

1. The problem

Formulating for delivery of actives into skin requires multiple compromises. The active has to be soluble in the delivery “chassis”, and the chassis needs to solubilise the correct part of the skin in order to aid the permeation of the active.

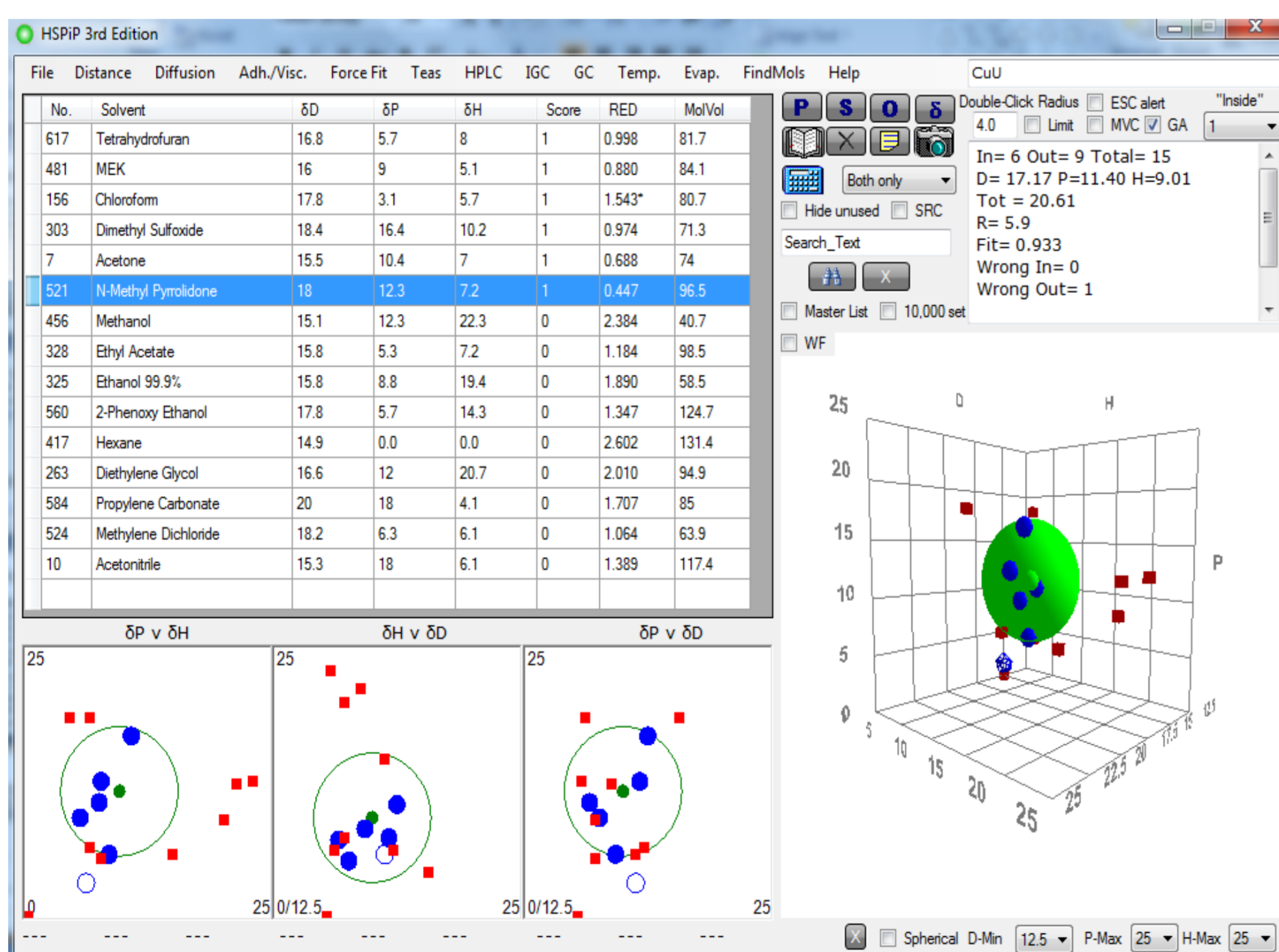
At the same time, the solvents/excipients in the chassis have to meet strict regulatory guidelines. Almost inevitably this requires a complex mixture and the solubility characteristics of the mixture need to be known in order to be optimized.

Without rational formulation guidelines, this task is often hit-and-miss, using simplistic and misleading terms such as “hydrophilic” or “lipophilic”, which don’t do justice to the complexity of chemical space.

Syntopix develops novel antimicrobials for the management of acne prone skin. The company was seeking a method of rational formulation design in order to ensure efficient delivery to the target site.

4. Measuring HSP

Although estimation methods are useful, there is no substitute for measurement. The classic method is to score solubility in a panel of ~20 test solvents. By scoring the solvents as “good” or “bad” it’s possible to calculate a Sphere in 3D HSP space with the centre at the HSP of the solute and a radius which describes how restrictive the solubility range is. Using this approach the HSP values of an active ingredient can be calculated and used to accurately predict solubilities in pure solvents or mixtures.



The polymer poly lactic acid being tested for its solubility in 27 solvents, with a Sphere calculation that gives HSP values of 19, 10, 6

Whilst the process for a single compound is relatively simple, it becomes rather tedious when lots of actives, polymers, excipients need to be measured in this way. It needs to be automated.

2. Understanding solubility characteristics

One proven, powerful method for understanding solubility is the use of Hansen Solubility Parameters. These 3 values provide a means of predicting whether one material will dissolve in another and form a solution:

- δD represents the energy from dispersion bonds
- δP represents the energy from dipolar intermolecular forces
- δH represents the energy from hydrogen bonds

If a solute has parameters δD₁, δP₁ and δH₁ and a solvent has parameters δD₂, δP₂ and δH₂ then the “Distance” between them is: $D^2 = 4 * (\delta D_1 - \delta D_2)^2 + (\delta P_1 - \delta P_2)^2 + (\delta H_1 - \delta H_2)^2$ where a small D means high compatibility (“like dissolves like”) and a high D means low compatibility.

The HSP of a mixture is simply the weighted average of the individual components. Using HSPs, it is possible to make a solvent from two non-solvents. Syntopix has exploited this approach to devise solvent mixtures for difficult to solubilise actives.

5. High Throughput Screening for Sphere measurements

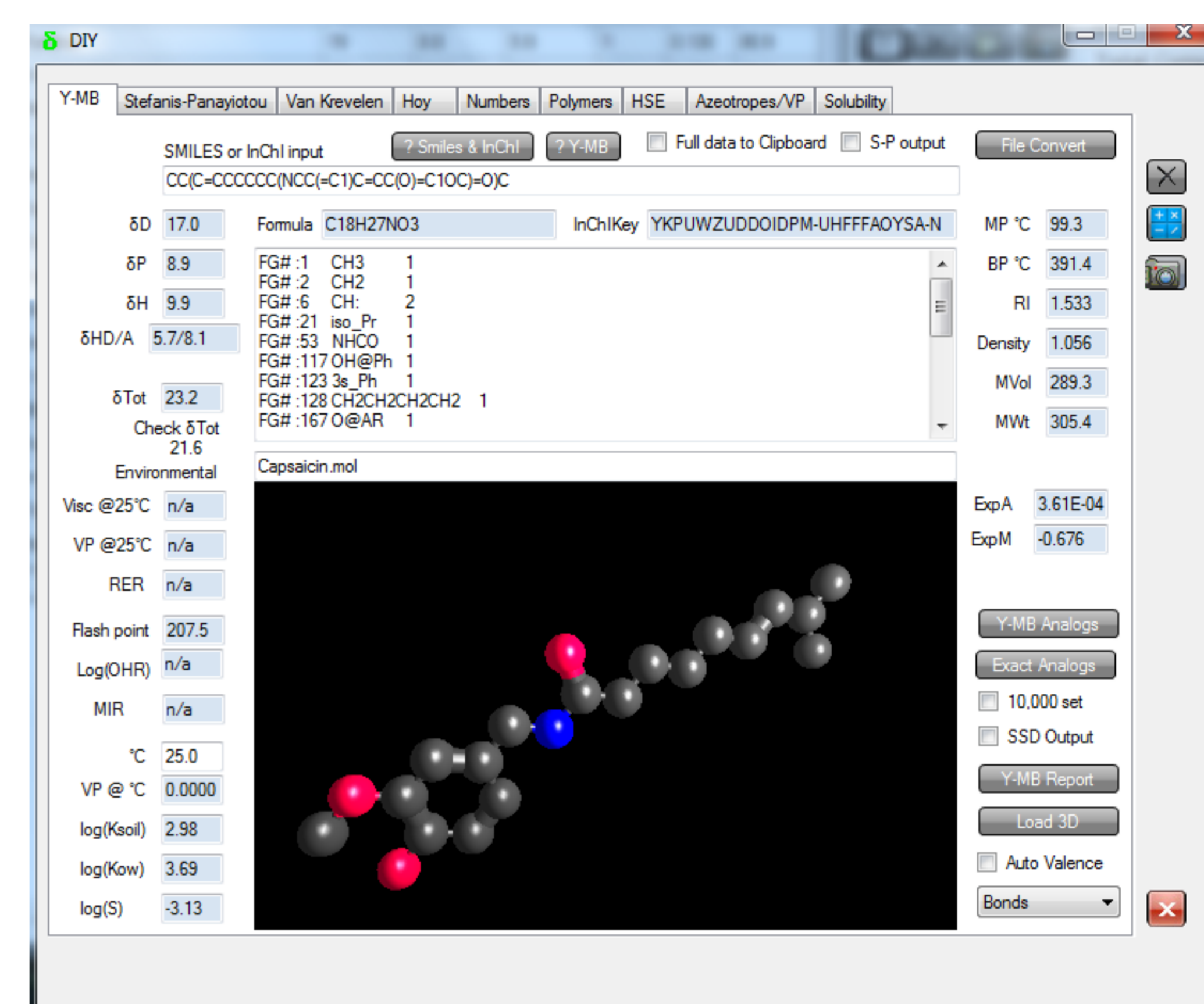
The Formax machine at VLCI (picture below) has been used to automate the process. The same, known amount of the test material is automatically dispensed (syringed for liquids, special dispenser for or solids) into each tube, the known amount of each solvent is pumped into the tube, the samples are then shaken vigorously (with optional glass beads as integral stirrers) for a known time, and finally scored by eye. The data are entered into the HSPiP software for an instant calculation.



Acknowledgements: We appreciate the help of Sander Van Loon, VLCI, Amsterdam, www.vlci.biz.

3. Knowing the HSP

If the active/solvent is well-known, the chances are that the HSP are also known and provided in databases such as HSPiP (Hansen Solubility Parameters in Practice). If they are not known, an estimate can be made from a SMILES or MolFile input via the Y-MB method.



Automatic estimation of the HSP of Capsaicin from its MolFile

6. The benefits

Initial HSP determinations for Syntopix active ingredients were done by the classic, manual process. The results enabled the design of a novel anti-acne formulation that produced positive in-vivo outcomes more efficiently than traditional approaches.

Availability of the HT method from VLCI permits customers like Syntopix to very efficiently build their own data set of HSP values for active ingredients and preferred excipients as well as for solvent mixtures which have to meet strict regulatory requirements.

Any other actives that have a close HSP match to the original vehicle (which has many features other than the right HSPs built into it) can now be used by Syntopix straight away. New vehicles can be developed for those actives that are in a very different HSP space and no time is wasted in trying to put those actives into the standard chassis, as they will certainly fail on simple solubility grounds.

The Syntopix team can now spend much more time focusing on actives and in-vivo testing rather than hit-and-miss formulation work. The pipeline of actives in advanced testing can therefore increase significantly.