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A study of the adhesive–skin interface: correlation between adhesion and passage of a drug

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Abstract

The phenomena taking place at the patch–skin interface, in particular the adhesion of a pressure sensitive adhesive (PSA) film loaded with drug and the partition of the drug between the patch and the skin were correlated. The kinetics of adhesion as well as those of drug passage were studied in detail. Adhesion data were collected from peel test either on skin or on a polymer model. Passage of the drug was studied in a simple system composed of PSA film stuck on skin. In some experiments the film was left on the skin throughout the experiment; in others, it was periodically removed and stuck on again to keep the adhesion force constant during the whole of the experiment. We observed a rapid increase of the drug content in the skin until a plateau was reached. One adhesion for the whole experiment or several adhesions gave a similar curve. The main difference was the rate of increase of skin drug content and the value of the plateau. Different hypotheses concerning the relationship between the adhesion of this PSA and changes in the flux of drug have been put forward. However, it is difficult to extrapolate from this model to the in vivo situation because of variation both between individuals and with time. © 2000 Elsevier Science B.V. All rights reserved.

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The percutaneous route is now a recognised way of administering drugs. Since the basic mechanisms are still unclear, many experiments have to be performed (Good et al., 1986) to design a new transdermal therapeutic system (TTS). These are mainly intended to evaluate adhesion of the system to the skin (Leterme et al., 1992; Lin, 1996), or to study the permeability of the drug (Potts and Guy, 1992).

The system we have studied is intended for hormonal replacement therapy (Gordon, 1995).

We wanted to investigate adhesion and passage at the same time in order to better understand their relationship.

Trimegestone [17β-(2-hydroxy-1-oxopropyl)-17α-methylestra-4,9(10)-dien-3-one], a drug

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derived from progesterone and patented by Hoechst–Marion–Roussel (Romainville, France), was used in this study. As a very potent progestative, this drug is a good candidate for transdermal administration. We chose to study a silicone-based transdermal therapeutic system (Ulman and Lee, 1988).

Drug and a heptane suspension of the silicone adhesive (BIO-PSA® High tack, Dow Corning Corporation) were mixed with a laboratory stirrer to obtain a formulation containing 3% w/w drug used for preparation of film by enduction.

In some experiments, semi-industrial patches prepared with the same materials and with comparable techniques of coating were used.

Adhesion onto the skin was estimated by the 90° peel test using a traction machine (Zwick). Samples (10 mm wide by 45 mm long) of placebo patch were stuck on the right forearm of healthy volunteers.

The mean adhesion force on the forearm of ten healthy volunteers was 1.2 ± 0.5 N.

Due to interindividual variations, supply difficulties and other problems related to biological material, we replaced the skin by a polymeric substrate: PTFE. Adhesion forces developed by silicone on this substrate are in the same range as those on skin because of quite similar surface properties for both total energy and polar/apolar components. Peel force studies as a function of adhesion time showed variations of adhesion forces (Fig. 1). Instantaneous adhesion between 1 and 2 N is comparable to the 1.2 N obtained on skin. After 180 min of contact the peel force reaches a plateau around 5 N.

This phase of increasing adhesion, lasting about 180 min, is worthy of particular study. When the plateau is reached, it probably means that the structural organisation of the adhesive at the interface and in the bulk is stabilised.

Some experiments were performed on placebo patches and others on patches loaded with 3% of drug as shown in Fig. 1. The two curves are quite similar, therefore adhesion seems to be indepen-

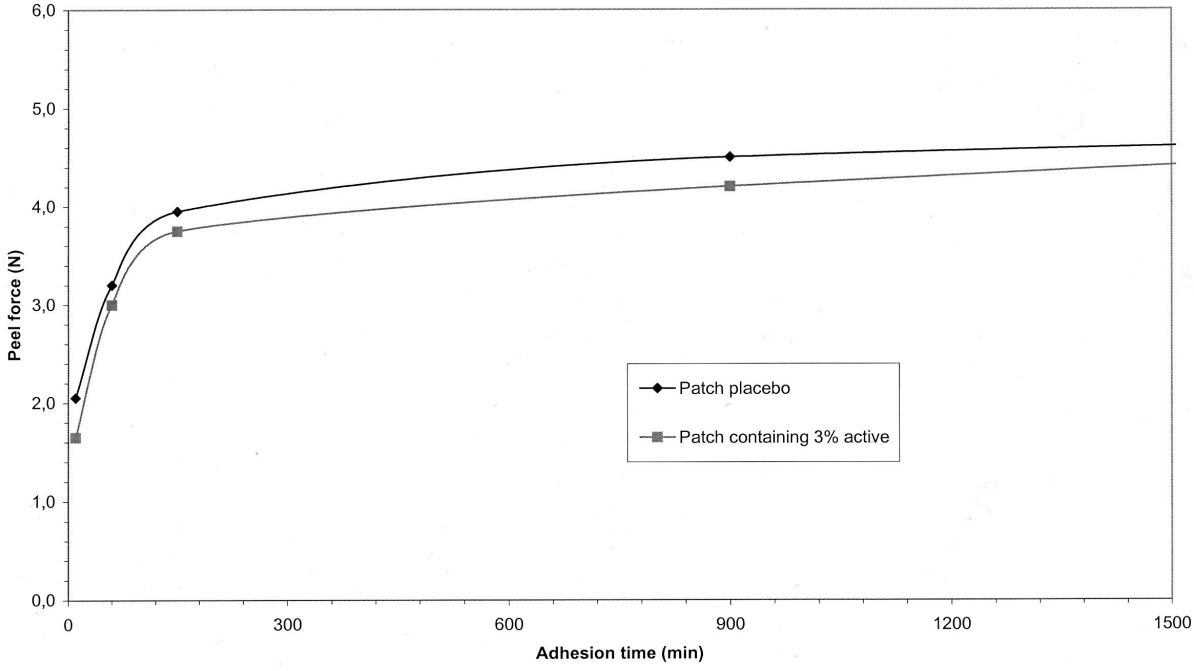

Fig. 1. Evolution with time of peel force needed to remove placebo and active patches from a PTFE (polytetrafluoroethylene) substrate.

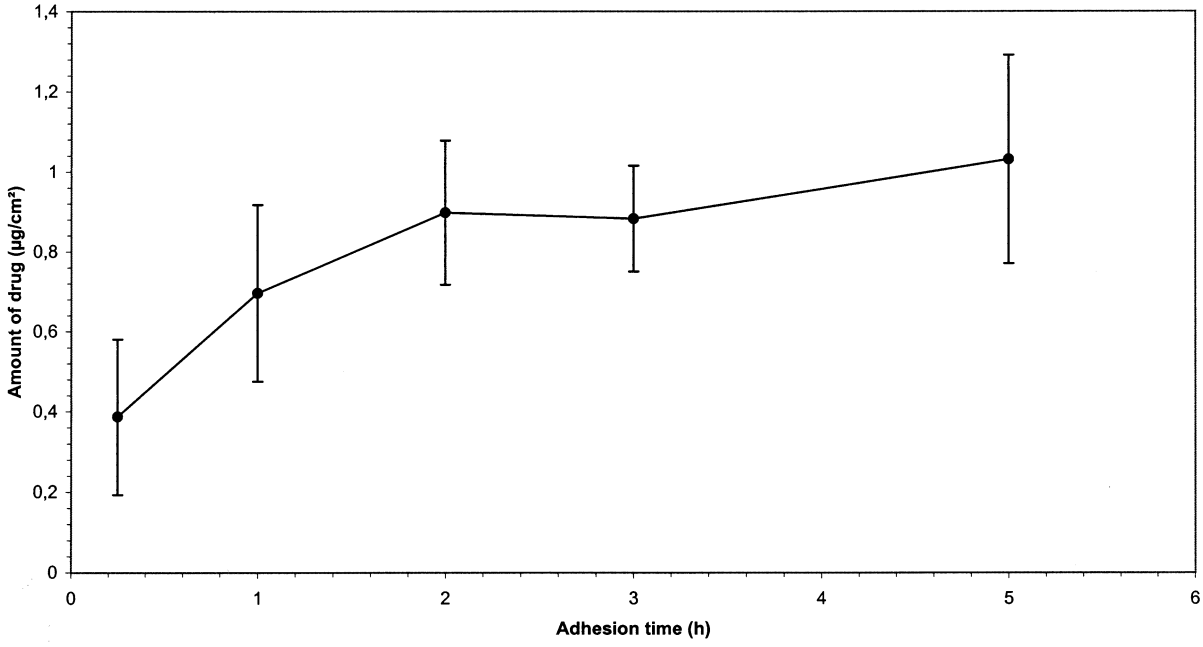

Fig. 2. Cumulative amount of drug detected in the skin as a function of adhesion time. A round patch (surface 1.74 cm^2) containing 3%w/w of drug was stuck on a 300 μm thick sample of human skin.

dent of the quantity of drug in the patch (in the range 0 to 3%). This means that the variations of adhesion observed during experiments are not due to the depletion of the drug content in the patch.

The results concerning drug release into human skin (Fig. 2) show that passage of the drug is quite substantial at the beginning and then reaches a plateau. A flux can be calculated as the difference of drug in the skin between two measurements. This was 1.600 $\mu g/cm^2$ per h during the first 15 min and fell to 0.400 and 0.200 $\mu g/cm^2$ per h during the first and second hour, respectively. After 2 h, a plateau of the total amount of drug in the skin was reached although the amount of drug released (1.6 $\mu g/cm^2$) was quite small compared with the initial amount in the patch (≈ 300 $\mu g/cm^2$).

However, the skin was not saturated with drug because other experiments with different methodologies (Figs. 3 and 4) resulted in a larger amount of drug release. Thus the slowing down of the drug passage from film to skin could be explained by film–skin interactions, partition properties, cutaneous permeability or adhesion conditions. This aspect will be considered further. During experiments described above, adhesion developed and improved with time, as shown by peel tests. This mechanism could affect the partition and diffusion of the drug into the skin and enhance the drug release. For a better understanding of this phenomenon we wanted to study the film–skin passage of the drug under conditions of constant adhesion.

In order to achieve constant adhesion conditions over a long period, the film was removed and re-stuck after a defined period.

Three films (containing 3%w/w of drug) of 95 μm, about 150 μm and about 210 μm thickness were manufactured for these experiments on 300 μm thick skin. 'Stabilised' adhesion methodology was used with a period of 1 h between each application. Results are reported in Fig. 3 for 1 h, twice 1 h, three times 1 h, and five times 1 h adhesion.

After 1 h, the drug concentration in the skin is close to 0.8 $\mu g/cm^2$, regardless of the film tested. For the 95 μm thick film, the drug content in the skin remained stable. For the 150 μm thick film, it

increased moderately. For the 210 μm thick film, there was a large increase during the second hour, and then a gradual augmentation of drug content.

The films used had the same drug concentration, so a thicker film contained a higher total amount of adhesive and drug. After 2 h, the mean amounts of drug released were 0.83 ± 0.15, 1.23 ± 0.38 and 2.95 ± 0.37 μg/cm^2, respectively for patch thicknesses of 95, 150 and 210 μm.

This results lead to the conclusion that increased film thickness can explain the higher quantities of drug passing in the skin in the absence of modifications in adhesion.

In some 'stabilised' adhesion trials we studied the influence of the elapsed time between each re-application.

Fig. 4 shows the amount of drug in the skin after each successive bonding. For adhesion intervals of 0.25 h the amount of drug increased slowly until a plateau is reached at 0.6 μg/cm^2. When the adhesion interval was increased from 0.25 h to 1 h and to 2 h, the mean amounts of drug found into the skin were 0.60 ± 0.05, 0.85 ± 0.14 and 1.48 ± 0.50 μg/cm^2, respectively.

These studies show that the overall capacity for cutaneous absorption differs as a function of the adhesion conditions. Removing the patch periodically limits the force of adhesion and keeps it constant. After the destruction of the first film–skin adhesion, the amount of drug in the skin can still increase. This could be due to a modification of the stratum corneum; essentially a stripping of keratinocytes. However, after this first event, the passage of new drug molecules slows down. The amount of drug in the skin does not increase further because subsequent bonding is too weak and adhesion no longer develops.

Thus this silicone transdermal therapeutic system has an adhesion which develops during the first 3 h and then stabilises. In this study we showed that the passage of Trimegestone occurs mainly during these first 3 h, after which it practically ceases. These results confirm the hypothesis that the passage is the result of two mechanisms taking place at the adhesive–skin interface.

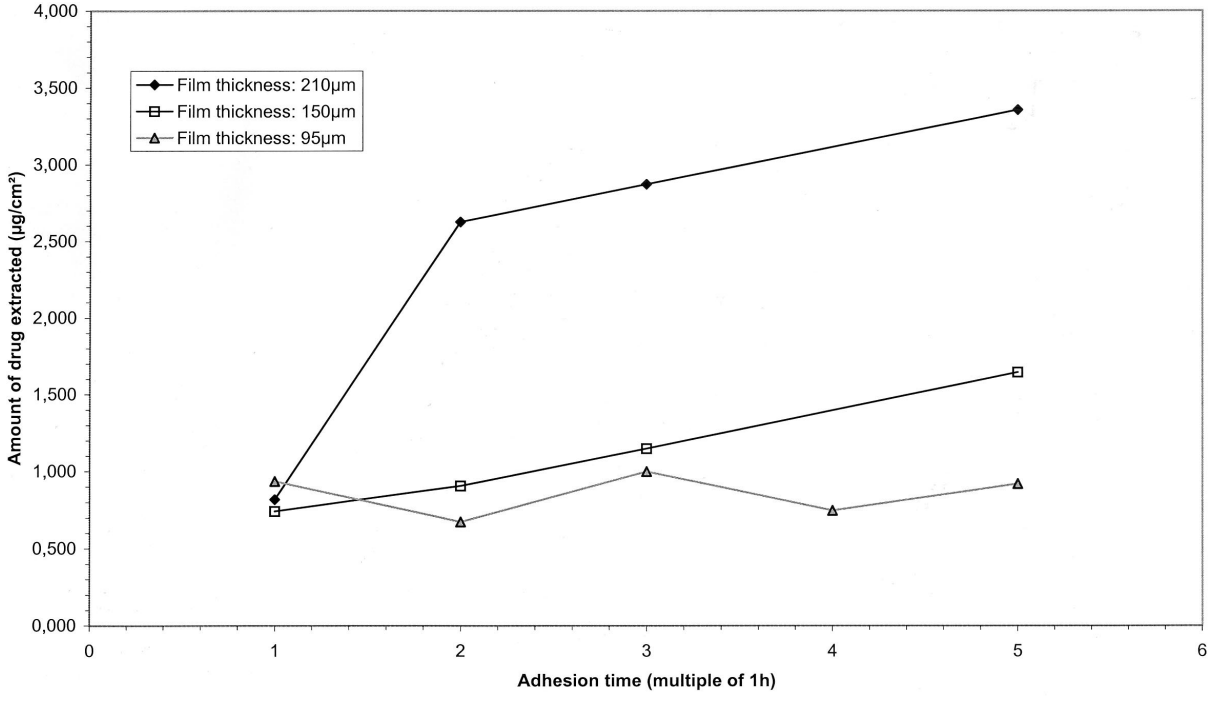

Fig. 3. Cumulative amount of drug in the skin as a function of adhesion time for films of various thicknesses (films containing 3% drug).

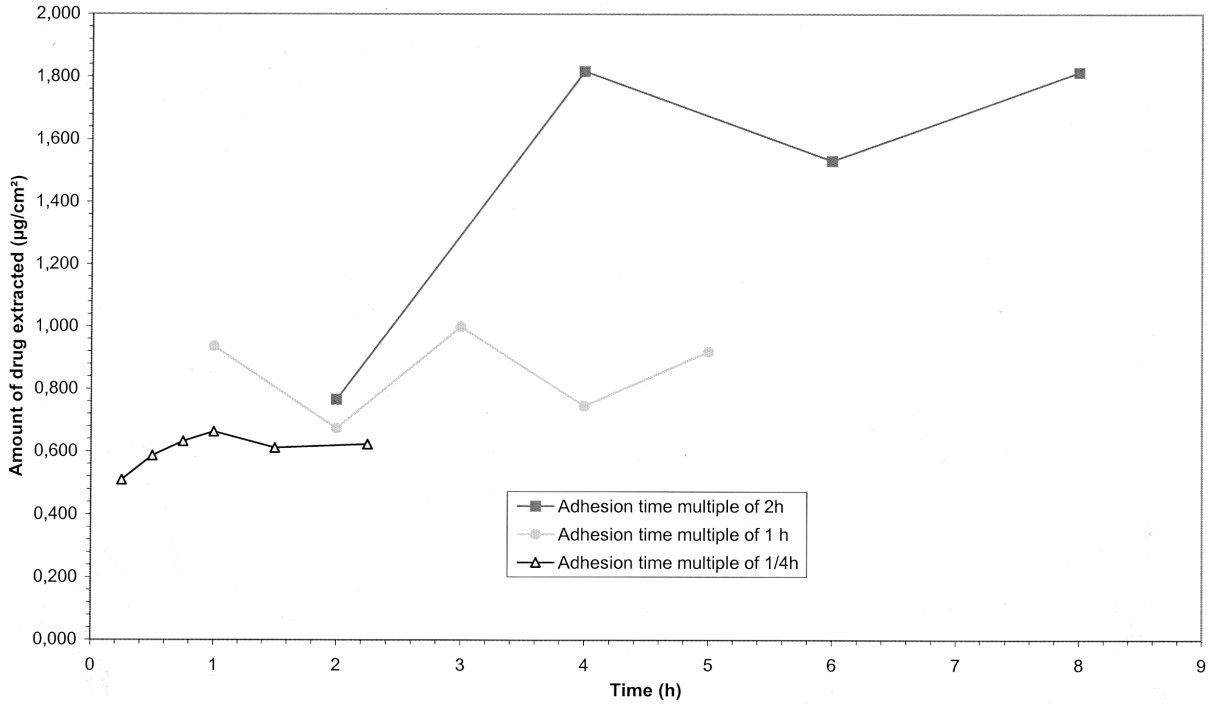

Fig. 4. 'Stabilized adhesion': cumulative amount of drug extracted from the skin as a function of time. The film was placed on the skin, removed periodically (every 1/4, 1 or 2 h) and stuck again at the same place. The time axis shows the global adhesion time.

An increase in film thickness may increase adhesion and passage of drug to the skin. This data is thus in favour of a passage dependent on the force of adhesion and number of bonds.

When adhesion is allowed to develop, substantial amounts of drug go quickly and easily through the interface until a limit imposed by the drug partition coefficient is reached (Gao and Singh, 1998).

The 'stabilised' protocol enhances the passage of the drug during an initial period. However, after several cycles of sticking and removal, patch–skin adhesion is weaker than previously because the interface patch–skin is not as tight. As a result, drug passage stops even if the skin is not totally saturated.

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