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Formulation and Evaluation of Floating tablets of Ondansetron Hydrochloride

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Abstract

The purpose of the present study was to develop an optimized gastric floating drug delivery system (GFDDS) containing Ondansetron Hydrochloride as a model drug by using various proportions of polymers such as HPMC K_4M and Ethyl cellulose. This was employed to enhance the bioavailability and therapeutic efficacy of the drug. The sustained release formulations of Ondansetron Hydrochloride using hydrophobic and hydrophilic polymers were prepared by wet granulation method. Optimization of formulation was done by studying effect of drug to polymer ratio on drug release. FT-IR studies indicated absence of any interaction between Ondansetron Hydrochloride, polymer (HPMC K_4M, Ethyl cellulose) and excipients. Six formulations were prepared and formulation F6 possessed good floating property with total floating time between 8-12 hours. The tablets were also evaluated for its hardness, friability, and *in-vitro* evaluation test. All parameters complied with IP limits. Results of this study indicated that the combinations of hydrophilic polymers with hydrophobic polymers are suitable to optimize sustained release formulation of Ondansetron Hydrochloride.

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Gastro retentive system, Floating property, Swelling index, Ondansetron Hydrochloride

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INTRODUCTION

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. From immediate release to site-

specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastro retentive delivery systems. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the Gastro Intestinal Tract (GIT) has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, rate systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. This technology benefits drugs that have a narrow window of absorption in the stomach and upper GI tract. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[1,2] Therefore, control of placement of a Drug Delivery Systems (DDS) in a specific region of the GIT offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem[3]. These considerations have led to development of a unique oral controlled release dosage form with gastro retentive properties. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT), i.e. Gastro Retentive Dosage Form (GRDF).

Floating systems or hydro dynamically balanced systems, are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and a better control of the fluctuations in plasma drug concentrations. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow micro spheres [4]. Floating drug delivery systems are designed to prolong the study of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drug having a better solubility in acidic environment and also having specific site of absorption in upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form [5]. Hence in the present wok is to design and develop the sustained release floating tablets of Ondansetron Hydrochloride using HPMC K_4M and Ethyl cellulose as a polymers in order to enhance the absorption followed by improving bioavailability.

MATERIALS AND METHOD

Ondansetron Hydrochloride and Micro crystalline cellulose (MCC) were obtained as a gift sample from Tablets India Pvt Ltd., Chennai, Hydroxy Propyl Methyl Cellulose (HPMC K_4M), Ethyl cellulose gift sample obtained by ATOZ Pharmaceuticals, Chennai, Magnesium stearate was obtained from Trishul reagents and chemicals, Chennai, Talc was obtained from S.S chemicals, Chennai, Starch was obtained from Indian research products, Chennai, Isopropyl alcohol (IPA) was obtained from Sd Fine chemicals, Chennai. All the chemicals and reagents required for the present experimental work are of analytical grade.

Method of preparation of Ondansetron Hydrochloride floating tablets [6]

The Ondansetron Hydrochloride floating tablets were prepared by blending the drug (Ondansetron Hydrochloride), polymer (HPMC K_4M / Ethyl cellulose) in different proportions respectively. To this starch, sodium bicarbonate was added and mixed well. The powder was passed through sieve no: 40. 3 ml of isopropyl alcohol was taken in a beaker and a required quantity of polyvinyl pyrrolidone is added and stirred well until the polyvinyl pyrrolidone is dissolved. This is added to the above powder and mixed well until to form a coherent mass. The mass was passed through sieve no: 10. The granules were dried at 60-70°C for 20 min in hot air oven. Purified talc and magnesium stearate were finally added as glidant and lubricant respectively and compressed finally.

In the present work, 6 formulations of (F1 to F6) floating tablets of Ondansetron Hydrochloride were prepared using variable concentrations of HPMC K_4M and Ethylcellulose as shown in the Table no.1.

Table no 1: Development of different formulations containing varying proportions of polymers

Ingredients (mg)	Formulations					
	F1	F2	F3	F4	F5	F6
Ondansetron Hydrochloride	10.1	10.1	10.1	10.1	10.1	10.1
HPMC K_4M	36	54	72	36	54	72
Ethyl cellulose	-	-	-	9	9	9
MCC	81.9	63.9	45.9	90.9	72.9	54.9
Starch	20	20	20	20	20	20
$NaHco_3$	10	10	10	10	10	10
PVP	9	9	9	9	9	9
IPA (ml)	0.3	0.3	0.3	0.3	0.3	0.3
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2

***In – vitro* characterization:**

a. Weight uniformity test [7] **:**

If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test.

20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

Calculate the average weight of tablets = Total weight of tablets/Number of tablets

Average weight of tablets (X) = $(X_1+X_2+X_3+.....+X_{20})$ / 20

b. Hardness uniformity studies [7] **:**

The hardness of prepared formulation was measured by using Monsanto Hardness tester. Six floating tablets were used for hardness uniformity studies. The hardness data used to calculate mean and standard deviation.

c. Thickness Uniformity Studies:

The thickness uniformity studies were carried out by using Vernier Calipers. Six tablets were used for thickness uniformity studies and denoted in millimeter. The data obtained was used to calculate mean and standard deviation.

d. Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%) 20 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 min (100 revolutions). The tablets were weighed again (W final). The % friability was then calculated by

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

e. Thickness and diameter:

Tablet thickness is important for tablet packaging; very thick tablets affect packaging either in blisters or plastic containers. The tablet thickness is determined by the diameter of the die, the amount of fill permitted to enter the die and the force or pressure applied during compression. The thickness of the tablet may be measured manually or by automatic equipment. The thickness and diameter of the tablets was measured by Vernier Caliper. It is expressed in mm.

f. Content Uniformity:

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100 mg of drug was transferred to 100 ml standard flask. The powder was dissolved in suitable solvent and make up the final volume with suitable (0.1N Hcl) solution. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer, using 0.1N Hcl solution as a blank.

g. *In vitro* buoyancy / floating study [8]:

In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing simulated gastric fluid, pH1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as Floating Lag Time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the Total Floating Time (TFT).

h. Swelling Index [9]:

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium pH 6.8 buffers at 37±0.5° C. After 0.5, one, two, three, four, five, six, seven, and up to twelve hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point, swelling index was calculated by using the following formula.

i . *In - vitro* dissolution studies [10]:

The release rate of Ondanestron Hydrochoride from floating tablets was determined using United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N Hcl for 12 hrs. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N Hcl for 12 hrs. Absorbance of these solutions was measured at 310 nm using a UV/ Visible spectrophotometer.

j. FI-IR Spectra [10]:

Fourier transform Intra red analysis (FI-IR) measurement of pure drug, polymers and drug loaded floating tablets formulations were obtained using a model name BX – Perkinelmer system 200 FT-IR Spectrophotometer. The pellets were prepared

on KBr press under hydraulic pressure of 150 kg / cm^2 at an ambient temperature.

k. Drug release kinetics [11] :

The success of HPMC K4M with ethyl cellulose in controlling the release of the drug was studied under the following heads to understand the order and probable underlying mechanism involved in the release pattern. To analyze the mechanism of drug release from the F6 formulation, the data obtained form *in -vitro* release studies were subjected to zero order model first order model, Higuchi's model, Korsemeyer's model and Hixson's Crowell kinetics.

RESULTS AND DISCLUSSION

EVALVATION OF TABLETS:

Weight variation, Thickness, Hardness and Friability:

The results showed that weight variation, thickness were lying within limits. Because of variation in the compressional forces there is a slight variation in hardness of tablets. As the proportion of polymers increases the hardness of the tablets was found to increase in case of HPMC K4 M and ethyl cellulose tablets. HPMC K4 M tablets are less harder and thickest tablets. The friability loss was found to be within the limits in all the formulations. As the amount of polymer increased, the friability of the floating tablet was found to decrease. The results of physical properties of Ondansetron Hydrochloride floating tablets are given in Table No:02 and the results revealed that the tables are mechanically strong.

Table no.2: Data of average weight variation, thickness, diameter, hardness and friability for all the formulation of Ondansetron Hydrochloride.

Formulation code	Weight variation (gm) Mean ± SD*	Thickness (cm) Mean ± SD*	Diameter (cm) Mean ± SD*	Hardness Kg/cm2 Mean ± SD*	Friability (%) Mean ± SD*
F1	0.1801±0.004	0.38±0.031	0.82±0.008	4.0±0.190	0.65±0.002
F2	0.1823±0.019	0.40±0.011	0.83±0.001	4.2±0.132	0.65±0.004
F3	0.1991±0.014	0.41±0.007	0.82±0.004	4.3±0.281	0.68±0.123
F4	0.1826±0.007	0.43±0.007	0.82±0.006	4.1±0.182	0.22±0.324
F5	0.1876±0.007	0.42±0.013	0.82±0.007	4.5±0.123	0.36±0.189
F6	0.1981±0.006	0.44±0.001	0.82±0.005	5.0±0.431	0.32±0.123

* - (n=6)

Buoyancy and total Flotation test:

From the results, it was observed that as the buoyancy lag time and the total floating time was studied for all the formulations. F1, F2, F3, F4, F5 and F6 total floating time were found to be 8, 6.5,9,11 and 12 hrs respectively as shown in Table no.3. The formulations with hydrophilic polymer (F1, F2, F3) showed less buoyancy lag time when compared to formulations with hydrophobic polymer (F4, F5, F6). The formulation with combination of polymers (F6) showed optimum buoyancy lag time. For all the F4, F5 and F6 formulations showed more total floating time when compared to F1, F2, and F3 due to the presence of hydrophobic polymer which decreased the solubility. When compared in between F1, F2, and F3 showed less total floating time. Thus with an increase in the concentration of the hydrophilic polymer total floating time was found to be decreased due to increase in the solubility. In case of F4, F5 and F6 showed less total floating time. Thus with an

increase in the concentration of the hydrophobic polymer total floating time was found to be increased due to decrease in the solubility.

Results revealed that as the concentration of the hydrophilic polymer increases, the buoyancy lagging time decreases. The increase in the concentration of the hydrophobic polymer resulted in the increase of the buoyancy lag time. Thus polymer HPMC K4 M and the combination of Ethyl cellulose were found to have optimum floating characters for a longer period.

Table no.3: Data of Buoyancy lag time and total floatation time for all the formulation of Ondansetron Hydrochloride

Formulation Code	Buoyancy lag time (min)	Total floatation time (hrs)
F1	2.5	8
F2	2.0	6.5
F3	2.3	10
F4	4.0	11
F5	3.5	9
F6	4.5	12

Swelling thickness:

As tabulated in Table no.4 the extent of swelling was found out by measuring the thickness of the tablet before and after one hours stay of the tablet in 0.1N Hcl at 37±0.5°C. Formulation F2 tablets were found to swell more and formulation F6 tablets were swelling to lesser extent.

Table no.4: Data showing swelling index for all the formulation of Ondansetron Hydrochloride

Formulation Code	Average Initial thickness (cm)	Average Final thickness (cm)
F1	0.27±0.031	0.37±0.031
F2	0.28±0.011	0.50±0.011
F3	0.29±0.007	0.41±0.007
F4	0.31±0.007	0.43±0.007
F5	0.30±0.013	0.44±0.013
F6	0.32±0.014	0.44±0.014

Drug content:

Drug content of all the formulations are within the acceptable range which shows the proper mixing of the drug with excipients as shown in Table no.5.

Table no.05: Data showing the drug content of various formulation of Ondansetron Hydrochloride:

Formulation Code	%Drug content
F1	98.6±0.021
F2	99.2±0.031
F3	103.1±0.021
F4	100.2±0.010
F5	99.75±0.021
F6	100.3±0.007

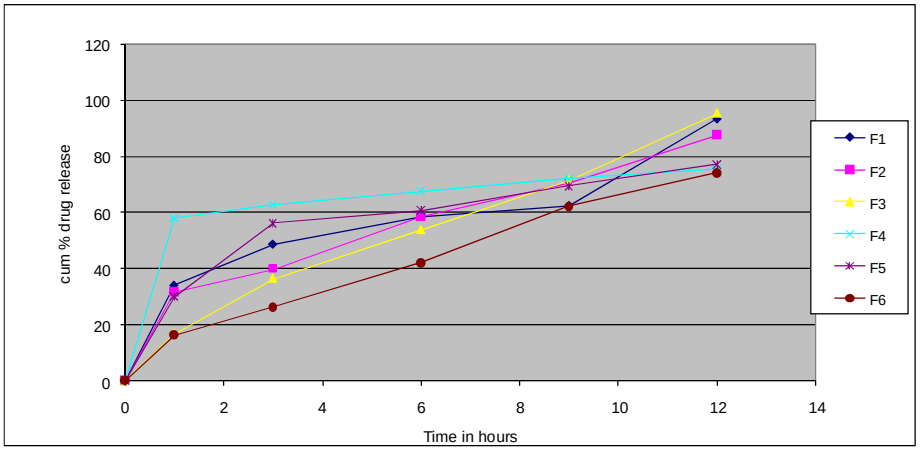
***In-vitro* drug release:**

In-vitro drug release study for all the formulations was conducted and tabulated in Table no.6: Formulation with both the polymers (F6) showed sustained release. Formulations with hydrophilic polymer (F1, F2, F3) showed high release of drug when compared to formulations with hydrophobic polymer (F4, F5, F6) as shown in the Figure no.1. The hydrophilic polymer solubilized more and drug release was high. The hydrophobic polymer solubilized less which retards the drug release to a greater extent. Thus the HPMC K4M with the combination of ethyl cellulose provides the optimum drug release.

Table no 6: Data showing comparative *In-Vitro %* drug release profiles for all the prepared formulations

TIME IN HOURS	Cumulative % Drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	34.03	31.81	16.76	58	29.96	16.42
3	48.72	39.97	36.46	62.7	56.3	26.32
6	58.55	58.44	53.78	67.5	60.83	42.16
9	62.55	70.78	71.46	72	69.49	62.17
12	93.52	87.71	95.29	75.4	77.32	74.22

Figure no.1: Comparative *in-vitro* % drug release profiles for all the prepared formulations.



Drug release kinetics:

From the data of drug release, it was found that, all the tablet formulations follow diffusion, erosion, mechanism for all drug release. The zero order, first order, mixed order root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion, erosion. Results revealed that F6 formulations follow mixed order kinetics as shown in Table no.7.

Table no.7: Data showing drug release kinetics for F6 formulations.

Formulation code	Zero order	First order	Higuchi	Korsmeyer	Hixson
F6	0.979	0.995	0.969	0.977	0.991

FT-IR data:

FT – IR of pure Ondanestron Hydrochoride , various polymers, other excipients and F6 formulation were recorded as shown in Figure no.2-6. The Ondanestron Hydrochoride present in the formulation F6 was confirmed by FT- IR. No predominant drug interaction was detected between drug and polymers along with excipients. Although there were some mild interactions in the wave number 1900-2100cm^{-1}.

The region 3600-3200cm^{-1} was stretching region of the functional group N-H, C-H of aromatic ring (3100-3000cm^{-1}), O-H (3200cm^{-1}) and C-H alkenes (3020-3100cm^{-1}) and C-H of alkane. The region 1500-800cm^{-1}, the week interaction was noticed at 756.93cm^{-1}. All the peaks have appeared in pure on and formulation F6 indicating no chemical interaction between Ondansetron Hydrochloride and excipients.

Figure no.2: FT-IR spectra of pure Ondensetrum Hydrochloride

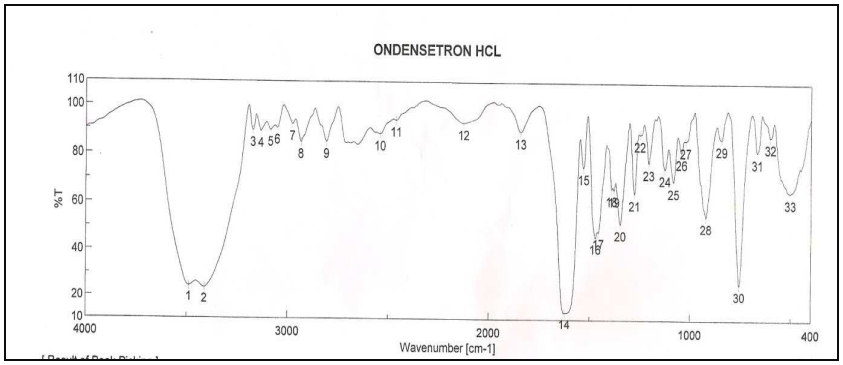


Figure no.3 : FT-IR spectra of pure HPMCK_4M

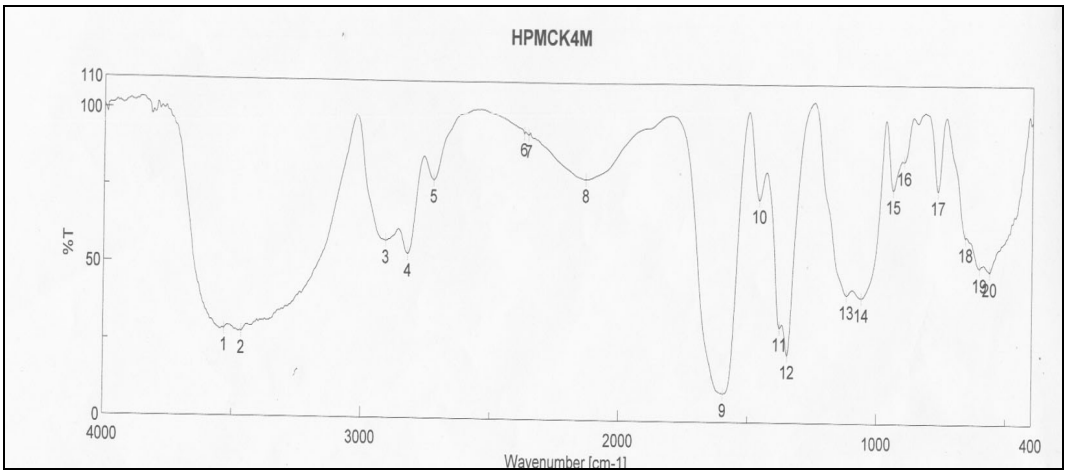


Figure no 4: FT-IR spectra of pure Ethyl cellulose

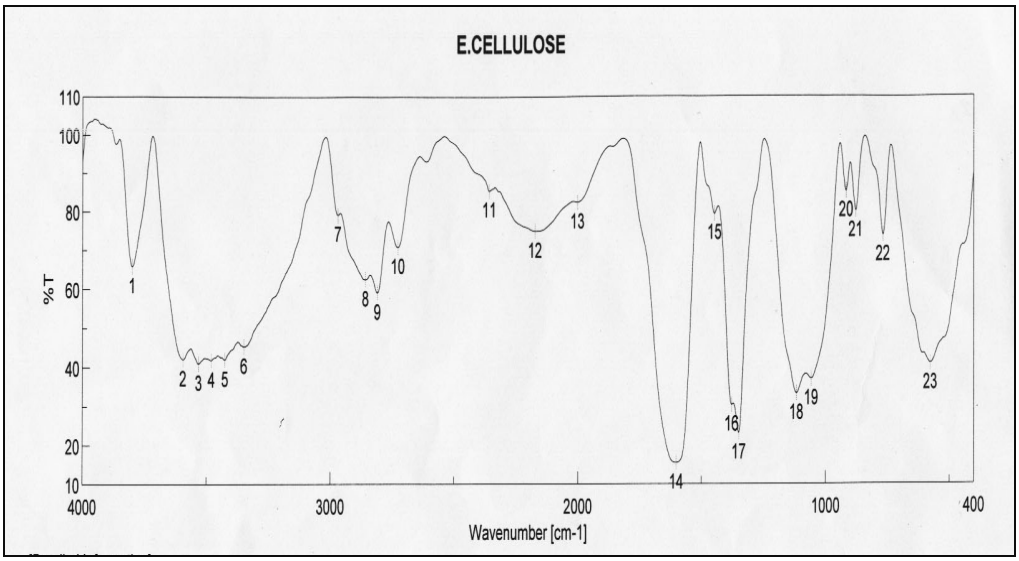


Figure no.5: FT-IR Data of physical mixture of pure Ondensetran Hydrochloride and polymers

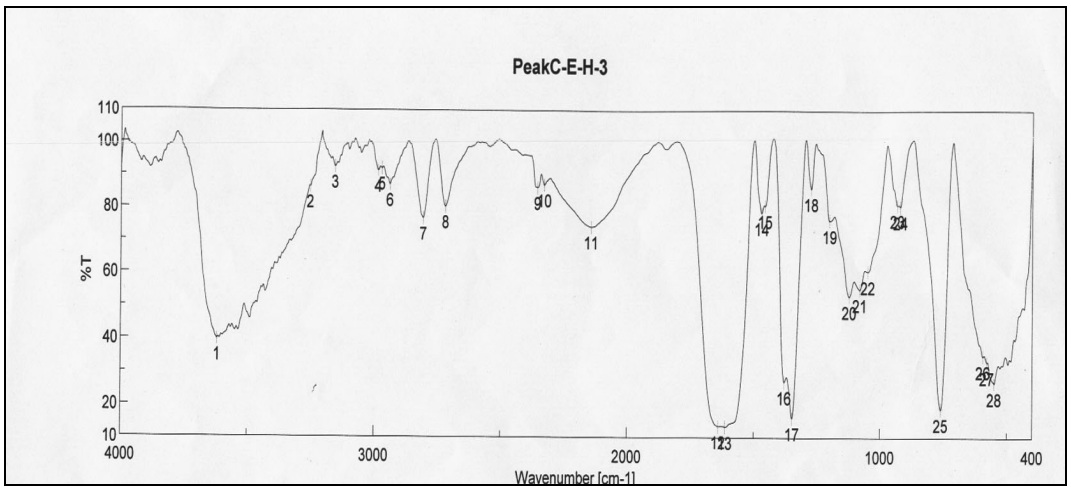
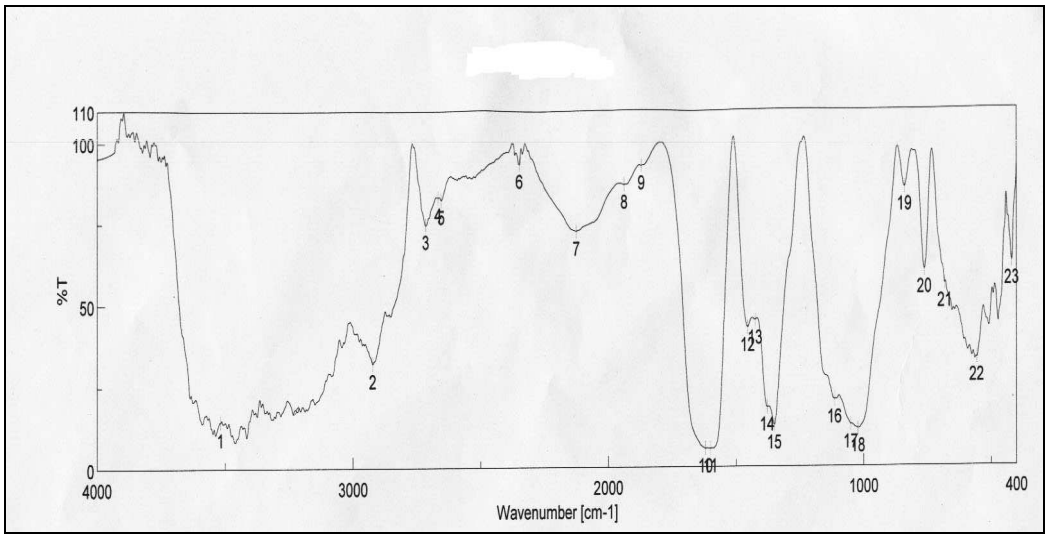


Figure no.6: FT-IR Data of F6 formulation



CONCLUSION

The research was undertaken with the aim to formulate and evaluate the sustained release floating tablets of Ondansetron Hydrochloride using HPMCK4M and Ethylcellulose as polymers. From results obtained, it was concluded that the formulation of sustained release tablet of Ondansetron Hydrochloride containing a combination of polymers (HPMCK4M, Ethylcellulose) was taken as ideal or optimized formulation for 24 hours release as it fulfills all the requirement of sustained release dosage form.

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