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Investigating a Calcium Alginate-Xylitol Coating Methodology for Controlled Release Profiles of Multivitamin Tablet as a Model Drug

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Author's contribution

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

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ABSTRACT

The drug delivery system promotes the release of the active pharmaceutical ingredient (API) to attain the desired therapeutic effect at the time most needed. Alginate is a natural polymer that is frequently employed in drug delivery systems. Calcium alginate can simply coat as a film type on the surface of a tablet, which might be created to be dissolved more quickly and predictably manners in the gastric fluid to deliver as needed in a patient-friendly system. In this study, the sodium alginate solution was reacted with a predetermined calcium compound and xylitol combination, while the multivitamin tablets' surface was coated with calcium suppliers such as calcium chloride. Then, the coated tablets were subjected to a dissolution test in a simulated gastric fluid. Our study results showed that the sphere formation was excellent in terms of strength and size in 1.0% sodium alginate with 4% calcium chloride. Average sphere sizes were 0.5 ~ 2.0 mm. Their break force was 3.5 N, And the dissolution was the fastest in the coated tablets with 1%

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sodium alginate and calcium chloride. The dissolution rate was changed proportionally with calcium concentration. A high feasibility of dissolution rate was positively found. When a high concentration of xylitol was mixed with 4% calcium chloride, the dissolution rate was proportional to the concentration of xylitol. In conclusion, the study demonstrated that the dissolution rate of tablets with API might be controllable with the calcium alginate film coating with xylitol.

Keywords: Alginate tablet coating technology; calcium alginate; drug delivery system; dissolution control.

1. INTRODUCTION

Drug delivery technologies have been developed as approaches, improved efficacies, manufacturing advancements, shelf-life systems, and technologies for delivering pharmaceutical ingredients to the areas most needed to establish [1,2]. Principles related to drug preparation, route of administration, site-specific targeting, metabolism, and toxicity are used to optimize efficacy and safety and to improve patient compliance [3,4]. Conventional drug delivery systems mostly have poor bioavailability and fluctuations in plasma drug level and fail to achieve sustained release since API is not delivered correctly for the time and region of action [5]. Therefore, it is crucial to an established methodology that can control the drug release rate by appropriately coating tablets [6].

Alginate is a natural polymer that is frequently employed in drug delivery systems. Using alginate chemical products can provide several advantages, including ease of preparation, biocompatibility, biodegradability, and nontoxicity [7,8]. It can be applied to various routes of drug administration, including targeted or localized drug-delivery systems. The increased effectiveness and safety of sodium alginate in the drug delivery system are evidenced by changing the drug's or proteins' physicochemical characteristics [9]. Calcium alginate can coat as a film type on the surface of a tablet, which is not quickly and predictably dissolved in gastric fluid to deliver as needed in a patient-friendly manner [10].

So, we cast a question about the feasibility of a controlled release of API as scheduled. While considering various advantages of alginate compounds, a unique idea was created from brainstorming that multiple xylitol combinations with alginate and calcium suppliers might be able to adjust the dissolution rate of a model drug since this technique, if it works, should apply to typical medicines on the market.

Our study could be summarized as follows. The reaction of sodium alginate (Concentration 0.5~2 w/l%) and calcium compounds (1~4w/l%) have been used in many areas, such as culinary sciences [11] and pharmaceutical technologies [12]. This study investigated various types of hydrogel coating film formations of calcium alginate and their properties. Further, the sodium alginate solution was combined with a predetermined amount of xylitol (0~60%w/l%) and coated the multivitamin surface with calcium suppliers such as calcium chloride. Then, the coated tablets were subjected to a dissolution test in a simulated gastric fluid [13].

Coating the multivitamin tablet gave us various insights into the possible applications for the controlled release of a tablet form of therapeutic pharmaceuticals [14]. We first tried to investigate the formation of hydrogel as a spherical form. The hardness and sizes with functions of concentrations have been investigated.

Secondly, we first tried to coat the multivitamin tablets with the reaction of sodium alginate with calcium lactate and calcium chloride. Their dissolution test has been done to understand their profile difference.

Thirdly, to modify the calcium alginate-coated film, a variable amount of xylitol was mixed with sodium alginate and then coated with the calcium compound to measure the dissolution rate change in a simulated gastric fluid, which was necessary for any favorable formulation delivering in a timely manner according to the purposes of each API.

2. EXPERIMENTAL METHODS

2.1 Procedures and Methods of Data Collection

2.1.1 Alginate and calcium compound solution preparations

Mostly, sodium alginate solutions for the predetermined concentration of 0.5~2% w/v were

prepared first since they were not easily dissolved in reverse osmosis (RO) water and needed a period of magnetic stirring procedure or blended in Midea Blender Mode 1forcibly. The sodium alginate solution should be used after 6~24 hours after being created to remove air bubbles that were captured in the solution [15]. In contrast, other calcium compounds, such as calcium chloride and calcium lactate, were readily dissolved without much agitation. We prepared 50 ~ 100 mL as much as we needed. As seen in Fig. 1, our chemical agents were weighed carefully for high accuracy, and created when used to maintain the freshness of the solutions.

2.1.2 Sphere creation and characterization

Calcium alginate hydrogel spheres were created by placing a drop of sodium alginate solution into the calcium compound solution, such as calcium chloride. Most spheres formed instantly when a drop of the sodium alginate solution fell into the beaker filled with a calcium compound solution [16]. The spheres were then picked up after 2 ~ 30 seconds as designed and moved into a revere osmosis (RO) water to stop further reaction as in Fig. 2. The RO water was used as just pure water, replacing distilled water. However, the role of water was as a chemical agent to stop further reaction by removing the calcium source.

Various combinations of variables could be examined, for example, the concentration of sodium alginate, calcium chloride, drop size, and reaction time. After the calcium alginate spheres were obtained, physical characterizations were performed. Their sizes were measured with a micrometer, while their hardness was estimated with a petri dish on balance and pressed until the spheres were broken.

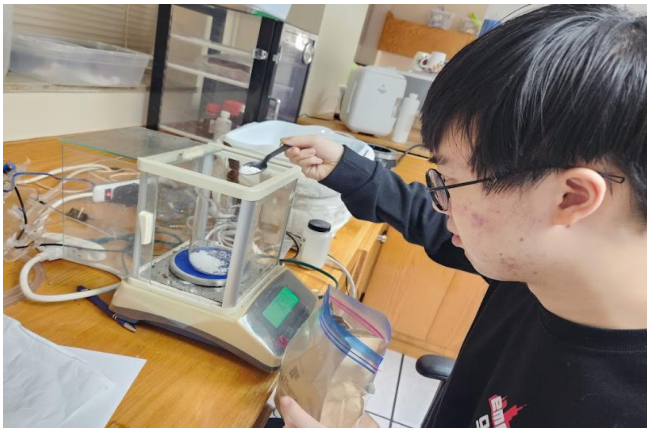

Fig. 1. Presents the weighing-out procedure from the calcium chloride container into the beaker zeroing in advance

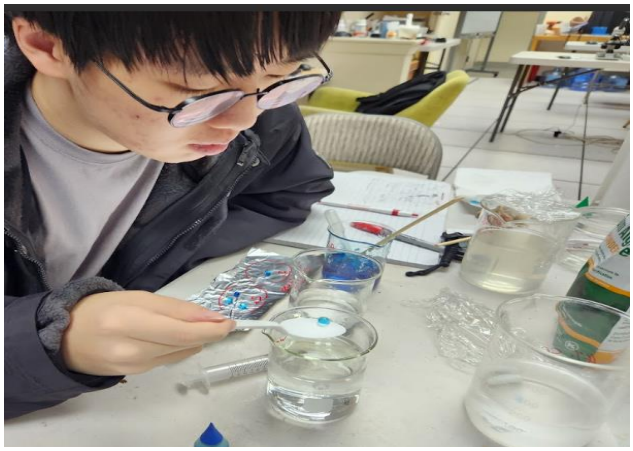

Fig. 2. Shows the pictorial illustration of procuring the hydrogel spheres dyed with blue food dye to facilitate sphere identification

2.1.3 Vitamin tablet coating procedures

We collected three beakers of 250 ml, properly labeled them with a permanent marker, and filled them with sodium alginate, calcium chloride solution prepared in advance, and RO water, respectively. A piece of aluminum foil was prepared and marked as circles for groups 1, 2, 3, and 4, which were different in concentration of Xylitol or amount of calcium compounds. A forceps and stopwatch were confirmed to be on hand. The three beakers were now aligned from sodium alginate, calcium chloride, and RO water. A vitamin tablet was picked with forceps and carefully dropped into the alginate solution beaker in which the sodium alginate should be stuck to the tablet's surface for 10 seconds or so. And it moved to the next calcium chloride beakers to make the sodium alginate react with the calcium ions for 10 seconds. Then, it moved to the RO water beaker to prevent the ongoing reaction of calcium ions into the alginate structure. The calcium alginate-coated tablets were transferred onto the aluminum foil as marked and moved into the dehumidifier dryer for approximately 2 hours, as shown in Fig. 3. A drop of olive oil was placed on the aluminum foil before the coated tablets were stuck.

2.1.4 Preparations of simulated gastric solution and dissolution test

As seen in Fig. 4, a dissolution test was carried out at 37 °C degrees with the coated tablets in a simulated gastric solution at pH 2 that was created with a 1:4 solution of Pedialyte to RO water ratio. The pH was adjusted by adding 2M HCl into the stirring solutions. The dissolution was performed on a 4-station core magnetic stirrer with approximately 60 rotations per minute (RPM). A spectrophotometer (Model 721) was used as absorbance to measure the drug's relative concentration to investigate the coated drugs' dissolution profile.

Fig. 3. Shows the beakers with sodium alginate (a) and calcium compounds with RO water. A forceps is found in (b), and the coated tablets (d) were placed on an aluminum foil (c)

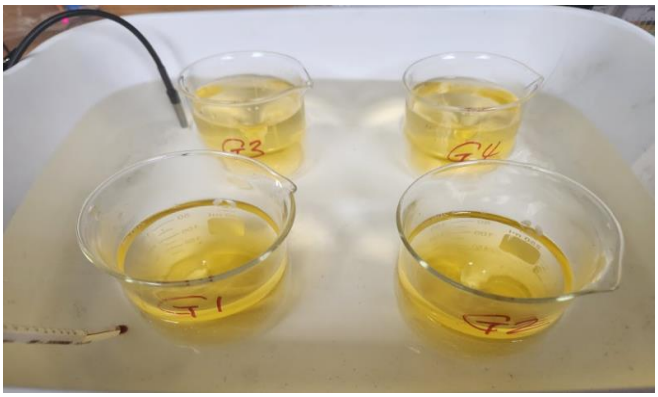

Fig. 4. Presents our four groups of dissolution testing beakers with a water bath for coated tablets in simulated gastric fluid. It had a heating-on water container in which the temperature sensor was connected to an Arduino microcontroller to maintain a constant temperature.

2.1.5 Dissolution sample analysis

The 721 Model of UV-Vis Spectrophotometer was used to measure the relative concentration of the solutions from the dissolution test beakers at the wavelength of 460 nm. A calcium alginate-coated multivitamin was placed and stirred while sampling the solution with time as in Fig. 5. It was not the scope of the study to get exact concentrations of each multivitamin ingredient. Instead, we used the absorbance of the sample solution to indicate the dissolving conditions in each group of solutions. Our magnetic stirrer is equipped with four stations of rotation cores.

2.2 Data Analysis

Data was summarized with mean and standard deviation in Microsoft Excel in which they were graphed and performed regression analysis. Sample number (n) was different for individual cases of study. Student's t-test ($P<0.05$) was performed if needed.

3. RESULTS AND DISCUSSION

3.1 Calcium Alginate Sphere Size with Time

The sphere size could be variable for various factors such as solution concentration and dropping tools such as spoons or tubes [17]. Fig. 6 below shows the bead sizes with respect to the stay time in the calcium chloride. As seen in the figure, sizes were not increased with time. However, bead size seemed to have a high relationship with sodium alginate concentration.

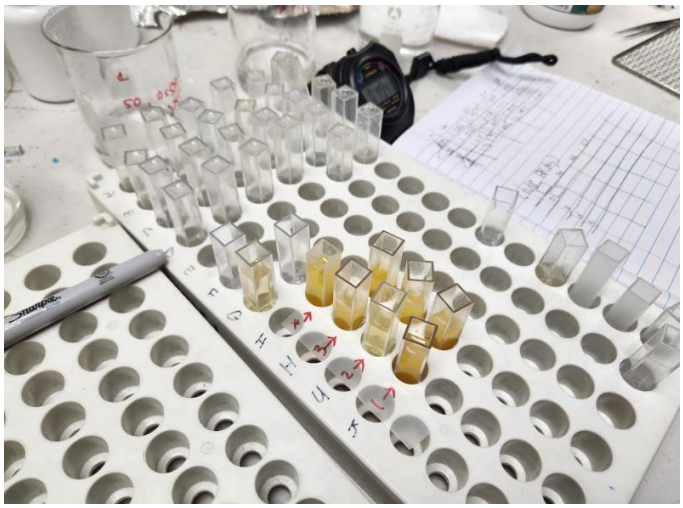

Fig. 5. Presents the aligned photometer cuvettes during our dissolution test. The samples were obtained every 20 minutes for up to 2 hours

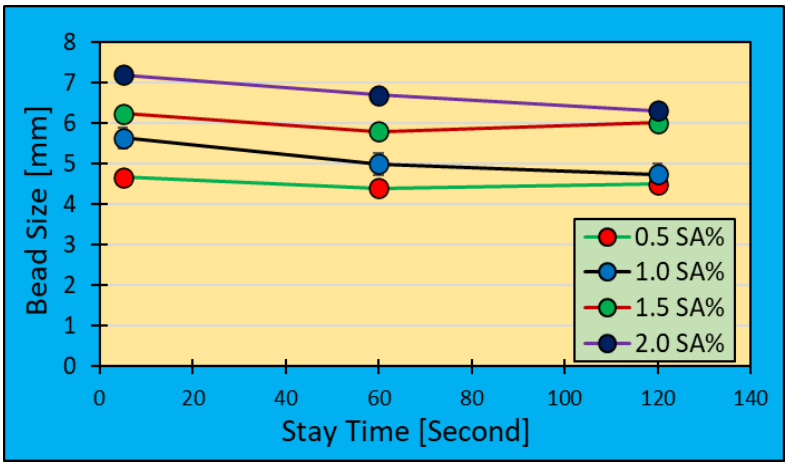

Fig. 6. Presents the bead sizes with respect to the stay time in the calcium chloride solution

3.2 Pressing Force on the Alginate Spheres with Calcium Lactate

After creating the hydrogel spheres, some beads were subjected to a pressing force test on a petri dish in an electric balance. The pressing force was the weight pressed by the index finger down with force up to breakage while reading the scale of maximum weight [18]. So, the pressing force might have the same meaning as the breakage or popping-out force of the spheres. Fig. 7 shows that the hardness was not much changed with the stay time in the calcium lactate; however, it was highly related to the sodium alginate (SA) concentration. The data was surprising because we expected the pressing force was proportional to the stay time. So, further study might be necessary to clarify.

3.3 Pressing Force on the Alginate Spheres with Calcium Chloride

The calcium alginate spheres were brought on the electrical balance and pressed down using an index finger until the spheres were broken. And, the maximal breakage force was recorded. As seen, the spheres were getting more resistant after 1.5 % sodium alginate with calcium chloride as in Fig. 8. However, it was not easy to dissolve after 1.5% sodium alginate. So, we mainly used 1% sodium alginate solution as long as it was satisfactory to generate film on the surface of the multivitamin.

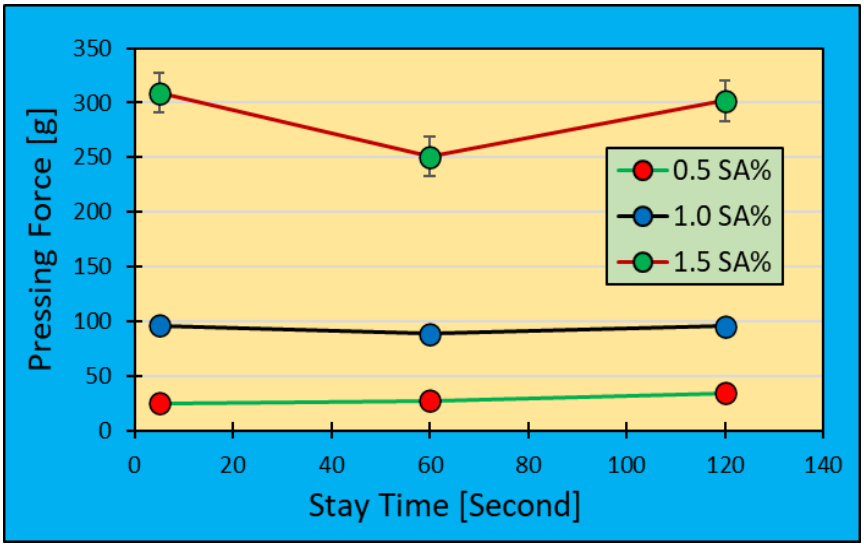

Fig. 7. Presents the pressing forces with respect to the stay time in the calcium lactate solution

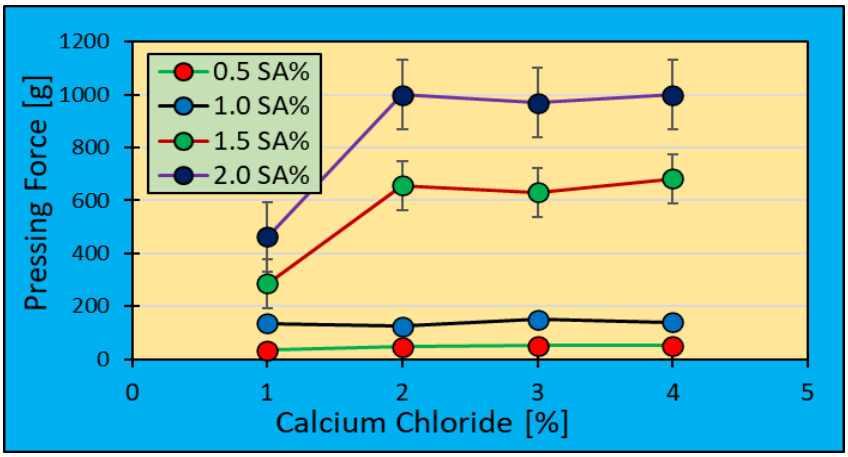

Fig. 8. Presents the pressing forces with respect to the stay time in the calcium chloride solution

3.4 Xylitol Effects on Sodium Alginate Concentration

The typical gelation mechanism involves the coordination and chelating structures in the model of egg-box during the process of binding of alginates to polyvalent metal ions, G-units selectively form higher-order junction zones, which is composed of two or more chains, together with the hydrogen-bonding interaction of these cross-linking agents with oxygen atoms in the G blocks of two adjacent polymer chains [19]. Various solutions of SA concentrations with Xylitol were examined. The absorbance from the first two groups was done with 0.5% SA, one with 0.0 XLT, and the other with 10g XLT as shown in Fig. 9. The absorbance from the high xylitol was higher than the low xylitol group. In the same way, the absorbance from the high xylitol group was higher than that of the low xylitol group. That is, the xylitol might facilitate dissolving in the simulated gastric fluid. When xylitol was mixed, their absorbance at 20 minutes was higher than no xylitol groups of tablets, which implied that the xylitol might have facilitated the dissolution rate by the alginate coating. The absorbance in 0.5% SA solution changed by 20%, while 25% changed when 2% SA.

3.5 Xylitol Effects of Coating with Calcium Chloride (CC) and 1% Sodium Alginate (SA)

The multivitamin was coated with calcium alginate created with 1% SA and 4% calcium chloride. The percentage was the xylitol concentration in sodium alginate.

The Fig. 10 below shows that the profiles were changed differently according to the concentration of xylitol concentration. The tablet coated with 15% xylitol dissolved faster than other groups. Faster dissolution might mean the yellow line's slope was most significant at 0 to 20 minutes.

3.6 Xylitol Effects of Coating with Calcium Lactate (CL) and 1% Sodium Alginate (SA)

As described above, the multivitamin was coated with 1% sodium alginate created with 4% calcium lactate. The percentage was the xylitol concentration in SA. The curves in Fig. 11 show that the tablet coated with 15% xylitol dissolved faster than the solution with no xylitol solution. But there might not be a significant difference in the case of sodium lactate. Another finding was that the dissolution profiles differed from those with calcium chloride.

3.7 High Concentration Xylitol Effects of Coating with Calcium Chloride (CC) and 1% Sodium Alginate (SA)

In this study, we used high concentrations of xylitol in a calcium chloride solution, hoping that any difference might be outstanding because of the xylitol particles in the calcium chloride solution as illustrated in Fig. 12. Our assumption was right based on the data, which said that the dissolution rate could be controllable while controlling the amount of xylitol. At this very moment, we couldn't figure out why the coated film's permeability depends on the concentration of xylitol. These data were supported by the result of others' research, that xylitol increased the thickness/mass of the coat and decreased its density by it [20]. During the study, sometimes, we faced some issues with the constant quality of coating film around tablets. We may need more development and study for increasing reproducibility.

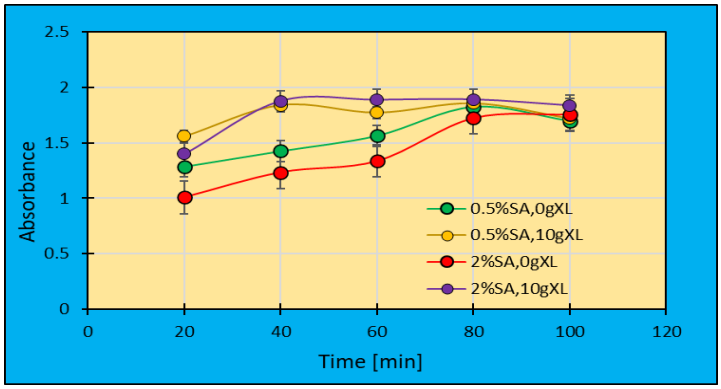

Fig. 9. Presents the absorbance with respect to different concentrations of sodium alginate and xylitol. The absorbance was treated to be a relative concentration dissolved drugs

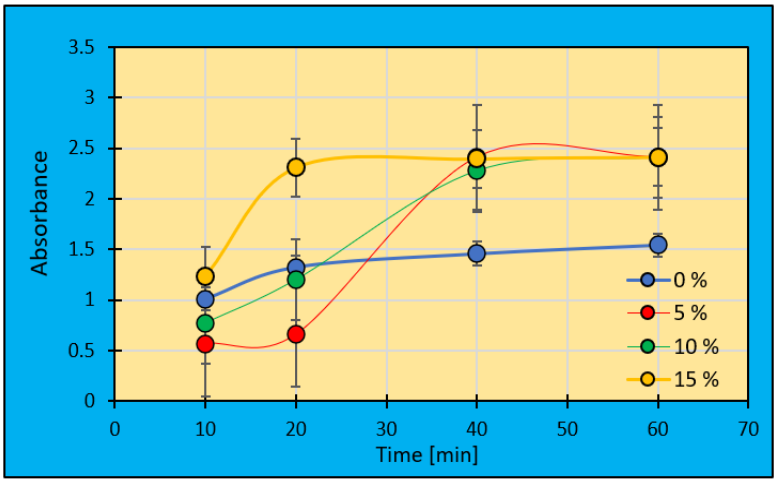

Fig. 10. Presents the dissolution profile of a multivitamin tablet coated with SA solution and calcium chloride with xylitol

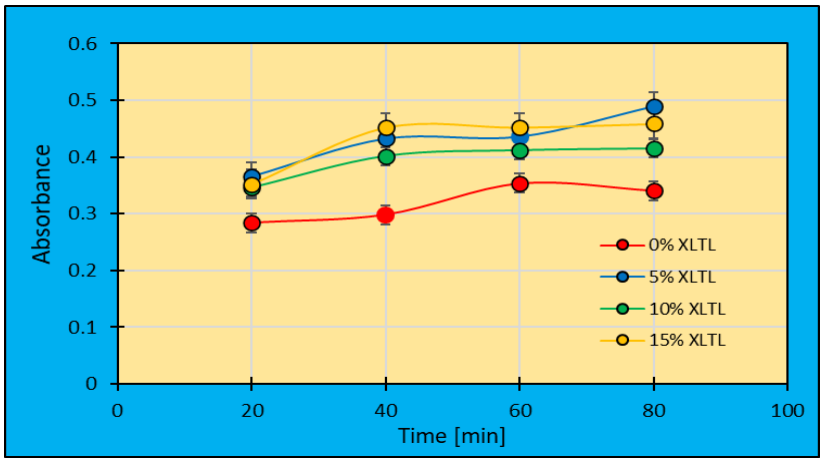

Fig. 11. Presents the dissolution profile of multivitamin tablets coated with SA solution and calcium lactate with xylitol. Legends: XLTL stands for Xylitol

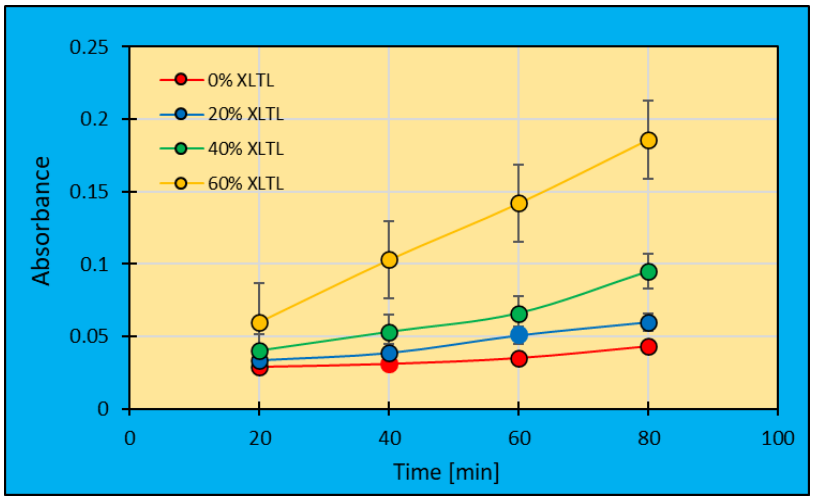

Fig. 12. Presents the absorbance changes with respect to dissolution time

4. CONCLUSION

The drug delivery system supports the release of the active pharmaceutical ingredient (API) to reach the desired effect. Therefore, it is important to control the drug release rate by appropriately coating tablets.

The sphere formation was found to be excellent in their strengths and sizes when reacted of 1.0 % sodium alginate with 4% calcium chloride. Average sphere sizes were 5.0± 0.12 mm. Their break force was 3.5 N. For coated vitamin tablets, the dissolution was the fastest in 1.0 % sodium alginate and calcium chloride. Based on the data, a high feasibility of dissolution rate was positively found. When a high concentration of xylitol was mixed with 4% calcium chloride, the dissolution rate was proportional to the concentration of xylitol. So, the study demonstrated that the dissolution rate of tablets with API should be controllable with the calcium alginate film coating if the xylitol is optimally added to the calcium compound. More studies might be needed for elaboration in the future.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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