International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 8 | Issue 1 | JAN-MAR| 2018 | 139-145
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

DESIGN AND EVALUATION OF FLOATING MULTI UNIT MINI TABLETS OF CEPHALEXIN MONO HYDRATE

Ramesh Romala, Saritha Chukka, Bhagya Bhoga and Shayeda*

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506009, Telangana State, India.

***Corresponding Author Email:** drshayeda@gmail.com

ABSTRACT

***Background**: The oral route currently represents the most predominant and preferable route of drug delivery. Gastro-retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. **Objective:** The purpose of the study was to prolong the gastric residence time of cephalexin monohydrate by designing floating multi-unit mini tablets after oral administration. With this objective, floating dosage form containing drug was designed. **Method:** Tablets were prepared by using different grades of hydroxy propyl methyl cellulose (HPMC) by varying concentrations of, either alone or in combination. The tablets were prepared by direct compression method and evaluated for various physico-chemical parameters. **Results**: The physicochemical parameters of formulated tablets were found to be within normal range. The results of in-vitro release study showed that the optimized formulation could sustain the drug release for 12 hrs. The optimized formulation was subjected to various kinetic release investigations and it was found that mechanism of drug release was predominantly by fickian diffusion. The developed formulation was found to be stable. **Conclusion:** In the present study, floating mini tablets of cephalexin monohydrate were successfully prepared and optimized formulation has shown better controlled release in 0.1N HCl. Hence it concluded that Cephalexin monohydrate suitable for floating drug delivery system. In vivo radiographic imaging studies revealed that the mean residence time of single mini tablet in stomach was found to be 4h in healthy human volunteers.*

KEY WORDS

Cephalexin monohydrate, floating minitablets, gastric residence time, gastroretentive drug delivery system.

INTRODUCTION

Gastroretentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance, Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics, enzymes that act locally in the stomach. These systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract, thus ensuring optimal bioavailability. Various gastroretentive techniques were used, including floating, swelling, high density and bioadhesive system, [1-4] has been explored to increase the gastric retention of dosage forms.

Cephalexin mono hydrate, β-lactam antibiotic is a broad-spectrum antibiotic for treatment of wide range of bacterial infections, including urinary tract infections and respiratory tract infections [5-7]. It is a lipophilic weak acid with pk_a values of 5.2 and 7.3 and is stable in gastric conditions but degrade in intestinal conditions. It is absorbed completely with a short bilological half-life of

approximately one hour. Thus, to maintain therapeutic range, its conventional dosage forms need to be administered 3-4 times a day leading to saw tooth kinetics and thus an ineffective therapy[8]. In order to reduce the frequency of administration, we made an attempt to develop multi-unit particulate system by encapsulated into the HPMC capsule. The advantages of this system include it reduces the dose dumping, minimizing the drug fluctuations in the plasma.

MATERIALS AND METHODS

Cephalexin monohydrate drug was gift sample received from Ranbaxy laboratory and HPMC K 100M, HPMC K15M Purchased from Orchid Chemicals & Pharmaceuticals Ltd, Chennai. MCC (Avicel pH 102), Sodium bi carbonate, Magnesium stearate and Talc was purchased from S.D. Fine Chemicals, Mumbai. All other chemicals used were analytical grade.

Preparation of gastro retentive floating multi-unit mini tablets (MUMTS)

Accurately weighed quantities of polymer and MCC Avicel (pH 102) were taken in a mortar and mixed geometrically. To this required quantity of Cephalexin monohydrate was added and mixed slightly with pestle. Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar and triturated with pestle. The powder was passed through sieve no. #40 and mixed with the drug blend which was also passed through sieve no. #40. The whole mixture was collected in a polyethylene bag and mixed for 3 minutes. To this talc was added and mixed for 15 minutes, later magnesium stearate was added and mixed for 3 min. The mixture equivalent to 80 mg was compressed into tablets with 6 mm round concave punches at a hardness of 5 kg/cm^2.

Table1. Composition of Cephalexin mono hydrate floating multi-unit mini tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Cephalexin Monohydrate	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K100M	40	50	60	70	80	-	-	-	-	-	55	55	55	55	55
HPMC K15M	-	-	-	-	-	100	110	120	130	140	115	120	125	128	130
$NaHCO_3$	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Avicel-102	120	110	100	90	80	60	50	40	30	20	20	15	10	7	5
Mg.Stearate	20	20	20	20	20	20	20	20	20	20	5	5	5	5	5
Talc	20	20	20	20	20	20	20	20	20	20	5	5	5	5	5
Total tablet weight	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800

Capsule filled with mini tablets; Capsule (size 00) capable of being filled with 10 mini tablets and each mini tablet contain 4mm diameter and 2.5 mm thickness.

Drug- excipient compatibility study by using Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) Study was carried out to know the interaction among drug and the excipients. Pure drug and optimized formulation were subjected to the study. 5-15mg of sample to be analysed was taken in the pierced DSC aluminium pan and Scanned in the temperature range of 50-400^{0}c. The heating rate was 20^{0}c/min; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyser (perkin elemer-4000) was used for this purpose.

Physical evaluation of multi-unit mini tablets

All the prepared mini tablets evaluated for their physicochemical parameters like hardness, thickness, friability, weight variation. Hardness (n=6) was calculated by using Monsanto hardness tester. Thickness (n=6) was determined by using Vernier calipers. Friability (n=20) tested with Roche friabilator and weight variation (n=10) was performed using digital balance.

Drug content estimation:

Twenty tablets were taken, powdered and the powder equivalent to one dose was transferred to a 100 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-Visible

spectrophotometer (Systronics -117, Hyderabad, India) at λ_{max}260 nm.

***In Vitro* Buoyancy Studies:**

In vitro buoyancy was determined by floating lag time and total floating time. The tablets were placed in a 100 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and the duration of time floated on surface called as total floating time.

***In Vitro* Dissolution Studies:**

In vitro drug release studies of Cephalexin monohydrate floating tablets (n = 3) were conducted using a USP 24 type-II paddle apparatus. The dissolution test was performed using 900 mL of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at pre-determined time intervals and replaced with fresh dissolution medium. The samples were filtered through a 0.45 µm membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these samples was measured at 260 nm using UV/visible double-beam spectrophotometer ((systronic-117, Hyderabad, India).

***In Vivo* Radiographic Studies:**

To make the tablet x-ray opaque, incorporation of $BaSO_4$ was necessary. For this purpose, 80 mg of the drug was replaced with $BaSO_4$ (80 mg $BaSO_4$ + 420 mg drug) and all other ingredients were kept constant. The protocol of radiographic studies on healthy human volunteers was approved by the Human Ethical Committee, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India. The study was conducted on three healthy male volunteers, each weighing between 55–75 kg and in the age group of 25± 2 years. The tablets prepared for radiography (F13) were administered orally with a glass of water. During the study, the subjects were not allowed to eat but water was available ad libitum. After ingestion of CEP 13 floating tablets containing barium sulphate, the volunteers were exposed to x-ray photography in the abdominal region. The x-ray photographs were taken at 0, 1, 2, 4, and 6 h after administration of the tablets. The mean gastric residence time was calculated.

RESULTS AND DISCUSSION

Drug - excipient compatibility study by Differential Scanning Calorimetry

DSC thermogram of pure drug and optimized formulaton are shown in figure 1&2. There were two significant events appeared in the DSC study of cephalexin monohydrate. Drug was shown sharp endothermic peak at 167.87°C and exothermic peak shown at 203°C and optimized formulation containing HPMC K100M and HPMCK15M was shown 76.45°C. From the DSC study, it can be concluded that there was no interaction between pure drug and polymers used in the study.

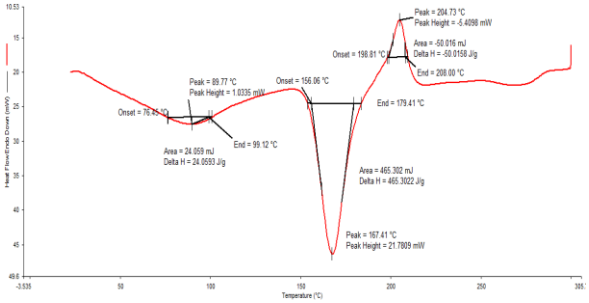

Fig1: DSC Thermogram of pure drug

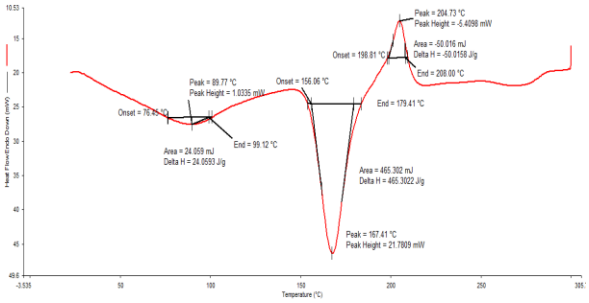

Fig2: DSC Thermogram of optimized formulation.

Physical characterization of all formulations:

The prepared mini tablets were evaluated for their physicochemical parameters like hardness, thickness, weight variation, friability, drug content, floating lag time (FLT) and total floating time (TFT). The values obtained were tabulated in Table No 3.

Table3: Physicochemical parameters of all formulations

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)	FLT (Sec)	TFT (h)
CEP1	79 ±3	5.1 ± 0.2	2.6±0.03	0.40	99.05	9	12
CEP2	81 ±5	5.3 ± 0.3	2.5±0.02	0.65	99.03	11	12
CEP3	80 ±6	5.5 ± 0.3	2.1±0.01	0.54	100.09	10	12
CEP4	80 ±4	5.1 ± 0.5	2.4±0.01	0.30	99.91	8	12
CEP5	80 ±6	5.0 ± 0.3	2.3±0.03	0.42	98.72	10	12
CEP6	81 ±5	5.8 ± 0.2	2.6±0.02	0.37	99.72	9	12
CEP7	79 ±3	5.5 ± 0.2	2.6±0.03	0.35	100.0	10	12
CEP8	80 ±2	5.3 ± 0.4	2.1±0.04	0.29	100.07	10	12
CEP9	80 ±5	5.1 ± 0.3	2.3±0.03	0.25	99.28	11	12
CEP10	81 ±2	5.9 ± 0.2	2.4±0.02	0.20	98.48	9	12
CEP11	81 ±4	5.1 ± 0.2	2.4±0.05	0.49	99.95	12	12
CEP12	80 ±3	5.3± 0.3	2.5±0.02	0.32	98.25	10	12
CEP13	80 ±3	5.5 ± 0.2	2.3±0.03	0.20	100.1	10	12
CEP14	80 ±5	5.0 ± 0.3	2.4±0.02	0.42	97.85	11	12
CEP15	81 ±2	5.5 ± 0.3	2.3±0.02	0.34	98.21	10	12

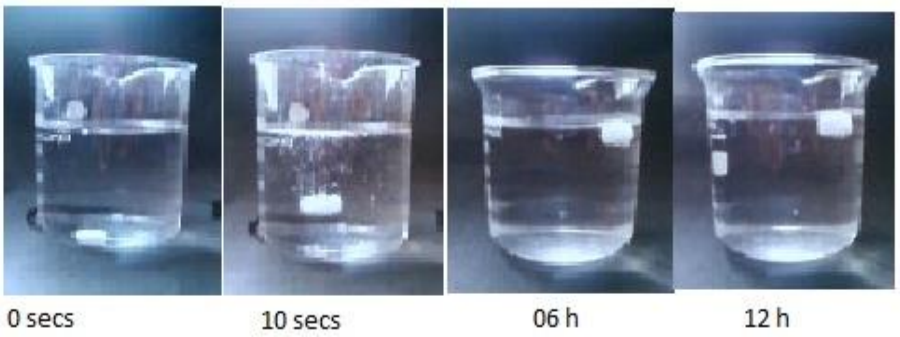

Figure 3: *In vitro* buoyancy studies of optimized (CEP-13) mini tablet.

***In vitro* drug release studies:**

In vitro dissolution studies of all the formulations of CEP MUMTS were carried out in 0.1 N HCl (pH 1.2). The study was performed for 12 h and cumulative drug release was calculated. The drug release profiles of the formulations, CEP1-CEP5 prepared with HPMC K 100M are shown in Figure 4. As the concentration of polymer increases, the drug release was decreased. CEP1 and CEP2 formulations releases the drug 97.5±1.9% in 8hrs and 92.9±1.5% in 10hrs and CEP3, CEP4, CEP5 formulations has shown the drug release up to 12hrs with 94.31±1.9, 89.9±1.7,85.9±1.5 respectively. From this result, it can be concluded that CEP3 was considered as optimized formulation, because it sustains the drug release for desired period of time and matched with the theoretical release profile.

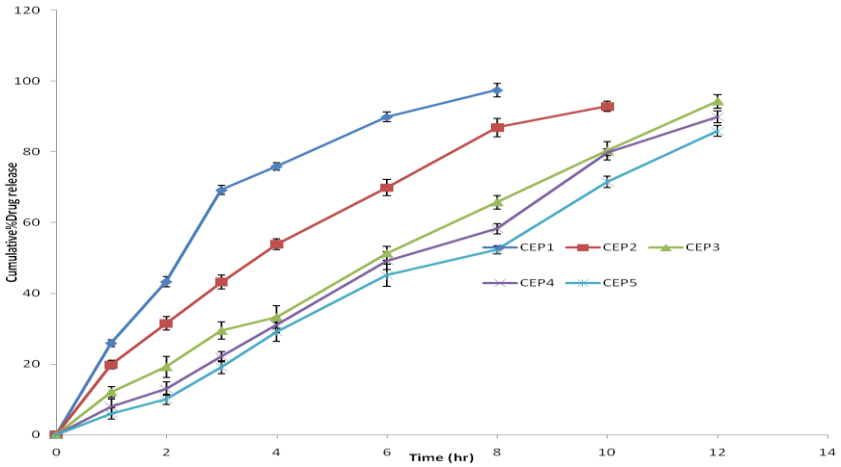

Fig 4*: In vitro* drug release profile of CEP in 0.1N HCL (HPMC K100M)

The results of the *in vitro* dissolution studies of the formulations CEP6- CEP10, prepared with HPMC K 15M are shown in Figure 5. CEP6 and CEP7 formulation has shown 97.9±2.2% in 8hrs and 95.9±3.1% in 10 hrs and CEP8, CEP9, CEP10 formulations has shown the drug release up to 12hrs with 96.31±1.4, 93.19±1.7,87.9±1.5 respectively. From this result, it can be concluded that CEP8 was considered as optimized formulation, because it sustains the drug release for desired period of time upto 12 hrs with the good theoretical release profile.

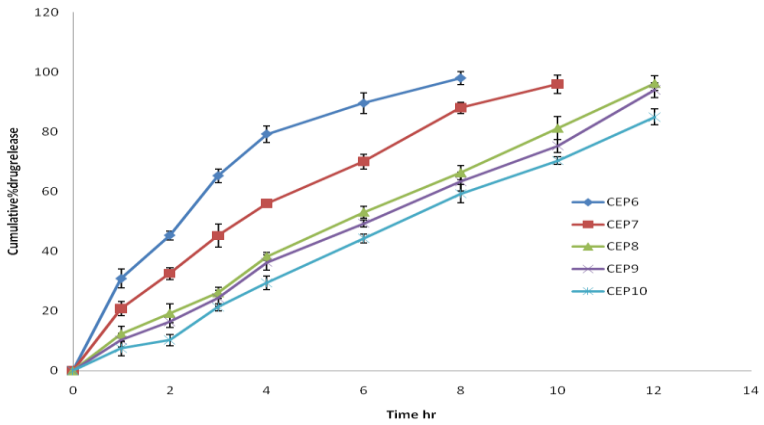

Fig5*: In vitro* drug release profile of CEP in 0.1N HCL (HPMC K15M)

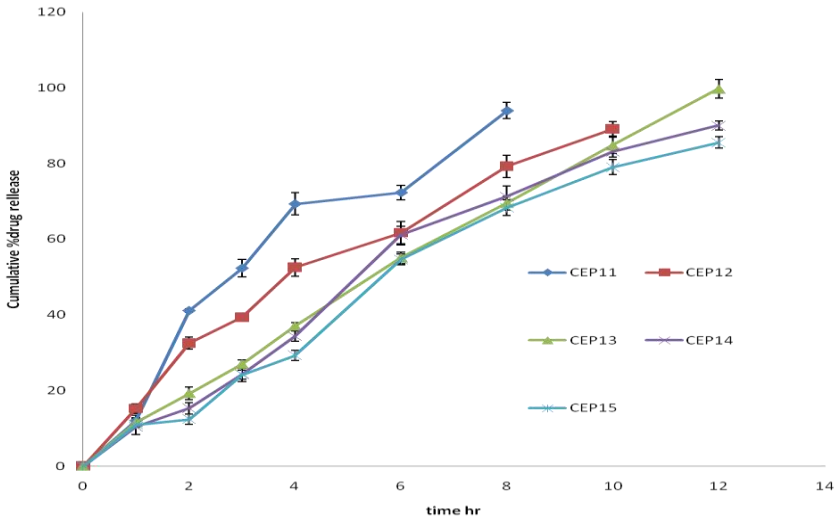

Fig6: *In vitro* drug release profile of CEP in 0.1N HCL (HPMCK100M+HPMCK15M)

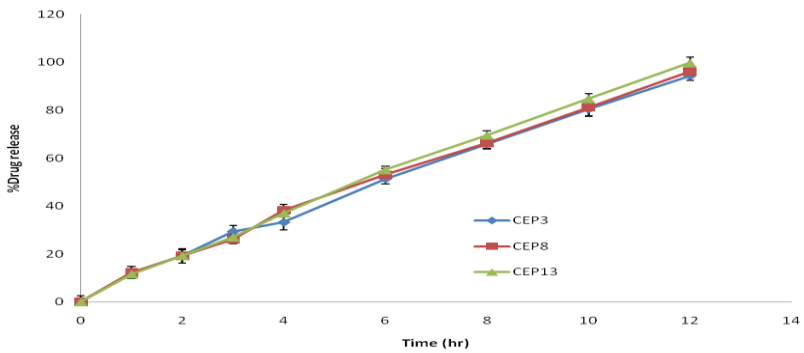

Fig7: Comparative release profile of all optimized formulations

The formulations CEP11-15 were prepared with different ratio of combination of polymers (HPMCK100M & HPMCK15M). The drug release from CEP11, 12&13 was 94.01±2.1, 89.1±1.9, 99.75±2.5, within 8, 10,12h respectively (Fig6). CEP14 and CEP15 has shown the drug release 90.05±1.2, 85.57±1.5 in 12 h. All the formulations (CEP11, CEP12, CEP13, CEP14 and CEP15) were floated for 12h. The difference in drug release was due to the presence of different concentration of combination of polymer. Among all formulations, CEP13 has shown better drug release 99.75±2.5% within 12h. So, it was selected as best formulations based on floating and drug release characteristics. Comparative release study was conducted for these three formulations (Fig7). Cumulative percentage drug release of CEP3, CEP8 and CEP13 was 94±1.9, 96.21±2.5, 99.75±2.5 within 12hrs respectively. From these results we can concluded that CEP13 has shown better release, so it can be considered as optimized formulation and used for further studies. From the radiographic images the tablet was retained in stomach for 4hr in all human volunteers after 4th h, the tablet was not found in the stomach. Therefore, from these studies, it was clearly observed that the floating tablets could retain in the stomach up to 4hrs (Fig 8).

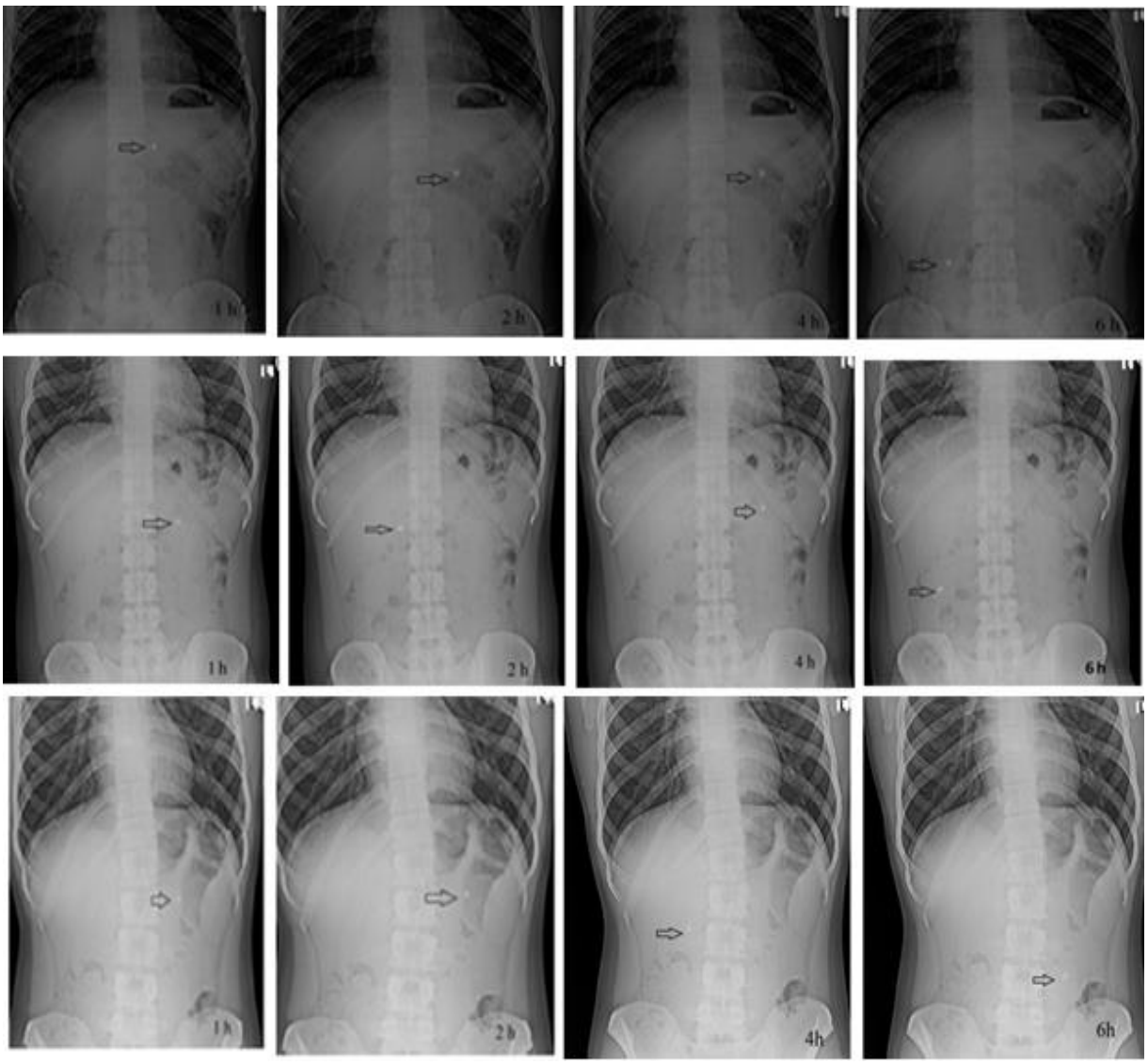

Fig 8: *In vivo* X-ray study of $BaSO_4$ loaded floating mini tablet (CEP13)

CONCLUSION

The floating multi-unit mini tablets of CEP were successfully developed using HPMC K15M, K100M and combination of both by direct compression technique. The optimized formulation (F13) showed satisfactory results with respect to FLT, TFT and sustained the drug release upto 12hrs. The in vivo radiographic studies showed that the $BaSO_4$-loaded floating tablets were retained in the stomach for 4 h.

REFERENCES

1. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J. Pharm. Res. 2008; 7 (3): 1055-1066.
2. Xiaoqiang X, Minjie S, Feng Z, Yiqiao H. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: in vitro and in vivo evaluation in healthy volunteers.Int. J. Pharm. 2006; 310: 139-145.
3. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm. Res. 1997; 14: 815-819.
4. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavia RR. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int. J. Pharm. 2006; 316 (1-2): 86-92.
5. Sweetman SC. Martindale: The Complete Drug Reference. 36th ed. Vol.1.London, Chigago: Pharmaceutical Press; c2009. p. 218-9.
6. Healthline: Connect to better health. San Fransisco, New York: Healthline Networks Inc.; 1999. Available from: http://www.healthline.com/ahfscontent/cephalexin.
7. Rx List: The Internet Drug Index. California. Rx List Inc.; 1995. Available from: http://www.rxlist.com/keflex-drug.htm. [Last cited on 2011 Jan 14].
8. Shin SC, Cho SJ. Kinetics of cephalexin release from Eudragit - Hydroxypropylcellulose membranes. Drug Dev Ind Pharm 1996; 22:299-305.

***Corresponding Author:**
Shayeda*
Email: drshayeda@gmail.com