Title	Investigation of drug dissolution and absorption from low-density inhalation budesonide formulations in a cell culture integrating impactor system
Keywords (up to 5)	Pulmonary drug delivery, drug disposition, alveolar cell line, new generation impactor, inhalation budesonide formulation
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Abstract	Besides alveolar deposition, pulmonary bioavailability is determined by dissolution of deposited particles in the scarce fluid of the epithelium and API absorption.[1,2] In this work an arrangement combining the next generation impactor (NGI) with the human alveolar epithelial cell line A549 that possesses type II alveolar cell characteristics is presented. The goal being to investigate drug absorption after particle deposition of previously developed powder formulations and to examine the suitability of this combination of in vitro pulmonary test models. Formulations of budesonide for deep lung deposition were manufactured by nano-milling in a stirred media mill and subsequent spray drying, containing albumin, ammonium carbonate and/or leucine as excipients to modulate porosity. The aerodynamic fine particle fraction of these formulations determined by the NGI ranged between 18.3 and 61.1%. The cups of stages 3, 4, and 5 of the NGI corresponding to aerodynamic particle size of 4.16 to 2.64 µm, 2.64 to 1.56 µm, and 1.56 to 0.88 µm, respectively, were modified to accommodate PTFE PICM0RG50 inserts while assuring minimal interference with air flow. A549 cells were cultivated in the air-liquid interface on the inserts coated by 3D printing with Corning® Matrigel®. After powder deposition in the NGI the inserts were returned to the 6-well plate. Budesonide absorption was monitored over time by determining drug amount in the basal solution, in the interior of the cell monolayer, and on the cell surface. Deposition in the three stages generally decreased in the order 3>4>5 to an extent depending on formulation. Between 10 and 35% of the deposited drug amount permeated in one hour into the basal solution, indicating fast dissolution and absorption. This amount, however, correlated with LDH release from the cells suggesting some membrane damage. Budesonide was for all formulations and stages most abundant within the cells, predominantly as its metabolic conjugate with oleate. The smallest part of drug, between 10 and 20%, remained on the cell surface after eight hours. Drug percentage increased in the basal solution in the three stages in the order 3<4<5 and decreased on the cell surface in the order 3>4>5. The results obtained with the present test model provide useful insights into the biopharmaceutical performance of the developed formulations.
References	1. M. Bur, B. Rothen-Rutishauser, H. Huwer, C-M. Lehr. Eur.J.Pharm.Biopharm. 72 (2009) 350. 2. M. Haghi, D. Traini, P. Young. Pharm. Res. 31 (2014) 1779.