DESIGN OF IN VITRO SKIN PERMEATION STUDIES ACCORDING TO THE EMA REGULATORY GUIDELINES ON THE QUALITY OF TRANSDERMAL PATCHES

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Transdermal patches and medicated plasters are designed to sustain effective systemic or loco-regional drug concentrations, respectively. In both cases, drug skin permeation is a critical attribute from the early stage of pharmaceutical development. In 2014, the EMA introduced the “Guideline on the quality of transdermal patches”, in which the importance of equivalence of drug fluxes (*J*) obtained from in vitro skin permeation study was particularly emphasized to generic or abridged applications for the marketing authorization or post-approval changes. The Agency proposed a similar approach in the “Draft guideline on quality and equivalence of topical products”, which was released for public consultation in 2018.

This work provides information on the set-up of in vitro skin permeation studies and the statistical evaluation of obtained *J*[1]. In particular, the impact of the inter-sample variability on the equivalence assessment was deeply investigated by using patch/plaster pairs containing propranolol, diclofenac or nitroglycerin.

The in vitro permeation studies were performed by Franz diffusion cell (permeation area: 0.636 cm^2; receptor volume ≈ 3 mL) using human epidermis as a membrane. The skin integrity was determined according to a standard internal procedure based on electrical resistance[2].

Considering the kinetic nature of the *J*, the same statistically approach for assessing bioequivalence in a parallel clinical trial was applied to the in vitro permeation studies. The parallel design was selected since the two tested treatments were assigned randomly at each experimental unit (i.e., Franz cells plus skin membrane) that was exposed univocally and independently to each treatment. The SAS Two One-Sided Test Procedure (TOST; $\alpha = 0.05$) was used for assessing the equivalence of the treatment *J* in the logarithmic form. The acceptability interval for the difference of the *J* means in the log scale is set at 0.8-1.25 in agreement with the EMA guideline. In the case of data presenting a high *J* variability, the interval was widened following the same statistical protocol accepted by the EMA for highly variable drug products in bioequivalence studies.

The main outputs were attributable to the definition of acceptability interval and number of replicates to be performed. For example, the equivalence of propranolol and nitroglycerin patches (*J* variability < 25%) was assessed using 6 replicas and a confidence limit within the 0.8-1.25 range. However, in the case of nitroglycerin patches, the equivalence could only be assessed if *J* were normalized for the effective patch area due to the different patch area activity of the tested formulations. In contrast, equivalence of diclofenac plasters, which exhibited a variability near the 50%, were demonstrated increasing the number of replicas for each tested formulation (i.e., 20 skin samples) and widening the acceptance range according to a statistical approach proposed (i.e. 0.69–1.43).

1. F. Cilurzo, U.M. Musazzi, S. Franzé, G. Fedele, P. Minghetti. Design of in vitro skin permeation studies according to the EMA guideline on quality of transdermal patches. Eur. J. Pharm. Sci. (2018) 125: 86-92;
2. U.M. Musazzi, A. Casiraghi, S. Franzé, F. Cilurzo, P. Minghetti. Data on the determination of human epidermis integrity in skin permeation experiments by electrical resistance. Data in Brief (2018) 21: 1258–1262.