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Formulation and evaluation of orally disintegrating tablet of ondansetron using natural superdisintegrant

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ABSTRACT

Introduction: Difficulty in swallowing is common among all age groups, especially elderly and pediatrics. Orally disintegrating tablets may constitute an innovative dosage form that overcome the problem of swallowing and provide a quick onset of action. This study was aimed to formulate and evaluate an orally disintegrating tablet (ODT) containing ondansetron while using semi-synthetic and natural superdisintegrants.

Methods: Orodispersible tablets were prepared by direct compression using natural superdisintegrant (Karaya gum) and semi-synthetic superdisintegrant (croscarmellose). The prepared tablets were evaluated for hardness, friability, thickness, drug content uniformity, water absorption and wetting time. A 3^2 factorial design was used to investigate the effect of independent variables (amount of croscarmellose and Karaya gum) on dependent variables (disintegration time, friability and Q_5 [cumulative amount of drug release after 5 minutes]). A counter plot was also presented to graphically represent the effect of independent variable on the disintegration time, friability and Q_5. The check point batch was also prepared to prove the validity of the evolved mathematical model. The systematic formulation approach helped in understanding the effect of formulation processing variable.

Results: According to the results of optimized batches, the best concentrations of superdisintegrant were as follows: 7.88 mg Karaya gum and 7.78 mg croscarmellose gave rapid disintegration in 31 seconds which showed 99% drug release within 5 minutes.

Conclusion: Karaya gum, a natural superdisintegrant, gives a rapid disintegration and high release when used with synthetic superdisintegrant in formulation of ODT.

Implication for health policy/practice/research/medical education:
Karaya gum is a natural superdisintegrant that showed a good disintegration time and wetting effect when used with synthetic superdisintegrant in formulation of orally disintegrating tablet (ODT) of Ondansetron.

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Introduction

Buccal route is a useful method of administration when rapid onset of actions is desired. The ease of usage, patient compliance and improved bioavailability are other advantages of this route (1). Tablets and capsules are the most popular solid dosage forms.

However, many people face difficulty in swallowing tablets and hard gelatin capsules (2). It has been found that this problem has been encountered in all groups of patients, especially with pediatric and geriatric populations. Thus, these conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing especially in the case of pediatric, geriatric, and any mentally retarded persons (3).

However, it offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size, and handling (4). Its ease of administration in the population especially for pediatric, geriatric, or any mentally retarded persons makes it a very popular dosage form. Due to the presence of superdisintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action (5).

Ondansetron has a high oral bioavailability of 60%. The half-life is 3 to 4 hours and the T_{max} is 1.5 hours for the conventional tablet and slightly longer for the oral drug

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therapy (ODT). In cancer chemotherapy, drug induced nausea and vomiting may occur so regularly that anticipatory vomiting occurs when patients return for treatment before the chemotherapeutic agent is given. If not controlled, the discomfort associate with drug induced emesis may cause a patient to refuse further chemotherapy. In this condition ondansetron hydrochloride is a drug of choice (6,7).

In market ondansetron is available in freeze dried dosage form which gives rapid disintegration. Main disadvantage of this method is very costly method, process is not feasible and product is highly sensitive to moisture. Freeze drying is cumbersome and it yields a fragile and hygroscopic product (8).

In this study natural superdisintegrants were utilized. Natural superdisintegrants are safer, more biodegradable, better compressible, easier to preparation and cheaper and these advantages can boost the production of ODTs (9). In the present study, the fast disintegrating tablets were prepared by the method of direct compression using various pharmaceutical excipients. The excipients used were avicel PH102, croscarmellose, Karaya gum, mannitol, aspartame, aerosil and magnesium stearate.

Materials and Methods

Ondansetron hydrochloride was a gift from Amin Pharmaceutical Company (Iran). Aerosil and aspartame were obtained as gift from Isfahan University of Medical Science Lab and other ingredients were bought from market. Croscarmellose (Macleods Pharmaceuticals, India), Karaya gum (Nutriroma, India), aspartame (Fluka, Switzerland), Avicel PH102, Magnesium stearate, Mannitol (Merck, Germany).

Preparation of orally disintegrating tablets

Orally disintegrating tablet (ODT) of ondansetron was prepared by direct compression method. All the ingredients were passed through 60 mesh sieve separately. The ondansetron, croscarmellose, Karaya gum, avicel PH102, mannitol and aspartame were mixed up using a mortar and pestle. The blends were lubricated with 1% magnesium stearate and 1% aerosil. The blends ready for compression were converted into tablets. Tablets were compressed at 3 mm size flat round punch to get tablet machine (Erweka AR 4100, Germany). The compositions of experimental factorial design are shown in Table 1.

3^2 Full factorial design

Response surface methodology (RSM) was characteristically employed to relate a response variable to the levels of the input variables and to generate a design matrix to choose the optimal formulations. A statistical model, which consisted of interactive and polynomial terms, was utilized to evaluate the responses (11,12). The responses were analyzed using analysis of variance (ANOVA) and the individual response parameters were evaluated using *F* test and polynomial equation was generated for each response using multiple linear regression analysis.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1 X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. A 3^2 full factorial design was employed to study the effect of independent variables, ie, amount of Karaya gum (X_1) and the amount of croscarmellose (X_2) on dependent variables friability, disintegration time and Q_5 (cumulative amount of drug release after 5 minutes).

After application of full factorial design and with the help of produced polynomial terms, amount of 2 formulation variable was optimized. The optimized amount of the croscarmellose and Karaya gum were incorporated in the tablet which was used as the check point of the regression analysis model (Tables 1 and 2).

Evaluation of mixed powder blend of drug and excipients

Evaluation of mixed blends of drug and excipients were carried out for all the formulations for angle of repose, bulk density, tapped density, Hausner ratio and Carr index.

Bulk density (D_b) and tapped density (D_t)

Both bulk density and tapped bulk density were determined. A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder.

Table 1. Factorial design batches

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Ondansetron hydrochloride	4	4	4	4	4	4	4	4	4
Croscarmellose	3	6	9	3	6	9	3	6	9
Karaya gum	5	5	5	10	10	10	15	15	15
Aerosil	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1
Aspartame	1	1	1	1	1	1	1	1	1
Mannitol	20	20	20	20	20	20	20	20	20
Avicel PH 102 up to	150	150	150	150	150	150	150	150	150

Abbreviations: F, formulation.

Table 2. Design and summary response data

Run	Independent variable in code form				Dependent variable		
	Coded form		Actual form				
	Factor A	Factor B	Karaya gum (mg)	C.C (mg)	F %	DT (s)	Q_5 %
1	-1	-1	5	3	0.54	50	93
2	-1	0	5	6	0.50	48	96
3	-1	1	5	9	0.47	42	102
4	0	-1	10	3	0.45	39	101
5	0	0	10	6	0.41	35	100
6	0	1	10	9	0.37	31	98
7	1	-1	15	3	0.34	28	99
8	1	0	15	6	0.33	24	98
9	1	1	15	9	0.35	27	92

Abbreviations: C.C: croscarmellose; F, Friability; DT, Disintegration time; Q5, Drug release after 5 minutes.

After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. Bulk density and tapped bulk density were calculate using following formula (13):

$$D_b = \frac{Weight\ of\ the\ power}{Volume\ of\ the\ packing}$$

$$D_t = \frac{Weight\ of\ the\ power}{Tapped\ volume\ of\ the\ packing}$$

Carr index

The compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the D_b and D_t of a powder and the rate at which it packed down. The formula for Carr index is as below:

$$Carr\ index = \frac{D_t - D_b}{D_t} \times 100$$

Where D_t is tapped density of the powder and D_b is bulk density of the powder.

Hausner ratio

Hausner ratio was calculated from bulk and tapped density of ondansetron blend powder formulation and it is expressed as:

$$Hausner\ ratio = \frac{D_t}{D_b}$$

Where D_t is tapped density and D_b is bulk density.

Angle of repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granular cone was measured and angle of repose was calculated using the following equation:

$$\tan\theta = \frac{h}{r}$$

Where h and r are the height and radius of the cone (Table 3).

Evaluation parameters of orally disintegrating tablets

Weight variation

Randomly, 20 tablets were selected after compression and the mean weight was determined (14). None of the tablets deviated from the average weight by more than ±7.5%.

Tablet thickness

The thickness was measured by placing tablet between two arms of the vernier calipers. Five tablets were taken and their thickness was measured (15).

Tablet hardness

Hardness of tablet is defined as the force applied across

Table 3. Powder flow properties of the ondansetron formulations

Code	Angle of repose (θ)	Bulk density (gr/cm³)	Tapped density (gr/cm³)	Carr index (I)	Hausner ratio
F_1	27.06 ± 0.02	0.58 ± 0.06	0.66 ± 0.07	12.12 ± 1.13	1.11
F_2	27.09 ± 0.03	0.57 ± 0.09	0.66±0.08	13.63 ± 1.01	1.10
F3	26.57 ± 0.02	0.56 ± 0.05	0.65 ± 0.04	13.84 ± 0.35	1.08
F4	24.62 ± 0.03	0.58 ± 0.05	0.66 ± 0.07	12.12 ± 1.27	1.07
F_5	24.42 ± 0.01	0.60 ± 0.03	0.69 ± 0.02	13.04 ± 1.05	1.10
F_6	24.17 ± 0.05	0.61 ± 0.04	0.69 ± 0.06	11.59 ± 1.11	1,10
F_7	24.51 ± 0.02	0.62 ± 0.04	0.67 ± 0.04	7.46 ± 1.36	1.07
F8	24.49 ± 0.01	0.58 ± 0.02	0.66 ± 0.08	12.12 ± 1.55	1.17
F9	24.45 ± 0.03	0.58 ± 0.04	0.66 ± 0.02	12.12 ± 0.35	1.08

Abbreviations: F, formulation.

the diameter of the tablet in order to break the tablet. The hardness of the tablets was determined by diametral compression using Erweka hardness tester (16).

Friability testing

This test was performed to determine the effects of friction and shock. Preweighed sample of 10 tablets was placed in the Erweka friabilator and rotated at 25 rpm for about 4 minutes. The tablets were dedusted and reweighed, and the friability percentage was calculated. Compressed tablets should not lose more than 1% of weight (17).

$$\text{Percentage friability} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Wetting time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The wetting times were measured (18).

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following equation (19).

$$R = \frac{W_a - W_b}{W_a} \times 100$$

Where, W_b is the weight of the tablet before water absorption and W_a is the weight of the tablet after water absorption.

In vitro disintegration test

The in vitro disintegration studies were carried out using a digital tablet disintegration test apparatus (Erweka ZT, Germany). One tablet was placed in each of the 6 tubes of the basket assembly and then disk was added to each tube. This assembly was then suspended in a 1-liter beaker containing water with its temperature being maintained at 37 ± 2°C. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for complete disintegration of the tablet was recorded (20).

Dissolution test

The release rate of ondansetron hydrochloride from ODTs was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 500 ml of 0.1N HCl pH 1.2 as a dissolution medium, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 3, 4, 5, 10, 20 and 30 minutes. The samples were filtered through a 0.45 membrane filter. Absorbance of these solutions was measured at 310 nm using a Shimadzu spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve (21).

Content uniformity

Ten tablets of each batch were weighed and powdered. Aliquot of this powder containing Ondansetron hydrochloride equivalent to 4 mg of Ondansetron was accurately weighed, suspended in approximately 50 ml of 0.1 N HCl and shaken for 15 minutes. Final volume was adjusted to 100 ml with 0.1 N HCl and filtered (Whatman No.1 filter paper). From this 10 ml was diluted to 100 ml. The final volume was made by taking 2 ml of above solution and diluted to 10 ml with 0.1 N HCl. Absorbance of this solution was recorded at 310 nm using UV/Vis spectrophotometer against a reagent blank and the content was compared from a calibration curve prepared with standard ondansetron hydrochloride in the same medium (Table 4). The mean percentage drug content was calculated as an average of 3 determinations (22).

Data analysis

Response surface model factorial designs with 2 independent formulation variables at 3 different levels were used to study the effect of dependent variables (23). All the batches of orally disintegration were statically (95% or $P < .05$) evaluated with regard to disintegration time, friability and drug release after 5 minutes.

Optimization of formulation ingredients

After generating the polynomial equations relating the dependent and independent variables, the process was optimized for responses, optimization was performed to obtain the value of X_1 and X_2, which targeted disintegration time (DT) = 30 seconds; friability (F) = 0.35; drug release after 5 minutes (Q_5) = 100. The optimized amount of croscarmellose and Karaya gum was incorporated in the tablet which was also used as the check point of the regression analysis model (24). The optimized ODT was prepared and evaluated for the physiochemical properties.

Results

Data analysis

A response surface model factorial design with 2 independents variable at 3 different levels was used to study the effects in dependent variables. Transformed values of the batches along their results are shown in Table 5. The dependent variables (DT, F, Q_5) obtained at various levels of the 2 independent variables (X_1 and X_2) were subjected to multiple regressions to yield a second-order polynomial equation, the obtained coefficient are shown in Table 5. The DT, F and Q_5 values measured form different batches

showed wide variations. These results clearly indicated that the DT, F and Q_5 were strongly affected by the variables selected for the study. This was also reflected by the wide range of value for coefficients of the term equation. The value of correlation coefficient (R^2) of polynomial regression equation was found to be greater than 0.99, indicating good fit for all dependent variables (Table 5).

X_1 and X_2 represent the average result if changing one variable at a time from its low level to its high level. The interaction terms (X_1X_2, X_1X_1 and X_2X_2) show how the DT, F and Q_5 changes when 2 variables are simultaneously changed. Using the polynomial equations, the optimized formulations were obtained for the response parameters.

Polynomial equation for disintegration time

$$Y=34.67-2.83X_1-10.17X_2+1.75X_1X_2+0.5X_1^2+1.5X_2^2$$

Polynomial equation for friability

$$Y=0.41-0.023X_1-0.082X_2+0.02X_1X_2+(6.667E-0.003)X_1^2+0.012X_2^2$$

Table 4. Evaluation of the prepared orodispersible tablets of ondansetron

Tests	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Weight variation (Mean±SD)	5.7±0.51	6.0±0.22	5.5±0.34	5.0±0.28	5.4±0.30	5.0±0.54	5.2±0.28	5.0±0.39	5.4±0.41
Hardness (kg/cm²)	3.2±0.39	3.2±0.67	3.0±0.46	3.0±.0.69	3.0±0.59	3.3±0.34	3.1±0.76	3.3±0.94	3.2±0.32
Friability	0.57±0.16	0.68±0.14	0.81±0.15	0.93±0.147	0.96±0.157	0.72±0.155	0.44±0.138	0.80±0.149	0.66±0.153
Thickness (mm)	3.45	3.49	3.42	3.53	4.13	3.53	3.54	3.42	3.46
Wetting time (s)	32	29	26	25	23	18	16	19	21
Water absorption ratio	79.22	81.34	84.43	87.11	89.56	91.57	92.76	93.76	91.25
In vitro disintegration time (s)	50	48	42	39	35	31	28	24	27
Assay	97.4	98.2	97.7	96.8	97.3	98.6	99.5	97.3	98.1

Abbreviations: F, formulation.

Table 5. Analysis of variance (ANOVA) response surface cubic model

	Source	Sum of squares	Df	Mean square	F value	Prob of P value< F value	R^2
For Fraibility	Model	0.045	5	9.049E-003	29.80	0.0093	0.9803
	X_1	3.267E-003	1	3.267E-003	10.76	0.0207	
	X_2	0.04	1	0.040	131.76	0.0747	
	X_1X_2	1.600E-003	1	1.600E-003	5.27	0.2048	
	X_1^2	8.889E-005	1	8.889E-005	0.29	0.2445	
	X_2^2	2.722E-004	1	2.722E-004	0.90	0.1755	
	Residual	9.111E-004	3	3.037E-004			
	Cor total	0.046	8				
For Disintegration time	Model	685.58	5	137.12	28.53	0.0098	0.9794
	X_1	48.17	1	48.17	10.02	0.0506	
	X_2	620.17	1	620.17	129.05	0.0015	
	X_1X_2	12.25	1	12.25	2.55	0.2086	
	X_1^2	0.50	1	0.50	0.10	0.7682	
	X_2^2	4.50	1	4.50	0.94	0.4046	
	Residual	14.42	3	4.81			
	Cor total	700.00	8				
For Drug release after 5 minutes	Model	274.69	5	54.94	9.06	0.0497	0.9379
	X_1	8.17	1	8.17	1.35	0.3298	
	X_2	1.50	1	1.50	0.25	0.6531	
	X_1X_2	210.25	1	210.25	34.67	0.0098	
	X_1^2	20.06	1	20.06	3.31	0.1666	
	X_2^2	34.72	1	34.72	5.73	0.0965	
	Residual	18.19	3	6.06			
	Cor total	292.89	8				

Polynomial equation for drug release after 5 minutes

$Y=100.78+1.17X_1-0.5X_2-7.25X_1X_2-3.17X_1^2-4.17X_2^2$

Response surface counterplot

The relationship between the dependent and independent variable was further elucidated by constructing counter plots. The effects of X_1 and X_2 with their interaction on DT, F and Q_5 at different levels (low, medium and high level) are displayed in Figures 1-3 .the interaction effect between X_1 and X_2 are shown in response surface plot Figures 4-6.

Optimization of orally disintegrating tablet

The optimization of the ODT was decided to target DT= 30 seconds, F= 0.35% and drug release Q_5= 100%.
Optimized concentrations obtained from the software and the counter plot are shown in Figure 7. Comparative values of predicted and observed responses along with the formulation components are reported in Table 6.

Discussion

An optimized formulation of Ondansetron ODT was prepared in this study using the "Direct compression" method. Formulation and optimization procedures were facilitated using 3^2 full factorial designs.
About the DT test, it was observed that with increasing croscarmellose and Karaya gum, DT was decreased; however, changes in the quantities of Karaya gum had more significant effect than croscarmellose (10,25).
On the other hand with increasing the percentage of Karaya gum, speed of drug release was decreased, hence to create a suitable response, an optimum limit in usage Karaya gum was found to have a proper amount of drug release.

Effect of formulation variable on friability

Value of prob>f less than 0.05 shows that the model for F is significant and Factor X_2 is found to be significant in this case. The positive coefficient for X_1 and X_2 indicates favorable effect on F (increasing the amount of C.C and K [Karaya gum] decreases the F). The results convey us that factor X_2 has significant effect on F than that of X_1.

Effect of formulation variable on disintegration time

Value of prob>f less than 0.05 shows the model terms are significant and Factor X_2 is found to be significant in this case The negative coefficient for X_1 and X_2 indicates favorable effect on disintegration time (DT) (increasing the amount of croscarmellose [C.C] and Karaya gum decreases the DT). The results convey us that factor X_2 has significant effect on DT than that of X_1.

Effect of formulation variable on Q_5

Value of prob>f less than 0.05 shows the model for Q_5 is significant, and X_1X_2 is significant. The positive coefficient for X_1 and X_2 indicates favorable effect on Q_5 (increasing the amount of C.C and Karaya gum increases the Q_5). The

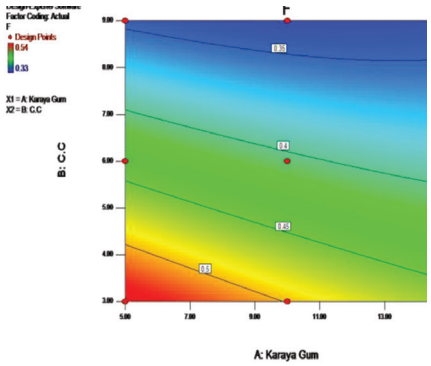

Figure 1. Counter plot for friability. F: friability, X1=A: Karaya gum, X2=B:C.C, C.C: croscarmellose.

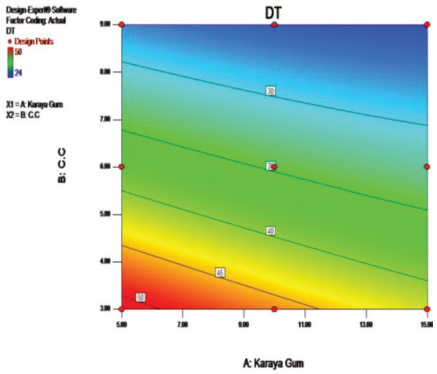

Figure 2. Counter plot for disintegration time. X1=A: K, X2=B:C.C, C.C: croscarmellose, DT: disintegration time.

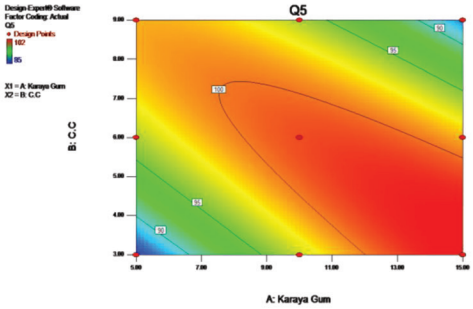

Figure 3. Counter plot for Q5. X1=A: K, X2=B:C.C, C.C: croscarmellose, Q5: drug release after 5 minutes.

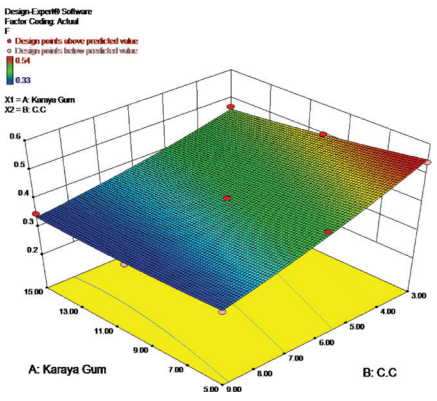

Figure 4. Response surface plot for friability. F: friability, X1=A: Karaya gum, X2=B:C.C, C.C: croscarmellose.

Table 6. Comparative value of predicted and observed responses

F_{NO}	Karaya gum (mg)	Croscarmellose (mg)	DT (s)		F%		Q_5		Desirability
			Predicted	Observed	Predicted	Observed	Predicted	Observed	
O_1	7.88	7.78	29.99	31	0.366	0.37	99.9	99.2	0.964

Abbreviations: F: friability; DT, disintegration time; Q_5, drug release after 5 minutes; O, optimized batch.

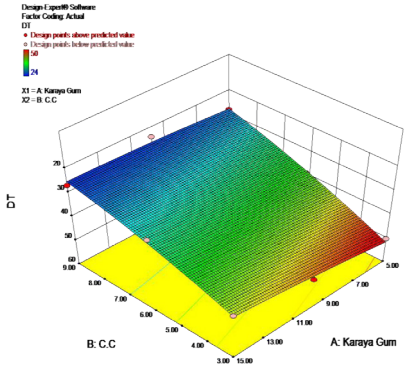

Figure 5. Response surface plot for disintegration time. DT: disintegration time, X1=A: Karaya gum, X2 = B:C.C, C.C: croscarmellose.

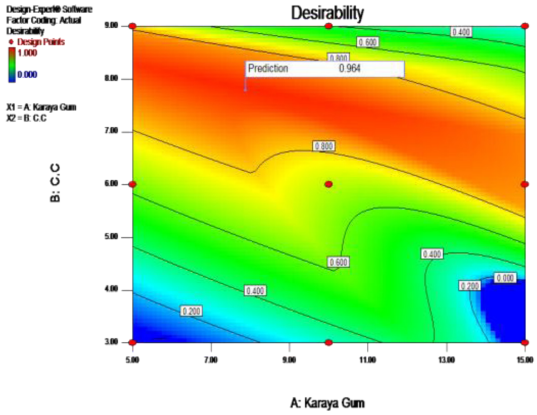

Figure 7. Counter plot for desirability. X1 = A: Karaya gum, X2 = B:C.P, C.C: croscarmellose.

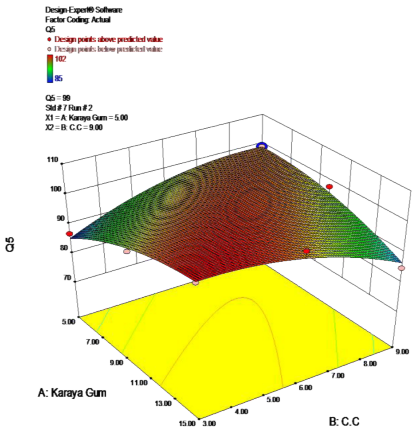

Figure 6. Response surface plot for Q5. X1 = A: Karaya gum, X2 = B:C.C, C.C: croscarmellose, Q5: drug release after 5 minutes.

results convey us that factor X_1 has significant effect on Q_5 than that of X_2.

Conclusion

Overall, the results convey us that optimized ODTs of Ondansetron containing 7.78 mg of C.C and 7.88 mg of Karaya gum as a superdisintegrant by direct compression method showed responses as we desired.

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Authors' contributions

All contributed to the study. MT, MAS and SK prepared the manuscript.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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