Lipid nanocarriers improve paclitaxel transport throughout human intestinal epithelial cells by using vesicle-mediated transcytosis

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Résumé en anglais	The use of lipid nanocapsules (LNCs) has enabled an improvement of the oral bioavailability of paclitaxel (Ptx). However, mechanisms that support this recent observation are not yet understood. By focusing on the well defined in vitro Caco-2 model, the purpose of this study was to evaluate the transport of LNCs across a model intestinal barrier. Firstly, four sizes of paclitaxel or dye (Nile Red)-loaded LNCs were formulated and LNCs with sizes between 26.3+/-2.7nm and 132.7+/-5.5nm were obtained. Different transport and uptake experiments were then performed across a Caco-2 cells culture model using these LNCs. Paclitaxel-loaded LNCs improved permeability of Ptx across intestinal epithelium compared with free Ptx or Taxol((R)) by a factor of 3.5. At 37 degrees C particle size did not influence transport efficiency. However, at 4 degrees C a decrease in Ptx transport was observed with increasing size of LNCs. Thus, with LNCs of 25nm size, the apparent permeability coefficient (P(app)) was 5.3+/-1.1cm s(-1) at 37 degrees C and 2.2+/-0.4cm s(-1) at 4 degrees C. In comparison in LNCs of 130nm size, the P(app) decreased from 5.8+/-0.8cm s(-1) at 37 degrees C to 0.5+/-0.1cm s(-1) at 4 degrees C. The uptake of LNCs by Caco-2 cells and the incapacity of LNCs to open tight junctions were also demonstrated. Furthermore, experiment transports were performed in the presence of different inhibitors of endocytosis. Findings indicated a reduction of Ptx transport of 30+/-6% when cell cholesterol was depleted, 65+/-12% when caveolae-mediated endocytosis was inhibited and 20+/-8% when clathrin-mediated endocytosis was inhibited. Finally, transmission electronic microscopy showed the presence of nano-objects on the basolateral side of the Caco-2 cell monolayers when LNCs were applied on the apical side.

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