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Original Article

Development of Glimepiride Solid Dispersion using the Coprocessed Excipients of Polyvinylpyrrolidone, Maltodextrin, and Polyethylene Glycol

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ABSTRACT

Objectives: The aim of this work was to produce the solid dispersion of glimepiride (GMP-SD) based on the coprocessed excipient of polyvinylpyrrolidon (PVP), maltodextrin (MD) and polyethylene glycol (PEG). **Methods:** The PVP-MD-PEG coprocessed excipients were prepared in the ratio of 1:1:1, 1:1:2, 1:2:1, 2:1:1, 2:2:1, 2:1:2, and 1:2:2; as well as characterized. Furthermore, GMP-SD was prepared by spray drying with a ratio of 1:2 for glimepiride and the excipients. The obtained GMP-SD were characterized by fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction, and scanning electron microscopy. Dissolution study of GMP-SD was carried out in a phosphate buffer pH 7.4 at ± 37°C for 120 min. **Results:** The PVP-MD-PEG coprocessed excipients displayed irregular shapes and rough and distributed in a wide range of particle sizes with mostly under 125 µm. The coprocessed excipients exhibited the moisture content of 5-8%, pH of 5-8, and the flow rate of 2.5-4.0 gr/s. The results revealed that there was no chemically interaction between GMP and the coprocessed excipients. Thermal analysis demonstrated that the crystal phase reduction was occurred, thus it was transfomed to amorph form. The dissolution study revealed that GMP-DP proved the dissolution enhancement of GMP compared to the pure GMP. **Conclusion:** GMP-SD with the PVP-MD-PEG coprocessed excipients has benefit to enhance dissolution rate of glimepiride.

Key words: Coprocessed excipient, Glimepiride, Maltodextrin, Polyethylene glycol, Polyvinylpyrrolidone, Solid dispersion.

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INTRODUCTION

Coprocessed excipient is a combination of two or more excipients that have a better visual advantage that cannot be achieved by using the common physical mixing with the same excipient.[1] Coprocessed excipient is prepared by a specific technique using drum-drying and spray drying process.[2] Coprocessed excipients can be modified physically without changing their chemical structure.[3] The combination of selected excipients can complement each other to cover the undesirable properties of each excipient while simultaneously maintaining or increasing the desired properties.[2]

Oral administration route is one of the most widely used routes today. Drugs with oral administration can not directly enter the circulation system and must undergo pharmaceutical processes before they can be absorbed.[4] Active compounds formulated in oral dosage forms must be released from the excipient to dissolve then diffuse and transferred between membranes which will eventually absorbed to produce therapeutic response.[5] However, most of the drugs belong to Biopharmaceutical Classification System (BCS) class II which means drugs with low solubility and high permeability. Drugs with low solubility in water often have a low dissolution profile that affects oral dosage form bioavalibility and their absorption. The bioavailibility will determine the effication, intensity, and drug therapeutic response duration.[6]

The rate of drug dissolving in the body can accelerate absorption process to produce therapeutic effects in patients, but not all drugs are soluble in water.[7] Modification can be done to increase drug solubility in water, i.e solid dispersion. Solid dispersion is a dispersion of one or more active compounds in an inert carrier or matrix in solid state. Solid dispersion can be prepared using melting, solvent, and melting-solvent method.[8]

Polyvinylpyrrolidone (PVP), maltodextrin (MD) and polyethylene glycol (PEG) are some of the excipients that are often used as carriers to increase dissolution rate in the form of solid dispersions. PVP is a hydrophilic polymer that can form an amorphous solid dispersion thereby increasing solubility and drug release. Maltodextrin is also a hydrophilic polymer with a high solubility in water and porous structure. Its circular structure creates a greater surface area resulting in a more efficient rehydration, thus a mixture of maltodextrin with other compound can increase solubility.[9] PEG is very effective in aqueous environment and forms a two different phases of polymer systems. When PEG is attached to other polymer molecule, it can affect the chemical properties and solubility of drug molecule so that they can dissolve easily in bodily fluids.[10]

Glimepiride is one of the drugs that needs a dissolution rate enhancer. Glimepiride is a sulfonylurea antidiabetic third-generation oral medicine indicated for diabetes mellitus type 2 patients. Glimepiride is a BCS class II drug,[11] which has a low solubility but high permeability. Physicochemical modification in surface properties, solubility, size, particle, polimorfism, molecule/atom/ion size and stability are needed to improve the absorption rate.[6] Glimepiride is practically insoluble in water, slightly

soluble in methanol, ethanol, ethyl acetate and acetone also sparingly soluble in dichloromethane but soluble in dimethylformamide.

In this study, the coprocessed excipients of Polyvinylpyrrolidone (PVP), maltodextrin (MD) and polyethylene glycol (PEG) was prepared, then applied in production of the solid dispersion of glimepiride (GMP-SD) by spray drying method to increase the dissolution rate of glimepiride.

MATERIALS AND METHODS

Materials

Glimepiride (Kimia Farma, Indonesia), PEG 4000 (Duchefa Biochemie, Germany), PVP K-30 (Nanhang Industrial Co, LTD, China.), MD DE 18-20 (Zhucheng Dongxiao Biotechnology Co, LTD, China), dichloromethane (Merck, Germany), methanol (Merck, Germany), potassium dihydrogenphosphate (Merck, Germany), natrium hydroxide (Merck, Germany), aquadest (PT. Ikapharmindo Putramas, Indonesia).

Preparation of the coprocessed excipients

PVP K-30, MD DE 18-20, and PEG 4000 was dissolved in water with a ratio of 1:1:1, 1:1:2, 1:2:1, 1:2:2, 2:1:1, 2:1:2, and 2:2:1 until a homogenous solution was formed. The solution was dried using drum dryer until a dry powder mass was formed. The excipient concentration ratio was chosen randomly and determined in Table 1.

Characterization of the coprocessed excipients
Shape and morphology

Scanning electrom microscope (SEM) was used to observe particle size and surface texture of PVP-MD-PEG powder. The powder was placed in a copper and coated with gold.[3]

Organoleptic observation

Excipient powder was evaluated for physical appearance, including color, and other physical properties.

Particle size distribution

One hundred miligrams of excipient sample was placed in sieve with mesh 120, 80, 60, 45, and 35 stacked from the highest size at the bottom and the smallest at the top. Shieving was set at 30 rpm for 20 min. The remaining powder in each shieve and container at the bottom was weighed and the weight percentage was calculated.

Moisture content

Moisture content analysis was done using moisture balance instrument that was heated for 10 min prior to use. Two grams of powder was placed on the alumunium container evenly and the temperature was set at 105°C. The reading was then recorded.

Flow rate

Flow rate evaluation of PVP-MD-PEG powder was done by placing 10 g of powder in flowmeter funnel and the surface was evenly leveled without any pressure and the instrument was started. The time for all powder to flow through the funnel was used to calculate the flow rate that was expressed in g/sec.

Table 1: Composition of the coprocessed excipient.

Composition	E1	E2	E3	E4	E5	E6	E7
PVP (g)	166	125	125	100	250	200	200
MD (g)	166	125	250	200	125	100	200
PEG (g)	166	250	125	200	125	200	100

Preparatios of the glimepirid solid dispersion

Glimepiride and coprocessed excipient were weighed with a ratio of 1:2. Glimepiride was dissolved in 400 ml methanol and coprocessed excipient was dissolved in 100 ml aquadest. Both solution was mixed and sprayed using spray dryer with a flow rate of 10 ml/min. The inlet and outlet temperature were set to 100°C and 70°C, respectively. The result was stored in dessicator at room temperature and characterized.[12]

Glimepiride assay

Glimepiride was weighted 2.4 miligrams and then dissolved in 50 ml dichloromethane. Thes solution was sonicated for 15 min and filtered. Filtrate was analyzed using UV-Vis spectrophotometer at 230.4 nm.[12]

Evaluation and characterization of solid dispersion
Fourier transform infrared spectroscopy (FT-IR)

The analysis was conducted on solid dispersion of glimepiride-coprocessed excipient and its physical mixture using KBr tablet. One miligram of sample was dispersed in 100 mg KBr and pulverized until homogenous then placed into FT-IR disc. The analysis was done at wavelenght 450-4000 cm^{1}. The spectrum was recorded in FT-IR at 4000-400 cm^{-1}.[13]

Differential scanning calorimetry (DSC)

Thermal analysis was conducted on glimepiride and solid dispersion using DSC. 5 to 10 miligrams sample was placed in a container and heated from 50-300°C with heating rate of 20°C/min. Endothermic or exothermic process can be observed in the thermogram.[13]

X-ray diffraction

X-ray diffraction analysis was conducted on glimepiride and glimepiride-coprocessed excipients solid dispersion. The analysis was recorded at an interval of 5°-80°/2θ using x-ray radiation diffractometer Cu.[13]

Scanning electron microscopy (SEM)

The morphology was analyzed using SEM to observe the shape and particle size. The sample was placed in a holder coated with conductive tape and coated with gold (Au) in a vacuum evaporator.

Dissolution study

Dissolution examination was done to glimepiride and glimepiride-coprocessed excipients solid dispersion using beaker glass and stirrer (100 rpm) for 120 min. Phosphate buffer pH 7.4 (250 ml) at 37°C was used as a medium. Four miligrams glimepiride and glimepiride-coprocessed excipients solid dispersion equal to 4 mg glimepiride were weighed and added to dissolution medium. Ten mililiter sample was taken at 5, 10, 20, 30, 45, 60, 90, 120 min. Each of the sample was added with 10 ml medium with the same temperature and filtered. The filtrate was analyszed using UV-Vis spectrophotometer at 230.4 nm.[13]

RESULTS

Preparation of PVP-MD-PEG coprocessed excipient

The preparation of coprocessed excipient was conducted by using drum-drying method. Process rendement result (Table 2) showed that all formulae had a varying value. Coprocessed excipient with the highest maltodextrin concentration showed the lowest percentage.

Coprocessed excipient characterization
Physical appearance

Organoleptic evaluation showed coprocessed excipient was in the form of flakes or thin small plates after drum-drying process. Particle size reduction process using a blender was needed to obtain fine powders.

Table 2: Properties of the PVP-MD-PEG coprocessed excipients.

Coprecess excipients PVP-MD-PEG	Yield (% w/w)	Moisture content (% w/w)	Flow rate (g/sec)
1:1:1	76.0	6.10 ± 0.03	3.53 ± 0.32
1:1:2	74.0	5.91 ± 0.17	3.26 ± 0.11
1:2:1	68.0	8.02 ± 0.02	2.54 ± 0.15
1:2:2	78.0	7.65 ± 0.05	3.99 ± 0.21
2:1:1	84.4	4.96 ± 0.23	4.33 ± 0.17
2:1:2	88.0	6.43 ± 0.03	3.22 ± 0.39
2:2:1	77.4	6.54 ± 0.06	3.13 ± 0.09

Table 3: The yield value and the glimepiride content of the glimepiride solid dispersion.

Coprocessed excipient PVP:MD:PEG	Yield value (%)	Content (%)
1:1:1	80.00	75.50
1:1:2	93.33	86.06
1:2:1	90.00	74.75
1:2:2	93.33	107.63
2:1:1	73.33	84.09
2:1:2	90.00	101.33
2:2:1	83.33	100.18

Table 4: Endothermic peak, melting enthalpy, and X-ray diffractogram height values of solid dispersions.

Sample	Endothermic peak (°C)	Melting enthalpy (J/g)	Diffractogram height
GMP	213.43	143.9287	11173.6
DP 1:1:1	191.53	104.9004	2773.3
DP 1:1:2	196.57	78.7598	5792.7
DP 1:2:1	193.07	78.7598	4157.54
DP 1:2:2	200.02	63.5221	5660.63
DP 2:1:1	186.26	63.6556	4921.57
DP 2:1:2	191.60	62.8997	5660.41
DP 2:2:1	192.41	68.5999	4670.99

Each of PEG, PVP dan Maltodextrin powders were white but after drum drying in high temperature, the powders became broken white.[14]

Morphology

Observation on morphology of the PVP-MD-PEG coprocessed excipients was performed using scanning electron microscope (SEM). Figure 1 shows that the PVP-MD-PEG coprocessed excipients possessed irregular-shaped of flakes and rough surfaces.

Particle size distribution

Figure 2 showed that coprocessed excipient was distributed in a wide range of sizes with mostly under < 125 µm. Coprocessed excipient PVP-MD-PEG 1:2:1 had 78% particles under < 125 µm which was the highest percentage while coprocessed excipient PVP-MD-PEG 2:1:2 had the lowest (38%).

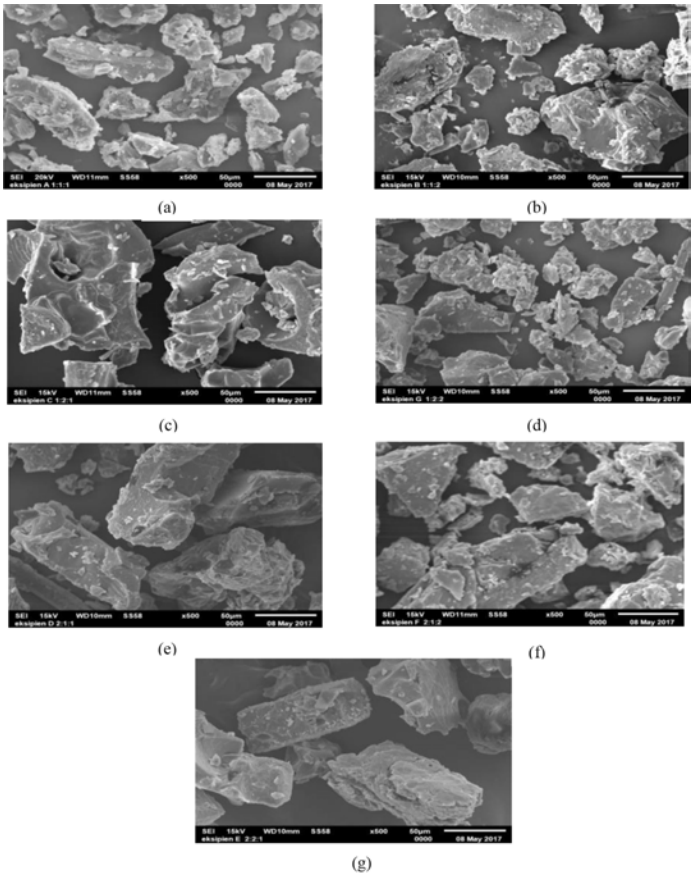

Figure 1: The SEM micrographs of the PVP-MD-PEG coprocessed excipients in the ratio of (a) 1:1:1, (b) 1:1:2, (c) 1:2:1, (d) 1:2:2, (e) 2:1:1, (f) 2:1:2, and (g) 2:2:1 with magnification of 500x.

Moisture content

As shown at Table 2, the coprocessed excipient 2:1:1 had the lowest moisture content and the coprocessed excipient 1:2:2 had the highest.

Flow rate

Table 2 showed that the coprocessed excipient 1:2:1 had the flow rate of 2.53 g/sec, while coprocessed excipient 2:1:1 had the highest flow rate of 4.33 g/sec. The flow rate of all the coprocessed excipient was under 10 g/sec, so the excipient powder revealed fair flow rate.

Solid dispersion preparation

Yield value of glimepiride solid dispersion is displayed in Table 3.

Glimepiride content

Glimepiride assay result (Table 3) would be used as a base for dissolution sample weight so the amount of glimepiride contained will be the same.

Solid dispersion characterization

Physical appearance

Solid dispersion drying process using spray dryer produced finer powders compared to coprocessed excipient powders using drum dryer. The powders were also smaller in size compared to pure glimepiride.[15]

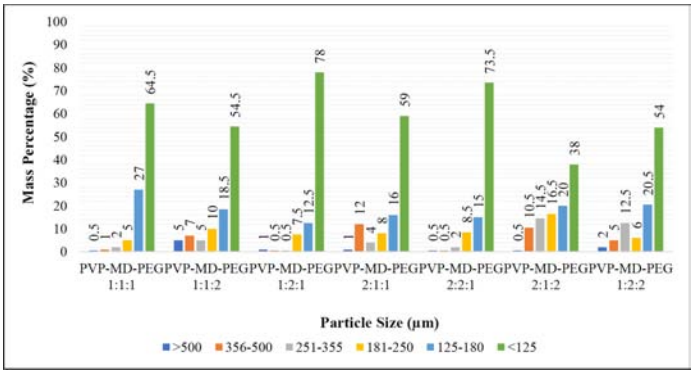

Figure 2: Particle size distribution of the coprocessed excipients.

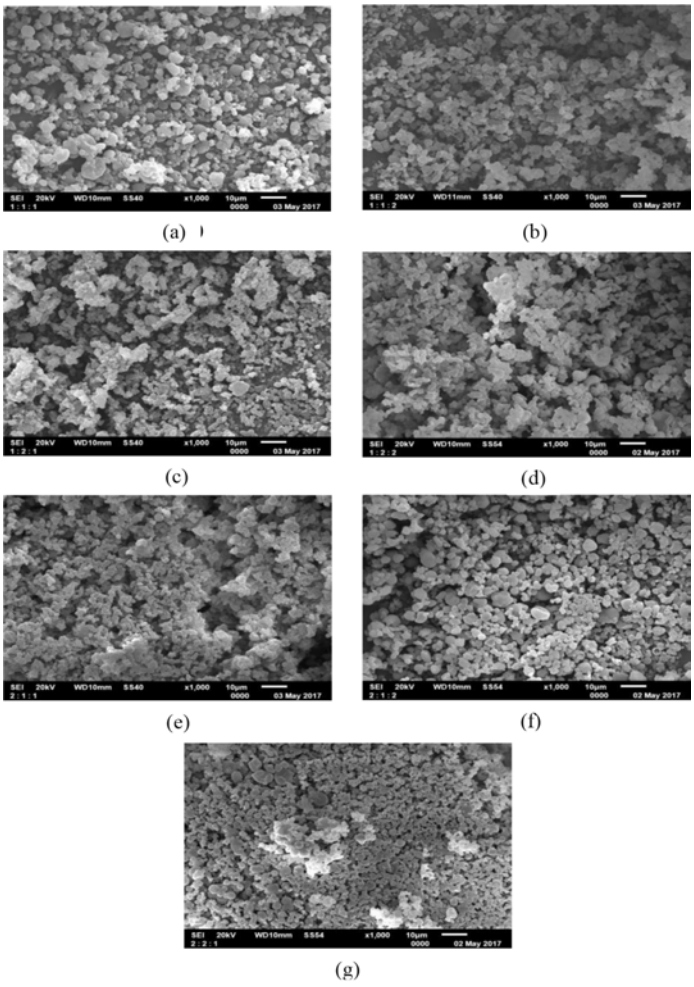

Figure 3: Solid dispersions morphology with magnification 1000x: (a): 1:1:1, (b): 1:1:2, (c): 1:2:1, (d): 1:2:2, (e): 2:1:1, (f): 2:1:2, (g): 2:2:1.

Morphology

Glimepiride was asymmetrical and different sizes. However, all solid dispersion formulation was spherical in form, showed in Figure 3.

Fourier transform infrared spectroscopy (FT-IR)

There was no difference in spectrum of physical mixture and solid dispersion, hence there were no chemical interaction during solid dispersion preparation.

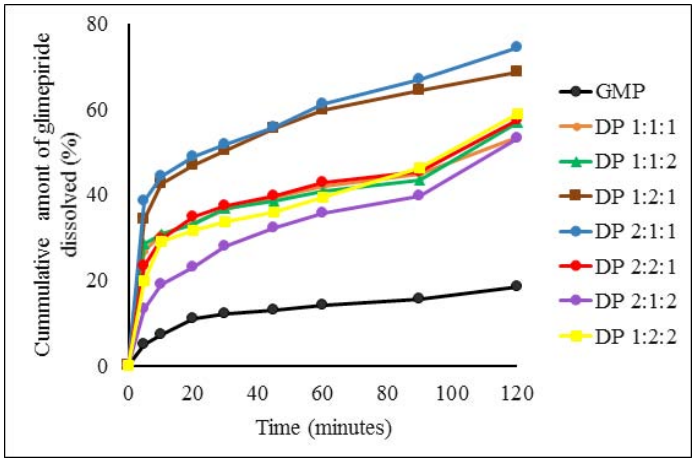

Figure 4: Dissolution profiles of the glimepiride solid dispersions.

Differential scanning calorimetry (DSC)

The significant change of pure glimepiride and glimepiride solid dispersion enthalpy showed the decrease of crystalline phase in solid dispersion so low energy was needed to melt the crystals present (Table 4).

X-ray diffraction

Solid dispersion characterization with x-ray diffraction was done to see if there's any different in crystal form of glimepiride and solid dispersion. X-ray diffraction results can be seen in Table 4.

Dissolution study

Figure 4 shows the dissolution profiles of the GMP-SD with the PVP-MD-PEG coprocessed excipients. In 5 min, there was an increase of dissolution rate up to 7.59-fold in solid dispersion with coprocessed excipient 2:1:1 compared to pure glimepiride. Pure glimepiride had only 5.06% of drugs released, while in solid dispersion 2:1:1 was 38.43%. These results were also supported in the data at 120 min which showed only 18.45% of pure glimepiride were dissolved and solid dispersion 2:1:1 showed an increase up to 4.02-fold compared to pure glimepiride (74.22%). Solid dispersion 2:1:2 showed the lowest increase of 2.87x with a percentage of 53.04% followed by coprocess 1:1:1, 1:1:2, 2:2:1, 1:2:2, and 1:2:1 with values of 53.40%, 56.76%, 57.32%, 58.90%, and 68.52%, respectively.

DISCUSSION

In this study, PVP, MD and PEG were prepared by coprocessed method. Then the coprocessed excipient and glimepiride were melted together and dried using the spray-drying method. Coprocessed excipient with the highest maltodextrin concentration showed the lowest percentage. This might be due to the high concentration of maltodextrin resulting in a stickier mass so the possibility of the mass to stick in container and drum dryer instrument was higher. The physical appearance of the coprocessed excipient showed that there is a change of appearance after drum drying was caused by the method used to dry the coprocessed excipient is drum dryer. In the drum-drying process, pureed raw ingredients are dried at relatively low temperatures over rotating, high-capacity drums that produce sheets of drum-dried product. That's what makes the powder produced using drum dryer were not fine as using spray-dryer.

The shape of PVP-MD-PEG coprocessed excipients possessed irregular-shaped of flakes and rough surfaces. This shape of powder was due to drying process using a double drum drier that break the granule of each excipient and turn it into irregular thin flakes form. However, the variation

of powder particle size was affected by the force and the length of particle size reduction process. Particle size affects the flow rate of an excipient. Flow rate will decrease with the decrease of particle size.[14]

The measurement of moisture content is used in this study for the moisture content influences the physical properties of a substance such as weight, density, viscosity, refractive index, and electrical conductivity in any form of powders. The measurement of the moisture content showed that coprocessed excipient 1:2:2 had the highest moisture content, which might be caused of the coprocessed excipient 1:2:2 contain higher amount of MD, as maltodextrin DE 18-20 is the most hygrosopic one.

The flow rate evaluation of PVP-MD-PEG powder was done by placing the powder in flowmeter funnel and the surface was evenly leveled without any pressure and the instrument was started. The result showed that the flow rate difference might be due to different concentrations of PVP, MD and PEG in each excipient. Maltodextrin hygroscopic properties caused the higher moisture content. Poor flow rate could also cause by particle size, since the flow rate will decrease as the particle size decrease.[14]

In this study, glimepiride was dissolved in 400 ml methanol and coprocessed excipient was dissolved in 100 ml aquadest. Both solution was mixed and sprayed using spray dryer. The inlet and outlet temperature were set to 100°C and 70°C, respectively. This method produced vary yield value that were caused by masses that sticks on spry dryer machine resulting in the decrease of dry powder produced.

The first solid dispersion characterization in this study was physical appearance. Solid dispersion by spray drying produced a white and finer powder. The result showed that the finer powders were produced by solid dispersion drying process might be caused by the method used for drying is using spray-dryer which produced a finer due to its drying system that involves atomizing and spraying a solution or dispersion containing iron and carrier materials in a hot chamber, resulting in evaporation of the water to leave a powder.[17] The smaller size in compared to pure glimepiride were caused by its reduction when glimepiride and the co-processed excipient were melted into one and dried with spray-drying.[16]

Morphology affects flow properties, glimepiride in solid dispersion had an ideal form to have good flow properties.[18] Solid dispersion morphology was finer and more uniform due to the use of spray dryer. The dry powders after spray drying are physically and chemically stable with minimal amounts of residual solvent. This makes a lot of differences compared to other ways of drying.

The FTIR analysis was conducted on solid dispersion of glimepiride-coprocessed excipient and its physical mixture using KBr tablet. Although the IR Spectrum is not displayed, the result showed that the absence of chemical interaction means solid dispersion did not change overall functional group of glimepiride.[19] This indicates that solid dispersion spectra were only the summation of glimepiride and co-processed excipient and reflected that there was no major interaction between glimepiride and the coprocessed excipient.

The result of thermal analysis using differential scanning calorimetry (DSC) which showed the decrease of crystalline phase in solid dispersion makes that it assumed to be a homogeneous solution and only low energy was needed to melt the crystals present. [20] Based on diffractograms height, solid dispersion peaks were smaller than pure glimepiride with lower intensity too, which indicate a transformation from crystalline phase into amorphous phase.[19]

Dissolution examination was conducted to glimepiride and glimepiride-coprocessed excipients solid dispersion. The result showed that from the dissolution profile of solid dispersion from all formulas, it shows the evident that there is a remarkable improvement in the dissolution rates of solid dispersion than pure glimepiride. [21]

CONCLUSION

PVP-MD-PEG coprocess excipient 2:1:1 was selected as the best excipient compared to other formulations with flow rate of 4.33 g/sec, moisture content of 4.96%, and acidity degree of 6.52. The glimepiride solid dispersion which was produced with the PVP-MD-PEG coprocessed excipient 2:1:1 was the best GMP-SD with dissolution rate up to 4-fold compared to pure glimepiride at 120 min.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ABBREVIATIONS

BCS: Biopharmaceutical Classification System; **DE:** Dextrose Equivalent **GMP:** Glimepiride; **GMP-SD:** Glimepiride Solid Dispersion; **DSC:** Differential Scanning Calorimetry; **FT-IR:** Fourier Transform Infrared; **MD:** Maltodextrin; **PEG:** Polyethylene glycol; **PVP:** Polyvinylpyrrolidone; **SEM:** Scanning Electron Microscope; **UV-Vis:** Ultraviolet-Visible

SUMMARY

In this study, the coprocessed excipients of polyvinylpyrrolidon (PVP), maltodextrin (MD) and polyethylene glycol (PEG) was prepared, then applied in production of the solid dispersion of glimepiride (GMP-SD) by spray drying method to increase the dissolution rate of glimepiride. GMP-SD with the PVP-MD-PEG coprocessed excipients has benefit to enhance dissolution rate of glimepiride

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