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Research Article

Granulation Methods Dependent Physical Characteristics of Chitosan Effervescent Granule Suspension from Mangrove Crab (*Scylla serrata*) Shell

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Abstract

The mangrove crab (*Scylla serrata*), a prevalent resource in coastal mangrove ecosystems, is widely utilized for consumption. Its shell offers a valuable source of chitosan, a biopolymer readily synthesized and recognized for its potential health benefits. Chitosan's unique structure, characterized by the presence of amine groups, imparts a strong positive charge, enabling it to effectively bind with negatively charged molecules such as oils and fats. This property makes chitosan a promising natural compound for managing cholesterol levels. Developing a palatable and convenient dosage form, such as an effervescent granule suspension, is crucial to enhance its public acceptance as a health supplement. This study investigated how different granulation methods (wet and dry) influence the physical properties of effervescent granules containing chitosan, both before and after reconstitution. Four distinct formulations were prepared: F1 and F2 employed dry and wet granulation, respectively, with a citric acid : tartaric acid ratio of 10% : 20%; while F3 and F4 utilized the same granulation methods but with a higher acid ratio of 13% : 26%. Comprehensive evaluation revealed that all formulations generally met quality requirements, except F3's pH (4.38 ± 0.57). Statistical analysis using an independent sample t-test indicated that the granulation method significantly affected parameters such as flow time, percentage of fines, dispersion time, and pH. Ultimately, the dry granulation method yielded the most favorable characteristics, with F1 exhibiting superior flow properties, optimal pH, and desired viscosity.

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INTRODUCTION

Indonesia is home to four prominent species of mangrove crabs: *Scylla serrata*, *Scylla olivacea*, *Scylla tranquebarica*, and *Scylla paramamosain*. Among these, *S. serrata* exhibits the highest abundance due to its superior tolerance for salinity, allowing it to colonize extensive estuarine areas[1]. This crab species is widely consumed; however, historically, only the meat has been utilized, resulting in significant waste of the shells. These shells, however, represent a valuable resource, containing approximately 20% to 30% chitin by dry weight[2]. Chitin can be efficiently converted into chitosan through sequential chemical processes: deproteination, demineralization, and deacetylation[3].

Chitosan is a versatile biopolymer with extensive applications across the pharmaceutical, agricultural, health, and food sectors, primarily owing to its biocompatibility, biodegradability, and non-toxicity[4]. One of its most distinctive health benefits is its potent hypocholesterolemic activity, characterized by its ability to effectively reduce serum Low-Density

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Lipoprotein (LDL) cholesterol levels while simultaneously promoting an increase in High-Density Lipoprotein (HDL)[5]. Clinical and *in vivo* studies have supported this potential, with a 55 mg dose of chitosan demonstrating a 67.69% reduction in cholesterol levels in animal models[6]. Our previous research[7] further confirmed this efficacy, showing that a chitosan solid dispersion system derived from *S. serrata* shell achieved a 29.56% reduction in cholesterol levels during *in vitro* testing. Despite its therapeutic promise, chitosan exhibits challenging physicochemical properties, specifically being insoluble in water and requiring acidic conditions for dissolution, which results in a highly viscous solution[4].

To overcome this poor aqueous solubility and enhance patient compliance, chitosan is formulated here as an effervescent granule suspension. Effervescent granules are designed as a mixture of acids and bases that rapidly liberate carbon dioxide upon contact with water, creating a palatable, soft-drink-like preparation. This formulation offers advantages such as enhanced physical and chemical stability compared to loose powders, and is particularly beneficial for patients who experience difficulty swallowing solid medications[8]. Effervescent granules can typically be prepared by two conventional methods: wet granulation and dry granulation. The wet granulation method is suitable for active ingredients that are resistant to moisture and heat, yet possess poor flow and compressibility characteristics[9]. Conversely, the dry granulation method involves powder compaction without the use of liquid binders and is generally preferred when the active ingredient is thermolabile or sensitive to moisture[10]. Given that chitosan's decomposition temperature is high, ranging between 200°C and 220°C[11], either the wet or dry granulation method is viable for its formulation.

This study aims to investigate the impact of wet granulation versus dry granulation methods on the physical properties of effervescent granules containing chitosan extract from *S. serrata* shells. Achieving optimal granule standards is crucial for producing a safe and effective final pharmaceutical product. The comprehensive evaluation of the effervescent granule suspension includes both pre-reconstitution tests (flow properties, moisture content, organoleptic analysis, and particle size distribution) and post-reconstitution tests (dispersion time, froth height, organoleptic analysis, pH, and viscosity). Statistical analysis involves initial tests for normality and homogeneity, followed by an independent samples t-test to compare the properties resulting from the two different granulation methods.

MATERIALS AND METHODS

Materials

The chitosan used in this study was synthesized from the discarded shells of *S. serrata*, sourced from Layar Restaurant in Surabaya, Indonesia. The identity of the crab was formally confirmed at the Zoology and Animal Engineering Laboratory at the Sepuluh Nopember Institute of Technology, Surabaya, as belonging to the species *S. serrata*. The formulation of the granular effervescent powder required several key excipients and reagents. These materials included anhydrous lactose (Pharma Chemical), effervescent acids (citric acid and tartaric acid; Dwilab Indonesia), and the base sodium bicarbonate (Mitra Wacana Media). Other auxiliary materials utilized were PVP K-30 (Aloin Labora) and Xanthan Gum (Aloin Labora) as binders and thickeners, PEG 6000 (Merck), and Tween 80 (Muda Berkah Jogja) as a surfactant. Solvents and diluents used included 70% ethanol (Medika) and distilled water (Aquadest). The instrumentation employed comprised an analytical balance (OHAUS-PA214), a sieve shaker (SS-200), an oven (Memmert UN55), a pH meter (Laqua PH-1100), a digital viscometer (NDJ-8S), along with standard laboratory equipment such as a mortar, pestle (stamper), beaker glass, and desiccator.

Methods

Formulation of effervescent granules via wet granulation

The effervescent chitosan granule suspension derived from *S. serrata* shells was prepared according to the methodology established by Rani *et al.*[12], with specific modifications detailed in **Table I**. The effervescent granules were prepared using the wet granulation method. Initially, all necessary instruments and materials were prepared and precisely weighed according to the formulation specifications. Lactose and PVP-K30 were combined and thoroughly mixed using a mortar and pestle until a homogeneous excipient mixture was achieved. This homogeneous mixture was then divided into two equal parts (0.5 parts each). The first half was mixed with citric acid and tartaric acid to form the acidic component, while the second half was combined with sodium bicarbonate to create the fundamental component. Each component (acidic and

basic) was transferred to separate containers, and 70% ethanol was carefully added as the granulating liquid. Both mixtures were stirred until a cohesive granular mass was formed. This mass was subsequently passed through a sieve with a 10-mesh size and dried in an oven at 50°C for 8 hours. The dried granules were then sieved again using a sieve with a 16-mesh opening. Finally, the required amount of chitosan powder was added to the sieved acid and basic granules, and the final mixture was homogenized in a tumbling mixer. The resulting effervescent granules were subjected to comprehensive evaluation both before and after reconstitution[12].

Table I. Effervescent granule suspension formulation.

Material	Use	Concentration (%)			
		F1 (Dry)	F2 (Wet)	F3 (Dry)	F4 (Wet)
Chitosan	Active agent	1.1	1.1	1.1	1.1
Effervescent system					
Citric acid	Acid compound	10	10	13	13
Tartaric acid	Acid compound	20	20	26	26
Sodium bicarbonate	Base compound	34.4	34.4	34.4	34.4
Excipients					
PVP K-30	Binder	1	1	1	1
Xanthan Gum	Suspending agent	1	1	1	1
PEG 6000	Lubricant	2	-	2	-
Wetting agents					
Tween 80	Wetting agent (liquid)	0.1	-	0.1	-
70% Ethanol	Wetting agent (solvent)	-	0.1	-	0.1
Lactose	Diluent/sweeteners	ad 100	ad 100	ad 100	ad 100

Formulation of effervescent granules via dry granulation

The effervescent granules were prepared using the dry granulation method, with components weighed precisely according to the formulation detailed in **Table I**. The required components included chitosan powder, citric acid, tartaric acid, sodium bicarbonate, PVP K-30, xanthan gum, PEG 6000, Tween 80, and lactose. First, the citric acid was ground and then sieved through a 60-mesh sieve. It was subsequently dried in an oven at 50°C for 30 minutes. The dried citric acid was subsequently combined with tartaric acid and sodium bicarbonate, and the mixture was stirred until homogeneous. Separately, the remaining excipients (chitosan powder, PVP K-30, xanthan gum, PEG 6000, Tween 80, and lactose) were mixed until a homogeneous mixture was achieved. Following this, the two primary mixtures were combined and stirred until a uniform blend was achieved. This powder mixture was then placed on a suitable tray and heated in the oven at 50°C for 15 minutes. During the heating phase, the powder was periodically turned using an acid-resistant spatula. Once the mixture reached a sponge-like consistency, it was removed and granulated by passing it through a 16-mesh sieve[12].

Evaluation of effervescent granules before reconstitution

Organoleptic assessment: The effervescent granules were subjected to an organoleptic evaluation which involved physically observing the texture, and assessing the odour and taste of the final preparation[13].

Flowability characterization: *Flow time*: The flow time test was executed using the funnel method. A sample of 100 g of effervescent granules was introduced into a funnel with the bottom aperture initially closed. The aperture was then opened, and the time required for the entire granule sample to exit the funnel was recorded as the flow time. A flow time of less than 10 seconds is generally required for preparations demonstrating adequate flowability[14]. *Angle of repose (°)*: The angle of repose was also determined using the funnel method. After pouring 100 g of the effervescent granules through the funnel, the resulting conical pile height (h) and the diameter of the cone base (d) were measured. The angle of repose (°) was calculated using the following **Equation 1**[15]:

$$\text{Tan } \alpha = \frac{2h}{d} \qquad [1]$$

Moisture content determination: The moisture content was assessed using a moisture content analyzer instrument. Approximately 5 g of granules were weighed, leveled on the instrument's pan, and the analysis was run for 10 minutes. The

moisture content, recorded directly from the instrument in percent units, was calculated as **Equation 2**[16], in which W_1 = initial sample weight (g) and W_2 = final sample weight (g).

$$\%\text{Moisture content} = \frac{(W1-W2)}{W1} \times 100\% \qquad [2]$$

Particle size distribution: The particle size distribution was analyzed using a mechanical sieve shaker equipped with a set of standard sieves. A 100 g sample of effervescent granules was loaded onto a stack of sieves with mesh sizes of 20, 30, 50, 60, 80, and 100. The stacked sieves were then vibrated for 20 minutes at a speed of 60 rpm. The weight of the granules retained on each sieve was meticulously weighed. The percentage of fines was calculated using the following **Equation 3**[12], in which W_b = Granule weight in the bottom sieve (pan) and W_t = Total weight.

$$\%\text{Fines} = \frac{Wb}{Wt} \times 100\% \qquad [3]$$

Data analysis

Several quality control parameters were evaluated for the effervescent granule formulation. For the dispersion time, 30 g of the effervescent granules were added to a 250 mL beaker containing 150 mL of deionized water. The mixture was gently stirred, and the time required for the granules to be entirely and uniformly dispersed was recorded[17]. To assess froth height, the same procedure was followed: 30 g of granules were poured into 150 mL of distilled water and stirred slowly until a stable foam formed. At this point, the height of the foam was measured and recorded[12]. Organoleptic evaluation was conducted after reconstituting 30 g of the effervescent granules with 150 mL of distilled water; this assessment included the qualitative description of the product's texture and savour (taste)[13]. The pH of the reconstituted solution (30 g of granules added to 150 mL of distilled water) was immediately measured using a calibrated pH meter[18]. Finally, the viscosity of a larger reconstituted sample (500 mL) was measured using a digital viscometer located at the Laboratory of the Faculty of Food Technology, Universitas Pembangunan Nasional "Veteran" Jawa Timur, Surabaya. This test is crucial as excessive viscosity can hinder homogeneous mixing with other ingredients, affecting the final product's quality and consumer acceptability[19].

RESULTS AND DISCUSSION

The physical properties of the effervescent granules were rigorously evaluated both before and after reconstitution, consistent with established pharmaceutical standards[20]. The pre-reconstitution characterization, detailed in **Table II**, focused on critical parameters necessary for ensuring product quality and manufacturability[12]. These evaluations included the flow properties test (assessing the angle of repose and flow time) to determine granule uniformity and handling efficiency, the moisture content test to predict stability and storage characteristics, the organoleptic test to ensure acceptable sensory attributes, and the particle size distribution test to confirm consistency in dosage and dissolution behavior.

Table II. Evaluation results of effervescent granule suspension (before reconstitution).

Evaluation Parameter	Sub-Parameter	F1 (Mean ± SD)	F2 (Mean ± SD)	F3 (Mean ± SD)	F4 (Mean ± SD)
Organoleptic	Texture	Coarse granular powder	Coarse granular powder	Coarse granular powder	Coarse granular powder
	Taste (Savour)	Slightly sour	Slightly sour	Sour	Sour
Flow properties	Flow time (sec)	2.25 ± 0.10	3.88 ± 0.30	4.66 ± 2.30	2.89 ± 0.20
	Angle of repose (º)	19.96 ± 1.76	22.60 ± 1.72	25.97 ± 1.09	26.50 ± 3.23
Moisture & fines	Moisture content (%)	2.00 ± 0.97	0.60 ± 0.57	1.30 ± 0.58	2.30 ± 2.31
	Fines (%)	1.90 ± 0.35	6.10 ± 0.72	3.00 ± 1.23	2.40 ± 0.86

The results of the organoleptic and physicochemical evaluations of the effervescent granule suspensions across all formulas before reconstitution are summarized in **Table II**. All formulations exhibited a texture consistent with a coarse granular powder, which aligns with established specifications for this dosage form[13]. Regarding the taste profile, F3 and F4 presented

a noticeably sourer flavor compared to F1 and F2. This difference is directly attributable to the higher concentration of the acid blend in F3 and F4 (a citric acid to tartaric acid ratio of 13%:26%) compared to F1 and F2 (a 10%:20% ratio). The choice of granulation method did not significantly influence the observed organoleptic properties.

Flow time is a critical parameter for effervescent granules as it directly impacts the ease with which the suspension can be poured from its packaging into a container for reconstitution. Flow rate is inversely related to cohesion, meaning larger, more uniform granules flow faster, while smaller granules increase cohesive forces, leading to agglomeration and slower flow[21]. All formulas successfully met the flow time requirement of less than 10 seconds, indicating good intrinsic flow characteristics[22]. The F1, prepared using the dry granulation method with a lower acid concentration (10%:20%), exhibited the fastest flow time at 2.25 ± 0.1 seconds.

To determine the impact of the granulation method, F1 (dry) was statistically compared with F2 (wet), and F3 (dry) was compared with F4 (wet). For the F1 vs. F2 comparison, preliminary statistical tests indicated that the data were homogeneous (homogeneity test, $p = 0.056$) but not normally distributed (normality test, $p = 0.043$). The subsequent Mann-Whitney U test yielded a significant p-value of 0.046 (<0.05), indicating a significant difference in flow time between the dry and wet granulation methods at this acid concentration. Conversely, the comparison between F3 and F4 yielded homogeneous and normal data (homogeneity test $p = 0.064$; normality test $p = 0.157$). The Independent Samples t-test showed $p = 0.267$ (>0.05), indicating no significant difference between the methods at the higher acid concentration.

Similarly, the angle of repose for all formulations was less than 30°, confirming the excellent flowability of the effervescent granule suspensions[23]. A smaller angle of repose, such as that achieved by F1, correlates directly with better flow characteristics, aligning with its superior flow time. Statistical analysis comparing the angle of repose between the corresponding formulas (F1 vs. F2 and F3 vs. F4) revealed no significant differences, with p-values of 0.136 and 0.729, respectively. This suggests that the granulation method did not significantly impact this parameter. The efficiency and cost-effectiveness of the dry granulation technique, along with its capacity to yield coarse granules with favorable flow characteristics, led to its selection as the preferred method for subsequent product testing and formulation[9,24].

The moisture content analysis, detailed in **Table II**, showed that all formulas met the requirement of being less than 5%[20], preventing premature carbonation reactions in the packaging that could damage the preparation. Although F2 (wet granulation) exhibited the lowest water content (0.6 ± 0.57%), statistical analysis using the Independent Samples t-test showed no significant difference in moisture content between the methods (F1 vs. F2: $p = 0.116$; F3 vs. F4: $p = 0.796$). This suggests that the final drying procedure effectively neutralized the influence of the initial granulation method on the final moisture level[9,20]. A low moisture content is crucial, as higher water content can lead to granule agglomeration, which negatively impacts flowability and stability.

The evaluation of particle distribution is visually represented in **Figure 1** via histograms for all tested formulas. Formulas F3 and F4 produced a characteristic bell-shaped histogram, indicating a homogeneous and desirable particle size distribution among the granules. A homogeneous particle size is critical as it directly enhances the flowability of the powder and facilitates the even penetration of water throughout the granule matrix, thus accelerating dissolution. Conversely, the histograms for F1 and F2 showed uneven distributions across sieve mesh sizes, indicating that their particle sizes were not uniformly distributed.

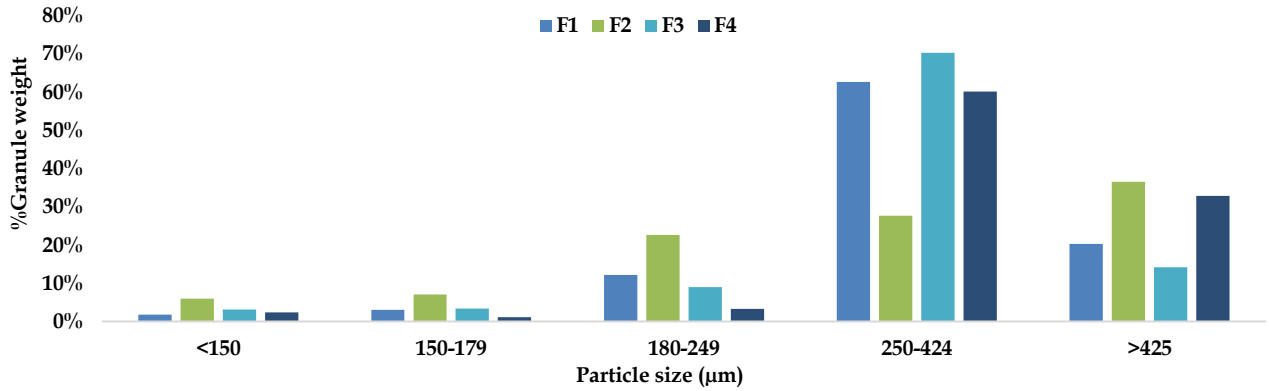

Figure 1. Particle size distribution of F1, F2, F3, and F4.

A crucial parameter in granule characterization is the percentage of fines, defined as particles smaller than 150 µm[25]. All tested formulas exhibited a fines percentage of less than 10%, which meets the established regulatory requirement for good powder flowability (10). Given the homogeneous and normally distributed nature of the fines data, an independent samples t-test was performed for statistical comparison. The analysis showed a statistically significant difference between F1 and F2 ($p = 0.001 < 0.05$), yet no significant difference was observed between F3 and F4 ($p = 0.507 > 0.05$). This indicates that the choice of granulation method (wet vs. dry) impacts the resulting percentage of fines, but this effect is highly dependent on the specific formulation. Although fine particles can sometimes slightly improve flowability by covering rough surfaces[26], excessive fines are generally detrimental, leading to poor flow properties due to increased inter-particulate adhesive-cohesive forces and challenging aeration/deaeration characteristics[27].

The stability and quality of the effervescent granules were comprehensively assessed through post-reconstitution evaluations, including the determination of dispersion time, froth height, organoleptic properties, pH, and viscosity; the detailed results for all four formulas are presented in **Table III**. The organoleptic evaluation across all formulas consistently yielded a suspension texture upon reconstitution. This characteristic is expected because the primary agent, chitosan derived from *S. serrata* shell, is a solid particle insoluble in water[12]. Taste, or savour, varied primarily based on the acid concentration: Formulas F3 and F4, containing a higher ratio of citric acid to tartaric acid (13%:26%), compared to F1 and F2 (10%:20%), exhibited a distinctly sourer profile. However, the variation in the granulation method itself did not significantly influence the overall organoleptic parameters.

Table III. Evaluation results of effervescent granule suspension (after reconstitution).

Evaluation Parameter	Sub-Parameter	F1 (Mean ± SD)	F2 (Mean ± SD)	F3 (Mean ± SD)	F4 (Mean ± SD)
Organoleptic	Texture	Suspension	Suspension	Suspension	Suspension
	Sourness	+	+	++	++
Dispersion time (minute)		2.60 ± 0.50	2.59 ± 0.59	2.70 ± 0.30	1.39 ± 0.04
Froth height (cm)		3.60 ± 0.36	3.30 ± 0.57	3.90 ± 0.60	4.60 ± 1.15
pH		5.65 ± 0.14	6.33 ± 0.11	4.38 ± 0.57	6.40 ± 0.09
Viscosity (cP)		2.22 ± 0.32	1.55 ± 0.39	1.91 ± 0.12	1.84 ± 0.18

The dispersion time is a critical functional parameter that directly affects the release rate of the active ingredient. All formulas successfully met the regulatory requirement for effervescent granules, achieving complete dispersion within 5 minutes. This rapid dispersion is linked to granule porosity, where greater porosity facilitates quick liquid penetration and disintegration[28]. Statistical analysis (Independent Sample T-Test) indicated a significant difference in dispersion time between F3 and F4 ($p = 0.05$). However, no significant difference was found between F1 and F2 ($p = 0.989 > 0.05$), suggesting the influence of the granulation method is dependent on the specific formula composition. Closely related to dispersion time, the froth height also met the requirements, consistently falling within the expected range of 3-5 cm. The concentration of the acid-base source influences the height of the froth, as higher concentrations generate more CO_2 gas[20]. Statistical tests for froth height showed no significant difference between F1/F2 ($p = 0.535 > 0.05$) and F3/F4 ($p = 0.609 > 0.05$), indicating that the choice between wet and dry granulation methods did not significantly affect this parameter.

However, the pH values upon reconstitution revealed a clear statistical distinction based on the formulation method. While most formulas fell within the acceptable near-neutral range of pH 5.00-7.00[20], formula F3 was found to be excessively acidic (pH 4.38 ± 0.57). Although F3 and F4 had identical acid compound concentrations, the dry granulation formulas (F1 and F3) contained excipients, Tween 80 (pH 5.5-7.5) and PEG 6000 (pH 4.4-7.5), which contributed to a lower pH. Statistical analysis (Independent Sample T-Test and Mann-Whitney test) confirmed a significant difference in pH between the two granulation methods for both F1/F2 ($p = 0.002 < 0.05$) and F3/F4 ($p = 0.043 < 0.05$), demonstrating that the presence of these excipients in the dry granulation process resulted in a significantly more acidic final pH.

Finally, the viscosity of the reconstituted suspensions was assessed to predict stability and consumer comfort. The final product exists as a suspension due to the insoluble nature of the chitosan[12]. All formulas met the standard viscosity requirement for oral preparations, falling within the range of 1-7.25 mPa.s[29]. Lower viscosity is desirable as it increases comfort during consumption. Statistical analysis revealed no significant difference in viscosity for both F1/F2 ($p = 0.084 > 0.05$) and F3/F4 ($p = 0.649 > 0.05$), indicating that the variation in the granulation method had no significant effect on the final viscosity of the preparation.

CONCLUSION

This study confirms that the choice of granulation technique has a significant influence on the critical physical and chemical properties of the effervescent formulation, specifically affecting flow time, percentage of fines, dispersion time, and pH. Based on the comprehensive evaluation, the dry granulation method yielded the optimal formula (F1, containing a 10%:20% ratio of citric acid to tartaric acid), demonstrating superior flow properties, a desirable pH, and an appropriate viscosity. Overall, the tested formulas met most of the regulatory requirements, except the pH test for formula F3, which registered a value of 4.38 ± 0.57.

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AUTHORS' CONTRIBUTION

Conceptualization: Hilya Nur Imtihani
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Writing - review & editing: Hilya Nur Imtihani, Andhika Dwi Aristyawan

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to this research.

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