Research Article

Formulation and Evaluation of Bilayer Floating Tablet Containing Antihypertensive Drug

***Anil Kumar AP, Felix Joe V., Vishwanath B. A.**

Department of Pharmaceutics, Aditya Bangalore Institute for Pharmacy Education & Research, Bangalore- 560064, India.

ABSTRACT

Enalapril is an angiotensin converting enzyme (ACE) inhibitor used in the treatment of hypertension, diabetic nephropathy, and some types of chronic heart failure. The serum concentration profile of Enalapril exhibits a prolonged terminal phase apparently representing a small fraction of the administered dose that has been bound to ACE.The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalapril following multiple doses of enalapril maleate is 11 hours.

The aim of the present investigation is to increase the gastric residence time by preparing gastro retentive floating bilayered tablet thereby by improving bioavailability. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymer interactions.

Eight formulations (FE1 to FE8) were prepared using various polymers such as HPMC K15M, Sodium Carboxymethylcellulose in different ratios. Direct compression was adapted to compress bilayer floating tablet. The prepared bilayer floating tablet were evaluated for hardness, weight variation, thickness, Friability, drug content, buoyancy lag time, total floating time and in- vitro dissolution studies. Drug content (98.23-99.75%) was found uniform for all batches. percentage drug release was found to be 87.84 % to 97.27 % after 12 hours. Release of bi layered formulations follows zero order kinetics (0.8661 to 0.9649) except formulation FE1. When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.603 to 0.6981) indicated that the drug release was by non-fickian mechanism. FE4 was considered as optimized formulation which exhibited 84.91% of drug releases in 14 hours. The values were within the permissible limits.

Keywords: Enalapril maleate, hydroxypropylmethylcellulose K15M, sodium carboxymethyl cellulose and bilayer floating tablets

Received 11 Nov 2014 Received in revised form 04 Dec 2014 Accepted 06 Dec 2014

***Address for correspondence:**
Anil Kumar AP,
Department of Pharmaceutics, Aditya Bangalore Institute for Pharmacy Education & Research, Bangalore- 560064, India.
E-mail: felixjoev@gmail.com

INTRODUCTION

Oral drug delivery has been known for decades as the most utilized route of administration. Among all the routes that have been explored for the systemic delivery of drugs via, various pharmaceutical products of different dosage forms and constitute about 50-60 % of total drug formulations. This trend is still continuing to be the most preferred route due to its manifold advantages, including ease of ingestion, prolonged release (in some cases) and most important of all is the patient compliance [1,2].

Controlled drug delivery implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingredients from a controlled release drug delivery systems proceeds at a rate that is predictable kinetically and also reproducible from one unit to another. Moreover, the rate and extent of drug absorption from conventional formulations may vary greatly depending on factors such as physicochemical properties of the drug, presence of excipients, various

physiological factors such as the presence or absence of food, pH of GIT, GI motility, and mucin turn over. Several terms have been used to describe the various types of drug delivery systems intended to provide long duration of action [3].

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at controlled rate or by targeted drug delivery in the GI tract using p^H dependent polymers [4].

Conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There are various applications of the bi-layer tablet which consists of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer, its delivery occurs into the whole oral cavity [5].

Enalapril is an angiotensin-converting-enzyme (ACE) inhibitor used in the treatment of hypertension, diabetic nephropathy, and some types of chronic heart failure. ACE converts the peptide hormone angiotensin I to angiotensin II. Enalapril was the first member of the group known as the dicarboxylate containing ACE inhibitors. Enalapril as a treatment for high blood pressure works by modulating the renin-angiotensin-aldosterone system. Enalapril belongs to a class of medications called angiotensin converting enzyme inhibitors. Normally angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II constricts blood vessels, increasing blood pressure. By inhibiting ACE, Enalapril decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure. Enalapril is a pro-drug following oral administration, it is bio activated by hydrolysis of the ethyl ester to enalapril, at which is the active angiotensin converting enzyme inhibitor [6]. The aim of the present investigation is to increase the gastric residence time by preparing gastro retentive floating bilayered tablet thereby by improving bioavailability.

MATERIALS AND METHODS

Enalapril maleate was obtained as a Gift sample of Micro Labs, Bangalore, HPMC K15M was procured from Ontop pharmaceuticals, Bangalore, Sodium carboxymethylcellulose was procured from Ontop pharmaceuticals, Bangalore, Sodium bicarbonate, Lactose was procured from SD Fine Chemicals Limited, Mumbai. All other reagents used were of analytical grade.

Pre-formulation studies

Pre-formulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of Physical and chemical properties of drug substance, alone and when combined with excipients.

FTIR Spectroscopy

The FTIR spectrum of the obtained sample of drug was compared with the standard FTIR spectra of the pure drug. FTIR spectrum of drug and physical

mixture of drug with polymers were obtained on FTIR instrument. The samples were mixed with KBr. The spectrum was scanned over the wave number range of 4000-400 cm^{-1}.IR helps to confirm the identity of the drug and to detect the interaction of the drug with the excipients.

Formulation of Bilayer tablet [7-10]

Bilayer floating tablets contain the two layers i.e, immediate release layer and floating sustained release layer. The immediate release layer contains the drug, sodium starch glycolate (as super disintegrants) and small amounts of lubricants and binder, the floating sustained release contains the drug and sodium bicarbonate (as gas generating agent), with polymers like Hydroxy-propylmethylcellulose & sodium carbo-xymethylcellulose and other excipients as given in (**Table 1 & 2**). The tablets are prepared by direct compression method. The drug and all the excipients were sifted through mesh # 40, weighed accurately, and then was mixed in a plastic bag for 5 minutes, and lubricated with magnesium stearate and mixed. The granules were compressed by using 6mm round flat punches with low hardness to produce floating layer tablets.

Table 1: Formulation of Immediate Release Layer

INGREDIENTS	FE1	FE2	FE3	FE4	FE5	FE6	FE7	FE8
Enalapril maleate	4	4	4	4	4	4	4	4
Sodium starch glycolate	20	20	20	20	20	20	20	20
Sodium bicarbonate	18	20	22	24	18	20	22	24
Lactose	2	2	2	2	2	2	2	2
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Total wt of each quick disintegrating layer is 27mg

Table 2: Formulation of sustained release layer

INGREDIENTS	FE1	FE2	FE3	FE4	FE5	FE6	FE7	FE8
Enalapril maleate	16	16	16	16	16	16	16	16
HPMC K 15M	60	60	60	60	80	80	80	80
Sodium carboxymethylcellulose	14	14	14	14	14	14	14	14
Lactose	22	20	18	16	22	20	18	16
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total wt. of tablet (I &II layer) in mg	160	160	160	160	180	180	180	180

All quantities were given in milligrams.

Pre compression Parameters

Angle of Repose

Angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane. The results are given in (**Table 3**).

Tan θ = h/r

Where, θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

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

Bulk Density

It is the ratio of total mass of powder to the bulk of powder. It is measured by pouring the weighed powder into a

measuring cylinder and the volume was noted. It is expressed in g/cm^3 and is given by; the results are given in (**Table 3**).

$$\text{Bulk Density} = \frac{\text{Mass of powder}}{\text{Bulk volume of the powder}}$$

Tapped density

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/cm^3 and is given by; the results are given in (**Table 3**).

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{Tapped volume of the powder}}$$

Carr's index

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by; the results are given in (**Table 3**).

$$\text{CI} = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Hausner's Ratio:

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density; the results are given in (**Table 3**).

Hausner's Ratio = Tapped density/Bulk density

Post compression parameters [10]

Tablet thickness

Thickness of tablets was important for uniformity of tablet size. Thickness were measured using vernier calipers, the results are given in (**Table 4**).

Hardness [11]

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2. The mean values are given in (**Table 4**).

Friability

The friability test was carried out to evaluate the hardness and stability instantly. In Roche friabilator in which twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w). The percent loss in weight or friability (f) was calculated by the formula given below and the results are given in (**Table 4**).

$f = (1\text{-}W/Wo) \times 100$

where, f= friability

Wo= initial weight

W= final weight

Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage and none deviate by more than twice the percentage. The mean and standard deviation were determined. The results are given in (**Table 4**).

Drug content estimation

Ten tablets were selected randomly, weighed and triturated a quantity of

triturate equal to 100mg of Enalapril maleate was transferred to 100ml volumetric flask and was dissolved in 0.1N Hydrochloric acid. It was sonicated for 30 min and filtered through 0.45µm membrane filter. The absorbance after suitable dilutions was measured in a UV-Visible Spectrophotometer at 215 nm using 0.1N Hydrochloric acid as blank. The results are given (**Table 4**).

***In vitro* buoyancy determination**

The floating characteristics of the Gastric floating drug delivery system are essential, since they influence the *in vivo* behaviors of the drug delivery system.

Floating Lag Time

The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37+_0.5°C, paddle rotation at 50 rpm and 900ml as volume, it is measured using stopwatch. The results are given in (**Table 5**).

Total Floating Time

The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temp 37±0.5°C, paddle rotation at 50 rpm ,it is measured using stopwatch. The results are given in (**Table 5**).

***In vitro* dissolution studies [12]**

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (Apparatus 2). The stirring rate was 50 rpm, 0.1N hydrochloric acid was used as dissolution medium 900ml and was maintained at 37±0.5°C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Enalapril maleate at 215 nm by using a double beam UV spectrophotometer (Shimadzu-1800). Each dissolution study was performed for three times and the mean values were taken. The results are given in (**Table 6 & 7**).

Drug Release kinetics [13-14]

The analysis of drug release mechanism from the pharmaceutical dosage form is an important but complicated process and it is practically evident in the case of matrix systems. As model-dependent approach, the dissolution data are fitted to four popular release model such as a zero-order, first order, Higuchi and peppas equations, which have been described in the literature .The order of drug release from matrix systems was studied by using Higuchi equation and erosion equation. The results of in vitro release studies were also fitted into five models to determine the release kinetics pattern.

The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n = 1.0 indicate non-fickian mechanism. In case of a cylinder n = 0.45 instead of 0.5, and 0.89 instead of 1.0.This model is used to analyze the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon being involved.

RESULTS AND DISCUSSION

Compatibility study of drug with polymers

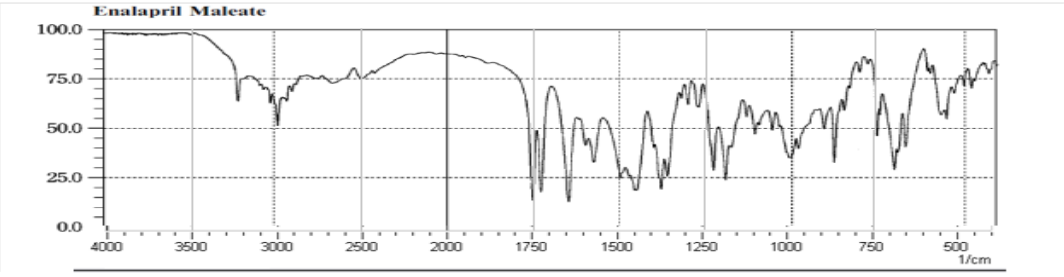

Figure 1: FTIR spectrum of Enalapril Maleate

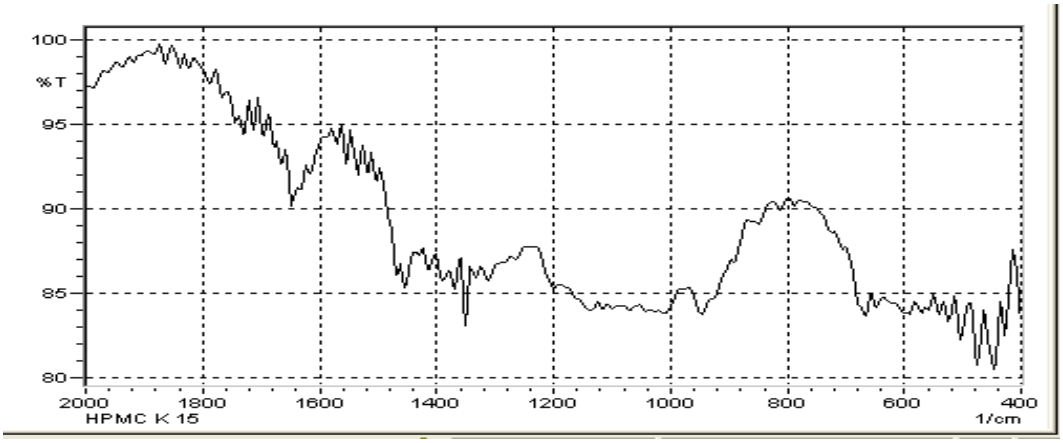

Figure 2: FTIR spectrum of HPMC K15M

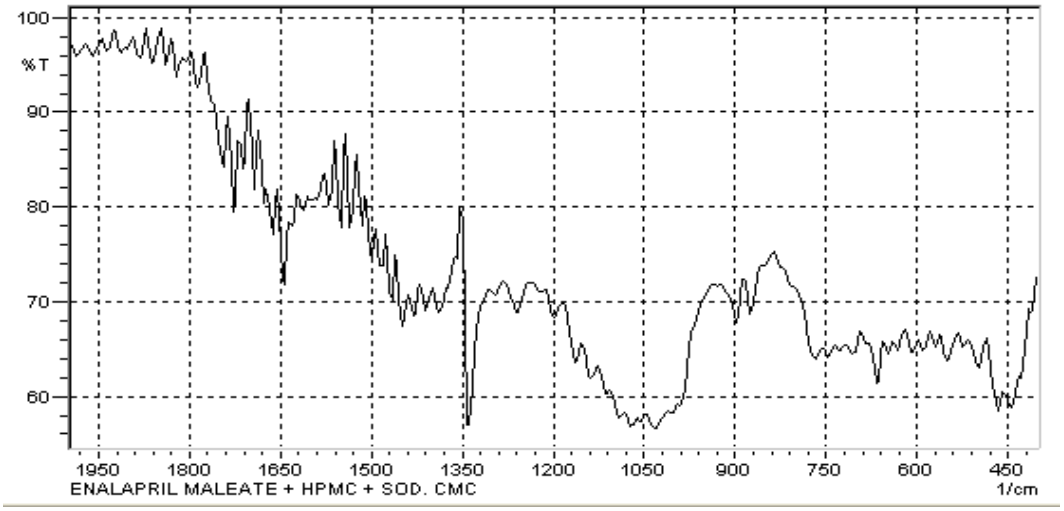

Figure 3: FTIR spectrum of Enalapril Maleate with HPMC K15M and Sodium Carboxymethylcellulose

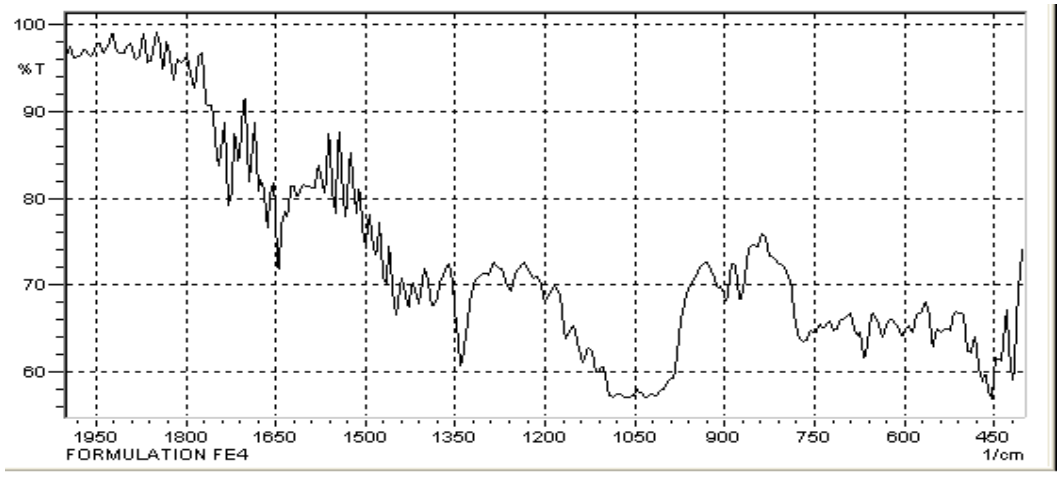

Figure 4: FTIR Spectrum of Optimized Formulation FE4

The above peaks can be considered as characteristic peaks of Enalapril maleate. These peaks were not affected and prominently observed in IR spectra of Enalapril maleate along with polymers. This indicates that there is no interaction between drug and polymers.

Pre compression parameters

Table 3: Physical parameters of the powder blend of Enalapril maleate

Formulation code	Angle of Repose (θ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio (%)
FE1	$29^0.69'$	0.57	0.77	19.73	1.26
FE2	$27^0.26'$	0.62	0.69	20.75	1.22
FE3	$30^0.48'$	0.64	0.71	15.43	1.10
FE4	$24^0.56'$	0.60	0.72	15.91	1.19
FE5	$29^0.29'$	0.62	0.65	16.34	1.14
FE6	$28^0.85'$	0.59	0.60	17.34	1.20
FE7	$27^0.49'$	0.61	0.71	15.02	1.32
FE8	$26^0.52'$	0.64	0.72	16.05	1.23

The Pre-compression parameters of all formulations prior to the compression were studied and the results are shown in the Table No.03. The angle of repose of all formulations shows values in the range of $24^0.56'$to $30^0.4'$ which indicates good flowability. The bulk density of the formulation ranged from 0.57 to 0.64 gm / ml and, tapped densities were found to be in the range of 0.60 to 0.77 gm / ml. The values of Carr's index and Hausner's ratio were found to be in the range of 15.02 % to 20.75% and 1.10 % to 1.32 % which also indicates good flow.

Post compression parameters

Post compression studies were carried out and the data are given in Table No.04.Weight variations, friability, Thickness, Hardness, Friability and Drug contents of the tablets are computed. All different batches of bilayer floating tablets were of uniform thickness, hardness (5.70-7.02 kg/cm^2), friability (0.15-0.40 %) and weight variation of different batches of bilayer floating tablets were found within prescribed limits. Drug content (98.23-99.75%) was found to be uniform for all batches.

Table 4: Post Compression evaluation of Enalapril maleate bilayer floating tablets

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
FE1	5.2±0.006	5.72±0.360	0.40	160±4.26	99.75±0.54
FE2	5.2±0.010	5.70±0.288	0.19	159±4.26	98.96±0.52
FE3	5.2±0.009	6.01±0.152	0.30	160±4.11	98.46±1.21
FE4	5.2±0.001	6.25±0.152	0.15	158±4.50	99.11±0.16
FE5	5.4±0.010	6.30±0.100	0.23	180±3.77	98.49±0.59
FE6	5.4±0.011	6.35±0.057	0.35	179±3.35	98.74±0.67
FE7	5.3±0.010	6.87±0.200	0.25	180±3.30	98.25±0.54
FE8	5.3±0.006	7.02±0.152	0.20	178±3.04	98.23±1.11

Dissolution release studies

The cumulative percentage drug release of Enalapril maleate bilayered floating tablets of FE1 to FE8 was carried out in 0.1 N HCl and the cumulative percentage drug was found to be 87.84 ± 0.95 % to 97.27 ± 1.11 % after 12 hours. The cumulative percentage drug release are shown in (**Table 6 & 7**) and (**Figure 5 & 6**).

Table 5: *Invitro* floating properties

Formulation Batch	Floating Lag time	Floating duration
FE1	3min, 50 sec	> 24 hrs
FE2	3 min, 13 sec	> 24 hrs
FE3	3 min, 42 sec	> 24hrs
FE4	2 min, 27 sec	> 24hrs
FE5	2 min 03 sec	> 24hrs
FE6	3 min, 27 sec	> 24hrs
FE7	2 min, 15 sec	> 24hrs
FE8	2 min, 57 sec	> 24hrs

Table 6: *In vitro* drug release of Enalapril maleate bilayered floating tablet formulations (FE1toFE4)

Time	Cumulative percentage (+ S.D) drug release			
In (hrs)	FE1	FE2	FE3	FE4
1.	29.19±0.48	25.11±0.27	25.18±1.64	22.13±0.10
2.	32.09±1.62	27.46±1.74	38.45±0.53	23.35±0.85
3.	41.51±0.07	35.58±0.87	49.54±0.66	31.27±1.29
4.	47.71±1.67	47.83±0.08	55.15±1.38	36.70±0.17
5.	54.95±1.86	59.23±1.72	67.41±1.45	43.88±0.10
6.	66.21±0.87	65.53±1.55	69.77±0.78	50.55±0.16
7.	74.09±0.11	73.14±2.41	76.22±0.05	55.53±0.94
8.	83.46±0.24	83.23±0.52	82.61±1.75	62.81±1.64
9.	85.57±0.97	84.04±0.23	84.96±1.19	67.23±0.08
10.	88.74±1.23	85.56±0.55	86.14±2.75	69.83±0.71
11.	90.89±0.34	87.34±1.24	87.69±0.88	74.47±0.08
12.	92.27±0.89	89.38±1.00	91.46±0.23	79.23±1.54
13.	95.32±1.02	93.30±0.97	93.86±1.08	81.03±0.45
14.	97.27±1.11	93.62±1.45	95.63±1.21	84.91±0.67

Table 7: *In vitro* drug release of Enalapril maleate bilayered floating tablet formulations (FE5 to FE8)

Time	Cumulative percent (+ S.D) drug release			
in (hrs)	FE5	FE6	FE7	FE8
1.	23.73±1.43	21.19±1.29	20.20±1.09	24.59±0.86
2.	36.36±0.66	32.09±0.84	26.55±0.54	29.64±0.43
3.	47.80±0.45	41.51±1.47	31.59±1.45	34.72±0.78
4.	54.49±0.87	47.71±0.98	45.53±0.88	38.60±0.87
5.	56.60±1.86	54.95±0.79	54.93±1.25	41.27±0.19
6.	61.62±0.75	66.21±0.58	66.37±0.78	47.64±2.69
7.	67.03±0.99	74.09±0.25	78.15±0.09	52.82±0.56
8.	73.00±0.81	83.46±0.75	83.37±0.65	61.71±0.40
9.	77.56±1.23	84.88±0.74	85.83±1.20	66.97±0.67
10.	80.24±1.67	86.67±0.76	90.84±0.45	74.70±0.76
11.	85.02±1.33	90.89±0.31	91.61±1.00	78.69±0.29
12.	88.67±1.00	92.73±1.23	92.74±0.66	82.48±1.85
13.	90.74±0.67	95.32±0.53	93.42±0.75	84.75±1.02
14.	96.34±0.55	97.27±1.11	94.10±0.56	87.84±0.95

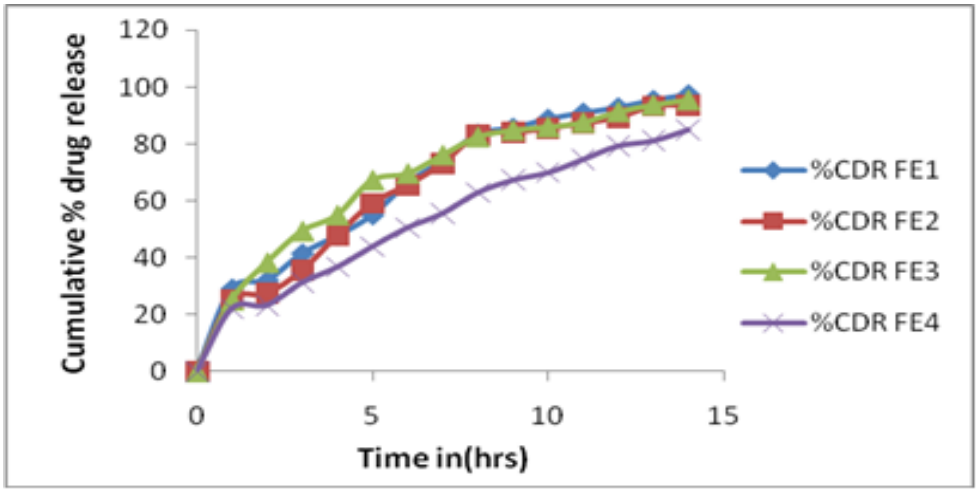

Figure 5: Cumulative Percentage drug release from Enalapril maleate bilayered floating tablet formulations (FE1 to FE4)

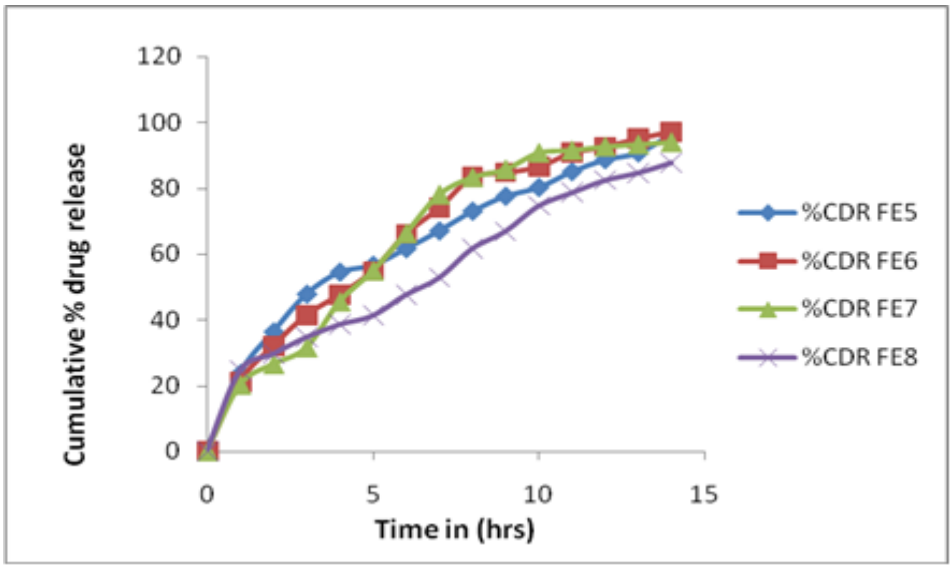

Figure 6: Cumulative Percentage drug release from Enalapril maleate bilayered floating tablet formulations (FE5 to FE8)

In vitro drug Release kinetic study

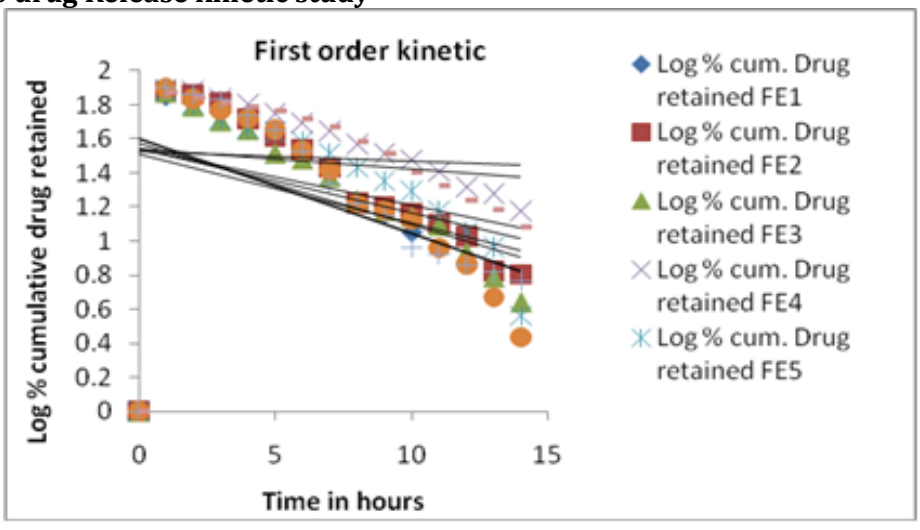

Figure 7: Cumulative percentage drug release Vs Time (Zero Order)

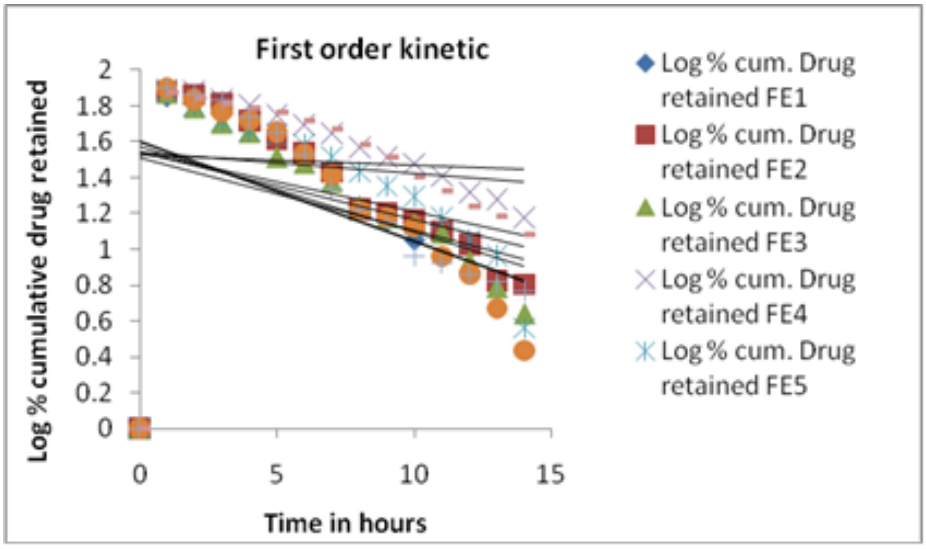

Figure 8: Log Cumulative Percent Drug Retained Vs Time (First order)

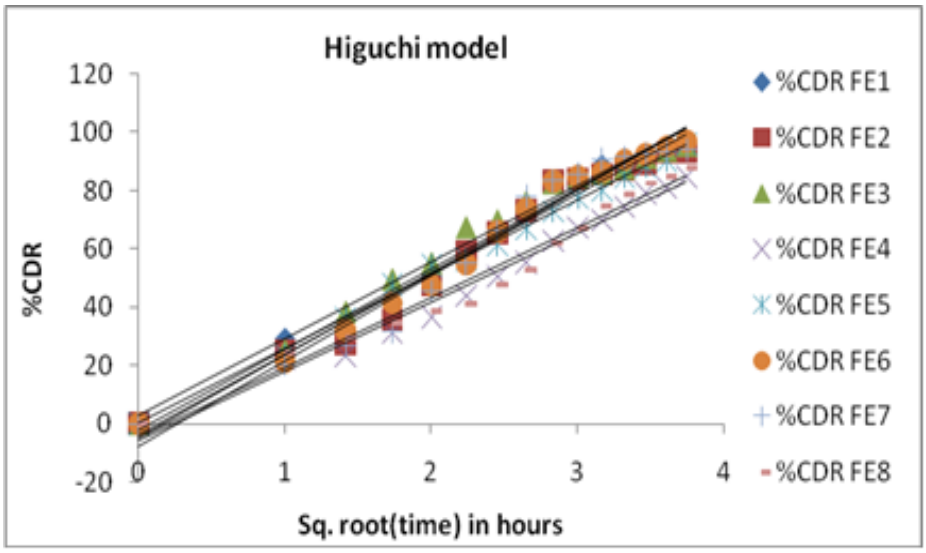

Figure 9: Cumulative Percentage drug release Vs Square root of time (Higuchi's Plot)

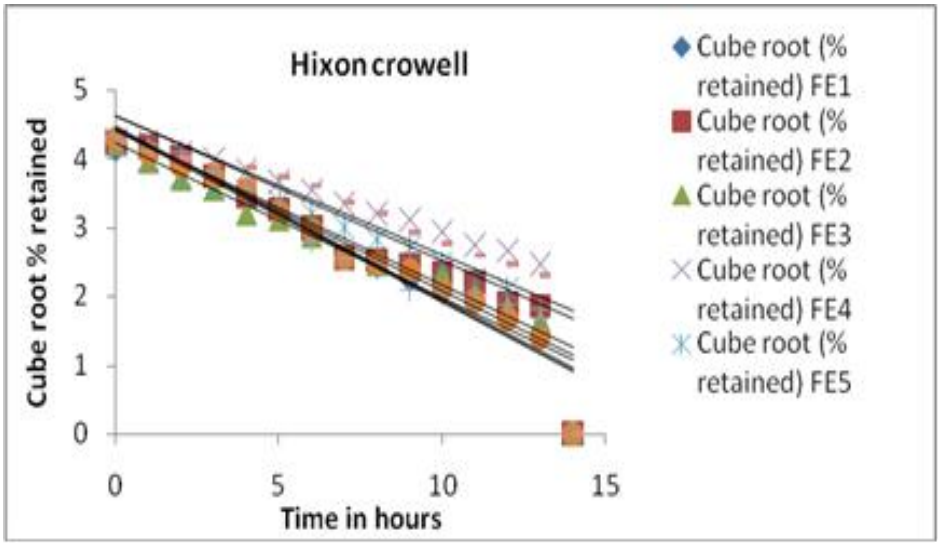

Figure 10: Cube root of % retained Vs Time (Hixon crowell cube root law)

Table 8: Regression coefficients (r^2) computed from different kinetic model

Formulation code	Zero order (r^2)*	First order (r^2)*	Higuchi Model (r^2)*	Hixon crowell (r^2)*	Korsmeyers-Peppas model (r^2)*
FE1	0.916	0.987	0.981	0.9363	0.6189
FE2	0.9029	0.924	0.9726	0.8897	0.6514
FE3	0.8661	0.936	0.9839	0.8975	0.603
FE4	0.9637	0.969	0.9834	0.7306	0.6674
FE5	0.9146	0.862	0.9969	0.8607	0.6094
FE6	0.9198	0.973	0.9839	0.939	0.6638
FE7	0.9035	0.909	0.9589	0.9152	0.6981
FE8	0.9649	0.925	0.9707	0.7654	0.6334

*is regression coefficient.

When the regression coefficient 'r²' value of zero order and first order plots were compared, it was observed that the 'r²' values of zero order were in the range of 0.8661 to 0.9649 whereas the 'r²' values of first order plots were found to be in the range of 0.862 to 0.987 indicating drug release from all the formulations were found to follow zero order kinetics except formulation FE1.

The good fit of the Higuchi model to the dissolution profiles of majority the formulations suggested that diffusion is the predominant mechanism limiting drug release since the 'r²' values of Higuchi's plots were near to unity and FE1 lies in first order linear kinetics.

The *in vitro* dissolution data as log cum percent drug release versus log time were fitted to Korsmeyer equation, values of the exponent 'n' was found to be in the range of 0.603 to 0.6981 indicating that the drug release is by non-fickian diffusion mechanism.

CONCLUSION

The aim of this study was to formulate and evaluate bilayered floating tablets of Enalapril maleate. From the present study it is concluded that FTIR spectroscopic studies indicates no drug-excipient interaction. Bilayered Gastric Floating Drug Delivery systems of Enalapril maleate with immediate release and sustained release layer was prepared by direct compression method using polymers as HPMC K15M, sodium carboxymethylcellulose, sodium bicarbonate as gas generating agent, and sodium starch glycolate as super disintegrant. Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K 15 M, and Sodium Carboxymethylcellulose has predominant effect on total floating time and drug release. The *in vitro* dissolution profiles of all the prepared Bilayered Gastric Floating Drug Delivery systems formulations of Enalapril maleate were found to extend the drug release over a period of 14 hours. Release of bi layered formulations follows zero order kinetics (0.8661 to 0.9649) except formulation FE1. When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.603 to 0.6981) indicated that the drug release was by non-fickian mechanism. While comparing all the formulations, bilayered floating drug delivery system formulation FE4 was considered as the optimized formulation which exhibited 84.91% of drug release in 14 hours, and floating lag time of 147 seconds with a floating time of 24 hours.

REFERENCES

1. Anand S, Suran, Rakhee K, Kotecha. An overview on various approaches to oral Controlled drug delivery system via, gastro retention. Int J Pharm Sci Rev Res. 2010; 2(2):68.
2. Ranade VV, Hollinger MA. Oral drug delivery; Drug Delivery System. 2nd edi. CRC Press; 2003. 149-152.
3. Xiaoling L, Bhaskara JR. Design of controlled release drug delivery system.173-189.

4. Panchal Hiten Ashok, Tiwari Ajay Kumar. A novel approach of bilayer tablet technology: A Review. IRJP. 2012; 3(5): 44-49.
5. Sowmya C, Suryaprakash Reddy C, Tabasum SG, Varma V .An overview on bi-layer tablets. IJPT.2012;2(4):2143-2156.
6. Drug profile from "http: //en. wikipedia. org/ wiki /Enalapril maleate# Mode_ of_ action".
7. Kulkarni A, Bhatia M. Development and evaluation of region selective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile. Iranian Journal of Pharmaceutical Research. 2009;8(1):15-25.
8. Rajashree masa reddy, Shiva kumar Yellanki, Bhushan R. Patil, Manvi FV, Development and Evaluation of Floating Matrix Tablets of Riboflavin. International Journal of PharmTech Research.2010; 2(2):1439-1445.
9. Lachman Leon., Lieberman Herbert A. Pharmaceutical dosage forms: Tablets. The theory and practice of industrial pharmacy. 3rd edition U.S.A: Lea and Febiger;1991:293-345
10. Gibson M. Pharmaceutical Preformulation and formulation. Int Pharm Washington; 2nd edi. 2004.247-252.
11. Sharma MC, Sharma S, Kohli DV, Chaturvedi SC, Formulation In-vitro Evaluation, study of effect of Hardness on Buoyancy the time of Gastro retentive Film and Floating Tablet. J optoelectronic and Biomedical Materials. 2009;1: 353-358.
12. Costa P, Souse lobo, Manuel J, Modeling and Comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 13(2001):123-133.
13. Higuchi T, Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963):1145–1149.
14. Peppas NA. Analysis of Fickian and non-fickian drug release from polymer. Pharm. Acta Helv.60 ;1985.110–111.