OPTIMIZING OF CHITOSAN CONCENTRATION AS MATRIX POLYMERS ON RANITIDINE HYDROCHLORIDE FLOATING TABLET DISSOLUTION

OPTIMASI KONSENTRASI KITOSAN SEBAGAI MATRIKS POLIMER PADA DISOLUSI TABLET *FLOATING* RANITIDIN HIDROKLORIDA

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ABSTRACT

Floating is a drug delivery system using polymer as matrix to control drug release. Chitosan has function as matrix polymer. This research aims at finding the optimum concentrations of chitosan on ranitidine HCl tablet. The granules was made into 6 formulas with different concentrations of chitosan (16.00%, 16.50%, 17.00%, 17.50%, 18.00%, 18.50%). The granules had been molded into a tablet and then evaluated. The dissolution test results from formula 4 and formula 5 are 120.19% and 99.45%. The statistical analysis of one-way ANOVA with 95% confidence level showed that there was no significant difference between the formulas 4 and 5. The conclussion that the optimization of the chitosan concentration as polymer matrix can increase the drug release of ranitidine HCl floating tablet.

Key words: *Chitosan, Floating Tablet, Polymer Matrix, Ranitidine HCl*

ABSTRAK

Sistem penghantaran obat secara *floating* adalah suatu cara yang dapat memperlama waktu kerja obat di dalam lambung. Dalam sistem *floating*, polimer digunakan untuk membentuk matriks yang memiliki kemampuan untuk mempertahankan pelepasan obat. Kitosan mempunyai fungsi sebagai matriks polimer karena dapat meningkatkan pelepasan tablet *floating* ranitidin HCl. Pada penelitian ini, kitosan diaplikasikan menjadi sediaan tablet *floating* yang bertujuan untuk mencari konsentrasi optimum kitosan pada tablet ranitidin HCl. Granul dibuat menjadi 6 formula dengan konsentrasi kitosan yang berbeda (16,00%, 16,50%, 17,00%, 17,50%, 18,00%, 18,50%). Tablet kemudian dievaluasi yaitu uji organoleptik, keseragaman bobot, keseragaman ukuran, kekerasan, kerapuhan, *swelling*, *floating*, menentukan panjang gelombang, membuat kurva kalibrasi, dan uji disolusi. Hasil uji disolusi yang diperoleh dari formula 4 dan formula 5 pada menit ke 480 yaitu 120,19% dan 99,45%. Dari analisa statistik ANAVA satu arah dengan taraf kepercayaan 95% menunjukkan bahwa tidak ada perbedaan bermakna antara formula 4 dan 5. Disimpulkan bahwa optimasi konsentrasi kitosan sebagai matriks polimer dapat meningkatkan pelepasan tablet ranitidin HCl.

Kata kunci : Kitosan, matriks polimer, ranitidin HCl, tablet *floating*

INTRODUCTION

Ranitidine HCl is an H_2-receptor antagonist that inhibits the action of histamine which competitively on H_2 receptor. H_2 receptor antagonists completely inhibit the secretion of gastric acid secretion induced by histamine and gastrin, but partially inhibit the secretion of gastric acid secretion induced by acetylcholine (Pediatri, 2002). Ranitidine HCl is used for gastric ulcer disease. Ranitidine HCl has a half life 2-3 hours, so it can be absorbed quickly and completely in the stomach (Tjay and Rahardja 2007). Ranitidine HCl is one of the drugs potentially to be formulated in floating tablet form. Ranitidine HCl is one of the drugs potentially to be formulated in tablet form floating. Floating tablets have the ability to swell then float and stay in the stomach for some time so that the drug can release slowly (Chawla *et al.* 2003).

Floating system are required to use the polymer to form a matrix that has the ability to maintain the drug release. Chitosan is a biopolymer that can form a gel layer so it can control the release of active substances and have resistance in inhibiting excessive erosion of the floating tablet (Tarirai 2005). This gel layer serves as a barrier in around a matrix that controls drug release from the matrix (Satpathy 2008).

In this research, optimization of chitosan was evaluated in variation concentration (16.00%, 16.50%, 17.00%, 17.50%, 18.00% and 18.50%). Pada penelitian ini dilakukan optimasi kitosan dengan variasi konsentrasi kitosan 16,00%, 16,50%, 17,00%, 17,50%, 18,00% dan 18,50%. Each concentration will be observed how the effect of increasing concentrations of chitosan on ranitidine HCl floating tablet dissolution. Chitosan is expected to provide the properties of slow-release tablet dosage form at ranitidine HCl ideal, which fulfill the physical requirements of tablets and able to maintain a more stable drug release for a certain time.

METHODOLOGY

A. Equipments

Equipments used in this study include the single punch printing machines, hardness tester, friability tester, dissolution tester, UV-Vis spectrophotometer, an analytical balance, weighing bottle, stopwatch, electric oven, beaker glass, stirrer,

measuring cup, volumetric flask, storey sieve, measuring pipette, granule flow tester, mortar, stamper, calipers and glass tools.

B. Materials

Ranitidine hydrochloride (Union Quimico Farmaceutica, S.A), chitosan (Biotech Surindo), Avicel pH 102, sodium bicarbonate, talc, magnesium stearate, HCl 0,1 N, aquadest and alcohol 96%.

C. Procedures

1. Production Method of Ranitidine HCl Floating Tablets

Table 1. Formula of Ranitidine HCl Floating Tablet

Materials	Total Material In Formula (mg)						Function
	F1	F2	F3	F4	F5	F6	
Ranitidine HCl	150	150	150	150	150	150	Active Substance
Chitosan	80	82,5	85	87,5	90	92,5	Matrix Polymers
Sodium Bicarbonate	125	125	125	125	125	125	Source Bases
MCC PH 102	25	25	25	25	25	25	Binder
Magnesium Stearate	5	5	5	5	5	5	Lubricants
Talc ad	500	500	500	500	500	500	Filler

The initial step is to conduct pre-mixing process by mixing ranitidine HCl, matrix polymers (chitosan) and avicel pH 102, and then stir until homogeneous. And then add 96% alcohol until it forms a a mass which can be clenched. Sieved the moist mass using a mesh number 8. Then dried at 50 ° C for 18 hours (Parrot 1971). After drying, the granules sieved again using mesh number 16. The granules which obtained, added the external phase of sodium bicarbonate, magnesium stearate and talc as a base resource, lubricant and filler, then mixed until homogeneous. Then evaluate the granules.

The granules already evaluated then molded into tablets (500 mg) and then tablet be evaluated.

2. The Granule Evaluation of Ranitidine HCl Floating Tablet

The granules evaluation of Ranitidine HCl floating tablet before compressed, include: flow time test, angle of repose test, compressibility test, and particle size distribution test.

3. The Evaluation of Ranitidine HCl Floating Tablet

The evaluation of Ranitidine HCl tablets, include: organoleptic test, size uniformity test, weight uniformity test, hardness test, friability test, swelling test, floating lag time test, the total floating time test, the assay test, and dissolution test.

4. Preparation of Ranitidine HCl Standard Solution

100.0 mg ranitidine HCl was weighed and added to 100.0 ml volumetric flask, then dissolved with 0.1N HCl until the mark boundaries, and we get a standard solution with a concentration of 1000 ug / ml.

5. Determination of Ranitidine HCl Maximum Wavelength

Pipetted from the standard solution as much as 1.0 ml and put 100.0 ml into a flask volumetric, 0.1 N HCl was added until the mark. Then the absorbance was measured using a spectrophotometer at a wavelength of 200-400 nm. It will get a maximum wavelength of Ranitidine HCl.

6. Preparation of Calibration Curve Ranitidine HCl

Made concentration series from standard solution (4, 6, 8, 10, and 12 ug / ml). Pipetted a standard solution put into a volumetric flask and then added a 100.0 ml solution of HCl 0.1 N to the mark. After that read the absorbance with using a spectrophotometer at a maximum wavelength of 227.60 nm, then made the plot between the concentration of Ranitidine HCl and absorption, it will obtain a regression line linear equation

RESULT AND DISCUSSION

1. The evaluation result of Ranitidine HCL

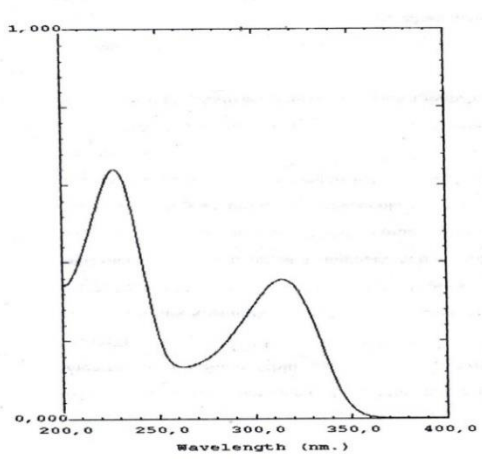
The evaluation result of Ranitidine HCL consisting of the examination of form, colour dan taste.

Table 2. The evaluation result of Ranitidine HCL

Evaluation	Result
a. Ranitidine HCl	
1) Organoleptic	Crystalline powder white to pale yellow, practically odorless
2) Absorbance of UV Spectrum	227,60 nm (HCl 0,1 N)

2. Maximum Wavelength of Ranitidine HCl

The maximum wavelength of ranitidine HCl determined at 200-400 nm using a Spectrophotometer Visibel. Determination of the maximum wavelength aimed to know the absorption can reach the maximum, thus increasing the absorption process of the solution to light. According to the Pharmacopoeia V edition, the maximum wavelength of ranitidine HCl is approximately 229 nm and 314 nm. The results obtained in the media 0.1N HCl solution shows maximum wavelength of 227.6 nm with the absorbance value of 0.6412. It concluded that the substance was ranitidine HCl and has a good quality of raw materials. This wavelength is used to create a calibration curve.



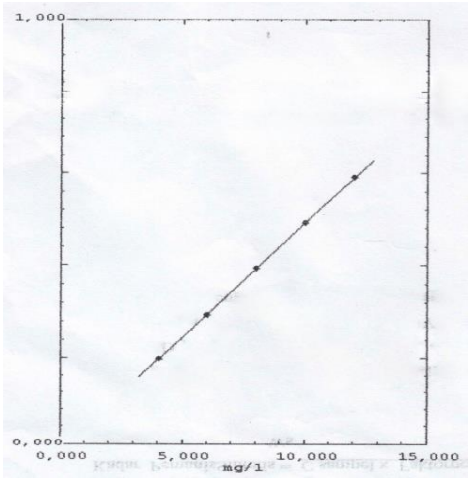
Picture 1. Maximum Wavelenght of Ranitidine HCl

3. Calibration Curve Of Ranitidine HCl

In the evaluation results of calibration curve using the equation A = a.b.c, obtained the minimum concentration (3.74 ppm) and maximum concentration (14.97

ppm). From a calibration curve can be made concentration of 4 ppm, 6 ppm, 8 ppm, 10 ppm and 12 ppm in 0.1 N HCl solution is then measured with a spectrophotometer.

The result has the value of the intercept (a) obtained is $-2x10^{-4}$, while the intercept good value is 0. Regression values obtained is 0.9999. A good regression value is the correlation coefficient has the value 1. Based on the results of the calibration curve can be concluded that the law Lambet-Beer has been fulfilled and ranitidine HCl eligible to continue for assay test.



Picture 2. Calibration Curve of Ranitidine HCl

4. Evaluation of Granules

Table 3. The Result of Granules Evaluation Ranitidine HCl Floating Tablet

Parameter	F1	F2	F3	F4	F5	F6	Requirement
Flow time (sec)	7,72	8,32	8,82	8,91	9,18	9,27	10 g/sec (Siregar dan Saleh 2010)
Angle of repose (°)	33,41	34,21	31,36	34,21	34,21	31,36	25 - 40° (Agoes 2012)
Compressibility (%)	3,99	2,00	4,33	5,00	4,00	4,00	< 20% (Siregar dan Saleh 2010)
Drying shrinkage (%)	2,45	3,76	2,86	2,77	3,28	4,05	3-5% (Voigt (1995)

Flow time test results obtained showed that all formulas have a flow that suitable with the specified requirements at less than 10 seconds (Siregar, 2010). This is possibly due to the formula contains magnesium stearate which serves as a lubricant.

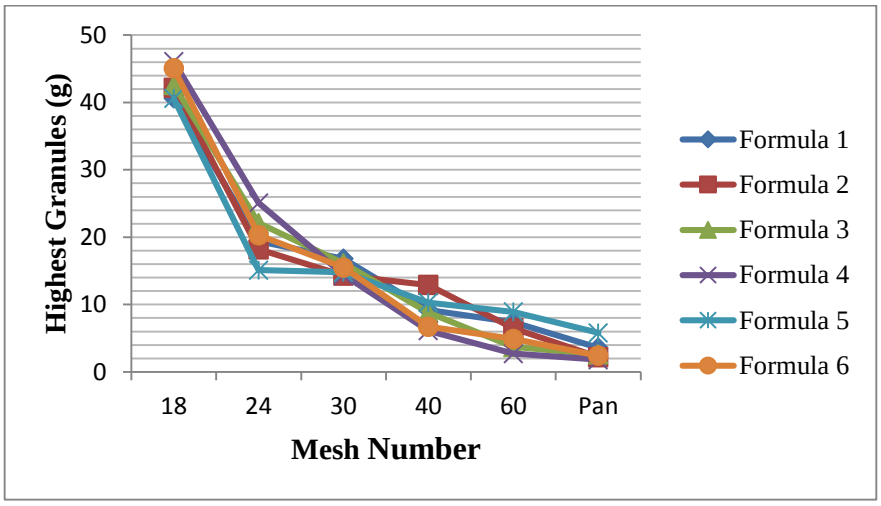
Then test the angle of repose, which showed that the granules entire formula accordance with the requirements is 25-45° (Agoes 2012). The more flat from the resultant corner, which means that the smaller the slope angle and the better the flow

properties of the powder. If a granule has good flow properties will be obtained tablet that has a good weight uniformity.

The test results granule compressibility formula 1 sampa 6 comply with the requirements ie <20% (Agoes 2012). This is influenced because the manufacture of tablets using wet granulation method, thus increasing the overall weight of the type of material and produce a mixture with good flow properties and homogeneous, and the presence of fillers and binders in the composition of the formula. The lower the compressibility obtained the better the flow properties, but if the higher value of its compressibility will make the tablet sink (hard float).

Drying shrinkage test aimed at the preparation using wet granulation method because of water usage or other solvents as binder activators that should be evaluated. Data of formula 1 to 6 shows the drying shrinkage test results are good, because the percentage obtained moisture content below 10%. But in Formula 1, Formula 3 and Formula 4 does not fulfill the requirements set is 3-5% for the water content of the granules (Voigt 1995). This may be due to differences in the length of time the heating granules. The lower the water content can cause the tablet to be easily cracked and split into two parts, while the greater the water content can cause adhesion of granules on a punch.

The result of the particle size distribution of all formula, showing that the granules much spread on the sieve mesh number 18, while the mesh number 24 to 60 has decreased by degrees. In this test the granules with a larger size resulting in large numbers, this is because the characteristics of chitosan that can absorb water, so that the resulting granules have high humidity. The good graphic are graphic representations showing the results of granules spread percentation which restrained in small mesh and large mesh numbers must be balance. The results of the evaluation of particle distribution in the entire formula is not consistent with the theory. The size distribution of granules can be affected by several things, including granulation method, the amount of binder solution, a process of making granules, and equipment (Hadisoewignyo and Fudholi 2013).



Picture 3. Distribution of Particle Size

5. The Result Of Evaluation Tablet

Organoleptic evaluation aims to control the uniformity of tablets appearance, consumer acceptance, and monitor the right making process. Floating tablet which generated from the sixth formula has a pale yellow color, round shaped, bitter tasted, and has a rough surface texture

Tablet weight uniformity test was conducted by examining the weight of 10 tablets. The results of the test weight uniformity tablet from formula 1 to formula 6 are qualifies, because no two tablets that weighs deviates 5% of the tablet weight average and there is no one tablet which has a tablet weight deviation 10% of the tablet average weight (Departemen Kesehatan RI 2014).

Table 4. The Result Of Evaluation Ranitidine HCl Floating Tablet

Parameter	Formula						Requirements
	F1	F2	F3	F4	F5	F6	
Weight uniformity (%)	2,50	1,9	1,9	1,7	2,6	1,8	< 2 tablet that deviates from the 5% and 1 tablet should not be deviated from 10% (Departemen Kesehatan RI 2014)
Hardness	2,76	2,13	2,66	3,67	3,49	3,35	4-8 Kg/cm^2 (Elhassan 2012)
Friability	0,09	0,09	0,29	0,09	0,16	0,23	< 1% (Ben 2008)
Diameter (cm)	1,7927	1,7956	1,7958	1,7953	1,758	1,7949	No less than 1 1/3 and not greater than 3x tablet thickness (Departemen Kesehatan RI 1979)
Thickness (mm)	2,6300	2,5850	2,6230	2,6120	2,5933	2,6060	-
Swelling index (%)	12,96	16,17	24,12	31,56	28,96	25,55	-
Floating lag time (s)	213	206	286	309	333	222	25-600 second (Rosa *et al.* 1994)
Floating time Total (hours)	07.46	07.48	07.30	12.45	08.30	08.05	> 12 hours (Rosa *et al.* 1994)
The assay (%)	95,77	95,98	99,48	103,18	103,60	109,16	90-110 % (Depkes RI 2014)

Hardness test results for 10 tablets in Table 4, it can be concluded that the tablet formula 1 to formula 6 does not fulfill the hardness requirements which already established as a tablet standard is 4-8 kg/cm^2 (Elhassan 2012). This possibility caused by the low compression pressure and material properties which compressed. But the tablet hardness values that are beyond the required range does not indicate that a tablet has a poor quality. Hardness values of tablet less than 4 kg still acceptable on condition of fragility does not exceed the limit (Sulaiman 2007).

Tablet friability test performed on a sample of 10 tablets. The test results showed that fragility tablet of formula 1 to 6 are fulfill the requirements because of its value below 1%. Therefore, it can be concluded that the tablets were tested had a good levels of compactness tablet, because the higher compactness of tablets, resulting the smaller tablet friability (Ben 2008).

Tablet size uniformity test was conducted by measuring the diameter and thickness of the tablet. Data results in table 10 it can be seen that the entire tablet formula fulfill the requirements of the size uniformity which established by the third edition Indonesian Pharmacopoeia, in which the tablet diameter should not be more than 3 times thicker and not less than 4/3 thickness. This occurs because of the amount of granules into the punch or die has the same mass and influenced by the good flow properties of granules.

Swelling time test is the most important parameter in floating tablet dosage. Swelling time test viewed and counted starting at the time of the tablet entry into the medium and then swelling. The increasing concentration of chitosan can make the result of swelling tablet will be greater. But the results of swelling was highest in formulas 4 and 5 as chitosan can slow the formation of CO_2, so the possibility of drug release can be slowed from the other formula (Rosa *et al.* 1994).

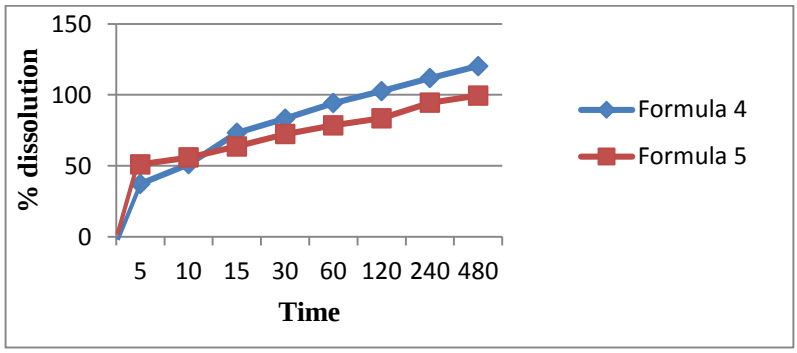
Floating lag time test influenced by the swelling power of the polymers used in the formula. The results of tests known that floating lag time from the sixth tablet formula fulfill the requirements that are in the range 25-600 seconds (0.4 to 6 minutes). This occurs because the CO_2 gas can be formed quickly so the tablet can float in the medium with the time span which fulfill the requirements.

Furthermore, the total time floating test is the time which the ranitidine takes to float in the stomach. Floating tablet caused by the formation of CO_2 as a result of the neutralization reaction between $NaHCO_3$ and HCl 0.1 N. When the tablet into the stomach, the gastric acid fluid will penetrates the pores of the matrix which consisting of gel polymer and react with alkaline of $NaHCO_3$ resulting CO_2. The gas was trapped in the hydrocolloid which formed and can not come out. That makes the tablet density decreases so it can float and last longer in the stomach. The evaluation result of the total floating time which fulfill the requirements only formula 4 (12:45:45) to determine how long the tablet floats in the medium HCl 0,1N (Rosa *et* al. 1994).

In the assay test of ranitidine HCl tablet from all formula, all of the formula fulfill the requirements established by the Indonesian Pharmacopoeia V edition that contains the levels of ranitidine HCl be within the range 90% -110% of the amount

ranitidine HCl listed on the formula. But all of formula does not fulfill the requirements of homogeneity that is the coefficient of variation more than 6%.

The main goal from the development of floating tablet dosage form is improves the bioavailability over an extended residence time in the stomach and extend preparation time by holding the drug release rate. Based on these goals, it can be concluded that the dissolution testing is an important parameter to examining the success from controlled release dosage of floating system. All of formula floating ranitidine HCl tablets, the dissolution test is only performed in the formula 4 and 5, because the results test in the swelling index of formula 4 and 5 that have a percentage of swelling tablet diameter greater than the other. It can be concluded that the larger of swelling potency of the tablet will make the percentage released of active substance in the tablet be increased.



Picture 4. Dissolution Profile of Ranitidine HCl Floating Tablets

Data dissolution of both formulas was obtained that the levels of ranitidine HCl were dissolved at minute 5, 10, 15, 30, 60, 120, 240, and 480 showed increased significantly with the different concentration, so there are differences between each tablet. The explanation of relationship between the concentration levels ratio of the polymeric matrix in the dissolution of ranitidine HCl can showed that chitosan can increase the release of the drug in controlled release dosage form and has resistance in inhibiting excessive erosion of the tablet.

CONCLUSSION

Based on this study, the use of chitosan as a matrix polymer in floating tablet can affect the physical characteristics of the tablet mass, swelling index, floating lag time, and total floating time. The optimum amount of chitosan as a polymer matrix for ranitidine HCl floating tablets based on the results of optimization is 90 mg.

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