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Aqueous Solubility of Liquid Monoterpenes at 293 K and Relationship with Calculated Log P Value

Krzysztof CAL

Department of Pharmaceutical Technology, Medical University of Gdansk, Hallera 107, 80–416 Gdansk, Poland

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Aqueous solubility is often a limiting factor in any concentration-dependent process and n-octanol/water partition coefficient, usually expressed as log P, is equilibrium between surrogate of nonaqueous biophases and water phase. The aqueous solubility of seven liquid monoterpenes: (±)-β-citronellol, (±)-linalool, linalyl acetate, (−)-α-pinene, (−)-β-pinene, eucalyptol and terpinen-4-ol were experimentally determined at 293 K. The obtained aqueous solubility data correlate well with log P values calculated by ACD/Log P software.

Key words——aqueous solubility; log P; monoterpenes; terpenes

INTRODUCTION

The solubility in water and n-octanol/water partition coefficient are the most important parameters for explaining diffusion-related biological processes. Solubility is an equilibrium distribution of a solute between solvent (e.g. water) and the solute phase. The maximum concentration that can be achieved is often a limiting factor in any concentration-dependent process.[1] Octanol/water partition coefficient, usually expressed as log P, is equilibrium between surrogate of nonaqueous biophases (n-octanol) and water phase.[1] In percutaneous penetration studies, solubility of a penetrant (or penetration enhancer) can explain partitioning events between vehicle/stratum corneum barrier and penetration into different skin layers and the skin permeation is always limited by log P value of penetrant.[2—4] As log P is sometimes difficult to measure and the values calculated using computer software are different,[3] solubility seems to be easy to appoint parameters. For liquid terpenes experimentally determined solubility and log P values are only sporadically or incompletely available in literature.[5—7]

In measurement of aqueous solubility of liquid solutes, like terpenes, equilibration step requires longer equilibration time and increasing interfacial area e.g. by vigorous agitation, which decreases the size of solute globules. Uncomplete separation of the phases, pure terpene and the saturated aqueous solution, can be a major source of error. At this step phase-separation by centrifugation is recommended.[1,8]

The aim of this study was to correlate the experimentally determined aqueous solubility of seven liquid monoterpenes with their log P values calculated by ACD/Log P software (Advanced Chemistry Development, Toronto, Canada). For the study both acyclic-: (±)-β-citronellol, (±)-linalool, linalyl acetate and cyclic-type terpenes: (−)-α-pinene, (−)-β-pinene, eucalyptol and terpinen-4-ol were chosen.

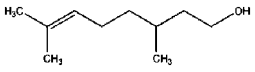
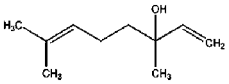
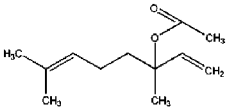
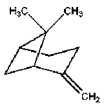
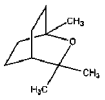
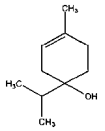
The investigated terpenes are compounds of many over-the-counter products, cosmetics and household chemicals.[9,10] In experimental dermopharmacy terpenes are widely used as penetration enhancers.[11] The structure of investigated terpenes is presented in Table 1. Among them hydrocarbon-, ester- and alcoholic-type compounds were included.

MATERIALS AND METHODS

All terpenes were >99.0% purity (Fluka, Buchs, Switzerland), and other chemicals were HPLC grade. The investigated terpene, in amount 0.5 ml, was added to 5.0 ml of highly purified water (Ph. Eur. 5), and the mixture in tightly closed chromatographic vials with Teflon® seals was placed for 24 h in a water bath-shaker at 293±1.0 K. After centrifugation (2000×g, 20 min), terpene upper layer was carefully removed by a pipette. The aqueous phase (1.0 ml) was triple extracted with portions of 1.0 ml of dichloromethane, and the combined organic phases were analysed by gas chromatography under the conditions described earlier.[3] The linearity of the

e-mail: kcal@wp.pl

Table 1. The Determined Aqueous Solubility (Mean±SD, $n=4$) and Calculated Log P Values of Investigated Terpenes

Parameters: / Terpenes:	Structural formula	Solubility in water (mg/ml)	Log P calculated by	
			ACD/Log P software	Proposed equation
Acyclic terpenes				
(±)-β-citronellol		0.322±0.0033	3.38±0.24	3.55
(±)-linalool		1.336±0.0087	3.28±0.26	3.14
Linalyl acetate		0.054±0.0007	4.12±0.40	4.07
Cyclic terpenes				
(−)-α-pinene		0.018±0.0005	4.37±0.24	4.39
(−)-β-pinene		0.023±0.0006	4.37±0.24	4.32
Eucalyptol		2.633±0.0084	2.82±0.27	2.94
Terpinen-4-ol		2.945±0.0093	2.99±0.24	2.91

method was demonstrated, and the detection limit was 0.5 μg/ml for all terpenes. The recovery of extraction was>95% for all terpenes. The experiments were repeated in quadruplicates.

RESULTS AND DISCUSSION

The determined aqueous solubility of terpenes together with the calculated log P values are shown in Table 1. The method employing centrifugation step allows to a very good reproducibility of the results. The maximum relative standard deviation (RSD) was calculated for (−)-α-pinene as 2.78%. This was not achieved when only ambient gravity separation (2 h) was employed (data not shown), e.g. for (−)-α-pinene RSD in such case was about 16%. The differences between the aqueous solubility determined after leaving in ambient gravity state and after centrifugation were greater for better soluble compounds (data not shown). This indicates that separation of the phases should be performed very careful.

Based on determined aqueous solubility, investigated terpenes can be grouped as follows: well soluble (>1 mg/ml) acyclic and cyclic alcoholic-type terpenes: (±)-linalool, eucalyptol and terpinen-4-ol; poor soluble (<0.1 mg/ml) acyclic and cyclic ester- and hydrocarbon-type terpenes: linalyl acetate, (−)-α-pinene, (−)-β-pinene; and medium soluble acyclic alcoholic-type terpene (±)-β-citronellol.

The relationship between log P values of the investigated terpenes calculated by ACD/Log P software (Table 1) and determined solubility in water (presented as logarithm) is describing by equation given in Fig. 1 and linear with the correlation coefficient 0.97. This proposed equation served to recalculation of log P values (Table 1). Obtained log P values of each terpene are enclosed within range calculated by ACD/Log P software. Considering also results of log P calculated by other software (ClogP, LogKow) for acyclic terpenes it can be ascertain, that calculated by equation presented in Fig. 1 values of log P are enclosed in the range formed by all three program: 3.25—3.56 for citronellol, 2.75—3.38 for

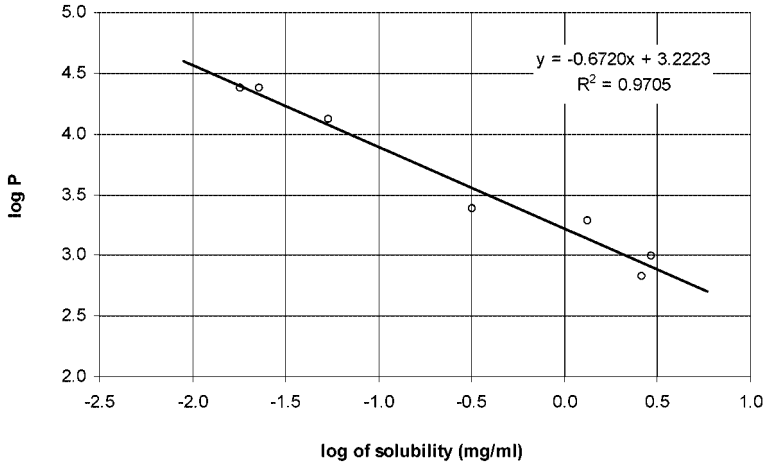


Fig. 1. The Relationship between Log P Values of Terpenes Calculated by ACD/Log P Software and Logarithm of Determined Aqueous Solubility

linalool and 3.91—4.39 for linalyl acetate.[3)]

CONCLUSION

The analysed in this study problem concern on the system consisted of liquid and volatile solute with the less density than water. It seems to be one of most difficult composition to obtain the absolute (in definite condition) value of solubility. This work signalises also how determined solubility data can be exploited alternatively for more time-consuming and more complex other determinations, because the proposed equation can be used for calculations of log P for other liquid monoterpenes.

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