International Journal of Pharmaceutics 370 (2009) 103–109

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Plasticizers in the manufacture of novel skin-bioadhesive patches

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ARTICLE INFO

Article history:
Received 9 September 2008
Received in revised form
19 November 2008
Accepted 20 November 2008
Available online 27 November 2008

Keywords:
Plasticizer
Roughness
Mechanical properties
Adhesion
Peeling

ABSTRACT

The effects of plasticizer inclusion (10%, w/w) on roughness, mechanical and adhesive properties of novel skin-bioadhesive patches produced from polyvinyl alcohol and polyvinyl pyrrolidone were studied. Dry, non-adhesive patches became adhesive upon wetting. Roughness profiles of the patches and a skin model were studied, by measuring average values of Ra (recognized as average roughness in practice) and Rz (average of the vertical distances from the highest peak to the lowest valley within five equal sampling lengths). These values ranged from 2.4 to 3.8 μm and from 10.9 to 12.5 μm, respectively. Plasticizers had no significant effect on them. The average Ra obtained for the skin model was six- to eightfold higher than that obtained for the patches. Plasticizer inclusion caused a reduction in patch tensile strength and an increase in its strain at failure—the lower the plasticizer's molecular weight, the greater its effect. Plasticizer inclusion also caused a significant reduction in peeling force: 1.5 ± 0.11 and 2.8 ± 0.13 g force/cm for patches with and without glycerol, respectively. Patch adhesion to the skin also depended on the time elapsed between application and removal. In summary, plasticizer inclusion widened the range of mechanical and adhesive properties of the patches.

1. Introduction

Topical and transdermal drug delivery may have some advantages over other drug-delivery routes. By using transdermal drug-delivery systems (TDDS), first-pass hepatic metabolism is circumvented, resulting in good customer compliance. In specific cases, there is also an increase in drug bioavailability (Alderborn, 2002; Zecchi et al., 2002; Washington et al., 2003). TDDS can be classified into several groups: creams and emulsions, gels and patches. There are two basic types of patches: drug-in-adhesive (DIA) systems in which the drug is dissolved/dispersed in the adhesive layer, and reservoir systems that contain a membrane controlling the drug-release rate from a reservoir layer (Dittgen, 1998; Venkatraman and Gale, 1998; Panchagnula and Jain, 2005).

Plasticizers are low-molecular-weight materials which cause a reduction in polymer–polymer chain secondary bonding (e.g. hydrogen bonding), forming secondary bonds with the polymer chains instead (Feldstein et al., 2001, 2007). With the inclusion of a plasticizer, elongation at break and flexibility are expected to increase, while tensile stress, Young's modulus and the glass transition temperature are expected to decrease (Rahman and Brazel, 2004). Plasticizers are used in many areas/markets, such as food packaging, agriculture, papers and tapes (Giam and Wong, 1987; Briston, 1989; Krochta et al., 1994; Nussinovitch, 1997, 2003). The effects of different plasticizers on tensile stress and elongation at break of films based on wheat gluten (Popineau et al., 2003), chitosan (Tighzert et al., 2005) and gelatin (Sorbal et al., 2005) have been investigated. Plasticizers have also been used in transdermal drug-delivery devices, and in many formulations, 5–20% (w/w, dry basis) plasticizer was added (Agrawal et al., 1996; Aqil and Ali, 2002; Biswajit and Priyanka, 2002; Jain et al., 2003; Minghetti et al., 2003; Aqil et al., 2004; Gupta and Jain, 2004; Kimura et al., 2005). Without the addition of a plasticizer, a very strong, but brittle film is produced. High brittleness means that external forces (e.g. bending, peeling or tensile) may lead to film tearing under very small strains (Tighzert et al., 2005). On the other hand, addition of a plasticizer has been reported to cause a significant increase in film ductility, accompanied by a decrease in its strength (Abd Karim et al., 2006). As regards transdermal patches, the decrease in patch strength is less important, so long as it remains sufficient to resist tearing while the patch is being positioned or repositioned on the skin (Nussinovitch et al., 2008). Plasticizers may also influence the adhesive properties of the patch. Patch adhesion to a substrate is achieved, at least in part, by the formation of secondary bonds between specific functional groups of molecules in the patch and the substrate (Ben Zion, 2007). As already mentioned, including a plasticizer in the patch formulation will produce new secondary bonds between polymer and plasticizer molecules, which may replace polymer–polymer chain secondary bonding (Rahman and Brazel, 2004). Furthermore, secondary bonding between the patch

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doi:10.1016/j.ijpharm.2008.11.015

and the substrate may, in and of itself, lead to changes in the adhesive properties of the patch. Recently, a single-layer DIA patch which was practically not adhesive in the dry state (having only remnant adhesion) and became adhesive upon wetting was formulated. The patch included polyvinyl alcohol (PVA) as a film-forming agent, Eudragit E100 (dissolves in water only in the presence of organic acids) as an adhesive and a plasticizer (glycerol or sorbitol, at 15%, w/w, dry basis). The effects of the plasticizers on tensile stress and elongation at break of the patch were studied (Santi et al., 2003, 2005). However, the effects of molecular weight of the plasticizers on those mechanical properties were not investigated. To the best of our knowledge, the possible effects of plasticizer inclusion on the adhesive and topographical properties of transdermal patches, which may be related to their adhesive properties (McBain and Hopkins, 1925; Ben Zion, 2007), have also not been investigated. Since in other research areas (e.g. films based on gluten and chitosan which are used in the food industry), plasticizer inclusion and its molecular weight may affect different physical properties of the products, our main tenet was that those parameters may also affect different physical properties of transdermal patches based on synthetic water-soluble polymers (such as PVA and polyvinyl pyrrolidone [PVP]). Therefore, the objectives of this study were to: formulate dry patches which are adhesive only upon wetting, with and without plasticizer inclusion; study the effects of plasticizer inclusion at relatively high concentrations on roughness (Ra and Rz values), mechanical (stress and strain at failure) and adhesive (peeling force) properties of the patches, and study the adhesive properties of the patches as a function of time elapsed between patch application and removal.

2. Materials and methods

2.1. Patch preparation

Four types of patches based on PVA as a film-forming agent and PVP as an adhesive were produced. Three of the four different types of patches also contained one plasticizer from a list of glycerol, polyethylene glycol (PEG) 200 or PEG 400 (with molecular masses of 92, 200 and 400 Da, respectively). PVA of 49,000 Da (degree of hydrolysis 87%) (Sigma Chemical Co., St. Louis, MO) was ground to a fine powder with particles smaller than 140 μm (Fritsch Pulverisette 6, Fritsch GmbH, Germany). PVA powder (12%, w/w, wet basis) was dissolved in hot double-distilled water (~80 °C) with stirring (~3 h) using a magnetic stirrer (Freed Electric, Haifa, Israel). Simultaneously, PVP powder (10%, w/w, wet basis) of 55,000 Da (Sigma) was dissolved in another beaker which contained hot double-distilled water (~80 °C) while stirring. After 3 h, both solutions were cooled to 60 °C and one of the plasticizers (either glycerol, PEG 200 or PEG 400) was added to the PVA solution (at 10%, w/w, wet basis). The two solutions were then combined to give one final solution, which was stirred for 2 h more. The final solution was laminated on siliconized paper (Armak Tape Co., Makati City, Philippines), using a film-casting knife (Elcometer, Rochester, MI), and oven-dried at 80 °C for 120 min. After additional drying of the patch samples at 105 °C for 48 h, water content was measured by the gravimetric method (Gardner, 1986) to be ~7% (w/w). Petri dishes filled with patch samples (10 cm × 10 cm) were placed in a desiccator. The average thicknesses of the patches were measured with a thickness meter (Elcometer).

2.2. Skin model preparation

A skin model was prepared in accordance with US Patent 4,877,454 (Charkoudian, 1989) to serve as a substrate in peeling tests. Porcine skin gelatin 225 bloom (7 g) (Sigma) was dissolved in 58.1 g of water at 50 °C with stirring. Then, 0.035 g of propylparaben as a preservative (Sigma), 3.15 mL of sodium hydroxide solution (4%, w/w) (Frutarom, Haifa, Israel) and 0.35 g of glycerol were added. Ceraphyl GA (3 g) was added (Van-Dyk, Belleville, NJ) as the lipid component in the skin model, resulting in a white emulsion. Before pouring the emulsion into a negative mold in accordance with Charkoudian's patent, 2.77 mL of formaldehyde solution (3%, w/w) was added. The mixture was allowed to set and dry under ambient conditions (Charkoudian, 1988, 1989). After 24 h, the resultant skin model was carefully removed from the mold. The average thickness of the skin model was measured with a thickness meter.

2.3. Topographical characterization of the skin model and patches

Roughness of the different patches and the skin model was measured using a portable surface-roughness tester (Surftest-301, Mitutoyo Corp., Tokyo, Japan). Ten measurements of Ra and Rz were taken, to characterize the aforementioned surfaces. The Ra and Rz measurements were taken in both the "*x*" and "*y*" dimensions of the plane surface of the patch or skin model. Results are given as arithmetic mean ± S.D. for an evaluation length of 7.5 mm at a speed of 0.5 mm/s. In order to further study the topography of the skin model and the different patches, photos were taken with a digital camera (Nikon Coolpix 600, Nikon Corp., Tokyo, Japan).

2.4. Tensile test

To study the mechanical properties of the patches, tensile tests were carried out. Samples were cut from the patches using a sharp-edged stainless-steel template. The dimensions of the bone-shaped samples were: length 65 mm, width at the top and bottom edges 24 mm, and at the center of the patch 12 mm (Nussinovitch et al., 1990). Thus, tearing of the samples was directed to their center. Each sample was connected to the upper and lower grips of a Universal Testing Machine (UTM) (Instron Model 5544, Canton, MA). Tensile tests were carried out in six replicates per sample (two batches for every patch type). The UTM was connected to an IBM-compatible personal computer with a card. Using "Merlin" software (Instron Corporation), data acquisition and conversion of the Instron's continuous voltage vs. time output into digitized force vs. time relationships was performed. The following equations were used to convert force vs. time data to stress vs. Hencky's strain relationships:

$$\Delta H = v \cdot t$$

$$\varepsilon_{\mathrm{H}} = \ln\left(\frac{H_0 + \Delta H}{H_0}\right)$$

$$\sigma_{\mathrm{corrected}} = \frac{F_t}{A_t} = \frac{F_t(H_0 + \Delta H)}{A_0 H_0}$$

where ΔH is the absolute deformation (m), v is the deformation rate (m/s), t is time (s), ε_{H} is the Hencky's strain, H_0 is the initial length of the sample (m), $\sigma_{\mathrm{corrected}}$ is the corrected stress (Pa = N/m^2), F_t is the force (N) at a given time and A_0 (m^2) is the initial cross-sectional area of the patch.

2.5. Peeling test

The adhesion properties of the patches were studied by peeling test. The patches were peeled from a skin model sample as previously described (Portelli, 1986; Ben Zion and Nussinovitch, 1997). The produced patches had to be wetted to become adhesive. Therefore, prior to the peeling tests, the skin model was immersed in double-distilled water for 5 s to reach a relative humidity of ~25%, which is typical for the stratum corneum (Charkoudian, 1989). Then, the skin model was wetted with a known amount of water

Fig. 1. Set-up for peel test.

($9\,\mu L/cm^2$). Finally, the patch was attached and left on the model surface for the specified period of time (15, 30 or 45 min) until the start of the peeling test. The peeling tests were carried out with the UTM (Fig. 1). Elapsed time from application was defined as the time passed from the instant the patch was attached to the wetted skin model till the start of the peeling test. During the test, a graph showing the peeling force (g force/cm) as a function of peeling length (cm) was obtained. Peeling force was examined as a function of elapsed time. Rectangular samples with dimensions of 10 cm × 2 cm (length by width) were used. Six replicates were carried out per sample.

2.6. Statistical analysis

Statistical analyses were conducted using JMP software (SAS Institute, 1995), including ANOVA and Tukey-Kramer Honestly Significant Difference test for comparisons of means, with $p \leq 0.05$ considered significant.

3. Results and discussion

Patch adhesion is influenced by its suitability to the substrate to which it is being applied. This suitability is affected, among other things, by the surface topography of the adhesive and the substrate (McBain and Hopkins, 1925; Hershko et al., 1998; Ben Zion, 2007). Therefore, it is necessary to examine the roughness of both surfaces. This property comprises the surface irregularities of relatively small distances (usually up to tens of microns) caused as a function of the preparation method and conditions, the chemical composition and the number of components in the adhesive system. The two main parameters used to characterize the roughness profile of a surface are Ra and Rz (particularly the former). Ra is defined as the average deviation of the absolute values of the roughness profile from the center line within the distance being measured and Rz is defined as the average of the vertical distances from the highest peak to the lowest valley within five equal sampling lengths. Figs. 2 and 3 present typical roughness graphs for a patch containing 10% glycerol and a skin model, respectively. Table 1 summarizes the Ra and Rz values obtained for the four different patches and the skin model, which all had a thickness of 200 ± 10 μm. All presented Ra and Rz values are the average ± S.D. of 10 measurements, which were taken in the "*x*" and "*y*" dimensions of the plane surface of the patches and skin model. Average Ra values for the four types of patches ranged from 2.4 to 2.8 μm, in the "*x*" and "*y*" dimensions. For a patch containing 10% glycerol, the average Ra values in the "*x*" and "*y*" dimensions were: 2.55 ± 0.12 and 2.58 ± 0.13 μm, respectively. In contrast, the average Ra values for the skin model in the "*x*" and "*y*" dimensions were 19.35 ± 0.91 μm and 19.25 ± 0.89 μm, respectively (Table 1), about six- to eightfold higher than the average Ra values obtained for any of the four types of patches. Average Rz val-

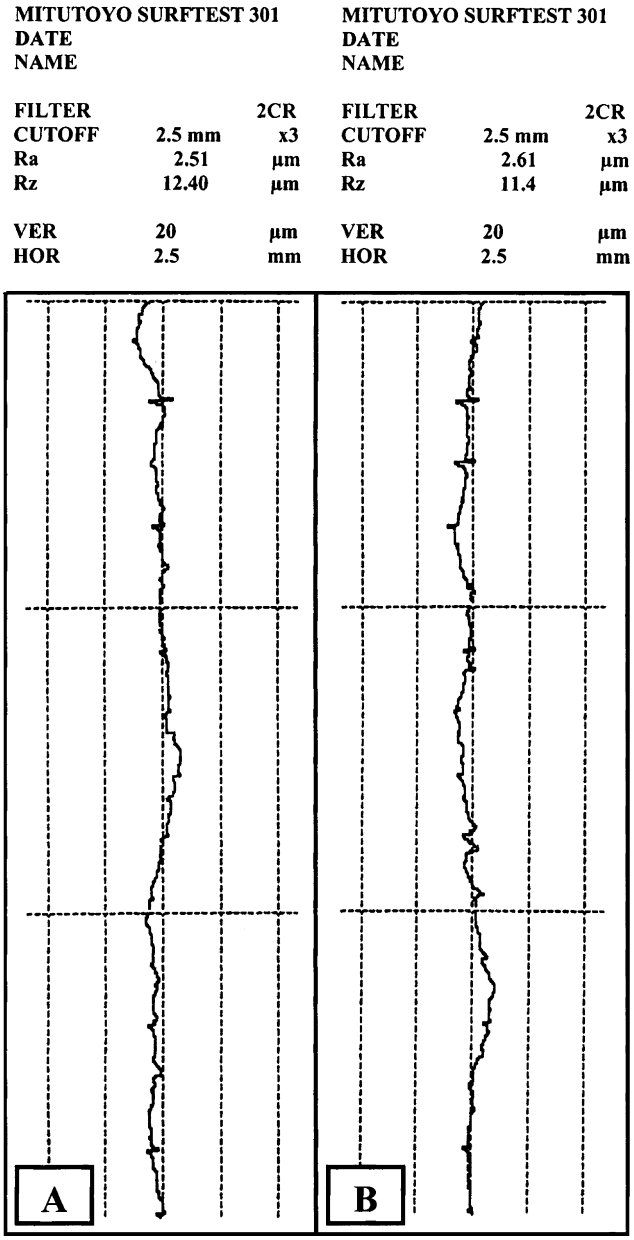

Fig. 2. Typical roughness profiles for a patch containing 10% glycerol: (A) measurement taken in "*x*" dimension; (B) measurement taken in "*y*" dimension.

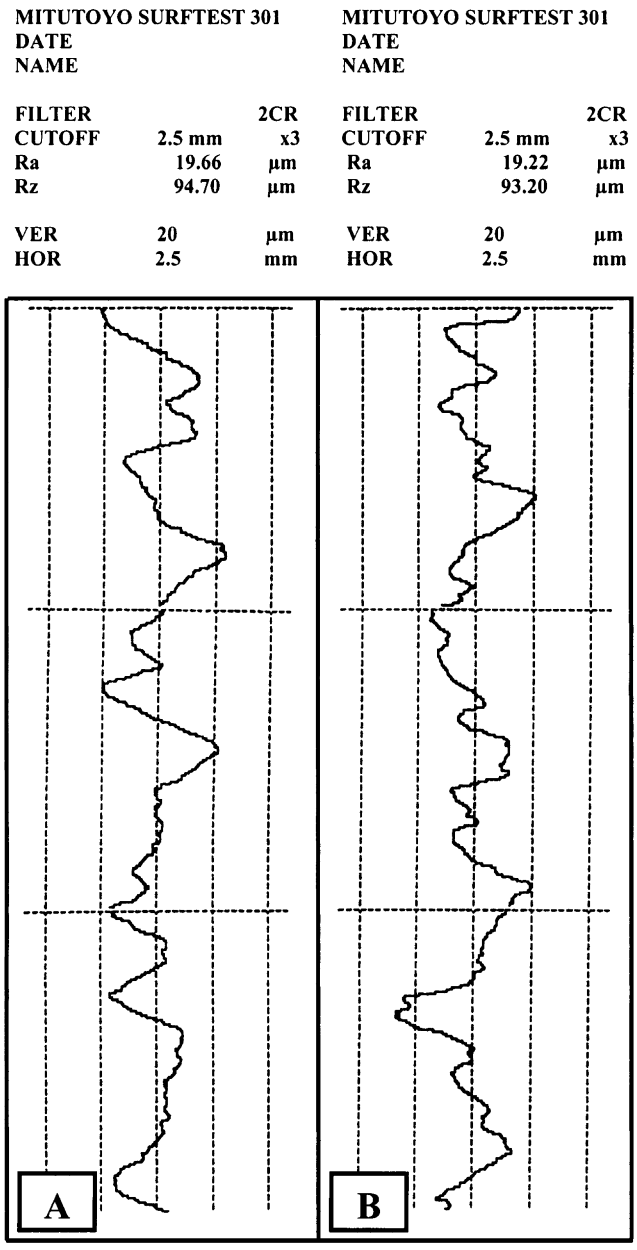

Fig. 3. Typical roughness profiles for the skin model: (A) measurement taken in "*x*" dimension; (B) measurement taken in "*y*" dimension.

ues for the four types of patches were also much smaller than those obtained for the skin model, e.g. for a patch containing 10% glycerol, average Rz values in the "*x*" and "*y*" dimensions were: 11.80 ± 0.68 and 11.82 ± 0.62 μm, respectively; for the skin model, these values were: 92.50 ± 3.48 and 91.80 ± 3.23 μm, respectively (Table 1). In summary, there were no significant differences in either Ra or Rz values between the "*x*" and "*y*" dimensions for the patches or the skin model. Moreover, there were no significant differences in Ra or Rz values between the different patches. It is important to note that the Ra values for both pig and human skin have been reported to be 20 ± 3 μm (De Paepe et al., 2000; Ben-Yaakov, 2007), similar to the Ra values obtained here for the skin model, indicating that the skin model mimics the topography of human skin. Neither plasticizer inclusion nor plasticizer type had any significant effect on the studied roughness parameters. The Ra and Rz values for the patches and the skin model were similar to those obtained in a previous study (Nussinovitch et al., 2008). Fig. 4 presents digital photos of the skin model (A) and of a patch containing glycerol (B). The photos support the results obtained in the roughness measurements in that the surface of the skin model appears much rougher than the surface of the glycerol-containing patch. The latter photo is quite similar to those taken of the other types of patches (data not shown).

Tensile tests enable studying the mechanical properties of the patches, such as strain and stress at failure (strength). These properties are important, since an adhesive patch needs to exhibit desirable resistance to external forces, so that damage, such as tearing, will not occur during storage or use. The patch should also be removable without tearing. In this study, relatively high concentrations of plasticizer were intentionally included to demonstrate the effects of plasticization on the mechanical properties of the patches. The patches included 10% (w/w, wet basis) plasticizer, ~28% (w/w) after drying (calculation not shown). For comparison, in the preparation of another DIA patch, plasticizer at a concentration of 4% (w/w, wet basis) was used to obtain 15% (w/w) after drying (Santi et al., 2003). Fig. 5 demonstrates typical tensile stress–strain relationships for patches containing no plasticizer or 10% glycerol, PEG 200 or PEG 400. The average stress at failure values were 39.3 ± 0.6, 3.5 ± 0.2, 5.5 ± 0.2 and 6.5 ± 0.3 MPa, respectively. The average strain at failure values were: 0.012 ± 0.002, 1.95 ± 0.10, 1.41 ± 0.09 and 1.00 ± 0.04 (dimensionless), respectively. Two conclusions could be derived from these results: plasticizer addition caused a significant decrease in tensile strength (stress at failure) and a significant increase in strain at failure. Those properties were also influenced by the molecular weight of the plasticizer: the lower the molecular weight, the greater the plasticizing effect obtained. The same weight of plasticizer was used in all patches. However, relative to the high-molecular-weight plasticizer, the lower molecular-weight plasticizers had more molecules per unit weight, and those molecules could more easily penetrate between the polymer chains of the film-forming agent and adhesive and interact with specific functional groups of those polymers. We assume that the resultant plasticizing effect was due to hydrogen bonding between O—H groups that were present in all of the plasticizers used and O—H and C=O groups of PVA and PVP, respectively, in agreement with other reports (Arvanitoyannis et al., 1997; Feldstein et al., 2001; Wang et al., 2003; Rajendran et al., 2004).

Table 1
Ra and Rz values for skin model and patches.

Property				
Composition	Ra (μm) in "*x*" dimension	Ra (μm) in "*y*" dimension	Rz (μm) in "*x*" dimension	Rz (μm) in "*y*" dimension
Skin model	19.35 ± 0.91^{b}	19.25 ± 0.89^{b}	92.50 ± 3.48^{g}	91.80 ± 3.23^{g}
PVA-PVP	2.65 ± 0.13^{a}	2.61 ± 0.12^{a}	11.77 ± 0.63^{f}	11.64 ± 0.71^{f}
PVA-PVP-Glycerol	2.55 ± 0.12^{a}	2.58 ± 0.13^{a}	11.80 ± 0.68^{f}	11.82 ± 0.62^{f}
PVA-PVP-PEG 200	2.60 ± 0.14^{a}	2.54 ± 0.11^{a}	11.68 ± 0.60^{f}	11.72 ± 0.66^{f}
PVA-PVP-PEG 400	2.64 ± 0.14^{a}	2.60 ± 0.14^{a}	11.67 ± 0.62^{f}	11.78 ± 0.65^{f}

Each result is the mean of 10 determinations ± S.D.
Means with the same superscript are not statistically different at $p \leq 0.05$.

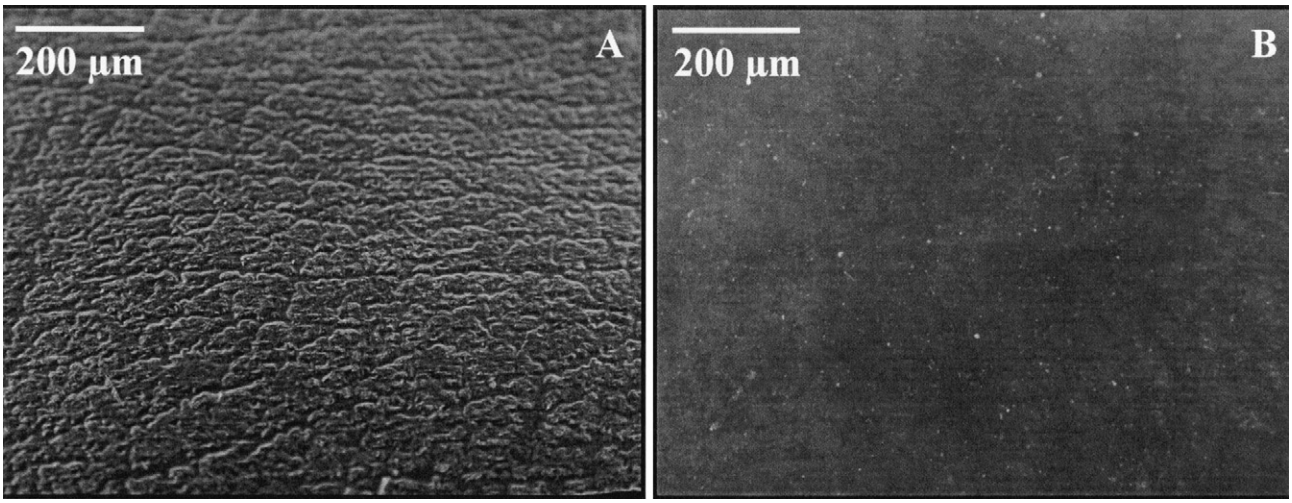

Fig. 4. Digital photos of the skin model (A), and of a patch containing glycerol (B). Magnification: ×4.

A topical and/or transdermal-drug-delivery patch should exhibit desirable adhesive properties (Venkatraman and Gale, 1998). Failures related to inappropriate adhesion may result in complete or partial removal of the patch and/or non-homogeneous adhesion (Wokovich et al., 2006). Peeling tests for different types of patches have been carried out elsewhere (Couarraze et al., 2000; McCarron et al., 2005; Nussinovitch et al., 2008). However, the effect of plasticizer inclusion on the adhesive properties of patches has never been studied. Therefore, we evaluated the adhesive properties of the patches. Different patches were peeled off of the skin model. This skin model has advantages over other substrates, i.e. steel or glass plates (Dimas et al., 2000; Jovanovic and Dube, 2005), in that it mimics the physical, chemical and topographical properties of human skin. The patch was attached to the wetted skin model for the specified period of time. Fig. 6A demonstrates the obtained peeling force (g force/cm) as a function of plasticizer inclusion: inclusion of 10% glycerol caused a significant decrease in average peeling force, from 2.8 ± 0.13 g force/cm for a patch containing no plasticizer to 1.5 ± 0.11 g force/cm for a patch that included glycerol. Inclusion of other types of plasticizers also caused a reduction in the obtained peeling force (data not shown). We assume that the hydroxyl groups of the plasticizer interacted with specific groups of the polymers (PVA and/or PVP). As a result, there was a decrease in the number of polymer functional groups that were available (before plasticization) to interact with specific groups on the skin model. Thus, a reduction in peeling force was obtained. Fig. 6B demonstrates peeling force as a function of time elapsed from application. For application periods of 15, 30 and 45 min, peeling forces of 2.8 ± 0.13, 5.5 ± 0.24 and 6.7 ± 0.26 g force/cm were obtained, respectively. Thus, the peeling force increases with time. This is in agreement with results obtained in our previous research (Nussinovitch et al., 2008). At this stage, we assume that with time, the system reaches equilibrium, as the distribution of

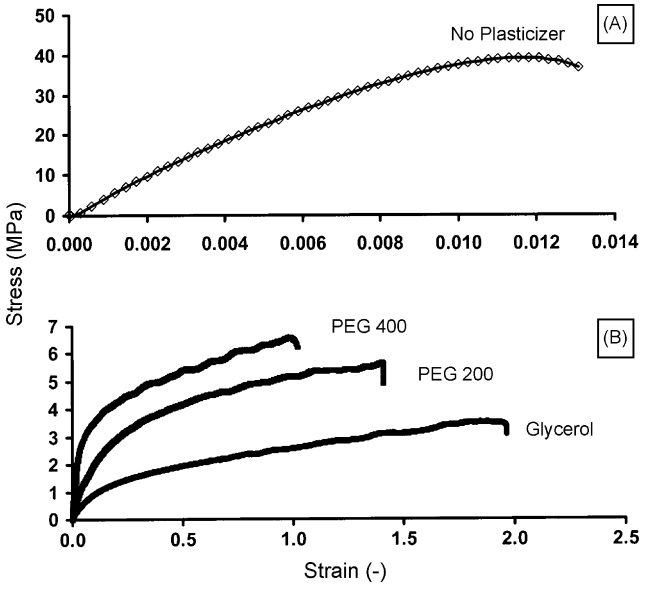

Fig. 5. Typical tensile stress–strain relationships: (A) for patches containing no plasticizer (◊); (B) for patches containing glycerol, PEG 200 and PEG 400.

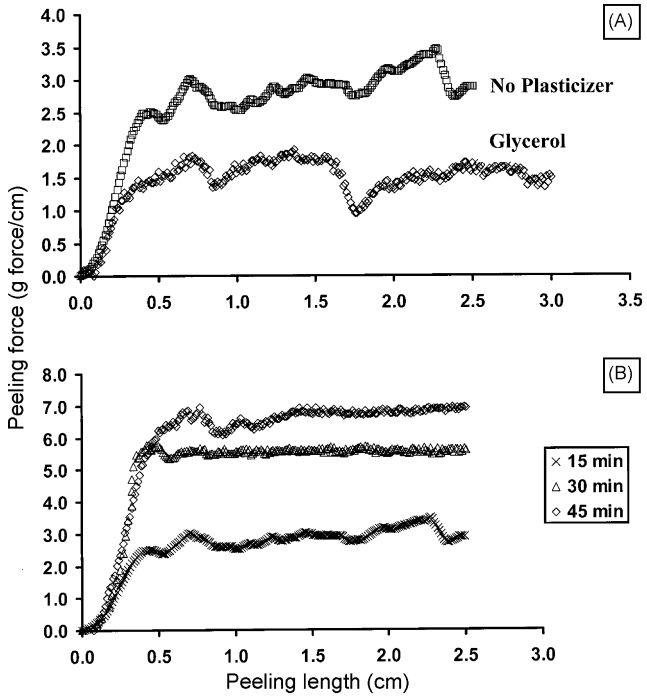

Fig. 6. (A) Peeling force as a function of added plasticizer: no plasticizer (□) and 10% glycerol added (◊); (B) peeling force as a function of time elapsed from patch application on skin model: (×) 15 min; (Δ) 30 min, (◊) 45 min.

the water wetting the patch and at the skin model-patch interface becomes more uniform. To the best of our knowledge, there are no data in the literature on 90-degree peeling tests performed with commercial transdermal patches on skin. This information is also limited with respect to non-commercial patches. The peeling of Durapore™ adhesive tapes (non-medical patches) from human skin revealed peeling force values of 0.2–1 N/cm (equivalent to 2.0–9.8 g force/cm) (Karwoski and Plaut, 2004). Silicone-based transdermal matrix systems peeled from human skin demonstrated an average peeling force of 1.2 N/cm, equivalent to 11.8 g force/cm (Couarraze et al., 2000). Our patches exhibited peeling force values of up to 7.0 g force/cm after 45 min of application. A desirable range of peeling force values has not yet been defined, because many factors, such as application site (i.e. back, forearm, etc.), moisture content in the stratum corneum and application time, can influence the results (Wokovich et al., 2006). Thus, a patch should exhibit the minimal peeling force necessary to remain well attached to the skin during the application period; on the other hand, peeling force values that are too high should be avoided, since these might cause skin irritation.

4. Conclusions

Novel patches were formulated based on PVA and PVP with the inclusion of plasticizer, the latter affecting the mechanical properties of the patch. In addition, the molecular weight of the plasticizer had a significant effect on both stress and strain at failure. The patches were not adhesive in the dry state, but became sticky upon wetting. Patch adhesion to the skin model increased with elapsed time of adhesion. Plasticizer inclusion caused a reduction in the resultant peeling force. The nature of the relationship between the molecular weight of the plasticizer and patch adhesive properties is not yet completely understood. Plasticizer inclusion had no significant effect on the roughness parameter values. Since the skin model had much higher Ra and Rz values than the patches, we assume that in addition to plasticizer inclusion, the roughness of the skin model also affects patch adhesive properties.

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