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Crystallization of stable doped mannitol polymorphs and *in vitro* assessment of their safety as carriers for lung delivery

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The aerosolization performance of dry powder inhalers (DPIs) for the administration of micronized APIs at low dosage depends, among other parameters, on the nature and solid-state properties of the carrier. Mannitol, being non-reducing and non-hygroscopic, is a promising compound to be used as carrier, since it is useful to overcome limitations of lactose, in particular with reference to patients' intolerance and incompatibility with APIs carrying amino groups [1].

On these bases, it is interesting to investigate the effect of different polymorphs on DPIs performances, provided that kinetically stable mannitol polymorphs are obtained, preferably by a simple and reproducible method. To this purpose, doping polymers [2], namely PVA 22K® and PVP K30®, were introduced into mannitol solutions to induce its recrystallization. Different amounts of doping agents were tested, and the minimal amount needed to obtain α and δ form identified. The lowest concentration of PVA 22K® necessary to obtain α form from saturated methanol solution was 2% w/w, with respect to mannitol, while δ form could be obtained with 1% w/w of PVP K30®, by using acetone as antisolvent. Powder X-ray diffraction and differential scanning calorimetry were used to monitor the stability of polymorphs which was confirmed up to 12 months of storage in accelerated conditions (40°C and 75% R.H.). Despite the low amount of doping agents, concerns may be raised about their safety as excipients for lung administration.

For this reason, in vitro assays were performed on two models of the airways, namely Calu3 and A549 cell lines, as a preliminary indication of cytocompatibility. The range of concentration tested was selected considering, on one side, the highest amount of respirable solid that was obtained by *in vitro* aerosolization of the content of a capsule of 20 mg of sole excipients, i.e. 2 mg, and, on the other side, the estimated volume of lung lining fluid (10 to 30 mL) [3]. On these premises, cells were exposed to different doped polymorphs of mannitol at concentrations up to 16 times higher than the worst-case-scenario (0.2 mg/mL). Viability with respect to β mannitol or untreated cells was evaluated by MTT assay. PVP K30® and PVA 22K® were also tested alone up to a concentration of 64 μg/mL.

No significant differences in viability were observed on both cell lines at all concentration tested, and viability never decreased below 80% with respect to control, providing substantial evidence of the safety of these substances as useful excipients for inhalation.

Literature:

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