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Optimization and *In vitro* evaluation of verapamil hydrochloride floating bilayer tablet

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ABSTRACT
The main objective of this investigation was to optimize bilayer gastric floating drug delivery system of Verapamil hydrochloride to study the effect of formulation variables especially, combination of polymers on drug release showing prolonged gastric residence time and optimized by using mathematical and statistical techniques. Three ratios of drug to total polymer content and three ratios of HPMC K4M to CP934 were chosen for an optimal design. In the preliminary trials the effect of sodium bicarbonate loading was studied on floating properties and 12% concentration was found to be optimum for floating buoyancy. Hardness of about 5 kg/cm^2 was found to be optimum for floating buoyancy and to keep two layers intact. Other physical parameters like weight variation, thickness and friability were within pharmacopoeial limit. Percentage drug content in all BFT formulations was found to be 98.47% - 99.96% which were within pharmacopoeial limit. Drug-polymer ratio and the HPMC K4M-CP934 significantly affect the buoyancy and drug release. It was concluded on the basis of buoyancy and *in-vitro* release kinetics that an optimized formulation containing a ratio of Drug to polymer 1:1 and polymer to polymer 1:1 gave the best *in-vitro* release of 99.42% in 12 hrs while for 3:1 and 1:3 *in-vitro* release was 91.05% and 93.71% respectively. A comparative study was done with the marketed formulation of Verapamil hydrochloride (Calaptin – SR). FTIR studies show no evidence of interaction between drug, polymers and other excipients. The *In vitro* data were fitted to different kinetic models.

Keywords: Gastro retentive floating tablets, Buoyancy, Dissolution equivalency.

1. Introduction
GRDDS is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption [1, 2]. As a mechanism to override this problem, erodible gastro retentive dosage forms have been developed that provide continuous controlled administration of these drugs at the absorption site [3]. In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteinoid microspheres and pharmacosomes etc. [4, 5]. Verapamil HCl was selected as the model drug to study the retardant efficiency of combination of polymers on the water soluble drug [6]. Verapamil HCl has short biological half-life, low pKa and good aqueous solubility that decrease with increase in pH due to which it is essential to confine its location in the upper gastro intestinal tract preferably in the stomach [7, 8]. Hence it was of prime importance to devise a floating drug delivery system that will help to minimize fluctuations in plasma drug concentration over the range of pH, help in readily absorption of the drug and also fulfill the requirements of spatial localization.

2. Materials and methods
2.1 Materials
Verapamil Hydrochloride was obtained as a kind gift sample from Flamingo Pharma. Ltd. Navi Mumbai (India), HPMC K4M and Microcrystalline cellulose were obtained from Zim Labs. Ltd. Nagpur (India). Carbopol 934P was obtained as a kind gift sample from Unijules Life Sciences Ltd. Nagpur (India). All other chemicals/reagents used were of analytical grade, available commercially and used as such without further processing.

2.2 Methods-Formulation for preliminary trials
2.2.1 Effect of sodium bicarbonate loading on floating property
Floating layer of BFT with different proportions of sodium bicarbonate (8%, 12% and 24%)

was prepared. Compression was controlled to produce a 5 kg/cm^2 tablet crushing strength. The tablets were subjected to buoyancy test. The time between introduction of dosage form and its buoyancy in the simulated gastric fluid and the time for which dosage form remained buoyant was measured. It was done to study the effect of sodium bicarbonate loading on the floating property and to optimize the immediate floating.

2.2.2 Formulation of bilayer floating tablets

The preparation process involved two steps. In the first step, immediate-release granules were prepared by mixing Verapamil hydrochloride and MCC using starch paste (used water with dissolved tartrazine yellow) as a granulating agent. The granules were dried at 60 °C for 30 minutes in an oven and then mixed with talc and magnesium stearate (the composition is shown in Table 7). In the second step, floating layer containing Verapamil hydrochloride (as a sustained dose) was prepared by mixing the drug with the excipients in a formulation as shown in Table 8 and 9. The blend was dried at 60 °C for 30 minutes in an oven. Granules of IRL and FL were weighed and compressed into bilayer tablets using 10 mm round tooling on a rotary tablet machine. Each bilayer tablet contained 120 mg (40 mg as immediate release dose and 80 mg as sustained dose) of Verapamil hydrochloride. Compression was controlled to produce a 5 kg / cm^2 tablet crushing strength. Time required for 33% drug release ($t_{33\%}$); 50% drug release ($t_{50\%}$); 80% drug release ($t_{80\%}$) and percentage of Verapamil hydrochloride release at 12 hours (Q12) were selected as dependent variables [9].

Table 1: Composition of Immediate-Release Layer (IRL) of the Bilayer Floating Tablet

Composition	Quantity (mg)
Verapamil hydrochloride	40
Soluble starch	6
Sodium starch glycolate	2
Magnesium stearate	1
Talc	1
Tartrazine yellow	-
Microcrystalline cellulose	50

Table 2: Composition of Floating Layer (in mg) of the Bilayer Floating Tablet

	FL1	FL2	FL3	FL4	FL5	FL6	FL7	FL8	FL9
Verapamil hydrochloride	80	80	80	80	80	80	80	80	80
HPMC K4M	60	40	20	90	60	30	120	80	40
Carbopol 934P	20	40	60	30	60	90	40	80	120

HPMC indicate hydroxypropyl methyl cellulose, each formulation contains 12%w/w Sodium bicarbonate ($NaHCO_3$), 1%w/w talc and 1%w/w magnesium stearate

2.2.3 Micromeritics evaluation of powder blend

The micromeritic evaluation of the powder blends was done by calculating the angle of repose, bulk density, tapped density, and Carr's index (% compressibility), Hausner's ratio [10, 12].

2.3 Evaluation of Tablets

2.3.1 Tablet Diameter and Thickness

Diameter and thickness of tablet are important for uniformity of tablet size. Thickness and diameter was measured by using Micrometer screw guage [13, 14].

2.3.2 Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by the Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

2.3.3 Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure.

Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

2.3.4 Uniformity of Weight

Twenty tablets were selected at random and average weight was calculated. The pharmacopoeial standards indicated that not more than two of the individual weights deviate from the average weight by more than the percentage and none deviates by more than twice that percentage.

2.3.5 Uniformity of content

One tablet was transferred to a 100 ml volumetric flask; to it 50 ml of 0.1N HCl was added and heated on steam bath for 50 minutes. The heated solution was sonicated for about 10 min. The solution was allowed to cool, diluted with 0.1N HCl to volume, mixed and finally filtered. The accurately measured amount (4 ml) of the filtrate was diluted up to 100 ml with 0.1N HCl to obtain a test preparation containing about 48 µg/ml of Verapamil HCl.

Concomitantly the absorbance of test and standard preparation was determined at 278 nm. The same procedure was repeated for nine tablets.

2.3.6 Floating Behavior

Floating behavior studies were performed on the floating tablet. The study was carried out in a USP Dissolution Test Apparatus (Type II) at paddle speed 50 rpm in 900 ml of 0.1 N HCl at 37 ± 0.5 °C to mimic *in-vivo* conditions. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time. Also the duration of system floatation and the relative matrix integrity was observed visually [15, 16]. The experiment was performed in triplicate.

2.3.7 Swelling behavior

Apparent swelling was ascertained by measuring the axial and radial expansion of matrix tablets following exposure to dissolution medium. Tablet hydration volume (%HV) and water uptake (%WU) tests were performed using the same conditions described in the dissolution studies and calculated using following equation [17, 18].

$$\%WU = Wh - Wi / Wi \times 100$$

Where,

Wh = mass of the tablet after placing in the dissolution medium (hydrated)

Wi = mass of the tablet before placing in dissolution medium

At various time intervals the tablets were removed from dissolution medium and weighed for % WU.

$$\%HV = Vf - Vi / Vi \times 100$$

Where,

Vf = final volume of tablet after placing in dissolution medium (hydrated)

Vi = initial volume of tablet before placing in dissolution medium

At various time intervals the tablets were removed from dissolution medium and measured in their height and width using a micrometer. The tablet volume was calculated considering a right circular cylinder form. The dimensions of each matrix were measured using a micrometer screw gauge prior to dissolution studies.

2.3.8 Dissolution Studies

The release rate of Verapamil hydrochloride from bilayer floating tablets was determined using USP Dissolution Test Apparatus (Type II). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5 °C with the paddle speed of 50 rpm. Aliquot (10 ml) of the solution was collected from the dissolution apparatus at time 10 min, 20 min, 30 min and then hourly upto 12 hrs and were replaced with fresh dissolution medium. The aliquots were filtered through Whatman filter paper. Absorbances of these solutions were measured at 278 nm. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. Release studies were performed in triplicate [19].

2.3.9 Dissolution equivalency

The $f1$ and $f2$ factors provide a simple measure of similarity between pairs of dissolution profiles. The difference factor ($f1$) is the percentage difference between two dissolution profiles at each time interval [20, 21].

$$f1 = \{[\Sigma \mid Rt - Tt \mid] / \Sigma Rt\} \times 100 \text{…….....(1)}$$

Where, Rt indicates the released amount of drug of reference formulation; and Tt, the released amount of drug of test formulation.

If the dissolution profiles are superimposed, $f1$ reaches a value of 0, whereas the factor value increases when the differences between dissolution profiles also increase from a practical point of view, values of $f1$ between 0 and 15 can be considered as superimposed dissolution profiles. The similarity factor ($f2$) can be calculated using the following expression:

$$f_2 = 50\log\left\{[1+(1/n\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\right\} \text{……..(2)}$$

Where, N indicates the number of experimental data.

Values of $f2$ between 50 and 100 can be considered as superimposed dissolution profiles.

2.3.10 IR analysis

The IR absorption spectra of pure drug, polymers and physical mixture of drug and polymer (1:1) were taken in the range of 400-4000 cm^{-1} using potassium bromide dispersion method. Fourier-transform infrared (FT-IR) spectrum of drug was obtained using FT-IR Spectrophotometer. The sample was mixed with KBr (ratio 5:95). The spectrum was scanned over the wave number range of 4000 to 400 cm^{-1}. [22, 23].

3. Results and discussion

3.1 Effect of sodium bicarbonate loading on floating property

Floating layer of BFT with different concentration of sodium bicarbonate (8, 12 and 24%) was prepared and introduced into SGF (pH 1.2) at 37±0.5 °C. At 12% sodium bicarbonate concentration; the tablets floated immediately (4-5 min) and remained buoyant for more than 12 hour. BFT with 8% sodium bicarbonate needed 7-9 min to float and remained buoyant for up to12 hours, whereas with 24% sodium bicarbonate concentration the tablets load floated immediately (3-4 min) and remained buoyant up to 10 hour. BFT with 12% sodium bicarbonate load requires less time for floating and remained buoyant for longer time. The powder mixtures for all nine FL were evaluated for bulk density, which ranged from 0.4021 to 0.4505 (g/ml), tapped density ranged from 0.4558 to 0.5056 (g/ml), Carr's index ranged from 9.81 to 12.51% and angle of repose ranged from 28.78 to 32.08°. For IRL bulk density was 0.6241 g/ml, tapped density 0.6957 g/ml, Carr's index 10.28% and angle of repose 27.05° All these results indicated that, the powder mixture possess satisfactory flow and compressibility properties.

Table 3: Evaluation of powder mixtures of bilayer floating tablets

Batches	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Angle of repose
FL-1	0.4021±0.02	0.4596±0.03	12.51	28.78±0.03
FL-2	0.4226±0.03	0.4736±0.04	10.77	32.08±0.02
FL-3	0.4439±0.04	0.5056±0.01	12.20	31.06±0.04
FL-4	0.4074±0.02	0.4521±0.02	9.89	29.67±0.01
FL-5	0.4242±0.02	0.4786±0.04	11.37	28.55±0.02
FL-6	0.4505±0.02	0.4995±0.02	9.81	32.08±0.01
FL-7	0.4054±0.02	0.4558±0.01	11.06	31.06±0.01
FL-8	0.4264±0.02	0.4734±0.04	9.93	29.67±0.02
FL-9	0.4495±0.03	0.5007±0.02	10.22	30.13±0.02
IRL	0.6241±0.02	0.6957±0.01	10.28	27.05±0.01

.* FL - Floating layer, IRL – Immediate release layer; (n=3).

Hardness of tablets of each formulation was measured and found in the range of 4-5 kg/ cm^2. Each sample was analyzed in triplicate. Percentage weight loss of the tablets of each formulation was measured and found to be in the range of 0.583 ± 0.058 to 0.813 ± 0.023 %. Tablets from each batch showed uniformity of weight as per IP limits. Tablets from each batch showed uniformity of content in the range 98.47% to 99.96% which is under pharmacopoeial specifications.

Table 4: Values of physical parameters for bilayer floating tablet formulation of Verapamil HCl prepared by employing direct compression technique

Batches	Weight Variation		Thickness (mm) ±SD	%Friability	Drug Content
	Avg.Wt (mg)	%Variation			
BFT-1	280.00	-1.43 to +1.78	2.9 ± 0.02	0.595 ± 0.044	99.24 ± 2.73
BFT-2	280.05	-2.32 to +1.25	3.0 ± 0.01	0.630 ± 0.046	99.87 ± 2.19
BFT-3	279.95	-1.41 to +1.80	3.0 ± 0.03	0.583 ± 0.058	98.95 ± 1.93
BFT-4	324.70	-1.85 to +1.54	3.3 ± 0.02	0.622 ± 0.029	99.52 ± 2.67
BFT-5	325.03	-1.54 to +1.85	3.2 ± 0.01	0.782 ± 0.031	98.73 ± 2.85
BFT-6	324.40	-1.54 to +1.23	3.2 ± 0.02	0.813 ± 0.023	99.08 ± 2.39
BFT-7	374.81	-1.60 to +0.82	3.4 ± 0.02	0.782 ± 0.031	99.96 ± 2.28
BFT-8	374.85	-1.87 to +1.33	3.5 ± 0.03	0.757 ± 0.047	98.47 ± 2.10
BFT-9	374.21	-2.67 to +1.07	3.5 ± 0.02	0.697 ± 0.027	99.44 ± 2.62

It was observed that all the tablets floated within 4-5 mins, and remained buoyant until the completion of release studies. The tablets float within 4-5 min after immersion into 900 ml 0.1 N HCl at 37 ± 0.5 °C in the dissolution vessels and the systems remain buoyant over the entire dissolution period in each case.

Table 5: Details of floating behavior of prepared batches

Batches	F_{lag} (sec.)	Floating Time (hr)
BFT-1	287 ± 3.2	21.07 ± 0.22
BFT-2	255 ± 2.8	22.07 ± 0.29
BFT-3	275 ± 1.6	20.15 ± 0.41
BFT-4	318 ± 1.3	19.08 ± 0.24
BFT-5	311 ± 2.9	19.32 ± 0.28
BFT-6	327 ± 0.9	18.35 ± 0.32
BFT-7	323 ± 1.4	15.03 ± 0.38
BFT-8	306 ± 2.7	17.37 ± 0.41
BFT-9	337 ± 1.5	12.31 ± 0.44

(n=3)

The matrices %WU and %HV increases at the beginning attains a maximum and then declines, as can be seen in Fig. 1 & 2. BFT with ratio 1:1.5 had shown greater hydration volumes than 1:1 and the ratio 1:2 had greater than 1:1.5. The curves for %WU and %HV of BFT containing the drug and polymer showed distinct intercepts. However, after 7-8 hr of dissolution the hydration volumes are practically same. Hydrophilic matrices in contact with water swell and increase their volume and weight due to water diffusion through the matrix. The increasing water content dilutes the matrix until a disentanglement concentration is attained. As the matrix polymer proportion increases, the hydration volume increases as well as the time necessary to attain its maximum. The time to reach the maximal hydration volume increases gradually as the matrix polymer content increases (Fig. 1, 2). A linear regression of the data indicated that the lines corresponding to optimized BFT formulation at different polymer ratio have distinct intercepts (BFT-2, $P < 0.0001$, BFT-3, $P<0.0001$ and BFT-6, $P<0.0001$) as well as distinct slopes (BFT-2, $P < 0.0001$, BFT-3, $P=0.0001$ and BFT-6, $P=0.0009$).

The results of the %WU and %HV data for BFT-2, BFT-3 and BFT-6 were plotted according to the Vernaud model. It is evident from Fig. 3 & 4 that tablets from batch BFT-6 hydrate and swells more rapidly than the BFT -2 and BFT-3 tablets as soon as the tablet makes contact with the dissolution test medium.

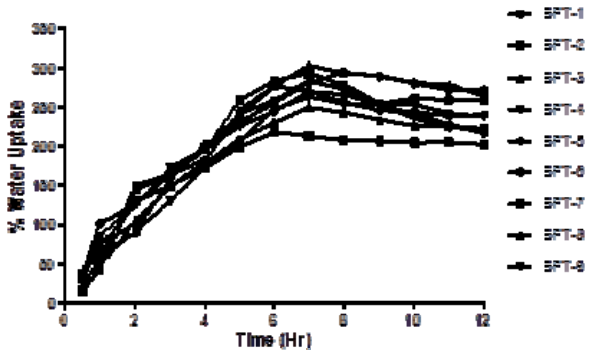

Fig 1: Plot of percent water uptake (% swelling) by tablets from batches BFT-1 toBFT-9 as a function of time (Mean, n = 3).

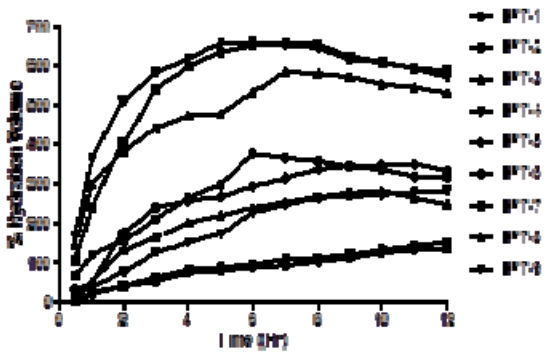

Fig 2: Plot of percent hydration volume by tablets from batches BFT-1 to BFT-9

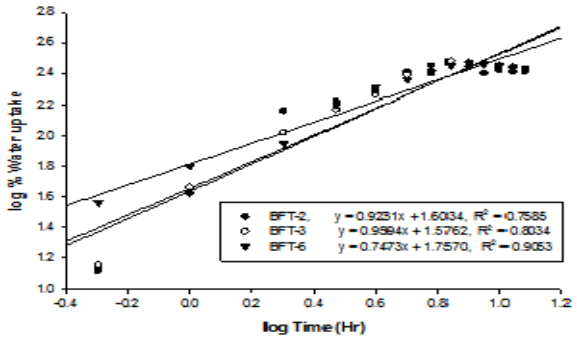

Fig 3: Plot of log percent water uptake by tablets from optimized batches BFT-2, BFT-3 and BFT-6 according to Vernaud model.

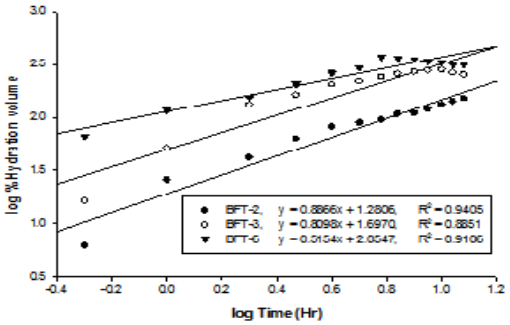

Fig 4: Plot of log percent hydration volume by tablets from optimized batches BFT-2, BFT-3 and BFT-6 according to Vernaud model.

It is clear from the figures that the formulations showed biphasic release of Verapamil hydrochloride. In the first phase, the first fraction of the dose (IRL) was released at ~30 minutes because of prompt disintegration of the fast releasing layer and the enhanced rate of dissolution of Verapamil hydrochloride from the system. This behavior was identical for all the formulations. After the release of the first fraction, the release of the sustained dose (FL) was depend upon the drug-to-total polymer and HPMC K4M:CP934 ratio. Formulation BFT-1, BFT-2 and BFT-3 which contained drug-to-total polymer ratio 1:1, control the release for longer period of time possibly because of the equal proportion of drug and polymer. BFT-2 had shown the best release as comparable to theoretical release profile as well as with Calaptin-SR (Table no.-6). For formulations BFT-7, BFT-8 and BFT-9, the drug release was 85% within 12 hours. Which contained a high polymer concentration. The first phase of the drug release profile depends on the concentration of drug in the upper layer as an immediate dose and hence followed first-order release kinetics. In the second phase of the release (1-12 hours), the data was fitted to Korsmeyer and Peppas model and the diffusion coefficient was found to be 0.4522 to 0.5458 and 0.7761 for Calaptin-SR (Table 26). As the polymer concentration in the matrix increases, the release rate decreases. Hence, the drug-to-total polymer ratio increased, the release decreased from 99.42% to 81.87%, which is due to the increased strength of the gel layer. The drug diffusion was controlled by the penetration of liquid through the gel layer. In almost all the formulations, 30% to 34% of Verapamil hydrochloride was released rapidly within 30 minutes of the experiment.

Table 6: Cumulative % release of marketed preparation (Calaptin – SR) and prepared batches.

Time (Hr)	Calaptin-SR	BFT-1	BFT-2	BFT-3	BFT-4	BFT-5	BFT-6	BFT-7	BFT-8	BFT-9
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.16	3.31	6.05	5.24	7.38	7.09	7.46	7.61	6.27	6.79	8.35
0.33	4.13	15.90	14.57	15.23	18.64	19.01	19.01	15.23	15.60	18.64
0.50	7.98	32.71	29.82	31.45	30.48	29.45	33.30	30.48	31.82	31.08
1.00	13.97	37.44	39.44	40.18	40.78	41.44	39.00	38.11	37.30	42.18
2.00	23.89	45.74	46.33	47.88	49.59	46.85	48.18	47.51	46.48	48.92
3.00	33.00	52.03	52.62	53.29	54.55	57.80	56.03	51.81	50.62	53.36
4.00	42.11	56.40	57.36	57.73	58.47	62.84	59.73	55.58	53.88	56.84
5.00	52.62	60.17	66.47	60.32	61.36	65.95	63.73	59.36	57.80	59.88
6.00	62.62	64.76	75.05	67.43	64.69	69.43	68.47	62.76	61.58	62.62
7.00	72.54	70.39	80.39	73.06	70.02	71.35	72.69	66.47	65.87	67.65
8.00	75.50	79.79	85.72	77.87	73.65	76.24	76.46	70.91	67.87	71.72
9.00	79.65	83.12	90.45	80.46	78.24	81.20	78.46	74.46	69.65	77.20
10.00	84.98	85.86	94.45	86.01	84.46	83.87	83.20	76.91	73.13	79.65
11.00	90.01	88.23	98.23	88.68	86.75	86.31	88.60	80.02	78.09	82.98
12.00	93.19	91.05	99.41	93.71	88.68	88.38	93.27	84.75	81.87	84.90

n=3

Table 7: Time required for x% drug release ($t_{x\,\%}$) i.e. $t_{33\%}$, $t_{50\%}$ and $t_{80\%}$.

Formulation	Time required for x% drug release ($t_{x\,\%}$) In Hours		
	$t_{33\%}$	$t_{50\%}$	$t_{80\%}$
Calaptin-SR	3.0	4.75	9.07
BFT-1	0.53	2.68	8.06
BFT-2	0.66	2.58	6.93
BFT-3	0.59	2.39	8.82
BFT-4	0.62	2.08	9.28
BFT-5	0.65	2.89	8.76
BFT-6	0.50	2.23	9.32
BFT-7	0.66	2.58	10.99
BFT-8	0.60	2.85	11.50
BFT-9	0.58	2.24	10.10

It is clear from the figures that the formulations showed biphasic release of Verapamil hydrochloride. In the first phase, the first fraction of the dose (IRL) was released at ~30 minutes because of prompt disintegration of the fast releasing layer and the enhanced rate of dissolution of Verapamil hydrochloride from the system. This behavior was identical for all the formulations. After the release of the first fraction, the release of the sustained dose (FL) was depend upon the drug-to-total polymer and HPMC K4M:CP934 ratio. Formulation BFT-1, BFT-2 and BFT-3 which contained drug-to-total polymer ratio 1:1, control the release for longer period of time possibly because of the equal proportion of drug and polymer. BFT-2 had shown the best release as comparable to theoretical release profile as well as with Calaptin-SR (Fig. 5 & 6).

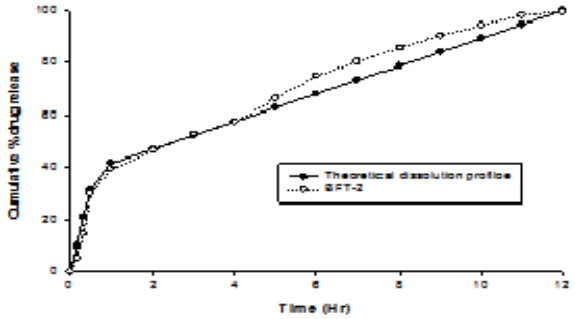

Fig 5: Comparison of *in-vitro* dissolution profiles of batch BFT-2 and theoretical dissolution profile as a function of time.

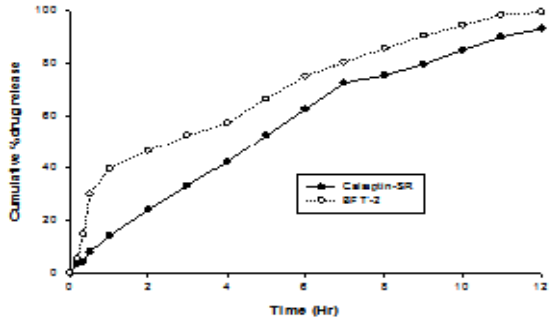

Fig 6: Comparison of *in-vitro* dissolution profiles of batch BFT-2 and Calaptin.

All dissolution profiles were described with the exponential expression attributed to Korsmeyer and Peppas model. Time required for $t_{33\%}$, $t_{50\%}$ and $t_{80\%}$ were calculated and are shown in Table 8 As expected, increasing polymer contents produce decreasing drug release rates. The effect of polymer content is attributed to an increasing tortuosity and length of the diffusion path through the matrix as the polymer content increases. Considering a linear regression, the relationship between the

dissolution parameters (k) and (n) against the polymer proportion of BFT can be seen from Table 8. The exponent (n) moves from a release mechanism predominantly controlled by diffusion toward a mechanism with a little more emphasis on relaxation, erosion and polymer dissolution as the drug release rate is restricted. This has been attributed to greater extension or exercise of hydration and dissolution of the polymeric matrix as the drug release is subject to limitation.

Table 8: Kinetic data for prepared batches and Calaptin-SR

Formulation	Best fit model	r^2	k	n (Peppas)
Calaptin-SR	Peppas	0.9976	24.1394	0.7761
BFT-1	Higuchi	0.9790	26.8592	0.4892
BFT-2	Higuchi	0.9897	29.3834	0.5458
BFT-3	Higuchi	0.9818	24.4383	0.4899
BFT-4	Higuchi	0.9683	26.8615	0.4579
BFT-5	Higuchi	0.9749	27.4506	0.4625
BFT-6	Higuchi	0.9774	28.0075	0.4604
BFT-7	Higuchi	0.9746	25.5345	0.4767
BFT-8	Higuchi	0.9647	25.6954	0.4641
BFT-9	Higuchi	0.9750	27.9262	0.4522

Table 9: Difference factor (f1) and similarity factor (f2) analysis between optimum formulation (F2) and reference product.

Time in hrs.	% Drug release		(Rt - Tt)	|(Rt - Tt)|	$(Rt - Tt)^2$
	Calaptin-SR	Optimized batch F2			
1	13.97	39.44	25.47	25.47	648.71
2	23.89	46.33	22.44	22.44	503.55
3	33.00	52.62	19.62	19.62	384.94
4	42.11	57.36	15.25	15.25	232.56
5	52.62	66.47	13.83	13.83	191.82
6	62.62	75.05	12.43	12.43	154.50
7	72.54	80.39	7.85	7.85	61.622
8	75.50	85.72	10.22	10.22	104.44
9	79.65	90.45	10.8	10.8	116.64
10	84.98	94.45	9.47	9.47	89.68
11	90.01	98.23	8.22	8.22	67.56
12	93.19	99.41	6.22	6.22	38.68
Sum (Σ)	724.16	885.92	161.82		2594.702

$$f1 = \{[\Sigma \mid Rt - Tt \mid] / \Sigma Rt\} \times 100 = 22.34$$
$$f2 = 50 \times \log \{[1 / (1 + (\Sigma (Rt - Tt)^2) / N)]^{1/2} \times 100\} = 67$$

Thus, it may be concluded that drug release from BFT is best explained by Higuchi and Peppas model and r^2 and n values represent Anomalous transport mechanism. The value of slope for best optimized batch, BFT-2 is -2.736 and P value <0.0001 (n = 0.5458, k = 29.3834 and r^2 = 0.9897). Difference factor (f1) and Similarity factors (f_2) were calculated and it was found to be 67 for optimized batch BFT-2 (Table 9). The dissolution profiles are considered to be similar when f_2 is between 50 and 100.

3.2 Infrared Absorption Spectrum

The FT-IR spectra of the pure Verapamil hydrochloride and physical mixture of drug and polymers were analysed to check for any interaction between drug and polymers. The characteristic peaks of Verapamil hydrochloride were appeared in the spectra without any significant change. The IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between Verapamil hydrochloride & the used polymers.IR spectrum showed all prominent peaks of Verapamil hydrochloride which was comparable with standard IR graph. The major IR peaks observed in Verapamil hydrochloride were (3030 and 2860) C-H stretching of methyl and methylene groups, (2838) C-H stretching vibrations of the methoxy groups, (2800 – 2300) N–H stretching vibrations of the protonated amine, (2237) C=N of stretching vibrations of the saturated alkyl nitrile, (1597, 1518 and 1462) C-H stretch of benzene ring, (1258) strong C-O stretching vibrations of the aromatic ethers Figure 7-10.

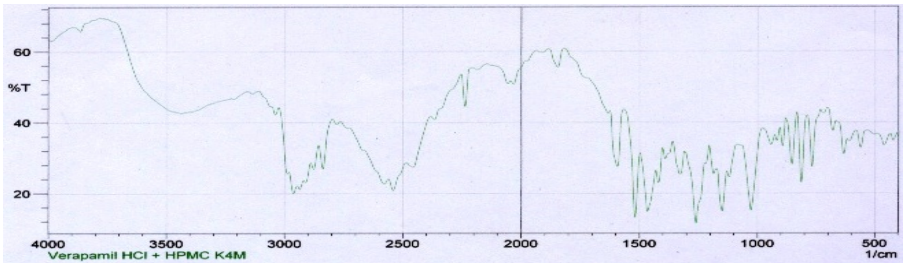

Fig 7: Verapamil HCl + HPMC K4M

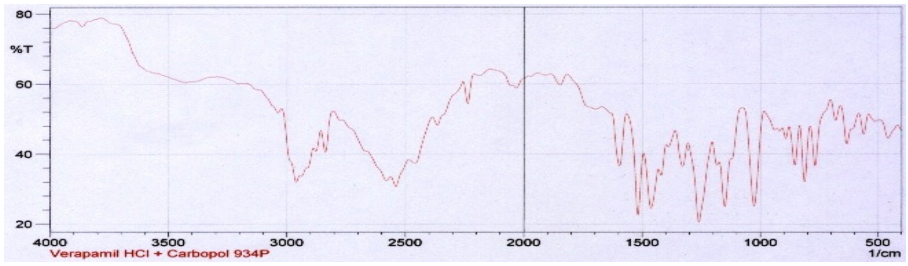

Fig 8: Verapamil HCl+CP934

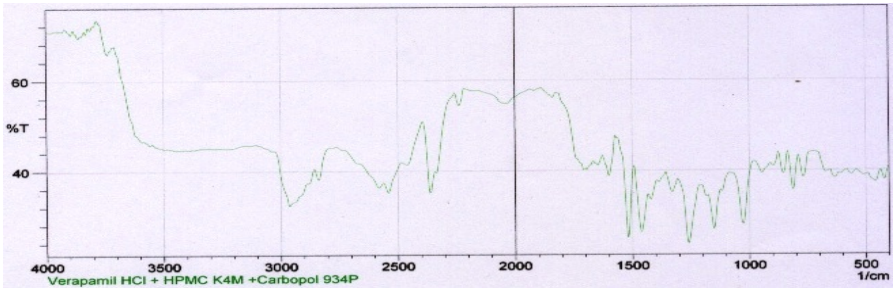

Fig 9: Verapamil HCl + HPMC K4M + CP934

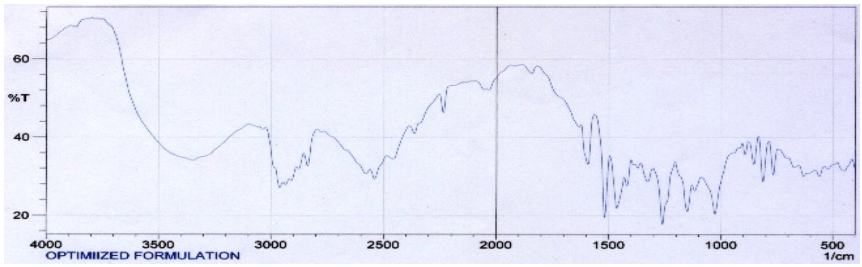

Fig 10: Optimized formulation (BFT-2)

4. Conclusion

In present work, a bilayer floating gastroretentive system for Verapamil hydrochloride was developed and optimized by using mathematical and statistical techniques. Verapamil hydrochloride was selected for this investigation because less biological half-life, to improve bioavailability by retaining the drug in acidic environment as its solubility decreases with increasing pH. It was concluded on the basis of buoyancy and *in-vitro* release kinetics that optimized formulation containing drug-polymer ratio 1:1 and HPMC K4M-CP934 1:1 gave the best *in-vitro* release of 99.42% in 12 hrs. Comparative study was done with marketed formulation of Verapamil hydrochloride (Calaptin – SR) the release of VRP from all batches of bilayer tablet followed Higuchi release kinetics. Increasing polymer contents increases the exponent (n) and reduces the release constant (k). This is attributed to an increasing restriction of drug release produced by increasing polymer proportions. This increasing restriction makes the matrices accessible for longer period of time for the action of the dissolution medium before a given quantity of the drug is released; producing a greater hydration and polymer dissolution that shift the release mechanism toward relaxation and erosion. The optimized dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolong floating time.

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