are hydrophilic molecules that do not rapidly penetrate cell membranes by diffusion and their absorption relies on specialized transporters. Therefore, the oral absorption of nucleoside prodrugs and the target organ concentration of the biologically active nucleotide can be limited due to poor permeation across the intestinal epithelium. In the present study, the specificity, concentration dependence, and effect of four classes of absorption promoters, i.e., fatty acids, steroidal detergents, mucoadhesive polymers, and secretory transport inhibitors, were evaluated in a rat in vivo model. Sodium caprate and alpha-tocopheryl-polyethyleneglycol-1000-succinate (TPGS) showed a significant effect in increasing liver concentration of nucleotide (5-fold). These results suggested that both excipients might be suited in a controlled release matrix for the synchronous release of the drug and absorption promoter directly to the site of absorption and highlights that the effect is strictly dependent on the absorption promoter dose. The feasibility of such a formulation approach in humans was evaluated with the aim of developing a solid dosage form for the peroral delivery of nucleosides and showed that these excipients do provide a potential valuable tool in preclinical efficacy studies to drive discovery programs forward.

Davies, L. B. et al. (2017). "Accelerating topical anaesthesia using microneedles." *Skin Pharmacol Physiol* 30(6):277–283.

BACKGROUND/AIMS: Topical anesthetics reduce pain during venous access procedures in children. However, clinical use is hindered by a significant anesthetic onset time. Restricted diffusion of the topical anesthetic through the stratum corneum barrier is the principal reason for the delayed onset. Microneedles can painlessly pierce the skin. This study evaluated microneedle pretreatment of ex vivo human skin as a means to increase the rate of tetracaine permeation, in order to accelerate the onset of anesthesia. METHODS: Franz-type diffusion cells were used to determine permeation of a commercial tetracaine formulation, Ametop gel, through human skin epidermis. Microneedle-assisted permeation was compared to untreated epidermis. Upon completion of the permeation studies, the epidermal membranes were visually characterized. RESULTS: At 30 minutes, 5.43 μg/cm^2 of tetracaine had permeated through the untreated membrane compared to 12.13 μg/cm^2 through the microneedle-treated membrane. Insertion of a hypodermic needle created a large single channel in the epidermis (approx. 4,250 μm^2), whilst the punctured surface area following microneedle treatments was estimated to be 75,000 μm^2. CONCLUSION: Pretreatment of skin with microneedles significantly enhances the permeation of tetracaine. Microneedles have the potential to more than halve the onset time for anesthesia when applying Ametop gel.

Dubey, S. and Y. N. Kalia (2014). "Understanding the poor iontophoretic transport of lysozyme across the skin: When high charge and high electrophoretic mobility are not enough." *J Control Release* 183:35–42.

The original aim of the study was to investigate the transdermal iontophoretic delivery of lysozyme and to gain further insight into the factors controlling protein electrotransport. Initial experiments were done using porcine skin. Lysozyme transport was quantified by using an activity assay based on the lysis of Micrococcus lysodeikticus and was corrected for the release of endogenous enzyme from the skin during current application. Cumulative iontophoretic permeation of lysozyme during 8 hours at 0.5 mA/cm^2 (0.7 mM; pH 6) was surprisingly low (5.37 ± 3.46 μg/cm^2 in 8 hours) as