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Original Article

IMPROVEMENT OF GLICLAZIDE'S DISSOLUTION RATE BY USING SURFACE SOLID DISPERSION WITH AVICEL PH 101

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ABSTRACT

Objective: The aim of this study was to improve the dissolution rate of gliclazide by developing a surface solid dispersion (SSD) with Avicel PH 101 as a carrier.

Methods: Solid dispersions of gliclazide were prepared, with various ratios of gliclazide and Avicel PH 101, using the solvent evaporation method. Evaluations of the dissolution rate for each ratio were carried out in order to find the optimal formula. The physical characteristic of solid dispersions was evaluated using Fourier transform infrared (FTIR), powder X-ray diffractometry (PXRD), and Scanning Electron Microscopy (SEM). The pure gliclazide powder and its solid dispersions were then blended with excipients and compressed into tablets by using the direct compression method.

Results: The optimum solid dispersion, which consists of gliclazide and Avicel PH 101 at ratio 1:5, showed the highest dissolution rate. The infrared spectrum of the solid dispersion showed that the spectrum was a combination of gliclazide and Avicel PH 101, and that there is no differences between the spectrum of the solid dispersion and its physical mixture. The diffractogram of PXRD showed that there was a change in the gliclazide's crystalline state in solid dispersion compared to its physical mixture. Whereas, SEM characterization indicated that the solid dispersion had an adsorption of gliclazide particles on the surface of Avicel PH 101 particles in the form of small particles.

Conclusion: The preparation of surface solid dispersion with Avicel PH 101 can be used to increase the dissolution rate of gliclazide. The compression process did not alter the dissolution profile of gliclazide solid dispersion.

Keywords: Gliclazide, Avicel PH 101, Surface solid dispersion, Dissolution rate.

INTRODUCTION

Gliclazide belongs to class two in the *Biopharmaceutical Classification System* (BCS), which means it has a characteristic of low water solubility and high permeability. Gliclazide is usually used as an antidiabetic for patients with diabetes mellitus type II. Bioavailability of this drug was governed by its dissolution in the GIT tract after oral administration [1-2]. One method that can be used to improve the bioavailability of drugs was the improvement of its dissolution rate. Various techniques have been used to enhance the dissolution rate of active ingredients, such as the formation of an inclusion complex, solid dispersion, co-grinding/co-micronization, lipid-based formulation, reduction of particle size into the nanometer range [3] etc. Solid dispersion is one of the promising techniques for solubility and dissolution improvement of poorly water soluble drugs. In this technique, one or more active ingredients are dispersed in an inert carrier by the melting (fusion), solvent or melting-solvent methods [4-5].

Conventional solid dispersion usually uses a water soluble material as a carrier. A lot of solid dispersion techniques have been developed to enhance the dissolution rate of gliclazide by using soluble hydrophillic materials, such as polyvinvl pirolidone, hydroxy prophyl methyl cellulose and various type of polyethilene glycol, as a carrier [6-9]. Polyethilene glycol has a sticky characteristic. Therefore it is difficult to handle in the preparation of tablets, especially in the milling, shieving and mixing processes. Surface solid dispersion is one alternative technique to improve the dissolution rate of a substances [10]. The carrier used in this method has material characteristics that are non-water soluble, porous and hidrophilic, such as microcrystaline cellulose. This carrier will be immediately dispersed in water after it makes contact with it, and will release the particles of the active ingredient [11]. Microcrystaline cellulose is usually used as a diluent in the preparation of tablets. Hence, this material can also play the same role when the solid dispersion is compacted into a tablet. Avicel PH 102 and PH 101 are two types of microcrystalline cellulose that are widely used in the preparation of tablets. The Avicel PH 101 has a larger surface area compared to Avicel PH 102. The larger the surface area, the higher the interaction between the active ingredient and the carrier [11]. This study was conducted to develop surface solid dispersion of gliclazide, using Avicel pH 101 as a carrier, and by using the solvent evaporation technique. The evaporation of the solvent in this technique can be done by simple evaporation. The dried mass obtained from surface solid dispersion was porous, and easier to pulverize compared to conventional solid dispersion. In addition, the Avicel pH 101 also plays a role as a diluent in the preparation of the tablets.

MATERIALS AND METHODS

Materials

Gliclazide (Calao, Italy), Avicel PH 101 (Mingthai, Taiwan), dichlorometane p. a, hydrochloric acid p. a, magnesium sterat, and talc were bought from the local suppliers.

Instruments

Analytical balance (Mettler Toledo XS204), magnetic stirrer (Thermolyne Nuova), pH meter (Mettler Toledo S20), Dissolution tester (Hanson Research SR8PLUS-HR), spectrophotometer UV-Visible (Beckman DU 650i), spectrophotometer infra red (FTIR-Shimadzu 8501), Scanning Electron Microscopy (JEOL JSM-6360LA), Powder X-Ray diffractometer (Diano type 2100 E), orbital shaker (GFL 1083), Mixer (Turbula type T2C), flow tester (Erweka tipe GDT), tableting machine (Stokes type 519-2), hardness tester (Erweka type TB 24), friability tester, frictibility tester (Erweka type TAP), disintegration tester (Erweka type ZT122), and other general laboratory glassware.

Preparation of solid dispersion

Solid dispersions were prepared using the solvent evaporation method, with the ratio of gliclazide and Avicel PH 101 being 2:1, 1:1, 1:2, 1:5, and 1:10 respectively. First, gliclazide was dissolved in

dichlorometane and Avicel PH 101 was then incorporated into the solution of gliclazide and stirred the by magnetic stirrer. Dichlorometane was then evaporated at room temperature. Furthermore, the material was dried in the oven with a temperature of 50°C until the weight was constant. The dried solid dispersion was ground and sieved, using the shiever that has a diameter of 315 µm, and then kept in a desiccator.

Preparation of physical mixture

The physical mixture of gliclazide and Avicel PH 101, of the same ratio state as above, were also prepared by grinding the mixtures in a mortar and then sieved by the 315 µm shiver, and then kept in a desiccator.

Evaluation of solid dispersion

Solubility test

Solubility tests were performed on the pure glicazide powder, its solid dispersion and its physical mixture. These determinations of glicazide solubility were done in solutions of hydrochloric acid of pH 1.2. An amount of 50 mg of each product was dissolved in 25 mL of hydrochloric acid solution of pH 1.2 and shaked in the orbital shaker at 100 RPM, with a temperature of 37°C for 96 hours. At the point of 24, 48, 72 and 96 hours, 2 mL of the solution were withdrawn and filtered. The concentration of soluble gliclazide in each solution was then measured using UV-VIS spectrophotometer.

Infrared spetrophotometri

Infrared spectrum indentifications were performed for pure glicazide powder, its solid dispersion and its physical mixture at a wave number of 4000-400 cm^{-1}.

X-ray Diffractometri

X-ray diffraction pattern identifications were also performed for pure glicazide powder, its solid dispersion and its physical mixture. These determinations were conducted at the range of 2θ of 5^0-44.98^0 with rate of 0.02^0 per 0.8 seconds radiation of Cu-Kα.

Scanning Electron Microscope (SEM)

SEM microphotographs of particle morphology were also performed for the pure glicazide powder, its solid dispersion and its physical mixture.

Dissolution test

Dissolution tests were performed on pure glicazide powder, its solid dispersion and its physical mixture. Tests using 50 mg of gliclazide powder from each sample were examined for its dissolution profile, using aparatus II in 900 mL of HCl 0.1 N medium, with a pH 1.2, at a temperature of 37°C, and with a rotation speed of 100 rpm. The concentration of gliclazide that was dissolving in the medium was determined at 10, 20, 30, 45, 60, 90, and 120 minutes by using a UV-Visible spectrophotometer.

Preparation of tablets

Tablets of pure gliclazide and its solid dispersion were prepared using the direct compression method. The weight of tablets was 310 mg and with a gliclazide concentration of 50 mg per tablet. All the ingredient was mixed in turbula mixer for 15 minutes and then blended with talc and magnesium stearate for 2 minutes. The characteristic of each mixture was evaluated before the mass was compressed into tablets.

Evaluation of Tablets

Evaluations of the tablets included aspects of the hardness, friability, frictibility, disintegration time, dissolution profile, content of uniformity and assay of gliclazide.

RESULTS AND DISCUSSION

In this study, Avicel PH 101 was choosen as a carrier because the size of its particles is smaller than those of Avicel PH 102, hence the particles' surface area will be larger and increase the ability to adsorb the active ingredient.

The mechanism for improving glicazide's dissolution rate in solid dispersion was due to the reduction of particle size. Beside that, there was a formation of a new solid phase between the active ingredient and carrier, which was more amorphous than its original pure glicazide. In addition to the hidrophyllic carrier being incorporated into the solid dispersion system, there would be an alteration in its wettability of the active ingredient and therefore an improvement in its dissolution rate [11].

In surface solid dispersion, the improvement of the dissolution rate mechanism was similar to conventional solid dispersion. The differences between both types of dispersion were between the carrier and the preparation process. The carrier that is usually used in conventional methods is a water soluble material, while in the surface solid dispersion it was a non-water soluble, porous and hydroplilic material. In the conventional solid dispersion technique both the active ingredient and carrier are dissolved, mixed and dried. While in surface solid dispersion, only the active ingredient was dissolved in the solvent, and this solution was mixed with the solid carrier and dried [11].

In this study, gliclazide was first dissolved in dichloromethane. This solvent was choosen because glicazide has a high solublity in dicholorometane. The carrier, Avicel PH 101, was then dispersed in the solution of gliclazide and stirred to make it homogenous. A part of dichoromethane was evaporated during the stirring and the rest of the dicholoromethane dried in the oven at a temperature of 50°C, until the weight was constant. Then dried mass was ground and shieved with a 315 µm shiever to obtain a homogenous particle size.

The study began by optimizing the formula of gliclazide surface solid dispersion to make five formulas with a different ratio of gliclazide and Avicel PH 101. The dissolution of each formula was tested using the paddle method. The dissolution profile of each formula is shown in fig. 1.

The one-way ANOVA technique was employed to analyze the differences between the five formulas. A *Post Hoc Test* type LSD (Least Significant Difference) was then administered on CI of 95% to found which of the formula that give an significantly different in the dissolution rate of gliclazide. The result obtained from the statistical analysis revealed that all the solid dispersion formulas have a significant difference in dissolution rates compared to pure gliclazide. The formula with the glicazide: Avicel PH 101 ratio of 1:10, gave the highest amount of glicazide dissolved after 120 minutes, which was 63.81%, followed by the formula with ratio of 1:5, 1:2, 1:1, and 2: 1 respectively. There was no significant difference between the dissolution rate of the solid dispersion formulas of ratios 1: 5 and 1: 10. Whereas, the dissolution rate between the formulas with a ratio of 1:5, 2:1, 1:1, and 1:2 were significantly different. Hence the solid dispersion with a gliclazide: Avicel PH 101 ratio of 1:5 was chosen as the optimum formula. This dessicion also considered the amount of the mass required for the preparation of the tablets.

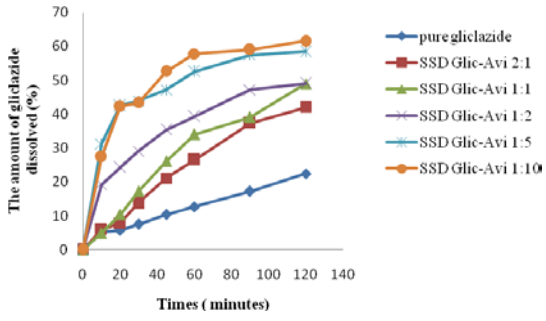

Fig. 1: Dissolution profile of pure gliclazide and its surface solid dispersion in various ratio

The next step was to determine the solubility of gliclazide from the pure subtance, its physical mixture with Avicel PH 101 and the

optimum formula of solid dispersion. This test was conducted in a HCl 0.1N medium with pH 1.2, using a temperature of 37°C and a rotation speed of 100 rpm. The gliclazide that was dissolved in the medium reached a relative constant after 48 hours. The result of this experiment is shown in fig. 2.

The sample that revealed the highest solubility quantitatively was a solid dispersion powder. Based on the statistical analysis, there was no significant difference between the solubility of solid dispersion of gliclazide: Avicel PH 101 and its physical mixture. So we can conclude that the solid dispersion technique did not improve the solubility of gliclazide, but significantly improved the rate of gliclazide dissolution.

Furthermore, the optimum solid dispersion formula was characterized using the Powder X-ray diffractometry method and a scanning electron microscope.

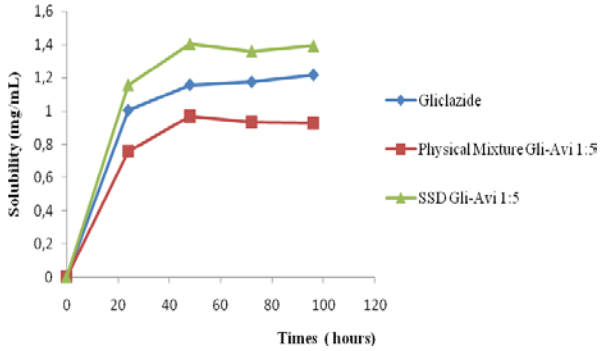

Fig. 2: Solubility profile of pure gliclazide, its surface solid dispersion and physical mixture of gliclazide-Avicel PH 101

The infrared spectrum of solid dispersion showed that the spectrum was a combination between gliclazide and Avicel PH 101, and that there was no differences between the spectrum of solid dispersion and its physical mixture.

The X-ray diffractogram samples showed that there was a differences between pure gliclazide, pure Avicel PH 101, solid dispersion of gliclazide: Avicel PH 101 of ratio 1:5, and the physical mixture of gliclazide and Avicel PH 101 with ratio of 1:5. The specific peaks of the glicazide crystall at 2θ were shown to be 10.44°, 14.86°, 16.72°, 16.76°, 17.84°, 18.08°, 20.72°, 21.04°, 21.96°, 26.14°, and 26.80° respectively.

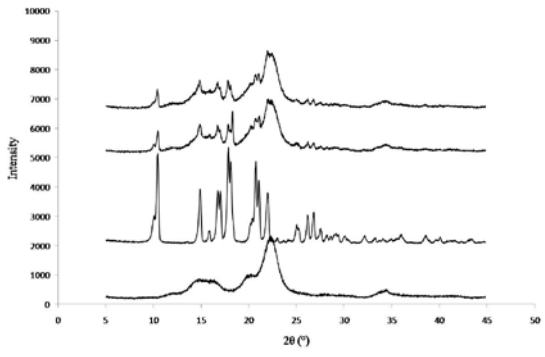

Fig. 3: Diffractogram of Avicel PH 101 (a), pure gliclazide (b), physical mixture of gliclazide: Avicel PH 101 of 1:5 (c) and solid dispersion of gliclazide: Avicel PH 101 of 1:5 (d)

In the gliclazide solid dispersion diffractogram, there were decreases of intensity, specifically for gliclazide at 2θ, and lost of peak at 2θ of 21.96^0 that was caused by Avicel PH 101. These differences have attributes in which the glicazide structure changes from a crystalline to an amorphous form [12]. The solid dispersion glicazide: Avicel PH 101 diffractogram was similar to its physical mixture that had a different intensity. The decrease of intensity in the solid dispersion diffractogram was larger than its physical mixture because of the formation of amorphous structrures in the solid dispersion sample.

The surface morphology of solid dispersion was observed using a Scanning Electron Microscope (SEM). The microphotograph of each sample is shown in fig. 4.

In microphotographs with a magnification of 10000 times, shows that solid dispersion consisted of a combination of Avicel PH 101 and gliclazide particles. The size of the gliclazide particles is smaller than its original size, and the surface of Avicel PH 101 adsorbed the gliclazide. The reduction of particle size occured in the solid dispersion process because during the evaporation of dichloromethane, the solution of gliclazide was recristallized in the form of smaller particles. The photo of the physical mixture of gliclazide with Avicel PH 101 displayed no absorption of gliclazide particles.

The solid dispersion of gliclazide with Avicel PH 101 was then compressed into tablets in order to check the influence of the compression force on the dissolution of gliclazide from solid dispersion, compared to its pure gliclazide. Magnesium stearat and talc were added to the formula as a lubricant and glidant in order to improve the flowability of the powder blend. The flowability of the powder blend should be more than 4g/sec. It was found that the flowability of pure gliclazide and the solid dispersion powder blend was only 1.84 and 3.37 g/sec.

This value indicated that the powder blends had a poor flowability and were unable to flow freely into the tablet die, so the tablets could not be compressed automatically. However, it can be compressed manually. Although the pre-compression powder blend did not fulfill the requirement, the objective of this experiment was to observe the effect of compression force on the dissolution characteristics of gliclazide derived from surface solid dispersion, therefore no additional of other excipient was used in the formula.

The disintegration time of a pure gliclazide tablet was around 26 seconds, while the solid dispersion tablet has a disintegration time of 12 minutes. Both tablets have disintegration times less then 1 minutes and fulfilled the requirements. The disintegration of both tablets was very fast because there was a dominant amount of Avicel PH 101. The hydrophyllic characteristic of Avicel PH 101 facilitated the water to enter the pores of the tablets and improved the disintegration of the tablets. The other evaluations of the tablets are shown in table 1.

For tablets weighing less than 400 mg, the hardness should be 4-6 kg/cm^{2,} and a good tablet has friability and frictibility of less than 1%. The hardness of both tablets fulfilled requirements while the parameters of friability and frictibility did not fulfill the requirements. This occured because there was no binder used in the tablet formulas, so the tablets were britle.

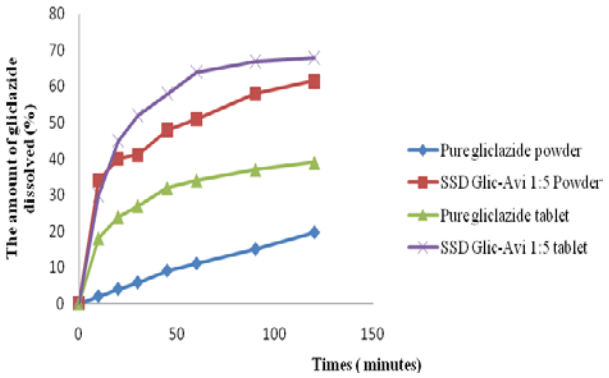

Fig. 5: Dissolution profile of gliclazide from powder and tablet

The content of gliclazide in both tablets fulfilled the requirements. The amount of drugs dissolved from pure gliclazid tablets were larger than pure gliclazide powder, this phenomenon may be due to the the presence of Avicel PH 101 in tablets. As shown at fig. 5, the amount of the drug that dissolved after 120 minutes, from pure gliclazide powder, were only around 19.6%, while the pure glicazide tablets were 39,0%. The compression process did not alter the dissolution profile of gliclazide solid dispersion.

The amount of the drug dissolved from solid dispersion powder was 61.5%, whereas the solid dispersion tablet was 68.6%.

In the surface solid dispersion that used the solvent evaporation technique, the solid dispersion powder was dried in the oven. The energy needed to evaporate the solvent was lower than the energy used in the spray drying method. Hence the solvent evaporation method is relatively simple compared to the spray drying method.

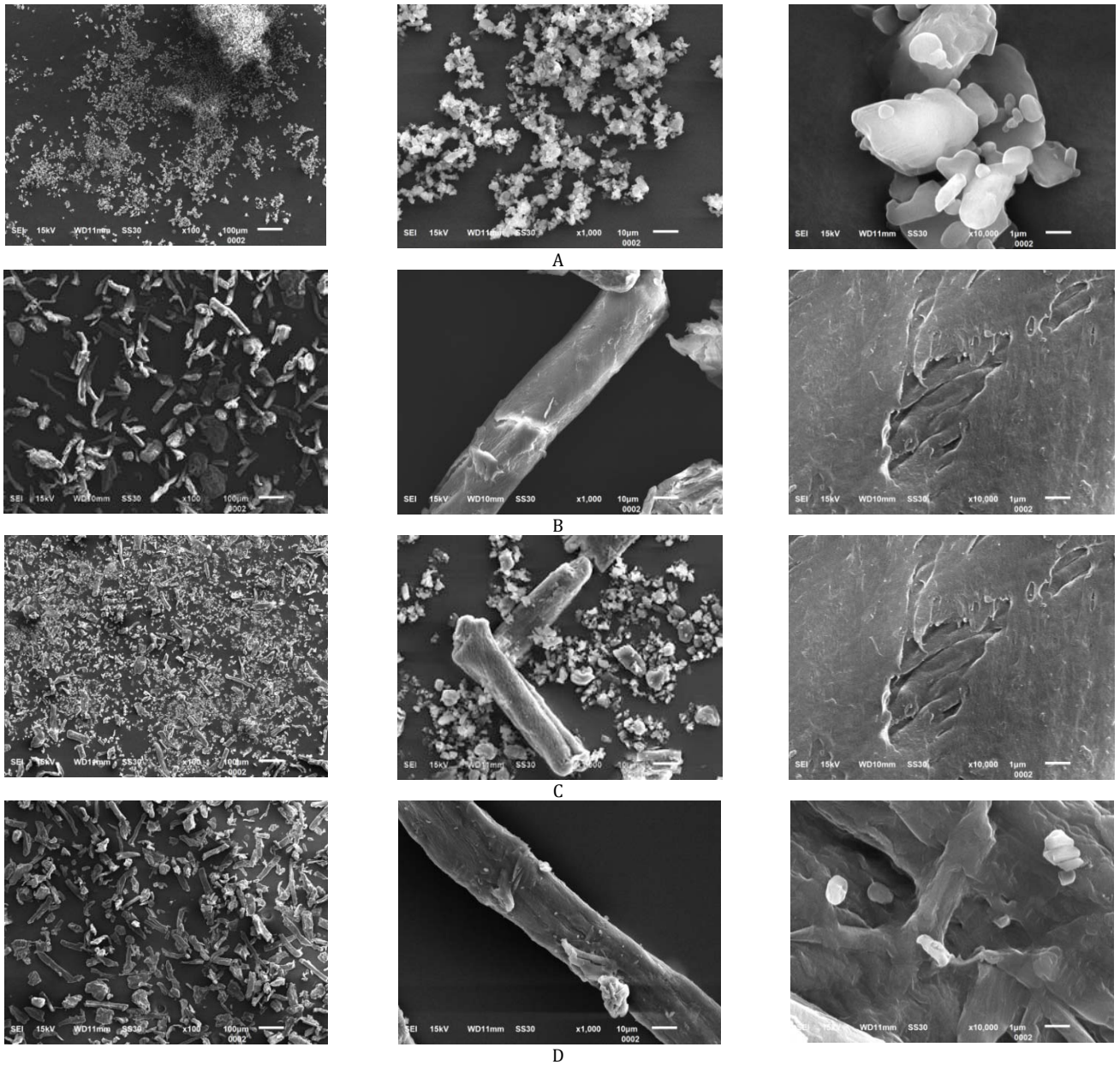

Fig. 4: Morphology of pure gliclazide (a), Avicel PH 101 (b), physical mixture of gliclazide: Avicel PH 101 1:5 (c), and solid dispersion of gliclazide: Avicel PH 101 1:5 (d), with magnification of 100 x, 1000 x, and 10000 x respectively

Table 1: Tablet evaluation

Parameter of evaluation	Pure gliclazide Tablet	Solid Dispersion Tablet
Hardness (kg/cm2)	4.04±0.41	4.79±0.48
Friability (%)	2.09±0.02	1.98±0,03
Frictibility (%)	1.68±0,02	2.21±0,01
Drug content (%)	100.54±3.25	99.25±7.63

ANOVA and LSD statistical analyses were also used to compare the dissolution efficiency of both tablets. Dissolution efficiencies were calculated from the ratio of the area under the curve (AUC), which was obtained from the dissolution profile of 0-120 minutes, to the AUC from the dissolution profile of where 100% of the drug dissolved. The dissolution efficiency of solid dispersion tablets and pure glicazide tablets were 58.74%±1.16 and 31.44%±1.79.

Based on the statistical analyses, the difference in the dissolution effeciencies of both tablets were significant. The dissolution rate of glicazide can be improved by the preparation of surface solid dispersion. The improvement of gliclazide dissolution was also found by Mahajan et al, by using a superdisintegrant and spray drying technique [13].

CONCLUSION

Preparing surface solid dispersion of glicazide with Avicel PH 101 can improve its dissolution rate. The optimum solid dispersion formula uses a gliclazide and Avicel PH 101 ratio of 1:5. Preparing solid dispersion into tablets did not change its dissolution profiles.

CONFLICT OF INTERESTS

Declared None.

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