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Design and optimization of *In-situ* floating gel containing ondansetron hydrochloride dihydrate using 3^2 factorial design

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Abstract
The aim of the present study was to develop an *in-situ* floating gel of Ondansetron HCl dihydrate. The Ondansetron HCl dihydrate has low gastro intestinal Transit time that result in low absorption of drug. Floating *in-situ* gel is most suitable form to achieve greater absorption of drug. *In-situ* gel floats on the gastric fluid for sufficient time and also increases the gastric transit time. An *in-situ* floating gel prepared by using various excipients like sodium alginate, calcium carbonate, sodium citrate, D-mannitol, methyl paraben, propyl paraben. The compatibility study was performed by using FT-IR. Formulations were optimized by using 3^2-factorial designs. Concentration of Sodium Alginate and calcium carbonate were selected as independent variables whereas floating lag time and drug release after 8 hrs (Q_8) were selected as dependent variables. The prepared formulations were evaluated for viscosity, floating lag time, duration of floating, *in- vitro* gelation and *in-vitro* drug release. All formulations showed floating within 60 s and had total floating time 24 hrs.
The concentration of Sodium Alginate and calcium carbonate had significant influence on floating lag time, cumulative percentage drug release in 8 hrs. Among different formulae tested, formulation A5 showed optimum floating lag time (38sec) and drug release after 8 hrs (98.56%). Therefore, floating *in-situ* gelling of Ondansetron HCl dihydrate containing Sodium Alginate as a gelling polymer to sustain the drug release for 8 hrs. All the formulations showed good pourability.

Keywords: Floating *in-situ* gelling system, Ondansetron HCl dehydrate (OSD), oral drug delivery, sustained release, sodium alginate

1. Introduction
Ondansetron hydrochloride is a 1,2,3,9-terahydro-9-methyl-(2- methyl-1-H- imidazol-1-yl)methyl -4H-carbazol-4- one, monohydrochloride [1]. Ondansetron hydrochloride is a short acting drug for the management of nausea and vomiting. Chemotherapeutic agents and radiotherapy cause release of 5HT in the small intestine initiating the vomiting reflux by activating vagal afferents via 5HT3 receptor. It blocks the initiation of these reflexes [2-3]. It has a short biological half-life of 3.1h.
Powder dosage form was traditionally used dosage form. Tablet taken by oral route which through GI tract reaches in stomach and intestine simultaneously, then it shows pharmacological action. Tablet is a most popular dosage form, but tablet also having limitation like it is difficult to administration in small children, unconscious patient and dose dumping [4].
The main limitation regarding tablet dosage form is gastro intestinal Transit time (6 to 8 hrs). Some drug having specific absorption site, they absorb only at that site. Even the gastro intestinal transit time if smaller, the drug has less time for absorption and when it misses the absorption window, further there is no any absorption site.
When we increase the residential time of tablet remain intact in stomach for more period and result in more absorption of drug. This can be achieve by various means, out of which preparation of floating *in-situ* gel is most suitable form, as it can be float on the gastric fluid for sufficient time and also increases the gastric transit time [5].

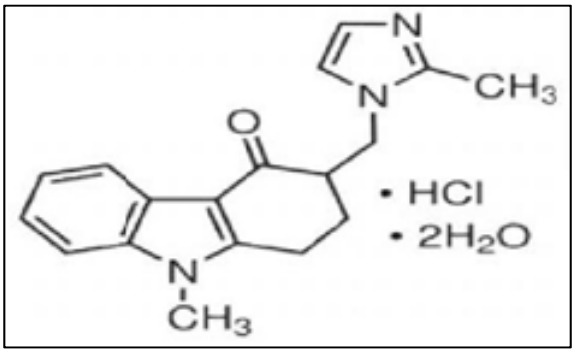

Fig 1: Structure of Ondansetron HCL Dihydrate

2. Material and method

2.1 Material

Ondansetron HCL Dihydrate USP was obtained from Naproid life science, Sodium Alginate (AR), Sodium Citrate (LR), Calcium Carbonate (LR), Methyl Parben (LR), Propyl Parben (LR) were procured from Chem Pure Lab. Pvt. Ltd., Mumbai.

2.2 Method

2.2.1 Preparation of *in-situ* floating gel

The weighed quantity of sodium Alginate was added in distilled water containing Sodium Citrate. This dispersion of sodium Alginate in Distilled water was heated at 60 ^{0}C with continuous stirring. Then, this solution was cooled below 40 ^{0}C. The calculated amount of drug, Calcium Carbonate, D-mannitol, Methylparaben, Propyl paraben were added with continuous stirring. The final volume was made with distilled water. Prepared gel was transferred in amber colored bottle. Stored at cool temperature [6-9]. the Quantity of ingredients listed in table 1.

2.2.2 Optimization of formulation Factorial Design:

An acceptable pharmaceutical formulation can be developed in shortest possible time using factorial design methods. Traditionally, trial and error method was utilized to develop an optimized pharmaceutical formulation by changing one variable at a time. This method having certain disadvantages like time consuming and requires a lot of imaginative efforts. Therefore, the complexity of pharmaceutical formulations can be understood by using established statistical tools such as factorial design. This study is based on the number of independent variables selected. The response, Y is measured for every experiment. The response for 3^2 Factorial design is calculated by using following formula

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

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine experiments and b_1 is the coefficient for the factor X_1 while b_2 is the coefficient for the factor X_2. 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_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate non linearity. The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative).[10]

In the present investigation, a 3^2 full factorial design was used. This method consists of two factors which were evaluated at three levels, and experiments were carried out for all possible combinations. Total nine trials were developed. The layout and coded value of independent factor is shown in Table 1. Selection of factors was based upon preliminary study.

Independent Variables: Concentration of Sodium Alginate (X_1) and Concentration of Calcium Carbonate (X_2), Dependent Variables: Percentage Floating Time and Percentage Drug Release. The no. of formulations as per 3^2 full factorial designs (F1 to F9) is shown in Table 2.

Table 1: 3^2 Full factorial design layout

Batch code	X_1	X_2
F_1	-1	-1
F_2	-1	0
F_3	-1	1
F_4	0	-1
F_5	0	0
F_6	0	1
F_7	1	-1
F_8	1	0
F_9	1	1

Table 2: No. of Formulations as per 3^2 Factorial Design

Name of Ingredient	Formulation Code								
	F1	F2		F3	F4	F5	F6	F7	F8	F9
OndansetronHCl Dihydrate	0.160	0.160		0.160	0.160	0.160	0.160	0.160	0.160	0.160
Sodium Alginate	1.25	1.25		1.25	1.75	1.75	1.75	2.25	2.25	2.25
Sodium citrate	0.25	0.25		0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium carbonate	0.375	0.5		0.625	0.375	0.5	0.625	0.375	0.5	0.625
D-Mannitol	2	2		2	2	2	2	2	2	2
Methyl paraben	0.09	0.09		0.09	0.09	0.09	0.09	0.09	0.09	0.09

2.3 Evaluation of *in-situ* floating gel

2.3.1 Drug Content Determination

Accurately 5 ml weighed *in-situ* gel was dissolved in 70 ml 0.1 N ml HCL. Kept this solution for sonication for 15 min. Volume was adjusted upto 100 ml with 0.1 N HCL. Further, 10 ml solution was withdrawl and made the volume up to 100 ml with 0.1 N HCL. Prepared solution was scanned by using UV-Visible Spectroscopy (Shimadzu) at 309 nm wavelengths [9].

2.3.2 Study of *in-vitro* Gelation

5ml *in-situ* gel was transferred in beaker containing 500 ml 0.1 N HCL with mild agitation that avoid breaking of *in-situ* gel. Gelling was observed visually [9, 11].

2.3.3 Study of *in-vitro* floating

The floating ability of *in-situ* gel was determined by adding 5 ml prepared gel in 500 ml 0.1 N HCl with mild agitation. The time required for floating the gel on surface was measured.

2.3.4 Study of *in-vitro* drug release

In-vitro drug release of drug was studied by using dissolution test apparatus USP. 0.1 N HCl was used as dissolution media. The temperature was maintained at 37 ^{0}C, paddle speed was enough that avoid breaking of gel. 5 ml prepared gel was transferred in dissolution media. Windrow solution after each interval maintains the sink condition by adding fresh dissolution media. The absorbance of windrow solution was observed under the UV-visible spectrophotometer at wavelength 309 nm3 [11-12].

2.3.5 Viscosity measurement

Viscosity of prepared *in-situ* gel was determined by using Brookfield viscometer. The prepared gel was kept in beaker and stirred at 60 rpm using spindle No. 3 at room temp.

2.3.6 Stability study

The stability study was performed for the optimized batch. The samples were stored at 40 ^{0}C and 75 ^{0}C +/- 2 ^{0}C Rh. for three month to assess their stability. The protocol of stability study were meet ICH guideline Q2R1 for stability testing intended in market. After 30 days, sample was windrow and determine the characteristic of gel like viscosity, Drug content, *In-vitro* gelation, Floating lag time and *in-vitro* drug release study [13- 16].

3. Result and discussion

3.1 Statistical Analysis

The purpose of 3^2 factorial designs was to conduct a comprehensive study of the effect of the process parameters like Sodium Alginate (X_1) and Calcium Carbonate (X_2). Their interactions using a suitable statistical tool (Design-Expert 8.0.4 software) by applying one-way ANOVA at 0.05 levels. A mathematical modeling was carried out by using Equation-I to obtain a first–order polynomial equation depending on significant influences among three factors (X_1, X_2 and X_3) and their interaction factors (X_1X_2, X_2X_3, and X_1X_3) of the factorial design model. (Table. 3)

$$Y=B_o + B_1X_1+B_2X_2+B_3X_1X_2^2+B_4X_1^2X_2^2+B_5X_1^2X_2^2 \ldots\ldots\ldots\ldots\ldots\ldots \text{(I)}$$

Where, Y = the dependent variable,

bo = the intercept, b_1, b_2, b_3, b_4, and b_5 = regression coefficients;

X_1, X_2 = main factors; X_1X_2, X_2X_3, and X_1X_3 = interactions between main factors.

The best-fitting mathematical model was selected by comparison of several statistical parameters, including the coefficient of variation (CV), the multiple correlation coefficient(R^2), the adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of squares (PRESS), provided by the software. PRESS indicates how well the model fits the data, and for the chosen model, it should be small relative to the other models under consideration. (Table 4 & Table 5) The 3-D response surface graphs and the 2-D contour plots were also generated by the Design Expert® software. These plots are very useful to see interaction effects of the factors on responses. (Fig. 2 & 3). The Floating lag time is improve with increasing concentration of Sodium alginate and Calcium Carbonate. Batch F1, F5, F9 shows 43%, 38%, and 34% respectively.

Table 3: Layout of Actual Design

Formulation Code	Factor 1 A: Sodium Alginate	Factor 2 B: Cal. Carbonate	Response 1 Q_8 (%)	Response 2 Floating Lag Time (Second)
F_1	1.25	0.375	95.94	43
F_2	1.25	0.5	98.70	42
F_3	1.25	0.625	93.60	36
F4	1.75	0.375	95.65	48
F_5	1.75	0.5	98.56	38
F_6	1.75	0.625	93.50	31
F_7	2.25	0.375	96.87	49
F_8	2.25	0.5	93.0	30
F_9	2.25	0.625	93.2	34

Model assessments for the dependent variables:

Q_8 (Drug release 8 hr):Q_8 = + 95.45 – 0.86*X_1-1.36 *X_2

Table 4: Analysis of Variance for Y_1 (Q_8)

Source	F-Value	p-value Prob>F	Significance
Model	1.85	0.0237	S
A-Polymer conc	1.06	0.0343	S
B- calcium carbonate	2.64	0.0155	S

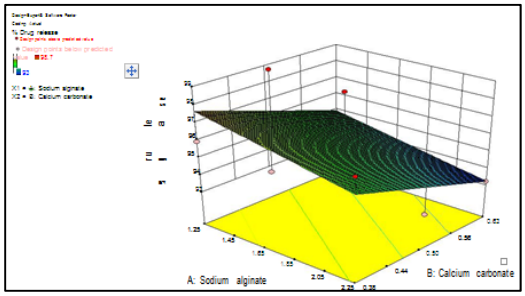

Fig 2: 3D Response Curve of Floating In-situ Gel of Ondansetron HCl Dihydrate.

Floating lag time: Floating lag time = +40.67 - 0.50 X_1 -7.50 X_2
Analysis of variance for Y_2

Table 5: Analysis of Variance for Y_2

Source	F Value	p-value Prob> F	Significance
Model	48.43	0.0002	S
A-polymer conc.	0.43	0.5370	-
B-calcium carbonate	96.43	-	-

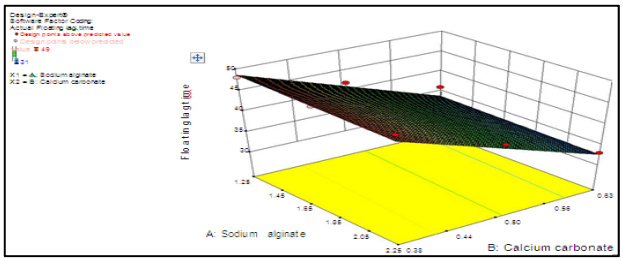

Fig 3: 3D Response Curve of Floating Lag Time for Floating *in-situ* Gel of Ondansetron HCldihydrate

3.2 Evaluation of *in-situ* gel
The *in-vitro* drug release studies reveled that formulation F1 to F9 containing 1.25, 1.75 and 2.25% of polymer sodium alginate respectively were able sustained the drug release for 8 hrs. in Table 6.

3.3 Viscosity
The viscosity Study was carried out by Brookfield viscometer. Formulations F3, F6, F9 showed a marked increase in viscosity with increasing concentration of sodium alginate & calcium carbonate as shown (Table 6).

3.4 Drug content
The drug content analysis determined in 0.1 N HCL result are tabulated in Table 6. The F5 formulation shows 99.63% release of drug over a period of 8 hrs.

3.5 *In-vitro* gelation Study
The formulation containing highest concentrations of calcium carbonate has lowest gelation time as shows in Table 6. Formulation F3, F6, F9 showed a lowest gelation time, whereas formulation F1, F4, F7 showed a highest gelation time.

3.6 *In-vitro* Floating Study
The floating ability of the prepared formulations was evaluated in 0.1 N HCL (pH 1.2).Floating lag time and duration of floating were tabulated in Table 6. The best formulation (F5) containing (0.5%) calcium carbonate showed floating lag time 38± 1.1 sec with duration of floating 24 hours.

Table 6: Evaluation Data for Factorial Formulations (F_1-F_9) *Mean± S.D., (n=3)

Formulation Code	Solution Viscosity (cps)	Gelling Time (Sec)	Floating Lag Time (Sec)	Duration Of Floating (Hrs)	Drug Content (%)
F1	120±0.12	11±0.1	43±0.32	22.6±0.54	95.7±0.26
F2	160±0.16	8±0.23	42±1.5	23.6±0.54	94.6±0.14
F3	200±0.028	6±0.16	36±1.1	24	98.7±0.066
F4	140±0.050	9±0.18	48±2.3	23.6±0.54	95.48±0.31
F5	200±0.2	6±0.021	38±1.4	24	99.63±0.11
F6	250±0.54	5±0.036	31±1.3	24	98.90±0.18
F7	160±0.36	8±0.052	49±3.1	24	98.73±0.22
F8	190±0.26	5±0.096	41±2.4	24	98.91±0.036
F9	280±0.04	4±0.045	33±1.8	24	99.27±0.23

3.7 *In-vitro* Dissolution
The *in vitro* drug release studies reveled that formulations F1 to F9 containing 1.25, 1.75 and 2.25% of polymer Sodium Alginate respectively were able to sustained the drug release for 8 hours. *In-vitro* dissolution is carried out by using USP Apparatus type II (Paddle), 0.1 N pH Dissolution medium and 75 speed of rotation of paddle at 37 ^{0}C. The F5 batch show 98.65% release of drug at 60 min. (Table 7)

Table 7: Data for Factorial Formulations (F1-F9) *Mean± S.D (n=3)

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	63.87±0.12	51.3±0.33	49.6±0.04	56.8±0.04	61.1±0.01	54.6±0.08	61.0±0.13	53.7±0.4	49.5±0.48
2	71.75±0.02	59.7	54.4±	62.7±	67.8±	61.6±	66.1±	58.3±	52.9±
	0.02	±0.39	0.089	0.032	0.34	0.09	0.28	0.45	0.03
3	81.3 ±	67.1	62.1±	67.8 ±	72.9±	67.4±	70.4±	63.9±	62.9±
	0.16	±0.43	0.19	0.76	0.89	0.47	0.45	0.20	0.045
4	87.25±	72.1±	66.1±	73.1±	78.7±	70.6±	76.3±	70.1±	69.1±
	0.34	0.018	0.39	0.24	0.97	0.12	0.034	0.47	0.012
5	92.94±	89.9	71.9±	80.5±	87.8±	75.6±	82.4±	73.0±	74.0±
	0.032	±0.011	0.48	0.049	0.1	0.75	0.02	0.13	0.034
6	99.94±	94.8±	79.0±	86.9±	91.1±	81.6±	88.4±	77.6±	83.9±
	0.012	0.78	0.75	0.039	0.023	0.38	0.23	0.29	0.045
7		99.7±	87.9±	90.7±	95.4±	87.9±	92.8±	85.2±	89.2±
		0.39	0.34	0.09	0.32	0.1	0.19	0.59	0.012
8		-----	96.6±	95.65±	98.56±	93.5±	96.87±	93.0±	93.7±
			0.13	0.34	0.19	0.34	0.3	0.96	0.1

The release kinetics of the formulation is shown in Table 8. Demonstrated that the regration coefficient is between 0.906 - 0.984. The best fit model representing the mechanism of drug release from the matrices was Peppas release (Fig. 4)

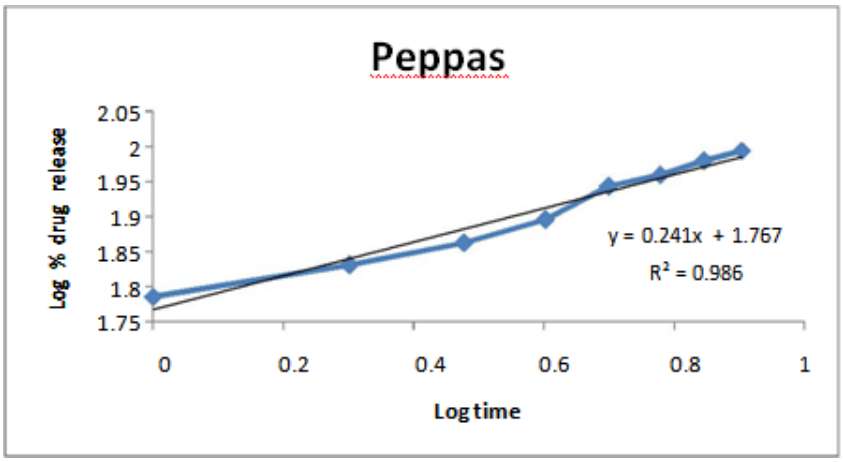

Fig 4: Korsmeyer-Peppas model

Table 8: Regression coefficients of models for optimized batch:

Batch	Zero order		First order		Higuchi		Peppas		Parameter for Peppas equation
	R^2	K	R^2	K	R^2	K	R^2	K	N
F5	0.984	5.522	0.906	-0.189	0.976	21.55	0.986	1.76	0.241

3.8 Stability study

The optimized formulation, stored at 40±1 ^{0}C, 75% RH. Formulations were found stable over 90 days. The stability study indicating that after storage drug release, viscosity, drug content, *in- vitro* gelation study, *in- vitro* floating study were found similar to at the time of preparation. Result are tabulated in table 8.

Table 9: Stability study *Mean± S.D., (n=3)

Evaluation parameters	MONTH			
	Initial	First	Second	Third
Viscosity	150±0.15	150±0.25	150±0.36	150±0.42
Gelling time	6±0.23	6±0.098	6±0.26	6±0.48
Floating lag time	38±0.069	39±0.25	36±0.056	37
Duration of floating time	24	24	24	24
Drug content	99.09± 0.21	98.96±0.063	98.88±0.31	98.55±0.11
In vitro drug release (%)	98.56	98.250	97.957	97.80

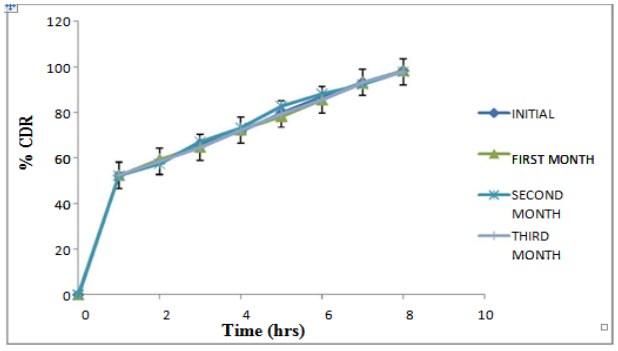

Fig 5: *In-vitro* dissolution profile for stability formulation

4. Acknowledgment

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5. Conclusion

In present investigation, formulation A5 showed optimum floating lag time (38sec) and drug release after 8 hrs. (98.56%). Therefore, Prepared *in-situ* floating gel was found to have better floating efficacy and *in-vitro* drug release profile characteristics. Hence, it may represent as a novel alternative. Formulation of ondansetron HCl dihydrate which may improve the patient compliance. The developed formulation promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to increase the residence time of drug in stomach which may increase bioavailability.

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