International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Special Issue 6, 2024

Original Article

FORMULATION AND EVALUATION OF SODIUM DICLOFENAC SLOW-RELEASE TABLET USING A COMBINATION OF MANGROVE FRUIT STARCH (*BRUGUIERA GYMNORRHIZA*) AND SODIUM CARBOXY METHYL CELLULOSE (CMC) AS MATRIX

SETYO NURWAINI[1*], ANITA FITRI ANGGRAINI[2], ANITA SUKMAWATI[3], TEGUH IMANTO[4], WAHYU UTAMI[5]

[1,2,3,4]Pharmaceutic and Pharmaceutical Technology Laboratory, Faculty of Pharmacy Universitas Muhammadiyah Surakarta Jl Ahmad Yani Kartasura, Surakarta, Indonesia. [5]Pharmaceutical chemistry laboratory, Faculty of Pharmacy Universitas Muhammadiyah Surakarta Jl Ahmad Yani Kartasura, Surakarta, Indonesia

*Corresponding author: Setyo Nurwaini; *Email: sn164@ums.ac.id

Received: 26 Mar 2023, Revised and Accepted: 20 Sep 2024

ABSTRACT

Objective: Mangrove fruit (*Bruguiera gymnorrhiza)* has a high starch content that potential as a matrix for slow-release tablets. This study aims to determine the optimum formula for diclofenac sodium tablets using a matrix combination of mangrove fruit starch and sodium Carboxy Methyl Cellulose (CMC).

Methods: Optimization of the formula was carried out using the Simplex Lattice Design method. Evaluation of the tablet includes the physical properties of the granules, tablet, and dissolution profile.

Results: The combination of mangrove fruit starch of 15-45% and 0-30% CMC fulfilled the requirements for granule flow properties and the release of active substances. The optimum formula obtained was a combination of mangrove fruit starch 32.30% (193.80 mg) and 12.70% Na-CMC (76.20 mg) with a desirability value of 0.805.

Conclusion: The results of this study clearly showed that the combination of mangrove starch and CMC was successfully used in the slow-release tablet formulation of diclofenac sodium

Keywords: Mangrove fruit starch (*Bruguiera gymnorrhiza*), CMC, Sodium diclofenac, Optimization, Simplex lattice design

DOI: https://dx.doi.org/10.22159/ijap.2024.v16s6.TY2040 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Bruguiera gymnorrhiza or what is often called mangrove fruit, is most commonly found in Indonesian waters. The natural resources of Indonesia can be used for medicinal development [1]. Mangrove fruit has a high carbohydrate content, namely 32.91%. High carbohydrate content indicates a high starch content of around 57.73% with amylopectin of 26.17% [2]. Other studies showed the material contained in mangrove fruit (*Bruguiera gymnorrhiza*) is starch by 14.23% [3]. According to a study by Afandi *et al.* (2018), mangrove fruit flour with *Sonneratia caseolaris* species can be used as a disintegrant in the formulation of paracetamol tablets with an added level of 15% [4]. Mangrove fruit flour (*Soneratia caseolaris*) and the type *Bruguiera gymnorrhiza* have similar content: carbohydrates, fat, protein, and water. The range between the two types, especially carbohydrates in *Bruguiera gymnorrhiza* is higher at 78.85% compared to *Sonneratia caseolaris,* which is only 68.41% [5].

High starch content allows mangrove fruit to be used as an additional ingredient in making medicine. Matrix is one of the ingredients in slow-release tablet preparations, which are usually made from starch. Starches found in tropical vegetables and fruits have long been used as a nutritious carbohydrate source. The majority of these crops grow in abundance with little or less agricultural help and include gluten-free carbs in the form of starch. They have been researched for their superior medicinal excipient capabilities in formulations such as fillers, glidants, binders, and disintegrants. These starches can be exchanged for chemically modified starches that are commercially available. The various versions of the native forms of these starches have also been studied and shown to have features that make them potential candidates for controlled drug delivery systems [6].

Slow-release tablets are formulated by mixing the drug ingredients homogeneously with a matrix to cover the active substance so that it is not immediately absorbed by body fluids. Slow-release tablet preparations with a hydrophilic matrix that are commonly used are avicel [7], xanthan gum [8], sodium Carboxy Methyl Cellulose (CMC) [8, 9], methylcellulose, carboxy polymethylene, Hydroxy Propyl Methyl Cellulose (HPMC) [10]. The advantage of making slow-release preparations is that it can reduce the frequency of drug administration so that patients do not take the drug repeatedly in a short time. Diclofenac sodium is a drug that is made in slow-release tablet preparations.

This research was optimized using expert design with the simplex lattice design (SLD) method to determine the potential of mangrove fruit starch (*Bruguiera gymnorrhiza*), which is used as a matrix of diclofenac sodium slow-release tablets on drug release time.

MATERIALS AND METHODS

Materials

The ingredients used were *Bruguiera gymnorrhiza* fruit (Mangrove) was obtained from Mangunharjo village, Semarang, Indonesia. Other materials: diclofenac sodium (Sigma Aldrich, Singapore), polyvinylpyrrolidone (PVP) (Sigma Aldrich, Singapore), sodium Carboxy Methyl Cellulose (CMC) (Brataco, Indonesia), lactose (Brataco, Indonesia), magnesium stearate (Brataco, Indonesia), distilled water (Brataco, Indonesia, sodium metabisulfite (Sigma Aldrich, Singapore), NaOH (Sigma Aldrich, Singapore), and KH_2PO4 (Sigma Aldrich, Singapore).

Extraction of *Bruguiera gymnorrhiza* starch powder

Mangrove fruit peeled and cut into thin slices. The mangrove slices were soaked one night with a change of water when the water looked brown. The mangrove pieces were blended and then squeezed to extract the starch. The starch was precipitated overnight and the water was removed. The starch extract was dried at 40 °C and then crushed and sieved using a 100-mesh sieve.

Evaluation of mangrove starch

Organoleptic examination

Starch was tested organoleptically by direct observation including color, odor, and shape of starch.

Identification tests for the presence of starch

For the starch identification test, 1 g of starch was boiled with 15 ml of water. 0.1 N iodine solution was applied to 1 ml of cooled mucilage, and color change was noticed.

Flowability

As much as 100 g of starch was weighed and put into the funnel with the lower mouth of the funnel closed. The mouth of the funnel was opened and the time was recorded until the starch comes out of the funnel.

pH test

Starch as much as 1 g was weighed and dissolved in distilled water. The starch solution was read for its degree of acidity using a pH meter (Hanna instruments).

Moisture content

Starch was weighed as much as 3 g and then put into the moisture content balance (Ohaus). The measurement temperature was 105±2 °C.

Ash content

Starch was weighed as much as 4 g and then put into the crush cup. The crush cup containing starch was put into the furnace (Vurnanche model Vulcan D-550) at 600 °C for 3 h. The ashing results were left for 3 h until the container and sample were cool when weighed. The result of starch which becomes ash was then weighed to calculate the ash content.

Swelling capacity

In a 100 ml measuring cylinder, the tapped volume occupied by 10 g of each starch will be documented. The powder was dispersed in 85 ml of distilled water, and the volume will be increased to 100 ml by adding more water. The amount of sediment was assessed after 18 h, and the swelling capacity and swelling index were calculated [11].

Preparation of granules

Granules were made using variations in mangrove starch and CMC levels by determining the upper and lower levels of the two ingredients (table 1). A wet granulation process was used for formulations 1-5 (table 2). PVP as a binder was dissolved in 100 ml of distilled water. Diclofenac sodium, CMC, mangrove starch, and lactose were mixed until homogeneous. The mixture was moistened with PVP solution binder until a good granular mass was formed. The granules were sieved using a 12-mesh sieve and then dried in an oven at 60 °C for 18 h. The dried granules were sieved using a 14-mesh sieve and added with a magnesium stearate lubricant.

Table 1: Lower and upper limit of mangrove starch and CMC as a matrix in diclofenac sodium slow-release tablet

Level	A (mangrove starch)	B (CMC)
Lower limit	15%	0%
Upper limit	45%	30%

Evaluations of granules

Flow rate and angle of repose

Granules weighing as much as 100 g were put into the funnel with the lid of the lower funnel closed. The lid of the funnel was opened and the time when the granules flowed out of the funnel was recorded. The powder cone's diameter was measured to calculate the granules' repose angle.

Bulk density and tapped density

A total of granules 100 g (M) was put into a 250 ml measuring cylinder with a 2 ml scale. The volume of the granule in the measuring cylinder was the initial volume (V0). The bulk density is calculated as the ratio of M to V0. The tapped density is obtained by mechanically tapping a measuring cylinder filled with granules. After being determined, the volume of granules volume was expressed as the final volume (Vf). The compressed density of granules is calculated by the formula M/Vf [12].

Compressibility index and Hausner's ratio

The compressibility and Hausner's ratio were calculated based on the results of the bulk density and tapped density of the granules.

Hausner's Ratio = tapped density/bulk density

Moisture content

The granules are put into the moisture content balance (Ohaus) which was previously equalized, as much as 3 g. The start button was pressed and then waited a few minutes until the reading process stopped. The measurement temperature was 105±2 °C.

Preparation of tablets

Tablets containing 75 mg of diclofenac sodium will be manufactured, and the different formulas used in the study use differences in mangrove starch and CMC levels (table 2.) The granules were compressed into tablets with a weight of 600 mg per tablet using a single punch tablet machine (Korsch EK-0).

Table 2: Formulas of diclofenac sodium slow-release tablet formula using mangrove starch and CMC

Ingredients (mg)	F1	F2	F3	F4	F5
Diclofenac sod	75	75	75	75	75
PVP	30	30	30	30	30
Mangrove starch	270	90	180	225	135
CMC	0	180	90	45	135
Laktose	210	210	210	210	210
Magnesium stearate	15	15	15	15	15
Total	600	600	600	600	600

Evaluation of tablets

Thickness

The thickness of the tablets was measured with a vernier caliper, and the findings were represented as the mean of 10 measurements with standard deviations.

Weight variation

A total of 10 tablets were weighed individually. Each tablet was crushed and then dissolved in a 50 ml measuring flask with phosphate buffer pH 6.8. The solution was taken 25 µl diluted in a 5 ml measuring flask. The absorption of the solution was read using a

UV spectrophotometer (Milton Roy, Genesys 10) with a wavelength of 203 nm. The level is calculated by entering the absorbance into the standard curve equation. The acceptance value for the first 10 tablets is no more than 15%.

Hardness

Tablet hardness is measured by placing the tablet into a hardness tester. The screw is rotated until the tablet cracks and breaks. The tablet hardness test was carried out to determine the hardness of the tablet against pressure. Hardness requirements for slow-release tablets are 10-20 kg.

Friability

The friability of the tablets was tested by inserting 11 tablets or at least the total weight of the tested tablets was 6500 mg. The tablets are dust-free and weighed. The tablets were put into the friability tester, rotated at 25 rpm for 4 min, and removed from the tool. The free tablets were dusted again and weighed. The tablet friability requirement is less than 1%.

Disintegration time

This test is carried out by inserting tablets one by one into six tubes from the basket. The tool is run by being filled with water at 37 °C±2 °C as a medium. The tablets should disintegrate completely in less than 15 min. The test is repeated with 12 tablets if 1 or 2 tablets are not completely disintegrated, so no less than 16 tablets out of the 18 tested must be completely disintegrated [12].

Drug content

The UV technique was used to determine the amount of diclofenac sodium in the tablets in triplicate. The drug content of six tablets from each batch was tested at random. The tablets were crushed, and the contents of all six tablets were thoroughly mixed. 130 mg of crushed tablet powder (equivalent to 15 mg of diclofenac sodium) was transferred to a 100 ml volumetric flask. Then 50 ml of methanol was added and sonicated for 15-20 min, after which the volume was brought up to the mark with methanol. After that, the solution was filtered using Whatman filter paper. The filtrate was properly diluted with the solvent to obtain a solution with a concentration of 15 g/ml. The sample's absorbance (203 nm) was compared to a blank solution. The concentration of drug content in each tablet was calculated using the standard curve [11].

Dissolution profile study

The dissolution test was carried out by inserting the tablets into USP type XXIII (RC-GD dissolution tester). The dissolution medium used was 900 ml of phosphate buffer pH 6.8. The medium temperature was set at 37±5 °C. The tool is rotated at 50 rpm. The dissolution test was carried out for 12 h at an interval sampling time of 1 h. After sampling, 5 ml of fresh medium was added to maintain sink condition. The collected samples were evaluated for the percentage amount of diclofenac sodium released at 203 nm using a UV spectrophotometer (Milton Roy, Genesys 10) [12].

Data analysis

The collected data was tested with a theoretical approach by comparing the data contained in the literature. Data optimization was performed using Design Expert 13 software using the Simplex Lattice Design (SLD) method with the equation Y = B1(A)+B2(B)+B12(AB) for the two independent variables. The results of design expert obtained the optimum formula out of the five formulas that have been made and tested. The optimum formula was then made and evaluated. The evaluation results were compared with the prediction results using the T-test on SPSS with a 95% confidence level. The results of the comparison were used to determine whether there were significant or insignificant differences.

RESULTS AND DISCUSSION

Mangrove starch (*Bruguiera gymnorrhiza*) has a brown color, is in the form of a fine powder, and has a slightly sweet odor. The brown color can be caused by the content of tannin compounds [13], so it is easily oxidized in the air and turns brown. As seen at the time of making the starch, after the mangrove fruit is peeled, the color turns brown in the air and it will get darker if it is not put in water. Starch in the form of fine powder is the result of sieving with a 100-mesh sieve number, and the sweet smell of starch arises from the starch content which has high carbohydrates, causing the starch to have a sweet odor.

Mangrove starch has a poor or negative flow rate. Poor flow rates are affected by the density or weight of the particles, and the frictional forces of the particles. The smaller the particle size, the greater the frictional force because the surface area of the particles increases, making it difficult for starch to flow. The pH of mangrove starch is 6.70, which tends to be weakly acidic. The degree of acidity of starch commonly is 5-8 [14], so mangrove starch is included in the general range of starch acidity. Mangrove starch has a moisture content of 9.08 %, which is lower than the moisture content of corn starch (12%) and potato starch (18%) [14].

Ash content is related to minerals in the form of two salts, organic and inorganic salts. The minerals contained in a substance or material can be determined by the remnants of burning mineral salts which will produce ash [15]. The test results for ash content in mangrove starch were 13.68%.

Table 3: Mangrove (*Bruguiera gymnorrhiza*) starch characteristics

No	Parameters	Specifications
1.	Organoleptic	Brown, fine powder, smooth texture, sweet odor
2.	Iodine test	Dark blue color (starch+)
3.	Flowability (g/s)	(-)
4	pH	6.70
5.	Moisture content (%)	9.08
6.	Ash content (%)	13.68
7.	Swelling index	2.52

Evaluation of granules aims to determine whether the quality of the granules produced meets the good requirements for making slow-release tablets. Granules that flow easily will have a small angle of repose. The higher the density of the granules, the better the flow properties of the granules so that the compressible density of the granules increases. The lower the moisture content, the smaller the bond between particles and the smaller the compressed density.

The granules that have been made have a granular shape are brown in color, and have a distinctive medicinal odor. The brown color of the granules is due to the brown mangrove starch, so it can dominate other white ingredients.

The granule flow rate is affected by a granule's size, shape, porosity, density, and friction force [16]. Granules with good flow properties have a flow time of 100 g granules of less than 10 seconds or a flow rate of more than 10 g/s [17].

The results showed that the flow rate (10.72-12.41 g/ml), and angle of repose (32.41-34.12^{o}) of all granules (F1-F5) had good flow properties and were within the permissible limits. The bulk densities of all formulas were in the range of 0.42-0.50 g/ml. The tapped densities of all formulas were in the range of 0.49-0.58 g/ml. Compressibility percentages of all formulas were 9.91-14.29 %, indicating that all granules from F1-F5 had a good ability to be compressed into tablets

with a certain pressure (<15%). The Hausner ratio of all formulas (1.11-1.17) indicated that all granules had adequate flow properties and were within the permissible limit, which is below 1.8. The data showed that all granules have acceptable flow quality (table 4).

Table 4: Physical properties of diclofenac sodium slow-release granules using mangrove (*Bruguiera gymnorrhiza*) starch and CMC

Physical properties	F1	F2	F3	F4	F5	Req
Flow rate (g/s)	11.91±0.16	10.72±0.37	10.90±0.16	12.41±0.19	11.08±0.08	>10
Angle of repose (ɵ)	33.95±0.35	34.12±1.85	33.65±0.43	32.93±0.69	32.53±1.07	<35
Bulk density (g/ml)	0.50±0.015	0.42±0.012	0.45±0.011	0.49 ±0.010	0.46±0.015	-
Tapped density (g/ml)	0.58±0.013	0.49±0.015	0.50±0.017	0.56±0.014	0.52±0.011	-
Compressibility (%)	13.00±0.10	14.29±0.21	9.91±0.24	11.76±0.32	11.01±0.15	<15
Hausner's ratio	1.15±0.005	1.17±0.009	1.11±0.005	1.13±0.008	1.12±0.005	<1.18
Moisture content (%)	3.93±0.010	5.56±0.015	5.00±0.028	4.73±0.056	3.89±0.037	-

Note: values are measured in mean±SD; n=3

Diclofenac sodium slow-release tablets in the five formulas had a flat round shape with a line in the middle, were brown in color, and had a distinctive medicinal odor. The brown color of the tablets was influenced by the mangrove fruit starch, which was brown in color so other white ingredients will turn brown.

The physical properties of all formulas met the requirements for good tablets, except for tablet hardness at F1 (table 5). The hardness of F1 was very low (8.11±1.72) (table 5), and did not meet the hardness requirements of slow-release tablets, while the other four formulas met the requirements. The addition of CMC can increase tablet hardness because the resulting cohesive forces between particles are getting stronger [18].

The disintegration time of F1 was the fastest compared to other formulas. F1 is a formula that only contains mangrove starch without the addition of CMC. Based on the optimization equation (expert design), it showed that CMC had a more role in increasing tablet hardness compared to the mangrove starch matrix, and prolonged the disintegration time of tablets in the body (table 6). There are no special requirements for the disintegration time of slow-release tablets, but for non-coated tablets, the disintegration time is less than 15 min.

Table 5: Physical properties of diclofenac sodium slow-release tablet using mangrove (*Bruguiera gymnorrhiza*) starch and CMC

Evaluations	F1	F2	F3	F4	F5	Req
Thickness (mm)	2.22±0.01	2.22±0.03	2.22±0.01	2.22±0.02	2.22±0.02	-
Weight variation (%)	14.89	12.20	11.83	10.83	13.56	<15
Hardness (kg)	8.11±1.72	12.10±0.84	14.62±1.76	13.06±2.14	11.66±0.62	10-20
Friability (%)	0.61± 0.12	0.53±0.05	0.21±0.05	0.47±0.13	0.37±0.05	<1
Disintegration time (min)	75±2.10	135±3.10	122±2.85	92±2.54	85 ±1.54	-
Drug content (%)	99.34±2.01	98.21±2.48	98.76±2.15	97.90±2.08	98.71 ±2.43	90-110
Dissolution (%)	97.78±1.80	83.30±2.87	81.15±4.01	89.65±3.26	90.04±2.70	>75

Note: values are measured in mean±SD; n=3

Table 6: Optimization results of diclofenac sodium slow-release tablet formula using design expert ver 13

Evaluation	Equation	Model of graphic	P value
Hardness	Y= 8,65971 (A)+11,2917 (B)+15,4743 (AB)	quadratic	0,2491
Friability	Y= 0,635714(A)+0,531714(B) – 1,16571(AB)	quadratic	0,1527
Weight variation	Y= 14,8844(A)+12,1964(B) – 7,016(AB) – 21,712(AB(A-B)	cubic	0,0256
Disintegration time	Y = 70,4(A)+133,2(B)	linier	0,0055
Dissolution	Y= 94,1(A)+82,6704(B)	linier	0,1962

The standard curve of the diclofenac was Y = 0.60367x – 0.00493 with an R-value of 0.99969. A drug release test on diclofenac sodium slow-release tablets was carried out by dissolution test for 12 h to determine the amount of release of the active substance or the percent dissolution rate. Diclofenac sodium slow-release tablets contain approximately 90% to 110% of the active ingredient per tablet [12].

Table 7: Zero order, first order, and Higuchi linear regression equations of diclofenac sodium slow-release tablet dissolution using mangrove starch and CMC

Code of formula	Zero orde (C vs T)		First order (log C vs T)		Higuchi (C vs root of time)	
	Equation	r	Equation	r	Equation	r
F1	Y = 0.230x+14.466	0.989135	Y = 0.0025x+1.219	0.885877	Y = 5.0161x-5.622	0.990665
F2	Y = 0.253x – 0.631	0.997448	Y = 0.0045x+0.597	0.859838	Y = 5.3888x-21.444	0.976589
F3	Y = 0.236x – 0.027	0.997122	Y = 0.0046x+0.564	0.856514	Y = 5.0571x-19.789	0.983303
F4	Y = 0.254x – 1.551	0.979405	Y = 0.0051x+0.448	0.882646	Y = 5.481x – 23.169	0.971418
F5	Y = 0.257x+2.720	0.988992	Y = 0.0047x+0.613	0.810464	Y = 5.6178x-19.812	0.986504

Table 7 showed that diclofenac sodium slow-release tablets followed two drug release mechanisms: diffusion and erosion. The relationship between dissolved concentration and time was more linear, a drug release mechanism that was controlled by matrix erosion, whereas if the relationship between dissolved levels and the root of time, the drug release mechanism was controlled by drug diffusion through the matrix.

The diffusion mechanism can be seen in F1 with the r value for the diclofenac sodium dissolution level curve line equation to the root of

time (Higuchi) greater than the r value at zero order and first order. F2-F5 followed the mechanism of erosion drug release with r values at order zero greater than r order values one and Higuchi. Based on the research results, drug release was controlled by two mechanisms: erosion and diffusion. The erosion mechanism was more dominant than diffusion. The erosion mechanism indicated that the drug was released through erosion on the tablet surface [19].

Using many parameters, the optimum formula was determined using the Simplex Lattice Design method through the Design Expert 13 program [20, 21] (table 8). The components that were optimized were mangrove starch and CMC as a matrix that controlled the release of the active substance diclofenac sodium. The optimum formula predicted value was obtained based on experimental data with a ratio of mangrove fruit starch of 32.30% (193.80 mg) and CMC of 12.70% (76.20 mg). From these predictions, it produced a desirability value of 0.805 (fig. 1). Desirability is the optimization target point to be achieved [22]. The desirability value has a range of 0-1, the higher the desirability value, the better the optimum formula is obtained to obtain the desired criteria.

Table 8: Criterias for granule and slow-release tablet test results of diclofenac sodium with a combination of mangrove starch and CMC

Parameters	Value	Criteria
Flow rate (g/s)	10-12.4	Maximize
Angle of repose (ɵ)	32.5-35	Minimize
Bulk density (g/ml)	-	None
Tapped density (g/ml)	-	None
Compressibility (%)	9.9-15	Minimize
Hausner's ratio	1.1-1.18	Minimize
Moisture content (%)	-	None
Hardness (kg)	10-20	In range
Friability (%)	0.2-1	Minimize
Dissolution (%)	80-100	In range
Weight variation (%)	10.83-15	Minimize
Disintegration time (min)	60-135	In range

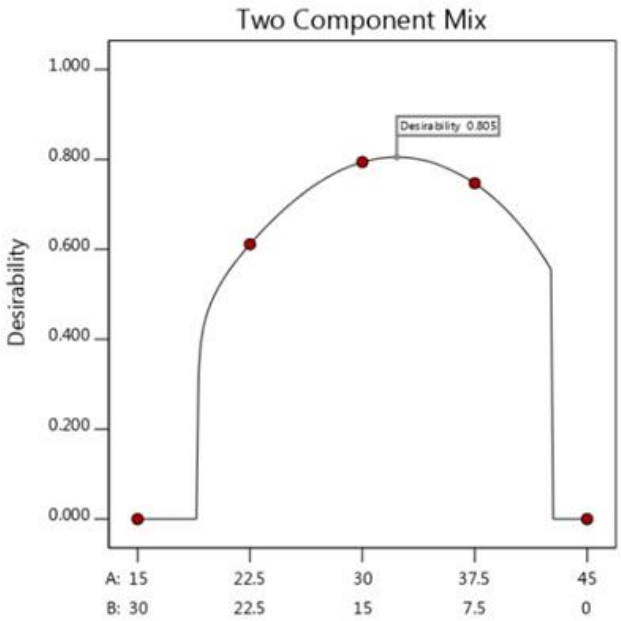

Fig. 1: The results of determining the optimum point using design expert 13

Table 9: Statistical test results of one t-test sample optimum formula of diclofenac sodium slow-release tablets with a combination of mangrove starch and CMC

Parameters	Prediction value	Verification results	P value
Flow rate (g/s)	11.518	11.440	0.263
Angle of repose (°)	32.577	32.497	0.891
Bulk density (g/ml)	0.471	0.477	0.252
Tapped density (g/ml)	0.535	0.533	0.520
Compressibility (%)	10.306	10.527	0.529
Hausner's ratio	1.115	1.127	0.842
Moisture content (%)	4.778	4.720	0.037
Hardness (kg)	13.552	13.598	0.932
Friability (%)	0.307	0.313	0.664
Dissolution (%)	89.261	89.800	0.718
Weight variation (%)	11.221	12.370	0.144
Disintegration time (min)	96.990	96.000	0.818

The data that has been obtained in testing the optimum formula is compared with the predicted value that has been obtained by the software design expert. Data comparison was carried out through the SPSS application using one t-test sample with a 95% confidence level. The results of the analysis are said to be significantly different if the significance value is<0.05. Based on the results obtained (table 9), there was one test result that is significantly different with a significance value of 0.030, namely the moisture content test, while the other test results show insignificant results.

CONCLUSION

The combination of mangrove fruit starch of 15-45 % and 0-30 % CMC fulfilled the requirements for granule flow properties and the release of active substances. The physical properties test of all formulas met the requirement of the slow-release tablet, except FI (only using mangrove starch without CMC) had a tablet hardness below 10 kg. The optimum formula obtained was a combination of mangrove fruit starch 32.30 % (193.80 mg) and 12.70 % CMC (76.20 mg) with a desirability value of 0.805.

FUNDING

This research was funded through research grant scheme: Hibah Integrasi Tridharma (HIT) from Universitas Muhammadiyah Surakarta, Indonesia.

AUTHORS CONTRIBUTIONS

Setyo Nurwaini has contributed to the overall study design and has produced the paper. Anita Fitri Anggraini and Anita Sukmawati have contributed to the supervised laboratory work. Teguh Imanto and Wahyu Utami have contributed to the data gathering and research report.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Wikantyasning ER, Setiyadi G, Pramuningtyas R, Kurniawati MD, Yee HO CY. Formulation of nanoemulgel containing extract of Impatients balsamina l. and its antibacterial activity. Int J App Pharm. 2023;15(3):67-70. doi: 10.22159/ijap.2023v15i3.46670.
2. Jacoeb AM, Nugraha R, Putu S, Dia S. Production of edible film from lindur fruit starch with the addition of glycerol and carageenan. JPHPI. 2014;17:14-21.
3. Amin MN, Pralebda S, Hasan M, Zakariya Z, Subekti S, Saputra E. Physicochemical properties of (Bruguiera gymnorrhiza) flour (BGF). Int Food Res J. 2018 Oct;25(5):1852-7.
4. Afandi I, Siagian II, Putri RC. Formulation design of mangrove Sonneratia caseolaris fruit powder as a disintegrant in paracetamol tablet formulations. Jurnal Seminar Nasional Kelautan XIII; 2018. p. 33-8.
5. Talib A, Tamrin A, Deni S. Study about potential fruit mangrove as a food alternative in the future. Int J Agron Trop Plants. 2018:1-8.
6. Pawar H, Varkhade C, Jadhav P, Mehra K. Development and evaluation of orodispersible tablets using a natural polysaccharide isolated from Cassia tora seeds. Integr Med Res. 2014;3(2):91-8. doi: 10.1016/j.imr.2014.03.002, PMID 28664083.
7. Ameen MS, Ibrahim NJ, Omar TA. Design and evaluation of sustained-release bilayer tablets of oxcarbazepine. J Pharm Innov. 2023;18(3):1213-28. doi: 10.1007/s12247-022-09694-2.
8. Quinten T, DE Beer T, Onofre FO, Mendez Montealvo G, Wang YJ, Remon JP. Sustained release and swelling characteristics of xanthan gum/ethylcellulose-based injection moulded matrix tablets: *in vitro* and *in vivo* evaluation. J Pharm Sci. 2011 Jul;100(7):2858-70. doi: 10.1002/jps.22480, PMID 21254067.
9. Nurwaini S, Yuliani R, Jannah W, Sinaka A, Yulistyanti DU. Formulation and antibacterial activity of ceremai (Phyllanthus acidus) lozenges using three different binders. Int J Pharm Res. 2020 Jan-Mar;12(1):485-9. doi: 10.31838/ijpr/2020.12.01.109.
10. Sirisolla J, Ramanamurthy KV. Formulation and evaluation of cefixime trihydrate matrix tablets using HPMC sodium CMC ethyl cellulose. Indian J Pharm Sci. 2015 May-Jun;77(3):321-7. doi: 10.4103/0250-474x.159663, PMID 26180278.
11. Varghese N, Komala M. Analysis of *in vitro* disintegration and dissolution effect of Cucurbita maxima starch in losartan FDT. Int J App Pharm. 2022 Jul 7;14(4):163-70. doi: 10.22159/ijap.2022v14i4.43852.
12. Ministry of Health of the Republic of Indonesia. Indonesian pharmacopoeia. 6th ed. Jakarta: Ministry of Health of the Republic of Indonesia; 2020.
13. Sulistyawati W, Kumalaningsih S. Low tannins and HCN of lindur fruit flour products as an alternative food. J Teknol Pertanian. 2012;13(3):187-98.
14. Rowe RC, Sheskey PJ, Owen SC. Handbook of pharmaceutical excipients. Pharmaceutical Press; 2006.
15. Swastawati F, Surti T, Agustini TW, Riyadi PH. Quality characteristics of smoked fish processed using different methods and types of fish. J Aplikasi Teknol Pangan. 2013;2(3):1-7.
16. Burhan L, Yamlean PV, Supriati HS. Formulation of effervescent granules of soursop fruit juice (Annona muricata L.). Pharmacon. 2012;1(2):72-8.
17. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy by Lachman and Lieberman. 3rd ed; 1986.
18. Laili N, Komala A, Maulida H, Suprapto S. Optimization of sago amylum concentration (Metroxylon rumphii) as co processed in theophylline tablets. Pharmacon: Jurnal Farmasi Indonesia. 2019;14(2):72-80. doi: 10.23917/pharmacon.v14i2.6422.
19. Suprapto S, Setiyadi S. Formulation of theophylline sustained release matrix tablets: optimization study of the effect of compression pressure and ethyl-cellulose matrix and HPMC with a factorial design model. J Sci Technol Res. 2010;2:100-16.
20. Alita GS, Suprapto S. Optimization of captopril slow release tablets using PVP as a binder and talc magnesium stearate as a lubricant using the simplex lattice design method. Usadha J Pharm. 2023;2(1):86-107. doi: 10.1234/ujp.v2i1.121.
21. Herzanti A, Suprapto S. Optimization of captopril slow release tablets using gelatin as a binding agent and talc magnesium stearate as a lubricating agent with the simplex lattice design method. Usadha J Pharm. 2023;2(2):218-35. doi: 10.1234/ujp.v2i2.148.
22. Widhiardani FA, Setiyadi G. Optimization of glycerol as a humectant and HPMC as a gelling agent in the antioxidant gel formula of carrot extract (*Daucus carota l.*). Usadha J Pharm. 2023;2(3):278-90. doi: 10.23917/ujp.v2i3.86.