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Research Article

Microencapsulation of Paracetamol with Polycaprolacone Coating

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ABSTRACT

Paracetamol is widely used as a medicine for fever and pain. Paracetamol has a normal half-life in the blood of 2 hours. If paracetamol is consumed frequently it will cause stomach irritation. This research aims to cover the unpleasant taste of paracetamol by microencapsulating using a coating and changing the release of paracetamol microcapsules. In this study, the coating material used was polycaprolactone because polycaprolactone is a biodegradable coating material. The amount of coating used in this study was 1.5g, 3g and 4.5g. Paracetamol microencapsulation was carried out in evaluation tests, namely organoleptic examination and particle size. Then a characterization test was carried out, namely the surface morphology test of the paracetamol microencapsulation using the Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR) method and the dissolution test. The research results showed that the concentration obtained by Formula 1 was 95.66%, Formula 2 was 97.17 and F3 was 98.81. The dissolution test results showed that the largest dissolution percentage of microcapsules in formula 1 was 97.85% at 50 minutes, formula 2 was 98.13 at 55 minutes and formula 3 was 98.91% at 60 minutes. Microencapsulation of paracetamol with polycaprolactone can cover the bitter taste and changing the release of paracetamol microcapsules into sustained release preparations.

Keywords: Microencapsulation, Paracetamol, Polycaprolactone.

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INTRODUCTION

Paracetamol is an analgesic drug that is used to reduce pain in the body ranging from mild to moderate. And it can also act as an antipyretic which can help reduce body temperature[1]. Paracetamol is used as an antipyretic and analgesic drug which is generally widely used for diseases in children and the elderly [2] . Paracetamol is one of the first choices used by pediatricians to treat fever and pain in accordance with national and international guidelines [3] . Paracetamol is an analgesic/antipyretic that is commonly known and used in combination and single formulations[4] .

Paracetamol (acetaminophen) is an analgesic and antipyretic drug that is sold freely and is widely used. It is usually widely used to relieve headaches and other minor aches and pains [5,6] . The World Health Organization (WHO) includes paracetamol on the list of essential medicines, namely drugs that are efficacious, safe and cost-effective for priority conditions [7] . Paracetamol has a characteristic bitter taste which is often considered to be a significant barrier to any drug administration [8] . Because the taste of paracetamol is bitter, some consumers avoid or are reluctant to take the medicine [9] . This bitter taste is one of the biggest problems in the world for the treatment of pediatric patients, causing less than optimal therapeutic value [2] . The therapeutic dose of paracetamol for adults is 1 g single dose or divided doses of 4x1 g every day with an administration interval of 4-6 hours. Children aged 2–12 years are usually given an individualized body weight-derived therapeutic dose of 10–15 mg/kg body weight [10,11] . The mechanism of action of paracetamol is not completely understood but likely involves inhibition of cyclooxygenase-2 (COX-2). Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase (COX), preventing the metabolism of arachidonic acid to prostaglandin (PG) G2 [12,13] . Taste masking is an appropriate technique used to mask the bitter taste of a drug [14] . There are several taste masking techniques that can be used to mask taste, including microencapsulation, polymer layer formation, ion exchange, inclusion complex formation, liposomes, prodrug approaches, adsorption, various emulsion techniques, gel formation and so on [12,15] . One of the most effective ways to mask the unpleasant taste of drugs is to use microencapsulation techniques [16] .

Microencapsulation technology began to emerge in the 1950s starting with the development of dyes for capsules and inclusion in packaging [17] . Microencapsulation is a method used to mask undesirable flavors and aromas, this is a simple technique used to mask flavors that have relatively fewer negative impacts on consumers [16,18] . And currently, microencapsulation can also be defined as a series of technologies that have the aim of protecting sensitive compounds from the external environment and will also control their release. If drug release exceeds a certain time threshold, the formulation is considered to lack taste masking [19] . Therefore, unstable compounds are often referred to as trap cores because they are surrounded by shell or wall material. Microencapsulated isolates are most widely applied in the pharmaceutical, food, textile, agricultural, biomedical and cosmetic industries [17,20] .

The microencapsulation method was chosen because it has several advantages, including being able to mask the unpleasant taste of drugs, producing micro-

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sized drug particles, and many choices of manufacturing methods [21,22] . Apart from that, this method was chosen because it has several advantages, including relatively low cost, efficiency, and microcapsules having high stability [23] .

METHOD

Tools and materials

The tools used in this research are analytical scales, UV-Vis spectrophotometer, SEM, FTIR, DSC, homogenizer, measuring flask, dissolution tester, Erlenmeyer, dropper pipette and glass beaker. The materials used in this research were paracetamol, polycaprolactone, paraffin liquid, acetone, n-hexane, phosphate buffer pH 5.8, magnesium stearate, distilled water and methanol.

Research procedure

Polycaprolactone and paracetamol were dissolved with chloroform in an Erlenmeyer flask (mass 1). Then Mg stearate was dissolved with acetone in an Erlenmeyer flask (mass 2). Mass 1 and mass 2 were put into an Erlenmeyer flask containing liquid paraffin and then stirred using a homogenizer at a speed of 250 rpm for 5 hours. The resulting microcapsules are then separated from the liquid paraffin by pouring it. The microcapsules obtained were washed using n-hexane by drying in the oven at 400 °C for 2 hours.

Evaluation of Paracetamol Microcapsules

Determination of Contents

a. Determination of the maximum absorption wavelength of paracetamol

Preparation of paracetamol mother liquor by dissolving 25mg paracetamol in 500 mL distilled water, resulting in a concentration of 0.05mg/mL. Solutions were made with concentrations of 2, 4, 6, 8, 10, and 12 by diluting the mother liquor. Then the absorbance was measured at a wavelength of 200-400 nm using a UV-Vis spectrophotometer.

b. Creation of Calibration Curve

From the dilution results, the maximum absorption was measured and then a calibration curve was created.

c. Determination of active substance levels

Paracetamol microcapsules equivalent to 120mg were weighed, then put into a 500 mL measuring flask, dissolved in 10 mL of methanol P, diluted with distilled water to the limit. Then pipette 5 mL and put into a 100 mL measuring flask, dilute with distilled water to the mark. Absorption was measured using the maximum wavelength that was obtained, the blank used was distilled water, the same treatment was carried out with each formula and the percentage of paracetamol content in the microcapsules was calculated [24] .

Particle Size Distribution

The microcapsules that have been obtained are then determined for their particle size distribution using a vibration sieve. Where the sieve is graded from the largest sieve size to the smallest sieve size, namely 2000, 1000, 600, 355, 212, 150, 125 µm. Then weigh 3 grams of paracetamol microcapsules and put them in a sieve, the sieving machine will run for 10 minutes. After that, the sieve and the fractions remaining in it are weighed, and each formula [25,26] is repeated three times .

Mycocapsule Morphology *Scanning Electron Microscopy* (SEM)

The surface morphology of the microcapsules was carried out to determine the characteristics between the coating polymer and paracetamol [27] . Morphological tests were carried out using a JEOL-JSM-6510LV *scanning electron microscopy (SEM) tool* [28] .

FTIR (*Fourier Transform Infrared Spectroscopy*) test

The FTIR test was carried out to determine the interaction between the coating and the active substance [27] . The powder sample is placed in a total reflectance (ATR) crystal device and then compressed using an axial screw [29] .

Dissolution Test

In the dissolution test, 900 mL of pH 5.8 phosphate buffer solution was used as a medium. The method used is the rowing method. The steps carried out are a) Preparation of dissolution media, namely 1 L of pH 5.8 phosphate buffer mixed with 250 mL of 0.2M potassium dihydrogen phosphate then added with 18 mL of 0.2N NaOH, diluted with CO2-free water. Adjust the pH of the solution until a pH of 5.8 ± 0.05 is obtained by adding 0.2 N NaoH and increasing the volume to 1 liter. b) Put 900 mL of pH 5.8 phosphate buffer solution into the dissolution flask. c) Install the dissolution apparatus, allow the dissolution medium to reach a temperature of 37 ± 0.5 ^{0}C then insert the microcapsules into the dissolution apparatus, at a speed of 50 rpm. d) Take 5 mL samples at 5, 10, 15, 20, 25, 30 and 60 minutes. The sampling position is not less than 1 cm from the wall of the container. Each solution that has been taken is replaced again so that the amount of medium remains. e) Take 5 mL of the solution then measure the absorbance with a UV-Vis Spectrovotometer, repeat it for each formula and calculate the percentage.

RESULTS AND DISCUSSION

The results of the examination of raw materials and coating materials have met the requirements according to the Indonesian Pharmacopoeia edition III and Indonesian Pharmacopoeia edition IV which include solubility, description, determination of levels, drying losses. The requirement for drying shrinkage is not more than 0.5%. Based on the results obtained, it was found to be 0.37%, not exceeding the provisions so that it meets the requirements. The results of determining the required levels according to the Indonesian Pharmacopoeia are 98.0%-101.0% and from the results obtained the results were 99.68, so it still meets the requirements.

Determination of Contents

Determination of the maximum absorption wavelength of paracetamol

The results obtained from the paracetamol wavelength were 243.3 nm. The wavelength results show that the results obtained are not much different from the literature, namely that the wavelength of paracetamol in water is 244.2 nm [30] .

After obtaining the wavelength, proceed with making a paracetamol calibration curve by making a paracetamol solution with concentrations of 2, 4, 6, 8, 10 and 12 µg/mL, then measuring the absorption with the maximum wavelength obtained. The regression equation y = 0.0568x + 0.0423 with r = 0.9997 which shows that there is a linear relationship between the absorbance value and the concentration of the solute being analyzed. A good linear relationship has a correlation coefficient value r in linear regression analysis y = bx + a. where the linear relationship is good if the value of b = 0 and the value of r is close to 1. After the calibration curve is carried out, a test is carried out to determine the active substance content of paracetamol microcapsules which is carried out according to the procedures in the Indonesian Pharmacopoeia VI edition, which is carried out using a UV spectrophotometer with medium Aquadest. The values obtained are then used to calculate the levels of paracetamol contained in paracetamol microcapsules.

The results obtained from weighing the weight of paracetamol microcapsules in formula 0 4.9324, formula 1 8.7685g, formula 2

Table 1. Paracetamol Microcapsule Formula.

Material name	Concentration			
	F0	F1	F2	F3
Paracetamol (g)	-	3	3	3
PCL (g)	1.5	1.5	3	4.5
Chloroform (mL)	10	10	15	20
Mg Stearate (g)	0.5	0.5	1	1.5
Acetone (mL)	5	5	8	11
Paraffin Liq (mL)	100	100	100	100

Table 2. Determination of Microcapsule Concentrations.

Microcapsules	Heavy Microcapsules	Acquisition Return Microcapsules	Acquisition Return Substance Active
F0	4.9324	98,365	-
F1	8.7685	95.6632	68.4537±2.31
F2	11.0142	97.1782	61.1492 ± 2.17
F3	13.2916	98.8197	56.3657±1.26

Table 3. Particle Size Distribution Measurement Results.

Sieve size (µm)	Fraction of sieve retained (%)		
	Formula 1	Formula 2	Formula 3
125 – 150	1.52	0.38	0.67
150 – 212	0.89	3.04	1.03
212 – 355	4.15	3.21	3.35
355 – 425	5.09	2.65	5.63
425 – 600	3.61	4.54	11.28
600 – 1000	33.11	35.76	19.34
1000 – 2000	25.47	31.64	27.48
0 – 2000	25.42	18.78	30.45

11.0142, formula 3 13.2916 and for the recovery of paracetamol microcapsules in each formula were 98.365, 95.6632, 97.1782, 98.8197. From the test results for determining the levels in paracetamol microcapsules from the three formulas with each comparison, it can be seen that the greater the coating ratio, the smaller the active substance obtained. Where F1 contains more active substances than F2 and F3. F1 68.4537, F2 61.1492, F3 56.3657, from the results obtained it is clear that F1 has the highest active substance content due to the effect of size on the microcapsules where the smaller the particle diameter, the greater the ability to absorb drugs [25] while F3 has the lowest active substance content because the thicker the coating used, the less drug content it contains [25,31] . Results can be seen in table 2.

From the results of examining the particle size distribution using a multilevel sieve, it was found that the particle size of paracetamol microcapsules with polycaprolactone coating was between 125-2000 µm. The sizes obtained have differences in particle size distribution which is greatly influenced by the amount of coating used as a layer to form the microcapsule walls. The particle size obtained meets the requirements for microcapsules, namely 5-5000µm [25.32] . Results can be seen in table 3.

Mycocapsule Morphology *Scanning Electron Microscopy* (SEM)

Microscopic evaluation of microcapsules was carried out using SEM tests with 500x magnification. The aim of this test was to see the morphology of each paracetamol microcapsules formula. The results of the paracetamol microcapsule test using SEM can be seen in Figure 2.

The results of observing the morphology of paracetamol with polycaprolactone at a magnification of 500 times using SEM showed that the surface of formula 3 was rougher than formulas 1 and 2. From the results it could be concluded that as the concentration of the coating used increased, the resulting surface became rougher.

FTIR (*Fourier Transform Infrared Spectroscopy*) test

The FTIR test was carried out to determine the interaction between paracetamol and polycaprolactone. The interaction between paracetamol and polycrolactone is indicated by the presence of a new peak or a shifted peak [29].

The FTIR spectrum results of paracetamol microcapsules formulas 1, 2 and 3 in table 4 show that the peak spectrum produced is not much different from the IR spectrum of the raw material, the three formulas have some of the same spectrum results as the spectrum of paracetamol and polycaprolactone. From the results of the wavelength numbers in formulas 1, 2 and 3, there is no visible shift in the wave numbers. This shows that there is no interaction between the active substance and the polymer used as a coating so that it does not produce new functional groups or new bonds.

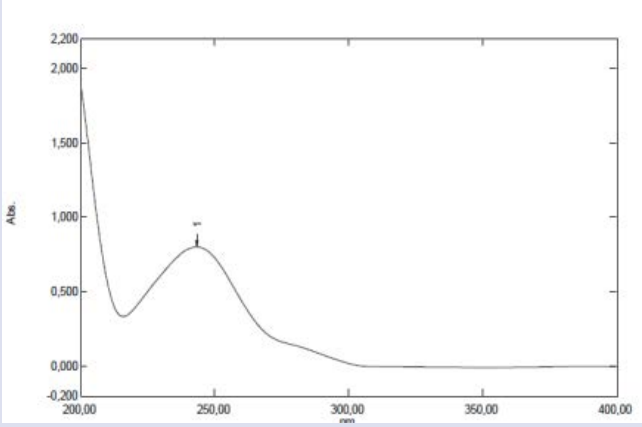

Figure 1. Maximum Absorption Wavelength of Paracetamol (λ = 244.2 nm).

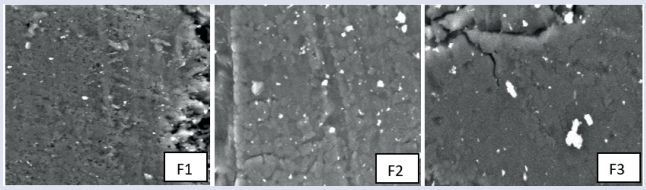

Figure 2. SEM micrograph.

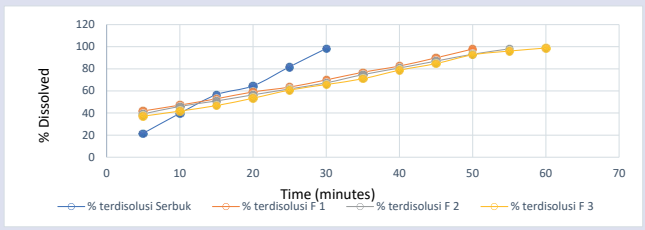

Figure 3. Dissolution Curve of Paracetamol Microcapsules for Each Formula.

Table 4. Wave Numbers of Paracetamol, Polycaprolactone, Formula 1, Formula 2 and Formula 3.

Functional groups	Paracetamol BPFI	Paracetamol	Polycaprolactone	F1	F2	F3
NH	3321.42	3323.37	-	3323.37	3323.37	3323.37
C=O	1732.08	1878.67	1722.43	1722.43	1722.43	1722.43
OH	3161.33	3151.36	-	3143.24	3143.24	3143.24
C.N	1327.03	1327.03	1363.67	1363.38	1363.38	1363.38
C=C Aromatic	1651.07	1651.06	-	1651.05	1651.05	1651.05
CH	1435.04	1445.06	1417.68	1435.06	1435.06	1435.06
CH_2	2929.87	2867.76	2864.29	2948.67	2948.67	2948.67
CO	968.27	968.27	960.55	967.21	967.21	967.21

Table 5. Percent of Dissolved Substances.

Time	% dissolved			
	Powder Paracetamol	F 1	F 2	F 3
5	21.58	41.88	39.08	37.16
10	39.67	47.16	45.97	41.77
15	56.54	52.87	50.88	46.75
20	64.53	59.06	56.43	53.43
25	81.85	63.45	61.81	60.79
30	98.32	69.95	67.32	65.81
35		76.83	74.76	71.08
40		82.49	80.78	78.82
45		89.91	87.05	84.81
50		97.85	93.28	92.75
55			98.13	96.14
60				98.91

Table 6. Kinetic Model of Active Substance Release from Microcapsules.

Kinetic Model	R^2		
	F1	F2	F3
Order 0	0.9167	0.8992	0.9657
Order 1	0.9364	0.9122	0.9477
Higuchi	0.9192	0.9132	0.9746
Kosmeyer-Peppas	0.8828	0.8623	0.9481
Langenburcher	0.8776	0.8769	0.9582

Dissolution Test

The dissolution test is carried out to measure and determine the amount of active substance dissolved in a known volume of liquid media at a certain time using a tool so as to determine the speed of release of the drug from the solid dosage form. The dissolution test results can be seen in table 5.

From the results of the dissolution profile test, it can be seen the difference in propyl release between paracetamol powder and paracetamol microcapsules for 60 minutes. The percentage obtained from dissolvable substances in paracetamol powder at 30 minutes was 98.32%. The percentage of dissolvable substances in paracetamol microcapsules for formula 1 at 50 minutes was 97.85%, formula 2 at 55 minutes was 98.13% and formula 3 at 60 minutes was 98.91%. From the results of the dissolution test it was found that the release of active substances from microcapsules was not the same as the release of active substances in powder form which did not undergo a microencapsulation process, for formula 1 the release of active substances was faster than formulas 2 and 3 because in the microencapsulation process each formulation had a ratio of each polymer. where formulation 1 is lower than formulations 2 and 3 so that the release of the active substance takes longer in formulation 3 [33,34-41] . From the results of the dissolution test it can be concluded that making paracetamol into microcapsules affects the release of the drug more slowly.

The results of determining the kinetic model for the release of paracetamol microcapsules have been carried out and are based on zero order, 1st order, Higuchi, Korsmeyer-Peppas and Langerburch equations. From the results of the five kinetic models, the relationship coefficient obtained from formulas 1, 2 and 3 which is closest to 0.999 is the 1st Order equation where the amount of drug released is proportional to the square root of the time to reach the maximum concentration, not depending on the dose but on the absorption rate constant [34, 35] .

CONCLUSION

From the research results, it was concluded that paracetamol can be made into microcapsules. Polycaprolactone used as a slow-release polymer can have an effect on paracetamol microcapsules and can slow down the process of releasing the active substance which can be seen from the dissolution results.

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