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Original Article

FORMULATION AND *IN VITRO* TESTS OF KETOPROFEN NANOSUSPENSION USING THE MILLING METHOD WITH POLYMER VARIATIONS

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ABSTRACT

Objective: The aim of this research was to formulate ketoprofen nanosuspension with a variety of polymers and to compare the dissolution rate of the nanosuspensions with ketoprofen suspension.

Methods: Ketoprofen nanosuspension was formulated by milling method using a different polymer such as Polyvinyl Pyrrolidone (PVP) K-30 (F1), Polyvinyl Alcohol (PVA) (F2) and Hydroxy Propyl Methyl Cellulose (HPMC) (F3). Nanosuspensions were prepared and characterized, including organoleptic, pH, particle size, zeta potential, Polydispersity Index (PI), specific gravity, crystalline state determination, physical stability at room temperature for 3 mo, and *in vitro* dissolution test compared with ketoprofen suspension.

Results: The ketoprofen nanosuspensions with PVP K-30 and PVA showed stable preparations, while those with HPMC showed less stability, as indicated by sedimentation during storage. The particle size values of PVP K-30 and PVA were 10.004±0.03 nm; and 9.560±0.01 nm; zeta potential and polydispersity index values met the test requirements. The dissolution rate of the ketoprofen nanosuspensions was higher with a cumulative of F1, F2, and F3 were 83.35%; 85.00%, and 81.09% after 60 min, while the ketoprofen suspension was only 7.62%.

Conclusion: The milling method of ketoprofen nanosuspensions with PVP and PVA has more stable physical characteristics than nanosuspension with HPMC. The ketoprofen nanosuspensions have a higher dissolution rate than the ketoprofen suspension.

Keywords: Ketoprofen, Nanosuspension, Milling, Dissolution

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INTRODUCTION

Ketoprofen belongs to the Biopharmaceutical Classification System (BCS) class II and it is a type of non-steroidal anti-inflammatory drugs that have analgesic and antipyretic effects. This drug works by reversibly inhibiting the cyclooxygenase 1 and cyclooxygenase 2 (COX-1 and COX-2) enzymes, which decreases the production of pro-inflammatory prostaglandin precursors. Rheumatoid arthritis, osteoarthritis, and menstrual cramps in the stomach are among the conditions for which ketoprofen is frequently prescribed [1]. Furthermore, because of the short half-life of 2-4 h, ketoprofen must be administered more frequently, which frequently results in adverse effects, including stomach bleeding and irritation [2].

Several formulation approaches can be used to solve the problem of low solubility in drugs, such as micronization, dissolution using cosolvents, use of permeation enhancers, surfactant dispersion, making solid dispersion preparations, adding salt, and precipitation techniques. These techniques are not applicable to drugs that are not soluble in water and organic solvents. Nanosuspensions may be able to solve issues related to the administration of medications that are insoluble in water [3]. Pharmaceutical nanosuspensions are defined as colloidal dispersions of submicron, biphasic, solid drug particles dispersed in an aqueous vehicle. Stabilizing nano suspensions smaller than 1 µm can be achieved by preparing surfactants and polymers using appropriate techniques for drug delivery applications [4-6].

There are several methods for making nanosuspensions, such as bottom-up technology and top-down technology. The bottom-up technology method is a method of forming drug nanoparticles from molecular form [1]. Meanwhile, in the top-down technology method, drug particles that are large or on a micron scale are ground in various ways to reduce the particle size [7]. The top-down technology method is divided into several methods, one of which is the milling method. The milling method is a method for making nanosuspensions that has several advantages; namely, the formulation can be carried out easily, requires a short grinding time, and does not require organic solvents so it does not cost a lot [8].

Several approaches have been taken in the development of ketoprofen nanosuspension, including using solvent evaporation method [9], precipitation-ultrasonication method [10] or ketoprofen nanoparticle from nanosuspension using freeze-drying method [11]. However, there is no research on the preparation of nanosuspension with milling method using polymer variation such as PVP K-30, PVA and HPMC.

Therefore, this study aimed to develop a ketoprofen nanosuspension using milling techniques with a variety of polymers (PVP K-30, PVA and HPMC). The physical characterization and the dissolution rate of the nanosuspension will be compared with ketoprofen suspension to get the optimize formulation.

MATERIALS AND METHODS

Materials

Ketoprofen was obtained from Kimia Farma, Indonesia. Concentrated hydrochloric acid, HPMC, sodium chloride, PVP K-30, PVA, and tween 80 were purchased from Merck, Germany. Distilled water was obtained from Smart Chemical Lab, Jakarta. All the chemicals used in this study were analytical grade.

Methods

Preparation of ketoprofen nanosuspension

Preparation of nanosuspension was develop based on modification from Das [11]. Ketoprofen pure was grinded using high energy ball-mill tool to reduce the particle size of ketoprofen. The sample was filled into the sample holder of the high-energy ball-mill tool at a speed of 300 rpm with a running time of 1 h. Tween 80 was dissolved in distilled water at 40 °Cin a beaker glass, then added the polymer (PVP-K30/PVA/HPMC) and distilled water to 20 ml, homogenizing to form an aqueous phase. Ketoprofen nanoparticle was then added into an

aqueous phase while stirred magnetically at 1500 rpm at 40 °Cfor 1 h until a clear nanosuspension was formed. Three formula of ketoprofen nanosuspension were formulated using various polymer along with suitable excipients using the milling method (table 1).

Preparation of ketoprofen suspension

A uniform organic solution was formed using the pure drug ketoprofen and ethanol at 40 °Cin a beaker glass. PVP K-30 was dissolved in distilled water, then put tween 80, then homogenizing to form an aqueous phase. Once homogeneous, the organic solution was then added to an aqueous phase (20 ml) in a gradual manner with the aid of syringe, then stirred magnetically at 600 rpm at 40 °C for 20 min until a suspension was formed. The ketoprofen suspension formula can be seen in table 1.

Evaluation of ketoprofen nanosuspension

Organoleptic test

The organoleptic test was carried out visually included odor, color, shape and texture of the nanosuspension.

Table 1: **Formula of ketoprofen nanosuspensions and suspension**

Formula	Ketoprofen (mg)	Tween 80 (ml)	PVP K-30 (mg)	PVA (mg)	HPMC (mg)	Ethanol (ml)	Distilled water ad (ml)
F1	400	3	200	-	-	-	20
F2	400	3	-	200	-	-	20
F3	400	3	-	-	50	-	20
F Suspension	400	0.1	200	-	-	2	20

Particle size, zeta potential and polydispersity index

The sample was placed into the sample holder before it was transferred to the instrument. Dynamic Light Scattering (Zetasizer, Malvern) was the tool used for determining particle size and zeta potential by analyzing the intensity of light scattered by sample molecules as a function of time at a scattering angle (90) and constant temperature (25 °C). This tool can measure particle size, polydispersity index and zeta potential value. Measurement of the average diameter and polydispersity index of the samples were done for every formula [13].

pH determination

The pH of the nanosuspensions was determined using a pH meter (Hanna). The readings were taken for an average of 3 times.

Specific gravity determination

A clean and dry pycnometer (A g) was weighed first. Water was added to the pycnometer until it was full and then weighed (A1 g). The water was removed from the pycnometer and cleaned. The pycnometer was filled with the preparation and weighed (A2 g). The specific gravity calculation was calculated using the following equation.

$$\text{Specific gravity} = \frac{A2-A}{A1-A} \times \rho\text{water}$$

Observation of the crystalline state of particles

Observations were carried out by placing the sample in an aluminum pan which was closed tightly and airtight. Differential Scanning Calorimetry (DSC) was calibrated with Indium p. a. with a melting point of 156 °Cand a comparison was used in the form of an empty aluminum pan. DSC measurements begin on samples with a temperature range of 25-150 °C(according to the melting point of the component to be tested) with a heating rate of 10 °C/min. Ketoprofen nanosuspension thermograms were recorded using Shimadzu DSC-60 plus.

***In vitro* studies**

Preparation of artificial gastric fluid pH 1.2 (without enzymes)

Two gs of sodium chloride were dissolved in 7 ml of concentrated hydrochloric acid and added distilled water until 1000 ml [14].

Preparation of ketoprofen standard solution

Artificial gastric fluid pH 1.2 (without enzymes) was used to dissolve ketoprofen (40 mg) until it was completely dispersed in a 100 ml volumetric flask, then filled with artificial gastric fluid pH 1.2 (without enzymes) until the mark line (ketoprofen concentration was 400 ppm).

Preparation of ketoprofen absorption curve

The standard ketoprofen stock solution was pipetted at 0.15 ml, then put into a 10 ml volumetric flask, then filled with artificial gastric fluid pH 1.2 (without enzymes) to the mark line (ketoprofen concentration was 6 ppm). The absorption was measured by UV spectrophotometer at a wavelength of 200-400 nm [14].

Preparation of ketoprofen calibration curve

Ketoprofen solutions were prepared in various concentrations by pipetting 0; 0.075; 0.1; 0.125; 0.15; 0.175; 0.2; 0.225; 0.25; 0.275 and 0.3 ml of ketoprofen standard stock solution into a 10 ml volumetric flask then added with artificial gastric fluid pH 1.2 (without enzymes) to the mark line (ketoprofen concentration is 0; 3; 4; 5; 6; 7; 8; 9; 10; 11 and 12 ppm). The absorbance was measured by UV spectrophotometer at a wavelength of 258 nm [14].

Determination of ketoprofen assays

The nanosuspension preparation was pipetted 5 ml and put into a 50 ml volumetric flask, then diluted with artificial gastric fluid pH 1.2 (without enzymes) to the mark line and homogenized (Flask I, ketoprofen concentration was 2000 ppm). The dilution result from flask I was pipetted 5 ml into a 50 ml volumetric flask and then diluted with artificial gastric fluid pH 1.2 (without enzymes) up to the mark line and homogenized (Flask II, ketoprofen concentration was 200 ppm). The dilution results from flask II were pipetted 5 ml into a 50 ml volumetric flask and then diluted with artificial gastric fluid pH 1.2 (without enzymes) up to the mark line and homogenized (Flask III, ketoprofen concentration was 20 ppm). The solution was measured by UV spectrophotometer at a wavelength of 258 nm [14].

***In vitro* dissolution test**

The prepared preparation was put into a dissolution tube containing 900 ml of artificial gastric fluid pH 1.2 (without enzymes) at a temperature of 37±0.5 °Cin a paddle-type dissolution apparatus at a speed of 100 rpm. 1 ml of sample was taken and the volume was maintained at 900 ml at time intervals of 0, 5, 10, 15, 30, 45, 50, 75, 90, and 120 min and carried out at the same place. The sample was put into a 10 ml volumetric flask then diluted with artificial gastric fluid pH 1.2 (without enzymes) to the mark line and homogenized. The samples were analyzed with a UV spectrophotometer at a wavelength of 258 nm.

Stability studies

Stability studies were observed on preparation during a storage period of 3 mo at room temperature (25±2 °C), including organoleptic, particle size, zeta potential, polydispersity index, and pH.

Data analysis

Data were presented as average value and Standard Deviation (SD). Data analysis was performed in this study IBM SPSS Statistics version 22 by pairwise Mann-Whitney-U-Tests to examine the *in vitro* dissolution test between the formula.

RESULTS AND DISCUSSION

Preparation ketoprofen nanosuspensions and suspension

Ketoprofen that has been ground using a high-energy ball mill has a smaller texture compared to ketoprofen that has not been ground. Then, the crushed ketoprofen particles were measured. The results of particle measurements produce powder particle sizes reaching 400 nanometers. This states that the ground ketoprofen powder is still in the nano-size range, namely 200-600 nm [13]. The results of the preparation ketoprofen nanoparticles are shown in fig. 1.

All the nanosuspension formula were shown in the form of a liquid with a slightly thick texture, clear color, had a distinctive smell, and there was no precipitation in all formulas. Meanwhile, ketoprofen suspension was form a liquid solution, had a milky white color and had a distinctive odor. The results were shown in fig. 2.

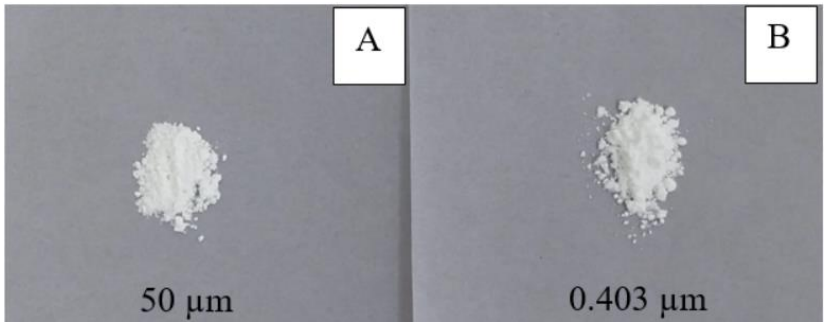

Fig. 1: The comparison of (A) ketoprofen before ground with (B) ketoprofen, which has been ground with a high-energy ball mill

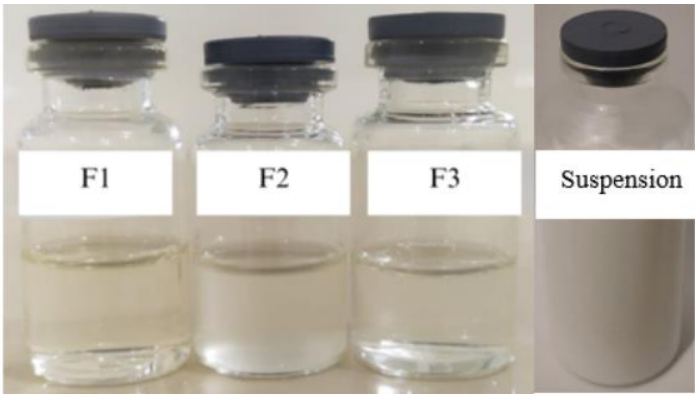

Fig. 2: Ketoprofen nanosuspensions and suspension

Evaluation of ketoprofen nanosuspension

Organoleptic

The ketoprofen nanosuspensions were inspected visually. All the nanosuspension formulas were shown in a clear liquid form, has a distinctive aroma and no sedimentation (table 2).

Particle size, zeta potential, and polydispersity index

The particle sizes shown in table 2 indicate that the nanosuspension preparation with PVA produces the smallest particle size, followed by PVP K-30 and the largest particle size using HPMC. These results showed that nanosuspensions formulated using the milling method produce particle sizes within the acceptable range of pharmaceutical nanosuspensions, namely less than 1 micron, with an average range between 200-600 nm [15]. The differences in particle size between polymers can occur due to several factors, such as the composition of the polymer used interactions between the polymer and other materials, which can influence particle formation and size. The properties of each polymer also vary, such as molecular weight, viscosity or bond strength between particles in the preparation, which can affect the size of the particles formed [16].

The stability of colloidal nanosuspension dispersions can be determined by analyzing the zeta potential value. The minimum zeta potential value for steric stabilizers is±20 mV [12]. The results shown in table 4 indicates that the zeta potential value does not meet the requirements where the zeta potential value exceeds+25 mV and is less than-25 mV and has a high level of stability. PI is a parameter that shows the particle size distribution, which is an important characteristic because it affects saturation solubility, dissolution rate, physical stability, and even bioavailability of nanosuspensions. The PI value should be as low as possible to provide long-term stability. The distribution of particles was fairly narrow with a value of 0.1–0.25, while a value of more than 0.5 indicates a wide distribution [17]. The PI value shown in table 2 indicates that all formula has a fairly narrow distribution. A small distribution size is needed to reduce the risk of Ostwald's ripening [2].

pH determination

All formula were in the pH range of 4.5-5 (table 2). The pH range requirements for acceptable oral preparations and pharmaceutical solutions are between 2-9 so the pH of the formulated ketoprofen nanosuspension was still within the range of pH requirements for preparations that can be consumed orally [17]. The pH in the solution preparation is an important factor that must be considered. The stability of the drug to be administered will depend on the potential impact of pH on solubility [18].

Specific gravity determination

The specific gravity of all formulas of ketoprofen nanosuspension has almost the same specific gravity and meets the suspension-specific gravity requirements, namely>1.00 g/ml [18]. Results were shown in table 2.

Table 2: Characterization of ketoprofen nanosuspension and suspension

Parameters	Formula			
	F1	F2	F3	F Suspension
Appearance	Clear	Clear	Clear	Milky white
Aroma	Specific	Specific	Specific	Specific
Form	Liquid	Liquid	Liquid	Liquid
Sedimentation	No	No	No	No
pH	4.7±0.1	4.8±0.1	5.0±0.1	4.6±0.1
Particle Size	10.004±0.03	9.560±0.01	11.413±0.08	901.3±0.2
Zeta Potential	-7.880±0.02	-6.640±0.03	-7.157±0.01	-
Polydispersity Index	0.175±0.01	0.145±0.005	0.195±0.01	-
Specific Gravity	1.036	1.114	1.049	-

Data of pH, particle size, zeta potential, and polydispersity index were presented as mean±SD with n = 3.

Observation of the crystalline state of particles

The results of the DSC analysis of ketoprofen pure drug and milled ketoprofen pure drug are shown in fig. 3**.** DSC is a technique commonly used to determine the state of crystals and amorphous fractions. The results showed a sharp and single endothermic peak at 90.1 ℃and 89.4 ℃, close to the melting point of ketoprofen. This peak indicates the melting of ketoprofen and the crystalline state of ketoprofen. In the ketoprofen nanosuspension, there was a difference in melting point with ketoprofen powder, namely at 104.7 ℃, which showed that there was a decrease in the crystal structure caused by the endothermic melting point, which shifts from the melting point of ketoprofen powder.

The presence of a wide peak indicates the change of ketoprofen into an amorphous form. The DSC study proved that ketoprofen experienced a reduction in crystallinity in the ketoprofen nanosuspension dosage form, which was characterized by changes in the ketoprofen particle structure based on a shift in the melting point [19].

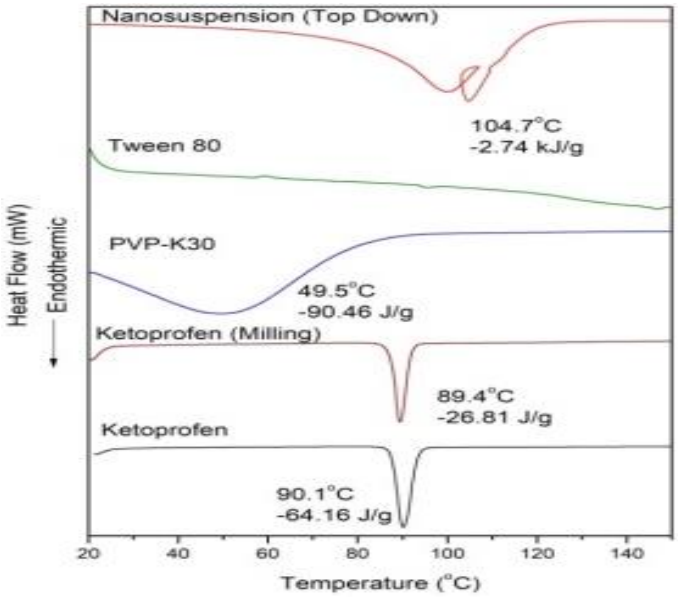

Fig. 3: Thermogram of measurement results of DSC nanosuspension, tween 80, PVP K-30, milled ketoprofen powder and pure ketoprofen powder

***In vitro* studies**

Ketoprofen assays

Based on the monograph listed in the VI edition of the Indonesian Pharmacopoeia, the requirement for ketoprofen is that it contains no less than 98.5% and no more than 101.0% of the amount of content stated on the label. From table 3, it can be seen that all formulated preparations meet the requirements, namely, they are within the specified range. The results of the ketoprofen assay were shown in table 3.

***In vitro* dissolution test**

Based on the monograph, the dissolution rate requirement for ketoprofen is the Q value, which states that the percentage of the amount of substance that is dissolved within 60 min must be no less than 80%. The results of the dissolution rate can be seen at table 3 and the result shown that all ketoprofen nanosuspension preparations meet the requirements, namely within the specified range. Meanwhile, the ketoprofen suspension does not meet the requirements because ketoprofen in suspension form has low solubility in a dissolution medium of pH 1.2 (acidic medium), and also, the particle size of the suspension affects the dissolution rate of the preparation [19]. The % cumulative of ketoprofen suspension showed a significant different compared with nanosuspension formula ($p<0.05$). The results showed that the nanosuspension increases the dissolution speed. Reducing the size of drug particles can produce a wider surface area which results in increased contact of the nanoparticles with the dissolution medium so that the dissolution rate increases (table 3) [19].

In previous studies [19], ketoprofen nanosuspension was prepared using the solvent evaporation method using PVP and Tween 80 as nanosuspension stabilizers to dissolve ketoprofen in ethanol before stabilizing it; the study indicated that the nanosuspension dosage

form had a higher rate of ketoprofen dissolution. Ketoprofen nanosuspension prepared by solvent evaporation method showed a similar value from *in vitro* dissolution test in an artificial gastric medium (pH 1.2) at 37 ℃

The kinetics of the release of active substances from preparation can be obtained using zero order, first order, Higuchi equations [19]. Determination of the kinetics of ketoprofen dissolution is carried out to find out what percentage of the drug is dissolved over time during the test by plotting the results of the ketoprofen dissolution test in graphs of time versus cumulative percent, time versus logarithm of cumulative percent, and the root of time versus cumulative percent so that a correlation value can be obtained (R^2) The data of dissolution kinetics of ketoprofen from nanosuspension preparations in gastric medium pH 1.2 were shown in table 3.

Based on the dissolution kinetics, the ketoprofen dissolution kinetics results for all preparations follow Higuchi order kinetics seen from the coefficient of determination value>0.95. According to Higuchi's equation, drugs dispersed in a water-insoluble matrix were released through a diffusion process. The release of drugs was influenced by time because it was directly proportional to the rate of time, as a result, the active substance will be released at a slower rate over time due to the longer diffusion distance [20].

Table 3: *In vitro* dissolution test

Formula	Ketoprofen assay (%)	T_{80}	% Cumulative	Coefficient of determination
F1	100.43±0.305	60th minute	83.35±0.13	0.9819
F2	100.82±0.227	60th minute	85.00±0.19	0.9748
F3	100.51±0.131	60th minute	81.09±0.28	0.9676
F Suspension	-	60th minute	7.62±0.01*	0.8930

Data were presented as mean±SD with n = 3; *Indicated a significant difference between the formulas with p value<0.05

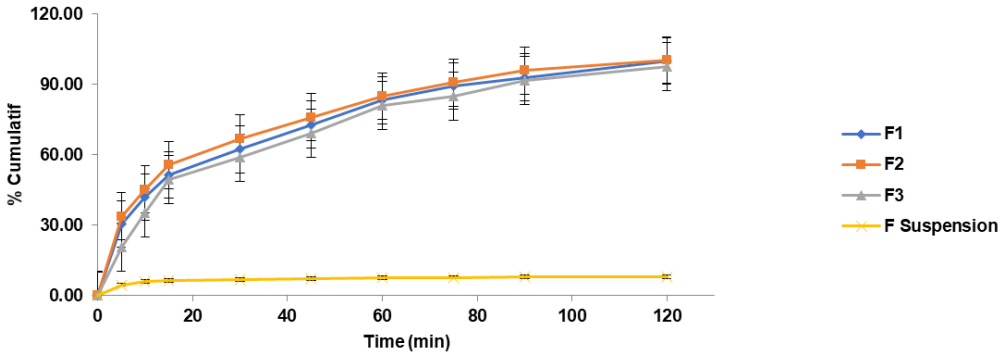

Fig. 4: Comparison of dissolution of F1, F2, F3 nanosuspension preparations with suspension in artificial stomach medium pH 1.2 (without enzymes) at 37 °C *in vitro,* (Data were presented as mean±SD, n = 3)

Stability studies

Organoleptic

The results of organoleptic evaluation were shown in table 4 and the results shown on F1 and F2 did not experience changes in color, shape, aroma, and no precipitation formed after storage for 3 mo. This shows that the ketoprofen nanosuspension preparation shows good physical stability in storage for 3 mo.

Meanwhile, in F3, it can be seen that the preparation shows instability during storage, characterized by sedimentation at the bottom of the container starting in the 6th week. This can be caused by loss of attraction between particles, HPMC has viscoelastic properties, which can affect the stability of the nanosuspension. Over time, the attraction between particles in the nanosuspension caused by the HPMC polymer can decrease, causing the particles in the nanosuspension to attract each other and form sediment [21].

The obstacle encountered in formulating nanosuspensions is their physical stability. Insoluble drug can separate from the carrier phase and settle to the bottom of the container. Sedimentation and aggregation can occur and form caking, which can be difficult to redisperse; this is a characteristic of a deflocculation system, where particles do not settle easily but are difficult to redisperse. Therefore, stabilizers are needed in the form of polymers to increase physical stability [21].

Suitable polymers are known to be important for controlling particle growth. The polymer functions as a stabilizer to prevent the release of molecules onto the particle surface and inhibit structural changes in the particle. The polymer will increase the viscosity of the solution and prevent aggregation. The affinity of the nanoparticles will determine the stability of the nanosuspension; the higher affinity between active substance and polymer will increase the stability [4].

Particle size, zeta potential, and polydispersity index

The evaluation of particle size, zeta potential, and polydispersity index at the beginning and after 3 mo of storage can be seen in table 4. After storage for 3 mo, the particle size of all nanosuspension formulations showed an increase. The increase in nanosuspension particle size during storage was caused by agglomeration and aggregation [22]. The F3 formula with HPMC showed a fairly large increase in particle size because the nanosuspension was not stable enough, so heavy particles settle to the bottom during storage to form sedimentation in the preparation.

HPMC is a non-ionic steric stabilizer which has the largest molecular weight between PVA and PVP K-30. A larger molecular weight can cause sedimentation in the preparation because the higher molecular weight can increase the viscosity of the solution. High viscosity can make it more difficult for the particles in the nanosuspension to remain homogeneously dispersed and settle more easily. Additionally, hydrogen bonds can form between ketoprofen and HPMC. HPMC is a polymer that has hydroxyl groups that can act as hydrogen bond acceptors, which can bind with ketoprofen, which has a carboxylic group (-COOH) that can act as a hydrogen bond donor. Hydrogen bond formation can cause the formation of complexes or associations between drugs and polymers. Hydrogen bond formation can affect the physicochemical properties of nanosuspensions and cause sedimentation. The complexes or associations formed can have a larger size and weight

compared to drug particles, so they tend to settle downwards due to gravitational forces and sedimentation occurs. Hydrogen bonds between ketoprofen and HPMC can also influence the stability of particle dispersion in nanosuspensions. This interaction can disrupt the dispersion forces that keep the particles apart and cause the particles to approach each other, thereby increasing the tendency for coalescence or particle clumping [17].

PVP K-30 and PVA are also steric stabilizers that can form a barrier layer or repulsion layer on the surface of the particles so that they do not come into contact with one another to avoid Ostwald's ripening, resulting in good physical stability of the dosage form [17]. Tween 80 as a non-ionic surfactant which has small particles and low molecular weight, is tasked with decreasing the interfacial stress between particles and the medium by forming a mechanical barrier which functions to prevent crystal growth and agglomeration [17]. After 3 mo, formulas F1, F2, F3 experienced a decrease in zeta potential values. This can happen because the nature of the zeta potential can be affected by the environment, for example, pH, ionic strength, and changes in the concentration of formulation components (polymer and surfactant) instead of just particle size or molecular weight [3]. This indicates that the zeta potential measurement used to measure nanosuspension stability cannot be considered absolute.

The surface charge and electrolyte concentration of the stabilizer used have a significant impact on the zeta potential value. As the value of the zeta potential increases, the repulsion between similar charged particles that are close together in the distribution will be greater, which causes the nanosuspension to be more stable because it reduces the risk of agglomeration [7]. In contrast, in F1 and F2, based on organoleptic observations, the nanosuspension was clear during three months of storage. The PI results show that F1 and F2 have good particle size distribution in a narrow range, namely<0.5, as indicated by the absence of sedimentation in the nanosuspension preparation. Meanwhile, in F3, the PI value shows a wide particle size distribution, characterized by the occurrence of sedimentation in the preparation. A small PI value indicates good homogeneity, thereby increasing the stability of the formula [23].

pH determination

The pH stability results were shown in table 4 and the results showed an insignificant decrease in pH. A decrease in pH in preparations can be caused by oxidation in the presence of oxygen from the environment and light, as well as microbial activity originating from raw materials or microbes obtained during the preparation stage [13].

Table 4: Results of stability of ketoprofen nanosuspension

Parameters	Storage time (Month)					
	F1		F2		F3	
	0	3	0	3	0	3
Appearance	Clear	Clear	Clear	Clear	Clear	Clear
Aroma	Typical	Typical	Typical	Typical	Typical	Typical
Form	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
Sedimentation	No	No	No	No	No	Yes
Particle Size (nm)	10.004±0.03	10.707±0.06	9.560±0.01	10.483±0.06	11.413±0.08	302.5±10.15
Zeta Potential (mV)	-7.880±0.02	-8.910±0.02	-6.640±0.03	-16.8±0.10	-7.157±0.01	-17.533±0.25
Polydispersity Index	0.175±0.01	0.175±0.006	0.145±0.005	0.162±0.01	0.195±0.01	0.526±0.05
pH	4.7±0.10	4.6±0.10	4.8±0.10	4.8±0.10	5.0±0.10	4.9±0.10

(Data of pH, particle size, zeta potential, and polydispersity index were presented in mean±SD, n=3)

CONCLUSION

Ketoprofen nanosuspension can be made using the milling method to produce a nanosuspension with liquid form, clear appearance, characteristic odor, and no sedimentation in the preparation. The polymer variations influence the characteristics of ketoprofen nanosuspension preparations. The ketoprofen nanosuspension with PVP K-30 and PVA showed a stable preparation, while the nanosuspension with HPMC was less stable when stored for 3 mo at room temperature. All ketoprofen nanosuspension formulas showed a faster dissolution rate compared to ketoprofen suspension.

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Nil

AUTHORS CONTRIBUTIONS

TIH: The main investigator that do the research and do the final approval for the manuscript; WF: The second investigator that helps in data collection and makes the draft of the manuscript; BEP: proofreader, supervisor.

CONFLICT OF INTERESTS

There is no conflict of interest

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