Research Article
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Nanosuspension Formula of *Curcuma xanthorriza* Rhizome Dry Extract: Impact of Tween 80-PEG 400 Ratio

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Keywords: Curcuma xanthorrhiza, Nanosuspension, Factorial design, Tween-80, PEG-400.

Abstract: Our previous research investigated nanosuspension using the ionic gelation method with a 2:1 ratio of chitosan to sodium tripolyphosphate (TPP) and 0.44% *Curcuma xanthorriza* rhizome extract. The results indicated an unstable nanosuspension with a particle size of 399.3 nm, a polydispersity index of 0.60, and an entrapment efficiency of 73.37%. This study aims to develop a nanosuspension using Tween 80-PEG 400 to improve the characteristics and dissolution at pH 6.8. Curcuma rhizome was macerated with 96% ethanol and dried using a spray dryer. The nanosuspension formulation was designed using a 2^2 factorial design with Tween 80 (0.1%-0.4%) and PEG 400 (0.1%-0.4%) as factors, and the formulation was analyzed using Minitab 18. The dissolution of the optimum formulation was tested. The best formulation, comprising 0.1% Tween 80 and 0.4% PEG 400, provided a spherical shape, a particle size of 111.26 nm, a polydispersity index of 0.27, a zeta potential of 30.77 mV, an entrapment efficiency of 84.30%, and a desirability value of 0.9058. The release of curcumin at pH 6.8 after 180 minutes was 37.85% ± 0.1375 with a DE180 of 83.60% ± 0.1457. The 2^2 factorial design proved effective for enhancing formulation attributes. Based on the result obtained, it can be concluded that the best formulation contains 0.1% Tween 80 and 0.4% PEG 400, with zero-order release kinetics and a diffusion mechanism.

Introduction

In Indonesia, Curcuma xanthorrhiza rhizome is among the Indonesian traditional medicinal plants (namely "*Jamu*") for treatment based on natural ingredients (1) locally famed as "*Temulawak*", which are used for type 2 diabetes mellitus therapy, antibacterial, anti-cancer, and other diseases (2). One of its main components is curcuminoid, it has relatively low solubility, absorption capacity, and bioavailability in the body. Therefore, there is a need to formulate a curcuma rhizome dry extract into nanosuspension by ionic gelation method to increase its solubility and bioavailability (3).

In our unpublished preliminary research, a nanosuspension formulated using a concentration of 0.44% curcuma rhizome dry extract and a ratio of chitosan:TPP (2:1). The characterization results include a spherical shape, a particle size of 114.7-399.3 nm, a polydispersity index of 0.43-0.60, a zeta potential of 35.1-48.6 mV, and entrapment efficiency of 61.08-73.37%. When stored at room temperature for the fifth day, it showed precipitation on the fifth day. Hence, it is necessary to improve its stability and character by adding Tween-80 and PEG-400 as surfactants and cosurfactants, respectively (4). Combining Tween 80 and PEG 400 as stabilizers has produced good nanosuspensions with approximately 77.90% entrapment efficiency. The characterization results include particle size ranges from 114.7 to 399.3 nm, a zeta potential of 35.1 to 48.6 mV, a polydispersity index of 0.43 to 0.6, entrapment efficiency of 61.08 to 73.37%, and spherical shape are among the characteristics reported in the characterization results. It began to show precipitation on the fifth day after being kept at room temperature for five days. As a result, Tween-80 and PEG-400 must be added as surfactants and cosurfactants, respectively, to increase their stability and character

(4). Using Tween 80 and PEG 400 as stabilizers has been demonstrated to produce good nanosuspensions with an entrapment effectiveness of roughly 77.90%. This is because Tween 80 coats the surface of the particles to prevent aggregation between particles, while PEG 400 reduces the inter-phase surface tension. The results then showed that PEG 400 is a cosurfactant that increases the entrapment efficiency in nanoparticle formulations.

This study utilized a 2^2 factorial design to investigate the optimal formulation for a stable nanosuspension with improved characteristics. The factors examined were Tween 80 (at 0.1%-0.4%) and PEG 400 (0.1%-0.4%). The nanosuspension was characterized using Transmission Electron Microscopy (TEM) and Particle Size Analyzer (PSA) to assess nanoparticle morphology, particle size, polydispersity index, zeta potential, entrapment efficiency, and preliminary physical stability over five days at room temperature. Data analysis was conducted using the Minitab 18 response optimizer to determine the optimal formula. To assess the release of curcumin, the nanosuspension from the optimal formula was subjected to spray drying, followed by a dissolution test under pH 6.8 conditions. Dissolution Efficiency (DE), kinetic modeling, and analysis of the release mechanism from the nanoparticle matrix were performed (5).

Materials and Method

Materials and Tools

In this research, the materials used were curcuma rhizome, 96% ethanol, curcuminoid (Merck), maltodextrin, chitosan (Sarchem Laboratories), sodium tripolyphosphate (Arrow Fines Chem.), tween 80 (Avantor), PEG 400 (DOW Chemical Company), glacial acetic acid (Merck), methanol, potassium dihydrogen phosphate, and NaOH. The morphology of the nanosuspension was carried out using transmission electron microscopy (JEOL TEM Type). The particle size, polydispersity index, and zeta potential were determined using a Particle Size Analyzer. At the same time, the entrapment efficiency of curcumin in nanosuspension was analyzed using a UV-Vis spectrophotometer (Shimadzu UV-1900). Furthermore, the nanoparticle powder was dissolved using a type 2 device (Erweka type DT 60).

Methods of Extraction and Drying

Curcuma rhizome dry powder was initially macerated four times with 96% ethanol to ensure thorough extraction of the active compounds. The resulting filtrate was then concentrated using a rotary evaporator to remove excess ethanol and concentrate the extract. Subsequently, maltodextrin was added, and dried by spray drying at an inlet temperature of 160°C and an optimum outlet of 80°C to obtain a dry extract (6).

Preparation of Curcuma Extract Nanosuspension

A 0.2% chitosan solution in 1% glacial acetic acid with 0.44% dry extract of Curcuma rhizome was added and stirred with a 300 rpm magnetic stirrer for 10 minutes. The solution was poured gradually into a mixture of Tween 80 (0.1% - 0.4%) and PEG 400 (0.1% - 0.4%) and stirred with a magnetic stirrer for 30 minutes. Subsequently, approximately 0.1% sodium tripolyphosphate was added with a ratio of 2:1 chitosan and sodium tripolyphosphate at a speed of 1 drop/3 s through a burette and stirred with a 300 rpm magnetic stirrer for 1 h to form a homogeneous nanosuspension. The four nanosuspension formulas were placed in each test tube, stored at room temperature (25°C) for five days, and observed for color, shape, odor, and precipitate (7). The formula can be seen in Table 1.

Table 1. The nanosuspension formula of Curcuma nanosuspension dry extract with 2^2 factorial design.

Ingredient	Concentration (%)			
	F1	F2	F3	F4
Curcuma Dry Extract	0.44%	0.44%	0.44%	0.44%
Chitosan	0.2%	0.2%	0.2%	0.2%
Na-TPP	0.1%	0.1%	0.1%	0.1%
Tween 80	0.1%	0.4%	0.1%	0.4%
PEG 400	0.1%	0.1%	0.4%	0.4%

Nanoparticle Morphological Examination

The nanosuspension liquid sample was diluted in a ratio of 1:10, and the solution was dried by dripping it into the Cu Substrated Grid and 2% uranyl acetate solution. The nanoparticle morphological examination used a Transmission Electron Microscope (TEM JEOL 1010) (8).

The distribution and particle size examination was determined using a Particle Size Analyzer (PSA) with Dynamic Light Scattering (DLS, Malvern) technique. A total of 2 drops of the nanosuspension sample were diluted with 20 mL of distilled water to produce the appropriate scattering intensity. Meanwhile, the DLS's average diameter and polydispersity index were used to measure the size distribution of nanoparticles. Subsequently, the diameter and polydispersity index of the sample were examined from the mean of three angle measurements at 173° in a 10 mm polystyrene plastic cell at 25°C (9). Zeta potential was characterized using a zeta sizer (Malvern type 1203893) to determine the electric charge parameters of nanosuspension. A sample volume was put in a cuvette containing electrodes, and two drops of nanosuspension were added to the 20 mL of distilled water.

Entrapment Efficiency

The nanosuspension sample was centrifuged at 14,000 rpm for 45 min, after which the residue was separated from the supernatant. Subsequently, the supernatant was homogenized using a vortex for 1 min, and the absorption was measured with a spectrophotometer at a wavelength of 429 nm. The obtained uptake was used to calculate the concentration of unabsorbed curcumin using the linear regression equation of the standard curcumin calibration curve. The entrapment efficiency was calculated using Equation 1 (10).

$$\%Entrapment = \frac{C_t - C_b}{C_t} \times 100\% \quad \textbf{Equation 1}$$

with Ct = Total curcumin in nanosuspension, and Cb = Concentration of unabsorbed curcumin.

Dissolution Test

The dissolution medium (900 ml of phosphate buffer at pH 6.8) was used with a type 1 dissolution device at a temperature of 37±0.5°C. Subsequently, a total of ±500 mg of dry powder nanosuspension was weighed, put in a basket, and rotated with a stirring speed of 100 rpm for 180 min, while 10 mL aliquots were taken at 10, 15, 30, 45, 60, 90, 120, 150, and 180 min, this method refers to Zhang (2022) with slight modification. When the aliquots were taken, the volume was replaced with a new solution of the same volume and temperature. Meanwhile, each aliquot was filtered, and the absorption of curcumin was determined using a UV-Vis spectrophotometer at 429 nm. The percentage dissolution value was used to calculate the Dissolution Efficiency (DE). Since DE180 was the percentage ratio of the area under the dissolution curve to the rectangular area of 100% curcumin dissolved in the medium at 180 min, it was expressed by DE (11) The value of DE180, as stated by Zhang et al. (2022), was the percentage ratio of the area under the dissolution curve to the rectangular area of 100% curcumin dissolved in the medium at 180 min.

Factorial Design

The nanosuspension formula optimization was analyzed using the response optimizer, namely Minitab 18. Meanwhile, the factors utilized were tween 80 at 0.1%–0.4% and PEG 400 at 0.1%–0.4%. The responses measured were polydispersity index, particle size, zeta potential, and entrapment efficiency. In the response optimizer, the polydispersity index and particle size were set at minimum conditions, while the entrapment efficiency and zeta potential were set at maximum conditions.

Result and Discussion

Physical and Morphological Observation

Based on the organoleptic examination results, the nanosuspension was viscous liquid, transparent yellow, had a characteristic aromatic odor, and was free of precipitate. After five days of storage at room temperature, it remained stable with no organoleptic changes observed (Figure 1).

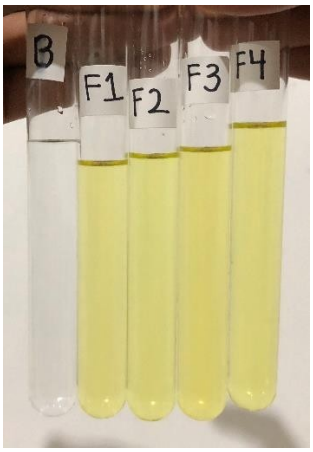

Figure 1. Nanosuspension of curcuma rhizome dry extract on day 5th.

Morphology examination of nanoparticles using TEM. The principle of the TEM is that the specimen will be fired using a beam of high-energy electrons, which illuminates the specimen and produces an image on the phosphor screen. Based on the morphology observation of the nanosuspension at 80.0 KV with a magnification of 30,000x, the morphology obtained is perfectly spherical with a flat surface and a particle size of ±200 nm (Figure 2). The spherical surface penetrates the cell more easily because surface morphology affects the nanoparticles' capability to pass through the target cell membrane.

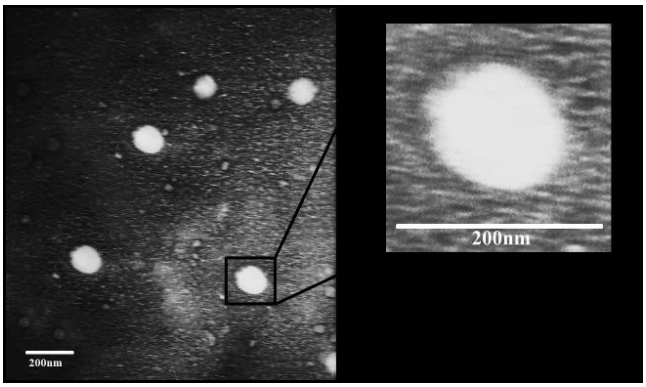

Figure 2. Morphology of Curcuma rhizome dry extract nanoparticles using TEM.

Particle Size

The measurement of particle size gave a value between 97.86 and 276.1 nm. Since the decrease in particle size causes an increase in the surface area of the active substance, it is easy to dissolve, thereby increasing the dissolution rate, absorption power, and bioavailability (12). The measurement of the particle size of curcuma rhizome dry extract nanoparticles is shown in Table 2.

Table 2. Significance of the effects of Tween 80, PEG 400, and their interaction.

Factor and interaction	P-value (95% confidence level)			
	PS	PDI	ZP	EE
Tween-80	0.024	0.073	0.000	0.000
PEG-400	0.055	0.145	0.000	0.000
Tween-80* PEG-400	0.099	0.565	0.001	0.000

Note: PS = particle size, ZP = zeta potential, PDI = polydispersity index, EE = entrapment efficiency.

The tween 80 factors had a significant effect (p<0.05) on the particle size (see Figure 3). Moreover, Tween 80 is a surfactant that covers the particles' surface to prevent aggregation. Based on the Tween 80 factor effect analysis, particle size increased due to high concentration, causing further adsorption of free Tween 80 on the particle surface. This can form a thin layer that gives a larger nanosuspension particle size (13).

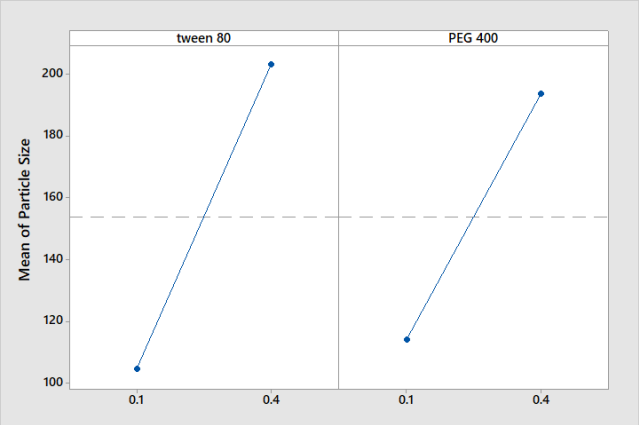

Figure 3. Effect of Tween 80 and PEG-400 on nanosuspension particle size.

In this research, the nanoparticle formulation with tween 80 and PEG 400 produced particle size within the 97.86-276.1 nm range. This is smaller than the 114.7-399.3 nm obtained in the previous research without addition. Meanwhile, particle size reduction to 100 nm occurs because the addition of Tween 80 and PEG 400 can form an optimal nanosuspension system. Furthermore, the hydroxyl group in Tween 80 synergistically bonds to the hydroxyl group on PEG 400, forming a hydrogen bond, making it easier for PEG 400 to be placed between Tween 80. Therefore, it can form a repulsion between particles, prevent aggregation, and make the particle size smaller (14).

Polydispersity Index

A range of 0.27-0.51 was obtained by measuring the F1-F4 PDI (see Table 3). A value near 0.00 suggests that the particle size of a dispersion system is more uniform. Furthermore, the PDI of each formula shows that the particles formed are uniformly dispersed. This indicates that the more uniform the particle size, the more stable the nanosuspension (15).

Table 3. Characterization of curcuma nanosuspension.

Formula	Particle size (nm)	Polydispersity Index	Zeta Potential (mV)	Entrapment efficiency (%)
F1	97	0.418	-31.50	74.35
F2	130	0514	-28.90	82.21
F3	111	0.272	-30.70	84.30
F4	276	0.447	-23.40	78.74

The polydispersity index is not significantly impacted by factors or their interactions (see Table 2). A higher polydispersity index resulted from an increase in the tween 80 concentration, whereas a lower index was observed when the PEG 400 concentration increased. Since an increase in the Tween 80 concentration causes a less uniform surface layer of particles, the distribution is less homogeneous. Therefore, PEG 400 fills the space between the surfactants, makes the particles more compact, and prevents aggregation (13, 14).

Zeta Potential

The measurement of zeta potential value from the four formulas produced a range of 23.4-31.5 mV (Table 3). Based on their electrostatic interactions, the nanoparticles' zeta potential was utilized to characterize the surface charge characteristics of the particles. Nanoparticles with a high value of more than ±30 mV possibly provide good stability because they prevent particle aggregation due to high repulsion forces. Meanwhile, a low zeta value probably causes the attractive force between particles to be greater and leads to aggregation between particles (16). It was reported that chitosan nanoparticles with small particle size can increase the zeta potential value (17). The nanoparticles with high zeta potential (more than ±30 mV) have greater repulsive forces, providing stability and preventing particle aggregation. Both factors and their interactions on the zeta potential response were significant (p<0.05). Based on the factor interaction graph, at 0.4% concentration of PEG-400, an increase in the Tween-80 concentration produced an average decrease in the zeta potential, more significant than the PEG-400 concentration of 0.1% (Figure 4A). This occurred because Tween-80 and PEG-400, used for formulation, are nonionic surfactants with no charge on their hydrophobic groups. Therefore, the surface of the particles coated by Tween-80 and PEG-400 is uncharged, as shown by their low zeta potential. At Tween-80 and PEG-400 concentrations of 0.4%, a low zeta potential of 23.4 mV was produced. Meanwhile, at concentrations of 0.1% Tween 80 and 0.1% PEG 400, the highest zeta potential of the four formulas was 31.5 mV. Lower amounts of Tween 80 and PEG 400 in the formulation result in higher zeta potential (18-20).

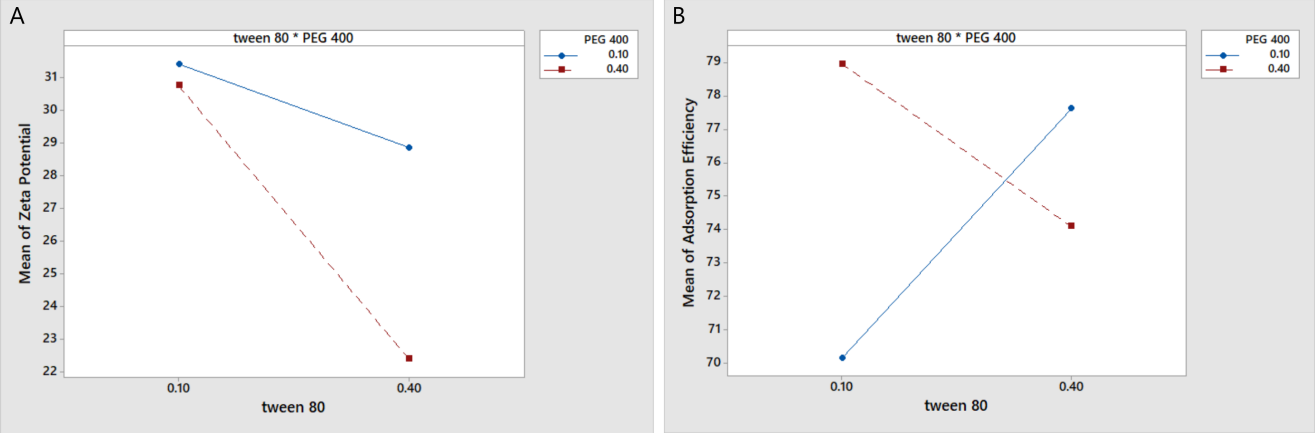

Figure 4. Effect of Tween 80 and PEG-400 on nanosuspension zeta potential (A) and entrapment efficiency (B).

Entrapment Efficiency

The amount of drug absorbed in the nanoparticles is known as the entrapment efficiency, and for each of the four formulas, its value gets within 74.35-84.30% (Table 3). Thanks to its high entrapment efficiency, an effective nanoparticle system can deliver enough medication to the target cells.

The high entrapment efficiency is advantageous because it transports enough drugs to the target cells. Meanwhile, the two factors and their interactions significantly affected the entrapment efficiency ($p<0.05$). Based on the factor interaction graph, at a PEG 400 concentration of 0.1%, an increase in the tween 80 concentration gave an average increase in entrapment efficiency higher than the 0.4% PEG 400 concentration (Figure 4B). This occurred because high zeta potential is produced at a PEG 400 concentration of 0.1%, as shown by the zeta potential factor interaction analysis. High zeta potential produces repulsion between particles; therefore, it prevents aggregation. Furthermore, the small particle size increases the contact area of the curcumin surface with the crosslinking matrix, which makes it absorb more curcumin.

In this research, the nanoparticle formulation with the addition of Tween-80 and PEG-400 produced entrapment efficiency within 74.35%-84.30%, which is greater than the 63.51% obtained in previous research This increase occurred because the use of Tween-80 and PEG-400 work synergistically for stabilization purposes. Tween-80 is a surfactant that coats the surface of the particles and is assisted by a PEG-400 cosurfactant, which fills the space between surfactants. Therefore, the coatings Tween-80 and PEG-400 applied to the particle surface can inhibit the disintegration of the nanoparticle structure (13, 14).

Formula Optimization

The optimum formula of Curcuma rhizome dry extract nanosuspension has the composition of the extract concentration of 0.44%, chitosan-TPP of 2:1, Tween 80 of 0.1%, PEG 400 of 0.4% with a particle size of 111.25 nm, polydispersity index of 0.27, potential zeta of 30.77 mV, entrapment efficiency of 84.30%, and desirability value of 0.91 (Figure 5). The desirability value reflects the range of factor values to the response that shows the degree of the accuracy of the optimal results. Meanwhile, its values ranged from 0 to 1.0, where a value closer to 1 indicates the more optimum formula (21).

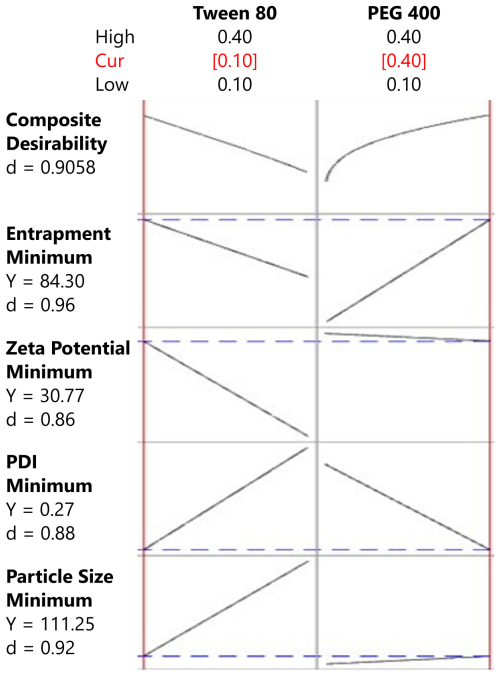

Figure 5. Optimization results for nanosuspension formula using a response optimizer.

Dissolution of Nanosuspension Dry Powder

The dissolution test's parameter, called DE (Dissolution Efficiency), is defined as the ratio of the area under the dissolution velocity curve to the area that, when combined, describes 100% of the drug dissolved in the medium. Meanwhile, the test results of curcuminoid

release from the dry powder of curcuma rhizome extract nanosuspension and Dissolution Efficiency (DE) are shown in Figure 6.

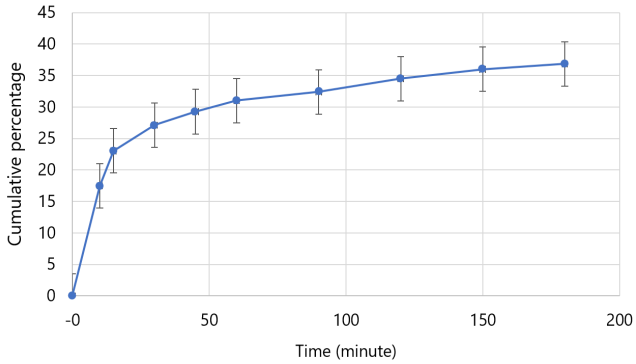

Figure 6. Cumulative percentage of dissolved curcumin released from nanosuspension dry powder in PBS medium at pH 6.8 for 180 min.

There was a diffusion of curcumin to the release medium through the chitosan nanoparticle matrix, and all curcumin was released constantly for an extended period. Drug release from the chitosan polymer matrix is strongly influenced by polymer concentration; the higher the viscosity of the surrounding medium becomes, the thicker the release becomes prolonged. Diffusion is a mechanism for the permeation of curcumin from the polymer matrix to the surrounding medium. However, the polymer chain becomes a barrier to diffusion that limits the release of curcumin. Furthermore, swelling is the process by which the dissolution medium enters the polymer matrix, causing the polymer chains to tangle and releasing curcumin slowly. The slow and constant release of curcumin is also influenced by the pH of the phosphate buffer medium at pH 6.8. Chitosan nanoparticles are stable at pH 6.8 because the ionic bond between chitosan and TPP is resistant to neutral pH and weak bases. Since the ionic bond between chitosan and TPP is easily broken or detached at pH 1.2, the release of curcumin from nanoparticles is not controlled. In this research, the parameter used to express the dissolution result is dissolution efficiency (DE), and the average DE180 obtained was 83.60% ± 0.1457. Moreover, the curcumin was gradually released from the matrix with a stable and relatively constant release (14).

Kinetics and Mechanism of Curcumin Release

The data from the curcuminoid release test from 3 replications were entered into the drug release kinetics model such as zero-order, one-order, Higuchi and Korsmeyer-Peppas (22), as shown in Table 4. Based on Table 4, the curcumin released from the nanoparticles in the 10th to 15th minutes produced an average of 17.46% and 23.04%. Meanwhile, it ended with a relatively slow and more constant release of curcuminoids from the 30th to 180th minutes of 27.13% to 36.85%. Furthermore, in phosphate buffer media at pH 6.8, the average release of curcumin was 36.85% for 3 hours.

Table 4. Kinetic model of the curcuminoid release.

Release Kinetic Model	Equation	(R2)	Exponential (n)
Zero-order	Qt = 22.481 + 0.0934.t	R2 = 0.8004	-
One order	Ln(Qt) = Ln(1.3504) +0.0014.t	R2 = 0.7082	-
Higuchi	Qt =1.6590.t1/2	R2 = 0.9049	-
Korsmeyer-Peppas	Qt = 11.6348.e0.2299.t	R2 = 0.9347	n = 0.2299

The results from the calculations using the Korsmeyer-Peppas equation gave an n value = 0.2299 (< 0.45). This indicated that the curcumin release mechanism follows Fick's diffusion law, with the release kinetics based on the zero-order (23).

Conclusion

The optimum formula composition obtained consisted of a Curcuma dry extract of 0.44%, a Chitosan-TPP ratio of 2:1, Tween-80 at 0.1%, and PEG-400 at 0.4%. The nanoparticles had a spherical shape with a particle size ranging from 97.86 to 276.1 nm, a polydispersity index between 0.272 and 0.514, a zeta potential of 23.4 to 31.5 mV, and an entrapment efficiency of 74.35% to 84.30%. Furthermore, the nanoparticles released 83.60% ± 0.1457 of curcumin in phosphate buffer media at pH 6.8, exhibiting zero-order release kinetics and a diffusion mechanism.

Declarations

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Conflict of Interest

The authors declare no conflicting interest.

Data Availability

The unpublished data is available upon request to the corresponding author.

Ethics Statement

Not applicable.

Funding Information

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