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FORMULATION AND EVALUATION OF BILAYER FLOATING TABLET CONTAINING VERAPAMIL HYDROCHLORIDE

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ABSTRACT

The objective of the present investigation was to develop a bilayer-floating tablet (BFT) for Verapamil Hydrochloride using direct compression technology using floating and viscosity enhancing polymers such as HPMC K100 and Carbopol 940. Sodium bicarbonate and citric acid were used as a gas generating agent. All the bi-layered floating tablet formulations were subjected to post-compression evaluation parameters such as hardness, friability, weight variation, thickness, drug content, lag time subsequently buoyancy time, and *in-vitro* dissolution studies. The assay of the formulation revealed that the drug content was within the limits. *In-vitro* floating revealed that all the formulations showed buoyancy of more than 12 hours. Dissolution tests were performed using USP dissolution apparatus at 75 rpm in pH 1.2 buffer. The tablet split in to 2 layers i.e. floating and immediate layer in the dissolution medium, which exhibited biphasic release of Verapamil Hydrochloride. The formulation F3 released 98.24% of drug at the end of 12hr. The *invitro* drug release data was fitted into various kinetic models and the best fit release kinetics was achieved with Peppas model.

Keywords: Verapamil hydrochloride, HPMC, Carbopol, Bilayer floating tablet.

INTRODUCTION

Development of oral controlled-release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable. When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, affecting a prolonged gastric residence time (GRT) [1,2]. This floating dosage form is well known as a hydrodynamically balanced system (HBS). It has been suggested for the following instances that an active material should be formulated in the form of an HBS to enhance bioavailability: (*i*) having a dissolution and/or stability problem in the small intestine fluids, (*ii*) being locally effective in the stomach, (*iii*) being absorbed only in the stomach and/or upper part of the intestine [3]. Floating tablets, capsules, beads, microspheres and chambers have been reported in literature [4].

Verapamil, an antihypertensive agent, has been widely used for the treatment of hypertension, angina and arrythmia. Verapamil has been shown to be effective and safe alone or in combination, in patients with hypertension and or coronary artery diseases. The profile of verapamil hydrochloride indicates that it is a drug with short half life(3-6 hrs) and hence requires frequent dosing like 3-4 tablets daily. This frequent dosing result in fluctuating drug levels in body and need for constant monitoring and counseling of patient for adherence to dose regimen. This consequently reduces the compliance of patients who are to take these medicines almost lifelong. Hence, the major task in treatment of hypertension and other such chronic ailments is of minimizing fluctuations of drug levels in blood by using dosage form which offer sustained, steady drug release profiles [5,6].

In comparison with the single layer tablet, a double layer matrix offers advantages; this formulation of the matrix dosage form with two distinct layers allows separate regulation of the floating capabilities and drug release kinetics. The present investigation aims to develop a BFT of Verapamil Hydrochloride with a view of prolonging GRT [7].

MATERIALS AND METHODS

Materials

Verapamil HCl was obtained as a gift sample from Apotex Research Pvt Ltd, Bengaluru, Carbopol-940 was purchased from Rolex Laboratories Chennai., HPMC-K-100

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was purchased from Shreeji chemicals, Sodium Bicarbonate and Citric acid were purchased from S.D. Fine Chemicals Mumbai. Other materials and solvents used were of analytical grade or better.

Methods

Formulation

Bilayer tablets consist of floating matrix layer as bottom and immediate release layer as top layer. The drug and all the excipients were sifted through mesh # 40, weighed accurately, and then was mixed in a plastic bag for 5 minutes, followed by lubrication which, was carried out in a plastic bag for 5 minutes by adding the weighed quantity of magnesium stearate and mixing. Tablets were prepared by direct compression technology using tablet punch machine. Bilayer floating tablets were prepared in two stages. First stage was formulation of floating layer tablets. The drug, polymer, gas generating agent such as sodium bicarbonate, citric acid and lactose are mixed geometrically and compressed by using 12 mm round flat punches with low hardness to produce floating layer tablets. Second stage was formulation of bilayer floating tablets. The drug and lactose are mixed separately for immediate release layer. Floating layer was placed in punching die. Then contents of immediate release layer were placed over the floating layer tablet and compressed to obtain hardness in the range of 8-9 kg/cm^2 to produce bilayer floating tablets [8].

Evaluation

Pre Compression Parameters

Bulk density (Db)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$Db = M / Vo$$

Tapped density (Dt)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$Dt = M / Vt$$

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

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

POST-COMPRESSION PARAMETERS

The tablets were subjected to the following tests:

Hardness

The hardness of the tablet was determined using a Pfizer Hardness tester. It is expressed in kg/cm^2.

Friability (F)

The Friability of the tablet was determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (W_{final}). The % friability was then calculated by

$$F = \frac{Winitial - Wfinal}{Winitial} \times 100$$

Thickness

The Thickness of the tablets was measured using Screw gauge and expressed in millimeter.

Weight variation

Weight variation was carried out for both immediate release and sustained release layers. 20 tablets were weighed and the average weight was calculated. Then the tablets were weighed individually. The percentage weight deviation of each tablet from average weight was calculated using the following formula

$$\%\ Deviation = \frac{Average\ weight - Individual\ weight}{Average\ weight} \times 100$$

Assay/drug content

Ten tablets were selected randomly, weighed and triturated; a quantity of triturate equal to 100mg of Verapamil HCl was transferred to 100ml volumetric flask and was dissolved in 0.1N HCl. 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 278 nm using 0.1N HCl as blank [9].

***In vitro* Buoyancy Studies**

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a beaker containing 100mL 0.1N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time [10,11].

***In vitro* Dissolution Studies**

Release rate of all the designed formulations were studied up to 12 hours using USP type II dissolution apparatus (Rotating Paddle method) at 75 rpm. A distance of 2.5 cm± 0.2 cm was maintained between the paddle and bottom of dissolution vessel. The dissolution medium (900 ml) consisted of 0.1N hydrochloric acid (1.2 pH), maintained at 37°C ± 0.5 °C. Sample of 5 ml was withdrawn at specific time intervals throughout the dissolution study of

12 hours for analysis and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed for Verapamil HCl using UV-Visible spectrophotometer at 278nm. The release studies were conducted in triplicate.

Stability Studies

The selected formulations were subjected for stability studies based on their drug content and *in-vitro* drug release characteristics. The formulations were stored in tightly closed amber coloured glass container in stability chamber. The formulations were stored at different storage conditions like 5^0C/Ambient, 25^0 C/ 60 % RH and 40^0C/ 75 % RH for 60 days. The formulations were subjected to different tests namely hardness, drug content and *in-vitro* drug release study after 60 days and reported [12].

RESULTS AND DISCUSSION

The physical characteristics of BLF tablets (F1, F2, and F3) such as tablet size, hardness, friability and weight variation were determined and the results are shown in Table 03. The hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in Pharmacopoeia. The drug content was found spectrophotometrically for all the formulations.

The values are shown in Table-03. The drug content was found to be within a narrow range as specified in Pharmacopoeia (90 - 110%) in all formulations. Buoyancy lag time and duration of floating were determined using 100 ml beaker containing 0.1N HCl medium are shown in Table 04. The Bilayer floating formulations F1, F2 and F3 were subjected for the dissolution studies using USP dissolution apparatus II (paddle) in 900 ml of 0.1N HCl medium. Average value were obtained from the triplicate values and taken as the final value. The results are given in Figures 1. The F3 BFT was chosen as the optimized formulation because it showed maximum drug release compared to other formulation [13-16].

To analyze the Verapamil Hydrochloride release mechanism the *in vitro* release data were fitted into various release equations and kinetic models first order, zero order, Higuchi and Korsemeyer and Peppas. As indicated by the value of R^2, the best fit model was found to be Peppas for all the formulation. The value of *n* for optimised formula F3 was 0.4079($R2$ = 0.9944), indicating release governed by Fickian diffusion.

All formulations were subjected to stability studies and results are given in Table06, 07 and08. From the results it was observed that there was no significant change in physicochemical properties and release profile after the storage at for two months at three different condition. It may be inferred that there was no degradation and change in the release system [17,18].

Table 1. Formulation of Maintenance And Loading Dose

Formulation and ingredients	Quantity taken in mg					
	MF1	MF2	MF3	LF1	LF2	LF3
Verapamil HCL	215	215	215	78	78	78
HPMC K100	60	60	60	-	-	-
Carbopol 940	140	120	100	-	-	-
Sodium Bicarbonate	80	80	80	-	-	-
Citric acid	50	50	50	-	-	-
Lactose	15	35	55	22	22	22

Table 2. Drug Evaluation

Sl. No	Parameters	Results
1	Bulk density (g/cc)	0.383
2	Tapped density (g/cc)	0.448
3	Angle of repose (ɵ)	23.55^0
4	Carr's index (%)	14.51

Table 3. Physical evaluation of Bilayer floating tablets of Verapamil Hydrochloride

Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation	Drug Content (%)
F1	8.9	4.0	0.305	2.06	95.31
F2	8.6	4.0	0.318	1.72	97.54
F3	8.8	4.15	0.397	1.84	96.66

Table 4. Floating Properties

Formulation Batch	Lag time or buoyancy time	Floating duration or buoyancy duration
F1	2 min, 07 sec	> 13 hrs
F2	1 min, 27 sec	> 13 hrs
F3	1min 12 seconds	> 13 hrs

Table 5. Regression co-efficient (r^2) values of different kinetic models and diffusion exponent (n) of Peppas model for Verapamil Hydrochloride Bilayer floating tablet

Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				r^2 value	'n' value
F1	0.8871	0.9383	0.9800	0.9850	0.3528
F2	0.8689	0.9907	0.9821	0.9862	0.4375
F3	0.8579	0.9743	0.9830	0.9944	0.4079

Table 6. Hardness data of the selected formulations at the end of 60 days

Stability condition	Sampling (days)	Hardness
5^0C/Ambient	60	8.8
25^0C/ 60 % RH	60	8.9
40^0C/ 75 % RH	60	8.8

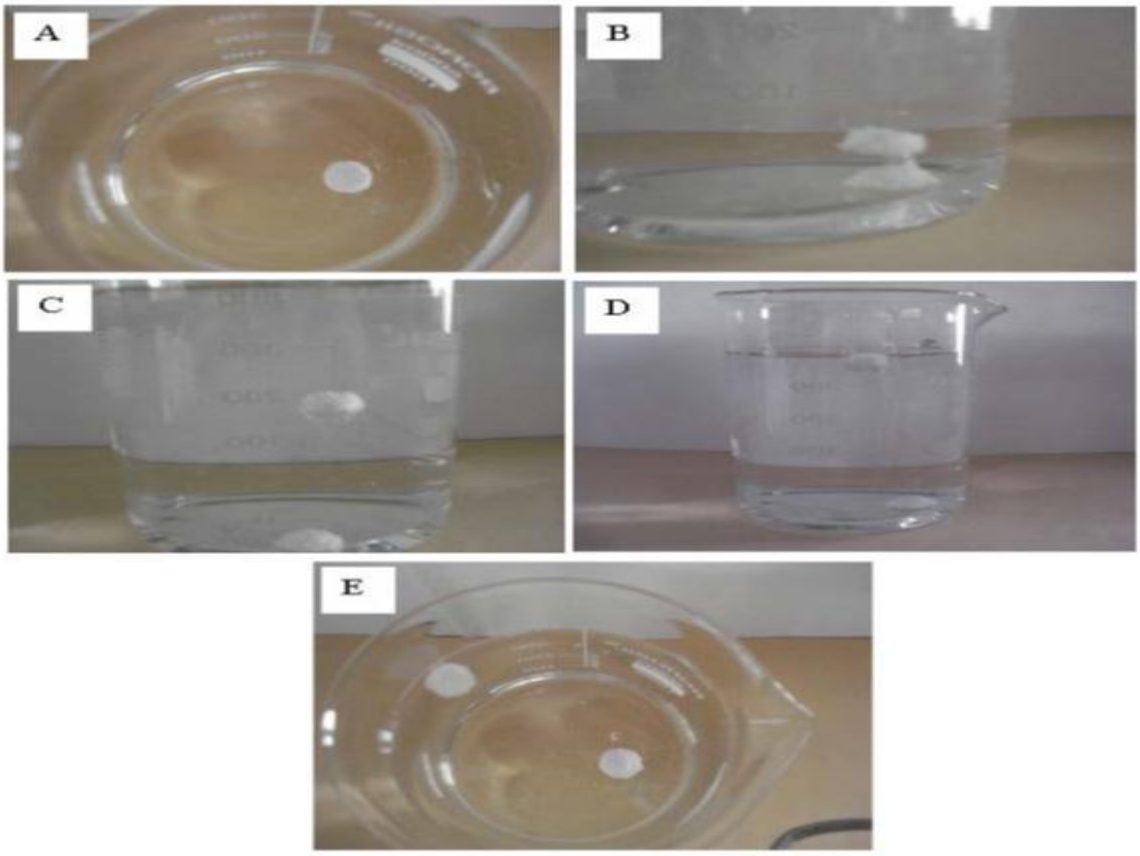
Table 7. Drug Content retained for selected formulations at the end of 60 days

Stability condition	Sampling (days)	Drug Content
5^0C/Ambient	60	96.3%
25^0C/ 60 % RH	60	96.39%
40^0 C/ 75 % RH	60	96.15%

Table 8. *In-Vitro* drug dissolution profile of the selected formulations at the end of 60 days

Stability condition	Sampling (days)	*In-Vitro* drug dissolution profile of F3
5^0C/Ambient	60	96.23
25^0C/ 60 % RH	60	96.14
40^0 C/ 75 % RH	60	95.56

Fig 1. *In-Vitro* floating of Bilayer Tablets



A-Tablet placed in 1.2 pH dissolution media,
B-Separation of immediate and sustained release layer from bi-layer tablet,
C-Floating sustained release layer separated from immediate release layer and floating On dissolution media.
E-Separate two layers i.e. immediate and sustained release layer,
D-Separated immediate and sustained release layer.

CONCLUSIONS

The present study was carried out to develop the Bi-layer floating tablet of Verapamil HCl using HPMC and carbopol. *In vitro* dissolution studies showed % CDR increased with increase in the polymer concentration. The drug release was characterized by an initial burst of higher release followed by a slow release. Analysis of drug release mechanism showed that the drug release followed Fickian diffusion and the best fit model was found to be Peppas. Stability studies revealed that no significant change in percentage drug content and physical characters. Stability studies indicated that the selected formulation (F3) was stable. Thus, results of the current study clearly indicate, a promising potential of the Verapamil Hydrochloride floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system for patients suffering from hypertension.

REFERENCES

1. Chien YE. Potential developments, new approaches in oral controlled release drug delivery systems. *Drug Dev. Ind. Pharm*, 9, 1993, 486–488.
2. Deshpande AA, Rhodes CT, Shah NH and Malick AW. Controlled release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev. Ind. Pharm*, 22, 1996, 531–539.
3. Uzdemir N, Ordu S and Ozkan Y. Studies of floating dosage forms of furosemide: *in vitro* and *in vivo* evaluation of bilayer tablet formulations. *Drug Dev. Ind. Pharm*, 26, 2000, 857–866.
4. Ingani HM, Timmermans J and Moes AJ. Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. *Int. J. Pharm*, 35, 1987, 157–164.
5. Triggle DJ. Calcium channel antagonists: clinical uses- past, present and future. *Biochemical pharmacology*, 74, 2007, 1-9.
6. Eisenberg MJ, Brox A, Bestwros AN. The Calcium Blockers: An update. *American Journal of Medicine*, 116, 2004, 35-43.
7. Dinesh Kumar P, Rathnam G, Prakash CR, Saravanan G, Karthick V, Selvam P, formulation and characterization of bilayer floating tablets of Ranitidine. *Rasayanj.Chem*, 3(2), 2010, 368-374.
8. Lakshmi A, Ashwini Kumar1 G, Karnaker Reddy T, Anand Kumar M. Development and invitro evaluation of gastroretentive Verapamil Hydrochloride floating tablets. *International Journal of Pharmacy and Pharmaceutical Sciences*, 4(1), 2012, 360-363.
9. Baumgartner S, Kristel J, Vreer F, Vodopivec P, and Zorko B. *Int. J. Pharm.*, 2(5), 2001, 95
10. ICH Harmonized Tripartite Guidelines, 2003. Stability testing of new drug substances and products. Q1A (R2).
11. Lokendra Pal Singh, Rajesh KS, Deepak G. Umalkar, Vijay Kumar Chauhan, ViralKumar Rana, Kamini S. Vasava. Floating Effervescent tablet: A review. *Journal of Pharmaceutical and biomedical sciences*, 5(11), 2011, 1-6.
12. Vishnu M Patel, Bhupendra G Prajapati, Anand K Patel. Controlled Release Gastroretentive dosage form of Verapamil Hydrochloride. *International Journal of PharmTech Research*, 1(2), 2009, 215-221.
13. Ziyaur Rahman, Mushirali, Khar RK. Design and evaluation of Bilayer Floating Tablets. *Acta Pharm*, 56, 2006, 49-57.
14. Borkar SN, Suresh R, Sawant VA, Shende VS, Mokale VJ and Dama G. An approach to Formulate Bilayerd Gastro Retentive Floating Drug Delivery System of Cefpodoxime Proxetil. *International Journal of Chem Tech Research*, 22(2), 2010, 1229-1242.
15. Rajashree Masa Reddy, Shivakumar Yellanki, Bhushan R.Patil, Manvi FV. Development and Evaluation of Floating Matri'x Tablets of Riboflavin. *International Journal of Pharm Tech Research*, 2(2), 2010, 1439-1445.
16. Aisha Khanum, Vinay Pandit and Shyamala Bhaskaran. Formulation and Evaluation of Bilayer Tablets of Propranolol Hydrochloride. *IJPER*, 43(3), 2009, 290-294.
17. Ravindra S.Dhumal, Samit Kumar T, Rajmore Sanjay T. Dhumal and Atmaram P. Pawar. Design and evaluation of Bilayer Floating tablets of Cefuroxime Axetil for Bimodel release. *J.scientific. Industrial Res*, 65, 2006, 812-816.
18. Lunana Perioli, Valeria Ambrogi, Stefano Giovagnoli, Maurizio Ricci, Paolo Blas I, and Carlo Rossi. Mucoadhesive Bilayerd Tablets for Buccal Sustained release of Flurbiprofen. *AAPS.PharmSciTech*, 8(3), 2007, 54.