Original Article

Formulation and Optimization of Effervescent Tablet Containing Bismuth Sub-citrate

Somayeh Taymouri[1], Abolfazl Mostafavi[2], Mohamad Javanmardi[2]

[1]Department of Pharmaceutics, School of Pharmacy and Novel Drug Delivery Systems Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Sciences and Isfahan pharmaceutical Sciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Objective: The objective of this study was to design, evaluate and optimize effervescent tablets containing bismuth sub-citrate with sufficient hardness and friability in treatment of peptic ulcer. **Materials and Methods:** Effervescent tablets were prepared by direct compression method and were optimized using irregular factorial design. Amount of citric acid, sodium bicarbonate to citric acid molar ratio, polyvinyl pyrrolidone K 30 (PVP k30), polyethylene glycol 6000 (PEG 6000) were selected as independent variables, whereas disintegration time, amount of carbon dioxide (CO_2), friability, pH, and hardness were selected as dependent variables. All the batches were assessed for various pre and post compression characteristics such as flowability, hardness, friability, effervescent time, pH, and content uniformity. For the enhancement of tablets' palatability, the components of optimized formulation were mixed with same amounts of different flavoring agents. **Results:** The best results obtained from effervescent tablets prepared by 500 mg citric acid, 5% PEG 6000 and 3% PVP k30 while the molar ratio of the sodium bicarbonate to citric acid was 3. The disintegration time, amount of CO_2, friability, pH, and hardness of optimized formulation were confirmed to be 95.33 ± 1.15 sec, 398.73 ± 1.46 mg, 0.73%, 6.0 ± 0.06 and 72.3 ± 5.5 N, respectively. The most pleasant taste according to volunteers' acceptability was the taste of cherry. **Conclusion:** These results suggest that developed effervescent tablets may be promising for delivery of bismuth sub-citrate in peptic ulcers therapy.

Keywords: *Bismuth sub-citrate, direct compression method, effervescent tablet, polyvinylpyrrolidone k 30*

Introduction

Gastric ulcer is one of the most common causes of hospitalization and surgery in the last century. In spite of the efforts taken to prevent and treat gastric ulcer, the number of patients continues to increase. Several therapies are available for the treatment of gastric ulcer, including surgery, drug therapy, and herbal medicine.[1] Bismuth sub-citrate is one of the most effective medications for the treatment of gastric ulcer. It has anti-*Helicobacter pylori* effects, in addition to its ability to cover the gastric mucosa in the ulcerous area, enhance mucus glycoprotein secretion, strengthen the viscoelastic gel properties of mucus, and stimulate the synthesis of endogenous prostaglandin. A proposed mechanism for the anti-*H. pylori* effect of bismuth sub-citrate is the formation of an inhibitory complex with glycoproteins in the stomach and preventing the migration of *H. pylori* to the gastric mucosa. Studies have shown the use of bismuth a week before the conventional triple therapy regimen increases the recovery significantly as compared to the conventional regimen.[2] The usual dosage of this drug is 120 mg tablet four times a day or 240 mg twice daily.[3] The amount of the drug absorbed from the gastrointestinal tract is negligible (approximately 0.16%–0.24%). Bismuth is safe at concentrations <50 ng/mL; however, it may lead to neurotoxicity when it produces concentrations >100 ng/mL. The drug is mainly excreted through the kidney and may be stored in bones. The side effects of bismuth include feces discoloration, nausea, abdominal pain, and black tongue. If blood level goes high, it will cause central and peripheral neurological complications, including headache and chills.[4]

The oral drug delivery is still the most accepted route of drug administration due to ease of administration, patient acceptance and cost-effectiveness. Effervescent tablets are interesting oral dosage forms, have drawn attention for some unique benefits when compared with simple tablets. Effervescent tablets are dissolved or dispersed in water and releases carbon dioxide (CO_2). They are generally obtained by compressing mixtures of

How to cite this article: Taymouri S, Mostafavi A, Javanmardi M. Formulation and optimization of effervescent tablet containing bismuth sub-citrate. J Rep Pharm Sci 2019;8:236-44.

Address for correspondence: *Dr. Abolfazl Mostafavi, Department of Pharmaceutics, Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, PO Box 81745-359, Isfahan, Iran. E-mail: mostafavi@pharm.mui.ac.ir*

Access this article online

Website: www.jrpsjournal.com

DOI:10.4103/jrptps.JRPTPS_11_19

Quick Response Code:

organic acids, such as citric acid or tartaric acid, with sodium bicarbonate. After the tablet is placed in water, a reaction between the acid and the bicarbonate begins, which is very fast and ends within approximately 3 min, and a transparent solution containing CO_2 is produced. Effervescent tablets are more stable and easily carried than liquid pharmaceutical forms. They are liquidized at the time of administration, so their absorption and onset of action is fast.[5] Furthermore, they have pleasant taste due to CO_2 production, good stomach and intestinal tolerance, high patient compliance, ease of use, accurate dosing, and capability to incorporate larger amount of active ingredients. This dosage form is also easier to use for patients in intensive care unit, children, people with dysphagia, and the elderly.[6]

Owing to the limitations of solid dosage form for certain groups of patients and the lack of liquid solution of bismuth sub-citrate in the Iran's pharmaceutical market, this study aimed to develop an effervescent form of this drug to facilitate its administration to certain groups of patients and therefore increase the acceptance of the drug.[7] In addition, it is possible to formulate larger amounts of the drug due to the larger size of effervescent tablets compared to conventional ones.[6]

Materials and Methods

Bismuth sub-citrate was purchased from Amin Pharmaceutical (Isfahan, Iran). Citric acid, sodium bicarbonate, mannitol, sucrose, polyvinylpyrrolidone k 30 (PVP k30), and polyethylene glycol 6000 (PEG 6000) were obtained from Merck (Darmstadt, Germany). Flavoring agents were gifted by Farabi Pharmaceutical (Isfahan, Iran).

Formulation studies

Irregular factorial design was used in the preparation, optimization, and evaluation of the effect of formulation variables, identified during preliminary trials, on the characteristics of the effervescent tablets containing bismuth sub-citrate. Table 1 shows different variables selected in the optimization study. All studied variables had two levels, and all experiments were carried out in triplicate. An overview of the investigated formulations is presented in Table 2. Each run involved the corresponding combination of levels to which the factors in the experiment were set. In all formulations, the amount of drug was constant (240 mg). The studied responses were effervescent time, amount of CO_2, friability, pH, and hardness. Design–Expert Software (version 10, USA) was used to analyze the experimental data and to graphically express the effect of each variable on the response.

According to Table 1, desired amount of citric acid, sodium bicarbonate, PVP k30, and PEG 6000, and 240 mg of bismuth sub-citrate, sucrose, and mannitol were weighed and mixed using glass mortar and pestle, and compressed using a single punch tablet machine (Kilian & Co, Germany).

Evaluation of blends before compression

Angle of repose

Repose angle was determined by means of funnel method. For this purpose, carefully weighed blend was poured in a funnel. The funnel's height was adjusted in a manner that its tip had contact with the apex of the blend's heap. The powder cone's diameter was measured, and the repose angle was calculated according to the following formula[8,9]:

$$Tan\theta = h / r$$

where h and r represent the height of cone and radius of cone base, respectively.

Bulk density

Apparent bulk density was determined by pouring a weighed amount of blend into graduated cylinder and measuring the weight and volume. Bulk density was calculated by the following formula:

Bulk density = Weight of the powder/volume of the packing

Tapped density

Tapped density was measured by a graduated cylinder that contained a specified mass of drug–excipients blend, and could fall under its own weight on a hard surface from a 10-cm height at 2-s intervals. The tapping continued until no further volume change was observed. Tapped density was measured using the following formula:

Tapped density = (Weight of the powder/volume of the tapped packing)

Compressibility index

Compressibility index was determined according to the following formula[8,10]:

$$\text{Compressibility index } (\%) = [(TD - BD) \times 100]/TD$$

Hausner's ratio

Hausner's ratio is an index to determine the flow properties, which is calculated by the following formula:

Table 1: Definition and trial levels of factors investigated by irregular full factorial design in production of effervescent tablets containing bismuth sub-citrate

Independent variables	Levels		Dependent variables
	I	II	
Citric acid (mg)	250	500	Tablet friability
Sodium bicarbonate to citric acid molar ratio	1:1	3:1	pH
PEG 6000 (%)	0.5	5	Hardness
PVP (%)	3	10	Amount of CO_2, disintegration time

Table 2: Composition of different formulations studied in the preparation of effervescent tablets containing bismuth sub-citrate

Formulations	Citric acid (mg)	Sodium bicarbonate to citric acid molar ratio	PEG 6000 (%)	PVP k30 (%)	Mannitol (mg)	Sucrose (mg)
P1	250	1:1	0.5	3	100	70
P2	500	3:1	0.5	3	100	70
P3	250	1:1	0.5	10	100	70
P4	500	1:1	0.5	10	100	70
P5	250	3:1	0.5	10	100	70
P6	500	3:1	0.5	10	100	70
P7	250	1:1	5	3	100	70
P8	500	1:1	5	3	100	70
P9	250	3:1	5	3	100	70
P10	500	3:1	5	3	100	70
P11	500	1:1	5	10	100	70
P12	250	3:1	5	10	100	70

Hausner's ratio = (Tapped density x 100) / (Bulk density)

Hausner's ratio < 1.25 – Good flow = 20% compressibility index

>1.25 – Poor flow = 33% compressibility index

Particle size distribution

To investigate particle size distribution, powders were sieved. Powders or granules were then disposed on a series of sieves with a size of 20, 25, 30, 35, 40, 70, and 100, and placed on the device. The remaining powders or granules on each sieve were weighed, and the mean particle size (d) was measured by the following equation:

$$d = \frac{\sum x_i d_i}{100}$$

where x_i is the average size of both upper and lower sieves and d_i is the percentage of d_i value in the range of that bulk.[9,11]

Evaluation of tablets

Hardness test

Hardness of tablets was determined by the tablet hardness tester. In this method, pressure was exerted to the tablet to break it into two halves. Hardness of 10 tablets from each formulation was determined.[12]

Weight variation

Weight variation test was performed on 20 tablets. Weight variation was determined by calculating the variation of each tablet weight from the average weight of 20 tablets. The weight variation of less than 7.5% was considered acceptable.[12]

Friability test

The friability of 20 tablets from each formulation was calculated by using Roche friabilator (Erweka,Germany). For this purpose, the pre-weighed tablets were placed in the friabilator plastic chamber and the friabilator was run for 4 min at 25 rpm. All tablets were de-dusted and weighed by the following equation[12,13]:

$$\%\ Friability = [(W_1 - W_2)100] / W_1$$

where W_1 and W_2 are the weights of tablet before testing and after testing, respectively.

Content uniformity test

To conduct content uniformity test, 10 tablets were weighed and triturated in a mortar and pestle. Powder blend equivalent to the weight of one single tablet was prepared, and the drug content was determined by UV-visible spectrophotometer at λ max, 240 nm.[10,14]

Amount of carbon dioxide content

Three tablets were placed in 100 mL of 1 N sulfuric acid solution in three beakers. The difference in the weight before and after tablet dissolving was calculated to obtain the amount of released CO_2 (mg).[15]

pH test

The pH value of the solution was measured by dissolving three tablets in three beakers containing 200 mL water by means of a pH meter (Metrohm, Herisau, Switzerland).[15]

Effervescent time

Three tablets were placed in three beakers containing water and the disintegration time was measured by a stopwatch. Effervescence completion was defined as the moment when the solution became completely transparent.[13,15]

Taste evaluation

For the enhancement of tablets' palatability, the component of optimized formulation then was mixed with same amount of different flavoring agents such as cherry, sour berry, raspberries, and tutti-frutti [Table 3].

Results and Discussion

By using the irregular full factorial design, several parameters, including amount of citric acid (A), sodium bicarbonate to citric acid molar ratio (B), PVP k30 (C), and PEG 6000 (D), in the formulations were assessed in order to achieve optimal preparation conditions. Table 4 shows the flow properties of blended powders in terms of Carr's index, angle of repose, and Hausner's ratio. The angle of repose of powder blend was

found to be in the range of 27.9–34.3°, indicating that the powder flow for all formulations was good. Hausner's ratio for all formulations was found to be in the range of 1.17–1.32, whereas compressibility index was in the range of 14.88–24.76. The compressibility index, angle of repose, and Hausner's ratio for the mixed powders were in acceptable range. A number of effervescent tablets containing bismuth sub-citrate were produced, and the basic characteristics of the products, including thickness, disintegration time, amount of CO_2, friability, pH, hardness, weight uniformity, and uniformity of content were determined, and results are presented in Table 5. Statistical analysis for effervescent time, hardness, friability, pH, and CO_2 is shown in Table 6. For the statistical data analysis and determination of the contribution effect of each factor, Design–Expert software (version 10) was used. Analysis of variance was performed to conclude the significance of the factor and their interaction.

Table 3: Composition of optimized formulations with different flavoring agents

Ingredients (mg)	Formulations			
	F_1	F_2	F_3	F_4
Bismuth	240	240	240	240
Citric acid	500	500	500	500
Na bicarbonate	656	656	656	656
PVP	45.5	45.5	45.5	45.5
PEG 6000	76	76	76	76
Mannitol	100	100	100	100
Sucrose	70	70	70	70
Cherry	20	-	-	-
Tutti-frutti	-	20	-	-
Sour cherry	-	-	20	-
Raspberry	-	-	-	20

Tablet hardness

As shown in Table 5, the effervescent tablets of bismuth sub-citrate showed uniform content and low weight variation. The hardness of tablets ranged from 31 to 72 N and was mostly affected by PEG 6000 content [Figure 1]. The effect of each factor on the hardness can be explained by the following equation:

$$Hardness = 102.81 - 4.63A + 4.13B + 4.25C + 36.37D + 1.62AB + 2.25AC + 6.88AD - 2.25BC - 2.87BD$$

where A, B, C, and D are the amount of citric acid, sodium bicarbonate to citric acid molar ratio, PVP k30, PEG 6000, respectively.

Figure 1 shows the effect of each studied variables on the hardness of the effervescent tablets. The formulations P2, P4, P5, and P6had the desirable hardness.

Table 4: Evaluation of pre-compression parameters for various batches of effervescent tablets containing bismuth sub-citrate

Formulations	Angle of repose (o)	Hausner's ratio	Compressibility index (%)	Tapped density (g/cm^3)	Bulk density (g/cm^3)	Particle size distribution
P1	31.97 ± 1.70	1.23	18.64 ± 0.12	0.44 ± 0.03	0.36 ± 0.01	314.88 ± 4.55
P2	29.50 ± 0.50	1.31	23.46 ± 0.22	0.47 ± 0.02	0.36 ± 0.02	447.56 ± 8.21
P3	31.73 ± 1.33	1.26	20.36 ± 0.18	0.35 ± 0.01	0.28 ± 0.01	386.75 ± 8.72
P4	32.30 ± 2.71	1.19	16.06 ± 0.05	0.32 ± 0.00	0.27 ± 0.01	376.54 ± 3.25
P5	30.00 ± 1.00	1.32	24.15 ± 0.11	0.35 ± 0.01	0.27 ± 0.01	342.69 ± 1.74
P6	31.97 ± 0.81	1.19	15.89 ± 0.09	0.39 ± 0.01	0.32 ± 0.02	333.64 ± 2.83
P7	31.50 ± 0.50	1.20	16.36 ± 0.09	0.42 ± 0.03	0.35 ± 0.03	482.46 ± 1.55
P8	33.07 ± 0.60	1.18	15.47 ± 0.04	0.37 ± 0.01	0.31 ± 0.02	350.92 ± 3.14
P9	32.33 ± 0.76	1.29	22.04 ± 0.16	0.43 ± 0.02	0.33 ± 0.02	394.15 ± 7.79
P10	27.90 ± 1.01	1.17	14.88 ± 0.08	0.37 ± 0.01	0.31 ± 0.01	351.25 ± 9.33
P11	32.50 ± 0.87	1.32	24.76 ± .014	0.36 ± 0.01	0.27 ± 0.01	489.63 ± 1.86
P12	34.33 ± 2.08	1.22	17.94 ± 0.09	0.31 ± 0.01	0.26 ± 0.02	342.69 ± 6.41

Table 5: Evaluation of different effervescent tablets containing bismuth sub-citrate

Formulations	Thickness (mm)	Disintegration time (s)	Amount of CO_2 (mg)	Friability (%)	pH	Hardness (*N*)	Weight uniformity (%)	Uniformity of content (mg)
P1	2.21 ± 0.01	180.33 ± 3.06	63.30 ± 2.75	3.46	3.2 ± 0.06	36.2 ± 2.4	1.13 ± 0.46	242.64 ± 2.45
P2	6.54 ± 0.04	106.33 ± 2.31	380.97 ± 4.06	2.31	5.5 ± 0.06	31.3 ± 1.9	1.11 ± 0.52	236.81 ± 1.50
P3	2.42 ± 0.01	176.33 ± 6.11	61.67 ± 0.90	1.78	3.3 ± 0.15	37.7 ± 2.1	0.91 ± 0.50	243.55 ± 3.17
P4	4.43 ± 0.03	141.00 ± 3.00	126.57 ± 3.99	2.03	3.5 ± 0.06	29.1 ± 0.8	0.93 ± 0.69	238.14 ± 4.21
P5	4.15 ± 0.02	86.33 ± 5.13	196.47 ± 4.30	1.94	5.4 ± 0.06	43.2 ± 2.2	1.10 ± 0.63	244.06 ± 2.62
P6	6.86 ± 0.05	90.67 ± 2.52	384.77 ± 5.06	2.24	5.8 ± 0.15	33.1 ± 1.8	0.60 ± 0.41	239.27 ± 4.15
P7	2.35 ± 0.01	181.00 ± 4.58	61.37 ± 0.96	0.81	3.5 ± 0.15	68.5 ± 5.4	0.92 ± 0.59	241.87 ± 1.94
P8	4.39 ± 0.02	134.00 ± 6.56	123.10 ± 1.54	0.65	3.8 ± 0.06	64.6 ± 4.7	1.05 ± 0.76	240.76 ± 2.04
P9	3.87 ± 0.01	108.00 ± 4.00	191.30 ± 2.09	0.91	5.5 ± 0.06	67.7 ± 7.2	0.34 ± 0.20	241.07 ± 5.12
P10	6.74 ± 0.03	95.33 ± 1.15	398.73 ± 1.46	0.73	6.0 ± 0.06	72.3 ± 5.5	0.79 ± 0.41	239.88 ± 1.06
P11	5.06 ± 0.03	401.0 ± 14.73	107.30 ± 0.66	0.62	3.3 ± 0.15	75.8 ± 0.8	0.71 ± 0.36	240.19 ± 3.52
P12	4.26 ± 0.01	92.00 ± 3.61	192.70 ± 2.50	0.77	5.4 ± 0.17	70.1 ± 8.8	0.94 ± 0.56	243.70 ± 3.48

Table 6: Statistical analysis for effervescent time, hardness, friability, pH, and carbon dioxide

Parameters	Effervescent time	Hardness	Friability	pH	CO_2
	P value	*P* value	*P* value	*P* value	*P* value
Model	0.0061	0.0071	0.0004	<0.0001	<0.0001
A	0.0135	0.0172	0.0599	0.0002	<0.0001
B	0.0052	0.0193	0.0095	<0.0001	<0.0001
C	0.0054	0.0187	0.0006	0.0024	-
D	0.0051	0.0022	<0.0001	0.0033	-
AB	0.0180	0.0489	-	0.0066	<0.0001
AC	0.0047	0.0353	0.0010	-	-
AD	0.0051	0.0116	0.0042	0.0072	-
BC	0.0044	0.0353	0.0013	0.0013	-
BD	0.0047	0.0277	0.0017	0.0029	-
CD	0.0041	-	0.0008	0.0002	-
ABC	-	0.0245	-	-	-
R-squared	1	1	0.9999	1	0.9965
Adj. *R*-squared	0.9999	0.9999	0.9996	1	0.9952

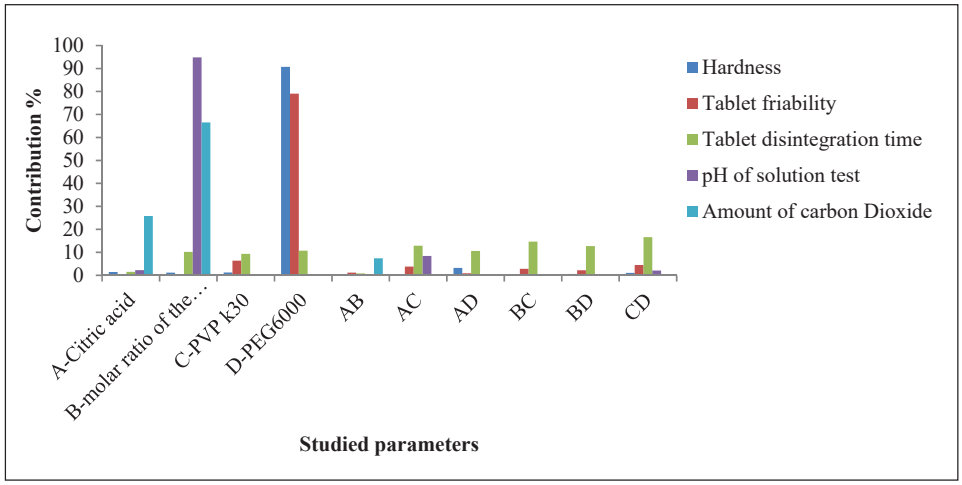

Figure 1: Contribution percent of different studied parameters and their interactions on hardness, friability, effervescent time, pH, and carbon dioxide content of effervescent tablets of bismuth sub-citrate

The analyses showed that increasing the amount of citric acid in the formulation of the tablets decreased the tablet hardness [Figure 2A–C]. This finding could be due to the plasticizing effect of citric acid that reduced interactions among the macromolecules.[16] Regarding the tablet hardness, the results of a study on the effervescent forms of ranitidine and potassium citrate are in agreement with the results of this study.[17,18] As shown in Figure 2B and C, increasing the amount of PVP k30 and PEG 6000 in the formulation of the tablets increased the tablet hardness due to their binding effect. This result was in good agreement with the previous result obtained in a study by Shiyani *et al.*[17] and Aslani and Fattahi.[18]

Tablet friability

Friability was mostly affected by the amount of PEG 6000 [Figure 1] used in each formulation, ranging from 0.5% to 5% [Table 5]. The following equation describes the effect of each factor levels on friability.

$$Friability = 1.59 + 0.069A + 0.069B - 0.22C - 0.85D + 0.22AC + 0.10AD + 0.19BC + 0.16BD + 0.20CD$$

Figure 3 shows the effect of each studied variables on the friability of the effervescent tablets. According to the pharmacopoeia, the friability less than 1% for tablets is acceptable.[13] Formulations P7–P12 had a friability less than 1%. Formulations P1–P6 had comparatively higher friability due to lower hardness. The results showed that increasing the amount of PVP k30 and PEG 6000 decreased the friability percentage. All of these changes were parallel with the increasing tablet hardness [Figure 3A–C].

Tablet effervescent time

Effervescent time of all formulations was found to be in the range of 86–401 s. As shown in Figure 1, the most effective variables on effervescent time of tablets were interaction of PVP% and PEG 6000%. Effect of each factor on effervescent time can be comprehended by the following equation:

$$Effervescent\ time = 161.25 - 11.75A - 30.50B + 29.21C + 31.21D + 8.83AB + 34.21AC + 31.04AD - 36.54BC - 33.96BD - 33.67CD$$

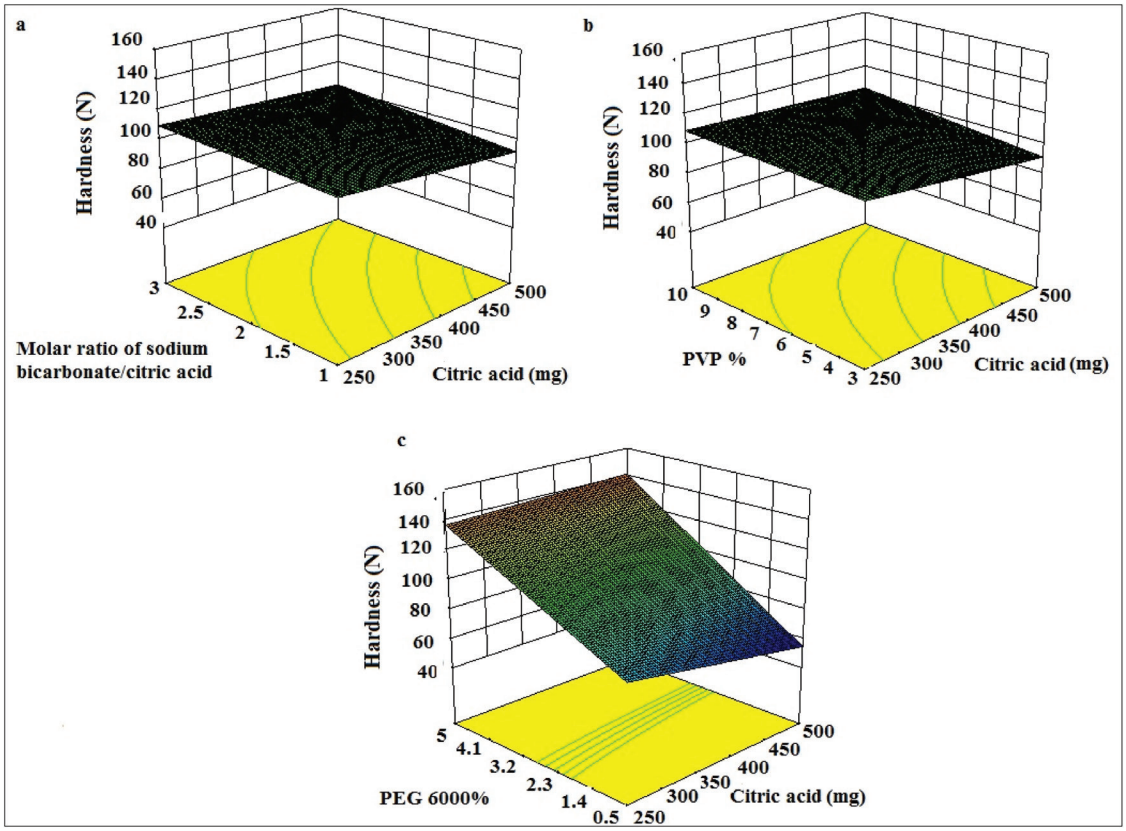

Figure 2: Response surface plots showing the effect of different levels of studied variables on the hardness of the tablet

According to the pharmacopoeia standards, effervescent time should be less than 3 min or 180 s.[12,13] In all formulations except P11, the effervescent time was less than 180 s, all within the range recommended by the pharmacopoeia [Table 5].

The results showed that increasing the amount of citric acid and the sodium bicarbonate/citric acid molar ratio reduced the effervescent time. This is due to increasing the available amounts of citric acid and sodium bicarbonate that result in faster reaction [Figure 4A].

The availability of a greater amount of base compared to the amount of acid leads to a comparatively more explosive and intense effervescence reaction, and more rapid dissolution of the tablet, which is presented by a shorter effervescent time. In a study conducted by Rahim *et al.*,[19] increasing sodium bicarbonate concentration from 10% to 20% wt/wt decreased the lag time of effervescent floating tablets containing pentoxifylline. With increasing PVP and PEG 6000, effervescent time increased, which is associated with increased hardness of the tablet [Figure 4B and C]. In agreement with our result, disintegration time of the formulation was further decreased, and the tablet hardness increased.

pH of solution test

pH of solution was in the range of 3.2–6.0 Figure 1. The most effective parameter on formulations pH was the molar ratio of the sodium bicarbonate to citric acid. The following equation also describes the effect of each factor on pH:

$$pH = 4.45 + 0.19A + 1.09B - 0.054C + 0.046D + 0.032AB + 0.027AD + 0.074BC + 0.049BD - 0.16CD$$

Formulations were divided into two parts with respect to pH. Formulations P1, P3, P4, P7, P8, and P11, all had pH value between 3.2 and 3.8. Formulations P2, P5, P6, P9, P10, and P12 had pH value in the range of 5.4–6.0. These differences are due to the types of formulations, which are mainly due to the citric acid/sodium bicarbonate molar ratio.

A ratio of 1:1 causes a substantial amount of un-neutralized acid to remain in the solution, and the pH tends to acidify, but the acid/base ratio of 1:3 causes the acid to be thoroughly neutralized, and the pH tends to neutralize[20] [Figure 5A and C]. An increase in the amount of effervescent constituents increases the neutralization reaction, which results in a slight increase in the pH of the final solution [Figure 5A and B].

Amount of carbon dioxide

Amount of CO_2 was in the range of 63.4–398.5 mg. Figure 1 shows that the most important effective parameter on the amount of CO_2 was the molar ratio of the sodium bicarbonate to citric acid. Following equation shows the effect of each factor on this response:

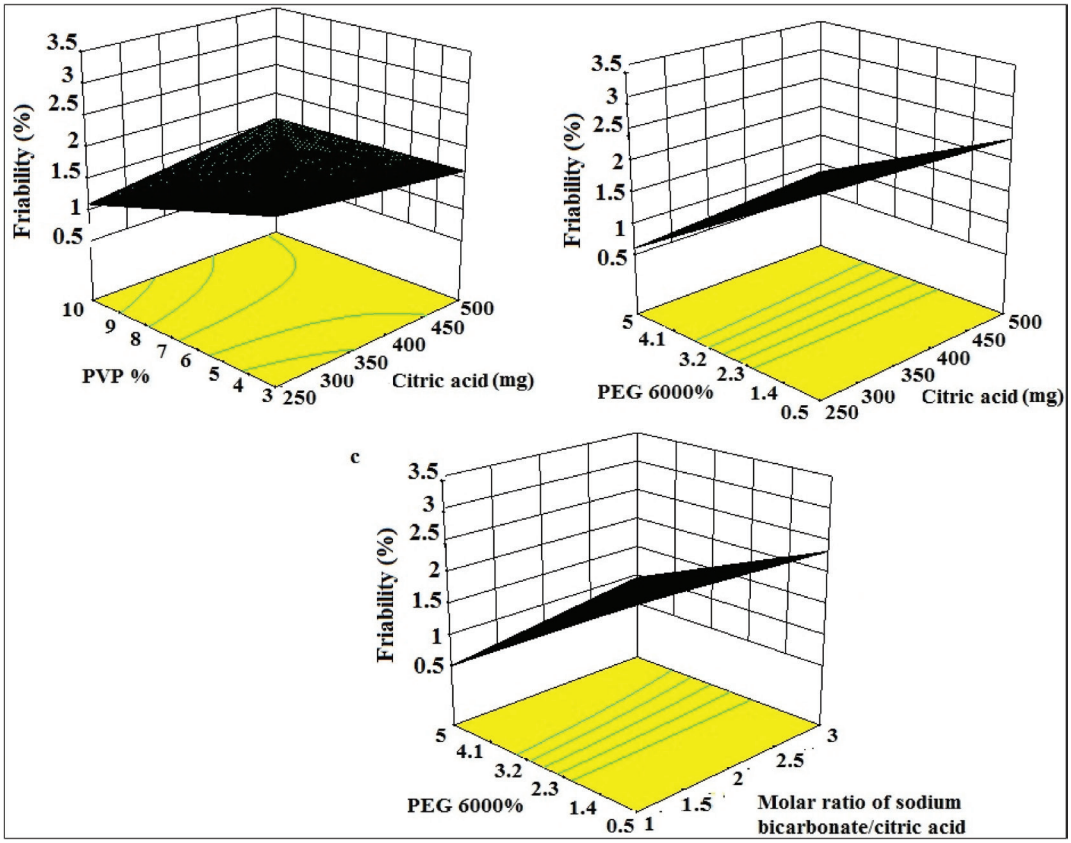

Figure 3: Response surface plots showing the effect of each studied variables on the friability of the effervescent tablets

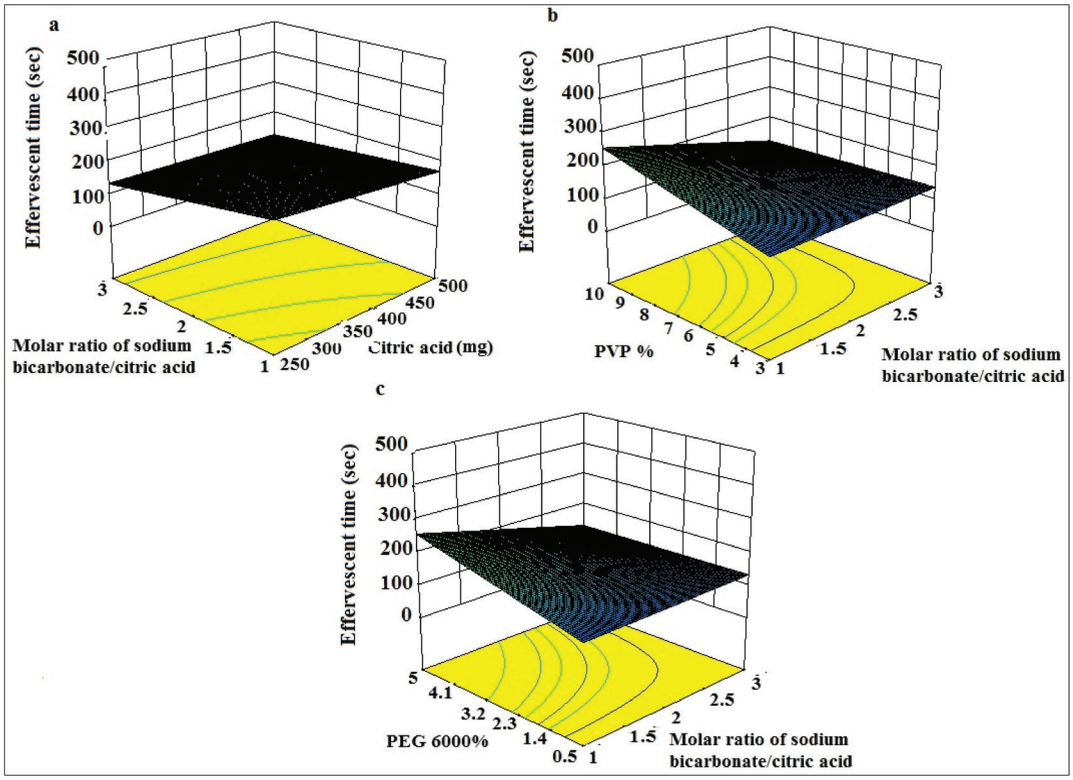

Figure 4: Response surface plots showing the effect of different levels of studied variables on the effervescent time of the tablets

$$Amount\ of\ CO_2 = 190.69 + 62.11A + 99.64B + 33.26AB$$

According to the results in Table 5, the amount of obtained CO_2 is directly correlated with base/acid molar ratio, indicating that the reaction is complete, and more CO_2 is produced when base/acid molar ratio is 3:1 [Figure 6]. Increasing the amount of effervescent constituents causes an increase in the amount of produced gas [Figure 6].

Optimization

Five dependent variables were optimized using Design–Expert software. Optimization was carried out to obtain the levels of each variable, which maximized CO_2 content and hardness, while minimizing disintegration time and friability, and targeting pH at 6. On the basis of obtained results, formulation P10 fulfilled the requirements of optimization by a desirability of 98%. The optimized formulation had a disintegration time of 95.33 ± 1.15 s,

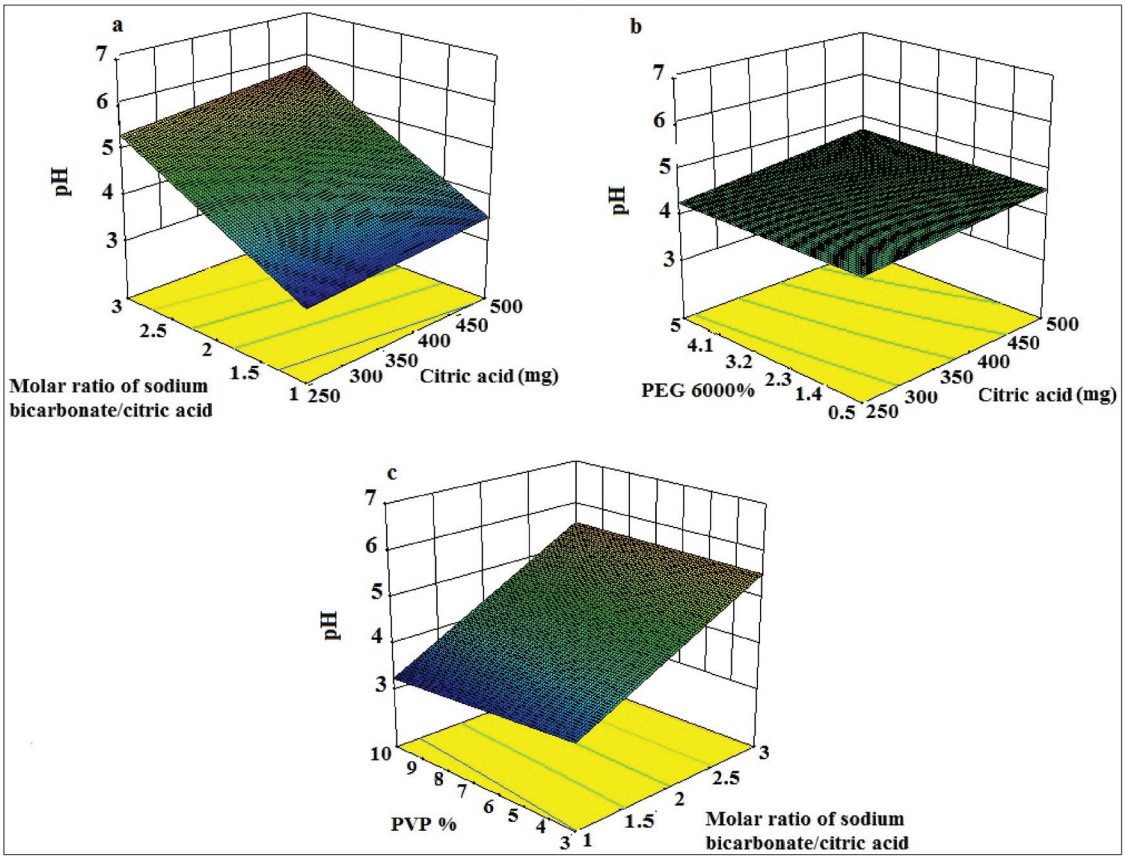

Figure 5: Response surface plots showing the effect of different levels of studied variables on the pH of solution test

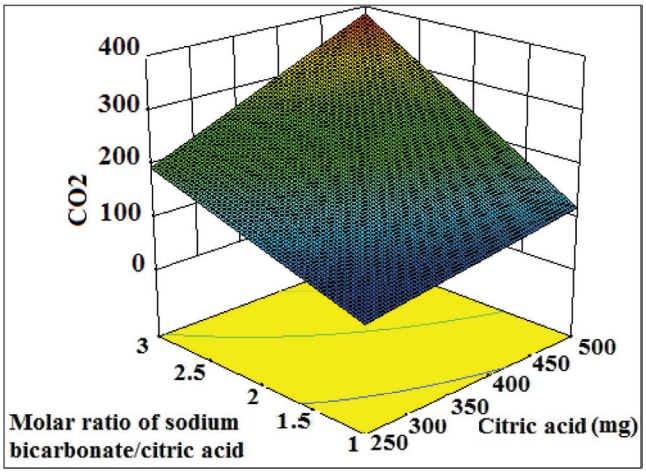

Figure 6: Response surface plots showing the effect of different levels of studied variables on the weight of carbon dioxide released from tablet

friability% of 0.73%, and pH value of 6.0 ± 0.06. Amount of CO_2 and hardness was 398.73 ± 1.46 mg and 72.3 ± 5.5 N, respectively.

Taste evaluation

To evaluate the taste of the formulation, as aforementioned, four flavoring types, cherries, tutti-frutti, sour cherries, and raspberries, were used, named A, B, C, and D, respectively. Thirty healthy volunteers were selected and divided into three groups. Group 1 was given formulation A followed by formulations C, D, and B, and group 2 formulation C followed by formulations A, D, and B.

Finally, group 3 was given formulation D, followed by formulations C, B, and A.

In group 1, the highest score was obtained for cherry flavor (3.8) followed by tutti-frutti and sour cherries (3.5). In groups 2 and 3, the highest score was obtained for cherry flavor and the rest was 3.8 and 3.7, respectively. At the end, the highest average score was obtained for cherry flavor (3.76) and this flavor was chosen as the best one. The mean scores of tutti-frutti (B), sour cherries (C), and raspberries (D) were 3.07, 3.33, and 2.9, respectively.

Conclusion

In this study, we successfully developed effervescent tablets containing bismuth sub-citrate. The process and formulation variables were optimized using Design–Expert software. The optimum condition suggested for the production of effervescent tablets included 500-mg citric acid, 5% PEG 6000, and 3% PVP k30, whereas the molar ratio of the sodium bicarbonate to citric acid was 3. This formulation had desirable flowability, hardness, and friability due to appropriate levels of PVP% and PEG 6000, which were used as binder and lubricant, respectively. This formulation also showed optimal pH, disintegration time, and amount of CO_2. All of these results suggest that developed effervescent tablets may be promising for delivery of bismuth sub-citrate in peptic ulcer therapy.

Financial support and sponsorship

This study was supported by the Isfahan University of Medical Sciences, Isfahan, Iran, as a thesis research project (number 4479).

Conflicts of interest

There are no conflicts of interest.

References

1. Delchier JC, Malfertheiner P, Thieroff-Ekerdt R. Use of a combination formulation of bismuth, metronidazole and tetracycline with omeprazole as a rescue therapy for eradication of *Helicobacter pylori*. Aliment Pharmacol Ther 2014;40:171-7.
2. Lee SP. A potential mechanism of action of colloidal bismuth subcitrate: Diffusion barrier to hydrochloric acid. Scand J Gastroenterol Suppl 1982;80:17-21.
3. Lahaie R, Farley A, Dallaire C, Archambault A, Fallone CA, Ponich T, *et al*. Bismuth-based quadruple therapy with bismuth subcitrate, metronidazole, tetracycline and omeprazole in the eradication of *Helicobacter pylori*. Can J Gastroenterol 2001;15:581-5.
4. Benet LZ. Safety and pharmacokinetics: Colloidal bismuth subcitrate. Scand J Gastroenterol Suppl 1991;185:29-35.
5. Tokola RA. The effect of metoclopramide and prochlorperazine on the absorption of effervescent paracetamol in migraine. Cephalalgia 1988;8:139-47.
6. Ipci K, Öktemer T, Birdane L, Altintoprak N, Muluk NB, Passali D, *et al*. Effervescent tablets: A safe and practical delivery system for drug administration. ENT Updates 2016;6:46.
7. Singh LP, Rajesh KS, Umalkar DG, Chauhan VK, Rana V, Vasava KS. Floating effervescent tablet: A review. J Pharm Biomed Sci 2011;5:1-6.
8. Zhou Q, Armstrong B, Larson I, Stewart PJ, Morton DA. Improving powder flow properties of a cohesive lactose monohydrate powder by intensive mechanical dry coating. J Pharm Sci 2010;99:969-81.
9. Aslani A, Jahangiri H. Formulation, characterization and physicochemical evaluation of ranitidine effervescent tablets. Adv Pharm Bull 2013;3:315-22.
10. Aslani A, Eatesam P. Design, formulation and physicochemical evaluation of acetaminophen effervescent tablets. JRPS 2013;2:140-9.
11. Wagh MP, Yewale CP, Zate SU, Kothawade PI, Mahale GH. Formulation and evaluation of fast dispersible tablets of aceclofenac using different superdisintegrant. Int J Pharm Pharm Sci 2010;2:154-7.
12. Thoke SB, Sharma YP, Rawat SS, Nangude SL. Formulation development and evaluation of effervescent tablet of alendronate sodium with vitamin D3. J Drug Delivery Ther 2013;3:65-74.
13. United States Pharmacopeial Convention. United States Pharmacopeia and National Formulary. 29th ed. Rockville, MD: United States Pharmacopeial Convention; 2006.
14. Blanco M, Alcalá M. Content uniformity and tablet hardness testing of intact pharmaceutical tablets by near infrared spectroscopy: A contribution to process analytical technologies. Anal Chim Acta 2006;557:353-9.
15. Yanze FM, Duru C, Jacob M. A process to produce effervescent tablets: Fluidized bed dryer melt granulation. Drug Dev Ind Pharm 2000;26:1167-76.
16. Shi R, Bi J, Zhang Z, Zhu A, Chen D, Zhou X, *et al*. The effect of citric acid on the structural properties and cytotoxicity of the polyvinyl alcohol/starch films when molding at high temperature. Carbohydr Polym 2008;74:763-70.
17. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of metoclopramide hydrochloride and ibuprofen. AAPS PharmSciTech 2008;9:818-27.
18. Aslani A, Fattahi F. Formulation, characterization and physicochemical evaluation of potassium citrate effervescent tablets. Adv Pharm Bull 2013;3:217-25.
19. Rahim SA, Carter PA, Elkordy AA. Design and evaluation of effervescent floating tablets based on hydroxyethyl cellulose and sodium alginate using pentoxifylline as a model drug. Drug Des Dev Ther 2015;9:1843.
20. Khan A, Iqbal Z, Rehman Z, Nasir F, Khan A, Ismail M, *et al*. Application of SeDeM Expert system in formulation development of effervescent tablets by direct compression. Saudi Pharm J 2014;22:433-44.