

Theory & Practice for Development of Enabling Formulations for Preclinical Studies

Sree Nadkarni, Ph. D.
FibroGen Inc.

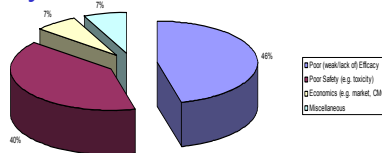
Bay Area Pharmaceutical Discussion Group Meeting
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OUTLINE

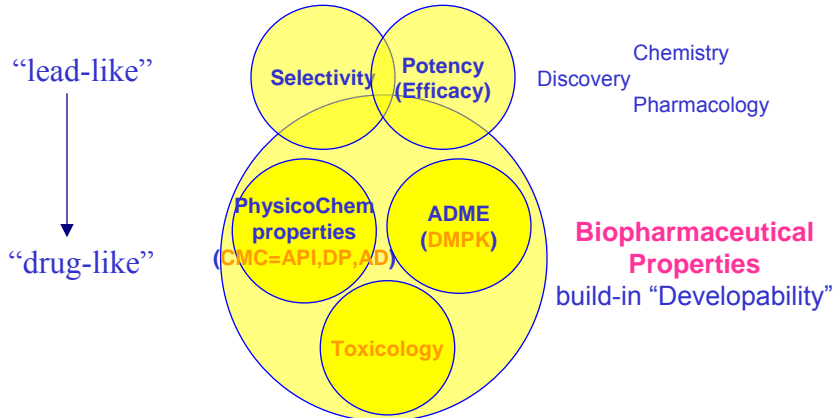
- ❖ Background
- ❖ Preclinical Formulation Development – Requirements & Challenges
- ❖ Preclinical Formulations for Early/Late Stage Drug Discovery
 - ❖ Standard Approaches
 - ❖ Intermediate Approaches
 - ❖ Advanced (Enabling) Approaches
- ❖ Conclusions

Drug Discovery Lead Optimization

- In early 1990s, approx. 40% of drugs failed in clinical trials due to pharmacokinetics and bioavailability problems.
- Since the incorporation of pharmacokinetics and toxicology (ADMET) assessment in lead optimization stage, 7-11% of drugs fail due to poor PK and bioavailability.
- Currently, the primary reasons for failures during clinical development are lack of efficacy and human toxicity.

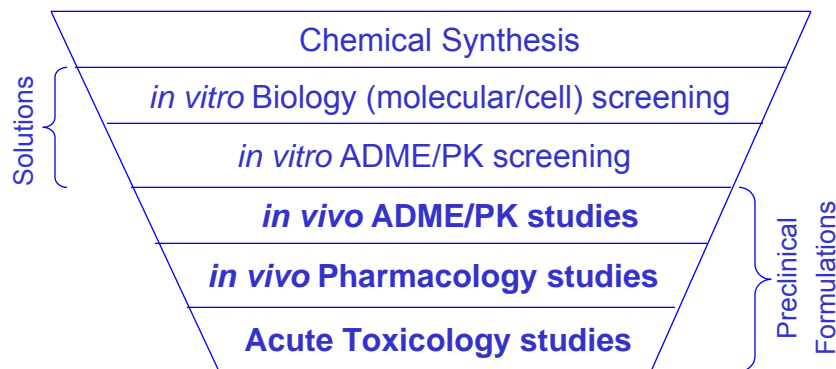


Lead Optimization/Selection: Multi-faceted Approach



- Early evaluation of “Developability”, i.e. biopharmaceutical properties, in conjunction with Selectivity & Potency will allow transition from “lead-like” → “drug-like” candidates.

Lead Optimization



Lead Optimization Pharmacology & ADME/PK Studies

Pharmacology Studies

- What a drug does to the body; evaluation of biological / pharmacological effects of drug.
- *in vitro* Biology/Pharmacology (molecular, cellular)
 - Potency, selectivity; initial ranking of compounds
- *in vivo* Pharmacology
 - Dose-activity/efficacy in normal animals (biomarker) and/or validated disease models; tolerability in animals (clin. chem., histopathology)

ADME/PK Studies

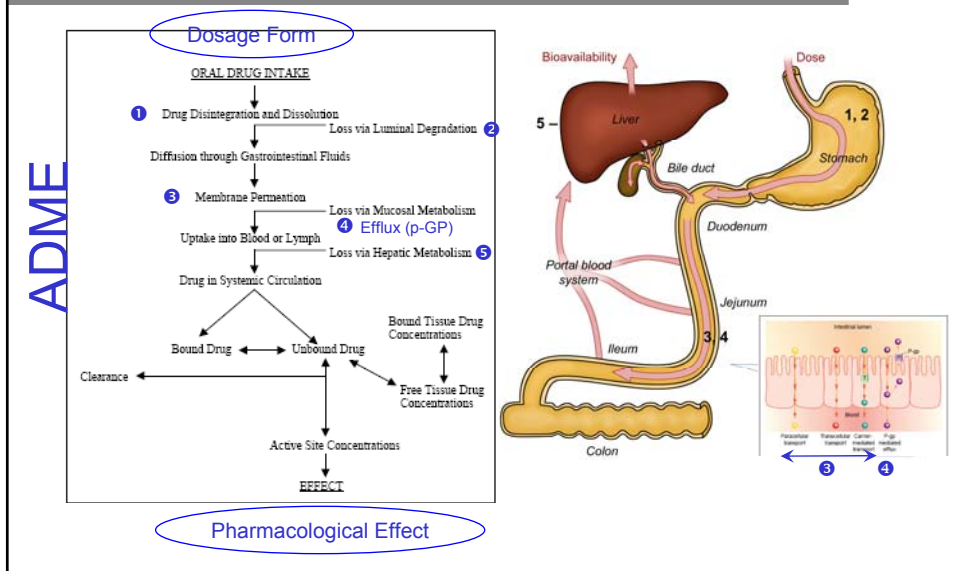
- What a body does to the drug; evaluation of absorption, distribution, metabolism, and excretion (ADME) of drug.
- *in vitro* ADME/PK
 - Microsomal stability, Caco-2 permeability, plasma protein binding, CYP induction/inhibition
- *in vivo* ADME/PK (rodent – mouse, rat; non-rodent – dog, pig, monkey)
 - IV PK profiling (AUC, C_0 , $t_{1/2}$)
 - Oral PK Profiling (AUC, C_{max} , t_{max} , $t_{1/2}$, %F); dose linearity; metabolite profile

Lead Optimization

Early (non-GLP) Toxicology Studies

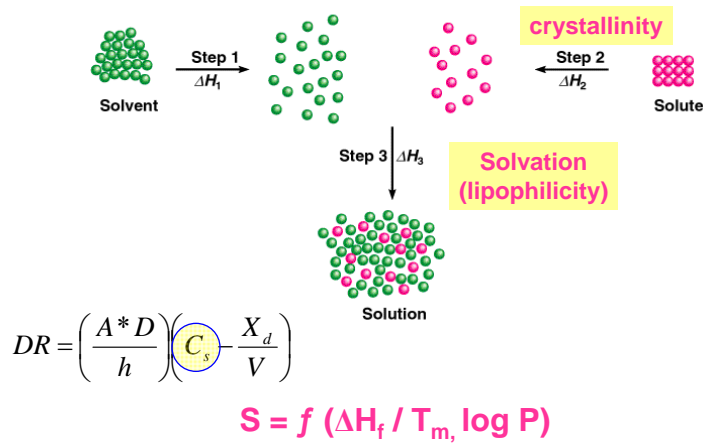
- Evaluation of adverse effects of drug at multiples of the effective dose range (MED).
- Oral Dosing
 - Acute/Short-term toxicity (3-5 dose levels): single dose, multiple dose (1-4 wk)
 - Rodent (mouse, rat) and non-rodent (dog, pig, monkey)
 - Target organs; signs of toxicity (clinical chemistry, histopathology)
 - Toxicokinetic evaluation (minimal PK)
 - Advisable to evaluate suspension formulation for assessing feasibility of oral dosing in clinical studies

Fate of Drug upon Oral Administration

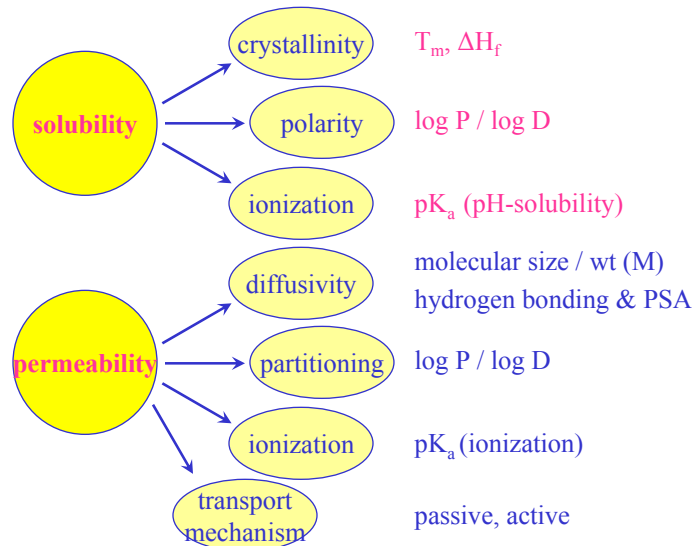


Factors influencing Solubility

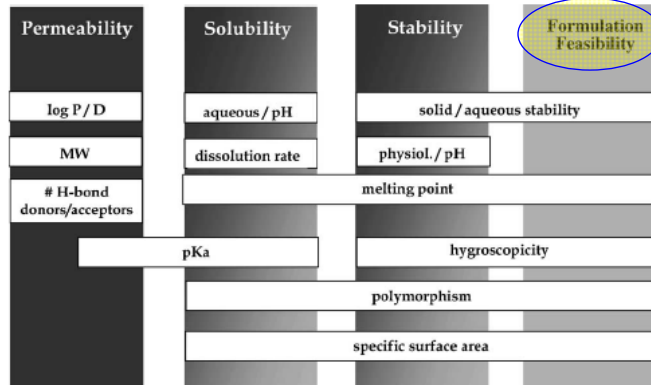
Molecular View of the Solution Process



Molecular / Physicochemical Factors Influencing Absorption



Considerations beyond Solubility & Permeability



- In addition to Solubility & Permeability, **Stability** and **Solid State Form** are important considerations for dosage form development
 - Stability: chemical (solution, solid state), physical (hygroscopicity)
 - Analytical Methods, Stress testing
 - Solid Form: salt, polymorph

Preclinical Formulation Development: Requirements & Challenges

Requirements for Preclinical Formulation Development

- Tolerability of Excipients
 - Ease of administration; no adverse effects;
 - May vary depending on animal species
- Maximum exposure
- Comparability of data across multiple studies
 - Little/no changes in formulations
- Dose linearity (PK, Toxicology studies)
 - High doses in toxicology studies pose challenge for low solubility drugs (solubility-limited absorption)

Challenges in Preclinical Formulation Development

- Short timelines
 - Develop fundamental formulation strategy based on compound series
- Limited compound availability.
 - Miniaturization of formulation screening/development
- Limited Information Physicochemical Properties
 - Utilization of in silico estimation softwares (S_w , log P, pKa)

Preclinical Formulations for Drug Discovery: Standard Approaches

Early Solution Formulations Basic Approaches

- pH Adjustment
 - *in situ* Salt (counterion)
 - Strong acid (HCl) or strong base (NaOH)
 - Weak acid or base
 - Buffer system
 - Formulation Considerations:
 - Formulation pH should be within physiological range (pH 2-9)
 - Avoid very high (could cause local irritation) and very low (chance of precipitation) buffer capacity
- Cosolvents
 - Tier 1: Ethanol, propylene glycol, polyethylene glycol (PEG) 300, PEG 400
 - Tier 2: DMA (10-30%, i.v.), DMSO (10-20%; i.v., p.o.), NMP (10-20%; i.v., p.o.), Transcutol / DGME (30%; p.o.),
 - Solubility in a cosolvent-water system:
 - $\log [S_{co}] = \log [S_w] + \sigma f_c$
Sw = solubility of drug in water (intrinsic solubility)
 σ = solubility power of cosolvent; inversely related to polarities of drug and cosolvent
 f_c = fraction of cosolvent (% v/v)
 - Normally, a mixture of cosolvents is used to improve solubility and increase tolerability; 10% ethanol, 40% PG is commonly used, e.g., Valium (diazepam), Lanoxin (digoxin), Nembutal (pentobarbital sodium), Dilantin (phenytoin)
 - Major limitation: drug precipitation upon administration; particularly i.v., but also p.o.
 - Precipitation after i.v. bolus injection will cause pain, inflammation (thrombophlebitis), obstruction of vein, local tissue damage (black tail in mouse)
 - Solutions: lower drug conc., slow injection (infusion), addition of a surfactant

Early Solution Formulations

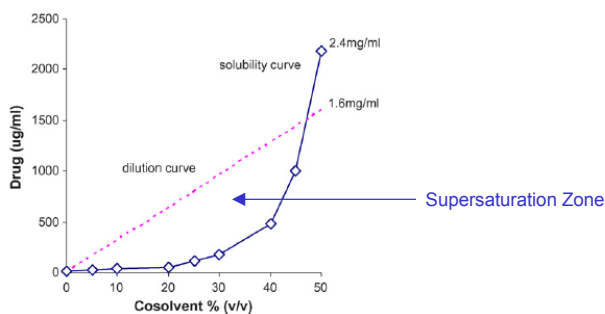
Basic Approaches: Cosolvents

- Tier 1: Ethanol, propylene glycol, polyethylene glycol (PEG) 300, PEG 400
- Tier 2: DMA (10-30%, i.v.), DMSO (10-20%; i.v., p.o.), NMP (10-20%; i.v., p.o.), Transcutol / DGME (30%; p.o.),
- Solubility in a cosolvent-water system:
 - $\log [S_{tot}] = \log [S_w] + \sigma f_c$
 - Sw = solubility of drug in water (intrinsic solubility)
 - σ = solubility power of cosolvent; inversely related to polarities of drug and cosolvent
 - f_c = fraction of cosolvent (% v/v)
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Solubilization by Cosolvents

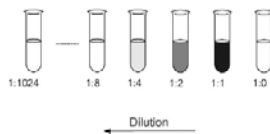
Precipitation Potential

- Drug solubility increases exponentially with % cosolvent.
- Upon dilution, the concentration of both the drug and the cosolvent decrease linearly.
- Dilution (i.v. bolus, p.o.) results in a supersaturated solution of drug which is prone to precipitation.



Solubilization by Cosolvents or pH Evaluation of Precipitation Potential

- Precipitation upon dosing is a challenge for cosolvent based formulation, as well as for pH based formulations (i.v., p.o.)
- Serial dilution method, which mimics in vivo dilution process
- i.v. formulations:
 - Isotonic Sorensen Phosphate Buffer (pH 7.4, Na₂HPO₄-NaH₂PO₄); buffer capacity of 0.036 (whole blood, 0.032-0.039)
 - If no cloudiness/precipitation is observed in 3-5 minutes, drug is unlikely to precipitate



- p.o. formulations:
 - Simulated gastric fluid (SGF, without pepsin) or simulated intestinal fluid (SIF, without pancreatin)

Early Solution Formulations Basic Approaches

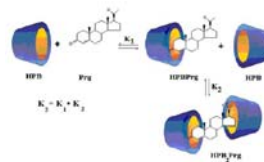
- Surfactants
 - Polysorbate 80, Polysorbate 20 (1-10%; i.v., p.o.)
 - Ethoxylated Castor Oils: Cremophor EL, Cremophor RH40, Cremophor RH60 (5-10%; i.v., p.o.)
 - Pluronics: Pluronic F68 / Poloxamer 188 (20-50%; i.v., p.o.),
 - Solutol HS15 (20-50%; i.v., p.o.),
 - Vitamin E TPGS, d- α -tocopheryl PEG 1000 succinate (20-50%; i.v., p.o.)

Early Solution Formulations Basic Approaches

- Cyclodextrins
 - Cyclic oligosaccharides
 - Solubilization by forming drug-ligand (cyclodextrin) complex

$$[Stot] = [S0] + (K [S0] / 1 + K [S0]) [Ctot]$$

[S0] = drug solubility in water (intrinsic solubility)
[Ctot] = cyclodextrin concentration
K = stability constant of drug-cyclodextrin complex
 - HPβCD, SBEβCD (10-40%; i.v., p.o.)
 - Evaluate solubility in 30% HPβCD
 - Addition of small quantities of a hydrophilic polymer (e.g. PVP, NaCMC) has been shown to increase solubility.



Aqueous Suspension (p.o.) Basic Approach

- Why use Suspensions?
 - Dosing of high concentrations required for toxicology studies
 - Evaluation of feasibility of oral dosing
- Suspending agent: hydrophilic polymer
 - Methyl cellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), carboxymethylcellulose sodium (NaCMC)
- Wetting agent (surfactant)
 - Polysorbate 80, polysorbate 20, Cremophor RH40, Solutol HS15
- Typical formulation: 0.5% MC / HEC, 0.2% Polysorbate 80 (w/v)
- Micronized suspension for improved dissolution and batch-to-batch uniformity
 - Micronized drug (fluid energy mill), wet milling (homogenizer), high pressure homogenization (microfluidizer)
- Concerns: physical stability (change in particle morphology, particle aggregation, sedimentation)
- Solutions: extemporaneous preparation, refrigerated storage, mixing prior to use, stability testing

Preclinical Formulations for Drug Discovery: Intermediate Approaches

Solution Formulations Intermediate Approaches

- Intermediate (Combination) Formulations
 - pH adjustment + surfactant
 - Cosolvent + surfactant
 - Cyclodextrins + surfactant
- Addition of a Surfactant or Polymer
 - Increases solubility
 - Reduces precipitation potential
 - Prevents agglomeration

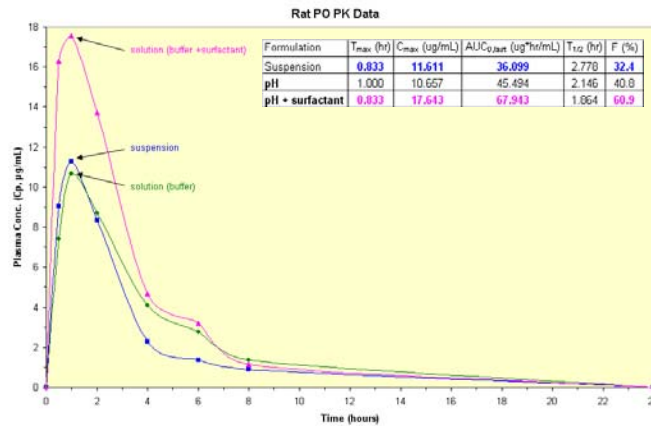
In combination with surfactants, pH control can be used to enhance the solubility of ionizable solutes. Li et al⁴ showed that the general equation for solubilization of a weak base by pH and a surfactant is as follows:

$$S_{TOT} = S_U + S_U (F/K_a) + \kappa_u C_{SDC} + (F/K_a) + \kappa_i C_{SDC} \quad (1)$$

where κ_u and κ_i represent the solubilization capacities for the un-ionized and ionized forms of the solute, respectively, and S_U represents the solubility of the un-ionized solute. Often, $\kappa_u \gg \kappa_i$, and the only effect of the surfactant is to solubilize the un-ionized solute. For example, in the case of surfactants

Intermediate Solution Formulation Case Study

- Drug: weak acid; low aqueous solubility



**Preclinical Formulations for Drug
Discovery:
Advanced (Enabling) Approaches**

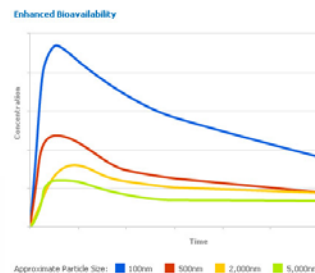
Solution Formulations Advanced (Enabling) Approaches

- To be used after thorough evaluation of standard and intermediate approaches
- Require more extensive development (API, resources, time)
- Technologies (p.o.)
 - Nanoparticle Suspensions
 - Lipid-based DDS
 - Self-emulsifying Drug Delivery Systems (SEDDS or SMEDDS)
 - Solid Dispersions

Advanced (Enabling) Approaches Nanoparticle Suspensions

- Nanoparticles, <600 nm p.o., <300 nm i.v.
- Benefits:
 - Increased solubility
 - Larger surface area for dissolution
 - Ostwald-Freundlich equation

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$



- Technologies (p.o.).
 - Wet milling (Nanocrystal, Elan)
 - Wet milling using highly crosslinked polystyrene beads; suspension stabilized by a wetting agent and a hydrophilic polymer
 - p.o. – Emend (aprepitant, Merck), Rapamune (sirolimus, Wyeth), Tricor (fenofibrate, Abbott), Megace ES (megestrol acetate, Par); i.v. – Invega Sustenna (paliperidone palmitate, Janssen)
 - Rapamune (sirolimus),
 - High pressure homogenization (DissoCube, SkyePharma)
 - Solvent Precipitation (NanoEdge, Baxter)
 - Spray Drying
 - Supercritical Fluid Technology

Advanced (Enabling) Approaches Lipid-based Formulations

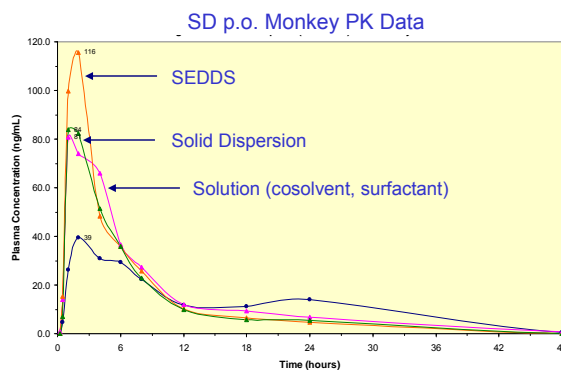
- SEDDS, SMEDDS
- Drug dissolved in digestible lipids; fine particle dispersion in vivo, providing high surface area for partitioning/dissolution
- Lipids:
 - Free fatty acids
 - Mono-/di-/tri-glycerides and derivatives
 - Mono-/di-propylene glycol esters
- Surfactants
 - Polyethoxylated fatty acids
 - Polyglycerol fatty acid esters
- Cosolvents

Advanced (Enabling) Approaches Solid Dispersions

- Drug dispersion in a hydrophilic carrier; drug may be in solubilized, or dispersed as a micro-crystalline or amorphous solid
- Generally prepared by solvent evaporation or hot melt extrusion
- Polymers: PVP, HPMC, HPMC phthalate, HPMC acetate succinate, PEG 3350 / 4000, Gelucire 44/14, Pluronic F68
- For stabilization of amorphous form of drug, stability under stress conditions needs extensive evaluation
- Commercial products: Gris-PEG (griseofulvin, Novartis), Cesamet (nabilone, Lilly), Kaletra (lopinavir/ritonavir, Abbott).
- Lab-scale preparation:
 - Solvent evaporation: low boiling solvent capable of solubilizing both drug and polymer (methanol, ethanol, isopropanol, acetone, dichloromethane, ethyl acetate)
 - Melting & Congealing: Drug solubilization in molten polymer (PEG 4000, Gelucire 44/14); may require use of a cosolvent

Advanced (Enabling) Approaches Case Study 2

- Drug: m.p. $\sim 260^{\circ}\text{C}$; $\log P = 3.6$; $\text{pK}_a = 8.5$; $S_w < 100 \text{ ng/mL}$
- Satisfied all criteria in Lipinski's Rule of 5 (MW, $\log P$, HBD, HBA)
- Standard formulation gave poor and highly variable exposures.



Conclusions

- Drug discovery strategy should be designed by taking into consideration the physicochemical and biopharmaceutical properties of the compound series (scaffolds).
- Strategies including in silico estimation of physicochemical properties and miniaturization of formulation screening should be adopted in light of time and drug availability constraints.
- Standard and Intermediate approaches should be thoroughly evaluated before embarking on advanced (enabling) approaches.
- A close collaboration between Chemistry, Biology (molecular/cellular), Pharmacology, DMPK, Toxicology and Pharmaceutics groups is essential for successful lead optimization in drug discovery.