Effect of pH and penetration enhancers on cysteamine stability and trans-corneal transport.

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Abstract

Ocular cystinosis is a rare metabolic disorder characterized by the presence of insoluble cystine crystals inside the corneal stroma, with consequent photophobia, keratopathies and frequent corneal erosions. The current therapy consists in the lifetime ophthalmic administration of cysteamine, drug characterized by extremely high hydrophilicity, low molecular weight (77g/mol), and easy oxidization to disulfide. Ocular delivery of cysteamine is very challenging, for its poor permeability and stability in solution. The purpose of the present paper was to study the impact of formulation pH and composition on (1) the trans-corneal delivery and (2) the stability in solution of cysteamine, with particular focus on the use of alpha-cyclodextrin (α-CD), benzalkonium chloride (BAC) and disodium edetate (EDTA). Permeation experiments were performed ex vivo through freshly excised porcine cornea; stability was evaluated for six months at -20°C, +4°C and +25°C; irritation potential was evaluated using HET-CAM assay. The results showed that cysteamine trans-corneal diffusion is strictly dependent on both pH (7.4 preferred to 4.2) and buffering capacity, that negatively impact on the permeation; EDTA did not enhance the trans-corneal diffusion of cysteamine neither at pH 7.4 nor at pH 4.2, while benzalkonium chloride (BAC), antimicrobial agent present within commercial eye-drops, significantly enhanced it. Notably, α-CD was able to promote the trans-corneal diffusion of cysteamine and, at a 5.5%, a 4-fold higher penetration compared to the BAC-containing formulation was obtained. EDTA and acidic pH demonstrated to be essential for cysteamine stability. The formulation obtained by combining α-CD and EDTA was characterized by significant permeation, good stability profile, and no irritation potential, even if the tolerability should be further confirmed by in vivo test.

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