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Research Article

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FORMULATION AND EVALUATION OF LISINOPRIL DIHYDRATE AS GASTRORETENTIVE FLOATING TABLETS

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ABSTRACT

Aim of the current study was to increase residence time of lisinopril dihydrate in specific site through formulating it as floating tablet. Floating tablet were prepared by direct compression using polymers; HPMC K100M, HPMC K4M, xanthan gum, ethyl cellulose either alone or in combination with other excipient such as sodium bicarbonate, citric acid, avicel pH 102, spray dried lactose [SDL] and dicalcium phosphate [DCP]. The prepared tablets were evaluated in terms of their physical properties, hardness, % friability, weight variation, content uniformity, *in-vitro* release, floating properties and swelling index. Most of the prepared batches of tablets were found to exhibit short FLT due to the presence of sodium bicarbonate and showed that as amount of HPMC K100M increased the drug release decreased; this is due to the increase in concentration of HPMC K100M that resulted in increased tortuosity or gel strength of the polymer. It was found that increase sodium bicarbonate concentration causes an increase in the floating time (FLT) and increased drug release. While floating time was decreased due to the increased amount of sodium bicarbonate; causing a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix. Avicel pH 102 was used as a diluent showed more retarded drug release when compared with SDL and DCP. It is concluded that HPMC K100M at concentration 50% [F5] gives the best result with high swelling index 157% with 75% drug release at 8h and TFT 24h.

Keywords: Lisinopril dihydrate; HPMC K100M; sodium bicarbonate; floting tablets.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve and maintain the desired drug concentration. The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation.

Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non- uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed[1].

Various approaches have been pursued to increase the retention of an oral dosage forms in the stomach, including high density sinking systems, low density floating systems, mucoadhesive systems, swellable, expandable or unfoldable systems, superporous hydrogel systems, and magnetic systems[2].

Floating drug delivery systems (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[3].

The floating drug delivery system classified in to non-effervescent FDDS which is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol[4], and effervescent systems which prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such way that when in contact with the acidic gastric contents, C02 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms[5].

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Lisinopril dihydrate is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE). Lisinopril is chemically described as (S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dehydrate[6]. It is slowly and incompletely absorbed after oral doses. About 25% of a dose is absorbed on average, but the absorption varies considerably between individuals, ranging from about 6 to 60%.It is used in the treatment of hypertension, heart failure, prophylactically after myocardial infarction, and in diabetic nephropathy[7].

MATERIALS & METHODS

Materials

Lisinopril dihydrate purchased from Hangzhou Hyper Chemicals Limited, China. HPMC K100M, HPMC K4M purchased from Shin-Etsu Chemicals Co.Ltd., Japan. avicel pH 102 gifted by Samara´a drug industry/Iraq. Sodium bicarbonate purchased from Riedel-deltaen/Germany.

Method

Formulation of lisinopril dihydrate floating tablet: Different formulas of Lisinopril dihydrate floating tablets were prepared as shown in table **1**. They were prepared using direct compression method. The previously weighed ingredients were homogeneously mixed in a mortar for fifteen minutes in order to obtain a homogeneous mixture of powder blend, a known weight of the powders blend of different ingredients were mixed with a calculated amount of magnesium stearate and talc powder for five minutes and then compressed using 9mm biconcave punch tableting machine[8].

Effect of polymer type: Formulas 1, 2 and 4 which contain xanthan gum, HPMC K4M,and HPMC K100M, respectively in concentration equal to 40%(w/w)of the total weight of the tablet were used to study the effect of the type of polymer used to retard the release from the floating matrix tablet.

Effect of polymer concentration: Formulas 3, 4 and 5 which contain HPMC K100M in concentration of 30%, 40%, 50% (w/w) respectively of the total weight of the tablet were used to study the effect of polymer concentration on the release profile.

Effect of polymer combination: Formulas 6, 7, 8 and 9 were used to study the effect of polymer combination and how the ratio of these combinations will affect the release from the floating matrix tablet, formulas 6 and7 contain HPMC K100M:carbopol 934p in a ratio of 3:1and 1:1 respectively, and effect of ethyl cellulose addition in formulas 8 and 9 which contain HPMC K100M:ethyl cellulose in a ratio 3:1and 1:1 respectively.

Table1. Composition of the float tablets using different ingredients types and concentrations.

Formula No. / Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Lisinopril dihydrate	10	10	10	10	10	10	10	10	10	10	10	10	10
Xanthan gum	80	-	-	-	-	-	-	-	-	-	-	-	-
HPMC K4M	-	80	-	-	-	-	-	-	-	-	-	-	-
HPMC K100M	-	-	60	80	100	60	40	60	40	80	80	80	80
Carbopol 934p	-	-	-	-	-	20	40	-	-	-	-	-	-
Ethyl cellulose	-	-	-	-	-	-	-	20	40	-	-	-	-
Sod. bicarbonate	30	30	30	30	30	30	30	30	30	25	-	30	30
Calcium carbonate	-	-	-	-	-	-	-	-	-	-	30	-	-
Citric acid	15	15	15	15	15	15	15	15	15	15	15	15	15
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5	5
Mg stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5
Avicel pH102	50	50	70	50	30	50	50	50	50	50	50	-	-
Spray dried lactose	-	-	-	-	-	-	-	-	-	-	-	50	-
Dicalcium phosphate	-	-	-	-	-	-	-	-	-	-	-	-	50
Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200	200	200

Concentration effect of sodium bicarbonate: Formula 10 was prepared to study the effect of sodium bicarbonate amount at 12.5% w/w concentration on drug release and floating properties.

The effect of gas generating agent type: In order to study the effect of the type of gas generating agent on drug release from the matrix tablet, sodium bicarbonate in formula 5 was replaced by calcium carbonate in formula 11 with the same amount.

Effect of types of diluents: Formulas 5, 12 and 13 which contain avicel pH102, spray dried lactose and dicalcium phosphate respectively, were prepared to study the effect of different types of diluent on the release profile. All the prepared formulas have the same amount of diluent.

Evaluation of the prepared floating tables

Weight variation: Twenty tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than7.5% for 200 mg tablets and none by more than double that percentage[9].

Hardness: The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2[10].

Friability: Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again .The observed value should not be more than 1 %. The percentage friability was measured using the following formula.

$$\%F = \left(1 - \frac{W_t}{W}\right) \times 100$$

Where, % F = friability in percentage, W = Initial weight of tablet, W_t = weight of tablets after revolution[11]

Drug content: Five tablets for each batch were taken and triturated, then added to 100ml of 0.1N HCL with sonicated for 15 minutes and filtered through Whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 206nm using UV/Visible spectrophotometer[12].

***In-vitro* buoyance studies:** The *in-vitro* buoyancy was determined by floating lag time, as per the method described by a Rosa et al, 1994. Here, the tablets were placed in a 100-ml, beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT)[13].

Swelling index: The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 100 ml beaker of 0.1 N HCl and after 1, 2, 3, 4, 5 and 6 h each, beaker containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. Swelling index was calculated by using the following formula[14].

$$Swelling\ index = \left(\frac{Wet\ weight\ of\ tablet - Dry\ weight\ of\ tablet}{Dry\ weight\ of\ tablet}\right) \times 100$$

***In-vitro* dissolution test:** The release rate of Lisinopril dihydrate from the floating tablets was determined using the dissolution apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl at 37±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper and diluted to a suitable concentration with 0.1 N HCl and analyzed spectrophotometrically at λmax of 206nm[15].

RESULTS AND DISCUSSION

Evaluation of lisinopril dihydrate floating tablets

Weight variation: The weight variation of floating tablets as shown in table **2**, the result was found in rang of 198±0.7 to 199.3±0.9 from all the formulations. This is fulfills the USP requirements in the limits ±7.5% of the average weight. That means no large difference observed in weight of individual tablet form the labeled to weight[16].

Hardness: As shown in table **2** the hardness for formulas was in range of 3.7 to 5.2 kg/cm^2 which indicated good mechanical strength and don't affect floating ability of the tablets.

Friability: As shown in table **2** all the prepared formulas having an acceptable weight loss which range between 0.35% to 0.76 % which indicated to be less than 1% which was in accordance to the IP[17]. Friability was unaffected with polymer concentration and viscosity[18].

Content uniformity: The content uniformity of the prepared lisinopril dihydrate floating tablets (table **2**) showed that all the formulas of prepared lisinopril dihydrate floating tablets, which results in a good content uniformity, which were subjected to this test, complied with USP specification, which is 85 - 115% of lisinopril dihydrate content in each individual tablet[16].

Table 2. Parameters of lisinopril dihydrate floating tablets.

Formula No.	Weight Variation (mg)±SD	Hardness (kg/cm) ±SD	Friability (w/w)	Lisinopril Contain (%) ±SD
F1	199±1.1	3.75	0.7	98.5
F2	198±0.7	3.75	0.73	97.5
F3	199.1±1.1	3.7	0.76	99.1
F4	198.6±1	3.8	0.72	102
F5	199.2±1.1	4	0.6	99.2
F6	198.6±1.2	5	0.41	98.4
F7	198.4±1.4	5.2	0.35	98.8
F8	198.7±0.9	4.2	0.72	98.7
F9	199.3±0.9	4.3	0.66	99.3
F10	199.2±1.1	4	0.72	99.2
F11	198.5±1.2	4	0.75	101
F12	199.1±0.76	4	0.63	99.4
F13	199.2±1	3.8	0.76	98

***In-vitro* buoyance studies:** All the tablets were prepared by effervescent method; the results are shown in table **3**. Sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1g/ml, the tablet becomes buoyant[19].

Tablets with xanthan gum concentration of 40% (F1) show high FLT (260) because xanthan gum has the tendency to form a viscous gel, this gel restricts the diffusion of dissolution media inside the matrix and delay the formation of CO_2, as a result floating lag time was prolonged dramatically and formation of viscous gel entraps the gas bubbles inside the matrix and minimizes chances of bubbles getting escaped from the polymer network channels. This in turn led to floating behavior of the matrix for longer duration[20].

F2 contain HPMC K4M in concentration of 40% shown FLT 12s and TFT 14h. The effect of polymer concentration on floating lag time and total floating duration was shown in formulas 3, 4 and 5 which contain HPMC K100M in concentration of 30% 40% and 50% respectively, which they have a lag time values of 10s, 18s and 26s and a TFT of 15h, 17h and 24h respectively. This can be explained by that a high polymer contents result in the formation of a strong gel; at low polymer levels the gel does not form quickly, as HPMC content is increased, the resulting gelatinous diffusion layer becomes stronger and more resistant to diffusion and erosion[21].

Incorporation of carbopol 934p with HPMC K100M F6 and F7 in concentration (1:3) and (1:1) gave FLT 25s and 20s and allow TFT 14 h and 12h respectively, this lead to prolongation of floating lag time and decrease in total floating duration. Carbopol 934p has a well-known negative effect on floating behavior of the delivery system; this can be explained by the fact that carbopol 934p has a much higher moisture absorption compared to HPMC. This result in a dramatic increase in the density of floating system which, in turn showed a corresponding decrease in the floating capacity of floating system[22].

Incorporation of ethyl cellulose with HPMC K100M F8and F9 in concentration (1:3) and (1:1) gave FLT 34s and 42s and allow TFT 19h and 23h respectively. Ethyl cellulose has a well-known release retardant effect due to its hydrophobic nature so it can retard the diffusion of dissolution medium to the matrix and this will delay the reaction between the dissolution medium and sodium bicarbonate; generation of CO_2 will be affected and hence

floating lag time will be prolonged and prolongation of floating lag time with increasing ethyl cellulose concentration[23]. Formula 10 which contain lower amount of sodium bicarbonate (25 mg) when compared with other formulas that contain same polymer and gas generating agent, gave increased FLT (42s) and decreased TFT (19h) because of FLT value decrease with increase in sodium bicarbonate concentration in tablets.

At lower concentration of sodium bicarbonate the more time was required to ditch the tablet from agar plate. But increased sodium bicarbonate the tablets were detached early and became buoyant. Further the entrapment of CO_2 bubbles within the tablet matrix was resulted in longer floating duration of matrix tablet[24]. The effect of addition of calcium carbonate as gas generating agent on floating behavior was studied in formula 11 in comparison with formula 4. It was shown that there is increase in floating lag time (16s) and floating duration (21h), Because of calcium carbonate is insoluble in pH 1.2 media and its hydrophobicity might be increase duration of floating for the tablets[25]. Two different fillers with different properties were used to study their effect on floating behavior and release. Formulas 12 and 13 contained spray dried lactose and dicalcium phosphate respectively. Lactose is a well-known water soluble filler[26]; while dicalcium phosphate, although it is hydrophobic in nature, but it is soluble in acidic solution[27], this property facilitates the penetration of medium to matrix and lead to floatation of the tablet in a short period.

Determination of the swelling index of the floating tablets: The swelling index of floating tablets illustrated in table **3**. The changes in weight and swelling was started from the beginning and continued until the end of experiment, which is 6h. Among, the result was found in range of 103% to 157% from all the formulations. The highest swelling was observed with the formulation F5; this may be due to type of polymer.

Table 3. The floating capacity and swelling index of the prepared lisinopril dihydrate floating tablets

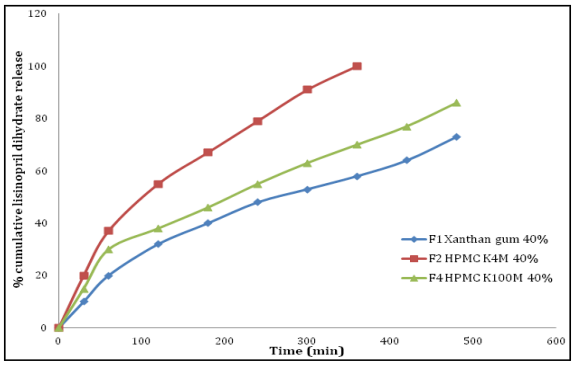
Formula No.	Floating lag time FLT(s)	Total floating time TFT(h)	Swelling index (%)
F1	260	30	155
F2	12	14	103
F3	10	15	134
F4	18	17	145
F5	26	24	157
F6	20	14	148
F7	25	12	154
F8	34	19	133
F9	42	23	126
F10	42	19	138
F11	16	21	135
F12	11	13	144
F13	19	15	140

Effect of polymer type: Formulas 1, 2 and 4 were designed with different types of polymers to show the effect of these different polymers on the release behavior from the matrix. The polymers used are xanthan gum, HPMC K4M and HPMC K100M. The concentration of polymer was kept constant in all formulas; the concentration used was 40%w/w.

Formula 1 was fabricated to study the effect of xanthan gum on the release of lisinopril dihydrate from the compressed matrix. Xanthan gum, a hydrophilic polymer, upon contact with aqueous fluid is able to form quite viscous gel, and hence retard the drug release from hydrophilic matrix[28] (figure **1**).

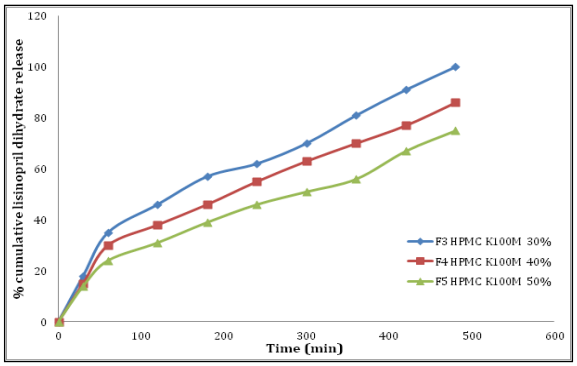
Formula 2 which contain HPMC K4M can retard the release of lisinopril dihydrate for 6h. In formula 4 HPMC K100M was used as matrix forming polymer, there is a retardation in lisinopril dihydrate release from this formula 87% in 8h; the results are shown in figure **1**. The release differences between HPMC K4M and HPMC K100M due to difference in polymer viscosity was mainly due to the differences in their molecular weight such increase in polymer viscosity grade results in a decrease in the drug release rate due to a decrease in the total porosity hence release is extended to long period[29].

Figure 1. The effect of polymer type on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.



The effect of polymer concentration: The effect of concentration of HPMC K100M in formulas 3, 4, and 5 which contained 30%, 40%, and 50% polymer respectively (figure **2**). The release of drug is decrease with increase polymer concentration. This might be due to the fact that HPMC K100M is a polymer with high molecular weight and viscosity; when contacted with water, it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded release of Lisinopril dihydrate from the floating tablets[30].

Figure 2. The effect of polymer concentration HPMC K100M on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.



The effect of polymer combination: Four formulas were prepared with different polymers to study the effect of polymer combination and how the ratio of this combination will affect the release from the floating matrix tablet.

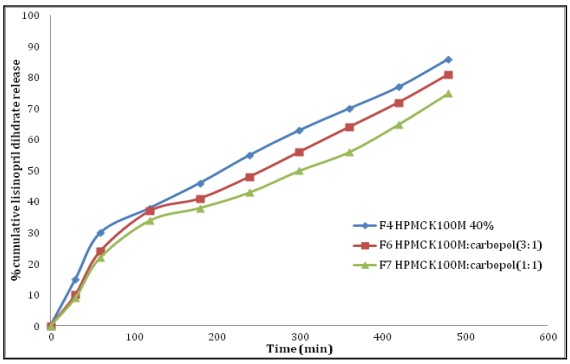
Carbopol 934p and ethyl cellulose were used in combination with HPMCK100M to retard the release of lisinopril dihydrate. These polymers were used in two different ratios of 3:1and 1:1 with respect to HPMCK100M.

Incorporation of carbopol 934p in the formulas 6 and 7 leads to reduction in the amount of lisinopril diydrate released from the matrix (as shown in figure **3**).

Carbopol 934p is a cross-linked polymer with high molecular weight and viscosity; it would swell and hold water inside its micro-gel network. This particular

property may be responsible for retarding the drug release. Carbopol 934p, when exposed to water, becomes viscous and tends to bind the mixed polymeric system together resulting in a reduced erosion of system[31]. Also, combination of anionic polymer (carbopol) with nonionic (HPMC) produces a synergistic increase in viscosity. This is probably due to the stronger hydrogen bonding between the carboxyl groups of carbopols and hydroxyl groups of HPMC, leading to stronger cross-linking between the two polymers, which could also diminish the release fluctuations[32].

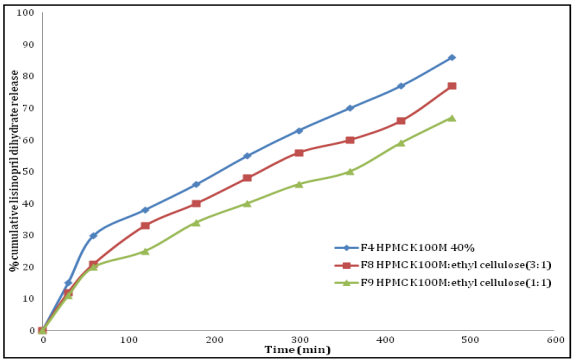
Figure 3. The effect of carbopol 934p concentration on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.



Formulas 8 and 9 were designed to study the effect of incorporation of ethyl cellulose on the release profile of lisinopril dihydrate. Addition of ethyl cellulose to formulas 8 and 9 lead to reduction in the release of lisinopril dihydrate from the matrix tablet in comparison with formula 4which contains no ethyl cellulose. As the ratio of ethyl cellulose in the matrix increase from 1:3 (ethyl cellulose to HPMC K100M) in formula 8 to 1:1 in formula 9, further decrease in the release was observed (figure **4**).

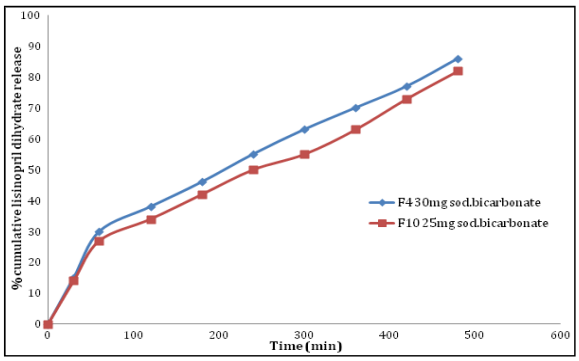
The retardation in the release from formulas containing ethyl cellulose is related to hydrophobic nature of ethyl cellulose which restricts the penetration of medium inside the matrix, leading to reduced diffusion of the drug from the matrix. This may be due to a more rigid complex formed by hydrophilic polymers HPMC K100 M in presence of ethyl cellulose, which helped in retaining the drug in the matrix and did not allow rapid diffusion of soluble drug from the matrix. According to penetration theory, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network[33].

Figure 4. The effect of ethyl cellulose concentration on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.



Concentration effect of sodium bicarbonate: Formulas 4 and 10 were used to study the effect of effervescent concentration on drug release which contain 15% and 12.5% respectively, as shown in figure **5**. The results obtained reduction in the release of lisinopril dihydrate from formula 10 containing 25mg sodium bicarbonate as gas generating agent with respect to formula 4 having 30mg sodium bicarbonate. The high release of formula 4 than formula 10 due to the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release[34].

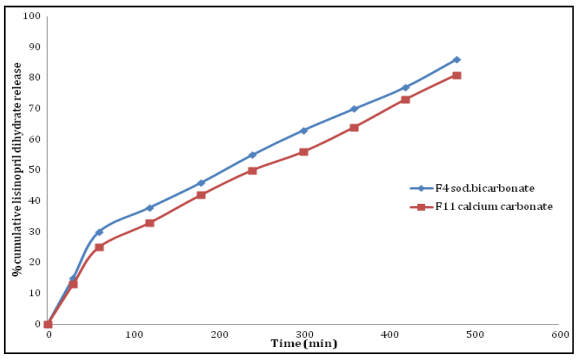
Figure 5. The effect of sodium bicarbonate concentration on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.



The effect of gas generating agent type: Sodium bicarbonate and calcium carbonate were used to prepare effervescent floating lisinopril dihydrate compressed matrix and the effect of them on the release behavior was studied. Results are shown in figure **6**.

The results obtained indicate reduction in the release of lisinopril dihydrate from formula 11 containing calcium carbonate as gas generating agent with respect to formula 4 having sodium bicarbonate. These results can be attributed to different gas forming capacity and the solubility of the particular gas-forming agent because of the high aqueous solubility of sodium bicarbonate than calcium carbonate[35].

Figure 6. The effect of gas generating agent type on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.

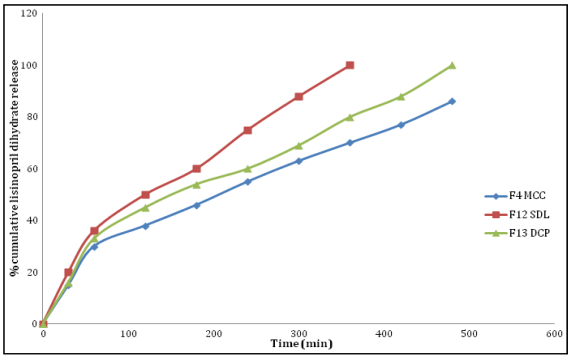


The effect of diluent type: The effect of different types of diluents on release profile was studied using three different diluents which differ in their properties, thus each one can affect the release in different manner. Microcrystalline cellulose (MCC) was used as diluents in formula 4; in formula 12 MCC was replaced by spray dried lactose, and in formula 13 dicalcium phosphate (DCP) was utilized as a diluent, so replacement of MCC with lactose in formula 12 and bicalcium phosphate in formula 13 lead to acceleration of release from compressed matrix as in shown in figure **7**.

Lactose is well known water soluble filler, so incorporation of lactose leads to increases in the hydration rate and relaxation of the polymer chains resulting in more dissolved drug diffusing out from the matrix. And also lactose, by its water-soluble and hydrophilic nature, facilitates gel formation and shortens the penetration time

of the dissolution medium into the matrix[36].

Figure 7. The effect of diluent type on the release of lisinopril dihydrate in 0.1N HCL at 37˚C.



Incorporation of DCP as filler in formula 13 instead of MCC leads to increase in release of drug. As floating drug delivery system should remain for long period of time, so the drug release kinetics should be important in acidic medium. Solubility of DCP was 17.39 mg/ml at pH of 1.2 while it was only 0.068 mg/ml at pH of 7.4 Thus, although DCP was characterized as water-insoluble filler, it acts as soluble component at low pH[37].

CONCLUSION

Lisinopril dihydrate was successfully formulated as controlled release floating tablet with a dose 10mg that extend the drug release for 24 hrs. This dosage form was prepared using effervescent technique by direct compression method. F5 was the best formula which contains HPMC K100M at concentration 50% gives the best result with high swelling index 157% with 75% drug release at 8h and TFT 24h.

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