A practical computational tool to predict formulation and process variables during the development of spray-dried amorphous solid dispersions.

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Agenda

Introduction

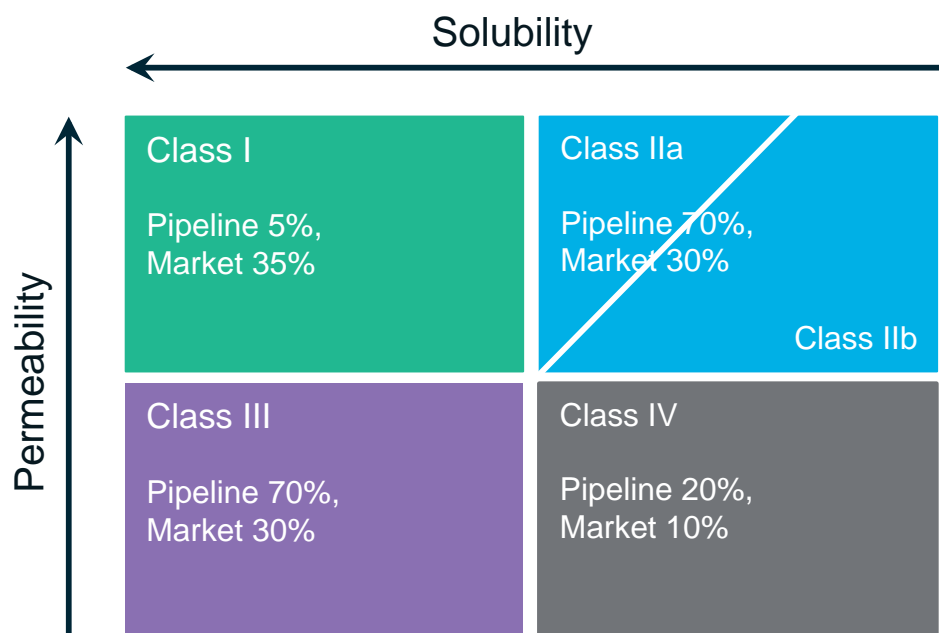ASDs screening program:

a) Case-study: early performance and physical stability evaluation;

b) Case-study: prototypes production and characterization;

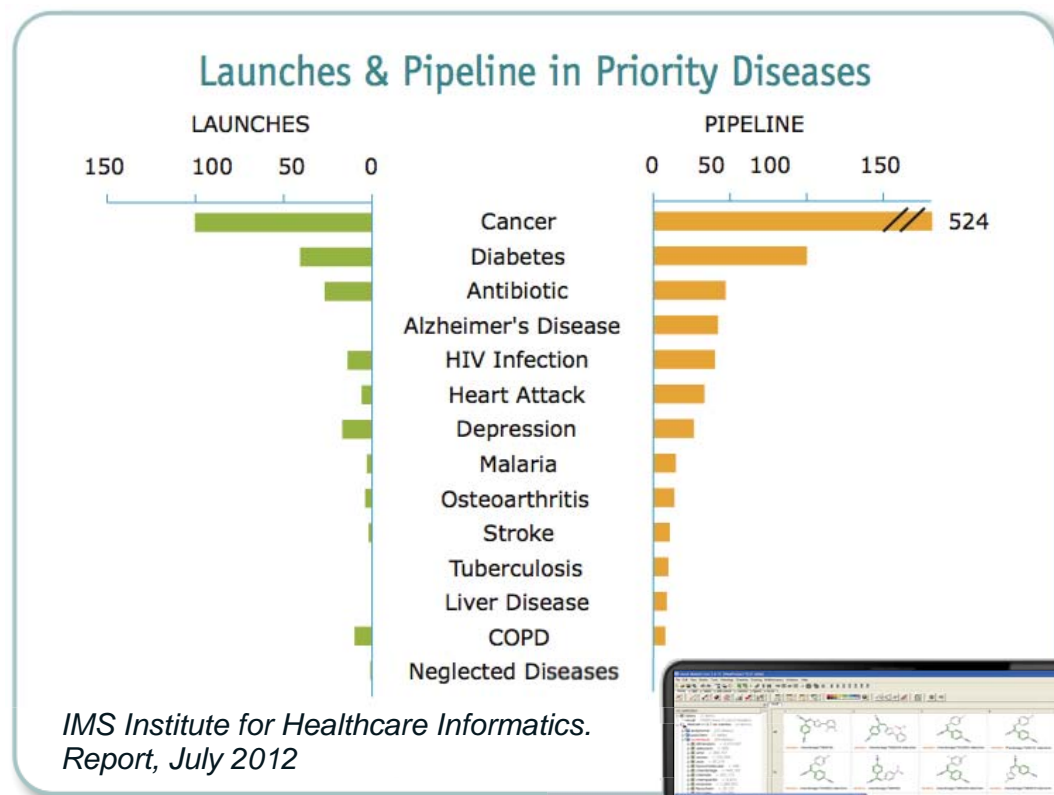c) Case-study: validation of the screening methodologies applied.

Conclusions

Introduction
The current solubility/bioavailability challenge…

Solubility

Permeability

Class I	Class IIa
Pipeline 5%, Market 35%	Pipeline 70%, Market 30%
	Class IIb
Class III	Class IV
Pipeline 70%, Market 30%	Pipeline 20%, Market 10%

Biopharmaceutical Classification System (BCS)*
Developability Classification System (DCS) **

Launches & Pipeline in Priority Diseases

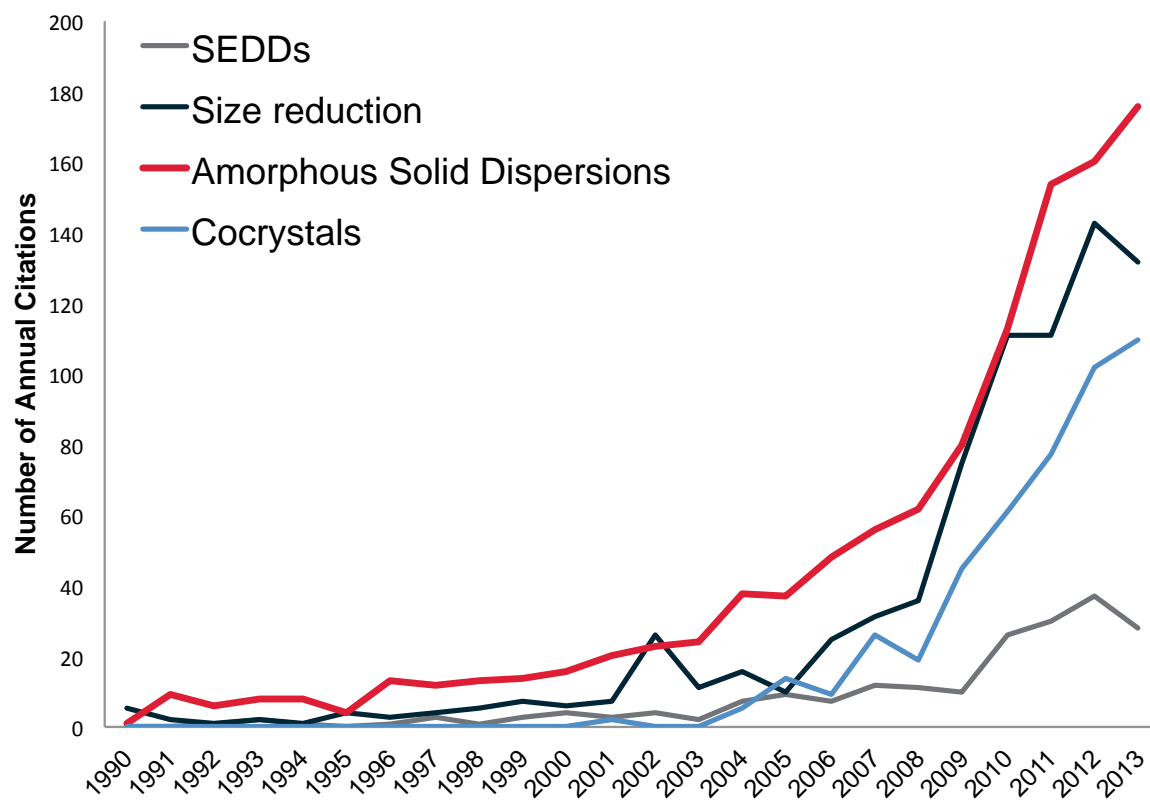IMS Institute for Healthcare Informatics.
Report, July 2012

- Complex drug-receptor targets;
- Combinatorial chemistry;
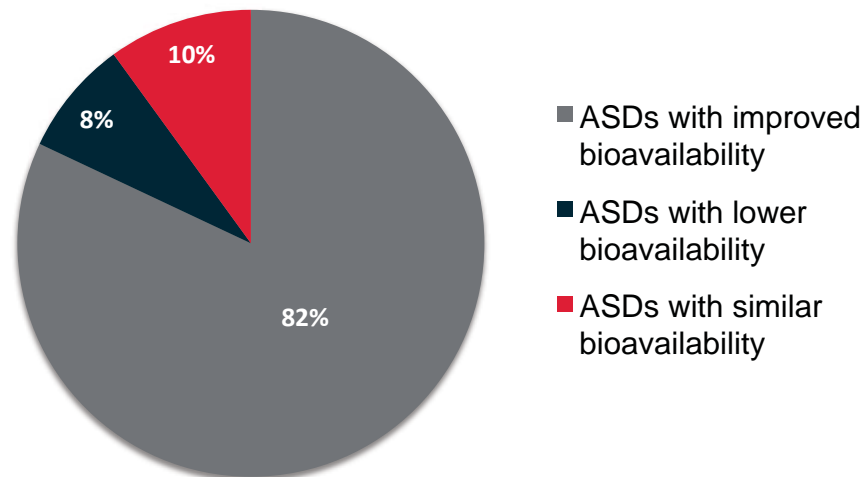- High-throughput screening.

Introduction
The panorama of current solubilization strategies

In 2010, the market size for solubility+bioavailability enhancing drug delivery platforms was **$139M USD.**
(*Cientifica Ltd., Report January 2012*)

General performance of ASDs with respect to the reference materials (42 research papers)*

- ASDs with improved bioavailability
- ASDs with lower bioavailability
- ASDs with similar bioavailability

Number of Annual Citations

- SEDDs
- Size reduction
- Amorphous Solid Dispersions
- Cocrystals

*Citations include articles, patents, reports, etc. *Data obtained from Scifinder*

ZELBORAF™ (vemurafenib) tablets

KALETRA® (lopinavir/ritonavir)

INTELENCE® (etravirine) tablets

Noxafil® (posaconazole) delayed-release tablets 100 mg

> 10 Commercial ASDs

Introduction
Paradigm shift in ASDs development

Past…the empirical approach
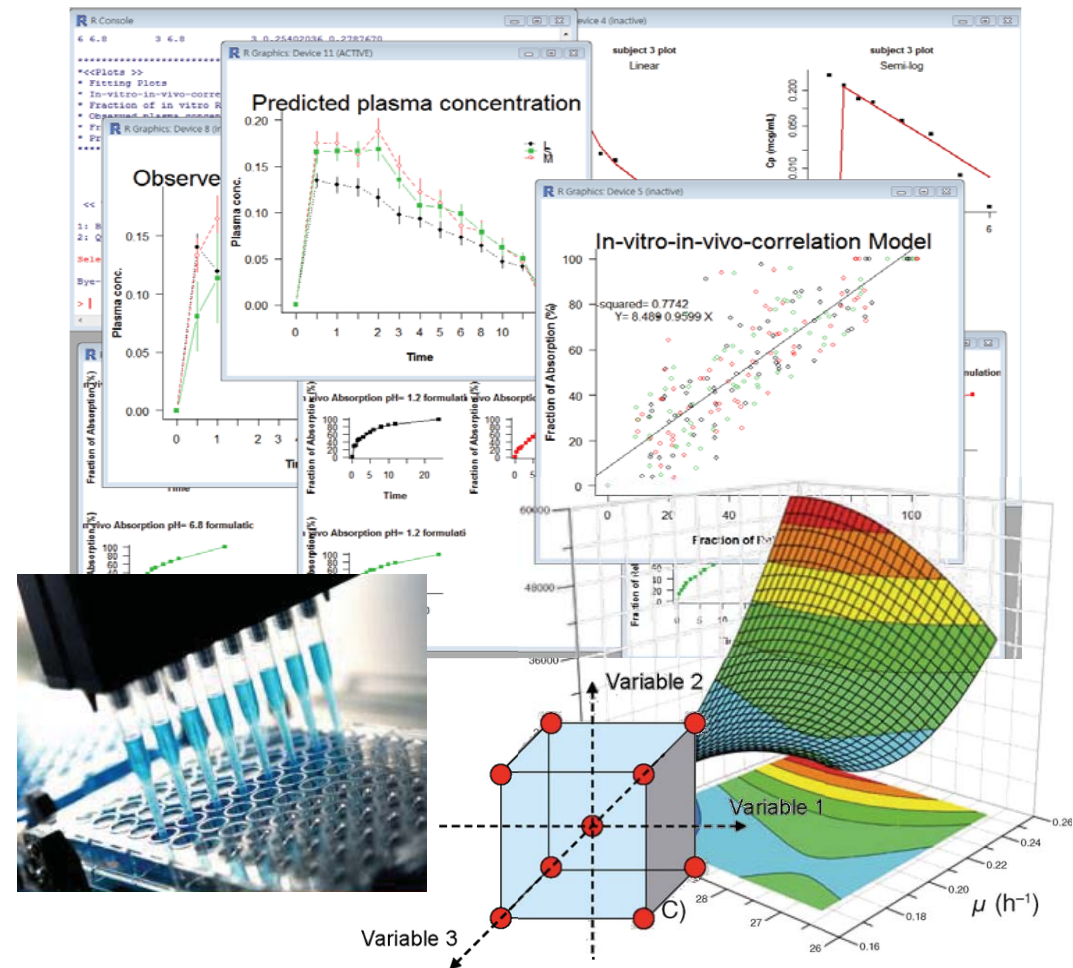
Present...science- and risk-based approach driven by QbD principles

'That's Dr Arnold Moore. He's conducting an experiment to test the theory that most great scientific discoveries were hit on by accident.'

Drawing by Hoff; © 1957
The New Yorker Magazine, Inc.

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ASDs Screening methodology

Validation of the screening program

Selection of polymeric carriers

Performance (supersaturation – solvent-shift method)

Physical stability (computational analysis and solvent casting)

Prototypes production

Prototypes analytical characterization

INPUTS:
- Relevant physicochemical properties of the drug;
- Target drug release profile;
- Target dose, etc.

OUTPUTS:
- Small group of potential polymeric excipients;
- Polymer physicochemical properties;
- Potential to promote drug-polymer interactions (*e.g.* H-bonding).

Performance:
- Polymers precipitation inhibition effect;
- Small-scale experiments;
- Non-sink conditions;
- Biorelevant media (unfavorable pH).

Physical stability:
- Drug-polymer miscibility estimates;
- Solvent casting = "Bench" screening = small-scale;
  - Fine-tuning.

Prototype production:
- Lab-scale spray-drying;
- Definition/optimization of drying process conditions;
- Fine-tuning of formulation variables.

Analytical Characterization:
- Physical stability (fresh product and long-term storage):
  - modulated DSC, XRPD;
  - 25ºC/60%RH and 40ºC/75%RH up to 12months.
- Performance (*in vitro*):
  - Powder dissolution;
  - ASDs *versus* crystalline;
  - Maintenance of biorelevant conditions and pH.

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ASDs screening methodology:

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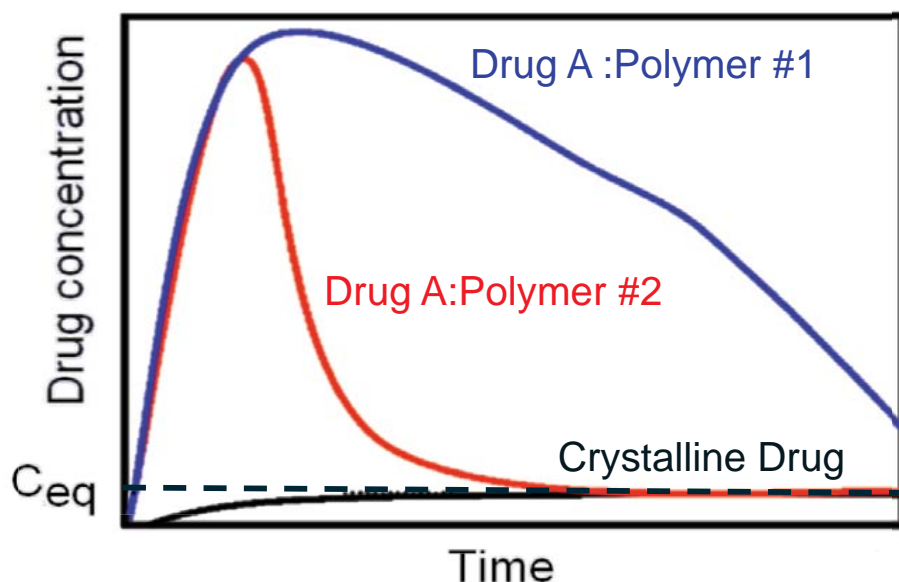b) Case-study: prototypes production and characterization;

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Conclusions

Drug A is poorly water soluble and has a $T_M \sim 200°C$.

Performance
(supersaturation – solvent-shift method *)

Physical stability
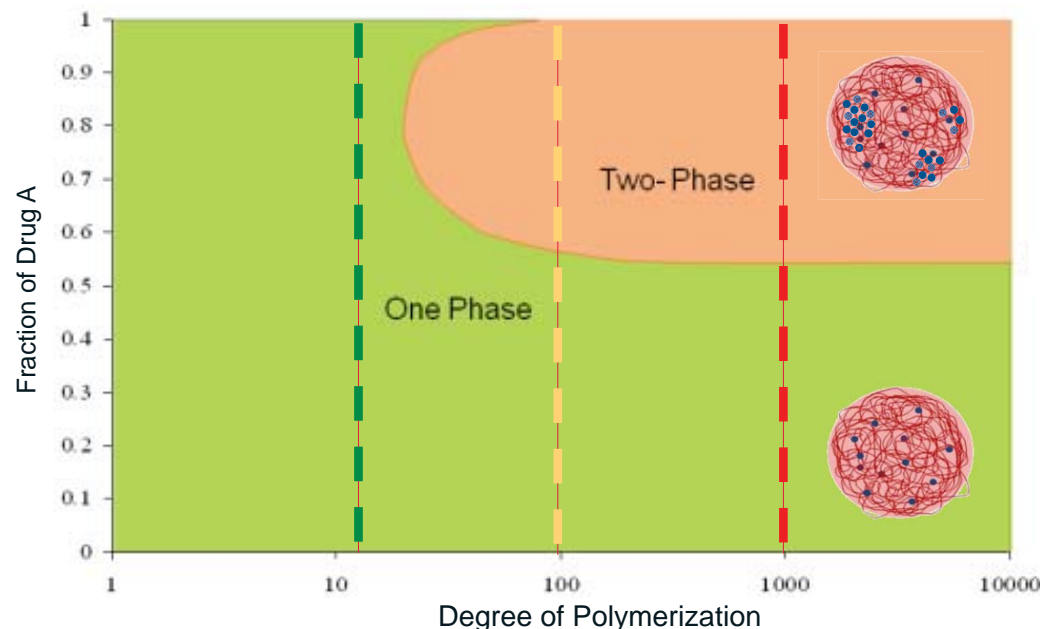(computational analysis and solvent casting)

Method*:
- Polymers are pre-dissolved in the medium;
- The amount of polymer pre-dissolved is constant among all the tests (0,05%w/v);
- An aliquot of a highly concentrated drug solution in a water-miscible organic solvent is transferred to the medium.

Method – computational analysis:
- Implementation of the Flory-Huggins theory (F-H);
- Thermodynamics of mixing;
- T–drug/polymer composition phase diagram;
- F-H Interaction parameter may be determined via solubility parameters, iGC, melting point depression.
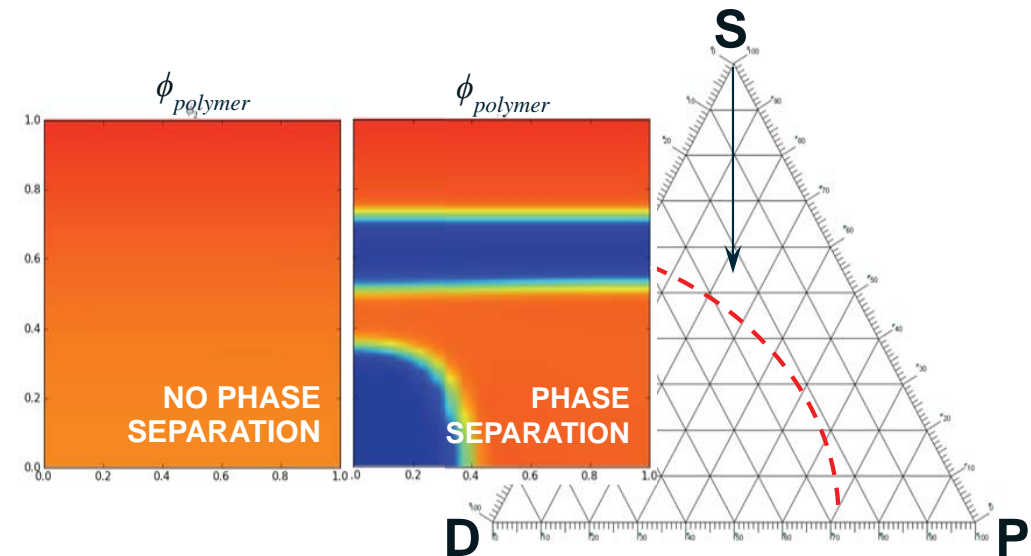
Drug A is poorly water soluble and has a $T_M \sim 200°C$.

Performance
(supersaturation – solvent-shift method *)

Physical stability
(computational analysis and solvent casting)

$\phi_{polymer}$ $\phi_{polymer}$

NO PHASE SEPARATION PHASE SEPARATION

S
D P

Purpose:

- To assess the inhibition effect of the polymer during the drug precipitation - "parachute" phase;
- To obtain a polymer ranking considering the area under the supersaturation curve (AUC_{SS});
- Low stabilizing polymers are excluded.

Thermodynamics + Kinetics + Evaporation*

Purpose:

- To obtain a polymer ranking based on drug-polymer miscibility and phase behavior;
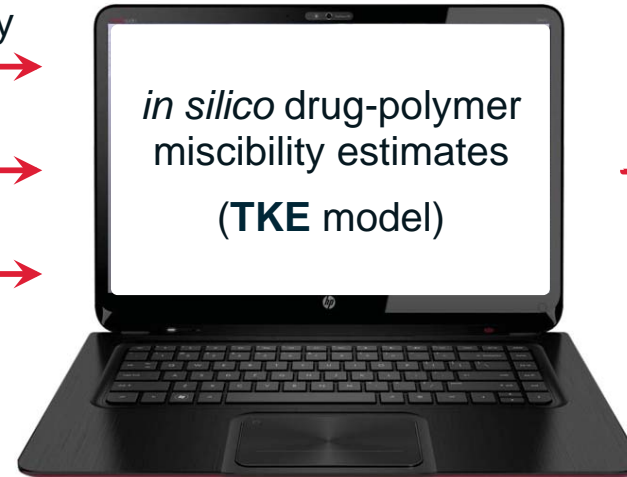- Preliminary assessment of optimal drug load range.

A practical computational tool to predict formulation and process variables during the development of spray-dried ASDs.
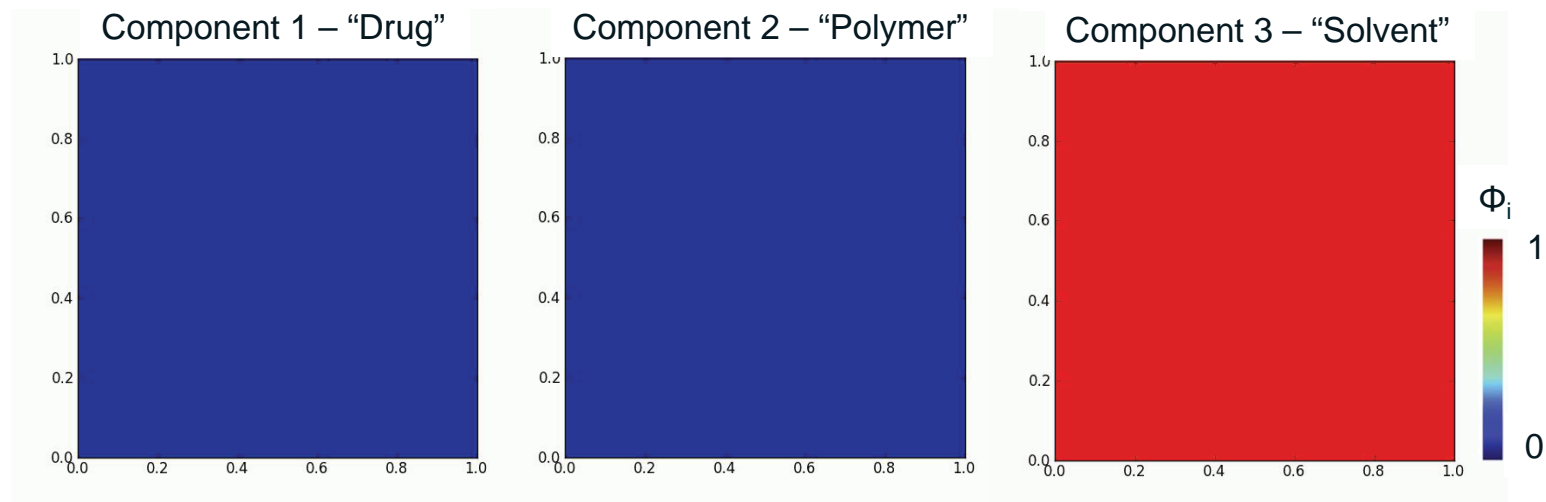
INPUTS

1) **T**hermodynamics: Flory-Huggins Theory

2) **K**inetics: Components Diffusion

3) Process: **E**vaporation Rate

OUTPUTS

in silico drug-polymer miscibility estimates

(**TKE** model)

Component 1 – "Drug"

Component 2 – "Polymer"

Component 3 – "Solvent"

Φ_i

Drug A is poorly water soluble and has a $T_M \sim 200°C$.

Computational analysis
Physical stability

Solvent casting ("bench" screening)
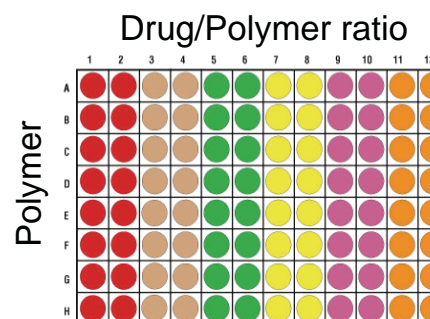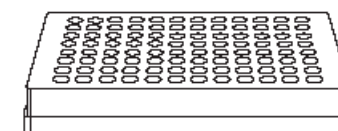### Physical stability

~40uL

96-well plate format

~2mL solutions

Drug/Polymer ratio

Polymer

Input variables for Drug A - TKE model *:

- F-H interaction parameters (χ_{ij}): determined using solubility parameters, obtained via iGC;
- Solid's diffusivity: Wilke-Chang equation;
- Evaporation rate: correlation for the evaporation of a single droplet in still air.

Purpose:

- Further narrow down the "polymer list" and optimize drug load range in formulation;
- Re-evaluate potential false-negative results;
- Fine-tune other formulation variables;
- Preliminary evaluation of experimental miscibility.

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Drug A is poorly water soluble and has a $T_M \sim 200°C$.

- Summary – Screening results

Drug A: HPMCAS   Drug A: Eudragit® L100   Drug A: HPMC   Drug A: PVPVA 64

YES / MAYBE / NO

Supersaturation / Miscibility / Solvent Casting

- Best drug-polymer formulations identified;
- Optimal drug load range selected for further evaluation;
- Other variables could have been included in the ranking.

Prototypes production

- SDDs were produced with 5% solids' concentration;
- Solvent(s): Pure MeOH or MeOH:DCM (60:40 %w/w);
- Drug loads tested: 15, 35, 45 and 65% (w/w).

Prototypes analytical characterization

- All SDDs produced were X-ray amorphous;
- All SDDs presented a single T_g (>75°C) using mDSC;
- All 65% (w/w) Drug A formulations were tested for powder dissolution and long-term stability.

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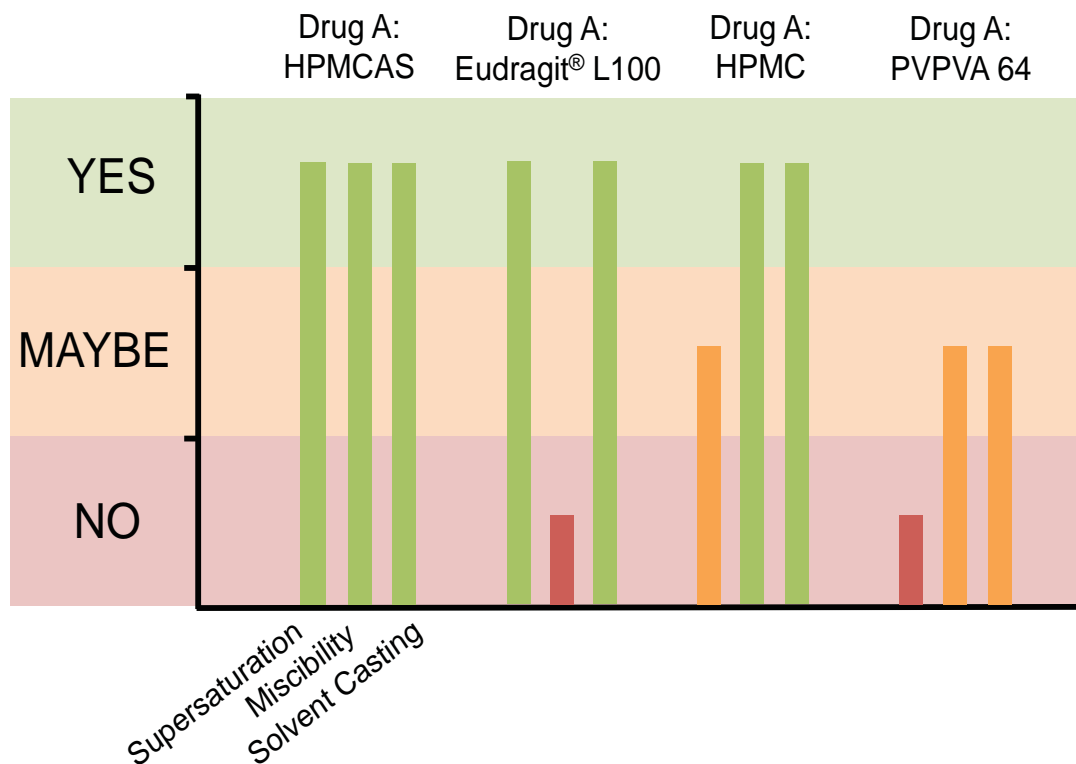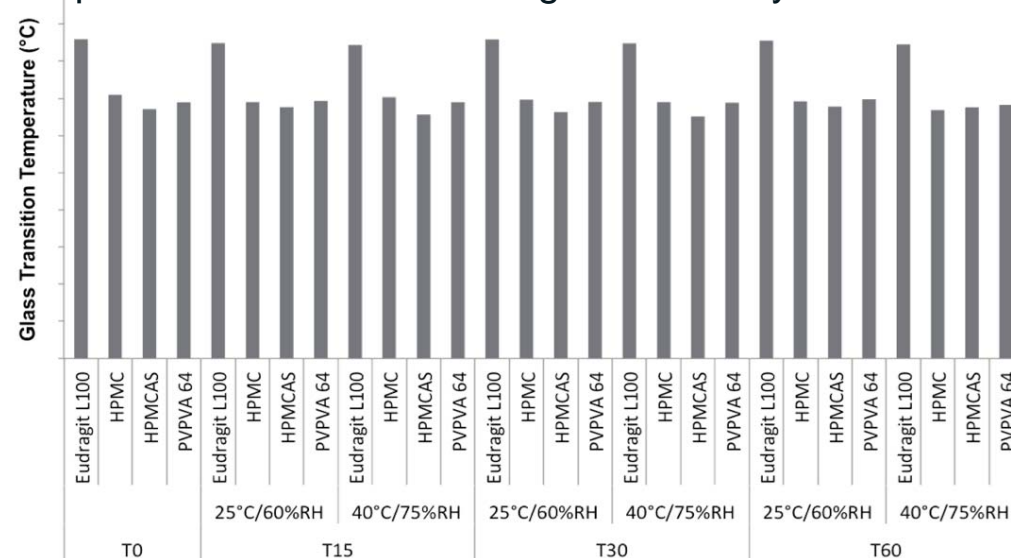
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Drug A is poorly water soluble and has a $T_M \sim 200^\circ C$.

Physical stability (computational analysis and solvent casting) *	Performance (supersaturation – solvent-shift method *)

- Correlation between experimental and screening data;
- False-negatives can be observed;
- Importance of small-scale "bench" screening to re-evaluate unexpected results.

- Correlation between the powder dissolution and the supersaturation screening results;
- Ability to maintain the performance ranking initially defined.

Conclusions

- **Screening program:**

  – promotes early formulation design and provide valuable insights on ASDs properties;

  – should include methods for assessing the behavior of the ASD, either in solution and dry conditions (*e.g.* solubility enhancement, miscibility, long-term physical stability, etc);

  – the performance (*i.e.* supersaturation) and physical stability screening results should be analyzed concurrently to guarantee proper selection of the most promising systems along the different phases of formulation development.

- **Computational Tool – TKE Model**:

  – useful to rank the most promising amorphous formulations in terms of physical stability, but also to narrow down the range of drug-polymer ratios to be tested in the following phases;

  – still need for new models to simulate the complex processes related with amorphous systems and more accurate methods for determining critical input variables.

- **Future work**:

  – Melting point depression experimental technique will be evaluated to obtain the FH interaction parameters of Drug A-based systems (benchmarking with iGC).

Acknowledgements

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Thank you for your attention.

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