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Original Article

ENHANCEMENT OF GLIBENCLAMIDE DISSOLUTION RATE BY SOLID DISPERSION METHOD USING HPMC AND PVP

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ABSTRACT

Objective: The aim of this study was to investigate the effects of changing in the proportions of the solid dispersion formula on the dissolution rate of glibenclamide.

Methods: Solid dispersions were prepared by solvent evaporation method by using methanol as solvent, hydroxypropyl methylcellulose (HPMC) and polyvinyl pyrrolidone (PVP) as polymers. The prepared product was evaluated by the saturated solubility test and the dissolution rate test. The prepared product was characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) and Scanning Electron Microscopy (SEM).

Results: The result showed solid dispersion with a ratio of glibenclamide: PVP: HPMC (1: 3: 6) has the highest increase in solubility (20 fold) compared to pure glibenclamide. This formula also showed an improvement in dissolution rate from 19.9±1.19% (pure glibenclamide) to 99±1.60% in 60 min. Characterization of FT-IR showed that no chemical reaction occurred in solid dispersion of glibenclamide. The results of X-ray diffraction analysis showed an amorphous form in all solid dispersion formulas. The results of DSC analysis showed that endothermic peak melting point of solid dispersion occurred, and the morphology of solid dispersion was more irregular than pure glibenclamide based on SEM characterization

Conclusion: The solid dispersion of glibenclamide using PVP: HPMC as carriers can increase the solubility and dissolution rate compared to pure glibenclamide.

Keywords: Dissolution Rate, Glibenclamide, Solid Dispersion, HPMC, PVP

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INTRODUCTION

One of the most widely used drug routes of administration is the oral route. The oral route has several advantages, including ease of administration, patient compliance, cost-effective and flexible dosage settings. However, the challenge in developing drugs with oral routes is their bioavailability, because many factors can affect bioavailability include permeability, solubility, dissolution rate and first pass metabolism [1].

Solubility is an important parameter of the absorption process of a drug. The poor water solubility of drug can exhibit poor bio-availability in the drug absorption [2]. Based on the BCS system, there are around 40% of drug drugs that have been marketed that have low solubility, which can cause poor dissolved in the GI fluids. One of a drug that belongs to class II, according to BCS is glibenclamide (has high permeability, but low solubility). The solubility of glibenclamide in water is equal to 4 mg/l [3]. The low solubility of glibenclamide in water causes a low ability of glibenclamide to reach the systemic circulation and results in poor bioavailability of the drug. The bioavailability of glibenclamide is known at 40-45% after oral dosing [4]. Therefore, increasing the solubility and dissolution of glibenclamide is important to improve the efficiency of administration of glibenclamide in oral preparations [5].

Several techniques can be used to increase the solubility and dissolution of the drug such as complexation, the salts formation, particle size reduction, cocrystallization and solid dispersion [1]. Solid dispersion applications have widely been used to improve the solubility and oral bioavailability of the drug [6]. Kaur and Kumar reported that the solid dispersion technique was able to increase glibenclamide solubility from 78.85±0.001 µg/ml to 260.00±0.006 µg/ml and increased the dissolution rate from 22.41% to 93.98% within 60 min. Some advantages of solid dispersion techniques are simple, do not require a lot of equipment and can increase dissolution rates [7]

In this study, glibenclamide solid dispersion was prepared using PVP K30 and HPMC as a polymer by solvent evaporation method in different ratios. Sangeetha *et al.* reported that using HPMC as a solid dispersion polymer can increase the solubility of drug 10 fold compared with pure drugs, while for PVP K30 can increase 2.5 fold. Dissolution rate at 5 min using HPMC as polymer was 98%, PVP 66.3% and pure drug 57% [8]. PVP and HPMC also can inhibit the crystallization of the drug from an amorphous state during the solvent removal process [9].

MATERIALS AND METHODS

Materials

Glibenclamide (PT. Indofarma Tbk), HPMC, PVP (Nanhang Industrial Co LTD), methanol, potassium hydrogen phosphate, potassium dihydrogen phosphate, Sodium Hydroxide (all reagents are analytical grade).

Methods

Preparation of solid dispersion

Solid dispersion of glibenclamide was prepared by mixing Glibenclamide and carriers according to the formula in table 1. Glibenclamide, HPMC and PVP K30 were dissolved in methanol and mixed using a magnetic stirrer until homogeneous solution. The mixture solution was evaporated at a temperature of 50-60 °C for 24 h to obtain a dried sample [10].

Determination of drug content

Solid dispersion of glibenclamide equivalent to 50 mg of glibenclamide was weighed and dissolved in methanol. The solution was filtered through a 0.45 µm membrane filter, and the amount of the drug dissolved was analyzed spectrophotometrically at 300 nm [11].

Table 1: Binary and ternary solid dispersion formula of glibenclamide

Formula	Glibenclamide (%)	PVP (%)	HPMC (%)
F1	10	90	
F2	20	80	
F3	30	70	
F4	40	60	
F5	50	50	
F6	60	40	
F7	70	30	
F8	80	20	
F9	90	10	
F10	10		90
F11	20		80
F12	30		70
F13	40		60
F14	50		50
F15	60		40
F16	70		30
F17	80		20
F18	90		10
F19	10	30	60
F20	20	20	60
F21	30	35	35

Evaluation

Solubility test

Solid dispersion of glibenclamide equivalent to 10 mg of glibenclamide was weighed and placed into Erlenmeyer flask that contained water. The samples were agitated using a mechanical agitator for 24 h and 48 h at room temperature. The saturated solutions were filtered through a 0.45 µm membrane filter, and the amount of the drug dissolved was analyzed spectrophotometrically at 300 nm [12, 13].

Dissolution test

Solid dispersions equivalent to 20 mg of glibenclamide were put into 900 ml of pH 8 phosphate buffer solution with a paddle speed of 75 rpm. 5 ml of samples were taken at intervals of 5, 10, 15, 20, 30, 45, 60 min. Each sample taken was replaced with 5 ml of dissolution medium. The dissolution samples were filtered through a syringe filter of 0.45 µm pore size and analyzed spectrophotometrically at 300 nm [12, 13].

Characterization of solid dispersion

Powder X-ray diffraction *(PXRD)*

Crystal structures were analyzed by PXRD (Phillips *PW1835*® diffractometer) with the following conditions: target/filter (monochromator) Cu, voltage 40 kV and a tube current 30 mA. Data was collected by scanning mode 0.2 °-0.5 ° per minute with scanning distances of 2θ = 5 °-60 ° [14].

Differential scanning calorimetry *(DSC)*

Thermal analysis of solid dispersion was conducted using DSC. A thermograph was recorded under a nitrogen gas flow at a flow rate of 50 ml/min. Samples were evaluated from 30 to 300 °C with a heating rate of 10 °C/min [15].

Fourier transform infrared (FTIR)

The infrared spectrum of the samples was recorded using an infrared spectrophotometer using the KBr pellet. The infrared spectrum was recorded at 4000-400 cm^{-1} wavenumbers [16].

Scanning electron microscope (SEM)

Sample powders were placed on the sample holder aluminum (each formula and pure glibenclamide) coated with gold. The sample was analyzed by SEM (JSM6510, JEOL) with voltage acceleration obtained at 15kV [15, 17].

Data analysis

Analysis of solubility and dissolution test data were presented as a mean of samples±standard deviation (SD) and were analyzed using the one-way analysis of variance (ANOVA) at the level of ($P<0.05$) [18].

RESULTS AND DISCUSSION

Preparation of solid dispersion

Solid dispersion was prepared using the solvent evaporation method. In this method, the drug and polymer were dissolved in an organic solvent and evaporated to obtain dried sample [19]. Through this process, the drug will be dispersed molecularly in the polymer matrix [20]. PVP is a hydrophilic polymer commonly used as carriers for solid dispersions to increase solubility and dissolution of poorly water-soluble drug [11, 21]. HPMC is a water-soluble polymer that can be used as carriers for solid dispersion. Many drugs have been successfully prepared for solid dispersion using HPMC as a carrier. HPMC in particular cellulose can adsorb hydrophobic drug surfaces by the presence of methoxyl or hydroxypropyl groups [20, 22].

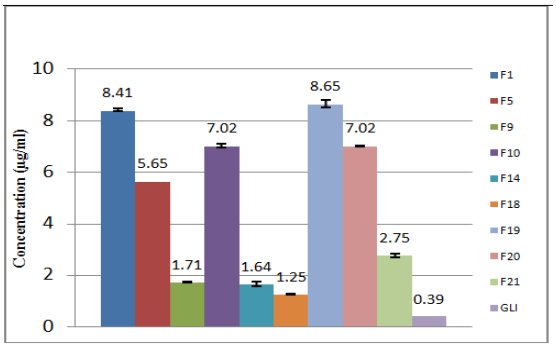
Content determination

Table 2: Result of content determination of glibenclamide solid dispersion

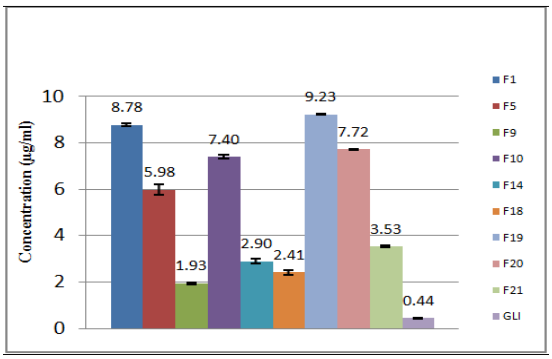
No	Formula	Average content	SD
1	F1	94.32	0.019%
2	F5	98.42	0.008%
3	F9	96.70	0.013%
4	F10	93.02	0.017%
5	F14	96.31	0.010%
6	F18	94.44	0.020%
7	F19	90.00	0.020%
8	F20	95.48	0.017%
9	F21	95.75	0.020%

Solubility test

The result of the solubility study of glibenclamide solid dispersion can be seen in fig. 1.



(a)



(b)

Fig. 1: The result of solubility study of glibenclamide solid dispersion (a) after 24 h and (b) after 48 h (All the values were calculated as mean±standard deviation) (n=3)

The result showed that all solid dispersion formulas increase the solubility of glibenclamide compared with pure glibenclamide. The highest increase in solubility was in Formula 19 (GLB: HPMC: PVP (1:6:3) with a saturated solubility of 9.23±0.012 µg/ml compared to the solubility of pure glibenclamide of 0.44±0.006 µg/ml. The increase in solubility of this solid dispersion can be caused by the molecular dispersion of the drug in the hydrophilic polymer so that the wettability of the drug will increase. The presence of HPMC and PVP can form the intermolecular hydrogen bonding with glibenclamide [11]. The result of the solubility study was analyzed statistically and showed that the solubility of all solid dispersion formula were significant differences ($\rho<0.05$) compared with pure glibenclamide.

Dissolution test

The dissolution test results of pure glibenclamide were 19.9±1.19% in 60 min. The highest dissolution result was formula 19 (99±1.60%). Based on these results, it is known that there was an increase in the dissolution rate of glibenclamide solid dispersion compared to pure drugs. The mechanism of solid dispersion for the improvement of dissolution rate of the drug are particle size reduction of drug, formation of an amorphous state and improved wettability. Based on the results, HPMC and PVP can form an amorphous state with intermolecular hydrogen bond, inhibit crystallization of drug and enhance wettability [22, 8].

In a ternary solid dispersion system with a mixture of PVP and HPMC polymers there is a combination of a mechanism for increasing dissolution rates of active substances. PVP has properties that can increase dissolution of the drug, whereas HPMC will produce high dispersion with high porosity having a synergistic effect that will increase dissolution rates compared with the use of single polymers. Ohyagi *et al.* reported that a synergistic effect was obtained from a combination of HPMC and eudragit which can increase the griseofulvin dissolution rate [15]. The result of the dissolution study was analyzed statistically and showed that the dissolution of the solid dispersion formula were significant differences ($\rho<0.05$) compared with pure glibenclamide.

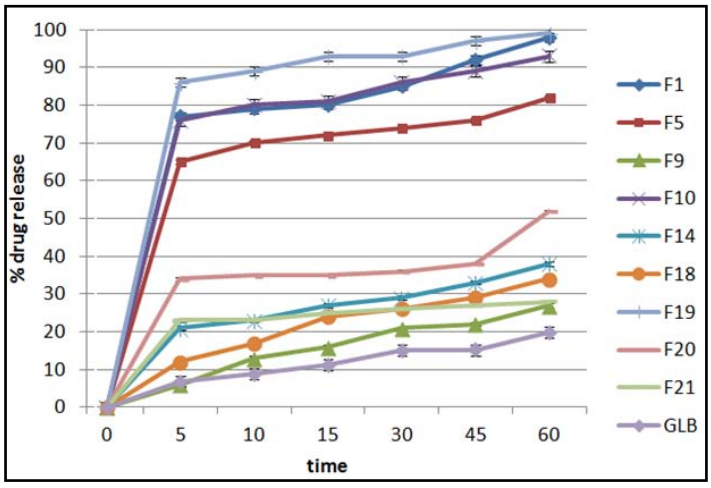


Fig. 2: The result of the dissolution study of glibenclamide solid dispersion (All the values were calculated as mean±standard deviation) (n=3)

Powder X-Ray diffractometer (PXRD)

The pure glibenclamide showed diffractogram peak with the highest intensity at an angle of 2Θ = 10.7 °, 12.3 °, 19.5 °, 19.8 °, 20.9 °, 22.1 ° which indicates that glibenclamide is in the crystalline state. Whereas for F1 solid dispersions containing 10% glibenclamide and 90% PVP, there is halo pattern diffractogram but still found the peak at 2Θ = 10.5 °, 11.3 °, 19.7 °, 20.8 °, 21.7 ° and 22.2 °, but the intensity was relatively lower compared to the intensity of the peak on a pure glibenclamide diffractogram. In the F10 solid dispersion containing 10% glibenclamide and 90% HPMC, there was also a halo pattern diffractogram with less peak observed, with relatively lower intensity compared to pure glibenclamide, the highest intensity obtained at an angle of 2Θ = 19.6 °, 20.1 °, 31.7 ° and 45.4 °. While the ternary solid dispersion formula does not appear diffractogram peak characteristic of glibenclamide. It is indicated that the molecular state of glibenclamide in ternary solid dispersion was in an amorphous state [23]. Any changes in diffractogram peak

characteristic of glibenclamide, when formulated into a solid dispersion, indicated that the molecular state of the drug already changed from crystalline state to amorphous state. Changes in crystallinity of glibenclamide could be one of the mechanisms responsible for improving the solubility and dissolution of glibenclamide [11].

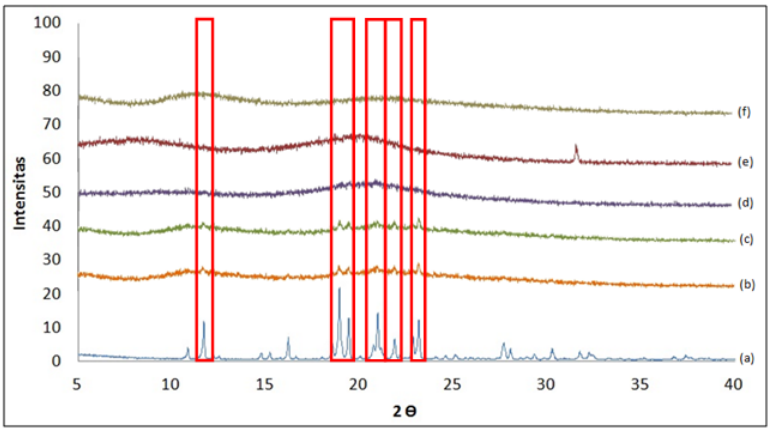


Fig. 3: PXRD result of glibenclamide (a), F1 (b), F10 (c), F19 (d), HPMC (e), PVP (f)

Differential scanning calorimetry (DSC)

In the thermogram of DSC, the endothermic peak of pure glibenclamide was on 176.6 °C, indicating its crystalline nature. The thermal behavior of the PVP and HPMC are amorphous substances, with a large endothermal effect in the 60-100 °C range due to polymer dehydration [11]. No endothermic peaks corresponding to glibenclamide were observed in solid dispersions prepared by the solvent evaporation method. This is assumed that HPMC and PVP in solid dispersion can inhibit the crystallization of glibenclamide through hydrogen bonding between polymers with glibenclamide [22].

According to gracin *et al.*, the solubility of a compound or material has a correlation with its thermodynamic properties, the thermodynamic properties can be either the melting or enthalpy of the substance [24]. In relation to solubility, enthalpy shows changes in the relative energy needed to break the bonds between solute molecules so that the smaller enthalpy energy needed to break down the solute bonds becomes lower and solubility becomes higher [25].

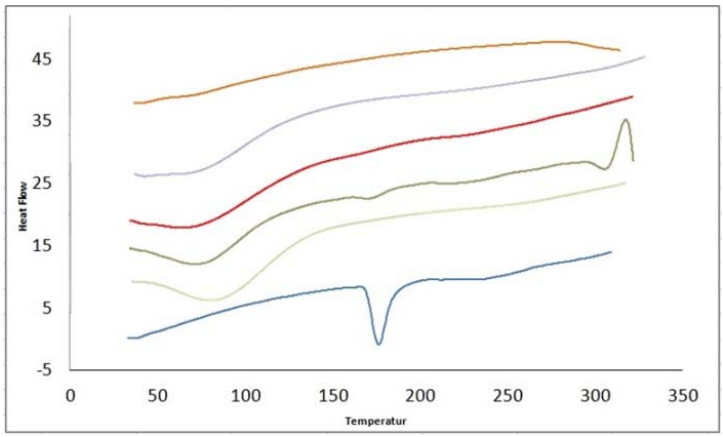


Fig. 4: DSC thermogram of glibenclamide (blue line), PVP (gray line), HPMC (green line), F1 (red line), F10 (purple line) and F19 (brown line)

Fourier transform infrared (FTIR)

The FTIR spectra of pure glibenclamide showed a peak at wave number 3413 cm^{-1} ((NH stretch), 3116^{-1} (OH stretch), 2390^{-1} (CH stretch), 1712^{-1} (C = O stretch) 1612^{1} (C = C stretch and 1350^{-1} (CH) amines according to the characteristics of the glibenclamide structure. The PVP polymer shows a peak at wave number 1655^{-1} caused by the presence of carbonyl groups, 2955-^{1} due to CH stretch and at 3450-^{1} (OH) which indicates the presence of moisture due to the hygroscopic nature of PVP. The HPMC FTIR spectra show that the wide peaks at wavenumber 3470^{-1} show OH stretch, this is consistent with the research conducted [26].

Whereas for the solid dispersion of F1, there are still peaks at 3439^{-1} (OH stretch), 2961^{-1} (CH stretch), 1651^{-1} (CO stretch) and CN at wave number 1299^{-1}. For solid dispersion F10, a cluster is still found. The OH function at wave number 3480^{-1}, CH at 2975-^{1}, C = C at 1628^{-1} and CN at 1350^{1}. For F19 solid dispersions, an OH functional group was found stretching at 3452^{-1}, CH at 2972^{-1}, C = C at 1650^{-1} and amine (CN) in 1297^{1}. This indicates that no chemical reaction occurred in the solid dispersion of glibenclamide.

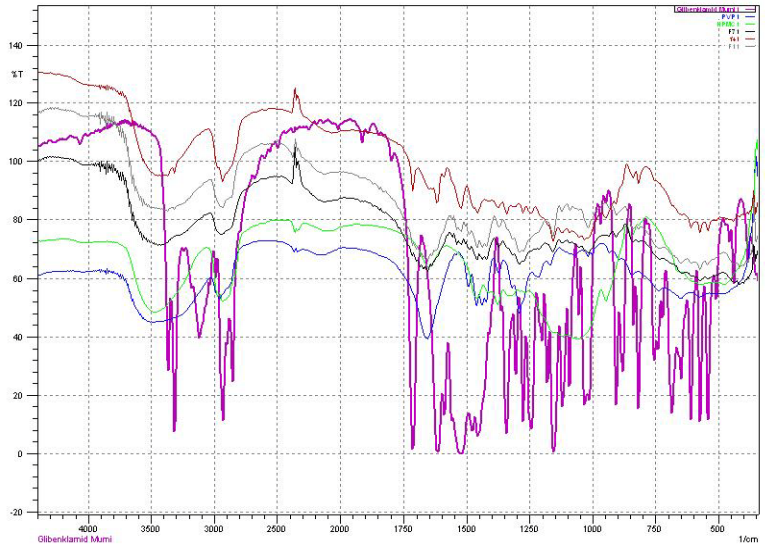


Fig. 5: FTIR spectrum of glibenclamide (purple line), PVP (blue line), HPMC (green line), F1 (black line), F10 (gray line) and F19 (brown line)

Scanning electron microscopy (SEM)

Morphology of pure glibenclamide, HPMC, PVP, and solid dispersion of glibenclamide can be seen in fig. 6. The morphology of solid dispersion did not show a characteristic of glibenclamide crystal. It is assumed that glibenclamide was dispersed in HPMC and PVP. The irregular shape of the solid dispersion is related to the wettability of a solid form, although the average solid dispersion particles have a larger size but irregular shapes can increase the wettability of the active substance so that the solubility increases [17, 27].

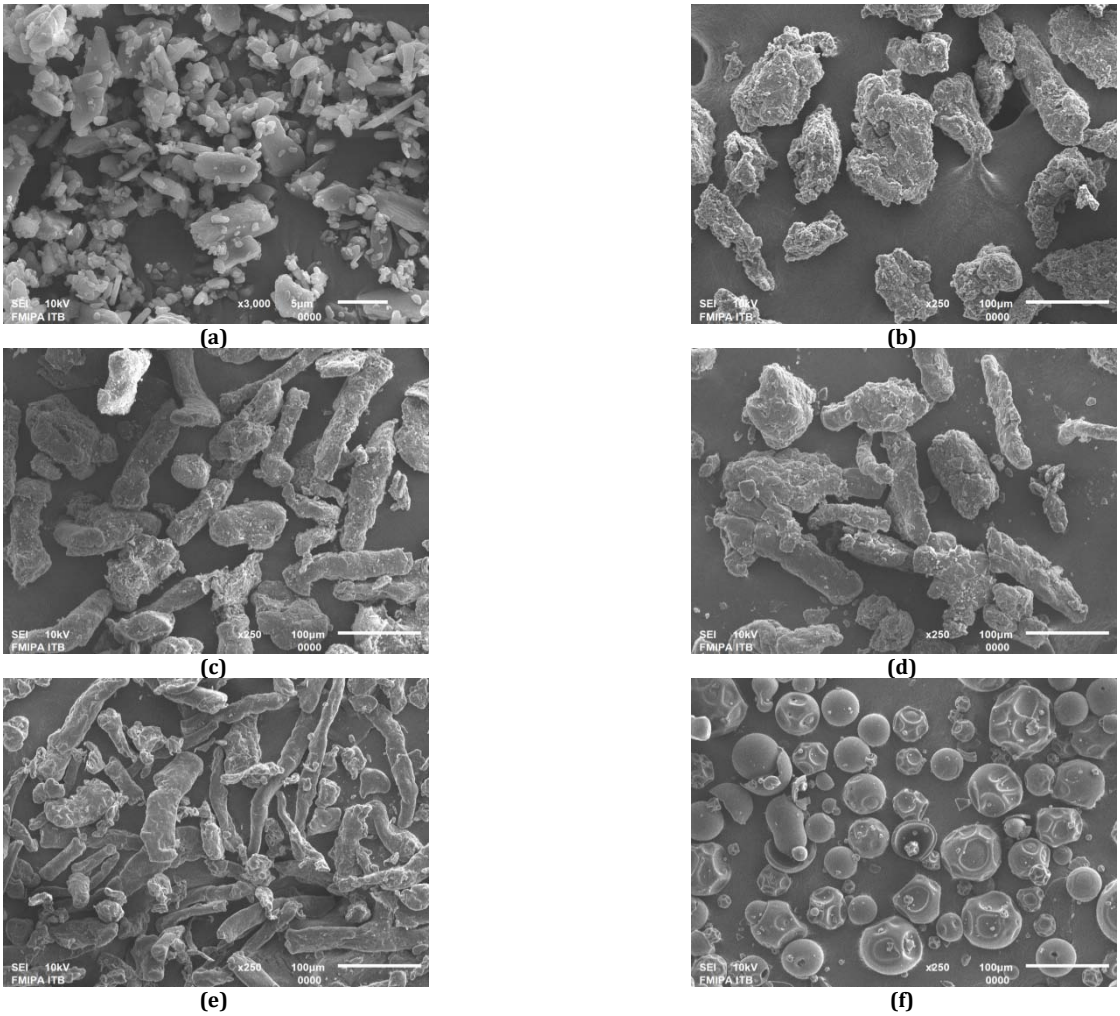


Fig. 6: SEM electromicrophotograph of (a) glibenclamide, (b) Solid dispersion of F1, (c) F10, (d) F19, (e)HPMC, (f) PVP

CONCLUSION

The solid dispersion of glibenclamide using PVP: HPMC as carriers can increase the solubility and dissolution rate compared to pure glibenclamide. Solid dispersion with a ratio of glibenclamide: PVP: HPMC (1: 3: 6) has the highest increase in solubility (20 fold) compared to pure glibenclamide. This formula also showed an improvement in dissolution rate from 19.9±1.19% (pure glibenclamide) to 99±1.60% in 60 min. Characterization of FT-IR showed that no chemical reaction occurred in solid dispersions of glibenclamide. The results of X-ray diffraction analysis showed an amorphous form in all solid dispersion formulas. The results of DSC analysis showed that endothermic peak melting point of solid dispersion occurred, and the morphology of solid dispersion was more irregular than pure glibenclamide based on SEM characterization.

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CONFLICTS OF INTERESTS

All authors have none to declare

AUTHORS CONTRIBUTIONS

All the authors contributed equally to this work

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