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DESIGN, FABRICATION AND IN-VITRO EVALUATION OF BILAYER TABLETS VERAPAMIL

Raju Manda[1]* , Dr. K.S.K. Rao Patnaik[2], T. Mangilal[2]

*[1] Department of Pharmaceutics and Drug Regulatory Affairs, Teegala Ram Reddy College of Pharmacy, Meerpet -500097, Telangana, INDIA.
[2] Department Of Pharmaceutics, University College of Technology, Osmania Universty, Hyderabad -500007, Telangana,(State) INDIA.

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ABSTRACT

The principle of the present research work was to formulate and evaluate floating sustained release bilayer tablet with biphasic release for verapamil hydrochloride. Verapamil hydrochloride shows pH dependent solubility and having coronary vasodilator, antihypertensive category therefore it is necessary to facilitate immediate onset of action followed by prolong duration of action. Biphasic means two phases, immediate release phase or layer, and sustained release layer, compressed in single unit tablet by direct compression. Immediate release layer contain sodium starch glycolate and crosspovidone as a superdisintegrants. Floating sustained release layer contain HPMC K- series polymers and carbopol 971 P for hydrogel forming. Gas-generating agent sodium bicarbonate and citric acid was incorporated in the tablet to generate the carbon dioxide gas upon contact with gastric fluid. Immediate release layer releases the drug immediately and starts onset of action and floating sustained release layer floats on gastric fluid for more than 12 hrs and releases the drug in sustained manner, subsequently it prolonged duration of action. Bilayer tablets were prepared by direct compression method. Prepared tablets were evaluated for in-vitro. In-vitro evaluation parameters are within the Pharmacopoeial limits.

Keywords: *Verapamil hydrochloride, Biphasic release, Release kinetics, In-vitro.*

INTRODUCTION

Oral Controlled Drug Delivery: [1-3]

The objective of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration. Recently a pharmaceutical formulation scientist is well versed with the fact that the overall action of a drug molecule is not merely dependent on its inherent therapeutic activity, rather on the efficiency of its delivery at the site of action. An ideal drug delivery system (DDS) should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. Hence, the DDS should deliver the drug at a rate dictated by the needs of the body over the period of treatment. DDS may be employed for spatial placement (i.e., targeting a drug to a specific organ or tissue) or temporal delivery (i.e., controlling the rate of drug delivery to the target tissue**.**

Bilayer Floating Tablet: [3, 4]

Bilayer tablets contain immediate and sustained release layer. Immediate release layer delivers the initial dose, it contains superdisintegrants which increase drug release rate and start onset of action whereas sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period.

The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics and antiallergenic agents are mainly used for this system. The biphasic system may contain one or two drugs for immediate release and sustained release layer.

***Corresponding author:**
Raju Manda
Department of Pharmaceutics and Drug Regulatory Affairs,
Teegala Ram Reddy College of Pharmacy,
Meerpet -500097, Telangana, INDIA.
Cell: +91-9966288297.
**E-Mail: 0502varma@gmail.com*

MATERIALS AND METHODS

Materials:

The following drug, polymers, excipients and Polymers were used for the formulation and evaluation of bilayer floating tablets.

Preformulation studies involving bulk density, angle of repose, tapped density, compressibility index, melting point range, pH, and solubility were carried out as per IP specifications. The results lied in between IP range

Bilayer Floating Tablets:

Formulation of Bilayer Floating Tablets: [4-6]

Bilayer tablet contains two layers i.e. immediate release layer and sustained release layer of verapamil hydrochloride. Bilayer tablets were prepared by using optimized immediate and sustained release layer. Accurately weighted 150 mg of immediate release layer and 250 mg of floating sustained release layer individually. Various batches of bilayer tablets were prepared by direct compression method according to formula **Table.** Initially immediate release powder blend was fed manually into the die of 10 stations Rimek minipress-1 tablet machine and then compressed at low compression force to form uniform layer. Subsequently floating sustained release layer powder blend was added over that layer and completely compressed on rotary tablet punching machine by using flat faced punch 12 mm.

Steps Involved in Bilayer Tablet Preparation:

1) Filling immediate release powder in to dies
2) Slightly compressed immediate release powder
3) Ejection of upper punch
4) Addition of floating sustained release powder over immediate release powder
5) Compression of both layer
6) Ejection of bilayer tablet

Evaluation of Bilayer Tablets (USP, IP):

Bilayer tablets were evaluated for hardness, friability, disintegration time, drug content, percent drug release, weight variation, thickness, floating lag time and total floating time.

Table No. 1: Compositions of bilayer floating tablet.

Ingredients	Formulation code (Quantity in mg)					
	AB1	AB2	AB3	AB4	AB5	AB6
Verapamil hydrochloride	50	50	50	50	50	**50**
Sodium starch glycolate	12	12	---	12	---	**12**
Crosspovidone	---	---	12	---	12	**---**
Dicalcium phosphate	88	88	88	88	88	**88**
Verapamil hydrochloride	102	102	102	102	102	**102**
HPMC K15 M	25	25	25	30	30	**---**
HPMC K100M	---	---	---	---	---	**25**
Carbopol 971 P	20	20	20	20	20	**20**
Sodium bicarbonate	40	40	40	40	40	**40**
Citric acid	4	4	4	4	4	**4**
Crosspovidone	0	54	54	49	49	**54**
Talc	**3.41**	**3.95**	**3.95**	**3.95**	**3.95**	**3.95**

Table No. 2: Compositions of bilayer floating tablet.*

Ingredients	Formulation code (Quantity in mg)				
	AB7	AB8	AB9	AB10	AB11
Verapamil hydrochloride	50	50	50	50	**50**
Sodium starch glycolate	--	12	--	12	**---**
Crosspovidone	12	---	12	--	**12**
Dicalcium phosphate	88	88	88	88	**88**
Verapamil hydrochloride	102	102	102	102	**102**
HPMC K15 M	---	---	---	30	**30**
HPMC K100 M	25	30	30	----	**---**
Carbopol 971 P	20	20	20	20	**20**
Sodium bicarbonate	40	40	40	50	**70**
Citric acid	4	4	4	----	**----**
Crosspovidone	54	49	49	49	**49**
Talc	3.95	3.95	3.95	3.91	**4.21**
Magnesium stearate	**3.95**	**3.95**	**3.95**	**3.91**	**4.21**

***HPMC – Hydroxypropyl methyl cellulose**

***In-vitro* Drug Release Study:** [7, 8]

In-vitro drug release study was performed using type-II(paddle) apparatus (Electrolab TDT- 08L plus, Dissolution tester USP Mumbai, India) at 100 rpm in simulated gastric fluid of 1.2 pH and simulated fed state fluid of 3.0 pH individually. Temperature was maintained at 37 ± 0.5°C. The 5 ml sample was withdrawn at predetermined time intervals and replaced with same dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by using UV spectrophotometer (UV Shimadzu 1700) at λ_{max} 278 nm. This test was performed on 6 tablets and mean ± SD was calculated.

Kinetics of *In-vitro* Drug Release:

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

RESULTS AND DISCUSSION

Evaluation of Bilayer Floating Sustained Release Tablets:

Prepared bilayer floating sustained release tablets were evaluated for postcompression parameters, results are shown in

Table No. 3: Evaluation parameters of bilayer floating tablets

Formulation Code	Drug content (%)	Percent drug release	Weight variation (mg)	Thickness (mm)
AB1	99.02±1.2	84.43±2.8	347.82±1.4	**4.06±0.010**
AB2	98.20±1.5	99.46±1.1	402.9±1.6	**4.08±0.013**
AB3	99.12±1.8	99.87±1.3	402.9±1.5	**4.06±0.011**
AB4	98.22±2.0	99.36±2.3	402.9±2.0	**4.04±0.012**
AB5	98.55±2.3	98.29±2.4	402.9±1.7	**4.06±0.014**
AB6	101.03±1.9	98.84±3.8	402.9±2.1	**4.06±0.012**
AB7	98.55±1.5	98.53±2.3	402.9±1.9	**4.07±0.014**
AB8	98.65±1.4	97.76±2.0	402.9±2.0	**4.07±0.015**
AB9	99.32±1.7	98.69±2.6	402.9±2.3	**4.08±0.013**
AB10	98.65±2.0	99.90±2.5	408.82±1.7	**4.06±0.013**
AB11	**98.77±2.4**	**93.28±1.1**	**429.42±2.3**	**4.08±0.011**

The data are presented as mean value ± S.D. (n = 3)

Table No. 4: Evaluation parameters of bilayer floating tablets

Formulation code	Hardness (kg/cm²)	Friability (%)	Disintegration Time (sec)	Floating lag time (sec)	Total floating time(hrs)
AB1	6±0.7	0.4±0.7	17±1.1	13±0.6	**>12**
AB2	6±0.4	0.5±0.5	19±1.3	16±0.9	**>12**
AB3	6±0.9	0.5±0.3	20±0.9	15±0.5	**>12**
AB4	6±0.3	0.7±0.4	16±1.4	13±0.6	**>12**
AB5	6±0.5	0.5±0.5	18±1.6	15±0.7	**>12**
AB6	6±0.8	0.6±0.7	17±1.2	18±0.9	**>12**

AB7	6±0.6	0.4±0.3	19±1.8	14±0.4	**>12**
AB8	6±0.4	0.5±0.5	20±1.2	16±0.6	**>12**
AB9	6±0.5	0.7±0.7	18±2.0	14±0.9	**>12**
AB10	6±0.3	0.4±0.9	16±1.1	17±0.4	**>12**
AB11	**6±0.4**	**0.5±0.5**	**19±1.4**	**19±0.8**	**>12**

The data are presented as (n = 3) mean value ± S.D.

Determination of Buoyancy Lag Time:

The buoyancy of tablets was studied at 37 ± 0.5°C in 500 ml of 1.2 pH buffer (simulated gastric fluid without pepsin). Buoyancy lag time was less than 20 sec because incorporation of gas generating agent.

The *in-vitro* dissolution study of verapamil hydrochloride bilayer tablets was performed using USP type II apparatus (paddle) (Electrolab TDT- 08L plus, Dissolution tester USP Mumbai, India).

This test was performed on 6 tablets and mean ± SD calculated.

***The in-vitro* Dissolution Study of Bilayer Floating Tablets:**

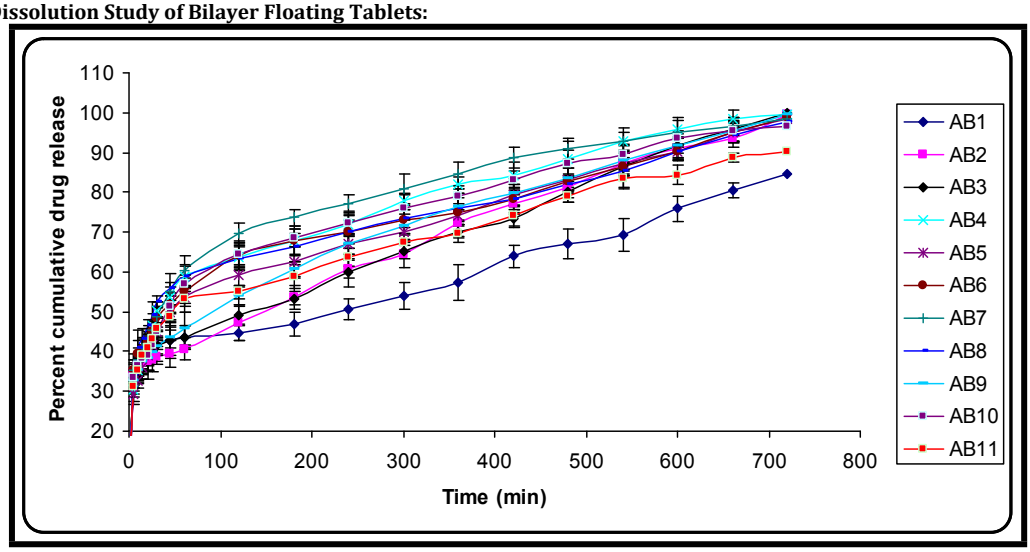

Fig. 1: Comparative dissolution of bilayer floating tablets of all AB1 to AB11 batches in 1.2 pH dissolution media (simulated gastric fluid without enzyme) (n = 6, mean ± S.D.).

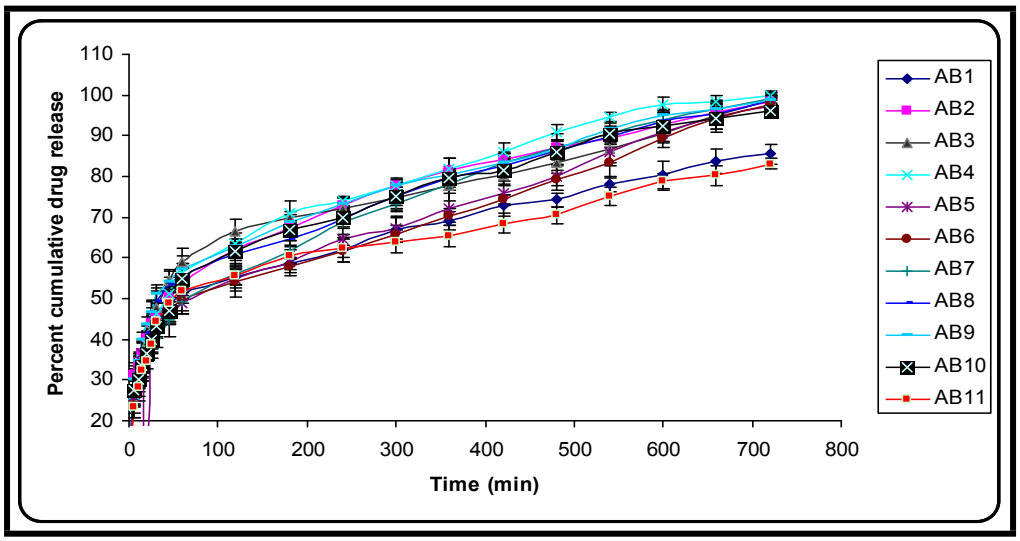

Fig. 2: Comparative dissolution of bilayer floating tablets of all AB1 to AB11 batches in citrate phosphate buffer, pH 3.0 (simulated fed state gastric fluid). (n = 6, mean ± S.D.).

Effect of Compression Force on Floating and Drug Release: [9, 10]

Compression force was significantly affect floating i.e. floating lag time, total floating time and *in-vitro* drug release. For study two sets of 6 tablets of batch AB2 with hardness 8 Kg/cm² and 10 Kg/cm² in addition to one set of tablets having hardness 6 Kg/cm² were subjected to *in-vitro* drug release and floating study. Results indicated that increase in the compression force diminish the drug release and total floating time, increase in the floating lag time.

Release Kinetics Study:

The zero-order release rate describes the systems where the drug release rate is independent of its concentration. First order, which describes the release from systems where the release rate is concentration dependent. Higuchi's model 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 was calculated 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 sustained release floating tablet was best explained by first order, plots showed the linearity (R^2= 0.8992- 0.9713) for Higuchi's equation (R^2 = 0.9225-0.9954) and for Korsmeyer Peppas (R^2 = 0.8978 - 0.9811), (n= 0.1619-0.200) of optimized batch in 1.2 pH buffer. For 3.0 pH, first order plot (R^2= 0.781 – 0.960), for Higuchi equation (R^2= 0.9456-0.987) for Korsmeyer Peppas (R^2= 0.9617-0.9870) and release exponent n was (n = 0.1582-0.2284). Drug release was found to be concentration dependent.

Mechanism of Drug Release:

The corresponding plot (log cumulative percent drug release Vs log time) for the Korsmeyer Peppas (equation 13) indicated linearity (R^2 = 0.8974-0.9811) and release exponent n was (n = 0.1619-0.200) in 1.2 pH buffer. For 3.0 pH (R^2= 0.9617-0.9870) and (n = 0.1582-0.2284). The release exponent 'n' indicated drug release mechanism is quasi Fickian diffusion.

Stability Study:

After storage the formulation was analyzed for various physical parameters, results are showed in Table No 4. No major difference was found between evaluated parameters before and after ageing / storage and all are in acceptable limits.

Table No. 4: Evaluation parameters of stability batch

Evaluation parameters	Before stability storage	After 1 month storage	After 2 months storage	After 3 months storage
Hardness (kg/cm²)	6 ± 0.6	6 ± 1.1	5 ± 1.6	**5 ± 1.1**
Friability (%)	0.4 ± 0.3	0.3 ± 0.6	0.2 ± 0.9	**0.3 ± 0.7**
Weight variation (mg)	402.9 ± 1.9	401.2 ± 2.5	400.4 ± 2.2	**401.1 ± 1.5**
Disintegration time (sec)	19 ± 1.8	18 ± 2.3	20 ± 1.5	**22 ± 1.3**
Drug content (%)	99.55 ± 1.5	99.32 ± 1.8	98.10 ± 2.0	**97.66 ± 2.4**
Percent drug release in 1.2 pH buffer	98.53 ± 3.8	98.85 ± .2.7	98.00 ± 3.2	**97.05 ± 2.1**
Percent drug release in 3.0 pH buffer	98.69 ± 1.3	98.21 ± 1.9	98.54 ± 2.4	**97.11 ± 2.5**
Floating lag time (sec)	14 ± 0.4	15 ± 0.9	18 ± 1.2	**16 ± 0.8**
Total floating time (hrs)	**>12**	**>12**	**>12**	**>12**

The data are presented as mean value ± S.D. (n = 3)

SUMMARY AND CONCLUSION

Initially immediate release tablets of verapamil hydrochloride was prepared by using various superdisintegrants i.e. sodium starch glycolate, crosspovidone and dicalcium phosphate as a diluent. Superdisintegrants increases the disintegration and ultimately dissolution of drug; consequently release rate of drug increases and its absorption lead to faster onset of action. Evaluation of postcompression parameters of immediate release tablets was performed. The results of optimized batches (A1 and A2) were found to be within limit, *in-vitro* study showed 95-100 % drug release within 15- 20 min. Subsequently floating sustained release tablets for prolonged drug release of verapamil hydrochloride were formulated and evaluated. Tablets were prepared by using various hydrophilic and hydrophobic polymers such as HPMC K15 M, HPMC K100 M and carbopol 971P. Hydroxypropyl methylcellulose (HPMC) a low density polymer that has been widely used. It was reported that carbopol increased the pharmacological availability of drug by protecting from being attached by luminal enzymes. Floating tablet contains sodium bicarbonate, citric acid as a gas generating agent. Crosspovidone is a superdisintegrant, which also used in floating sustained release tablets as a drug release modifier due to its capillary mechanism. Evaluation of floating tablets was performed. All parameters were found to be within Pharmacopoeial limits. Also formulations were evaluated for floating behaviour, which showed floating lag time less than 20 sec, and total floating time more than 12 hrs. *In-vitro* drug release study was performed in simulated gastric fluid i.e.1.2 pH buffer. Optimized batches (B1 – B4) showed that the drug released at floating sustained manner for 12 hrs. Finally bilayer floating tablets were formulated by using optimized immediate (A1 and A2) and floating sustained release layer (B1 - B4) of verapamil hydrochloride. Bilayer tablets when comes in contact with gastric fluid quickly releases the immediate release layer and start onset of action, subsequently floating sustained release layer floats over gastric fluid and release the drug in sustained manner, which would be required in above diseased conditions. *In-vitro* drug release was carried out in 1.2 pH (simulated gastric fluid) and 3.0 pH (simulated fed state fluid) results showed that no major difference in drug release in both dissolution media. This indicates that slightly increased in pH did not affect the drug release from the formulation. Stability study also showed no changes in results.

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