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Research Article

Formulation and Evaluation of Gastroretentive Drug Delivery System of Cefuroxime Axetil

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ABSTRACT

Cefuroxime Axetil is a second generation antibacterial belongs to Cephalosporin Group. The drug undergoes rapid metabolism in intestinal mucosa due to change in pH Environment and hence has decreased oral bioavailability. The aim of present investigation is to increase the gastric residence time by preparing gastroretentive tablets here by improving bioavailability of Cefuroxime Axetil. A simple UV spectrophotometric method has been employed for the estimation of Cefuroxime Axetil at 281 nm. A floating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, sodium alginate and hydrocolloids like hydroxyl propyl methyl cellulose (HPMC) and guggul. The prepared tablets were evaluated in terms of their precompression parameters, physical characteristics, In vitro release, buoyancy lag-time and swelling index. The formulations were optimized for the different grades of HPMC, and its concentrations and combinations. The results of the In vitro release studies showed that the optimized formulation F3 could sustain drug release of 92% and remain buoyant for 10h. The optimized formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominately Higuhci with non fickian diffusion. Finally the tablets formulations found to be economical and may overcome the draw backs associated with the drug during its absorption.

Keywords: Gastroretentive Drug Delivery System, Cefuroxime Axetil, lag time

INTRODUCTION

The Floating drug delivery system (FDDS) is one of the Gastroretentive technique becomes most promising drug delivery to improve the bioavailability of drug which is unstable in the intestinal environment and also FDDS provides prolonged drug release by increasing the residence time of the drug in GIT due to its buoyancy capacity in stomach fluid.[1, 2] To achieve the buoyancy of dosage form in stomach fluid, the dosage form should have less density than the density of stomach fluid which is approximately 1.004 g/cc. The drugs which are unstable in intestine and the drug with short biological half-life are more suitable for the floating drug delivery system [3,4].Cefuroxime Axetil (CA) is 1-acetoxyethyl ester of ab-lactamase-stable cephalosporin, cefuroxime with a broadspectrum of activity against Gram-positive and Gram-negative microorganisms. After oral administration CA is absorbed and rapidly hydrolyzed by esterases to produce cefuroxime. The 1-acetoxyethylester group at 4th position of CA ensures lipophilicity and promotes the absorption of cefuroxime but at the same time compromises on solubility and hence, the prodrug shows poor and variable oral bioavailability. [5] CA exists in crystalline as well as amorphous forms; of these, latter exhibits higher bioavailability owing to

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improved solubility. The bioavailability of CA is variable and limited to 30% in fasted and 50% in fed state in humans.CA is known to have good absorption from upper parts of GIT. Thus, retaining CA in this region for longer time would be beneficial in improving its bioavailability.[6]In the present work, floating delivery system approach was used in developing hydroxyl propyl methyl cellulose (HPMC)based dosage form. Various grades of HPMC (K4M, K15M) along with sodium alginate were tested for their usefulness in formulating GFDDS of CA.

MATERIAL AND METHODS

Cefuroxime axetil was obtained as a gift sample from Covalent labs Pvt.Lmt. Hyderabad. Hydroxypropyl Methylcellulose K4M (HPMC K4M) and Hydroxypropyl Methylcellulose K15M(HPMC K15M) were obtained from ISP, Hyderabad, India. Guggul was obtained from Tirupathi. Other excipients were procured from S.D. Fine Chemicals, Mumbai, India.

Calibration curve of Cefuroxime axetil

Accurately weighed 10 mg of Cefuroxime axetil was transferred to 100 ml volumetric flask, dissolved in 20 ml 0.1N HCL by shaking manually for 10 min. The volume was adjusted with the same up to the mark to give final strength i.e. 100 µg/ml. Appropriate volume 0.2 ml of standard stock solution of Cefuroxime axetil was transferred into 10 ml volumetric flask, diluted to mark with 0.1N HCL to give concentration of 2µg/ml. The resulting solution was scanned in UV range (200 nm – 400 nm). . The absorbance of the solutions was measured at 281 nm using double beam UV-Visible spectrophotometer against 0.1N HCl as a blank. The plot of absorbance vs. concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft Excel.

Formulation of floating tablets of Cefuroxime Axetil using HPMC k4M , HPMC k15M .

Floating tablets of Cefuroxime axetil was prepared by direct compression method. Cefuroxime axetil was mixed with the required quantitiesof polymer blend (HPMC k15M, HPMC k4M), sodium alginate, guar gum, $NaHCO_3$, guggul by geometric mixing The powder blend was then lubricated with Mg. stearate (1%) & compressed on a single punch machine (Rimek mini press, Ahmedabad) using 12mm standard flat punch.

HPMC K4M , HPMC K15M are used as viscosity grade polymer , guar gum is used as binder , Guggul which is the Gum of the Commiphora Mukul obtained by solvent extraction isused as taste masking agent and also increases the drug release, sodium bicarbonate is used as gas generating agent agent, sodium alginate is used as tablet disintergent.

EVALUATION OF POWDER BLENDS[7,8,9,10]

Angle of repose

Angle of Repose of powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \alpha = h/r$$

Bulk density and tapped density

An accurately weighed quantity of the blend (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder with lid, set into the density determination apparatus (Tapped Density Apparatus, (ElectrolabLTD1020). The density apparatus was set for 500 taps and after that the volume (Vf) was measured which was tapped volume. The bulk density and tapped

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density were calculated by using the following formulas.
Bulk density = W/ V0
Tapped density = W/ Vf

Compressibility index (CI)/ Carr's index
It was obtained from bulk and tapped densities. It was calculated by using the following formula.

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio
Hausner's ratio is a number that is correlated to the flowability of a powder. It is measured by ratio of tapped density to bulk density.

$$\text{Hausner' index} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

EVALUATION OF TABLETS

Thickness
Thickness of the tablets was determined using a digital vernier caliper MITUOTYO.

Weight variation Test
To study weight variation, 20 tablets of each formulation were weighed using an electronic balance Aqua and the test was performed according to the official method.

Drug content (assay)
Drug content of the tablets was determined spectrophotometrically.

Hardness
Hardness of the tablets was determined using a Monsanto tablet hardness tester. A tablet hardness of about 3 to 5 kg/cm2 is considered adequate for mechanical stability.

Friability
Friability of the tablets was measured in a friabilator (Roche). 20 tablets were accurately weighed (W0) and placed in friability test apparatus. They were observed for 100 rotations. After 100 rotations they were weighed again (W). The weight loss should not be more than 1% w/w.
%Friability = (W0-W)/ W0 X100

Buoyancy study
Buoyancy study was done in a glass beaker containing 900ml of 0.1 N HCl. Prepared tablets were put in the medium for observation. From this study floating lag time and total floating time were noted with the help of a stop watch. Floating lag time is the time taken by the tablet to move upward to the surface of the medium. The duration for which tablet floats constantly on the surface of the medium is called total floating time.

***In-vitro* drug release study** [11]
Dissolution of the tablets of each batch was carried out using USP type-I apparatus using basket. The dissolution medium consisted of 900mlof 0.1N HCl (pH 1.2) for 10h, maintained at 37 $\pm$ 0.5°C. One tablet was placed in basket of each dissolution vessel and the basket rotation speed was set at 50rpm. 5ml of the sample was withdrawn every hour for 10h and for every 1h to 10 h the same volume of the fresh medium was replaced every time. The samples were analyzed for drug content at a wavelength of 281 nm using double beam UV-Visible spectrophotometer. The content of the drug was calculated using the equation generated from the standard curve. The percentage cumulative drug released was calculated.

Kinetic drug release[12]
Various models such as Zero order kinetics (cumulative percentage amount of drug release versus time), First order kinetics (log cumulative percentage of drug remaining to release versus time), Higuchi (fraction of drug release, Mt/Mi, versus square root of time), Hixon Crowell (cube root of drug percentage remain, W01/3- Wt1/3 versus time) and Korsermeyer-Peppas (log fraction of drug released, log Mt/Mi, versus log

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time) were applied to assess the kinetics of drug release from prepared tablets. Most suited model for drug release was predicted on the basis of regression coefficient i.e. nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism.

RESULTS AND DISCUSSION

The present study was aimed to make the formulation remain in the stomach for longer period of time and to release the drug (cefuroxime axetil) in controlled rate. Sodium bicarbonate generates carbon dioxide gas in the presence of hydrochloric acid present in gastric dissolution medium. No drug polymer incompatibility was noted in their FTIR spectra (Fig. 6 to 7).

The tablets were evaluated for physical characteristics, weight variation, friability, hardness and dissolution studies. Hardness, thickness and friability was found to be in range of 5.2 ± 0.2293 to 5.38 ± 0.3542 kg/cm2, 5.08 ± 0.0816 to 5.103 ± 0.080 and 0.79 to 0.91 respectively, which is acceptable criteria in tablet formulation. In all formulations, hardness test indicates good mechanical strength; friability is less than 1% which indicates that tablets had a good mechanical resistance. Drug content was found to be high (90.4%-98.367%). The FTIR spectrum showed that both drug and polymer were not interacted with each.(Table 3)

Due to low densities all formulations floated for 10hr except F5 (9 hrs) on the simulated gastric fluid USP (Table No. 4). This help to improve bioavailability of the drug. *In vitro* drug release studies were performed in 0.1 N HCl for 10 hrs at 100 rpm. All formulations showed more than 75 to 92% of drug release in 10 hrs of dissolution study. The drug release data obtained were fitted into equations for zero-order, first-order and Higuchi release and Korsemeyer-Peppas models (Fig. 1 to 5). The interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for Higuchi [**F3**] indicating diffusion to be the predominant mechanism of drug release. (table 5)

CONCLUSION

In the present study gastro-retentive floating tablets of Cefuroxime axetil were successfully prepared by direct compression method using polymer HPMC k4M, HPMC k15M. *In vitro* data obtained for floating tablets of Cefuroxime axetil showed good buoyancy and prolonged drug release. Diffusion was found to be the main release mechanism. The drug release form the tablets were sufficiently sustained (10 hours) due to the presence of polymer and guar gum. The floating lag time of F3 formulation was 40 sec and total floating time was 10 hours. This is mainly due to to sodium bicarbonate which induced CO_2 generation in the presence of dissolution medium (0.1N HCl). The gas generated was trapped and protected with in the gel, formed by hydration of polymer, thus decreasing the density of tablet. Cefuroxime axetil floating drug delivery system showed improved *In-vitro* bioavailability and extended drug release which may favour the reduced dose frequency and patient compliance.

Table 1: Composition of floating tablets of Cefuroxime axetil (in mgs)

Ingredients	F1	F2	F3	F4	F5	F6	F7
Cefuroxime Axetil	250	250	250	250	250	250	250
HPMC- k15M	-	-	50	50	52	-	51
HPMC- k4M	71	74	50	53	48	79	47
Guggul	0.5	1	0.5	1	1	1	-

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Guar Gum	8	10.5	4	6	8	8	6
$NaHCO_3$	60	60	60	60	60	60	60
Sodium Alginate	28.5	27	17	10	10	22	16
Lactose	72	67.5	58.5	60	61	70	60
Mg.Sterate	10	10	10	10	10	10	10

* Weight of each tablet equals 500 mg

Table 2: Evaluation of physical properties of powder blend of all formulations

Batch	ANGLE OF REPOSE	BULK DENSITY(g/cm^3)	TAPPED DENSITY(g/cm^3)	CARR'S INDEX	HAUSNER RATIO
F1	22.76	0.27	0.312	11.36	1.12
F2	26.04	0.22	0.26	16.34	1.19
F3	22.5	0.30	0.33	8.85	1.09
F4	21.38	0.27	0.32	11.36	1.17
F5	25.53	0.29	0.34	15.31	1.18
F6	21.53	0.33	0.416	19.68	1.24
F7	25.53	0.29	0.34	15.31	1.18

Table 3: Physical Properties of different formulations (F1 to F7)

Batch	Thickness (mm)	Friability (%)	Hardness (Kg/cm^2)	Drug content (%)	Weight variation(mg)	Diameter (mm)
F1	5.083	0.89	5.33	95.2	498	10
F2	5.093	0.91	5.38	92.6	499	10
F3	5.103	0.87	5.9	96.7	499	10
F4	5.101	0.91	5.21	94.5	502	10
F5	5.085	0.90	5.32	98.1	498	10
F6	5.084	0.89	5.28	90.4	500	10
F7	0.094	0.79	5.30	93	498	10

Table 4: Result of buoyancy study of prepared formulations (F1-F7)

FORMULATION	LAG TIME(Sec)	FLOATING DURATION(Hour)
F1	48	10
F2	50	10
F3	40	10
F4	45	10
F5	42	9
F6	57	10
F7	61	10

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Table 5: Kinetic evaluation data for various formulations (F1 to F7)

Formulation No.	Cumulative %Drug Release	Zero Order R^2	First order R^2	Higuchi R^2	Korsemeyer-Peppas R^2
F1	82.3	0.84	0.96	0.96	0.99
F2	75.1	0.79	0.92	0.93	0.98
F3	92.5	0.90	0.96	0.97	0.96
F4	83.5	0.58	0.79	0.77	0.83
F5	85.9	0.46	0.71	0.66	0.77
F6	79.4	0.75	0.91	0.91	0.98
F7	84.8	0.71	0.91	0.87	0.98

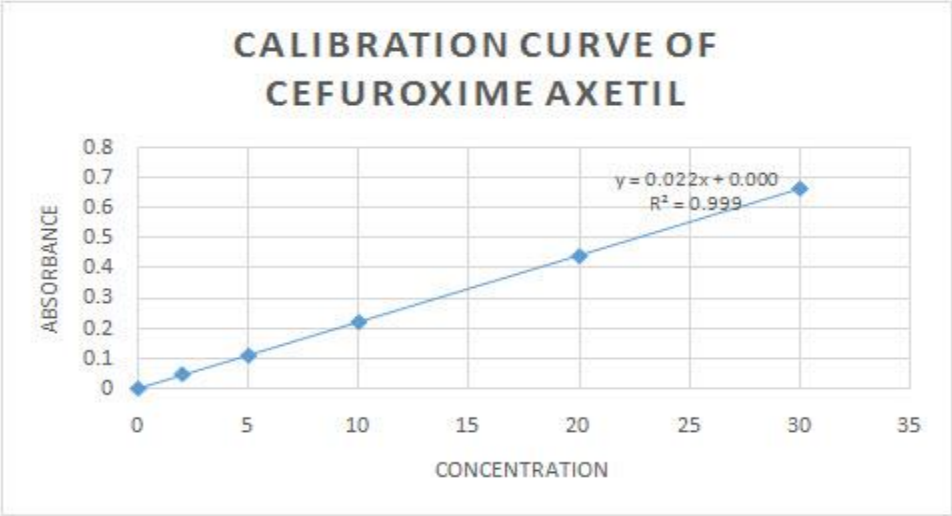

Figure 1 : Standard curve of Cefuroxime axetil

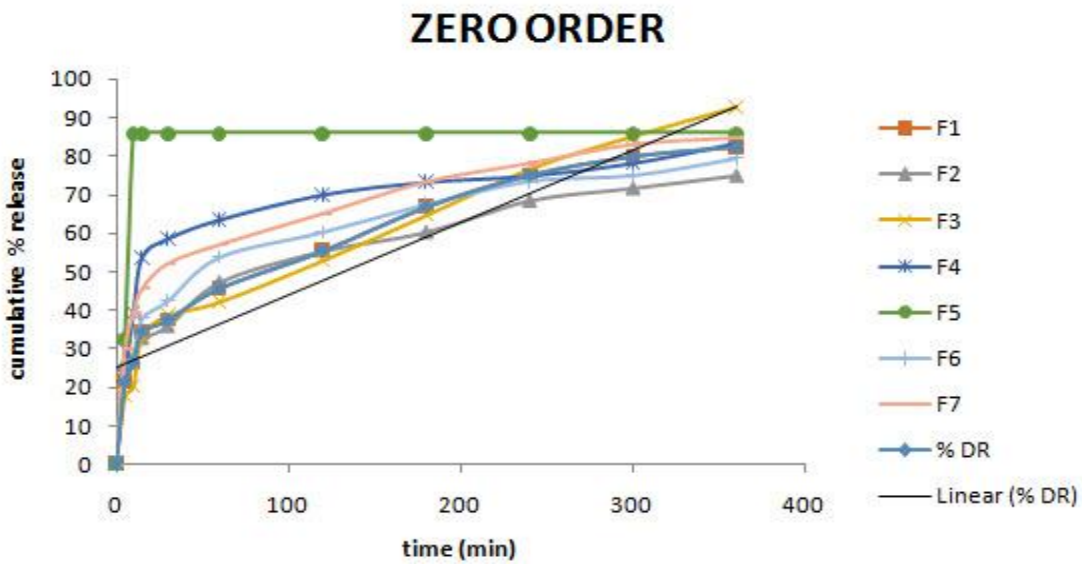

Figure 2: Zero order plot of different formulations

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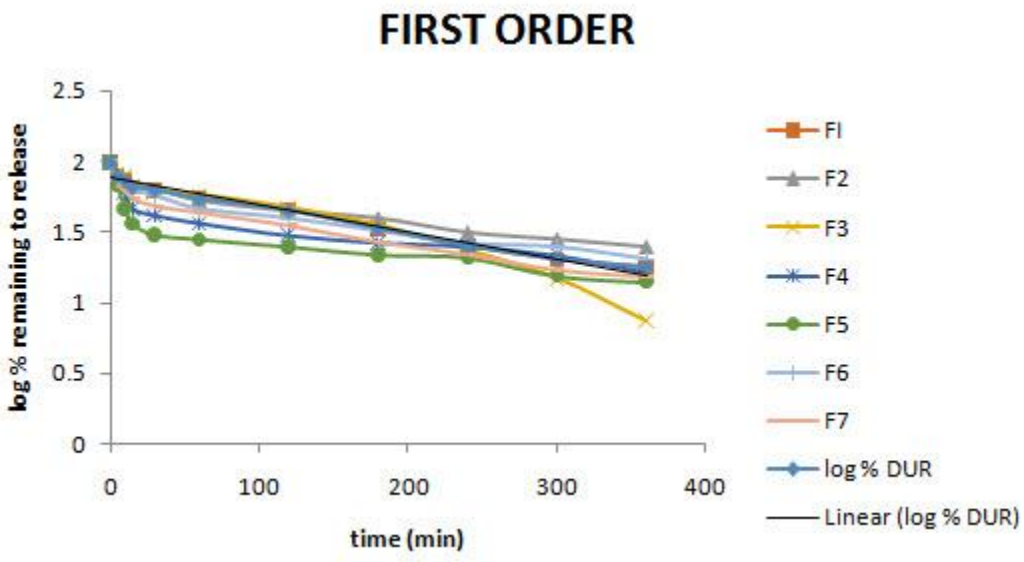

Figure 3: First order plot of different formulations

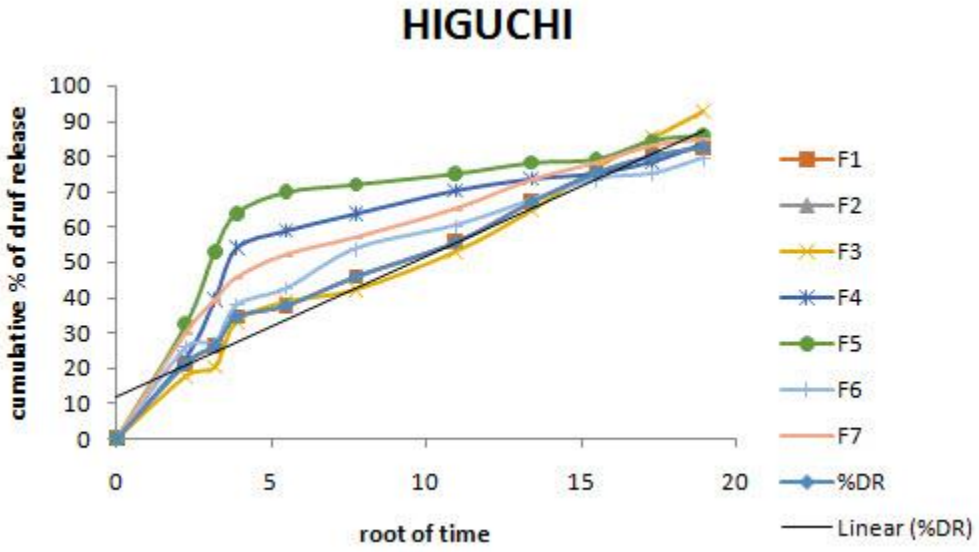

Figure 4: Higuchi's plot of different formulations

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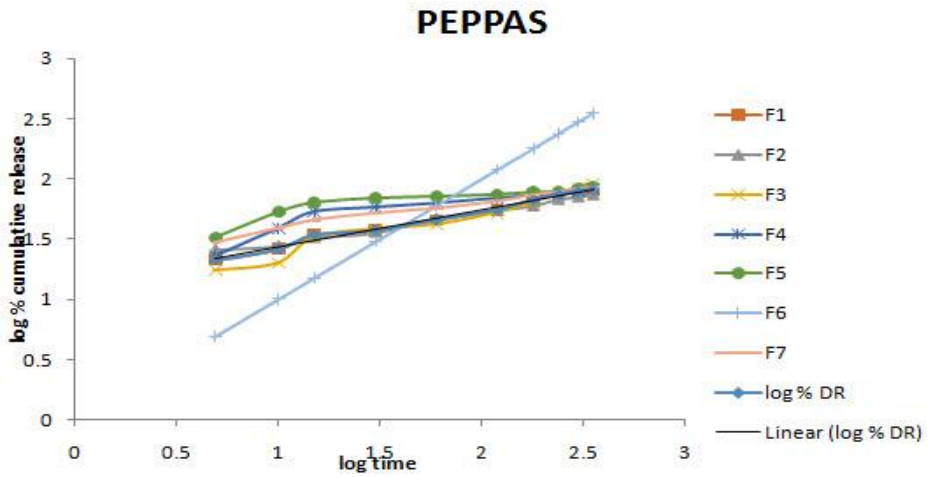

Figure 5: Korsemeyer-Peppas plot of different formulations

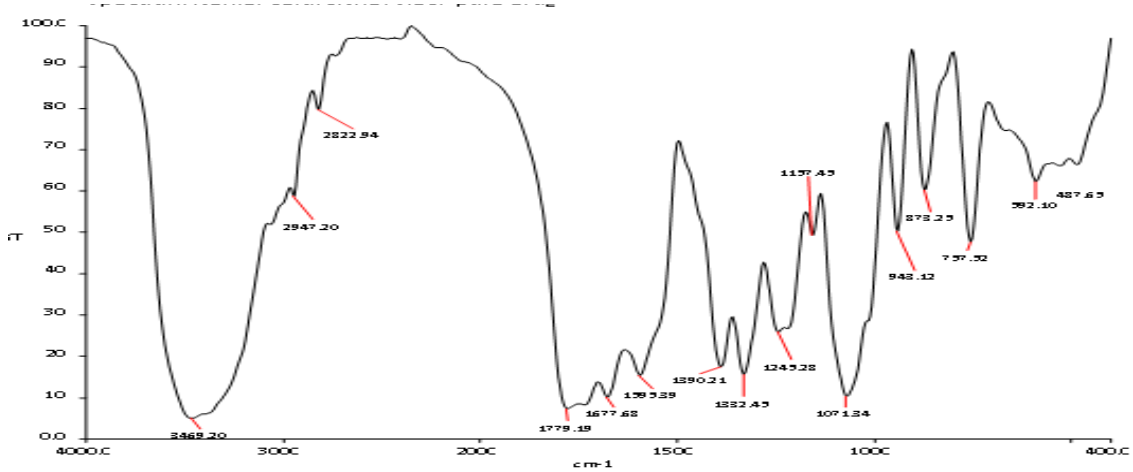

Figure 6: FTIR Study of Cefuroxime axetil

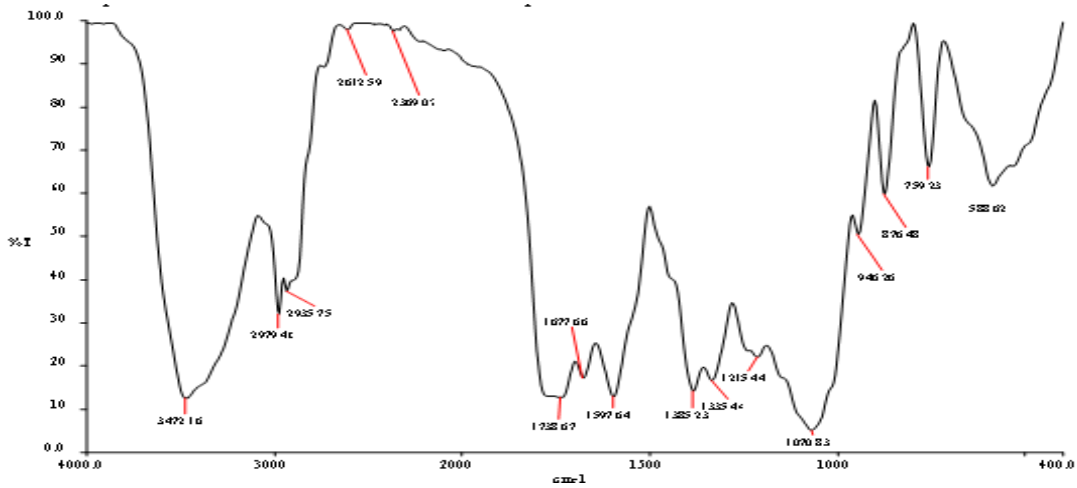

Figure 7: FTIR Study Complete Cefuroxime axetil formulation

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