RESEARCH ARTICLE

Formulation, Statistical Optimization and Stability Study of Ondansetron Films

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ABSTRACT

Nausea and/or vomiting is common in patients of all ages. Nausea and vomiting can occur for a variety of reasons and may be related to illness or treatment. Careful study of the receptors involved has aided in the selection of drug classes to treat patients (34). This study aimed to prescribe an oral dissolving film of the antiemetic drug ondansetron for treating vomiting patients and nausea and vomiting (NVP) in pregnancy. The goal for optimizing the orally dissolving ondansetron film was to reduce disintegration time and maximize drug release from the film.

The formulation of the mouth-dissolving film contains carefully selected additives to impart aesthetic and performance properties such as taste masking, rapid dissolution, physical mouth feel and tactility. From a regulatory perspective, all excipients used in the formulation of oral dissolution films are generally considered safe (i.e., on the GRAS list) and are approved for use in oral pharmaceutical dosage forms.

Keywords: Anti-emetic, Films, Mouth dissolving, Tensile strength

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INTRODUCTION

The oral route of administration has always been preferred over other routes of administration: parenteral, topical, rectal, and intravaginal.

Mouth-dissolving films are oral solid dosage forms that disintegrate without absorbing water and dissolve in the mouth. Mouth-dissolving films are popular and accepted among children, the elderly, and people with dysphagia who fear choking. Oral dissolving films allow drugs to be absorbed via the oral mucosa, bypassing first-pass metabolism. and enter the systemic circulation, offering convenience, ease of administration, and rapid onset of action.[1]

EXPERIMENTAL

Formulation of Ondansetron MDF

Step 1: Select a film preparation method

A solvent casting process was used to manufacture the films. The polymer was soaked overnight in 3/4 of the solvent. The polymer solution was mixed with a magnetic stirrer for about 30 minutes until a uniform dispersion was obtained. Plasticizers, film modifiers, and sweeteners were then added and stirred for 10 minutes after each ingredient was added. The polymer solution was mixed with a magnetic stirrer for 60 minutes. The polymer solution was sonicated for 30 minutes to remove air bubbles. The polymer solution was then added into pre-lubricated 9 cm diameter round glass petri dishes. Petri dishes were smeared with glycerol. After the film was dried at room temperature, the film was peeled off, cut into 2 x 2 cm films, wrapped in butter paper, and stored in a desiccator. The key quality attributes considered in the formulation were film clarity, peelability, stiffness, and disintegration time.[2-5]

Step 2: Selection of Vehicle

Water was chosen as the film's solvent because the drug ondansetron is highly water soluble. However, using water increased the drying time of the film. Therefore, co-solvent ethanol was used to reduce film drying time.[6]

Step 3: Selection of Film Forming Polymer

Hydroxypropyl methylcellulose (HPMC) proved to be the best film former among the various polymer grades investigated. An oral dissolving film was prepared using the solvent casting method. HPMC E3, E5, and E15 have been found to make good clear-release films. HPMC E3 (F9) and E5 (F14) produced good films at 5% concentration but were found to be soft. HPMC E15 is the best film-forming polymer, produces clear films at low concentrations, is hard, peelable and not too soft.[7]

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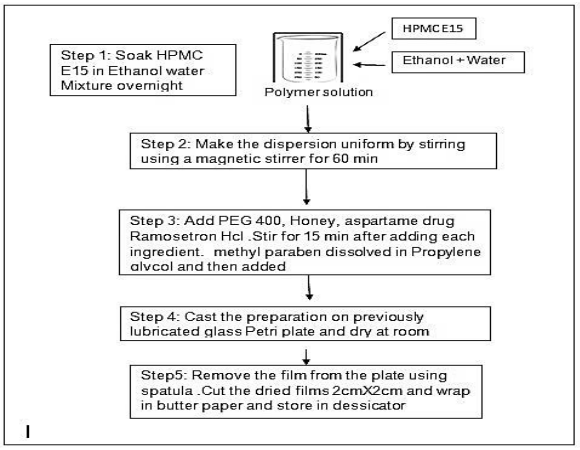

Figure 1: Flowchart of the Steps involved in the processing of Ondansetron Mouth Dissolving Film.

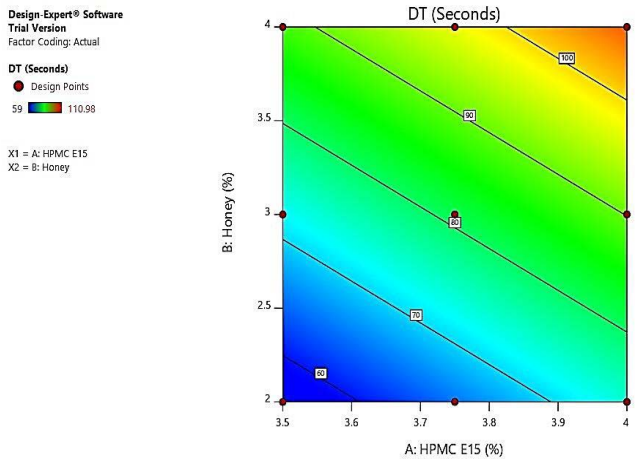

Figure 2: Contour Plots for Response Y1 Disintegration Time.

Table 1: Composition of Placebo Film with HPMC E15 and Honey

CODE	*F15*	*F16*	*F17*	*F18*	*F19*	*F20*
HPMC E15%	3	3.5	4	3	3.5	4
PEG 400%	1	1	1	1	1	1
Honey%	2	2	2	4	4	4
Ethanol (mL)	5	5	5	5	5	5
Water qs (mL)	10	10	10	10	10	10
Film properties	Good Stiff film	Good Stiff film	Good Stiff film	Good Stiff film	Good. Stiff film	Good. Stiff film
Peelability	Y	Y	Y	Y	Y	Y
Tachyness	Non-Sticky	Non-Sticky	Non-Sticky	Non-Sticky	Non-Sticky	Non-Sticky
Transparency	Y	Y	Y	Y	Y	Y
Disintegration time (minutes)	1.10	1.45	2	1	1.20	2

X: No result Y: Yes is positive

Table 2: Formulation of Ondansetron Mouth DissolvingFilm

S. No	*Ingredients*	*Quantity*	*Use*
1	Ondansetron	0.1 mg /film	Anti-Emetic Drug
2	HPMC E15	3.5–4%	Film forming Agent
3	Honey	2–4%	Film Modifying agent
4	PEG 400	2%	Plasticizer
5	Propylene Glycol	1%	Cosolvent
6	Methyl Paraben	0.01%	Preservative
7	Ascorbic Acid	10 mg	Antioxidant
8	Citric Acid	10 mg	Saliva Stimulating Agent
9	Aspartame	5 mg	Sweetener
10	Ethanol	5 mL	Cosolvent
11	Water	qs	Solvent

Table 3: Solubility of various solubilizers

S. No	*Solid solubilizers*	*Total concentration (% w/v)*	*Solubility (mg/ mL)*	*Solubility enhancement ratio*	*AG°tr JK 'mof1*
1	DW+OND	—	0.152	—	—
2	UR	40.00	2.673	17.575	-7107.12
3	SC	40.00	0.951	6.190	-4520.34
4	PEGFT	40.00	1.135	7.474	-4987.86
5	PEGST	40.00	1.267	8.334	-5257.96

Table 4: Composition of 3 ^{2} Factorial Ondansetron MDF Formulation

Contents	*R1*	*R2*	*R3*	*R4*	*R5*	*R6*	*R7*	*R8*	*R9*
Ramosetron HCL (mL)	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48
HPMC E15	3.50	3.75	4.00	3.50	3.75	4.00	3.50	3.75	4.00
Honey (%)	2	2	2	3	3	3	4	4	4
PEG 400 (%)	1	1	1	1	1	1	1	1	1
Methyl Paraben (%)	0. 01	0. 01	0. 01	0. 01	0.01	0.01	0.01	0.01	0.01
Citric acid (%)	1	1	1	1	1	1	1	1	1
Ascorbic Acid (%)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Aspartame (%)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Propylene glycol) (%)	1	1	1	1	1	1	1	1	1
Ethanol (mL)	5	5	5	5	5	5	5	5	5
Water qs (mL)	10	10	10	10	10	10	10	10	10

Table 5: Layout of Two Factor Three Level Design [24-26]

	Independent Variables					
Factors	*Code Values*			*Actual Values (in %)*		
X1	-1	0	+1	3.5	3.75	4.0
X2	-1	0	+1	2	3	4
Dependent Variables (Response)						
Y1		Y2		Y3		
Disintegration-Time (in Seconds)		Tensile strength of the film (in g/cm2)		Drug Release in % at 9 minutes		

Table 6: Evaluation Parameters for Placebo Film of HPMC E15

CODE	*F1*	*F2*	*F3*	*F4*
Folding endurance	355 ± 3.51	385 ± 3.67	389 ± 2.5	401 ± 2.01
Surface pH	6.60 ± 0.01	6.72 ± 0.02	6.65 ± 0.01	6.70 ± 0.01
DT (s)	120 ± 2.51	176 ± 3.6	123 ± 4.5	180 ± 2.05
Thickness(mm)	0.11 ± 0.01	0.12 ± 0.005	0.11 ± 0.01	0.12 ± 0.01
Surface texture	Very Smooth	Very Smooth	Very Smooth	Very Smooth
Clarity	Very Clear	Very Clear	Very Clear	Very Clear

Results are expressed as mean ± SD (n=3)

Step 4 Selection of plasticizer

HPMC in combination with glycerin produced sticky films (F1, F2), so PEG 400 was tested. PEG 400 produced tack-free films that peeled off easily but were slightly soft (F3, F4).

Step 5 Film Modifier Selection

Maltodextrins produced translucent films when used in combination with HPMC grades. Using HPMC grade honey produced a transparent film with the required stiffness, the film could be removed without tearing, and the disintegration time (F15-F20) was unaffected. Feasibility test 1. The configuration for testing on the HPMC E15 is shown in Table 1. HPMC E15 is an excellent film-forming polymer that produces clear, hard, and easily removable films. The minimum concentration for film formation was 3%. It was found that films containing 10% glycerin as plasticizer gave tacky films, while films containing 10% PEG 400 gave less tacky films. Therefore, we decided to use a lower concentration of PEG 400.[8-12]

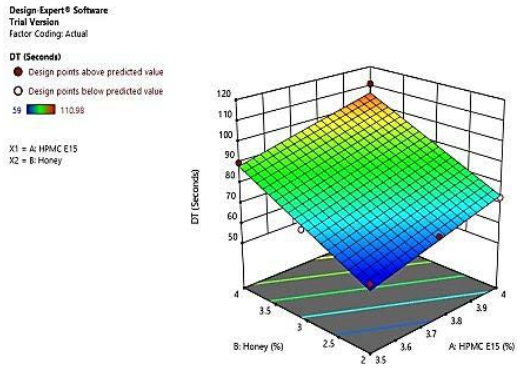

Figure 3: Response Surface Plot for Response Y1 Disintegration Time.

Optimization with Selected Excipients

In feasibility studies 1, 2 and 3, HPMC E15 in combination with the plasticizer PEG 400 proved to be the best film-forming

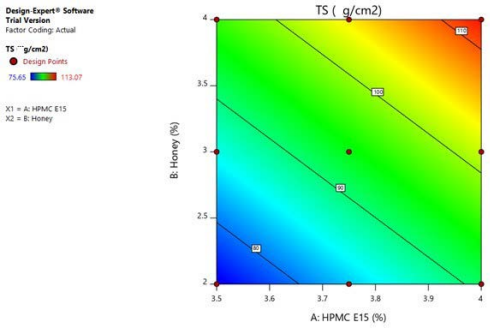

Figure 4: Contour Plot for Response Y2 Tensile Strength.

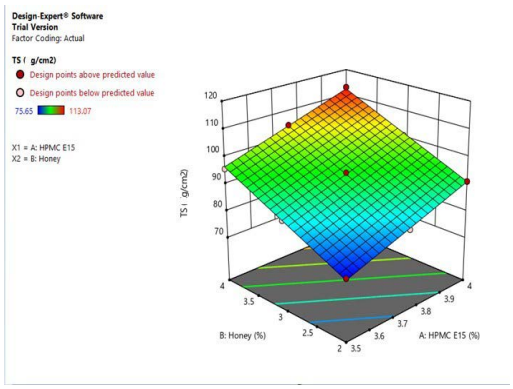

Figure 5: Response Surface Plot for Response Y2 Tensile Strength.

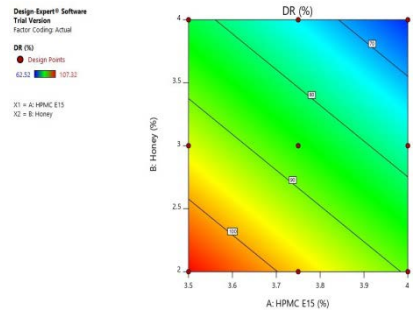

Figure 6: Contour Plot for Response Y3 Drug Release at 9 min.

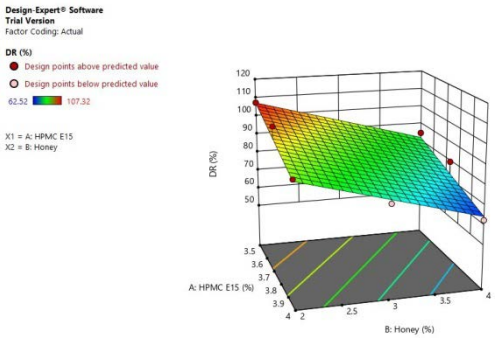

Figure 7: Response-Surface Plot for Response Y3 Drug Release in 9 min

Table 7: Evaluation Parameters for Placebo Film HPMC E5

CODE	*F10*	*F11*	*F12*	*F13*	*F14*
Folding endurance	-	-	247 ± 3.60	405 ± 4.50	556 ± 3.50
Surface pH	-	-	6.60 ± .01	6.67 ± 0.02	6.65 ± 0.01
DT(s)	-	-	125 ± 2.51	150 ± 3.6	160 ± 2.51
Thickness(mm)	-	-	0.11 ± 0.01	0.12 ± 0.005	0.12 ± 0.01
Surface texture	-	-	Smooth	Smooth	Smooth
Clarity	-	-	Clear	Clear	Clear

Result is expressed as mean±SD (n = 3)

Table 8: Evaluation Parameters for Placebo Film for Optimization Trial 4

CODE	*F15*	*F16*	*F17*	*F18*	*F19*	*F20*
Folding endurance	722 ± 5.00	745 ± 4.50	790 ± 3.60	801 ± 4.50	845 ± 5.00	866 ± 5.00
Surface pH	6.66 ± 0.01	6.67 ± 0.03	6.65 ± 0.04	6.60 ± .02	6.63 ± 0.04	6.66 ± 0.03
DT (s)	70 ± 2.51	90 ± 3.60	120 ± 1.30	60 ± 3.03	80 ± 3.61	120 ± 2.51
Thickness (mm)	0.11 ± 0.01	0.12 ± 0.02	0.13 ± 0.01	0.11 ± 0.02	0.12 ± 0.01	0.12 ± 0.02
Surface texture	Very Smooth	Very Smooth	Very Smooth	Very Smooth	Very Smooth	Very Smooth
Clarity	Very Clear	Very Clear	Very Clear	Very Clear	Very Clear	Very Clear

Result is expressed as mean±SD (n = 3)

polymer. Since PEG 400 produced a very flexible film, we reduced the concentration of PEG 400 and added honey as a film modifier to change the properties of the film. Honey has been found to stiffen the foil making it easier to remove without tearing (F15–F20).[13-15]

Formulation Development of Ondansetron the Mouth Dissolving Films[16-20]

Based on the placebo trials of F1-F20, the following formulation (Table 2) was decided for the formulation of the ondansetron mouth-dissolving film.

Table 9: Summary of Regression Analysis and ANOVA for Disintegration Time.

Outputs	*D F*	*S S*	*M S*	*F*	*p-Value Prob >F*
Model	2	2053.16	1026.58	91.00	< 0.0001
HPMC E15	1	485.64	485.64	43.05	0.0006
Honey	1	1567.52	1567.52	138.96	< 0.0001
Residual	6	67.68	11.28	-	-
Total	8	2120.84	-	-	Significant

Response	*p-value*	*R2*	*Adjusted R2*	*Predicted R2*	*Adequate precision*	*S D*	*C V%*
Y1	< 0.0001	0.9681	0.9574	0.9224	25.9499	3.36	4.14

Reduced Model equation: Y1 = 81.14 + 9.0 X1+16.16 X2

where: D F = Degree of Freedom, S S = Sum Square, M S = Mean Square

Table 10: Summary of Regression Analysis and ANOVA for Tensile Strength.

Outputs	*D F*	*S S*	*M S*	*F*	*p- Value Prob>F*
Model	2	1070.99	535.50	1113.70	< 0.0001
HPMC E15	1	383.84	383.84	798.29	< 0.0001
Honey	1	687.15	687.15	1429.11	< 0.0001
Residual	6	2.88	0.4808	-	-
Total	8	1073.88	-	-	Significant

Response	*p-value*	R^2	*Adjusted* R^2	*Predicted* R^2	*Adequateprecision*	*S D*	*C V%*
Y_2	<0.0001	0.9973	0.9964	0.9934	93.4195	0.693	0.739

Reduced Mode equation: $Y_2 = 93.72 + 8.00X_1 + 10.70X_2$

where: D F = Degree of Freedom, S S = Sum Square, MS = Mean Square

Table 11: Summary of Regression Analysis and ANOVA for Drug Release

Outputs	*D F*	*S S*	*M S*	*F*	*p-Value Prob>F*
Model	2	1415.48	707.74	24.59	0.0013
HPMC E15	1	474.73	474.73	16.49	0.0066
Honey	1	940.75	940.75	32.68	0.0012
Residual	6	172.71	28.79	-	-
Total	8	1588.19	-	-	Significant

Response	*p-Value*	*R2*	*Adjusted R2*	*Predicted R2*	*Adequate precision*	*S D*	*C V%*
Y3	0.0013	0.8913	0.8550	0.8013	13.8279	5.37	6.25

Reduced Mode equation: Y3 = 85.79-8.90X1 -12.52X2

where: D F = Degree of Freedom, S S = Sum Square, MS = Mean Square

The procedure followed for the preparation of the mouth-dissolving film of the antiemetic drug Ondansetron is given in Figure 1 i.e. in the form of a flow chart.

Solubility check for various solubilizer was performed and results are depicted in Table 3.

Optimization of Ondansetron Mouth Dissolving Film using 32 Factorial Design.[20-23]

An experimental design was used to optimize an orally soluble film of ondansetron. A formalized full factorial experimental design was constructed with two factors at three levels. The independent variables were numerical coefficients: X1 - HPMC E15 and X2 - concentration of honey. The responses selected for statistical optimization were Y1 - disintegration time in seconds, Y2 - tensile strength of film (g/cm^2) and Y3 - release rate of drug in 9 minutes. Table 4 shows the composition of ondansetron films that disintegrate in the mouth (F15 to F20) and Table 5 shows the layout of two factor three-level design..

Formulation of Ondansetron MDF.[27-29]

Preliminary Screening for Placebo Films i.e., without drug

The preliminary screening was done for the selection of various excipients namely the film-forming agent, plasticizer, and film modifier.

Feasibility Trial 1 with HPMC E15[30]

Filming experiments with HPMC E15 showed that HPMC E15 has good film-forming properties. The test batch results are shown in Table 6 and 7. All films were clear, smooth, non-sticky, removable, and had good stiffness.

Table 12: Optimization Output from Software for Ondansetron MDF

Number	*HPMC E15*	*Honey*	*DT*	*TS*	*DR*	*Desirability*	
1	3.500	2.000	55.984	75.020	107.211	0.999	Selected
2	3.500	2.014	56.216	75.174	107.031	0.997	
3	3.521	2.000	56.733	75.685	106.471	0.990	
4	3.788	2.000	66.331	84.218	96.982	0.813	

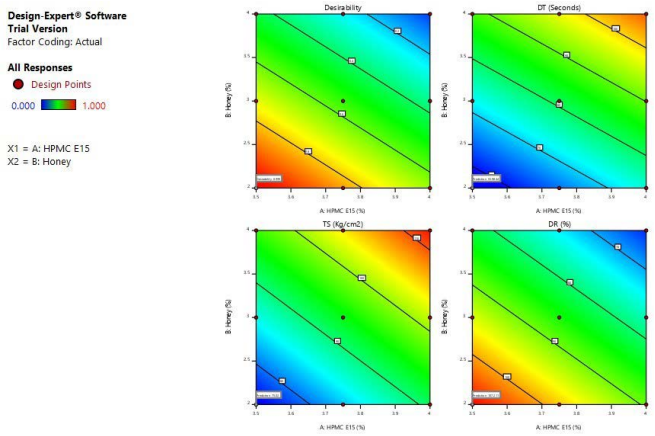

Figure 8: Contour Plot Showing the Desirability of the Selected Design.

Optimization of Excipients[31]

The film former HPMC E15 was chosen for this study because it produces smooth, transparent, and easy-to-peel films. A small amount of PEG 400 was used as a plasticizer and honey was added to modify the properties of the film. Table 8 shows the evaluation results of the placebo film.

Statistical Optimization of Ondansetron MDF[32]

The model selected for the study with the best correlation between dependent and independent variables was determined using software. The best-fitting model was selected based on regression analysis parameters: *p-value*, fitted and predicted R2 values. A value of $p < 0.05$ indicates whether the modal term was significant. ANOVA was performed at the 5% significance level.

Study of Effect of Formulation Variable on Disintegration Time[33]

The 32-aspect design records confirmed that the linear model became the first-class healthy for the Y1 response variable. A precis of the regression evaluation and ANOVA is shown in Table 9. The p-fee become observed to be <0.0001, so the version was labeled as great. The predicted R2 values were in affordable settlement with adjusted R2 values of 0.9224 and 0.9574, respectively. The distinction changed into much less than 0.2. an inexpensive accuracy for measuring the sign-to-noise ratio become determined to be 25.950. version F scored 91 points

Data from ANOVA of response Y1, namely H. H. decay time, showed that the linear model was the best. Table 9 shows the software-generated polynomial for response Y1. As shown in Figures 3 and 4, we found that X1 and X2 were the key factors and had an agonistic effect on the decay time.

Using the contour plots in Figure 2 and the response surface plots in Figure 3, we found that the higher the HPMC E15 and honey concentration, the longer the film degradation time. The factor X2, H. Honey, also significantly impacted the decay time, as shown by the coefficient value of 16.16 for X2 and 9.00 for X1.

Study of Effect of Formulation Variable on Tensile Strength of R MDF[34]

Screening the tensile strength of the 32-factor design data in a trial of Design Expert 11.0 software, a linear model was found to be the best for the Y2 response. H. Indicates tensile strength. A summary of the regression analysis and ANOVA is shown in Table 10. The *p-value* was found to be <0.0001, so the model was classified as significant. The predicted R2 values were in reasonable agreement with approximate R2 values of 0.9934 and 0.9964, respectively. H. The difference was less than 0.2. A reasonable measurement accuracy for the S/N ratio was found to be 93.4195.

Data from ANOVA for response Y2, i. H. Tensile strength, showed the linear model as the best fit model. Table 10 shows the software-generated polynomial for response Y2. X1 and X2 were found to be important factors and have agonistic effects on tensile strength as shown in Figures 5 and 6.

From the contour plots in Figure 6 and the response surface plots in Figure 7, it was found that increasing the concentrations of HPMC E15 and honey increased the tensile strength of the films. Also, the X2 coefficient, or H. As can be seen from the X2 coefficient value of 10.70, it is larger than the X1 value of 8.00.

Study of Effect of Formulation Variables on Drug Release[35-37]

A 32-factor design data for a 9 minute drug release screen in the Design Expert Software 11.0 study showed that a linear model best fit the Y3 response. H. drug release at 9 minutes A regression analysis and ANOVA. The model was found to be significant as the *p-value* was found to be 0.0013. The predicted R^2 value was in reasonable agreement with the adjusted R^2 value of 0.801.

Data from the ANOVA of response Y3, drug release at H. 9 minutes, indicated that the linear model was the best. Polynomials generated by the software for answer Y3. X1 and X2 are found to be significant factors, having an antagonistic effect on drug release as the coefficient estimates of X1 and X2 are negative values of -8.90 and -12.52, respectively.

Optimization Goals[38,39]

The goal for optimizing the ondansetron orally dissolving film was to reduce disintegration time and maximize drug release

from the film. The software provided four solutions (Table 12), one of which gave a desirability of 0.999 and was the lot R1 formulation (Figure 9). Batch R1 was therefore considered to be the best formulation, with the shortest disintegration time and highest drug release.

CONCLUSION

The orally soluble ondansetron film was successfully developed using solvent-casting technology. The combination of HPMC E15 as film former with honey as film modifier and PEG as plasticizer resulted in homogeneous, transparent, stiff and easily peelable films. The experimental design has proven to be a useful utensil for understanding the effects of excipients on film performance.

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