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Hydrocolloid Gel-Formers and Polyvalent Cations in the Formation of Microparticles

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1. Introduction

Hydrocolloid drug delivery systems can be used through various application routes both for tissue regeneration or the delivery of peptides and proteins or targeted release.

Polymers of natural (chitosan, alginate, xanthan or guar gum), semisynthetic (cellulose derivatives) and synthetic (polyacrylic acid derivatives) origin can also be used as hydrocolloid gelling agents, of which naturally occurring materials are distinguished by their excellent tolerability and –in many cases- their biodegradability. The release is influenced by the swelling capacity of the macromolecules, that precedes the liberation of the active ingredient, namely diffusion through the swollen layer, or erosion of the hydrated polymer. In the swelling behavior, intermolecular cross-links play a significant role [1].

Among the numerous test methods (SEM, TEM, MPM) Micro-CT is suitable for studying the microstructure formed by cross-linking. Micro-CT is a non-invasive technique that has successfully been used to study the internal structure of freeze-dried calcium alginate microspheres [2].

The structure of the microspheres of high liquid content in the hydrated state can be inferred indirectly through texture analysis and image analysis.

Positron Annihilation Lifetime Spectroscopy (PALS) is a well-known assay in polymer chemistry, which has successfully been used in pharmaceutical technology in several cases to detect polymeric aging [3], macro- and microstructural changes in cast films [4] or gels [5]. The method is based on the interaction between free volume and o-positronium (o-Ps), and the lifetime of o-Ps is proportional to the free volume of the polymers. PALS measurements allow the structure to be compared based on the free volume of the voids in the polymer structure.

The aim of the study was to evaluate the effect of different divalent cations on the coacervation process, the morphology and microstructure of alginate microparticles.

2. Materials and methods

Medium viscosity sodium alginate from brown algae (Merck, Hungary) was used as a hydrocolloid gelling agent. The microspheres were formed by vibration extrusion, and gelation was facilitated by ionic coacervation. Solutions of Ca^{2+}, Zn^{2+}, and Ca^{2+}: Zn^{2+}= 1: 1 served as the coacervation medium.

Physical properties and morphological parameters were analyzed by texture analysis (Brookfield Texture Pro CT3), image analysis, and PALS. Statistical analysis was performed by bivariate regression analysis (Table Curve® 3D). A polynomial function characterized the effect of the two independent variables on the response parameter.

3. Results

Calcium ions are most frequently used to coacervate alginate gels; however, many di- and trivalent ions form bonds with sodium alginate. The strength of the formed bonds is influenced by several factors (concentration of coacervation medium, conditions of application, time of coacervation, use of any excipients, temperature). After drying, they are partly able to absorb a significant volume of liquid. This is due to their porous structure, which is in relation to the nature of the ion.

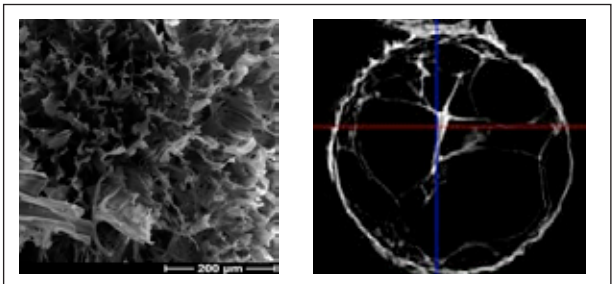

Figure 1 *Internal structure of freeze-dried calcium alginate microparticles a) SEM; b) Micro-CT*

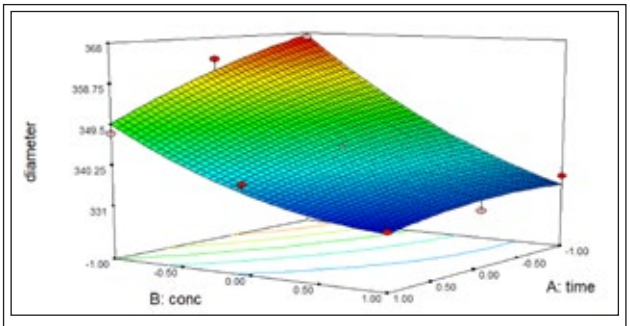

Figure 2 *Effect of coacervation time and medium concentration on diameter (µm) of particles*

It is observed that by increasing the concentration of the medium, the size of the formed particles significantly ($p < 0.05$) reduces and the compression force increases. As a result of faster coacervation with calcium ions, morphological parameters show a more irregular, less spherical shape than zinc alginate, especially at high concentrations.

4. Conclusions

Solutions of calcium (II) and zinc (II) ions in the concentration range of 0.05-0.25 M are suitable for forming a stable microsphere gel carrier system. The concentration of solutions used for coacervation and the reaction time in them affects both the macromorphological properties (size, sphericity) and the micromorphology of the spheres, resulting in different physical properties (hardness, fragility). PALS measurements support conclusions based on mechanical properties and morphological parameters.

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References

1. *Lengyel, M., Kállai-Szabó N., Antal V., Laki A.J., Antal Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery, Sci. Pharm. (3) 87 (2019)*
2. *Lengyel, M., Balogh E., Szerőczei D., Dobó-Nagy Cs., Pápay Zs., Antal, I. Study on process parameters and optimization of microencapsulation based on phase separation, Eur. J. Pharm. Sci. 25:273-278 (2018)*
3. *Zelkó, R.; Süvegh, K. Tracking of the physical aging of amorphous pharmaceutical polymeric excipients by positron annihilation spectroscopy, Eur. J. Pharm. Sci. 21: 519-523 (2004).*
4. *Szabó, B.; Sebe, I.; Kállai, N.; Süvegh, K.; Zelkó, R. Comparison of the micro- and macrostructural characteristics of biopolymer cast films. Eur. Polym. J. 49(9): 2422-2425 (2013)*
5. *Palcsó, B.; Moldován, Z.; Süvegh, K.; Herczegh, A.; Zelkó R, Chlorine Dioxide-Loaded Poly(acrylic Acid) Gels for Prolonged Antimicrobial Effect, R. Mater. Sci. Eng. C 98: 782–788 (2019)*