Permeability coefficients and vapour pressure determination for fragrance materials

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Abstract

OBJECTIVE: This study aims to correlate new experimental data relevant to the description of the combined evaporation/permeation process of a perfume applied onto the skin.

METHODS: The vapour pressure data were measured by thermogravimetric analysis (TG-DTA). The Antoine constants and the Clarke and Glew parameters were determined for the same set of fragrance molecules to describe its low vapour pressures at new temperature ranges. The permeability coefficient of a set of 14 fragrance molecules in ethanolic solution was determined by Franz diffusion cell experiments, using porcine skin. The samples were analysed by gas chromatography with a flame ionization detector (GC/FID) and high-performance liquid chromatography with UV visible detector (HPLC/UV). A QSAR model was proposed to correlate the experimental data.

RESULTS: The Antoine constants were determined and presented low standard deviations. The Clarke and Glew physically significant parameters were obtained along with its statistical analysis. The fitting is good since the magnitude order is in accordance with the literature, associated with the low correlation between the estimated parameters and low standard deviations. The presented correlation, based on a mixture using only ethanol as solvent, showed better results than previous QSAR models with a standard relative deviation (σ_r) of 0.190, a standard error (SE) of 0.397 and a determination coefficient (R^2) of 0.7786.

CONCLUSION: The dataset is still small compared to larger and more general QSAR models; however, it is much more specific as to the type of solvent and class of materials studied. This work represents an advance for the modelling of the perfume diffusion process since it specifies important properties that until then had been treated in a more general way.

Rèsumè

OBJECTIF: Cette étude vise à corréler de nouvelles données expérimentales pertinentes à la description du processus combiné d'évaporation/perméation d'un parfum appliqué sur la peau.

MÉTHODES: Les données de pression de vapeur ont été mesurées par analyse thermogravimétrique (TG-DTA). Les constantes d'Antoine et les paramètres de Clarke & Glew ont été déterminés pour le même ensemble de molécules de parfum afin de décrire ses faibles pressions de vapeur à de nouvelles plages de température. Le coefficient de perméabilité d'un ensemble de 14 molécules de parfum en solution éthanolique a été déterminé par des expériences de cellules de diffusion de Franz, en utilisant de la peau de porc. Les échantillons ont été analysés par chromatographie en phase gazeuse avec un détecteur à ionisation de flamme (GC / FID) et chromatographie liquide haute performance avec détecteur UV visible (HPLC / UV). Un modèle QSAR a été proposé pour corréler les données expérimentales.

RÉSULTATS: Les constantes d'Antoine ont été déterminées et ont présenté de faibles écarts types. Les paramètres physiquement significatifs de Clarke & Glew ont été obtenus avec son analyse statistique. L'ajustement est bon car l'ordre de grandeur est conforme à la littérature, associé à la faible corrélation entre les paramètres estimés et les faibles écarts types. La corrélation présentée, basée sur un mélange utilisant uniquement de l'éthanol comme solvant, a montré de meilleurs résultats que les modèles QSAR précédents avec un écart relatif standard (σr) de 0,190, une erreur standard (SE) de 0,397 et un coefficient de détermination (R2) de 0,7786.

CONCLUSION: L'ensemble de données est encore petit par rapport aux modèles QSAR plus grands et plus généraux ; cependant, il est beaucoup plus spécifique quant au type de solvant et à la classe de matériaux étudiés. Ce travail représente une avancée pour la modélisation du processus de diffusion des parfums car il précise des propriétés importantes jusque-là traitées de manière plus générale.

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Introduction

The description of the combined phenomena of fragrance evaporation/permeation is complex due to its chemical nature, the interaction with other formulation ingredients, subtracts (e.g. clothing) and external factors (e.g. temperature) [1, 2]. Regarding the use of a perfume, two main processes describe the phenomena: evaporation and absorption. The evaporation process is clearly dependent on the fragrance concentration in the liquid phase, as well as external factors such as temperature, wind and other surface properties. On the other hand, the absorption of any chemical through

the skin depends upon multiple factors (skin hydration, transepidermal water loss, temperature), and it determines the amount of fragrance substances available for human perception, since it also impacts the liquid phase concentration.

Most of the perfume raw materials (PRMs) used in cosmetic products have a lipophilic character and, therefore, the potential to be absorbed through the skin. Due to this feature, terpenes – some of the main perfume constituents – are even used as skin permeation enhancers in transdermal drug delivery [3]. The literature vastly explores this property by measuring the permeability coefficient of drugs enhanced by the terpene lipophilic property [4–6]. Due to the lipophilic nature of skin, the optimal permeant has relatively low molecular weight and reasonable solubility in both hydrophilic and lipophilic media [7]. The permeability coefficient of a substance is also strongly dependent on the vehicle it is dissolved in, due to the solvent or solid–matrix interactions and the permeation enhancement/decreasing factor [8]. The permeation and safety of various PRMs have been investigated [9–11]. The process controlling parameters are also well determined: physicochemical properties (including size, lipophilicity, and solubility in oil and in water), the vehicle in which it is dissolved in, the "skin environment," and the extent of exposure [12].

Several predictive permeation models have been proposed on cutaneous drug delivery and toxicology [13–15]. However, such models are more reliable when confined within well-defined chemical classes, and their applicability is often limited by the narrow property space of the set of permeants under study [16, 17]. Mathematical models describing the absorption of chemicals through the skin have been also reported in the literature [15, 18–20], but just a few kinetic models describe the combined fragrance evaporation/permeation phenomena [2, 21].

The evaporation process of volatiles at atmospheric pressure relies on the interface vapour–liquid equilibrium. Such systems are easily represented by the modified Raoult's law, which requires the pure component vapour pressure and the mixture activity coefficients [22]. Group contribution methods (UNIFAC) or predictive models (COSMO-SAC) are used to predict the mixture property [23]. However, few data are available for the terpenes vapour pressure, and the corresponding states/group contribution methods frequently demand other unspecified properties [24]. The thermogravimetric analysis (TG–DTA) has been proved to be a useful tool for determining low vapour pressure, because it is a fast test and requires small samples [25, 26]. There are studies applying the TG–DTA technique through a modified Langmuir equation, to evaluate the vapour pressure of terpenes and essential oils [27, 28].

Recently, a mathematical model based on a differential mass balance for predicting the evaporation and permeation profiles of fragrance systems applied to skin was reported [29]. In this previous study, three fragrance systems were studied: ethanol/limonene, ethanol/linalool and ethanol/α-pinene. This method requires the terpene permeability coefficient (K_p) to estimate the whole diffusion system. As far as we know, this is the only study regarding the specific evaluation of permeability coefficients for terpenes in ethanolic solutions. The correlations for its estimation available in the literature are poorly accurate for lipophilic compounds, once they were developed for aqueous systems, mostly for pharmaceuticals and hydrophilic substances. The International Fragrance Association (IFRA) uses the correlation developed based on the findings of the Research Institute of Fragrance Materials (RIFM) [30], which gathers data regarding the safety of fragrance materials, along with the EDETOX [31] database (containing *in vitro* and *in vivo*
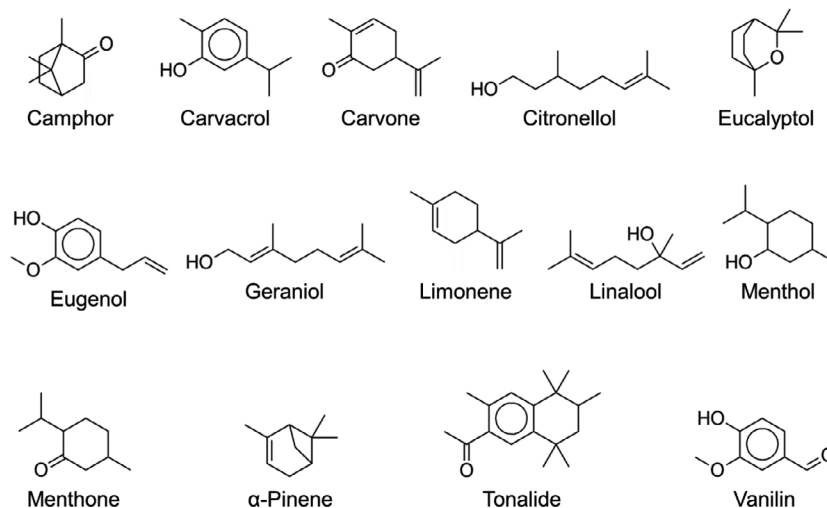
percutaneous penetration data). In addition, the enhancer effect attributed to terpenes in pharmaceutical formulations is also observed for perfumes, proving that K_p values are also related to the vehicle [7, 32]. For this reason, a correlation for K_p values specific for terpenes in ethanolic solutions would represent a breakthrough.

Therefore, this investigation aims to evaluate the two main properties, vapour pressure and permeability coefficient, related to the evaporation/permeation process concerning ethanolic solutions of PRMs applied to the skin. A quantitative structure–activity relationship (QSAR) based on the two main current models [30, 33] is proposed in order to correlate the experimental data, only when ethanol is used as the vehicle. Antoine constants and Clarke and Glew parameters [34] are fitted to the experimental low vapour pressure data. The determination of these two properties aims to aid in the design and evaluation of fragrance materials [35].

Materials and methods

Chemicals

Camphor (96%), carvacrol (99%), (L)-carvone (99%), E-caryophyllene (≥98%), citronellol (≥95%), eucalyptol (99%), eugenol (≥98%), geraniol (≥97%), R-(+)-limonene (≥98%), (±)-linalool (>97%), (±)-menthol (≥98%), (−)-menthone (96%), α-pinene (98%), tonalide (≥98%), vanillin (99%) and Tween® 20 were all obtained from Sigma-Aldrich. Ethanol (P.A. 99.8%), 1-propanol (67-63-0 ≥ 99.5%), methanol (67-56-1 P.A. 99.9%), phosphate buffer solution (pH 7.4) and glacial acetic acid (64-19-7) were obtained from Merck. The perfume raw materials are listed in Table 1 with their chemical structure presented in Fig. 1. All the PRMs are miscible with ethanol (Hazardous Substances Data Bank

Table 1 Properties of the fragrance materials

Compound	CAS#	Molecular formula[a]	MW (g mol⁻¹)[a]	P_i^{sat}(Pa)[b]	log K_{ow}[c]
Camphor	76-22-2	$C_{10}H_{16}O$	152.23	9.60	2.38
Carvacrol	499-75-2	$C_{10}H_{14}O$	150.22	3.09	3.49
Carvone	99-49-0	$C_{10}H_{14}O$	154.22	13.70	2.71
Citronellol	106-22-9	$C_{10}H_{20}O$	156.27	5.88	3.91
Eucalyptol	470-82-6	$C_{10}H_{18}O$	154.25	253.0	2.74
Eugenol	97-53-0	$C_{10}H_{18}O_2$	164.2	3.01	2.27
Geraniol	106-24-1	$C_{10}H_{18}O$	154.25	4.0	3.56
Limonene	5989-27-5	$C_{10}H_{16}$	136.23	192.0	4.57
Linalool	78-70-6	$C_{10}H_{18}O$	154.25	21.3	2.97
Menthol	89-78-1	$C_{10}H_{20}O$	156.27	8.49	3.2
Menthone	14073-97-3	$C_{10}H_{18}O$	154.25	0.37	3.05
Tonalide	21145-77-7	$C_{18}H_{26}O$	258.41	0.0471	5.70
Vanillin	121-33-5	$C_8H_8O_3$	152.15	0.057	1.21
α-Pinene	80-56-8	$C_{10}H_{16}$	136.23	633.0	4.83
Ethanol	64-17-5	C_2H_6O	46.1	7910	-0.31

Molecular Weight (MW), Vapour Pressure (P_i^{sat}) at 25°C and Octanol–Water Partition Coefficient (K_{ow}).
[a]From EPI Suite Database.
[b]Experimental values from EPI Suite Database, at 25°C.
[c]Experimental values of log K_{ow} from EPI Suite Database.

Figure 1 Fragrance chemical structures studied

Pig ears skin preparation

The pig ears were obtained from the local slaughterhouse Cooperativa Ouro do Sul Carnes (Harmonia, RS, Brazil) within few hours *post-mortem*. No approval of the ethics committee of animal research was required as the ears were taken from pigs not slaughtered specifically for the purpose of this study. Ears were washed with water, and any visible hairs were trimmed carefully with scissors and scalpel. The full-thickness skin of the dorsal side was removed from the underlying cartilage using a scalpel and served as the starting material for further preparation. Then, the stratum corneum (SC) was isolated by trypsin treatment as recommended by Kligman and Christophers [36]. For that, the SC facing upwards was saturated with trypsin solution (0.5% in phosphate buffer at pH 7.4) in a glass Petri dish and stored for 4 h at 37°C (310.15 K) in a saturated vapour atmosphere. The digestion occurred from the dermis end of the tissue, ensuring that the SC remained undamaged. The top layer representing the SC was carefully removed using forceps and washed with purified water. The tissue was washed again with purified water and stored in aluminium foil at 253 K.

In vitro skin permeation

In vitro skin permeation assays were carried out on Franz diffusion cells with an orifice diameter of 9 mm, corresponding to a skin area of 0.64 cm^2, and a receptor volume of 15.0 mL was used in the diffusion cell experiments. Two jacketed cells were mounted in a magnetic stirrer (MS-H280-Pro - DLAB) and kept at 33°C (306.15 K), to mimic human skin surface temperature, by means of circulating water from a thermostatic water bath (TECNAL TE-2000). The skin was placed horizontally on Franz diffusion cells, between the donor and receptor compartments. The receptor solution was composed of phosphate buffer solution (pH 7.4), Tween® 20 and 1-propanol (97:2:1 w/w) and was equipped with small

Teflon-coated magnets, maintaining the receptor medium thoroughly stirred during the entire experiment. In this study, the fragrance systems studied had the initial concentrations of 10 mg mL^{-1} (ethanolic solution). The applied volume to the skin was 2 mL of solution for the infinite dose experiments. The infinite dose experiments aim to define the permeability coefficient in steady state; the donor solution large volume is not representative of the product and this exposure scenario was determined just in order to maintain the external concentration constant over the 24 h and to establish a steady-state flux. The fragrance system was capped with parafilm and tin foil in order to avoid the evaporation or photodegradation over time. For the liquid phase analysis, aliquots of 1 mL were withdrawn from the receptor medium at fixed times (i.e. 0, 1, 2, 4, 6, 24 h) with a syringe and immediately replaced with an equivalent amount of fresh buffer solution.

Quantification

The fragrance components in the liquid phase were firstly isolated by liquid–liquid extraction with the addition of 1 mL of cyclohexane to 1 mL of receptor phase. The mixture was submitted to a vigorous vortex agitation for 1 min, 10 min of ultrasonic bath, followed by 24 h freezing in order to improve phase separation [37]. The organic phase containing the target compounds was then analysed using an Agilent 7890A gas chromatograph (Agilent Technologies, USA). The injector used was in split mode (1:10) at 523 K. The capillary column used was a HP-5MS (30 m × 250 µm i.d., 0.25 µm phase thickness, Agilent Technologies, USA), coated with 5% phenyl methyl silane. The oven temperature started at 333 K, raised to 523 K at 20 K min^{-1}, then held for 2 min. Carrier gas was helium with a flow rate of 1 mL min^{-1}. The FID detector was maintained at 523 K. The quantification of the components was achieved using the respective calibration curve, using concentrations of 10, 5, 2.5, 1.25, 0.625, 0.312 and 0.152 mg mL^{-1} of each terpene dissolved in the receptor buffer solution and isolated as above described for the samples.

In the case of vanillin and tonalide, which have higher boiling points, the analysis was carried out by HPLC/UV. An Agilent Technologies 1200 Series with an Agilent Zorbax Eclipse XDB-C18

(5 μm, 150 × 4,6 mm) column was used. The analysis methodology was the same as used by [38]. The UV wavelengths used were 231 and 252 nm, for the vanillin and tonalide, respectively. The mobile phase consisted of two solvents with a flow rate of 1 mL min^{-1}: (A) water: acetic acid (98: 2), (B) methanol: acetic acid (98: 2). The flow starts at 40% of solvent A and decreases constantly to 0% in 5 min when it increases until 40% in the next 5 min. The ratio 40% of Solvent A and 60% of Solvent B is then kept constant for 5 min. Each run lasted 15 min [38]. To quantify the samples, calibration curves were made using the ≥98% standards.

Vapour pressure

The vapour pressure of each compound was experimentally determined by thermogravimetry with differential thermal analysis (TG-DTA) using the TA Instruments STD Q600 equipment. For that, 10 mg of samples were placed in an alumina crucible with a cross-sectional area of 0.28 cm^2, with a heating rate of 10 K min^{-1}, in an atmosphere of nitrogen with a 50 mL min^{-1} flow and temperature ranging from 293 to 573 K. The Langmuir equation (Eq. 1) relates the vapour pressure, at a given temperature, to the mass loss rate [26]. The constant k was determined per calibration with a well-known compound (E-caryophyllene) following the same methodology.

$$P_{exp}{}^{sat} = k\left[\left(\frac{T}{MW}\right)^{\frac{1}{2}}\left(\frac{dm}{dt}\right)\right] \tag{1}$$

where, $P_{exp}{}^{sat}$ is the experimental TG-DTA vapour pressure (Pa), T is the temperature (K), MW is the molar weight (g mol^{-1}) and $\frac{dm}{dt}$ is the mass loss rate (g s^{-1}).

The Antoine equation (Eq. 2) was used to model the obtained vapour pressure curve.

$$\ln\left(P^{sat}\right) = A - \frac{B}{T+C} \tag{2}$$

where P^{sat} is the vapour pressure (Pa), T is the temperature (K), A, B and C are adjustable parameters. These three parameters are highly correlated, and they are not physically significant, despite the good model adherence. In this way, several different models were proposed for a better property description. Clarke and Glew [34] have proposed a model based on the evaluation of thermodynamic functions from equilibrium constants, initially presented for chemical reactions but lately expanded for pure compounds [39] describing the equilibrium between the two phases. The most significant model improvement is the parameters physical representation; dG_θ^0 is the Gibbs free energy of the phase change process, dH_θ^0 is the enthalpy involved in the process and $dC_{p,\theta}^0$ is the specific heat of the gas formed in the process, all at the reference temperature θ which corresponds to a reference pressure P^0, as presented by Eq. 3.

$$\ln\left(\frac{P^{sat}}{P^0}\right) = -\frac{dG_\theta^0}{\theta} + dH_\theta^0\left(\frac{1}{\theta} - \frac{1}{T}\right) + dC_{p,\theta}^0\left(\frac{\theta}{T} - 1 + \ln\left(\frac{T}{\theta}\right)\right) \tag{3}$$

Due to the nonlinearity of the models used to describe this property, there are few works that assess the statistical significance of the estimated parameters, which could be performed using a hybrid estimation method. The particle swarm optimization method [40] is used first to provide a set of initial guesses, which is used for fine-tuning of model parameters with the help of a Gauss–Newton procedure [41].

Permeability coefficient and QSAR model

The diffusion process involving the skin – considered as a simple membrane – occurs in accordance with Fick's first law, which can be described in terms of permeability (related to diffusivity) as shown by Eq. 4.

$$J(t) = K_{p,i}\left(C_{i,d}(t) - C_{i,r}(t)\right) \tag{4}$$

where $K_{p,i}$ is the skin permeability coefficient (cm h^{-1}) and $C_{i,d}$ and $C_{i,r}$ are the component i concentrations in the donor and receptor chambers (mg cm^{-3}), respectively. The maximum flux at which a material diffuses across the skin is theoretically achieved when it is maintained as a saturated solution on the surface ($C_{i,d} \gg C_{i,r}$). The infinite dose condition leads to a constant mass flux trough the membrane after a diffusion lag time [42].

The flux J (mg cm^{-2} h^{-1}) is then calculated from the slope of cumulative uptake of a substance through a unit of skin surface area (Q in mg cm^{-2}) as a function of time, once the maximum flux is established (constant mass transfer rate) and a linear behaviour is recorded. The permeability coefficient is then obtained from Eq. 5, which gives:

$$K_{p,i} = \frac{J}{C_{i,d}} = \frac{Q}{\Delta t C_{i,d}} \tag{5}$$

A finite dose model, which accounts quantitatively for depletion of chemical due to skin uptake and its evaporation from the skin surface was presented by and, among other properties, it requires permeability coefficient data [29]. The experimental flux for each substance is obtained from the *in vitro* skin permeation experiments (Franz diffusion cell). From these experimental data, a quantitative structure–activity relationship (QSAR) is proposed based on the significant properties related to the absorption of fragrance compounds into the skin. Guy [33] proposed a correlation in order to predict the rate and extent of fragrance absorption, in which it is also pointed out that chemicals with the highest values of steady-state flux have the highest values of vapour pressure. Based on the previous assumptions proposed by the RIFM [30] and Guy [33], the molecular weight (MW) and the octanol–water partition coefficient were considered for this new proposal.

Results and discussion

Vapour pressure

The experimental vapour pressure of all the studied perfume raw materials was determined by the TG-DTA technique. All the compounds presented a zero-order kinetics, which can be attributed to the evaporation. An example of nonzero-order kinetics is a thermal dissociation process. Since sublimation and evaporation are zero-order processes, the rate of mass loss of a sample due to vaporization should be constant, providing that the free surface area does not change. In this way, the absence of chemical decomposition was evaluated in terms of its kinetics, as stated by different papers before [25, 27, 43, 44]. The Langmuir equation (Eq. 1) relates the vapour pressure at a given temperature to the rate of mass loss from the thermogravimetric tests. The percentage mass loss and its derivative (% K^{-1}) are presented in Fig. 2. A calibration constant
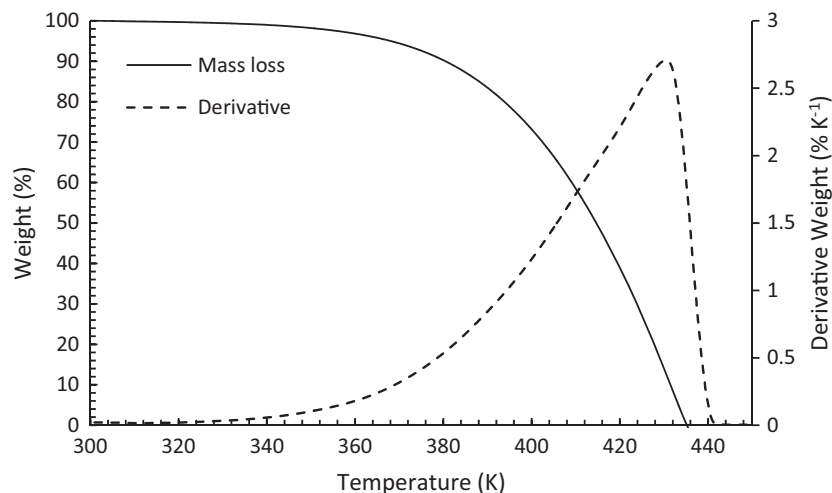
Figure 2 Geraniol TG-DTA analysis
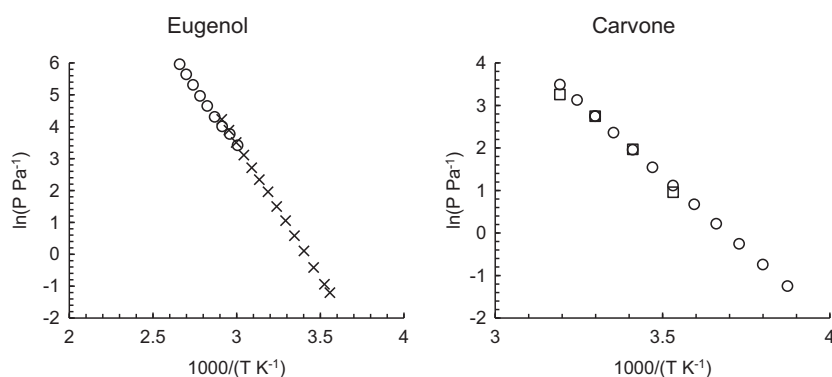
Figure 3 Comparison between experimental and literature vapour pressures of eugenol and Carvone. Experimental data from this work (○); literature data for eugenol (×) [43] and carvone (□) [44]

was used for the specific method and equipment ($k = 4.971 \times 10^4$ Pa g$^{-0.5}$ mol$^{-0.5}$ s^{-1} K$^{-0.5}$).

The Antoine vapour pressure curve for all the compounds were built based on Eq. 2. Although the vapour pressure of several PRMs is available in literature, most of the existing data belongs to that of room temperatures (298.15 K) and the atmospheric pressure. Eugenol and carvone were selected in order to compare the obtained results with those reported in the literature (Fig. 3). The Antoine constants were estimated (Table 2), along with its standard relative deviations.

The experimental and estimated values obtained from public sources such as PubChem, ChemSpider and EpiSuite were all investigated. For these compounds, the experimental values presented are mostly at room temperature (293.15 or 298.15 K). Estimated values from correlations and predictive models are also available at these sources, but as discussed by Almeida et al. [45], at low temperatures the error of such models increases and should only be used when no experimental data is available. At the NIST database, a few Antoine constants are available at higher temperature ranges

(camphor, carvone, carvacrol, eugenol, menthol) and only α-pinene presents Antoine constants for the same temperature range.

The resulting parameters of the Clarke and Glew equation (Eq. 3) along with the standard deviation of the fit, σ_r, are presented in Table 3. Some of the compounds used in this study have similar data reported in the literature [46–49]; however, the vapour pressure experimental data ware obtained by different methods, or at different temperature ranges. The most relevant estimated parameter, the enthalpy of vaporization, of ten of the studied molecules is available at the NIST database, although the reference temperature is not the same (all of them are determined at higher temperatures). This property is mostly used in the thermodynamic modelling of separation processes, such as distillation, along with the vapour pressure. In case of a more complex model for the diffusion of perfume from the skin, including heat and mass transfer, the enthalpy of vaporization is required.

The correlation coefficient obtained from the covariation matrix for each pair of parameters results in 42 correlation coefficients in the range of -0.7396 to 0.8751, for the set of 14 compounds. The

Table 2 Antoine estimated vapour pressure parameters

Compound	A	B	C	Temperature Range (K)	σ_r[a]
Camphor	28.86	7827.78	6.59	298.1–353.1	0.033
Carvacrol	27.09	8226.41	27.86	298.1–383.2	0.050
Carvone	28.08	8364.89	27.02	298.2–308.2	0.019
Citronellol	23.04	6026.10	14.10	298.1–426.4	0.066
Eucalyptol	20.57	4495.92	20.40	298.0–381.2	0.087
Eugenol	26.34	7722.42	3.59	298.1–459.1	0.012
Geraniol	23.54	6374.41	20.14	298.0–427.7	0.109
Limonene	26.30	6392.22	19.97	298.1–333.2	0.031
Linalool	25.26	6494.80	5.59	298.1–423.5	0.022
Menthol	29.56	8648.66	12.83	298.1–360.0	0.077
Menthone	29.72	8265.75	12.66	298.2–336.5	0.034
Tonalide	30.62	9400.46	12.86	298.1–329.0	0.001
Vanillin	26.79	8632.73	12.14	299.2–355.0	0.004
α-Pinene	24.27	5760.66	15.45	298.1–372.3	0.064

[a] σ_r is the standard relative deviation of the fit defined as $\sigma_r = \left[\sum_{i=1}^{n}(\Delta \ln p)^2_{i}/(n-m)\right]^{\frac{1}{2}}$, where $\Delta \ln p$ is the difference between logarithms of the experimental and the fitted values, n is the number of experimental points used in the fit and m is the number of adjustable parameters.

fitting is good, since the magnitude order is in accordance with the literature, associated with the low correlation between the estimated parameters and low standard deviations. The confidence region for the carvacrol is presented in Fig. 4, where the more circular and less elliptical the region, the better the fitting.

The vapour pressure data are fundamental regarding the modelling of perfume diffusion process from skin, but it is also important concerning the modelling of any mass transfer process associated to the phase equilibrium such as distillation or any other separation process. In this way, the collected data and curve fitting comprehend an advance towards a better representation of different systems and applications.

Permeability coefficient

The experimental permeability coefficient (K_p^{exp}) was calculated for all the compounds from the infinite dose Franz cell experiments. The infinite dose condition allows a constant permeation of a substance through the skin surface once the maximum flux is established and a linear behaviour is recorded. The permeability coefficient for each substance was then obtained according to Eq. 5. Table 4 presents the results for the experimental values, along with the relative volatilities at 25°C (298.15 K), which are more available in this condition and it can be obtained from its standard vapour pressure. Fig. 5 illustrates the results for the citronellol and geraniol as representative of all the studied perfume raw materials.

The experimental values agreed with those expected when compared to the two main current models recommended by the RIFM (Research Institute for Fragrance Materials), which assists the regulation of safety assessment process. The SAM (skin absorption model) [30] is an extension from the one developed by Guy [33], being both based on a dataset of "fragrance-like" materials. The two models are of great importance in the toxicological field, serving as guideline along with the parameters used in the threshold of toxicological concern (TTC) technique [11] for the safety evaluation of cosmetic ingredients. The EDETOX and RIFM's datasets are bigger than the one presented here, however most of the experimental data is obtained with different vehicles and most of them do not present the experimental values of K_p (the permeability coefficients were then calculated using predicted water solubility values and experimental maximum absorption flux).

One of the main goals of the present work is to correlate the experimental fragrance material data obtained from the permeation experiments with an ethanolic solution, an essential solvent of perfumes. In our previous work, a model for the combined process of permeation and evaporation from skin was proposed [29]. Differences were found between the experimental permeability coefficients and those obtained by Guy [33], and the relevance of the vehicle–skin interaction, as well as the saturation on the surface were demonstrated.

Table 3 Parameters of Clarke and Glew equation derived from vapour pressure data at the reference temperature $\theta = 298.15$ K and pressure $P^0 = 10^5$ Pa

Compound	$dG_\theta^0 \left(J mol^{-1}\right)$	$dH_\theta^0 \left(J mol^{-1}\right)$	$dC_{p_\theta}^0 \left(J mol^{-1} K^{-1}\right)$	Temperature Range (K)	σ_r[a]
Camphor	20135.0	54664.0	−62.1	298.1–353.1	0.451
Carvacrol	24302.0	53398.0	−38.0	298.1–383.2	0.002
Carvone	22721.0	57294.0	−44.0	298.2–308.2	0.243
Citronellol	22444.0	73017.0	−59.7	298.1–426.4	0.124
Eucalyptol	13850.0	37027.0	−50.7	298.0–381.2	0.117
Eugenol	23622.0	65905.0	−63.6	298.1–459.1	0.138
Geraniol	20447.0	62447.0	−56.3	298.0–427.7	0.439
Limonene	14682.2	47239.7	−67.2	298.1–333.2	0.766
Linalool	20560.0	54704.0	−68.5	298.1–423.5	0.008
Menthol	24809.0	65028.0	−44.4	298.1–360.0	0.004
Menthone	21409.0	66924.0	−45.3	298.2–336.5	0.007
Tonalide	27556.0	72133.0	−35.3	298.1–329.0	0.037
Vanillin	31121.0	67998.0	−37.6	299.2–355.0	0.076
α-Pinene	12333.0	44565.0	−62.7	298.1–372.3	0.242

[a] σ_r is the standard relative deviation of the fit defined as $\sigma_r = \left[\sum_{i=1}^{n}(\Delta \ln p)^2_{i}/(n-m)\right]^{\frac{1}{2}}$, where $\Delta \ln p$ is the difference between logarithms of the experimental and the fitted values, n is the number of experimental points used in the fit and m is the number of adjustable parameters.
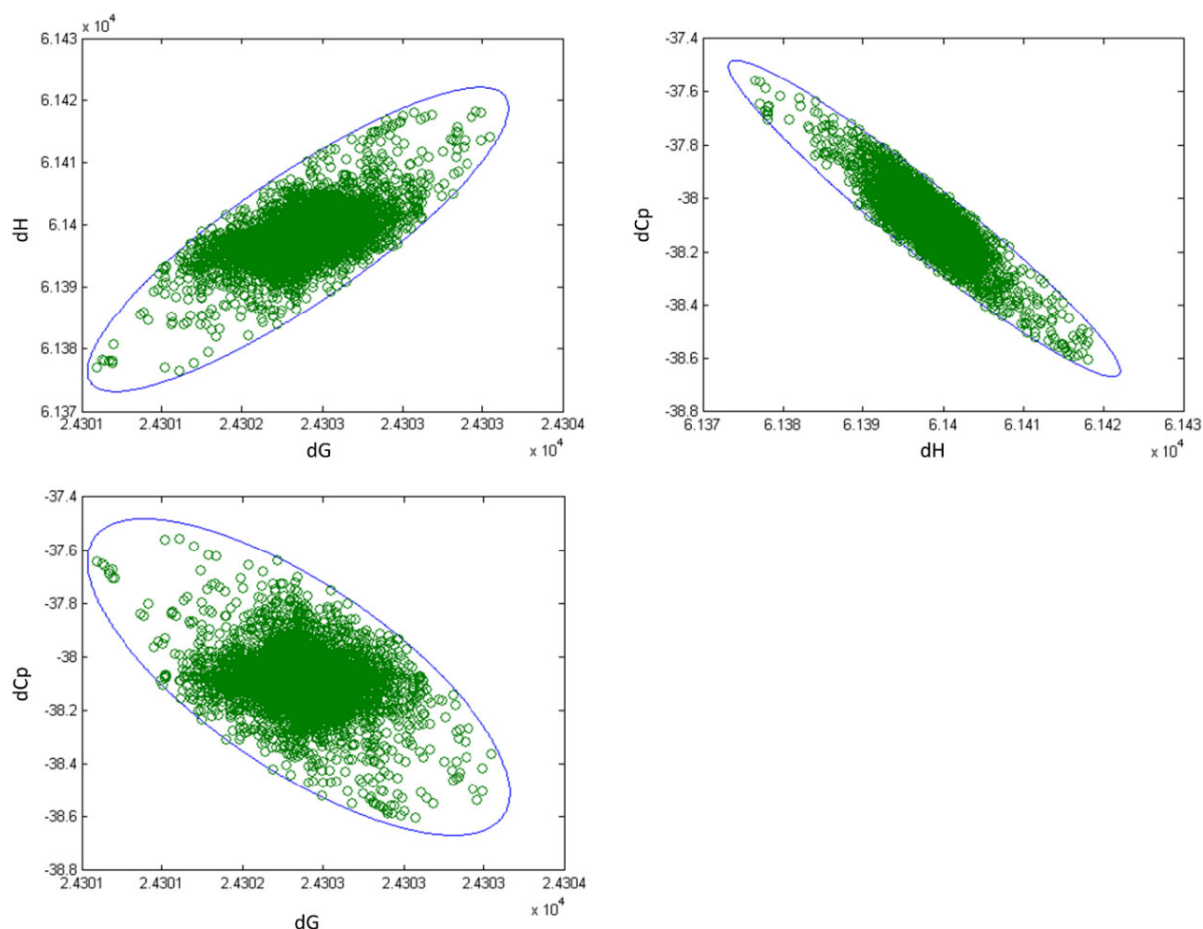
Figure 4 Confidence regions for the Clarke and Glew fitted parameters for the carvacrol vapour pressure data at the reference temperature $\theta = 298.15$ K and pressure $P_0 = 10^5$ Pa

Table 4 Experimental and correlated skin permeability coefficients of the studied fragrance materials

| Compound	MW (g mol^{-1})[a]	$\alpha . 10$[a]	logK_{ow}[c]	$K_p^{exp}.10^2$ (cm h^{-1})	logK_p^{exp}	logK_p^{calc}[d]
Camphor	152.23	12.14	2.38	1.0027	−1.999	−1.827
Carvacrol	150.22	3.91	3.49	5.3023	−1.276	−1.504
Carvone	154.22	17.32	2.71	1.6062	−1.794	−1.733
Citronellol	156.27	7.43	3.91	2.3467	−1.630	−1.387
Eucalyptol	154.25	319.85	2.74	1.9617	−1.707	−1.715
Eugenol	164.2	3.80	2.27	2.5244	−1.598	−1.869
Geraniol	154.25	5.06	3.56	4.4223	−1.354	−1.487
d-Limonene	136.23	242.73	4.57	8.0363	−1.095	−1.172
Linalool	154.25	26.93	2.97	0.9671	−2.015	−1.657
Menthol	156.27	10.73	3.2	3.7304	−1.428	−1.592
Menthone	154.25	0.467	3.05	2.1702	−1.664	−1.635
Tonalide	258.41	0.059	5.7	11.0262	−0.958	−0.950
Vanillin	152.15	0.072	1.21	0.6866	−2.163	−2.167
α-Pinene	136.23	800.20	4.83	8.0641	−1.093	−1.080

[a]From EPI Suite Database.
[b]Relative volatility determined from vapour pressure values from EPI Suite Database, at 25°C.
[c]Experimental values of log K_{ow} from EPI Suite Database.
[d]From the correlation proposed in this work.
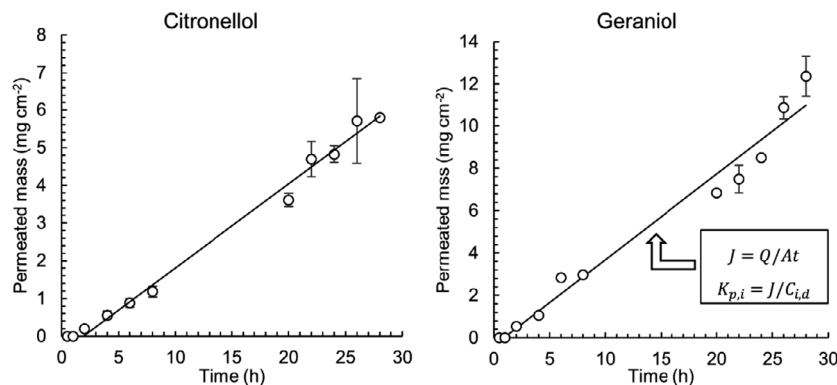
Figure 5 Citronellol and geraniol cumulative amount absorbed at the receptor compartment for the infinite dose experiment. Experimental data (○) and continuous line representing the constant mass rate (maximum flux)
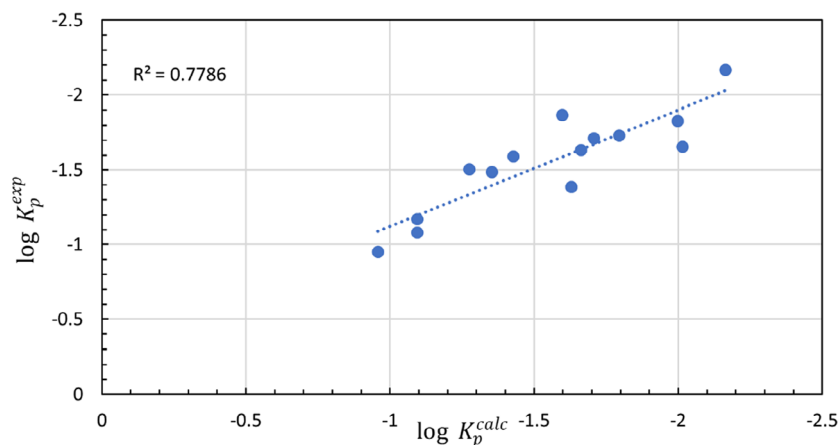
Figure 6 The correlation of experimental values vs estimated values of log K_p

In this way, a new correlation (Eq. 6), for the use only when ethanol is present as vehicle and inside the specific ranges of $\log k_{ow}$ (1.21–5.70) and MW_i (136.2–258.4 g mol^{-1}), is proposed based on the experimental permeability coefficients obtained in this work:

$$\log K_p = -2.383 + 0.294 \log k_{ow} - 0.00094 MW_i \qquad (6)$$

The presented correlation has a standard relative deviation (σ_r) of 0.190, a standard error (SE) of 0.397 and a determination coefficient (R^2) of 0.7786 (Fig. 6). The two previous models, Guy (SE = 0.712, R^2 = 0.578) and SAM (SE = 0.594, R^2 = 0.703), presented slightly worse results although based on a larger dataset.

In order to validate the proposed correlation, three compounds from the RIFM and EDETOX database were selected (coumarin, isoeugenol and musk ketone). Comparing the values obtained through SAM and the correlation proposed in this work, the permeability coefficient differences vary from 2% to 11%. It is important to note that for the same compound under different experimental conditions, different values are found in the literature. For this reason, the application of experimental values (whenever possible) or the use of a correlation that best suits the studied system is highly recommended [30]. The reader is cautioned that the experimental Kp values in this report or those predicted by Eq. 6 must not be used

as a substitute for aqueous Kp values when conducting risk assessments according to the method of Guy [32] or Shen et al. [33]. They will not yield comparable results.

The results suggest that the proposed correlation is a complementary tool in the assessment of permeability coefficients specifically for the design of fragrance systems. The present work does not intend to replace the SAM model, which is mainly developed for toxicological purposes, instead it was designed to assist during pre-formulation stages of scented products using ethanol as vehicle. The QSAR model meets the principles for validation (according to the OECD) and has a defined endpoint, an unambiguous algorithm, and a well-defined domain of applicability (perfumes). It has also appropriate measures of goodness-of-fit and a mechanistic interpretation. The dataset used for the SAM correlation has 131 compounds (54 fragrance materials and 72 "fragrance-like" materials), 27 of which had an experimentally determined K_p on different solvents (ethanol/water solution, PEG, acetone). Most of the RIFM database consists of toxicological experiments in which the main goal is to determine the amount absorbed from the applied dose (permeability coefficient is not determined). The experimental data and the correlation presented in this work are a first step towards achieving a more specific range of applicability and thus becoming

available for predictions of perfume raw materials when in ethanol solution.

Conclusions

In this work, a range of fragrance chemicals had its vapour pressure and permeability coefficients determined. The permeability coefficients were assessed by Franz diffusion cell experiments, measuring the steady-state flux through the skin and using a simple mathematical model based upon Fick's first law of diffusion. Low vapour pressures were evaluated by thermogravimetric analysis and a modified Langmuir equation. The dataset is still small compared to larger and more general QSAR models; however, it is much more specific as to the type of solvent and class of materials studied. The QSAR model proposed presented good fitting to the experimental data and lower errors (SE = 0.397 and R^2 = 0.7786) than more general models (Guy correlation and Skin Absorption Model).

Acknowledgements

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