2440

# DEVELOPING A METHOD FOR SKIN PAMPA™ TO TEST TRANSDERMAL PATCHES

Gábor Vizserálek[3], Bálint Sinkó[1,2], Konstantin Tsinman[2], Krisztina Takács-Novák[3]

*1) SinkoLAB Scientific, Budapest, HUNGARY 2) Pion Inc., Billerica, MA, USA 3) Semmelweis University, Budapest, HUNGARY*

## PURPOSE

Using the skin as absorption site presents unique challenges that have facilitated the progression of transdermal drug delivery in the past decades. Efforts in drug research have been devoted to find a quick and reproducible model for predicting the skin penetration of molecules, because the in vitro or in vivo animal models are expensive, labor-intensive and suffer from poor reproducibility.

The Parallel Artificial Membrane Permeability Assay [1] (PAMPA) has been extended for prediction of transdermal penetration by developing the "skin-mimetic" artificial membrane [2]. Having a high standardization potential and being a high throughput method, PAMPA can become an ideal model for prediction of skin penetration in early stages of drug development.

In the present study commercially available transdermal patches (3 nicotine, 2 fentanyl, 1 rivastigmine and 1 ketoprofen) are studied. Data are compared to the declared permeation speed that is indicated by the manufacturers.

## METHODS

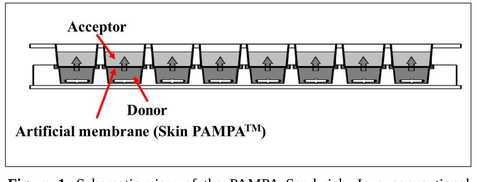



**Figure 1.** Schematic view of the PAMPA Sandwich. In a conventional PAMPA application the permeation is going from the bottom (donor) compartment to the top (receiver) compartment.

The pre-coated Skin PAMPA™ plates were purchased from Pion, Inc., and were used after an overnight hydration. The traditional method was modified to study transdermal patches. Patches were applied as they are without any chemical treatment.

The bottom part of the Skin PAMPA™ Sandwich has been replaced with a deep well reservoir to provide enough space for patches to be applied in whole pieces from the bottom side of the membrane. Britton-Robinson buffer at pH = 7.4 has been used as acceptor solution. Acceptor solution has been sampled after 0.5, 1, 3 and 6 hours (in some cases 12 and 24 hours were also included) of incubation. Direct UV spectrometry (nicotine, ketoprofen and rivastigmine) and LC-MS (fentanyl) have been used to analyze the samples.

## RESULTS

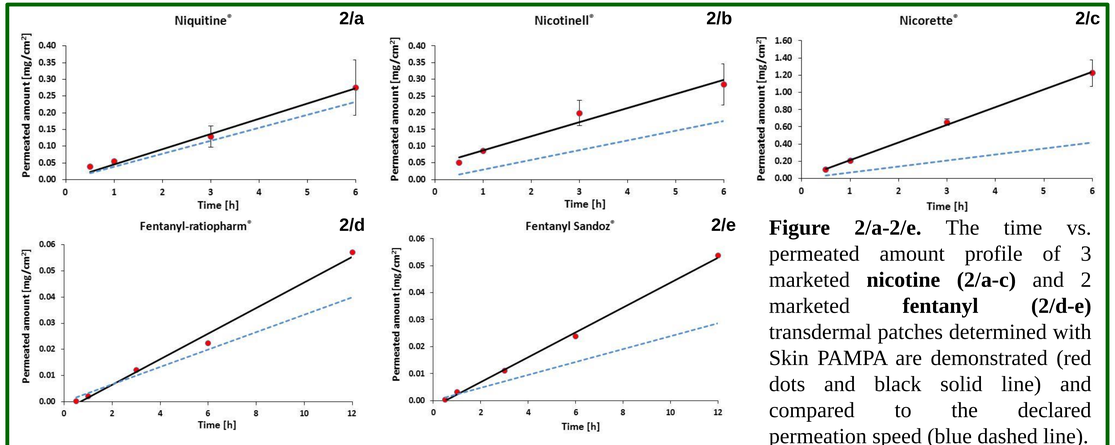



**Figure 2/a-2/e.** The time vs. permeated amount profile of 3 marketed **nicotine (2/a-c)** and 2 marketed **fentanyl (2/d-e)** transdermal patches determined with Skin PAMPA are demonstrated (red dots and black solid line) and compared to the declared permeation speed (blue dashed line).

The established time profiles are 20-40 % higher than the expected curves that is caused by the well described edge-effect [3-4]. The edge effect means a lateral diffusion within the adhesive film of the patch that increase virtually the assay surface if the total surface of the patch is not covered by the assay cell. This effect occur in Franz cell assay and in PAMPA assay as well and cause a tendentious error that can be taken into account. Regardless of this effect Skin PAMPA™ assay appears to be useful for comparison and to determine ranking order.

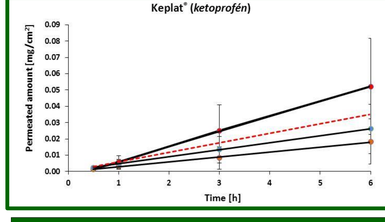



**Figure 4.** The time vs. permeated amount profile of a marketed transdermal patch containing **ketoprofen** is shown. Study of 3 same patches has been performed (3 solid lines), and the mean of these 3 measurements is demonstrated by the red dashed line. Declared permeation speed is not indicated by the manufacturer. Higher standard deviation was experienced than in cases of other products. This may be caused by the inhomogeneous distribution of the API on the surface of the patches.

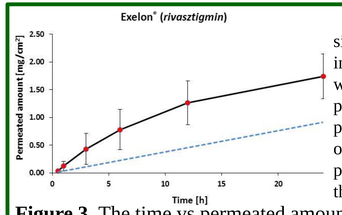
## REFERENCES

[1] A. Avdeef: Absorption and Drug Development, 2nd edition, Wiley-Interscience, 2003

[2] B. Sinkó, T.M. Garrigues, G.T. Balogh, Z.K. Nagy, O. Tsinman, A. Avdeef, K. Takács-Novák: Skin PAMPA: A new method for fast prediction of skin penetration. Eur. J. Pharm. Sci., 2012, 45, (5): 698-707

[3] J. Hadgraft, d. Lewis, D. Beutner, H. M. Wolff: In vitro assessments of transdermal devices containing nitroglycerin. Int J. Pharm. 1991, 73, 125-130

[4] J. C. Olivier, S. Rabouan, W. Couet: In vitro comparative studies of two marketed transdermal nicotine delivery systems: Nicopatch® and Nicorette®. Int. J. Pharm. 2003, 252, 133-140.




The measured data are significantly higher than the indicated permeation speed, which can caused by a penetration enhancer of the patch. The artificial membrane of the Skin PAMPA™ is probably more sensitive to this than the human skin.

**Figure 3.** The time vs permeated amount profile of a transdermal patch containing **rivastigmine** is shown.

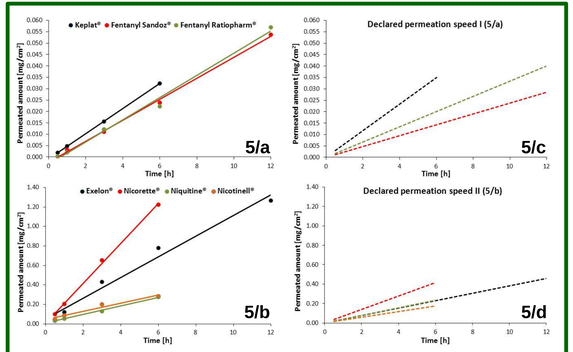



**Figure 5/a-5/d.** All the measured data (**5/a-b**) and the declared permeation speed (**5/c-d**) can be observed in this figure. Our results indicate that the Skin PAMPA™ model can determine the ranking order of the transdermal patches thus it can provide very valuable information about the behaviour of the patches during the development process of the transdermal drug delivery systems.

## CONCLUSIONS

The present study demonstrated the usage of Skin PAMPA™ skin penetration model system for transdermal patch testing. The results suggest that Skin PAMPA system can serve as a useful tool for rapid evaluation of transdermal patches, though this system is also affected by the edge-effect similarly to most of the available in vitro permeation models. Considering the edge-effect results serve as a good estimation for API permeation.