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Optimization of Melt in Mouth Tablets of Palonosetron HCl using 3^2 Full Factorial Design

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ABSTRACT

Palonosetron HCl is a 5HT3 antagonist licensed for the prevention of acute chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy agents (HEC) and the prevention of CINV associated with moderately emetogenic cancer chemotherapy (MEC). It has a substantially longer half-life (Approximately 40 h). So, it was plan to prepare melt in mouth tablet which could rapidly dissolved and absorbed which may produce rapid onset of action. Melt in mouth tablets were prepared by direct compression method using various superdisintegrants like Kyron T314 and Vivasol, and evaluated for pre compression and post compression parameters. A 3^2 full factorial design was applied systematically to optimize responses. The concentration of Kyron T314 (X_1) and concentration of Vivasol (X_2) were selected as independent variables and disintegration time (Y_1) and wetting time (Y_2) as dependent variables. The prepared tablets were evaluated for hardness, friability, disintegration time, wetting time, drug content and *in vitro* drug release. The results indicated that concentration of X_1 and X_2 significantly affected Y1 and Y2. Regression analysis and numerical optimization were performed to identify the best formulation. Similarity (f_2) and dissimilarity (f_1) study for optimized batch was also carried out. Batch P9 was found to be best batch with 10.43 s. disintegration time, 19.53 s. wetting time and 99.02% drug release in 30 min. There was no drastic change in the result of tablets of optimized batch at end of six month accelerated stability study.

INTRODUCTION

Tablet is the most widely used dosage form, because of its convenience in terms of self administration, compactness and unit dose. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have designed innovative drug delivery system known as "Melt in mouth" or "Mouth dissolving (MD)" tablets.

The adoption of the term “Melt in mouth tablet” in European Pharmacopoeia justifies its growing significance. “Melt in mouth tablet” is defined as a tablet to be placed in mouth where it disappears rapidly before swallowing and which disintegrates in less than 3 min (Shaikh *et al*., 2010).

Actually melt in mouth tablets are preferred by an increasing number of patients especially children and elderly, and also adult consumers who like to have their medication readily available at any time. Patients appreciate the convenience and the discreteness of these products which can be taken without water and which guarantee a rapid onset of action. These tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease. As tablets disintegrate in mouth this could enhance the clinical effect of drug through pre gastric absorption from the mouth, pharynx and esophagus (Shrivastava *et al*., 2012). Palonosetron hydrochloride is an antiemetic and anti nauseant agent; selective inhibitor of type 3 serotonergic (5-HT3) receptors, with molecular weight of 332.87g/mol. Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, & slightly soluble in ethanol and 2- propanol.

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It prevents acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Palonosetron hydrochloride is being administered intravenously, as a single dose, 30 min before chemotherapy, or administered as a single oral capsule one h before chemotherapy. (Bodar *et al*., 2011) The objective of the study was to achieve better patient compliance, solve the problems of difficulty in swallowing and enhance onset of action by developing melt in mouth tablets of Palonosetron HCl. The effect of concentration of different super disintegrants such as Kyron T 314, and Vivasol on the tablet properties, disintegration time, wetting time and *in vitro* drug release also considered.

MATERIALS AND METHODS

Materials

Palonosetron HCl was gifted from Intas Pharmaceuticals, Gujarat. Kyron T314 was received as a gift sample from Corel Pharma Chemicals, Ahmedabad. Vivasol and Vivastar were gifted sample from Zhaveri Pharma Chemicals, Mumbai and used as superdisintegrants. Ludiflash and Spray dried lactose were obtained from Signet Chemical Corporation Pvt. Ltd., Mumbai and Foremost Farms USA, respectively. Magnesium stearate and Talc were purchased from S. D. Fine Chemicals, Gujarat.

Drug-excipients compatibility study by DSC

DSC was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60) and operating software (TA 60). The samples (drug alone or mixture of drug and excipients) were heated in sealed aluminum pans at a scanning rate of 5ºC/min from 50 to 300ºC. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the drug and drug-excipient mixture. The physical mixtures of drug with different excipients for compatibility studies were prepared by triturating drug and additives in a dried mortar for 5 min (Kolhe *et al*., 2011).

3^2 Full factorial design

A 3^2 full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The concentration of Kyron T- 314 (X_1) and concentration of Vivasol (X_2) were chosen as independent variables, while disintegration time (Y_1) and wetting time (Y_2) were taken as dependent variables (Table 1). Polynomial equation generated by this design is as follow:

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

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 to b_2 are the regression coefficients. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The response values are subjected to Multiple linear regression analysis (MLRA) to find out relationship between the factors used and response values obtained. After application of full factorial design and with the help of produced polynomial terms, amount of formulation variable was optimized (Patel and Mehta 2014; Patel and Mehta, 2013).

Table 1: Selection of Levels for Independent Variables and Coding of variable.

Levels	Coded value	Independent Variables	
		Conc. of Kyron T-314 (mg) X_1	Conc. of Vivasol (mg) X_2
Low	-1	5	5
Intermediate	0	6	6
High	1	7	7

Preparation of melt in mouth tablets by using 3^2 full factorial design

Palonosetron HCl melt in mouth tablets were prepared by direct compression method according to formula given in Table 2. A total number of nine formulations were prepared as per the standard experimental design protocol. All ingredients were weighed accurately and shifted through sieve no. # 40 and were mixed well to get a uniform mixture expect magnesium stearate and talc. They were sifted through sieve no. # 60, and then mixed with other ingredients. The lubricated directly compressible blend was compressed using rotary tablet punching machine (4 mm punch diameter). The total weight of the formulation was maintained 100 mg.

Table 2: Composition of Factorial Design Batches.

Formulation Ingredients	P1	P12	P13	P4	P5	P6	P7	P8	P9
Palonosetron HCl	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56
Kyron T-314	5	6	7	5	6	7	5	6	7
Vivasol	5	5	5	6	6	6	7	7	7
Spray dried lactose	76	75	74	75	74	73	74	73	72
Ludiflash	8	8	8	8	8	8	8	8	8
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Vanillin	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44
Total weight (mg)	100	100	100	100	100	100	100	100	100

Evaluation of mouth dissolving tablets

Weight variation

Twenty randomly selected tablets were weighed individually and all together. The average weight and the percentage deviation were calculated. The percentage difference in the weight variation should be within the permissible limits (±7.5%) (Bhanja and Hardel 2012). The percentage deviation was calculated using the following formula:

$$\text{Percentage Deviation} = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Individual Weight}}$$

Thickness and diameter

Tablets of each batch were selected and measured for thickness and diameter using verniour caliper (Bhanja and Hardel, 2012).

Hardness

The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using Monsanto hardness tester (Bhanja and Hardel, 2012).

Friability test

The friability of tablets was determined by using Roche Friabilator (Electrolab EF2, Mumbai, India). It was expressed in percentage (%). Five tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W_{final}) (Bhanja and Hardel, 2012). The percentage friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

Drug content

The drug content was carried out by weighing 10 tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to specified weight of Palonosetron and dissolved in 100 ml volumetric flask containing 100 ml of 0.1 N HCl and volume was made to 100 ml with 0.1 N HCl. The volumetric flask was shaken using sonicator and after suitable dilution with 0.1 N HCl, the drug content was determined using UV-Visible Spectrophotometer at 251 nm (Goswami, 2014).

Disintegration time

Disintegration time was measured using disintegration test apparatus (Electrolab ED-2L, Mumbai, India). Place 1 tablet in each of the six tubes of the basket, insert disc and operate the apparatus for the specified time, using distilled water maintained at 37 ± 2°C as the immersion fluid.

Note down the time in second when tablets disintegrate completely. The tablet complies with the test if all six have disintegrated. If one or two tablet fails to disintegrate completely repeat the test on 12 another tablets. From total 18 tested tablets, 16 tablets should comply the test i.e. should disintegrate completely. (Reddy *et al*., 2011)

Wetting time

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petri dish with a 10 cm diameter. 10 ml of 0.1 N HCl was poured into the tissue paper placed in the petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. (Reddy *et al*., 2011)

***In vitro* dissolution study**

The developed formulations of Palonosetron HCl were subjected to release studies using USP-II dissolution apparatus (Electrolab TDT-06 P, Mumbai, India) at 50 RPM. Dissolution medium used was 500 ml 0.1 N HCl maintained at 37 ± 0.5°C, which was found to provide sink conditions. The 5 ml samples were withdrawn at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples, after filtration through 0.45-mm nylon membrane filters, were analyzed using a validated UV spectroscopic method at 251 nm (Goswami, 2014).

***In vitro* evaluation of bitter taste of drug**

An accurately weighed tablet and 10 ml of 0.1 N HCl was taken in volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals, dispersion was filtered and the concentration of Palonosetron HCl in filtrate was determined. Time for tablet to achieve drug concentration corresponding to threshold bitterness in 10 ml 0.1 N HCl is recorded (Patil *et al*., 2013; Kandliya *et al*., 2013).

Statistical analysis

Statistical Analysis of the 3^2 factorial design batches was performed by multiple regression analysis using Microsoft excel. To evaluate the contribution of each factor with different levels to the response, the two- way analysis of variance (ANOVA) was performed using the Design Expert 8.0.5.2 (STAT – EASE) demo version software. To graphically demonstrate the influence of each factor on the response, the response surface plots, Normal plot of residual, Two- Dimensional counter plot, 3-D graph, and overlay plot, were generated using the Design Expert 8.0.5.2 (STAT – EASE) demo version software (Patel and Mehta, 2014; Patel and Mehta, 2013).

Checkpoint analysis

A check point analysis was performed to confirm the role of the derived polynomial equation and counter plots in predicting the responses. Values of independent variables were taken at 3 points, 1 from each counter plot, and the theoretical values of disintegration time and wetting time were calculated by substituting the values in the polynomial equation. The tablets were formulated using the chosen optimal composition and

evaluated for disintegration time and wetting time. The observed and predicted responses were critically compared (Patel and Mehta, 2014; Patel and Mehta, 2013).

Optimization of formulation

The optimization formulation was obtained by applying goals on dependent and independent variables. The models were evaluated in terms of statistically significant coefficients and R^2 values. Various feasibility and grid searches were conducted to find out the optimum parameters. Various 3D responses surface graphs were provided by the Design Expert 8.0.5.2 (STAT – EASE). The optimized formulation factors were evaluated for various parameters (Patel and Mehta, 2014; Patel and Mehta, 2013).

Similarity and dissimilarity study

Comparison between innovator product and test batches was done using two statistical factors called difference factor (f_1) and similarity factor (f_2) (Kattamuri *et al*., 2013; Sumudeepthi *et al*., 2014).

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles of products were compared using f_2. The similarity factor is calculated by following formula.

$$f_2 = 50 \text{ X } \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} w_t \left(R_t - T_t \right)^2 \right]^{-0.5} \text{X } 100 \right\}$$

Where, n = No. of time points

Rt = The reference profile at the time point t

Tt = The test profile at the same point

The difference factor (f1) calculate the percentage difference between two profiles i.e. innovator dissolution profile and test sample dissolution profile at each sampling points and corresponds to a relative error measure between the two profiles.

$$f1 = (\Sigma \, |R\text{-}T| \, / \, \Sigma \, R) * 100$$

Where,

|R-T|- Absolute difference of % drug released at each time points between innovator or reference product & test product

R- % drug released of reference product at each time points

f1 value should be less than 15 ideally it should be as close as possible to 0.

Accelerated stability studies

Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists deterioration. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Deterioration of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2ºC/ 75 ± 5 % RH for time period of 6 Months in stability chamber (Thermo lab stability chamber, Mumbai, India).

Tablets were evaluated for disintegration time, wetting time, drug content and for in-vitro dissolution study and were compared with initial tablets results.

RESULT AND DISCUSSION

Drug excipients compatibility study by DSC

DSC thermogram of drug exhibits sharp peak at 88.18°C as shown in Fig. 1. The thermal analysis study of Palonosetron HCl and excipients clearly suggest that there is no interaction of the drug with superdisintegrants and excipients.

Characterization of melt in mouth tablets

Weight Uniformity

Weight variation of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value.

Thickness and Diameter

Thickness and diameter of all the tablets were found in the range 2.30 ± 0.31 to 2.36 ± 0.24 mm and 3.98 ± 0.02 to 4.02 ± 0.01 mm respectively.

Hardness and Friability

Hardness of the prepared tablets was observed within the range of 4.98 ± 0.42 to 5.15 ± 0.31 kg/cm^2. Friability of all the tablets was found below 1%.

Drug Content

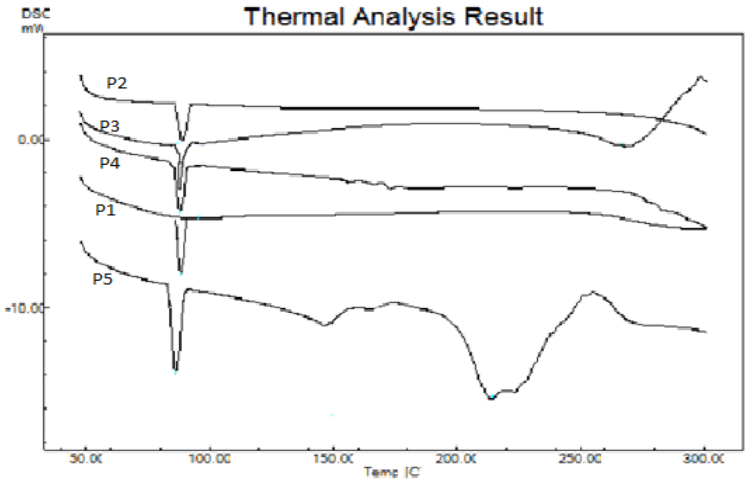
The drug content in all the tablets was in the range of 96.12 ± 0.53 % to 99.54 ± 0.58 % as shown in Table 3. This ensured the uniformity of the drug content in the tablets.

Disintegration Time and Wetting Time

Disintegration time is very important for melt in mouth tablets which desired to be less than 60s for orally disintegration. Disintegration time in all the batches was found in the range of 10.43 ± 2.37 to 13.49 ± 2.46s and wetting time was found in the range of 19.53 ± 2.41 to 24.34 ± 2.87s (Table 3). Wetting time is used as an indicator from the ease of the tablet disintegration in buccal cavity.

Table 3: Post compression Evaluations of Batches P1 to P9.

Batch	Diameter (mm) (n = 5)	Thickness (mm) (n = 5)	Hardness (kg/cm$^{2)}$ (n = 5)	Disintegration time (s) (n = 6)	Wetting time (s) (n = 3)	Friability (n=5)	Weight Variation (n=20)	Drug Content (n = 10)
P1	3.99 ± 0.01	2.31 ± 0.22	5.15 ± 0.31	13.23 ± 2.31	24.34 ± 2.87	0.36 ± 0.04	100.02 ± 3.51	97.12 ± 0.43
P2	4.01 ± 0.01	2.35 ± 0.23	5.10 ± 0.62	12.59 ± 2.34	23.24 ± 2.54	0.43 ± 0.03	97.84 ± 3.56	98.32 ± 0.45
P3	3.98 ± 0.02	2.36 ± 0.24	5.02 ± 0.41	11.47 ± 2.87	21.47 ± 2.41	0.87 ± 0.05	98.42 ± 3.56	96.12 ± 0.53
P4	4.01 ± 0.02	2.33 ± 0.27	4.99 ± 0.32	13.49 ± 2.46	23.43 ± 2.54	0.65 ± 0.03	97.21 ± 3.77	96.13 ± 0.21
P5	3.99 ± 0.02	2.31 ± 0.28	5.11 ± 0.21	11.54 ± 2.45	20.32 ± 2.87	0.05 ± 0.75	97.32 ± 2.41	96.21 ± 0.34
P6	3.99 ± 0.02	2.34 ± 0.26	5.12 ± 0.22	11.41 ± 2.54	20.42 ± 2.14	0.83 ± 0.04	98.18 ± 2.56	98.87 ± 0.49
P7	4.02 ± 0.01	2.30 ± 0.31	4.98 ± 0.42	12.38 ± 3.12	22.32 ± 2.43	0.43 ± 0.03	102 ± 2.45	97.25 ± 0.56
P8	4.01 ± 0.02	2.32 ± 0.34	5.11 ± 0.31	11.58 ± 3.21	20.32 ± 2.32	0.98 ± 0.05	99.43 ± 2.56	97.34 ± 0.43
P9	4.01 ± 0.02	2.33 ± 0.21	5.14 ± 0.21	10.43 ± 2.37	19.53 ± 2.41	0.71 ± 0.04	100.31 ± 2.45	99.54 ± 0.58
Marketed Product	6.1 ± 0.01	2.30 ± 0.21	5.0 ± 0.31	11.28 ± 2.43	19.49 ± 2.32	0.56 ± 0.03	100.32 ± 2.43	99.01 ± 0.61



P1 = Palonosetron HCl, P2= Palonosetron HCl + Kyron T-314, P3= Palonosetron HCl + Vivasol, P4 = Palonosetron HCl + Ludiflash, P5 = Palonosetron HCl + Spray dried lactose.

Fig. 1: Drug – Excipients Compatibility Study by DSC.

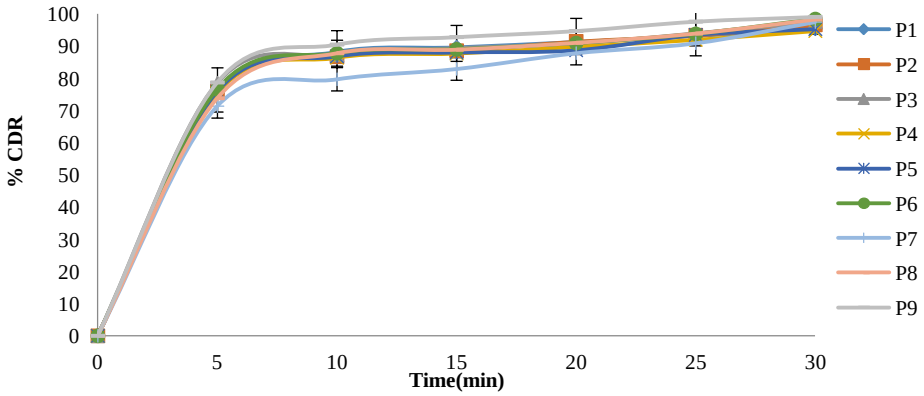


Fig. 2: % Drug Release of Batches P1 to P9.

In-Vitro Dissolution Study of Factorial Batches P1 to P9

Batches P1 to P9 were prepared using different concentrations (5%, 6%, and 7%) of Kyron T -314 and Vivasol as superdisintegrants. *In vitro* drug release study (Fig. 2) of these batches indicated that batches P1 to P3 containing 5%, 6%, and 7% of Kyron –T 314 and 5 % of Vivasol has shown 95.32 % to 97.63 % drug release. While batches P4 to P6 containing 5%, 6%, and 7% of Kyron –T 314 and 6 % of Vivasol has shown 94.63 to 98.36% drug release within 30 min. Compared to these batches, batches P7 to P9 containing 5%, 6%, and 7% of Kyron –T 314 and 7 % of Vivasol has shown 98.21 to 99.12 % drug release within 30 min. From the results, it was concluded that batch P9 containing 7% of each super disintegrant has shown less disintegration time as well as good drug release. So, this batch was considered as optimized batch from all the batches.

In vitro Evaluation of Bitter Taste

The time for this threshold bitterness concentration to be achieved in buffer of salivary pH showed that the drug is not released in saliva to attain threshold bitterness concentration there by masking the bitter taste satisfactorily.

Statistical analysis

The experimental runs with independent variables and corresponding responses for the 9 formulations are presented in Table 4.

Table 4: Result of Effect of Independent variables on Responses.

Batch code	Independent variables		Dependent variables	
	X_1	X_2	Y_1	Y_2
P1	5	5	13.23	24.34
P2	6	5	12.59	23.24
P3	7	5	11.47	21.47
P4	5	6	13.49	23.43
P5	6	6	11.54	20.32
P6	7	6	11.41	20.42
P7	5	7	12.38	22.32
P8	6	7	11.58	20.32
P9	7	7	10.43	19.53
X_1 = Conc. of Kyron T -314 (mg)			Y_1 = Disintegration Time (s)	
X_2 = Conc. of Vivasol (mg)			Y_2 = Wetting Time (s)	

Table 5: Results of ANOVA for Full and Reduced Models.

ANOVA for Response Y_1					
ANOVA	**DF**	**SS**	**MS**	**F value**	**P value**
Regression					
Full model	5	7.132492	1.426498	7.464561	0.064351
Reduced model	3	0.573308	0.191103	-	-
Residuals					
Full model	4	7.07842	1.76951	11.27511	0.018829
Reduced model	4	0.627758	0.15694	-	-
ANOVA for Response Y_2					
Regression					
Full model	5	21.66087	4.332173	10.26798	0.041877
Reduced model	3	1.2657	0.421911	-	-
Residuals					
Full model	5	21.66087	4.332173	10.26798	0.041877
Reduced model	3	1.265733	0.421911	-	-

Corrected text: ANOVA indicates analysis of variance; Df, degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio.

The dependent variables were the disintegration time (Y_1), and wetting time (Y_2). Based on the 3^2 factorial design, the factor combinations resulted in different results. Various models, such as linear, 2FI, quadratic and cubic, were fitted to the data for these responses simultaneously using Design Expert software and adequacy and good fit of the model was tested using analysis of variance (ANOVA). The multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS) provided by Design-Expert software were used as factors for selection of adequate models. Results of ANOVA for response disintegration time (Y_1) and wetting time (Y_2) are listed in Table 5.

A mathematical relationship in the form of polynomial equation for disintegration time and wetting time are as follows:

$Y_1 = 11.71 - 0.965X_1 - 0.32X_2 + 0.1975\ X_1 X_2 + 0.165X_1^2 + 0.29\ X_2^2$

$R^2 = 0.9240$

$Y_2 = 20.67 - 1.445X_1 - 0.9983X_2 + 0.2425X_1 X_2 + 0.625X_1^2 + 0.925\ X_2^2$

$R^2 = 0.9262$

The r^2 was high indicating the adequate fitting of the linear model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative. The negative coefficient of variable X_1 i.e. concentration of Kyron T314 and X_2 i.e. concentration of Vivasol in case of responses i.e. disintegration time (DT) and wetting time (WT) indicates that, as the Kyron T314 and Vivasol concentration was increased, the DT and WT was decreased. The data clearly indicate that the dependent variables are strongly dependent on the independent variables. The relationship between the variables was further elucidated by using the response surface plot (Fig. 3 & 4). A high level of factor X_1 and X_2 gave a least disintegration and wetting time. The "Pred R-Squared" is close to the "Adj R-Squared" as one might normally expect. This may indicate a good fitting of the model. The faster disintegration time and wetting time of Kyron T314 and Vivasol may be attributed to its rapid disintegration property.

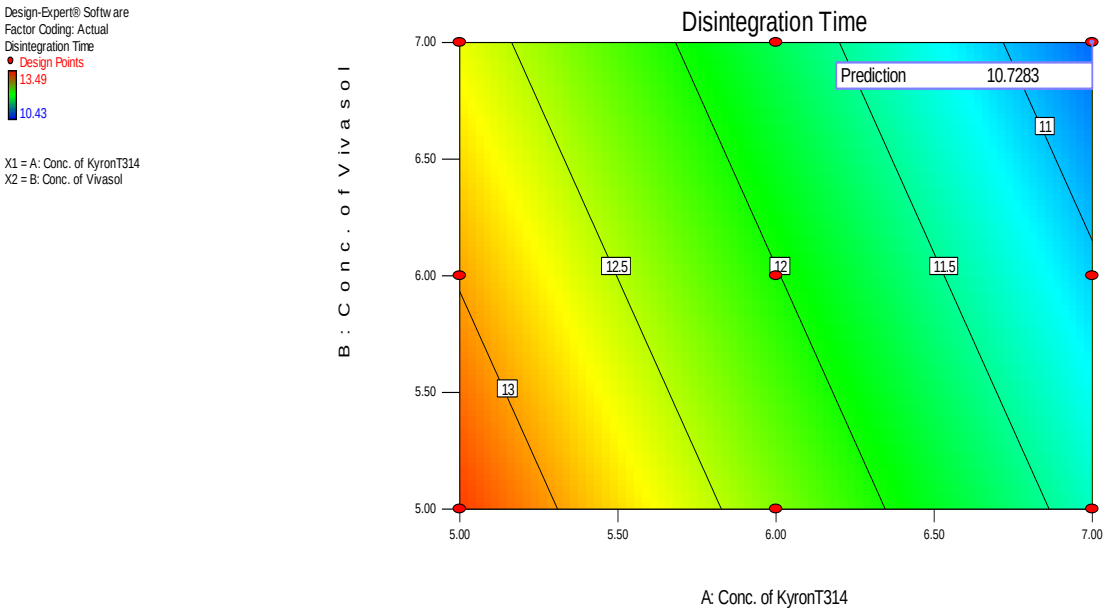


Fig. 3:..

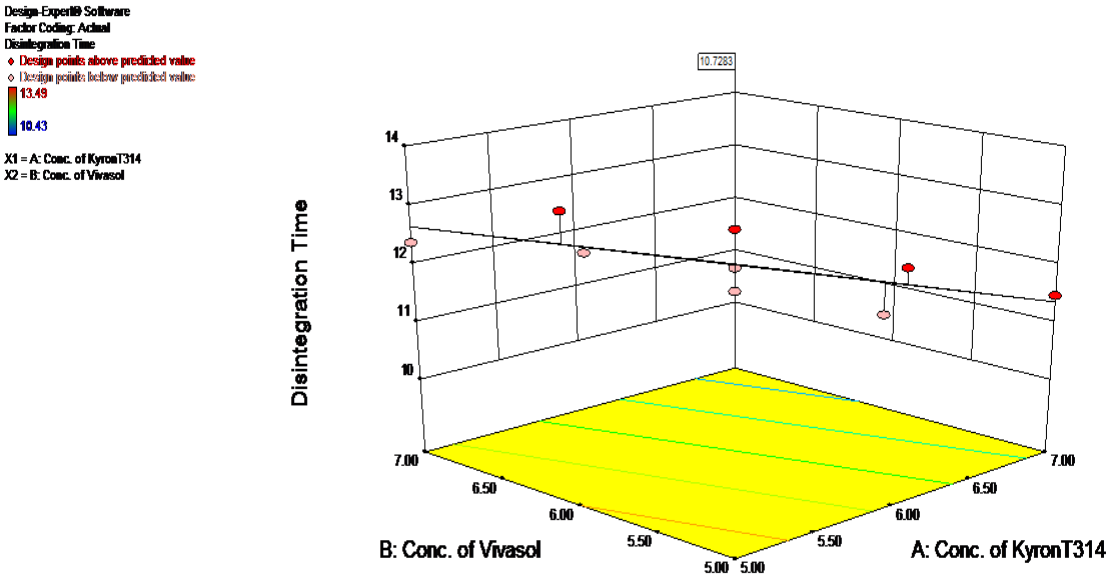


Fig. 3: (A) Contour plot and (B) 3D Graph showing effect of Kyron T- 314(X_1) and Vivasol (X_2) on Disintegration Time (Y_1)

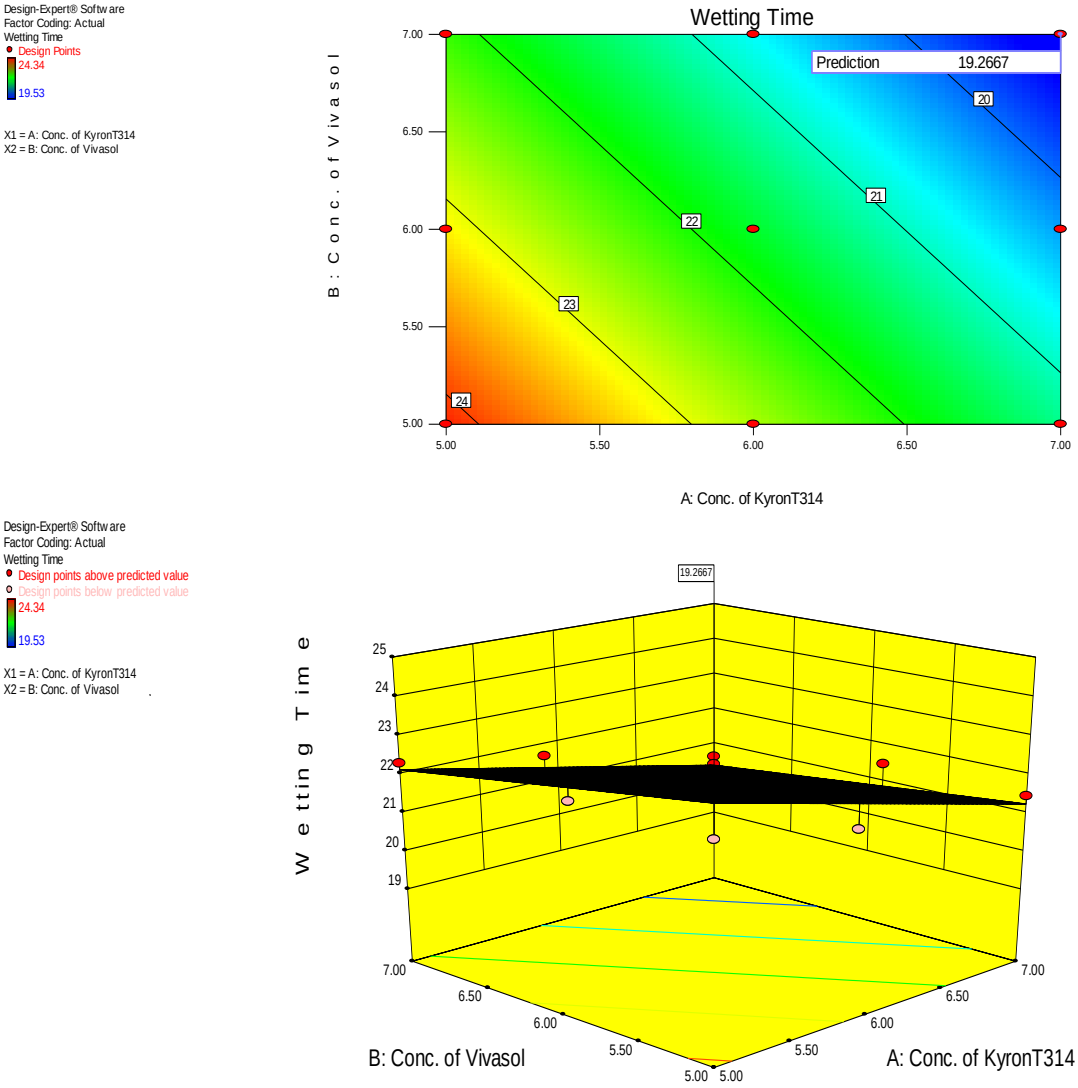


Fig. 4: (A) Contour plot and (B) 3D graph showing effect of Kyron T- 314(X_1) and Vivasol (X_2) on Wetting Time (Y_2).

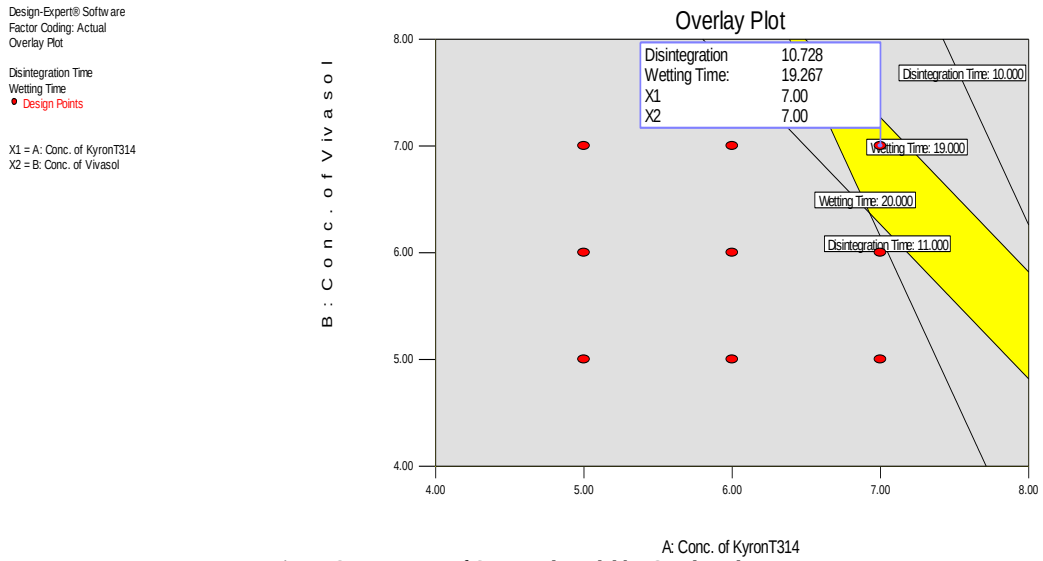


Fig. 5: Optimization of Statistical Model by Overlay Plot.

Check point analysis

Three check point batches were prepared and evaluated for disintegration time and wetting time as shown in Table 6. Results indicated that measured values matches well with expected values. When measured disintegration time and wetting time values were compared with predicted disintegration time and wetting time values, the difference were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicted values.

Table 6: Checkpoint batches with predicted and measured Disintegration Time and Wetting Time.

Batch code	X_1	X_2	Disintegration time (Y_1)		Wetting time (Y_2)	
			Measured	Predicted	Measured	Predicted
P10	0	0.5	11.54	11.62	20.27	20.40
P11	0.5	1	11.23	11.23	20.02	20.14
P12	1	0.5	10.81	10.92	19.59	19.69

Optimization of formulation

An optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. The optimum formulation was selected based on the criteria of attaining minimum disintegration time and wetting time and desirability was kept at 1. Upon "trading off" various response variables, constraints like minimizing the disintegration time and wetting time were set at appropriate limits and importance. Upon comprehensive grid searches, the formulation composition with 7mg of Kyron T -314, and 7mg of Vivasol fulfilled maximum requisites of an optimum formulation because of less disintegration time and wetting time.

Similarity and dissimilarity study

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. The standard for similarity factor and dissimilarity factor are 50-100 and 0-15. The similarity factor obtained is 89.84 which was between 50 to 100 and dissimilarity factor is 3.10 which was between 0 to 50. The similarity and dissimilarity factor obtained for Palonosetron HCl was found to be within the standards. So, it is concluded that the optimized batch P9 is similar to the marketed product (EME-OD).

Stability study

Stability study of melt in mouth tablet of Palonosetron HCl was carried out for 6 Months at specified condition using thermolab stability chamber. All data are mentioned in table 7. The stability studies of the optimized formulation (P9) shown no significant changes in the disintegration time, wetting time, % drug content and % drug release in 30 min. when stored at temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH. So, it was considered that formulation having good stability.

Table 7: Stability Study of Optimized Formulation (P9) carried out at 40 ± 2°C/ 75 ± 5 % RH.

No. of Months	Disintegration Time (sec)	Wetting Time (sec)	%Drug Content	% Drug release in 30 min
0	10.43 ± 2.37	19.53 ± 2.41	99.43 ± 2.03	99.30 ± 2.45
6	10.31 ± 2.42	19.32 ± 2.31	99.38 ± 2.43	99.12 ± 2.91

All values are expressed as mean ± standard deviation, n=3

CONCLUSION

Palonosetron HCl has been used for the prevention of nausea and vomiting associated with cancer chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) is an important adverse effect to control in cancer patients. It can impair patient's quality of life, cause dehydration, electrolyte imbalances, malnutrition and may result in refusal of treatment. Melt in mouth tablets containing Palonosetron HCl were prepared by direct compression method using various superdisintegrants like Kyron –

T 314 and Vivasol. These superdisintegrants were used in different concentrations. Sweetening agents like Ludiflash was evaluated. Results of formulation studies of the Palonosetron HCl indicate that, it has good flow property and compressibility property. Drug excipient compatibility study also confirms that there was no interaction between drug and excipients. 3^2 full factorial design was prepared using different concentrations (5%, 6% and 7%) of superdisintegrants, Ludiflash as sweetening agent and vanillin as flavoring agent for removing the bitterness of drug. Among the different formulations prepared in this study, batch P9 containing 7 % of Kyron T- 314 and Vivasol as superdisintegrants agent has shown better disintegration time, wetting time and drug release profile. There was no significant variation in drug assay and release profile of Palonosetron HCl, during stability studies of batch P9 in accelerated conditions over the period of six month.

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REFERENCES

Bhanja S, Hardel DK, Sudhakar M. Mouth dissolving tablets of losartan potassium: formulation and evaluation. Int J Pharma Sci Res, 2012; 3(9): 3444-3453.

Bodar J, Yadav YC, Kumar S. Development of the chromatographic method for the estimation of palonosetron in palonosetron hydrochloride injection. Int J Pharma Sci, 2011; 2(3): 24-31.

Goswami KK. M. Pharm Thesis, Development and evaluation of melt in mouth tablets of palonosetron. Gujarat Technological University. April 2014.http://www.drugs.com/ppa/palonosetron-hydrochloride.html [Accessed Date: 20th November 2014]. http://en.m.wikipedia.org/wiki/Palonosetron [Accessed Date: 20th November 2014].

Kadliya PN, Chauhan KV, Patel KN, Patel PA. Comparison and evaluation of bitter taste masked Levocetrizine diHCl using β-Cyclodextrin and Kyron T-114. Int J Pharma Res Scholars, 2013; 2(2): 114-124.

Kattamuri SB, Mogili R, Potti L, Bandi V, Prasada Rao M. Formulation and evaluation of Zafirlukast oral disintegrating tablets. Int J Uni Pharm and Bio Sci, 2013; 2(5): 87-101.

Kolhe SR, Chaudhari PD, More DM. Development and evaluation of melt-in-mouth tablets by sublimation technique. Int J Pharma Sci Res, 2011; 2(1): 65-76.

Patel KN, Mehta TA. Formulation design and characterization of an elementary osmotic pump tablet of Flurbiprofen. PDA J Pharm Sci and Tech, 2014; 68: 333-346.

Patel KN, Mehta TA. Development and optimization of elementary osmotic pump tablet of Nicardipine Hydrochloride using central composite experimental design. Int J Drug Dev & Res, 2013; 5(3): 382-395.

Patil SM, Ghatge GA. Review on taste abatement techniques. Int J of Inst Pharm Life Sci, 2013; 3(5): 43-67.

Reddy B, Sai Ram S. Rapimelts: A Review, J. Pharma Biomed. Sci, 2011; 6(10): 1-8.

Shaikh S, Khirsagar RV, Quazi A. Fast disintegrating tablets: an overview of formulation and technology. Int J Phar Pharma Sci, 2010; 2(3): 1-20.

Shrivastava S, Bala R, Joshi AC, Single V. Mouth dissolving tablets: A future compaction, Int Res J Pharm, 2012; 3(8): 98-109.

Sumudeepthi B, Nagaraju G, Ramakotaiah M, Rao MP. *In vitro* evaluation of newly formulated Metaxolone tablets for immediate release by wet granulation technique. Int J Innovative Pharma Sci and Res, 2014; 2(10): 2425-2437.

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