

FORMULATION AND PROCESS OPTIMIZATION OF GASTRO-RETENTIVE FLOATING TABLET OF ONDANSETRON HCL

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ABSTRACT

Ondansetron HCl is a potent, highly selective 5-HT₃ receptor-antagonist used to prevent nausea and vomiting, mainly in patients undergoing chemotherapy and radiation treatments. The aim of present work was to formulate, evaluate and optimize gastro-retentive tablet of Ondansetron HCl which would be advantageous, that can provide prolong gastric retention and increase efficacy of the dosage form. In formulation optimization, different formulation of HPMC polymer, NaCMC and NaHCO₃ were studied with help of 3² full factorial designs. It was found that HPMC K4M with concentration 40%, NaCMC 5% and NaHCO₃ with 17% concentrations showed good

sustained and floating ability and it releases 94.51% drug within 24 hrs. During study of effect of process parameters, it was concluded that release of drug decreases with decreasing granular size. The drying time (10 and 20 min) and drying temperature (40° and 50°C), does not have any significant effect on the release profile of drug.

KEY WORDS

Ondansetron HCL, gastro retentive, 5-HT₃ receptor-antagonist, 3² full factorial design, HPMC(Hydroxy Propyl Methyl Cellulose) K4M, NaCMC (Na Carboxy Methyl Cellulose), NaHCO₃

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a significant adverse side effect for patients receiving chemotherapy. Patients treated with chemotherapy may experience anticipatory, acute, and delayed nausea and vomiting. The choice of antiemetic therapy is a vital part of preventing these symptoms and enhancing patient satisfaction. In addition, consideration of the emetogenic potential of chemotherapy agents is important for appropriate prescribing of antiemetics. This program will review the pathophysiology of CINV, antiemetic pharmacology, and appropriate guidelines for prophylaxis of CINV.

Ondansetron is used to prevent the nausea and vomiting that may occur after therapy with anticancer medicines (chemotherapy) or radiation, or after surgery. Ondansetron hydrochloride has a short biological half-life (3.5 ± 1.2 hours) and 62 % absolute bioavailability. Dose of the drug is 0.15 mg/kg, 3 times/day beginning 30 minutes prior to chemotherapy or 0.45 mg/kg once daily or 8-10 mg 1-2 times/day or 24 mg or 32 mg once daily.^[2]

To reduce frequency of administration of the drug and for patient compliance, gastro retentive tablet of Ondansetron HCl were prepared in order to release loading dose as well as maintenance dose of Ondansetron HCl through increasing residence time in stomach with the help of floating mechanisms. Tablets were prepared by wet granulation method using different polymer like HPMC, Klucel HXF, Carbopol 934P, and NaCMC. Sodium bicarbonate used as a gas

generating agents. Tablet was also tested with physicochemical properties.^[1-3]

MATERIALS & METHODS

Materials

Ondansetron HCl was obtained as a gift sample from Lincoln Pharmaceuticals Ltd, Ahmedabad, India. HPMC K4M was obtained as gift sample from Jaxani Pharma, Ahmedabad, India. Klucel HXF was obtained from Cadila Pharma, Ahmedabad. Carbopol 934P, Sodium carboxy methyl cellulose, Sodium bicarbonate was obtained from S. D. Fine chemicals, Mumbai, India. All other ingredients were of laboratory grade.

Methods

Preparation of standard calibration curve of ondansetron HCL

Ondansetron HCl (10 mg) was dissolved in 0.1 N HCl (P^H=1.2) and volume was made up to 100 ml in 100 ml volumetric flask. This solution (100 µg /ml) was further diluted with 0.1 N HCl to obtain solution of 5 to 25 µg /ml. Absorbance of each solution was measured at 310 nm using Shimadzu UV-1700 UV/VIS double beam spectrophotometer and 0.1 N HCl as reference standard. The standard calibration curve was generated for the entire range from 0 to 25 mcg/ml.

Calculation of total dose and theoretical drug release profile^[3,4]

The pharmacokinetic parameters of Ondansetron HCl were utilized for the calculation of theoretical drug release profile for 24 hrs dosage form. The immediate release part (loading dose) of Ondansetron HCl was calculated using following equation.

$$IRD = \frac{C_{ss} \times V_d}{F}$$

Where, C_{ss} is steady-state plasma concentration, V_d is volume of distribution, and F is fractional bioavailability. The total dose of Ondansetron HCl required for 24 hrs release profile was calculated using following equation.

Dose = Immediate release part $\{1 + (0.693 * t/t_{1/2})\}$

Drug excipients interaction study^[5]

The pure drug, Ondansetron HCl and a mixture of drug with the polymer HPMC K4M and NaCMC was examined by DSC using a shimadzu DSC-50 differential scanning calorimeter at 20° C/min over a temperature range of 50° - 300° C.

Measurement of viscosity of polymer^[6]

To prepare 2% (w/v) an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, and then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume. The viscosity of solution was measured using Brookfield digital viscometer.

Optimization of HPMC concentration using 3² full factorial design

A 3² randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The factors were selected based on preliminary study. The Content of HPMC (X1) and Viscosity of HPMC (X2) were selected as independent variables. The time required for 50% drug release ($t_{50\%}$), release at 24hrs (Q_{24hrs}) and similarity factor f_2 were selected as dependent variables.

In vitro dissolution study^[1]

The release rate of Ondansetron HCl from sustained release tablets was determined 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 ($P^H=1.2$), at 37 ± 0.5°C and 50 rpm.

Comparison of dissolution profile^[7]

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 are considered to be similar when f_2 is between 50 and 100⁷. The dissolution profiles of products were compared using f_2 . This similarity factor is calculated by following formula,

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

Where, n is the number of dissolution time and R_t and T_t are the reference and test dissolution values at time t .

In vitro buoyancy study^[8]

The tablets were placed in 100 ml beaker containing 0.1 N HCl ($P^H=1.2$). The time required for the tablets, to rise to the surface and float, was determined as floating lag time.

Optimization of NaCMC & NaHCO₃

A 3² randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The Content of NaCMC (X1) and Content of NaHCO₃ (X2) were selected as independent variables. The time required for 50% drug release ($t_{50\%}$), release at 24hrs (Q_{24hrs}) and similarity factor f_2 were selected as dependent variables.

Evaluation of physical parameters of prepared tablets^[9]

Prepared gastro retentive tablets of Ondansetron HCl tablet were evaluated for various parameters like, weight variation test, hardness, friability etc.

Kinetic modeling and mechanism of drug release^[10]

Data obtained from *In vitro* drug release studies were fitted to dissocalculation software. The kinetic models used are zero order, first order, Korsmeyer's, Hexon crowell and Higuchi equation.

$$\frac{M_t}{M_\infty} = kt^n$$

Where, M_t/M_∞ is the fraction of drug released at time t , k the kinetic constant, and n the release exponent.

Process Optimization of Ondansetron floating tablet

- ✓ Effect of granule size,
- ✓ Effect of drying time & drying temperature,
- ✓ Effect of thickness.

RESULTS & DISCUSSIONS:

Calculation of total dose

$$\begin{aligned} \text{IR} &= \frac{C_{ss} \times V_d}{F} \\ &= \frac{39 \text{ ng/ml} \times 1.9}{0.62} \\ &= 39 \times 10^{-6} \text{ mg/ml} \\ &= 7.17 \text{ mg} \end{aligned}$$

$$\frac{\text{lit/kg}}{x 1.9 \times 10^3 \text{ ml} \times 60}$$

$$\begin{aligned} \text{Total Dose (TD)} \\ \text{TD} &= \text{IR} [1 + (0.693 \times t_{1/2})] \\ &= 7.17 [1 + (0.693 \times 23/4.1)] \\ &= 35 \text{ mg.} \end{aligned}$$

Drug excipient compatibility study

From the drug excipient compatibility study, it is concluded that the given drug ondansetron is compatible with all excipients.

Measurement of viscosity of polymers

The viscosity of polymer of different grade of HPMC K4M, HPMC15M & HPMC K100M solution was measured using Brookfield digital viscometer.

In vitro dissolution profile of factorial batches

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel 2003. The data clearly indicated that the values of $Q_{24\text{hrs}}$, $t_{50\%}$, and f_2 were strongly dependent on the independent variables. The fitted Equations relating the response $Q_{24\text{hrs}}$, $t_{50\%}$, and f_2 to the transformed factor are shown in following Equations.

$$\begin{aligned} Q_{24\text{Hrs}} &= 88.17 - 3.44 X_1 - 12.24 X_2 - 0.475 X_1 X_2 - 0.42 X_1^2 - 3.32 X_2^2 \\ (R^2 &= 0.9965) \end{aligned}$$

$$\begin{aligned} t_{50\%} &= 9.94 + 1.5 X_1 + 4.07 X_2 - 0.14 X_1 X_2 + 0.38 X_1^2 + 1.21 X_2^2 \\ (R^2 &= 0.9935) \end{aligned}$$

$$\begin{aligned} f_2 &= 51.08 + 0.71 X_1 - 10.38 X_2 - 9.13 X_1 X_2 + 3.95 X_1^2 - 2.75 X_2^2 \\ (R^2 &= 0.8090) \end{aligned}$$

The value of correlation coefficient indicates good fit. The polynomial Equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, (i.e. positive or negative).

In case of depended variable $Q_{24\text{hrs}}$, p value for factor X1 and X2 was found to be 0.0042 and 0.0001 respectively which clearly depicts that the both the factors i.e content of HPMC and viscosity of HPMC has individually influence on drug release. All other factor has P values greater than 0.005 ($p > 0.005$). Thus, it was concluded that the percentage of drug release depends on both, content and viscosity of HPMC.

In case of depended variable $t_{50\%}$, p value for factor X2 was found to be 0.0002 which clearly depicts that factor X2 i.e. viscosity of HPMC has influence on drug release. All other factor has P values greater than 0.005 ($p > 0.005$). Thus, it was concluded that the percent of drug release depends on viscosity of HPMC.

Comparison of dissolution profiles

In vitro drug release profile of all batches of factorial design was compared with theoretical drug release profile. The result shows that Batch N3 (120mg of HPMC K4M) shown highest f_2 value which is 77.33 and it releases the loading dose (18.73%) which is nearest to theoretical drug release profile (20.48%).

Swelling Index ^[11]

The swelling index of tablets was determined in 0.1 N HCl (P^H 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation. Determinations were made in triplicate.

$$\text{Swelling index} = \frac{W_t - W_0}{W_t}$$

Where, W_0 is the initial weight of tablet, and W_t is the weight of the tablet at time t.

Physical parameters of prepared tablets ^[9,12]

All the tablet formulations showed acceptable pharmacopoeial properties and complied with the in-house specifications for weight variation, hardness and friability.

Effect of granule size

So it was clearly seen that the tablets prepared with 20# granules has high porosity. Due to its high porosity it has the low hardness and thus it has low floating lag time (35 sec). This batch showed highest f_2 value which is 81.37. So, granules pass through mesh 20# was kept optimum.

Effect of drying time & drying temperature

Effect of drying time and drying temperature were not so much on release of drug. So, 10 min drying time and 50°C drying temperature were kept optimum.

Effect of tablet thickness

As the thickness of tablet decrease, tablet became harder and thus friability of the tablets decreases and drug release is also retarded. So, batch T2 having 3.6 mm thickness of tablet was kept optimum.

Formulations Code	A	B	C	D	E	F	G	H	I
Ondansetron HCl	35	35	35	35	35	35	35	35	35
HPMC K4M	120	120	120	120	120	120	120	120	120
NaCMC	15	15	15	30	30	30	45	45	45
NaHCO ₃	42	51	60	42	51	60	42	51	60
PVP K-30	20	20	20	20	20	20	20	20	20
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lactose	59	50	41	44	35	26	29	20	15
Mg-stearate	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6
Total weight	300	300	300	300	300	300	300	300	300

*All weights are in mg

Table 1 : Formulation using 3² full factorial design in optimization of NaCMC.

Ingredients	Quantity (mg)
Ondansetron HCl	35
HPMC K4M	120
NaCMC	15
NaHCO ₃	51
PVP K-30	20
IPA	q.s.
Lactose	50
Mg-stearate	3
Talc	6
Total weight	300

CONCLUSION :

A 3² full factorial design was applied to systemically optimize polymer concentration. The content of HPMC (X1) and Viscosity of HPMC (X2) were selected as independent variables. The time required for 50% drugs released ($t_{50\%}$), Q_{24hrs} , similarity factor f_2 were selected as dependent variables. The results of full factorial design was indicated that the X2 (content of HPMC) and X2 (Viscosity of HPMC) both have significant effect on *in vitro* drug release profile. Optimized area was obtained with help of counter plot. From contour plot, it was conclude that HPMC having content 120 mg and viscosity 5600 cps will give the satisfactory drug release. The similarity factor f_2 was applied between the *in vitro* drug release profile of factorial design batches and theoretical drug release

Table 2 : Optimized formula of ondansetron floating tablet

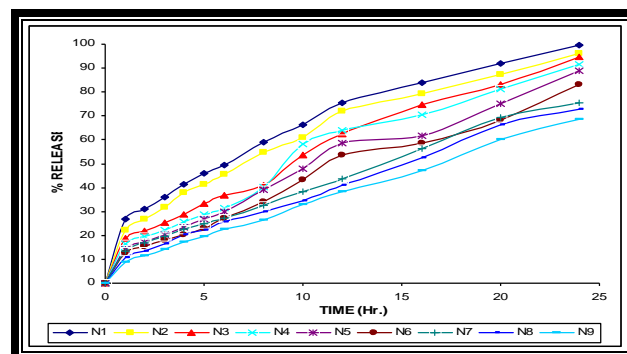


FIG 1 : Drug release profile of factorial batches in HPMC optimization

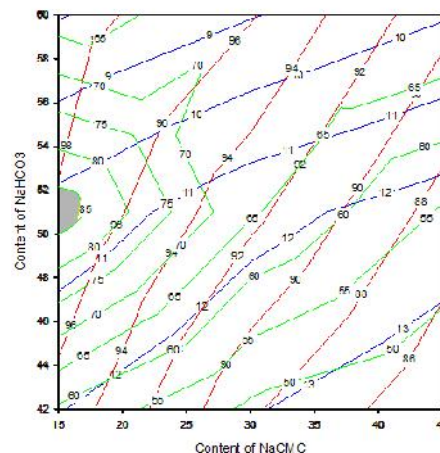


FIG 2 : Overlapping Counter plot of content of NaCMC (X1) and content of NaHCO₃(X2) versus Q_{24hrs} , $t_{50\%}$, f_2

profile. It was conclude that batch N3 containing HPMC K4M, 40% was optimize for further work. From *in-vitro* buoyancy studies, it was found that floating lag time of all factorial batches was less than two minutes. From all above study it was cleared that process parameters like thickness, granules size, drying time and drying temperature have great influence on performance of the floating tablets. So such parameters are critically maintain or put at their optimum level during the manufacturing of the floating tablets to obtained desired properties of floating tablets, like floating lag time and floating time, optimum hardness and friability and drug release.

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