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 3^2 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.

KEY WORDS

Ondansetron HCl, gastro retentive, 5-HT3 receptor-antagonist, 3^2 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]
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.

\[
IRD = \frac{CSS \times Vd}{F}
\]

Where, \(CSS\) is steady-state plasma concentration, \(Vd\) 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.

\[
\text{Dose} = \text{Immediate release part} \{1 + (0.693 \times t_{1/2})\}
\]

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 (\(Q_{24hr}\)) 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 (PH=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 100. The dissolution profiles of products were compared using \(f_2\). This similarity factor is calculated by following formula,

\[
f_2 = 50 \log \left( \frac{1}{n} \sum_{i=1}^{n} \left( \frac{R_i - T_i}{R_i} \right)^2 \right)^{0.5} \times 100
\]

Where, \(n\) is the number of dissolution time and \(R_i\) and \(T_i\) 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 (PH=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 (\(Q_{24hr}\)) 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, \(M_t/M_\infty\) 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

\[ IR = \frac{Css \times V_d}{F} \]

\[ = \frac{39 \text{ ng/ml} \times 1.9}{0.62} \]

\[ = \frac{39 \times 10^{-6} \text{ mg/ml}}{0.62} \]

\[ = 7.17 \text{ mg} \]

Total Dose (TD)

\[ TD = IR \left[ 1 + (0.693 \times \frac{t}{t_{1/2}}) \right] \]

\[ = 7.17 \left[ 1 + (0.693 \times 23/4.1) \right] \]

\[ = 35 \text{ mg.} \]

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_{24hrs}, t_{50%}, and f_2 were strongly dependent on the independent variables. The fitted Equations relating the response Q_{24hrs}, t_{50%}, and f_2 to the transformed factor are shown in following Equations.

\[ Q_{24h} = 88.17 - 3.44 X_1 - 12.24 X_2 - 0.475 X_1 X_2 - 0.42 X_1^2 - 3.32 X_2^2 \]

\[ (R^2 = 0.9965) \]

\[ t_{50%} = 9.94 + 1.5 X_1 + 4.07 X_2 - 0.14 X_1 X_2 + 0.38 X_1^2 + 1.21 X_2^2 \]

\[ (R^2 = 0.9935) \]

\[ f_2 = 51.08 + 0.71 X_1 - 10.38 X_2 - 9.13 X_1 X_2 + 3.95 X_1^2 - 2.75 X_2^2 \]

\[ (R^2 = 0.8090) \]

Swelling Index
The swelling index of tablets was determined in 0.1 N HCl (PH 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.

\[ \text{Swelling index} = \frac{W_t - W_0}{W_i} \]

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

Physical parameters of prepared tablets
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
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<th>Quantity (mg)</th>
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<tbody>
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<td>35</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>120</td>
</tr>
<tr>
<td>NaCMC</td>
<td>15</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>51</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>20</td>
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<td>IPA</td>
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<tr>
<td>Talc</td>
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<tr>
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Table 1: Formulation using 3² full factorial design in optimization of NaCMC.

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 (t₅₀%), Q₂₄hrs, similarity factor f₂ 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 f₂ was applied between the in vitro drug release profile of factorial design batches and theoretical drug release 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.

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 Q₂₄hrs, t₅₀%, f₂

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