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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF BILAYERED FLOATING TABLET OF DILTIAZEM DRUG

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ABSTRACT
Aim of study was to develop bilayered floating drug delivery for treatment of hypertension by delivering loading and maintenance dose for fast achievement of peak plasma concentration and maintaining the same respectively. The prepared drug loaded bilayered floating tablets were evaluated for pre and post compression parameters. Stability study of the promising formulation was also performed. The tablets were prepared by direct compression method. The loading dose was delivered in the form of immediate release layer prepared by different super-disintegrations and maintenance dose was delivered through sustained release layer prepared by using polymers like HPMC K15M and Carbopol 934P. Both the immediate release layer and sustained release layers were separately optimized and then combined to optimize the bilayered floating tablets. No interactions were found between drug and excipients. Formulation containing crosscarmellose sodium shows immediate drug release. Formulation Containing HPMC K15M shows sustained release action and bilayered formulations FB7 shows releases up to 12 hours with good buoyancy and total floating time. All the Bilayered floating formulations buoyant up to 12 hrs. Bilayered floating tablets with release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.
Key words: Diltiazem, Bilayered floating tablet, sustain release tablet

INTRODUCTION

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface.[1,2]

The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.[1]

Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged gastric retention time of the floating forms, improved bioavailability of drugs and improved clinical situations.

These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcelluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy time.[1]

Bilayer tablet is new era for developing a combination of two or more active pharmaceutical ingredient in single dosage form, Promoting patient convenience and compliance. Two or more ingredients to be formulated together inspite of active having different physico-chemical characteristics (active incompatibility). Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as multi-layer matrix tablet.[1]

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.[1]

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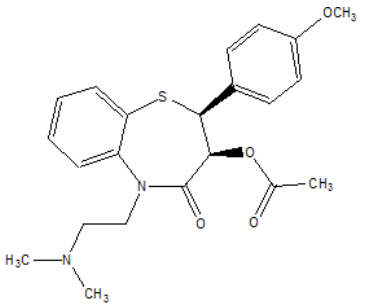

Chemical name: Cis-(+)-[2-(2-dimethylaminoethyl)-5-(4-methoxyphenyl) -3-oxo-6-thia-2-azabicyclo [5.4.0] undeca-7, 9, 11-trien-4-yl] ethanoate [1]

Diltiazem is similar to other peripheral vasodilators. Diltiazem inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ioncontrol gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.[1,2]

FORMULATION

Table 1: Formulation of Immediate Release Tablets

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Diltiazem HCL	30	30	30	30	30	30	30	30
Sodium starch glycolate	**10**	**20**	-	-	-	-	-	-
Croscarmellose Sodium	-	-	**10**	**20**	-	-	-	-
Crospovidone	-	-	-	-	**10**	**20**	-	-
Sodium bicarbonate	-	-	-	-	-	-	**10**	**20**
Micro crystalline cellulose	60	50	60	50	60	50	60	50
Total	100	100	100	100	100	100	100	100

Table 2: Formulation of Sustained Release Floating Tablets

Ingredients (mg)	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Diltiazem HCL	60	60	60	60	60	60	60	60
HPMC K15M	75	150	75	150	75	150	75	150
Sodium bi carbonate	10	10	20	20	10	10	20	20
Tartaric acid	10	10	10	10	20	20	20	20
Microcrystalline cellusoe	141	66	131	56	131	56	121	46
Mg. Stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Total (mg)	300	300	300	300	300	300	300	300

Table 3: Formulation of Bilayered Floating Tablets

Ingredients (mg)	**FB1**	**FB2**	**FB3**	**FB4**	**FB5**	**FB6**	**FB7**	**FB8**
Immediate Release								
Diltiazem HCL	30	30	30	30	30	30	30	30
Croscarmellose sodium	10	10	10	10	10	10	10	10
Sustained Release								
Diltiazem Hcl	60	60	60	60	60	60	60	60
HPMC K15M	75	150	75	150	75	150	75	150
Sodium bi carbonate	10	10	20	20	10	10	20	20
Tartaric acid	10	10	10	10	20	20	20	20
Microcrystalline cellulose	151	76	141	66	141	66	121	56
Mg. Stearate	2	2	2	2	2	2	2	2

1. post-compression parameters: immediate release tablets

Batch	Weight Variation (mg) (n=3)	Thickness (mm)	Hardness (kg/cm^2)(n=3)	Disintegration time (sec)
Fl	100.0±1.92	1.80±0.02	4.4±0.12	79.66±1.32
F2	100.2 ±1.93	1.12±0.04	*4.3=0.05*	58.00±1.00
F3	1011±1.77	1.75±0.07	4.8=0.16	4800=1.57
F4	100.3 ±1.25	1.26=0.09	*4.5=0.25*	84.33=1.98
F5	103.5±2.72	1.92±0.03	4.7±0.15	73.30±1.63
F6	102.3±1.98	1.65±005	4.9±0.10	75.33±1.51
F7	102.1 ±*1.85*	1.70±0.08	4.2±0.05	62.33±1.84
F8	102.4 =1.98	1.90±0.0 1	4.0=0.03	64.34=1.72

2. post-compression parameters: for sustained release floating tablets

Batch	Weight Variation (mg) (n=3)	Thickness (mm)	Hardness (kg/cm^2)(n=3)	Buoyancy Lag time (sec)	% Swelling
F9	300.0±1.92	3.21±0.04	5.4±0.13	99	96.98
F10	299.5±196	3.22±002	50±0.05	78	97.1
F1l	300,3±1,58	3.23±0.01	5,9±0,19	65	97.57
F12	304 ±1.62	3.26±0.09	6.2±0.24	101	97.79
F13	299.6±1.72	3.10±0.05	6.7±0.15	89	98.11
F14	3003±158	3.11±003	5.1±0.12	120	98.15
F15	300.1±1.55	3.10±0.07	5.2±.07	108	99.8
F16	300.0 ±1.78	3.12±0.08	5.0±.03	109	99.11

3. post compression parameters: for bilayered floating tablets

Batch	Weight Variation (mg) (n=3)	Thickness (mm)	Hardness (kg/cm^2)	Buoyancy lag rime (sec)
FB1	350.00±085	351±004	50±013	100
FB2	349.08±0.74	352±0.02	5.1±0.05	99
FB3	35010±099	3A9±0O1	5.3±019	66
FB4	3495O±0.91	*358±0O9*	59±024	102
FB5	349.90±1.12	3.67±0.05	5.7±0.15	101
FB6	350.00±0.79	3.66±0.03	5.2±0.12	115
FB7	350.09 ±0.77	369±007	50±018	105
FB8	350.00±1.78	3.78±0,08	5.6±0.11	110

EVALUATION STUDY[1,2]

1. Hardness

The resistance of tablets to breakage under the conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulationwas measured by Monsanto hardness tester.[1]

2. Friability

Friability was measured by Roche friability tester. 10 tablets were kept in the friability tester and it was rotated at 25 rpm for 4 minutes. Initial and final weights were then recorded and friability was calculated by following formula.[2]

Friability= Initial weight-Final weight/ Initial weight ×100

3. Weight variation test

To study weight variation, 20 tablets were taken and were weighed individually and the weight variation was calculated with the use of standard deviation weight values were reported in mg.[1]

4. *In vitro* drug release studies:

In Vitro drug release studies were performed using USP dissolution test apparatus (Type 2). The dissolution studies were performed in 900 ml of 1.2 pH dissolution medium which was stirred at 50 rpm at 37±0.5°C.[1]

5. Swelling index

Swelling index was done on the prepared tablet by using 200ml beaker containing 0.1NHCL.The Temperature maintained at 37^0 C .the tablets were tested for 12hrs.the -tablets were carefully removed using a small basket, and the weight of each tablet was determined. [2]

$$\text{Swelling index} = (Wt - W_0) \times W_0 / 100$$

Where, W_t=Weight of tablet at time t, W_0 = Initial weight of tablet at 0 time

6. Buoyancy lag time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. The tablets were placed in a 100 ml glass beaker containing 0.1M HCL as per IP. The time required for the tablet to rise to the surface and float was determined as floating lag time. [2]

7. Floating time

Test for buoyancy is usually performed in Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time. [2]

8. Stability studies

The optimized formulation was charged for the accelerated stability studies according to ICH guidelines (40 ± 2ºC and 75 ± 5% RH) for a period of 3 months in a stability chamber. The optimized formulations were placed in USP type-I flint vials and hermetically closed with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at 30, 60 and 90 days and evaluated for the drug content and In Vitro drug release.[2,20]

9. *In Vitro* Drug Release

1. Immediate release

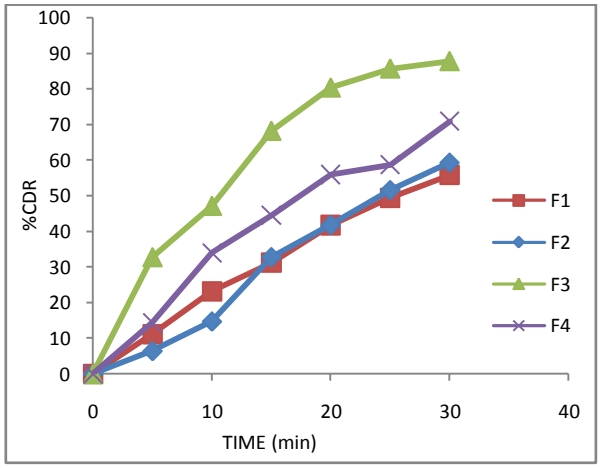

Figure 1: % Cumulative drug release for F1-F4

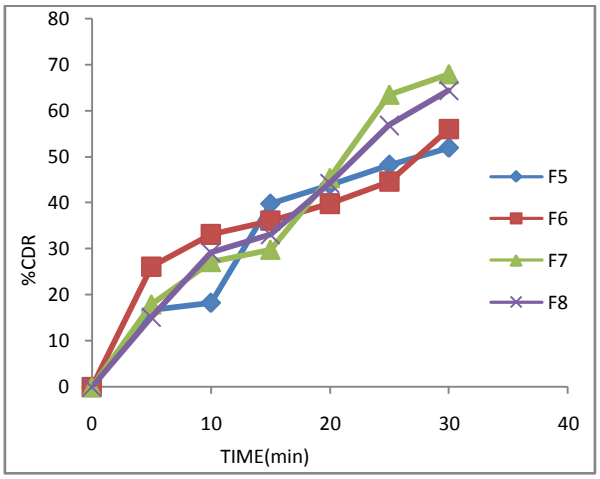

Figure 2: %Cumulative drug release for F5-F8

2. Sustained release

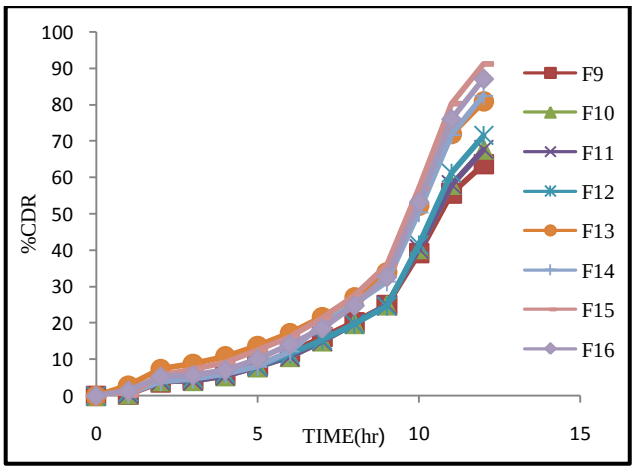

Figure 3: %Cumulative drug release for F9-F16

3. Bilayered release

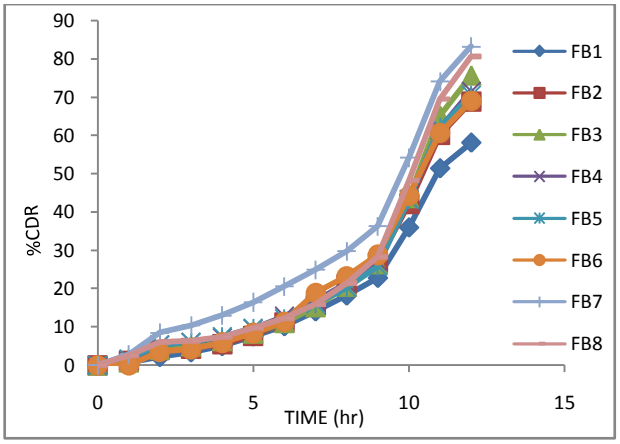

Figure 4: % Cumulative drug release for FB1-FB8

6. Stability study

Formulation code	Parameter	Storage time			
		Initial	1 month	2 months	3 months
FB7	Drug content (%)	99.97	99.60	99.45	98.05

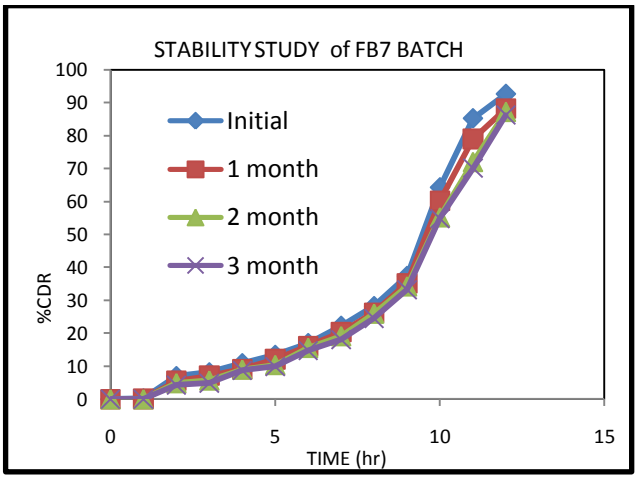

Figure 5: %Cumulative drug release for FB7

CONCLUSION

Bilayer floating tablet of Diltiazem HCl tablet was prepared by direct compression method. The Tablets Containing HPMC K15M polymer Showed The high degree of swelling. All the floating formulations buoyant up to 12 Hr. Formulation F15 containing HPMC K15M show better sustained release action. Formulations **FB7** releases up to 12 hours and it shows good buoyancy and total floating time. Bilayered floating tablets with release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site of absorption.

REFERENCES

1. Seth P Tossounian J, "The hydrodynamically balanced system HBS^{TM}, A novel drug delivery system for oral use."Drug Dev.Ind.Pharm.1984,10,313-339
2. Lachman L, Liberman H Koing J, The theory and Practice of Industrial Pharmacy,3rd Ed.Vargheese Publishing House,Bombay,1991,430
3. Yie WC,Text Book of Novel drug delivery system, 2nd Marcel Dekker Inc.New York,1992,2
4. Desai S and Bolton S, A Floating Controlled Release Drug Delivery System: In vitro–In vivo Evaluation. *Pharmaceucal ti. Res*., 1993, 10, 321-325.
5. Panchal HA, Tiwari A, A novel approach of bilayer tablet technology: A review. *Int. Res. J. Pharm.*, 2012, *3*, 44-49
6. Pujara ND, Gokani RK, Paun JS, Bilayer tablet – an emerging trend., *Int. J. pharm. Res. Dev*. 2012, *4*, 102-111
7. U.S.National library, Drug information, May 2007 www/in/wikipedia/org/Wiki/Diltiazem
8. Kumar P.D and Rathnam g , Formulation and characterization of bilayer floating tablets of ranitidine, *Rasayn, J*.2010**,**3 ,368-374
9. Kumar P.D and Rathnam g , Formulation and characterization of bilayer floating tablets of ranitidine, *Rasayn, J*.2010**,**3 ,368-374
10. Hilton AK, Deasy PB, In Vitro and In *Vivo* Evaluation of an Oral Sustained-release Floating Dosage Form of Amoxycillin Trihydrate.*Int. J. Pharma*.1992**,** 2 , 79-88.
11. Gowtham. M, Vasanti S, Formulation and evaluation of Immediate release folic acid tablets, *Der.harma.Lettre*, 2011, 3 , 157-162
12. Santhanalakshmi G, Elango K, Ramesh Kumar K and Farheen F, Formulation and Evaluation of Bilayer Floating Tablets of Trimetazidine hydrochloride and Metoprolol succinate, Ind J Pharm Edu Res, Jul-Sep, 2012, 46, 3
13. Divya A,K Kavitha,M.rupeshkumar An overview of Bilayer tablet technology Journal of Applied pharmaceutical science 01, 08; 2011: 43-47
14. Dey Sanjay, Dutta Snigdha, Mazumder Bhaskar, Formulation and evaluation of floating matrix tablet of atenolol for gastro retentive drug delivery , 4, 3,2012,434
15. Natarajan R, Kaveri Naveen, Rajndran N N R, Formulation and evaluation of Aceclofenac gastro retentive darug delivery system, RJBPS, 2, Jan-March, 767
16. Z.Rahman,Kumar A**,** Formulation and Evaluation of Sustain released Bilayer tablets of captopril, Acta.Pharm,2006, 56, 49-57
17. Kannan C, Karunanithi V, Janarthanan S, Dheivasigamani V, Formulation and in vitro Evaluation of Gastroretentive Rosiglitazone maleate Floating Tablets, 27-28.
18. Robinson J R, Sustain and Controlled released drug delivery system, MarcelDekker, New York, 1987,72-76
19. Toti U, Aminabhavi T, Modified guar gum matrix tablet for controlled release of Diltiazem hydrochloride, J.Controlled Release, 2004, 95, 567-577
20. Aulton M, Pharmaceutics the science of dosage form design,1st Ed,ELBS, Hongkong, 1990, 316