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Gastric Floating Matrix Tablets of Metformin Hcl: Design and Optimization Using Combination of Polymers

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A B S T R A C T

The objective of this study was to develop a floating drug delivery system (FDDS) from metformin hydrochloride to enhance gastro residence time (GRT), with floating properties which remain in the stomach more than gastric empting time (GET). Eight batches were prepared using hydrophilic polymers as release-retarding, and sodium bicarbonate as a gas former by direct compression technique. The effects of effervescent agent (sodium bicarbonate) and a binary combination of hydroxypropyl methylcellulose (HPMC) K4M with polyvinylpyrrolidone (PVP) or carbopol934 on floating properties and drug release profile were investigated. Drug release study was evaluated for 12 hours using USP paddle-type dissolution apparatus using 0.1N HCl in 37±0.5˚C as dissolution medium. The swelling index, floating behavior and kinetic parameter were found to be regulated by polymers and CO_2 generating agent content. The results of powder ingredients and compressed tablets showed acceptable physicochemical properties. It was found that polymer content affected in the release rate constant and diffusion exponent. Statistical analyses of formulations data exhibited that F7 formulation was promising systems revealing excellent floating properties and sustained drug release characteristics. The MDT and DE_{12h} of F7 formulation were calculated to be 5.26h and 49.88%, respectively. Drug release profile of F7 formulation followed non-Fickian diffusion with Hixson-crowell model.

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Introduction

Generally, rapid and unpredictable gastric emptying time (GET) close to 0.5–2.0 h, could result short residence time of the conventional dosage form through the oral administration. This phenomenon can cause inadequate drug absorption from the device above the absorption site leading to reduced efficacy of the administered dose. Obviously, therapeutic efficacy of well absorbed drugs in the stomach or the upper part of the gastrointestinal tract may be enhanced with a long gastric residence time and achieved gastro retentive dosage forms (GRDFs)[1,2]. Possibly, fabrication of gastro retentive dosage forms can possess many benefits such as: persisting nearly constant drug level at the site of action, prevention of peak-trough irregular rises, reduction in dose and dosage frequency, side effect avoidance, and improved patient adherence [3]. Consequently, different approaches such as Floating Drug Delivery System (FDDS) as the sub collection of GRDFs with a bulk density lower than gastric fluids have been proposed to retain the dosage form in the stomach. While, such buoyant system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. And In the end, the residual system is emptied from the stomach [2,4]. Certain types of drugs can benefit from using gastric retentive dosage forms. These includes (I) locally active drugs in the stomach (II) drugs with a narrow absorption window (III) drugs which are unstable in the intestinal or colonic environments, (IV) and eventually drugs which have low solubility at high pH values [4,5].

Floating tablet consisted of hydrocolloidic polymer such as hydroxypropylmethylcellulose, hydroxyl propyl cellulose, carbopol, sodium carboxy methylcellulose and chitosan from synthetic, semi-synthetic or natural origin [6].

Non-effervescent and effervescent systems have been developed as FDDS: (a) non-effervescent system prepared by using a high amount of one or more hydrocolloid polymer that become hydrated in gastric fluid, by water absorption. This swelled matrices bulk density is less than 1, thus buoyant in the stomach fluid for up to 6 hours; (b) effervescent systems commonly composed of swellable polymers and various effervescent compounds such calcium carbonate and sodium bicarbonate in combination with citric acid or tartaric acid. [4]. The liberation of carbon dioxide via the acidity of gastric contents and its trap in the polymeric network provides the better floating characteristics to the dosage form and prepares the effervescent systems [7].

Many reviews mentioned Levodopa, Magnesium hydroxide, Diazepam, and Misoprostol as the good candidate for designing of floating tablets [5].

Metformin, a BCS class III drug comes under the class of biguanides exhibited an anti-hyperglycemic agent, improves glucose tolerance in non-insulin dependent diabetes mellitus and chronic hyperglycemia and disturbances of carbohydrate [8]. Bioavailability issues have been an increasing concern to drug regulatory authorities once assessing the safety and efficacy of drug products. It was reported that the bioavailability of metformin in oral administration is 33-55%. Plasma elimination half-life of metformin HCl is 1.52-4.50 h and the main site of absorption is proximal small intestines [9, 10].

It is seem that unique pharmaceutical dosage form of metformin with gastro retentive properties would allow an extended absorption phase of the drug with continues supplying to its absorption site in the upper gastrointestinal tract. This would lead to improve the bioavailability of the drug. In another research published on the formation of floating matrix tablets of metformin hydrochloride [10], Metformin HCL floating tablets were prepared by means of granulation method containing HPMC K4M as swellable polymer, where the most of the entrapped drug released during the first 8 h and the maximum floating time was about 8.4 h. In this study, floating matrix tablets of metformin hydrochloride were developed by direct compression method using three hydrophilic swellable polymer; HPMC K4M , carbopol 934 and PVP and the effect of different combination of polymers on various physicochemical characterization such as dissolution profile and in vitro buoyancy were evaluated. In this study, the release profiles of Metformin HCL from different floating tablets were improved up to 12 hrs and total floating time was increased up to 16.8 h.

Materials and Methods

Materials

Metformin HCl (Raha pharmaceutical industry as a gift), hydroxypropyl methylcellulose (HPMC) K4M, carbopol934 (Colorcon, England), poly vinyl pyrrolidone (PVP), magnesium stearate, sodium bicarbonate, citric acid (Merck, Germany).
All other chemical excipients were analytical grade.

Method

Metformin controlled release floating tablets were prepared by direct compaction method. For preparation of tablets, all the ingredients were weighed accurately and were screened through sieve (no.18). For this purpose, Metformin and other polymers were mixed for 10 minutes using a mortar and pestle, and lubricated with 5 mg of magnesium stearate. Then the tablets were compressed by using oval shape single punch tablet compression machine (GMBH-KS Kilian, Germany).
Rotary tablet punching machine was fitted with 14mm flat-faced punches with 60N in hardness. Formulation compositions were noted in Table1.

Table1. Composition of Metformin HCL floating tablets.

Formulations	Metformin	HPMC K4M	Cp_{934}	PVP	$NaHCO_3$	Citric Acid
F1	500	400	-	-	70	30
F2	500	400	-	-	90	30
F3	500	400	-	-	120	30
F4	500	350	50	-	70	30
F5	500	300	100	-	70	30
F6	500	250	150	-	70	30
F7	500	350	-	50	70	30
F8	500	300	-	100	70	30

Pre compression parameters

To evaluate the Pre-compression study of floating tablets were evaluated as a standard procedure below:

Carr's index

To calculate the Carr's index, the bulk and tapped density of the powder was used. It is expressed via the given equation:

Carr's Index (%) = $\frac{ty - B}{}$

Bulk density was measured to evaluate the ratio of total mass of powder to the bulk volume via passing the weighted powder through standard sieve # 18 into a measuring cylinder. Tapped density was obtained by dividing the mass of powder to tapped volume of the powder .Tapped volume was indicated via tapping the sample with the graduated measuring cylinder [11].

Angle of repose (θ)

To elucidate the maximum angle possible between the surface of the pile of the powder or granules and the horizontal plane, angle of repose was calculated.
The powder mixture was allowed to pass through the funnel fixed to a stand at definite height. The angle of repose was then obtained by calculating the height and radius of the heap of the powder formed [12].

Tan θ = –

θ = angle of repose, h = height of the heap, r = radius of the heap.

Post compression parameters
Physical properties of floating tablets

The hardness, weight variations, friability and content uniformity were determined for tablets by procedure stated in the US pharmacopoeia 35 [13].

Floating lag time (FLT) and total floating time (TFT)

FLT and TFT of floating tablets were measured visually in 100ml acidic environment (pH 1.2) at 37±0.5 ◦C and 50rpm [14].

Swelling index (%S.I.)

The dosage form was placed in glass containing 200ml of similar gastric medium (0.1 N HCl) at 37 ± 0.5. Percentage swelling at characterized time interval was calculated by the below equation [15].

$$\%S.I. = \frac{\quad}{\quad}$$

S.I. = Swelling index, W_t = Weight of tablet at time t., W_o = Weight of the dry tablet before placing in the glass.

In vitro drug release

The evaluation of release rate of Metformin HCl from floating tablets carried out using *United States Pharmacopeia (USP) apparatus* II (paddle method) (USP 29; ERWEKA dissolution test, Germany). The dissolution test was performed for six tablet using 900 mL 0.1N HCl solution (pH=1.2) and 100 rpm. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus at appropriate time intervals 0.5, 1, 2, 4, 6, 8, 10 and 12h and the samples were replaced with equal volume of medium. The samples were diluted to a suitable concentration with same buffer. These solutions samples were analyzed by atomic spectrophotometer at 228nm[16] Cumulative percentage drug release versus time was calculated using an equation obtained from a standard curve.

Kinetic analysis of dissolution data

To clarify the mechanism of release, the in vitro profiles were fitted to Zero order, First order, Higuchi matrix, Korsmeyer-Peppas and Hixson-Crowell cube root law (Table2).

Table2. Kinetic models used for analysis of metformin HCl release data.

No.	Model name	Model equation
1	*Zero order*	$Q_t = Q_0 + K_0 t$
2	*First order*	$Log\ Q_t = log\ Q_o + K_1 t/2.303$
3	*Higuchi*	$Q_t = K_H\ t_{1/2}$
4	*Hixson-Crowell*	$W_0^{1/3} - W_t^{1/3} = \kappa\ t$
5	*Korsmeyer-Peppas*	$M_t / M_\infty = K.t^n$

Where Q_t is amount of drug dissolved in time, Q_0 is initial amount of drug in the solution, t is the release time, W_0 is initial amount of drug in the pharmaceutical dosage form, W_t is remaining amount of drug in the pharmaceutical dosage form at time, Mt / M∞ is the fraction of drug release, *n* is the diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form, K_0 & K_1 is rate constant, K_H is Higuchi dissolution constant, κ is constant incorporating the surface-volume relation

The accuracy and prediction ability of models were compared by calculation of squared correlation coefficient (r^2 value). Based on the r^2 value, the best-fitted model was selected.

In Korsmeyer-Peppas model, the value of *n* characterizes the drug release mechanism from matrix. For the case of cylindrical tablets, $n \leq 0.5$ corresponds to a Fickian diffusion mechanism, 0.5

< n < 1 to non-Fickian transport, n = 1 to Case II transport, and n > 1 to super case II transport [17].
The release rate was compared between different formulations by calculation of tow release model parameters that are mean dissolution time (MDT) and dissolution efficacy (DE). These calculated by the below equations:

$$\text{MDT} = \frac{\sum_0^\infty (M \quad t) d}{}$$

Where M_t is amount of the drug dissolved at time (t) and M_∞ is amount of drug dissolved at infinite [18].
DE_{12h} of profiles were calculated from dividing by AUC (area under the curve) at 12 hours to area of the rectangle at the same time (expressed as a percentage)[19].

In vivo radiographic studies

X-ray technique was used to determine the gastric residence time of the tablets. Floating tablets of the formulation F7 were selected to make the tablet X-ray opaque, by way of replacement of 20 mg of the drug with $BaSO_4$ (all other ingredients were kept constant). The amount of barium sulfate in tablet should be sufficient to provide visibility by X-ray and at the same time preserve floating ability. For *In vivo* evaluation of gastrointestinal residence time asked three healthy volunteers to swallow the tablet with a glass water. The radiographic image of the tablet was recorded at intervals of 0.5, 1, 3, and 5 h [20, 21].

Result

Physical characterization of the powders

Results from characterization of powder blend are shown in Table 3. Values for angle of repose and Carr's index were found in the range of 21.4 to 27.6° and 12.8-17.1. Angle of repose and Carr's index parameters was measured with the acceptable limits (Table3).

Table3. Powder properties of all the batches.

Formulations	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's index %	Angle of repose (θ) °
F1	0.506	0.58	12.8	24.2
F2	0.435	0.526	17.1	23.7
F3	0.472	0.554	14.8	21.4
F4	0.428	0.502	14.7	27.6
F5	0.463	0.546	15.2	26.3
F6	0.457	0.531	13.9	27.4
F7	0.458	0.546	15.3	26.1
F8	0.479	0.566	15.3	24.5

Physical characterization of the tablets

Table 4 shows the physicochemical properties of floating matrix tablet of metformin. The floating tablets of metformin HCl showed the uniform content and appropriate friability. The weight variation for all formulations calculated accurately with his acceptable limits. The hardness was obtained at 50–65 N (Table4).

Table 4. Tablet properties of metformin HCl floating tablet.

Formulations	Weight variation (mg)	Friability (%)	Hardness (kg/cm3)	Content uniformity
F1	1053.8±11.6	0.56±0.1	51.3±4.1	497.6±12.2
F2	1032.9±12.1	0.63±0.04	59.1±2.4	513.2±9.5
F3	977.3±11.3	0.67±0.03	65.4±1.7	486.1±10
F4	978.8±10.2	0.6±0.02	56.3±3.8	508.2±14.7
F5	980.3±7.1	0.58±0.03	64.7±5.2	512.5±11.8
F6	1019.4±3.9	0.59±0.01	61.4±2.9	504.6±18.4
F7	968.3±8.1	0.59±0.01	61.4±2.9	504.6±18.4
F8	991.3±17.4	0.61±0.02	53.6±3.7	509.7±16.3

In vitro buoyancy studies

FLT was less than 1min for all formulations (Table5) and TFT was longer than 12 h for most of formulations. FLT showed meaningful change by increasing the sodium bicarbonate concentrations from 70 to 120 mg. It was found that as sodium bicarbonate increased the FLT decreased. Increasing in the carbopol content in tablet containing varying amount of (HPMC K4M)/ Carbopol increased the FLT of tablet. Incorporation of PVP in dosage forms decreased FLT significantly. In the optimized formulation (F7), dosage form to buoy after 19 s and floated for 15h (Fig. 1). Formulations (F7, F8) containing HPMC K4M/PVP demonstrated a decrease in total floating time. At the Fig1 floated tablet of optimized formulation in HCl medium has illustrated.

Table 5. Physical properties of metformin HCl tablets.

Formulations	FLT (sec)	TFT (h)	Maximum swelling (%)
F1	27±5	16.3±0.8	143±14
F2	23±2	16.8±1.1	140±14
F3	20±4	15.9±0.6	148±12
F4	33±8	16.5±1.8	152±8
F5	39±8	15.7±2.1	165±15
F6	50±10	13.4±1.5	177±13
F7	19±6	15.7±1.0	129±9
F8	24±4	13.5±0.6	118±17

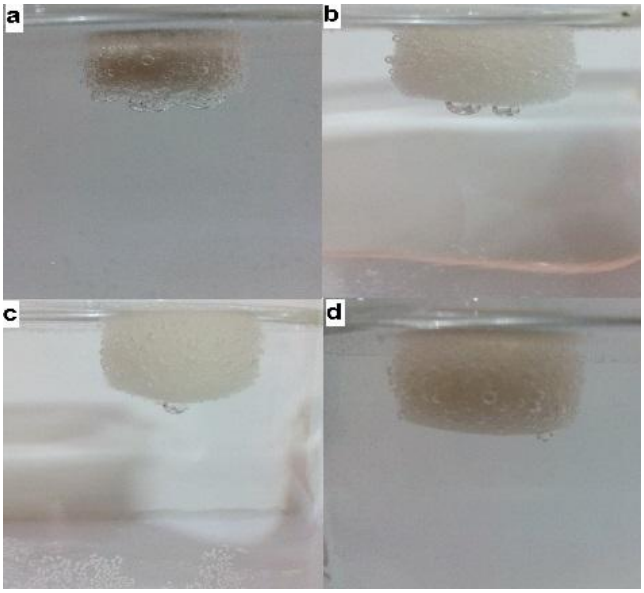

Fig 1. Photographs of floating tablet (F7) in HCl 0.1N (a: 25s, b: 1 h, c: 8h, d: 12h after immersion).

Swelling index

The swelling percent of tablets were determined by the mentioned method (*2.4.3*) at different time intervals. The maximum swelling was observed at 8 h in all formulations and swelling percent was determined at the end of 8 h for all the developed formulations (Fig2). There was a significant ($P< 0.05$) increase in swelling of the tablet containing varying amount of Carbopol (F4, F5, F6) with an increase in the Carbopol /HPMC content. In formulations F7 and F8, increasing the concentration of PVP resulted in decrease in swelling index ($P< 0.05$). Incorporation of varying amount of sodium bicarbonate in the formulations had no effect on the swelling index ($P> 0.05$). Swelling percent at 1, 2, 4, 6, 8 and 12 h has showed at Fig3.

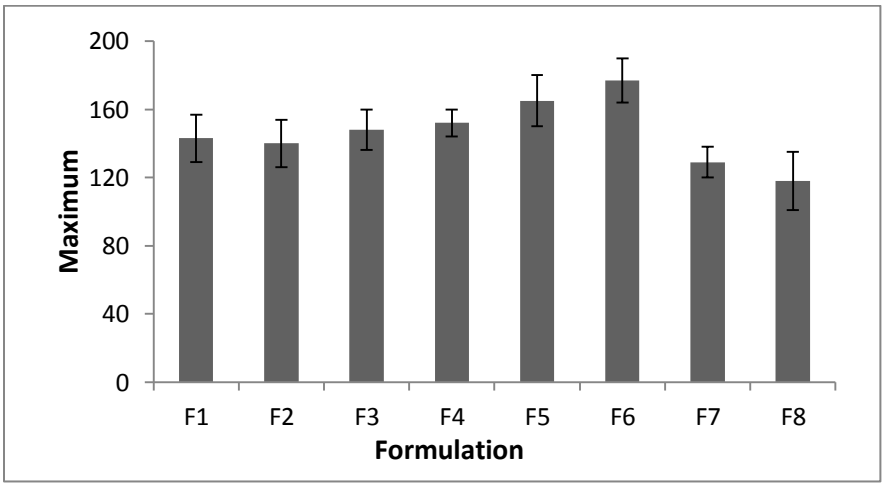

Fig 2. Effect of various concentrations of excipients on maximum swelling percent.

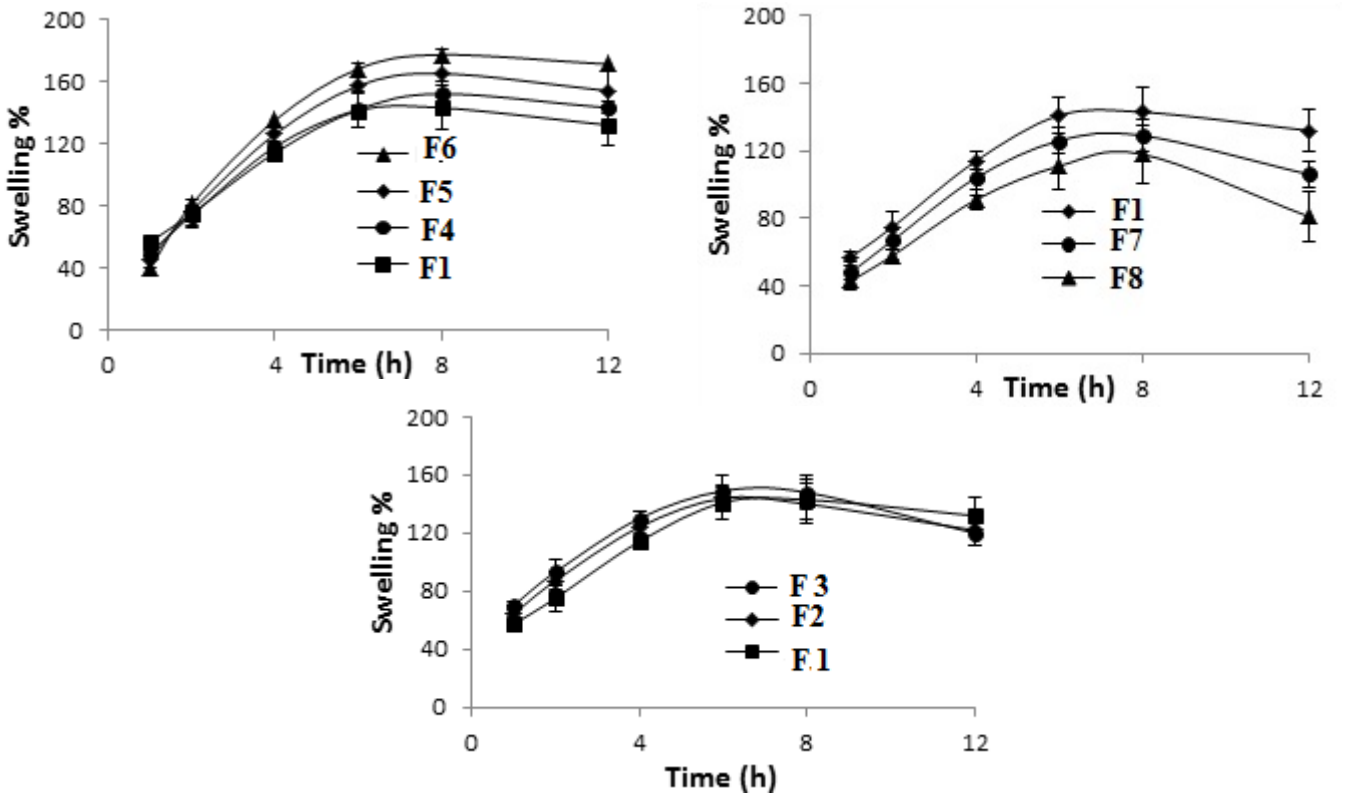

Fig. 3. Swelling percent of formulations at different times.

In vitro Drug release and kinetics of release

In vitro release studies of all formulations were carried out in 0.1N HCL .The study was performed for 12 h. The drug release profiles of different formulations are illustrated in Fig. 4. MDT and DE_{12h} were used to express the effect of polymers on drug release profiles. The reverse order exists between MDT and release rate. MDT value is the highest (7.98 h) for F6 formulation and lowest (4.3 h) for F8. Release parameters of all the formulations of metformin release presented at table 6. Increasing the percentage of effervescent increased the drug release rate. The influence of HPMC k4M/PVP and HPMC k4M /carbopol were shown in Fig 4. Higher concentration of PVP facilitates the drug release but as concentration of carbopol increased, the drug release rate was decreased compared to formulation containing just HPMC k4M (comparison of DE_{12h} % for F4, F5, F6 and F1 presented in Table 6).

Table 6. Drug release kinetic of Metformin HCL.

Formulations code	Kinetic models(r^2)				Peppas parameter			
	Zero order	First order	Higuchi	Hixson-Crowell	n	r^2	MDT	DE_{12h} %
F1	0.982	0.997	0.975	0.987	0.76	0.998	6.32	42.33
F2	0.976	0.972	0.981	0.997	0.73	0.998	5.89	45.7
F3	0.945	0.994	0.982	0.983	0.72	0.993	5.62	48.5
F4	0.987	0.995	0.961	0.996	0.84	0.998	6.7	39.31
F5	0.987	0.99	0.963	0.997	0.86	0.994	7.24	35.09
F6	0.979	0.987	0.962	0.996	0.86	0.997	7.98	29.7
F7	0.99	0.968	0.964	0.991	0.81	0.99	5.26	49.88
F8	0.961	0.957	0.985	0.991	0.76	0.99	4.3	57.78

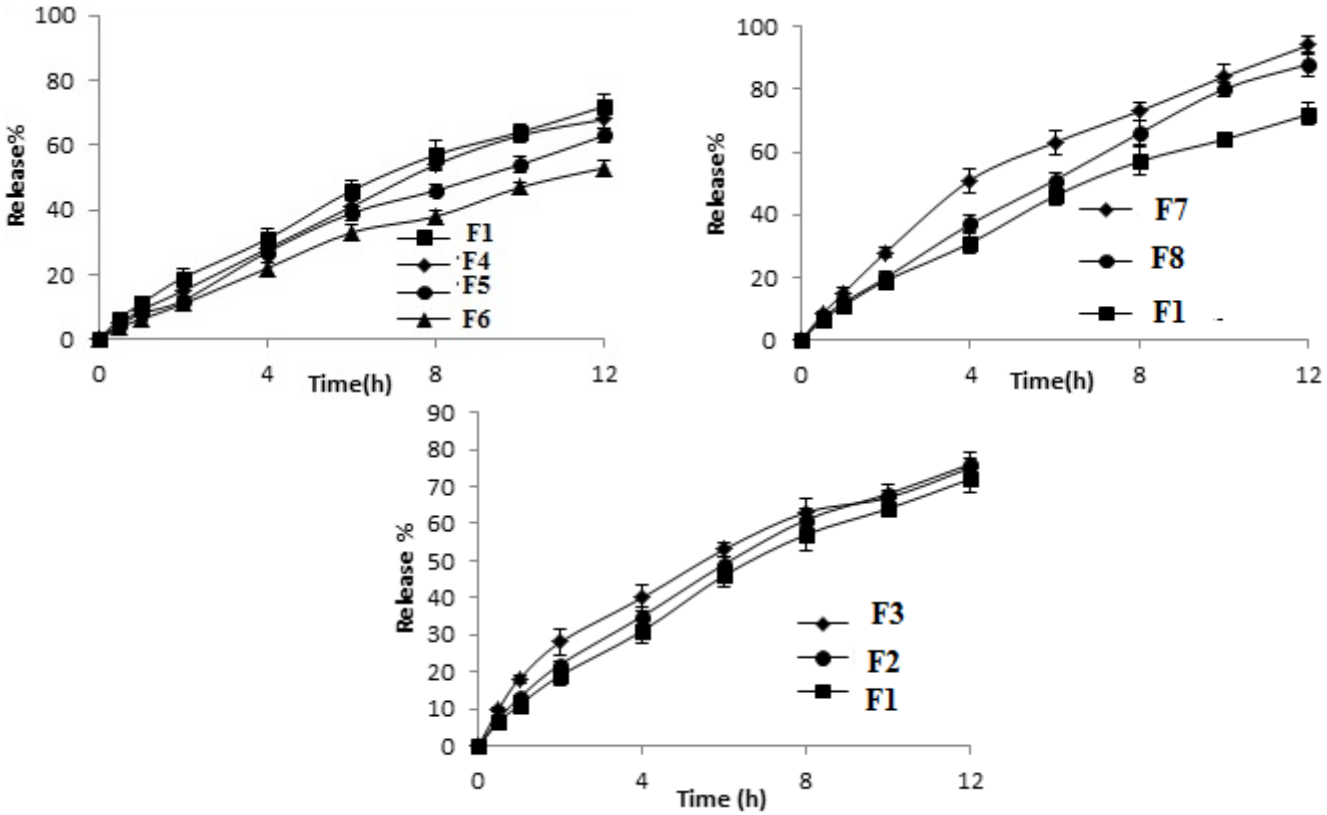

Fig. 4. The effect of different amounts of excipients on drug release properties.

Dissolution Kinetics and drug release mechanism

Based on higher correlation coefficient values, except F1 and F3 formulations that were best fitted with First order model, metformin release profile from all other formulations was best fitted with Hixon-Crowel equations model. (Table6). Investigation on exponents from korsmeyer-peppas equation is often useful in characterizing

drug releasing mechanism from matrix tablets. When n value is equal and less than 0.45, Fickian diffusion is dominant mechanism of drug release. When 0.45<n<0.89, the release mechanism follows non Fickian model and for n value =0.89, drug release mechanism is case II transport. By using Korsmeyer-Peppas equation, the *n* values obtained for developed formulations were between 0.72 and 0.86 indicating the non-fickian behavior coupling with the both diffusion and erosion mechanism.

Result- floating tablets behavior in stomach

Floating lag time and hardness of the BaSO4-containing floating tablets showed 23 ± 5 s and 65 ± 3.42 kg cm^3. The tablets were seen in the stomach at different time interval. The residence time of optimized formulation (F7) in stomach was 5±1.15 h. In Fig. 5 tablet position and its swelling are visible.

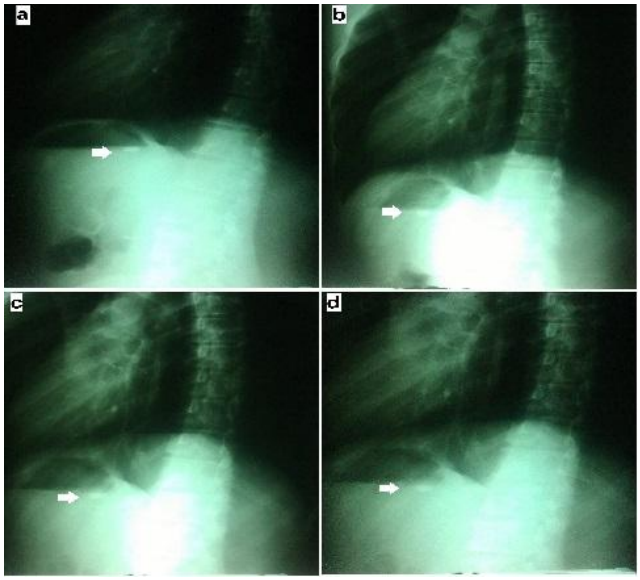

Fig 5. X-ray photographs of the $BaSO_4$-loaded floating tablets in the stomach. Images were taken at a) 0.5h, b) 1h, c) 3h and d) 5h.

Discussion

At the present study we attempt to develop optimized dosage form of Metformin HCl to obtain predictable sustained release floating tablets in 12 hours. Tablets were prepared by direct compression methods. The tap density, Carr's Index, and angle of repose generally considered as appropriate criteria for evaluation of the flow properties of solids. The results of angle of repose (<30) indicate good flow properties of the granules. This was also supported by lower Carr's index values. Generally, Carr's index values up to 18% indicate well to excellent flow properties. Therefore the prepared blends had good flow properties and can be used for tablet manufacture. Weight variation, drug content and friability of all formulations were in acceptable range. Content uniformity was within acceptable limits; indicate the prepared powders were uniformly mixed before tableting. Friability was found to be below 1% indicating good mechanical resistance of the tablets during handling on machines and or shipping. In previous studies, Gambhire et al [22] showed tablet hardness had little or no effect on the release kinetics but the FLT increased as tablet hardness increased by affecting the rate of penetration dissolution medium in tablet. In contrast, in study conducted by Basak et al [10], increasing the hardness of tablets resulted in better floating duration of gasteroretentive tablet of metformin which was explained by better protection of gas generated within the polymer gel formed by hydration in presence of water. However in present study, it isn't possible to evaluate the effect of hardness on FLT, due to changes several parameters simultaneously. CO2 generated from exposure sodium bicarbonate to acidic contents of stomach; which captured inside the hydrophilic matrix, consequently, built buoyant system. Increasing of the sodium bicarbonate amounts led to increase pore formation and earlier swelling, so the floating lag time (FLT) was reduced. It was resulted from increasing in CO2 liberating and its entrapment in matrix network and reduced density of FDDS [23].
Hydrophilic polymers were used to form floated tablet matrix like HPMC K4M and carbopol. The role of hydrophilic polymers is very important in

floating tablet. They hydrated with the exposure of gastric fluids and form low gravity matrix, with buoyant properties. Eventually, active pharmaceutical ingredients were captured inside the polymeric structures with the controlled release kinetic [24]. HPMC K4M was the most important ingredients of the floating tablet based polymers to adjust the release profile of metformin HCl and bouancy properties, because of the ability for producing rapidly viscose gelatin layer, pH- independent hydration, and high capacity for loading of therapeutic agents. The gelling compact ability was increased while the amounts of the polymers enhanced, so that diffusion pathway becomes long leading to slow releasing rate of the drug and increasing of mean dissolution time [25, 26].Because of the carboxylic groups inside the in carbopol structure and slow separation with the low swelling of the polymeric chain, incorporation of carbopol in the formulations increased the FLT [27, 28]. Indeed, carbopol tends to absorb more waters to increase the density as consequence TFT decreased [27, 29]. PVP, as a swelling polymer was implicated for designing of the famotidine floated tablet. It was thought that PVP effects on the dosage form buoyancy and drug dissolution, because of the water penetration to the matrix and facilitate gelling formation. Incorporation of PVP in dosage forms led to decrease FLT .This may be due to lower density of PVP compared with that of HPMC which caused rapid floating of the tablets [30]. Swelling index depends on percentage and type of polymer used in the formulation. Buoyancy properties, drug dissolution and drug release kinetic was impressed from the swelling index [26]. There was increase in swelling index of the tablet with increase carbopol content [25] the drug release from the formulations which have the better swelling index was slower, thus, this formulation can trap the higher amounts of active ingredients. As concentration of carbopol increased, the drug release rate was decreased. This finding is in agreement with study of Tavakoli, et al [30] .This effect was explained with sustaining effect of carbopol on drug release rate. Increasing the percentage of effervescent increased the drug release rate. This may be attributed to an increase in rate of pore formation and rapid hydration of the tablets. Certainly, drug release was the most important factor which affected from the incorporation of PVP[31-33]. Comparison of drug release from tablets containing combination of HPMC k4M/PVP or HPMC k4M alone demonstrated that PVP increased release rate. This was due to the fact that PVP is hydrophilic in nature allowed easy penetration of medium into the matrix and a more rapid release of metformin.

HMPC as the based polymer conveyed with other polymers to achieve optimized formulations. Tablets (F7) containing 350 mg HPMC K4M, 50 mg PVP, 70 mg $NaHCO_3$, 30 mg citric acid showed desirable in vitro properties. The optimized formulation demonstrated a short buoyancy lag time, total floating time of at least 15 h. For optimized formulation, the MDT and DE_{12h} were calculated to be 5.26 h and 49.88%, respectively and obtained good drug release profile with the Hixson-crowell kinetic and the non-Fikian transport. It seems that the both diffusion and erosion mechanism had the meaningful effect on the releasing mechanism.

Conclusion

The present study demonstrates the development of a metformin effervescent floating tablet with gastroretentive ability formulation using direct compression. Tablets containing 350 mg HPMC K4M, 50 mg PVP, 70 mg $NaHCO_3$, 30 mg citric acid showed acceptable results in respect to invitro evaluation. Finally, it can be claimed that the floated tablet of metformin HCl based HPMC K4M and PVP polymers can be noted as a drug delivery system with sustained release property in management of diabetes type II. The offered optimized formulation may reduce loaded dose, dosage frequency of metformin HCl tablet, prevent of peak-trough irregular rises and increase bioavailability. All of these properties can adjust blood glucose level better and improve patient compliance.

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Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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