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Original Research Paper

DESIGN AND CHARACTERIZATION OF FLOATING TABLET OF ONDANSETRON HYDROCHLORIDE FOR GASTRICRETENTION

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ABSTRACT

Floating drug delivery system is the gastro retentive systems can remain in the stomach for many hours and can significantly prolong the gastric residence time of drugs. The aim of the work is to design floating tablets of Ondansetron for gastric retention by using 3^2 factorial designs. Chitosan and Sodium Bicarbonate is used as independent variables were as time taken to release 50% and floating lag time is dependent variables. Floating tablets of Ondansetron were prepared by direct compression method using polymers and sodium bicarbonate. Floating tablets were evaluated for floating time, floating lag time, drug content and *in vitro* dissolution profile. The lag time is between 25-10 sec and floating time of the formulations stopped on 12 hrs, Drug release percentage is upto 90-94 % and kinetic studies were carried out and best batch is F9, The best fit model is Korsemeyer Peppas Model. From the study it is proof that the sustain release by floating tablets of Ondansetron can be develop.

Keywords: Floating tablets, Sustained release, Gastric retention time, Ondansetron, Factorial design.

INTRODUCTION

FDDS have a bulk density less than gastric fluids and so remain floatable in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the system is eliminated from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentrations. The floating sustained release dosage forms exhibit most of the characteristics of hydrophilic Matrices and are known as 'hydrodynamically balanced systems'. These forms are expected to remain buoyant (3-4 h) in the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. The results obtained have also demonstrated that the presence of gastric contents is needed to allow the proper achievement of the buoyancy retention effect. Among the different hydrocolloids recommended for floating form formulations. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy. In parallel with formulation studies**,** Investigations have been undertaken in animals and humans to evaluate the intragastric retention performance of floating forms. These assessments were carried out either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the transit through the GI tract. When a floating capsule is administered to subjects who have consumed a fat and protein meal, it remains buoyant at the surface of the gastric contents in the upper part of the stomach and moves to the lower region progressively as the meal empties from the stomach. The reported gastric retention times range from 4 to 10 h. Pharmacokinetic and bioavailability evaluation studies confirm the favourable effect of this prolonged gastric residence time.

(Shahaa, *et al.*, 2009). Ondansetron is a short acting serotonin 5-HT^3 receptor antagonist used for management of nausea and vomiting. This drug is removed from the body by the liver and kidneys. Its Bio availability is ~60 %, protein binding is 70%-76% and is metabolized in liver through (CYP3A4, CYP1A2, CYP2D6). Its half life is about 5.7 hours. In present investigation, Ondansetron is formulated as the gastro retentive drug delivery system in the form of floating tablets by using polymers and other excepients in different ratios and evaluated. (Kumari, S. Daisy Chella; *et al.*, 2012).

MATERIAL AND METHODS

Materials

Ondansetron, polymers are the samples all the other excipients were bought from the Central Drug House, New Delhi. (Vankatesh, *et. al.*, 2012).

Full Factorial Design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amounts of chitosan and sodium bicarbonate were selected as independent variables. The times required for 50% drug dissolution (*T50%*), and the Floating lag time (*FLT*) was selected as dependent variables trials were performed at all 9 possible combinations.

Effect of Formulation Variables on T50%

The result of two ways ANOVA clearly shows that the coefficient of *X1, X2* and *X1X2* were found to be significant at $P < 0.01$(Naruka, PS *et al.* 2012).

Preparation of Floating Tablets of Ondansetron

Floating tablets containing Ondansetron as an active material were prepared by direct compression method by effervescent approach. Briefly drug and Chitosan, Xanthan Gum, Citric Acid, Sodium Bicarbonate, Microcrystalline Cellulose and Magnesium stearate were mixed geometrically with each of the polymer. Various formulations were prepared by a formulation design using different ratios of polymers and floating agent. Sodium Bicarbonate helpful for floating. These powders were grinded and blended together and punched into tablets in direct compression method by using punching machine in a die (13 mm diameter) at 50 kg/cm2 pressure for 1 min to produce floating tablets. As a part of preformulation studies, the UV-VIS λ-max of Ondansetron was determined using UV-VIS Spectrophotometer (Shimadzu) and the calibration curve of Ondansetron was designed by measuring absorbance at 310 nm in 0.1 N HCl making dilutions to yield concentration of 20,40,60,80,100 µg/ml. FTIR studies for the compatibility study of drug to polymers were performed for Pure Drug, polymers and formulation using FTIR spectrophotometer (Thermo Nicolet) (Kumari, S Daisy Chella *et al.*, 2012).

Physical Evaluation of Tablets

Floating Study

In vitro floating 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) (Leena, Jagat S *at el*., 2011)

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 (Rao, Raghavendr *et al.*, 2012).

Swelling Index

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±0.5º 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 done; swelling index was calculated by using the following formula. (Railkar, Anirudh *et al.*, 2001).

In-Vitro Dissolution Studies

Dissolution Testing Automatic Apparatus (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl for 12 hrs. Sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. Sampels were 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. Cumulative %drug release was calculated using an equation obtained from a standard curve. The data obtained from *in vitro* release studies were subjected to Zero order, first order Higuchi's model and Korsemeyer's model (PS, Naruka *et al.*, 2012).

RESULTS AND DISCUSSION

Drug Content

All the formulations were tested for Percentage drug content and it was found that drug content in all formulations is under limit. (Gupta, Amit *et al.*, 2011)

Floating Lag Time

Formulations were prepared using different ratios of polymers. The prepared formulations were evaluated for floating lag time and buoyancy time. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N HCl). It was observed that the gas generated is trapped and as the concentration of Sodium bicarbonate increases FLT decreases in F3, F6, F9 and floating time of formulation F9 is 12 hrs as the concentration of chitosan increases floating time increases, thus density of the tablet decreased and it becomes buoyant, Sodium bicarbonate and Chitosan had significant effect on lag time of floating tablet.

In Vitro Dissolution Studies

In Vitro dissolution studies were done for floating tablets containing Ondansetron in 0.1 N HCl. The tablet swelled during in vitro floating studies. The results from the dissolution studies carried in 0.1 N HCl. Nine formulations were sustained release and it releases for a period of 12 hrs .It was found that F9 provided better-sustained release characteristics with best *in vitro* floating with much floating lag time because of amount of Chitosan present in the formulation. As the concentration of Sodium bicarbonate increases FLT decreases in F3, F6, and F9, floating time of formulation F9 is 12 hrs as the concentration of chitosan increases floating time increases.

Release Kinetics Study

Most of the formulations best fit to Higuchi model, Korsemeyer's model, First Order and zero order which shows that the release of drug is dispersed uniformly in polymer. The best fit model of formulation 9 is Korsemeyer's model Chitosan and Sodium Bicarbonate help successfully to release drug in sustained manner which understands the release pattern as well as order.

CONCLUSION

- A systemically study using a factorial design revealed that the amount of Chitosan and amount of Sodium Bicarbonate had significant effect on release rate and Floating lag time

- The formulation F9 was selected as the best formulation because it gave the best result in terms of the required in vitro buoyancy study and drug release in sustained manner.
- The result of two ways ANOVA clearly shows that coefficient of *X1, X2* and *X1X2* were found to be significant at P<0.01.
- The kinetic study revealed the drug release mechanism best fitted Korsemeyer's model and Zero order.

Table 1: Amount of Variables in Full Factorial Design Formulations

Code values	Actual values (mg)	
	X1	X2
-1	80	45
0	100	55
+1	120	65

X1 values are Chitosan; **X2** values are Sodium bicarbonate

Table 2: Preparation of floating tablets of Ondansetron

Ingredients (mg)	Formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Chitosan	80	80	80	100	100	100	120	120	120
Xanthan Gum	60	60	60	60	60	60	60	60	60
Sodium Bicarbonate	45	55	65	45	55	65	45	55	65
Citric Acid	30	30	30	30	30	30	30	30	30
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Microcrystalline Cellulose	65	65	65	65	65	65	65	65	65
Ondansetron	10	10	10	10	10	10	10	10	10

Batch	% Drug Content
F1	95.5
F2	96.0
F3	95.6
F4	98.16
F5	98.87
F6	96.8
F7	99.6
F8	98.7
F9	100.9

Table 1.1: Evaluation parameters of preliminary trial's formulation

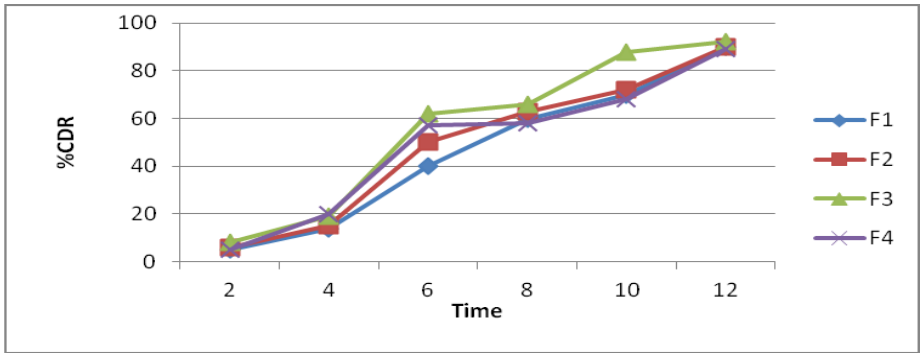
Batch	Weight Variation (Mg) (N=20)	Hardness (Kg/Cm2) (N=10)	Friability (%) (N=10)	Thickness (cm)Mean ± SD	Diameter (cm) Mean ± SD
F1	295±5	4.5±0.50	0.58±0.0019	0.38±0.031	0.82±0.008
F2	305±5	4.6±0.41	0.53±0.0022	0.40±0.011	0.83±0.001
F3	315±5	5±0.350	0.64±0.0018	0.41±0.007	0.82±0.004
F4	315±5	4.7±0.270	0.62±0.0015	0.43±0.007	0.82±0.006
F5	325±5	4.8±0.477	0.71±0.0028	0.42±0.013	0.82±0.003
F6	335±5	4.5±0.130	0.65±0.0031	0.44±0.001	0.82±0.006
F7	335±5	5.0±0.431	0.61±0.0021	0.40±0.001	0.83±0.001
F8	345±5	4.3±0.280	0.63±0.0025	0.43±0.007	0.82±0.002
F9	355±5	4.0±0.190	0.52±0.0016	0.44±0.001	0.82±0.007

Table 1.2: Data showing comparative In-Vitro % drug release profile

Time (hrs)	Cumulative % Drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
2	5	6	8	5	11	20	37	39	8
4	14	15	19	20	25	30	55	41	18
6	40	50	62	57	55	54	57	49	34
8	60	63	66	58	69	59	68	53	54
10	70	72	88	68	82	65	76	60	75
12	90	90	92	89	97	91	94	88	94

Table 1.3: Data showing FLT and Floating Time

Batch	Floating Lag Time (second)	Floating Time (hrs)
F1	15	7
F2	25	9
F3	10	11
F4	25	8
F5	12	10
F6	10	11
F7	15	9
F8	12	11
F9	10	12



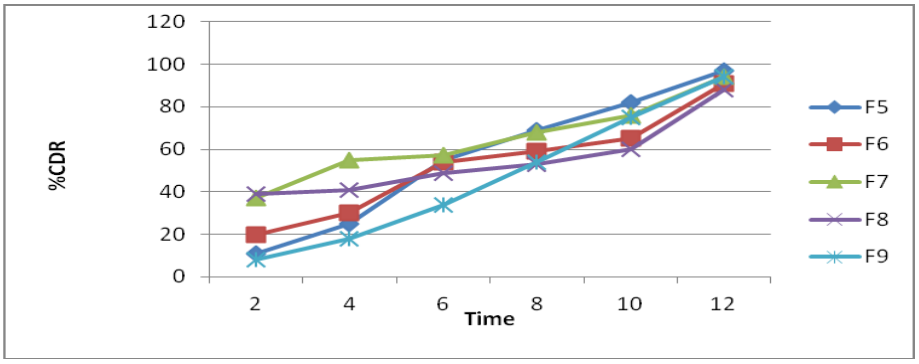


Figure 1: *In Vitro* Dissolution Data for the Formulation of F1-F9

Table 1.4: Model fitting of release profile of formulation

Formulation Code	Mathematical Model (Kinetics)				
	Zero order R^2	First order R^2	Higuchi Kinetics R^2	Korsemeyer Peppas model R^2	Best Fit Model
F1	0.985	0.699	0.969	0.982	Zero Order
F2	0.962	0.776	0.965	0.963	Peppas Model
F3	0.928	0.951	0.947	0.907	First Order
F4	0.934	0.477	0.945	0.944	Higuchi Kinetics
F5	0.980	0.862	0.984	0.951	Higuchi Kinetics
F6	0.912	0.778	0.899	0.855	Zero Order
F7	0.960	0.798	0.941	0.889	Zero Order
F8	0.832	0.673	0.755	0.646	Zero Order
F9	0.988	0.834	0.948	0.993	Peppas Model

Table 1.5: *In vitro* release profile of formulation F9 for studying the Release kinetics

Time	Square root	Log time	%CDR	Log % CDR	Cumulative % Drug Retained	Log Cumulative % Drug Retained
2	1.414	0.301	8	0.903	92	1.96
4	2.00	0.602	18	1.255	82	1.91
6	2.449	0.778	34	1.530	66	1.81
8	2.828	0.903	66	1.732	46	1.66
10	3.162	1	46	1.870	25	1.39
12	3.464	1.07	25	1.970	6	0.77

Table 1.6: *In vitro* T50% release of formulations F1-F9

Batch	T50 %(hrs)
F1	5.0
F2	6.0
F3	5.0
F4	5.6
F5	6.0
F6	6.2
F7	6.4
F8	6.9
F9	7.0

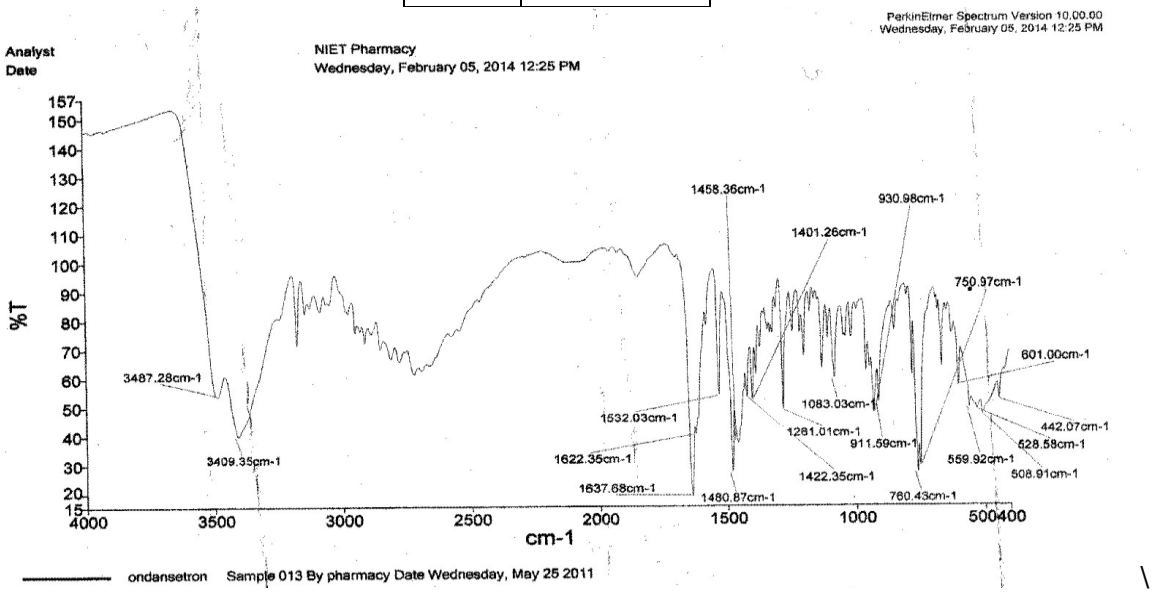


Figure 1.1: FTIR (Fourier Transform Infra-red Spectroscopy) of Drug

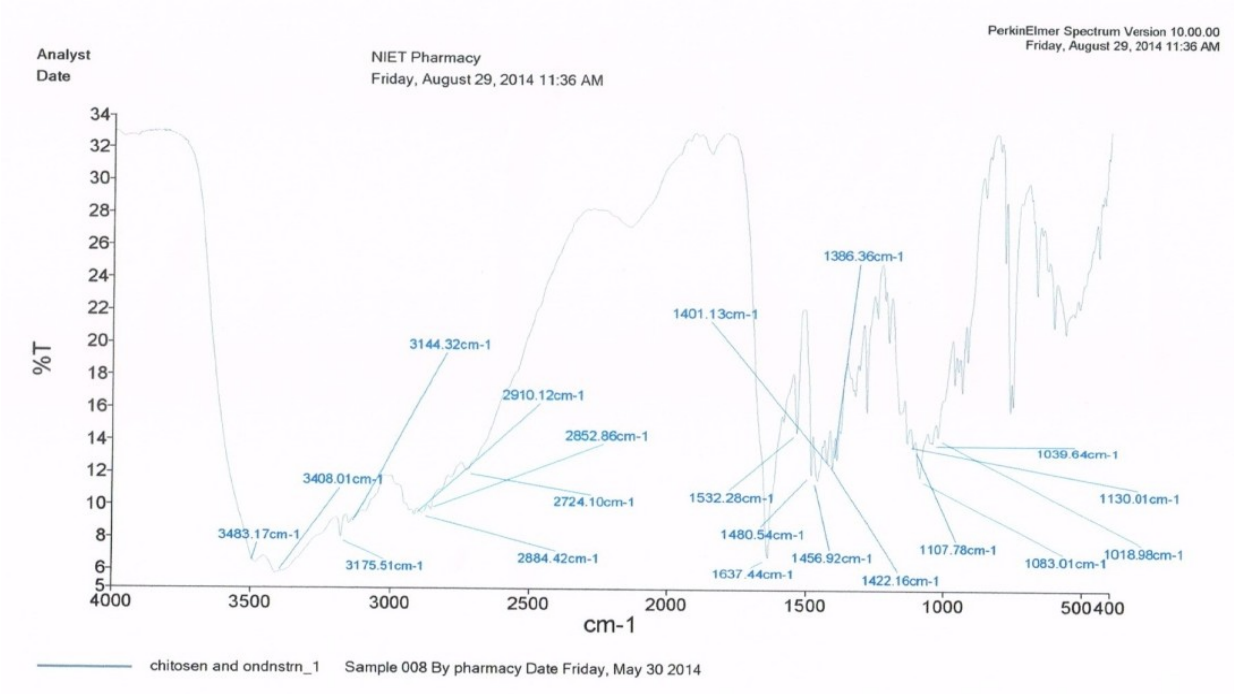


Figure 1.2: FTIR Spectrum of Drug and Chitosan

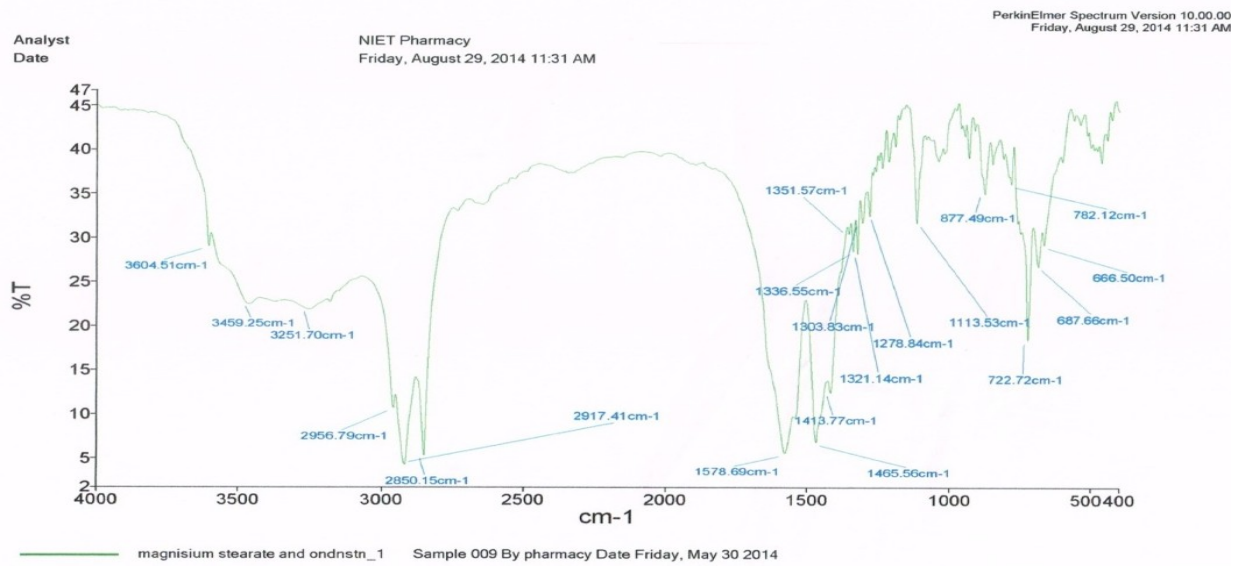


Figure 1.3: FTIR Spectrum of Drug and Magnesium Stearate

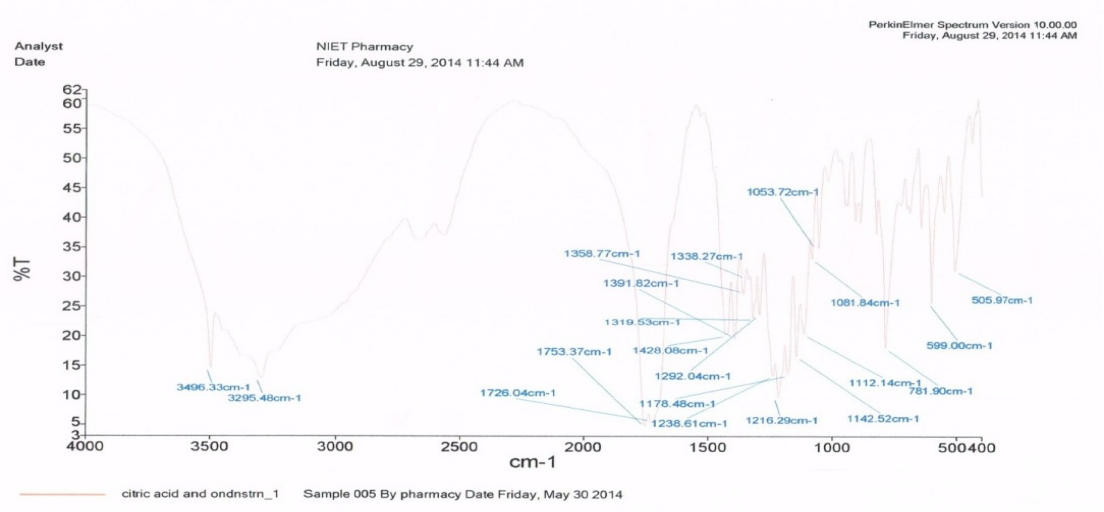


Figure 1.4: FTIR Spectrum of Drug and Citric Acid

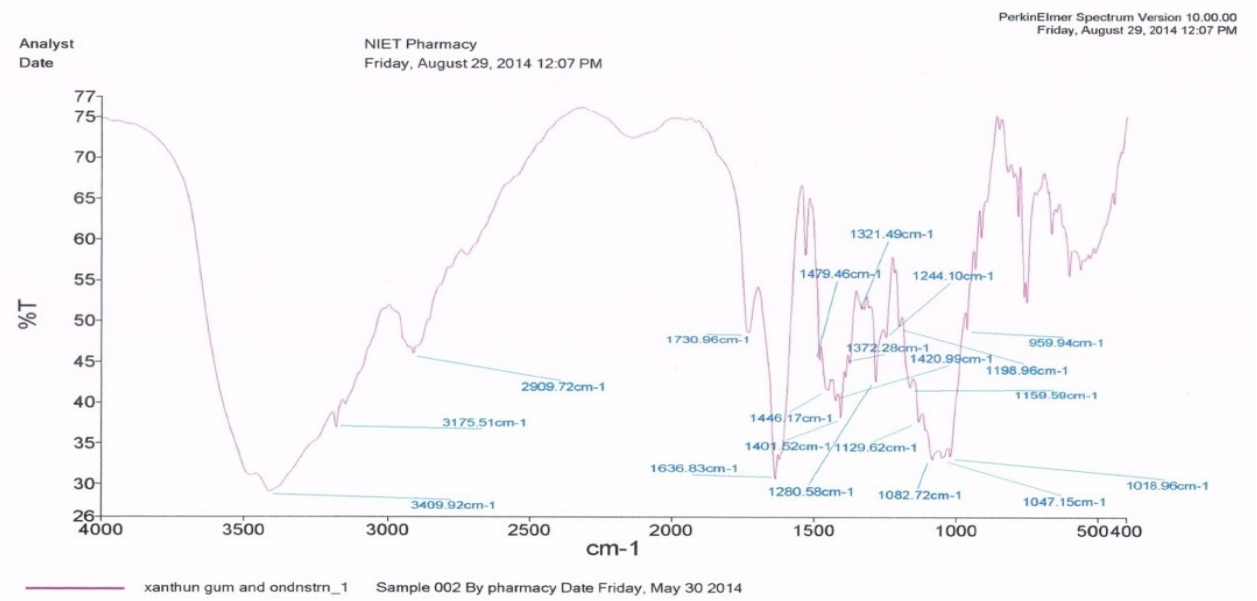


Figure 1.5: FTIR Spectrum of Drug and Xanthan Gum

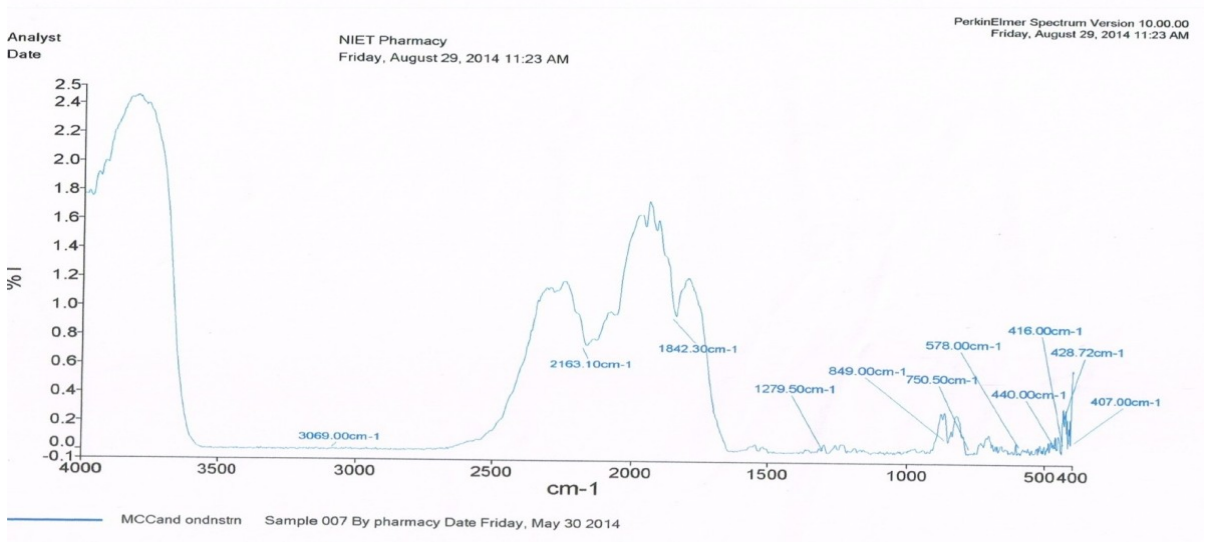


Figure 1.6: FTIR Spectrum of Drug and MCC

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