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Retention of Sodium Alginate-Based Mucoadhesive Ranitidine

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Abstract: Ranitidine, a histamine H2-antagonist, has an oral bioavailability of 50-60% and an elimination half-life of approximately 2 to 3 hours. To enhance its therapeutic efficacy, ranitidine must remain in the stomach for an extended period. A mucoadhesive gastroretentive drug delivery system can improve its bioavailability. This study aimed to formulate ranitidine granules using sodium alginate as a polymer via wet granulation. Formulations with varying sodium alginate concentrations (7-11%) were prepared and evaluated for flow properties, tapping properties, moisture content, swelling capacity, and dissolution. The formulation with 11% sodium alginate exhibited acceptable properties. It achieved a flow rate of 12.3±0.23 g/s, an angle of repose of 27.13±0.63°, a compressibility index of 21.35±2.23%, a Hausner ratio of 1.32±0.07, a moisture content of 2.59±0.2%, a swelling index of 72.85±3.48%, and a wash-off time of 77.34±48.75 minutes. Additionally, over 80% of the drug was dissolved. In conclusion, the 11% sodium alginate formulation is the most promising for mucoadhesive ranitidine delivery.

Keywords: Ranitidine, Gastroretentive, Mucoadhesive, Sodium alginate

Introduction

Ranitidine is a medication classified as an H2 histamine receptor antagonist. It is commonly available in the form of an HCl salt and is widely used to reduce stomach acid production, particularly in conditions such as gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, and peptic ulcer disease [1]. However, ranitidine has a limited oral bioavailability of approximately 50-60% and a short half-life of 2-3 hours [2]. To ensure effective action in the stomach, a sufficient and sustained concentration of the drug in the body is required [3]. Therefore, an effective drug delivery system is essential for ranitidine to achieve optimal therapeutic effects.

Gastroretentive drug delivery is a strategy designed to prolong the retention time of a drug in the stomach, enabling targeted release at specific sites within the gastrointestinal tract for localized or systemic therapeutic effects. Gastroretentive formulations can remain in the stomach for extended periods, thereby significantly increasing the drug's residence time [4]. Recently, several gastroretentive drug delivery systems have been developed,

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including high-density (sinking) systems that settle at the bottom of the stomach, low-density (floating) systems that float on gastric fluids, mucoadhesive systems that adhere to the gastric mucosa, swelling systems, and magnetic systems [5].

Among these, mucoadhesive systems are particularly effective in enhancing the bioavailability of ranitidine. As a type of controlled drug delivery method, mucoadhesive systems are characterized by their ability to adhere to the mucosal lining, which prolongs the residence time and contact duration at specific sites. This prolonged adherence enhances drug effectiveness by increasing its bioavailability [6]. In these formulations, polymers are essential for enhancing the residence time of the drug at the target location [7].

The development of mucoadhesive formulations has shown promising results with various drugs, including nifedipine, simvastatin, amoxicillin, and ketoprofen [8–11]. Building on these successes, this study aims to develop a mucoadhesive system for ranitidine, with the expectation that this formulation will allow the drug to remain in the stomach for a longer duration, thereby enhancing its therapeutic efficacy

Sodium alginate is a polymer particularly well-suited for such formulations. In pharmaceutical manufacturing, sodium alginate serves as a thickening agent, binder, and disintegrant in tablet formulations [10]. It is commonly combined with antacids for the management of GERD. In the stomach, sodium alginate reacts with gastric acid to form a viscous gel, often referred to as a "raft," which floats on the stomach contents and acts as a mechanical barrier to reduce reflux [12]. Due to its critical properties, such as its ability to form a gel in the stomach, sodium alginate has been chosen as the polymer for formulating mucoadhesive ranitidine granules [10].

The development of this formulation is anticipated to contribute valuable insights into the formulation of mucoadhesive ranitidine granules using sodium alginate. Additionally, testing on rabbit stomachs is expected to provide more realistic data regarding the gastroretentive capabilities of the formulation. Therefore, the aim of this study was to formulate the most promising mucoadhesive for ranitidine delivery using sodium alginate.

Materials And Methods

Materials

The main materials used are ranitidine (HCl form; Shadong Biotech), sodium alginate (Sigma-Aldrich), lactose (DMV Fontera), PVP K-30 (Hangzhou Nanhang), HCl and KCl (Merck).

Methods

Mucoadhesive granule production

Ranitidine, sodium alginate, and lactose were mixed until a homogeneous blend was achieved. A PVP K-30 solution was then added to the mixture, and it was stirred until homogeneous and a cohesive mass formed. This mixture (Table 1) was passed through a

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No. 14 sieve, followed by drying in a drying cabinet at a temperature of 40-50°C for 3 hours. The dried granules were then sieved using a No. 16 sieve [4,13].

Table 1. Formulations of mucoadhesive ranitidine granules

Materials (mg)	F1	F2	F3
Ranitidine	300	300	300
Sodium alginate	35	45	55
Lactose	143	133	123
PVP K-30	qs	qs	qs

Preparation of Test Animals

Prior to preparation, the research protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Islam Indonesia. Rabbits were selected as test subjects based on the biological similarities between their mucosal systems and those of humans. The study utilized the gastric mucosa of rabbits, with the number of test subjects corresponding to the number of formulation variations, totalling four. The health criteria for the test subjects were determined by their active physical movement and the absence of any macroscopic morphological abnormalities. Animals were provided with adequate, fresh, and clean nutritious food, as well as unlimited access to clean drinking water. Cage bedding was replaced 1 to 3 times per week to ensure a dry environment.

Subjects were fasted 24 hours before testing. On the day of the experiment, the test animals were anesthetized with ether. Once fully anesthetized and immobile, an abdominal incision was made to extract the stomach for analysis. Post-mortem disposal of the test animals was conducted by burying them at a location distant from residential areas and water sources.

Preparation of Simulated Gastric Fluid

Simulated gastric fluid without enzymes was prepared by combining 250 mL of 0.2 M KCl with 425 mL of 0.2 M HCl in a 1000 mL volumetric flask, followed by the addition of distilled water to reach the final volume. The pH of the solution was then adjusted to 1.2 [14].

Physical Properties Testing of Granules

The granules were primarily evaluated by assessing their organoleptic properties, moisture content, and flow characteristics (Table 2). The color and aroma of the granules were evaluated organoleptically. Moisture content was determined using approximately 500 mg of granules with a moisture analyzer. Flow properties were measured using the flow funnel and tapping method; 100 g of granules were tested in a flow funnel to determine the flow rate and the angle of repose [15]. Subsequently, 100 mL of granules were placed in a graduated cylinder and tapped 100 times using a tapping device. This

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process was repeated until the granule volume stabilized, after which the compressibility index was calculated based on the final volume [16].

Swelling Test

A sample of 200 mg of granules was placed in 10 mL of simulated gastric fluid with a pH of 1.2 at 37°C. The swelling capacity was evaluated at intervals of 15, 30, 45, and 60 minutes by determining the percentage change in weight [16].

Wash-Off Test

The wash-off test was carried out using a disintegration tester (Erweka 2T-502) with simulated gastric fluid maintained at 37 ± 5°C as the medium. A strip of gastric mucosa was affixed to the testing cylinder, and 500 mg of granules were evenly applied to the mucosal surface. The cylinder was then moved up and down 30 times per minute. The amount of granules remaining adhered to the mucosa was assessed every 30 minutes, with a final measurement taken after 2 hours [17].

Dissolution Test

The dissolution test was conducted on the formulation that demonstrated the best results in the wash-off test. The medium consisted of 500 mL of 0.2 M HCl at pH 1.2, maintained at 37°C. A 500 mg sample of granules was placed in the basket of a dissolution apparatus, which was rotated at 100 rpm. Aliquots of 5 mL were withdrawn at 5, 10, 15, 30, 45, and 60 minutes, filtered, and their absorbance was measured using UV-Vis spectrophotometry [17].

Results And Discussion

Organoleptic Properties

The granules formulated in this study have a distinctive aroma and a white to yellowish-brown color (Figure 1). The yellowish-brown color is due to the presence of sodium alginate. The characteristic aroma of the granules is derived from the active ingredient, ranitidine.

Flow Properties

The flow rate of granules is critical for producing high-quality tablets that comply with manufacturing specifications. Good flowability is essential for the efficient mixing of ingredients, ensuring uniformity in both weight and active ingredient content in the final product. Particle size and shape are key factors influencing the flow properties of granules. The evaluation of flow rate revealed that all three formulations exhibit a flow rate greater than 10 g/s, which indicates excellent flow characteristics. Furthermore, all formulations demonstrated an angle of repose of less than 30°, confirming that the granules have good flowability through the test funnel [18].

A slightly different outcome is observed in the compressibility index (CI), which ranges from 21.35% to 24.1%, classifying the granules as acceptable (Table 2). Ideally, a

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CI value below 20% is preferred, as it indicates superior flow properties. A lower CI suggests that the granules exhibit better flow characteristics. The CI value is primarily influenced by the granules' ability to fill the spaces between them when poured into a graduated cylinder. Better flow results in tighter packing of granules, minimizing the remaining void spaces. During tapping, the granules shift minimally to fill any remaining gaps, leading to slight compression and a lower CI value [16]. The wet granulation process, which employs PVP K30 as a binder, enhances the flow properties of the granules compared to the original powder form of each component [19, 20].

Table 2. Properties of mucoadhesive ranitidine granules

Formula	Flow rate (g/s)	Repose angle (°)	CI (%)	Hausner ratio	Moisture content (%)	Wash off (min.)
F1	14,28±0,31	27,25±0,47	21,38±2,28	1,27±0,04	1,6±0,0	22,4±8,19
F2	12,64±0,23	26,84±0,24	21,35±2,23	1,27±0,04	1,9±0,4	19,4±4,15
F3	12,3±0,23	27,13±0,63	24,1±0,27	1,32±0,07	2,59±0,2	77,34±48,75

Moisture Content

The moisture content test results indicate values ranging from 1.60 - 2.59%. Higher moisture content can impair the flowability of granules, while excessively low moisture content may cause the granules to disintegrate into their constituent powders. This is because the binder, PVP K30, requires a certain level of moisture to maintain its effectiveness and produce well-formed granules. The moisture content can be controlled through the drying process, by adjusting both the duration and temperature of drying [21].

Swelling Test

This test is conducted to evaluate the effectiveness of the mucoadhesive formulation. The test is performed in simulated gastric fluid. Swelling capacity is determined by measuring the change in weight of the granules at specific time intervals, which is influenced by the polymer's ability to absorb liquid [17]. Higher liquid absorption corresponds to a greater swelling capacity of the formulation. The test results indicate that each formulation exhibited an average swelling capacity of more than 50%. Among the three formulations, F3 showed the highest swelling capacity, making it the most effective. This outcome is likely due to the higher concentration of sodium alginate in F3 compared to the other formulations. An increase in sodium alginate concentration enhances the swelling capacity [17].

Wash-Off Test

This evaluation aims to assess the mucoadhesive properties of the granules over a period of 2 hours. The wash-off test results show that F1, F2, and F3 have wash-off times

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of 22.40, 19.40, and 77.34 minutes, respectively. In contrast, the control formula without polymer had a wash-off time of only 1.6 minutes, due to the absence of sodium alginate, which serves as a binder. Without sodium alginate, the granules have reduced adhesion to the gastric mucosa, resulting in a shorter attachment duration. The polymer in the granules interacts with the mucus, creating attractive forces between the two surfaces, which facilitates adhesion. Among all the formulas, F3, which contains the highest concentration of sodium alginate, is the best formulation due to its longest wash-off time compared to the others [17].

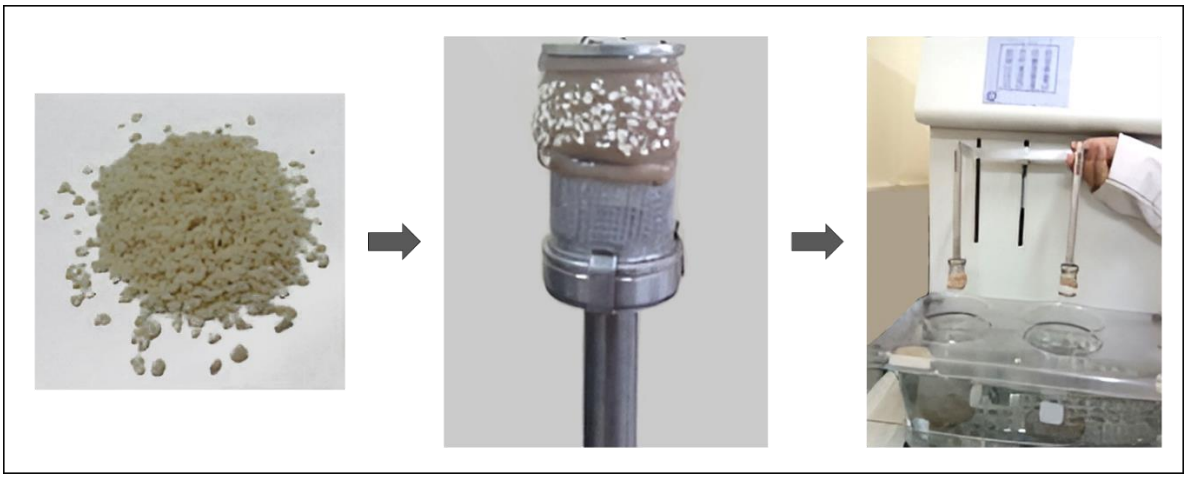

Figure 1. Wash-off test for mucoadhesive ranitidine granules

Dissolution Test

The dissolution test evaluates the amount of drug that dissolves within a specific time frame. This test was performed exclusively on formulation F3, which exhibited the best wash-off performance and is therefore considered suitable for large-scale development (Figure 2). The results showed that 90.04% of the drug dissolved within the first 5 minutes, and the entire dose of ranitidine was completely dissolved by 30 minutes. These findings indicate that the mucoadhesive formulation does not negatively impact the active ingredient. In fact, the combination of sodium alginate and PVP K-30 in the mucoadhesive formulation facilitates the efficient release of the active ingredient from the matrix. The polymers in the formulation improve the dosage form's adherence to the mucosa, allowing for complete drug release prior to gastric emptying [22].

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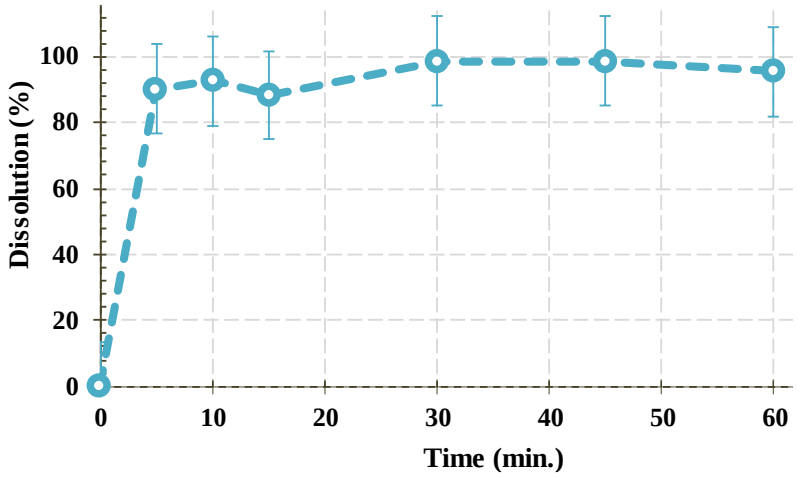

Figure 2. Dissolution profile of mucoadhesive ranitidine granules (F3)

All study parameters indicate that increasing the concentration of sodium alginate enhances the formulation's characteristics, including granule flow, swelling capacity, and wash-off resistance — key properties for a gastroretentive mucoadhesive system. Therefore, developing mucoadhesive formulations using natural polymers like sodium alginate could be beneficial for a wide range of drugs with low bioavailability. In the study framework, this effect was observed to peak at a concentration of 11%. Based on the case example, optimizing sodium alginate up to this threshold contributes significantly to the overall performance of the formulation. However, the impact of using concentrations beyond this level could not be clearly determined within the scope of this study.

Conclusion

Sodium alginate enhances the adhesion of granules to the gastric mucosa. Of the three tested formulations, F3 proved to be the optimum formula, demonstrating the best swelling capacity and dissolving over 90% of the drug within the first five minutes.

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