

SELF-REGULATING 'SMART CARRIERS' FOR NON-INVASIVE AND TARGETED DRUG DELIVERY

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The skin of mammals is an excellent anatomical and biochemical barrier. Non-invasive transport across the skin is therefore only feasible for relatively small molecules (MW > 400 Da) [1]. Special tile-like cell organisation in the skin and the sealing of intercellular contacts by the lipids that are tightly packed and attached covalently to cutaneous cell membranes are both responsible for this [2]. At least partial barrier destruction using mechanical, electrical, thermal, or sonic micro-poration of outer skin layers, until recently, was the only possibility to overcome transcutaneous transport problem.

Ultra-deformable and extremely hydrophilic vesicles, Transfersomes[®] (a trademark of IDEA AG) were designed to open and utilize new pathways through the skin [3-5]. Such nano-porous transcutaneous pathways follow the track of lowest resistance but are only accessible to most adaptable (mixed lipid) aggregates [2]. The proviso is that the aggregates are driven through the skin by sufficiently large external force or pressure [3]. Transcutaneous osmotic (hydrotactic), electrical or hydrostatic gradients are three possible sources of such force/pressure [1].

Maximum ultradeformable vesicle adaptability is achieved by allowing the vesicle membrane to optimize its local composition under exposure to an external, spatially anisotropic stress [5]. The reaction involves spontaneous and reversible mixed lipid aggregate relaxation and deformation. Transfersome[®] membrane thus behaves as an extremely adaptable and responsive - 'smart' - material. This allows specially designed vesicles to slip through pores much narrower than the average vesicle diameter in an optimum, self-regulated fashion [5].

The resulting process of non-invasive transport through the skin consequently involves: 1) reversible vesicle-mediated opening of intercellular hydrophilic pathways, typically between epidermal cells and/or lipids; 2) strong response of epicutaneously applied ultradeformable vesicles to a naturally occurring transdermal hydration gradient or to an external transdermal electrical gradient; these ensure adequate vesicle hydration / electrical energy, respectively. Pursuing the goal, the ultradeformable vesicles seek to reach the water rich / low potential, viable tissue below the skin barrier. To the effect, they use the above-mentioned transcutaneous pathways, which normally play a key role in transdermal water evaporation. This allows the ultradeformable carrier mediated transcutaneous agent transport into the skin or into the body by means other than

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the skin poration. Examples of transdermal drug administration with ultradeformable vesicles [3,6] resulting in perfectly noninvasive and/or targeted delivery through the skin will be given.

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