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Study of Formulation Factors Influencing Phenytoin Release Rate from Alginate–Chitosan Microparticles using an Experimental Design Approach

N. CEKIĆ [1], B. ČALIJA [2], S. SAVIĆ [2], J. MILIĆ [2]

[1] DCP Hemigal, Leskovac, Serbia
[2] Faculty of Pharmacy, Belgrade University, Belgrade, Serbia

E-mail: nesafarm@gmail.com (N. Cekić)

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Alginate-based microparticles have been widely investigated for applications like enzyme immobilization, immunoisolation in cell transplantation and drug release systems. Using the custom made air-jet device, by varying processing as well as several formulation factors, we aimed to prepare and investigate alginate-chitosan microparticles loaded with phenytoin, a standard antiepileptic agent. The extended-release formulations of antiepileptics simplify treatment of this chronic condition. Such commercial formulations with phenytoin appear to be well designed, with one possible shortcoming being the potential for irregular absorption that appears to occur particularly in elderly patients [1]. The final aim of the project was to investigate microparticles loaded with phenytoin with possibly improved liberation profile. In order to evaluate the influence of formulation factors and hardening time in a chitosan solution on drug release rate, 2^4 full factorial design was used. The independent variables (inputs) investigated were the calcium chloride concentration (X_1), chitosan molecular weight (X_2), chitosan concentration in coating solution (X_3) and hardening time (X_4). The times for 50% and 90% of the drug to be released – $t_{50\%}$ and $t_{90\%}$ for each formulation were calculated and used as response parameters (outputs). ANOVA analysis revealed that among investigated factors X_2, X_3, X_4 as well as interactions X_2–X_3 and X_3–X_4 have statistically significant influence on drug release from microparticles ($p<0.05$). Since no significant influence of X_1 on drug release rate was observed, it was excluded from further statistical analysis. Calculated factor effects of investigated variables indicate that lower level of X_2 (combination of high and low molecular weight chitosan), higher levels of X_3 (0.2% w/w chitosan concentration in coating solution) and X_4 (24h hardening time) favour sustained release of phenytoin. The present study suggests that alginate-chitosan microparticles may be used as a delivery system for sustained release of phenytoin with key factor affecting the release rate being the combination of hardening time, chitosan concentration and molecular weight.

[1] Pellock JM, Smith MC, Cloyd JC, Uthman B, Wilder BJ. Extended-Release Formulations: Simplifying Strategies in the Management of Antiepileptic Drug Therapy. Epilepsy Behav. 2004; 5: 301–307. doi:10.1016/j.yebeh.2004.01.009