Design of a New Water-Soluble Pressure-Sensitive Adhesive for Patch Preparation

Paola Minghetti[1], Francesco Cilurzo[1], Leila Tosi[1], Antonella Casiraghi[1], and Luisa Montanari[1]

[1]Istituto di Chimica Farmaceutica e Tossicologica, Università degli Studi di Milano, Milan, Italy

ABSTRACT

This work was intended to improve the adhesion properties of an available medical water-soluble pressure-sensitive adhesive (PSA) through the addition of cellulose ethers or polyvinylpyrrolidone (PVP). The adhesion properties were evaluated by means of peel adhesion test and creep resistance test. Possible interactions between the polymethyl methacrylate (PMMA) and hydrocolloid were investigated by Fourier-transformed infrared spectroscopy. Moreover, a central composite design was used to estimate the effects of hydrocolloids and plasticizers and their interactions on the PSA performance. The addition of PVP made it possible to obtain a patch with a 40-fold improved creep compliance and a reduced peel adhesion. The significant increase of the matrix cohesion was due to attractive interactions between the amide group of PVP and the carboxylic acid group of PMMA. The water vapor permeability of the prepared systems was very high. Furthermore, no primary skin irritation was observed. The presence of plasticizers at high level increased both the peel values and creep compliance, showing an opposite behavior with respect to PVP. The new PSA system can be easily removed from the skin, is suitable for repeated applications on the same site, and has adhesive properties that can be modified by changing the component ratios.

Corresponding Author: Paola Minghetti, Istituto di Chimica Farmaceutica e Tossicologica, Università degli Studi di Milano, Viale Abruzzi, 42, 20131 Milano, Italy. Phone: +39 (0)2 50317518; Fax: +39 (0)2 50317565; Email: paola.minghetti@unimi.it.

INTRODUCTION

Medical-grade pressure-sensitive adhesive (PSA), widely used in wound dressing and in the development of (trans)dermal patches, has to be biologically inert, nonirritating, and nonsensitizing at skin level and should confer good adhesive properties to the final product.

Ideally, medical PSA adheres strongly to the skin but can be easily removed with little or no trauma (adhesion properties) and without adhesive residues (cohesion properties). Aggressive PSA can cause skin irritation as well as pain. In the case of long-term wearing of the PSA on the skin, low shear strength values make a patch or bandage aesthetically unacceptable, as the adhesive oozes leave adhesive residues on the outside edges of the backing layer. Moreover, when detached, the patch can leave visible residues. Thus, highly critical PSA adhesive properties are peel adhesion and shear strength.

PSA with some hydrophilic characteristics, solventless and water-borne PSA, could improve patch/skin contact[1] and make it possible to avoid skin irritation and sensitization and reduce environmental contamination risks. A water-soluble system based on polymethyl methacrylate, (PMMA—Eudragit L 100), plasticized with polyethylene glycol 400 (PEG 400) and glycerol (GLY), was proposed by the manufacturer mainly to make a thin adhesive layer in bilayer transdermal patches.[2] Such a PSA is a soft adhesive not suitable for the production of medical devices or monolayer transdermal patches, which have to be thicker than bilayer transdermal patches; adhesion to the skin is ensured, but the patch splits on removal because of its low cohesive strength.[3] However, the system appears interesting because it permits the production of PSA by using well-known materials without final curing.

The addition of bivalent ions such as zinc (usually in the form of zinc sulfate) into anionic PSA is the conventional approach to increasing the cohesive properties of PSA with carboxylic groups.[4] However, the

addition of even small quantities of zinc sulfate causes the aggregation of PMMA because of the strong interaction between the carboxylic groups of the polymer and the zinc ion. An alternative approach to improve matrix cohesion could be the addition of a compatible polymer. This approach was successfully used in a previous work where the performance of a PSA based on an aminomethylmethacrylate was improved by adding a high-molecular-weight poly(ethyl acrylate, methyl methacrylate).[5]

The work currently being reported was aimed to improve the adhesive performance of PSA based on PMMA by adding to the system a hydrocolloid chosen among materials widely used for plaster formulation. In particular, cellulose ethers and high-molecular-weight polyvinylpyrrolidone (PVP) were evaluated. Moreover, to estimate the effects of the hydrocolloid, which was selected based on a preliminary screening, and of plasticizers on the adhesive properties of the prepared patches, a central composite design was used.

The adhesion properties of the patches were determined by a creep resistance test, which indicates the cohesion of the PSA, and a peel adhesion test, which measures the tenacity of the bond between the patch and another surface performed at the rate of 100 and 300 mm/min. The 300 mm/min rate was selected because it is recommended by standard control procedures; the 100 mm/min rate represents the real speed of patch removal from the skin.[6]

As occlusion may act as a primary skin irritant, leading to maceration of the skin and favoring growth of pathogenic microorganisms,[7,8] particularly in the case of repeated applications on the same site, all the patches were prepared by using a backing layer with very high water vapor permeability (WVP) selected on the basis of previous results.[9]

The WVP of the developed PSA was evaluated in vitro by using the previously described method.[9,10] Moreover, although the materials used for the preparation of the PSA are widely used in pharmacies for topical preparations, the tendency to produce skin irritation was evaluated in rabbit.[11]

MATERIALS AND METHODS

Materials

PMMA of molecular weight 135 000 d and molar proportions of the monomer units 1:2 (Eudragit L 100) was purchased from Röhm (Darmstadt, Ger-many). PEG 400 and glycerol (GLY) were purchased from Azienda Chimica e Farmaceutica ([ACEF], Fiorenzuola d'Arda, Italy). PVP, $\mu_{rel} = 1.6$, was purchased from Carlo Erba (Rodano, Italy). Methocel E 4M (Hydroxypropylmethylcellulose [HPMC], E4M), Methocel K 4M (HPMC K4M), Methocel E 50 (HPMC E50), Methocel A 15 (Hydroxymethylcellulose [HMC], A15), Natrosol 250MR (Hydroxyethylcellulose [HEC]) were purchased from Eigenmann & Veronelli (Rho, Italy). Artificial silk (rayon acetate) was purchased from Bouty (Milano, Italy), technical specifications: thickness 130 µm; weight 70 g x m²; warp/weft 42/26 yarns/cm, WVP: 2777 ± 129 g/m²/24 h.[6]

All substances were used as received. All solvents were of analytical grade.

Preparation of Polymeric Solutions

The composition of the aqueous polymeric mixtures used for the hydrocolloid selection is shown in **Table 1**.

The hydrocolloid was dissolved in an appropriate amount of water at the temperature of $60 \pm 1°C$.

The PMMA was dispersed separately in the water using a paddle stirrer and stirred at room temperature at 150 rpm for 10 minutes; NaOH 10% m/m aqueous solution was added rapidly to the PMMA suspension, stirring at 350 rpm for 20 minutes. After PMMA was solubilized by neutralization (PMMA-Na), PEG 400 and GLY were added and the mixture was stirred at 150 rpm for a further 20 minutes. The previously prepared hydrocolloid solution was finally added and the system stirred at 150 rpm for 60 minutes. A mixture without hydrocolloid (formulation A, Table 1) was also prepared. The PSA solutions were used after 12 hours of rest.

Patch Preparation

The patches were prepared by using a laboratory coating unit Mathis LTE-S (M) (Mathis, Zurich, Switzerland). The polymeric systems were spread on the artificial silk at the constant rate of 1.5 m/min. The coating thickness was set to obtain patches with the same weight per surface unit, and the patches were dried at 60°C for 15 minutes, covered with the protecting foil, and stored in an airtight container.

Table 1. Composition of the Formulations Used for the Hydrocolloid Selection*

Component	Formulation (% wt/wt)						
	A	B	C	D	E	F	G
PMMA	7.35	7.65	7.51	2.43	6.25	2.91	9.10
PEG 400	11.0	11.5	11.3	3.65	9.38	4.36	13.7
GLY	4.80	5.00	4.90	1.59	4.08	1.90	5.95
Water	12.7	54.0	58.2	85.3	62.5	82.3	48.6
NaOH 10%	13.5	15.1	14.8	4.80	12.3	5.73	18.2
HPMC E50	—	6.77	—	—	—	—	—
HPMC E4M	—	—	3.33	—	—	—	—
HPMC K4M	—	—	—	2.23	—	—	—
HMC A15	—	—	—	—	5.45	—	—
HEC	—	—	—	—	—	2.15	—
PVP	—	—	—	—	—	—	4.55

*PMMA indicates polymethyl methacrylate; PEG 400, polyethylene glycol 400; GLY, glycerol; HPMC, hydroxypropylmethylcellulose; HMC, hydroxymethylcellulose ; HEC, hydroxyethylcellulose; PVP, polyvinylpyrrolidone.

Adhesion Properties Evaluation

Peel Adhesion 180° Test

One week after preparation, the adhesive patches were cut into strips 2.5 cm wide, applied to an adherent plate, smoothed 3 times with a 4.5-kg roller, maintained for 10 minutes at 20°C, and pulled from the plate at a 180° angle at 2 different rates: 300 and 100 mm/min. The 300 mm/min rate is recommended by the standard procedure[12]; the 100 mm/min rate represents the speed of patch removal from the skin.[7] The peel adhesion test was performed by using a stainless steel plate, recommended by the standard method, or a polyethylene plate, a material with a lower-energy surface. The polyethylene plate was used when the adhesion strength was higher than the elongation of the backing layer at break, because the test performed by using the stainless steel plate had produced unreliable results.[13] The test was performed with a tensile testing machine Acquati model AG/MC 1 (Acquati, Arese, Italy). The force was expressed in cN/cm width of the patch under test. Peel adhesion values were the average of 3 replicates.

Creep Resistance Test

One week after preparation, the adhesive patches were cut into strips 2.5 cm wide and 6.0 cm long. Exactly 1.27 cm of the specimen was applied at the tab end of an adherent panel made of stainless steel. The specimen was laid with no pressure exactly parallel to the length of the test surface and smoothed 3 times with a 2.04-kg roller. The prepared sample was placed in the shear adhesion rack to hold panels 2° inclined from vertical so that the back of each panel formed an angle of 178° with the extended piece of sample. A weight of 500 g was secured to the free end of the patch. The shear adhesion value is the time taken for the sample to separate from the panel. The test was performed with an apparatus made in our lab according to PSTC-7 (Pressure Sensitive Tape Council) specification.[14] Each value is the average of 5 replicates.

WVP Evaluation

The WVP of the patch was determined with the previously described method.[6] The apparatus consists of a cylindrical glass chamber with a separate lid, completely closed except for a circular opening (40 mm in diameter), which is covered with the material being examined. About 20 mL of water was poured into the chamber, and the sample was mounted at the center of the top surface of the cell. The chambers were placed into a natural air circulating oven and maintained for

Table 2. Patch Composition and Cube Central Composite Design*

Patch	PMMA-Na	PVP		GLY		PEG 400	
		Real Values	**Coded** **Values**	**Real** **Values**	**Coded** **Values**	**Real** **Values**	**Coded** **Values**
1	5.31	1.80	−1	2.36	−1	5.41	−1
2	5.31	2.70	1	2.36	−1	5.41	−1
3	5.31	1.80	−1	3.52	1	5.41	−1
4	5.31	2.70	1	3.52	1	5.41	−1
5	5.31	1.80	−1	2.36	−1	8.09	1
6	5.31	2.70	1	2.36	−1	8.09	1
7	5.31	1.80	−1	3.52	1	8.09	1
8	5.31	2.70	1	3.52	1	8.09	1
G	5.31	2.25	0	2.94	0	6.75	0

*PVP indicates polyvinylpyrrolidone; GLY, glycerol; PEG 400, polyethylene glycol 400.

24 hours at $37 \pm 1°C$. The chambers were weighed 1 hour before the test and again 1 hour after the removal from the oven.

The WVP is given by the following equation:

$$WVP = W/A \qquad (1)$$

where WVP is expressed in g/m^2 x 24 hours, W is the amount of vapor permeated through the patch expressed in g/24 hours, and A is the effective area of the exposed samples expressed in m^2. Each WVP value represents the average of 5 sample readings.

Experimental Design

The cube central composite design used was a 2^3 design, and the investigated variables were PVP, PEG 400, and GLY. The levels of each excipient were set at 20% m/m (high level; 1), and -20% m/m (low level; -1) of the standard formulation (**Table 2**). The run of the central point of the design (formulation G, **Table 1**), where all the factor levels were 0, was replicated. For each response variable (creep adhesion, peel adhesion 100 and 300 mm/min), a multiple regression model was fitted to the data ($P < .05$). The results were evaluated using a model including the main effects and the interaction terms. Standard analyses of variance (ANOVAs) were performed, and the models were subsequently tested for overall curvature using the statistical factorial design and the software Statistica (Statsoft, Tulsa, OK).

Fourier-Transformed Infrared Spectroscopy

Fourier-transformed infrared (FT-IR) spectra of PVP, PMMA neutralized with NaOH (PMMA-Na) in the same PMMA/NaOH ratio used in patch G preparation (**Table 1**), and a mixture of such materials obtained by spray-drying (PMMA-Na/PVP; ratio 70/30 wt/wt) were recorded with a FT-IR spectrometer Paragon 1000 PC (Perkin Elmer, Wellesley, MA). Sixteen scans were collected for each sample at a resolution of 4 cm^{-1} over the wavenumber region 4000 to 450 cm^{-1}. Samples were prepared in KBr dies by compaction (compaction force of 10 tons and holding time of 15 minutes). The weight ratio of KBr to powder was about 100:1.

The PMMA-Na/PVP mixture was prepared by spraying through a standard nozzle (inner diameter: 0.75 mm) 3% wt/wt solution of the components in water by using the spray-dryer Lab-Plant model SD04 (Lab-Plant LTD, West Yorkshire, UK). The process parameters were set as follows: flux rate 350 mL/h, air flux rate 44 m^3/min, inlet temperature 130°C, outlet temperature 60 to 70°C.

Table 3. Peel Adhesion and Creep Resistance Values of Patches Used for the Cube Central Composite Design*

Patch	Coded Values			Peel Adhesion (cN/cm ± SD)		Creep Resistance (min ± SD)
	PVP	GLY	PEG 400	100 mm/min	300 mm/min	
1	−1	−1	−1	3.9 ± 0.8	5.2 ± 1.1	164 ± 13
2	1	−1	−1	1.7 ± 0.2	1.8 ± 0.2	697 ± 42
3	−1	1	−1	20.1 ± 1.1	17.8 ± 3.6	97 ± 6
4	1	1	−1	12.7 ± 1.8	11.7 ± 2.2	558 ± 4
5	−1	−1	1	38.0 ± 3.1	29.7 ± 1.4	20 ± 5
6	1	−1	1	33.1 ± 3.7	66.8 ± 11.2	70 ± 8
7	−1	1	1	57.5 ± 14.2	82.1 ± 12.7	4 ± 1
8	1	1	1	56.4 ± 19.1	57.8 ± 2.5	50 ± 2
G	0	0	0	29.0 ± 4.5	53.8 ± 13.2	264 ± 16
G	0	0	0	34.3 ± 2.1	51.8 ± 10.6	279 ± 20
A	—	—	—	—†	609.0 ± 19.0	6 ± 1

*PVP indicates polyvinylpyrrolidone; GLY, glycerol; PEG 400, polyethylene glycol 400.
†Not performed.

Acute Skin Irritation Test

The skin irritation evaluation was performed according to International Organization for Standardization (ISO) 10993-10 specifications by using rabbits.[11]

Three healthy young adult New Zealand albino male rabbits of a single strain weighing 2.5 to 3.5 kg were used. On the day before the test, the fur on the backs of the animals was closely clipped at a sufficient distance on both sides of the spine (240 cm^2) for application of 2 sample specimens of 10 cm^2. The application site was covered with a non-occlusive dressing and wrapped with a semiocclusive bandage for 4 hours. At the end of the contact time the dressing was removed and the position of the application site marked. The appearance of each application site was recorded after 1 hour, 24 hours, 48 hours, and 72 hours according to the following grading system: no erythema 0, very slight erythema 1, well-defined erythema 2, moderate to severe erythema 3, severe erythema to slight eschar formation 4; no edema 0, very slight edema 1, well-defined edema 2, moderate edema 3, severe edema 4.

Results were analyzed by means of the software Statistica using Wilcoxon signed rank tests.

RESULTS AND DISCUSSION

Selection of the Hydrocolloid

The solutions based on HPMC E50 and HPMC E4M (formulations B and C, **Table 1**) did not produce homogeneous mixtures when the PMMA adhesive system was used. Therefore, the patches were prepared by using all the other polymeric mixtures (formulations D, E, F, and G, **Table 1**).

The patches made with the matrices based on HPMC K4M, HMC A15, and HEC had no adhesive properties.

The addition of the PVP to the PMMA adhesive system (formulation G, **Table 1**) led to a reduction in peel adhesion values and a roughly 40-fold decrease in creep compliance of the corresponding patch (patch G) in comparison with the reference patch (patch A) obtained with the formulation A (**Table 3**). The reduction in peel adhesion suggests that the patch will be easily removed from the skin with little or no trauma to the wearer. This could be especially useful for patients with fragile skin, such as the elderly or people needing repeated applications on the same site. Moreover, the adhesive layer of patch A did not strip
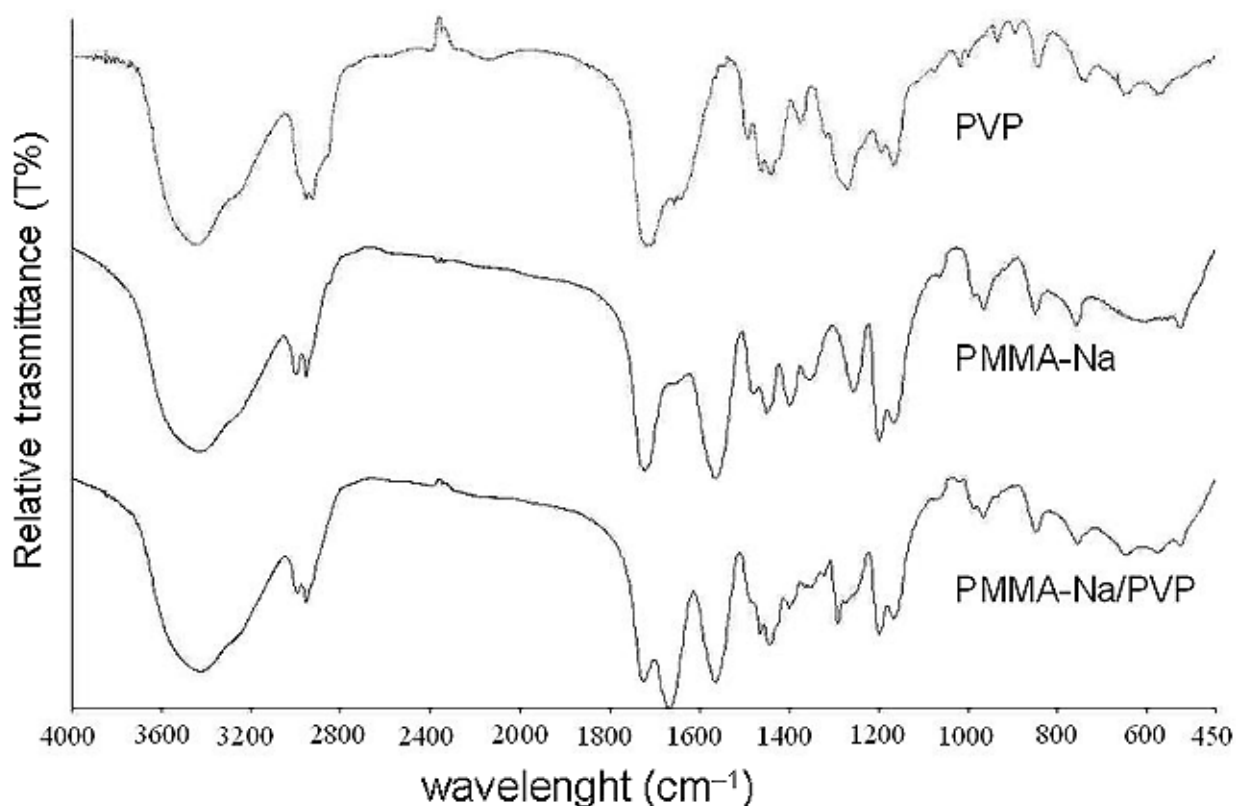
Figure 1. FT-IR spectra of PMMA-Na, PVP, and their mixture.

cleanly from the plate, leaving noticeable residues, which was evidence of cohesive failure. The intra-assay standard deviations obtained within each sample of patch A (coefficient of variation [CV], > 15%) were higher than those registered within each sample of patch G (CV < 6%). This could be due to the observed lower cohesion properties of the patches made of anionic copolymer. The increased creep resistance of patch G confirms the previous considerations and suggests a reduced risk that the matrix could ooze and leave adhesive residues on the outside edges of the backing layer after in vivo application.

The observed increased creep resistance could be due to a specific interaction between the 2 polymers investigated by FT-IR spectroscopy (**Figure 1**).

The spectrum of PMMA-Na showed the characteristic bands at 1560 cm^{-1} and between 1400 and 1300 cm^{-1} corresponding to the asymmetrical and symmetrical vibration of the -COO$^-$ structure; the esterified group absorption band[15] was at 1720 cm^{-1}.

The most significant band of PVP is the cyclic amide C=O stretching band at about 1700 cm^{-1}. A shift of this band in the PMMA-Na/PVP mixture to a higher

frequency (1664 cm^{-1}) was registered. This shift could be due to an interaction between the amide group of PVP and the carboxylic acid salt of PMMA. As a matter of fact, the shift of the PVP C=O stretching band was also verified in PVP solid dispersions by other authors that postulated H-bond[16] or ion dipole interaction[17] formation between the amide group of PVP and the carboxylic acid group of another substance.

The WVP measured for patch G (WVP = 1989 ± 97 g/m^2/24 hours) is very high. On the basis of previous results, it is possible to conclude that skin hydration will be not modified by the application of the patch for a period of 24 hours.[10]

Patch G was also submitted to an acute skin irritation test. The scores of the Draize test were 0 in every determination both for the edema and for the erythema evaluation in all tested rabbits, indicating that primary skin irritation was absent.

On the basis of these results and considerations, PVP was considered suitable to improve the technological performance of the PMMA adhesive system (patch A). As a result, this hydrocolloid was selected for the subsequent study.

Table 4. Statistical Analyses of the 100 mm/min Peel Values*

Factor	100 mm/min Peel Values ($R^2 = 0.98$)		300 mm/min Peel Values ($R^2 = 0.77$)		Creep Resistance Values ($R^2 = 0.78$)	
	Estimates	*P* Value	Estimates	*P* Value	Estimates	*P* Value
PVP	−0.094	0.248	0.014	0.942	0.543	0.002
GLY	0.424	0.019	0.275	0.254	−0.121	0.042
PEG 400	0.888	0.004	0.835	0.041	−0.684	0.001
PVP by GLY	−0.009	0.895	−0.268	0.264	−0.038	0.282
PVP by PEG 400	0.021	0.752	0.093	0.646	−0.448	0.003
GLY by PEG 400	0.095	0.247	0.086	0.668	0.085	0.081
Curvature	−0.081	0.304	−0.280	0.249	−0.114	0.047

*PVP indicates polyvinylpyrrolidone; GLY, glycerol; PEG 400, polyethylene glycol 400.

Cube Central Composite Design

The creep resistance and the peel adhesion values of the placebo patches of the cube central composite design are reported in **Table 3**.

The peel force of patch G (53.8 ± 13.2 cN/cm) from polyethylene was lower than that registered with the stainless steel plate (361 ± 8 cN/cm). This behavior can be justified considering that the carboxylated adhesive did not fully wet the polyethylene plate because of its low-energy surface.[13]

The matrices of the tested patches stripped cleanly from the plate and left no noticeable residues. This adhesive failure of all formulated patches at both peel rates is a clear indication that the matrix will not easily leave noticeable residue when disbonded in vivo.

The statistical analysis for the peel adhesion tests performed at 100 and 300 mm/min rates is shown in **Table 4**. The presence of PEG 400 and/or GLY at high level increased the peel values. The PEG 400 concentration effect was statistically significant at both peel rates. GLY concentration was significant only for the peel rate of 100 mm/min. The same effect on adhesion strength was observed by adding these plasticizers to poly(butyl methacrylate, (2-dimethylaminoethyl)methacrylate methyl methacrylate) (PAMA) films plasticized with triacetin.[18]

PVP did not significantly affect the adhesion strength as plasticizers did. ANOVAs of the peel values presented in **Table 4** suggested good fit of the lowest peel rate ($R^2 = 0.98$). In conclusion, the simple interaction model supported by this 2-level factorial design adequately described the peel response surface (**Figure 2**); furthermore, the lowest peel rate discriminated better the effect of the considered variables. The different pattern at the 2 different peel rates can be explained when considering that a part of the measured peel force is lost in deforming the adhesive and that this loss was higher in the case of the higher peel rate.

The creep resistance was affected in a significant way by all main factors and by the PVP/PEG 400 interaction term (**Table 4**). As expected on the basis of the previous considerations, the 2 plasticizers, which promote the polymer chain mobility, reduced the creep resistance values, while PVP, which interacts with PMMA-Na, reduced its mobility with a consequent improved resistance to shear (**Figure 3**). The creep resistance value of patch 7 (**Table 2**) was not statistically higher than that of patch A (**Table 1**).

CONCLUSION

The addition of PVP to the PSA based on plasticized PMMA-Na permitted us to obtain patches with high adhesive thickness having satisfactory creep resistance and peel adhesion. The significant increase of the matrix cohesion was due to attractive interactions between PMMA-Na and PVP. The water vapor permeability of the prepared systems was very high. Furthermore, no primary skin irritation was observed.
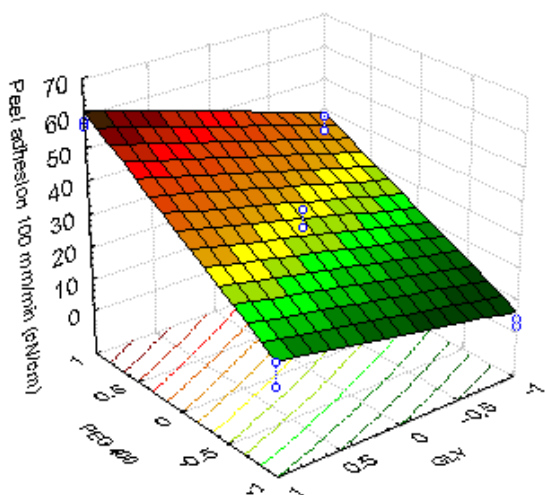
Figure 2. Effect of PEG 400 and GLY on peel adhesion force (speed rate 100 mm/min).
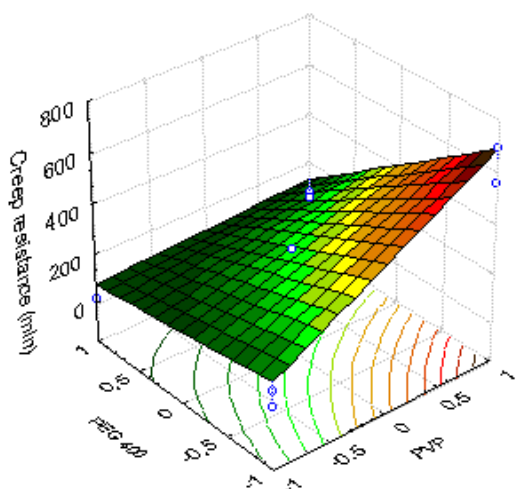
Figure 3. Effect of PVP and PEG 400 on creep resistance.

The proposed PSA is suitable when repeated applications on the same site are required. The analyses of the factorial design results made it possible to identify the contribution of PSA components. With the proposed approach, it is possible to modify the properties of the adhesive simply by changing the ratio of the excipients. A wide range of different percentages can be used, this being evidence of formulation flexibility making it possible to optimize the properties of the adhesive according to therapeutic requirements. Moreover, the possible alteration of patch adhesion properties because of the addition of low-molecular-weight molecules (as in the case of transdermal patches, cosmetics, or medical devices) can be easily offset.

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