OPTIMIZATION OF SODIUM CROSCARMELLOSE AND SODIUM STARCH GLYCOLATE IN ORALLY DISINTEGRATING TABLETS (ODT) ACETOSAL

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Abstract

Acetosal is a drug that is included in the NSAID class which has anticoagulant properties. Acetosal has low bioavailability due to first-pass effect metabolism, so it is formulated in ODT form to increase the bioavailability of acetosal. This research aims to determine the effect of croscarmellose sodium and sodium starch glycolate concentrations as superdisintegrants on the physical characteristics of acetosal ODT and to determine the concentrations of croscarmellose sodium and sodium starch glycolate as superdisintegrants that produce acetosal ODT with optimum physical characteristics. The ratio formula for CCS and SSG obtained from design expert 10.0.1 using the simplex lattice design method, namely FI (0:6); FII (3:3); FIII (6:0); FIV (4.5:1.5); FV (6:0); FVI (0:6); FVII (3:3); FVIII (1.5:4.5). Based on the research results, the optimum ODT formula for acetosal was obtained with a concentration of CCS 1.232% and SSG glycolate of 4.768%. The optimum formula test results obtained a flow rate of 19.706 grams/second, MC 2.574%, compressibility 24.00%, hardness 3.70 kg, friability 0.668%, disintegration time 40.574 seconds, wetting time 46.002 seconds, and dissolution 95.142%. Based on the t-test between theoretical and experimental results, the results show that the results are not significantly different ($p>0.05$) so they are said to be valid.

Keyword : Orally Disintegrating Tablet (ODT), acetosal, croscarmellose sodium, sodium starch glycolate, Simplex Lattice Design (SLD).

1. INTRODUCTION

Acetosal is one of the drugs from the Non-Steroidal Anti-Inflammatory (AINS) group that has an anticoagulant effect (BNF, 2017; Sweetman, 2009). Acetosal bypasses metabolism first pass effect and hydrolysis into salicylate in the intestinal wall of has low bioavailability (Tjay and Rahardja, 2015). Acetosal in conventional tablet preparations induces an irritating effect in the stomach, while acetosal in enteric coated tablet form causes decreased absorption (AHFS, 2002). To overcome this, acetosal can be made in preparations Orally Disintegrating Tablet (ODT). Orally Disintegrating Tablet (ODT) is a solid preparation containing active compounds, which disintegrate rapidly when in contact with saliva on the tongue (Allen et.al., 2011). The acetosal ODT dosage form can reduce the number of drugs that undergo first-pass effect Because some of the drugs are absorbed in the pregastic area when saliva descends into the gastric area, so that it can increase the bioavailability and therapeutic effects of acetosal (Alğin Yapar, 2014).

The components that most affect the time of ODT destruction are superdisintegrant or crushing materials (Bhowmik DK., 2010). Superdisintegrant not only accelerates the destruction of tablets, but has an influence on the solubility of active substances so that it can increase the bioavailability of a preparation (Zarmpi et.al., 2020). Examples of superdisintegrant (Nurdianti et.al, 2018) which is commonly used in ODT preparations, namely croscarmellose sodium and sodium starch glycolate (Kumar and Devi, 2022). Croscarmellose sodium has a dual mechanism, namely water absorption (water wicking) and rapid swelling (rapid welling) (Dalimbe et.al, 2021), but has a smaller development power than SSG, which is 4-8 times the original volume (Rowe et al., 2009). Sodium starch gycolate have the ability swelling or inflate 200-300 times in water (Bhusnure et.al., 2015), but SSG at high concentrations will cause Gelling so that the ability to disintegrate will be reduced because it can inhibit water penetration (Siregar and Wikarsa, 2010). The combination of high water absorption strength of croscarmellose sodium and swelling of sodium starch glycolate will result in a time of destruction that relative Shorter (Rachmawati et.al, 2015).

Optimization was carried out to determine the right composition by using a comparison of croscarmellose sodium and sodium starch glycolate as a superdisintegrant to produce acetosal ODT with optimal physical characteristics.

2. RESEARCH METHODS

The object of this study is the physical characteristics of a mixture of powder and the physical characteristics of acetosal ODT preparations using croscarmellose sodium and sodium starch glycolate as superdisintegrants.

The independent variable in the study was a comparison of the concentration of 0 – 6 % croscarmellose sodium and sodium starch glycolate at a concentration of 0 – 6 % as a superdisintegrant in atopic ODT. The tests carried out include testing the physical characteristics of the powder mixture, namely moisture test, compressibility test, flow speed test, and stationary angle. The characteristics of ODT include, hardness, fragility, disintegration time, *wetting time*, uniformity of content and profile of solution.

The tools used are glass tools, mortars, tampers, analytical balances, single punch tablet printing machines, moisture analyzers, flow velocity test equipment, hardness tester, friability tester, disintegration tester, dissolution tester type 2 paddle, petri dish (pyrex), stopwatch, UV-VIS spectrophotometer (UV-1800 Shimadzu). The materials used are Acetosal, croscarmellose sodium, sodium starch glycolate, mannitol, aspartame, talcum, magnesium stearate, avicel PH 102, methanol pro analysis, sodium acetate trihydrate and glacial acetic acid.

Acetosal ODT is made using the direct print method. The acetosal ODT optimization design is shown in table 1. Asetosal, croscarmellose sodium, sodium starch glycolate, mannitol, aspartame, avicel PH 102, talcum and mg stearate are mixed until homogeneous. The powder mixture is tested for flow velocity, stationary angle, compressibility and moisture. The mixture was printed with a weight of approximately 250 mg. ODT preparations are tested for hardness, brittleness, crushing time, wetting time, solution, and uniformity of content (Nurdianti et.al., 2018).

Table 1. Acetosal ODT Optimization Design Based on *Design Expert* 10.0.1

Material	**FI**	**FII**	**FIII**	**FIV**	**FV**	**FVI**	**FVII**	**FVIII**
Acetosal (mg)	80	80	80	80	80	80	80	80
Sodium Croscarmellose (% b/b)	**0**	**3**	**6**	**4,5**	**6**	**0**	**3**	**1,5**
Sodium starch Glycolate (% b/b)	**6**	**3**	**0**	**1,5**	**0**	**6**	**3**	**4,5**
Manitol (%b/b)	20	20	20	20	20	20	20	20
Aspartam (% b/b)	1,5	1,5	1,5	1,5	1,5	1,5	1,5	1,5
Talc (% b/b)	2	2	2	2	2	2	2	2
Mg Stearat (% b/b)	1	1	1	1	1	1	1	1
Avicel PH l02 add (mg)	250	250	250	250	250	250	250	250

Remarks: the weight of each tablet of 250 mg is made as many as 250 tablets

The optimal formula is obtained from several parameters, namely flow speed, moisture content, compressibility, hardness, brittleness, crushing time, wetting time, and resolved. The optimal formula is obtained based on the program design expert, then a test is carried out one sample t-test to find out the difference between theoretical results and practical results using IBM SPSS Statistics 23.

3. RESULTS AND DISCUSSION

The results of testing the physical characteristics of the acetosal powder mixture and acetosal ODT can be seen in table 2. The equation of *simplex lattice design* mixed powder and acetosal ODT can be seen in table 3.

Table 2. Physical Characteristics Test of Acetosal Powder and ODT Mixture

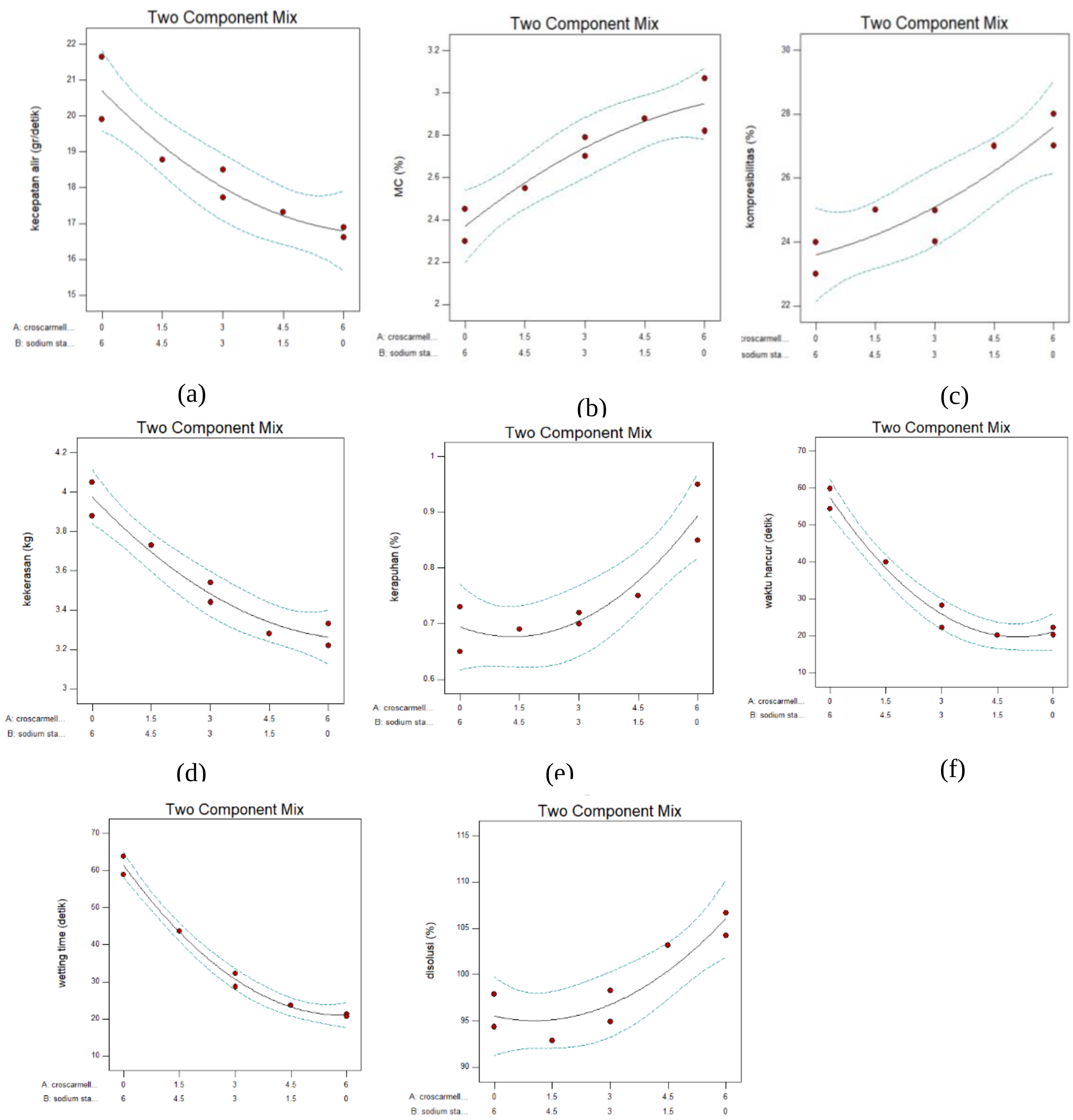
Testing	Formula							
	FI	**FII**	**FIII**	**FIV**	**FV**	**FVI**	**FVII**	**FVII**
Flow rate (grams/sec)	19,91	17,73	16,62	17,31	16,89	21,64	18,49	18,78
Moisture Content (%)	2,30	2,70	3,07	2,88	2,82	2,45	2,79	2,55
Compressibility (%)	23,00	24,99	27,01	27,00	28,00	24,00	24,01	25,01
Hardness (kg)	4,05	3,54	3,22	3,28	3,33	3,88	3,44	3,73
Friability (%)	0,73	20,72	0,95	0,75	0,85	0,65	0,70	0,69
Crushing time (seconds)	59,86	28,32	0,27	20,18	22,18	54,34	22,18	39,98
Wetting time (seconds)	63,80	28,66	20,62	23,66	21,34	58,88	32,16	43,66
Content Uniformity (%)	101,13	102,95	103,40	101,94	102,95	100,36	101,50	104,42
NP	2,74	6,92	4,18	4,33	4,98	4,30	7,80	6,59
Dissolution Q_{20} (%)	94,34	98,27	104,21	103,13	106,63	97,86	94,89	92,84

Table 3. Equation of *Simplex Lattice Design* Mixture of Acetosal Powder and ODT

Testing	Simplex Lattice Design *Equations*
Flow rate (grams/sec)	Y = 2,79951 (A) + 3,44951 (B) – 0,082745 (A)(B)
Moisture content (%)	Y = 0,49155 (A) + 0,3948 (B) + 9,06318 x (A)(B)10^{-3}
Compressibility (%)	Y = 4,60033 (A) + 3,93330 (B) – 0,056732 (A) (B)
Hardness (kg)	Y = 0,54366 (A) + 0,66255 (B) – 0,015207 (A) (B)
Friability (%)	Y = 0,14902(A) + 0,11569 (B) – 9,93464 x (A) (B)10^{-3}
Crushing time (seconds)	Y = 3,52068 (A) + 9,556883 (B) – 1,48693 (A) (B)
Wetting time (seconds)	Y = 3,50735 (A) + 10,22735 (B) – 1,16993 (A) (B)
Dissolution Q20 (%)	Y = 17,67897(A) +15,91711 (B) – 0,44876(A) (B)

Information:
Y : response
A : Sodium Croscarmellose (CCS)

In flow speed testing, SSG components have a dominant effect in increasing flow speed because they have the property of free flowing, so that it has a good flow speed (Rowe e.al., 2009). The interaction of CCS and SSG has a small effect on decreasing the flow rate. The moisture content is inversely proportional to the flow rate, the higher the moisture content produced, the worse the flow speed. This can be seen from the CCS component which is more dominant in increasing the moisture content of the powder mixture and can be seen in figures 1 (a) and (b) which show the graph between the flow velocity and the moisture content have opposite directions. The increase in moisture content is affected because CCS has hygroscopic properties so that it can absorb water from the air (Anbrasson Duck., 2018).



B : Sodium Starch Glycolate (SSG)

Figure 1. Graph of the Effect of Superdisintegrant Addition

(a) Flow rate, (b) Moisture Content, (c) Compressibility, (d) Hardness, (e) Friability, (f) Crushing Time, (g) Wetting Time, (h) Dissolution

Based on the equation in table 3, it shows that CCS has a more dominant influence in increasing the compressibility of the powder mixture. The hygroscopic nature of CCS can increase the moisture content of the powder thereby increasing the percent compressibility value which means that the compressibility of the powder is getting worse (Irawan et.al., 2022). The mixture of CCS and SSG components can lower the compressibility value of the powder mixture.

In the hardness test, SSG components have a dominant effect in increasing the hardness of tablets. This is because SSG is a starch derivative, so it can bind tablet particles and can increase the hardness of the tablet (Bala et.al., 2012). The tablet brittleness test is inversely proportional to the hardness value of the tablet. The smaller the hardness value of the tablet, the higher the percentage of fragility obtained. This is evidenced by CCS which has a dominant influence in increasing the percentage of tablet fragility because CCS has hygroscopic properties.

Based on the equation in table 3, it is shown that the addition of CCS (+3.52068) separately can accelerate the tablet destruction time. The value of the coefficient obtained by SSG is (+9.56883) which indicates that the ODT destruction time will be longer with the use of SSG compared to CCS. The high water absorption ability of CCS is more influential in destroying the formation of the tablet (Dalimbe et.al., 2021). High concentrations of SSG can form a gel so that it takes longer to destroy (Berlian and Subarnas, 2018).

The dismemberment time capability of tablets has a linear relationship with testing *wetting time*. This is evidenced by the dominant CCS component in accelerating *wetting time* tablet and also seen in Figure 1 (f) and (g) which shows the time of destruction and *wetting time* have the same graph shape so that it shows that the two tests have a linear relationship or are the same. CCS has a dual mechanism i.e. *Wicking* and *swelling* while SSG only has a mechanism *swelling* (Bhowmik et al., 2010; Shihora and Panda, 2011). In addition, the higher the concentration of SSG, the thicker the gel layer formed so that it can inhibit the penetration of water into the tablet (Bala et al., 2012)

The dialysis test showed that the CCS component was more dominant in increasing the percentage of aesthetic ODT dissolution. CCS has a water absorption action (*wicking*) and also development (*swelling*), water enters the tablet and expands rapidly then causes the tablet to collapse so that the amount of dissolved active substance is large (Desai et al., 2016).

In all responses, each test showed a significance value of ANOVA <0.05 which showed that the difference in CCS concentration at 0 – 6 % and SSG at concentration at 0 – 6 % had a significant influence on each test response. In addition, all test parameters had a p-value at lack of fit of (p>0.05) indicating that the results of the replication test of each formula were not significantly different.

Based on the results of the study, the results were obtained that the optimum formula for acetosal ODT was obtained with a concentration of croscarmellose sodium of 1.232% and sodium starch glycolate of 4.768%. The results of the optimum formula test obtained a flow rate of 19.706 grams/second, mouiture content 2.574%, compressibility 24.00%, hardness 3.70 kg, friability 0.668%, crushing time 40.574 seconds, wetting time 46.002 seconds, and dissolution profile 95.142%. The results of testing this optimal formula are then validated with the T-test. The results of the T-test show that from all the tests on the optimization parameters, the results are not significantly different, it is known from the significance value which > 0.05 so that it can be concluded that the equation of the experimental results with the theory can be concluded to be valid (Table 4).

Table 4. Significant Sample T-test between Theoretical and Practical Results

Parameters	Theoretical results	Practical results	Significance	Conclusion
Flow rate (g/sec)	19,411	19,706	0,660	Not sig
Mouisture Content (%)	2,542	2,574	0,400	Not sig
Hardness (kg)	3,740	3,7680	0,671	Not sig
Friability (%)	0,677	0,668	0,572	Not sig
Crushing time (sec)	41,233	40,574	0,549	Not sig
Wetting time (sec)	46,218	47,002	0,645	Not sig
Disolusi (%)	95,037	95,142	0,838	Not sig

4. CONCLUSIONS

Based on the results of the study, croscarmellose sodium is able to improve MC, compressibility, brittleness, and dissolution profile as well as be able to reduce the flow velocity of hardness, crushing time, and wetting time. The sodium starch glycolate has the opposite effect, namely increasing flow speed, hardness, crushing time, and wetting time and being able to reduce MC, compressibility, brittleness, and dissolution. The interaction between croscarmellose sodium and sodium starch glycolate increases MC, decreasing flow velocity, compressibility, hardness, brittleness, crushing time, wetting time and dissolving. Comparison of croscarmellose sodium and sodium starch glycolate concentrations with levels of 1.232 % and 4.768 % can produce acetosal ODT preparations with optimal physical characteristics.

Suggestions that can be made in this study are that further research is needed on the acetosal ODT stability test and pharmacological tests on acetosal ODT preparations to determine the efficacy of the preparations produced.

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