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# Spray-drying of inhalable prodrug-enzyme systems with antibacterial properties

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Rising numbers of multidrug-resistant bacteria and the desire to avoid systemic drug exposure are among the key challenges of current pharmaceutical development. Inhalable powders with prodrug-enzyme systems may contribute to progress in both areas, using natural defence mechanisms as inspiration. For instance, plants of the genus *Allium*, i.e., garlic, onion, leek, rely on the broad and strong antimicrobial effect of thiosulfinates. They are synthesized from sulfoxides, i.e., prodrugs, using the enzyme alliinase. This happens only when the plant cells are attacked by microbes. Moreover, thiosulfinates are volatile and unstable, leading to hindered onset of microbial resistance. However, unstable compounds cannot be put safely into a drug product with long-term stability. Therefore, we propose to formulate sulfoxides and alliinase into inhalable spray-dried powders, where the reaction is triggered by contact with the moist environment of the lungs. Delivering antibiotics directly to the place of action and avoiding systemic drug exposure is of high importance here because it decreases the necessary dose and limits the damage caused to the gut microbiome. Moreover, thiosulfinates are the only antibiotics active in a vapour state[1], which may enable them to overcome mechanical barriers posed by chronic lung diseases.

In this work, we used the three-fluid atomization nozzle to spray dry powders containing alliinase and sulfoxide alliin in all particles, together with carrier maltodextrin. This nozzle allows for the entry of two separate feeds, i.e., alliin-maltodextrin and alliinase-maltodextrin, which only meet at the nozzle orifice. This approach limits the alliin-alliinase contact in liquid state, while enabling their presence in one particle and, thus, facilitating thiosulfinates production at the place of action. We evaluated the effect of different designs on the amount of thiosulfinates produced during spray drying. Moreover, we studied the antibacterial effect of prepared powders and their storage stability. In the future, we plan to test the deposition and antibacterial effect of these powders in a simplified lung model.

1. Mašková, L., et al., *Development of compartmentalized antibacterial systems based on encapsulated alliinase.* Advanced Powder Technology, 2021. **32**(8): p. 2720-2732.

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