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Development of Floating Drug Delivery System with Biphasic Release for Verapamil Hydrochloride: *In vitro* and *In Vivo* Evaluation.

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Abstract:
The purpose of the research work was development and evaluation bi-layer floating tablets for verapamil hydrochloride. Verapamil hydrochloride has pH dependent solubility. It has coronary vasodilator, antihypertensive category therefore necessary to facilitate immediate onset of action followed by prolong duration of action of drug. Verapamil hydrochloride bi-layer floating tablets have two layers one immediate release layer and second floating sustained release layer. Verapamil hydrochloride bi-layer floating tablet releases drug in two phases i.e immediate and sustained drug release. Direct compression method was used to formulate bi-layer floating tablets. All bi-layer formulation float more than 12 h and sustained drug release above 12 h. Kinetic release study suggests that release mechanism is quasi Fickian. The optimized formulation was selected based on in *vitro* characteristics and used in *vivo* radiographic studies in rabbits by incorporating BaSO4. This showed that, tablet significantly float in rabbit stomach for more than 7 h.

Keywords: *Verapamil Hydrochloride, Bi-layer floating tablets, Biphasic release, Release kinetics, In vivo study.*

Introduction:

The aim 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. In oral drug delivery system not all drugs or therapeutic agents are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed in a particular portion of GIT.

One of the novel approaches in the area of oral sustained release drug delivery is gastroretentive drug delivery system (GRDDS). Drugs those are having a narrow absorption window and having more solubility in gastric region are suitable candidates for GRDDS[1]**.** GRDDS prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract, as to improve solubility, bioavailability and 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], hydrodynamically balanced system[4]**,** expanding or swelling system, bio/mucoadhesive system[5]**,** sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time.

The biphasic system is used mostly when maximum relief needs to be achieved quickly 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. Literature showed that biphasic release tablets containing two drugs ketoprofen and Praziquantel[6].

Verapamil hydrochloride is the first calcium channel blocker. It is used for the treatment of angina pectoris, hypertension and supraventricular tachyarrhythmias. Verapamil hydrochloride is approximately 90 % absorbed from gastrointestinal tract, but has low bioavailability of 22 ± 8 %. Biological half life of verapamil hydrochloride is 4.0 ± 1.5 h[7].

Verapamil hydrochloride was chosen as a model drug because of its pH dependent solubility. It is highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH)[8].

Literature showed low density microparticles and tablets of verapamil hydrochloride were prepared by using low density polypropylene foam powder[8].

The present work relates to the formulation and evaluation of bi-layer floating tablets 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[9].

Materials and Methods:

***Materials*:**

Verapamil hydrochloride was received as a gift sample from Nicholas Piramal India Ltd. (Mumbai, India), HPMC K15M and HPMC K100M were received as a gift sample from Colorcon Asia Pvt. Ltd. (Goa, India), Carbopol 971 P received from Noveon Asia Pacific Ltd. as a gift sample. Crosspovidone was kindly supplied by Cadila Pharmaceutical Ltd (Ahmedabad, India), sodium starch glycolate (Explotab) was received as a gift sample from JRS Pharma, (Rosenberg, Germany). Dicalcium Phosphate (DCP), Sodium bicarbonate, Citric acid, Talc and Magnesium stearate were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). All other chemicals and regents used were of analytical grade.

Formulation of bi-layer floating tablets:

Bi-layer floating tablet contains two layers one immediate release layer and second sustained release layer of verapamil hydrochloride. Accurately weighted 150 mg of immediate release layer powder blend and 250 mg of floating sustained release layer powder blend individually. Batches of bi-layer tablets were prepared by direct compression method according to formula given in Table 1. Initially immediate release powder blend fed manually into the dies of 10 stations Rimek minipress-1 tablet machine and then compressed at low compression force to formed uniform layer of powder. Subsequently floating sustained release layer's powder blend was added over precompressed immediate release layer then increased compression force then compressed on 10 stations Rimek minipress-1 tablet machine by using 12 mm flat faced punch.

Evaluation of bi-layer floating tablets:

Prepared bi-layer floating 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. The results are shown in Table 2.

In vitro 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°C in 900 ml of 1.2 pH buffer (simulated gastric fluid without enzyme). The duration of buoyancy lag time was observed visually and record by using stop watch**.**

In vitro drug release study:

In vitro drug release study was performed using USP XXII paddle apparatus (Electrolab TDT- 08L plus, Dissolution tester USP Mumbai, India) at 100 rpm in simulated gastric fluid without enzyme of pH 1.2. Temperature was maintained at 37 ± 0.5°C. Sample 5ml was withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by using UV spectrophotometer (UV Shimadzu 1700 Pharmaspec) 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 *in vitro* drug release data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

Zero order

$$C = K_0 t \qquad (1)$$

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

First order

$$Log C = Log C_0 - Kt/2.303 \qquad (2)$$

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

Higuchi

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

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Table 1: Composition of bi-layer floating tablet

Sr. No	Ingredients	Formulations code (quantity in mg)										
		AB 1	AB2	AB 3	AB4	AB5	AB6	AB7	AB8	AB9	AB 10	AB 11
	Immediate release layer formula											
1	Verapaml hydrochloride	50	50	50	50	50	50	50	50	50	50	50
2	Sodium starch glycolate	12	12	-	12	-	12	-	12	-	12	-
3	Crosspovidone	-	-	12	-	12	-	12	-	12	-	12
4	Dicalcium phosphate	142	88	88	88	88	88	88	88	88	88	88
	Floating sustained release layer formula											
5	Verapamil hydrochloride	102	102	102	102	102	102	102	102	102	102	102
6	Hydroxypropyl methyl cellulose K15M	25	25	25	30	30	-	-	-	-	30	30
7	Hydroxypropyl methyl cellulose K100 M	-	-	-	-	-	25	25	30	30	-	-
8	Carbopol 971 P	20	20	20	20	20	20	20	20	20	20	20
9	Sodium bicarbonate	40	40	40	40	40	40	40	40	40	40	40
10	Citric acid	4	4	4	4	4	4	4	4	4	4	4
11	Crosspovidone	0	54	54	49	49	54	54	49	49	49	49
12	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
13	Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Table 2: Evaluation of bi-layer floating tablets

Formulation code	Hardness (kg/cm2)	Friability (%)	Disintegration time for immediate release layer (s)	Drug content (%)	Percent drug release	Weight variation (mg)	Thickness (mm)	Floating lag time (s)	Total floating time (h)
AB1	5±0.7	0.4±0.7	17±1.1	99.02±1.2	84.43±2.8	405.8±1.4	5.06±0.010	13±0.6	>12
AB2	8±0.4	0.5±0.5	19±1.3	98.20±1.5	99.46±1.1	404.1±1.6	5.08±0.013	16±0.9	>12
AB3	6±0.9	0.5±0.3	20±0.9	99.12±1.8	99.87±1.3	398.9±1.5	5.36±0.011	15±0.5	>12
AB4	7±0.3	0.3±0.4	16±1.4	98.22±2.0	99.36±2.3	401.4±2.0	5.04±0.012	13±0.6	>12
AB5	5±0.5	0.5±0.5	18±1.6	98.55±2.3	98.29±2.4	402.7±1.7	5.75±0.014	15±0.7	>12
AB6	7±0.8	0.4±0.7	17±1.2	101.03±1.9	98.84±3.8	390.6±2.1	5.43±0.012	18±0.9	>12
AB7	6±0.6	0.4±0.3	19±1.8	98.55±1.5	98.53±2.3	402.2±1.9	5.07±0.014	14±0.4	>12
AB8	5±0.4	0.5±0.5	20±1.2	98.65±1.4	97.76±2.0	405.6±2.0	5.27±0.015	16±0.6	>12
AB9	6±0.5	0.54±0.7	18±2.0	99.32±1.7	98.69±2.6	401.7±2.3	4.88±0.013	14±0.9	>12
AB10	7±0.3	0.4±0.9	16±1.1	98.65±2.0	99.90±2.5	404.2±1.7	4.96±0.013	17±0.4	>12
AB11	7±0.4	0.5±0.5	19±1.4	98.77±2.4	93.28±1.1	403.4±2.3	4.68±0.011	19±0.8	>12

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

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

Where M_t represents amount of the released drug at time t, M is the overall amount of the drug (whole dose) released after 12 h K is the diffusional characteristic of drug/polymer system constant and n is a diffusional or release exponent that characterizes the mechanism of 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 quasi-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 case II diffusion, n> 1.0 mechanism is non Fickian super case II[10].

Formulation of tablets for in vivo study:

Tablets for *in vivo* study were prepared by reformulating batch AB2 in this batch instead of drug, various concentration of BaSO4 (Barium sulphate) i.e. 15%, 20% and 25% was used. BaSO4 used as a radio contrast agent. Tablets containing various concentrations of BaSO4 were studied to check the *in vitro* floating ability.

Results and Discussion:

Bi-layer floating tablets were prepared by using optimized immediate release and floating sustained release formula. It was observed from *in vitro* drug release study that immediate release layer disintegrated rapidly in 0.1 N hydrochloric acid buffer pH 1.2 (simulated gastric fluid without enzymes) from bi-layered tablet. Subsequently, floating sustained release layer started floating in 0.1 N hydrochloric acid buffer pH 1.2 and sustained drug release. This showed biphasic drug release i.e. immediate drug release from immediate release layer and then sustained drug release from floating sustained layer.

Evaluation of bi-layer floating tablets:

The hardness of all formulations was found to be 5-7 kg/cm^2. The thickness of formulations was between 4.88 mm to 5.75 mm. The friability was between 0.3% – 0.5 % for all the formulations, which was an indication of good mechanical resistance of the tablet. The average drug content of tablets (n = 10) between 98.20 % to 101.03 % and percent drug release was found to be 84.43% to 99.90%. Floating lag time was between 13 s to 19 s. Total floating time of floating sustained release was observed more than 12 h.

In vitro dissolution study:

Bi-layer floating tablets of verapamil hydrochloride were prepared using polymers such as HPMC K4M, HPMC K100M and carbopol 971 P. Bi-layer floating tablets were float more than 12 h in 900 ml 0.1 N hydrochloric acid buffer pH 1.2 (simulated gastric fluid without enzyme) at 37 ± 0.5^{o}C. During dissolution, dissolution media goes in to tablet matrix, the interaction of acidic fluid with sodium bicarbonate resulted in to formation of carbon dioxide gas and that entrapped in swollen gel thus causing floatation.

The *in vitro* dissolution study of verapamil hydrochloride bi-layer floating tablets were performed using 900 ml 1.2 pH buffer dissolution media (simulated gastric fluid without enzymes). The study was done 37 ± 0.5^{o}C temperature and 100 rpm. Immediate release layer get completely dissolved within 15-20 min and 30-45% drug released among the total dose. Concurrently floating sustained release layer releases the drug up to 12 h. Results showed in Figure 1.

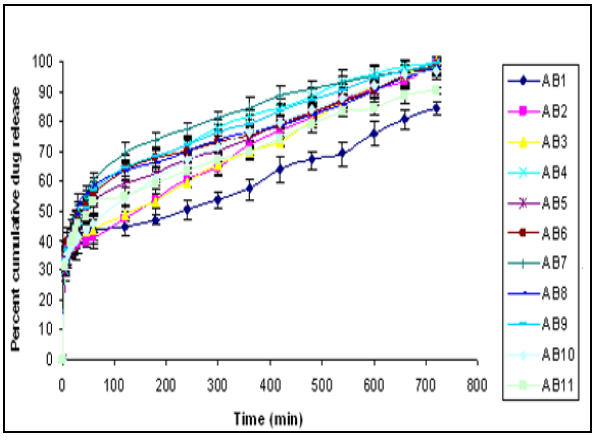

Figure 1. Comparative dissolution of bi-layer floating tablets of batches AB1 - AB11 in 1.2 pH dissolution media (simulated gastric fluid without enzymes). (n = 6, mean ± S.D.).

Bi-layer floating tablet when immersed in 1.2 pH buffer media, immediate release layer separated from bi-layer tablet within seconds and start to release drug subsequently floating sustained release layer start to float and sustained drug release, showed in Figure 2.

Effect of stirring rate:

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 53.64± 3.1%, 64.65 ±3.5%, and 72.21 ±1.0% respectively at the end of 4 h results showed in Figure 3

Drug release study:

The zero-order release rate Equation 1 describes the systems, where the drug release rate is independent 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 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 = 0.8974 - 0.9811), (n= 0.1619-0.200) of optimized batch in 1.2 pH 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 3.

The mechanism of drug release corresponding plot log cumulative percent drug release Vs log time for the Korsmeyer Peppas equation 4 indicated linearity (R^2 = 0.8974-0.9811) in 1.2 pH. The release exponent n was (n = 0.1619-0.200), (R^2= 0.9617-0.9870). The release exponent 'n' indicates drug release mechanism is quasi Fickian diffusion.

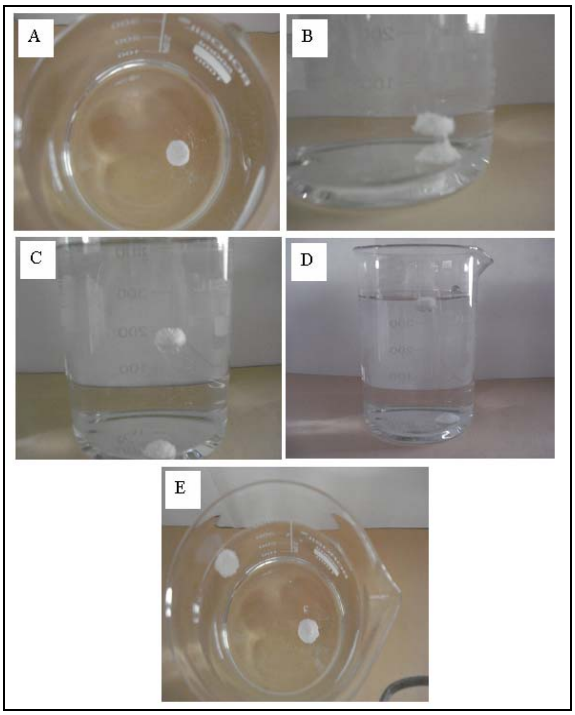

Figure 2: Photograph shows

- **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,
- **D-** Separate two layers i.e. immediate and sustained release layer,
- **E-** separated immediate and sustained release layer.

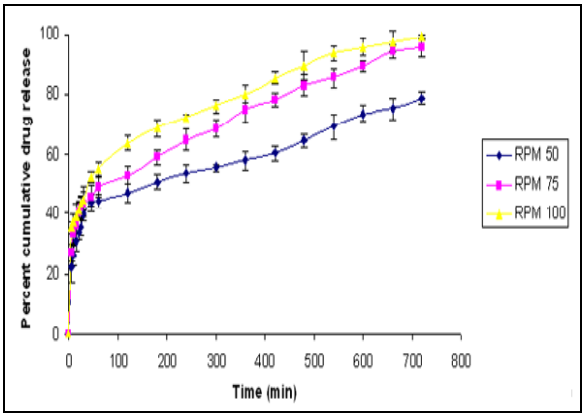

Figure 3. Effect of stirring rate on *in vitro* release of verapamil hydrochloride (n =6)

In vivo study:

In vivo study was performed in New Zealand Albino rabbits by using X ray imaging technique. Prior permission was taken from institutional animal ethical board of R C Patel Institute of Pharmaceutical Education and Research, Shirpur. This X-ray study was performed in 6 healthy New Zealand Albino

Table 3: Analysis data of optimized bi-layer floating tablets in 1.2 pH buffer

Formulation Code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer Peppas R^2	Korsmeyer peppas N
AB1	0.8189	0.9519	0.9845	0.9625	0.177
AB2	0.83	0.9127	0.9802	0.9576	0.1817
AB3	0.8915	0.95	0.9801	0.8974	0.1794
AB4	0.8037	0.9607	0.9485	0.9811	0.1986
AB5	0.8374	0.8992	0.9735	0.9694	0.200
AB6	0.7972	0.9362	0.9572	0.9542	0.1712
AB7	0.7667	0.9327	0.9225	0.9576	0.1863
AB8	0.7641	0.9225	0.9730	0.9786	0.1619
AB9	0.8741	0.9713	0.9954	0.9317	0.1973
AB10	0.8117	0.9586	0.9692	0.9506	0.1937
AB11	0.8219	0.9433	0.9543	0.9053	0.1762

Values shown in the table are mean ± S.D.

rabbits of either sex, weight 2kg - 2.5kg. Animals were fasted for 12 h before study apart from drinking water. Prepared tablets for *in vivo* study of various concentration of barium sulphate were evaluated for *in vitro* floating study. It was observed that tablets containing 15% barium sulphate showed good floating behavior i.e floating lag time and total floating time as compared to 20% and 25% barium sulphate containing tablets. Therefore tablets containing 15% barium sulphate were selected for *in vivo* study and administered to rabbits followed by 30 ml water. Rabbit was placed upright posture for checking the position of tablet in gastric region by using X-ray machine[11], (Wipro GE DX-300 with horizontal X- ray system, model SI-0146-3128 capacity 300 MA-100 KVP, Pune, India) at different time intervals like 10 min, 1 h, 2 h, 5 h, and 7 h after administration of tablet. X ray imaging studies results showed that tablet was float more than 7 h in gastric region of the New Zealand Albino rabbits Figure 4

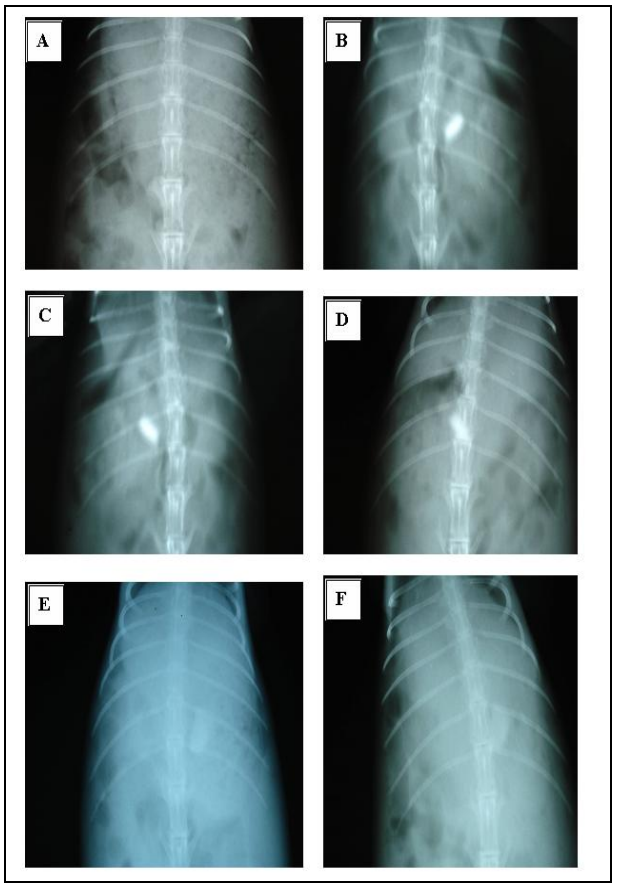

Figure 4.

A: X-Ray without tablet,
B: X-ray after 10 min administration of tablet
C: X-Ray after1h
D: X-Ray after 2 h
E: X-Ray after 5 h
F: X-Ray after 7 h

Conclusion

In conclusion, the results of this study based on *in vitro* characterization. Biphasic drug releases from bi-layer floating tablets which float more than 12 h in dissolution media. Stirring rate is directly proportional to the drug release rate. *In vivo* study was done New Zealand Albino rabbits. X ray imaging studies showed that tablet was float more than 7 h in gastric region.

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