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Optimization Matrix Formulas Using Hypromellose and Carboxymethylcellulose Sodium for Metformin HCl Extended Release Caplets

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ABSTRACT

The first-line pharmacological therapy in type II diabetes patients in people who are overweight and have normal kidney function is metformin. However, metformin with immediate release has been found to have some weaknesses, namely that a maximum dose of 2,000 mg/day requires use 2 to 3 times a day, which leads to a potential patient's non-compliance, in addition to causing disorders in the intestinal tract. To overcome this problem, a formulation was developed that was modified with extended release using the direct compressed method. This study aims to determine the influence of variations in the concentration of hypromellose and carboxymethylcellulose natrium (Na-CMC) matrices in the extended-release of metformin HCl 500 mg to obtain an optimal and similar extended-release system capsule formula to the originator drug, as well as to prove the quality of the selected formula through stability monitoring. This research is expected to produce the optimum formula for metformin HCl capsules extended release and can be applied in the pharmaceutical industry into commercial products.

Keywords: Diabetes, Metformin HCl, Extended release, Direct compressed, Hypromellose, Carboxymethylcellulose natrium.

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1. Introduction

Diabetes mellitus is a chronic metabolic disorder with multiple etiologies characterized by high blood sugar levels accompanied by disorders of carbohydrate, lipid, and protein metabolism because of insufficient insulin function (1–4). The first line of pharmacological therapy in patients with diabetes mellitus, especially type II diabetes mellitus in people who are overweight and obese and those who have normal kidney function and are not dependent on insulin, is metformin (5,6).The conventional dosage form of metformin, namely immediate release, is usually given as 500 mg caplets, which are taken twice a day with food; in addition, there are 850 mg caplets, which can be taken once daily. The maximum metformin dose is 2550 mg daily in divided doses (5,7). There is also an extended version of metformin that only needs to be taken once daily with food. The maximum total daily dose of this type of metformin is 2000 mg. It also has fewer side effects and lasts longer than regular metformin (8,9).

Metformin has low permeability across cell membranes and high solubility in water, so metformin is classified as a class 3 compound according to the biopharmaceutical classification system (BCS) and biopharmaceutics drug disposition classification system (BDDCS) (10,11). Pharmacokinetically, metformin shows slow and incomplete absorption after oral administration. The absolute bioavailability of metformin after a single dose of 500 mg is approximately 50-60%. Its bioavailability can also be reduced if consumed with food (11,12).

Continuous maintenance of sugar levels in the body by consuming several doses (2 - 3 times), such as metformin HCl caplets in immediate release (IR), can increase the potential for patient non-compliance in taking medication, it can cause problems with the digestive system. Gastrointestinal in some patients (5,7). To overcome this, a modified formulation was developed, namely extended release (XR) with a direct compressed method, where the drug works and is effective on specific targets, for example, the blood vessels. Another advantage of the extended-release system is that medication administration is not too frequent, improving the healing process and increasing patient compliance in administering medication (8,13).

Extended-release drug delivery systems are designed to achieve therapeutically effective drug concentrations in systemic circulation over extended periods. The matrix system is the most popular among other oral drug delivery systems because it is simple, low cost, easy to manufacture, has less dosing frequency, and has better patient compliance and efficacy (10,14). Metformin tablets with an extended-release system (metformin XR) are an antihyperglycemic drug formulation that can be administered once daily (15). The polymer matrix of metformin XR 500 mg tablets will swell in gastric fluid, causing the preparation to be retained in the stomach and food. Over 8 hours, the drug will dissolve and diffuse through the matrix to be absorbed in the upper gastrointestinal tract (16–18). A *matrix* is a well-mixed composite of one or more drugs with a gelling agent, namely a polymer (19,20). The matrices commonly used in matrix tablets are matrices from hydrophilic and hydrophobic polymers, both cellulose derivatives (hydroxyethyl cellulose, hydroxypropyl methylcellulose 25, 100, 4000 and 15000 cps, Na-CMC and methylcellulose 400 and 4000 cps), natural non-cellulose and semi-synthetic

polymers (gum arabic, alginate, polysaccharides from mannose and galactose, chitosan and modified starch) as well as acrylic acid polymers (carbopol 934, alginic acid, gelatin and natural gum). In contrast, the hydrophobic polymer matrix is polyvinyl chloride, ethyl cellulose, cellulose acetate, and polystyrene(8,21,22).

The method for making extended-release tablets can be done using wet granulation or direct compressed method. However, several research results show that the final dissolution profile results from the two methods are similar (23,24). That way, the direct compressed method is considered in the research carried out because it is more efficient. In addition, preparations are formulated with varying drug and polymer/matrix ratios, and design expert® 13 software assists in determining variations. The matrix used is hypromellose, which can form a hydrogel layer with high viscosity when in contact with the media. Hypromellose is generally used as a rate-controlling polymer, viscosity-increasing agent, and water absorber in slow-release preparations (25). The advantage of using hypromellose is that it is easy to manufacture and can inhibit drug release (26). In addition, the Na-CMC matrix was also used to optimize formula selection (27). The choice of hypromellose and Na-CMC matrices is expected to slow down the release of the drug from the preparation due to the ability of the combination of the two matrices to form a gel layer around the caplet surface area (28). Therefore, several formula developments were carried out with variations in matrix composition to achieve optimum conditions through an extended-release system using the direct compression method.

2. Method

2.1. Materials

The materials used in this study consist of the originator drug Glucophage XR 500 mg tablets, (Merck Sante's s.a.s France, imported and packaged by PT. Merck Tbk, Indonesia), metformin HCl (Sohan Healthcare Pvt. Ltd./Hildose, India), microcrystalin cellulose PH 102 (JRS Pharma GmbH Co. KG, China), hypromellose (Shin-Etsu Chemical Co.Ltd, Japan), Na-CMC (Anqiu Eagle Cellulose Co., Ltd, China), water absorbing agent, colloidal silicon dioxide (Anhui Sunhere Pharmaceutical Excipients Co.,Ltd), mg stearate (FACl Asia Pacific Pte Ltd, Singapore), sodium 1-heptansulfonate (PT, Merck, Indonesia) sodium chloride, natrium hydroxide, sodium dihydrogen phosphate monohydrate, 1-pentana sulfonic acid (Sigma aldrich, Germany), acetonitrile, monobasic potassium phosphate (JT Baker, Indonesia), metformin HCl (PT. InfaLabs, Indonesia), and aluminium foil (PE 12/PE 15/AL 12/ PE 30) (PT Avesta Continental Pack, Indonesia).

2.2. Originator Study

The originator study includes the characterization of the originator drug by carrying out several physical and chemical examinations. The physical examination carried out by organoleptic; dimensions; weight uniformity; and hardness. The chemical examination includes measuring the levels of active substances and dissolution tests by United States Pharmacopoeia (USP) 44 (29).

2.3. Determination of Hypromellose and Na-CMC Ratio Using Design Expert® 13 Software

In determining the concentration ratio of the combination of hypromellose and Na-CMC matrices, design expert® 13 software was used with study type factorial, subtype randomized, design type 2 level factorial, and replication was carried out three times.

2.4. Formulation of Metformin HCl XR 500 mg Caplet

The metformin HCl XR formula was selected based on the basic formula containing matrix excipients, fillers, glidants, and lubricants.Then, the hypromellose and Na-CMC matrix ratio was determined based on the optimization results of the expert design expert® 13 software. The complete Metformin HCl XR 500 mg caplet formula can be seen in Table 1.

Table 1. Formulation of Metformin HCl XR Caplets

Formulation	Composition (mg)				Composition (g)			
	F1	F2	F3	F4	F1	F2	F3	F4
Metformin HCl	500	500	500	500	300	300	300	300
Avicel PH 102	290	90	190	0	174	54	114	0
Hypromellose	100	300	100	300	60	180	60	180
Na-CMC	100	100	200	200	60	60	120	120
Colloidal silicon dioxide	5	5	5	0	3	3	3	0
Mg stearate	5	5	5	0	3	3	3	0
Total	1.000	1.000	1.000	1.000	600	600	600	600

2.5. Characterization of Intermediate Product

2.5.1. Determination of Moisture Content

A granule (5 grams) was put into a moisture balance, then the temperature was set at 85°C (30). The moisture content was calculated using the following formula (1), including initial granule weight, grams (W1), granule weight after drying, grams (W2).

$$\text{Moisture content} = \frac{(W1-W2)}{W1} \times 100\% \quad (1)$$

2.5.2. Determination of Flow Properties

2.5.2.1. Flow Speed

A granule (100 grams) was put into a flow tester, and the flow time was recorded (31). Flow speed was calculated using the following formula (2), including granule weight, gr (W) and granule flow time, seconds (t).

$$\text{Flowability} = \frac{W}{t} \quad (2)$$

2.5.2.2. Angle of Repose

A granule (100 grams) was put into a funnel, which is installed at a certain height until the top of the pile formed by the powder reaches the funnel (32). The angle of repose was calculated using the following formula (3), including the height of the cone (h) and the radius of the cone (r).

$$\text{Angle of Repose} = \tan^{-1}(h/r) \quad (3)$$

2.5.2.3. Bulk and Tapped Density

The granules, which weighed as much as 100 grams, were put into a 250 mL measuring cup. Subsequently, the measuring cup was erected and shaken rapidly to even out the granule surface. The volume read was used to calculate the bulk density (33). Bulk density was

calculated using the following formula (4), including mass (m) and volume (Vo).

$$\text{Bulk Density} = \frac{m}{Vo} \quad (4)$$

Using a tapped density tester, the granules in the measuring cup were later tested for tapped density. This was done at certain tapping intervals from 100 to 500 taps (34). Tapped density was calculated using the following formula (5), including mass (m) and constant volume (Vt).

$$\text{Tapped Density} = \frac{m}{Vt} \quad (5)$$

2.5.2.4. Hausner Ratio and Compressibility Index

The bulk and tapped density results were used to calculate the derived parameters of the granule flow characteristics, namely the Hausner ratio and compressibility index (35–37).

Characterization of the Finished Product

Physical Properties

Uniformity of Mass

A total of twenty metformin HCl XR caplets were weighed one by one on an analytical balance, and then the average weight of each caplet was calculated. The criterion for accepting weight uniformity is that no more than two caplets deviate more than the average weight value specified in column A (5%). There should not be a single caplet whose weight deviates more than the average weight value in column B (10%) (38).

Uniformity of Size

The size uniformity test was carried out on twenty caplets by measuring the length, width and thickness of the caplets using a caliper (38).

Hardness

The hardness test was carried out using twenty caplets resulting from dimensional inspection; ten caplets were taken for hardness testing using a hardness tester (38).

Friability

The friability test was carried out on twenty caplets, cleaned, weighed, and put into a friability tester. The test lasted four minutes or 100 rounds (38).

Chemical Properties

The chemical examination tests active substance levels using HPLC-UV and dissolution testing using a dissolution tester with conditions according to the USP 44 (2021). In the dissolution test, additional sampling times were set at t (time) to 12, 18 and 24 hours. Instrument conditions for analysis of Metformin HCl can be seen in Table 2 and 3.

Table 2. Instrument conditions for analyzing Metformin HCl levels

LC System	Instrument Conditions
Detector	UV 218 nm
Column	Waters µ Bondapak, C18 300x3,9 mm; 10 µm (L1)
Temperature	30°C
Flow rate	1,0 mL/seconds
Injection volume	10 µL
Run time	20 minutes
Retention time	±7 minutes

Table 3. Instrument conditions for the Metformin HCl dissolution test

Dissolution System	Instrument Conditions
Media	Buffer Phosphate pH 6,8
Volume	1.000 mL
Tool	Type 2 (*paddle*)
Rotating speed	100 rpm
Time	1 hours, 3 hours, and 10 hours
Specification	20 minutes
	Q (60) = 20,0 – 40,0%
	Q (180) = 45,0 – 65,0%
	Q (600) ≥ 85,0%

Comparative Dissolution Test (CDT)

Comparative dissolution test is carried out to show the similarity or difference in dissolution profiles between the test drug and the innovator/comparator drug. This test was carried out in dissolution media with a pH adjusted to in vitro conditions, namely at pH 1.2, 4.5, and 6.8 (39) using paddle method type 2, HCl buffer media pH 1.2; acetate buffer pH 4.5; 1000 mL of phosphate buffer pH 6.8 with a stirring speed of 100 rpm at a temperature of 37^{o}C + 0.5^{o}C. Testing was carried out for 12 hours with time intervals of 1, 2, 3, 5, 6, 10 and 12 hours.

Primary Caplet Packaging

Primary packaging of metformin HCl XR caplets is carried out on a Wufu stripping machine using aluminum foil composition PE 12/PE 15/AL 12/ PE 30 as the strip material.

Stability Test of Caplets

The stability tests carried out were long-term and accelerated stability tests. Stability studies were carried out to predict shelf life, thereby reducing the duration of testing time with monitoring duration during the study being six months at temperature/humidity conditions of 30±2°C/75±5% (long-term) and 40±2°C/75±5% (accelerated) using a climatic chamber (40).

Data Analysis

After obtaining the results of granule flow rate, caplet hardness and dissolution from all formulas, the formulation results were analyzed using design expert® 13 software by entering all the response results in the granule flow rate, caplet hardness and dissolution test.

3. Result

3.1. Original Study

The originator study was carried out by conducting physical and chemical examinations of the originator drug Glucophage XR 500 mg tablets. Complete results can be seen in Table 4 below:

Table 4. Characteristics of the Originator Drug (Glucophage XR 500 mg Tablets)

Parameters	Results
Organoleptic	The tablet is odourless and white; on one side, the number 500 is written, and on the other, it is plain
Dimensions	Diameter 13,00 mm, tebal 6,82 mm
Average weight	1018,4 mg
Hardness	30,02 kP
Active substance level	106,34%
Dissolution	
a. Q (60') = 20,0% - 40,0%	37,54%
a. Q (180') = 45,0% - 65,0%	57,60%
a. Q (600') ≥ 85,0%	96,85%

3.2. Characterization of Intermediate Product

Granule characterization includes determining the water content and flow properties of the granules. The results of the characterization test can be seen in Table 5 below:

Table 5. The Result Characterization of Intermediate Product

Formula	Moisture Content (%)	Flow Speed (g/s)	Angle of Repose (º)	Hausner Ratio	Compressibility Index (%)
1	2,71 ± 0,34	7,6 ± 1,29	32,7 ± 2,06	1,143 ± 0,02	12,494 ± 1,26
2	2,45 ± 0,06	4,7 ± 0,42	29,8 ± 0,34	1,127 ± 0,02	11,265 ± 1,18
3	2,74 ± 0,34	5,8 ± 0,17	33,7 ± 0,28	1,143 ± 0,01	12,453 ± 0,72
4	2,90 ± 0,12	0,6 ± 0,06	35,6 ± 0,53	1,292 ± 0,01	22,592 ± 0,64

3.3. Characterization of the Finished Product

Caplet characterization includes physical and chemical examination. The physical examination includes the uniformity of weight, thickness, length, width, hardness, and friability of the caplets, while the chemical examination includes testing the levels of active substances and dissolution. The characterization results can be seen in Tables 6 and 7 below:

Table 6. Physical Properties of the Finished Product

Formula	Uniformity of Mass (mg)	Thickness (mm)	Length (mm)	Width (mm)	Hardness (kP)	Friability (%)
1	1007,10 ± 1,35	6,52 ± 0,03	19,59 ± 0,00	8,58 ± 0,01	24,32 ± 0,24	0,141 ± 0,10
2	1007,13 ± 1,91	6,55 ± 0,03	19,59 ± 0,01	8,57 ± 0,01	28,92 ± 1,16	0,187 ± 0,02
3	1007,17 ± 0,97	6,58 ± 0,04	19,58 ± 0,01	8,58 ± 0,01	29,47 ± 0,84	0,237 ± 0,13

Table 7. Chemical Properties of the Finished Product

Formula	Active substance level	Dissolution					
		Q (60')	Q (180')	Q (600')	Q (720')	Q (1080')	Q (1440')
1	101,41 ± 0,92	31,85 ± 0,41	57,92 ± 0,41	107,54 ± 0,33	80,89 ± 0,11	79,41 ± 0,26	77,17 ± 0,55
2	102,28 ± 1,79	31,13 ± 1,22	55,60 ± 2,00	99,04 ± 5,43	98,64 ± 7,21	98,55 ± 9,28	98,63 ± 9,43
3	100,32 ± 1,30	30,97 ± 0,73	56,75 ± 1,64	104,71 ± 2,20	81,32 ± 0,64	79,41 ± 0,80	78,19 ± 0,98

3.4. Comparative Dissolution Test (CDT)

CDT was evaluated on formula F2 with the originator drug Glucophage XR 500 mg tablets in HCl buffer medium pH 1.2, acetate pH 4.5, and phosphate pH 6.8. UDT results on various media are shown in Table 7 below:

Table 8. *Comparative Dissolution Test* (CDT)

Dissolution Media	Difference Factors (F1)	Similarity Factors (F2)	Results
Buffer HCl pH 1,2	9,7	56,4	Similar
Buffer Acetate pH 4,5	1,67	88,9	Similar
Buffer Phosphate pH 6,8	6,87	64	Similar
Specification	0-15	50≤ F2 ≤ 100	x

3.5. Stability Test of Caplets

The caplet stability test was carried out using an accelerated and long-term stability method with observation periods of 0, 3, and 6 months. The stability test results can be seen in Tables 9 and 10 below:

Table 9. Accelerated Stability

No.	Parameters	Specifications	Testing Interval (Month)		
			0	3	6
Primary Packaging					
1	Organoleptic	There is no discoloration, no peeling, and no leaking.	There has been no change	There has been no change	There has been no change
Caplets					
1	Organoleptic	The caplets are white, odorless, and plain on both sides.	According to specifications	According to specifications	According to specifications
2	Length	19,40 mm - 19,80 mm	19,58 mm	19,60 mm	19,62 mm
3	Width	8,40 mm - 8,80 mm	8,57 mm	8,57 mm	8,57 mm
4	Thickness	6,00 mm - 7,00 mm	6,58 mm	6,45 mm	6,55 mm
5	Average weight	980 mg - 1.020 mg	1.007,4 mg	1.005,8 mg	1.000,6 mg
6	Identification	The retention time of the principal peak produced by the test solution is the same as the reference solution.	According to specifications	According to specifications	According to specifications

7	Active substance levels	Each caplet contains: Metformin HCl 500 mg ±10% or (90 % -110 %)	102,6%	98,9%	93,5%
8	Dissolution		Min = 32,0%	Min = 26,8%	Min = 30,3%
		$Q_{(60)}$ = 20,0% - 40,0%	Max = 33,3%	Max = 31,3%	Max = 34,2%
			$\bar{x}$ = 32,6%	$\bar{x}$ = 28,4%	$\bar{x}$ = 32,2%
			Min = 54,8%	Min = 47,6%	Min = 57,5%
		$Q_{(180)}$ = 45,0% - 65,0%	Max = 58,6%	Max = 55,4%	Max = 60,6%
			$\bar{x}$ = 56,83%	$\bar{x}$ = 50,7%	$\bar{x}$ = 58,8%
			Min = 92,1%	Min = 89,6%	Min = 97,8%
		$Q_{(600)} \geq$ 85,0%	Max = 96,88%	Max = 94,5%	Max = 101,5%
			$\bar{x}$ = 94,0%	$\bar{x}$ = 93,0%	$\bar{x}$ = 99,1%
9	Hardness	20,00 kP - 36,00 kP	29,4 kP	27,12 kP	29,8 kP

Table 10. Long-term Stability

No.	Parameters	Specifications	Testing Interval (Month)		
			0	3	6
Primary Packaging					
1	Organoleptic	There is no discoloration, no peeling, and no leaking.	There has been no change	There has been no change	There has been no change
Caplets					
1	Organoleptic	The caplets are white, odorless, and plain on both sides.	According to specifications	According to specifications	According to specifications
2	Length	19,40 mm - 19,80 mm	19,58 mm	19,58 mm	19,68 mm
3	Width	8,40 mm - 8,80 mm	8,57 mm	8,55 mm	8,63 mm
4	Thickness	6,00 mm - 7,00 mm	6,58 mm	6,43 mm	6,59 mm
5	Average weight	980 mg - 1.020 mg	1.007,4 mg	997,6 mg	1002,5 mg
6	Identification	The retention time of the principal peak produced by the test solution is the same as the reference solution.	According to specifications	According to specifications	According to specifications
7	Active substance levels	Each caplet contains: Metformin HCl 500 mg ±10% or (90 % - 110 %)	102,6%	97,9%	95,2%
8	Dissolution		Min = 32,0%	Min = 26,8%	Min = 29,9%
		$Q_{(60)}$ = 20,0% - 40,0%	Max = 33,3%	Max = 31,1%	Max = 30,9%
			$\bar{x}$ = 32,6%	$\bar{x}$ = 28,5%	$\bar{x}$ = 30,5%

			Min = 54,8%	Min = 48,4%	Min = 54,6%
		$Q_{(180)}$ = 45,0% - 65,0%	Max = 58,6%	Max = 56,8%	Max = 56,3%
			$\bar{x}$ = 56,83%	$\bar{x}$ = 51,2%	$\bar{x}$ = 55,5%
			Min = 92,1%	Min = 89,7%	Min = 94,9%
		$Q_{(600)} \geq$ 85,0%	Max = 96,88%	Max = 94,3%	Max = 96,1%
			$\bar{x}$ = 94,0%	$\bar{x}$ = 92,9%	$\bar{x}$ = 95,5%
9	Hardness	20,00 kP - 36,00 kP	29,4 kP	30,15 kP	29,3 kP

3.6. Data Analysis

The analysis was done using 2-level factorial design by design expert® 13 software. The results of this analysis were in the form of the most optimal linear formula based on the lack of fit response factors for granule flow rate, hardness, and caplet dissolution. The complete analysis results can be seen in Figures 1, 2, and 3 below:

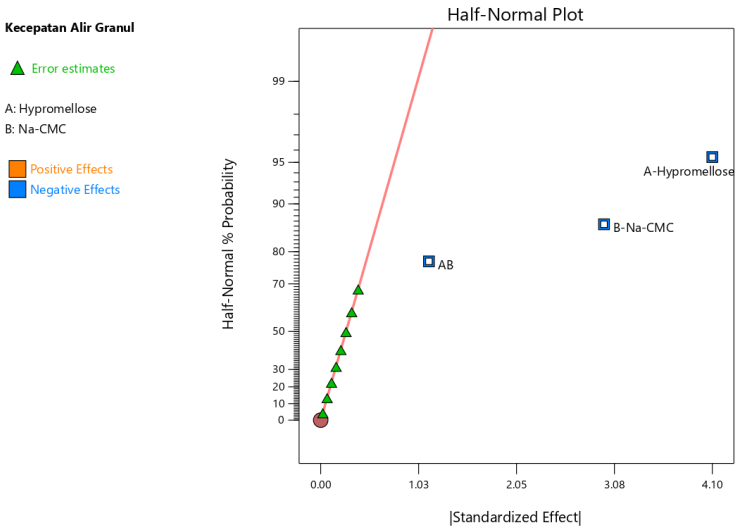

Figure 1. Matrix Effects on Granule Flowability

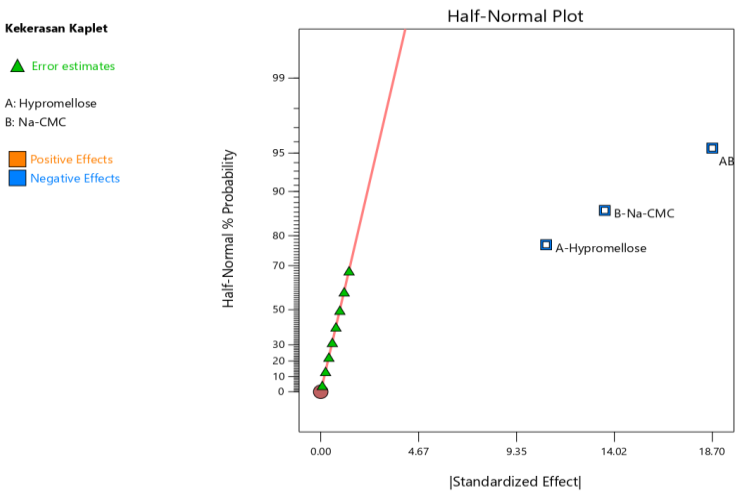

Figure 2. Matrix Effects on Hardness

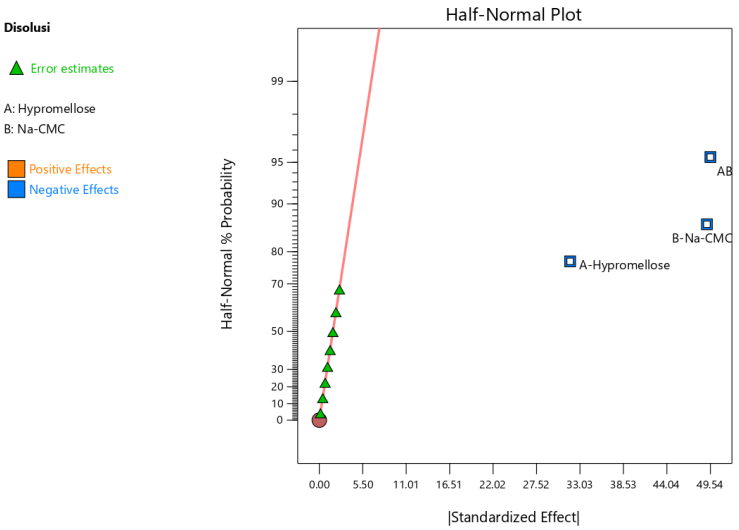

Figure 3. Matrix Effects on Dissolution

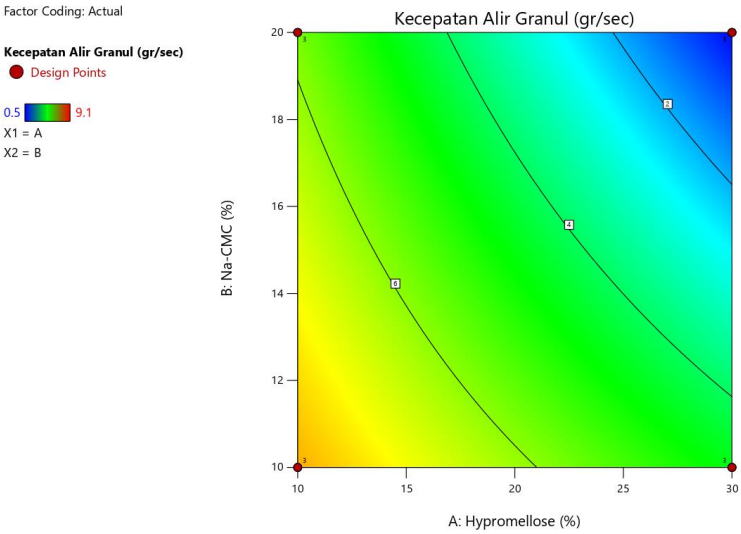

Figure 4. Contour Plot of Granule Flowability Response

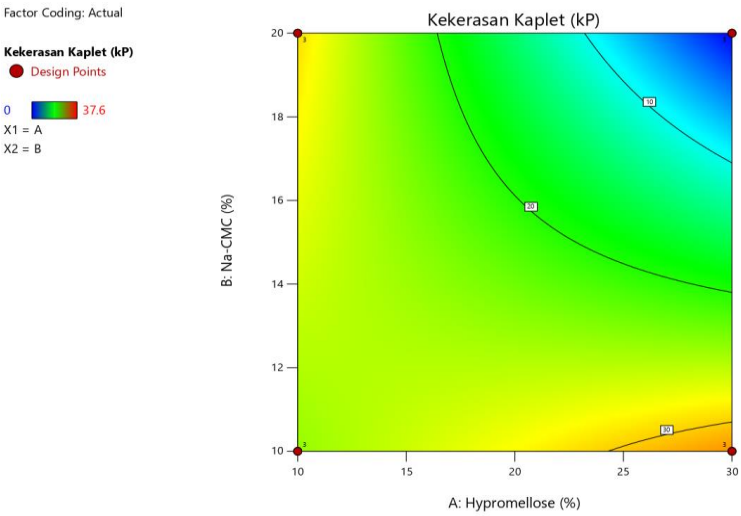

Figure 5. Contour Plot of Hardness Response

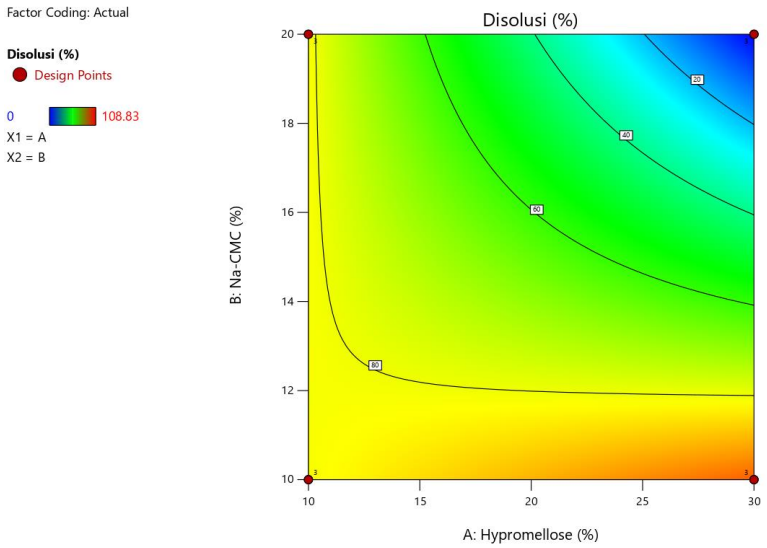

Figure 6. Contour Plot of Dissolution Response

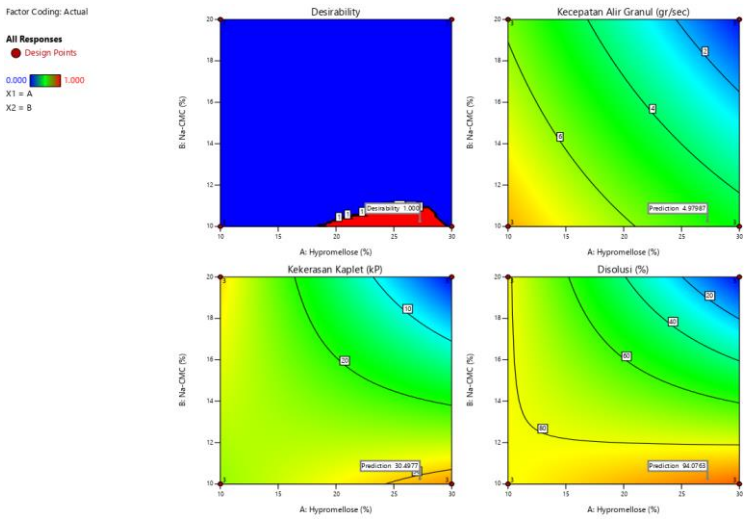

Figure 7. Desirability Value

4. Discussion

The dosage form of metformin with an immediate release system was found to have several weaknesses, namely that the maximum dose that must be achieved is 2,000 mg/day, requiring use 2 - 3 times a day; this creates the potential for patient non-compliance, besides that, it can cause gastrointestinal disorders (7). To overcome this, a modified formulation was developed in this research, namely extended release, using the direct compressed method. The development methods for this research include originator studies, searching for hypromellose and Na-CMC ratios using design expert® 13 software, formulation of metformin HCl caplets with an extended-release system, granule characterization, characterization of metformin HCl caplets, evaluation of optimal caplet formulas, primary packaging of caplets and caplet stability test.

Originator studies are carried out on comparator drugs determined by the Food and Drug Supervisory Agency (BPOM) with the criteria that the drug used in the equivalence test as a comparison must be an innovator drug with a distribution permit in Indonesia (41).The innovator drug specified for metformin HCl extended release is Glucophage XR 500 mg tablets. The results of the originator study show that the physical and chemical properties of the Glucophage have complied with the acceptance criteria requirements according to USP 44 (2021) so that the originator drug for Glucophage XR 500 mg tablets can be used as a research reference product. Complete results can be seen in table 4.

Based on the results of determining the ratio of hypromellose and Na-CMC matrix in the metformin HCl XR formulation using design expert® 13 software, four basic variables for matrix comparison were obtained, including F1 (hypromellose: Na CMC ratio of 10:10), F2 (hypromellose: Na CMC ratio of 30:10), F3 (hypromellose: Na CMC ratio of 10:20), and F4 (hypromellose: Na CMC ratio of 30:20). The complete caplet formula design can be seen in Table 1. Each formula was replicated three times; then, characterization was carried out on the intermediate and finished products.

Granule characterization determines that the bulk used has reached the minimum granule requirements for tablet compression, so a product with a good formulation is obtained. Complete granule characterization results can be seen in Table 5. The results of determining water content show that the water content in granules F1, F2, F3, and F4 is relatively homogeneous; the results of determining the flow properties show that the flow rates of F1, F2, and F3 have good flow properties, but F4 has very difficult flow properties which tend not to flow; the results of determining other flow properties, namely the angle of repose, show that the angle of repose values F1, F2 and F3 have adequate flow properties, but F4 has very poor flow properties; the results of the compressibility index show that the compressibility index F1, F2 and F3 have good flow properties but F4 has poor flow properties; and the results of the Hausner ratio show that the Hausner ratio values F1, F2 and F3 have good flow properties but F4 has medium flow properties. Based on the results of the granule characterization, it can be concluded that formulas F1, F2, and F3 can be continued to the caplet compression process, while formula F4 is not continued.

Caplet compression was carried out using a Rimex machine with punches type tooling D, namely caplets with a length of 19.6 mm and a width of 8.6 mm. The test parameters for compressing these caplets follow the specifications of USP 44 (2021), including physical and chemical examination. The complete results of the examination of the physical and chemical properties of the caplets can be seen in Table 6 and 7. The physical examination results in Table 6, including uniformity of weight, thickness, length, width, hardness, and friability, are to the specifications set by USP 44 (2021). Furthermore, the results of the chemical examination in Table 7 include the levels of active substances and dissolution in

the caplets following the specifications set by USP 44 (2021). The active substance content test results show a 100.32-102.28% value with a 90-110% specification. The dissolution test results show that the F1 and F3 formulas for sampling points Q (60'), Q (180'), and Q (600') still meet dissolution requirements, but at the 12th, 18th, and 24th hour, levels decreased below 85%. In contrast, the F2 sampling point formula, after 10 hours, or Q (600'), could still maintain levels above 85%, so this F2 formula was declared the most optimal compared to formulas F1 and F3. Then, the F2 formula will be tested for similarity through a comparable dissolution test (UDT) on the originator drug of the Glucophage XR 500 mg tablet.

Comparative dissolution test (UDT) on the test drug with the originator drug Glucophage XR 500 mg tablets was carried out using HCl buffer medium pH 1.2, acetate pH 4.5, and phosphate pH 6.8. The complete UDT results can be seen in Table 8. The results show that the metformin HCl XR 500 mg caplet formula F2 is similar to the Glucophage. Therefore, F2 formula products can proceed to packaging and stability.

The primary packaging process is carried out using strips using a Wufu machine. The parameters observed include sealing roll temperature, yield, and strip leak test. Observation results show that the sealing roll temperature is 120°C, and the packaging yield is 95%. Apart from that, a leak test was carried out to assess the quality of the strips resulting from the primary packaging process, using a vacuum chamber with a pressure of -50 mmHg for 5 minutes, and the results showed that none of the strips experienced any leaks.

The product stability test for metformin HCl XR 500 mg was carried out using the long-term and accelerated stability method using a climatic chamber with observation periods of 0, 3, and 6 months. Observation of the stability of long-term and accelerated conditions as shown in Tables 9 and 10, conditions at initial (0 months), third month, and sixth month, both physical and chemical parameters, the results are by the established acceptance criteria, especially on the target extend solubility, up to the sixth month the product dissolution results still meet the requirements of Q (600) ≥ 85.0%, namely 99.1% (accelerated stability) and 95.5% (long term stability).

Based on the analysis results with design expert® 13 software, the linearity values of the granule flow rate response, caplet hardness, and dissolution were found to be 0.9559, 0.9978, and 0.9912, and the lack of fit value was the same, zero. With these validation results, the test can be validated with a linearity value close to 1 and a lack of fit < 2. The results of the ANOVA (Analysis of variance) analysis show that the ANOVA results on the response of granule water rate, caplet taper, and dissolution provide a significant p-value for each matrix, which is smaller than the α value = 0.05, so it can be proven that the granule flow rate response, caplet hardness, and dissolution have a relationship with the concentration and matrix combination in the metformin HCl XR 500 mg caplet formula. The half-normal plot analysis produced in this data analysis can be used to see the factors that most

influence the evaluation parameters of the analysis data, which can be seen in Figure 2, 3 and 4. In the granule flow rate response, the most influential factor is hypromellose (A), with a value of the contribution, was 59.746%, followed by Na-CMC (B) at 31.281% and the combination of both (AB) at 4.565%. These three factors harm the granule flow rate. This can be interpreted as the addition of hypromellose, the largest contributor to the flow rate, further decreasing the flow rate, making the flow less smooth. In the caplet hardness response, the most influential factor was the combination of the two matrices (AB) with a contribution value of 52.630%, followed by Na-CMC (B) at 27.701% and then hypromellose (A) at 17.477%. These three factors harm caplet hardness. This can be interpreted by adding a combination of the two matrices, which contribute the most to caplet hardness; the hardness of the caplets formed will further decrease. In the dissolution response, the most influential factor is the combination of the two matrices (AB) with a contribution value of 41.401%, followed by Na-CMC (B) at 40.674%, followed by hypromellose (A) at 17.041%. These three factors harm the dissolution value. It can be interpreted that with the combined effect of the two matrices as the largest contributor to the dissolution value, the dissolution value will decrease if they continue to be added.

Recommendations for optimal formulas from the design expert® 13 software can be seen in contour plot graphs and regression equation models. The contour plot graph shows how the matrix combination affects the response of granule flow rate, caplet hardness, and dissolution. The results of the matrix response to granule flow rate, caplet hardness, and dissolution can be seen in Figure 4,5 and 6. It can be seen in the contour plot of the granule flow rate response that the good formula recommendation is formula F1 with a hypromellose concentration of 10% and Na-CMC of 10%. In contrast, for the contour plot on the caplet hardness response and the contour plot on the dissolution response, the good formula recommendation is the F2 formula, with a hypromellose concentration of 30% and Na-CMC of 10%.

The optimum formula obtained from the design expert® 13 software can be seen from the desirability value. The desirability value provides a relationship between the response value produced by the factor and the ideal requirement value, namely 0 - 1. The closer the desirability value is to number one; it shows the software's ability to produce a good optimum formula (42). In Figure 7, the results of the desirability analysis show that the optimal formula is formula F2, a combination of hypromellose and Na-CMC of 30:10 with desirability values for granule flow rate, hardness, and caplet dissolution of 1, which shows that design expert® 13 software has produced the optimum formula. The results of the desirability analysis also correlate well with stability; in the F2 formula, the stability test results up to the sixth month still follow the acceptance criteria regarding physical and chemical properties.

5. Conclusion

This research focuses on developing a Metformin HCl caplet formula with variations in the composition of the hypromellose and Na CMC matrix to achieve optimum conditions through an extended-release system using the direct compression method. The optimum formula produced is the F2 formula, a combination of hypromellose and Na-CMC with a ratio of 30:10. This was determined based on the results of comparative dissolution tests, stability, and data analysis with design expert software. Comparative dissolution test (CDT) results show that the F2 formula is similar to Glucophage XR 500 mg tablets. The long-term and accelerated stability results for six months show that the physical and chemical properties comply with USP 44 specifications, and based on data analysis with expert design, the granule flow rate desirability, hardness, and dissolution values for the F2 formula caplets were 1, which indicates that the F2 formula is the optimum formula.

6. References

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