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Multi-Objective Optimization (Pareto Sets) and Multi-Response Optimization (Desirability Function) of Microencapsulation of Emamectin

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Abstract : Emamectin Benzoate (EB) is a crystal antiparasitic that belongs to the avermectin family. It is one of the most common treatments used in Chile to control Caligus rogercresseyi in Atlantic salmon. However, the sea lice acquired resistance to EB when it is exposed at sublethal EB doses. The low solubility rate of EB and its degradation at the acidic pH in the fish digestive tract are the causes of the slow absorption of EB in the intestine. To protect EB from degradation and enhance its absorption, specific microencapsulation technologies must be developed. Amorphous Solid Dispersion techniques such as Spray Drying (SD) and Ionic Gelation (IG) seem adequate for this purpose. Recently, Soluplus® (SOL) has been used to increase the solubility rate of several drugs with similar characteristics than EB. In addition, alginate (ALG) is a widely used polymer in IG for biomedical applications. Regardless of the encapsulation technique, the quality of the obtained microparticles is evaluated with the following responses, yield (Y%), encapsulation efficiency (EE%) and loading capacity (LC%). In addition, it is important to know the percentage of EB released from the microparticles in gastric (GD%) and intestinal (ID%) digestions. In this work, we microencapsulated EB with SOL (EB-SD) and with ALG (EB-IG) using SD and IG, respectively. Quality microencapsulation responses and in vitro gastric and intestinal digestions at pH 3.35 and 7.8, respectively, were obtained. A central composite design was used to find the optimum microencapsulation variables (amount of EB, amount of polymer and feed flow). In each formulation, the behavior of these variables was predicted with statistical models. Then, the response surface methodology was used to find the best combination of the factors that allowed a lower EB release in gastric conditions, while permitting a major release at intestinal digestion. Two approaches were used to determine this. The desirability approach (DA) and multi-objective optimization (MOO) with multi-criteria decision making (MCDM). Both microencapsulation techniques allowed to maintain the integrity of EB in acid pH, given the small amount of EB released in gastric medium, while EB-IG microparticles showed greater EB release at intestinal digestion. For EB-SD, optimal conditions obtained with MOO plus MCDM yielded a good compromise among the microencapsulation responses. In addition, using these conditions, it is possible to reduce microparticles costs due to the reduction of 60% of BE regard the optimal BE proposed by (DA). For EB-GI, the optimization techniques used (DA and MOO) yielded solutions with different advantages and limitations. Applying DA costs can be reduced 21%, while Y, GD and ID showed 9.5%, 84.8% and 2.6% lower values than the best condition. In turn, MOO yielded better microencapsulation responses, but at a higher cost. Overall, EB-SD with operating conditions selected by MOO seems the best option, since a good compromise between costs and encapsulation responses was obtained.

Keywords : microencapsulation, multiple decision-making criteria, multi-objective optimization, Soluplus®
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