International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.9, No.8, pp 140-153, 2016

Controlled - Release Effervacent Floating Tablet of Verapamil Hydrochloride: Development and Opitmization

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Abstract : The objective of this study was to controlled - release effervescent floating tablet of verapamil hydrochloride, development and optimization in combination with natural polymer Xanthan Gum.Tablets were prepared by direct compression, using Xanthan Gum, HPMC K15 M, PVP K30, polymer in various proportions in combination, Further, the Prepared Floating Tablet were characterized for Weight variation, Friability, Hardness, Thickness, Uniformity, Drug-excipient compatibility, *In vitro* floating, Swelling Index and Stability studies. Complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations. The formulations F1, F5, F6, F9, and F10 exhibited more than 75% drug release at 12 h. The formulation F1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost upto 12 h. Based on the *in vitro* evaluation data, formulation F1 was considered as optimized formulation. On calculating and comparing R2 values for Higuchi, Korsmeyer-Peppas, matrix, and other models, F4, F5, F7, and F12 gave a good fit to the matrix model, F10 fitted the Higuchi model, and the remaining formulations were best fitted in the Korsmeyer-Peppas model. From the studies, it has been observed that effervescent based floating drug delivery system is a promising approach to achieve controlled release behavior containing Xanthan Gum, HPMC K15 M rate controlling polymer for the effective treatment high blood pressure and to control angina.
Keywords: Verapamil Hydrochloride, Xanthan Gum, floating tablets, Release kinetics.

Introduction:

Oral delivery of drug is by-far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Floating system or hydrodynamically controlled system are low density system that have sufficient buoyancy to float over the gastric contents and tending to keep afloat in the stomach without affecting the gastric emptying rate for a prolong period of time[1]. Release of ingredients may be controlled by several mechanisms for the delivery of pharmaceuticals and biopharmaceuticals[2]. Gastric retention is an approach for the drug delivery in which desirable for optimizing the therapeutic benefit of drug. The retention of drugs with narrow absorption window in the small intestinal region, longer residence time in stomach and advantageous for local action in the upper part of the small intestine. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach[3,4].This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into Non-effervescent and gas-generating system[5].

Verapamil hydrochloride, a calcium channel blocker, is weakly basic in nature and demonstrates poor bioavailability in the small intestine because of pH-dependent solubility (poorly soluble at high pH values,

highly soluble at low pH values)[6,7]. In medical practice, it is most widely used in conventional tablet form with a minimal dose of 40 mg and a maximal dose of 180 mg, and for slow release doses ranges between 120–240 mg. Only 10–20 % of total dose absorbed from the digestive tract penetrates to the systemic circulation in an unchanged form. This is due to the narrow absorption window of the drug[8].

Oral Controlled release drug delivery systems (OCRDDS) that can be retained in the stomach for a long time have many advantages over sustained release formulations. Controlled drug delivery system releases the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract[9].

Development of controlled release oral drug delivery system (CRDDS) by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. controlled release gastro retentive dosage form (CRGRDFS or GRDDS).4 Controlled release Gastroretentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a prolonged period of time and thereby improved the bioavailability. GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form[10].

Materials and Methods:

Verapamil hydrochloride (Glenmark Pharmaceutical Ltd, Indore), Polyvinyl Pyrrolidone (PVP) (SRL, Mumbai, India), Xanthan Gum (LobaChemie, Mumbai, India), Sodium bicarbonate Gum (LobaChemie, Mumbai, India), HPMC (Ranbaxy, Baddi, India), Magnesium Stearate,(LobaChemie, Mumbai, India), Lactose (LobaChemie, Mumbai, India).

Reagents

Hydrochloric acid buffer (pH 1.2) 50.0 ml of 0.2 M potassium chloride was placed in a 200 ml volumetric flask, to this 85.0 ml of 0.2 M hydrochloric acid was added and then made up to the volume with water.

4.3 Analytical Methods 4.3.1.

Verapamil hydrochloride:

The method described by Florey K was followed.81 **Stock solution:** Verapamil hydrochloride in pH 1.2 hydrochloric acid (HCl) buffer (100 g/ml). **Scanning:** From the stock solution, a suitable concentration (10 g/ml) was prepared with pH 1.2 Hydrochloric acid buffer solution and UV scan was taken between 200-400 nm. The spectrum is given in fig.1. The absorption maxima of 278 nm were selected and utilized for further studies.

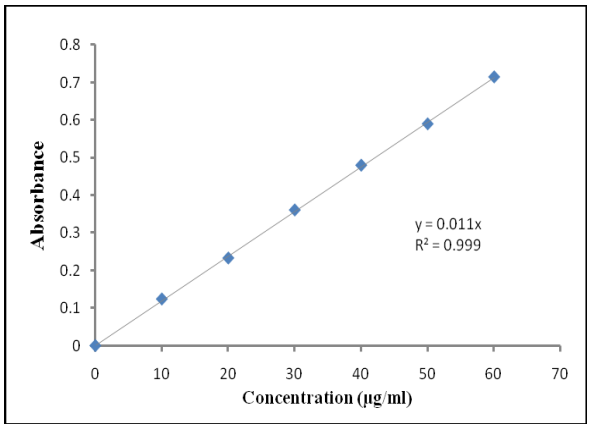

Fig.1

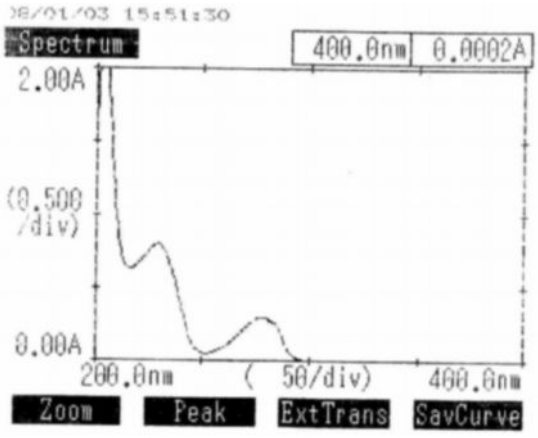

Fig. 2

Fig.1: UV-Spectra of Verapamil hydrochloride in pH 1.2 hydrochloric acid buffer

Fig. 2:Standard plot graph of Verapamil hydrochloride in pH 1.2 hydrochloric acid buffer solution

Standard Plot:

From the stock solution, 10, 20, 30, 40, 50, and 60 g/ml solutions of Verapamil hydrochloride were prepared in pH 1.2 hydrochloric acid buffer solution. The absorbance was measured at 278 nm and a graph of concentration versus absorbance was plotted. Standard plot data of Verapamil hydrochloride in pH 1.2 hydrochloric acid buffer solution is reported in table 1 and graph in fig.2

Standard plot data for Verapamil hydrochloride in pH 1.2 hydrochloric acid buffer

*Standard deviation, n = 3

Formulation of Effervescent floating tablets

The floating tablets of verapamil hydrochloride were prepared by direct compression technique. For each tablet formulation, drug, HPMC-K15M, Xanthan Gum, sodium bicarbonate, and diluents were blended homogeneously for 10 min followed by addition of magnesium stearate. The total weight of each tablet was 300 mg. The amount of Xanthan gum used was in the range of 40–90 mg, whereas HPMC was used in the range of 20-40 mg. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a Rimek Rotary Tablet Machine. Thirteen formulations were prepared by changing the amount of the ingredients as shown in table1.

Table 1: Formulation chart of effervescent floating Verapamil hydrochloride tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Verapamil Hydrochloride	120	120	120	120	120	120	120	120	120	120	120	120	120
Xanthan Gum	40	40	40	40	70	70	70	70	70	90	90	90	90
HPMC K15 M	20	40	30	30	20	40	20	40	30	20	40	30	30
Sodium Bicarbonate	20	20	10	30	10	10	30	30	20	20	20	10	40
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	70	50	70	50	60	40	40	20	40	30	10	30	00
Total weight	300	300	300	300	300	300	300	300	300	300	300	300	300

Technological characteristics of floating tablets

Weight variation:

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. For the tablets of average weight 350 mg, the % deviation allowed is ± 5 %.[11]

Percentage of weight variation = (average weight of tablet-individual tablet weight/average weight of tablet) ×100

Friability:

10 tablets were weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated using the equation[12].

% F = {1-(Wt/W)} ×100

Where, % F is percentage friability, W is the initial weight of tablet and Wt is the final weight of tablets after revolutions. Compressed tablets with a loss of less than 1 % are generally considered acceptable.

Hardness:

The hardness of core tablets was measured using Inweka hardness tester. A total of five tablets from each formulation were taken for the study and the average of the three is reported. It is expressed in kg.

Thickness and diameter:

Thickness and diameter of the tablets were determined by using Mitutoyo micrometer screw gauge[13]. The average of five tablets from each formulation was taken. It is expressed in millimeter.

Uniformity of drug content:

Drug content uniformity was determined by randomly selecting 5 tablets were powdered. The quantity equivalent to single dose of the drug was dissolved in HCl buffer solution, pH 1.2 for 5 hours with occasional shaking and diluted to 100 ml with buffer[14]. After filtration to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with the buffer. The absorbance was measured at the required λmax using a UV visible spectrophotometer. The experiments were carried out in triplicate for all formulations and average values were recorded[15].

The drug content was calculated using the following equation:

% Drug content = conc. (µg/ml) × Dilution factor × 100/ 50

Drug-excipient compatibility studies

Fourier transform infra-red spectroscopy (FT-IR):

In order to evaluate the integrity and compatibility of the drug in the formulation, drug-excipient interaction studies were performed. Pure drug and optimized formulations were analyzed by Fourier transform infra-red (FTIR) spectroscopy[16]. FTIR spectra of pure drug and its formulations were obtained by a FT-IR Shimadzu 8400S (Japan) spectrophotometer using the KBr pellet method. The samples were scanned from 400 to 4,000 cm−1 wave number.

Differential scanning calorimetry (DSC):

Differential scanning calorimetry was performed on pure sample of drug and its formulation. Calorimetric measurements were made with empty cell (high purity alpha alumina discs) as the reference[17]. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10 °C min-1. The energy was measured as Joules per kilocalorie.

***In vitro* floating studies:**

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type-II (basket) using 900 ml of 0.1 N HCl buffer solution at 100 rpm at 37 ± 0.5°C. The time required for the formulation to rise to the surface of the dissolution medium and the duration for which the formulation constantly floated on the dissolution medium were noted as floating lag time and total time, respectively[18].

Swelling Index studies:

The swelling of the polymers was measured by their ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals[19], the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of **Swelling Index** (SI) as:

Swelling Index(%) = (weight of swollen Tablet-Initial weight of tablet/initial weight of tablet) ×100

Stability studies:

The optimized formulation of Verapamil Hydrochloride were packed in screw capped bottle and aluminum foil laminated on the upper part of the bottle and these packed formulation was stored in ICH certified stability chambers. The stability studies were carried out at 25ºC/60% RH, 30ºC/65% RH for 12 months and 40ºC/75% RH for 6 months. The samples were withdrawn periodically and evaluated for their content uniformity, in vitro buoyancy studies and for in vitro drug release[20].

Result and Discussion

Tablets were prepared by direct compression. Technological characteristics of floating tablets were within the Pharmacopoeial limit. In all the formulations, weight variation of Verapamil hydrochloride gastroretentive effervescent floating tablets was in ranges, Hardness test indicated good mechanical strength and percentage friability of the tablets of all the batches remained in the range of 0.32± to 0.67±0.50 kg/cm2. Friability is less than 1%, indicated that tablets had a good mechanical resistance and thickness of the tablets was ranges from4.0±0.68 to .44±0.28 mm. The results of quality control tests reveal that all the Verapamil hydrochloride gastroretentive tablets are meeting the official pharmacopoeia requirements Table 2.

Table2: Physical properties of effervescent floating tablets of Verapamil Hydrochloride

Batch	Weight Variation	Hardness* (Kg)	Friability* (%)	Content Uniformity* (%)	Thickness* (mm)	Floating lag*time(s)	Max swelling* (%)
F1	Passes	4.2±0.05	0.58±0.05	99.05±0.30	4.44±0.28	62±2.3	395±5.5
F2	Passes	5.5±0.20	0.37±0.30	98.14±0.42	4.10±0.64	66±1.2	226±0.9
F3	Passes	5.2±0.50	0.32±0.10	99.11±0.27	4.12±0.74	90±1.8	224±5.6
F4	Passes	5.9±0.25	0.37±0.44	96.72±0.27	4.11±0.48	35±1.4	325±9.4
F5	Passes	4.5±0.51	0.55±0.86	100.01±0.64	4.0±0.68	89±1.6	265±8.6
F6	Passes	4.4±0.45	0.59±0.76	102.03±0.52	4.1±0.47	95±1.6	312±4.5
F7	Passes	4.2±0.21	0.52±0.53	97.52±0.50	4.1±0.62	31±4.8	407±4.3
F8	Passes	4.2±1.72	0.48±0.49	98.27±0.50	4.0±0.22	64±8.2	477±4.2
F9	Passes	4.4±2.35	0.47±0.45	97.45±0.27	4.0±0.54	29±2.4	258±4.2
F10	Passes	3.2±2.51	0.64±0.46	99.86±0.98	4.1±0.55	58±4.5	290±4.2
F11	Passes	3.7±0.58	0.58±0.17	100.21±0.4	4.0±0.44	63±2.2	371±4.5
F12	Passes	3.2±0.48	0.67±0.50	98.27±0.50	4.2±0.72	97±4.6	281±3.7
F13	Passes	3.1±0.56	0.62±0.05	99.47±0.18	4.2±0.54	27±3.5	361±7.2

*Standard deviation, n=3

Fourier transform infrared spectroscopy (FT-IR)

The spectrum was measured in the solid state as Potassium bromide dispersion. The bands were recorded using the FT-IR technique. FT-IR spectral study revealed that similar characteristic peaks appear with minor differences, for the pure drug and drug formulation, as shown in fig.3. Hence it was confirmed that no chemical interaction had taken place between the drug and the polymer used. The data for the same is given in table 3.

Table 3: FT-IR Spectral data of effervescent floating tablet of Verapamil hydrochloride (F1) and Verapamil hydrochloride pure drug

Functional groups	Frequency of pure drug (cm-1)	Frequency of formulation (cm-1)
C-H Stretching vibrations of methyl and methylene groups	3030.5-2860	3051.49–2789.16
C-H stretching vibrations of the methoxy group	2840	2843.17
C-O stretching vibrations of the aromatic ethers	1262	1255.70
sharp weak bond due to C=N stretching vibrations of the alkyl nitrile	2236	2235.57
skeletal stretching vibrations of the benzene ring	1607, 1518	1599, 1518

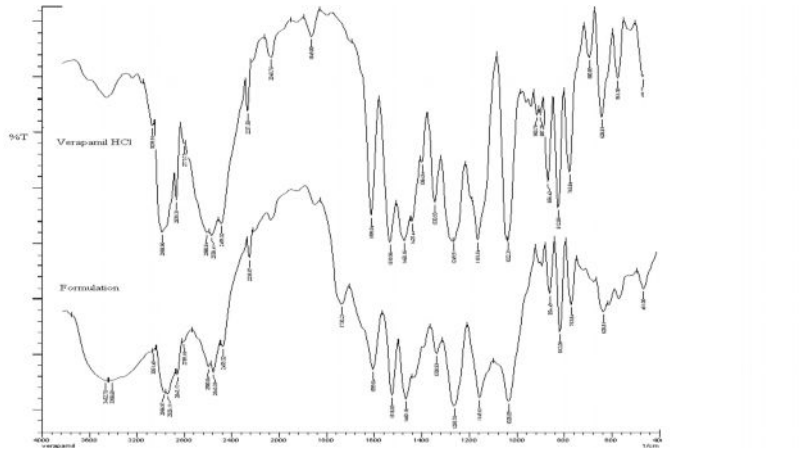

Fig.3: FT-IR Spectra of effervescent floating tablet of Verapamil hydrochloride (F1) and Verapamil hydrochloride pure drug

Differential scanning calorimetry (DSC)

DSC is a fast and reliable method to screen drug and excipient compatibility, and to provide maximum information about the possible interactions. DSC study was carried out for Verapamil hydrochloride and its formulation F1. Thermogram of pure drug shows a sharp endothermic peak at 138.25 ^{o}c, which corresponds to its melting point. Matrix tablet formulation F1 also showed endothermic peak at 139.53 ^{o}c, which corresponds to the melting point of the drug. The evaluation of thermograms obtained from DSC revealed no interaction between the drug and the excipients. From the thermograms, it was evident that melting point of Verapamil hydrochloride had not changed when it was formulated as a floating matrix tablet. The thermogramsobtained are presented in fig.4 and the data is given in Table 4

Table 4: DSC thermogram data of effervescent floating tablet of Verapamil hydrochloride (F1) and Verapamil hydrochloride pure drug

Drug and formulation	TO(°C)	Tm(°C)	Tc(°C)	Melting range(°C)
Verapamil Hydrochloride	131.20	139.53	145.73	14.10
Formulation F1	130.99	138.25	144.85	13.86

To - Onset of melt, Tm - Melting point, Tc - Completion of melt,

DSC data obtained at 10°C/min

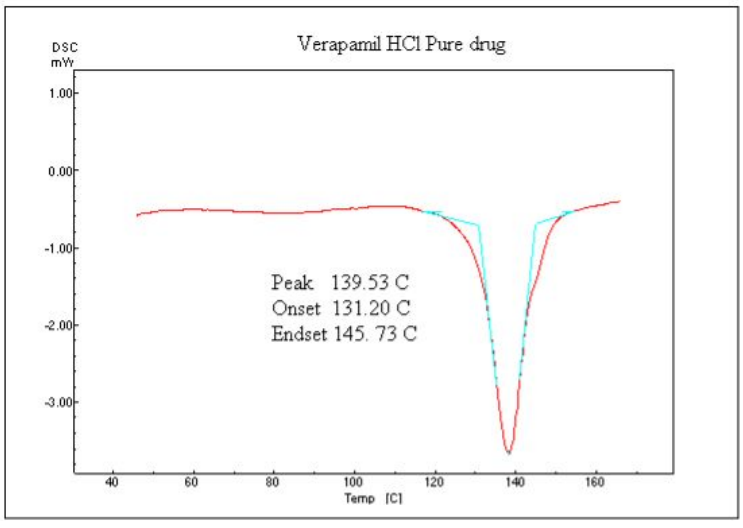

Fig.4: DSC thermograms of effervescent floating tablet of Verapamil hydrochloride (F1) and Verapamil hydrochloride pure drug

***In vitro* buoyancy studies**

Sodium bicarbonate was added as a gas-generating agent. As the dissolution medium (0.1 N HCl) got imbibed into the tablet matrix, the acidic fluid interacted with Sodium bicarbonate resulting in the generation of CO_2. The generated gas was entrapped and protected within the gel, formed by the hydration of polymer and Xanthan gum, and thereby decreased the density of the tablet. As the density of the tablet fell below 1g/ml, the tablet became buoyant. Xanthan gum with HPMC produced tablets with good gel strength, entrapping CO_2 gas within and thereby imparting stable and persistent buoyancy. The results demonstrated that the time taken by the system to float in the medium, decreased with increasing amount of effervescent agent and increased with increasing levels of Xanthan gum, which was true in F13. The higher amount of effervescent agent caused faster and higher CO_2 generation. Thus, Sodium bicarbonate was essential to achieve optimum buoyancy. In general, gastric emptying time was 4 h. The extended gastric residence time of the drug in the stomach caused increased absorption due to the fact that the proximal part of the intestine was the main absorption site for Verapamil hydrochloride. Moreover, during formation of the floating tablets, evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix. The amount of sodium bicarbonate also played an important role in floating lag time of tablets, the higher the amount the lesser the floating lag time, and vice versa. Fig. 5 shows the effect of concentration of Sodium bicarbonate on floating lag time,duration of floating and floating behavior and concentration of the tablet is shown in the Table 5 and Figure. 6.

Table 5: Effect of Sodium bicarbonate on onset and duration of floatation of effervescent floating tablet of Verapamil hydrochloride (F1)

Amount of sodium bicarbonate (mg)	Onset of floating (s)	Duration of floating (h)
10	92±3.86	16±0.81
20	62±2.96	21±0.36
30	32±2.50	24±0.69
40	27±0.05	18±0.75

*Standard deviation, n=3

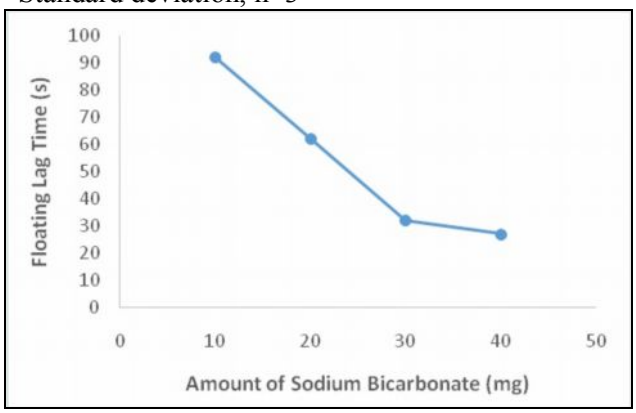

Fig. 5: Effect of amount Sodium bicarbonate on floating lag time of effervescent floating tablet of Verapamil hydrochloride (F1)

At initial time **At 18th Sec** **At 8th h**

Fig. 6: Photographs of *in vitro* floating behavior of effervescent floating tablet at different time intervals

Swelling Index of effervescent floating : The swelling of the polymers used could be determined by water uptake of the tablet. The percent swelling of the tablet was determined at different time intervals. The complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations. The maximum percentage of swelling of F8 was found to be higher, when compared to other formulations, and least percentage of swelling was found in F3. Water uptake data is presented in Table 6 and Figure. 7 shows effect of various ingredients on dynamic water uptake of formulations at the end of 8 h. There was rapid increase in percentage swelling of the F4, F6, and F7 at 1 h. F8 showed a gradual increase in percentage of swelling at the end of 8 h. The increase in the concentration of Xanthan gum retarded the water uptake during the first hour. F2, F3, and F5 showed a decrease at the end of 8 h. There was no significant difference observed in the swelling property by varying the concentration of Sodium bicarbonate, but less concentration of lactose in F8 showed maximum swelling ($p \geq 0.05$).

Table 6: % Swelling Index of effervescent floating tablet of Verapamil hydrochloride formulations in pH 1.2 hydrochloric acid buffer

Time (h)	Swelling Index (%)Time (hrs) (n=3) Mean±SD												
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	226± 2.3	189± 2.8	213± 1.4	247± 1.6	139± 3.1	263± 2.5	249± 1.2	183± 1.1	111± 4.3	113± 3.2	111± 2.9	77±1 .1	119± 3.6
2	234± 4.1	206± 3.2	217± 2.5	250± 2.1	196± 6.0	235± 1.5	252± 1.5	265± 0.9	155± 5.5	162± 4.2	171± 1.1	135± 2.6	208± 2.2
3	245± 5.6	247± 3.6	243± 1.9	250± 5.3	261± 4.2	267± 2.1	257± 1.8	299± 1.5	188± 6.5	191± 1.6	197± 0.4	152± 3.2	226± 3.5
4	271± 3.7	277± 7.1	268± 4.3	259± 4.2	263± 3.8	276± 2.6	323± 2.4	340± 2.1	216± 5.1	228± 1.9	235± 1.2	164± 4.3	245± .33
5	291± 5.2	284± 2.4	289± 5.1	341± 5.5	271± 4.3	309± 1.6	337± 3.6	345± 2.6	237± 6.5	260± 2.2	271± 1.9	205± 4.7	262± .15
6	312± 2.3	296± 1.6	295± 6.2	318± 3.6	277± 1.9	325± 2.5	349± 4.0	411± 2.3	257± 4.3	264± 3.7	302± 2.0	233± 2.1	290± .23
7	327± 5.2	305± 2.9	266± 2.3	350± 6.4	270± 5.2	332± 4.1	372± 5.8	441± 2.5	251± 1.3	291± 2.3	299± 2.2	257± 1.1	311± 3.6
8	396± 4.5	226± 3.1	223± 4.4	325± 2.2	265± 5.5	311± 3.9	407± 6.9	477± 2.1	258± 1.7	290± 2.2	372± 0.5	281± 2.1	361± 5.1

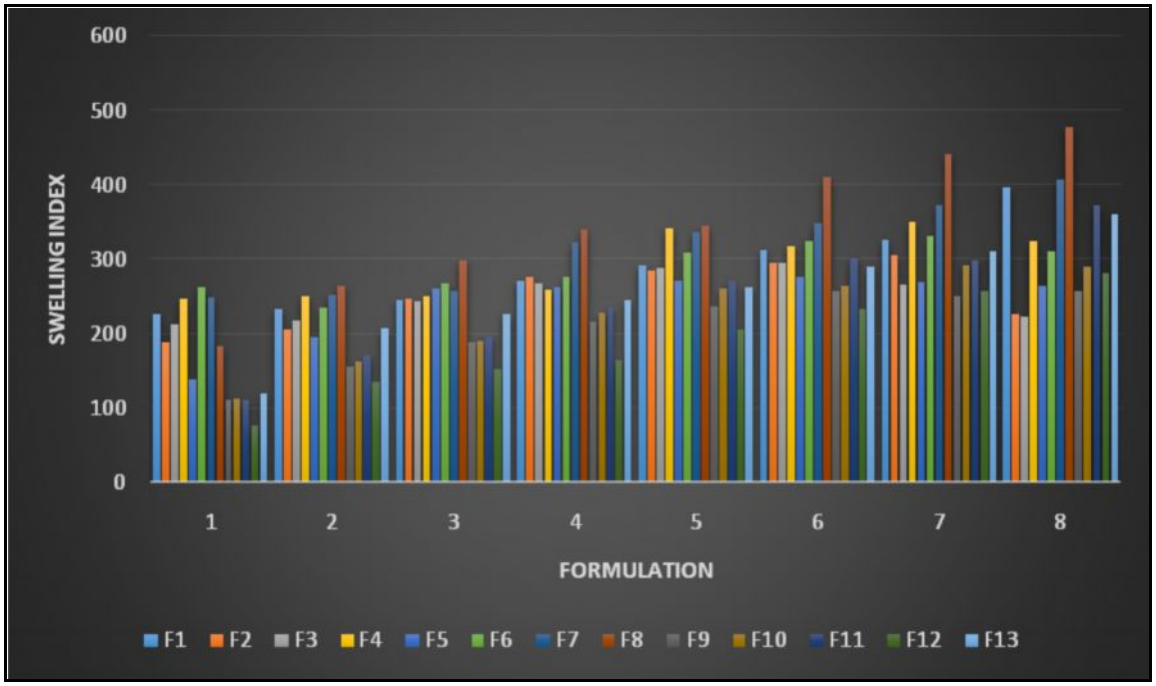

Fig. 7: Effect of various concentrations of ingredients on swelling index of floating tablets of Verapamil hydrochloride at the end of 8 h

***In vitro* drug release studies:**

The concentration of gum, polymer, and diluent had a remarkable influence on the drug release. Increase in the concentration of gum with decrease in lactose concentration, decreased the drug release. This may be due to the formation of thick gel barrier. The *in vitro* drug release data is presented in Table 7 and 8 and profile is presented in Figure 8 and 9. The F1, F5, F6, F9, and F10 exhibited more than 75% drug release at 12 h. The F1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost upto 12 h. F8 showed the least drug release among all other formulations; this may be due to the formation of a thick gel barrier on the tablet. As the thickness of the gel barrier increased, the drug took more time to diffuse through it; this was observed in other formulations which showed higher swelling index.

Table 7: *In vitro* drug release data of effervescent floating tablets of Verapamil hydrochloride in pH 1.2 Hydrochloric acid buffer(F1-F6)

Time (h)	% Cumulative drug release*					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	30.86±0.21	15.20±0.45	17.41±0.13	19.43±0.32	21.32±0.18	15.57±0.91
2	40.74±0.43	21.62±0.33	26.25±0.10	25.58±0.18	29.96±0.21	24.91±0.85
3	46.05±0.14	29.44±0.12	33.87±0.22	30.73±0.43	34.27±0.29	34.15±0.48
4	52.74±0.19	33.55±0.32	40.49±0.31	35.99±0.89	45.63±0.43	45.64±0.39
5	58.12±0.26	38.21±0.33	45.29±0.41	39.85±0.56	51.56±0.47	53.78±0.31
6	62.66±0.43	42.91±0.42	52.16±0.26	44.32±0.71	56.03±0.59	62.20±0.11
7	65.54±0.56	46.72±0.21	55.37±0.39	47.58±0.23	60.30±0.62	68.49±0.39
8	66.48±0.20	47.47±0.19	56.21±0.43	48.40±0.28	64.22±0.47	69.41±0.29
12	78.36±0.25	63.45±0.12	71.02±0.56	61.35±0.17	76.97±0.67	77.09±0.35

*Standard deviation-mean±SD, n=3

Table 8: *In vitro* drug release data of effervescent floating tablets of Verapamil hydrochloride in pH 1.2 Hydrochloric acid buffer (F7-F13)

Time (h)	% Cumulative drug release*						
	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
1	18.86±0.34	12.73±0.32	16.50±0.45	15.92±0.32	13.23±0.66	20.92±0.55	10.35±0.33
2	25.20±0.45	18.68±0.43	27.19±0.55	26.40±0.67	21.38±0.21	26.92±0.32	18.03±0.01
3	28.00±0.56	22.74±0.56	34.63±0.32	34.44±0.52	26.46±0.45	34.75±0.46	22.52±0.60
4	36.64±0.12	28.49±0.76	41.20±0.43	41.03±0.33	31.18±0.67	39.74±0.76	26.94±0.07
5	43.61±0.44	31.77±0.89	48.47±0.58	47.69±0.90	35.91±0.32	47.30±0.24	31.21±0.55
6	46.10±0.21	36.40±0.71	52.53±0.92	52.44±0.12	39.14±0.71	50.33±0.54	34.58±0.32
7	48.55±0.26	38.82±0.44	59.34±0.13	58.62±0.32	44.17±0.67	57.31±0.77	39.50±0.15
8	49.45±0.78	39.42±0.64	63.39±0.33	62.40±0.45	47.11±0.56	59.31±0.89	42.32±0.31
12	61.59±0.92	51.83±0.13	75.74±0.41	78.22±0.22	59.92±0.34	73.46±0.87	54.96±0.60

*Standard deviation-mean±SD, n=3

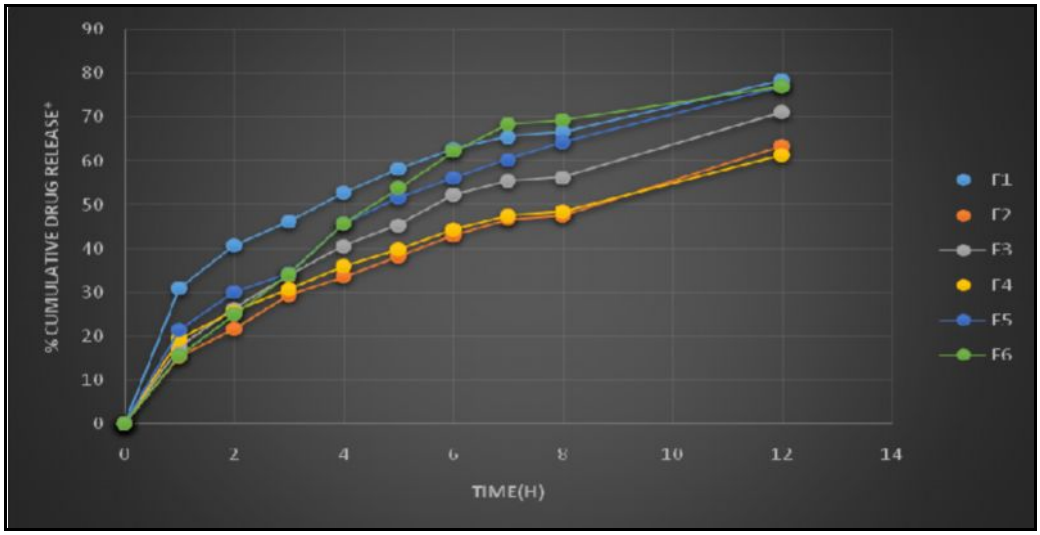

Fig.8: *In vitro* drug release profiles of Verapamil hydrochloride effervescent floating tablets (F1-F6)

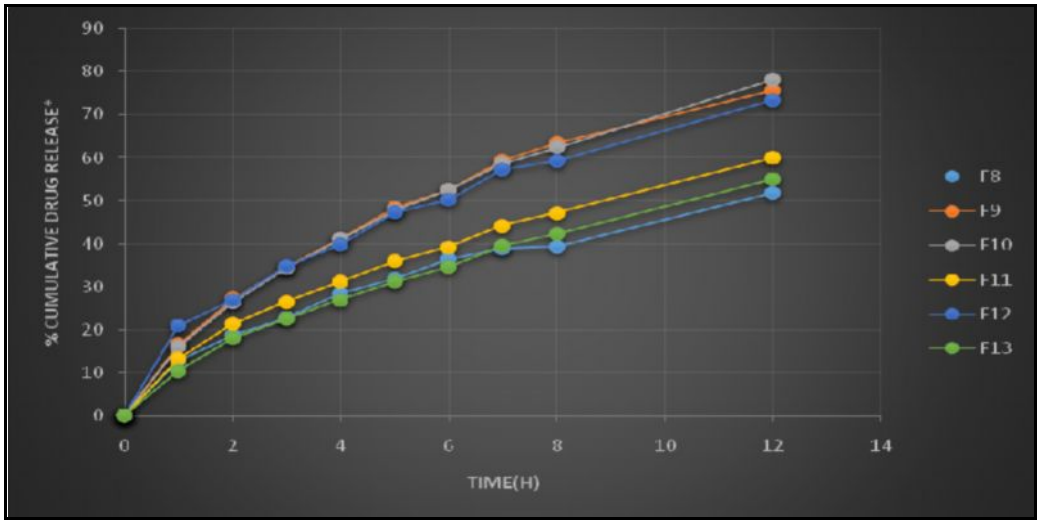

Fig. 9: *In vitro* drug release profiles of Verapamil hydrochloride effervescent floating tablets (F7-F13)

Mathematical model fitting of obtained drug release data

The *in vitro* drug dissolution profiles were fitted to various models and release data was analyzed on the basis of Korsmeyer-Peppas equation and Higuchi kinetics. The diffusion exponent ranges from 0.3771–0.6997. The release rates *k* and *n* values of each model were calculated by PCP disso v2.08 software. Co-efficients of correlation (R2) were used to evaluate the accuracy of the model fitting. The R2, *k*, and *n* values are given in table 6.08. On calculating and comparing R2 values for, Korsmeyer-Peppas, Matrix, and other models, F4, F5, F7, and F12 gave a good fit to the Matrix model, and the remaining formulations best fitted the Korsmeyer-Peppas model.

F1, F4 and F7 exhibited Fickian release and other formulations showed non-Fickian or anomalous release. F4 and F7 best fitted to the matrix model with Fickian release; F5 and F12 best fitted to the matrix model with non-Fickian release. If the value of „*n*" in Korsmeyer-Peppas is 0.5 or less, the release mechanism follows a Fickian diffusion, and for anomalous or non-Fickian, release the release is mainly by diffusion with *n* values between 0.5-1. This model was used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well-known or, when more than one type of release phenomenon could be involved. The fundamental of diffusion is based on Fick"s laws, which describes the macroscopic transport of molecules by a concentration gradient show in Table 9.

Table 9: Kinetic treatment of dissolution profile of tablets (Values of r2, k, and n for tablets) and mechanism of drug release

Batch	Korsmeyer – Peppas			Matrix		Mechanism of drug release	Release kinetics
	n	R2	k	R2	K		
F1	0.3771	0.9981	31.1077	0.9811	24.7943	Fickian	Peppas
F2	0.5737	0.9981	15.1110	0.9950	17.3367	Non-Fickian	Peppas
F3	0.5714	0.9975	17.8613	0.9966	20.3088	Non-Fickian	Peppas
F4	0.4660	0.9982	18.9024	0.9986	17.7889	Fickian	Matrix
F5	0.5380	0.9948	20.8757	0.9967	22.3909	Non-Fickian	Matrix
F6	0.6997	0.9868	16.2306	0.9775	23.3020	Non-Fickian	Peppas
F7	0.4963	0.9899	18.1986	0.9949	18.0932	Fickian	Matrix
F8	0.5675	0.9981	12.6702	0.9956	14.3660	Non-Fickian	Peppas
F9	0.6208	0.9975	17.2819	0.9937	21.5235	Non-Fickian	Peppas
F10	0.6405	0.9985	16.6296	0.9919	21.5147	Non-Fickian	Peppas
F11	0.5997	0.9992	13.6038	0.9941	16.3669	Non-Fickian	Peppas
F12	0.5254	0.9962	19.8444	0.9976	20.8679	Non-Fickian	Matrix
F13	0.6597	0.9986	10.7988	0.9867	14.5388	Non-Fickian	Peppas

Stability studies

Stability studies were performed for the optimized formulation F1 to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25ºC/60% RH, 30ºC/65% RH for 12 months and 40ºC/75% RH for 6 months. There was no significant change in the physical appearance and drug content during the study period. The results of drug content determination during stability testing period are reported in Table 10. The drug content in the formulation(F1) in long-term storage conditions and accelerated storage conditions along with 95% confidence interval was plotted using Sigmaplot software 12.0. The observations of long-term storage conditions and accelerated conditions are shown in the Figure10, Figure 11 and Figure 12. Results showed that changes in the parameters evaluated, were very small and were not significant.

Table 10: Stability study data of effervescent floating tablet formulation (F1) of Verapamil hydrochloride

Stability condition	Sampling interval (months)	Physical appearance	% Drug content F1 (mean ± S.D*)
25o±2oC/60±5% RH	**0**	No change	99.25 ± 0.25
	3	No change	99.30 ± 0.42
	6	No change	98.47 ± 0.25
	12	No change	98.25 ± 0.27
30o±2oC/65±5% RH	**0**	No change	99.44 ± 0.25
	3	No change	99.14 ± 0.15
	6	No change	98.47 ± 0.57
	12	No change	98.13 ± 0.13
40°±2oC/75±5% RH	**0**	No change	99.25 ± 0.83
	6	No change	98.50 ± 0.89
	12	No change	96.24 ± 0.56

*Standard deviation- mean±SD, n=3

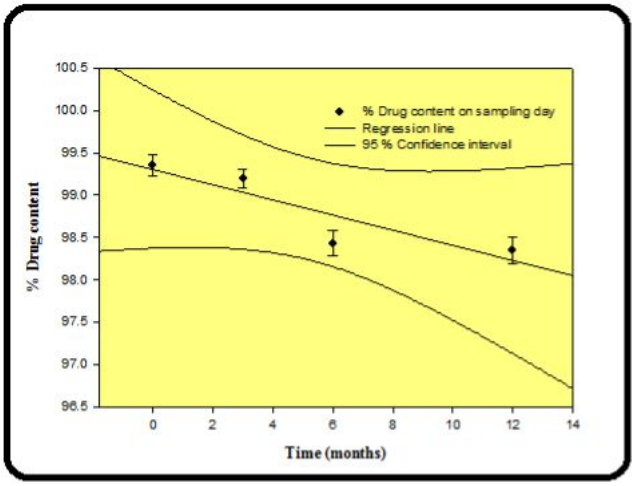

Fig. 10: % Drug content in the effervescent floating tablet of Verapamil hydrochloride (F1) when stored at 25 ± 2 °C & 60 ± 5 % RH for 12 months

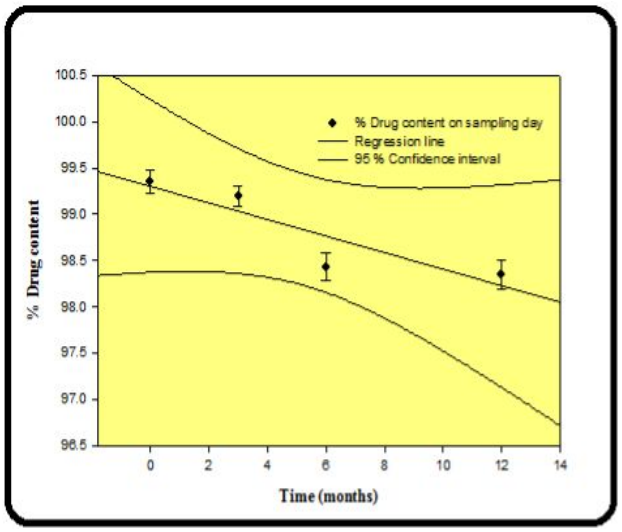

Fig. 11: % Drug content in the effervescent floating tablet of Verapamil hydrochloride (F1) when stored at 30 ± 2 °C/65 ± 5 % RH for 12 months

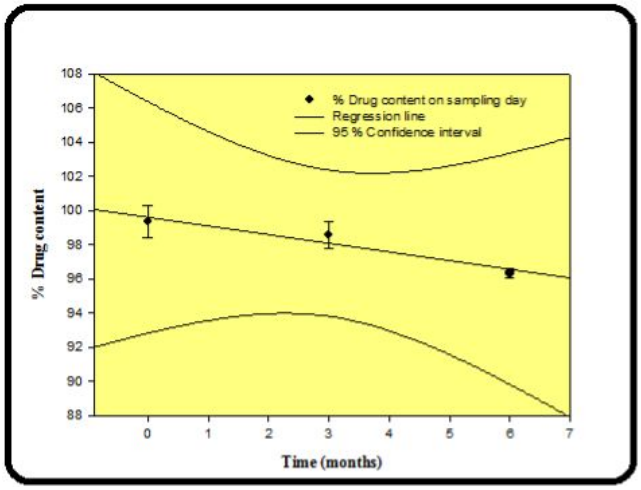

Fig. 12: % Drug content in the effervescent floating tablet of Verapamil hydrochloride (F1) when stored at 40 ± 2 °C/75 ± 5 % RH for 06 months

Conclusion:

From the above studies, it has been observed that effervescent based floating drug delivery system is a promising approach to achieve increase gastric residence time and thereby improve its bioavailability, All the prepared formulation was found to be of circular shape with no cracks. Friability and hardness were within the standard limits thus showing good mechanical strength of tablets. The drug content was well within the Pharmacopoeial limits indicating uniform distribution of drug within the effervescent based floating tablet dosage form. The formulations of F1, F5, F6, F9, and F10 exhibited more than 75% drug release at 12 h and F1 exhibited a maximum of 30 % drug release in the 1st hour and constant release for almost upto 12 h. Based on the *in vitro* evaluation data, formulation F1 was considered as optimized formulation. Short-term stability studies of optimized formulations F1 indicate, that there are no significant changes in drug content and dissolution parameter values. Thus the objective of formulating a floating dosage form Verapamil hydrochloride has been achieved.

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