Thiomers: A potent tool for the non-invasive administration of efflux pump substrates?

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The past several years have witnessed the potential of thiolated polymers - designated thiomers – as useful excipients in oral drug delivery. Due to their comparatively strong mucoadhesive properties being based on the formation of disulfide bonds between the thiomer and cysteine-rich subdomains of the mucus gel layer an intimate contact with the absorption membrane can be achieved. By the immobilization of thiol groups on chitosan and poly(acrylic acid) the mucoadhesive properties of these polymers, for example, were 20-fold and 140-fold improved, respectively (1,2). Furthermore, as thiomers can reversibly open tight junctions, the oral uptake of numerous drugs can be strongly improved. In the presence of 0.5% thiolated polycarbophil, for instance, the apparent permeability coefficient of insulin and LMWH could be 1.3-fold and 2.0-fold improved, respectively (3,4). Such in vitro results could meanwhile be verified in numerous in vivo studies demonstrating the potential of thiomers in absorption enhancement of orally given drugs. Studies in pigs demonstrated a significantly improved uptake of a model peptide drug when being incorporated in thiomers (5).

More recently Werle and Hoffer revealed efflux pump inhibitory capability of thiomers (6). Transmucosal transport of the P-gp substrate rhodamine 123 was strongly improved in the presence of thiolated chitosan. These in vitro results could meanwhile be confirmed by in vivo studies in rats. Föger et al. (7) showed that the oral bioavailability of rhodamine 123 is even 3.0-fold improved when this model P-gp substrate is embedded in thiolated chitosan minitablets given orally to rats. The results of this study are shown in Fig. 1. In addition, poly(acrylic acid)-cysteine conjugate showed to inhibit effectively Mrp2 efflux pump transporter, improving the permeation of sulforhodamine 101 4.67-fold. The inhibitory effect of thiomers is thereby strongly dependent on their molecular mass. As shown in Fig. 2 thiolated polyacrylates of 250 kDa exhibit the highest P-gp inhibitory effect, whereas thiolated poly(acrylic acid) of higher and lower molecular mass display significantly lower inhibitory activity.

The postulated mechanism of efflux pump inhibition is based on an interaction of thiomers with the channel forming transmembrane region of P-gp. P-gp exhibits 12 transmembrane regions forming a channel through which substrates are transported outside of the cell. Two of these transmembrane regions – namely 2 and 11 – exhibit on position 137 and 956, respectively, a cysteine subunit. Thiomers seem to enter in the channel of P-gp and likely form subsequently one or two disulfide bonds with one or both cysteine subunits located within the channel. Due to this covalent interaction the allosteric change of the transporter being essential to move drugs outside of the cell seems to be blocked. The theory is supported by the size dependent activity of thiomers and the observation that corresponding unthiolated polymers show no or significantly lower efflux-pump inhibitory properties. The theory is additionally supported by the observation that the efflux pump inhibitory effect of thiomers is only to a minor extent influenced by the type of polymer backbone.
Thiolated chitosans show for instance a similar effect as obtained by using thiolated polyacrylates. Based on this theory, calculations on the diameter of the channel might be feasible by utilizing thiolated polymers of a defined diameter. Apart from their oral use, thiomers might also be helpful in order to improve the efficacy of parenterally administered anticancer drugs.

References