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Formulation and Pharmaceutical Evaluation of Ferric-Maltol Floating Table

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A B S T R A C T

The new drug delivery systems have been developed, which can remain in the stomach for prolonged period of time. The effervescent floating tablet is one of these systems. Iron deficiency anaemia is a common disease in the world. Ferrous sulphate is the most common ferrous preparation used to treat and prevent iron deficiency, but it has little bioavailability and several complications. Ferric-maltol complex (FMC) is a ferric compound which doesn't have ferrous complications. In this study FMC was used for preparing effervescent floating tablets that are designed to prolong the gastric residence time of drug, increase drug bioavailability and treat iron deficiency. At first the active ingredient (FMC) was synthesized from maltol and ferric chloride, the formation of complex was confirmed. Eleven tablet formulations were designed using different amounts of gel-forming agents (HPMC K4M, Carbopol 934 P), and effervescent agents (sodium bicarbonate and citric acid). Pre-compression parameters of powder blend (bulk density, tapped density, angel repose, Carr's index, hausner's ratio) were measured; the tablets from each formulation were prepared by direct compression method. Buoyancy study of tablets was investigated. The F3-F11 tablets were selected for further post compression evaluations (thickness, hardness, friability, weight variation, drug content, *in vitro* dissolution study, swelling ability, drug release mechanism determination). F9, F10, F11 were the most appropriate formulations. They were very similar in consideration of swelling property, total floating time and drug release kinetic & mechanism. Among these three formulations, F11 was selected as the best formulation with more suitable buoyancy behavior. The F11 tablets were able to float immediately and remained buoyant for more than 18 hours. The drug release pattern followed zero order kinetic with non-fickian diffusion. 98.54% of FMC released from F11 floating tablets after 12 hours. Physical stability of F11 tablets was evaluated according to ICH guidelines. This formulation showed no-significant change in physical properties after storage at 40°C and 75% RH for 3months.

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Introduction

The oral administration of drugs is the most convenient route of drug delivery due to the ease of administration and patient compliance [1]. But this way has some limitations and physiological problems, for example short gastrointestinal passage time and subsequently non-complete absorption of some drugs, especially drugs with a narrow absorption window in proximal part of the small intestine, is one of the major problems. In addition , the period of time that drugs stay in the stomach and the evacuation rate of gastric content are not predictable[2].Investigators have developed several drug delivery systems which can remain in the stomach for a prolonged time so that the duration of drug existence in the stomach will be predictable. Four main groups of these systems include floating systems, bio-adhesive systems, high density systems, expandable systems [3]. Application of the floating drug delivery systems (FDDSs) is one of the methods to prolong the retention time of drugs in stomach and increase their bioavailability. Drugs with a narrow absorption window in upper part of GIT, unstable and insoluble drugs in intestinal lumen, and drugs which are mainly absorbed in stomach or have a local effect in stomach can be formulated as floating system[4].The floating systems can stay buoyant on the surface of the gastric fluids, and resist the evacuation force of stomach contents, because the density of these systems is lower than that of gastric fluids, and the gastric emptying rate doesn't have any influence on buoyancy time of these systems. A desired rate of drug release from the floating system and suitable total floating time can be obtained using different amounts of various gel-forming polymers [5]. The floating drug delivery systems (FDDSs) have two different types of buoyancy mechanism including effervescent and non- effervescent types. In the formulation of effervescent type, gel- forming polymers like HPMC and carbopol, and gas- generating agents such as citric acid and sodium bicarbonate are used. Effervescent floating dosage forms generate CO_2 after contact with gastric fluids, thus reduce the density of system and remain buoyant in stomach for a prolonged period of time and release the drug slowly at desired rate [6, 7] .Iron deficiency anaemia is one of the common diseases in the human's society. It is reported that 30% of people in the world are anaemic. Iron is a necessary trace elemental in body. It is a part of haemoglobin, a protein which carries oxygen from longs throughout other organs, so iron deficiency can make many problems. 18mg of daily iron administration prevents iron deficiency [8]. Ferrous (Fe^{+2}) compounds are widely used for treatment iron deficiency anaemia [9]. These preparations have several side effects such as irritation, because the ferrous ions (Fe^{+2}) produce hydroxyl radicals and these radicals damage the mucosal layer of gastrointestinal tract. Ferrous sulphate is the most common iron product used in prevention and treatment of iron deficiency. Acidity of this compound is also an irritant [10]. The use of Ferric (Fe^{+3}) preparations avoids these problems (Fe^{+3} ions don't produce hydroxyl radicals), but they are generally much less soluble at physiological pH and, therefore, have poor bioavailability within pH>3(as in the intestine). Thus the use of compounds that hold ferric iron in soluble and absorbable form within alkaline pH of intestine has a therapeutic benefit [11]. 2-methyl-3-hydroxypyran-4-one (maltol) is a natural and safe compound present in some plants (Fig 1).

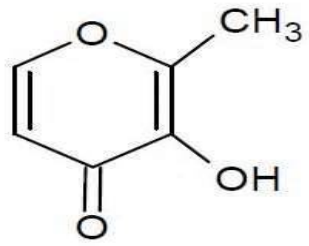

Fig. 1. Chemical structure of 2-Methyl-3-Hydroxy-pyran-4-on (MALTOL)

It has applications in food and cosmetic industry, and has a very high affinity for Fe^{3+}, so that Ferric- maltol complex (FMC) will be hold in soluble form in the gastrointestinal tract (within 1<pH< 9). FMC can easily deliver its iron to apotransferrin after reduction of $Fe^{3+}$to Fe^{2+} in gut lumen [12, 13]. The absorption of Fe from FMC has beencompared with that from FeSO4 in previous studies .Fe^{+3} in this complex was absorbed almost as well as Fe^{+2} after oral treatment with the same quantities of FMC and FeSO4 preparations. It can be claimed that FMC

is a suitable successor for ferrous compounds to prevent and treatanaemia related to iron deficiency, because not only doesn't ferric-maltolproduce free hydroxyl radicals, but also can hold Fe^{+3} in soluble forms within alkaline PH of intestinal lumen [11]. As iron mainly has a narrow absorption window in proximal part of the small intestine, slow delivery of it to the duodenum will increase its bioavailability. So iron compounds are good candidates to be formulated as floating drug delivery system [14].In this study, we tried to develop the best formulation of FMC effervescent floating tablet which allows the medicine to be released slowly at a desired level to maximize iron bioavailability and minimize its complications in patients.

Material and Methods

Materials

HPMC K4M powder was obtained from Colorcon (England) and citric acid, maltol, ferric chloride hexa hydrate, lactose, NaOH, sodium bicarbonate and Carbopol934 were from Merck (Germany).PVP was obtained from Amin Pharmaceutical Co.IR.

Synthesis of ferric-maltol complex

The iron-maltol complex (Fig 2) was synthesized from the 2-methyl-3-hydroxypyran-4-one (Maltol) and ferric chloride hexa hydrate as the following method:

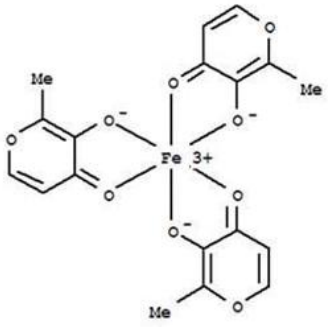

Fig. 2. Chemical structure of ferric-maltol complex (FMC)

A solution of ferric chloride hexa hydrate (4.3g, 0.016 mol) in 40 ml of warm ethanol was added to a solution of maltol (6g, 0.048mol) in 50 ml of warm ethanol. After the removal of solvent by rotary evaporation, the resulting purple oil/solid was taken-up in 60 ml of hot water and filtered, then NaOH (1.93 g, 0.048 mol) dissolved in 5 ml of the water added, Storage at 4^0 C for 18 h caused precipitate to form, filtration followed by freeze-drying, giving ferric-maltol as a red powder, 5.70 g (88 %). The resulting compound was purified by recrystallization from $CHCl_3$ / hexane to isolate the mineral and non-reacted iron and to form iron complex as a deep-red powder, in a 61 % yield 5.31 g. This complex was heated in a vacuum oven (0.1mmHg, 120^0C) for 8 h to give purple Fe-maltol, 4.12 g (60%). This end stage was preformed to evaporate the trapped chlorophorm in the structure of the complex during formation of this. Mp (decomposition) 315-318 ºC ((lit. value (Reference No12)320^{o}C)) Anl. Calcd. For $C_{18}H_{15}O_9Fe$ (M_w: 431g/mol), %:Fe12.95. Found, %: Fe, 12.5.

IR and UV-Visible spectrums of the final sample and its ligand were evaluated to confirm the formation of ferric- maltol complex, λ_{max} in these spectrums was compared with obtained results in previous study (Reference No 12). To determinate the purity and iron percentage, the formed complex was analyzed by an atomic spectrophotometer at 248.3 nm. A linear correlation (R^2 =0.995) was obtained over the iron range of 5-25 mg/ml, high precision and accuracy were obtained. The absorption of the complex before and after recrystallization was determined and iron percentage was calculated.

Preparation of effervescent floating tablets

Effervescent floating tablets containing 170 mg of ferric-maltol were prepared by direct compression method using different amounts of hydrocolloid polymers including HPMC K4M, carbapol934P, and gas-generating agents (sodium bicarbonate and citric acid), lactose as a filling agent, PVP as a binder, and magnesium stearate as lubricant. All the ingredients for preparation of 50 tablets from each formulation were accurately weighed and passed through sieve No #20. All ingredients (except magnesium stearate) were blended using a cylinder mixer for 20 minutes, then magnesium stearate was added, and mixed for 2-3 additional minutes, tablets were compressed in compression machine with 12mm oval punch (Table1).

Table1. Formulations of ferric-maltol effervescent floating tablet.

Formulation code	FMC (mg)	HPMC K4M (mg)	Carbopol (mg)	PVP (mg)	Na-bicarbonate (mg)	Citric acid (mg)	Mg-stearate (mg)	Lactose (mg)
F1	170	60	30	-	50	-	5	135
F2	170	60	30	15	50	-	5	120
F3	170	60	30	25	50	-	5	110
F4	170	60	40	25	50	-	5	100
F5	170	60	50	25	50	-	5	90
F6	170	90	30	25	50	-	5	80
F7	170	120	30	25	50	-	5	50
F8	170	120	40	25	50	-	5	40
F9	170	140	30	25	50	-	5	30
F10	170	140	30	25	50	10	5	20
F11	170	140	30	25	50	20	5	10

Evaluation of effervescent floating tablet formulations

Evaluations of pre- compression parameters

To determine the flow properties of powder blend before compression of the tablets, the following parameters were measured [15]:

Bulk density

Pre-sieved ingredients blend of tablets was placed in a graduated cylinder and measured the volume and weight as it is, then bulk density was calculated by following formula:

$Db=M/Vb$

Where, M = Weight of powder taken; Vb = bulk volume [15]

Tapped density

Pre-sieved ingredients blend of tablets was placed in a graduated cylinder, then cylinder was fallen down at an interval of 2 inch from the surface of a desk, this action was repeated for several times until the powder bed volume reached the minimum volume, thus tapped density was calculated by bellow formula:

$D_{T=}M/Vt$

Where, M = Weight of powder taken; VT = tapped volume [15]

Compressibility index

This parameter was calculated by this formula:

Compressibility index = $(D_t- D_b/ D_T) \times 100$

Where, D_T = tapped density; D_b = bulk density[15]

Angle of repose

Pre-sieved ingredients blend of tablets was poured from a funnel to a flat surface, thus a cone was formed, the height and diameter of this cone was measured, and then repose angle (∞) was calculated by this formula:

$Tan\infty =2H/D$

Where, H= height of cone; D = diameter of con [15]

Hausner's ratio

Hausner's ratio was calculated by the following formula:

Hausner's ratio = D_T/ D_b

Where, D_T = tapped density; D_b = bulk density [15]

Evaluation of post compression parameters

In vitro buoyancy study

In vitro buoyancy study was performed for all the formulations. Ten randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of the medium, was determined as the total floating time (TFT) [16].

Evaluation of suitable formulations

Formulations that showed suitable buoyancy behaviour (F3–F11) were selected for following tests.

Tablet thickness

Twenty tablets were randomly picked, and their thickness was measured by a digital micrometer (d: 0.001 mm).The average values were calculated and reported as the mean values ±SD**.**

Tablet hardness

The hardness of ten randomly selected tablets was determined by Euweka hardness tester. The average values were reported in N as the mean± SD.

Tablet weight variation

Twenty tablets were randomly selected, and accurately weighed individually. Results were reported as mean values ± SD.

Tablet friability

Twenty pre-weighed tablets were placed in afriabilator. The friabilator was operated at 25rpm for 4min. The tablets were dusted and reweighed (W_f). The results of friability were calculated by the following formula:

Friability= $(W_0-W_f/W_0) \times 100$ [14]

Where, W_0 - initial weight of tablets, W_f - final weight of tablets.

Drug content estimation

Ferric-maltol content

Twenty tablets from each formulation were weighed individually, the average weight was calculated, then all twenty tablets were triturated and the powder equivalent to the average weight was dissolved in100ml of suitable buffer (buffer was prepared by using deionised water and HCl, NaOH, PH were stabilized at 7.4).The solution was filtered through a 0.45µ membrane filter. After diluting suitably, absorption of the prepared solution was determined using a UV-Visible spectrophotometer at wavelength of 411 nm, the mentioned buffer was employed as blank.

Swelling ability

Three tablets from each formulation were randomly picked. At first each tablet was weighed accurately; tablets were placed in 100ml of 0.1 N HCl. Then the tablets were removed every 2h up to 12 h, and weighed after draining free water by a filter paper. Swelling index were expressed in terms of water uptake percentage (WU %). Swelling index was calculated by the following equation:

Swelling index = $(W_t - W_0) /W_0 \times 100$

Where, W_t= Weight of tablet at time t [14]

W_0 = Initial weight of tablet

In vitro dissolution test

In vitro dissolution test was carried out using USP I apparatus in 900 ml of 0.1 N HCl (pH 1.2) for 12 hours at 37±0.5°C and 50 rpm. A 4ml sample of the solution was withdrawn at 1 h interval of time. The samples were filtered through a 0.45µ membrane. The volume of dissolution medium was fixed with adding 0.1N HCl. The absorption of the withdrawn samples was measured at 248.3 nm using an atomic absorption spectrophotometer.

Determination of dissolution parameters

The percentage of dissolution efficiency (DE %) and the mean dissolution time (MDT) are used to compare dissolution profiles of drugs. These two parameters for ferric-maltol were calculated by the following formulas:

MDT=$\sum^{n} t_{mid} \times \Delta M / \sum^{n} \Delta M$ [17]

ii

Where, t_{mid}= the meantime between times t_i and t_{i-1}; ΔM =amount of the dissolved drugs between times t_i and t_{i-1}.

DE % = $(\int_0^t y.\,dt / y_{100}.\,t) \times 100$[17]

Where, $\int_0^t y.\,dt$ =the area under the dissolution curve up to the time t; y_{100}=the loading dose. In this study DE12% was calculated.

Determination of release kinetics and mechanism

The obtained data from dissolution study of ferric-maltol were analysed as per zero order. Firstorder and Higuchi's models. The highest correlation coefficient value (R^2) determined the drug release kinetic. The mentioned data were fitted into Korsmeyer-Peppas equation, and the mechanism of drug release from tablet was

distinguished using the slope (n) of the formed line.

Physical stability study

Physical stability study of F11 tablets were performed according to the ICH guidelines [18]. Tablets were kept in oven at 40^{oC}/ 75% RH (a saturated solution of sodium chloride provided the necessary humidity) for 3 months. At intervals of one month, tablets were evaluated with regard to physical characteristics including: weigh variation, hardness, friability, drug content, TFT and FLT, the percentage of drug release after 12h.

Statistical analysis

In statistical analysis of the obtained data, comparison between more than two means was performed using ANOVA followed by LSD test. P-value less than 0.05 were considered significant.

Results

Synthesis of ferric-maltol complex

The ferric-maltol complex was synthesised according to the procedure described in literature [12]. The Identification, the structure and the purity of complex were achieved by IR and UV- Visible spectroscopy, atomic absorption method and through physical constants. IR and UV-Visible spectrums of ferric-maltol complex and its ligand (maltol) were evaluated (Fig3, 4, 5, 6) .The obtained results were compared with previous studies [12] (Table 2, 3). Results were very similar to each other, so the formation of complex was proved.

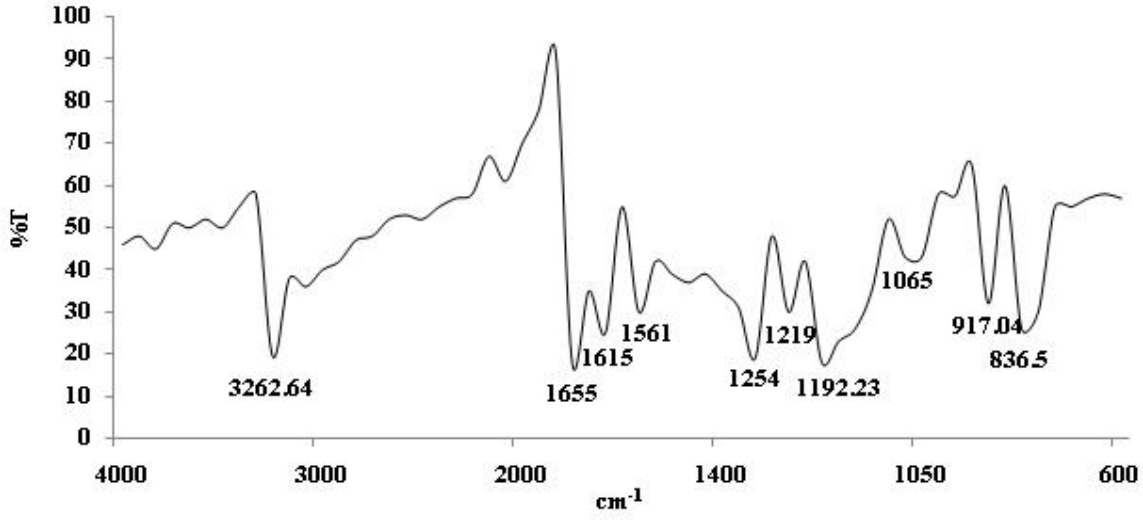

Fig. 3. IR-spectrum of maltol.

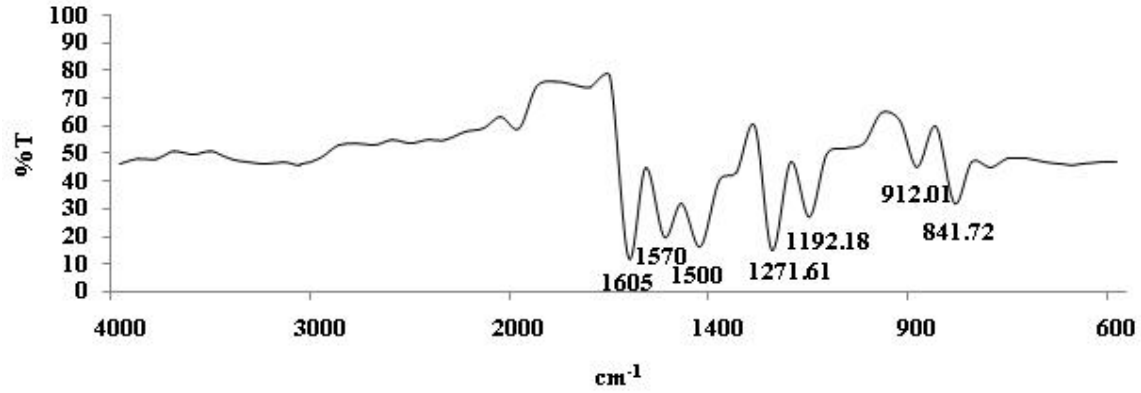

Fig. 4. IR-spectrum of ferric-maltol complex.

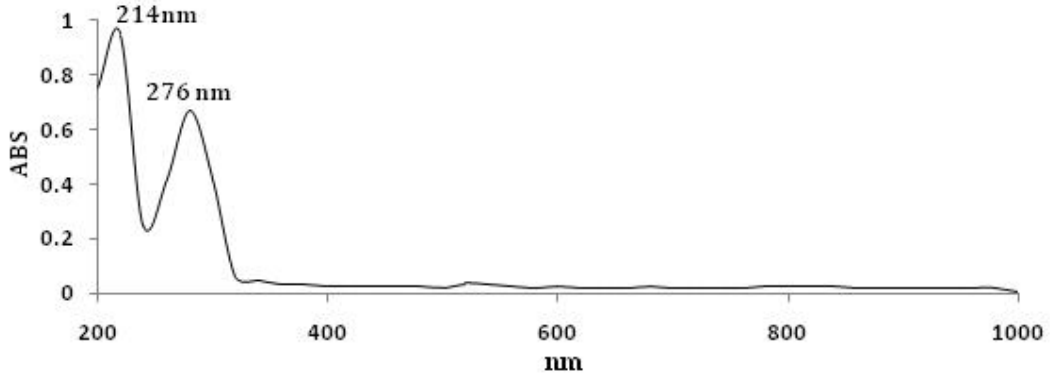

Fig. 5. UV-Visible spectrum of maltol.

Table 2. Maximum absorption (λ_{max}) in the UV-Visible spectrum of maltol and ferric-maltol complex.

	λ_{max} ofmaltol (nm)	**λ_{max} of ferric-maltol complex (nm)**
In previous study	215,275	225,305,412
In our study	214,276	224,304,411

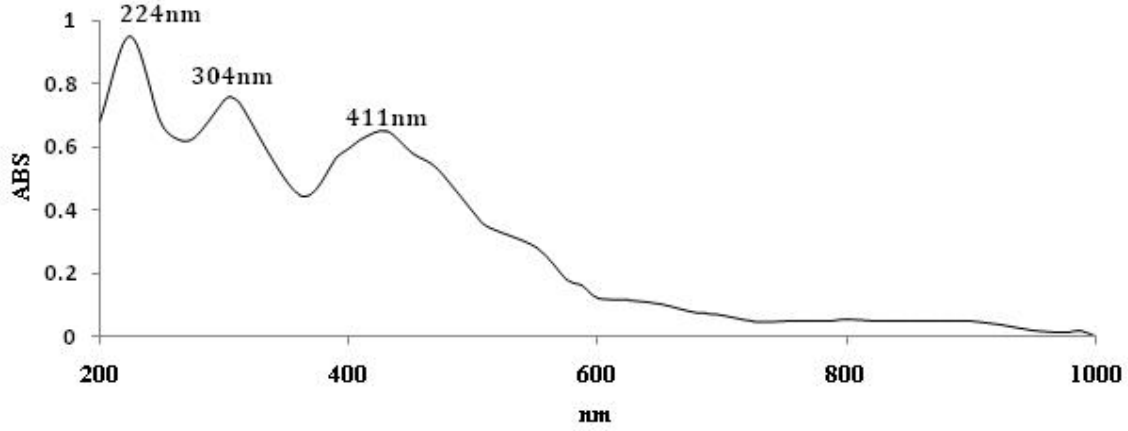

Fig. 6. UV-Visible spectrum of ferric-maltol complex.

The determination of iron percent in prepared complex (before and after recrystallization) was performed using atomic absorption method at 248.3nm .The standard curve of iron was obtained over the range 5-25mg/ml (Fig7). The obtained result (after recrystallization) was similar to the expected Value. The distinguished difference between the quantities of iron before and after recrystallization was due to non-reacted and excess mineral iron. But the mineral iron was isolated after recrystallization of the complex using chlorophorm.

Table 3. Frequencies (ν) in the IR- spectrum of maltol and ferric-maltol complex.

Compound	Maltol			Ferric-maltol complex		
	ν(C=O)	ν(C=C)	ν(O-H)	ν(C=O)	ν(C=C)	ν(O-H)
In previous study	1660	1625,1565	3240	1600	1576,1500	-
In our study	1655	1615,1561	326.64	1605	1570,1500	-

Before recrystallization absorption by atomic spectrophotometer: 0.059, %:Fe14.25. After recrystallization, absorption: 0.052, %:Fe12.5 Calculated, %:Fe12.95.

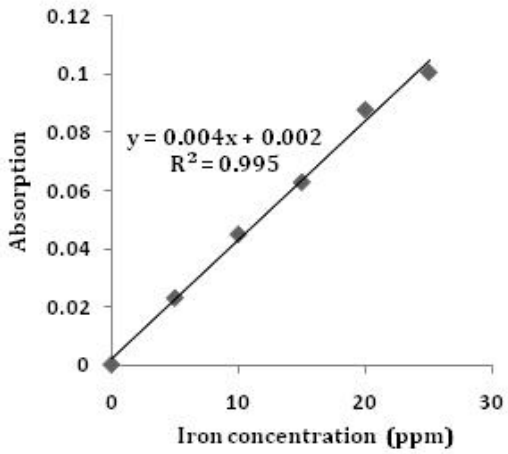

Fig. 7. Calibration curve of iron in atomic spectrophotometer

Pre compression evaluation

The fluidity of the powder blend was evaluated in terms of tapped density, bulk density, Carr's index, angle of repose and Hausner's ratio (Table 4). The calculated results showed that the powder blend had a suitable fluidity, so the direct compression method was used intablet preparation.

Table 4. Results of pre-compression evaluation.

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr'sindex (%)	Hausner's ratio
F1	0.58±0.02	0.65±0.02	28.54±1.30	10.67±0.58	1.12±0.01
F2	0.57±0.01	0.63±0.02	30.11±1.63	9.52±0.80	1.10±0.01
F3	0.55±0.02	0.62±0.02	31.38±1.05	11.29±0.43	1.12±0.02
F4	0.59±0.02	0.65±0.02	28.81±2.30	9.23±1.50	1.10±0.01
F5	0.60±0.01	0.67±0.01	30.96±1.50	10.44±0.60	1.11±0.01
F6	0.57±0.03	0.64±0.02	29.68±1.30	10.93±0.79	1.12±0.01
F7	0.62±0.01	0.70±0.01	28.81±1.00	11.42±0.20	1.12±0.00
F8	0.61±0.01	0.68±0.03	27.47±2.40	10.29±1.00	1.11±0.01
F9	0.59±0.03	0.66±0.02	29.24±2.00	10.6±0.70	1.11±0.02
F10	0.58±0.03	0.64±0.03	26.65±2.40	9.37±1.00	1.10±0.03
F11	0.61±0.04	0.69±0.05	28.36±1.00	11.59±0.40	1.13±0.01

Table5. Results of buoyancy behaviour of tablets.

Formulation code	Floating lag time (s)	Total floating time (h)
F1	246±2	Failed
F2	185±3	Failed
F3	155±2	5.3±0.2
F4	124±4	4.5±0.3
F5	103±3	3.8±0. 1
F6	132±5	8.0±0.4
F7	158±1	10.5±0.2
F8	115±5	9.3±0.4
F9	184±5	>14
F10	85±4	>18
F11	12±2	>18

Post compression evaluations In vitro buoyancy study

Average values ± SD obtained from buoyancy study have been shown in table5. The Addition of PVP (as binder) protected the tablet construction and improved buoyancy behavior of tablets. Increase in amount of HPMC (as gel-forming agent) had an important effect on the total floating time enhancement. But the enhancement in quantity of carbapol mainly improved the beginning of tablet buoyancy. Inthe end, using citric acid (as effervescent agent) decreased the floating lag time.

TheF3-F11 tablets were evaluated for other post compression tests because of their suitable buoyancy behavior. Tablet hardness was in the range of 72.3±1.6 to 78.6± 1.2 N. Weight loss in friability test was in the range 0.59 to 0.79%. All the prepared tablets contained ferric-maltol complex within the range of 96.12% ±2.3 to 102.04%±1.8 of the labeled claim (Table 6).

Swelling study

Swelling study was performed for F3-F11 tablets for 12h. The tablet swelling percentage was measured at intervals of one hour .The maximum swelling was observed after 8-10 h in all formulations (Fig8).

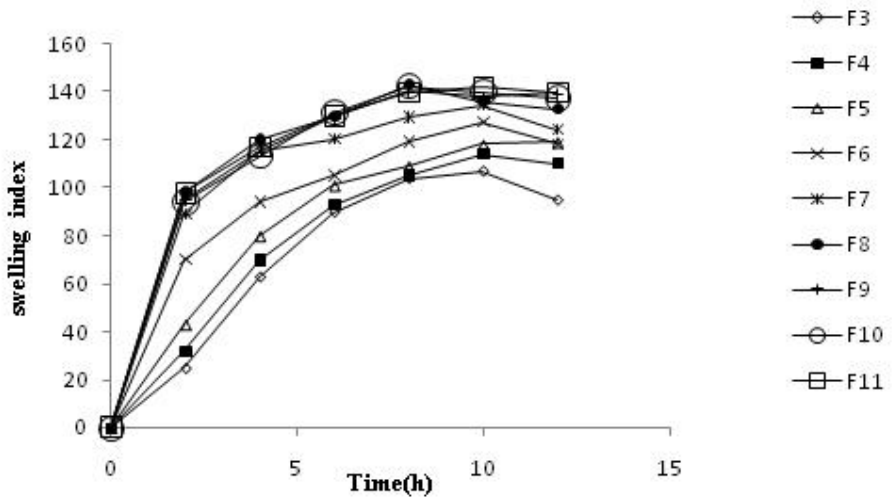

Fig. 8. Swelling index of the F3-F11 formulations.

Table 6. Results of post compression properties of tablets.

Formulation code	Thickness (mm)	Hardness (N)	Friability (%)	Weight Variation (mg)	FMC Content (%)
F3	3.980±0.001	78.60±2.07	0.63±0.06	448.50±4.80	97.90±1.41
F4	3.979±0.005	74.40±1.10	0.68±0.01	447.00±2.40	99.27±1.09
F5	4.030±0.014	73.00±1.96	0.74±0.05	449.00±3.31	98.77±0.59
F6	3.999±0.003	75.00±1.36	0.64±0.07	448.20±5.10	97.49±1.87
F7	4.001±0.003	72.30±1.60	0.73±0.14	446.50±3.05	96.12±2.03
F8	3.980±0.005	74.40±2.10	0.59±0.12	450.00±1.70	99.41±0.98
F9	4.030±0.012	75.00±2.60	0.70±0.08	448.80±1.44	97.32±1.34
F10	3.983±0.005	75.30±1.60	0.68±0.13	447.00±2.13	98.00±1.80
F11	3.980±0.030	74.00±1.80	0.79±0.10	450.30±2.52	98.45±1.63

In vitro dissolution study

The results of dissolution study during 12 hours have been reported in Fig 9 as released cumulative quantities of ferric –maltol. It was observed that the type and concentration of gel-forming and effervescent agents had effects on drug release pattern. The results showed that higher concentration of gel-forming agents would cause reduction in the rate of drug release. Addition of citric acid enhanced drug release.

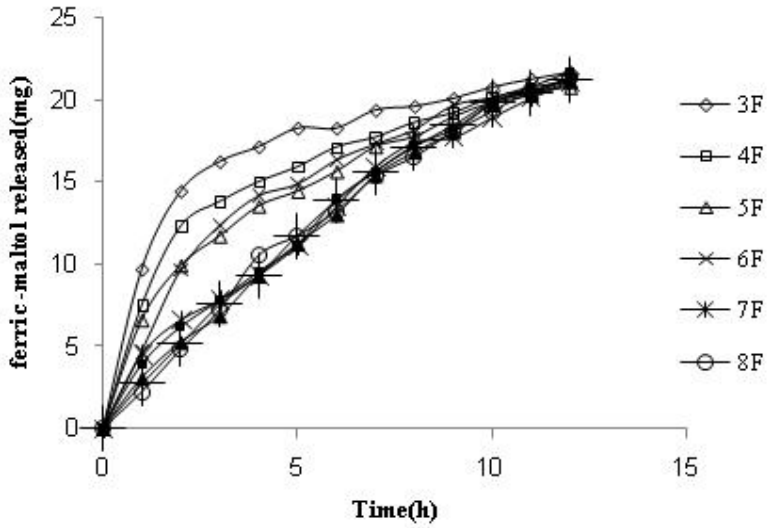

Fig. 9. Result of dissolution study of ferric-maltol in F3-F11 formulations.

Table7.The release parameters of ferric-maltol.

Formulatin code	Ferric-maltol	
	DE12%	MDT(h)
F3	80.07±0.35	2.10±0.15
F4	74.75±0.12	3.19±0.23
F5	66.6 ±0.21	3.53±0.26
F6	66.87±0.25	3.53±0.18
F7	59.72±0.43	4.70±0.23
F8	56.67±0.16	4.95±0.19
F9	57.54±0.45	4.81±0.27
F10	60.10±0.13	4.68±0.14
F11	62.43±0.17	4.50±0.28

Determination of release kinetics and parameters

The release parameters have been brought in table 7, and the results of release kinetic evaluation have been shown in table 8. The R^2 values showed that the *in vitro* release profile of drug from F3-F5 tablets could be best expressed by the first order model. The changes made in the concentration of gel-forming agents (in subsequent formulations) could shift the drug release kinetic from first order to zero order. The dissolution data were fitted in to Peppasequation. The slope (n) value was in the range of 0.289 to 0.826, so the drug release mechanism was diffusion.

Table 8. The release kinetic parameters of F3- F11 for ferric-maltol.

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsemeyerpeppas (n)
F3	0.683	0.954	0.900	0.289
F4	0.796	0.962	0.961	0.378
F5	0.877	0.984	0.933	0.454
F6	0.868	0.832	0.982	0.550
F7	0.968	0.941	0.973	0.660
F8	0.974	0.921	0.956	0.896
F9	0.975	0.947	0.965	0.838
F10	0.980	0.941	0.963	0.825
F11	0.978	0.916	0.964	0.826

Table 9. The results of physical stability of F11tablets at 40°C/75%RH.

Physical characteristic	At the beginning	1nd month	2nd month	3nd month
Weight variation(mg)	449.03±1.02	450.06±1.00	449.18±0.99	449.82±1.02
Hardness (N)	75.02 ±0.30	73.00±1.00	74.80±0.03	74.18 ± 0.15
Friability (%)	0.79 ± 0.02	0.80±0.01	0.85±0.00	0.80 ± 0.03
FMC Content (%)	99.75±1.07	101.06±1.67	98.80±1.50	100.14±1.00
Floating lag time(s)	13±2	15±4	16±3	15±2
Total floating time(h)	>18	>18	>18	>18
FMC released after 12h (%)	98.54±1.25	97.60±1.86	98.30±1.07	97.72±1.59

Physical stability studies

The optimized floating tablets (F11) were selected for stability study (Table9)**.** This formulation showed no-significant change in weigh variation, hardness, friability, drug content, TFT, FLT and drug release after storage at 40°C and 75% RH for three months.

Discussion

Iron is a vital mineral. Our bodies need the enough amount of it for several functions. It is a part of many enzymes and proteins such as hemoglobin, a protein which carries oxygen in blood. If we have too little iron, we may develop iron deficiency. It has a narrow absorption window in duodenum. Inadequate iron absorption from iron supplements available in markets is observed. So many factors help to optimize iron absorption such as slow drug release to its absorption site and the increase of gastric emptying time [8, 14]. The preparation of floating tablet is one of the novel drug delivery system. A floating tablet allows the medicine to be released slowly at a desired level during a suitable period of time. So this system can be used to increase bioavailability of drugs with narrow absorption window in GIT [4, 5]. In a previous study, floating tablets of $FeSO_4$ were prepared to increase iron absorption [14]. It is supposed that ferrous compounds are more effective in the oral treatment of iron deficiency than ferric preparations because of low bioavailability of ferric iron [13]. A major difficulty in ferrous compounds administration is the production of free hydroxyl radicals. These radicals are toxic [10]. As Ferric ions don't produce free hydroxyl radicals, the use of acompound that can hold ferric iron in an absorbable form in gut lumen is a therapeutic advantage [13]. Ferric-maltol complex (FMC) was selected as a successor for ferrous compounds, sinceits bioavailability in duodenal lumen is similar to $FeSO_4$ [11] .The aim of this study was the preparation of effervescent floating tablets of

FMC. After the synthesis of FMC, the formation of it was evaluated using the atomic absorption method, through studying the found electron-spectrums and IR-spectrums of FMC and its ligand and determining the melting point. The results were similar to the previous study, so it can be claimed that mentioned complex was formed (Table2, 3). In the found IR-spectrum of maltol (Fig3) and IR-spectrum of FMC (Fig 4) in our study, it was observed that the $\nu_{c=o}$, C=O stretching frequencies (cm^{-1}), in complex ($1605cm^{-1}$) is significantly lower than $\nu_{c=o}$ in the corresponding ligand ($1655cm^{-1}$). This variation in $\nu_{c=o}$ ($\Delta\nu_{c=o}$, $50cm^{-1}$), indicated that the complex

was successfully synthesized (Table 3). In fact, complex formation is associated with the formation of some new metal- oxygen bonds (Fe-O=C). The presence of new bonds causes an increase in the C=O bond order which leads to driving the C=O stretching frequencies down. The ligand (maltol) showed a broad O-H stretches in the region 2500-3400 cm^{-1}which disappeared in the iron complex. The comparison of the maximum absorption in the UV-Visible spectrum of maltol (Fig5) with the maximum absorption of FMC (Fig6) showed a bathochromic shift of the absorption band related to $\pi \rightarrow \pi^*$ transition. The found spectrum of maltol, nm is λ_{max} 214, 276, and in the spectrum of FMC, nm is λ_{max}224, 304. In addition of these two bands in the spectrum of FMC, the absorption band in 411nm related to d→d* transition emerged. All of these pieces of evidence confirmed the formation of ferric-maltol complex. The purpose was to obtain the best formulation of FMC floating tablets in different aspects. In the formulation of effervescent floating tablets, gel-forming polymers such as HPMC with different grades and carbopols are employed. Using HPMC K4M and carbopol 934 dompridone, floating tablets have been designed [19]. In addition, in a previous study phenoporlamine with a combination of HPMC K4M and carbopol 934 were buoyant for 6 hours and drug release was controlled during 12 hours [20]. Carbopol has suitable bio-adhesive and fluidity properties, so that in the research done by Khanna and his collaborators, it was established that the accompaniment of Carbopol with HPMC causes enhancement of the system adhesion [21]. We used HPMC K4M and Carbopol 934 as gel-forming agents. Na-bicarbonate and citric acid are used as effervescent agents. Citric acid could decrease floating lag time in the previous study [14].PVP is employed as a binder agent in direct tablet compression [22]. To prevent iron deficiency anaemia, at least 18mg of daily elemental iron is required [8]. Tablets with more than 170mg of FMC (22mg elemental iron) didn't float, so 170mg of FMC was considered as a critical point, and we used 22mg of elemental iron in each tablet.After designing eleven formulations, the fluidity of powder blend was evaluated in terms of different parameters (Table 4). Calculated values showed that the powder fluidity is suitable [15], so the direct compression method was selected for tablet preparation. The results of the tablet physical tests were compared with the standard limits. For example friabilities less than 1% and the hardness more than 40N are acceptable. Tablet hardness was between 72.3±1.6 to 78.6±1.2, the friability was less than 1%(0.59to0.79) .For tablets with more than 324mg of weight, the maximum percentage difference allowed is 5, and no more than 2 tablets can be outside this limit[23]. The tablets contained FMC within the range of96.12% ±2.3 to 102.04% ± 1.8 of the labeled claim. All the formulations passed the mentioned tests. The results of the buoyancy study (table 5) show that the first and the second formulations (F1, F2) didn't have suitable total floating time. The F1 floating tablets were decomposed after several hours, while the construction of the F2 tablets was more consistent. The more consistency of F2 tablets could be due to the addition of PVP. A brief decrease in the floating lag time, and an increase in the total floating time was observed by the addition of PVP. The F3 tablets had more PVP (25mg) than F2 tablets and their construction was protected during the floating time, so PVP was employed at the optimized amount (25mg) in all subsequent formulations. Several changes were made in the type and amount of gel-forming agents & gas-generating agents to obtain the best formulation with more suitable FLT &TFT. In the same amounts of HPMC K4M, an increase in the quantity of carbopol decreased both TFT and FLT; on the contrary, in similar amounts of carbopol, the addition of HPMC increased these two parameters. The addition of citric acid improved buoyancy behavior of the tablets. Among all the prepared formulations, F11 tablets, with 37.7% of gel-forming agents and 15.5% of gas-producing agents, were proved the most suitable TFT &FLT. The swelling index of all formulations increased regularly during the initial hours (up to 8 hours), and after this time gradually decreased (Fig8). When tablets met the dissolution medium, the hydrophilic nature of polymers caused water penetration inits construction, and subsequently gel layer formation around it. The initial increasing of the swelling index was due to the continuous water penetration to the formed system, but after several hours (8h) polymers erosion caused the lower rate of swelling and even its reduction. In the fixed quantity of HPMC, by increasing the

amount of carbopol 934(from 6% in F3 to 8% inF4 and 11% in F5) a brief enhancement in the initial swelling index values was observed. The swelling capability increased by changing the percentage of HPMC (from 13% in F3 to 20% inF6 and 26%in F7) with the same quantity of carbopol. In general it can be said that a larger amount of polymers increases the swelling capability. HPMC could influence the initial swelling more, but carbopol had more significant role in the protection of tablet construction. The type and amount of a gas generating agent didn't have any important effects on swelling properties. Obtained results from famotidine effervescent tablets' evaluation in one research confirmed our results [24].We can determine the effects of the exercised changes in type and amount of tablet ingredients on drug dissolution profile using the percentage of dissolution efficacy (DE%) and mid dissolution time(MDT). A Brief increase in the amount of Carbopol had a distinguished effect on the dissolution profile of the drug (compare DE12% and MDT of F3, F4, F5; $p<0.05$). The enhancement of HPMC (in fixed quantity of carbopol) also retarded the drug release (compare DE12% and MDT of F6 with F3, F6 with F7 and F7 with F9; $p<0.05$). The increase of the amount inHPMC contemporaneous with the reduction of quantity in Carbopol(for example changing HPMC from 13% and Carbapol from11% in F5 to 20% HPMC and 6% Carbapol in F6) had no significant effect on the dissolution profile($p>0.5$). The addition of citric acid as an effervescent agent with no change in other agents increased drug release. The enhancer-drug release effect of citric acid was dependent on the employed quantity of this (compare DE12% and MDT of F9, F10, F11; $p<0.05$).The comparison of the drug release profile of the formulations (F3-F11) showed that F7-F11 formulations had a close drug release process (Fig9). The *in vitro* dissolution data was fitted in to a different kinetic model. At relatively higher polymer contents, the formulations displayed better fitting with zero order release kinetic. These data were fitted in Peppas equation and the slope of formed lines (n) was calculated to determine the drug release mechanism. When $n\leq0.5$, the drug release follows Fickian diffusion, and when $0.5 < n < 1$, the drug release mechanism is non-Fickian diffusion. In a non-Fickian diffusion in addition to diffusion, chain relaxation phenomenon has also an important role in drug release from its reservoir [25].

Conclusion

This study discusses the preparation of effervescent floating tablets of ferric-maltol complex (FMC). Development of gastro retentive tablets of FMC is a suitable drug delivery method to increase bioavailability and to decrease complications of oral iron administration. The results of pharmaceutical tests were evaluated. F9, F10, F11 were the most appropriate formulations. They were very similar regarding theswelling property, the total floating time and the drug release kinetic & mechanism. But among these three formulations, F11 was selected as the optimized formulation due to having the best pharmaceutical properties. The F11 tablets were able to float immediately and showed buoyancy for more than 18 hours. 98.54% of the ferric maltol was released from the tablets after 12 hours. The release pattern followed the zero order kinetic with a non-Fickian diffusion. No statistically significant change in the physical characteristics of tablets was observed after the storage of F11 tablets at $40^{o}C/75\%$ RH for 3month. Thus it was found that the F11 floating tablets of FMC were stable under these storage conditions for at least 3 months.

Conflict of interest

Authors certify that there exists no actual or potential conflict of interest associated with this article.

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