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PREPARATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF ENALAPRIL MALEATE

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ABSTRACT

The purpose of this research was to develop a novel gastro retentive floating tablets of Enalapril Maleate. The main objective is to increase bioavailability and increase gastric residence time. There are 12 formulations were prepared by using different ratios of natural gums & synthetic polymers. Xanthum gum is used for floating property so as to target the delivery of drug to a specific region in the GIT. HPMC K 100 is used as hydrophilic polymer. sodiumbicarbonate, citric acid is used as gas generating agent, Lactose is used as adsorbent, suspending agent. F11was the optimized formulation having floating time more than 20 hrs.

KEY WORDS

Enalapril maleate, gastric floating tablet, floating drug delivery, controlled release, HPMC K100

INTRODUCTION

Enalapril maleate is oral long acting non-sulphydryl ACE inhibitor. It is class I antihypertensive drug. Oral dosage forms are most convenient route of drug delivery. The formulations are developed to improve the great patient compliance and clinical efficacy of drug. It has short biological half-life. The oral bioavailability of enalapril maleate is 40-60% due to narrow absorption window and is absorbed in upper part of small intestine. In the present investigation, the gastro retentive tablet dosage forms are prepared by using enalapril maleate as drug candidate and evaluating the prepared tablets for physicochemical properties, buoyancy lag time[1].

MATERIALS AND METHODS

Materials

Enalapril Maleate was obtained as a gift sample from Cipla laboratory, Bangalore. Xanthan gum, Xanthum gum was received from FINAR labs, Hyderabad, India. HPMC K100M was obtained from Signet chemicals corporation, Mumbai. Citric acid, sodium bicarbonate, talc, magnesium stearate and lactose were purchased from S.D. chemicals, Mumbai.

Methods

Formulation of Floating tablets of Enalapril Maleate were prepared by direct compression method according to the formula given in Table 1. Enalapril Maleate (200 mg) was mixed with the required quantity of polymer using Xanthan gum, HPMC K 100 M, sodium bicarbonate (20 mg), citric acid (10 mg), lactose is taken in a mortar and pestle for 15 min. The powder blend was then lubricated with talc (5 mg) and magnesium stearate (5 mg) for additional 3min prior to the compression. The powder was then compressed into tablets.

Preparation of standard curve of Enalapril maleate

The samples of different concentration were analyzed at 216nm using UV-Spectrophotometer against 0.1N Hcl buffer as blank.

Compatibility Studies: [1, 2]

The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy.

Formulation design: [3-5]

Floating tablets containing Enalapril maleate were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and lactose. The compositions of all formulations are given in Table No. 1.

Table 1: Composition of Gastroretentive Floating Tablets of Enalapril maleate (F1 to F12)

Formulation	HPMCK100M	Xanthum gum	Sodium bicarbonate	Citric acid	Lactose
F1	20	--	20	10	130
F2	40	--	20	10	110
F3	60	--	20	10	90
F4	80	--	20	10	70
F5	100	--	20	10	50
F6	120	--	20	10	30
F7	--	20	20	10	130
F8	--	40	20	10	110
F9	--	60	20	10	90
F10	--	80	20	10	70
F11	--	100	20	10	50
F12	--	120	20	10	30

EVALUATION PARAMETERS:

Precompression parameters:

Bulk density and tapped density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD were calculated using following formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder

Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

Compressibility index: Percentage compressibility of powder mix was determined by Carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is calculated by following formula.

Carr's index (%) = [(TBD -LBD) × 100]/TBD

Angle of repose (Θ): The frictional forces in a loose powder or granules can be measured by the angle of repose.

$\tan \theta = h / r$

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

Where, θ is the angle of repose

h is height of pile

r is radius of the base of pile

Post compression parameters:

Weight variation test: [6]

Twenty tablets from each formulation were selected randomly and weighed individually average weight was determined. Individual tablets weighed were then was compared with average weight.

Hardness test: [6]

The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Pfizer hardness tester. The hardness was measured in terms of Kg/cm2.

Friability:

Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Content uniformity test:[6]

Twenty tablets were finely powdered; quantities of the powder equivalent to 5mg of Enalapril maleate were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCl (pH 1.2 buffer) solution and mixed thoroughly. The solution was made up to volume 100ml and filtered. Dilute 1 ml of the resulting solution to 10 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 216 nm using a Shimadzu UV-visible spectrophotometer.

In vitro Dissolution Studies: [8-10]

The In vitro dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900

ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at 37 ^{o}C ± 0.5 ^{0}C.

RESULTS AND DISCUSSION

Standard calibration curves of Enalapril maleate: Figure 1 (Table 2) shows the standard calibration curves for Enalapril maleate with slope, regression co-efficient and intercept.

Table 2: Standard Calibration curve of Enalapril maleate at 216 nm in pH 1.2 Buffer.

Concentration (µg/ml)	Absorbance
0	0
4	0.14
8	0.23
12	0.33
16	0.43
20	0.57
24	0.67
28	0.74
32	0.86
36	0.95

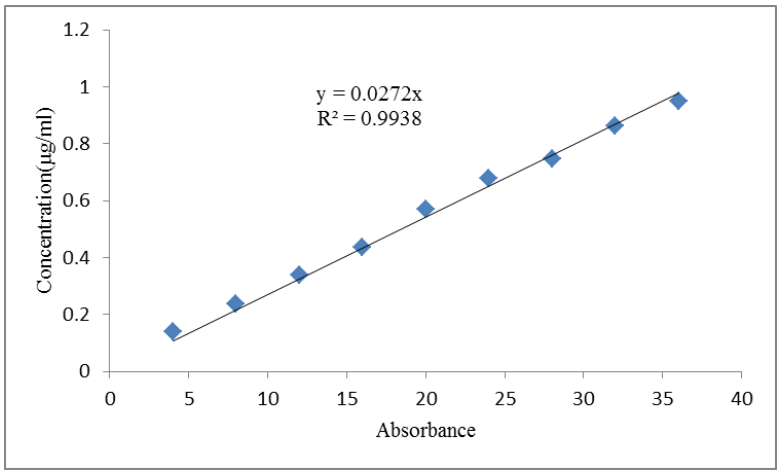

Fig.1 Calibration curve of Enalapril maleate of 0.1N HCL at 216nm

Compatibility Studies: Compatibility studies of pure drug Enalapril maleate with all excipients were carried out prior to the preparation of floating tablets. I.R spectra of pure drug Enalapril maleate and combination of Enalapril maleate and excipients were obtained.

Formulation development of floating tablets: The floating tablets of Enalapril maleate were prepared using direct compression method.

Pre-compression Parameters:

Angle of repose: The values were found to be in the range of 22^{0} to 29^{0}. All the formulation showed angle of repose below 30^{0} which indicates a good flow property of the granules.

Compressibility index: Carr's index lies within the range of 19.8 to 24.1%. All formulations show good compressibility. The results are shown in Table 3.

Table 3: Pre-compression parameters from formulation F1 to F12

Formulation Code	Carr's Index (%)	Bulk density(gm/cc)	Tapped density(gm/cc)	Angle of repose(^{0})
F1	20	0.45	0.55	22
F2	22	0.43	0.60	24
F3	24	0.42	0.59	23
F4	22	0.50	0.58	25
F5	21	0.51	0.59	23
F6	22	0.47	0.66	28
F7	25	0.46	0.61	27
F8	23.5	0.45	0.55	26
F9	24.1	0.47	0.59	23
F10	21.4	0.58	0.62	24
F11	19.8	0.49	0.64	27
F12	23.8	0.44	0.63	29

Post compression Parameters:

Weight variation test: The values of tablets ranged from 197±1.1 to 202±1.2 mg. All the tablets passed weight variation test as the % weight variation was within the Pharmacopeia limits of ±10 % of the weight and is shown in Table 4.

Hardness test: The hardness of all formulations was in the range of 4.1±0.2 to 5.7±0.3 kg/cm2.

Friability test: The friability values of prepared tablets are given in Table 4. The values ranged from 0.22 to 0.51%

Content uniformity test: The percent drug content of tablets was found to be in between 95 to 98 of Enalapril maleate and all results are shown in Table 4.

Table 4: Physical Characterization of Gastroretentive Floating Tablets of Enalapril maleate (F1 to F12)

Formulation Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	197 ±1.1	4.5±0.5	3.76±0.06	0.23	98
F2	199 ± 1.7	5.6±0.3	4.56±0.03	0.48	95
F3	202 ± 1.2	4.4±0.5	4.66±0.04	0.51	96
F4	199 ± 1.7	4.5±0.2	4.43±0.06	0.22	95
F5	201 ± 1.7	5.4±0.5	4.68±0.05	0.35	97
F6	198 ± 1.2	4.1±0.2	4.55±0.25	0.38	97
F7	197 ± 1.1	5.5±0.5	4.55±0.04	0.41	96
F8	201 ± 1.7	5.5±0.3	4.62±0.07	0.29	96
F9	199 ± 1.7	5.7±0.3	4.46±0.07	0.25	97
F10	197 ± 1.1	4.9±0.1	4.48±0.04	0.28	98
F11	198 ± 1.2	5.4±0.2	4.71±0.06	0.39	96
F12	199 ± 1.7	5.5±0.5	4.94±0.08	0.48	95

***In vitro* Buoyancy Studies:** On immersion in 0.1N Hcl solution pH (1.2) at 37±0.5 ^{0}c, the tablets floated, and remained buoyant without disintegration. Formulation F1 to F6 containing HPMC K100 showed highest floating lag time of 52-63 sec, and total floating time of upto12 hrs. The formulation F7 to F12 containing xanthum gum showed floating lag time of 51 sec to 66 sec. This may be due to the amount of polymer. As the polymer concentration got increased the floating lag time got increased (Table 7).

***In vitro* Dissolution Studies:** The tablets containing HPMC K100M (F1, F2, F3andF4, F5, F6) showed the release of 92.91%,91.01%,94.49%,72.79%,93%,102.85% in 5, 6, and 12 hours respectively. These variations in drug release were due to changes in polymer concentrate on

the tablets. However, formulations are failed to meet the desired drug release profile in 12hrs. The results are showed in Fig. 2, Table. 5.

Table 5: *In vitro* Dissolution Data for Formulation F1 to F6 by using HPMC K 100

Time(hrs)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	18.32±1.3	15.69±1.6	13.27±1.5	10.57	16.16±1.3	22.38±1.1
1	24.85±1.7	28.51±1.3	22.05±1.8	16.82±1.1	21.29±1.3	33.79±1.3
2	39.84±1.7	39.14±1.4	35.42±1.5	29.78±1.9	38.42±1.7	49.08±1.4
3	44.24±1.8	42.35±1.5	40.62±1.5	35.59±1.5	56.75±1.9	51.89±1.8
4	58.38±2.4	55.49±1.5	53.31±1.2	46.84±1.7	79.64±1.4	66.46±1.9
5	65.77±0.9	72.47±1.9	69.15±1.7	53.85±1.4	85.83±1.1	78.17±1.4
6	79.68±1.9	81.82±1.3	75.55±0.9	65.45±1.1	93±0.9	85.74±1.3
10	86.47±1.8	91.01±1.9	85.86±1.8	72.79±0.9	--	97.74±1.3
12	92.12±1.4	--	94.49±1.6	--	--	102.85±1.1

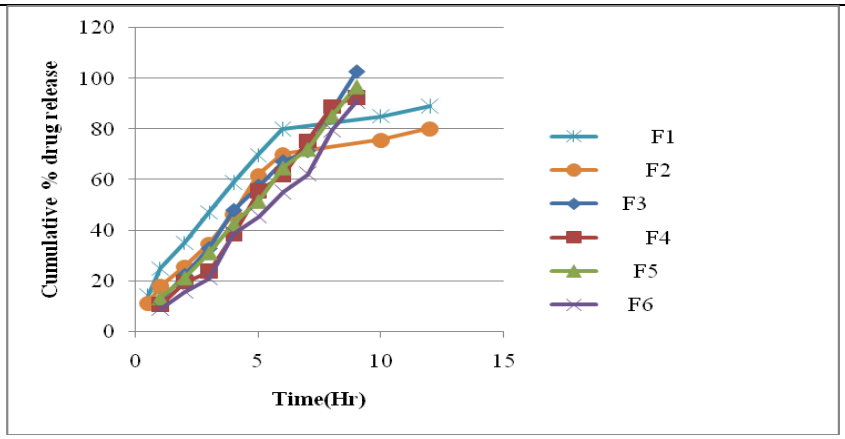

Fig 2: *In vitro* release of Enalapril maleate from HPMC K100M containing formulations

The tablets containing xanthum gum (F7, F8, F9, F10, F11, F12) showed release of 79.97%, 80.26%, 102.14%, 92.75%, 96.85%, 90.89% respectively at the end of 12 hrs. Formulations F11 met the desired drug release profile in 12 hr therefore, considered the best formulation among all the formulations of this series. The results are shown in Fig. 3, Table.6.

Correlation coefficient (R^2) and release exponent (n) values for different kinetic models were shown in Table 8.

Table 6: In vitro Dissolution Data for Formulation F6 to F12 by using xanthum gum

Time(hrs)	Cumulative % drug release					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
0.5	14.29±1.5	11.1±1.4	12.18±1.3	10.56±1.1	13.29±1.5	9.08±1.4
1	25.09±1.0	17.96±1.1	22.35±1.7	19.62±0.3	21.18±1.0	15.94±1.1
2	35.22±1.8	25.72±1.6	32.88±1.9	23.81±1.4	31.15±1.8	21.25±1.9
3	47.18±1.5	34.81±1.5	47.95±0.6	38.35±1.8	42.47±1.5	38.74±1.7
4	58.98±1.5	46.48±1.7	57.57±0.9	55.65±1.9	51.55±1.1	45.59±1.2
5	69.67±1.9	61.79±1.4	67.13±1.8	62.08±1.3	64.75±1.9	55.17±1.4
6	79.97±1.9	70.07±1.1	71.38±1.1	75.5±1.3	72.09±1.4	62.12±1.1
10	--	75.7±0.9	87.5±1.4	89.04±1.5	85.19±1.6	79.49±0.9
12	--	80.26±1.2	102.64±1.8	92.75±1.9	96.85±1.8	90.89±1.2

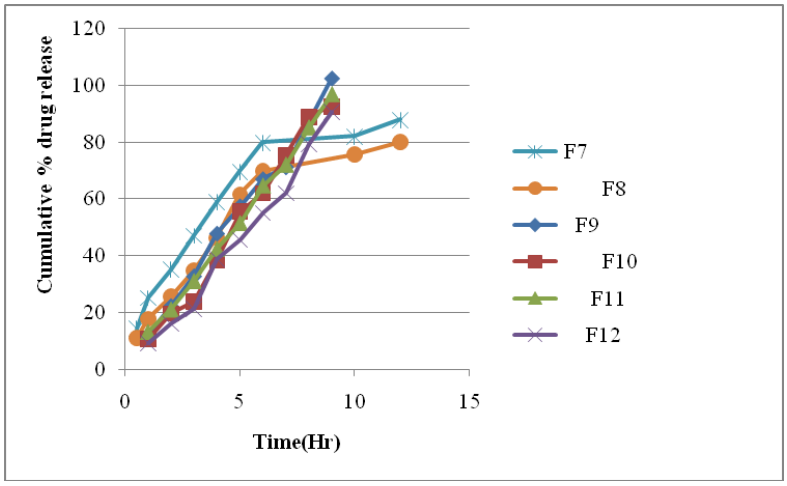

Fig.3: *In vitro* release of Enalapril maleate from xanthan gum containing formulations

Table 7: Floating properties of prepared tablets.

Formulation	Floating lag Time(sec)	Floating time(h)
F1	63	Upto 12
F2	61	Upto 12
F3	55	Upto 12
F4	52	Upto 12
F5	55	Upto 12
F6	63	Upto 12
F7	66	Upto 12
F8	58	Upto 12
F9	57	Upto 12
F10	51	Upto 12
F11	54	Upto 12
F12	53	Upto 12

Table:8 Correlation coefficient (R^2) and release exponent (n) values for different kinetic models.

Formulations	ZERO ORDER	FIRST ORDER	HIGUCHI	HIXSON -CROWELL	KORSEMEYER - PEPPAS	"n"
1	0.88689	0.956916	0.859262	0.251061	0.959653	0.541
2	0.86602	0.979420	0.862597	0.251061	0.966432	0.3706
3	0.90141	0.884218	0.906426	0.251061	0.975166	0.5699
4	0.86339	0.952467	0.922173	0.251061	0.979423	0.6975
5	0.82222	0.35059	0.574517	0.251061	0.877999	0.7462
6	0.87079	0.855388	0.9579	0.251061	0.936897	0.4064
7	0.84203	0.970613	0.982301	0.251061	0.988531	0.5656
8	0.86689	0.963381	0.973684	0.251061	0.989872	0.5933
9	0.92376	0.827966	0.991741	0.251061	0.979567	0.68
10	0.90550	0.822782	0.97419	0.251061	0.855984	0.5744
11	0.99557	0.988557	0.999527	0.251061	0.992406	0.625
12	0.86340	0.85031	0.977652	0.251061	0.881909	0.766

CONCLUSION

By incorporating alkalizing agents into a hydrophilic matrix formulation, it is possible to effectively control the pH within the matrix surrounding the Enalapril maleate molecules and thereby enhance the drug's solubility in the body. This has been accomplished by incorporating electrolyte sodium bicarbonate with a HPMC gel matrix, so that as the dosage form hydrates, a pH is induced that allows Enalapril maleate to solubilize within the hydrated gel region prior to release. The tablets (F11) showed satisfactory results with short buoyancy lag time, long total buoyancy time and controlled drug released up to 12 hrs.

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