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Controlled Release in Transdermal Pressure Sensitive Adhesives using Organosilicate Nanocomposites

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Abstract

Polydimethyl siloxane (PDMS) based pressure sensitive adhesives (PSA) incorporating organo-clays at different loadings were fabricated via solution casting. Partially exfoliated nanocomposites were obtained for the hydroxyl terminated PDMS in ethyl acetate solvent as determined by X-ray diffraction (XRD) and atomic force microscopy (AFM). Drug release studies showed that the initial burst release was substantially reduced and the drug release could be controlled by the addition of organo-clay. Shear strength and shear adhesion failure temperature (SAFT) measurements indicated substantial improvement in adhesive properties of the PSA nanocomposite adhesives. Shear strength showed more than 200 % improvement at the lower clay loadings and the SAFT increased by about 21% due to the reinforcement provided by the nano-dispersed clay platelets. It was found that by optimizing the level of the organosilicate additive to the polymer matrix, superior control over drug release kinetics and simultaneous improvements in adhesive properties could be attained for a transdermal PSA formulation.

Keywords

Organoclay; Polydimethyl Siloxane; Diffusion; Drug Delivery; Shear Strength; Mass Transport; Nanotechnology

Introduction

Polymer clay nanocomposites have been extensively studied in the last decade. For the dispersion of the hydrophilic nano-clay platelets in a lipophilic polymer matrix, the clay is usually modified with a long chain fatty acid surfactant. Substantial improvements in the mechanical and barrier properties of the nanocomposite materials have been observed.^{11, 14, 20, 21} More recently, their role as modifiers in pressure sensitive adhesive (PSA) systems have also been examined.^{4, 17} Organo-clays can impart substantial improvements in adhesive properties such as shear strength, and offer additional advantages in commercial production by reducing the build up on adhesive processing equipment.¹⁷

For a drug to effectively permeate the skin in a transdermal delivery system, the drug should pass through the *stratum corneum* (SC), a protective layer of skin that is known to offer

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significant resistance to permeation of hydrophilic material. Several literature reports review the different approaches adopted for transdermal drug delivery.^{2, 18-28} These include passive drug diffusion enhancement techniques such as modification of the nature of the drug molecule to facilitate permeation or the concurrent use of chemical permeation enhancers such as alcohols, fatty acids and esters.¹⁸⁻²⁸ Physical drug delivery enhancement technologies that have been utilized include iontophoresis (application of a low level electrical current), technologies which puncture the SC (such as micro-needle based devices) and other miscellaneous methods such as the application of pressure, ultrasound, laser radiation, magnetic fields and temperature differences.² However, most commercial transdermal formulations still currently use polymer matrix based release technologies where a drug is dispersed uniformly within the adhesive layer. Commercially available patches such as 3M's Climara® (an estradiol transdermal patch) and Smith Kline Beecham's Androderm® (a testosterone patch), have a fatty acid ester in the formulation to enhance permeability.²⁸ Excipients and surfactants such as sodium lauryl sulfate (SLS) and dimethyl sulfoxide (DMSO) are also known to enhance skin permeation.¹⁸⁻²⁹ It has also been shown that SLS has the potential to enhance diffusion by as much as four to five times, in guinea pig skin.²⁹ However, even though an improvement in skin permeability is obtained, the surfactant may seriously affect the adhesive properties such as tack, peel and shear and result in insufficient adhesion to skin.^{22, 28}

This study aims to develop a transdermal PSA formulation which offers better control over the drug release kinetics and simultaneously improves adhesive properties. In this study, we examined the effect of organo-clay on adhesive strength properties and drug-release characteristics of PDMS based PSA samples. To our knowledge, this is the first study to examine the role of organo-clay nanocomposites in pressure sensitive adhesives with applications in transdermal drug delivery. In addition to improvements in PSA adhesive properties, it is expected that the nanodispersion will offer an added degree of control over the rate of release of the drug. The presence of a surfactant bound to the clay and at the interface of the adhesive and skin may also enhance skin permeation.

Materials and Methods

Chemicals

Montmorillonite clay (Na-MMT, Mineral Colloid BP) was obtained from Southern Clay Products, (Gonzales, TX) and contains exchangeable cations of primarily Na⁺. Mineral Colloid BP, a fine powder with an average particle size of 75 µm in the dry state and a cation exchange capacity of 90mEq/100g. Octadecylamine (C18 amine), was supplied by Aldrich (St. Louis, MO) and was used as received. Solvent blue 35 dye (MW: 350.45), a hydrophobic dye used to simulate drug release from the polymer matrix, was obtained from Sigma (St. Louis, MO). Hydroxyl terminated poly-(dimethyl siloxane) (PDMS-OH, BIO-PSA® grade 7-4601) and trimethyl terminated PDMS (PDMS-CH₃, BIO-PSA® grade 7-4302) in ethyl acetate solvent were obtained from Dow Corning Corp. (Midland, MI) and used for synthesizing the adhesive nanocomposite samples.

Synthesis of Organo-Clay

The C18-MMT organo-clay (OC) was synthesized by ion-exchange between the Na-MMT and the octadecylamine according to a previously described procedure.⁹⁻¹⁰ 10 g of MMT was suspended in 1 liter of distilled water and stirred for 30 minutes. An aqueous solution of 12 mmoles of the C18 amine surfactant was then added with continued stirring. After 30 minutes, 2 ml of concentrated HCl (38 weight % aqueous solution) was added to neutralize the mixture and then stirred for an additional 3 hours. The solution was left idle for another 14 hours. The product was then filtered and washed several times with hot distilled water until no chloride

was detected using a 0.1 M AgNO₃ solution. The resulting cation exchanged clay was vacuum dried and then ground using a mortar and pestle. Particles of size of less than 65 µm were collected by passing through a sieve. The modified clays are referred to as C18-MMT.

PDMS Nanocomposite Preparation

PDMS based PSA formulations are typically composed of two components, a polysiloxane polymer and a silicate resin in solvent systems such as ethyl acetate or xylene. During the curing process, a crosslinking reaction between the polymer and silicate resin results in the formation of a three dimensional network of polymer chains. In this study, we used –OH terminated (7-4601) and tri-methyl terminated PDMS (7-4302) adhesives. The former was chosen because it was anticipated that the –OH groups would have an affinity to hydrogen bond with the clay platelets, thus enhancing their dispersion. The latter was chosen because of its enhanced chemical stability in the presence of amine functional drugs. 10 g of PDMS adhesive (~6 g of polymer) were added to a 50 ml flat-bottom conical flask (PYREX 4980, Corning). 3 mL of ethyl acetate solvent along with the appropriate amount of C18-MMT organo-clay (OC) and solvent blue dye were added to the flask. Several OC concentrations (0, 2, 5 and 10% based on dry weight of adhesive) were used for preparing the PDMS nanocomposite adhesive. The samples were mechanically stirred for one hour and then sonicated to evenly disperse the OC in the PDMS adhesive solution. The PDMS adhesive flasks were then vacuum dried at 50 °C for 48 hours until a uniform PDMS nanocomposite (PNC) layer at the bottom of the flask was obtained. The layer has a surface area of 18 cm² and a thickness (mean ± std. dev) of 2.22 ± 0.04 mm.

Material Characterization

X-ray diffraction (XRD) patterns of the OCs and the PNC adhesives were obtained by using a Phillips XRG 3100 X-ray generator equipped with a Ni-filtered Cu-Kα (1.5418 Å) source that was connected to a Phillips APD 3520 type PW 1710 diffractometer controller. The SEM images were taken using a scanning electron microscope (Hitachi S4500) equipped with a field-emission gun, two secondary electron detectors, a backscatter detector, and an infrared chamber scope. Atomic force microscopy (AFM) was carried out using the air tapping mode and a scan rate of 1.61 Hz. Cantilever tips used were silicon nitride (Veeco Instruments Inc., Woodbury, NY) with an average spring constant of 0.58 N/m.

Release Study

To determine drug transport from the PNC formulations, release studies were conducted using the Solvent Blue 35 dye. Release studies of the PSA formulations were conducted in a temperature controlled Environ-Shaker (Lab-Line®, Thermo Scientific, MA) at 37 °C and 150 RPM. The PNC formulation was prepared in a 50 ml flask as mentioned previously, and 30 mL of dimethyl sulfoxide was added as a solvent. The model dye was readily soluble in DMSO and the PDMS adhesive was insoluble in DMSO. Samples (100 µL) were taken at frequent intervals over a period of twenty-five days and stored for subsequent analysis. The dye levels were determined by measuring the absorbance of the sample at a wavelength of 644 nm using a spectrophotometer (SpectraMax M2, Molecule Devices, Sunnyvale, CA).

Adhesive manufacture and testing

The PDMS adhesive nanocomposites were solution cast on a fluorinated silicone release liner. The adhesive samples were dried in an oven at 80 °C for 1 hour and then were pressure rolled onto a poly-(ethylene terephthalate) (PET) backing liner. Three samples per adhesive were tested at each condition. The peel adhesion test was run as per ASTM D903-98 at an angle of 180° and a speed of 12 inches per minute. The static shear strength was measured according to ASTM D-3654 (500 g/0.5 in²). The shear adhesion failure temperature (SAFT) was run as per

ASTM D4498-00. Briefly, one square inch of adhesive contact was applied to a standard stainless steel panel and then placed in an oven starting at 25 °C. A 500-gram weight was applied and the temperature was raised by 5 °C every ten minutes. The point at which the sample failed was recorded.

Results and Discussion

Morphology Characterization

X-ray diffraction (XRD) is a commonly applied technique for examining surfactant intercalation and expansion of MMT, and the morphology of organoclay nanocomposites.^{14, 15, 20, 21} As MMT interlayer spacing expands or contracts, the d_{001} peak shifts proportionally to the left or right. The d-spacing is calculated from the XRD peak position using Bragg's law ($d = \lambda/2\sin\theta$), where d is a reflection of the interlayer clay spacing, λ is the x-ray wavelength equal to 1.5418 Å, and θ is the incidence angle of the x-ray. An increase in the d-spacing of the clay indicates intercalation/exfoliation of the clays by surfactant or polymer molecules. XRD patterns can be used to pre-screen the nanocomposite samples for OC exfoliation. The XRD patterns for the OC and the PNC samples are shown in Figures 1A and 1B. Figure 1A is a typical diffraction pattern of an unmodified Na-MMT. It shows a strong peak corresponding to a 2θ value of 7.1. After the clay was modified with the C18-surfactant, the peak shifted to a lower angle corresponding to a 2θ value of 4.3. When we compared the peak intensity of the composite PDMS-CH₃/C18-MMT (Plot 4 in Figure 1B) to the intensity pattern of C18-MMT (Figure 1A), only a very small increase in the 2θ value was observed suggesting that the d-spacing was unchanged and the PDMS molecules was not able to fully penetrate the clay layers. A similar result can be observed when the XRD pattern of PDMS-CH₃/Na-MMT (Plot 3 in Figure 1B) was compared to that of Na-MMT (Figure 1A). However, when XRD pattern of PDMS-OH/C18-MMT (Plot 2 in Figure 1B) was compared to that of C18-MMT (Figure 1A), it can be observed that the former had no clear peak because the 2θ value was shifted to a very low angle. A similar but not as strong observation can be made when XRD pattern of PDMS-OH/Na-MMT (Plot 1 in Figure 1B) was compared to that of Na-MMT (Figure 1A). This featureless XRD pattern indicates possible exfoliation of the clay platelets. There are several reasons for the better dispersion of the OC platelets in the -OH terminated PDMS adhesives as compared to PDMS-CH₃. Silicate oxygen groups on the clay surface in addition to hydroxy groups along the clay edges are more likely to hydrogen bond with the free hydroxy terminated chain ends (as compared to the -CH₃ chain ends), thus increasing the possibility of intercalation/exfoliation of the clay layers.^{15, 26} Also in the case of PDMS, the polymer backbone is incompatible with the OC. Therefore, with minimal backbone contribution to the dispersion, end-group polarity plays a key role in the dispersion and exfoliation of the clay platelets.²³ With decreasing molecular weight, the end-group effects will become even more prominent in the case of associating or H-bonding chain ends. Thus, with a judicious choice of end-groups, an appropriately low molecular weight and suitable surfactant chain length, it is possible to develop a thermodynamically stable nanocomposite adhesive dispersion with minimal mixing.

An SEM image of the PDMS-OH adhesive (Figure 2A) indicates a uniform layer of adhesive between the PET backing liner and the release liner. The thickness of the adhesive layer measured after drying was 38 ($\pm$ 1.23) microns. Due to the softness of the PDMS adhesive, it was not possible to ultra microtome a sample for a TEM image. However, tapping mode AFM has been successfully used to study dispersion of organo-clay in polymers²³ and was applied in this study to determine dispersion of OC in the PDMS adhesives. An AFM image of the PDMS adhesive layer (Figure 2B) indicates an even dispersion of the OC nanoparticles. The brighter white areas indicate the OC platelets and the darker areas represent the less resilient adhesive areas. Particles in the range of 50 to 70 nm (intercalated structures) could be seen. In

addition, at higher magnifications, diffuse patterns (exfoliation) between these particles can also be observed (Figure 2C).

Transport Characterization

The multiple layers in skin serve as an excellent barrier to water loss and provide sensation, heat regulation and protection from UV as well as bacterial invasions among other functions. For a transdermal drug to overcome transport limitations and penetrate through the outermost layer of skin layer, the *stratum corneum*, the size, charge and lipophilicity of the drug molecule become important factors. Chemical permeation enhancers (CPEs) such as surfactants and organic solvents alone or in combination are used to enhance diffusion through skin.^{13, 18, 25} In our study, we used the Solvent Blue 35 dye as a model molecule to characterize the transport properties and the release kinetics of the PSA formulations. The hydrophobic characteristics and the molecular weight of the dye (Log P (log₁₀ partition coefficient) = 5.2, MW (molecular weight) = 350) are similar to most drugs currently used in transdermal systems, such as β -estradiol (for hormone therapy, Log P = 3.94, MW = 272), nitroglycerin (vasodilator for cardiac pain)²⁸ and oxybutynin (for overactive bladder, Log P = 4.9, MW = 357).²⁴

The release of the solvent blue dye was studied from the PDMS – OH/OC polymer matrix (Figure 3A) at four different organo-clay loadings (0, 2, 5 and 10%). It can be observed that as OC loading increased, the percent of dye release decreased. It was shown that addition of 2% OC decreases the total dye release by about 50% after a 10 day period and by about 75% for higher values of organo-clay loading (5 and 10%). Although the dye release decreased with OC levels, the reduction in the dye release seemed to reach saturation at about 10% OC loading. This result is in agreement with earlier published work reporting controlled release of drug molecules by organo-clays in polymer pellets⁷ and hydrogels.¹⁶ The rate of drug release in a polymer nanocomposite system is based on several factors such as the amount of organo-clay in the matrix, the type of surfactant used to modify the clay, the degree of exfoliation of the clay as well as the charge of the drug moieties. It has been shown in Figure 3A that the extent of dye release was controlled by varying the organo-clay loading in the polymer matrix. More importantly, the initial burst release was substantially reduced (Figure 3B), and a more constant sustained release profile was maintained for the desired time period. The initial burst release is usually undesirable because the drug level may be above the therapeutic window and result in toxicity or other side effects.

Many polymeric resin matrices show Fickian release.^{5, 6} For a planar surface similar to the one employed in this work, the equation governing Fickian release³ is

$$\frac{M_t}{M_0} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left(\frac{-D(2n+1)^2 \pi^2 t}{4\delta^2}\right) \quad (1)$$

where M_t is amount of dye released from the polymer matrix at time 't', M_0 is the initial amount of dye in the device and ' δ ' is the thickness of the PNC adhesive layer. D is an effective diffusivity of the dye in the polymer-nanocomposite. For short times, Equation (2) can be truncated to the following form.³

$$\frac{M_t}{M_0} = \frac{2}{\delta} \left(\frac{Dt}{\pi} \right)^{1/2} \quad (2)$$

Effective diffusivity values were estimated from the slopes of M_t/M_0 vs. $t^{1/2}$ (Figure 4A). The plots resulted in linear trends initially for all organo-clay compositions. D_0 was defined as the diffusivity for the PDMS resin without nanocomposite and D_n was the diffusivity value for the PNC for increasing OC loading respectively. The ratios of D_n/D_0 , were plotted against increasing weight % (n) of nanocomposite (Figure 4B). The predicted diffusivities (lines in Figure 4B) were obtained by models used for estimating gas and liquid diffusivities through polymer filled composite systems with flake like particulates.^{8, 19} These models have been used recently to describe gas^{21, 30} as well as liquid⁷ permeability in clay based nanocomposite systems.

The Nielson model predicts the effect of filler level on diffusivity.¹⁹ The clay platelets are assumed to be oriented parallel to the surface of the polymer and perpendicular to the path of diffusing molecules. The model is defined as

$$\frac{D_n}{D_0} = \frac{1}{1 + \frac{L}{2W} \varphi_s} \quad (3)$$

where L is the length of a face of the clay platelet, W is the thickness of the platelet and φ_s is the volume fraction of clay in the polymer matrix. The Cussler model also assumes the flakes to be aligned parallel to the direction of diffusion and having one very long dimension.⁸ The reduction in diffusivity depends on three factors; the tortuous wiggles to get around the flakes, the tight slits between the flakes and resistance in going from the wiggle to the slit. The model assumes that the diffusion depends on the volume fraction of the filler and the aspect ratio of the platelets and is given by

$$\frac{D_n}{D_0} = \frac{1}{1 + \frac{(\frac{L}{2W})^2 (\varphi_s)^2}{(1-\varphi_s)}} \quad (4)$$

The models were fitted to the experimental data using the 'Solver' algorithm in Excel (Microsoft, Redmond, WA) to determine the aspect ratio (L/2W) values for Equations 3 and 4. It can be seen from Figure 4B that the decrease in diffusivity can be well predicted using the Nielson model using an L/2W value of 498 which is in the range of those reported for organosilicate fillers. The Cussler model fits the experimental data at a lower value of the aspect ratio (L/2W=231). Both models predicted L/2W values that are within the range of those reported for organosilicate fillers.¹ However, the Nielson model fitted the data slightly better than the Cussler model. Average absolute percentage error between experimental and predicted values for the Nielson model is 35% whereas it is 47% for the Cussler model.

Adhesion Strength Characterization

To characterize the adhesion strength of the PSA formulations, we determined the shear strength, shear adhesion failure temperature (SAFT), and peel strength of the adhesives made of them. Figure 5 shows the results of adhesion strength of the PSA formulations as a function of different organo-clay loadings. The shear strength (**5A**) showed a marked improvement as compared to the unmodified PSA (2.65 times the initial value at 1% OC loading, and 1.4 times the initial value at 2%). In comparison, the shear strength for the unmodified clay (Na-MMT) decreased to only 28% of the initial shear strength. In the OCs, the increase in shear strength is expected because of the reinforcement of the PDMS matrix due to exfoliation/intercalation of the OC platelets.¹⁷ However, at higher clay loadings, the clay may form aggregates or

agglomerates, which could work as stress concentrators and thus reduce shear strength.²⁷ This explains the reduction in shear strength at the higher OC loadings. In the case of the Na-MMT/PDMS system, the Na-MMT forms agglomerates even at low filler loading, and acts not as a nanocomposite but as a usual filler where the clay layers are dispersed in the matrix but not exfoliated or intercalated, which is reflected in the reduction in shear strength. The SAFT measured in a ramping oven also indicated substantial improvement for the OC nanocomposites over the control formulation and Na-MMT (Figure 5C). The increase in SAFT was about 21% and remained constant at the higher nanocomposite loading. The peel strength of the adhesives decreased only slightly with increasing OC levels (Figure 5B). The decrease was about 3% at 1% OC loading and about 10% at 2% OC loading. This could possibly be attributed to the presence of the plasticizing effect of the C18-amine surfactant at the interfacial layer between the adhesive and the substrate. It has been shown recently that a combination of chemical permeation enhancers acting in synergy are able to increase the permeability up to 100-fold, of even large molecules.^{12, 13} Therefore, a surfactant or a combination of surfactants, if appropriately selected for organo-clay modification can possibly act as a chemical permeation enhancer at the interfacial layer between the skin and the transdermal adhesive.

Conclusions

Organoclay based PSA formulations were developed for transdermal drug delivery. The exfoliation of the clay nanolayers in the PDMS matrix resulted in a more uniform release rate and substantially reduced the initial burst release. Considerable improvements in the shear strength and SAFT of the PSA were obtained due to the reinforcement provided by the nano-dispersed clay platelets. It can be concluded that by optimal addition of organosilicates to a PSA formulation, enhancements in PSA properties as well as accurate control over drug release rate could be obtained simultaneously. It may be possible to design transdermal PSAs with a higher initial drug concentration but with little or no burst release. A steady concentration of the active ingredient can be delivered and thus provide the lowest effective blood level of the drug while minimizing adverse side effects, due to toxicity. This attribute could be potentially significant in the design of effective PSA systems for transdermals with extended release.

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Figure 1.
 (A) XRD patterns of Na-MMT (unmodified clay) and C18-MMT (modified organo-clay).
 (B) XRD patterns of PDMS-nanocomposites: PDMS-OH/Na-MMT (1), PDMS-OH/C18-MMT (2), PDMS-CH₃/Na-MMT (3), and PDMS-CH₃/C18-MMT (4).

Figure 2. (A) Cross-sectional SEM image (X 400) of the transdermal pressure sensitive adhesive. (B) AFM image of the adhesive layer (bar=1 micrometer). (C) AFM image of the adhesive layer at a higher magnification (bar=100 nanometer).

Figure 3.

(A) Percent normalized drug release from a PDMS-OH adhesive at different C18-MMT levels. (B) Rate of drug release showing the difference in burst release from a PDMS-OH adhesive at two different organo-clay loading levels (0 and 2%).

Figure 4.

(A) Transport coefficient estimation from drug release data. Square root of time vs. percentage release plot at different OC loadings. (B) D_n/D_0 values for various nanocomposite loadings. Marker indicates results from experiments, and lines indicate model fits.

Figure 5.

(A) Values of shear strength vs. clay loading in the PSA. (B) Values of 180° peel strength vs. clay loading in the PSA. (C) Shear adhesion failure temperature (SAFT) vs. clay loading.