International Research Journal of Pharmaceutical and Applied Sciences
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2012; 2(2):44-56

IRJPAS **ISSN-2277-4149**

Research Article

FORMULATION AND IN-VITRO EVALUATION OF FLOATING MATRIX TABLETS OF CEPHALEXIN

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(Received: 10 March, 2012; Accepted: 25 March, 2012; Published: 29 April, 2012)
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ABSTRACT

Floating matrix tablets of Cephalexin were prepared by using a combination of synthetic and natural polymers in two different concentrations. The floating properties and in-vitro drug release properties were optimized by 2^3 factorial design and total 8 formulations were developed. The synthetic and natural polymers used in combination were HPMC K4M, HPMC K15M and Xanthan Gum, Guar gum respectively. Each formulation consists of a combination of one synthetic and one natural polymer in any one ratio of 1:1 or 1:4. In this study it was confirmed that the formulations containing HPMC K4M, have shown better floating properties and finally the formulation containing a combination of HPMC K4M and Xanthan Gum in 4:1 ratio, has shown better in-vitro release properties.

Key words: Floating matrix tablets, Cephalexin, HPMC K4M, Xanthan Gum, Gastric retention.

INTRODUCTION

Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from upper GIT. Floating drug delivery systems (FDDS) offer a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract [1].

The ideal drug candidate for FDDS are drugs that are acting locally in upper gastro intestinal tract (GIT) or drugs that are degrading in lower GIT or drugs that show poor intestinal absorption or drugs that are absorbed only in the initial part of

the small intestine and stomach. Acid labile drugs and other drugs that are causing gastric lesions are unsuitable for such formulations. The gastric retention of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states. Out of all available gastro retentive systems floating tablets, floating beads, floating granules, and floating microspheres have gained major importance in the formulation development more recently [2].

Cephalexin, chemically (6*R*, 7R)-7-{[(2*R*)-2-amino-2-phenylacetyl] amino} - 3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene- 2-carboxylic acid, is a first generation cephalosporin antibiotic. It inhibits synthesis of bacterial cell wall, causing cell death. Cephalexin is a weak acidic drug with pKa of 3.6 and half life of 0.5-1.2 hours. According to Handerson-Hesselbach equation, the weak acidic drugs with pKa in the range of 2.5-7.5 show poor absorption in the intestine because of more ionization and show more absorption in stomach because of predominant unionization at gastric pH. Thus the Cephalexin is suitable to formulate as floating tablets in order to increase the bioavailability. As the half life of the drug is less, it can be formulated as matrix tablets to decrease the dose frequency.

In the present study, Cephalexin floating matrix tablets were prepared to increase the absorption of drug through gastric mucosa and to decrease the dose frequency. The prepared tablets were evaluated for their floating properties and in-vitro drug release.

MATERIALS AND METHODS

The chemicals used in this study were pure drug like Cephalexin (Venkateswara scientific traders) and polymers like HPMC K4M, HPMC K15M, Xanthan gum (Venkateswara scientific traders), Guar gum (Accord labs) and other excipients like Micro crystalline cellulose (Venkateswara scientific traders), Magnesium stearate, Talc, Sodium bicarbonate (Accord labs), Citric acid (Fischer labs).

1. Preformulation study

Preformulation studies were conducted to identify the compatibility of drug with polymers. These studies were conducted by using FTIR method. In this method, the sample along with KBr was used to get the IR spectrum. The IR spectra of pure drug and physical mixtures containing drug and polymers were produced and analysed.

2. Preparation of floating matrix tablets

Cephalexin was mixed manually in polybags with gastro retentive polymers separately as per formulae and MCC was added as diluent and sodium bicarbonate, citric acid were added as effervescent agents (Table 1) and mixed for 10 mins. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. The mixed blend was then compressed into tablets by direct compression method using 12.5 mm punches on a sixteen station rotary tablet punching machine (Cadmach machineries). Total eight formulations were developed by 2^3 factorial design i.e 3 factors were optimized, each at 2 levels.

Table 1: Formulation composition of Cephalexin floating tablets of F1 to F8

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Drug	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg
HPMC K4M	125mg	200mg	-	-	125mg	200mg	-	-
HPMC K15M	-	-	125mg	200mg	-	-	125mg	200mg
Guar gum	-	-	-	-	125mg	50mg	125mg	50mg
Xanthan gum	125mg	50mg	125mg	50mg	-	-	-	-
MCC	72mg	72mg	72mg	72mg	72mg	72mg	72mg	72mg
NaHCo3	45mg	45mg	45mg	45mg	45mg	45mg	45mg	45mg
Citric acid	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Mg. Sterate	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg
Talc	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg	6.5mg

The three factors, each at two levels used in the study were as follows

The three factors, each at two levels used in the study were as follows:

Factor	**Levels**
1. Ratio of synthetic polymer and natural polymer	1:1 and 4:1
2. Type of synthetic polymer	HPMC K4M and HPMC K15M
3. Type of natural polymer	Xanthan gum and Guar gum

3. Evaluation

a) Characterization of tablets for physicochemical parameters

The prepared Cephalexin floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

b) In vitro floating lag time

The in vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37^{o} C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

c) In vitro floating duration time

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration.

d) In vitro drug release

The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5^{o}C temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbances of the diluted samples were measured at 257nm for Cephalexin by using UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve.

e) Characterization of drug in Floating tablets

FTIR studies were conducted for characterization of drug in tablets of selected optimized formulation (F2). The

floating tablets were compressed and powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectra of pure Cephalexin and pelletized powder of tablets were taken, interpreted and compared with each other.

RESULTS AND DISCUSSION

1. Preformulation study

In IR spectrum (figure 1) of pure Cephalexin, the presence of peaks at 3447.82, 3616.29 cm^{-1} (>N-H stretching), 1690.25, 1752.75 and 1835.12 cm^{-1} (>C=0 stretching), 3038.97 cm^{-1} (Aromatic >C-H stretching), 1645.79 (Aromatic -C=C-stretching) were characteristic to that of the pure drug and all of them remained unaltered in the IR spectra (figure 2) of physical mixtures containing drug and polymers. IR analysis revealed that there was no evidence to the presence of known chemical interaction of drug with polymers and other ingredients.

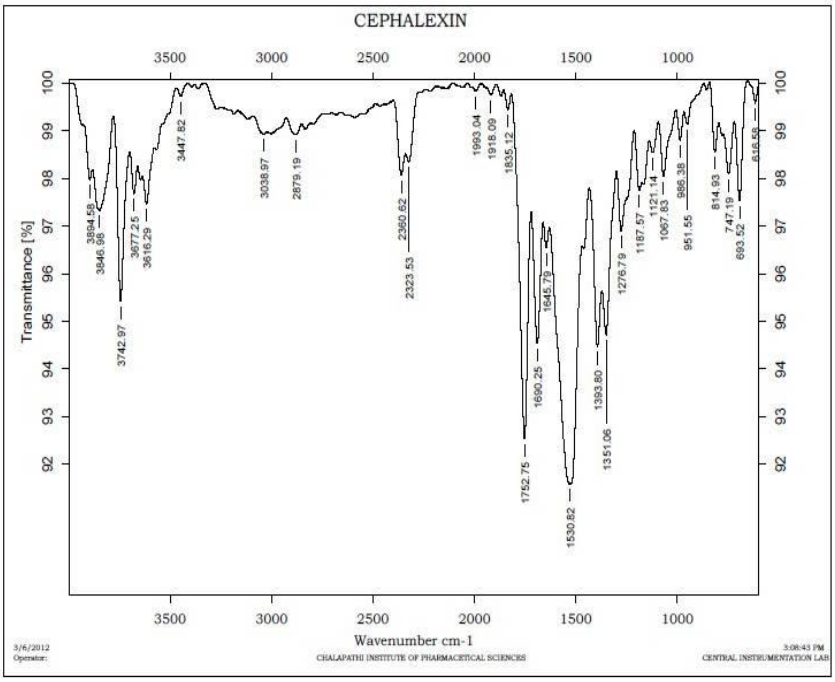

Figure 1: IR spectrum of pure Cephalexin.

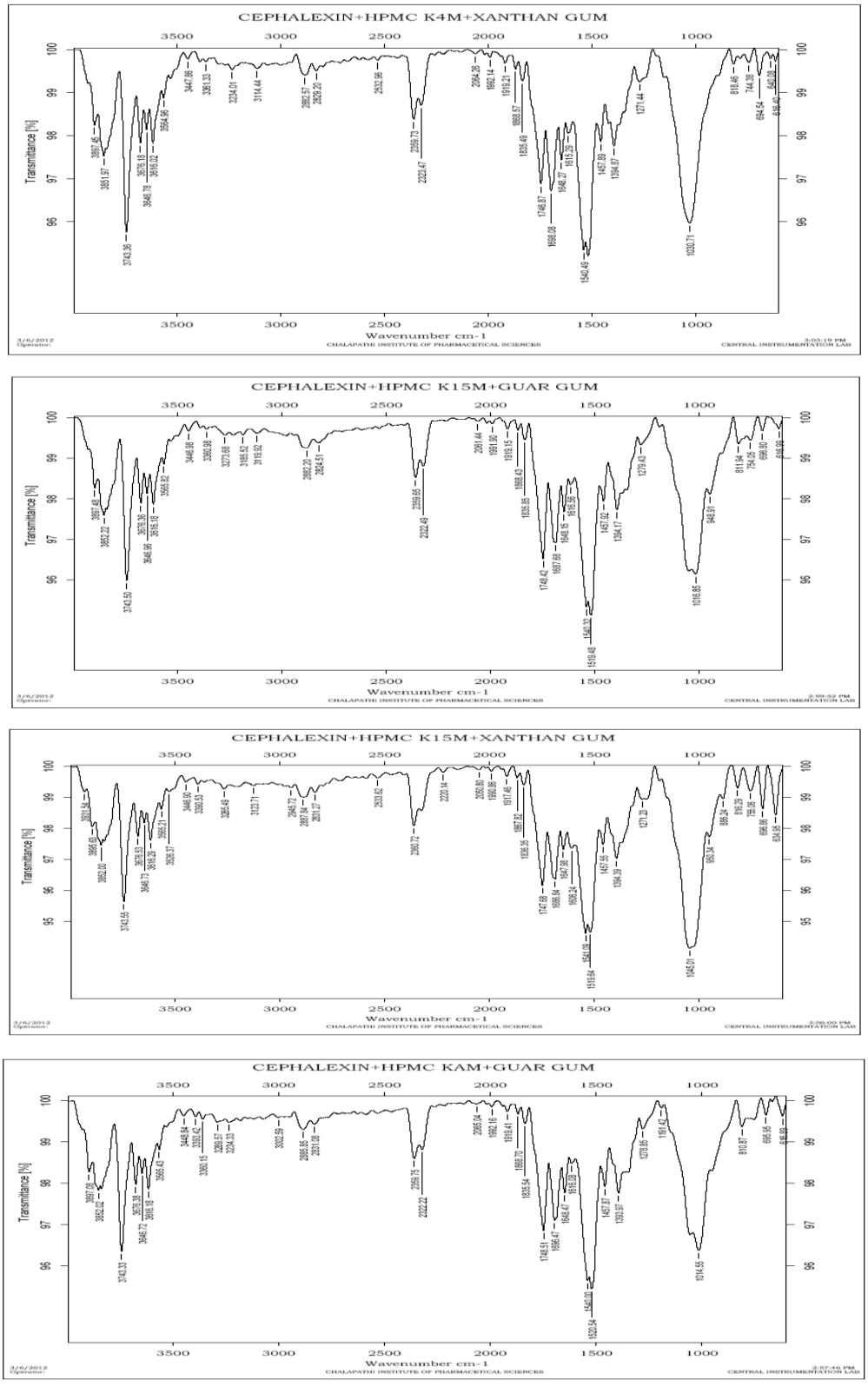

Figure 2: IR spectra of physical mixtures containing drug and polymers

2. Weight variation, hardness, friability and assay

The weight variation of the tablets (Table 2) was within the limits of uniformity. The mass ranged from 647.50 to 652.40 mg with SD values 0.69–1.30. The mass of all compressed tablets were within the limits as per USP. The drug content ranged from

97.50 ± 0.36 % in formulation F1 to 90.38 ± 0.36 % in formulation F8 and the friability was ranged from 0.25 to 0.98. Friability and assay of all compressed tablets were within the limits as per USP. The hardness of all prepared tablets was in the range of 3.5 to 4 kgs.

Table 2: Weight variation, Friability and Assay

Formulation	Mass (mg) Mean ± SD	Friability (%)	Assay (%)
F1	649.80 ± 1.00	0.50	97.50 ± 0.36
F2	648.70 ± 0.76	0.25	101.25± 0.47
F3	651.10 ± 0.69	0.32	109.25± 0.59
F4	650.40 ± 0.75	0.98	110.88±1.01
F5	652.40 ± 1.24	0.87	91.38±0.75
F6	649.00 ± 0.89	0.51	102.00±0.36
F7	648.20 ± 1.30	0.45	104.38± 0.48
F8	647.50 ± 0.99	0.30	90.38±0.36

3. In vitro floating lag time and floating duration

The formulations like F1, F2 and F5, F6 had floating lag times below 5 minutes, where as the formulations like F3, F4 and F7, F8 has shown floating lag time of more than two hours (Table 3). From these results it was found that the formulations containing HPMC K4M as one of the polymers, has shown less floating lag time and formulations containing HPMC K15M as one of the polymers, has taken more time to float on the surface of 0.1 N HCl.

All the formulations were allowed to float constantly on dissolution medium. The formulations F1, F2 and F5, F6 containing HPMC K4M as one of the polymers, were floated up to more than 12 hours where as the formulations F3, F4 and F7, F8 containing HPMC K15M as one of the polymers, have shown their floating duration of less than 8 hours.

This may be due to less capacity of HPMC K15M to form hydrophilic barrier around the tablet and to decrease the total density of the tablet. The other reason may be due to inefficiency of 10 % w/w effervescent agent in tablet to reduce its total density in the presence of HPMC K15M.

Table 3: Floating lag time and Floating duration

Formulation	Floating lag time (sec)	Floating duration time(hrs)
F1	120 sec	More than 12 hrs
F2	300 sec	More than 12 hrs
F3	More than 2 hrs	5 hrs 12 min
F4	More than 2 hrs	4 hrs 24 min
F5	10 sec	More than 12 hrs
F6	35 sec	More than 12 hrs
F7	More than 2 hrs	4 hrs 35 min
F8	More than 2 hrs	3 hrs 23 min

4. In vitro drug release

The in vitro dissolution study was performed to those formulations that have shown better floating properties i.e. F1, F2 and F5, F6. The release of Cephalexin from gastro retentive floating tablets (Table 4 and Figure 3) varied according to the type of matrix forming polymers. The drug release from the formulations F1 and F2 was controlled up to 8hrs. The drug release in case of formulation F5 was not extended up to 8 hrs and immediate drug release pattern was observed; and incase of formulation F6 the complete drug release was observed at the end of 8 hours. The matrix forming ability was more in case of formulations F1 and F2 containing polymers like HPMC K4M and Xanthan gum, where as matrix forming ability was less in case of formulations F5 and F6 containing polymers like HPMC K4M and Guar gum. However the more controlled drug release was observed in the formulation F2 containing a combination of polymers like HPMC K4M and Xanthan gum in 4:1 ratio. It may be due to high capacity of HPMC K4M in combination with Xanthan gum at 4:1 ratio, to form the matrix in the tablet.

Table 4: In-vitro release profiles of formulations F1, F2 and F5, F6

Time (hrs)	F1	F2	F5	F6
0	0	0	0	0
1	25.38 ± 0.85	25.78 ± 1.24	98.49 ± 1.33	63.09 ± 0.84
2	37.85 ± 0.69	34.67 ± 1.04	**103.42 ± 0.63**	65.29 ± 0.96
4	49.85 ± 0.64	45.78 ± 1.33	**111.30 ± 1.49**	77.65 ± 1.41
6	68.92 ±0.86	68.00 ± 0.66	-	84.71 ± 0.81
8	73.38 ±0.99	77.78 ±0.87	-	**108.53 ±1.11**

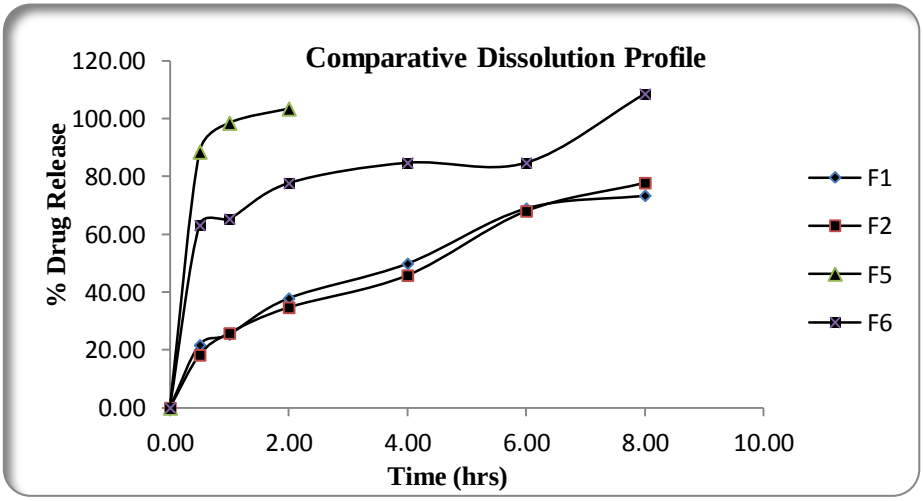

Figure 3: Dissolution Profile of F1, F2 and F5, F6

In the dissolution study of formulations F1, F2 and F5, F6, it was revealed that only three formulations like F1, F2 and F6, have released the drug in controlled manner up to 8 hours. Hence kinetics of drug release and mechanism of these three formulations were studied. The release data of all three formulations seem to fit better with the first order kinetics and Higuchi model i.e. the release rate in these formulations, is dependent of its concentration or amount of drug in tablet at given time and the release mechanism is Fickian diffusion.

Based on the results from in-vitro floating studies and in-vitro drug release studies, the formulation F2 containing a combination of polymers like HPMC K4M and Xanthan gum in 4:1 ratio was selected

as best formulation with optimum floating and drug release properties.

5. Characterization of drug in floating tablets

IR analysis (figure 4) revealed that there was no evidence to the presence of known chemical interaction of drug with polymers and other ingredients in selected best formulation.

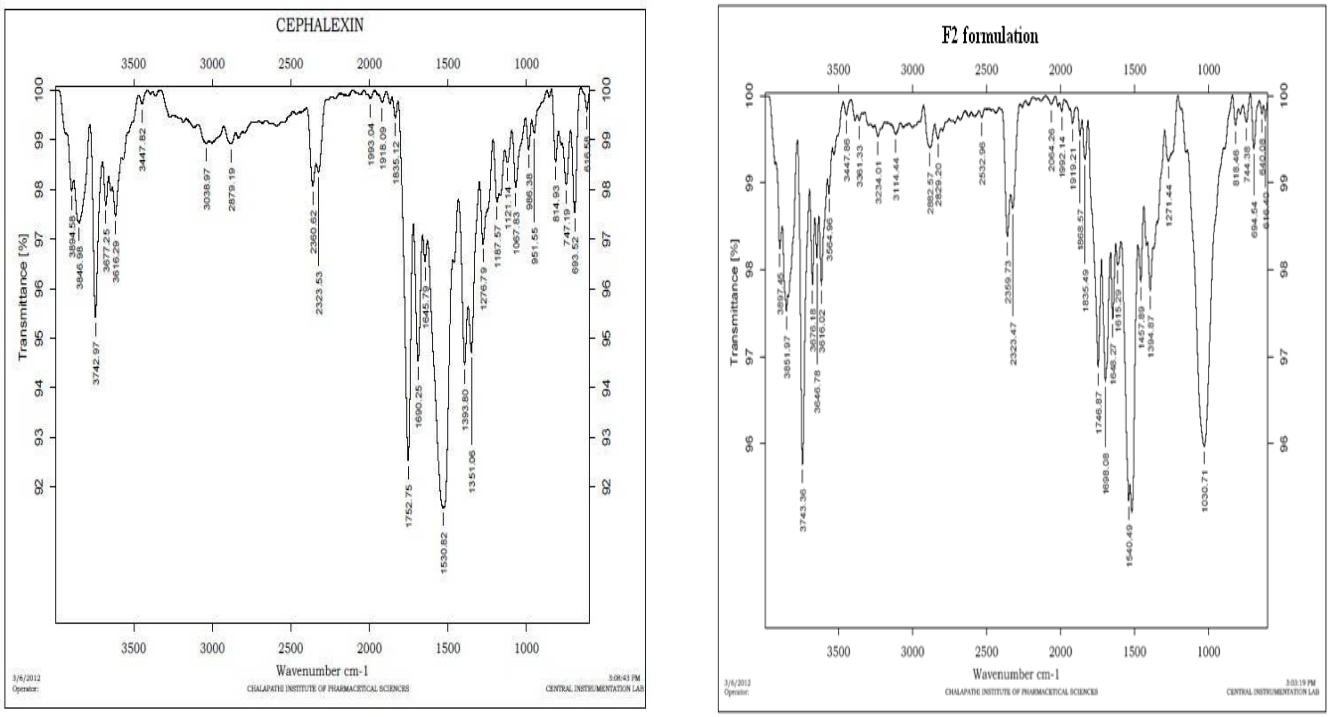

Figure 4: IR spectra of Pure Cephalexin and F2 formulation

CONCLUSION

New gastro retentive delivery systems for Cephalexin were developed and evaluated. The results propose that synthetic polymer HPMC K4M in combination with natural polymer like Xanthan gum in 4:1 ratio can increase the retention time of formulation in stomach and also can control the drug release from formulation due to matrix formation thereby increasing drug absorption and reducing the dose frequency. It can be concluded that the antimicrobial action of Cephalexin may be increased in the stomach due to increased retention and absorption by using formulation F2. The results obtained for used combination and ratio of polymers in the presence of MCC (diluent), were not reported earlier in any work. Further work is needed to claim the results in human beings by in-vivo studies.

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