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Formulation Development and Evaluation of Ondansetron Hydrochloride sustained release Matrix tablets

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Abstract

The objective of the present study was to develop sustained release matrix tablets of Ondansetron hydrochloride [5mg] formulated employing Hydroxy Propyl Methyl Cellulose polymer and the sustained release behaviour of the tablets was investigated. Tablets were prepared by wet granulation methods. The granules were evaluated for angle of repose, bulk density and drug content .The tablets were subjected to thickness, diameter, weight variation test, hardness, friability, drug content and in vitro release studies. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The results of dissolution studies indicated that formulation FV (drug to polymer ratio 1:3) the most successful of the study, exhibited drug release pattern very close to theoretical release profile. All the formulations (except FV) exhibited diffusion – dominated drug release. The mechanism of drug release from FV was diffusion coupled with erosion.

Keywords: Ondansetron, Hydroxy Propyl Methyl Cellulose, Sustained release, Matrix tablets.

Introduction

Ondansetron is a 1,2,3,9-tetrahydro – 9 – methyl – (2 - methyl – 1-H- imidazol – 1- yl) methyl - 4H – carbazol – 4 – One, monohydrochloride[1]. Ondansetron is a short acting drug for 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 $5HT_3$ receptor. It blocks the initiation of these reflexes [2,3]. It is short biological half life 3.1 h.

The sustained release drug delivery is to ensure safety and to improve efficacy of the drug as well as patients compliance. The dosage release properties of matrix devices may be dependent upon the solubility of the drug in the polymer matrix. Hydroxy Propyl Methyl Cellulose (HPMC) is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems [4]. Numerous studies have been reported in literature review of the control the release of drug from matrixes [5-7]

The objective of the present study was to formulate Ondansetron sustained release dosage form using HPMC [K4M, K15M, K100M] polymer and to elucidate the release pattern of drug form SR matrix tablets, and compare with the theoretical sustained release profile.

Materials and Methods

Ondansetron hydrochloride USP was obtained from Natco Pharma Ltd. Hyderabad. Microcrystalline cellulose IP was obtained from FMC Biopolymer, Mumbai, HPMC IP (K4M, K15M, and K100M), Pregelatinized starch IP (starch 1500) was procured from Colorcon Asia Pvt. Ltd., Mumbai. Other materials and excipients used in preparing tablets were I.P Grade. All other ingredients used throughout the study were of analytical grade.

Calculation of theoretical release profile of Ondansetron Hydrochloride from Sustained Release tablets:

The total dose of Ondansetron for a once daily sustained release formulation was calculated by the following equation [8] using available pharmacokinetic data [9]. The zero order drug release rate constant (ko) was calculated using equation K^0=DI ×Kel, where DI is the initial dose (2mg) and Ke is first order rate constant for overall elimination and was found to be 0.2235mg/h. The loading dose was calculated as 0.447mg/h. Hence an oral controlled release formulation of Ondansetron hydrochloride should contain a total dose of 5.69mg (≈5mg) and should

release 0.447 mg in first h like conventional tablets and 0.2235 mg/h up to 12h thereafter.

Preparation of matrix tablets:

Different tablet formulations were prepared by wet granulation technique (table1). All the powders were passed through mesh 60 # sieve. Required quantity of drug and polymer were mixed thoroughly and a sufficient volume of granulating agent was added slowly. After enough cohesiveness was obtained the mass was sieved through 22/44 # mesh. The granules were dried at 40^o C for 12 h. Avicel pH 10.1, Magnesium stearate as lubricant. The practical weight of tablet was calculated based on the drug content of the granulation, and the tablets were compressed using a single punch tablet compression machine. Each tablet contains 5 mg of Ondansetron and other ingredients as listed in table 1.

Evaluation of tablets:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets were tested using a strong – Cobb hardness tester (Tab machine, Mumbai). Friability of the tablets was determined in a Roche friabilator (Campbell electronics, Mumbai). The thickness of the tablet was measured by Vernier calipers. Weight variation test was performed according to official method[10]. Drug content of Ondansetron Hydrochloride was carried out by HPLC method and the chromatographic conditions are column - Lichrosphere, CN, 250 × 4.6mm, 5 µm, wavelength: 247nm, flow rate: 1ml\min, injection volume: 20µl, run time: 15 min, UV-detector and the mobile Phase composition is buffer and acetonitrile 50:50 v/v, comparing the content from the calibration curve prepared with standard Ondansetron hydrochloride in the same medium.

In vitro drug release studies:

The in vitro dissolution studies were carried out using USP 24 dissolution apparatus type II [10] (Paddle method) at 100 rpm. Dissolution test was carried out for a total period of 12 h using 0.1 N HCl (pH 1.2) solution (750 ml) as dissolution medium at 37 ± 0.5^o C for first 2 h, and pH 6.8 phosphate buffer solution (1000 ml) for the rest of the period. 10 ml of the sample was withdrawn at regular interval and replaced with the same volume pre-warmed (37 ± 0.5^o C) fresh dissolution medium. The samples withdrawn were filtered through 0.45µ membrane filter, and the drug content in each sample was analyzed after suitable dilution by above – mentioned HPLC method. The actual content in samples was read from a calibration curve prepared with standard Ondansetron hydrochloride.

Stability studies:

One selected fabricated tablet batch was strip packaged and kept at RT & 40^o C with 75% RH. Samples were withdrawn at 0, 30 days for evaluation of drug content and in vitro drug release.

Results and Discussion

The granules of different formulation were evaluated for Loose Bulk Density (LBD), Tapped Bulk density (TBD) and angle of Repose (Table 2). The result of LBD and TBD ranged from 0.424 ± 0.02 to 0.496 ± 0.03 and 0.570 ± 0.03 to 0.696 ± 0.02 respectively. The result of angle of repose was found to be 27^o.17 ± 0.02 to 27^o.66 ±0.02.

The thickness of the tablets ranged from 2.51 ± 0.01 to 2.53 ± 0.06 mm. the hardness and percentage friability of the tablets in all batches ranged from 48 ± 2 to 65 ± 4 kg/cm^2 and 0.28 ± 0.02 to 0.79 ± 0.03 respectively (Table 3).

Drug content was found to be uniform among different batches of the tablets and ranged from 97.5 ± 0.1 to 101.5 ± 0.2 (Table 3). All the batches of the

Table 1

Formulation of sustained release tablet of Ondansetron hydrochloride

i) For Core Tablet

Batch (Ingredients)	F – I (mg)	F – II (mg)	F – III (mg)	F – IV (mg)	F – V (mg)
Ondansetron HCl	5.02	5.02	5.02	5.02	5.02
Lactose Monohydrate	45.73	45.73	45.73	45.73	45.73
Micro crystalline Cellulose (Avicel pH 101)	10.00	10.00	10.00	10.00	10.00
Pregelatinized Starch	7.5	7.5	7.5	7.5	7.5
Purified Water	26 ml	27 ml	25.5 ml	25.5 ml	27 ml
Micro crystalline Cellulose (Avicel pH 101)	7.5	7.5	7.5	7.5	7.5
HPMC K 4M	12.55	15.06	-	-	-
HPMC K 15M	-	-	12.55	15.06	-
HPMC K 100M	-	-	-		15.06

ii) For film coating

Batch / Ingredients	F – I (mg)	F – II (mg)	F – III (mg)	F – IV (mg)	F – V (mg)
HPMC 15 cps	1.230	1.230	1.230	1.230	1.230
Dibutyl phthalate	0.015	0.015	0.015	0.015	0.015
PEG 6000	0.055	0.055	0.055	0.055	0.055
Talc	0.500	0.500	0.500	0.500	0.500
Titanium Dioxide	0.200	0.200	0.200	0.200	0.200
Dichloromethane	q.s	q.s	q.s	q.s	q.s
Isopropylalcohol	q.s	q.s	q.s	q.s	q.s
Ratio of polymer	1:2.5	1:3	1:2.5	1:3	1:3

Table 2
Evaluation of granules

Sr. No.	Formulation	Loose Bulk Density	Tapped Bulk Density	Angle of Repose
1	F – I	0.4967 ± 0.03	0.6102 ± 0.02	27°56 ± 0.02
2	F – II	0.4244 ± 0.02	0.5703 ± 0.03	27°17 ± 0.02
3	F – III	0.4377 ± 0.02	0.6212 ± 0.03	27°56 ± 0.01
4	F – IV	0.4955 ± 0.03	0.6968 ± 0.02	27°66 ± 0.02
5	F – V	0.4951 ± 0.03	0.6899 ± 0.02	27°58 ± 0.01

Mean ± SD n = 3

Table 3
Physical Parameters and Percentage Drug Release of Fabricated Tablets

Sr. No.	Formulation	Average tablet weight (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Diameter (mm)	Friability (%)	Percentage of Drug Release
1	F-I	93.50	52 ± 2	2.53 ± 0.03	5.92	0.54± 0.03	101.5 ± 0.3
2	F-II	93.01	65 ± 4	2.52 ± 0.02	5.92	0.28± 0.02	102.5 ± 0.2
3	F-III	94.10	50 ± 5	2.52 ± 0.01	5.92	0.56± 0.03	100.1 ± 0.3
4	F-IV	92.55	48 ± 2	2.53 ± 0.06	5.92	0.71± 0.03	97.7 ± 0.1
5	F-V	92.32	60 ± 1	2.51 ± 0.01	5.92	0.79± 0.03	98.9 ± 0.4

Mean ± SD n = 6

Table 4
In vitro release Profile of F – V & Ms – I Tablets kept after storage at 40°C/75% RH, Room temperature for 30 days

Time Interval in hrs	Percentage Drug release (Mean ± SD) n = 3			
	F – V		MS I	
	Initial	After 30 days	Initial	After 30 days
1	23.2	24.0	25.2	26.2
4	45.8	47.1	43.0	46.0
8	71.2	70.6	75.0	75.2
12	104.4	102.5	101.2	101.5
Assay (%)	98.9	97.9	101.9	101.18

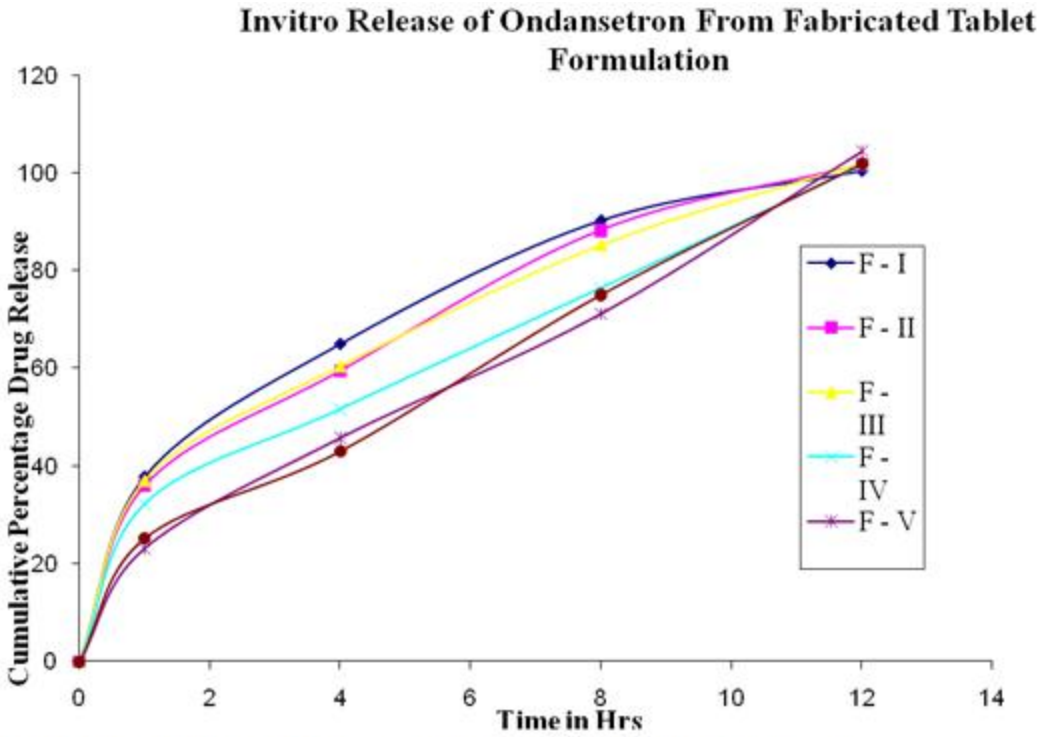

Fig 1. In vitro Release of Ondansetron from Fabricated Tablet Formulation

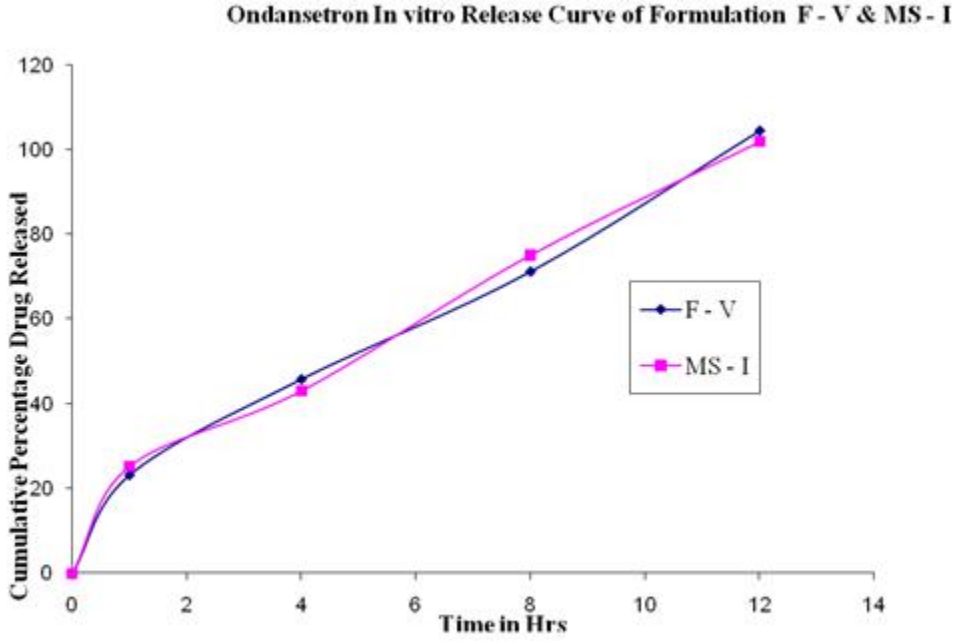

Fig 2. Ondansetron In vitro Release Curve of Formulation F - V & MS – I

fabricated tablets were of good quality with regard to hardness, thickness, friability and drug content. All the tablets complied with pharmacopeial specification for weight variation and friability.

The result of dissolution studies of formulation FI to FV are shown in figure 1. Drug release from the matrix tablets was found to be decrease with increase in drug polymer ratio. Formulation FI compared of drug polymer (HPMC K4M) ratio of 1:2.5 failed due t release is fast. Formulation FII, FIII and IV formulated HPMC K4M (1:3), HPMC K15M (1:25) HPMC K15M (1:3) respectively. FII, III and IV released 57.49, 60.42, 51.65 of Ondansetron at the end of 4 h and drug release is not similar to that of marketed sustained release tablets. F V was composed drug. Polymer HPMC K100M ratio 1:3 and gave release profiles were satisfactory.

The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. HPMC used in hydrophilic matrix drug delivery systems has been employed to formulate sustained release tablets of Ondansetron. The hydration rate of HPMC depends n the nature of these substitutions. The hydration rate of HPMC increase with an increase in the Hydroxy Propyl content. The solubility of HPMC is pH independent [11,12] HPMC K100 M was used FV formulation because it forms a strong viscous gel on contact with aqueous media which may be useful in controlled delivery of highly water soluble drug.

The in vitro drug release characteristics were studied in simulated gastric and intestinal fluid for a period of 12 h using USP 24 dissolution apparatus. the theoretical release profile calculation is important to evaluate the formulation with respect rates and ascertain whether it release the drug in a predetermined manner [12] according to the theoretical sustained release profile an sustained release formulation of Ondansetron hydrochloride should provide a release of 23.2% in 1 h, 45.8% in 4 h, 71.2% in 8 h and 104.4% in 12 h. formulation V tablets gave release profile near to theoretical sustained release needed for Ondansetron. The release from formulation was also comparable to that f a commercially available SR tablet tested fig 2.

The data for stability studies carried out for FV batch at 45^{o}C with 75% RH for 30 days revealed that no changes occurs in drug contents and dissolution rate were observed table 4 .

It may be calculated from the present study that slow, controlled and complete release of Ondansetron over a period of 12 h was obtained from matrix tablet (FV) formulated employing drug polymer ratio of 1:3. It is also evident from the results that formulation V is a better system for twice daily SR of Ondansetron hydrochloride.

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