

Physicochemical Characterization and Drug Release Behavior of Theophylline with Chitosan–Alginate Polyelectrolyte Complexes Microparticle

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Abstract

Theophylline is a methylxanthine alkaloid commonly used in the management of bronchial asthma; however, its clinical use is limited by a short biological half-life, gastric irritation, and an unpleasant bitter taste. Encapsulation of theophylline into polymeric microparticles has been proposed as an effective approach to improve its therapeutic performance by providing sustained drug release and reducing adverse gastrointestinal effects. This study investigated the influence of chitosan concentration on the physical characteristics, drug content, and in vitro release behavior of theophylline-loaded alginate–chitosan polyelectrolyte complex microparticles. Microparticles were prepared using the orifice–ionic gelation technique with sodium alginate and chitosan at ratios of 1:0.25, 1:0.50, and 1:1. The resulting microparticles were evaluated for morphology, particle-size distribution, chemical interactions, drug content, and in vitro drug-release profiles. An increase in chitosan concentration led to larger particle sizes and the formation of smoother, more spherical microparticles. The highest drug content was obtained at an alginate–chitosan ratio of 1:0.25. All formulations exhibited a sustained-release profile compared with pure theophylline, indicating effective drug encapsulation within the polymeric matrix. The slowest drug release was observed in the formulation containing the highest chitosan concentration (1:1 alginate–chitosan ratio). These findings suggest that alginate–chitosan polyelectrolyte complex microparticles are a promising delivery system for theophylline and that chitosan concentration plays a crucial role in controlling microparticle characteristics and drug-release behavior.

Keywords: Theophylline; Chitosan; Microparticles; Controlled Release; Polyelectrolyte Complex.

1. Introduction

Theophylline is a naturally derived methylxanthine alkaloid commonly prescribed to treat bronchial asthma for its ability to relax bronchial smooth muscle [1]. It has a relatively short half-life, approximately 8–9 hours in

adults and 3.5 hours in children, and is primarily metabolized in the liver, with only a small fraction excreted via the kidneys [1]. Despite its therapeutic benefits, theophylline is associated with numerous side effects, including tachycardia, nausea, vomiting, and

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increased gastric acid secretion. Encapsulation into microparticles offers a potential strategy to mitigate these adverse effects, improve bioavailability, mask its bitter taste, reduce gastric irritation, and prolong its half-life [2, 3].

Microparticles are spherical solid particles ranging in size from 1 to 1000 μm , typically consisting of a core and a surrounding polymeric coating, such as waxes or synthetic/natural polymers [4]. They are widely used in drug delivery systems to mask unpleasant tastes and odors, protect active compounds from environmental factors (e.g., moisture, heat, light, and oxygen), inhibit volatilization, improve powder flow properties, and provide sustained or controlled drug release profiles [5, 6].

Among various fabrication methods, orifice-ionic gelation is a well-established technique for producing microparticles through the interaction between a positively charged polymer (e.g., chitosan) and a negatively charged crosslinker (e.g., sodium alginate) [7]. Several factors, including the drug-to-polymer ratio, polymer molecular weight, processing temperature, dripping rate, nozzle size, crosslinker concentration, and contact time, influence the physicochemical characteristics of microparticles prepared using this method [8, 9]. This method can produce uniformly sized microparticles with controlled release properties [10].

Chitosan, a biopolymer derived from chitin, is a water-insoluble polysaccharide with free amino groups and a near-neutral to alkaline pH. It has been widely used in microparticle systems due to its high encapsulation efficiency, smooth spherical morphology, and compatibility with acidic drugs [11,12]. Under acidic conditions, the amino groups of chitosan become protonated (R-NH_3^+), rendering the polymer water-soluble. Chitosan can form a polyelectrolyte complex (PEC) with sodium alginate (SA) via ionic interactions between the R-NH_3^+ groups and the carboxylate residues of alginate [9].

The combination of chitosan and SA is particularly advantageous for controlled-release applications, as both polymers are biocompatible and biodegradable and can form stable PECs [13, 14]. Alginate enhances the structural integrity of the system by preventing drug leakage and stabilizing chitosan in both acidic and alkaline environments [8, 12]. To facilitate gelation, a

suitable crosslinker is required. Commonly used agents include glutaraldehyde, sodium hydroxide (NaOH), formaldehyde, and tripolyphosphate (TPP) [11, 12].

TPP is a non-toxic, multivalent anionic crosslinker that interacts ionically with the protonated amino groups of chitosan, thereby reinforcing the bond between chitosan and SA [9]. This interaction significantly influences key microparticle attributes such as density, surface morphology, particle size, and encapsulation efficiency, which, in turn, affect the drug-release profile, bioavailability, and therapeutic performance of the system [11, 15].

Recent studies have demonstrated the potential of alginate-chitosan systems as controlled drug delivery carriers, owing to their excellent biocompatibility and ability to form stable polyelectrolyte complexes. Ahmad et al. [16] reported that alginate-based microgels could effectively modulate drug release behavior; Cheng et al. [17] successfully developed chitosan-containing particulate systems for sustained theophylline delivery. More recently, Al-Assady et al. [18] investigated sodium alginate/chitosan polyelectrolyte microparticles and demonstrated that polymer composition determines particle characteristics and drug release performance. However, studies specifically evaluating the effect of chitosan concentration on the physicochemical properties and release behavior of theophylline-loaded alginate–chitosan microparticles prepared using the orifice–ionic gelation method remain limited.

Therefore, the novelty of the present study lies in the systematic investigation of chitosan concentration as a critical formulation parameter that affects particle morphology, particle size distribution, encapsulation efficiency, physical characteristics, and the *in vitro* release behavior of theophylline-loaded alginate–chitosan polyelectrolyte complex microparticles. Unlike previous studies that primarily focused on formulation development or drug release performance alone, this study provides a comprehensive physicochemical characterization and establishes the relationship between chitosan concentration and microparticle performance. Such information is important for optimizing alginate–chitosan systems as controlled-release carriers for highly water-soluble drugs such as theophylline.

This study aims to investigate the effect of chitosan concentration on the physicochemical characteristics of

theophylline-loaded alginate–chitosan microparticles, with a specific focus on particle morphology, size distribution, physical state, encapsulation efficiency, and in vitro release.

2. Materials and Methods

2.1. Chemicals and Reagents

Theophylline (Kimia Farma, Indonesia; Batch No: 200702025), SA (Wako Pure Chemical Industry, Japan), chitosan (Biotech Co. Ltd, South Korea; Batch No: CS6153S), sodium tripolyphosphate (TPP) (Nacalai Tesque, Japan), and acetic acid (Merck, Germany) were used in this study. All chemicals were of analytical grade.

2.2. Microparticle Preparation

Theophylline-loaded chitosan–SA microparticles were prepared via the orifice-ionic gelation method using varying chitosan concentrations as described in [Table 1](#). Theophylline was first sieved through a No. 140 mesh and dispersed into a chitosan solution prepared in 10 mL of 4% (v/v) acetic acid to form a uniform viscous dispersion. This dispersion was then introduced dropwise into a 20 mL solution containing 15% (w/v) sodium tripolyphosphate (TPP) and 5% (w/v) sodium alginate, using a syringe fitted with a 23G needle at a constant dripping rate. The solution was stirred continuously at 500 rpm for 30 minutes to facilitate gelation and microparticle formation. The resulting microparticles were collected by membrane filtration, rinsed thoroughly with cold distilled water to remove unreacted components, and dried at 40 °C for 3 hours.

Table 1. Theophylline sodium alginat-chitosan microparticle formulations

Materials	Formula		
	F1	F2	F3
Theophylline	1 g	1g	1g
Sodium Alginate	1 g	1 g	1 g
Chitosan	0.25 g	0.50 g	1 g

2.3. Fourier Transform Infrared Spectroscopy (FT-IR)

Approximately 3 mg of dried microparticles were mixed with 300 mg of potassium bromide (KBr) and compressed using a hydraulic press to form a transparent

disc. Infrared spectrum were recorded using a Jasco FT-IR 5300 (USA) over a range of 4000–450 cm⁻¹.

2.4. Microparticle Morphology and Particle Size Distribution

Surface morphology, shape and particle size distribution were evaluated under an optical microscope.

Particle size distribution was analyzed using a calibrated optical microscope (Olympus, Japan), with the diameters of 300 particles from each formulation recorded. The data were then classified into intervals to calculate the average particle size for each sample, offering insights into how chitosan concentration affects the uniformity and size of the theophylline-loaded microparticles.

2.6. Encapsulation Efficiency

To determine encapsulation efficiency, 100 mg of microparticles were sonicated in 10 mL of distilled water for 10 minutes at 60 MHz. The solution was filtered through a 0.45 µm membrane filter and analyzed at 270.94 nm using a UV–Vis spectrophotometer (Cary 50 Conc, Agilent, United States). All measurements were performed in triplicate. Encapsulation efficiency (EE) was calculated using the formula:

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug amount}}{\text{Theorirical drug amount}} \times 100$$

2.7. In Vitro Drug Release

In vitro release of theophylline from microparticles was evaluated using an Erweka DT 700 dissolution tester (Erweka, Germany) with a basket apparatus. Microparticles equivalent to 50.0 mg of theophylline were added to 900 mL of distilled water maintained at 37 ± 0.5 °C and stirred at 50 rpm. At predetermined time intervals (0, 15, 30, 60, 90, 120, and 180 minutes), 5.0 mL samples were withdrawn and filtered through a 0.45 µm Millipore filter. Drug release was quantified at 270.94 nm using a UV–Vis spectrophotometer. An equal volume of fresh dissolution medium was replaced after each sampling to maintain sink conditions. All experiments were performed in triplicate.

Dissolution efficiency (DE) at 180 min was calculated as the ratio of the area under the dissolution curve (AUC) up to 180 min to the area of the rectangle

representing 100% dissolution over the same time period, expressed as a percentage, according to the following equation:

$$\%DE = \frac{\text{Area Under the Dissolution Curve}}{\text{Total area Representing 100\% Dissolution}} \times 100\%$$

where the area under the dissolution curve was determined using the trapezoidal rule.

3. Result and Discussion

Fourier Transform Infrared (FTIR) spectroscopy was performed to identify specific functional groups involved in microparticle formation and to evaluate possible interactions between chitosan and SA (Figure 1).

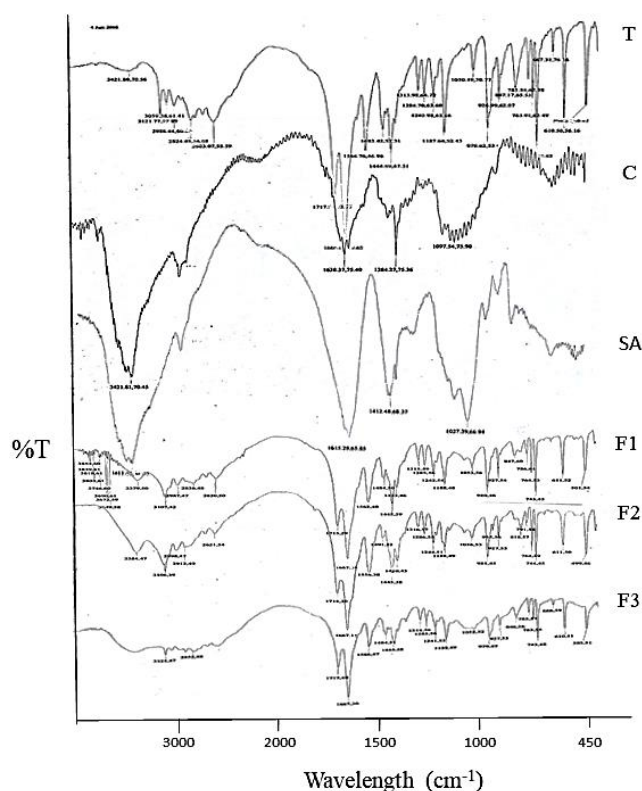


Figure 1. FTIR spectra of pure theophylline (T), chitosan (C), sodium alginate (SA), and theophylline-loaded microparticles prepared with varying chitosan-to- SA ratios: 1:0.25 (F1), 1:0.50 (F2), and 1:1 (F3)

The characteristic absorption bands of chitosan were observed at 3421.81 cm^{-1} ($-\text{OH}$ stretching), 1384.27 cm^{-1} ($-\text{NH}_2$ bending), and 1638.37 cm^{-1} ($\text{C}=\text{O}$ stretching), confirming the presence of hydroxy, amine, and carbonyl functional groups, respectively. All formulations exhibited a prominent carbonyl absorption in the range of 1600–1700 cm^{-1} . Interestingly, the intensity of the hydroxy group band increased with increasing chitosan concentration, suggesting enhanced hydrogen bonding. However, no distinct amine group absorption was detected in any of the microparticles, which may indicate that the $-\text{NH}_2$ groups of chitosan were involved in strong ionic interactions with the carboxylate groups ($-\text{COO}^-$) of SA [19, 20]. This suggests the successful formation of polyelectrolyte complexes between chitosan and SA via hydrogen bonding and electrostatic interactions [21].

The shift and broadening of several characteristic absorption bands in the microparticle formulations, compared with those of pure chitosan and sodium alginate, further support the formation of a polyelectrolyte complex. In particular, changes in the amine- and carboxylate-related absorption regions indicate electrostatic interactions between protonated amino groups of chitosan and negatively charged carboxylate groups of alginate. Similar spectral changes have been reported in previous studies investigating alginate–chitosan polyelectrolyte complexes [19–21].

Morphological observations of the theophylline-loaded microparticles, conducted under an optical microscope at 40 $\times$ magnification, revealed significant changes in shape and surface characteristics as chitosan concentration increased (Figure 2). Lower chitosan concentrations (F1 and F2) produced irregular or moderately spherical particles with rough surfaces [22, 23], while higher concentrations (F3) resulted in more uniformly spherical microparticles with smoother surfaces [17,23]. This improvement in morphology is attributed to the increased availability of protonated amine groups ($\text{R}-\text{NH}_3^+$) at higher chitosan concentrations, which facilitated stronger ionic interactions with the alginate's negatively charged carboxylate groups. The formation of a well-defined polyelectrolyte complex under these conditions likely contributed to the improved sphericity and surface smoothness [21].

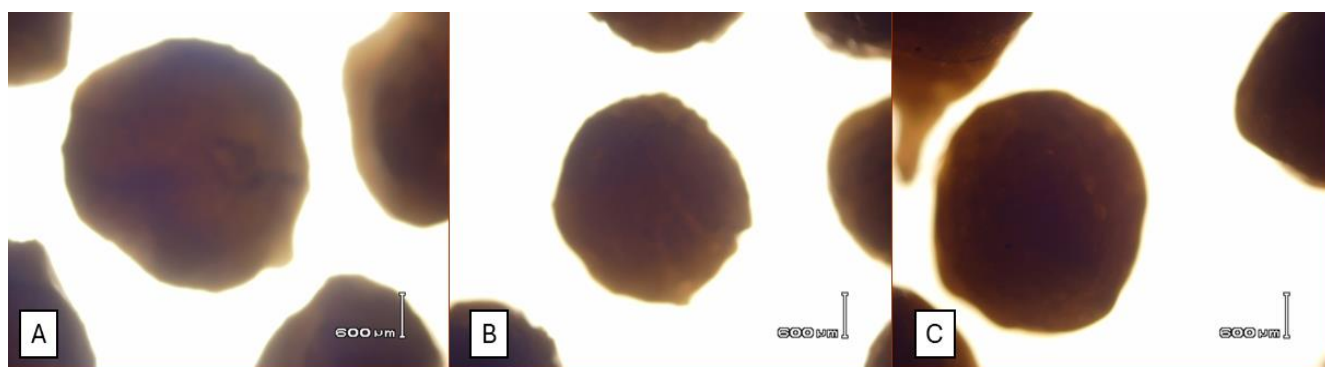


Figure 2. Optical microscopy images of theophylline-loaded microparticles formulated with varying chitosan-to- SA ratios at 40× magnification. (A) F1 (1:0.25), (B) F2 (1:0.50), and (C) F3(1:1).

The particle size distributions shown in [Table 2](#) illustrate the effect of increasing chitosan concentration on the formation of theophylline-loaded SA microparticles. Although F1 contained the lowest amount of chitosan, it exhibited the largest average particle size. This counterintuitive result may be attributed to weaker electrostatic interactions between SA and chitosan at low chitosan concentrations, resulting in a less cohesive polymer matrix during gelation. The lower viscosity of the formulation in F1 could also lead to larger droplets during extrusion, resulting in larger microparticles. In contrast, the moderate chitosan concentration in F2 facilitated optimal ionic interactions and enhanced matrix cohesion, resulting in smaller, more uniform particles. Further increasing the chitosan content in F3 enhanced crosslinking density and viscosity [24, 25], resulting in larger, more cohesive gel matrices during orifice-ionic gelation and agglomeration [25]. These findings align with the principle that the balance between polymer concentration and charge interactions critically influences particle formation dynamics and final size.

Table 2. Mean Particle size of theophylline-loaded microparticles with chitosan-to- SA ratios of 1:0.25 (F1), 1:0.50 (F2), and 1:1 (F3). Size analysis was performed by measuring 300 microparticles per formulation using a calibrated optical microscope and categorizing them into defined size intervals.

Sample	Diameter (µm)
F1	1603.42
F2	1126.74
F3	1637.71

The mean particle sizes obtained in this study ranged from 1126.74 to 1637.71 µm. These values are considerably larger than those reported for chitosan–TPP nanoparticles, which are in the nanometer range, but are comparable to those of microparticles produced by ionic gelation techniques. The larger particle size observed in the present study may be attributed to the use of a relatively concentrated polymer system, the formation of alginate–chitosan polyelectrolyte complexes, and the extrusion process through a 23G needle. Previous studies have demonstrated that increasing chitosan concentration increases solution viscosity and promotes the formation of larger droplets during gelation, resulting in larger particles. Similar observations were reported by Sreekumar *et al.* [24] and Gan *et al.* [25], who found that polymer concentration and crosslinking density significantly influence particle growth and aggregation during ionic gelation.

Encapsulation efficiency results showed a decreasing trend with increasing chitosan concentration. F1, F2 and F3 showed encapsulation efficiencies of $62.17 \pm 0.08\%$, $45.13 \pm 0.35\%$, and $29.55 \pm 0.25\%$, respectively ([Table 3](#)). The reduced encapsulation at higher chitosan levels may be due to the increased viscosity of the chitosan dispersion, which can lead to aggregation and poor drug entrapment during microparticle formation [26,27]. Furthermore, the high aqueous solubility of theophylline may have contributed to drug loss during preparation, particularly in the alginate-TPP solution and washing steps, reducing the amount of drug retained in the microparticles.

The encapsulation efficiencies obtained in this study ranged from 29.55% to 62.17%. These values are within the range reported for chitosan-based microparticle systems containing highly water-soluble drugs. The relatively moderate encapsulation efficiency can be explained by theophylline's high aqueous solubility, which facilitates its diffusion into the external aqueous phase during gelation and washing. Similar reductions in drug entrapment have been reported for water-soluble compounds incorporated into chitosan-based delivery systems, where increasing polymer concentration may further decrease encapsulation efficiency due to aggregation and non-uniform drug distribution within the polymer matrix [26, 27].

The *in vitro* release profiles of the theophylline microparticles over 180 minutes revealed that F1, F2, and F3 released $107.49 \pm 3.62\%$, $97.41 \pm 3.66\%$, and $82.08 \pm 1.54\%$ of the drug, respectively, while pure theophylline exhibited a release of $96.26 \pm 2.56\%$ (Figure 3). Correspondingly, the dissolution efficiencies (DE_{180}) for F1, F2, and F3 were 83.70%, 61.96%, and

46.60%, respectively, with pure theophylline showing a DE_{180} of $83.32 \pm 2.40\%$ (Table 3). These results indicate that higher chitosan concentrations generally led to reduced drug release and dissolution efficiency.

The sustained-release behavior observed in formulations with higher chitosan concentrations is consistent with previous reports on alginate–chitosan delivery systems. Increasing chitosan concentration promotes the formation of a denser polyelectrolyte complex network, thereby reducing matrix porosity and increasing the diffusion path length of the drug molecules. Consequently, water penetration and drug diffusion through the polymer matrix become slower. Similar findings were reported by Cheng et al. [17], who observed reduced theophylline release from chitosan-containing particulate systems due to enhanced polymeric barrier properties. Therefore, the reduced dissolution efficiency observed in F3 can be attributed to stronger intermolecular interactions and a more compact polymer network.

Table 3. Encapsulation efficiency and dissolution efficiency at 180 minutes for theophylline-loaded microparticles formulated with varying chitosan-to- SA ratios: F1 (1:0.25), F2 (1:0.50), and F3 (1:1).

Sample	Encapsulation Efficiency (%)	Dissolution Efficiency (%)
Theophylline	-	83.32 ± 2.40
F1	62.17 ± 0.08	83.70 ± 2.57
F2	45.13 ± 0.35	61.96 ± 1.89
F3	29.55 ± 0.25	46.60 ± 0.79

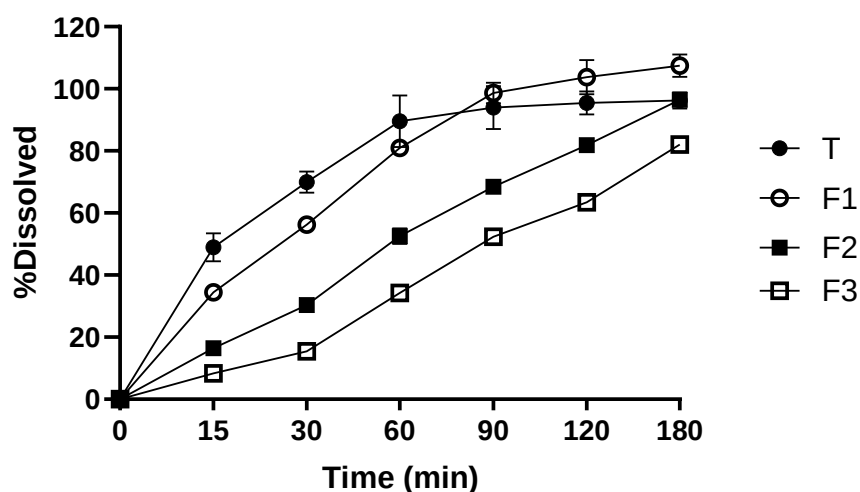


Figure 3. *In vitro* drug release profiles of pure theophylline (T) and theophylline-loaded microparticles: F1 (1:0.25), F2 (1:0.50), and F3 (1:1). Drug release was conducted in 900 mL of distilled water at 37 ± 0.5 °C using a USP dissolution apparatus with basket method at 50 rpm. Replications were done in triplicate ($n = 3$).

This study highlights the significant impact of chitosan concentration on the physicochemical properties, drug entrapment efficiency, and release behavior of theophylline-loaded alginate–chitosan microparticles. The formation of polyelectrolyte complexes through hydrogen bonding and ionic interactions between chitosan and SA was confirmed by FTIR analysis and was shown to influence microparticle morphology and functionality. As chitosan concentration increased, microparticles became larger, smoother, and more spherical. However, encapsulation efficiency decreased at higher chitosan levels, likely due to increased viscosity and drug loss during preparation.

In vitro drug release studies demonstrated that microparticles formulated with the highest chitosan concentration (F3) achieved more sustained release profiles, suggesting a denser crosslinked network that slowed drug diffusion. These results underscore the importance of optimizing the polymer ratio to balance particle formation, drug loading, and release kinetics. The alginate–chitosan system shows promise as a biocompatible, tunable platform for controlled drug delivery, particularly for drugs with narrow therapeutic windows, such as theophylline. Future work should explore the feasibility of scale-up and in vivo performance to assess its clinical applicability fully.

4. Conclusion

Theophylline-loaded alginate–chitosan polyelectrolyte complex microparticles were successfully prepared using the orifice–ionic gelation method. FTIR analysis confirmed interactions between chitosan and sodium alginate, indicating the successful formation of a polyelectrolyte complex. Increasing chitosan concentration influenced microparticle morphology, particle size, encapsulation efficiency, and drug release behavior. Higher chitosan concentrations produced larger, more spherical microparticles, but decreased encapsulation efficiency and slowed drug release. Among the investigated formulations, the formulation with the highest chitosan concentration (F3) exhibited the most sustained release profile. These findings demonstrate that chitosan concentration is a critical factor in tailoring the physicochemical properties and release profiles of alginate–chitosan microparticles for the controlled delivery of theophylline.

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Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors Contributions

Concept: R.S., D.S.; Design: L.A.W., R.S.; Control: R.S., D.S.; Sources: L.A.W., R.S.; Materials: R.S.; Data Collection and/or Processing: L.A.W., A.P., R.S.; Analysis and/or Interpretation: L.A.W., A.P., R.S.; Literature Review: L.A.W., A.P., R.S., A.P; Manuscript Writing: A.P., R.S., A.P; Critical Review: R.S., D.S., A.P Other.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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