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Development of an effervescent tablet formulation which contains ferrous salt and ascorbic acid combination

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Abstract

This study aimed to develop the formulation of effervescent tablets containing ferrous sulfate and ascorbic acid combination to increase intestinal iron absorption and reduce gastrointestinal side effects related to iron supplementation.

In this study, the prototype formulation was calculated precisely and then prepared by three different methods for compression and evaluation. The flowability of powders and granules was investigated. Effervescent tablets were produced by direct compression and two different wet granulation methods. The produced tablets were then evaluated for acceptable hardness, friability <1 %, effervescence time <5 minutes, solution pH <6, water content <0.5 %, and optimum content uniformity.

The powder mixture prepared for the direct compression method had acceptable flowability but required a high compression force. Flowability and other physicochemical properties of this powder, including compressibility and hardness, were improved by granulation. The taste and color of the effervescent solution had good acceptability for the volunteers.

The results of the effervescent tablets produced by the GM2 method, which contain a higher percentage of granulated content were better than the other two methods. The PVP binder solution is suitable to produce effervescent granules that are compressed into tablets, due to improvements in flowability and compactibility.

Keywords

Direct compression method, effervescent tablets, ferrous sulfate, iron deficiency, wet granulation method

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INTRODUCTION

Effervescents consist of a soluble organic acid and an alkali metal carbonate salt that release carbon dioxide in contact with water. Effervescent tablets are usually made by compressing the active ingredients with a mixture of sodium bicarbonate and organic acids, such as citric acid and tartaric acid (Lachman *et al.*, 1986).

In general, these tablets contain drugs that dissolve quickly upon entry into the water and are recommended as a clear, palatable solution (Allen *et al.*, 2011). Therefore, they can be prescribed for patients suffering from swallowing tablets or capsules (Swarbrick and Boylan, 2002). The main advantage of effervescent tablets is the fast onset of action due to the quick production of buffered effervescent solution (Altomare *et al.*, 1997).

Excipients such as water-soluble lubricants (e.g., PEG 6000 and sodium benzoate), sweeteners, flavors, and pharmaceutical dyes (Mohrle, 1989), polyvinylpyrrolidone K-30 is an effective binder for effervescent tablets and can be used both in wet granulation and in direct compression (Callahan *et al.*, 1982; Mohrle, 1989).

Low relative humidity (maximum 25 % or less) and moderate to cool temperatures (25 °C) in the manufacturing areas are essential to prevent granules or tablets from sticking to the machinery and from picking up moisture in the air, which may cause product degradation (Mohrle, 1989).

In direct compression manufacturing method, powder mixtures with excellent flowability without particle segregation are required, and the particle size of all raw materials should be equal. Granulation is necessary when the particle size is small (Saleh *et al.*, 1988; Swarbrick and Boylan, 2002). The granulating fluids, which are being used, are non-reactive solutions containing ethanol or isopropanol, in which most of the tablet components are insoluble (Mohrle, 1989).

Effervescent tablets are manufactured and controlled in the same way as conventional tablets. These quality controls include physicochemical properties such as hardness, weight variation, friability, dissolution time, pH, and content uniformity (Mohrle, 1989).

Anhydrous ferrous sulfate ($FeSO_4$) is an odorless greyish-white powder. It is slowly but almost completely soluble in water and practically insoluble in ethanol. Relative molecular mass for the anhydrous form of $FeSO_4$ is 151.91 g/mol (WHO, 2019).

$FeSO_4$ supplements are prescribed for conditions such as iron deficiency, pregnancy, heavy menstrual periods, prevention and treatment of anemia, blood

loss, frequent blood donors, hemodialysis patients, and following gastrectomy or intestinal resection (Boccio and Iyengar, 2003).

Although oral products containing ferrous sulfate in various dosage forms such as capsules, tablets, chewable tablets, syrup, suspension, and elixir are available in the pharmaceutical market, patients are reluctant to continue taking them due to gastrointestinal side effects such as constipation, stomachache, nausea and vomiting, change in color of stool, metallic taste, and diarrhea (Tolkien *et al.*, 2015). These patients have to take vitamin C supplements at the same time to increase iron absorption and minimize the side effects of taking them.

Until now, in the pharmaceutical market especially in Turkey and Iran, an effervescent tablet that provides 100 % of iron RDA (18 mg/day) in combination with a high dose of ascorbic acid (500 mg) was not produced. Therefore, this is a new and functional study.

The aim of this study was to design, develope and evaluation of the effervescent tablets, which contain ferrous sulfate and ascorbic acid combination.

MATERIALS AND METHODS

Chemicals

Sodium bicarbonate (EMBOY), citric acid monohydrate (Sigma-Aldrich®), ascorbic acid (ZAG Kimya®), PVP K-30 (ZAG Kimya®), sodium benzoate (Mediko Kimya), aspartame (Amino Sweet®), sucrose (Alfa Aesar®), lactose monohydrate (Sigma-Aldrich®), polyethylene glycol 6000 (Merck KGaA), isopropyl alcohol 99.7 % (emirkimya) and saccharin (Sigma-Aldrich®) were supplied by Eastern Mediterranean University Pharmaceutical Department. Ferrous sulfate heptahydrate (FreyBG), red powder food colorant (Chefmaster®), and lemon aroma (Scrapcooking®) were purchased from a Chinese supplier.

Pre-formulation Studies and Prototype Formulation Development

Among the food acids, citric acid is more preferred because it is widely available and relatively inexpensive, has excellent solubility and a pleasant taste. It is very hygroscopic and must be used with caution to prevent exposure to moisture during manufacturing and storage. Sodium bicarbonate is the most commonly used carbonate source because it is completely soluble in water, non-hygroscopic, inexpensive and abundant (Mitul, 2010; Mohrle, 1989).

The stoichiometric ratio between the effervescent ingredients is 1:1.3 for the citric acid anhydrous:sodium bicarbonate.

However, it is advisable to leave a small amount of citric acid unreacted to enhance palatability and taste (Allen *et al.,* 2011).

Ferrous sulfate is suitable for the formulation of effervescent tablets because of its water solubility and high elemental iron content. Ascorbic acid should be added to the formulation due to its reducing properties that cause a stabilizing effect on the iron-II salt. The recommended daily allowance (RDA) for elemental iron depends on a person's age and sex but generally for adults is 18 mg/day (Heinrich, 1974).

The diluents used should be highly water-soluble, have a particle size in the range of other effervescent ingredients, and possess excellent compressibility. Diluents may also be selected from lactose, mannitol, sorbitol, or mixtures thereof, and spray-dried lactose is also commonly used. Spray-dried lactose is particularly preferred because it facilitates the blend flowability and thus improves compressibility and tableting of the formulation (Mitul, 2010; Mohrle, 1989).

Water-soluble binders are necessary for effervescent tablets to bring the tablet hardness to a point where handling is possible. However, binder levels should be kept to a minimum to avoid delay of disintegration. PVP K-30 is an effective binder for effervescent tablets, as it dissolves rapidly in water and forms a clear solution. It is suitable for wet granulation method and direct compression. It can be used in wet granulation processes in two ways, dissolved in a granulating liquid (isopropyl alcohol) as a binder solution or added to powder blends in dry form and then granulated (Hadisoewignyo *et al.*, 2016; Kasperek *et al.*, 2016; Mohrle, 1989).

Lubricants such as magnesium stearate are not used because their water insolubility results in cloudy solutions and extended disintegration times. Spray-dried leucine and PEG are water-soluble alternatives. The micronized polyethylene glycol 6000 was prepared by freezing PEG 6000 before grinding to make it brittle and then added to the formulated mixture in the final step prior to the tableting. PEG 6000 has a low melting point of 55-63 °C, so it should be added to precooled granules to prevent stickiness problem (Conway, 2008; Rowe *et al.,* 2009).

Both artificial and natural sweeteners are used. However, in most formulations, sodium cyclamate is used in combination with saccharin sodium to mask the off-tastes of both sweeteners, often in a ratio of 10:1 (Conway, 2008; Rowe *et al.*, 2009). Water-soluble flavoring agent in dry form should be used in the formulation. Flavors such as mint, lemon or orange can help mask a bitter or metallic

taste in the mouth (Conway, 2008; Mohrle, 1989).

All ingredients must be converted to anhydrous form to prevent the components within the formulation from reacting with each other during storage. Therefore, citric acid monohydrate and ferrous sulfate heptahydrate were heated to lose their water of crystallization using the oven until they reached a constant weight. Citric acid monohydrate can be converted to the anhydrous form at about 78 °C. Ferrous sulfate heptahydrate green crystals lost their crystallization water after drying at 150 °C for 10 hours and turned to a brown-colored anhydrous solid (Conway, 2008; Heinrich, 1974). The prototype formulation was first calculated for the 2000 mg tablets, and then the formulation materials were mixed and granulated. Afterward, the prepared granules were compressed using a tablet press machine (ERWEKA EP-1) with a 20 mm diameter punch. The pressed tablets were evaluated for their weight, thickness, and hardness using an electronic balance and ERWEKA (TBH 125) hardness tester. According to the results, the tableting machine was adjusted to obtain the desired tablet thickness, hardness, and weight. Finally, the formulation was modified based on the average tablet weight (Ozyurt and Evcin, 1994; Ozyurt and Evcin, 1994).

Methods of Production

Direct Compression

The formulation materials were weighed according to Table 1, then sodium bicarbonate was dried at 100 °C for 1 hour and mixed with the other components for 15 minutes. After preparing the primary mixture, saccharin sodium sweetener and lemon flavor were passed through a 0.8 mm sieve and added to the mixture and mixed for 5 minutes. Finally, the PEG 6000 lubricant was added and mixed with other materials for about 2-5 minutes again. The powder mixture was then compressed into tablets using a tablet press machine (ERWEKA EP-1) with a 20 mm punch at a maximum of 25 % RH. In the end, the tablets were dried in an oven with air circulation at 50 °C for 1 hour and then packed in plastic tubes after cooling. Figure 1 shows direct compression of ferrous sulfate plus ascorbic acid effervescent tablets.

Table 1: Prototype formulation of ferrous sulfate and ascorbic acid combination based on preformulation studies.

Mixture or Solution	Material Name	Tested Concentrations (%)	Selected Concentration (%)	mg/tablet
I.	Sodium bicarbonate	25-50	25	500
	Citric acid anhydrous (powder)	10-22.5	21.5	430
	Red dye	0.1-0.5	0.3	6
II.	Povidone, PVP K30	0.5-5	0.5	10
	Isopropanol	q.s.*	q.s.*	0.20 mL
III.	Ascorbic acid (powder)	25	25	500
	Ferrous sulfate anhydrous (powder)	2.5	2.5	50
	Sucrose (fine crystals)/Lactose anhydrous	q.s.*	21.87	438
IV.	Lemon flavor	0.03-0.5	0.03	0.6
	Saccharin sodium	0.075-0.6	0.05	1
V.	Micronized PEG 6000	2-5	3.25	65

*q.s: quantum sufficit

Figure 1: Direct compression of ferrous sulfate plus ascorbic acid effervescent tablets.

Wet Granulation Method

Wet granulation was performed using two different procedures.

1- According to Table 1, mixture I was passed through 35 mesh sieve (<0.5 mm) and blended for 10 minutes. Then, 5 % w/v PVP K-30 solution in isopropanol was added dropwise using a pipette to the mixture until an orange pasty mass formed. This wet mass was passed through sieve No. 10, and the resulting granules were dried in an oven at 50 °C until dry. The dried mass was then passed through 10 mesh sieve. Mixture III was also dried at 60 °C and mixed with the granule mass and mixture IV for 5 minutes. At last, the PEG 6000 lubricant was added to other materials and mixed for 2-5 minutes. The granule mixture was compressed into tablets using a tablet press machine (ERWEKA EP-1) with a 20 mm punch at a maximum of 25 % RH. The prepared tablets were dried in an oven with air circulation at 50 °C for 90 minutes, then covered with aluminum foil and packed in plastic tubes. Tableting of granules produced by wet granulation method-1 is shown in Figure 2.

Figure 2: Tableting of granules produced by wet granulation method-1.

Figure 3: Tableting of granules produced by wet granulation method-2.

2- In this method, the active ingredients were mixed with acid and base and then granulated with the binder solution. That is, mixtures I and III were first blended, and then granulated with solution II in the same manner explained. The resulting granules were then dried and mixed with mixture IV. At the last step, by adding lubricant, the granule mixture was prepared for the tableting process (Figure 3). Better results were observed when lactose anhydrous was used instead of sucrose in this method.

Evaluation of Pre-compression Parameters

Angle of Repose

The angle of repose was measured by the fixed funnel method. Approximately 10 g of granule or powder was poured through a funnel that was fixed at a certain height (10 cm) above graph paper. The diameter (D) and the height of the formed cone (h) were measured to calculate the angle of repose (θ) using the following trigonometric relationship (Aulton and Taylor, 2013):

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left[\frac{\text{height of the heap (h)}}{0.5 \times \text{diameter of the base (D)}}\right]$$

This test was repeated three times for each method, and the mean of three measurements was interpreted (USP31–NF26, 2008).

Carr's Compressibility Index and Hausner Ratio

These terms describe the flow properties of powders. The compressibility index is expressed in percentage and calculated by the following equation (Ashish *et al.*, 2011; Aulton and Taylor, 2013):

$$\text{Compressibility Index} = 100 \times \left[\frac{\text{tapped density (}\rho\text{ tapped)} - \text{bulk density (}\rho\text{ bulk)}}{\text{tapped density (}\rho\text{ tapped)}}\right]$$

The Hausner ratio was calculated from the following equation (Ashish *et al.*, 2011):

$$\text{Hausner Ratio} = \frac{\text{tapped density (}\rho\text{ tapped)}}{\text{bulk density (}\rho\text{ bulk)}}$$

Compressibility Index and Hausner ratio parameters were obtained using the mean

of three measurements of ρ bulk and ρ tapped and compared (USP31–NF26, 2008).

Bulk Density

To measure bulk density, a quantity of accurately weighed granules and powders (100 g) was poured into the graduated cylinder (250 mL) using a funnel without compacting, and then its volume was recorded. Bulk density is expressed in grams per milliliter and calculated by the following formula (Aulton and Taylor, 2013; Palanisamy *et al.*, 2011):

$$\text{Bulk Density } (\rho\text{bulk}) = \frac{\text{weight of powder (m)}}{\text{volume of powder (V bulk)}}$$

Tapped Density

After measuring bulk density, the cylinder was tapped from a height of 2.5 cm until powder volume remained constant. Tapped density was calculated from the following formula (Remington, 2011):

$$\text{Tapped Density } (\rho\text{tapped}) = \frac{\text{weight of powder (m)}}{\text{minimum volume occupied after tapping (V tapped)}}$$

Determination of Particle Size Distribution

The mean particle size of the granules was determined by the sieving method. Selected sieves with different meshes (18, 35, 60, 120) were placed on the sieve shaker. 100 g of granules were placed on the upper sieve. After 10 minutes of shaking, the amount of granule retained on each sieve was weighed. The mean diameter of powders was calculated by the following equation (Moghimipour *et al.*, 2010; Yanze *et al.*, 2000):

$$\text{Mean Particle Diameter (d)} = \frac{\Sigma x_i d_i}{100}$$

x_i = The average size of both the upper and lower sieve

d_i = The percentage of the value i in that range of bulk.

Evaluation of Post-compression Parameters

Tablet Dimensions

Thickness and diameter of 10 tablets from each method were measured using a micrometer. The mean deviation of

thickness should not exceed 5 % of its acceptable limits (Lachman *et al.*, 1986).

Hardness

Tablet hardness was measured for 10 tablets of each method using the ERWEKA (TBH 125) hardness tester, and the average hardness was calculated. The hardness of effervescent tablets is usually lower than that of conventional tablets, and the minimum acceptable hardness for uncoated tablets is approximately 40 N (Patel and Chauhan, 2012).

Uniformity of Weight

Twenty tablets of each method were weighed individually using an analytical balance and the average weight was calculated. According to the EP for tablets

with average weight more than 250 mg, not more than two tablets can deviate 5 % from the average weight and none deviates by more than twice that percentage (Aslani and Fattahi, 2013).

Friability

A total of 20 tablets of each method were weighed together and placed in the ERWEKA friability tester and then rotated at 25 rpm for 4 minutes. The tablets were then re-weighed and the percentage loss calculated from the following equation (Aslani and Sharifian, 2014); If weight loss is not greater than 1 %, it is acceptable (Lachman *et al.*, 1986).

$$\% \text{ Friability} = \frac{\text{Weight of tablets before test} - \text{Weight after test}}{\text{Weight of tablets before test}} \times 100$$

Disintegration Time Measurement

One tablet was dissolved in a beaker containing 200 mL of purified water at 15-25 °C, and the effervescent time was measured using a stopwatch. Whenever a clear, particle-free solution was obtained, the effervescence time has finished. The average of six measurements was calculated for each method (WHO, 2019).

Effervescent Solution pH

One tablet was dissolved in 200 mL of purified water at 20±1 °C. Immediately after completing dissolution, the solution pH was measured using a pH meter. This test was repeated three times for each method (Aslani and Fattahi, 2013).

Water Content

A total of 10 tablets of each formulation were weighed before and after drying in a desiccator containing activated silica gel for 4 hours. The percentage of their water content was calculated from the following equation (Aslani and Sharifian, 2014); The water content of 0.5 % or less is acceptable (Yanze *et al.*, 2000).

$$\text{Water content} = \frac{\text{weight before drying} - \text{weight after drying}}{\text{weight before drying}} \times 100$$

CO_2 Content

One effervescent tablet was dissolved in 100 mL of 1 N sulfuric acid solution, and weight changes were determined after the dissolution completed. The obtained weight difference showed the amount (mg) of CO_2 per tablet. The average of 3 determinations was calculated for each method (Moghimipour *et al.*, 2010).

Assay

First, 14 effervescent tablets of dried ferrous sulfate were triturated, and the crushed powder containing 700 mg of anhydrous ferrous sulfate was weighed and dissolved in a mixture of 20 mL of water and 20 mL of dilute sulfuric acid, then 2 mL of phosphoric acid was added. This solution is immediately titrated against 0.02 M potassium permanganate VS to a

pink endpoint. Each mL of 0.02 M potassium permanganate VS is equal to 15.1908 mg of anhydrous ferrous sulfate (Japanese Pharmacopoeia, 2002).

Uniformity of Content

10 tablets of each manufacturing method were selected randomly to determine the amount of active ingredient by the method described in the assay and calculate the amount of active ingredient per tablet. The acceptance limits are 94.3-105.8 % for 10 sample tablets (USP26, 2002).

RESULTS

The preformulation study results showed that the optimum stoichiometric ratio is 1:1.3 for the citric acid: sodium bicarbonate that produces a clear effervescent solution in the shortest effervescent time. The amount of ferrous sulfate anhydrous per tablet should be considered 50 mg equal to 18 mg of elemental iron that is recommended daily allowance of iron for adults.

The pre-compression evaluation results for parameters including angle of repose, compressibility index, Hausner ratio, and particle size distribution are presented in Table 2 and Figure 4.

Table 2: Pre-compression evaluation of blends.

Flowability Tests	Methods GM1	GM2	D
Angle of Repose	23.01	22.73	26.42
Compressibility Index (%)	10	8.57	22.22
Hausner Ratio	1.11	1.09	1.28

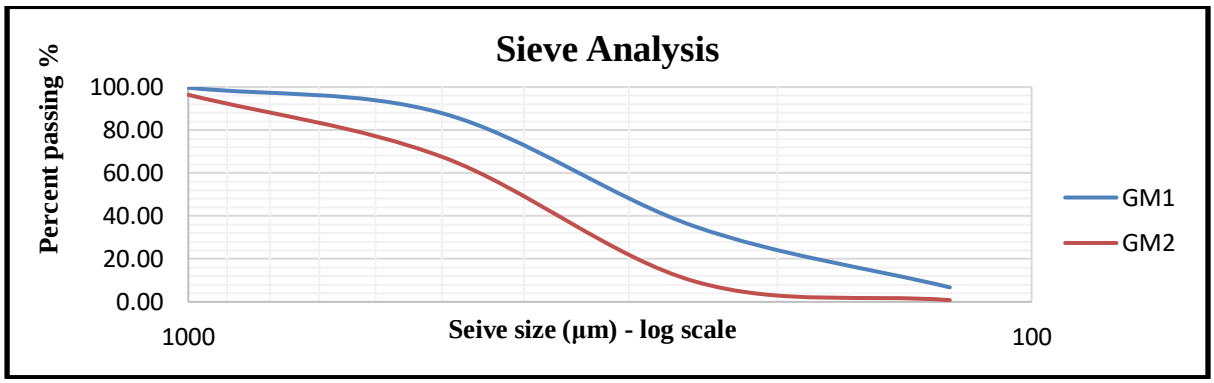

Figure 4: Particle size distribution graph of the formulation in wet granulation methods.

The post-compression evaluation results for parameters such as tablet thickness, diameter, hardness, friability, weight, variation, effervescence time, pH of the solution, moisture and CO_2 content, and content uniformity are presented in Table 3.

Table 3: Post-compression evaluation of produced effervescent tablets.

QC Tests for Effervescent Tablets	Methods		
	GM1	**GM2**	**D**
Thickness (mm)	7.84 ± 0.03	7.99 ± 0.03	8.95 ± 0.05
Diameter (mm)	19.95 ± 0.02	20.06 ± 0.01	20.05 ± 0.02
Hardness (*N*)	40.6	44.5	45.3
Friability (%)	0.78	0.93	0.97
Weight variation (g)	2.21 ± 0.05	2.2 ± 0.07	2.94 ± 0.02
Effervescence time (sec)	90.6 ± 2	108.6 ± 2.19	117 ± 2
pH of solution	5.18 ± 0.05	5.32 ± 0.08	5.11 ± 0.02
Water content (g)	0.034	0.028	0.046
CO_2 content (mg)	227	236	214
Content uniformity (mg)	47.82 ± 0.16	48.68 ± 0.10	47.45 ± 0.29

DISCUSSION

In comparison to other iron salts, anhydrous ferrous sulfate provides more elemental iron (36 %) and has more water solubility. For these reasons, ferrous sulfate was selected to be used in the formulation of effervescent tablets (WHO, 2019).

Approximately 5–10 % of dietary iron is absorbed. Although the absorption percentage increases by up to 30 % in iron deficiency states, unabsorbed dietary iron lead to gastrointestinal disturbances. Ascorbic acid consumption is the most efficient enhancer of iron absorption (Abbaspour *et al.,* 2014). Therefore, the main aim of this study was the development of effervescent tablets containing these two ingredients to reduce the side effects of iron supplementation. The ratio of effervescent components in the formulation should result in a clear solution at acceptable effervescent time and pH <6. The amount of anhydrous citric acid was calculated slightly more than this stoichiometric ratio to enhance effervescent solution taste and reduce the rate of sodium ascorbate formation. In comparison, acid: base ratios that show low solubility and precipitation were not selected for the formulation.

The mean diameter of particles is increased by wet granulation due to the adhesion of smaller particles and the formation of larger particles. According to the curves of Figure 4, the mean particle size for the granule mixture prepared by the wet granulation method-2 is larger than the other two methods because more ingredients of the formulation were granulated in this method.

As the results are shown in the Table 2, the angle of repose is decreased with increasing granulated content of mixtures due to the increase in particle size and shape-changing into the sphere (Agrawal and Naveen, 2011). The Hausner ratio and the compressibility index are also reduced due to less significant inter particulate

interactions and closer bulk and tapped densities in mixtures containing higher granulated content, thus indicating improved powder flow.

Wet granulation improves tablet hardness due to the internal porosity of granules and plastic deformation (Agrawal and Naveen, 2011). In the direct compression method, the dry form of the PVP K-30 binder was used, and the powder mixture was pressed with a higher compression force to achieve the desired tablet hardness. The formulation was also granulated using a PVP K-30 binder solution in the wet granulation methods. Using an appropriate binder percentage in the formulation can eliminate capping problem during tablet processing. With the increase of PVP percentage, an increase in hardness and effervescence time was observed (Yanze *et al.*, 2000).

The thickness of the tablets must be within the range of 7.9 ± 0.1 mm so that the results are acceptable according to the pharmacopeia criteria (USP31–NF26, 2008). According to the EP, in the tablets weighing more than 250 mg, out of 20 tablets, only two tablets can exceed ± 5 % of the average weight, that the results are acceptable.

A pH of less than six is required to increase the absorption of effervescent solutions that the pH of the developed formulation is between 5.09 and 5.4 which is lower than six. Similar results of pH measurements in different samples of one formulation show that the granule mixtures were uniform (Yanze *et al.*, 2000). The effervescence time must be less than 5 minutes for the produced effervescent tablets that the results follow this requirement (WHO, 2019).

As each tablet contains 500 mg of sodium bicarbonate, so this amount will react with the anhydrous citric acid in the presence of water to produce a maximum of 262 mg of CO_2 per tablet which is comparable with the results. Lower levels of CO_2 content indicate that the moisture absorbed by the hygroscopic ingredients existing in the formulation has initiated a small-scale effervescent reaction.

As shown in Table 3, the friability of the tablets is acceptable. It was also observed that in large dimension tablets such as effervescent tablets with increasing hardness, the fragility also increases.

Anhydrous ingredients are extremely hygroscopic since they try to absorb moisture and return to their stable crystalline form. As a result, the possibility of initiating effervescent reaction and instability in effervescent tablets is high. The use of lactose anhydrous instead of sucrose in the GM2 provided better results because lactose anhydrous is less hygroscopic compared to powder sucrose. Also, sucrose crystalline is less

hygroscopic compared to powder sucrose, so crystalline form was used in the direct compression method. The produced tablets by the wet granulation method contain lower water content due to receiving heat during the drying process.

Since the amount of active ingredient ($FeSO_4$) can be variable in the range of 47.16 to 48.78 mg, the content uniformity of prepared effervescent tablets by all three methods was in the limits of USP acceptance criteria.

It was preferred to use orange or lemon flavors to mask the metallic taste of iron. However, when the amount of ferrous sulfate is calculated at the maximum recommended daily dose, full masking of metallic taste will become a challengeable problem.

CONCLUSION

This study attempted to formulate and produce effervescent tablets containing ferrous sulfate and ascorbic acid combination using direct compression and wet granulation methods. The results of this study show that both methods are applicable, but wet granulation is a more suitable method to produce ferrous sulfate effervescent tablets. This method is performed by adding a granulator solution to the powder mixture to obtain a wet mass. In this study, the evaluation results are in accordance with the pharmacopoeia criteria.

The produced effervescent tablets by the wet granulation method were more compact and uniform in content. They did not have any of the processing problems, but generally, effervescent tablets should be pressed using PTFE coated punches at a maximum of 30 % RH to overcome their sticking problem.

The developed formulation is acceptable for all physicochemical properties, including effervescent time less than 5 minutes, pH <6, friability below 1 %, water content under 0.5 %, low weight variation, and proper content uniformity. The metallic taste of ferrous sulfate was also masked by adding lemon flavor as much as possible.

These tablets are very useful in iron deficiency conditions because their ascorbic acid content can increase iron absorption and reduce iron supplementation related gastrointestinal side effects.

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