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Layer-By-Layer Coating of Sesame Oil in Alginate-Chitosan Beads for Enteric Coating and Sustained Release

Somaia Abueta[1], Hazrina Hadi[1,*], Abd Almonem Doolaanea[2], and Abdullah Mohammed Aloqyli[3]

ABSTRACT

Introduction: Medical uses of alginate-chitosan beads have been growing widely in recent years due to their varied applications in pharmaceutical and biomedical technology. Moreover, a variety of research have used drug encapsulation in the alginate-chitosan matrix to facilitate the enteric coating and sustained release of therapeutic molecules. Sesame oil has various medical applications as it contains a significant amount of lignans, which enhance its antioxidant function and anti-inflammatory effects for external or internal medical uses. In addition, it has contributed to the treatment of several inflammatory bowel diseases. Layer-by-layer assembly provides an effective coating for drugs, improving the oil instability in the gastric media, preventing drug leakage, and elongating the release time for sesame oil. This study aims to encapsulate sesame oil in alginate-chitosan beads and to optimize the formulation for enteric coating.

Method: Consuming sesame oil directly will not enable gastrointestinal tract to obtain the desired quantity of active ingredients in the oil due to the early degradation of oil. Therefore, the beads were prepared by using the external gelation method with layer-by-layer technique to provide multicoated layers. To illustrate, the usage of layer-by-layer assembly for the encapsulated alginate-sesame oil beads was accomplished by alginate and chitosan polysaccharides. A stability test was held to ensure the formulation stability during the study. In addition, the beads were characterized for particle size, roundness, and in-vitro drug release in different simulated buffers.

Results: This study revealed that the layer-by-layer approach is a viable method to obtain a sesame oil alginate-chitosan bead formulation for enteric coating and sustained release. Formulation coated layer-by-layer provided a successful pass of the stomach system whereas 68% of cumulative drug release occurred in the intestine within 5 h. To illustrate, during 135 min uncoated beads showed a cumulative drug release of 65% while the same percentage was achieved in 255 min for coated beads.

Conclusion: Sesame oil alginate-chitosan beads could be introduced as a promising carrier for encapsulating essential oils with favourable features.

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***Corresponding author:**

Email address: hazrina@iium.edu.my

Authors' Affiliation:

[1] *Dermatopharmaceutics Research Group, Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia*

[2] *Research and Development, Sabrena Experience, 1500 Dragon Street, Suite 160, Dallas, Texas 75207, USA.*

[3] *Department of Histology, Faculty of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia.*

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Introduction

The interest in natural products has been revitalized as they are considered as drug leads (Atanasov et al., 2021). Sesame oil (SO) is an example of natural compound that has been widely used for a long time in both pharmaceutical and food industries (Esmaeilzadeh Kenari & Razavi, 2022), and its efficiency has been documented in different diseases treatment in both aspects of traditional medicine and preventive medicine. Sesamin and sesamolin are the main phenolic components with high content compared to other oil ingredients (Akhila & Beevy, 2015; Esmaeilzadeh Kenari & Razavi, 2022), and several pharmacological properties, including antioxidant, anti-inflammation, and anticancer action, were related to them (Mekky, Abdel-Sattar, Segura-Carretero, & Contreras, 2019; Ostovan, Fazljou, Khazraei, Araj Khodaei, & Torbati, 2020). Several studies have revealed the potency of SO on a variety of health problems, such as colon cancer, cardiovascular diseases (CVD), osteoarthritis (OA), ulcerative colitis (UC), and oxidation stress inhibition (Anilakumar, Pal, Khanum, & Bawa, 2010; Hsu & Parthasarathy, 2017). One study revealed an inhibition effect of free radical formation that works against oxidative stress (Kheirati Rounizi et al., 2021). Another research has reported that it provides a valuable protective property for CVD (Jayaraj, Narasimhulu, Rajagopalan, Parthasarathy, & Desikan, 2020). In addition, the ability to suppress carcinogenesis will enable it to have a wide effect on the prevention and treatment of colon cancer (Valaei et al., 2022). Moreover, ulcerative colitis (UC) is a chronic inflammatory bowel disorder that infects the colon; a medical trial on rats has reported the decline in ulcerative colitis inflammation by using mastic and sesame (Ostovan et al., 2020).

According to the sesame oil medical potency, the enteric coating was the goal of this study which would enhance the therapy availability and effectiveness throughout long-term exposure and specific delivery. Reducing the drug side effect, increasing drug effectiveness, and enhancing oral delivery are all advantages of enteric coating. The intestinal sites have unique chemical properties, including a high pH value and increased enzyme activities compared to other gastrointestinal tract (GIT) parts. Therefore, enteric coating increases drug protection from unsuitable environments in the GIT. It was attained in our research by alginate and chitosan polysaccharides that had an opposite pH property.

Recently, the microencapsulation of alginate and chitosan polysaccharide has shown great promise in large clinical studies due to their biocompatibility, biodegradability, and nontoxicity properties that enable them to be important biopolymers in medicinal and therapeutic aspects (Bakshi, Selvakumar, Kadirvelu, & Kumar, 2020; Hariyadi & Islam, 2020). Alginate is an anionic polymer with high solubility in basic pH media (H. A.-O. Choukaife, Doolaanea, & Alfatama) while chitosan is a cationic polymer with high solubility in acidic pH media (Bakshi et al., 2020). They are strong alternatives due to their high availability, low cost, and environmentally friendly aspect (Bakshi et al., 2020; H. A.-O. Choukaife et al.). Besides that, the alginate "egg-box" structure, which is formed by ion exchange between calcium and sodium ions, provides the gelation property, and hydrophilic feature that will maintain its structure while absorbing a large amount of water (H. A.-O. Choukaife et al.; Hariyadi & Islam, 2020). Furthermore, enteric coating has been improved with the usage of layer-by-layer (LbL) technique, which is presented as a multi-layered structure for the desired drug, and it is demonstrated for a wide spectrum of pharmaceutics by using chemical bonds, such as electrostatic interactions between opposite charges that have been used in this study (Shende, Patil, & Prabhakar, 2020; Zhang et al., 2019). The ability of LbL assembly to coat large surface areas without changing or damaging the active ingredients is one of its advantages that broaden its applications (Alkekhia, Hammond, & Shukla, 2020). Eventually, using external gelation and LbL techniques for enteric coating has provided a successful enteric coating for SO, and improved the drug bioavailability in the targeted site with sustained release properties.

The study aimed to optimize alginate-SO formulation for enteric coating, and to estimate the cumulative drug release percentage throughout the stomach and intestine by using simulated buffers.

Methodology

Sodium alginate with low molecular weight and viscosity at 20°C (grade IL-6G, high G, 30-60 mPa.S) was procured from Kimica (Tokyo, Japan). Chitosan (plant-based) source: aspergillus niger with deacetylation ≥90 was attained from Modernist Pantry LLC (Eliot, USA). Calcium chloride anhydrous (fused), $CaCl_2$ was obtained from Techno Pharmchem (India). Citric acid 5% was produced in Saudi Arabia by Al Faris Food Industries LTD (Riyadh, SA). SO was purchased from Soybean Crushing CO. & Derivatives LTD (Yanbu, Saudi Arabia).

Preparation of Alginate SO Emulsion

Three different emulsions with different concentrations of alginate (0.5%, 1%, 2% w/v) were prepared. A homogenizer was used to mix SO (10% w/v relative to the total emulsion volume) with three different concentration of sodium alginate (0.5%, 1%, 2% w/v) consecutively for 5 min The outcome was three emulsions with a variation in alginate concentration and the total volume was 100 ml for each.

Alginate SO Emulsion Stability Test

A sample of 10 ml from the resulting emulsion was dispersed into a centrifuge tube (n = 3) that was held for 6 h to check for the sesame oil alginate emulsion separation. Every 30 min, a visual inspection was performed to evaluate the detachment during the experiment time of 6 h.

Preparation of Alginate SO Beads

The SO alginate beads were prepared by using an electrospray technique with an external gelation method. Alginate SO emulsion of 2% sodium alginate was selected for beads preparation as weight by volume (w/v). The emulsion was pumped through a 22G needle using a syringe pump (Shenchen Lab2015, Baoding, China) to provide a flow rate of 15 ml/min. At the same time, a beaker for a gelling bath of 100 ml calcium chloride (2% w/v) was prepared to provide the cross-linking of beads. SO beads were kept in calcium chloride solution while stirring for 30 min to confirm the complete gelation. Then, stainless steel sieve was used to collect the beads from the solution, and they were washed with distilled water. An oven of 60°C was used to dry out the beads for 24 hours.

Characterization of the Beads

MS2 digital microscope was used to capture images for wet and dry beads. Afterward, ImageJ program was used to determine the beads' size and shape. The beads roundness was evaluated using sphericity factor (SF). The SF was calculated using the following equation (Almurisi et al., 2020):

$$SF = \frac{D_{max} - D_{per}}{D_{max} - D_{per}}$$

where D_{max} is the maximum diameter passing through a bead centroid (mm), and is the diameter perpendicular to the Dmax passing through the bead centroid (mm). A perfect sphere is presented by zero SF while a higher SF directs to a higher shape distortion. Furthermore, all bead with SF ≤ 0.05 is considered as a spherical bead

LbL Assembly of Alginate SO Beads

The dried SO beads were encapsulated in a matrix comprised of two alternating layers of 1% w/v chitosan and 1% w/v alginate. The beads were poured in 100 ml of 1% w/v chitosan solution that was prepared by adding 1 g of chitosan (powder) to 74 ml of DW, and 25 ml of 5% citric acid was added to confirm the complete solubility of chitosan. The beads were transferred to 100 ml of DW to prevent beads' adhesions, then 100 ml of 2% w/v alginate was added. These two layers were obtained by electrostatic LbL technology, and it was held for 15 min for each. Lastly, the beads immersed in 2% w/v CaCl2 gelling bath for 5 min to ensure the alginate crosslinking and micro-gel formation. The beads were dried out on the laboratory bench for 6 h.

In-Vitro Drug Release profile of Coated Beads Vs Uncoated Beads

Initially, an experiment was held to ensure the efficiency of the coated beads vis uncoated beads in the basic 6.8 pH media. Briefly, 0.5 g of coated beads and 0.5 g of uncoated beads (control sample) were added to 100 ml of simulated intestine fluid (SIF; pH 6.8). During three hours of experiment, 3 ml aliquot of samples were withdrawn every 10 min. with a plastic dropper, and it was returned to the dissolution media. The spectrophotometer (Jenway 7305, Bibby Scientific Ltd Stone, Staffs, UK) at 600 nm was used to measure the absorbance while the calculation of cumulated drug release was accomplished by the following equation:

$$\text{Drug Release (DR\%)} = \frac{\text{Buffer volume (100)} \times \text{Actual oil conc.} \left(\frac{\text{mg}}{\text{ml}}\right)}{\text{Theoretical oil conc.} \left(\frac{\text{mg}}{\text{ml}}\right)}$$

value in counts per second (cps). The system software was then used to translate the intensities for various isotopes in the tested samples into concentrations and compared them to those obtained from calibration standard solutions. Each sample underwent analysis for a total of one minute and forty seconds.

To investigate the sequence in-vitro drug release (DR%) of SO beads, the dissolution was carried out at 37 ± 1°C and 60 rpm using an orbital incubator shaker under continuous stirring (Innova™ 4000 Benchtop Orbital Shakers, New Brunswick Scientific™, Edison, NJ, USA). Then, 0.5 g for each coated and uncoated SO beads was weighed and poured into 100 ml of simulated gastric fluid (SGF; pH 1.2) for 2 hours, separately. Afterwards, the beads were removed and filtered using a metal mesh, and they were dispersed in 100 ml of pH 6.8 SIF for 3 hours. Then, 3 ml aliquot of samples were withdrawn every 10 min. with a plastic dropper from each aliquot, and it was returned to the dissolution media. The spectrophotometer (Jenway 7305, Bibby Scientific Ltd Stone, Staffs, UK) at 600 nm was used to measure the absorbance whereas cumulated drug release was calculated through the following equation:

$$\text{Drug Release (DR\%)} = \frac{\text{Buffer volume (100)} \times \text{Actual oil conc.} \left(\frac{\text{mg}}{\text{ml}}\right)}{\text{Theoretical oil conc.} \left(\frac{\text{mg}}{\text{ml}}\right)}$$

Linearity, LOD, LOQ, Accuracy and Repeatability

The validation parameters that were assessed and calculated included linearity, LOD, LOQ, accuracy and repeatability. To assess the linearity of the method, calibration graphs for each element were generated by the system software at final concentrations of 0.02 g/mL, 0.04 g/mL, 0.06 g/mL, 0.08 g/mL, 0.1 g/mL, and 0.12 g/mL.

Statistical Analysis

Minitab and imageJ programs were used to perform statistical optimization. Each measurement was done in triplicate (n = 3) and the measured data were expressed as the mean ± standard deviation (SD). T-test and one-way ANOVA were used to compare the data, while considering $p < 0.05$ as indication of significant difference.

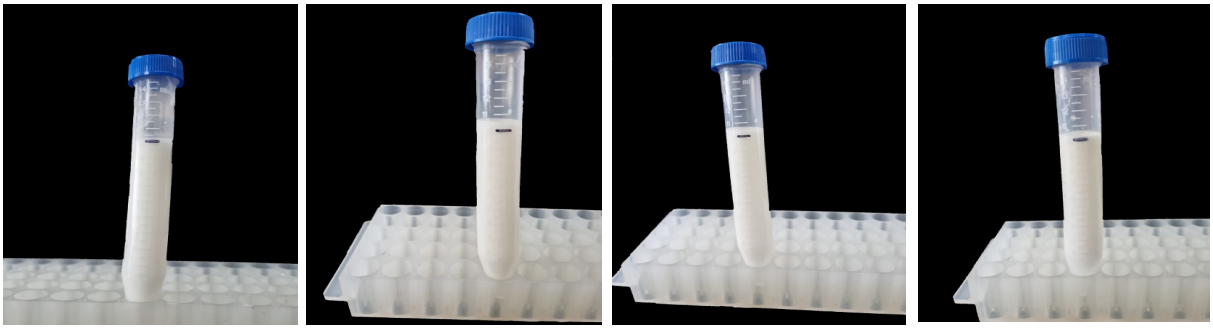
Results

Characterization of Alginate-SO Emulsion

In the present study, a homogenizer was used to confirm the complete mix of the alginate and SO emulsion for 5 min. Therefore, the emulsion stability was checked to ensure its stability during the experiment. It was shown by visual inspection that the emulsion was not separated or detached for 6 hours, meaning that the emulsion was stable for more than the time needed for preparation as shown in Figure 1. Therefore, the result during the testing period has indicated no change in the emulsion.

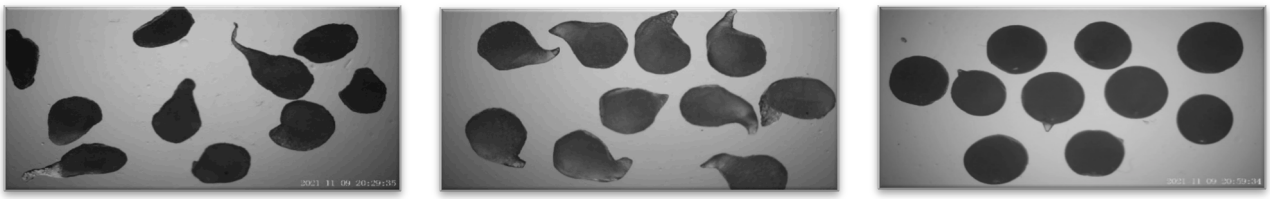
Characterization of Alginate-SO Beads

The emulsion was optimized by variation of alginate (0.5%, 1%, 2% w/v) concentrations to ensure the optimal spherical shape. To illustrate, we found that as alginate concentration increased, the shape distortion of hydrogel beads declined as shown in Figure 2. Moreover, the beads' roundness increased with the increase of alginate as shown in Figure 3. According to the statistical analysis of ANOVA test, 0.5% alginate concentration was significantly different from 1% and 2% while no significant difference was shown between 1% and 2% concentrations. A research paper (Wong et al., 2021) mentioned the usage of 2% alginate to form hydrogel beads that had spherical shape with higher stability against structural deformation. Therefore, 2% alginate emulsion was chosen for external gelation method which was applied for SO beads encapsulation with the incorporation of 2% w/v CaCl2 for 30 min. alongside a continued stirring to facilitate alginate crosslinking and micro-gel formation.



A)10% SO w/v 2%Alg. B) 10% SO w/v 2%Alg. C) 10% SO w/v 2%Alg. D) 10% SO w/v 2%Alg.

Figure 1: Alginate SO emulsion mixed with homogenizer for 5 min. (a) at zero time, (b) after 2 hours, (C) after 4 hours, and (d) after 6 hours.



a)10% SO w/v, 0.5% Alg. B) 10% SO w/v, 1% Alg. C) 10% SO w/v, 2% Alg.

Figure 2: Microscopic image of alginate SO beads. (a) Alginate conc. of 0.5% w/v, (b) Alginate conc. of 1% w/v, and (c) Alginate conc. of 2% w/v. Magnification at 10×.

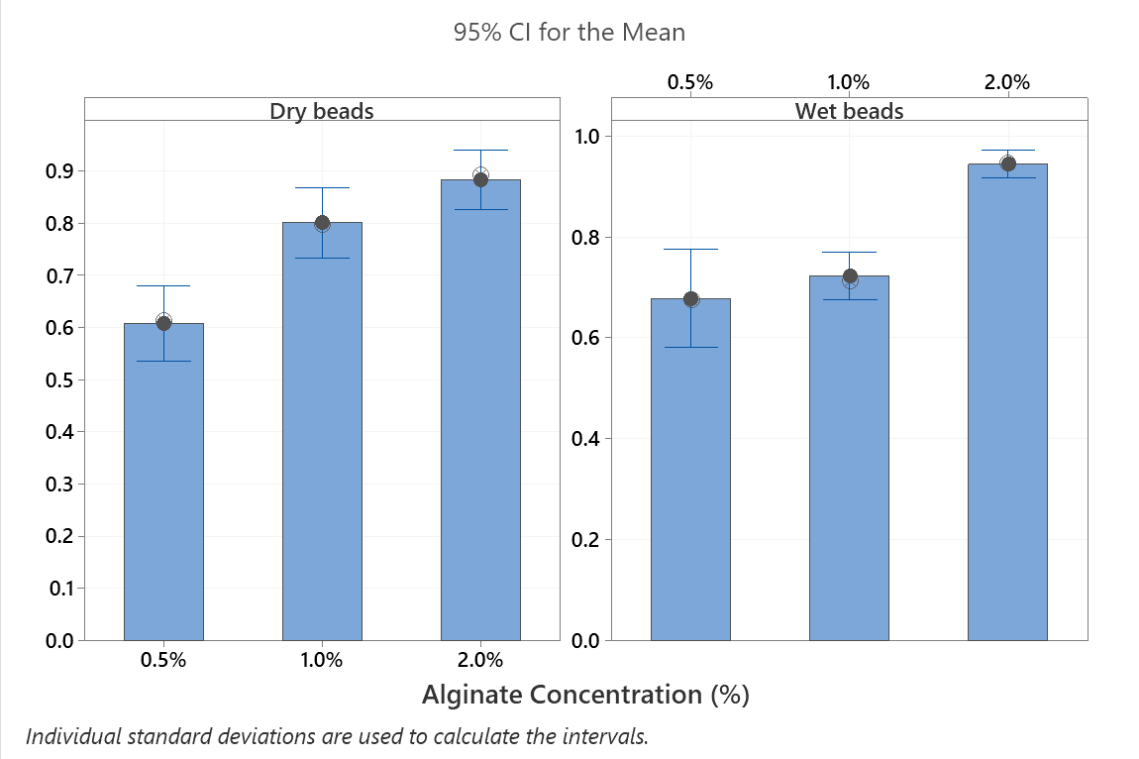


Figure 3: Dry and wet beads' roundness measurements correlation with alginate concentration. On the left side are the dry beads bars and on the right side are the wet beads bars (mean ± SD; n = 3).

A) Wet SO-alginate beads B) Dry SO-alginate beads

Figure 4: (A) The wet SO-alginate beads, and (b) dried beads.

Afterward, the beads were dried out by oven to provide dry alginate SO beads that were ready for LbL-encapsulation. Bead size and roundness measurements were checked by using the imageJ program for wet and dry beads, and the result showed a significant difference between the wet and dry beads' area while no significant difference was shown in roundness property (t-test $P < 0.05$) as shown in Table 1. Thus, we achieved a successful SO microencapsulation as shown in Figure 4.

In vitro drug release measurements in SGF and SIF of LbL coated and uncoated beads

SO-alginate beads were LbL coated with chitosan and alginate. To investigate the effectiveness of LbL coated beads vis-uncoated beads, the beads were dispersed in pH 6.8 SIF for three hours. The free beads showed 61% drug release in SIF for 3 hours, while zero percent was released

Table 1: The difference between wet and dry beads were observed based on the roundness property. Wet beads had a roundness mean value of 0.94 with low SD of 0.035 compared to dry beads (mean ± SD; n = 3).

	Wet Beads		Dry Beads	
Beads No.	Area (mm^2)	Roundness	Area (mm^2)	Roundness
1	1.74 ± .099	0.952 ± .035	0.518 ± .032	0.778 ± .078
2	1.715 ± .099	0.892 ± .035	0.493 ± .032	0.926 ± .078
3	1.78 ± .099	0.978 ± .035	0.436 ± .032	0.985 ± .078
4	1.785 ± .099	0.969 ± .035	0.496 ± .032	0.931 ± .078
5	1.896 ± .099	0.974 ± .035	0.455 ± .032	0.855 ± .078
6	1.623 ± .099	0.932 ± .035	0.538 ± .032	0.744 ± .078
7	1.56 ± .099	0.888 ± .035	0.508 ± .032	0.858 ± .078
8	1.79 ± .099	0.962 ± .035	0.474 ± .032	0.86 ± .078
9	1.651 ± .099	0.966 ± .035	0.489 ± .032	0.946 ± .078
10	1.647 ± .099	0.9 ± .035	0.449 ± .032	0.952 ± .078
Mean value	1.7187	0.9413	0.4856	0.8835

from coated beads as shown in Figure 5. According to the t-test statistical analysis, there was a significant difference between the two different beads ($p < 0.05$). This increased viability of coated beads was contributed to the LbL efficiency of the beads' outer surface.

Regarding to oral administration, the uncoated beads of SO would be degraded and digested in a short time because of the low pH in the stomach and the high absorbance in the intestine due to enzyme actions. Therefore, maintaining an adequate quantity of SO beads until they reach the last part of the intestine would be a key factor in improving the therapeutic impact. To investigate the in-vitro drug release (DR%) of SO beads, the method by Samah (Almurisi et al., 2020) was used with slight modifications. The beads were poured into pH 1.2 SGF for 2 hours, followed by pH 6.8 SIF for 3 hours. The cumulative drug release of 65% was reached in 135 min for uncoated beads whereas the same percentage was achieved in 255 min for coated beads. After 300 min, the dry coated beads showed a cumulative drug release of 68% while uncoated beads showed 83.7% of cumulative drug release as shown in Figure 6. In addition, a significant difference (t-test $P < 0.05$) was shown between both beads (coated and uncoated).

Discussion

The preparation of alginate-SO emulsion was the first step in our study. A recent study indicated the possibility of using sesame oil as the fat base of an emulsion, and the long-term stable emulsion by mixing SO with lecithin and carboxymethylcellulose (Kowalska & Żbikowska, 2016). According to oil encapsulation, several polysaccharides were used for oil encapsulation, such as sodium alginate which was successfully used to control the release of black seed oil (Azad et al., 2020). The ability of alginate to form hydrogels supports its uses as a gelling agent, stabilizer, thickener, and emulsifier in several studies (Ahmad Raus, Wan Nawawi, & Nasaruddin, 2021; Gheorghita Puscaselu, Lobiuc, Dimian, & Covasa, 2020). In addition, thyme oil encapsulated with sodium alginate was achieved effectively in another study (Volić et al., 2018).

Alginate concentration had a significant influence on SO beads formation as it plays the most important role regarding shape and size (H. Choukaife, Doolaanea, & Alfatama, 2020; Lotfipour, Mirzaeei, & Maghsoodi, 2012; Narin, Ertugrul, Tas, Sahin, & Oztop, 2020). Therefore, the emulsion in this study was optimized by variation of alginate (0.5%, 1%, 2% w/v) concentrations to ensure the optimal spherical shape. A similar study used alginate in different concentrations and reported that the shape of the beads was deformed when they decreased the alginate concentrations to 0.5% and 1% (Wong et al., 2021). This deformation happened when water consisted in the wet hydrogel beads evaporated throughout the drying process, causing volume shrinkage of hydrogel beads. Therefore,

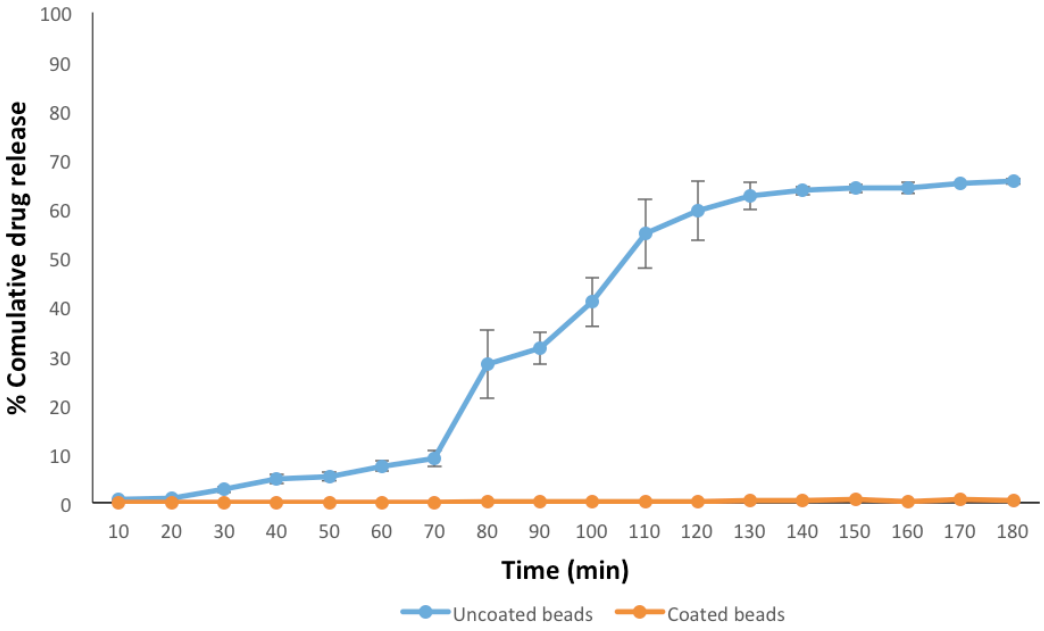


Figure 5: In vitro drug-release profile of LbL coated and uncoated alginate-SO dry beads in simulated intestinal fluid pH 6.8 (mean ± SD; n = 3).

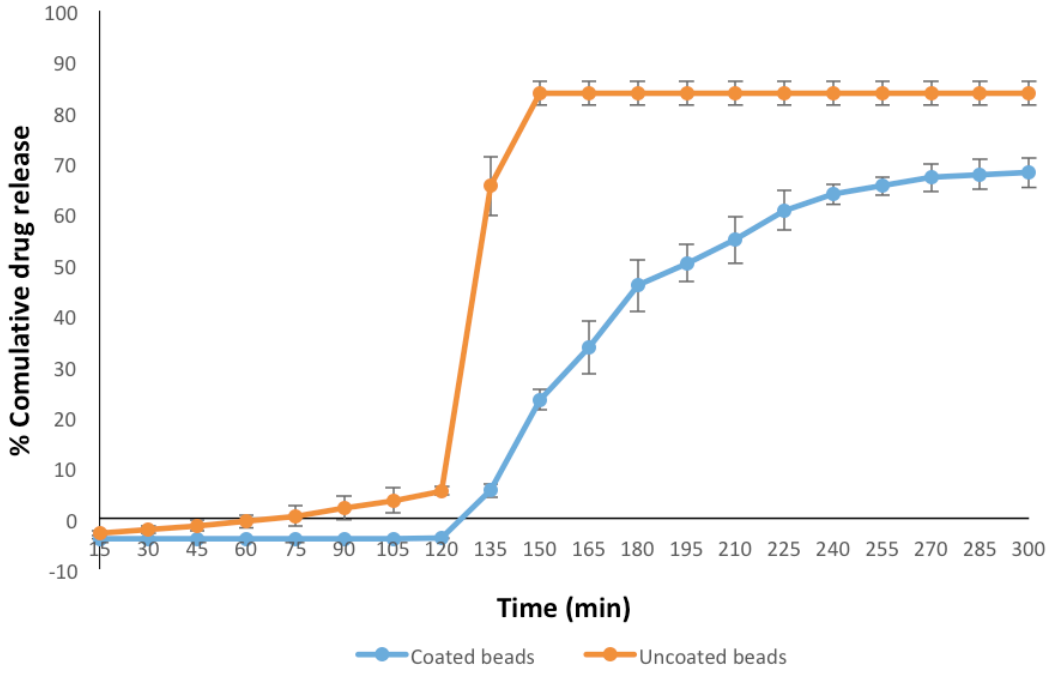


Figure 6: In vitro drug-release profile of LbL coated and uncoated alginate-SO dry beads in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 6.8 (mean ± SD; n = 3).

the presence of high alginate concentration will minimize the loss of water due to the formation of larger wet beads (Wong et al., 2021).

Multifunctional controlled drug release has been improved with the usage of LbL encapsulation. Alginate and chitosan were the chosen polymers for SO delivery as alginate is an anionic polymer and chitosan is a cationic polymer. Besides that, both hydrophilic and hydrophobic drugs can be delivered by using chitosan (Shafabakhsh et al., 2020). Doxorubicin was successfully delivered in the study by Chai et al. who prepared alternative multilayer of chitosan and alginate to control doxorubicin release for antitumor activity (Chai et al., 2017). Another study has synthesized an EcN encapsulated in a chitosan-alginate matrix with LbL assembly and CaCl2 cross-linking, and suggested an improvement of probiotic viability in the stomach environment (Luo et al., 2020). According to the control drug delivery via oral administration, chitosan and alginate polysaccharides have shown a promising efficiency in the drug delivery as mentioned in a study of emodin-encapsulated micelles into alginate and chitosan matrix. The beads showed sustained-release properties, and they could be used for site-specific drug delivery systems for hydrophobic drugs (Cong et al., 2018).

Conclusion

To enhance the oral administration and prevent drug leakage in the stomach, this study represented a double protection for active ingredients, the external gelation of SO and LbL coating of alginate-SO beads. The outcome of the study showed that LbL coated beads had zero release of SO in SIF compared to uncoated beads because it did not pass through the SGF. On the other hand, when beads passed through both buffers of pH 1.2 and 6.8, the coated beads showed a very low cumulative drug release in SGF while a higher drug release occurred in SIF. Uncoated beads showed a high drug release in both media, SGF and SIF. The previous results showed that the enteric coating designed in this study has the potential to be applied in intestinal treatments and colon delivery if it is inside the capsules. Furthermore, we are looking for further studies that will verify the drug biodistribution on animal models to show in-vivo mechanism of action.

Author Contribution

All authors made a great contribution to design the study, collect, and analysis data. In addition, the corresponding author revised the draft critically and gave a final approval for the paper to be published.

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Conflict of Interest

The authors declare no conflict of interest.

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