ELASTIC VESICLES: INTERACTION WITH HUMAN SKIN AND DRUG TRANSPORT

JOKE A. BOUWSTRA, ANKO DE GRAAFF, WOUTER GROENINK and LOAN HONEYWELL
Leiden/Amsterdam Center for Drug Research, Gorlaeus Laboratories, Einsteinweg 55, 2300 RA, Leiden, The Netherlands

The most superficial layer of the skin, the stratum corneum, is the major barrier for permeation of most drugs. In order to increase the efficiency of drugs delivered via the skin, there is a demand for new transdermal drug delivery systems. Over the last two decades vesicles have been explored as potential carriers for drugs with the aim to facilitate drug transport across the stratum corneum. Recently a new series of vesicles have been introduced in which in addition to a fluid state of the membranes, the vesicles are also elastic. It is proposed that when applied onto the skin, these vesicles are able to deform, which is expected to facilitate partitioning into the stratum corneum and to increase the permeation rate of drugs across the skin. The new generation of elastic vesicles developed in Leiden, are entirely prepared from surfactants. It is the simultaneous presence in one membrane of different stabilizing molecules (such as bilayer forming surfactants) and destabilizing molecules (such as micelle forming surfactants), and their tendency to redistribute in the bilayers, that enables these vesicles to be more elastic than conventional vesicles. It has been postulated that elastic vesicles are transported intactly through the skin. We questioned the mechanism of action of this new generation of elastic vesicles. For this purpose permeation studies were carried out with two drugs, pergolide and lidocain. The formulations were loaded with the drug and applied onto human skin in vitro. The studies revealed a significant increase in drug transport after application in elastic vesicles compared to application in rigid vesicles. The drug permeation rate depended on the pH of the formulation and the volume of application. Furthermore drug co-treatment with vesicles was more successful than pretreatment, indicating that permeation enhancement of the vesicle components is not the only mechanism of action. Besides the permeation characteristics of drugs applied in vesicle containing formulations, we are also interested in the permeation pathways and whether or not an intact transport of these vesicles occurs. For this purpose vesicles were applied onto human skin in vitro and in vivo. When a fluorescent label was intercalated in the bilayers of the elastic vesicles, an inhomogeneous label distribution was observed. Thread-like penetration channels were formed never observed in previous studies. These channels might serve as penetration pathways for drugs. These results obviously demonstrate that elastic vesicles exert extraordinary interactions with stratum corneum compared to rigid
vesicles. Very recently elastic vesicles were applied onto human skin in vivo. Using visualization studies it was observed that after one hour of application, vesicular structures were present in deeper layers of the stratum corneum also in channel-like regions. However, no vesicles were visualized in the deepest layers in the stratum corneum. Intact permeation of vesicles into the stratum corneum was an exceptional observation. The electron microscopic and two-photon excitation studies were in excellent agreement both strongly suggesting a channel-like permeation. The mechanism by which the vesicles act as permeation enhancing formulation is most probably an extremely fast partitioning of the vesicles into the stratum corneum, after which the drug is released and permeate to deeper layers in the skin.