A Study into the Application of Ultrasound and Liposome Combination on Skin Permeability

A. Dahlan, O.H. Alpar and S. Murdan
Department of Pharmaceutics
The School of Pharmacy, University of London,
29-39 Brunswick Square, London WC1N 1AX
Email: afendi.dahlan@pharmacy.ac.uk

The skin is a good barrier and drug permeation has to be assisted for transdermal delivery. Enhancers include physical techniques such as application of electricity, ultrasound (US), chemical enhancers e.g. azone and vehicles e.g. elastic liposomes. Often, enhancers are used in combination for synergistic activity. Surprisingly, a combination of liposomes and electric pulses was found to decrease permeation of drugs through the skin compared to electricity alone (Essa et al, 2003); liposomal lipids were thought to accelerate the repair of electric-induced skin damage by infiltrating into skin lipid bilayers and thereby reduce drug flux.

The aim of our study was to determine whether such skin repair ability of liposomes would also apply to damage caused by low-frequency ultrasound. The latter is being investigated in our laboratories for skin vaccination. Thus, the effects of US and liposomes on the in vitro skin permeation of a model antigen (bovine serum albumin (BSA)) and the in vivo trans-epidermal water loss (TEWL - an indicator of skin barrier properties) were determined.

Permeation studies were conducted using Franz diffusion cells and full thickness rat skin. US waves (30% amplitude, 0.5s ON, 0.5s OFF, sonication time 2 min, 5 mm probe distance from skin) were applied to the skin via a coupling medium (PBS or SDS 1%w/v aqueous solution), followed by liposomes (MLVs or SUVs) for 5 or 60 minutes followed by the application of BSA. In vivo experiments were conducted in rats, with the same experimental protocols except that no vaccine was applied and TEWL was measured at different times post-liposome application.

The effect of liposome application on in vitro antigen flux through skin and on TEWL is shown in Tables 1 and 2 respectively. When coupling medium was PBS, application of liposomes (for either 5 or 60 min) post-sonication decreased BSA permeation into and through the skin compared to the controls (US, but no liposome). This negative effect of liposomes on permeation enhancement correlates with similar negative effect of liposomes on electrically-assisted enhancement. Liposomal lipids seem to repair the skin barrier post-sonication, before protein is applied. Interestingly, a 5 minute liposome application was as good as a 60 minute application. In vivo, 5 minute liposome application seems to reduce TEWL, with smaller vesicles being more effective than larger ones at skin repair.

When SDS was included in the coupling medium, liposomes reduced the protein flux, but did not have any significant effect on TEWL. SDS, a surfactant, is expected to be integrated within skin lipid bilayers and the subsequent addition of lipid (from the liposomes) to the skin does not seem to have any skin repair effect in vivo.

To conclude, liposomes have been shown to be effective in repairing skin which has been disrupted by ultrasound, but not when SDS is also present.

Table 1 Protein sonophoresis through rat skin.
(Data represents mean±SD, n=5)

Treatment	Radiolabelled protein permeated (cpm)
US	85770±3054
US+MLVs (5min)	58090±649
US+MLVs (60 min)	48880±2447
US(SLS)+MLVs (5 min)	57290±3870
US(SLS)	74840±3501

Table 2 TEWL values for animal treatment groups
(Data represents mean±SD, n=5)

Time	0 min	5 min	15 min	30 min	45 min	60 min
US	10.6	24.7	21.9	18.6	18.3	20.3
	±0.7	±5.9	±4.4	±3.1	±3.3	±3.9
US+MLVs	10.3	18.2	14.9	14.5	13.9	13.1
	±0.9	±3.9	±5.0	±3.8	±3.7	±3.5
US+SUVs	10.9	15.8	11.2	10.5	11.1	11.1
	±1.3	±1.7	±2.2	±1.5	±1.7	±1.9
US(SDS)	10.0	33.5	31.7	28.6	27.2	27.2
	±1.3	±1.8	±1.7	±2.6	±2.3	±3.4
US(SDS)+	10.9	31.0	24.8	24.8	23.6	23.0
MLVs	±0.6	±2.1	±3.5	±5.0	±4.3	±3.3
US(SDS)+	10.2	33.5	24.9	22.0	20.9	22.1
SUVs	±0.8	±2.5	±4.4	±5.1	±5.0	±4.5
SDS	11.4	15.8	11.3	10.3	10.5	10.0
	±1.1	±2.4	±1.2	±0.4	±1.3	±1.2

Essa, E.A. et al (2003) J. Control. Rel. **92**: 163-172