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Original Article

Formulation, Design, and Optimization of Taste Masked Effervescent Tablet Containing Methocarbamol

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Abstract

Methocarbamol is a skeletal muscle relaxant drug. In this study, we investigated the potential of developing methocarbamol effervescent tablets to facilitate drug administration. Effervescent tablets containing 1000 mg methocarbamol were prepared using the direct compression method. The effect of various formulations parameters such as citric acid, sodium bi-carbonate, PEG 6000, and PVP k30 on different physicochemical properties of tablets was evaluated at two levels. Different formulations with various amounts of mentioned excipients and the constant amount of methocarbamol, sucralose, mannitol, and different flavoring agents were prepared, and their properties included hardness, friability, pH effervescent time, CO2 content, and taste were studied. The optimized formulation was B8, which contained 400 mg of citric acid, 525 mg of sodium bicarbonate, 226.5 mg of PVP k30, 113.2 mg of PEG 6000, 100 mg of mannitol, and 30 mg of sucralose. This formulation had an effervescent time of 112.67± 2.05 seconds, hardness of 71.10± 2.51 N, and pH of 6.01±0.02. Statistical analysis by Design-Expert software showed that the hardness of tablets is mainly affected by the amount of PEG 6000. Volunteers reported that sour cherry had the most pleasant taste to them. In conclusion, current effervescent tablets are shown to be suitable vehicles for methocarbamol with potential for use in patients with swallowing problems and will enhance patient compliance.

Keywords: Full Factorial Design, Methocarbamol, Direct Compression Method, PEG 6000, PVP K-30, Effervescent Time, Hardness.

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1. Introduction

The oral administration route is the most popular and desirable way of taking medication due to its convenience of administration and manufacturing. Liquid dosage forms have several outstanding advantages such as easy formulation,

increased bioavailability and faster onset of action in comparison to solid products. In addition, liquid dosage forms are favorable for certain patients due to the increased dose flexibility and ease of swallowing. However, liquid dosage forms are often unstable and have short expiration dates [1]. Thus, solid effervescent tablets can be considered as a good replacement for liquid oral dosage forms [2, 3].

Effervescent tablets are intended to be dissolved or dispersed in water before consumption. These tablets disintegrate quickly in water as a consequence of the interaction between acid and base agents and the release of CO_2. Acid agents which are used in making effervescent tablets usually are citric acid, tartaric acid, and citric acid monohydrate and their interaction with base agents, which predominantly are carbonates or bicarbonates salts, result in dissolving or dispersing drugs in water [4]. Effervescent tablets are more stable than liquid dosage forms. But, they are in liquid form at the time of administration, so their absorption and onset of action are fast. In addition, they are easily administered in patients with swallowing problems. The release of CO_2 rises the transport of active pharmaceutical ingredients in a para cellular pathway leading to drug absorption [5].

Methocarbamol acts as a skeletal muscle relaxant by inhibiting polysynaptic reflexes in the spinal cord and subcortical centers [6-7]. Methocarbamol is easily absorbed in the gastrointestinal tract after oral administration, and its bioavailability is about 94% [8]. The onset of action is within 30 minutes, and after 2 h, it reaches to its maximum effect [9]. Methocarbamol is available in the forms of 500 and 750 mg tablets and an injection solution of 100 mg/ml. The usual dosage of this drug is 1500 mg 4 times a day for 2 to 3 days. In severe conditions, 8 gr per day may be administered [7]. Due to the inherent limitations of solid dosage forms for certain groups of patients and compliance issues of injection form, designing and manufacturing effervescent tablets seems promising. Compared to conventional ones, incorporation of larger amounts of the drug is possible in effervescent tablets.

Considering all of the above, in this study, effervescent tablets containing 1000 mg methocarbamol were prepared. The effect of various formulations parameters on their characterization was evaluated. Finally, the taste of prepared tablets was evaluated in healthy volunteers as well.

2. Materials and Methods

2.1. Materials

Methocarbamol was purchased from Amin pharmaceutical Co (Iran). Citric acid, sodium bicarbonate, mannitol, sucrose, PVP k30, PEG 6000 were obtained from Merck (Germany). Flavoring agents were gifted by Farabi Pharmaceutical Company (Iran).

2.2. Preparation of Effervescent Tablets and Formulation Studies

Effervescent tablets of methocarbamol were prepared by direct compression method. To optimize the condition for preparation of

formulation, four independent variables, including citric acid, sodium bicarbonate to citric acid molar ratio, PVP k30, and PEG 6000 were selected based on preliminary studies. All these variables had two levels as shown in Table 1. Using full factorial design, sixteen formulations were designed as exhibited in Table 2. In all formulations, the amount of the drug was constant (1000 mg). The desired amount of citric acid, sodium bicarbonate, PVP k30, PEG 6000, sucralose, mannitol, and 1000 mg of methocarbamol were weighed and mixed using mortar and pestle and compressed using a single punch tablet machine (Kilian & Co, Germany). Compositions of different formulations are shown in Table 2. The studied responses or the dependent variables were hardness, friability, PH, and effervescent time. Design-Expert Software (version 10, USA) was employed to the analysis of the experimental data and graphically expressed the effect of each variable on the response.

2.3. Evaluation of Blends before Compression

2.3.1. Angle of Repose

The angle of repose (Θ) measured by assessment of the height (h) and radius (r) of the powder's pile that emerged after flowing powder through a funnel in distinct height using following equation (10):

$$Tan\theta = h/r$$

where θ is the angle of repose, h represents the height of the pile, and r shows the radius of the base of the pile. The angle of repose lower than 40° shows good flowability, while an angle of repose greater than 40° is an indication of cohesiveness [11].

2.3.2. Bulk Density

Bulk density (ρ_b) was measured by calculating occupied volume of weighed amount of powder using below equation [12]:

$$\rho b = \frac{Weight\ of\ powder}{volume\ occupiedby\ the\ powder}$$

2.3.3. Tapped density

Certain amount of powder was placed in graduated cylinder and then the cylinder was dropped from 10 cm height until the volume became constant. Then, tapped density (ρ_t) was measured using the following equation [12]:

$$\rho t = \frac{Weight\ of\ the\ powder}{volume\ occupied\ by\ the\ tapped\ powder}$$

2.3.4. Compressibility Index and Hausner's Ratio

Compressibility index, also known as Carr's index, was used to evaluate the flowability of powder and can be determined using the following formula [13]:

$$\text{Carr's index (\%)} = \frac{\rho t - \rho b}{\rho t} \times 100$$

A powder with a compressibility index lower than 20% is considered to have a good flowability [11].

Hausner's ratio was also used to determine the flowability of a powder and calculated using following equation [13]:

$$\text{Hausner's ratio} = \frac{pt}{pb}$$

Hausner's ratio lower than 1.25 characterizes a free-flowing powder [11].

2.3.5. Particle Size Distribution

Particle size distribution was measured using the sieve method. Powders put on a series of sieves with a size of 20, 25, 30, 35, 40, 70, and 100 and then placed in the device. The remaining powders on each sieve were weighed, and the mean particle size (d) was measured using the following equation (4):

$$d = \frac{\Sigma xidi}{100}$$

in which xi is the mean size of both upper and lower sieves and di is the percent of remaining powder on the lower sieve.

2.4. Physicochemical Evaluation of the Effervescent Tablets

2.4.1. Hardness Test

The hardness of 10 tablets from each batch was measured using Erweka hardness tester (Erweka, TPA, Germany) [14].

2.4.2. Weight Variation

A weight variation test was carried out to determine the uniformity of dosage units. Twenty tablets from each batch were randomly selected and weighed, and then the weights of tablets were compared with the calculated mean weight [10].

2.4.3. Friability Test

Ten pre-weighed tablets of each formulation were put into Erweka friabilator (Erweka TAP, Germany). After the friabilator ran for 4 min and at a speed of 25 rpm, tablets were weighed again and friability calculated using the following equation [10]:

$$\text{Friability\%} = \left(\frac{W1 - W2}{W1}\right) \times 100$$

W1 represents the initial weight of tablet and W2 is the final weight of tablet. A friability below 1% is desirable [10].

2.4.4. Drug Content Analysis

Ten tablets were randomly selected. Each tablet was grounded into a fine powders using mortar and pestle. Then, the fine powders were dissolved in 1000 ml purified water. The solution was filtered through a cellulose acetate membrane (0.45 μm), diluted and analyzed by UV-visible spectrophotometer (Shimadzu, Japan) at 273 nm [15].

2.4.5. Measurement of CO2 Content

One tablet was put in 100 ml of 1 N sulfuric acid solution and content of CO_2 was determined by measuring weight change after complete dissolution. The weight difference considered to be the amount of CO_2 (mg) per tablet. This test was performed in triplicate [4].

$$2NaHCO_3\ (aq) + H_2SO_4\ (aq) \longrightarrow Na_2SO_4\ (aq) + 2CO_2\ (g) + 2H_2O\ (l) \quad (21)$$

2.4.6. Evaluating the Solution pH:

The pH of solution was measured after a tablet dissolution in 200 ml of water at 20 °C ± 1° via a pH meter (Metrohm Herisau, Switzerland). This test was performed in triplicate.

2.4.7. Effervescent Time of the Tablets

A tablet was immersed in the beaker containing 200 ml of purified water at 20 °C ± 1°, and the disintegration time was measured by a stopwatch. Effervescence completion was considered as the moment when the clear

solution without particles was obtained. This test was performed in triplicate [4].

2.4.8. Water Content

Ten tablets from each batch were kept in a desiccator containing activated silica gel for 4 h, and then water content % was calculated using the following equation:

$$\text{Water content \%} = \frac{(Tablet\ weight\ before\ drying - Tablet\ weight\ after\ drying)}{Tablet\ weight\ befor\ drying} \times 100$$

Water content of 0.5% or less is acceptable [4].

2.4.9. Tablet Thickness

The thickness of three randomly selected tablets from each batch was measured using an vernier caliper (For-Bro Engineers, India) [16].

2.5. Taste Evaluation

To increase tablets' palatability, a constant amount of flavoring agent including cherry, Tutti-frutti, sour berry, and orange was added to the optimized formulation (Table 3), and four new formulations were prepared, named F1, F2, F3, and F4, respectively. Thirty volunteers were involved in the study. Group A received F2 followed by F3, F4, and F1, while group B received F3 followed by F1, F4, and F2, and group C received F1 followed by F4, F2, and F3.

3. Results and Discussion

Effervescent tablets contain multiple ingredients such as acid or acid salts, carbonate or bicarbonate salts, lubricants, binders, fillers, sweeteners, and flavors. Excipients are used in making effervescent tablets should be soluble in water. Because these products are sensitive to moisture and temperature, the environment of producing effervescent tablets should have relative moisture of 25% or less and keep it at moderate temperature [4]. In this study, sixteen formulations were prepared using full factorial design, and the effect of different formulation variables was determined for optimal conditions.

3.1. Evaluation of Powders Blend

Table 4 shows blended powders' flow properties, including Carr,s index, angle of repose, Hausner ratio, and particle size distribution. The angle of repose of powder blend was found to be in the range of 26.97 - 33.63^{o} (Table 4). Formulation B_7 had the lowest angle of repose (26.97 ±0.49^{o}), and formulation B_4 had the highest angle (33.63 ±0.68^{o}). Hausner ratio for all formulations was found to be in the range of 1.08 – 1.21, and compressibility index was 7.05–17.59 (Table 4), demonstrating that all formulations had good flowability.

3.2. Physicochemical Evaluation of Tablets

Tablets were prepared by direct compression method. Physicochemical tests were conducted on prepared tablets, including effervescent time, content uniformity, solution pH, hardness, friability, thickness, weight variation, CO_2 content, and water content, and

results are shown in Table 5. According to USP, the content uniformity of tablets should be in the range of 90-110 % of claimed amounts in each formulation, and the coefficient of variation (CV) should not be more than 6 % (10). Therefore, based on our findings (Table 5), all the formulations had uniform content. As shown in Table 5, all prepared formulations' water content was less than 0.5 %, which confirms that the produced tablets had desirable water content [4]. The CO_2 content of tablets was found to be in the range of 154.90 – 510.83 mg (Table 5). In another study, the CO_2 content of effervescent tablets of acetaminophen containing 384-768 mg of the citric acid monohydrate and 231-924 mg of sodium bicarbonate was in the range of 314-772, which is approximately similar to these results [17]. According to USP, the weight variation of produced tablets must be less than 5% of the tablets' average weight [10]. All the prepared formulations had a weight variation of less than 5% (Table 5).

3.2.1. Tablet Hardness

As shown in Table 5, the hardness of tablets ranged between 35.30 and 76.00 N. B_7, B_8 and B_5 formulations had the greatest hardness and B_2, B_1 and B_4 formulations had lowest hardness. Desired hardness for effervescent tablets is 40 to 80 N [4]. Four batches (B_1-B_4) were out of the range. As shown in Fig. 1, the hardness of tablets is mostly affected by the amount of PEG 6000. Rising PVP and PEG 6000 increased tablet hardness (Figure 2 c, d), which had already been shown in other studies [16, 18]. This finding could be related to the binding effect of PEG 6000 and PVP. The increasing citric acid amount decreased tablet hardness (Figure 1), possibly due to the plasticizer effect of citric acid leading to decreased interaction among the macromolecules [19].

3.2.2. Tablet Friability

According to USP, the acceptable limit of friability is less than 1% (10). The friability of prepared tablets ranged from 0.32 to 3.29 % (Table 5). Half of the formulations had a friability in the acceptable limit. B_8 formulation had the lowest (0.32%), and B_2 formulation had the highest friability (3.29%). Fig. 3 shows the effect of each studied variable on the friability of the effervescent tablets. Studies showed that every variable that increased the hardness of tablets decreased friability; three formulations that had the highest hardness also had the lowest friability (B_7, B_8, and B_5). Similar results were obtained in our previous study on the preparation of effervescent tablets containing bismuth sub-citrate where there was a decrease in friability of tablets with increasing the amount of PEG 6000 and PVP [20].

3.2.3. Tablet Effervescent Time

The acceptable limit for effervescent time is less than 180 seconds [10]. From Table 5, four formulations had more effervescent time than 180 seconds (B_1, B_5, B_9, and B_{16}), and the best effervescent time was observed in the B_4 formulation (98.67 sec). As it can be seen in

Fig. 4, increase in the amount of citric acid and sodium bicarbonate / citric acid molar ratio led to decrease in effervescent time. The effervescent time mostly influenced by sodium bicarbonate / citric acid molar ratio, as demonstrated in Figure 1. This is because of presence of greater amounts of citric acid and sodium bicarbonate in formulation and therefore a faster reaction (Figure 4a, b). The more quantity of base versus acid can lead to an intense and prompt reaction and therefore a faster and better dissolution of tablet [21]. The analysis also showed that the increase in amount of PEG 6000 and PVP raised the effervescent time (Figure 4c, d). This is due to increase in tablet hardness which slows down dissolution and increases the effervescent time [20]. In a study conducted by Aslani et al [19] increment of PVP content increased the hardness of effervescent tablets containing potassium citrate.

3.2.4. pH of Solution

The pH of solution was found to be in the range of 3.54 -6.32 (Table 5). B_{12}, B_4 and B_8 solution had highest pH and B_9, B_5 and B_1 had the lowest pH. Figure 5 shows the effect of studied variables on pH of solution. As demonstrated in Figure 1, Sodium bicarbonate / Citric acid molar ratio had the most effect on pH of solution. The formulations with 1:1 ratio had lowest pH, while formulations with 1:3 ratio had the highest pH which showed that some acid molecules remain un-neutralized in ratio of 1: 1, but completely neutralized in 1:3 ratio. This is in agreement with previous study that reported highest pH in batches with higher base/acid ratio [4].

3.3. Optimization of Formulations

The optimal condition for preparation of optimized formulation was determined using design expert based on the set criteria including constraints and target goals of all dependent variables. Optimization was done in a way that pH of solution was maximized, hardness was in the range of 40-80 N, friability and effervescent time were less than 1% and 180 seconds, respectively. The B_8 formulation was selected as optimized formulation with desirability of 82%. The B_8 formulation had effervescent time of 112.67± 2.05 seconds, friability of 0.32 %, hardness of 71.10± 2.51 N and pH of 6.01±0.02.

3.4. Taste Evaluation

The components of optimized formulation were mixed with same amount of mentioned flavors and four new formulations were prepared (Table 3). Based on obtained data, the F_3 formulation containing sour cherry had the best taste with the average score of 3.92 followed by F_1, F_2 and F_4 with average score of 3.54, 3.26 and 3.10, respectively.

4. Conclusion

In this study, we designed and produced a new and effective effervescent tablet containing methocarbamol and their physicochemical properties were investigated. After doing all tests and analysis of collected data, the optimization carried out by using Design Expert software and eventually the

optimized formulation containing 400 mg of citric acid, 525 mg of sodium bicarbonate, 10% PVP, and 5% PEG 6000 alongside 1000 mg of methocarbamol, 100 mg of mannitol, 30 mg of sucralose were selected. This formulation had suitable hardness, pH, friability, and effervescent time because of a proper amount of excipients. Although *in vitro* findings showed that produced effervescent tablets could be a practical and new way of delivery of methocarbamol, however, further study is required to confirm the therapeutic potential of the effervescent tablet of methocarbamol *in vivo*

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Tables:

Table 1. Variables used in full factorial design.

Independent variables	Levels		
	I	II	Dependent variables
Citric acid (mg)	200	400	Friability
Sodium bicarbonate to citric acid molar ratio	1-1	3-1	pH
PEG 6000(%)	0.5	5	Hardness
PVP (%)	3	10	Effervescent time

Table 2. Composition of different formulations studied in preparation of effervescent tablets containing 1000 mg methocarbamol.

Formulations	**Citric acid (mg)**	**Sodium bicarbonate (mg)**	**Sodium bicarbonate to citric acid molar ratio**	**PEG 6000 (%)**	**PVP k30 (%)**	**Mannitol(mg)**	**Sucralose(mg)**
B_1	200	87.5	1-1	0.5	3	100	30
B_2	400	175	1-1	0.5	3	100	30
B_3	200	262.5	3-1	0.5	3	100	30
B_4	400	525	3-1	0.5	3	100	30
B_5	200	87.5	1-1	5	10	100	30
B_6	400	175	1-1	5	10	100	30
B_7	200	262.5	3-1	5	10	100	30
B_8	400	525	3-1	5	10	100	30
B_9	200	87.5	1-1	0.5	10	100	30
B_{10}	400	175	1-1	5	3	100	30
B_{11}	200	262.5	3-1	0.5	10	100	30
B_{12}	400	525	3-1	5	3	100	30
B_{13}	400	175	1-1	0.5	10	100	30
B_{14}	200	262.5	3-1	5	3	100	30
B_{15}	400	525	3-1	0.5	10	100	30
B_{16}	200	87.5	1-1	5	3	100	30

Table 3. Panel test for flavors by Latin Square method (on 30 volunteers) for effervescent tablets containing 1000 mg methocarbamol.

Ingredients(mg)	**Formulations**			
	F_1	**F_2**	**F_3**	**F_4**
Methocarbamol	1000	1000	1000	1000
Citric acid	400	400	400	400
Na bicarbonate	525	525	525	525

PVP	226.5	226.5	226.5	226.5
PEG 6000	113.2	113.2	113.2	113.2
Mannitol	100	100	100	100
Sucralose	30	30	30	30
Cherry	50	-	-	-
Tutti-frutti	-	50	-	-
Sour cherry	-	-	50	-
Orange	-	-	-	50

Table 4. Evaluation of pre compression parameters for various effervescent tablet formulations containing 1000 mg methocarbamol.

Formulations	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility Index (%)	Hausner ratio	Mean particle size (µm)
B_1	32.70 ±1.90	0.29± 0.03	0.33± 0.01	14.09± 1.50	1.17± 0.09	285.25± 2.13
B_2	31.67 ±0.37	0.30± 0.02	0.34± 0.02	11.64± 0.18	1.13± 0.04	291.87± 1.28
B_3	30.60 ±0.16	0.26± 0.02	0.29± 0.03	12.22± 0.83	1.14± 0.05	422.49± 3.61
B_4	33.63 ±0.68	0.34± 0.01	0.40± 0.01	14.98± 0.57	1.18± 0.03	381.97± 2.08
B_5	29.40 ±0.22	0.24± 0.02	0.27± 0.02	11.00± 1.03	1.12± 0.01	299.78± 3.83
B_6	30.10 ±0.16	0.26± 0.02	0.29± 0.03	10.06± 0.68	1.12± 0.08	354.69± 2.35
B_7	26.97 ±0.49	0.28± 0.02	0.30± 0.02	8.80± 0.94	1.10± 0.02	323.25± 2.82
B_8	28.40 ±0.36	0.31± 0.02	0.33± 0.02	7.05± 0.85	1.08± 0.02	431.80± 3.10
B_9	30.40 ±0.36	0.34± 0.02	0.38± 0.03	10.46± 0.73	1.12± 0.03	295.84± 4.32
B_{10}	31.50 ±0.14	0.28± 0.01	0.32± 0.02	12.17± 1.40	1.14± 0.06	323.47± 1.51
B_{11}	32.00 ±0.29	0.33± 0.02	0.38± 0.01	13.30± 1.33	1.16± 0.06	413.80± 4.27
B_{12}	29.37 ±0.65	0.30± 0.03	0.33± 0.02	10.03± 1.18	1.11± 0.06	383.02± 1.01
B_{13}	30.80 ±0.37	0.28± 0.01	0.32± 0.01	13.37± 1.54	1.15± 0.02	351.37± 1.31
B_{14}	33.07 ±0.73	0.29± 0.02	0.33± 0.01	10.99± 0.49	1.13± 0.08	396.36± 2.18
B_{15}	28.63 ±0.40	0.31± 0.01	0.33± 0.01	12.25± 0.11	1.14± 0.04	411.84± 2.96
B_{16}	33.57 ±0.50	0.31± 0.02	0.38± 0.02	17.59± 0.82	1.21± 0.03	303.00± 1.28

Table 5. Evaluation of different effervescent tablets containing 1000 mg methocarbamol.

Formulations	Thickness (mm)	Effervescence time (sec)	Co_2 content (mg)	Friability (%)	Hardness (N)	Weight variation (%)	Drug content %	pH	water content (%)
B_1	4.14± 0.08	183.33± 2.05	154.90 ± 0.98	2.92± 0.03	39.20± 1.14	1.08±0.25	99.85±0.56	3.64±0.05	0.02±0.003
B_2	5.12± 0.07	157.67± 2.62	262.47 ± 1.06	3.29± 0.03	35.30± 1.34	0.91±0.14	100.49±0.57	3.92±0.03	0.02±0.002
B_3	4.68± 0.10	125.33± 3.30	373.80 ± 1.15	2.35± 0.06	39.60± 2.22	0.97±0.18	99.52±0.50	5.09±0.02	0.02±0.003
B_4	6.59± 0.07	98.67± 2.62	492.57 ± 1.75	2.50± 0.02	39.50± 1.27	0.75±0.23	99.60±0.32	6.13±0.04	0.01±0.002
B_5	4.66± 0.09	195.00± 3.74	169.90 ± 1.37	0.52± 0.03	66.80± 2.10	1.03±0.13	100.00±0.43	3.55±0.01	0.01±0.002
B_6	5.51± 0.13	176.33± 1.25	285.67 ± 1.54	0.59± 0.03	65.60± 1.58	0.83±0.08	99.93±0.25	3.97±0.03	0.02±0.004
B_7	5.29± 0.13	146.33± 2.05	393.43 ± 1.40	0.45± 0.01	76.00± 2.05	0.95±0.10	99.89±0.29	5.79±0.01	0.02±0.003
B_8	7.30± 0.09	112.67± 2.05	510.83 ± 1.10	0.32± 0.02	71.10± 2.51	0.57±0.11	100.07±0.29	6.01±0.02	0.02±0.003
B_9	4.67± 0.09	191.00± 3.56	161.40 ± 0.70	1.61± 0.02	44.00± 1.05	1.01±0.06	100.47±0.28	3.54±0.02	0.01±0.002
B_{10}	5.19± 0.07	165.00± 1.41	271.97 ± 1.16	0.84± 0.02	55.20± 1.32	0.93±0.13	99.93±0.21	4.11±0.01	0.01±0.003
B_{11}	5.10± 0.06	134.33± 1.70	380.63 ± 0.67	1.22± 0.02	53.80± 2.78	0.97±0.13	99.96±0.21	5.72±0.01	0.02±0.003

B_{12}	7.05± 0.09	108.00± 1.63	502.17 ± 0.32	0.64± 0.02	58.30± 2.50	0.71±0.1 0	100.15±0.1 9	6.32±0.0 3	0.01±0.004
B_{13}	5.35± 0.15	171.33± 2.05	279.86 ± 1.42	2.12± 0.02	41.30± 0.95	0.66±0.1 6	100.18±0.1 6	4.05±0.0 5	0.01±0.003
B_{14}	4.82± 0.07	130.33± 1.70	377.39 ± 1.14	0.73± 0.04	61.60± 1.51	0.74±0.1 6	99.86±0.42	5.32±0.0 2	0.01±0.004
B_{15}	7.13± 0.06	115.00± 2.16	506.98 ± 1.32	1.86± 0.06	51.60± 1.51	0.66±0.0 5	100.01±0.2 1	5.94±0.0 5	0.02±0.004
B_{16}	4.37± 0.08	187.00± 1.63	158.74 ± 3.84	0.92± 0.02	57.60± 2.27	1.03±0.1 1	99.90±0.20	3.75±0.0 2	0.01±0.003

Figures:

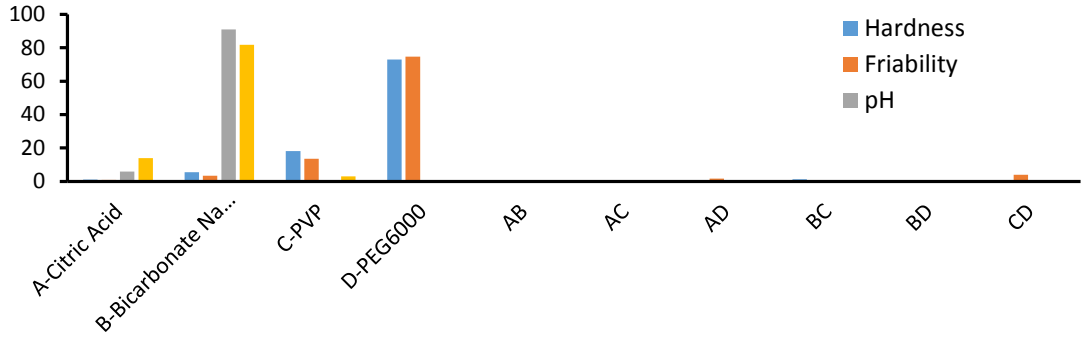

Figure 1.Contribution percent of different studied parameters and their interactions on physicochemical characteristics of effervescent tablet containing methocarbamol. A: Citric acid (mg), B: Sodium bicarbonate to citric acid molar ratio, C: PEG 6000(%), D: PVP (%) and AB, AC, AD, BC, BD and CD is combined effect of two factors.

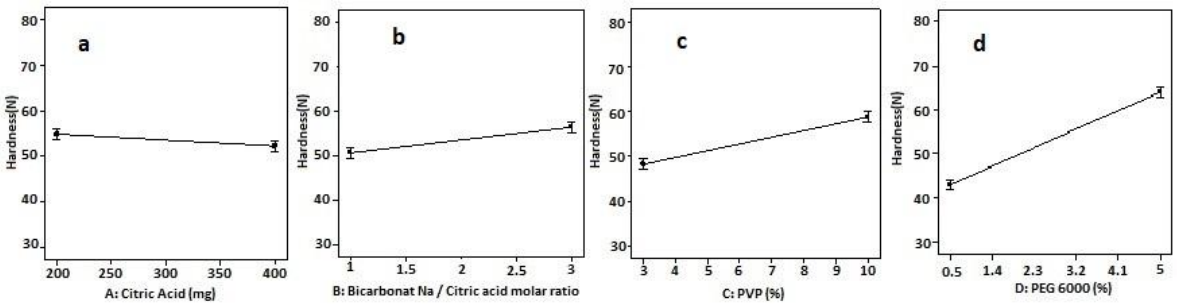

Figure 2. Effect of studied variables on tablets hardness.

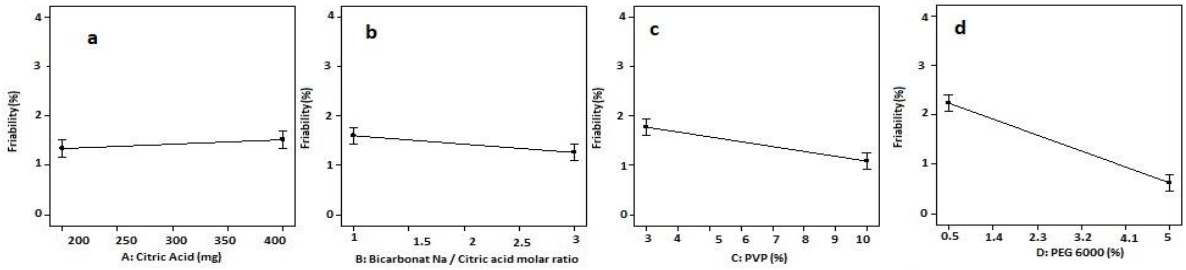

Figure 3. Effect of studied variables on tablet friability.

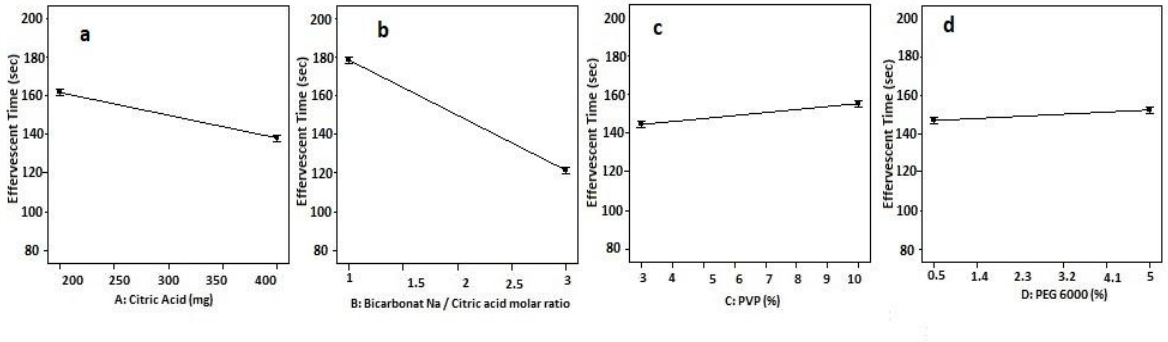

Figure 4. Effect of studied variables on effervescent time.

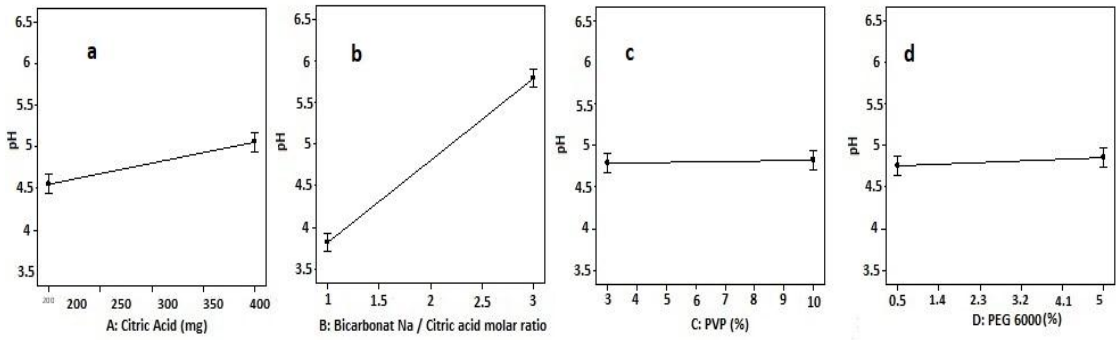

Figure 5. Effect of studied variables on pH of solution.

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