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Preparation and Pharmaceutical Evaluation of Ferrous Sulfate and Ascorbic acid Floating Matrix Tablet for Prevention of Anemia

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A B S T R A C T

For prolonging the time that drug remains in stomach, new methods used as floating drug delivery systems, that available in various forms such as floating tablets. These systems enhance drug absorption and decrease plasma concentration fluctuations. Iron deficiency and its inadequate absorption in diet are of community health problems. Common forms of iron available in the market have little bioavailability and due to greater excretion of drugs from the gastrointestinal tract has many complications such as constipation. Using floating systems to enhance drug absorption can reduce the dose required and drug side effects. In this study, preparation of floating tablets of ferrous sulfate plus ascorbic acid is considered since it has proven that vitamin C enhances iron absorption. Tablets were prepared with swollen polymers like HPMC K4M and carbopol$_{934}$ by direct compression method. Sodium bicarbonate and citric acid was used to create the CO_2 then drug properties such as buoyancy, release percentage and physical properties were tested on that. Tablet formulation No. 10, started to float in 27 seconds and floating state lasts 18 hours in environments like stomach. According to the great drug release and long floating state (12 h), tablet formulation 10 is recommended as a drug supplement to prevent anemia.

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Introduction

Oral tablets have been so far the most accepted drug delivery method due to ease of administration, patient compliance and flexibility in formulation. The important factors affecting the delivery method is quality of gastric emptying that depends on the physiological state of the individual and formulation's design. This process can be very different. These differences can lead to unpredictable bioavailability and the time reaching to maximum plasma concentration. To solve this problem and to slow down the drug in the stomach, several methods such as bio adhesive systems, swollen systems, floating systems have been developed [1]. Floating tablet is one of these products. While the tablet is floating in the stomach, the drug is released at a rate of favorable outcome that controls plasma concentration fluctuations in a good manner [2]. Floating systems techniques can be applied in many different drugs such as those absorbed in the beginning of intestine, drugs with low stability in alkaline media, poorly soluble drug in intestinal fluids and topical medications with effects on the stomach [3]. Among the drugs that are affected by gastric emptying is iron, prescribed to prevent and treat anemia. Iron absorption is very sensitive and can be easily influenced by various factors. Since the normal body iron, excretion is limited and unregulated; generally, the amount of iron in the body is regulated by iron absorption sites [4]. Heme and non-Heme iron is mainly absorbed by the duodenal mucous cells with a bioavailability of about 20-35 percent for Heme iron and 2 percent for non-Heme iron [5]. Foods contain the trivalent form of iron. The iron in the food, at pH of more than 3, forms the ferric hydroxide precipitate immediately which is highly insoluble and increase the iron abso- rption in the presence of stomach acid due to inhibition of sediment formation [4]. Low iron absorption observed in patients with low acid secretion compared with normal people is a good proof for this claim [6]. Other factors affecting iron absorption are gastric emptying time and bowel transport time. Generally, slow gastric emptying provides the opportunity to greater amounts of insoluble iron in stomach to form soluble complexes and therefore increases iron absorption [7]. Recently researches shows that ascorbic acid can increase absorption of ferrous sulfate to 2 to 3 times, however this increase is dose-dependent [8-10]. Increasing the duration of drug retention in the gut, the chance of drug absorbance and its bioavailability is increased. Providing more contact time and absorption area [11] slow release of iron to the duodenum causes a greater amount of drug absorbed [5]. Elemental iron that the body needs to prevent anemia is 18 mg daily and this value should be provided by iron salts such as ferrous sulfate. 32% ferrous sulfate salt is natural iron, therefore, to provide 18 mg of iron daily; approximately 60 mg of dried ferrous sulfate is required [5].

Based on the mechanism of buoyancy, two distinctly non-effervescent and effervescent technologies have been introduced to make these systems that it was selected kind of effervescent [12]. Effervescent floating matrix tablets are systems that are created by swollen polymers like HPMC, Sodium alginate, Chitosan and Carbopol also effervescent compounds such as sodium bicarbonate, tartaric acid and citric acid [13]. These tablets release carbon dioxide when exposed to acidic stomach contents and trapped within the swollen hydrocolloid polymer then dosage form will float [14]. In this study, preparation of floating tablets of ferrous sulfate plus ascorbic acid is considered to enhance drug absorption and reduce iron complications in patients.

Materials and Methods

Materials

Hepta hydrate crystals of Ferrous sulfate were obtained from Amin Pharmaceutical Co Iran ascorbic acid from Osvah Pharmaceutical Co IR, HPMC K4M powder was obtained from Colorcon (England) and citric acid, lactose and Microcrystaline cellulose, sodium bicarbonate and Carbopol$_{934}$ Merck (Germany).

Preparation of Floating Tablets

Prolonged-release gastro retentive formulations containing 60mg ferrous sulfate and 20 mg

ascorbic acid were prepared by a direct compression method using formula shown in Table1.

The tablets were prepared by mixing required quantities of HPMC K4M, CP 934, lactose, Microcrystaline cellulose and sodium bicarbonate and citric acid. All excipients were passed through sieve no.18, mixed using a mortar and pestle for10 min, and lubricated with 5mg of magnesium stearate. The blended powders were compressed in to tablets using a single punch tablet compression machine, fitted with 10mm punches with 50N in hardness.

Table 1. The ingredients of floating tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Ferrous sulfate	60	60	60	60	60	60	60	60	60	60	60
Ascorbic acid	20	20	20	20	20	20	20	20	20	20	20
CP 934 P	70	-	50	70	40	30	-	60	60	40	40
HPMC K4M	-	70	50	70	70	100	120	80	100	100	100
Sodium Bicarbonate	40	40	40	40	40	40	40	40	40	30	30
Citric Acid	-	-	-	-	-	-	-	-	-	10	10
Lactose	95	95	65	25	55	45	45	25	25	25	-
MCC	-	-	-	-	-	-	-	-	-	-	25
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5
Total weight	290	290	290	290	290	290	290	290	290	290	290

Physical properties of floating tablets

The thickness, hardness, weight variations, and content uniformity of fabricated tablets were determined by procedure stated in the US pharmacopoeia (Table 2).

In-vitro buoyancy studies

On immersion of tablets of different formulations in beaker containing 100mL 0.1N HCl at 37±5°C, and their physical state was observed for 20 h. the results of the buoyancy lag time and total floating time were shown in Table 3.

Swelling studies

The swelling behavior of tablets were measured in glass containing 200 ml of HCL (0.1 N) which was maintained at 37±0.5 ◦C. At regular time intervals, the tablets were removed from glass and the percentage of swelling was calculated using the following equation

$$\% \text{ swelling} = \frac{W2 - W1}{W1} \times 100$$

Table 2. Physical properties of floating tablets

Batch No	Friability (%)	Hardness (N)	Weight Variation (mg±SD)	ferrous sulfat (%)	Ascorbicacid (%)
F1	0.45	66± 3	279 ± 4	98.0 ± 2.0	98±3
F2	0.66	58± 4	277 ± 3	96.5 ± 1.0	94±2.1
F3	0.58	56 ± 5	279 ± 2	98.9 ± 1.8	97±0.8
F4	0.85	38 ± 3	278 ± 4	97.4 ± 1.6	98±0.6
F5	0.68	48 ± 4	279 ± 4	100.5 ± 0.5	97±0.5
F6	0.87	39 ± 6	278 ± 2	98.0 ± 2.6	98±0.9
F7	0.62	45 ± 2	279 ± 4	96.2 ± 1.1	97±1
F8	0.95	35 ± 2	278 ± 5	98.0 ± 2.1	99±1.1
F9	0.63	42 ± 4	279 ± 4	101. 4± 1.8	97±0.9
F10	0.89	48 ± 5	278 ± 3	98.0 ± 0.9	98±0.1
F11	0.91	46 ± 3	279 ± 2	97.0 ± 1.1	97±1

Drug release studies

Six tablets of each formulation were used in the release experiment. The release rates of ferrous sulfate were determined using basket apparatus at 37 ◦C in 900 ml 0.1N HCL solution [pH, 1.2] with the rotation speed of 50 rpm. At appropriate time intervals 1, 2, 3, 4, 6, 8, 10, 12,14,18 and 24h, 2ml of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed by atomic spectrophotometer at 248.3 nm. A linear correlation ($R^2 > 0.991$) was obtained over the range of 5–25 mg of iron. High precision and accuracy were also obtained. The dissolution data obtained were plotted as percent cumulative drug released versus time in figure 3.

Kinetics of drug release

To investigate the mechanism of drug release from selected formulations, the results of drug release of these formulae were examined in all models for kinetic studies. These kinetic studies were designed and evaluated in EXCEL software.

Results

Physical properties of floating tablets

Using direct compression method, floating tablets were successfully created. Physical properties such as hardness and corrosion, uniform distribution, floating lag time, floating time were evaluated and the results are shown in Tables 2 and 3.Tablets with desired characteristics were selected for following study procedures.

Table 3. Buoyancy and floating time of floating tablets

Batch No	Buoyancy lag time (sec)	Floating duration (hrs)
F1	16	2.5
F2	29	4
F3	21	5
F4	14	4
F5	20	5.5
F6	45	10
F7	Fail	Fail
F8	11	8.5
F9	15	14
F10	24	>18
F11	26	>18

In-vitro buoyancy studies

By study of tablets buoyancy (Table 3) it was discovered that neither hydroxy propyl methyl cellulose, nor Carbopol alone were good floatability (F1, F2). Formulations containing Carbopol (Formulation 1), though got to floating state quickly but they stayed in floating state for short time (about 2.5 hours) On the other side formulations containing hydroxyl propyl methyl cellulose (Formulation 2) got to floating state with some hesitancy in

comparison with formulation 1 and kept this state more. Formulations containing equal amounts of both polymers showed better buoyancy (formulations 3 and 4). In order to increase the buoyancy term in the Next formulations (formulations 5, 6, 7, 8 and 9) the amounts of Carbopol reduced compared to hydroxy propyl methylcellulose and favorable results were reached, shown in Table 3. Replacing sodium bicarbonate by citric acid reduced floating lag time in the formulation10.Also replacing lactose by cellulose microcrystalline in formulation 11 did not cause significant changes in the buoyancy of tablets. Formulations by better buoyancy were selected and were evaluated for swelling index and drug release testing.

Swelling studies

The percent swelling of tablets were determined at different time intervals. Since the maximum swelling was observed after 10 h in most formulations, percent swelling was determined at the end of 10 h for all the developed formulations (Fig 1).

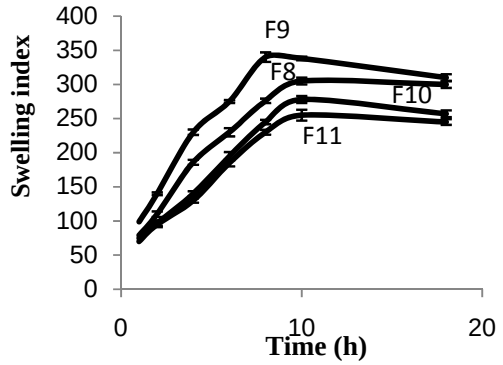

Fig. 1. Swelling index of optimized formulations

Drug release studies

A linear correlation ($R^2 > 0.991$) was obtained over the range of 5–25 mg of iron. High precision and accuracy were also obtained (Fig 2).

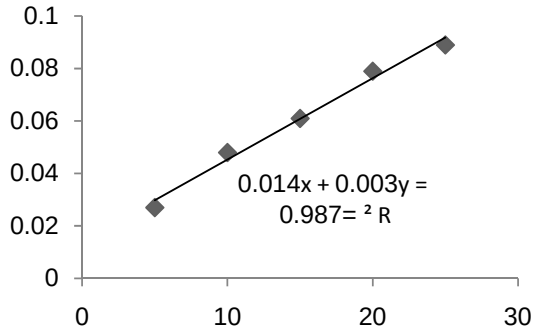

Fig. 2. Calibration curve of ferrous sulfate

Polymers (hydroxyl propyl methylcellulose, Carbopol, lactose and cellulose microcrystalline Ferrous sulfate) effect on rate of release of Ferrous sulfate from the respective matrix is shown in Figure 3.

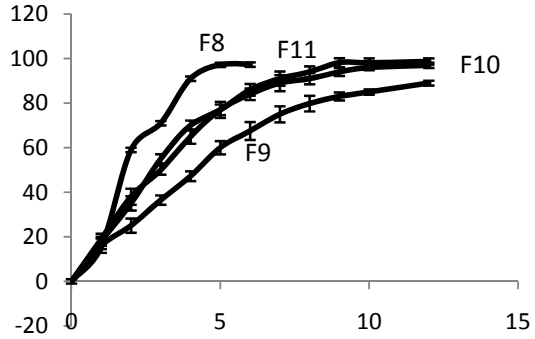

Fig. 3. Dissolution studies of optimized formulations

The results showed that increasing hydroxyl propyl methylcellulose polymer concentration would cause reduction in the rate of drug release (Compare formula8 with 9) so that increasing polymer content from 80 to 100mg would reduce amount of drug release from 59 percent to 25 percent within 2 hours. In formulation 10, presence of citric acid increased the amount of drug release. This figure also shows that replacing microcrystalline cellulose instead of lactose in the formu- lation 11 to somewhat increased rate of drug release; however, this increase was not significant. Finally, formulation 10 was select- ed as the best formulation because of 97% drug-content release in12-hour period (Figure 4).

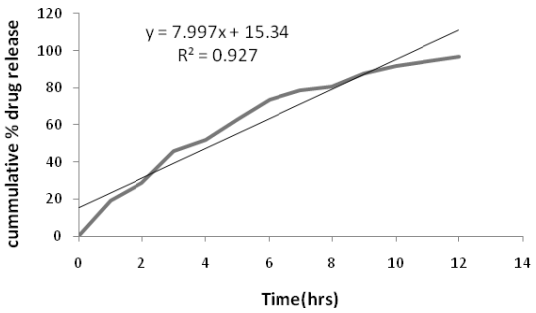

Fig. 4. Zero order release plot

Discussion

Iron as a trace element necessary to our body is vital. Since of inadequate intake of iron using iron supplements is inevitable, however products available in markets are of incomplete absorption because of rapid bowel transport. Increasing iron supplements floating time in stomach will provide longer iron- mucosal contact in duodenum. It would skip complications associated with high loading dose iron to meet body needs such as nausea, vomiting, constipation, black stools and in some cases, diarrhea. In this research, in addition to adjusting the dose of iron, vitamin C is placed in tablets. It has been proven that vitamin C can increase iron absorption [15]. Other factors that may increase iron absorption such as increasing the gastric emptying time, slow release of drugs to the site of absorption and acidic environment of the stomach will help to maximize absorption of the drug. In this research, by creation of conditions for long floating time and complete absorption, Iron amount in stool was minimized, as the gastrointestinal disturbances. To prove this hypothesis and to ensure complete absorption of iron, formulations with desired features tested in lab were taken by some volunteers and they were asked about the drug complications. It was concluded the floating tablets are more accepted in comparison to conventional oral tablets of ferrous sulfate. Hardness of tablets is an important factor in buoyancy. Tablets with little filler and little hardness showed uninterrupted buoyancy [tablet was floating from the beginning] and increased erosion ensued. Also high tablet hardness will prolong floating lag time of the tablets, most likely be due to the reduction of water penetration into tablets [12]. Table1 shows the more absorbent polymer component engaged in formulation, cause the less filler component included in the pills and this factor reduces the hardness of tablets especially in formulations with high levels of Carbopol. Increasing the amount of HPMC K4M with higher compressibility than of Carbopol in subsequent formulations, required hardness was provided. The survey revealed that 40-50 Newton hardness is suitable for tablets and drug release. Buoyancy characteristics of tablets are depicted in Table3. The Carbopol had a significant role in reducing the interruption before buoyancy of tablets but has a negative effect on the duration of the buoyancy that probably is due to greater absorbance of water compared with hydroxy propyl methylcellulose and also increases the density of the pills [16]. As is clear from Figure 3 with the increasing amount of polymer HPMC, drug release is reduced since this polymer is able to absorb water from the surrounding matrix to form a layer of gel. Therefore, with increasing polymer concentration, the viscosity of this layer increases and decreases drug release from the matrix [16]. Importing citric acid ratio of 1 to3, compared to sodium bicarbonate will increase the drug release (Compare formulation 9withformulation10). The results of the effect of lactose [formulateon 10] and Microcrystaline cellulose [formulation 11] are compared in Fig 3. Finally formulation 10 was selected as the best formulation because of 97% drug-content release in 12-hour period.

The *in vitro* release data of best formulation (F10) were examined with various release equations and kinetic models [first order, zero order, Higuchi and Korsmeyer and Peppas]. The slope and R^2 are shown inTable.4 and graphs in Figure 4 to 7.

Table 4. *In vitro* release kinetic data for the optimized formulation (F10)

Model	Slope	R^2 Value
Zero order R^2	7.99	0.927
First order R^2	-0118	0.963
Higuchi's R^2	30.94	0.982
Korsmeyers R^2	0.685	0.981

Optimized formulation F10 fitted best for Higuchi equation with R^2 value of 0.982. From the kinetic data analysis it was found that the release of the drug from the formulation follows the Higuchi order and non-fickian transport of diffusion ($0.5<n<1.0$).

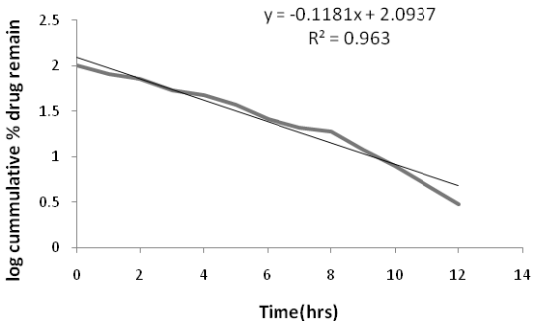

Fig. 5. First order plot

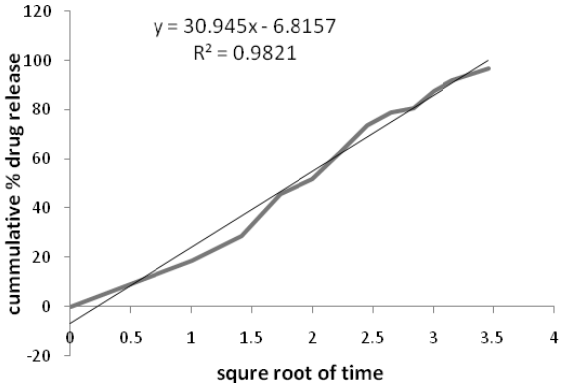

Fig. 6. Higuchi plot

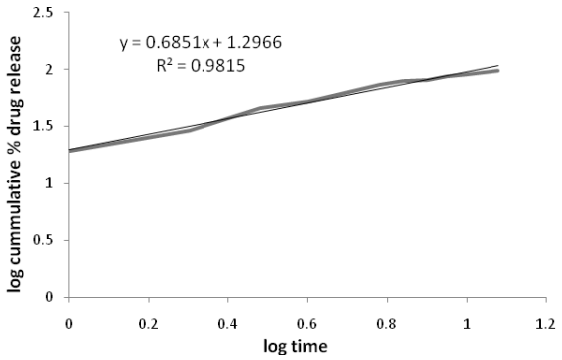

Fig. 7. Korsemayerpeppas plot

Conclusions

Effervescent gastro retentive tablets of ferrous sulfate plus ascorbic acid were successfully formulated. Tablets containing 100 mg HPMC K4M and 60 mg Carbopol as retarding polymers showed desirable in-vitro properties. The optimized formulation released the drug in a Higuchi-order fashion demonstrated a short buoyancy lag time, total floating time of at least 18 h and could maintain drug release for 12 h. Based on pharmacokinetic parameters, once-daily administration of this new formulation can be a suitable alternative formulation compared to common forms of iron available in the market.

Conflict of interest

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

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