HSP50 York, 6th April 2017

Lack of correlation of polymer-drug dispersion stability with Hildebrand or Hansen Solubility Parameters

M.C.Garnett [1], E. Turpin [1], V. Taresco[1], C.A.Laughton[1], J. Burley[1], C. Alexander[1], J.Booth[2] and K.Treacher [2]

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Polymers in Pharmaceutical formulations

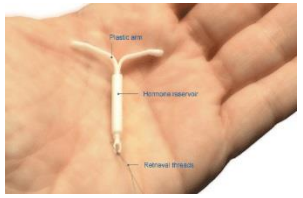
Polymers increasingly important in complex drug delivery systems

Examples:

Implants:

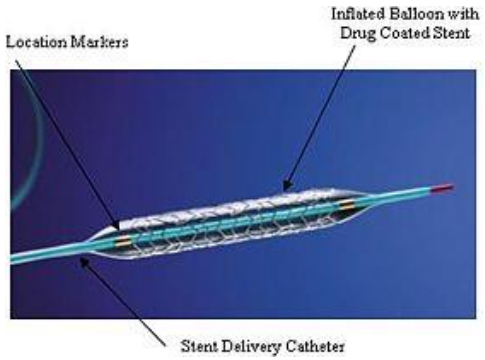
Zoladex

Gliadel

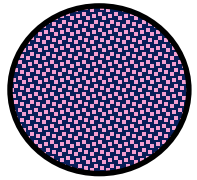


Mirena contraceptive IUD

Coatings:
Drug eluting stents



Microparticles and Nanoparticles
Polymer matrix containing drug



Important features of polymer drug delivery systems

- Incorporation of drug to protect from environment (e.g. hydrolysis, degradation, biological components)
- High drug loading (maximise amount of drug delivered, minimise dose of medicine)
- Give a slow drug release (Allow drug to reach target, control over release of drug at target site)

Drug- Polymer interactions in Pharmaceutical formulations

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Need to accommodate:

- Wide variety of drugs
- Wide range of structures
- Diverse physicochemical properties

Choosing Suitable Polymers

A few useful polymers which can accommodate a range of different drugs?
Lots of polymers with properties tailored to the drug?

Understanding compatibility/interaction of polymers with drugs

Solubility parameters widely discussed in Pharmaceutical publications – but
Which solubility parameter? (Hildebrand, Hansen, Flory Huggins, other?)
Which method of calculation?
How do you measure drug compatibility/phase separation/drug-polymer interactions?

Wide variety of parameters and methods used:

No clear indication of which parameter or method is most accurate
No indication of how useful solubility parameters are for polymer applications

Polymer dispersions as a test system

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Relevant and important Pharmaceutical formulation
- experimentally accessible

Polymer dispersions - to aid solubility of hydrophobic drugs
Using amorphous drug, molecularly dispersed in polymer
Uses water soluble polymers to release drug in gastrointestinal tract at site of absorption

Stability issues

- Drug can easily phase separate from polymer and recrystallise
- Difficult to determine drug compatibility → Need a better screening tool
- Hydrophobic drugs not very compatible with hydrophilic polymer?

Could use a very biodegradable hydrophobic polymer instead

Project Objectives and Progress

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Set of well defined polymers:
Range of characteristics

Diverse set of drugs:
Range of structures
Range of functional groups
Range of physicochemical characteristics
(Mainly hydrophobic)

Matrix of drugs and polymers

Experimentally Assess:-
Compatibility/Interaction:
High Throughput method

Assess various:
Solubility Parameters, Other interaction parameters
Theoretical, Computational,
(MD, QM, Equations of state).

Correlate Experimental and Theoretical results

Improve understanding of drug-polymer interactions/compatibility

Devise simple predictive methods for drug-polymer interactions/compatibility

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Biodegradable Polymer with Chemically Functionality

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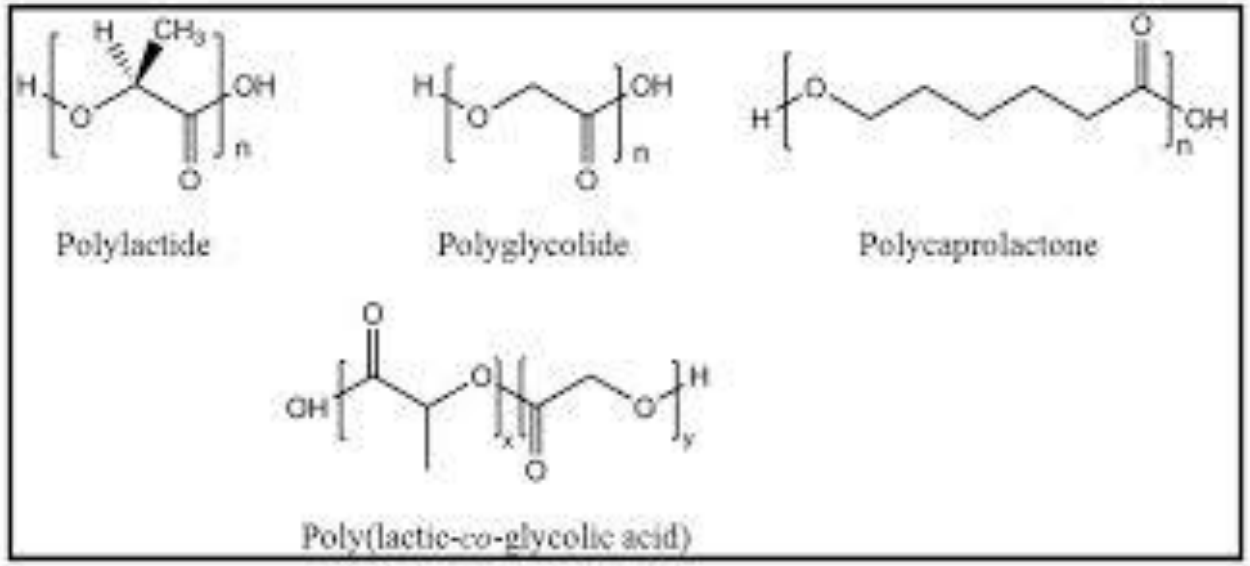
Most common synthetic biodegradable polymers: Pros and cons



Advantages

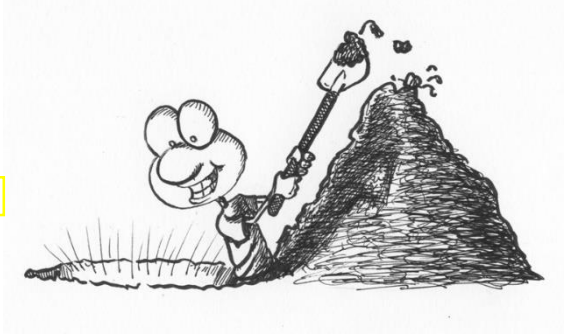
- Hydrolytically and enzymatically biodegradable:
- Biocompatible;
- FDA approved;
- Low cost;
- Easy to synthesise

Crucial limitations for Drug Delivery

Lack of chemical functionality for conjugation

Lack of compatibility with drugs and biomolecules

Enzymatic polymerization is Game-changing



Huang, M.-H.; Li, S.; Hutmacher, D. W.; Coudane, J.; Vert, M.. *Journal of Applied Polymer Science* **2006**, *102*, 1681-1687.

Poly(Glycerol Adipate) and derivatives: synthesis and characterization

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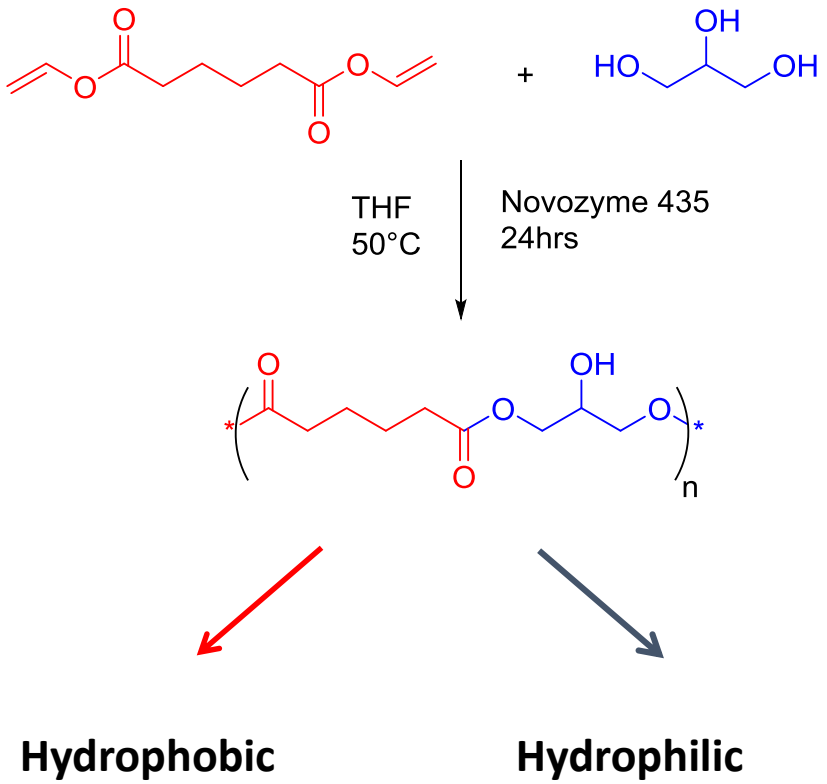
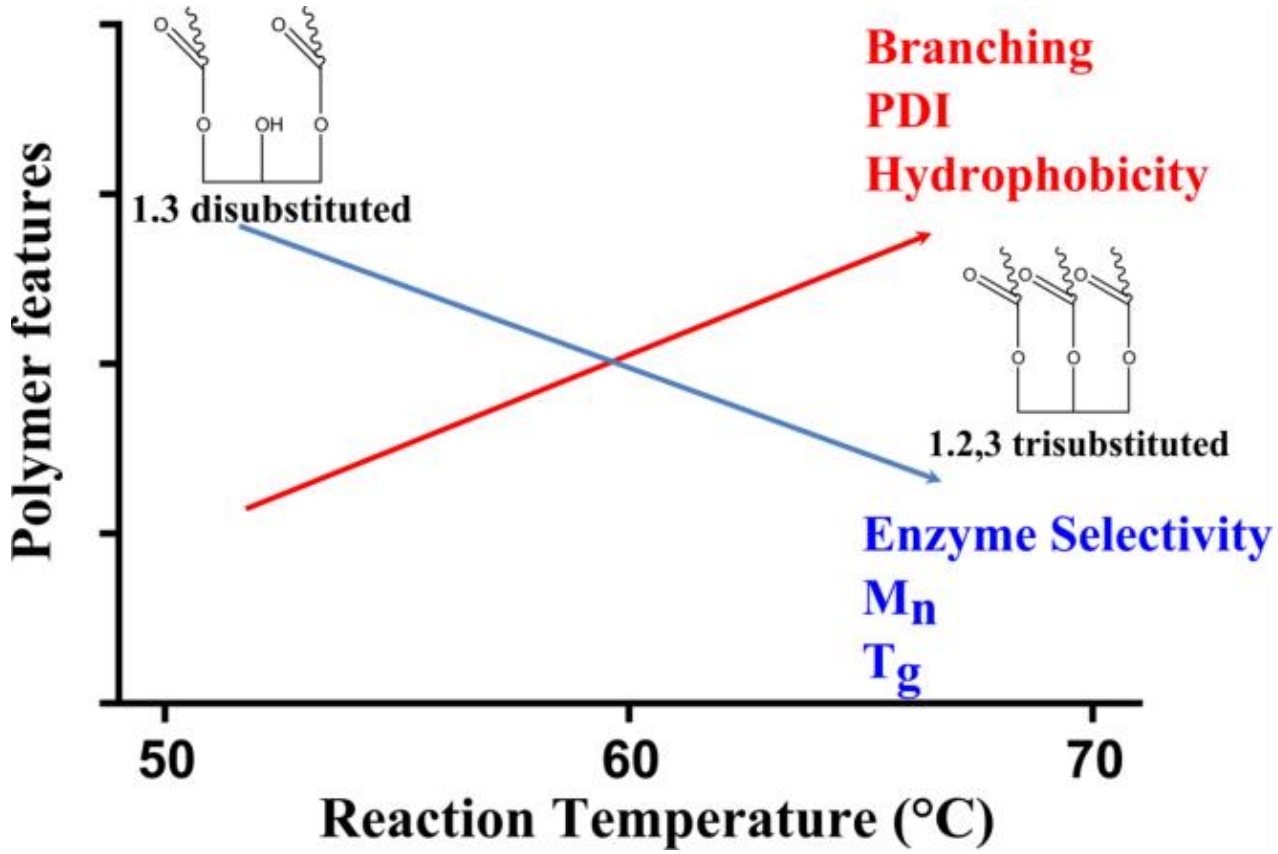
Polymer backbone synthesis





Taresco V., et al, Polymer 89, 41-49 (2016)

Poly(Glycerol Adipate) and derivatives: synthesis and characterization

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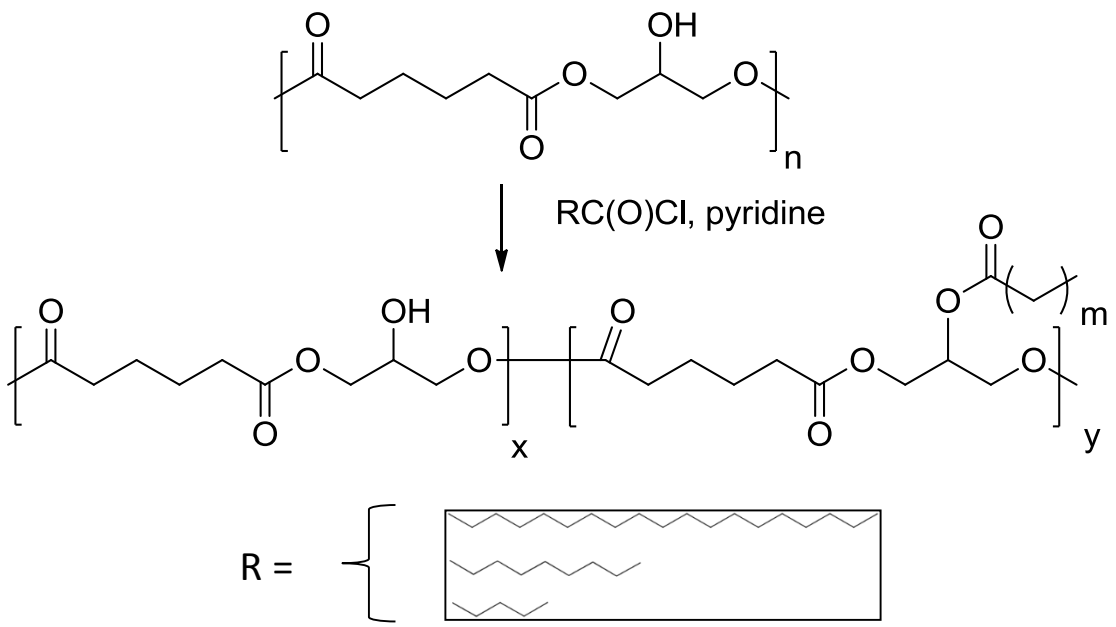
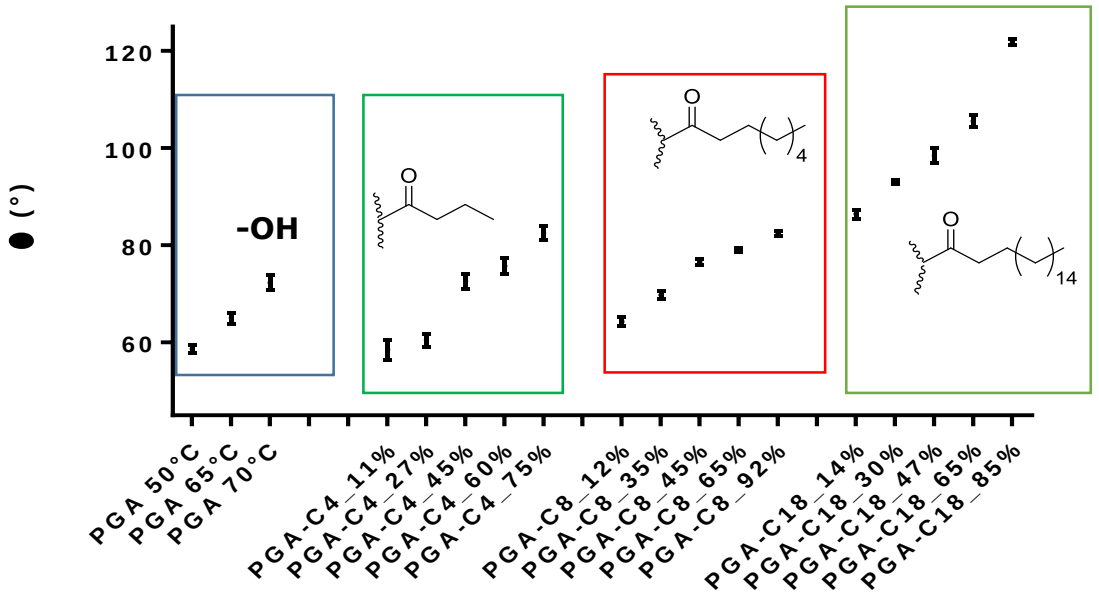
Acyl derivatives – Physicochemical properties



PGC18 = Semicrystalline polymers

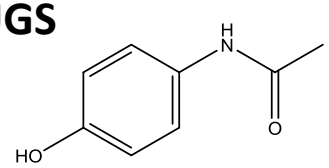


All PGA acyl derivatives prepared from the same batch of PGA
All Tg <0°C so in liquid state

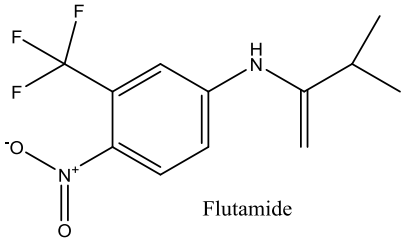
Taresco et al. J. Polymer Sci 54,(20) 3267-3278 (2016)

Differing Drug structures: GFA Class I

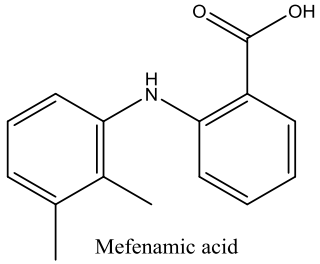
DRUGS



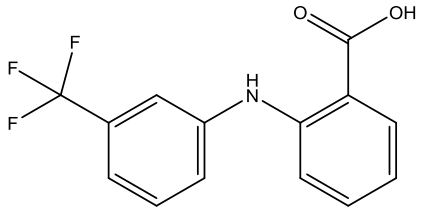
Paracetamol



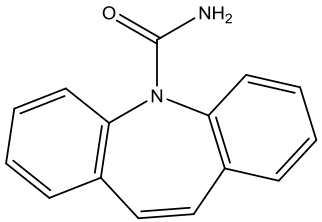
Flutamide



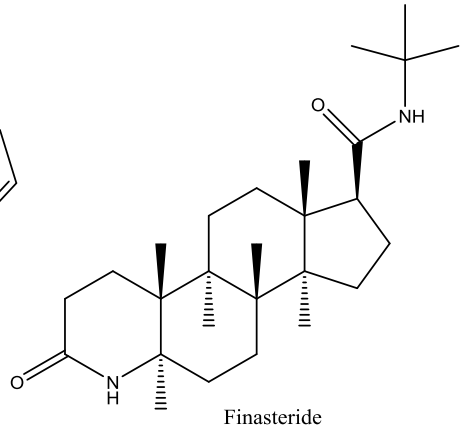
Mefenamic acid



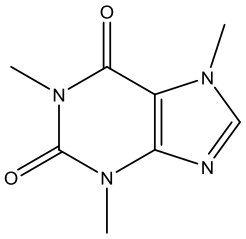
Flufenamic acid



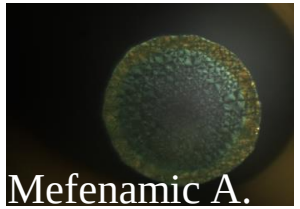
Carbamazepine

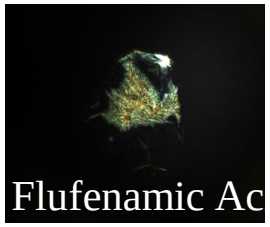


Finasteride



Caffeine





Glass Forming Ability Classification System

Class I Crystal forming drugs
Class II Weakly glass forming drugs
Class III Strongly glass forming drugs

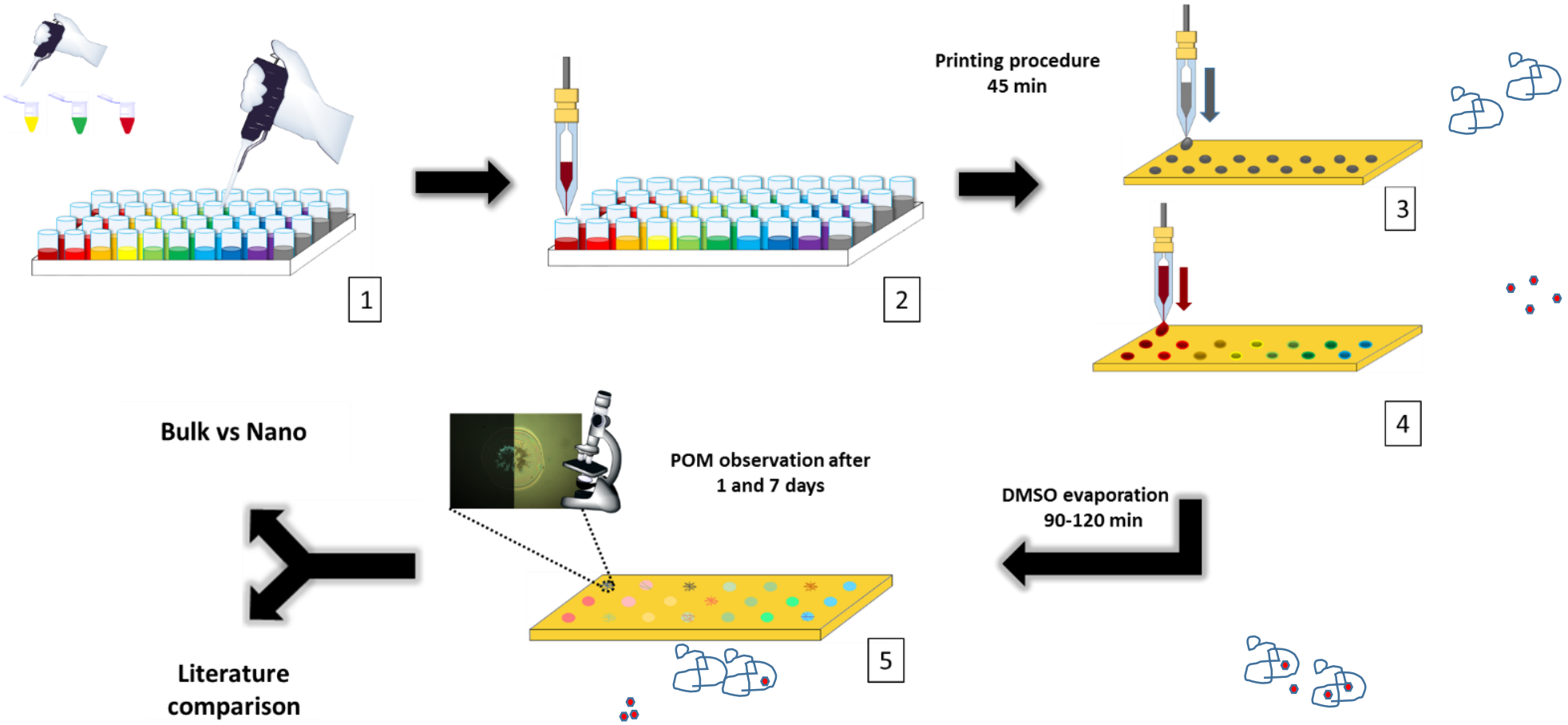
Class 1 drugs chosen:

- Easily detected by POM
- Difficult to stabilise with polymers

J. A. Baird, B. Van Eerdenbrugh and L. S. Taylor, *J. Pharm. Sci.*, 2010, **99**, 3787–3806.

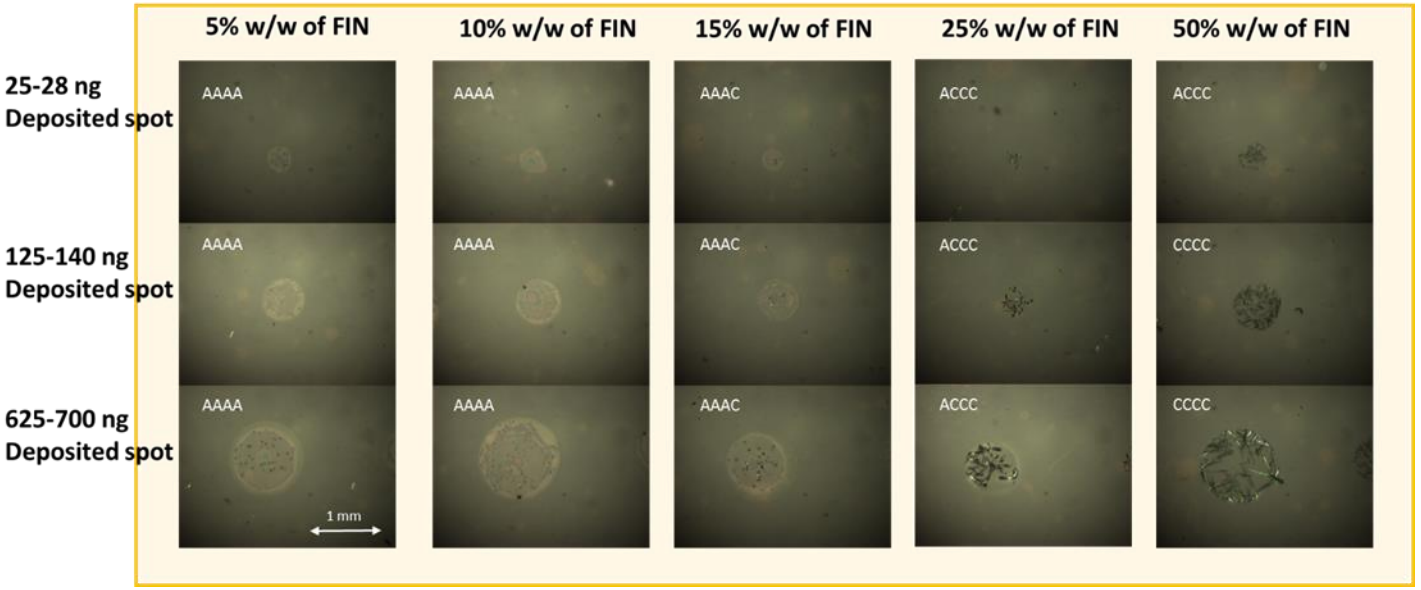
High Throughput Screening

Printing and assessing polymer drug mixtures



High Throughput Screening

Spot sizes and drug Polymer ratios

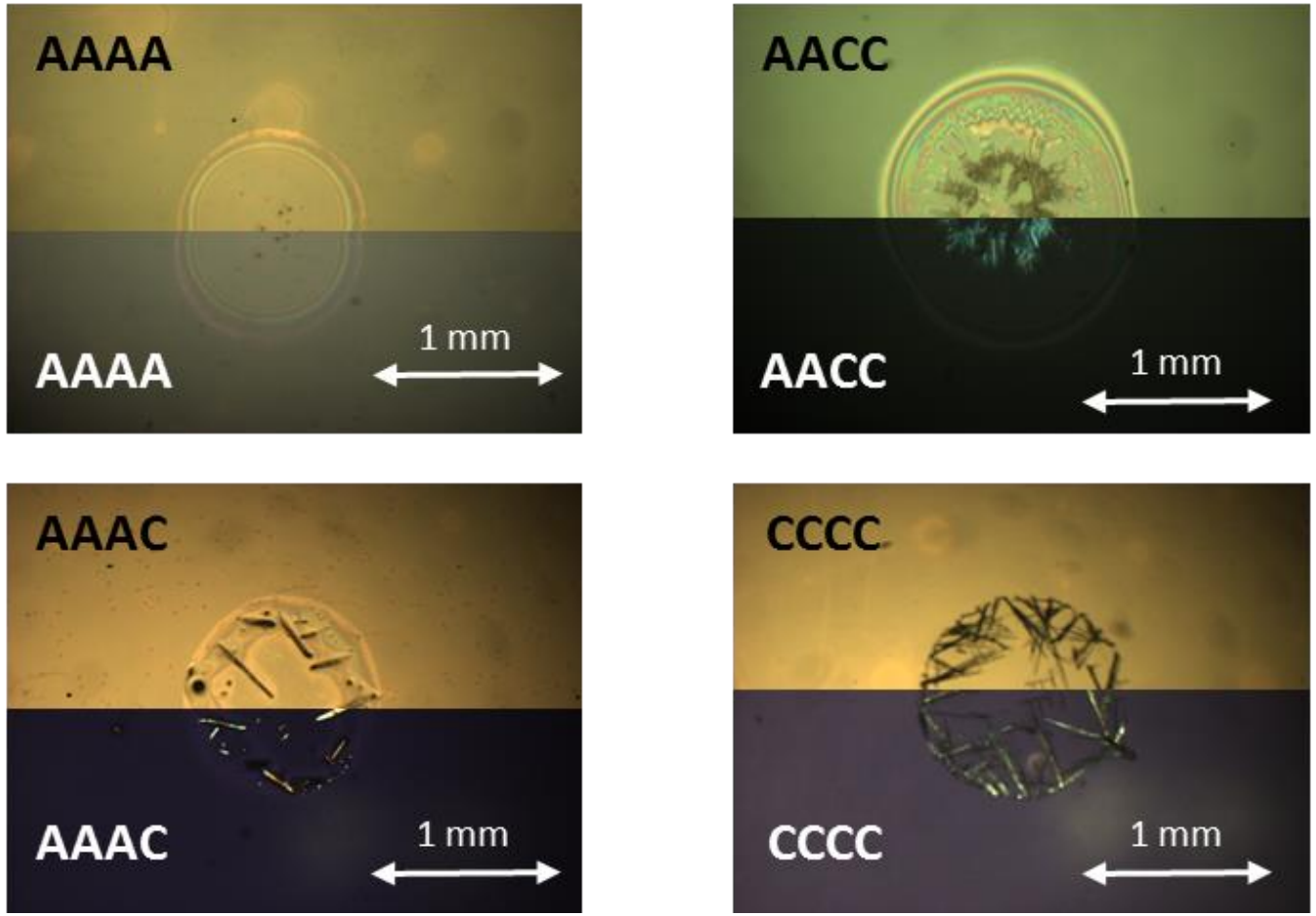


An array section with the cross polarized filters in place for Finasteride-PVPVA spots at different drug to polymer ratios after 7 days from solvent evaporation.

In each row there is the same amount of printed materials (25-28ng top row, 125-140ng center and 625-700ng bottom row) and in each column the same drug/polymer ratio.

Crystallisation dependent on both amount of material and drug polymer ratio. Largest spot size corresponds to behaviour of bulk material

High Throughput Screening
Amorphicity Index evaluation



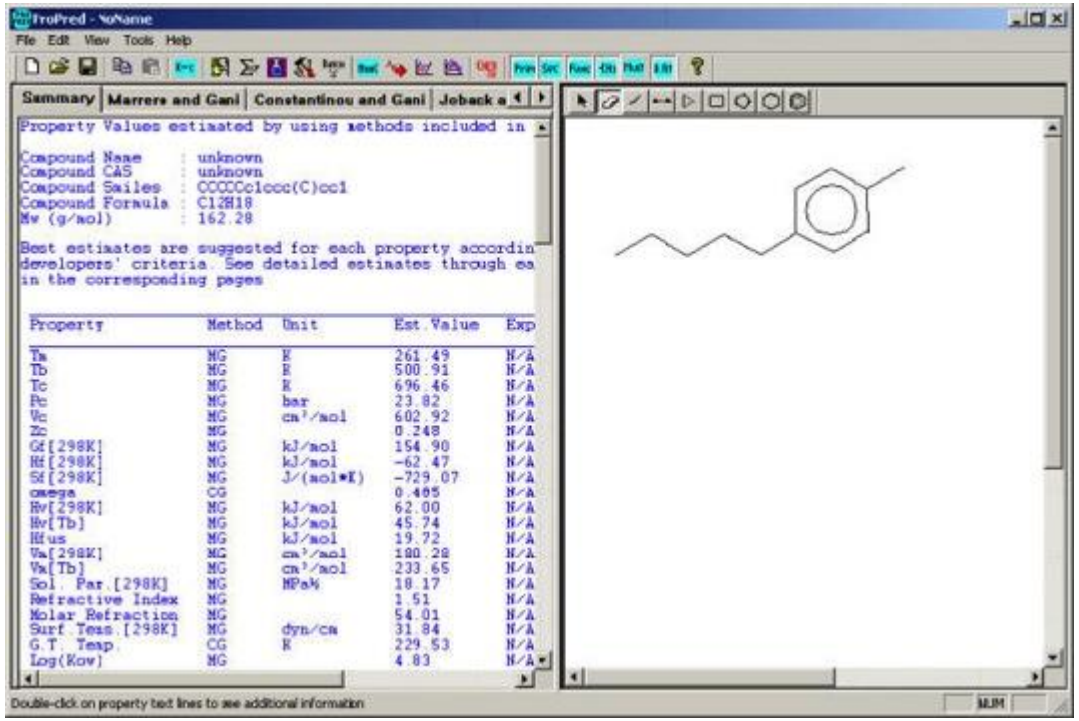
AI% = [number of A attributed at each spot (assigned by POM)/total number of A]*100

Over a range of different drug:polymer ratios (5, 10, 15, 25, 50 % w/w), at 1 day and 7 days time points

B. Van Eerdenbrugh and L. S. Taylor, *Mol. Pharm.*, 2010, **7**, 1328–1337.

Methods for determination of Solubility parameters

1. ProPred Group contribution method (Hildebrand)

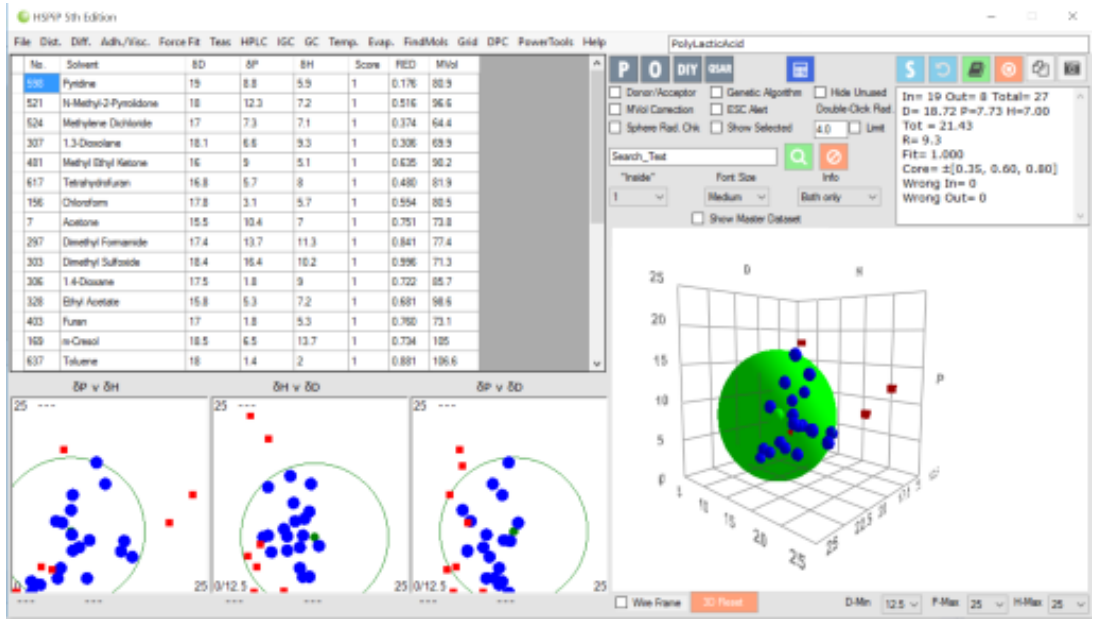


The ProPred tool in the ICAS suite of software was used for calculation of Hildebrand solubility parameters. Parameterised from a large group of small organic molecules

1.J. Marrero & R. Gani, 2001, Fluid Phase Equilibria, pp. 183-208
2.www.capec.kt.dtu.dk/Software/ICAS-and-its-Tools

Methods for determination of Solubility parameters

2. HSPIP (Hansen Group contribution method)



Hansen Solubility Parameters are comprised of partial cohesive energy density components for dispersion, δ_d, polarity, δ_p, and hydrogen bonding, δ_h. These are combined into the Hansen radius, Ra, using the relation:

$$Ra^2=4(\delta_{d1}-\delta_{d2})^2+(\delta_{p1}-\delta_{p2})^2+(\delta_{h1}-\delta_{h2})^2$$

The HSPiP software was used to calculate the Hansen Solubility Parameters (HSPs) by the Yamamoto-MB method.

1.Hansen Solubility Parameters: A User's Handbook, 2007, 2nd ed, CRC Press, Inc., Boca Raton: FL

2.hansen-solubility.com

Methods for determination of Solubility parameters

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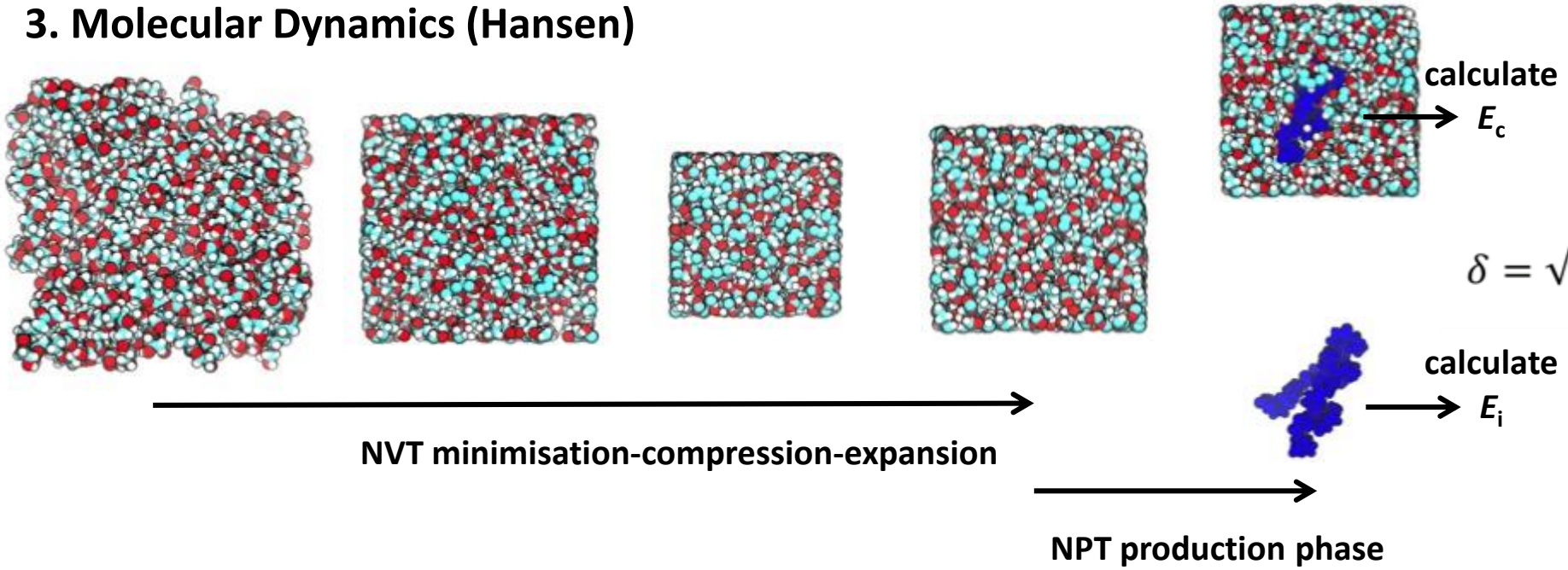
3. Molecular Dynamics (Hansen)



$$\delta = \sqrt{CED} = \sqrt{\frac{\sum_{i=1}^{n} \langle E_i^k - {E_c^k}/{n} \rangle}{N_0 \langle V_c \rangle}}$$

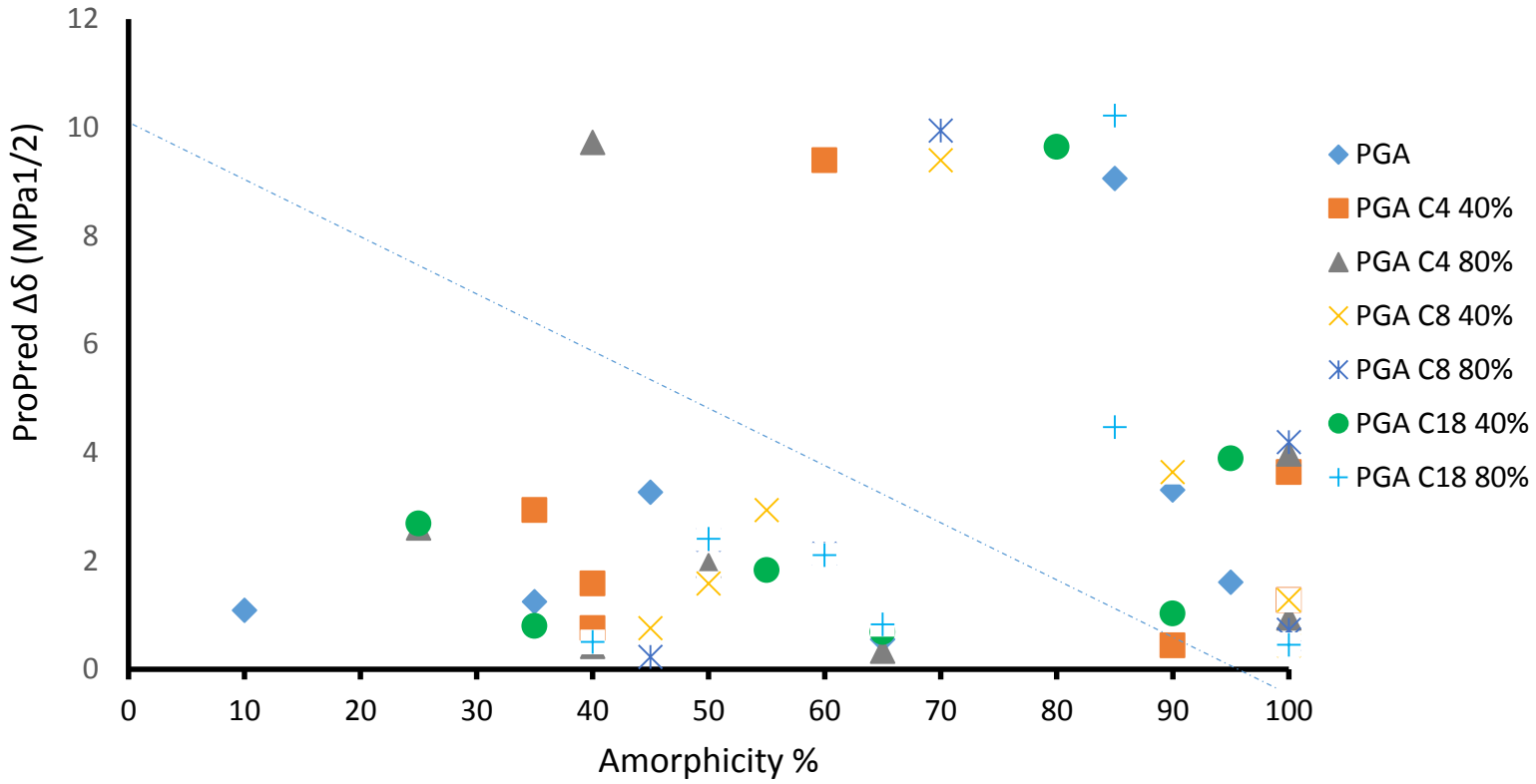
All simulations and analysis of the drug, polymer and drug-polymer systems were performed in GROMACS using parameters from the CHARMM-36 force field[1,2]. Hansen solubility parameters have been calculated from MD simulations following the methodology as described by Belmares *et al.*[3].

[Charmm does not include an explicit term for hydrogen bonding, this being treated implicitly within the electrostatics term; therefore the Hansen parameters from MD only include δ_{elec} and δ_{disp}.]

1. www.gromacs.org: 2. K. Vanommeslaeghe et al., 2010, J. Comput. Chem. 31, pp. 671-690
3. M Belmares *et al.,* 2004, J. Comput. Chem. 25, pp. 1814-1826.

Results
Hildebrand with Amorphicity Index

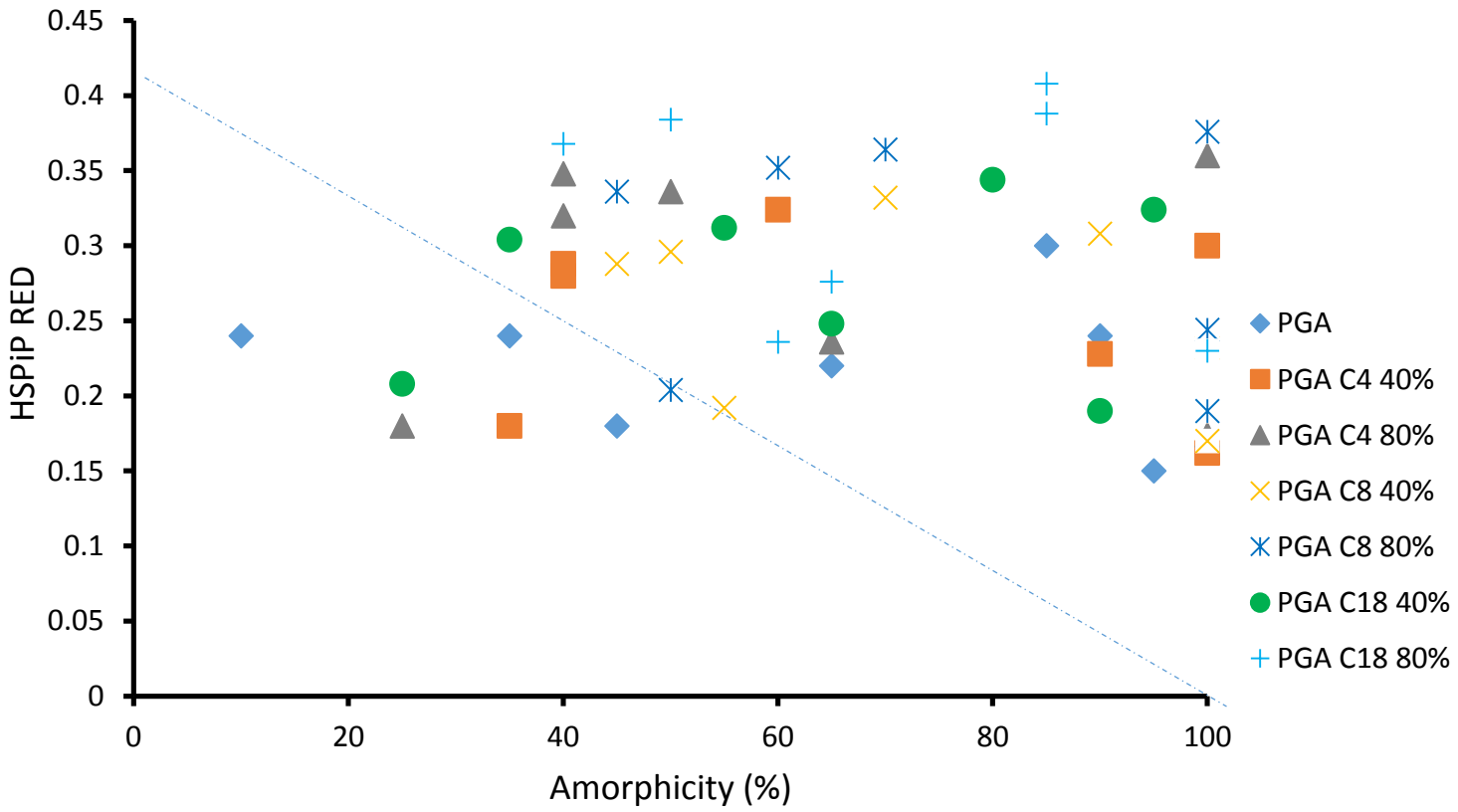
Correlation of Hildebrand Solubility Parameter (calculated by the group contribution method) versus Amorphicity Index as measure of Drug Polymer Compatibility



Expected correlation trendline

Results
Hansen GC with Amorphicity Index

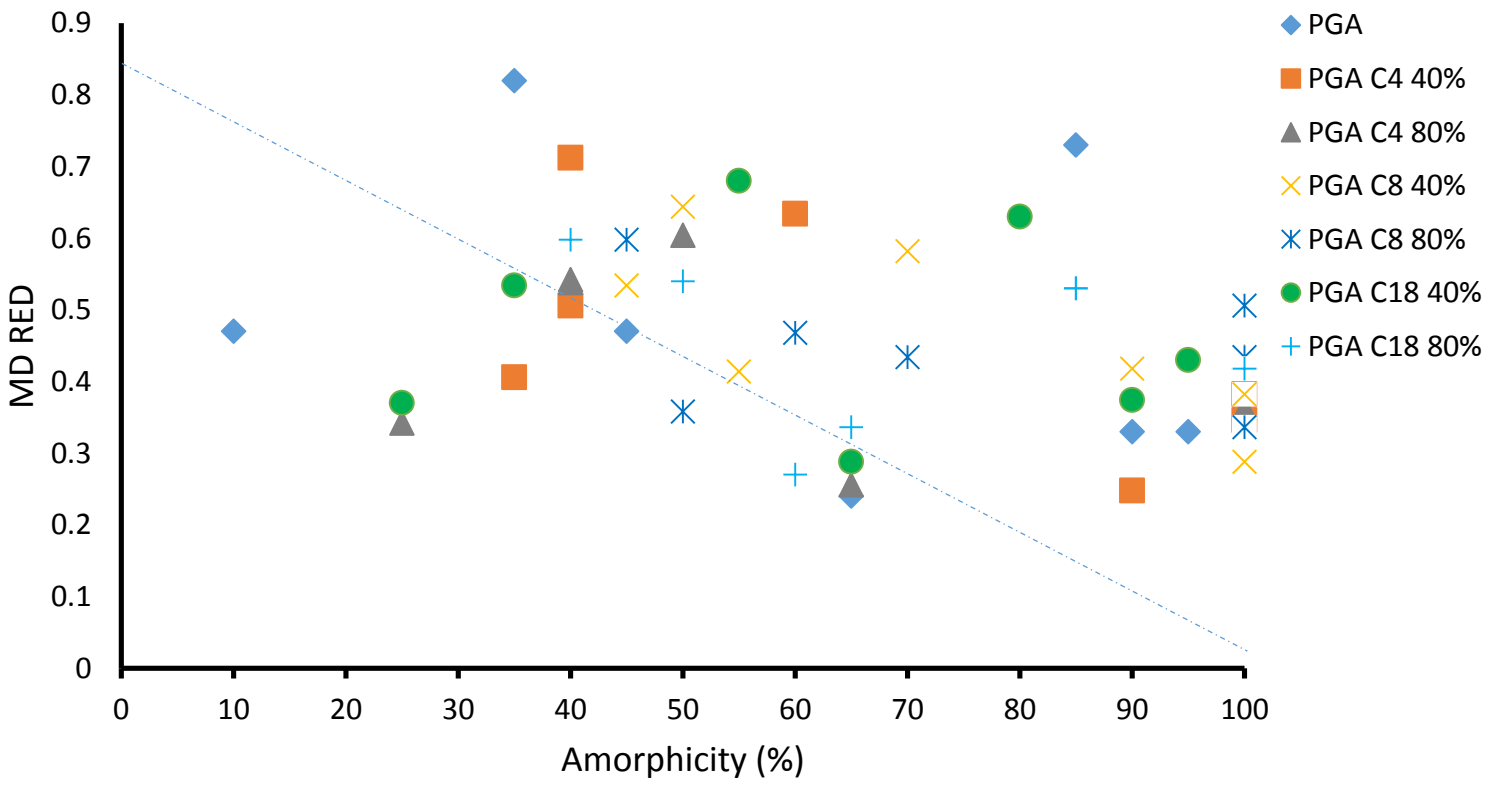
Correlation of Hansen Solubility Parameters (Calculated from HSPIP) versus Amorphicity Index as measure of Drug Polymer Compatibility



Expected correlation trendline

Results
Hansen MD with Amorphicity Index

Correlation of Hansen Solubility Parameters (calculated from molecular dynamics simulations) versus Amorphicity Index as measure of Drug Polymer Compatibility



Expected correlation trendline

Conclusions

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7 polymers in molecular dispersion with 7 drugs were assessed for Amorphicity (49 points)
Solubility parameters were calculated by 3 different methods

There was no apparent correlation between amorphicity and :

- The **Hildebrand parameter** as estimated using the ProPred tool in the ICAS software suite.
- The **Hansen RED parameter** as estimated by a **Group Contribution** method using the HSPiP programme.
- The **Hansen parameter** as estimated using a **Molecular Dynamics** method (Belmares et al).

- These methods should have yielded an increasingly accurate estimate of the solubility parameters, but showed no obvious improvement in correlation.
- Polymer structure entropy may be an additional factor influencing drug-polymer compatibility. However, the polymers had a high level of similarity despite the differences in physicochemical properties.

- ➢ The in silico determined solubility parameters are not predictive for polymer dispersions.
- ➢ Are there other areas of pharmaceutics and drug delivery for which the prediction of solubility parameters do not correlate to experimental data?
- ➢ Is there a fundamental flaw in the theory, or in the predictive power of in-silico generated solubility parameters?

Acknowledgements

Investigators

University of Nottingham

Alexander Cameron	Polymer Chemistry
Charlie Laughton	Computational Modelling
Jonathan Burley	Physical chemistry, HTS

Research Fellows

Vincenzo Taresco	Polymer chemistry, HTS
Eleanor Turpin	Solubility Parameters, Computational Modelling

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Jonathan Booth	Formulation of poorly soluble APIs
Kevin Treacher	Polymer physical chemistry
Jim McCabe	Solid state interactions
David Buttar	Computational modelling
Simone Tomasi	Computational modelling

EPSRC
Engineering and Physical Sciences Research Council