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DEVELOPMENT AND *IN VITRO* EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF VERAPAMIL HCl

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ABSTRACT

Gastro retentive controlled release drug delivery system of Verapamil HCl was formulated to increase the gastric retention time of the dosage form with controlling the drug release pattern. Different grades of hydroxy propyl methyl cellulose derivatives; Methocel K4M and Methocel K15MCR were incorporated for their gel forming properties. Tablet buoyancy was achieved by incorporating a mixture of gas generating agents; sodium bicarbonate and anhydrous citric acid. *In vitro* dissolution studies were carried out for eight hours using USP XXII paddle type apparatus using 0.1N HCl as the dissolution medium. All the gastro retentive tablets showed good *in vitro* buoyancy. Tablets swelled radially and axially during buoyancy study. The release kinetics were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be governed by polymer type and content. Formulations were characterized by physical characterization, drug loading content and Fourier Transform Infrared spectroscopy (FT-IR). Good results were obtained in the tests and the FT-IR spectroscopic studies indicating no interaction and the stability of Verapamil HCl in the used excipients. Based up on the results, it was proved that a proper balance between rate retarding polymer and gas forming agents is obligatory for efficient buoyancy and controlled drug release.

INTRODUCTION: Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. Oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady

state by delivering drug in a controlled and reproducible manner. One of the novel approaches in the area of oral sustained release drug delivery is to formulate a gastro retentive 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 to improve the solubility, bioavailability and the therapeutic efficacy of the drugs [2].

Several techniques have been proposed to increase the gastric residence time of the dosage forms such as buoyancy or floating system [3], hydrodynamically balanced system [4], expanding or swelling system, biomucoadhesive system [5], sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time.

Gastro retentive floating tablet can be prepared by incorporating hydrophilic cellulose derivatives that swell remarkably to reduce the bulk density, and gas generating agents that form CO_2 in presence of aqueous media to make the dosage form float initially. Once a drug floats by the emitted gas, it remains buoyant in the gastric fluid for a longer period due to the reduction in the bulk density that finally cause a prolonged gastric residence time. This floating dosage form is well known as a Hydrodynamically Balanced System (HBS) [6].

Verapamil HCl is a calcium channel blocker used in treatment of angina pectoris, hypertension and supraventricular tachyarrhythmia [7]. In atrial fibrillation, Verapamil HCl is more effective than digoxin for controlling ventricular rate [8]. Though it is well absorbed from GIT still it has low bioavailability (10–20%) and short half-life (4 hr) making its dosing frequency high due to the first-pass effect.

Moreover, Verapamil HCl shows pH dependent solubility. It is highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH) [9]. Thus, the physicochemical properties of Verapamil HCl and its short half-life make it a suitable candidate for preparation of floating tablet.

The objective of the present study is to prepare gastro retentive floating tablets of Verapamil HCl and to evaluate the rate retarding ability of gel forming polymers. Effects of polymer loading upon the floating lag time of tablets, release rate, mean dissolution time and release mechanism were evaluated with the help of various mathematical model.

MATERIALS: Verapamil HCl, Methocel K4M and Methocel K15MCR were found as gifts from Incepta Pharmaceuticals Ltd. Polyvinyl pyrrolidone (PVP K-30), sodium bi carbonate and citric acid were collected from ACI Pharmaceuticals Ltd. All other ingredients were of analytical grade and procured from local market.

METHODS:

Preparation of floating tablets of Verapamil HCl: Different formulation variables were used to prepare the tablets of Verapamil HCl by mixing required quantities of various ingredients as per **Table 1**. Particular attention was given to ensure uniform mixing of the components. Buoyancy of tablets was achieved by adding an effervescent mixture of sodium bi carbonate and anhydrous citric acid. Each item was accurately weighed by an electronic balance (SHIMADZU AY-200, Japan) and finally compressed by using a single punch tablet compression machine fitted with 13 mm flat faced punches. Compression stage was controlled to produce a 5 kg/cm^2 tablet crushing strength. Die and punch were lubricated each time before compression. Tablets of each batch were stored in airtight container at room temperature in a desiccator.

Evaluation of Tablets: The tablets of each batch were evaluated for thickness, diameter, weight variation, hardness, and friability.

Randomly collected 10 tablets of each batch were evaluated for thickness and diameter by digital slide calipers and then they undergo weight variation test. Each tablet was individually weighed and the average weight & standard deviation of 10 tablets was calculated. Then the tablets were tested by Monsanto hardness tester. Another ten tablets were weighed and placed in the Electorlab friabilator and the apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again.

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS FOR FLOATING TABLETS OF VERAPAMIL HCl (IN MG)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Verapamil HCl	120	120	120	120	120	120	120	120	120	120
Methocel K4M	130	140	150	160	170	–	–	–	–	–
Methocel K15MCR	–	–	–	–	–	130	140	150	160	170
Avicel PH 101	150	140	130	120	110	150	140	130	120	110
PVP K-30	20	20	20	20	20	20	20	20	20	20
Sodium bi carbonate	50	50	50	50	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Purified talc	5	5	5	5	5	5	5	5	5	5

The percentage of friability was measured using the formula of Gendle *et al*., 2010 [10].

$$\% F = \{1- (W_t/W)\} \times 100$$

where, %F= friability in percentage; W = Initial weight of tablets; W_t = weight of tablets after revolution

The averages of diameter, thickness, hardness of tablets of each formulation along with the weight variation and % friability of each batch have been provided in **Table 2**.

***In vitro* Buoyancy Studies:** *In vitro* buoyancy was determined by buoyancy lag time by the method of Sharmin *et al*., 2011 [11]. The test was performed by placing three tablets of each batch in a 250 ml beaker, containing 200 ml of 0.1 N HCl having pH of 1.2, maintained at 37±0.5°C in a water bath. Their physical state was observed for 24 hr. The time between introduction of the dosage form and its buoyancy on the 0.1 N HCl (lag time) and the time during which the form remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.

Swelling Study: The floating tablets were weighed individually and placed separately in a glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1 hr interval until 24 hr, the tablets were taken from the beaker and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed and swelling index (SI) was calculated using the following formula [11].

$$SI = \{(W_t-W_0)/W_0\} \times 100$$

where, W_t is the weight of tablet at time t and; W_0 is the initial weight of tablet.

Compatibility Studies by FT-IR: FTIR spectra were taken in IR-Prestige 21, Shimadzu, Japan by scanning the sample in potassium bromide (KBr) discs. Before taking the spectrum of the sample, a blank spectrum of air back ground was taken. To examine any degradation and/or interaction with drug and used excipients, Infrared spectra of Verapamil HCl and physical mixture of drug-excipients which were recorded between 400 to 2000 cm-1 on FT-IR.

***In vitro* Dissolution Studies:** The *in vitro* dissolution study was performed by using a USP XXII paddle apparatus at 50 rpm [12]. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and was maintained at 37±1°C. 5 ml of the dissolution medium was withdrawn at specified time interval until 8 hr. Exact 5 ml of fresh medium was replaced to the dissolution vessel after each withdrawal to maintain a constant volume. The samples withdrawn were analyzed by using a UV spectrophotometer (Shimadzu, Japan) at 278 nm.

***In vitro* Drug Release Kinetic Studies:** The dissolution profile of all the batches were fitted to zero order, first order, Higuchi and Korsemeyer-peppas [13] model to ascertain exact mechanism of drug release from the tablets. To characterize the drug release rate in different experimental conditions, $T_{25\%}$, $T_{50\%}$ (mean dissolution time) and $T_{80\%}$ were calculated from dissolution data according to the following equations [14]:

$$T_{25\%} = (0.25/k)^{1/n}$$

$$T_{50\%} = (0.5/k)^{1/n}$$

$$T_{80\%} = (0.8/k)^{1/n}$$

Mean dissolution time (MDT) value is used to characterize the drug release rate from the matrix. A higher value of MDT indicates a lower drug releasing

ability of the solid dispersion and vice-versa. Mean Dissolution Time can also be calculated by the following equation.

$$MDT = (n/n+1).\ K^{-1/n}$$

where *k* is the antilog of intercept & *n* is a release exponent of Korsmeyer's plot.

RESULTS AND DISCUSSION: The intra gastric floating tablets of Verapamil HCl were off-white, smooth and flat shaped in appearance and were prepared by direct compression method. The diameter and thickness of floating tablets was measured by digital slide calipers and were ranged between 13.13 to 13.22 mm and 2.84 to 3.08 mm respectively. The hardness of the floating tablets was measured by Monsanto hardness tester and was found uniform for all the batches ranging from 18 to 25 kg/cm^2. Weight variation and friability for the formulations yielded satisfactory results that indicate the compression stage was controlled. The results are summarized in **Table 2**.

TABLE 2: PHYSICAL PROPERTIES OF FLOATING TABLET OF VERAPAMIL HCl

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Average weight (mg)	Friability (%)
F1	13.18±.07	3.01±0.08	21.2±.13	500±1.04%	0.28
F2	13.22±.09	3.07±0.12	24.5±.16	500±1.10%	0.24
F3	13.15±.02	3.05±0.08	20.2±.11	500±0.78%	0.34
F4	13.21±.04	3.05±0.06	21.5±.14	500±0.94%	0.32
F5	13.17±.06	3.08±0.05	24.1±.09	500±1.04%	0.19
F6	13.17±.05	3.33±0.06	19.9±.16	500±0.87%	0.29
F7	13.16±.09	2.96±0.13	25.1±.09	500±1.01%	0.16
F8	13.16 ±.02	2.99±0.04	24.3±.13	500±0.69%	0.21
F9	13.13±.02	2.84±0.03	19.8±.14	500±0.84%	0.41
F10	13.15±.03	2.91±0.05	18.6±.16	500±1.03%	0.45

The buoyancy lag time and total floating time of each formulation was determined triplicate in 0.1N HCl and the results are presented in **Table 3**. Nine out of twelve formulations floated very quickly and had floating lag time below 1 minute. Those formulations floated on acidic media for more than 8 hrs to more than 18 hrs. Formulation F4 and F8 showed shorter buoyancy lag time (18 sec and 15 sec) with a total floating time of more than 12 hrs to more than 18 hrs respectively.

But formulation F1 failed to float and settled on the vessel after disturbing on the media. Effervescent floating tablets float over a long period initially by emitting CO_2 gas and then by the reduced bulk density of the matrix that was achieved by rapid swelling of the incorporated polymer.

Formulation F1 was found to go upward due to the release of gas in the acidic medium and then again turned down probably due to the lack of necessary bulk density reduction. The polymer used (Methocel K4M) in the matrix failed to swell instantaneously and hence, was unsuccessful to float over the medium. But, Methocel K15MCR was found to have better swelling capacity compared to Methocel K4M when incorporated at same ratio in formulation F1 and F6. Formulation F6 floated within 20 seconds after placing in the acidic media.

FIGURE 1: FLOATING OF TABLETS OF VERAPAMIL HCl

TABLE 3: *IN VITRO* BUOYANCY STUDIES

Formulation	Buoyancy lag time (sec)	Total floating time (hr)
F1	No floating found	
F2	28	>8
F3	26	>8
F4	18	>12
F5	25	>12
F6	20	>12
F7	25	>18
F8	15	>18
F9	30	>18
F10	31	>18

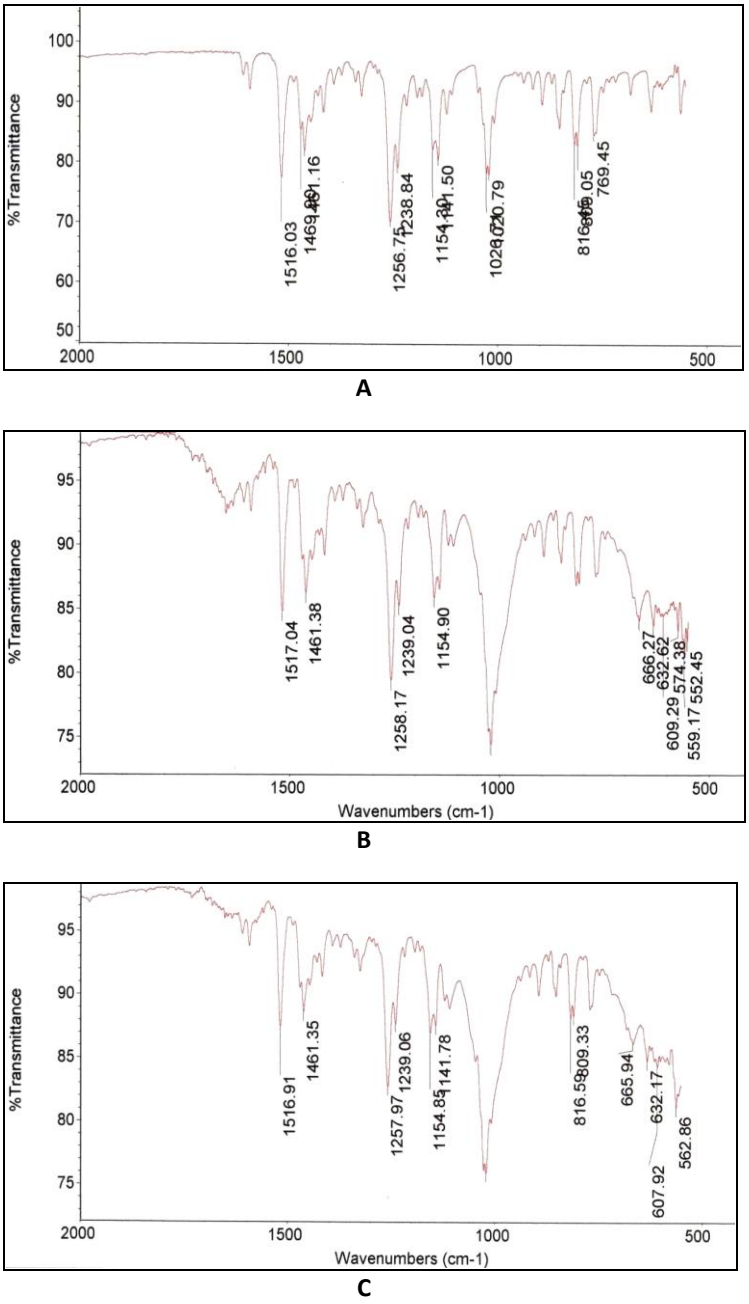
Swelling is a key weapon for buoyancy of a floating tablet. The hydrophilic polymers absorbed the available water around it as soon as it gets in contact. This water intake makes the matrix swell and thus reduces the bulk density that is responsible for buoyancy. The total floating time hence, depends on the decrease of bulk density. An increasing order of swelling index was observed for formulations having higher total floating time. The results are summarized the **Table 4**.

TABLE 4: STUDY OF SWELLING INDEX

Formulation	% Swelling Index				
	1 hr	2 hr	3 hr	4 hr	5 hr
F1	62.91	86.99	90.87	104.66	113.59
F2	85.38	99.03	106.43	117.54	139.96
F3	73.98	100.00	113.20	130.10	141.17
F4	89.43	113.11	134.44	146.97	162.82
F5	86.35	97.86	112.28	126.32	138.79
F6	97.02	102.78	110.54	112.52	129.62
F7	92.28	110.30	120.00	129.90	141.58
F8	76.74	100.60	124.06	158.65	175.35
F9	81.96	109.02	130.20	149.41	172.55
F10	72.85	112.50	131.25	158.98	180.47

No significant alteration was observed when pure drug and physical mixture were subjected to FT-IR study as shown in **Figure 2**. The spectra of pure Verapamil HCl displayed characteristic peaks at 1516.03 cm^{-1} and 1469.16 cm^{-1} for C=C in aromatic bond, at 1256.75 cm^{-1} and 1154.20 cm^{-1} for C-O stretching in aromatic and aliphatic chain and at 1026.20 cm^{-1} for C-N aliphatic stretching vibration, at 816.05 cm^{-1} and 769.45 cm^{-1} for meta substituted benzene. The FT-IR spectra obtained from two physical mixtures showed peaks obtained from the pure drug that indicted no chemical interaction of drug with excipients.

If the drug and polymer would interact, the functional groups in FT-IR spectra would show band shifting and broadening compared to pure drug and polymers [15].



A

B

C

FIGURE 2: FT-IR SPECTRA OF A) VERAPAMIL HCl, B) PHYSICAL MIXTURE CONTAINING METHOCEL K4M AND C) PHYSICAL MIXTURE CONTAINING METHOCEL K15 MCR

The cumulative percent drug release data obtained from formulations F2 to F10 are shown in **Figure 3** and **4**. As formulation F1 failed to float over the media, release study of the batch was not performed. Drug release from different formulations was found to be dependent on the polymer viscosity grade and polymer loading.

Formulation F2, F3, F4 and F5 containing Methocel K4M showed 68.67%, 76.47%, 51.05% and 49.64% drug release in 8 hrs, respectively. In the same way, formulation F6, F7, F8, F9 and F10 containing Methocel K15MCR revealed 74.04%, 64.64%, 53.88%, 51.30%, and 42.76% drug release respectively. This decreasing order of drug release was obtain on using the polymer at ratio of 26%, 28%, 30%, 32% and 34% respectively.

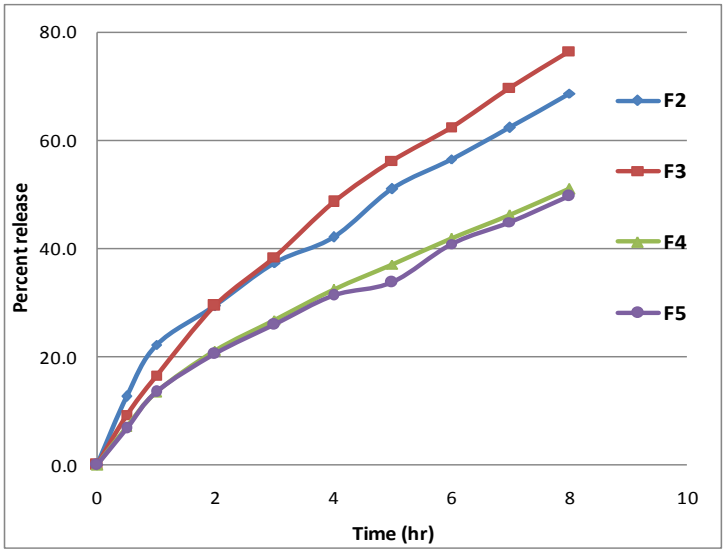


FIGURE 3: PERCENT RELEASE CURVES OF VERAPAMIL FROM METHOCEL K4M BASED FLOATING TABLETS

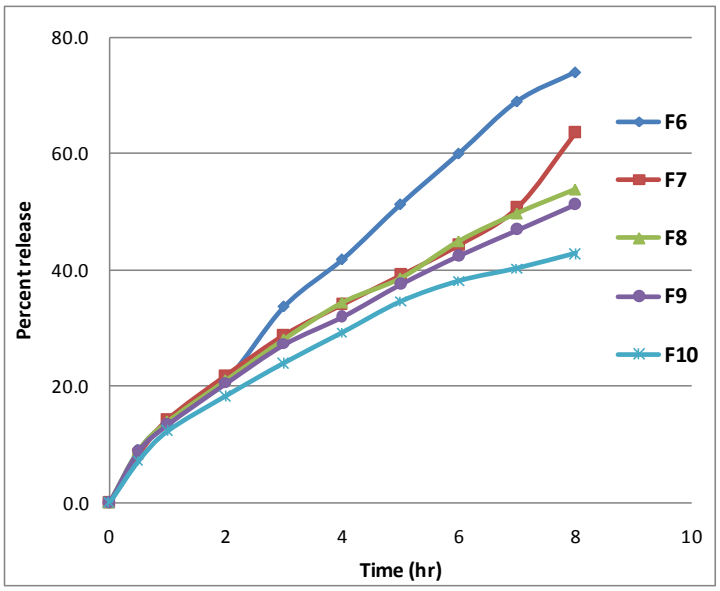


FIGURE 4: PERCENT RELEASE CURVES OF VERAPAMIL FROM METHOCEL K15MCR BASED FLOATING TABLETS

The discrete differences in percent drug release were observed due the varying polymer content in the tablet matrix. The MDT values, $T_{50\%}$, $T_{80\%}$ also indicate the same. Formulations containing Methocel K4M have an increasing order of $T_{50\%}$ values on growing order of polymer incorporation (4.85, 4.35, 7.59 and 8.04 hrs on using the polymer at 28% to 34% of the matrix). While formulations containing Methocel K15MCR also showed similar results. Formulation F6, F8 and F10 showed MDT values of 5.07, 8.26 and 9.66 hrs respectively.

Higher values of MDT, $T_{50\%}$ and $T_{80\%}$ indicate the stronger retention capacity of the polymer in the matrix. Therefore higher the polymer loading in the matrix better the retention was obtained. Besides, Methocel K15MCR showed better retention than Methocel K4M when used at same ratio in formulation F5 and F10. Similar findings were reported by Sharmin *et al.*, 2011 [11]. The results are summarized in the **Table 5**.

TABLE 5: MDT, $T_{50\%}$ AND $T_{80\%}$ VALUES OF FORMULATIONS OF VERAPAMIL HCl (IN HR)

Formulation	$T_{50\%}$	$T_{80\%}$	MDT
F2	4.85	10.92	5.89
F3	4.35	8.10	4.69
F4	7.59	15.09	8.49
F5	8.04	15.99	9.00
F6	4.72	8.74	5.07
F7	5.74	10.84	6.23
F8	7.21	14.90	8.26
F9	7.84	16.43	9.07
F10	8.01	17.86	9.66

The obtained *in vitro* drug release data was fitted with zero order, first order, Higuchi and Korsmeyer-peppas model to predict the exact drug release mechanism. All the formulations showed good linearity to Higuchi and first order curve having R^2 value ranging from 0.979 to 0.997 and 0.982 to 0.998 respectively (**Table 6**). This indicated that the rate of release is dependent on the initial drug loading and diffusion is the predominant mechanism of drug release.

Good correlation coefficients values were observed when the release data was compared to Korsmeyer-peppas model (R^2 value from 0.989 to 0.999) with slope *n* values ranging from 0.563 to 0.731 indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$).

It can be postulated that the release from the hydrophilic matrix was dependent on both drug diffusion and polymer relaxation, which appears to indicate a coupling of diffusion and erosion mechanisms so called anomalous diffusion [16].

TABLE 6: *IN VITRO* RELEASE KINETICS OF FORMULATIONS OF VERAPAMIL HCl

Formulation	Zero order		First order		Higuchi		Korsmeyer	
	k_0	R^2	k_1	R^2	k_h	R^2	n	R^2
F2	6.278	0.991	-0.045	0.998	21.348	0.982	0.731	0.997
F3	6.577	0.994	-0.049	0.993	22.235	0.979	0.680	0.996
F4	5.479	0.991	-0.037	0.993	18.559	0.988	0.685	0.995
F5	5.286	0.991	-0.035	0.990	17.875	0.984	0.684	0.989
F6	5.626	0.949	-0.034	0.982	17.679	0.997	0.563	0.998
F7	6.294	0.969	-0.040	0.994	19.494	0.989	0.659	0.998
F8	6.371	0.975	-0.040	0.996	19.636	0.986	0.648	0.999
F9	6.011	0.974	-0.037	0.995	18.562	0.988	0.635	0.999
F10	5.791	0.959	-0.036	0.988	18.075	0.994	0.586	0.999

CONCLUSION: Floating tablets of Verapamil HCl were successfully formulated by effervescent technique using two hydrophillic cellulose derivatives; Methocel K4M and Methocel K15MCR. The later one showed a strong retardation of the drug release compared to Methocel K4M when used in higher quantity. The release mechanism was mainly diffusion controlled in formulations with higher polymer content. No interaction was observed when pure drug and physical mixture were subjected to FT-IR study. Based on the dissolution data and floating time formulation F-3 containing Methocel K4M and F7 containing Methocel K15MCR may be considered as the best formulations.

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