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Design, Optimization and Evaluation of Orally Disintegrating Tablet of Antiemetic Drug

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ABSTRACT

This work describes Design, Optimization & Evaluation of Orally Disintegrating Tablet (ODT) of Antiemetic Ondansetron HCl. The bitter taste of the drug was masked by Kyron T 114, a weak cation exchange resins with the method of ion exchange resin complexation, Which was prepared by the batch technique and resin ratio & pH was optimized to successfully formulate the resinate into ODT and it was confirmed by FTIR and DSC study. In preliminary trials selection of superdisintegrants (i.e., crosspovidone XL 10, cross carmellose sodium and sodium starch glycolate) and selection of diluent (i.e. mannitol SD 200, Avicel pH 102 Avicel pH 112, Starch and pregelatinized starch) were made. The cohesive force of mannitol increase wetting time and disintegration time so drug release was delayed. 3^2 factorial design was applied in which superdisintegrant and diluent ratio were taken as independent factor and disintegration time and wetting time were taken as response. The prepared tablets were evaluated for weight variation, hardness, friability, disintegration time, content uniformity, and % drug release. Dissolution studies were performed in 0.1 N HCl. The optimized batch was compared with the marketed formulation and charged for stability study. Results from an evaluation by a panel of ten human volunteers demonstrated that the orally disintegrating tablets prepared by Kyron T 114 improved the taste significantly. In 3^2 full factorial design, Quadratic model was suggested and contour and 3D Graph was generated. By using Overlay plot batch was optimized. ODT prepared with 9.92 % crosspovidone XL 10 and 27.32:44.46 Mannitol: Avicel pH 112 ratio decrease DT and Wetting time i.e. 13 and 19 second respectively, produced tablet with desired properties and showed satisfactory drug release profile.

KEYWORDS

Orally disintegrating tablets; Ondansetron HCl; Taste masking; Kyron T 114; Drug Resin Complex; Superdisintegrants; 3^2 full factorial Design.

INTRODUCTION

Recently, ODTs have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patient life, which includes dysphasic, bed ridden, psychic, geriatric and pediatric patients, who have difficulty in swallowing conventional tablets and capsules.

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The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue[2]."

Ondansetron HCl is a potent antiemetic drug indicated for the treatment and/or prophylaxis of postoperative or chemotherapy or radiotherapy induced emesis and also used in the early onset of alcoholism[3]. Ondansetron HCl is a selective

serotonin 5-HT3 receptor antagonist. The antiemetic activity of the drug is brought about through the inhibition of 5-HT3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract).This inhibition of 5-HT3 receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone[4,5]. Ondansetron HCl is an intensely bitter drug; hence, in the present study an attempt has been made to mask the taste of ondansetron HCl and to formulate orodispersible with good mouth feel so as to prepare a "patient friendly dosage form."

Ion Exchange Resin (IER) are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking[6]. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected. In this study, Kyron T 114 is used as taste masking agent. Kyron T114 is weak cation exchange resin derived from crosslinked polymer of Methacrylic acid and has carboxylic acid functionality which is enables its use as a taste masking agent. [7,8,9]

MATERIALS AND METHODS

Materials

Ondansetron Hydrochloride and all excipients were gifted by Cadila Healthcare Ltd, Ahmedabad, Gujarat. Ion Exchange Resin Kyron T 114 was gifted by Corel Pharma Chem, Ahmedabad.

Methods

Drug excipients Compatibility study by FTIR

FT-IR spectrum of the Powder mixture containing drug and excipients was obtained by using FTIR Spectrophotometer. A Pellet of the powder blend prepared with KBr (Spectroscopic Grade) using hydraulic pellet pressure at a pressure of 7-10 tones. The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Taste Masking by Formation of Complexes with Ion Exchange Resin [10]

Batch Technique

100 mg of Kyron T 114 was allowed to swell separately in 100 ml of deionized water for 60 minute on a Magnetic Stirrer at moderate speed. 100 mg of Ondansetron HCl was added to each of them and stirred for 4 hrs. Slurry was filtered and the residues i.e. resinate or drug resin complex (DRC) was washed again with 25 ml of deionized water. The combined filtrate was evaluated for drug content. The difference between amount of drug used initially and that remaining in the filtrate is the amount of drug loaded on the resin.

Optimization of various parameters for maximum drug loading[11]

Drug loading process was optimized for maximum drug loading considering parameters like effect of activation, drug: resin ratio and pH.

Resin Activation

24 mg of resin, placed on a Whatmann filter paper in a funnel, was washed with deionized water and subsequently with 1N HCl (100 ml). The resin was rewashed with water until neutral pH was reached. DRC was prepared by in the same way as discussed earlier using 100 mg each of Ondansetron HCl and acid activated resin. Similarly, alkali activation of resin was done, replacing 1 N HCl with 1 N NaOH. Finally, Kyron T 114 was also activated with combined treatment of 1 N HCl and 1 N NaOH solutions. Drug loading efficiency in each case was determined.

To study the effect of other parameters, activated resin was used.

Optimization of drug: resin ratio

100 mg of Ondansetron HCl was added to each of the five beakers containing 100, 200, 300, and 400 mg of resin swelled in 100 ml of deionized water. The mixture was stirred for 4 hr. DRC was collected by filtration, washed with 50 ml of deionized water and evaluated for drug content.

Optimization of pH

pH was optimized by preparing DRC using 100 mg each of Ondansetron HCl and 300 mg resin in 100 ml of deionized water and adjusting pH like 1.2, 2, 3, 4, 5, 6, 7, and 8 using standard solutions of hydrochloride and sodium hydroxide. Loading efficiency was determined at these conditions.

Characterization of DRC[12]

***In-vivo* taste evaluation**

The time intensity method were used. A panel of ten healthy human volunteers was selected for the study. Each volunteer held a quantity of DRC equivalent to 4 mg of Ondansetron HCl in oral cavity for 30 seconds. The taste of the DRC was reported by them immediately, then after 5, 10, 15, 30, 60, 120, and 180 seconds on the scale described earlier.

Confirmation of complexation

FTIR studies

Ondansetron HCl, Kyron T 114, and DRC were subjected for FTIR studies. Samples were prepared using KBr disc method and spectra were recorded over the range 500 cm^{-1} to 4500 cm^{-1}. Spectra were analyzed for drug- resin interactions and functional groups involved in the complexation process.

Thermal analysis

Differential scanning calorimetry (DSC) was performed using Mettler Toledo STAR^{e}SW 8.10 instrument equipped with intra cooler. Indium zinc standards were used to calibrate the temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated over the temperature range 40 °C to 220°C with heating rate of 10.00 °C/min. inert atmosphere was provided by purging nitrogen gas flowing at 90 ml/min.

Estimation of drug content

16 mg of DRC was stirred with 100 ml of 0.1 N HCl for 60 min so as to release the entire drug from DRC. The mixture was filtered and 1 ml of the filtrate was diluted to 10 ml using 0.1N HCl. The absorbance of this solution was measured at 310 nm using 0.1 N HCl as blank and the content of Ondansetron HCl was estimated.

***In-vitro* drug release study**[13]

DRC equivalent to 4 mg of Ondansetron HCl was subjected to dissolution studies using USP Type I dissolution test apparatus at 37±2°C at 50 rpm speed. 500 ml of 0.1 N HCl was used as dissolution medium. Here, DRC equivalent to 4 mg of Ondansetron HClwas placed in basket surrounded by muslin cloth which retained the formulation. Aliquot equal to 5 ml was withdrawn after every 2 Min. intervals (For total 10 Min.) and amount of Ondansetron HCl released from DRC was determined at 310 nm.

Formulation Development of Orally Disintegrating Tablets of Ondansetron Hcl [14]

Selection of superdisintegrant and diluent[15]

In preliminary trial batches, different concentrations i.e. 2, 4, 6 and 8 % of Crospovidone XL 10, sodium starch glycolate, Croscarmellose sodium were screened. Based on the objective of the work, different diluents like Starch, Pregelatinised starch Avicel pH 102, Avicel pH 112 with Mannitol SD 200 in ratio of 1:1, were evaluated.

Method: Direct Compression[16,17]

Composition of tablets is mentioned in Table 1and 2. DRC and other materials except Aerosil and Magnesium Stearate were passed through sieve no. 40. Prepared blend is lubricated with Aerosil and Magnesium Stearate which is previously passed through sieve no. 80. Tablets were compressed using 8/32 mm flat punch on 8 station (D-tooling) Compression machine. Tablet weight was maintained at 100 mg.

Evaluation of Orally Disintegrating Tablet [18]

Weight variation

Weight variation was calculated as per method descried in Indian Pharmacopoeia (I.P. 1996). 20 tablets were weighed individually and the average weight is calculated.

Hardness

Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

Thickness

Ten Tablets were selected at random from individual formulations and thickness was measured by using Vernier caliper scale, which permits accurate measurement.

Friability (%F)

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability:

$$\%F = 1-(\text{loss in weight}/\text{initial weight})* 100$$

Disintegration time

In a simplest method, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37 ± 2 °C. ODT was put into it and time required for complete disintegration of the tablet was noted.

Wetting time[19]

A Petri dish containing 6 ml of distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. A small quantity of amaranth red color was put on the upper surface of the tablet. Time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet.

Drug content

Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 4 mg of Ondansetron HCl was dissolved in 100 ml of 0.1 N HCl, stirred for 60 min and filtered. 1 ml of the filtrate was diluted to 10 ml with 0.1 N HCl. Absorbance of this solution was measured at 310 nm using 0.1 N HCl as blank and content of Ondansetron HCl was estimated.

In Vitro drug release study[20]

Dissolution test was carried out using USP Type II dissolution test apparatus at37±2°C and 50 rpm speed. 500 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 ml was withdrawn after every 2 Min. intervals (For total 10 Min.) and amount of Ondansetron HCl released from tablets was determined at 310 nm.

Full Factorial Design [21,22,23]

A 3^2 Factorial design was chosen for the current formulation optimization study. In this design two factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combination. In the preliminary trial runs, 8 % Crospovidone XL 10 and 36.85:36.85 Mannitol SD 200: Avicel pH 112 ratio showed good results. So these levels were selected and subjected to further optimization. Ratio of: Mannitol SD 200: Avicel pH 112 and Crospovidone XL 10 were selected as independent factors whereas disintegration time (DT) and wetting time (WT) were measured as responses. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign. The responses were analyzed for ANOVA using Design Expert version 8.7.1. A mathematical equation was generated for each response parameter. The mathematical models were tested for significance. Response surface plots were generated for each response to study the behavior of the system.

Table: 1 3^2 Full Factorial Design Layout for factorial Batches

Run	Independent Variable in coded form		Independent Variable in actual form		Dependent variable	
	Factor 1	**Factor 2**	**Superdisintegrant conc. (%)**	**Mannitol SD 200 : Avicel pH 112 ratio (mg)**	**Disintegration Time (Sec.)**	**Wetting time (Sec.)**
1	+1	+1	10	55.28:18.42	19	23
2	+1	0	10	36.85:36.85	14	21
3	+1	-1	10	18.42:55.28	10	16
4	0	+1	8	55.28:18.42	25	30
5	0	0	8	36.85:36.85	21	26
6	0	-1	8	18.42:55.28	18	22
7	-1	+1	6	55.28:18.42	34	38
8	-1	0	6	36.85:36.85	30	34
9	-1	-1	6	18.42:55.28	26	30

Table: 2 Formulation of Factorial Design FT1-FT9 Batches

Ingredients (mg)	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Drug Resin complex	16	16	16	16	16	16	16	16	16
Crosspovidone XL 10	10	10	10	8	8	8	6	6	6
Mannitol SD 200	55.28	36.85	18.42	55.28	36.85	18.42	55.28	36.85	18.42
Avicel pH 112	18.42	36.85	55.28	18.42	36.85	55.28	18.42	36.85	55.28
Mg. Stearate	1	1	1	1	1	1	1	1	1
Aerosil	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Aspartame	1	1	1	1	1	1	1	1	1
Total Weight	100	99	100	101	101	100	99	101	99

Validation of statistical model [24]

From overlay plot of responses,optimized formulation was selected as checkpoint to validate RSM. The tablets were formulated using chosen optimal composition & evaluated for DT & WT.

Stability study of optimized batch [25]

Stability study was carried out for the optimized formulation for 40° C / 75% RH for 1 months and 15 days and samples were withdrawn at the end of 0, 2, 4 and 6 week and evaluated for active drug content, disintegration time and *in-vitro* drug release.

RESULTS AND DISCUSSION

Drug excipients compatibility study by FTIR

It was found that there was no interaction of the excipients with the drug .The characteristic peaks of Ondansetron HCl (N-Hstretch at 3379.05 cm^{-1}, C-H stretch at 2985.60 cm^{-1}, O-H stretch at 3494.77 to 3294.19 cm^{-1}, C-O stretch

at 1639.38 cm^{-1} and C-C stretching at 3174.61, 2985.60) were not affected. The FTIR spectra of physical mixture retain all the peak of pure drug. So there was no significant shift in peak corresponding to the drug were observed.

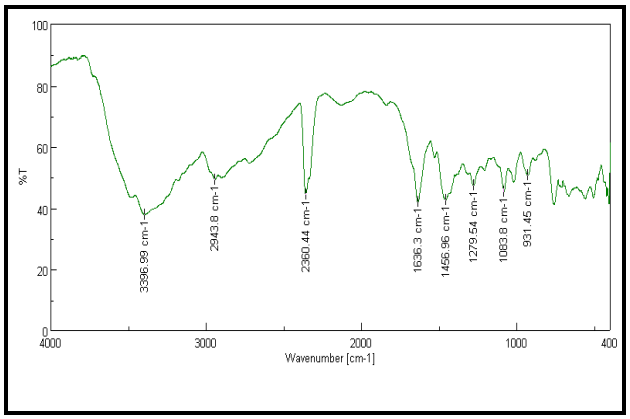

Figure: 1 FTIR of Ondansetron HCl + Physical Mixture

Optimization of various parameters for maximum drug loading

Optimization of Resin Activation and Drug: Resin ratio

Acid-Alkali combined treated 1:3 ratio gave optimum drug loading i.e. 99.91 % because impurities associated with industrial scale manufacture or absorbed during storage or handling may be neutralized by treating with combined solution.

Table: 3 Effect of Resin activation on Drug loading

Resin Activation	Drug Resin Ratio	%Drug Loading
Acid	1:1	11.67
Alkali	1:1	19.50
Acid-Alkali	1:1	26.34
Acid	1:2	20.28
Alkali	1:2	24.33
Acid-Alkali	1:2	40.16
Acid	1:3	44.00
Alkali	1:3	83.75
Acid-Alkali	1:3	99.91
Acid	1:4	43.43
Alkali	1:4	78.31
Acid-Alkali	1:4	92.76

Optimization of pH

It was observed that optimum drug loading was achieved at neutral pH 7 i.e. 97.23 % (near to pKa of Drug) and was not much increased at pH higher than this. At pH 1.2, minimum drug loading was obtained i.e. 22.20 % because of at an acidic pH, resin which is weak cationic in nature occupied H^+ ion of acid and there is no space for drug binding.

Table: 4 Optimization of pH

P^H	% Drug loading
1.2	22.20
2	48.36
3	53.99
4	61.20
5	69.19
6	89.32
7	97.23
8	85.10

Characterization of DRC

***In-vivo* taste evaluation**

The volunteers did not report any bitterness for DRC throughout the study. The majority of the volunteers found the DRC to be tasteless and agreeable.

Confirmation of complexation

FTIR studies [26]

FTIR spectra of Ondansetron HCl, Kyron T 114 and Drug resin complex are shown in figure 2, 3, 4. The absence of Ondansetron HCl peak i.e. $-NH_2$ stretch at 3379.05 cm^{-1} in DRC confirms the complexation of the secondary amine group in the drug with resin. The spectrum of Kyron T 114 showed distinct C=O *stretch* at 1738.43 of the –COOH functional group of the resin, which was not seen in the spectrum of DRC. The functional groups involved in the complexation process were –COOH of Kyron T 114 along with the Secondary amines of Ondansetron HCl.

Table: 5 Rating by the volunteers for evaluation of taste of DRC (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness)

Volunteer No.	Bitterness level after						
	5 sec.	10 sec.	15 sec.	30 sec.	60 sec.	120 sec.	180 sec.
1.	1	1	0	0	0	0	0
2.	0	0	0	0	0	0	0
3.	1	0	0	0	0	0	0
4.	1	0	0	0	0	0	0
5.	2	1	1	1	0	0	0
6.	1	1	1	0	0	0	0
7.	0	0	0	0	0	0	0
8.	0	1	0	0	0	0	0
9.	1	1	0	0	0	0	0
10.	0	0	0	0	0	0	0

The absence of other peaks of Ondansetron HCl in the spectrum of DRC indicated that the drug was completely embedded in the resin polymer matrix and thus the complexation was confirmed.

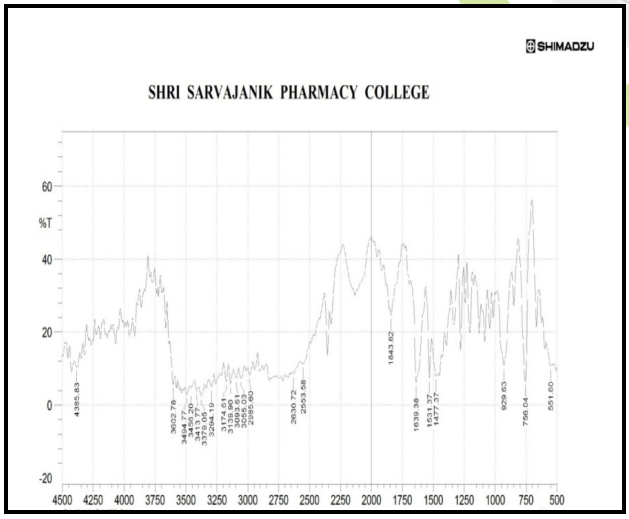

Figure: 2 FTIR Spectra of Ondansetron HCl

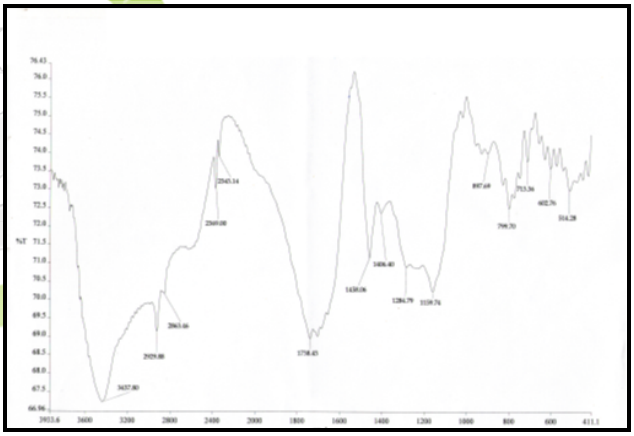

Figure: 3 FTIR Spectra of Kyron T 114

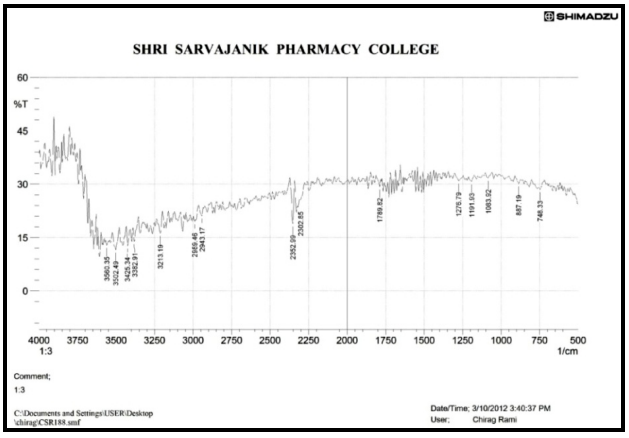

Figure: 4 FTIR spectra of DRC

Thermal analysis

Thermograms of pure Ondansetron HCl, Kyron T 114 and Drug resin complex are shown in below figure 5, 6, 7. In the case of pure Ondansetron HCl, a sharp endotherm was observed at 183.86 ºC, corresponding to the melting point of Ondansetron HCl. While in Kyron T 114 and DRC, a sharp endotherm was observed at 253.98 ºC and 243.60 ºC respectively, corresponding to the melting point of Kyron T 114 and DRC. In DSC curve of DRC total disappearance of drug melting temperature was occurred.

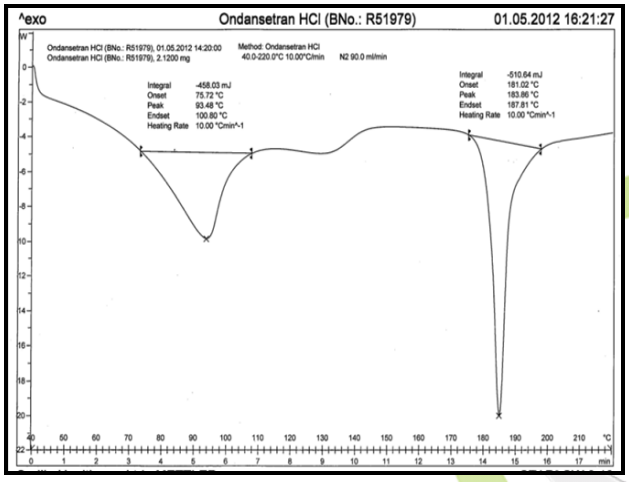

Figure: 5 DSC thermogram of Ondansetron HCl

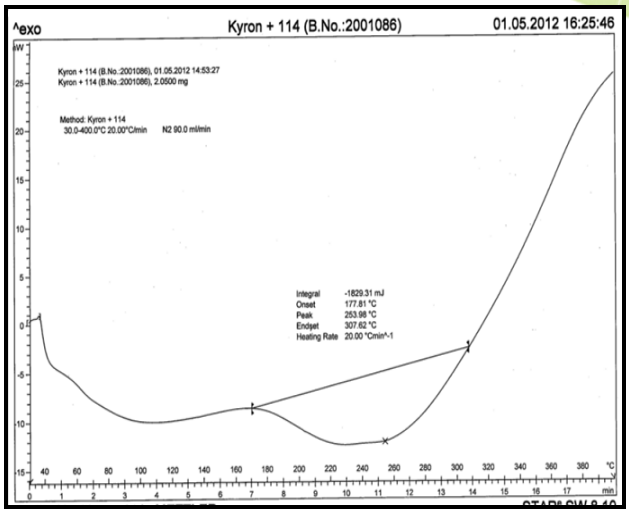

Figure: 6 DSC thermogramof Kyron T 114

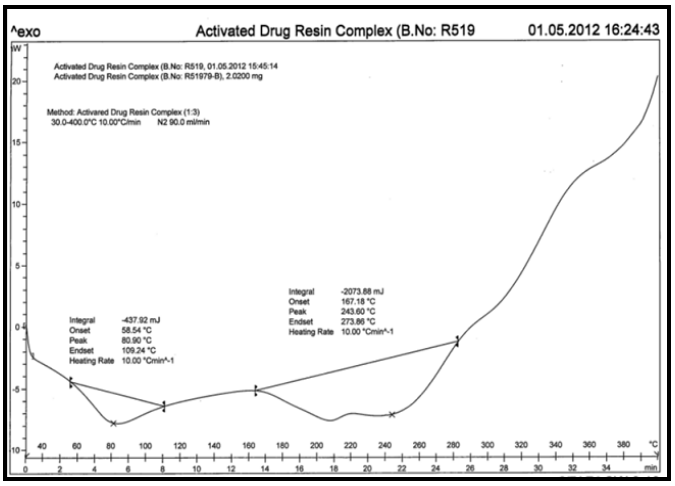

Figure: 7 DSC thermogram of DRC

Estimation of drug content

When DRC was prepared using all of the optimized parameters for drug loading, the percent drug loading was found to be 99.16% and hence the drug content was 98.57 % w/w.

***In-vitro* drug release study**

The dissolution profile of DRC showed complete drug release within 10 minutes in 0.1 N HCl. Thus DRC releases the drug quickly upon contact with acidic environment although it does not release any drug at salivary pH. Ondansetron HCl is eluted rapidly from the DRC because of its highly hydrophilic nature and having low selectivity for the carboxylic acid functional groups of the resin. It was concluded that Acid-Base Combined treated DRC gives optimum Drug release.

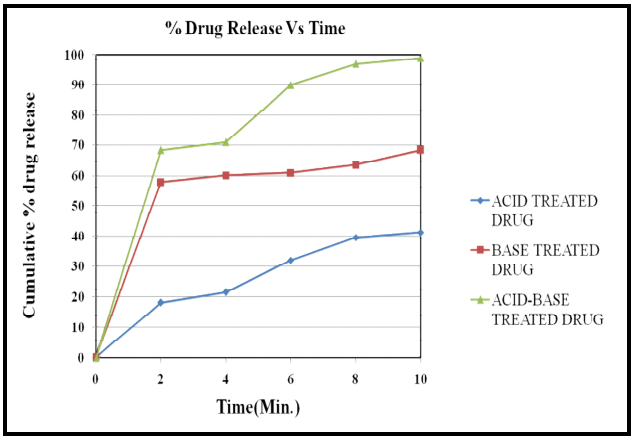

Figure: 8 Cumulative Percentage Release of Acid, Base and Acid-Base treated Drug Resin Complex

Table: 6 Cumulative Percentage Release of Acid, Base and Acid-Base treated Resin

Time	Acid treated DRC(1:3)		Base treated DRC(1:3)		Acid – Base treated DRC(1:3)	
(Min.)	Absorbance	% CDR	Absorbance	% CDR	Absorbance	% CDR
0	0	0	0	0	0	0
2	0.999	18.12	0.24	57.90	0.277	68.34
4	0.111	21.5	0.248	60.16	0.286	7.088
6	0.148	31.94	0.251	61.00	0.353	89.79
8	0.175	39.56	0.26	63.54	0.378	96.84
10	0.181	41.25	0.227	68.34	0.385	98.81

Evaluation of Orally Disintegrating Tablet

Thickness of all batches was in the range of 6.13-6.15 mm. Hardness of all batches was in the range of 3.5-4.5 Kg/Cm^2 that ensures good handling characteristics of all batches. Friability of all batches was in the range of 0.39 – 0.48 % that ensuring that the tablets were mechanically stable. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopeial limits of i.e. ±7.5. % of the weight .DT & WT range was found to be in range of 12-33 Sec & 19-37 Sec. The percentage of drug content for FT1 to FT9 was found to 96.67 % to 102.58 %, it complies with official specifications.

***In Vitro* Drug Release study of Factorial Design FT1 – FT9 batches**

FT1 to FT9 batches releases more than 80 % drug in 10 min. FT3 batch gives highest drug release that is 99.27%.

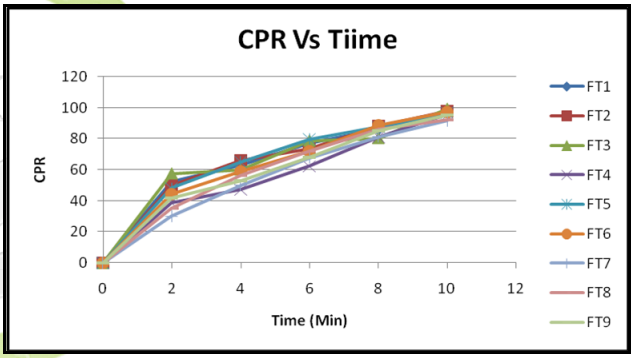

Figure: 9 Cumulative Percentage Release of FT1-FT9 batches

Table: 7 Evaluation of Factorial FT1-FT9 Batches

Test	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Weight variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Hardness (kg/cm$^{2)}$	3.5-4.5	3.7-4.2	3.6-3.9	3.5-4.5	3.8-4.5	3.7-4.0	3.8- 4.3	3.7- 4.3	3.9 - 4.5
% Friability	0.40 ± 0.08	0.42 ± 0.05	0.48 ± 0.01	0.39 ± 0.05	0.45 ± 0.05	0.42 ± 0.08	0.39 ± 0.05	0.45 ± 0.01	0.42 ± 0.05
Thickness (mm)	6.15 ±0.02	6.13± 0.02	6.14 ±0.02	6.13± 0.02	6.14± 0.02	6.15 ±0.02	6.13± 0.02	6.15 ±0.02	6.15± 0.02
Wetting time (sec.)	25 ± 1.57	22 ± 1.23	19 ± 1.20	29 ± 1.23	30 ± 1.23	24 ± 1.57	37 ± 1.23	36 ± 1.20	31± 1.23
Disintegration time(sec.)	21 ± 1.05	16 ± 0.77	12 ± 0.61	23 ± 0.77	19 ± 0.77	20 ± 1.05	33 ± 0.77	31± 0.61	24 ± 0.77
Drug content (%)	98.89 ± 0.15	101.26 ± 0.12	96.67 ± 0.25	100.23 ± 0.11	102.58 ± 0.14	97.89 ± 0.15	99.91 ± 0.14	96.35 ± 0.25	10.02 ± 0.12

Factorial equation for dependent variables

Factorial equation for Disintegration time

$$Y= 21.11 – 7.83 X1 +4 X2 +0.25 X1X2 +0.83 X_1^2 + 0.33 X_2^2, R^2= 0.9982$$

Positive sign in front of terms indicate synergistic effect while negative indicate antagonistic effect upon responses. So, sign of b_1 was negative shows that as a concentration of CP XL 10 increases, DT decreases. As the R^2 value nearer to 1 indicate selected model was significant.

Factorial equation for wetting time

$$Y= 26.33 -7 X1 + 3.83 X2 – 0.25 X1X2 + 1 X^2 -0.5 X_2^2, R^2= 0.9972$$

Positive sign in front of terms indicate synergistic effecy while negative indicate antagonistic effect upon responses. So, sign of b_1 was negative shows that as a concentration of CP XL 10 increases ,WT decreases. As the R^2 value nearer to 1 indicate selected model was significant.

ANOVA of quadratic model for DT and WT

ANOVA table used to generate mathematical models. The high values of correlation coefficient for DT and WT indicate a good fit i.e. good agreement between the dependent and independent variables. The mathematical model was evolved by omitting insignificant term ($p > 0.05$). So, the main effect X1 & X2 were found significant as p value was < 0.05.

Response surface plots

Response surface plots for Disintegration Time

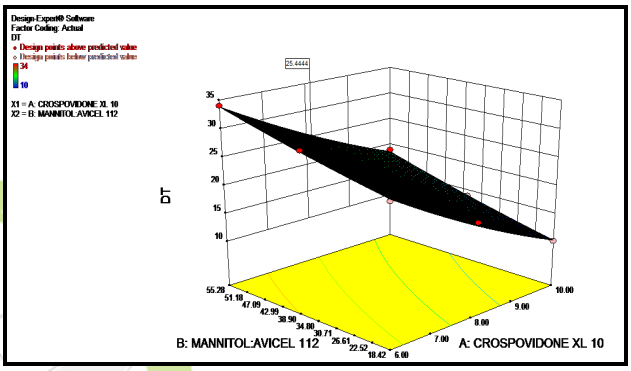

Figure: 10 3D graph of Disintegration Time

Table: 8 ANOVA Response surface quadratic model for DT

Source	SS	Df	MS	F Value	p-value probe> F	R^2
Model	466.03	5	93.21	324.72	0.0003	**0.9982**
A superdisintegrant concentration	368.17	1	368.17	1282.65	<0.0001	
B-Dilution ratio	96	1	96	334.45	0.0001	
AB	0.25	1	0.25	0.87	0.4195	
A^2	1.39	1	1.39	4.84	0.1152	
B^2	0.22	1	0.22	0.77	0.4437	
Cor Total	466.89	8	0.29	-	-	

Table: 9 ANOVA Response surface quadratic model for WT

Source	SS	df	MS	F Value	p-value prob> F	R^2
Model	384.92	5	76.98	213.18	0.0005	**0.9972**
A superdisintegrant concentration	294	1	294	814.15	<0.0001	
B-Dilution ratio	88.17	1	88.17	244.15	0.0006	
AB	0.25	1	0.25	0.69	0.4664	
A^2	2	1	2	5.54	0.1	
B^2	0.50	1	0.5	1.38	0.3242	
Cor Total	386	8	-	-	-	

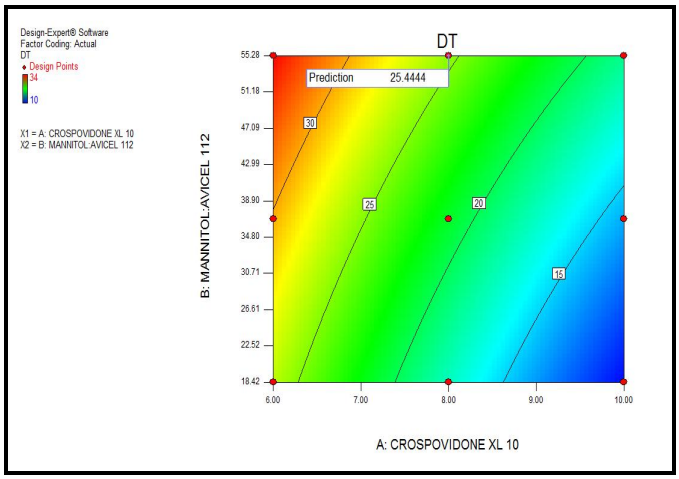

Figure: 11Contour plots of disintegration time

Response surface plot for wetting time

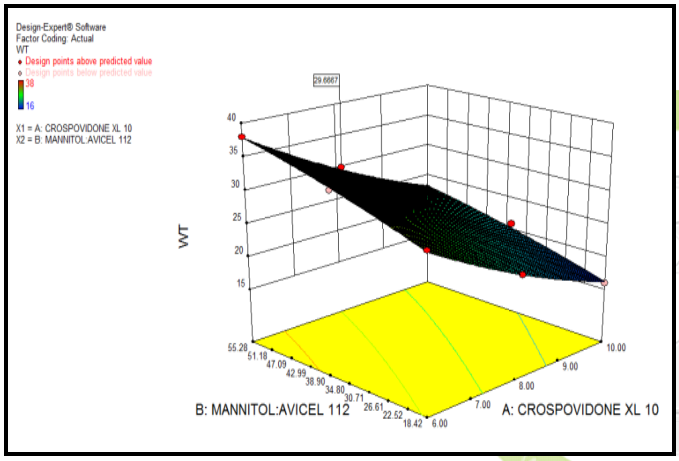

Figure: 12 3D graph of wetting time

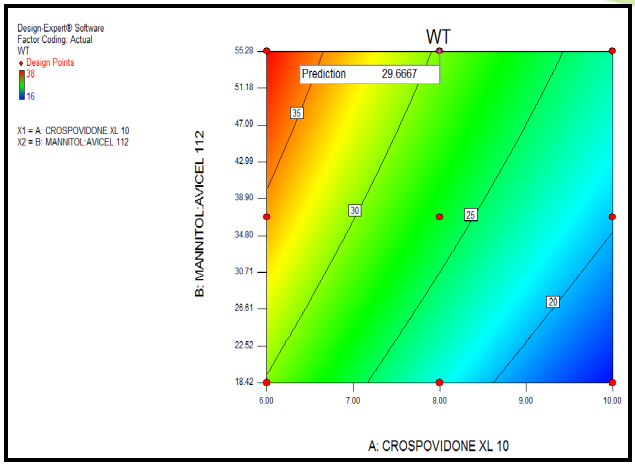

Figure: 13 Contour plot of wetting time

The counter plot & 3D plot shows the effect of concentration of CP XL 10 & Mannitol SD 200: Avicel pH 112 on DT & WT. As the conc. of X1X2 increases the value of response Y decreases. It was observed from the 3D and contour plots that both the factors had influence on DT & WT of the tablets. There was a linear increase in the values of DT & WT as the levels of crospovidone and Mannitol SD 200: Avicel pH 112 was increased. Mannitol SD 200: Avicel pH 112 being a diluent increases the mechanical strength of the tablet and crospovidone is also known to produce mechanically strong tablets.

Validation of Statistical Model by overlay plot

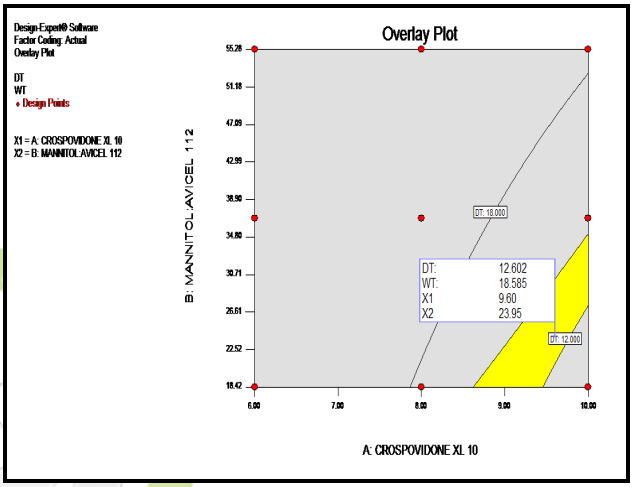

Figure: 14 Validation Of Statistical Model by overlay plot

From overlay plot of responses, optimized formulation was selected as checkpoint to validate RSM. The Overlay plot of responses generates an optimized area as per desired criteria of DT should be 12 sec & WT should be 18 sec. So, it can be concluded that by adopting systemic formulation approach one can reach to an optimum point in shortest time with minimum effect. Thus, we can conclude that statistical model is mathematically valid.

Optimum formulation for orally disintegrating tablets of Ondansetron HCl

The optimized concentrations were obtained from the software as clear areas in Overlay plot. A checkpoint was prepared at X1 = 9.60 & X2 = 23.95 to obtain DT & WT 12 & 18 sec respectively. The optimized formula was characterized for its blend properties and tablet characterization.

Table: 10 Optimum formulation of orally disintegrating tablets of Ondansetron HCl.

Ingredient	Quantity (mg)
DRC (eq. to 4 mg of Ondansetron HCl)	16
Crospovidone XL 10	9.92
Mannitol SD 200	27.32
Avicel pH 112	44.46
Magnesium Stearate	1
Aerosil	0.3
Aspartame	1
Total Weight (mg)	100

Evaluation parameters of Optimized batch

Table: 11 Evaluation parameters of Optimized batch

Precompression Parameters	
Bulk Density (gm/ml) ±SD	0.54±0.01
Tapped Density (gm/ml) ±SD	0.60±0.02
Hausner ratio	1.11
Compressibility index (%)	10±0.09
Angle of repose (°)	30.95±0.08
Precompression Parameters	
% Weight variation	Pass
Thickness (mm)	6.14 ± 0.02
Hardness (Kg/cm^2)	3.8 – 4.2
% Friability	0.40 ± 0.05
Disintegration time	13 ± 0.18
Wetting time	19 ± 0.15
% Drug Content	100.32 ± 0.32

Table: 12 Cumulative Percentage release of optimized batch

Time (Min)	CPR
0	0
2	65.02 ± 0.62
4	77.56 ± 1.26
6	84.33 ± 1.86
8	94.09 ± 0.70
10	99.93 ± 0.58

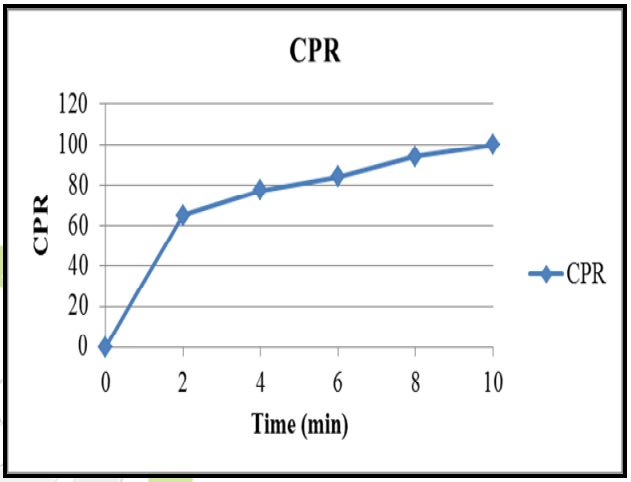

Figure: 15 Cumulative Percentage release of optimized batch

From the evaluation of optimized batch, it was observed that all parameters were found within desire limits and the derived polynomial equation & Response surface plots aid in predicting the values of selected independent variables for preparation of optimum Ondansetron HCl Orally Disintegrating Tablet with the desired properties.

Comparison of Optimized batch with marketed product

***In-vitro* drug release study**

According to I.P., Ondansetron HCl ODT should release not less than 80 % of the stated amount of drug.Optimized batch, ONDEM & ONDET releases 99.93, 99.97, 99.95 % drug respectively within 10 min. From the above graph, it is observed that Optimized Ondansetron HCl Orally Disintegrating tablet

gives nearer drug release profile to two marketed product.

Table: 13 Cumulative Percentage release comparison of optimized batch two marketed products

Time (Min)	Optimized batch	ONDEM	ONDET
0	0	0	0
2	65.02 ± 0.62	57.23 ± 1.20	44.09 ±0.58
4	77.56 ± 1.26	65.29 ± 0.64	59.32 ± 1.16
6	84.33 ± 1.86	73.22 ± 0.82	67.45 ± 0.33
8	94.09 ± 0.70	93.08 ± 0.39	88.67 ± 0.85
10	99.93 ± 0.58	99.97 ± 0.62	99.95 ± 0.47

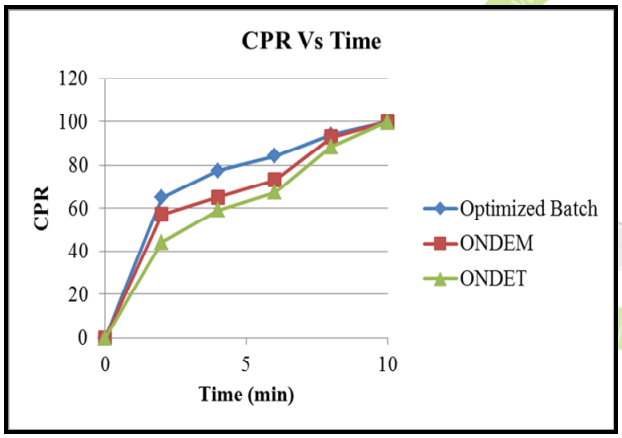

Figure: 16 Cumulative Percentage release comparison of optimized batch with two marketed products

Stability study of optimized batch

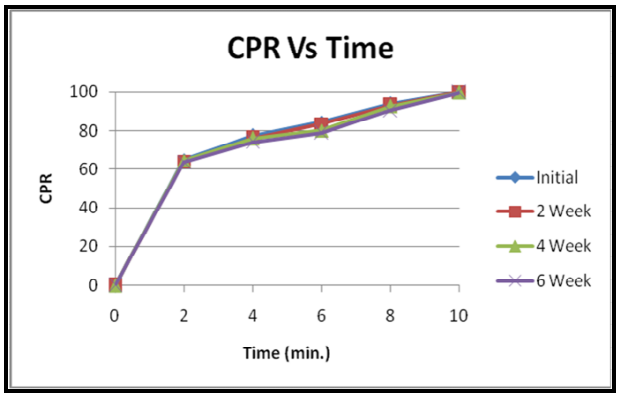

Figure: 17 Cumulative Percentage release for 40ºC

Table: 14 Stability study Result

Parameters	Initial	2 Week	4 Week	6 Week
Disintegration Time(Sec.)	13	13	14	14
Wetting time	19	19	21	21
Assay (%)	100.32	100.15	100.0	99.99
Dissolution (10 Min.)	99.93	99.90	99.76	99.71

From the above stability data at 40°C/75% RH, it reveals that the product is stable at 40 °C/75% RH for 6 Weeks (1 months & 2 Week).

CONCLUSION

In the present study, an attempt was given to mask bitter taste of Ondansetron HCl by Kyron T-114 & prepare palatable dosage form. Molecular properties of resinate were studied using DSC and FTIR, both suggested complexation between drug and resin. The complexes were successfully formulated into orodispersible tablets. The 3^2 full factorial design applied in thisstudy was used to provide details of the influence of independent variables on the responses. The results of analysis of variance showed that two independent variables had significant effect on the selected response. The quadratic model showed high degreeof reliability. It is thus concluded that by adopting a systematic approach, an optimum point can be reached in the shortest time with minimum efforts. The dissolution profiles of the optimized batch with DT & WT 13 & 19 Sec respectively was compared with that of marketed product and showed matching *in vitro* drug release to that Marketed product. Stability study indicate that the optimized batch was stable. Hence Ondansetron HCl can be successfully formulated as an Orally Disintegrating tablet with desired property.

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