

Formulation, Characterization and Physicochemical Evaluation of Potassium Citrate Effervescent Tablets

Abolfazl Aslani*, Fatemeh Fattahi

Department of Pharmaceutics, School of Pharmacy and Novel Drug Delivery Systems Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

ARTICLE INFO

Article Type:

Research Article

Article History:

Received: 7 November 2012

Revised: 18 November 2012

Accepted: 22 December 2012

ePublished: 7 February 2013

Keywords:

Effervescent tablets

Potassium citrate

Direct compression method

Fusion method

Wet granulation method

ABSTRACT

Purpose: The aim of this study was to design and formulation of potassium citrate effervescent tablet for reduction of calcium oxalate and urate kidney stones in patients suffering from kidney stones. **Methods:** In this study, 13 formulations were prepared from potassium citrate and effervescent base in different concentration. The flowability of powders and granules was studied. Then effervescent tablets were prepared by direct compression, fusion and wet granulation methods. The prepared tablets were evaluated for hardness, friability, effervescent time, pH, content uniformity. To amend taste of formulations, different flavoring agents were used and then panel test was done by using Latin Square method by 30 volunteers. **Results:** Formulations obtained from direct compression and fusion methods had good flow but low hardness. Wet granulation improves flowability and other physicochemical properties such as acceptable hardness, effervescence time ≤ 3 minutes, $\text{pH} < 6$, friability $< 1\%$, water percentage $< 0.5\%$ and accurate content uniformity. In panel test, both of combination flavors; (orange - lemon) and (strawberry - raspberry) had good acceptability. **Conclusion:** The prepared tablets by wet granulation method using PVP solution had more tablet hardness. It is a reproducible process and suitable to produce granules that are compressed into effervescent tablets due to larger agglomerates.

Introduction

Effervescent tablets were designed to produce solutions that release carbon dioxide simultaneously. Usually, these tablets are prepared by compressing the active ingredients with mixture of sodium bicarbonate and organic acids such as citric and tartaric acid.¹

Generally, these tablets are included drugs that are solved rapidly when entered to water and they are recommended as a clear and palatable solution.² So, they can be prescribed to patients who suffered from swallow capsules or tablets.³ The main advantages of effervescent tablets are quick production of solution. Thus, it is faster and better to absorb.⁴

As a source of acid, citric acid is the most used acid. Also other acids such as tartaric, fumaric, adipic, malic acid and anhydrides and salts of acid can be used. Potassium and sodium carbonate, sodium and potassium bicarbonate, arginine carbonate are used as a sources of alkali. Sodium bicarbonate is one of the most used carbonate because of high solubility, severe reaction and low cost.⁵ So, excipients such as water soluble lubricants (e.g. PEG 4000, 6000 and sodium benzoate), sweeteners, flavorings and water-soluble colors are applied.⁵

Polyvinylpyrrolidone (PVP) is an effective binder of effervescent tablets. It can be added as dry powder or in

a wet form as an aqueous or hydroalcoholic solution. Mannitol, PEG 6000 and water in small amounts can be used as effective binder.^{5,6}

Low relative humidity (maximum of 25% or less) and moderate to cool temperatures (about 25 °C or 77 °F) in the environment are essential to prevent sticking granule or tablets to tablet press machine.⁵

In producing direct compression method, the mixtures of powder with excellent flowability, and without particles segregation are needed and particle size of all raw materials should be equal. It is necessary to prepare granules, if particle size is small.^{3,7}

In fusion method, mostly monohydrate citric acid, released its water at 54 °C in order to obtain the granules by agglomeration of the particles. Granulation with nonreactive solution contain of ethanol or isopropanol, that the most components of tablets are insoluble in them. So, a very small amount of water (0.1-0.5%) is active solution.⁵

Effervescent tablets are produced and controlled same as conventional tablets. These controls are included physicochemical properties such as hardness, weight variation, friability, solution time, pH and content uniformity.⁵

*Corresponding author: Abolfazl Aslani, Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98(311)7922617, Fax: +98(311)6680011, Email: aslani@pharm.mui.ac.ir

Potassium citrate is very soluble in water and almost insoluble in alcohol with very salty taste. Each g of potassium citrate (monohydrate) consists of about 9.3 mmol of potassium and 3.08 mmol of citrate.⁸

Potassium citrate is used to replace sodium bicarbonate in the treatment of metabolic acidosis in patients, alkalizing agent of urine and symptomatic relief of mild urinary tract infections. Studies were shown that it is effective in reduction of calcium oxalate and urate kidney stones formation and prevent from bone loss.⁹⁻¹² So, studies are shown that oral supplements of potassium prevents hyperkalaemia from it due to the high absorption from the gastrointestinal tract but slowly.¹²

Products of potassium citrate are available in pharmaceutical world market in the forms of: tablet (5, 10, and 15 mEq potassium citrate, Urocit®-K), effervescent powder (1500 mg equivalent to 13 mEq potassium citrate, Effercitrate®) and oral solution.⁸ Although the mentioned dosage form are available in the pharmaceutical market, none of them are held accountable for patient requirement, because high doses of drug are needed for patients with calcium and urate kidney stones.

These patients are using the drug into two forms: 1) a pharmaceutical dosage form with a low dose and high frequency consumption or 2) the bulk of the raw materials. Until now in the pharmaceutical market, this potassium citrate effervescent tablet with 25 meq does not exist. It is a new and applications design.

The aim of this study is design, formulation and preparation of the potassium citrate effervescent tablets containing 25 mEq monohydrate potassium citrate. These tablets will help to physicians prescribing and

convenience consumption for patients suffering from calcium oxalate and urate kidney stones.

Materials and Methods

Material

Potassium citrate (monohydrate), sodium bicarbonate, citric acid (monohydrate), tartaric acid, PEG 6000, sodium benzoate, mannitol, sorbitol and aspartame were procured by Merck (Darmstadt, Germany). Povidon k-30 (PVP) was purchased from Rahavard Tamin (Tehran, Iran). Orange flavoring agent was procured from Kagawa (China) and raspberry, strawberry, cherry and lemon flavoring agents were prepared by Farabi pharmaceutical Company, (Isfahan, Iran).

Preformulation

Firstly, the formulas were made up in the different stoichiometric ratios from tartaric acid, citric acid and sodium bicarbonate based on below reactions. According to Table 1, materials of each formulation were weighed and then 2700 mg of monohydrate potassium citrate was added to each formulation. Finally, after preparation of appropriate mixture, the lubricants including 30 mg of PEG 6000 and 10 mg of sodium benzoate were added the mixture and then the tablets compressed by using a single-punch press machine (KILIAN & CO, Germany). For next stages, the better stoichiometric ratios were selected with regard to three factors: solubility, effervescence time and pH.



Table 1. Composition of preliminary formulations (ratio) with their effervescence time, pH and solubility (Mean \pm SD).

Formulations	Tartaric acid	Citric acid	Na bicarbonate	Effervescent time(s)	pH	*Solubility
S ₁	-	0.5	0.5	105 \pm 2.08	5.9 \pm 0.05	3
S ₂	-	0.5	1	40 \pm 1.52	6.2 \pm 0.1	3
S ₃	1	0.5	1	39 \pm 1.51	6.1 \pm 0.04	1
S ₄	0.5	1	1	36 \pm 2	6.1 \pm 0.05	2
S ₅	-	1	1	50 \pm 2.13	5.9 \pm 0.06	5
S ₆	1	1	1	48 \pm 2.01	6.1 \pm 0.06	2
S ₇	1.5	0.5	1	52 \pm 1.8	6.1 \pm 0.1	2
S ₈	2	0	1	55 \pm 1.83	6.1 \pm 0.08	1
S ₉	-	1	1.5	43 \pm 1.51	6.1 \pm 0.7	4
S ₁₀	-	1	0.5	30 \pm 3.11	5.6 \pm 0.4	4
S ₁₁	-	1.5	1.5	25 \pm 2.13	5.6 \pm 0.05	5
S ₁₂	-	1.5	1	49 \pm 1	5.6 \pm 0.04	4
S ₁₃	-	2	2	20 \pm 2.07	5.5 \pm 0.06	4

*Solubility was defined by Likert Scale from 1= very poor, 2 = poor, 3 = average, 4 = good and 5 = excellent

Methods of Potassium Citrate Effervescent Tablets Production

Direct Compression

According to Table 2, raw materials of each formulation were weighed and were mixed in a tumbling cubic blender for 15 minutes.

After the preparation of the primary powder mixtures, sweeteners including aspartame, sorbitol, mannitol and fruit flavoring agents were passed through the appropriate mesh and were added to the powders and these were mixed altogether for 5 minutes. Finally, the selective lubricants including sodium benzoate (10 mg) and PEG 6000 (30 mg) were added and again mixed for about 2-5 minutes with other material.

Then, the powders were compressed into tablets by using a single-punch press machine (KILIAN & CO, Germany), with 25 mm punch set. Weight of each tablet was considered about 4.5 g. At the end, the tablets were dried in an oven with air circulation at 54°C for 1 hr and after cooling were packed in plastic tubes.

Table 2. Different components of prepared tablets from the direct compression (D) and fusion (f) methods.

Ingredients (mg)	Formulations					
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
K citrate	2700	2700	2700	2700	2700	2700
Citric acid	570	850	850	850	850	850
Na bicarbonate	500	750	750	750	750	750
Mannitol	-	-	60	120	-	60
Sorbitol	-	-	-	-	60	-
Aspartame	-	-	-	-	-	1.5

Fusion Method

According to the formulations which are shown in Table 2, amounts of citric acid, sodium bicarbonate, potassium citrate and mannitol (sorbitol) were weighted accurately and were mixed for about 15 minutes in a tumbling cubic blender. Then, the obtained mixture was placed in an oven at 54 °C. The powder was mixed regularly until the crystallization water of citric acid was released as binder factor (approximately 30 minutes). After obtaining an appropriate pasty mass, this wet mass was passed through sieve No. 20 and the obtained granules were dried in an oven at 54 °C for 1 hr. After drying, for second times the granules were passed through sieve No. 20.

In the next stage, sweeteners and flavors were added with the granule mass and mixed for 5 minutes with other material.

At last, the lubricants including sodium benzoate (10 mg) and polyethylene glycol 6000 (30 mg) were added and mixed for 2-5 minutes with other material. The granule mixtures compressed into tablets by a single-

punch press machine (KILIAN & CO, Germany), with 25 mm punch set. Finally, they were dried and packed with the previous methods.

Wet granulation Method

Wet granulation was performed on F₅ and F₆ formulations. First, citric acid and sodium bicarbonate and potassium citrate were milled by using miller so that all powders were passed through sieve No. 35 and were blended for 10 minutes. Then 9.5 % w/v PVP solution in absolute ethanol was added with the mixture, so that white pasty mass was formed. This wet mass was passed through sieve No. 20 and the granules were dried in an oven at 54 °C for 75 minutes. So, the dried mass was passed through sieve No. 20 and the other ingredients were added to them like as fusion method. The granule mixtures were compressed into tablets by using a single-punch press machine (KILIAN & CO, Germany), with 25 mm punch set. Prepared tablets were dried in an oven with air circulation at 54 °C for 90 minutes, then were wrapped in Aluminum foil and were packaged in plastic tubes.

Precompression Tests

Particle Size Analysis

The average particle size of powder mixture was determined by sieve analysis method. 100 grams of powder mixtures and granules poured on the upper sieve. Series of sieve were placed on ERWEKA shaking apparatus for 10 minutes after this period; the amount remaining on each sieve was measured.¹³

The mean diameter of the powders was calculated by equation (1).

$$d = \sum \frac{x_i d_i}{100} \quad \text{Eq.1}$$

x_i = The average size of both upper and lower sieve

d_i = The percentage of the amount of i in limited area by two sieves.

Flowability

For evaluation of powder flow, the angle of repose, compressibility index and Hausner's ratio can be used.

Angle of Repose (α): The powder or granule mass was passed from the funnel. Angle of repose was determined by equation 2.

The average of three measurements was interpreted according to USP NF. 2008.¹⁴

$$\tan(\alpha) = \frac{\text{Height}}{0.5 \text{ Base}} \quad \text{Eq. 2}$$

Height: The height of the formed cone

Base: Diameter of the formed cone

Compressibility Index and Hausner's Ratio: For measurement of bulk density, 100 grams of powders and granules was poured into the graduated cylinder (250 ml) using a glass funnel and its volume is recorded.

$$\rho_{\text{bulk}} = \frac{m}{V_{\text{bulk}}} \quad \text{Eq. 3}$$

Tapping to cylinder containing the powder continued until no further volume changes occur. Tapped density is obtained from the following equation.

$$\rho_{\text{tapped}} = \frac{m}{V_{\text{tapped}}} \quad \text{Eq. 4}$$

Compressibility Index and Hausner's ratio parameters obtained by using the mean of three measurements from ρ_{bulk} and ρ_{tapped} and were compared according to the USP NF.2008.¹⁴

$$\text{Compressibility Index} = 100 \times \left[\frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \right] \quad \text{Eq. 5}$$

$$\text{Hausner's Ratio} = \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \quad \text{Eq. 6}$$

Post compression Tests

Measurement of Tablet Hardness

Hardness of tablets was determined according to the USP for 10 tablets of each formulation by using a hardness tester (Erweka, 24-TB, Germany).

Hardness of effervescent tablets is usually lower than conventional tablets and minimum of acceptable hardness of uncoated tablets is 40 N approximately.¹

Measurement of Tablet Thickness

The thickness of 10 tablets from each formulation was determined by using calibrated collies. Average fluctuations of thickness, should not exceed more than 5 % of its normal limits.¹

Friability

20 tablets of each formulation was taken randomly and after weighting altogether, were placed in the friabilator chamber (Erweka, TAP, Germany) for 4 minutes at 25 rpm. If weight loss is greater than 1% is unacceptable.¹

Evaluation of Weight Variation

20 tablets of each formulation were weighed individually and the mean of weight were determined. According to the USP for tablets with weight more than 324 mg, among 20 tablets; just two tablets can be out of the 5% of the average weight and none deviated by more than twice that percentage.¹⁴

Measurement of Effervescence Time

A single tablet was placed in a beaker containing 200 ml of purified water at $20 \pm 1 \text{ }^\circ\text{C}$. Whenever a clear solution without particles was obtained effervescence time has finished.¹⁵

The mean of three measurements of each formulation was reported.

Determination of Effervescent Solution pH

pH solution was determined with one tablet in 200 ml of purified water at $20 \pm 1 \text{ }^\circ\text{C}$ by using pH meter (Metrohm, 632, Switzerland), immediately after completing the dissolution time.¹⁵ This experiment was repeated 3 times for each formulation.

Measurement of CO₂ Content

One effervescent tablet solved in 100 ml of 1N sulfuric acid solution and weight changes were determined after

dissolution end. The obtained weight difference was shown the amount (mg) of CO₂ per tablet. The CO₂ content reports are averages of 3 determinations.¹⁵

Evaluation of the Water Content

10 tablets of each formulation were dried in a desiccator containing of activated silica gel for 4 hours. Water content of 0.5% or less is acceptable.¹⁵

Assay

The first, 3 effervescent tablets of potassium citrate was triturated and 347 mg of crushed powder (Equivalent to 200 mg of anhydrous potassium citrate) accurately weighed and was dissolved in 25 ml of acetic acid glacial. Added 2 drops of crystal violet TS solution and titrated with 0.1N perchloric acid VS (USP) to a green end point. The same steps was done on a blank solution prepared from effervescent tablets of potassium citrate without active ingredient and was made any necessary correction. In the titration, the prepared blank was consumed perchloric acid and corrected volumes were required. Each ml of 0.1N perchloric acid is equivalent to 10.21 mg of anhydrous potassium citrate.¹⁴ 2700 mg of hydrated potassium citrate is equivalent to 2550.194 anhydrous potassium citrate. Of course, in this assay other alternative methods such as atomic absorption can also be used.

$$N \times V(\text{corrected by blank}) = \frac{\text{mg}}{108.14} \quad \text{Eq.7}$$

N: Normality of standardized acid by potassium biphthalate according to USP

mg: milligram of hydrated potassium citrate

108.14: Eq of hydrated potassium citrate

Evaluation of Content Uniformity

10 tablets of each formulation were selected at random to measurement of the active ingredient amount. None of the tablets should not be out of range (90-110 %) of mention amounts in formula, and coefficient of variation (CV) should not be more than 6. If only one tablet was out of previous range and range of 80 – 120 %, 20 tablets must be tested. Among these 20 tablets, anything of them should not be out of range 90-110 percent.¹⁴

Determination of the Equilibrium Moisture Content

Three desiccators were prepared containing saturated salt solutions of potassium nitrate (for creation 90% RH, at 18 °C), sodium chloride (for creation 71% RH, at 18 °C) and sodium nitrite (for creation 60% RH, at 18 °C). Three tablets of each formulation were placed in desiccators. Then, the equilibrium moisture content was determined by Karl Fischer method and the autotitrator device (Mettler, TOLEDO-DL53, Switzerland) in the first day and after 7 day.¹⁴

Evaluation of Prepared Tablets Taste

Before beginning the evaluation, the taste ability of volunteers was measured by four base tastes (salt,

sweet, sour, bitter) by 20 ml of 0.2% sodium chloride, 2% sucrose, 0.07% citric acid, and 0.07% caffeine in water respectively.¹⁶

To evaluate the taste, panel tests were performed by Latin Square method. The first, with the help of 5 volunteers, 7 flavors which were added to F₆ formulation (optimum formulation), were examined (Table 3). Thus, the volunteers were asked to score each of the formulation from 1 = very bad, 2 = bad, 3 = no taste, 4 = good and 5 = excellent taste based on Likert Scale.

At next stage, another 30 volunteers were asked to give points to the 2 selected flavors of early stages from 1 = very bad, 2 = bad, 3 = no taste, 4 = good and 5 = excellent taste based on Likert Scale.

Table 3. Different flavors were used for panel test of potassium citrate effervescent tablets.

Code	Flavoring agent	Amount (mg)
A	Raspberry	4.4
B	Strawberry	4.4
C	Cherry	4.4
D	Orange	4.4
E	Lemon	8.8
F	Orange & Lemon	4.4 & 8.8
G	Raspberry & strawberry	4.4 & 4.4

In all time of experiments, the standard conditions of panel test were considered such as temperature equal to 21°C, 20 minutes distance from the previous samples, samples with similar concentrations of drugs and have been done without exchanging the volunteers' idea.¹⁶

Results

Results of preformulation study is shown that formulations with stoichiometric ratios 1:1 and 1.5:1.5 (S₅, S₁₁) were selected as the appropriate base formulations in tableting process, and with better physicochemical characteristics.

Results from characterization of the powder formulations containing of the particle size distribution, angle of repose, compressibility index and Hausner's ratio are given in the Tables 4, 5 and Figure 1.

The results of obtained from tablets evaluation are presented for hardness, friability, tablet thickness, effervescence time, pH, weight variation, water and CO₂ content, content uniformity and equilibrium moisture content properties are given in the Tables 5,6,8, too.

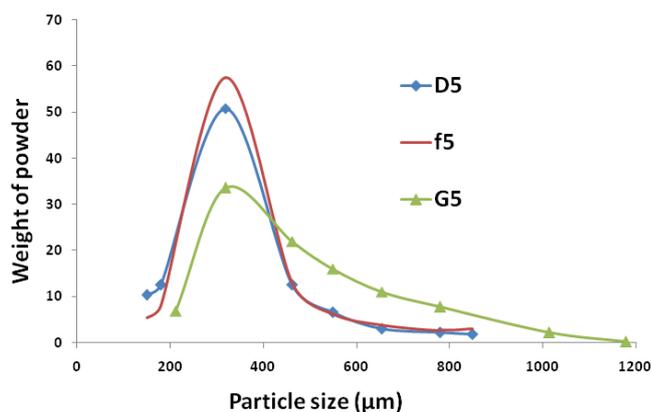
The particle size distribution of three manufacturing methods is listed in Tables 4 and 5. The mean diameters of granules were greater than the powders. Figure 1 shows the particle size distribution diagram of F₅ formulation which has normal distribution.

Table 4. The mean diameter, particle size distribution and percentage on each sieve of the obtained formulations from direct compression (D) and fusion (f) methods.

Formulations	Sieve number								Mean diameter(μ)
	<20	20-25	25-30	30-35	35-40	40-70	70-100	>100	
D ₁	1.69	1.46	5.64	5.29	1.62	47.9	16.13	20.28	311.42
f ₁	2.59	3.08	8.06	5.74	1.25	48.41	12.73	18.15	340.63
D ₂	1.9	2.73	6.62	6.66	1.28	45.42	16.1	19.29	326.08
f ₂	2.33	2.17	6.57	6.62	1.44	67.74	7.08	6.05	360.47
D ₃	1.52	2.01	4.59	5.67	1.17	48.04	13.63	23.38	307.95
f ₃	3.05	3.47	7.69	7.91	1.92	55.45	12.41	8.09	367.03
D ₄	1.8	2.09	5.25	4.52	1.6	44.47	13.85	26.42	304.59
f ₄	7.02	4.31	7.39	6.64	0.62	51.63	8.76	13.62	381.84
D ₅	1.84	2.24	3.06	6.56	12.55	50.86	12.51	10.38	347.48
f ₅	3.02	2.74	3.9	6.26	12.94	57.55	8.08	5.51	373.05
D ₆	1.41	2.06	4.5	4.43	1.77	44.66	16.36	24.82	299.12
f ₆	8.53	3.07	6.33	5.04	0.75	44.93	13.36	17.98	363.39

Table 5. Particle size distribution, mean diameter and flowability of obtained granules in wet granulation method together with tablets characteristics for G₅ and G₆ formulations.

Formulations	-	G ₅	G ₆
Sieve number	<16	0.28	0.04
	16-20	2.26	2.68
	20-25	7.73	21.17
	25-30	11.09	33
	30-35	16.08	6.74
	35-40	22	0.51
	40-70	33.66	30.33
	>70	6.9	5.52
	Mean diameter (μ)	471.2	556.71
Flow Properties	Hausner's ratio	1.06±0.01	1.08±0.02
	Compressibility index	5.73±0.66	7.6±2.14
	Angle of repose	15.076±0.12	14.713±0.59
Tablets characteristics	Weight variation	4.401 ± 0.113	4.416 ± 0.063
	Hardness	78.85 ± 2.26	65.05 ± 2.72
	Content uniformity, (%CV)	2744 ± 97.5 (3.55)	2742 ± 54.9 (2.0)
	Water content	0.0405 ± 0.01	0.0096 ± 0.005
	Tablet thickness	5.97 ± 0.06	6.048 ± 0.06
	Effervescence time(s)	132 ± 2	112.7 ± 2.52
	pH solution	5.8 ± 0.02	5.8 ± 0.02
	CO ₂ content	313 ± 13	423 ± 16
	Assay (mg)	2700 ± 40	2720 ± 20
	Friability (%)	0.973±0.02	0.936±0.05

**Figure 1.** Particle size distribution diagram of F₅ in direct compression (D), fusion (f) and wet granulation (G) methods

According to the results in Table 7, PVP 0.5 % (w/w) and sieve No. 20 were chosen considering hardness and effervescence time.

Range of hardness in obtained formulations of direct compression method (D) was varied from 15 N to 22 N and obtained granules from the fusion method (f) were shown a slight increase from 20 - 25 N (Table 6). Produced tablets were evaluated by hardness, weight variation, tablet thickness, friability, effervescent time, pH, content uniformity, water and CO₂ content. These values are reported in Table 5. In Table 5, hardness was shown threefold increase in wet granulation method. In this study, at 60 % RH and 18°C, the variation in percentage of equilibrium moisture content after 7 days was nothing, but, at 90 % RH and 18°C, it was most. For correcting the potassium citrate effervescent tablet tastes, in the first stage, volunteers selected orange – lemon and strawberry - raspberry flavors. Figure 2 is shown means of obtained results from the 30 volunteers in the panel test by Latin Square method. Both of desirable flavors had good acceptability.

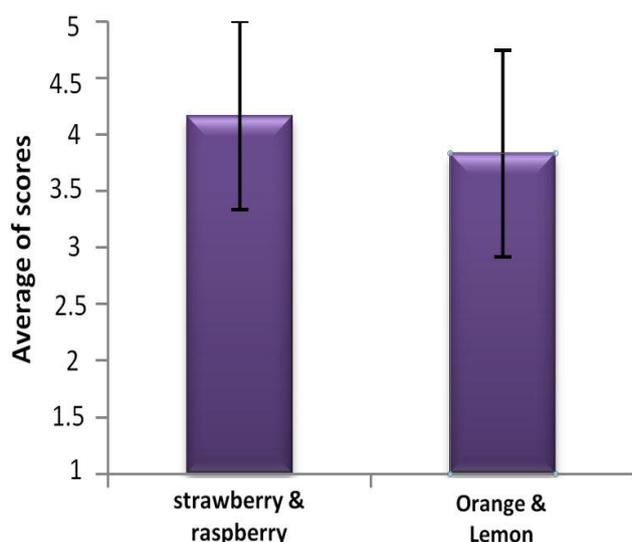


Figure 2. Evaluation of prepared tablets taste by Latin Square method.

Discussion

The pharmaceuticals which are suitable for formulation of the effervescent tablets should have specific particulars such as quick absorption of drug, good dissolution in water and high dose.¹⁷ These particulars were existed in potassium citrate.

Potassium citrate recommended for the people who suffer from urate and calcium kidney stones. One study which was done on 500 patients with recurrent kidney stones showed potassium citrate have been reduced the prevalence of kidney stones from two stone to half stone in a year.⁸ Also, these patients need to consume large amount of water daily, thus, solution of effervescent tablet in the water could remove this need. Currently, patients are taking potassium citrate into form of raw material powder. This kind of usage is not desirable for flavor and is not the exact for the consumption dosage. Therefore, the main objective of this study is design and formulation of potassium citrate effervescent tablets which have good taste and also have certain dosage. The main uses of these tablets are reduction of calcium oxalate and urate stones in patients with kidney stones.

Table 6. Flowability properties and hardness of tablets obtained from direct compression (D) and fusion (f) methods (Mean \pm SD).

Flowability properties	Formulations					
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
Angle of repose (D)	27.42 \pm 1.06	29.9 \pm 0.75	26.7 \pm 0.02	26.06 \pm 0.85	27.05 \pm 0.0	26.38 \pm 1.37
Angle of repose (f)	24.03 \pm 1.17	25.17 \pm 1.13	24.48 \pm 1.33	24.12 \pm 1.73	26.06 \pm 0.99	24.9 \pm 1.76
Hausner's ratio(D)	1.103 \pm 0.06	1.142 \pm 0.0	1.099 \pm 0.01	1.087 \pm 0.01	1.13 \pm 0.01	1.12 \pm 0.0
Hausner's ratio (f)	1.083 \pm 0.01	1.095 \pm 0.01	1.073 \pm 0.01	1.066 \pm 0.0	1.083 \pm 0.01	1.08 \pm 0.01
Compressibility index (D)	9.33 \pm 1.94	12.48 \pm 0.64	9.08 \pm 1.33	7.99 \pm 0.66	11.50 \pm 1.02	11.07 \pm 0.65
Compressibility index (f)	8 \pm 0.78	8.75 \pm 1.26	6.813 \pm 0.75	6.2 \pm 0.62	7.677 \pm 0.7	7.437 \pm 0.64
Hardness (Newton) (D)	15 \pm 2.34	17 \pm 3.54	17 \pm 3.96	17.5 \pm 5.11	22 \pm 4.26	17.5 \pm 5.16
Hardness (Newton) (f)	20 \pm 4.81	20 \pm 5.21	20 \pm 2.85	23 \pm 3.49	25 \pm 6.53	22 \pm 4.73

Table 7. Relationships between (%PVP /tablet, Sieve No) and (hardness, effervescence time) in formulation G₆ (Mean \pm SD).

Independent properties		Dependent properties	
PVP (% W/W) /tablet	Sieve No.	Hardness (N)	Effervescence time (s)
0.34	20	52.9 \pm 6.5	125 \pm 1.11
0.36	20	55.5 \pm 4.81	138 \pm 1.52
0.43	40	68.25 \pm 5.49	180 \pm 1.83
0.43	20	68.75 \pm 3.51	162 \pm 1.74
0.45	16&20	53.5 \pm 4.16	140 \pm 2.21
0.45	20&25	36.66 \pm 2.32	130 \pm 1
0.5	20	66.75 \pm 2.12	170 \pm 2.03
0.67	16&20	112.4 \pm 3.95	187 \pm 0.57
1	20	90.83 \pm 4.45	240 \pm 1.51

Table 8. Equilibrium Moisture Content (%) in the G₅ and G₆ effervescent tablets (Mean ± SD).

Microclimates	G ₅			G ₆		
	1st Day	7th Day	Variation	1st Day	7th Day	Variation
60% RH, 18°C	11.31±0.96	11.42±0.77	0.10	10.02±0.46	10.13±0.74	0.11
71% RH, 18°C	11.81±0.47	14.86±0.51	3.05	10.64±0.84	13.51±1.43	2.88
90% RH, 18°C	12.09±1.1	22.39±0.96	10.30	11.28±0.61	14.44±0.82	3.15

Ratios of effervescent components in the formulations of S₅ and S₁₁ were led to better solubility, pH less than 6, and an appropriate effervescent reaction. In the next steps, this stoichiometric ratios were used for the preparation of effervescent tablets (Table 1). In comparison of formulations containing tartaric acid, this result was obtained: tartaric acid should remove from the formulations because of low solubility and much precipitation.

The mean diameter of particles in the wet granulation method is larger than the average diameter of the particles in the two other methods due to the adhesion of smaller particles and formation of larger particles (Tables 4 and 5).

Accordingly to Figure 1, diagram peak of f₅ is drawn upward and is drawn to the right for G₅ which is representative of particle size increase in granulation.

Angle of repose is lessened in the produced granules due to shape changing into sphere and contact level deduction.

As results showed, angle of repose reduced in fusion and wet granulation methods. For example, angles of repose of D₆, f₆, G₆ (the same formulations, but different manufacturing methods) report: 26.38, 24.496 and 14.713, respectively (Tables 5 and 6). Hausner's ratio and compressibility index are reduced in fusion and wet granulation methods. Granulation (fusion or wet) increases flowability and decreases angle of repose due to increasing of particle size and shape changing into sphere, but these changes are higher in the wet granulation. In other study, the results were extracted similar to our results.¹⁸

Tablets' hardness of D₅, f₅ and G₅ (the same formulations but different manufacturing methods) were 22, 25, and 78.85 respectively. Wet granulation improves hardness of tablet due to internal porosity granules and the plastic deformation.¹⁸ Also, for hardness increasing, the dry forms of binder such as mannitol, sorbitol and PVP were used, but, the desired results were not found. Then wet granulation method using PVP was performed on the best formulations (G₅ and G₆). These formulations were better because of flowability and they had not capping and sticking in the manufacturing process. Increasing PVP percentage was found to enhance the hardness and effervescence time (Table 7). In the other study was shown that wet granulation technique could improve compressibility and flowability properties and hardness that the results were in agreement with this study.¹⁵

Thickness of the tablets must be between 6.1 ± 0.3 mm, that the results are acceptable regarding to pharmacopoeia standards (USP NF.2008).

According to the USP, in the tablets which their weight are more than 324 mg, among 20 tablets, just 2 tablets can be exceed from $\pm 5\%$ of the weight average (for G₅ ± 221.14 and for G₆ ± 221.21) that the result are acceptable.¹⁴

pH less than 6 is necessary to increase the absorption of effervescent tablets, that pH of two optimum formulations is less than 6. The equal pHs in different samples of one formulation indicate that granule mixtures are uniform. In other study on effervescent granules containing citric acid and sodium bicarbonate has been done, solution pH which is obtained from dissolving granules was measured at 5.64. It is comparable with the results in this study.¹⁵

Effervescence time of tablet must be less than 3 minutes that the results are indicated this subject.¹⁵

In the studied formulations, CO₂ contents of G₅ and G₆ were 313 and 423 mg, respectively. One study has been shown that amount of carbon dioxide in 2.5 g effervescent tablets containing of aspirin (prepared by direct compression method) were measured at 242 mg¹⁹ and other study reported that in each grams of formulas containing of citric acid and sodium bicarbonate CO₂ content was 292 mg which is comparable with the results.¹⁵ In the formulation G₅, lower level of CO₂ was obtained. In this formulation, sorbitol exists which is a hygroscopic matter. Absorbed moisture by sorbitol causes beginning of an effervescent reaction in the small scale.

As Table 5 shows, the friability of tablets was satisfactory, attributed by the acceptable hardness.

In the formulation G₅ and G₆, water content was gained 0.0405 and 0.0096, respectively. Reason of higher water content in formulation G₅ is the presence of sorbitol and the absorption of moisture. The prepared tablets by the wet granulation have very low water content due to getting temperate during drying process. Effervescent materials are hygroscopic highly and they are susceptible for degradation by air humidity. Of course potassium citrate is a hygroscopic substance since potassium citrate effervescent tablets are containing large amounts of active ingredient; much ability will have to absorb moisture. Consequently, possibility of effervescent reaction beginning and instability is high in these tablets. So it is necessary to determined that the provided tablets are stable up to

what moisture percent. At 60 % RH and 18°C, the variation in percentage of equilibrium moisture content after 7 days was alittle, thus, the granules ready to be compressed into tablets aren't hygroscopic mostly up to 60 % RH at 18°C. Also G₅ formulation equilibrium moisture content after 7 days showed more variation because the presence of sorbitol that is a hygroscopic substance.

Since, the amount of active ingredient (hydrated potassium citrate) can fluctuate in ranges from 2430 to 2970 mg and coefficient of variation percents (CV %) were not upper than 6%, content uniformity of G₅ and G₆ were in the acceptable range and the prepared tablets have USP standard about amount of active ingredient and the content uniformity.

As depicted in Figure 2, volunteer gave more scores to both the combination flavor of orange-lemon and raspberry-strawberry. Strawberry-raspberry flavors took more scores compare to orange-lemon but closed results showed, selection of flavor is depending on individual relish.

Conclusion

In this work, it was tried to produce potassium citrate effervescent tablets by using direct compression, fusion and wet granulation techniques. The results of this study show that wet granulation is a suitable method to produce effervescent tablets of potassium citrate due to the large size of these tablets in the pharmaceutical industry. Wet granulation is one of the most common methods used for granulation in the industry. This method is obtained by adding a solution with (or without) adhesive to the powder to form a wet mass. In this study, the prepared tablets were acceptable under the terms of pharmacopoeia standards only when PVP was added as a binder during the granulation process.

Due to particle adhesion, the prepared tablets through wet granulation technique had better compression and uniformity. They had not processing problems such as sticking, capping, and friction.

Among the studied formulations, only the formulation G₆ was desirable for all physiochemical characteristics, including effervescent time under 3 minutes or less, pH <6, friability under 1 percentage, the water content below 0.5 percentage, low weight variation, and correct content uniformity. Finally, its taste was also amended by adding strawberry - raspberry flavor.

These tablets will help to convenience consumption of potassium citrate and more acceptances of patients who are affected by urate and calcium kidney stones.

Conflict of Interest

The authors report no conflicts of interest in this work.

References

1. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Philadelphia: lea and febiger; 1986.
2. Allen LV, Popovich NG, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery

systems. 8th ed. Philladelphia: Lippincott Williams & Wilkins; 2010.

3. Swarbrick J, Boylan JC. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker; 2002.
4. Altomare E, Vendemiale G, Benvenuti C, Andreatta P. Bioavailability of a new effervescent tablet of ibuprofen in healthy volunteers. *Eur J Clin Pharmacol* 1997;52(6):505-6.
5. Monrle R. Effervescent tablet in: Liberman HA, Lachman I, Schwartz J. Pharmaceutical dosage form: tablets, 2nd ed. New York: Marcel Dekker Inc; 1980.
6. Callhan JC, Cleary GW, Elafant M, Kaplan G, Kensler T, Nash RA. Equilibrium Moisture Content of Pharmaceutical Excipients. *Drug Dev Ind Pharm* 1982 8(2):355-69.
7. Saleh SI, Boymond C, Stamm A. Preparation of direct compressible effervescent components: spray- dried sodium bicarbonate. *Int J pharmaceut* 1988; 45(1-2):19-26.
8. Sweetman SC. Martindle: The complete drug reference, 35th ed. London: pharmaceutical press; 2007.
9. Tekin A, Tekgul S, Atsu N, Bakkaloglu M, Kendi S. Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol* 2002;168(6):2572-4.
10. Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int* 1986;30(3):422-8.
11. Pak CY, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. *J Urol* 2002;168(1):31-4.
12. McEvoy GK. AHFS Drug information. Bethesda, MD: American society of health-system pharmacists; 2005.
13. Aulton ME. The science of dosage form design. 2nd ed. New York: Churchill living stone; 2002.
14. United States Pharmacopeia 31/National Formulary 26. Rockville MD USA: United States Pharmacopeial Convention; 2008.
15. Yanze FM, Duru C, Jacob M. A process to produce effervescent tablets: Fluidized bed dryer melt granulation. *Drug Dev Ind Pharm* 2000;26(11):1167-76.
16. Brich GG, Green LF, Coulson CB. Sweetness and sweetners. London: Applied science publisher LTD; 1981.
17. Prabhakar CH, Krishna KB. A review on effervescent tablet. *Int J Pharm Technol* 2011; 3(1): 704-12.
18. Agrawal R, Naveen Y. Pharmaceutical processing – A review on wet granulation technology. *Int J Pharm Front Res* 2011; 1(1): 65-83.
19. Amela J, Salazar R, Cemeli J. Methods for the determination of the carbon dioxide released from effervescent pharmaceuticals. *J pharm bely* 2000; 55(2): 53-6.