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Investigating the Feasibility of Xylitol and Gelatin for Controlled Release System in Drug Delivery using Calcium Alginate

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Calcium Alginate-based beads have been recognized to have high potential for pharmaceutical applications thanks to their ease of use and biocompatibility. This study aims to investigate how xylitol and gelatin could be used for a controlled drug delivery system and how to manipulate such a delivery system. For the study, calcium alginate beads were synthesized using two different calcium compounds: calcium lactate (CL) and calcium chloride (CC). Varying concentrations of the calcium compounds in the beads were prepared to measure their effects on their characteristics, such as size, weight, strength, and, most importantly, the diffusion rate. The study attempted to manipulate the diffusion rates by incorporating xylitol and gelatin into the calcium alginate membrane. A comparative analysis revealed that CC and CL affected the beads differently. For instance, bead size increased with CC concentration up to 5%, after which it decreased, while CL

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showed a more consistent decrease in size as concentration increased. Weight generally decreased with higher concentrations of both CC and CL, but the reduction was more pronounced with CL. The popping force increased with CC concentration but had a non-linear relationship with CL, reaching around 7% concentration before decreasing. The study also examined the percentage change in weight after 48 hours of drying. For smaller beads (3mm), the weight change decreased with higher CC concentration, but for larger beads (7.05mm), the trend reversed, showing an increase in weight change at higher concentrations. Similar patterns were observed for CL, with weight change initially decreasing but increasing with higher concentrations. Our diffusion studies found that the xylitol concentration generally enhanced diffusion rates, with CL beads showing a greater initial diffusion than CC beads. In contrast, gelatin concentration has less predictable effects on diffusion rates. For CL beads, more gelatin results in less dye diffusion, suggesting that gelatin may impact the initial release of dye from the beads.

Keywords: Calcium alginate; controlled release system; dissolution test; drug delivery; gastro-spherification.

1. INTRODUCTION

Drug delivery at the right time, in the right area, and at the right concentration should be warranted for therapeutic efficacy [1,2]. The drug delivery system enables the release of the active pharmaceutical ingredient to achieve a desired therapeutic response [3,4]. Conventional drug delivery systems such as tablets, capsules, syrups, and ointments typically suffer from poor bioavailability and fluctuations in plasma drug levels and cannot achieve sustained release [5,6]. The therapeutic process can only be rendered functional with an efficient delivery mechanism. Moreover, the drug has to be delivered at a specified controlled rate as precisely as possible to achieve maximum efficacy and safety [7]. A challenging aspect of insulin delivery to diabetes patients is the constant fluctuation of blood sugar levels throughout the day [8]. Controlled insulin delivery devices stabilize blood sugar levels for diabetes patients. These systems can release insulin steadily over time or in response to changing glucose levels to stabilize blood sugar levels [9,10]. Diabetes is just one example in the real world that shows us that timely or controlled drug delivery is crucial.

The controlled release of pharmaceutical compounds in tablets is defined as the release of drugs according to a predictable diffusion rate to reach the desired drug concentration in a certain amount of time [11]. Calcium alginate is a polymer derived from seaweed that can be utilized in drug-delivery systems [12,13]. The alginate can form hydrogels by interacting with calcium ions, creating a unique and optimal way to coat and package drugs. Calcium alginate capsules are commonly used in controlled-release systems [14]. Alginate is versatile and suitable for oral, topical, and targeted drug delivery [15,16]. For instance, alginate beads can be infused with a dye that gradually diffuses, serving as a model for drug delivery.

Many factors influence the diffusion of molecules through a calcium alginate film. Generally, the smaller the size of the molecules, the faster the diffusion rate. Additionally, the molecule's shape can also affect its diffusion rate [17,18]. The thickness of the film is also a significant factor. Thicker films reduce the rate at which molecules can pass through due to the longer path that the molecules must take to diffuse out of the membrane. Higher concentrations of alginate result in denser films with smaller pore sizes, which can slow down the rate of diffusion [19]. The concentration of calcium ions influences the degree of cross-linking. Higher cross-linking reduces diffusion rate due to its compact structure [20,21]. Other factors, such as temperature, pH, and other environmental ions or molecules, can also affect diffusion [22,23]. The amount of water in the film also influences its diffusion rate. Fully hydrated films allow faster diffusion than dry films.

The diffusion of molecules through sodium alginate films is influenced by various factors, including the type of calcium compound used [24]. Calcium alginate films are formed when sodium alginate reacts with calcium ions, creating a network of a gel-like substance [25]. Different calcium salts, such as calcium chloride and calcium lactate, can be used, and each affects the film properties and diffusion rates differently [26]. Calcium chloride is expected due to its high solubility and rapid gelation, resulting in a dense network that can slow down diffusion [27]. Calcium lactate has moderate solubility [28].

Therefore, the choice of the calcium source provides a way to manipulate the properties of a calcium alginate film.

Using calcium alginate beads release of food dye as a model drug is a common experimental method to study diffusion properties. This setup simulates drug delivery systems. The food dye, serving as a model drug, is mixed into the sodium alginate solution. Once the beads are formed, they are placed in water or some medium for release, and the release of the dye is monitored over time. Spectroscopic methods, like UV-Vis spectrophotometry, can be used to measure the concentration of the dye in water at different intervals.

Xylitol is a common substitute for sugar due to its lower risk of cavities and tooth decay. Thanks to its lower calorie content than sugar and fewer health risks, it is a popular ingredient in gums, candies, and dental hygiene products [29]. Because xylitol is very similar to sugar, it can be used in a membrane to, rather than merely diffuse the model drug, form a membrane that slowly dissolves, resulting in a controlled release that can be controlled by the amount of xylitol present in the membrane [30].

Gelatin is a common food ingredient used as a gelling agent [31]. It is derived from collagen and is a collection of peptides and proteins. Gelatin is produced by partial hydrolysis, which classifies gelatin as a hydrogel. Traditionally, gelatin was used to encapsulate medicine. Gelatin is soluble in warm temperatures and lower pH levels [32]. In our simulation, gelatin denatures if the gastrointestinal conditions are 30-37 degrees Celsius and pH is 2. We hypothesize that this weakening gelatin structure in such conditions should result in a predictable change in diffusion rate as we increase the gelatin concentration in the membrane of our alginate beads. This study might contribute to developing improved pharmaceutical formulations in controlled drug release systems.

2. EXPERIMENTAL METHODS

2.1 Materials and Reagents

Sodium alginate (Cape Crystal Brands, NJ) was purchased and used as our source of SA Calcium chloride (PURE Original Ingredients), Calcium lactate (Bulk Supplements), pipette, electric balance, stirrer (Model: Bell-Stirr Magnetic Stirrer 4 Position, BELLCO), UV Visible Spectrophotometer (Model: V722, Amazon.com), Gelatin (Medley Hills Farm, unflavored gelatin, CA), Xylitol (NOW Real Food, NY)

2.2 Creation of Calcium-Alginate Beads

Targeted concentrations of calcium compounds were prepared in distilled water, such as 10%, 5.0%, 3.0%, and 1.0%, as labeled below as B, C, D, and E. To create the calcium compound solution, an estimated amount was carefully placed directly into a 500 ml beaker on a tared electric scale to measure the mass of each sample of calcium compound. Then, an exact amount of water was poured to create the desired solution concentration. The sodium alginate solution was prepared using the same method as described and added with red food dye as in the beaker labeled A. Distilled water was prepared in a plastic container (F), which was used to stop the calcium and alginate reaction. The plastic spoon (G) was utilized to transfer beads created after reacting.

Briefly, the dyed sodium alginate solution was obtained into a plastic pipette and dropped into the beaker filled with CC or CL. The beads were formed instantly and moved into the distilled water using the plastic spoon to stop further reaction. Fig. 2 shows the collections of beads of four groups. The beads were dried for 48 hours at room temperature before being subjected to the diffusion study.

2.3 Bead Size Measurement

A simple caliper was used to measure the diameter of our beads, as illustrated in Fig. 2. After letting the beads rest on the paper towels for a few seconds, we measured the beads by hand with calipers that measured up to tenths of centimeters. This meant that values observed between tenths of centimeters were estimations. Each bead was measured separately in order of highest to lowest CC concentrations. All five 10 % CC solution beads were measured in no particular order, and the diameters for each were. We then measured the diameters of the five 5% CC beads in no specific order and recorded the values. This procedure was repeated for the 3% and 1% CC concentration beads. Microsoft Excel calculated the mean and standard deviation of the diameters in centimeters.

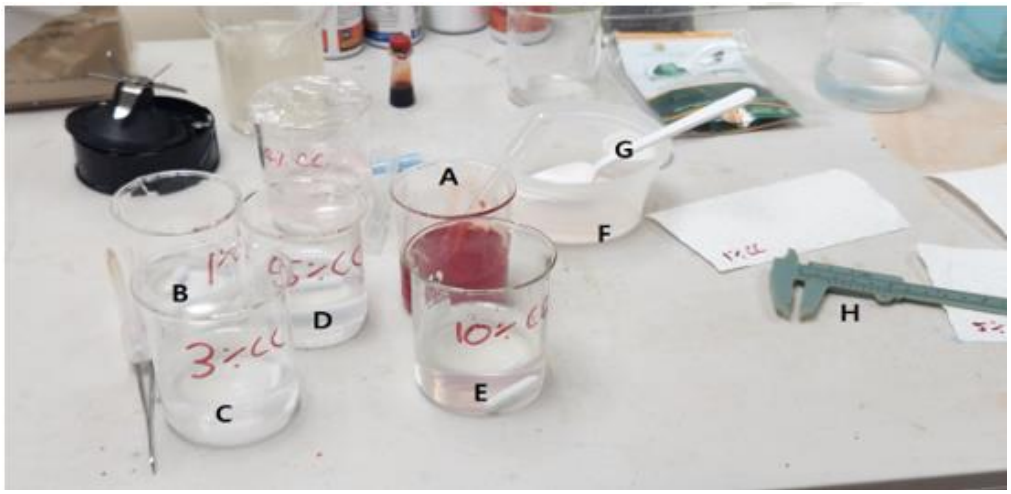

Fig. 1. Presents collections of our experimental materials

Fig. 2. Presents the collections of our calcium alginate beads after creation

Fig. 3. Presents the methods of measuring bead size with a micrometer

2.4 Bead Weight Measurement

An electric scale that was accurate to the hundredth of a gram was used to measure the weight of the beads. Paper weighing boats were created to hold the beads as their mass was measured. We first measured the five 10% CC beads by placing the weight boat on the scale and zeroing the scale. After the scale was zeroed, the first bead was moved on the weighing boat, and its mass was recorded. The beads were chosen randomly without any particular order. After recording the mass of the first 10% concentration bead, we simply zeroed the scale, placed the next bead on the weighing boat, and recorded the mass. The scale was tared to zero again to place the next bead and record its mass. This process was repeated for the rest of the 10% concentration group of beads. We then removed the beads from the weighing boat and placed them aside. The scale was tared again with the weighing boat still on the scale, and began to repeat the procedure for the next group of beads, the 5% CC concentration group. The same procedure was repeated for the 10% concentration group to record the masses of the 5% concentration group. This process was repeated until all beads in all concentration groups had their masses recorded.

2.5 Popping Force Evaluation

A force gauge that was accurate to the hundredth of a Newton was used to measure the popping force of the beads, as seen in Fig. 5. Before using the force gauge, we configure the settings so that only the maximum force recorded would be shown on the display to reduce human error in the form of poor reaction time or memory. Then, starting with a 10% concentration bead, we applied force to the bead with the force gauge slowly until the bead popped. The maximum force was recorded on the force gauge and was logged into our data. This procedure was repeated for all of the beads in our experiment and recorded all maximum force applied by the force gauge as popping force.

2.6 Simulated Gastric Solution Preparations

Temperature and acidity were considered essential to simulate the conditions of the human digestive system where the drug will be acting. The human body's internal temperature is about 37 degrees Celsius, so a water container that heated our beaker with solution to around 37 degrees Celsius was prepared. To replicate the stomach's acidity, hydrogen chloride solution was added with a plastic pipette until a pH of 2 was reached, which was checked with a pH strip. Additionally, Pedialyte was used to simulate gastric fluid since it is a mixture of various ions and electrolytes in our stomach. In this stomach-like condition, alginate beads full of red dye simulating a drug substitute were added, and a magnetic stirrer was used to replicate the digestive system’s movement at 37 °C. Four beakers with solutions of different concentrations could be used, as in Fig. 6. Every ten minutes, the testing solutions were sampled to examine how much of the red dye had diffused into the solution.

Fig. 4. Shows our method of measuring the bead weight using an electric balance

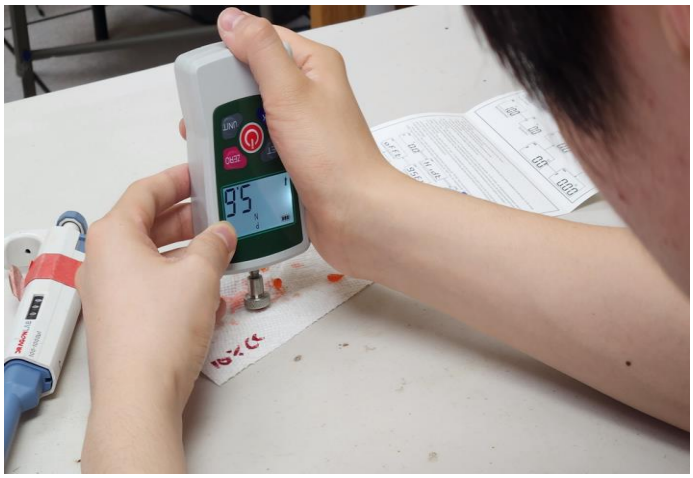

Fig. 5. Presents the manner of measuring the popping force of the beads

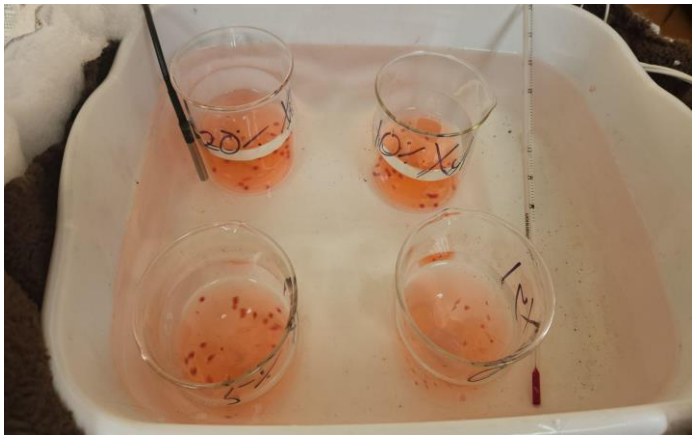

Fig. 6. Shows the diffusion study of red food dye embedded in the beads

2.7 Xylitol Solution Preparation

To add xylitol into the membrane of the alginate beads, xylitol was added to the 2% SA solution while keeping the calcium compounds alone. An electric scale was used to measure a quantity of xylitol to add to our beakers of SA to reach 20%, 10%, 5%, and 0% xylitol concentrations in our SA. Then, these xylitol-infused solutions were dropped into our existing calcium compound solutions to create alginate beads with xylitol incorporated into their membrane.

2.8 Gelatin Solution Preparation

To add gelatin to the membrane of the alginate beads, varying amounts of gelatin were used in 10% CC and CL solutions to create 15%, 10%, 5%, and 0% gelatin solutions. Then, previously prepared 2% SA was added to the gelatin-calcium compound solutions to create our gelatin-incorporated CL and CC beads.

2.9 Spectrophotometer

Four groups of beads were dropped into our diffusion mediums at different time intervals to measure the diffusion rate of our beads. The time that the beads were added to the solution was measured with a stopwatch, and 3 ml solution was sampled at ten-minute intervals for each group of beads. After 60 minutes for each group of beads, six samples were collected. A blank sample of 3 ml of our diffusion medium without any dye was prepared to measure the background absorbance from the spectrophotometer. The absorbance of each sample was measured, and the data was recorded in Microsoft Excel Worksheet.

2.10 Data Summary and Analysis

All the data was typed into Microsoft (MS) Excel Worksheet, from which the raw data's mean and standard deviation were calculated. When any

graph was inserted, it was created as a scattered plot. Background color, line thickness, and font sizes were chosen carefully for maximum contrast. For the regression analysis, the trendline function in MS Excel was used. The regression equations were selected by comparing the regression coefficient R squared.

3. RESULTS AND DISCUSSION

3.1 Relation of Size with CC Concentration

Fig. 7 presents the relationship between calcium chloride concentration and size. The results indicate that the bead sizes were not highly dependent on the concentration, with a poor regression coefficient of R squared equal to 0.1321 when plotted under linearity. However, its regression coefficient was more significant (R squared 0.908) when plotted as a polynomial function. Therefore, the bead sizes seemed to be correlated with the concentration of CC with a polynomial relation, not linearly. A separate study showed data similar to ours [33].

3.2 Relation of Weight with CC Concentration

Fig. 8 presents the relationship between CC concentration and bead weight. When a linear trendline was plotted with this data, we observed a value for our coefficient of determination of 0.765. Conversely, when a polynomial trendline was plotted with this data, we found a value for our coefficient of determination of 0.9227, significantly higher than when a linear trendline was plotted. This showed that a polynomial trendline better represented the trend of the data. The trend of the bead weight was negatively correlated. Our data looked similar to the study done by Gina [34].

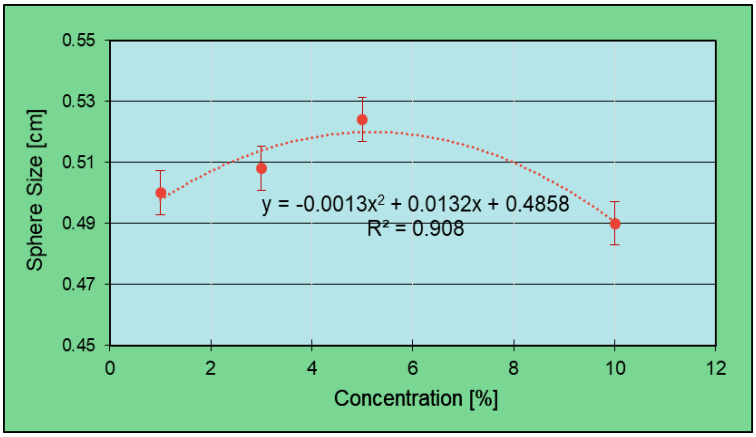

Fig. 7. Presents the relationship between CC concentration and bead size

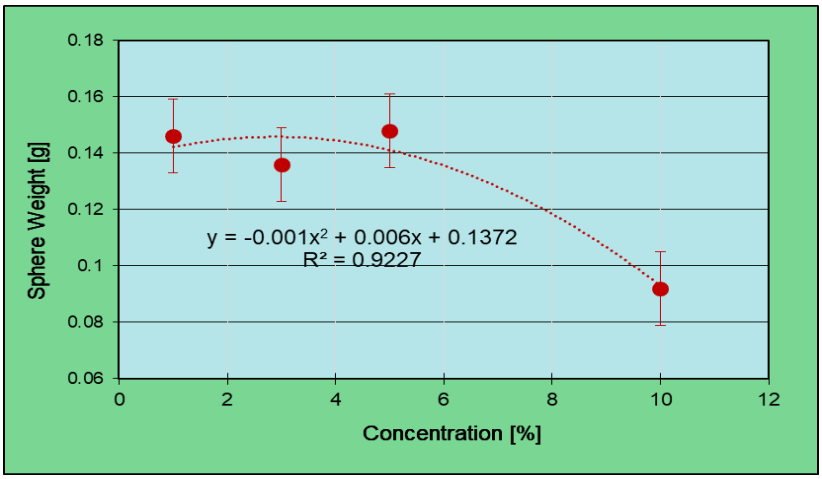

Fig. 8. Presents the relationship between CC concentration and bead weight.

3.3 Relation of Popping Force with CC Concentration

Fig. 9 presents the relationship between CC concentration and popping force. The relationship was positive and linear, with a strong coefficient of determination of 0.9459. This was interesting as, unlike the relationships between CC concentration and size or weight, this relationship was best represented as a linear relationship rather than a polynomial. Our data was predictable based on other groups of scientists [35].

3.4 Relation of Size with CL Concentration

Fig. 10 presents the relationship between CL concentration and size. The relationship was approximately polynomial. This was interesting because although the coefficient of determination was indeed higher when plotted as a polynomial relationship compared to the linear relationship, the magnitude of the coefficient of determination was not very strong.

3.5 Relation of PP with CL Concentration

Fig. 11 presents the relationship between CL concentration and popping force. The relationship was approximately polynomial. This was interesting because although the coefficient of determination was indeed higher when plotted as a polynomial relationship compared to the linear relationship, the magnitude of the coefficient of determination was not very strong. The relationship was also negative, unlike the relationship between CL concentration and size.

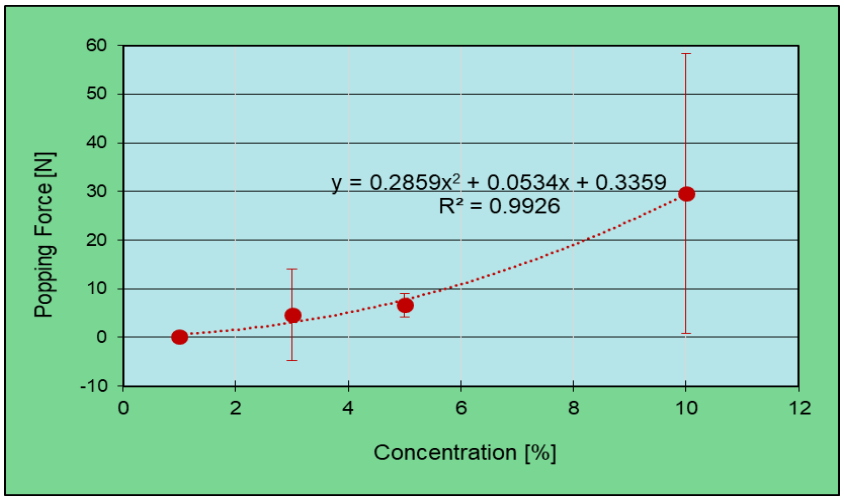

Fig. 9. Presents the relationship between CC concentration and popping force

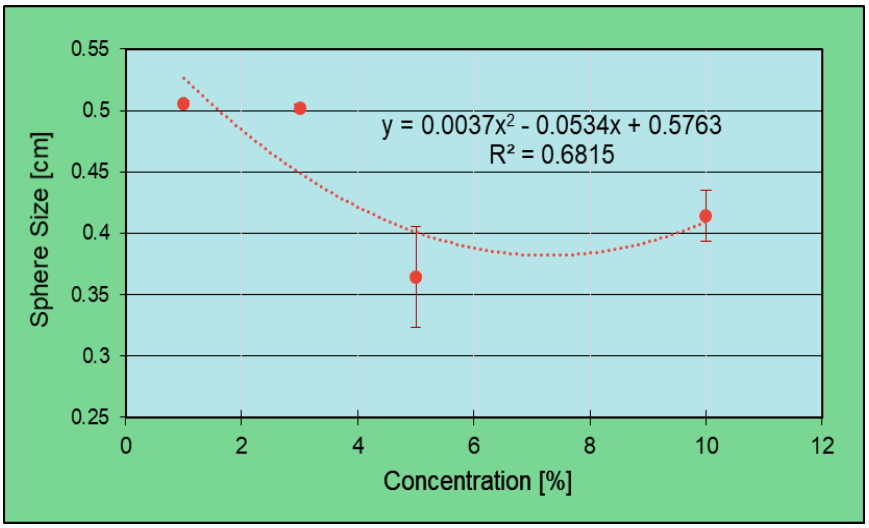

Fig. 10. Presents the relationship between CL concentration and size

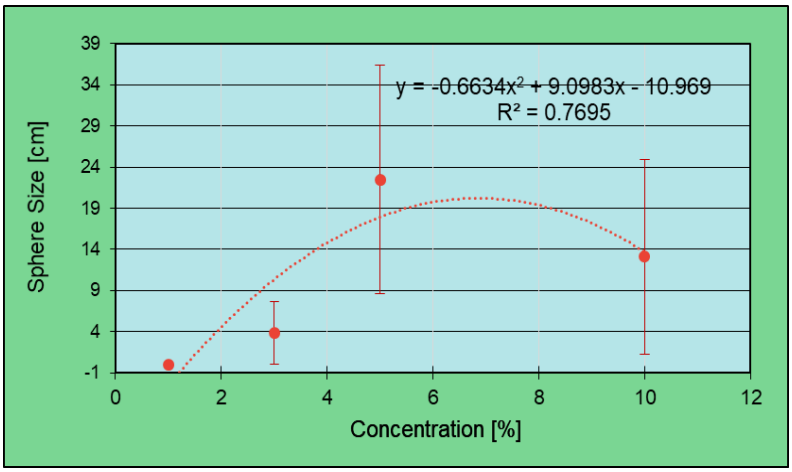

Fig. 11. Presents the relationship between CL concentration and popping force

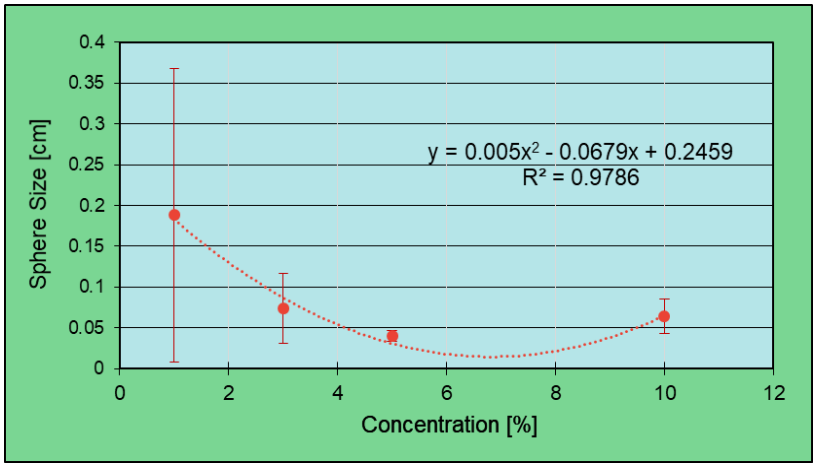

Fig. 12. Presents the relationship between CL concentration and weight

3.6 Relation of weight with CL Concentration

Fig. 12 presents the relationship between CL concentration and weight. This relationship was also best modeled with a polynomial trendline. The coefficient of determination for this relationship was highest compared to the relationships between CL concentration and size or popping force. This was interesting because, with CC concentration vs. popping force, the data was best modeled linearly but polynomially in this case.

3.7 Size Comparison of CC and CL

Fig. 13 compares the relationships between CC and CL Concentration vs. Size. This comparison shows that size reacts in nearly opposite directions as a function of the concentration of CL and CC. As CC concentration increased, the bead size increased, but only until approximately 5 percent concentration, where the bead size began to decrease as a function of CC concentration. As CL concentration increased, the bead size decreased much faster than it did for CC, but at approximately 7 percent concentration, the bead size began to increase.

3.8 Weight Comparison of CC and CL

Fig. 14 compares the effect on weight by CC concentration and CL concentration. For both CL and CC, it appears that bead weight decreases with higher concentration. However, CL's change was much more drastic, whereas the CC vs. weight line showed little difference. Only the CL beads increased again at higher concentrations.

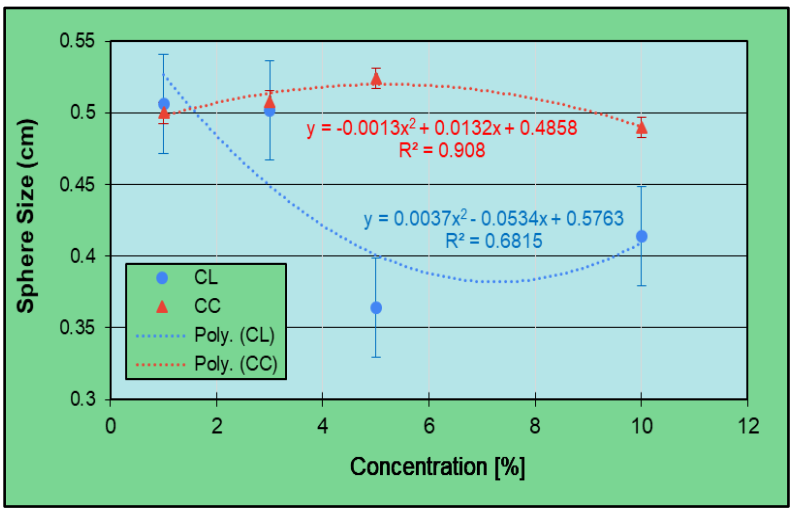

Fig. 13. Presents the comparison of the graphs of Fig. 7 and Fig. 11

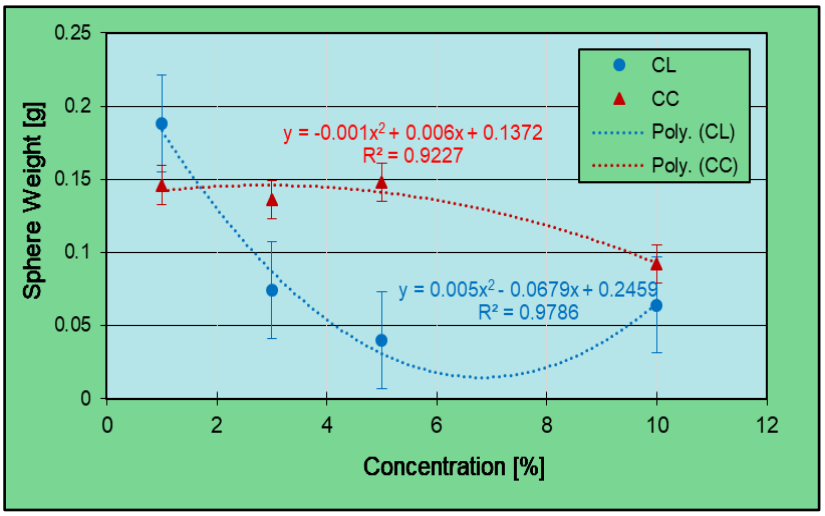

Fig. 14. Presents the comparison of the graphs of Fig. 8 and Fig. 13

3.9 Popping Force Comparison of CC and CL

Fig. 15 compares how the force required to pop a bead differed as concentrations of CC and CL increased. As CL concentration increased, the popping force increased until around 7% concentration, where the popping force decreased. As CC concentration increased, the popping force increased at an increasing rate. This is interesting because it was assumed that a higher concentration of CC or CL would result in a stronger membrane, automatically resulting in a higher required popping force.

3.10 Percent Change in Weight of 3mm CC Bead after 48 Hours of Drying

Fig. 16 represents the percent change in weight of 3mm CC beads after 48 hours of drying as a function of CC concentration. The percent change in weight decreases as a function of CC concentration. However, it should be noted that the percent weight change did not vary significantly between 1 and 5 percent concentration. The percent change in weight for the 10 percent concentration CC bead was significantly lower than the rest of the beads.

3.11 Percent Change in Weight of 3mm CL Bead after 48 Hours of Drying

Fig. 17 represents the percent change in weight of 3mm CL beads after 48 hours of drying as a function of CL concentration. The relationship follows a parabolic pattern where the percent weight change initially decreased as CL concentration increased. Still, at approximately 6 percent concentration, the percent weight

change began to increase with CL concentration. A notable aspect of this figure is that for the one percent bead, nearly all of its weight was lost after drying. This implies that a weaker membrane will result in more or at least a faster water loss. Another interesting part of this figure is that the percent weight change increased for the 10 percent CL bead compared to the 3 and 5 percent membranes. This is interesting because Fig. 17 suggests that a stronger membrane will keep water inside of the membrane.

3.12 Percent Change in Weight of 7.05mm CC bead after 48 Hours of Drying

Fig. 18 represents the percent change in weight of 7,05mm CC beads after 48 hours of drying as a function of CC concentration. The percent change in weight initially decreases as the concentration of the beads increases. However, at approximately 5 percent concentration, the percent change in weight begins to increase with the CC concentration. This results in the ten percent CC bead having the highest percent change in weight. This is interesting because this result was not observed in the previous experiment where smaller beads were used.

3.13 Percent change in weight of 7.05mm CL bead after 48 hours of drying

Fig. 19 represents the percent change in weight of 7,05mm CL beads after 48 hours of drying as a function of CL concentration. The percent weight change decreases as CL concentration increases initially. The percent changes in weight of the 3 percent, 5 percent and 10 percent beads do not vary significantly. This is interesting because it is nearly opposite to the relationship in Fig. 12.

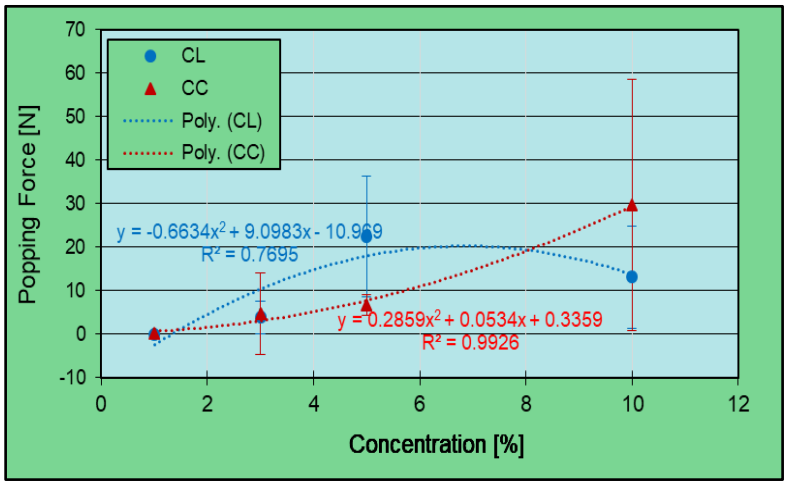

Fig. 15. Presents the comparison of the graphs of Fig. 9 and Fig. 12.

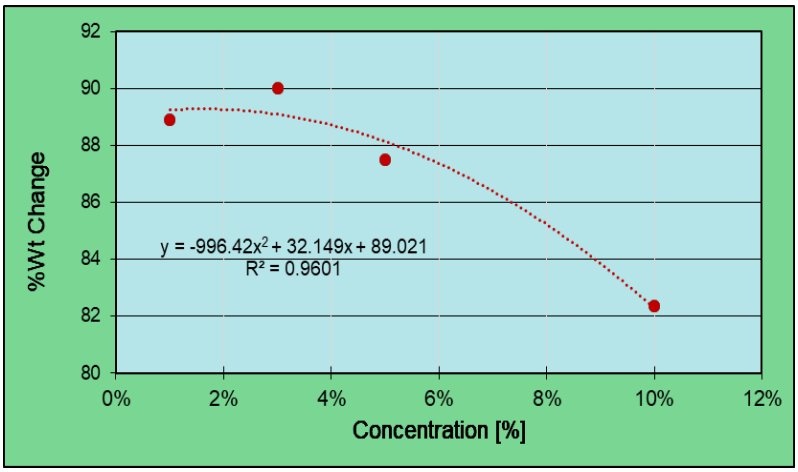

Fig. 16. Presents the relationship between CC concentration and the % change in weight in 3mm beads after drying for 48 hours

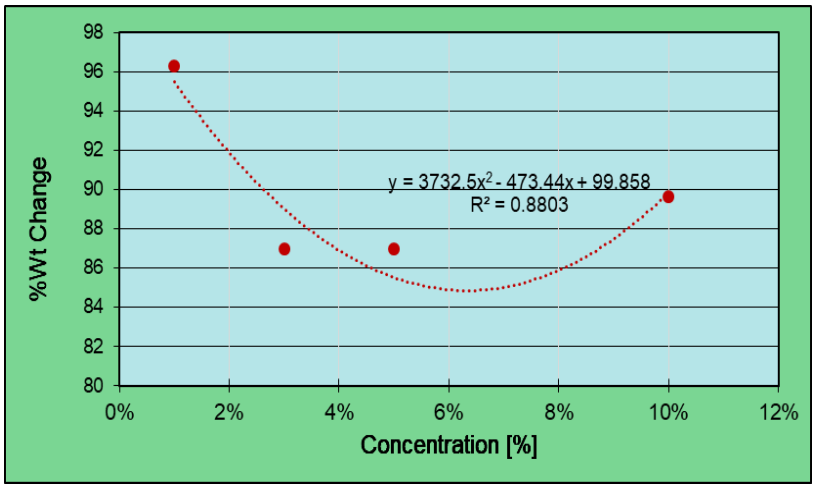

Fig. 17. Presents the relationship between CL concentration and the % change in weight in 3mm beads after drying for 48 hours

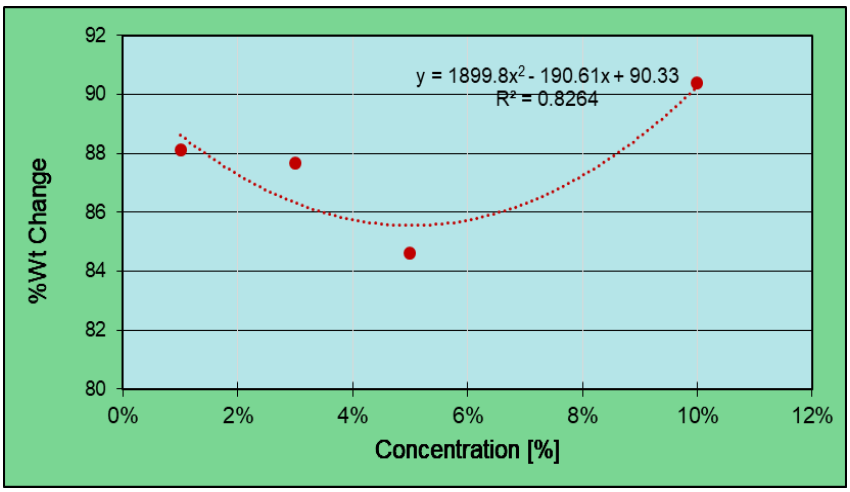

Fig. 18. Presents the relationship between CC concentration and the % change in weight in 7.05mm beads after drying for 48 hours

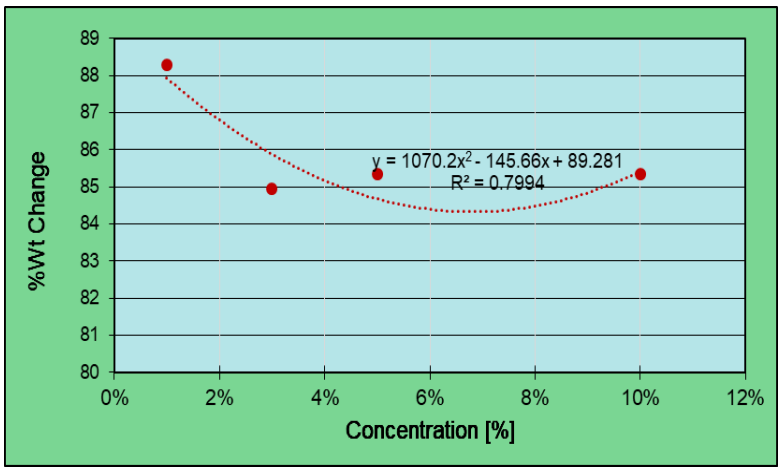

Fig. 19. Presents the relationship between CL concentration and the % change in weight in 7.05mm beads after drying for 48 hours

3.14 Standard Deviation in CC beads Produced by different Dispenser Sizes

Fig. 20 represents the comparison between the size of CC bead dispensers and the standard deviation in the sizes of CC beads before and after drying. The graph shows that before drying, the variability in bead sizes increased as the bead dispensers increased. However, after drying, the variability of all beads was roughly the same. This is interesting because it suggests that a larger bead size is favorable for experiments because of the increased amount of food dye and ease of use, which means there is no need to worry about the variation in size.

3.15 Dye Diffusion Test with 10% CC Beads in Varying Xylitol Concentration

Xylitol is a naturally occurring sugar, alcohol, and carbohydrate found in fruits, vegetables, corn cobs, and woody plants. It's also produced by the human body. Xylitol is a white, crystalline powder that tastes and looks like sugar but has half the calories. It's also known as wood sugar, birch sugar, and birch bark extract. It was chosen as a chemical compound that might modify the diffusion rate. As said in the Introduction, it was assumed that any compound that controls the diffusion rate of the food dye with respect to the compound concentration in beads might equally facilitate the controlled release of drug compounds capsuled with calcium alginate.

Our data, as seen in Fig. 21, shows that the diffusion rate increased up to 20%, even though the magnitude of the diffusion rate was somewhat reversed at 10% and 20% xylitol concentration. Further clarification study might be needed, but the trend of diffusion rate dependency on xylitol concentration left no doubt positive. The magnitude of absorption from our spectrophotometer was assumed to be that food dye concentration was diffused with the time of the beads in a simulated gastric solution at 37.5 °C, controlled in a water bath.

3.16 Dye Diffusion Test with 10% CL Beads in Varying Xylitol Concentration

Our data in Fig. 22 presents a similar trend to what we observed in Fig. 15. However, unlike our initial trial using CC beads, the diffusion rate has an increasing relationship with xylitol concentration that does not reverse in the higher xylitol concentrations within the interval. At some values of time, the difference in absorption between CL and CC beads was as large as .26 AU. However, the average diffusion rates between the two types of beads did not differ by such a significant magnitude. This could mean that the initial diffusion of dye as the beads rehydrate in the diffusion medium is more significant in the CL beads with xylitol compared to the CC beads with xylitol. This conclusion is supported by the larger increase in absorbance in CL beads between 0 and 10 minutes compared to CC beads.

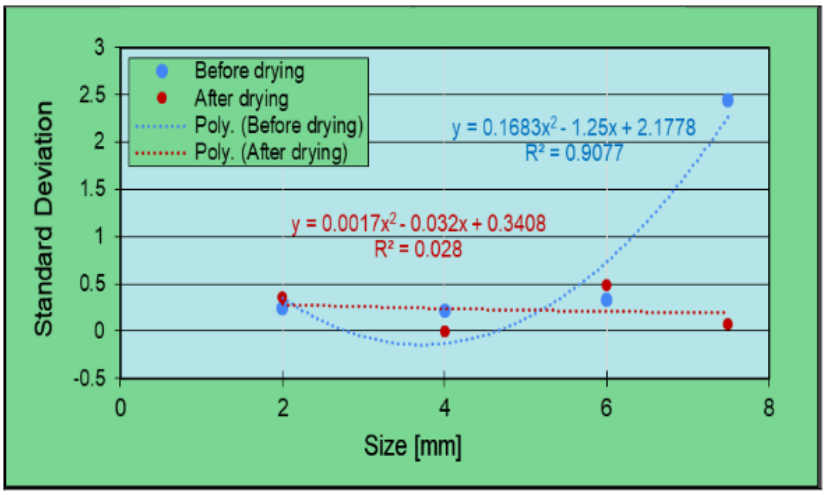

Fig. 20. Presents the comparison between standard deviation in 10% CC concentration bead sizes before and after drying for 48 hours

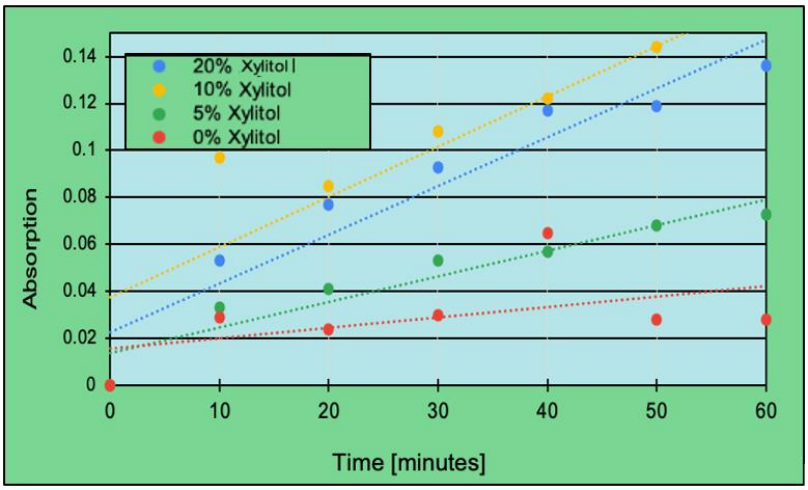

Fig. 21. Presents the spectrophotometric absorption change with time in a dissolution test in a gastric simulated solution at 37 °C with calcium alginate beads for various xylitol concentrations

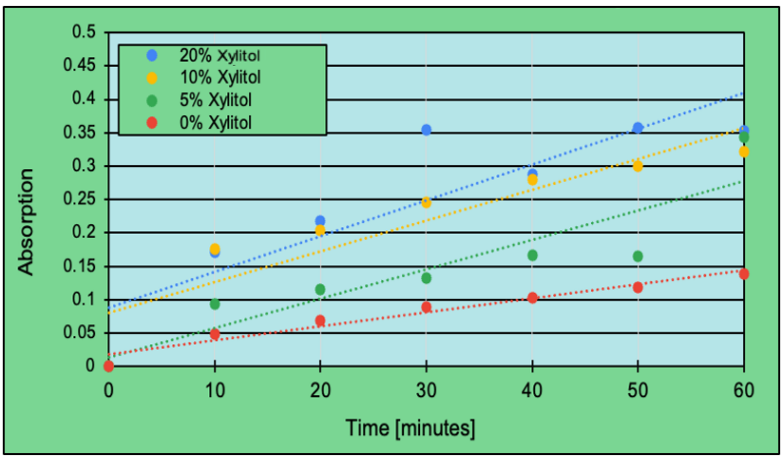

Fig. 22. Presents the spectrophotometric absorption change with time in a dissolution test in a gastric simulated solution at 37 °C with calcium alginate beads for various xylitol concentrations

3.17 Dye Diffusion Test with 10% CC Beads in Varying Gelatin Concentration

Our observations in Fig. 23 do not suggest a significant difference in diffusion rate when gelatin is a factor. The average rate of diffusion varied across the different groups. Still, the 5% gelatin concentration group appeared to have the fastest diffusion rate, while the other groups were very similar in their diffusion rates. At the end of the 60-minute interval, the 5% gelatin concentration group diffused the most dye, and the 10% group diffused the least. Because there was no clear trend in this data, it is likely that gelatin does not act as an efficient agent that creates a predictable diffusion rate.

3.18 Dye Diffusion Test with 10% CL Beads in Varying Gelatin Concentration

Our data in Fig. 24 show a clearer trend than what we observed in Fig. 23. In this trial, the data shows that all gelatin concentration groups present the same diffusion rates. However, the quantity of dye diffused had a negative relationship with the gelatin concentration in the beads. As the gelatin concentration in the beads decreased, the more dye was diffused. This may suggest that more gelatins will reduce the initial amount of dye diffused from the beads when they are rehydrated from the diffusion medium.

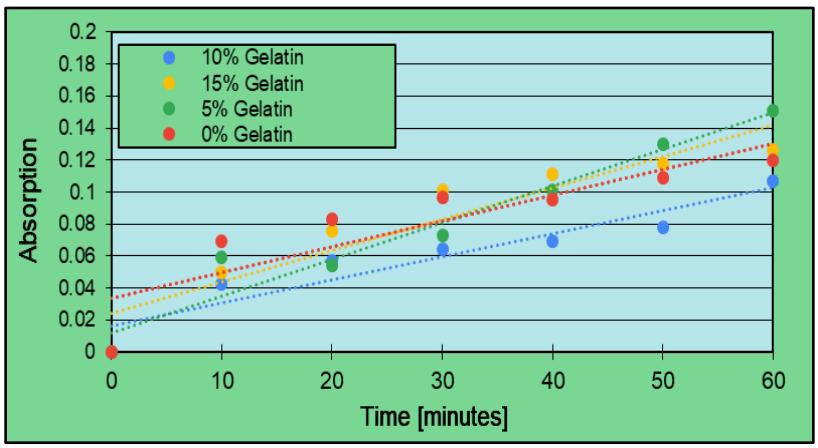

Fig. 23. Presents the spectrophotometric absorption change with time in a dissolution test in a gastric simulated solution at 37 °C with calcium alginate beads for various gelatin concentrations

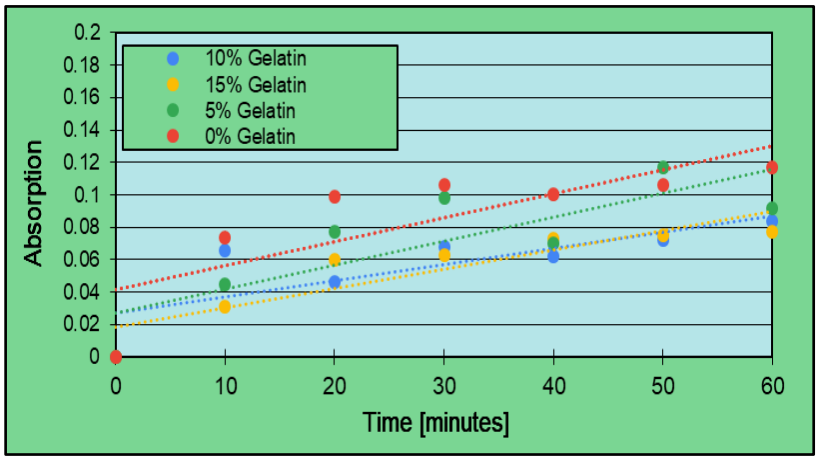

Fig. 24. Presents the spectrophotometric absorption change with time in a dissolution test in a gastric simulated solution at 37 °C with calcium alginate beads for various gelatin concentrations

4. CONCLUSIONS

This study demonstrates the potential of calcium alginate beads as a controlled release system for drug delivery. By experimenting with different concentrations of CC and CL, we could observe clear relationships with varying characteristics of the beads, such as size, weight, and popping force. Our data found that as concentrations of CC increase in alginate beads, size increases to about 5 percent concentration, where it begins to fall. We also found that as CL concentration increases, size decreases in alginate beads until about 7 percent concentration, where it begins to increase. We found that weight generally decreases as concentration increases, but the relationship is reversed at very high concentrations for CL beads. Additionally, we found that as concentration increases, the force needed to pop the beads generally increases between both types of beads; however, in CL beads, there was a diminishing effect as the concentrations got very high.

We also found relationships between concentrations of xylitol and gelatin in the alginate membrane with the diffusion rates of the beads. Our findings indicate that CL beads showed higher variability in diffusion rates. Our findings show that xylitol will enhance diffusion, especially in CL beads, but the effect was less predictable with gelatin.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models

(ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that he has no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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