

Simple design of miniaturized cabinet for compounding Vitamin C effervescent tablet in laboratory scale

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ABSTRACT

Aim: The aim of this study was to design miniaturized cabinet that needs the tight requirements in formulating the effervescent tablets ingredients to minimize the relative humidity value to prevent the initial effervescent reaction. **Materials and Methods:** The compounding workspace was created by designing cabinet arranged with special equipment so that the humidity and temperature of the mixing chamber could be monitored. The conditioning of the workspace was carried out using a variety of methods, i.e., lights, active silica gel, and a combination of both during certain observation times. In this study, all of the components in the effervescent tablet formula were mixed using two steps of the wet granulation method. The evaluation of effervescent tablets included the appearance of the tablet, diameter, tablet thickness, weight uniformity, hardness, friability, tablet disintegration time, pH of the solution, and hedonic test. **Results and Discussion:** The results of moisture control optimization indicated that the most rapid method of lowering moisture was using a combination of active light and silica gel. After 100 min, this method could decrease the relative humidity (RH) by 0.415% per min. Based on the evaluation result, all formulas achieved the requirements of good effervescent tablets. However, based on the hedonic test, a formula using a 1.2% lemon flavor was the most preferred formula of the panelist. **Conclusion:** In this research, the design of compounding cabinets with dimensions of 60 cm × 40 cm × 59.5 cm was proven to produce effervescent tablets that fulfill the requirements.

KEY WORDS: Cabinet, Compounding, Control, Effervescent, Miniaturized, Relative humidity

INTRODUCTION

Vitamin-specific supplements are fast becoming more popular than traditional multivitamins, with Vitamin C potentially being one of the most trusted. Especially for those who need extra vitality because it has many activities that deplete stamina. Humans cannot biosynthesis Vitamin C and we are also unable to store this in our bodies; therefore, it is essential that we consume a sufficient amount of this vitamin regularly. Approximately 70–90% of Vitamin C is absorbed in moderate intakes of 30–180 mg/day. However, at doses above 1 g/day, absorption falls to <50% and absorbed, unmetabolized ascorbic acid is excreted in the urine.^[1] An inadequate intake of Vitamin C can lead to scurvy, which manifests in symptoms such as fatigue, malaise, inflammation of the gums, poor wound healing, and joint pain.^[2-4] Vitamin C has low toxicity and is safe at high intakes.^[5] The most

common complaints are abdominal cramps, diarrhea, nausea, and other gastrointestinal disturbances due to the osmotic effect of unabsorbed Vitamin C in the gastrointestinal tract.^[2,5]

One of the most widely available forms of Vitamin C supplements is in effervescent tablets. There are several reasons why Vitamin C effervescent tablets are popular, for example, easy to take, exhibit more stability than liquid dosage forms, and offer the possibility to improve the absorption of the active ingredients due to prior dissolution.^[6] Other advantages of an effervescent tablet such as the fast onset of action, good stomach and intestinal tolerance, more portability, improved palatability, superior stability, more consistent response, incorporation of large amounts of active ingredients, accurate dosing, and improved therapeutic effect.^[7,8] The effervescent tablet is a tablet which is dissolved or dispersed in water before administration. In addition to active ingredients, it generally contains a mixture of acids/acid salts, carbonate, and hydrogen carbonates which release CO₂ when reacted with water.^[9] The CO₂ was

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liberated to improve the drug absorption and taste of the pharmaceuticals.^[10,11]

The effervescent tablets are generally manufactured in the same way as a conventional tablet manufacturing process but need controlled environmental conditions. The prerequisite for the controlled environment is due to the hygroscopic nature of the raw materials used for its production and chances of initiation of an effervescent reaction due to the uptake of moisture by these materials. Low relative humidity (maximum of 25% or less) and moderate to cool temperatures (25°C) in the manufacturing areas is essential to prevent the granulations or tablets from sticking to the machinery and from picking up moisture from the air, which may cause product degradation.^[8] Effervescent preparations are very sensitive to moisture, which may compromise their chemical stability and promote a premature reaction releasing carbon dioxide. It is desirable to develop an optimum formulation that improves effervescent stability.^[12,13] Thus, humidity and temperature control in the production area is an essential step in the manufacturing of these tablets. The cost of temperature and humidity control equipment and energy required for its operation is high, thus environmental control area needs to be kept to a minimum. Therefore, for the manufacture of laboratory-scale effervescent tablets which do not permit the use of such expensive tools and equipment, should consider the cost of manufacture. In this research, a cabinet was designed to maintain the humidity condition of the compounding place with optimization method that can reduce RH value in a short time and use a simple and inexpensive method.

MATERIALS AND METHODS

Materials

The materials used in this study include Vitamin C (Roche), sodium bicarbonate (Brataco), tartaric acid (Brataco), powdered sugar, sodium chloride, aspartame (Brataco), lemon yellow, lemon flavor (Givaudan), silica gel (Brataco), aquadest, ethanol (95%), and buffer pH.

Humidity Cabinet Design

The cabinet is made using a material made up mostly of glass equipped with a drawer where silica gel, handhole equipped with rubber gloves, lamp, hygrometer, thermometer, socket, and aluminum bars. The dimensions of the cabinet size are the length × width × height (60 cm × 40 cm × 59.5 cm). The top, side, and rear of the cabinets are surrounded by the glass while the front part consists of glass parts (#) and plywood (where the handhole). The cabinet design was performed in Figure 1.

In this humidity cabinet, some formulation process such as material weighing, material mixing, and



Figure 1: Humidity cabinet. a (length 60 cm); b (width 40 cm); c (height 59.5 cm); c1 (height 50 cm); c2 (drawer height 9.5 cm); 1 (roof of humidity cabinets); 2 (drawer where silica gel placed); 3 (handholes equipped with rubber gloves); 4 (lamp); 5 (hygrometer and thermometer); 6 (electric socket); and 7 (aluminum bars)

granulation process was done. The function of the drawer is to store the silica gel. The wristwatch in this cabinet is equipped with long rubber gloves that are glued to the hole making it easy to carry out the activity inside the closet and minimize the entry of air. While the function of the lamp is to illuminate the inside of the cabinet and is used to help the active silica gel in accelerating the decrease of moisture in the closet. For completeness, this cabinet was equipped with hygrometer and thermometer so it could be monitored directly. Hygrometer served to measure the humidity in the cabinet, while the thermometer was used to measure the temperature in the cabinet. The function of the outlet was used as an electronic weighing balancer with an electric voltage source. While the aluminum bars were used as a barrier with drawers and as a support tool used.

Conditioning Humidity Cabinets

The conditioning of these humidity cabinets was done by various methods, as follows: Lamp, active silica gel, the combination of lamp and active silica gel, and non-active silica gel. Conditioning the cabinets using a 10-watt lamp was performed for 100 min, then the RH value and the temperature were monitored every 5 min. Before use, 1 kg of silica gel was heated using an oven at 110°C for 24 h, thus forming an active silica gel. The active gels silica was then placed in the drawer of the humidifier cabinet. Optimized conditioning methods reduced Rh to 25% rapidly, used in subsequent cabin conditioning.

Formulation of Effervescent Tablet Vitamin C with Lemon Flavor

The prepared effervescent Vitamin C tablet that meets the requirements as a good effervescent tablet is a strong indicator that shows moisture cabinets conditioning has been successfully performed. For the formulation of effervescent tablets, other excipients such as sweeteners,

flavorings, water-soluble lubricants, and water-soluble colors are utilized.^[14] Before formulated, the ingredients that make up the effervescent Vitamin C tablet were dried first. Sugar powder, aspartame, dye, and tartaric acid were dried in the oven at 35°C for 1–3 h; sodium bicarbonate at a temperature of 100°C for 45 min; sodium chloride at a temperature of $\pm 105^\circ\text{C}$ for 2 h. After that, the process of compounding and granulation was done in humidified cabinets that have been conditioned. The granulation method used was a wet granulation method with two mixing steps so that tartaric acid and sodium bicarbonate did not react in the beginning with the presence of water at the initial granulation stage. Components of Vitamin C effervescent tablets consisted of Vitamin C, tartaric acid, sodium bicarbonate, powdered sugar, aspartame, and yellow lemon. Each tablet contained 500 mg of the Vitamin C and 20 mg aspartame as the sweetening agent. Total tablet weights were fixed at 2000 mg, where sufficient sugar powder was used as a diluent. The composition of the prepared effervescent tablets is shown in Table 1. The difference of each formula was in the ratio of NaHCO_3 :tartaric acid (1:0.6; 1:0.7; and 1:0.8). Each of these materials was sieved and weighed. Vitamin C, tartaric acid, powdered sugar, aspartame, and yellow lemon were mixed in one container and then stirred until homogeneous. Then, ethanol (95%) and water (15:1) were mixed in a spray bottle and shaken. The ethanol solution was then sprayed on the first mixture of the ingredients, to form a mass that could be clenched. The mass was then dried in the oven for 24 h at a temperature of 50°C. The dried mass was then passed by sieve number 30 to form a fine granule. Sodium bicarbonate (some only), sodium chloride, and lemon flavor were mixed and stirred until homogeneous. Then, the fine granules and sodium bicarbonate mixture were mixed with residual sodium bicarbonate, then stirred to homogeneous and molded into tablets.

Tablet Evaluation

The tablet evaluation was observed on the granule mass and the final tablet. The granules mass evaluation consisted water content determination, flow velocity and rest angle, true density, real density, and incompressible density. Whereas, the final evaluation of effervescent tablets included tablet appearance,

tablet diameter, tablet thickness, weight uniformity, hardness, friability, tablet disintegration time, and solution pH.

Water Content

The water content was determined by weighing 10 g of sample and then putting it into a desiccator containing active silica gel. Losing weight was calculated after 4 h.

Flowability and Angle of Repose

A total of 30 g of granules were placed in a funnel and then measured the granules that coming out from the flow velocity testers. The flow rate was determined by calculating the time required by the amount of powder to descend through the funnel. The resting angle was determined from the result of the granule pile that descends from the flowability tester.

True Density

The true density was determined by weighing 25 mL of the empty pycnometer, weighing the pycnometer with a non-solvent solvent, in this case, liquid paraffin, pouring 2–3 mL solvent into a clean reaction tube, weighing 1–1.5 g sample, and inserting the sample into a pycnometer containing the solvent until the pycnometer volume then weighing it. The result was reduced by the weight of the empty pycnometer.

Real Density

The real density was determined by inserting the powder or granule into the measuring cup to a limit of 100 mL. The weight of the granule was determined by weighing the granules in the measuring cup.

Tapped Density

The tapped density was determined in the same manner as in the actual density. However, the powder volume was compressed by tapping the measuring glass at a speed of one beat per second until the compressive volume was constant.

Diameter and Thickness

A total of 20 tablets from each formula were measured for its diameter and thickness using a caliper. The tablet's diameter should be no more than 3 times and not $<4/3$ of the thickness of the tablet.^[15]

Weights Variation

A total of 20 tablets from each formula were individually weighed in grams (g) on an analytical balance and then the average weight was calculated. No more than two tablets might have a weight deviation greater than 5% of the weight of the average tablet and there should be no tablets having a weight deviation of more than 10% of the average weight.^[15]

Table 1: Composition of effervescent tablets formula

Component (mg)	Formula I	Formula II	Formula III
Vitamin C	500	500	500
NaHCO_3	510	590	510
Tartaric acid	357	413	410
Sugar powder	565.2	429.2	512.2
NaCl	20	20	20
Aspartame	20	20	20
Lemon yellow	3.8	3.8	3.8
Lemon flavor	24	24	24

Hardness

A total of 10 tablets, each tablet were measured in hardness using a hardness test apparatus. The hardness of effervescent tablets is generally 70–120 N.^[15]

Friability

A total of 10 tablets were weighed and put into the friabilator. The tool operated the tool with a rotation speed of 25 rpm for 4 min. The intact tablet was weighed after it has been cleansed of the dust and debris formed during the rotation of the tool. Losing weight can still be allowed up to 0.8%.^[15]

Disintegration Time

The effervescent disintegration time is the effervescent degradation mechanism of the tablet. The effervescent time is determined by dipping one effervescent Vitamin C tablet into a beaker containing 100 mL cold water at a temperature of $20 \pm 1^\circ\text{C}$. The effervescent time was calculated by a stopwatch starting from the tablet dropped until the soluble tablet forms a clear solution without any small particles. Effervescent time usually lasts for 1–2 min.

Solution pH

Each tablet is put into 100 mL of distilled water at a temperature of $20 \pm 1^\circ\text{C}$. After the solution was clear at the end of the effervescent reaction, then the pH of the solution is measured using a pH meter.

Hedonic Test

Panel taste was performed using 30 volunteers within 20 min intervals with the numbers of 1–5; (1) very bad taste, (2) bad taste, (3) acceptable taste, (4) good taste, and (5) perfect taste. Consequently, the preferred flavoring agent was approved and then its content was determined.^[16] Each panelist was given three samples for taste and the panelist was asked to rate spontaneously based on his/her favorite level of the sample, by marking the appropriate questionnaire. After tasting one sample, the panelist must first rinse while waiting for the next sample to be presented, between samples approximately there was an interval of 2 min. The obtained data were statistically analyzed by ANOVA, where differences were considered statistically significant at $P \leq 0.05$.

RESULTS AND DISCUSSIONS

Condition of Moisture Cabinets

The result of conditioning using lamps obtained the result that there was a high-temperature rise, but the humidity decreased gradually. After 100 min, the RH value decreased to 0.06% per min. In the method of using active silica gel, heating of inactive silica gel (purple color) in the oven 110°C for 24 h to form active silica gel (dark blue in color). The obtained results

were a greater decrease in humidity after 100 min of 0.395% per min with constant temperature. The color change of active silica gel into non-active was dark blue - purple - pink - clear. In the method using a combination of light and active silica gel the obtained results were a rapid decrease in humidity after 100 min of 0.415% per min, followed by a rise in temperature that is not too high. While on the method using non-active silica gel purple (not heated first), the obtained results were a decrease in humidity that faster than using the lamp, and the decrease was 0.145% per min after 100 min. Based on the observations, it could be concluded that the most rapid conditioning method of lowering the humidity in the 0.1428 m^3 cabinet was using a combination of active silica gel and lamp. The result of moisture cabinet conditioning could be seen in Table 2.

Thus, it could be concluded that the use of moisture cabinets was by heating the silica gel in the oven 110°C for 24 h. A weight of 1 kg active silica gel was put into the drawer of the humidifier. After the lamp was turned on, all the equipment and materials could be put in the cabinet. All possible gaps were closed and allowed to achieve the RH value to 25% for at least 80 min. After reaching these conditions, then activities such as weighing materials, mixing materials, and granulation could be done. If the temperature in the cabinet was too high, the lamp could be turned off.

Effervescent Tablet Formulation Results

Effervescent tablets are faster absorbed than conventional tablets with plasma concentrations peaking after 45 min. The buffer itself does not affect the rate of absorption. While conventional tablets have a slower rate of absorption, they can only reach peak plasma concentrations after 90 min.^[15] However, the process of making effervescent tablets requires special conditions. The main problem of effervescent products is the loss of reactivity with time caused by premature reactions. Herein lies the stability of effervescent products. Hence, a formulator should consider the factors that can disrupt the effervescent product's stability. This particular condition is essential to avoid the occurrence of premature effervescent reactions caused by moisture. The presence of moisture can catalyze the reaction between NaHCO_3 and tartaric acid which produces water and CO_2 so that when the tablet is consumed, it cannot produce an effervescent reaction anymore. This can be reduced by draining all hygroscopic raw materials, conditioning the mixing area, and accelerating the compressing process. Drying of all hygroscopic raw materials is done to minimize the water content of the print mass so it is not easy to get wet and sticky. The mixing area must be strived to achieve 25% RH, one of which is by mixing the materials in the conditioned moisture cabinet. It can also reduce the water content of the

Table 2: Results of moisture cabinet conditioning

Time (min)	Lamp		Active silica gel		Combination of active silica gel and lamp		Non-active silica gel	
	RH (%)	T (°C)	RH (%)	T (°C)	RH (%)	T (°C)	RH (%)	T (°C)
0	50	26.5	67	24	65	24	56	26.5
5	49.5	27	60.5	24.75	60	24.5	55.5	26.75
10	49	27	54	24.75	54	25.25	55	27
15	48.5	27.25	48	25	49	26	55	27
20	48.5	27.5	44	25	45.5	26.5	54	27.25
25	48.5	27.75	41	25	43.5	26.5	53.5	27.25
30	47.5	27.75	39	25	40	27	52	28
35	47	28	37	25	37.5	27	51.5	28.25
40	46.5	28	35.5	25	35	27	50	28.5
45	46.5	28	34	25	33.5	27.5	49.5	28.5
50	46	28	32.5	25	31.5	27.5	49	28.5
55	46	28.25	31.5	25	30	27.5	48	29
60	46	28.25	30.5	25	29	28	47	29
65	45.5	28.25	29.5	25	28	28	46	29
70	45	28.25	28.5	25	26.5	28	45.5	29
75	45	28.25	28	25	25.5	28	45	29.25
80	44.5	28.25	27.5	25	25	28	44	29.25
85	44.5	28.5	27.5	25	25	28	43	29.5
90	44	28.5	27.5	25	24.5	28	43	29.5
95	44	29	27.5	25	24	28	42	29.5
100	44	29	27.5	25	23.5	28	41.5	29.25

granule mass and can prevent the onset of premature effervescent reactions. In addition to the humidity factor, the temperature must also be considered because Vitamin C is not stable at temperatures that are too high. Thus, it is necessary to control moisture and temperature during the process of mixing the material. Starting from the selection of materials to the treatment, conditioning the mixing area and the compressing process. Selection of raw materials is very important in making an effervescent tablet formula. The raw materials used must have low humidity. Its solubility in water is also important because if the component in the effervescent tablet is not soluble in water then the effervescent reaction will not occur and the shatter time of the tablet will be longer. Ideally, all components in the effervescent tablet should have the same dissolving speed.^[17] For binders, although soluble in water, some of binders can slow down the destruction time of effervescent tablets. Binders such as gum cellulose, gelatin, and amylum paste cannot be used because of their low solubility and high moisture content. Partially soluble citrate acid in ethanol or isopropanol can also act as a binder once the solvent is evaporated.^[15] Some lubricants can be effective at certain concentrations but at the same concentrations may also inhibit the effervescent tablets disintegration.^[17] Lubricants such as talc and magnesium stearate cannot be used because it is difficult to dissolve in water so that the effervescent tablet's disintegration time will be longer.^[18] NaCl can also be used as a lubricant. Although hygroscopic, NaCl may reinforce the taste in effervescent tablet formulas and may decrease the pH if the active ingredients used are acidic, for example, Vitamin C.

The principle of effervescent tablet granulation is essentially the same as conventional tablets. The wet granulation technique involves mixing dry ingredients with granulation fluid so as to produce a mass that can be clenched. After that sieved so that formed wet granules which then dried into dry granules that have the power of compression. In addition to the way, the mass formed can also be dried before sieving. After that mixed with other dry materials or outer phase. The mixture is then molded and dried in the oven.^[17] In addition, all the tablets were stored in airtight containers for further study.

Results of Granule Mass and Tablets Evaluation

The granule mass evaluation was performed to determine the mass characteristics before being compressed into tablets. The granule mass quality will determine the quality of the tablet. These checks include observation on moisture content, flowability and repose angles, true density, real and compressible, porosity, and compressibility. The results of the water content test on granule mass were 0.4%. This is good because it still qualifies moisture content of an effervescent preparation that is $\pm 0.5\%$, so the granules will not sticky with a punch and die on the tablet machine. The result of the granule flowability indicated that 30 g of print mass was capable of passing through the funnel for 2.9 s. While the angle of repose was 28.704 ± 0.55 degrees (without vibration) and 31.18 ± 0.705 degrees (with vibration). From those results showed that mass print had a good flow type. The density test results showed that the true density obtained was 0.0319 ± 0.0002 g/cm³ while the actual density was 0.682 ± 0.001 g/cm³, the density was 0.791 ± 0.002 g/cm³. From this data, it could be obtained a value of

porosity of tablet was 14.45% and compressibility value was 13.78%. Hence, from the results of granule mass examination, it could be stated that the granule mass met the requirements and could be compressed into tablets.

Evaluation of effervescent tablets is similar to conventional tablets that include the physical appearance of tablets, weight uniformity, thickness, diameter, hardness, friability, abrasion, disintegration time, and pH of the solution. The physical appearance of tablets is an esthetic factor that must be considered because it can affect the acceptance or absence of such preparations by consumers. The physical appearance of the prepared tablet included light yellow, smooth surface, and flat edges. The results of the average weighting of 20 tablets, obtained an average of 2.0148 ± 0.04 g, while the desired theoretical weight was 2 g. The weight uniformity requirement should not exceed two tablets which had a weight deviation $>5\%$ of the average weight and there should be no tablets having a weight deviation of more than 10% of the weight of the average.^[19] Thus, a weighting deviation which was still allowed was not <1.813 g and not more than 2.216 g. It found to be within the limit, and hence, all formulations passed the test for uniformity of weight as per official requirement.^[20] The thickness examination results obtained 4.4 ± 0.0229 mm while the examination results of the diameter obtained 20.0575 ± 0.040 mm. The results of the hardness examination were 70.825 ± 1.8 N. These results are considered good hardness and meet the effervescent ranges that generally between 70 and 120 N. Hardness is a factor that is also important because it shows the quality assurance and state of the tablet to get into the hands of the consumer in good condition. The result of friability examination was obtained 0.05% which was (that is $<1\%$) in the acceptable limit, as well as with abrasion obtained 0.05%.^[21] While the weight loss is still allowed for effervescent tablets of up to 0.8%. Thus, the results of friability and abrasion tablets that have been done still meet the range. The result of disintegration time was 63.7 ± 7.9 s. Hence, the effervescent tablets had disintegration time that satisfies an effervescent preparation of 1–2 min. The effervescence times of the all formulations were <2 min and all were in the range mentioned in British pharmacopeia.^[11] The disintegration time was controlled by the content of sodium bicarbonate present in the effervescent mixture.^[22] The results of the pH solution of the effervescent tablet had an average pH of 5.35 ± 0.16 . The pH of formulations should be within the range of 5.7 and 6.2. In another study on effervescent granules containing citric acid and sodium bicarbonate has been done, the pH of the solution was obtained by dissolving granules was measured at 5.64. It was comparable with the results in this study.^[23]

Hedonic Test Result

The results of panelist questionnaires were processed using ANOVA statistical analysis. The result of statistical analysis could be seen in Table 3.

Table 3: Statistical analysis

Source	DF	Sum	Mean	F	F 0.05
Interaction	29	4.01775			
Within	60	430.33	7.17217		
Formula	2	365.534	182.767	163.597	3.16
Error	58	64.7962	1.11718		
Total	89	434.348			

From table ANOVA above, $F_{\text{arithmetic}} > F_{\text{table}}$, then H_0 was rejected which means that there were differences in the effect of the formula on panelist preferences with the risk of error 0.05. Based on the calculations, it could be concluded that the formula III was an unlikely formula while the formulas I and II were the formulas which had the level of panelist preferences that were not significantly different. Thus, according to interval data, both were preferred formulas, but when viewed from the average interval data it could be concluded that the formula I was preferred by panelists compared to formula II. In addition, the average disintegration time of formula I was faster so that formula I was the best formula.

CONCLUSION

It can be concluded that using moisture cabinets conditioned by the combination of active silica gel and lamps; it can produce eligible effervescent tablets using simple and applicable tools for laboratory scale.

REFERENCES

- Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. *J Nutr* 2007;137:2171-84.
- Jacob RA, Sotoudeh G. Vitamin C function and status in chronic disease. *Nutr Clin Care* 2002;5:66-74.
- Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr* 1999;69:1086-107.
- Weinstein M, Babyn P, Zlotkin S. An orange a day keeps the doctor away: Scurvy in the year 2000. *Pediatrics* 2001;108:E55.
- Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press;
- Maximiano FP, Costa GH, Sa-Barreto LC, Bahia MT, Cunha F. Development of effervescent tablets containing benzimidazole complexed with cyclodextrin. *J Pharm Pharmacol* 2011;63:786-93.
- Robert LE. Amerilab Technologies, Effervescent Tablets. New York: CSC Publishing; 2002.
- Prabhakar CH, Krishna KB. A review on effervescent tablets. *Int J Pharm Technol* 2011;3:704-12.
- Kabir AK, Huda NH, Jhanker YM, Shamin K. Formulation development of verapamil hydrochloride tablet by effervescent method. *S J Pharm Sci* 2010;3:34-7.
- Wadhvani AR, Prabhu NB, Nandkarni MA, Amin PD. Consumer friendly mucolytic formulations. *Indian J Pharma Sci* 2004;7:506-7.
- Lieberman HA, Lachman L, Schwartz JB. *Pharmaceutical Dosage Forms: Tablets*. 2nd ed. New York: Marcel Dekker Inc.; p. 285-328.
- Wells ML, Wood DL, Sanftleben R, Shaw K, Hottovy J, Weber T, *et al.* Potassium carbonate as a desiccant in effervescent tablets. *Int J Pharm* 1997;152:227-35.
- Jacob S, Shirwaikar A, Nair A. Preparation and evaluation of

- fast-disintegrating effervescent tablets of glibenclamide. *Drug Dev Ind Pharm* 2009;35:321-8.
14. Rajalakshmi G, Vamsi CH, Balachandar R, Damodharan N. Formulation and evaluation of diclofenac potassium effervescent tablets. *Int J Pharm Biomed Res* 2011;2:237-43.
 15. Swarbrick J. *Encyclopedia of Pharmaceutical Technology*. 5th ed. New York: Marcel Dekker, Inc.; p. 52.
 16. Aslani A, Eatesam P. Design, formulation and physicochemical evaluation of acetaminophen effervescent tablets. *J Rep Pharma Sci* 2013;2:140-9.
 17. Mohrle R. *Effervescent Tablets. Pharmaceutical Dosage Forms*. 1st ed. New York: Marcel Dekker, Inc.; p. 285-320.
 18. Amela J, Salazar R, Cemelli J. Effervescent tablets of ascorbic acid. I. physical study of the possible components to be used. *Drug Dev Ind Pharm* 1996;22:407-16.
 19. Aslani A, Fattahi F. Formulation, characterization and physicochemical evaluation of potassium citrate effervescent tablets. *Adv Pharm Bull* 2013;3:217-25.
 20. Aslani A, Daliri A. Design, formulation and evaluation of its physicochemical properties of acetaminophen, ibuprofen and caffeine as effervescent tablet. *J Rep Pharma Sci* 2016;5:122-34.
 21. Patel AA, Parikh RH, Mehta TA. Development optimization and evaluation of effervescent tablets of chlorpheniramine maleate using box behnken design. *Int J Pharm Pharm Sci* 2015;7:317-23.
 22. Cunha-Filho MS, Gustmann PC, Garcia FS, Lima EM, Sá-Barreto LC. Development and physical evaluation of *Maytenus ilicifolia* effervescent granules using factorial design. *Braz J Pharm Sci* 2014;50:244-6.
 23. 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