Title	Pharmacokinetic disposition of cox-inhibitors for the prevention/treatment of colorectal cancer
Keywords (up to 5)	Pharmacokinetic disposition, COX-inhibitors, Colorectal cancer, Caco-2, Ussing Chamber
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Abstract	COX-inhibitors show promising results for the prevention of colorectal cancer, yet multiple uncertainties remain about the pharmacokinetics of the drugs, especially at the level of the colon. We pursue a full pharmacokinetic profiling of celecoxib and sulindac on a systemic, intraluminal, and tissue level. The translatability of intestinal models (Caco-2, Ussing Chambers) to humans in relation to the pharmacokinetics of the selected compounds will be evaluated as well. *In vivo*: a single dose of celecoxib (200 mg) was administered orally to a healthy volunteer. We observed that celecoxib gets extensively metabolized to carboxy-, and hydroxy celecoxib. Celecoxib gets excreted mostly through urine (3,5 %) and feces (43,9 %) with carboxy celecoxib as the predominant metabolite. *In vitro/ex vivo*: Experiments with β-blockers as reference compounds demonstrated that the Caco-2 model and the Ussing Chamber setup using human biopsies are reliable setups to study efflux and passive transport, as well as accumulation. Based on the assessment of the apparent permeability of a Caco-2 monolayer for celecoxib (absorption: $17.99 \pm 1.47 \times 10^{-6}$ cm/s, secretion: $9.78 \pm 2.15 \times 10^{-6}$ cm/s) and sulindac (absorption: $8.08 \pm 0.45 \times 10^{-6}$ cm/s, secretion: $6.32 \pm 0.41 \times 10^{-6}$ cm/s) these COX-inhibitors can be considered highly permeable compounds. Additionally, intestinal cells function as a depot for celecoxib upon uptake: the latter reversibly binds to cellular constituents, and thus can subsequently be released. Intracellular accumulation is sufficient (0.27 ± 0.03 nmol) to inhibit COX-2 activity [1]. We can conclude that celecoxib is a highly permeable compound that accumulates intracellularly in enterocytes. Oral intake leads to rapid and high systemic exposure to celecoxib and carboxy celecoxib, which is excreted mostly in feces and urine with little parent drug left unchanged.
References	1. Entezari Heravi, R., et al. Novel selective Cox-2 inhibitors induce apoptosis in Caco-2 colorectal carcinoma cell line. Eur. J.Pharm. Sci. (2011), doi:10.1016/j.ejps.2011.09.005