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Original Research Article

Development and Standardization of an Effervescent Granule Formulation of Pomegranate Peel Extract with Potential Antioxidant Activity

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ABSTRACT

Free radicals are unstable compounds that can cause oxidative stress, which plays an important role in the development of degenerative diseases such as cancer, diabetes, and cardiovascular disorders. Natural antioxidant compounds can help mitigate the negative impact of free radicals. Pomegranate peel has highly potent antioxidant activity, but its application in stable, effective, and pharmaceutical grade dosage forms requires improvement. This study aimed to develop, standardize, and optimize an effervescent granule formulation of pomegranate peel extract, and evaluate its antioxidant activity. Pomegranate peel extract was prepared by maceration in ethanol (70%). Phytochemical screening and standardization of the extract were done following standard procedures. Effervescence granules preparations of pomegranate peel extract was made in five formulas (Formula 1 – 5). The physical characteristics of the effervescence granules formulations were assessed based on relevant parameters to ensure that the resulting preparation is stable, effective, and easy to consume the antioxidant activity of the effervescence granules formulations was evaluated using the 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging assay. Formula 3 of the effervescent granule preparation of pomegranate peel extract showed the best physical characteristics, with optimal moisture content, flow rate and dissolution time. Furthermore, this formula exhibited strong antioxidant activity with IC_{50} value of 48.71 ± 0.42 µg/mL. Therefore, the effervescent granule formulation of pomegranate peel extract shows potential as an effective and practical pharmaceutical preparation, with strong antioxidant activity. However, more research is needed to assess its long-term stability.

Keywords: Pomegranate peel extract, Effervescent granule, Antioxidant activity, Oxidative stress, Standardization.

Introduction

Free radicals are unstable reactive compounds that can cause oxidative stress. Oxidative stress is a contributing factor to various degenerative diseases, such as cancer, diabetes, and cardiovascular disorders.[1] Therefore, it is important to mitigate the negative impact of these free radicals by the use of antioxidant compounds that can effectively neutralize free radicals. As the awareness of the dangers of free radicals increases, the use of natural antioxidant compounds as a safer alternative to synthetic antioxidants is gaining attention. In contrast to synthetic compounds, natural antioxidants from plant materials are considered safer and have a wider range of potential health benefits.[2,3] Pomegranate peels are rich source of natural antioxidant compounds. Pomegranate peels contain various bioactive compounds, such as flavonoids, tannins, saponins, and polyphenols, which have been shown to have strong antioxidant activity.[4–6] These compounds, such as gallotannin, ellagitannin, anthocyanins, hydroxycinnamic acid, and hydroxybenzoic acid, contribute to the prevention of free radical-induced cellular damage and provide additional health benefits, such as anti-inflammatory and antimicrobial properties.[7–9]

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Therefore, pomegranate peel extract can be a good choice as a natural source of antioxidants. Effervescent granules are one of the pharmaceutical dosage forms that are commonly used for improved drug delivery. They dissolve easily in water and provide a fresh sensation, which can improve the acceptability of the product by patients, especially those who have difficulty swallowing tablets or capsules. The formulation of effervescent granules with pomegranate peel extract do not only maintains the stability of the bioactive compounds in the extract but also increases its effectiveness in providing health benefits. Furthermore, the effervescent component can help enhance the release of active substances from the formulation.[10]
Although many studies have explored the antioxidant activity of pomegranate peel, the application of this extract in effervescent granule dosage forms that are stable, effective and meet pharmaceutical quality standards needs to be investigated. To produce a quality product, effervescent granule formulations must undergo careful development and standardization, by optimizing their physicochemical parameters such as moisture content, compressibility index, and dissolution time. This standardization is important to ensure that the resulting product is not only effective, but also safe, stable, and convenient to use.
This study aimed to develop an optimal formulation of effervescent granules of pomegranate peel extract and to standardize the formulation according to relevant pharmaceutical parameters. It is hoped that the results of this study will not only produce products that meet quality and safety standards but also provide a practical and innovative alternative to plant-based medicine for patients who need easy-to-consume preparations while increasing the efficiency of active substance release.

Materials and Methods

Chemicals
Ethanol (96%) (PT. Brataco, Indonesia), polyvinylpyrollidone (PVP K30) (Sigma Aldrich, St. Louis, MO, USA), citric acid (PT Brataco, Indonesia), tartric acid (PT Brataco, Indonesia), sodium bicarbonate (PT Brataco, Indonesia), xanthan gum (Sigma Aldrich, St. Louis, MO, USA), 1,1-diphenyl-2-picrylhydrazyl (DPPH) (Sigma Aldrich, St. Louis, MO, USA), maltodextrin and lactose (PT Brataco, Indonesia).

Collection of plant material
Pomegranate were obtained from Subang, Indonesia, the peels were carefully removed, dried and ground into a fine powder. The plant material was collected in December 2023 and has been identified at Herbarium Jatinangoriensis, Biosystematics and Molecular Laboratory, Department of Biology, Universitas Padjadjaran, Indonesia (No.250/LBM/IT/XII/2023).

Preparation of pomegranate peel extract
Powdered pomegranate peels (1 kg) were macerated in 70% ethanol at room temperature for 72 h with occasional stirring. Extract was collected every 24 h, and the solvent replaced. The combined extracts were evaporated using a rotary evaporator (Rotavapor R-300, PT. BUCHI, Indonesia) at a speed of 30 rpm and a temperature of 40°C until a thick extract was obtained.

Phytochemical screening and standardization of pomegranate peel extract
Pomegranate peel extract was subjected to phytochemical screening to detect the presence of alkaloids, flavonoids, saponins, quinones, tannins, and steroids/triterpenoids. The phytochemical tests were performed using specific reagents for each compound, such as Dragendorff's reagent for alkaloids, aluminum chloride for flavonoids, and hydrochloric acid for saponins.[11] Standardization of the extracts was carried out by evaluating quality parameters, namely; total ash, acid insoluble ash, and drying shrinkage, to ensure the stability and purity of the extracts produced.[12]

Effervescent Granule Formulation of Pomegranate Peel Extract
The formulation of effervescent granules (Table 1) was carried out in five replicates. The formulation consists of the active substance (pomegranate peel extract) at a concentration of 19%, and other additives, including polyvinylpyrrolidone (PVP), citric acid, tartaric acid, sodium bicarbonate, maltodextrin, xanthan gum, and lactose.

Evaluation of the physical properties of pomegranate peel extract effervescence granules
Determination of organoleptic properties
Organoleptic tests were performed by assessing parameters such as shape, colour, taste, and aroma.

Determination of moisture content (weight loss on drying)
A total of 1 g of the effervescent granule formulation was placed on the plate of the moisture analyzer (Moisture Analyzer MA 50. R, Radwag, Miami, FL, USA). The device was set at a temperature of 105°C, and heating was continued until a constant weight was achieved. Data were documented after the device exhibited a stable weight during heating.

Determination of flow rate, angle of repose, and compressibility index
A total of 25 g of the effervescent granules were placed in a flowmeter funnel. The flow rate was determined by observing the time it took to pass through the funnel until it completely ran out. The angle of repose was obtained by measuring the diameter and height of the formed pile. A total of 25 g was put into a measuring cup in a volumenometer (Tapped Density Tester Erweka SVM 221, Erweka, Germany). The compressibility index was determined from the final volume after 250 taps.[13]

Determination of solubility, sedimentation volume, foaming index, and pH
The granule dissolution time test was performed by weighing multiple samples and dissolving them in water at a 1:10 ratio (sample to solvent).[14] After 15 minutes, the sedimentation volume is measured to determine how much granule has settled to the bottom of the container. The sedimentation volume provides information on the stability and availability of the active ingredient in the solution. The measurement of foam height during acid and base reactions in effervescent granules is essential in preparation analysis. The data obtained from this measurement provide insight into reaction efficiency, preparation quality, and stability, all of which contribute to developing better and more effective formulations. pH was measured using a pH meter (Mettler Toledo S-220-KIT / S220-Kit pH Meter, Swiss), and the value obtained was recorded.

Determination of shape, morphology, and particle size
The shape and surface morphology of the formulation were observed using a scanning electron microscope (SEM) (JSM-6360, Jeol, Tokyo, Japan) with magnifications of 50 and 200×. The particle size was determined using a particle size analyzer (Horiba SZ-100, Horiba Ltd., Kyoto, Japan).

Table 1. Effervescent granule preparation formula

Materials	Function	Composition (%)				
		F1	F2	F3	F4	F5
Polyvinylpyrolidon	Binder	3	3	3	3	3
Citric acid	Acid source	0.3	2	0.725	1.15	1.575
Tartric acid	Acid source	25	10	21.25	17.5	13.75
Sodium bicarbonate	Base source	25	25	25	25	25
Maltodekstrin	solubility enhancers	3	3	3	3	3
Xanthan gum	Suspending agent	1	1	1	1	1
Lactose	Filler	Ad 100	Ad 100	Ad 100	Ad 100	Ad 100
Total		100	100	100	100	100

Determination of antioxidant activity

The antioxidant activity of the pomegranate effervescence granules formulation was evaluated using the DPPH radical scavenging activity. The samples and positive control (ascorbic acid) were prepared at concentrations ranging from 30 to 80 ppm, and from 1 to 5 ppm, respectively. DPPH solution (100 µL) at a concentration of 0.2 mg/mL in ethanol was added to 100 µL of the different concentrations of the sample and positive control. The mixtures were left in the dark for 30 minutes at 25°C, after which the absorbance was measured at 515 nm (Spectrophotometers Shimadzu UV-1800 - UV-Vis, Japan). The IC_{50} values for the test sample and the positive control were calculated from the linear regression equation of the percentage inhibition vs. concentration.[15]

Results & Discussion

Extract yield and phytochemical constituents of pomegranate peel extract

Extraction of 1 kg of powdered pomegranate peel resulted in 213.5 g of extract, which is equivalent to a percentage yield of 21.35%. phytochemical screening detected the presence of six secondary metabolites in pomegranate peel extract. The secondary metabolites detected include alkaloids, flavonoids, saponins, quinones, tannins, and steroids/triterpenoids.[16] Alkaloids are compounds often found in various medicinal plants and are known to have anti-inflammatory and antibacterial properties. On the other hand, flavonoids are compounds with strong antioxidant properties. Saponins are known to have antitumor effects and can boost immunity. Quinones also have antioxidant activity and protect body cells from damage due to free radicals. Tannins are compounds that can bind to proteins and have potential as anti-inflammatory and antiviral agents.[3] Steroids/triterpenoids are known to have anti-inflammatory properties and can play a role in the treatment of various diseases.[17] Therefore, pomegranate peel extract is known to have a high antioxidant protective value. [9,16] The presence of these phytochemicals in pomegranate peel extract suggest that the plant has great potential as a natural remedy that can be used in traditional medicine or as a natural ingredient that can be used in the manufacture of various health products.

Standardized pomegranate peel

The standardized moisture content was 7.33%, which is below the reference limit of 17.8%. Low moisture content prevents microbial growth, and improve stability of the formulation. The total ash content was 0.27%, which is well below the reference limit (<3.7%), indicating that there were few mineral or inorganic contaminants in the powdered pomegranate peel. The acid-insoluble ash content was 0.043%, below the reference (<0.2%), reflecting a high purity with very low insoluble material. Based on the results obtained, pomegranate peel met the specifications for crude herbal products.[18]

Physical properties of the effervescent granule of pomegranate peel extract

The effervescent granules containing pomegranate peel extract appeared as small brown particles. They possess a slightly bitter and sour taste, characteristic of the natural compounds found in pomegranate peel. These granules are formulated to dissolve quickly in water, releasing bubbles, and providing a refreshing sensation when consumed (Figure 1).

There were no significant variations in the organoleptic properties among the various replicate formulations of pomegranate peel extract effervescence granules (Table 2). All the formulas have a brown colour, a distinctive aroma of pomegranate peel extract, a granular shape, and a taste that tends to be sour and bitter. This shows that the organoleptic properties of the preparation are consistently maintained in each formula.

The moisture content (loss on drying) showed similar results in all the formulas, with values ranging from 0.85% to 1.06%. Formula 3 had the lowest moisture content of 0.85 ± 0.15%, which indicated that the formula had an optimal moisture to maintain the stability of the granules without causing clumping or damage to the preparation.[19]

Figure 1: Granule of pomegranate peel extract.

The granule flow rate increased as the formula improved, with formula 3 showing the highest flow rate of 12.06 ± 0.46 g/s, indicating that this granule had good flow properties and was easy to process in the production stage. Formula 4 had a slightly higher flow rate (12.61 ± 0.99 g/s) but was not significantly different from the other formulas.[20]

The granule flow rate increased as the formula improved, with formula 4 showing the highest flow rate of 12.61 ± 0.99 g/s, indicating that this granule had good flow properties and was easy to process during the production stage. Formula 3 had a slightly lower flow rate (12.06 ± 0.46 g/s) but was not significantly different from that of formulas 4 and 5.

Formula 3 had the lowest angle of repose value (23.03 ± 0.15°), which indicates that the granules of this formula are stable and flow easily. Meanwhile, formula 4 had the largest angle of repose (28.07 ± 0.96°), which indicates a higher tendency to agglomerate.[20]

The compressibility index in formula 3 showed the best value (10.57 ± 0.32%), indicating that the granules in this formula had optimal compressibility. Formula 2 and Formula 4 showed higher values (14.40 ± 3.04% and 14.28 ± 0.64%, respectively), which may indicate the tendency of granules to agglomerate more rapidly.[21,22]

The dissolution time showed varying results, with formula 3 having the fastest dissolution time at 3.22 ± 0.97 min, while formula 2 had a longer dissolution time (5.20 ± 0.23 min). This suggests that formula 3 dissolves faster in solution, which is important to ensure effective release of the active substance.[23]

The height of the foam formed also showed significant differences among the various formulas. Formula 5 produced the highest foam (3.00 ± 0.00 cm), while Formula 2 produced the lowest foam (0.63 ± 0.32 cm). Higher froth may indicate the efficiency of the effervescent component in improving the sensation of freshness and CO_2 release.[24]

The pH of the preparation varied between 4.71 ± 0.04 (formula 1) and 7.07 ± 0.08 (formula 2), indicating a variation in its acidity. Higher pH tends to be better accepted by the body and can improve compliance. Lastly, the relatively low sedimentation volume in all formulas, especially formula 3 (0.95 ± 0.01 mL), indicates that this preparation has good stability and does not easily sediment.[25,26]

In general, formula 3 showed the most optimal results with good moisture content, flow rate, angle of repose, dissolution time, and sedimentation volume and had significant antioxidant activity. Further evaluation of the long-term stability and clinical effectiveness of these formulas is necessary to ensure the quality of the final product.

Morphology and particle size

The results of the morphological test of the effervescent granules of pomegranate peel extract using a scanning electron microscope (SEM) at 50× and 200× magnifications is presented in Figure 2. The results showed that formula 3 is the best formula based on the physical properties of the previously tested granules. From the scanning electron microscopy, it was observed that the surface of the granule had a hollow structure and did not form tight crystals.

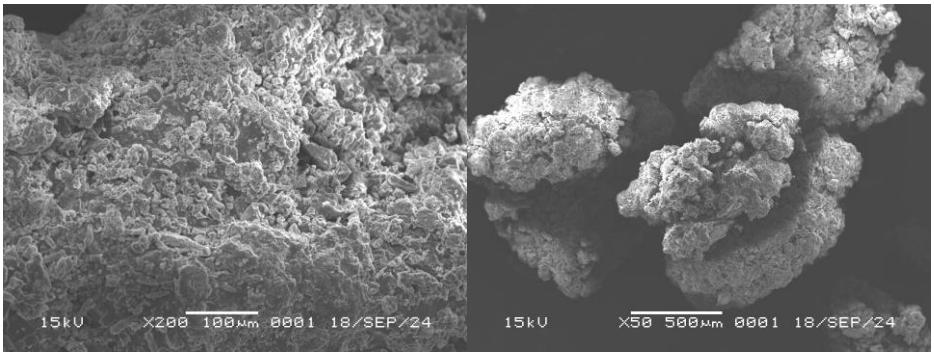

Figure 2: Typical morphology of the pomegranate peel extract granules.

Table 2. Physical characteristics of effervescent granules of pomegranate peel extract

Parameter	Formula				
	1	**2**	**3**	**4**	**5**
Colour	Brown	Brown	Brown	Brown	Brown
Aroma and flavour	Pomegranate peel extract	Pomegranate peel extract	Pomegranate peel extract	Pomegranate peel extract	Pomegranate peel extract
Shape	Granule	Granule	Granule	Granule	Granule
LoD* (%)	1.06 ± 0.12	0.88 ± 0.06	0.85 ± 0.15	0.89 ± 0.12	0.86 ± 0.09
Flow rate (g/s)	10.26 ± 1.48	10.76 ± 0.83	12.06 ± 0.46	12.61 ± 0.99	12.11 ± 0.34
Angle of repose (°)	24.15 ± 1.02	24.31 ± 2.42	23.03 ± 0.15	28.07 ± 0.96	27.37 ± 0.49
Compressibility Index (%)	13.03 ± 2.40	14.40 ± 3.04	10.57 ± 0.32	14.28 ± 0.64	12.17 ± 0.76
Dissolution time (min)	3.67 ± 0.68	5.20 ± 0.23	3.22 ± 0.97	3.33 ± 0.15	3.70 ± 0.39
Foaming index (cm)	1.40 ± 0.17	0.63 ± 0.32	2.50 ± 0.30	2.73 ± 0.25	3.00 ± 0.00
pH	4.71 ± 0.04	7.07 ± 0.08	4.90 ± 0.52	6.23 ± 0.71	6.26 ± 0.17
Sedimentation volume (mL)	1.05 ± 0.01	1.20 ± 0.00	0.95 ± 0.01	1.00 ± 0.00	1.00 ± 0.00

*LoD: Loss on Drying

These morphological characteristics can affect the solubility of granules in liquids. Granules with a hollow structure tend to dissolve more easily because of empty spaces, allowing wider contact between the particles and the solvents, which can accelerate the dissolution process.
The presence of voids on the surface of the granules is likely due to the evaporation of solvents that were previously bound to the surface of the particle during the heating and drying process. This evaporation of the solvent leads to the formation of small cavities on the surface of the granule, which in turn increases the solubility of the preparation in liquid.[13,27] These cavities can also serve as channels for the release of effervescent gases, providing a fresh sensation when the preparation dissolves in water. The presence of these cavities can improve the physical characteristics of the preparation by improving the dissolution rate and release potential of the active substance.[27]
Furthermore, formula 3, recognized as the best formula, was further analyzed using a scanning electron microscope (SEM) and a particle size analyzer (PSA) for more accurate particle size measurement. The results showed that formula 3 granules had a particle size of 1209 µm (Figure 2). This advanced technique confirmed the particle size distribution and provided further insights into the structure of the granules, reinforcing formula 3 as the most suitable option due to its favorable dissolution properties. However, in effervescent formulations, this slightly larger particle size can improve product stability and provide sufficient time for effervescent reactions to occur optimally.[28,29]

The morphology and particle size of the effervescent granule of the pomegranate peel extract revealed the appropriate characteristics needed to produce a stable and effective preparation. The hollow structure of the granule supports good solubility, while the relatively large particle size favors efficient release of the active substance and improved product acceptability. However, to ensure long-term consistency and quality, further evaluation of the stability of the preparation, as well as the influence of other factors, such as humidity and temperature, on the morphology and particle size, is necessary.

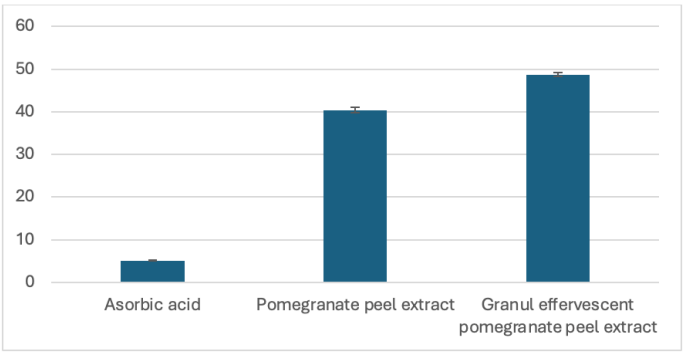

Figure 3: Antioxidant activity (**IC_{50}** value) of pomegranate peel extract, effervescence granules of pomegranate peel extract, compareded to ascorbic acid.

Antioxidant activity of the formulation

The antioxidant activity of the pomegranate peel extract as well as its effervescence granule formulation is presented in Figure 3. The results were presented as IC_{50} values of DPPH radical scavenging activity. The IC_{50} value denotes the sample concentration required to inhibit 50% of DPPH free radical. The lower the IC_{50} value, the stronger the antioxidant activity of the sample.[1]

The results showed that vitamin C had a very low IC_{50} value of 5.13 ± 0.08 µg/mL, indicating its strong antioxidant activity. This is consistent with its role as an antioxidant effective in counteracting free radicals.[30] On the other hand, the pomegranate peel extract has an IC_{50} value of 40.41 ± 0.64 µg/mL, indicating that pomegranate peel extract has good antioxidant activity, although not as strong as vitamin C. Pomegranate peel extract is known to be rich in polyphenolic compounds, such as flavonoids, which may play a role in the antioxidant effects.

The effervescent granule containing pomegranate peel extract showed a slightly higher IC_{50} value of 48.71 ± 0.42 µg/mL. Although the antioxidant activity was slightly lower than that of pure pomegranate peel extract, these results indicate that the effervescent granule preparation retains good antioxidant potential. The decrease in IC_{50} value may be attributed to the formulation and processing process, which may have affected the stability or presence of active compounds in the preparation.

Although the effervescent granule preparation had lower antioxidant activity than the pure pomegranate peel extract and vitamin C, it still exhibited significant potential as a source of antioxidants, which could be used as a plant-based natural alternative to synthetic antioxidant compounds.

Conclusions

This study successfully designed and developed a pomegranate peel extract-based effervescent granule formulations with good physical characteristics, especially Formula 3. Formula 3 showed optimal results, with a moisture content of 0.85 ± 0.15%, a flow rate of 12.06 ± 0.46 g/s, an angle of repose of 23.03 ± 0.15°, compressibility index of 10.57 ± 0.32%, a dissolution time of 3.22 ± 0.97 min, a foaming index of 2.50 ± 0.30 cm, a pH of 4.90 ± 0.52, and a sedimentation volume of 0.95 ± 0.01 mL. Furthermore, formula 3 also showed strong antioxidant activity with IC_{50} value of 48.71 ± 0.42 µg/mL, indicating a high potential of pomegranate peel extract to neutralize free radicals.

These findings indicate that the effervescent granule formulation of pomegranate peel extract has good physical quality and significant antioxidant activity, making it an effective and practical alternative pharmaceutical preparation. However, further studies are needed to assess the stability of the effervescent granule preparation in more depth to ensure the long-term quality of this product.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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