iFormulate

Introduces…

A Quick Guide to Hansen Solubility Parameters

Dr David Calvert
and
Dr Jim Bullock
iFormulate Limited

David@iformulate.biz and Jim@iformulate.biz

An iFormulate *Skills* Formulation Training 2017 Webinar

Overview:

1. Why is Solubility Important?
2. Hansen Solubility Parameters
3. Case Studies
4. Summary and Learning More

This webinar is being recorded and will be made available

The audience is muted and you may ask questions using the question function in GoToWebinar

This webinar will last about 30 minutes

Your Speakers

Dr David Calvert
iFormulate Ltd

Dr Jim Bullock
iFormulate Ltd

iFormulate *Skills* Formulation Training 2017

A Little About iFormulate

A company founded in 2012 by two experienced industry professionals…

Combining diverse experiences, knowledge and wide range of contacts:

…polymers, materials science, chemistry, imaging, dyes, pigments, emulsion polymerisation, biocides, anti-counterfeiting, environmental, formulation, consultancy, marketing, business development, strategy, regulatory, training, events, R&D, innovation

Complementary network of Associates

Dr Jim Bullock
E: jim@iformulate.biz
M: +44 (0)7450 436515

Dr David Calvert
E: david@iformulate.biz
M: +44 (0)7860 519582

Our Services

iFormulate Consult

iFormulate Strategic

iFormulate Skills

Definition of Solubility*

“The analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent, is the solubility of that solute. The solubility may be expressed as a concentration, molality, mole fraction, mole ratio etc”

*IUPAC Gold Book

Terms and Influences

- Solvent
- "Poorly soluble"
- Units
  - Often g/litre
- Saturated Solution
  - At equilibrium

- Temperature
- Pressure
- Particle size
- Counter-ion
- Purity

Sometimes "solubility" means "compatibility"

Importance of Solubility to Formulators

- Pharmaceuticals
- Agrochemicals
- Coatings
- Inks
- Personal Care/Cosmetics
- Home Care

- Efficacy
- Delivery
- Cost
- Regulations

Sometimes relative solubility (Partition Coefficent) is more relevant..
Sometimes insolubility is important…..

iFormulate *Skills* Formulation Training 2017

Agrochemicals Delivery

- Soluble Liquids (SL)
  - Simplest, most traditional formulations
  - Glyphosate, most successful herbicide is an SL formulation
  - Number of salts give different solubilities
  - Not an area where HSP is very helpful
- Emulsifiable Concentrates (EC)
  - A solution of active ingredient with emulsifying agents in a water insoluble organic solvent which forms an emulsion when added to water
  - HSP can help with choosing alternative solvents

Pharmaceuticals Delivery

- More than 40% of New Chemical Entities (NCEs) developed in pharmaceuticals are practically insoluble in water
- Techniques to solve
  - Particle size reduction
  - Particle engineering
  - Salt formation
  - Solid dispersions
  - Surfactant

Regulations

- To Comply
  - VOC regulations
  - Move away from more traditional solvents
- To minimise toxic effects
- To minimise environmental impact

How to Measure Solubility*

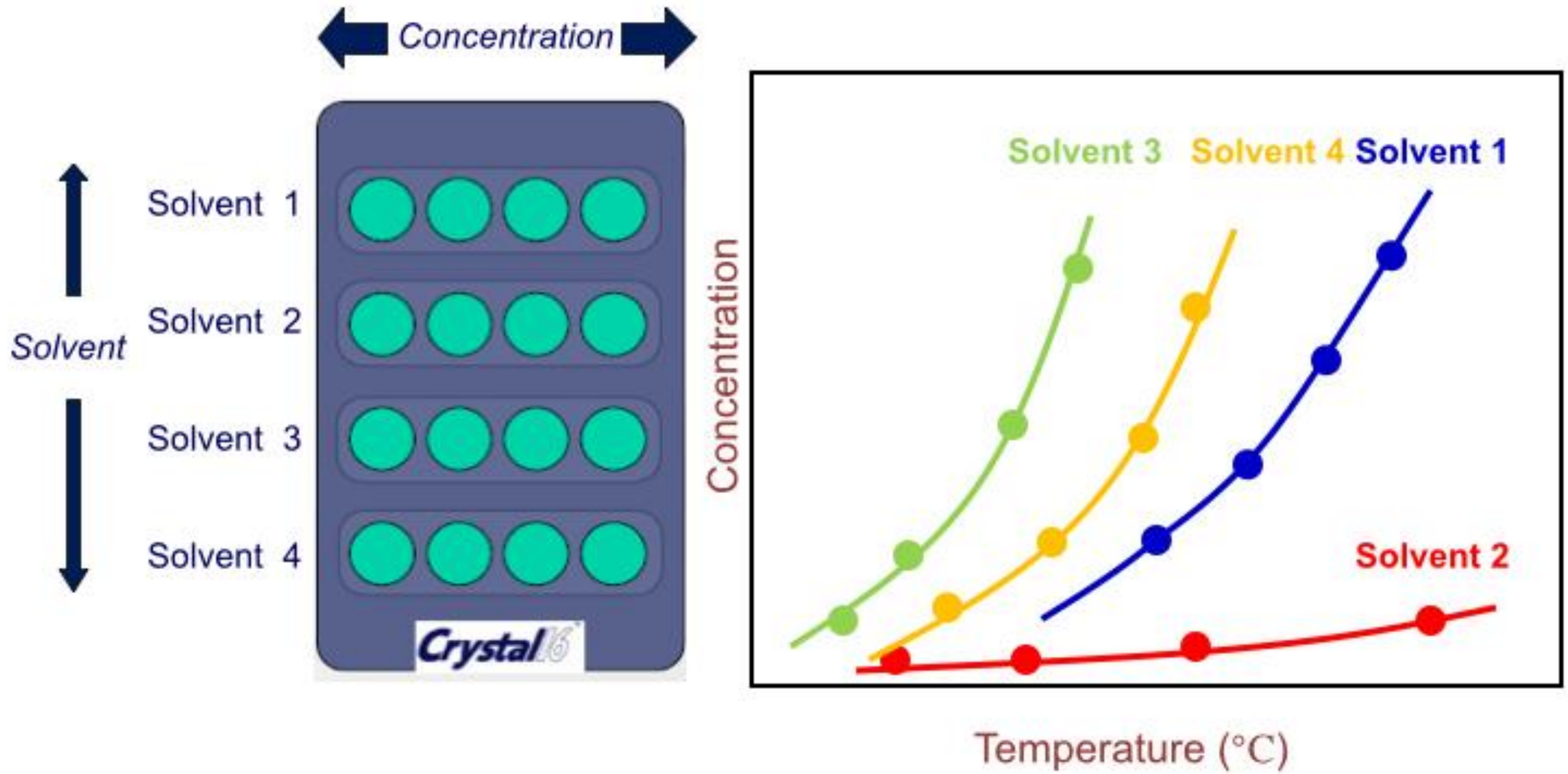
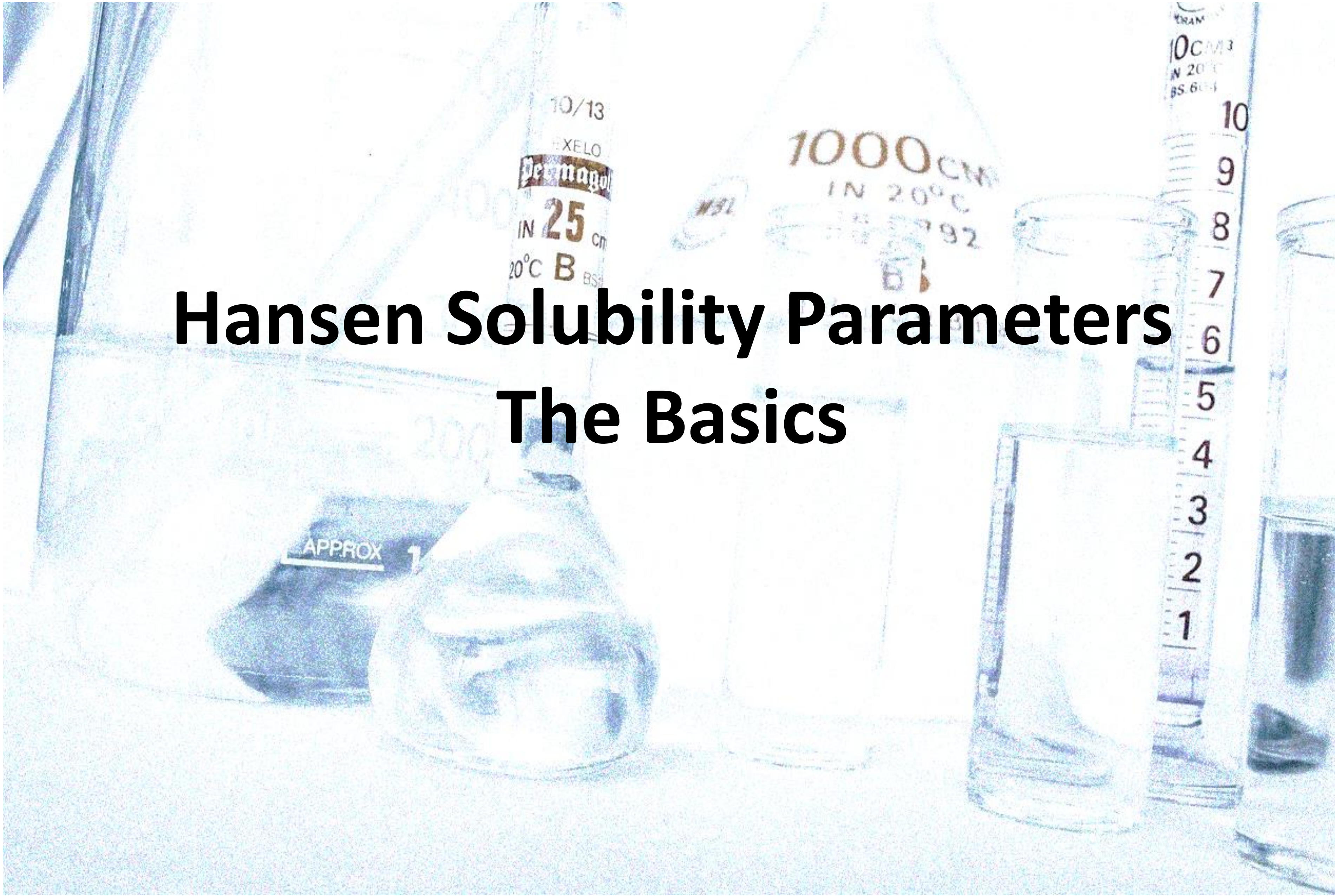


*Figure courtesy of Technobis

Can you predict Solubility/Compatibility?



Hansen Solubility Parameters
The Basics

Solubility: The Challenge

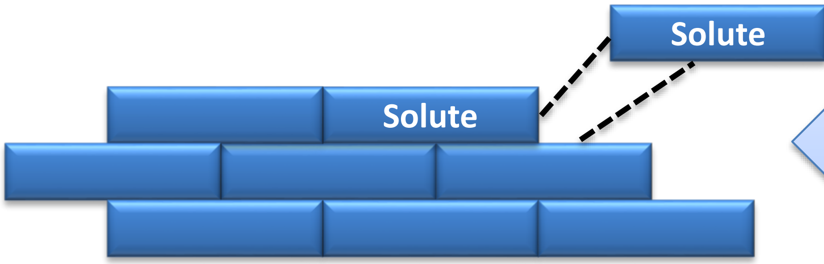
- But how can I predict solubility **well enough** to choose new (or replacement) solvents and other ingredients which are compatible with my formulation?
- For a practical formulator "**well enough**" does not have to mean "**perfectly**" – narrowing the extent and amount of experimental work is often justification enough…

Hansen Solubility Parameters: The Basics

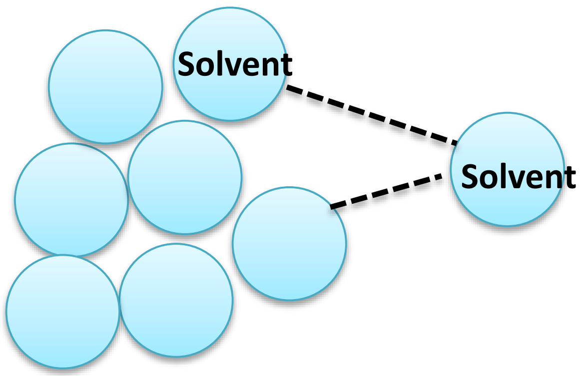
Simply speaking (i.e. without any mathematics)…

- **Solubility is all about interactions (or forces, in some case called bonds):**
  - Interactions between solute and solute molecules
  - Interactions between solvent and solvent molecules
  - Interactions between solvent and solute molecules
- **Thermodynamics tells us:**
  - Pulling molecules apart requires energy
  - Attractive interactions between molecules produce energy
  - Systems tend towards their lowest energy (stable) state
- **Observation tells us:**
  - "Like dissolves like" (e.g. hydrocarbons dissolve other non polar things)
  - But how do we measure "like"?

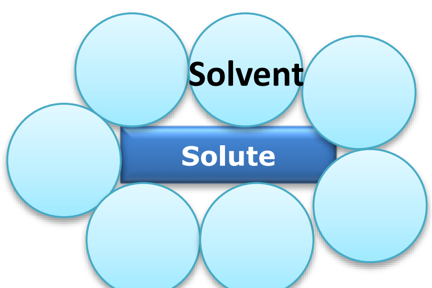
Interactions Between Molecules



Remove solute molecules from the bulk: Doesn't depend on solvent – doesn't really matter when comparing solvents



Break solvent molecules apart: Need to know about forces that have to be overcome



Create interaction between solvent and solute molecules: Need to know about types of interactions created

iFormulate *Skills*
Formulation Training 2017

What Are Those Interactions Anyway?

To cut a long story short, the main things you need to think about are:

Dispersion forces

- Weak intermolecular forces related to polarizability of a molecule and hence to the number of electrons
- Essentially related to the Van der Waals interactions that exist between all molecules

Polar (dipolar) interactions

- Molecules that have a degree of charge separation form an electrical dipole and hence can attract one another electrostatically

Hydrogen bonds

- A special type of polar interaction
- Some atoms on molecules act as donors or acceptors of electrons
- Typically a (partially) positively charged hydrogen atom is attracted to a lone pair of electrons on an electronegative atom (e.g. F, O, N)
- Often seen as “part-way” to a covalent bond

“Like Dissolves Like”: How Do We Quantify This?

- Hansen Solubility Parameters quantify the degree of “like” by describing the solvent and the solute using three numbers (HSP)
- You won’t be surprised to hear that these numbers relate to the three types of forces we have just heard about:

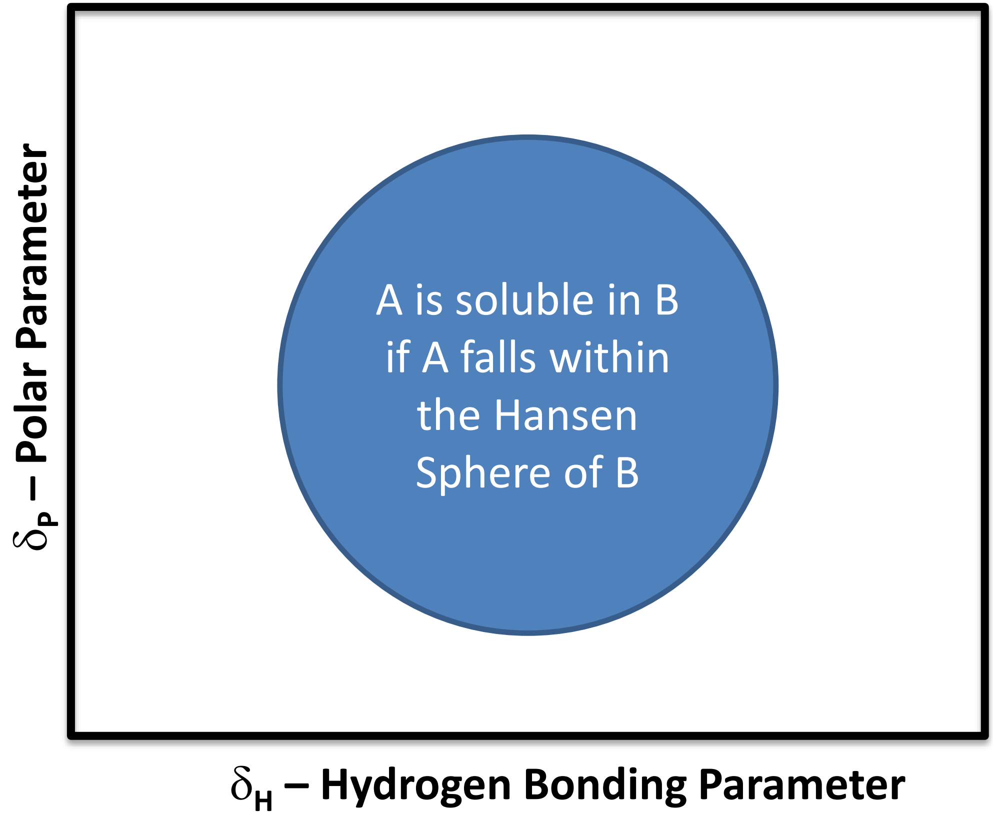
δ_D – Measure of dispersion forces

δ_P - Measure of polar (dipolar) interactions

δ_H – Measure of hydrogen bonding

- The closer the HSP values of solvent and solute, the better the solvent is for that solute
- The ”distance” of solvent from solute needs to take into account all three parameters (dimensions):
- $\text{Distance}^2 = 4(\delta_{D1} - \delta_{D2})^2 + (\delta_{P1} - \delta_{P2})^2 + (\delta_{H1} - \delta_{H2})^2$

“Like Dissolves Like” and The Hansen Sphere



In real examples the above circle is a sphere and the third dimension is δ_D the Dispersion Parameter

Two components will be mutually soluble (“in the sphere”) when their parameters are close together, i.e. if the HSP Distance is small

$$\text{Distance}^2 = 4(\delta_{D1} - \delta_{D2})^2 + (\delta_{P1} - \delta_{P2})^2 + (\delta_{H1} - \delta_{H2})^2$$

An Aside: How Is This Related To Thermodynamics and Energy?

E (cohesive energy, = ΔE_{vap}) = $E_D + E_P + E_H$

D - Dispersion (Hydrocarbon)

P - Polar (Dipolar)

H - Hydrogen Bonds (Electron Interchange)

We can normalise the energy to V (Molar Volume), so:

$E/V = E_D/V + E_P/V + E_H/V$, i.e.:

$$\delta^2 = \delta^2_D + \delta^2_P + \delta^2_H$$

HANSEN SOLUBILITY PARAMETERS (HSP)

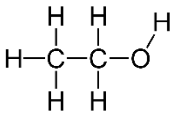
δ = Square Root of Cohesive Energy Density

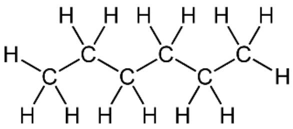
- Charles Hansen: "Hansen Solubility Parameters: A User's Handbook", Second Edition published 2007, CRC Press.
- Charles Hansen: Doctoral Thesis, 1967.

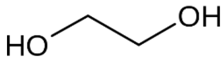
What Are Some Typical HSP Values?

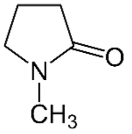
Example HSP values for common solvents – related to molecular structure

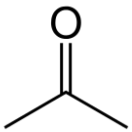
Solvent	δ_D	δ_P	δ_H
Ethanol	15.8	8.8	19.4
Hexane	14.9	0	0
Ethylene Glycol	17	11	26
N-Methyl-2-Pyrrolidone	18	12.3	7.2
Acetone	15.5	10.4	7











Limitations – or care needed:

- Water (very small and H-bonding - choose HSP values depending on conc.)
- Ionic or metallic materials (parameters don't describe bonding adequately)
- Complexes or molecular aggregates or ordering (e.g. surfactants)
- Size plays a role in solubility

How Do I Know What HSP Values To Use?

- **Literature**
  - HSP values are published for many common (and uncommon) solvents and other materials
- **Commercial software**
  - Extensive databases within the HSPiP software
- **Estimation**
  - QSAR methods
- **Measurement**
  - Choose solvents from across Hansen space - construct a Hansen sphere by measuring solubility of an unknown material in solvents of known HSP
  - Inverse Gas Chromatography (IGC) – HSP related to retention times

How Do I Calculate?

- **The "Eyeball Method"**
  - May be able to find solvents or combinations by selecting "by eye" or inspecting lists of HSP values
  - Not quantitative and subject to luck

- **Own spreadsheet or algorithms/macro**
  - Many of the calculations (e.g. HSP distance) are not too complex
  - Need to integrate published values
  - Need to "QA" the calculations

- **Commercial software**
  - Does all calculations, integrates comprehensive database
  - Manual and other support available
  - Costs money

How Could I Use HSP?

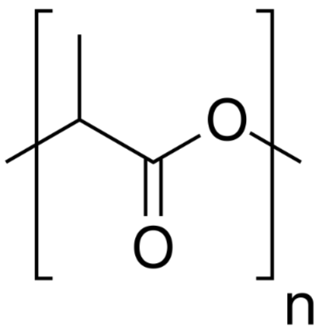
- Numerous applications are known from many industries including:
  - Coatings: Choosing solvent-resin combinations
  - Pharmaceuticals: Predicting solvents for APIs
  - Skin delivery: Of pharmaceutical and cosmetic actives
  - Cleaning solvents: Solvent mixtures with an HSP match for soils
  - Choice of solvents for stabilising nanoparticles, e.g. organic photovoltaics
  - Etc.
- Making use of “unexpected” solvent blends
  - Mix two “bad” solvents to get a “good” solvent
- Introduction to HSP, HSPiP software and database:
  - www.hansen-solubility.com and many publications
- Now, some examples…

Case Study: Plasticisers for Poly(lactic acid)

Example from Chapter 7 (S.Abbott) of “Poly(lactic acid): Synthesis, Structures, Properties, Processing, and Applications” (Wiley 2010)

Challenge:

- PLA - Poly (lactic acid) is a “green polymer” of growing importance
- Biodegradable and from renewable sources
- To enhance market opportunities, plasticisers are needed
- Ideally such plasticisers should also be “green”



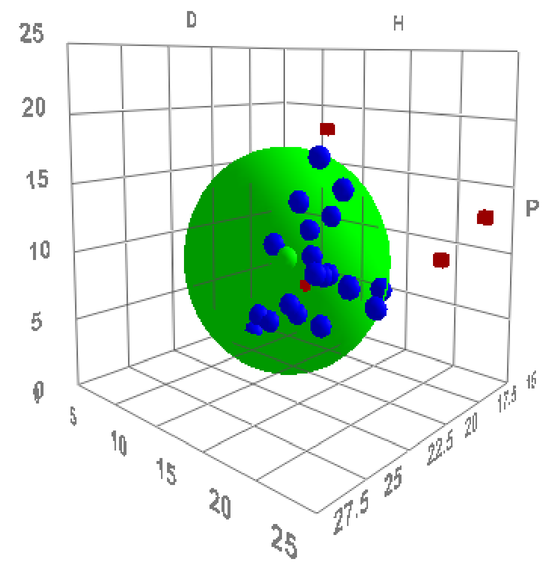
Approach:

1. Determine where PLA sits in HSP space
2. Evaluate what solubility properties are likely in common (“old”) solvents
3. Determine where current plasticisers sit in HSP space
4. Select new plasticisers

Case Study: Plasticisers for Poly(lactic acid)

1. Where is PLA in HSP space?

- Test set of solvents – measured to be "good" or "bad". Good includes swelling solvents.
- Fits to **δ_D = 18.6, δ_P = 9.9, δ_H = 6.0**
- HSP sphere quite wide (R = 10.7)



2. What are likely solubility properties in common materials?

- Best solvents will have lower distance
  - Distance < R
- Can also plot for mixtures

Solvent	δ_D	δ_P	δ_H	**Dist.**
Cyclohexanone	17.8	8.4	5.1	2.35
NMP	18	12.3	7.2	2.75
Isophorone	17.0	8.0	5.0	3.67
Butyl benzoate	18.3	5.6	5.5	4.18
1,3-Dioxolane	18.1	6.6	9.3	4.39
Nitropropane	16.6	12.3	5.5	4.49
MEK	16	9	5.1	5.10
Dimethyl acetamide	16.8	11.5	10.2	5.40
Benzyl benzoate	20.0	5.1	5.2	5.40
Caprolactone	19.7	15	7.4	5.40
THF	16.8	5.7	8	5.51
Tributyl phosphate	16.3	6.3	4.3	5.81
Acetone	15.5	10.4	7.0	6.02
DMF	17.4	13.7	11.3	6.53

Case Study: Plasticisers for Poly(lactic acid)

3. Where do where current plasticisers sit in HSP space?

- Lactide monomer is too small and oligomeric LA affects mechanical properties
- Citrates ("green") have been tried but HSP distances are rather large
  - Acetyl triethyl citrate. δ_D **= 16.6,** δ_P **= 3.5,** δ_H **= 8.6**, HSP distance = 8
  - Acetyl tributyl citrate. δ_D **= 16.7,** δ_P **= 2.5,** δ_H **= 7.4**, HSP distance = 8.4
  - Therefore citrates tend to bleed from PLA
- Triacetin also has a rather large HSP distance
  - Triacetin. δ_D **= 16.5,** δ_P **= 4.5,** δ_H **= 9.1**, HSP distance = 7.4
- Dipropylene glycol dibenzoate has a lower distance, but not "green enough"
  - DPG dibenzoate. δ_D **= 18.0,** δ_P **= 6.6,** δ_H **= 5.6,** HSP distance = 3.5
- PPG or PEG oligomers have a low HSP distance (~4) but problems of separation or crystallisation

Case Study: Plasticisers for Poly(lactic acid)

4. How can we select new plasticisers?

- PEG and lactide oligomers are good plasticisers but have other problems
- Consider lactide (or similar) esters with PEG
- Calculated 50:50 PLA/PEG: δ_D **= 17.6,** δ_P **= 8.6,** δ_H **= 7.9**, HSP distance = 3
- **OLA (oligomeric lactic acid) – capped with short chain PEG is the subject of a patent (U.S. Patent 7,351,785)**

Some Case Studies from HSP50

HSP for smart formulations of organic electronics:

- Replacing chlorobenzene as a solvent for coating of organic photovoltaics
- Binary solvent mixtures chosen using HSP
- Mixtures allow use of evaporation of good solvent to control phase separation
- Stefan Langner (University of Erlangen-Nuremberg): http://iformulate.biz/news-and-views/stefan-langner-using-hsp-smart-formulations-organic-electronics/ and in Solar Energy Materials & Solar Cells 100 (2012) 138–146.

HSP for stabilisation of nanoparticles:

- The compatibility of particles with solvents can be assessed by assigning HSP values to the particle (surface)
- Stability of dispersions of nanoparticles is related to sedimentation rate and correlates with the HSP match of the particle to solvent
- Examples: Carbon black, zinc oxide (quantum dots), talc-based pigments
- Dietmar Lerche (Lum GmbH): http://iformulate.biz/news-and-views/understanding-stability-behaviour/ and in Dispersion Letters 6, 2015, 5.

Some Case Studies from HSP50

Sustainable Reformulation using HSP:

- Replacement of methylene chloride in gel-based paint strippers
- Styrene replacement in vinyl ester resins driven by concerns over VOCs
- Identifying greener solvents for two polymers such as poly(3-hexylthiophene) (P3HT) and poly(butylene succinate) (PBS), a biodegradable replacement for low-density polyethylene.
- Identifying bio-derived solvents for polystyrene foam recycling
- Daniel Schmidt (U.Mass Lowell / Toxics Use Reduction Institute – TURI): http://iformulate.biz/news-and-views/sustainable-reformulation-using-hansen-solubility-parameters/

HSP50

Fifty Years of Hansen Solubility Parameters
University of York, UK, 5-7 April 2017

Invited Presentations and Submitted Papers/Posters

- Prof Jean-Marie Aubry, U. Lille: The predictive power of HSP in formulation science
- Prof James Clark, U. York: HSP for Green Chemistry
- Dr Charles Hansen: How HSP were developed
- Stefan Langner, U. Erlangen-Nürnberg, HSP for Organophotovoltaics and beyond
- Prof Daniel Schmidt, U. Mass. Lowell: HSP for polymer formulations
- Sander van Loon (VLCI) and Bart Wuytens (Agfa Labs): High Throughput measurement techniques for HSP
- Dr Hiroshi Yamamoto: The new HSP methodology

HSP Workshop

- Getting the most out of HSP

http://www.hansen-solubility.com/conference.php/

UNIVERSITY of York

Green Chemistry Centre of Excellence

HSPiP

iFormulate

LUM

The Next STEP in Dispersion Analysis & Materials Testing

HSP50

Fifty Years of Hansen Solubility Parameters
University of York, UK, 5-7 April 2017

Information:

- http://www.hansen-solubility.com/conference.php/

Registration (Early Bird discount before 15 Feb):

- http://store.york.ac.uk/browse/product.asp?compid=1&modid=2&catid=10

Abstract Submission (Papers and Posters):

- http://www.hansen-solubility.com/conference/abstract.php

Exhibition/Sponsorship Opportunities:

- http://www.hansen-solubility.com/conference/sponsorship.php

UNIVERSITY of York

Green Chemistry Centre of Excellence

HSPiP

iFormulate

LUM

The Next STEP in Dispersion Analysis & Materials Testing

Any Questions?

- Participants remain muted
- Please use the GoToWebinar question boxes
- Any follow up questions or other enquiries:
  info@iformulate.biz
- Participants will be sent details of how to access a recording of this webinar
- Training and webinars: http://iformulate.biz/training-and-events/

W: www.iformulate.biz
E: info@iformulate.biz

iFormulate *Skills* Formulation Training 2016