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FORMULATION AND EVALUATION OF NON EFFERVESCENT FLOATING TABLETS OF CEFUROXIME AXETIL

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Keywords:

Cefuroxime Axetil, Melt granulation, Meltable binders, gastric residence time, Non Effervescent floating, Buoyancy time

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ABSTRACT: The objective of this work was to develop non effervescent floating tablets by Melt granulation technique. Cefuroxime axetil is having shorter half life of 80 min and hydrolyzed by intestinal esterase to the non absorbable cefuroxime in the gut lumen and is, therefore, suspected as a possible cause of incomplete bioavailability. So there is a need to increase the gastric residence time of the drug. These tablets were prepared by different meltable binders such as paraffin wax, bees wax and carnauba wax as release retardants. Various formulations have been developed by varying concentration of waxes, buoyancing agent and disintegrating agent. The FTIR spectrum indicated the stability and compatability of drug and excipients. All the formulations (F1 to F9) were evaluated for weight variation, hardness, friability, buoyancy studies and *In-vitro* drug release studies. Among all the formulations, dissolution studies data indicated that F9 formulation exhibited good drug release 0f 91.67% and has shown floating time more than 24hrs with a lag time of 30 min. The mechanism of drug release of NEF tablets of Cefuroxime Axetil was determined by the application of Korsmeyer-Peppas model, Higuchi's model, Zero order and first order kinetics. From the drug release plots it was observed that the drug release was following zero order kinetics and non – fickian diffusion (n value 0.5 to 1) fitting in to Korsmeyer -Peppas equation. This indicates that drug release depends on erosion of waxes.

INTRODUCTION: Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effects. Drugs that are easily absorbed from gastro intestinal tract and having shorter half-lives are quickly eliminated. So for this type of drugs gastroretentive drug delivery systems have been designed to retain the system in gastro intestinal tract for longer time.

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While the system is floating on the gastric contents, the drug is released slowly at the desired rate [1, 2]. Cefuroxime is a broad spectrum, second generation and β - lactum antibiotic. Since cefuroxime is not absorbed orally, cefuroxime axetil an orally absorbed prodrug of cefuroxime is used in the treatment of commonly acquired infections. It is active against both gram positive and gram negative organisms.

It has a half life of 80 min and bioavailability of 30 to 40% when taken on empty stomach and 5 to 60% taken after food. Cefuroxime Axetil is absorbed from the gastrointestinal tract & rapidly hydrolyzed by non specific esterase's in intestinal mucosa & blood to non absorbable cefuroxime.

The axetil moiety is metabolized to acetaldehyde & acetic acid. So this may be cause for incomplete bioavailability. All the cephalosporins inhibit cell wall production and selective inhibitor of peptidoglycon synthesis. The initially drug binds to the cell receptors called penicillin binding proteins. After a beta lactum antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycon synthesis is blocked. Finally bacterial lysis takes place [3, 4]. In order to increase bioavailability and gastric residence time is increased by formulating into non effervescent floating systems. So meltable binders which are having low density i.e. less than gastric fluid (1.004g/cm^3). Based on low density property meltable binders were selected.

MATERIALS AND METHODS:

Materials:

The drug cefuroxime axetil was received as a gift sample from Aurobindo Pharma limited Hyderabad, Carnauba wax supplied by Oxford laboratory, Thane. Paraffin wax, Bees wax, Lactose Monohydrate, Microcrystalline cellulose, Sodium bicarbonate, Magnesium stearate, Talc, Concentrated HCl and Methanol supplied by SD Fine Chem. Ltd Mumbai.

Preparation of standard plot of cefuroxime Axetil:

10 mg Cefuroxime axetil was accurately weighed and transferred to 10ml volumetric flask. It was dissolved in methanol. Then from the above stock required concentrations were taken and diluted with 0.1N HCl. The absorbances were measured against 0.1NHCl as blank at 280nm using UV-spectrophotometer. Coefficient of correlation was found to be 0.998 [4, 5].

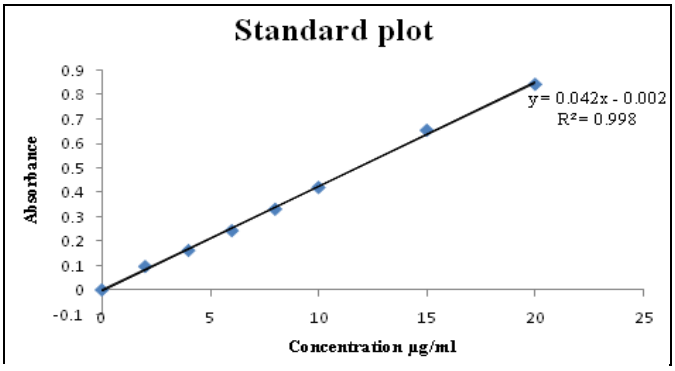


FIG.1: STANDARD PLOT OF CEFUROXIME AXETIL IN 0.1 N HCL AT 280nm

IR spectroscopy for pure drug and combination of drug and excipients:

The spectrum analysis of pure drug and combination of drug and waxes (1:1) were analyzed by FTIR. FTIR spectra were recorded using potassium bromide (KBr) disk method. KBr disk was prepared by mixing the sample with KBr by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resulted disk was mounted in a suitable holder in IR Spectrophotometer and it was recorded from 4000cm-1 to 400cm-1.The spectrum was observed for characteristic peaks of Cefuroxime Axetil and waxes [6].

Formulation of non effervescent floating tablets of Cefuroxime Axetil using meltable binders:

Each non effervescent floating tablets of containing 300mg Cefuroxime Axetil were prepared by melt granulation technique. Tablets were prepared by different meltable binders paraffin wax, bees wax and carnauba wax and using variable concentration of wax, buoyancing agent and disintegrant. Required quantities of materials were weighed. The granules were prepared by using hydrophobic binders. The meltable binders like paraffin wax, carnauba wax and bees wax were separately melted in porcelain dishes on water bath maintained at temperatures 46-69^{o}C, 80-86^{o}C and 61-65^{o}C respectively.

Required quantity of Cefuroxime axetil and lactose was weighed and gradually added to the molten wax with continuous stirring. To this mass lactose was added. Then solidified mass was pulverized in motar and sieved through 30 # screen to form granules. Then sodium bicarbonate was added and mixed well. Then to this magnesium stearate and talc are added and mixed well. The granules were compressed into tablet form by using 8mm to 12mm punches [6, 7, 8].

Preformulation studies of Cefuroxime axetil and formulations:

The pure drug and granules were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio

Angle of Repose:

This is the maximum angle possible between the surface of a powder pile and the horizontal plane. It

is the characteristic related to inter-particulate friction (or) resistance to movement between particles. Angle of repose was carried out by funnel method [9, 10, 11].

Angle of repose is calculated by the formula

$$\theta = Tan^{-1}(h/r)$$

Where θ =angle of repose, h =the height of the pile, r= radius of the pile.

Bulk Density:
It is determined by pouring drug or granules into 50ml graduated cylinder and the volume (V) occupied is noted [9, 10]. Bulk density is calculated as

$$\text{Bulk density} = M/V$$

Tapped Density:
Pure drug or granules were poured into 50ml graduated cylinder and it was tapped for affixed time (around 100 taps).The minimum volume (V) occupied in the cylinder was measured [9, 10].
Tapped density was calculated by the formula

$$\text{Tapped density} = M/V$$

Compressibility index:
It is an indirect method for measurement of bulk density, size, shape, surface area and cohesiveness of the material [9, 10].

It is determined by Carr's compressibility index.

$$\text{Compressibility index} = \frac{100(\text{Bulk density} - \text{Tapped density})}{\text{Bulk density}}$$

Hausner's ratio:
Hausner's ratio is a number that is correlated to flowability of a powder [9, 10, 11].

It is calculated by the formula

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

Evaluation of non effervescent floating tablets:
The prepared granules were evaluated for weight variation, hardness, friability and buoyancy studies.

Weight Variation Test:
Twenty tablets were selected randomly and they were weighed individually and the weights of tablets were compared with mean weight. In this method, not more than two tablets should have a deviation greater than pharmacopoeia limits ±5 % of the weight [12, 13].

Hardness:
For each formulation, hardness of 6 tablets was measured using Monsanto hardness tester. A tablet was placed between the two anvils of hardness tester, force was applied to the anvils and the crushing strength that causes the tablet to break was recorded in Kg/cm^2.Three tablets were tested and average reading was noted[12, 13].

Friability:
Friability of the tablets was determined using Electro Automated Roche Friabilator model EF-2, Bombay. This device consists of a circular plastic chamber which is set to revolve around 25rpm for 100 revolutions dropping the tablets at a height of 6 inches for each revolution. Pre-weighed tablets were placed in Friabilator and operated. After 100 revolutions the tablets were collected and were reweighed [12, 13].

Friability is calculated by the formula

$$\% \text{ Friability} = (\text{Initial Weight} - \text{Final weight} / \text{Initial weight})_x 100$$

***In-vitro* Buoyancy study / Floating Test:**
The tablets were placed in 100 ml glass beaker containing 0.1N HCl. The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT)[14, 15].

***In-vitro* drug release:**
In-vitro drug release of the tablets (n=3) was carried out using type-II dissolution apparatus (paddle type). 900 ml of 0.1N HCl dissolution medium was prepared and transferred in to dissolution baskets. The medium was maintained at temperature of 37°c±5°c and paddles were operated at 50 rpm. The tablets were then placed in each dissolution basket. A sample (5ml) of the solution was withdrawn from dissolution apparatus at predetermined time intervals (0.5, 1, 2, 3 …12 hrs) and the samples were replaced with 5ml of 0.1 N HCl in order to maintain sink conditions. The

collected samples were then analyzed for drug release against 0.1N HCl as blank using UV-Visible spectrophotometer at 280 nm[14, 15, 16].

Kinetics of *In-vitro* drug release:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order (cumulative percentage drug release versus time), first order (log cumulative percent of drug remaining versus time), Higuchi (cumulative percentage drug release versus √t), and Korsmeyer-Peppas (log percentage of drug released versus log time)release model [3, 7, 17].

Stability studies:

An accelerated stability study was conducted for the selected formulation for a period of one month at 40°C ± 2°C, 75% ± 5%RH. After one month tablets were evaluated for appearance and *in-vitro* drug release and release rate kinetics[13].

RESULTS AND DISCUSSION:

FTIR: Fourier transform infrared spectroscopy for drug, meltable binders and granules were performed. The drug and waxes retains all the peaks. Hence there was no interaction between drug and waxes. The other excipients used in the formulation are already compatible with Cefuroxime Axetil [5, 7].

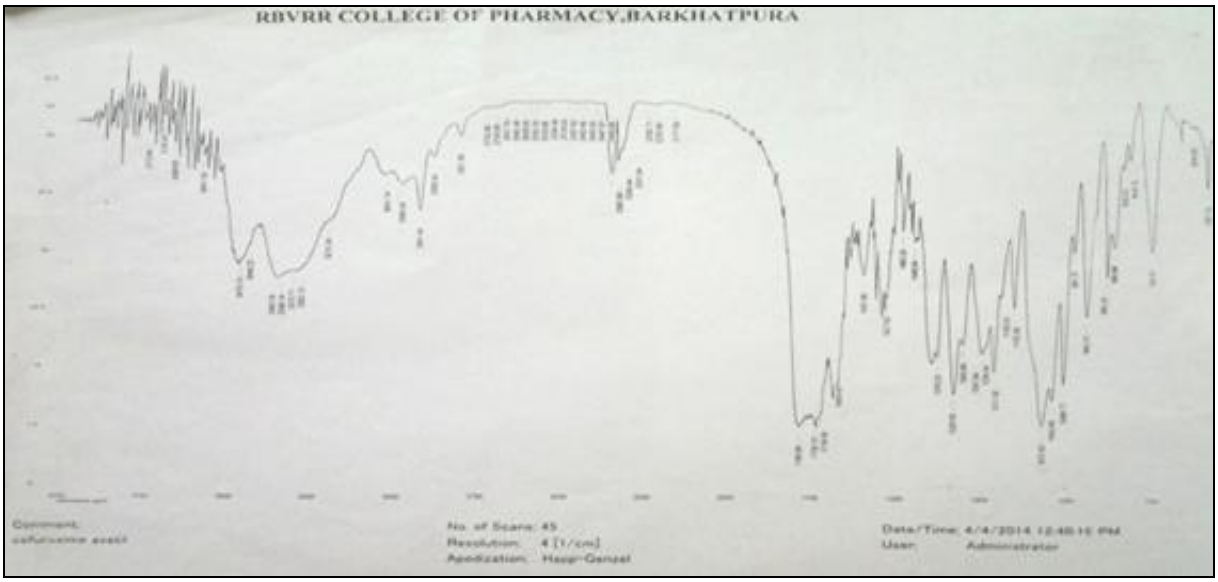


FIG. 2: FTIR OF CEFUROXIME AXETIL

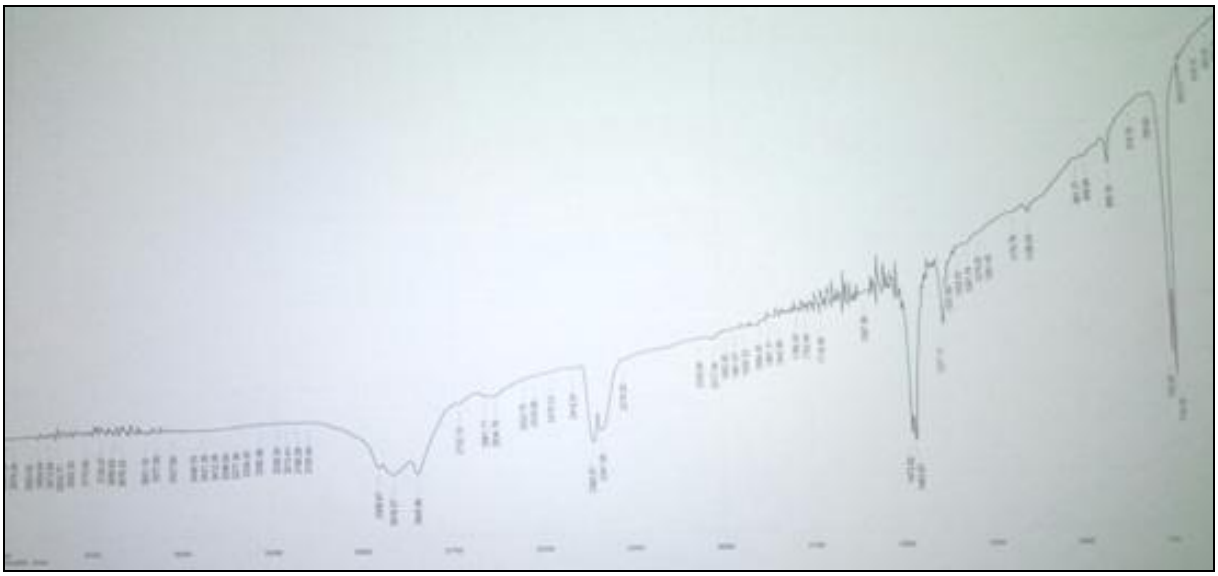


FIG.3: FTIR OF PARAFFIN WAX

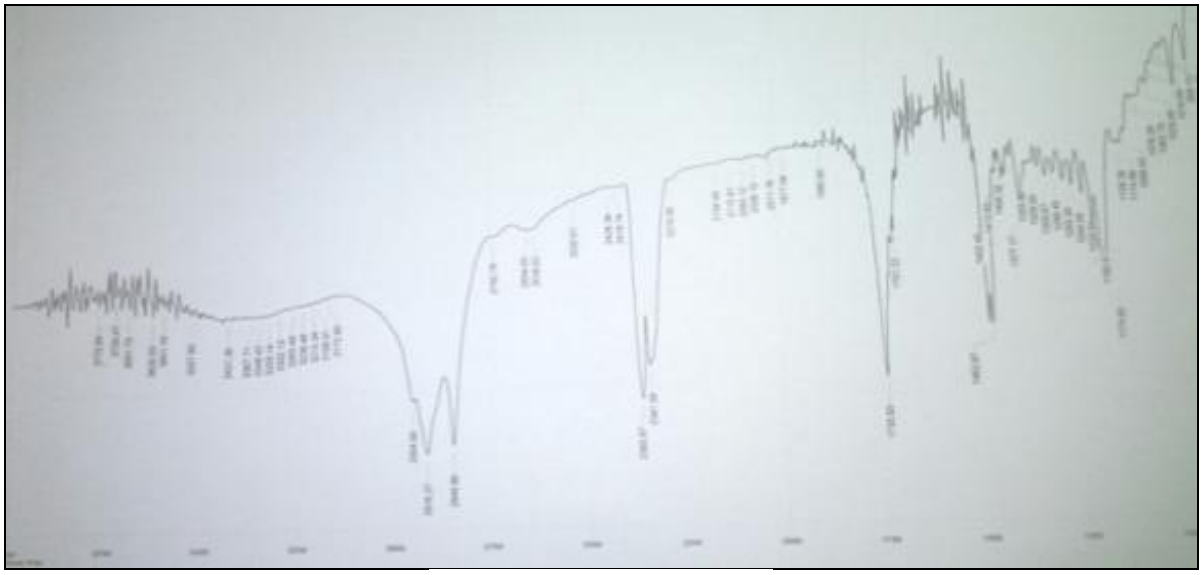


FIG. 4: FTIR OF BEES WAX

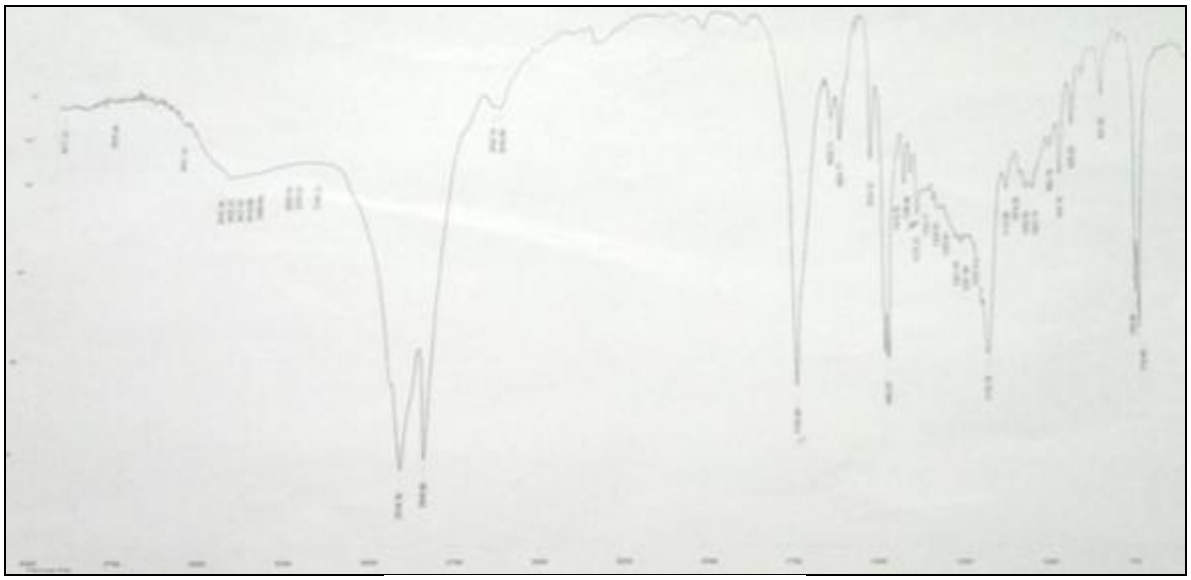


FIG.5: FTIR OF CARNAUBA WAX

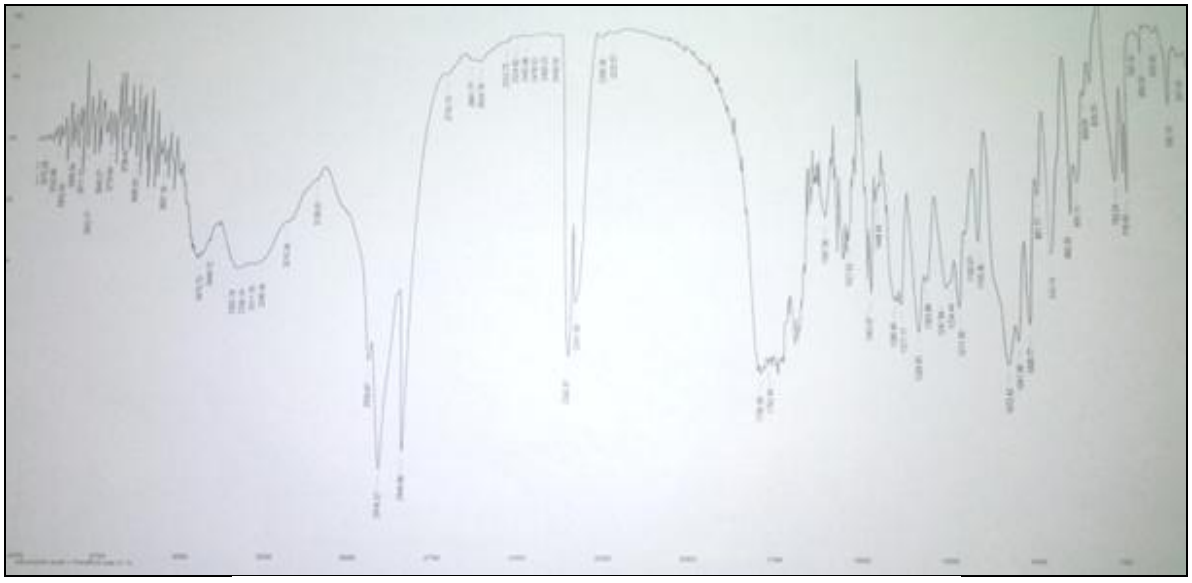


FIG.6: FTIR OF CEFUROXIME AXETIL + PARAFFIN WAX

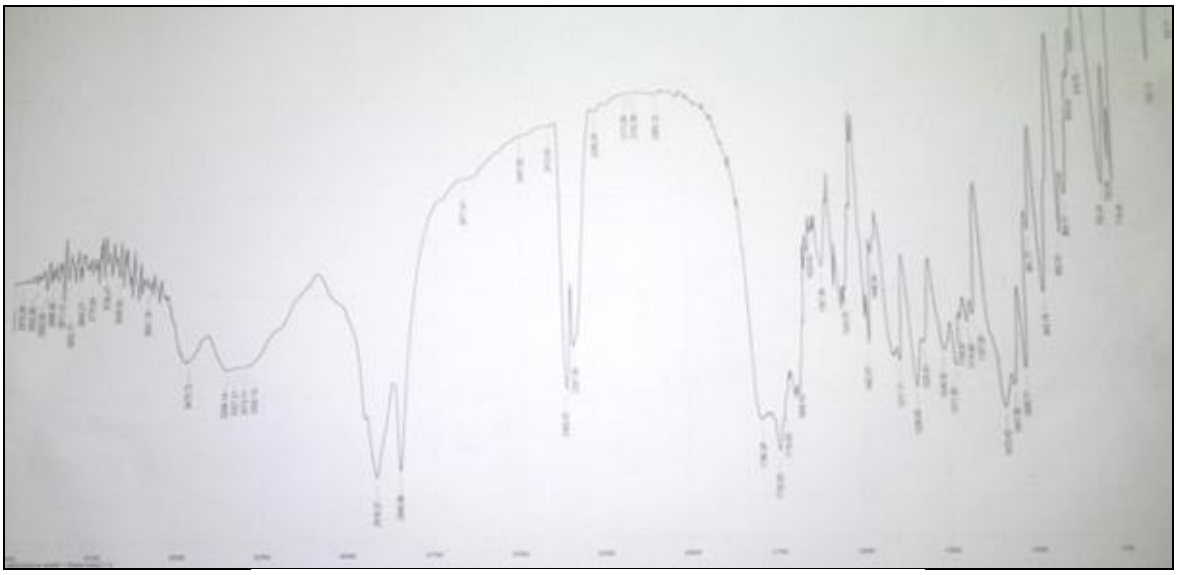


FIG.7: FTIR OF CEFUROXIME AXETIL + BEES WAX

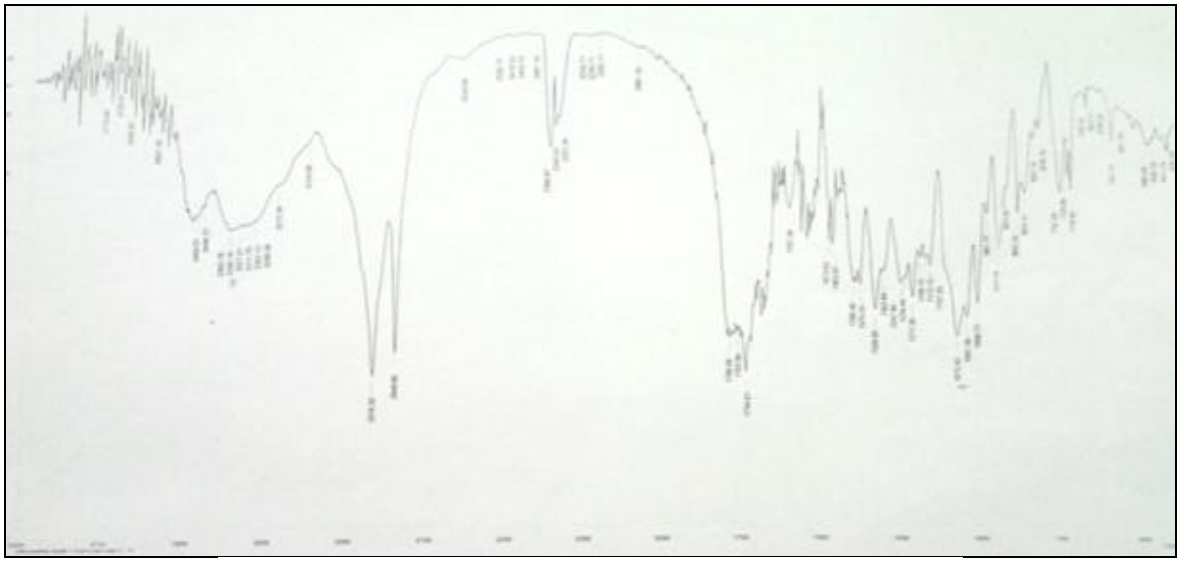


FIG.8: FTIR OF CEFUROXIME AXETIL + CARNAUBA WAX

TABLE 1: FORMULATIONS OF NON EFFERVESCENT FLOATING TABLETS

Formulation ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefuroxime Axetil	300	300	300	300	300	300	300	300	300
Lactose monohydrate	60	60	60	60	60	60	60	60	60
Paraffin wax	100	-	-	-	-	-	-	-	-
Bees wax	-	100	-	-	-	-	-	-	-
Carnauba wax	-	-	100	60	30	30	30	30	30
Sodium bicarbonate	-	-	-	-	-	60	120	120	120
MCC	-	-	-	-	-	-	-	15	30
Mg streate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total wt (mg)	470	470	470	430	400	460	520	535	550
Punch size (mm)	8	8	8	8	8	8	12	12	12

Pre formulation studies of pure drug and formulations: The pure drug and formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. For pure drug angle of repose was found to be 33.2^{o} showing that the drug has fair flow

property. Carr's Index and Hausner's ratio was found to be 23.66 and 1.46 respectively indicating that pure drug has poor flow property.

Angle of repose for all the formulations ranged from 28.16^{o} to 22.37^{o}indicating good flow properties except F1 and F2. The values of Carr's index ranged from 14.54 to12.45 indicating good flow properties. Hausner's ratio ranged from 1.124 to 1.146 indicating good flow properties. The result of angle of repose and compressibility index indicates good and excellent flow properties for granules shown in **Table 2**.

TABLE 2: PRE FORMULATION STUDIES OF PURE DRUG AND FORMULATIONS

Parameter	Pure drug	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of Repose(θ)	33.2	31.9	32.4	27.11	28.16	27.6	25.06	23.18	24.21	22.37
Bulk Density(g/ml)	0.579	0.632	0.598	0.562	0.583	0.597	0.579	0.586	0.582	0.585
Tapped Density(g/ml)	0.716	0.716	0.685	0.632	0.659	0.669	0.655	0.665	0.659	0.662
Hausner's Ratio	1.236	1.132	1.145	1.124	1.130	1.121	1.131	1.134	1.132	1.131
Compressibility Index (%)	23.66	13.29	14.54	12.45	13.03	12.06	13.12	13.48	13.23	13.16

Evaluation of prepared tablets:

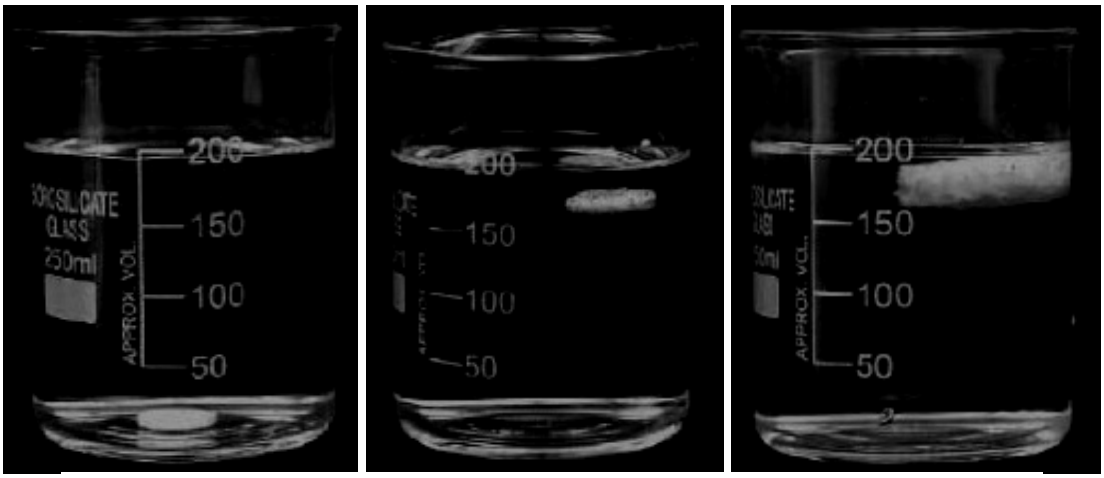
Various formulations of non effervescent floating tablets of Cefuroxime Axetil were prepared mentioned in **Table 1** and were evaluated for weight variation, hardness, friability and buoyancy mentioned in the **Table 3.** All the parameters for all the formulations were within the limits.

***In-vitro* buoyancy studies:**

Buoyancy studies were performed by immersing the tablet in 0.1 N HCl and the tablets remained buoyant without disintegration shown in **Fig.9**. From the results it can be concluded that F7, F8, F9 showed lag time of 30 min and total floating time more than 24 hrs.

TABLE 3: EVALUATION OF NON EFFERVESCENT FLOATING TABLETS OF CEFUROXIME AXETIL

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation (mg)	0.468± 0.038	0.467± 0.045	0.469± 0.053	0.428± 0.042	0.395± 0.046	0.455± 0.051	0.518± 0.06	0.533± 0.04	0.548± 0.055
Hardness (Kg/cm^2)	3.6	3.5	5.5	4.5	4.3	4.2	4.2	4.3	4.3
Friability (%)	0.86	0.83	0.763	0.81	0.87	0.85	0.89	0.85	0.84
Buoyancy	-	-	-	-	-	-	>24 hrs	>24 hrs	>24 hrs



AT INTIAL STAG **AT 30 MIN** **AT 24 HRS**

FIG. 9: BUOYANCY STUDIES

***In-vitro* drug release:** Dissolution study was initially carried out for marketed Immediate Release tablet of Cefuroxime Axetil equivalent to 250 mg of Cefuroxime tablets in 0.1NHCl. *In-vitro* drug release was performed for marketed Cefuroxime Axetil immediate release formulation had showed drug release of 99.42% in 100 min shown in **Table 4** and release profile shown in **Fig. 10**.

According to the formulations mentioned in **Table 1** NEF tablets of Cefuroxime Axetil were prepared and were subjected for dissolution studies. Various formulations were developed by using different waxes. In order to select the wax F1, F2 and F3 formulations are done by using 33.3% of paraffin wax, bees wax and carnauba wax. But due to the high concentration of waxes F1, F2, F3 has shown drug release of 5.82%, 8.42% and 12.71% in 12 hrs. From these three waxes F3 formulation containing carnauba wax has shown optimum release.

Then wax concentration was decreased. F4 and F5 formulations were formulated by using 20% and 10% of carnauba wax. F5 has shown drug release of 42.5% when compared to F4. F6, F7 are formulated by using different concentrations of buoyancing agent. 10% carnauba wax and 20% of sodium bicarbonate in F6, and in F7 formulation 40% sodium bicarbonate was used. F6 and F7 have shown drug release of 51.1% and 53.9%. F7 has shown floating more than 24 hrs. Among F6, F7 – F7 was the best formulation taking floating time into account. Taking F7 as base formulation F8 and F9 formulations were designed. To increase the disintegration of the drug MCC was taken. In F8 and F9 5% and 10% MCC was taken. F8 and F9 have shown drug release of 78.3% and 91.67%. Among these two formulations F9 was the best formulation. F9 has shown floating more than 24 hrs show in **Fig.9**. Release profiles are mentioned in **Table 4 and in Fig. 10**. As the preliminery studies showed that the concentration of lactose is influencing floating properties Concentration of lactose was kept constant. Hence the weight of the formulations was not kept equal during study.

Carnauba wax is less dense in nature, hence the tablets should have good floating property. But due to the hydrophobic nature of carnauba wax the wetting process of the tablet usually gets delayed which influences the floating of the tablet. In order to achieve the floating sodium bicarbonate is added to the preparation. When wetting process, occurs a reaction between the sodium bicarbonate present in the formulation and HCl present in the surrounding dissolution medium. As a result, it leads to the evolution of CO_2 gas, causing buoyancy to the tablet. This NEF tablet of Cefuroxime Axetil have shown lag time of 30 min and floating time was observed to be more than 24hrs.

As compared with the marketed tablets the drug release was prolonged for the prepared formulation.

TABLE 4: CUMULATIVE DRUG RELEASE PROFILES OF ALL FORMULATIONS

Time (min)	Marketed CA	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	19.07	0.5	-	-	-	-	-	-	-	16.28	17.07
10	28.92	1	2.05	1.88	3.10	6.64	5.57	11.14	11.89	20.78	21.48
20	42	2	2.93	2.63	4.95	10.39	10.5	12.64	13.19	27.87	28.97
30	53.14	3	3.06	3.57	6.69	12.96	16.82	14.78	15.89	32.87	35.78
40	65.14	4	3.38	4.09	7.96	15.42	19.60	18.64	18.19	41.78	44.67
50	76.92	5	3.68	5.121	9.73	19.28	21.85	19.56	20.56	52.78	54.64
60	85.07	6	4.2	5.87	10.36	17.78	26.57	22.28	23.34	59.49	60.64
70	90.85	7	4.65	6.38	10.77	22.60	29.78	36.67	29.43	62.789	67.07
80	96.21	8	4.88	6.79	12.53	24.21	31.5	42	34.45	64.88	77.67
90	98.35	9	5.12	7.39	12.44	25.60	36.75	44.14	43.29	68.48	81.32
100	99.42	10	5.27	8.12	12.46	28.28	39.53	45.23	48.23	70.56	82.98
-	-	11	5.61	8.18	12.62	28.96	41.14	48.64	49.49	75.29	83.67
-	-	12	5.82	8.42	12.71	30.12	42.53	51.12	53.90	78.27	91.67

Kinetic profiles of NEF tablets of Cefuroxime axetil:

The mechanism of drug release of NEF tablets of Cefuroxime Axetil was determined by the application of Korsmeyer-Peppas model, Higuchi's model, Zero order and first order kinetics shown in **Table 5** and respective plots of F3 to F9 formulations shown in **Fig. 11 to 14.** The correlation coefficient (r^2) values are from 0.896 to 0.992. From the drug release plots it was observed that the drug release was following zero order kinetics and non – fickian diffusion (n value 0.5 to 1) fitting in to Korsmeyer-Peppas equation. This

indicates that drug release depends on erosion of waxes.

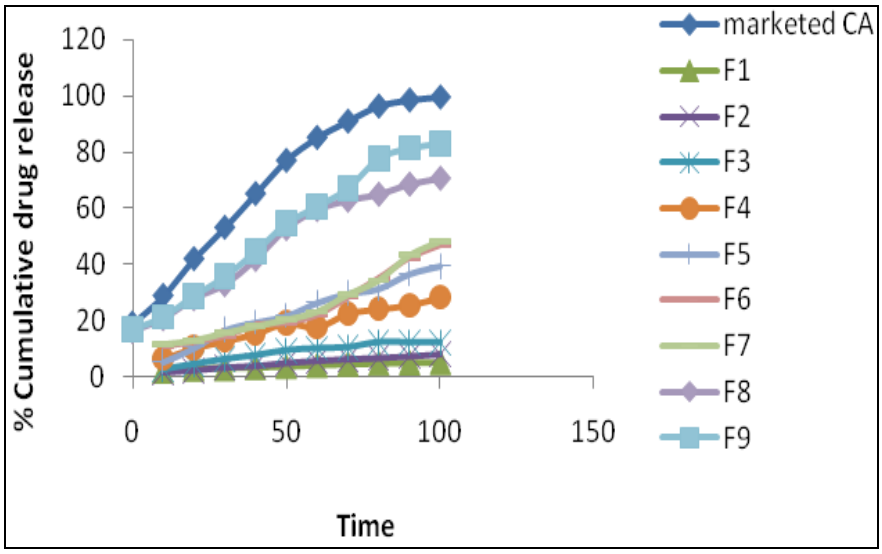


FIG.10: DRUG RELEASE PROFILES OF ALL FORMULATIONS

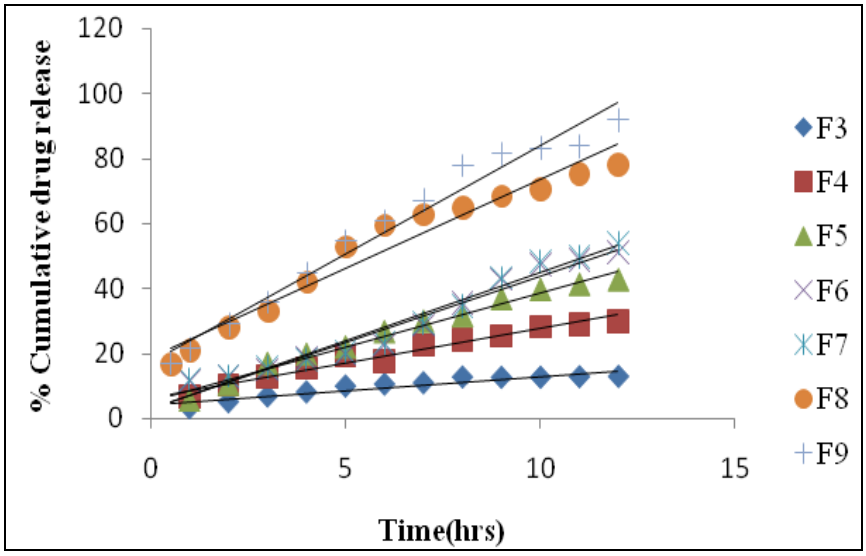


FIG.11: ZERO ORDER PLOTS OF F3-F9 FORMULATIONS

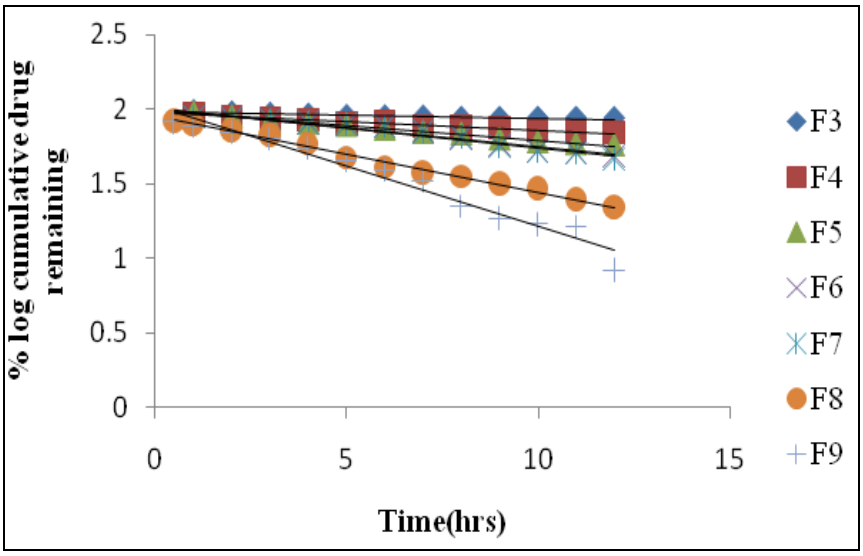


FIG.12: FIRST ORDER PLOTS OF F3-F9 FORMULATIONS

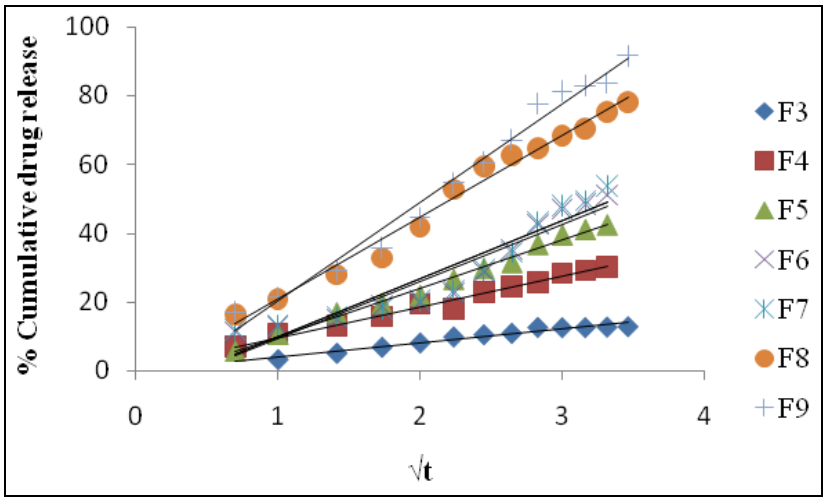


FIG. 13: HIGUCHI PLOTS OF F3-F9 FORMULATIONS

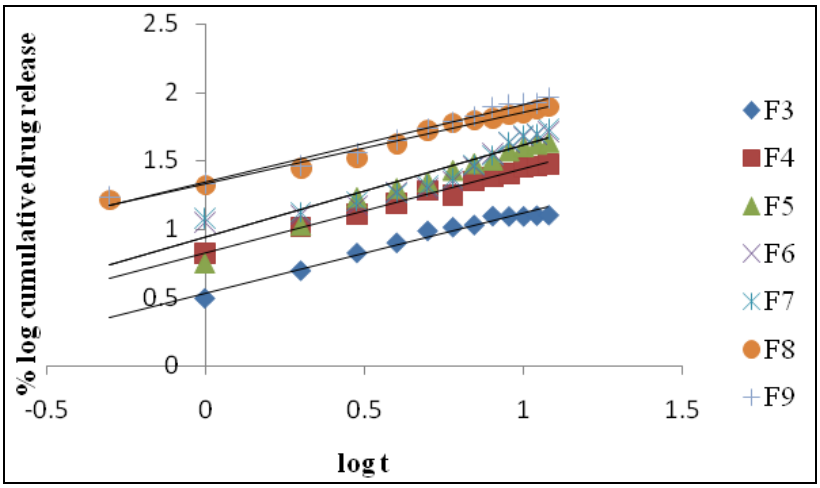


FIG. 14: KORSMEYER-PEPPAS PLOTS OF F3-F9 FORMULATIONS

Stability studies: An accelerated stability study was conducted for the selected formulation F9 for a period of one month at 40°C ± 2°C, 75% ± 5%RH. There was no change in physical appearance, color, hardness, weight variation and content uniformity. The samples were collected were collected after one month and were evaluated. Results given in **Table 6** for F9 showed that there was no change in drug release and the formulation was stable.

TABLE 5: CORRELATION COEFFICIENT VALUES

Formulations	Zero order K_o value	Zero order (r^2)	First order $K_{1\ value}$	First order (r^2)	Higuchi (r^2)	Peppas (r^2)
F3	0.861	0.986	0.009	0.982	0.993	0.990
F4	2.140	0.973	0.025	0.980	0.992	0.991
F5	3.354	0.982	0.043	0.992	0.985	0.990
F6	4.072	0.962	0.059	0.946	0.901	0.901
F7	4.155	0.963	0.062	0.941	0.896	0.899
F8	5.451	0.953	0.117	0.990	0.983	0.982
F9	6.636	0.973	0.184	0.964	0.982	0.981

Formulation was analyzed at the end of one month for assay and dissolution studies. *In vitro* dissolution profile and assay showed that there was no significant change in the release rate of the drug from optimized tablet at the end of one month. From all the above results it can be made clear that the attempt made to formulate non effervescent floating tablets was achieved. *In-vitro* drug release comparative plots of before and after stability are shown in **Fig. 15.** The correlation coefficient (r^2) values are from 0.972 to 0.979. From the drug release plots it was observed that the drug release

was following zero order kinetics and non – fickian diffusion (n value 0.5 to 1) fitting in to Korsmeyer-Peppas equation. This indicates that drug release depends on erosion of wax.

TABLE 6: EVALUATION OF NEF TABLETS OF CEFUROXIME AXETIL AFTER ONE MONTH STABILITY STUDY

Parameters	F9
Weight variation (mg)	0.549±0.043
Hardness (Kg/cm^2)	4.2
Friability (%)	0.84
Buoyancy	>24 hrs

TABLE 7: *IN VITRO* DISSOLUTION STUDY OF F9 FORMULATION AFTER ONE MONTH STABILITY STUDY

Time (hrs)	Before stability F9 (n=3)	After stability F9 (n=3)
0.5	17.071±0.03	16.178±0.05
1	21.48±0.06	20.389±0.03
2	28.97±0.03	26.29±0.08
3	35.78±0.02	35.68±0.04
4	44.67±0.028	43.87±0.01
5	54.64±0.052	54.89±0.033
6	60.64±0.035	61.79±0.024
7	67.07±0.039	68.9±0.038
8	77.67±0.046	76.47±0.017
9	81.32±0.027	80.98±0.042
10	82.98±0.053	81.49±0.012
11	83.67±0.042	85.78±0.085
12	91.67±0.025	91.08±0.027

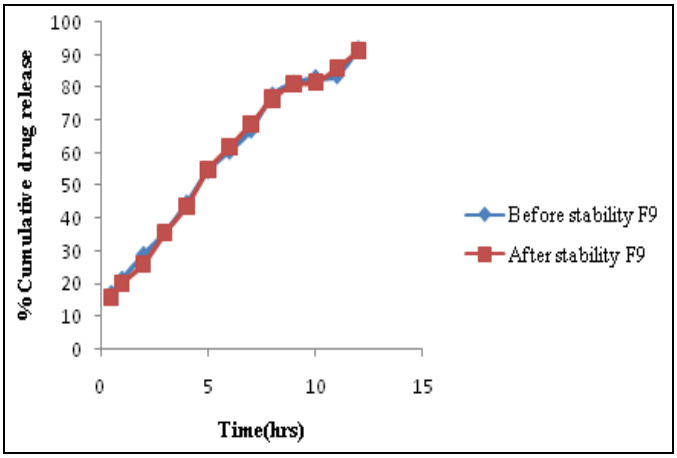


FIG.15: COMPARATIVE DRUG RELEASE PROFILE OF F9 FORMULATION BEFORE AND AFTER STABILITY STUDIES

CONCLUSION: Non effervescent floating tablets of Cefuroxime Axetil were prepared using Melt granulation technique. These tablets were prepared by using different waxes. The process variables such as concentration of wax, buoyancing agent and disintegrating agent were varied. Using these variables, nine formulations were prepared (F1-F9). The prepared formulations were evaluated for weight variation, friability, hardness, buoyancy studies and *in-vitro* drug release studies. All the formulations were within the limits for the above evaluated parameters. Drug release from all the formulations showed a sustained release pattern. The prepared formulations followed zero order kinetic model as the r^2 values were between 0.953-0.982 when compared to first order kinetics which have less r^2 values i.e. 0.941-0.992.

Among all the formulations prepared, F9 formulation had shown sustained drug release, i.e. 91.678% in 12 hrs and it has also showed floating time more than 24hrs. Thus, this was considered to be the best among all the nine formulations. Hence it shows the suitability of caurnauba wax as a polymer for preparing non effervescent gastric floating tablets.

This best formulation (F9) was therefore subjected for stability studies. From the stability data, it was confirmed that the formulation was stable without any degradation. And also the *in-vitro* drug release as well as floating time for this F9 formulation was observed to be same when conducted again after a time period of 30 days.

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