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Research Article

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Formulation and Evaluation of Gastroretentive Tablet of Ondansetron hydrochloride Using 3^2 Factorial Design

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Abstract The purpose of this research was to formulate and optimize an effervescent Gastro retentive tablet formulation of Ondansetron hydrochloride using 3^2 factorial design. Gastroretentive tablets were prepared by direct compression method by incorporating HPMC K4M, HPC, Carbopol 934P, sodium bicarbonate and citric acid. A 3^2 Factorial design was applied systemically; the amount of HPMC K4M (X_1) and Carbopol 934P (X_2) were selected as independent variables. The time required for 50% drug release ($T_{50\%}$), release rate (K_o) and floating lag time (FLT) were selected as dependent variables. It was found that HPMC K4M, Carbopol 934P and their interaction had significant influence on the $T_{50\%}$, release rate (K_o) and floating lag time of the delivery system. The decrease in the release rate was observed with an increase in the concentration of the polymer system. Polymer with lower concentration HPMC K4M was shown to be beneficial than the absence of polymer Carbopol 934P in improving the floating properties of gastroretentive tablet. The observed difference in the drug release and the floating capacity of gastroretentive drug delivery system could be attributed to the difference in the water uptake capacity of the selected polymer.

Keywords Ondansetron hydrochloride, HPMC K4M, HPC, Carbopol 934P

Introduction

Floating drug delivery systems were first described by Davis in 1968. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine [1].

The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergoes disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood.

It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastroretentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage forms would be retained in the stomach and release the drug there in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of sustain release-dosage form for these drugs [2,3].

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems [4]. These efforts resulted in GRDFs that were designed in large part based on the following approaches: (a) low density form of the DF that causes buoyancy above gastric fluid [5,6]; (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the stomach mucosa [7]; (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients; (e) expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

Various approaches for preparation of gastroretentive drug delivery system include floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension system and sachet systems. Among these, the floating dosage form has been used most commonly. The floating systems include gas-generating systems, non-effervescent systems and raft forming systems.

Ondansetron HCl is a potent, highly selective 5-HT_3 receptor-antagonist. Ondansetron HCl is widely prescribed to control or prevents nausea and vomiting, particularly in patients undergoing chemotherapy and radiation treatments. Chemotherapy and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT_3 receptors. Ondansetron blocks the initiation of this reflex. This drug is mainly absorbed in stomach. Hence, the focus of present work is to prepare and evaluate gastro-retentive floating tablet of the Ondansetron HCl to increase its residence time in the stomach to achieve prolonged therapeutic action. Once a day Ondansetron HCl gastroretentive tablet offer better patient compliance through less frequent administration and thus would lower the cost of total therapy. Gastroretentive tablet of Ondansetron HCl will be prepared to give sustained therapeutic effect for up to 24 hrs.

Material and Methods

Materials

Ondansetron HCl was received as a gift sample from Lincoln Pharma. Ltd, Ahmedabad, India. HPMC K4M, HPC and Carbopol 934P were received as gift samples from R&D Department Kusum Health Care Pvt. Ltd. India. Citric acid, sodium bicarbonate, PVP K30 and Lactose were purchased from Central Drug House (P) Ltd., New Delhi. Talc were purchased from Loba Cheme Pvt Ltd., Mumbai, India. Magnesium stearate was purchased from E. Merck (India) Ltd., Mumbai, India.

Methods

Preparation of Floating Tablet of Ondansetron HCl

The composition of preliminary trial's formulation is shown in Table 1. Gastroretentive tablets of Ondansetron HCl were prepared by direct compression methods employing sodium bicarbonate as a gas generating agent. HPMC K4M, HPC and Carbopol 934P were used as a rate controlling polymers.

All the ingredients (Table 1) were weighed accurately. The required quantity of drug was mixed with release rate retarding polymers and other excipients in ascending order of their weight. The powder mix was blended for 20 minutes so as to have uniform distribution of drug. The powder mix, 300mg was weighed accurately and fed into die of single punch tablet machinery (Cadmach, Ahemedabad, India.) and compressed at 3 N compression force using 10mm concave punches.

Weight variation

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighting up to 120 mg is ±10%, 120 mg to 300mg is ±7.5%, and more than 300 mg is ±5%.

$$PD = \frac{W_{avg} - W_0}{W_{avg}} \times 100$$

Where *PD*= Percentage deviation;
W_{avg} = Average weight of tablet;
W_0 = Initial weight of tablet

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet which was expressed in kg/cm^2.

Friability

It is measure of mechanical strength of tablet. Roche friabilator (Camp-bell Electronics, Mumbai) was used to determine the friability by following procedure. A pre-weighed tablet was placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping that tablet at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for a fixed time (100 revolutions). At the end of test tablet were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\%Friability = \frac{W_0 - W}{W_0} \times 100$$

Where W_0 = Initial weight of the tablet;
W = Final weight of the tablet.
The weight loss should not be more than 1 %.

***In vitro* buoyancy studies**

The *In vitro* buoyancy study was determined by floating lag time and floating duration. The floating lag time and the duration of floating were determined in the USP dissolution apparatus II paddle type apparatus using 900ml of 0.1 N HCl at paddle rotation of 50 rpm at 37± 0.5°C. The time interval between the introduction of the tablet into the dissolution medium and its floating to the top of dissolution medium was taken as floating lag time and the floating duration of the tablets were determined by visual observation.

***In vitro* dissolution profile**

In vitro drug release of the formulation was carried out by using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at a regular interval of one hour for initially six hours ; every two hours up to 12 hours and every four hours till 24 hours. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 μ membrane filter. Absorbance of these solutions was measured at 310.00 nm using a Shimadzu UV-1700 double beam Spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Full Factorial design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amounts of HPMC K4M (X_1) and Carbopol 934P (X_2) were selected as independent variables. The times required for 50% drug dissolution ($T_{50\%}$), release rate (K_0) and the floating lag time (*FLT*) were selected as dependent variables.

Results and Discussion

Results of Preliminary Screening

For preliminary Screening, three different polymers were used at different concentration level as indicated in Table 1. The weight of the tablet varied between 295 mg to 300 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of ±5% complying with pharmacopoeial specifications. The hardness for different formulations was found to be between 4.5 to 5.1 kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The findings are presented in Table 2. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, hardness and friability.

Table 1: Formulation of preliminary trial's-screening of polymers

Formulation Code	B1	B2	B3	B4	B5	B6	B7	B8	B9
Ondansetron HCl	38	38	38	38	38	38	38	38	38
HPMC K4M	90	-	-	120	-	-	150	-	-
HPC	-	90	-	-	120	-	-	150	-
Carbopol 934P	-	-	90	-	-	120	-	-	150
Citric acid	20	20	20	20	20	20	20	20	20
$NaHCO_3$	51	51	51	51	51	51	51	51	51
PVP K-30	20	20	20	20	20	20	20	20	20
Lactose	72	72	72	42	42	42	12	12	12
Mg-stearate	3	3	3	3	3	3	3	3	3
Total weight	300	300	300	300	300	300	300	300	300

In vitro buoyancy results of all the preliminary trial's formulations are shown in Table 2. As the concentration of swellable polymer was increased floating lag time also increased. The floating lag time for the formulation B1 containing 90% HPMC K4M was found to be lowest (27 sec.) followed by formulation B3 containing 90% Carbopol 934P (51 sec.). Total floating lag time for all the Preliminary trial's formulations was found to be more than 24 hrs.

Table 2: Evaluation parameters of preliminary trial's formulation

Batch	Weight variation (mg) (n=20)	Hardness (kg/cm^2) (n=10)	Friability (%) (n=10)	Floating lag Time (Second)	Floating Time (hrs)
B1	300 ± 2.51	4.5 ± 0.048	0.64 ± 0.0018	27	> 24
B2	300 ± 2.53	5 ± 0.127	0.58 ± 0.0019	68	>24
B3	300 ± 2.87	4.5 ± 0.052	0.53 ± 0.0022	51	>24
B4	299 ± 3.25	4.5 ± 0.034	0.61 ± 0.0021	33	> 24
B5	300 ± 2.88	5 ± 0.15	0.63 ± 0.0025	75	>24
B6	295 ± 2.90	5.1 ± 0.137	0.52 ± 0.0016	55	>24
B7	300 ± 2.48	4.5 ± 0.028	0.62 ± 0.0015	40	> 24
B8	297 ± 2.89	5 ± 0.164	0.71 ± 0.0028	80	>24
B9	300 ± 2.75	5 ± 0.025	0.65 ± 0.0031	59	>24

From *in vitro* dissolution study of preliminary trial's formulation, it was concluded that the desired release rate of drug was observed from the polymer matrix of HPMC K4M and Carbopol 934P. The amount of drug released was found to decrease with the increase in the polymer concentration as shown in Figure 1. This could be due to the increase in the diffusion layer with the increase in the polymer concentration.

On the basis of the results obtained from preliminary screening HPMC K4M and Carbopol 934P were selected as a polymer of choice for the further studies.

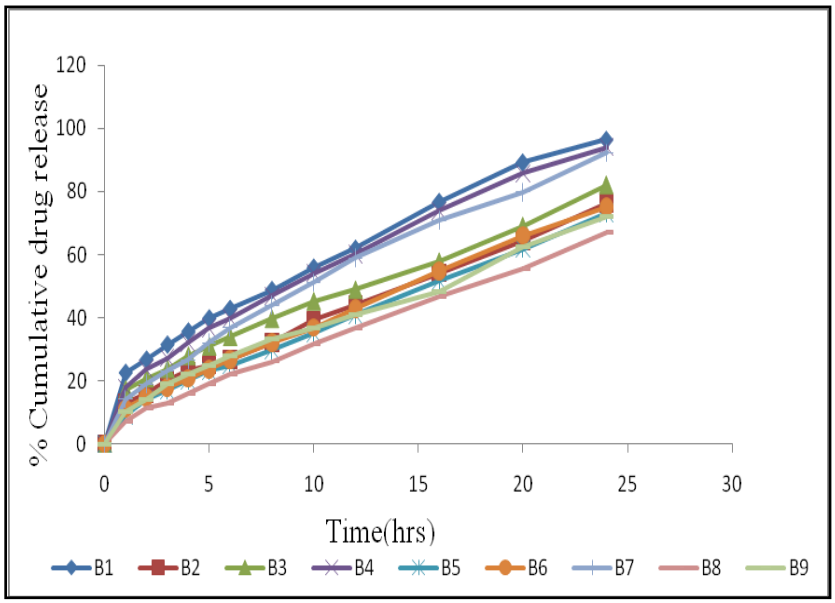

Figure 1: *Zero order plot of preliminary trial formulations*

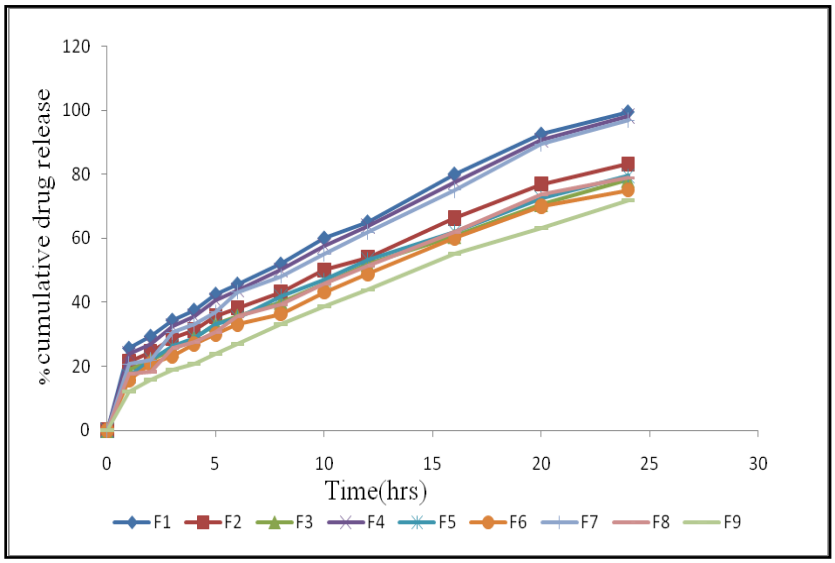

Figure 2: *Zero order plot of 3^2 factorial design formulations*

Factorial design:

A 3^2 randomized factorial design was used in the present study. In the design 2 factors (selected from the preliminary investigation) were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of HPMC K4M (X_1) and the amount of Carbopol 934P (X_2) were selected as independent variables. The time required for 50% drug release ($T_{50\%}$), release rate constant (K_0) and floating lag time (*FLT*) were selected as dependent variable. The design was evaluated by following interactive model.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2$$

Where *Y* is the dependent variable ($T_{50\%}$, K_0, *FLT*), b_0 is the arithematic mean response of the 9 runs and b_i (b_1,b_2 and b_{12}) is the estimated coefficient for the corresponding factor X_i (X_1,X_2 and X_1 X_2) which represents the average results of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) shows how the response changes when 2 Factors are simultaneously changed. The $T_{50\%}$, release rate constant (K_o), floating lag time for nine formulation (F1 – F9) showed wide variation (i.e, 5.587 – 7.352 hrs, 2.5843 – 3.4007 and 17 – 35 sec respectively). The responses of the formulations prepared according to 3^2 factorial design formulation are indicated in Table 3. The data clearly indicate that the $T_{50\%}$, releaserate(K_o), floating lag time values are strongly dependent on the selected independent variables. The fitted equation relating the response $T_{50\%}$, release rate constant (K_o), floating lag time (*FLT*) are shown in following equations, respectively.

Final Equation in Term of Coded factors:

$$T_{50\%} = 6.9 - 0.057\ X_1 + 0.790\ X_2 + 0.00875\ X_1X_2 \quad (1)$$

$$K_0 = 2.71 + 0.027\ X_1 - 0.0363\ X_2 - 0.013\ X_1X_2 \quad (2)$$

$$FLT = 29.22 + 4\ X_1 + 5.83\ X_2 + 0.5\ X_1X_2 \quad (3)$$

Table 3: Coded levels as per 3^2 Full Factorial Design with the Observed Responses

Formulation code	Variable level in coded form		$T_{50\%}$ (hours)	Release rate constant	Floating lag time (second)
	X_1	X_2			
F1	-1	-1	5.756	3.3008	17
F2	-1	0	6.914	2.7478	23
F3	-1	+1	7.352	2.5843	27
F4	0	-1	5.727	3.3175	19
F5	0	0	7.045	2.6966	29
F6	0	+1	7.244	2.6228	32
F7	+1	-1	5.587	3.4007	22
F8	+1	0	6.871	2.7651	35
F9	+1	+1	7.218	2.6322	34

Effect of formulation variables on $T_{50\%}$:

The result of multiple regression analysis and two way ANOVA, clearly shows that the coefficient of X_1, X_2 and X_1X_2 were found to be significant at $P < 0.05$ hence they were retained in polynomial equation. According to polynomial equation 1, Increasing the amount of HPMC K4M (X_1) resulted in retardation of $T_{50\%}$ as suggested by the negative sign of the coefficient of X_1, however increasing concentration of Carbopol 934P (X_2) increases $T_{50\%}$, also their interaction terms had a enhancement effect on the $T_{50\%}$.The relationship between the dependent and independent variables was further elucidated using Response surface plot (Figure 3) which confirms the result obtained from the multiple regression analysis.

Effect of formulation variables on Release rate (K_o):

The result of multiple regression analysis and two way ANOVA, clearly shows that the coefficient of X_1, X_2 and X_1X_2 were found to be significant at $P < 0.05$ hence they were retained in polynomial equation. According to polynomial equation 2, increasing the amount of HPMC K4M (X_1) resulted in the higher value of release rate. However ascending the amount of Carbopol 934P (X_2) is having reducing effect on release rate constant. While their interaction term is having increasing effect on release rate (K_o). The relationship between the dependent and independent variables was further elucidated using Response surface plot (Figure 4) which confirms the result obtained from the multiple regression analysis.

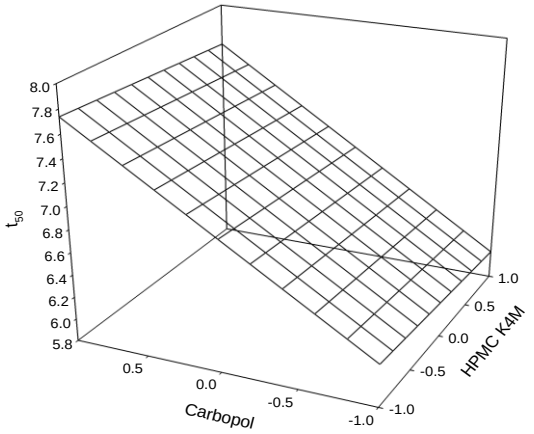

Figure 3: *Response surface plot for $T_{50\%}$*

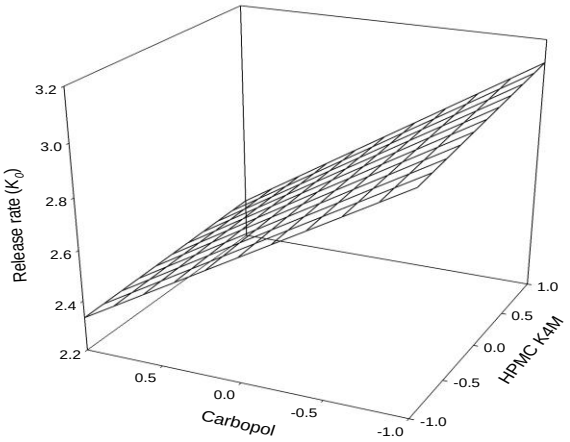

Figure 4: *Response surface plot for Release rate (K_o)*

Effect of formulation variables on Floating lag time (*FLT*)

The tablet floating lag time (FLT) for the 3^2 factorial design formulations was found to be in the range of 17 to 35 seconds. The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated in situ. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix. On the other hand, as solvent front penetrated the glassy polymer layer, the swelling of HPMC K4M and Carbopol 934P caused an increase in volume of the tablet. From this study it was concluded that as the concentration of swellable polymer increase floating lag time is also increased. The floating lag time was observed to be less with formulation containing HPMC K4M as compared to those containing Carbopol 934P.

The result of multiple regression analysis and two way ANOVA, clearly shows that the coefficient of X_1, X_2 and X_1X_2 are significant at $P < 0.05$ hence they were retained in the polynomial equation. According to polynomial equation 3, Increasing the amount of either HPMC K4M *(X_1)* and Carbopol 934P *(X_2)* resulted in enhancement of floating lag time as suggested by the positive sign of the coefficient of X_1 and X_2 and also their interaction terms had a enhancement effect on the floating lag time (*FLT*) of floating tablet. The relationship between the dependent and independent variables was further elucidated using Response surface plot (Figure 5) which confirms the result obtained from the multiple regression analysis.

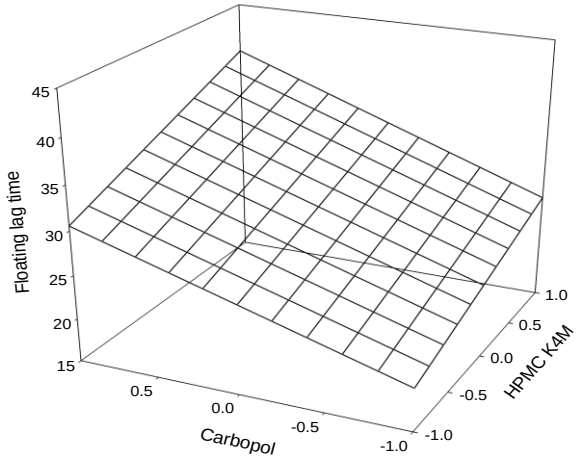

Figure 5: *Response surface plot for Floating lag time (FLT)*

Conclusion

A systemically study using a 3^2 factorial design revealed that the amount of HPMC K4M (X_1) and amount of Carbopol 934P (X_2) had a significant effect on ($T_{50\%}$), Release rate (K_o) and Floating lag time (*FLT*). The formulation F1 was selected as an optimized formulation because it gave the best result in terms of the required *in vitro* buoyancy study and drug release in sustained release manner which is shown in figure 2. In dissolution study of all the formulation it was observed that by increasing concentration of polymer, release rate of drug retarded.

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