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Once daily sustained release tablets of Ondansetron, a novel Anti-emetic

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ABSTRACT

The study aimed to formulate and evaluate sustained release ondansetron tablet. Conventional ondansetron tablets not only produce rapid and relatively high peak blood levels resulting in adverse effects but also should be administered three to four times daily. These drawn backs can be overcome by designing a suitable sustained release formulation. Sustained release tablets of ondansetron to be taken once daily were formulated with ondansetron hydrochloride equivalent to 8 mg of ondansetron base. Matrix system based on swellable as well as non-swellable polymers was selected for sustaining the drug release. Different polymers such as hydroxypropylmethylcellulose (HPMC), Carbopol were studied. Combinations of non-swellable polymers with HPMC were also tried in order to get the desired sustained release profile over a period of 24 h. The effect of drug to polymer ratio on in vitro release was studied. The marketed formulation was evaluated for different parameters such as appearance, weight variation, drug content and in vitro drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. In vivo studies were carried out for the optimized formulation in six healthy human volunteers and the pharmacokinetic parameters.

Keywords: Ondansetron; Matrix system; Hydroxypropylmethylcellulose; Carbopol; In vivo studies

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INTRODUCTION

Ondansetron is a serotonin (5-hydroxytryptamine) subtype 3 (5-HT_3) receptor antagonist used in the management of nausea and vomiting[1-3]. 5-HT_3 receptors, located centrally in the chemoreceptor trigger zone of the area postrema as well as peripherally on vagal nerve terminals, are key receptors in the nausea and vomiting response [4]. Ondansetron has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy and surgery [5-6]. Intravenous and oral dosage forms of the drug are commercially available. Following oral administration, ondansetron hydrochloride is well absorbed and undergoes first-pass metabolism. The absolute oral bioavailability averages 67%. A single 8 mg dose administered either in tablet or in solution form produces peak plasma concentrations of about 0.03 to 0.04 μg/ml after 1.5 to 2 hours of administration. The recommended oral dosing regimen of ondansetron hydrochloride for emeogenic neoplastic agents is 8 mg, three times a day. Sustained-release formulations may enable the ondansetron dosing-frequency to be reduced, and therefore increase patient compliance.

The present research endeavour was directed towards the development of a sustained release dosage form of ondansetron in the form of tablets to be taken once daily. Different polymers hydroxypropylmethyl cellulose (HPMC), Carbopol were tried. Combinations of non-swellable polymers with HPMC were also tried in order to get the desired sustained release profile over a period of 24 h. The tablets were evaluated for different physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and in vitro release. The drug release data were plotted using various kinetic equations to evaluate the drug release mechanism. The marketed formulation was evaluated for different physico-chemical parameters and the in vitro release of Ondansetron from the developed formulations was compared with the marketed one. The marketed product is available as tablets containing Ondansetron hydrochloride equivalent to Ondansetron 8 mg in the form of Immediate Release tablets. The optimized formulation was subjected to accelerated stability studies as per ICH guidelines[7]. Pharmacokinetic studies were carried out for the optimized formulation and compared with the internationally marketed formulation.

At present there are no sustained release ondansetron hydrochloride tablets available in the market. A sustained release ondansetron tablet can lead to the reduction of the number of doses administered, less of a chance of overdose, and it is good dosage form for treatment of chemotherapy induced nausea and vomiting in patients with cancer.

MATERIALS AND METHODS

Materials

Ondansetron hydrochloride (OND) was obtained from Micro chem. Services (Bangalore, India), HPMC (Methocel – K100–CR, apparent viscosity, 2% in water at 20°C is 80,000-12000 cP) and starch 1500 were gift samples from Colorcon (Goa, India). Polyvinyl pyrolidine (PVP-K-30) was a gift sample from Anshul Agencies (Mumbai, India). Aerosil was purchased from Degussa (Mumbai, India). Lactose was

purchased from Lactose Limited (Mumbai, India). All the other chemicals were of analytical grade or HPLC grade.

Preparation of OND tablets

Ondansetron hydrochloride SR tablets were prepared by the wet granulation method. All the composition, with the exception of magnesium stearate and aerosil were thoroughly mixed in a tumbling mixer for 5 min and wetted in a mortar with isopropyl alcohol. The wet mass was sieved (16 mesh) and granules were dried at 60°C for 2 h. The dried granules were sieved (22 mesh) and these granules were lubricated with a mixture of magnesium stearate and aerosil (2:1). The ondansetron tablets were prepared using an electrically operated punching machine. Compression was performed after granulation process with a single punch press applying a compression force of a 9 KN (preliminary work) or 12 KN (experimental design), equipped with a 6 mm concave punch. For the preliminary work, batches of 100 tablets were prepared. Each batch of experimental design consisted of 100 tablets (drug content in the tablet was 8 mg). Three batches were prepared for each formulation and the compositions of different batches of ondansetron hydrochloride SR tablets are given in Table 1. The compressed tablets were evaluated for average weight and weight variation, thickness, diameter, drug content & content uniformity, hardness, friability, disintegration and In vitro drug release.

Table 1. Formulation prepared by wet granulation method (F_1-F_{17})

F[a]	OND	HPMC	Carbopol	Avicel	Magnesium Sterate	Aerosil	PVP-k-30	Total (mg/tab)
F_1	8	5	---------	75.5	1	0.5	10	100
F_2	8	10	---------	70	1	0.5	10	100
F_3	8	15	---------	65.5	1	0.5	10	100
F_4	8	20	---------	60.5	1	0.5	10	100
F_5	8	25	---------	55.5	1	0.5	10	100
F_6	8	30	---------	50.5	1	0.5	10	100
F_7	8	------	5	75.5	1	0.5	10	100
F_8	8	------	10	70	1	0.5	10	100
F_9	8	------	15	65.5	1	0.5	10	100
F_{10}	8	------	20	60.5	1	0.5	10	100
F_{11}	8	------	25	55.5	1	0.5	10	100
F_{12}	8	------	30	50.5	1	0.5	10	100
F_{13}	8	2.5	2.5	75.5	1	0.5	10	100
F_{14}	8	5	5	70	1	0.5	10	100
F_{15}	8	7.5	7.5	65.5	1	0.5	10	100
F_{16}	8	10	10	60.5	1	0.5	10	100
F_{17}	8	12.5	12.5	55.5	1	0.5	10	100

[a] Code of formulations

Granule properties

The granules were evaluated for angle of repose [8], loose bulk density (LBD), tapped bulk density (TBD) using USP tapped density tester [9] and Carr`s index [10].

Compatibility studies

Infrared spectral matching approach was employed to detect any possible chemical interaction between ondansetron hydrochloride and the polymer. Physical mixtures of the drug and the polymer (1:1) were mixed with 400 mg of potassium bromide (IR grade). About 100 mg of the mixture was taken and compressed to form a transparent pellet in a hydraulic press at 15 tonnes pressure. The samples were scanned from 4000 to 400 cm^{-1} in a Shimadzu FT IR spectrophotometer. Similarly, the IR spectra of ondansetron hydrochloride, ondansetron hydrochloride and the polymer were also recorded. Physical appearance of the samples and appearance /disappearance of peaks in the spectra were observed to assess any possible physical and chemical interactions.

Tablet properties

The average weight, thickness (Digital slide calipers, Mitutoyo, Japan), hardness (Monsanto hardness tester, Cadmach machineries, Ahmedabad, India), Friability (friability testing apparatus, Electrolab, Mumbai, India), drug content and in vitro drug release of the formulated tablets were evaluated.

Drug content

Two tablets were weighed individually and crushed in mortar. An accurately weighed quantity of powdered tablets (8 mg) was extracted with pH 7.5 buffer and the solution was filtered through 0.45 µ membrane. The drug content was estimated by HPLC under suitable optimized condition after suitable dilution.

In vitro dissolution studies

Dissolution was performed for the manufactured tablets according to the USP 26 "Dissolution procedure over a 24-hour period, using an Electro lab – Tablet dissolution Tester, USP XXIII Model. The media was 0.1N Hcl at pH 2.0 and a volume of 700 ml for the first 2 h after which 200 ml of 0.2 M sodium phosphate tribasic, was added to give a final pH of 7.5 and maintained at 37°C. Dissolution tests were performed on six tablets and the amount of drug released was analyzed by HPLC at a wavelength of 305 nm. The stationary phase was a Princeton SPHER HPLC column C_{18} (250 x 4.6 mm i.d., 5µ) column. The mobile phase was mobile phase was 60:40 (v/v) acetonitrile-50mM Dihydrogen ortho phosphate buffer (pH 7.0). The injection volume was 50 µL and the flow-rate was 1mL min^{-1}. The eluent was monitored by UV detection at 305 nm. Dissolution samples were collected at the following times 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 h. Percentage of drug release and cumulative drug release were calculated.

Kinetics and Mechanism of Drug Release

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetics models: zero order as cumulative amount of drug released vs time, first order as log cumulative percentage of drug remaining vs time, and Higuchi`s model as cumulative percentage of drug released vs

square root of time.

The in vitro drug release profiles were plotted according to zero – order, first- order, Higuchi[11] and Peppas[12] equations to understand the mechanism of drug release and to compare the differences in the release profile of different batches of matrix tablets.

Stability study

The optimized ondansetron formulations were strip packed and subjected to accelerated stability studies as per ICH guidelines (40 °C±2 °C/75% RH±5% RH). The samples were withdrawn periodically (0, 15, 30 and 60 days) and evaluated for the different physico-chemical parameters viz. appearance, weight variation, thickness, hardness, drug content, and in vitro release studies.

Bioavailability Studies

Six healthy male volunteers (aged 18–30 years) were included in the study, after having undergone a thorough medical examination. The Bioavailability was performed in accordance with the guidelines set by the World Medical Assembly (Declaration of Helsinki). All volunteers gave written informed consent to participation in the study, after having been informed of the nature and implications of the study. A total of six male healthy subjects completed this study. There were no dropouts. Their mean age was 24.8±3.8 years (range 21–30 years), their mean weight was 72.4±7.3 kg (range 64–84 kg) and their mean height was 180.6±6.7 cm (range 167–192 cm). All cardiovascular measurements and laboratory values at screening were within prescribed limits. The study was an open, randomized, three-period, three-group crossover trial with an 7-day washout interval. During the first period, volunteers from group A received a single 8 mg dose of immediate release Ondansetron hydrochloride tablets from Sun pharma, Mumbai, India (Reference, EMSETRON), while volunteers from group B received a single 8 mg dose of slow sustained-release tablets (Test, In house). While volunteers from group C received a single 8 mg dose of fast sustained-release tablets (Test, In house). During the second and third period, the procedure was repeated on the groups in reverse. The tablets were administered to the volunteers in the next morning after an overnight fast, with 250 ml of water. Volunteers received standard lunch and supper, respectively, 4 and 10 h after drug administration. Volunteers did not ingest any alcoholic drink coffee or other xanthine-containing drinks during the trial. Furthermore, they did not take any other drug, 2 weeks before the study and during the execution. Blood samples were taken at pre-dose (0 h) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24 h. During each hospitalization period, the subjects remained under constant medical surveillance by a physician. During the three study sessions, the subjects maintained daily contact with the clinical investigator and reported any adverse events, whether related or not to the ongoing drug treatment in his opinion. An indwelling catheter was used for blood sampling during day 1, remaining blood samples were obtained by puncture of a forearm vein. The 5mL of blood were collected in evacuated polypropylene tubes containing sodium citrate solution 3.8% w/v. immediately after blood collection, the tubes were centrifuged for 10 min at 4000 rpm. After centrifugation, at least 2mL plasma were rapidly transferred into two polypropylene tubes and stored in appropriately labeled freeze resistant

bags at −70◦C until sent to the analytical laboratory.

High-performance liquid chromatography (HPLC) analysis of plasma samples

A sensitive and rapid HPLC method was developed and validated for the quantitative determination of ondansetron in human plasma. The compound and the internal standard (I.S.) (etrocoxib) were extracted from the plasma samples by solid phase extraction. The extracts were analyzed by a reversed-phase HPLC with C_{18} analytical column and 60:40 Compounds were monitored by UV detection at 305 nm. The calibration curves were linear in the range between 0.5-50.0 ng/ml. Calibration standards, validation QC samples and healthy volunteer plasma samples were prepared by adding 0.5 mL plasma to Eppendorf tube followed by adding 10.0 µL internal standard solution (1.0 µg/mL). All samples were mixed by vortexer for 30 s. After these procedures, Samprep SPE Columns C_{18} (50µm, 70A) 100mg/1mL solid phase extraction cartridge was conditioned with methanol, water sequentially. To this load the above sample. The cartridge was washed with 2.0 ml of water. The drug and internal standard was eluted from the cartridge using 0.5ml of Methanol. The resulting solution used for the analysis.

Pharmacokinetic analysis

The Pharmacokinetic parameters $C_{max,}$ $t_{max,}$ $AUC_{0\text{-}t,}$ $AUC_{0\text{-}\infty,}$ $t_{1/2}$ and k_{el} were determined using WinNonlin-Standard edition version 5.1 for individual drug treatments from the observed plasma concentration-time data. The measured plasma concentrations were used to calculate the area under the plasma concentration-time profile from time zero to the last concentration time point ($AUC_{(0\text{-}t)}$). The $AUC_{(0\text{-}t)}$ was determined by the trapezoidal method.

$AUC_{(0\text{-}\infty)}$ was determined by the following equation:

$$AUC_{(0\text{-}\infty)} = AUC_{(0\text{-}t)} + C_{(t)} / k_{el}$$

k_{el} was estimated by fitting the logarithm of the concentrations versus time to a straight line over the observed exponential decline. The Wagner-Nelson method was used to calculate the percentage of the dose absorbed,

$$F_{(t)} = C_{(t)} + k_{el}\, AUC_{(0\text{-}t)},$$

where $F_{(t)}$ is the amount absorbed. The percent absorbed is determined by dividing the amount absorbed at any time by the plateau value, $k_e\, AUC_{(0\text{-}\infty)}$ and multiplying this ratio by 100:

$$\% \text{ dose absorbed} = \left(\frac{C_{(t)} + k_{el}\, AUC_{(0\text{-}t)}}{k_e\, AUC_{(0\text{-}\infty)}} \right) \times 100$$

RESULTS AND DISCUSSION

Granulation is the key process in the production of many dosage forms. The sustained release tablets were prepared by wet granulation technique. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The granules of different formulations were evaluated for angle

of repose, loose bulk density (LBD), tapped bulk density (TBD), and Carr`s index as shown in Table. 2. The results of angle of repose indicate good flow properties of the granules. However the granules had fair to poor Carr`s index values. Aerosil therefore was added to dried granules prior to compression to improve the flow.

Table . 2. Comparison of the physical properties of the matrix tablets containing Ondansetron hydrochloride

F[a]	Hardness (N)	Thickness (cm)	Weight (g)	Friability (%)
F_1	5.00±0.35	3.50±0.07	0.1028±0.002	0.42± 0.01
F_2	4.98±0.01	3.52±0.07	0.1039±0.001	0.41± 0.02
F_3	4.95±0.01	3.48±0.16	0.1025±0.003	0.40± 0.02
F_4	4.92±0.07	3.51±0.14	0.1020±0.001	0.43± 0.02
F_5	4.99±0.26	3.49±0.18	0.1027±0.000	0.39± 0.02
F_6	5.01±0.03	3.43±0.27	0.1015±0.000	0.38± 0.02
F_7	5.04±0.27	3.42±0.15	0.1021±0.000	0.43± 0.01
F_8	4.98±0.06	3.44±0.12	0.1020±0.001	0.45± 0.01
F_9	4.90±0.13	3.54±0.09	0.1036±0.000	0.39± 0.04
F_{10}	4.91±0.39	3.53±0.16	0.1018±0.000	0.35± 0.03
F11	4.99±0.02	3.48±0.18	0.1022±0.000	0.44± 0.02
F_{12}	4.98±0.03	3.55±0.06	0.1020±0.002	0.36± 0.03
F_{13}	5.06±0.25	3.53±0.02	0.1047±0.000	0.35± 0.03
F_{14}	5.01±0.12	3.82±0.07	0.1038±0.001	0.36± 0.03
F_{15}	4.94±0.15	3.69±0.06	0.1035±0.000	0.36± 0.03
F_{16}	4.95±0.18	3.84±0.08	0.1040±0.007	0.45± 0.05
F_{17}	4.91±0.32	3.85±0.17	0.1062±0.006	0.46± 0.02

The physical properties of different batches of developed tablets are given in Table 3. All the batches showed uniform thickness. The average percentage deviation of 20 tablets of each formula was less than ± 5% and hence all formulations passed the test for uniformity of weight as per official requirements [13]. Good uniformity content was found among three different batches of tablets.

Table .3. Granule properties of the different formulations of Ondansetron hydrochloride (OND)

F[a]	Angle of repose (°C)	LBD[b] (gm/cm^3)	TBD[c] (gm/cm^3)	Carr`s Index (%)
F_1	37.23	0.51	0.58	13.06
F_2	38.3	0.30	0.35	12.89
F_3	36.5	0.36	0.42	14.29
F_4	38.65	0.28	0.34	16.52
F_5	36.26	0.29	0.36	19.44
F_6	37.88	0.35	0.42	16.67
F_7	32.45	0.38	0.47	19.15
F_8	31.63	0.34	0.41	17.07
F_9	33.42	0.42	0.48	12.5
F_{10}	32.76	0.43	0.48	10.42
F_{11}	31.25	0.39	0.5	22
F_{12}	32.65	0.42	0.53	20.75
F_{13}	34.21	0.43	0.48	10.42
F_{14}	27.66	0.49	0.58	15.52
F_{15}	28.73	0.47	0.55	14.55
F_{16}	29.98	0.44	0.57	22.81
F_{17}	31.54	0.45	0.56	19.64

[a] Code of formulations

[b] Loose Bulk Density

[c] Tapped Bulk Density

Another measure of tablets strength is friability. Conventional compressed tablets with less than 1% w/w of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1% w/w, indicating that the friability is within the prescribed limits. All the tablets formulations showed acceptable pharmaco technical properties and complied with the specifications for weight variation, drug content, hardness, and friability. Small values in friability imply much less friability during transportation, which is important in terms of sustained release of tablets.

In all the batches, we observed that as the polymer concentration increases, the drug release rate decreases (Figure 1-3).

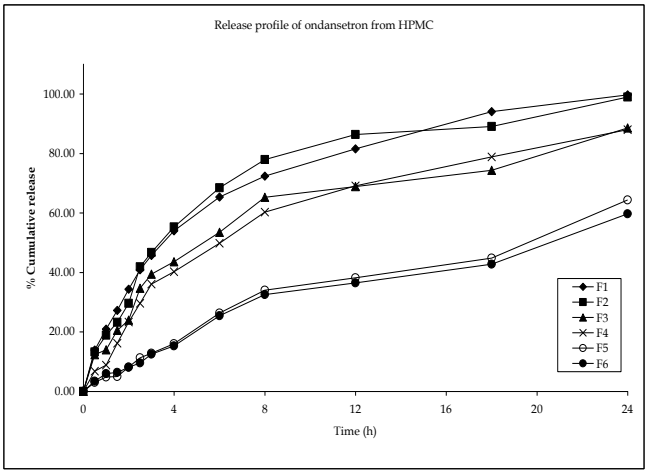

Figure .1: Release profiles of Ondansetron from HPMC (polymer) containing Formulations (F_1-F_6)

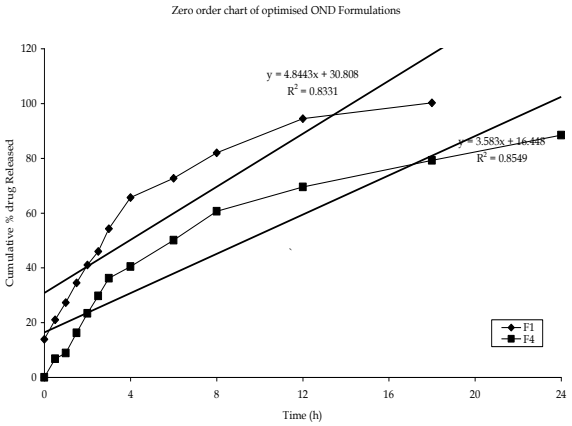

Figure 2: Zero order chart of optimized OND Formulations (F_1-F_4)

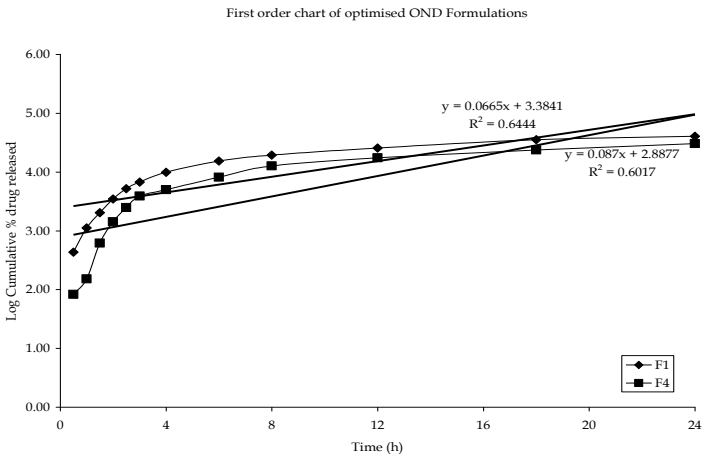

Figure. 3: First order chart of optimized OND Formulations (F_1-F_4)

The in vitro drug release characteristics of the developed SR and the marketed IR tablets were studied. Dissolution data for all the experiments were highly reproducible and hence only the average values were plotted. The dissolution of the marketed IR tablets indicated that more than 80% of the drug is released within 1 hr, which complies with the pharmacopoeial specifications. In all the batches, we observed that as the polymer concentration increases, the drug release rate decreases.

To know the mechanism of drug release from these formulations, the data were treated according to zero-order (cumulative amount of drug released versus time), first-order (log cumulative percentage of drug released versus time), Higuchi (Cumulative percentage of drug released versus square root of time) and Peppas (log cumulative percentage of drug released versus log time) equations which are clearly revealed in Figure. 4-6.

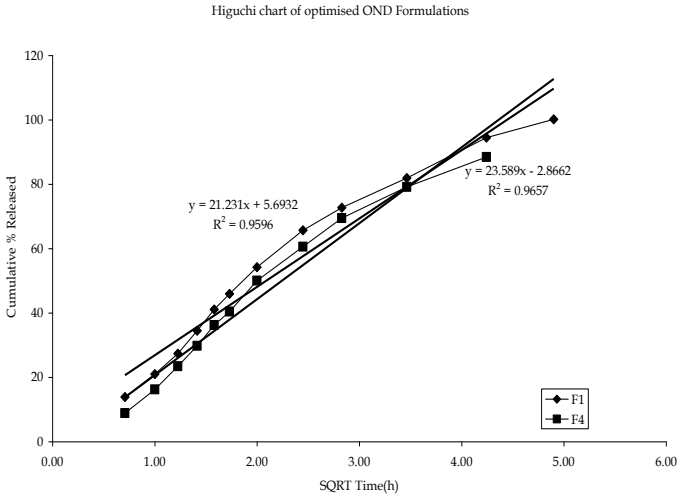

Figure. 4: **Higuchi chart of optimized OND Formulations (F_1-F_4)**

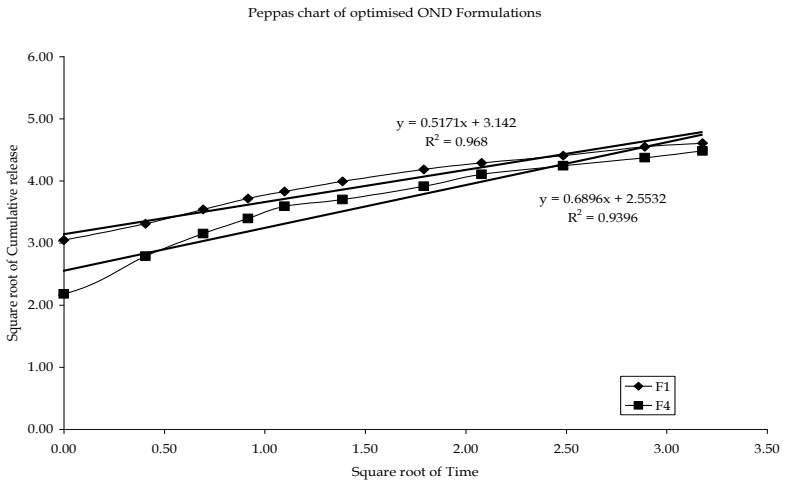

Figure 5: Peppas chart of optimized OND Formulations (F_1-F_4)

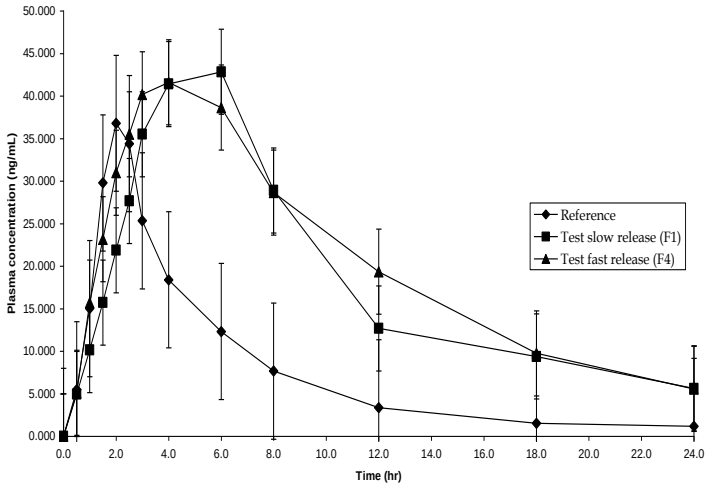

Figure 6: Mean plasma concentration-time profile of Ondansetron from developed Sustained release tablets (test) and marketed immediate release tablet (Reference)

The release profiles the OND, when plotted according to Higuchi's equation and Peppas equation confirm that drug release is diffusion control as evident by the values of correlation (r^2). The estimated values of pharmacokinetics parameters are also listed in table and figure. Formulated sustained release tablets were compared to a standard .the Tmax of the test (slow, fast) formulations showed a smooth and extended absorption phase was significantly longer than that obtained for conventional. The relative bioavailability of the SR 8 mg tablets (slow, fast) given daily was compared with one dose of the marketed 8 mg Ondansetron hydrochloride tablet. The developed SR tablet produced a plasma concentration-time profile typical of the prolonged dissolution characteristic of a SR formulation, as evident from Figure .7 and Table. 4. The developed SR tablets demonstrated a longer time to reach a peak concentration than the marketed tablets and appeared to be more consistent overall performance. This was no significant difference in extent of absorption as assessed by measurement $AUC_{0\text{-}t.}$ However AUC $_{0\text{-}\infty}$ values for the

SR tablets was higher than the marketed IR tablets indicating more efficient and controlled drug delivery, which would maintain plasma ondansetron levels well. This also was evident by the lower elimination rate constant and higher $t_{1/2}$ values. A good correlation between the dissolution profiles and bioavailability was observed. The relationship between percent drug released and percent drug absorbed [14] is illustrated in Figure 7.

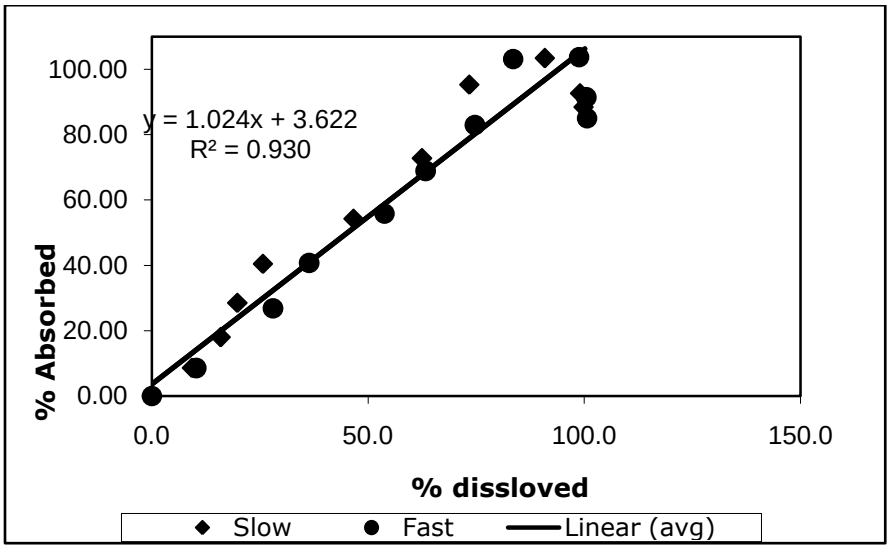

Figure. 7: Linear regression plots of percentage absorbed vs percentage dissolved for the slow and fast tablets using pH 4.5,50 rpm

Table 4. Pharmacokinetic parameters of the developed sustained release (SR) tablets and marketed immediate release (IR) tablets of Ondansetron hydrochloride

S. No	Pharmacokinetic Parameters	Developed SR tablets Slow Release	Developed SR tablets Fast Release	Marketed IR tablets
1	AUC_{0-24}	464.205 ± 46.103	445.162 ± 48.581	184.162 ± 29.951
2	$AUC_{0-\infty}$	475.353 ± 43.481	460.293 ± 47.668	188.973 ± 29.502
3	C_{max}	44.732 ± 2.259	44.992 ± 2.276	40.429 ± 2.383
4	T_{max}	5.333 ± 1.033	4.667 ± 1.033	2.000 ± 0.316
5	K_{eli}	0.166 ± 0.022	0.148 ± 0.011	0.175 ± 0.010
6	$T_{1/2}$	4.248 ± 0.611	4.695 ±0.328	4.030 ± 0.190

CONCLUSION

Once daily sustained release tablets of ondansetron were successfully formulated using Methocel – K100–CR. Release kinetics was found to follow Higuchi kinetics in all the developed formulations. The optimized formulation was found to be stable at all the stability conditions. The sustained release tablets of ondansetron hydrochloride were well absorbed and the extent of absorption was higher than that of the marketed tablet. The sustained and efficient drug delivery system developed in the present study will

maintain plasma ondansetron levels better, which will overcome the drawbacks associated with the conventional therapy.

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