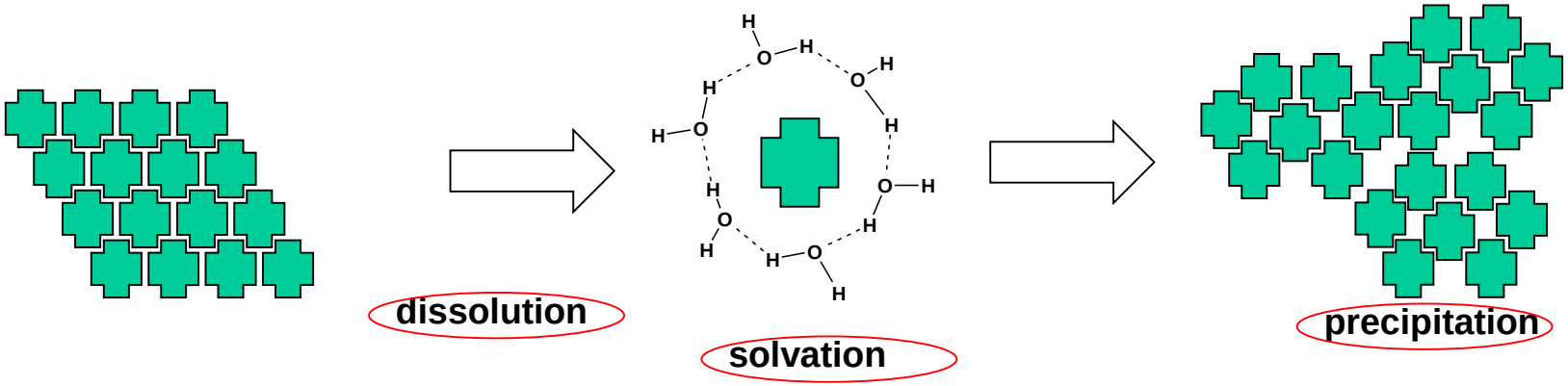
Solubility

Drug Absorption Process

Both physiological factors and physicochemical factors can affect the absorption process

Solubility risk assessment

Solubility is not a simple number…



Dissolution depends on:

- ➢ Properties of the crystal lattice
- ➢ Hydrophilic character of external surfaces
- ✓ melting point can be used as a surrogate of lattice strength
- ✓ logP as a surrogate for hydrophobicity

Dissolution is amenable to improvement by formulation

Solvation depends on:

- ➢ Hydrophobicity of compound (logP, or logD)
- ➢ pKa; ionized species are better solvated in GI track
- ➢ Hydrogen-bond donor/acceptor sites; however these may also lead to stronger lattices

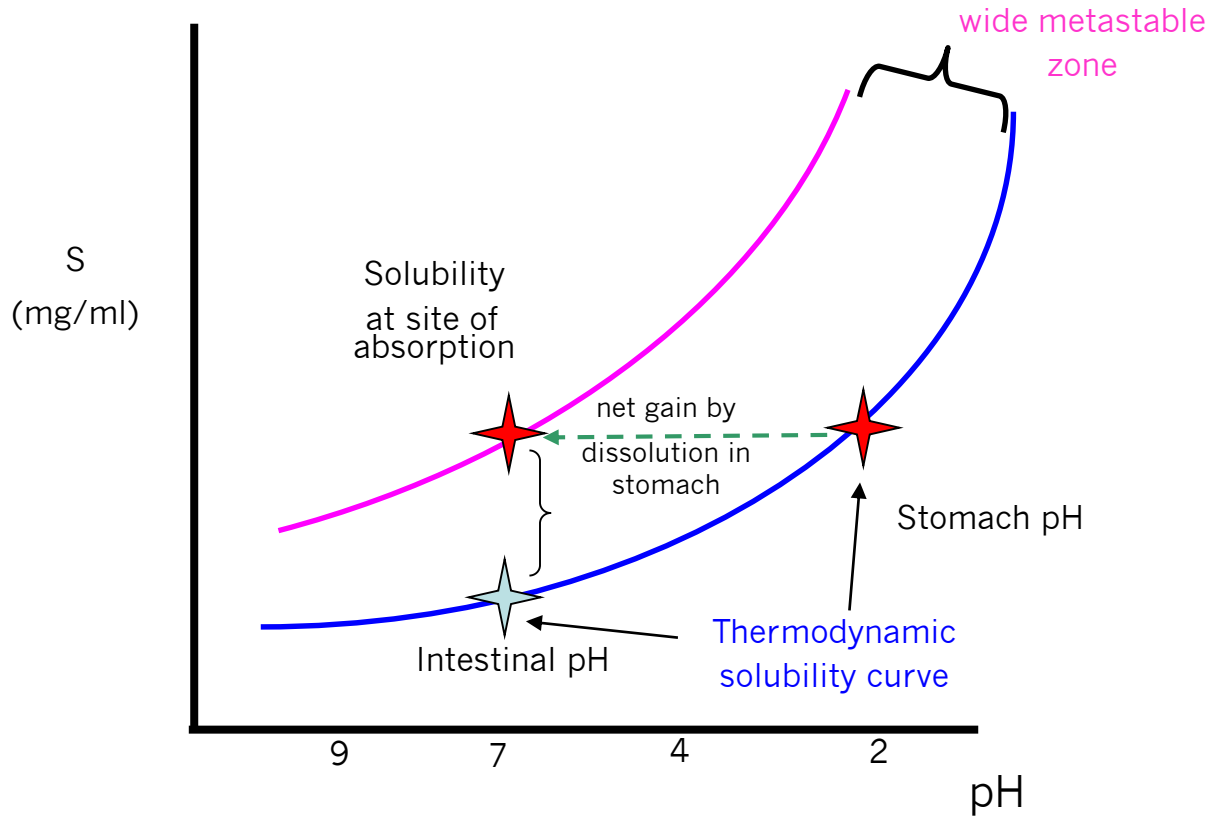
Precipitation depends on:

- ➢ Lattice strength of precipitating form
- ➢ Solvation energy; well solvated entities will take longer to precipitate
- ➢ Solvent and surrounding in solution

Solvation and precipitation are a function of the molecule's structure, and can not be altered by formulation

Solubility and pH Effects

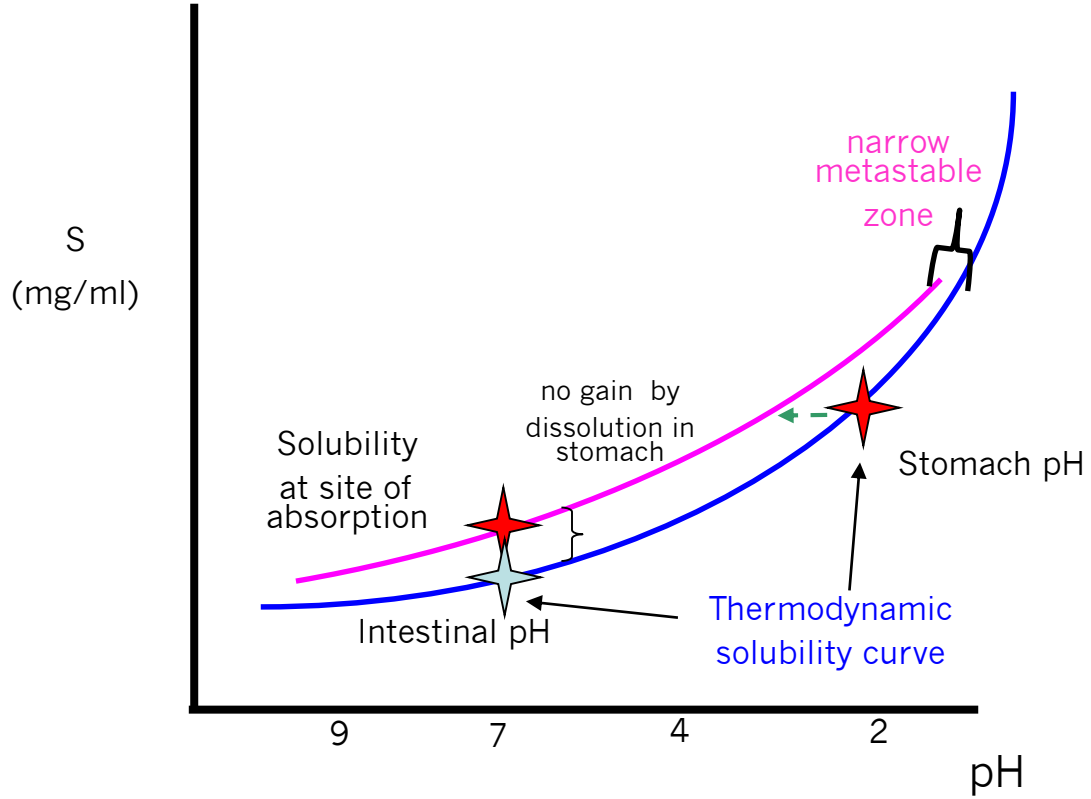
"good" solvation/precipitation



"Good" solvation/precipitation balance has a positive effect on absorption

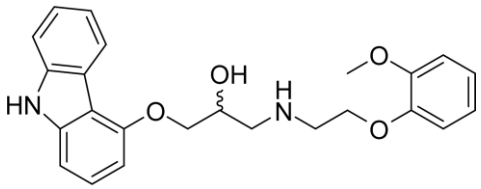
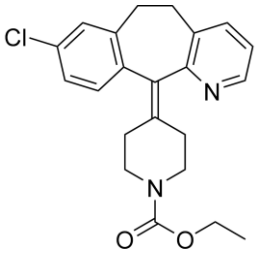
Solubility and pH Effects

"poor" solvation/precipitation



"Poor" solvation/precipitation balance has a negative effect on absorption

Solubility: Buffers vs Simulated GI Fluids

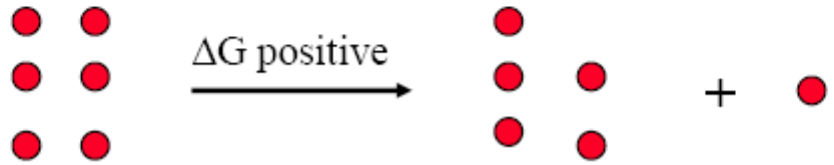
Compound	Structure	Solubility in Phosphate buffer (µg/ml)	Solubility in (FaSSIF) (µg/ml)
Carvedilol		22	99
Loratidine		4	35

FaSSIF – Fasted state Simulated Intestinal Fluid

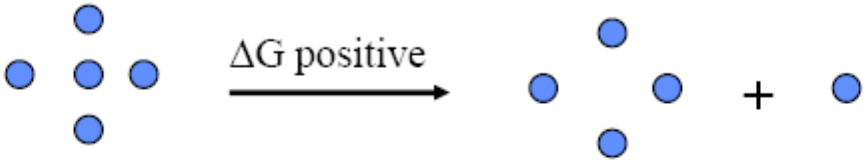
What do We Mean by the Term SOLUBILITY?

Solubility can be thought of as a Three Step Process

1. Removal of a Molecule from its Crystal Lattice



2. Creating a Void in the Solvent



3. Release of Solvation Energy

Hildebrand & Scott, 1950. Solubility of Non-electrolytes, New York, Reinhold

Definitions

Solubility is a physical property referring to the ability for a given substance, the solute, to dissolve in a solvent. It is measured in terms of the maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution. Certain substances are soluble in all proportions with a given solvent, such as ethanol in water. This property is known as miscibility.

Under various conditions, the equilibrium solubility can be exceeded to give a so-called supersaturated solution, which is metastable. The solvent is often a liquid, which can be a pure substance or a mixture. The species that dissolves, the solute, can be a gas, another liquid, or a solid. Solubilities range widely, from infinitely soluble such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly soluble compounds, though strictly speaking there are very few cases where there is absolutely no material dissolved.

Solubility and Dissolution

Solubility:

- Equilibrium solubility: It is the saturation concentration of the drug, at a defined temperature and pressure, in equilibrium with the specific solid form of the drug. Aqueous solubility of drugs is traditionally determined using the equilibrium solubility method that involved suspending an excess amount of a solid drug in a selected aqueous medium.
- Kinetic Solubility: It is the concentration when an induced precipitate first appears in a solution. While results may be similar, kinetic solubility is often much higher than equilibrium solubility.

Dissolution should be conceptually separated from solubility. Dissolution is a kinetic process and it is quantified by its rate. Solubility quantifies the dynamic equilibrium state achieved when the rate of dissolution equals the rate of precipitation.

Pro's and Con's

Thermodynamic

- Equilibration with most stable crystalline form for given solvent/buffer system
- Pros: accurate value system understanding later development
- Cons: need analytical methods (for solid and solution)

  laborious

  compound intensive limits number of compound screened

Kinetic (Apparent)

- Rapid determination often from metastable system with non specific assay
- Pros: high thoughput solubility ranking early development

  minimal analytical small compound consumption
- Cons: may mislead (over or underestimate) limited system understanding cosolvent effects

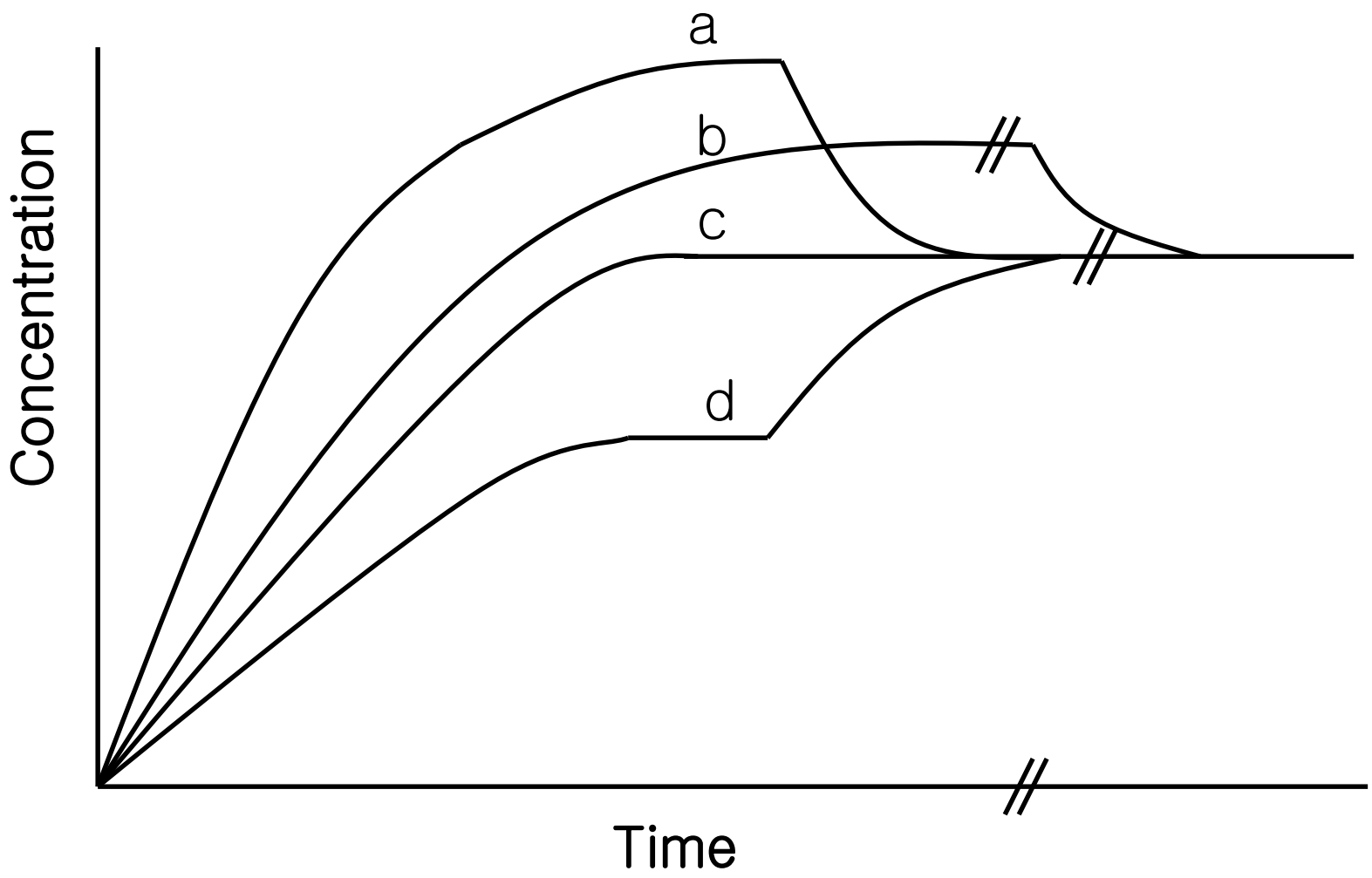
FDA Definitions

- **High solubility**
  - **when highest dose strength is soluble in ≤ 250 ml aqueous media**

    over pH range 1 to 7.5
- **High Permeability**
  - **≥90% of an administered dose is absorbed, based on mass balance or IV comparison**
- **Rapidly dissolving**
  - **≥85% of the drug substance dissolves in 30 min using USP Apparatus I at 100 rpm in 900 ml or less of:**
    - **0.1 N HCl or Simulated Gastric Fluid USP I w/out enzymes**
    - **pH 4.5 buffer**
    - **pH 6.8 buffer or Simulated Gastric Fluid USP I w/out enzymes**

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, US FDA, August 2000

Dissolution patterns by solid-state modification



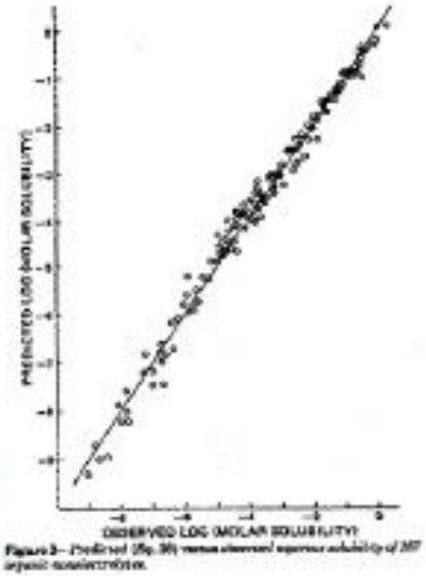
Solubility and Partitioning I: Solubility of Nonelectrolytes in Water

SH Yalkowsky and SC Valvani

J. Pharm. Sci. 69 (1980) 912-922

$\log S_w = -1.05 \log PC - 0.012MP + 0.87$

$n = 155 \quad r^2 = 0.979 \quad s = 0.308$



General Solubility Equation (GSE)

$$\text{Log } S_w = 0.5 - 0.01(T_M - 25) - \log P$$

General solubility equation for nonelectrolytes

$\log S_w(M/L) = 0.5 - \log P - 0.01(T_M - 25)$

If melting point is high → alter crystal to decrease MP

Micronize, microprecipitate, polymorph, amorphous

Change only apparent solubility and the dissolution rate

If logP is high → alter vehicle

Cosolvent, surfactant, complexant, buffer

General equation for solubilization by a cosolvent

$$\log S_{mix} = \log S_w + \sigma f_c$$

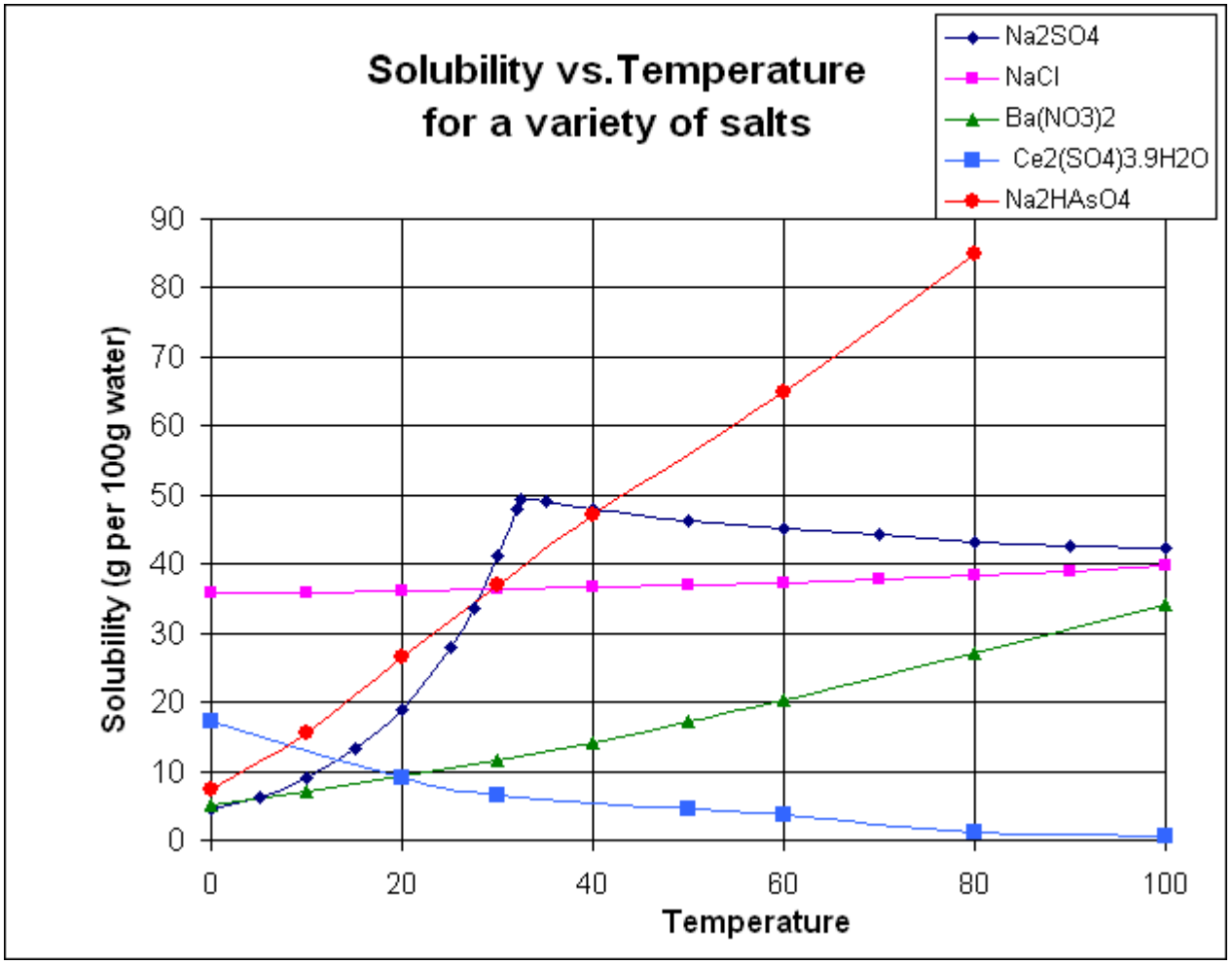
Smix: solubility of a non-polar solute in a mixed solvent

Sw: aqueous solubility of the solute

σ: solubilizing power of the cosolvent for the solute

fc: volume fraction of water and cosolvent in the mixture

Temperature effects



Polarity Effect

A popular aphorism used for predicting solubility is "*Like dissolves like*" This indicates that a solute will dissolve best in a solvent that has a similar polarity to itself. This is a rather simplistic view, since it ignores many solvent-solute interactions, but it is a useful rule-of-thumb. For example, a very polar (hydrophilic) solute such as urea is highly soluble in highly polar water, less soluble in fairly polar methanol, and practically insoluble in non-polar solvents such as benzene. In contrast, a non-polar or lipophilic solute such as naphthalene is insoluble in water, fairly soluble in methanol, and highly soluble in non-polar benzene.

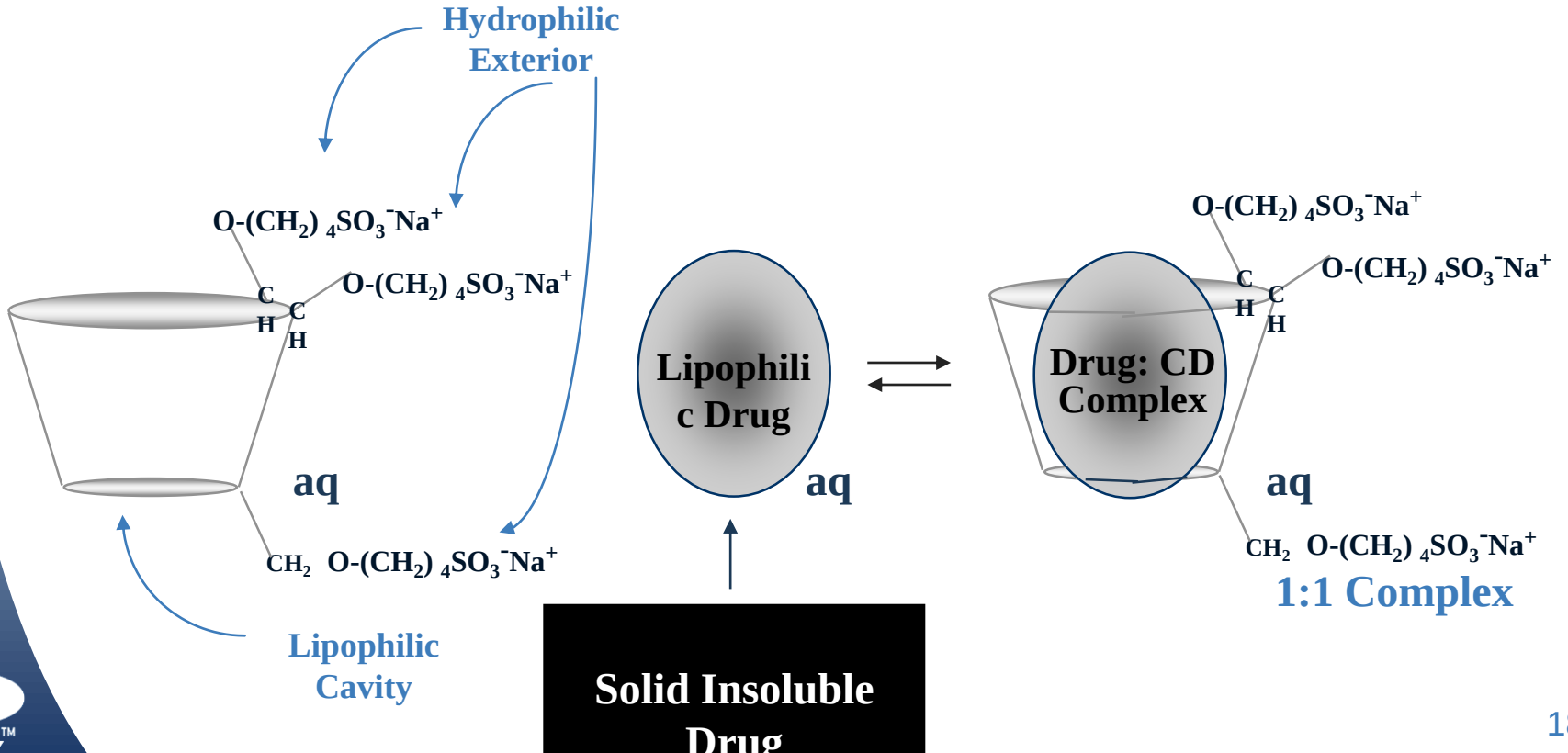
Cyclodextrin Drug Complexes

Enhance the Drug's Water Solubility

Increase Drug's Aqueous Solution Stability

Improve Solubility & Dissolution: Improve Oral Bioavailability

Effective Delivery



Phase Solubility Diagram-CD Drug Complexation

Higuchi and Connors Phase Solubility Method

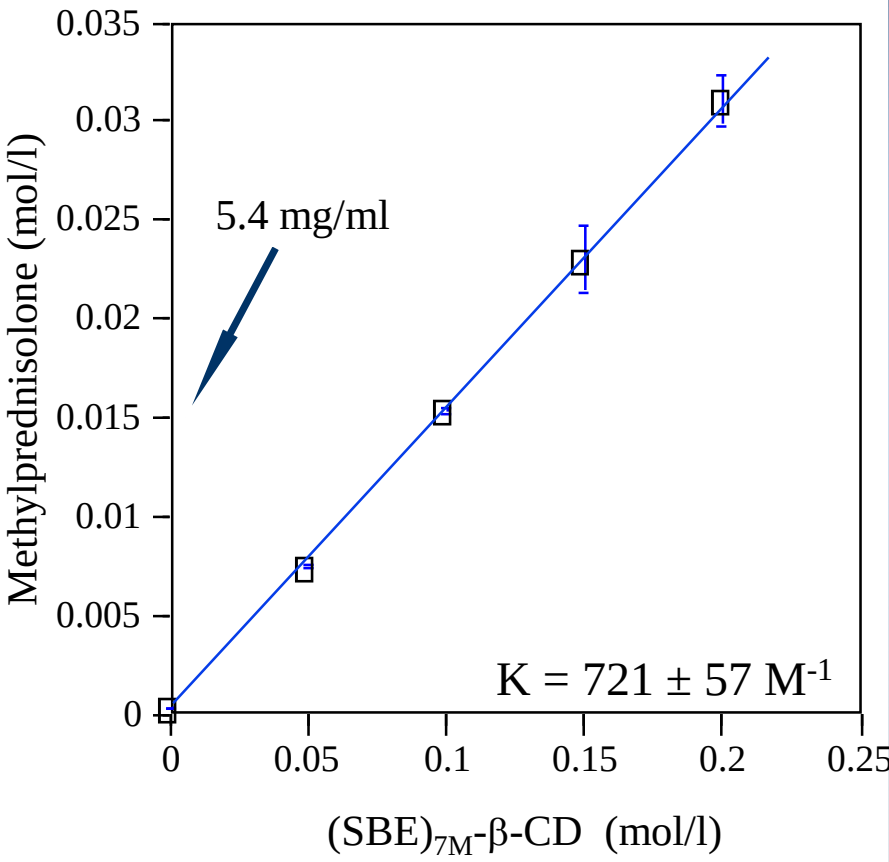
$$Drug_{free} + CD_{free} \underset{}{\overset{K}{\rightleftharpoons}} CD\text{-}Drug_{complex}$$

$$Drug_{free} \underset{}{\overset{S_o}{\rightleftharpoons}} Drug_{solid}$$

$$K = \frac{[CD\text{-}Drug]_{complex}}{[Drug]_{free}[CD]_{free}}$$

$$[Drug]_{total} = S_o + \frac{KS_o}{1 + KS_o}[CD]_{total}$$

Drug Solubilization with Captisol

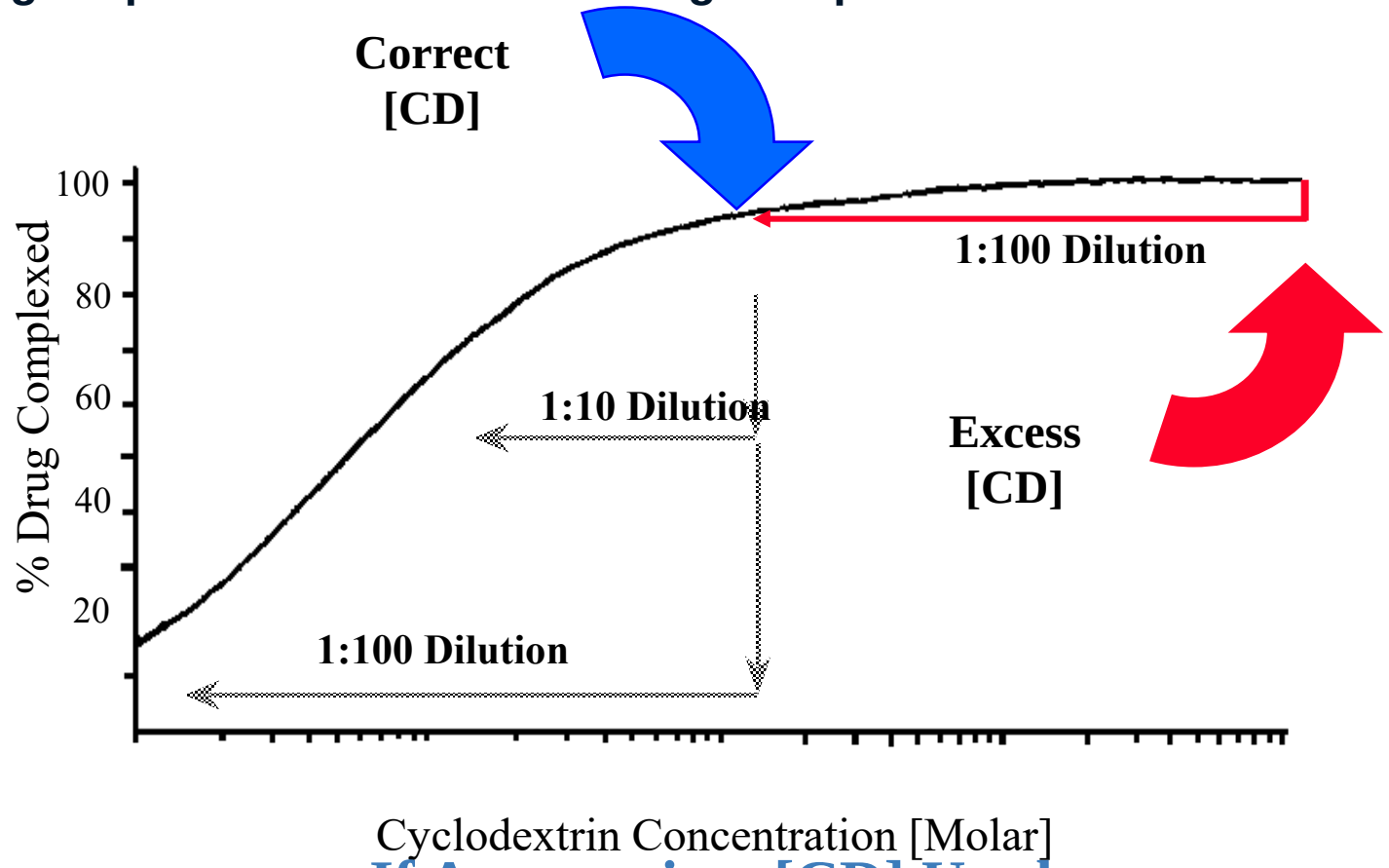


Higuchi and Connors, *Advances in Analytical Chemistry and Instrumentation*, 4 (1965) 117-212.

Optimize CD Concentration For Effective Delivery

$$K = \frac{[\text{CD-Drug}]_{complex}}{[\text{Drug}]_{free}[\text{CD}]_{free}}$$

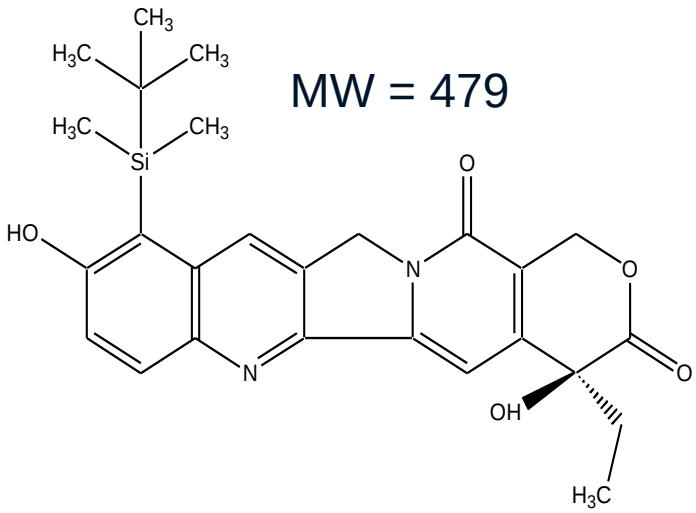
Rearrange Equation and Plot as % Drug Complexed vs CD Concentration



If Appropriate [CD] Used

1:100 Dilution Will Fully Dissociate Drug: CD Complex

Standard Formulations Are Not Working



Silatecan
Modified Camptothecin Analog
NCI Cancer Chemotherapeutic

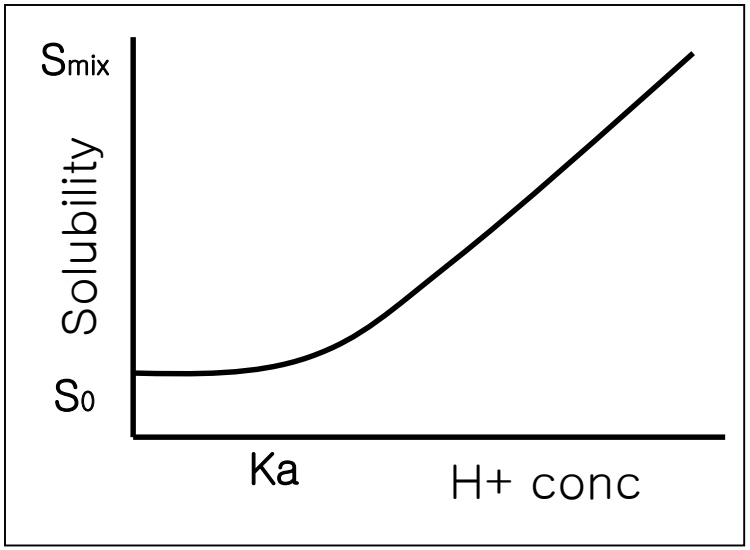
Target – 2 mg/ml

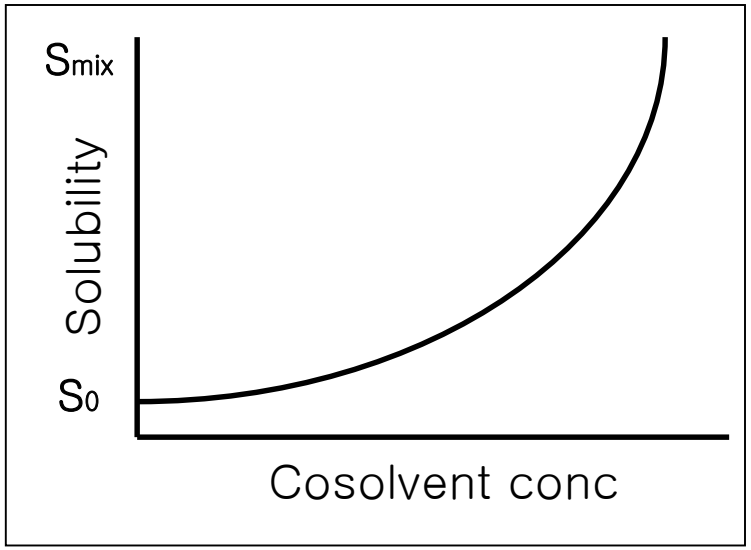
- **Solvent** **Solubility (mg/ml)**
- Water pH ~7.4 ~0.001
- Water pH 10.2 17.8
- Cosolvents in Water
- 40% PG 10% EtOH 0.173
- 50% PEG 400 0.200
- Emulsion 0.206

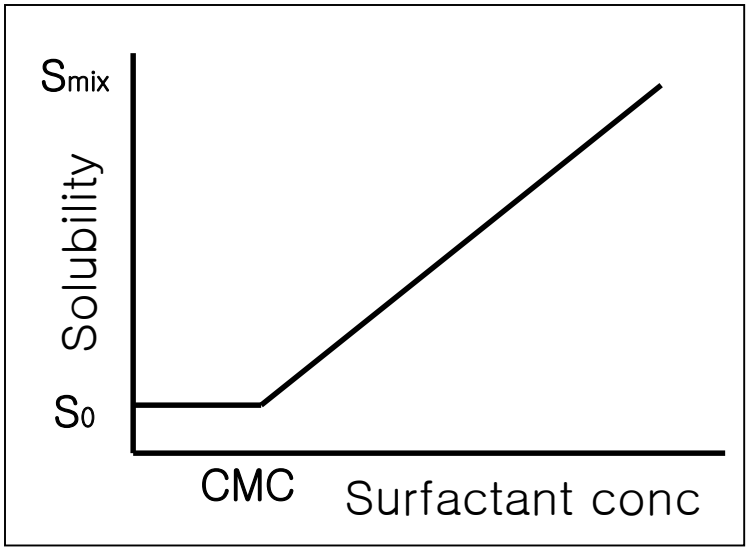
Stable Supersaturated Aqueous Solutions of Silatecan 7-t-butyldimethysilyl-10-Hydroxycamptothecin via Chemical Conversion in the Presence of a Chemically Modified b-Cyclodextrin, T. Xiang and B. Anderson, Pharm. Res., 19 (8), 1215-1222, 2002

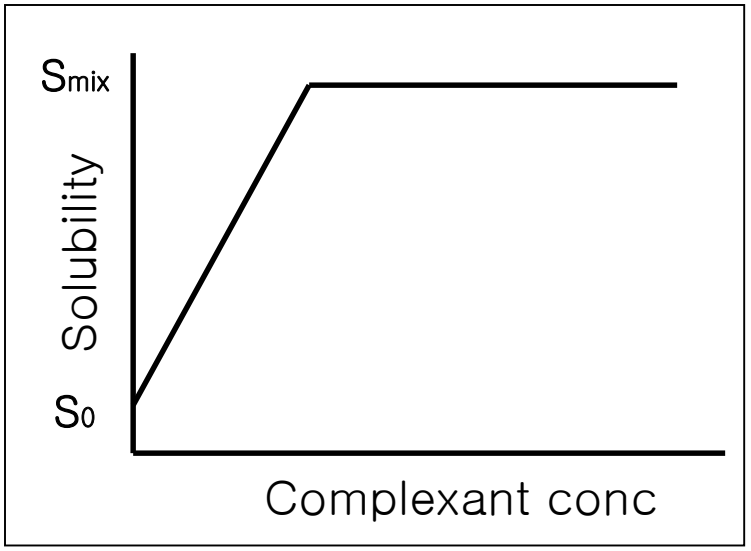
CyDex™

Solubilization

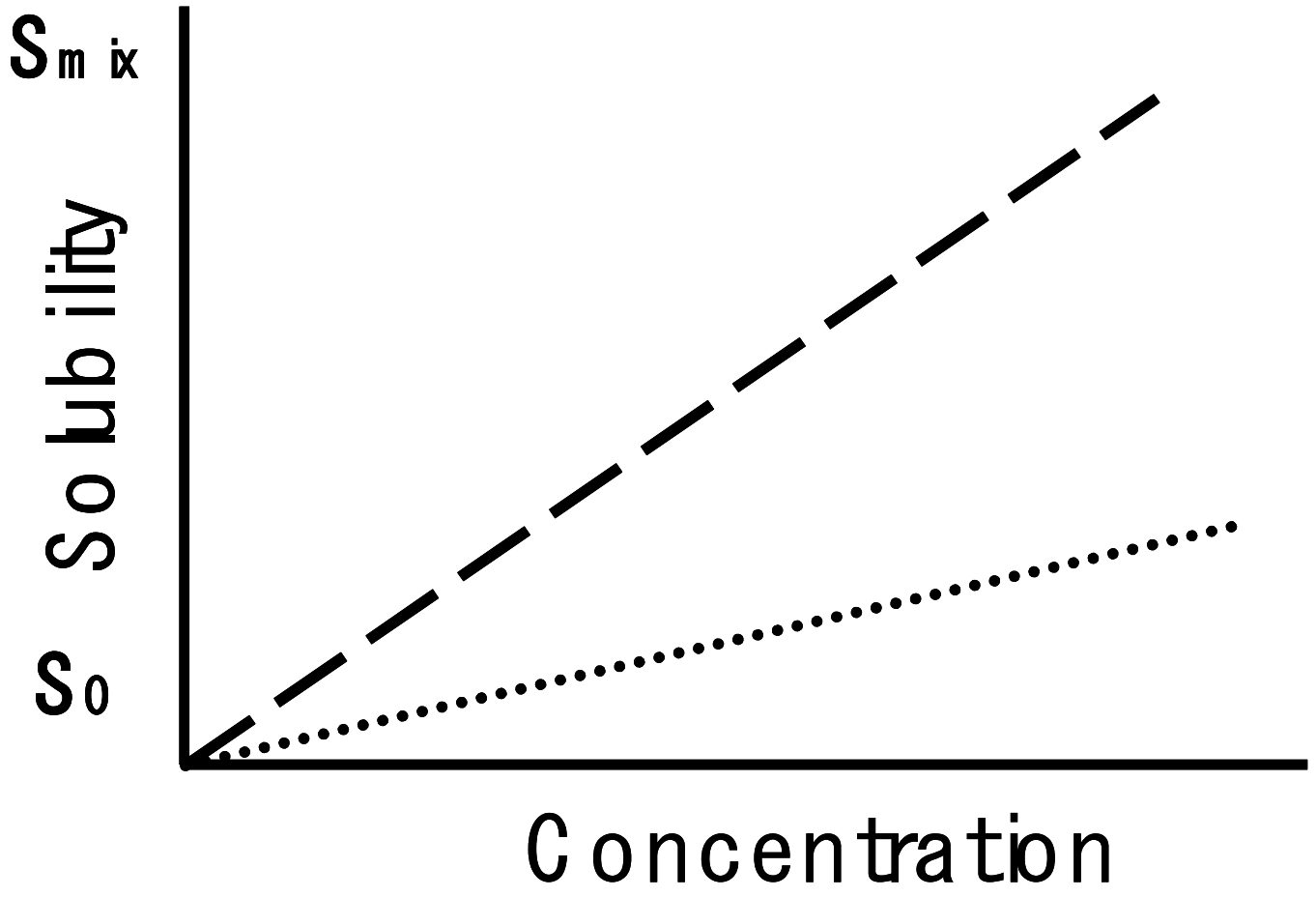




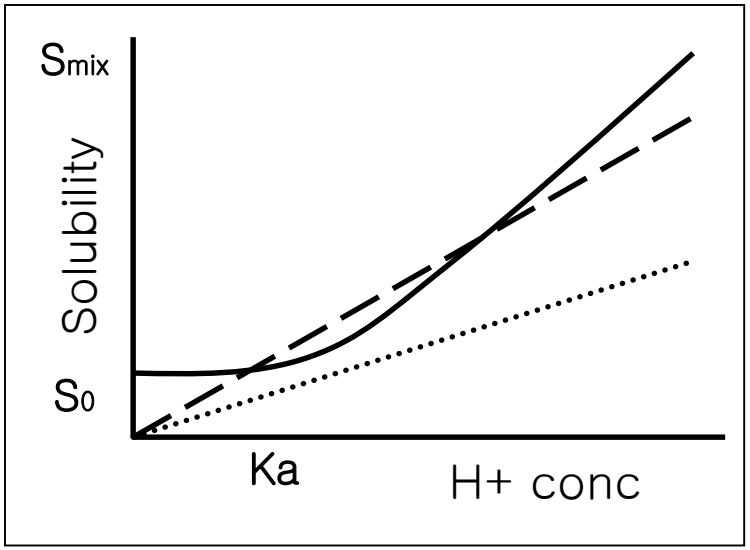


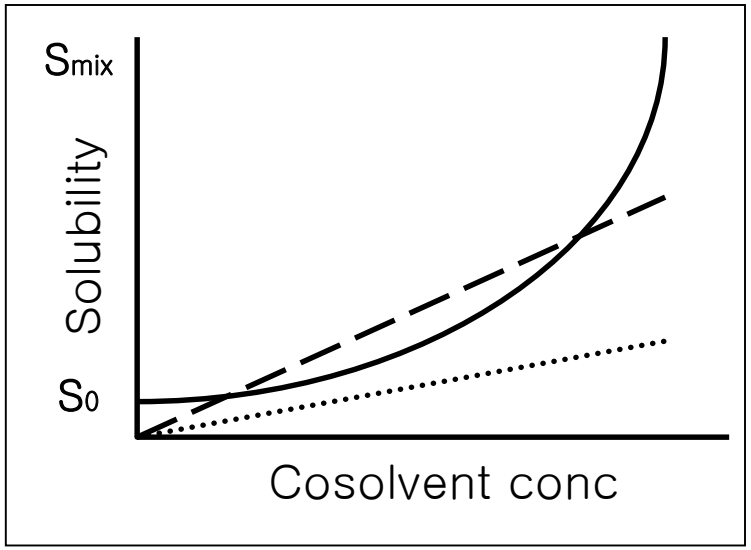


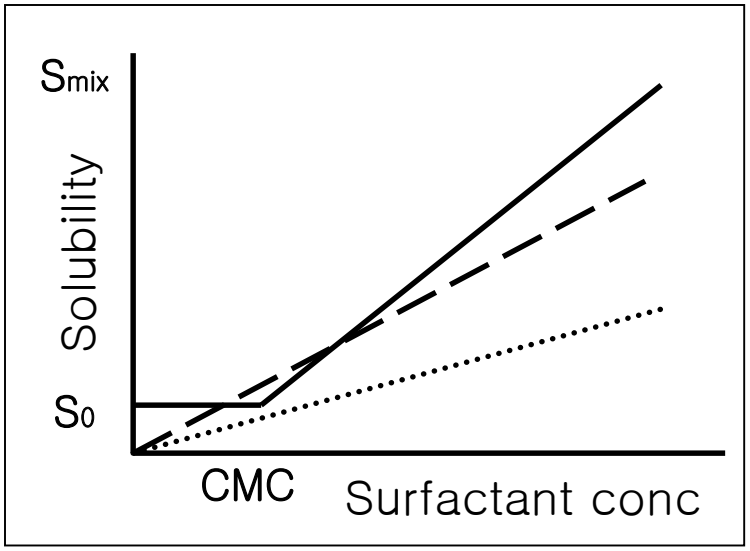
Dilution

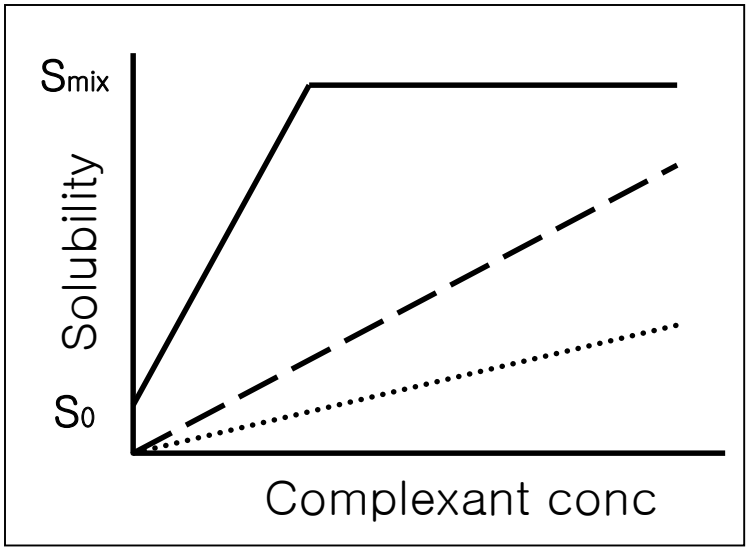


Dilution & precipitation



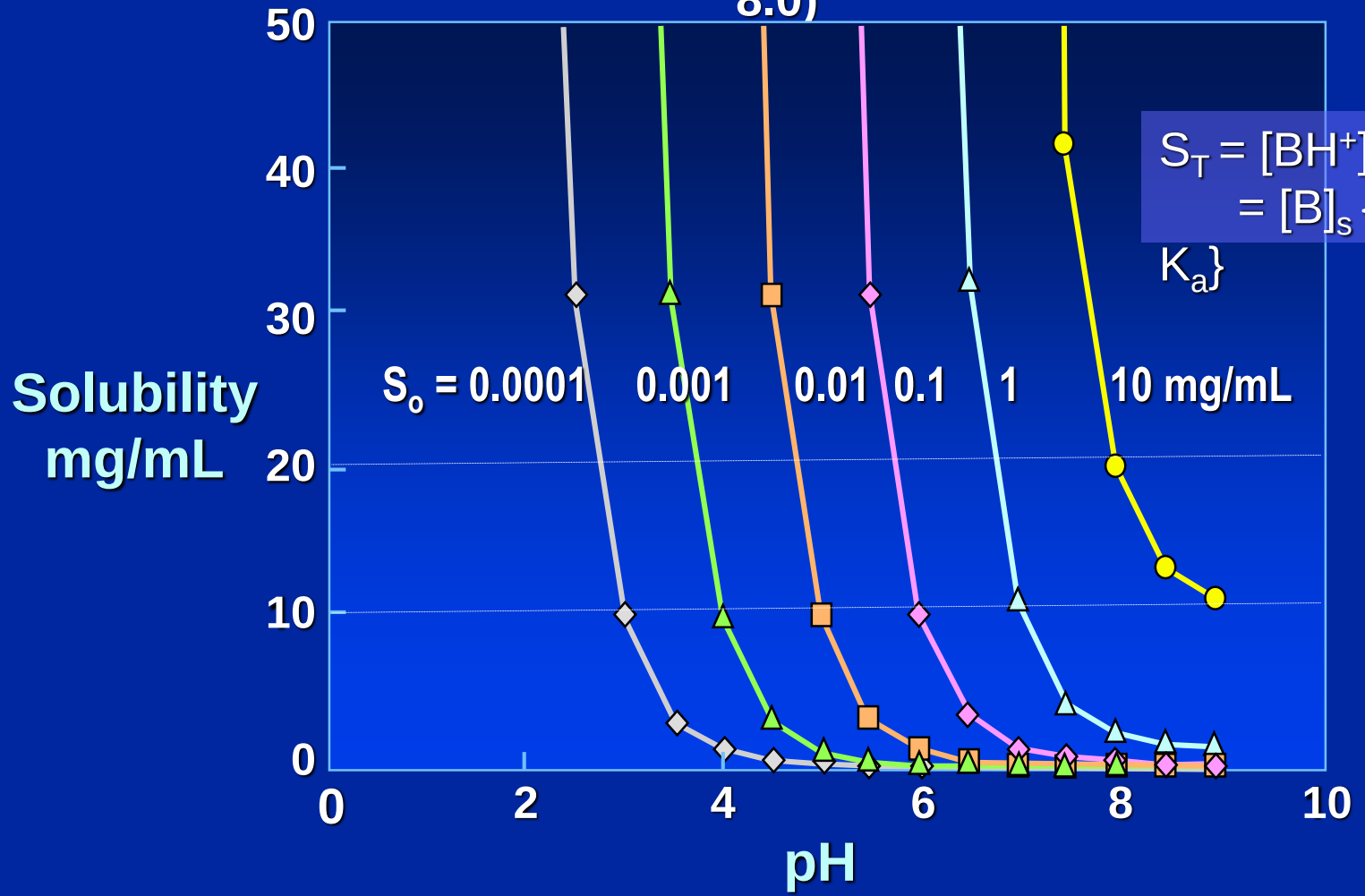






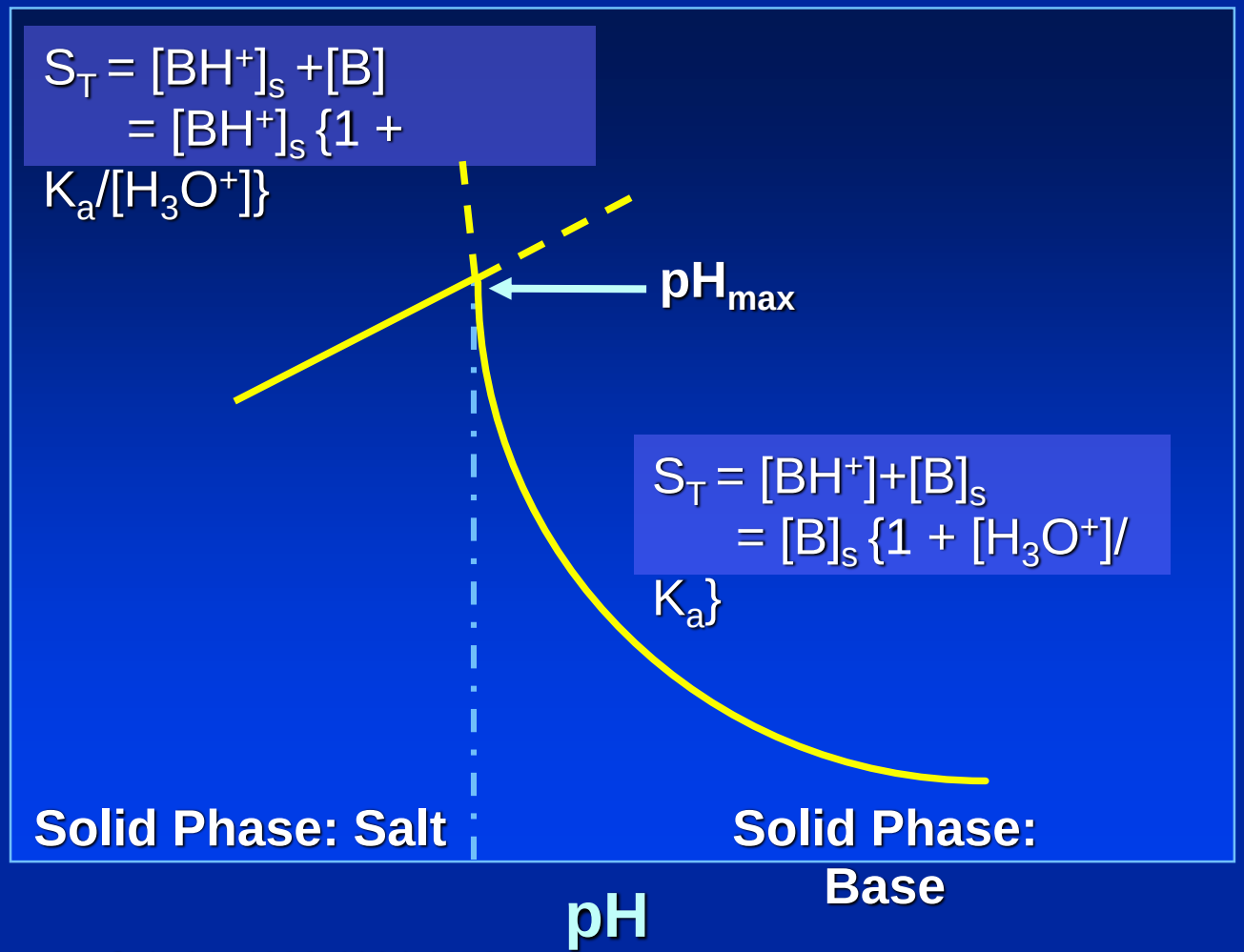
Theoretical Modeling of pH-Solubility Profiles

Effect of Intrinsic Solubility (S_o) on pH_{max} of a Base (pK_a = 8.0)



General pH-Solubility Considerations

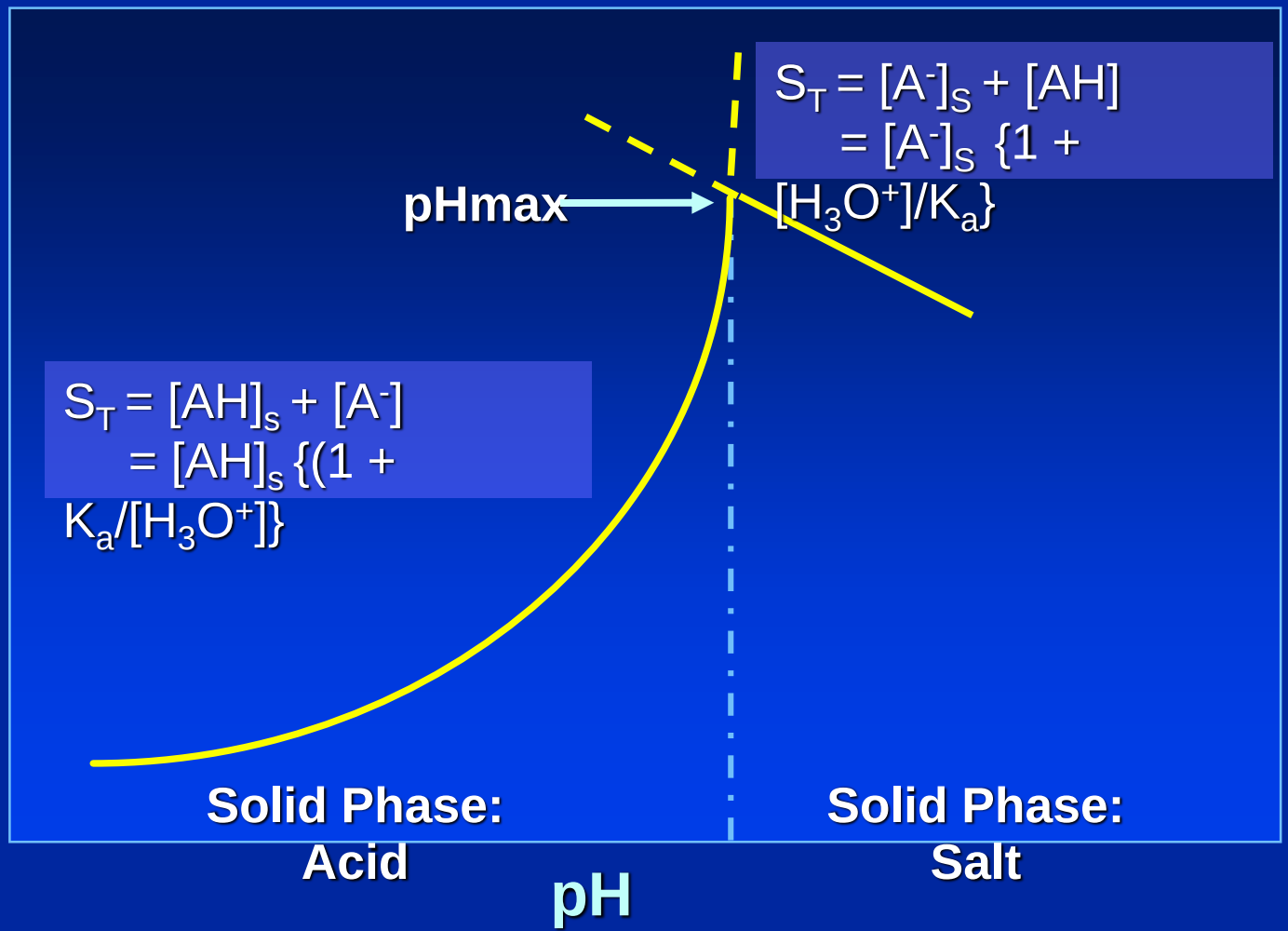
Monobasic Compound



Ref: Kramer & Flynn, *J. Pharm. Sci.*, 61, 1896-1904,1972.

General pH-Solubility Considerations

Monoprotic Acid



Ref: Chowhan, *J. Pharm. Sci.*, 67, 1257-1260,1978.

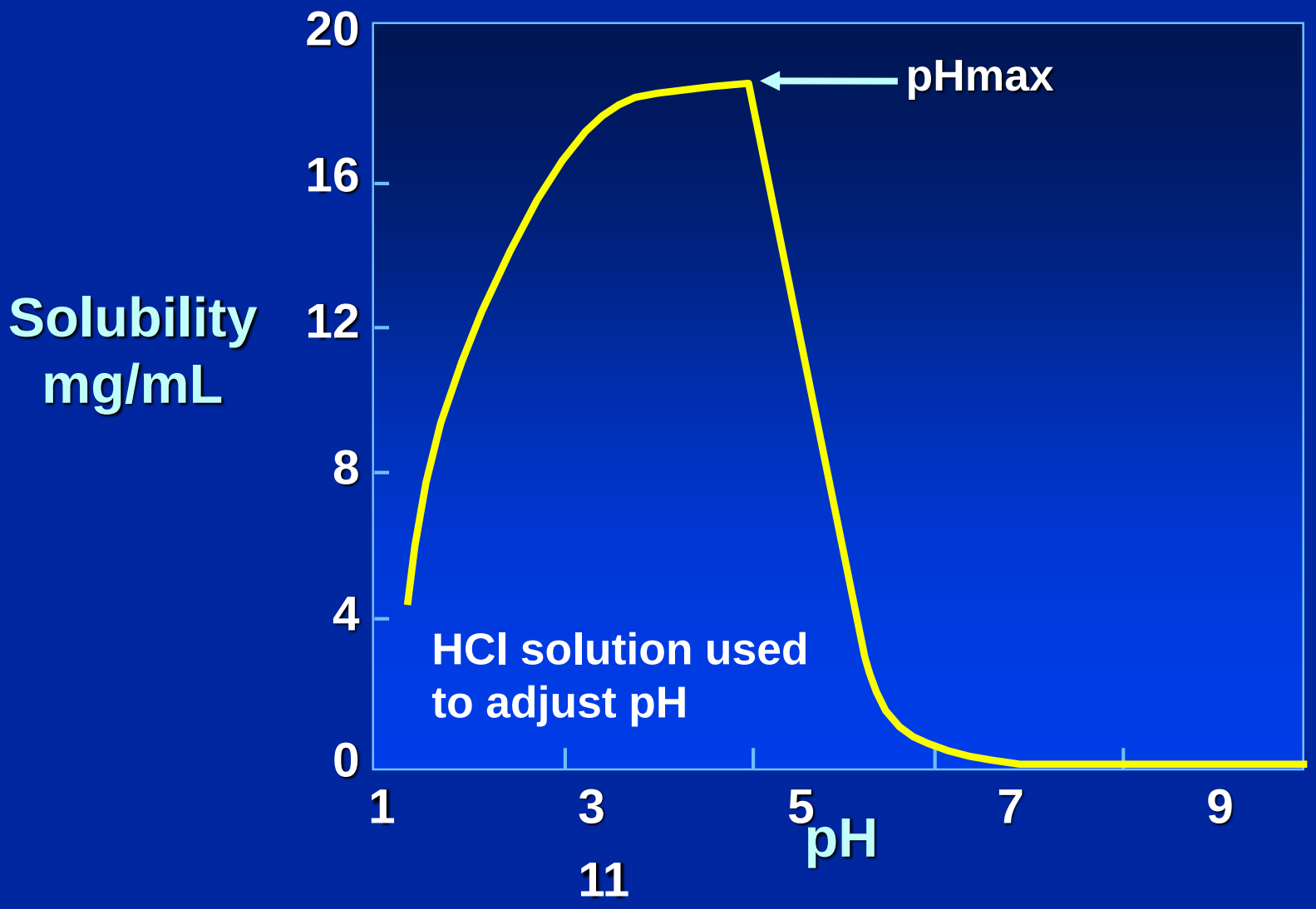
Feasibility of Salt Formation - Compound A

How can pH-solubility principle be used for Compound A?

pKa = 8 1

S_o = 0 06 mg/mL

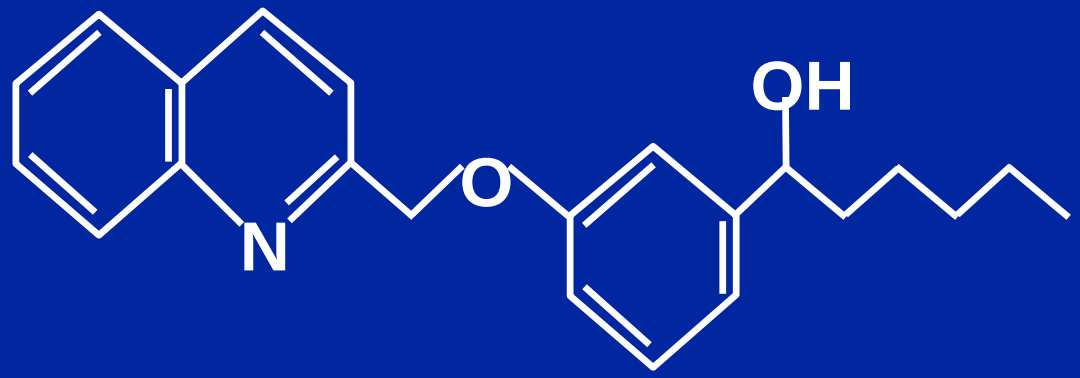
pH-Solubility Profile of Compound A



Feasibility of Salt Formation - Compound A

- pH_{max} ~ 5.5
- pH can be lowered below 5.5 with strong as well as relatively weak acids
- Salt formation with most common counter-ions might be feasible
- Acetate, fumarate, succinate and hydrochloride salts had acceptable crystallinity
- A relatively simple case!

Another Example - Compound B

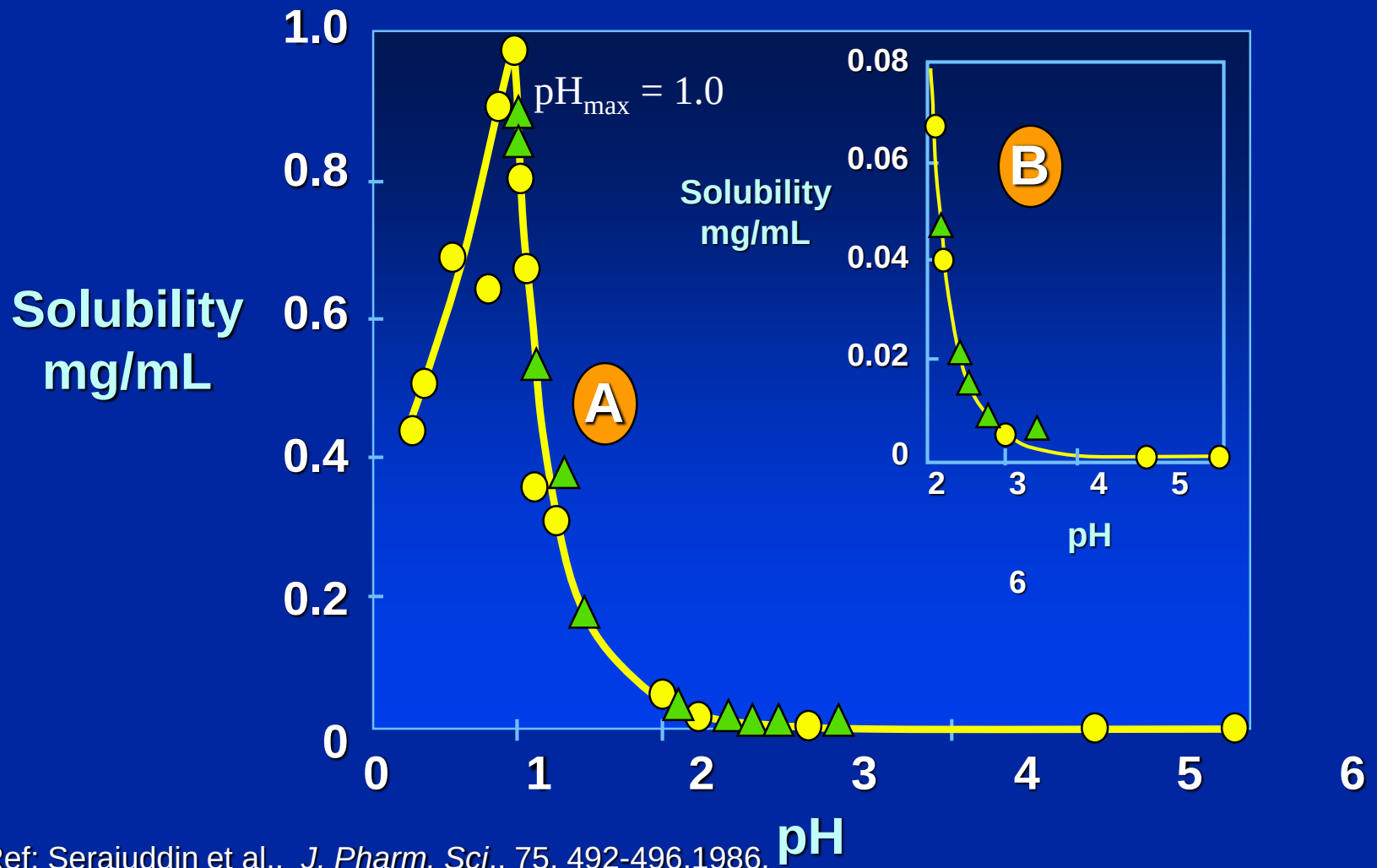


pK_a = 3.6; S_o = 0.002 mg/mL

- Will it form a salt?
- Only with relatively strong acids?

Lets first look at the pH-solubility relationship

pH-Solubility Profile of Compound B



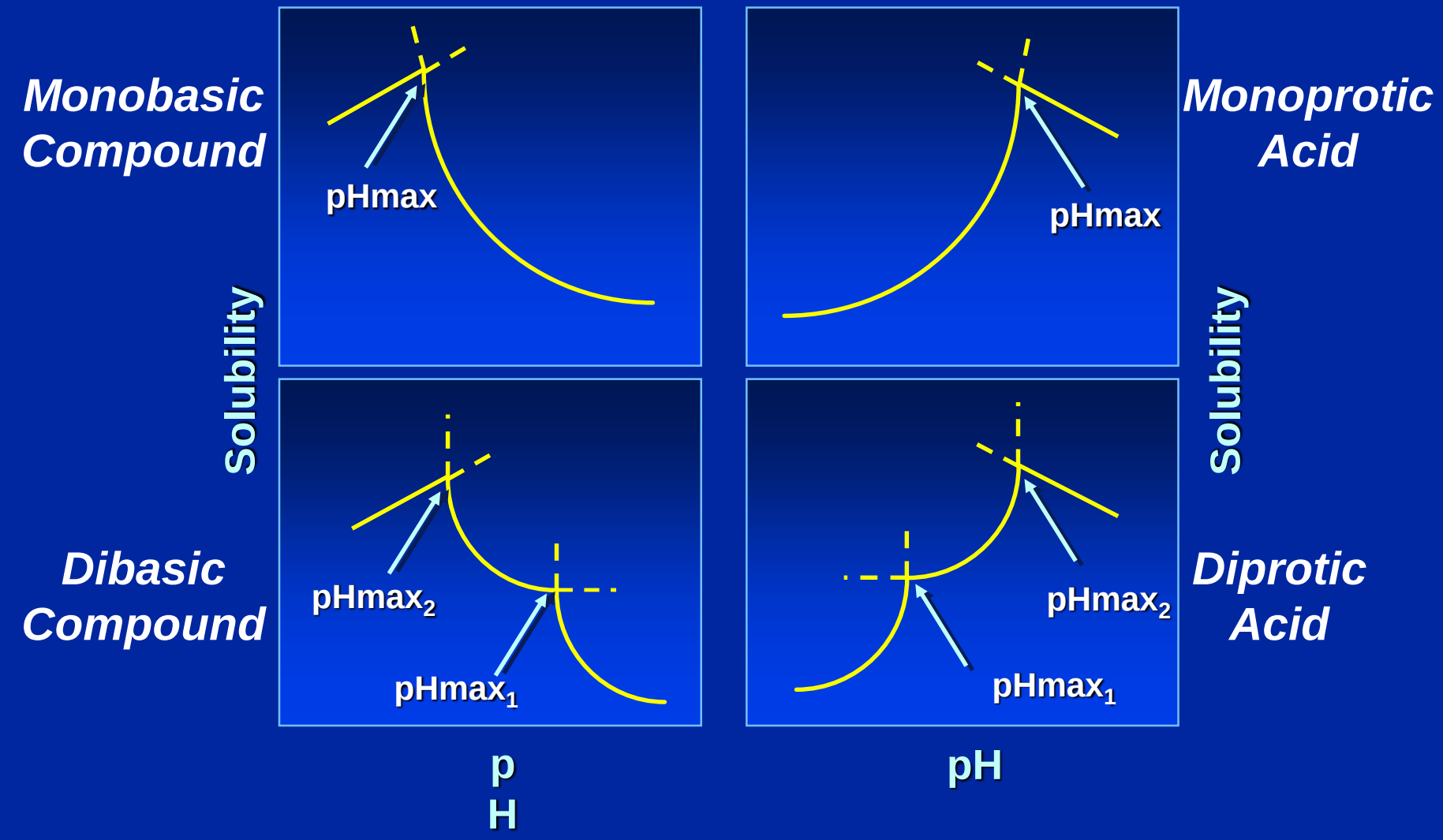
Ref: Serajuddin et al., *J. Pharm. Sci.*, 75, 492-496,1986.

Feasibility of Salt Formation: Compound B

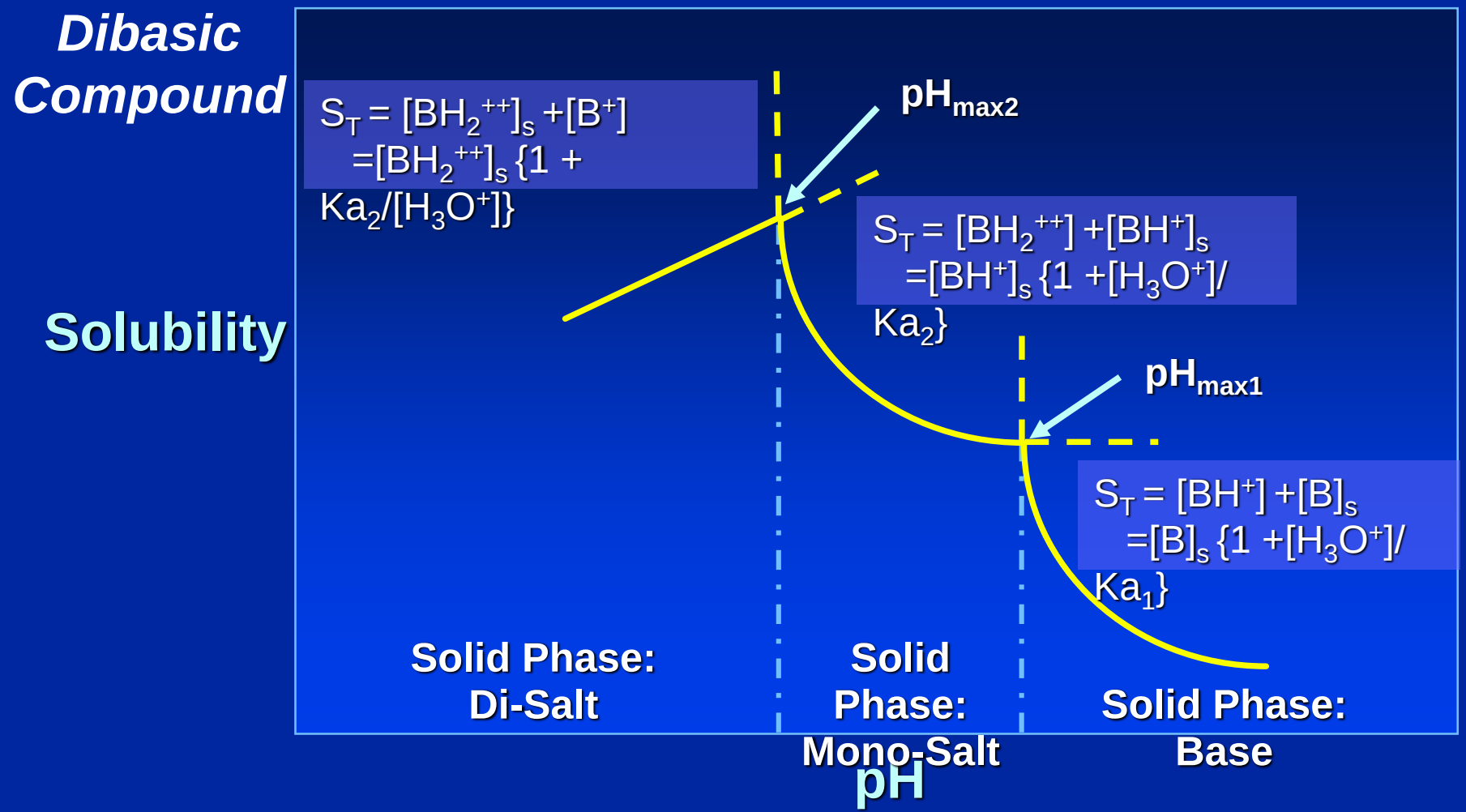
What did we learn from pH-solubility profile?

- **pH_{max} = 1.0; pH in aqueous media must be lowered below 1 to form salt**
- **Salt formation with strong acids could possibly be feasible**
- **Indeed, hydrochloride and sulfate salts could be prepared with difficulty; hygroscopic, chemically unstable, easily converted to free base, dissolved poorly**
- **Free base was selected for development**

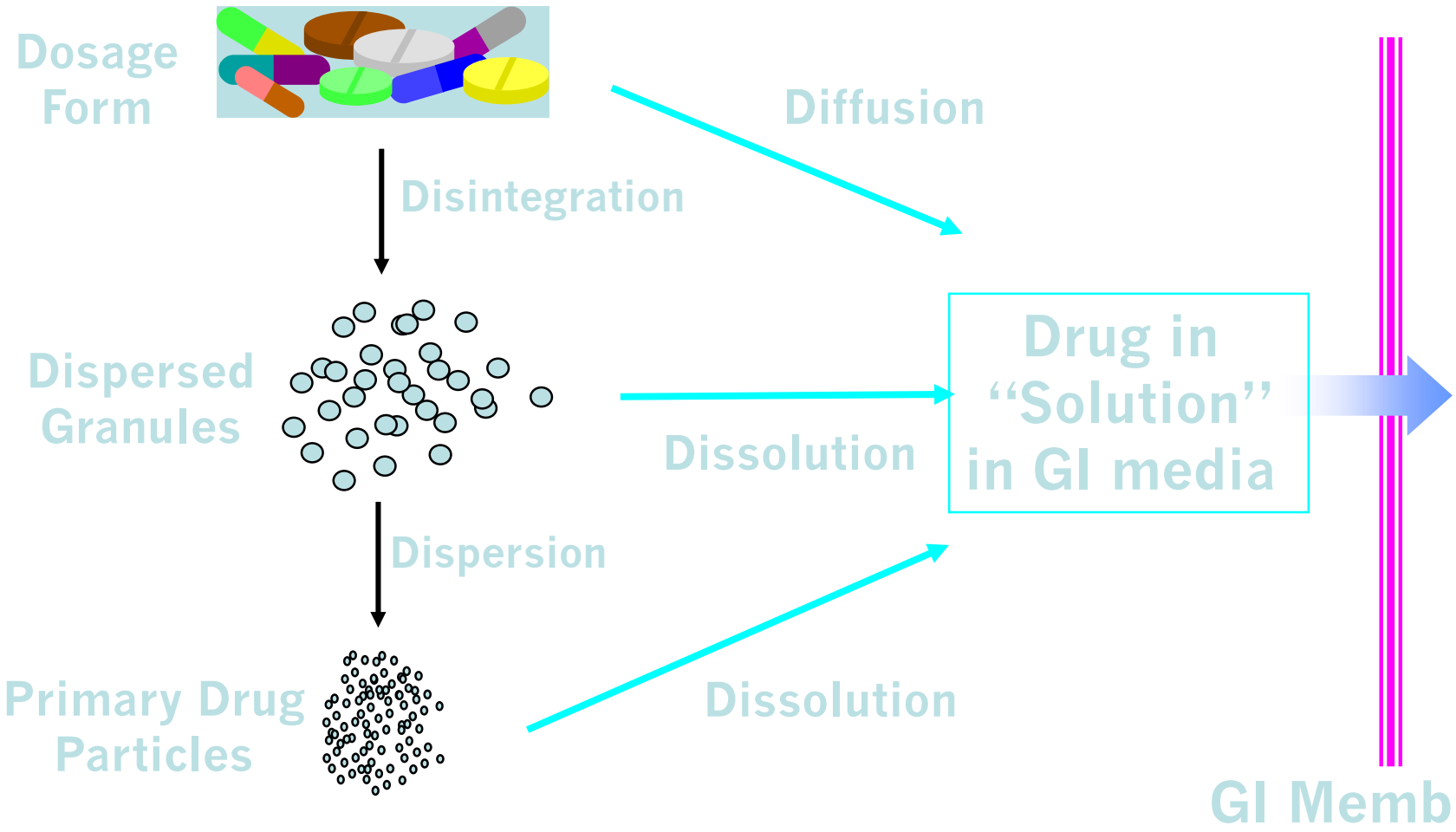
Considerations for Di-Salt Formation



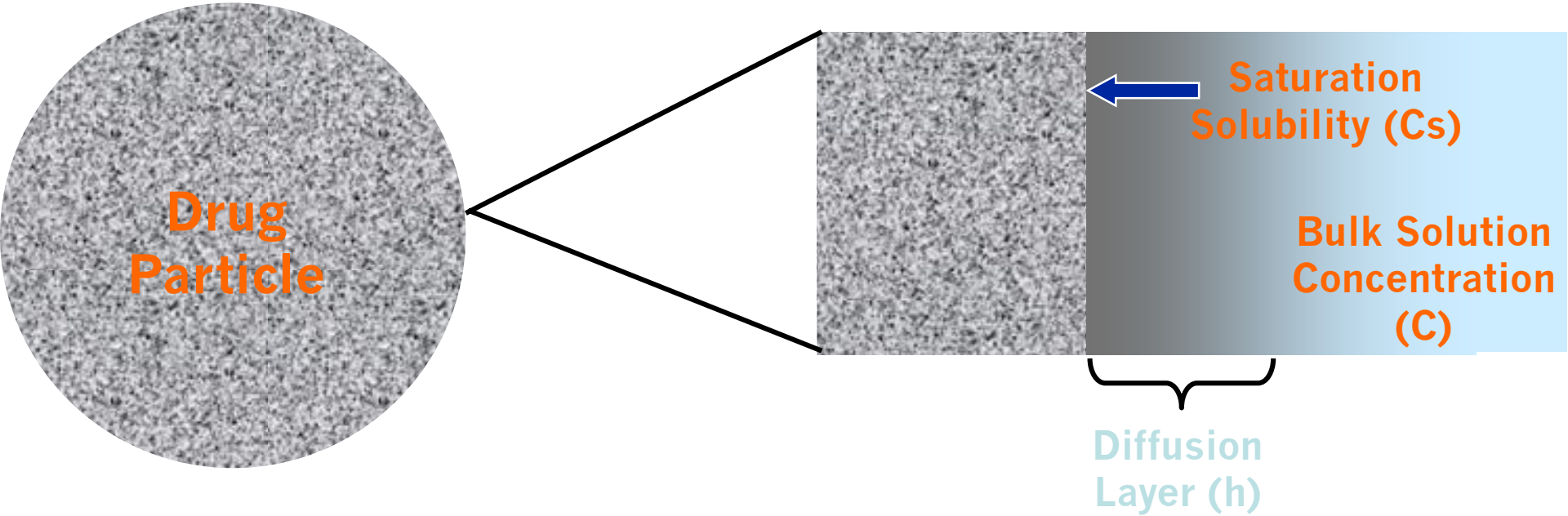
Considerations for a Dibasic Compound



Drug Delivery from Solid Dosage Forms



Dissolution



$$\text{Rate of Dissolution} = \frac{\left[\text{Diffusion Coefficient}\right]\left[\text{Surface Area}\right]}{h}\left[Cs - C\right]$$

What factors can affect dissolution rate?

In the pure drug

Solubility

Particle size

pH

Form (salts, hydrate, polymorphs, amorphous)

Defects of crystal

In the formulation

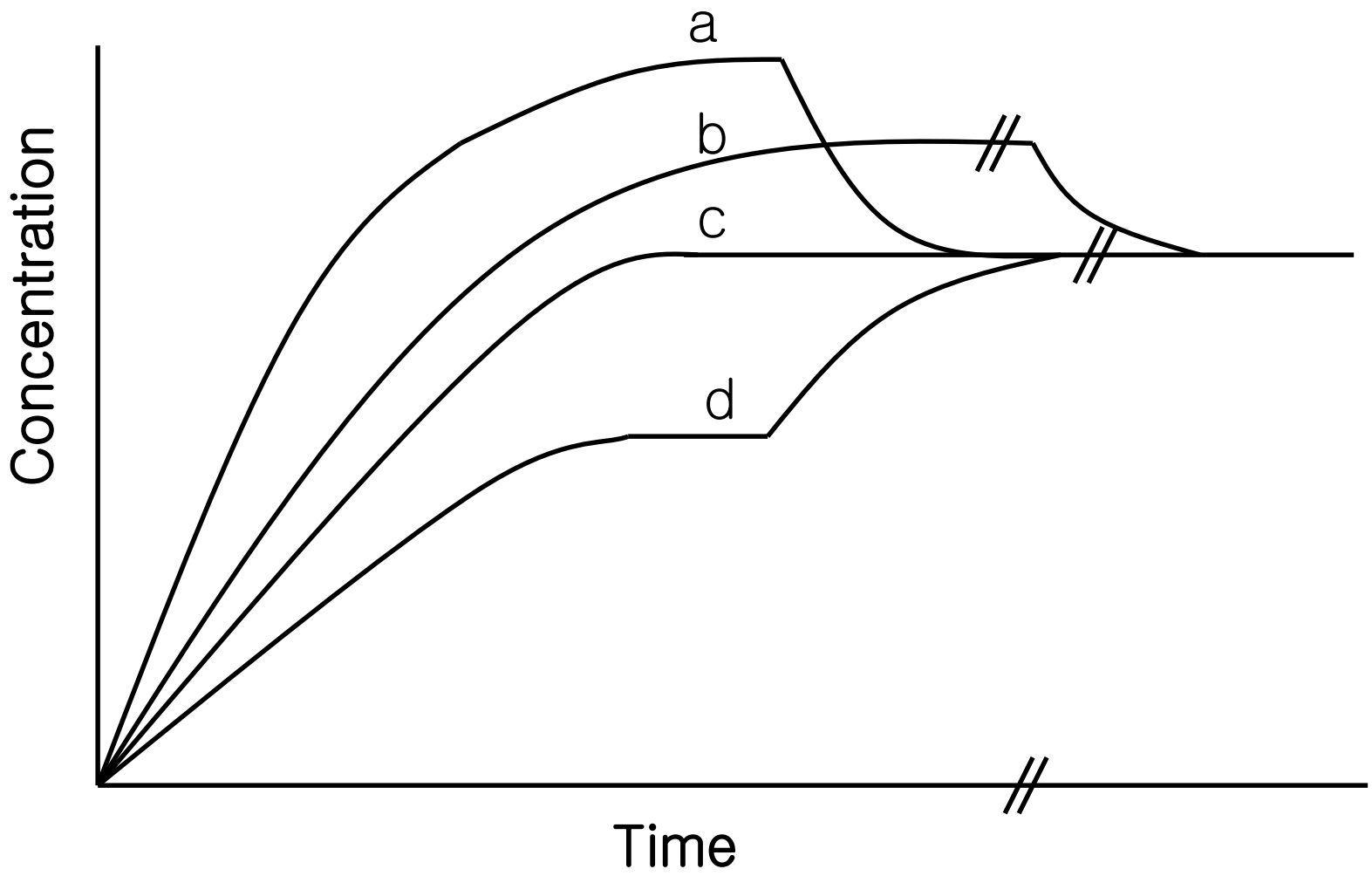
All the above plus:

Disintegration rate and mechanism

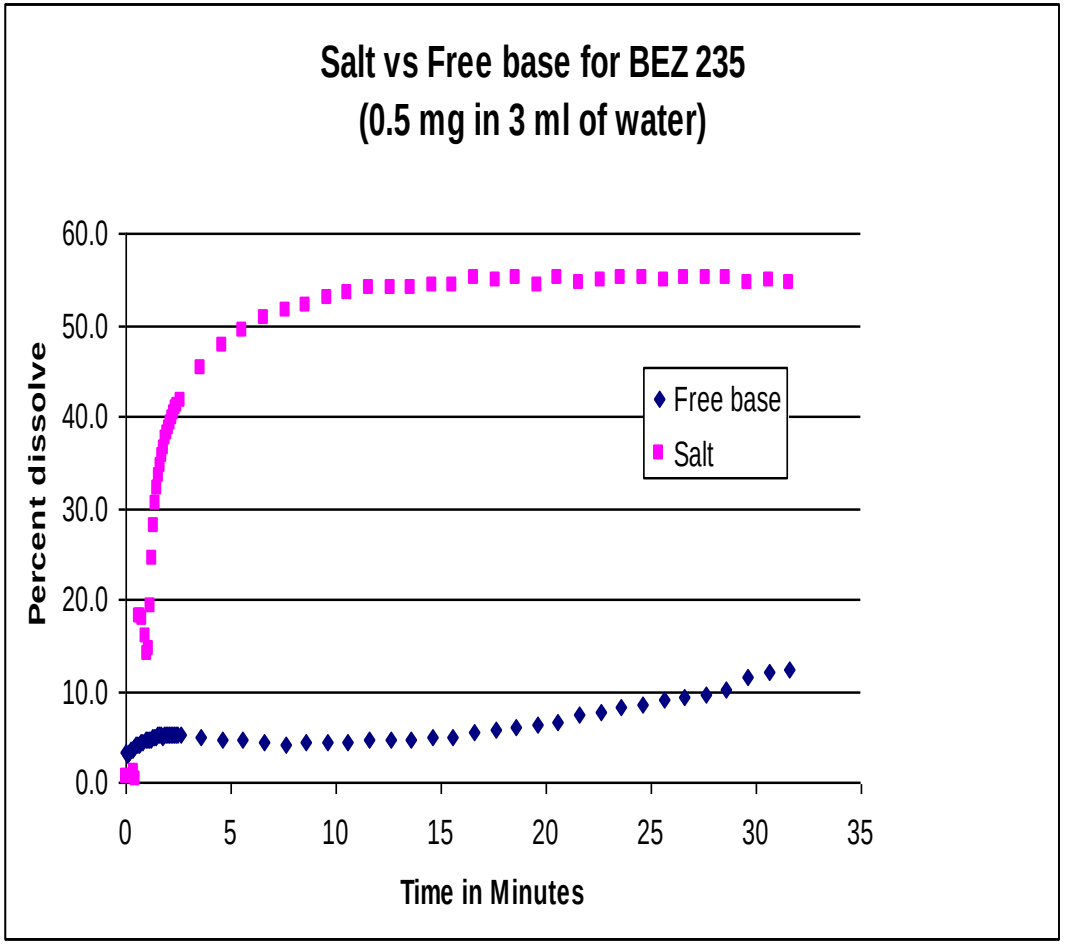
Excipients

Process variation (drying rates/compression etc.)

Dissolution patterns by solid-state modification



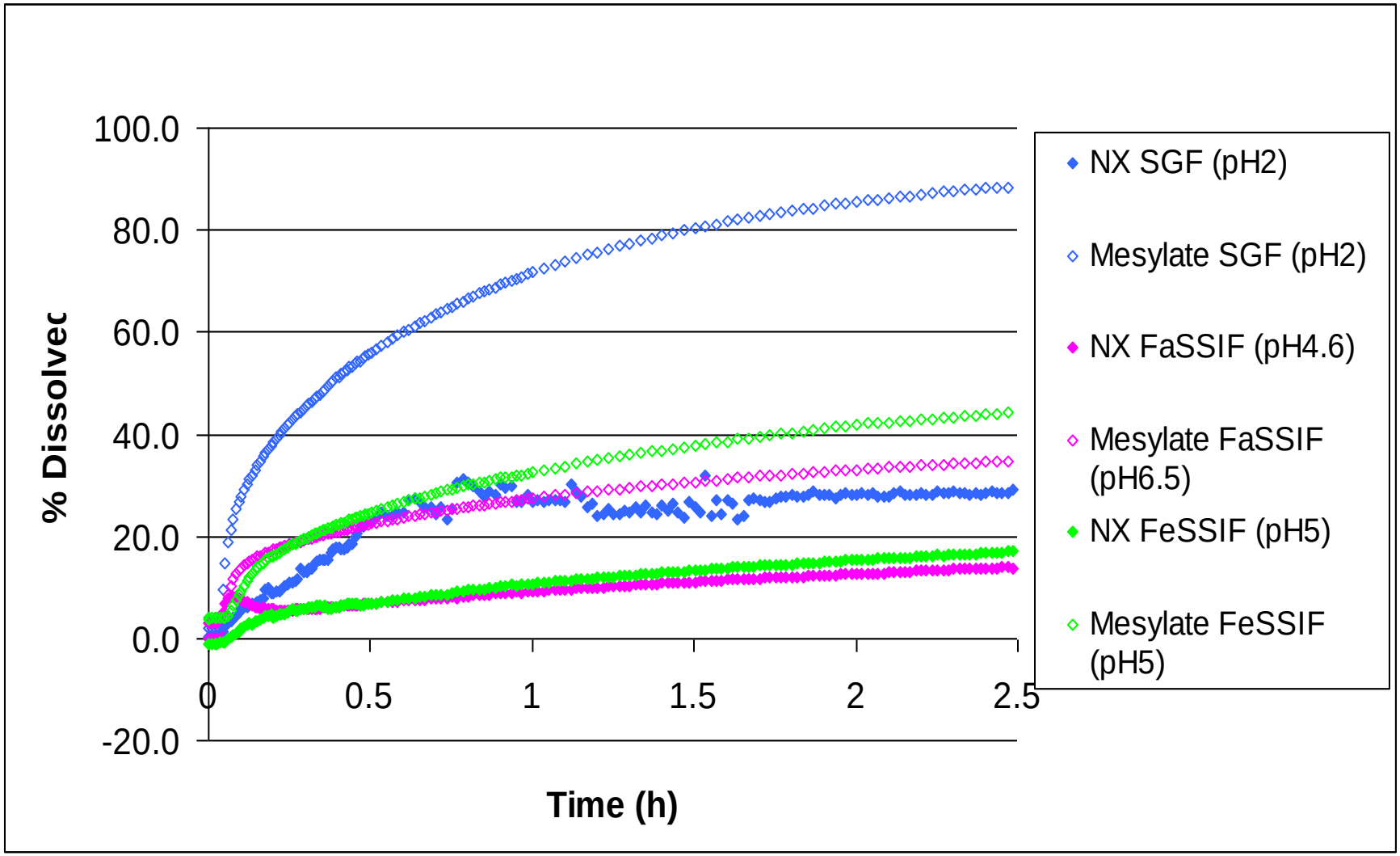
Dissolution of BEZ235 in Water



Oral Rat PK at 20 mg/Kg

	NX Solution	Sulfate Suspen.
Cmax umol/L	1.1	2.7
AUC hr.umol/L	18.5	31
%BAV	30	52

Dissolution Profiles for LCF369 in Different Media



Solubilization Techniques

Salt formation

Particle size reduction

Altered or reduced crystal structure

Solid dispersion

Emulsion

Co-crystallization

Complexation

Cosolvents

pH control

Surfactant

Formulations to improve the oral bioavailability of poorly water-soluble compounds

Natural and synthetic surfactants

Co-solvents

Complexations (cyclodextrins)

Nano- and micro- suspensions

Oil/surfactant mixtures

Co-solvent/surfactant mixtures

Self emulsifying drug delivery systems

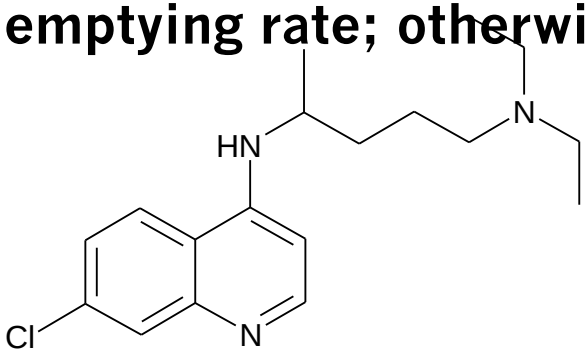
Solid dispersions

Formulations and related activities for the oral administration of poorly water-soluble compounds in early discovery animal studies, Pharm. Ind. 64, Nr. 8, 800-807,2002

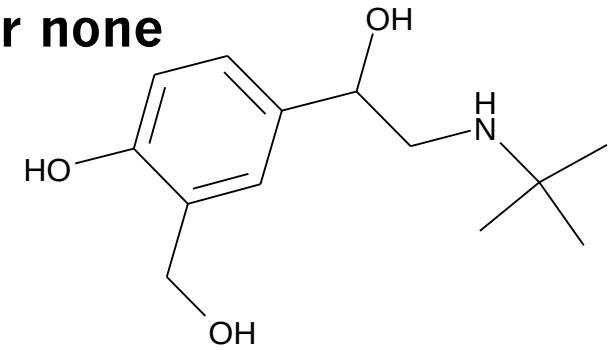
Class I: High Solubility – High Permeability

- **well absorbed**
  - **rate limiting step for drug absorption is dissolution (or gastric emptying if if dissolution is rapid)**
  - **gastric half emptying time = 12 or 22 min for 50 or 200 ml**
  - **immediate release dose forms that dissolve 85% in 15 min should**

    provide bioequivalence
- **In vitro – in vivo (IVIV) correlation: only if dissolution rate < gastric emptying rate; otherwise limited or none**



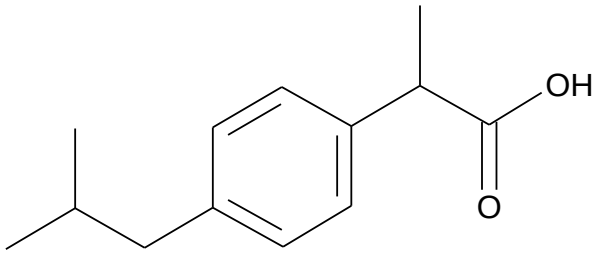
Chloroquine



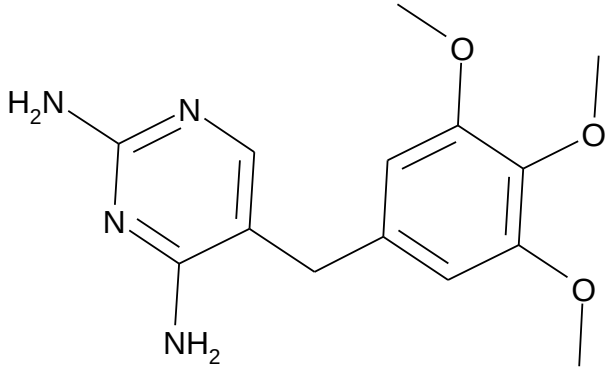
Salbutamol

Class II: Low Solubility – High Permeability

- **Must have a clearly defined and reproducible dissolution profile for these drugs**
- **Dissolution is the rate controlling step in absorption**
  - **Needs to be determined for several physiological pHs and over 4-6 time points**
- **Absorption is often variable; and less than that of Class I drugs**
- **Need to consider food, formulants, and surfactants**
- **IVIV correlation: if in vitro dissolution rate similar to in vivo, unless dose is very high**



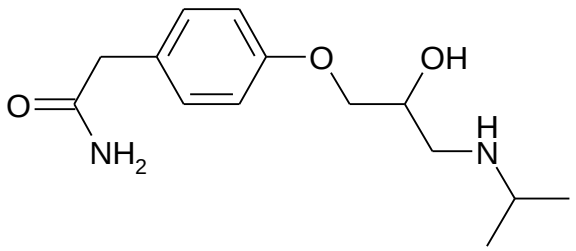
Ibuprofen



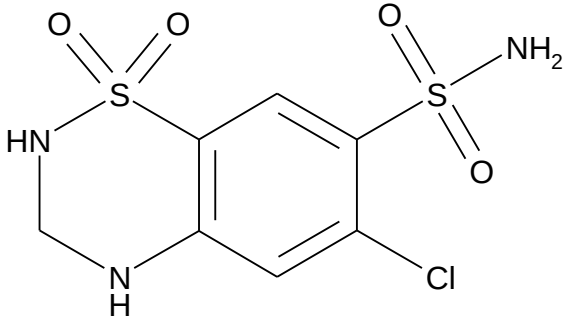
Trimethoprim

Class III: High Solubility – Low Permeability

- **Absorption is the rate determining step**
- **If dissolution is fast (85% in 15 min) then variations in absorption are due to:**
  - **gastrointestinal transit time**
  - **luminal contents**
  - **membrane permeability**
- **This means formulation cannot help as much for these compounds**
- **IVIV correlation: absorption governs**



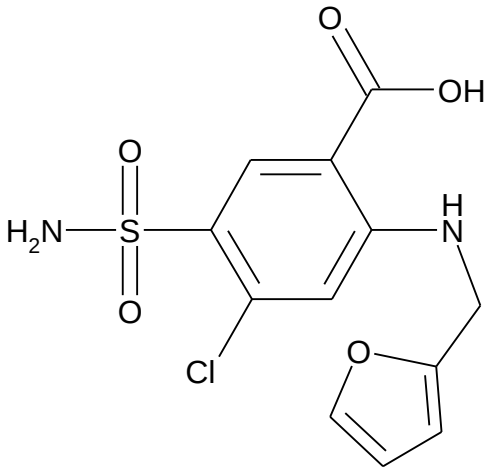
Atenolol



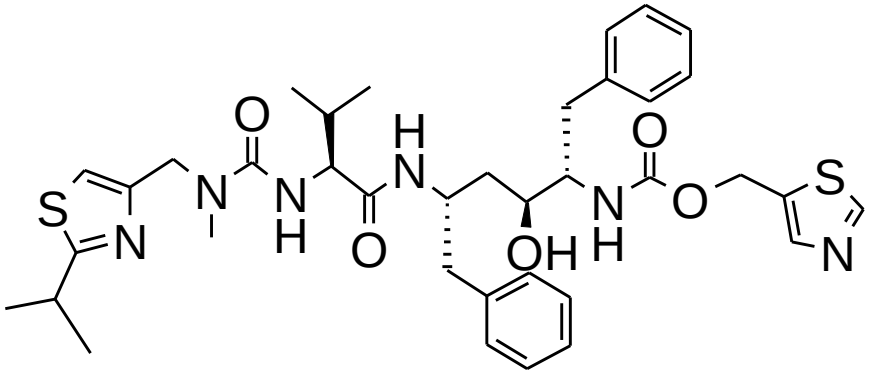
Hydrochlorothiazide

Class IV: Low Solubility – Low Permeability

- **‘‘This class of drugs present significant problems for effective oral delivery’’**
- **IVIV correlation: limited or none expected**



Furosemide



Ritonavir