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Abstract. Ketoprofen has low solubility in water with unpleasant taste. Efforts to improve solubility and taste are by forming inclusion complexes using β-cyclodextrin. In its development to release Ketoprofen quickly, fast disintegrating tablets (FDT) were prepared. The speed of drug release is influenced by the speed of disintegration tablets. The combination of sodium starch glycolate (SSG) and crospovidone (CP) combines swelling and wicking action which speeds up the disintegration of tablets. This study aims to obtain the optimum value of the combination of both in order to obtain FDT with optimum evaluation parameters according to the requirements. The study made 8 run FDT directly with variations in the concentration of SSG 2–8% and CP 2-5%. Evaluations carried out at each run included flow velocity tests, uniformity of preparation, hardness, friability, disintegration time, wetting time and dissolution. Data were analyzed using simplex lattice design method. The optimum formula predicted results are verified by analysis of one sample t-test. The results showed increasing the proportion of SSG increases hardness, disintegration time and wetting time and decreases fragility of FDT. The optimum formula found at combination of 2% SSG and 5% CP with optimum physical properties and percent release and sweet taste.

1. Introduction

Ketoprofen is an NSAID drug that has deficiencies in the development of solid dosage forms because of its bitter taste [1]. There are several ways that can be done to prevent direct contact between drugs that have an unpleasant taste with a sensory sensor in the oral cavity, one of which is the method of complexation with β-cyclodextrin.

The mechanism of developing complex techniques of inclusion with β-cyclodextrin can be done using kneading method. The kneading method is the most common and simple method of forming complexes with relatively inexpensive costs in the production process. Kneading is a mixture of cyclodextrin with a little water or a hydro alcohol solution so that it forms a paste, then the medicine is added slowly, pressed and kneaded for the specified time. The mixture is then dried and sifted [2]. In previous study, the mechanism for the formation of Ketoprofen-β-cyclodextrin inclusion complexes is considered more efficient because of the large number of complex formation results [3].

The development of Ketoprofen dosage forms with the aim of providing rapid action and increasing comfort and compliance in use is by formulating Ketoprofen in the form of Fast Disintegrating Tablets (FDT). FDT is a tablet that can disintegrate in a fast time of less than or equal to 30 seconds when placed on the tongue. Making FDT with the addition of superdisintegrant can facilitate the rapid destruction of the tablet matrix or in other words capable of causing tablet disintegration and release in saliva as soon as the tablet is placed on the tongue. Superdisintegrants used in this study were sodium starch glycolate (SSG) and crospovidone (CP).

The mechanism of SSG disintegration is the absorption of water followed by a rapid development process in large numbers, but SSG facilitates the formation of a gel layer on the surface of the tablet when dissolved so that water penetration into the tablet is blocked [4]. Based on these conditions, it is necessary to do a combination with CP which has a mechanism of porosity-capillarity action. CP particles will deform during the compression process, but when in contact with water, these particles will quickly return to normal shape and then swell, giving a hydrostatic pressure that causes the tablet to break without forming a gel on the surface of the tablet [5]. Based on the mechanism of the two superdisintegrants, the combination of both is expected to increase the speed of disintegration of tablets so as to produce tablets with better physical properties and percent release of active substances compared to tablets using one type of superdisintegrant.

Therefore, this study was conducted to obtain optimum formulas from several FDT preparation formulations resulting from the Ketoprofen-β-cyclodextrin inclusion complex with variations in the concentration of superdisintegrant sodium starch glycolate-crospovidone so that it is expected to obtain preparations with physical properties and the optimum percent release of active substances and flavors a lot of fun.

2. Method

The tools used in this study were: UV-Vis spectrophotometer; mixer; single punch tablet printing machine; oven; friability tester, hardness tester; flowmeter; in vitro dissolution test equipment; pH meter; analytical scales; stop watch; and a number of glassware. The materials used in this study were Ketoprofen, β-cyclodextrin, ethanol, eosin, HCl buffer pH 1.2, distilled water, SSG, CP, mannitol, avicel PH 102, aspartame, PEG 6000, stearic acid. All ingredients used are pharmaceutical grade.

2.1. Formation of Ketoprofen-β-cyclodextrin Inclusion Complex with Kneading Method

Inclusion complex was made with a 1: 2 molar ratio between β-cyclodextrin (223.16 g) with a mixture of 96% ethanol : water (1:1) as much as 140 ml, then added 25 g of Ketoprofen and kneading for 1 hour. The kneading mass was then roasted at a temperature of 50 ° C to a constant weight, then sifted with a sifter no. 30.

2.2. Ketoprofen Powder and Ketoprofen- β-cyclodextrin Inclusion Complex Flavor Response Test

Performed on healthy volunteers (n = 20) who have a normal sense of taste. Taste parameters consist of, 1 = very bitter, 2 = bitter, 3 = sweet, 4 = very sweet.

2.3. Preparation of Ketoprofen - β-cyclodextrin Inclusion Complex Fast Disintegrating Tablets

The formula design by SLD method used 2 factors, namely SSG (A) with an upper limit of 8% and a lower limit of 2%, while CP (B) with an upper limit of 5% and a lower limit of 2% were presented in Table 1.

Table 1 Formula Design by Simplex Lattice Design Method

Composition		Run							
		1	2	3	4	5	6	7	8
Design	A	50	0	75	100	0	50	100	25
(%)	B	50	100	25	0	100	50	0	75
Actual (%)	A	5.0	2.0	6.5	8.0	2.0	5.0	8.0	3.5
	B	3.5	5.0	2.75	2.0	5.0	3.5	2.0	4.25

2.4. Tablets Evaluation

The evaluation of tablets includes uniformity of weight, uniformity of drug content, hardness, friability, in vitro disintegration time and wetting time.

2.5. In vitro Dissolution Study

Dissolution test was carried out using a basket method with HCl buffer dissolution media pH 1.2 as much as 900 mL at 37 ± 0.5 °C. The tool run at 50 rpm (Mura et al., 2005). The test was carried out for 20 minutes and the samples were taken at minute 1, 3, 5, 10, 15 and 20. The samples that had been taken were filtered and their absorption was measured with a UV-Vis spectrophotometer at the maximum wavelength of Ketoprofen [8].

2.6. Determination of the Optimum Formula

The evaluation parameters of tablet data which is the variable to get the optimum point, namely hardness, friability,in vitro disintegration time, wetting time, Q_1 (drug release in the first minute) and DE_{20} (complete drug release for 20 minutes).

2.7. Verify Predictive Formula

Verification was done by comparing the value of the FDT evaluation response between the predicted FDT and the optimum formula FDT produced by one sample t-test analysis.

2.8. Hedonic Test

Sensitivity evaluation was carried out on healthy volunteers (n = 20) who had a normal sense of taste.

3. Result and Discussion

3.1. Tablets Evaluation Results

Results of the physical evaluation of the FDT inclusion complex of Ketoprofen-β-cyclodextrin are presented in Table 2.

Table 2 Evaluation of Ketoprofen-β-Cyclodextrin inclusion complex FDT

Runs	Evaluation Parameters (mean ± SD)					
	Uniformity of Weight (Acceptance Value)	Uniformity of Drug Content (Acceptance Value)	Hardness (kg/cm^2)	Friablity (%)	In Vitro Disintegration Time (seconds)	Wetting Time (seconds)
Run 1	1.63	12.45	3.48 ±0.35	0.62±0.21	34.15±1.31	70.60±2.61
Run 2	1.23	9.34	3.06±0.09	0.87±0.28	17.20±2.62	44.40±3.99
Run 3	3.48	8.74	3.60±0.11	0.65±0.05	37.63±4.67	87.20±3.90
Run 4	2.37	10.34	3.62±0.21	0.25±0.07	38.72±4.03	93.00±4.47
Run 5	2.80	13.04	3.11±0.07	0.83±0.03	16.95±4.67	44.20±3.19
Run 6	1.52	11.36	3.49±0.11	0.62±0.06	34.88±3.80	70.80±3.77
Run 7	2.33	12.87	3.61±0.23	0.23±0.06	39.28±3.06	92.30±2.59
Run 8	2.08	9.71	3.17±0.26	0.72±0.10	25.40±4.23	61.40±4.51

The results of the evaluation of in vitro dissolution of the Ketoprofen-β-cyclodextrin inclusion complex FDT are presented in Table 3.

Table 3 Evaluation of in vitro dissolution of Ketoprofen-β-Cyclodextrin inclusion complex FDT

Runs	Evaluation Parameters (mean ± SD)	
	Q_1 (%)	DE_{20} (%)
Run 1	19.28±0.71	66.36±1.53
Run 2	21.02±2.25	69.05±1.17
Run 3	15.44±0.85	69.54±1.00
Run 4	14.09±3.98	61.15±0.62
Run 5	21.58±1.57	70.83±1.62
Run 6	20.00±1.58	69.79±0.61
Run 7	16.13±0.51	63.60±0.67
Run 8	21.98±0.97	59.81±0.65

The results of the FDT evaluation of the Ketoprofen-β-cyclodextrin inclusion complex were then analyzed using Design Expert® version 7 software and provided the SLD equation as shown in table 4.

The mixture of each component has a positive influence on the violence and fragility of FDT. SSG has a slightly greater effect in increasing violence. The interaction of SSG and CP with a greater proportion of SSG increases FDT violence. CP has a porous and hollow structure [10] which reduces the compactness of the tablet when pressed and has an effect on reducing the hardness of the tablet.

CP has a greater effect than SSG in increasing fragility. This is shown in Run 2 and run 5 with a greater proportion of CP giving a higher percentage of fragility compared to other runs that have a greater or comparable proportion of SSG. The interaction of SSG and CP components with the greater proportion of SSG components shows the greatest coefficient (+1.25), which means increasing the fragility of FDT. CP is a superdisintegrant that works with the action of forming porous tablets, this will cause tablets with higher CP concentrations to be more fragile [11].

SSG has a greater coefficient than CP so that it can be said SSG has a greater effect than CP in increasing wetting time and disintegration time. The proportion of SSG and CP has a positive influence in increasing percent of Ketoprofen release, but CP has a greater coefficient (+21.26) than SSG (+15.06), so it can be said that CP has a greater effect compared to SSG in increasing percent release of Ketoprofen. CP gives a smaller effect on increasing wetting time compared to SSG because CP's highly porous and hygroscopic structure facilitates water to enter into the tablet [12].

Increasing the proportion of CP causes more water to be absorbed thus accelerating the time needed for the tablet to be thoroughly wetted and eventually the tablet is destroyed quickly [13]. Tablets with rapid disintegration time will immediately disintegrate into aggregate granules then disaggregation into fine particles will eventually release the active substance quickly.

SSG and CP components have a positive influence in increasing DE20, but CP has a greater coefficient (+69.71) compared to SSG (+62.15). The SSG mechanism that forms a gel layer when in contact with water prevents water penetration into the tablet thereby increasing wetting time and disintegration time, consequently it will inhibit the release of active substances and reduce the amount of Ketoprofen dissolved in dissolution media [14].

Table 4 Response Analysis of Ketoprofen-β-Cyclodextrin Inclusion Complex FDT by SLD

Parameters	Model	The SLD equation	*p –value*
Hardness	Cubic	Y = 3.61(A)+3.08(B)+0.44(A)(B)+0.88(A)(B)(A-B)	0.0006
Friability	Cubic	Y = 0.25(A)+0.86(B)+0.43(A)(B)+1.25(A)(B)(A-B)	0.0011
In Vitro Disintegration Time	Quadratic	Y = 39.03(A)+16.83(B)+23.74(A)(B)	<0.0001
Wetting Time	Quadratic	Y = 93.16(A)+44.45(B)+15.42(A)(B)	<0.0001
Q_1	Cubic	Y = 15.06(A)+21.26(B)+4.87(A)(B)–18.39(A)(B)(A-B)	0.0037
DE_{20}	Cubic	Y = 62.15(A)+69.71(B)+3.09(A)(B)+72.07(A)(B)(A-B)	0.0494

3.2. Results of Determination of Optimum Formula

The grading and weighting for each response can be seen in Table 5.

Table 5 Grading Value and Weight on Response

The Response	Goal	Lower	Upper	Importance
Hardness	In range	3 kg	4 kg	+++
Friability	Minimize	0.2 %	1 %	+++
In Vitro Disintegration	Minimize	10 detik	60 detik	+++++
Wetting Time	Minimize	30 detik	90 detik	+++++
Q_1	Maximize	14.09 %	21.98 %	+++++
DE_{20}	Maximize	59.81 %	70.83%	+++++

Software Design Expert version 7 then presents the formula with the highest desirability, which is the optimum formula that can provide the best evaluation parameter values. The proportion of SSG and CP in the optimum formula is 2%: 5% of the weight of tablets with desirability of 0.698.

3.3. Optimum Formula Verification Results

The optimum formula of Design Expert version 7 prediction that has been made was then evaluated to find out whether the tablets made can meet the quality and meet the requirements. Evaluation of tablets tested was the response of evaluation tablets used to determine the optimum formula, namely hardness, friability, in vitro disintegration time, wetting time, Q_1 and DE_{20}. The optimum formula evaluation results can be seen in table 6. Based on the results obtained, the values of the six parameters meet the specified conditions.

Comparison of the response value of the evaluation results of the optimum prediction formula and the optimum formula of the experiment can be seen in table 6. The results of the comparison of the response values show a significance value> 0.005 which means that the six different parameters are not significant, so it can be concluded that the equation is verified.

Table 6. Comparison of response value evaluation results of optimum prediction formula and optimum formula experiment

Evaluation parameters	Prediction results	Experimental results	Sig. (2-*tailed*)
Hardness	3.08 kg/cm2	3.17 kg/cm2	0.394
Friability	0.86 %	0.80 %	0.065
In vitro disintegration	16.83 detik	17.80 detik	0.633
Wetting time	44.44 detik	43.56 detik	0.223
DE_{20}	69.71%	69.21 %	0.353

3.4. Response Evaluation Results

As many as 20 respondents stated that the Ketoprofen-β-cyclodextrin inclusion complex was made to have a sweet taste. This shows that the method of forming the Ketoprofen-β-cyclodextrin complex with a molar ratio of 1:2 used has been able to improve the taste of Ketoprofen perfectly. The ability of cyclodextrins to trap the hydrophobic portion of Ketoprofen can prevent the interaction between Ketoprofen and taste sensors [9], resulting in the bitter taste of Ketoprofen being covered with complex formation.

4. Conclusion

The combination of sodium starch glycolate-crospovidone affects the physical properties of the FDT inclusion complex of Ketoprofen-β-cyclodextrin. Increasing the proportion of sodium starch glycolate increases hardness, decreases friability, prolongs disintegration time in vitro and prolongs the wetting time of the Ketoprofen-β-cyclodextrin inclusion complex. An increase in the proportion of crospovidone

applies vice versa. The concentration of SSG 2% and CP 5% can produce Ketoprofen-β-cyclodextrin inclusion complex FDT with optimum physical properties and percent release and sweet taste.

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