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Design, Formulation and Evaluation of Physicochemical Properties of Valacyclovir Effervescent Tablet

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Abstract

Valacyclovir (VA) displays antiviral activity against Herpes simplex virus (HSV) and Varicella zoster virus (VZV). The aim of this study was to design, formulate and evaluate the physicochemical properties of effervescent tablets containing VA in order to facilitate pill swallowing for the pediatric, elderly and bed-ridden patients. Sixteen formulations with different amounts of effervescent base were prepared by modified direct compression for the loading of 500 mg VA. The Design-Expert® software was then used to generate formulations using a full factorial design with four different variables: citric acid (A), sodium bicarbonate to citric acid molar ratio (B) 6000 (D). The prepared tablets were assessed for weight variation, hardness, thickness, friability, drug content, CO2 content, effervescence time and pH. To improve the taste of formulations, several sweeteners and fruity essences such as raspberry and cherries were used. F2 formulation was selected as the optimized formulation with the desirability of 72.8%. The optimized formulation had an effervescent time of 98.33±3.51 seconds, friability % of 0.55, pH value of 4.67±0.06, CO_2 amount of 261.33 ± 20.26 mg and hardness of 77.23±3.12 N. It, therefore, seems that optimized effervescent tablets may be helpful for the delivery of VA in the treatment of herpes simplex or herpes zoster and chikenpox.

Keywords: Valacyclovir, Effervescent Tablet, Dry Granulation, Direct compression method.

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1. Introduction

Solid oral dosage forms are the most favorite methods of taking medication. However, they suffer from several problems such as slow absorption and delayed onset of action. To overcome these disadvantages, the drug was administered in liquid form; however, several active pharmaceutical agents have limited the level of stability in the liquid form. Hence, effervescent tablets are a suitable substitute of liquid oral dosage forms (1). Effervescent tablets are a solid dosage form intended to be dissolved or dispersed in water before administration. Effervescence, which is defined as the evolution of gas bubbles in a liquid, is the result of the generation of CO_2 during the reaction of effervescent agents upon the formulation contact with water (2). Produced CO_2 elevates the penetration of active ingredients in the para cellular pathway and subsequently, drug absorption (3). Effervescent tablets have numerous advantag-

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es including fast onset of action, no need to swallow, good stomach and intestinal tolerance, better palatability, superior stability, precise dosing, and improved therapeutic effect (4).

Valacyclovir (VA) is the L-valine ester of acyclovir with the molecular formula $C_{13}H_{20}N_6O_4$.HCl. FDA-approved indications of VA include herpes simplex virus type 1 and 2 and varicella zoster virus (VZV) infections. VA has some advantages relative to the acyclovir. Due to the active transporter in the intestines, VA absorption is faster when compared to acyclovir, thus achieving 3-5 fold higher total plasma acyclovir levels than that is possible with oral acyclovir. Hence, the relative bioavailability of acyclovir after VA administration is about 70% (5, 6). VA is available in the forms of 500 and 1000 mg tablets. For the treatment of chickenpox, children dose is calculated based on the body weight, which is usually 20 mg/kg three times a day for five days (7). Since the liquid dosage form of drugs is not accessible in market, commercially available tablets are usually divided or fractioned by hand, which may result in an improper dosage. In addition, due to the inherent limitations of solid dosage forms for certain groups of patients, e.g., elderly or immunocompromised patients with swallowing problems, manufacturing effervescent tablets seem to be promising.

In light of the above points, in the present study, we prepared and evaluated the physicochemical properties of effervescent tablets containing 500 mg VA. The characteristics of the effervescent tablets were controlled by several formulation parameters. For this multi-factor optimization, the traditional method of "changing one factor at a time" could have been applied, but this was avoided because it could be tedious and would not guarantee getting the optimum set of parameters. Instead, the "full factorial design" method was preferred here. Based on a mathematical model of the combined effect of the processing factors, this approach is known to be much more reliable (8). Thus, the effect of various formulations parameters on their characterization were evaluated using the full factorial design. Finally, the taste of the prepared tablets was evaluated in healthy volunteers as well.

2. Materials and methods

2.1. Materials

VA was obtained from Abidi Pharmaceutical Company (Iran). Citric acid, sodium bicarbonate, mannitol, sucrose, povidone k-30 (PVP), and polyethyleneglycol 6000 (PEG 6000) were provided from Merck (Germany). Flavoring agents such as raspberry and cherries were purchased from Farabi Pharmaceutical Company (Isfahan, Iran).

2.2. Preparation of effervescent tablets and Formulation studies

EEffervescent tablets of VA were prepared by the modified direct compression method (2). In order to prepare the optimized formulation, formulation variables were optimized using the Design–Expert software (version 10, USA). The amount of citric acid, sodium bicarbonate to citric acid molar ratio, PVP k30, and PEG 6000 were selected as the variables. All these variables had two levels, as shown in Table 1. By using the full factorial design, sixteen formulations were designed, as exhibited in Table 2. For the preparation of tablets, the required amount of VA was compressed into slugs using a single punch tablet machine (Kilian & Co, Germany) having 12 mm flat punches; then it was milled and screened through sieve 20. Afterward, 500 mg of VA granules and the desired

Table 1. Variables used in full factorial design.

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

PVP: Povidone k-30 , PEG 6000: Polyethyleneglycol 6000

Table 2. Composition of different formulations studied in preparation of effervescent tablets containing 500 valacyclovir.

Formulations	Citric acid (mg)	Sodium bicarbonate (mg)	Sodium bicarbonate to citric acid molar ratio	PEG 6000 (%)	PVP k30 (%)	Mannitol (mg)	Sucralose (mg)
F1	400	525	3-1	0.5	3	100	30
F2	400	525	3-1	5	3	100	30
F3	400	525	3-1	5	10	100	30
F4	400	525	3-1	0.5	10	100	30
F5	400	175	1-1	0.5	10	100	30
F6	400	175	1-1	0.5	3	100	30
F7	400	175	1-1	5	10	100	30
F8	400	175	1-1	5	3	100	30
F9	200	262.5	3-1	5	10	100	30
F10	200	262.5	3-1	5	3	100	30
F11	200	262.5	3-1	0.5	3	100	30
F12	200	262.5	3-1	0.5	10	100	30
F13	200	87.5	1-1	5	10	100	30
F14	200	87.5	1-1	0.5	3	100	30
F15	200	87.5	1-1	5	3	100	30
F16	200	87.5	1-1	0.5	10	100	30

PVP: Povidone k-30 , PEG 6000: Polyethyleneglycol 6000.

amounts of citric acid, sodium bicarbonate, PVP k30, PEG 6000, sucralose and mannitol, as shown in Table 2, were blended using mortar and pestle. After that, compressing was done by using a single punch tablet machine. The studied responses variables were hardness, friability, pH and effervescent time. Design Expert Software was then employed for the analysis of the experimental data, generation of polynomial equations and 3D graphs showing the effect of each variable on the response.

2.3. Evaluation of blends before compression

2.3.1. Angle of repose

Angle of repose is defined as the highest probable angle between the surface of a powder pile and the horizontal plane. For this, the powder was allowed to flow via a funnel fixed to a stand at a definite height. Then, the angle of repose (Θ) was calculated by determining the height (h) and radius (r) of the formed powder heap and putting the values into the following formula (Eq. 1):

$$Tan\ \theta = (h/r) \quad \text{(Eq. 1)}$$

According to the literature (9), the angle of repose between 25-30°, 31-35° and 36-40° indicates excellent, good and fair flowability, respectively (9, 10).

2.3.2. Compressibility index

The flowability of the powder can be calculated by comparing the bulk density (ρb) and tapped density (ρt) of it. According to this, Carr's index and Hausner's ratio were determined using the following formula (Eq. 2):

$$Carr's\ index\ (\%) = \frac{\rho t - \rho b}{\rho t} \times 100 \quad \text{(Eq. 2)}$$

According to the literature (9), Carr's index≤10% and between 11-15 and 16-20 can indicate excellent, good and fair flowability, respectively.

Hausner's ratio was determined by the following formula (Eq. 3):

$$Hausner'sRatio = \tilde{n}t / \tilde{n}b \quad \text{(Eq. 3)}$$

Hausner's Ratio between 1.00-1.11 , 1.12-1.18 and 1.19-1.25 can indicate excellent , good and fair flowability, respectively (9, 10)

2.3.3. Particle size

TThe sieve method was used to determine the particle size distribution. In this method, 100 grams of the powder mixture was passed through

several sieves with different meshes (20, 25, 30, 35, 40, 70 and 100) on top of each other. After 10 minutes of mild shaking, the remaining powders on each sieve were weighed and the mean particle size was determined via the following equation (Eq. 4) (11).

$$Mean\ particle\ size = \frac{\sum xiwi}{w} \quad \text{(Eq. 4)}$$

where xi is the average size of both upper and lower sieves, wi is the amount of the powder remaining in the lower sieve and w is the amount of the powder passed from the sieves.

2.4. Physicochemical Evaluation of the Effervescent Tablets

2.4.1. Weight variation

To investigate weight variation (WV), 10 tablets of each formulation randomly were chosen and then weighed individually. Then, the acceptance value (AV) was calculated in accordance with the formula from USP <905> weight variation of dosage units.

2.4.2. Content uniformity

In order to evaluate the content uniformity (CU) of tablets, 10 of each formulation randomly were selected. Each tablet was grounded into a fine powder using mortar and pestle. Then, the fine powders were dissolved in 1000 ml purified water. Further dilution was carried out to obtain the concentration of 25 µg/ml. The solution was filtered through a cellulose acetate membrane (0.45 µm). Afterward, the amount of the drug was measured by UV-visible spectrophotometer at λ max of 254 nm. Then, the acceptance value (AV) was calculated in accordance with the formula from USP <905> content uniformity of dosage units (12).

2.4.3. Thickness

The thickness of 10 tablets from each formulation was measured using vernier caliper (For-Bro Engineers, India). It should be controlled within ± 5 % of its normal standard (13).

2.4.4. Friability

TTo determine the friability of tablets, ten of them were weighed and placed in the friabilator machine (Erweka, TAP, Germany) on Erweka motor. The device rotated at 25 rpm for 4 minutes. Then, the tablets were thrown from a distance of 15 cm. After that, the tablets were reweighed. Finally, the Friability percent was calculated using the following equation (Eq. 5).

$$Friability\ percent = \frac{\text{Weight of tablets before test} - \text{Weight after test}}{\text{Weight of tablets before test}} \times 100 \quad \text{(Eq.5)}$$

The friability percent value greater than 1 % is unacceptable (14).

2.4.5. Hardness

The hardness of the tablets was measured for 10 tablets by using a hardness tester (Erweka, TPA, Germany)

2.4.6. Effervescence time

Three tablets of each formulation were placed individually in three beakers of water containing 200 ml of purified water at 20±1 °C. Effervescence time was considered as the moment when a clear solution was obtained and determined by the chronometer (15).

2.4.7. Water content

Ten tablets were placed in a desiccator containing activated silica gel for 4 h. The percentage of water content was determined via the following formula (Eq. 6).

$$Water\ content = \frac{\text{Tablet weight before drying} - \text{Tablet weight after drying}}{\text{Tablet weight before drying}} \times 100 \quad \text{(Eq. 6)}$$

A water content value of greater than 0.5% is considered unacceptable (16).

2.4.8. Solution pH

The pH of the solution was measured after the complete dissolution of tablet in 200 ml of water. This test was repeated 3 times (16).

2.4.9. Carbon dioxide (CO_2) content

Three tablets of each formulation were individually put in 100 ml of 1N sulfuric acid solution and the weight variations were measured at the end of dissolution. The obtained weight difference was regarded as the amount of CO_2 (mg) per tablet (17). This experiment was performed three

Table 3. Panel test for flavors by Latin Square method (on 30 volunteers) for effervescent tablets containing 500 mg valacyclovir.

Ingredients(mg)	Formulations			
	G1	G2	G3	G4
valacyclovir	500	500	500	500
Citric acid	400	400	400	400
Na bicarbonate	525	525	525	525
PVP	46.5	46.5	46.5	46.5
PEG 6000	77.6	77.6	77.6	77.6
Mannitol	100	100	100	100
Sucralose	30	30	30	30
Tutti-frutti	50	-	-	-
orange	-	50	-	-
lemon	-	-	50	-
cherry	-	-	-	50

times.

2.5. Taste evaluation

The formulations which showed optimum physicochemical properties were prepared with fixed amounts of different flavoring agents such as Tutti-frutti, orange, lemon and cherries (Table 3). Thirty volunteers were then selected to evaluate the taste of the formulation. Formulations containing berry flavors (G1), orange (G2), lemon (G3) and cherry (G4) were given to them randomly. Candidates were then asked to rate the formulations from bad (score 1) to excellent (score 5) (11).

3. Results and Discussion

Different methods including direct compression, wet granulation, dry granulation and fusion method were used for the preparation of effervescent tablets (2, 18, 19). In our preliminary study, the flow of powder blends was poor, and the angle of repose, Hausner ratio and Carr's index were more than 45 °, 1.45 and 28, respectively. So

Table 4. Evaluation of pre compression parameters for various formulations (n=3).

formulation	Particle size (µm)	Bulk density (g/cm3)	Tapped density (g/cm3)	Compressibility index (%)	Hausner Ratio	Angel of repose (degree)
F1	387.47 ±5.06	0.90±0.01	1.02±0.01	7.45±0.29	1.08±0.01	25.70±0.51
F2	404.02±7.65	0.86±0.01	0.96±0.01	10.72±0.51	1.12±0.00	28.11±0.60
F3	362.05±7.34	0.79±0.00	0.90±0.01	12.60±0.60	1.14±0.02	31.84±0.85
F4	377.98±7.40	0.79±0.02	0.92±0.01	13.76±0.36	1.16±0.03	32.01±0.67
F5	374.17±2.16	0.83±0.01	0.91±0.02	9.56±1.08	1.11±0.02	27.27±0.30
F6	375.08±3.67	0.83±0.02	1.02±0.01	17.96±1.95	1.22±0.04	35.50±0.45
F7	353.72±4.63	0.91±0.02	1.02±0.02	10.12±0.56	1.11±0.01	29.93±0.24
F8	411.87±9.80	0.81±0.01	1.02±0.01	20.36±2.11	1.26±0.03	36.56±0.17
F9	332.51±10.98	0.79±0.02	0.91±0.01	13.85±0.96	1.16±0.01	31.64±0.39
F10	374.33±11.31	0.85±0.01	0.95±0.01	10.94±0.97	1.12±0.01	29.67±0.36
F11	358.95±6.34	0.80±0.01	0.94±0.01	14.77±0.64	1.17±0.03	33.59±0.39
F12	364.06±11.00	0.80±0.01	0.95±0.02	16.04±0.66	1.19±0.01	37.02±1.63
F13	420.28±8.42	0.75±0.02	0.91±0.01	18.26±0.78	1.22±0.02	35.41±0.34
F14	404.67±8.19	0.73±0.02	0.87±0.01	16.21±0.99	1.19±0.03	35.78±0.32
F15	444.38±7.66	0.81±0.02	0.99±0.01	18.07±1.04	1.22±0.02	35.49±1.09
F16	406.64±5.02	0.73±0.01	0.88±0.01	17.34±1.01	1.21±0.01	37.89±0.50

Table 5. Evaluation of different effervescent tablets containing valacyclovir (n=3).

formu-lation	Thickness (mm)	Effervescent time (sec)	Amount of CO2 (mg)	Friability (%)	pH	Hardness (N)	Drug content (mg)	Water contents (%)	Acceptance value for content uniformity (%)	weight variation	
										content, ex-pressed of label claim(%)	Acceptance value(%)
F1	4.55±0.05	101.00±7.21	259.33±16.26	0.64±0.12	6.03±0.21	72.25±2.49	506.62±7.87	0.23±0.01	5.09	99.97±0.19	0.46
F2	4.67±0.05	98.33±3.51	261.33±20.26	0.55±0.08	4.67±0.06	77.23±3.12	514.45±11.33	0.25±0.01	8.31	100.00±0.35	0.84
F3	4.88±0.06	157.67±2.52	267.33±26.08	0.48±0.08	6.03±0.21	87.25±1.95	480.79±17.13	0.14±0.01	10.58	100.02±0.61	1.46
F4	4.55±0.07	123.67±5.13	278.67±31.56	1.03±0.12	6.07±0.15	78.25±1.70	460.67±16.04	0.26±0.01	14.07	99.43±0.65	1.56
F5	4.08±0.06	145.67±6.11	128.13±5.29	1.08±0.10	4.08±0.10	75.50±1.58	519.92±8.99	0.13±0.02	8.30	101.15±1.30	3.12
F6	3.52±0.04	121.33±4.93	113.15±11.53	1.24±0.05	4.09±0.10	58.75±1.77	500.95±10.59	0.31±0.03	5.28	101.86±3.85	9.6
F7	3.52±0.04	135.67±5.86	124.14±5.00	0.38±0.08	5.67±0.15	77.75±1.84	480.71±19.19	0.12±0.04	9.58	100.00±0.95	2.28
F8	3.52±0.04	127.30±6.03	125.43±5.00	0.72±0.10	4.83±0.06	70.25±1.84	470.27±11.81	0.28±0.05	10.11	99.91±0.81	1.94
F9	3.50±0.05	174.33±4.04	62.33±3.21	0.32±0.06	6.07±0.15	86.75±1.21	501.26±8.99	0.24±0.03	4.32	99.73±0.76	1.82
F10	3.27±0.05	136.00±5.29	59.23±17.75	0.46±0.06	6.13±0.06	71.30±1.89	474.71±13.27	0.14±0.02	9.92	99.81±0.63	1.51
F11	3.28±0.04	97.67±5.69	67.65±11.50	0.89±0.08	5.90`±0.15	59.50±1.58	473.55±19.49	0.23±0.02	4.07	99.84±0.48	1.15
F12	3.65±0.08	113.33±2.89	58.65±9.17	0.75±0.08	6.13±0.06	72.50±2.04	502.24±10.06	0.25±0.03	5.27	100.56±1.11	2.66
F13	3.03±0.05	192.33±3.51	62.33±6.43	0.26±0.07	4.97±0.17	95.00±2.36	486.15±14.32	0.28±0.02	8.13	99.78±0.72	1.73
F14	2.48±0.22	151.67±3.79	59.32±9.54	0.94±0.12	4.83±0.06	58.75±1.77	488.23±9.30	0.17±0.02	5.31	100.07±1.49	3.58
F15	2.64±0.05	162.67±4.04	65.67±2.52	0.66±0.07	4.67±0.06	72.25±2.19	487.76±9.64	0.31±0.03	5.58	100.26±2.38	5.71
F16	2.69±0.03	171.00±2.65	58.42±6.08	0.70±0.09	4.67±0.02	82.75±2.19	487.73±15.50	0.24±0.02	8.39	97.99±1.48	4.06

dry granulation method was used to prepare VA granules; then the sieved granules were blended with other excipients to prepare VA tablets using the direct compression method.

3.1. Evaluation of the powders blend

Table 4 shows the flow properties of the mixed powders in terms of the angle of repose, Hausner ratio and Carr's index. As can be seen, angle of repose, Carr's index and Hausner ratio values were found in the range of 25.70 to 37.89°, 7.45 to 20.36 and 1.08 to 1.26, respectively. According to the results in Table 4, the flowability of most formulations was within good, excellent

Table 6. Statistical analysis for effervescent time, hardness, friability and pH.

parameters	Effervescent time	Hardness	Friability	pH
	p value	p value	p value	p value
A	0.0040	-	0.0332	-
B	0.0034	0.0007	0.0564	0.0002
C	0.0030	<0.0001	0.0352	0.0056
D	0.0057	<0.0001	0.0038	-
AB	0.0124	<0.0001	0.1113	0.0053
AC	-	<0.0001	0.0730	0.0125
AD	0.0130	0.0001	-	0.0778
BC	0.0456	0.0001	0.0311	0.1325
BD	0.0135	-	0.1762	0.0080
CD	0.0467	0.0245	0.0644	0.0058
ABC	0.0663	0.0018	0.1613	0.1668
R2	0.9985	0.9999	0.9954	0.9964
Adjusted R^2	0.9891	0.9995	0.9651	0.9822

A: Citric acid amount, B: Sodium bicarbonate to citric acid molar ratio, C: PVP k30 amount and D: PEG 6000 amount.

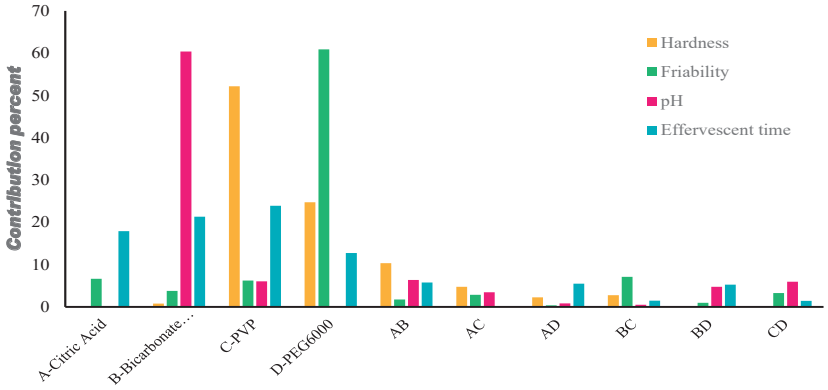

Figure 1. Contribution percent of different studied parameters and their interactions on hardness, friability, effervescent time and pH of effervescent tablets of valacyclovir

and fair range. The particle size distribution was in the range of 353.72-444.38 µm.

3.2. Evaluation of the physicochemical properties of effervescent tablets

The physicochemical properties of the prepared tablets are summarized in Table 5. The results of the physicochemical examination of the formulated tablets are shown in Table 5. For weight variation and content uniformity, the acceptance values ranged from 0.46 to 4.8% and 4.07 to 14.07 %, which met the passing criteria of 15% .Therefore, based on our findings (Table 5), all formulations had a uniform content. The water content of all tablets was less than 0.5 %, thus indicating the desirable water content of them. The CO_2 content of the tablets was found to be in the range of 58.42 -278.67 mg (Table 5). The results of the statistical analysis for effervescent time, hardness, friability and pH are shown in Table 6.

3.2.1. Tablet hardness

The tablet hardness ranged from 58.75 to 95.00 N (Table 5). The effect of each factor on the hardness can be explained by the following equation (Eq. 7).

$$Hardness(N) = 74.75 + 0.88B + 7.21C + 4.97D + 3.21AB - 2.18AC - 1.50AD - 1.66BC - 0.25CD \quad \text{(Eq. 7)}$$

where A, B, C and D are the amount of citric acid, sodium bicarbonate to citric acid molar ratio, PVP k30 and PEG 6000, respectively. Phrases composed of two factors indicate the interaction terms showing how the response changes when two parameters are changed simultaneously. The positive sign for the coefficient of each factor and their interaction in the polynomial equation can indicate the synergistic impact on response, while the negative sign represents an antagonism relationship.

Figure 1. presents the effect of each variables on the hardness of the effervescent tablets. According to the analysis done by design expert software, the hardness of the tablets was mainly affected by the amount of PEG 6000 and PVP k30. As can be seen in Figure 2-a, hardness has in-

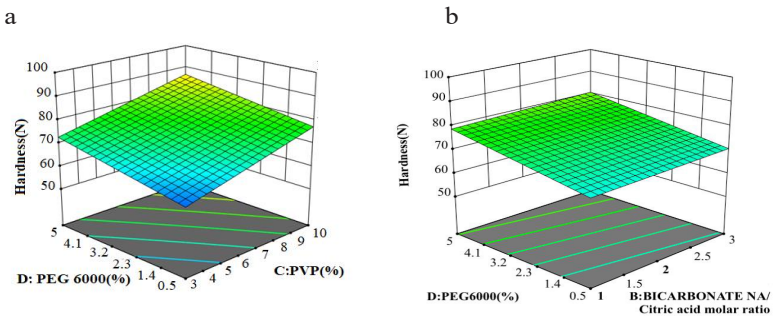

Figure 2. Response surface plots showing the effect of PEG and PVP(a) , bicarbonate Na /citric acid molar ratio and PEG (b) on the hardness of the effervescent tablets.

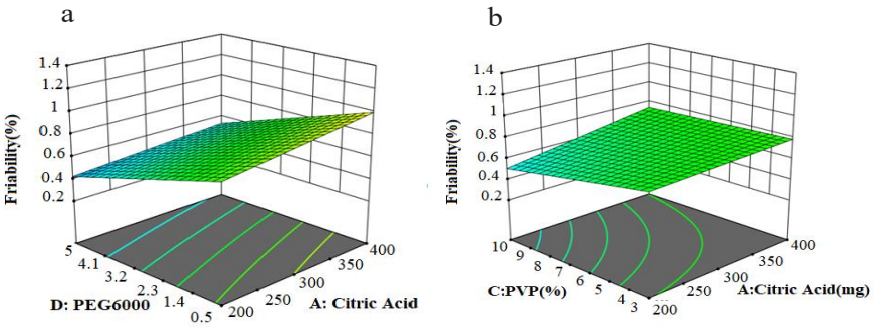

Figure 3. Response surface plots showing the effect of PEG 6000 (a), PVP (b) and citric acid (a,b) on the friability of the effervescent tablets.

creased with raising PVP and PEG. This was due to the binder nature of PVP and PEG, which allowed the formulation components to bind together, thus increasing their resistance (10, 16). According to Figure 2-b, increasing the molar ratio of sodium bicarbonate to citric acid causes a significant increase in hardness.

3.2.2. Tablet friability

Based on pharmacopoeia, the acceptable limit of friability is < 1% (14). In the present study, tablet friability varied from 0.26 % to 1.24 % (Table 5). Except for F4, F5 and F6 formulations, the rest of the formulations had an acceptable friability. The fallowing equation describes the effect of each factor levels on friability (Eq. 8).

$$Friability\ (\%) = 0.69 + 0.07A - 0.05B - 0.07C - 0.21D - 0.04AB + 0.05AC + 0.07BC + 0.03BD - 0.05CD \quad \text{(Eq. 8)}$$

As shown in Figure 1, friability was mostly affected by the amount of PEG 6000. The other factors significantly influencing the hardness of the tablets were citric acid and PVP content. According to Figure 3a-b, increasing the concentration of PEG 6000 and PVP decreased friability %, which was due to the increased hardness of tablets, as previously reported (10, 20). Increasing the amount of citric acid also significantly enhanced friability (Figure 3-a.).

3.2.3. Tablet effervescent time

According to Pharmacopoeia standards, the effervescent time should be less than 5 minutes (21). Our data showed that the effervescent time in all formulas was within the range suggested by Pharmacopoeia (Table 5). The effect of each factor on the effervescent time can be understood by the following equation (Eq. 9)

$$\text{Effervescent time} = 138.102 - 11.77A - 12.86B + 13.60C + 9.94D + 6.69AB - 6.52AD + 3.40BC + 6.40BD + 3.35CD \quad \text{(Eq. 9)}$$

In addition, the effervescent time of the tablets was mainly influenced by the amount of PVP. The other factors with significant effects were PEG 6000, citric acid and sodium bicarbonate/citric acid molar ratio. Increasing PVP and

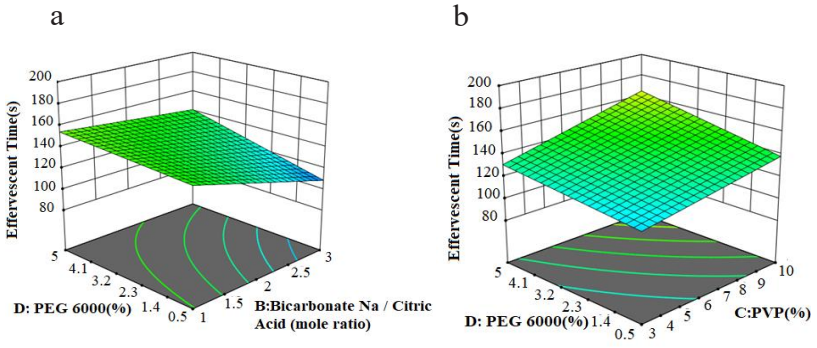

Figure 4. Response surface plots showing the effect of different levels of PEG 6000 and Bicarbonate Na/ Citric Acid (a), and PVP and PEG 6000 (b) on the effervescent time of the table.

PEG 6000 raised the effervescent time, which could be attributed to an increase in the hardness of the tablet 9 (Figure 4a, b). This result was in line with those of the other studies (16).

Conversely, increasing the molar ratio of sodium bicarbonate to citric acid reduced the effervescent time (Figure 4-a). Compared to the amount of acid, the availability of a larger amount of base leads to a relatively fast reaction, as well as the faster dissolution of the tablet, thus leading to a shorter effervescent time. Also, other studies have come up with similar results (22).

3.2.4. pH of solution test

The pH of the solution was assessed to be in the range of 4.67 - 6.13 (Table 5). pH was mostly influenced by the molar ratio of sodium bicarbonate to citric acid (Figure 1). The following equation also describes the effect of each factor on pH (Eq. 10).

$$pH = 5.40 + 0.48B + 0.15C - 0.16AB + 0.12AC - 0.06AD + 0.04BC - 0.14BD + 0.15CD \quad \text{(Eq. 10)}$$

The acid/base ratio of 1:3 had the highest pH, while the 1:1 one had the lowest solution pH. In a ratio of 1:1, a substantial amount of unneutralized acid remains in the solution, and pH tends to acidify, whereas the acid/base ratio of 1:3 causes the acid to be completely neutralized, and the pH tends to neutralize (Figure 5).

3.3. Optimization of the formulations

To select the optimized formulation, five variables were optimized using the Design-Expert software. Optimization process was performed to obtain the levels of each variable; hardness was considered to be maximum, friability and effervescent time were assumed to be minimum, and pH was taken to be in the range. Finally, according to the data, F2 formulation was selected as the optimized one with the desirability of 73%. The optimized formulation had an effervescent time of 98.33±3.51 seconds, friability of 0.55%, and pH value of 4.67±.06. Amount of CO_2 and hardness were 261.33±20.26 mg and 77.23±3.12 N, respectively.

3.4. Taste evaluation

Thirty healthy volunteers were chosen and divided into three groups. In each group, G1, G2, G3 and, G4 formulations were given to volunteers in a pattern which was different from that in other groups. Group A was given G2, followed by G3 ,G4 and G1, while group B was given G3, followed by G1 , G4 and G2; group C was given G1, followed by G4, G2 and G3. After collecting the responses given by the volunteers in each group , the G3 formulation was found to have the best taste (lemon) with the average score of 3.33. The average score of G1 (Tutti-frutti), G2 (orang) and G4 (cherry) was 1.43, 1.8 and 2.53, respectively.

4. Conclusion

Effervescent valacyclovir tablets were prepared successfully using the modified direct compression method. The process and formulation variables were optimized using the Design–Expert software; formulation F2 was selected as the final

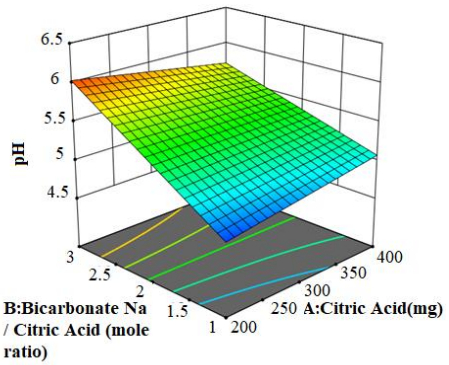

Figure 5. Response surface plots showing the effect of different levels of Bicarbonate Na/ Citric Acid and citric acid on the pH of solution test.

one. This formulation, due to the amount of citric acid and sodium bicarbonate, and the appropriate ratio of sodium bicarbonate to citric acid, which was equal to 3:1, had a good effervescence time (98.33 seconds) and a suitable pH (4.67). This formulation had good hardness (77.25 N) and friability (0.55 %), too. Thus, prepared effervescent tablet was found to have desirable characteristics to facilitate oral delivery of valacyclovir.

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Conflict of Interest

None declared.

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