Current Trends in Complex Oral Formulations & Digital Developments

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NEXT-GENERATION DELIVERY INNOVATIONS

“Complex” Definition by FDA*

Complex Active Ingredients	Complex Formulations	Complex Routes of Delivery	Drug-Device Combinations	Complex Dosage Forms
• large molecules, peptides • polymeric compounds • nature derived substances	• liposomes • colloids • long-acting injectables • emulsions • solid dispersions	• inhalation • transdermal • ophthalmic • nasal delivery	• auto-injectors • drug-coated stents	• extended-release tablets • implants • microspheres

* FDA Guidance for Industry - M13A Bioequilvalence for Immediat-Release Solid Oral Dosage Forms, Oct. 2024
FDA MAPP 5240.10 „Classifying Approved New Drug Products and Drug-device Combination Products as Comple Products for Generic Drug Development Purposes
Rainer Dobrawa, CRS Conference 2025 – MarComm-2025-00177

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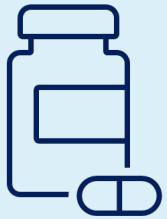
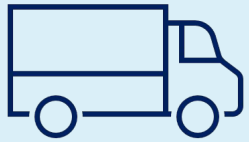
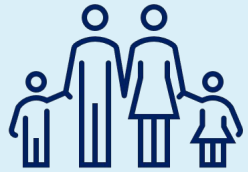
AI/ML in Drug Development & Marketing

Discovery	Development	Manufacturing	Supply Chain	Access
• Targets • Lead Molecules	• Developability • Phys/Chem • Formulation Development • Clinical Trials	• Continuous Manufacturing • Process Analytical Technologies • 3D Printing	• Logistics • Demand vs Supply • Drug Shortages	• Digital Health

Slide courtesy of Daniel Schaufelberger, Ph.D. Adj. Assistant Professor Johns Hopkins University, School of Medicine, Neurology, Nov 2016.

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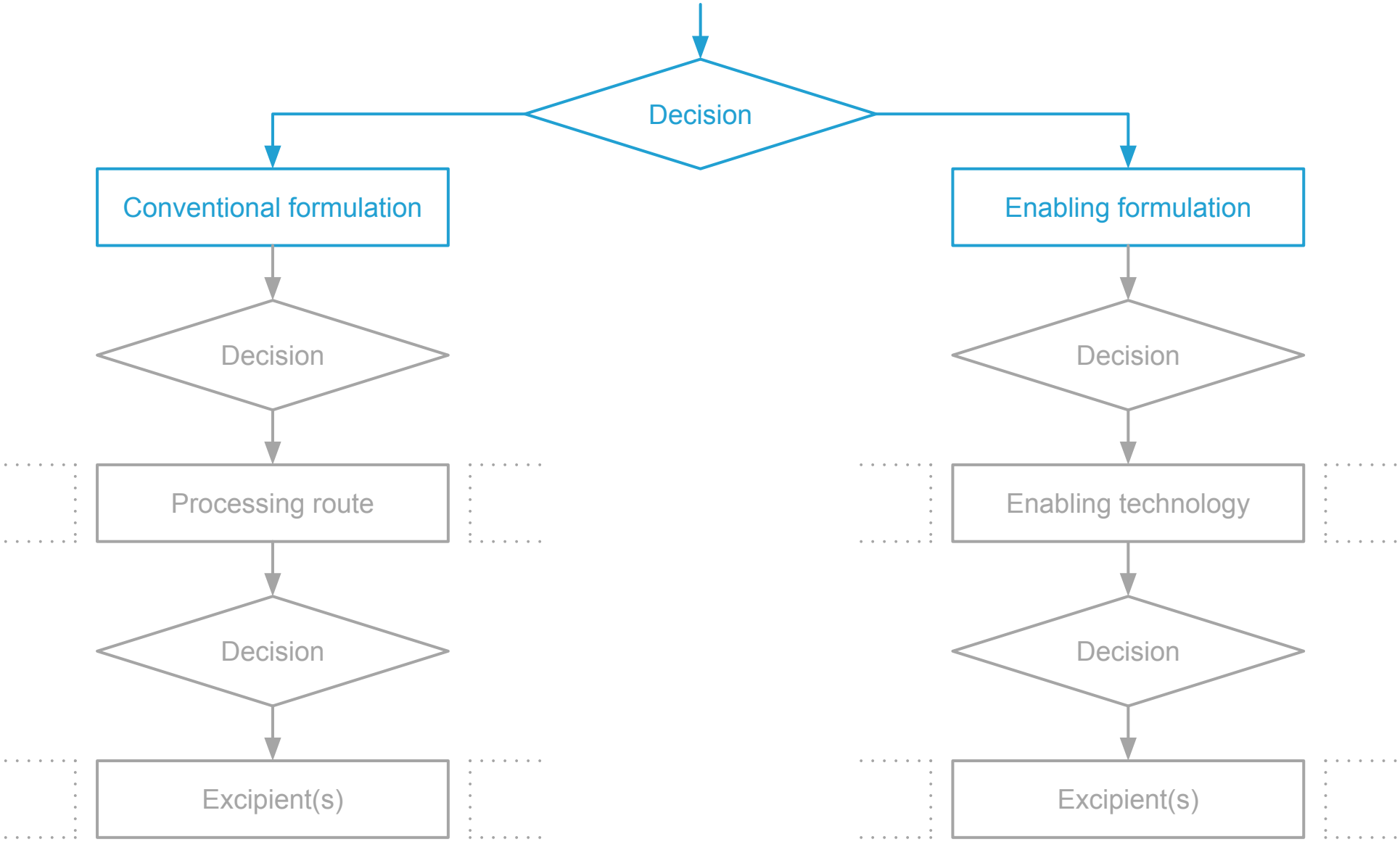

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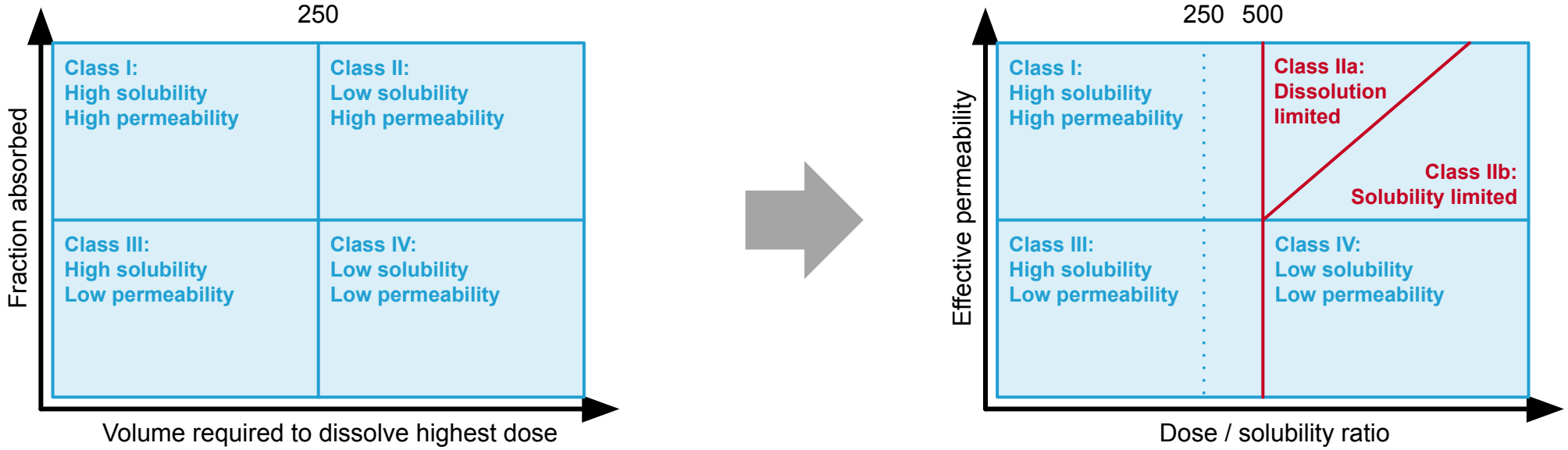
A revised version of the BCS helps assessing the developability of drugs for oral immediate-release dosage forms



Biopharmaceutics Classification System (BCS)

- **Regulatory** framework to reduce bioequivalence studies
- Oral bioavailability of active ingredients estimated based on **solubility** in 250 mL of aqueous **buffer** (pH 1–7) and **fraction absorbed**
- **Low predictive power** for in vivo performance

Developability Classification System (DCS)

- Solubility in 500 mL of **FaSSIF** to calculate dose number
- **Effective permeability** in humans instead of fraction absorbed
- Differentiation between **dissolution rate** limited and **solubility** limited absorption (i.e., particle size taken into consideration)

Butler JM, Dressman JB. The developability classification system: Application of biopharmaceutics concepts to formulation development. Journal of Pharmaceutical Sciences. 2010;99(12):4940-54.

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Formulation Wizard

The app identifies suitable excipients and calculates potential formulations depending on the selected dosage form, defined target profile, and properties of the active ingredient.

Formulation wizard | Beginner

Developability Classification

The core functionality of this app is based on the Developability Classification System (DCS) proposed by Butler and Dressman. An active ingredient is categorized into one of the classes I, IIa, IIb, III and IV based on its dose number and absorption number.

Active ingredient | Expert

Tabletability of Active Ingredient

The app calculates the compaction pressure at zero porosity, compressibility resistance, tensile strength at zero porosity, and bonding capacity of pharmaceutical powders (e.g., active ingredients or excipients).

Active ingredient | Expert

Processability of Active Ingredient

The app evaluates the processability of pharmaceutical powders (e.g., active ingredients). The app can be used to estimate the risk of different processing routes for solid oral dosage forms.

Active ingredient | Expert

Content Uniformity Check

The content uniformity of pharmaceutical dosage forms can be affected by the particle size and size distribution of the active ingredient. With this app, it is possible to set particle size limits for a given dose and eliminate problems of content uniformity.

Active ingredient | Expert

Dissolution Profile of Active Ingredient

The app predicts the dissolution profile of an active ingredient based on the Johnson dissolution model. The particle size distribution of the active ingredient is assumed to be log-normal and particles are assumed to be spherical in shape.

Active ingredient | Expert

d_{90} Value		µm
Solubility in FaSSIF at 37 °C *	1.80E-3	mg/mL

- ○ Use effective intestinal permeability for calculation
- ◉ Predict effective permeability from molecular properties

Molecular properties of the active ingredient

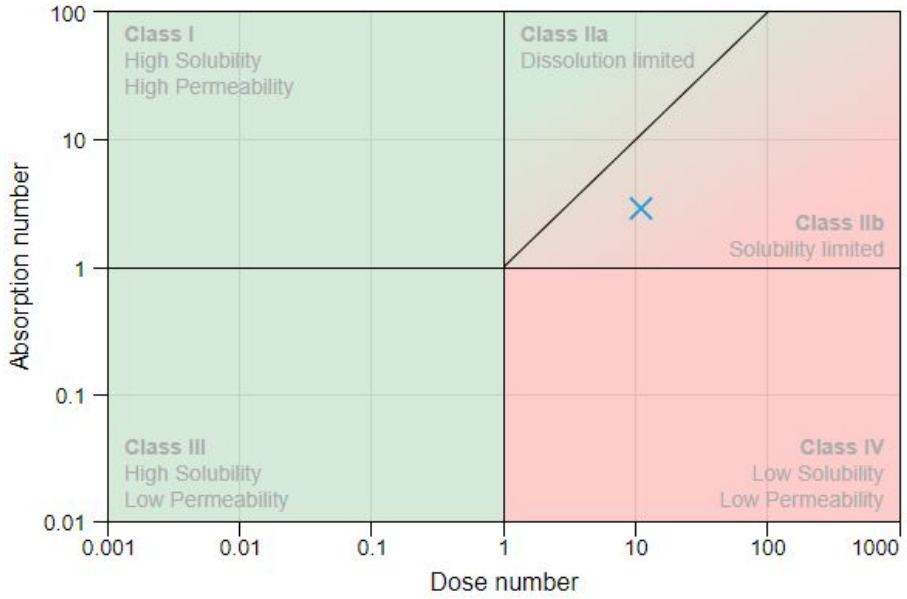
Search PubChem database and import available data

Chemical name or CAS registry no. | Import

Molecular weight *	409.40	g/mol
Number of hydrogen bond acceptors *	5	
Number of hydrogen bond donors *	2	
Computed partition coefficient (XLogP3) *	4.00	
Topological polar surface area *	60.80	Å^2

Finished

Developability Classification System

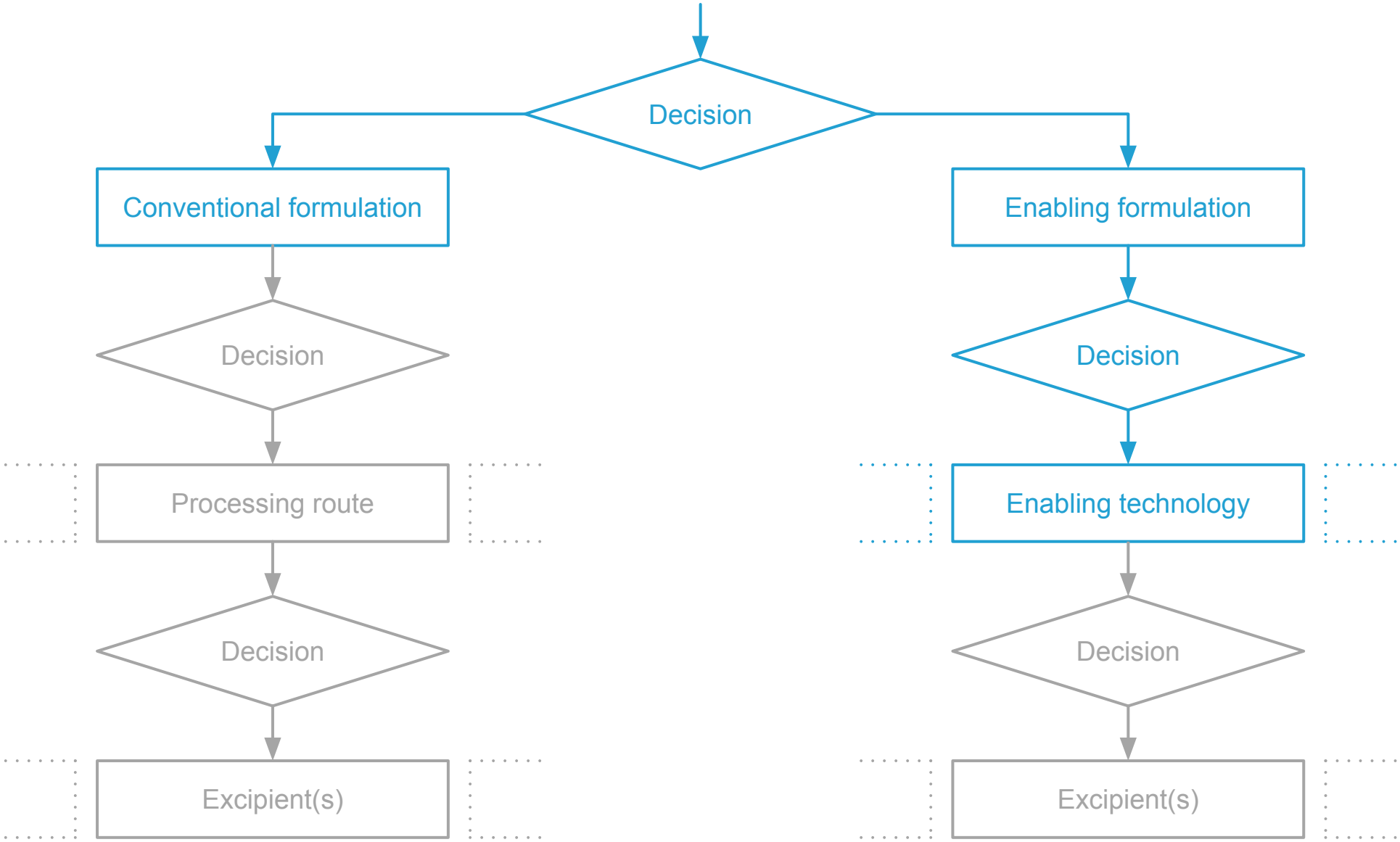


Formulation Advice

The topological polar surface area of the active ingredient is between 60 and 120 Å². As a result of this, moderate intestinal absorption of the active ingredient via paracellular diffusion is expected. No violations of Lipinski's "Rule of Five" were detected. Based on the molecular properties (molecular weight, number of hydrogen bond acceptors and donors, partition coefficient etc.), good oral bioavailability of the active ingredient is expected.

The active ingredient is assigned to DCS class IIb. The oral bioavailability of the active ingredient is limited by its solubility. The active ingredient should be solubilized (e.g., by adding surfactants) or processed using enabling formulation strategies (e.g., lipid-based systems or amorphous solid dispersions).

Decision Support for Solubilization



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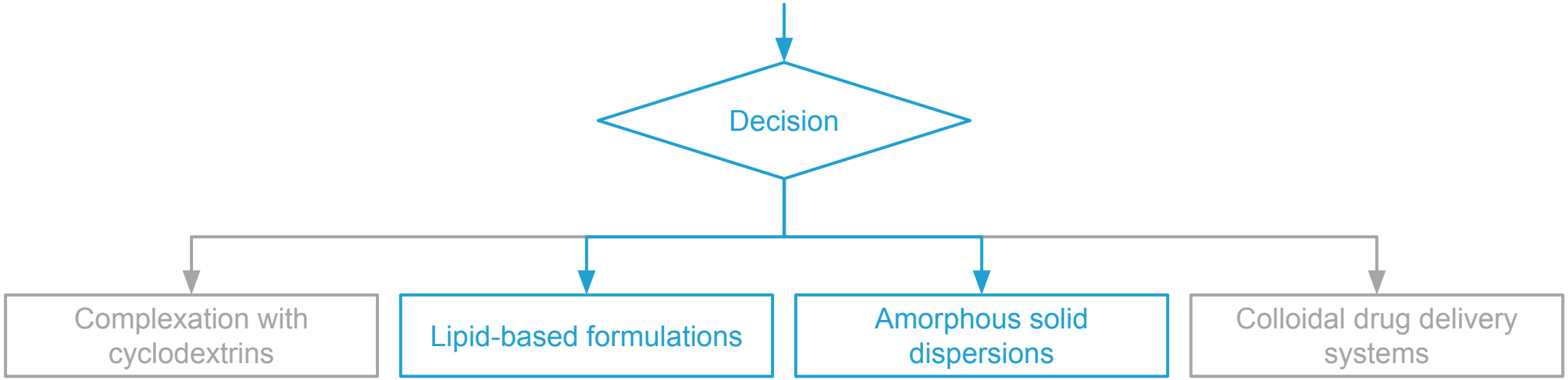
Active ingredients in DCS class IIb / IV can be formulated as lipid-based formulations or amorphous solid dispersions



- "Grease ball" molecules
- **Low melting point**
- **"High" lipophilicity**
- Low polar surface area
- Elongated, flexible structure
- …

- "Brick dust" molecules
- **High melting point**
- **"Low" lipophilicity**
- Strong crystal lattice
- Flat, rigid structure
- High aromaticity
- …

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Dissolution Method Selection

The app recommends suitable dissolution test methods for solid oral dosage forms. A complete protocol with instructions and background information is created. The app is based on the ORBITO decision tree for dissolution methods.

Sustained release | Beginner

Dissolution Profile Comparison

The app compares two dissolution profiles using a parametric approach. Several pairwise procedures are available, including the difference factor (f1) and similarity factor (f2).

Sustained release | Expert

Solubility Parameter Calculation

The app calculates the Hansen solubility parameters (HSP) of an active ingredient using group contribution methods. The algorithm requires the SMILES string of the molecule as input parameter.

Solubilization | Expert

Decision Support for Solubilization

The app analyzes experimental and computed properties of an active ingredient and assists formulators in identifying the most suitable formulation approach (lipid-based formulation or amorphous solid dispersion).

Solubilization | Expert

Polymer and Solvent Finder

The formulation of amorphous solid dispersions (ASD) requires suitable polymers and solvents that exhibit good miscibility with the active ingredient. The app ranks excipients and solvents based on computed solubility parameter differences.

Solubilization | Expert

Self-Emulsifying Drug Delivery Systems

The app identifies suitable self-emulsifying drug delivery system (SEDDS) carrier formulations for an active ingredient. Based on experimental and computed properties, the solubility of the active ingredient in the formulation is estimated and used to assess the feasibility of the approach.

Solubilization | Expert

Decision Support for Solubilization

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Properties of Active Ingredient

Active ingredient (leave blank for new active ingredient)

- Select active ingredient -

Load data

Melting point *	156.40	°C
Glass transition temperature	80.00	°C

Molecular properties of the active ingredient

Search PubChem database and import available data

Chemical name or CAS registry no.

Import

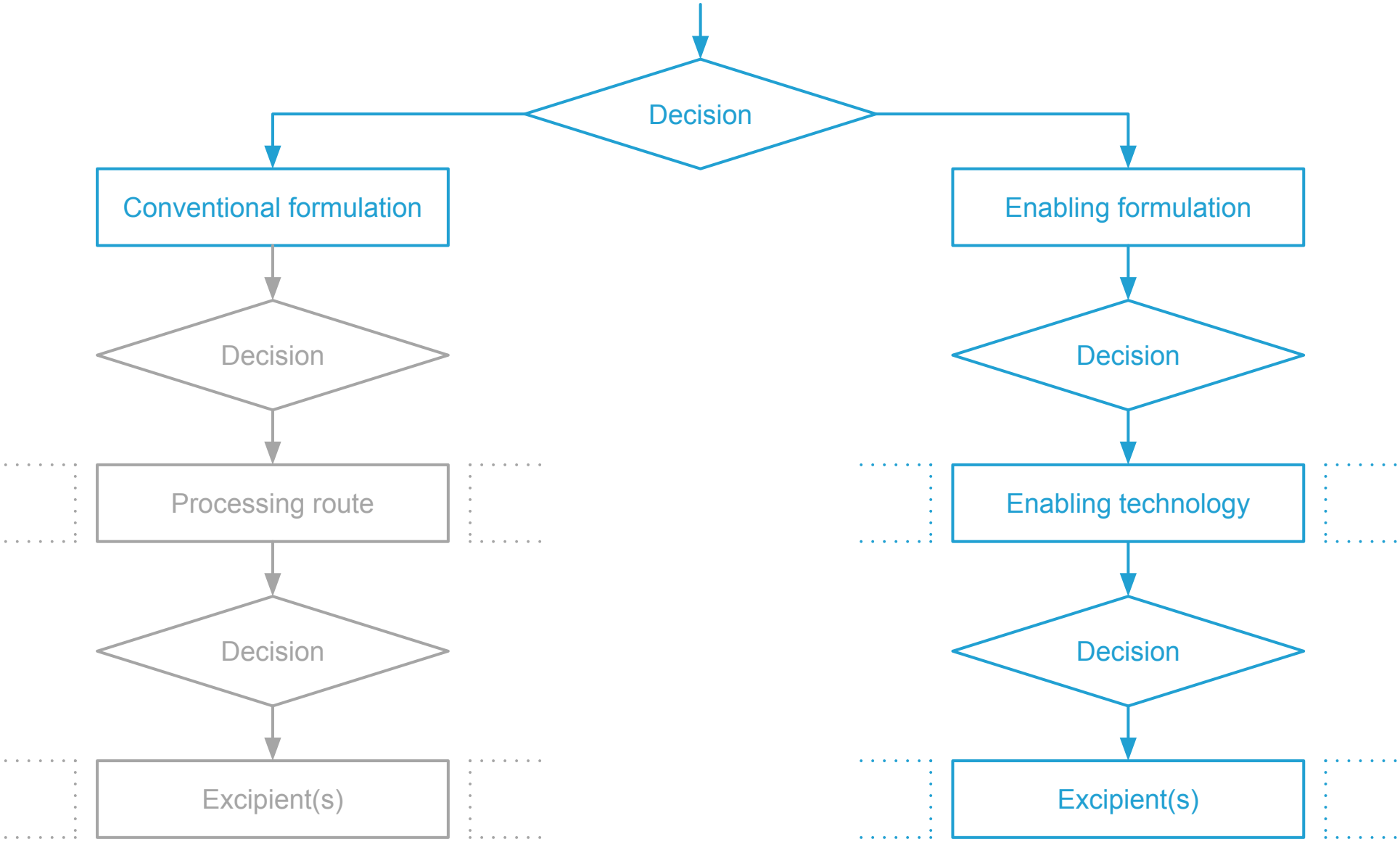
Molecular weight *	409.40	g/mol
Number of hydrogen bond acceptors *	5	
Number of hydrogen bond donors *	2	

Evaluation of Formulation Strategies

Parameter	Result
Estimated solubility in soybean oil	9.0 mg/g
Estimated glass-forming ability	good
Proposed formulation (logistic regression model)	Amorphous solid dispersion
Share of solid dispersions (logistic regression model)	55.8%
Proposed formulation (decision tree model)	Lipid-based formulation
Share of solid dispersions (decision tree model)	14.3%

Based on molecular descriptors and comparison with available drug products, the logistic regression model proposes formulating the active ingredient as an amorphous solid dispersion. The decision tree model proposes formulating the active ingredient as a lipid-based system. Using molecular descriptors, the algorithm has identified the top 10 most similar active ingredients. Among these, 8 molecules are exclusively formulated as amorphous solid dispersions, and 2 molecules are exclusively formulated as lipid-based systems. Therefore, formulating the active ingredient as an amorphous solid dispersion seems appropriate.

In conclusion, based on the performed assessment, formulating the active ingredient as an amorphous solid dispersion is recommended.



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Identification of solvents / polymers with / in which the active ingredient is miscible / soluble

Hildebrand Solubility Parameter: $\delta_t = \sqrt{\frac{E_{coh}}{V_m}}$

"Like dissolves like" – Solutes are soluble in solvents with similar solubility parameter (i.e., similar strength of intermolecular interactions)

Hansen Solubility Parameters: $\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + d_h^2}$

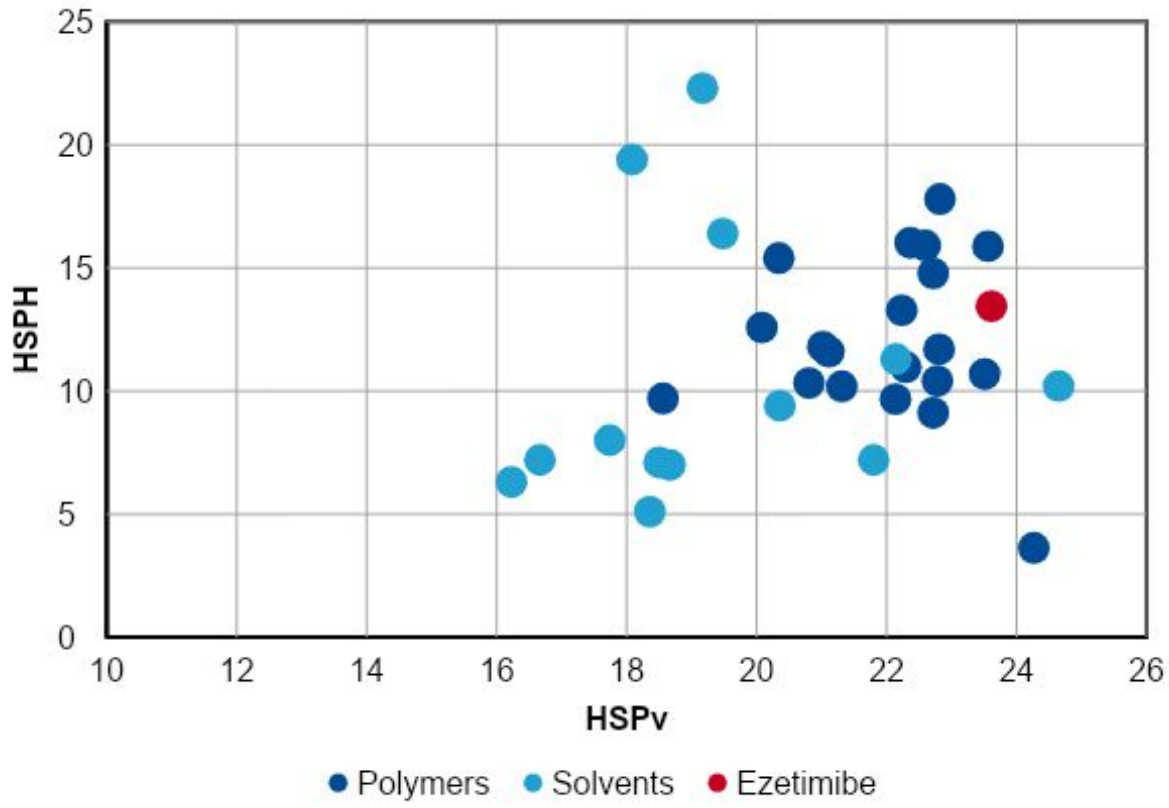
Contributions from dispersion, dipolar and hydrogen bond interaction forces

Determination of solubility parameters:

Measure solubility in a range of solvents with known solubility parameters and determine center point of a "solubility sphere"

Estimate solubility parameters with the help of group contribution methods

Bagley plot to screen for suitable solvents / polymers



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Sustained release | Beginner

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Solubilization | Expert

Polymer and Solvent Finder

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Properties of Active Ingredient

Active ingredient (leave blank for new active ingredient)

- Select active ingredient -

Load data

Hansen solubility parameters calculated by the van Krevelen method

Contribution from dispersion forces (δ_d) *	22.87	$MPa^{0.5}$
Contribution from dipolar forces (δ_p) *	5.88	$MPa^{0.5}$
Contribution from hydrogen bonds (δ_h) *	13.44	$MPa^{0.5}$

Ranking of Polymers and Solvents

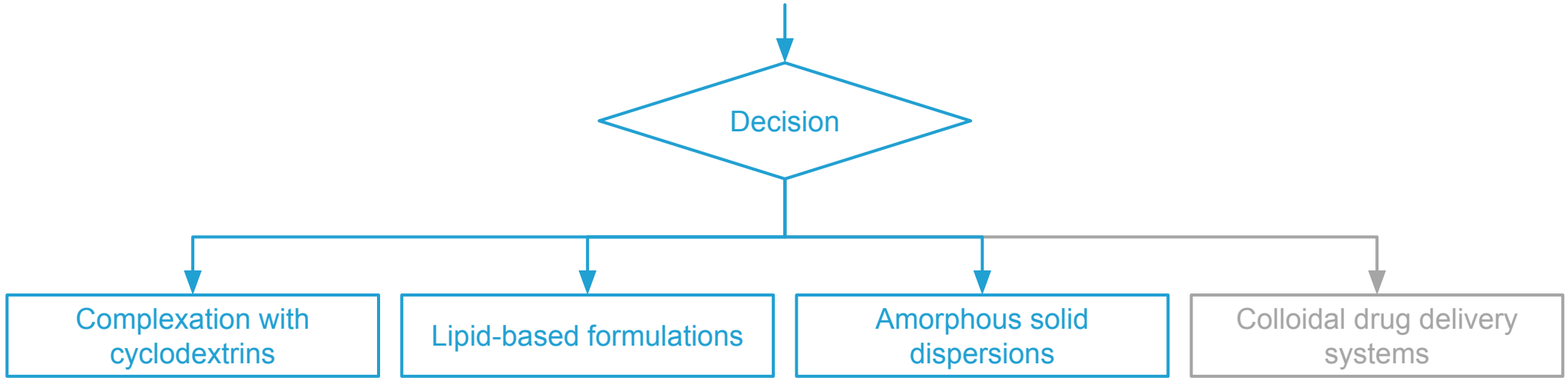
The algorithm has arranged the available solvents in descending order of "goodness". Select a ranking method from the dropdown menu and review the results.

Euclidean distance in Bagley plot

Polymers and solvents | Polymers | Solvents

Ingredient(s)	Process(es)	Result
Kollidon® VA 64 (BASF)	Coating, aqueous ⊞ Show more	1.4 $MPa^{0.5}$
Kollidon® 90 F (BASF)	Cold processing ⊞ Show more	1.6 $MPa^{0.5}$
Hydroxypropylmethylcellulose phthalate (Type HP 50)	Hot melt extrusion Spray drying	1.9 $MPa^{0.5}$
Kollidon® 30 (BASF)	Hot melt extrusion Spray drying	2.4 $MPa^{0.5}$
Kollidon® 12 PF (BASF)	Hot melt extrusion Spray drying	2.7 $MPa^{0.5}$

ZoomLab® provides tools for cyclodextrins, self-emulsifying drug delivery systems and amorphous solid dispersions



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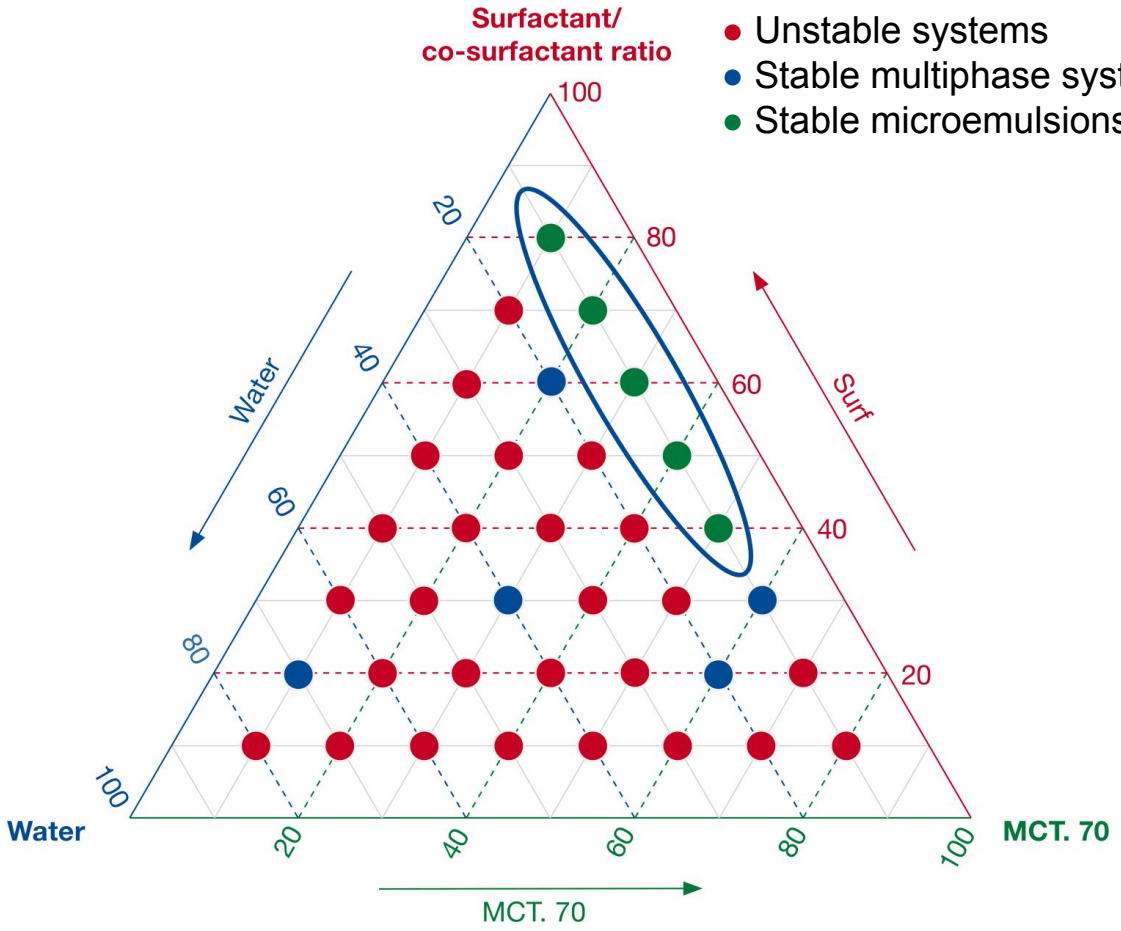
Self-emulsifying drug delivery systems (SEDDS) can effectively deliver poorly water-soluble drugs to the body

The Screening Approach



- Identifying stable microemulsions often requires thousands of formulation trials
- BASF used high-throughput screening to design 10 unique SEDDS carrier formulations that can be easily reproduced by formulators
- The formulations differ regarding digestibility, hydrophilicity and droplet size
- Formulations with high drug loading capacity can be filled into soft-shell capsules
- ZoomLab® supports the formulator in selecting suitable SEDDS carrier formulations

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Solubilization | Clear filters

Developability Classification

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Solubilization | Expert

Solubilization with Cyclodextrins

The app recommends suitable cyclodextrins and estimates the amount of cyclodextrin required for solubilization of the active ingredient. The app has been developed in cooperation with CycloLab – Pioneers in cyclodextrin-based innovation.

Solubilization | Expert

1 to 6 of 6 items

observed droplet size may vary for other active ingredients or drug loadings.

Number of nitrogen atoms * 1

Number of non-aromatic double bonds * 1

Computed partition coefficient (XLogP3) * 4.00

Biopharmaceutical Aspects

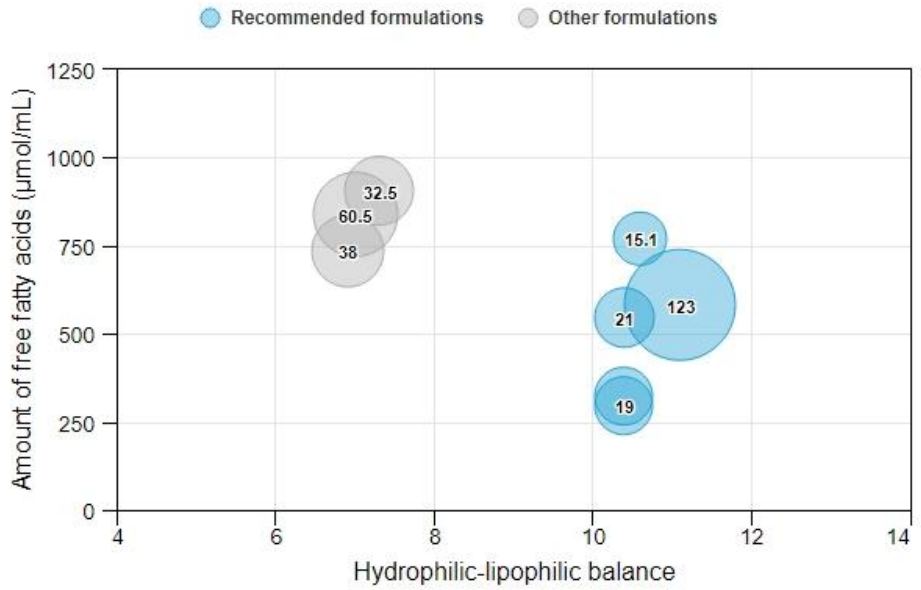
Capsule size: Capsule size 16 (max. 16 minim)

Lipid digestibility: No preference

Cosolvent content: Formulation must not contain ethanol

Finished

SEDDS Carrier Formulations



The amount of free fatty acids (in µmol/mL) is the amount of KOH (in µmol) required to titrate the free fatty acids after in vitro digestion, normalized to the formulation volume (in mL). The values depicted in the BASF SEDDS Formulary (digestibility in µmol) are not normalized to the formulation volume. Please check the documentation for further information.

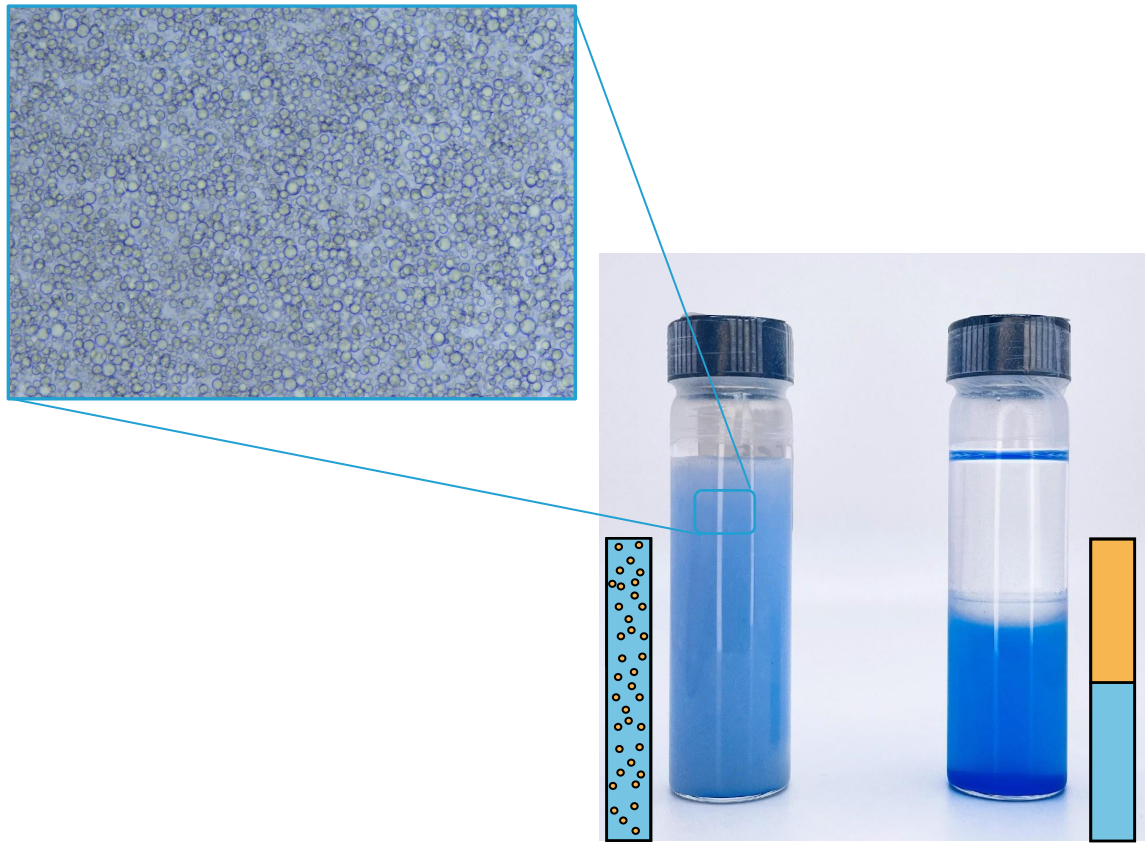
Composition of SEDDS Carrier Formulations

The algorithm has identified the most suitable self-emulsifying drug delivery system (SEDDS) carrier formulations. Select a formulation from the dropdown menu to review its composition.

SEDDS carrier formulation #02 without ethanol

Emulsion-based formulations are challenging to design

- Oil/Water emulsions will inevitably separate
- Emulsifiers help stabilize emulsions, but formulating is a balancing act between multiple competing forces
- Current formulation approaches are insufficient and inaccurate
- New, innovative approaches are needed to streamline development



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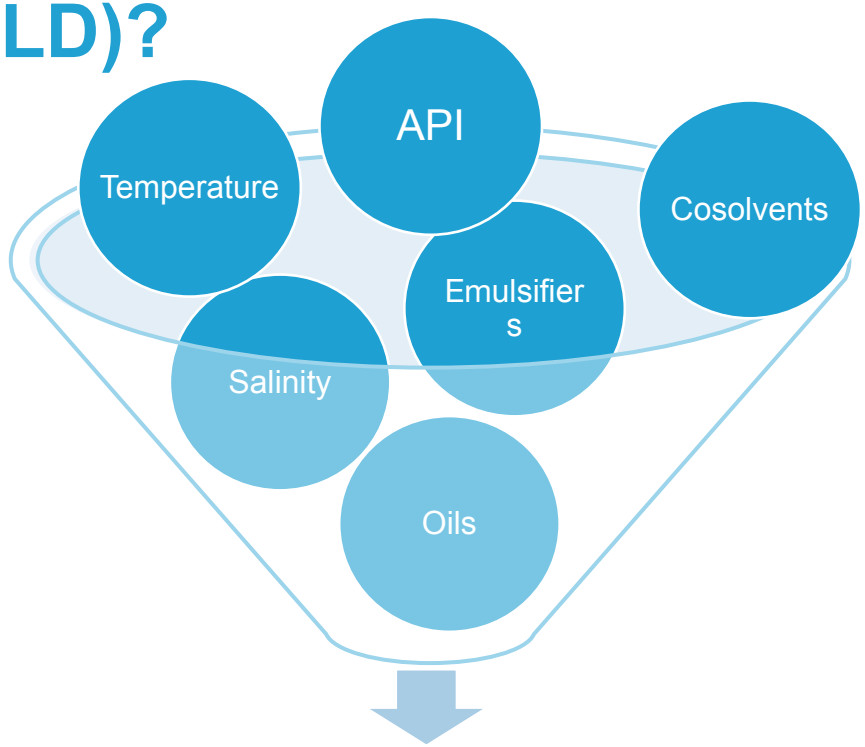
What is Hydrophilic-Lipophilic Difference (HLD)?

HLD…

- Is an easy-to-use empirical equation[1,2]
- Addresses existing formulation design shortcomings
- Considers multiple formulation effects[3]
- Provides insight on emulsion type, stability and improvement areas



HLD = Salinity – Oiliness + Temperature + Surfactant

1: Acosta et al., J. Surfact Deterg., 2008
2: Acosta, Curr. Opin. Colloid Interface Sci., 2020
3: Acosta et al, Int J Pharma, 2021

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What is Hydrophilic-Lipophilic Difference (HLD)?

$$HLD = Salinity - Oiliness + Temperature + Surfactant$$

$$HLD = f(S) - k\ EACN + \alpha\ (T\text{-}25) + C_c$$

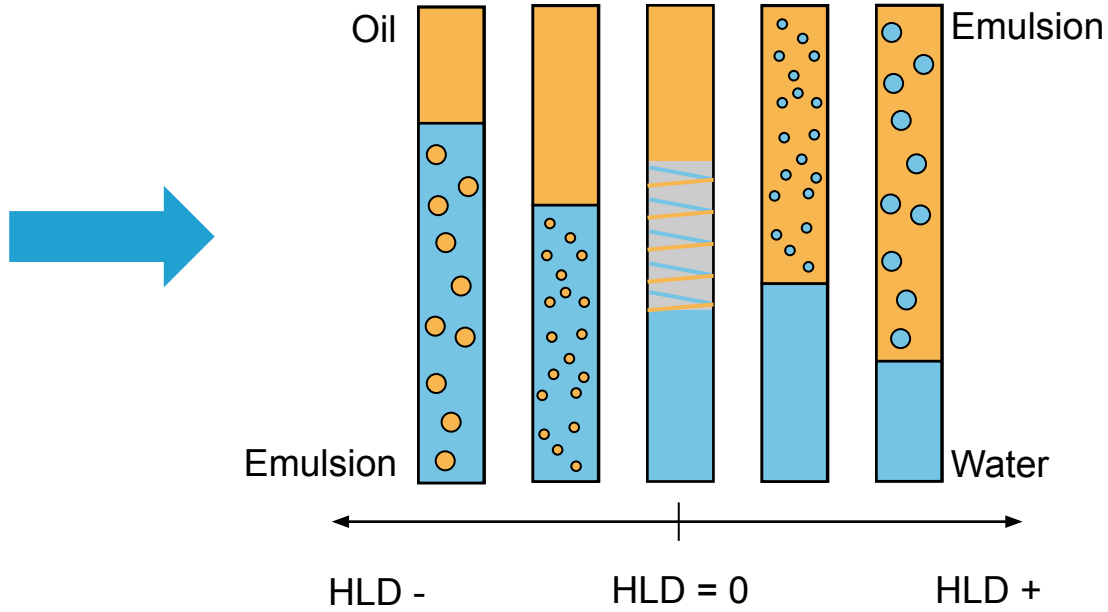
Salinity

Oil Effective Carbon Number

Surfactant Curvature

- HLD < 0 indicates oil-in-water emulsion
- HLD > 0 indicates water-in-oil emulsion
- HLD = 0 is the phase – inversion point[1]

- HLD principles have been rigorously validated in the petroleum field for > 40 years[2-4]



1: Kiran & Acosta, Ind & Eng Chem, 2015
2: Salager et al., J. Surfactants Deterg., 2005
3: Harwell et al., J Petrol Sci & Eng., 2015
4: Salager et al., Soc Petrol Eng, 1979

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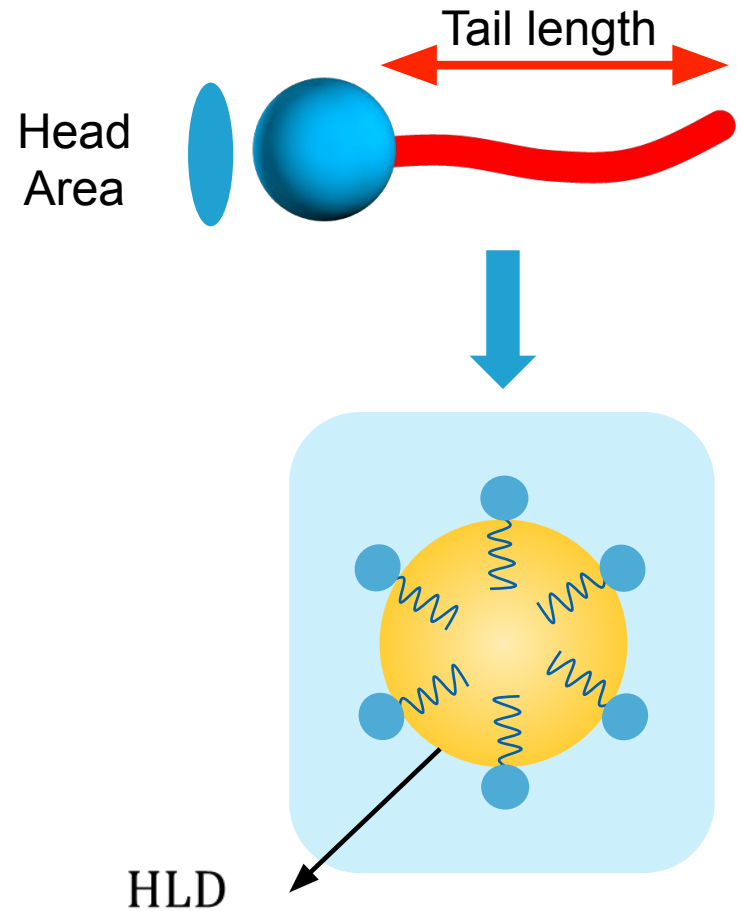
HLD is expanded by Net-Average-Curvature (HLD-NAC)

- NAC theory combines HLD and surfactant geometry to understand droplet curvature and size[1,2]
- Curvature is used to predict formulation properties and potential instabilities
- Current methods can explore rates of coalescence, creaming, and Ostwald ripening



$$H_{net} = \frac{1}{R_{oil}} - \frac{1}{R_{water}} = \frac{HLD}{L_{tail}}$$

1: Sabatini et al., Langmuir, 2003
2: Kiran & Acosta, Ind & Eng Chem, 2015

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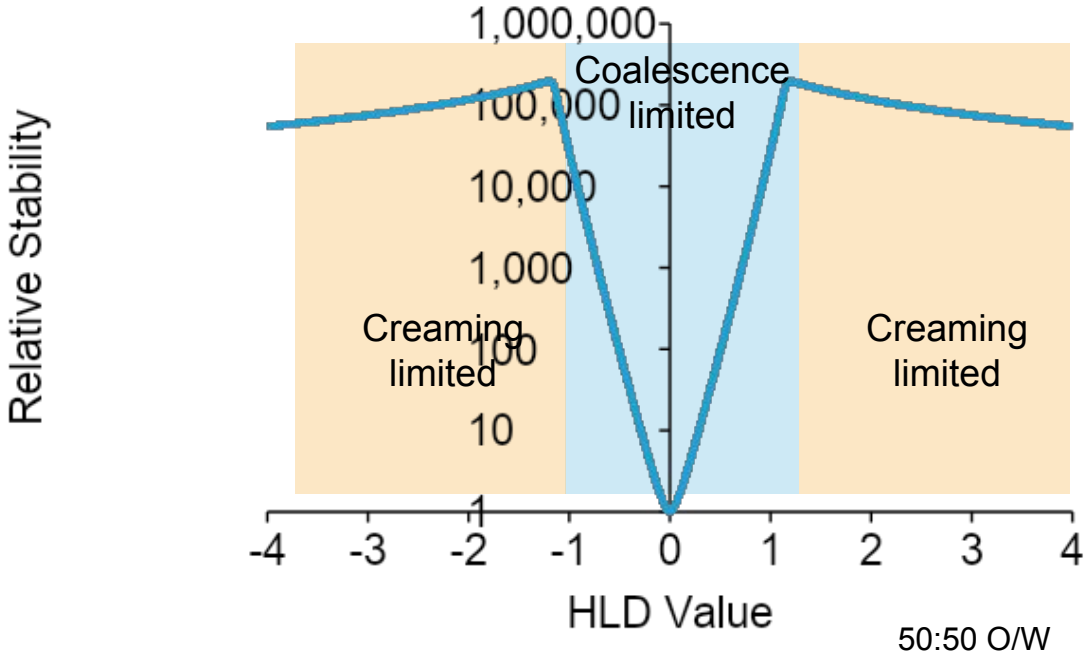
HLD is expanded by Net-Average-Curvature theory (HLD-NAC)

Using HLD-NAC can…

- Predict droplet sizes from mixing conditions
- Provide optimal HLD values
- Allow formulator to identify areas of improvement



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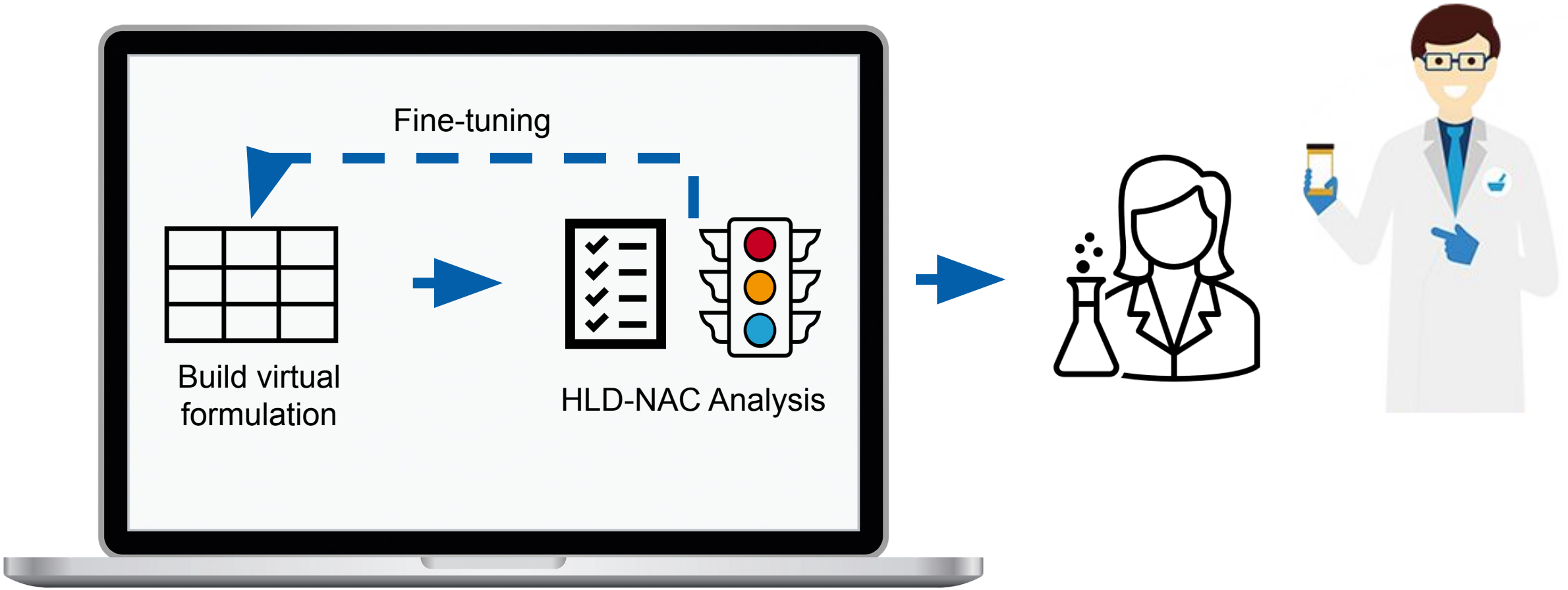

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Introducing BASFs HLD-NAC Toolkit, featuring ZoomLab®

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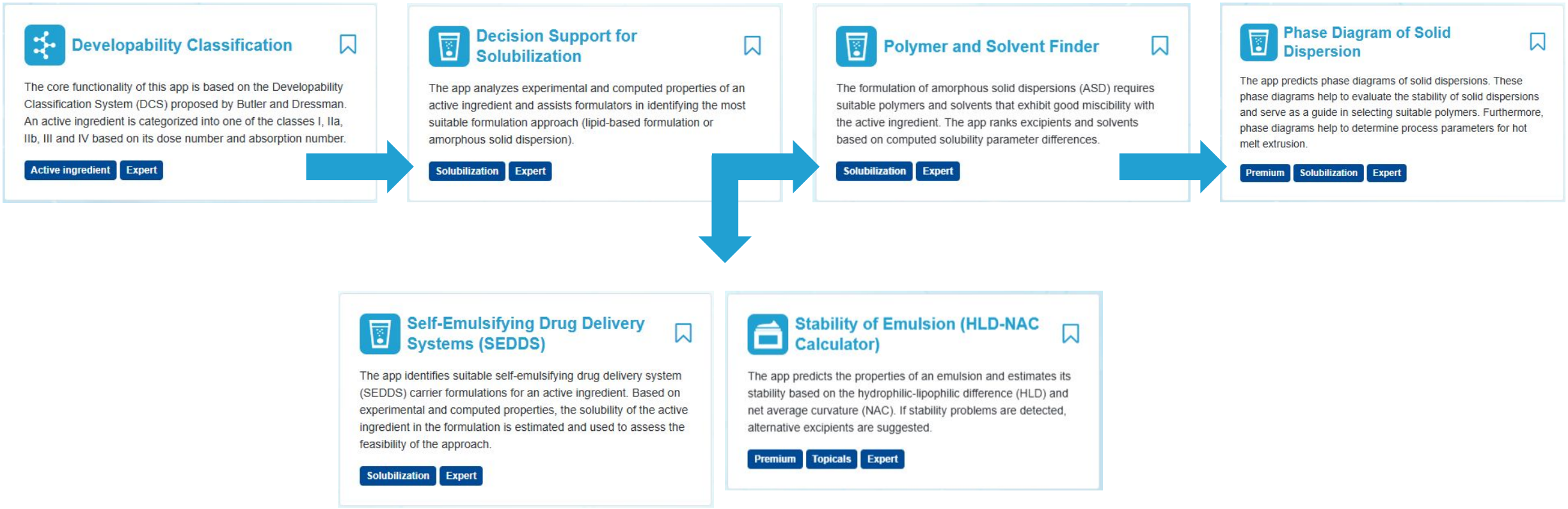
Today's Solubilization Journey within ZoomLab® - more to come…



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Nitrosamine Risk Assessment and Mitigation

New Formulation Project

Related content

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Project name (leave blank for default name)

New Formulation Project

Definition of Target Profile

Enter the dose of the active ingredient per tablet, the tablet weight, and the maximum daily dose of the active ingredient (provided as maximum number of tablets per day). This information is required to calculate the potential daily intake of the nitrosamine.

Dose of active ingredient * mg

Tablet weight * mg

Maximum number of tablets per day *

Properties of Degradation Product

ZoomLab® offers
various solutions for formulators
beyond Formulation Development

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