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SHORT COMMUNICATION

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A study of MacroDerm A and MacroDerm L monolayers and their two-dimensional compatibility

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Abstract Spread monolayers of two new skin permeation enhancers, MacroDerm A and MacroDerm L were investigated at the water/air interface as a function of temperature and of subphase composition. Both components did not seem to be markedly affected by changes in ionic strength and by the presence of metal ions in the subphase. The two-dimensional binary system MacroDerm A –MacroDerm L was also studied at the water/air interface at 298 K on pure water subphase. The behavior of surface areas, surface compressional moduli and collapse pressure as a function of molar ratios of components shows that MacroDerm A and MacroDerm L are miscible.

Key words Monolayers – bidimensional compatibility – miscibility – MacroDerm A – MacroDerm L – penetration enhancers

Introduction

Transdermal administration of drugs suffers from the fact that the stratum corneum is a barrier to all but a small number of compounds with favorable physico–chemical properties. Therefore, there is an increasing interest in compounds, called penetration enhancers, that can favor and increase the adsorption of substances across the stratum corneum. Several types of penetration enhancers have already been discussed in literature, such as solvents, like ethanol, or amphiphilic substances like detergents, fatty acids, monoglycerides [1]. Also Azone®, another amphiphilic molecule, has shown to be very effective in enhancing the permeability of many compounds through the stratum corneum [2–5]. In this work two new penetration enhancers, MacroDerm A and MacroDerm L, are presented. The properties of these two water-insoluble amphiphilic substances are investigated at the water/air interface as a function of temperature and subphase composition. Spread monolayers are a simple system that allows the investigation of the two penetration enhancers in a bidimensional array, thus mimicking the two-dimensional disposition of molecules in the stratum corneum. The two molecules differ for the presence of a polyethylene oxide segment (PEO) in the polar head of MacroDerm A (where A stands for amphiphilic), while in MacroDerm L (where L stands for lipophilic) a polypropylene oxide segment (PPO) substitutes the PEO chain. The hydrophobic part of the molecules is represented in both cases by two saturated linear chains of 16 atoms of carbon. The two different molecules have been thought in order to favor the penetration across regions of different polarity of the stratum corneum: MacroDerm L, due to the presence of the PPO segment, has a more lipophilic nature than MacroDerm A, and the use of the two compounds together could have a synergistic effect on enhancing the permeation of the stratum corneum and thus increase the

penetration of drugs, both polar and nonpolar, through skin. Thus, the study of bidimensional interactions between the two compounds could be very useful because interactions between the two substances could affect their effectiveness in the permeation of the stratum corneum; in view of this a study of the two-dimensional compatibility of the two compounds is presented in this paper.

Experimental

MacroDerm A (monostearyl $(PEG)_{20}$–methylenebis-cyclohexyldicarbamoyl–$(PEG)_{20}$ monostearyl) and MacroDerm L (monostearyl $(PPG)_{15}$–methylenebis-cyclohexyldicarbamoyl–$(PPG)_{15}$ monostearyl) were supplied by MacroChem Co., Lexington MA, USA; the purity was 99% for both compounds. Chloroform (analytical grade) was supplied by Fluka and used as spreading solvent for the isotherms. NaCl and $CaCl_2$ (analytical reagents) were provided by Merck and used for the preparation of the subphases. Water was purified with a Millipore Milli RO 6 and a Milli-Q water system (organex system) obtaining a specific resistance $\geq 18\ M\Omega \cdot cm$. Surface pressure – are a isotherms were recorded using a Lauda Filmwaage with continuous compression at a compression rate of 5 mm/min, that was shown to allow monolayers to reach the equilibrium during compression. The accuracy in measuring the surface pressure was ± 0.05 mN/m, while the accuracy in measuring the surface areas was $\pm 0.01\ m^2/mg$.

Results and discussion

Pure components

The π/A isotherms of MacroDerm A and L at different temperature on pure water subphase are shown in Fig. 1. The very large A_0 values (see Tables 1 and 2) for both components account for the presence of very large polar heads containing 40 units of PEO (polyethylene oxide) for MacroDerm A (a limiting area of 376 Å^2/molecule is obtained at 30 °C on pure water subphase, for example) and 30 units of PPO (polypropylene oxide) for MacroDerm L (a limiting area of 609 Å^2/molecule is obtained at 30 °C on pure water subphase). The calculated magnitudes of area/PEO unit and area/PPO unit are ca 18.5 and 40 Å^2, respectively: this shows that the molecules are lying flat, and increase in a $-CH_2-$ group from the PEO to the PPO unit is as expected ca. 20 Å^2. MacroDerm L shows an inflexion in the π/A isotherm at a surface pressure of about 20 mN/m that could be due to a change in the orientation of the molecule at the interface: this inflexion is not present in the corresponding isotherm of MacroDerm A and this could be explained by the presence of the PPO groups in MacroDerm L, which have lower affinity for the subphase and thus undergo a change in conformation with increasing surface pressure. The surface compressional moduli C_s^{-1} (defined as $C_s^{-1} = -A(d\pi/dA)_T$) were calculated for the monolayers in order to point out the bidimensional phases of the two compounds: the $C_{s,max}^{-1}$ values for both substances are typical of liquid expanded

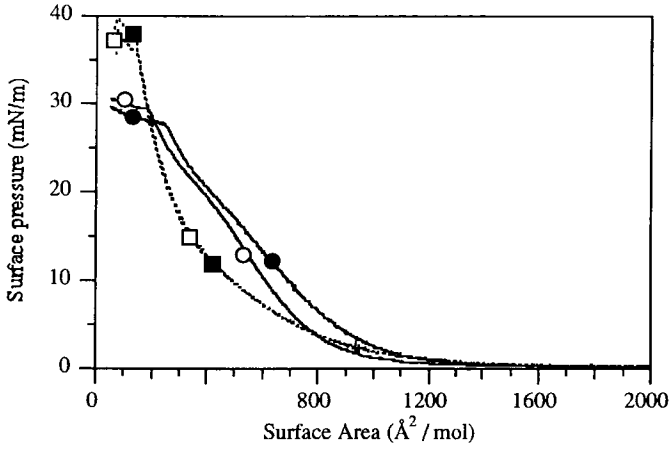

Fig. 1 π vs. A isotherms of MacroDerm A at 25 °C (●●□●●) and 40 °C (●●■●●) and MacroDerm L at 25 °C (–○–) and 40 °C (–●–) on pure water subphase

Table 1 Thermodynamic parameters of MacroDerm A

Subphase	T [°C]	A_0 [Å^2/mol]	π_{coll} [mN/m]	C_s^{-1} [mN/m]
Pure water	20	374	36.3	28.8
Pure water	25	370	35.5	29.0
Pure water	30	376	37.2	28.5
Pure water	40	380	37.3	28.3
NaCl 0.01N	25	398	35.1	26.0
NaCl 0.9N	25	409	37.4	26.5
$CaCl_2$ 0.01N	25	405	36.4	26.9

Table 2 Thermodynamic parameters of MacroDerm L

Subphase	T [°C]	A_0 [Å^2/mol]	π_{coll} [mN/m]	C_s^{-1} [mN/m]
Pure water	20	617	29.6	28.4
Pure water	25	592	29.6	29.3
Pure water	30	609	27.9	26.0
Pure water	40	721	28.5	27.1
NaCl 0.01N	25	610	28.0	26.8
NaCl 0.9N	25	644	28.4	27.5
$CaCl_2$ 0.01N	25	657	28.9	28.1

phases in the temperature range studied: this could be due to a loose packing because of the bulky polar heads of the molecules (Tables 1 and 2). Tables 1 and 2 report the thermodynamic parameters of spreading monolayers of MacroDerm A and L on different subphases. The dependence on the subphase composition (different ionic strength and variations of ions concentration) and on temperature does not seem to be very marked, especially for MacroDerm A.

MacroDerm A/MacroDerm L mixtures

MacroDerm A/MacroDerm L mixed monolayers were investigated at 25 °C on pure water subphase (see Fig. 2). Figure 3 shows the surface areas vs. MacroDerm A weight fraction at $\pi = 5$ mN/m and $\pi = 10$ mN/m, Fig. 4 shows the surface compressibility moduli vs. MacroDerm A weight fraction at the same surface pressures. The surface pressure values of 5 and 10 mN/m were chosen because they are both below the phase transition region of the isotherm of MacroDerm L, and thus only one homogeneous phase is present for MacroDerm L monolayers for those surface pressure values. The trend of the surface areas as a function of the weight fractions is not additive at all the surface pressures chosen, as it should be in case of ideal mixing or total immiscibility [6, 7], but is positive for increasing concentrations of MacroDerm A. Only slightly negative deviations from additivity are found at high concentrations of MacroDerm L at $\pi = 5$ mN/m and at low concentrations of MacroDerm L at $\pi = 10$ mN/m. The trend of the C_s^{-1} values presents globally slightly negative deviations from additivity for high concentrations of MacroDerm L, but deviations are more negative both at

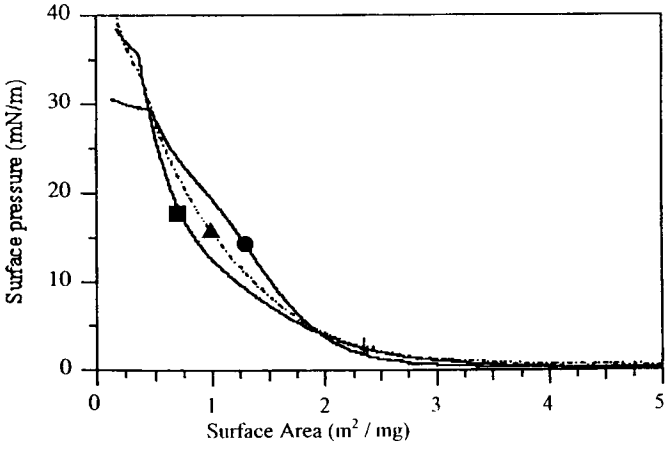

Fig. 2 π vs. A isotherms of MacroDerm A at 25 °C (—■—), MacroDerm L at 25 °C (--○--) and 1:1 MacroDerm A/MacroDerm L mixture at 25 °C (—▲—) on pure water subphase

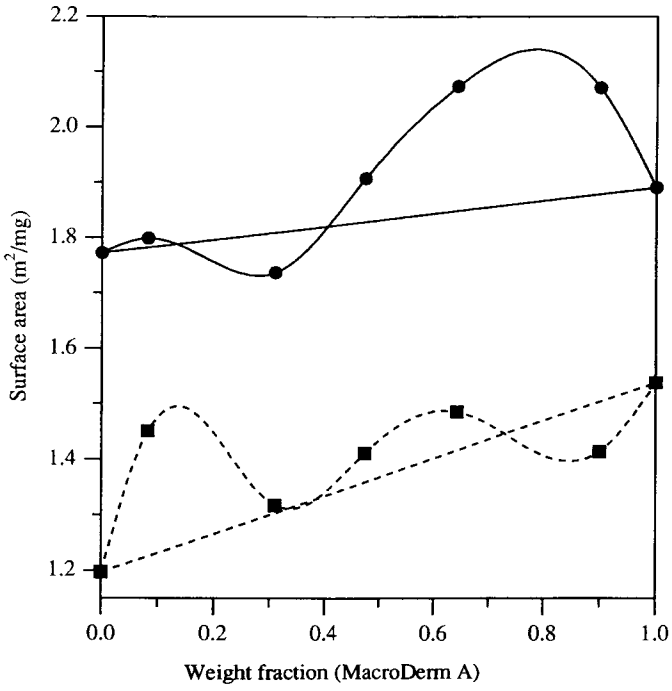

Fig. 3 Surface areas vs. MacroDerm A weight fraction for MacroDerm A/MacroDerm L system on pure water subphase at 25 °C; $\pi = 5$ mN/m (○); $\pi = 10$ mN/m (■)

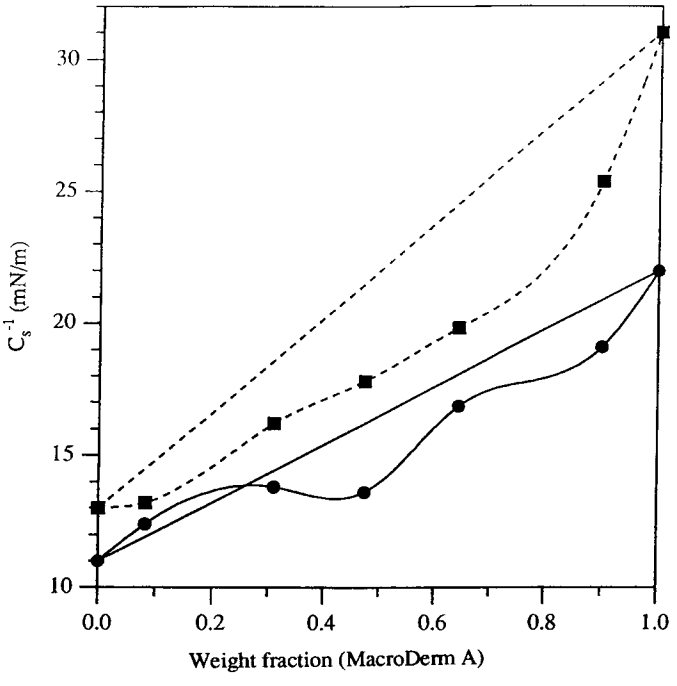

Fig. 4 Surface compressibility moduli plotted against MacroDerm A weight fraction for MacroDerm A/MacroDerm L system on pure water subphase at 25 °C; $\pi = 5$ mN/m (○); $\pi = 10$ mN/m (■)

Table 3 Thermodynamic parameters of MacroDerm A/MacroDerm L mixtures

Weight fraction (MacroDerm A)	A_0 [m²/mg]	π_{coll} [mN/m]	$C_{s,max}^{-1}$ [mN/m]
0.082	1.42	29.4	25.1
0.310	1.26	30.0	21.5
0.473	1.27	32.1	20.6
0.643	1.35	36.0	25.1
0.900	1.12	36.5	32.4

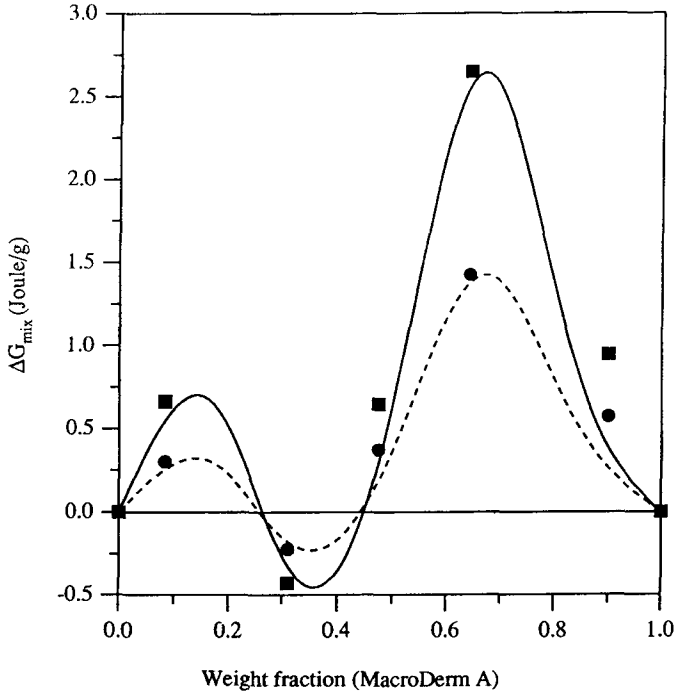

Fig. 5 Excess free energy of mixing for MacroDerm A/MacroDerm L system on pure water subphase at 25 °C; $\pi = 5$ mN/m (○); $\pi = 10$ mN/m (■)

$\pi = 5$ and $\pi = 10$ mN/m with decreasing concentrations of MacroDerm L: deviations from additivity could indicate a not ideal mixing of the two components [6, 7]. The collapse pressure values (Table 3) show high variations as a function of weight fractions of the components, and this is the clear proof of the miscibility of the two components, according to the surface phase rule [8], that is confirmed by the trends of the C_s^{-1} and surface areas as a function of weight fractions. Once the miscibility of the two components is ascertained, ΔG_{mix} values are calculated at different MacroDerm A weight fractions as in previous studies [9, 10] (see Fig. 5). ΔG_{mix} values are all positive, except for the mixture with MacroDerm A weight fraction of 0.31, which shows a negative value, thus indicating a slight stabilization with respect to the pure components that could be due to a favorable packing of molecules within the monolayer for that mixture. The lower stability of the mixtures in comparison with the pure components shown by the positive ΔG_{mix} values found for nearly all mixtures could be ascribed to less favorable interactions, in comparison with those in the pure components, between the PEO and PPO segments of the polar heads, probably due to their different structure and degree of polarity.

Conclusions

Spread monolayers of MacroDerm A and MacroDerm L are both characterized by the presence of a liquid expanded phase. The isotherms do not seem to be substantially influenced by the presence of different metal ions in the subphase and, more generally, by variations of the ionic strength. The two components show bidimensional miscibility at the air–water interface at 25 °C on pure water subphase. The miscibility of the two transdermal penetration enhancers and their low sensitiveness to variations of temperature and to the presence of ions could be very important in order to exploit these substances for effective pharmaceutical applications. Work is in progress in order to study the interactions of the two penetration enhancers with a mixture of substances simulating the composition of the stratum corneum in monolayers and the effectiveness of drug penetration in model systems such as monolayers and vesicles.

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