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Modelling Flavour Release through Quantitative Structure Property Relationships (QSPR)

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Abstract: The use of QSPR to explain the partition behaviour of flavour compounds in different matrices and to predict dynamic flavour release from certain food systems is described. QSPR has been applied in the pharmaceutical and environmental areas to predict properties like the efficacy of drugs (with different substitutions) or behaviours like the accumulation of pollutants in fish, despite the fact that the exact mechanisms are unknown. QSPR relies on the fact that the physicochemical properties of the molecules are responsible for their behaviour and properties in these systems. The models are relatively easy to produce but there are limitations associated with their use outside the defined experimental conditions. The background to modelling flavour partition and release is given, along with examples of relevant QSPR models.

Keywords: Dynamic · Flavour · Model · Partition · QSPR

Introduction

For many years, scientists have studied the link between the flavour chemicals present in a food and the perceived flavour experienced by humans, when they consume foods containing those flavour chemicals. It is now accepted that the way flavours are released from food, and delivered to the flavour receptors in the mouth and nose, determines our perception of flavour. Release of flavours from food and their transport to the receptors is governed by a complex series of physicochemical and thermodynamic parameters and various theoretical models and simulations have been published. The models can be used in two different ways. On the one hand, they can be used commercially to assist in the formulation of flavours for a particular food matrix so that it delivers the desired flavour profile to the flavour receptors. On the other hand, by building and verifying models, the fundamental scientific principles governing flavour release can be identified, improving the academic understanding of the subject. Since food is consumed in a variety of different forms (solutions, solids, emulsions) the models need to consider the sequence of mass transfer for each particular food system. Generally speaking, the key stages are the transfer of flavours from the food to the saliva phase, followed by partition of volatile aroma compounds from the saliva to the air phase in-mouth[1]. Further dilution and interactions with mucus membranes occurs during transport of volatile aroma compounds from the air phase in-mouth to the olfactory receptors in-nose. These stages (and the mass transfer mechanisms involved) have been described previously in reviews of flavour release [2–6].

Several authors have written theoretical models for flavour release, although few have been systematically tested and their validity remains unproven. One of the problems is obtaining meaningful values for the fundamental parameters that drive mass transfer *in vivo*. For instance, how can the change in surface area of a food during eating be predicted? What is the partition value for a volatile compound in a saliva solution containing sucrose, salt and other solutes and in which the concentrations are changing rapidly with time? deRoos and colleagues [1][7] approached the problem using a combination of theoretical modelling and empirical pragmatism. To overcome a lack of information on the mass transfer properties at the saliva-air interface, they obtained experimental data and developed a semi-empirical relationship that allowed them to produce predictive models. These were then tested and found to correlate well with the observed behaviour from foods. A series of paper from Hills and co-workers [8–14] have considered flavour release from a wide range of food systems (solids, liquids, emulsions) as well as the way that human physiology affects the mouth-to-nose transport of volatile compounds. Testing of these models has been limited and the main difficulty is the problem mentioned above, the determination of suitable values for the key parameters (partition, diffusion coefficient *etc.*).

An alternative approach is to abandon the theoretical, mechanistic approach and simply model the observed behaviour empirically. The advantage is that models can be produced, tested and validated, fairly rapidly. The disadvantage is that they only apply for the conditions pertaining in the experiment and cannot be easily extended to cover other situations. An example is a dairy product where any change in the protein content, fat content,

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pH or added hydrocolloid, will require a new empirical model, whereas a good mechanistic model will contain these parameters and so is better able to predict behaviour over a wider range of conditions. However, given the problems associated with purely mechanistic models and the fact that the only accepted model [15–17] contains some empiricism, the development of empirical models has attractions. Similar problems exist in several other scientific disciplines and one, universal, approach has been to apply Quantitative Structure Property Relationships to develop empirical models. This approach assumes that the behaviour observed experimentally is a result of the different physicochemical and/or topological properties of the compounds exhibiting the behaviour. Experimental data is first collected to determine the behaviour of a range of compounds in the system under study. Physicochemical parameters are usually calculated using group contribution methods [18]. With the advent of more powerful computers and software, it is now possible to type in the formula of the compound into a software program, optimise the geometry of the molecule in the phase of choice and then calculate several hundred physicochemical and topological parameters. These are then screened using a statistical software package to identify those that correlate with the observed behaviour. The selected parameters are further modelled to give the best correlation with the observed behaviour. Fig. 1 shows the process schematically.

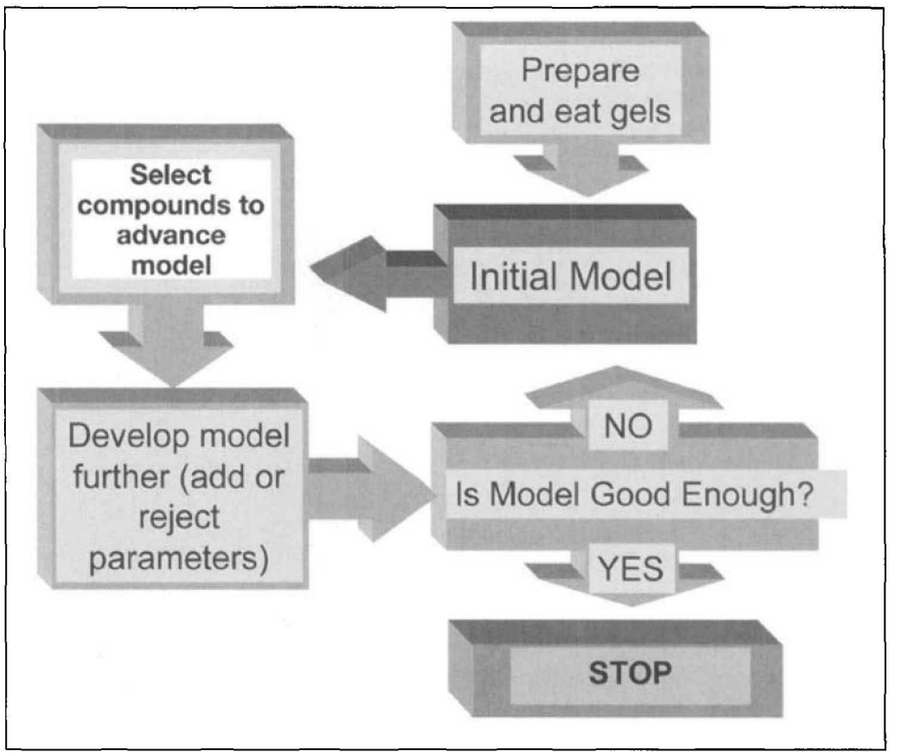

Fig. 1. Schematic representation of the stages of QSPR model development

To produce a robust model, it is important to use the full range of conditions to be found in the system. In the case of flavour volatile compounds, the range can be represented by plotting the hydrophobicity of the compounds against the volatility of the compounds. Fig. 2 shows the distribution for aroma compounds where the extremes are bounded by compounds like acetaldehyde (high volatility and hydrophilic), octadecane (low volatility and hydrophobic) and maltol (medium volatility and hydrophilic). Volatile compounds lie within this roughly triangular region. When selecting compounds with which to develop QSPR models, Fig. 2 can be used to ensure that the compounds selected not only cover the extremes, but are also evenly distributed throughout the volatile 'space'. This avoids undue 'leverage' in the correlations and modelling steps shown in Fig. 1.

Although QSPR models have been quite widely used elsewhere, applications relevant to food flavour seem to be limited to estimation of air-water partition coefficients [19], Henry's constant [20], prediction of pungency [21] and receptor binding attributes [22]. Here we report their use in predicting changes in partition coefficients in the presence of solutes as well as release from food systems *in vitro* and *in vivo*.

Solute-volatile Interactions in Aqueous Solutions

It is well-established that the partition of a volatile compound between the liquid and gas phases can be affected by the presence of solutes in the liquid phase. For flavour release, the liquid phase may be the food itself (beverages for example) or it may be the saliva phase in mouth which contains salivary salts and proteins as well as sugar, salts and acid released from the food matrix. The effects of single salts on the gas liquid partition K_{gl} of a volatile (i) have been studied [23] and a thermodynamic equation developed to describe behaviour (Eqn. 1)

$$K^i_{gl} = \left(\frac{\gamma_i P^0_i(T)}{P_T}\right)\frac{\bar{V}_l}{\bar{V}_g} \qquad \text{Eqn. 1}$$

where $P^o_i(T)$ is the vapour pressure for the pure component i (Pa) at temperature T, P_T, the total pressure in the gas phase (Pa) and $\bar{V}_l$, $\bar{V}_g$ are the molar volumes of the liquid and the gas phases respectively ($m^3\ mol^{-1}$). The practical difficulty of Eqn. 1 is determining the activity coefficient (γ_i) for each compound and for each solute. For a QSPR model, a rapid, direct headspace analysis (Atmospheric Pressure Ionisation Mass Spectrometry; API-MS; [24]) was used to determine the partition of around 40 volatile compounds in sucrose solutions [25]. Physicochemical parameters were calculated and, through the process shown in Fig. 1, the following model was obtained, where the effect value is the change in headspace concentration relative to the equilibrium headspace concentration of the volatile above water:

Effect Value = Eqn. 2

0.190
− 0.139 *(Log P)²
+ 0.276 *Carbonyl Group Count
+ 0.781 *Connectivity Index
− 0.072 *(Connectivity Index)²
− 0.073 *Dipole Vector X (Å³)
+ 0.600 *Lumo Energy (eV)
− 0.074 *(Lumo Energy)²
− 0.319 *Ring Count
+ 0.092 *Electrostatic Energy (kcal mol⁻¹)

The model was validated with a test set and with some data from the litera-

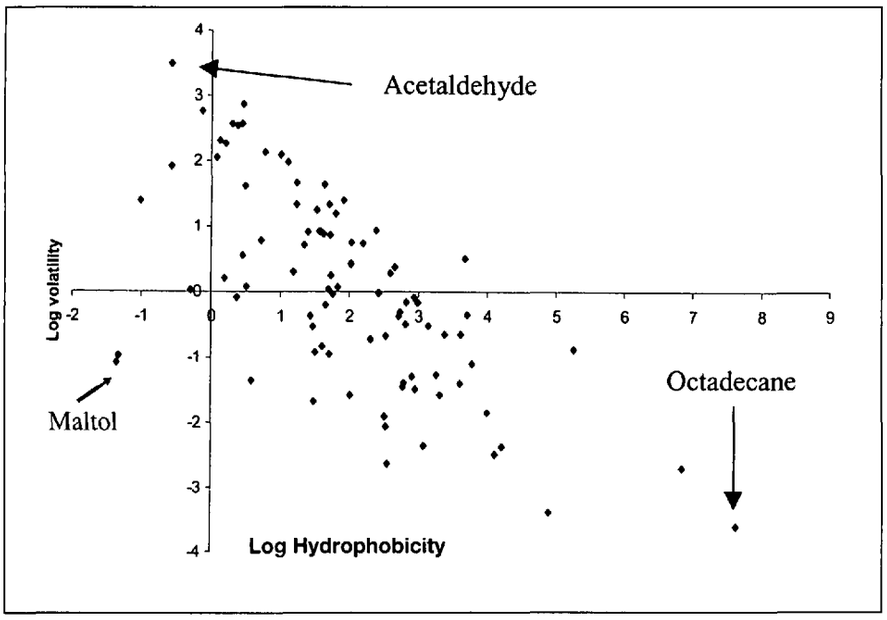

Fig. 2. Log-log plot of hydrophobicity against volatility of 40 compounds showing the range of physical properties found in volatile aroma compounds

ture. The predicted and actual headspace data are shown in Fig. 3. Separate studies indicated that the effect value increased linearly for each volatile compound over the range 20–60% sucrose [25] and significant differences were only noted above 20% sucrose. Measurement of sucrose concentrations in-mouth, during eating of sugar confectionery products gave values between 10 and 30% so these effects may be sensorially significant, especially given the fact that the effect values can show halving or doubling of the headspace concentration (see Fig. 3). The correlation coefficient for these data was 0.76, a value considered acceptable in terms of the validity of the QSPR model but a value that shows the spread of data points around the line of best fit. This demonstrates a limitation of this QSPR model; it gives a good guide to behaviour but does not give a high degree of precision.

Volatile Partitioning in Cloud Emulsions

Although various authors have published models for partitioning of volatiles between emulsions and the air phase above [14][26–30], the amount of experimental validation is low, with no systematic study published. Using cloud emulsion, (designed to give citrus beverages their opacity), experiments were performed to study partitioning between the emulsion and the air phase. Cloud emulsions contain low levels of lipid (around 2g/kg) and the effect of oil content, oil type (solid/liquid fat), emulsifier type and particle size on equilibrium partitioning were determined. By measuring under static equilibrium headspace conditions, any changes in viscosity between the samples was irrelevant as viscosity affects dynamic release but not partition, providing the system is given time to reach equilibrium. The two factors that affected partitioning were the oil content of the emulsion and the nature of the volatile compound that was partitioning. Again this type of behaviour is ideal for QSPR modelling and, using 39 volatiles at three different oil contents and 72 descriptors, obtained from group contribution software, a model was constructed with a correlation coefficient of 0.83 containing the parameters shown in Eqn 3.

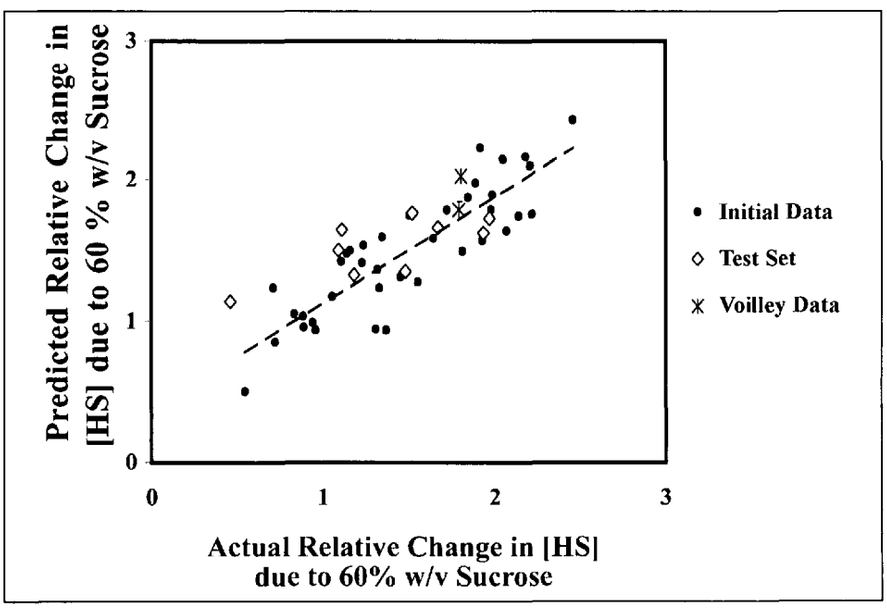

Fig. 3. Comparisons of actual and predicted headspace values (expressed as relative change) above a 60% sucrose solution. Initial data were used to build a model which was then tested and refined using the nine compound test set. Values from the literature are also included and show good agreement with the model [23]

Lipid Effect = Eqn. 3
+107
$-6.3*(LogP)^2$
-3.2* Log Solubility
$+0.28*(\text{dipole vector})^2$
+10* Lipid Concn (g/kg)
$+0.39*(\text{Log P})^4$
$-2*(\text{Log P})^2*$ Lipid Concn (g/kg)
+7.6 * Log Solubility* Lipid Concn (g/kg)
$-0.93*(\text{dipole vector})^{2*}$ Lipid Concn (g/kg)

Of the factors in Eqn. 3, log P was highly significant and a crude relationship between the oil content of the emulsion and the hydrophobicity index of the volatile compound could be constructed as shown in Fig. 4. The model was validated with a test set of compounds and comparison of actual and predicted values showed a correlation coefficient of 0.83. Again the model serves as a good guide to behaviour but lacks precision.

Volatile Flavour Release from Gels *in vivo*

The QSPR examples above both considered flavour release under equilibrium conditions where dynamic factors are not relevant. To test the applicability of QSPR to model a dynamic release situation, the in-nose concentration of volatiles release from gelatin gels (a model wine gum system) were measured in a small group of people eating the gels. There were variations between the people but these were relatively small compared to the differences found in-nose for different volatiles (variation by a factor of 10,000, even though all volatiles were incorporated into the gelatin gel at the same concentrations). A model was then constructed to predict the maximum in-nose concentration (I_{max}) for any compound [31]. The key factors were the volatility, the hydrophobicity and the Hartree energy (representative of the molecules' size and shape). A slice through this three dimensional model is shown in Fig. 5 at a Hartree energy of 94 and shows the contour lines for log I_{max} where a value of 0 represents an actual I_{max} of 1 ppm (µl of volatile per litre of air). Development of models for other time points during release allowed the production of models to predict the time course of release from the gels and there was good agreement between actual and predicted values (data not shown). The interesting finding of this experiment is that, despite the complex sequence of mass transfers undergone by the volatile compounds on their way to the nose, the whole process can be expressed in terms of just three parameters. This dynamic model led to a study of the persistence of volatiles after ingestion (the so-called aftertaste) and this too was amenable to modelling using QSPR [32].

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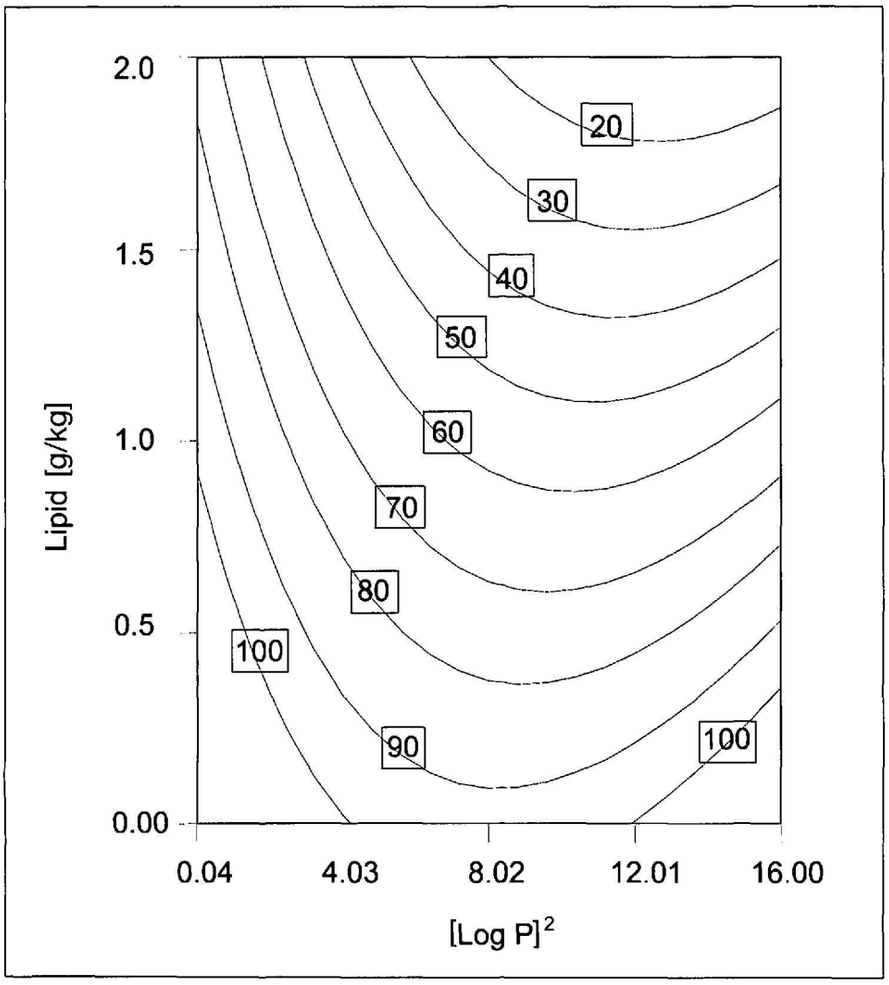

Fig. 4. Effect values (numbers on contour lines) for volatile compounds in emulsions with different lipid contents as a function of compound hydrophobicity (log P).

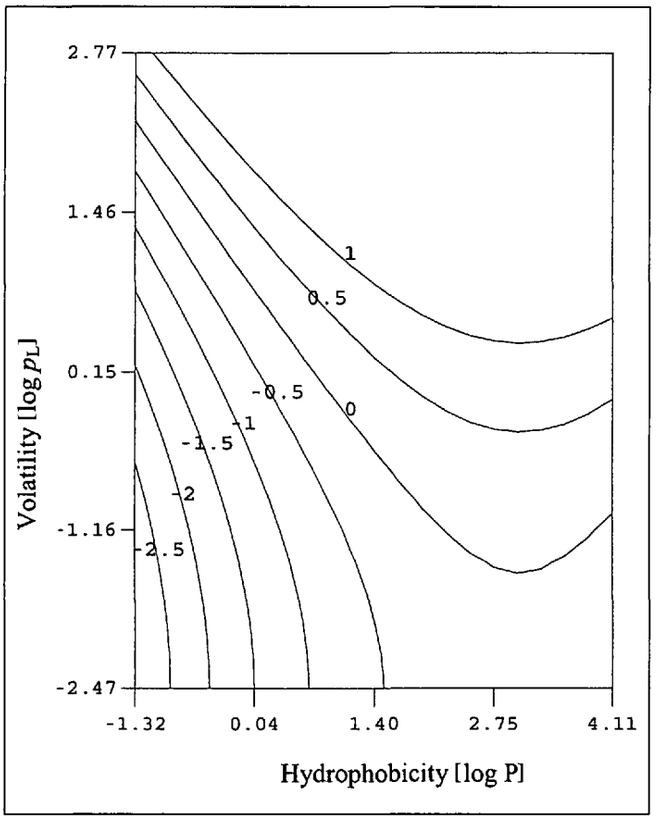

Fig. 5. Prediction of maximum in-nose concentration (l_{max}) from gelatin-sucrose gels as a function of hydrophobicity and volatility. The plot is taken at a Hartree energy of 94. Values on the contour lines are log l_{max} and a value of 0 is equivalent to an actual concentration of 1ppm by volume (1 µl per litre air).

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