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Original article

FLOATING MATRIX TABLET OF LOSARTAN POTASSIUM BY USING HYDROPHILIC SWELLING POLYMER AND NATURAL GUM

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Abstract

The main purpose of this study was to prepare the losartan potassium controlled release floating tablets by using effervescent technique to extent the gastric residence time and enhance its bioavailability. The floating matrix tablets were prepared by using different proportion of polymers such as hydroxypropylmethylcellulose, karaya gum and sodium bicarbonate used as gas generating agent, by direct compression technique. Before compression the particulate matter of the series of formulations were evaluated for various micromeritic properties. The prepared floating tablets were evaluated for weight uniformity, drug content uniformity, friability, hardness, floating characteristics such as floating lag time, total floating time, water uptake studies, compatibility studies of drug with polymers and in vitro drug release. The mathematical models were also used to investigate the principle release mechanism of drug release. The results showed that all prepared floating tablet were have excellent swelling, floating capabilities with short floating lag time within 100 seconds and maintain controlled release up to 12 hours.

Key words: *Floating matrix tablet, Losartan potassium, Hpmc, Karaya gum.*

Hidrofilik Şişebilen Polimer ve Doğal Zamk Kullanılarak Üretilen Losartan Potasyum Yüzen Matriks Tableti

Bu çalışmanın temel amacı efervesan teknik kullanılarak losartan potasyumun kontrollü salım gösteren yüzen tabletlerini hazırlayarak, gastrik bulunma süresini ve biyoyararlanımını arttırmaktır. Yüzen matriks tabletleri, hidroksipropilmetilselüloz ve karaya zamkı polimerlerin değişik oranlarda kullanımı ve gaz oluşturucu madde olarak sodyum bikarbonatın direkt basım tekniğiyle hazırlanmıştır. Partiküllerin basımından önce, formülasyonlar seri şeklinde çeşitli mikromeritik özelliklerine göre değerlendirilmiştir. Hazırlanan yüzen tabletler ağırlık tekdüzeliği, etkin madde tekdüzeliği, friyabilite, sertlik ve yüzme gecikme zamanı, toplam yüzme zamanı ve su alım özellikleri gibi yüzme özellikleri, etkin maddenin polimerlerler ile geçimliliği ve in vitro ilaç salımı değerlendirilmiştir. Ayrıca ilaç salımının mekanizmasını incelemek amacıyla matematiksel modeller kullanılmıştır. Sonuçlar, hazırlanan tüm yüzen tabletlerin mükemmel şişme ve yüzme özellikleri gösterdiği, yüzme gecikme zamanının 100 saniye kadar düşük olduğu ve kontrollü salımın 12 saate kadar sağlandığını göstermektedir.

Anahtar kelimeler: *Hareketli matrix tablet, Losartan potasyum, HPMC, Karaya zamkı*

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INTRODUCTION

Oral route is the most suitable and commonly employed form of drug delivery systems. The conventional peroral dosage forms cannot achieve prolongation of effective plasma concentration and effective bioavailability due to erratic changing environment in the GIT (1). This is because of various physiological problems like gastric emptying, motility, pH of the stomach etc., which can be overcome by developing appropriate dosage form (2).

In last decades, many types of controlled release formulations have been developed, to improve the bioavailability and release of drug from the system which should be predictable, reproducible and improves patience compliance (3). The drugs having narrow absorption window, shorter half-life, targeted therapy for local ailments in the upper GI tract, stability problem and which need to act locally in stomach can be formulated as a gastroretentive drug delivery systems (4). To achieve controlled gastric retention of solid dosage forms, several approaches have been attempted in the preparation of gastroretentive drug delivery systems (GRDDS) one of the following mechanisms: mucoadhesion (5), flotation (6), sedimentation (7), swellable and expansion systems (8), erosion system (9), bioadhesive systems (10), gel forming (11), modified shape systems (12), or by the simultaneous administration of pharmacological agents that delay gastric emptying (13) and suspension systems (14) etc.

The Floating drug delivery system (FDDS) is one of the GRDDS to prolong the gastric residence time (GRT) within the GIT to obtain sufficient bioavailability. The FDDS have much lower density than the gastric fluids and thus to remain buoyant in the stomach contents for a long time (15). Drug dissolution and release from the dosage form at desired rate in the stomach under fairly controlled conditions (16).

Losartan potassium (LP) is the first member of a new class of non peptide angiotension II receptor antagonist. It reduces effectively hypertension by suppressing the effects of angiotension II receptor, there by blocking the rennin-angiotension system. It is readily absorbed from GIT by oral administration, it undergo rapid first pass metabolism, bioavailability is only 32% and has short biological half life of 2 hrs (17), hence it is suitable candidate for floating drug delivery system.

The main principle objectives of the present study were to develop single unit floating tablet using hydrophilic swellable hydroxypropylmethyl cellulose (HPMC) 90 SH 15000 and natural karaya gum with gas generating agent for novel anti hypertensive drug. To evaluate the potency of KG to control the release of water soluble drug, LP in floating drug delivery system, the various proportions of drug and polymers on drug release and *in vitro* buoyancy of the drug delivery system were investigated. In addition, micrometrics properties, post compression parameters, water uptake and mechanisms were studied.

EXPERIMENTAL

Materials

Losartan Potassium, HPMC (Metlose 90 SH 15000), Microcrystalline cellulose (PH 105) and Lactose were gift samples from Adwya Lab (Tunis, Tunisia), Shin etsu Chemicals Co. (Paris, France), FMC biopolymer (Brussels, Belgium) and BDH Chemicals Ltd. (U.K) respectively. Karaya gum, sodium bicarbonate (SB) and magnesium stearate were purchased from reckitt benckier healthcare (U.K). All other reagents were analytical or pharmaceutical grade.

Micromeritic properties of powder mixture

For each formulations the drug, polymers (LP: HPMC+KG) and SB along with diluents were blended homogeneously for ten minutes in mortar, as shown in Table 1. The resultant

powder mixtures were evaluated for micromeritic properties such as tapped density, bulk density, angle of repose, hausner ratio and carr's index. The angle of repose was determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated using the following equation.

$$\text{Carr's index} = \frac{Df - D0}{Df} \times 100$$

Where, Df = Poured bulk or bulk density, $D0$= Tapped or consolidated bulk density.

Table 1. Composition of Losartan potassium floating tablets (all quantities are given in mg).

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Losartan Potassium	50	50	50	50	50	50	50	50	50	50
HPMC SH 9000	50	40	25	10	00	100	75	50	25	00
Karaya gum	00	10	25	40	50	00	25	50	75	100
MCC	15	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	36	36	36	36	36	36	36	36	36	36
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3
Lactose	150	150	150	150	150	100	100	100	100	100
Total wt. (mg)	300	300	300	300	300	300	300	300	300	300

Preparation of LP floating matrix tablets

The floating matrix tablets of LP were prepared by direct compression method. The above resultant powder mixture were blended homogeneously for 10 min followed by addition of magnesium stearate. The resultant mixture was compressed into tablets using a Rimek rotary tablet machine (Rimek Minipress, Karnavati Engg. Pvt. Ltd, Ahmedabad, India) at 12 mm, circular, flat punches at compression force of 8 KN. The total weight of each tablet was 300 mg, the compositions of floating tablets are given in Table 1.

Evaluation of the floating matrix tablets

The prepared floating matrix tablets (FMT) were evaluated for various evaluation parameters, such as,

Hardness

Tablet hardness has been defined as the force required to break a tablet in a diametric compression test. To perform this test Erweka hardness tester was used, it was expressed by kg/cm^2. In this test 10 tablets were selected randomly, each tablet is placed between two anvils, force is applied to the anvil, and the crushing strength that just causes the tablet to break is recorded as hardness and then takes the average. The hardness, thickness and diameter followed by mathematical evaluation of tensile strength (Ts) by using formula, $T S = 2F/rh$.

Friability

The pharma test *(PTFE)* instrument was used at 25 RPM for 4 minutes.

Drug content uniformity

The test was carried out as per USP.

Drug -excipients interaction studies

In order to evaluate the integrity and compatibility of the drug in the formulation, drug-excipient interaction studies were performed. Pure drug and optimized tablet formulation were analyzed by fourier transform infra-red (FTIR) spectroscopy. FTIR spectra of pure drug and its formulations were obtained by Perkin Elmer, (Germany) by using KBr pellet method.

In vitro floating studies

The *in vitro* floating studies were characterized by floating lag time and total floating time. The time required for the tablet to rise to the surface of the dissolution medium and the duration for which the tablet continuously floated on the dissolution medium were noted as floating lag time and total floating time respectively (18). The test was performed using a Erweka DT-600 dissolution tester (USP XXVI) paddle type using 900 ml of 0.1 N HCl solution at 100 rpm at 37± 0.5^0C (19)

Water uptake studies (Swelling index)

The swelling of the polymers can be measured by their capability to absorb water and swell up. The water uptake study of the tablet was done by Erweka DT-600 dissolution (Germany) basket type, using 900 ml of distilled water at 100 rpm. The medium was maintained at 37 ± 0.5 ^{0}C throughout the study. At regular time intervals, the tablets were removed, blotted to eliminate excess water and weighed (20). The swelling characteristics of the floating tablets were expressed as:

$$W\ U\ (\%) = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

In vitro dissolution studies

The *in vitro* drug release rate of LP from FMT was determined using Erweka DT-600 dissolution paddle type, by using 900 ml of 0.1N HCl, at 37 ±0.5°C and 100 rpm speed. The samples (5 ml) of the solution were withdrawn from the dissolution apparatus at predetermined time intervals for up to 12 h, and the samples were replaced with fresh dissolution medium at each time interval. The samples were filtered through 0.45 μm membrane filter and diluted suitably with 0.1N HCl. Absorbance of these solutions was measured at the wavelength of 205nm (21), Analytikajena, Specord 40 UV-Visible spectrophotometer (Germany).

Mechanism of drug release

The different mathematical models may be used for describing the kinetics of the drug release process from tablets; the most suitable being the one which best fits to the experimental results. They describe the best models for drug release from pharmaceutical systems resulting from a simple phenomenon, or when this phenomenon, by being the rate-limiting step, conditions all the process occurring in the system.

The release kinetics of LP from the FMT formulations were determined by finding the most excellent fit of the release data to Zero order, First order, Higuchi matrix, Hixson-Crowell and Korsmeyer-Peppas plots, respetively.

To study release of high and low aqueous soluble drugs incorporated in the semisolid and/or solid matrices, Higuchi has developed several theoretical models. According to this model, the drug release was described as a square root of time dependent diffusion process based on Fick's

law. This relation can be used to describe drug dissolution from few types of modified release pharmaceutical dosage forms.

$$Q_t = K_H \sqrt{t}$$

Where Q_t is the amount of drug released at time t, K_H is Higuchi's rate constant. If a plot of square root of time v/s cumulative amount of drug released yields a straight line, and the slope is one or more than one, then the particular dosage form is considered to follow Higuchi kinetics of drug release. Under some experimental situations the release system deviates from the Fick's equation, following an anomalous behavior i e non-fickian release. In such cases a more general equation can be used. Korsmeyer developed a simple, semi-empirical, relating exponentially the drug release to the lapsed time (22).

$$Q_t/Q_\alpha = Kt^n$$

Q_t/Q_α is the portion of drug released at time t; K is the constant comprising a structural and geometric characteristics of the tablets; and n, the release exponent is a parameter that depends on the release mechanism and is thus used to characterize it. Peppas used this n value in order to describe different release mechanisms. For Fickian diffusion release mechanism, if the n=0.5 or less, if the n value is more than 0.5 and less than 1.0 the release mechanism follows a Non-Fickian model or anomalous transport (Table 2). Hixson-Crowell recognized that particle regular area is proportional to the cubic root of its volume, derived an equation that can be describe in the following manner.

$$W_0^{1/3} - W_t^{1/3} = K_S t$$

Where W_0 is the initial amount of drug in dosage form, W_t remaining amount of drug in dosage form at time t and K_S is a constant incorporating the surface volume relation.

Table 2. Interpretation of diffusional release mechanisms.

Release exponent (n)	Drug transport mechanism	rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case II transport	Zero order release
Higher than 1.0	Super case II transport	t^{n-1}

RESULTS AND DISCUSSION

The particulate matter of the series of the formulation (F1-F10), were subjected to the determination of various micromeritic parameters to evaluate the flow properties and compressibility. The bulk density and tapped density were within range as shown in table 3, it shows that the packing arrangement of all the formulations in the particulate form do not statistically vary despite the variation in the composition with the respect to the polymer (HPMC & KG) relative to each other from 0% to 100% visversa, similarly the angle of repose was also found to be varying not significantly, the values of all formulation were within the range 30 θ indicative of flowability complying to good for compression (23). Further calculating the derived properties we can arrive at following two conclusions, a) the hausner ratio which reflects the interparticle friction was found to be less than 1.20 revealing the

spherical nature of the particulate, b) the carr's index which measure of potential compression bonds and their stability was found to be significantly different, all formulation was found to be excellent compressibility, whereas F1, and F5 compressibility was good as shown in the Table 3.

Table 3. Micromeritic properties of formulation.

Formulations	BD (g/mL) ±SD	TD (g/mL) ±SD	Hauser ratio	Carrs index (%)	Angle of repose ±SD
F1	0.520±0.023	0.595±0.022	1.041	12.612	28.224±0.086
F2	0.612±0.047	0.641±0.014	1.047	4.836	29.960±0.071
F3	0.595±0.021	0.641±0.018	1.077	7.176	29.840±0.092
F4	0.620±0.064	0.657±0.034	1.056	5.61	29.922±0.285
F5	0.615±0.018	0.727±0.056	1.182	15.442	30.242±0.126
F6	0.413±0.121	0.445±0.052	0.912	10.354	29.424±0.029
F7	0.522±0.012	0.571±0.411	0.909	8.282	28.860±0.054
F8	0.423±0.331	0.581±0.068	0.912	8.872	27.440±0.076
F9	0.502±0.012	0.497±0.014	1.027	8.011	25.782±0.082
F10	0.415±0.022	0.487±0.023	0.826	9.962	26.322±0.427

BD= Bulk density, TP= Tapped density

Evaluation of floating tablets

The prepared FMT hardness ranged between 4.4±0.238 to 5.6±0.922 kg/cm^2 depending upon the various proportion of the polymer used. The tablet friability varied between 0.760±0.398 to 1.04 ±0.554%. The weight variation of FMT formulation within the range of 5% deviation, complies with USP limits. The tensile strength of the tablets was varied between 25.64 ±0.872 to 35.63 ±0.212. The assay for drug content varied between 97.93±0.543 to 101.24±0.618%. The results of these parameters are given in Table 4.

Table 4. Evaluation test for floating tablets.

Formulations	WV (%)	Hardness (Kg/cm^2)	Thickness (mm)	TS	Friability (%)	DCU (%)
F1	2.652	4.9±0.246	4.0±0.24	35.63±0.212	0.76±0.398	100.05±0.213
F2	2.975	5.1±0.338	4.1±0.62	25.64±0.872	1.04±0.554	98.29±0.622
F3	3.622	4.4±0.834	4.1±0.76	29.36±0.345	0.86±0.388	99.88±0.466
F4	1.358	5.2±0.682	4.2±0.62	33.44±0.481	0.95±0.871	98.98±0.286
F5	1.681	5.6±0.922	4.1±0.84	31.89±0.422	0.86±0.744	101.21±0.618
F6	1.034	5.1±0.564	4.2±0.33	27.22±0.299	1.01±0.666	97.93±0.543
F7	1.034	4.4±0.238	4.1±0.29	27.76±0.345	0.92±0.281	99.88±0.412
F8	1.034	4.8±0.916	4.2±0.34	31.83±0.481	0.89±0.123	98.28±0.776
F9	1.358	5.4±0.202	4.1±0.65	32.32±0.422	0.88±0.875	99.10±0.334
F10	2.005	5.1±0.554	4.2±0.57	30.36±0.262	0.87±0.412	100.21±0.221

WV= Weight variation, TS = Tensile strength, DCU= Drug content uniformity.

Drug -excipients interaction studies

The spectrum was measured in the solid state as potassium bromide dispersion. The bands were recorded using FTIR technique. FT-IR spectral study revealed that similar characteristic peaks appear with minor differences for the pure drug and drug formulation as shown in Figure 1. Hence it was confirmed that there was no chemical interaction has taken place between the drug and polymer used.

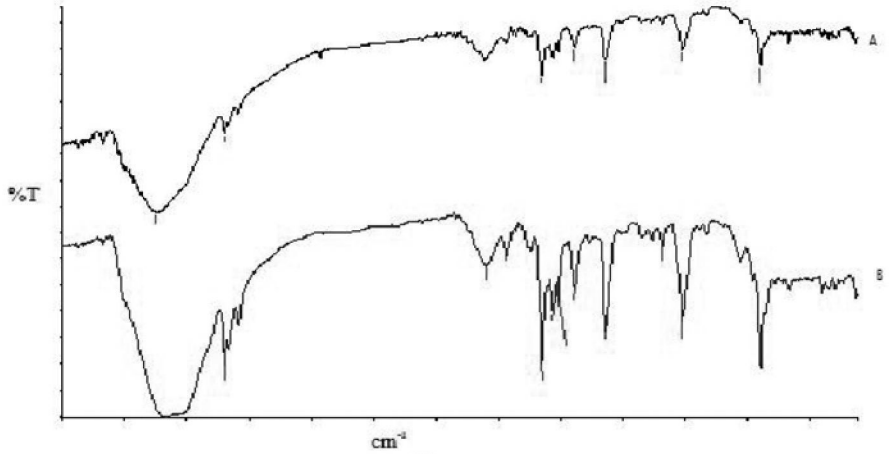

Figure 1. FTIR spectra floating tablet formultion and pure losartan (A=Floating matrix tablet, B= pure losartan).

In vitro characterization studies

LP matrices prepared from HPMC and karaya gum without gas generating are no floating behavior in gastric medium. To provide *in vitro* floating, an effervescent approach was adopted. The system should be float in a few minutes after contact with gastric fluid, thus the gas generating agent was essential to achieve optimum floating. Sodium bicarbonate was added as a gas-generating agent, it is the key component as a variable for floating matrix tablet. The concentration of SB on *in vitro* floating studies was optimized between 5-15%, these results clearly shows that, as the concentration of SB increases, the floating lag time were decreases and visversa vers. Thus, the concentration at 10-12% SB gives optimum buoyancy, after this if an increase the concentration of SB also does not shows much difference in the lag time and total floating time (24). Therefore in this study the 10% SB has selected for the whole study. When the matrix tablet comes in contact with acidic fluid (0.1 N HCl without pepsin) resulted in the generation of CO_2 bubbles. The generated gas was entrapped and confined within the gel, formed by hydration of polymer and gum, and thus falling density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. Karaya gum with HPMC produced the tablets with good gel strength, entrapped CO_2 gas and imparting steady and persistent buoyancy (25). Thus sodium bicarbonate was essential to achieve optimum buoyancy to extended gastric residence time of the LP matrix in the stomach could cause increased absorption. Table 5 shows the lag time and total floating time, all formulations are in between 29-96 seconds and continuously floating for more than 12 hours respectively.

Table 5. Evaluation of Lag time, Total floating time and swelling index.

Formulations	Lag time	Total floating time	Swelling index
F1	81	>12	110.42
F2	74	>12	221.84
F3	96	>12	280.86
F4	52	>12	489.20
F5	83	>12	483.20
F6	39	>12	160.11
F7	80	>12	451.32
F8	57	>12	480.86
F9	43	>12	839.20
F10	29	>12	723.20

Water uptake study

The swelling index of the polymers can be determined by water uptake of the floating tablet. The complete swelling was achieved by the end of 8 h, percent swelling was determined for all the developed formulations. The highest percentage of swelling was F9 as shown in Fig.2 (839.20%), when compared to other formulations and least percentage of swelling was F1 (110.42%) at the end of 8 h. There was significant difference observed on the swelling property by varying concentrations of HPMC and Karaya gum. There was considerable increase in percent swelling of the tablet with increase in karaya gum similarly increasing concentrations of HPMC also showed increase in swelling but relatively less compared to karaya gum as shown in Table 5. The diffusion of drug significantly depends on the water content of the tablet; this may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling of the system as shown in Figure 3. Also this higher water content could predict the higher penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation and thus reducing the floating lag time. Consequently, faster and higher swelling of the tablet led to increase in dimensions of the tablet leading to increasing the diffusion pathways and thus decreasing diffusion rates (26). So the drug release was found to be high initially and then gradually decreased. All the floating tablets showed better radial and axial swelling.

At 0 h At 8 h

Figure 2. Swelling behavior of floating matrix tablet of LP (F9) after 8 h.

In vitro dissolution studies

The floating drug delivery systems can extend the GRT and thus increase the overall drug bioavailability of drugs like LP that shows better absorption at stomach rather than intestine. The different concentration of natural gum, hydrophilic polymer and diluents had a remarkable influence on the *in vitro* drug release; the results were shown in Figure 3 and 4. The F1exhibited nearly 100% drug release at 8.3 h, nearly 44% drug in the 1st hour and control release for almost 8 h. The F6, F7, F8 exhibited more than 75% of drug release at 12 h. The F5 shows the least drug release among other formulations, these results clearly shows that as increase in the concentration of KG without HPMC concentration, decreases the drug release this may be due to formation of thick gel barrier on the tablet. As the thickness of the gel barrier increases drug takes more time to diffuse through it and this proved in other formulations, which showed more swelling index. But this was not true in F1 and F6, may be because of increased in the concentration of HPMC and absence of karaya gum. The controlled release of drug from the formulations may be because of release medium being diffused in to the matrix, whereby drug may have diffused out of the tablets. The ideal controlled drug delivery systems should release the drug in predetermined manner. The objectives of the systems are to ensure safety and efficacy of the drugs, as well as to improve the patient compliance. The results showed that the Karaya gum could be used for the preparation of gastric floating controlled delivery systems.

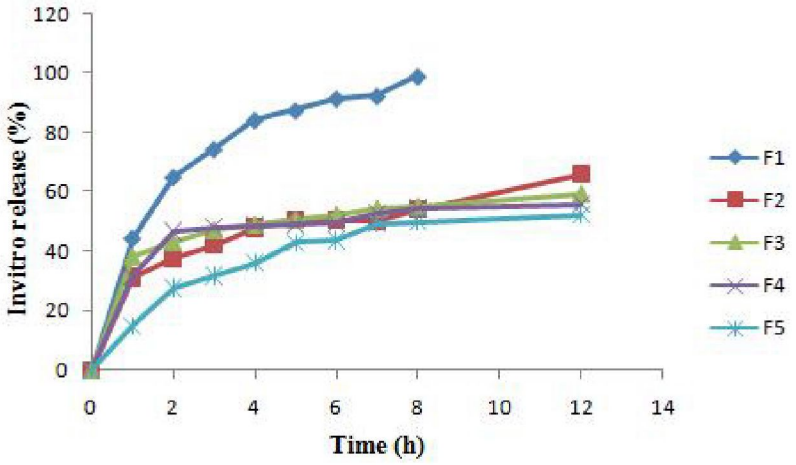

Figure 3. In vitro release behavior of Losartan potassium floating tablets (F1-F5).

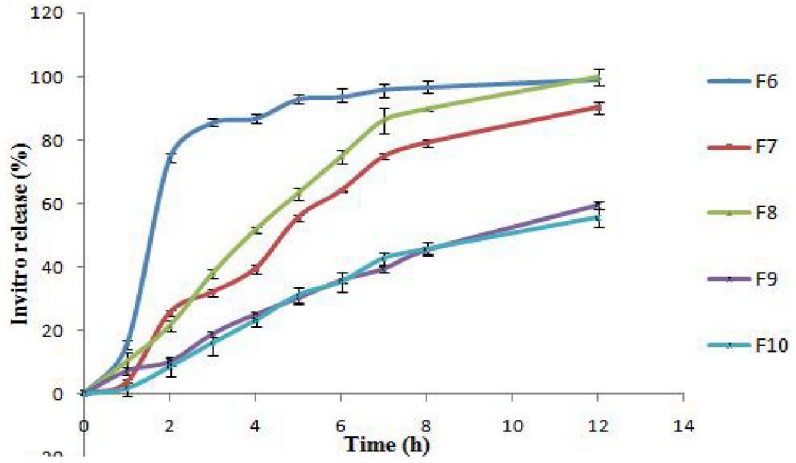

Figure 4. In vitro release behavior of Losartan potassium floating tablets (F6-F10)

Mechanism of drug release

The *in vitro* drug dissolution profiles were fitted to various models and release data were analyzed on the basis of Korsmeyer-Peppas equation and matrix release. The release rates k and n values of each model were calculated by PCP disso v2.08 software. The diffusion exponent ranges from 0.2231 to 0.5982. Coefficients of correlation (r^2) were used to evaluate the accuracy of the model fitting. The n, k and r^2 values are given in the Table 6. On calculating and comparing r^2 values for Korsmeyer-Peppas and other models, F8 and F9 gave good fit model to matrix model, and the remaining formulations were best fitted in the Korsmeyer-Peppas model, in this model, more than one type of release phenomenon could be involved or when release mechanism is not well known, and matrix release model applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablet with water soluble drug (27). In Korsmeyer-Peppas model, n value was in order to characterize the different release mechanisms, all formulations exhibited Fickian diffusion release, except F5 and F8 Non fickian diffusion release or anomalous transport. The fundamental of diffusion is based on Fick's laws, which describe the macroscopic transport of molecules by a concentration gradient.

Table 6. Kinetic treatment of dissolution profile of tablets (Values of r^2, k, and n for tablets) and mechanism of drug release.

Formulations	Korsmeyer – Peppas			Mechanism of drug release	Release kinetics
	N	r^2	K		
F1	0.2623	0.9942	53.4301	Fickian	Peppas
F2	0.2231	0.9944	36.1640	Fickian	Peppas
F3	0.4371	0.9962	14.210	Fickian	Peppas
F4	0.4876	0.9981	23.31	Fickian	Peppas
F5	0.5987	0.9931	17.054	NonFickian	Peppas
F6	0.2050	0.9894	12.387	Fickian	Peppas
F7	0.4935	0.9937	15.944	Fickian	Peppas
F8	0.5226	0.9904	13.040	Non fickian	Matrix
F9	0.2241	0.9929	19.562	Fickian	Matrix
F10	0.2974	0.9911	23.954	Fickian	Peppas

CONCLUSION

This study discusses the preparation of LP floating tablets using HPMC and KG by effervescent technique was a promising approach to achieve *in vitro* buoyancy and to improve the absorption of losartan. In order to prolong the GRT, a sodium bicarbonate was optimized, to keep the tablets floating over the medium and addition of gel forming polymer and gum was essential to achieve *in vitro* floating. The results data obtained from the experiment concluded that the release of drug from the tablets occur by Fickian and non-Fickian diffusion. The release kinetics profiles of tablets followed matrix and Korsmeyer-Peppas model.

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