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Evaluating the taste-masking ability and sensory attributes of alginate-encapsulated black seed oil

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ABSTRACT

Introduction: This study aimed to evaluate the sensory attributes of alginate-encapsulated black seed oil in 12 healthy volunteers. Black seed oil, derived from *Nigella sativa* seeds, is known for its therapeutic properties but is characterized by a pungent taste. Alginate, a hydrophilic polysaccharide polymer derived from brown seaweeds, forms water-insoluble gels in the presence of divalent metal ions such as calcium ions. Alginate finds applications in various fields, including food, pharmaceuticals, and biotechnology engineering.

Method: The ionic gelation method was employed to encapsulate black seed oil within alginate beads for taste-masking and to enhance its sensory characteristics. Sensory analysis was conducted to assess the smell, taste, taste masking, aftertaste, and texture acceptability of different formulations, including blank beads (negative control), black seed oil (positive control), black seed oil-alginate beads with and without added flavours (vanilla, chocolate, orange, and sugar), in both dried and wet forms, and a commercial black seed oil soft-gelatine capsule.

Results: The results showed that encapsulating black seed oil within alginate beads significantly improved its taste and aftertaste, and the addition of flavours further enhanced the smell. Vanilla and orange flavours were found to be the most effective in improving palatability and taste masking ability of the beads in both wet and dried forms, surpassing sugar and chocolate flavours. However, sugar is preferred in the dried form alone.

Conclusion: Overall, the study demonstrated the potential of alginate encapsulation to mask the taste of black seed oil and improve its sensory attributes, offering broad applications for enhancing the palatability of other unpleasant bio-compounds

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Introduction

A broad spectrum of medications possesses low organoleptic properties and, unless formulated meticulously, may be highly unpalatable. Therefore, there is significant interest in taste masking for active pharmaceutical ingredients with unpleasant tastes, as well as certain food supplements. This aspect has gained importance in the formulation of medications for paediatrics and other sensitive patient populations. Palatability, encompassing the acceptability of orally administered medications, is closely linked to various organoleptic properties such as mouthfeel (the texture of medications) and aroma (Andrews et al., 2020). While medications effectively treat illnesses, their unappealing taste remains a primary obstacle, hindering a considerable number of patients from consuming them easily. The application of taste masking to these medications enhances patient compliance, thereby improving their overall quality of life (Al-Kasmi et al., 2018).

However, numerous techniques have been employed to mask the bitter taste of drugs in pharmaceutical applications. These methods include introducing flavours and sweeteners (Abay & Ugurlu, 2015), utilising lipophilic vehicles (Abay & Ugurlu, 2015), forming solid dispersions (Zheng et al., 2018), employing salting-out layers (Abay & Ugurlu, 2015), employing complexation with ion exchangers and cyclodextrins (Al-kasmi et al., 2017), encapsulation into microspheres and microcapsules (Zheng et al., 2018), and applying physical barriers or coatings (Zheng et al., 2018).

In a recent study, sucrose octa-acetate served as a model for bitter-tasting drugs encapsulated in lipid microspheres. These microspheres were then integrated into rapidly dissolving edible films containing both masking and flavouring agents (Smutzer et al., 2020). The formulation was employed in a study focusing on suppressing bitter taste, with taste-masking efficacy evaluated in 24 healthy volunteers. Results demonstrated a significant reduction in the bitter taste of sucrose octa-acetate with this formulation (Smutzer et al., 2020). Another study utilised three techniques to assess taste-masking effectiveness: *in vivo* testing with healthy volunteers, *in vitro* drug dissolution, and electronic tongue analysis (Wasilewska et al., 2020). This investigation aimed to develop orodispersible minitablets containing rupatadine fumarate, formulated in taste-masked ethylcellulose-based microparticles produced through spray drying. Rupatadine fumarate, a recent antihistamine, served as a model bitter drug. The study concluded that the three aforementioned methods were valuable for evaluating taste-masking effectiveness, confirming that the fabrication of rupatadine fumarate in ethylcellulose microparticles and subsequent preparation in orodispersible minitablets yielded a satisfactory taste-masking outcome (Wasilewska et al., 2020). Furthermore, *in vitro* assessment and palatability evaluation were conducted to gauge the taste-masking efficacy of microencapsulated paracetamol in chitosan-coated alginate beads (Almurisi et al., 2020). Palatability was assessed with 12 human participants. Results indicated that the ability of dried beads to mask the bitterness of paracetamol surpassed that of wet beads. Even though wet beads were evaluated similarly to the marketed paracetamol suspension, the aftertaste evaluation was superior (Almurisi et al., 2020).

Utilising alginate beads for the microencapsulation of unpleasant drugs is a promising and straightforward approach applicable for a wide range of active compounds, offering scalability for large-scale preparation. Alginate, a hydrophilic polysaccharide polymer derived from brown seaweeds, has witnessed increasing utilisation across diverse fields, including food, pharmaceuticals, and biotechnology engineering. Its widespread application is attributed to its remarkable qualities of non-toxicity, biocompatibility, biodegradability, and the ability to form water-insoluble gels in the presence of divalent metal ions such as Ca^{2+}. Alginate is composed of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues, arranged in chain homo sequences of MMMMM and GGGGG, interspersed with MGMGMG hetero sequences (Jain & Bar-Shalom, 2014; Leong et al., 2016). The carboxylic acid groups of G units can crosslink with Ca^{2+}, and this gelation process follows the "egg-box" mechanism, where one divalent cation interacts with four –COOH groups (Abasalizadeh et al., 2020). Alginate encapsulation acts as a physical barrier, effectively shielding drugs or supplements from interacting with taste buds and, consequently, masking unpleasant tastes (Chirag J et al., 2013). This encapsulation process relies on the capacity of alginate to undergo water-insoluble gelation in the presence of divalent metal ions like calcium, leading to the formation of cross-linked beads (Chirag J et al., 2013; Liu et al., 2017).

Black seed oil (BSO), extracted from the seeds of *Nigella sativa*, commonly known as black cumin or black seeds, has garnered significant attention in recent studies (Majeed et al., 2020). Several investigations have documented the therapeutic effects of BSO, highlighting its anti-hypertensive, anti-microbial, anti-cancer, anti-inflammatory, and anti-diabetic properties (Majeed et al., 2020; Mazaheri et al., 2019; Mukhtar et al., 2019). Traditionally, BSO has served as a natural remedy for various ailments, such as relieving pain in osteoarthritis, treating influenza, asthma, headaches, rheumatism, and bronchitis (Begum & Mannan, 2020; Majeed et al., 2020; Mazaheri et al., 2019; Mukhtar et al., 2019). Moreover, a separate study suggested that genetically incorporating

BSO into a gene delivery carrier could potentially enhance therapeutic benefits for Alzheimer's disease treatment (Doolaanea et al., 2016).

Nevertheless, BSO is characterised by a bitter and pungent taste and, similar to other oils, is susceptible to oxidation and degradation during storage. This necessitates the use of high-quality packaging that can delay the process of oxidation and degradation over time (Chakraborty et al., 2017; Martins et al., 2017). Employing the technique of ionic gelation to encapsulate BSO within alginate beads could serve as an excellent strategy to mask its taste and enhance its sensory characteristics. Therefore, the aim of the present study was to assess the effectiveness of the ionic gelation method in masking the taste of BSO and evaluating the sensory attributes of the developed beads.

Methodology

Materials

Black seed (*Nigella sativa*) oil (BSO) was purchased from Blessed Seed Sdn. Bhd. (Kuantan, Malaysia). High stiffness gelation type sodium alginate IL-6G (KIMICA Corporation, Tokyo, Japan). Calcium chloride dihydrate was purchased from CFL-Chemische Fabrik Lehrte GmbH & Co. KG (Köthenwaldstraße, Germany). Polysorbate 80 (Tween 80) was purchased from Guangdong Runhua Chemistry Co., Ltd (Yingde, China). BSO soft-gelatine capsules (Baraka, 450 mg) were purchased from a local pharmaceutical outlet in Malaysia. Sugar and flavouring agents of vanilla, chocolate, and orange were purchased from a local market in Malaysia.

Formulation of BSO-alginate beads following ionic gelation

The emulsification of BSO was achieved by incorporating BSO into an alginate solution using Tween 80 as a stabiliser. The BSO-alginate beads were then fabricated using the ionic gelation method (Alkhatib et al., 2022). The concentrations of the ingredients used in the formulation of BSO-alginate beads are presented in Table 1. To create the beads, the BSO-alginate emulsion was slowly dripped through a 22-gauge stainless-steel needle using a syringe into a gelation bath containing a 1% w/v calcium chloride solution, as depicted in Figure 1. Following the gelation process, the beads were allowed to cure in the bath for 20 minutes. Subsequently, the beads were collected using a metal mesh, rinsed with distilled water, and filtered in preparation for their use in the sensory analysis study.

Table 1: Ingredients of BSO-alginate emulsion formulation.

No	Ingredients	Percentage (w/w %)	Quantity (g)
1	BSO	10	1
2	Alginate	2	0.2
3	Tween 80	3	0.3
4	Sugar / Flavouring agents	1	0.1
5	Distilled water	84	8.4
	Total	100 %	10.00

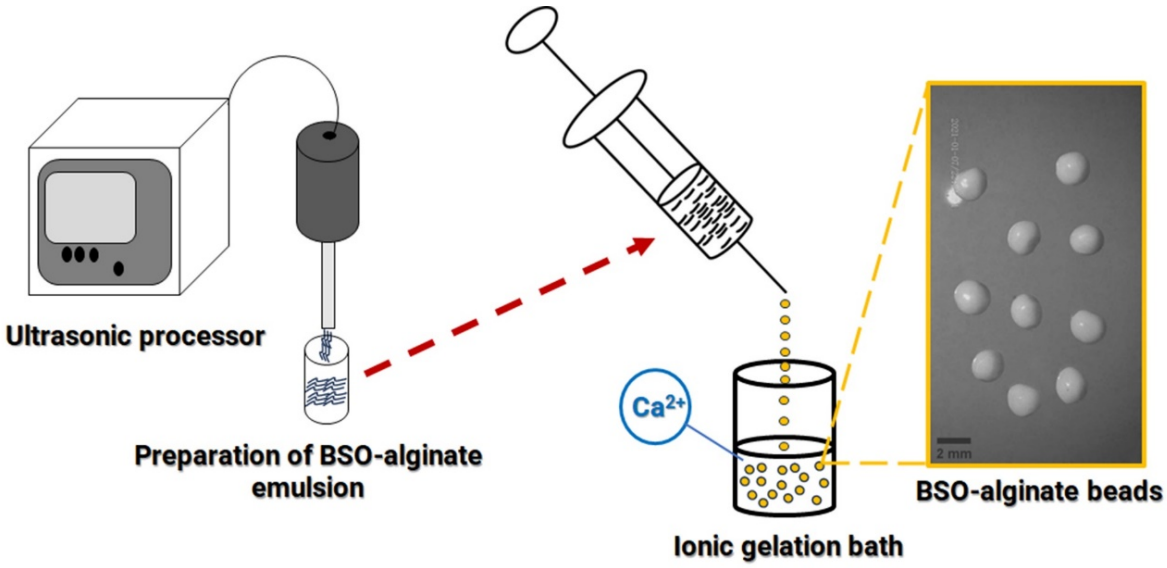

Figure 1: Formulation of BSO-alginate beads by the ionic gelation.

Sensory analysis of BSO in alginate beads

A blinded palatability study involving 12 healthy volunteers was carried out, and their informed consent was obtained in accordance with the university's procedure (IIUM Research Ethics Committee (IREC) reference no: IIUM/504/14/11/2/IREC 2019-156). The study protocol followed the methodology described by Alkhatib et al. (2020). The eligibility criteria included healthy individuals aged 18 to 35 years, while exclusion criteria encompassed smokers, individuals with cough and flu symptoms, use of prescribed medication, pregnant women, and individuals with known allergies to any component present in the formulations.

Six males and six females evaluated the smell, taste, taste masking, aftertaste, and texture acceptability of the following formulations: 100 mg of blank beads (alginate beads without BSO were used as a negative control), 100 mg of BSO (positive control), wet BSO-alginate beads, vanilla wet BSO-alginate beads, chocolate wet BSO-alginate beads, orange wet BSO-alginate beads, sugar wet BSO-alginate beads, dried BSO-alginate beads, vanilla dried BSO-alginate beads, chocolate dried BSO-alginate beads, orange dried BSO-alginate beads, sugar dried BSO-alginate beads, and BSO soft-gelatine capsule (used as a commercial product for comparison). The content of BSO in all beads formulations was 100 mg. The dried beads were made by overnight drying in an oven at 30□C. All the additive flavours and sugar were added to the BSO-alginate beads formulations at the concentration of 1 % w/w.

The participants were instructed to refrain from consuming any food or beverages for one hour prior to the test. A disposable plastic teaspoon was used to administer the tested material to the participants. Each participant tested each sample once. They were asked to place the material in the centre of their tongue and hold it there for 20 seconds before spreading it across their tongue for an additional 20 seconds, after which they spat it out. Feedback from the participants was collected five minutes after spitting out the product. To neutralise the taste of the oil, the participants consumed unsalted crackers and thoroughly rinsed their mouth with plenty of water. A 10-minute interval was provided between the introductions of each product. Palatability and taste-masking attributes were evaluated using a Likert scale, ranging from 1 (very unpleasant) to 5 (very pleasant) (Han et al., 2019).

Alongside the Likert scale, the participants were also requested to provide a taste score ranging from 0 to 100, indicating the perceived intensity of the BSO taste (Albertini et al., 2004). This scoring system assigned a value of 100 to BSO liquid and 0 to blank beads.

Statistical analysis

The statistical analysis in the present study was conducted using Minitab software, version 17.1.0. For the sensory analysis data, a non-parametric Mann-Whitney test was utilised, and the results were reported as medians (n = 12). The taste score results were analysed using One-Way ANOVA, followed by a Tukey's post-hoc test, and are presented as mean ± SD (n = 12).

Results and Discussion

Sensory analysis of BSO in alginate beads

An *in vivo* palatability and taste-masking efficacy evaluation study were conducted to optimise additive flavours for the BSO-alginate beads formulation, namely vanilla, chocolate, orange, and sugar. Pure BSO served as a positive control, compared with all BSO-alginate beads formulations, while blank alginate beads were used as a negative control to neutralise the alginate bead taste and for comparing the textures of BSO-alginate beads formulations, i.e. the gritty feeling in the mouth (Table 2 and Table 3). A Likert scale, ranging from 1 (very unpleasant) to 5 (very pleasant), was utilised for the evaluation, with 3 indicating a neutral feeling.

The lowest scores for smell, taste, and aftertaste were given to pure BSO, receiving ratings of 2, 1, and 1, respectively, as shown in Table 2 and Table 3. The unpleasant smell and very unpleasant taste and aftertaste of BSO present a genuine challenge when attempting to consume this oil in its raw form. The disagreeable taste of medications/supplements is widely acknowledged as a primary reason for non-compliance with treatments, particularly among children who tend to be more sensitive to the unpleasant and unfamiliar tastes of medications than adults (Moreira & Sarraguça, 2020).

Sensory analysis of the wet BSO-alginate beads formulations

The encapsulation of BSO in alginate beads in wet form, with no flavours added, did not improve the smell of BSO, as the wet BSO-alginate beads formulation still exhibited an unpleasant smell when compared with pure BSO (p = 0.972), as shown in Table 2. The addition of flavours significantly enhanced the smell in the wet form, particularly when vanilla and orange flavours were utilised (p = 0.013 and p = 0.029, respectively), as indicated in Table 2. Although the smell of chocolate wet BSO-alginate beads and sugar wet BSO-alginate beads was rated higher than the smell of pure BSO, no significant difference was observed (p = 0.283 and p = 0.137, respectively). This lack of significance was attributed to the low scores given by volunteers when evaluating the smell of these two formulations. Moreover, the ability of vanilla and orange flavours to improve the smell of BSO in wet bead forms surpassed the ability of the commercial product of BSO

soft-gelatine capsules, which did not show a significant difference in smell compared to the smell of pure BSO (p = 0.05) (Table 2). Additionally, the evaluation results indicated a significant improvement in the taste and aftertaste feeling of BSO in the mouth cavity, as well as in taste-masking ability, after encapsulation in the matrix of wet BSO-alginate beads (p = 0.002, p = 0.007, and p = 0, respectively). Despite the statistical significance of these results, they suggest a limited ability of the wet BSO-alginate beads formulation to enhance the taste and aftertaste sensation of BSO, or to exert a substantial taste-masking impact, as shown in Table 2.

BSO droplets were initially dispersed in the aqueous phase to formulate a BSO-alginate emulsion. Subsequently, during the gelation process, these BSO droplets became entrapped within the alginate matrix. The homogeneous distribution of BSO droplets within the alginate bead matrix resulted in the presence of oil droplets among the bead walls. The encapsulation's objective is to establish a barrier between pure BSO and taste receptors, aiming to minimise the inherent taste of BSO. However, the existence of BSO droplets throughout the entire alginate bead matrix, including the bead walls, allowed some of the pure BSO taste and aftertaste sensation to persist, along with a limited taste-masking effect. In contrast, the wall of the BSO soft-gelatine capsule completely prevented the BSO material from reaching taste receptors, resulting in the highest evaluation scores for taste, aftertaste feeling, and taste-masking ability (p = 0, p = 0, and p = 0, respectively), as detailed in Table 2 and Table 3. Al-kasmi et al. (2017) reported that microencapsulation, as a taste-masking method, is employed to render medications completely insoluble in saliva. This observation is based on the understanding that the bitter taste of medications becomes apparent only when the drug is dissolved in saliva and comes into contact with the tongue's taste buds. Encapsulation in alginate beads does not alter the taste or smell of BSO, particularly when carried out without the use of additives such as flavours. In this process, encapsulation minimises the original unpleasant palatability of pure BSO, which received the lowest scores in evaluations by volunteers. However, the addition of vanilla or orange flavour significantly enhances the evaluation scores of taste, aftertaste feeling, and taste-masking in their wet alginate beads formulations (p = 0), as shown in Table 2. Conversely, using chocolate or sugar as additive flavours in the wet formulations did not contribute to the improvement of taste, aftertaste feeling, and taste-masking ability during the encapsulation process, as the evaluation results closely resembled those of wet BSO-alginate beads (Table 2).

Sensory analysis of the dried BSO-alginate beads formulations

Drying the beads generally improved the smell, except in the case of dried BSO-alginate beads with no flavours added. There was no significant difference between the smell of dried BSO-alginate beads and the smell of pure BSO (p = 0.081), even though the smell was evaluated to be higher than that of pure BSO (Table 3). Notably, the smell significantly improved in the formulation of sugar

Table 2: Scores of palatability and taste-masking evaluation of wet BSO-alginate beads formulations. The texture scores were compared with blank beads. Data were analysed using non-parametric Mann-Whitney test and are presented as medians (n = 12).

Formulation	Smell	Taste	Aftertaste	Taste-masking	Texture
Blank beads	-	-	-	-	3
Pure BSO	2	1	1	1	-
Wet BSO-alginate beads	2 p = 0.972	2* p = 0.002	2.5* p = 0.007	2* p = 0.000	3 p = 0.899
Vanilla wet BSO-alginate beads	4* p = 0.013	3* p = 0.001	3* p = 0.003	3* p = 0.000	3 p = 0.948
Chocolate wet BSO-alginate beads	2.5 p = 0.283	2* p = 0.002	3* p = 0.002	2* p = 0.000	3.5 p = 0.975
Orange wet BSO-alginate beads	4* p = 0.029	3* p = 0.000	3* p = 0.002	3* p = 0.000	3 p = 0.400
Sugar wet BSO-alginate beads	3 p = 0.137	2* p = 0.004	2* p = 0.015	2* p = 0.000	3 p = 0.547
BSO soft-gelatine capsule	3 p = 0.050	4* p = 0.000	5* p = 0.000	5* p = 0.000	-

*A statistically significant difference was indicated at $p < 0.05$.

dried BSO-alginate beads, reaching the levels of vanilla dried BSO-alginate beads and orange dried BSO-alginate beads (p = 0.002, p = 0.006, and p = 0.004, respectively). However, this improvement in smell was not observed in sugar wet BSO-alginate beads (Table 2 and Table 3). On the other hand, there was an improvement in the smell of chocolate dried BSO-alginate beads compared to the smell of pure BSO, but it did not reach the levels achieved by using vanilla and orange flavours (p = 0.029), as shown in Table 3.

The general observation from these results is that the drying process was more effective in improving the smell of BSO compared to the wet beads. In fact, pure BSO, or crude BSO, is divided into two major fractions: a fixed oil fraction (triglyceride) accompanied by a minor fraction of volatile oil (E. Edris, 2021). It is expected that the volatile oil is responsible for the strong smell of BSO. The evaporation of water content from the formulations during the drying process might combine with some of the volatile content of BSO, thereby minimising the strong smell of BSO. Moreover, two major factors control the rate of aroma release from products, namely the volatility of the aroma compounds in the product base (thermodynamic factor) and the resistance to mass transfer from the product to air (kinetic factor) (de Roos, 2003). This observation aligns with the obtained results in the current study, where the smell transfer of pure BSO was limited after encapsulation in alginate beads, preventing the BSO smell from reaching the surrounding air in comparison with the smell of pure BSO. Furthermore, the high-water content in the wet formulations (≈ 80%) made the smell transfer to the surrounding air easier in wet beads compared to the dried beads, as this water content could act as an intermediate phase between the beads (solid phase) and the surrounding air (gas phase).

Additionally, the concentration of the additive flavours increased in the beads after the drying process due to water loss, enhancing the effect of the additive flavours. This was particularly evident in sugar-dried BSO-alginate beads, where this formulation obtained the highest evaluation scores with significant improvements in taste, aftertaste feeling, and taste-masking ability among the dried beads (p = 0). Moreover, chocolate dried BSO-alginate beads also achieved a level comparable to vanilla and orange dried BSO-alginate beads in terms of the significant ability to enhance the palatability aspects of taste and aftertaste feeling, in addition to the taste-masking efficacy (p = 0), as shown in Table 3.

Evaluation of the texture of BSO-alginate beads

The texture of blank beads received favourable evaluation scores, suggesting that the use of alginate beads is preferred as an oral formulation. Furthermore, the incorporation of BSO into alginate beads, with or without the addition of flavourings, did not result in a significant decrease in mouthfeel texture for both wet and dried bead forms (p > 0.05), as shown in Tables 2 and 3.

Table 3: Scores of palatability and taste-masking evaluation of dried BSO-alginate beads formulations. The texture scores were compared with blank beads. Data were analysed using non-parametric Mann-Whitney test and are presented as medians (n = 12).

Formulation	Smell	Taste	Aftertaste	Taste-masking	Texture
Blank beads	-	-	-	-	3
Pure BSO	2	1	1	1	-
Dried BSO-alginate beads	3 p = 0.081	2.5* p = 0.000	3* p = 0.001	2* p = 0.000	3 p = 0.318
Vanilla dried BSO-alginate beads	4* p = 0.006	3* p = 0.000	3* p = 0.001	3* p = 0.000	3 p = 0.182
Chocolate dried BSO-alginate beads	3* p= 0.029	3* p = 0.000	3* p = 0.000	3* p = 0.000	3 p = 0.367
Orange dried BSO-alginate beads	4* p =0.004	3* p = 0.000	3* p = 0.001	3* p = 0.000	2.5 p = 0.058
Sugar dried BSO-alginate beads	4* p = 0.002	4* p = 0.000	4* p = 0.000	4* p = 0.000	3 p = 0.190
BSO soft-gelatine capsule	3 p = 0.050	4* p = 0.000	5* p = 0.000	5* p = 0.000	-

*A statistically significant difference was indicated at p < 0.05.

Evaluation of the taste feeling of BSO

The results of BSO taste feeling in the fabricated alginate beads formulations were consistent with the findings obtained from the palatability evaluation, as shown in Figure 2. The taste feeling of BSO significantly decreased following encapsulation in alginate beads, measuring 67.17 ± 21.62% in wet BSO-alginate beads and 45.5 ± 22.43% in dried BSO-alginate beads ($p < 0.05$). The additive flavours generally enhanced the efficacy of alginate beads in reducing the taste feeling of BSO. Sugar dried BSO-alginate beads were the only formulation that reached the level of the commercial product of BSO soft-gelatine capsule with no significant difference ($p > 0.05$), as shown in Figure 2. The taste feeling of BSO in both sugar dried BSO-alginate beads and BSO soft-gelatine capsule was significantly reduced to 21.08 ± 16.31% and 2.67 ± 4.92%, respectively ($p < 0.05$). However, the efficacy of adding sugar or chocolate flavour to reduce the taste feeling of BSO in wet BSO-alginate beads formulations was less than the efficacy of vanilla and orange flavours (Figure 2).

The overall observation from the palatability, taste-masking, and BSO taste feeling evaluation studies showed that both vanilla and orange flavours surpassed sugar and chocolate flavours in improving the acceptability of BSO in wet beads formulations, and their efficacy remained stable in the dried beads formulations. In a study conducted by Lopalco et al. (2019), orange flavour was found to be the preferred taste corrector for the bitter-salty taste of sodium dichloroacetate. The palatability assessment in their study covered a range of flavours, including orange, tropical fruits, berries, and vanilla. Orange flavour emerged as a preferred flavouring agent and yielded satisfactory results in the current study for enhancing the palatability of BSO, masking its unpleasant taste, and reducing its taste feeling in the alginate beads formulation. Therefore, it is recommended to be selected as a flavouring agent in the formulation of BSO-alginate beads.

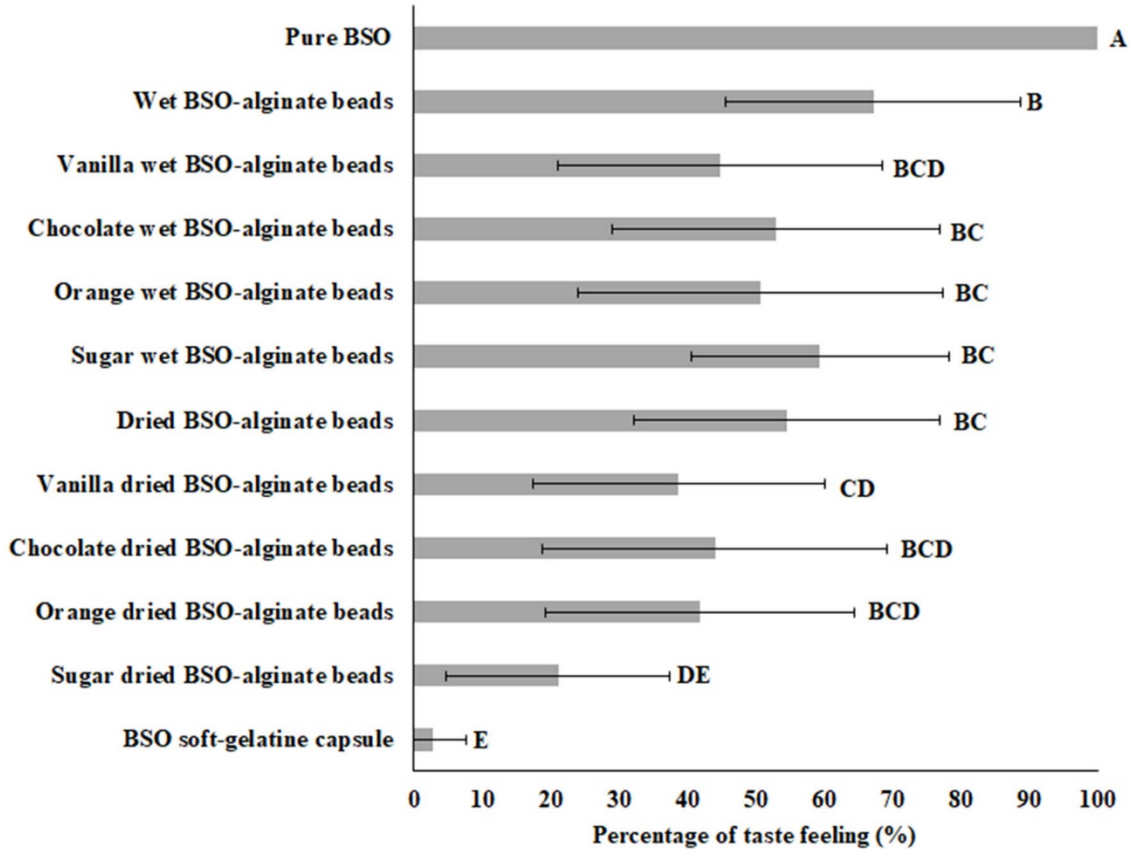

Figure 2: Percentage of BSO taste feeling score. Different letters indicate significant differences among means after Tukey Post-Hoc test ($p < 0.05$). Error bars represent the standard deviation of the mean values (n = 12).

Conclusion

In conclusion, this study demonstrated that alginate-encapsulated BSO successfully enhanced its sensory attributes and masked its unpleasant taste. Wet BSO-alginate beads, particularly those formulated with vanilla and orange flavours, exhibited significant improvements in smell, taste, and aftertaste compared to pure BSO. The alginate encapsulation method effectively shielded the taste buds from interacting with BSO, thereby enhancing its acceptability. Drying the beads further improved the texture and mouthfeel, making the dried formulations more pleasant for consumption. Overall, this approach holds promising implications for enhancing the palatability and patient compliance of BSO and similar compounds, thereby improving the quality of healthcare delivery.

Author Contribution

H. A.: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualisation; Writing - original draft; Writing - review & editing. A. S.: Project administration; Supervision; Writing - review & editing. A. R. S.: Writing - original draft; Writing - review & editing; Formal analysis. M. A.: Data curation; Methodology; Formal analysis. F. M.: Resources; Supervision; Writing - review & editing. A. D.: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Visualisation; Writing - review & editing.

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Ethical Approval Statement

Ethical approval for this study was obtained in accordance with the university's procedure. The study protocol was reviewed and approved by the IIUM Research Ethics Committee (IREC) under reference no: IIUM/504/14/11/2/IREC 2019-156.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Conflict of Interest

The authors declare no conflict of interest.

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