PHARMACIA

Pharmacia 70(1): 209–215
DOI 10.3897/pharmacia.70.e96593

Research Article

Physical stability and dissolution of ketoprofen nanosuspension formulation: Polyvinylpyrrolidone and Tween 80 as stabilizers

Tengku Ismanelly Hanum[1,2], Azizah Nasution[1], Sumaiyah Sumaiyah[1,2], Hakim Bangun[1,2]

1 *Faculty of Pharmacy, Universitas Sumatera Utara, Medan, 20155, Indonesia*

2 *Nanomedicine Center of Innovation, Universitas Sumatera Utara, Medan, 20155, Indonesia*

Corresponding author: Azizah Nasution (azizah@usu.ac.id)

Received 21 October 2022 ♦ **Accepted** 27 February 2023 ♦ **Published** 14 March 2023

Citation: Ismanelly Hanum T, Nasution A, Sumaiyah S, Bangun H (2023) Physical stability and dissolution of ketoprofen nanosuspension formulation: Polyvinylpyrrolidone and Tween 80 as stabilizers. Pharmacia 70(1): 209–215. https://doi.org/10.3897/pharmacia.70.e96593

Abstract

This study was conducted to improve the dissolution of ketoprofen in nanosuspensions. Ketoprofen nanosuspensions were prepared by a solvent evaporation method using polyvinylpyrrolidone (PVP) and Tween 80 as stabilizers at varied ratios with ketoprofen. Ethanol was used as a solvent for ketoprofen. Physical stability and dissolution of the produced ketoprofen nanosuspensions and conventional suspension were analyzed and compared. The parameters evaluated for their stability for a three-month period were pH, appearance, odor, color, particle size, zeta potential, polydispersity index (PI), and dissolution compared with ketoprofen suspension. Ketoprofen and PVP ratios of 1:1 and 1:1.5 had nano-scale particle sizes of 78.47±0.61 and 156.9±1.55, respectively. These nanosuspensions had stable pH, appearance, odor, color, particle size, and PI at room temperature. The dissolution rates of ketoprofen nanosuspensions were higher compared to that of ketoprofen conventional suspension. PVP and Tween 80 improved ketoprofen nanosuspension dissolution and was stable at room temperature for three months.

Keywords

dissolution, nanosuspension, ketoprofen, polyvinylpyrrolidone, Tween 80

Introduction

The pharmacological activity of a drug is determined by its bioavailability and dissolution at the absorption site. Thus, any problems associated with dissolution will decrease the required pharmacological effect. Ketoprofen is classified into non-steroidal anti-inflammatory drugs (NSAIDs) that have a mechanism of action of inhibiting cyclooxygenase (COX) and lipo-oxygenase (LOX) enzymes. Ketoprofen's therapeutic dose is 150–300 mg/day. Few problems are associated with ketoprofen. It is included in class II of the Biopharmaceutical Classification System (BCS) in which it has low solubility in water with high membrane permeability, thus only slightly absorbed in the digestive tract (Shohin et al. 2012). In addition, other problems with ketoprofen are that it has a short half-life (about 1–3 hours), a low area under the plasma concentration-time curve, and a short duration of action, consequently requiring repeated administration to maintain its therapeutic effect. Its multiple dose administration produces high plasma level fluctuations which tend

to result in adverse effects, including irritation and gastric bleeding for patients. Therefore, efforts to improve ketoprofen dissolution and reduce its particle size should be sought.

Various strategies have been suggested to improve the dissolution of drugs with low solubility, including salt formation, surfactant use, and micronization. Micronization alone is not sufficient to increase the bioavailability of insoluble drugs. Therefore, this problem is a challenge to motivate researchers to develop nano-size pharmaceutical preparations (< 1 μm) that could increase the dissolution rates of the drugs as well as their bioavailabilities (Shid et al. 2013; Yadollahi et al. 2015; Gadhari et al. 2022). Nanosuspension is a colloidal submicron dispersion of pure drug particles in a liquid phase stabilized by surfactants and polymers. Nanosuspensions can be manufactured by applying bottom-up and top-down technologies. One of the bottom-up technologies is the dissolution of water-insoluble drugs in volatile organic solvents. While top-down technology includes ball milling with high-pressure homogenization, in which particles are fragmented into submicron units (Thakkar et al. 2011).

A previous study undertaken to improve the dissolution of ketoprofen was the utilization of high-pressure homogenization techniques with variations of hydrogenated phosphatidylcholine, poloxamer 188, and sodium lauryl sulphate. This study indicated that the nanosuspension produced had a particle size of 322.7 nm and was stable for more than one month (Amin et al. 2013). Another study also indicated that ketoprofen nanosuspension could be manufactured utilizing a solvent evaporation technique with few polymers as stabilizers (PVP, HPMC, poloxamer) and surfactant (Tween 80). These stabilizers could increase the dissolution rate of ketoprofen (Wais et al. 2017). Additionally, a study argued that to enhance the solubility of ketoprofen by using DenaDM100 consisting of a soft polymeric fast rotating conical rotor sitting within a conical polymeric sleeve produced nanoparticles with a size of below 200 nm (Khan et al. 2019).

In the present study, the solvent evaporation method was chosen to prepare ketoprofen nanosuspension by a solvent evaporation technique since this technique is fast and easy to perform in a laboratory scale (Afifi et al. 2015; Ainurofiq et al. 2021).

Methods

Preparation of artificial gastric medium (pH 1.2)

Two grams of sodium chloride were added with 7 ml of concentrated hydrochloric acid and then added with distilled water to make up the final solution of 1000 mL (USP. 2019).

Preparation of ketoprofen standard stock solution and absorption curves

As much as 15 milligrams of ketoprofen were dissolved in a sufficient amount of 0.1 N HCl in a 50-ml volumetric flask. The solution was diluted with the solvent to make up the final solution of 50 ml. The concentration of this stock solution was 150 ppm (μg/ml). The standard stock solution (2.6 mL) was pipetted, then transferred into a 25-ml volumetric flask. Hydrochloric acid (0.1 N) was then added into the flask to make up the final solution volume of 25 ml. The obtained ketoprofen concentration was 32 ppm (μg/mL) and was measured using a UV spectrophotometer at a wavelength of 200–400 nm to obtain its maximum absorption wavelength, 260 nm. This wavelength was set to measure the dissolution of all samples.

Preparation of ketoprofen calibration curves

The standard stock solutions of 0.7, 1.7, 2.7, 3.7, 4.7, 5.7, 6.7, and 7.7 milliliters were withdrawn, transferred into 25-ml volumetric flasks, and added with 0.1 N HCl up to the marked lines to obtain ketoprofen with concentrations of 10, 20, 30, 40, 50, 60, 70, and 80 ppm, respectively. Each of these solutions was shaken to obtain homogeneous solutions. The absorption of each of these solutions was measured using a UV spectrophotometer at a wavelength of 260 nm.

Determination of ketoprofen saturation solubility

The saturation solubility of ketoprofen in various media was determined by using a shake flask method. An excess amount of ketoprofen was placed separately in three different closed Erlenmeyer flasks, each containing 10 mL of 0.1 N HCl (pH 1.2), demineralized water, and phosphate buffer pH 7.2, respectively. Subsequently, each flask was shaken using a shaking water bath (Stuart SBS40) at a controlled temperature of 37 °C for 24 hours until equilibrium was achieved. A visual inspection was performed to check for drug particle precipitation in the three flasks. The solutions were filtered through a membrane filter (0.45 μm), and the dissolved ketoprofen in each flask was measured spectrophotometrically at a wavelength of 260 nm. Each sample was analyzed in triplicate (Wais et al. 2017).

Preparation of conventional and nano-size ketoprofen suspensions

The composition of conventional and nano-size ketoprofen suspensions is listed in Table 1. Ketoprofen nanosuspensions were prepared by applying the solvent evaporation technique. The ketoprofen powder (400 mg), equivalent to 100 mg/5 mL, was dissolved in 2 ml of 96% ethanol at room temperature. The obtained ketoprofen solution was then dripped through a plastic syringe positioned with a needle directly into the PVP solution and Tween 80 which was later added up with distilled water to obtain a final mixture of 20 ml in each formula as shown in Table 1. Next, the temperature of each mixture was maintained at 40 °C and then stirred at 650 revolutions per minute (rpm) on a magnetic stirrer for about one hour to allow the ethanol to evaporate (Wais et al. 2017).

Table 1. Compositions of conventional and nano-size ketoprofen suspension formulas.

Formula	Ketoprofen (mg)	PVP (mg)	Tween 80 (mL)	Ethanol (mL)
1	400	–	3	2
2	400	400	3	2
3	400	600	3	2
4	400	800	3	2
5	400	200	0.1	2

The composition of the conventional suspension (Formula 5) was referred to as those used in the previous studies (Jadhav et al. 2018). PVP was dissolved in distilled water, then added with Tween 80, mixed homogeneously, and subsequently added with distilled water to obtain 20 ml of suspension.

Physical stability studies

The ketoprofen nanosuspensions were stored at room temperature for 3 months and observed organoleptically for changes in odor, color, and sedimentation. Changes in appearance, pH, particle size, zeta potential, and PI were recorded over the three months.

Particle size, PI, and zeta potential

The particle size of each formula was determined using a Dynamic Light Scattering method (HORIBA SZ-100), with a mechanism of measuring the light intensity scattered by the molecular sample as a function of time at a scattering angle of 90° and constant temperature of 25 °C without sample dilution. The sample was inserted into the sample cell (quartz cuvette) and placed into the sample holder. The particle size, PI, and zeta potential were determined using this instrument. The mean diameter and PI were measured for each formula (Wais et al. 2017).

Morphological Observations of Ketoprofen Nanosuspensions

The morphology and particle size of each of the nanosuspensions were analyzed using Transmission Electron Microscopy (TEM). In a brief, double-distilled water was used to dilute the ketoprofen nanosuspension 20 times the nanosuspension volume before dying it with 0.01% (w/v) phosphotungstic acid. A drop of dyed ketoprofen nanosuspension was placed on a Cu grid coated with carbon film and allowed to dry at room temperature. The treated nanosuspension was evaluated for morphology at TEM JEOL-1010, 80.0 KV (Eijkman Lab, Jakarta) at a magnification of 40.000× (Malkani et al. 2014).

In vitro dissolution test

The dissolution test was performed using a rotating paddle method at 37 °C ± 0.5 °C with a rotating speed of 100 rpm in 900 mL of 0.1 N HCl (pH 1.2) as a dissolution medium. A sample of each nanosuspensions (equivalent to 100 mg of ketoprofen) was just added into the dissolution medium. One milliliter of the sample was taken from the dissolution medium at intervals of 5, 10, 15, 20, 30, 40, 50, and 60 minutes, then filtered with Whatman paper. The volume of dissolution medium must always be maintained by adding 1 ml of the dissolution medium to replace the withdrawn sample. Ketoprofen concentrations in the withdrawn samples were analyzed using UV spectroscopy at a wavelength of 260 nm. The same procedure was carried out for ketoprofen suspension (Wais et al. 2017).

Statistical analysis

The dissolution data were analyzed applying a parametric technique at 95% confidence level in the program of Statistical Product and Service Solution (SPSS) version 19 with analysis of variance followed by Tukey HSD to determine if the relationship between two sets of data statistically showed significant difference.

Results and discussion

Ketoprofen saturation solubility

The results of ketoprofen saturation solubility in 10 mL of 0.1 N HCl (pH 1.2), distilled water, and phosphate buffer pH 7.2 are shown in Table 2. As shown in Table 2, the solubility of ketoprofen was higher in phosphate buffer compared to that in HCl 0.1N (pH 1.2) and distilled water.

Solubility determination of pure ketoprofen saturation at pH 1.2 and pH 7.2 was required to maintain a sink condition, i.e the media volume was at least three times larger than the volume required to form a saturated solution with the medicinal substance during the dissolution test. Based on the Biopharmaceutical Classification System (BCS), ketoprofen is classified as a Class II drug that has low water solubility and good absorption in the gastrointestinal tract due to its high permeability and lipophilicity. Ketoprofen is a weak acid that will ionize at high pH.

The result of the solubility study, as shown in Table 2, proved that rank of the ketoprofen solubility in increasing order was 0.062, 0.081, and 0.141 in HCl 0.1 N (pH 1.2), distilled water, and phosphate buffer (pH 7.2), respectively. Distilled water has a pH of 7. This finding supported a source of information in literature in which the solubility of ketoprofen increases with the increase in pH medium. However, the magnitude of ketoprofen solubility in the same dissolution media was higher as conducted in other study (Shohin et al. 2012). This difference may result from pH changes in the dissolution media during execution of the study.

Table 2. Ketoprofen saturation solubility in various media.

No	Medium	Solubility (mg/mL)
1	HCl 0.1 N (pH 1.2)	0.062
2	Distilled water	0.081
3	Phosphate buffer (pH 7.2)	0.141

Physical stability studies

Physical stability of the ketoprofen nanosuspensions for three-month storage at room temperature are shown in Fig. 1 and Table 3.

As demonstrated in Fig. 1 and Table 3, of the 4 nanosuspension formulas, it was proved that F2 and F3 nanosuspensions were stable for 3 months of storage in terms of odor and color. In addition, the present study revealed that there was no sedimentation detected for F2 and F3. These results indicated that F2 and F3 nanosuspensions were stable in storage for 3 months, while the F1 and F4 nanosuspensions changed in shape after three-month storage. Further increase in the PVP amount, as seen in F4, reduced the nanosuspension stability. The higher the concentration of the polymer, the thicker the layer on the surface of the drug particles. This condition resulted in aggregation of the nanosuspension. The use of different polymer concentrations as suspension stabilizers greatly affects the nanosuspension stability produced. Therefore, it is necessary to optimize the concentration of stabilizers in a nanosuspension system (Mansouri et al. 2011; Tehrani et al. 2019). Additionally, according to pH testing conducted, all formulas did not experience significant changes in pH, they remained in the pH range of 4.0–4.53, which was in accordance with ketoprofen's pH that is 4.6 (Shohin et al. 2012).

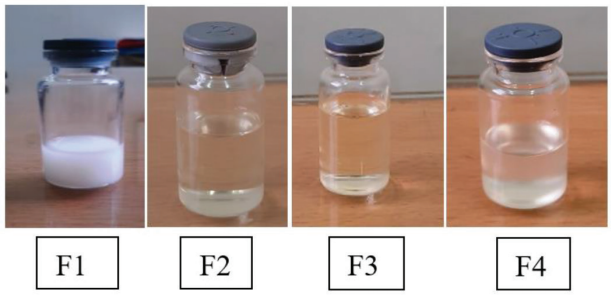

Figure 1. Physical stability of ketoprofen nanosuspensions for three-month storage.

The nanosuspensions were prepared by utilizing the solvent evaporation method (Wais et al. 2017) and using PVP and Tween 80 as nanosuspension stabilizers, and ketoprofen was previously dissolved in ethanol. PVP and Tween 80 act as non-ionic stabilizers for nanosuspensions by forming a physical barrier on the surface and preventing from contact with the adjacent particles. Non-ionic stabilizers with amphiphilic groups will provide steric stabilization (stabilization caused by adsorbed polymer layer and hydrated on particle dispersion) dominated by the wetting effect (Wang et al. 2015). The advantages of steric stabilization are not affected by changes in pH or ionic strength, etc., like in the varying conditions of the GI tract. (Kallum et al. 2015; Tuomela et al. 2016), When a non-ionic stabilizer is added to nanosuspension, it will be adsorbed by the drug particle surface through the head and strongly interact with the suspended particles, while the tail mixes well between the solvent and solution that will spread to the dispersion medium. PVP is a good

Table 3. Physical stability of the ketoprofen nanosuspensions for three-month storage.

Formula	Parameters	Length of Observation (month)			
		0	1	2	3
F1	Color	Clear yellowish	Clear yellowish	Clear yellowish	Milky white
	Odor	Specific	Specific	Specific	Specific
	Sedimentation	No	No	No	Yes
	pH	4.27 ± 0.06	4.33 ± 0.15	4.33 ± 0.06	4.50 ± 0.10
F2	Color	Clear	Clear	Clear	Clear
	Odor	Specific	Specific	Specific	Specific
	Sedimentation	No	No	No	No
	pH	4.30 ± 0.00	4.33 ± 0.15	4.33 ± 0.06	4.50 ± 0.10
F3	Color	Clear	Clear	Clear	Clear
	Odor	Specific	Specific	Specific	Specific
	Sedimentation	No	No	No	No
	pH	4.47 ± 0.06	4.50 ± 0.10	4.77 ± 0.06	4.87 ± 0.06
F4	Color	Clear	Clear	Clear	Turbid
	Odor	Specific	Specific	Specific	Specific
	Sedimentation	No	No	No	Yes
	pH	4.33 ± 0.06	4.43 ± 0.21	4.53 ± 0.38	4.00 ± 0.36
F5	Color	Milky white	Milky white	Milky white	Milky white
	Odor	Specific	Specific	Specific	Specific
	Sedimentation	No	Yes	Yes	Yes
	pH	4.60 ± 0.00	4.50 ± 0.03	–	–

stabilizer, preventing particle aggregation through repulsive forces originating from hydrophobic carbon chains that spread into the solvent and interact with each other (steric hindrance effect) (Kallum et al. 2015).

Particle size, PI, and zeta potential

The particle size and zeta potential of these nanosuspensions were compared with those of the ketoprofen conventional suspension formula. Mean particle size, PI and zeta potential in initial (0 month) and three-month storage are presented in Table 4.

This study revealed that the particle size of the entire nanosuspension formulas was still at the nanoscale size ranging from 14.33 ± 0.06 to 345.6 ± 3.13 at the initial storage. Similarly, the particle sizes of the whole formulas were still at the nanoscale after three-month storage. However, the particle size of the ketoprofen suspension was at the micro-scale (15.11 μm) at the beginning of storage. This result was due to the insufficient use of Tween 80 as a wetting agent and the low duration of the stirring process in the suspension preparation. The particle size reduction process in the manufacturing of nanosuspension dosage form will increase surface area and the surface free energy or interfacial free energy (ΔG) of the particles. Theoretically, the lower the ΔG of a system, the higher its stability. The relationship is as follows: $\Delta G = \gamma_{S/L}\ \Delta A$, where $\gamma_{S/L}$ is the interfacial tension between solid and liquid and ΔA is the increase in surface area. One of the strategies to produce a stable nanosuspension system is to lower its Δ G (Jacob et al. 2020). Therefore, the addition of stabilizers is often necessary to avoid particle agglomeration and reduce the possibility of Ostwald Ripening (Yadollahi et al. 2015).

In Ostwald ripening, small particles diffuse from higher concentrations with higher saturation solubility to the area

around larger particles with a lower drug concentration. This results in the formation of a supersaturated solution throughout the large particles, which ultimately leads to crystallization of the drug and the growth of the large particles (Shariare et al. 2018). These are the reasons why we need stabilizers in the nanosuspension formulation. Stabilizers commonly used to produce nanosuspensions include polysorbate (Tween), polyvinylpyrrolidone, poloxamer, lecithin, poly oleate, and cellulose polymers. Surfactant and polymer mixture has been found to produce long-term stable nanosuspensions (Yadollahi et al. 2015).

Tween 80 as a non-ionic surfactant and PVP as a non-ionic polymer played a significant role in the size reduction process as proved by the present study. Both of these stabilizers cause steric hindrance. One of the main mechanisms of stabilizer-induced inhibition of aggregation and agglomeration is the formation of a steric barrier around the particles. In fact, steric stabilizers reduce particle contact with the medium as well as particle attraction forces. As a result, polymer-coated drug nanoparticles have lower Brownian motions, which is another mechanism for particle attraction and aggregation inhibition. Furthermore, polymer adsorption prevents the attachment/detachment of molecules on the particle surface, inhibiting Ostwald ripening. In addition, polymers and non-ionic surfactants tend to increase solution viscosity, which acts as a barrier against aggregation (Tehrani et al. 2019).

PVP used in this study has a quite low molecular weight, thus it forms small particles faster (Tuomela, 2016). The hydrophobicity of the polymer chain is responsible for polymer adsorption on hydrophobic surfaces. On the other hand, the hydrophilic moiety of the polymer interacts with the medium. As a result, chain morphology is critical in polymer adsorption and steric stabilization. Long-swinging hydrophilic chains, in particular, appear to provide better steric stability and protection against aggregation (Tehrani et al. 2019). This study found that an increase in polymer concentration in the nanosuspension formula leads to the enlargement of the drug particle size. This finding may be due to the formation of thick layers that coated the drug particles as a consequence of adding too much polymer which subsequently led to aggregation of the drug particles (Wang et al. 2013).

Nanosuspensions will not be formed without the addition of Tween 80. Tween 80 functions as a wetting agent at low concentrations or below its critical micelle concentration (CMC) and as a solvent at concentrations above CMC, because surfactant is adsorbed to the solid-liquid interface leading to decrease in interfacial tension, increase in the nucleation rate, and lead to a decrease particle size (Mansouri et al. 2011).

A PI is a parameter used to determine particle size distribution (PSD) obtained from analyzing particle size. PSD is a critical and integral evaluation parameter for nanosuspension. By reduction of particle size into the submicron range, then drug solubility, dissolution, and bioavailability will increase. Therefore, it has become an essential quality attribute of nanodispersion. Furthermore, the particle size distribution in the formulation was evaluated as PI, which gave a degree of PSD. The PI is an important evaluation parameter that controls the physical stability of nanosuspensions and should be kept as low as possible to achieve the long-term stability of a nanosuspension (Ubgade et al. 2021). The present study indicated that the PIs of the produced ketoprofen nanosuspensions after three-month storage at room temperature were varied ranging from 0.374 ± 0.003 to 0.504 ± 0.035 depending on formulation compositions as shown in Table 4. Formula 1 had the lowest IP value (0.374 ± 0.003). The particle size uniformity was determined by the PI value, where the low value exhibited the best uniformity. A PI of a nano-dispersion between 0.1 and 0.25 indicates a narrow size distribution, while a PI of greater than 0.5 indicates a broad distribution. A narrow size distribution is suggested to avoid particle growth due to Ostwald ripening while also maintaining nanosuspension stability (Kavitha et al. 2014).

Table 4. Mean particle size, PI, and zeta potential of the nanosuspensions for three-month storage.

Formula	Mean particle size (nm)		PI		Zeta Potential (mV)	
	0 month	3 months	0 month	3 months	0 month	3 months
1	14.33 ± 0.06	19.3 ± 0.5	0.407 ± 0.009	0.374 ± 0.003	-11.2 ± 0.265	-0.97 ± 0.25
2	78.87 ± 7.92	78.47 ± 0.61	0.419 ± 0.061	0.496 ± 0.033	-5.4 ± 0.3	-1.33 ± 0.4
3	179.9 ± 4.79	156.9 ± 1.55	0.438 ± 0.032	0.446 ± 0.031	-8.2 ± 0.2	-1.1 ± 0.21
4	345.6 ± 3.13	223.17 ± 1.11	0.312 ± 0.053	0.504 ± 0.035	-2.2 ± 0	-1.13 ± 0.32
5	15,110	–	–	–	–	–

As shown in Table 4, the present study revealed that the zeta potential values of the entire formulas were in the range of -11.2 ± 0.265 to -0.97 ± 0.25. The zeta potential value was calculated by determining the particles' electrophoretic mobility and converting it into zeta potential. The zeta potential is the value of the electrostatic potential on the imaginary slipping plane (also termed the surface of hydrodynamic shear), which is the surface where particles interact with one another or with other surfaces. As shown in Table 4, the present study revealed that the zeta potential value of F1 was the highest, however, it had the lowest zeta potential after storage for three months. F4 had the lowest zeta potential out of all formulas. This study proved that the zeta potential values of all formulas after three-month storage were near zero. Theoretically, if the zeta potential value of a dispersion system achieves a value near zero, it becomes unstable and shows agglomeration. In contrast, F2 and F3, based on organoleptic observation, showed clear nanosuspension during three-month storage. The zeta potential property is not only affected by particle size or molecular weight but also influenced by its environment, e.g., pH, ionic strength, changes in the concentration of a formulation component (e.g polymer, surfactant), coating, and the presence of organic matter (Lowry, 2016). The present study indicated that the media had low pHs ranging from 4.00 to 4.87. These low pHs lead to the aggregation of PVP-coated particles. A Previous study found that surfactant choice and the physical stability of nanosuspensions were affected by pH. This

study proved that a low pH of the media promoted aggregation of the nanosuspensions (Donoso et al. 2012). Relying on the nature of PVP, it could decrease the zeta potential by pushing the shear plane outward, thereby decreasing the overall magnitude of the zeta potential even though the particles are more stable against aggregation. Consequently while interpreting the zeta potential, researchers must also think about the effect of adsorbed polymer (Louie, 2015). This indicates that the zeta potential measurement for nanosuspension stability is not an absolute measure.

Morphological observations of ketoprofen nanosuspension

Fig. 2 shows that the nanosuspension particles are spherical and amorphous with a particle size of 100 nm, following the determination of particle size with the particle size analyzer or a dynamic light scattering method. PVP and Tween 80 used as stabilizers cause no crystal growth so they can maintain the stability of the nanosuspension in long-term storage.

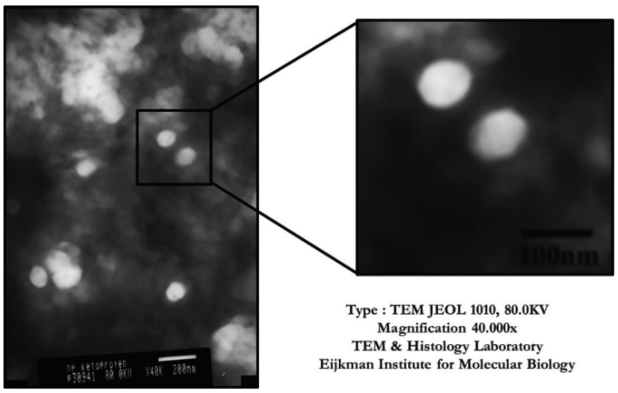

Figure 2. Transmission electron microscopy of ketoprofen nanosuspension.

In vitro dissolution test

A comparison of in vitro dissolution among nanosuspension dosage forms (F2, F3, and F4) and F suspension in the artificial gastric medium (pH 1.2) at 37°C is shown in Table 5.

Fig. 3 exhibited that ketoprofen dissolution was higher in the nanosuspension dosage form. Rank of the amount of ketoprofen dissolved in decreasing order was: nanosuspension of F2 > F3 > F4 > F5. This finding was caused by the increase in the particle size and polymer concentration which could affect the dissolution rates of the nanosuspensions (Shid et al. 2013). The high concentration of stabilizers in the formulation is most likely due to the formation of micelles that solubilizes the drug, resulting in Ostwald ripening and further destabilizing nanosuspensions (Shariare et al. 2018). While the cumulative percentage of ketoprofen suspension at the 60th minute was only 5.39%, this finding caused ketoprofen to have a low dissolution in the dissolution medium of pH 1.2 (acid medium).

Table 5. In vitro dissolution test nanosuspension dosage form and ketoprofen suspension.

Formula	Cumulative % (in the 60th minute)
2	82.47 ± 0.04
3	81.18 ± 0.09
4	80.09 ± 0.01
5	5.39 ± 0.34*

Data were presented as mean ± SD with n=3; * indicated a significant difference between the formulas.

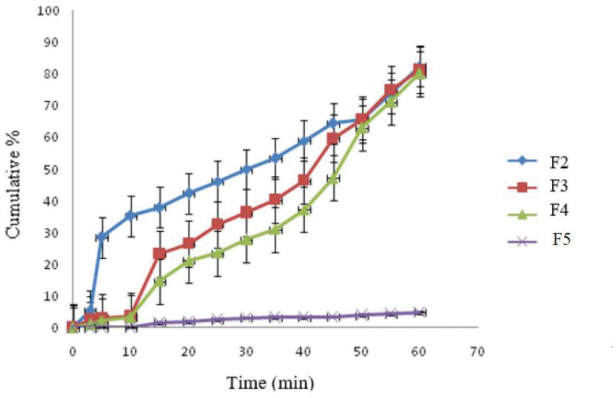

Figure 3. Comparison of in vitro dissolution between nanosuspension dosage forms (F2, F3, and F4) and F5 in artificial gastric medium (pH 1.2) at 37 °C.

Similarly, the ketoprofen suspension had a larger particle size compared to the three nanosuspension formulas. The drug particle size reduction leads to an increase in surface area, and consequently, increased nanoparticle contact with the dissolution medium. The results obtained were coordinated with the Noyes–Whitney equation:

$$\frac{dc}{dt} = \frac{D \cdot A}{h}(Cs - Cx) \quad (1)$$

Based on equation 1, the particle dissolution velocity (dc/dt) was inversely proportional to the diffusion distance (h) and was directly proportional to the particle surface area (A) and the saturation solubility (Cs). Therefore, the increase in saturation solubility and decrease in particle size could lead to an increase in the dissolution rate (Tehrani et al. 2019).

Conclusion

The present study confirmed that ketoprofen nanosuspension with PVP and Tween 80 as stabilizers was stable for three-month storage at room temperature and had a higher dissolution rate compared to that of ketoprofen suspension.

Acknowledgments

This research was supported by TALENTA University of Sumatera Utara year 2020 with contract no. 48/UN5.2.3.1/PPM/SPP-TALENTA USU/2020.

References

Afifi SA, Hassan MA, Abdelhameed AS, Elkhodairy KA (2015) Nanosuspension: An emerging trend for bioavailability enhancement of etodolac. International Journal of Polymer Science 2015: 938594. https://doi.org/10.1155/2015/938594

Ainurofiq A, Putro DS, Ramadhani DA, Putra GM, do Espirito Santo LDC (2021) A review on solubility enhancement methods for poorly water-soluble drugs. Journal of Reports in Pharmaceutical Sciences 10(1): 137–147. https://doi.org/10.4103/jrptps.JRPTPS_134_19

Amin MA, Osman SK, Aly UF (2013) Preparation and characterization of Ketoprofen nanosuspension for solubility and dissolution velocity enhancement. International Journal of Pharma and Bio Sciences 4(1): 768–780.

Chaurasia T, Singh D, Nimisha Srivastava DA (2012) Review on nanosuspensions promising drug delivery strategy. Current Pharma Research 3(1): 764–776. https://doi.org/10.33786/JCPR.2012.v03i01.010

Donoso MD, Haskell RJ, Schartman RR (2012) Surfactant choice and the physical stability of nanosuspensions as a function of pH. International Journal of Pharmaceutics 439(1–2): 1–7. https://doi.org/10.1016/j.ijpharm.2012.09.012

Gadhari AR, Tidke VN, Pawar RG (2022) Nano-suspension a tool for enhancing bioavailability: A systematic review. International journal of advanced research in science, communication and technology. IJARSCT 2(2): 1–14. https://doi.org/10.48175/568

Jacob S, Nair AB, Shah J (2020) Emerging role of nanosuspensions in drug delivery systems. Biomaterials Research 24: 1–16. https://doi.org/10.1186/s40824-020-0184-8

Jadhav AB, Gawandar PR, Vitore G (2018) Formulation and evaluation of amoxicillin nanosuspension. International Journal of Universal Print 4(4): 212–215.

Koczkur KM, Mourdikoudis S, Polavarapu L, Skrabalak SE (2015) Polyvinylpyrrolidone (PVP) in nanoparticle synthesis. Dalton transactions (Cambridge, England: 2003) 44(41): 17883–17905. https://doi.org/10.1039/C5DT02964C

Kavitha VB, Neethu CS, Dineshkumar B, Krishnakumar K, John A (2014) Nanoscience and nanotechnology: An international journal ISSN: 2278-1374. Review Article Nanosuspension Formulation: An Improved Drug Delivery System 4(1): 1–5.

Khan J, Bashir S, Asif Khan M, Ghaffar R, Naz A, Khan W, Ahmad S, Ullah A, Liaqat Ali F, Isreb M (2019) Enhanced dissolution rate of Ketoprofen by fabricating into smart nanocrystals. Pakistan Journal of Pharmaceutical Sciences 32(6Supplementary): 2899–2904.

Louie SM, Spielman-Sun E, Small MJ, Tilton RD, Lowry GV (2015) Correlation of the physicochemical properties of natural organic matter samples from different sources to their effects on gold nanoparticle aggregation in monovalent electrolyte. Environmental Science & Technology 49(4): 2188–2198. https://doi.org/10.1021/es505003d

Lowry GV, Hill RJ, Harper SL, Rawle AF, Hendren CO, Klaessig FC, Nobbmann U, Sayre P, Rumble JR (2016) Guidance to improve the scientific value of zeta-potential measurements in nanoEHS Environmental Science: Nano 3: 953–965. https://doi.org/10.1039/C6EN00136J

Malkani A, Date AA, Hegde D (2014) Celecoxib nanosuspension: Single-step fabrication using a modified nanoprecipitation method and in vivo evaluation. Drug Delivery and Translational Research 4(4): 365–376. https://doi.org/10.1007/s13346-014-0201-3

Mansouri M, Hamid R, Vida V (2011) Preparation and characterization of ibuprofen nanoparticles by using solvent/antisolvent precipitation. The Open Conference Proceedings Journal 2: 88–89. https://doi.org/10.2174/2210289201102010088

Shariare MH, Sharmin S, Jahan I, Reza HM, Mohsin K (2018) The Impact of Process Parameters on Carrier Free Paracetamol Nanosuspension Prepared Using Different Stabilizers by Antisolvent Precipitation Method. Journal of Drug Delivery Science and Technology 43: 122–128. https://doi.org/10.1016/j.jddst.2017.10.001

Shid RL, Dhole SN, Kulkarni N, Shid SL (2013) Nanosuspension: A Review. International Journal of Pharmaceutical Sciences Review and Research 22(1): 98–106.

Shohin IE, Kulinich JI, Ramenskaya GV, Abrahamsson B, Kopp S, Langguth P, Dressman JB (2012) Biowaiver monographs for immediate-release solid oral dosage forms: Ketoprofen. Journal of Pharmaceutical Sciences 101(10): 3593–3603. https://doi.org/10.1002/jps.23233

Tehrani AA, Omranpoor MM, Vatanara A, Seyedabadi M (2019) Formation of nanosuspensions in bottom-up approach: theories and optimization. DARU Journal of Pharmaceutical Sciences 27: 451–473. https://doi.org/10.1007/S40199-018-00235-2

Thakkar H, Thakkar S, Patel B (2011) Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. Journal of Pharmacy and Bioallied Sciences 3(3): 426. https://doi.org/10.4103/0975-7406.84459

Tuomela A, Hirvonen J, Leena P (2016) Stabilizing agents for drug nanocrystals: Effect on bioavailability. Pharmaceutics 8: 16. https://doi.org/10.3390/pharmaceutics

The United States Pharmacopeia 42 The National Formulary 37 (2019) Vol. 1, The United States Pharmacopeial Convention 12601. Twinbrook Parkway, Rockville, Md 20852.

Ubgade S, Bapat A, Kilor V (2021) Effect of various stabilizers on the stability of lansoprazole nanosuspension prepared using high shear homogenization: Preliminary investigation. Journal of Applied Pharmaceutical Science 11(9): 085–092. https://doi.org/10.7324/JAPS.2021.110910

Wais FMH, Abood AN, Abbas HK (2017) Preparation and evaluation of ketoprofen nanosuspension using solvent evaporation technique. Iraqi Journal of Pharmaceutical Science 26(2): 41–55. https://doi.org/10.31351/vol26iss2pp41-55

Wang Y, Zheng Y, Zhang L, Wang Q, Zhang D (2013) Stability of nanosuspensions in drug delivery. Journal of Controlled Release 172(3): 1126–1141. https://doi.org/10.1016/j.jconrel.2013.08.006

Yadollahi R, Vasilev K, Simovic S (2015) Nanosuspension technologies for delivery of poorly soluble drugs. Journal of Nanomaterials 2015: 216375. http://doi.org/10.1155/2015/216375