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International Journal of Pharmaceutics 333 (2007) 24–33
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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# Rheological studies on pressure-sensitive silicone adhesives and drug-in-adhesive layers as a means to characterise adhesive performance

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Received 19 December 2005; received in revised form 6 July 2006; accepted 26 September 2006
Available online 29 September 2006

**Abstract**

Pressure-sensitive adhesives are viscoelastic polymers used in the formulation of transdermal patches that allow attachment of a patch onto the skin. Established criteria exist that correlate viscoelastic parameters with adhesive performance. In this study, fulfilment of the adhesive performance criteria was examined using two silicone adhesives with different tack properties. The viscoelastic parameters of high and low tack silicone adhesives (BIO-PSA® High Tack 7-4302 and BIO-PSA® Low Tack 7-4102) were determined and compared with the criteria described by Chu and Dahlquist. Drug-in-adhesive layers were prepared using the high tack adhesive combined with nortriptyline HCl or paracetamol. The effect of drug addition on the viscoelastic properties of the adhesive was examined. The high tack adhesive showed congruence with the established criteria although with a modified range of viscoelastic moduli to that described by Chu. Examination of the low tack adhesive showed that it did not possess the appropriate viscoelastic properties for bonding onto the skin. The addition of the drugs into the high tack adhesive caused a concentration-dependent increase in its cohesive strength. This effect was independent of the physicochemical properties of the drugs tested.


*Keywords:* Pressure-sensitive adhesive; Silicone polymer; Drug-in-adhesive; Viscoelasticity; Rheology; Transdermal

## 1. Introduction

The pressure-sensitive adhesive (PSA) is a vital component of the transdermal patch system. The adhesive performance of a PSA is commonly monitored using tack, peel and shear strength tests (Muny, 1999; Minghetti et al., 2004; Venkatraman and Gale, 1998). Tack is a measure of the instantaneous adhesion of the adhesive onto the skin. It is a unique property of PSAs because, according to definition, an adhesive is pressure sensitive only if tacky at room temperature (Satas, 1999). Peel adhesion is a measure of the energy required to remove the adhesive from the skin after a period of application. Shear strength reflects the cohesive strength or the ability of the adhesive to remain attached without overspreading and to be removed without leaving a residue.

Tack, peel and shear measures are not inherent properties of a PSA but a response to the adhesive's bulk and surface properties. Their suitability for monitoring adhesive performance has, therefore, been questioned (Wokovich et al., 2006). The viscoelastic nature of PSAs controls their adhesion to the skin surface and determines the duration of their application, thus affecting the whole drug delivery process. The viscoelastic nature of PSAs enables them to exhibit both solid- and liquid-like behaviour depending on variables such as temperature and frequency of the applied stress. This behaviour of PSAs is described by viscoelastic parameters such as elastic modulus ($G'$), viscous modulus ($G''$) and creep compliance ($J$). The elastic modulus describes the solid-like character, whereas the viscous modulus describes the liquid-like character of the adhesive.

A correlation exists between the degree of adhesion and the viscoelastic properties of PSAs. Tack or bonding is a low rate process where the adhesive should be liquid-like and hence able to flow sufficiently to promote intimate contact between itself and the skin. Peel or debonding is a high rate process where the adhesive should be solid-like, i.e. cohesive and internally strong. The interpretation of these characteristics in terms of oscillatory viscoelastic parameters demonstrate that low oscillatory frequencies are associated with tack whereas high frequencies are associated with the peel process. Therefore, the viscous modulus should predominate ($G'' > G'$) at low frequencies, and the

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doi:10.1016/j.ijpharm.2006.09.043

**Nomenclature**

| | |
|---|---|
| $f$ | frequency |
| $f^*$ | cross-over frequency |
| $G'$ | elastic modulus |
| $G''$ | viscous modulus |
| $G^*$ | complex modulus |
| HCl | hydrochloride |
| HT | high tack |
| $J$ | compliance |
| LT | low tack |
| LVR | linear viscoelastic region |
| PSA | pressure-sensitive adhesive |
| $t_R$ | relaxation time |
| $T_g$ | glass transition temperature |
| $T^*$ | cross-over temperature |

*Greek letters*

| | |
|---|---|
| $\gamma$ | shear strain |
| $\delta$ | phase angle |
| $\sigma$ | shear stress |
| $\omega$ | angular frequency |

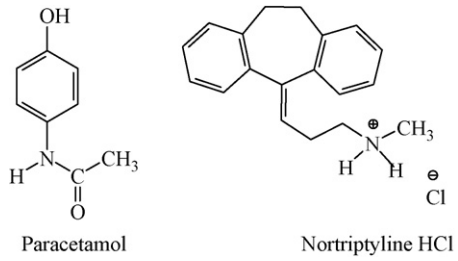
elastic modulus should predominate ($G' > G''$) at high frequencies (Chu, 1991). Moreover, throughout the application period, the PSA should remain attached on the skin without overspreading, and on removal should not leave any residues, i.e. it should have appropriate shear properties. In rheological terms, the creep compliance (cold flow) of the adhesive should be low enough at low stress values that describe gravitational effects but with a minimum limit so as to maintain its tackiness, and the ability to flow and adhere on the skin with the application of light pressure. The requirements for the performance of PSAs have been quantified using natural rubber blends with resin and are described in the criteria reported by Chu and Dahlquist (Chu, 1991; Dahlquist, 1999).

Chu criteria:

(i) $G'$ ($\omega = 0.1$ rad/s) $\sim 2$–$4 \times 10^4$ Pa, and
(ii) $5 < [G'(\omega = 100)/G'(\omega = 0.1)] < 300$.

*Dahlquist's criterion of tack*: $G' < 10^5$ Pa or equivalently $J_c > 10^{-5}$ Pa$^{-1}$, at low frequencies. This criterion is similar to the Chu criterion.

There are many different designs of transdermal patches, including the drug-in-adhesive and the reservoir systems. In the drug-in-adhesive design, the target drug is mixed with the adhesive to form a drug-in-adhesive layer. A drug can be delivered transdermally only when it possesses certain physicochemical and therapeutic properties. Two drugs with different physicochemical properties and potential therapeutic advantages by transdermal delivery were used in this study (Scheme 1). Nortriptyline HCl is the salt of a secondary amino group and has a bulky hydrophobic aromatic moiety. Paracetamol has an amide group and a phenol group, its molecular size is low and is also less bulky than nortriptyline HCl. Table 1 shows the properties of the chosen drugs compared with the ideal drug physicochemical and therapeutic requirements for passive transdermal delivery. Nortriptyline HCl is a tricyclic antidepressant. A recent study showed that combination therapy of transdermal nicotine (21 mg/day) and oral nortriptyline HCl (25–75 mg/day) significantly reduced withdrawal symptoms during smoking cessation therapy, representing an option for smokers where transdermal nicotine monotherapy had failed (Prochazka et al., 2004). The formulation of nortriptyline HCl as a transdermal patch either alone or in combination with nicotine, may therefore increase patient compliance. Treatment of nocturnal childhood enuresis (10–35 mg/night) provides another potential therapeutic indication for transdermal formulation of nortriptyline HCl. Nortriptyline HCl, like most antidepressants, requires a gradual withdrawal of administration due to gastrointestinal disturbances and other side effects that accompany sudden discontinuation of the oral dosage form. Transdermal administration of antidepressants is advantageous because cessation does not carry the same side effects. Paracetamol is a widely used analgesic and antipyretic agent for adults and children. It is the drug of choice for childhood post-immunisation pyrexia (60 mg every 4–6 h). Paracetamol is currently available in oral and rectal dosage forms. The transdermal route could provide a useful alternative route of administration for children suffering from diarrhoea, vomiting or refusal of the oral dosage form. Initial pharmacokinetic data of a formulated paracetamol




Paracetamol Nortriptyline HCl

Scheme 1. Structure of the model drugs.

Table 1
Physicochemical and therapeutic properties of nortriptyline HCl and paracetamol and ideal drug properties for passive transdermal delivery

| Properties | Ideal | Nortriptyline HCl | Paracetamol |
|---|---|---|---|
| Molecular weight | <500 Da | 299.8 | 151.2 |
| Aqueous solubility | >0.1 mg/ml | 20 mg/ml | 14 mg/ml |
| log $K_o/w$ | −2 to 3 | 1.7 | 0.49 |
| Melting point | <200 °C | 213–215 °C | 169–170 °C |
| Daily dose | <10 mg | 10–75 mg | 60 mg or 10 mg/kg (paediatric) |

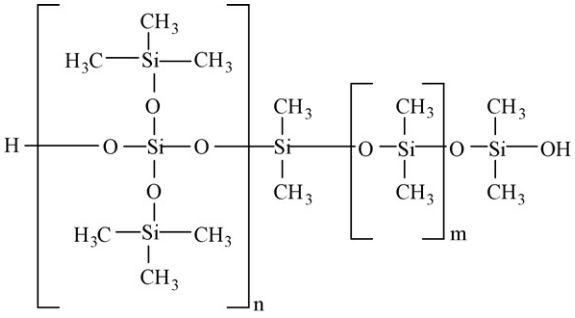
Table 2
Amount of drug used and the corresponding drug concentration in the high tack adhesive layers

| Drug | Amount of dry adhesive (mg) | Amount of drug (mg) | Concentration (%, w/w) |
|---|---|---|---|
| Nortriptyline HCl | 2080 | 50 | 2.35 |
| | 1337 | 50 | 3.6 |
| | 1630 | 80 | 4.7 |
| | 1770 | 150 | 7.8 |
| | 1070 | 120 | 10.1 |
| | 1440 | 400 | 21.75 |
| Paracetamol | 1986 | 100 | 4.8 |
| | 1392 | 200 | 12.6 |
| | 1530 | 450 | 22.7 |
| | 1710 | 800 | 31.9 |

transdermal patch from rat studies has been reported (Sintov et al., 2003). In our study, the amount of nortriptyline HCl and paracetamol used in the drug-in-adhesive layers (Table 2) was within the guidelines set for therapeutic daily dosage (Table 1).

Silicone adhesives are relatively inert with minimum risk of skin intolerance and incompatibility with other patch ingredients (Tan and Pfister, 1999). They are made up of a polymer (polydimethylsiloxane) and a silicate resin (Scheme 2). The resin has a high glass transition temperature ($T_g$) but the polymer has a low $T_g$. The adhesive properties of silicones are dependent on the ratio of resin to polymer. High polymer content (BIO-PSA® High Tack 7-4300 with 55/45 ratio) gives a soft but tacky adhesive, whereas high resin content (BIO-PSA® Low Tack 7-4100 with 65/35 ratio) gives a less tacky but stronger adhesive.

In this study, we investigated the use of a rheological approach to the monitoring of adhesive performance of drug-in-adhesive layers. Adhesive performance is an important factor of transdermal dosage forms directly related to drug delivery and therapeutic effect, but no consistent methodology exists to test adhesive properties (Wokovich et al., 2006). A series of viscoelasticity tests were performed and correlations of the adhesive performance with the dynamic mechanical properties of the drug–adhesive mixtures were carried out. Silicone adhesives with amino group compatibility were used in order to prevent H-bond interactions between the silanol (Si–OH) groups of the adhesive and the amine groups of the chosen drugs. Potential drug–polymer interactions that would be depicted as changes in



Scheme 2. Structure of silicone adhesives.

the viscoelastic parameters were of interest in this study. The overall aim of the study was to characterise the adhesive performance in terms of viscoelastic behaviour and identify the effect of drug addition on the viscoelastic properties of the adhesive layers.

## 2. Materials and methods

### 2.1. Materials

The BIO-PSA® 7-4302 High Tack and BIO-PSA® 7-4102 Low Tack silicone adhesives in ethyl acetate were donated by Dow Corning Corporation (Midland, USA). Nortriptyline HCl was supplied by Sigma® and 4′-hydroxyacetanilide (paracetamol) was supplied by Merck. The fluoropolymer SCOTCHPAK 9742 Release Liner was donated by 3M (St. Paul, USA).

### 2.2. Preparation of calibration plots

Calibration graphs of liquid adhesive versus dry adhesive were plotted for each adhesive material. A set of four to five samples of liquid adhesive were accurately weighed into glass containers cushioned with a release liner. The plate, liner and liquid adhesive were accurately weighed using a Mettler AT460 Delta Range® electronic balance. The weight of the dry adhesive in each sample was then determined 4 h after preparation, overnight and after 15 days.

### 2.3. Preparation of the drug-in-adhesive layers

The drug and the liquid adhesive were weighed and mixed in a small beaker until visibly homogeneous. The drug–adhesive mixtures were transferred onto a liner and allowed to dry overnight. The concentration of the drug in the dry adhesive was calculated using the calibration plots. The amount of each drug used in the preparation of the drug-in-adhesive layers was representative of therapeutic dosages (Table 1). Table 2 shows the amount of drug used and the corresponding drug concentration in the high tack adhesive layers. Each layer was divided into three samples for rheological measurements.

### 2.4. Rheological tests

The rheological measurements of dried bulk silicone and drug-in-adhesive layers were performed on a Bohlin Gemini™ Advanced Rheometer (Malvern Instruments, Malvern, UK) attached to a Julabo F12 water bath and Jun-Air 2000 compressor.

All tests, apart from the temperature sweep tests, were performed at 32 ± 0.1 °C (the temperature of the skin surface). A 20 mm diameter stainless steel parallel plate and a gap size of 1000 μm were used. The high tack adhesive was also studied using a 40 mm diameter parallel plate at 1000 μm gap size (HT*) and using a 20 mm diameter parallel plate at 500 μm gap size (HT**).

Oscillatory rheometry and creep testing were used to characterise the viscoelastic properties of the adhesives. Utilising

oscillatory rheometry the sample was subjected to sinusoidal deformation with the following tests performed in triplicate for each of the adhesive and drug-in-adhesive layers:

- *Stress amplitude sweep*. The linear viscoelastic region (LVR) of the sample was determined using a stress amplitude sweep, whereby a range of incremental shear stresses (10–10,000 Pa) at constant frequency (1 Hz) and temperature (32 °C) were applied on the sample. Within the LVR the shear stress ($\sigma$) is proportional to the shear strain ($\gamma$) and the magnitude of the complex modulus $G^*$ is constant with the stress amplitude, but dependent on frequency. At this region of applied stresses the material behaves as an elastic solid. The position and length of the LVR indicate the ability of the sample to resist flow and its stability over a range of stresses.
- *Single frequency*. The sample was subjected to a constant frequency ($f$ = 1 and 10 Hz), temperature (32 °C), and monitored shear stress (1000 Pa) within the LVR, for 300 s. The viscoelastic moduli ($G'$, $G''$) and the phase angle $\delta$ were observed as a function of time to confirm linear viscoelastic behaviour. The single frequency test was also carried out using a temperature gradient from −5 to 75 °C at 2 °C/min, and the temperature with $G' = G''$ was identified.
- *Frequency sweep*. The sample was oscillated over a range of frequencies (0.1–100 Hz), with a monitored shear stress (1000 Pa) within the LVR at a constant temperature (32 °C) and then at temperatures of −5, 5, 15, 25, 35, 45, 55, 65 and 75 °C. From the frequency sweep at 32 °C, the "cross-over" frequency, at which the $G' = G''$, was identified. At that specific frequency, the materials are viscoelastic with equal elastic and viscous components and the phase angle is equal to 45°. From the "cross-over" frequency, the relaxation time $t_R$ of the sample can be estimated from the equation $t_R = 1/(2\pi f^*) = 1/\omega^*$, where $f^*$ and $\omega^*$ are the cross-over frequency and cross-over angular frequency, respectively. For valid oscillatory studies, $t_R$ should be lower than the duration of the test. A master curve was derived from the frequency sweep at different temperatures, according to the time–temperature superposition principle described by the Williams–Landel–Ferry equation (Williams et al., 1955), using 32 °C as the reference temperature. The master curve provided the magnitudes for the viscoelastic moduli over a broad range of frequency values.

Creep testing was performed at 32 °C, with a constant stress of 500 Pa applied to the sample for 480 s followed by a recovery time of 480 s. The creep compliance $J_c$, transient recoverable compliance $J_r$, elastic creep compliance $J_{oc}$, elastic recoverable compliance $J_{or}$, and the steady state status, were recorded for all samples.

### 2.5. Particle size analysis

A small amount of drug powder was spread evenly on a glass slide and secured with a cover film. The size of the drug particles was examined using a Swift M4000-D microscope (Swift Instruments International S.A.) fitted with an eyepiece graticule, using a (10×) objective for nortriptyline HCl and a (4×) objective for paracetamol.

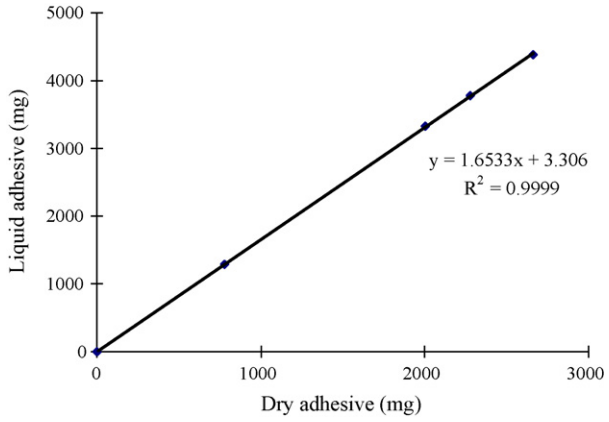



Fig. 1. Calibration plot for the high tack (HT) adhesive.

### 2.6. Solubility studies of the drugs in the high tack adhesive polymer

Several concentrations of drug–adhesive mixtures using the high tack adhesive were prepared, equivalent to drug concentrations between 0.1% and 5% (w/w) in dry adhesive. A few drops of the mixture solution were spread evenly onto a microscope slide and left to dry for 15 min before examination. The microscopic examination was performed using a Swift M4000-D microscope (Swift Instruments International S.A.) fitted with a Quodmaster® 100 polarising (10×) objective.

## 3. Results

### 3.1. Calibration plot

The calibration graphs for the high and low tack adhesives are presented in Figs. 1 and 2. Drying of the liquid adhesive for 4 h, overnight, and 15 days showed that approximately 60% of weight would remain as the dry adhesive, so overnight drying was sufficient. The addition of nortriptyline HCl or paracetamol in the high tack adhesive did not affect the solvent evaporation,

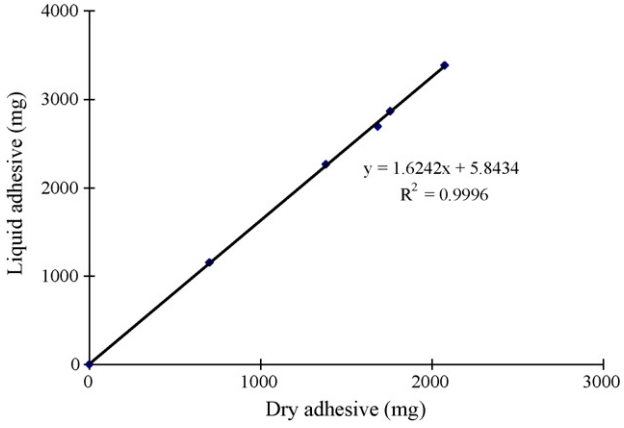



Fig. 2. Calibration plot for the low tack (LT) adhesive.

as shown by comparison of the actual weight of the dry adhesive and the weight calculated from the calibration plot.

### 3.2. Viscoelastic properties of the adhesive material

The adhesive materials were tested alone in order to establish the reference viscoelastic parameter values against which the drug-in-adhesive layers would be compared. All rheological measurements were performed in triplicate using three samples from each layer. Graphical data points show the mean of the three values. Due to negligible deviation between the values, error bars were omitted from the final graphs.

#### 3.2.1. High tack adhesive

The high tack adhesive was tested initially (HT-1st) and 1 month after opening (HT-2nd) in order to establish the stability and reproducibility of the measured parameters following storage. Preliminary analysis using a 40 mm diameter parallel plate at 1000 μm gap size (HT*) and a 20 mm diameter parallel plate at 500 μm gap size (HT**) was carried out. The different plate dimensions represented the effect of the application area of the adhesive layer on its viscoelastic properties, whereas the different gap sizes represented the effect of the layer thickness on its viscoelastic properties.

The linear viscoelastic region of all high tack samples (HT-1st, HT-2nd, HT* and HT**) was found between stresses of 251 and 3981 Pa (Fig. 3) indicating that it was independent of the dimensions of the adhesive layer and unaffected by storage. However, the magnitude of $G^*$ decreased for HT-2nd (Fig. 3) demonstrating that the adhesive had become softer following storage of the container at 25 °C for a month after opening. The magnitude of $G^*$ for HT** and HT-1st was identical, therefore the thickness of the layer did not affect the observed strength of the adhesive. The difference of the $G^*$ magnitude between HT* and HT-1st indicated that the application area of the adhesive layer may affect the observed strength of the adhesive. The linear region was verified by applying the three pairs of ($\sigma$, $\gamma$) values representing the beginning, middle and end of the LVR to the single frequency test at 1 and 10 Hz. These three pairs of ($\sigma$, $\gamma$) values were similarly applied to the frequency sweep and creep

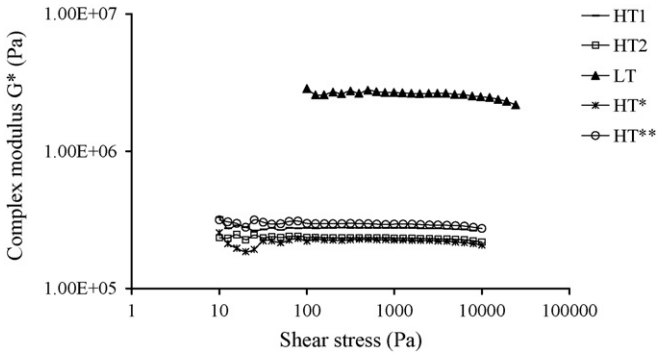



Fig. 3. Linear viscoelastic region of the high tack and low tack adhesives, at 1 Hz.

Table 3
Elastic modulus and phase angle of BIO-PSA 7-4302 High Tack (HT) and BIO-PSA 7-4102 Low Tack (LT), from the single frequency tests at 1 and 10 Hz

| BIO-PSA | $f$ (Hz) | $\sigma$ (Pa) | $G'$ ($10^6$ Pa) | $\delta$ (°) |
|---|---|---|---|---|
| HT-1st | 1 | 251 | 0.160 | 58.0 |
| | 1 | 1000 | 0.160 | 58.0 |
| | 1 | 3981 | 0.157 | 57.5 |
| HT-2nd | 1 | 1000 | 0.120 | 60.0 |
| HT* | 1 | 1000 | 0.15 | 48.8 |
| HT** | 1 | 1000 | 0.14 | 59.0 |
| LT | 1 | 6294 | 5.380 | 13.8 |
| HT-1st | 10 | 1000 | 0.725 | 46.0 |
| HT-2nd | 10 | 1000 | 0.642 | 48.0 |
| HT* | 10 | 1000 | 0.51 | 25.5 |
| HT** | 10 | 1000 | 0.7 | 45.0 |
| LT | 10 | 6294 | 7.350 | 10.0 |

* Gap size = 1000 μm and parallel plate size = 40 mm.
** Gap size = 500 μm and parallel plate size = 20 mm.

Table 4
Elastic and viscous modulus at 0.1 and 100 rad/s, obtained from the master curves for all the adhesive and drug–adhesive layers, at 32 °C

| Adhesive layer | Drug concentration (%, w/w) | $G'$ ($10^4$ Pa) | | $G'$ ($\omega$ = 100)/$G'$ ($\omega$ = 0.1) | $G''$ ($10^4$ Pa) | |
|---|---|---|---|---|---|---|
| | | $\omega$ = 0.1 rad/s | $\omega$ = 100 rad/s | | $\omega$ = 0.1 rad/s | $\omega$ = 100 rad/s |
| HT-1st | 0 | 0.63 | 100 | 157.5 | 1.3 | 91 |
| HT-2nd | 0 | 0.57 | 90 | 157.8 | 10.0 | 85 |
| HT* | 0 | 0.60 | 61 | 101.7 | 1.25 | 21 |
| HT** | 0 | 0.50 | 100 | 200.0 | 10.0 | 84 |
| HT with nortriptyline HCl | 2.35 | 0.66 | 100 | 151.5 | 1.2 | 89 |
| | 3.60 | 0.53 | 100 | 188.6 | 1.2 | 90 |
| | 4.7 | 0.63 | 100 | 158.7 | 1.4 | 100 |
| | 7.80 | 0.63 | 116 | 184.1 | 1.4 | 104 |
| | 10.10 | 0.77 | 130 | 168.8 | 1.7 | 120 |
| | 21.75 | 1.20 | 200 | 165.3 | 2.6 | 160 |
| HT with paracetamol | 4.8 | 0.60 | 100 | 166.7 | 1.3 | 94 |
| | 12.6 | 0.76 | 120 | 157.9 | 1.7 | 120 |
| | 22.7 | 1.00 | 160 | 160.0 | 2.2 | 140 |
| | 31.9 | 1.50 | 270 | 180.0 | 3.4 | 210 |
| LT | 0 | 190.00 | 580 | 3.0 | 83.0 | 68 |

Table 5
Effect of temperature on phase angle of the adhesive and drug–adhesive layers under oscillatory stress of 1000 Pa at 1 Hz

| Adhesive layers | Drug concentration (%, w/w) | δ (°) | | |
|---|---|---|---|---|
| | | −5 °C | 32 °C | 75 °C |
| HT-1st | 0 | 35.0 | 58.0 | 61.5 |
| HT-2nd | 0 | 36.3 | 60.0 | 61.7 |
| HT* | 0 | 10.6 | 48.8 | 60.0 |
| HT** | 0 | 30.0 | 59.0 | 61.0 |
| HT with nortriptyline HCl | 2.35 | 35.5 | 58.5 | 61.5 |
| | 3.6 | 36.2 | 58.5 | 61.5 |
| | 4.7 | 36.0 | 58.5 | 61.4 |
| | 7.8 | 34.9 | 58.5 | 61.2 |
| | 10.1 | 33.5 | 58.0 | 61.5 |
| | 21.75 | 31.8 | 56.4 | 60.9 |
| HT with paracetamol | 4.8 | 36.9 | 59.2 | 61.4 |
| | 12.6 | 33.9 | 58.2 | 61.2 |
| | 22.7 | 33.3 | 57.7 | 61.1 |
| | 31.9 | 29.5 | 56.0 | 60.8 |
| LT | 0 | 7.6 | 13.8 | 29.3 |

Table 6
Effect of temperature on the phase angle of the adhesive and drug–adhesive layers under oscillatory stress of 1000 Pa at 10 Hz

| Adhesive layers | Drug concentration (%, w/w) | δ (°) | | |
|---|---|---|---|---|
| | | −5 °C | 32 °C | 75 °C |
| HT-1st | 0 | 24.0 | 46.0 | 59.5 |
| HT-2nd | 0 | 24.8 | 48.0 | 60.1 |
| HT* | 0 | 6.0 | 25.5 | 55.0 |
| HT** | 0 | 18.2 | 45.0 | 60.0 |
| HT with nortriptyline HCl | 2.35 | 24.4 | 46.5 | 59.5 |
| | 3.6 | 24.2 | 47.0 | 59.5 |
| | 4.7 | 24.1 | 47.0 | 59.3 |
| | 7.8 | 23.9 | 46.4 | 59.6 |
| | 10.1 | 21.8 | 45.4 | 59.5 |
| | 21.75 | 20.0 | 43.2 | 58.9 |
| HT with paracetamol | 4.8 | 24.0 | 47.4 | 59.7 |
| | 12.6 | 23.3 | 45.9 | 59.3 |
| | 22.7 | 20.7 | 45.0 | 58.9 |
| | 31.9 | 16.7 | 42.4 | 58.9 |
| LT | 0 | 2.8 | 10.0 | 15.0 |

tests for HT-1st. The pair of ($\sigma$, $\gamma$) values from the middle of the LVR ($\sigma = 1000$ Pa) was chosen for the oscillatory and creep tests for HT-2nd, HT* and HT**.

The high tack adhesive samples HT-1st and HT-2nd were viscous-like with a phase angle of 58–60° at 1 Hz and viscoelastic with a phase angle of 46–48° at 10 Hz (Table 3). The lower $G'$ values of HT-2nd at both frequencies compared with HT-1st, are consistent with the previous observations of softening of the adhesive following storage. Additionally, the higher phase angle showed that the viscous component of the adhesive increased on storage. The dimensions of the parallel plate or adhesive layer, similarly affected the viscoelastic measurements with more obvious differences present at 10 Hz; the adhesive was softer (lower $G'$) and behaved solid-like ($\delta = 25.5°$, $G' > G''$) using a 40 mm parallel plate (Table 3). The same observation is also clearly demonstrated in Table 4 at 16 Hz ($\omega = 100$ rad/s), where $G' > G''$ for HT*, and $G'$ (HT-1st) > $G'$ (HT*).

At −5 °C the adhesive was solid-like ($\delta \sim 25$–$35°$) and as the temperature gradually increased up to 75 °C, it gradually became viscous ($\delta \sim 60°$) (Tables 5 and 6). This behaviour was characteristic of the high tack adhesive material, where the adhesive is elastic at low temperatures and viscous at high temperatures, in contrast to the low tack adhesive, which remains elastic throughout the temperature range −5 to 75 °C.

The cross-over frequency of the adhesive increased on storage (Table 7) also indicative of an increased viscous component. Using a 40 mm parallel plate, the adhesive (HT*) behaved more elastically than with the 20 mm plate (HT-1st). As before, the gap size did not affect the viscoelastic parameters. It is also noteworthy that the cross-over frequency of HT-1st increased with the increasing shear stress (Table 7). Consequently its relaxation time $t_R$ decreased, i.e. the adhesive behaved liquid-like with an increase in the applied stress, within the LVR. This latter behaviour was confirmed by creep testing of the adhesive (Table 8). The elastic creep compliance $J_{oc}$ decreased as the applied constant stress increased from 251 to 3981 Pa. At 251 Pa, the $J_{oc}$ and $J_{or}$ values were found in the same order of magnitude at $10^{-4}$ $Pa^{-1}$, in agreement with the criterion described by Dahlquist. At 1000 and 3981 Pa, the adhesive did not recover equally when the stress was released ($J_{oc} > J_{or}$) and subsequent application of 251 Pa did not give the same values as previously found. This suggests that the adhesive fractured on application of the constant high shear stress values, in agreement with the increase in relaxation time at high stress values reported previously. On application of 500 Pa for 480 s, similar $J_{oc}$ and $J_{or}$ and steady state values were obtained for the rest of the adhesive samples (Table 8). The HT-2nd sample showed a higher $J_c$ due to the increase of its viscous component on storage. The elastic creep and recoverable compliances were also higher when the 40 mm plate was used, consistent with previous observations of a higher surface area of the plate enhancing solid-like behaviour of the high tack adhesive.

The high tack adhesive had lower $G'$ ($\omega = 0.1$ rad/s) values compared to the Chu range (Table 4) under all different conditions. This showed that the $G'$ ($\omega = 0.1$ rad/s) range for the silicone high tack adhesive was $0.5–4 \times 10^4$ Pa, instead of $2–4 \times 10^4$ Pa. The BIO-PSA 7-4302 adhesive therefore had a high viscous component at low frequencies, indicating good tack

Table 7
Cross-over frequency $f^*$ of BIO-PSA 7-4302 High Tack (HT) and BIO-PSA 7-4102 Low Tack (LT) at 32 °C, from the frequency sweep tests

| BIO-PSA | $f$ (Hz) | $\sigma$ (Pa) | $f^*$ (Hz) | $t_R$ (s) |
|---|---|---|---|---|
| HT-1st | 0.1–100 | 251 | 10.0 | 0.016 |
| | | 1000 | 12.0 | 0.013 |
| | | 3981 | 15.8 | 0.010 |
| HT-2nd | | 1000 | 16.9 | 0.009 |
| HT* | | 1000 | 1.3 | 0.122 |
| HT** | | 1000 | 13.5 | 0.012 |
| LT | | 6294 | <0.1 | >1.592 |

Table 8
Creep and recovery compliance of BIO-PSA 7-4302 High Tack (HT) and BIO-PSA 7-4102 Low Tack (LT) at 32 °C

| BIO-PSA | Creep/recovery time (s) | $\sigma$ (Pa) | $J_{oc}$ ($10^{-4}$ Pa$^{-1}$) | $J_{or}$ ($10^{-4}$ Pa$^{-1}$) | $J_c$ ($10^{-4}$ Pa$^{-1}$) | Steady state |
|---|---|---|---|---|---|---|
| HT-1st | 600 | 251 | 5.11 | 2.92 | 12.9 | 0.604 |
| | | 1000 | 2.91 | 0.493 | 2.91 | 0.001 |
| | | 3981 | 0.161 | 0.0659 | 0.161 | 0.001 |
| | | 251 | 0.558 | 0.271 | 0.547 | 0.019 |
| | 480 | 5 | 2.25 | 2.97 | 12.6 | 0.823 |
| | | 500 | 2.74 | 3.35 | 13.7 | 0.800 |
| HT-2nd | | | 3.02 | 3.36 | 17.5 | 0.828 |
| HT* | | | 2.82 | 3.70 | 13.4 | 0.800 |
| HT** | | | 2.67 | 3.40 | 14.3 | 0.813 |
| LT | | | 0.012 | 0.013 | 0.04 | 0.700 |

properties. The [$G'$ ($\omega = 100$)/$G'$ ($\omega = 0.1$)] ratios (Table 4) were towards the upper limit of the Chu range indicative of a high slope of $G'$ versus $\omega$, and therefore adequate peel or debonding properties. The creep compliance $J_c$ was also greater than $10^{-5}$ Pa$^{-1}$, according to the Dahlquist criterion, for all high tack samples.

Although all high tack samples complied with the "good PSA" criteria, these results demonstrated that the adhesive layer thickness and surface area of application, represented by gap size and parallel plate size, respectively, affected the viscoelastic behaviour of the adhesive.

### 3.2.2. Low tack adhesive

The LVR of the low tack adhesive was shifted towards greater stress values than the LVR of the high tack adhesive and hence the magnitude of $G^*$ was much greater compared with the $G^*$ of the high tack adhesive (Fig. 3). In the single frequency test of 1 and 10 Hz, the phase angles were similar, 13.8° and 10.0°, respectively. Together with high $G'$ values this indicated that the low tack adhesive behaved solid-like and was much stronger than the high tack adhesive. The phase angle remained low even at 75 °C (Tables 5 and 6) and although $G'$ and $G''$ values were getting closer with increasing temperature, a cross-over point would be observed at much higher operating temperatures that are not representative of the use or storage conditions of a transdermal patch.

The frequency sweep test did not show any cross-over point within the frequency range of 0.1–100 Hz (Table 7), and $G'$ (190 and $500 \times 10^4$ Pa at $\omega = 0.1$ and 100 rad/s) was much higher than $G''$ (83 and $68 \times 10^4$ Pa at $\omega = 0.1$ and 100 rad/s) over a wide range of frequencies (Table 4). The $G'$ ($\omega = 0.1$ rad/s) was $190 \times 10^4$ Pa. This was much higher than the Chu range and showed high cohesive strength at low frequencies and a lack of the necessary flow properties for bonding with the skin. The creep test showed that the $J_{oc}$ and $J_{or}$ were in the same order of magnitude $\sim 1 \times 10^{-6}$ Pa$^{-1}$ (Table 8); they did not meet the Dahlquist criterion and were also much lower than the compliance values of the high tack adhesive. The low tack material was therefore found to be highly elastic with a comparatively small viscous component and so did not possess the appropriate viscoelastic properties for adhesion on the skin. Due to this lack of practical applicability, the preparation of drug-low tack adhesive layers was not considered necessary.

### 3.3. Viscoelastic properties of the drug-in-adhesive layers

The incorporation of increasing concentrations of nortriptyline HCl or paracetamol into the high tack adhesive caused a gradual increase in the magnitude of the complex modulus $G^*$ and a gradual decrease in the length of the LVR (Figs. 4 and 5). On addition of the drug, the adhesive became more rigid, and was more likely to fracture over a range of stresses. This was confirmed by the decreased strain values recorded, at the same applied stress of 1000 Pa; for example, strains of $3.8 \times 10^{-3}$ for

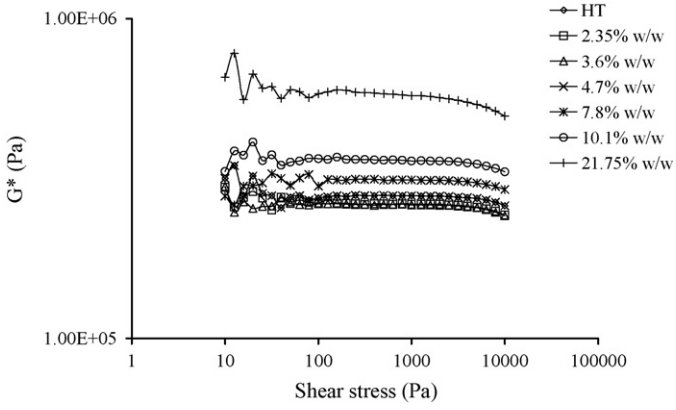



Fig. 4. Effect of nortriptyline HCl concentration on the linear viscoelastic region of the drug–adhesive layers, at 1 Hz.

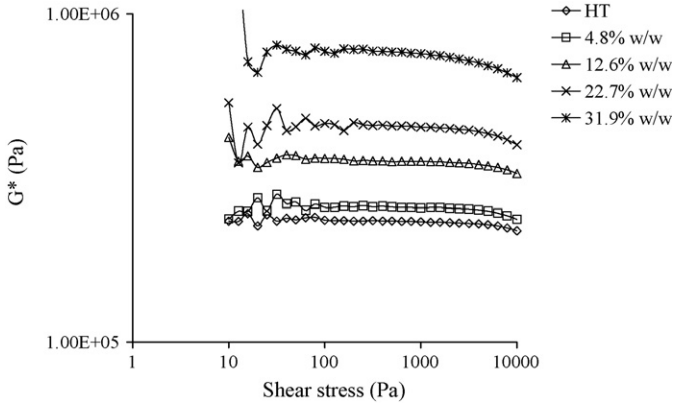



Fig. 5. Effect of paracetamol concentration on the linear viscoelastic region of the drug–adhesive layers, at 1 Hz.

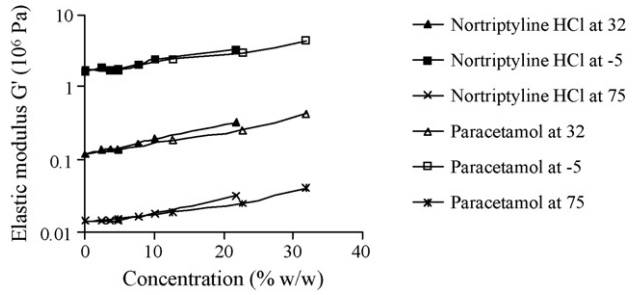



Fig. 6. Effect of drug concentration and temperature on the elastic modulus of the adhesive, at 1 Hz: squares, −5 °C; triangles, 32 °C; star, 75 °C.

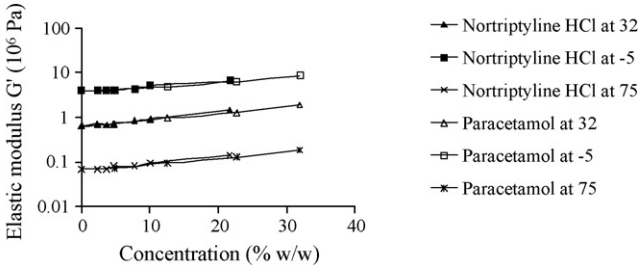



Fig. 7. Effect of drug concentration and temperature on the elastic modulus of the adhesive, at 10 Hz: squares, −5 °C; triangles, 32 °C; star, 75 °C.

2.35% (w/w) nortriptyline HCl decreased to $1.741 \times 10^{-3}$ for 21.75% (w/w) (data not shown).

The drug–adhesive samples at 1 and 10 Hz showed an increase in $G'$ (Figs. 6 and 7) and decrease in the phase angle (Tables 5 and 6) with increasing drug concentration. This behaviour was consistent at low and high temperatures. At temperatures above the cross-over temperature $T^*$, where $G' = G''$, the viscous component of the samples became predominant with increased $T^*$ of the samples corresponding to increased drug concentration (Fig. 8). Therefore, the viscoelastic point for the drug–adhesive mixtures was present at higher temperatures than that for the pure adhesive. This again indicated the higher elastic component of the drug–adhesive mixtures.

According to these findings, the magnitude of the moduli at a constant temperature was related not only to frequency but also to the drug concentration. The $G'$ and $G''$ values were similar for alike concentrations of nortriptyline HCl and paracetamol; for example at 1 Hz, $G' = 0.138 \times 10^6$ Pa for 4.7% (w/w)

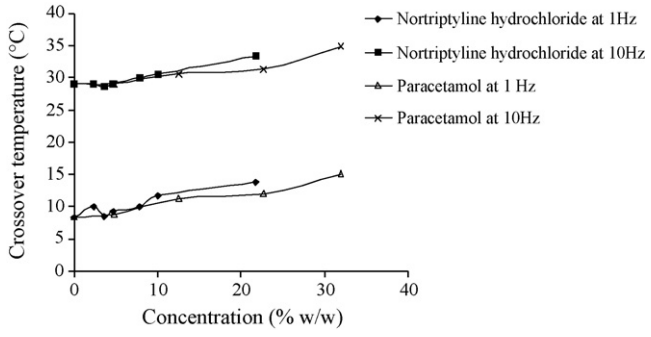



Fig. 8. Effect of drug concentration on the cross-over temperature of the moduli.

Table 9
Cross-over frequency $f^*$ of BIO-PSA 7-4302 High Tack (HT) with different drug concentrations at $\sigma = 1000$ Pa, from the frequency sweep tests at 32 °C

| Adhesive layer | Drug concentration (%, w/w) | $f^*$ (Hz) | $t_R$ (s) |
|---|---|---|---|
| HT | 0 | 12.0 | 0.013 |
| HT with nortriptyline HCl | 2.35 | 15.0 | 0.011 |
| | 3.60 | 15.8 | 0.010 |
| | 4.7 | 15.8 | 0.010 |
| | 7.80 | 15.8 | 0.010 |
| | 10.10 | 12.6 | 0.013 |
| | 21.75 | 7.9 | 0.020 |
| HT with paracetamol | 4.8 | 16.0 | 0.010 |
| | 12.6 | 12.1 | 0.013 |
| | 22.7 | 10.5 | 0.015 |
| | 31.9 | 6.8 | 0.023 |

and $0.194 \times 10^6$ Pa for 10.1% (w/w) of nortriptyline HCl, and $0.133 \times 10^6$ for 4.8% (w/w) and $0.186 \times 10^6$ for 12.6% (w/w) of paracetamol. Drug concentration, irrespective of drug type, affected the viscoelastic moduli of the adhesive at a constant temperature.

Table 9 shows that the cross-over frequency decreased as the corresponding concentrations of the drugs were increased, i.e. the relaxation time $t_R$ of the drug–adhesive layer increased. This was in agreement with results from single frequency tests indicating that samples with higher drug concentration will behave more solid-like than the adhesive alone, at any given frequency.

The $G'$ values at $\omega = 0.1$ rad/s were 0.5–1.5 × $10^4$ Pa. This complied with the requirement for a low $G'$ at low frequencies and, consequently, good bonding with the skin. The [$G'$ ($\omega = 100$ rad/s)/$G'$ ($\omega = 0.1$ rad/s)] values were also towards the upper limit of the Chu range indicating good debonding properties (Table 4). The samples with high drug concentrations showed the highest magnitudes of moduli, in agreement with previous observations of gradual strengthening of the adhesive as the drug concentration increases.

The $J_{oc}$ and $J_{or}$ values of the creep tests were in the same order of magnitude (Table 10) and, together with the $J_c$ and $J_r$, were found to decrease with the increasing drug concentration, indicating that the drugs increased the cohesive strength of the adhesive. All drug–adhesive samples had $J_c > 10^{-5}$ $Pa^{-1}$, indicating appropriate shear strength properties.

### 3.4. Solubility and particle size analysis studies

Drug crystals were observed in the samples at concentrations as low as 0.2% (w/w) of nortriptyline HCl and 1.9% (w/w) of paracetamol. The drug concentrations used for the viscoelastic studies were therefore much higher than the saturation solubility of these drugs in the dry adhesive. The median particle size was $20.6 \pm 0.2$ μm for nortriptyline HCl particles and $63 \pm 0.5$ μm for paracetamol particles. The shape of the nortriptyline HCl particles was circular–rectangular. Paracetamol particles were a mixture of rods and plates.

Table 10
Effect of drug concentration on the creep behaviour of the adhesive layers, under a constant stress of 500 Pa for 480 s

| Adhesive layer | Drug concentration (%, w/w) | $J_{oc}$ ($10^{-3}$ $Pa^{-1}$) | $J_{or}$ ($10^{-3}$ $Pa^{-1}$) | $J_c$ ($10^{-3}$ $Pa^{-1}$) | $J_r$ ($10^{-3}$ $Pa^{-1}$) | Steady state |
|---|---|---|---|---|---|---|
| HT | 0 | 0.302 | 0.335 | 1.368 | 1.033 | 0.800 |
| HT with nortriptyline HCl | 2.35 | 0.289 | 0.344 | 1.480 | 1.136 | 0.804 |
| | 3.6 | 0.267 | 0.357 | 1.599 | 1.242 | 0.833 |
| | 4.7 | 0.297 | 0.341 | 1.440 | 1.099 | 0.806 |
| | 7.8 | 0.235 | 0.275 | 1.218 | 0.943 | 0.807 |
| | 10.1 | 0.212 | 0.254 | 0.995 | 0.741 | 0.787 |
| | 21.75 | 0.133 | 0.158 | 0.578 | 0.419 | 0.771 |
| HT with paracetamol | 4.8 | 0.278 | 0.331 | 1.463 | 1.132 | 0.810 |
| | 12.6 | 0.201 | 0.257 | 1.045 | 0.787 | 0.808 |
| | 22.7 | 0.164 | 0.200 | 0.748 | 0.549 | 0.781 |
| | 31.9 | 0.093 | 0.121 | 0.444 | 0.324 | 0.790 |

## 4. Discussion

The results showed that the incorporation of the drugs into the silicone adhesive increased its solid-like behaviour at any given frequency and temperature, in a drug concentration-dependent manner. According to the correlation of viscoelasticity with adhesive performance, the implications of such an effect would be a decrease in tackiness, easier peel and a decrease in the tendency of the adhesive layers to creep outside of their application area. Despite this increase in the solid-like behaviour of the adhesive layers, the measured viscoelastic parameters remained within the quantitative range for good PSA performance. Viscoelastic measurements therefore allowed a qualitative prediction of the adhesive performance, based on the initial viscoelastic behaviour of the pure adhesive and the quantitative range criteria.

Similar results on the effect of drug incorporation into adhesives have been reported using peel force instead of viscoelastic measurements. Addition of steroids into silicone adhesives resulted in a reduction of the peel force of the adhesive layer, even at drug loading doses as low as 3% (w/w). It was concluded that drug incorporation in high concentrations results in loss of adhesiveness (Toddywala et al., 1991). Likewise, the addition of miconazole nitrate into acrylic-based adhesives resulted in a decrease in the peel adhesion values (Minghetti et al., 1999). These findings are consistent with our reported results; a reduction in the peel force indicates easier removal from the substrate. In terms of viscoelastic parameters, this is interpreted as an increase in the elastic modulus at high frequencies. Similarly, a loss of adhesiveness or tack is equivalent to an increase of the solid-like properties of the polymer at low frequencies. Therefore, we have shown that the effect of drug concentration on the adhesive performance can be demonstrated by measuring the viscoelastic parameters. This can also provide a qualitative prediction of the changes in the peel, tack and shear strength properties of the adhesive layers.

The lack of a quantitative correlation between peel test data and viscoelastic measurements has divided opinion as to their advantage over the peel test for determining adhesive performance (Demarteau and Loutz, 1996; Maillard-Salin et al., 2000). Considering the inadequacies of the currently used tack, peel and shear strength techniques (Wokovich et al., 2006), further investigation on the viscoelastic properties is justified. One disadvantage of viscoelastic measurements is their dependence on test parameters such as plate surface area and gap size. In this work we correlated plate surface area with area of application and gap size with thickness of adhesive layer. Further studies will investigate this relationship and attempt to minimise the effect of the test parameters on the viscoelastic measurements.

Nortriptyline HCl and paracetamol have different physicochemical properties (Table 1). Their concentration in the drug-in-adhesive layers was above their saturation solubility in the adhesive polymer, hence their particulate properties, such as size and shape, may have affected the viscoelastic behaviour of the layers. Nortriptyline HCl particles had a smaller median size than paracetamol particles. The shape of paracetamol particles was also more elongated. The addition of either drug resulted, however, in the same trend of changes in the viscoelastic properties of the adhesive. Therefore, we report that addition of drugs into the adhesive layer at concentrations above their saturation solubility in the dry adhesive polymer causes an increase in the cohesive strength of the adhesive layers in a drug concentration-dependent manner, irrespective of the drug particulate properties. This finding will be further investigated in future work. According to other studies, the interaction between the drug and polymer physicochemical properties has shown to affect the drug release behaviour without any mention on the adhesive properties (Toddywala et al., 1991).

## 5. Conclusions

The rheological tests carried out were useful for the evaluation of the adhesive performance. The high tack silicone adhesive BIO-PSA 7-4302 was found to comply with the "good PSA" criteria. In contrast, the low tack silicone adhesive BIO-PSA 7-4102, was lacking the necessary fluid-like properties for bonding onto the skin. A new range of $G'$ ($\omega = 0.1$ rad/s) values were established for the silicone high tack adhesive BIO-PSA 7-4302. This was found to be $0.5–4 \times 10^4$ Pa, in place of the literature range $2–4 \times 10^4$ Pa described by Chu, in agreement with a similar finding (Wolff, 2005). The addition of drug into the high tack adhesive led to an increase in the cohesive strength of the drug-in-adhesive layers, especially at drug concentrations above 20% (w/w), without deviating from the "good PSA" criteria. The

drug physicochemical properties did not affect the viscoelastic behaviour of the layers, although additional investigations are required. Considering that the test settings, such as size of parallel plate and gap size, affected the viscoelastic behaviour of the adhesive, further studies are required to establish any correlation with the area of application and layer thickness, respectively.

## Acknowledgement

The authors would like to thank the Institute of Chemical Engineers Pharma Subject Group for the funding of Mr. Ho's summer placement research.

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