ELSEVIER

International Journal of Pharmaceutics 199 (2000) 29–38

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

# Physical evaluation of a new patch made of a progestomimetic in a silicone matrix

D.G. Maillard-Salin [a,b], Ph. Bécourt [a], G. Couarraze [b,*]

[a] *Hoechst Marion Roussel, Pharmaceutics, 102 Route de Noisy, 93235 Romainville Cedex, France*
[b] *Laboratoire de Physique Pharmaceutique, UMR CNRS 8612, University of Paris-South, 5 rue Jean Baptiste Clement, 92296 Chatenay-Malabry, France*

Received 11 May 1998; received in revised form 12 August 1999; accepted 26 January 2000

**Abstract**

The adhesion of a new Transdermal Therapeutic System (TTS) made of silicone and loaded with a progestomimetic drug was characterised. The goal of this study was to use well-known methods or to adapt them to collect representative data. Individually, methods such as surface tension, peel test and rheology are already widely used. Results show that the choice of a substrate for peel tests can be made in the light of surface tension data and that polymers like poly(tetrafluoroethylene) (PTFE) are good alternatives to skin. Peeling characterisations are made a function of thickness of films, drug content in active, conditions of preparation and conditions of use such as pressure. Dynamic rheology is more difficult to link to other methods as it mainly reflects internal phenomena and properties that arise in the bulk, as opposed on its surface. Master curves enable results to be used more easily, but the theories to interpret the data are still not powerful enough to replace peel testing. 

*Keywords:* Surface tension; Peel testing; Rheology; Adhesion; Silicone; Transdermal Therapeutic System

## 1. Introduction

Hormones are used in many treatments. The administration of steroid hormones may prove very effective in a substitutive treatment for women after the menopause especially against bone ageing and loss of bone minerals.

Patches may be helpful for long term administration of progestatives because they can keep the desired concentration of drug in the body for some days without repeated administration (a major constraint leading some patients to break the cycle).

Silicone products seem to be very interesting because of their relative inert state that minimises the risk of skin intolerance and of chemical reaction with the drug. Among polymers, many silicones are classified as pressure sensitive adhesives (PSA) (Merrill, 1979; Kenney et al., 1992). This is

* Corresponding author: Tel.: +33-1-46835616; fax: +33-1-46835882.
*E-mail address:* guy.couarraze@presidence.u-psud.fr (G. Couarraze)

0378-5173/00/$ - see front matter 
PII: S0378-5173(00)00357-4

because their adhesion can be enhanced or even initiated by a light pressure.

The TTS studied is a multilaminate.

The aim of this study is mainly to characterise the adhesive properties of the matrix (Shanker et al., 1995). An attempt is made to determine the mechanics of adhesion between polymer and substrate, and to identify the factors that intervene.

Surface energy and rheology characteristics of the materials may be predictive of its adhesive behaviour (Kenney et al., 1992).

## 2. Materials and methods

### 2.1. Raw materials

#### 2.1.1. Drug

The RU27987 (patent Roussel-Uclaf) or 17β-(2-hydroxy-1-oxopropyl)-17α-methylestra-4,9(10)-dien-3-one is a very potent derivative of progesterone. Produced by Hoechst Marion Roussel, it was used as a micronised powder.

#### 2.1.2. Silicone adhesive

A solution of polydimethylsiloxane with resin in heptane named BIO PSA® High Tack 7-4301 (Dow Corning) was chosen. A similar preparation containing less resin and named BIO PSA® Medium Tack 7-4201 was used for the matrix and the backing side layer of the trilayer TTS.

#### 2.1.3. Backing

A total of 74 μm thick, fluoropolymer on polyester (Scotchpak 1022, 3M).

Table 1
Surface tension of different probe liquids

| Probe liquid | Surface tension (mN m$^{-1}$) | | |
|---|---|---|---|
| | $\gamma$ | $\gamma^d$ | $\gamma^p$ |
| Deionised water (Millipore) | 72.8 | 21.8 | 51.0 |
| Diiodomethane (Acros Organics) | 50.8 | 50.8 | 0 |
| Ethylene glycol (Merck) | 47.7 | 30.9 | 16.8 |
| Formamide (Merck) | 58.2 | 28.7 | 29.5 |

#### 2.1.4. Release

A multilaminate polyester of 72 μm was used (Scotchpak 1006 3M).

#### 2.1.5. Film

A heptane solution of BIO PSA® (35% of *n*-heptane) was coated on the backing using a knife (Braive) fitted for an enductor (Erichsen). Then the film was dried at ambient temperature and in an oven (Werner Mathis) for 10 min at 60°C and 10 min at 80°C. The release was rolled to the film to protect its adhesive side until use.

#### 2.1.6. Patch

They were similar to the films, but prepared in an industrial environment.

When used, the drug was suspended in the solution of polymer before coating. Thickness was measured with a gauge (type VRZ103-MT12 by Heidenhain).

#### 2.1.7. Skin

The skin was excised from women of 35–41 years old during plastic surgery. Samples were dermatomed to a thickness of 300 μm including stratum corneum and part of its attached epidermis and stored at −30°C until use.

### 2.2. Methods

#### 2.2.1. Surface energy from contact angle

The contact angle method was used to measure the angle formed between a probe liquid and the solid studied (Buckton, 1990) with a video goniometer G2 (Krüss). The image of the drop was recorded and digitised with a CCD video camera (Sony). Four liquids were successively used as probe (Table 1).

The surface tension $\gamma_S$ of the solid is calculated using Young's relation:

$$\gamma_S = \gamma_{SL} + \gamma_L \cos\theta$$

completed by Owens–Wendt–Rabel and Kaelble's method:

$$\gamma_{SL} = \gamma_S + \gamma_L - \sqrt[2]{\gamma_S^d \gamma_L^d} - \sqrt[2]{\gamma_S^p \gamma_L^p}$$

$\gamma_{SL}$, interfacial free energy; $\gamma_S$ and $\gamma_L$, surface free energy of the solid and of the liquid; $\gamma^d$ and $\gamma^p$,

dispersive and polar contributions of the surface free energy.

*2.2.2. Peel test on skin*

These tests were performed in-vivo on the inner surface of the right forearm of ten healthy volunteers (average age around 30 years). Adhesion of a 10 × 45 mm piece of patch was enhanced with a light pressure of the thumb during approximately 20 s. The forearm being maintained on the table of a traction machine (Zwick 1435), a 90° peel test was performed on a length of 35 mm at a rate of 100 mm $min^{-1}$ dwell time.

*2.2.3. A 90° peel test on substrates*

This test was performed on different kinds of substrates: poly(tetrafluoroethylene) (teflon, PTFE), polycarbonate, poly(methyl methacrylate) (PMMA), glass. Adhesive sample (film or patch with the backing) of 10 × 45 mm was stuck on the substrate. Commonly, the adhesion of the sample was developed for 1 h under a mass of 1 kg.

*2.2.4. Rheology*

The measurements were made on a controlled stress rheometer CSL100 (Carri-med) on oscillatory mode. The rheological experiments were carried out on bulk silicone (concentration of 91% dry polymer). The measuring system comprised parallel stainless steel plates (10 mm diameter, with a gap of 500 μm). The measure of $G'$ (storage modulus) and $G''$ (loss modulus) took place at a frequency range varying between 20 and 0.03 Hz. A deformation of 1% was imposed. Five series of measures were carried out on the same sample at temperatures of 5, 20, 37, 70, and 90°C, respectively.

## 3. Results

### 3.1. Surface energy

Surface tensions of TTS calculated by Owens method are reported in Table 2. The active formulation of monolayer TTS included 3% w/w of drug in the matrix. The bilayer TTS had an additional adhesive layer on the release side that was mainly intended to improve the adhesion to the skin. The trilayer TTS had a drug free layer on the release side and one on the backing side. These systems have surface tensions close to 7 mN $m^{-1}$.

Table 2
Surface tension of different types of patches

| Patch composition | | Surface tension (mN $m^{-1}$) | | |
|---|---|---|---|---|
| | | $\gamma$ | $\gamma^d$ | $\gamma^p$ |
| Monolayer | Placebo | 6.9 | 5.2 | 1.7 |
| | Active | 6.3 | 5.9 | 0.3 |
| Bilayer | Placebo | 7.4 | 7.3 | 0.1 |
| | Active | 5.3 | 4.1 | 1.2 |
| Trilayer | Placebo | 10.0 | 7.6 | 2.4 |
| | Active | 9.5 | 5.8 | 3.7 |

Table 3
Surface tension of films containing 3, 6 or 9% w/w of drug

| Drug content | Surface tension (mN $m^{-1}$) | | |
|---|---|---|---|
| | $\gamma$ | $\gamma^d$ | $\gamma^p$ |
| Film 3% w/w | 7.8 | 5.7 | 2.1 |
| Film 6% w/w | 9.6 | 5.4 | 4.2 |
| Film 9% w/w | 9.4 | 6.7 | 2.6 |

The contact angles on films were measured and the surface tensions calculated for different proportions of active (Table 3). Values of surface tension were in the range of 8–9 mN $m^{-1}$ whatever the drug concentration.

Skin samples were washed with water before contact angle measurement. Other samples were washed and delipidated for 2 min in a bath of acetone. Table 4 shows that the skin has a surface tension under 40 mN $m^{-1}$, with a major dispersive component. When aggressive washing with acetone is carried out, this surface tension decreases to 25 mN $m^{-1}$.

### 3.2. Peel testing

Peel tests were performed on skin in-vivo with 85 μm thick placebo patches. Results are given in

Table 4
Surface tension of skin

| Substrate | Surface tension (mN $m^{-1}$) | | |
|---|---|---|---|
| | $\gamma$ | $\gamma^d$ | $\gamma^p$ |
| Skin | 38.9 | 29.6 | 9.3 |
| Skin washed in acetone | 25.3 | 22.8 | 2.5 |

Table 5. The mean peel force on human skin is close to $1.2 \pm 0.5$ N.

Peel properties of TTS were also studied on polymers such as PTFE, polycarbonate, PMMA. Glass was chosen to produce a comparison with substrates of higher surface energy. The force needed to peel the patch increases in a logarithmic way when peel rate increases (Fig. 1). This result is in accordance with other data previously described in literature. All the results with polymeric substrates seem quite similar, showing that either of those polymers can be indifferently used for peel tests. Adhesion is higher on glass.

A patch prepared in industrial conditions was compared to a film prepared in laboratory on a PTFE substrate. In Fig. 2 it is seen that adhesion properties of film and patch are similar. The presence of drug in the film reduces the adhesion of the polymer, the slightness of this variation being probably due to the low drug content (3%).

Some trials were carried out on films of various thickness, but the results can be extended to patches as they showed a similar adhesive be-

Table 5
Peel force measured on the skin

| Volunteer no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Peel force (N) | 1.0 | 1.1 | 1.7 | 0.5 | 2.3 | 1.1 | 1.2 | 1.4 | 1.2 | 0.5 | $1.2 \pm 0.5$ |

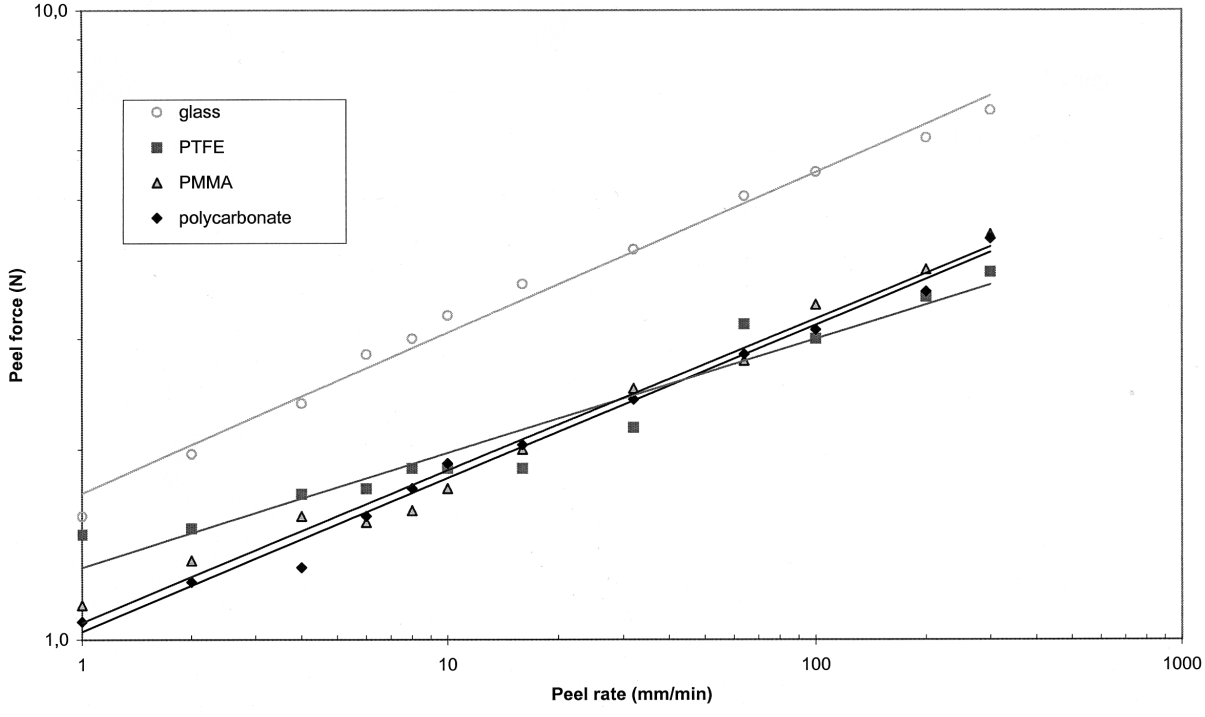


Fig. 1. Peel force on various substrates.

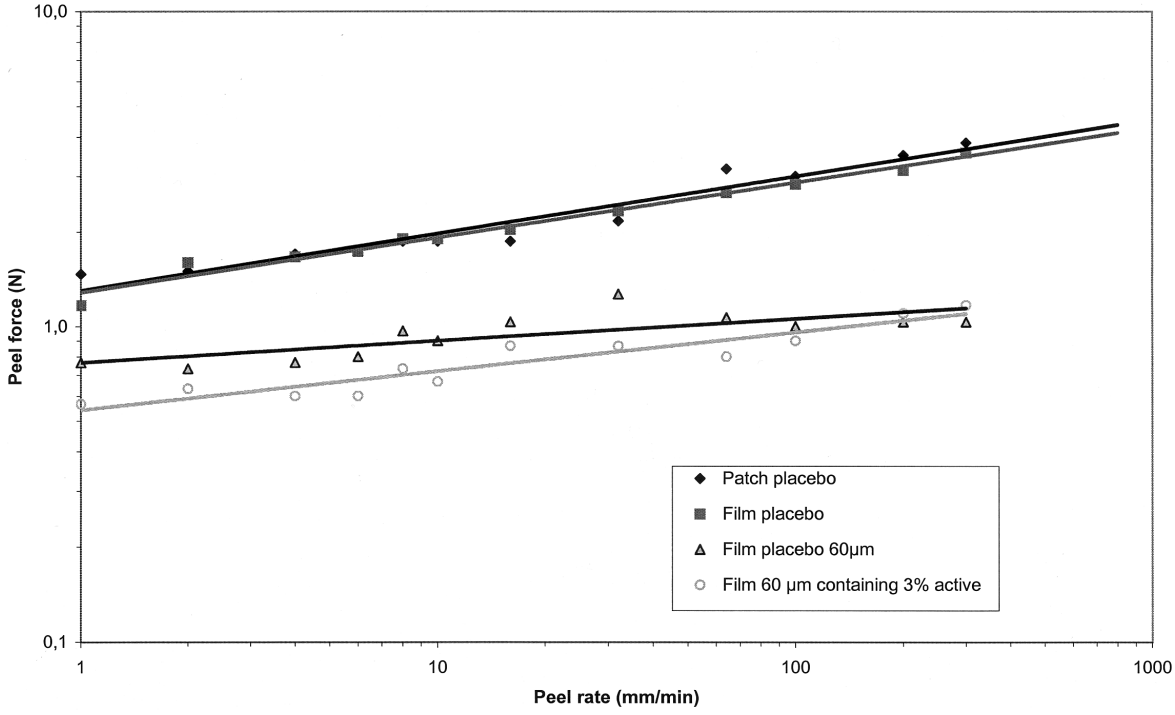


Fig. 2. Peel force of a patch compared to films (active and placebo).

haviour. Films of 60, 90, and 130 μm were tested (Fig. 3). Peel force is similar for thicker adhesives whatever the peel rate. But the peel force is lower for thinner films, as shown by the 60 μm thick film.

The peel force was studied as a function of the mass applied on the patch during development of the adhesion (Fig. 4). The mass has little or no influence on the peel force. For a 60 min adhesion time, the peel force is close to 3 N whatever the mass applied to the patch.

However, the peel force of the silicone polymer depends on the time of adhesion as shown in Fig. 5. During the first minutes a high adhesion of around 2 N is noted, then the force necessary to break the adhesive bonds increases with time. After 3 h a maximal adhesion is reached and peel forces greater than 4 N are required.

### 3.3. Rheology

Storage ($G'$) and shear ($G''$) moduli have been obtained by dynamic mechanical measurements at 20°C in a frequency range between 20 and 0.03 Hz (Fig. 6).

To obtain a master curve on a broader range of frequency, the time–temperature superposition principle was used as described in the theory of Williams–Landel–Ferry. $G'$ and $G''$ were measured at different temperature between 5 and 90°C on a same frequency range. To construct a master curve, a vertical translation of $G'$ or $G''$ has to be made with a factor $b_T$. This factor depends on the temperature chosen as a reference: $b_T = T_{ref}/T$ (for negligible variations of density). $T_{ref}$, temperature (K) of the desired master curve; $T$, temperature (K) used for the measurement.

Then a horizontal translation following the axe of frequencies has to be made in order to superimpose these curves (measured at temperatures ranging from 5 to 90°C) on the data measured at reference temperature (20°C). Fig. 7 corresponds to the master curve obtained in a frequency range as extreme as between 0.004 and 40 Hz when working at 20°C.

## 4. Discussion

As adhesion implies energetic phenomenon arising mainly at the interface between a substrate and an adhesive, surface tension should give valuable information related to adhesion. In the theory of Sharpe–Schonhorn, the surface tension of the adhesive has to be lower or equal to the one of the substrate.

All surface tension of the devices are under 10, and around 8 mN $m^{-1}$ for most of them. Studies on the patches show that including active in the matrix does not change the surface tensions. The dispersive component has a value around 6 mN $m^{-1}$, while the polar component is always under 4 mN $m^{-1}$.

Films and patches having surface tensions in the same range, it can be deduced that their surface properties are similar. Moreover, for low drug contents (between 3 and 9% w/w), all the films have identical surface properties.

Measurements on the skin show broad variations as with most of the biological substrates. The surface tension of 40 mN $m^{-1}$ is composed for three fourths of a dispersive part and a polar part of 10 mN $m^{-1}$. These results are in accordance with the data of the literature (Ginn et al., 1968; Kenney et al., 1992). Trials were made with skin drastically washed and partly delipidated by a bath in acetone. The surface tension value is around 25 mN $m^{-1}$, in the lower range of literature data.

One of the goals was to find a substrate that could mimic the skin to evaluate adhesive properties of the patch. This should then be used in peel tests to predict the way the skin would react, without the uncertainty due to biological variations. Substrates are needed that give a better representation of the forces on contact with skin than substrates of very high surface tension usually used for this approach as glass (80 mN $m^{-1}$) or steel (500 mN $m^{-1}$) (Lin, 1996). Polymers seem to be ideal as their surface tension is under 50 mN $m^{-1}$. Three polymers have been chosen with surface characteristics given in Table 6.

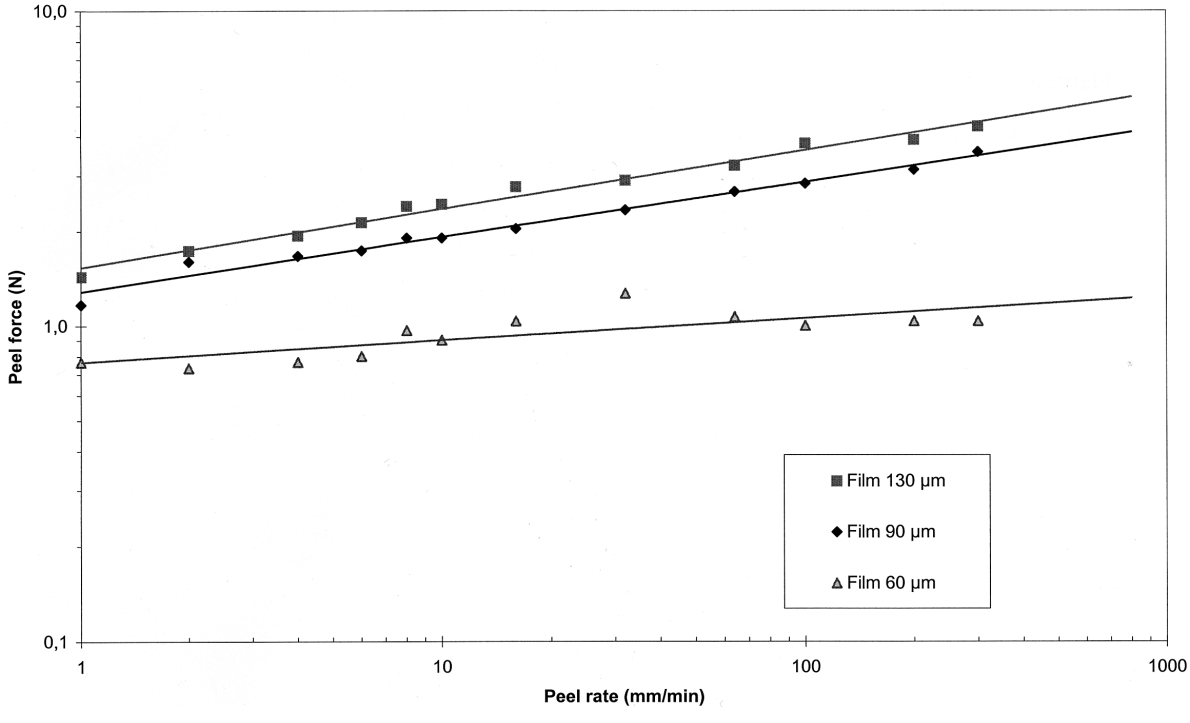


Fig. 3. Peel force for films of various thicknesses.

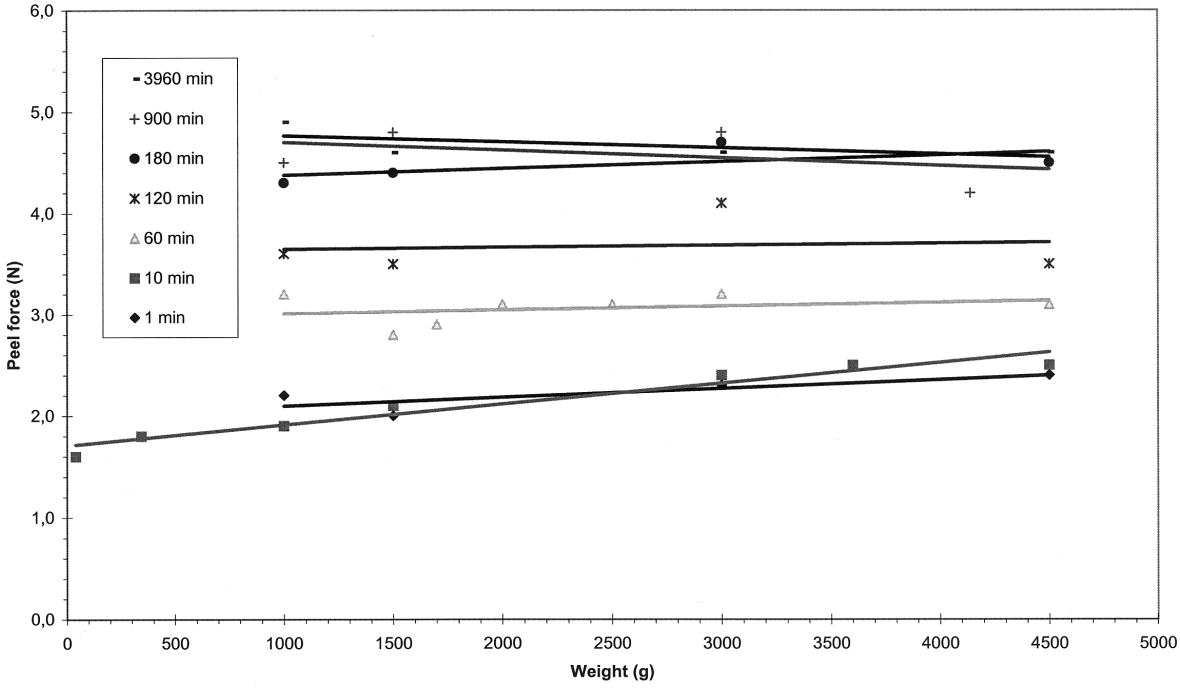


Fig. 4. Peel force as a function of pressure to enhance adhesion (patch placebo).

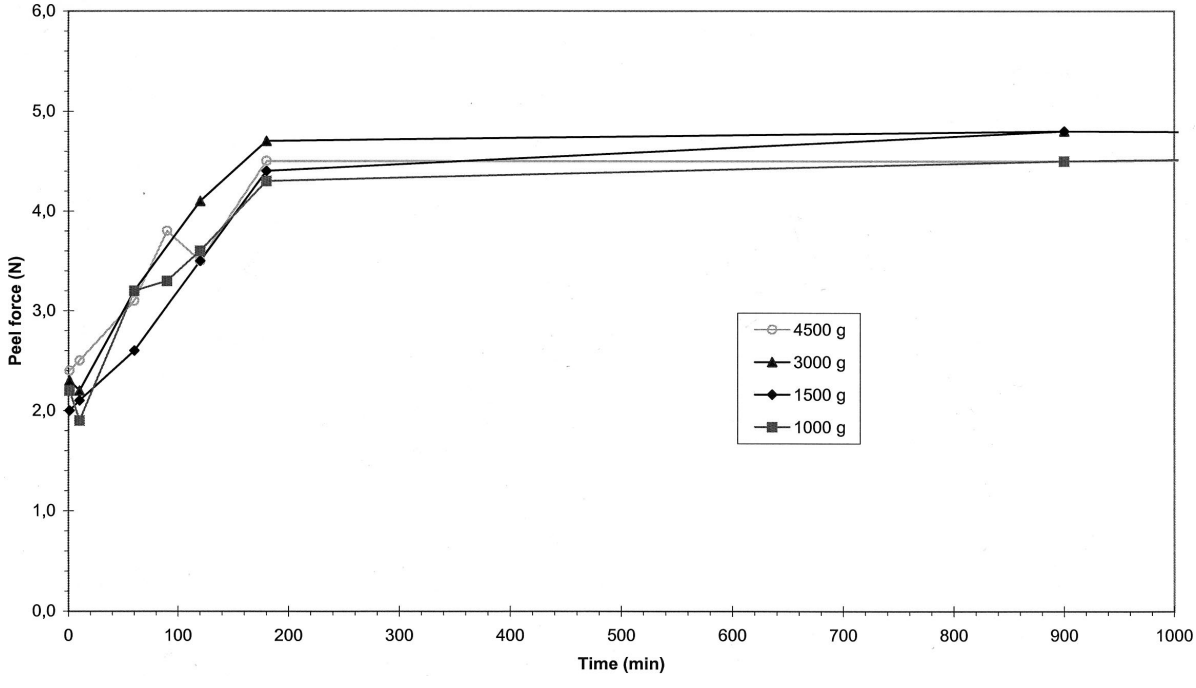


Fig. 5. Peel force as a function of adhesion time (patch placebo).

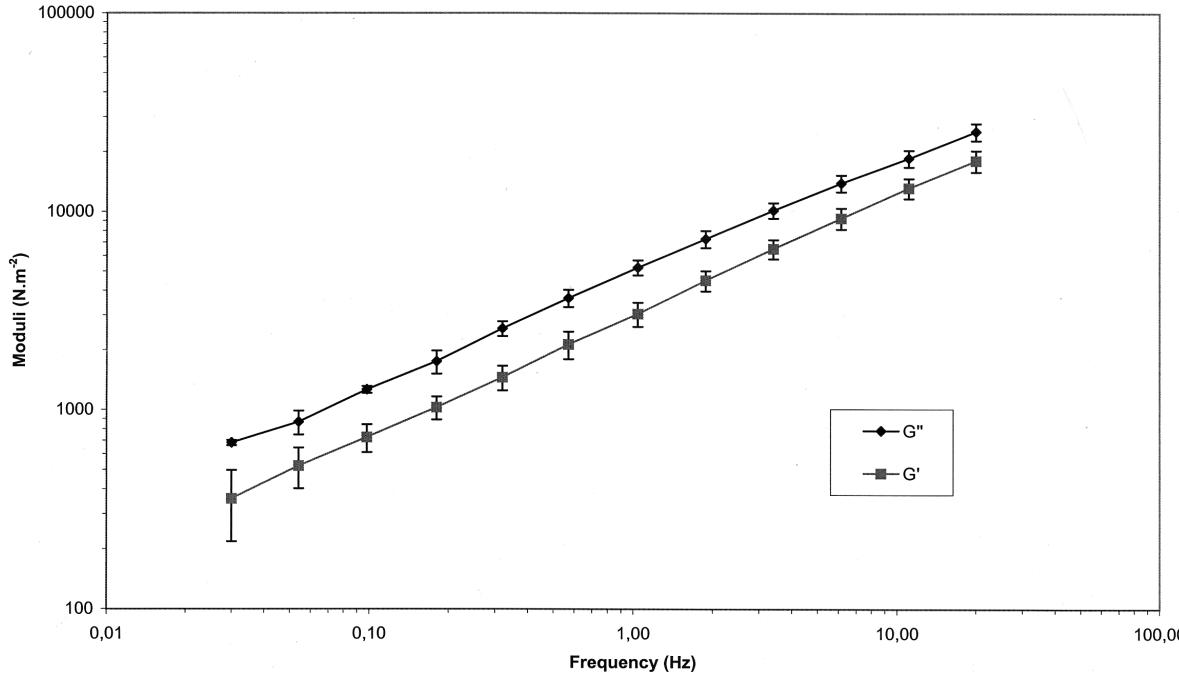


Fig. 6. Conservation ($G'$) and shear ($G''$) moduli measured at 20°C by dynamic rheology.

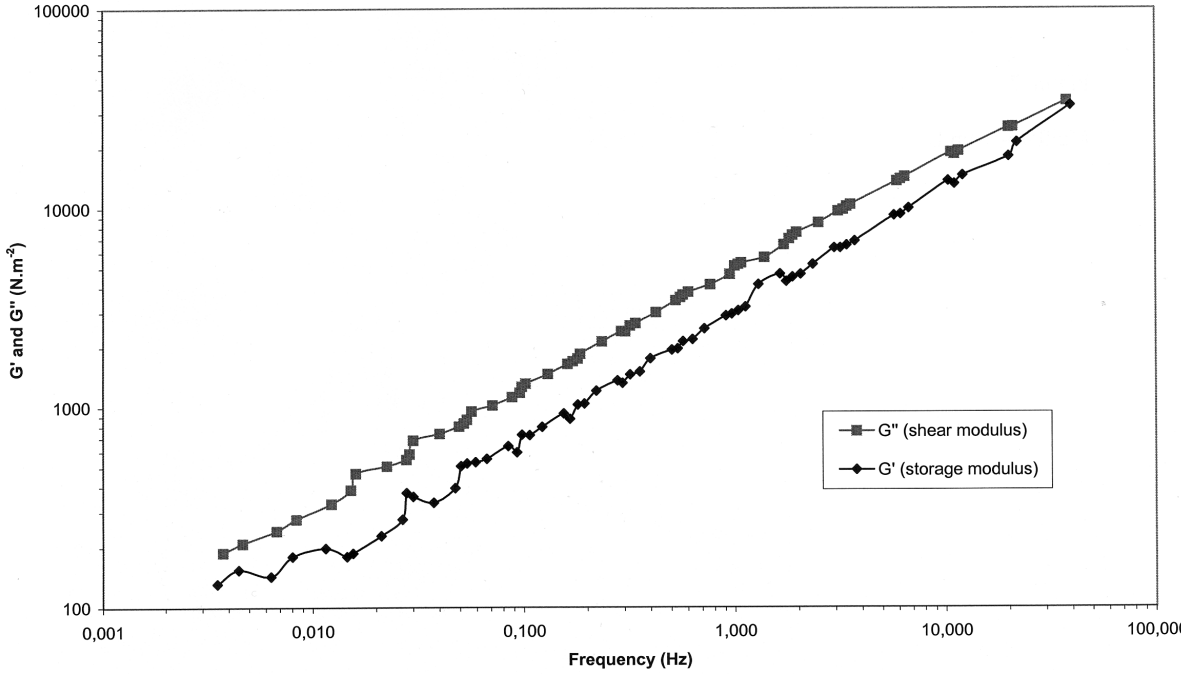


Fig. 7. Master curves of $G'$ and $G''$ at 20°C.

Table 6
Surface tension of some polymers

| Polymer | Surface tension (mN $m^{-1}$) | | |
|---|---|---|---|
| | $\gamma$ | $\gamma^d$ | $\gamma^p$ |
| PTFE | 19.1 | 18.6 | 0.5 |
| PMMA | 40.2 | 35.9 | 4.3 |
| Polycarbonate | 42.9 | 32.3 | 10.6 |

The peeling of placebo patches on skin gives an idea of the rate of the forces involved. Results on PTFE, PMMA and polycarbonate were quite similar, between 3 and 3.5 N at 100 mm $min^{-1}$ after 1 h of adhesion. It must be noted that the trials on skin were performed after 10 s while the adhesion lasts 1 h on the polymer trial. If the experiment takes places 1 min after adhesion, a force of 2 N is needed for the peeling of PTFE, results similar to the value obtained in vivo on skin. Among PTFE, PMMA, and polycarbonate, PTFE was arbitrarily chosen because of its lower surface tension.

No differences were seen on monolayer adhesives, films and patches had rigorously the same behaviour. This trial is of importance for the experiments. It shows that trials on laboratory films can be predictive for batches prepared on larger scale with somewhat dissimilar machines.

The adhesive thickness can sometimes be the source of variations in adhesion. The thinnest film presents more irregular results and sticks less. The 130 μm film adheres as well as the 90 μm but not better. The design of a new TTS with the adhesive cannot improve adhesion by increasing thickness beyond 90 μm. But 60 μm is not enough to obtain the optimum adhesion.

Among adhesion properties, the time of adhesion is a more important factor than pressure. It was shown that the adhesion is not constant over time. At the beginning, meaning the first minutes of adhesion, an instantaneous adhesion takes place. The peel force at around 2 N is quite high. This could probably be related to a high tack and due to a good stretch possibility of the adhesive. Then, there is an increase of adhesion that reaches around 4 N after 3 h. Bonds are probably forming through the time, reinforcing adhesion. After 3 h, the peel force is stabilised at around 4 N.

The rate of peeling is one of the important operating conditions (Satas, 1988). Rates were studied between 1 and 300 mm $min^{-1}$. In this range, peel force is often multiplied by a factor of 3! The conditions used to perform the trial must be standardised, taking values close to the studied phenomenon. In this case 100 mm $min^{-1}$ seems representative of peeling a TTS from skin at a good rate.

Among trials of peeling, some films were composed of adhesive only, while others contained the drug. Even if the adhesion of charged films is not as good as that of placebo, there is not much difference. This is probably due to the low active concentration. This result is in accordance with former results on surface energy of adhesive films.

Rheology is a method which easily and rapidly gives data on the bulk adhesive (Foley and Chu, 1986). That could then reflect what happens inside of adhesive (Sweet and Ulman, 1997) and even help to explain the behaviour at the interface with the substrate too. It is of interest to find a link between results obtained by rheology and by peeling (Tse, 1996).

In peeling, at the front where adhesive bonds break, adhesive is subject to shearing. It is admitted that peel rate divided by adhesive thickness is equivalent to a shear frequency.

$$N_{eq}(\text{peel}) = \frac{v}{e}$$

where $v$ is the shear rate and $e$ is the shear thickness.

Under these conditions, the increase of rheological moduli function of frequency (Fig. 7) gives a justification to the increase of peel force function of peel rate (Figs. 1–3).

For peel rate ranging from 1 to 300 mm $min^{-1}$, a 100 μm thick film has an equivalent frequency between 0.17 and 50 Hz. This is in the same order of magnitude as shear frequencies (Fig. 7). However, shear modulus obtained by rheological measurements is much lower than traction modulus evaluated by peel testing. It can then be deduced that true equivalent frequency corresponding to peel testing is higher than frequency calculated

with overall thickness of the film. In other words, it is possible to conclude that adhesive shear during peel test does not include the entire film but only part of it.

This conclusion is coherent with previous peel results showing that peel force does not increase anymore over a given thickness of film.

## 5. Conclusion

The tailoring of a TTS is a complex work, especially because of the difficulty in finding good adhesion characteristics. This study shows the advantages of developing new physicochemical methods of investigation to characterise adhesion of a TTS.

Describing and understanding the surface tension properties of a film and its components enables interactions between the compounds and the external environment to be understood and adapted. It leads to the choice of appropriate formulation of films. This study demonstrated that most polymers, and especially PTFE, are substrates of choice to mimic the skin in peel tests.

Furthermore, the rheological tool is essential (Satas, 1988). But it is shown that the actual theories are still insufficient to correlate exactly dynamic rheology to some particular surface properties of the adhesive. Peel testing remains an essential work to be carried out.

## References

Buckton, G., 1990. Contact angle, adsorption and wettability — a review with respect to powders. Powder Technol. 61 (3), 237–249.

Foley, K.F., Chu, S.G., 1986. Rheological characterization of elastomer latexes for PSAs. Adhesives Age Sep., 24–28.

Ginn, M.E., Noyes, C.M., Jungermann, E., 1968. The contact angle of water on viable human skin. J. Colloïd Interface Sci. 26, 146–151.

Kenney, J.F., Haddock, T.H., Sun, R.L., Parreira, H.C., 1992. Medical-grade acrylic adhesives for skin contact. J. Appl. Polym. Sci. 45, 355–361.

Lin, S.B., 1996. Silicone pressure-sensitive adhesives with selective adhesion characteristics. J. Adhesion Sci. Tech. 10 (6), 559–571.

Merrill, D.F., 1979. Silicone PSAs: types, properties, and uses. Adhesives Age March, 39–41.

Satas, D., 1988. Rheological properties and performance of PSAs. Adhesives Age Aug. 28–32.

Shanker, R.M., Baltusis, P.J., Hruska, R.M., 1995. Development of a new technique for the assesment of wettability of powders. Pharm. Res. Abstracts of papers 11 (Suppl. 10), 243.

Sweet, R.P., Ulman, K.L., 1997. Integrating rheological tools into the development and characterization of silicone adhesives. Proc. Int. Symp. Control. Release Bioact. Mater. 24 (5290), 621–622.

Tse, M.F., 1996. Pressure sensitive adhesives based on Vector® SIS polymers I. Rheological model and adhesive design pathways. J. Adhesion 56 (1–4), 79–95.