Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 4| Issue 4|OCT-DEC|2014|01-19

Research Article
Pharmaceutical Sciences

FORMULATION AND EVALUATION OF FLOATING BILAYER TABLETS OF ATENOLOL AND LOVASTATIN BY USING NATURAL POLYMERS

KALAKUNTLA SAIKRISHNA[1]*, SHIREESH KIRAN[1], UMA MAHESHWAR RAO[1], KEERTHI LEELA[1], B. RAJU[1], K.N. SAI SAINDHYA[1], PRATHIMA BATHINI[2], MUNIRAI NARENDER[2], VEMUNURI NAGARAJU[2] & PENDYALA ANUDEEP

[1]CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad

[2]Care College of pharmacy, Ogulapur, Atmakur Mandal, Warangal

*Corresponding Author Email: sairao.krishna@gmail.com

ABSTRACT

The objective of the present research was to develop a floating bilayer tablet of Atenolol and Lovastatin to control the hypertension. The preparation was done by both wet granulation and direct compression, it consisting of two layers, release retard layer Atenolol and immediate release layer Lovastatin. The sustained layer consists of natural polymers xanthun gum and chitosan and immediate release layer consists of super disintegrant cross povidone and cross carmellose sodium. Sodium bicarbonate was used as gas generating agent which leads to floating in the sustained layer. The immediate layer (FS3) containing 30% of cross povidone and carmellose sodium along with starch was found to be optimum and released 98.6% of lovastatin in 15min. The sustained released layer (FM2) containing 10% of chitosan and 20% of xanthum gum showed sustained released up to 12hr and above. The final optimized formulation (FM2) released 98.9% of Atenolol in 12hrs. The floating lag time and log time of optimized sustained layer showed 5.2 min and above 12hr respectively.

KEY WORDS

Floating bilayer tablet, Atenolol and Lovastatin, Hypertension, Natural Polymers.

INTRODUCTION

Atenolol is a beta-1-blocker which acts primilarily by blocking the beta-1 Adrenoreceptor. Various antihypertensive drug classes are there some of them areDiuretics, Beta-adrenergic blocking agents, Calcium channel blockers, Angiotensin converting enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARBs), Vasodilators, etc. Atenolol is poorly absorbed from intestine, lower GIT and oral bioavailability has been reported to be 50%. The lower intestinal permeability to Atenolol and the extent of absorption is low. So, that increase in gastric residence time will increase in absorption and permeability from stomach, there intern leads to increase in bioavailability. Lovastatin is a HMG coA reductase enzyme inhibitor. This HMG coA reductase enzyme will helps in Synthesis of cholesterol in the body. Inhibition of this enzyme intern inhibits the development of cholesterol. These drugs used in treatment of hyperlipidemia. Lovastatin has a very short half-life of 1.1 to 1.7 hr with a very low bioavailabilty. Hypertension and hypercholestremia will frequently co-exist and requires concomitant or treatment at same time. Safety and efficacy profile of lovastatin given in presence of antihypertensive medication has been evaluated by various researchers. In

the present study, we have attempted to formulate a bilayer floating system of lovastatin and atenolol. The optimized formulation was then considered according to buoyancy studies, lag time, log time, dissolution and drug release studies.

MATERIALS AND METHODS

Drugs: Atenolol, lovastatin. Natural gums like xanthum gum, guar gum, chitosan, pectin, karaya gum and caragenan. Excipients like MCC, crosspovidone, PVP-30, sodium bicarbonate, etc. are brought from the commercial labs.

Preparation of bilayer floating tablets:

Bilayer floating tablets contains two layers i.e., immediate release layer and floating sustained release layer. The immediate release layer contains lovastatin, starch, mannitol, crosspovidone (super disintegrant), and other excipients given in the (table 1). Immediate layer is made by wet granulation. Sustained release layer directly compressed and over it immediate layer is punched. The floating sustained release layer contains Atenolol, sodium bicarbonate as gas releasing agent and other excipients given in (Table 2).

Table 1: Formulation of Lovastatin

S.No	Ingredients(mg)	FS1	FS2	FS3	FS4	FS5
1	Lovastatin	50	50	50	50	50
2	MCC	30	-	-	-	15
3	Lactose	-	30	-	-	-
4	Mannitol	-	-	-	30	-
5	Starch	-	-	30	-	15
6	PVPK-30	5	5	5	5	5
7	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
8	Crospovidone	6	8	4		
9	Croscormellose sodium			4	6	8
10	Talc	2	2	2	2	2
11	Magnesium stearate	5	5	5	5	5
12	Yeellow Iron Oxide	q.s	q.s	q.s	q.s	q.s
13	Total weight(mg)	100	100	100	100	100

Table 2: Formulation of Atenolol layer:

S.No	Ingredients (mg)	FM1	FM2	FM3	FM4	FM5	FM 6	FM 7	FM 8	FM9	FM 10	FM 11	FM 12	FM 13
1	Atenolol	50	50	50	50	50	50	50	50	50	50	50	50	50
2	NAHCO3	50	50	50	50	50	50	50	50	50	50	50	50	50
3	PVP k30	45	45	45	45	45	45	45	45	45	45	45	45	45

4	Xanthan gum	40	80	--	--	--	--	80	120	--	--	--	--	20
5	Chitosan	80	40	--	--	--	--	--	--	--	--	--	--	20
6	Gaur gum	--	--	40	80	--	--	--	--	80	120	--	--	20
7	Pectin	--	--	80	40	--	--	--	--	--	--	--	--	20
8	Karaya gum.	--	--	--	--	40	80	--	--	--	--	80	120	--
9	Carrageenan	--	--	--	--	80	40	--	--	--	--	--	--	--
10	MCC	110	110	110	110	110	110	150	110	150	110	150	110	150
11	Aerosil	5	5	5	5	5	5	5	5	5	5	5	5	5
12	Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10	10
13	Talc	10	10	10	10	10	10	10	10	10	10	10	10	10
14	Total weight (mg)	400	400	400	400	400	400	400	400	400	400	400	400	400

Compression of bilayer tablets:

In this compression process same as a simple tablet, to it some modification using the two die fillings, two hoppers and compressing the tablet for twice. In bilayer tablets first layer punched with low pressure then after second layer punched together in high pressure. If the first layer is punched so hard that the second layer will not bond it, or poorly bond after ejection of tablet the two layers will be separated easily. Through the two hoppers and feed frames assures uniform filling without segregation of particles sizes they may otherwise carry over to the second layer affect layer weight, tablet hardness, content variation, so used colored granulation taken for one layer (immediate layer).

Pre-compression parameters:

a) Bulk density (BD):

It is the total mass per bulk volume of powder. It is measured by pouring the weighed amount of powder (passed through standard sieve#20) into a measuring cylinder and then the initial volume is noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by

BD=m/Vo

Where,

m=mass of the powder

Vo= bulk volume of the powder

b) Tapped density (TD):

It is the total mass per tapped volume of powder. The volume is measured by tappingthepowderfor500times.Againthetappingisdone for 750 times and the tapped volume is noted (the difference between these two

volumesshouldbelessthan2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume is noted. It is expressed in g/cc and is given by:

TD=m/Vi

Where,

m= mass of the powder.

Vi=tapped Volume of the powder

c)Hausner's Ratio (H.R):

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2– 1.5, and is determined by dividing tapped density to bulk density.

H.R = T.D / B.D

d) Compressibility Index (C.I):

The flowability of the powder material can be evaluated by comparing the Bulk density (BD) to the Tapped density (TD) of powder and the rate at which it gets packed down. Compressibility index is calculated using the following formula;

C.I = 100 X (1 – 1/H.R.)

e) Flow properties (angle of repose):

This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The angle of repose of granules is determined by using funnel method. The funnel is fixed at a particular height (2.5cm) on a burette stand. The powder sample is then passed through the funnel until it forms a heap. Further addition of granules is stopped as soon as the heap touches the tip of the funnel. A circle is drawn across it without disturbing the pile. The radius and height of the heap is then noted. The same procedure is repeated for three times and the average value is taken. The angle of repose is calculated by using following equation.

Tan θ =h/r

θ = tan–1(h/r)

Where,

θ =Angle of repose

h =Height of the heap

r =Radius of the heap

Post-compression parameters:

Tablet Thickness:

In this three tablets are randomly taken and then their thickness and diameter are measured by using vernier calipers or by calibrated screw gauze.

Weight Variation Test:

Twenty tablets are selected and weighed individually. Then the average weight and standard deviation is calculated. Test passes when not more than two tablets deviate from the average weight.

Hardness:

It is expressed in kg/cm2 and is measured using Monsanto hardness tester by randomly picking three tablets. Hardness helps in knowing the ability of tablet to withstand mechanical shock during handling.

Friability:

Ten tablets are selected, weighed and then placed in friabilator, which is rotated for 4 minutes at 25 rpm. After 4 minutes, the tablets are weighed again.

%F= [1-(Wt/W)]*100

If % Friability of tablets is less than 1% is considered acceptable.

Disintegration Time:

In this, one tablet is placed in disintegration apparatus containing buffer 0.1N HCl or PBS pH 6.8. The test is carried out at 37^{o}C. The time taken by the tablet to disintegrate is noted as disintegration time.

***In Vitro* Dissolution Studies:**

Dissolution study is performed using USP paddle apparatus. Study is carried out at 37°C temperature and 50 rpm. At various time intervals, 5 ml sample is withdrawn and is replaced with same amount of buffer solution.

Floating Lag Time:

It is the time interval taken by the tablets to start floating. It should be less than one minute. It is measured by using dissolution test apparatus containing 0.1 N HCl (900ml).

Floating Time:

It is the total time, of which the tablet remains in floating state in the given media.

Drug Content Uniformity:

Ten tablets are taken and powdered, equivalent weight of drug dose is measured and transferred to volumetric flask and then buffer is added. Absorbance is determined using U.V spectrophotometer.

Swelling Study:

Initially tablet is weighed (W0) and placed in a glass beaker, containing 200 mL of 0.1 N HCl. This is placed in a water bath maintained at 37 ± 0.5°C. At different time intervals, the tablet is taken out and the excess of liquid is carefully blotted by using a filter paper. The swollen tablet is reweighed (Wt). The swelling index (SI) is calculated using the formula.

SI = (Wt -W0/W0)*100

Wt (Weight of swollen tablet)

W0 (Initial weight of tablet)

RESULTS

Drug excipient compatibility study:

FT-IR studies of pure drug, polymers and drug polymer mixture were done separately to investigate the drug-excipients interactions.

FT-IR spectrum:

The spectrum FT-IR was measured in the solid state as potassium bromide dispersion. The spectrum FT-IR of pure Atenolol, lovastatin and the mixture of Atenolol, lovastatin, xanthum gum and chitosan are presented in Fig. 1, Fig. 2 and Fig. 3 respectively.

Fig.1: FTIR spctraof Pure drug of Atenolol

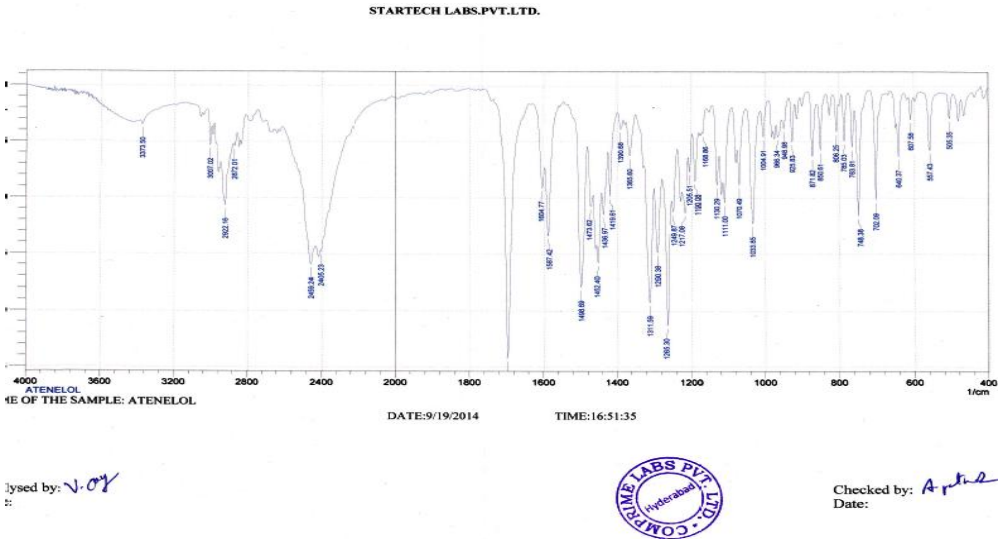


Fig.2 : FTIR spctra of Pure drug of Lovastatin

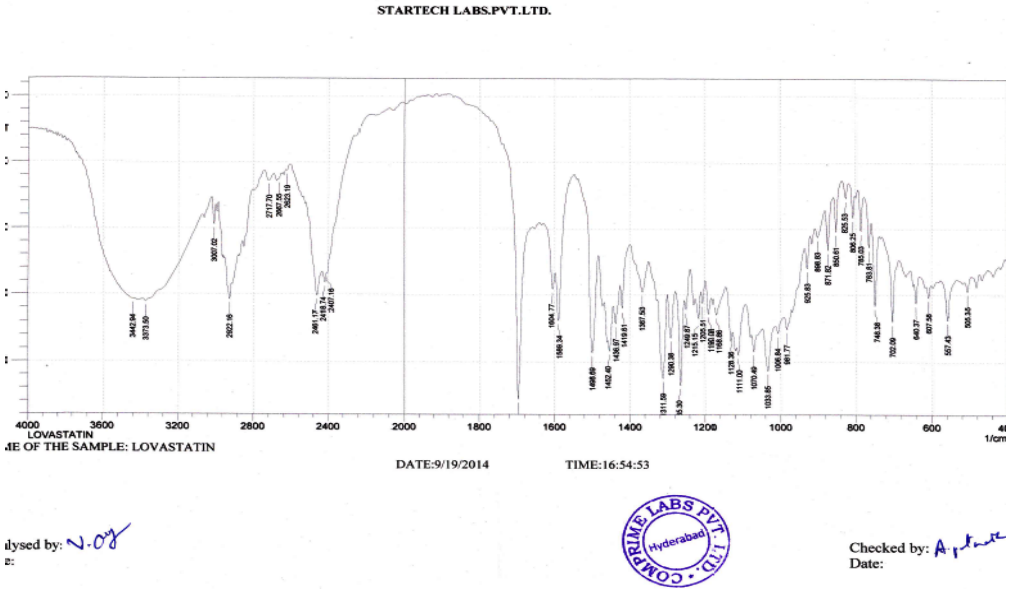
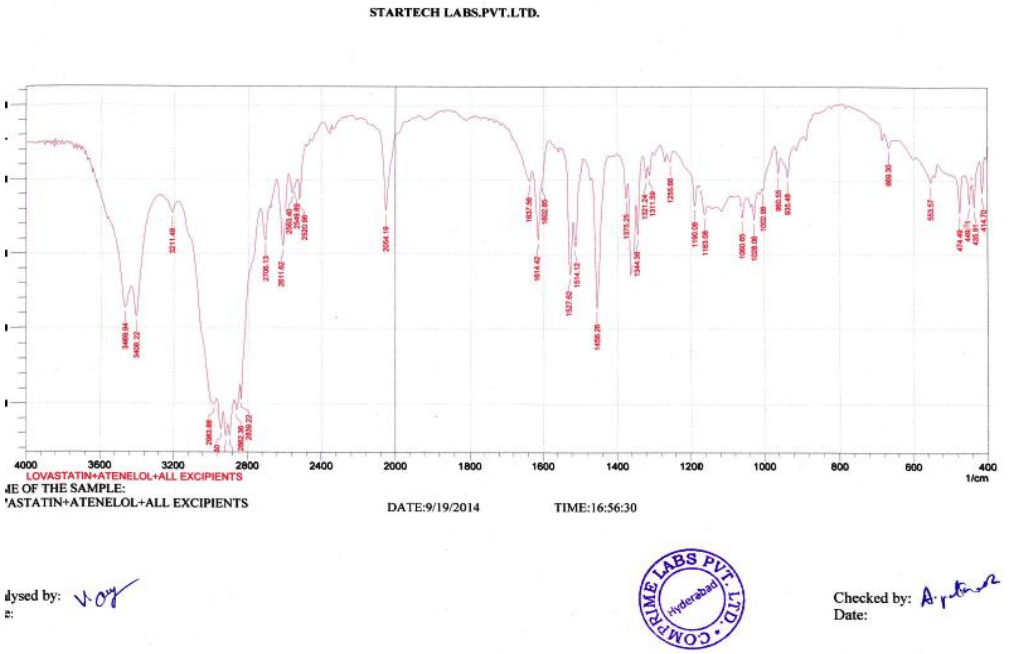


Fig.3: FTIR spctra of Optimised formula



The FT-IR spectra of drug and polymers revealed that, the major frequencies of functional groups of pure drug remain intact in the mixture containing different polymers. Hence there is no interaction between the drug and polymers used in the study.

Floating characteristics:

Maximum formulations are floated more than 12hrs with in a lag time of up to 5.2 min. swelling of the tablets was observed, which gave floating ability to formulations. 12.5% concentration of sodium bicarbonate was found to be optimum

for obtaining low lag time and prolonged floating time.

Drug content:

Atenolol FM2 (99.75±0.1) and lovastatin (99.63±0.7) contents was found to be within the acceptable range.

IN VITRO DRUG RELEASE

Atenolol

The release of Atenolol was found to be a function of the polymer concentration. All formulations retarded the release of drug for 12hr. The effect of xanthum gum and chitosan at different concentrations (30% of different combinations) on release of Atenolol from tablet matrices was studied. Figure 3 shows the release profile of drug from the different combination in different polymers matrices respectively. It was observed that xanthum gum and chitosan (FM2) retarded the drug release more than the guar gum and pectin combination. The diffusion exponent of 'n' values (0.471-0.626) indicated that the release mechanism is non-fickian or anomalous transport. The release data were fitted to different kinetic models and based on correlation R, the best fitted models were determined (Table-19).The formulation FM3 followed zero order kinetics while other formulations followed either Korsmeyer-Peppas model or Hixson-Crowell model.

Lovastatin:

The immediate release layer of the floating bilayer tablets disintegrated, and liberated lovastatin. All the formulations liberated or released more than 90% lovastatin content within 30min (Table-9). A concentration of 15% of starch was found to be optimum.

Hardness: Hardness of all formulations was found to be between (6.7±0.5Kg/cm^2) and did not affect the floating characteristics and the drug release (Table-8).

Table 3: Evaluation of precompression parameters of Lovastatin

Blend Formulation code	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index	Hausner's ratio
FS1	25.6±0.31	0.50±0.01	0.57±0.02	12.0±1.2	1.14±0.02
FS2	25.1±0.45	0.48±0.08	0.57±0.01	15.7±1.62	1.18±0.02
FS3	25.6±0.21	0.46±0.06	0.55±0.08	16.3±0.79	1.19±0.01
FS4	25.2±0.23	0.47±0.047	0.54±0.04	14.2±0.78	1.16±0.01
FS5	25.6±0.15	0.48±0.047	0.55±0.04	12.7±0.44	1.14±0.05

Table 4: Evaluation of pre compression parameters of Atenolol blend

Pre compression parameters	Angle of Repose (θ) (± SD)	Bulk Density (g/cc) (± SD)	Tapped Density (g/cc) (± SD)	Carr's Index (%) (± SD)	Hausner ratio (± SD)
FM1	23.26±0.11	0.301±0.07	0.350±0.05	14.1±0.06	1.16±0.05
FM2	23.7±0.08	0.306±0.09	0.341±0.09	11.7±0.05	1.11±0.07
FM3	24.7±0.16	0.304±0.09	0.361±0.11	15.5±0.09	1.18±0.05
FM4	24.7±0.12	0.314±0.12	0.351±0.08	10.2±0.06	1.11±0.09
FM5	24.2±0.09	0.308±0.14	0.350±0.09	12.3±0.13	1.13±0.06
FM6	25.1±0.11	0.304±0.08	0.351±0.08	13.3±0.08	1.15±0.09
FM7	24.2±0.12	0.318±0.09	0.361±0.13	11.9±0.11	1.13±0.07
FM8	23.7±0.09	0.304±0.12	0.343±0.09	11.3±0.05	1.12±0.05
FM9	24.2±0.13	0.312±0.15	0.360±0.11	13.8±0.05	1.16±0.07
FM10	25.5±0.13	0.3051±0.17	0.354±0.16	13.5±0.05	1.15±0.07
FM11	23.7±0.07	0.310±0.13	0.352±0.04	11.9±0.07	1.13±0.08
FM12	22.7±0.06	0.301±0.11	0.347±0.07	13.2±0.10	1.15±0.11
FM13	22.2±0.04	0.30±0.10	0.345±0.10	13.0±0.12	1.13±0.13

Table 5: Preformulation characters of Optimized Floating bilayer tablet of Atenolol and Lovastatin

S.No	Preformulation characters	Atenool	Lovastatin
1	Bulk density	0.306g/cc	0.46g/cc
2	Tapped density	0.34g/cc	0.55g/cc
3	Hausner's ratio	1.11	1.19
4	Angle of repose	23.7^0	25.6^0

Table 6: Evaluation of postcompression parameter of Lovastatin

Formulation	Uniformity of weight(mg)	Mean Thickness (mm)	Mean Hardness (Kg/cm^2)	Friability (%)	Mean % Drug Content
FM1	88	0.87±0.05	3.3±0.5	0.535	96.70±0.31
FM2	87	0.80±0.11	3.4±0.2	0.692	98.75±0.13
FM3	87	0.87±0.04	3.3±0.4	0.505	99.67±0.73
FM4	84	0.80±0.05	3.2±0.1	0.473	98.65±0.73
FM5	88	0.87±0.06	3.3±0.5	0.648	97.24±0.41

Table 7: Evaluation of post compression parameter of Atenolol

Formulation	Uniformity of weight(mg)	Mean Thickness (mm)	Mean Hardness (Kg/cm^2)	Friability (%)	Mean % Drug Content
FM1	399.3±1.64	2.75±0.07	5.1±0.3	0.435	98.70±0.3
FM2	400.1±1.91	2.85±0.08	5.4±0.2	0.492	99.75±0.1
FM3	400.7±1.24	2.8±0.13	5.3±0.4	0.501	99.42±0.7
FM4	400.3±1.02	2.8±0.11	5.5±0.6	0.463	98.52±0.7
FM5	400.5±1.61	2.85±0.15	5.3±0.5	0.478	98.54±0.4
FM6	400.7±1.81	2.8±0.04	5.2±0.7	0.342	98.63±0.7
FM7	400.5±1.62	2.85±0.03	5.5±0.9	0.414	98.85±1.1
FM8	400.3±1.02	2.85±0.05	5.5±0.2	0.417	99.42±1.0
FM9	400.7±1.43	2.8±0.03	5.2±0.4	0.318	99.14±1.2
FM10	400.1±1.56	2.85±0.06	5.1±0.5	0.412	98.86±0.5
FM11	400.1±1.53	2.85±0.07	5.2±0.6	0.416	98.70±0.7
FM12	400.6±1.44	2.8±0.04	5.2±0.4	0.514	98.65±0.8
FM13	400.1±1.42	2.78±0.05	5.1±0.3	0.355	98.92±0.4

Table 8: Post compression parameters of the floating bilayered tablet formulation

Bilayered Tablet	Average Weight mg (n=20) (± SD)	Hardness Kg/cm^2 (n=3) (± SD)	Thickness mm(n=3) (± SD)	Friability %(n=3) (± SD)	Drug content	
					Lovastatin	Atenolol
FS3 &FM2	**487.07±1.3**	**6.7±0.5**	**3.74±0.63**	**0.73±0.13**	**99.63±0.7**	**99.17±0.42**

Table 9: Disintegration Time for Lovaststin IR tablets

S.no	Formulation	Disintegration time (sec)
1	FS1	28 ± 2.52
2	FS2	33 ± 1.02
3	FS3	30 ± 2.85
4	FS4	41 ± 1.75
5	FS5	38 ± 1.96

Buoyancy studies

All the formulations showed satisfactory results for buoyancy studies and they were as reported in the Table 10.

Table 10: Buoyancy Studies of Batches FM1 – FM13 and FO1

Formulation	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
FM1	380	>12
FM2	330	>12
FM3	352	>12
FM4	360	>12
FM5	350	>12
FM6	342	>12
FM7	364	8
FM8	347	9
FM9	364	10
FM10	340	>10
FM11	358	>12
FM12	336	8
FM13	372	10

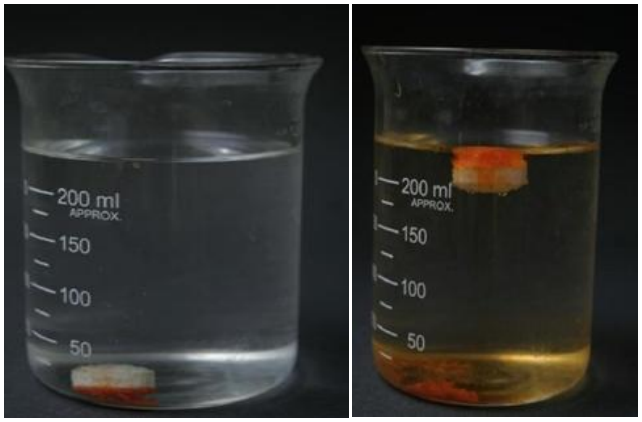
Swelling study

Swelling study was performed on all batches (FM1 to FM13) for 3 hrs. The results of % swelling index are shown in table 11.

Swelling Index of Batches FM1 – FM13 Table no: 11

Time (hrs)	% Swelling Index												
	FM1	FM2	FM3	FM4	FM5	FM6	FM7	FM8	FM9	FM10	FM11	FM12	FM13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	25.2	29.4	31.3	20.5	31.3	39.7	34.5	42.7	44.9	32.7	42.0	26.2	36.3
2	35.5	41.9	45.3	37.5	40.2	43.8	42.5	45.0	47.1	41.8	51.7	32.3	42.9
3	40.9	44.6	48.7	39.5	47.0	54.6	46.6	53.3	61.2	45.0	59.7	35.2	45.3

Fig no. 4



At 0 time **At 5 Min**

Table 13: *In Vitro* Dissolution Data for Batches FM1 – FM13

Time (hrs)	FM1	FM2	FM3	FM4	FM5	FM6	FM7	FM8	FM9	FM10	FM11	FM12	FM13
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	18.7	14.2	9.25	25.2	38.1	18.4	17.2	20.6	17.6	19.1	17.6	37.1	15.6
1	24.7	19.9	13.6	38.3	43.5	25.2	25.7	26.6	24.2	23.5	27.3	40.5	23.7
2	31.5	28.5	20.1	51.0	49.3	38.3	36.4	41.4	39.5	31.8	40.6	49.2	39.5
3	47.0	39.5	27.2	59.1	54.4	45.6	46.6	47.1	43.4	39.9	54.6	55.8	45.1
4	58.7	45.1	35.6	61.5	61.3	51.9	52.4	55.3	47.7	47.3	55.4	58.6	49.3
5	63.5	54.1	46.4	68.1	69.6	53.4	57.6	59.8	58.3	55.3	56.6	60.1	58.4
6	75.2	59.3	52.6	71.2	71.5	55.3	62.2	63.5	64.8	63.4	58.6	64.3	59.2
7	84.8	65.4	63.8	81.4	75.2	59.5	82.9	86.4	82.9	69.3	60.6	67.5	60.1
8	87.1	74.5	68.7	99.5	79.3	63.4	99.6	96.4	91.2	74.3	63.7	68.5	61.6
9	91.2	81.1	77.7	-	81.4	66.4	-	100	92.5	81.4	65.5	-	63.2
10	95.1	88.7	84.2	-	85.7	68.6	-	-	94.5	84.1	69.4	-	65.3
11	95.1	93.8	89.3	-	87.1	71.3	-	-	-	-	71.2	-	-
12	102.0	98.3	92.5	-	89.4	77.4	-	-	-	-	74.5	-	-

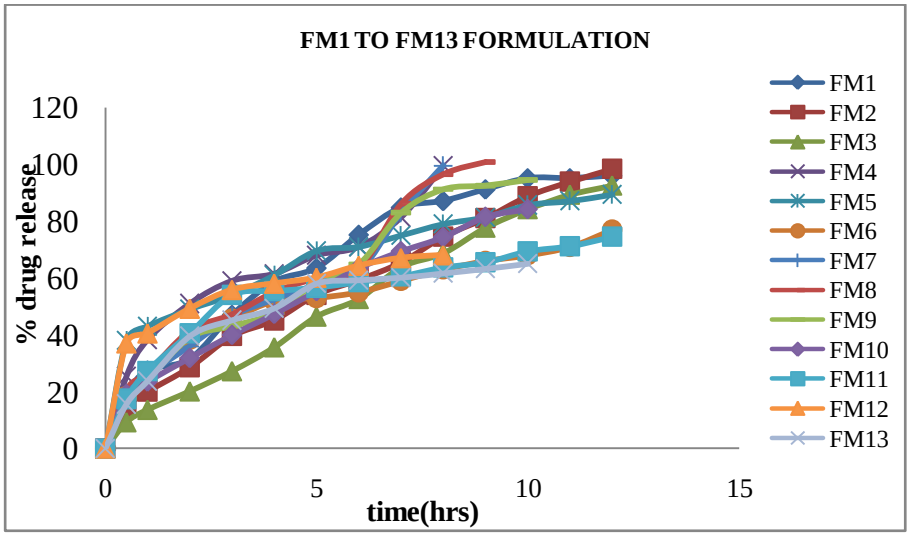


Fig 5: Dissolution profile of Atenolol (FM1 to FM13)

Table 14: *In Vitro* Dissolution Data for Batches FS1 – FS5

Time (mins)	Cumulative % drug release				
	FS1	FS2	FS3	FS4	FM5
0	0	0	0	0	0
5	84.15	70.65	45.0	58.0	20.2
10	85.05	71.11	60.5	91.8	70.2
15	85.95	71.54	77.0	91.8	71.5
20	-	-	81.0	91.9	71.5
30	-	-	99.7	92.4	72.4

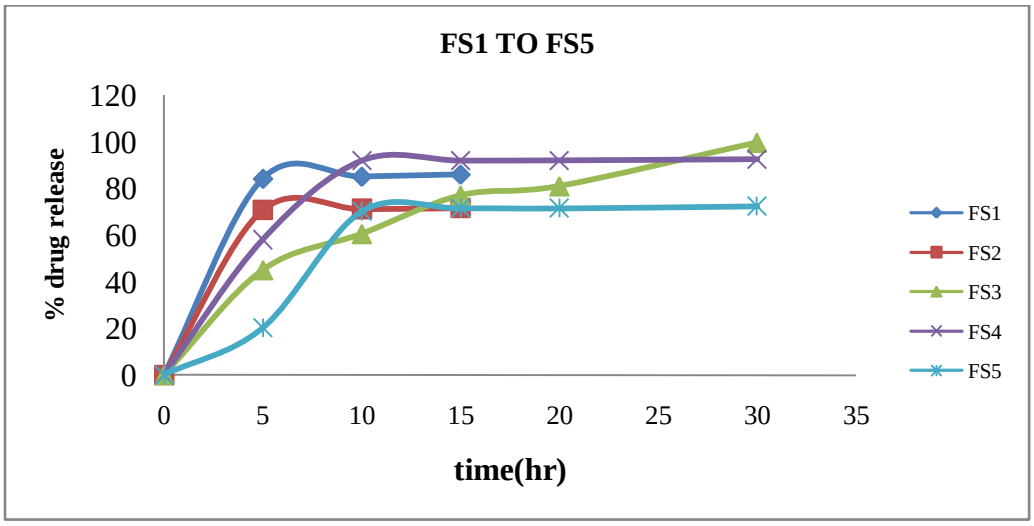


Fig 6: Dissolution profile of Lovastatin(FS1 ToFS5)

Table 15: Floating Behaviour of the bilayer tablets:

S.NO	Floating lag time	Floating time
1	5.2 Min	12-24hr

Table 16: Treatment of Dissolution Data in to Different Models of Atenolol

Formulation	Zero order(R^2)	First order (R^2)	Higuchi(R^2)	Koresmeyer peppas(R^2)	(n)
FM1	0.930	0.977	0.987	0.981	0.557
FM2	0.982	0.839	0.980	0.994	0.626
FM3	0.992	0.942	0.954	0.987	0.771
FM4	0.889	0.611	0.968	0.961	0.423
FM5	0.816	0.976	0.955	0.979	0.290

FM6	0.918	0.958	0.981	0.986	0.427
FM7	0.956	0.582	0.938	0.977	0.579
FM8	0.958	0.778	0.955	0.966	0.543
FM9	0.962	0.927	0.968	0.979	0.577
FM10	0.963	0.984	0.990	0.983	0.523
FM11	0.791	0.908	0.947	0.949	0.421
FM12	0.700	0.845	0.899	0.985	0.226
FM13	0.810	0.893	0.958	0.960	0.471

Tab 17: Treatment of Dissolution data in different models of Lovastatin

Formulation	Zero order(R^2)	First order(R^2)
FS1	0.616	0.633
FS2	0.609	0.643
FS3	0.859	0.831
FS4	0.581	0.677
FS5	0.644	0.504

Tab 18: Results of kinetic studies for optimized formulation FO1

S.no	Formulation	Zero order R^2	First order R^2	Higuchi R^2	Kores meyer peppas R^2	n	Mechanism of drug release
1	FO1	0.295	0.110	0.245	0.996	0.661	Non fickian diffusion

Tab.19: Best Fitting Model for the Formulated Batches

Formulation	n value	Drug release mechanism	Best fit model
FM1	0.557	Non Fickian Anomalous transport	Higuchi-Matrix
FM2	0.626	Non Fickian Anomalous transport	Korsmeyer-Peppas
FM3	0.771	Non Fickian Anomalous transport	Zero order
FM4	0.423	Fickian diffusion	Higuchi-Matrix
FM5	0.347	Fickian diffusion	Korsmeyer-Peppas
FM6	0.290	Fickian diffusion	Korsmeyer-Peppas
FM7	0.579	Non Fickian Anomalous transport	Korsmeyer-Peppas

FM8	0.543	Non Fickian Anomalous transport	Korsmeyer-Peppas
FM9	0.577	Non Fickian Anomalous transport	Korsmeyer-Peppas
FM10	0.523	Non Fickian Anomalous transport	Higuchi-Matrix
FM11	0.421	Fickian diffusion	Korsmeyer-Peppas
FM12	0.226	Fickian diffusion	Korsmeyer-Peppas
FM13	0.471	Non Fickian Anomalous transport	Korsmeyer-Peppas

DISCUSSION

In the present work, the main objective was to Design and Evaluation of Floating bilayer tablets of Atenolol and Lovastatin. Atenolol is the most widely used oral antihypertensive in the world. Atenolol shows high aqueous solubility and low cell membrane permeability. Atenolol has absorption window in stomach and upper part of GIT up to intestine, there is a need to develop gastro retentive drug delivery. Lovastatin is HMG coA reductase inhibitor, when combination of Atenolol and Lovastatin it is a broad and complementary spectrum of antihypertensive action. In order to achieve the development of a combination of conventional and sustained release dosage forms, currently, the bilayer technology with multiple layers having a rapid and sustained phase has been investigated. This formulation can be used for the treatment for type-hypertension. Atenolol and Lovastatin in 0.1N HCl was scanned in the UV wavelength region of 200 – 400 nm for maximum absorption. The Atenolol λ_{max} was found to be at 263nm and Lovastatin was at 265nm. Standard curve of the drug prepared in 0.1N HCl showed a linear relationship between the concentration and absorbance values in the range of 0-30µg/ml, R^2 value was found to be 0.999 for Atenolol, and for Lovastatin absorbance values in the range of 0-20µg/ml, R^2 value was found to be 0.999.

Compatibility studies:

The IR Spectrum of pure Atenolol, Lovastatin and other excipients was compared with the IR spectrum of formulated Atenolol sustained release and immediate release of Lovastatin tablets. The IR spectrums of the formulation werematching with the IR spectrum of pure Atenolol and Lovastatin (Fig no. 1, 2 and 3). There is no appearance or disappearance of any characteristics peaks. This shows that there is no interaction between the drug, excipients and polymers used in the tablets. (Ajit Kulkarni et al., 2009 p.15-25)

Evaluation of blend materials of Bilayer tablets:

The preformulation studies of both drugs Atenolol and Lovastatin were evaluated for various physical properties individually and the values are present in the table no. (Table no: 3 and 4). From the observations Atenolol has shown poor compressibility and poor flow then by addition of 5% glidant it show the good flow properties. Lovastatin shows good flow properties.

Angle of repose for layer 1 granules (Atenolol SR layer) was found to be between22.2°–25.1° and layer 2 granules (Lovastatin IR layer) was found to be between 25.1°–25.67°, which is well within the specified limit of 20^0-30^0 and the type of flow is good.

Bulk density for layer 1 granules was found to be between 0.301–0.318g/ml and layer 2 granules was found to be between 0.47-0.5g/ml.

Tapped density for layer 1was found to be between 0.343–0.361g/ml and layer 2 granules was found to be between 0.54– 0.57g/ml.

Carr's index for layer 1 was found to be in the range of 10.2–15.5 and for layer 2 was found to be in the range of 12.01–16.3. All the granules are well within the specification limit.

Hausner's ratio for layer 1 was found to be between 1.11–1.16 and for the layer 2 was found to be between 1.14–1.19 With this the granules were found to be free flowing material and showed suitability to be compressed as tablets of expected weight.

Evaluation post compression parameters

For Atenolol layer:

The mean thickness of the tablets was in the range of 2.85±0.08mm. The measured hardness of the tablets was in the range of 5.42-5.6 kg/cm^2. The % friability was in the range of 0.493 – 0.495. The mean % drug content was found to be in the range of 98 – 99.7%. The average weight of the formulated tablets was in the range of 400.1±1.91. The % deviations were within the prescribed limits as per USP.

For Lovastatin layer:

The mean thickness of the tablets was in the range of 0.87±0.05mm. The measured hardness of the tablets was in the range of 3.2-3.3 kg/cm^2. The % friability was in the range of 0.53-0.69. The mean % drug content was found to be in the range of 96.7 – 99.6%. The average weight of the formulated tablets was in the range of 88. The % deviations were within the prescribed limits as per USP.

Evaluation of Floating Bilayer tablets:

All the formulations of bilayer tablets fulfilled the official requirements of uniformity of dosage units. The average percentage of deviation of 20 tablets of each formula was less than ±3% (Table no: 8). The thickness of all the formulations of bilayer tablet rangedfrom3.74±0.63mm (Table no: 8).

The hardness and percentage friability of all batches ranged from 6.7-8Kg/cm2and 0.5 – 0.73% respectively (Table no: 8), and the average weight of the formulated tablets was in the range of 487.07±1.3mg.

***In-vitro* drug release studies of Bilayer tablets:**

Based on the preformulation data, Xanthun gum along with chitosan and MCC was taken as drug release retardants for sustained release layer of Atenolol. MCC acting as a filler and Xanthun and chitosan is the release controlling polymer.

The formulation consists of two layers, Sustained release layer of Atenolol (400 mg), layer -1.

An immediate release layer of Lovastatin (100 mg), layer2

Layer 1 – Atenolol:

Batches FM 1 and FM 2 sustained layer consists of xanthan gum along with chitosan. The xanthan gum along with chitosan concentration of 30%. PVP concentration was 10.5 In the two formulation the weight of the tablet was adjusted with MCC to 400 mg, exhibited mean cumulative % drug release of 102%, 98.3% and 92.5% at the end of 12 th hr.

Batches FM 3 and FM4 sustained layer consists of Guar gum along with Pectin. The Guar gum along with Pectin concentration of 30%. PVP concentration was 10.5 in the two formulations the weight of the tablet was adjusted with MCC to 400 mg, exhibited mean cumulative % drug release of 92.5% and 89.4% at the end of 12 th hr.

Batches FM 5 and FM6 sustained layerconsists of Karaya gum along with Carrageenan. The Karaya gum along with Carrageenan concentration of 30%. PVP concentration was 10.5 in the two formulations the weight of the tablet was adjusted with MCC to 400 mg, exhibited mean cumulative % drug release of 89.4% and 77% at the end of 12 th hr.

In case of FM7 & FM8 formulation only xanthum gum polymer is used. But concentration is different. In order to retard the release of the drug to be meet the specification limits, the Xanthum gum conc. was increased from20 to30%. (Table no: 1). FM7 formulation exhibited cumulative % drug release was 99.6% at the end of 8thhr, and in FM8 formulation 100.7% drug release was observed at the end of 9th hr.

In FM9 and FM10 guar gum concentration 20% and 30% are used.

Where the release of the drug in FM 9 and FM10 formulations exhibited 94.5% and 84.1% at the end of 10th hr.

In case of FM11 and FM12 Carrageenan concentration 20% and 30% are used. In FM11 formulation exhibited 84.1% mean cumulative % drug release observed at the end of 10th hr.In case of FM12 formulation cumulative % drug release was 68% at the end of 12th hr.

In FM13 all the four natural polymers were used xanthan gum, guar gum, chitosan and pectin were used. In case of FM13 formulation the concentration are taken 5% each and exhibited drug release was 65% at the end of 10th hr.

The tablets on contact with 0.1N Hcl medium, the hydrochloric acid in medium reacted with the sodium bicarbonate in the tablet matrix inducing the formation of CO_2 gas. This CO_2 was trapped in the matrix by the gel formed by hydration of polymers, which contributed the buoyant force required for floating of the tablets.

The floating lag time increased with the increase in polymer concentration. In layer 1 formulation FM1, FM2, FM3, FM5, FM6, and FM11 formulations are floated for more than 12h formulation. In case of FM3 formulation compared to FM1 and FM2 formulation the polymer conc. is more, it helps the retard the drug release more compared to FM1 & FM2. In FM4 formulation the polymer conc. is less compared to FM5 & FM6, the drug is easily disintegrated in the 0.1 N HCl. In case of FM1 formulation % drug release in the initial hrs was predicted but at the end of 12thhr the drug release was more. In FM5 & FM6 this both formulations are showing good floating time up to 12hrs, but drug release is less, so this is not optimized formula. In this FM7 and FM8 formulation the matrix of the batch FM7 & FM8 started to disintegrate causing erosion and formed a viscous gel like layer on the top of the dissolution medium which to an extent retarded the drug release. FM10 &FM11 formulation the swelling index increased with increased in the polymer conc. The combination of polymers had more index than with than with individual polymers. FM12 & FM13 are also the same.

In FM2 formulation the outer matrix got hydrated by the dissolution medium and formed into a viscous gel like layer around the tablet.

Tablets with both xanthan gum along with chitosan showed higher drug retardation than when either of the polymers was used alone. Initially the burst release of drug in the first few hours was attributed to the time needed by the polymer to get hydrated and form a release retarding gel layer, MCC is used as gel forming agent.

Layer– 2 (Lovastatin)

In the FS all formulation, immediate release layer of Lovastatin was prepared by wet granulation method with CP & CCS, Magnesium stearate, PVPK-30, Yellow Iron Oxide but diluents is changed.

From FS1 –FS5 formulation CP & CCS values are constant i.e., 3.25 mg. But the diluents is different , but concentration is same that is 43.5 mg the weight of the tablet was adjusted with diluents up to 100 mg, in FS1 formulation MCC is used, the mean cumulative % drug release 85.9% was observed, with in the 15 min.

In case of FS2 formulation lactose is used as diluents, the 71.5% drug release was observed in 15 min.

The immediate release layer FS3 combination of cross povidone and croscarmellose sodium along with starch is used 99.7% drug release was observed in 30 min.

In FS4, formulation the diluents mannitol is used, the 92.45%drug release was observed in 30 min. But in case of FS5 formulation the combinations of diluents are used that are starch and MCC. The 72.4% drug release was observed in 30 min.

Among all formulations from FS1 to FS5 the FS3 formulation is the best formulation because in this the starch and mannitol are used as a diluents and CP and CCS are used as a super disintegrating agents, and starch also acting as a disintegrating agent, so it helps the release of the drug is more and quickly . These super disintegrating agents are responsible for burst mechanism.

Super disintegrants are the agents that promote fast disintegration of the tablets by increasing water penetration and dispersion of the matrix. Here, in this study cross povidone, croscarmellose were used a super disintegrants and were evaluated for their effect on dissolution and disintegration of Lovastatin layer. Fixed dose combinations (or) combination therapy (Two or more active ingredients in one dosage form) offer several advantages such as lower cost, improved efficacy, better compliance as number of doses/ pills per day decreases, and fewer side effects. Thus currently focus is shifting fast to fixed dose combinations in the form of bi layer (or) multi-layer dosage forms to treat diseases like Diabetes, Hypertension, Tuberculosis, HIV etc.

Mathematical model fitting of the data obtained from in vitro release study of formulation FO1 for sustained release layer:

The data obtained from in vitro release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion for optimized formulation (FO1). Thus the release of the drug from the dosage form was found to be diffusion and non-fickian release.

CONCLUSION

The present research work was carried out to develop a floating bilayer tablet of Atenolol as sustained release layer was prepared by

xanthum gum along with chitosan and filler MCC. From results obtained, it was conclude that the Atenolol containing xanthan gum and chitosan with MCC was taken as optimized formula. The Immediate release layer was prepared by using super disintegrant such as Crospovidone, Croscormellose sodium in order to match the innovator product. The result demonstrated that initially burst release was due to CP and CCS as Super disintegrants in immediate release formulation & followed by Sustained release formulation

SuccessoftheInvitrodrugreleasestudiesrecommendstheproductforfurtherin vivo studies, which may improve patient compliance. From the literature Atenolol and Lovastatin, individual dosage form was used in the management of hypertension. Combination of Lovastatin as immediate release layer and Atenolol as sustained release layer improves the patient compliance. From the results formulation FM2 and FS3 has been selected as best formulation among all the other formulations. By using FM2 and FS3 formulation compress a tablet of FO1. It provides better *invitro* release from layer 1as well as layer 2. The data obtained from *in vitro* release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion for optimized formulation (FO1).

Thus the release of the drug from the dosage form was found to be diffusion and non- fickian Anomalous transport release.

REFERENCES

1. S Gilbert Banker, R NeilAnderson., tablets. In LeonLachman, HerbertaLiebermann, Joseph L Kanig. (Edition), thetheory and practice of Industrial pharmacy,3rded.Leaand Febiger,Philadelphia,1987,page.no.(a)293-294,(b)330-331, (c) 430-431.
2. Available on online URL:www.wikipedia.com.
3. M.AAbraham., A Shirwaikar., Formulation of multilayered sustain release tablets using insoluble matrix systm e., Indian Journal of Pharmaceutical Science.1997;59(6): pageno. 312-315.
4. C William Gunsel and G Robert. Busel.,compressioncoatedandlayertablets,
1. 1987, In: Herbert A Libermann, LeonLachman, Joseph.B.SchwartzPharmaceutical dosageform: Tablets2ndeditionmarcelDekkar,Inc.,Newyork1989,pageno.1,274.
5. V Iannucelli , G Coppi, MT Bernabei , R Camerorni . Air compartment multiple-unit System for prolonged gastric residence.Part-I.Formulation study.Int J Pharm 1998; 174:47-54.
6. R Garg , GD Gupta . Progress in controlled gastroretentive delivery systems. Trop J Pharm Res 2008; 7(3):1055-1066.
7. SP Vyas , RK Khar . Controlled drug delivery: Concepts and advances.VallabhPrakashan Delhi; 2002;1:123-231
8. BSDave,AF Amin ,M Patel . Gastrorentive drug delivery system of Ranitidine HCl formulation and in vitro evaluation. AAPS PharmaSci Tech., 2004; 5:1-10.
9. .RHejazi, M Amiji,. Stomach-specific anti-H.Pylori therapy. I: Preparation and characterization of tetracycline of a floating multiple-unit capsule, high-density loaded chitosan microspheres. Int J Pharm 2002; 235:87-94.
10. W Sawicki .Pharmacokinetics of verapamil and nor verapamil from controlled release floating pellets in humans. Eur J Pharm Biopharm 2001; 53:29-35.
11. VBMBabu , RK Khar . In vitro and In vivo studies of sustained release floating dosage forms containing salbutamol sulphate.Pharmazie 1990; 45:268-270.
12. SSangekar Evaluation of effect of food and specific gravity of the tablets on gastric retention time. Int J Pharm 1985; 35:34-53.
13. BN Singh ,KH Kim . Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release.2000; 63:235-259.
14. S Gopalakrishnan ,AChenthilnathan . Floating Drug Delivery Systems: A Review. J PharmaSciTechnol 2011;3(2):548-554.
15. SP Yyas ,KKRoop . Controlled Drug Delivery Concepts and Advances, First Edition, New Delhi, 2002; 196-217.

16. PDHaan ,CF Lerk . Drug delivery systems: an approach to oral controlled drug delivery via gastric retention 1984.
17. SJ Hwang, H Park. Gastro retentive drug-delivery systems. Cri Rev Ther Drug Carr.Syst, 1998; 15:234-284.
18. GS Banker, CT Rhodes. Modern Pharmaceutics. Marcel Dekker, New York 1996; 3:125.
19. MMarvola , A Kannikoski ,H Aito . The effect of food on gastrointestinal transit and drug absorption of a multiparticular sustained-release Verapamil formulation. Int J Pharm 1989; 53: 145-55.
20. SP Vyas ,RK Khar . Controlled drug delivery: Concepts and advances. Vallabh Prakashan Delhi; 2002;1:123-231
21. BS Dave ,AF Amin ,M Patel. Gastrorentive drug delivery system of ranitidine HCl formulation and in vitro evaluation. AAPS PharmaSci Tech 2004; 5:1-10.
22. RHejazi ,M Amiji .Stomach-specific anti-H. Pylori therapy. I: Preparation and characterization of tetracycline of a floating multiple-unit capsule, a high-density loaded chitosan microspheres. Int J Pharm 2002; 235:87-94.
23. Harkrishan Sinsh & V.K Kapoor. Medicinal and pharmaceutical chemistry, second edition-2005, reprint-2007, page no; 377.
24. K. Dtripathi: Essentials of Medical pharmacology 5th edition, page no; 235-45.
25. K.Dtripathi: Essentials of Medical pharmacology 5th edition, page no; 246-50.

***Corresponding Author:**
Kalakuntla Saikrishna