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Formulation, Optimization, and Evaluation of Extemporaneous Potassium Chloride-Loaded Alginate Beads

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ABSTRACT

Potassium chloride is an oral replacement therapy for hypokalemia, although its metallic taste is usually complained about and significantly reduces treatment compliance. This study aimed to develop an extemporaneous preparation of potassium chloride-loaded alginate beads for unpleasant taste masking. Formulation and factors influencing the preparation of potassium chloride-loaded alginate beads were determined. The optimized beads with satisfying spherical shape and size distribution were successfully prepared by dropping 2% alginate solutions into 5% calcium chloride containing 10% potassium chloride solutions. The optimal distance between the drip tip and the surface of the calcium chloride solutions was 10 cm. After bead fabrication, the beads were maintained for 5 min in calcium chloride solutions with constant stirring at the rate of 250 rpm for complete crosslinking. The average diameter of the resulting beads was 5.8 ± 0.2 mm with a sphericity index of 0.96. The average weight of prepared beads was 95.9 ± 2.3 mg. The prepared beads contained 3.8 ± 0.1 %w/w potassium ions and 3.3 ± 0.1 %w/w chloride ions that were calculated to have 50.3 ± 0.5 % and 71.3 ± 1.1 % entrapment efficiency, respectively. Moreover, the related compounds of sodium and calcium ions were also assayed, and were found to be 1.3 ± 0.3 %w/w and 0.9 ± 0.5 %w/w, respectively. In conclusion, the extemporaneous potassium chloride-loaded alginate beads were prepared successfully with high entrapment efficiency.

Keywords: Alginate beads; Extemporaneous; Formulation; Potassium chloride; Taste masking

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1. Introduction

Hypokalemia is a condition in which serum potassium is lower than 3.5 mmol/L. Potassium replacement is recommended for patients presenting with hypokalemia. Oral potassium is administered in patients with mild to moderate hypokalemia. Potassium chloride is available in either liquid or solid formulations. Slow-release potassium chloride tablets have been associated with gastrointestinal tract irritation, while potassium chloride solutions have a metallic taste. These problems often cause the patients to be unable to tolerate oral potassium chloride [1, 2]. To solve these problems, encapsulation is an attractive technique for taste masking, with research done on it in several publications [3-5]. Alginate is a natural, water-soluble, biodegradable, and non-toxic polysaccharide that is mainly produced from marine brown algae. Alginate has a wide variety of applications, particularly in drug delivery, cell and enzyme encapsulation, and wound dressing. Alginate can form gel *via* an ionotropic mechanism. These alginate gels form particularly well in the presence of divalent cations such as calcium [6, 7]. The ability to control the introduction of the crosslinking ions is necessary [8]. Extrusion dripping is famously applied and is the simplest method to create alginate beads. Factors influencing the size and shape of alginate beads, such as the concentration of calcium ions, crosslinking time of beads in gelation bath, collecting distance, and stirring rate, were previously observed [9,10]. However, most studies have aimed to load small or large molecule drugs into alginate beads. Studies on ion loading, such as with potassium ions, into these systems has not been found.

Therefore, the purpose of this study was to develop extemporaneous preparations of potassium chloride-loaded alginate beads to mask the unpleasant taste of potassium chloride, and to optimize the conditions for the preparation.

2. Materials and Methods

2.1 Material

Sodium alginate, calcium chloride, and potassium chloride were purchased from P.C. Drug Center Co., Ltd., Thailand. Red colorant (Winner's, Thailand) was used as a colorant. All other materials/reagents were of analytical grade. The simultaneous ICP emission spectrometer IPCE-9800 series (Shimadzu, Japan) was used to analyze the quantity of potassium, sodium, and calcium ions.

2.2 Alginate beads preparation

The alginate beads were prepared according to the technique of ionotropic gelation. Briefly, the sodium alginate solutions were prepared by dissolving an appropriate amount of sodium alginate in deionized water. The red colorant was also added in this solution to observe the initial changes in particle formation and color retention in the beads. The mixtures were stirred using a magnetic stirrer until the solutions were clear and were then stored at 2-8^{o} C for 24 h to give a uniform solution. The calcium chloride solutions were prepared by adding an appropriate amount of calcium chloride into deionized water and stirring using a magnetic stirrer until the solutions were clear. Then, the sodium alginate solutions were dropped by burette or squeeze bottle into the 200 mL of calcium chloride solutions. They were continuously stirred using a magnetic stirrer for a specific crosslinking time.

2.3 Optimization of alginate bead preparation conditions

Effect of solution concentrations: The sodium alginate solutions of varying concentrations (1%, 2% w/v) were dropped into calcium chloride solutions of varying concentrations (3%, 5%, 10% w/v, stirring at 250 rpm) at a rate of 8-12 mL/min by burette at the fixed distance of 10 cm (measured end of burette tip to surface of calcium chloride solution). After continuous stirring for 5 min, the beads were collected by sieve, excess aqueous phase was drained using blotting

paper, and the beads were desiccated at room temperature for up to 72 h.

Effect of crosslinking time: The 2% sodium alginate solutions were dropped in the 5% calcium chloride solutions with the same process as described above. The conditions were fixed, i.e., the distance between the end of burette tip and the surface of calcium chloride solutions at 10 cm, the drop rate at 8-12 mL/min, the stirring at 250 rpm. In this step, the crosslinking time (with continuous stirring) was varied to be 5, 10, 15, 20, or 30 min after the beads were fabricated.

Effect of collecting distance: The 2% sodium alginate solutions were dropped in the 5% calcium chloride solutions with the same process as described above. The conditions were fixed, i.e., the drop rate at 8-12 mL/min, the stirring at 250 rpm, and the crosslinking time at 5 min. In this step, the distance between the end of the burette tip and the surface of calcium chloride solutions varied from 10 or 20 cm.

Effect of stirring rate: The 2% sodium alginate solutions were dropped in the 5% calcium chloride solutions with the same process as described above. The conditions were fixed, i.e., the distance between the end of the burette tip and the surface of calcium chloride solutions at 10 cm, the drop rate at 8-12 mL/min, and the crosslinking time at 5 min. In this step, the stirring rate was varied at 250 or 500 rpm.

2.4 Potassium chloride-loaded alginate bead preparation

The solutions containing 2% sodium alginate and 10% potassium chloride: The 7.5 g of potassium chloride was dissolved in 25 mL of deionized water and then poured out into a portion of 50 mL of 3% sodium alginate. The mixture solution was then stirred using a magnetic stirrer to obtain a homogeneous solution and then finally was degassed for 1 h using an ultrasonic bath.

The solutions containing 5% calcium chloride and 10% potassium chloride: The 10.0 g of calcium chloride and 20.0 g of potassium chloride were weighed and subsequently added into 200 mL of deionized water. The mixture was stirred using a magnetic stirrer to obtain a homogeneous solution.

Formulation K1: The solutions containing 2% sodium alginate and 10% potassium chloride solutions were dropped in the 5% calcium chloride solutions.

Formulation K2: The 2% sodium alginate solutions were dropped in the solutions containing 5% calcium chloride and 10% potassium chloride.

For both K1 and K2 formulations, the sodium alginate phase was dropped in the calcium chloride phase with the same process as described above. The conditions were fixed, i.e., the distance between the end of the burette tip and the surface of calcium chloride solutions at 10 cm, the drop rate at 8-12 mL/min, the stirring at 250 rpm, and the crosslinking time at 5 min.

Preparation of potassium chloride-loaded alginate beads via plastic squeeze bottle: The preparation process was further scaled-up by dropping the alginate phase from a plastic squeeze bottle in the calcium chloride phase with the same process as described above. All preparation conditions were optimized again in the same step as described above.

2.5 Evaluation of alginate beads

Morphological analysis: The size and shape of the beads were measured on graph paper. Size is indicated by the diameter and shape is indicated by the sphericity index. The mean diameter and sphericity index were obtained from the measurement of 30 beads in each formulation. The sphericity index can be calculated by the following equation:

$$Sphericity\ index = \frac{width}{length}. \qquad (2.1)$$

Mean size reduction: Due to the size reduction of beads by water loss during 24 or

72 h of desiccant, the size of the beads at different periods was observed.

The ion content was calculated as the percentage ion load and entrapment efficiency (*EE*) or percentage of the content was estimated as the entrapped quantity of ions with respect to the total quantity incorporated in the preparation that can be calculated by using direct or indirect methods [11]. In this study, %*EE* was calculated by using a direct method that calculates the amount of ions contained in the beads. Ion load and *EE* were determined by accurately weighted alginate beads $\left(W_{beads}\right)$ that were crushed, sonicated in deionized water for 15 seconds/cycle, 4 cycles, and finally adjusted to the volume. The solution was analyzed for the chloride ion content $\left(W_{calculated\ ion}\right)$ using precipitation titration according to USP41 [12], and potassium, sodium, and calcium ion content $\left(W_{calculated\ ion}\right)$ using inductively coupled plasma-optical emission spectrometer (ICP-OES). The ion loading and *EE* were calculated by comparing $W_{calculated\ ion}$ with W_{beads} and the amounts of ion that were added in the preparations $\left(W_{theoretical\ ion}\right)$, respectively, using the following equation:

$$\%\ \text{Ion load} = \frac{W_{calculated\ ion}}{W_{beads}} \times 100, \qquad (2.2)$$

$$\%\ EE = \frac{W_{calculated\ ion}}{W_{theoretical\ ion}} \times 100. \qquad (2.3)$$

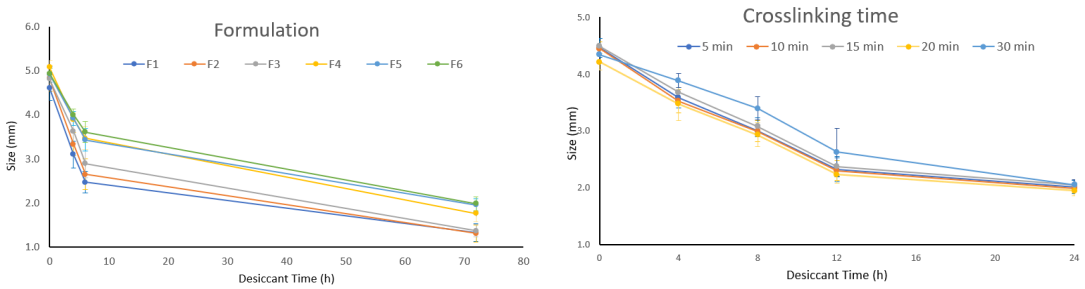
3. Results and Discussion

Alginate beads were successfully fabricated by the ionotropic gelation method. When sodium alginate solutions were dropped into calcium chloride solutions, the beads were formed immediately. From the previous study, the concentrations of sodium alginate used in bead preparation varied from 1% to 4% [13-16]. In this study, 1% and 2% sodium alginate concentrations were selected for testing as these concentrations are uncomplicated to prepare in a hospital, following the proposed use as extemporaneous preparation. The size and shape of the freshly prepared beads are presented in Table 1. Other preparation conditions held equal, the size of the beads was not different between the 1% and 2% sodium alginate solutions. This indicated that these fixed conditions could give reproducible products. Beads from both concentrations of sodium alginate were transparent and smooth on the surface. However, the physical characteristics of beads from 1% sodium alginate were of an inconsistent size and irregular shape, while those from 2% sodium alginate were of equal size and spherical shape. The lower standard deviation of size and the sphericity index close to the unity of 2% sodium alginate beads indicated a better bead character. For different concentrations of calcium chloride solutions, the physical characteristics were not different between the beads from 2% sodium alginate with all studied concentrations of calcium chloride. Increasing alginate concentration led to an increase in the viscosity of alginate solution. Additionally, the diameter of the beads decreased as the viscosity of the solution increased. Alginate solution with high viscosity was not suitable for encapsulated preparation because of the difficulty in the bead forming process [9]. The size and shape of the beads from 3%, 5%, and 10% calcium chloride were similar.

The resulting beads were then dried at room temperature in order to study the physical stability. The size of the beads gradually reduced over time (Fig.1).

The evaluation of crosslinking conditions on beads' appearance showed that the crosslinking time had a major effect on bead size, but the influence on shape was less intense. The shape of all beads was spherical regardless of the studied crosslinking times. The size of the beads obtained was quite similar (Fig.1). The diameter of the alginate beads formed after 20 and 30 min in calcium chloride solutions was found to be significantly smaller than those at the 5, 10, and 15 min times. This could be attributed to

the ionic crosslinking between calcium and alginate ions, which made the structure of alginate capsules more compact with the increased in crosslinking time. Another observation was that increasing the crosslinking time led to the formation of faded red beads. This implied the risk of a decrease in % loaded potassium chloride with increasing crosslinking time.



(a) (b)

Fig. 1. Changes in the size of beads (n=30) with different desiccant times at room temperature (a) formulations F1-F6 prepared by using burette with 0-72 h desiccant times, (b) formulation F5 prepared by using burette in different 5-20 min crosslinking times with 0-24 h desiccant times .

Table 1. Size and shape of the freshly prepared beads at different concentrations by using burette (n=30).

	Formulations	Mean diameter (mm)	Sphericity index
F1	1% sodium alginate + 3% calcium chloride	4.6 ± 0.3	0.88
F2	1% sodium alginate + 5% calcium chloride	4.8 ± 0.3	0.86
F3	1% sodium alginate + 10% calcium chloride	4.8 ± 0.3	0.85
F4	2% sodium alginate + 3% calcium chloride	5.1 ± 0.2	0.94
F5	2% sodium alginate + 5% calcium chloride	4.9 ± 0.2	0.96
F6	2% sodium alginate + 10% calcium chloride	5.0 ± 0.1	0.96

The drop distance between the tip of burette and the surface of calcium chloride solutions was also varied to observe its effect on bead formation in terms of bead size and shape. The beads which were prepared using either a 10 or 20 cm drop distance were spherical. However, the drop distance was also found to have affected the yield of the obtained beads; the greater the distance, the lower the yield. Using a 20 cm drop distance, some beads were broken when they fell and hit the bottom of the container. Thus, the distance of 10 cm was taken as the optimum drop distance in this study.

The size and shape of the alginate beads prepared at different stirring speeds were compared with two different mixing speeds, 250 and 500 rpm. Alginate beads prepared at 250 rpm were consistently spherical while stirring at 500 rpm tended to produce alginate beads with increased elongation and decreased roundness. Therefore, in the next study steps of potassium chloride addition, a 2% sodium alginate 5% calcium chloride ratio was selected, and the drop distance, stirring speed, and crosslinking time were 10 cm, 250 rpm, and 5 min, respectively. Using these conditions, the physical characteristics of the blank beads were transparent, and the size and sphericity index were 4.9 ± 0.2 mm and 0.96, respectively. Calcium alginate gel is chemically unstable. It is sensitive to chelators such as phosphate, citrate, lactate, and monovalent cations such as sodium and magnesium that may be present in some storage solutions. Consequently, calcium alginate gel beads may be destabilized and eventually dissolve after a certain period of

time [9]. The shrinking size of the beads was observed when the storage period increased, leading to increased crosslinking time between calcium ions and alginate molecules.

To increase the size of the prepared beads, a plastic squeeze bottle with a larger tip inner diameter (5.5 mm) than that of the burette (2.0 mm) was chosen to be used in the dropping of sodium alginate. The optimal drop rate was 80-120 drops per minute and was achieved through manual operation with consistent force. The increase in average bead size was as expected, reaching 5.8 ± 0.2 mm with a sphericity index of 0.96, which was 18% larger than the size of the beads prepared using a burette.

Using the optimal conditions as described above with the preparation of the alginate beads by plastic squeeze bottle, the appearance of alginate beads loaded with potassium chloride are shown in Fig.2. The physical appearance of the sodium alginate solution containing potassium chloride was slightly opaque with homogeneous solution and the physical appearance of the sodium alginate solution without potassium chloride was a clear colorless solution. The physical appearance of these solutions affected the physical appearance of the obtained beads as shown in Fig.2. The opacity of the beads can be explained by two factors. Firstly, based on the crosslinking effect of calcium on alginate, the latter is expected to precipitate in the presence of calcium [15]. Secondly, the presence of both sodium alginate and potassium chloride in the same solution results in decreasing solubility of alginate from the salting-out effect. The slightly opaque appearance of the K1 formulation may be the result of the salting-out effect. The size of the alginate beads from the placebo formulation, K1 formulation, and K2 formulation was 5.1 ± 0.1 mm, 5.9 ± 0.1 mm, and 5.8 ± 0.1 mm, respectively. The average weight of the alginate beads from the placebo formulation, K1 formulation, and K2 formulation was 78.8 ± 2.2 mg, 96.2 ± 3.9 mg, and 95.9 ± 2.3 mg, respectively. The sphericity index of the alginate beads from the placebo formulation, K1 formulation, and K2 formulation was 0.98, 0.97, and 0.95, respectively. Medications of size greater than 8 mm, there can be associated swallowing difficulties [17]. The size of potassium chloride loaded alginate beads was smaller than 8 mm, thus patients could swallow the alginate beads easily with water or other liquid.

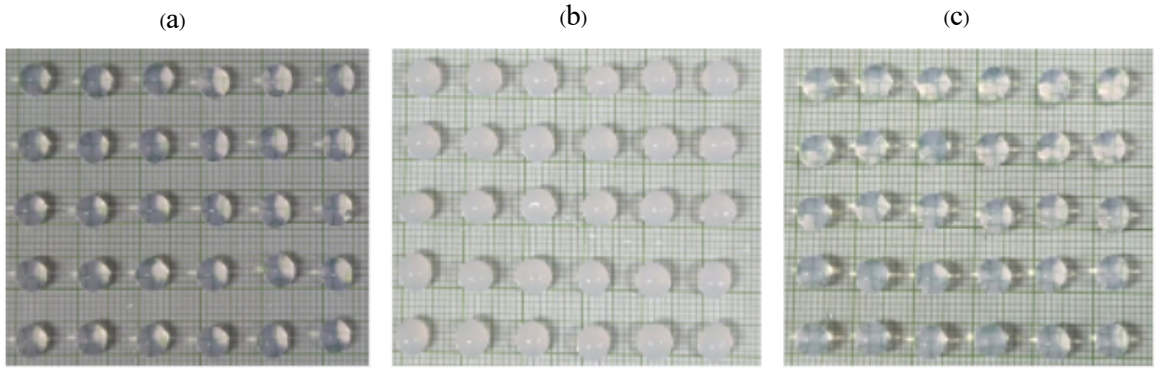


Fig. 2. The appearance of alginate beads prepared by using plastic squeeze bottle; (a) Placebo, (b) Formulation K1, (C) Formulation K2.

Besides control factors, i.e., the concentration of sodium alginate/calcium chloride solutions, collecting distance, stirring rate, and crosslinking time affecting the physical characteristics of beads, the bottle squeeze force also affected the size of the

beads which also affected drop rate. When using a burette, sodium alginate droplets grow at the tip and detach by the influence of gravity, which controls the constant flow rate by burette stop cork. However, sodium alginate droplets from the plastic squeeze bottle depended on the squeeze force, which varied by the individual squeezing the bottle. For scaled-up production, using a plastic squeeze bottle for potassium chloride-loaded alginate beads is a more appropriate choice than a burette because plastic squeeze bottles are generally more available, easy to use, and produce spherical beads. The squeeze force should be controlled consistently during the preparation process.

Table 2. The content of chloride, potassium, sodium, and calcium ions in the K2 formulation prepared using a plastic squeeze bottle.

Formulations	Chloride		Potassium		% Sodium (%w/w)	% Calcium (%w/w)
	% Loaded (%w/w)	%EE	% Loaded (%w/w)	%EE		
K1	2.7 ± 0.1	58.5 ± 2.5	1.3 ± 0.1	18.1 ± 2.5	1.0 ± 0.1	0.9 ± 0.2
K2	3.3 ± 0.1	71.1 ± 1.1	3.8 ± 0.1	50.3 ± 0.5	1.3 ± 0.3	0.9 ± 0.5

The amount of ion load and the ability of beads to entrap the ion are the determining factors for selecting the optimum bead preparation method and bead composition [15]. As shown in Table 2, %ion loaded and %EE of both potassium and chloride ions in the K2 formulation were higher than those in the K1 formulation; however, the contents of sodium and calcium ions were similar to the others. The preparation method was one of the major factors affecting the content entrapped in the beads. For potassium chloride in the calcium chloride phase, both potassium and chloride ions could diffuse easily into the beads, possibly in the interfacial surface during bead formation. This resulted in the high %EE for potassium chloride in the sodium alginate phase. In other words, both ions also diffused into the external aqueous phase resulting in the lower %EE. Because the potassium ion content from the K2 formulation was the highest, potassium chloride loaded alginate beads should be prepared by dropping sodium alginate into potassium chloride with calcium chloride solution. Sodium and calcium ions could also be found in the beads because they were composed in the raw sodium alginate and calcium chloride. For administration, the beads were weighed equivalent to the therapeutic potassium contents and then administered orally with water or other liquid. The typical dose of commercial potassium chloride medicine (10% w/v) is 30 mL which was equivalent to potassium ion 1.57 g/dose. The patient should intake approximately 488 beads or approximately 42 g of the freshly prepared beads calculated from % potassium loaded from the K2 formulation.

4. Conclusion

Optimal conditions used to prepare extemporaneous potassium chloride-loaded alginate beads are: 2% sodium alginate solution, 5% calcium chloride solution, collecting distance at 10 cm, stirring rate of 250 rpm, and a crosslinking time of 5 min. For scaled-up production, a plastic squeeze bottle was found to be suitable for producing the desired size and shape of the alginate beads. The addition of potassium chloride in the calcium chloride phase gave better EE than the sodium alginate phase. The assay results indicated that potassium chloride could be entrapped in alginate beads for in extemporaneous preparation. However, the storage of these beads and their stability should be further studied.

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