

Original Research Article

EFFECT OF VARYING PARAMETERS ON THE PROPERTIES OF EFFERVESCENT PARACETAMOL TABLETS FOR PAEDIATRICS

ABSTRACT

Aims: This study was aimed to determine the effect of varying parameters on the properties of effervescent paracetamol tablets for paediatrics.

Study design: This analytical study was carried out on effervescent paracetamol tablets formulated with differing formulation parameters.

Place and Duration of Study: This study was carried out in the Faculty of Pharmacy, Delta State University and Abraka from April 2017 to November, 2017

Methodology: Different formulations of effervescent paracetamol tablets were produced through wet granulation method using varied concentrations of citric acid (15, 20 and 25 %) and sodium bicarbonate (15, 20 and 25 %) as the major effervescent ingredients. The powder blends were evaluated for angle of repose, tapped and bulk density to determine its flow property. The prepared tablets were further evaluated using the unofficial test for hardness, friability and thickness as well as the official tests for weight uniformity, disintegration time, carbon dioxide (CO₂) content, water content and pH.

Results: Angle of repose ranged from $23.96 \pm 1.97^\circ$ - $28.84 \pm 0.91^\circ$, Hausner's ratio ranged from 1.16 ± 0.02 - 1.25 ± 0.02 while Carr's index ranged from 14 ± 1.73 - 20 ± 1.15 . All the granules had good flow properties while granules for F3 was the optimized formulation. Friability values were from 0.38 - 0.39 %. Tablets disintegrated between 3 ± 43.06 to 5 ± 16.3 min. The effervescence time in all formulations was between 3 to 5 mins with batch F3 giving the best effervescence time.

Conclusion: Granules made with Formulation F3 had the optimized flow characteristics. Effervescent paracetamol tablets containing 25% each of citric acid and sodium bicarbonate had the most desired properties as increase in both the concentration of the citric acid and sodium bicarbonate led to a decrease in the disintegration and effervescence time.

Keywords: [Effervescent, paracetamol tablets, paediatrics]

1. INTRODUCTION

The most frequent route of drug administration is through the mouth. The intrinsic difficulties of sluggish start and slow absorption, however, are unfavorable [1]. This improves effervescent drug delivery because the solution is produced quickly, making it easier to absorb [2,3]. Carbon tablets, also known as effervescent tablets, are tablets that dissolve in water and release carbon dioxide [4]. "Uncoated tablets typically containing acid compounds and carbonates or hydrogen carbonates, which react swiftly in the presence of water to release carbon dioxide," according to the European Pharmacopoeia. They should be dissolved or distributed in water before being administered [5]. Effervescent tablets are defined by the United States Pharmacopoeia (USP) as tablets that contain, in addition to the drug substance(s), mixtures of acids (e.g. citric acid or tartaric acid), carbonates, and/or sodium bicarbonate [6]. Carbon dioxide donors like sodium carbonate and sodium bicarbonate are combined with organic acids or carbon dioxide inducers like citric and tartaric acid to make effervescent tablets [7]. When effervescent tablets are dissolved in

water, they produce a clear, palatable solution [7]. In some cases, they may be coloured and sweeteners incorporated to facilitate patients' compliance. People who have trouble swallowing capsules or pills, especially youngsters and the elderly, are administered effervescent tablets. In comparison to normal tablets, this formulation facilitates swallowing, masks flavor, and provides quicker onset and absorption [8]. Furthermore, as compared to syrup or suspension forms, effervescent tablets offer storage benefits for keeping the medicine dry, stable, and safe. The CO₂ reaction is caused by an interaction of tartaric acid or citric acid with alkali metal carbonates or bicarbonates in the presence of water, and the tablet breaks up. Effervescent pills can be made from drugs that are recommended in large doses, such as vitamin C and paracetamol [9]. Acids and bicarbonates or carbonates salts of alkali metals are therefore key components of such tablets, containing the active medicinal ingredient [9,10]. Fillers, binders, sweeteners, flavors, and lubricants are also present. To avoid tablet adherence to the device and the generation of insoluble scum on the water surface, water soluble lubricants are utilized. Sweeteners are also necessary in some recipes. Because sucrose is hygroscopic and increases tablet mass, alternative sweeteners, such as aspartame, are employed instead [11].

Wet granulation, fusion technique, fluid-bed granulation, and direct compression are some of the ways for making effervescent tablets. In order to make effervescent pills, it's crucial to have a controlled atmosphere. Because these products are sensitive to moisture and temperature, production environments must have a relative humidity (RH) of 25% or less and moderate temperatures (25 °C) to prevent granulation or adherence of tablets to machinery due to absorbed moisture [12]. When put in 200 mL of water at 15–25 °C, effervescent tablets should effervesce and dissolve within 5 minutes, according to the European Pharmacopoeia [5]. These compositions emit carbon dioxide when mixed with water, resulting in the distinctive effervescent effect. They're classified as non-coated pills that should dissolve in 15 minutes [5]. Different medications, such as ranitidine [1] and benzodiazepines like lorazepam [13], have been developed into effervescent dosage forms. It appears that ingesting the medicine as a half glass of drink is less difficult than swallowing a huge pill. This administration strategy enhances the quality of life for people with a sore throat or a swallowing issue by allowing for simpler and quicker medication intake. Furthermore, as compared to syrup or suspension forms, effervescent tablets offer storage benefits for keeping the medicine dry, stable, and safe [8]. Because of their greater flavor, **tendency to rapidly form solution** and acceptance, effervescent pills of some medications, such as paracetamol, are more acceptable for children. **The appearance of effervescent paracetamol tablets could as well simplify ease of administration, and the utilization of appealing colors and tastes in this formulation can all help to promote paediatric compliance to the drug [8]. Furthermore, its tendency to rapidly form solution prior to oral administration has been exploited to improve the absorption of the drug compared to oral tablets.** This study therefore seeks to investigate some formulation parameters of effervescent tablets for delivery of paracetamol

2. MATERIAL AND METHODS

2.1 Materials

All materials were purchased from suppliers and they include paracetamol powder B.P (Wilkinson Vickers Ltd, England), microcrystalline cellulose (BDH Chemicals Ltd Poole, England) Sodium bicarbonate (Loba Chemie Pvt Ltd, India) maize starch, talc, magnesium stearate, lactose, citric acid and glucose was obtained from Pharmaceutical Technology Laboratory, Delta State University, Abraka, Delta State.

2.2 Preparation of Effervescent Paracetamol Granules

Using the wet granulation method of massing and screening, effervescent paracetamol granules were produced based on the formula used in table (Table 1). Several batches of

granules were produced with varying concentrations of lactose as a filler and glucose as a sweetener. The granules were formed by weighing appropriately paracetamol powder and lactose at varying concentrations of 20%, 15%, 10%. The sweetener, glucose at varying concentrations of 20%, 15%, 10%, the disintegrant (maize starch) the super-disintegrant (microcrystalline cellulose). The binder was prepared as mucilage by adding a little water to the weighed amount of starch and then boiling water till it gelatinized. Sufficient quantity of the mucilage obtained was added to the powder mix in a mortar and homogenized with the aid of a pestle to obtain a wet mass. The wet mass obtained was passed through a sieve size of 1.18 mm and the granules were dried in a hot air oven at 60 °C for 20 minutes. The granules were then passed through a 0.600 mm sieve and then dried again at 60 °C for 5 minutes. Varying concentrations of both the acid phase (citric acid) and base phase (sodium bicarbonate) were added using the formula in Table 1 after the granules were formed.

Table 1: Composition of Effervescent Paracetamol Tablets

Table Ingredients	F1	F2	F3
Paracetamol powder B.P (mg)	250	250	250
Disintegrant (%)	5	5	5
Super-disintegrant (%)	30	30	30
Binder (%)	15	15	15
Lubricant (%)	1	1	1
Glidant (%)	1	1	1
Filler (lactose) (%)	20	15	10
Sweetener (glucose) (%)	20	15	10
Citric acid (%)	15	20	25
Sodium bicarbonate (%)	15	20	25
Total (mg)	530	530	530

*Formulation table

2.3 Granule Characterization

2.3.1 Angle of Repose.

The angle of repose was determined by the funnel method 20 g of accurately weighed powder was taken in a funnel. The height of the funnel was adjusted with a height of term from the top to the base. The powder was allowed to flow through the funnel freely into the

surface. The diameter of the powder heap formed was measured and angle of repose was calculated using equation 1.

$$\tan \theta = \frac{h}{r} \quad (1)$$

Where h and r indicate the height and radius of the powder heap formed respectively.

2.3.2 Bulk Density and Tapped Density

About 20 g of the powder blend was weighed into a 100 ml measuring cylinder. The volume of the powder blend was noted as the bulk volume (B_v). The measuring cylinder was then tapped on a padded surface until there was no change in powder volume (100 taps) and the new volume of the powder blend was noted and recorded as the tapped volume (T_v). The procedure was carried out in triplicate for each of the batch (F1 – F3).

Both the bulk density and the tapped density were calculated from equations 2 and 3

$$\text{Bulk density} = \frac{\text{weight of powder blend}}{\text{bulk volume}} \quad (2)$$

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{tapped volume}} \quad (3)$$

2.3.3 Compressibility Index

The compressibility index (Carr's index) was determined using equation 4

$$\text{Carr's index (\%)} = \frac{TD - BD}{TD} \times \frac{100}{1} \quad (4)$$

Where TD = Tapped density

BD = Bulk density

2.3.4 Hausner's Ratio

The Hausner's ratio was determined using the formula in equation 5

$$\text{Hausner's ratio} = \frac{TD}{BD} \quad (5)$$

Where TD = Tapped density

BD = Bulk density

2.3.5 Evaluation of Tablets

2.3.5.1 Effervescent Time

A chronometer was used to track the effervescent time. At 20 degrees Celsius, three tablets of each formulation were submerged in a beaker containing 200 ml filtered water. The time the solution became clear and the particles evaporated marked the end of the effervescence reaction. Each formulation's average effervescence time was recorded for three tablets. [14].

2.3.5.2 pH Test

A pH meter was used to determine the pH of the combination shortly after the tablets completely dissolved. This was done in triplicate of each formulation and the average reported [14].

2.3.5.3 Hardness Time

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 Mosanto Hardness Tester (Pharmalab, Ahmedabad, India) and the hardness was gotten in KgF. The force required to break a tablet in a compression is defined as the hardness or crushing strength of a tablet.

2.3.5.4 Thickness

Thickness of ten (10) tablets was randomly measured by micrometer screw gauge and the average taken [2].

2.3.5.5 Diameter

Diameter of 10 tablets was randomly measured by micrometer screw gauge and the average taken [2].

2.3.5.6 Carbon dioxide (CO₂) Content

One tablet was dissolved in 100 ml of 1.0 N sulfuric acid. CO₂ content was determined by the weight difference before and after dissolution.. This test was performed for 3 tablets and the average value was reported.

2.3.5.7 Water Content

Ten tablets of each formulation were placed in a desiccator containing activated silica gel for 4 hours. Water content percentage was calculated from equation 6.

$$\text{Water content (\%)} = \frac{\text{weight before drying} - \text{weight after drying}}{\text{weight before drying}} \quad (6)$$

2.3.5.8 Weight Variation

Twenty tablets were selected randomly and weighed. Their average weight was calculated. [2].

2.3.5.9 Friability

Ten tablets were weighed and placed in a USP type-II Roche friabilator (Pharmalab, Ahmedabad, India). The device was rotated at 25 rpm for 4 minutes. The segregated particles of the tablets were carefully removed and tablets were reweighed.

Friability percentage was obtained from equation 7

$$F (\%) = \frac{w1-w2}{w1} \times 100 \quad (7)$$

Where W1 = initial Weight and W2 = Final Weight

3.1 RESULTS AND DISCUSSION

Effervescent tablets are dosage forms that give quick release of active substances by in-vitro breakdown, without causing gastrointestinal discomfort, and decrease swallowing problems, particularly in children and the elderly. Before being compacted into tablets, the formulation was manufactured as granules.

3.1.1 Flow Properties of Granules

Table 2 represents the granules' flow characteristics. Granules have lower bulk and tapped densities than powders due to higher porosity and lower cohesive force. As a result of their low moisture content, granulation generates granules with a lower potential for adhesion. The higher particle size achieved via granulation, on the other hand, would result in a smaller particle contact area. This would reduce particle friction resulting in greater flowability [15]. The angle of repose of a powder or granule gives information on the degree of cohesiveness and hence flowability of the powder. Powders having a greater than 30° angle of repose have poor flow [16]. The angle made with horizontal sides of the heap formed is called the angle of repose [17]. It is the measure of the flowability of the powder [18]. Angle of repose in the formulations of effervescent granules was in the range of 24 - 29, indicating acceptable to good flowability. With increasing concentration of citric acid and sodium bicarbonate, Hausner's ratio and Carr's index reduce and flow properties improved. In a similar study, sodium bicarbonate and citric acid had been found to affect the effervescent pH and solubility of certain formulations but did not affect the flow time, angle of repose and bulk density [19]. The differences observed in these studies may be due to different samples studied and possibly the varying concentrations of the citric acid and sodium bicarbonate.

Table 2: Flow characterization of Effervescent Paracetamol Granules. *Values are mean ± S.D*

Batch	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner Ratio	Carr's index (%)	Flow Rate (g/sec)	Angle repose (°)
F ₁	0.40± 0.00	0.50 ± 0	1.25± 0.02	20 ± 1.15	3.83± 0.33	23.96± 1.97
F ₂	0.38± 0.00	0.45± 0.01	1.18± 0.03	16 ± 2.30	2.58± 0.17	28.21± 1.34
F ₃	0.43± 0.01	0.50± 0.00	1.16± 0.02	14 ± 1.73	4.00 ± 0.01	28.84± 0.91

In a study by Abolfazi and Sharifan [15], on amoxicillin, the angle of repose was found to be between 30 - 45° which was higher. The Hausner's ratio (i.e the ratio of tapped density to bulk density) previews the degree of densification which could occur during tableting. The higher the Hausner's ratio, the greater the probability of the powder to densify. Hausner ratio of ≤ 1.25 indicates good flow while values > 1.25 indicates poor flow [20]. From the results obtained, the granules exhibited good flowability. The % compressibility which is the direct measure of the potential powder area or bridge strength and stability gave a range of 14 – 20 %. The prepared blend hence has a good flow property which is impacted by the presence of talc as the glidant and micro-crystalline cellulose which has a good flow property

and can be incorporated into the tablets. The values for tapped density of all the batches were higher than the bulk density values due to the densification of the granules upon tapping.

3.1.1 Properties of Effervescent Paracetamol Tablets

The results of official and non-official test from tablet evaluation are shown in Table 3. All the batches of tablets produced a tablet thickness of 3.22 ± 0.05 - 3.43 ± 0.08 mm and diameter of 12.98 ± 0.07 mm. This indicates that there was uniform die filling during compression.

Table 3: Characteristics of Effervescent Paracetamol Tablets (mean \pm SD)

Physico-chemical properties	F ₁	F ₂	F ₃
Effervescence time (mins)	5 \pm 0.00	4 \pm 0.00	3 \pm 0.00
PH	7.0 \pm 0.00	6.9 \pm 0.00	6.8 \pm 0.00
Hardness (kg/F)	5.4 \pm 0.54	6.6 \pm 0.54	2.0 \pm 0.54
Thickness (mm)	3.43 \pm 0.08	3.27 \pm 0.05	3.22 \pm 0.05
Diameter (mm)	12.98 \pm 0.07	12.98 \pm 0.07	12.98 \pm 0.07
CO ₂ content (mg)	40 \pm 0.00	20 \pm 0.00	30 \pm 0.00
Water content (%)	0.02	0.03	0.04
Uniformity of weight (mg)	519 \pm 11.45	513 \pm 18.52	505 \pm 15.72
Friability (%)	0.38	0.39	0.38
Disintegration test (mins)	5 \pm 16.30	4 \pm 39.85	3 \pm 43.06

**Physicochemical characteristics of the formulated paracetamol tablets*

The British Pharmacopoeia specifies that hardness of an uncoated conventional tablet should be within the range of 4 – 10 kg [16]. All the batches produced tablets that conformed to this specification. The tablet hardness of all the batches was within the range of (2 – 7 kg/F). The physical strength of tablets cannot be determined just by their hardness. The friability values of a tablet which will withstand handling during packaging, transport and storage should be less than or equal to 1% [16]. In addition to the hardness test, the friability test was used to assess the physical strength of tablets. Friability was less than 1% for all formulations. Wet granulation method has been reported to increase compressibility, flowability, and hardness of powders in earlier research [21,22], and the results were consistent with our investigation. In this study, all the batches gave friability values of less than 1 %. The disintegration time is important because it evaluates the ability of the compressed tablets to break up when it comes in contact with the body fluid. From the study, it was shown that disintegrants can be effective in the formulation of effervescent tablets; this is due to the wicking and swelling nature of the disintegrants [20]. The mechanism involved in the use of disintegrants is that, when it comes in contact with water it swells to a large extent to disintegrate the tablet. Furthermore, they have fibrous nature that allows intra-particulate as well as extra-particulate wicking of water at low concentrations [23]. All the

batches gave disintegration time within the range of 3 – 5 minutes which complies with the time in which an effervescent tablet should disintegrate. The effervescence time for effervescent tablet should be less than 3 minutes [16]. All the batches gave effervescence time within the range of 3 - 5 minutes due to the strong binder effect. A key finding of this present study is that as the concentration of citric acid and sodium bicarbonate increases from F₁ to F₃, effervescent time reduces. Thus the batch F₃ with optimized flow properties had lower effervescence time (3 mins) and lower disintegration time. Less concentration of the reacting molecules gave rise to longer effervescent time and high concentration gave rise to shorter effervescent time as evidenced in this study. This was higher than that reported by Abolfazi and Sharifan [15] however on amoxicillin effervescent tablets. The water content of all the batches were within the range of (0.02 - 0.04) and they were all in acceptable range (under 0.5%). The CO₂ content changes the taste and effervescence time, and Batch F1 had the highest CO₂ content. The shorter effervescence time of tablets indicate that the process is efficient.

4. CONCLUSION

Wet granulation can be used to make effervescent paracetamol tablets. Effervescent materials are very hygroscopic, making them prone to atmospheric humidity deterioration. The granules that were created have excellent flow characteristics. The study had shown that increasing the concentrations of the acid phase (citric acid) and the base phase (sodium bicarbonate) led to decrease in disintegration time and effervescence time. Therefore, the batch F₃ (filler 10 %, citric acid 25 %, sodium bicarbonate 25 %, sweetener 10 %) had optimized flow properties, lower effervescence time and lower disintegration time.

COMPETING INTERESTS DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. THE PRODUCTS USED FOR THIS RESEARCH ARE COMMONLY AND PREDOMINANTLY USE PRODUCTS IN OUR AREA OF RESEARCH AND COUNTRY. THERE IS ABSOLUTELY NO CONFLICT OF INTEREST BETWEEN THE AUTHORS AND PRODUCERS OF THE PRODUCTS BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

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