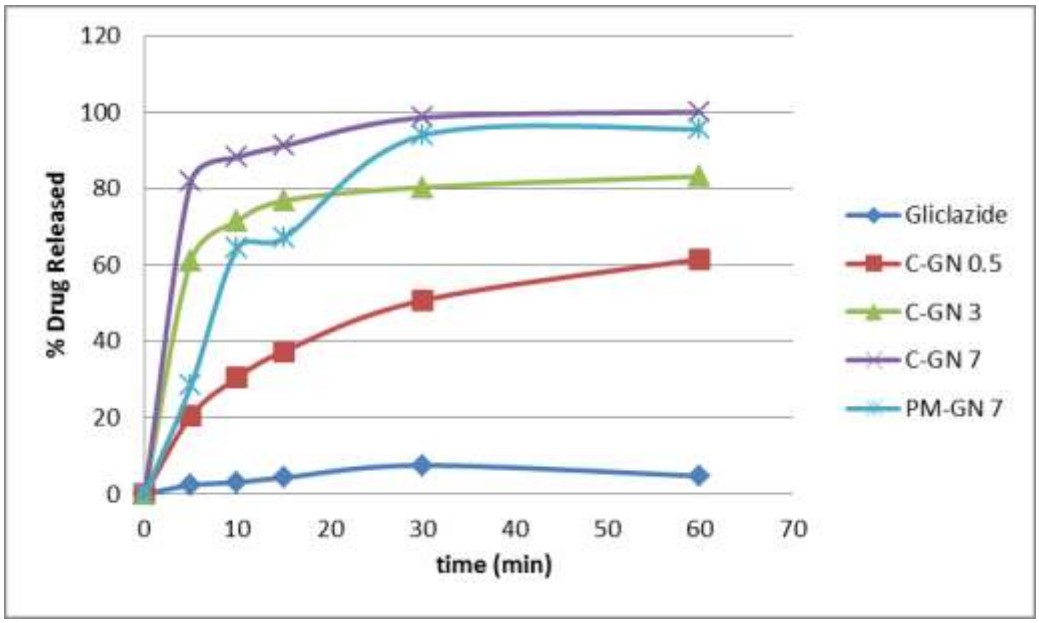

Fig. 6: Dissolution profile of Pure Gliclazide, Co-crystal Gliclazid-Nicotinamide, and Physical Mixtures Gliclazide-Nicotinamide

4. CONCLUSION

Intermolecular interactions between _ gliclazide and nicotinamide was apparent from a molar ratio of 1: 7 as indicated by changes in FTIR spectra for gliclazide. Gliclazide solution treatment with nicotinamide showed an increase in dissolution rate, and the highest dissolution rate was obtained from Co-Crystal gliclazide-nicotinamide 1: 7. Tests with DSC and XRD on samples 1:0.5, 1:1 and 1:2 showed a decrease in endothermic peak level of gliclazide and nicotinamide as well as a decline in the degree of crystalline of gliclazide. f_2 analysis results showed differences in dissolution rate for all samples (gliclazide, C-GN 0.5, C-GN 3, C-GN 7, and PM-GN 7) when compared to one another.

5. REFERENCES

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