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Dissolution and pharmacokinetics profile of acetylsalicylic acid in rabbit plasma following oral ingestion of acetylsalicylic acid microcapsules

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ABSTRACT: Acetylsalicylic acid (80 mg) suppresses thromboxane A2 (TXA-2) formation, thereby reducing platelet aggregation and is used as an antiplatelet agent. Oral administration of acetylsalicylic acid causes gastrointestinal bleeding; therefore, acetylsalicylic acid microcapsules have been developed, which are less soluble in stomach acid but dissolve in intestinal fluid. This study aimed to evaluate the concentration, dissolution, and bioavailability of acetylsalicylic acid (ASA) microcapsules. Microcapsules were prepared using the microencapsulation method with an alginate crosslinking technique, with calcium chloride as the crosslinker. The concentration of acetylsalicylic acid and the dissolution of microcapsules were determined in vitro. The bioavailability of 80 mg acetylsalicylic acid microcapsules was studied in rabbits that were orally administered of 80 mg. Blood sampling was carried out at 0, 0.5, 1, 2, 4, 6, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, and 30 h. In this study, the percentage of acetylsalicylic acid in the microcapsules was 24.08±0.59%. The dissolution test at the acid stage showed that acetylsalicylic acid was still released at 40.09% in 90 min. In the bioavailability test, a lag time of absorption of less than 1 h was obtained, peak plasma levels of 2.06 µg/mL were achieved within 9.16 h after microcapsule administration, and the area under the curve was 15.98 µg ·h/mL. It can be concluded that the release of acetylsalicylic acid from microcapsules in the acidic medium indicates incomplete entrapment, and there is a lag time, indicating inhibition of drug release due to the microencapsulation process.

KEYWORDS: Acetylsalicylic acid, bioavailability, dissolution, microcapsule, pharmacokinetic.

INTRODUCTION

Acetylsalicylic acid is an acidic nonsteroidal anti-inflammatory drug that is poorly soluble in water [1]. Acetylsalicylic acid is rapidly absorbed, with absorption occurring almost completely in the upper duodenum. However, because it is acidic, some acetylsalicylic acid is absorbed in the stomach. The bioavailability of acetylsalicylic acid decreases due to hydrolysis during absorption [2]. At low doses, acetylsalicylic acid can inhibit platelet aggregation; therefore, it is used in the treatment of myocardial infarction and stroke [3]. Acetylsalicylic acid can be administered orally; however, it can cause severe side effects, including gastrointestinal bleeding [4]. Acetylsalicylic acid has an onset of action after 30 min and lasts for 3-6 hours, and its half-life (t½) is 2-3 hours [5]. The mechanism of action of acetylsalicylic acid involves acetylation of the cyclooxygenase enzyme and inhibition of the formation of cyclic endoperoxide enzymes. Acetylsalicylic acid also inhibits thromboxane A-2 (TXA-2) synthesis in platelets, thereby inhibiting platelet aggregation [6].

Acetylsalicylic acid 80 mg remains the primary choice as an antithrombotic [7]; therefore, a bioavailability test for acetylsalicylic acid 80 mg is needed as a quality control measure to protect consumers from preparations of acetylsalicylic acid 80 mg that do not meet standards, ensuring that consumers receive the correct dosage of acetylsalicylic acid 80 mg.

The microencapsulation technique is one way to modify the release of active substances so that they can be used to reduce adverse side effects [8]. The most frequently used microcapsule formation technique is the emulsification-evaporation of organic solvents [10]. However, owing to toxicity and limitations in choosing organic solvents, polymer crosslinking microencapsulation techniques have been developed, which can be used for hydrophilic or lipophilic substances [11]. The polymer used in the formulation of microencapsulation was sodium alginate, a salt of alginic acid that is hydrophilic and can form a gel in the presence of calcium

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[12]. Clinically, alginate has been used as an anti-ulcer agent that can protect the surface of the gastric mucosa; however, research on the oral administration of acetylsalicylic acid is still ongoing in the pharmaceutical field [13].

Based on this, the study was conducted in vitro to determine the percentage of acetylsalicylic acid content, dissolution profile of the acetylsalicylic acid microcapsules prepared, and bioavailability of acetylsalicylic acid microcapsules resulting from cross-linking of alginate and calcium chloride in experimental rabbits. To determine the concentration of acetylsalicylic acid in plasma, a selective and sensitive analytical method is required. Visible light spectrophotometry offers the advantages of being fast, simple, and selective. Acetylsalicylic acid is hydrolyzed to salicylic acid and acetic acid under alkaline conditions, after which it is neutralized with acid. The salicylic acid formed is complexed with iron (III) nitrate, which reacts with the phenol group of salicylic acid to produce a purple complex [14].

▪ MATERIALS AND METHODS

Materials

Alginate (HiMedia Laboratories, USA), calcium chloride (Merck, Germany), male New Zealand White rabbits, heparin (Pfizer, US), ethanol (Merck, Germany), nitric acid (Merck, Germany), NaOH (Merck, Germany), iron (III) nitrate (Merck, Germany), distilled water, trichloroacetic acid (TCA) (Fengchen Group Co., China), phenolphthalein (Runtai Chemical, China), sulfuric acid (PT Merck Chemicals and Life Sciences, Indonesia), iron (III) chloride (PT Merck Chemicals and Life Sciences, Indonesia), potassium dihydrogen phosphate (PT Merck Chemicals and Life Sciences, Indonesia), and aqua demineralized were used in this study.

Instruments

UV-Vis spectrophotometry (Shimadzu-1800, Japan), microcentrifuge (Beckman Coulter, US), vortex, micropipette (Eppendorf, Germany), syringe, and oral sonde were used.

Methods

Microcapsules were prepared by crosslinking sodium alginate with calcium chloride. The microcapsules were prepared using a ratio of aspirin: $CaCl_2$ of 0.5%:0.15 M. Sodium-alginate was weighed and added to the water while stirring to obtain a solution. Acetylsalicylic acid was added to a solution of sodium alginate while heating. A 10 mL mixture of alginate-aspirin was added dropwise to 40 mL of calcium chloride solution, and the mixture was stirred constantly with a stirrer. The formed calcium-alginate granules were allowed to harden in calcium chloride solution for 20 min, then decanted and washed with deionized water. The microcapsules were then formed in an oven at 37 °C until dry microcapsules were obtained. Microcapsules were characterized by measuring the yield of the process (%), particle size (µm), dissolution profile in acidic and alkaline media, and percent entrapment of acetylsalicylic acid in microcapsules. The pharmacokinetic profile and bioavailability were evaluated after obtaining approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (approval number: 616/UN2.F1/ETIK/PPM.00.02/2023). The bioavailability test of 80 mg acetylsalicylic acid microcapsules was conducted using rabbits. Male rabbits of New Zealand White strain, body weight 3.2±0.3 kg, age 4-5 months, as many as six rabbits were kept and acclimatized at the Pharmacology Laboratory, Faculty of Pharmacy, Pancasila University. Each rabbit was placed in an individual cage with dry wood chip bedding, which was replaced periodically during the test. The room temperature of the cage was 19±2 °C, with a light: dark cycle of 8:16 h. The rabbits were provided with adequate food and water.

Preparation of acetylsalicylic acid standard solution

A 250 mg acetylsalicylic acid working standard was weighed, 5 mL of ethanol was added, and the mixture was shaken until it dissolved. Distilled water was added to 100 mL to obtain a 2500 µg/mL solution.

Plasma blank preparation

The rabbit ear sections were shaved and cleaned with ethanol. One milliliter of blood was taken from the marginal vein, heparin 5000 UI 1-3 drops, vortexed, and centrifuged at 3500 rpm for 10 min. Plasma (0.5 mL) was collected, 4 mL of 20% TCA was added, vortexed, and centrifuged at 3500 rpm for 5 min. Then, 2 mL of

supernatant was taken, and 1.35 mL of 2 N sodium hydroxide was added (let stand for 5 min), 1 mL of 1 N nitric acid (pH 4-6), and the mixture was placed in a 10 mL volumetric flask. Then, 1 mL of 1% iron (III) nitrate was added, and distilled water was added to the mark. Used as a blank.

Pharmacokinetic profile of microcapsule acetylsalicylic acid in plasma after oral administration

The rabbits were fasted for 24 h (n = 6). Oral administration of acetylsalicylic acid microcapsules to rabbits. Blood sampling through the marginal vein at time intervals of 0, 0.5, 1, 2, 4, 6, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, and 30 h, with up to 1 mL of blood sample per collection, and then treated the same as blank. The absorbance was measured at the maximum wavelength of the sample. The results of the determination of acetylsalicylic acid levels in rabbit plasma were used to create a pharmacokinetic profile and calculate the pharmacokinetic parameters.

RESULTS

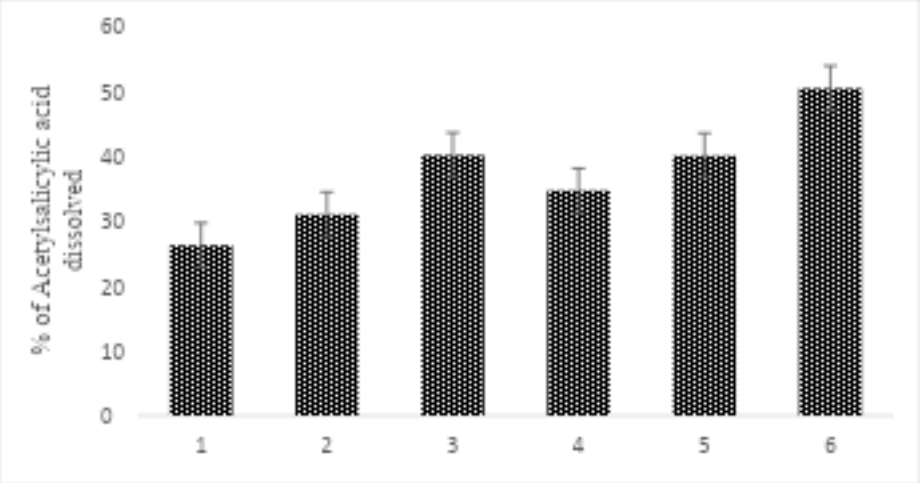

Figure 1. Acetylsalicylic acid dissolution profile of microcapsules in acidic and alkaline media.

Table 1. Linearity test of acetylsalicylic acid solution in plasma.

No.	Concentration (µg/mL)	Absorbance
1	0	0.000
2	1	0.012
3	2	0.018
4	4	0.034
5	10	0.074
6	20	0.159
7	40	0.312
8	100	0.752

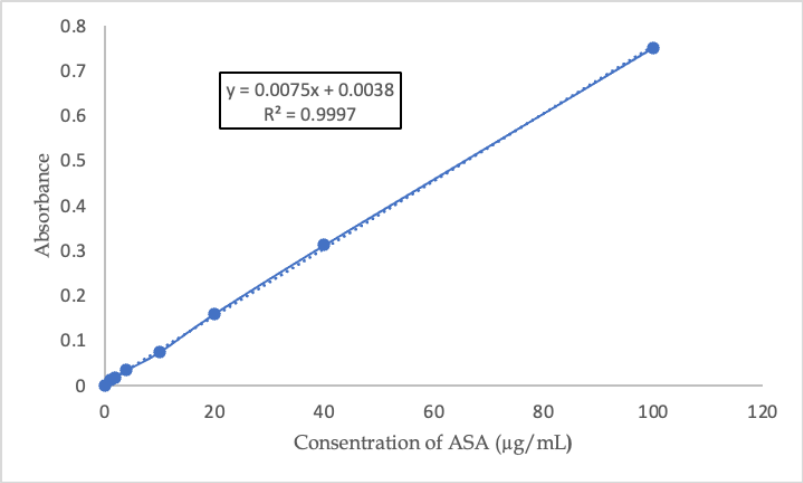

Figure 2. Correlation curve between the concentration (ppm) and absorption (A) of the acetylsalicylic acid solution in plasma at λ 525 nm.

The results of the acetylsalicylic acid microcapsule bioavailability test in rabbits are as follows:

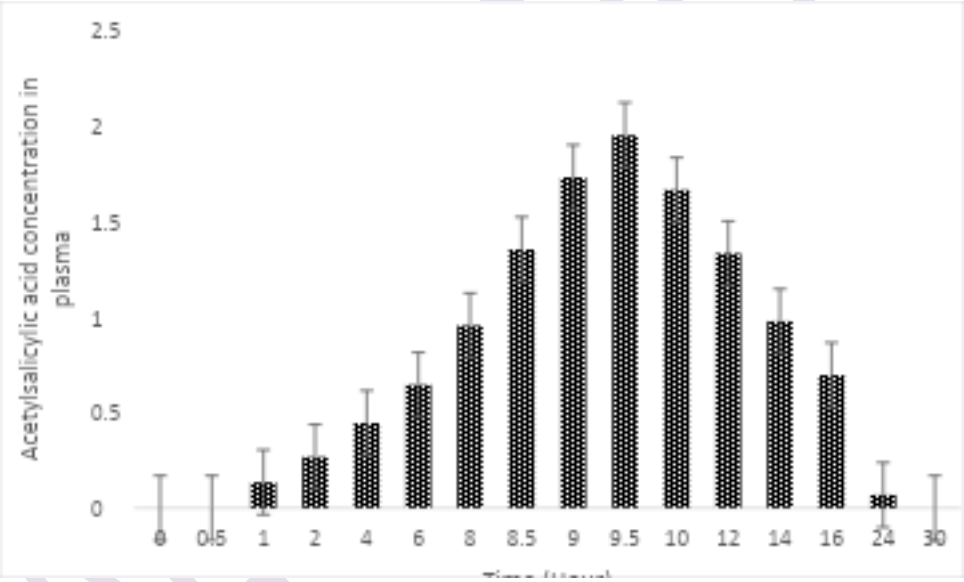

Figure 3. Plasma concentration-time curve of acetylsalicylic acid after oral administration of microcapsules containing 80 mg acetylsalicylic acid. These results were obtained 30 h after the oral administration of the drugs. *Each point represents the mean ± SE (n = 6).

Table 2. Pharmacokinetic parameters.

Pharmacokinetic Parameters	Rabbits no.						Mean±SD
	1	2	3	4	5	6	
AUC (µg.h/mL)	19.5	15.8	15.3	12.7	16.3	16.3	15.98±2.18
C_{max} (ppm)	2.01	2.15	2.02	2.02	2.02	2.15	2.06±0.07
T_{max} (h)	9.0	9.5	9.5	9.0	8.5	9.5	9.16±0.41

▪ DISCUSSION

The microcapsules used in this study aimed to increase the bioavailability of acetylsalicylic acid, thereby increasing its efficacy. Producing microcapsules by crosslinking alginate with calcium chloride can be advantageous because alginate also has anti-ulcer activity that can protect the surface of the gastric mucosa

[12]. In this study, the average yield of the acetylsalicylic acid microcapsules was 99.97±7.34%, and the average particle size was 308.59 (µm).

Percentage of acetylsalicylic acid in the microcapsules

In this study, the concentration of acetylsalicylic acid in the microcapsule formula was determined to evaluate the efficiency of the microencapsulation process. The average acetylsalicylic acid concentration of the microcapsules was 24.08±0.59. The percentage of acetylsalicylic acid in microcapsules that meets the theoretical requirements is ±50% [15]. However, in this study, the percentage of acetylsalicylic acid in the microcapsules was 24.08±0.59%. This could be caused by the loss of acetylsalicylic acid during the manufacturing process due to the incomplete entanglement of acetylsalicylic acid in the microcapsules formed. The loss of acetylsalicylic acid can also occur during microcapsule washing for acetylsalicylic acid that is entangled on the surface.

Dissolution profile

The dissolution profile of the acetylsalicylic acid microcapsule formula in this study was observed at two degrees of acidity: pH 1.2, which corresponds to the pH of artificial stomach acid without enzymes, and pH 6.8, which corresponds to artificial intestinal fluids without enzymes. This dissolution profile was used to determine the release profile of acetylsalicylic acid in the body. The percentage dissolution of the acetylsalicylic acid microcapsules at 30, 60, and 90 min is shown in Figure 1.

The results of the dissolution of the acetylsalicylic acid microcapsules showed that the microcapsules were not perfect in resisting the release of acetylsalicylic acid in an acidic environment. This is due to the Acetylsalicylic acid attached/trapped in the microcapsule skin layer because the acetylsalicylic acid is not properly micro-encapsulated, so that it is easily released and dissolves in the dissolution medium in an acidic environment. This may also be due to the presence of pores on the surface of the microcapsule, which can also play a role in the rate of release of the acetylsalicylic acid [16]. This is consistent with another study that stated that increasing the amount of drug in the dispersed phase can produce microcapsules with larger pores [17]. Dissolution continued at a pH of 6.8. At this stage, approximately 85% of the acetylsalicylic acid was released from the microcapsule for 90 min.

Bioavailability test of acetylsalicylic acid microcapsules

The bioavailability of acetylsalicylic acid microcapsules was tested in experimental rabbits by oral administration. Before determining the acetylsalicylic acid levels in rabbit blood, a linearity test was performed, and the lowest quantification limit in spiked plasma was determined.

Linearity test

The linearity test using a series of acetylsalicylic acid solutions in plasma at different concentrations produced the following absorption values, as shown in Table 1. The linearity test results show that the relationship between absorption and concentration has a linearity that corresponds to the equation of the line, and the price of the coefficient of variation is close to 1, as shown in Table 1 and Figure 2

Lower limit of quantification (LLOQ)

In the search for LLOQ, experiments were conducted at concentrations of ½ and ¼ times the LOQ values. The LOQ was obtained from a linearity test at a concentration of 1 µg/mL. Based on these experiments, it can be concluded that the LLOQ level is 0.5 µg/mL, because the accuracy at 0.5 µg/mL still meets the requirements of LLOQ according to the FDA, namely, % error ≤ +20% and -20%, while the accuracy at 0.25 µg/mL does not meet the requirements of LLOQ, and recovery at 0.5 µg/mL is still said to be good because it is in the range of 80-120%.

Bioavailability test of acetylsalicylic acid microcapsules in rabbits

Bioavailability is the percentage and speed of the active substance in a drug product that reaches/is available in the systemic circulation in an active/intact form after administration of the drug product, measured by its level in the blood over time or by its excretion in urine [18], [19]. A bioavailability test was performed in experimental animals in the initial stage. Blood sampling was performed for 30 h. In this study, rabbits were used as experimental animals because they have several advantages, including a large blood volume, so there was no concern of a shortage of blood samples from experimental animals compared to mice

or rats, an easy sampling method through the marginal ear vein, and easy handling compared to other experimental animals. Such as monkeys, dogs, or cats, so that the experimental animals were not stressed during the research.

In this study, when viewed from the dissolution profile, there was a release of acetylsalicylic acid in the acid. However, acetylsalicylic acid levels in plasma were detected at 1 h, indicating a lag time for drug absorption. The pharmacokinetic parameter area under curve (AUC) describes the bioavailability of 80 mg microcapsules in rabbit plasma as 15.98±2.18 µg.h/ml. C_{max} indicated that the peak level of acetylsalicylic acid in blood plasma was 2.06±0.07 µg/ml.

This study also calculated the T_{max}, which is the time to reach peak acetylsalicylic acid levels in the blood, and found that T_{max} was 9.16 h. Moreover, the time required for acetylsalicylic acid to reach its peak serum concentration (T_{max}) was prolonged with the microencapsulated acetylsalicylic acid formulation. These results are in line with those of a study on gliclazide microcapsules in rats, where T_{max} was significantly prolonged ($p < 0.05$) with the microencapsulated gliclazide formulation compared to the gliclazide suspension [20]. Low-dose acetylsalicylic acid (ASA; aspirin) is used for secondary prevention to reduce the risk of cardiovascular disease and mortality. ASA acetylates cyclooxygenase in the portal circulation and is rapidly hydrolyzed (half-life, 20 min) [21].

▪ CONCLUSION

Although the acetylsalicylic acid microcapsules exhibited good characteristics, acetylsalicylic acid was still released from the microcapsules in an acidic atmosphere and showed incomplete binding. In the in vivo test, a lag time of more than 0.5 h was observed, indicating the inhibition of drug release due to the drug microencapsulation process.

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