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Original Article

OPTIMIZING FORMULATION OF MINI TABLETS FLOATING RANITIDINE HCL USING FULLY PREGELATINIZED STARCH (*MANIHOT ESCULENTA CRANTZ*) WITH SIMPLEX LATTICE DESIGN

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ABSTRACT

Objective: The main objective of this study was to optimize the noneffervescent floating mini tablets (NEFT) formula of ranitidine hydrochloride (ranitidine HCl) using the simplex lattice design (SLD) with parameters, granule flow rate, hardness, friability, floating lag time and ranitidine HCl dissolution test (%).

Methods: The material was prepared using the SLD model was cassava starch fully pregelatinized (CSFP), hydroxypropyl methylcellulose K4M (HPMC K4M), and magnesium stearate. The formula obtained was tested for critical parameters, namely flow rate, hardness, friability, floating lag time and ranitidine HCl dissolution test (%). The dissolution test was carried out by using the USP type II method (paddle method). The beaker is immersed in the water bath of temperature 37 °C. It is filled with 900 ml of 0.1 N HCl, and the apparatus was set at 75 rpm. The samples were taken in the interval of 10 min and estimated content by a spectrophotometer at 312 nm.

Results: The optimum formula based on superimposed graphs of various contour plots with SLD. From the experimental data for all test parameters, the experimental results are approaching with the results of the prediction. The condition for optimum functional components in NEFT was 80 mg for CSFP, HPMC K4M 30 mg, and 10 mg magnesium stearate to obtain a yield of 7.85 kg hardness, 0.34 % friability, 15.27 floating lag time and 91.31 % ranitidine HCl dissolved.

Conclusion: It can be concluded that the optimum formula using the Design-Expert® program the SLD concept is obtained in the range of 70-80 mg CSFP, 30-40 mg HPMC K4M, 0-10 mg magnesium stearate.

Keywords: Cassava starch fully pregelatinized, Noneffervescent, Floating mini tablets, Optimization, Simplex lattice design

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INTRODUCTION

Amylum as an excipient in pharmaceutical formulations is very widely used because it can be mixed with almost all drugs and is inert without causing chemical reactions [1]. Amylum is often used as an excipient, such as binders. Binder functions to power the mass cohesion of powder at press time. Binding materials influence the dissolution rate of the drug [2]. The more strongly bound an active substance is with excipients and will not be able to dissolve in the body, and not achieve the expected bioavailability [3-5].

Amylum is a reserve polysaccharide that is abundant in plants. In general, starch consists of water-soluble components (amylose) as much as 20 % and water-insoluble parts (amylopectin) as much as 80 % [6]. Amylose is a straight molecule, consisting of 250–300 D-glucose units and is uniformly linked by α-1,4-glucoside bonds, which tends to cause the molecule to be shaped like a helix [7-9]. Amylopectin consists of 1,000 or more glucose units, most of which is also associated with α-1.4 bonds. However, there are also a number of α-1.6 bonds found at the branching points [10, 11]. This number of bonds are approximately 4 % of the total number of relationships or one for every 25 glucose units. Amylopectin in water can form colloidal solutions [12, 13]. When the colloidal solution is heated a sticky period occurs, this property is used as a binder. Amylose has the ability to expand when in contact with liquids, this property is used as a destroyer [14-16].

Modification of the physical properties of starch was carried out in a pregelatinized manner. The purpose of this modification is to improve the flow properties and its compatibility so that it can be used as a binder in printed tablets directly and can reduce glidan and antiadherent use [17]. The use of glidan and antiadherent can extend dissolution rates because it can form a film layer [18]. Modification of pregelatinized starch was carried out by giving the treatment in the form of adding the right amount of water and heating at the appropriate temperature. This method produces starch with larger particle size and higher particle density [19]. In pregelatinized starch due to the addition of proper water and heating, a gel formation process causes the starch granules to absorb water and expand to form a thick mass [20].

One of the local plants producing starch that can be modified in this way is cassava amylum. In addition to its relatively cheap price, cassava amylum is relatively easy to obtain, so it is potential to be used as a solid dosage excipient [21]. Amylopectin content is high, which is equal to 83 %, making cassava starch potential to be used as a binder in the manufacture of pharmaceutical preparations [22]. The aim of the study was to optimize the NEFT formula of ranitidine HCl using the CSFP base on SLD design.

MATERIALS AND METHODS

Materials

The study used tubers of cassava (*Manihot esculenta* Crantz) as the basic ingredient to make starch. The cassava was obtained from Banyuning Village in Bali, Indonesia. The botanical identity of the plant and determination already done in the Eka Karya Bali plant conservation center, voucher specimen number B-451. The starch was prepared using fully pregelatinized methods [23], with the addition of distilled water and then heating above the starch gelatinating temperature, ranitidine HCl (Chemo Lugano), HPMC K4M® (Colorcon), magnesium stearate, all ingredients mentioned have pharmaceutical qualities. Sodium chloride, methanol (Merck p. a), distilled water, aquabides, acetonitrile (Merck p. a), and raw material ranitidine HCl (catalog number 66357-59-3 SIGMA).

Instrumentation and software

Tablet machine (Korsh® USA single punch), JASCO FT-IR-4200 type A model, Electromagnetic Sieve Shaker EMS-8, Electrolab Tap density tester EDT-1020, Oakton pH 510 series, oven, Erweka Type TA/TR 120, Erweka Disintegrator tester ZT X20, Electrolab Dissolution tester (USP) TDL-08L, and UV-Vis spectrophotometry (Genesys). DoE was computed and analyzed applying Design-Experts® software 7.1.5 (computer lab Gadjah Mada University).

CSFP preparation

The CSFP was made with a starch: distilled water ratio of 1:1 (w/v). The mixture was then stirred until a homogenous suspension was formed. The suspension was heated with water vapour at a temperature 80 °C in a drum, which was closed for 15 min, until gelatinization occurred. The pregelatinized starch was then dried in an oven at 50 °C or 48 h. Once dried, it was sieved using a 20-mesh sieve [24-26].

Preparation of granules

The wet granulation method of massing and screening was used 150 g batches of formulated mixtures of ranitidine HCl, CSFP, HPMC K4M, and magnesium stearate were mixed [27]. In small batches the ingredients may be mixed in stainless steel bowls or mortars. They were then moistened with polyvinylpyrrolidone K 30 (PVP K-30) binder solution to yield 2 % w/w, PVP in the final dried granulation. The resulting wet masses were granulated by passing them manually through a 10 mesh sieve, dried oven at 50 °C for 7 h, and then re-sieved through a 20 mesh sieve. The dried granules were lubricated by using magnesium stearate [28-30].

Preparation of NEFT

Quantities (150 g) of granules from each batch were compressed into tablets with predetermined loads on single tablet press with a 8 mm die and flat faced punch assembly. A set of tablets was produced from each pressure. After ejection, the tablets were stored in airtight containers to allow for elastic recovery and hardening, prevent falsely low yield values before the tablets were subjected to analysis [31, 32].

Dissolution test

The dissolution test was carried out by using the USP type II method (paddle method). The beaker is immersed in the water bath of temperature 37 °C. It is filled with 900 ml of HCl 0.1 N and the apparatus was set at 75 rpm. The samples were taken in an interval of 10 min and estimate the content by spectrophotometer at 312 nm. The same procedure was repeated at different time intervals and absorbance was noted and the percentage drug release was calculated [33, 34].

Formula design according to SLD

Based on the Design-Expert® version 7.1.5, for the optimization method with SLD, with 3 independent variables (mixture of 3 components) 14 experiments were conducted on various mixed compositions for the three components, there are repetitions of several formulas according to those suggested by the Design-Expert® program [35, 36].

In this study, the variables to be optimized are CSFP (X1), HPMC K4M (X2) and magnesium Stearate (X3). The total mixture of X1+X2+X3 for each formula was 120 mg, with a total weight of 150 mg mini tablets containing 33,48 mg ranitidine HCl. Determination of the minimum and maximum limits for the three components optimized based on the results of the literature study and preliminary research [37, 38].

The SLD was used to optimize the NEFT formula for ranitidine HCl tablets with variations in the levels of CSFP 70-80 mg, and HPMC K4M 30-40 mg, magnesium stearate 0-10 mg. The optimum formula using the Design-Expert® program is based on parameters: granule flow rate, hardness, friability, floating lag time, and ranitidine HCl dissolution test (%) [39].

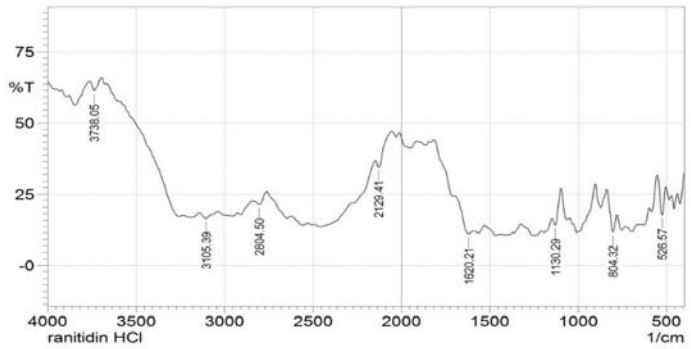

Fig. 1:Fourier transform infrared (FT-IR) spectroscopy analysis of ranitidine HCl

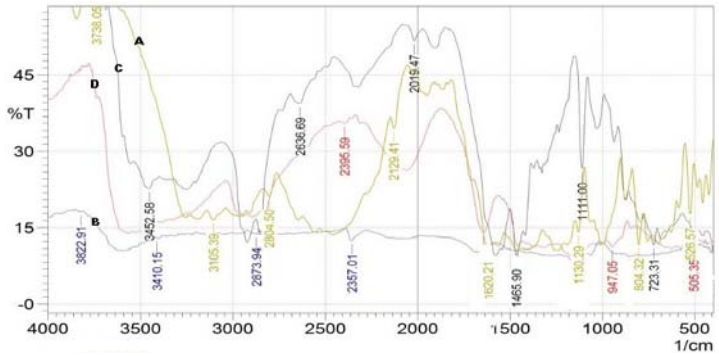

Fig. 2:Overlay ranitidine HCl+CSFP+magnesium stearate+HPMC K4M, Where: A: ranitidine HCl, B: CSFP, C: magnesium stearate, D: HPMC K4M

RESULTS AND DISCUSSION

Interaction study of ranitidine HCl with excipients in formulas

By comparing the spectrum of single ranitidine HCl, a mixture of ranitidine HCl and CSFP and a mixture of ranitidine HCl with components present in the tablet gastroretentive formula (fig. 1 and fig. 2), it can be concluded that there is no chemical interaction (no chemical incompatibility) between components in the formula. The IR spectra showed that there was no chemical interaction that caused the formation of a bond between ranitidine HCl and

excipients in the formula. The presence of a new peak and loss of the original peak, indicates an interaction. [40]. Ranitidin HCl is incompatible with lactose fillers, PVP (polivinil pirolidone) polymers and there is mild interaction with eudragit E100 [41].

Simplex lattice design

The SLD was used to optimize the NEFT formula for ranitidine HCl tablets with variations in the levels of CSFP 70-80 mg, and HPMC K4M 30-40 mg, magnesium stearate 0-10 mg. The optimum formula using the Design-Expert® program (table 1.)

Flow properties

Material flow properties can be illustrated with parameters of flow velocity and angle of repose. The pregelatinized fully produced starch can flow through the funnel with a flow rate for 100 g less than 10 s. At the parameters of flow velocity, CSFP has a flow rate of 6.23 s, while for the parameters of the angle of repose, and has an angle of repose of 32.570. This indicates that the modified material of the starch produced better flow properties.

From the data of the flow velocity test from all runes with the ANOVA test, the p-value value obtained with a 95 % significance level obtained the value of 0.0004 (<0.05). The p-value value with the quadratic model is lower than 0.05, indicating that there are significant differences in flow velocity due to the use of the three optimized ingredients. The lack of fit analysis with the results of the p-value of 0.0806 (>0.05) with a confidence level of 95 %, shows that there is no significant difference between the experimental data and the predicted data from the suggested model (table 2)

Table 1: Proportion of each component according to the SLD

Trial code	Material (mg)/*mini* tablet		
	CSFP	HPMC K4M	Magnesium stearate
1	76.67	36.67	6.67
2	80	40	0
3	78.33	33.33	8.33
4	75	35	10
5	80	35	5
6	80	40	0
7	80	30	10
8	80	30	10
9	70	40	10
10	70	40	10
11	75	40	5
12	78	38.33	3.33
13	75	35	10
14	73.33	38.33	8.33

*Formula using the Design-Expert® program the SLD concept

Table 2: Analysis of variance (ANOVA) of the flow properties

Source	Sum of squares	df	Mean square	F Value	p-value prob>F	
Model	45.08	5	9.02	17.16	0.0004	Significant
Linier mixture	32.1	2	16.05	30.54	0.0002	
AB	0.56	1	0.56	1.06	0.3341	
AC	0.55	1	0.56	1.05	0.3345	
BC	12.28	1	12.28	23.37	0.0013	
Residual	4.2	8	0.53			
Lack of fit	3.47	4	0.87	4.74	0.0806	Not significant
Pure error	0.73	4	0.18			
Cor total	49.29	13				

*The p-value value indicating that there are significant differences in flow velocity due to the use of the three optimized ingredients. The values are mean±standard deviation of n=5.

From the data of the flow velocity ready for the press, the equation according to the SLD is obtained as follows:

Flow rate (g/s) =-0,045 (A)+2,36 (B)+2,71 (C)-0,024 (A) (B)+0,029 (A) (C)–0,14 (B) (C)

Where:

A = starch component fraction CSFP

B = fraction of HPMC K4M components

C = fraction of the Magnesium stearate component

From the equation, it can be seen that the starch matrix component is fully pregelatinized, HPMC K4M and magnesium stearate and component interactions, influence the flow velocity. Individually CSFP has a negative effect, which means it can reduce flow velocity. For HPMC K4M and magnesium stearate individually, it is positive, which means it can increase flow speed. While the optimized two-component interaction of CSFP with HPMC K4M and HPMC K4M with magnesium stearate has a negative effect which means it can reduce flow velocity, while the interaction between CSFP with magnesium stearate has a positive effect which means it can increase flow speed.

Hardness test

For each formulation, the hardness of the tablets was determined individually using a hardness tester. The batch of all batches was found 8.52+0.231 kg.

From the hardness test data from all runes with the ANOVA test, the p-value value obtained with a 95 % significance level obtained a value of 0.002 (<0.05). The p-value value with the quadratic model is lower than 0.05, indicating that there are significant differences in flow velocity due to the use of the three optimized ingredients.

The lack of fit analysis with the results of the p-value 0.0879 (>0.05) with a confidence level of 95 %, shows that there is no significant difference between the experimental data and the predicted data from the suggested model (table 3).

Table 3: Analysis of variance (ANOVA) of the hardness test

Source	Sum of squares	df	Mean square	F value	p-value prob>F	
Model	7.88	5	1.57	11.05	0.002	Significant
Linier mixture	4.36	2	2.18	15.34	0.0018	
AB	2.47	1	2.47	17.4	0.0031	
AC	1.01	1	1.01	7.11	0.0288	
BC	0.025	1	0.025	0.18	0.0058	
Residual	1.14	8	0.14			
Lack of fit	0.93	4	0.23	4.48	0.0879	Not significant
Pure error	0.21	4	0.052			
Cor total	0.99	13				

*The p-value value indicating that there are significant differences in flow velocity due to the use of the three optimized ingredients. The values are mean±standard deviation of n=5.

From the data on tablet hardness, the equation according to the SLD is obtained as follows:

Hardness (g/s) =-0.82(A)-2.28(B)-1.20(C)+0.05(A)(B)+0.04(A)(C)-6,23(B)(C)

Where:

A = starch component fraction fully pregelatinized

B = HPMC K4M component fraction

C = fraction of the Magnesium stearate component

From the equation, it can be seen that the starch matrix component is fully pregelatinized, HPMC K4M and magnesium stearate and component interactions, influence the hardness. Individually the starch is fully pregelatinized, HPMC K4M, and magnesium stearate has a negative effect, which means it can reduce violence. While the optimized two-component interaction, which is CSFP with HPMC K4M and CSFP with magnesium stearate, has a positive effect which means it can increase hardness, while the interaction between HPMC K4M and magnesium stearate has a negative effect which means it can reduce violence. In fig. (fig. 5B), for the red area to get the optimum formula.

Tablet friability

According to the USPNF23, 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min then the tablets were removed from the drum, dedusted, and accurately weighed. The percent weight loss was calculated. The friability test of tablets of entire batches. Depicted that the tablets of entire batches had passed the USP criteria of variability testing (0.5–1 %, w/w). The results revealed that tablets possess good mechanical strength.

From friability testing data from all runes with ANOVA test, p-value obtained with a significance level of 95 % obtained a value of 0.0046 (<0.05). The p-value value with the quadratic model is lower than 0.05, indicating that there are significant differences in probability tests due to the use of the three optimized ingredients.

The lack of fit analysis with the results of the p-value of 0.0786 (>0.05) with a confidence level of 95 %, indicates that there is no significant difference between the experimental data and the predicted data from the suggested model (table 4).

Table 4: Analysis of variance (ANOVA) of the friability test

Source	Sum of squares	df	Mean square	F value	p-value prob>F	
Model	5.261	5	1.05	8.52	0.0046	Significant
Linier mixture	3.52	2	1.76	1.43	0.2947	
AB	1.032	1	1.03	0.84	0.3874	
AC	4.5	1	4.5	36.51	0.0003	
BC	5.864	1	5.86	4.75	0.061	
Residual	9.88	8	1.23			
Lack of fit	8.18	4	2.04	4.81	0.0786	Not significant
Pure error	1.7	4	4.25			
Cor total	6.24	13				

*The p-value value indicating that there are significant differences in probability tests due to the use of the three optimized ingredients. The values are mean±standard deviation of n=5.

From the data friability of the tablet, the equation according to the SLD is obtained as follows:

Friability (%) = 7.87 (A)+1.16 (B)+0.05 (C)-1.05 (A) (B)-8.36 (A) (C)+3,014 (B) (C)

Where:

A = starch component fraction fully pregelatinized

B = HPMC K4M component fraction

C = fraction of the Magnesium stearate component

From the equation, it can be seen that the starch matrix component is fully pregelatinized, HPMC K4M and magnesium stearate and component interactions, have an effect on variability. Individually the starch is fully pregelatinized, HPMC K4M, and magnesium stearate has a positive effect, which means it can improve friability. While the optimized two-component interaction, which is CSFP with HPMC K4M and CSFP with magnesium stearate, has a negative effect which means it can reduce friability, while the interaction between HPMC K4M and magnesium stearate has a positive effect which means it can improve friability.

Floating lag time

Comparison of excipients

The floating tablets were prepared by wet granulation. Each tablet contained ranitidine HCl (33.4 mg), matrix-forming polymers 30 mg (different grades of HPMC) combination with CSFP (80 mg) and magnesium stearate (10 mg). Different grades of HPMC are HPMC K100LV combination with CSFP, HPMC K4M combination with CSFP, HPMC K15M combination with CSFP. The results showed that the HPMC K4M combination with CSFP could provide immediate floatation upon contact with the dissolution medium and were able to continuously float over 24 h (table 5).

Table 5: Floating lag time

Comparison of excipient	Floating lag time (min)+SD
HPMC K4M combination with CSFP	15.304+0.089
HPMC K100LV combination with CSFP	16.402+0.085
HPMC K15M combination with CSFP	23.874+1.706

*HPMC K4M combination with CSFP could provide immediate floatation upon contact with the dissolution medium. The values are mean±standard deviation of n=5.

Floating lag time describes the time needed by the tablet when it starts to be inserted into the test medium until the tablet floats. Floating time parameters are very important for gastroretentive tablet preparations with floating systems. The results of the literature study do not yet have information about what is the best floating lag time for gastroretentive tablets. The results of the study show that gastroretentive tablets have a floating time of 13-32 min.

The results of testing for flotation for up to 24 h of observations, the tablet is still floating. The tablet floats because the starch is fully pregelatinized by the medium and causes the tablet to expand, and the gel is formed by the presence of the HPMC K4M matrix in tablet formulas so as to maintain the integrity of the tablet.

From the floating lag time test data from all runs with the ANOVA test, the p-value value obtained with a 95 % significance level obtained a value of 0.0318 (<0.05). The p-value value with the quadratic model is lower than 0.05, indicating that there are significant differences in flow velocity due to the use of the three optimized ingredients.

The lack of fit analysis with the results of p-value 0.0746 (>0.05) with a confidence level of 95 %, shows that there is no significant difference between the experimental data and the predictive data from the suggested model (table 6).

Table 6: Analysis of variance (ANOVA) of the floating lag time test

Source	Sum of squares	df	Mean square	F value	p-value prob>F	
Model	469.12	5	93.62	4.4	0.0318	Significant
Linier mixture	215.4	2	107.7	5.05	0.0381	
AB	241.31	1	241.31	11.32	0.0099	
AC	11.34	1	11.34	0.53	0.4866	
BC	1.73	1	1.73	0.081	0.7828	
Residual	170.52	8	21.31			
Lack of fit	142	4	35.5	4.98	0.0746	Not significant
Pure error	28.52	4	7.13			
Cor total	639.64	13				

*The p-value value with the indicating that there are significant differences in flow velocity due to the use of the three optimized ingredients. The values are mean±standard deviation of n=5.

From the floating lag time tablet data, the equation according to the SLD is as follows:

Floating lag time (min) =-7.27 (A)-25.47 (B)+4.62 (C)+0.51 (A)(B)+0.13 (A)(C)-0,052 (B)(C)

Where:

A = starch component fraction fully pregelatinized

B = HPMC K4M component fraction

C = fraction of the Magnesium stearate component

From the equation, it can be seen that the starch matrix component is fully pregelatinized, HPMC K4M and magnesium stearate and component interactions, have an effect on friability. Individualism CSFP has a negative effect, while HPMC K4M, and magnesium stearate have a positive effect, which means it can increase the floating lag time. While the optimized two-component interaction, which is CSFP with HPMC K4M and CSFP with magnesium stearate, has a positive effect which means it can increase the floating lag time, while the interaction between HPMC K4M and magnesium stearate has a negative effect, which can reduce the floating lag time.

Dissolution test

Validation method

Table 7: Analysis LOD and LOQ

Concentration	Absorbancy (y)	y'	y'-y	(y'-y)2
10	0.461000	0.466400	0.005400	0.000029
12	0.558000	0.547400	-0.010600	0.000112
13	0.592000	0.587900	-0.004100	0.000017
14	0.615000	0.628400	0.013400	0.000180
15	0.671000	0.668900	-0.002100	0.000004
17	0.752000	0.749900	-0.002100	0.000004
18	0.789000	0.790400	0.001400	0.000002
			Σ	0.000349
			Sy/x	0.008351
			LOD	0.592247
			LOQ	1.974158

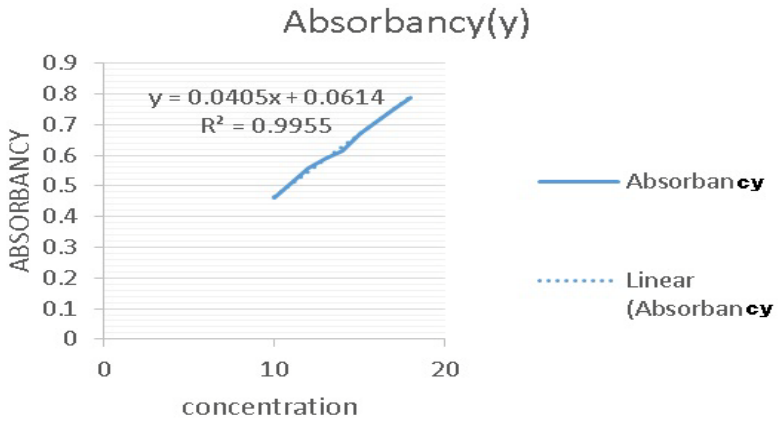

Fig. 3:The curve of ranitidine HCl in 0.1 N HCl dissolution medium

The maximum wavelength of ranitidine HCl was obtained in 0.1 N HCl medium at 312 nm. The linear regression equation obtained y = 0.0405X+0.0614 (Y = absorbancy and X = ranitidine HCl content) with a correlation coefficient of 0.9955

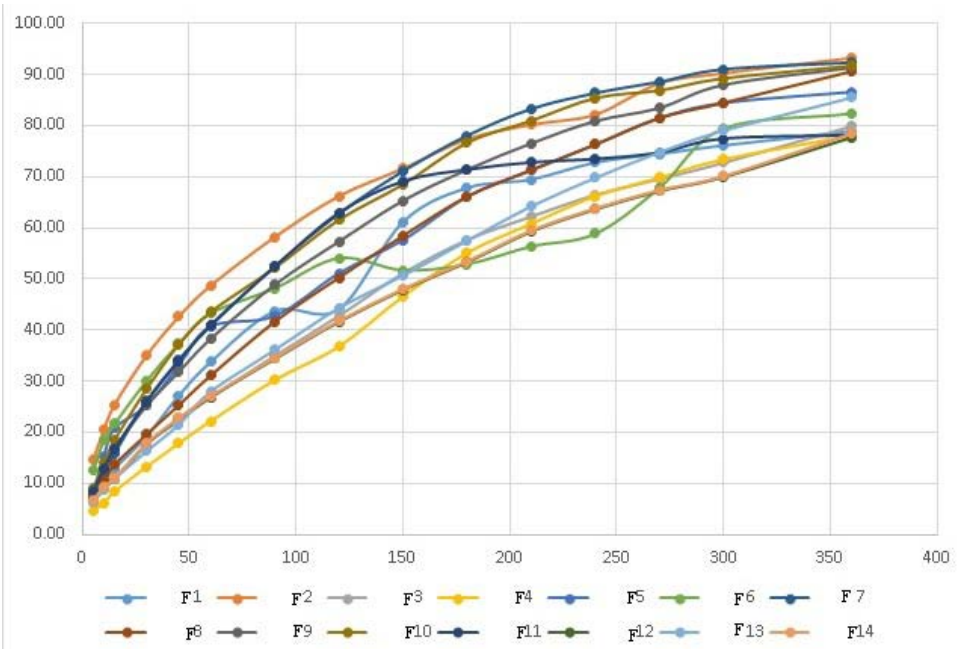

Fig. 4:Profil average dissolved of ranitidine HCl in the HCl 0.1 N, the values are mean±standard deviation of n=5

Table 8: Analysis of variance (ANOVA) of the dissolved of ranitidine HCl in the HCl 0.1 N

Source	Sum of squares	df	Mean square	F value	p-value prob>F	
Model	390.23	5	78.05	5.63	0.0162	significant
Linier mixture	15.03	2	7.52	0.54	0.0016	
AB	162.29	1	162.29	11.7	0.0091	
AC	172.59	1	172.59	12.44	0.0078	
BC	23.37	1	23.37	1.68	0.2304	
Residual	110.97	8	13.87			
Lack of fit	22.7	4	5.68	0.26	0.8915	not significant
Pure error	88.27	4	22.07			
Cor total	501.2	13				

*The release profile of ranitidine HCl from a tablet has a similar profile, which is slow release. The values are mean±standard deviation of n=5.

Abbreviations: F: formulations.

Fig. 4 shows that the release profile of ranitidine HCl from a tablet has a similar profile, which is a slow release. In the initial phase until the 60th min, the release is still quite large and is followed by slower release until it reaches steady state.

From the data of ranitidine HCl dissolved (%), the equation obtained:

Ranitidine HCl dissolved (%) = 7.39(A)+20.88(B)+34.84(C)-0.42(A)(B)-0.52(A)(C)-0.19(B)(C)

Where:

A = starch component fraction fully pregelatinized

B = HPMC K4M component fraction

C = fraction of the Magnesium stearate component

ANOVA results of the quadratic model, the calculated probability value (p-value) = 0.0162. The calculated p-value is less than 0.05 indicating the model/equation obtained is significant (model fit) at the 95% confidence level. The equation model obtained can be used to navigate the design space.

From the above equation shows that each component individually has a positive effect which means it can increase dissolitidine HCl dissolved (%). Two-component interaction produces a coefficient that is negative, which means it can reduce the speed of release.

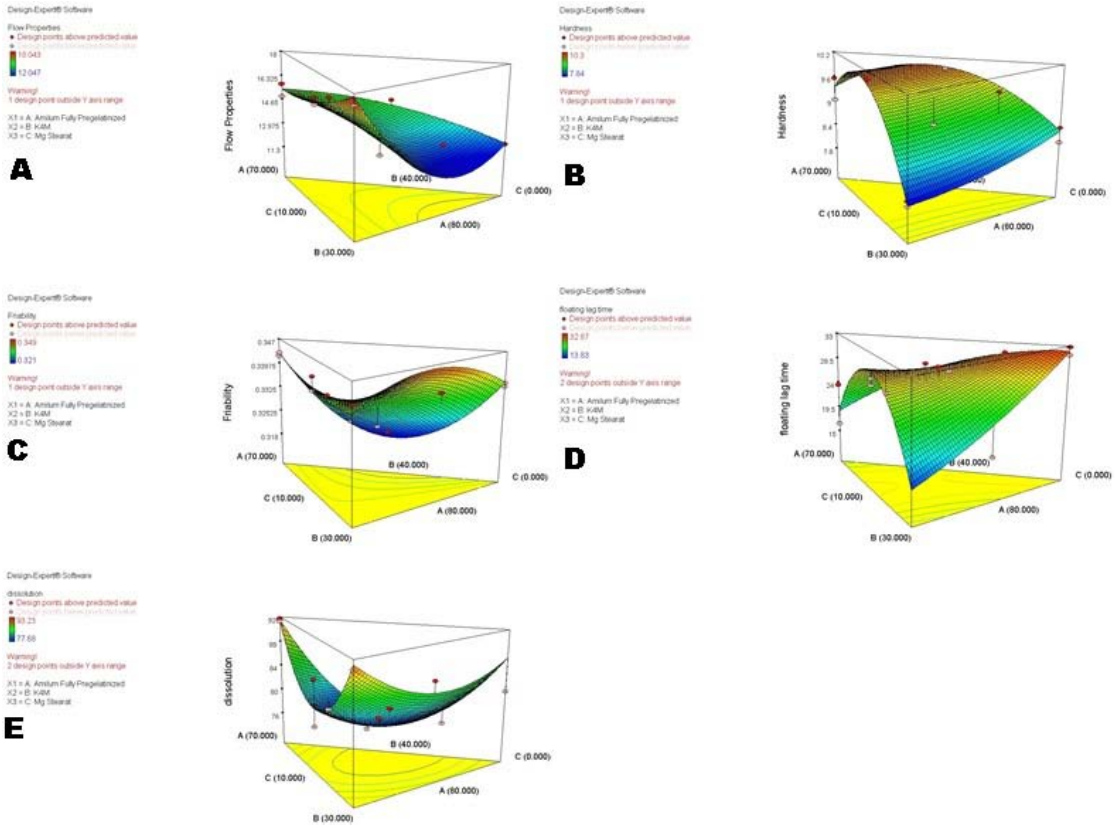

Fig. 5: Interaction factors A, B, and C on flow properties (A), interaction factors A, B, and C on hardness (B), Interaction factors A, B, and C on friability (C), Interaction factors A, B, and C on floating lag time (D), Interaction factors A, B, and C on dissolution (E)

Optimization

The selection of the optimum condition (fig. 6) is formula 1, focused on the highest desirability value (table 8). The optimization process for NEFT has been evaluated by desirability value, the condition for optimum functional components in NEFT was 80 mg for CSFP, HPMC K4M 30 mg, and 10 mg magnesium stearate to obtain a yield of 7.85 kg hardness (fig. 5B), 0.34 % friability (fig. 5C), 15.27 floating lag time (fig. 5D) and 91.31 % ranitidine HCl dissolved (fig. 5E).

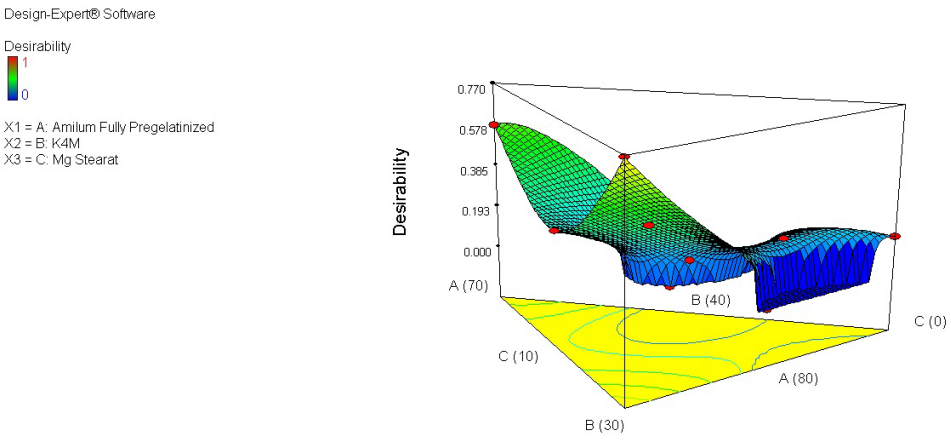

Fig. 6: Superimposed graphs of various contour plots

Table 8: Solutions for 3 combinations of category factor levels

	CSFP(mg)	HPMC K4M (mg)	Magnesium stearate (mg)	Floating lag time (min)	Dissolution (%)	Desirability	
1	80	30	10	15.27	91.31	0.764	Selected
2	70	40	10	19.73	89.77	0.587	
3	70	40	10	18.87	91.55	0.577	
4	79	39	2	30.88	82.66	0.216	
5	79	40	1	31.80	82.19	0.202	

*The selection of the optimum condition is formula 1, focused on the highest desirability value.

Table 9: Verification optimum formula

Response	Sample		p-value
	Experiment	Prediction	
Flow rate (g/s)±SD	18.02+0.18	17.84+0.15	0.51
Hardness (kg)±SD	8.11+0.27	7.85+0.35	0.44
Friability (%)±SD	0.32+0.02	0.34+0.05	0.38
Floating lag time (min)±SD	15.12+0.09	15.27+0.06	0.63
Dissolution (%)±SD	91.28+0.45	91.31+0.65	0.82

*The values are mean±standard deviation of n=5.

The experimental response data for the selected optimum formula was analyzed using the independent sample test for the T-test in the open state software to find out whether there was a difference in the response value of the SLD prediction. At the 95% confidence level, the p-value for all responses is greater than 0.05. This means that all response data have no significant difference in the response value of the SLD prediction. It can be concluded that between the verification data and predicted data statistically have no difference or have the same value.

CONCLUSION

The optimization process for NEFT has been evaluated by desirability value, the condition for optimum functional components in NEFT was 80 mg for CSFP, HPMC K4M 30 mg, and 10 mg magnesium stearate to obtain a yield of 7.85 kg hardness, 0.34 % friability, 15.27 floating lag time and 91.31 % ranitidine HCl dissolved.

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CONFLICT OF INTERESTS

The author declares there is no conflict of interest.

AUTHORS CONTRIBUTIONS

All author the author contributed equally

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