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Original Article

PREPARATION AND CHARACTERIZATION OF GLICLAZIDE SOLID DISPERSION IN BINARY AND TERNARY SYSTEM

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ABSTRACT

Objective: The objective of this research was to improve the dissolution rate of gliclazide by solid dispersion technique with poloxamer 188, HPMC, and Eudragit® E100 as carriers.

Methods: Solid dispersions were prepared by solvent evaporation methods in the binary and ternary system. In binary system gliclazide was mixed with poloxamer188 in the ratio of 1:0.5, 1:0.75, 1:1, 1:1.5 and 1:2, with HPMC in the ratio of 1:0.1, 1:0.125, and 1:0.25, and with Eudragit® E100 in 1:0.25 ratio. In ternary system gliclazide was prepared with poloxamer188 and HPMC in the ratio of 1:2:0.1 and 1:2:0.25, and with poloxamer188 and Eudragit® E100 in the ratio of 1:1:0.25 and 1:2:0.25. Pure gliclazide, solid dispersions, and physical mixtures were characterized by dissolution testing, DSC, FTIR, dan XRD.

Results: At the 15th minute, the highest dissolution rate observed from binary and ternary solid dispersions of gliclazide were from gliclazide-poloxamer188 1:2 dan gliclazide-poloxamer188 and Eudragit® E100 1:2:0,25 which showed 12 and 15 fold increase in dissolution rate compared by pure gliclazide. The decrease of endothermic peak (DSC) and the intensity of the diffraction pattern by XRD of solid dispersions showed the decrease of crystallinity rate. Characterization by FTIR virtually showed no shift of absorption peaks of gliclazide on solid dispersion.

Conclusion: The results of this study indicate that the solid dispersion of gliclazide using poloxamer and Eudragit®E100 in 1:2:0, 25 ratio of weight was the best in enhancing the dissolutions characteristics and bioavailability.

Keywords: Dissolution, Gliclazide, Solid dispersions, Poloxamer 188, HPMC, Eudragit®E100

INTRODUCTION

Drugs with low solubility which belongs to a class II and IV BCS (Biopharmaceutics Classification System) will have less bioavailability because the drug particles dissolve slowly. One technique that can improve the drugs dissolution which can improve its bioavailability is through solid dispersion [1]. Solid dispersion is a dispersion of one or more active ingredients in an inert carrier or matrix prepared by the melting, solvent, or melting-solvent method. Solid products consisting of generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly [2]. Gliclazide (GLK) is a second-generation sulfonylurea of an antihyperglycemic oral, widely used for the treatment of type II diabetes mellitus (NIDDM or Non-Insulin Dependent Diabetes Mellitus) [3]. Gliclazide includes in the class II biopharmaceutics, which has a high permeability and low solubility [4]. Solid dispersion used on gliclazide is intended to increase its dissolution rate. Poloxamers are nonionic copolymers composed of a central hydrophobic chain of polypropylene flanked by two hydrophilic chains of polyoxyethylene. Most poloxamers function are as surfactants, emulsifying agents, cleansing and/or solubilizing agents. Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer that is soluble in water, which is stable and hygroscopic. HPMC used as stabilizers, suspending agents, tablet binders and viscosity enhancer [5]. Eudragit® E100 is a cationic polymer consisting of dimethylamino ethyl methacrylate, butyl methacrylate, and methyl methacrylate in the ratio 2: 1: 1. Eudragit® E100 has a low viscosity and its solubility is influenced by physiological conditions of the gastrointestinal tract. Eudragit® E100 dissolve at a pH of up to 5 and will develop and permeable at a pH above 5 [5, 6]. Less investigation on a ternary system of gliclazide solid dispersion has been found. Therefore, the present study was meant to obtain a dissolution formulation of gliclazide with a better method solid dispersions with poloxamer 188, HPMC, Eudragit® E100, as the combination of carrier poloxamer 188-HPMC, and poloxamer 188-Eudragit® E100.

MATERIALS AND METHODS

Materials

Gliclazide (PT. Kalbe Farma Tbk), poloxamer 188 (BASF), HPMC/Methocel E6 LV (PT. Kalbe Farma Tbk), Eudragit® E100 (PT. Sanbe Farma), hydrochloric acid (HCl) 37% pro analysis (Merck), methanol, dichloromethane, distilled water and other reagents associated with the research.

Preparation of the solid dispersion by solvent evaporation

The solid dispersion was made by mixing the active ingredient and the carrier according to the comparison in table 1. Gliclazide was dissolved in methanol, poloxamer 188 was dissolved in distilled water, HPMC was dissolved in a mixture of water: methanol (1: 1), Eudragit® E100 was dissolved in dichloromethane. Then gliclazide and the carrier solution were mixed until homogeneous using a magnetic stirrer. Solid dispersion solution mixture was then evaporated on a water bath at a temperature of 50-60 °C, then dried in an oven 50 °C for 1-2 h. Dry mass was stored in desiccators. Furthermore, the mass of dry solid dispersion crushed and sieved to gain a size<125 µm particle [7].

Preparation of physical mixture

The physical mixture was made by mixing gliclazide and the carrier in a mortar without crushing. Eudragit® E100 first crushed and sieved to gain a size<354µm particle.

In vitro dissolution study

The dissolution test carried out in acidic media 0,1N HCl pH 1.2 900 ml using a type II dissolution apparatus with a rotation speed of 100 rpm and a temperature of 37±0.5 °C. The sample used is equivalent to 80 mg gliclazide. The sampling is done in minutes: 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240. The diluted test solution was then measured absorbance at a wavelength of 228 nm.

Table 1: Composition of solid dispersion and physical mixture gliclazide

Formulation	Carrier	Ratio drug: carrier	Methods
SD PLX 1	Poloxamer 188	1: 0.5	Solvent evaporation
SD PLX 2		1: 0.75	
SD PLX 3		1: 1	
SD PLX 4		1: 1.5	
SD PLX 5		1: 2	
PM PLX		1: 2	Physical Mixture
SD HPMC 1	HPMC	1: 0.1	Solvent evaporation
SD HPMC 2		1: 0.125	
SD HPMC 3		1: 0.25	
PM HPMC		1: 0.25	Physical Mixture
SD EUD 1	Eudragit®E100	1: 0.25	Solvent evaporation
PM EUD		1: 0.25	Physical Mixture
SD PLX-HPMC 1	Poloxamer 188–HPMC	1: 2: 0.1	Solvent evaporation
SD PLX-HPMC 2		1: 2: 0.25	
PM PLX-HPMC		1: 2: 0.25	Physical Mixture
SD PLX-EUD 1	Poloxamer 188-Eudragit®E100	1: 1: 0.25	Solvent evaporation
SD PLX-EUD 2		1: 2: 0.25	
PM PLX-EUD		1: 2: 0.25	Physical Mixture

SD: Solid Dispersion, PM: Physical Mixture

Characterization of solid dispersions

Solid dispersions were characterized by differential scanning calorimetry (DSC), the FTIR spectra, and X-Ray Diffraction of pure drug and their solid dispersions. DSC curves of Solid Dispersions and Physical Mixture were obtained by Differential Scanning Calorimetry (Perkin Elmer). The FTIR spectra of pure drug and their solid dispersions were obtained on a Perkin–Elmer type one by using KBr disc method. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm-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.

Data analysis

The similarities between the results of dissolution testing of solid dispersion and physical mixture 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

RESULTS AND DISCUSSION

The dissolution test gliclazide from solid dispersions showed that 50% gliclazide had been released after the 10th minute on all-poloxamer188 comparison gliclazide, for gliclazide-HPMC after the 60th minute, and the gliclazide-Eudragit® E100 after the 15th minute.

The dissolution test solid dispersions of gliclazide-poloxamer 188 shows that the greatest dissolution rate obtained from solid dispersion gliclazide-poloxamer 188 in the ratio of 1: 2 (BD1) which is reached at minute 120. In the solid dispersions of gliclazide-HPMC greatest dissolution rate indicated by gliclazide-HPMC at a ratio of 1: 0.25 (BD2). Gliclazide-solid dispersion Eudragit® E100 is made only at a ratio of 1: 0:25 (BD3) [8]. This study focused on the use of Eudragit® E100 in the ternary system wherein solid dispersion is made with a combination of the two carriers.

The dissolution test solid dispersion with a combination of two carriers results dissolution rate of solid dispersions of gliclazide-poloxamer188-HPMC (TD1) and gliclazide-poloxamer188-Eudragit®E100 greater in the ratio 1: 2: 0.25 (TD2).

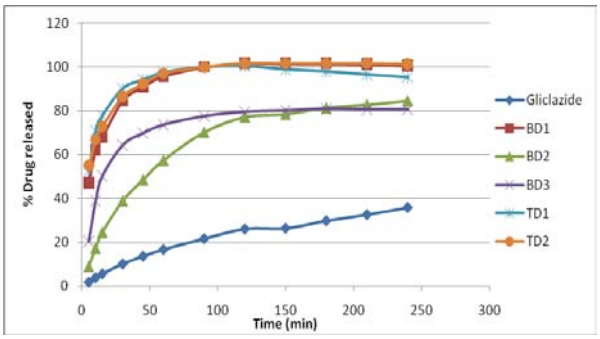

Fig. 1: Dissolution profile of pure drug and solid dispersion system of binary and ternary

*note: error bars have been omitted for simple presentation

Statistical analysis ƒ2 between BD1 and BD3 with 2 BD, TD 1 and TD2, against BD3 BD2, BD3 TD1, and TD2 and against TD1 and TD2 ƒ2 value<50, which means no Similar dissolution rate. Similar results of the dissolution rate (ƒ2>50) were obtained from BD1 comparison with TD1, TD2, and BD1 with TD1 to TD2.

Comparison between physical mixture of binary and ternary systems gliclazide-poloxamer188 1: 2 (BC1), gliclazide-HPMC 1: 0.25 (BC2), gliclazide-Eudragit®E100 1: 0.25 (BC3), gliclazide-poloxamer 188-HPMC 1: 2: 0.25 (TC1) and gliclazide-poloxamer 188-Eudragit®E100 1: 2: 0.2 (TC2) gives the following results:

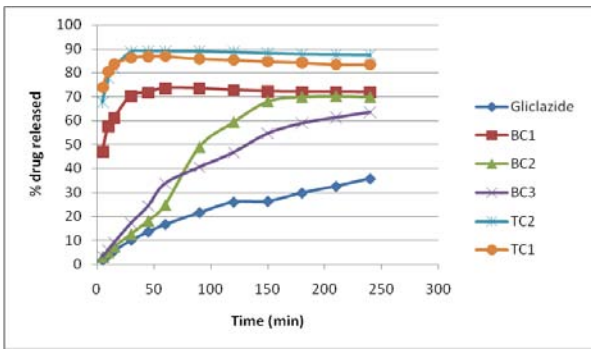

Fig. 2: Dissolution profile of pure drug and physical mixture of binary and ternary systems

*note: error bars have been omitted for simple presentation

Statistical analysis ƒ2 for pure gliclazide with BC1, BC2, BC3, TC1 and TC2, BC1 to BC2, BC3, TC1 and TC2, TC1 and TC2 BC3 with the obtained results<50. These results give meaning between the dissolution rate of a physical mixture of the above is no Similar, Similar dissolution rate were obtained between a physical mixture of BC2 to BC3 danTC1 comparison with the value TC2 54.55 and 70.65. For statistical analysis ƒ2 BC2 with TC1 and TC2 cannot be done because RSD for BC2 on the first point>20% while for the point of the 2nd, 3rd and 4th of>10%.

The dissolution rate of solid dispersions between BD1 with TD 1 and TD2 was similar, the addition of this shows the carrier (HPMC and llEudragit® E100) does not provide a different dissolution rate.

Solid dispersion either in binary or in the ternary system by using carrier poloxamer 188 showed increased dissolution rate is quite high. In the 15th minute a solid dispersion gliclazide-poloxamer 188 1: 2 gives the dissolution rate 12 times greater than pure gliclazide, gliclazide-HPMC 1: 0.25 dissolution rate increased 5 times, gliclazide-Eudragit®E100 1: 0.25 increases 10 times, gliclazide-poloxamer188-HPMC 1: 2: 0.25 14 times and gliclazide-poloxamer188-Eudragit®E100 1: 2: 0.25 15 times greater than pure gliclazide. Solid dispersion gliclazide-poloxamer188 1: 2, gliclazide-poloxamer188-HPMC 1: 2: 0.25 and gliclazide-poloxamer-Eudragit® E100 1: 2: 0.25 in the 90th minute almost 100% gliclazide has been dissolved.

Increase mechanism in dissolution rate in the presence of amphiphilic surfactants such as poloxamer 188 through a reduction in surface tension between the drug with solvents, wetting and solubilization micelles increase of drug [9]. Another possibility is the formation of intermolecular interactions between the polymer gliclazide. Interactions that occur due to the formation of hydrogen bonds between the H atoms from the group NH gliclazide with O atoms of poloxamer 188. But solubilization mislead in this study did not happen because of solubilization micellar can only occur if the surfactant concentration above the critical micelle concentration (CMC). CMC to poloxamer 188 is 1.25 x 10-4 M [10].

HPMC carrier increases the dissolution rate of the solid dispersion as HPMC would slow down the process of re-crystallization of gliclazide. Medicinal compounds will lose its crystalline form in an HPMC matrix so that the dissolution rate becomes larger in the form of solid dispersions [11].

Dissolution rate improvement with Eudragit® E100 as the carrier was possibly made as the interaction between a tertiary amine group of Eudragit® E100 with gliclazide through molecular interactions and dipolar interactions. Molecular interactions also occurred due to weak acidic gliclazide while Eudragit® E100 is a weak base [11].

A physical mixture of binary and ternary systems also provide increased dissolution rate compared to pure gliclazide can occur because when the physical mixture was added to the dissolution medium carrier will dissolve over time so will alter the hydrophilicity/lipophilicity or wetting of active substances that will enhance the dissolution. Another mechanism was a weak complex formation of the carrier with the active substance on the surface of the particles so that it will produce greater dissolution rate [12].

Pure Gliclazide characterization, solid dispersion, and physical mixture gliclazide-carrier by Differential Scanning Calorimetric (DSC) provide data calorimetric as shown below:

In the solid dispersion and physical mixture decreased the melting point of gliclazide, followed by a decrease in enthalpy which indicates the amount of energy required for a lower dissolution due to a decrease in the crystalline degree.

The spectra FTIR of pure drug, solid dispersions and physical mixture has been shown in fig. 6, 7, 8 and 9.

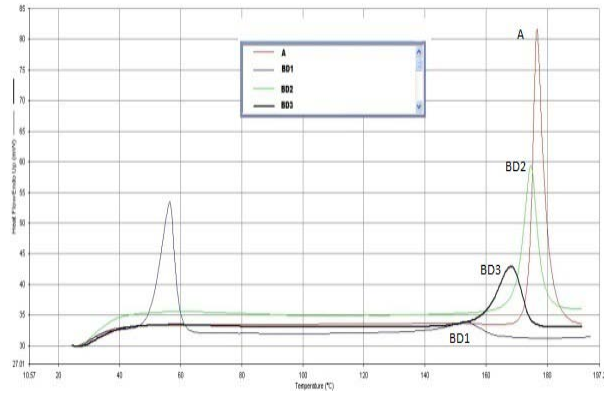

Fig. 3: DSC thermogram BD1, BD2, and BD3

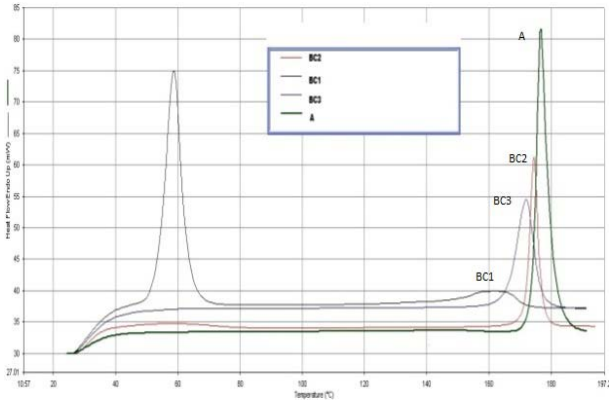

Fig. 4: DSC thermogram BC1, BC2, and BC3

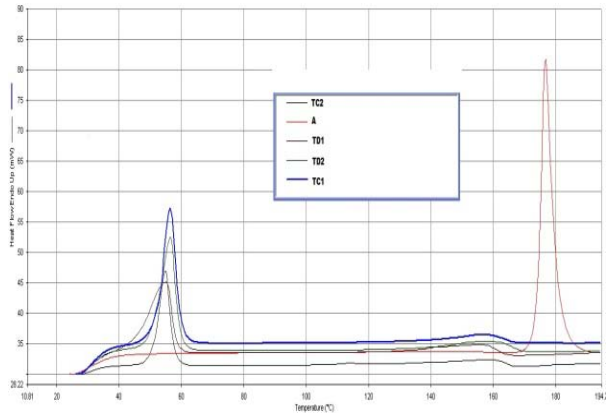

Fig. 5: DSC thermogram TD1, TD2, TC1, and TC2

In the solid dispersion and physical mixture, peak characteristic for gliclazide still apparent at specific hardly shifted wavelength. The interaction between the active substance and the carrier can be determined if there was a change in the functional groups spectrum C = O, S = O, and NH. Hydrogen chain can occur on the hydroxyl on poloxamer 188 group with the carbonyl on gliclazide group and the interaction between the hydrogen atoms of the NH gliclazide group with an oxygen atom of poloxamer 188 (Patil and Galkwad, 2009). In the FTIR spectra of all samples (BD1, BD2, BD3, BC1, BC2, BC3, TD1, TD2, TC1, and TC2) did not indicate a shift so revealed no interaction between the carrier gliclazide [12].

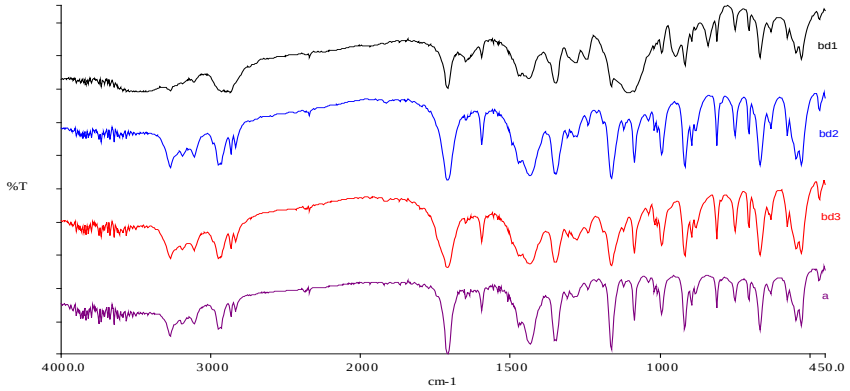

Fig. 6: FTIR spectra of pure drug (a), BD3, BD2, and BD1 (from bottom to top)

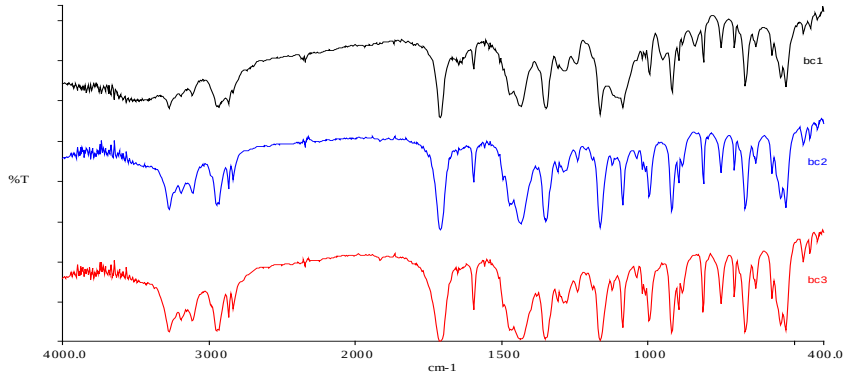

Fig. 7: FTIR spectra BC1, BC2, and BC3 (from top to bottom)

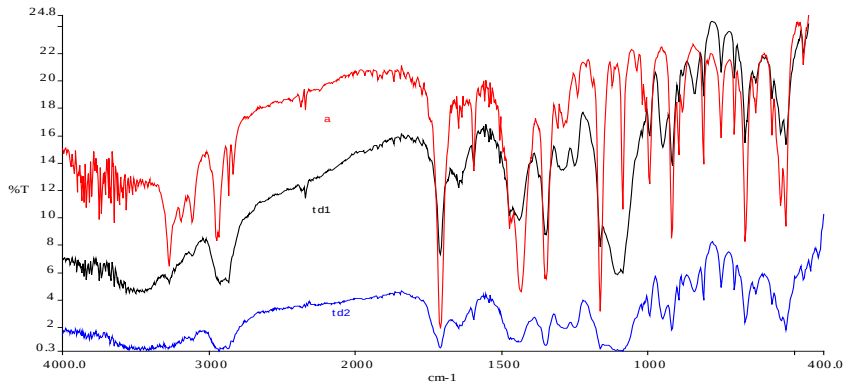

Fig. 8: FTIR spectra of pure drug (a), TD1, and TD 2 (from top to bottom)

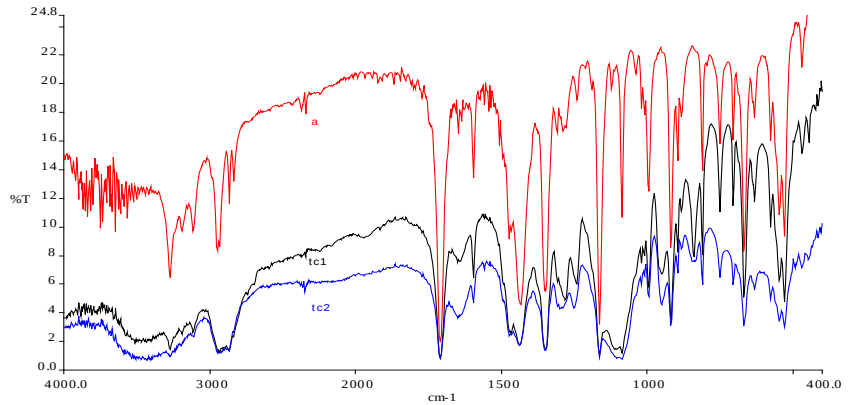

Fig. 9: FTIR spectra of pure drug (a), TC1, and TC2 (from top to bottom)

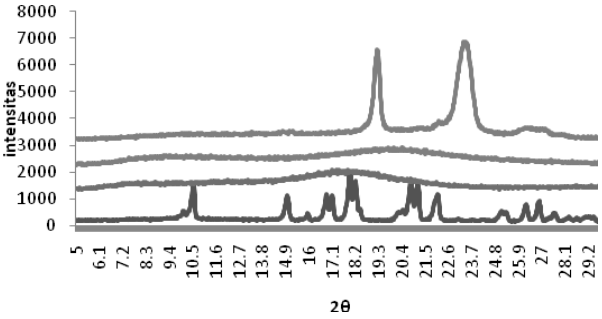

Fig. 10: X-ray diffraction pattern of gliclazide, Eudragit®E100, HPMC, and poloxamer 188 (from bottom to top)

X-ray diffraction spectra of pure gliclazide gave high-intensity peaks at 2θ 10.56, 17.94, 18.20, and 20.84. X-ray diffraction pattern on poloxamer 188 carrier, two peaks apparent at 2θ with high intensity at 19.24 and 23.36 shows the crystalline the character of the poloxamer 188. The peak was not appeared at HPMC and Eudragit®E100, which means the second form of this carrier, is amorphous.

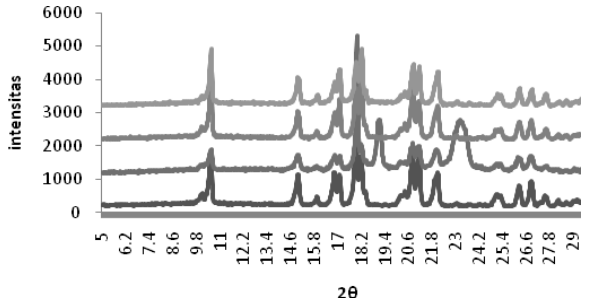

Fig. 11: X-ray diffraction pattern of gliclazide Pure, BD1, BD2, and BD3 (from bottom to top)

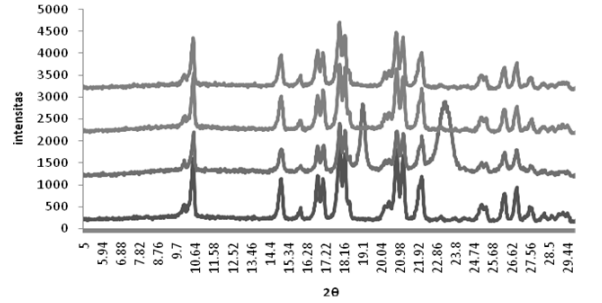

Fig. 12: X-ray diffraction pattern of pure gliclazide, BC1, BC2, and BC3 (from bottom to top)

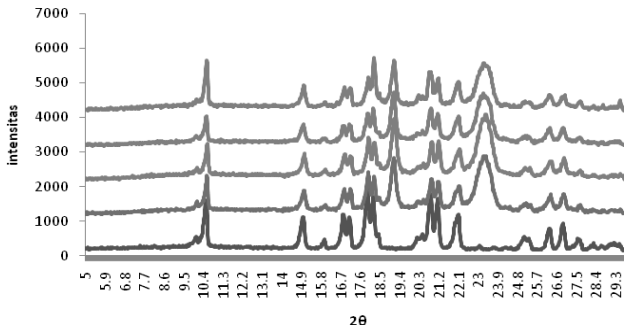

Fig. 13: X-ray diffraction patterns of pure gliclazide, TD1, TD2, TC1, and TC2 (from bottom to top)

In general, the decrease in intensity of the diffraction pattern for solid dispersion gliclazide and physical mixture compared with pure gliclazide showed a decline in the crystalline gliclazide degree. This might improve the dissolution rate [13].

The decrease in intensity occurred in the solid dispersion systems with poloxamer 188, because the concentrations of poloxamer 188 are large enough to make a diffraction pattern dominant. At the same time as the carrier of Eudragit®E100 HPMC is relatively small due to low carrier concentration and does not change the character of the drug crystalline when compared to poloxamer 188. The peak of poloxamer 188 in solid dispersion same with the diffraction pattern of pure poloxamer 188, it indicates the absence of chemical interactions between gliclazide with poloxamer 188 [12].

CONCLUSION

Gliclazide solid dispersion with poloxamer 188 1: 2 compared with solid dispersions of gliclazide-poloxamer188-HPMC 1: 2: 0.25 and gliclazide-poloxamer 188-Eudragit® E100 1: 2: 0.25 provide the similar dissolution rate

In the 15th minute the dissolution rate of solid dispersions of gliclazide-poloxamer 188 1:2, gliclazide-HPMC 1:0.25, gliclazide-Eudragit® E100 1:0.25, gliclazide-poloxamer188-HPMC 1:2:0.25 and gliclazide-poloxamer 188-Eudragit® E100 1:2:0.25 respectively giving the dissolution rate 12 times, 5 times, 10 times, 14 times, and 15 times greater than the rate of dissolution of pure gliclazide.

Characterization by DSC showed a decrease of gliclazide endothermic peak due to the decrease in gliclazide crystalline degree. FTIR spectra showed no absorption peak movement from functional groups of gliclazide. A decrease in intensity of the gliclazide diffraction pattern in solid dispersions showed a decrease in the degree of crystalline gliclazide.

CONFLICT OF INTERESTS

Declared none

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