Preparation And In-Vitro Evaluation For Captopril Floating Capsules

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□ ABSTRACT □

Floating drug delivery system (FDDS) is the gastro retentive system that can remain in the stomach for many hours and can significantly prolong the gastric residence time of drugs. The aim of this study was to obtain controlled release floating capsules of captopril, as one of the most ACE inhibitor used to manage hypertension and congestive heart failure. Therefore we investigated the effect of three excepients (HPMCK4M, HPMC K100M, ethyl cellulose) on the floating time and release rate of the drug. The drug: polymer ratio used was (1/6). The prepared capsules have shown good flowability for more than eight hours. It was observed that as the molecular weight of HPMC increased the floating time and dug release decreased. However, mixing of different grades of HPMC improved the floating time and sustained drug release in compare with high viscosity polymer alone. The results revealed that EC could improve the floating time as well as the drug release. According to the findings of this investigation, the superior dissolution profiles achieved by mixing the three used polymers and the prepared capsules could float and prolong the drug release for 10 hours.

Keywords: Floating drug delivery system, Floating capsules, Captopril, Hydroxypropyl methylcellulose, Ethyl cellulose

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تحضير كبسولات كابتوبريل طافية ودراسة خصائصها في الزجاج

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□ ملخّص □

الأنظمة الدوائية الطافية هي عبارة عن أنظمة دوائية تبقى في المعدة لفترة طويلة وتطيل بذلك من زمن البقاء المعدي بشكل كبير. كان الهدف من هذه الدراسة تحضير كبسولات طافية مضبوطة التحرر من الكابتوبريل، باعتباره أكثر مثبطات الأنزيم المحول للأنجيوتنسين استخداماً لتدبير ارتفاع الضغط وفشل القلب الاحتقاني. لذلك قمنا بالتحري عن تأثير ثلاثة سواغات هي (HPMC K100M , HPMC K4M, EC) على زمن الطفو الكلي ومعدل تحرر المادة الفعالة من الكبسولات الطافية. كانت نسبة الدواء إلى السواغ المستخدمة (1:6). أظهرت جميع الكبسولات المحضرة زمن طفو جيد لأكثر من ثمان ساعات، وقد لاحظنا زيادة زمن الطفو الكلي وتناقص معدل تحرر الدواء بزيادة الوزن الجزيئي ل HPMC ، وعلى الرغم من ذلك فإن استخدام مزيج من بدرجات لزوجة مختلفة من ال HPMC أدى إلى زيادة زمن الطفو الكلي وانخفاض معدل تحرر الدواء مقارنة باستخدام HPMC عالي الوزن الجزيئي وحيداً. وكشفت النتائج أن استخدام EC يزيد زمن الطفو الكلي ويقلل معدل تحرر الدواء.

وفقاً لنتائج هذا البحث إن مخططات التحرر الفضلى تم الحصول عليها عن طريق استخدام مزيج من البوليميرات الثلاثة المستخدمة، وتمكنّا بذلك من إطالة تحرر المادة الفعالة حتى 10 ساعات.

الكلمات المفتاحية: الأنظمة الدوائية الطافية، الكبسولات الطافية، كابتوبريل، هيدروكسي بروبيل ميتيل سيللوز، إيتيل سيللوز.

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INTRODUCTION

Oral controlled-release drug delivery systems release the drug at a predetermined, predictable, and controlled rate, so it have drawn great attention [1]. However, heterogeneity of the gastrointestinal system created many problems needed to be overcome, among these problems variable transition time [2]. Floating drug delivery system (FDDS) were described in 1960s to prolong the residence time of dosage forms [3]. FDDS remain buoyant in the stomach releasing drug slowly at the desired rate [4]. Being in the stomach improves bioavailability of drugs that have narrow upper gastrointestinal absorption window, a short half-life time, instability in the distal intestine or poor soluble in alkalin pH [5,6,7,8].

Captopril (1-[(2S)-3-mercapto-2-methyl propionyl]-L-proline) is the first orally active inhibitor of angiotensin-converting enzyme (ACE) [9,10], has been used widely to manage hypertension and congestive heart failure [11,12]. Captopril is freely soluble in water with aqueous solubility 0.1g/ml, and has elimination half-life after an oral dose of 1.7 h [13,14] . captopril is stable at pH 1.2 and as the pH increases, Captopril becomes unstable and undergoes pseudo-first order degradation reaction [15]. Approximately 70% of the ingested oral dose is absorbed in healthy fasting human subjects with an absolute bioavailability of 60%, compared to iv dose [16]. Captopril has a narrow absorption window in the stomach and the proximal small intestine by an active transport process via the peptide carrier system with a considerable passive component to the absorption process [16,17].

Plentiful benefits of sustained release therapy for captopril have been reported [18] .In this study we aimed to prolong the gastric residence time (GRT) of captopril by designing FDDS in the form of floating capsules using hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) alone or in combination. We had tried to prolong the drug release and increase the gastric residence time, in order to increase bioavailability and therapeutic efficacy of the drug compared to conventional oral dosage forms.

MATERIALS AND METHODS

1. Material

Captopril was obtained from Unipharma. Hydroxypropyl methylcellulose K4M and K100M premium CR were gifted from City Pharma and Universal pharmaceutical industries respectively, Ethyl cellulose from Sigma-Aldrich (Germany) and Magnesium stearate (MgSt) and poly vinyl pyrrolidone (PVP- K30) were obtained from Otokemi (Mumbai, India). Hydrochloride acid (37%) and isopropanol from Prolabo (France). Hard gelatin capsules of size number (0) were kindly supplied by a local company. All the other chemicals used were of analytical grade.

2. Methods

1.2 Formulation and Preparation of capsules

Tow different approaches have been used in order to prepare floating capsules

1- Preparation of floating capsules filled with powders

Captopril and used polymers were weighed and physically blended in a mortar for 10 min, then magnesium stearate was added to the mixture and mixed for 3 min. Hard gelatin capsules were filled using manual capsule filling machine. The different prepared formulas of captopril are listed in table 1.

Table 1: Formulations of floating captopril capsules filled with powders (all quantities are given in mg)

Formulation code	Captopril	EC	HPMC K4M	HPMC K100M	MgSt	Total weight
F1	25	50	50	50	1.75	176.5
F2	25	0	0	150	1.75	176.5
F3	25	75	75	0	1.75	176.5
F4	25	0	75	75	1.75	176.5

2- preparation floating capsules filled with granules

All ingredients except magnesium stearate were weighed and manually mixed in a mortar for 10 min and granulated using 15% (w/w) PVP K30 isopropanol solution as granulating agent. The granules were dried at 40°c in an oven. Dry granules were sieved and granules with dimensions (500-800) µm were mixed with 1% w/w magnesium stearate manually for 3 min before being filled into hard gelatin capsules. The composition of prepared floating capsules is given in table 2.

Table 2: Formulations of floating captopril capsules filled with granules (all quantities are given in mg)

Formulation code	Captopril	EC	HPMC K4M	HPMC K100M	MgSt	Total weight
F5	25	0	150	0	1.75	176.5
F6	25	50	50	50	1.75	176.5
F7	25	0	0	150	1.75	176.5
F8	25	75	75	0	1.75	176.5
F9	25	0	75	75	1.75	176.5
F10	25	150	0	0	1.75	176.5
F11	25	0	50	100	1.75	176.5
F12	25	75	0	75	1.75	176.5
F13	25	50	25	75	1.75	176.5
F14	25	50	75	25	1.75	176.5
F15	25	25	25	100	1.75	176.5
F16	25	25	100	25	1.75	176.5
F17	25	25	75	50	1.75	176.5

2.2 PHYSICAL PROPERITIES OF FINAL BLEND

The flow properties of powders and granules were determined in terms of bulk density, tapped density, Carr's index and Hausner ratio [19], tapped density using a density tester (SOTAX- TAP DENSITY TESTER (USP)). Carr's index and Hausner ratio were calculated using eqs 1and 2:

$$\text{Carr's index} = \{D_t - D_b / D_t\} \times 100 \quad (1)$$

$$\text{Hausner ratio} = D_t / D_b \quad (2)$$

Where, D_t and D_b are tapped density and bulk density

3. EVALUATION OF FLOATING CAPSULES

1.3 WEIGHT VARIATION

Twenty capsules were randomly selected from each batch individually weighed and reopened the content weight was calculated by subtracting the weight of gelatin shells from the weight of the capsule. the average weight and standard deviation of 20 capsules were calculated [19].

2.3 DRUG CONTENT UNIFORMITY

Ten capsules of each formulation were dissolved in 250 ml of 0.1N HCl. From the stock solution 1 ml sample was withdrawn, filtered through a 0.45µ membrane filter and diluted to 10 ml with 0.1N HCl. The absorbance was measured at wavelength 206 nm using UV spectrophotometer (Jasco V-530/ vis spectrophotometer/Japan)

3.3 IN-VITRO BUOYANCY STUDIES

Floating capsules were designed in such a way that its density becomes low enough to float over gastric fluid. Six capsules of each formulation were placed in 250 mL of HCl 0.1N pH 1.2 (simulating the pH of the stomach contents in the fed state), 37±5°c. total floating time was defined as the total duration of time by which capsules remain buoyant [20,21].

4.3 IN-VITRO RELEASE STUDIES

Dissolution was measured with a fully calibrated dissolution apparatus, using the paddle method (Erweka DT 600/ Germany). The paddle speed was 50 rpm, temperature 37.5±5°c, and volume of the medium 900ml HCl 0.1N, simulating gastric conditions. At predetermined time intervals (2-4-6-8-10)h, 5ml samples were withdrawn with replacement. The collected samples were filtered through the 0.45 µm filters, suitably diluted with the release medium and the absorbance was measured using a UV spectrophotometer (Jasco V-530/ vis spectrophotometer/Japan) at 206nm to quantify the captopril. Experiments were performed with all six capsules. and the results were expressed as the cumulative percentage of the released drug as a function of time.

5.3 RELEASE KENITIC DATA ANALYSIS [22][23][24][25]

Several kinetic models were tested in order to describe the release mechanism of captopril from the prepared floating capsules.

The Higuchi model:

$$Q_t = K \times t^{1/2} \quad (3)$$

Where Q_t represents the amount of drug released at the time t, and K is the release rate constant incorporating the design variables of the system. A liner relationship between the released drug and the square root of time indicates that the drug release follow fickian diffusion .

Korsmeyer–Peppas model :

$$Q_t/Q_a = k \times t^n \quad (4)$$

Where Q_t/Q_a is the fractional solute release. k is a constant incorporating structural and geometric characteristics of the dosage form, and n is the release exponent. For cylindrical devices, if n = 0.45 then the drug release follows Fickian diffusion, while n = 0.89 is related to a mechanism of case-II transport and values between 0.45 and 0.89 indicates both phenomena (non-fickian transport).

Zero order model:

$$W_0 - W_t = k_0 \times t \quad (5)$$

where $k_0$is the zero order release constant, W_0 is the initial amount of drug in the dosage form and W_t is the amount of drug in the dosage form at time t. In this model, the amount of drug released is the same per unit of time and is independent of the initial concentration.
First order model:

$$\log Q_t = \log Q_0 + k_1 t /2.303 \quad (6)$$

Where Q_0 is the initial amount of drug, Q_t is the amount of drug released at time t and K_1 is the first order release constant. the dosage forms following this model releases the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

4. RESULTS AND DISCUSSION

1.4 PHYSICAL PROPERITIES OF FINAL BLEND

Powders and granules with Hausner ratio of 1.25 have good flow properties [26], so values in table 3 show the final blend has acceptable flow properties.
Carr's index values were in the range of 5.555 to 10 for granules and 10.071 to 17.391 for powders as it shown in table 3.The value between 5 to 10 has excellent flowability while the value between 12-20 has good flowability [26], which indicate that final blend is an acceptable range.

Table 3: Carr's index and hausner ratio for all formulations

Formulation code	Carr's index	Hausner ratio
F1	10.071±0.468	1.112±0.168
F2	17.391±0.753	1.210±0.195
F3	16.037±0.752	1.191 ±0.268
F4	15.625±0.66	1.185±0.218
F5	8.823±0.385	1.096±0.187
F6	5.555±0.874	1.058±0.84
F7	5.633±0.853	1.059±0.152
F8	8 ±0.478	1.086±0.184
F9	8.771±0.387	1.096±0.147
F10	9.090±0.593	1.1±0.147
F11	10±0.548	1.111±0.386
F12	10±0.569	1.111±0.274
F13	10±0.753	1.111±0.176
F14	6.944±0.523	1.074±0.145
F15	7.857±0.659	1.085±0.178
F16	9.836±0.963	1.109±0.157
F17	9.357±0.592	1.103±0.184

2.4 WEIGHT VARIATION

In all the formulations, the weight variation of floating capsules was ranges between 0.18 – 3.98 %. All the formulated capsules were passed the weight variation test as the % weight variation was within the pharmacopoeia limits of 10% ± of the average weight[19]. Table 4 shows the weight variation test results.

Table 4: Weight uniformity and drug content for all formulations

Formulation code	Average weight ±sd (mg)	Content uniformity (%)
F1	174.9±2.65	102.60 ±7.71
F2	178.22±3.20	104.86±8.08
F3	177.857±3.97	102.18±7.24
F4	179.295±3.51	102.82±8.16
F5	173.78±3.98	102.02±9.06
F6	179.015±2.61	103.83±6.84
F7	178.96±3.31	101.7±8.9
F8	178.115±3.54	107.7±6.42
F9	177.975±3.91	100.05±4.52
F10	180.05±3.86	97.79±3.73
F11	178.295±3.92	101.68±4.21
F12	178.845±2.49	101.22±7.54
F13	176.02±2.72	103.43±5.09
F14	180.565±3.91	99.66±6.78
F15	179.675±2.93	100.08±6.00
F16	179.5±3.67	101.36±4.97
F17	179.61±3.87	101.97±8.50

3.4 DRUG CONTENT UNIFORMITY

The percentage drug content of all formulations (F1-F17) was found to be between 97.79% – 107.7% which ensured the uniformity of drug content. This showed that the drug was uniformly distributed in all formulations. Hence the percentage of drug content of all formulations complies with official specifications in E.ph (Limits: not less than 85% and not more than 115%). Table 4 shows the results.

4.4 IN-VITRO BUOYANCY STUDIES

All the prepared formulations were buoyant instantaneously without any lag time. All formulations remained buoyant on dissolution medium (HCl 0.1N) for more than 10 h except F2 and F7.

As it was shown in table 5 formulations F6 – F8 – F9 showed total floating time more than F1-F3-F4 respectively, which indicates that granulation increased total floating time. However, the granulation effect was not clear with F5 in comparison to F7 and that could be attributed to used polymer (HPMC K100M).

The F5-F7-F9 formulations reveal that the combination HPMC K4M and K100M had the longest floating time, this may be accounted to increased gel strength of the polymeric matrices through hydration and swelling [27]. It was observed that EC increases the total floating time which may be explained by the hydrophobic nature of EC [28]. In addition, F6,F13,F14,F15,F16,F17 Formulations indicated that the mixture of all three used polymers has increased total floating time compared to those containing two polymers.
Moreover, magnesium stearate, which was mixed with captopril granules as lubricant in capsule filling, is reported as material that help to produce buoyancy [29].

Table 5: Total floating time of floating capsules

Formulation code	Floating time (h)
F1	11
F2	8
F3	11
F4	10
F5	11
F6	13
F7	8
F8	12
F9	12
F10	13
F11	10
F12	11
F13	11
F14	13
F15	13
F16	12
F17	12

5.4 IN-VITRO RELEASE STUDIES

Table 6 shows the released amount of captopril (%) for all formulations.

Table 6 : Released amount of Captopril (%) for all formulations as a function of time

Time (H)	F1	F2	F3	F4	F5
2	45.751±1.222	58.256±1.762	89.379±2.379	59.721±3.965	69.543±3.037
4	63.282±1.778	67.180±2.658	102.455±3.954	73.620±4.991	73.453±1.837
6	63.743±1.852	73.587±2.436		73.983±4.097	83.168±2.658
8	77.396±3.414	80.781±3.057		78.913±5.437	87.75±0.682
10	87.939±1.664			59.721±3.965	
Time (H)	F6	F7	F8	F9	F10

2	40.937±1.008	53.831±1.233	53.343±2.562	48.1777±1.049	71.566±0.948
4	51.428±1.070	69.540±0.902	61.252±4.680	48.894±1.073	73.188±0.702
6	59.142±1.852	80.483±0.749	67.298±4.532	59.376±1.232	82.233±1.272
8	66.796±2.22	82.096±1.249	77.004±5.616	62.791±1.872	
10	81.731±0.588		83.113±3.115	100.040±1.848	
Time (H)	F11	F12	F13	F14	F15
2	43.013±1.127	43.160±4.921	53.542±1.962	59.854±2.159	45.206±0.310
4	46.9359±0.988	48.754±4.502	54.333±1.398	63.484±3.187	56.464±0.333
6	55.1528±0.718	57.842±5.457	76.696±0.738	76.624±2.665	70.786±1.322
8	59.85±0.348	63.852±5.138	79.384±0.808	79.403±2.550	73.929±1.024
10	84.4188±0.932	82.885±2.919	81.609±1.909	84.366±1.371	82.752±1.045
Time (H)	F16	F17			
2	36.654±2.719	49.487±1.677			
4	43.667±4.170	51.626±2.912			
6	50.4102±0.771	57.452±8.099			
8	61.4978±0.449	61.957±6.902			
10	83.108±1.238	80.522±4.819			

In order to indicate the preparation method formulations F1-F2-F3-F4 were compared to F6-F7-F8-F9 respectively using IBM® SPSS® Statistics 20 software, significance was accepted at $p < 0.05$. The amount of released drug from floating capsules reduced significantly after granulation ($P<0.05$), as it shown in figures 1,2. It could be explained by the increased particle size of the granules [30], and the effect of PVP which delays the penetration of dissolution medium into the polymeric matrix and delays the hydration and degradation of polymeric chains [31].

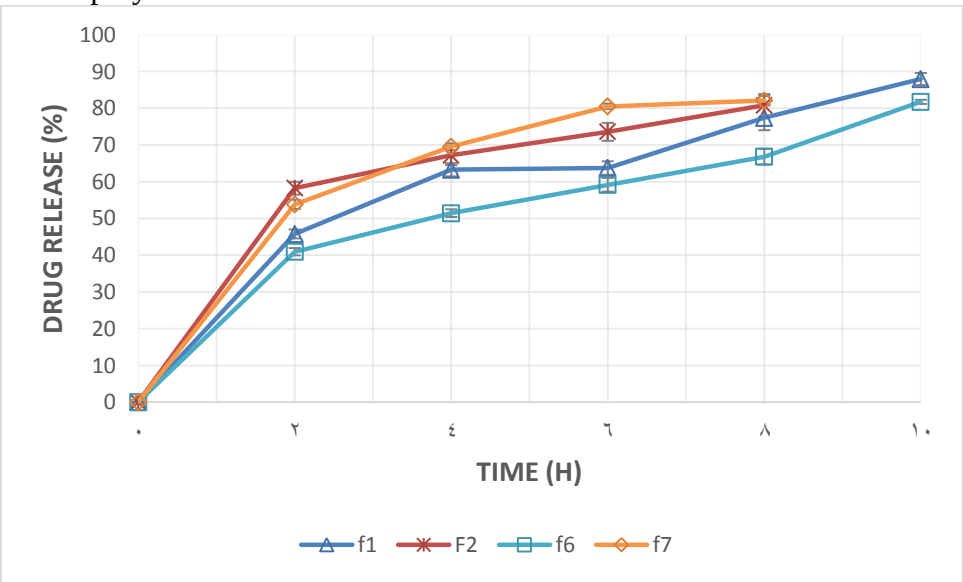

Fig 1: in vitro drug release profile for formulations F1-F2-F6-F7

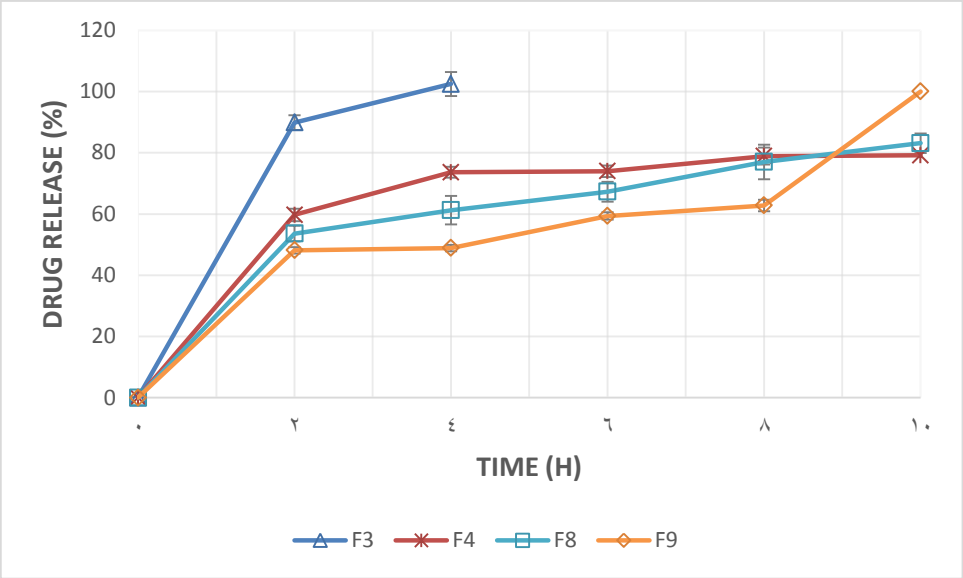

Fig 2: In vitro drug release profile for formulations F3-F4-F8-F9

it was observed by comparing F5 to F7, that the increase of molecular weight of HPMC reduces the amount of released drug ($P<0.05$), as it shown in figure 3. This could be caused by the increased density of the polymer matrix which increases diffusion path length and decreases the overall drug release from the polymer matrix [32].

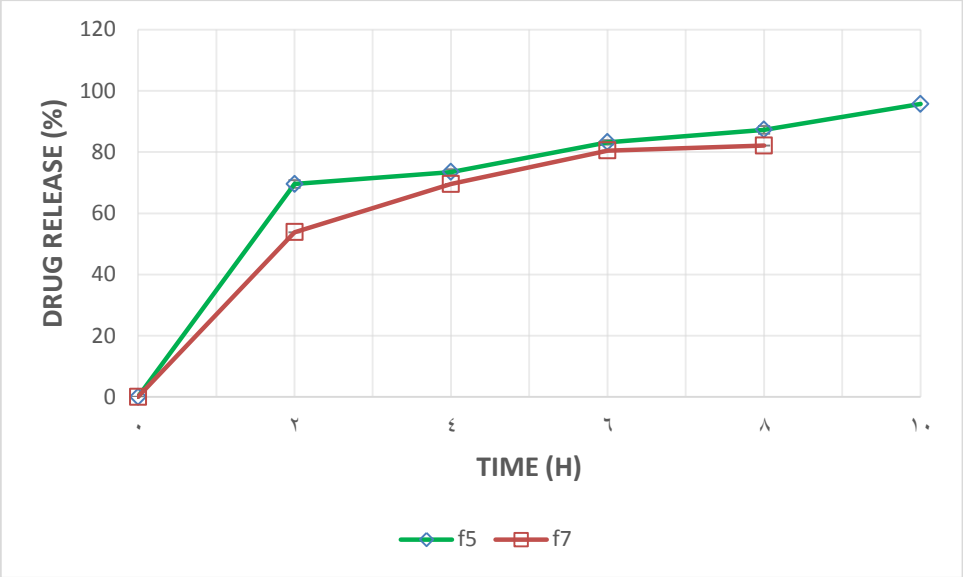

Fig 3: In vitro release profile for formulations F5-F7

It was clear from the dissolution profile in figure 4 of formulation F9 that mixing the low and high viscosity HPMC reduced the amount of released drug as compared to manufacturing F7 high viscosity HPMC alone.

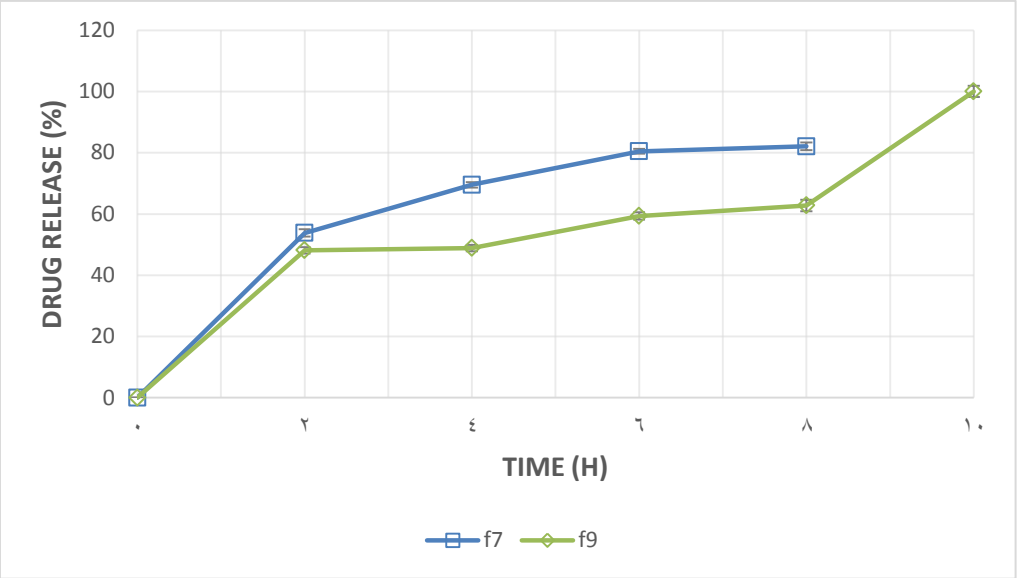

Fig 4: In vitro release profile for formulations F7-F9

The floating capsules prepared using HPMC were compared to those prepared using EC , HPMC mixture, the result showed that EC can significantly reduce drug release rate from floating capsules as it shown in figure 5. This may be caused by EC hydrophobic nature which makes EC chains more stable and less perceptible in the dissolution medium [33,34,35].

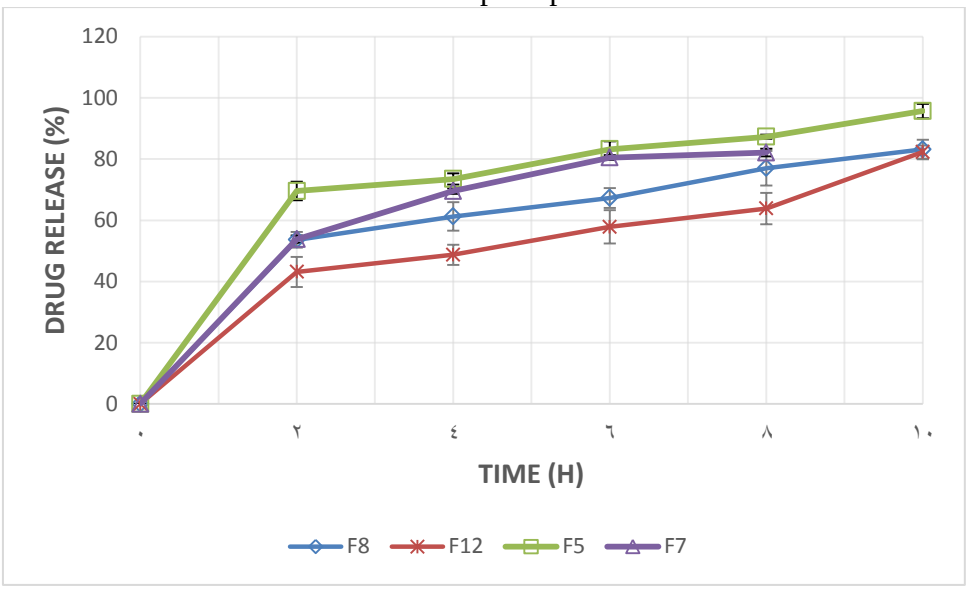

Fig 5: In vitro release profile for formulations F5-F7-F8-F12

It was found from dissolution profiles in figure 6 of formulations F6- F13 -F14 that the increased amount of high viscosity polymer (HPMC K100M) used in combination of three polymers (HPMC K100M , HPMC K4M, EC) reduced the release rate from captopril floating capsules when the EC amount is 25mg. Although the increasing amount of HPMC K100M in formulations F15-F16-F17 which contain EC 50mg didn't lead to decrease the amount of released drug from the prepared floating capsules. this could be explained by the prevention of HPMC hydration caused by the increased amount of ethyl cellulose.

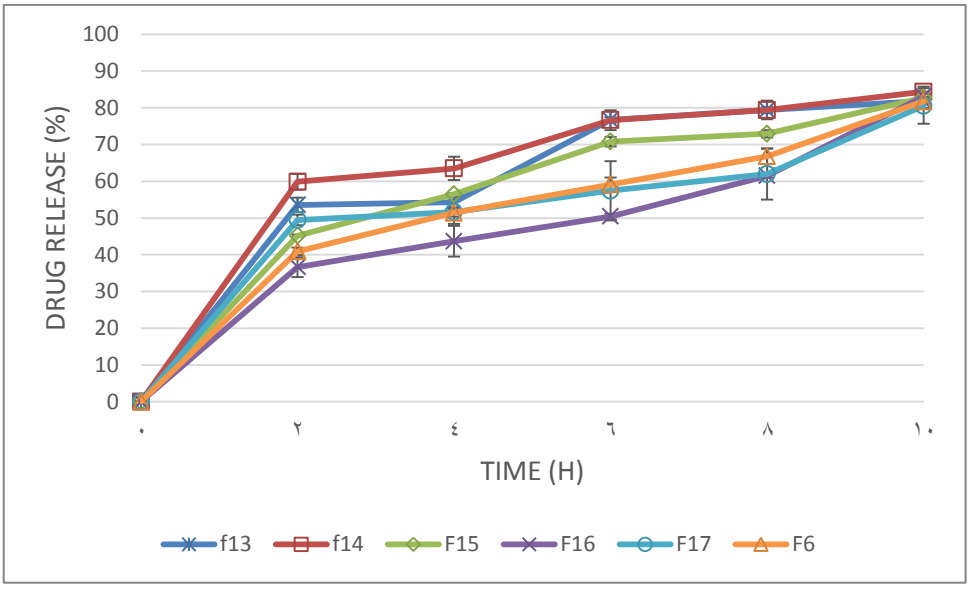

Fig 6: In vitro release profile for formulations F6-F13-F14-F15-F16-F17

6.4 RELEASE KINETIC DATA ANALYSIS

The captopril release process from the developed capsules is the result of the combination of different mechanisms. Although it was difficult to find a mathematical model that describes all the processes taking place, in the present study, the modeling of the release data versus time has allowed characterizing the limiting kinetic process in each case.
Table 7 shows correlation coefficient values for all formulations except F3.

Table 7: Correlation coefficient values in the analysis of release data of the captopril floating capsules prepared as per Zero order, First order, Higuchi and Peppas Equation Models

Formulation code	R^2 values				Best fit model
	Zero order	First order	Higuchi model	Krosmeyer-peppas	
F1	0.9505	0.9175	0.9389	0.9478	Krosmeyer-peppas
F2	0.9953	0.993	0.978	0.9911	Zero order
F4	0.7795	0.8366	0.9159	0.9019	Higuchi
F5	0.9854	0.9016	0.9159	0.9296	Zero order
F6	0.9833	0.9016	0.9241	0.9628	Zero order
F7	0.9004	0.9397	0.9743	0.9719	Higuchi
F8	0.9554	0.9764	0.9887	0.967	Higuchi
F9	0.7686	0.5796	0.6153	0.669	Zero order
F10	0.8603	0.9412	0.7092	0.7498	First order
F11	0.9789	0.9798	0.9655	0.983	Crosmeyer-peppas
F12	0.9441	0.8477	0.8374	0.8882	Zero order
F13	0.8449	0.8788	0.8168	0.831	First order

F14	0.9449	0.9637	0.9133	0.9276	First order
F15	0.963	0.9784	0.9423	0.9856	Krosmeyer peppas
F16	0.9302	0.819	0.8115	0.8794	Zero order
F17	0.8568	0.7697	0.7142	0.7486	Zero order

CONCLUSION

It was possible to formulate floating drug delivery system in the form of floating capsules containing captopril using a mixture of hydrophilic and hydrophobic polymers. Floating time and drug release rate varies with the type and molecular weight of the polymers. Capsules containing HPMC K100M, HPMC K4M and EC have shown the best floating time and dissolution profile.

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