Controlled Release Floating Matrix Tablet of Captopril
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Abstract

The present study was done to prepare a gastroretentive floating tablet of captopril (CAP) which is an angiotensin converting enzyme inhibitor (ACE-inhibitor) used in the treatment of hypertension and heart failure. CAP is mainly absorbed from the proximal intestine and to a lesser extent from the stomach, also CAP stability decreases as the pH raised above 1.2 and this makes it a suitable candidate for floating dosage form.Effervescent floating tablets of CAP were prepared in order to prolong the gastric residence time and increase the bioavailability of the drug. The floating tablets of CAP were prepared by direct compression and wet granulation technique, using the polymer hydroxypropylmethylcellulose (HPMC) as the primary retarding polymer together with carboxymethylcellulose(CMC) ,ethyl cellulose(EC) and pectin as a secondary release modifying polymers in different ratios of (1:1, 3:1 and 9:1). Different formulation parameters were studied such as type of diluents, amount of effervescent agent, methods of preparation and their effects on buoyancy and the *in vitro* drug release profile as well as their physical characteristics. The wet granulation method shows a good flow and compressibility characteristics and a better dose uniformity in comparison with direct compression technique. Pectin together with HPMC in the ratio of 1:1 was found to meet the requirement for a good matrix formation and floating characteristics and the drug release was sufficiently sustained for 12 h with floating time >24h and floating lag time of 2 min. Kinetic modeling of the release data for the selected formula showed that the mechanism of drug release pattern follows anomalous or non –fickian diffusion.
Key words: Captopril, floating, matrix tablet, pectin.

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الخلاصة

الغرض من هذه الدراسة تحضير صيغة دوائية طافية ذات قابلية بقاء في المعدة لدواء الكابتوبريل والمثبط لعمل الانزيم المحول للانجيوتنسين ويستخدم الكابتوبريل لعلاج امراض ارتفاع ضغط الدم وعجز القلب. الكابتوبريل يمتص بشكل رئيسي من الامعاء الدقيقة وبقابلية اقل من المعدة , تقل ثباتية الدواء كلما ازدادت قاعدية المحيط , مما يجعله مرشح مثالي للتقنيات الدوائية الطافية.الصيغ الدوائية الطافية لدواء الكابتوبريل المصنعة بالطريقة الفوارة قد حضرت وذلك لغرض زيادة فترة بقائها في المعدة من اجل زيادة التوافرية الحيوية للدواء . التركيبة الدوائية الطافية المفردة لدواء الكابتوبريل صنعت باستخدام بوليمر الهايدروكسي مثيل سليلوز(HPMC) كمعيق تحرر اولي مع أو بدون معيقات تحرر ثانوية مثل بوليمر الاثيل سليلوز (EC) والكاربوكسي مثيل سليلوز الصوديوم (SCMC) والبكتين (Pectin) وبنسب مختلفة (١:١,١:٣,١:٩). كما شملت الدراسةمقارنة عدد من العوامل المؤثرة على التصنيع كطريقة التصنيع وكمية العامل المولد لغاز ثاني اوكسيد الكاربون والمضافات الاخرى وقد وجد ان الصيغة التي تستخدم بوليمر الهايدروكسي مثيل سليلوز مع البكتين وبنسبة (١:١) تلاقي المتطلبات اللازمة لتشكيل قالب جيد وخصائص طفو للجرعة الدوائية. حيث كان معدل تحرر الدواء من الصيغة قد استمر لاكثر من ١٢ ساعة وبوقت للطفو دقيقتان ومعدل طفو لاكثر من ٢٤ ساعة.ولقد تم مطابقة بيانات التحرر الدوائي للصيغة المنتقاة (١١) مع مختلف النماذج الحركية لتحرر الدواء وقد لوحظ ان الية تحرر الدواء تتبع (Non-fickian).

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Introduction

It is widely accepted that gastric emptying of a conventional dosage form in humans is affected by numerous factors and the time taken shows wide inter- and intra-subject variation [1].This variability, in turn, can lead to unpredictable times to achieve peak plasma drug levels and bioavailability, since many drugs are absorbed to the greatest extent in the upper part of the small intestine [1, 2].The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several drug delivery systems, such as intragastric floating drug delivery systems (FDDS) [3], swelling and expandable systems [4], bioadhesive systems [5], modified shape systems [6], high density systems [7], delayed gastric emptying systems [8] and low density super porous systems [9].The intragastric FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. 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. This results in increasing gastric residence time (GRT) and a better control of fluctuations in plasma drug concentration [10].

Captopril (CAP) is a 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline, It is an angiotensin converting enzyme inhibitor. It has been widely used for the treatment of hypertension and congestive heart failure. It has been reported that the duration of antihypertensive action after a single oral dose of CAP is only 6–8 h, so clinical use requires a daily dose of 37.5–75 mg to be taken three times [11].The drug is freely water soluble and has elimination half-life after an oral dose of 1.7h. It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction [12].Various attempts have been made to develop floating systems to control drug release; among them is the so called hydrodynamically balanced system [13, 14].Such a system is useful for drugs acting locally in the proximal gastrointestinal (GI) tract or for drugs that degrade in the intestinal fluid.The aim of the present investigation is to develop a sustained release single unit floating matrix tablet of CAP with a view of prolonging GRT and controlled release properties.

Materials and methods
Materials
CAP and sodium carboxymethyl cellulose (Na CMC) were obtained from Samara´a drug industry/Iraq, metolose 90SH100000SR, a brand of HPMC obtained from Nutrer Farma/Japan, pectin was obtained from HIMEDIA /India, ethyl cellulose (EC) obtained from PDH/England; other materials and solvents used were of analytical grade.
Methods
Preparation of CAP matrix tablets
The composition of different formulas of CAP floating tablets is shown in table (1), Effervescent Floating tablets containing CAP were prepared by direct compression technique using varying concentrations of polymers with sodium bicarbonate. All the ingredients were accurately weighed and blended uniformly in a mortar. After sufficient mixing of drug and excipients, magnesium stearate was added as post lubricant with further mixing for 5 minutes. The tablets were compressed using double punch and die tablet machine (Manesty/England) with a diameter of 10mm biconcave punch and die.Formulas F11, F12 and F13 were selected and prepared by wet granulation method using 1% solution of polyvinylpyrolidon (PVP-K30) in isopropyl alcohol as a granulating agent. A sufficient quantity of the granulation solution was added until a positive ball test consistency was resulted, then the wet mass was passed through sieve (10 mesh) and dried in pre warmed oven

at 60 ºC for one hour. The dried granules were reduced in size by screening them through 12 mesh size sieve. A known weight of granules was mixed with the calculated amount of magnesium stearate and talc powder for 5 minutes.
Evaluation of powder blends.
Angle of Repose
Flow property of the granules was evaluated by determining the angle of repose and the compressibility index.
Static angle of repose was measured according to fixed funnel method and free standing cone method of Banker and Anderson [15]. The angle of repose was calculated using the following equation,

$$\text{Tan } \theta = h/r \qquad \text{............ (1)}$$

Where (h) is the height of the cone, (r) is the radius of the cone base.

Compressibility Index& Hausner Ratio
Carr's Compressibility Index (CI) for the prepared granules was determined utilizing the equation (2),

$$CI (\%) = (V_{o} – V_{f}/V_{o})x \ 100 \ \text{....... (2)}$$

Where (Vo) is the untapped apparent volume, (Vf) is the tapped apparent volume of the powder.
The Hausner ratio (HR) is closely related to Compressibility Index (CI). It can be calculated using equation (3), where (V_O) is untapped apparent
volume and (Vf) is tapped apparent volume[16].

$$HR = V_{o} / V_{f} \qquad \text{.......... (3)}$$

Evaluation of CAP tablets
Tablets from all of the prepared formulas were evaluated for their physical properties such as hardness, friability, content uniformity, *In-vitro* dissolution and the floating behaviour (floating time (FT) and floating lag time (FLT).

Tablet hardness and friability
The compression force was controlled to keep the tablet hardness 5 kg, Tablet crushing strength was measured using Monsanto hardness tester, The friability was determined as the percentage of weight loss after 100 revolutions of 20 tablets using Erweka friabilator, Germany.

Drug content uniformity
Ten tablets from each prepared formula were crushed in a mortar then a weight of one tablet were assayed for drug content using 0.1N HCl as the solvent and the samples were analyzed spectrophotometrically at 205nm λmax[17] using UV-Visible spectrophotometer (Carry UV, Varian, Australia).

Floating behaviour

The floating ability was determined using USP II apparatus (50 rpm, 37 ± 0.5°C, 900ml, 0.1N HCl), One tablet was placed in the medium; the time needed to go upward and float on the surface (floating lag time) was recorded also the floating duration and relative matrix integrity were measured (the results were done in triplicate and the average values were taken). The latter parameter was determined on the basis of mass loss by gravimetry and visual inspection after the floating studies .

In vitro dissolution

The CAP release from all the prepared formulas was determined using a USP XXX paddle apparatus 2. The dissolution medium was 900 ml (0.1 N HCl, no enzyme) at 37 ± 0.5 °C; paddle speed 50 rpm. All experiments were done in triplicate and the average values were taken. The prepared formulas were subjected to dissolution tests for 7h. Sample (5 ml) was withdrawn at predetermined time intervals, filtered through a Millipore filter membrane (0.45 μ) and replaced by an equal volume of dissolution medium to maintain sink condition. Drug content in the dissolution sample was determined specrophotometrically at its λmax at 205nm according to USPXXX specification[17].

Selection of the Best Formula

The selection of the best formulas was done depending on the correlation of the resulted floating matrix tablet, with respect to a reference adapted from previous research that match the release profile of gastroretentive floating dosage form of CAP obtained by Meka et al [18]. The similarity factor (f_2) introduced by Moore and Flanner [19], was used as criterion for assessment of the best formula.

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}|R_t - T_t|^2\right]^{-0.5} \times 100\right\} \cdots (4)$$

Where n is the number of dissolution time points, R_t and T_t are the reference and test dissolution values at time t. The ($f2$) value was found to be more than 50 (between 50 and 100), means that the two dissolution profiles are considered to be similar.

Kinetic Modelling of Drug Release

To analyze the CAP release mechanism from the selected formula F11, the *in vitro* release data were fitted into various release kinetic models, first order, zero order, Higuchi and Korsmeyer and Peppas, and the model with the highest correlation coefficient was considered to be the best model:

- **First order kinetic**

$$log\, M_t = log\, M_o + k_1\, t\, / 2.303 \ldots\ldots\ldots (5)$$

- **Zero order kinetic**

$$M_t = M_o + K_o\, t \qquad\qquad \ldots\ldots\ldots (6)$$

- **Higuchi model**

$$M_t\, /\, M\infty = k_H\, t^{1/2} \qquad\qquad \ldots\ldots\ldots (7)$$

- **Korsmeyer-Peppas model (Power Law)**

$$M_t\, /\, M\infty = K_{KP}\, t^{\,n} \qquad\qquad \ldots\ldots\ldots (8)$$

$$log\,[M_t\, /\, M\infty] = log\, K_{KP} + n\, log\, t \ldots\ldots (9)$$

Where M_t is the amount of drug released in time t, M_o the initial amount of drug, $M\infty$ is the cumulative amount of drug released at infinite time, K is respective release constant and n is the release exponent, which characterizes the mechanism of drug release. For Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet (cylinder), when n takes the value of 0.45 it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (anomalous transport). [20, 21]

Statistical Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

Results and Discussion

The effervescent floating tablets of CAP were formulated in 13 different formulas (table 1) using direct compression technique except, F11, F12 and F13 which were prepared by wet granulation technique using 1% PVP in isopropyl alcohol as a granulating agent.The pre-compression parameters like Angle of Repose, compressibility index and Hausner's Ratio were evaluated and all parameters are within the pharmacopoeial prescribed limits as shown in table (2).The physical property of the final blend for the selected formula (F11) showed excellent flow characteristics, the angle of repose <31° and the value of the Compressibility Index (C.I) which is <10 further supported the results of the flow property. The prepared tablets of all the formulas were evaluated for their post compression parameters like hardness, friability, buoyancy lag time, total floating time, drug content and in-vitro drug release as shown in table (2).The % friability was less than 1% in all of the prepared formulas ensuring that the tablets were mechanically

stable. The drug content uniformity of the selected formula (F11) showed a value of (99.5%) which reflects a good uniformity in drug content. All the tablets passed weight variation test and they were within the Pharmacopoeial limits[17].

Table 1 : Different formulas of captopril floating matrix tablet.

Ingredient In (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11*	F12*	F13*
CAP.	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMC	200	180	150	100	180	150	100	180	150	100	100	100	100
EC	-	20	50	100		-	-	-	-	-		-	-
SCMC	-	-	-	-	20	50	100	-	-	-		-	-
Pectin	-	-	-	-	-	-	-	20	50	100	100	100	100
NaHCO3	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	52.5	70	87.5
MCC PH102	37	37	37	37	37	37	37	37	37	37	37	19.5	2
Mg. Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	7	7	7	7	7	7	7	7	7	7	7	7	7

* formulas were prepared by wet granulation method using 1%PVP solution in isopropyl alcohol as a granulating agent.

Table 2 : Characterization of powder blend and the prepared captopril tablets.

formulas	Angle of Repose	C.I.%	H.R.	Hardness	%Friability	Content uniformity	FLT(min)	TFT(hours)	Matrix integrity
F1	34.9	20	1.25	5	0.215	97.6	4.5	>24	+
F2	35	25	1.33	5	0.226	99.45	4.25	>24	+
F3	37.5	23.3	1.3	5	0.253	90.5	4.2	20±0.5	+
F4	36	20	1.25	5	0.432	93.3	3.5	17±0.6	+
F5	38.8	13.3	1.15	5	0.402	90	12	>24	+
F6	41.3	16.6	1.2	5	0.321	91.2	10	21±0.7	+
F7	46.3	20	1.25	5	0.085	105.2	5	14±0.3	+
F8	38.1	25	1.33	5	0.095	104	5	>24	+
F9	41.2	21.7	1.27	5	0.167	102.5	9.5	19	+
F10	42.8	21.5	1.14	5	0.428	99.5	12	14±0.5	+
F11	30.9	6.6	1.07	5	0.672	99.5	1	>24	+
F12	25.6	15.6	1.17	5	0.571	97.7	0.15	17±0.6	+
F13	30.05	16.1	1.2	5	0.742	94.8	0	14±0.3	+

+means a good matrix integrity during the test duration.

The selected formula (F11) showed a FLT of (1 min) and a TFT of more than (24h), as would be expected slower floating and longer buoyancy duration were achieved with formulas containing smaller amount of effervescent agent and this could be due to less gases evolved and less matrix expansion, and by increasing the ratio of the effervescent agent from 15% in formula F11 to20% and 25% (formulas F12 and F13 respectively) showed a high decrease in FLT, but a faster release was shown for formulas F12 and F13 (Fig.1) that containing higher amount of effervescent agent, this is because the elevation of the gas-forming agent would generate larger amounts of effervescence leading to an increase in the rate of pore formation, rapid hydration of the tablets matrices and consequently a faster drug release rate [22].All the formulas were subjected to *in vitro* dissolution studies.
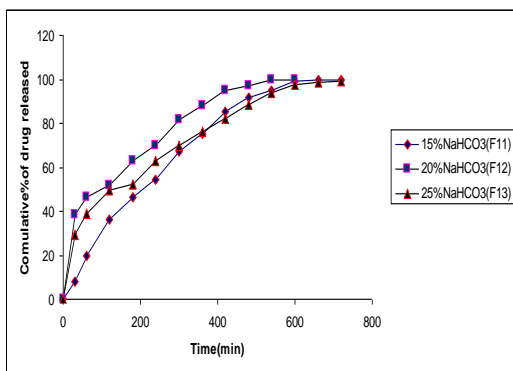
Figure 1: Effect of effervescent agent on Captopril release profile in 0.1N HCl at 37ºC.

The results of *in vitro* percentage release at different time intervals are plotted against time to obtain the release profile. A preliminary study showed that the drug to polymer (HPMC) ratio of (1:4) in F1 was the best to sustain the drug release for the desired profile. From the *in vitro* drug release studies, it was concluded that a partial replacement of HPMC with EC (F2, F3 and F4 in Fig.2) showed an increase in final drug release rate, and the burst effect was also increased compared to F1 which contain HPMC alone, and that could be due to the presence of as little as 10% fibrous insoluble excipients which might disturb the formation of the gel layer and prevent uniform swelling [23].
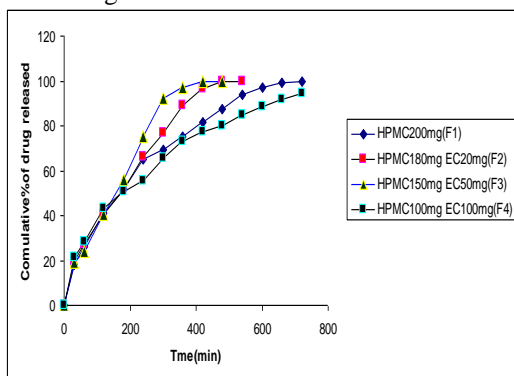
Figure 2: Effect of EC on Captopril release profile in 0.1N HCl at 37ºC .

In the other hand, the partial replacement of HPMC with SCMC (F5, F6 and F7 in Fig.3) showed a significant decrease in final drug release ($p<0.05$) compared to F1, but there was no significant difference between F5 (HPMC/SCMC ratio 9:1) and F6 (HPMC/SCMC ratio 3:1), that might be caused by the low solubility of SCMC at pH 1.2 to 3 [24].
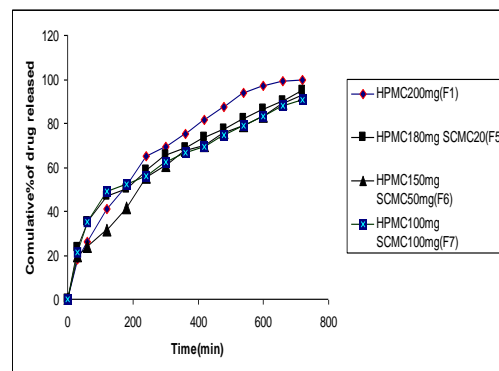

Figure 3: Effect of SCMC on Captopril release profile in 0.1N HCl at 37ºC.

Formulas containing pectin together with HPMC showed different behaviour, at lower ratio (9:1) of HPMC to pectin in F8 the final drug release rate showed no significant difference compared to F1, but as the ratio of HPMC to pectin decreased to (3:1) in F9 and (1:1) in F10 the final drug release rate was also decreased ($p<0.05$) in addition to a little improvement in burst releasing effect (Fig.4), this is due to the formation of a denser gel and slower erosion at higher pectin content [25], formulas (F11) was prepared by wet granulation technique using 1% of PVP K30 in isopropyl alcohol showed a significant increase ($p<0.05$) in the last phase of drug release compared to formula (F10) that prepared with direct compression technique, as shown in (Fig.5). This was because PVP-K30, which is hydrophilic in nature, allowed penetration of the medium into the matrix and a more rapid release of CAP in the last phase [26].
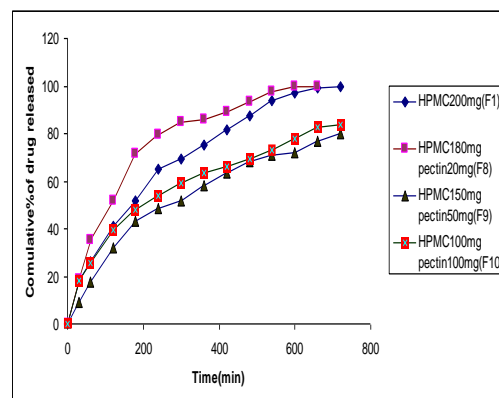

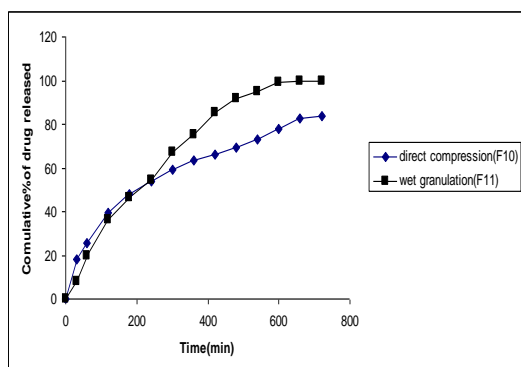**Figure 4: Effect of pectin on Captopril profile in 0.1N HCl at 37ºC.**

Figure 5: Effect of the method of preparation on Captopril release profile in 0.1N HCl at 37ºC.
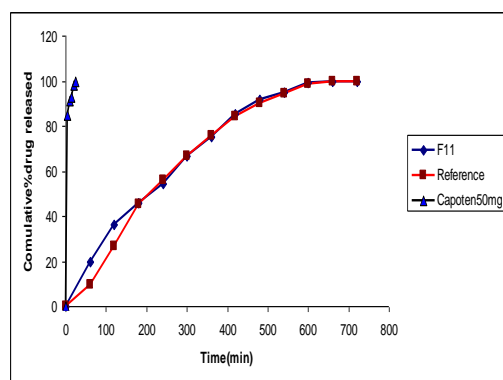

Figure 6: The Release Profile of Captopril Floating Matrix tablet from selected formula (F11) and the Reference Floating Mini-matrices and conventional tablet ofCapoten®50 mg tablet (Squibb), at 0.1N HCl at 37ºC.

A comparison in the release profile between the suggested formula F11 and the reference standard as well as the release profile of Capoten® conventional tablet is shown in (Fig.6), the floating system (Fig.7) was able to control the drug release for 12h compared to Capoten® conventional tablet which released the drug within a 30min.

Table 3 : Drug Release Kinetic Parameters for Captopril from Selected Formula (F11).

Model	R^2	Slope		Intercept
Zero order	0.9806	11.865	*ko*	6.0287
First order	0.9714	-0.1102	*k/2.303*	2.0278
Higuchi model	0.9711	33.702	*k_H*	–9.4228
Korsmeyer – peppas model	0.9791	0.8772	*n*	2.8546

The drug release data of the selected formula (F11) was fitted to various models like zero order, first order, Higuchi's model and Korsmeyer's model. The calculated slope, the intercept and R^2 are shown in table (3). This formula (F11) was best fitted for zero order model with regression value 'R^2' of 0.9806. To know the exact mechanism of drug release the data of F11 was also fitted to Korsmeyer's model. Slope value of $(0.45<n<0.89)$ suggested that the release of CAP from floating tablets followed non Fickian or anomalous transport mechanism.
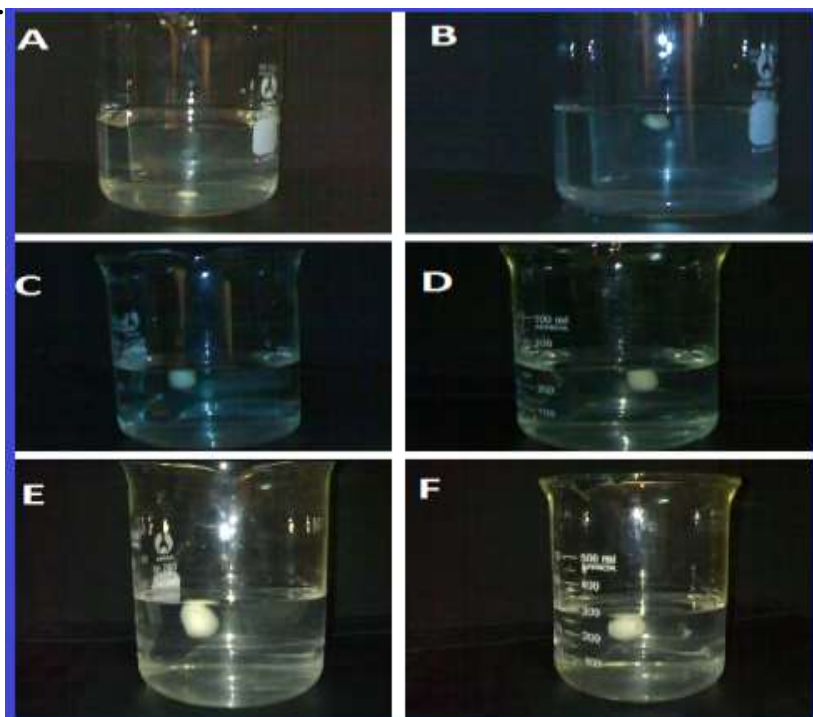

Figure 7: Photographs taken during in vitro buoyancy study of formula F10 in 300 mL 0.1 N HCl at different time intervals, (A) at zero time, (B) after 2 min, (C) after 1 hr., (D) after 8 hr., (E) after 12 hr., (F) after 24 hr.

Conclusion

The present study was done to develop a controlled release floating gastro-retentive dosage form of CAP to produce an effective treatment of hypertension to reduce the fluctuation in drug level caused by conventional tablets. The result of the *in vitro* dissolution study shows a controlled release of CAP for 12h with a zero order release and prolonged residence time. Thus, results of the current study clearly indicate, a promising potential of the CAP floating system as an alternative to the conventional dosage form.

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