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Optimization of Formula Fast Disintegrating Tablet (FDT) Antacids with Simplex Lattice Design Method

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ABSTRACT

Antacids are compounds that can neutralize stomach acid. Antacid preparations on the market are generally in the form of powders, suspensions, and chewable tablets. However, this dosage form is considered less practical, so an alternative dosage form is needed. FDT antacids are one of the quick-dissolving tablet strategies to neutralize stomach acid. The combination of Avicel PH 101 with a wicking mechanism and Sodium Starch Glycolate (SSG) with swelling action is expected to increase the effectiveness of the super disintegrant. The simplex lattice design method (Design Expert 7.1.5) was used to optimize the super disintegrant of SSG (A) and Avicel PH 101 (B). Tablets were prepared using the wet granulation method in an 8-run formula. The optimum formula for FDT antacids was determined by disintegration time and acid neutralization capacity parameters. The results showed that increasing Avicel PH 101 in combination with SSG decreased the disintegration time and increased the value of the acid neutralization capacity of the FDT antacid. Based on the optimization of the numerical method, the optimum composition of the FDT antacid formula was obtained with a combination of 38 % SSG and 101 % Avicel PH 101.

***Keywords*:** Antacids; Sodium starch glycolate; Avicel PH 101; Simplex lattice design; Fast disintegrating tablet

INTRODUCTION

Basic Health Research (Riskesdas) results show that the incidence of gastritis in Indonesia is relatively high at 40.8%.[1] Antacids are compounds that can neutralize stomach acid. Antacids on the market are generally in the form of powders, suspensions, and chewable tablets. However, this dosage form is considered impractical, so an alternative dosage form, namely fast disintegrating tablets (FDT) antacids, is needed. FDT can provide a faster onset because it disintegrates rapidly in the mouth.[2]

In the FDT formula, one of the essential ingredients is a super disintegrant, so the tablet undergoes a rapid disintegration process in the mouth.[3] One example of a commonly used super disintegrant is sodium starch glycolate (SSG). SSG results from modified starch with carboxymethyl substitution and has very high swelling power, but the concentration required is only a small amount, namely 2-8%.[4,5] To obtain FDT antacids with a shorter disintegration time, add Avicel as a super disintegrant combined with SSG. Apart from being widely used as a filler binder, Avicel is also widely known for its use as a disintegrant. Avicel is the trade name for microcrystalline cellulose.[5,6] Avicel can shorten the disintegration time of FDT papaverine HCl.[7] The addition of Avicel as a hydrophobic polymer is expected to increase the neutralization capacity of antacid FDT. To get the exact composition

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of Avicel and SSG, the simplex lattice design (SLD) optimization approach is used. With this SLD optimization approach, the optimum composition of SSG and Avicel can be estimated, avoiding trial and error experiments. Besides that, the effect of the interaction of SSG and Avicel PH 101 on the quality of FDT antacids can also be analyzed.[8]

METHODS

Materials

Aluminum hydroxide (Par Drugs & Chemicals Pvt. Ltd.), Magnesium Hydroxide (Par Drugs & Chemicals Pvt. Ltd.), Sodium Starch Glycolate (Gujarat Overseas Inc.), Avicel PH 101, Mannitol (Qingdao Bright Moon Seaweed Group Co., Ltd.), Lactose, Manihot Starch, Magnesium Stearate (pharmaceutical grade, Brataco Indonesia), Hydrochloric Acid (analytic grade, Merck), Sodium Hydroxide, and Aquades (Brataco Indonesia).

Equipment

Single punch tablet machine (Korsch, Germany), friabilator (Erweka), hardness tester (Stokes Monsanto), analytical balance (Sartorius BP 221S), pH meter (Hanna 8514), and glassware.

Preliminary trials

This step aims to obtain the excipient composition of antacid FDT, especially superdisintegrant. In the preliminary experimental formula, SSG was used as the superdisintegrant (Table 1).

Optimization of the antacid FDT formula

The design of the FDT antacid tablet formula uses SLD optimization with the Design Expert 7.1.5 program. In this case, two variables were used, SSG and Avicel PH 101, to obtain eight formulas (table 2).

Production of FDT antacids

Tablets were prepared using the wet granulation method. Aluminum hydroxide, magnesium hydroxide, avicel, SSG, mannitol, lactose, and manihot starch were mixed until homogeneous.

Table 1. Formula of FDT antacid: preliminary trials

Materials	Formula 1	Formula 2 (mg)	Formula 3
$Al(OH)_3$	200	200	200
$Mg(OH)_2$	200	200	200
SSG	70	105	140
Mannitol	70	70	70
Lactose	83	48	13
Amylum	70	70	70
Magnesium Stearate	7	7	7
Tablet Weight	700	700	700

Aquadest was added to form a granular mass, sieved with no. 16 mesh, the granules were dried in a drying cabinet at 60°C. The dry granule mass was sieved with no.18 mesh. Magnesium is added and stirred until homogeneous. The tablet mass was compressed with a die diameter of 12 mm and a weight of 700 mg.

Evaluation of physical properties of tablets

The weight uniformity test was carried out by weighing 10 tablets and calculating the NP (%) as an evaluation parameter. Hardness test using Hardness Tester. The friability test was carried out using 20 tablets with an friabilator, and the % weight loss was calculated.

Tablet disintegration time test

FDT tablets were placed in a petri dish containing 20 ml of distilled water. FDT is placed slowly into a petri dish containing distilled water, and then the disintegration time required by the tablet is recorded.[9]

Acid neutralizing capacity test

Weigh 20 tablets and then calculate the average weight. All tablets were powdered and weighed accurately for the dose. Put the powder into a 250 ml beaker glass. Add 70 ml of distilled water and mix for 1 minute with a magnetic stirrer.

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Table 2. FDT antacid formula according to the SLD optimization design

Std	Run	Materials (mg)							
		$Al(OH)_3$	$Mg(OH)_2$	SSG	Avicel PH 101	Mannitol	Lactose	Amylum	Magnesium Stearate
3	1	200	200	70	70	70	13	70	7
1	2	200	200	140	0	70	13	70	7
2	3	200	200	0	140	70	13	70	7
6	4	200	200	140	0	70	13	70	7
5	5	200	200	35	105	70	13	70	7
7	6	200	200	0	140	70	13	70	7
8	7	200	200	70	70	70	13	70	7
4	8	200	200	105	35	70	13	70	7

While stirring, add 30 ml of 1.0 N HCl. Then, go for precisely 15 minutes, and immediately titrate with 0.5 N NaOH until a stable pH of 3.5 is reached. Calculation of the amount of acid mEq used with the following formula:

Total mEq = (30 x N HCl) – (V NaOH x N NaOH)

Note: N HCl = normality of HCl, N NaOH = normality of NaOH

The results are expressed in mEq of the acid used in the titration for each g of the substance in the test sample.[10,11]

Data analysis

Statistical analysis of SLD optimization using the Design Expert 7.1.5 program. The effect of SSG and Avicel PH 101 on the FDT properties of antacids was determined based on the correlation coefficient (X) in equation (1).

$$Y = X0 + XA\ (A) + XB\ (B) + XAB \quad \text{..... (1)}$$

Note: Y = tablet properties, X = correlation coefficient, A = SSG (mg), B = Avicel PH 101 (mg)

The optimum composition of FDT antacids was determined by a numerical method using parameters of disintegration time and acid neutralization capacity.

RESULTS AND DISCUSSION

Preliminary trials

The evaluation results of the preliminary trial of FDT antacid tablets are presented in Table 3. The data in Table 2 also shows that increasing the amount of SSG can increase tablet hardness and reduce friability. This is due to the nature of SSG, which can absorb the moisture of 40-50% by weight to strengthen the bonds between granules in tablets and increase compressibility.[12,13]

The results of the disintegration time test showed that increasing the level of SSG reduced the disintegration time of the tablets even though the hardness of the tablets was different between formulas. SSG has a swelling destruction mechanism because it has an excellent affinity for water and a very high swelling power when in contact with water. As a result of which, the tablet constituent particles will be pushed and broken.

Table 3. Physical properties of FDT antacid tablets: preliminary trials

Parameters	Formula 1	Formula 2	Formula 3
Weight (Mean±SD, mg) (n=10)	700.25±0.43	700.80±0.21	700.20±0.75
Hardness (Mean±SD, kg/cm²) (n=3)	6.32±0.13	8.28±0.18	8.55±0.48
Friability (%)	0.11	0.07	0.09
Disintegration time (minute) (n=3)	4.20±0.01	3.32±0,01	2.53±0.01
Acid neutralization capacity (mEq) (n=3)	7.35±0.35	5.92±0,08	5.67±0.10

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Table 4. Physical properties of FDT antacid: formula optimization

Run	Weight (mg) (n=10)		Hardness (kg/cm²)(n=5)	Disintegration time (minute) (n=3)	Friability (%)	Acid neutralization capacity (mEq) (n=5)
	Mean	NP (%)				
1	708.10	11.94	8.19±0.33	5.72±1.46	0.07	9.64±0.37
2	710.50	11.93	7.83±0.27	25.86±0.62	0.21	8.77±0.69
3	711.40	11.93	7.57±0.48	5.05±1.18	0.14	7.72±0.98
4	712.00	14.40	7.74±0.98	28.89±0.61	0.29	9.35±0.88
5	708.70	14.22	7.68±0.61	2.30±0.22	0.07	8.85±1.11
6	747.30	11.76	8.53±0.34	5.11±1.50	0.14	8.39±0.76
7	705.00	10.31	7.80±0.46	6.81±0.41	0.14	10.24±0.26
8	710.00	13.90	7.95±0.50	6.83±0.59	0.07	9.03±1.16

SSG can absorb 200-300% water, so the ability to absorb water from the medium is more significant. As a result, the disintegration time of antacid FDT tablets is faster.[13] However, decreased disintegration time due to increased SSG content was not accompanied by increased acid neutralization capacity. Increasing the amount of SSG decreases the FDT neutralization capacity of antacids. This is thought to occur due to the formation of a gel layer due to the SSG development process, thereby reducing the neutralizing capacity of the acid.[4,14,15] To overcome this, Avicel PH 101 was added to the optimization study of the antacid FDT formula.

Optimization of the antacid FDT formula

All tablet run 1-8 formulas met good tablet weight uniformity requirements. This can be seen in table 2, the NP values of all formulas do not exceed 15%.[16] This shows that the wet granulation method can produce good granule fluidity so that the weight is uniform. The hardness test results also showed that tablets run 1-8 met the requirements of a good tablet, namely 4-10 kg/cm² and friability <1%.[17]

The results of the disintegration time test showed that, in general, the antacid FDT formulations did not meet the requirements of less than 3 minutes except for run 5.[18] Further analysis of tablet disintegration time used Design Expert 7.1.5. Equation (2) and contour plot are obtained in Figure 1a.

$$Y = 26.311 (A) + 5.482 (B) – 46. 426 (A) (B) \quad \ldots\ldots (2)$$

Y = disintegration time (minutes)
A = SSG (mg)
B = Avicel PH 101 (mg)

Based on equation (2), Avicel PH 101 shows the dominant effect in reducing disintegration time. Avicel PH 101, as a disintegrating agent, has a high effectiveness with a wicking action mechanism. The mechanism of wicking action through the capillary action is the initial step when the tablet is in contact with the medium. Water will penetrate through the pores of the tablet to replace the air in the particles, then weaken the intermolecular bonds and damage the tablet so that it breaks into smaller sizes.[19] Avicel's wicking ability allows the tablet to absorb water faster, causing swelling. As a result, the tablet breaks and dissolves.[20]

The interaction between SSG and Avicel PH 101 produces a negative coefficient (–46.426), meaning that combining the two ingredients can reduce tablet disintegration time. This can be seen in contour plot 1a, which is concave in shape. The concave area in the figure shows the lowest disintegration time with the combination of 35 mg SSG and 105 mg Avicel PH 101 (run 5).

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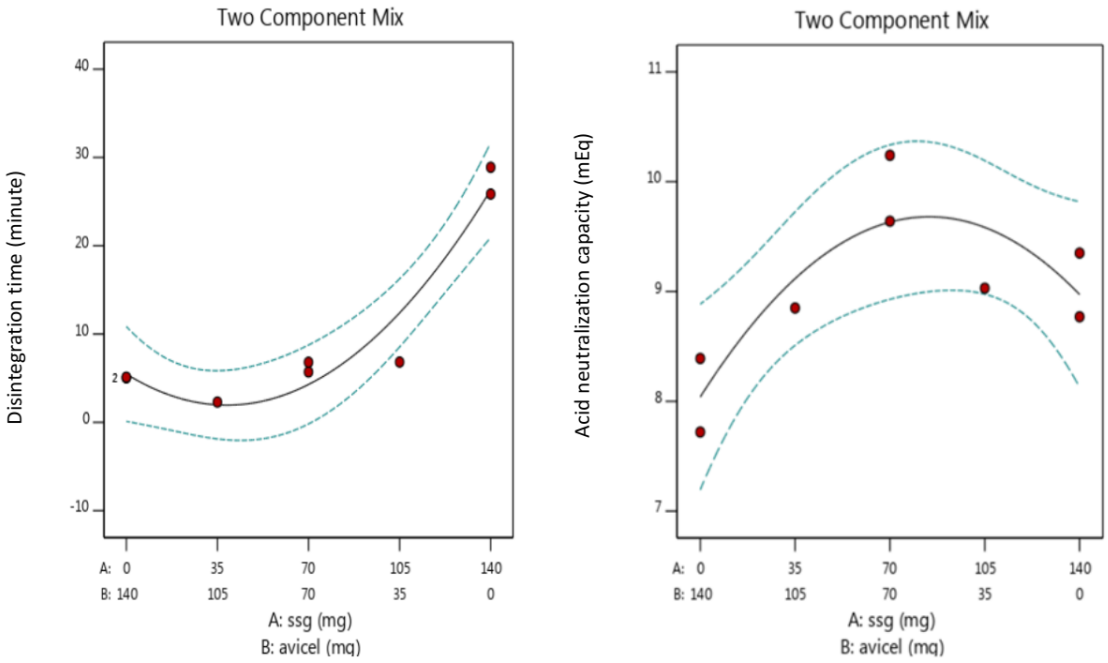

1a **1b**

Figure 1. Contour plot of response disintegration time (1a) and acid neutralization capacity (1b) of FDT antacids

Avicel PH 101, as a superdisintegrant can increase the effectiveness of SSG. Avicel PH 101 neutralized the viscous gel layer formed due to the expansion of SSG as a hydrophobic polymer. In addition, the combination of SSG's swelling mechanism and Avicel PH 101's wicking mechanism disintegrates the tablet more quickly. The wicking action of Avicel PH 101 will draw water into the tablet.

Furthermore, the water in the tablet comes in contact with the SSG, and through the swelling action, the tablet expands upon contact with water. As a result, the tablet constituents will be pushed so that the tablet breaks.[17] Water entry into the tablet causes the SSG to expand up to 300 times its volume. It results in the tablet particles being pushed out more quickly, breaking the intermolecular bonds of the tablet into a finer size into small particles.[5,21,22]

The results of the acid-neutralization capacity test in Table 4 show that all run formulas 1-8 meet the requirements > 5 mEq.[23] The acid neutralization ability of an antacid preparation is an important quality parameter related to the effectiveness of antacid FDT. Further analysis of acid neutralization capacity using Design Expert 7.1.5. Equation (3) and contour plot are obtained, as shown in Figure 1b.

$$Y = 8.972\ (A) + 8.039\ (B) + 4.503\ (A)(B) \quad ....(3)$$

Y = acid neutralization capacity (mEq)
A = SSG (mg)
B = Avicel PH 101 (mg)

Based on equation (3), there is no dominant factor affecting the acid neutralization capacity, but the combination of SSG and Avicel PH 101 can significantly increase the acid neutralization capacity with an interaction coefficient value of +4.503. The effectiveness of combining these two materials can also be seen in Figure 1b. The convex upward contour plot shows that the ratio SSG: Avicel PH 101 (1:1) produces the optimum neutralization capacity. This phenomenon occurs because combining the two materials results in a faster tablet disintegration time. The faster the tablet disintegrates, the smaller the particle size, and the larger the surface area, the dissolution of FDT antacids increases, resulting in a higher acid neutralization capacity.[4]

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FDT antacid optimum formula

The optimum formula of FDT antacids was determined by parameters of disintegration time (< 3 minutes) and acid neutralizing capacity (> 5 mEq).[18,23]

Table 5. The optimum formula of FDT antacid

Material	Amount/tablet (mg)
Aluminum hydroxide	200
Magnesium hydroxide	200
SSG	38
Avicel PH 101	101
Mannitol	70
Lactose	13
Amylum	70
Magnesium stearate	7

Optimization results using the Design Expert 7.1.5 program with numerical methods obtained the optimum formula composition with a desirability value of 0.523. The optimum FDT antacid formula is presented in Table 5. The predicted value of the optimum formula describes a good antacid FDT profile with a disintegration time of 2 minutes 15 seconds and an acid neutralization capacity value of 9.19 mEq.

To determine the validity of the theoretical optimum formula for SLD optimization results in the Design Expert 7.1.5 program, FDT antacid tablets were prepared according to the formula in Table 5. The statistical analysis results of the optimization parameters with the Openstat 12 program at a 95% confidence level (table 6) show that the value of the theoretical optimization parameters (tablet disintegration time and acid neutralization capacity) resulting from the model were not significantly different from the experimental results. This means that the optimum formula produced is by the predictions determined by the SLD optimization model in the Design Expert 7.1.5 program.

CONCLUSION

The increase in Avicel PH 101 in combination with SSG as a disintegrating agent has been shown to decrease disintegration time and increase the neutralization capacity of FDT antacids. The optimum formula for FDT antacids based on the SLD method is a combination of 38 mg SSG and 101 mg Avicel PH 101 with a desirability of 0.523.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article.

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Table 6. Verification parameters optimized formula of FDT antacids

Parameters	Prediction	Experiment	$t_{calculated}$*	t_{table}	Conclusion**
Disintegration time (minute)	1.95	1.25	0.142	4.475	Unsignificantly different
Acid neutralization capacity (mEq)	9.19	9.70	0.570	4.475	Unsignificantly different

Note: *data processed by open stat 12, **based on the level of 95%

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