Journal of Reports in Pharmaceutical Sciences 2016, 5(2), 122-134

Design, Formulation and Evaluation of Its Physiochemical Properties of Acetaminophen, Ibuprofen and Caffeine as Effervescent Tablet

Abolfazl Aslani*, Ali Daliri

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: 2016-09-15
Revised: 2016-11-20
Accepted: 2016-11-25
ePublished: 2016-11-29

***Keywords*:**
Effervescent tablets
Acetaminophen
Ibuprofen
Caffeine
Direct compression method
Fusion method

A B S T R A C T

The aim of this study was to design, formulate and evaluate the physicochemical properties of acetaminophen, ibuprofen and caffeine as effervescent tablets, since, they can overcome the problems with drug swallowing for the pediatric, elderly and bed-ridden patients. Effervescent tablets were prepared in a dosage of 325 mg acetaminophen, 200 mg ibuprofen and 40 mg caffeine by fusion and direct compression methods. Pre-compression characteristics of the mixed powders and granules, such as angle of repose, compressibility index, mean particle size and Hausner's ratio were evaluated. Then, they were evaluated for post-compression properties including weight variation, hardness, friability, carbon dioxide content, effervescence time, pH, content uniformity, assay and water content. Panel taste was performed using 30 volunteers. After performing the required procedures, citric acid and sodium bicarbonate were selected as effervescent materials. It was resulted that the fusion method was exhibited more flowability than direct compression and the G_5 formulation was selected as the optimized formulation. It is significant that fusion method resulted in better tablets compared to direct compression method.

*Corresponding Author: **Abolfazl Aslani, E-mail:** aslani@pharm.mui.ac.ir

Introduction

The oral dosage forms are the most popular method of drug administration, in spite of, some disadvantages like slow absorption and thus onset of action is time consuming. This can be overcome by administrating the drug in liquid form but, many active pharmaceutical ingredients have limited level of stability in liquid form. Therefore, effervescent tablets acts as an alternative dosage form [1]. As per revised definition suggested to US FDA, effervescent tablet is a tablet which is dissolved or dispersed in water before administration. In addition to active ingredients, it generally contains mixture of acids/acid salts, carbonate and hydrogen carbonates which release CO_2 when reacted to water [2]. The CO_2 liberated to improve the drug absorption and taste of the pharmaceuticals [3, 4]. The acidic substance for the effervescence reaction can be prepared from three main sources such as; 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 alkali substances of effervescent dosage forms are alkali metal carbonates or bicarbonates [4]. Effervescence is the result of a chemical reaction [5].

$C_6H_8O_7 + 3NaHCO_3 \rightarrow Na3C_6H_5O_7 + 4H_2O + 3CO_2 \uparrow$

This reaction performs in presence of water, even with small amount as catalyzing agent, and because water is one of the reaction products, it increases the rate of reaction, leading to difficulty in stopping the reaction. For this reason, the whole manufacturing and storage of effervescent products is planned by reducing of the contact with water [5]. For formulation of effervescent tablets, other excipients such as sweeteners, flavorings, water-soluble lubricants (e.g. PEG 4000, 6000 and sodium benzoate) and water soluble colors are utilized [6].

The effervescent tablet advantages are; no need to swallow, no gastrointestinal irritation, increasing the stability of the medicine, faster absorption, ease of portability and possibility of having more amounts of active ingredients [7].

Various methods including wet granulation, fusion method, fluid-bed granulation and direct compression are carried out to produce the effervescent tablets with controlling of the environmental conditions. Since these products are sensitive to the moisture and temperature, it appears that a relative humidity (RH) of 25% or less and moderate temperatures (25°C) are necessary in manufacturing areas to prevent granulation or adhesion of tablets to the machinery as a result of absorbed moisture [7].

Acetaminophen is the most common non-opioid analgesic and non-salicylates with antipyretic effects and moderate anti-inflammatory. Acetaminophen relieves mild osteoarthritis pain in which aspirin use can cause contraindication or harm. Absorption of acetaminophen in edible use is fast and approximately completes [8].

Ibuprofen is a non-steroidal anti-inflammatory drug, that is commonly used for the relief of symptoms of arthritis, fever, primary dysmenorrhea (menstrual pains), and as an analgesic [9].

Caffeine is a central nervous system (CNS) stimulant of the methyl xanthine category. It reversibly blocks the action of adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system [10].

The main purpose of this study is to design and formulate the 325 mg acetaminophen, 200 mg ibuprofen and 40 mg caffeine as effervescent tablet for patients who cannot swallow, such as the pediatric, elderly, geriatric and psychiatric patients, bed-ridden patients, and eventually patient who suffer from renal failures. Also it can 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

The pharmaceuticals including acetaminophen, caffeine, ibuprofen and flavoring agents such as cherry, lemon, orange, raspberries and tutti frutti were provided by Farabi Pharmaceutical

Company (Isfahan, Iran). Citric acid, tartaric acid, sodium bicarbonate, mannitol, sucrose, propylene glycol (PG), povidone k-30 (PVP), polyethylene glycol 6000 (PEG 6000), polyethylene glycol 400 (PEG 400) and ethanol 96% were purchased from Merck (Germany).

Solubility improvement of acetaminophen and ibuprofen

One of the properties essential to candidate screening is the solubility of the compound. When the aqueous solubility of a drug candidate is inadequate to permit solution formulations, co-solvents are often employed to improve solubility. Co-solvent is a second solvent added in small quantities to enhance the solvent power of the primary solvent such as PVP, PG, PEG, and ethanol. Due to low solubility of acetaminophen and ibuprofen in water, so it was used co-solvents to increase the solubility of them.

For increase of acetaminophen water solubility, different amounts of PG, PEG 400 and PVP were used [11-13].

For increase water solubility of ibuprofen, different amounts of PG, PEG 400, Ethanol 96%, glycerin, and tween 80 were used [13, 14].

Determination of effervescent components and design formulations by Design-Expert software

The effervescent components and the ratios between them were calculated according to the neutralization of acids and alkali materials and effervescence reaction.

The effects of citric acid and tartaric acid on pH, solubility and effervescence time were investigated via changing the acid amounts as follows; 0.5, 0.75, 1 and 1.5 times. The experiment was repeated for sodium bicarbonate via changing the amounts as follows; 0.75, 1 and 2 times (Table 1).

Table 1. Determination of effervescent components based on ratio of effervescent materials.

Code	Citric acid(mg)	Tartaric acid(mg)	Sodium bicarbonate(mg)	Effervescent time(sec)	Solubility	pH
P_1	147	294	500	135	2	5.4
P_2	147	73.5	500	117	3	6.0
P_3	147	147	500	120	3	5.9
P_4	147	220	500	130	2	5.7
P_5	73.5	147	500	125	2	6.0
P_6	220	147	500	118	3	5.7
P_7	294	147	500	117	3	5.4
P_8	73.5	-	500	123	4	6.3
P_9	147	-	500	110	5	6.1
P_{10}	220	-	500	98	5	6.0
P_{11}	294	-	500	94	5	5.7
P_{12}	147	-	375	93	5	5.8
P_{13}	220	-	375	91	5	5.6
P_{14}	294	-	375	88	5	5.5
P_{15}	147	-	750	123	4	6.6
P_{16}	220	-	750	120	4	6.5
P_{17}	294	-	750	118	4	6.4
P_{18}	147	-	1000	136	2	6.9
P_{19}	220	-	1000	132	2	6.8
P_{20}	294	-	1000	130	3	6.7

*Solubility of formulations using a standard table[15] (1=insoluble: 2=slightly soluble: 3=sparingly soluble: 4=soluble: 5=freely soluble)

To find the optimal conditions for determining effervescent components the Design-Expert software (ver.7.2 US) was used by taking the appropriate output responses including

effervescence time and pH. Two different processing variables including citric acid (factor A) and sodium bicarbonate (factor B) were studied, each in three levels. According to the results in Table 1, three levels for citric acid are in (147-294 mg) range and three levels for sodium bicarbonate are in (375-500 mg) range. Nine different formulations were designed by a general full factorial design (Table 2). The optimum conditions were determined by an optimization process to yield a heightened performance.

Table 2. Ingredients for final tablet formulations. F_1-F_9 and G_1-G_9 granules had same components

Ingredients (mg)	Formulations								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Acetaminophen	325	325	325	325	325	325	325	325	325
Ibuprofen	200	200	200	200	200	200	200	200	200
Caffeine	40	40	40	40	40	40	40	40	40
Citric acid (A)	147	147	147	220	220	220	294	294	294
Sodium Bicarbonate (B)	375	437	500	375	437	500	375	437	500
PVP	50	50	50	50	50	50	50	50	50
PEG 400	150	150	150	150	150	150	150	150	150
Ethanol 96%	150	150	150	150	150	150	150	150	150
PEG 6000	200	200	150	200	150	100	150	100	100
Mannitol	100	100	100	100	100	100	100	100	100
Sucrose	70	70	70	70	70	70	70	70	70
Flavoring agents	20	20	20	20	20	20	20	20	20

Evaluation of powder mixtures and granules

The main flowability properties of granules and powders (before compression) were characterized by the angle of repose, compressibility index (Carr's index), and Hausner's ratio. These tests and physicochemical tests were repeated 3 times for each formulation.

Angle of repose

Angle of repose is described as the maximum possible angle between the surface of a powder pile or granules and the horizontal plane.

The granules were allowed to flow through a funnel fixed to a clamp at a definite height. The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the formed granules heap and putting the values into the equation; Tan θ = (h/r) [15].

Compressibility index

The flowability of powder may be calculated by comparing the bulk density (ρb) and tapped density (ρt) of powder and the rate at which it packs down. The percentage of compressibility index was measured as $\left[\frac{\rho\ tapped-\rho\ bulk}{\rho\ tapped}\right] * 100$ [16].

Hausner's ratio

Hausner's ratio is an important character to determine the flow property of powder and granules. This can be measured via following formula; ρt/ρb [17].

Particle size distribution

Various mesh size sieves were arranged from the larger mesh size at the top to the smaller ones at the bottom. Powders or granules were then poured on a series of sieves and placed on the device. The remaining powders or granules on each sieve were weighed and the mean particle size (d) was calculated as $d = \frac{\sum xidi}{100}$ where xi was the average size of both upper and lower sieves and di was the percent of value i in the range of that bulk [18].

Preparation of F_1-F_9 tablets by direct compression method

Acetaminophen, caffeine and ibuprofen were first triturated with sweeteners and subsequently mixed with the effervescent materials. As mentioned above, for increasing of the water solubility of ibuprofen, optimized combination between PEG 400 and ethanol was added to formulations. To increase the water solubility of acetaminophen, PVP was added to formulations. After mixing of the dried powders with appropriate characteristics, the F_1-F_9 series tablets were prepared. The powders were pressed in a single punch machine (Kilian & Co, Germany) with a rod number 18. The prepared tablets were dried in an oven at 60°C for 1 hour (Table 2).

Preparation of G_1-G9 *tablets by fusion method*

The selected acid and alkali materials were placed on a heater at 54°C to release the crystallization water of citric acid. The formed granules were dried in an oven at 60°C. Afterwards, the mixture of acetaminophen, caffeine and ibuprofen and the sweeteners were added. The granules were pressed in a single punch machine (Kilian & Co, Germany) with a rod number 18. The G_1-G9 tablets were dried in an oven at 60°C for 1 hour and finally packaged (Table 2).

Physicochemical evaluation of the effervescent tablets

The following physicochemical tests were conducted to evaluate the tablet physicochemical properties.

Weight variation

20 tablets were randomly selected and weighed individually and the weights of tablets were compared with the calculated mean.
Through this method, not more than 2 tablets should have a deviation greater than pharmacopoeia limits ± 5% of the weight [19].

Friability test

Friability of the 10 tablets was determined via friabilator (Erweka, TAP, Germany). It highlighted tablets are resistance to the combined abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes. The friability was measured through this equation;

$$\frac{Initial\ weight\ of\ tablets - final\ weight\ of\ tablets}{Initial\ weight\ of\ tablets} * 100$$

[19].

Thickness

A vernier caliper (For-Bro Engineers, India) was used to determine the thickness of 10 selected tablets which recognized randomly [20].

Hardness test

The force required to break down a tablet in a compression is characterized as the hardness or crushing strength of a tablet. In this study, 10 tablets were randomly selected and individually placed in a hardness tester (Erweka, 24-TB, Germany) and then the hardness of tablets reported in N [21].

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 [22].

Evaluating the solution pH

Just after the complete dissolving of a tablet in a beaker containing 200 ml of water, pH was determined by pH meter (Metrohm, 632, Switzerland) [22].

Effervescence time

Effervescence time was measured by chronometer. One tablet was 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 [22].

Assay

For acetaminophen 20 tablets were weighed and powdered. Powdered tablet equivalent to one tablet was weighed and taken into volumetric

flask in mixture of methanol and water to obtain concentration of 65 µg/ml. To calculate assay, this solution was analyzed by UV spectrophotometery (Secoman, Anthelie, France) at 244 nm [23].
For ibuprofen assay analysis, this procedure was performed for 20 tablets and a solution with concentration of 40 µg/ml in NaOH 0.1N was prepared and analyzed by spectrophotometery (Secoman, Anthelie, France) at 265 nm [24].
For caffeine assay analysis, this procedure was performed for 20 tablets, and solution with concentration of 40 µg/ml in purified water was prepared and analyzed by spectrophotometery (Secoman, Anthelie, France) at 270 nm [25].

Content uniformity

After randomly selecting 10 tablets, the content of each tablet was determined separately [18].

Water content

10 tablets were dried for 4 hours in a desiccator containing silica gel. The percentage of water content was calculated as $\frac{tablet\ weight\ before\ drying - tablet\ weight\ after\ drying}{tablet\ weight\ before\ drying} * 100$ [21].

Equilibrium moisture content

Three tablets of each formulation were placed in 3 desiccators containing saturated salt solutions of sodium nitrite (RH, 60%), sodium chloride (RH, 71%), and potassium nitrate (RH, 90%). The percentage of equilibrium moisture content was determined on the first and seventh days by using Autotitrator (Mettler, TOLEDO-DL53, Switzerland) [22].

Taste Evaluation

Formulations were prepared with various flavoring agents such as cherry, lemon, orange, raspberries and Tutti frutti but the same amounts of sweeteners and the same content of active drug and excipients. Then 30 volunteers gave scores to each formulation, within 20-minutes intervals with the numbers of 1 to 5 (1: very bad 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 [26].

Results

The standard curve of acetaminophen in methanol and purified water was obtained spectrophotometry via curve equation, $y=0.004x+0.0165$ and the regression $R^2 = 0.998$.
The standard curve of ibuprofen in NaOH 0.1N was drown led to the curve equation, $y=0.002x+0.0061$ and the regression $R^2 = 0.999$.
The standard curve of caffeine in purified water was obtained led to the curve equation, $y=0.0096x+0.0305$ and the regression $R^2 = 0.998$.
50 mg of PVP was showed better water solubility for acetaminophen. Although, a combination of 150 mg PEG 400 and 150 mg ethanol 96% was showed better water solubility for ibuprofen.
Finally, some of the formulations were obtained by measuring effervescent components and 20 formulations which explained in Table 1.
The formulations were selected with the suitable solubility, effervescence time and pH. The formulations with an effervescence time of over 180 seconds or a sediment formation were deleted. The P_1-P_4 formulations were fixed in amount of citric acid and sodium bicarbonate but variable in amount of tartaric acid. The P_5-P_7 formulations varied in the amount of citric acid and according to the previous results, tartaric acid was 147 mg but sodium bicarbonate was fixed. Thus, citric acid was not less than its original value because of its pH increased. The P_8-P_{20} formulations varied in the amount of sodium bicarbonate and citric acid, but tartaric acid was removed. After altering the ratio of effervescent components, the materials had a lot of effect on solubility, effervescence time and pH. The results show that formulations without tartaric acid have better characteristics of solubility and effervescence time.

Evaluation of mixed powders and granules

The results for evaluation of mixed powders and granules were provided in Table 3 and Table 4.

Table 3. Evaluation of physical characteristics of mixed powders (Mean ± SD)

Physical Characteristics	Formulations								
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Angle of repose (θ)	29.63± 1.21	26.41±2. 42	27.83±1. 74	26.24±1. 02	28.44±3. 12	25.31±2. 84	30.43±3. 41	28.63±2. 84	27.63±1. 69
Compressibility Index	6.0± 0.12	9.07± 0.25	7.19± 0.19	3.84± 0.09	4.95± 0.14	6.03± 0.30	3.43± 0.12	6.42± 0.25	7.14± 0.29
Hausner´s ratio	1.063± 0.02	1.099±0. 06	1.077±0. 05	1.040±0. 01	1.052±0. 08	1.064±0. 02	1.035±0. 03	1.048±0. 05	1.076±0. 04
Mean particle size	335.98 ±4.36	340.08± 5.87	338.22± 4.21	331.74± 6.58	343.71± 2.78	344.85± 3.97	349.22± 1.29	342.16± 6.47	333.64± 2.94

Table 4. Evaluation of physical characteristics of mixed granules (Mean ± SD). F_1-F_9 and G_1-G_9 granules had same components

Physical Characteristics	Formulations								
	G_1	**G_2**	**G_3**	**G_4**	**G_5**	**G_6**	**G_7**	**G_8**	**G_9**
Angle of repose(θ)	28.54±2. 31	25.84±1. 05	26.14±1. 23	26.01±2. 48	27.53±1. 68	25.10±1. 97	29.65±1. 81	27.94±2. 14	26.63±1. 09
Compressibility index	5.75± 0.14	4.39± 0.11	4.42± 0.10	6.66± 0.19	7.50± 0.25	4.31± 0.14	6.39± 0.26	8.61± 0.21	5.05± 0.18
Hausner´s ratio	1.061±0. 01	1.045±0. 02	1.046±0. 01	1.071±0. 03	1.081±0. 02	1.045±0. 04	1.068±0. 03	1.094±0. 06	1.053±0. 05
Mean particle size	414.25± 7.25	418.73± 6.41	423.17± 7.47	412.15± 5.69	433.71± 5.94	420.38± 6.48	427.97± 7.15	428.63± 4.96	430.82± 6.19

Physicochemical evaluation of prepared tablets

Formulations of F_1-F_9 and G_1-G_9 granules had same components, but the method of preparation were dry granulation and fusion method respectively. They were encountered to all of the physicochemical tests. The weight of formulated effervescent tablets was in accordance of the pharmacopoeia criteria [18].

Physicochemical tests were conducted on tablets including assay, content uniformity, hardness, friability, thickness, weight variation, CO_2 content, water content and equilibrium moisture content (Tables 5, 6).

Table 5. Physicochemical properties of the effervescent tablets by direct compression method (Mean ± SD)

Physicochemical Evaluation	Formulations								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Effervescence time (s)	93.24±2.52	97.13±2.49	110.43±1.53	91.91±4.16	93.81±3.31	98.12±2.93	88.61±5.31	90.23±1.13	94.53±3.64
pH	5.81±0.14	6.07±0.27	6.18±0.11	5.63±0.43	5.77±0.57	6.01±0.22	5.52±0.47	5.54±0.39	5.72±0.18
Hardness (N)	50.73±2.41	52.61±1.55	45.53±4.40	60.81±3.41	63.84±1.25	58.31±4.14	56.39±6.47	65.37±2.38	51.91±5.38
Thickness (mm)	4.95±0.02	4.32±0.06	4.61±0.03	5.12±0.02	5.31±0.03	4.15±0.03	5.26±0.05	4.80±0.07	5.83±0.06
CO2 content (mg)	207.32±1.53	211.38±3.61	213.64±2.62	216.01±1.21	217±1.02	221.53±1.73	222.50±4.57	224.13±1.04	225.64±2.51
Water content (%)	0.13±0.04	0.16±0.09	0.11±0.05	0.20±0. 17	0.15±0.06	0.14±0.06	0.18±0. 12	0.17±0.08	0.12±0.03
Weight variation (g)	1.67±0.07	1.74±0.05	1.74±0.08	1.75±0.06	1.77±0.07	1.77±0.13	1.78±0.09	1.79±0.08	1.84±0.11
Friability (%)	0.27±0.01	0.25±0.01	0.34±0.02	0.30±0.02	0.36±0.03	0.29±0.04	0.32±0.02	0.28±0.05	0.38±0.03
Content uniformity of acetaminophen (mg)	325.24±3.61	321.61±4.81	329.73±7.92	331.52±3.61	324.14±3.64	326.23±5.86	321.81±4.75	327.93±2.67	322.82±6.12
Content uniformity of ibuprofen (mg)	203.34±5.91	197.63±3.82	199.51±4.01	205.73±3.09	202.81±5.12	195.42±1.87	204.67±3.74	201.52±2.63	196.13±3.01
Content uniformity of caffeine (mg)	44.13±2.13	37.03±1.82	41.33±2.72	39.52±3.71	40.43±2.91	43.71±4.51	38.48±3.21	41.66±2.51	42.81±1.82
Assay of acetaminophen (mg)	327.12±2.12	325.24±4.06	321.31±6.56	320.62±5.84	324.24±5.84	328.17±4.36	329.62±3.07	326.32±3.27	323.62±2.39
Assay of ibuprofen (mg)	204.14±3.01	198.13±3.24	200.71±4.77	202.43±2.15	199.22±3.92	196.72±5.54	203.41±2.89	206.92±3.81	195.31±4.01
Assay of caffeine (mg)	40.14±1.10	42.21±1.63	38.78±2.13	41.92±2.08	40.47±0.92	43.57±3.04	37.31±1.23	39.12±3.12	42.51±1.11

Table 6. Physicochemical properties of the effervescent tablets by fusion method (Mean ± SD)

Physicochemical Evaluation	Formulations								
	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9
Effervescence time (s)	91.64±1.43	96.71±3.13	106.81±2.81	89.37±4.01	92.64±2.91	96.51±3.87	85.81±2.23	87.67±3.47	93.76±4.15
pH	5.79±0.29	6.09±0.16	6.15±0.12	5.65±0.54	5.76±0.28	5.98±0.36	5.51±0.61	5.56±0.41	5.70±0.29
Hardness (N)	57.21±6.21	62.42±2.41	51.64±1.11	62.33±3.31	70.73±1.33	63.61±5.38	60.91±2.56	68.40±6.28	55.66±4.28
Thickness (mm)	4.99±0.09	4.35±0.01	4.66±0.08	5.40±0.02	5.38±0.05	4.21±0.05	5.27±0.06	4.83±0.04	5.89±0.08
CO2 content (mg)	191.56±02.51	198.63±1.31	204.67±3.12	208.36±1.53	210.67±5.63	215.13±2.00	218.64±1.05	223.73±4.58	225.44±2.08
Water content (%)	0.01±0.008	0.02±0.016	0.01±0.004	0.01±0.011	0.01±0.006	0.01±0.005	0.01±0.009	0.01±0.003	0.01±0.007
Weight variation (g)	1.68±0.01	1.75±0.11	1.75±0.06	1.75±0.03	1.77±0.02	1.77±0.01	1.79±0.04	1.79±0.10	1.84±0.09
Friability (%)	0.20±0.02	0.22±0.01	0.28±0.06	0.23±0.01	0.33±0.08	0.24±0.04	0.29±0.01	0.22±0.01	0.34±0.03
Content uniformity of acetaminophen (mg)	328.14±3.81	324.74±6.98	325.13±3.13	330.53±4.12	326.83±5.23	322.12±3.81	321.45±4.24	323.67±7.18	320.43±2.93
Content uniformity of ibuprofen (mg)	206.62±3.13	208.51±2.82	196.72±4.98	198.31±2.84	202.32±5.84	204.72±3.33	197.42±5.94	201.13±4.23	207.24±3.83
Content uniformity of caffeine (mg)	37.21±1.31	43.12±2.65	38.42±2.22	41.71±1.08	40.72±3.31	39.80±2.88	41.41±3.01	42.52±2.37	39.92±3.11
Assay of acetaminophen (mg)	321.21±5.64	324.31±4.51	328.71±4.92	322.17±3.18	325.72±5.21	327.21±3.14	322.33±3.35	324.41±1.04	326.52±4.97
Assay of ibuprofen (mg)	202.21±4.21	206.44±3.36	204.31±2.14	197.51±3.02	201.13±1.09	199.31±2.14	196.42±5.84	198.13±4.71	200.72±3.04
Assay of caffeine (mg)	41.52±1.43	43.31±1.05	37.93±2.10	39.90±1.01	40.32±2.51	42.51±1.84	38.12±0.91	41.23±2.01	39.12±1.07

Weight variations of all formulations were in the acceptable range. The drug content of all formulations was put down in the range of 85-115%.

Friability of the all formulations was found to be lower than 1%. The hardness values were within the range of 45-75 N. The thickness of the tablets varied between 4 and 6 mm. The formulations produced by the fusion method were thicker. The effervescence test was carried out in 200 ml of water. Effervescence times of all formulations were 85-110 seconds. During this time excipients and medicines were dissolved in water completely. The G_3 and F_3 formulations had the longest effervescence time (106 and 110 seconds, respectively). Effervescent compounds basically absorb a lot of moisture. Water content of all formulations was lower than 0.5%.

Among tablets, the F_1 and G_1 formulations had the lowest friability. In both methods of granules preparation, the G_5 and F_3 formulations had the highest and lowest hardness, respectively. The pH of formulations should be within the range of 5.7 and 6.2, otherwise they may not be acceptable due to lack of stability and sediment production. The percent of equilibrium moisture content of effervescent powders and granules formulations (F_1, F_5 and F_9) are provided in Table 7.

Table 7. Equilibrium moisture content (%) in effervescent powders and granules formulations of the F_1, F_5 and F_9 in temperature 18 °C (Mean ± SD)

Formulation	Microclimates	Effervescent powders		Variation	Effervescent granules		Variation
		1st Day	7th Day	(%w/w)	1st Day	7th Day	(%w/w)
F_1	**RH 90%**	12.64±0.14	16.13±0.22	21	14.84±0.11	21.32±0.31	30
	RH 71%	5.73±0.08	6.84±0.02	16	7.91±0.07	10.93±0.03	27
	RH 60%	1.43±0.02	1.45±0.05	1	4.15±0.03	4.17±0.02	0
F_5	**RH 90%**	11.36±0.07	17.01±0.02	33	14.13±0.11	22.34±0.01	36
	RH 71%	6.32±0.07	9.01±0.04	29	7.88±0.03	10.31±0.02	23
	RH 60%	2.58±0.02	3.02±0.03	14	4.47±0.04	5.38±0.01	16
F_9	**RH 90%**	12.93±0.04	16.63±0.01	22	14.87±0.09	21.33±0.01	30
	RH 71%	6.43±0.02	7.84±0.03	17	7.52±0.02	10.63±0.03	29
	RH 60%	3.85±0.01	4.51±0.02	14	5.72±0.013	6.92±0.03	17

The saturated salt solution: Sodium nitrite (RH, 60%), Sodium chloride (RH, 71%) and Potassium nitrite (RH, 90%)

In panel test for taste evaluation of formulations, according to the average scores of volunteers, the cherry flavor was selected among various flavoring agents such as cherry, lemon, orange, raspberries and tutti frutti with the same of sweetener.

Discussion

Most of the oral pharmaceutical dosage forms such as conventional tablets are formulated to be swallowed. Old people and children frequently have difficulties in swallowing these dosage forms. Such problems are more serious for those confined to bed patients. Despite the attractiveness of effervescent dosage forms, the compound of acetaminophen, ibuprofen and caffeine is not available in this form. Since, it is better tolerated by patients and results in a faster recovery, Therefore, it was decided to design and formulate the effervescent tablets containing acetaminophen, ibuprofen and caffeine.

Since the effervescent reaction in effervescent products requires acid and alkali resources, so they were used in all formulations. Then, pH of the solution, the solubility and the effervescence time were tested. Formulations containing tartaric acid (P_1-P_7) were eliminated due to the formation of

clearly observed sediment and a lower pH. The P_{18}-P_{20} formulations with a higher amount of sodium bicarbonate were eliminated due to the observed sediment and the highest pH. Ratios of effervescent components in the formulations of P_9-P_{14} led to a better solubility, a pH less than 6.1 and an appropriate effervescent reaction.

Addition of co-solvents to formulations was increased water solubility of acetaminophen and ibuprofen. PVP was increased solubility of acetaminophen, also PEG400 and ethanol were increased the ibuprofen solubility [11-14].

Each of the physicochemical properties listed in Tables 4 and 5 were compared with USP tables [18]. In both methods of granule preparation, most of the formulations had suitable flowability. As the results showed, angle of repose was reduced in fusion method. Mostly, Hausner´s ratio and compressibility index are reduced in fusion method. Fusion method increases flowability and decreases angle of repose due to increasing the particle size of granules and its spherical shape. Compressibility index of the granules was higher due to internal porosity of granules.

The mean diameter of particles in the fusion method is larger than the average diameter of the particles in the direct compression due to the adhesion of smaller particles and formation of larger particles. Effervescent granules had the particle size larger than of the effervescent powders blend. In other study, the results were agreement with these results [28].

All of formulations had the weight variation and friability of pharmacopoeia limits. The F_1, F_2, F_4-F_9, G_1-G_9 formulations had the desired hardness. Due to a lower hardness of direct compression method, the friability of tablets was increased compared to the fusion method. Other study found similar results [28].

CO_2 content of fusion method is lower than that of the direct compression method. These differences are found in manufacturing process of the granules. Other study reported that in each grams of formulas containing citric acid and sodium bicarbonate CO_2 content, was 292 mg which is comparable with these results [22]. In formulation G_1, lower level of CO_2 was obtained.

The pH of formulations should be within the range of 5.7 and 6.2. Therefore, all formulations of tablets were selected except F_4, G_4, F_7, G_7, F_8 and G_8. In other study on effervescent granules containing citric acid and sodium bicarbonate has been done, the pH of solution is obtained from dissolving granules was measured at 5.64. It is comparable with the results in this study [22].

The effervescence times of the all formulations were less than 2 minutes and all were in the range mentioned in BP [4]. All of the formulations showed effervescence within 85 to 110 seconds.

Drug content was established in a range of 320.62-329.62 mg for acetaminophen, 195.31-206.92 mg for ibuprofen and 37.31-43.57 mg for caffeine which was within the normal range. Drug content of all formulations was in the range mentioned in USP [18].

Water content was lower in formulations of fusion method, since they had lost some water during granulation process. In a similar study on the effervescent tablets of potassium citrate, water content was reported within 0.04 and 0.096 that was in agreement with the results of this study [19].

Measurements of relative humidity in some formulations revealed more moisture absorption in the fusion method, compared with direct compression method. Moreover, formulations with higher amounts of sodium bicarbonate absorbed more moisture. A previous study also reported similar findings [29]. Therefore, the F_3, F_6 and F_9 formulations absorbed the highest amount of moisture.

Five flavoring agents were used and 30 volunteers chose the best formulation. Formulation with cherry flavor was selected as the best.

Conclusion

Effervescent acetaminophen, ibuprofen and caffeine tablets were prepared by fusion and direct compression methods for treatment of ache, fever, and inflammation specifically for elderly, pediatrics and bed ridden patients.

After performing the required procedures, citric acid, sodium bicarbonate was selected as effervescent materials. Pre and post-compression tests were conducted on the prepared tablets. Finally, the G_5 was selected as the optimized formulation because of its preferred

physicochemical characteristics. It is significant that fusion method resulted in better tablets compared to direct compression method.

Acknowledgments

This study was supported by Isfahan University of Medical Sciences as a thesis research project numbered 394235.

Conflict of interest

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

References

[1] Srinath K, Chowdary P, Palanisamy P, Krishna A, Aparna S. Formulation and evaluation of effervescent tablets of paracetamol. Int J Pharm Res Dev. 2011;3:76-104.

[2] Kabir AK, Huda NH, Jhanker YM, Shamin K. Formulation development of verapamil hydrochloride tablet by effervescent method. S J Pharm Sci. 2010;3:34-7.

[3] Wadhwani AR, Prabhu NB, Nandkarni MA, Amin PD. Consumer friendly mucolytic formulations. Indian J Pharma Sci. 2004;7:506-7.

[4] Liberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets. 2nd ed. New York: Marcel Dekker Inc; 1989:285-328.

[5] Patel AA, Parikh RH, Sharma OP, Mehta TA. Development and optimization of effervescent tablets of promethazine. Int J Pharm Sci Res. 2015;6:5077.

[6] Rajalakshmi G, Vamsi CH, Balachandar R, Damodharan N. Formulation and evaluation of diclofenac potassium effervescent tablets. Int J Pharm Biomed Res. 2011;2:237-43.

[7] Prabhakar CH, Krishna KB. A review on effervescent tablets. Int J Pharm Technol. 2011;3:704-12.

[8] Wilson CG, Clarke CP, Starkey YY, Clarke GD. Comparison of a novel fast-dissolving acetaminophen tablet formulation (FD-APAP) and standard acetaminophen tablets using gamma scintigraphy and pharmacokinetic studies. Drug Dev Ind Pharm. 2011;37:747-53.

[9] Chen H, Chang X, Du D, Li J, Xu H, Yang X. Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. Int J Pharm. 2006;315:52-8.

[10] Kamimori GH, Karyekar CS, Otterstetter R, Cox DS, Balkin TJ, Belenky GL, et al. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. Int J Pharm. 2002;234:159-67.

[11] Kumar SD, Bihari GV, Suresh P. Solubility improvement using solid dispersion; Strategy, mechanism and characterization: Responsiveness and prospect way outs. Int Res J pharm. 2011;2:55-60.

[12] Yadav PS, Kumar V, Pratap Singh U, Raj Bhat H, Mazumder B. Physicochemical characterization and in vitro dissolution studies of solid dispersions of ketoprofen with PVP K30 and D-mannitol. Saudi Pharm J. 2013;21:77–84.

[13] Rubino JT. Cosolvents and cosolvency. Encyclopedia of pharmaceutical technology. 1988;3:375-98.

[14] Spiegel AJ, Noseworthy MM. Use of nonaqueous solvents in parenteral products. J Pharm Sci. 1963;52:917-27.

[15] Carter SJ. Eds: In Copper and Gun's: Tutorial Pharmacy, 6th ed., CBS Publishers and Distributors, Delhi, 1998, pp. 225.

[16] Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, Sharma R, Gupta N. Orally disintegrating tablets: formulation, preparation techniques and evaluation. J Appl Pharm Sci. 2011;1:35-45.

[17] Patil MG, Kakade SM, Pathade SG. Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique. J Appl Pharm Sci. 2011;1:178.

[18] United State Pharmacopeia 31- National Formulary 26. Washington: Board of Trustees; 2008. Vol 2: 639-41, 676, 1269.

[19] Aslani A, Fattahi F. Formulation, characterization and physicochemical evaluation of potassium citrate effervescent tablets. Adv Pharm Bull. 2013;3:217-25.

[20] Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro–in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm. 2010;74:332-9.

[21] Masareddy R, Yellanki SK, Patil BR, Manvi V. Development and evaluation of floating matrix tablets of riboflavin. Int J PharmTech Res. 2010;2:1439-45.

[22] Yanze FM, Duru C, Jacob M. A process to produce effervescent tablets: fluidized bed dryer melt granulation. Drug Dev Ind Pharm. 2000;26:1167-76.

[23] Behera S, Ghanty S, Ahmad F, Santra S, Banerjee S. UV-visible spectrophotometric method development and validation of assay of paracetamol tablet formulation. J Anal Bioanal Techniques. 2012;3:1-6.

[24] Kesur BR, Salunkhe VR, Magdum CS. Development and validation of UV spectrophotometric method for simultaneous estimation of ibuprofen and famotidine in bulk and formulated tablet dosage form. Int J Pharm Pharma Sci. 2012;4:271-4.

[25] Sethuraman S, Radhakrishnan K, Arul T. Analytical method development and validation of caffeine in tablet dosage form by using UV-spectroscopy. Int J Novel Trends Pharm Sci. 2013;3(4):82-6.

[26] Aslani A, Eatesam P. Design, formulation and physicochemical evaluation of acetaminophen effervescent tablets. JRPS. 2013;2:140- 9.

[27] Moghimipour E, Akhgari A, Ghassemian Z. Formulation of glucosamine effervescent granules. Sci Med J. 2010;9:22-34.

[28] Aslani A, Jahangiri H. Formulation, characterization and physicochemical evaluation of ranitidine effervescent tablets. Adv Pharm Bull. 2013;3:315-22.

[29] Aslani A, Sharifian T. Formulation, characterization and physicochemical evaluation of amoxicillin effervescent tablets. Adv Biomed Res. 2014;3:209.