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Optimization of FDT Turmeric Rhizome Extract (*Curcuma domestica* Val.) Using a Combination of Crospovidone and Croscarmellose Sodium

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Abstract

Turmeric rhizome (*Curcuma domestica* Val.) is a plant that has anti-diarrheal activity. To get an immediate effect and action in the treatment of diarrhea, turmeric rhizome is formulated into a fast-disintegrating tablet (FDT) dosage form. FDT is strongly influenced by super disintegrant (crushing material). Crospovidone is used as a super disintegrant, as it has a wicking effect (capillary action), while croscarmellose sodium has a swelling effect. The study aims to determine the effect of variations in the concentration of crospovidone and croscarmellose sodium on the physical properties of FDT and determine the optimal concentration of crospovidone and croscarmellose sodium. The sample used was a dry extract of turmeric rhizome. The dried extract of turmeric rhizome was made 5 runs with variations of crospovidone 2–5% and croscarmellose sodium 2–5%. Run 1 (2.75%: 4.25%), run 2 (3.5%: 3.5%), run 3 (5%: 2%), run 4 (2%: 5%), and run 5 (4.25%: 2.75%). The responses used included disintegration time, hardness, and restriction tests. The results utilized to determine the optimum formula were derived from the simplex lattice design (SLD) method. The outcomes of the optimal formula testing experiment were based on the findings from 13.0.5 predictive software experts, employing a one-sample t-test analysis at a 95% confidence level. The results of this study indicate that the combination of crospovidone and croscramellose sodium can reduce the response time of disintegration, hardness, and FDT. The optimum formula was obtained with the variation of crospovidone 3.5% and croscarmellose sodium 3.5%.

Keywords: Optimum Formula; Fast-Disintegrating Tablets; Super Disintegrant; Simplex Lattice Design

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INTRODUCTION

Diarrhea is defecation characterized by soft or liquid consistency or can even only be water [1]. Even though there are many drugs available to treat diarrhea, other alternatives are needed because the current dosage forms are difficult to swallow, causing long drug disintegration times [2]. In fact, diarrhea drug formulations should be able to provide rapid efficacy.

Thus, anti-diarrhea drugs are very suitable to be formulated into fast-disintegrating tablet (FDT) dosage forms to provide fast disintegration times.

One of the potential ingredients to treat diarrhea is turmeric rhizome. The turmeric content that is efficacious for treating diarrhea is found in tannin. Tannin is efficacious as an *adstringent*, as it can shrink the intestinal mucous membrane [3]. Hence, it can reduce diarrhea fluid output and inhibit electrolyte secretion [4].

Apart from tannins, flavonoid compounds also play a role in treating diarrhea. The way flavonoids work is to stop diarrhea by inhibiting or reducing intestinal motility without changing fluid transport in the intestinal mucosa, thereby reducing fluid and electrolyte secretion [5]. Several tannin and flavonoid derivative compounds have antisecretory (inhibiting or reducing fluid secretion into the intestine), antimotility (slowing intestinal movement), and antibacterial activities.

Turmeric rhizome extract at a dose of 80 mg/kg weight of male mice revealed a stronger anti-diarrhea effect compared to Loperamide HCl at a dose of 1 mg/kg weight of male mice, which was tested on male mice [5]. In its use, turmeric can be formulated into a dosage form to obtain immediate drug action effects as a treatment for diarrhea.

Additionally, fast-disintegrating tablets (FDT) are solid preparations in the form of tablets that disintegrate quickly when placed on the tongue, generally in less than 60 seconds [6]. Using FDT, rapid drug therapy intervention of diarrhea can be achieved since it can achieve increased bioavailability absorption through the absorption of drugs in the mouth. FDT also provides immediate effects and drug action, making it suitable for anti-diarrhea drug formulation.

Excipients that are influential in making FDT are super disintegrants (destroying agents). Super disintegrant is a disintegrating agent in tablets that can accelerate the destruction of the tablet matrix so that the tablet can be released immediately after being placed on the tongue [7]. Super disintegrants that can be used in making FDT include crospovidone and croscarmellose sodium with a concentration of 2-5% [8].

Crospovidone has a main mechanism—wicking (water absorption/capillary action). Crospovidone is capable of rapid capillary action and has good compressibility. Good compressibility will produce tablets that are easy to compress so they are suitable for making using the direct compression method [9]. Meanwhile, croscarmellose sodium has the main mechanism, i.e., swelling. Croscarmellose sodium is used because it can absorb water and expands more quickly when in contact with water, thereby speeding up the tablet disintegration process [10].

However, super disintegrants, which have a swelling mechanism, have a longer disintegration time compared to the wicking mechanism [11]. Therefore, it is necessary to use a combination to cover this deficiency. The combination of crospovidone and croscarmellose sodium is expected to produce an optimum FDT formula according to the requirements.

The combination of crospovidone and croscarmellose sodium will affect the physical properties of FDT, so

optimization needs to be carried out. Optimization is conducted to obtain the optimum formula to produce good-quality preparations. The method employed in optimization is the Simplex Lattice Design (SLD) method. The SLD method is used to determine the optimum formula for a mixture of ingredients, where the proportion of the total amount of different ingredients must be 1 (100%) [12].

Moreover, turmeric rhizome is an ingredient that is greatly influenced by pH stability, so it requires the addition of PEG in the formulation. PEG in the formulation can help regulate environmental conditions so that it is not too alkaline or acidic and prevents degradation, thereby making the turmeric FDT formulation more stable and effective [13].

Based on this background description, it is necessary to research the optimization of fast-disintegrating tablets (FDT) of turmeric rhizome extract (*Curcuma domestica* Val.) with a combination of 2-5% crospovidone and 2-5% croscarmellose sodium as super disintegrants. The use of sections to divide the text of the paper is optional and left as a decision for the author. Where the author wishes to divide the paper into sections, the formatting shown in Table 2 should be used.

METHODS

Optimization of Fast-Disintegrating Tablets

Optimization of the fast-disintegrating tablet was carried out using the simplex lattice design method with the help of software design expert v.13.0.5 on crospovidone and croscarmellose sodium. The formula is shown in Table 1.

Table 1. Fast-Disintegrating Tablets Formula

Ingredients	Composition (%)				
	Run 1	Run 2	Run 3	Run 4	Run 5
Turmeric rhizome extract	25.84	25.84	25.84	25.84	25.84
Avicel PH 102	56.16	56.16	56.16	56.16	56.16
Crospovidone	2.75	3.5	5	2	4.25
Croscarmellose sodium	4.25	3.5	2	5	2.75
Manitol	6	6	6	6	6
PEG 4000	5	5	5	5	5
Total	100	100	100	100	100

Preparation for Turmeric Rhizome Extract

Four kg of turmeric rhizomes were washed thoroughly with water flow and dried using an oven at a temperature of 50 ± 2⁰C [14]. The dried turmeric rhizomes were ground using a blender and sieved with sieve No. 60. Forty grams of turmeric rhizome powder were wrapped in filter paper, tied with thread at both ends and put into a socket tube. The Soxhlet flask was filled with 400 ml of 96% ethanol solvent. The socket device was equipped with a reverse cooler and was heated to the boiling point of the solvent, allowing it to circulate until the solvent became clear or approximately eight cycles at a temperature of 81-96⁰C. The soxhletation

results obtained were then evaporated using a rotary evaporator until a thick extract was obtained [15].

Making Dry Extract of Turmeric Rhizome

The mortar and stamper were sterilized first by heating them with hot water. A total of 100 grams of thick extract was dried by adding lactose little by little, 2x the weight of the thick extract, namely 200 grams. The dry mass was added with ±300 ml of hexane solvent and then stirred thoroughly several times for two hours, allowed to settle and then poured into the liquid. Then, the remaining mixture was mixed again with 300 ml of hexane, stirred thoroughly, and the excess hexane was separated; the process was repeated once with hexane, dried at a temperature of ±70^{0}C [16].

Making the Fast-Disintegrating Tablets Formula

FDT extract turmeric rhizome was made by direct compression method, in which each tablet weight was 300 mg. All ingredients were mixed using mortar and stamper, then pressed into tablets utilizing a single punch tablet pressing machine. FDT of turmeric rhizome extract was made in five runs with varying concentrations of crospovidone (2 – 5%) and croscarmellose sodium (2 – 5%), determined by design expert software using the simplex lattice design method.

The Compressed Mass and Physical Properties Test of Turmeric Rhizome Extract Fast-Disintegrating Tablet

While the evaluation of compressed mass encompassed flow speed test, angle of repose test, and compressibility test, the evaluation of physical properties of tablets included weight uniformity test, disintegration time test, tablet hardness test, friability test, and wetting time test. The data results of the hardness test, friability test, and disintegration time test were carried out using SLD to obtain optimum formula results.

Flow Speed Test

The flow speed test was carried out by weighing 25 grams of powder/granule. Then, they were put into the flowmeter funnel with the bottom closed funnel. The funnel cover was opened, so the powder flowed up completely and drained into a dust heap. The funnel cover was opened at the same time as turning on the stopwatch. Then, the time it took for the powder to flow was noted down and calculated, thus showing the powder flow time [17].

Angle of Repose Test

The angle of repose test was conducted by weighing 25 grams of powder/granule. Then, they were put into the flowmeter funnel with the bottom of the funnel closed. Then, the cover on the end of the funnel stem was opened, and the powder was in, forming a cone. Then, the height of the powder pile and the radius of the powder pile were measured [18].

Compressibility Test

The compressibility test was performed by calculating the bulk destiny, slowly pouring 20 g of powder into a measuring cup until the volume was 100 ml as V0. Then, the tap destiny was calculated by pouring 20 g of powder slowly into a measuring cup up to a volume of 100 ml (V0). Then, a measuring cup on the tool was set up, and the motor was started. The powder was compressed 500 times with a

tap test with tap test equipment and noted volume after compression (Vt). Then, the tap specific gravity, tapping index, and carr index were calculated [24].

Weight Uniformity Test

The weight uniformity test was carried out with 20 tablets weighed one by one and calculated on average. The tablet qualifies for the uniform weight requirement if no more than two tablets have a deviation of more than 7.5% from the average weight and no tablets have deviations of more than 15% from the average weight [18].

Disintegration Time Test

The disintegration time test was performed by placing the FDT tablet into a petri dish containing 20 ml of distilled water. FDT was placed slowly into a petri dish containing distilled water, and then the time was recorded disintegration required by tablet [19].

Hardness Test

A hardness test was conducted on 10 tablets. One by one, the tablets were placed in the center and perpendicular to the hardness tester. At first, the scale showed zero position, and then the tool was rotated slowly until the tablet broke or crumbled [25].

Friability Test

The friability test was carried out by taking 20 tablets without dust and weighing them first in the analytical balance to know the beginning weight. Then, they were put into a friability tester with a rotation of 25 rpm for 4 minutes or 100 rotations. The tablet was taken out of the device. The tablet was then shaken free and then weighed again to find the final weight. Tablets are considered good if they have no friability value, maybe more than 1% 20.

Wetting Time Test

The wetting time test was conducted by putting down a piece of filter paper that had been folded twice into a 5 cm diameter petri dish. The petri dish had previously been filled with 5 ml of distilled water containing a strawberry red substance, and a tablet was then placed on the filter paper. The time required for the entire surface of the tablet to turn red was calculated as the wetting time [21].

RESULTS AND DISCUSSION

Evaluation of Compressed Mass

The flow speed test results uncovered that the five runs met the requirements for a very good flow speed value, having a value of <10 grams/second. Powder with good flow properties will also have good weight uniformity. FDT of turmeric rhizome extract was made in five runs with varying concentrations of crospovidone (2 – 5%) and croscarmellose sodium (2 – 5%), determined by expert design software using the simplex lattice design method. The optimization design used was 2 factors (crospovidone and croscarmellose sodium) in FDT. The results of Soxhlet extraction obtained 138.7 grams of extract, with an extract yield value of 86.69%. Testing of the extract included organoleptic extract tests, drying shrinkage tests, and calculation of extract yield.

The angle of repose test was carried out to determine the maximum angle formed by the drug surface. The results of the angle of repose test in the fifth test showed an angle of repose value of $<30^0$, meaning that the flow properties are very good[26].

Furthermore, the standard compressibility value is 5-15%. The five runs have met the standard compressibility test values. Powder with a good compressibility value will be able to flow easily into the molding chamber, after which it deforms to become compressible and forms a compact mass 8. The evaluation of compressed mass is displayed in Table 2.

Table 2. Results of Evaluation of Compressed Mass FDT Turmeric Rhizome Extract

Run	Evaluation of Compressed Mass		
	Flow Speed Test (gram/second)	Angle of Repose Test (⁰)	Compressibility Test (%)
1	5.99 ± 0.56	18.33 ± 1.29	11.26 ± 0.58
2	5.59 ± 0.59	23.48 ± 1.26	7.60 ± 0.48
3	5.82 ± 0.36	26.89 ± 1.19	11.76 ± 1.26
4	6.06 ± 0.58	26.99 ± 2.63	6.91 ± 0.17
5	5.58 ± 0.58	23.17 ± 0.97	11.58 ± 0.37

Evaluation of Physical Properties

Evaluation of physical properties encompassed weight uniformity test, disintegration time test, hardness test, friability test, and wetting time test. The results of the evaluation of physical properties are presented in Table 3.

Table 3. Results of Evaluation of Physical Properties FDT Turmeric Rhizome Extract

Run	Evaluation of Physical Properties				
	Weight Uniformity Test (mg)	Disintegration Time Test (second)	Hardness Test (kg/cm2)	Friability Test (%)	Wetting Time Test (second)
1	285.35 ± 12.04	20.91 ± 1.63	3.50 ± 0.16	0.58 ± 0.20	26.15 ± 0.95
2	283.20 ± 10.93	22.15 ± 1.25	3.04 ± 0.04	0.58 ± 0.00	23.78 ± 0.59
3	284.20 ± 11.52	26.63 ± 0.34	3.60 ± 0.24	0.71 ± 0.12	22.22 ± 1.21
4	282.20 ± 11.28	27.66 ± 0.38	3.80 ± 0.06	0.65 ± 0.10	22.88 ± 0.46
5	286.25 ± 12.45	20.25 ± 0.17	3.10 ± 0.16	0.59 ± 0.00	27.13 ± 2.00

According to the Indonesian Pharmacopoeia Edition III, the requirements for a weight uniformity test with an average weight of 151-300 mg are that there must be no more than 2 tablets, each weight deviating by 7.5% from the average weight of the tablet, and there must not be a single tablet, whose weight deviates by 15% from the average weight. After calculating the deviations for the five runs, the results showed that no tablet deviated 7.5% from the average weight of the tablet, and there was not a single tablet whose weight deviated 15% from the average weight. This denotes that the FDT made in the five runs met the weight uniformity requirements in accordance with the Indonesian Pharmacopoeia Edition III [22].

Additionally, the disintegration time test was carried out to determine the time required for FDT tablets to disintegrate quickly when placed on the tongue. In this case, a disintegrating tester was used.

Based on Table 3, the results demonstrated that the five runs had a disintegration time between 20.91 and 27.66 seconds. This aligns with the literature, asserting that, generally, the disintegration time of FDT is less than 60 seconds [6].

Hardness tests were then performed to assess the tablet's resistance to shock or pressure. Based on Table 3, the results revealed that the five runs met the criteria requirements—in the range of 3–5 kg/cm² [23].

Lastly, the wetting time test relates to the time it takes for the tablet to be wetted by water. There are no special requirements for the FDT wetting time test, but from the wetting time test, it can be seen how quickly the FDT absorbs water [9]. Based on Table 3, the results showed that from run one to run five, the wetting time range was 22.22–27.13 seconds. Meanwhile, in research by Edityaningrum et al. (2018), the wetting time test showed a shorter time, between 9.14 and 12.64 seconds. Another study stated in the test results that the wetting time with crospovidone and croscarmellose sodium as super disintegrants was in the range of 99.33–150.67 seconds [8]. The reason for the difference in wetting time in this study and the study by Edityaningrum et al. (2018) is that it is caused by differences in the active substances and concentrations used in the formula, even though they both used the same combination of super disintegrants.

Although this study exhibited a longer wetting time, it is still in accordance with the literature that the greater the crospovidone used, the faster the wetting time will be. This is because the porous structure of crospovidone makes it easily wetted by water. This was shown in run 3 with a crospovidone concentration of 5%, resulting in a wetting time of 22.22 ± 1.21.

Optimization FDT Formula

The optimum formula was determined from the response time of disintegration, hardness, and brittleness. The scoring and weighting of responses is presented in Table 4.

Table 4. Assignment of Values and Weights to Responses

Name	*Goal*	*Lower*	*Upper*	*Importance*
Disintegration time	*Minimize*	20.25	27.66	+++++
Hardness	*In range*	3	3.8	+++
Friability	*Minimize*	0.58	0.71	+++

The disintegration time test values were analyzed using Design Expert software version 13.0.5 to determine the effect of crospovidone and croscarmellose sodium on disintegration time.

The coefficient value produced by crospovidone was +26.28, and croscarmellose sodium was +27.36. The combination of crospovidone and croscarmellose sodium can reduce the disintegration time of FDT with a

coefficient value of –26.42. The results of this study indicate that when used alone, both crospovidone and croscarmellose sodium can increase the time of disintegration. However, using a combination of both can reduce the disintegration time. Thus, the combination of both is more because the faster the FDT disintegration time, the greater the dissolution rate of the tablet when it dissolves in water. A contour plot diagram of the disintegration response of the FDT is presented in Figure 1.

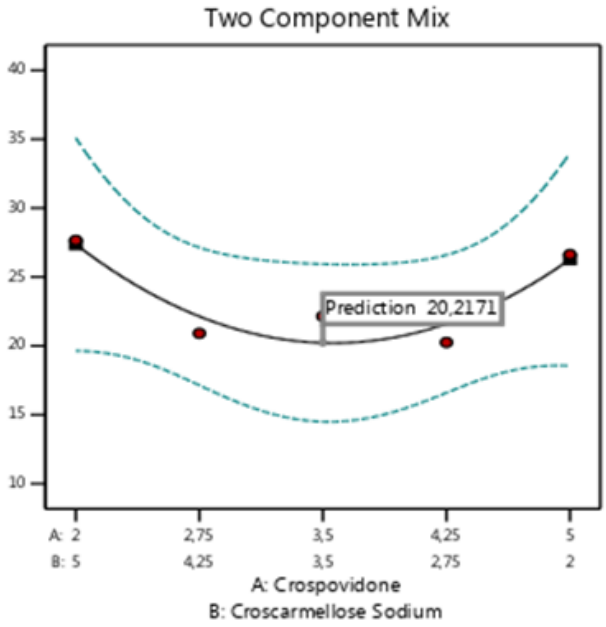

Figure 1. Contour plot diagram of the disintegration time response of the FDT

This is the basis for determining the optimum formula response criteria; disintegration time has a very important level of importance (+++++).

According to research by Putranti et al. (2021), the combination of crospovidone and croscarmellose sodium can reduce tablet disintegration time because crospovidone has a wicking mechanism, and croscarmellose sodium has a swelling mechanism so that it can speed up the disintegration of the tablet. The particle arrangement in crospovidone is very porous so it can accelerate the absorption of water into the tablet. Meanwhile, croscarmellose sodium has a rapid swelling mechanism so that when it comes into contact with water, it will cause the particles that make up the tablet to break up quickly and speed up the disintegration time [8].

Hardness test values were analyzed using Design Expert software version 13.0.5 to determine the effect of crospovidone and croscarmellose sodium on hardness. When used alone, both had a positive effect, with crospovidone +3.55 and croscarmellose sodium +3.87. This means

that crospovidone, the use of both croscarmellose sodium alone, can increase the hardness of FDT. However, using a combination of both had a negative response of –2.51. This indicates that the combination of crospovidone and croscarmellose sodium as super disintegrants can reduce the hardness response of FDT. These results are consistent with research by Edityaningrum et al. (2018), stating that the combination of crospovidone and croscarmellose sodium is a super disintegrant that can reduce the violent response of FDT. A contour plot diagram of the hardness test response of the FDT is depicted in Figure 2.

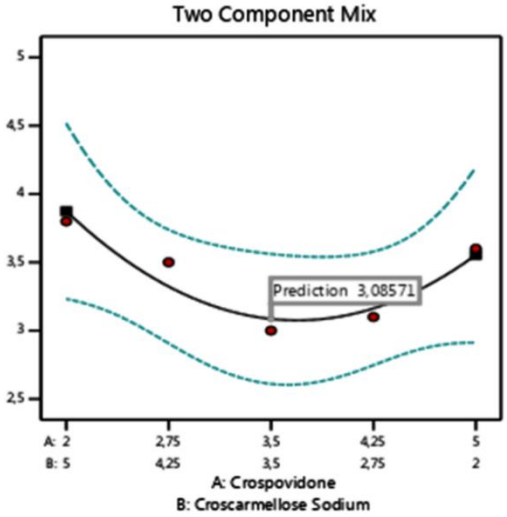

Figure 2. Contour plot diagram of the hardness response of the FDT

Afterward, the friability test was carried out to describe the bond strength of the particles at the edge of the tablet surface due to the influence of friction or abrasion. In this case, 20 tablets were tested for friability test in each run. Based on Table 3, the results revealed that the five runs met the friability value requirements of <1% [23]. The tablets met the required friability values due to the need for Avicel PH 102 as a filler and binder in rather large quantities in Formula 9. The friability test values were analyzed using Design Expert software version 13.0.5 to determine the effect of crospovidone and croscarmellose sodium on friability.

Based on the equation, there was an interaction between crospovidone and croscarmellose sodium, which could reduce the friability presentation value seen in the coefficient value –0.44. Single-

use of super disintegrant obtained a higher friability presentation. The coefficient resulting from single use between crospovidone (+0.70) and croscarmellose sodium (+0.65) has almost the same value. This aligns with research by Edityaningrum et al. (2018), which states that the use of a combination of the super disintegrant crospovidone and croscarmellose sodium can reduce the friability value.

A contour plot diagram of the friability response of the FDT is illustrated in Figure 3.

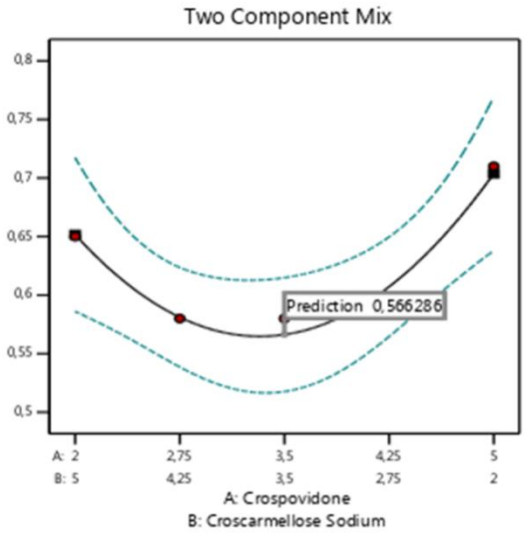

Figure 3. Contour plot diagram of the friability response of the FDT

The optimum formula was determined based on the target response to be achieved as well as the degree of importance and based on the desirability value. The design expert software version 13.0.5 then presented the formula with the highest desirability value. The proportions of crospovidone and croscarmellose sodium in the formula optimum were 3.5%: 3.5% with a desirability value of 1.

Physical Properties Evaluation Results Optimum Formula

Test results evaluating the physical properties of the optimum formula included hardness, friability, and disintegration time tests. The test results are presented in Table 5.

Table 5. Evaluation of Physical Properties Optimum Formula

Hardness	Friability	Disintegration Time
$\bar{x}$ ± SD (kg/cm²)	$\bar{x}$ ± SD (%)	$\bar{x}$ ± SD (second)
3.06 ± 0.07	0.5 ± 0.10	19.88 ± 2.08

Optimum Formula Verification Results

Based on Table 6, all responses tested had a significance value (p-value) > 0.05, indicating that the difference is not significant. Hence, it can be concluded that the optimum formula has been verified.

Table 6. Optimum Formula Verification Results

Response	Predicted Value	Result Value Test	*p-Value*	Information
Disintegration Time	20.21	19.88	0.812	statistically significant
Hardness	3.08	3.06	0.894	statistically significant
Friability	0.56	0.5	0.423	statistically significant

CONCLUSIONS

There is an effect of varying concentrations of crospovidone and croscarmellose sodium on the physical properties of FDT of turmeric rhizome extract (Curcuma domestica Val.). The effect of the combination of crospovidone and croscarmellose sodium is in the form of reducing the disintegration time, hardness, and friability of FDT. A comparison of the concentrations of 3.5% crospovidone and 3.5% croscarmellose sodium produced the optimum formula for FDT of turmeric rhizome extract (Curcuma domestica Val.).

CONFLICT OF INTEREST

There is no potential for conflict of interest with research, authorship, and/or article publication with all authors.

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REFERENCES

1. Kemenkes RI. (2012). *Profil Kesehatan Indonesia Tahun 2011.* Jakarta: Kementerian Kesehatan Republik Indonesia.
2. Rachmawati, W. d.Optimasi Formula Tablet Dispersible Ekstrak Daun Jambu Biji Dengan Kombinasi Bahan Penghancur Croscarmellose Sodium dan Sodium Starch Glycolate. *Traditional Medicine Journal*. 2015
3. Permata, H. *Tanaman Obat Tradisional.* Titian Ilmu. 2007
4. Tjay, T. H. *Obat - Obat Penting.* Jakarta: PT Gramedia. 2007
5. Meliala L., Sari W., Tarigan P. *Uji Efek Antidiare Ekstrak Rimpang Kunyit (Curcuma domestica val.) Pada Mencit Jantan*. Jurnal Penelitian Farmasi Herbal, 2020; Vol.2 No. 2. 15-21. https://doi.org/10.36656/jpfh.v2i2.208
6. Bhowmik D., C.B., Krishnakanth, Pankaj, Chandira R.M. *Fast Disolusing Tablet: An Overview*. Journal of Chemical and Pharmaceutical Research. 2009; 1(1): 163-177.
7. Hidayati, Nurul., Sulaiman T.N.S. & R Nurhaini R. *Optimization formula of fast disintegrating tablets Ketoprofen-cyclodextrin inclusion complex with sodium starch glycolate and crospovidone as the superdisintegrants*. Journal of Physics: Conference Series; 2020

8. Putranti, Widyasari., C. A. *Formulasi Fast Disintegrating Tablet Ekstrak Etanol Daun Salam dengan Kombinasi Crospovidone dan Croscarmellose Sodium sebagai Superdisintegrants*. Jurnal Sains Farmasi & Klinis, 2021; 285–295.
9. Edityaningrum, T. S. *Optimasi Formula Fast Disintegrating Tablet Ekstrak Daun Belimbing Wuluh (Averrhoa Bilimbi L.) dengan Kombinasi Superdisintegrant Crospovidone dan Croscarmellose Sodium*. Traditional Medicine Journal, 2018; 23(I), 62-69.
10. Rowe, R. C. *Handbook of Pharmaceutical Excipients Sixth Edition.* Washington DC: Pharmaceutical Press. 2009
11. Didi, G. Pengaruh Kombinasi Krospovidon, Ac-Di-Sol, dan Primojel Terhadap Waktu Hancur Sediaan Orally Disintegrating Tablet Dimenhidrinat. *BIMFI*. 2015; 26-31.
12. Hidayat Rifki, I. A. Z. *Design Expert Software Sebagai Alat Optimasi Formulasi Sediaan Farmasi*. Majalah Farmasetika, 2021; 99-120.
13. Fortunata, I. M.R. Pembuatan dan karakterisasi Konjugat Nanopartikel Emas- Kurkumin Termodifikasi Polietilen Glokol = Synthesis and Characterization of Curcumin Conjugated Gold Nanoparticles with Polyethylene Glycol Modification. 2016. https://lib.ui.ac.id/detail?id=20431264&lokasi=lokal
14. Bintoro, M. d. *Analisis dan Identifikasi Senyawa Saponin Dari Daun Bidara (Zhizipus mauritania L.).* Jurnal ITEKIMA, 2017; 84-94.
15. Cobra, H. W. *Skirining Fitokimia Ekstrak Sokhletasi Rimpang Kunyit (Curcuma longa) dengan Pelarut Etanol 96%*. Jurnal Ilmiah Kesehatan Karya Putra Bangsa, 2019; 12-17.
16. Rivai, Harrizul., Putri Eka, and Humaira Fadhilah. *Pembuatan dan Karakterisasi Ekstrak Kering Daun Sirih Hijau (Pipper betle L.)*. Jurnal Farmasi Higea, 2014; Vol 6 No 2.
17. Syukri, Y. *Teknologi Sediaan Obat dalam Bentuk Solid*. Yogyakarta: Universitas Islam Indonesia; 2018
18. Kemenkes RI. *Farmakope Indonesia Edisi V*. Jakarta: Kementerian Kesehatan Republik Indonesia; 2014
19. Garg A and Gupta MM. *Review Article Mouth Dissolving Tablets: a Review.* J Drug Deliv Ther. 3 (2), 207-214.
20. DepKes RI. *Farmakope Indonesia Edisi IV*. Jakarta: Departemen Kesehatan Republik Indonesia; 1995
21. Jain, C.P and Naruka, P.S. *Formulation and evaluation of Fast Dissolving Tablets of Valsartan*. International Journal of Pharmacy and Pharmaceutical Science. 2009; 1: 219-221.
22. DepKes RI. *Farmakope Indonesia Edisi III*. Jakarta: Departemen Kesehatan Republik Indonesia; 1979
23. Panigrahi, R. &. A review on Fast Dissolving Tablets; 2010
24. Sulaiman. (2007). *Teknologi & Formulasi Sediaan Tablet.* Yogyakarta: Pustaka Laboratorium Teknologi Farmasi Fakultas Farmasi Universitas Gadjah Mada.
25. Goeswin A. 2007. Pengembangan Sediaan Farmasi. Edisi Revisi dan Perluasan. Bandung. Penerbit ITB.

26. Syaifullah, M. Y. (2016). Physicochemical and flow properties of fruit powder and their effect on the dissolution of fast dissolving fruit powder tablets. *Powder Technology*, 396–404.