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RESEARCH ARTICLE

Formulation and Evaluation of Sustained release Ondansetron hydrochloride pellets by extrusion spheronization technique

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ABSTRACT

The aim of the present study was designed and develops model sustained release pellets formulations for Ondansetron HCL. Ondansetron HCL is widely used in the management of vomiting sensation at the time of cancer chemotherapy. The bioavailability of Ondansetron HCL is high and protein binding was found to be 91-93 %. The half-life of Ondansetron hydrochloride is about 7 hours. But the short half-life of Ondansetron hydrochloride leads to poor compliance and adverse reactions; that is why Ondansetron hydrochloride in sustained release dosage form is needed to achieve better therapeutic effects and to improve patient compliance. Ondansetron hydrochloride at different drug to polymer ratios was prepared by extrusion and spheronization technique. The influence of the proportion of the polymer on the release rate of the drug from the pellets was studied. The in-vitro release studies of pellets were carried out in 0.1N HCL for 12 hours. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero-order to evaluate the kinetics and mechanism of the drug release. Kinetic modeling of in-vitro dissolution profiles revealed the release mechanism ranges from Quasi-Fickian transport to Anomalous (non-Fickian transport), which was only dependent on the type and amount of polymer used. The drug release of the optimized formulation (F5) follows Zero order kinetics and the mechanism was found to be diffusion controlled. The compatability studies were performed by using FTIR and DSC which reveals that there is no interaction between the drug and the polymer/excipients mixture.

Keywords: Sustained-release, Ethylcellulose, HPMC, Pellets, Ondansetron hydrochloride

Introduction

The oral route of drug administration is traditionally the most preferred for systemic drug delivery by physicians and patients. The population of patient with chronic diseases has recently been increasing. So there is necessity of taking drug for a long period and/or multiple doses of same and/or different medicines simultaneously, which can lead to increase in non-compliance. The drugs with short half-life could be a problem for administration. So a method to find a dosage form to release the drug gradually is necessary to solve these kinds of problems.[1]

Conventional Drug Therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. Conventional forms often cause problems to the patient, because they maintain therapeutic drug level for only brief duration. This gives rise to sharp fluctuations of drug levels in plasma and in tissue. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels controlled drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively.[2]

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. Numerous studies have been reported in literature review of the control the release of drug from matrixes.[3]

Pellets: Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration) obtained from diverse starting materials utilizing different processing techniques and conditions.[4]

Ondansetron (5-hydroxytryptamine) subtype 3 (5-HT3) receptor antagonist used in the management of nausea and vomiting. 5-HT3 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. Ondansetron has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy and surgery. Intravenous and oral dosage forms of the drug are commercially available.[5,6]

Nausea is the unpleasant urge to vomit. Vomiting is the forceful ejection of stomach contents through the mouth. This is generally a protective mechanism to remove harmful ingested substances, but can occur from many unrelated infectious and inflammatory conditions in the body. Muscles in the abdominal wall contract vigorously to create the pressure necessary for vomiting (retching). Retching, also called 'dry heaving' can also occur without vomitcan precede or follow vomiting. Similarly, nausea can occur without vomiting or may precede vomiting.[7]

Causes: The etiologies of nausea and vomiting include iatrogenic, toxic, or infectious causes; gastrointestinal disorders; and central nervous system or psychiatric conditions. [8,9,10]

MATERIALS AND METHODS

Materials

Ondansetron HCL, MCC, Talc, Ethyl cellulose were purchased from yarrow chemicals tumkur, all other reagents and chemicals used were for analytical grade.

Equipments used: The following Equipments were used for the formulation: mini extruder and spheronizer: cronimach, UV-Spectrophotometer: Shimadzu UV-1800, digital weighing balance: essaeteraoka limited, tap density tester: electrolab, micro pipette: tarson products pvt ltd, digital pH meter: millennium industries.

Methods: Pellets are prepared by extrusion spheronization method by dry mixing of materials to achieve homogeneous dispersion. Wet granulation of the resulting mixture was done to form wet mass and extrusion of wet mass form rod shaped particles which were rounded off (in spheronizer).

Drying: These dried rounded particles can be optionally screened to achieve a targeted mean size.

EVALUATION OF PELLETS:

1) Percentage yield of pellets:

The prepared pellets were collected and weighed from different formulations. The measured weight was divided by total amount of drug and polymers which were used for the preparation of the pellets to obtained

percentage yield.

% Yield =(Weight of pellets) X 100
(Weight of drug+ Weight of polymer)

2) Fourier-transform infrared spectroscopy (FT-IR):

Drug-polymer interactions were studied by FTIR spectroscopy. Pure drug and excipients were subjected to FT-IR studies. The samples were intimately mixed with dry powder potassium bromide. The powder mixture was taken in a diffused reflectance samples and the spectra recorded by scanning in the wavelength of 500-4000 cm-1 in a FT-IR spectrophotometer.

3) *In vitro* Drug Release study:

The in-vitro release study of the pellets was carried out using USP rotating basket method at 50 rpm at 37 ºC. Dissolution study was performed in acidic buffer pH 1.2 taking 900 ml for each study. 100 mg of the pellets was placed in the dissolution medium and testsamples were taken from the medium at predetermined time intervals over a period of 12hours and the samples were analyze ondansetron content in UV spectrophotometer.[7]

4) Drug Release Kinetics:

Data obtained from In vitro release studies were fitted to various kinetic equations to find out the mechanism of drug release from the pellets. The kinetic models used were:

Zero-order equation: (Cooper and Gunn, 1986) Q = k0 t where, Q is the amount of drug released at time t, and k0is the release rate.

First-order equation

Log Q = Log Q0 - k1t/ 2.303

where, Q is the amount of drug un-dissolved at t time, Q0 is drug concentration at t = 0 and k1 is the release rate constant.

Higuchi's equation

Q = k2t1/2 where

Q is the percent of drug release at time t, and k2 is the diffusion rate constant.

Results and Discussion

The present study was undertaken to formulate sustained release. Ondansetron pellets with different grades of HPMC(K15,K100,E15). Drug coated pellets prepared by extrusion and spheronization technique using mini melt extruder. Initially Analytical method was developed; preformulation studies were performed for active pharmaceutical ingredient as well as excipients. After preparing pellets evaluation tests like assay, dissolution, FTIR, DSC studies etc were carried out.

Table 1: Drug and polymer combination in different concentrations

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Ondansetron HCL	24	24	24	24	24	24	24	24	24
HPMC K15M	25	50	75	-	-	-	-	-	-
HPMC K100M	-	-	-	25	50	75	-	-	-
HPMC E15	-	-	-	-	-	-	25	50	75
Ethyl cellulose	10	10	10	10	10	10	10	10	10
MCC	50	50	50	50	50	50	50	50	50
Talc	20	20	20	20	20	20	20	20	20
Starch	30	30	30	30	30	30	30	30	30
Iso propyl alchol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Ondansetron hydrochloride show maximum absorption at 248 nm this value is used for further analysis and calculations.

Figure 1: λ max of Ondansetron HCL in pH 1.2 acidic buffer (0.1N HCL)

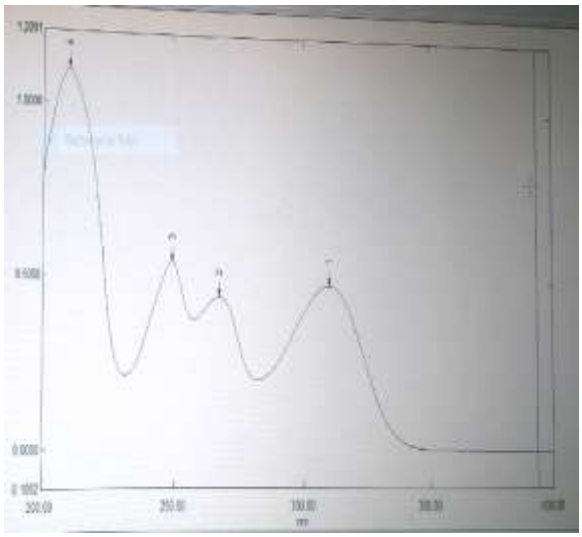


Table 2: Calibration curve of ondansetron hydrochloride in acid buffer (pH 1.2)

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.122
3	4	0.238
4	6	0.351
5	8	0.473
6	10	0.594
7	12	0.712
8	14	0.821
9	16	0.941

Figure 2: Calibration curve of ondansetron hydrochloride

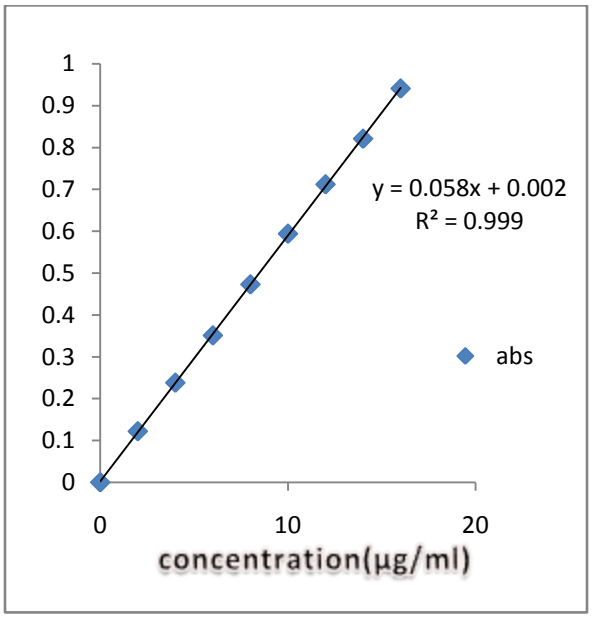
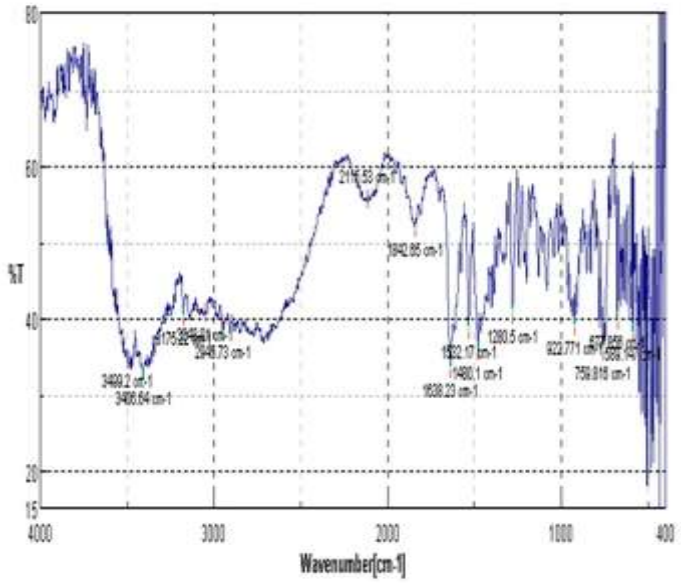


Figure 3: FTIR Spectroscopy of pure drug (Ondansetron hydrochloride)



FTIR Spectra

FTIR spectrum of Ondansetron hydrochloride showed in figure 3. FTIR spectra of polymers like HPMC K100M, K15M, E15 and excipients like ethylcellulose, MCC and talc and physical mixture of drug, polymers and excipients are shown in figures (4-7). The characteristic peaks of the drug were observed in the spectra of mixture of drug and polymer mixture, however the intensity of the peaks were reduced this might be due to very low concentration of drug in the mixture this indicates that there is no interaction between the drug and polymer mixtures.

Figure 4: FTIR Spectroscopy HPMC K100M + Ondansetron hydrochloride

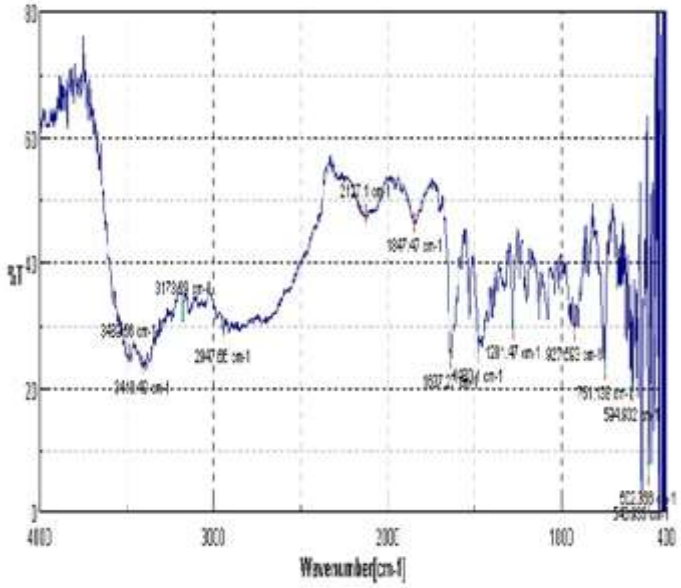


Figure 5: FTIR Spectroscopy of HPMC E15 + Ondansetron hydrochloride

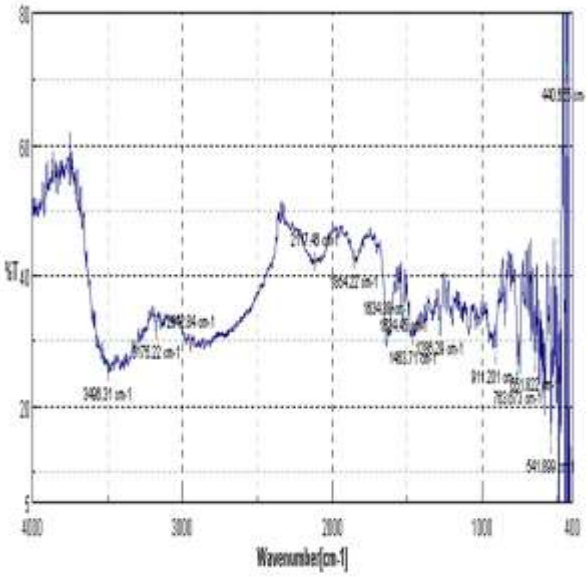


Figure 6: FTIR Spectroscopy of Ethyl cellulose + Ondansetron hydrochloride

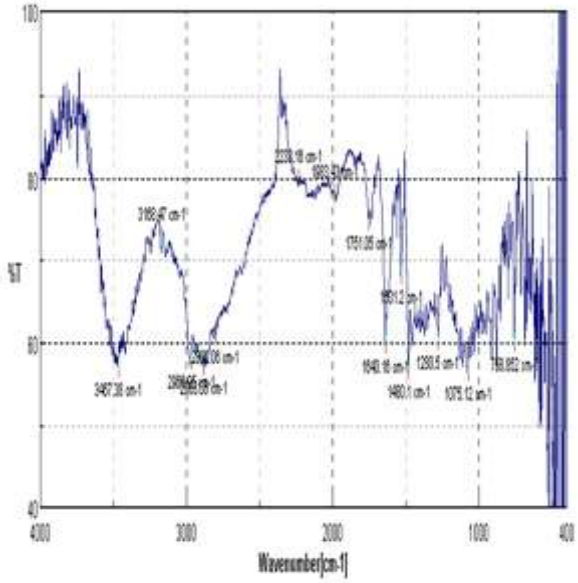


Figure 7: FTIR Spectroscopy of Optimised formula

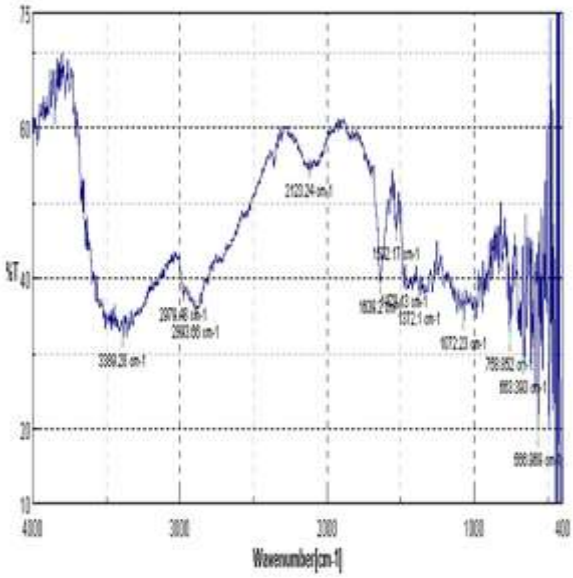


Figure 8: DSC thermogram of optimized formulation, F5

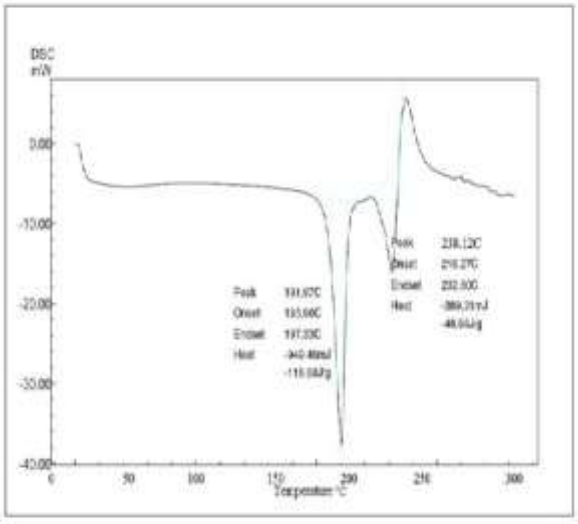


Figure 9: DSC thermogram of pure drug ondansetron HCl

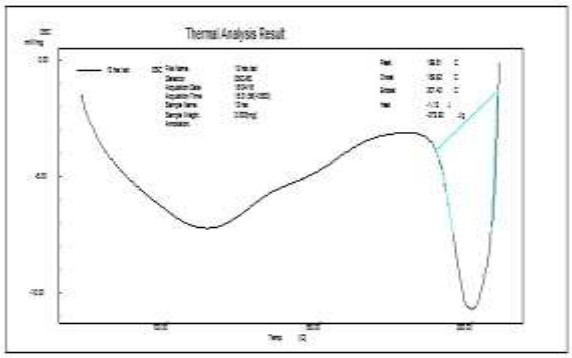


Table 3: Physicochemical parameters of Ondasetron HCl sustained release pellets (F1-F5)

Parameters	FORMULATION CODE				
	F1	F2	F3	F4	F5
Angle of repose	20.56 º	22.35 º	21.2 º	23.2 º	22.01 º
Loose bulk density (LBD)(g/ml)	0.35	0.282	0.27	0.27 9	0.268
Tapped bulk density (TBD) (g/mL)	0.39	0.31	0.29 5	0.29 5	0.291
Compressibili ty index (%)	10.25	9.032	8.47 4	8.42	7.903
Hausner"s ratio	1.114	1.099	1.09 2	1.05 7	1.085
Flow rate (g/s)	9.235	7.843	7.62 5	7.38 9	7.764
Loss on drying (%)	0.263	0.199	0.24 9	0.19 8	0.197
Moisture content (% w/w)	1.8	1.21	1.25	1.26 7	1.255
Assay (%)	98.2	98.68	97.3 2	99.1 5	99.86

Table 4: Physicochemical parameters of Ondasetron HCl sustained release pellets (F6-F9)

Parameters	FORMULATION CODE			
	F6	F7	F8	F9
Angle of repose	20.1º	21.65º	23.48º	24.1º
Loose bulk density (LBD)(g/ml)	0.262	0.276	0.268	0.254
Tapped bulk density (TBD) (g/ml)	0.289	0.296	0.291	0.273
Compressibility index (%)	9.342	6.756	7.903	6.959
Hausner"s ratio	1.103	1.072	1.085	1.074
Flow rate (g/s)	8.913	8.782	8.478	8.652
Loss on drying (%)	0.198	0.235	0.242	0.238
Moisture content (%w/w)	1.683	1.958	1.751	1.899
Assay (%)	99.5	99.35	99.97	98.86

Table 5: In vitro drug release of ondansetron from formulations

TIME IN HOURS	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	30.75	29.31	26.25	30	26.29	26.25	30.37	23.64	20.76
2	37.87	37.8	37.85	37.7	37.87	34.45	45.45	31.12	26.21
3	49.37	45.2	38.41	49.2	41.83	38.04	49.50	37.20	33.33
4	51.54	51.5	45.76	52.75	45.83	15.15	50.12	41.11	39.91
5	57.5	56.5	47.12	65.4	53.62	48.66	50.12	41.11	45.29
6	58.15	58.5	57.75	73.29	54.66	50.80	58.25	52.51	51.39
7	65.66	64.6	73.08	77.45	65.54	54.12	73.29	55.93	57.49
8	66.37	68.1	75.35	81.66	77.2	73.25	81.20	64.01	65.46
9	73.91	73.9	76.45	85.87	85.16	77.41	85.75	73.34	69.21
10	76.16	76.1	77.95	86.08	86.75	85.00	85.87	78.94	72.90
11	82.5	80.5	79.35	87.45	93.62	88.50	86.33	84.54	79.06
12	86.87	84.16	83.3	91.95	94.51	90.86	90.50	87.19	89.94

Figure 10: *In-vitro* Drug release profile of Ondansetron hydrochloride F1-F5

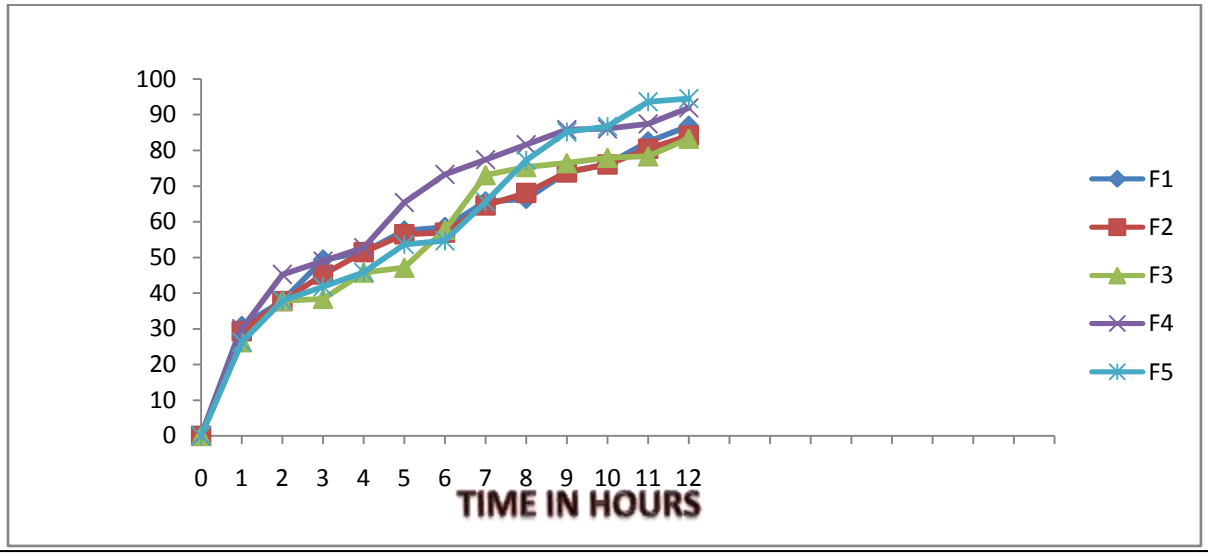


Figure 11*: In-vitro* Drug release profile of Ondansetron hydrochloride F6-F9

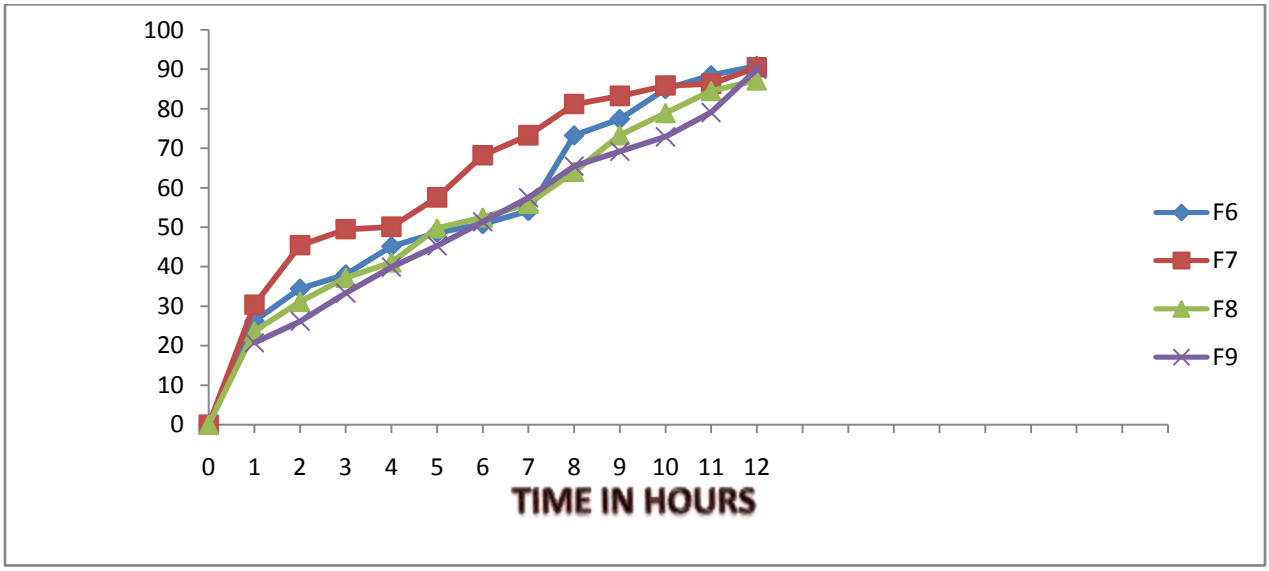


Table 6: Kinetic model fitting for optimized formulation (F5)

TIME	LOG TIME	SQRT	%CDR	LOG%CDR	%CRR	LOG%CRR
1	0	1	26.29	1.419	73.71	1.867
2	0.301	1.414	37.87	1.578	62.13	1.793
3	0.477	1.732	41.83	1.621	58.17	1.764
4	0.602	2	45.83	1.661	54.17	1.733
5	0.698	2.236	53.62	1.729	46.38	1.666
6	0.778	2.449	54.66	1.737	45.34	1.656
7	0.845	2.645	65.54	1.816	34.46	1.537
8	0.903	2.828	77.2	1.887	22.8	1.357
9	0.954	3	85.16	1.93	14.84	1.171
10	1	3.162	86.75	1.938	13.25	1.122
11	1.041	3.316	93.62	1.971	6.38	0.804
12	1.079	3.464	94.51	1.975	5.49	0.738

Conclusion

In this study sustained release pellets of ondansetron hydrochloride was prepared by extrusion and spheronization technique, using different grades of HPMC like K15M, K100M, E15 as polymers alone as retardant. It was found that increase in the concentration in polymeric ratio decreases the drug release and able to sustain for 12 hours. The formulation F5 containing 0.75% of HPMC K100M F5 showed good drug release over a period of 12 hours and in-turn the release was found to be within the limits specified in monograph. The entire pellet formulations showed acceptable quality control properties like moisture content, loss on drying, drug content uniformity etc. and complied with in the specifications for tested parameters. Thus, formulation F-5was found to be the most promising formulation on the basis of acceptable pellets properties. The kinetic treatment of selected optimized formulation shows that the regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics and the "n"-value lies between 0.373 to 0.860 (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release of formulations F-1 to F-4 was Quasi-Fickian diffusion, whereas the mechanism of drug release of formulations F2 to F5 and F6, F9 was Anomalous (non-fickian) diffusion. The mechanism of drug release from the formulation F13 was found to be fickian diffusion. Therefore, the results of the kinetic study obtained permit us to conclude that an orally sustained ondansetron pellet delivers the drug through a complex mixture of diffusion, swelling and erosion. Based on the FT-IR studies, there appears to be no possibility of interaction between ondansetron hydrochloride and polymers/ other excipients used in the pellets DSC studies for optimized formulation it was concluded that there is no interaction between the drug and polymers/other excipients.

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