

# IN VIVO EVALUATION OF SKIN PERMEABILITY OF DRUGS AFTER APPLYING ADHESIVE TRANSDERMAL PATCHES

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## Introduction

The skin permeability of drugs can be evaluated by analyzing the drug concentration in the stratum corneum before reaching steady state. We demonstrated that the steady state penetration rate of steroids was predicted under in vivo conditions on the basis of the tape stripping method [1]. At two time intervals,  $t_1$  and  $t_2$ , following the onset of skin absorption experiment, the drug amount entered in the stratum corneum was measured by tape stripping, and then the ratio of the amounts at  $t_1$  and  $t_2$ ,  $t_1/t_2$ , can be related to the dimensionless quantity,  $Dt_1/h^2$ , where  $D$ ,  $t_1$  and  $h$  are the diffusion coefficient in the stratum corneum, the duration of patch application ( $t_1 < t_2$ ) and the thickness of the stratum corneum, respectively.

This method is simple and useful to evaluate the skin permeability in vivo after application of drug solution, ointments and non adhesive transdermal devices. If the device is an adhesive patch, on the other hand, the appreciable amount of the drug molecules distributed near the surface of the stratum corneum is removed together with a part of stratum corneum. The value of  $m_1$  and  $m_2$  may, therefore, be significantly underestimated for adhesive transdermal patches. For conventional adhesive devices, the effect of the drug molecules removed together with the device must be corrected before evaluating the weight ratio  $m_1/m_2$ .

In this study, we propose a simple and safe in vivo method for evaluating the skin permeability following various adhesive transdermal drug delivery systems. The steady state flux can be determined after correcting for the effect of drug amount removed together with the adhesive patch at each time interval  $t_1$  or  $t_2$ . The skin permeability of four model drugs is then evaluated from the present in vivo method. In vitro skin penetration experiments are also carried out using side-by-side diffusion cells. The skin permeability of the model drugs evaluated from the present in vivo method is compared to those obtained from the conventional in vitro skin permeation experiments.

## Method

In initial transient stage shortly after the onset of transdermal drug application, the drug concentration near the boundary between the stratum corneum and viable skin remains zero or at very low level. Under such conditions, the ratio of the amount of the drug entering in the stratum corneum at two time intervals,  $t_1$  and  $t_2$ , is given by [1,2]:

$$\frac{M_1}{M_2} = \frac{1 - \sum_{n=0}^{\infty} 8 \exp\left\{-D(2n+1)^2 \pi^2 t_1 / h^2\right\} / \{(2n+1)^2 \pi^2\}}{1 - \sum_{n=0}^{\infty} 8 \exp\left\{-kD(2n+1)^2 \pi^2 t_1 / h^2\right\} / \{(2n+1)^2 \pi^2\}} \quad (1)$$

If the transdermal delivery system is an adhesive patch, the surface layers of stratum corneum are partly removed together with the device. The apparent amounts,  $m_1$  and  $m_2$ , are therefore appreciably underestimated. It is obvious that the amounts,  $m_1$  and  $m_2$ , should be corrected for the drug molecules removed with the adhesive device in order to evaluate the diffusion coefficient by using Eq.(1) and the resulting concentration on the surface of the stratum corneum  $C_s$ .

$$C_s = \frac{2M\pi^2}{ah \left\{ \pi^2 - 8 \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(\frac{-D\pi^2 t n^2}{h^2}\right) \right\}} \quad (2)$$

The amount of drug in the stratum corneum is completely removed by tape stripping at two time intervals,  $t_1$  and  $t_2$ , shortly after the patch application. The apparent amount ratio  $m_1/m_2$  at the two time intervals is then calculated based on these experimental values. The diffusion coefficient  $D$  can be evaluated from Eq.(1) by using the apparent  $m_1/m_2$  value obtained as the first approximation.

In general, the amount of drug removed together with the adhesive patch would be more appreciable for the shorter time intervals because of the steeper concentration gradient near the surface of the skin. In some cases, therefore, the ratio  $m_1$  and  $m_2$  becomes smaller than the square root of  $(1/k)$  where the diffusion coefficient can not be determined. Under these circumstances, we assume that the diffusion coefficient is  $4 \times 10^{-11} \text{ cm}^2/\text{s}$  as the first approximation for the present model drugs [3].

The concentration distribution in the skin is given by [4]:

$$C = C_s \left(1 - \frac{x}{h}\right) - \frac{2}{\pi} \sum_{n=0}^{\infty} C_s \sin \frac{n\pi x}{h} \exp\left(-\frac{Dn^2 \pi^2 t}{h^2}\right) \quad (3)$$

where  $C_s$  is the drug concentration on the surface of stratum corneum. If the fraction of the stratum corneum removed with the patch is known, the surface concentration  $C_s$  can be evaluated by integrating the concentration distribution Eq.(3) on the basis of the amounts of the drug,  $m_1$  and  $m_2$ , corrected for the amount of drug removed with the patch respectively. The surface concentration  $C_s$  was then evaluated as the average value of  $C_s$  at two time intervals.

## Materials and Experimental Method

In order to determine the amount of drug removed together with the stratum corneum, a matrix-type drug delivery system containing various loading dose has been developed and applied on the surface of the hairless mouse skin. Various amount of model drugs, progesterone, 17 $\beta$ -estradiol, testosterone or hydrocortisone were dispersed in the EVA toluene mixture with 41% VA content. The drug-EVA polymer mixture was poured onto PET film by using a doctor blade. The drug containing matrix device was then formulated with the thickness of 45 $\mu$ m. The drug loading dose for hydrocortisone, estradiol, testosterone and progesterone is 0.8%, 5%, 7% or 15% by weight, respectively.

The matrix type adhesive device was applied on the surface of the hairless mouse abdominal skin for 5 min ( $t_1$ ) and 30 min( $t_2$ ) and then the device was removed. The stratum corneum was removed completely by 20 tape stripping. The total amount of drug molecules in the tape was then measured after total extraction with methanol. The amount of the stratum corneum removed together with the device was also determined by weighing the device before and after application using the matrix device. In order to compare the penetration rate, the in vitro penetration experiment was also carried out using side-by-side diffusion cells [2]. The in vivo rate of penetration was then compared with the in vitro profiles.

## Results and Discussion

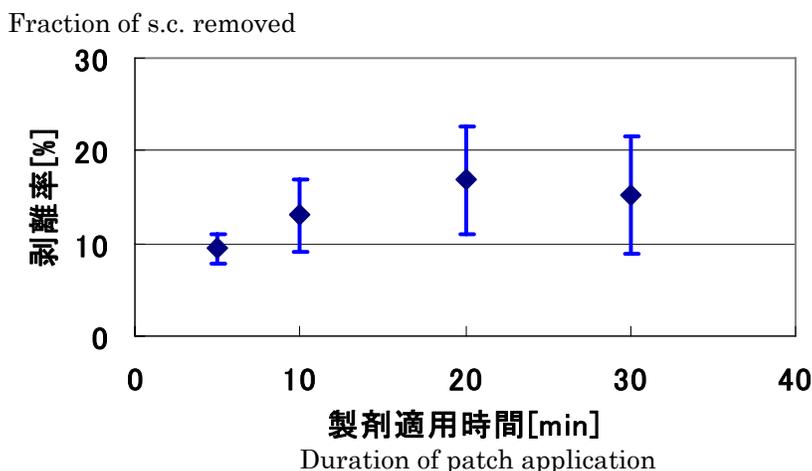


Fig. 1. effect of the duration of patch application on the fraction of the stratum corneum removed together with the transdermal patch.

Figure 1 shows the fraction of the stratum corneum removed with the transdermal device. The amount of the stratum corneum removed initially increased rapidly with increasing the duration of application of 30 min or longer. The fraction is not significantly influenced by the presence of the drug molecules during the patch application from 5 min to 30 min. For the application period of 5 min, 10min, and 30 min, the fraction of the skin removed is 11% and 16 %, and 22%, respectively.

The steady state rate of penetration evaluated from the present approach was listed in Table 1. As can be seen, the surface concentration at  $t_1$  and  $t_2$  was found to be constant. The steady state flux determined from the present in vivo approach was plotted as a function of the octanol/water partition coefficient of drugs in Fig.2. As can be seen, the present in vivo flux predicted agreed reasonably well with the in vitro profiles. The in vitro penetration rate of testosterone is a little higher than the in vivo rate indicating that the hydration during the long-term penetration experiment (24 hours) may give rise to the increased penetration rate under the in vitro conditions.

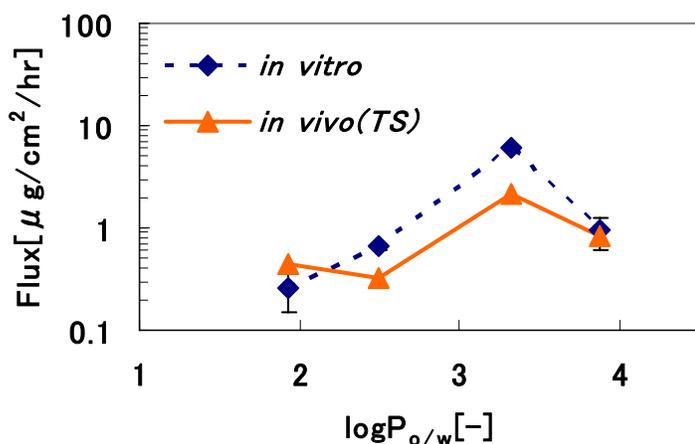


Fig.2. Comparison of the steady-state flux of hour model drugs (hydrocortisone, estradiol, testosterone, progesterone). Triangles: the present in vivo method, Diamonds: in vitro long-term penetration experiment.

The present in vivo method neglects the effect of drug binding in the stratum corneum. If the drug is appreciably bound in the stratum corneum, the amount of drug accumulated in the skin at the initial two time intervals is obviously overestimated. The present in vivo approach should therefore be applied to the drug whose skin binding is not significant. We have reported that the drug binding in the stratum corneum for the present model drugs is insignificant from the in vitro penetration and release experiment [5].

## References

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