PP-020

NEW VERSATILE DIFFUSION CELL FOR RAPID AND HANDY PERMEABILITY ASSESSMENTS IN EXPERIMENTAL MEDICINE DEVELOPMENT IN HOSPITAL PHARMACY

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Introduction

The development of experimental medicines (EM) for clinical trials is a tedious but lucrative activity for hospital pharmacies (HP). This activity requires the compounding of poorly described compounds with often unfavorable biopharmaceutical characteristics. National competent authorities (NCA) now require a high level of proof to approve such preparations. To evaluate (i) security of use and (ii) potential efficiency of EM, *in vitro* characterization of tissular bioavailability can be performed on devices called diffusion cells.

Purpose

Available diffusion cells are research devices that are not well adapted to the context of HP. We developed and validated a new, easy to use, inexpensive and versatile diffusion cell called VitroPharma, meant to obtain permeation and penetration data across a wide rang of biological or artificial membranes. Photographic operating protocol for VitroPharma is displayed in figure 1.

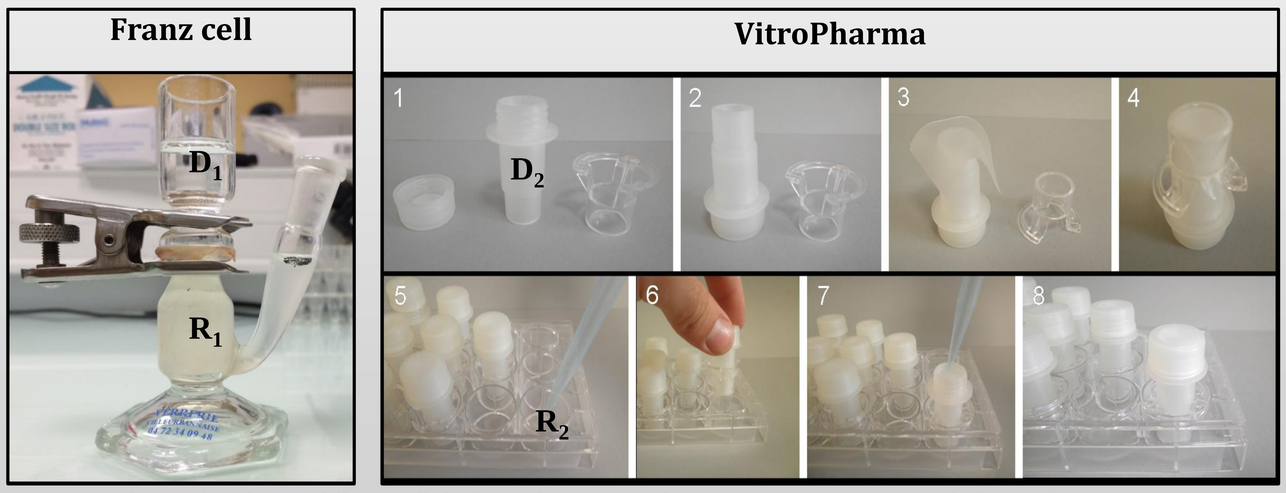

Figure 1 : Photography of Franz diffusion cell displaying donor (D1) and receptor (R1) compartments and photographic operating protocol for VitroPharma: (1) Presentation of the device including donor compartment (D2) with its screwable cap and sealing system. (2) Empty donor compartment is turned head down. (3) Membrane (e.g., silicone membrane) is deposited onto donor compartment. (4) Sealing system is hermetically applied by simple pressure. (5) Receptor fluid is poured in multiple well plate receptor compartment (R2). (6) Donor and membrane assemblage is positioned on receptor compartment. (7) Donor fluid is poured in donor compartment at t = 0. (8) Permeability assay takes place under controlled temperature conditions.

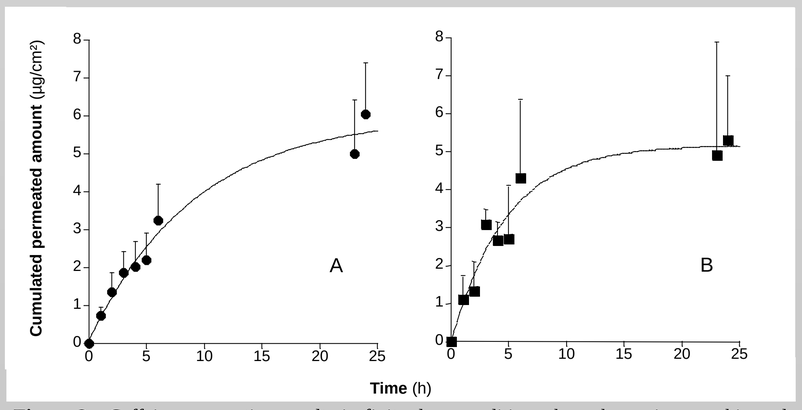

Figure 2 : Caffeine permeation results in finite dose conditions through porcine ear skin and modelization thereof obtained (A) using Franz cell with an aqueous liquid receptor (i.e., 0.9% NaCl solution) and (B) using VitroPharma with same aqueous liquid receptor. Each value is the mean ± SD of at least 4 experimental determinations

		10^7.Kp *(cm/s)*	Jss *(µg/cm²/h)*	Tlag *(h)*
caffeine	Franz cell	8.40 ± 1.10	30.25 ± 3.95	3.14 ± 1.12
	VitroPharma	8.35 ± 0.48	30.08 ± 1.73	0.43 ± 0.25*
testosterone	Franz cell	10.46 ± 1.32	3.77 ± 0.47	3.09 ± 0.09
	VitroPharma	10.15 ± 0.32	3.65 ± 0.11	0.76 ± 0.24*

* Significant difference as compared to Franz cell

Table 1 : Permeability parameters for caffeine and testosterone through silicone membrane obtained in infinite dose conditions in Franz cell and VitroPharma

Materials & Methods

VitroPharma was developed in collaboration with a local plasturgist. Validation studies were performed using caffeine and testosterone as model hydrophilic and lipophilic compounds, respectively. Finite dose conditions where performed *ex vivo* on porcine ear skin explants and using commercially available formulations of model compounds, as to simulate real in-use administration conditions. Oppositely, infinite dose conditions where performed *in vitro* on silicone membranes and using simple solutions of model compounds, as to obtain reproducible permeability parameters. VitroPharma was compared to reference widely used diffusion cell (i.e., Franz cell, figure 1)

Results

Permeation results in both type of cells were fitted to mathematical models following Fick's laws of diffusion for finite (figure 2) and infinite dose (figure 3 and 4 for caffeine and testosterone, respectively). Permeability characteristics given by model could be compared using non-parametric tests. Concerning finite dose assays, no significant difference was observed between Franz cell and VitroPharma for (i) maximum quantity of caffeine retrieved in receptor compartment after 24 hours (i.e., 6.04 ± 2.70 µg/cm² and 5.32 ± 3,34 µg/cm² for Franz cell and VitroPharma, respectively), and (ii) area under the cumulated permeated amount curve (AUC) over 24 hours (i.e., 85.01 ± 44.44 µg.h.cm² and 96.17 ± 41.62 µg.h.cm² for Franz cell and VitroPharma, respectively).
Concerning infinite dose conditions, no significant difference was observed between Franz cell and VitroPharma for permeability coefficient (Kp),and steady state fluxes (Jss) given by model as exposed in table 1. Only a reduced lag time (T lag) was evidenced in VitroPharma, that could turn out to be profitable for rapid comparison of permeability profiles.

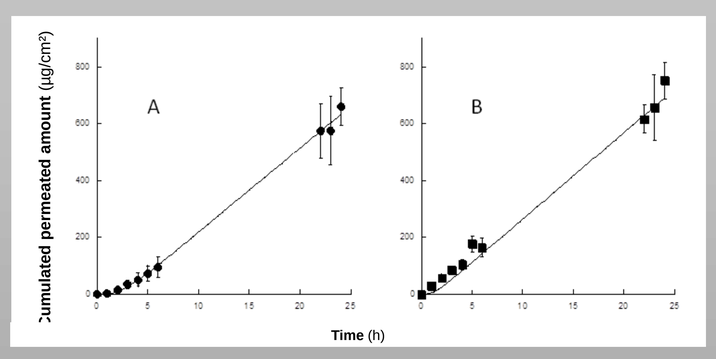

Figure 3 : Caffeine permeation results in infinite dose conditions through silicone membrane and modelization thereof obtained (A) using Franz cell with an aqueous liquid receptor (i.e., 0.9% NaCl solution) and (B) using VitroPharma with same aqueous liquid receptor. Each value is the mean ± SD of at least 4 experimental determinations

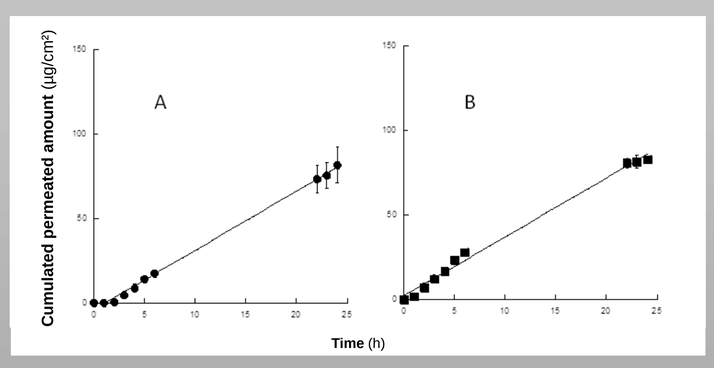

Figure 4 : Testosterone permeation results in infinite dose conditions through silicone membrane and modelization thereof obtained (A) using Franz cell with an aqueous liquid receptor (i.e., 2% albumin solution) and (B) using VitroPharma with same aqueous liquid receptor. Each value is the mean ± SD of at least 4 experimental determinations

Discussion

VitroPharma was found equivalent to Franz cell in harmonized experimental conditions. Furthermore, VitroPharma enables to determine tissular penetration kinetic (figure 5) which in return enables to prefigure EM medicine active ingredient exposure and safety profile in future clinical trial. Such data is presented to NCA in EM pharmaceutical dossier to apply approval.

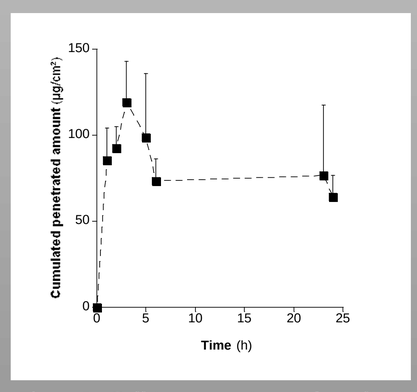

Figure 5 : Caffeine penetration results in finite dose conditions into porcine ear skin and modelization thereof obtained using VitroPharma with an aqueous liquid receptor (i.e., 0.9% NaCl solution). Each value is the mean ± SD of at least 4 experimental determinations

Conclusion

VitroPharma is adapted to EM development. Furthermore, it can be used in quality control of hospital preparations containing BSC class III and IV compounds and in other assessments where penetration and permeation data in a biological or artificial (i.e., gloves, smooth conditioning device) membranes is required in HP.

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Références

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