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Incidence of chirality on the properties of mixtures containing an amide type anesthetic compound

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ABSTRACT

Thermal analysis carried out on the two binary systems between lidocaine and D-camphor, on the one hand, and DL-camphor, on the other hand, has shown that both systems form eutectic mixtures which are liquid at room temperature. Since these three substances present anesthetic properties, the mixtures elaborated from them are suitable for topical anesthesia. The similar behavior of D- and DL-camphor, regarding melting and crystallographic properties, implies similar binary temperature–composition phase diagrams when they are mixed with lidocaine.

1. Introduction

A large number of pharmaceutical compounds fall within the class of chiral molecules. Due to the difficulty in separating enantiomers one from the other, many chiral drugs are initially prepared in their racemic form. However, one enantiomer may have substantially different pharmacological and toxicological effects from the other [1]. Each enantiomer displays opposite optical activity. An equimolar mixture of two enantiomers is called a racemate. Crystalline racemates can be classified into three categories [2]: conglomerates, which correspond to the mechanical mixture of the pure enantiomers, racemic compounds, which have their own well-defined crystalline arrangement, and pseudoracemates, which result from the formation of a solid solution between two enantiomers. The behavior of enantiomers and racemates with temperature has shown that some of them do not systematically recrystallize once melted, as is the case with ibuprofen, an anti-inflammatory drug [3,4]. Moreover, in the presence of another constituent, such as stearic acid, the stability of the solid phases of the ibuprofen enantiomer, as well as the racemate one, is modified [5]. Even if both compounds form eutectic mixtures in the whole range of composition with stearic acid, the enantiomer and the racemic compound do not behave in the same way. It may be suggested that they behave differently when they are mixed with another component, because the enantiomer and the racemate of ibuprofen present distinguishable temperature and enthalpy of melting as well as different crystal structures. On the basis of this hypothesis, one can wonder what may happen when the enantiomer and the racemate have close crystallographic and thermodynamic properties as, for instance, in the case of camphor [6]. In addition, its equimolar compound has been described as a pseudoracemate and presents, as its enantiomer, a sequence of three crystal structures depending on the temperature: $S_{III} \rightarrow S_{II} \rightarrow S_{I}$. Interestingly, for the enantiomer and the racemate, the phases S_{III} have the same orthorhombic symmetry, the phases S_{II} the same hexagonal symmetry, and the phases S_{I} the same cubic symmetry [7]. As far as lidocaine is concerned, it crystallizes in the monoclinic system [8]. From a pharmaceutical point of view, camphor (D- and/or DL-camphor) is readily absorbed through the skin and acts as a slight local anesthetic and antimicrobial substance [9–11]. Therefore, this terpene can be combined with lidocaine in order to develop pharmaceutical oil mixtures able to form emulsion for topical anesthesia. The latter compound, otherwise known as xylocaine or lignocaine, is a common anesthetic and antiarrhythmic drug used topically to relieve itching, burning and pain from skin inflammations or as a local anesthetic for minor surgery. An emulsion containing equal masses of lidocaine and prilocaine, known as "Eutectic Mixture of

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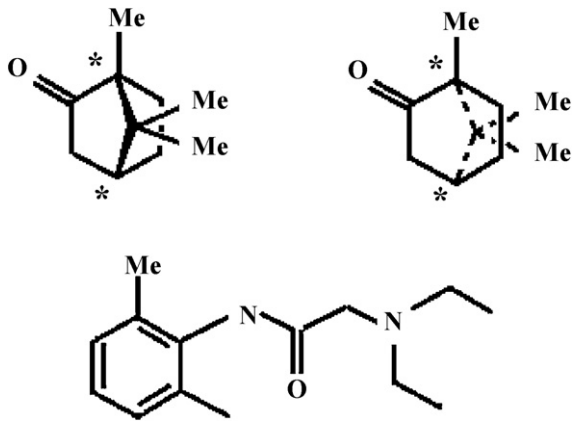

Scheme 1. Structures of D-camphor (top left), L-camphor (top right), and lidocaine (bottom). The two asymmetric carbons of camphor are indicated by an asterisk. DL-camphor is composed of D- and L-camphor in equimolar proportions.

Local Anesthetics" (EMLA®), was developed for topical anesthesia in the early 80s [12,13]. The particular property of this eutectic mixture is that it is liquid at room temperature. After it had been shown that prilocaine could provoke methemoglobinemia [14,15], other eutectic mixtures based on lidocaine were patented [16]. Pharmacological compounds such as menthol, thymol, salicylate, and so on, were suggested to replace prilocaine to form, by mixing with lidocaine, eutectic mixtures with melting points below room temperature [16]. The first issue discussed in this paper is to determine, whether or not camphor may form a eutectic mixture remaining liquid at room temperature when D- or DL-camphor are respectively mixed with lidocaine. The other issue is to apprehend the effect of the nearby physical properties of D- and DL-camphor on the properties of the binary systems formed with the anesthetic compound.

2. Experimental

2.1. Materials

Lidocaine $C_{14}H_{22}N_2O$ (M = 234.34 g mol^{-1} with a purity of 97.5%) and DL-camphor $C_{10}H_{20}O$ (156.27 g mol^{-1} with a purity >98%) were purchased from Acros Organics and Sigma–Aldrich, respectively. D-Camphor was obtained from Prolabo (purity of ~95%) and was purified under secondary vacuum by a slow sublimation/condensation process using a tubular oven with temperature gradient function to improve the purity up to 99.9%. The thus-obtained crystals were studied by thermal analysis in order to ascertain that they were in their stable state (S_{II}) at room temperature.

The molecular structures of both camphor and lidocaine are drawn in Scheme 1.

2.2. Thermal analyses

The DSC runs were performed on a differential scanning calorimeter 822e (Mettler-Toledo, Switzerland) at a scanning rate of 10 K min^{-1}. The calibration was made using high purity indium (T_{fus} = 429.75 K; $\Delta_{fus}H$ = 3.27 kJ mol^{-1}).

The temperature of isothermal processes – pure compounds melting, and eutectic or metatectic reaction – was determined at the onset of the corresponding endothermic peak as previously described [5]. For binary mixtures, the end of the thermal transformation (*i.e.*, when the liquidus, or solubility curve, is reached) was determined at the extremum of the last broad signal [5].

Three independent measurements were carried out for each sample. The uncertainties on the enthalpies and the temperatures were obtained by adding the standard deviation from the average value to the accuracy of the DSC ($\Delta T = \pm 0.3$ K and $\Delta(\Delta H)/\Delta H = \pm 3\%$). For clarity, the uncertainties on the experimental points were not reported on the phase diagrams.

2.3. Sample preparation

The binary mixtures were prepared by mixing both components at different ratios in lidocaine. The samples were then introduced at room temperature in DSC aluminum pans, which were hermetically sealed prior to being inserted within the thermal device. The homogenization of the mixtures was performed *in situ* by heating–cooling cycles.

3. Results and discussion

From the hypothesis that either D-camphor/lidocaine or DL-camphor/lidocaine binaries form eutectic mixtures, a theoretical determination of the invariant temperature as well as of the eutectic composition was made by calculating the ideal phase diagram using the Schröder–van Laar equation [19–21]. For this purpose, we had to take into account that D- and DL-camphor exhibit a solid (S_{II})/solid (S_I) transition before melting (the temperature and enthalpy changes are given in Table 1). This study showed that a eutectic invariant exists at a temperature close to 307 K for both systems and the eutectic composition is set between 0.55 and 0.6 in mole fraction of lidocaine. This eutectic temperature is well below the solid–solid transition point of camphor. This implies that the eutectic point is reached at the crossing of the solubility curve of lidocaine and the one of camphor S_{II}, and not at the solubility curve of the high-temperature phase S_I. The S_{II}–L equilibrium goes through the melting point of camphor S_{II}, which is a metastable melting triple point. To originate the corresponding liquidus curve, the melting data of camphor S_{II} have to be calculated by means of Khirchoff's law using previously reported data for the S_{II}/S_I and

Table 1
Temperatures and enthalpies for the solid/solid and solid/liquid transitions of D- and DL-camphor as well as for the solid–liquid transition of lidocaine (s and m stand for stable and metastable transition points, respectively).

		S_{II}–S_I (s)	S_I–L (s) [6]	S_{II}–L (m)	S–L (s) [18]
D-Camphor	T_{trans} (K)	370.4 ± 0.1 [17]	451.8 ± 0.7	449 ± 3[a]	
	$\Delta_{trans}H$ (kJ mol^{-1})	0.16 ± 0.02 [6]	6.1 ± 0.5	6.3 ± 0.6	
DL-Camphor	T_{trans} (K)	367.1 ± 0.1 [17]	448.0 ± 0.7	445 ± 4[a]	
	$\Delta_{trans}H$ (kJ mol^{-1})	0.17 ± 0.02 [6]	6.0 ± 0.3	6.2 ± 0.4	
Lidocaine	T_{fus} (K)				340.6 ± 0.4
	$\Delta_{fus}H$ (kJ mol^{-1})				16.4 ± 0.2

[a] The calculated uncertainty (±53 K) does not take into account thermodynamics reality. Indeed, the metastable melting point cannot be set at higher temperatures than the stable melting point, otherwise, it would correspond to the stable state data. Therefore, the uncertainty was adjusted to the difference between the highest acceptable value of the stable melting point and the average value of the metastable melting point.