Formulation for Stability: Moving Beyond Excipient Compatibility

Kenneth C. Waterman, Ph.D.
FreeThink Technologies, Inc.
Branford, CT USA

Reactive Excipients

- Some degradation due to direct excipient-drug reaction
- Example: Maillard reaction between secondary amines (amino acids) and reducing carbohydrates (e.g., lactose)—leads to brown colors + multiple products
- **Relatively uncommon** (other than this reaction)

Reaction with Excipient Impurities/Degradants

- Peroxides
- Formaldehyde (and other aldehydes)
- Acids
  - Formic acid
  - Acetic acid

Non-reactive Excipient Impact

- Effects proportional to interfacial contact
- Specific degradation will show different effects
- Some degradation mechanisms will be more sensitive than others to excipients

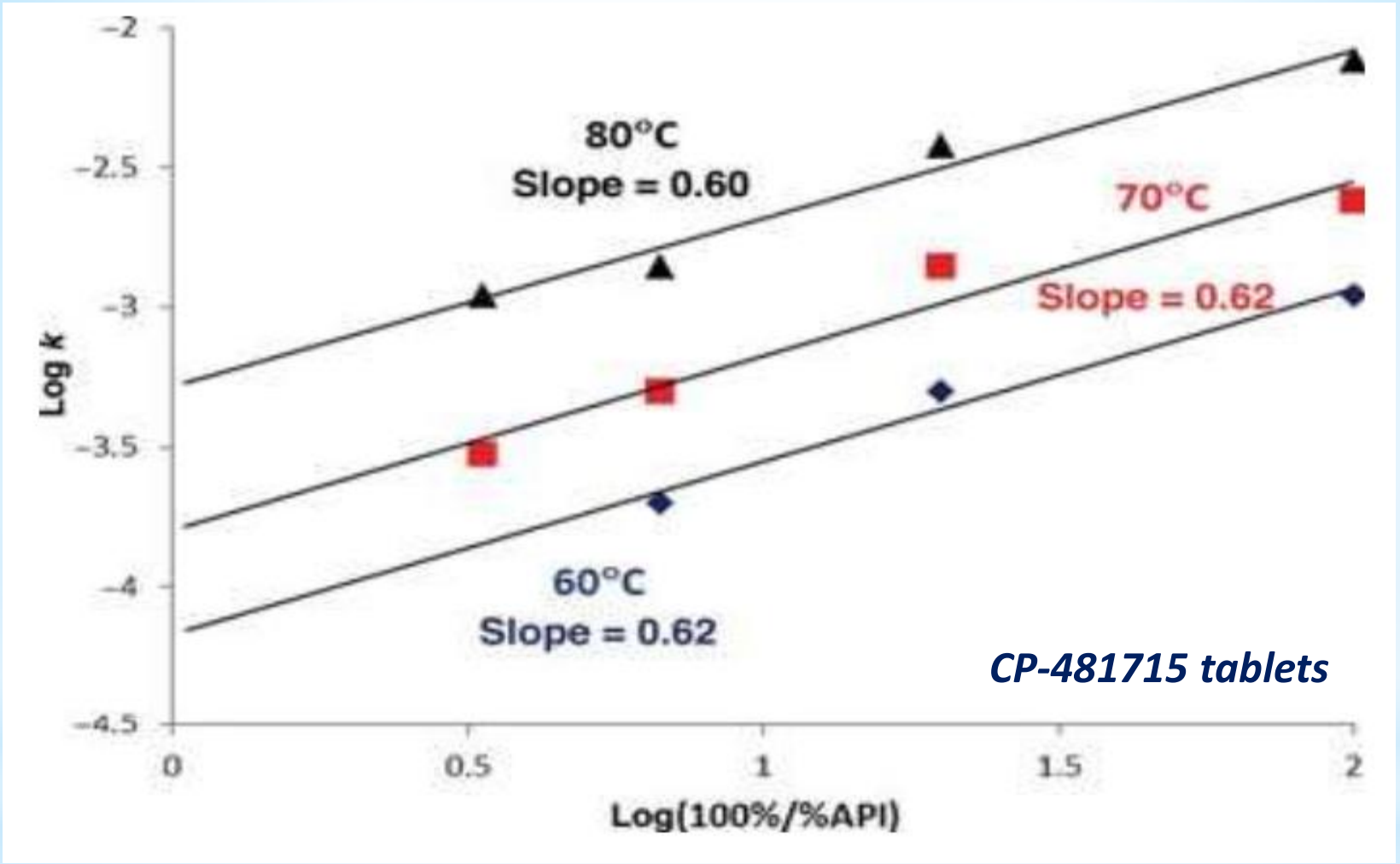
Drug Concentration Impact in Solid Formulations

- Impact of concentration (approximation):

$$\log k = \alpha log \frac{100\%}{\%active} + log k_0$$

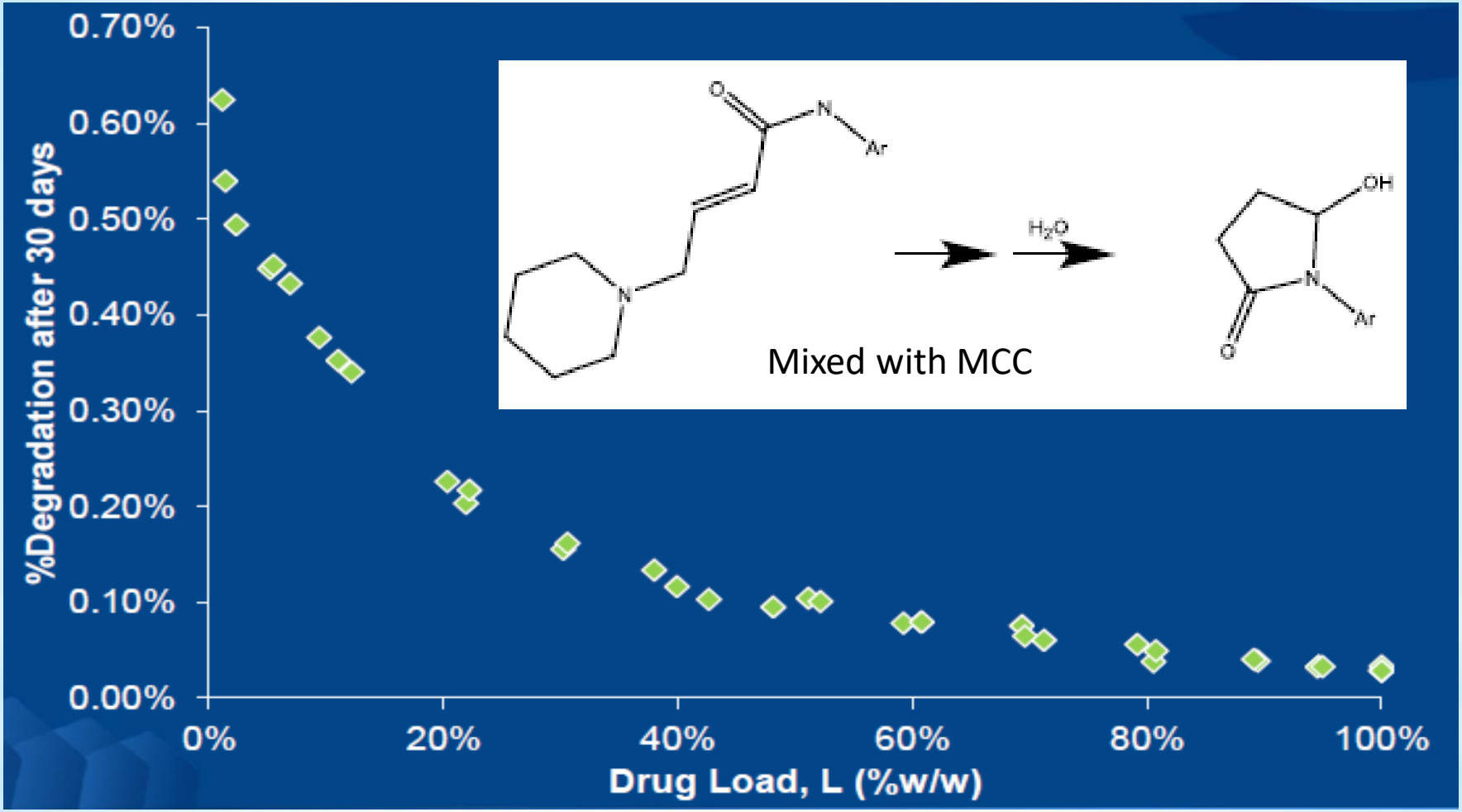
- α may be independent of temperature/RH
- α may depend on T/RH (catalysis)

Example



From J Pharm Sci 2012, 101, 4170-4177.

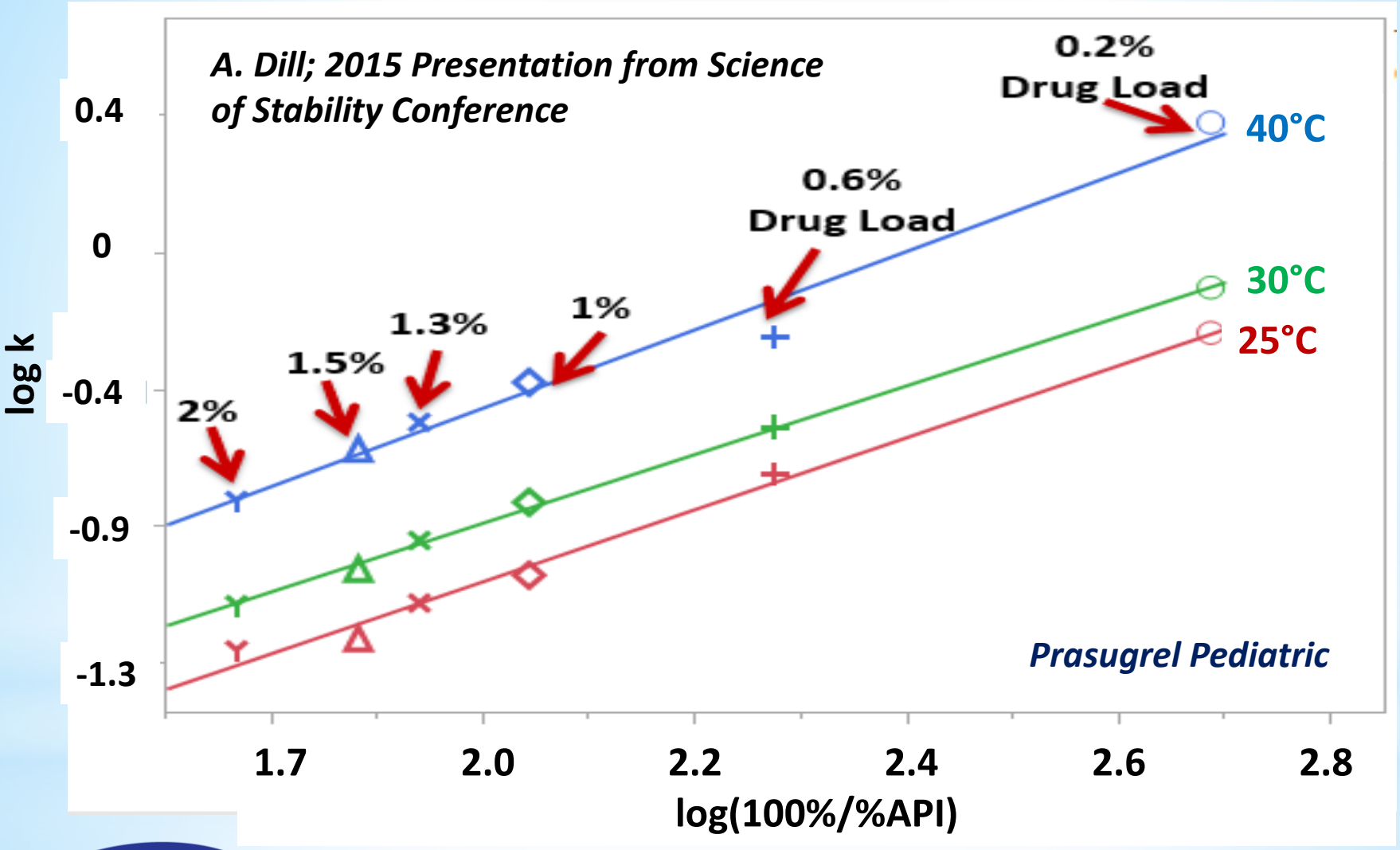
Example



G. Scrivens; 2017 Presentation from Science of Stability Conference

FreeThink Technologies

Example


A. Dill; 2015 Presentation from Science of Stability Conference
0.2% Drug Load
0.6% Drug Load
2%
1.5%
1.3%
1%
40°C
30°C
25°C
Prasugrel Pediatric
log k
0.4
0
-0.4
-0.9
-1.3
1.7
2.0
2.2
2.4
2.6
2.8
log(100%/%API)

Excipient Compatibility

- Binary blend stability (often rank order)
  - 1:1 API:Excipient
  - Representative API level:Excpient level

Problems with Binary Excipient Compatibility

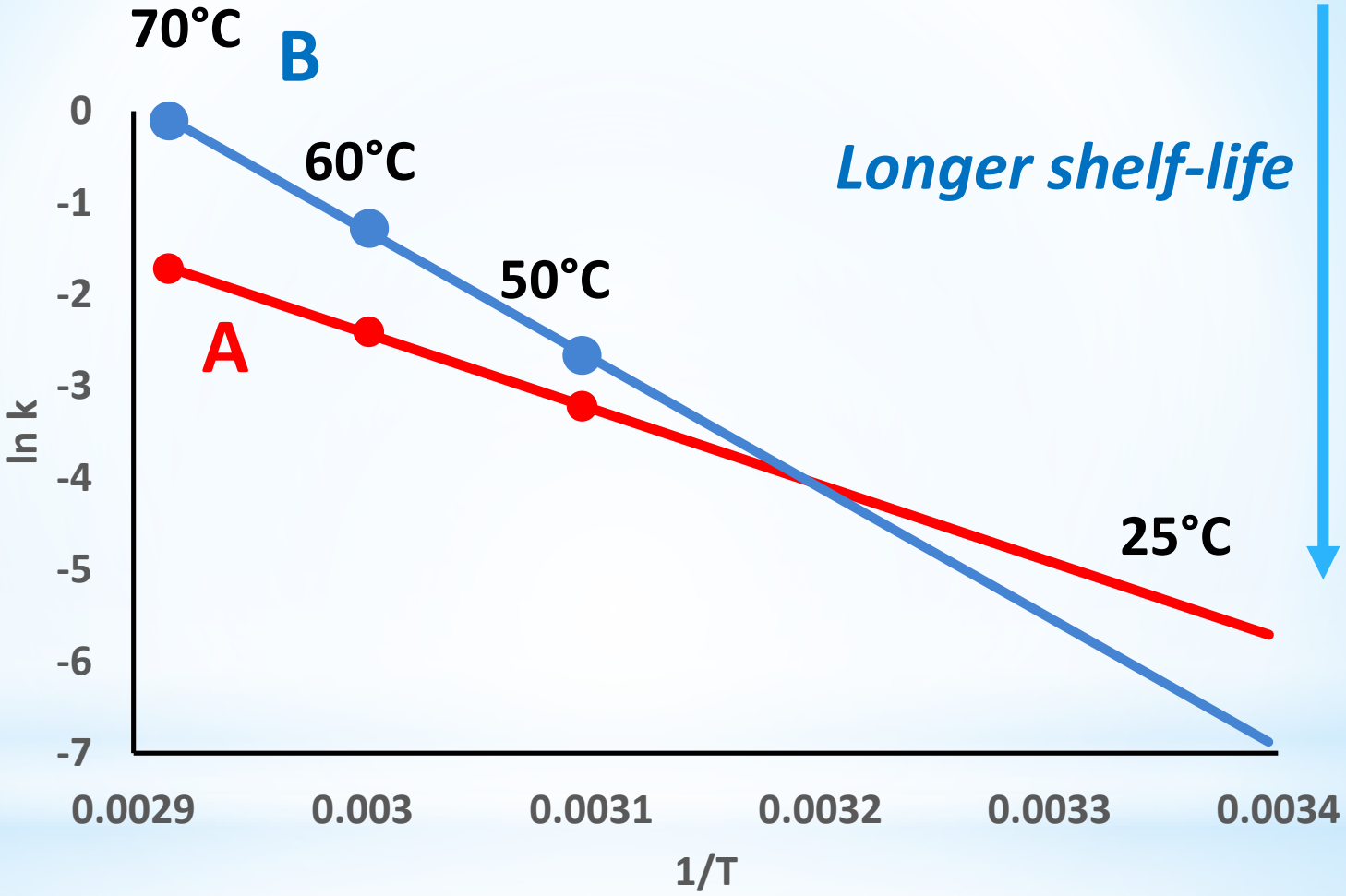
- For low level excipient, greatly exaggerates issues
  - Often leads to excluding magnesium stearate
- Since true interaction is base on log-log scaling, formulation stability is not a weighted average of the binary stabilities
- Rank order not appropriate
  - Excludes good enough excipients
- Stability studies can be slow delaying product development

Screening Stability (Rank Order)

Two formulations screened 2 weeks, 70°C/75%RH

Formulation	70°C
A	0.18
B	0.90

Which formulation should you proceed with for ambient (25°C/60%RH) storage?



FreeThink Technologies

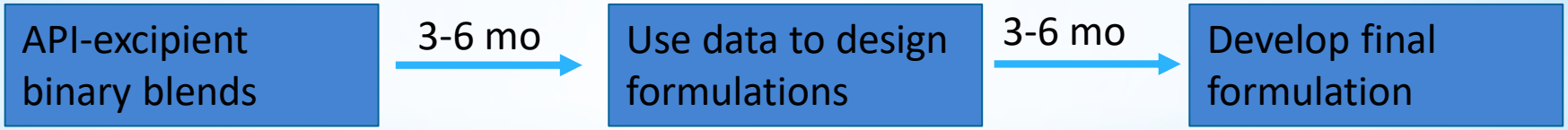
Screening Stability (Rank Order)

- Rank order from high temperature often opposite to room temperature
- Rank order does not distinguish formulations that are all good or all bad

Excipient Compatibility Formulation Development (Real Time Stability)

Long development time for stable formulations

Traditional Formulation Development: 6-12 mos.

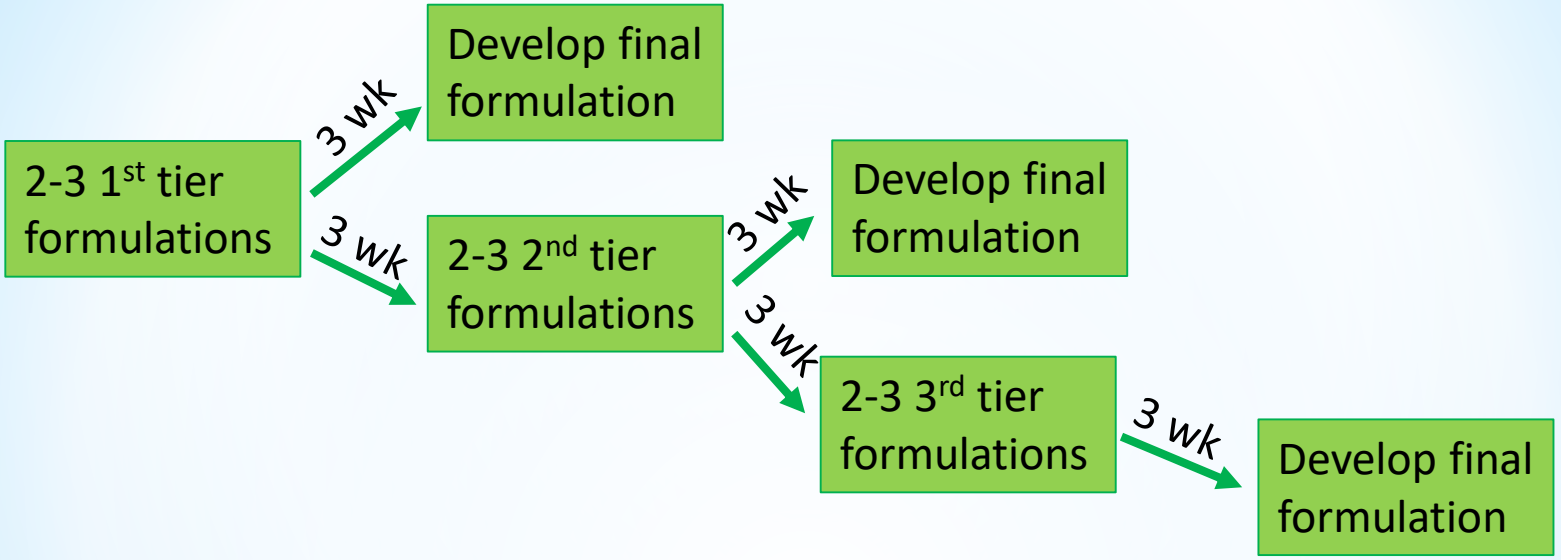


Rapid Formulation Development: ASAPprime® Tiered Approach

- Full formulations prepared (e.g., tablets, capsules)
  - 3-4 Tier 1 full formulations
  - Low API concentration (worst case)
- ASAP studies conducted
- Tier 1 formulations work for most APIs and enable fast development
- If Tier 1 fails, Tier 2 formulations used
- Rare that we need to go past this
- Must justify formulation used: do not need excipient compatibility for regulatory submissions.

Rapid Formulation Development

ASAP-Based Formulation Development using Tiers: 1-4 mos.



Example Tier 1 Tablet Formulations

Function	Ingredient	Formulation 1 wt%	Formulation 2 wt%
Active	API	5	5
Diluent (ductile)	MCC	54	54
Diluent (brittle)	Lactose	25	
Diluent (brittle)	Mannitol		25
Disintegrant	Croscarmellose sodium	10	
Disintegrant	Crospovidone		10
Binder	HPC	5	
Binder	Povidone		5
Lubricant	Magnesium stearate	1	
Lubricant	Stearic acid		1

Tiered Approach to Formulation Development

Advantages to ASAP Approach

- Fewer resources, much shorter time-line
- Most cases can go straight to experienced (manufacturable) formulation (and processing) space
- Does not rule out effective excipients based on rank-order or exaggerated binary results