

Thermal conductivity measurement: a promising tool for the study of drug skin penetration

¹Giovannelli L., ²Gustavsson M., ³Cossi R., ⁴Salmi L., ¹Segale L., ¹Pattarino F.
¹DISCAFF Dept., School of Pharmacy – University of Piemonte Orientale, Italy
²Hot Disk AB, Gothenburg, Sweden
³Qi srl, Pomezia, Roma, Italy
⁴Primary Health Care, Gothenburg, Sweden

Skin and in particular the stratum corneum, the more superficial layer of the epidermis, represents the main hindrance to the therapeutic effect of an active principle applied by the topical way.

Different approaches may be employed to enhance the percutaneous penetration of a drug in the skin: physical methods for instance ionophoresis, sonophoresis, etc or chemical substances (DMSO, alcohol, propylene glycol, etc...) which exercise their promoting effect through various mechanisms such as the modulation of the hydration of the skin, the alteration of the chemical-physical properties or the composition of the stratum corneum.

Among the chemical absorption enhancers, cyclodextrins (CD) represent one of the most recent attraction. These cyclic oligomers are able to interact with the lipid components and to extract them from the corneous layer (cholesterol and triglycerides), or to induce the alteration of cellular membranes by structural modifications, or they can modify the permeability of the skin and promote the penetration of molecules.

The evaluation of percutaneous absorption of bioactive molecules is performed through *in vitro* experiments using biological substrates as pig, rabbit and mouse on horizontal or vertical diffusion cells.

The aim of this work was to compare the results obtained with various semisolid preparations containing caffeine in permeation studies through pig skin with those obtained in *in vivo* with a new technique, Transient Plane Source (TPS) method. TPS is a patented technique, not invasive, fast (measurement time approximately 20 seconds) that does not require the employment of radiations; TPS is able to determine simultaneously thermal conductivity, thermal diffusivity and specific heat capacity of several materials.

The TPS technique can be also applied in the research field in order to estimate the modifications of the skin after the application of dermatological formulations.

The topical preparations used in this work contained 1% of caffeine; they were hydrogels made of Carbopol[®], Carbopol[®] and liposomes (prepared by high pressure homogenization) and the same systems added of hydroxypropyl- β CD, a synthetic derivative of native β CD. The rheological behavior of the formulations was comparable, as evaluated by means of a Brookfield rotational viscometer.

The permeation experiments were carried out using vertical Franz type diffusion cells, with available diffusion area equal to 1.77 cm² and volume of receptor compartment of 14 ml, (phosphate buffer solution 0.1 M, pH 7.4 \pm 0.1, 37 °C under stirring).

The receiving solutions were completely removed at specified time intervals. To maintain sink conditions, the receptor compartment was immediately refilled with fresh warmed buffer solution. At the end of the permeation experiments the skin was cut by a cryostat microtome into thin slices (100 μ m), that were opportunely treated for the extraction of the entrapped caffeine. The amount of caffeine in each sample was determined by HPLC.

The performances of semisolid formulations used as donor phases in the permeation experiments were also studied by the TPS technique, in order to measure the thermal conductivity of human skin after the application of caffeine-containing topical formulations. In a previous work it was observed that the values of skin thermal conductivity were different if lesions were present. In particular, the thermal conductivity of normal skin was greater than that of skin with lesions.

The TPS technique was therefore employed for preliminary experiments on volunteers, in order to inquire if the application of a semisolid preparation leads to

structural modifications of the skin and if such alterations are affected by the time of application.

The results obtained from the diffusion experiments indicated that liposomes and/or cyclodextrin significantly influence the permeation and distribution of caffeine in the skin.

These findings are in agreement with those achieved by *in vivo* thermal conductivity experiments. In fact, significant differences were observed in skin before and after applying formulations containing liposomes and CD. In particular the presence of liposomes and especially of cyclodextrin induces a reduction of the thermal conductivity. The values of conductivity observed for epidermis are comparable with those found in skin affected by pathology such as actinic keratitis. The reduction of thermal conductivity observed mainly for the stratum corneum of the skin has been associated to the potential interaction/disorganization caused by the phospholipids of liposomes and by hydroxypropyl- β CD; in particular CD is able to extract the lipid components of the corneous layer through formation of inclusion complexes.

Moreover, TPS technique evidenced that the structural modifications of the skin are related to the time of contact with the formulations.

Further trials are in progress in order to confirm the correlation between the results achieved by the *in vitro* permeation study with those obtained by Transient Plane Source method; a wider number of volunteers will be enlisted and preparations containing different drugs and absorption enhancers like mixtures of phospholipids and β - or γ - modified cyclodextrins will be employed.