

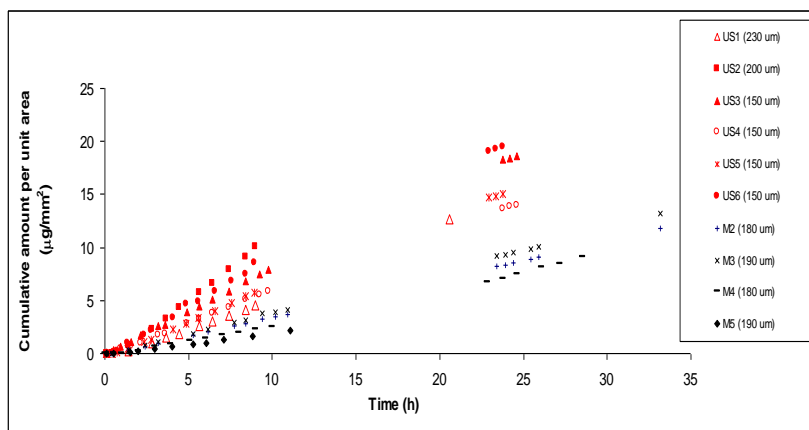
Low-frequency ultrasound to enhance topical drug delivery to the nail.Ana Torkar^a, Julijana Kristl^a, Sudaxshina. Murdan^b^aFaculty of Pharmacy, University of Ljubljana, Slovenia.^bThe School of Pharmacy, University of London, WC1N 1AX, UK.

The two most common disorders of the nail are onychomycosis (fungal infections of the nail plate and/or bed) and psoriasis. Onychomycosis is usually treated with oral antifungals, while psoriasis necessitates repeated monthly injections of corticosteroids into the nail folds. Ideally, these diseases would be treated topically to eliminate the inherent side effects of the current treatments such as pain, systemic adverse events and drug interactions, and to increase patient compliance. The effectiveness of topical therapy is, however, limited mainly by the very poor permeability of drugs in the nail plate. So far, only a few unguinal enhancers, such as N-acetyl cysteine, mercaptoethanol, N-(2-mercaptopropionyl) glycine, have been identified.

The aim of this study was to investigate the potential of low-frequency ultrasound as a physical technique to enhance the unguinal permeation of topically applied drugs.

Bovine hoof membranes (thickness \approx 150-200 μ m) were used as a model for the nail plate and metformin was used as a model drug. Low frequency ultrasound was applied to hoof membranes using a 13mm ultrasound probe placed at 1cm from the hoof membrane, via a coupling medium. A 50% intensity level (of the machine) was used for 1 min total sonication time, applied in a pulsatile manner (2 sec on – 2 sec off). Subsequently, the hoof membranes were removed from the sonication setup, disks were punched out and the membranes were sandwiched between donor and receptor compartments of modified Franz diffusion cells for permeation studies. The drug concentration in the receptor phase was measured at time intervals using UV spectroscopy.

Greater drug movement was found through ultrasound-treated hoof membranes (US) compared to control membranes (M) as shown in the Figure below. The transport parameters of the model drug, metformin, are shown in the Table below. Statistical analyses showed the flux and permeability coefficient were significantly different ($P < 0.05$) for ultrasound-treated and control membranes. These preliminary studies indicate the promise of low-frequency ultrasound as a physical unguinal enhancer and the need for further investigations. Optimisation of the ultrasound parameters – sonication time, intensity, duty cycle, probe shape, size and distance from the membrane – is expected to increase the enhancement of drug permeation.



	Control	Ultrasound-treated
Diffusion coefficient ($\times 10^{-4}$ mm ² /min)	1.4 (0.7)	1.1 (0.3)
Partition coefficient	2.3 (1.6)	6.5 (3.0)
Permeability coefficient ($\times 10^{-3}$ mm/min)	1.3 (0.3)	3.4 (1.3) *
Lag time (min)	55.8 (36.7)	66.6 (41.0)
Flux ($\times 10^{-3}$ µg/mm ² per min)	2.6 (0.6)	6.8 (2.6) *