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Design, Formulation and Physicochemical Evaluation of Acetaminophen Effervescent Tablets

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A B S T R A C T

The main objective of this study was to design, formulate and evaluate the physicochemical properties of 500 mg acetaminophen effervescent tablets, in order to accelerate its analgesic and antipyretic effects in patients with pill swallowing problems. Formulations with 500 mg of acetaminophen were prepared with effervescent bases including tartaric acid, citric acid, sodium bicarbonate, and PEG6000. Flowability of powders and granules was determined by measurement of bulk and tapped density, compressibility index and Hausner's ratio. Three methods were applied to prepare tablets: direct compression, wet granulation and fusion. The effervescence time, hardness, pH, thickness, CO_2 content, water content, weight variation, and content uniformity of the prepared tablets were investigated. In order to overcome the bitter taste of acetaminophen, different sweeteners and fruity essences such as orange, lemon, and cherry flavors were applied. Panel taste was performed using 20 volunteers. The physicochemical characteristics of three different methods of preparing tablets were pretty similar. Wet granulated formulations had higher hardness and better flowability while direct compressed tablets had stable effervescence time and better solubility. According to the panel taste, orange flavor was more acceptable. Wet granulated tablets which were prepared using alcohol and PVP had higher hardness and variable effervescence time in comparison to direct compressed tablets. Flowability of wet granulated formulations was better than the one with direct compressed formulations.

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Introduction

Edible drugs are the most important and the most acceptable forms of drug delivery systems. Among them tablets are preferable when compared to the liquid dosage forms due to the accurate dose of medication, less microbial contamination, and better taste covering. The downsides of tablets are late activation and slow absorption. Effervescent formulations can solve the instability problems of many drugs in liquid form, by providing a pharmaceutical solution at the time of consumption [1].

Effervescent tablets are uncoated in which the effervescence reaction occurs between acid and base in the presence of water, and causes carbon dioxide release; this makes an edible pharmaceutical solution [2].

Some advantages of the effervescent tablets are: no need to swallow, no gastrointestinal irritation, increasing the stability of the drug substance, faster absorption, ease of portability, and possibility of having more amounts of active ingredients [3].

The acidic substance for the effervescence reaction can be obtained from three main sources: food acids, anhydride acids and acid salts. Food acids such as citric acid and tartaric acid are commonly used because they are natural, more available, and more compatible with gastrointestinal system. The base substance of effervescent formulation is composed of alkali metal carbonates or bicarbonates [4]. Other ingredients of effervescent formulation such as binders, sweeteners, internal or external lubricants, etc are water-soluble [2].

Three methods were used in preparation of effervescent tablets: direct compression, wet granulation and fusion [4]. Direct compression is more preferable in comparison with other methods due to lower dependence on equipment, easier manufacturing process, faster dissolution, and increased stability of drugs which are sensitive to heat or humidity [5]. Because of sensitivity of effervescent tablets to humidity and temperature, controlling the relative humidity under 25% and temperature less than 25°C is necessary during manufacturing process and storage [4].

Acetaminophen is the most common non-opioid analgesic and non-salicylates with antipyretic effects and moderate anti-inflammatory [6]. Acetaminophen relieves mild osteoarthritis pain in which aspirin use can cause contraindication or harm, e.g. patients who receive anticoagulant drug or uricosuric agent, hemophilia or other bleeding disorders, diseases of the upper gastrointestinal and intolerance or hypersensitivity to aspirin [7]. Acetaminophen is used for children more than aspirin and other non-steroidal anti-inflammatory drugs because of its safety, lower toxicity, and lower gastrointestinal side effects [8, 9]. Absorption of acetaminophen in edible use is fast and approximately complete; it reaches its maximum plasma concentration within 0.5-2 hours [7].

Solubility of acetaminophen in water is low (1 part in 70 parts) [9]. Micronization, using co-solvent and dispersion in PVP or mannitol can be used to improve the solubility. [10, 11]. Acetaminophen is available in various edible forms such as tablet, capsule, solution, drop, suspension and rectal suppository [7].

The main purpose of this study is to design and formulate the 500 mg acetaminophen effervescent tablet in order to overcome the problems with drug swallowing and obtain faster drug effect on relieving the pain and fever. We have tried to provide desirable formulations with appropriate solubility and flavor, using the least amounts of excipients.

Materials and methods

Materials

Acetaminophen, citric acid, tartaric acid, sodium bicarbonate, mannitol, poly vinyl pyrrolidone (PVP), PEG 6000, aspartame and potassium acesulfame were provided from Merck company (Germany). The used flavoring agents were cherry and lemon from Osveh Pharmaceutical Company (Tehran, Iran), and orange from KAGAwa Company (China).

Methods

Pre-formulation

At first, according to effervescence reaction (equations 1 and 2) in table 1, some initial formulations were prepared according to effervescence reaction with various ratios of citric acid, tartaric acid, and sodium bicarbonate. 500 mg acetaminophen powder was then added to each formulation and mixed well. Afterwards, in each formulation 25, 30, 60, 75, 80 mg of PEG6000 was added to the formulations and the mixtures were transferred to single punch tablet press machine (Kilian & Co, Germany) in order to produce tablets.

According to the weights of tablets, the punch with 18 mm in diameter was applied.
Subsequently, the best proportions of acid and base of the initial formulations according to the solubility and the effervescence time were selected.

$3NaHCO_3 + C_6H_8O_7.H_2O \rightarrow 4H_2O + 3CO_2 + Na_3C_6H_5O$ Eq. 1

$2NaHCO_3 + C_4H_6O_6 \rightarrow 2H_2O + 2CO_2 + Na_2C_4H_4O_6$ Eq. 2

Direct compression method

According to tables 1 and 2 the different ratio of materials were mixed and ground. 20, 40, 60 and 80 mg of PVP were then applied. The selected formulations which contained PVP and had the best solubility are listed in table 2. Powders were then transferred to single punch tablet press machine (Kilian & Co, Germany) in order to produce tablets. According to the weights of tablets, the punch with 18 mm in diameter was applied. Afterwards, tablets were placed in coats of foil and stored at controlled humidity and temperature conditions.

Table 1. Initial formulations with various amounts of acids and base and in the brackets is proportions of them

Formulations	Sodium bicarbonate (mg)	Citric acid (mg)	Tartaric acid (mg)
A_1	462(1)	136(1)	272(1)
A_2	462(1)	136(1)	408(1.5)
A_3	462(1)	204(1.5)	272(1)
A_4	462(1)	272(2)	272(1)
A_5	693(1.5)	136(1)	272(1)
A_6	462(1)	204(1.5)	408(1.5)
A_7	462(1)	384(1)	-
A_8	462(1)	576(1.5)	-
A_9	462(1)	768(2)	-
A_{10}	693(1.5)	384(1)	-
A_{11}	924(2)	384(1)	-
A_{12}	231(0.5)	384(1)	-
A_{13}	231(0.5)	450(1.17)	-

Table 2. Required ingredients for final formulations in direct compression method

Ingredients (mg)	Formulations							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Acetaminophen	500	500	500	500	500	500	500	500
Citric acid	384	576	768	384	384	450	450	450
monohydrate	462	462	462	693	924	231	231	231
Sodium	75	75	75	75	75	60	30	30
bicarbonate	-	-	-	-	-	60	60	60
PEG6000	-	-	-	-	-	100	150	200
PVP								
Mannitol								

Wet granulation method

Formulation of wet granulated tablet (F_9) was similar to the F_8 sample. PVP was dissolved in 96% ethanol as binder solution and mixture of acetaminophen, sodium bicarbonate and citric acid powders as granulated agents were used. Then the prepared paste were passed through a 25 mesh sieve and dried with oven at 54°C for 1 hour. During drying process, granules were mixed every 15 minutes in order to perform more uniform drying process.
Then sodium bicarbonate and mannitol were added and mixed. Mixture of powders and granules were then placed in the oven at 54°C for 30 minutes to remove residual moisture. Finally, PEG6000 as the lubricant agent was added to the granules and mixed for 2-5 minutes, and tablet was prepared by single punch tablet press machine (Kilian & Co, Germany) with 18 mm in diameter-punch.

Fusion method

Formulation of fusion granulated tablet (f_{10} sample) was similar to f_8 sample. Mixture of citric acid monohydrate and sodium bicarbonate were placed in oven at 54 °C for 1 hour, while the powders were mixed every 10 minutes in order to release the moisture that exists in citric acid monohydrate and consequently form the granules. Then other ingredients of the formulation were added. The mixture of powders and granules were dried in the oven at 54°C for 15 minutes. Then, tablet was prepared by single punch tablet press machine (Kilian & Co, Germany) with 18 mm in diameter-punch.

Pre-formulation studies

Flowability

Powders flowability is determined using angle of repose, Hausner's ratio, or compressibility index.

Angle of repose

To determine angle of repose, 100 g of powder is poured in a glass funnel which is placed at 4 cm height on a constant basis. Angle of repose is calculated from the following equation [12].

$$Tan(\alpha) = \frac{2H}{D} \quad \text{Eq. 3}$$

H: Height of the pyramid
D: Diameter of the pyramid

Hausner's ratio and compressibility index

Hausner's ratio and compressibility index are obtained from the following equations [12].

$$Hausner's\ ratio = \frac{\rho\ tapped}{\rho\ bulk} \quad \text{Eq. 4}$$

$$Compressibility\ Index(\%) = \left[\frac{\rho\ tapped - \rho\ bulk}{\rho\ tapped}\right] * 100 \quad \text{Eq. 5}$$

In these equations, ρ tapped and ρ bulk are:

$$\rho\ \text{bulk} = \frac{M}{\text{V bulk}} \quad \text{Eq. 6}$$

$$\rho\ \text{tapped} = \frac{M}{\text{V tapped}} \quad \text{Eq. 7}$$

M: initial weight of powder
V_{bulk}: initial volume of powder before hitting
V_{tapped}: second volume of powder after hitting [12]

Particle size distribution

Various mesh size sieves were arranged from the larger mesh size at the top to the smaller ones at the bottom. 100 g of powders were poured on the upper sieve. Sieves were then shaken with vibrator machine (Erweka) for 10 minutes. Afterwards the remained powders on each sieve were weighed and particle size distribution curve was plotted for F_8, F_9 and F_{10} samples [12].

Evaluation of effervescent tablets

Effervescence time

Effervescence time was measured by chronometer. Three tablets of each formulation were immersed in a beaker containing 200 ml of purified water at 20 ± 1°C. The end of effervescence reaction was the time that the solution became clear and the particles disappeared [13]. Average effervescence time of 3 tablets of each formulation was reported.

pH test

Just after the complete dissolving of the tablets in the mentioned solution, pH of the mixture was determined by pH meter (Metrohm, 632, Switzerland). This test was performed for 3 tablets of each formulation and the average values were reported [13].

Hardness test

The force required to break a tablet in a compression is defined as the hardness or crushing strength of a tablet. In this study, ten tablets were randomly selected and individually placed in a hardness tester (Erweka, 24-TB, Germany) and the hardness of tablets reported in N [1].

Thickness

Thickness of 10 tablets was randomly measured by micrometer. Tablets thickness variation should not be out of ± 5 % of normal standard [1].

CO_2 content

One tablet was dissolved in 100 ml of 1 N sulfuric acid. Weight variation before and after dissolution, is a measure of CO_2 content. This test was performed for 3 tablets and the average value was reported [13].

Water content

10 tablets of each formulation were placed in a desiccator containing activated silica gel for 4 hours. Water content percentage was calculated from the following equation [13].

$$\text{water content (\%)} = \frac{\text{weight before drying} - \text{weight after drying}}{\text{weight before drying}} \quad \text{Eq. 8}$$

Weight variation

20 tablets were selected randomly and weighed. Their average weight was calculated. According to the average weight of tablets which is more than 324 mg, the maximum acceptable error was considered within ± 5% [1].

Friability

Ten tablets were weighed and placed in friabilator machine (Erweka, TAP, Germany) on Erweka motor. Device was rotated with 25 rpm rate for 4 minutes. The segregated particles of the tablets were carefully removed and tablets were reweighed. Friability percentage was obtained from the following equation [1, 12].

$$F(\%) = (1 - \frac{W}{W0}) * 100 \quad \text{Eq. 9}$$

W_0: weight of tablets before test
W: weight of tablets after test

Conventional tablets with less than 1 % weight loss are acceptable. Effervescent tablets have more friability because of their larger size in comparison with the normal tablets [1, 12].

Content uniformity

Ten tablets were randomly selected from each formulation and the active drug content of each one was determined. The average value of active substance in each tablet should be in the range of 85-115% of the nominal content of tablet in order to be acceptable [1].

Assay

120 mg of acetaminophen powder was carefully weighed and dissolved in 10 ml of methanol. It was then diluted with purified water to the volume of 500 ml. Afterwards 5 ml of this solution was transferred to a 100 ml volumetric flask and it was diluted with water to the desired volume. The absorbance of this solution at 240 nm was measured with spectrophotometer (Secoman, Anthelie, France). For standard absorption, different concentration of sample was prepared and standard curves were plotted. Acetaminophen content in milligrams was obtained using $10C\frac{Au}{As}$, where C is the concentration of acetaminophen in the standard solution (μg/ml) and Au and As are the absorbencies of acetaminophen and standard solutions, respectively [12].

Equilibrium moisture content

Three tablets of each formulation were placed inside three different desiccators containing saturated salt solution of potassium nitrate (18°C, relative humidity 90%), sodium chloride (18°C, relative humidity 71%) and sodium nitrite (18°C, relative humidity 60%). Equilibrium moisture content was determined at the first and seventh day using Autotitrator (Mettler, TOLEDO-DL53, Switzerland) [13].

Evaluation of flavor of the prepared tablets by volunteers

This test was performed within 2 steps; at first, formulations were prepared with various flavoring agents such as lemon, orange and cherry but the same amounts of sweeteners and the same content of active drug and excipients as the optimized sample (F_8). Then 20 volunteers gave scores to each formulation, within 20-minutes intervals with the numbers of 1 to 5 (1: disgusting taste, 2: bad taste, 3: acceptable taste, 4: good taste, 5: perfect taste). Consequently the preferred flavoring agent was approved and then its content was determined. At the second step, different sweeteners with various contents (as listed in table 3) were used to omit unpleasant taste of acetaminophen. Then the volunteers were asked to assign a score in the range of 1 to 5 to each formulation within 20-minutes intervals. According to the volunteers average assigned scores and approaching the results to the score of 5 based on Likert scale, the final formulation sweetener content and flavoring agent was chosen [14-16].

Table 3. Modification of taste in the final formulation by different sweeteners and flavoring agents

Ingredients (mg)	Formulations											
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**
Acesulfame K	6	6	6	60	60	12	60	-	-	-	-	-
	0	0	0	-	-	0	-	1	4	4	-	-
Aspartame	-	-	-	10	50	-	10	5	5	5	-	-
	-	-	-	0	0	10	0	-	-	-	10	20
Sucrose	-	-	-	-	-	0	-	-	-	-	0	0
Maltitol	3	-	-	30	30	-	50	3	3	5	50	50
Orange fla.	0	2	-	-	-	30	-	0	0	0	-	-
	-	0	3	-	-	-	-	-	-	-	-	-
Cherry fla.	-	-	0			-		-	-	-		
Lemon fla.												

Results

Pre- formulation studies

The pre-formulation results which are listed in table 4 show that formulations without tartaric acid have better characteristics of solubility and effervescence time. Samples A_1-A_6 have effervescence time over 600 seconds and after 30 minutes there was particles at the bottom of the container.

Table 4. Results of studies on solubility and effervescence time of the base formulations.

Physicochemical Properties	Formulations						
	A_7	**A_8**	**A_9**	**A_{10}**	**A_{11}**	**A_{12}**	**A_{13}**
Effervescence time(s)	196 ± 4	164.3 ± 4	134 ± 4	196.7 ± 3	213±4	141.7±4	126.3±2
*Solubility	3	4	5	3	3	4	5

*Solubility in water was defined by Likert scale [5: freely soluble, 4: soluble, 3: sparingly soluble, 2: slightly soluble, 1: very slightly soluble] [17]

Flowability

Flowability studies of all direct compression formulations show moderate and acceptable flowability. The best flowability is related to the formulation of wet granulation (F_9). Results of the flowability studies are reported in table 5.

Table 5. Flowability results of prepared formulations of direct compression (F_1-F_8), wet granulation (F_9), and fusion (F_{10}) methods.

Flowability characteristics	Formulations									
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
Angle of repose (Ø)	43.2	38.9	36.5	37.2	36	34.6	34.1	33.7	26.2	34.7
Bulk density (g/ml)	0.66	0.68	0.67	0.69	0.70	0.71	0.72	0.72	0.75	0.71
Tapped density(g/ml)	0.84	0.83	0.81	0.84	0.84	0.83	0.83	0.82	0.82	0.84
Compressibility index	21.4	18.1	17.3	17.9	16.7	14.5	13.3	12.2	8.5	15.5
Hausner's ratio	1.27	1.22	1.21	1.22	1.2	1.17	1.15	1.14	1.09	1.18

Particle size distribution

Particle size distribution curves, for three methods of direct compression, wet granulation, and fusion, are shown in figure 1.

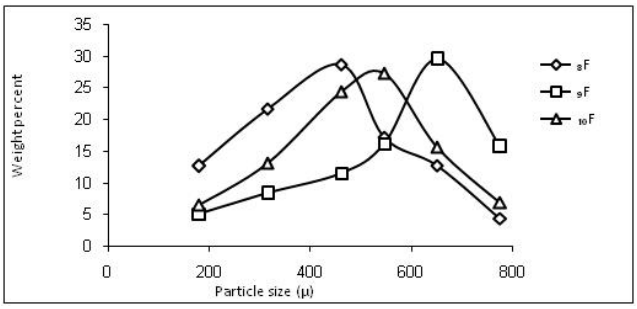

Fig. 1. Particle size distribution curves based on weight percentage in direct compression (F_8), wet granulation (F_9) and fusion (F_{10}) methods

Physicochemical properties of the prepared tablets

The results of physicochemical characteristics of the prepared tablets are listed in table 6. Effervescence time in F_1-F_8 was less than 3 minutes and in F_9, F_{10} it was over 3 minutes. pH in all formulations except the F_5 was less than 6. Results of the hardness measurement in effervescent tablets in direct compression formulation showed values in the range of 40-48.5 N. The highest value of hardness is assigned to the wet granulation formulation (F_9). Thickness of all tablets was within 4.3-5.6 mm. The most CO_2 content was found in F_3 and F_5 formulations. Water contents of all formulations were acceptably under 0.5%. Weight variations of all formulation were in the acceptable range. Friability of all formulations was less than 1% and the least one was assigned to the F_9 formulation. Content uniformity set according to the standard curve. The standard curve at wavelength of 240 nm obeys $y=0.0737x + 0.0239$, ($R^2 = 0.9983$).

Table 6. The results of physicochemical properties of the prepared formulations by direct compression (F_1-F_8), wet granulation (F_9) and fusion (F_{10}) methods (mean ± SD)

Physicochemical properties	Formulations									
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
Effervescence time (s)	163.7 ± 4	135.7±4	110±5	157.7±3	169±4	101.7±3	89.7± 4	77.7±3	243.3±23	274 ±9
pH	5.3±0.1	4.6±0.1	3.8±0.1	5.9±0.2	6.2±0.2	4±0.1	4.2±0.1	4.2±0.1	4.9±0.4	4.2±0.1
Hardness (N)	36.5±3.9	33± 4	31.5±3.2	29±3.8	29±3.4	27.5±4.5	28.5±3.4	29.5±3.1	68±1.7	44±2.1
Thickness (mm)	4.3±0.1	4.7±0.1	5.4±0.1	5±0.1	5.6±0.1	4.5±0.1	4.6±0.1	4.8±0.1	4.5±0	4.7±0
CO_2 content (mg)	314 ±4.6	246±4.4	772±4.1	365±5.3	572±3.6	161±2	154±2.7	94±1.7	112±3.5	47±5.6
Water content (%)	0.06	0.09	0.09	0.06	0.05	0.13	0.12	0.12	0.2	0.14
Weight variation (g)	1.4	1.6	1.8	1.6	1.9	1.4	1.4	1.5	1.5	1.5
Friability (%)	0.91	093	0.95	0.95	0.95	0.97	0.94	0.94	0.55	0.85
Content uniformity(mg)	492 ±7.7	494±13	494±8	492± 11	493±10.7	492±9	499± 7.8	500±9.5	499±9.1	501±14
Assay(mg)	487.3	484	503.8	491.2	503.3	496.7	490.6	496.7	503.3	518.7

Results of Equilibrium moisture content in the first and seventh days, for F_8, F_9 and F_{10}, showed that the most variations of humidity at 90% and temperature at 18°C. The results are listed in table 7.

Table 7. Equilibrium moisture content in the first and seventh days for F_8, F_9 and F_{10} in environments with sodium nitrite (RH, 60%), sodium chloride (RH, 71%) and potassium nitrate (RH, 90%) at 18°C.

Formulations		RH, 60%	RH, 71%	RH, 90%
	1st Day	2.85 ± 0.33	4.43 ± 0.35	7.54 ± 0.53
F_8	7th Day	5.59 ± 0.65	8.13 ± 0.41	13.52 ± 0.75
	Variation	**2.74**	**3.7**	**5.98**
	1st Day	3.27 ± 0.31	5.72 ± 0.19	7.55 ± 0.29
F_9	7th Day	7.47 ± 0.15	11.15 ± 0.49	16.95 ± 0.47
	Variation	**4.2**	**5.43**	**9.45**
	1st Day	3.14 ± 0.19	3.93 ± 0.17	9.29 ± 0.13
F_{10}	7th Day	4.82 ± 0.23	6.66 ± 0.24	16.27 ± 0.32
	Variation	**1.68**	**2.76**	**6.98**

In first level of studying for improving the taste of formulation, according to the average scores of volunteers, the orange flavor was selected among various flavors such as lemon, cherry and orange with the same of sweetener,. In the second level, some formulations were prepared, using different sweeteners and various contents of acceptable flavor. The mean scores of volunteers in this level for the better formulations contain maltitol (k) and acesulfame K and sucrose (g) listed in table 3 are presented in figure 2.

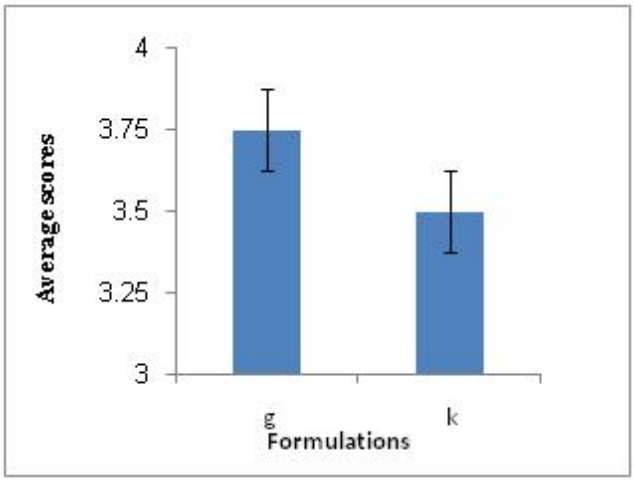

Fig. 2. The mean scores of 20 volunteers to the best prepared formulations in table 3; 100 mg sucrose and 60 mg acesulfame K (g) and 100 mg maltitol (k)

Discussion

Effervescent tablets are dosage forms which provide immediate release of active ingredients, without gastrointestinal irritation and improve swallowing difficulty especially in elderly and bed patients. Unfortunately, in pharmaceutical market, effervescent tablets of acetaminophen with mentioned advantages do not exist. The aim of this study was to develop appropriate products to increase physician and patients' compliance due to better effect in relieving fever and pain.

The effervescence time is the time that the solution becomes free of particles and clear, the acceptable range of this time is under 3 minutes [13]. Among A_1-A_{11} formulations, the A_1-A_6 samples that contained tartaric acid were excluded from this study because of the very low solubility of them and appearance of insoluble particles at the bottom of container, consequently, A_7-A_{11} were selected for the next steps due to the appropriate effervescence time. In the next step, the effect of increasing the co- solvents on F_1-F_5 was investigated. Amount of PEG6000 was decreased in later formulations due to the existence of fine particles inside the container that was probably the excess of PEG6000.

Since the best effervescence time among F_1-F_5 is assigned to F_3, in order to decrease the excipients and consequently the weight of tablets, the next formulations were prepared with the ratio of 2 to 1 from citric acid to sodium bicarbonate in the base formulation.

PVP was used in order to improve the drug solubility. In other studies similar results were obtained [11, 18]. When different contents of PVP were used, the best effervescence time observed with the contents of 60 and 80mg. consequently, 60 mg of PVP was used for the other formulation in order to lessen the excipients content. To improve the flowability of powders,

formulation with optimized solubility and effervescence time was prepared by wet granulation and fusion methods. In wet granulated formulations when minimum alcohol and PVP contents was applied as binder and the mixture of acetaminophen and citric acid was used as granulated agent, angle of repose, compressibility index, and hausner's ratio were decreased, consequently, improved the flowability. In similar studies, the use of wet granulation improved flowability, which is in conformance with the results of this study [13, 19].

Improving the flowability in granulation method is related to the formation of spherical particles and particle size increase. Variable and inappropriate effervescence time of formulations is related to the particle size distribution curve, the high particle size average, and the deviation from normal distribution curve. High particle size average in wet granulated formulations is related to the coalescence of particles and forming larger granules. According to figure 1, the peak of diagram is appeared at larger sized articles for F_9 while it is appeared at smaller ones for F_8; it means that the particles are bigger in granulation technique.

When higher contents of alcohol (twice or triple) were used, effervescence time in different tablets were more uniform and lower, but the drying time of granules was increased (more than 8 hr). Co-solvents of propylene glycol and glycerin were applied in order to improve solubility, but the effervescence time and the time of granules formation increased in comparison with the time that alcohol was used, and there was no solubility improvement. Also improving of the solubility and effervescence time was not observed in the fusion method compared to F_8, and the preparation time of formulas was increased due to the additional steps of forming and drying the granules. In older studies on prepared tablets, the hardness was less than 50 N in direct compression method, which can be related to some factors such as larger size of the effervescent tablets than conventional tablets and less stickiness of particles in direct compression method. It can be shown that the solution of PVP in F_9 is the cause of higher hardness of the prepared tablets in comparison with the direct compression formulations, which results in sticking of the particles together and using much force to break the tablets.

In all formulations except the F_5, the pH of effervescence solutions were lower than 6, which is in an acceptable range for effervescent tablets [13]. Higher pH of F_5 is resulted from the ratio of 2 to1 of sodium bicarbonate to citric acid. The results of this section were different from the ones reported for diclofenac potassium tablet [20].

The CO_2 content changes the taste and effervescence time, and most of the CO_2 content was observed in F_3. In formulations with PVP (F_6-F_8), the CO2 content was reduced significantly and effervescence time was decreased which may be corresponding to the formation of hydrogen bonding between PVP and acetaminophen [18]. In a similar study on effervescent tablet of diclofenac potassium, the CO_2 content is comparable with these results [20]. CO_2 content in direct compression method is higher than fusion method. Another study found similar results [21].

Water contents of all formulations were in acceptable range (under 0.5%) [13]. In a similar study on the effervescent tablets of citrate potassium, water content was reported within 0.04 and 0.096 that was in agreement with the results of this study.[19] Higher water content of F_9 may be because of the use of alcohol as binder and the presence of that in the granules with large particle size.

Friability was near 1% for all formulations except the F_9. Lower friability of F_9 may be related to its higher hardness value. Due to higher hardness in fusion method friability is decreased compared to direct compression. The results of this section were similar to the ones reported for ranitidine tablet.[21] According to the tablets weight which were more than 324 mg, weight variations were less than ±5% and it was acceptable for all formulations [1]. Content uniformity of tablets can vary in the range of ±15% of the 500 mg active ingredient (425-575 mg) that is in the acceptable range for all tablets [1].

The orange flavor was chosenby volunteers at the first level of evaluating the taste of the products, according to the average assigned scores. Then, different sweeteners with various contents were prepared. This time the preferred sweeteners were a mixture of acesulfame potassium and sucrose according to the average assigned scores and it is tactual.

Conclusion

In this study, we tried to produce effervescent tablet of acetaminophen by direct compression method, wet granulation and fusion techniques. The main factors

of preparing the optimal formulation were lower weight and thickness, lower manufacturing process, suitable flowability, effervescence time less than 3 minutes, CO_2 content, and the least excipients. F_8 was selected as the optimal formulation because of its best effervescence time and suitable weight, despite the lower release of CO_2 than F_3 and lower flowability than F_9.

Wet granulation technique was found to be more desirable method in industrial scale because it improves the flowability. To improve the taste of products, flavor of orange and acesulfame and sucrose sweeteners were selected.

Conflict of Interests

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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