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Pharma & Biopharma
Raw Material Solutions

Strategies and Enabling Technologies for Enhancing API Solubility

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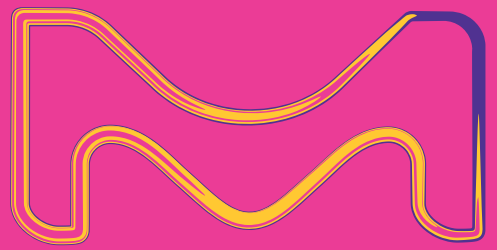
Webinar – April 2023



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The Life Science business
of Merck KGaA, Darmstadt, Germany operates as
MilliporeSigma in the U.S. and Canada

agenda

01 Introduction to Developability Classification System (DCS)

02 Strategies to enhance solubility of DCS Class IIa molecules

03 Strategies to enhance solubility of DCS Class IIb molecules

04 Summary

Drug exposure

The exposure of the drug in the bloodstream, is essential for a physiological effect

Speed up Liberation

- Type of dosage form
- Disintegration time

Increase Absorption

- **Solubility**
  - Chemical approaches
  - Physical approaches
- **Permeability**
  - Administration route
  - Permeation enhancers
  - API lipophilicity
- **Other**
  - Efflux (P-gp)
  - API stability

Influence Distribution

- Tissue targeting
- Protein binding

Reduce Metabolism

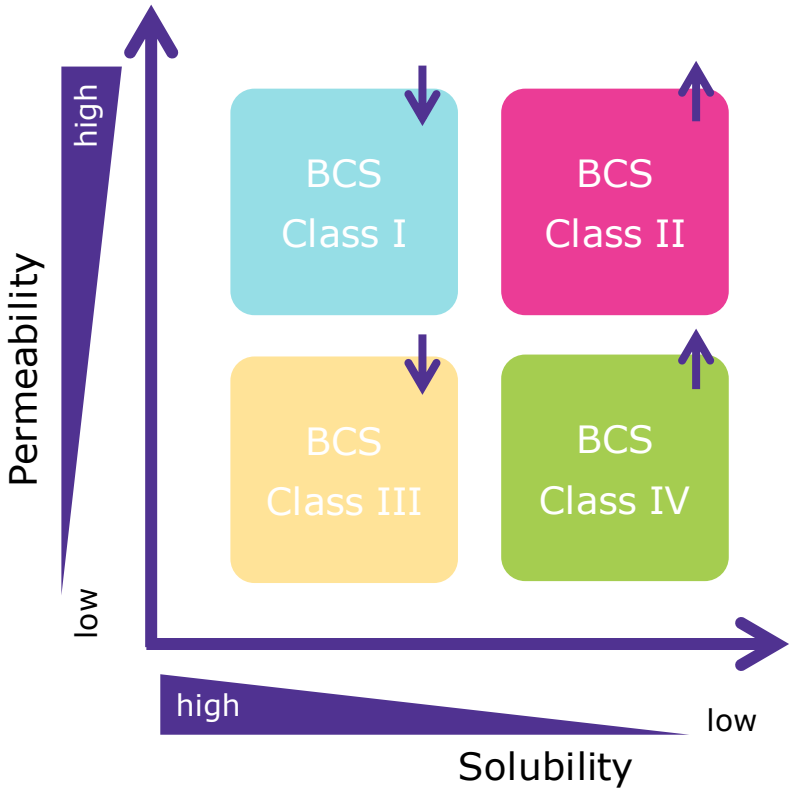
- Avoid the first pass effect
- Reduce enzymatic bio-transformation

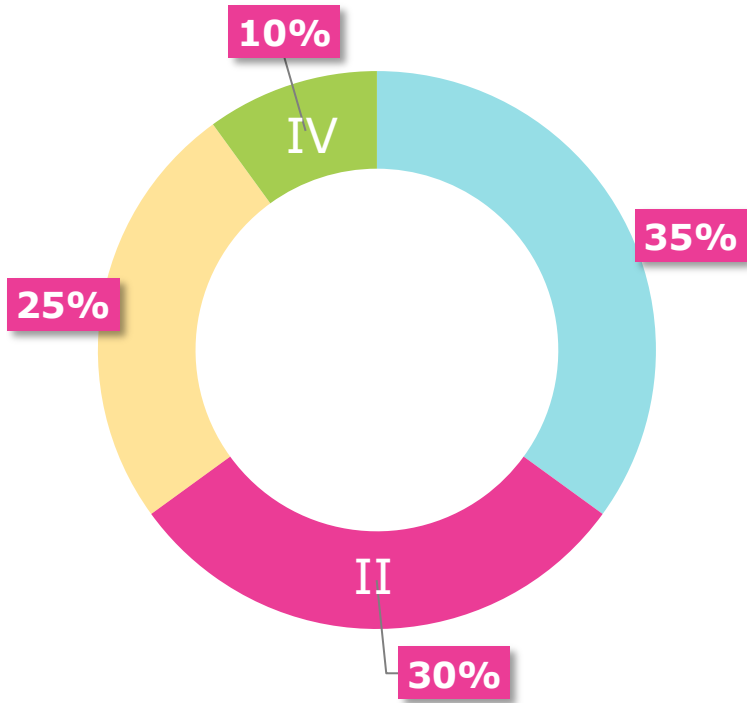
Postpone Elimination

- Increase circulation lifetime
- Increase size

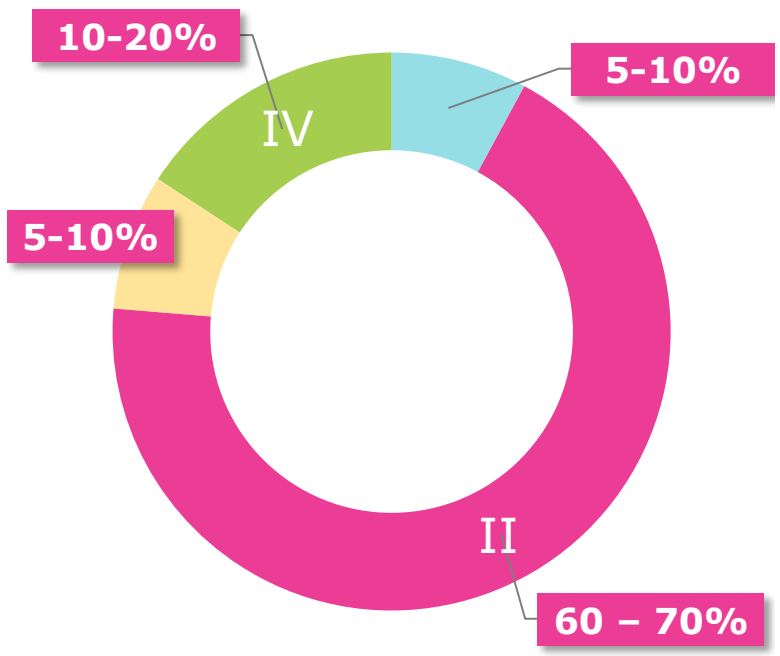
Absorption of the API from the intestinal tract to systemic circulation is governed primarily by **solubility and permeability**

Solubility of APIs in development
Poor soluble molecules are becoming more prevalent





Distribution of **marketed** drug substances



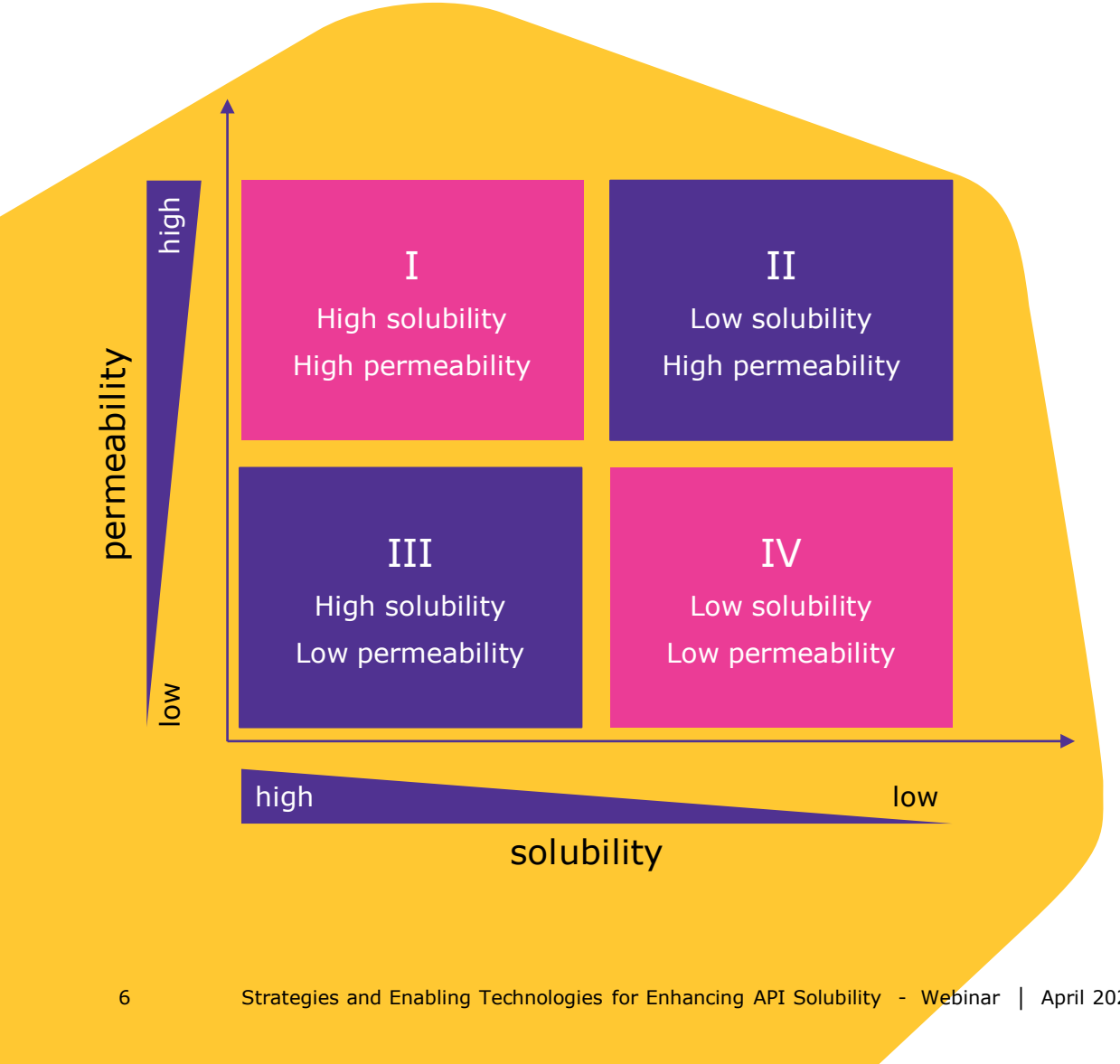
Distribution of **pipeline** drug substances

Poor solubility can lead to low and variable absorption

Distribution of drug substances according to their respective BCS classification modified from Ting et al. Advances in Polymer Design for Enhancing Oral Drug Solubility and Delivery. Bioconjugate Chemistry. 2018;29(4):939-52.

Solubility and the BCS

The BCS classifies molecules based on solubility and permeability



Originated in the 1990s

Correlates *in-vitro* to *in-vivo* performance based on aqueous solubility and permeability, and classifies APIs based on these factors

Adopted by regulatory Authorities

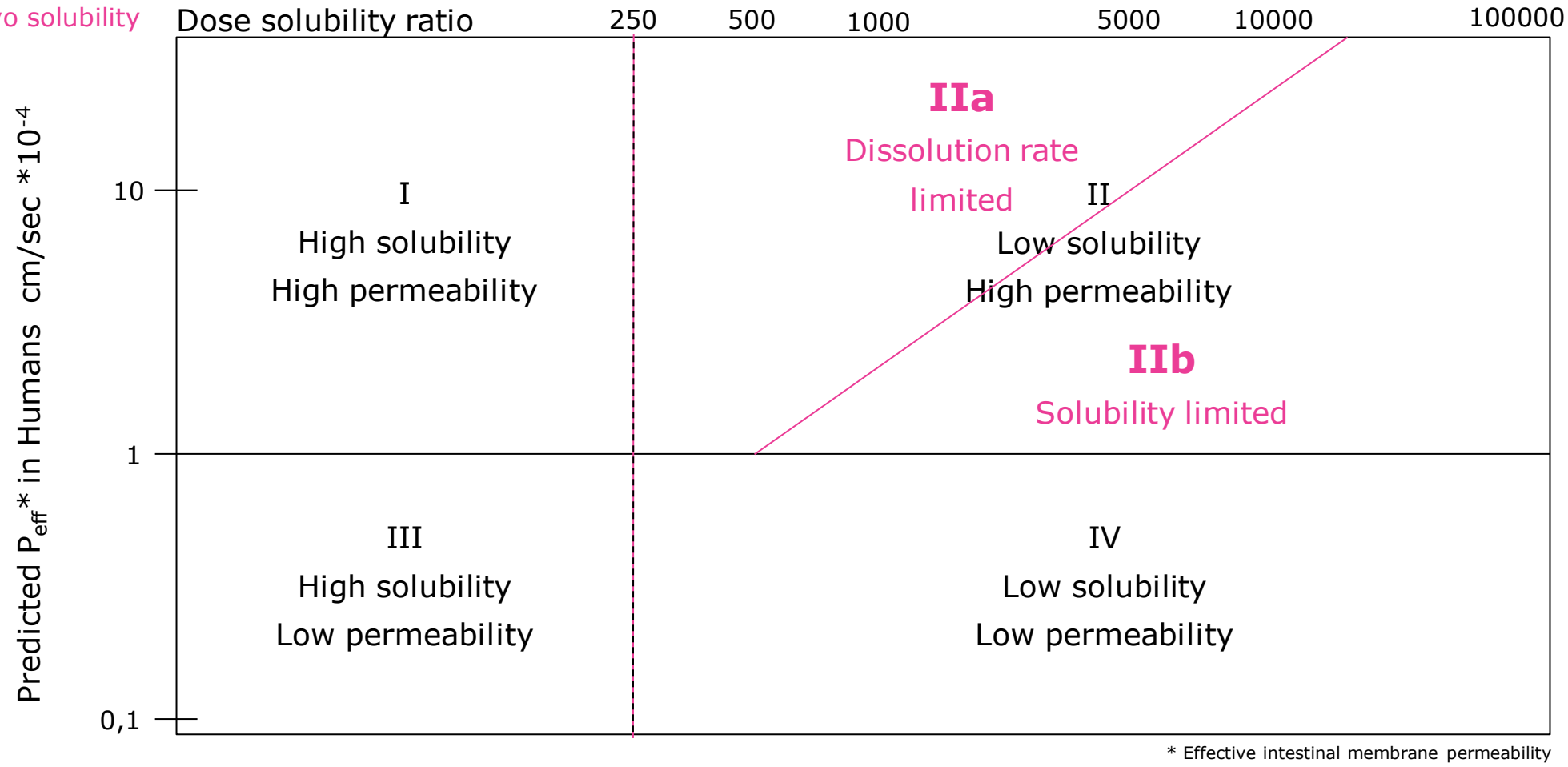
Used by FDA as basis for so called „Biowaiver" applications for immediate-release formulations in order to reduce unnecessary additional in-vivo studies for bioavailability and bioequivalence.

Amidon et al. (1995). Pharmaceutical Research 12(3): 413-420.

The Developability Classification System (DCS)

The DCS is based on the BCS and can be used to optimize formulations of poorly soluble molecules

Using FaSSIF for an estimate of in vivo solubility



* Effective intestinal membrane permeability

General approach

Applying DCS in formulation development

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Solubility Determination

- Thermodynamic solubility
- Describes the maximum saturation concentration
- Measured in FaSSIF
- Described using the Dose/Solubility ratio, the minimum amount of "solvent" required to dissolve the maximum dose

Permeability Determination

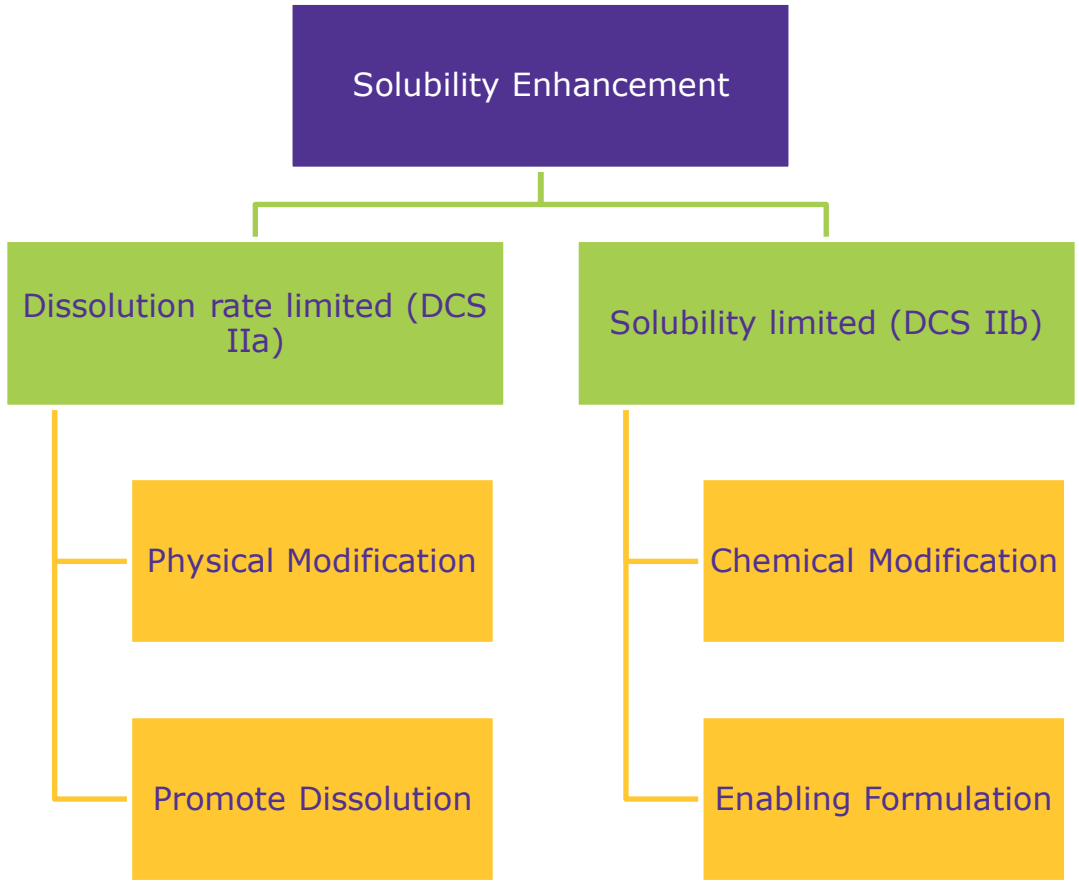
- Description of flux through cell membrane
- Measured using Caco-2 cells
- Can also be predicted using software

DCS Class Assignment

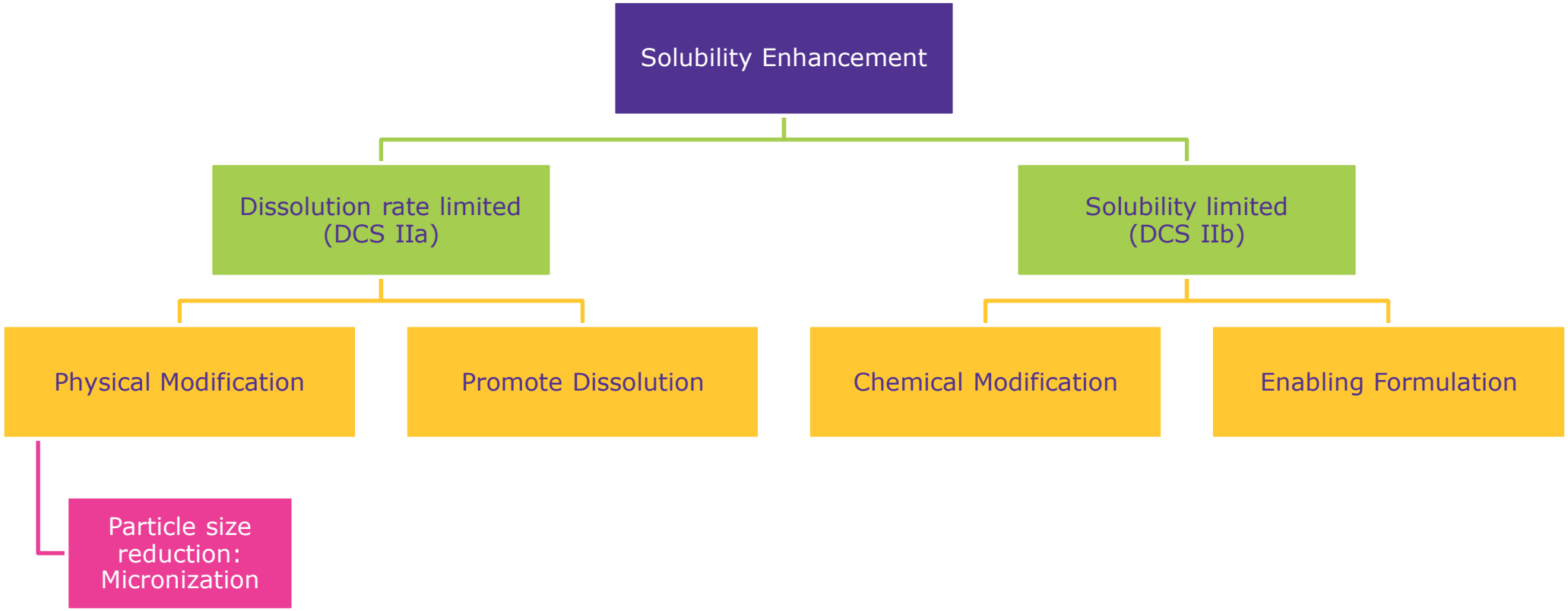
- Based on the combination of solubility and permeability
- Determines its DCS class
- For DCS II molecule, devided by the solubility limited absorbable dose (SLAD) line

The DCS class of a molecule can be determined using readily accessible laboratory methods and equipment

Strategies and Enabling Technologies for Enhancing API Solubility



Strategies and Enabling Technologies for Enhancing API Solubility



Micronization

- According to Noyes-Whitney equation, dissolution rate of a drug particle is related to its surface area ➔ **smaller particles means higher dissolution**[1]
- Micronization aims at reducing particle size to µm range, but no generally defined borders
- Frequently used methods are **mechanical milling** (coarse particles) and **jet milling** (fine particles)[2]

Mechanical Milling

- Typically particle sizes in the range 50 – 75 µm
- Established, easy to handle, rather cheap
- Moving / rotating parts with mechanical wear
- Abrasion of machinery possible -> contamination
- Limited control of particle size distribution

Jet Milling

- Particle sizes down to approx. 1 µm possible
- Employs pressurized gas at >sonic speed
- No moving parts, low / no mechanical wear
- Contamination risk strongly reduced
- Higher control of particle size distribution

[1] The rate of solution of solid substances in their own solutions, Noyes & Whitney, 1897
[2] Overview of nanoparticulate strategies for solubility enhancement of poorly soluble drugs, Khan *et al.*, 2022

Micronization

In-Situ Micronization

- Principle: Drug is precipitated with a non-solvent, followed by drying
- Poorly water-soluble drugs: solubilized with an organic solvent; aqueous solvent (including stabilizing agent) is used as precipitator
- Common stabilizers: PEG, PVA, PVP, Cellulose (API-dependent)
- Particle sizes down to approx. 1 µm possible

Benefits:

- No specialized mechanical equipment needed
- Tight particle size distribution, drug amount in preparation relatively high[2]
- Polymer-hydrophilized surface increases dissolution and prevents aggregation

Milling

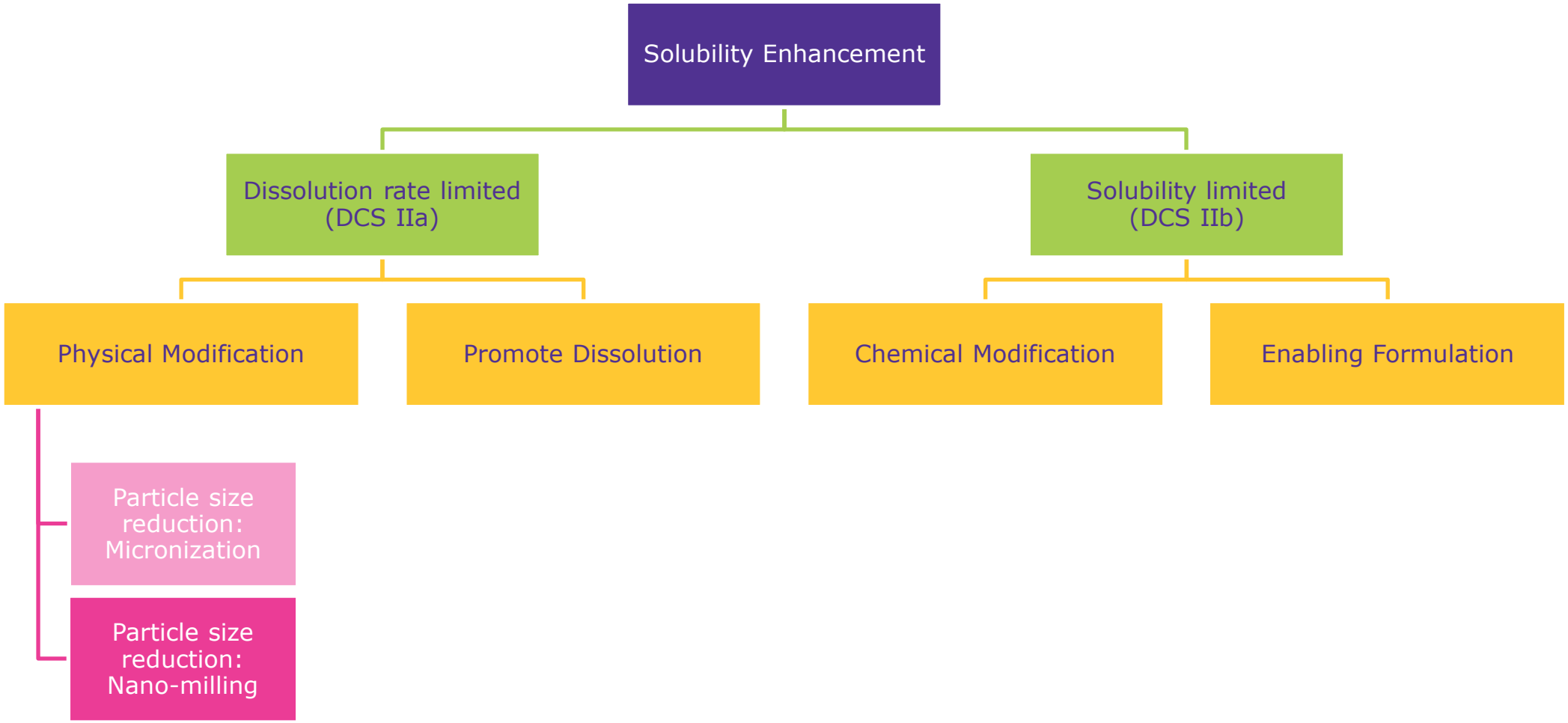
- Well-established techniques
- Thermal and physical stress
- Mechanical equipment needed
- Size control depends on method

***In-Situ* Micronization**

- No stress, tight size control
- Process rather demanding
- Stabilizers needed

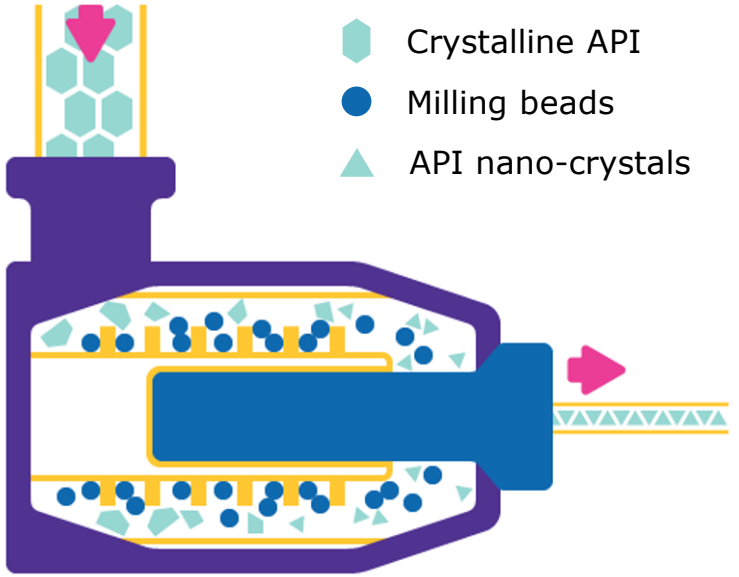
[1] An overview on in situ micronization technique – An emerging novel concept in advanced drug delivery, Vandana *et al.*, 2013
[2] Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs, Rasenack & Müller, 2002

Strategies and Enabling Technologies for Enhancing API Solubility



Nano-Milling

- API **nano-milling is an established procedure** to enhance dissolution by strongly increasing the drug surface area[1]
- Target is usually a reduction of **particle size below 1000 nm**, typically 100 nm range
- **Can be converted into diverse dosage forms** like oral liquids, capsules, tablets, injectables, aerosols, etc.[1]
- Milling is **performed using a medium with beads** made of ceramics or highly crosslinked polystyrene[2]
- **Outcome is a nanosuspension** comprised of water, stabilizer(s), and API



stabilized drug nano-crystal

[1]: Nanomilling of Drugs for Bioavailability Enhancement: A Holistic Formulation-Process Perspective, Li *et al.*, 2016
[2]: Nanomilling: A Key Option for Formulating Water-Insoluble APIs, Lee & DiFranco, 2022

Nano-Milling

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Examples Marketed Nano-Milled Drugs[1]:

Product	API	Company
Rapamune®	Rapamycin, Sirolimus	Wyeth
Emend®	Aprepitant	Merck & Co.
Tricor®	Fenofibrate	Abbott Laboratories
Ritalin LA®	Methylphenidate HCl	Novartis
Zanaflex®	Tizanidine HCl	Acorda
Invega Sustenna® / Trinza®	Paliperidone Palmitate	Janssen Pharma
Yonza®	Abiraterone Acetate	Sun Pharma

Benefits of Nano-Milling

- Well established
- No chemical modification
- No limitation for dosage form

Challenges

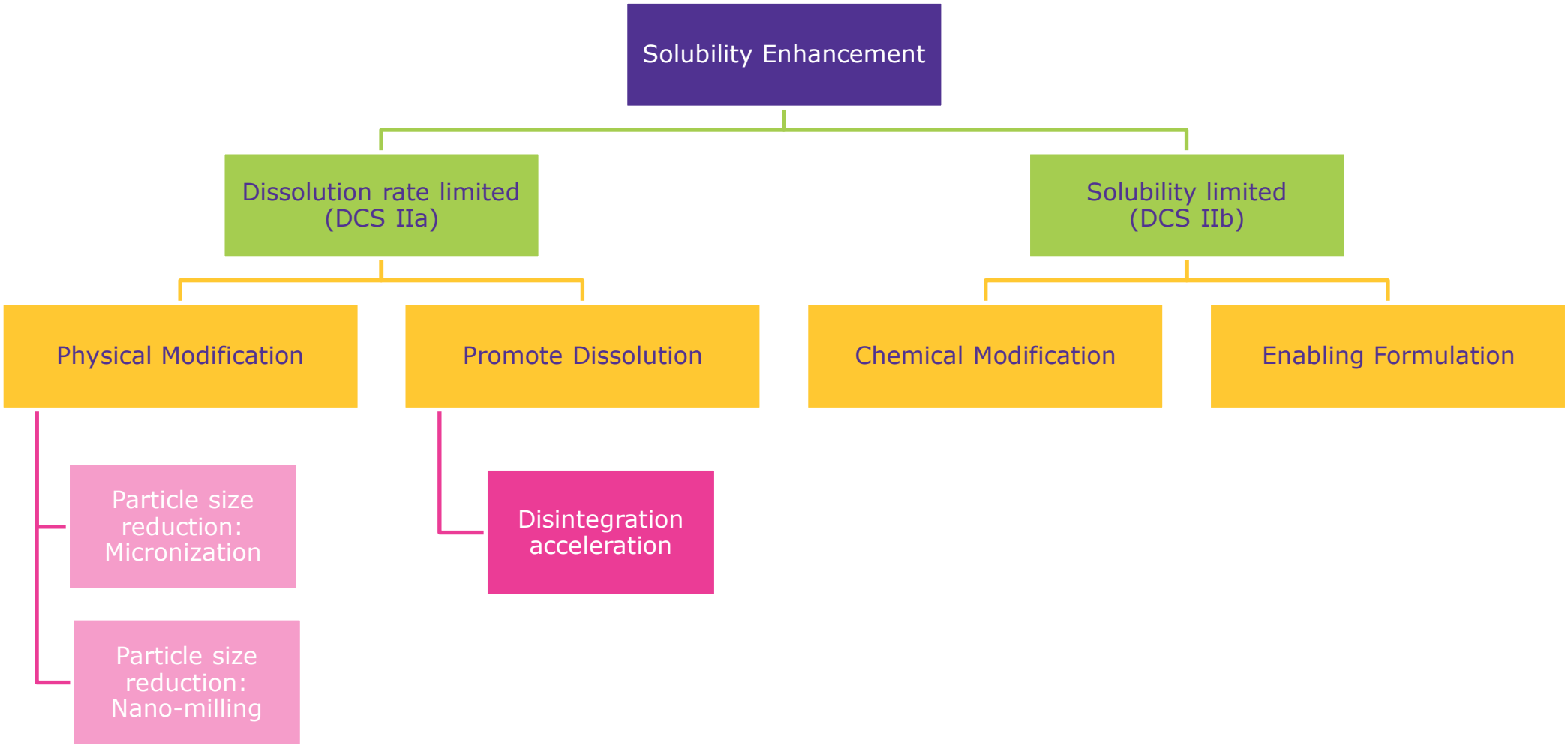
- Mechanical stress to API
- Re-aggregation can occur
- Stabilizers needed

Due to high re-aggregation tendency stabilizers are required:

Poloxamer	Polyethylene glycol
Tween	Polyvinyl alcohol
Sodium dodecyl sulfate	

[1]: Nanomilling: A Key Option for Formulating Water-Insoluble APIs, Lee & DiFranco, 2022

Strategies and Enabling Technologies for Enhancing API Solubility



Accelerate disintegration
Disintegrants are important for the dissolution rate

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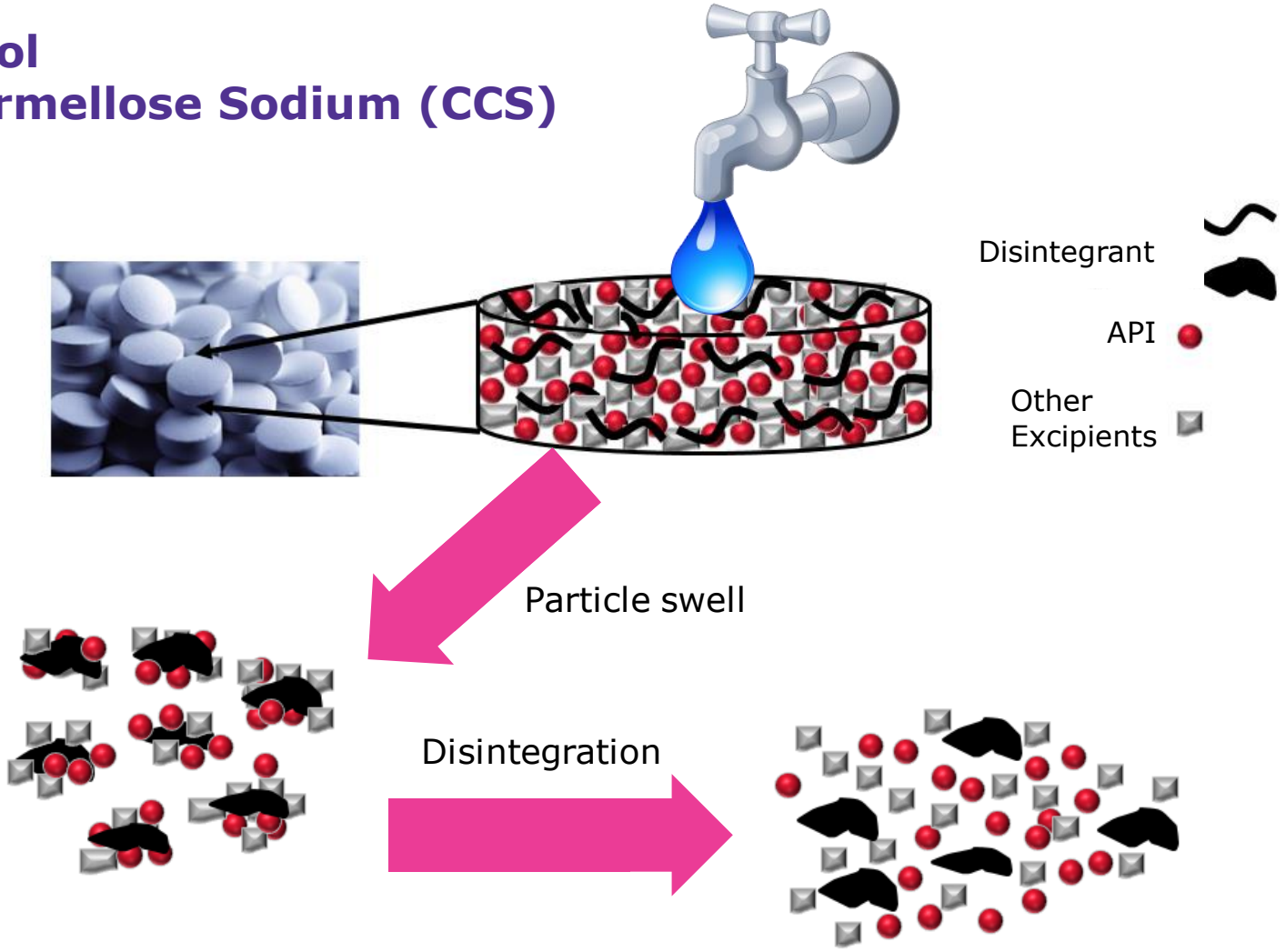
Mannitol
Croscarmellose Sodium (CCS)

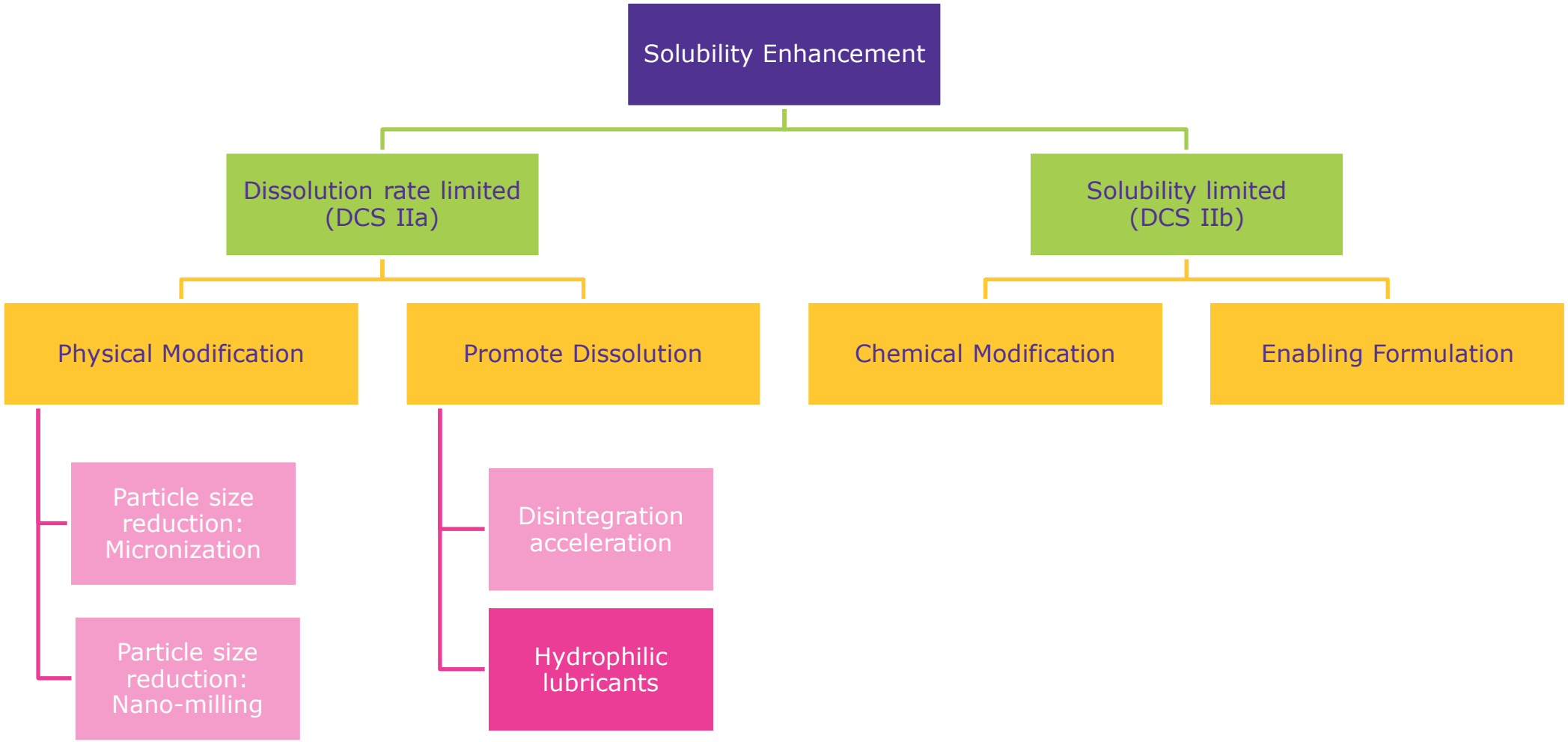
Disintegrant features

- Good hydration capacity
- Surface structure
- Compressibility
- Compatible with enabling technology

Fast disintegration

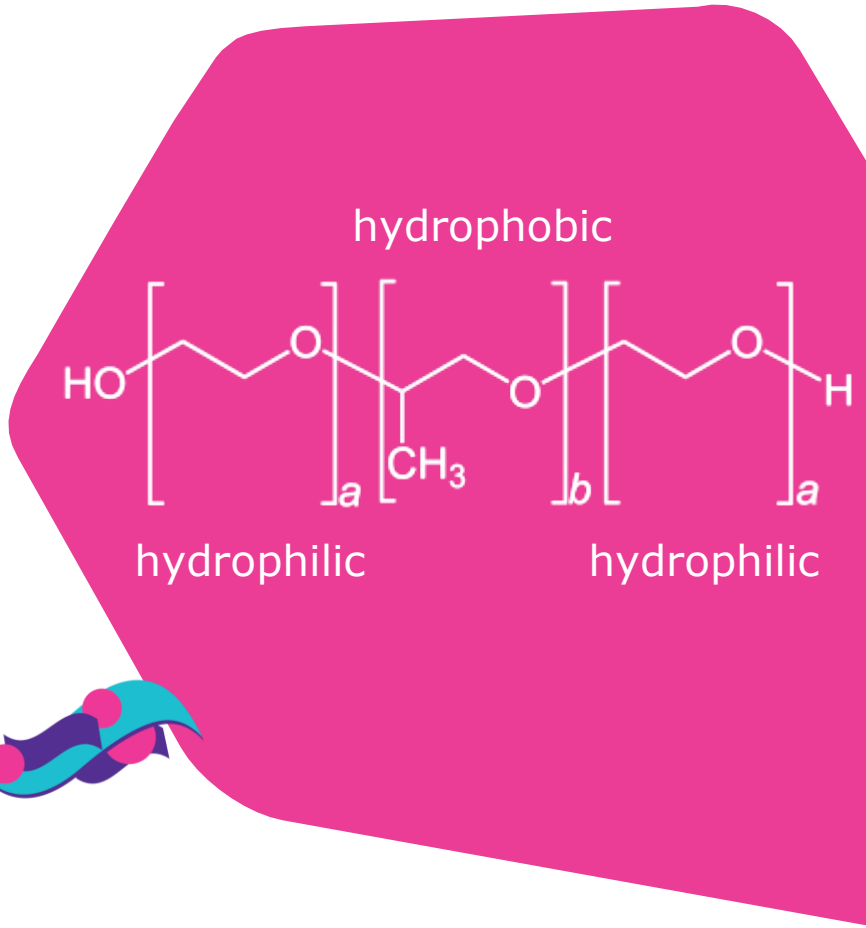


Strategies and Enabling Technologies for Enhancing API Solubility



Hydrophilic Lubricant – Dissolution enhancement
A multi-functional excipient

- **Poloxamer 188**, a block copolymer of poly(ethylene oxide) and poly(propylene oxide)
- Functional excipient for oral solid dosage forms acts as a **dissolution rate enhancer** via a surfactant like effect
- Additional functionality as a **hydrophilic lubricant**
- Compatible for: DC, continuous manufacturing and 3D printing



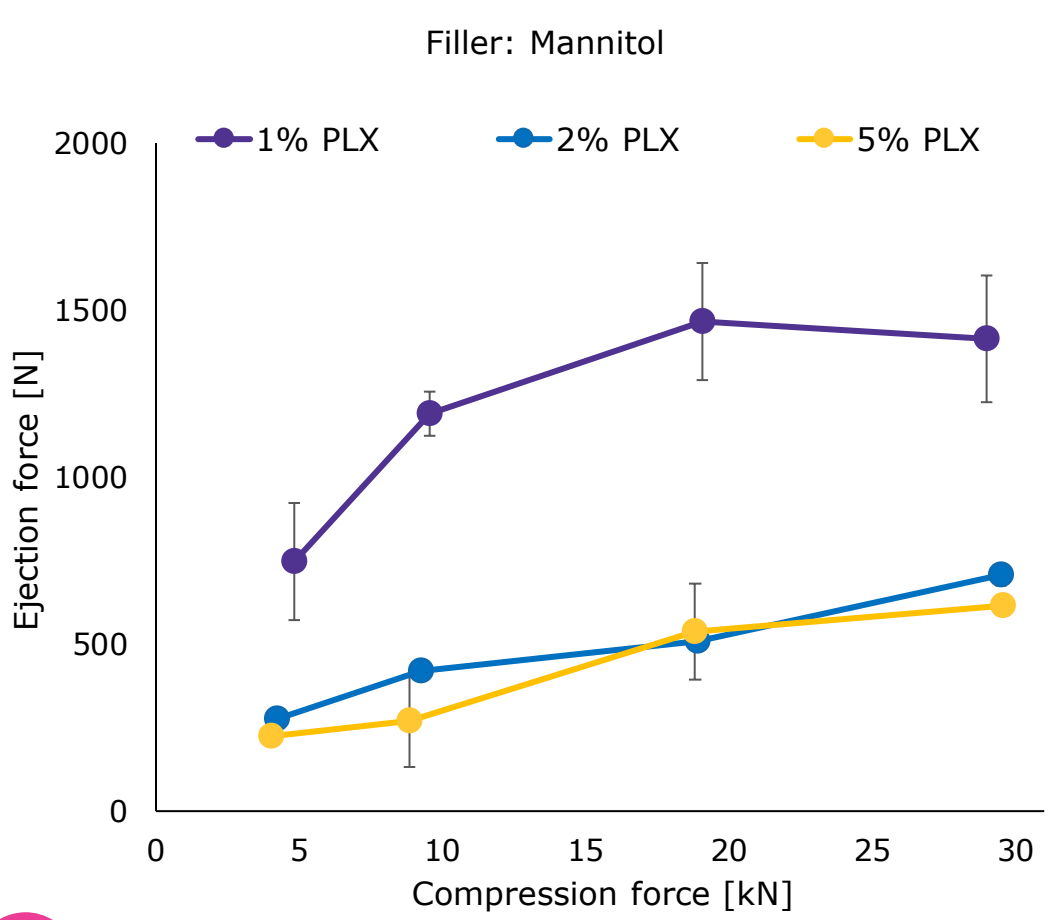
Parteck® PLX 188

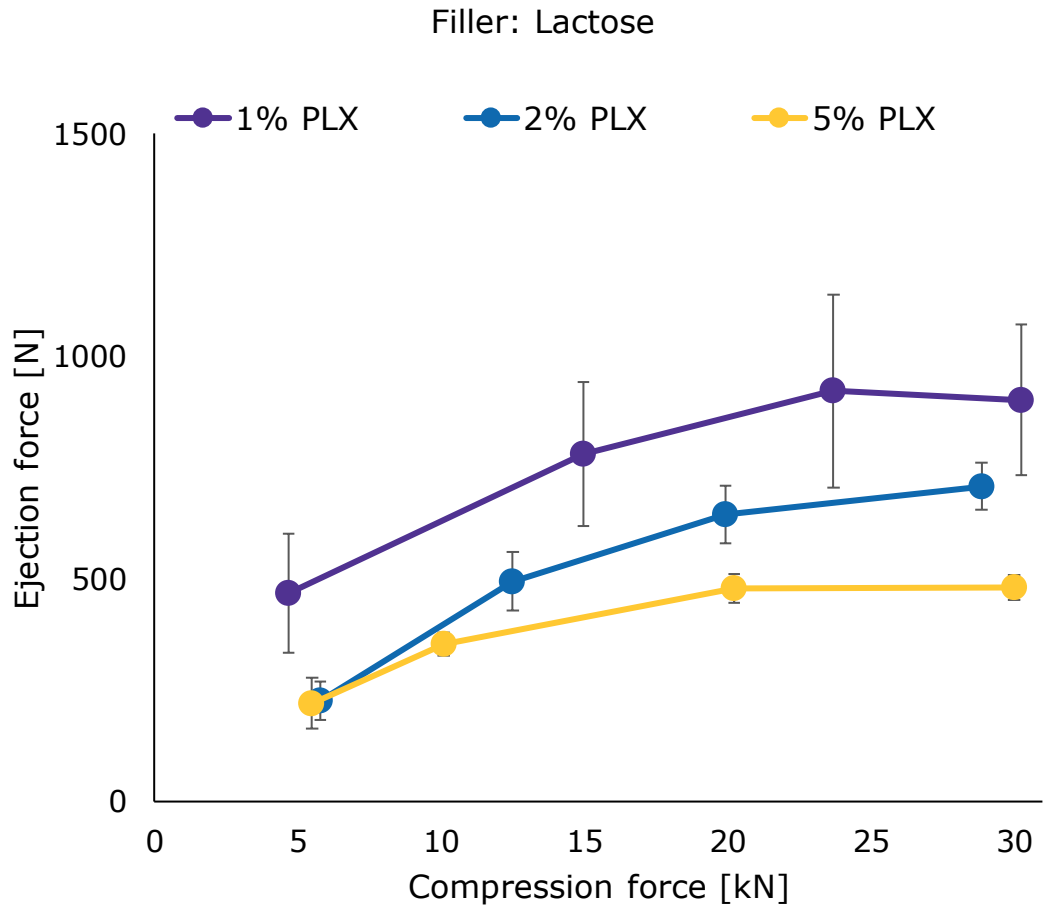
Dissolution enhancer	1 – 15 %
Lubricant	2 – 5 %

One excipient, multiple functionalities:
Improving process efficiency and unlock future manufacturing capabilities

Poloxamer 188 – Hydrophilic lubricant

Effective lubrication is achieved even when combined with brittle, deforming fillers

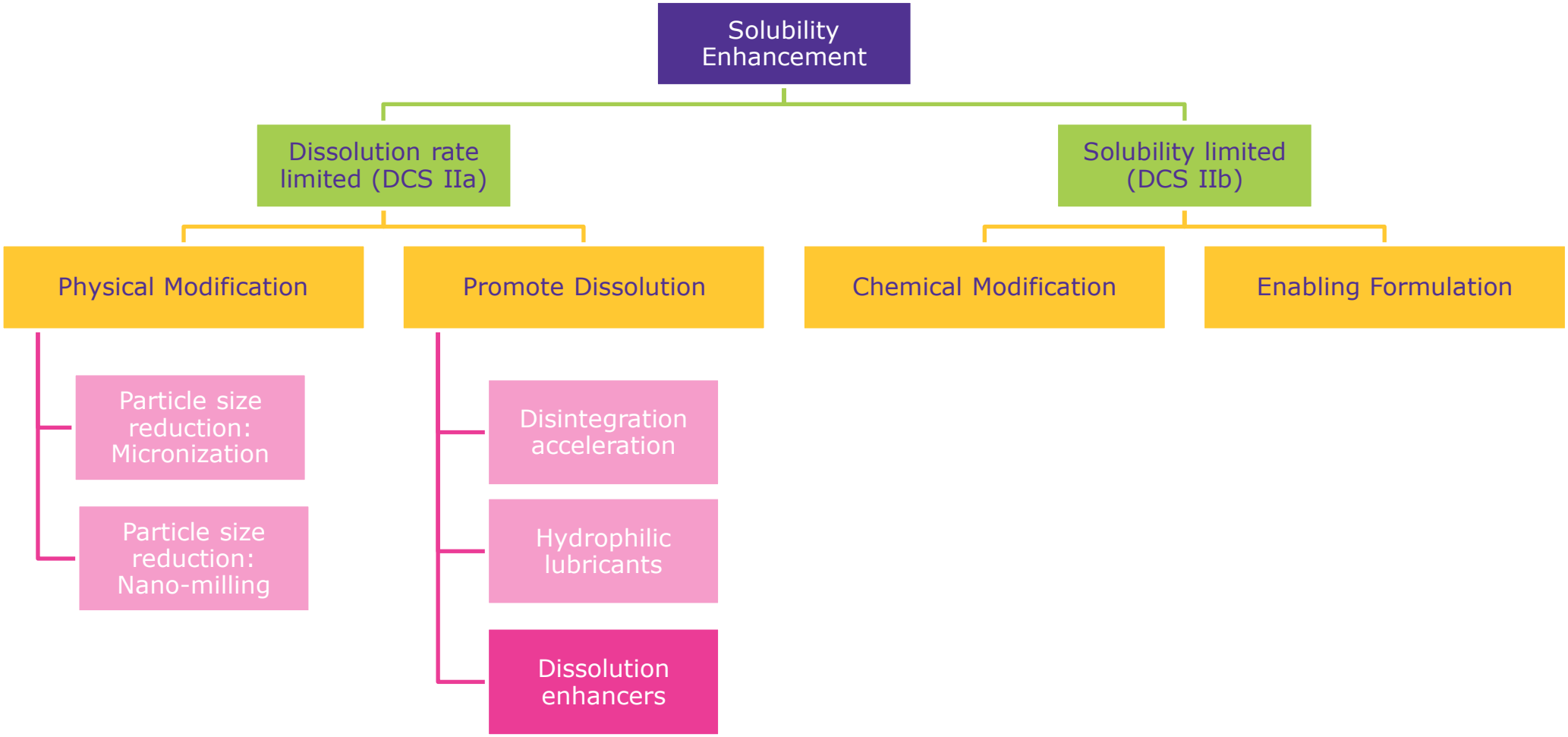




A minimum of 2% Poloxamer 188 is recommended for lubrication effect

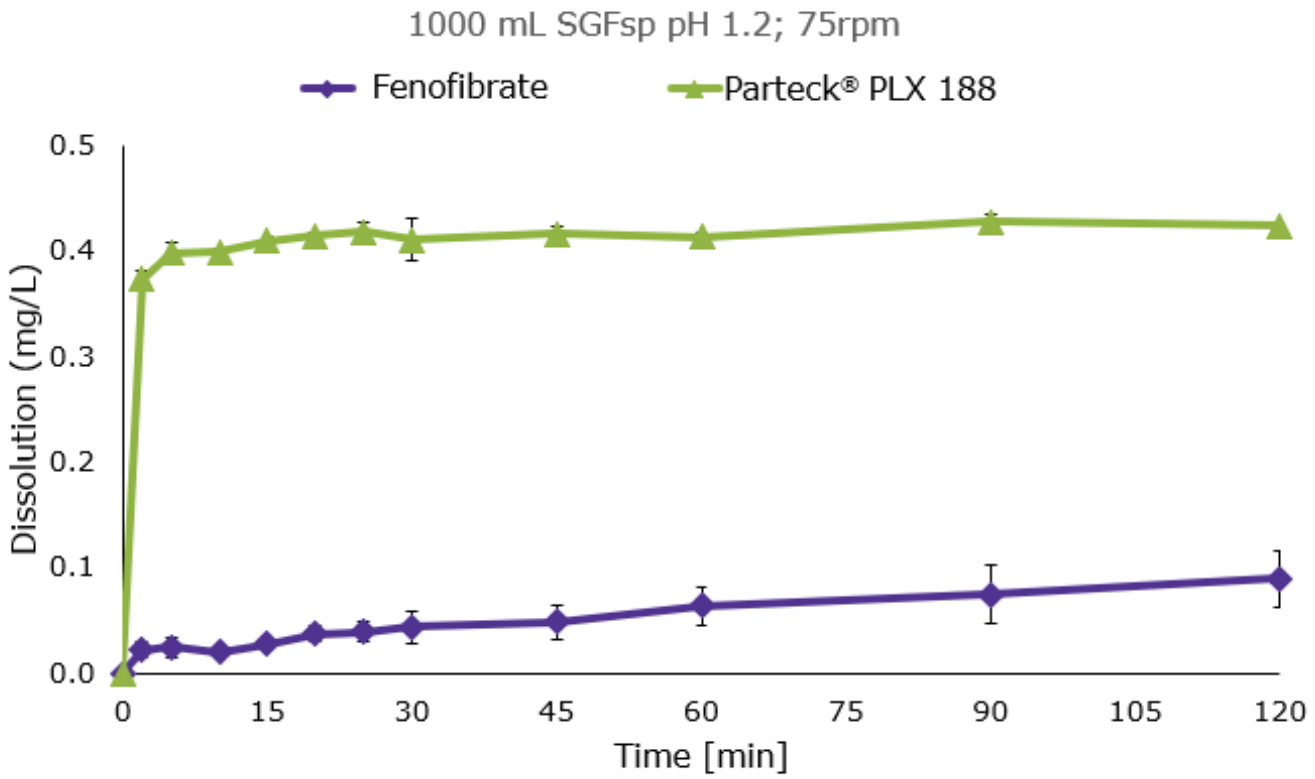
➔ **Perfect fit for direct compression**

Strategies and Enabling Technologies for Enhancing API Solubility



Poloxamer 188 – Dissolution enhancement

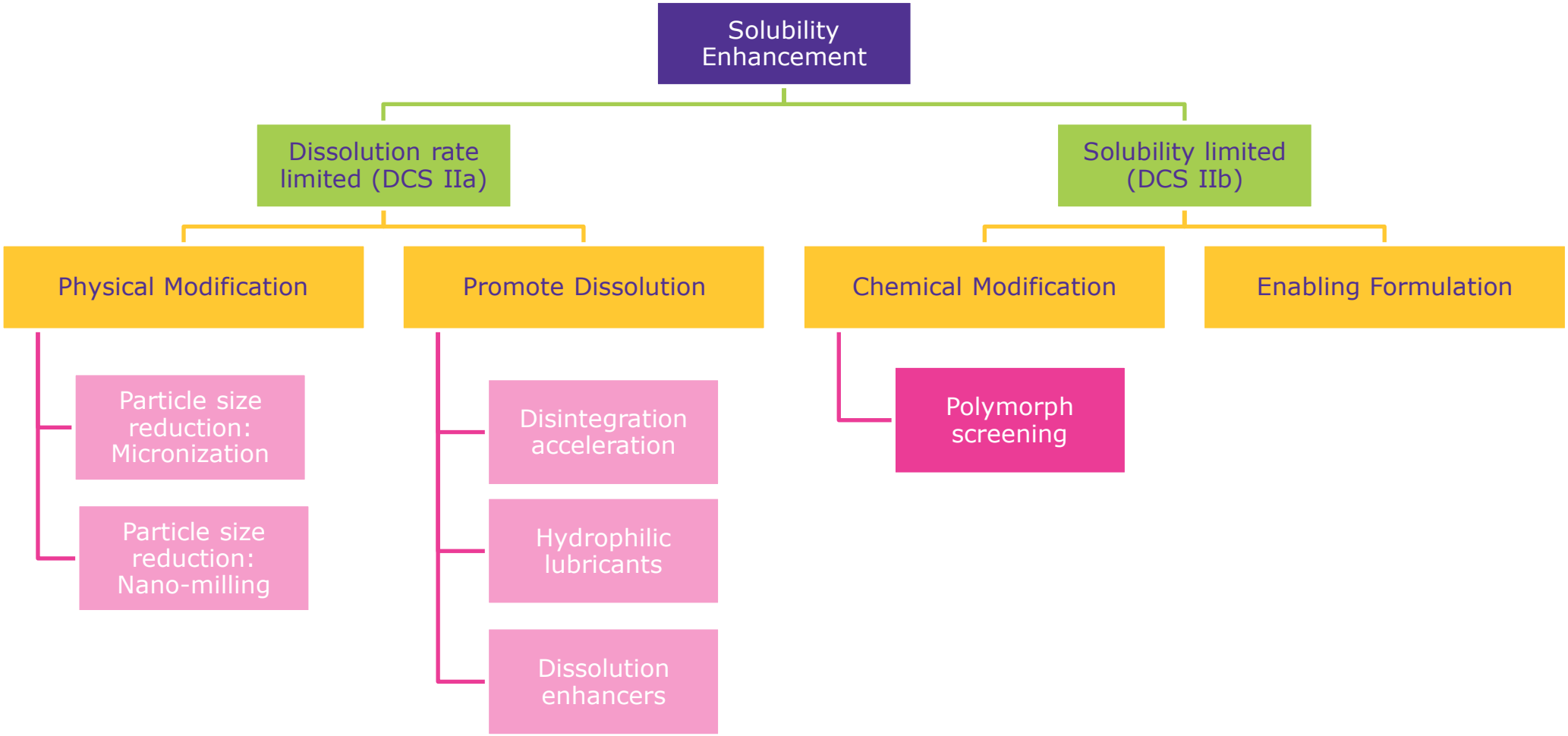
Dissolution is enhanced via increased wetting and micelle formation



Component	Content [%]
Parteck® PLX 188	**5**
Fenofibrate	**20**
Parteck® M 200	69
Crosscarmellose sodium (CCS)	5
Magnesium stearate	1

Adding Poloxamer 188 to the formulation is a fast and easy solution to enhance the dissolution rate

Strategies and Enabling Technologies for Enhancing API Solubility



Polymorph Screening

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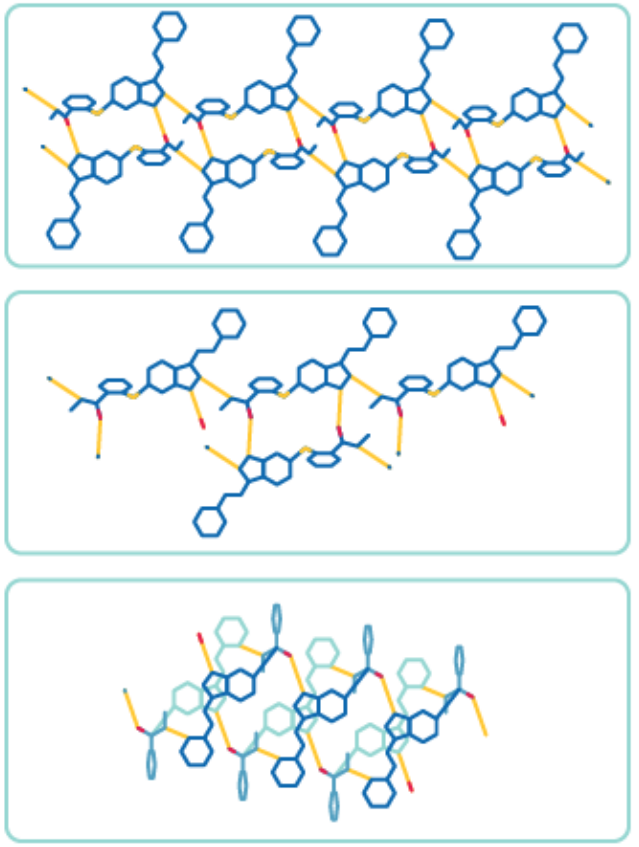
- **Polymorphism** means that drugs can have several crystalline forms – which is true for **>50 % of APIs**[1]
- Polymorph screening is **mandatory due to safety reasons**, e.g. regarding thermodynamic stability and toxicity (-> ICH Q6A)
- Polymorphs can be considerably different regarding[2]
  - Solubility
  - Biological activity
  - Melting Point
  - Dissolution rate
  - Pharmaco-dynamics
- Polymorphic forms are considered **different chemical entities**



...

[1] Development of a Targeted Polymorph Screening Approach for a Complex Polymorphic and Highly Solvating API, Campeta *et al*., 2010
[2] Polymorphism: The Phenomenon Affecting the Performance of Drugs, Raza *et al*., 2014

Polymorph Screening

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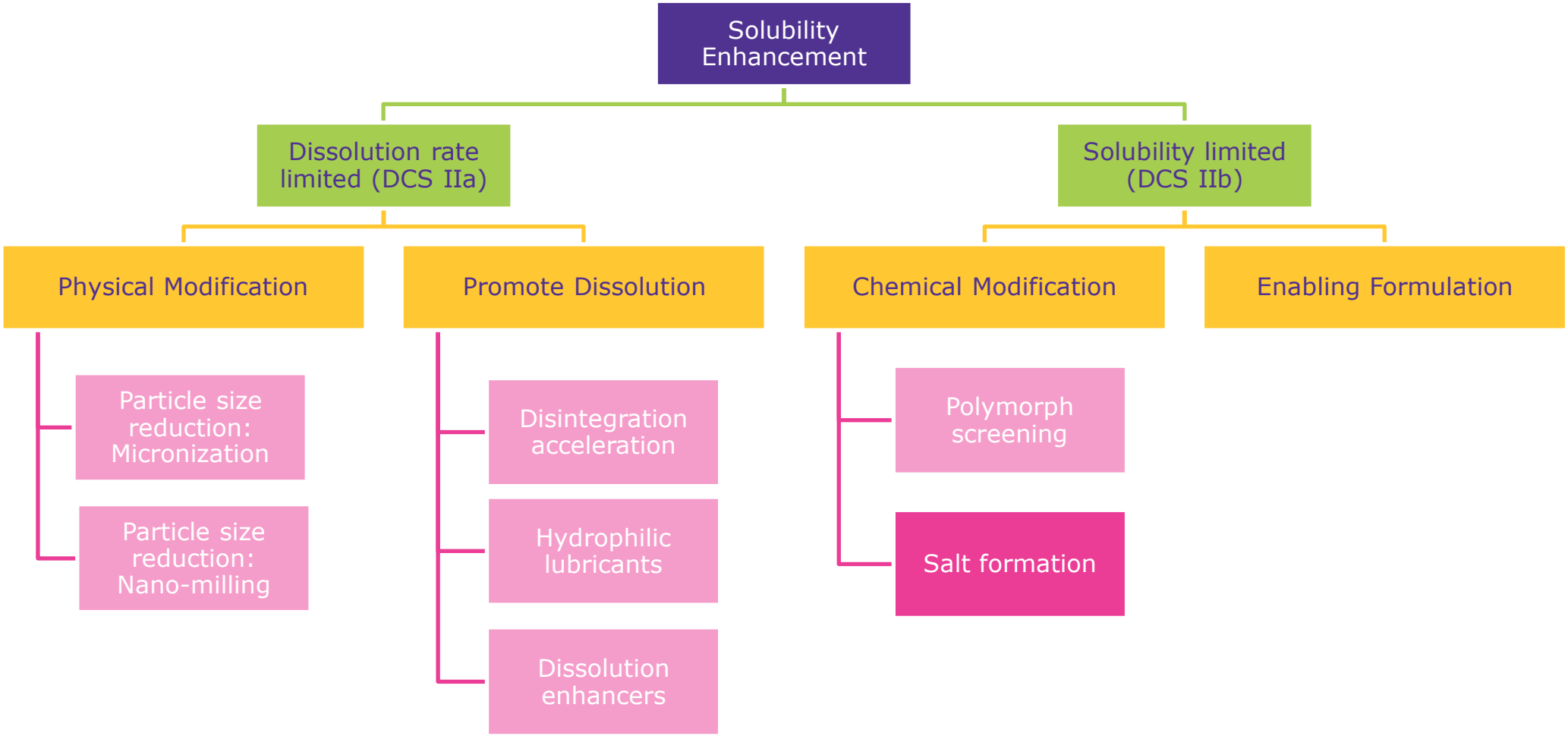
- API polymorphs are a **very important factor for IP protection**:
  - Innovators screen and identify as many polymorphs as possible and protect the related IP, thus **preventing generics entering the market**
  - Non-protected, viable polymorphic forms are **opportunities for generic companies** to enter markets earlier

- Diverse **solvents are broadly used** for polymorph screening, e.g.:

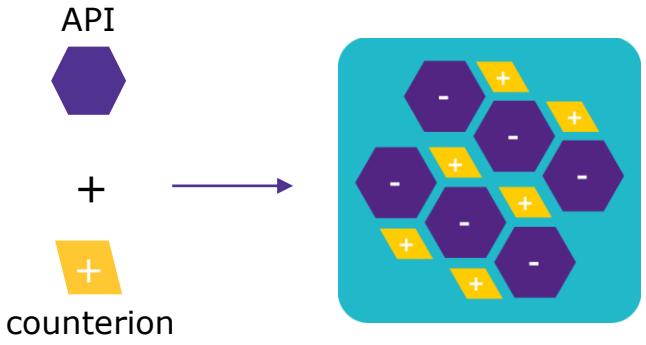
1-Butanol	Chloroform	Ethyl acetate
2-Propanol	Dichloromethane	Formic acid
Acetic acid (glacial)	Diethyl ether	Methanol
Acetone	Dimethyl Sulfoxide	Tetrahydrofuran
Acetonitrile	Ethanol absolute	

Strategies and Enabling Technologies for Enhancing API Solubility

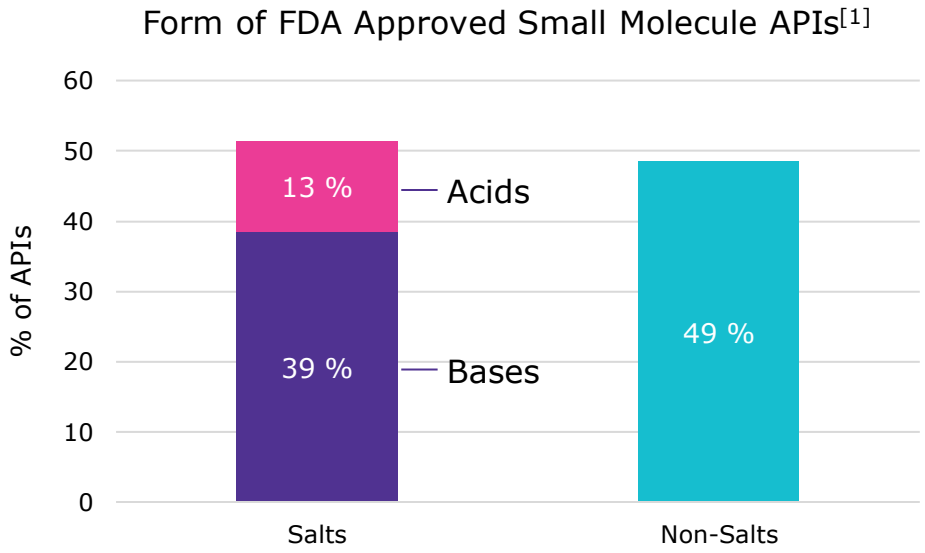


Salt Formation

- Salt formation is a **well-established** technique, employed for several decades
- Currently marketed drugs are **predominantly in salt form** (~50%), still with increasing trend
- **Principle:** API is ionized with the aid of a counterion (acid or base, typically H^+ transfer)



➔ **for ionizable drugs**



~ 50 %
of drug molecules are administered in salt form[1]

[1] Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database, Paulekuhn *et al.*, 2007

Salt Formation – Why Salts?

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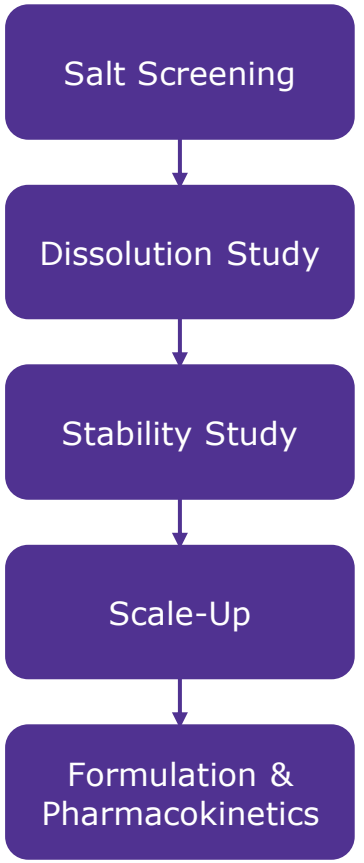
Opportunity: Optimizing solid state properties

- Enhanced bioavailability[1]
  - Solubility
  - Dissolution rate
- May also result in beneficial impact on:
  - API purity
  - Physical & chemical stability
  - Manufacturability
  - Particle size
  - Flowability

Typical Process Flow



Benefits of Salts

- Well established
- Simple & cost-effective
- High regulatory acceptance

Challenges

- API needs to be ionizable
- Common Ion Effect
- Disproportionation
- Hygroscopicity

[1] Use of pharmaceutical salts and cocrystals to address the issue of poor solubility, Holm *et al.*, 2013

Salt Formation – Examples

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Examples marketed drugs in salt form[1]:

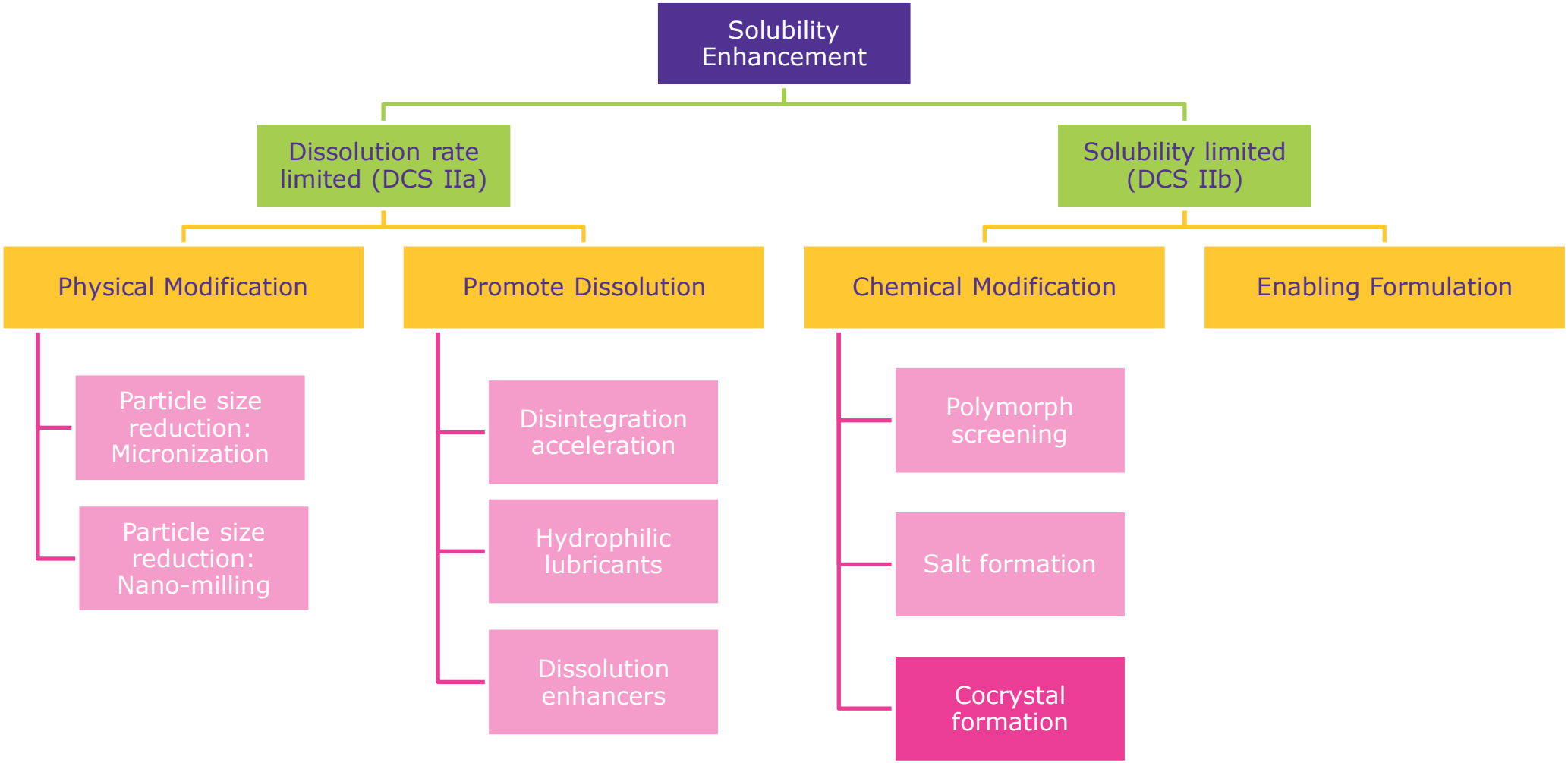
Product	API	Counterion	Company
Clindac (antibiotic)	Clindamycin	Phosphate	Sandoz
Baytril (antibiotic)	Enrofloxacin	Mesylate	Bayer
Trimeton (antihistaminic)	Chlorpheniramine	Maleate	MSD
Escitalopram (antidepressant)	Escitalopram	Oxalate	Hexal
Gastrografin (contrast agent)	Diatrizoate	Meglumine	Bayer
Ketorol (anti-inflammatory)	Ketorolac	Thromethamine	Dr. Reddy`s

Common salt former / counterions:

Acetic acid	Citric acid	Imidazole	Salicylic acid
Adipic acid	Formic acid	Lactic acid	Sorbic acid
Benzenesulfonic acid	Fumaric acid	Maleic acid	Succinic acid
Benzoic acid	L-Glutamine	Malic acid	Sulforic acid
Boric acid	Hydrochloric acid	Ortho-Phosphoric acid	Tartaric acid

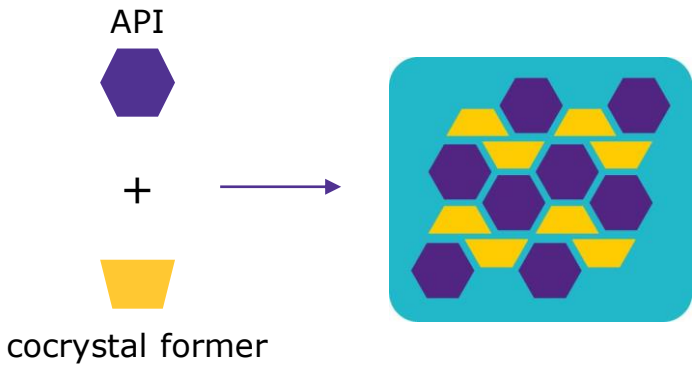
[1] Pharmaceutical salts: A summary on doses of salt formers from the Orange Book, Saal & Becker, 2013; [2] Internal Evaluation

Strategies and Enabling Technologies for Enhancing API Solubility

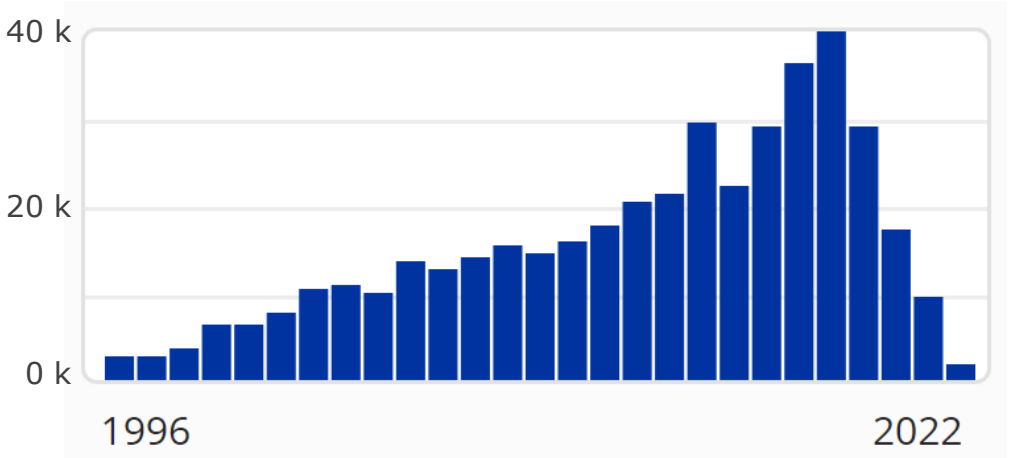


Cocrystal Formation

- Pharmaceutical cocrystal formation is a **relatively new approach**
- **Alternative for non-ionizable compounds**, as nearly all kinds of APIs can form cocrystals
- **Principle:** API and co-former interact by certain forces and build one joint crystal lattice



➔ **for non-ionizable drugs**



Reference hits for "co-crystals" in Formulus database search (patents applications) per year (2018: 39 k; date 10/22).

Marketed API cocrystals are still rare (<10) but increasing[1]

[1] Recent Advances in Pharmaceutical Cocrystals: From Bench to Market, Bandaru *et al.*, 2021

Cocrystal Formation – Why Cocrystals?

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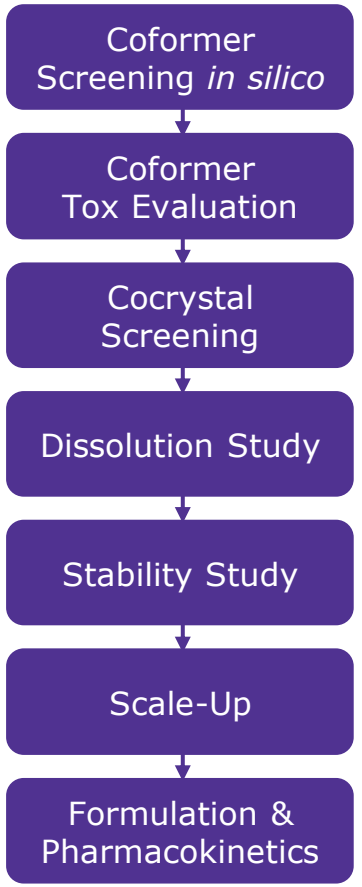
Opportunity: Optimizing solid state properties

- Enhanced bioavailability[1,2]
  - Solubility
  - Dissolution rate
- May also result in beneficial impact on:
  - API purity
  - Physical & chemical stability
  - Manufacturability
  - Particle size
  - Flowability

Typical Process Flow



Benefits of Cocrystals

- Alternative if non-ionizable
- No common ion effect
- No disproportionation effects
- Less prone to hygroscopicity

Challenges

- Coformer selection
- Crystallization process control
- Regulatory acceptance

[1] N. R. Hornedo, S. J. Nehm, A. Jayasankar in Encyclopedia of Pharmaceutical Technology, Third Edition, Informa Healthcare, 2006, pp. 615–635.
[2] N. Upadhyay, T. P. Shukla, A. Mathur, J. S. K. Manmohan, Pharmaceutical Sciences Review and Research 2011, 8, 144–148.

Cocrystal Formation – Examples

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Examples marketed cocrystal drugs[1]:

Product	API : Coformer	Company
Suglat®	Ipragliflozin : L-Prolin	Astellas / MSD
Entresto®	Valsartan : Sacubitril	Novartis
Steglatro®	Ertugliflozin : Z-Pyroglutamic acid	MSD
Depakote®	Valproic acid : Valproate sodium	Abbott
Beta chlor®	Chloral hydrate : Betaine	Mead Johnson

Common cocrystal former:

2,4-dihydroxybenzoic acid	Nicotinamide	L-proline
3,4-dihydroxybenzoic acid	Tert-butyl hydroquinone	Maltol
Tartaric acid	Resorcinol	Oxalic acid
Citric acid	Orotic acid	Urea
Fumaric acid	Sorbic acid	Glycerol
Phloroglucinol	L-tyrosine	Sulfamic acid

Diverse techniques exist for cocrystal formation:

- Slurrying
- Grinding (solvent-assisted)
- Solvent evaporation
- Sublimation
- Hot melt extrusion (DSC screening)

Computational co-former screening is a promising approach to save time and resources

[1] Recent Advances in Pharmaceutical Cocrystals: From Bench to Market, Bandaru et al., 2021; [2] Internal Evaluation

Cocrystal Formation – Regulatory Implications

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EMA – Reflection on Cocrystals[1]

"[…] There is no strict borderline between the salt formation in the one end with complete proton transfer and cocrystals formation in the other end with no proton transfer. […] Cocrystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied."

FDA – Guidance on Cocrystals for Industry[2]

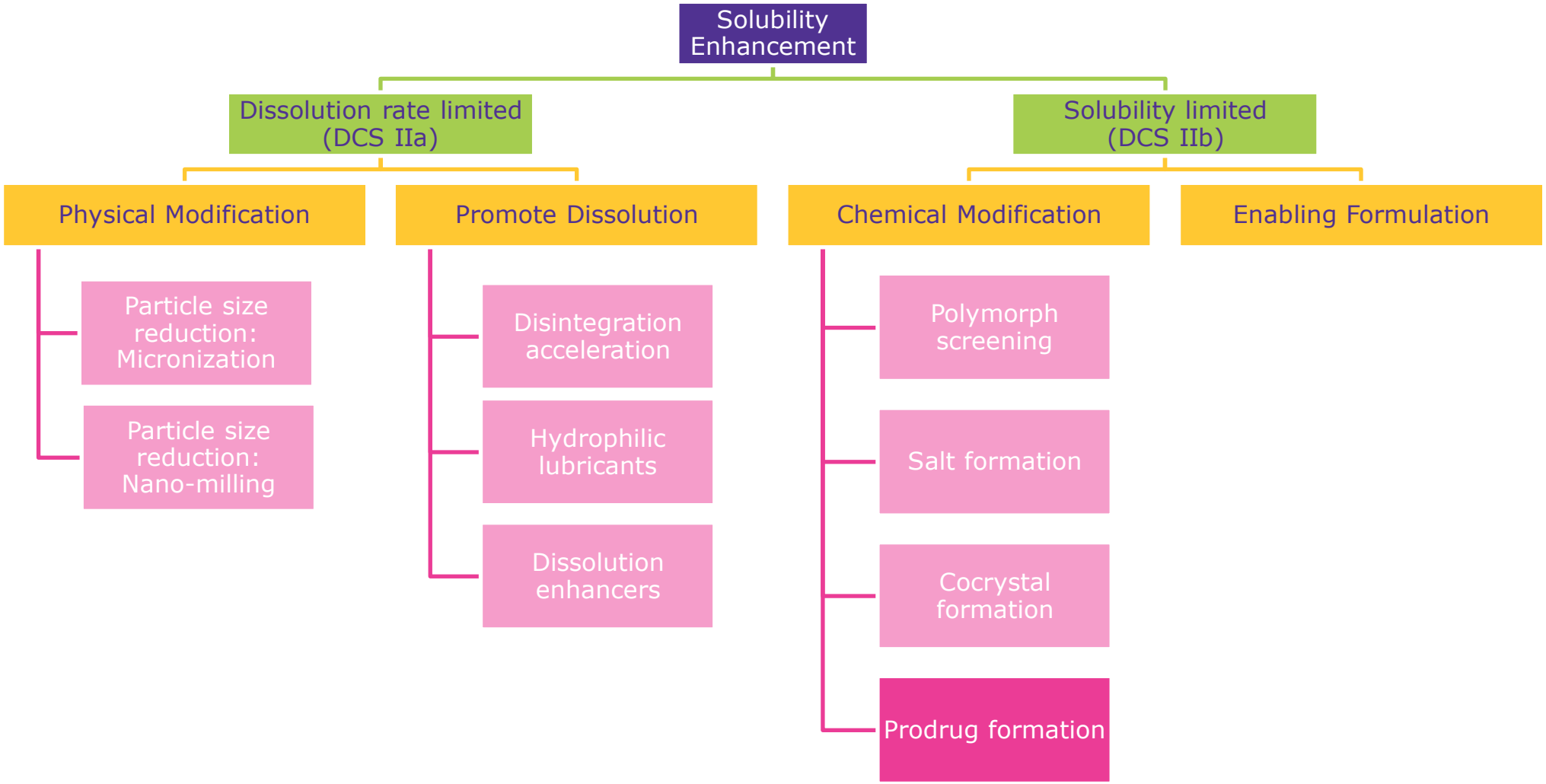
"[…] Co-crystals are distinguished from salts because unlike salts, the components that co-exist in the co-crystal lattice with a defined stoichiometry interact nonionically. […] A co-crystal with a pharmaceutically acceptable coformer […] can be considered to be a pharmaceutical cocrystal and has a regulatory classification similar to that of a polymorph of the API. Specifically, it is not regarded as a new API."

Regulatory Implications of Cocrystals

- Reflections on cocrystals (still) strongly differ between FDA and EMA
- Both FDA and EMA provide little guidance regarding co-former

[1] Reflection paper on the use of cocrystals of active substances in medicinal products, EMA, 2015
[2] Regulatory Classification of Pharmaceutical Co-Crystals – Guidance for Industry, FDA, 2018

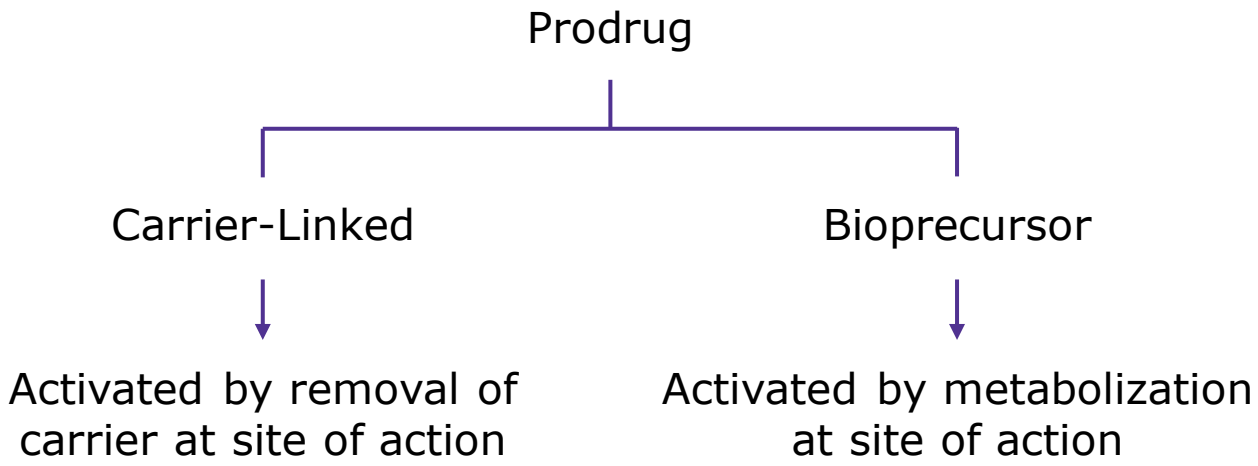
Strategies and Enabling Technologies for Enhancing API Solubility



Prodrug Formation

- **Prodrugs** are molecularly modified APIs with improved physicochemical characteristics
- They have no or **low activity until converted** to the active parent drug ***in vivo***
- Often regarded as "strategy of last resort", but offers **various opportunities**[1]

Approx. 10 % of all marketed drugs are prodrugs – with increasing trend[2]



Objectives of prodrug approach:

- Improved solubility
- Targeted release
- Improved membrane permeability
- Reduced side effects

[1] The Prodrug Approach: A Successful Tool for Improving Drug Solubility, FDA, 2015
[2] The expanding role of prodrugs in contemporary drug design and development, Rautio *et al.*, 2018

Prodrug Formation

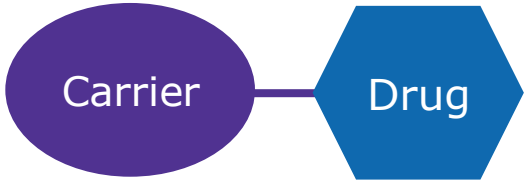
SAFC®

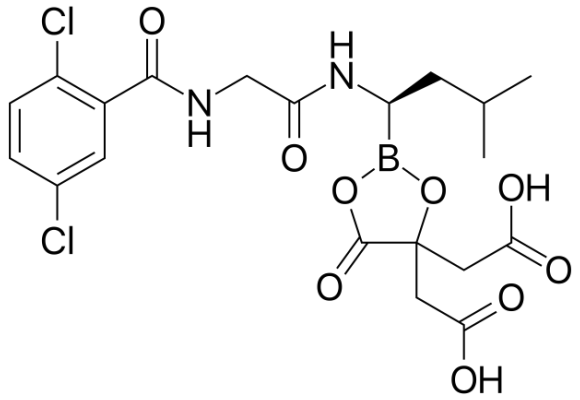
Carrier-Linked Prodrugs

- Common carriers are e.g.: Polymers (e.g. PEGs), proteins, antibodies
- Linkage of carrier to drug possible by diverse covalent binding types, e.g.: ester, amide, carbamate, carbonate, ether, imine, phosphate etc.

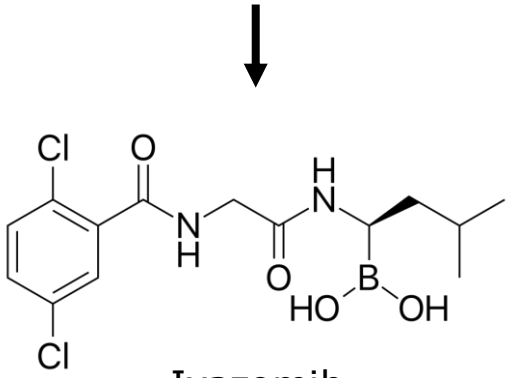
Example: Ixazomib (Takeda, approval 2015[2])

- Indication: Multiple myeloma, reversible proteasome inhibitor
- Prodrug hydrolyzes under physiological conditions to active form





Ixazomib Citrate (Prodrug)



Ixazomib

[1] Prodrug approach: An overview of recent cases, Abet *et al.*, 2017
[2] The expanding role of prodrugs in contemporary drug design and development, Rautio et al., 2018

Prodrug Formation

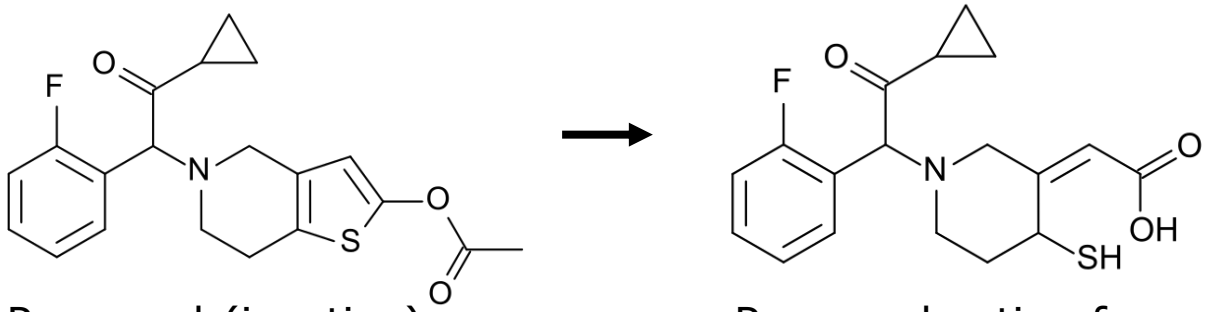
SAFC®

Bioprecursors

- No carrier or linker, precursor acts as substrate to enzymatic activation[1]
- Activation by diverse chemical modification spossible, e.g. reductive or oxidative activation, phosphorylation, decarboxylation, etc.

Example: Prasugrel (Daiichi Sankyo, Eli Lilly, approval 2009[2])

- Indication: Thrombotic and cardiovascular events



Prasugrel (inactive) → Prasugrel active form

Benefits of Prodrugs

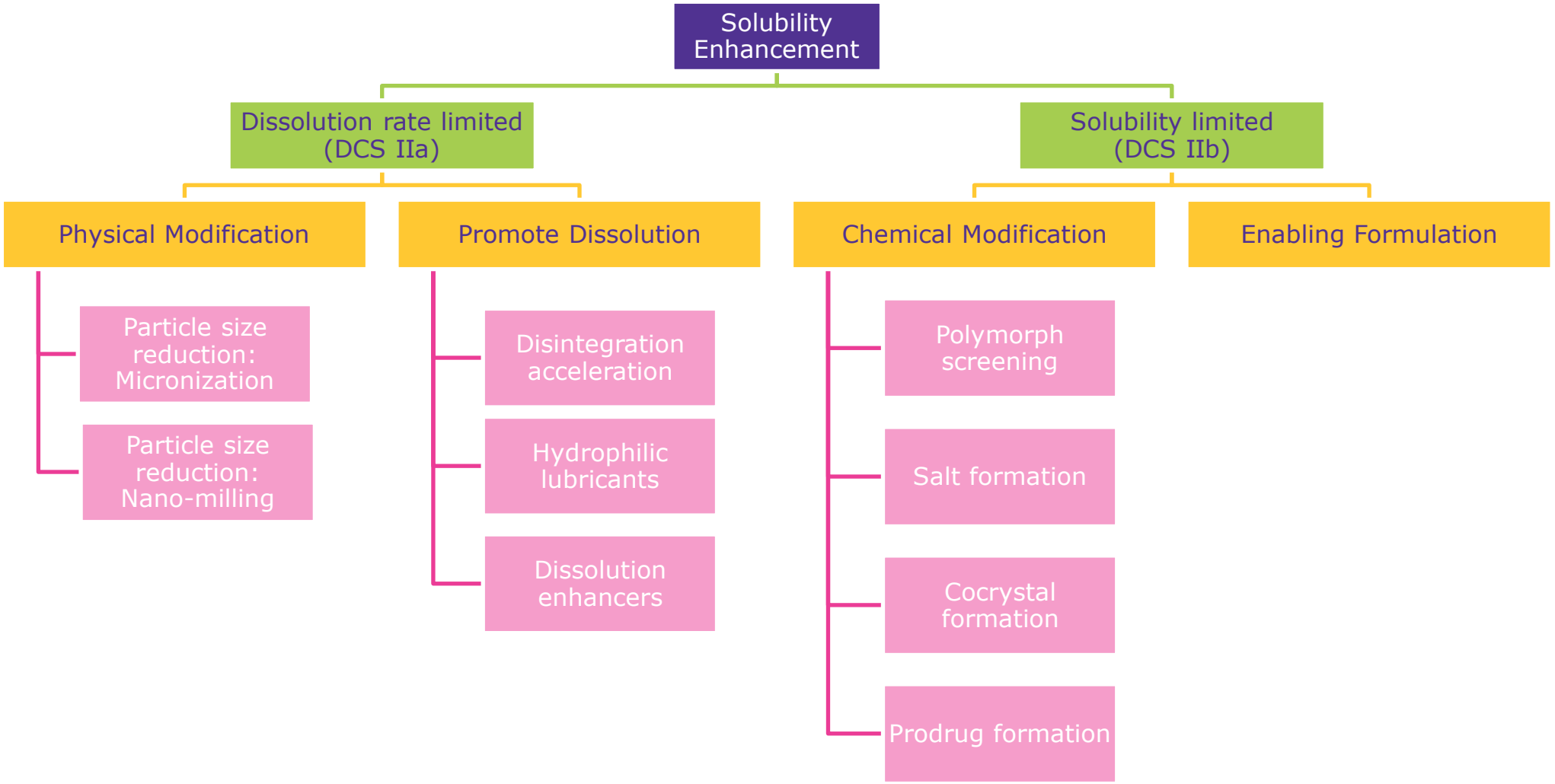
- Versatile approach
- Can improve several properties
- Alternative if other strategies are not feasible

Challenges

- Demanding development
- Cleaved groups must be safe

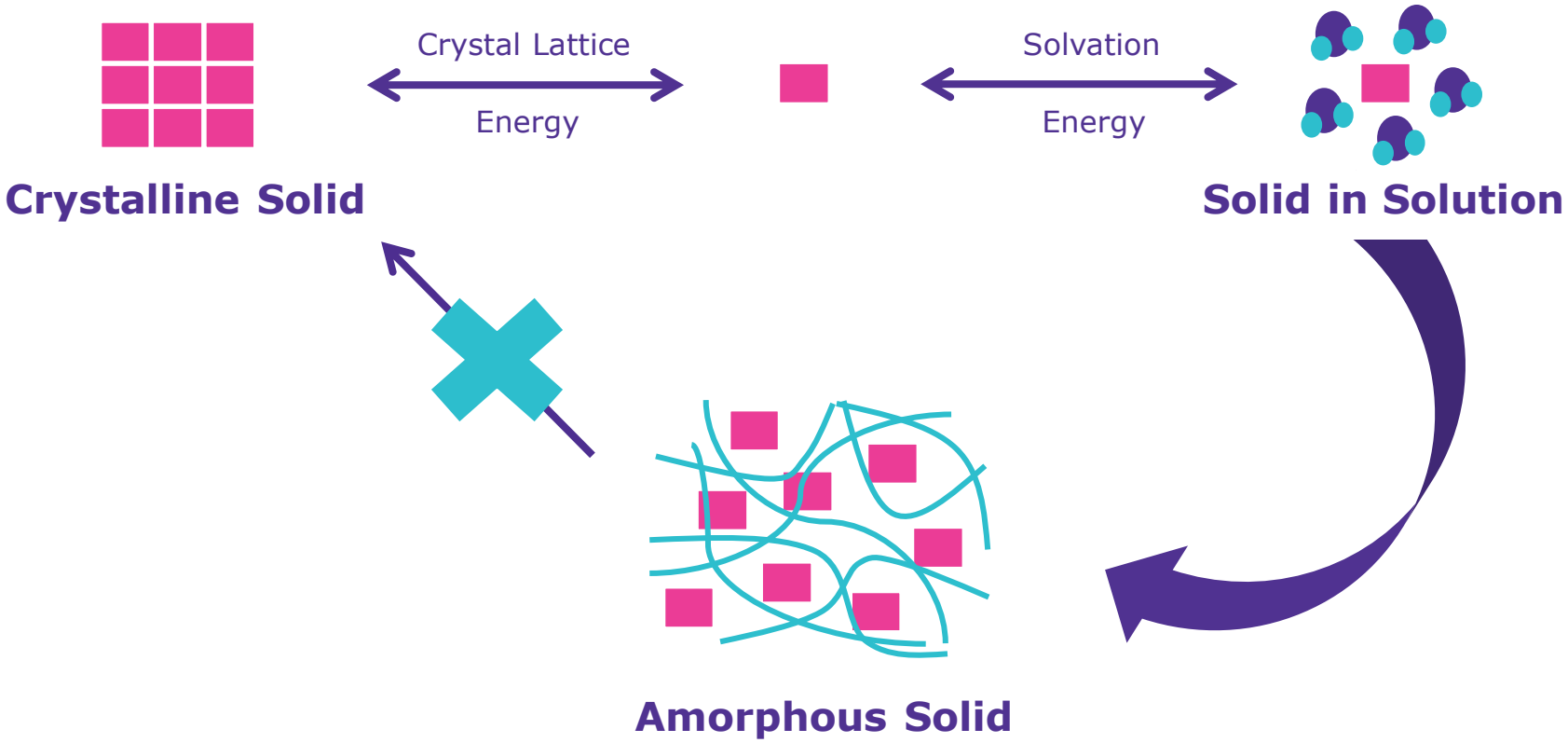
[1] Prodrug approach: An overview of recent cases, Abet *et al.*, 2017
[2] Pharmacokinetics and pharmacodynamics of prasugrel, a thienopyridine P2Y12 inhibitor, Dobesh, 2009

Strategies and Enabling Technologies for Enhancing API Solubility



Solid dispersion technologies - Solid state modification

Solubility of DCS IIb molecules can be enhanced via the amorphous form



The amorphous solid-state can be leveraged to enhance solubility of DCS IIb

Amorphous solid dispersions

The most common amorphous formulation have a polymeric matrix

SAFC®

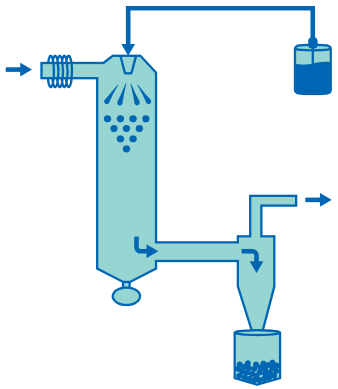
API

Polymer

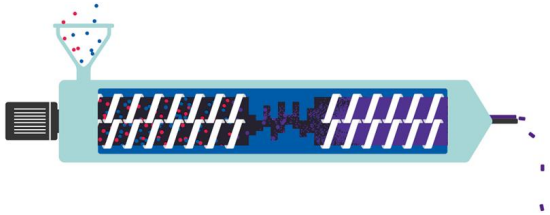
Dissolve

Mix & melt

spray drying

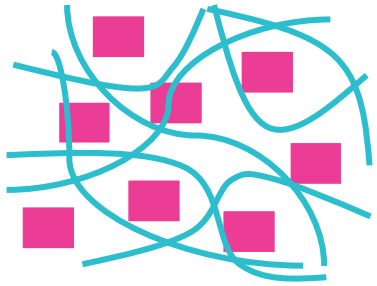


Melt extrusion



Spray dried dispersion (SDD)

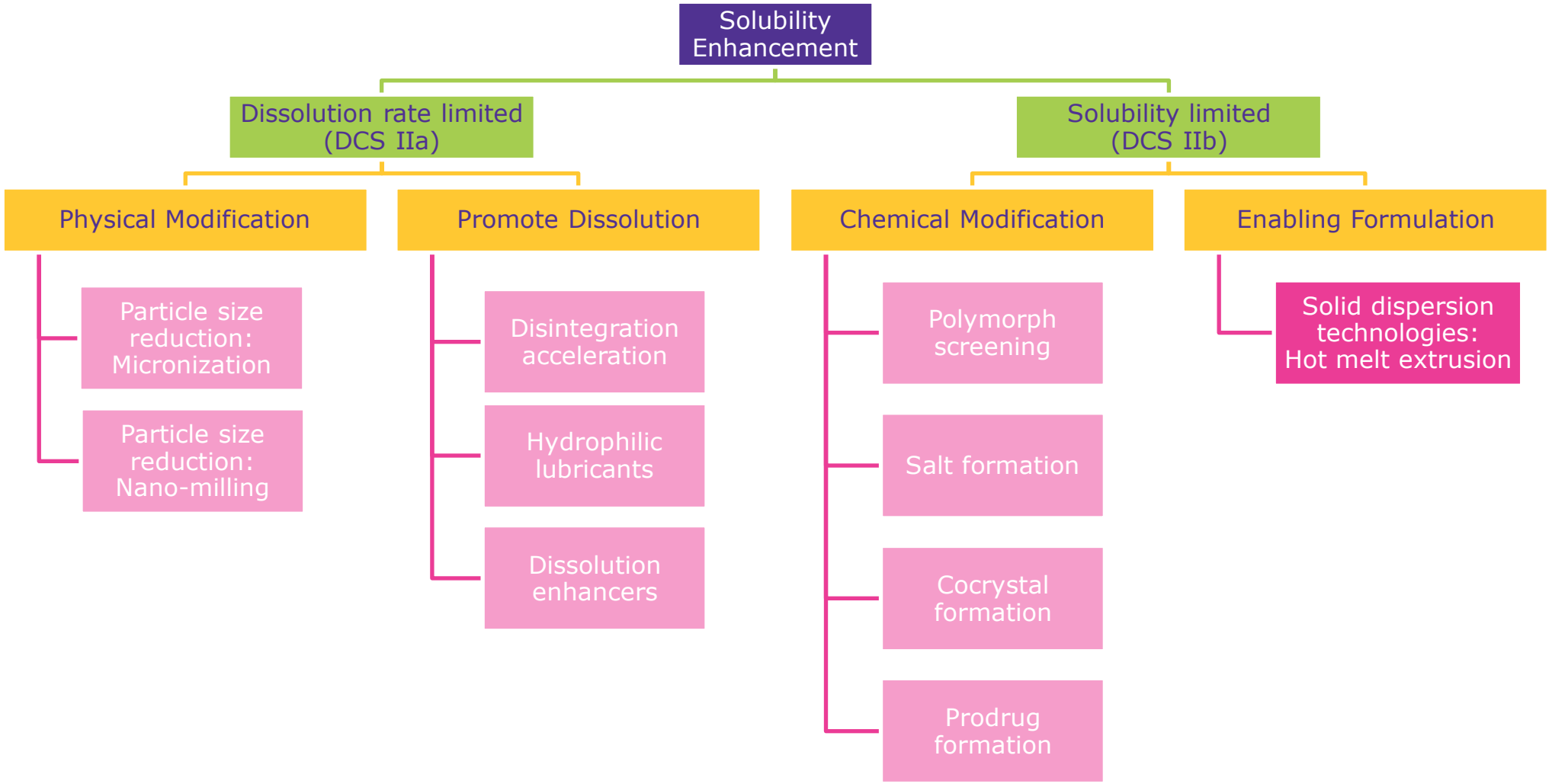
Hot Melt Extrusion (HME)



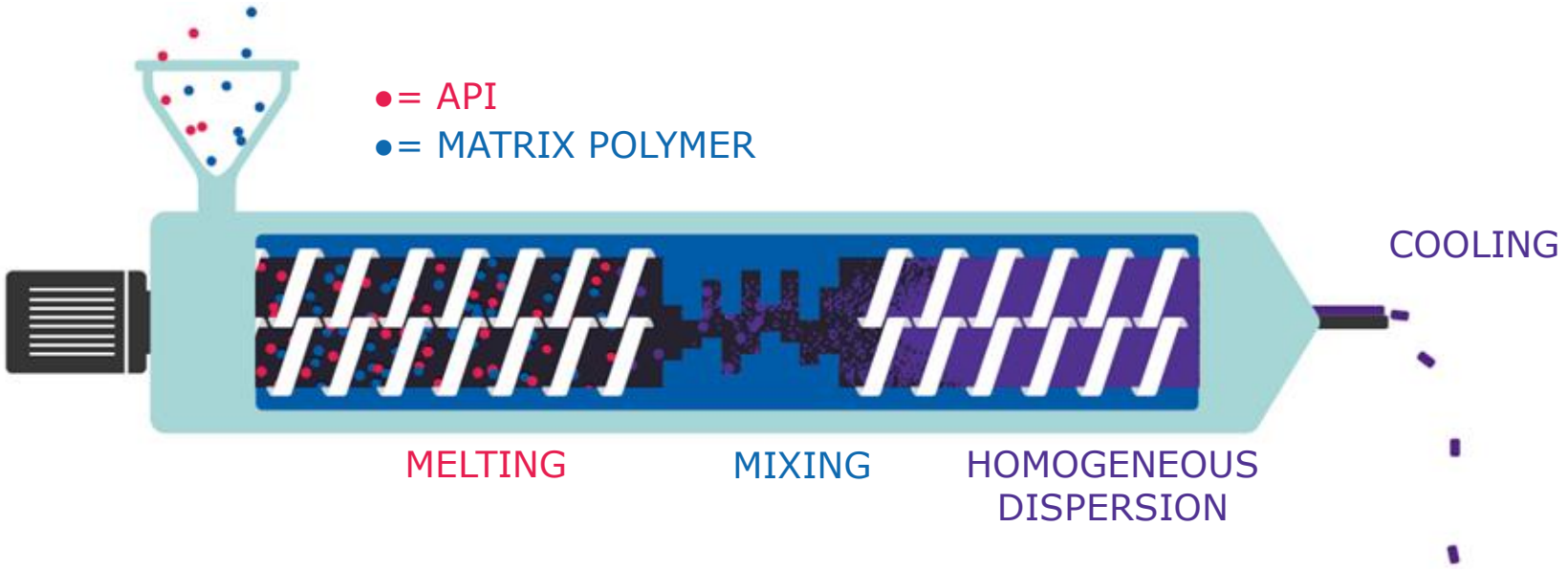
Amorphous solid dispersion (ASD)

Goal is a homogenous dispersion of drug and polymer

Strategies and Enabling Technologies for Enhancing API Solubility



Amorphous solid dispersions
Advantages of the HME process



MIX. MELT. PERFORM.

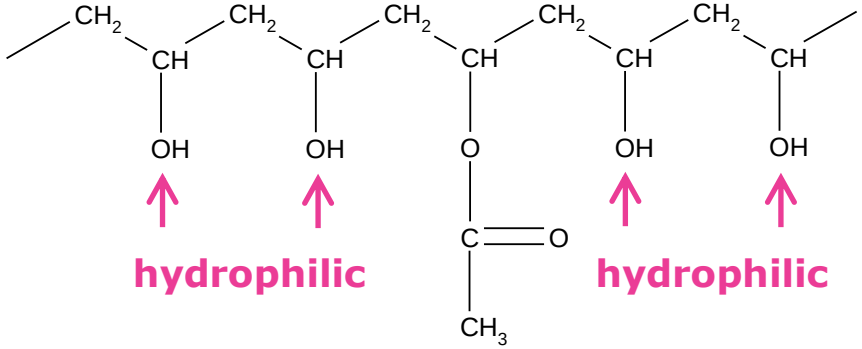
Advantages of HME

- Enhanced solubility & bioavailability
- Stable, high drug loading
- Controlled release
- Continuous effective process
- Solvent-free manufacturing
- Support of various dosage forms

Amorphous solid dispersions
Which polymers are suitable for the HME process

- Multiple Polymers can be used for HME
  - Natural origin
  - Synthetic
- Polyvinyl alcohol (PVA) suitable for HME
  - PVA Amphiphilic nature
  - PVA Stable high drug loads
  - PVA Optimized hydrolysis grade
  - PVA Flexible downstream processability
  - PVA Various options to modify release profile

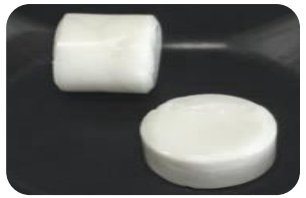
Polyvinyl alcohol



PVA 4-88 / 3-82

PVA for Hot Melt Extrusion – Downstream flexibility

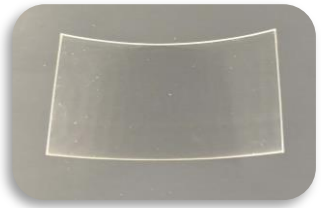
Excellent downstream processability



Direct shaping Tablet

Tablet

Milling



Film extrusion

Hot Melt Extrusion

Pelletizing

*Drug loaded

Capsule

3D Printing

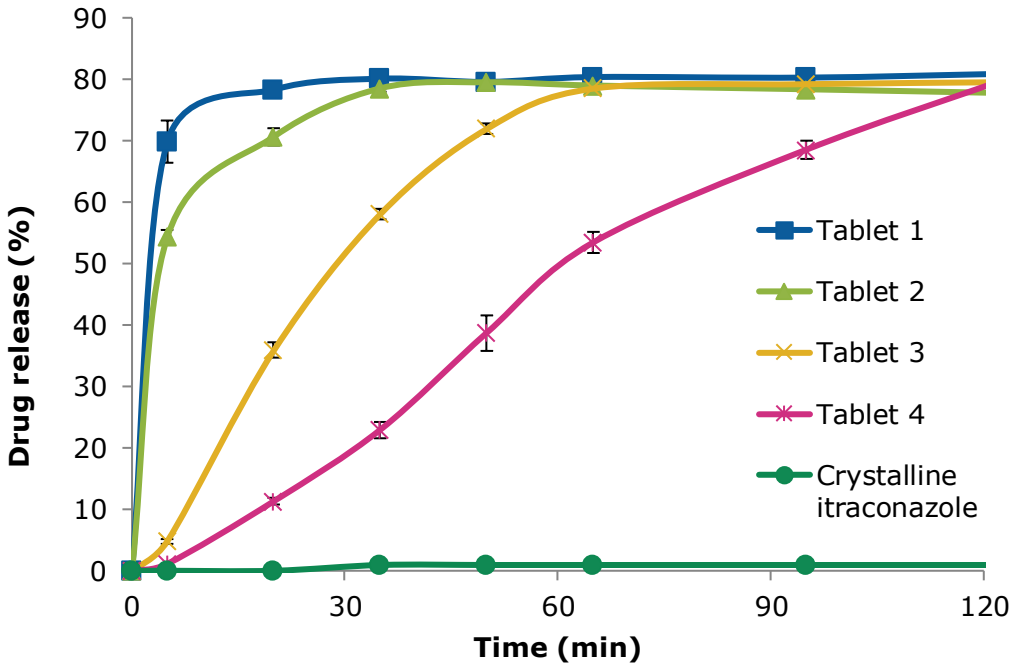
3D Printing Reagents

Versatile polymer extrudates can be processed into various dosage forms

PVA for Hot Melt Extrusion – Release profile

Addition of other excipients allow flexible release profiles

	Tablet 1	Tablet 2	Tablet 3	Tablet 4
Extrudate (%)	50	50	50	60
Microcrystalline cellulose (%)	10	10	10	10
K_2CO_3 (%)	-	-	14.75	10
NaCl (%)	14.75	14.75	-	-
Magnesium stearate (%)	0.5	0.5	0.5	0.5
Lactose (%)	16.25	16.25	16.25	11
Silica (%)	1	1	1	1
Crospovidone (%)	7.5	7.5	7.5	7.5
Compressed force (kN)	15	10	10	10
T_{max} (min)	15	30	60	120



Dissolution of compressed tablets based on milled itraconazole:PVA (FDA-recommended conditions for itraconazole, 900 mL SGF, 37 °C, 100 rpm, formulated extrudate with 30 % drug load; n=3)

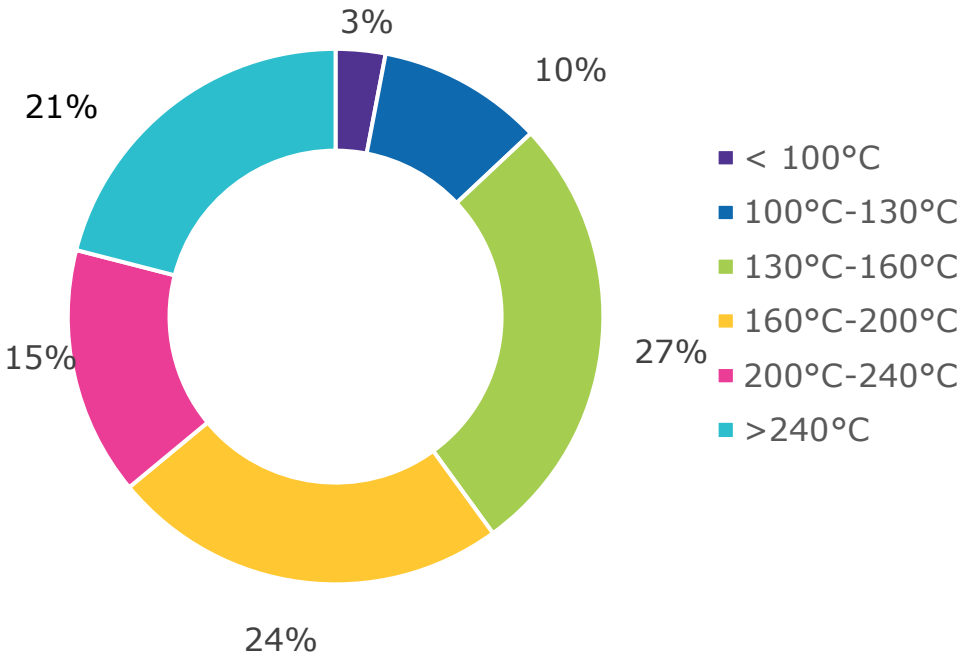
Single polymer, single extrudate, many options to modify dissolution kinetics

PVA for Hot Melt Extrusion – Hydrolysis optimization (PVA 4-88)

Parteck® MXP 4-88: Thermo-stabile polymer for high melting point APIs

API BCS II&IV	T_m of API	Loading Capacity	Solubility Enhancement (max.)
Ibuprofen*	78 °C	> 30 %	2 x
Cinnarizine	118-122 °C	< 20 %	10 x
Indomethacin	151 °C	> 50 %	3 x
Ketoconazole	146 °C	> 35 %	17 x
Naproxen	152 °C	> 30 %	4 x
Atorvastatin	159-160 °C	> 55 %	154 x
Itraconazole	167 °C	> 30 %	80 x
Carbamazepine	204 °C	> 30 %	2 x
Telmisartan*	260 °C	> 15 %	35 x

*Plasticizer required

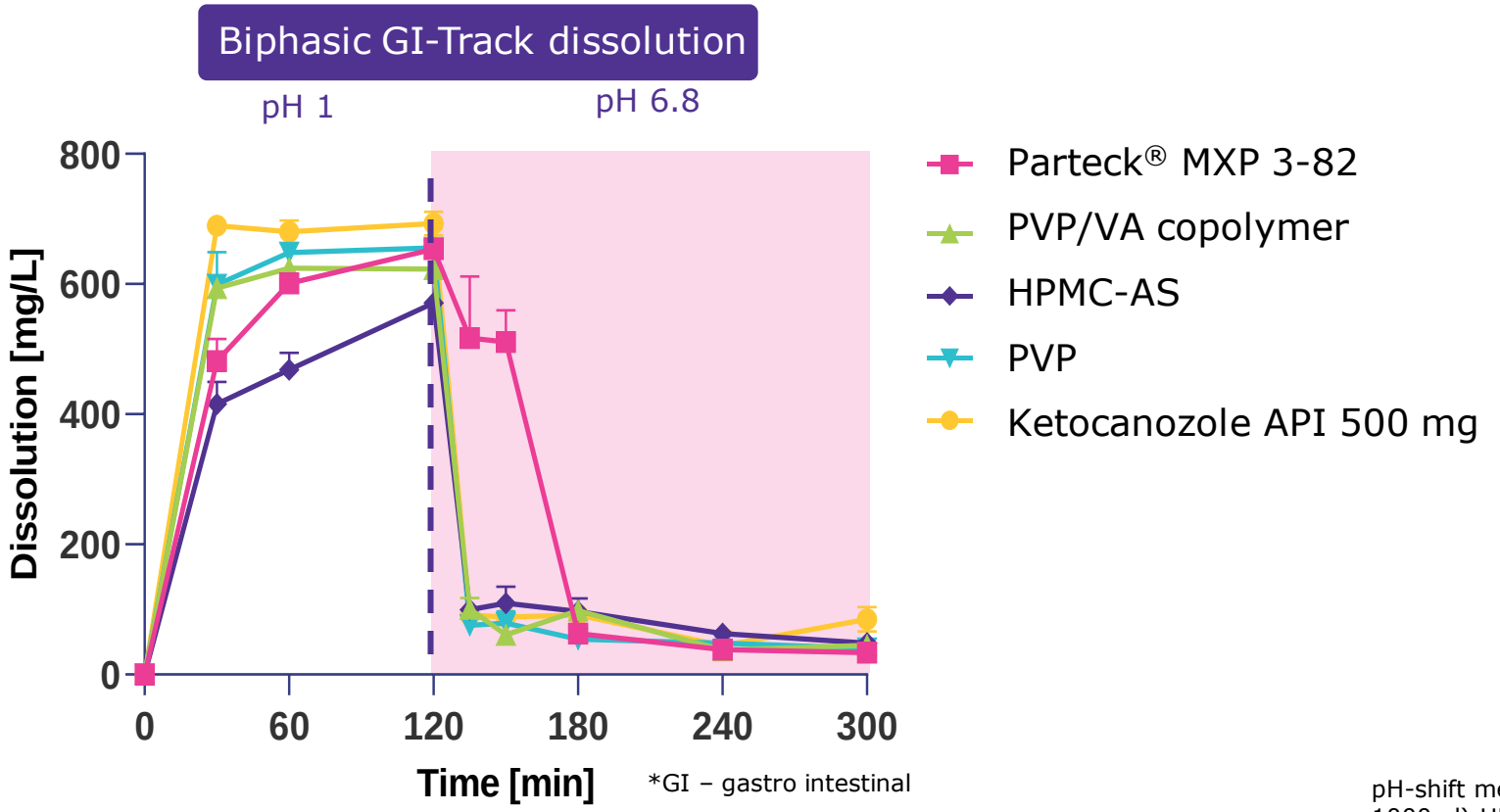


T_m Breakdown of 67 BCS II and IV compounds:
Sarah Shugarts and Leslie Z. Benet, The Role of Transporters in the Pharmacokinetics of Orally Administered Drugs, Expert Review, Pharmaceutical Research, Vol. 26, No. 9, September 2009

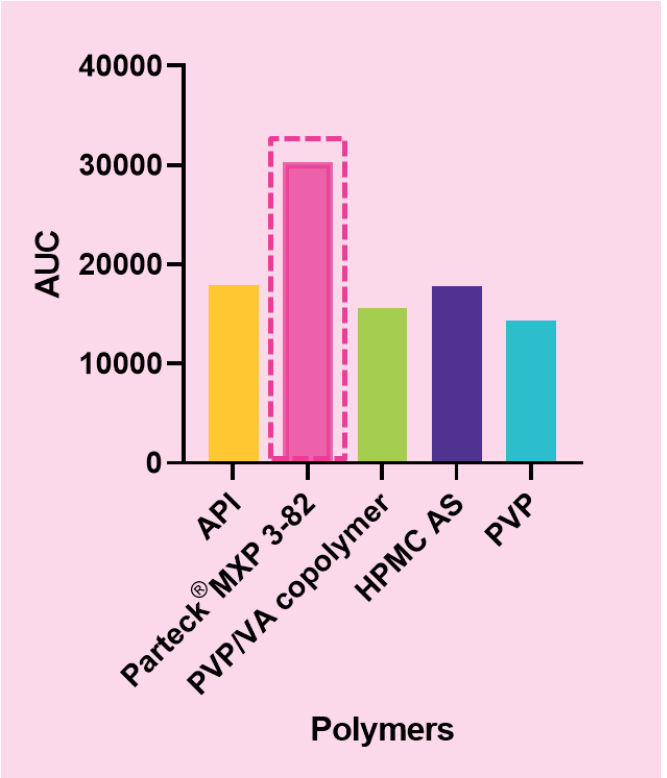
APIs have a range of melting points:
Good thermo-stability is needed to cover a wide range (PVA 4-88)

PVA for Hot Melt Extrusion – Hydrolysis optimization (PVA 3-82)

Parteck® MXP 3-82: Formulation performance, prolongated supersaturation of Ketoconazole



*GI – gastro intestinal

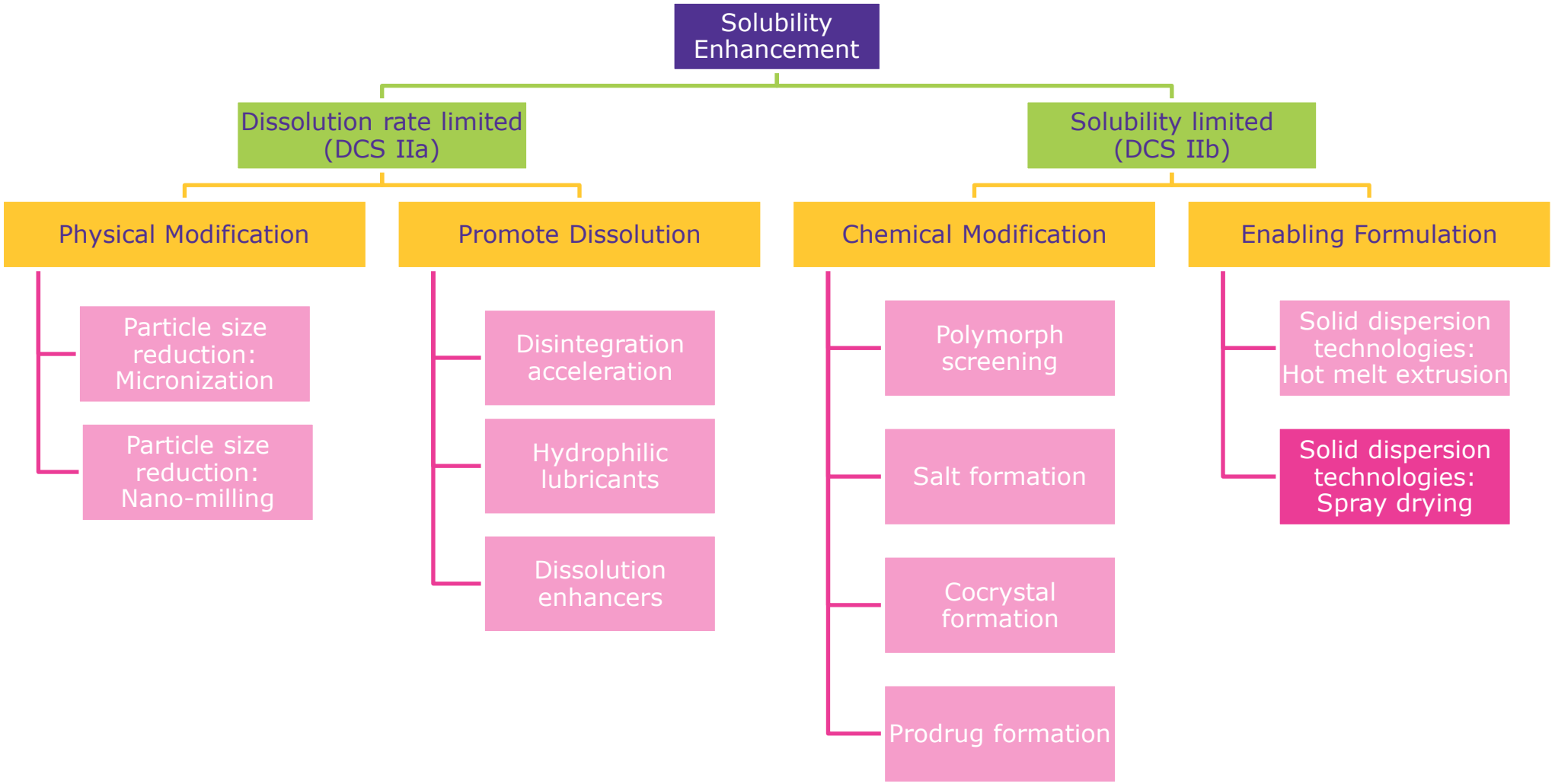


pH-shift method (750ml 0.1M HCl for 120 min, add 250ml PP pH 6.8 final 1000ml) HME formulation with 20% Ketoconazole, Paddle: 50 rpm, n=3

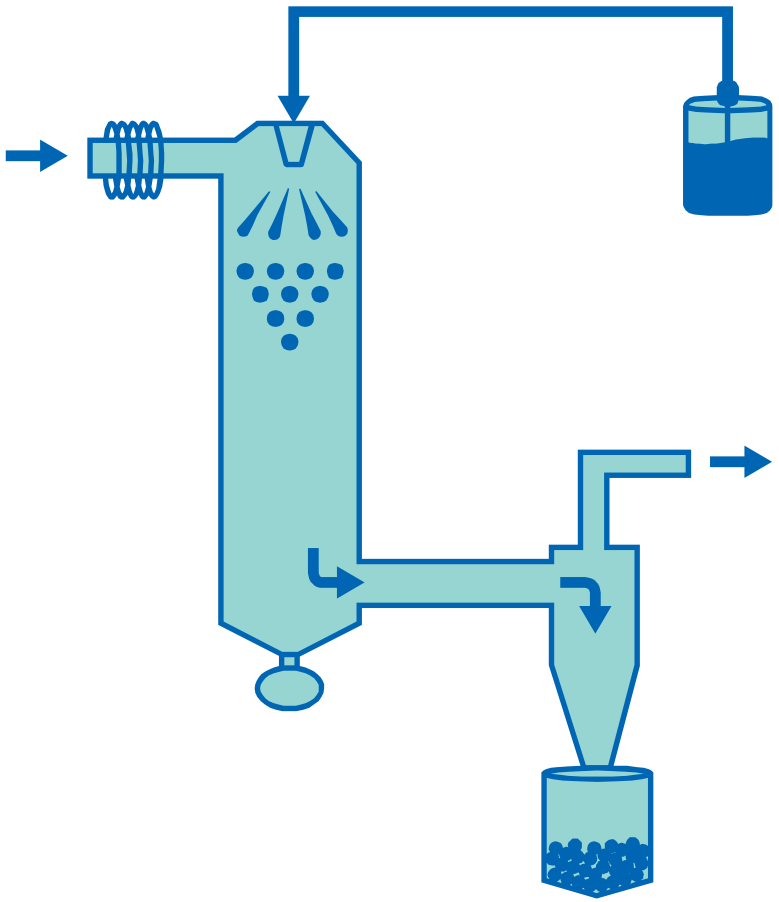
*AUC – area under the curve

Improved hydrophobicity leads to **superior supersaturation maintenance via precipitation inhibition** and prolongates the release profile (PVA 3-82)

Strategies and Enabling Technologies for Enhancing API Solubility



Amorphous solid dispersions
Advantages of spray drying

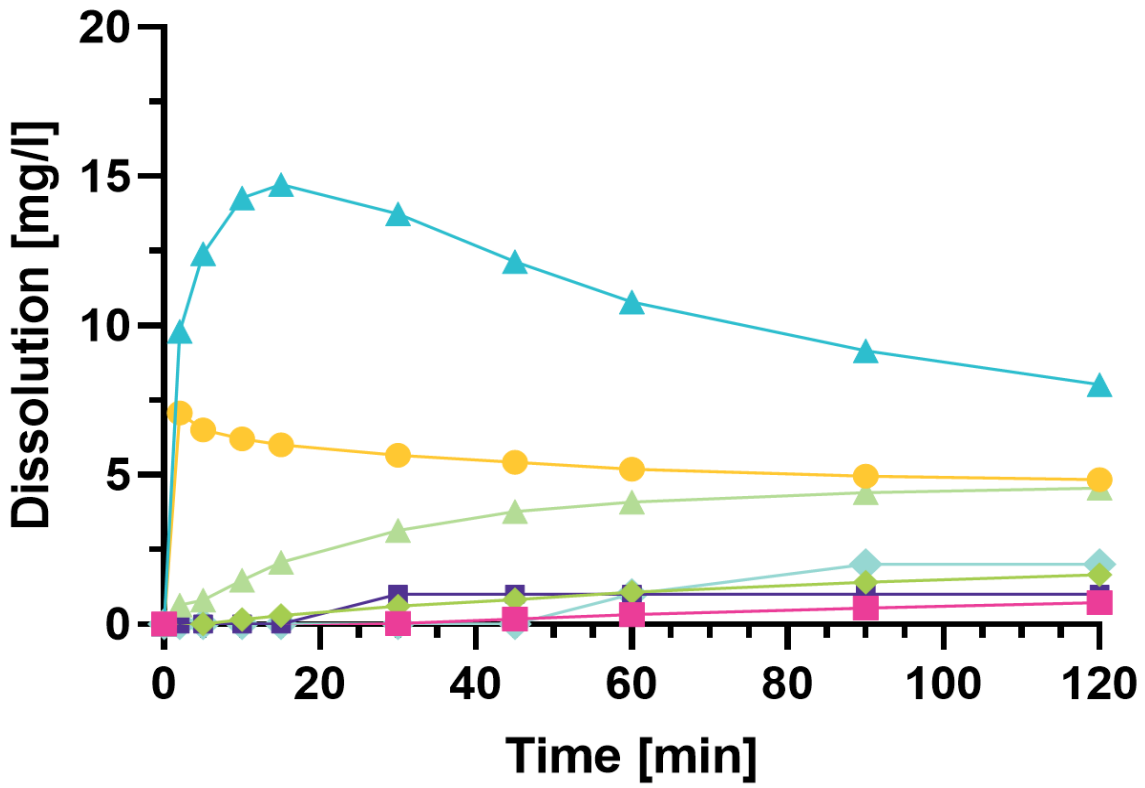


Advantages of spray drying

- Enhanced solubility & bioavailability
- Low API amount needed
- Heat sensitive APIs
- Upscaling & high throughput
- Continuous technologies
- Particle engineering

dissolve. spray. PERFORM.

PVA for spray drying
Dissolution of Indomethacine with an ASD of PVA



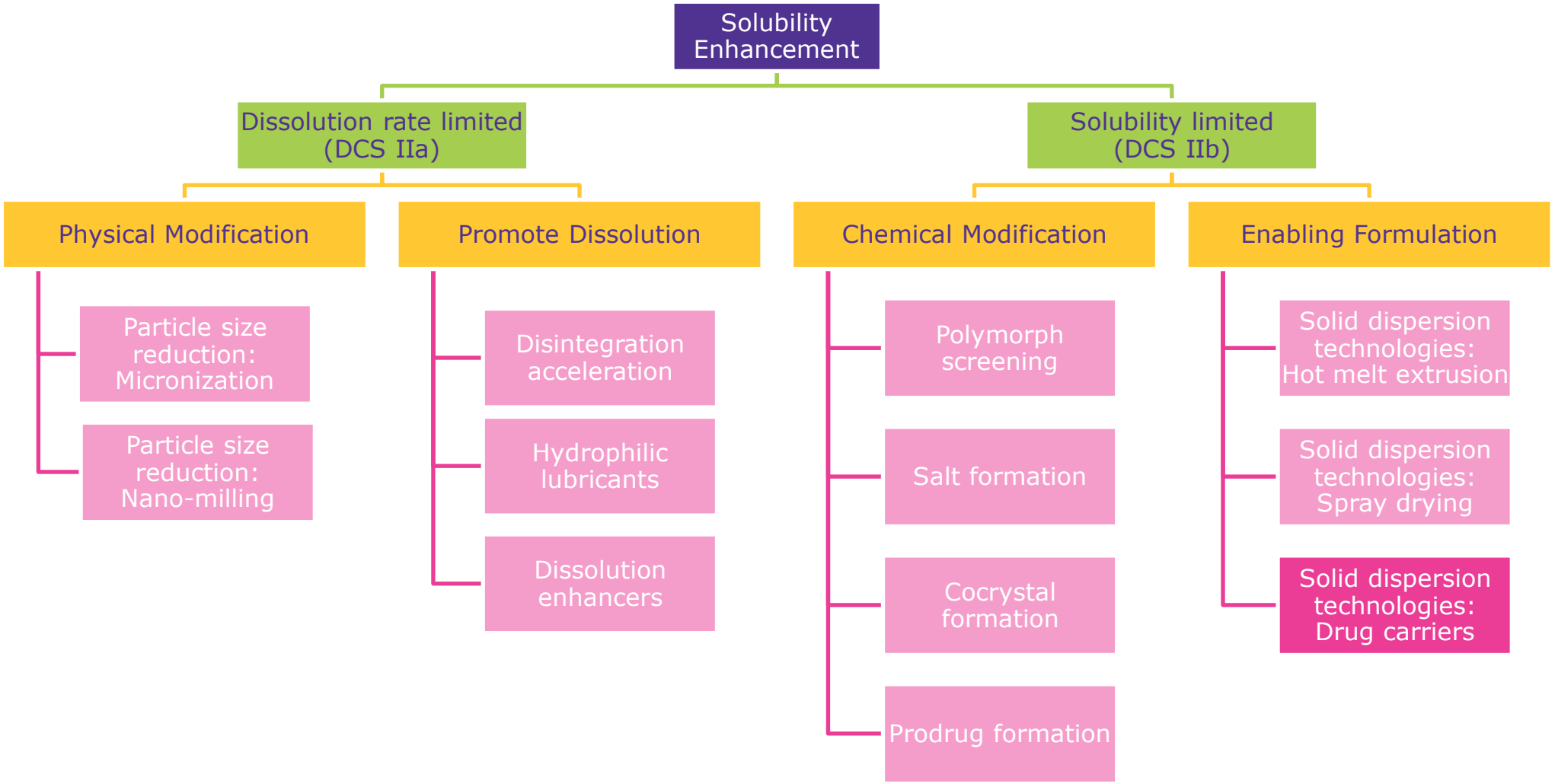
- Indomethacin API 25 mg
- SD: Parteck® MXP 3-82
- SD: Parteck® MXP 4-88
- SD: Grafted copolymer
- SD: PVP K30
- HME: PVP/VA copolymer
- HPMC-AS

- ✓ Fast spring
- ✓ Extended parachute
- ✓ Superior performance

SD process, Büchi B295
SD via two/three-fluid nozzle: Inlet temperature of 90°C, Outlet temperature of 50°C Drying air (N_2) flow rate of 35 m^3/h (Aspirator: 100%) Atomization air flow rate of 670 L/min (N_2: 55mm) Dissolution: Indometacine SGF with 30% DL

Excellent dissolution enhancement & performance

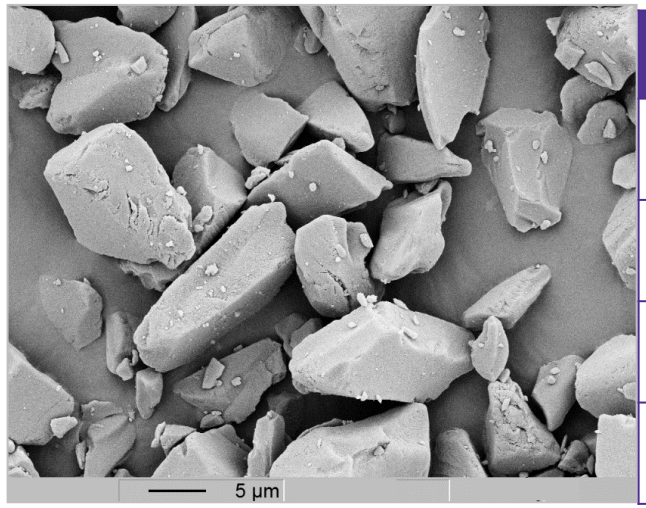
Strategies and Enabling Technologies for Enhancing API Solubility



Carrier for amorphous formulation – Mesoporous silica

Stabilize the amorphous solid-state within the pores of silica

- **Chemical formula:** SiO_2
- **Pharmacopoeial monograph:** Silicon Dioxide (USP) and Silica, colloidal hydrated (Ph Eur)
- **Regulatory status:** Generally Regarded As Safe (GRAS)*



Typical values	
Particle size	5 – 20 µm
Bulk density	0.32 g/mL (0.56 g/mL**)
Surface area	~ 500 m^2/g
Pore size	~ 6 nm (disordered)

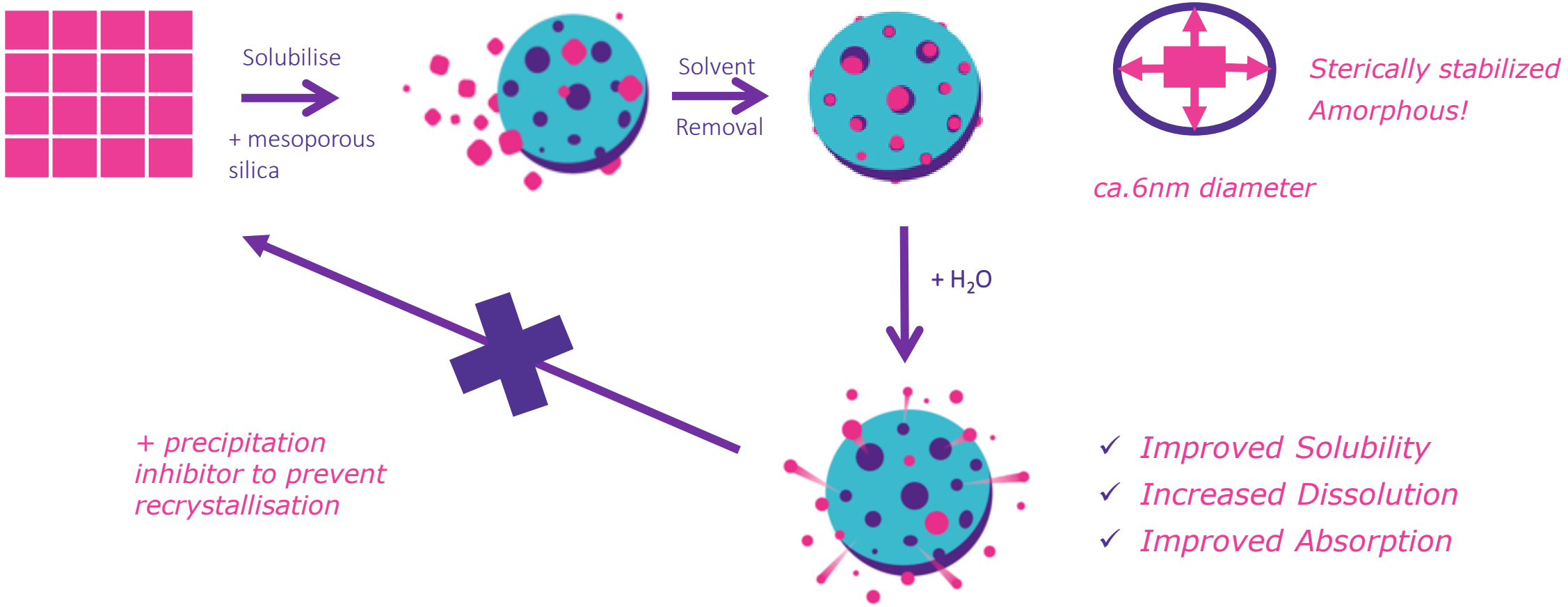
Parteck® SLC

* By the U.S Food and Drug Administration

** Loaded particle

Mesoporous silica for amorphous formulation

Stabilize the amorphous solid-state within the pores of silica

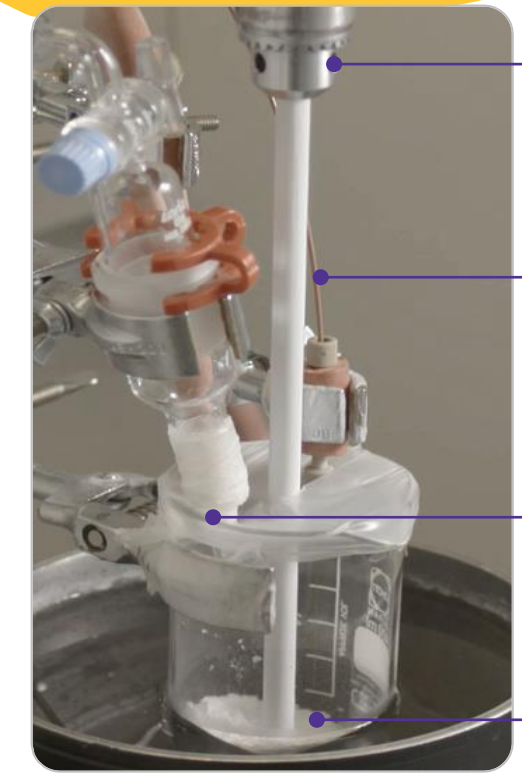


Pore adsorption and nanoconfinement are the key steps for formulation with mesoporous silica

Mesoporous silica for amorphous formulation
Lab-scale loading of APIs onto mesoporous silica

SAFC®

Impregnation method



- Overhead stirrer
- Canulla (API solution)
- Vacuum nitrogen
- Silica powder

Suspension method

+ Silica powder

↓

API solution

⇒Stirring
⇒Evaporation

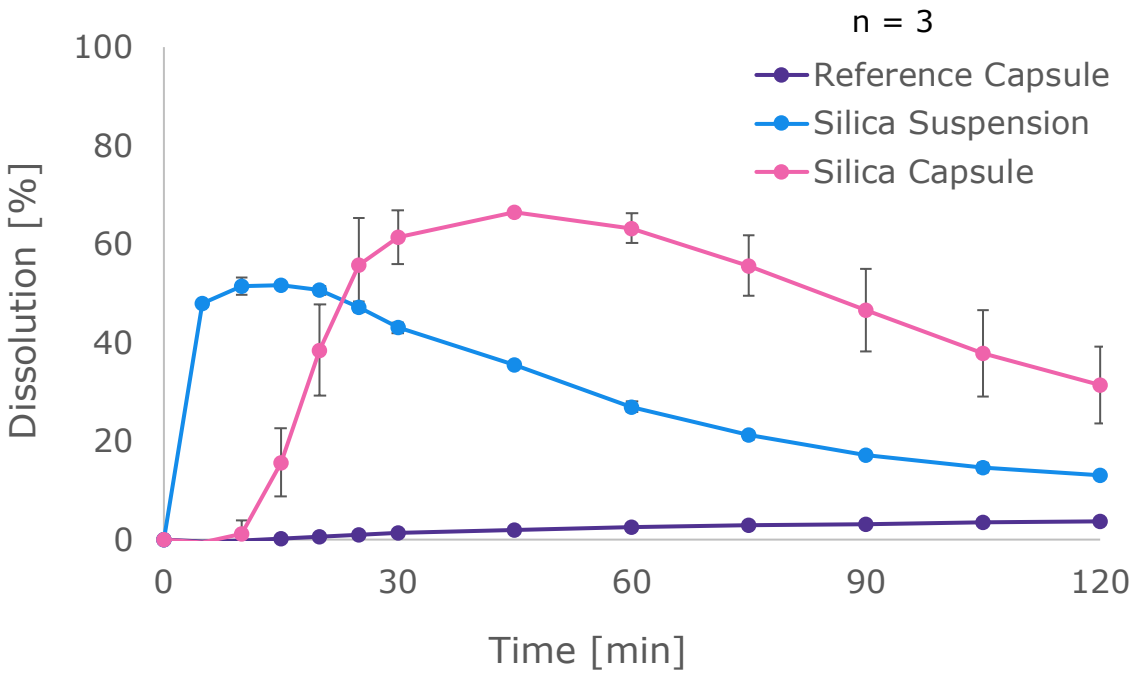
NO specialized equipment

NO extra capital investment

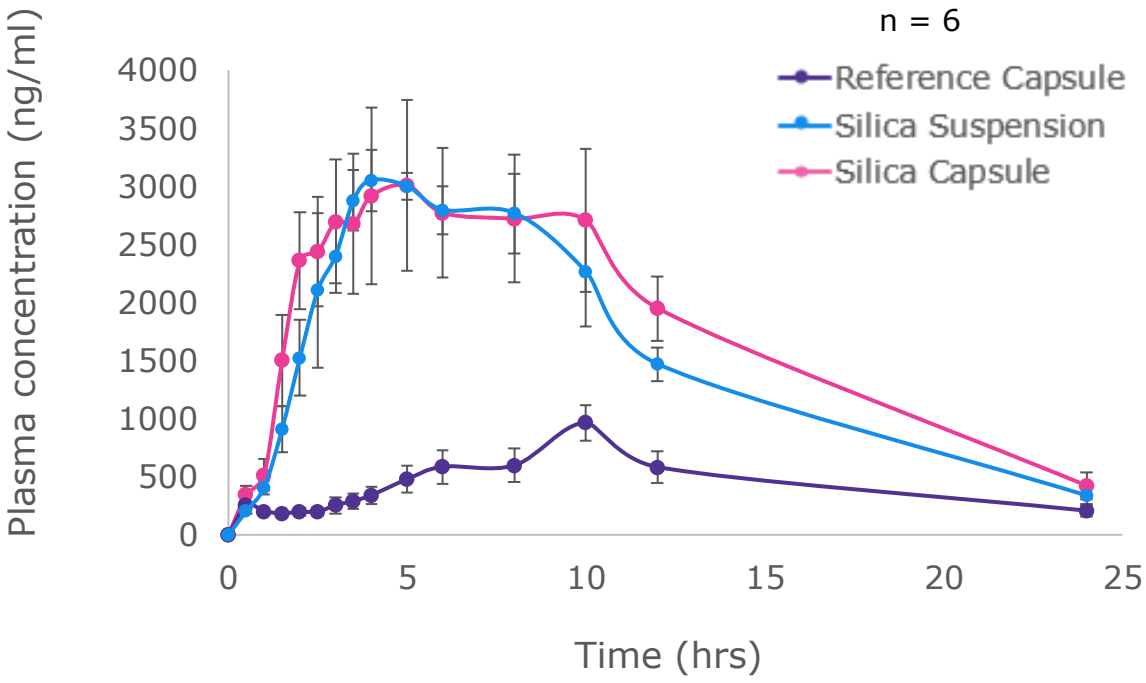
Mesoporous silica for amorphous formulation
***In-vitro* and *in-vivo* dissolution profile of fenofibrate**

SAFC®

Biorelevant *in-vitro* dissolution



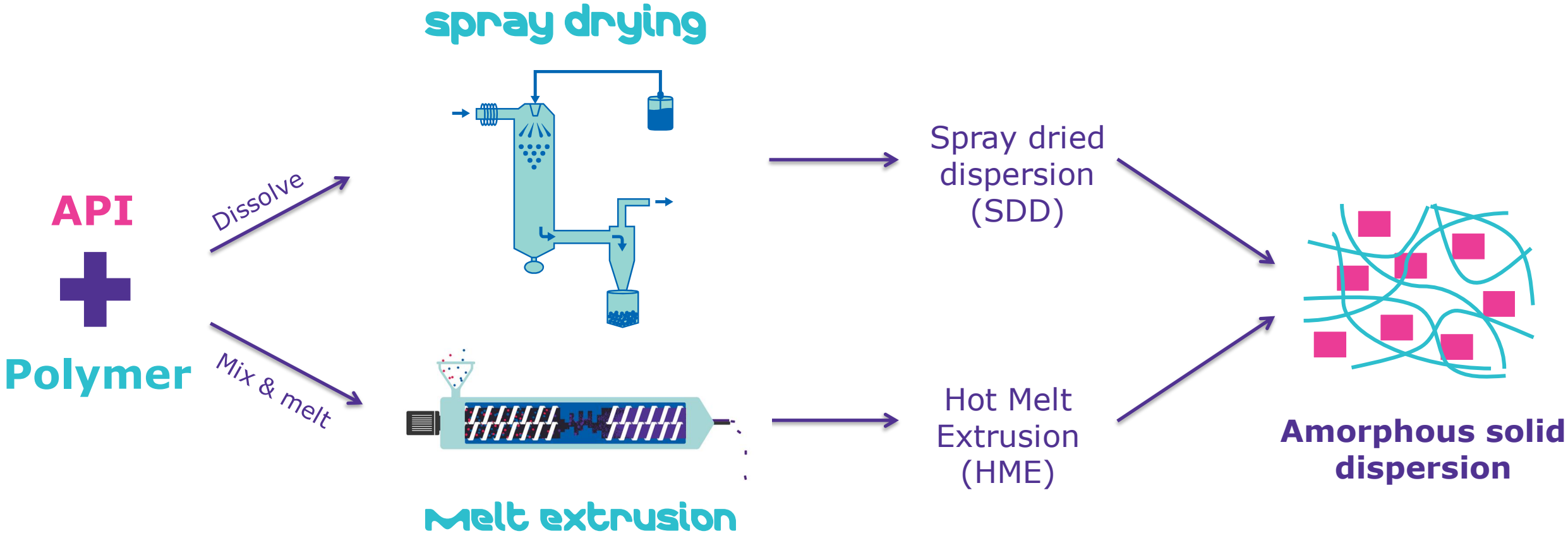
In-vivo bioavailability in fasted pigs



Biorelevant dissolution provides a good prediction of relative bioavailability
PK study in pigs indicates a significant bioavailability enhancement

Amorphous stability

Polymeric ASDs can lead to phase separation and recrystallization

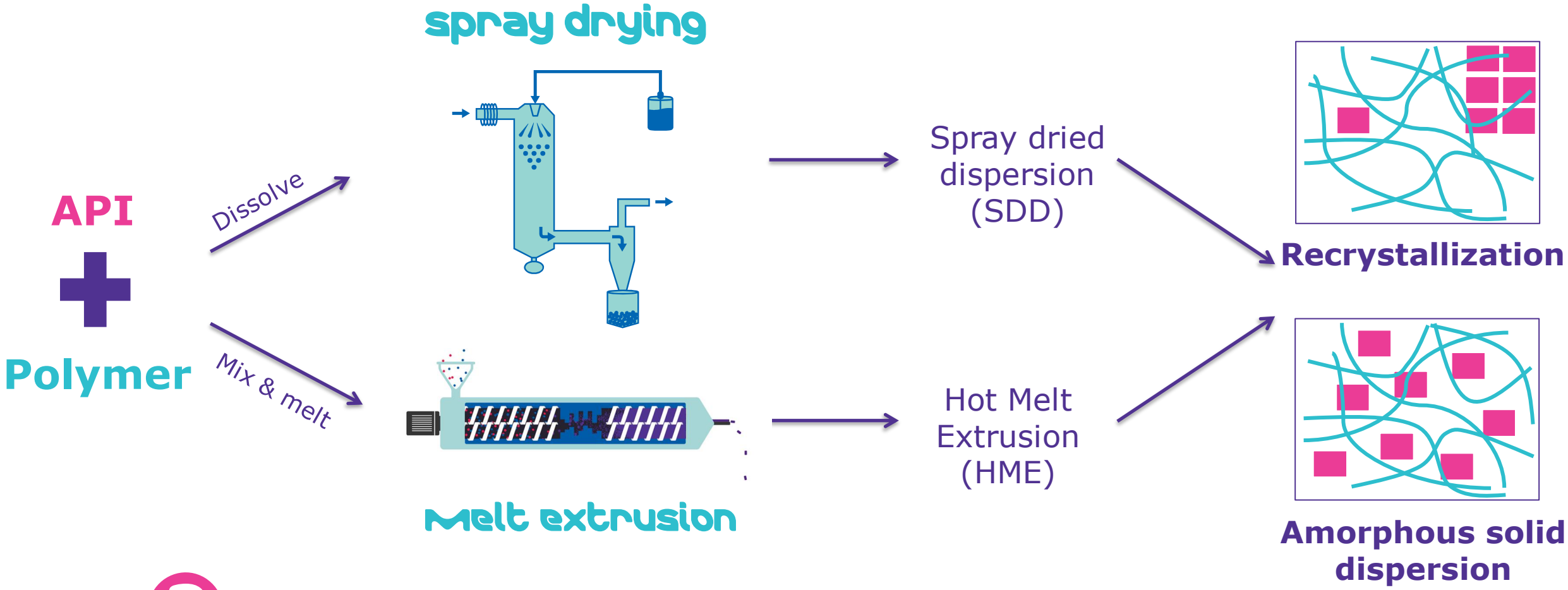


Goal is a homogenous dispersion of drug and polymer

Amorphous stability

Polymeric ASDs can lead to phase separation and recrystallization

SAFC®



How can we predict if our drug will be unstable?

Amorphous stability

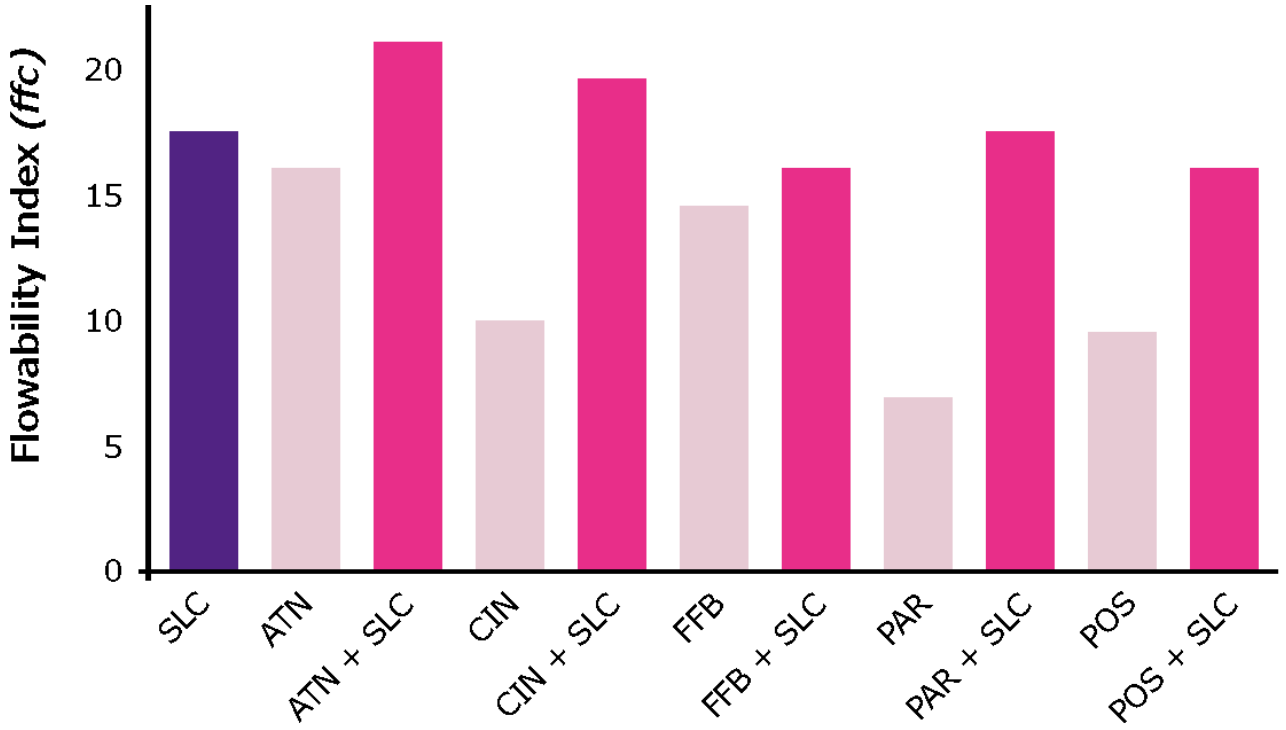
The Glass Forming Ability (GFA) describes the stability in the amorphous form

Poor glass formers (GFA-I) have a higher propensity for re-crystallization. They are more fragile in the amorphous form.

Mesoporous silica is the best-in-class technology to stabilize poor glass formers *

* Felix Ditzinger, et al. 2019. Opportunities for Successful Stabilization of Poor Glass-Forming Drugs: A Stability-Based Comparison of Mesoporous Silica Versus Hot Melt Extrusion Technologies

Mesoporous silica for amorphous formulation
Platform technology to stabilize unstable amorphous APIs



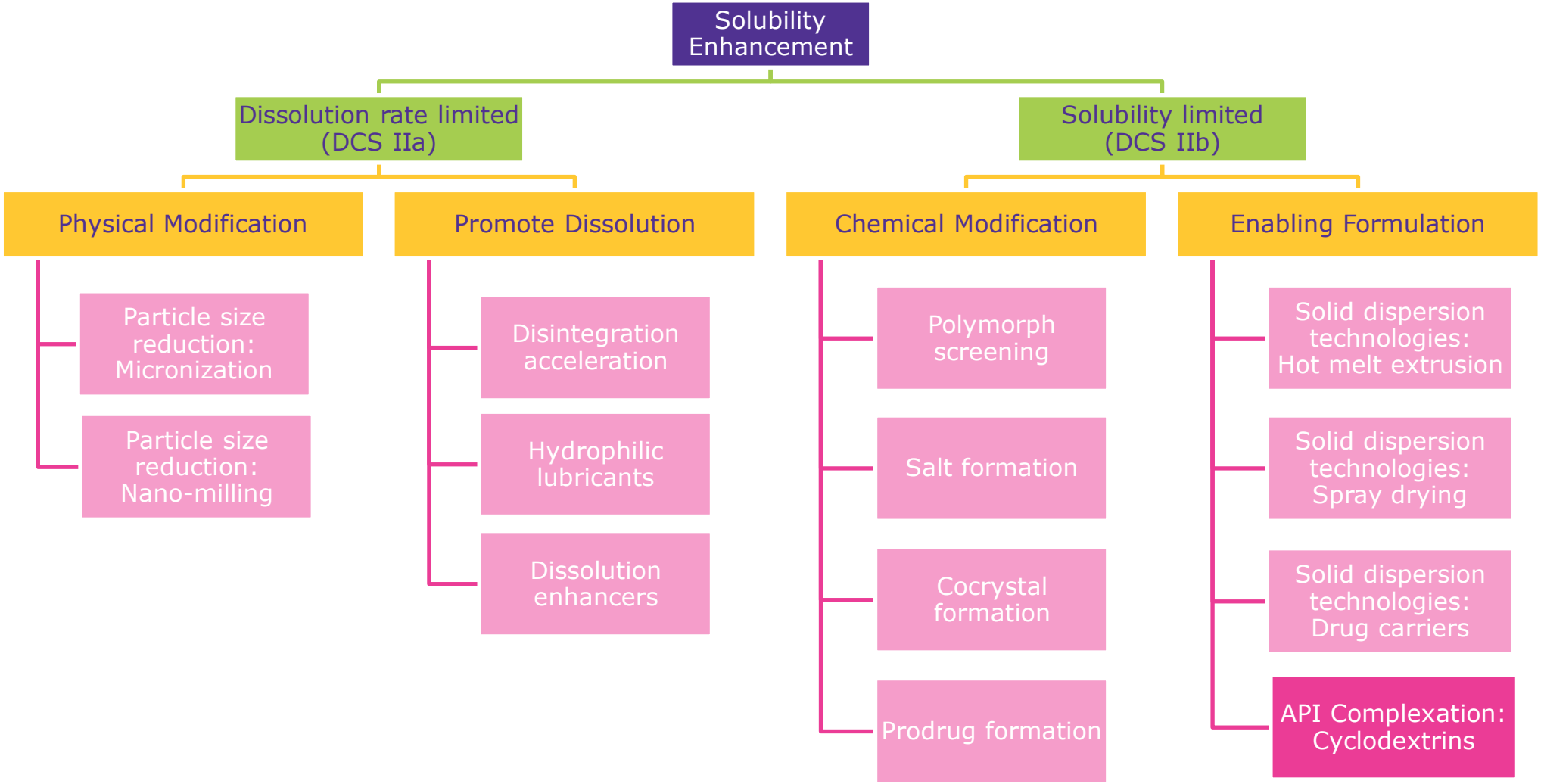
Platform technology approach

Uniformity & consistency:

- **Particle size**
- **Flowability**
- **Tablet hardness**
- **Friability**

De-risk unexpected polymorphic changes and challenges in drug development

Strategies and Enabling Technologies for Enhancing API Solubility



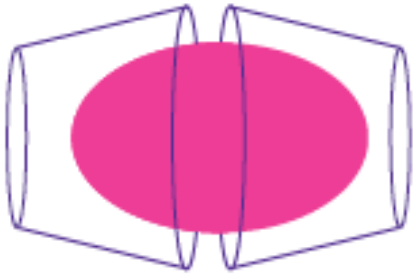
Cyclodextrins

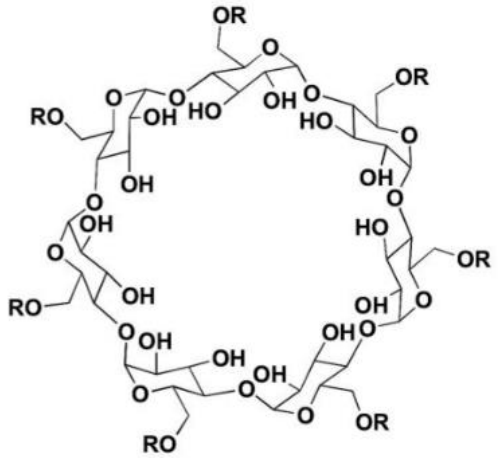
Cyclodextrins strongly gained importance during past years

- Cyclodextrins are cyclic oligosaccharides derived from natural starch
- Units arranged in the form of hollow cone with hydrophilic exterior and hydrophobic cavity
- First discovered in the 19th century; nowadays increasing use as pharmaceutical excipient

Benefits of Cyclodextrins[1]:

- Increases solubility and stability
- Enhances bioavailability
- Masks odors and tastes
- Reduces aggregation behavior of biologics





[1] Cyclodextrins, Kurkov & Loftsson, 2012

Cyclodextrins

SAFC®

Derivates offer enhanced solubility

- Currently, there are >120 products formulated with Cyclodextrins on the market
- SBE-β-CD containing drugs nearly doubled during past years

Route	α-CD	β-CD	γ-CD	RM-β-CD	HP-β-CD	SBE-β-CD	HP-γ-CD
Oral	3 [0]	37 [0]	2 [0]	1 [0]	12 [1]	0 [1]	2 [0]
Buccal	0 [0]	0 [0]	0 [0]	0 [0]	4 [0]	0 [0]	0 [0]
Topical	1 [0]	7 [0]	0 [0]	0 [0]	1 [0]	0 [0]	0 [0]
Ophthalmic	0 [0]	1 [0]	0 [0]	1 [0]	2 [0]	0 [0]	0 [0]
Parenteral	6 [0]	0 [0]	0 [0]	0 [0]	19 [3]	25 [5]	1 [0]
Total	**10 [0]**	**45 [0]**	**2 [0]**	**2 [1]**	**38 [4]**	**25 [6]**	**3 [0]**

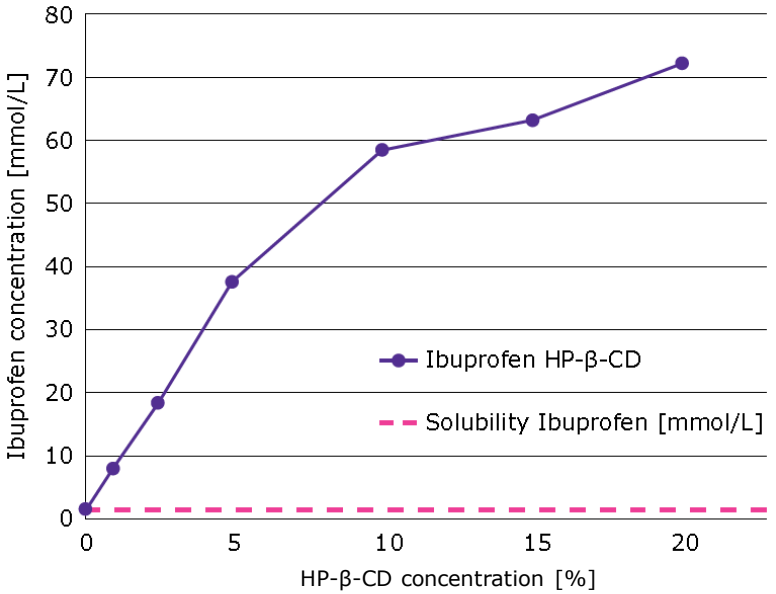
Marketed products employing the respective CD; numbers in brackets indicate new products currently in clinical phase
Not shown here: studies ongoing to broaden indication of existing drugs; PharmaCircle database, March 2022

RM: randomly methylated; HP: hydroxypropyl; SBE: sulfobuthylether

Cyclodextrins

HP-β-CD and SBE-β-CD have very good safety profiles

- Part of FDA list of inactive ingredients
- Marketed drugs exist for parenteral administration
- Usually renally excreted intact without metabolization[1]
- Shielding effects can help minimizing gastrointestinal irritation[1]
- Very versatile for liquid, semi-solid and solid formulations



Solubility of Ibuprofen as a function of HP-β-CD concentration, internal data

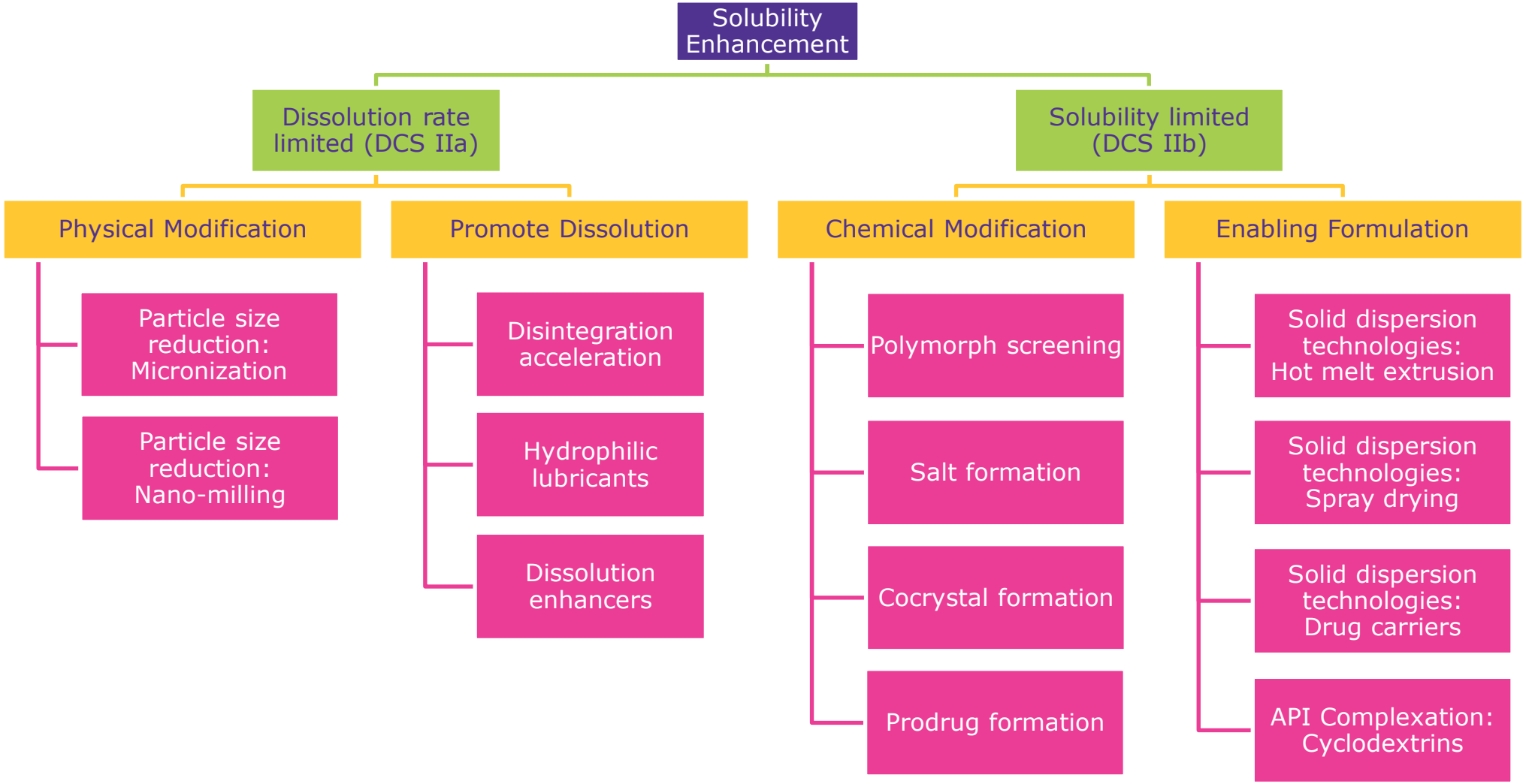
Cyclodextrins and COVID-19

- Remdesivir (Gilead): SBE-β-CD to increase solubility[2]
- COVID-19 vaccine (J&J): HP-β-CD to protect proteins[3]

HP: hydroxypropyl; SBE: sulfobuthylether

[1] Questions and answers on cyclodextrins used as excipients in medicinal products for human use, EMA, 2017
[2] Sulfobutylether-β-cyclodextrin, Stella & Rajewski, 2020
[3] Cyclodextrins in Antiviral Therapeutics and Vaccines, Braga *et al.*, 2021

Strategies and Enabling Technologies for Enhancing API Solubility



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