Preliminary physicochemical evaluation of effervescent granules of *Anogiessius leocarpus* stem bark extract

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Abstract
The plant *Anogeissus leiocarpus* is traditionally used in the treatment of ulcers including gastric ulcers. Effervescent granules are unique, pleasant-tasting oral formulations which are ingested as liquids. This study is a preliminary development and evaluation of effervescent granules of the aqueous extract of the stem bark of *Anogeissus leiocarpus*. The extract was obtained by drying the filtrate gotten from maceration of the dried, crushed stem bark in water. The acids (citric and tartaric acid) were each combined with the base (sodium bicarbonate) in 1:1 and 1:2 ratios and these were mixed with the extract using either the fusion or wet granulation method of preparation of effervescent granules. The granules were evaluated for their flow properties, moisture content, pH after dissolution, effervescent time and *in vitro* dissolution. Results show that granules prepared by the fusion method possessed better flow properties than those prepared by wet granulation. Moisture content of the granules was similar. Granules containing higher base content had higher pH (7.29 and 7.30) and faster effervescent time (86 -99 sec) than those containing equal ratio of acid and base with pH of 5.85 and 5.96 and effervescent time of 104 -150 sec. *In vitro* release was faster release from formulations containing higher base content (100 and 90.32 % respectively) than the other batches. Aqueous extract of the stem bark of *Anogeissus leiocarpus* can be suitably formulated into effervescent granules.

Keywords: *Anogeissus leiocarpus*, effervescent granules, fusion method, wet granulation method, effervescent time

Introduction
Peptic ulcer (PU) is a common disorder of the digestive system which involves lesions of the inner lining of the gastrointestinal tract as a result of exposure to aggressive factors such as acidic secretion and pepsin. These lesions are typically found in the stomach and proximal duodenum but they could also occur in the lower esophagus, distal duodenum, or jejunum (Malik *et al.*, 2023). Peptic ulcer disease (PUD) accounts for an estimated lifetime prevalence of 5 - 10 % and an annual incidence of 0.1 - 0.3 % in the general

population in Western countries (Lanas & Chan, 2017). Nigeria has been listed as a high area of PUD prevalence with more than 100,000 cases reported annually while in US alone, more than six million people are affected each year (Eniojukan *et al*., 2017; WHO, 2018). It is predicted that about 10 % of population will develop PUD, with the ratio slightly higher in men than in women (1.3:1), although it occurs in all age (Lanas & Chan, 2017).

The predominate causes of PUs are *Helicobacter pylori* (*H. pylori*) infections, ingestion of non-steroidal anti-inflammatory drugs; NSAID and stress factors like smoking, alcohol and a variety of other infections are believed to increase its occurrence (Narayanan *et al*., 2018).

Although, PU heals upon satisfactory suppression of gastric acid; therapy is found to be very effective with pharmaceutical agents such as antacids, anticholinergic drugs, histamine H_2-receptor antagonists, proton pump inhibitors which regains the balance between the aggressive factors and the defensive factors and neutralizes or reduces gastric acid production. Unfortunately, adverse effects such as constipation, diarrhoea, dizziness, dry mouth, abdominal cramps, edema, development of tolerance and incidence of relapses of these drugs affect patient compliance and ultimately overall therapy (Alhammadi *et al.,* 2020). This has led to investigations of alternative pharmacologically active leads such as crude plant extracts which are cheap, readily available, better cultural acceptability and have relatively fewer side effects making it a desirable, better and safer approach (Olayemi *et al*., 2021).

Plants have been used for treatment of various diseases from medieval times and their uses are being passed down from generation to generation. They are potential sources in the discovery and development of new therapeutic agents (Blunt *et al*., 2018).

Ethnobotanical claims show some plants that have been used as antiulcer; these include bulbs of *Allium sativum,* root extracts of *Cassia sieberiana,* stem bark extract of *Anogiesuss leiocarpus,* seedpods of *Acacia nolitica* (Bello *et al*., 2016, Datok *et al*., 2022, Abdulazeez & Balogun, 2023).

The plant investigated in this study is *Anogeissus leiocarpus* belongs to the family Combretaceae and is widely distributed in Central, East, and West African countries. It is commonly called the "African Birch" and known in Nigerian local languages as *Otra* (Idoma), *Kwankila* (Hausa), *Atara* (Ibo) and *Orin-odan* (Yoruba) (Rufa'i H. *et al*., 2022). Anecdotal reports from the South-Western and South-Eastern parts of Nigeria reveal that the plant can be used in treatment of bacterial infections. Scientific investigations of these folklore beliefs show the plant is useful for management/treatment of stomach ulcers (Fokam-Tagne *et al*., 2021, Rufai'H *et al.,* 2022).

Although plant extracts offer good pharmacological efficacy in treatment of diseases, their use is often times limited because of the mode of presentation which is usually in form of decoctions or infusions. Formulation into presentation dosage forms, like effervescent granules in this case, is a step towards achieving good patient compliance and overall successful therapy. Effervescent granules are formulations containing medicinal agents in a dry mixture, they are easy to carry and administer, mask unpleasant tastes, have rapid onset of action, fast dissolution and disintegrating properties hence an immediate therapeutic effect. In addition, their ability to produce fizzy gases gives some form of aesthetic value (Maysarah *et al.,* 2020).

The aim of this study is to prepare effervescent granules containing the aqueous extract of stem bark of *Anogiessius leocarpus* by the fusion method and wet granulation methods and to evaluate the physicochemical properties of the prepared granules.

Materials and Methods

Materials

Citric acid (BDH chemicals Ltd, UK), tartaric acid (Fluka Chemika, Switzerland), Sodium bicarbonate (BDH chemicals Ltd, UK), Lactose (BDH chemicals Ltd, UK), Ethanol (Analytical grade), Aqueous extract of stem bark *Anogiessius leocarpus* (prepared in the National Institute for Pharmaceutical Research and Development, NIPRD, Abuja, Nigeria).

Methods

Collection and preparation of aqueous extract of stem bark of *Anogiessius leocarpus*

The stem bark of *Anogiessius leocarpus* was collected from the botanical garden in National Institute for Pharmaceutical Research and Development (NIPRD), it was identified in the Institute's herbarium and assigned a voucher number (NIPRD/H/7286). The bark materials were crushed in a mechanical grinder to coarse powder. The crushed material was macerated in water (1:5) at room temperature for 24 h, afterwards, the mixture was filtered using a muslin cloth, the filtrate was concentrated over a water bath (Karl Kobb, Dreieich, West Germany) at 70 °C. the resulting dried powdered material; the aqueous extract of *Anogiessius leocarpus* stem bark (AGLE).

Preparation of effervescent granules of aqueous extract of stem bark *Anogiessius leocarpus*

Four (4) different batches were prepared according to the compositions stated in Table 1. Different ratios of acid to base were employed for the preparation of two (2) batches using the fusion method and similar ratios were also used for the preparation of two (2) using the wet granulation method.

For the preparation by fusion method; appropriate quantity of citric acid was weighed in a mortar and mixed with tartaric acid, the extract was added with gentle stirring then sodium bicarbonate was incorporated into the contents of the mortar, lactose was added to the mortar and mixed. The powder mixture was poured into a heated porcelain dish placed over a water bath and mixed well until a uniform mass produced as a result of release of water of crystallization from citric acid is obtained. The mass was passed through a sieve with mesh size of 250 µm to obtain granules then the granules were dried in an oven at 55 ^{o}C for 4 h.

Effervescent granules obtained by wet granulation were prepared by mixing appropriate quantities of citric acid, tartaric acid, AGLE, sodium bicarbonate and lactose as done in the fusion method. Some quantity of ethanol sufficient to make a damp mass was incorporated in the powdered mixture, the mass was passed through a sieve with mesh size of 250 µm to obtain granules and the granules were dried in an oven 55 ^{o}C for 4 h.

Table 1: Composition of ingredients for preparation of effervescent granules

Ingredients/Batches	F1	F2	G1	G2
AGLE (g)	0.5	0.5	0.5	0.5
Lactose (g)	8.5	1.0	8.5	1.0
Citric acid (g)	1.5	1.5	1.5	1.5
Tartaric acid (g)	1.5	3.0	1.5	3.0

Sodium bicarbonate (g)	3.0	9.0	3.0	9.0
Ethanol (mL)	-	-	qs	qs

Evaluation of effervescent granules

Organoleptic properties

The color, appearance and odor of the granules were determined by visual assessment.

Determination of angle of repose

The angle of repose was measured by the fixed funnel method using the internal angle subtended by the surface of a heap of powder against the plane that supports it. The internal angle between the surface of the heap and the horizontal surface which is the angle of repose (AOR) was calculated as the ratio of the tan inverse of the height (h) of the cone and the radius of the cone (r).

$AOR = tan - 1h/_r$..1

Determination of moisture content

The effervescent granules (1g) were weighed, placed into a porcelain dish and dried in a hot air oven at 60 ºC for 2 h and reweighed. This process was continued until a constant weight was obtained. The difference in granule weight was calculated and the moisture content was computed in percentage.

Determination of effervescence time

The effervescence time of the effervescence granules was determined by weighing a dose of the granules into a beaker containing 250 mL of water, the time taken for effervescence to cease and the solution to become clear was noted (Grajang & Wahyuningsih, 2019).

Determination of pH

This was done by dissolving the granules in distilled water to make 1% w/v solution. The pH of the solution was determined using a digital pH meter (Mettler Toledo). Three determinations were made and the average was computed.

***In vitro* dissolution studies**

Calibration curve of the aqueous extract of *Anogiessius leocarpus* stem bark (AGLE) was constructed by preparing varying concentrations of the extract; 0.02 - 50 µg and the corresponding absorbance was gotten from the UV-Visible Spectrophotometer (Agilent Cary 60, USA) at the scanned maximum wavelength of 230 nm.

Dissolution studies was carried in the Apparatus II type Dissolution tester (RC-6, India) containing 0.1 N Hydrochloric acid (900 mL) maintained at 37 ± 0.5 ºC. the apparatus was set to rotate at 50 rpm, at specified time intervals (1, 3, 5, 10, 15 min), 5 mL aliquot was withdrawn and immediately replaced with equal volume of fresh dissolution medium. The sample withdrawn was filtered and diluted with the medium, the absorbance was determined at 230 nm using the UV Spectrophotometer and the percentage of extract released per time was calculated from the calibration curve.

Results

All the effervescent granules were light brown in color with a characteristic odor, and granular texture. The color of the effervescent granules upon dissolution in water was dull yellow.

Moisture content of all the prepared effervescent granules as displayed in Table 2 fell between 1.46 and 1.72 % with formulations F2 and G2 having higher amount of moisture than F1 and G1.

The flow properties of the effervescent granules (Table 2) show that the angle of repose of all the effervescent granules was between 31.36 and 37.04 ° with the highest value being for formulation G2. The flow rate of the granules was between 0.48 and 1.74 g/s with formulation G2 having the longest flow time.

Table 2: Organoleptic and physicochemical properties of prepared effervescent granules

Parameters/Batch	F1	F2	G1	G2
Color	Light brown	Light brown	Light brown	Light brown
Appearance	Granular	Granular	Granular	Granular
Odor	Characteristic	Characteristic	Characteristic	Characteristic
Moisture content (%)	1.46	1.58	1.64	1.72
Angle of repose (°)	37.04 ± 1.15	32.16 ± 0.64	31.36 ± 5.42	36.51 ± 3.33
Flow rate (g/sec)	0.77	1.30	0.64	0.48
pH	5.96 ± 0.02	7.29 ± 0.01	5.85 ± 0.01	7.30 ± 0.01
Effervescence time (sec)	150	86	104	99

The pH of the granules after reconstitution in water was observed to be between 5.85 and 7.30; formulation F2 and G2 had similar high pH (7.29 and 7.30 respectively) while F1 and G1 had similarly low values (5.96 and 5.85 respectively).

Formulations F2 and G2 with the highest amount of sodium bicarbonate had the lowest effervescence time (86 and 99 sec respectively); while formulations F1 and G1 with equal amount of acid to base ratio had the longest effervescence time (150 and 104 sec respectively).

The amount of extract released from the effervescent granules is also displayed as Figure 1. The release at 1 minute was found to be higher from formulations F2 and G2 (68.82 and 63.29 % respectively) while G1 and F1 had the least release (51.23 and 36.54 % respectively). Similarly, at 5 minutes, the release was observed to follow the same pattern with F2 having the highest release. At the end of the period the order of release was G2>F2>G1>F1.

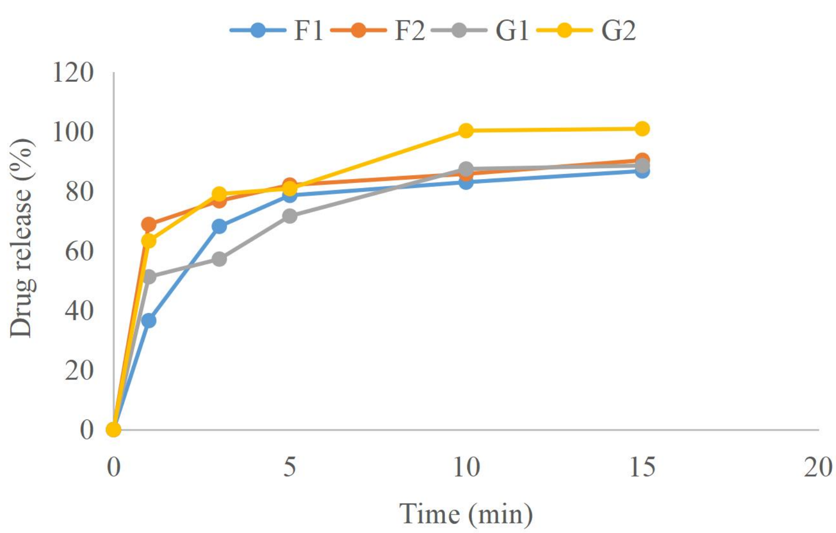

Figure 1: dissolution profile of effervescent granules containing *Anogiessius leocarpus* extract

Discussion

The organoleptic features of the effervescent granules were found to be characteristic as a result of the extract incorporated into the formulation.

Moisture content plays a crucial part in product formulation and stability, excessive moisture could lead to crystallization, decrease in powder flow and promotion of microbial growth during storage (Kumadoh *et al*., 2023). Although the main ingredient used in formulation of effervescent granules is rather hygroscopic, it is important to limit excessive moisture in the preparation so as to prevent premature effervescent reaction. The acceptable limit set of moisture content for effervescent granules is between 0.5 % (Giyatmi and Lingga, 2019). However, our results fell outside the acceptable limit due to high relative humidity of the room where the preparations were made. Efforts to reduce the humidity of the room to 25 % which is the requirement for preparation of effervescent granules (Wati & Saryanti, 2019) proved abortive as the least humidity achieved was about 30 % at a temperature of about 31 ^{o}C. It is important to state here that such high humidity and temperature are not uncommon in tropical regions of the world including Nigeria. Other studies also recorded similar high values in their formulations (Giyatmi and Lingga, 2019; Wati & Saryanti, 2019).

The high amount of moisture found in formulations F2 and G2 could be due to the large amount of sodium bicarbonate used in the preparations. Sodium bicarbonate although not hygroscopic, has ability to absorb moisture as such, its presence in the preparations (F2 and G2) could be responsible for the increased moisture content. On the other hand, low moisture content points to the ability of these granules to flow more freely and retain better effervescence quality. Generally, the granules prepared by fusion technique had lower moisture content and is attributed to the fact that unbound water in these granules evaporated more readily than from those prepared by the wet granulation method (Jassim *et al.*, 2018).

The evaluation of flow properties of granules is important in ensuring reproducibility of filling, dose consistency and weight uniformity of each batch. The flow properties of the effervescent granules as investigated by the angle of repose are presented in Table 2. Generally, granules with <25 ^{o} are said to have excellent flow, with 25-30 ^{o} considered as good flow, 30-40 ^{o}; moderate flow and >40 ^{o}; poor flow (Al-Mousawy *et al.,* 2019). According to Widayanti *et al.*, (2012), the difference in concentration of citric acid to tartaric acid (1:2), as contained in F2 and G2 can affect good flow properties. Tartaric acid is known to have greater density than citric acid so that granules containing more tartaric acid will have greater density; these large densities show large molecular weights that will flow more easily due to greater force of gravity (Grajang & Wahyuningsih, 2019). Other factors that influence the flow of a material includes the particle size, shape, density, porosity, particle frictional forces and experimental conditions. Our results show no particular pattern in values of angle of repose obtained by the fusion or wet granulation technique. However, all the effervescent granules prepared by both techniques were observed to have moderate flow with low cohesiveness.

The flow rate of the granules was found to be within the acceptable limit of 10g/s for flow of granules (Maysarah *et al*., 2020). Our results show that for formulations prepared by the fusion method, flow time decreased with increase in amount of sodium bicarbonate. However, for those prepared by wet granulation, flow time increased with increase in amount of sodium bicarbonate.

This implies that the granules prepared by fusion technique had better flow than those prepared by wet granulation method. Consequently, the amount of citric acid, tartaric acid, and sodium bicarbonate and method of preparation are observed to significantly influence the flow of the effervescent granules.

Determination of pH of effervescent granules is important to predict the acidity of the solutions. Solutions with low pH are acidic and can cause irritation in the mouth and stomach while highly alkaline solutions with high pH have bitter/sour tastes both of which affects patient compliance (Grajang & Wahyuningsih, 2019). The difference in the ratio of citric acid to sodium bicarbonate was observed to affect the pH of the formulations. F2 and G2 which had the highest amount of sodium bicarbonate had the highest pH which is due to higher ratio of citric acid to base (1:3). On the other hand, formulations F1 and G1 with lower citric acid to base ratio (1:2) had lower pH. Increase in acid proportion has been reported to play significant role in increasing the concentration of unreacted (H_3O^+) ions. The acceptable pH of effervescent solutions is said to be close to neutral; between pH 6 and 7 (Herlina *et al.,* 2020) and our results show that F2 and G2 met this specification. However, formulation F1 and G1 can also be considered suitable because their pH appeared to be close to the acceptable range.

Effervescence time is an indication of disintegration, dispersion and cessation of gas evolution in solution containing effervescent granules and is also known as the granule soluble time which is specified to be within 5 min (Forestryana *et al*., 2022). The process of disintegration begins with the penetration of water into the effervescent granules which brings about the acid and base reaction resulting in evolution of carbon dioxide (Grajang & Wahyuningsih, 2019). Our results show effervescence time of all the granules was within the required time limit. Formulations F2 and G2 with the highest amount of sodium bicarbonate had the shortest effervescence time; high concentration of sodium bicarbonate causes faster evolution of carbon dioxide and consequently, faster granule disintegration. Furthermore, effervescent granules containing smaller amount of citric acid in the presence of high sodium bicarbonate concentration are known to dissolve faster in water due to the action of sodium bicarbonate which improves porosity of the granules resulting in increased rate of carbonation (Herlina *et al*., 2020). Another reason for the faster effervescence time observed in these formulations could be ascribed to the presence of high amounts of base to acid then which led to more intense effervescence reaction, hence more rapid disintegration and dissolution of the granules than in other formulations (Giyatmi & Lingga, 2019). However, formulations F1 and G1 with equal amount of acid to base ratio had the longest effervescence time.

In vitro dissolution profile of the prepared effervescent granules is shown in Figure 1. Generally, there was rapid extract release from all the formulations which can be attributable to burst effect of the granules facilitated by production of carbon dioxide upon effervescence. The initial release at 1 minute was higher from F2, then G2 and G1, formulation F1 had the least release. The release pattern was similar at 5 min however, at the end of the dissolution period, extract release was observed to be significantly higher ($p < 0.05$) in formulation G2 prepared by wet granulation than in F2, G1 or F1 in that order. Rapid release from the wet granulation formulation may be due to breakdown and subsequent weakening of bonds during the granulation process resulting in faster release than F2 prepared by fusion method. On the other hand, faster release from formulations G2 and F2 could be due to the fact that they contain high amount of sodium bicarbonate which is responsible for generation of carbon dioxide which in turn leads to rapid drug release.

Conclusion

In this preliminary study, we have been able to successfully prepare effervescent granules containing the aqueous extract of *Anogiessius leocarpus* by the fusion and wet granulation method. The ratio of acid to base and the method preparation were observed to affect the physicochemical properties of the granules. Effervescent granules containing higher ratio of acid to base and prepared by the wet granulation method (G2) and fusion method (F2) were considered the optimum formulations based on the parameters investigated. However, further studies would be necessary to fully optimize the process.

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Conflict of interest

There is no conflict of interest. No external financial support was obtained for this study.

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