

DISSOLUTION IMPROVEMENT OF KETOPROFEN TABLETS BY SOLID DISPERSION METHOD

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ABSTRACT

Ketoprofen is practically water-insoluble drug and has low bioavailability. A solid dispersion method is one of the methods to increase the solubility of an active pharmaceutical ingredient in water. The aims of this study are to develop a solid dispersion of ketoprofen using PVA (polyvinyl alcohol), hydrolyzed PVA and the mixture of PVP K-25 (polyvinylpyrrolidone K-25) with lactose and to evaluate dissolution profile and solubility of ketoprofen solid dispersion. In addition, influence of the tableting processes of ketoprofen solid dispersion loaded tablets is also studied to their dissolution profile. Solid dispersions were prepared by solvent-evaporation technique. Ketoprofen was mixed with PVA and hydrolyzed PVA at ratio 4:1 also with combination of PVP K-25 and lactose at ratio 4:1:3. Solubility and dissolution profile of the solid dispersions were evaluated. Furthermore the solid dispersions were also characterized by scanning electron microscope (SEM), and X-ray diffractometry (XRD). Then all obtained solid dispersions were incorporated into tablets using wet granulation and direct compression methods. The solid dispersion can improve the solubility of ketoprofen and its rate dissolution. The highest increasing of solubility was revealed by hydrolyzed PVA solid dispersion (1.71 times). The alteration on the crystallinity of ketoprofen in all solid dispersions polymer were characterized by SEM and XRD. The highest rate dissolution was showed by hydrolyzed PVA solid dispersion, followed by PVA solid dispersion, and the combination of PVP K-25 with lactose. The dissolution profiles of solid dispersions were better than physical mixture and pure ketoprofen. The dissolution rate of ketoprofen from solid dispersions tablet were faster than the pure ketoprofen tablet. The preparation of ketoprofen solid dispersion tablets was not affect to their dissolution rate.

Keywords: Ketoprofen, Dissolution, Solid Dispersion, Tableting Process

INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug which has good analgesic properties, but ketoprofen has a low solubility in water so that it can cause problems in formulating and limiting the bioavailability (1). One way to increase the solubility of poorly soluble drugs is through the formation of solid dispersion. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs (2). Other methods, such as salt formation (3), complexation with cyclodextrins (4, 5, 6, 7, 8), solubilization of drugs in solvents (9, 10), and particle size reduction (11) have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly watersoluble drugs.

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption in vivo will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs (12). Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs (13).

Increased solubility of drugs in solid dispersions can be through several mechanisms, including increasing the wetting and the formation of amorphous or metastable crystal because of the hydrophilic polymer, decreasing particle size, the formation of complex drugs and hydrophilic polymers that are more soluble, or combinations of these mechanisms (14). The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles (13).

The objective of this research is to develop solid dispersions of ketoprofen with various carriers, such as PVA, hydrolyzed PVA and

PVP K-25 combined with lactose to enhance the solubility and dissolution rate of ketoprofen. In addition, the aim of the study is also to investigate the influence of tablet-making process to dissolution rate of ketoprofen solid dispersion from a tablet.

MATERIAL AND METHODS

Material

The material were used including to ketoprofen (Baselux S.A obtained from PT Meprofarm), PVP K-25 (BASF), PVA (Merck), PVA hydrolyzed (Merck), ethanol, lactose, Ac-Di-sol, Amprotab, Avicel pH 102, Starch 1500, Aerosil, magnesium stearate, talcum and hydrochloride acid.

METHODS

Solid Dispersion (SD) Preparation

Formation of solid dispersions were prepared by solution method. Weighing ketoprofen with PVP K-25 and lactose are in comparison of 4:1:3, whereas for ketoprofen with PVA or hydrolyzed PVA was prepared with the weight ratio of 4:1. PVP K-25 was dissolved first in ethanol until completely dissolved. Ketoprofen solutions were then added to those solution while lactose dissolved in water. In other hand, PVA and hydrolyzed PVA dissolved in water, ketoprofen was dissolved in ethanol as little as possible. Solution of the active substance and the carrier were then mixed and heated over a water bath to form a thick mass. The mass was condensed and dried for 24 hours to form a dried mass which can be crushed into powder. The obtained powder was sieved to generate powder with size of 125-315 μm .

Preparation of Physical Mixture (PM)

Ketoprofen with the carrier are mixed in the mortar with a weight ratio of 4:1:3 for ketoprofen mixture with PVP K-25 and lactose, and the weight ratio of 4:1, either to a mixture of ketoprofen with PVA or PVA hydrolyzed. The resulting powder and then sieved to obtain powders with a size of 125-315 μm . Physical mixture obtained is stored in a desiccator for subsequent experiments.

Solubility Testing

Ketoprofen mixture equivalent to 50 mg is dissolved in 100 mL of water and stirred with an orbital shaker at 37 °C and a speed of 150 ppm. Within certain times, dissolved ketoprofen were measured using ultraviolet-visible spectro-photometer at 260 nm.

Solid Dispersion Evaluation

Powder x Ray Diffraction (PXRD)

Pure ketoprofen, hydrolyzed PVA, physical mixture of ketoprofen-PVA hydrolyzed and solid dispersions were analyzed by X-ray diffraction at 2θ in a range $5-50^\circ$ with the speed of 0.02° per 0.8 seconds.

Disolution test

The dissolution test was carried out using type 2 (paddles) at $37 \pm 0.5^\circ\text{C}$ and a speed of 50 ppm in HCl medium pH of 1.2. The sample was placed into a vessel containing 900 mL of HCl medium pH of 1.2. Samples were taken after 15, 30, 45, 60, and 90 minutes and dissolved ketoprofen was measured using UV-visible spectrophotometer at 260 nm (Mura, 2005).

Scanning Electron Microscope

Pure ketoprofen, polymers (PVA, PVA hydrolyzed, PVP K-25 and lactose) and ketoprofen solid dispersion was coated with gold-palladium. Samples were then inserted into the container on SEM equipment to capture an image.

Tablet Formulation

250 mg tablets were prepared with contained 50 mg of ketoprofen. Beside excipients, reference tablets contain pure ketoprofen (Table 1). The formula tablets will be used subsequently in the manufacture of solid dispersions loaded tablets (Table 2). Reference and solid dispersion tablets were prepared by wet granulation and direct compression method.

Table 1: Formulation of Reference Ketoprofen tablet

Bahan	F1	F2	F3	F4	F5	F6	F7	F8
Ketoprofen (mg)	50	50	50	50	50	50	50	50
Starch paste (%)	10	-	-	-	-	-	-	-
PVP K-25 (%)	-	2	-	-	-	5	-	-
PVA (%)	-	-	5	-	-	-	5	-
Hydrolyzed PVA (%)	-	-	-	5	-	-	-	5
Avicel pH 102: Starch 1500 7:3 (%)	-	-	-	-	72	72	72	72
Ac-Di-Sol (%)	8	8	8	8	5	5	5	5
Lactose (%)	59	59	59	59	-	-	-	-
Talc (%)	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5
Mg-stearate (%)	1	1	1	1	1	1	1	1
Aerosil (%)	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5

Notation : F1, F2, F3, and F4 prepared by wet granulation method; F5, F6, F7, and F8 prepared by direct compression method

Table 2: Tablet formulations of Ketoprofen solid dispersion

Bahan	F1A	F1B	F1C	F5A	F5B	F5C
Ketoprofen : PVP K-25 : Lactose (mg)	100	-	-	100	-	-
Ketoprofen : PVA (mg)	-	62,5	-	-	62,5	-
Ketoprofen : hydrolyzed PVA (mg)	-	-	62,5	-	-	62,5
Starch paste (%)	10	10	10	-	-	-
Ac-Di-Sol (%)	8	8	8	5	5	5
Lactose (%)	39	54	54	-	-	-
Avicel pH 102 : Starch 1500 7:3 (%)	-	-	-	52	67	67
Talc (%)	1,5	1,5	1,5	1,5	1,5	1,5
Mg-stearate (%)	1	1	1	1	1	1
Aerosil (%)	0,5	0,5	0,5	0,5	0,5	0,5

Notation : F1A, F1B, and F1C prepared by wet granulation method; F5A, F5B, and F5C prepared by direct compression method

Solid dispersions can improve dissolution rate of active substance due to increased wetting ability of the active substance and formed a mixture of the active substances with hydrophilic polymers which are more soluble in water (15). PVA and PVP were chosen because those polymers have high solubility in water and can increase the hydrophilic active ingredient so that the active substance is more easily wetted. This carrier can interact with molecular physics of active ingredient so that any change of crystallinity of the active substance is occurred (16). The melting point of ketoprofen, PVP and PVA are above 100°C (17, 18), therefore the solution method is the most suitable method for forming a solid dispersion.

Ketoprofen when only mixed with PVP K-25 formed mass that alike caramel. Therefore, it is necessary to add lactose for obtaining dry mass which can be crushed to be powder again. In manufacturing of dispersion systems of ketoprofen with PVA or hydrolyzed PVA, ketoprofen was dissolved in ethanol, whereas hydrolyzed PVA or PVA dissolved in water.

Solution of ketoprofen and the carrier were mixed and heated in a water bath to form a thick mass. Based on the literature, ketoprofen is stable to heat so the mixture can be heated without any

decomposition of the active substance. The mass was dried at 60°C in order to avoid destruction of the active substance and carrier. Dry mass was then crushed. The obtained powder was sieved in the size range of $125-315\ \mu\text{m}$ to generate a homogeneous particle size distribution powder.

Solubility of the physical mixture of ketoprofen with PVA, hydrolyzed PVA and PVP K-25 combination with lactose are statistically not differ ($p < 0.05$) with pure ketoprofen (Figure 1). Instead, each form of solid dispersion provides a significant increase in solubility ($p < 0.05$). The highest increasing solubility was given by the solid dispersion of ketoprofen in hydrolyzed PVA by 1.71 time compared to pure ketoprofen.

Dissolution rate of ketoprofen was tested in HCl medium pH of 1.2. This is consistent to the pH of the stomach. In addition, ketoprofen has a maximum absorption in the stomach (19). Figure 2 is dissolution profiles of a pure ketoprofen, physical mixture and solid dispersion of ketoprofen in various carriers.

An increasing in powder dissolution of ketoprofen solid dispersion was observed in comparison with pure ketoprofen and physical

mixtures. Within 15 minutes, ketoprofen-hydrolyzed PVA solid dispersion provided the highest dissolved ketoprofen by 73.54 %. In contrast, only 25% of pure ketoprofen and 30% of physical mixture

were dissolved in the same time. This result shows the dissolution rate of solid dispersion powder faster than the physical mixture and pure ketoprofen (Figure 2).

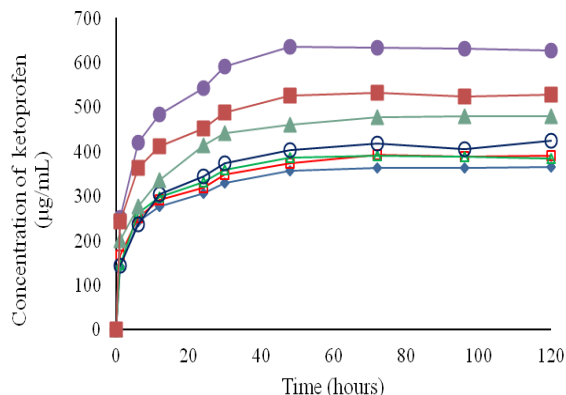


Fig. 1: Solubility of ketoprofen (♦), PM ketoprofen PVP : lactose (4:1:3) (Δ), PM ketoprofen : PVA (4:1) (□), PM ketoprofen : hydrolyzed PVA (4:1) (○), SD ketoprofen : PVP : laktosa (4:1:3) (▲), SD ketoprofen : PVA (4:1) (■), SD ketoprofen : hidrolized PVA (4:1) (●) in water at 37°C.

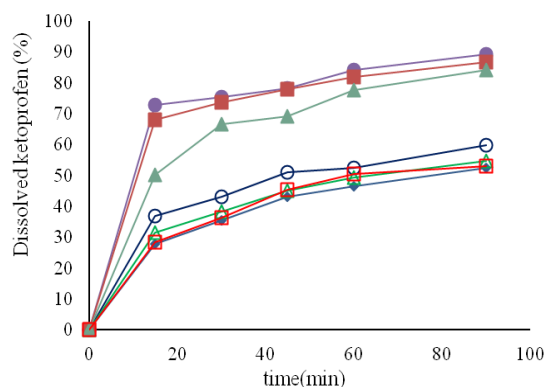


Fig. 2: Dissolution of ketoprofen (♦), PM ketoprofen : PVP : lactose (4:1:3) (Δ), PM ketoprofen : PVA (4:1) (□), PM ketoprofen : hydrolyzed PVA (4:1) (○), SD ketoprofen : PVP : lactose (4:1:3) (▲), SD ketoprofen : PVA (4:1) SD ketoprofen : hidrolized PVA (4:1) (●) in HCl medium pH of 1.2

Since ketoprofen solid dispersion with hydrolyzed PVA provided the highest dissolution rate and solubility, evaluation X-ray diffractometry is only performed to ketoprofen solid dispersions with hydrolyzed PVA. The diffraction pattern of physical mixture did not show a change in crystallinity, whereas diffraction pattern of the solid dispersion revealed a slight decrease of crystallinity compare to pure ketoprofen. Crystallinity changes in solid dispersion can be observed especially with the decrease of intensity at 2θ of 22.72° , although the declining intensity was only a little (Figure 3).

Scanning Electron Microscopy (SEM) was employed to study surface morphology of solid dispersion. Evaluation by SEM indicated a change in crystallinity of the all ketoprofen solid dispersions over than pure ketoprofen. Figure 6, 7, and 8 are morphology of solid dispersion of ketoprofen that revealed a rough surface. In contrast, a smooth surface formation are revealed by pure ketoprofen.

The process of making tablets may cause changing in the dissolution rate of active substances. Therefore increasing dissolution rate of the active substance in powder form due to increasing solubility of solid dispersion is not automatically increasing dissolution rate of ketoprofen solid dispersion loaded tablet. Therefore dissolution testing is necessary to perform so that releasing ketoprofen from the tablet can be evaluated.

Tablets were made using two methods, wet granulation and direct compression. The best tablet formulation of the granulation method was showed by F1. Therefore F1 was chosen as reference tablet and subsequently to develop solid dispersion tablets (F1A, F1B, F1C). In the direct compression method, reference tablets were made in four formulas. F5 was not added polymer of solid dispersion, while the F6, F7, and F8 polymer were added polymer. In the fourth formula, only the F5 and F8 (added PVA hydrolyzed) could produces eligible tablets.

F6 and F7 produces masses that can not be compressed into tablets. F5 was chosen to manufacture solid dispersion tablet. Excipients were used in this formula, namely Ac-Di-Sol as a disintegrant, a combination of Avicel pH 102: Starch 1500 as a filler with a ratio of 7:3, Mg-stearate as a lubricant, talc as glidan and Aerosil as adsorbent. Solid dispersion tablets are made in three formulas based on the difference of the carrier used for the manufacture of solid dispersions of ketoprofen. In the direct compression method, the materials were mixed and then evaluated. The tablet evaluation includes evaluation of the uniformity of tablet size, weight variation, hardness, friability, disintegration time and also frictibility. Based on the tablet evaluation indicate reference tablets (F5 and F8) and solid dispersion tablets (F5A, F5B, and F5C) met the requirement of a good tablet.

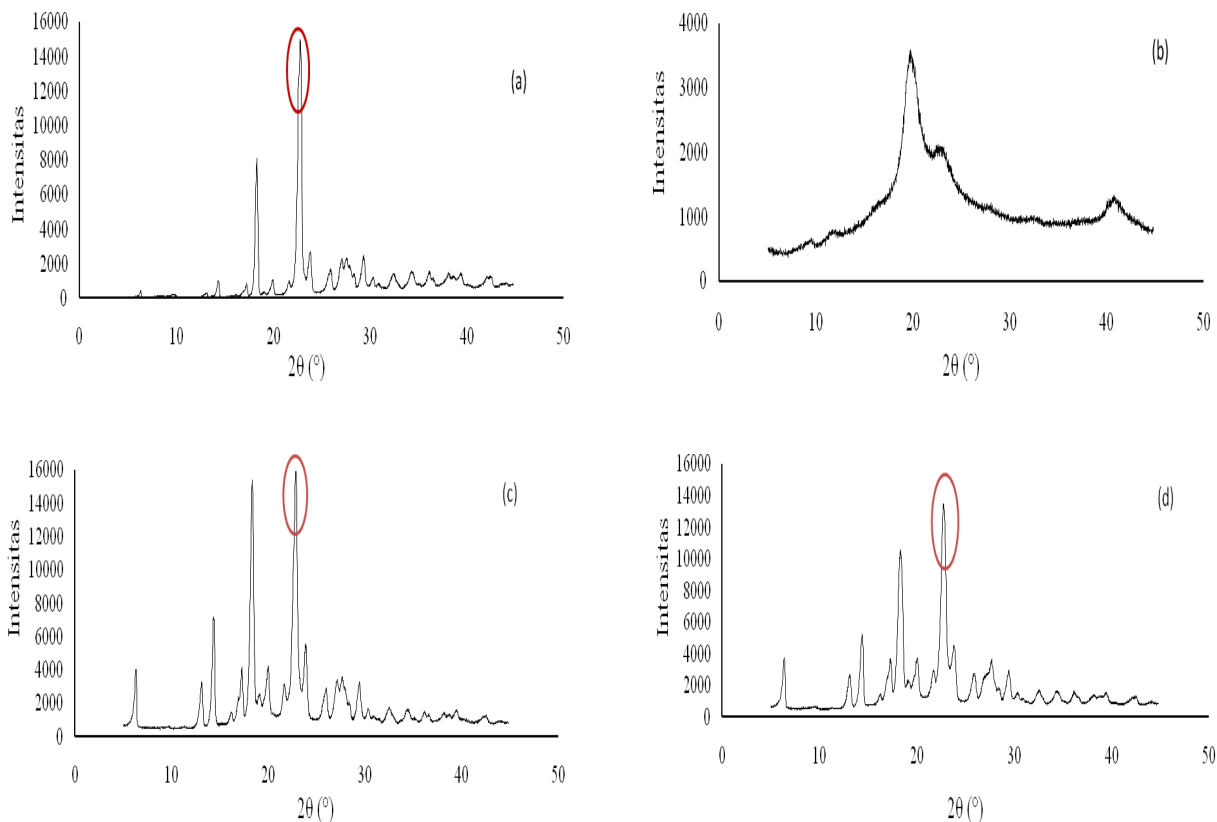


Fig. 3: Diffractogram pure ketoprofen (a), hydrolyzed PVA (b), physical mixture ketoprofen : PVA terhidrolisis 4:1 (c), and solid dispersion ketoprofen: PVA terhidrolisis 4:1 (d).

According to the evaluation, disintegration time of direct compression tablet was shorter than wet granulation tablets. It can be attributed to difference in used materials. The addition of starch paste on wet granulation tablets increase the binding between the particles. Meanwhile in direct compression, binder tablet is not added. All wet granulation and direct compression tablets were also conducted to dissolution performance.

Dissolution profiles of solid dispersion tablets by wet granulation method and direct compression method were significantly different ($p < 0.05$) compare to reference tablets. In wet granulation tablet, within 15 minutes highest dissolved ketoprofen are given by solid dispersion with hydrolyzed PVA tablet by 63.04%. In contrast, only 25% of ketoprofen was dissolved by reference tablet (F1). For direct compression tablet, reference tablet is using F5 and F8 tablet

which dissolution of both tablets are not significantly different ($p < 0.05$). F5 and F8 tablet released only 25% and 37% of ketoprofen within 15 minutes. Whereas solid dispersion tablet with hydrolyzed PVA by direct compression method could release of 68.94% of ketoprofen in period of 15 minutes. Wet granulation and tablet direct compression of the three solid dispersion system provides a better dissolution profile compare to reference tablets (Figure 4 and 5).

According to dissolution performance, profile dissolution of solid dispersion powder did not differ significantly ($p < 0.05$) with solid dispersion tablets which are made in direct compression or wet granulation. It indicates that the process of making tablets do not affect the dissolution rate of ketoprofen solid dispersions from a tablet.

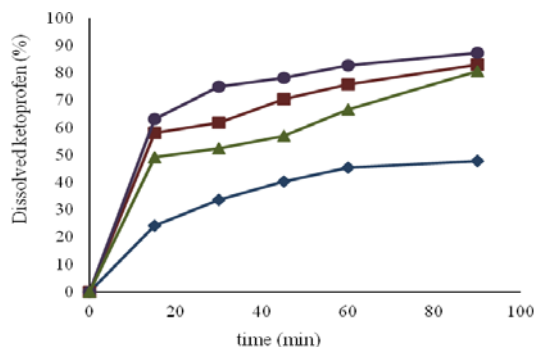


Fig. 4: Dissolution profile of wet granulation method, F1 (♦), F1A (▲), F1B (■), and F1C(●) in HCl medium pH of 1.2

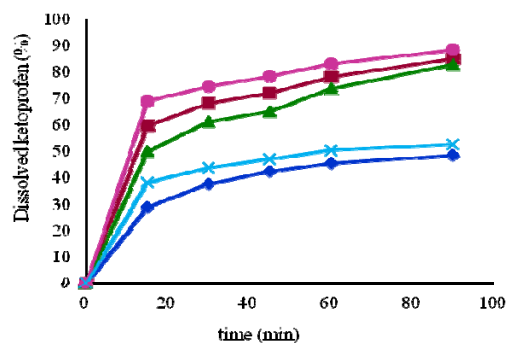


Fig. 5: Dissolution profile of direct compression method, F5 (♦), F8 (×), F1A (▲), F1B (■), and F1C (●) in HCl medium pH of 1.2

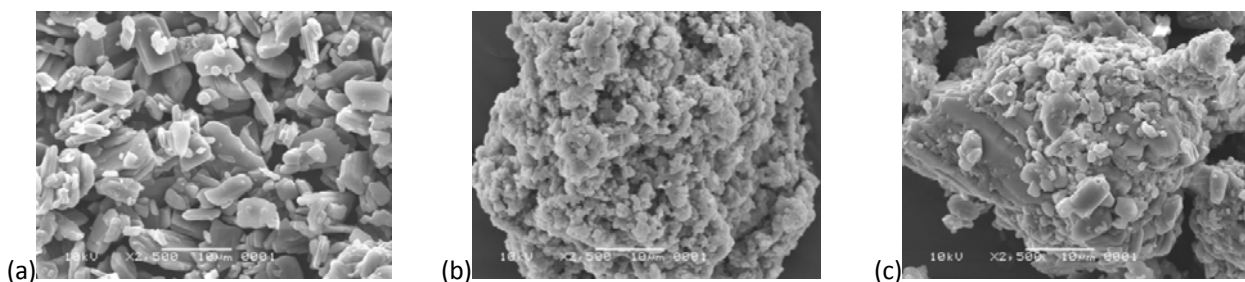


Fig. 6: The morphology of pure ketoprofen (a), PVA (b), and ketoprofen solid dispersions with PVA 4:1 (c) at 2500 times magnification

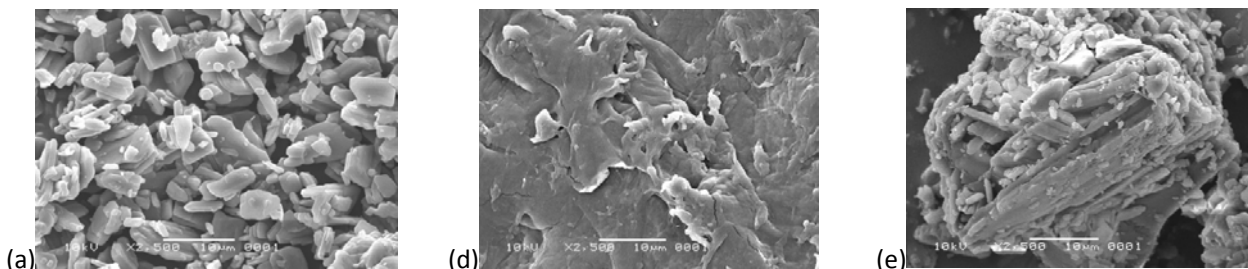


Fig. 7: The morphology of pure ketoprofen (a), PVA hydrolyzed (d), and solid dispersions of ketoprofen with hydrolyzed PVA 4:1 (e) at 2500 times magnification

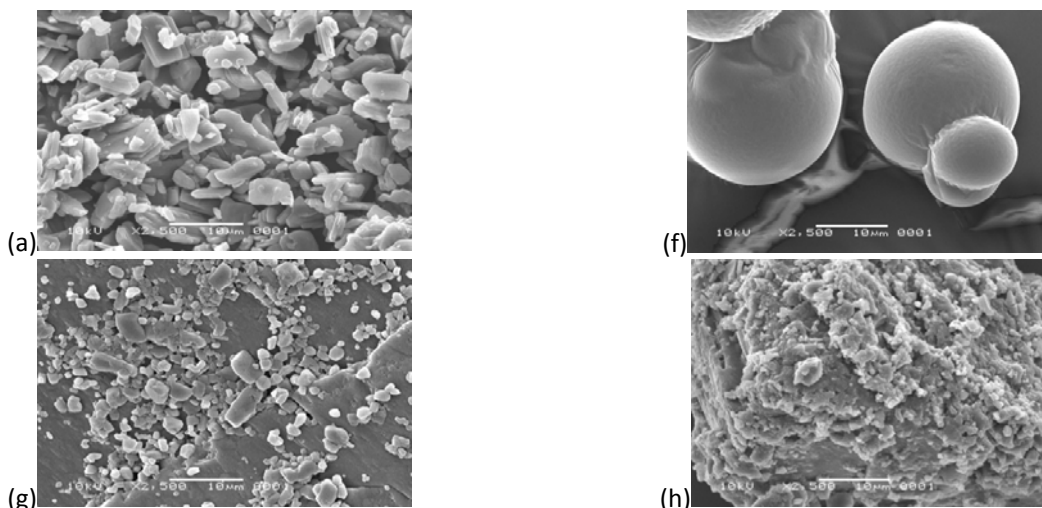


Fig. 8: The morphology of pure ketoprofen (a), PVP K-25 (f), lactose (g), and solid dispersion of ketoprofen: PVP K-25: Lactose 4:1: 3 (h) at 2500 times magnification

CONCLUSION

Solid dispersions of ketoprofen with various carriers, such as PVA, PVA hydrolyzed, and the combination of PVP K-25 with lactose could increase the solubility of ketoprofen in water thereby increasing the dissolution rate. The highest increase in solubility is given by the solid dispersion of ketoprofen in PVA hydrolyzed by 1.71 times over pure ketoprofen. Powder solid dispersion showed better dissolution profile than the physical mixture and pure ketoprofen. The highest dissolution rate was indicated by the ketoprofen solid dispersions with hydrolyzed PVA. Wet granulation and direct compression tablet of the three solid dispersion system provide a better dissolution profile than reference tablets.

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