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Expandable Ranitidine HCl tablets with Salak Bali seed matrix (*Salacca zalacca*)

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ABSTRACT

This research aims to develop ranitidine HCl tablets that can be expanded with a matrix from Balinese salak seeds (Salacca zalacca) as a natural matrix material. This formulation is expected to prolong the release time of the drug in the body, thereby increasing the effectiveness of ranitidine therapy in the treatment of gastric diseases. The research method included the extraction of the active components from Balinese salak seeds and the process of making tablets using the wet granulation method, followed by physical tests of the tablets which included the hardness, crushing time, and ability of the tablets to expand. The results showed that ranitidine HCl tablets with Balinese salak seed matrix had physical characteristics that met the requirements of pharmacopooeia, with a slower drug release time than tablets without a developer matrix. Analysis of development capabilities shows that Balinese salak seeds are effective as natural matrix agents to prolong the release time of ranitidine HCl. In conclusion, Balinese salak seed matrix can be used as an alternative in the development of expandable ranitidine HCl tablets, potentially increasing the therapeutic effect of the drug.

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INTRODUCTION

The rapid development of industrial technology in the pharmaceutical field causes high consumer expectations for a product. The ever-increasing cost of production is one of the challenges that must be faced by manufacturers in the pharmaceutical industry. To be able to answer these challenges, producers are required to continue to explore all the potentials they have, such as the development of production equipment or product development in terms of excipients. Innovations that can be carried out are in the form of finding new excipients that have the potential to replace the excipients that have been used so far. The new excipients that are being tried to be developed are physically and chemically modified excipients. The use of new excipients, especially in tablet products, is expected to reduce production costs but not experience changes in the safety, quality and quality of the tablet products produced (Uddin et al., 2011)

The development of formulation technology is mostly carried out towards the development of controlled release dosage forms. The controlled release of active substances in the digestive tract can be achieved by several methods, namely expandable systems, high density systems, mucoadhesive systems, extendable or expandable systems and superporous hydrogels. Expandable systems can be achieved in several ways, including using a matrix that has a low bulk density; is highly porous; and experiences a decrease in density if it comes into contact with gastric fluid caused by the development of the matrix. A potential source of amylum that can be developed in Indonesia and can increase economic value is salak seeds. Physical modification of salak seed amylum that meets SNI (Indonesian National Standard) standards for chemical characteristics and pharmaceutical physical parameters can be done through a fully gelatinized process. Modification is carried out by heating the amylum of salak seeds above the gelatinization temperature, which is at a temperature of 80°C. The fully gelatinized process can cause the amylose to be damaged, so the amylopectin component will be more and increase the swelling ability (Asrofi et al., 2018)

The optimization method that can be done to determine the optimal proportion of the material mixture is the SLD (simplex latice design) method. The SLD method is used to determine the relative proportion of the mixture of ingredients in the formula, with the hope that an optimal formula will be produced from the mixture

according to the predetermined criteria. Controlledly released ranitidine HCl in the stomach is expected to be absorbed immediately in the stomach or in the upper part of the small intestine. With such properties, it is hoped that ranitidine HCl formulated in the form of gastroretentive preparations can release the drug in the stomach and can be immediately absorbed (give a linear correlation). Many methods can be used to evaluate the release model of a drug from a modified release preparation, including zero-order kinetics, first-order kinetics, Higuchi, Korsmeyer-Peppas and a compartment-based model (WinSAAM) that can describe the dissolution profile of ranitidine HCl from gastroretentive tablet preparations with *an expandable system* (Khattab & Zaki, 2017; Mohammad Yusif et al., 2016)

In synergy with the Udayana Research Master Plan (RIP) for 2022-2026, in the field of health and drug excellence (C3.2), which is related to the development of raw materials, pharmaceutical preparation auxiliary ingredients and phytopharmaceutical formulations, where the position of this research as a new approach for expandable sustained-release tablet preparations is physically modified (fully gelatinized) to amylum derived from the amylum of salak seeds (*Salacca Zalacca*) to produce excipients that conform to standardized matrix characteristics.

METHOD

The ingredients used in this study are salak seeds (*Salacca Zalacca*) taken from Tabanan Bali Indonesia, ranitidine HCl (Chemo Lugano), hydroxypropyl methylcellulose K4M® (Colorcon), magnesium stearate (Bratachem), sodium chloride (p.a Merck), methanol (p.a Merck), aquaades (Bratachem), acetonitrile (p.a Merck), and raw ranitidine HCl (catalog number 66357-59-3 SIGMA), raw ornidazole (catalog number 16773-42-5 SIGMA), male beagel (certificate perkin number 27121).

The tools used in this study are a tablet machine (single punch Korsh® USA), hardness tester (stokes mosanto® USA), thickness gage (mitutoyo Japan), spectrophotometer (Hitachi® U-2810 Japan), HPLC (Shimatzu® Japan), Phenomenex® USA column (LiChrosorb particle size 10µm, RP-18, 100 Å, length 250 mm x inner diameter 4.00 mm), magnetic stirrer (Heidolph MR3001®) analytical balance (Mettler Toledo® USA), USP type II dissolution test equipment (Erweka DT-700® Germany), disintegration tester (Erweka Z.T.21 Germany), friability tester (Erweka, Germany), Stable Micro System TA. XT *plus*, Forrie Transform Infra Red (FTIR) Shimadzu Brand, Type: IRPrestige 21, SEM or Scanning Electron Microscope HITACHI FLEXSEM 100 equipped with EDS (Energy Dispersive X – Ray Spectroscopy), Olympus BHA 2 Trinocular Polarization Microscope Adapter with Canon EOS 700 D DSLR Camera and Digital Monitor, Rapid Visco Analysis RVA 4500 (Perten Instruments, Sweden), X-Ray Diffraction (XRD) PanAnalytical Brand, Type: E'xpert Pro with Software High Score Plus and PDF2, differential scanning calorimetry (DSC)(NETZSCH, Selb, Germany).

The amylum of fully gelatinized salak seeds was made with the parameters of the modified process that had been optimized (Table 1). The ratio of amylum : aqueous is with a ratio of 1 : 1 (w/v). The mixture is then stirred until a homogeneous suspension is formed. The suspension is heated at 80oC for 15 minutes until a viscous period is formed. The thick period is dried in an oven at 60oC for 48 hours, after drying then ground and sifted using mesh 20.

Table 1. Process conditions of fully gelatinized *Salacca Zalacca* starch (FGSS)

Parameter	Process Conditions
The temperature of fully gelatinized	80ºC
Heating time period	15 minutes
Oven temperature	60ºC
Oven period	48 hours

Analysis of pharmaceutical properties characteristics includes characteristics of amylum granules using polarization microscope and SEM (Scanning Microscope Electron), RVA (Rapid Visco Analysis) profile, XRD (X-ray Diffraction) criticality, microscopic, macroscopic analysis, crystallin and amorphous region analysis using FTIR (Fourier Transform Infrared), Viscosity, Energy Dispersive X-Ray Spectroscopy (EDS/EDX), TPA and retrograde degree analysis with Differential Scanning Calorimetry/DSC. The tablet formulation method uses the granulation method, because all the ingredients in the formula are fine powders, so they cannot be directly flattened. The data analysis of WinSAAM-based solution and HPLC system for the determination of ranitidine levels of HCl in vivo tests and data from in vitro and in vivo test results was carried out IVIVC correlation analysis.

In this study, the variables to be optimized are FGSS (X1), HPMC K4M (X2) and Mg Stearate (X3). The total mixture of X1 + X2 + X3 for each formula is 120 mg, with a total weight of 150 mg tablets containing 33.48 mg of ranitidine HCl. Determination of minimum and maximum limits for the three optimized components based on the results of literature studies and preliminary research.

Simplex lattice design was used for the optimization of the formula of expandable ranitidine HCl tablets with FGSS levels of 20-80 mg, and HPMC K4M 10-40 mg, Mg stearate 0-10 mg. The optimal formula using the Design-Expert® program is based on the following parameters: granule flow properties, physical properties of tablets, and drug release. Based on the simplex lattice design for 3 independent variables, 14 experiments are needed on various mixture compositions for the three components (FGSS, HPMC K4M, and Mg stearate) the mixture composition can be seen in tables 2 and 3.

Table 2. Ranitidin HCl tablet formula with expandable tablets system

Material	Amount (mg)
Ranitidin HCl	33,48a
Amilum FGSS	20-80 [b]
HPMC K4M	10-40 [c]
mg stearate	0-10 [d]

Information:
a : (Mohammad Yusif et al. , 2016)
b : (Sugiura et al., 2017)
c : (Yin et al., 2018)
d : (Ali et al., 2018)

Table 3. Proportions of each component according to simplex lattice design

Run	Ingredients (mg)/tablet		
	FGSS (X1)	HPMC K4M (X2)	Mg stearat (X3)
1	76,67	36,67	6,67
2*	80,00	40,00	0,00
3	78,33	33,33	8,33
4#	75,00	35,00	10,00
5	80,00	35,00	5,00
6*	80,00	40,00	0,00
7¥	80,00	30,00	10,00
8¥	80,00	30,00	10,00
9∞	70,00	40,00	10,00
10∞	70,00	40,00	10,00
11	75,00	40,00	5,00
12	78,00	38,33	3,33
13#	75,00	35,00	10,00
14	73,33	38,33	8,33

Information:
Run 2 with 6, 4 with 13, 7 with 8, F9 with 10 with the same formula

Determination of formula and plot contour related to the physical properties of tablets and drug release

The equation used in the simplex lattice design is for 3 factors:

$Y = b1X1+b2X2+b3X3+b12X1X2+b23X2X3+b13X1X3$ .. ……..…….(1)

Description: Y = Reply
X1,X2,X3 = fraction of each component
b1,b2,b3 = regression coefficient of X1,X2,X3
b12, b23, b13 = regression coefficients of X1-X2, X2-X3, X1-X3

Determination of the optimal formula based on the equations obtained

Based on the data of the results of the physical properties and release of ranitidine HCl from slow-release tablet preparations with system expandable, then the coefficients B1, B2, B3, B12, B23, B13 can be calculated for each test result. Next is to determine the equation and create a profile of each parameter tested using software Design-Expert®, from each contour plot created curve superimposed so that the optimal formula region is obtained (Sreeja et al., 2018).

Analyze the Results

The data from the test results of the physical properties of granules and tablets and the release of ranitidine from the tablets were analyzed using Design-Expert® software, so that *a contour plot* was obtained from each test result. The determination of the optimum formula begins by determining the optimized parameters, namely flow velocity, tablet hardness, tablet brittleness, *expandable* time and ranitidin HCl release rate.

The data from the dissolution test results made a relationship curve between the number of drugs dissolved versus time and time root, and the regression equation was sought. The value of the correlation coefficient of the number of dissolved drugs versus time and root time was compared to determine the kinetics and mechanism of drug release from tablet preparations. The slope value of the regression equation is the speed of drug release. Drug release kinetics modeling was made according to: zero order kinetics, first order kinetics, Higuchi, Korsemeyer-Peppas and curve fitting with WinSAAM. The data from the dissolution test results were also calculated with f2 (similarity factor) and f1 (difference factor) values.

Data from in vivo absorption test results made a relationship curve between drug levels in the blood versus time. The calculated parameters include: AUC, C max, t max, t1/2 elimination and K elimination. The data from the in vitro and in vivo tests were then analyzed for in vitro - in vivo correlation (IVIVC). Relative bioavailability is calculated by equation 3.6.

F = (AUC mini tablet expandable/AUC conventional tablet) X 100% …….(3.6)

Pharmacokinetic parameter data obtained from mini expandable tablets and conventional tablets were analyzed by statistical paired sample test with a confidence level of 95%.

RESULTS AND DISCUSSION

Optimal Formula and Manufacturing of Mucoadhesive Nanoparticle Tablets of Salak Fruit Peel Extract

The process of making mucoadhesive nanoparticle tablets of salak fruit peel extract was carried out in the Pharmacy Laboratory of the Pharmacy study program, Faculty of Mathematics and Natural Sciences, Udayana University using 16 formulas that have been produced. The tablets that have been made are then evaluated by tests. The tablet evaluation tests carried out were organoleptics test, weight uniformity test, brittleness test, hardness test, crush time test, and adhesive lag time test. From the results of the evaluation test, the optimum formula of mucoadhesive nanoparticle tablets of salak fruit peel extract containing SNEDDS (Self-Nano Emulsifying Drug Delivery System) salak fruit peel extract was obtained by 77%, fully gelatinized kimpul taro amylum by 9.67%, sodium alginate by 9.5%, and magnesium stearate by 3.83%. The optimal formula of the tablets that have been obtained, then a solution test is carried out to determine the solubility of the active substances from the tablet preparations made.

Total Flavonoid Levels Mucoadhesive Nanoparticles Tablets Salak Fruit Peel Extract

The total flavonoid content in mucoadhesive nanoparticles of salak fruit peel extract was measured quantitatively using a UV-Vis spectrophotometry tool based on the colorimetric reaction of AlCl3 and quercetin as a standard solution. The measurement of total flavonoid levels was carried out using UV-Vis spectrophotometry because the flavonoid compounds contain conjugated aromatic groups so that they can show strong absorption bands in the ultraviolet light spectrum and visible light spectrum (Makuasa & Ningsih, 2020; Nurlinda et al., 2021). The AlCl3 colorimetric reaction has the principle of forming a complex between AlCl3 and the group contained in flavonoid compounds so that there is a shift in wavelength in the visible direction which is marked by a change in the color of the solution to become more yellow. Flavonoids have keto groups on the C-4 atom and hydroxy groups on the C-3 or C-5 atoms which are neighbors of the flavone and flavonol groups (Suharyanto & Hayati, 2021). This is also what causes the use of quercetine as a benchmark solution (Quercetine Equivalent/QE). Quercetin is included in flavonol compounds that can react to form complexes with AlCl3 and its glycosides are easy to find, which ranges from 60-75% of the total flavonoids (Solikah et al., 2023). The mechanism of formation of flavonoid complexes with AlCl3 can be seen in the figure below.

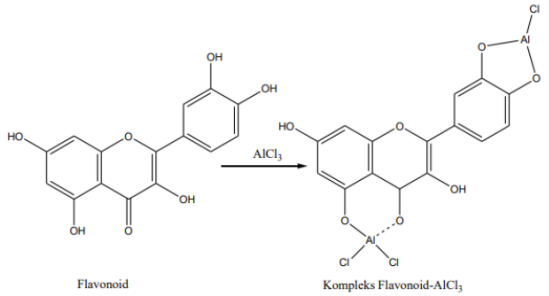


Figure 1. Formation of Flavonoid Complexes with AlCl3 (Suharyanto & Hayati, 2021)

The standard solution of quercetin is made into several concentration series, namely 25 ppm, 50 ppm, 75 ppm, and 100 ppm. Each series solution is measured for absorption using a UV-Vis spectrophotometer to obtain a standard curve. However, before measuring the absorbance of the series solution, it is necessary to measure the maximum wavelength. This is a very important factor in the analysis method with a UV-Vis spectrophotometer because when the maximum wavelength has maximum sensitivity so that the largest change in absorption occurs at each concentration, the absorption curve produced is linear, the repetition of errors that can occur will be small, and the Lambert-Beer law can be fulfilled (Suharyanto & Hayati, 2021). Maximum wavelength measurements are made by running from the wavelength 400-500 nm. The running results showed that the maximum wavelength of the quercetin standard was at a wavelength of 425 nm. The maximum wavelength will later be used to measure the absrobance of the series solution so as to obtain a standard curve and a mucoadhesive tablet sample of salak fruit peel extract nanoparticles.

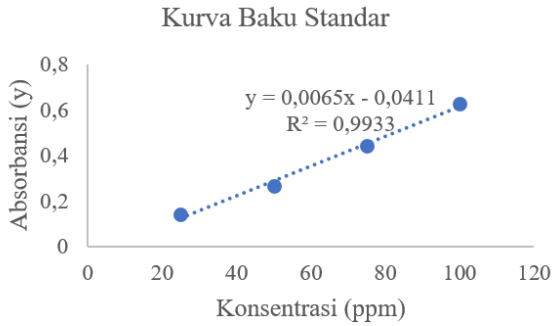


Figure 2. Standard Standard Curve

The quaercetin standard curve is obtained from the relationship between the concentration of the quercetin series and its absorption which can be seen in Figure 6. It can be seen that the resulting standard curve is linear. This means that the increased concentration is also accompanied by an increase in absorption (Suharyanto & Hayati, 2021). The linear regression equation obtained based on the quatercetin standard curve is y = 0.0065x – 0.0411 with a value of R2 = 0.9933. The value of the correlation coefficient (r), which is almost close to 1, shows a strong correlation between absorbance and concentration (Solikah et al., 2023). The linear regression equation obtained was then used to calculate the total flavonoid content in the mucoadhesive nanoparticle tablets of salak fruit peel extract by inserting the absorbance of the sample into the regression equation.

In order to obtain relevant results in determining the total flavonoid content of the mucoadhesive nanoparticle tablets of salak fruit peel extract, it is necessary to validate the method first before determining the level. The validation of the method carried out is to determine accuracy, precision, linearity, detection limit (LOD) and quantity limit (LOQ). The results of method validation can be seen in table 3.

Table 4. Results of Validation Analysis of Total Flavonoid Levels Determination Method

Concentration (ppm)	Absorbansi installment	Precision (%RSD)	Accuracy (%*recovery*)	Linearity (R2)	LOD (ppm)	LOQ (ppm)
25	0,139	1,1578	110,831	0,9933	8,201	27,337
50	0,2654	1,9906	94,308			
75	0,4425	2,3809	99,2			
100	0,6256	0,8392	102,574			
Installment			1.5921 101.728			

Based on the precision calculation indicated by the relative standard deviation value (%RSD), an average result of 1.5921% was obtained. The results obtained have met the %RSD requirement, which is ≤2% (Harmita, 2004). Then, the accuracy indicated by the value of the percentage of recovery (%recovery) obtained an average of %recovery of 101.728%. The results obtained have met the %recovery requirement, because they are in the range of 98–102% (Harmita, 2004). Then, the value of the determination coefficient (R2) aims to see the proximity of the approximate value for the regression analysis that represents the actual data. the coefficient of determination (R2) obtained was 0.9933. This correlation coefficient gives linear results because it meets the acceptance criteria, which is ≥ 0.98. The next method validation carried out is to determine the detection limit (LOD) and quantity limit (LOQ) for the UV-Vis spectrophotometry method based on the deviation of the response and slope of the standard curve, which are obtained at 8.201 ppm and 27.337 ppm, respectively. The purpose of determining the detection limit is to find out the smallest number of analytes that

can still be detected but do not need to be measurable and the purpose of determining the quantitative limit is to find out the smallest number of analytes that can still be measured accurately (Currie, 1968; Klymus et al., 2020). Based on the results of the validation of the method that has been carried out, it can be said that this method is valid and can produce precise and accurate results in determining the total flavonoid levels of mucoadhesive nanoparticle tablets of salak fruit peel extract. The total flavonoid content in the mucoadhesive nanoparticle tablets of salak fruit peel extract can be seen in table 5.

Table 5. Total Flavonoid Levels Mucoadhesive Nanoparticles Tablets Salak Fruit Peel Extract

	Up to Flavonoids Total (MagK/Tablet)	**Average Rate Flavonoid Total (MagK/Tablet)**	**SD**	**%RSD**
Replication 1	4,879			
Replication 2	4,998	4,913	0,0746	1,52
Replication 3	4,861			

Based on table 5, after three replications, the average total flavonoid content contained in the mucoadhesive nanoparticle tablets of salak fruit peel extract was 4.913 ± 0.0746 mg QE/tablet with a %RSD value of 1.52%. This means that in each mucoadhesive tablet nanoparticles of salak fruit peel extract contain flavonoid compounds equivalent to 4.913 ± 0.0746 mg of quercetin and have good precision in the replication results because the RSD value ≥ 2% (Harmita, 2004).

Salak Fruit Peel Extract Nanoparticle Mucoadhesive Tablet Dissolution Test

The dissolution test is a parameter used in the development of drug preparations to measure the speed of release and dissolution of active substances from the preparation. The disolution test is used for in vitro bioavailability tests, because it is related to the bioavailability of drugs in the body (Evard et al., 2016). The dissolution test on the mucoadhesive nanoparticle tablet preparation of salak fruit peel extract was carried out to determine the percentage of release of active substances, namely flavonoids that can be released from the matrix and dissolved in the solution medium during a certain time interval.

The solution test in this study was carried out using a USP 2 model solution device with a paddle type on an artificial gaspitude fluid medium with pH 1.6. This mucoadhesive nanoparticle tablet of salak fruit peel extract is designed to stay in the stomach for a long time. Therefore, the medium used is an artificial gastric fluid medium that describes the condition of the fasting stomach with a pH of 1.6. The duration of time used in the test of this tablet solution is 360 minutes or 6 hours. Then, a stirring speed of 50 rpm and a medium temperature of 37 ± 2°C are used to adjust to the hull conditions. Sampling was carried out 8 times at intervals of 30, 60, 90, 120, 280, 240, 300, and 360 as much as 5 mL. Each sampling is also filled with a new solution medium with the same volume, namely 5 mL, to keep the volume of the solution medium the same from the beginning of the test to the end. In addition, it also aims to maintain a sink condition so that the media is not saturated with drugs.

The samples that have been taken are then measured for absorption using a UV-Vis spectrophotometer. Before measuring the total flavonoid content from the results of the disolution test, it is necessary to determine the maximum wavelength and standard curve of quercetin in the disolution medium. The results of the maximum wavelength measurement showed that the maximum wavelength used to determine the total flavonoid level was resolved at a pH medium of 1.6, which was 423 nm. Then, the standard curve obtained from the four series of concentrations of the standard quercetin solution that have been measured for absorption and connected with the concentration of the series solution produces a linear regression equation of $y = 0.0038x–0.0504$ with a value of $R^2 = 0.9874$ (can be seen in figure 3).

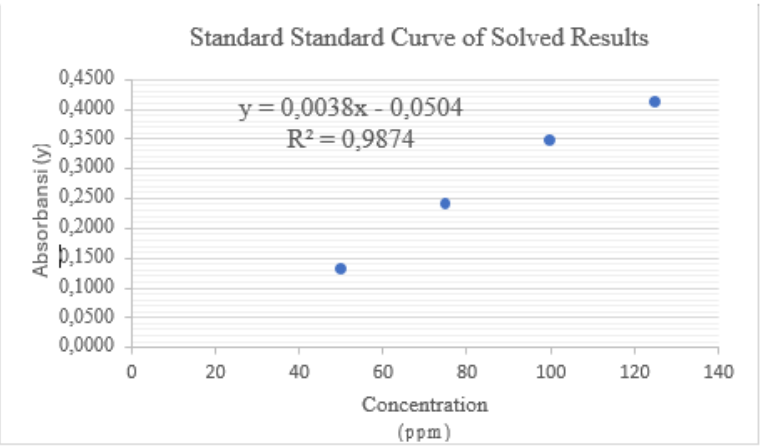


Figure 3. Standard Standard Curve of Solved Results

Then, method validation was carried out to determine the total flavonoid level of the solution result based on the calibration curve obtained. The validation of the method carried out is to determine accuracy, precision, linearity, detection limit (LOD) and quantity limit (LOQ). The results of method validation can be seen in table 6.

Table 6. Results of Validation of the Method for Determining Total Flavonoid Levels Solved

Concentration (ppm)	Absorbansi installment	Precision (%RSD)	Accuracy (%recovery)	Linearity (R2)	LOD (ppm)	LOQ (ppm)
25	0,1308	1,168	95,585			
50	0,2391	0,418	101,579			
75	0,3471	1,547	104,605	0,9874	10,93	36,43
100	0,4115	1,312	97,242			
Average		1,111	99,703			

Based on the precision calculation indicated by the relative standard deviation value (%RSD), an average result of 1.111% was obtained. The results obtained have met the %RSD requirement, which is ≤2% (Harmita, 2004). Then, the accuracy indicated by the value of the percentage of recovery (%recovery) obtained an average %recovery of 99.703%. The results obtained have met the %recovery requirement, because they are in the range of 98–102% (Harmita, 2004). Then, the value of the determination coefficient (R2) aims to see the proximity of the approximate value for the regression analysis that represents the actual data. the coefficient of determination (R2) obtained was 0.9874. This coefficient of determination gives linear results because it meets the acceptance criteria, which is ≥ 0.98. The next method validation carried out is to determine the detection limit (LOD) and quantity limit (LOQ) for the UV-Vis spectrophotometry method based on the deviation of the response and slope of the standard curve, which are obtained at 10.93 ppm and 36.43 ppm, respectively. Based on the results of the validation of the method that has been carried out, it can be said that this method is valid and can produce precise and accurate results in determining the total flavonoid level of the mucoadhesive nanoparticle tablets of salak fruit peel extract as a result of the solution.

After measuring the absorbance of the dissolved sample at the appropriate maximum wavelength using a UV-Vis spectrophotometer, the absorbance is then substituted into a linear regression equation to obtain the total flavonoid content of the tablet from the results of the dissolved test expressed in the form of % dissolved content which can be seen in table 6. Based on the data in table 5, the average level of % dissolution of mucoadhesive nanoparticles of salak fruit peel extract tablets for 6 hours was 18.173%. The % disolution data obtained will then be used to determine the mechanism of flavonoid release from mucoadhesive nanoparticle tablets of salak fruit peel extract.

Table 7. % Content Data Dissolution of Mucoadhesive Nanoparticles Salak Fruit Peel Extract pH 1.6

Time	Up to %Disolution		
	R1	R2	R3
0	0	0	0
30	15,876	15,868	15,885
60	16,606	16,597	16,614
90	17,573	17,565	17,582

120	18,420	18,411	18,429
180	21,290	21,272	21,285
240	23,355	23,346	23,364
300	24,413	24,422	24,422
360	26,032	26,024	26,015

Mucoadhesive Nanoparticle Tablet Release Study of Salak Fruit Peel Extract

Drug release studies are aimed at finding out how the mechanism of drug release from the dosage form is. By knowing the drug release mechanism from the dosage form, it can be used as a reference in efforts to develop drug formulations, such as designing drugs according to needs and predicting drug release in vivo so that it can increase the therapeutic efficacy of the drug and ensure drug safety (D'Souza, 2014). Because, there are qualitative and quantitative changes in the formulation of a drug can change the drug release mechanism and drug performance in vivo (Nugroho et al., 2021). Therefore, this study was conducted to find out how the mechanism of release of flavonoids as active substances in mucoadhesive nanoparticles of salak fruit peel extract tablets.

The data from the tablet solution that has been carried out is processed statistically or using several kinetic model equations contained in an add-in program in Microsoft Excel software, namely DDSolver. DDSolver is a program developed to analyze the kinetics of dissolved data with a non-linear regression approach. The reason for using DDSolver in data modeling is that it is simpler and easier to use, can speed up calculations, and reduce errors in data analysis (Zhang et al., 2010). The data of the results were solved in the form of the percentage of solved (% solved) and time in minutes were entered into the DDSolver program. In this study, the drug release kinetics models used were Zero Order, First Order, Higuchi, and Korsmeyer-Peppas. Some of the parameters used to assess which kinetic model is in accordance with the drug release profile are seen from the three most important parameters, namely the adjusted determination coefficient (R2adjusted), the Akaike Information Criterion (AIC), and the selection criterion (MSC) model (Zuo et al., 2014). R2-adjuste is a measure of how far the regression line represents the data. Whereas, AIC is and MSC are a form of reciprocity that has been modified from AIC and has been normalized so that it does not depend on data point scaling. The lowest AIC value and the largest MSC value indicate the most appropriate drug release kinetic model. Meanwhile, the R2adjusted value closest to 1 indicates the best drug release kinetic model (Nugroho et al., 2021).

The results of the study of total flavonoid release from tablets using DDSolver can be seen in table 8.

Table 8. Results of the Study on the Total Flavonoid Release of Mucoadhesive Nanoparticles of Salak Fruit Peel Extract

Model	R2adjusted	AIC	MSC	Discharge Rate (mgQE/hr)
Zero order k0 = 0,093	-0,093	58,278	-1,496	0,0046
First order k1 = 0,001	0,072	56,812	-1,333	0,00005
Korsmeyer - Peppas kKP = 7,128 n = 0,213	0,986	20,066	2,749	0,3502
Higuchi k = 1,557	0,781	43,798	0,112	0,0765

The zero-order kinetics model is a drug release mechanism whose drug release rate is constant and is not affected by drug concentration. This kinetic model can be used to describe the drug release mechanism of several types of modified release dosage forms, such as transdermal preparations and matrix tablets with drugs that have low solubility. Based on the data from the release study that can be seen in table 7, the zero-order kinetics model shows an R2adjusted value of -0.093 with AIC and MSC values of 58.278 and -1.496. Based on these values, the zero-order kinetics model does not match the total flavonoid release mechanism from the mucoadhesive nanoparticle tablets of salak fruit peel extract because the resulting R2adjusted value has a small value compared to other kinetic models. In addition, the AIC and MSC scores are also not qualified compared to other kinetic models. Meanwhile, the value of the drug release rate produced is 0.0046 mgQE/hour**.** The graph of the dissolution profile in the zero-order kinetics model can be seen in figure 4.

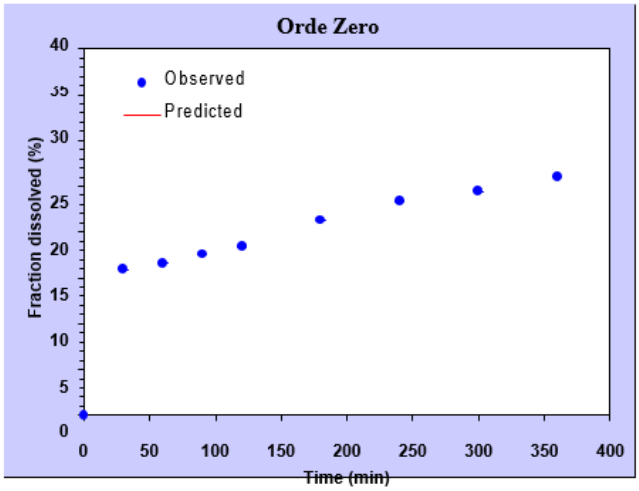


Figure 4. Profile of Zero-Order Kinetic Model Solution

The first-order kinetics model is the concentration-dependent release of the drug where the velocity at a given time is proportional to the concentration of the drug remaining in the preparation at that time. This kinetic model can be used to describe the dissolution of drugs in the form of pharmaceutical preparations such as water-soluble drugs in a porous matrix system. Based on the data from the release study that can be seen in table 7, the first-order kinetics model shows an R2adjusted value of 0.072 with AIC and MSC values of 56.812 and -1.333. Based on these values, the first-order kinetics model is not in accordance with the total flavonoid release mechanism from mucoadhesive nanoparticle tablets of salak fruit peel extract because the resulting R2adjusted value has a greater value than the zero-order kinetics model, but it is still far closer to 1. In addition, the AIC and MSC scores are also not qualified compared to other kinetic models. Meanwhile, the resulting drug release rate value is 0.00005 mgQE/hour**.** The graph of the dissolution profile in the zero-order kinetics model can be seen in figure 5.

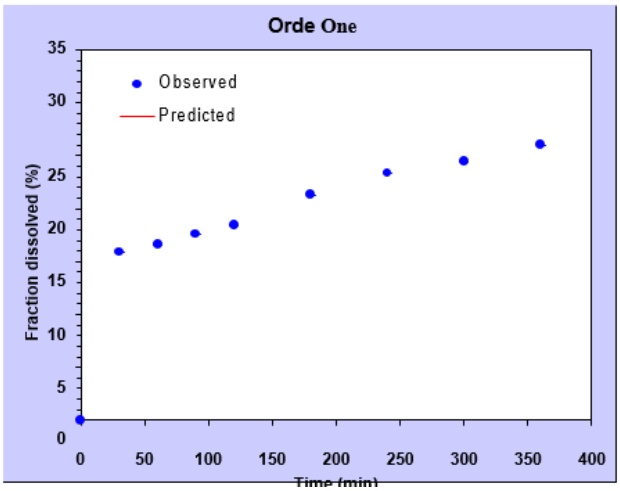


Figure 5. Profile of the First-Order Kinetic Model Solution

The Higuchi release kinetics model is the first example of a kinetic model equation describing the release of drugs from a matrix system. This kinetic model can be used to describe drug solutions of several types of modified release pharmaceutical preparations, such as some transdermal systems and water-insoluble matrix tablets. In this model, the drug release system from a water-insoluble matrix is directly proportional to the time root (t) and is based on fickian diffusion, which means that the release of an active substance can be affected by time. The longer the diffusion time interval of the active substance, the lower the dissolution velocity of the active substance to be released (Mahdi et al., 2016).

Based on the data from the release study that can be seen in table 7, the Higuchi kinetics model shows an R2adjusted value of 0.781 with AIC and MSC values of 43.798 and 0.112. Based on these values, the Higuchi kinetics model does not match the total flavonoid release mechanism of the mucoadhesive nanoparticle tablets of salak fruit peel extract because the resulting R2adjusted value has a larger value (almost close to 1) compared to the zero-order and first-order kinetics models. In addition, AIC and MSC values are

also the most qualified compared to zero-order and first-order kinetics models. Meanwhile, the value of the drug release rate produced is 0.0765 mgQE/hour**.** The graph of the dissolution profile in the Higuchi kinetic model can be seen in figure 6.

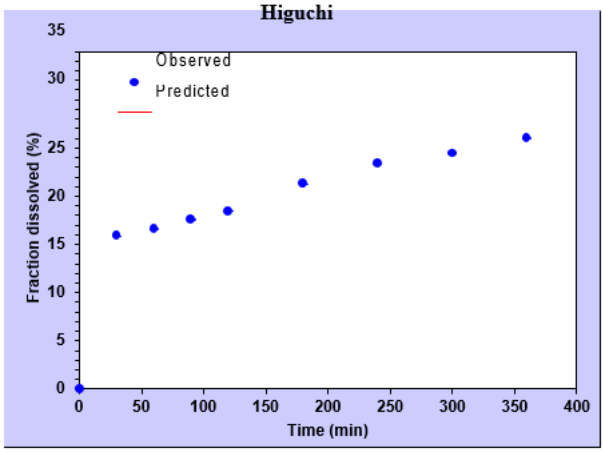


Figure 6. Profile of Higuchi Kinetic Model Disolution

The Korsmeyer-Peppas kinetics model is a kinetics model developed to describe the kinetics of drug release from polymer matrices. This model describes a semi-empirical model, where diffusion is the primary mechanism for drug release that exponentially links drug release to time. In the Korsmeyer-Peppas equation, there is a value of n, which is a diffusion exponent that can provide important information about the mechanism of drug diffusion release from polymers (Mahdi et al., 2016). In cylindrical matrix preparations such as tablets, the n-value on this model should be considered as it can describe how the mechanism of drug release is. The relationship between n and the release mechanism can be seen in Table 9.

Table 8. Relationship of n-Value with Drug Release Mechanism

n (emission exponent)	Discharge mechanism
< 0.45	Fickian diffusion
0,45 < n < 0,89	Non fickian (anomaly)
> 0,89	case-II transport

If 0 < n < 0.45 means that the release of the drug follows Fickian diffusion, which means that the release is affected by time where the longer the time, the lower the speed at which the active substance will be released. This is due to the longer diffusion distance of active substances. If 0.45 < n < 0.89 means abnormal release or non-Fickian diffusion and if n > 0.89 indicates the drug release rate independent of time indicating the release kinetics run through the order of zero and the mechanism is named Case-II transport (Ge et al., 2021).

Based on the data from the release study that can be seen in table 8, the Korsmeyer-Peppas kinetics model shows an R2adjuste value of 0.986 with AIC and MSC values of 20.066 and 2.749. Based on these values, the total flavonoid release mechanism from mucoadhesive nanoparticle tablets of salak fruit peel extract follows the Korsmeyer-Peppas kinetic model because the resulting R2adjusted value has the largest value or is closest to 1 compared to other kinetic models. In addition, AIC and MSC values are also the most qualified, namely with the lowest AIC value and the highest MSC compared to other kinetic models. Meanwhile, the resulting drug release rate value was 0.350 mgQE/hour and the value of n (diffusion exponent) was 0.213. This n value shows that the total flavonoid release mechanism of the mucoadhesive nanoparticle tablets of salak fruit peel extract follows fickian diffusion because n < 0.45 which means that the release is affected by time where the longer the time, the lower the speed of the active substance to be released. This is due to the longer diffusion distance of active substances. Based on the release profile graph on the Korsmeyer-Peppas kinetics model (figure 7), it can be seen that there is a spike in drug release in the first 30 minutes. This is in accordance with the theory of sustained release preparations where drug release occurs by releasing an appropriate dose of initial drug therapy (loading dose) followed by a slower and constant drug release (Maderuelo et al., 2011). In addition, the surge in release is caused by the polymer matrix used, namely fully gelatinized kimpul taro amylum which is a natural binder in tablets. Due to this natural nature, it causes the tablets to have a faster disintegration time so that there is a spike in the first minutes of drug release.

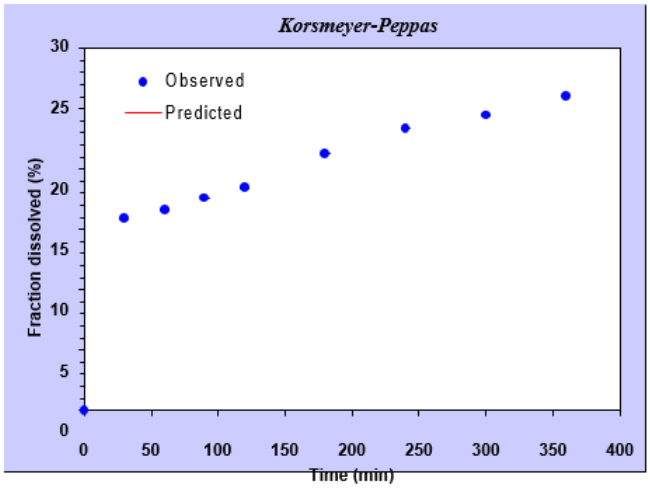


Figure 7. Profile of the Dissolution of the *Korsmeyer-Peppas Kinetic Model*

Diffusion occurs when the active substance of a drug flows through the pores of a polymer matrix or through the space between the polymer chains. When it hits gastric fluid, the polymer matrix expands and makes it easier for the active substance to diffuse. Once all the active substances are released, the polymer matrix will degrade as a result of the hydrolysis of the polymer matrix into small molecules that can be accepted by the body's systems. The existence of this diffusion process causes the active substance of the drug to slowly release from the matrix so as to avoid drug fluctuations and the concentration of the drug in the blood circulation remains stable (Maderuelo et al., 2011). This diffusion process can be caused by the hydrophilic properties of the sodium alginate and taro fully gelatinized polymers used as mucoadhesive polymers in the manufacture of these tablets. Hydrophilic polymer matrix systems are generally used for sustained release delivery systems such as in mucoadhesive nanoparticle tablets of salak fruit peel extract because they are flexible to obtain the desired dissolution profile, are cost-effective, and can resist the release of the active substance of the drug by trapping on the polymer layer that expands when in contact with gastric fluid . In addition, the sodium alginate polymer matrix is an anionic polymer with a carboxyl group in development has shown good survival during repeated contact with gastric fluids. The mechanism of action that occurs between sodium alginate and the gastric mucosa is an ionic interaction between the amino groups of positive and negative charges in the lining of the gastric mucosa. This mechanism is also supported by the existence of adhesion force, which is the force of attraction between particles with different charges. Thus, mucoadhesive tablets nanoparticles of salak fruit peel extract can stick to the gastric mucosa and cause the drug to stay longer in the stomach. This can increase the bioavailability of drugs, drug effectiveness, more effective drug absorption and drug bioavailability increase and the frequency of drug doses to be low (Al-Enizi et al., 2018).

CONCLUSION

This research succeeded in developing ranitidine HCl tablets that can be expanded by using Balinese salak seed matrix as a natural matrix material. The resulting formulation exhibits physical characteristics that meet pharmacopoeia standards, with a slower drug release time compared to tablets without a developer matrix. The results of the analysis showed that Balinese salak seeds were effective as a natural matrix agent that could extend the release time of ranitidine HCl, potentially increasing the effectiveness of therapy in the treatment of gastric diseases. Therefore, the use of Balinese salak seed matrix can be an interesting alternative in the development of drug preparations with a controlled release system.

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