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Diffusion rate of quercetin from chitosan-TPP nanoparticles dispersion of onion (*Allium cepa* L.) ethanol extract in medium phosphate buffer pH 7.4

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ABSTRACT

Onion extract contains quercetin, which has anti-inflammatory properties. The absorption of quercetin in the extract can be improved by using the ionic gelation method to composition the extract into a nanoparticle system. Chitosan is a polymer that is used to make nanoparticles that impact medicinal drug absorption. Although many studies of nanoparticle coatings with chitosan have been performed, the effect of the chitosan concentration used remains an intriguing research issue, especially as a natural compound carrier. The goal of this study was to examine how varying chitosan polymer concentrations affected the rate of quercetin diffusion from onion (*Allium cepa* L.) ethanol extract nanoparticles. With 0.1% tripolyphosphate (TPP) as a crosslinker, the concentrations of chitosan used were 0.1% (F1), 0.2% (F2), 0.3% (F3), and 0.4% (F4). Organoleptic test, particle size measurement, zeta potential, polydisperse index, entrapment efficiency, density, and determination of quercetin diffusion rate using a phosphate buffer medium pH 7.4 were all used to analyze each composition. Transparent yellow nanoparticles with particle sizes ranging from 199.89 nm to 514.97 nm, a zeta potential of 47.73 mV to 51.36 mV, a polydispersity index of 0.57, an entrapment efficiency of 54.78 % to 59.06 %, and a density of 1.012 g/mL to 1.042 g/mL are the result of this system. In each composition, the rate of diffusion follows the Higuchi reaction kinetics. Increased chitosan concentration decreases the diffusion rate of onion ethanol extract nanoparticles (*Allium cepa* L). The fastest diffusion rate value with requirements-meeting physical properties was obtained in nanoparticle systems containing a 0.1 % chitosan solution.

Keywords: nanoparticles, chitosan, ionic gelation, diffusion rate onion (*Allium cepa* L.)

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INTRODUCTION

Onion have an anti-inflammatory effects (Nasri et al., 2012). At a dose of 300 mg/kgBW, onion ethanol extract exhibits anti-inflammatory actions when taken orally (Syafaat, 2015). Onion extract's anti-inflammatory activities are attributable to the presence of quercetin components in the extract. Oral administration of 150 mg/kgBW of quercetin can be effective as an anti-inflammatory in experimental animals (Hussain et al., 2014). Quercetin is classified as a class 2 biopharmaceutical in the Biopharmaceutical Classification System (BCS). BCS class 2 compounds have a high permeability but are less soluble in water (Madaan et al., 2016). By incorporating onion extract into a nanoparticle technology system, this lack of solubility in water can be resolved. According to earlier research, incorporating quercetin into a nanoparticle system can improve quercetin penetration when used topically (Tan et al., 2011).

Nanoparticles are drug delivery devices that can improve the solubility of insoluble active chemicals, the absorption of natural medicinal ingredients, and the stability of a pharmacological molecule (Saryanti et al., 2020). The ionic gelation method, which involves a cross-linking process between polyelectrolytes in the presence of multivalent ion pairs, is one of the nanoparticle production methods. Chitosan and tripolyphosphate are one of the polymer couples that can be utilized for ionic gelation (Iswandana et al., 2013). Chitosan is a biocompatible, biodegradable, mucoadhesive, and nontoxic polymer that can be used in drug delivery nanoparticles (Del Prado-Audelo et al., 2020). Tripolyphosphate (TPP) is the most popular polyanion crosslinker because it is multivalent. The crosslinker technique protects the active chemicals enclosed in chitosan nanoparticles from any harm. The crosslinking method of nanoparticle production creates a more stable nanoparticle system with lower particle sizes than the deprotonation method of nanoparticle formation (Ribeiro et al., 2020).

In a previous study, it was discovered that the chitosan concentration in the nanoparticle system was 0.2%, with a TPP concentration of 0.1% and a chitosan TPP volume ratio of 5:1, resulting in nanoparticles measuring less than 10 nm, which were fairly consistent and stable (Mardliyati et al., 2012). Another study discovered that using chitosan concentrations of 0.025%, 0.05%, and 1% in the nanoparticle composition with doxorubicin and PGV-1 resulted in nanoparticles with a release rate that followed the Higuchi kinetic model and order 0 (Sukmawati et al., 2017). Because the active ingredient model employed in previous studies was still synthetic active ingredients, more study on the creation of nanoparticle systems as drug delivery systems derived from natural components is required. The goal of this research was to determine how increasing chitosan concentrations affected quercetin diffusion rate in ethanol onion extract nanoparticle prepared using ionic gelation method.

MATERIALS AND METHOD

Materials

A magnetic stirrer (MS-H-Pro), pH meter (Lamonte), Transmission Electron Microscopy (TEM), particle size analyzer and zeta sizer (DELSA MAX), UV-Vis spectrophotometer, centrifugation (EPPENDRORF), vortex (VM-300), and modified Diffusion Cell were among the tools utilized in this work. Onion extract (Purchased from PT. Lansida Herba Teknologi Yogyakarta), standard quercetin (Sigma Aldrich), chitosan (CHIMULTIGUNA), sodium tripolyphosphate, aquadest, standard quercetin (SIGMA-ALDRICH), and a 0.22 µm Millipore cellulose membrane (MF-Millipore ^{TM}) all required materials.

Methods

Onion ethanol extract preparation

Lansida Herba Teknologi Yogyakarta provided the onion (*Allium cepa* L) extract, which was used in this study. Maceration with ethanol solvents was used to produce the extract. After that, a rotary evaporator was used to condense the extract it becomes viscous.

Onion extract phytochemical screening

The condensed extract was weighed up to 0.5 g, and 5 ml of ethanol was added before stirring and filtering. Two drops of concentrated HCl and 200 mg of magnesium metal were added to 1 ml of filtrate. The presence of a discoloration ranging from red orange to red purple suggests the presence of flavonoid compounds in the extract (DITJEN POM, 2020).

An investigation of onion extract's characteristics (Kemenkes RI, 2017)

An examination of the organoleptic system

The form, smell, color, and taste of onion extract were all examined organoleptically.

Water content determination

A spherical volumetric flask was filled with several properly weighed extracts that were expected to contain 2 ml-4 mL of water. The setup was set up after the flask was filled with 200 mL of toluene. Toluene was injected into the receiving tube via a chiller. The flask was heated for 15 minutes. When the toluene starts to boil, it was distilled at a rate of roughly 2 drops per second until all of the water has been distilled, at which point it was increased to 4 drops per second. For another 5 minutes, the distillation process was continued. The cooling receiver tube was then allowed to cool down until it reaches room temperature. After the water and toluene had completely separated, the volume of water was measured. The amount of water in a sample was given as a percentage.

Calculation of yield

The extract yield was determined by dividing the amount of condensed extract obtained by the amount of simplicia powder before extraction and multiplying by 100.

The quantification of quercetin compounds in onion extract

Quercetin standard stock solution preparation

A total of 10.00 mg of quercetin was weighed and placed in a 10 mL volumetric flask, where it was dissolved with ethanol to 1000 ppm.

Maximum wavelength and calibration curve determination

At wavelengths of 400-800 nm, a UV-Vis Spectrophotometer was used to determine the maximum wavelength of quercetin standard solution. Color reagent consisting of 1.5 mL ethanol, 0.1 mL 10 % $AlCl_3$, 0.1 mL sodium acetate 1 M, and 2.8 mL distilled water was added to a total of 0.5 ml of standard solution quercetin. Following that, the absorbance of the solution was determined. After determining the maximum wavelength, a series of quercetin solutions with concentrations of 22, 32, 44, 55, and 65 ppm were used to create calibration curves. A color reagent was added to each solution. The absorbance of each solution was measured at the quercetin's maximal wavelength.

Onion ethanol extract quercetin content determination

A total of 100,00 mg of onion extract (*Allium cepa* L) was weighed and dissolved in ethanol in a 100 mL volumetric flask to obtain a solution concentration of 1000 ppm, following which 10 mL was taken and diluted with ethanol in a 100 mL volumetric flask to obtain a test solution concentration of 100 ppm. A color reagent was added to the test solution at 0.5 mL. The absorbance of the test solution at the maximum wavelength of quercetin. Three times the measurements were taken. (Januarti et al., 2020).

Nanoparticles of onion ethanol extract

A total of 200 mg, 400 mg, 600 mg, and 800 mg of chitosan were dissolved in acetic acid (0,1%) to form a 200 ml chitosan solution with concentrations of 0.1 %, 0.2 %, 0.3 %, and 0.4 %. Onion extract (300,00 mg) was dissolved in each of the chitosan solutions (M_1), yielding solutions with the codes F1,

F2, F3, and F4 showed in Table 1. Sodium tripolyphosphate solution (40 mL) was prepared in different containers by soaking 40.00 mg sodium tripolyphosphate with aqua demineralization to get a solution with a concentration of 0.1 % (M_2). The M_2 solution was then added to the M_1 solution and stirred at 1000 rpm at room temperature (25ºC) for 15 minutes to create nanoparticles dispersion (Iswandana et al., 2013; Mardliyati et al., 2012).

Table 1. Composition of a nanoparticle

Components	Composition			
	F1	F2	F3	F4
Onion extract	300 mg	300 mg	300 mg	300 mg
0.1 % chitosan solution	200 mL	-	-	-
0.2 % chitosan solution	-	200 mL	-	-
0.3 % chitosan solution	-	-	200 mL	-
0.4 % chitosan solution	-	-	-	200 mL
0.1 % sodium tripolyphosphate solution	40 mL	40 mL	40 mL	40 mL

*The Chitosan:TPP volume ratio is 5:1

Physical properties of onion extract nanoparticles dispersion

Organoleptic evaluation, particle size testing, zeta potential, density, morphological tests using TEM, and calculating the % efficiency of quercetin entrapment in onion extract nanoparticles were all part of the evaluation of nanoparticle preparations.

Particle size distribution and zeta potential determination

Nanoparticle dispersion was diluted with aquadest at 25ºC at a ratio of 1/100 (v/v) to determine particle size, zeta potential, and polydispersity index. A particle size analyzer and a zeta sizer were utilized in the three measurements (Amalia et al., 2021).

Entrapment efficiency of quercetin in onion ethanol extract nanoparticles dispersion expressed as a percentage of total entrapment

A total of 1.5 mL of nanoparticle dispersion was centrifuged for 30 minutes at 10000 rpm, resulting in two layers. The crushed material was collected and mixed with 10 mL of ethanol before being spun in a vortex to form two layers. The crush was collected and measured at the quercetin's maximum wavelength. The amounts of quercetin in the sample were estimated using the quercetin in ethanol solvents linear regression equation. The percentage of quercetin trapped in nanoparticle dispersion was calculated using the results gained in the equation 1 (Shahab et al., 2020; Taurina et al., 2017):

$$\text{Entrapment efficiency (\%)} = \frac{\text{quercetin in precipitate}}{\text{quercetin in 1,5 ml nanoparticle dispersion (theoretical)}} \text{x}100 \quad (1)$$

Density

Density was measured with pycnometers. Clean and dry the pycnometer before calibrating it by weighing the empty pycnometer (Wo) and the water placed into it (W1). Nanoparticle dispersion was then injected and weighed into a drained pycnometer (W2). The formula for calculating density was presented in equation 2 (DITJEN POM, 2014).

$$\text{Density} = \frac{W2-Wo}{W1-Wo} \quad (2)$$

Study of diffusion

The maximum wavelength of quercetin in buffer phosphate pH 7.4 (medium for diffusion studies) was first determined, then a quercetin calibration curve was created. In vitro diffusion testing was performed utilizing a modified diffusion cell. A donor compartment, a receptor compartment, a 0.22 µm Millipore cellulose membrane, a peristaltic pump, and a stirrer make up the diffusion cell. Before being flattened on the membrane, each nanoparticle dispersion composition (F1, F2, F3, and F4) was weighed at 1.00 g. The receptor fluid was a 330 ml pH phosphate buffer with a pH of 7.4 and a temperature of 37^{o}C. Diffusion tests lasted 5 hours, and the receptor fluid was taken as much as 10.0 ml at minutes 5, 10, 15, 30, 45, 60, 80, 100, 120, 150, 180, 210, 240, and 300. In each sampling, add a 10.0 mL 7.4 pH phosphate buffer to extend the diffusion medium volume at 330 ml. Color reagent was added to samples taken from the receptor fluid, and the sample absorbance was measured at the maximum wavelength of quercetin in a pH phosphate buffer of 7.4. The obtained absorbance value was then integrated into the linear regression equation, yielding quercetin amounts that are diffused into the receptor compartment. The rate of diffusion of quercetin from the dispersion of onion extract nanoparticles was determined subsequently. The rate of quercetin diffusion was obtained by plotting the amount of quercetin diffused against time (kinetics of order 0), the logarithm value of the number of quercetin diffused against time (kinetics of order 1), the amount of quercetin against the heritage of time (Higuchi kinetics model), and the logarithmic value of the amount of quercetin diffused to the logarithm value of time (Korsmeyer-Peppas kinetic model) The kinetic rate of diffusion was determined using the correlation coefficient (r) value that is closest to 1 (Amalia et al., 2021; Amalia et al., 2021; Januarti et al., 2020).

Data Analysis

To identify the significant difference between each composition, the results on the diffusion rate constant for the ethanol extract of onion (*Allium cepa* L) were analyzed using one-way ANOVA (One Way ANOVA). Tukey's test a follow-up to the ANOVA test, which used to determine the significant of differences between compositions.

RESULT AND DISCUSSION

Onion extract characteristics and quality

Lansida Herbal Teknologi Yogyakarta was in charge of the onion extract analysis. The simplicia utilized was the onion type *Alium cepa* L. from the Alliaceae family, according to the results of the determination. The simplicia extraction resulted in a thick blackish brown extract with a distinct odor. The toluene distillation method was used to determine the water content of the onion extract, which came out to 5.46%. Because the standardization of extract water content in general is less than 10%, these results meet the standards (Kemenkes RI, 2017). The yield of onion ethanol extract was 9.0669%, according to the calculations. The material's characteristics are an important phase in the composition process since it ensures that the material used has the properties specified in the monograph, preventing counterfeiting of the material obtained.

Onion extract phytochemical screening

The results of this screening were limited to looking for flavonoid compounds in onion extract, which would be utilized as a standard, especially quercetin (a flavonoid group). The color of the extract changes to orange after using the reagent, showing the presence of flavonoid molecules. The results of this screening are confirmed once again by quantifying the quantities of quercetin in the extract.

Quantification of quercetin in onion extract

The total colorimetric method was used to determine total quercetin levels, which involved adding $AlCl_3$ to the sample, which can form a complex and cause a shift in wavelength towards visible light, as indicated by a yellow solution, and then adding sodium acetate to keep the wavelength in the visible region (Januarti et al., 2020). This analysis used quercetin as a marker, with a concentration of 50 g/mL,

a wavelength of 436 nm, and an absorbance of 0.4902. The linear regression equation for the quercetin calibration curve is y = 0.0093 + 0.0314x, where y is the absorbance value of quercetin in the extract and x is the concentration of quercetin in the extract. This linear regression equation was then used to calculate the quercetin concentration of the onion extract. The concentration of quercetin, according to the estimates, was 0.1731 ± 0.00%.

Evaluation of onion extract nanoparticle dispersion

Organoleptic

On the organoleptic aspect, onion extract nanoparticles F1–F4 have a bright yellow color, a distinct odor, and are in the form of a liquid.

Polydispersity index and particle size

The particle size distribution of a sample can be determined by evaluating particle size determination. A zetasizer was used to determine the particle size distribution of the four compositions. Each composition has particle sizes of 199.87 ± 26.68 nm (F1), 239.87 ± 45.82 nm (F2), 347.40 ± 41.85 nm (F3), and 514.97 ± 44.40 nm (F4), according to the test results. Figure 1 shows the results of determining the particle size values. Particles with a diameter of less than 300 nm are ideal for use in medication delivery systems (Gredi et al., 2017). The particle size of the four compositions can be categorized as nanoparticles, with particle sizes ranging from 10 to 1000 nanometers. The results indicates that higher the chitosan concentration employed, the larger the particle size of the nanoparticle system produced, and each formula has a significant difference ($p < 0.05$). Because the amount of chitosan employed exceeds the amount of extract, a leading chitosan that has not been connected with the active ingredient binds back to the bound active component, causing the particle size to increase. (Napsah & Wahyuningsih, 2014).

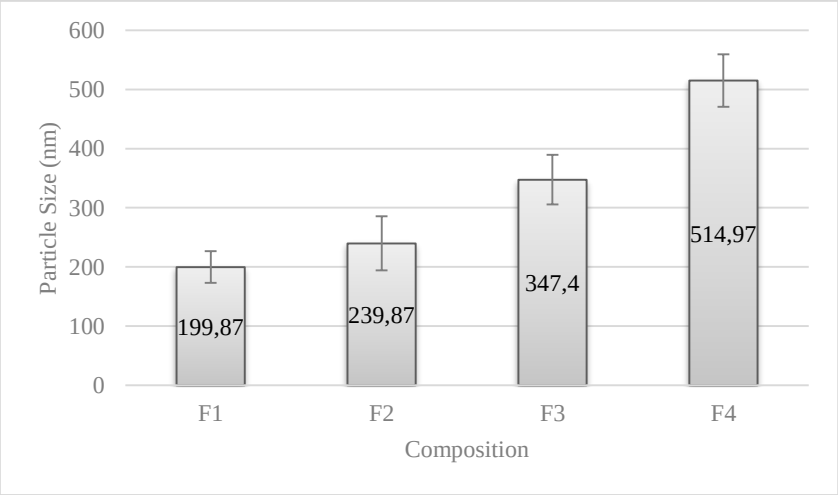

Figure 1. Onion extract nanoparticle particle size

The polydispersity index (PI) is a tool for determining the range of particle sizes in a sample. Monodispersed is indicated by a PI value less than 0.150, while polydispersity is indicated by a PI value more than 0.3000. A PI value of 0.571 ± 0.00 indicated that the system generated was included in the polydispersity system, based on the evaluation of the polydispersity index performed on each composition (Anonim, 2013).

Zeta Potential

The zeta potential test measures the nanoparticles' stability. The repulsion between the particles is affected by the charge between them. The higher the repulsive force, the less likely the particles will interact and form aggregates. The zeta potential of stable nanoparticles is greater than 30 mV (Flareyanti et al., 2017). Figure 2 shows the zeta potential value in each composition. Each composition has a zeta potential of 47.73 ± 1.88 mV (F1), 51.73 ± 6.56 mV (F2), 49.51 ± 2.68 mV (F3), and 48.80 ± 1.45 mV (F4), respectively. Because the outer layer of the nanoparticle system is chitosan, which has a lot of positive charges, the test findings demonstrate that the zeta potential value of nanoparticles has a positive charge (Sarwono, 2010). Because the nanoparticles generated have a zeta potential greater than 30 mV, the results demonstrate that they are stable. The higher the zeta potential value, the more stable the colloidal nanoparticles formed (Amalia, et al., 2021).

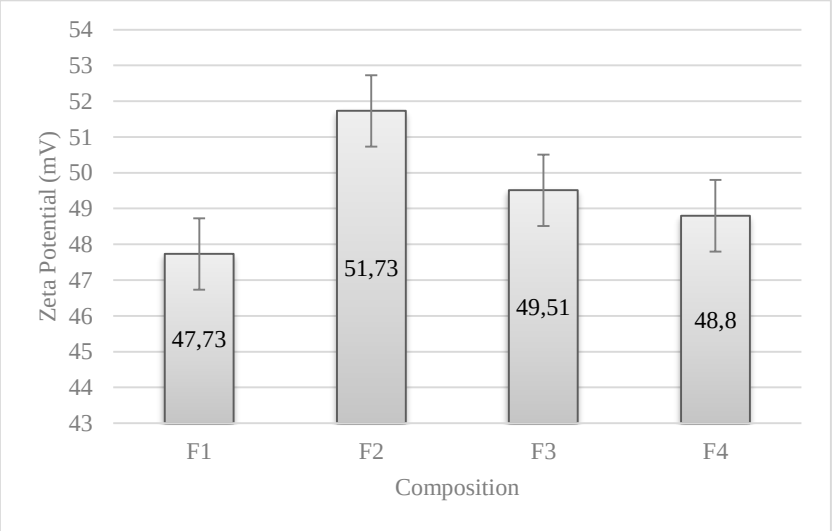

Figure 2. Onion extract nanoparticles zeta potential measurement

Quercetin entrapment's effectiveness

The entrapment efficiency is a measurement of how many active compounds are trapped in the nanoparticle dispersion. Quercetin entrapment effectiveness in onion extract nanoparticles is 59.062 ± 0.11 % (F1), 55.620 ± 0.40 % (F2), 54.780 ± 0.43 % (F3), and 55.640 ± 0.22 % (F4). According to statistical analysis, the value of % efficiency of entrapment between formulations significantly differences ($p < 0.05$). The difference in entrapment efficiency between compositions is attributable to the different concentrations of chitosan utilized in each composition. Composition 1 has the highest entrapment efficiency, followed by compositions 2, 3, and 4. This is because chitosan forms a thin layer on the surface of nanoparticles at low concentrations, and the carboxyl groups in chitosan are able to bond strongly with drug materials and tripolyphosphate, trapping more active chemicals. High chitosan and tripolyphosphate concentrations form a viscous liquid that can obstruct the encapsulation process (Iswandana et al., 2013; Shi & Berkland, 2006).

Density

The density of a substance is defined as the mass-to-volume ratio of the substance to water. Based on the findings of density measurements, it can be determined that the higher the concentration of chitosan added, the higher the density of the preparation. This is because the higher the chitosan content, the more solid mass is supplied to the nanoparticle system, resulting in the highest density value for F4 onion extract nanoparticles dispersion (Sinko, 2006).

Transmission electron microscopy morphological test (TEM)

The morphology of nanoparticles was examined using transmission electron microscopy. Figure 3 shows the results of morphological tests on nanoparticles with the smallest particle size (F1). Onion extract is seen trapped inside the particles, which are roughly spherical but have a less smooth surface. The parameters of the nanoparticle manufacturing process, such as the stirring speed and the amount of anionic chemicals, determine the shape and surface of the resultant particle (Efiana et al., 2013).

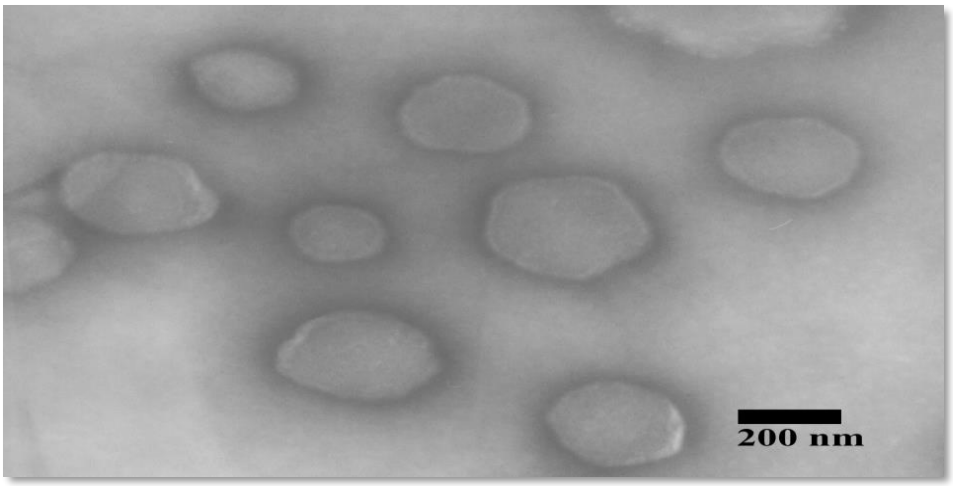

Figure 3. Onion extract nanoparticle morphology (Composition 1)

Study of diffusion rate

On onion extract nanoparticle dispersion, a diffusion test was done to investigate how increasing the concentration of chitosan affected the rate of quercetin diffusion over the membrane.

The amount of total flavonoid, measured as quercetin, that diffused was evaluated after an 8-hour test. Figure 4 presents the results of the nanoparticle dispersion diffusion test. In comparison to other formulas, the percentage of quercetin diffused in F1 has the highest value. This could be because the particle size in F1 is the smallest, making quercetin diffusion easiest (Sinko, 2010).

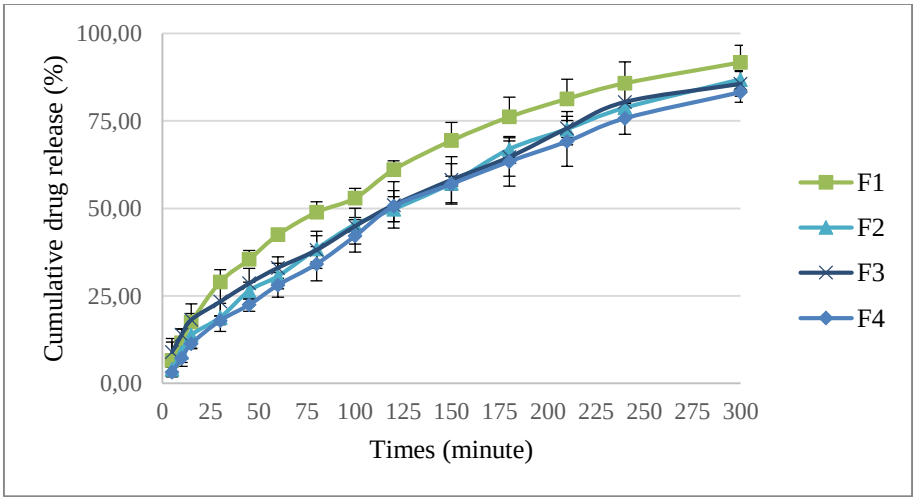

Figure 4. Diffused cumulative amount of quercetin

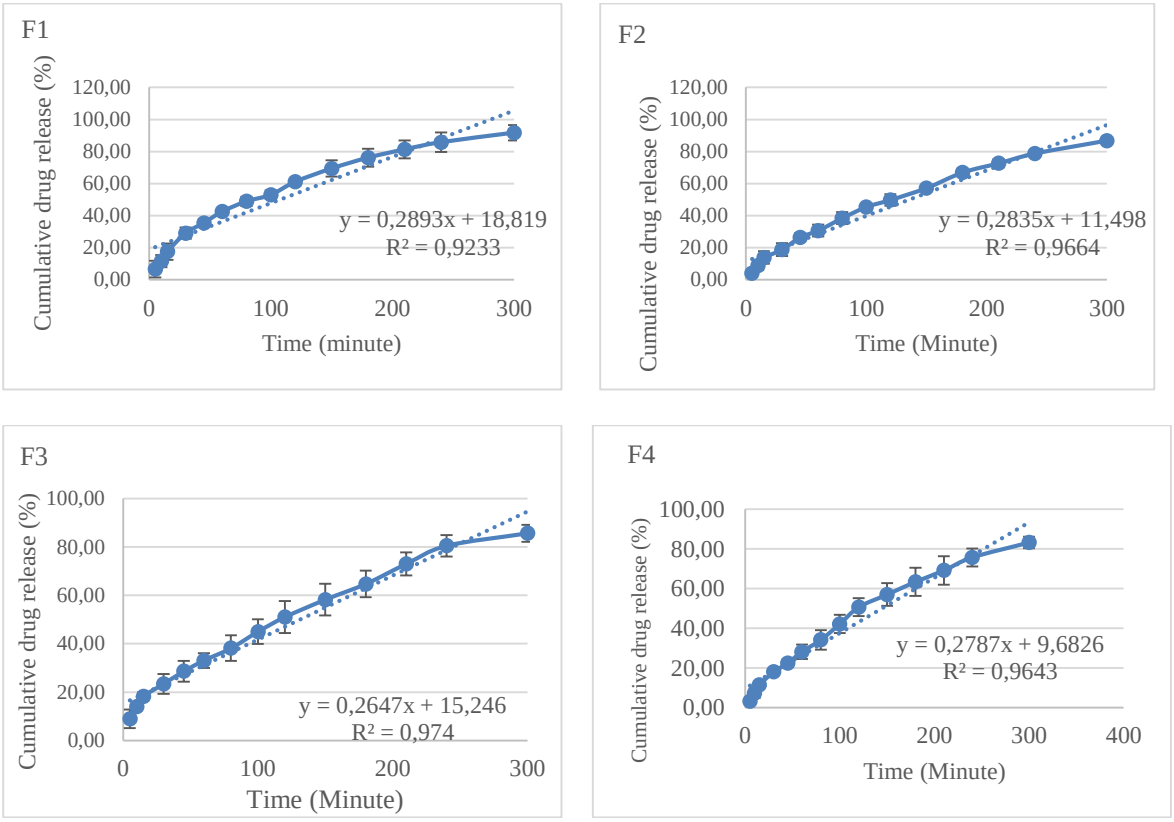

Figure 5. Zero order kinetic release of quercetin

The % value of quercetin diffusion is then explored in the zero order, first order, Higuchi model, and Korsmeyer-Peppas model kinetic equations. Figure 5 shows an analysis of the kinetic rate of release that follows the zero order. Based to the results, quercetin diffusion rates in compositions 1, 2, and 4 follow the Higuchi model's kinetics, while composition 3 follows the Korsmeyer-Peppas model's kinetics, as shown in Table 2. Because the amount of drug in the carrier is greater than the amount of drug in the diffusion medium, quercetin can diffuse from a high concentration to a low concentration after the diffusion medium penetrates the membrane and dissolves the drug, the drug can be released according to Higuchi's kinetics. While the drug's release follows the Korsmeyer-Peppas model's kinetics, the mechanism of release is determined by the value of n (exponent of Peppas diffusion). The Fickian diffusion mechanism, erosion/dissolution mechanism, or diffusion-erosion mechanism are all used to release drugs from dosage forms. A value of n larger than 0.45 indicates drug release via the Fickian diffusion mechanism, but a value of $0.45 < n < 0.89$ indicates a non-Fickian mechanism, i.e., a discharge mechanism including the diffusion and erosion processes. The value n = 0.89 also indicates that the drug's release mechanism in the dosage form is similar to zero-order kinetics, while a n value higher than 0.89 indicates a non-Fickian release profile, and a n value approaching 0.5 indicates a Fickian diffusion release profile (Gouda et al., 2017; Mohamed & Damodharan, 2020).

Each composition's quercetin release rate is 5.8560 %/minute (F1), 5.6130 %/minute (F2), 1.3353 %/minute (F3), and 5.1890 %/minute (F4), with F3's quercetin release mechanism being a non-Fickian mechanism due to the value n = 0.6303. Following that, a one-way ANOVA analysis was performed on the diffusion rate data. The results of this analysis revealed that the value of sig 0.05 indicated a significant difference. On the basis of these results, F1 appears to be the formula with the highest rate of quercetin release. The size of the particles has an impact on this; the smaller the particle size, the easier it is for the quercetin to release and diffuse (Amalia et al., 2021; Sinko, 2010). Furthermore, an increase

in the concentration of polymers in nanoparticle dispersion might cause the viscosity of the dispersion to increase, inhibiting quercetin release. Because one of the factors that might affect the diffusion of quercetin compounds is the gradient of concentration, the amount of quercetin entrapped in dispersion can also affect the rate of drug release (Sinko, 2010). The quercetin diffuses more rapidly when the gradient concentration was higher. In comparison to other formulas, F1 has the highest entrapment efficiency value. Based on these results, the gradient concentration of F1 is higher than that of other formulations, implying that quercetin released from the dispersion of onion extract nanoparticles will diffuse more efficiently and rapidly.

Table 2. Onion extract nanoparticles release kinetics

Diffusion rate kinetics	Parameter	Composition			
		F1	F2	F3	F4
Zero-order	r^2	0.9233	0.9664	0.9740	0.9643
	Slope (k)	0.2893	0.2835	0.2647	0.2787
First-order	r^2	0.6924	0.7296	0.8186	0.9643
	Slope (k)	0.7296	0.0083	0.0067	0.2787
Higuchi	r^2	0.9945	0.9961	0.9911	0.9942
	Slope (k)	5.8560	5.6130	5.2060	5.1890
Korsmeyer-Peppas	r^2	0.9847	0.9883	0.9945	0.9890
	ln intercept (k)	1.0702	0.4972	1.3353	0.1847
	Slope (n)	0.6303	0,7125	0.5440	0.7652

CONCLUSION

According to the results, increasing the chitosan concentration decreases the rate of quercetin diffusion from onion (*Allium cepa* L) ethanol extract nanoparticles dispersion. The release kinetics of quercetin in the F1, F2, and F4 compositions follow Higuchi's kinetic model, while the release kinetics of quercetin in the F3 formula follow the Korsmeyer-Peppas model.

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