Development of hyaluronan/mannitol dry powders for flucytosine repositioning in local therapy of lung infections.

1)Tramontano T.. 2)D'emmanuele di villa bianca R.. 3)Mitidieri E.. 4)Costabile G.. 5)D'angelo I.. 6)Pompili B.. 7)Del porto P.. 8)Leoni L.. 9)Visca P.. 10)Miro A.. 11)Quaglia F.. 12)Imperi F.. 13)Ungaro F.. 14)Sorrentino R..

Department of Pharmacy, University of Naples, Federico II

Flucytosine (5-fluorocytosine, 5-FC) is a fluorinated analogue of cytosine that is currently used for the systemic treatment of fungal infections (Nett et al., 2016). Recently, in a mouse model of pulmonary infection, it was revealed that systemic administration of 5-FC was also able to reduce the virulence of the bacterium Pseudomonas aeruginosa (Imperi et al., 2013), one of the most dreaded opportunistic pathogens in hospital and the main cause of lung infection and mortality in individuals with cystic fibrosis (CF) (Driscoll et al., 2007). Taking into account that pulmonary administration represents an ideal way to treat local lung infections (Flume et al., 2015; Langan et al., 2015), in this study we have developed novel inhalable composite hyaluronic acid [HA]/mannitol dry powders for repositioning 5-FC in local treatment of lung infections. As first step, studies were performed in order to identify the 5FC/HA/mannitol formulation with convenient aerosolization properties and drug release profile in simulated lung fluids. The optimized powder for inhalation (HyaMan_FC#3) was delivered from different breath-activated dry powder inhalers (DPI) already available to CF patients, and we observed that HyaMan_FC#3 well fit with a low-resistance DPI. Additional studies have shown that HyaMan_FC#3 was able to inhibit in vitro both the growth of Candida albicans and the virulence of P. aeruginosa at concentration that did not caused cytotoxic effects in wild type (16HBE14o-) and CF (CFBE41o-) human bronchial epithelial cells cultures. In view of the encouraging in vitro findings, we moved to in vivo studies and compared pharmacokinetics of HyaMan_FC#3 inhalation powder and 5-FC solution after intratracheal administration in rats. Our bio-distribution results clearly demonstrated that the optimized 5-FC dry powder offers the possibility to control local 5-FC concentration over time and significantly increases the drug levels in both bronchoalveolar lavage fluid and lung tissue as compared to 5-FC solution. Of note, when the same amount of 5-FC was administered intravenously, no significant 5-FC level was found in the lung at each time point from the injection. To reach a 5-FC lung concentration similar to that obtained by using HyaMan_FC#3, a 6-fold higher dose of 5-FC should be administered intravenously. In conclusion, our data demonstrate for the first time the feasibility to develop effective 5-FC formulations for pulmonary delivery by inhalation, reasonably limiting the well-known associated systemic side effects. Furthermore, our results highlight that an appropriate formulation design can improve the persistence of the drug at lungs, where microorganisms causing severe infections are located.

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