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Original Article

Impact of preparation techniques on formulation and characterization of captopril effervescent granules

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ABSTRACT

Captopril aqueous solution prepared using the drug as a powder dissolved in water was stable only for approximately twenty-seven days. The present work aimed to prepare captopril as stable dry solid effervescent granules that form a suitable swallowing aqueous liquid dosage for pediatrics. Six formulas were prepared, by wet, and; fusion methods, using different ratios of citric acid and tartaric acid with potassium bicarbonate as the effervescent base. The granules evaluation was done concerning their flowability, tapped density, bulk density, and the angle of repose, as well as pH, Carr's; Index, effervescent time, particle size, drug content, and the dissolution study, all were performed in vitro. F2, prepared by wet granulation method at a ratio of 1:2:4.8 citric acid, tartaric; acid, with; potassium bicarbonate respectively was chosen as the selected formula as it exerts an accepted flow property, good distribution, and drug content of 97.5%. Fast effervescence time with 100% releases within 48.44 sec, and 2 min respectively. Captopril was successfully prepared as an effervescent granule, especially using the wet granulation technique.

Keywords: Effervescent granules, Captopril, Wet method, Fusion method, Effervescent time

Introduction

Nowadays Angiotensin-Converting Enzyme (ACE) inhibitors are considered a cornerstone in the treatment of heart failure in adults, as well as playing an important role in children with cardiac failure. Captopril (as an ACE inhibitor) is added to the Essential Medicines List for children [1-3].

Captopril is a white crystalline powder with a melting point of about 106°C, freely soluble in water, ethanol, chloroform, and methanol, log P (0.8-0.9). Captopril has two p Ka values 3.7 and 9.8 respectively [4, 5].

Figure 1 shows the structure of captopril. The aqueous solution of captopril is prepared by dispersing the drug powder in water which is stable for approximately twenty-seven days upon storage at 5 °C [6, 7].

European Pharmacopoeia defines granules as; dry aggregates, and solid, powder, particles that can tolerate handling. Usually, oral administration is what granules are used for. They can be given out in single, or multi-dose presentations for different types of use. Granules show more stability, better flowability, and uniformity in particle size [8, 9].

Usually, effervescent preparations contain three main constituents: the drug, the acid source represented by citric acid, and tartaric acid accompanied by a base source like potassium bicarbonate. In the presence of water, alkaline and acid bases react spontaneously releasing carbon dioxide. They added water just before administration to the patient. The resulting

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carbonated solution provides a pleasant taste masking any medicinal agent [10-12]. This is a unique feature of the effervescent granule's dosage form, unlike the rest of the fast-release dosage forms that require using different methods for masking the unpleasant taste of drugs. Different excipients like binders, flavors, diluents, surfactants, disintegrating agents, anti-foaming agents, colors, and sweeteners could be added. The active ingredients that were readily soluble could be added directly to the; effervescent, formulation; as, active ingredients, or during the dissolution process, it can be solubilized via salt production, while poorly soluble active ingredients can be dispersed in the formulation [13-15].

This study aimed to solve the aqueous stability problems of captopril by formulating captopril as dry solid effervescent granules to be dissolved in water just before administration allowing a high increase in the stability of the drug.

The drug concentration, flowability, particle size, pH, effervescence time, and in vitro drug release of the formed granules were all assessed.

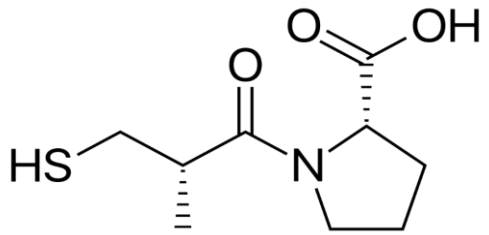

Figure 1. The chemical structure of captopril [6]

Materials and Methods

Captopril was supplied by Awa-medica Company in Iraq. Hi-Media, India, provided potassium bicarbonate, citric acid, and tartaric acid. The analytical-grade substances utilized in this study were used.

Preparation processes, of captopril effervescent; granules by wet and fusion methods

Three distinct effervescent base ratios of citric acid, tartaric acid, and potassium bicarbonate were used to create three separate formulations. F1, F2, and F3 were prepared using ratios of 1:2:3.4, 1:2:4.8, and 1:2:3.67 respectively. These formulations were prepared twice, once using the wet method and the other using the fusion approach, as shown in **Table 1**. The basic quantities required to make 20 g of effervescent granules with a single dose of 12.5 mg captopril were determined using The Stoichiometric calculation [16, 17].

Wet method

All the dry anhydrous ingredients were combined in a mortar, then ethanol was added gradually until a wet dough was formed which then passed through Sieve no. 10, and the granules were dried in a 50°C oven for 10 minutes before being stored in tightly sealed containers [18, 19].

Fusion method

Water molecules available in citric acid monohydrate were used as the binding agent in the fusion process, which acts as a binder for the formula mixture1 (instead of ethanol in the wet method) [20]. A precise amount of citric acid monohydrate was placed in a mortar on a hot plate. The citric acid monohydrate was heated to release the crystallization water, after which all other ingredients were added with continuous mixing, the pliable mass formed was sieved with Sieve no. 10 and dried at room temperature, and the granules were placed in specific containers and tightly sealed [14, 21].

Table 1. The constituents of captopril effervescent granules

ingredient	F1 (g)	F2 (g)	F3 (g)	F`1 (g)	F`2 (g)	F`3 (g)
Captopril	0.25	0.25	0.25	0.25	0.25	0.25
Citric acid	3	2.46	2.88	3	2.46	2.88
Tartaric acid	6	4.92	5.76	6	4.92	5.76
Potassium bicarbonate	10.18	11.8	10.57	10.18	11.8	10.57
Mannitol	0.15	0.15	0.15	0.15	0.15	0.15
Saccharin	0.1	0.1	0.1	0.1	0.1	0.1

Evaluation of captopril effervescent granules

Particle size distribution

Granule's size and distribution of the granule were measured by a sieve shaker which was supplied with standard sieves that were arranged progressively. The agitation time was 5 min. The mean granule diameter was calculated for each formula by weighing the granules retained on each sieve. Then the graph of particle size distribution was plotted [21, 22].

Angle of repose

The angle of repose is determined by measuring the angle formed by the powder stack's surface and the horizontal plane. The formula granules allowed them to fall freely onto graph paper on a horizontal surface due to gravity flowing smoothly through the funnel nozzle. From the cone formed on the graph sheet, the diameter and the peak of the resulting stack were determined.

The following equation was used to calculate the angle of repose [23, 24]:

$$\text{Tan } Ø = h/r \quad (1)$$

Ø is the angle of ribose, h is the powder cone's height, and r is the powder cone's radius.

Bulk density (BD)

A weighed quantity of granules was added to a dry 100 mL graduated cylinder. The unsettled volume (Vo) was measured after carefully leveling the granules (without compacting). The following formula was used to compute the bulk density (gm/ml) [25].

$$\text{BD} = \text{weight of granules/Bulk volume} \quad (2)$$

Tapped density (TD)

The same measuring cylinder used in measuring the bulk density was used. The sample's granules were tapped 1000 times. The volume of tapped granules was measured to the nearest graduation. The following equation was used to calculate tapped density [26, 27].

$$\text{Tapped density (TD)} = \text{Granule's weight/Tapped volume} \quad (3)$$

Hausner's ratio

It is also known as the Packing factor. The Hausner's ratio is correlated to the flowability of granules [28].

$$\text{Hausner's ratio} = \text{TD/BD} \quad (4)$$

Where TD is the tapped density, BD is the bulk density.

Carr's index / Compressibility index

Carr's index is a simple test for determining the granules' bulk and tapped densities and the space at which they are packed down. The following equation was used to calculate Carr's Index [29].

$$\text{Carr's Index} = [(\text{TD} - \text{BD}) * 100]/\text{TD} \quad (5)$$

Effervescence time and pH

1 g of granules (one dose) was poured into a beaker containing 50 ml of water to determine in vitro effervescence time. Random samples from each batch were chosen randomly, and the effervescence duration was monitored from the start to the appearance of a clear solution, after which the solution's pH was measured using a pH meter [30, 31].

Drug content

In a volumetric flask, one dose of effervescent granules from each batch was carefully weighed and added to 100 mL phosphate buffer pH 6.8. The samples were assayed for drug content by UV-spectrophotometer (Shimadzu1800) at 206 nm after suitable subsequent dilutions using the following equation [32]:

$$\text{Percent drug entrapmen} = \frac{\text{calculated drug concentration}}{\text{theoretical drug concentration}} \times 100 \quad (6)$$

Taste evaluation

For this evaluation, six human volunteers were selected, upon placing the effervescent solution in the mouth for 60 seconds [33].

In vitro dissolution study

The USP dissolution test apparatus Type II was used to conduct in vitro dissolution investigations for the selected formulas F2 and F′2 (paddle). At 37 ± 0.5°C and 50 rpm, 900 cc of 0.1N HCl (pH 1) was used in the dissolution test. For the first 5 minutes, 5 ml of dissolving medium was withdrawn at 1-minute intervals, then every 5 minutes for 15 minutes and replaced with a new dissolution medium. The withdrawn sample was filtered before being examined in a UV spectrophotometer. An equation derived from a standard calibration curve which was used to calculate the drug concentration [34].

Results and Discussion

Particle size distribution

Instead of a microscopic method, the sieving method was utilized in this experiment because it is rapid, easy to use, economical, automated (no need for an experienced person), and provides a wide range of particle sizes, especially for coarse particles. The particle size results from **Table 2** and **Figure 2** showed that the particle sizes varied from 968 to 1516 m. Because the water of crystallization released from the fusion method was not enough for complete granulation, there was a lot of loss in paste forming the granules, and a lot of powder was not granulated because of fast drying, the formulas prepared by the fusion method showed lower particle size than those prepared by wet method. The unbound water in granules evaporated during the drying stage in the fusion process, resulting in lower moisture content than granules produced by the wet granulation method. **Figure 2** depicts the particle size distribution [35].

Flow property of granules

Table 2 shows the results of flow qualities such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The flow characteristics of all of the formulations were good to exceptional. Carr's index findings were ≤15 showing flow properties varied from good to excepted. The angle of repose was 30°, suggesting excellent flow and quality of the

granules. The Hausner's ratio of 1.19 indicated that effervescent granules have good to exceptional flow properties [36].

Effervescence time and pH

Table 2 declares that the effervescence time ranged from 38.53 to 50.89 seconds. The presence of unreacted citric acid caused the solution to become acidic after effervescence, which enhanced taste perception. This is why the pH of the solution was 5. Because of the high proportion of potassium bicarbonate, F2 produced using the wet approach had the highest pH of all the formulae. The pH of the dry method was generally lower than that of the wet method formulations, possibly due to the higher amount of unreacted citric acid in this procedure [37].

Drug content

Drug content was in the range of 93.8-98 for all six formulations that are listed in **Table 2**. So, it was within the accepted range of content uniformity labeled in United States Pharmacopeia (USP) which varied from 90 % to 110 % [38].

In vitro dissolution study

Figure 3 shows that F2 and F′2 demonstrated >80% release in 0.1 N HCl after 1.5 minutes. The drug's fast release could be due to captopril's free solubility with the effervescence effect that causes an efficient release of the granules. The selected formulas showed a good release i.e., enhanced rapid dissolution. F22 released 1000% of the drug in just 2 min, F′2, on the other hand, was produced using the fusion procedure and released 95.12 percent of the medication in just 2 minutes [39].

Table 2. Evaluation of flow property parameters of captopril effervescent granules

Constituents of Formula	Type of test								
	Particle1 size (µm),	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Carr's1 index (%)	Hausner's ratio	Effervescence time (s)	pH	Drug content (%)
Captopril powder		42.27± 2.1	0.602 ±0.21	1.003±0.48	40.1 ±5.5	1.66±0.04		6.5	100±0.0
F1	968.969± 10.35	27.7± 0.8	0.545± 0.32	0.631±0.31	13.6±1.2	1.15±0.03	50.62±2.4	4.51	93.8±2.9
F2	1516.263± 25.12	19.6± 0.5	0.545± 0.14	0.6±0.17	9.16±0.89	1.1±0.02	48.44±3.5	4.92	97.5±7.5
F3	994.8329± 14.78	23.05± 0.7	0.545±0.57	0.591±0.47	7.7±0.43	1.05±0.7	46±5.7	4.75	97.1±3.1
F`1	1133.745± 31.42	27.45± 0.99	0.645±0.42	0.686±0.51	5.97±0.21	1.06±0.4	38.53±2.8	3.97	96.4±3.7
F`2	981.6142± 22.38	24.4± 0.35	0.669±0.46	0.75±0.22	10.8±0.98	1.12±0.07	50.89±6.7	4.2	98±2.7
F`3	989.9689± 12.14	29.05± 0.62	0.609±0.38	0.693±0.47	12±1.2	1.137±0.05	40.83±4.2	4.13	94.2±3.4

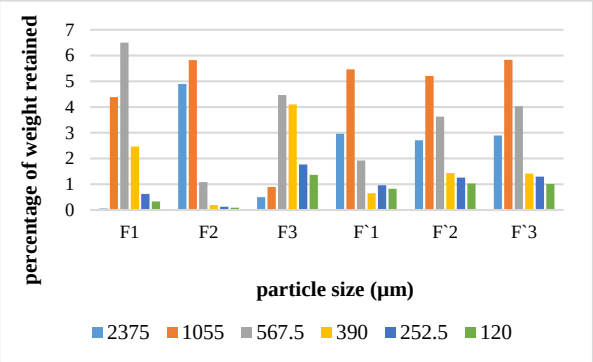

Figure 2. Distribution of particle size

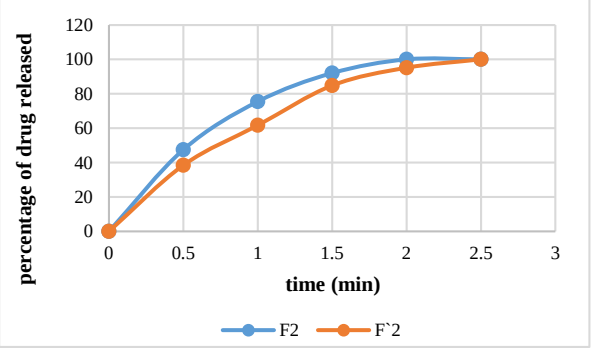

Figure 3. Captopril effervescent granules dissolution profile

Conclusion

Two distinct techniques (wet and dry) had been used to produce captopril-effervescent granules successfully. All formulated effervescent granules had predicted satisfactory results for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, good effervescence time, accepted drug content, drug release, and other physicochemical parameters. The F2 formula was selected as the best one according to its physicochemical characteristics with a 100% release within 2 min. In general, when compared to the fusion approach, the wet method produced better granules.

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