Solubilization Selection

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What You Will Learn

- The fundamental physical chemistry of drug solubility, its interplay with intestinal absorption, and the role of different mechanisms for solubilization
- The advantages of oil-based formulations including self-emulsifying dispersions
- When particle size reduction is the right answer
- When to use amorphous solid dispersions and whether to prepare them using a hot melt extrusion or spray drying

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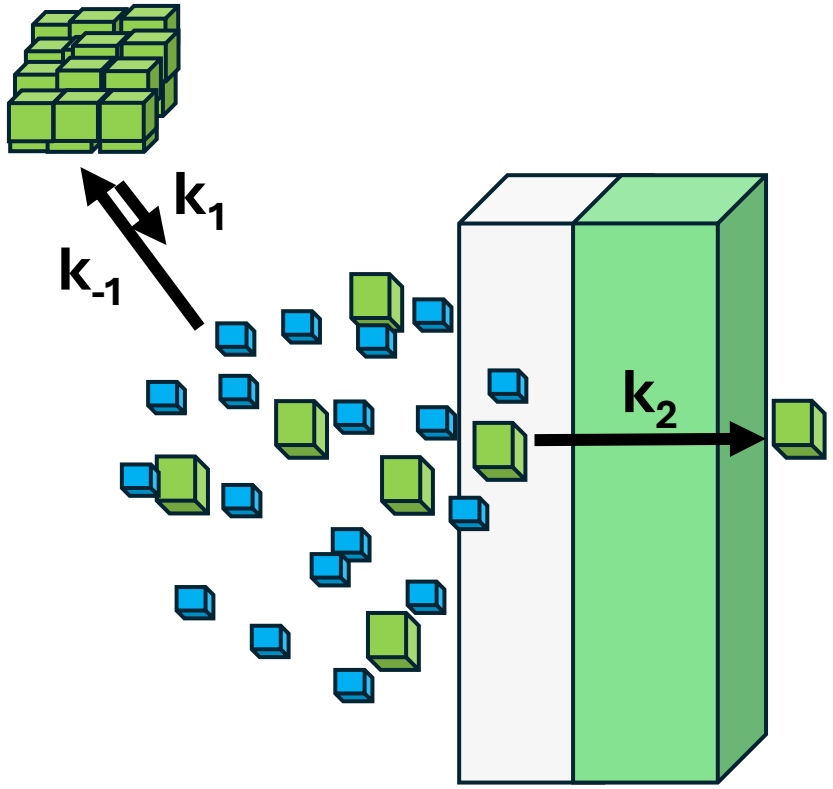
Intestinal Drug Absorption



Limiting Conditions

- When $k_2 >> k_1$ absorption rate proportional to dissolution rate (k_1)
- When $k_1 >> k_2$ absorption rate proportional to drug solubility (k_1 / k_2)

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Is Solubilization Needed?

Maximum Absorbable Dose (MAD)

$$MAD = k_2 S V t \qquad S = \frac{MAD}{k_2 V t}$$

k_2 absorption rate (0.001 to 0.050 min^{-1})

S solubility (mg/mL),min value in pH 6.1-7.5

V water volume of small intestine (250 mL)

t residence time in small intestine (270 min)

Biopharmaceutics Classification System (BCS)

To be considered “high solubility” (BCS I or III):

$$solubility \geq \frac{dose[mg]}{250\ [mL]}$$

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Is Solubilization Needed?

Dose (mg)	Absorption Rate (min^{-1})	Minimum Solubility Needed (µg/mL)	BCS I or III Solubility Needed (µg/mL)
50	0.005	150	200
50	0.025	30	200
200	0.025	119	800

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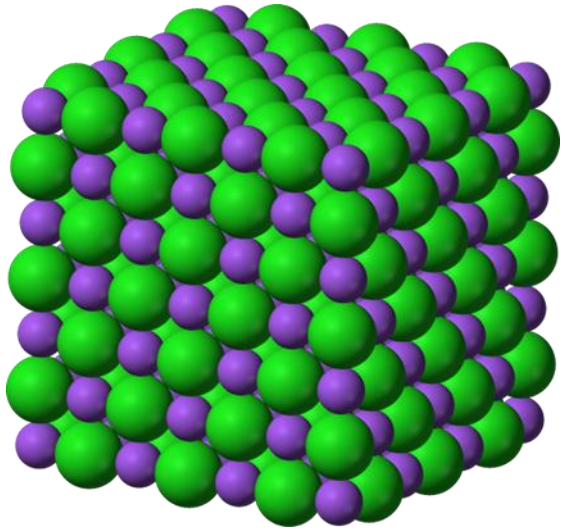
Physical Chemistry of Solubility



Representation of an ionic crystal

Drug Crystals

- Molecules interact strongly together (cooperatively) → enthalpy favors the lattice
  - Charge interactions (ionic)
  - Hydrogen bonds
  - Van der Waals interactions
- High degree of order (low entropy) → entropy favors loss of lattice structure (amorphization, dissolution)

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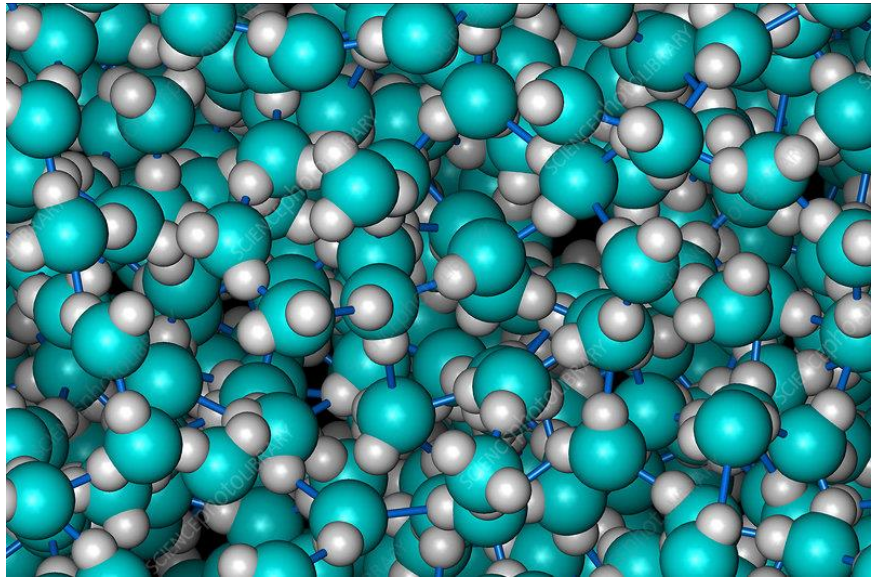
Physical Chemistry of Solubility



Water

- Molecules interact together → enthalpy favors pure water
  - Hydrogen bonding strong
- Pure water has order → entropy favors impure water

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Physical Chemistry of Solubility

Low Solubility Root Causes

- **Hydrophobicity**
  - Drug-water interactions are poor (low H_2O-API enthalpy)
- **Strong Crystal Lattice**
  - Drug-drug interactions very good (high crystal lattice enthalpy)
  - API has high melting point

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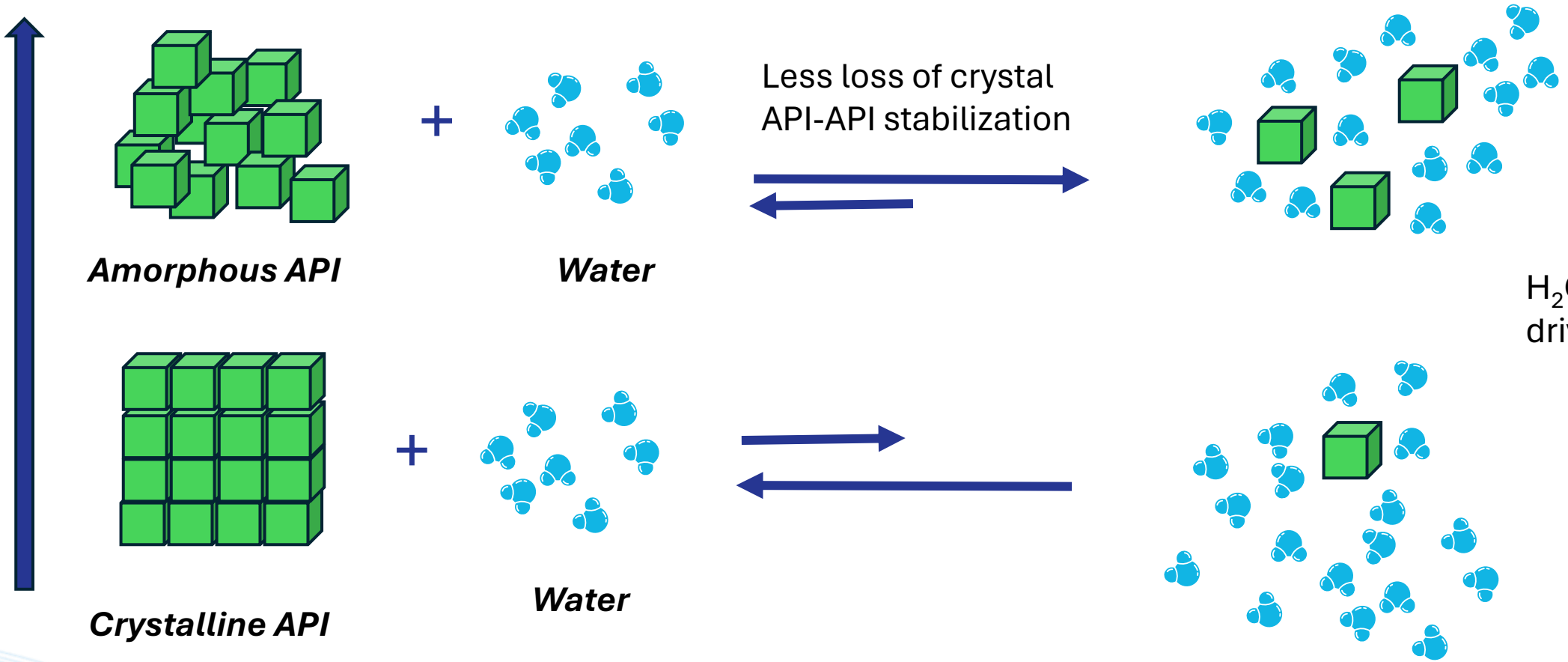
Energetics of Dissolution



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Improving Overall Absorption of Poorly Soluble Drugs

- Increase API dissolution rate [k_1] (fast intestinal absorption)
  - Salt form
  - Complexation
  - Particle size reduction
  - Drug dissolved in oil/surfactant
- Increase (supersaturated) API concentration [k_1/k_2]
  - Amorphous API
    - Precipitated *in vivo*
    - Amorphous solid (dispersion)

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Increasing API Dissolution Rate: Salt Formation

- APIs generally have higher solubility in salt form (ionized) compared to free form; however, only neutral APIs absorb through intestinal walls
- Dissolved salts of APIs can often rapidly replenish drug as it absorbs
- In some cases, dissolved basic drugs in the stomach can precipitate into **amorphous** free base in intestine (depending on pK_a) giving higher kinetic solubility

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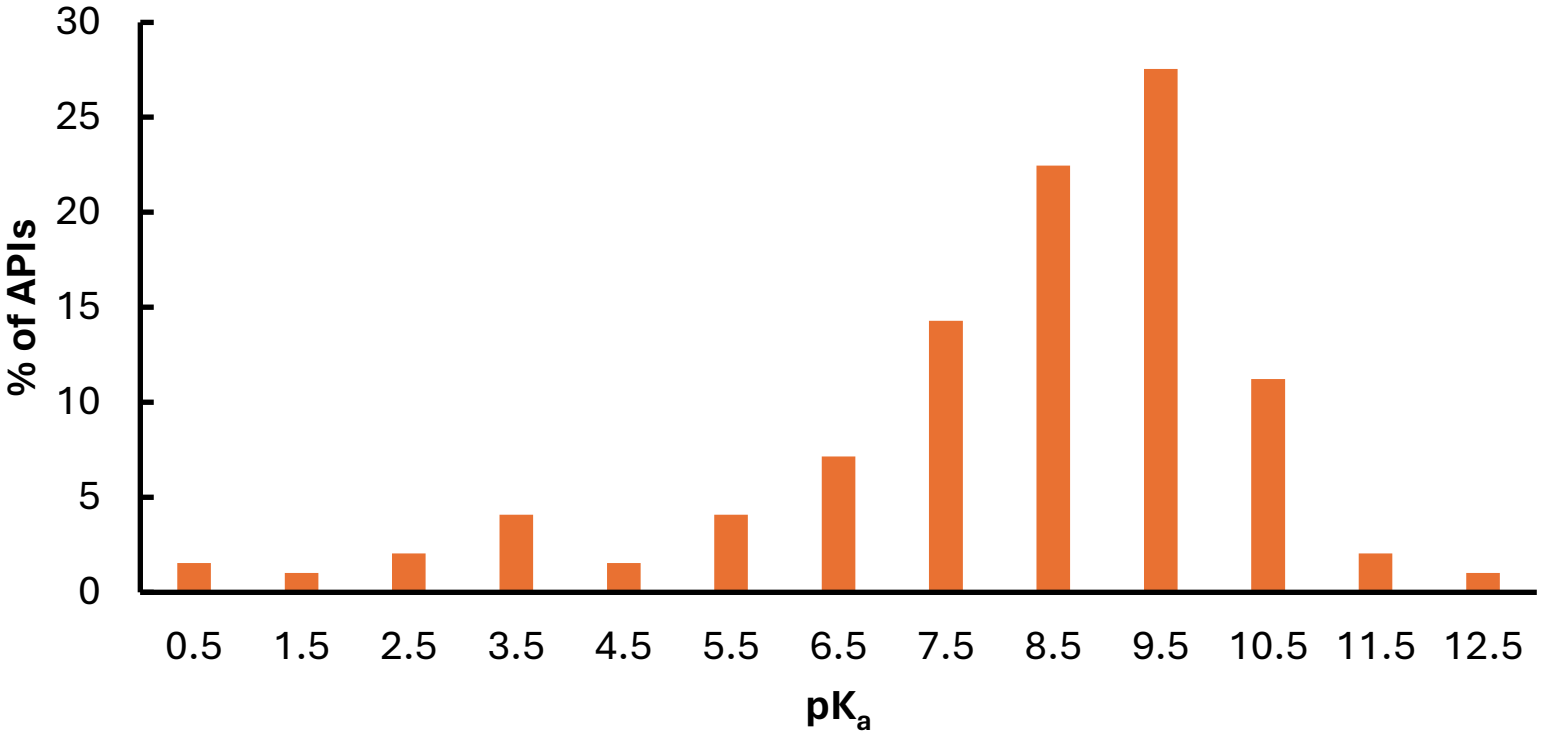
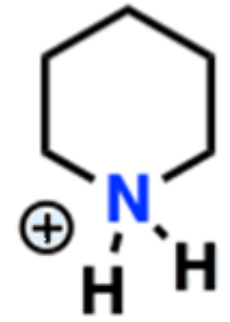
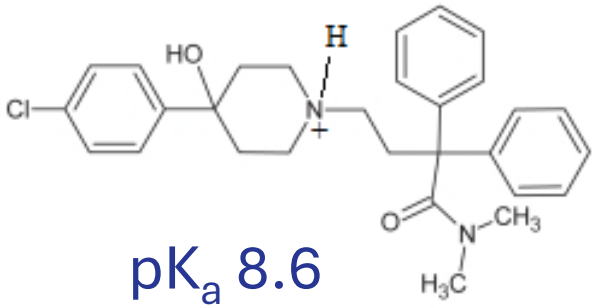
Increasing API Dissolution Rate: Salt Formation



From Manallack DT, Perspect Medicin Chem 2007; 1: 25-38



pK$_a$ 11



pK$_a$ 8.6

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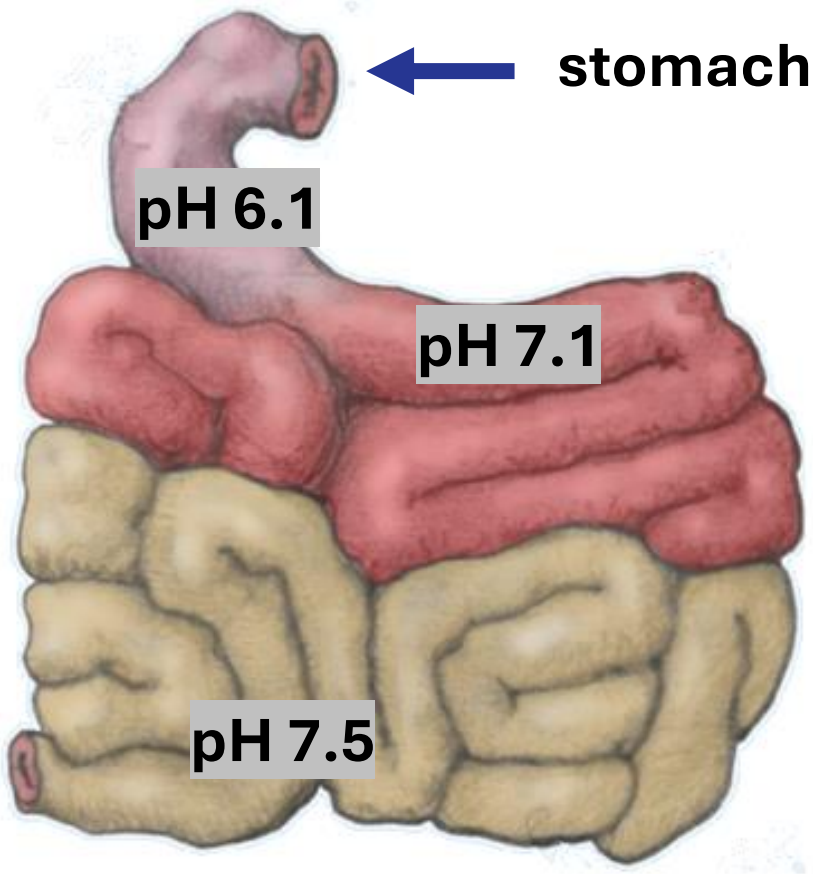
Increasing API Dissolution Rate: Salt Formation

pK_a	% Ionized @ pH 6.1	% Ionized @ pH 7.5
6.5	71.5	9.1
9	99.8	96.9
11	99.9	99.9



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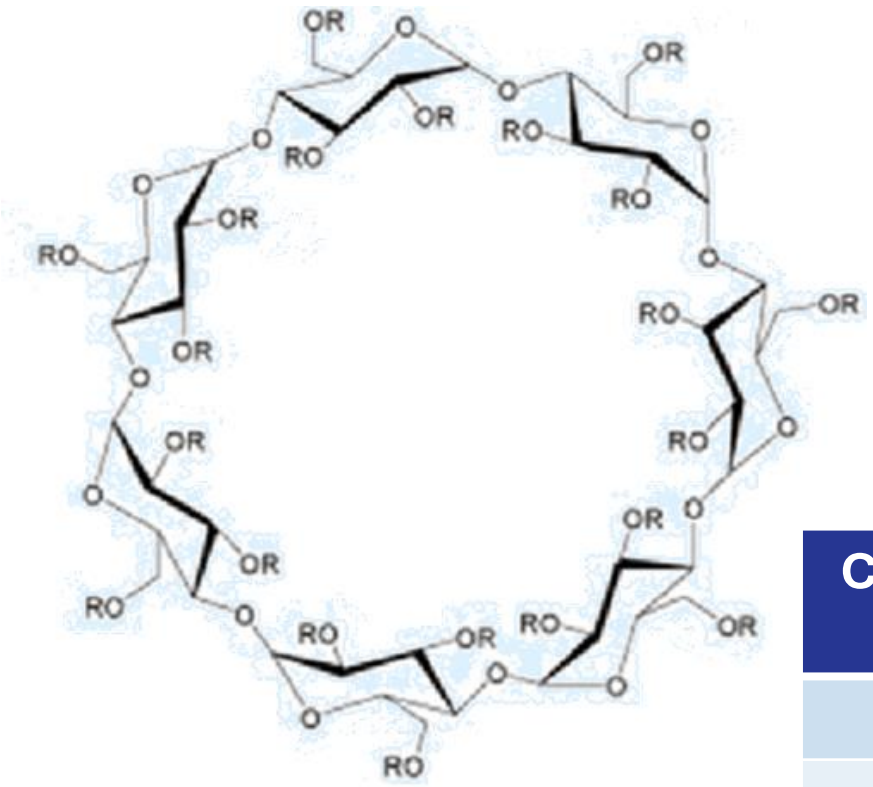
Increasing API Dissolution Rate: Complexation



- Cyclodextrins can solubilize APIs that fit into the ring cavity (0.60-0.65 nm)
- Typically, only one API per cyclodextrin
- API needs to dissociate from complex to absorb
- Complexed API can replenish absorbed drug quickly unless binding constant is too high

Cyclodextrin	R	MW	API Maximum Dose (mg)
β	H	1153	150
SBECD	$(CH_2)_4SO_3^-$	2163	75

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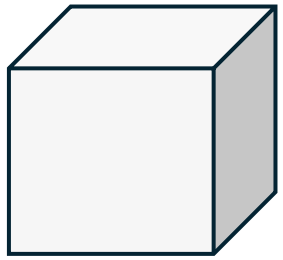
Increasing Water Dissolution Rate: Particle Size Reduction

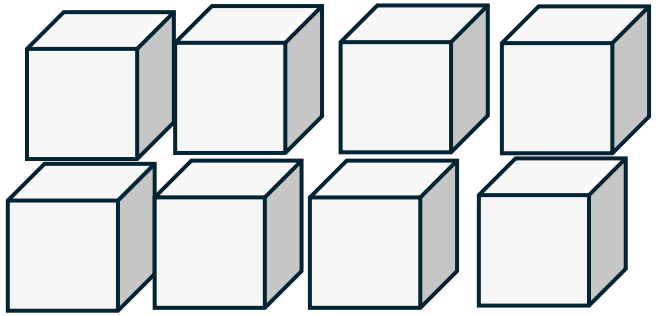
Dissolution rate of crystal depends on surface area to volume ratio and the API concentration at the particle surface vs. saturation (Noyes/Whitney)

$surface\ area = 6d_1^2$



d_1

$surface\ area = 8*[6*(d_1/2)^2] = 12d_1^2$



$d_2 = ½\ d_1$

Overall, dissolution rate directly proportional to particle diameter

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Increasing API Dissolution Rate: Particle Size Reduction – Processing

- Processes can be simple using well-established techniques
  - Milling
    - Ball milling: API particles plus beads (usually steel) are rotated in a drum generating shear
    - Hammer milling: API particles fed into fixed drum with rotating hammers
    - Jet milling: Very high-speed air shears API particles
    - Cryomilling: Using low temperature to make particles more brittle such that mechanical shear will shatter them
  - Crystal Engineering
    - Antisolvent addition to generate small crystals
    - Rapid expansion of supercritical solution (typically CO_2)
- Extremely small crystals (<10 nm): surface molecules have higher energy (greater solubility), but impractical for solid dosage forms due to flow, agglomeration issues

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Increasing API Dissolution Rate: Particle Size Reduction – Challenges

- While particle size reduction may increase solubility, there are some challenges with this approach
  - Stability
    - Milling or rapid crystallization can result in amorphous API which is much less stable chemically (drug degradation) and physically (recrystallization)
  - Diminishing returns
    - Need to remain dissolution limited: may quickly saturate solution near API particles when solubility is low
  - Manufacturability
    - Smaller particles generally flow more poorly
    - Smaller particles can agglomerate
    - Particle size distribution may be difficult to keep consistent batch to batch

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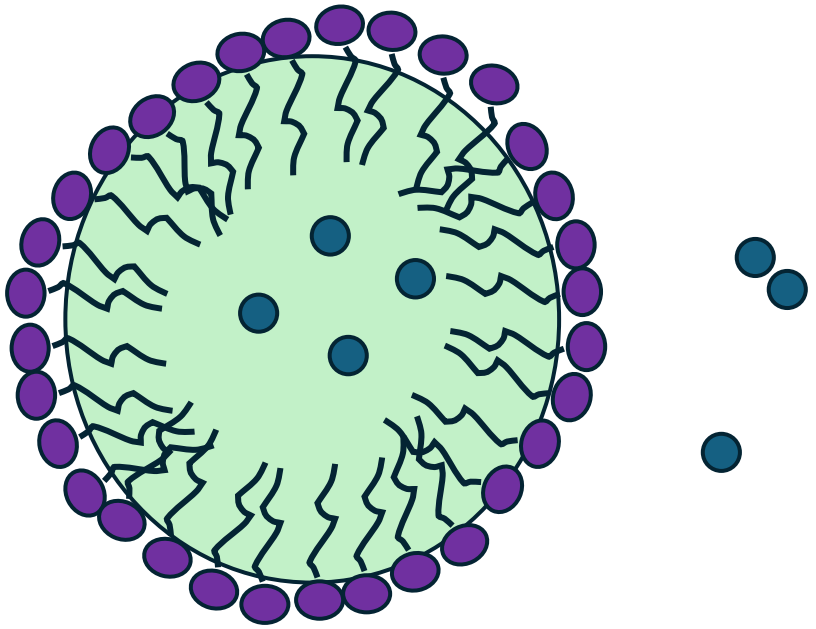
Increasing API Dissolution Rate: Emulsions

- Self-Emulsifying Drug Delivery System (SEDDS) or Self Micro-Emulsifying Drug Delivery System (SMEDDS)
  - API dissolved in oil + surfactant + solvent (can be solid dosage form)
  - When exposed to water in GI system, forms micro- or nano-emulsion
    - High surface area: equilibration between drug in micelle and bulk water phases rapid



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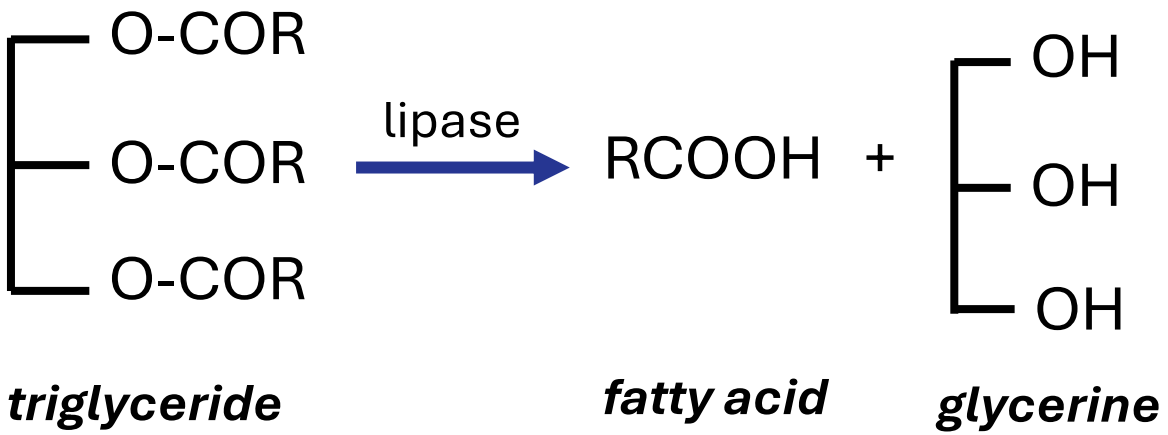
Increasing API Kinetic Solubility: Lipid Digestion

- Lipid digestion from oil-based formulations
  - When API solubility is lower in fatty acid: API precipitates as amorphous solid providing higher kinetic solubility
  - When API solubility is higher in fatty acid: fatty acid self-assembles to form micelles, which solubilize and disperse API (similar to SEDDS)



Lipid digestion by lipases

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Increasing API Dissolution Rate: Dissolved Drug Formulations

Type	Description	Weight % Inactive				Dispersion Diameter (nm)
		Tri- or Mixed Mono- + Di-glycerides	Hydrophobic Surfactant (HLB < 12)	Hydrophilic Surfactant (HLB > 12)	Hydrophilic Cosolvent	
I	Lipid	100	-	-	-	-
II	SEDDS	40-80	20-60	-	-	250-2000
IIIA	SEDDS	40-80	-	20-40	0-40	100-250
IIIB	SMEDDS	< 20	-	20-50	20-50	< 100
IV	Oil-free	0	0-20	30-80	0-50	< 100

$$HLB = 20\frac{mass\ of\ hydrophilic\ part}{molecular\ mass}$$

Holm, et al. Eur J Pharm Sci. 2023, 189, 106556

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Amorphous Solid Dispersions (ASDs) Basics

- Amorphous solid APIs have greater kinetic solubility – usually sufficiently long to enable absorption
- Polymer plus API form a molecular dispersion – slows crystallization both during shelf life and once exposed to water in GI tract
- Solubility enhancement 2-200 fold!
- Two predominant methods for forming ASDs
  - Hot melt extrusion
  - Spray-drying

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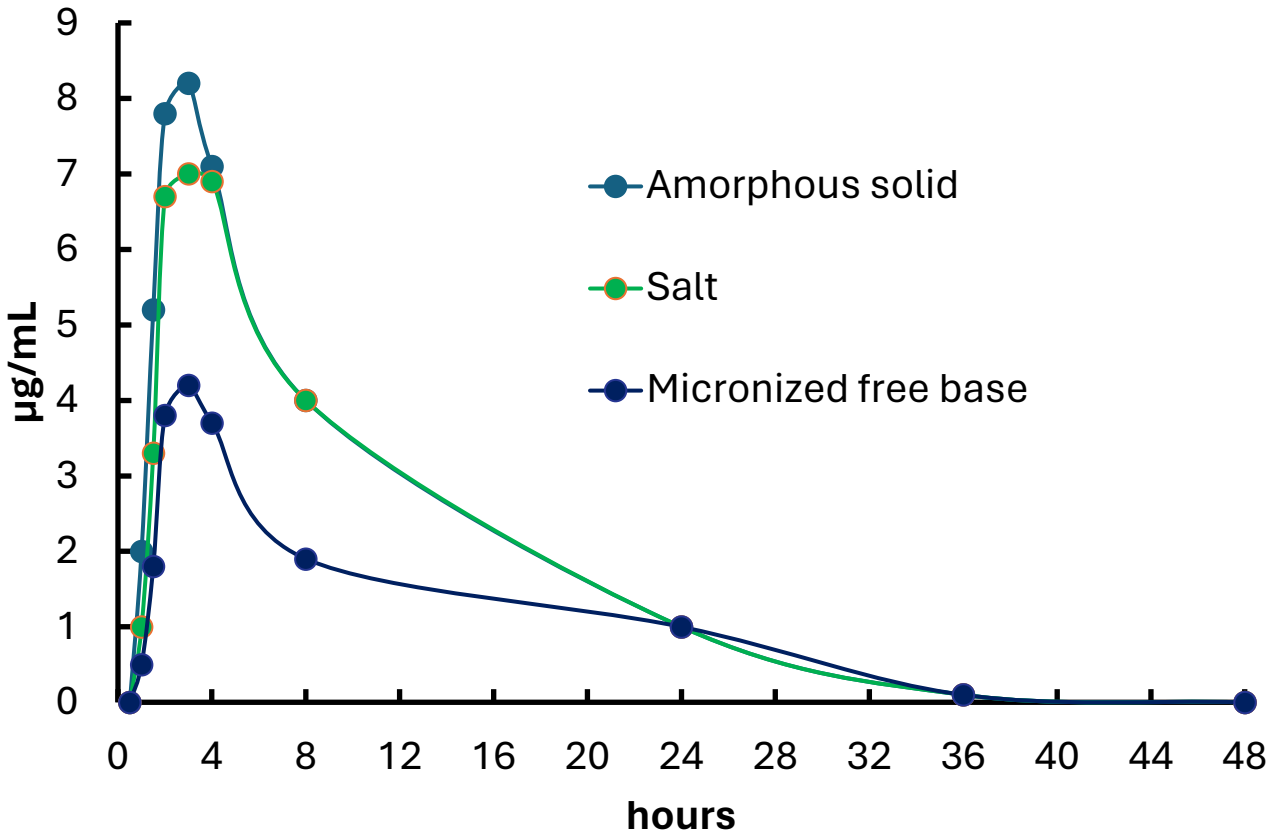
Supersaturation Impact on Absorption



Both salt form and amorphous solid provide good bioavailability

Mol. Pharmaceutics 2023, 20, 11, 5888–5900

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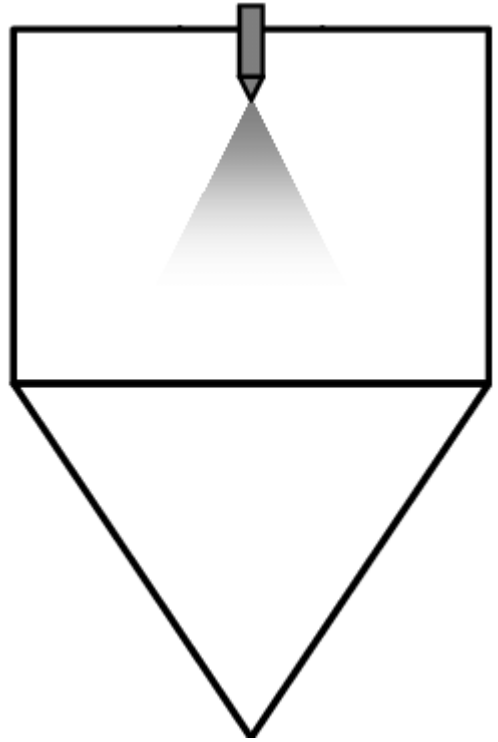
Amorphous Solid Dispersions: Spray-Dried Dispersions (SDDs)

- API and polymer need to dissolve in a volatile solvent (need to handle solvent vapor)
- Amorphous form locked in with rapid drying of droplets during spray-drying: need optimization at each scale
- Stability related to T_g and drug:polymer ratio
  - Want T_g at least 20°C above storage conditions
  - 25:75 drug:polymer ratio is often stable, but concerns with dose level and SDD loading in dosage form
  - ASAP approach works for crystallization rate determination (fast stability data)!



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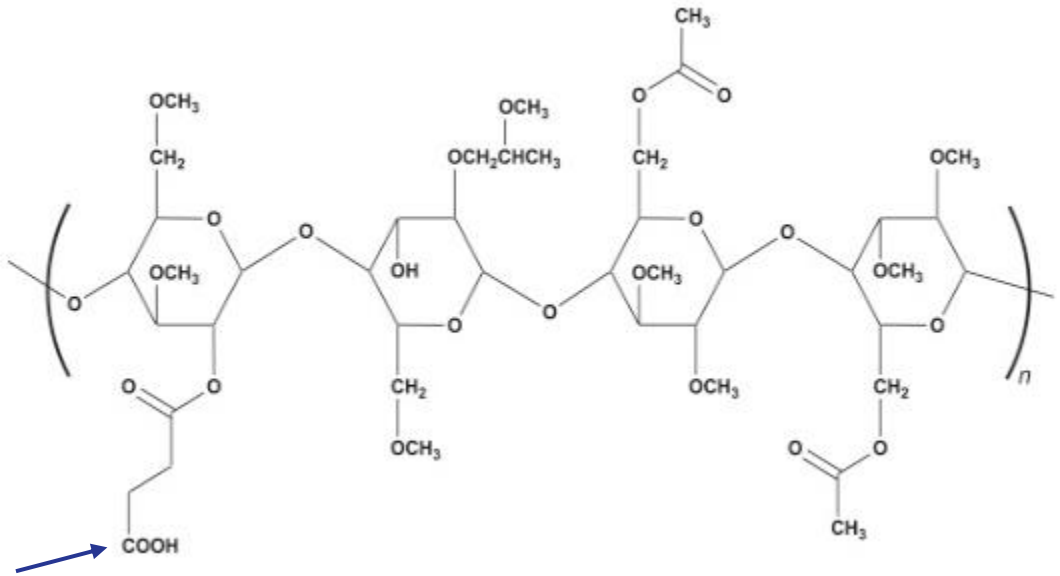
Spray-Dried Dispersions (SDDs): Polymer Selection

Polymer generally has both hydrophilic and hydrophobic groups

Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS)



Ionized in intestine

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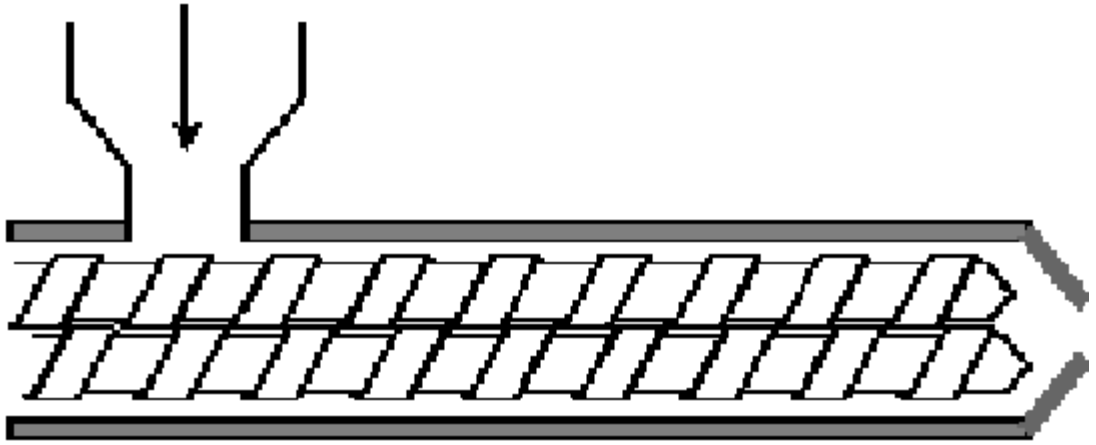
Amorphous Solid Dispersions: Hot Melt Extrusions (HME)

- Polymer needs to melt and dissolve API to form a solution
  - API needs to be stable at melt conditions
  - Can add plasticizers to lower extrusion temperature
- Cooling locks in amorphous form
- Continuous process using twin screw extruder
  - No solvents
  - Can scale-up easily
- Common pharma polymers
  - PVP/VA, PVA, PEG, PVP



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Summary

- MAD calculations useful to determine likelihood of needing solubilization based on preclinical data
- Low solubility results from high lattice energy (strong API-API molecular interactions) and/or hydrophobicity (weak H_2O-API interactions)
- Absorption can be limited by dissolution rate or API concentration in solution
- Increase API dissolution rate by salt formation, complexation, particle size reduction, or with oil/surfactant formulations
- Increase dissolved API concentration by use of amorphous solids, including *in vivo* precipitation and amorphous solid (dispersion)

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Questions?

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