

OPTIMIZATION OF CROSCARMELLOSE AND SODIUM STARCH GLYCOLATE ON ORALLY DISINTEGRATING METOCLOPRAMIDE HCL TABLETS

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32

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ABSTRACT

The dosage form of metoclopramide HCl with high solubility but low permeability is an Orally Disintegrating Tablet (ODT) because it can decrease first-pass-effect metabolism so that its bioavailability and effectiveness increase. Superdisintegrant is an excipient that plays a significant role in formulating ODT. The combination of croscarmellose and Sodium Starch Glycolate (SSG) can accelerate tablet disintegration time, making the resulting ODT suitable for its intended use. This study aimed to determine the effect of each and the interaction of the use of croscarmellose and SSG on the physical characteristics of ODT metoclopramide HCl, and to get the optimum formula of ODT metoclopramide HCl. Tablets were prepared by direct compression method. Optimization process by using simplex lattice design (design expert 10.0.1.R program) with eight formulas, including FI (5.25%A:1.75%B), FII (0%A:7%B), FIII (7%A:0%B), FIV (1.75%A:5.25%B), FV (7%A:0%B), FVI (3.5%A:3.5%B), FVII (3.5%A:3.5%B) and FVIII (0%A:7%B). Component A is the concentration of croscarmellose, and component B is the concentration of SSG. Based on the SLD equation, the single-use croscarmellose and SSG components could be increased flowability, hardness, moisture content, friability, water ratio absorption, weight uniformity, uniformity of content, accelerated disintegration time, wetting time, and dissolution. The interaction of the two components was increased flowability, moisture content, water ratio absorption and dissolution, decreased hardness, friability, uniformity of content, weight uniformity, accelerated disintegration time, and wetting time. The optimum formula of ODT metoclopramide HCl with proportion 5.145% croscarmellose and 1.855% SSG. Based on the one sample t-test between theoretical and experimental results, there were no significant differences between them.

Keywords: Croscarmellose; Metoclopramide HCl; Optimization; Orally disintegrating tablets; Sodium starch glycolate

1. INTRODUCTION

Metoclopramide HCl is an antiemetic drug to prevent nausea and vomiting as a dopamine receptor antagonist (Aronson, 2015). Metoclopramide HCl metabolism occurs rapidly after administration, indicating that metoclopramide HCl undergoes first-pass-effect metabolism (Litou et al., 2019). The absorption of metoclopramide HCl when given orally, is about 75% (Vinarov et al., 2021). Metoclopramide HCl has high solubility and low permeability, so it is categorized in BCS (Biopharmaceutical class system) class 3 (Shakeel et al., 2014). Metoclopramide HCl, an Orally Disintegrating Tablets (ODT), can reduce the first-pass-effect metabolism because some drugs are also absorbed in the pre-gastric area such as the mouth, pharynx, and esophagus when saliva descends into the stomach. Therefore, the bioavailability of the drug will increase and ultimately increase the therapy's effectiveness (Dawadi et al., 2020).

Disintegrants are excipients that have a significant role in the formulation of tablet dosage forms to accelerate disintegration in the gastrointestinal environment, consequently increasing the release of active ingredients (Sadeghi et al., 2019). The formulation of the ODT preparation with

the direct compression method requires the presence of a vital component, including a superdisintegrating material that quickly disintegrates in the mouth so that it has greater disintegration than conventional tablet preparations. Superdisintegrants in the preparation have been shown to not only accelerate the disintegration of tablets but also affect the solubility of the active substances to increase their bioavailability (Zarmpi et al., 2020).

Croscarmellose has a dual mechanism: water wicking and rapid swelling (Setyawan et al., 2010). However, its expansion power is more minor than SSG, which is 4-8 times its original volume (Sheskey et al., 2017). Sodium Starch Glycolate (SSG) is a superdisintegrant that has an immense expansion power, which is 200-300 times its original volume (Berlian & Subarnas, 2018), but often forms a gel layer when in contact with water. Hence, it blocks the penetration of water into the tablet (Sa'adah & Fudholi, 2011). The combination of the high-wicking power of croscarmellose and the enormous swelling of SSG is expected to result in a disintegration time of less than three minutes. Research Rachmawati et al (2015) states that the development of a formulation combining SSG and croscarmellose sodium will produce tablets with better physical quality parameters and can accelerate the disintegration time, dispersion time, and tablet wetting time. This study uses the direct printing method because according to Berkenkemper et al (2020), the disintegrating effect of croscarmellose sodium would be damaged due to the granulation process.

Optimization uses the Simplex Lattice Design (SLD) method. The combination of the two ingredients is expected to produce tablets with better physical characteristics than tablets using one type of disintegrant. Therefore, it is necessary to optimize croscarmellose and SSG on the physical characteristics of ODT metoclopramide HCl using the SLD method, which has never been done before. This study aims to determine the respective effects and interactions of the use of croscarmellose and SSG on the physical characteristics of metoclopramide HCl ODT and to obtain the optimum formula for metoclopramide HCl ODT preparations.

2. METHOD

The tools are analytical balance (P.A.C.I.S.A), digital balance (Shimadzu), tablet printing machine, flow time tester, hardness tester (Prima), friability tester (Prima), disintegration tester, stopwatch, thermometer, moisture content tester (Mettler Toledo), water absorption ratio tester, type 2 dissolution tester (Veego), and UV-Vis mini 1240 spectrophotometer (Shimadzu).

Pharmaceutical grade materials use metoclopramide HCl (Ipca Laboratories Ltd.), croscarmellose use Ac-Di-Sol® (FMC Biopolymer), sodium starch glycolate (Gujarat), magnesium stearate (Faci Asia Pacific Pte. Ltd.), talcum, mannitol (Danisco), aspartame (Sinosweet), and spray dried lactose (Meggle). In contrast, the material with technical grade is aqua destillata.

The preparation of orally disintegrating tablets of metoclopramide HCl uses the direct compression method. Table 1 presents the optimization design of the ODT formula. Metoclopramide HCl, croscarmellose, SSG, Spray Dried Lactose (SDL), aspartame, talcum and mannitol were weighed and then mixed until homogeneous. The powder mixture was tested for flow time and moisture content. Then, magnesium stearate is added to the mixture and mixed until homogeneous. The mixture is then compressed into tablets weighing 200 mg per tablet approximately. The printed tablets were tested for weight uniformity, friability, hardness, disintegration time, content uniformity, wetting time, water absorption ratio, and dissolution of metoclopramide HCl tablets.

Determination of the optimum formula is based on parameters including flowability, moisture content, hardness, friability, disintegration time, wetting time, water absorption ratio, content uniformity, weight uniformity, and dissolution. The optimum formula is obtained by considering the total responses from the design expert program 10.0.1.R through the simplex lattice design (SLD) equation, $Y = Ba(XA) + Bb(XB) + Bab(XA)(XB)$. Y is the response, and Ba, Bb

and Bab are coefficients that describe the effect of the interaction (can be calculated from the experiment). XA and XB are factors with 0 to 1 value. The optimum formula is obtained from the design expert program 10.0.1.R, then a t-test is performed with a 95% confidence level using IBM SPSS Statistics 23.

Table 1. Optimization Design Based on Design Expert 10.0.1.R

Ingredients (gram)	FI	FII	FIII	FIV	FV	FVI	FVII	FVIII
Metoclopramide HCl	3	3	3	3	3	3	3	3
Croscarmellose	3.15	0	4.2	1.05	4.2	2.1	2.1	0
SSG	1.05	4.2	0	3.15	0	2.1	2.1	4.2
34 Day Dried Lactose (SDL)	39	39	39	39	39	39	39	39
Aspartame	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Magnesium Stearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Talcum	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mannitol	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6

Note: Ingredient's calculation and weighing for 300 tablets.

3. RESULTS AND DISCUSSION

The optimization parameters determine the powder mixture's quality and the ODT metoclopramide HCl results. The test results include flowability, moisture content, weight uniformity, hardness, friability, disintegration time, wetting time, water absorption ratio, content uniformity, and dissolution as shown in Table 2.

The test results of each optimization parameter were analyzed using the design expert program 10.0.1.R with the SLD method until the respective equations were obtained, as shown in Table 3. These equations can identify the single effect of croscarmellose, SSG, and the interaction between the two on each optimization parameter by looking at the obtained coefficient values. The optimization equation can also predict the value of each response as the value of Y, so that the optimal formula and prediction of the value of each parameter can be calculated.

Table 2. Parameter Test Results Optimization of Powder Mixture and ODT Metoclopramide HCl

Test	FI	FII	FIII	FIV	FV	FVI	FVII	FVIII
Flow rate (gram/second)	53.21	59.03	54.16	57.49	52.25	57.3	56.46	59.12
Moisture content (%)	0.62	0.46	0.68	0.56	0.7	0.59	0.58	0.5
Hardness (kg)	3.33	3.83	3.42	3.75	3.42	3.5	3.5	4
Friability (%)	0.69	0.53	0.77	0.48	0.74	0.64	0.68	0.51
Disintegration time (second)	61.37	80.32	62.5	72.26	62.37	65.02	65.34	80.23
Wetting time (second)	64.5	105	65.38	85.35	65.25	72.12	70.3	105.36
Water absorption ratio (%)	60.1	36.27	48.08	39.6	49.01	47.14	48.02	38.61
Weight uniformity (mg)	199.95	203.95	203.65	201.35	203.1	203.65	206.3	204.2
Content uniformity (%)	101.16	99.92	101.53	99.93	100.06	99.52	98.48	99.09
Dissolution (%)	103.93	93.51	95.11	95.89	95.39	94.02	97.22	93.23

Table 3. Equation of Simplex Lattice Design of Mixed Powder and Metoclopramide HCl ODT

Test	Equation of Simplex Lattice Design
Flow rate (gram/second)	$Y = 7.56 X_a + 8.45 X_b + 1.74 \times 10^{-2} X_a X_b$
Moisture content (%)	$Y = 9.80 \times 10^{-2} X_a + 6.93 \times 10^{-2} X_b + 1.60 \times 10^{-4} X_a X_b$
Hardness (kg)	$Y = 0.49 X_a + 0.56 X_b - 1.37 \times 10^{-2} X_a X_b$
Friability (%)	$Y = 0.11 X_a + 7.20 \times 10^{-2} X_b - 3.85 \times 10^{-4} X_a X_b$
Disintegration time (second)	$Y = 8.89 X_a + 11.50 X_b - 0.50 X_a X_b$
Wetting time (second)	$Y = 9.32 X_a + 15.04 X_b - 1.13 X_a X_b$
Water absorption ratio (%)	$Y = 7.21 X_a + 5.15 X_b + 0.48 X_a X_b$
Weight uniformity (mg)	$Y = 28.99 X_a + 29.13 X_b - 2.64 \times 10^{-2} X_a X_b$
Content uniformity (%)	$Y = 14.42 X_a + 14.22 X_b - 5.36 \times 10^{-2} X_a X_b$
Dissolution (%)	$Y = 13.77 X_a + 13.28 X_b - 0.25 X_a X_b$

Notes: Y= response; Xa= croscarmellose concentration; Xb= SSG concentration

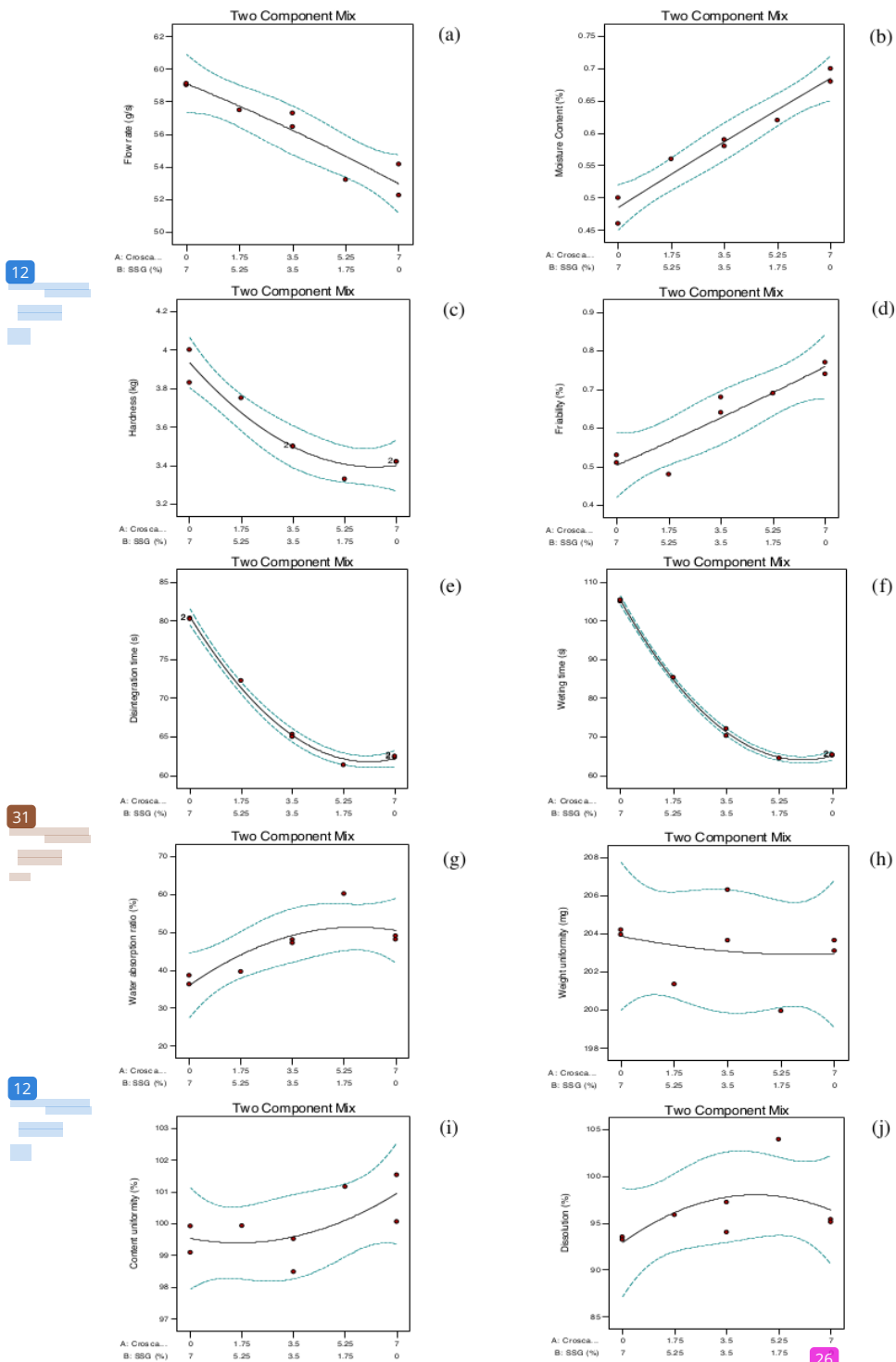


Figure 1. Graph of Effect of Superdisintegrant Addition on: (a) Flowability; (b) Moisture Content; (c) Hardness; (d) Friability; (e) Disintegration Time; (f) Wetting Time; (g) Water Absorption Ratio; (h) weight uniformity; (i) Content uniformity; (j) Dissolution based on Software Design Expert

The equation in Table 3 shows that the positive coefficient values in the single use of the croscarmellose and the SSG component increase the flow rate. The use of SSG components has a dominant effect in increasing the flow rate. The interaction of the two components also increases the flowability, but the effect is negligible. Figure 1a shows that the higher the concentration of croscarmellose, the lower the flowability because croscarmellose is hygroscopic. Table 3 shows that the coefficient value of the croscarmellose component is $+9.80 \times 10^{-2}$, indicating the effect of increasing the moisture content of the powder mixture because croscarmellose is a hygroscopic material. Therefore, water from the air can be absorbed. The interaction between the two components showed an increase in the moisture content of the powder mixture. Figure 1b presents that the higher the concentration of croscarmellose, the greater the moisture content in the powder mixture.

The hardness test based on the equation in Table 3 shows that the coefficient value of the SSG component is $+0.56$, while the croscarmellose coefficient is $+0.49$. If used alone, croscarmellose and SSG can increase the hardness of ODT. The interaction of croscarmellose and SSG components has a negative coefficient, indicating that the interaction of croscarmellose and SSG reduces tablet hardness. Figure 1c presents that the interaction of the components of croscarmellose and SSG decreases the tablet hardness response.

The friability of tablets in Table 3 shows that the friability response is influenced by the croscarmellose component, SSG, and the interaction of the two components. The positive coefficient value indicates that using the croscarmellose and the SSG component in single-use increases the friability of ODT. The component that most affected the friability was croscarmellose, with a coefficient of 0.11 ; therefore, the greater the concentration of croscarmellose, the higher friability of the tablet. Figure 1d presents the interaction between croscarmellose and SSG on the friability response, showing that the interaction between croscarmellose and SSG has the best effect on tablet friability than single-use because the interaction between croscarmellose and SSG can improve tablet compactness.

In Table 3, the value of the croscarmellose coefficient is $+8.89$, showing that adding croscarmellose separately will increase the disintegration time of the tablet. The SSG coefficient value obtained is greater than that of croscarmellose, which is $+11.50$. Therefore, the disintegration time of using SSG can be longer. SSG, under certain conditions, will be able to change its mechanism from swelling to the formation of a gel matrix causing a decrease in the rate of hydration and dissolution due to the formation of a thick interfacial layer and causing the tablet not to disintegrate immediately (Wren et al., 2017). Croscarmellose has a better disintegration time of its consistency and stability. Croscarmellose has wicking and swelling action (Sheskey et al., 2017). The swelling ability (expands quickly) in croscarmellose is more dominant so that it can change the formation of the tablet. Figure 1e shows an interaction between croscarmellose and SSG, which causes a change in disintegration time. The interaction of croscarmellose and SSG will increase the wicking speed and swelling power in water by minimizing gel formation so that the tablet disintegrates quickly.

The value of the croscarmellose coefficient based on the equation in Table 3 is $+9.32$, indicating that adding croscarmellose separately will increase the wetting time. The SSG coefficient value is greater than croscarmellose, which is $+15.04$. Figure 1f shows the two components' interaction with the wetting time response. The value of the interaction coefficient between the two components is negative, -1.1 , indicating that the interaction can reduce or speed up wetting time. Figure 1f shows that the graph pattern is higher on the formula containing the most SSG. It shows that the more SSG, the longer the wetting time than adding croscarmellose separately, which indicates the reduced nature of the tablet matrix that can absorb water and the reduced hydrophilicity of the tablet (Kumar & Saharan, 2017).

The effect of each component of croscarmellose and SSG or the combination of the two can increase the water absorption ratio, as shown in Table 3, all the coefficients of the equation are

positive (+). The increase in the water absorption ratio due to the effect of croscarmellose was greater than that of SSG, as shown in Figure 1g where the water absorption ratio curve increased along with the increase in the concentration of croscarmellose. The same result is also seen from the content uniformity test in Figure 1i, which is dominated by the single effect of croscarmellose. In Figure 1h, the weight uniformity test of SSG has a more dominant effect than croscarmellose with a slight difference in coefficient values (Table 3).

The dissolution test parameters based on the equation in Table 3, positive coefficient values indicate that the single use of croscarmellose and SSG components increases the dissolution of ODT. The value of the croscarmellose coefficient is + 13.77; this indicates that adding croscarmellose separately will further increase the dissolution time. The interaction between the two components on the dissolution response can be seen in Figure 1j. The value of the interaction coefficient between the two components is positive, + 0.25, indicating that the interaction of the two components can also increase or prolong the dissolution time, but the effect is very small because croscarmellose has a wicking and swelling action (Hussain et al., 2020).

The experimental results of each test are compared with the theoretical results from the optimization of the simplex lattice design. Each test parameter showed $P > 0.05$. In conclusion, the results of each parameter were not significantly different between the theoretical and experimental results.

4. CONCLUSION

The single-use of croscarmellose and SSG increased the flowability, hardness, moisture content, friability, water absorption ratio, weight uniformity, content uniformity, accelerated disintegration and wetting time, and increased the dissolution of ODT metoclopramide HCl. The interaction between croscarmellose and SSG increased the flowability, moisture content, water absorption and dissolution ratio, decreased hardness, friability, disintegration time, and wetting time. Comparing 5.114% croscarmellose and 1.886% SSG can produce ODT metoclopramide HCl preparations with optimal physical characteristics. Based on the results of the disintegrant combination, it can be considered for research on the superdisintegrant potential of natural ingredients in ODT preparations.

5. CONFLICT OF INTEREST

The author declares that there are no competing conflicts of interest.

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