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Original article

Synthesis and Characterization of Alginate Microparticles for Oral Delivery of Alpha-Tocopherol

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SUMMARY

Introduction/Aim. Microencapsulation technology can be used for the protection of alpha-tocopherol from degradation in unfavorable environments and enhancement of bioavailability and shelf-life of vitamin E. The aim of this study was the synthesis and characterization of alginate microparticles for the oral delivery of α-tocopherol.

Methods. Four different formulations of alpha-tocopherol loaded calcium alginate microparticles for oral delivery were synthesized by external ionotropic gelation method. The vitamin E content in microparticles was 0.5%, 1% and 2% (w/w); the vitamin E/sodium alginate ratio was 1:1 and 1:2. All microparticles were characterized by average particles size, swelling degree, vitamin E content, loading capacity, and encapsulation efficiency.

Results. Spherically shaped microparticles with the diameter of 500 to 1000 μm were obtained after the drying process. The size and the swelling degree did not change significantly in 0.1 M HCL, while they were increased in base conditions of phosphate buffer of pH 6.8 and 7.4. Encapsulated vitamin E content was not significantly different between formulations (0.30 ± 0.010 - 0.60 ± 0.021 mg/mL). The loading capacities were in the range between 10 ± 0.11% and 20.45 ± 0.22%, while encapsulation efficiency percentages were between 18.94 ± 0.32% and 31.91 ± 0.41%.

Conclusion. The optimum conditions for alpha-tocopherol encapsulation with the highest percentage of loading capacity and encapsulation efficacy were obtained using 1% sodium alginate, 2% calcium chloride, and vitamin E/polymer in the ratio 1:1. All four formulations showed the expected behavior in different mediums, which simulated gastrointestinal fluids *in vivo* (0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4): gastroresistance, increasing in the size, and swelling degree in intestinal fluids. This emphasizes the use of alginate microparticles as a carrier for the oral delivery of vitamin E.

Keywords: **alpha-tocopherol, vitamin E, calcium alginate, alginate particles, encapsulation**

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INTRODUCTION

Alpha tocopherol (vitamin E), as a lipid-soluble vitamin, is widely utilized because of its antioxidant properties. It possesses the ability to stabilize reactive oxygen species (ROS or free radicals) and protect cells from damage which could cause different diseases in perspective, like cardiovascular disease and cancer (1, 2). However, in the presence of oxygen and oxidative reactions mediated by free radicals, vitamin E can be decomposed quickly. It can be mostly solved by using the microencapsulation technology for the protection of α-tocopherol from unfavorable environments and solubilization in aqueous environments. Also, biological activity after ingestion and shelf-life of vitamin E could be improved by encapsulation (1, 3).

Microencapsulation technology is based on entrapping sensitive substance by protective encapsulation excipient (4). One of the most frequently used natural polymers for bio-encapsulation is sodium alginate. Sodium alginate is commonly used as a gelling agent because of its ability to create gels in the presence of di- or tri-cations in aqueous environments (5). Alginate particles can be produced by dropping an aqueous sodium alginate solution in a calcium chloride solution (6). Due to its properties such as biocompatibility, low toxicity, swelling, mucoadhesiveness, and sol/gel transfer ability, alginate has taken a privileged place in the development of drug delivery systems (5). Several studies have shown that the bioavailability of drugs encapsulated in alginate hydrogels is higher than that of the free drug applied directly, thereby increasing the therapeutic efficacy (7 - 10). Alginate is frequently used as an excipient in drug delivery systems, serving as a stabilizing ingredient in a variety of pharmaceutical formulations and also for targeted and localized delivery systems (7, 12).

The aim of this study was to formulate alginate microparticles with different concentrations of sodium alginate for oral delivery of α-tocopherol and characterize them by average particle size, swelling degree, vitamin E content, loading capacity, and encapsulation efficiency.

MATERIALS AND METHODS

Materials

The following materials were used for synthesis of alginate microparticles: alpha-tocopherol (Zhejiang Medicine Co. Ltd., China), sodium-alginate (Erba Pharm, France), and calcium chloride (Centrochem, Serbia).

Synthesis of microparticles

The synthesis of alpha-tocopherol loaded microparticles was performed using the external ionotropic gelation method (12). Four different formulations were prepared, according to Table 1. In the first phase, sodium-alginate was dissolved in purified water with constant stirring in order to obtain solutions of 1% w/w and 2% w/w concentration. After that, alpha-tocopherol was added to sodium alginate solution; hence, the vitamin E/polymer ratio was 1:1 and 1:2 (Table 1). Also, 2% (w/w) aqueous solution of calcium chloride was prepared. The vitamin E microparticles were formed by dropping vitamin E suspension in aqueous solution of sodium alginate into calcium chloride solution using a syringe with 0.45 mm inner diameter needle (with constant stirring on magnetic stirrer). The mixture remained on the magnetic stirrer for the next half an hour. After the incubation period, microparticles were filtrated, rinsed by purified water, and collected into a Petri dish. The microparticles were dried at the room temperature to a constant weight (13).

Table 1. *Composition of alpha-tocopherol microparticles*

Formulation label	Sodium alginate (%w/w)	Calcium chloride (%w/w)	Alpha-tocopherol/sodium alginate ratio
F_1	2	2	1:1
F_2	2	2	1:2
F_3	1	2	1:1
F_4	1	2	1:2

Determination of microparticle size

Determination of the size of microparticles was performed using an optical microscope (Motic, Germany). The particle size is presented as an average value of the diameter of 20 dried particles. The diameter of particles before drying, after drying, and after swelling in different pH value mediums was compared (1).

Determination of alpha-tocopherol content

Alpha-tocopherol content in microparticles was analyzed spectrophotometrically at the wavelength of 285 nm (Shimadzu UV-1800, Japan). Stock solution was prepared by dissolving 50 mg of alpha-tocopherol in 25 mL of 96% ethanol. The following dilutions were made from the stock solution: 10, 30, 50, 70 and 90 μg/ml. The calibration curve was obtained by measuring the absorbance of dilutions at 285 nm (14).

The preparation of the samples included pulverization of 100 mg of microparticles and mixing with 5 mL ethanol on ultrasonic bath until the particles were completely destroyed. After membrane filtration (0.45 μm MF-Millipore®, Milipore Corporation, Bedford, SAD), the absorbance of the filtrate was measured at 285 nm. The concentration of vitamin E (mg/mL) was calculated from the calibration equation (1).

Vitamin E loading and encapsulation efficiency determination

The following formula was used for the vitamin E loading (DL%) determination:

$$DL\% = 100 \times Qe/Qm$$

Qe represents the encapsulated amount of vitamin E in the measured quantity of dried microparticles;
Qm represents the measured quantity of dried microparticles.
All formulations were analyzed in triplicate and results were presented as average value ± standard deviation (15).

Encapsulation efficiency is defined as the percentage of the encapsulated substance. The preparation of the sample included a transfer of dried microparticles in phosphate buffer at pH 7.4 and stirring on ultrasonic bath for 24 h. The obtained dispersion was filtered through a 0.45 μm MF-Millipore® filter (Milipore Corporation, Bedford, SAD) and the concentration of vitamin E in the filtrate was determined spectrophotometrically at 285 nm. (Shimadzu UV-1800, Japan). Encapsulation efficiency (EE%) was calculated using the following equation (15):

$$EE\% = 100 \times Qe/Qt$$

Qe – incapsulated amount of vitamin E in the measured quantity of dried microparticles
Qt – the content of vitamin E initially used in the preparation procedure

All formulations were analyzed in triplicate and the results were presented as an average value ± standard deviation.

Swelling degree determination

A swelling experiment was performed in order to investigate the microparticle ability of water uptake from the medium. 0.1 M HCl (simulated gastric fluid), phosphate buffer at pH 6.8 and 7.4 (simulated intestinal fluids) were used as mediums. The purpose of the swelling study was to evaluate the possible mechanism of vitamin E release from microparticles. 50 mg of dried microparticles were transferred to a bottle with 20 mL of each medium. The bottles were immersed in a water bath heated to 37 °C. At specific time intervals (30, 60, 120 and 180 minutes), the microparticles were removed from media by filtration, transferred to filter paper to remove excess of water and right after that weighed at analytical scale. The swelling degree (SD) was calculated by the following equation (1, 15):

$$SD = (Wt - Wi)/Wi$$

Wt - the weight of the swollen microparticles at specific time t
Wi - the initial weight of dried microparticles

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois, US). One-way analysis of variance (ANOVA) and appropriate nonparametric test were used to identify significant differences in the data. Differences were considered statistically significant if $p < 0.05$ and highly significant if $p < 0.01$. The results were expressed as mean ± standard deviation (SD).

RESULTS

Four test formulations with different sodium-aliginate/alpha-tocopherol ratio were prepared. All

alginate microparticles were characterized by determining weight, average particle size, alpha-tocopherol content, loading capacity (DL%), encapsulation efficiency (EE%), and swelling ability. Table 2 shows the total weight of alginate microparticles of F1, F2, F3 and F4 formulations, immediately after synthesis and after drying period. During the drying process, the weight of all tested formulations was reduced due to evaporated water. Dried alginate microparticles of F1 formulation (vitamine E/sodium-alginate 1:1) retained the largest percentage of weight (7.51%), while microparticles of F4 formulation (vitamine E/sodium-alginate 1:2) retained the lowest percentage of weight (2.71%). There was a significant difference between the total weight of dried microparticles of F1 and F4 formulation ($p = 0.012$).

Table 2. *Total weight of alpha-tocopherol loaded alginate microparticles*

Total weight (g)	After synthesis	After drying	%
F1	2.607	0.196[a]	7.51
F2	2.508	0.149	5.94
F3	2.412	0.078	3.23
F4	2.624	0.071[b]	2.71

Different letters in superscript in the same column significantly differ from each other at $p < 0.05$

Determination of alginate microparticle size

The average size of alginate microparticles of all formulations with alpha-tocopherol after synthesis, drying and swelling in mediums (0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4) is shown in Table 3. Spherically shaped particles with the diameter of 0.5 to 1 mm which is 500 to 1000 μm were obtained after the drying process. Therefore, the obtained particles belong to the category of microparticles. The used mediums served to simulate biological fluids in the gastrointestinal tract. The diameter of the microparticles increased with increasing the pH value of the incubation medium. A statistically significant difference was observed between the dried microparticles of F1 and F2 formulation size and microparticle size of the same formulations in the phosphate buffer of pH 7.4 ($p < 0.05$). The diameter of F3 and F4 alginate microparticles, after incubation in the phosphate buffer with pH 7.4 was immeasurable because the particles were completely decomposed.

Table 3. *The average size of alginate microparticles with alpha-tocopherol after synthesis, after drying, and after swelling in mediums (0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4)*

Average size (diameter in mm)	After synthesis	After drying	0.1 M HCL	Phosphate buffer pH 6,8	Phosphate buffer pH 7,4
F1	2±0.01	1±0.03[a]	1±0.03[a]	3±0.15	4±0.20[b]
F2	1.9±0.01	0.9±0.02[a]	0.8±0.01[a]	2.5±0.12	5±0.23[b]
F3	1.7±0.02	0.5±0.05	0.7±0.02	1.5±0.10	immeasurable
F4	1.8±0.02	0.8±0.01	1±0.09	2±0.17	immeasurable

Different letters in superscript in the same row significantly differ from each other at $p < 0.05$

Determination of alginate microparticle swelling degree

The swelling degree of alginate microparticles of all formulations with alpha-tocopherol in three different mediums (0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4) for 180 minutes is shown in Figures 1, 2, 3 and 4, respectively. Microparticles of all four formulations remain almost intact during 3 hours in 0.1 M HCL which simulate the gastric fluid; hence, the synthesized particles are gastro resistant. The intensive swelling started after about 1 hour in the phosphate buffer with pH 6.8. The highest swelling index was reached in phosphate buffer 7.4 after 3 hours for all formulations, while microparticles of F3 and F4 were completely destroyed.

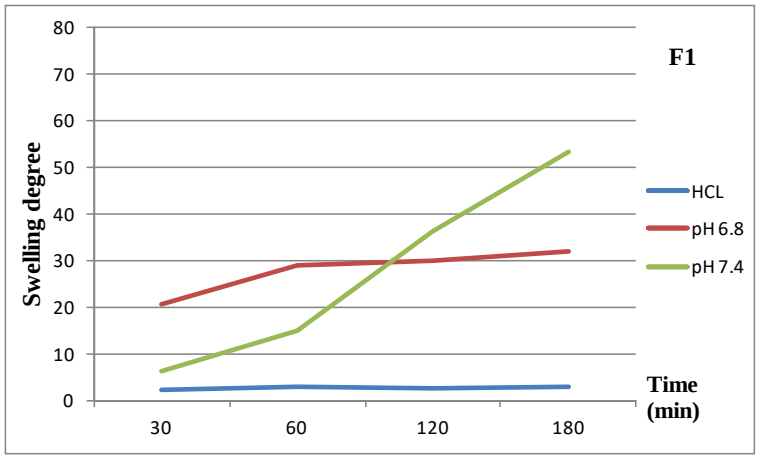

Figure 1. *Swelling degree of F1 formulation in 0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4 within the three-hour period*

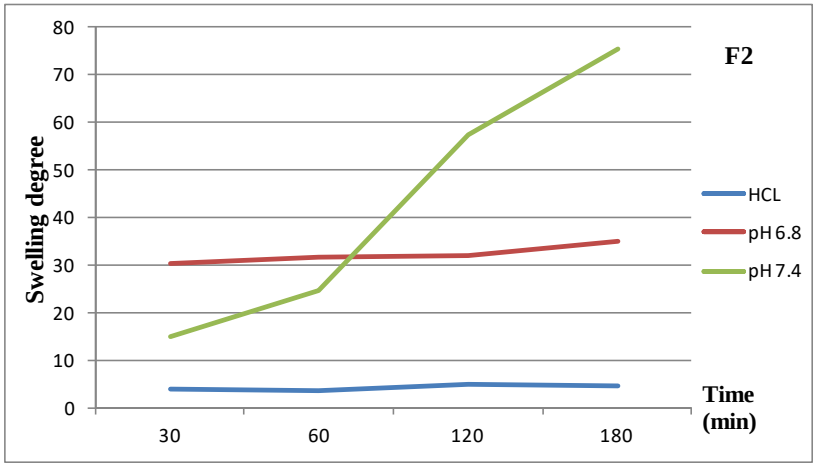

Figure 2. *Swelling degree of F2 formulation in 0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4 within the three-hour period*

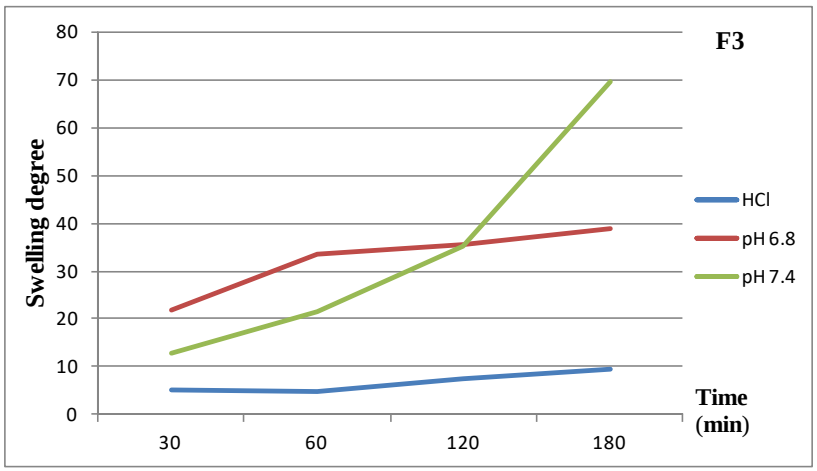

Figure 3. *Swelling degree of F3 formulation in 0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4 within the three-hour period*

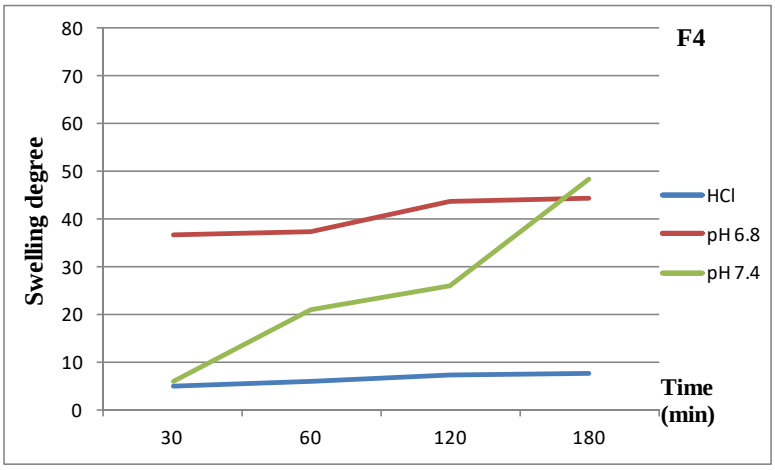

Figure 4. *Swelling degree of F4 formulation in 0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4 within the three-hour period*

Alpha-tocopherol content in alginate particles, loading capacity (DL%), and encapsulation efficiency (EE%)

Table 4 shows the content of alpha-tocopherol in alginate microparticles, loading capacity, and encapsulation efficiency of F1, F2, F3 and F4 formulations. The content of alpha-tocopherol in all-tested formulations was similar; however, the highest concentration was present in the microparticles of F1 formulation. The highest percentage of loading capacity and encapsulation efficiency was recorded in microparticles of F3 formulation (1% alginate in 2% calcium chloride, vitamin E/polymer ratio 1:1). There was a significant difference in DL between microparticles of F1 and F3 formulations ($p < 0.05$). In addition, a significant difference in EE between microparticles of F3 and F4 formulations was observed ($p < 0.05$).

Table 4. *Alpha-tocopherol content in alginate microparticles, loading capacity (DL%) and encapsulation efficiency (EE%)*

Formulation	Vitamin E content (mg/mL)	DL (%)	EE (%)
F_1	0.60 ± 0.021	10.00 ± 0.11^a	29.31 ± 0.72
F_2	0.50 ±0.020	12.50 ± 0.02	24.42 ± 0.2
F_3	0.45 ± 0.012	20.45 ± 0.22^b	31.91 ± 0.41^a
F_4	0.30 ± 0.010	12.50 ± 0.03	18.94 ± 0.32^b

All data are average value ± standard deviation (n = 3). Different letters in superscript in the same column significantly differ from each other at $p < 0.05$

DISCUSSION

Alginate has shown as suitable biomaterial for many biomedical applications like drug delivery systems, wound healing material, and bioink in 3D bioprinting because of biocompatibility, low toxicity, swelling ability, mucoadhesiveness, and mild gelation conditions (5). Microencapsulation in alginate beds can protect different substances such as vitamins and essential oils from unfavorable environmental conditions, including oxidative degradation, instability at high temperature, and volatility (4). Therefore, the antioxidant ability of vitamin E can be provided and supported by alginate microencapsulation. Alginate microparticles loaded by vitamin E were synthesized using external ionotropic gelation method and characterized by average particles size, swelling degree, vitamin E content, loading capacity,

and encapsulation efficiency. The obtained particles of all formulations are characterized as microparticles with diameter in the range from 500 to 1000 μm (12). Particles of F3 formulation showed the smallest diameter (500 μm). Singh J et al. described the vitamin E loaded pectin/alginate microparticles (PSA) with the diameter around 500 μm (460 - 620 μm) (1). Specifically, we can compare the particle diameter of the test F3 formulation with PSA sample from the previously mentioned study, both made from 1% sodium-alginate. There was a little difference in the diameter of compared samples (500 and 540 μm, respectively) (1). The size of calcium alginate microparticles can be reduced by using calcium chloride solution of a lower concentration because lower calcium content in the gelling medium causes grater shrinkage of hydrogel structure (15).

The swelling ability of tested microparticles was analyzed by monitoring the changes in particle size in three mediums (0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4) for 180 minutes and by determining the swelling degree. Mediums are chosen in order to simulate the behavior of microparticles in *in vivo* gastrointestinal fluids. Swelling degrees as well as diameters of all tested microparticles were increased with increasing of medium pH value. In acidic conditions (0.1 M HCL) which simulate the gastric fluid, the tested alginate microparticles showed the swelling degree below 10 for the entire three hours. Also, we conclude that there was no significant difference in the size of microparticles after incubation in 0.1 M HCL solution. The alginate particles remained almost intact in 0.1 M HCL medium because aginate forms strong hydrogel networks under gastric conditions and shows a low swelling ability (16, 17). As shown in Figures 1 - 4, all tested formulations started to swell intensively after 30 minutes in the phosphate buffer of pH 6.8, which simulate small intestinal fluid. Rapid swelling of alginate at the pH 6.8 conditions form gel-barrier which control the drug diffusion, therefore, we assume that release of incorporated vitamin E start in small intestinal fluid (17). In the end of monitoring period, the swelling degree of tested formulations in phosphate buffer of pH 7.4 was between 50 and 80. It was observed that particles of F3 and F4 formulations made with lower concentration of sodium-alginate (1%) were completely disintegrated. Such behavior of tested microparticles can be explained by pH sensitivity of alginates (18). Alginate hydrogel network becomes weaker by increasing the pH value because calcium chelators present in the intestinal environment scavenge Ca^{2+} from the calcium-alginate hydrogel matrix (17, 19).

Table 3 shows that vitamin E content is similar in all four formulations, ranging between 0.30 ± 0.010 and 0.60 ± 0.021. The loading capacities (DL) were in the range between 10 ± 0.11and 20.45 ± 0.22, while encapsulation efficiency percentages were between 18.94 ± 0.32% and 31.91 ± 0.41%. The best results were obtained for F3 formulation (1% sodium-alginate, 2% calcium-chloride, and vitamin E/polymer ratio 1:1) which show the highest DL percentage and the highest EE%. The properties of formulation F3 indicate that 31.91% of the used vitamin E was entrapped into the microparticles, and 20.45% of the microparticle mass was composed of vitamin E. Our results for encapsulation efficiency of vitamin E were lower than in the study conducted by Singh et al. (45.12 ± 0.41 - 50.53 ± 0.13); perhaps, the addition of pectin to microparticles structure influenced these results (1).

The literature data indicate different drug delivery systems of alpha-tocopherol in order to protect its antioxidant properties. For example, lipid nanoparticles or protein-based particles coated with alginate can provide gastroresistance and release of vitamin E in intestinal fluid (20, 21).

CONCLUSION

The optimum conditions for alpha-tocopherol encapsulation with the highest percentage of loading capacity and encapsulation efficacy were 1% sodium-alginate, 2% calcium-chloride, and vitamin E/polymer ratio 1:1 (formulation F3). Alginate proved to be a good protective excipient for encapsulation in order to improve characteristics of vitamin E such as lipophilicity and chemical instability. All four formulations showed the expected behavior in different mediums, which simulated gastrointestinal fluids *in vivo* (0.1 M HCL, phosphate buffer pH 6.8 and pH 7.4): gastroresistance, increase in the size, and swelling degree in intestinal fluids. This emphasizes the potential of using alginate microparticles as a carrier for the oral delivery of vitamin E, which are able to protect it from oxidative degradation.

Conflict of interest

The authors declare no conflict of interest.

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Sinteza i karakterizacija alginatnih mikročestica za oralnu primenu alfa-tokoferola

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SAŽETAK

Uvod/Cilj. Tehnika mikroinkapsulacije može se koristiti za zaštitu alfa-tokoferola od degradacije u nepovoljnoj sredini, kao i za poboljšanje bioraspoloživosti i produžetak roka trajanja vitamina E. Ciljevi ovog istraživanja bile su sinteza i karakterizacija alginatnih mikročestica za oralnu primenu alfa-tokoferola.
Metode. Napravljene su ukupno četiri test-formulacije kalcijum-alginatnih mikročestica za oralnu primenu sa 0,5%, 1% i 2% (w/w) alfa-tokoferola metodom eksternog jonotropnog geliranja. Odnos između vitamina E i natrijum-alginata bio je 1 : 1 i 1 : 2. Sve alginatne čestice okarakterisane su određivanjem prosečne mase i veličine čestica, procentualnog sadržaja alfa-tokoferola, efikasnosti inkapsulacije i sposobnosti bubrenja.
Rezultati. Nakon sušenja dobijene su čestice sfernog oblika, veličine od 500 do 1000 μm, što ih svrstava u kategoriju mikročestica. Veličina i stepen bubrenja nisu se značajno menjali u 0,1 M HCl, dok su u baznim uslovima fosfatnog pufera pH 6,8 i 7,4 bili povećani. Sadržaj inkapsuliranog vitamina E nije se značajno razlikovao među formulacijama (od 0,30 mg/mL ± 0,010 mg/mL do 0,60 mg/mL ± 0,021 mg/mL). Kapacitet punjenja kretao se u opsegu 10% ± 0,11% i 20,45% ± 0,22%, a procentualna efikasnost inkapsulacije bila je između 18,94% ± 0,32% i 31,91% ± 0,41%.
Zaključak. Ispostavilo se da su optimalni uslovi za inkapsulaciju alfa-tokoferola, sa najvećim kapacitetom punjenja i stepenom inkapsulacije, postignuti korišćenjem 1% natrijum-alginata, 2% kalcijum-hlorida i odnosa vitamin E/polimer 1 : 1. Sve četiri formulacije pokazale su očekivano ponašanje u različitim medijumima, koji su simulirali gastrointestinalne tečnosti *in vivo* (0,1 M HCl, fosfatni pufer pH 6,8 i 7,4): gastrorezistenciju i porast veličine i sposobnosti bubrenja u intestinalnim tečnostima. Na osnovu svega navedenog može se govoriti o primeni alginatnih mikročestica kao nosača za oralnu primenu vitamina E.

Ključne reči: **alfa-tokoferol, vitamin E, kalcijum-alginat, alginatne čestice, inkapsulacija**