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FORMULATION AND EVALUATION OF FLOATING BILAYER TABLETS OF FUROSEMIDE

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ABSTRACT

The present work was carried out to design the floating drug delivery system to minimize the side effects, improve the prolongation of action, to reduce the frequency of administration. The objective of the present investigation was to develop a bi-layer floating tablets and to evaluate furosemide using direct compression technology. Xanthium gum, sodium bicarbonate, pvpk30 and some other ingredients are used and formed floating layer. The sustained layer contained furosemide and various ratios of polymers such as HPMC-K100M, HPMC-K4M. The floating behavior and in vitro dissolution studies were carried out in a USP XXIV type 2(paddle) apparatus in a stimulated gastric fluid. Final formulation released approximately 105% drug in 12 h in vitro, while the floating lag time was 105 sec and the tablet remained floatable throughout all the studies. Statistically significant differences were found among the drug release profile from different formulations. Final formulation that showed no change in appearance and the results generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug.

KEYWORDS: floating drug delivery, furosemide, bilayer tablets, HPMC-K100M, HPMC-K4M.

INTRODUCTION

It is known that the short stay of active material released from controlled-release oral preparations in the region that they are absorbed, specifically in the gastrointestinal (GI) tract, leads to bioavailability problems. Thus, to prolong the passage time of the preparations through the GI tract, it has been suggested that (a) addition of certain fatty acids such as triethanolamine and cetyl palmitate to the formulations used since it is known that they may reduce the gastric emptying rate; (b) preparation of bioadhesive systems by adding polymers to the formulations, which may attach to the surface of GI epithelium and (c) development of floating dosage forms that may remain on the contents of the stomach because of they have a lower density than that of the stomach.[1]

Floating dosage forms (hydrodynamic balanced systems, HBS) are oral dosage forms of tablets, capsules, or microbeads and contain hydrocolloids that allow floating by swelling. Effervescent granules or floating chambers may also be added to the formulations to provide floating.[2] For the following instances, it has been suggested that an active material should be formulated in the form of an HBS to enhance its bioavailability: (a) having dissolution and/or stability problems in the fluids of the small intestine, (b) being effective locally in the stomach and (c) being absorbed only in the stomach and/or upper part of the small intestine.[2]

It has been reported that furosemide (FR), the active material used in the present study, has a bioavailability problem and it initially shows an adverse temporary peak diuretic effect.[3] To eliminate such an effect, various efforts have been made for the preparation of FR in prolonged-release forms. However, it has been reported that the bioavailability of such preparations has been decreased to 40–60% compared to conventional tablet forms.[4] Although it has not been shown for humans, it has been pointed out in all animal studies of bioavailability that there may be regions in the stomach and/or upper the part of the small intestine in which FR is specifically absorbed; it has been thought that the short stay of controlled release preparations in this specific region of absorption leads to bioavailability problems.[5-7] Accordingly, this study was designed to enhance the bioavailability of FR by prolonging its duration in the stomach via the floating dosage forms with controlled release**.**

MATERIALS AND METHODS

Furosemide was obtained as gift sample from Sura labs Hyderabad. Magnesium stearate, Talc, Sodium bicarbonate, sodium lauryl sulphate were procured from sd fine-chem. Ltd Mumbai, and micro crystalline cellulose, HPMCK4M, HPMCK15M, HPMCK100M, Xanthium gum, poly vinyl pyrolidineK30 were obtained from essel fine chem, Mumbai and all other chemicals/solvents used were of AR grade.

Preparation of Bilayer Floating Tablets

Tablets were prepared by direct compression technology using camdach single punch machine. Bilayer floating tablets were prepared in two stages. First stage was formulation of floating layer tablets. The active ingredients such as xanthium gum, talc magnesium stearate, pvpk30, NAHCO3, micro crystalline cellulose, are mixed geometrically and compressed to produce floating layer tablets. Second stage was formulation of bilayer floating tablets.[8] The drug, polymer, SLS, Talc, magnesium stearate are mixed separately for sustained release layer. Floating layer was placed in punching die. Then contents of sustained release layer were placed over the floating layer tablet and compressed to produce bilayer floating tablets. The composition details of Bilayer floating tablets are given in Table-1a &1b.

Composition of floating layer tablets Table 1a:

INGREDIENTS	F1	F2	F3
Xanthium gum	300mg	300mg	300mg
Talc	4mg	4mg	4mg
Magnesium Stearate	4mg	4mg	4mg
PVPk30	20mg	20mg	20mg
NAHCO3	35mg	52.5mg	70mg
MCC	QS	QS	QS
Total weight	400mg		

Composition of sustained release layer tablets Table 1b:

INGREDIENTS	F4	F5	F6	F7	F8	F9	F10	F11	F12
HPMCK4M	40mg	80mg	120mg						
HPMCK15M				40mg	80mg	120mg			
HPMCK100M							40mg	80mg	120mg
SLS	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	300mg								

EVALUATION OF FLOATING BILAYER TABLETS[9-12]

The formulations were evaluated for weight variation, thickness, friability, hardness, disintegration time, (The data is presented in Table-2) and in vitro dissolution study.

Weight variation

Weight variation was done by selecting 20 tablets randomly and weighing individually. Average weight was calculated and the weight of individual tablet was compared with it.

Thickness

The thickness was measured using Vernier Caliper and expressed in mm.

Friability

Friability test was performed using a Roche friability testing apparatus. It is performed 100 to access the effect of friction and shocks which may often cause table to chip, cap or break. This device subjects a number of tablets to the combine effect of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm, dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed tablet sample is placed in friabilator which is then operated for 100 revolutions. The tablets are then dusted and re-weighed. The % friability was measured using following formula:

$$\% F = [(W\text{-}W0)/W0] \times 100$$

Where; %F = Friability in percentage, W = initial weight of tablet, W0 = Weight of tablet after test.

Hardness

The strength of tablet is expressed as tensile strength (kg/cm^2). The tablet crushed load, which is the force required to break a tablet into halves by compression. It was measured using a tablet hardness tester (Monsanto hardness tester).

Disintegration time

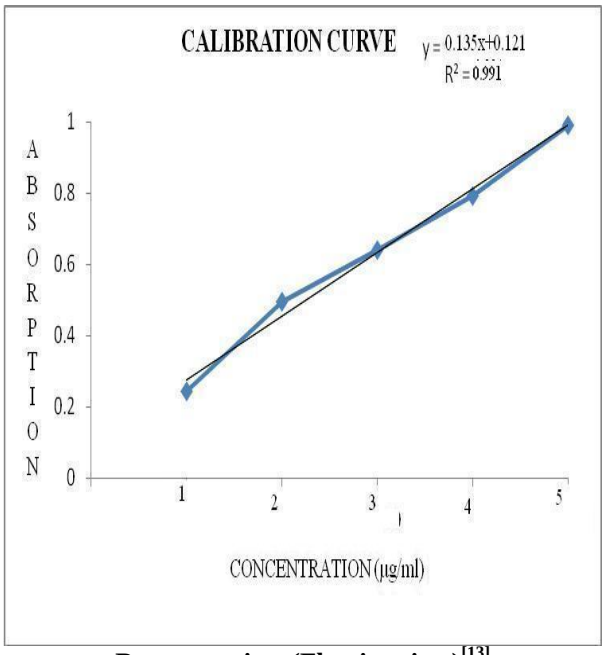
One tablet was placed in each of six tubes of disintegration test apparatus. The test was carried out at 37 ± 2^0C according to USP XX11 at 50 rpm. Disintegration test apparatus was used without disc. Time required for complete disintegration of tablet fragments through sieve (#10) was considered as a disintegration time of tablet.0.1N HCL, pH 1.2, 900 ml was used as disintegrating medium and time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Table 2: floating evaluation parameters-:

PROPERTIES	F1	F2	F3
Weight variation(mg)	694mg	700mg	704mg
Hardness(kg/cm$^{2)}$	4.5±3	4.4±2	4.3±5
Thickness (mm±S.D)	2.3±0.03	2.1±0.01	2.2±0.02
%Friability	o.31	0.21	0.28
Disintegration time (sec)	40	35	45

Procedure for standard curve

First the stock solution was prepared by dissolving 10mg of furosemide in 9 ml of acetone (1000µg/ml). From this the second solution was prepared by diluting 1ml to 10ml of mixed 0.1N HCL (10$^{0\mu}$ g/ml). from the second stock solution, third solution was prepared by diluting 1ml to 10ml of mixed 0.1N HCL (10µg/ml).from the third stock solution 1, 2, 3, 4, 5 and 6 and 10µg/ml dilution were prepared. The absorbance of each sample was measured at 248nm. Standard curve of concentration vs. absorbance was plotted. R^2=0.991.



Buoyancy time (Floating time)[13]

A tablet was introduces in to beaker containing 100ml of 0.1 N HCL. The time taken by the tablet to come up to the surface and floated was taken as the buoyancy time. An average of three determinations was taken for the floating forms.

Table 3a:

	F1	F2	F3
Floating lag time	240sec	120sec	78sec
Floating Duration	>24hrs	>24hrs	18hrs

Table 3b:

Floating Lag time	105 sec
Floating Duration	>24hrs

In vitro dissolution studies

The in vitro dissolution studies were performed by using the USP XX1V type 11 (paddle) apparatus at 37 ± 0.5^{0}C and at 50 rpm and 0.1 N HCL (Ph 1.2) as dissolution media. The samples were removed at predetermined intervals by maintaining sink condition. Each removed samples was filtered by using 0.45µ filter. The samples were analyzed at 248 nm for estimation of furosemide by UV/VIS spectrophotometer.

TABLE 4: F4 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.198	1	13.94366	12.5493	15.68662
1	0.298	1	20.98592	18.88732	23.60915
2	0.398	1	28.02817	25.22535	31.53169
3	0.458	1	32.25352	29.02817	36.28521
4	0.587	1	41.33803	37.20423	46.50528
5	0.645	1	45.42254	40.88028	51.10035
6	0.745	1	52.46479	47.21831	59.02289
7	0.898	1	63.23944	56.91549	71.14437
8	0.121	10	85.21127	76.69014	95.86268
12	0.132	10	92.95775	83.66197	104.5775

TABLE 5: F5 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.077	1	5.422535	4.880282	6.100352
1	0.17	1	11.97183	10.77465	13.46831
2	0.372	1	26.19718	23.57746	29.47183
3	0.626	1	44.08451	39.67606	49.59507
4	0.833	1	58.66197	52.79577	65.99472
5	0.045	10	31.69014	28.52113	35.65141
6	0.078	10	54.92958	49.43662	61.79577
7	0.098	10	69.01408	62.11268	77.64085
8	0.111	10	78.16901	70.35211	87.94014
12	0.124	10	87.32394	78.59155	98.23944

TABLE 6: F6 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.055	1	3.873239	3.485915	4.357394
1	0.087	1	6.126761	5.514085	6.892606
2	0.124	1	8.732394	7.859155	9.823944
3	0.175	1	12.32394	11.09155	13.86444
4	0.21	1	14.78873	13.30986	16.63732
5	0.354	1	24.92958	22.43662	28.04577
6	0.412	1	29.01408	26.11268	32.64085
7	0.468	1	32.95775	29.66197	37.07746
8	0.512	1	36.05634	32.4507	40.56338
12	0.542	1	38.16901	34.35211	42.94014

TABLE 7: F7 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.102	1	7.183099	6.464789	8.080986
1	0.145	1	10.21127	9.190141	11.48768
2	0.156	1	10.98592	9.887324	12.35915
3	0.168	1	11.83099	10.64789	13.30986
4	0.187	1	13.16901	11.85211	14.81514
5	0.296	1	20.84507	18.76056	23.4507
6	0.387	1	27.25352	24.52817	30.66021
7	0.459	1	32.32394	29.09155	36.36444
8	0.545	1	38.38028	34.54225	43.17782
12	0.782	1	55.07042	49.56338	61.95423

TABLE 8: F8 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.05	1	3.521127	3.169014	3.961268
1	0.062	1	4.366197	3.929577	4.911972
2	0.082	1	5.774648	5.197183	6.496479
3	0.121	1	8.521127	7.669014	9.586268
4	0.132	1	9.295775	8.366197	10.45775
5	0.235	1	16.5493	14.89437	18.61796
6	0.345	1	24.29577	21.8662	27.33275
7	0.452	1	31.83099	28.64789	35.80986
8	0.478	1	33.66197	30.29577	37.86972
12	0.512	1	36.05634	32.4507	40.56338

TABLE 9: F9 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.057	1	4.014085	3.612676	4.515845
1	0.115	1	8.098592	7.288732	9.110915
2	0.356	1	25.07042	22.56338	28.20423
3	0.625	1	44.01408	39.61268	49.51585

4	0.094	1	6.619718	5.957746	7.447183
5	0.143	1	10.07042	9.06338	11.32923
6	0.169	1	11.90141	10.71127	13.38908
7	0.209	1	14.71831	13.24648	16.5581
8	0.231	1	16.26761	14.64085	18.30106
12	0.332	1	23.38028	21.04225	26.30282

TABLE 10: F10 FORMULATION

TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.078	1	5.492958	4.943662	6.179577
1	0.112	1	7.098592	7.098592	8.873239
2	0.156	1	9.887324	9.887324	12.35915
3	0.189	1	11.97887	11.97887	14.97359
4	0.219	1	13.88028	13.88028	17.35035
5	0.256	1	16.22535	16.22535	20.28169
6	0.279	1	17.6831	17.6831	22.10387
7	0.306	1	19.39437	19.39437	24.24296
8	0.371	1	23.51408	23.51408	29.39261

TABLE 11: F11 FORMULATION

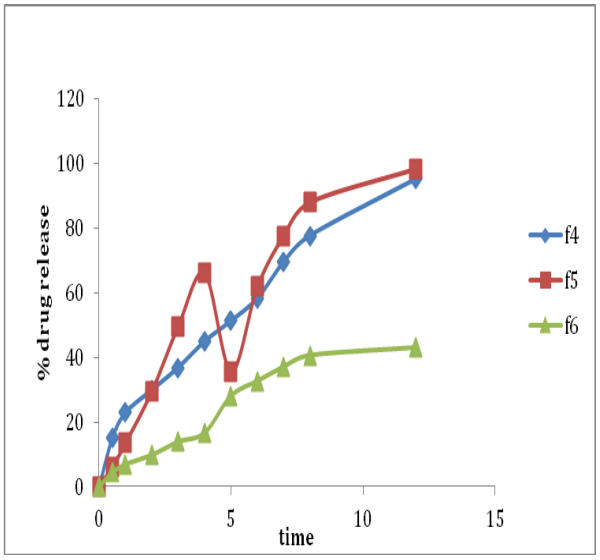
TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.052	1	3.661972	3.295775	4.119718
1	0.071	1	0.5	0.45	0.5625
2	0.074	1	0.521127	0.469014	0.586268
3	0.084	1	0.591549	0.532394	0.665493
4	0.974	1	6.859155	6.173239	7.716549
5	0.984	1	6.929577	6.23662	7.795775
6	0.123	10	8.661972	7.795775	9.744718
7	0.135	10	9.507042	8.556338	10.69542
8	0.147	10	10.35211	9.316901	11.64613

TABLE 12: F12 FORMULATION

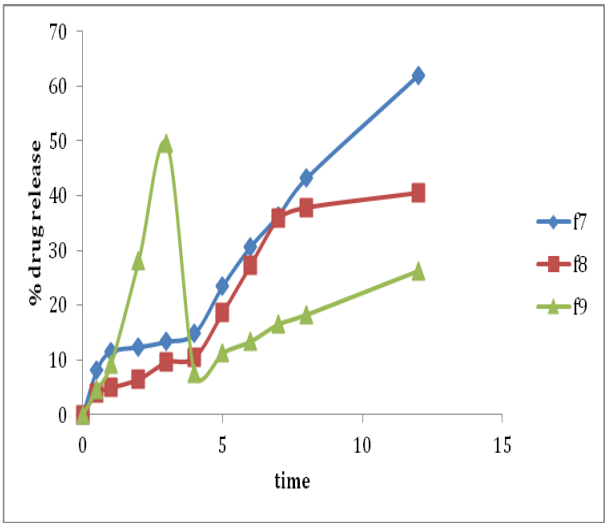
TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.343	1	2.415493	2.173944	2.71743
1	0.446	1	3.140845	2.826761	3.533451
2	0.494	1	3.478873	3.130986	3.913732
3	0.564	1	3.971831	3.574648	4.46831
4	0.57	1	4.014085	3.612676	4.515845
5	0.645	1	4.542254	4.088028	5.110035
6	0.656	1	4.619718	4.157746	5.197183
7	0.698	1	4.915493	4.423944	5.52993
8	0.726	1	5.112676	4.601408	5.751761

TABLE 13: OPTIMISED FORMULATION F4

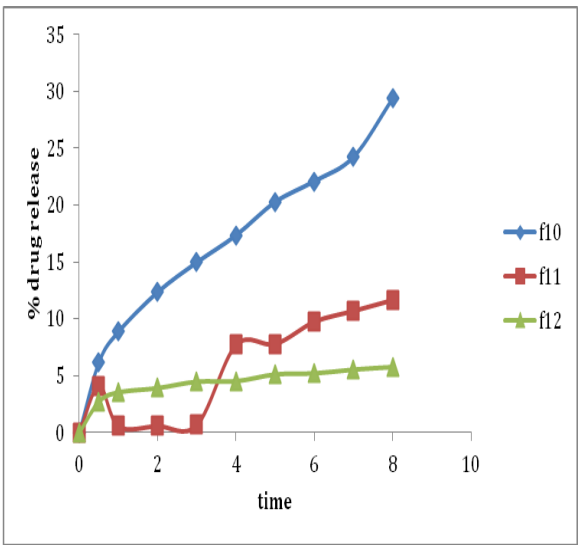
TIME	ABSORBANCE	D.F	CONCENTRATION	AMOUNT	%D.R
0.5	0.189	1	13.30986	11.97887	14.97359
1	0.289	1	20.35211	18.3169	22.89613
2	0.378	1	26.61972	23.95775	29.94718
3	0.465	1	32.74648	29.47183	36.83979
4	0.567	1	39.92958	35.93662	44.92077
5	0.647	1	45.56338	41.00704	51.2588
6	0.735	1	51.76056	46.58451	58.23063
7	0.878	1	61.83099	55.64789	69.55986
8	0.098	10	69.01408	62.11268	77.64085
12	0.12	10	84.50704	76.05634	95.07042



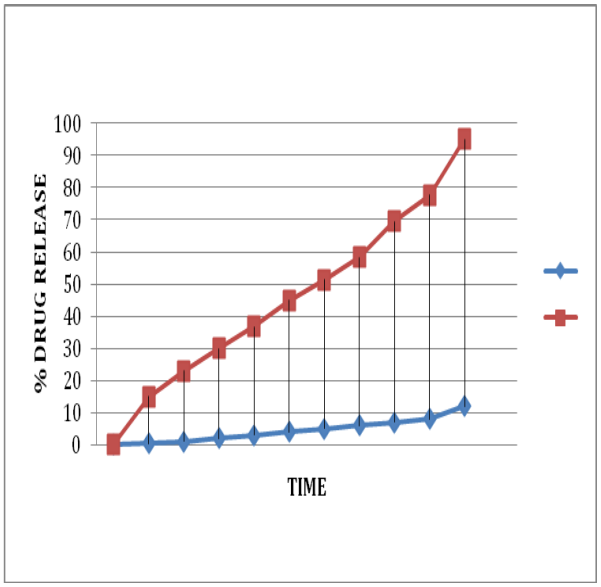
Comparisons of % drug release for formulations F4, F5, F6:



Comparisons of % drug release for formulations F7, F8, F9:



Comparisons of % drug release for formulations-F10, F11, F12:



OPTIMISED FORMULATION GRAPH %D.R vs. time:

8. RESULTS AND DISCUSSION

The evaluation parameters of floating bilayer tablets (F4 to F 12) such as weight variation, thickness, friability, and hardness were determined in table-1a. The hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in pharmacopoeia. Buoyancy lag time and duration of floating were determined using 100ml beaker containing 0.1N HCL medium as shown in table 3a & 3b. The floating bilayer formulations F4 to F12 were subjected for the dissolution studies using USP dissolution apparatus 2 (paddle) in 900ml of 0.1N HCL medium. The results and values are given in tables 4 to 13. The formulation F4 showed a constant rate of release in a sustained manner with good buoyancy property. Hence F4 was chosen as the best formulation. The first three formulations (F1 to F3) are performed for optimizing the formulations by altering the sodium bicarbonate concentrations; from this the F2 formulation was suitable for performing all the formulations. From that F4 was the optimized formulation showed best results.

9. CONCLUSION

The present work was done to produce floating bilayer tablet of furosemide with good sustained release property. The tablets were obtained by direct compression for all the formulations F1to F12 and evaluated for the buoyancy lag time and floating time. Based on the performance with respect to the buoyancy lag time, floating time and the release characteristics, the formula (F4) was selected as the best formula, as it showed a buoyancy time 105 sec and a floating time >24hrs. This formulation (F4) showed a sustained release rate throughout its release period.

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