INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

DEVELOPMENT AND CHARACTERIZATION OF BIVARIENT TABLETS FOR ANTI HYPERTENSIVEDRUGS- A NOVEL APPROACH

[1]Keerthiprathyusha.S*, [2] Durga Srinivasarao. M
[1]Department of Pharmaceutics, Tvm College of Pharmacy, Bellary
[2] Department of Pharmaceutics, S.Chaavan College Of Pharmacy, Nellore

ABSTRACT

The Bivarient tablet regimen is used when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drug. The Bivarient system has Hydrochlorothiazide for immediate release with superdisintegrants which increase rate and start onset of action whereas Verapamil hydrochloride sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period. Verapamil hydrochloride has pH dependent solubility. It has antihypertensive category therefore necessary to facilitate prolong duration of action of drug. Hydrochlorothiazide, a diuretic used necessary to facilitate immediate onset of action. The purpose of the present work was to design development and characterisation of Bivarient tablet for antihypertensive drug delivery. A floating drug delivery system was developed using gas forming agents, like sodium bicarbonate, citric acid and hydrocolloids like HPMC and Carbopol. This Bivarient formulation floats more than 10h. Kinetic release study reveals that release mechanism is following First order. The optimized formulation was selected based on *in vitro* dissolution characteristics and disintegration time in 0.1N HCl. Finally the tablet formulations found to be economical and may overcome the drawbacks associated with the drug during its absorption.

Keywords: Bivarient tablet regimen, Verapamil hydrochloride, Hydrochlorothiazide, biphasic release, release

Author for correspondence:
Keerthiprathyusha.S,
Department of Pharmaceutics,
Tvm College of Pharmacy, Bellary.

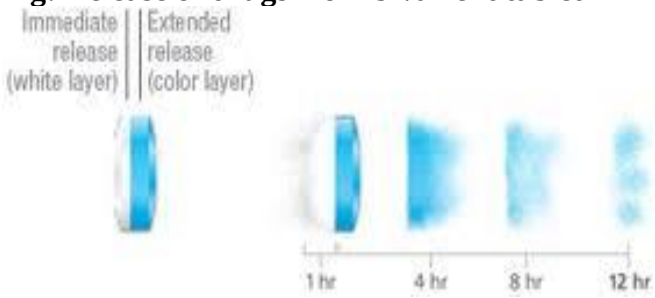
Email:prathyushaarchan@gmail.com

INTRODUCTION:

The aim of any drug delivery system is to affort a therapeutic amount of the proper site in the body and to maintain the desired drug concentration.one of the novel approaches in the area of oral sustained release the stomach or upper GIT, as to improve solubility, Bioavailability & the therapeutic efficacy of the drugs [2]. Several techniques have been proposed to increases the gastric residence time of dosage forms such as buoyancy or floating system[3]. The biphasic system is used mostly when maximum relief needs to be achieved quickly followed by sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics & anti allergic agents are mainly used for this system. The biphasic system may contain one or two drugs for immediate release & sustained release layer [4].

The Bi-varient tablet is innovative drug delivery system. This is novel type of dosage form for oral administration in which one layer contains sustained release drug and another layer contains immediate release drug. Combination therapy has various advantages over mono therapy such as problem of dose dependent side effects minimized. A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects of the other.

Fig: Release of drugs from bivarient tablet



Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced.

The term Bi-varient tablets refers to tablet containing subunits that may be either the same or different. Bi-varient tablets allow for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release. Bi-varient tablets are preferred when the release profiles of the drugs are different from one another. While second layer designed to release drug latter, either as second dose or in an extended release manner [5].

The goal in designing sustained or controlled drug delivery system is to reduce the frequency of the dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period time, either systemically or to a specified target organ. Sustained release dosage forms, extends the life of the drug so that people shift from 3 times a day dosing to the new extende release tablets, taking them just once or twice a day [6]

The present work relates to the formulation of bivarient tablet having immediate release layer and floating sustained release layer. These tablets showed biphasic drug release means immediate release layer releases drug immediately after contact with dissolution media this as a loading dose. Floating sustained release layer releases drug for prolong time as a maintenance dose. Due to prolong gastric retention of drug, it increases the solubility, bioavailability and reduces drug waste.

Materials and methods

This work is to prepare and evaluate bivarient tablet for antihypertensive drugs such as verapamil hydrochloride, a calcium channel blocker having $t_{1/2}$ 3-4.5 hrs formulated as sustained release effervescentfloating tablets to improve drug bioavailability by prolongation of gastic residence time and hydrochlorthiazide, a diuretic having $t_{1/2}$ 5.6 hrs formulated as immediate release tablet.

Verapamil hydrochloride was received as a gift sample from Microlabs Pharma limited & Hydrochlorthiazide was received as a gift sample from Aurobindo pharma Ltd, HPMC K 100M and HPMC K15 were received as a gift sample from Orchids Lab. Pvt. Ltd, Carbopol & aerosol received from Himedia Lab.Pvt.Ltd, Starch, PVP & Magnesium stearate received from Otto chemicals, Sodium bicarbonate, Citric acid, sodium starch glycolate, Dicalcium phosphate received from Sd Fine.Chem.Ltd, Talc received from ozone international(Mumbai, India), cross povidone received from Isp sales. All other chemicals used were of analytical grade.

FORMULATION OF BIVARIENT TABLETS

***(a)* Formulation of immediate release granules**

Various formulation batches of Hydrochlorthiazide were prepared by wet granulation method. The working formulae were given in the table no.5.

Procedure

1. Hydrochlorothiazide, dicalcium phosphate and cros povidone as super disintegrant was mixed properly in motar and pestle according to their compositions.

2. The resulting mixture or blend was passed through sieve #40.
3. To the above mixture, 10 % starch paste which is previously prepared was added slowly to make damp mass. The wet mass was passed through sieve # 60 and dried at 50^0C for suitable time. After drying the solid particles were passed through sieve # 40 with lubricants. Their granules were stored for further purpose.

Note: The dye was mixed with binder solution.

***(b)* Formulation of sustained release granules**

Granules were made by wet granulation method. All the ingriedients were drug, diluents, mixed thoroughly and the binding agent was added slowly to form cohesive mass. The damp mass was passed through sieve #60 and was dried at 50^0C for 45 min. Again the granules were passed through sieve no #40 and were mixed with lubricants. The granules were stored in well packed polythene cover for further purpose. The formula for sustained release layer was given in the table

Working formulae for Immediate release layer

Note: Total weight of each tablet= 200mg

Ingredient (mg/tablet)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Hydro chlorothiazide	25	25	25	25	25	25	25	25	25
Sodium starch glycolate	**25**	**35**	**45**	**--**	**--**	**--**	**22.5**	**30**	**15**
Crospovidone	**--**	**--**	**--**	**25**	**35**	**45**	**22.5**	**15**	**30**
Dicalcium phosphate	120	110	100	120	110	100	100	100	100
Aerosil	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Starch	15	15	15	15	15	15	15	15	15

Working formulae for sustained release granules

Ingredients (mg/tablet)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
Verapamil hydrochloride	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**
HPMC K 100M	**30**	**40**	**50**	**--**	**--**	**--**	**25**	**50**	**--**	**--**
HPMC K 15M	**--**	**--**	**--**	**30**	**40**	**50**	**--**	**--**	**25**	**50**
Carbopol	-	**--**	**--**	**--**	**--**	**--**	**25**	**25**	**25**	**25**
Starch	60	50	40	60	50	40	40	15	40	15
Sodium bicarbonate	50	50	50	50	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20	20	20	20	20
PVP	10	10	10	10	10	10	10	10	10	10
Mg. Stearate	5	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

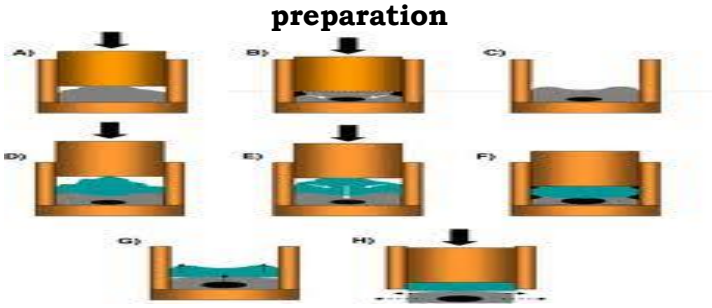
Note: Batch size for each formula: 100 tablet, Total weight of granules: 30g

Compression of bivarient tablet

Bivarient tablets were prepared using Rimek mini press (16 station) machine. Bivarient tablets were compressed using 6mm oval shaped punches with **"SPSP"** embossing in the middle.

Bivarient tablet contains two layers i.e., immediate release layer and sustained release layer of Hydrochlorothiazide and Verapamil hydrochloride. Bivarient tablets were prepared by using optimized immediate and sustained release layer. Accurately weighed 200mg of immediate release blend and 300mg of floating sustained release blend individually. Initially immediate release granules blend was fed manually into the die and then compressed at low compression force to form uniform layer. Subsequently floating sustained release layer granules blend was added to the die over that layer and completely compressed on tablet punching machine.

Fig: 13 Steps involved in Bivarient tablet preparation



Steps involved in Bivarient tablet preparation:

- Filling immediate release granules into die.
- Slightly compressed immediate release granules.
- Ejection of upper punch.
- Addition of floating sustained release granules over immediate release granules.
- Compression of both sustained release granules and immediate release granules.
- Ejection of bivarient tablet.

CHARACTERIZATION OF BIVARIENT TABLETS

Physical Evaluation of tablets

Prepared Bivarient tablets were evaluated for hardness, friability, disintegration time for immediate release layer, drug content, percent drug release, weight variation, thickness, floating lag time and total floating time for floating sustained release layer.

Invitro buoyancy lag time:

Buoyancy lag time is the time required for the tablet to rise towards surface and float. The buoyancy of tablets was studied at 37 ± 0.5^0C in 900 ml of 1.2 p^H buffer (simulated gastric fluid without enzyme). The duration of buoyancy lag time was observes visually and recorded by using stop watch.

In vitro Dissolution Studies (by UV method)

The *in vitro* drug release study was performed using United States Pharmacopoeia (USP) XXII paddle apparatus

Instrument: UV- spectrophotometer

Wavelength: 272nm (for Verapamil) and 273nm (for Hydrochlorothiazide)

Dissolution parameters

Medium : 0.1N HCl, Phosphate buffer pH 7.4
Volume : 900ml
Apparatus : USP XXII paddle type
RPM : 50
Time intervals: 30sec, 60sec, 90sec, 120sec, 1, 2,3,4,5,6,7,8 hrs.
Temperature: 37.0 ± 0.5^0 C.

Kinetics of *in vitro* drug release

To study the release kinetics *in vitro* drug release data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-peppas. To analyse the mechanism of the drug release rate kinetics o the dosage form, the data obtained were plotted as

1) Log cumulative percentage drug remaining Vs time(first order plots)
2) Cumulative percentage drug released Vs square root of time (Higuchi's plots)
3) Log percentage drug released Vs log time (Korsmeyer peppas).

Zero order

$C = K_0t$ (1)

Expressed in units of concentration/time and t is the time in h.

First order

$\text{Log } C = \text{Log}C_0K_t/2.303$ (2)

Where C is the concentration, C_0 is the initial concentration of drug, Kis the first order constant, and t is the time.

Higuchi

$Q_t = Kt^{1/2}$ (3)

Where Q_t is the amount of the release drug in time t, K is the kinetic constant and t is the time in h.

Korsmeyer peppas

$M_t / M_\infty = Kt^n$ (4)

where M_t represents amount of the released drug at time t,

M is the overall amount of the drug released after 8hrs

K is the diffusional characteristic of drug/polymer system constant and

n is a diffusional or release exponent that characterizes the mechanism of the drug release of drug.

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n=0.5, then the drug release mechanism is fickian diffusion. If n<0.5 the mechanism is quassi-fickian diffusion, and $0.5 < n < 1.0$, then it is non fickian or anomalous diffusion and when n=1.0 mechanism is non fickian super case II

Effect of stirring rate

The effect of stirring rate study was performed using United States Pharmacopoeia (USP) XXII paddle apparatus. The stirring rate study was performed using 900 ml of 0.1N HCl, at 37 ± 0.5^0 C and 50, 75 and100 rpm. A sample (1ml) of the solution was withdrawn from the dissolution apparatus at

specified time intervals and the samples were replaced with 1ml of fresh medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 272-273 nm using a Shimadzu UV-1601 UV/Visible spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Short term stability studies

Stability studies were carried out as per ICH guidelines for tablets for a period of three months (at 40^0 C, RH 75%) using stability chamber (Indeecon company). The tablets were analyzed for weight variation, hardness, friability, buoyancy lag time, total floating time, buoyancy on distributing, drug content. Samples were assayed for percentage drug release once in a month for 3 months time period.

Note: For stability studies reproducible batch of selected optimized formulation was used.

Results and discussion:

Bivarient tablets were prepared by using optimized immediate release and floating sustained release formula.

It was observed that **variation in individual weight of formulated tablets** was within the range of ± 5%. The **hardness** of all formulations was found to be 5.5 kg/cm^2. The **thickness** of formulation was between 5.5- 5.6mm. The **friability** was found to be 0.8%, which was indication of good mechanical resistance of the tablet, **the drug content** was found to be in the range of ± 1%. Floating lag time was between 30-40 sec. Total floating time of bivarient tablet was observed for more than 10hrs.

Invitro dissolution study

Bivarient floating tablets of Verapamil hydrochloride and hydro- chlorthiazide were prepared using polymer such as HPMC K 100 and carbopol 971P. The *in vitro* dissolution study of Verapamil hydrochloride and Hydrochlorothiazide bivarient floating tablets were performed using 900 ml 0.1N HCl and 7.2 pH phosphate buffer dissolution media. The study was done 37±0.5^{0}C temperature and 50 rpm.

During dissolution, dissolution media goes into tablet matrix, the interaction of acidic fluid with sodium bicarbonate result into formation of carbon dioxide gas and that entrapped in swollen gel thus causing flotation.

Bivarient floating tablets were float more than 10 hrs in 900 ml 0.1N HCl at 37±0.5^{0}C. It was observed from *in vitro* drug release study that immediate release layer disintegrated rapidly in 0.1N HCl from bivarient tablet. Subsequently, floating sustained release layer started floating in 0.1N hydrochloric acid for 2hrs followed by 8hrs in 7.2pH phosphate buffer. This shows biphasic drug release i.e., immediate drug release from immediate release layer and then sustained drug release from floating sustained layer.

Immediate release layer get completely dissolved with in 2 min and 99% drug released among the total dose. Concurrently floating sustained release layer releases the drug upto 10hrs.

(a) Dissolution profile of immediate release layer of bivarient tblet(F1- F10)

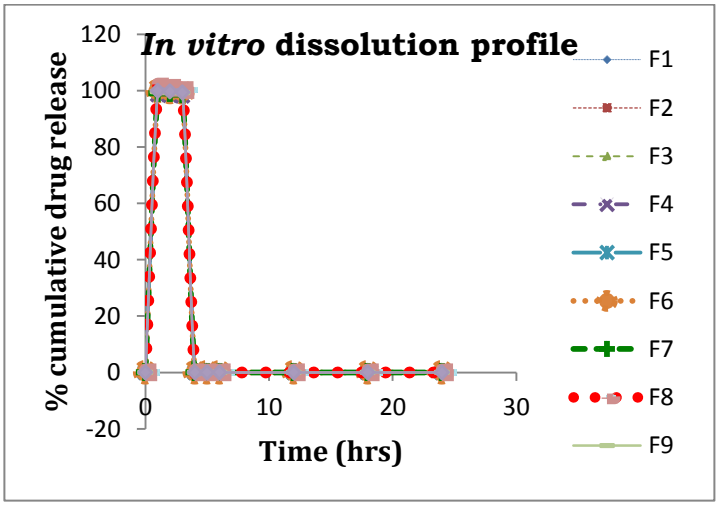


Fig: Dissolution profile of immediate release layer of BMR tablet

ISSN: 2395-0536

***(b)* Dissolution profile of sustained release layer of bivarient tablet (F1 – F9)**

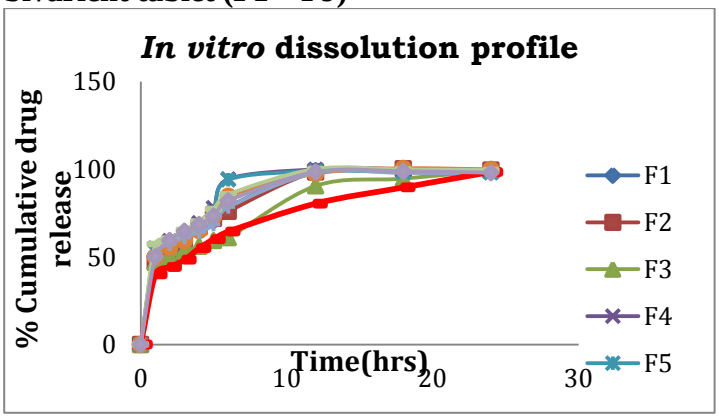
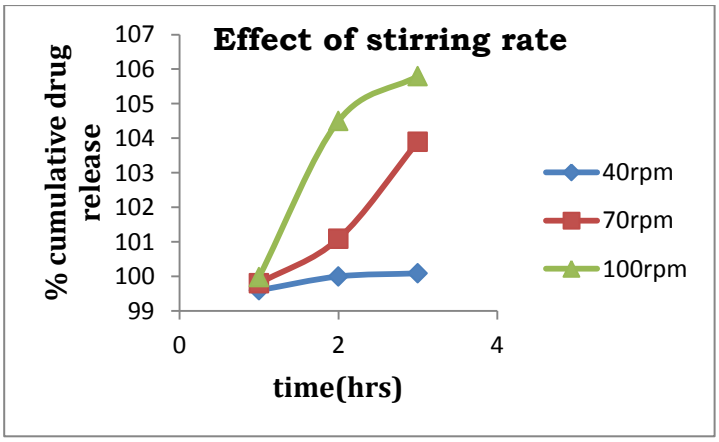
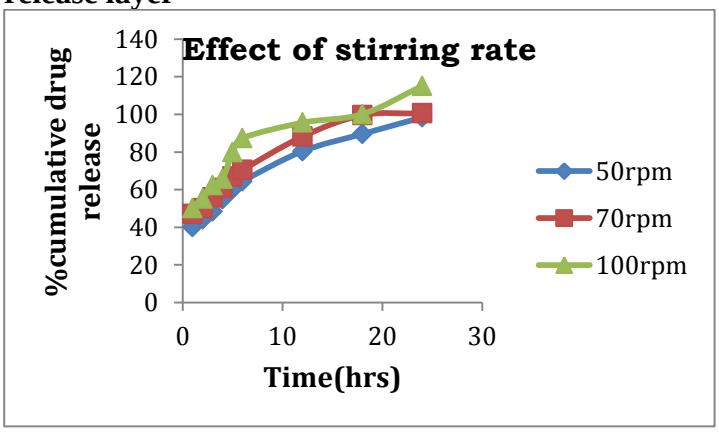


Fig: Dissolution profile of sustained release layer of BMR tablet

***Effect of stirring rate* ON RELEASE (DISSOLUTION RATE) OF BIVARIENT TABLETS**



Results of effect of stirring rate on immediate release layer



Results of effect of stirring rate on sustained release layer

Result indicated that stirring rate is directly proportional to the drug release rate. Drug release at 50, 75 and 100 rpm was found to be 99.6%, 99.8%, 99.98% for immediate release layer at the end of 1st hour and 80.42%, 88.2% and 95.6% for sustained release layer respectively at the end of 8th hr.

Drug release study:

The **zero order release rate equation 1** describes the systems, where the drug release rate is dependent of its concentration. **First order Equation 2,** which describes the release from systems, where the release rate is concentration dependent. **Higuchi's model Equation 3** describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. The release rate constant from the slope of the appropriate plots, and the regression coefficient (R^2) and release exponent (n) was calculated.

It was found that the *in vitro* drug release of Bivarient modified release tablet was best explained by first order of optimized batch in 1.2pH buffer medium. Drug release was also found to be very close to first order kinetics, indicating that the drug release is concentration dependent. The results are shown in Table 20. The mechanism of drug release corresponding plot log cumulative percent drug release Vs log time for the Korsmeyer Peppas equation 4 indicated linearity in 1.2 pH. The release exponent 'n' indicates drug release mechanism is non fickian super case II diffusion

Coefficient of regression R^2 values for F8.

F8	Coefficient of regression R^2				Korsmeyer peppas n value(release exponent)
	Zero order	First order	Higuchi	Korsmeyer peppas	
SR	0.761	0.947	0.947	0.734	0.975
IR	0.590	0.914	0.834	0.873	0.86

ISSN: 2395-0536

SHORT TERM Stability studies OF BMR TABLETS

Results of stability study (40^0C/75%RH) of optimized formulation (F8)

Parameters	1st month	2nd month	3rd month
Thickness	5.6 ± 0.24mm	5.6 ± 0.24mm	5.6 ± 0.24mm
Weight variation (mg)	501 ± 0.32 mg	501 ± 0.32 mg	501 ± 0.32 mg
Hardness	5.5 ± 1.42 kg/cm^2	5.49 ± 1.42 kg/cm^2	5.49 ± 1.42 kg/cm^2
Friability	0.8	0.8	0.8
Buoyancy lag time (sec)	40 sec	40 sec	40 sec
Total floating time	12 hrs	12 hrs	12 hrs
Buoyancy on distributing	Float	Float	Float
Drug content (%)	98.52 ± 0.18	98.49 ± 0.18	98.49 ± 0.18
In vitro release(%)12hr	99.45	99.32	99.74

The promising formulation was tested for a period of 3 months at 40^0C with 75% RH, for their drug release and other parameters. From the data, the formulation was found to be stable under the conditions mentioned before since there was no significant change in percentage amount of drug content, *in vitro* release, weight variation, thickness, buoyancy studies. Thus, it was found that the bivarient tablets of Verapamil hydrochloride and Hydrochlorothiazide were stable under these storage conditions for atleast 3 months.

CONCLUSION:

Bivarient tablets of Verapamil hydrochloride and Hydrochlorthiazide were prepared by wet granulation method and superdisintegrants sodium starch glycolate and crospovidone. The drug release from the tablets was sufficiently immediate and sustained following non Fickian super case II transport of drug from tablets was confirmed. Based on *in vitro* characterization, biphasic drug release was observed from bivarient floating tablets which float more than 10 hrs in dissolution media. Good stability was observed for 3 months during stability studies.

Stability study shows that there was no significant change in hardness, friability, drug content, and dissolution profile of the selected formulation. Since the formulation showed sufficient stability for prolonged period, this work concludes that the formulation showed sustained release and immediate release, so dose can be reduced and because of more buoyancy complete absorption of the drug can be achieved.

REFERENCES:

1. Hoffman.A,Stepensky.D, Lavy.E, Eyal.S, Klausner. Friedman.M Pharmacokinetics and pharmacodynamic aspects of gastroretentive dosages forms. Int J Pharm. 2004: 277; 144.
2. R.Talukder.R, Fassihi.R. Gastroretentive delivery systems. A mini review, drug dev Ind Pharm. 2004: 1019.
3. Tanwar.Y, Jaimini.M, Rana.A. Formulation and evaluation of famotidine floating tablets. Current drug delivery.2007: 4; 51-55.
4. Londhe S., Gattani S., Surana. Development of floating drug delivery system with biphasic release for verapamil hydrochloride: invitro & invivo evaluation.journal of pharmaceutical science and technology.2010: vol2(11); 361-367.
5. Vinoth kumar G., Anand babu.K, Ramasamy.C. formulation and evaluation of bilayered tablets of cefixime trihydrate and dicloxacillin sodium. International journal of pharm tech research. 2011: 3(2); 613-618.
6. Branmankar D.M., Jaiswal B.S. "Biopharmaceutics and Pharmacokinetics"."A Treatise," 2004: 1; 335-347