Fundamental Determinants for Justifying Low and Very Low Biopharmaceutics Risk When Dissolution is Not Critical to Product Performance

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Contents

Suggested API & formulation properties and data/evidence that can justify dissolution as non-critical to absorption (low to very low risk), but with caveats in red text indicating risk

Low Permeability

- BE over a wide range of dissolution (PK studies or PBPK modelling)
- BE supported by validated biorelevant methods
- Long T_{max}
- Discrimination can still be observed, but has no in vivo implication
- Food effect if observed (due to longer gastric emptying and/or solubilization) could elevate risk

Rapid dissolution

- Rapid dissolution
- Rapid disintegration
- Linear PK
- Short T_{max} (not always)
- Discrimination unlikely except for DCS IIb compounds
- pH dependent solubility (basic drugs) rendering precipitation in small intestines could elevate risk level for PPI users
- Food effect could elevate risk level, especially for DCS IIb
- Discrimination observed for DCS IIb such API PS

pH independent solubility (acid or basic)

- BE over a wide range of dissolution (PK studies or PBPK modelling)
- BE supported by validated biorelevant methods
- pH independent dissolution
- No food effect observed
- Minimum PPI effect
- Discrimination can still be observed
- Food effect if observe could elevate risk level, especially for DCS IIb

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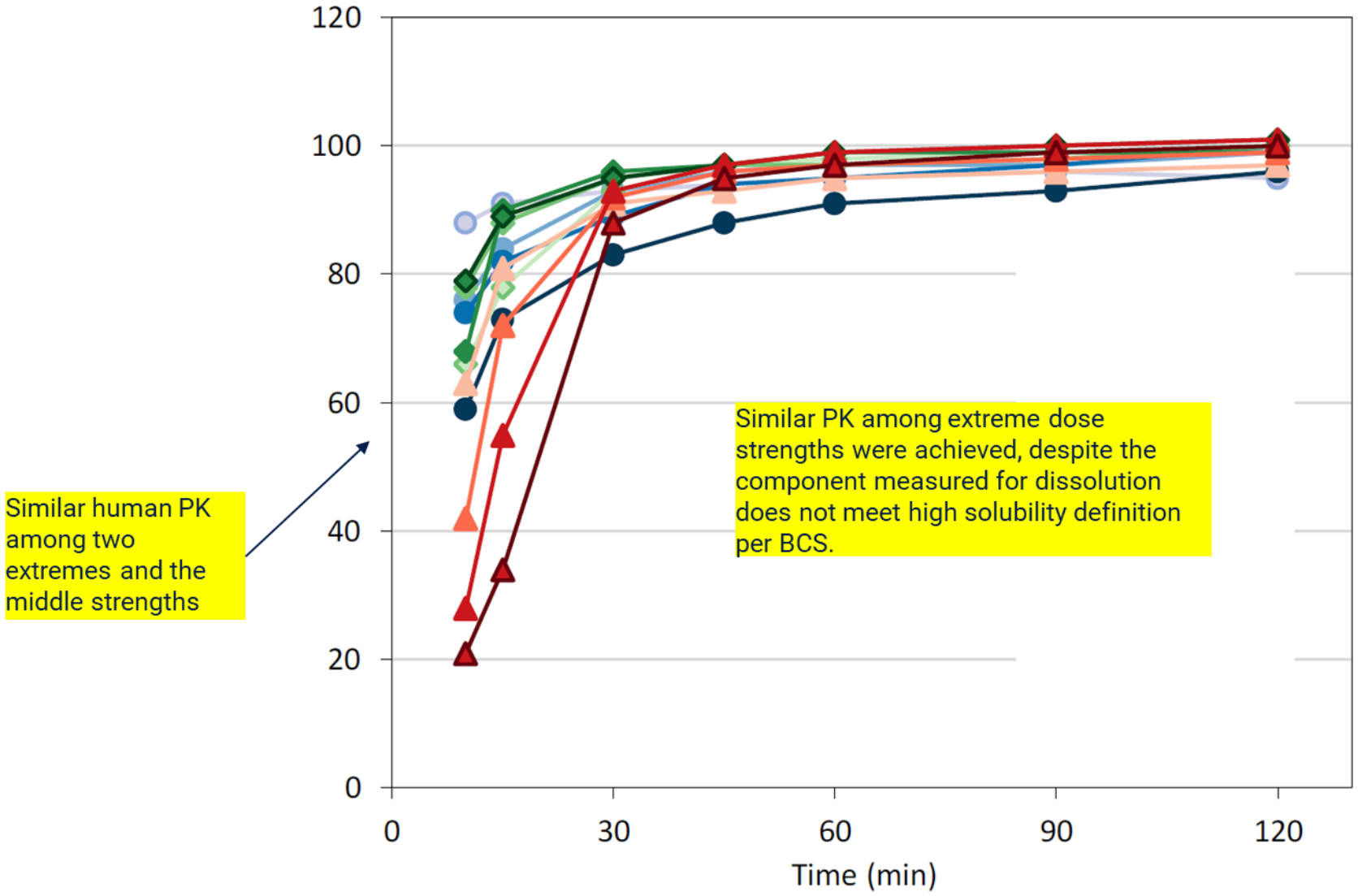
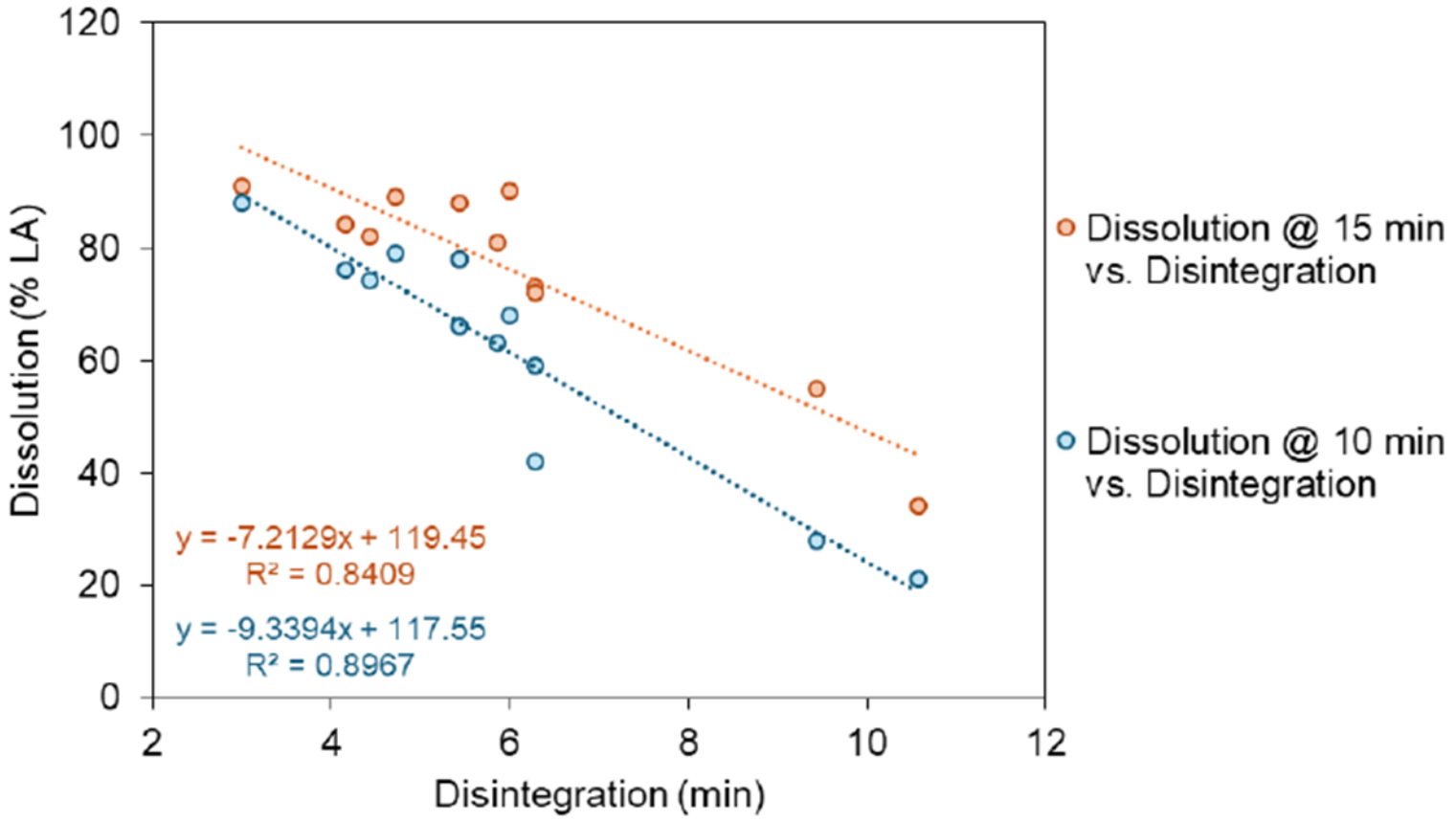
Case Study 1

A rapidly disintegrated tablet that gives similar bioavailability across all strengths and exhibits correlation and similar discrimination power between dissolution and disintegration

A safe space covered by the highest and lowest dose strengths is supported by (1) similar human PK covering the extreme dose ranges and (2) a wide range of dissolution profiles from multiple dose strengths



Correlation between dissolution and disintegration from PSBs were observed



Both dissolution and disintegration show discrimination against two variables, with a common variable of solid fraction

Drug/Product Information	Rapidly disintegrating tablets	
	Variables	**Risk Level on Dissolution Performance (High, Medium, Low)**
Potential CMAs	Drug substance properties (particle size, morphology)	Low: No discrimination
	Excipient CMAs	N/A (not studied)
Potential CFVs (≤ ± 20%)	Drug loading	Low: Discrimination observed at high drug load
	Filler (dextrose) level	Low: No discrimination
	Binder level	N/A (not studied)
	Disintegrant level	Low: No discrimination
	Filler level	N/A (not studied)
	Lubricant level	Low: No discrimination
Potential CPPs	Granulation particle size	Low: No discrimination
	Lubrication time	Low: No discrimination
	Compression force (Solid Fraction)	Low: Discrimination observed at SF = 0.9
Effect of Temperature and Moisture	Moisture	Low: No discrimination
	Temperature	Low: No discrimination
Method Conditions	pH	Low: pH XX selected for solubility and stability
	Enzyme	Low: Protease selected due to highest enzyme activity
	Ionic strength (buffer concentration)	Low
	Medium volume	Low
	Apparatus type	Low: Apparatus 2 small volume vessels selected due to size limitations with Apparatus 1 small volume baskets. Flat-bottom vessels selected to minimize coning artifact.
	Agitation rate	Low

Notes: SF quantifies how much of the tablet is solid (the inverse of porosity); used as a measurement to normalize tablet compactness across the range of tablet sizes/strengths.

Potential CMAs, CFVs, and CPPs		Level / Range	Discrimination Observed at USP Criterion (NMT 15 mins)
Target	Target	DS particle size: $D_{90} \leq 51$ µm Disintegrant level: 4% (w/w) Lubricant level: 1.5% (w/w) Milled granule PSD: D_{50}=57.2 µm Final-blend time and speed (K value): 200 Compression force (SF): 0.8 12.6% Drug load 7.9% Dextrose	N/A
CMA	DS particle size	Larger DS particle size (D_{90} = 63.3 µm)	Yes
CFV	Disintegrant (sodium starch glycolate) level	3.2% (-20% of Target level)	No
		4.8% (+20% of Target level)	No
	Lubricant (Calcium stearate) level	1.2% (-20% of Target level)	No
		1.8% (+20% of Target level)	No
	Drug loading	15.1% Drug load	No
		10.1% Drug load	No
	Filler (dextrose) level	9.5% (+20%) of Target Level	No
		6.3% (-20%) of Target Level	No
CPP	Milled granule particle size	Larger PSD: D_{50}=67.1 (+17.3% of Target)	No
		Larger PSD: D_{50}=96.1 (+68.0% of Target)	No
		Larger PSD: D_{50}=108.6 (+72.5% of Target)	No
	Final blend blending time and speed	Over-blending: K* value = 250 (+20% of Target)	No
	Compaction force and speed	Low SF = 0.72 (-10% of Target)	No
		High SF = 0.90 (+12.5% of Target)	Yes

*K Value is a dimensionless parameter that accounts for sensitivity to lubrication during blending process. SF quantifies how much of the tablet is solid (the inverse of porosity); used as a measurement to normalize tablet compactness across the range of tablet sizes/strengths.

Summary of Case Study 1

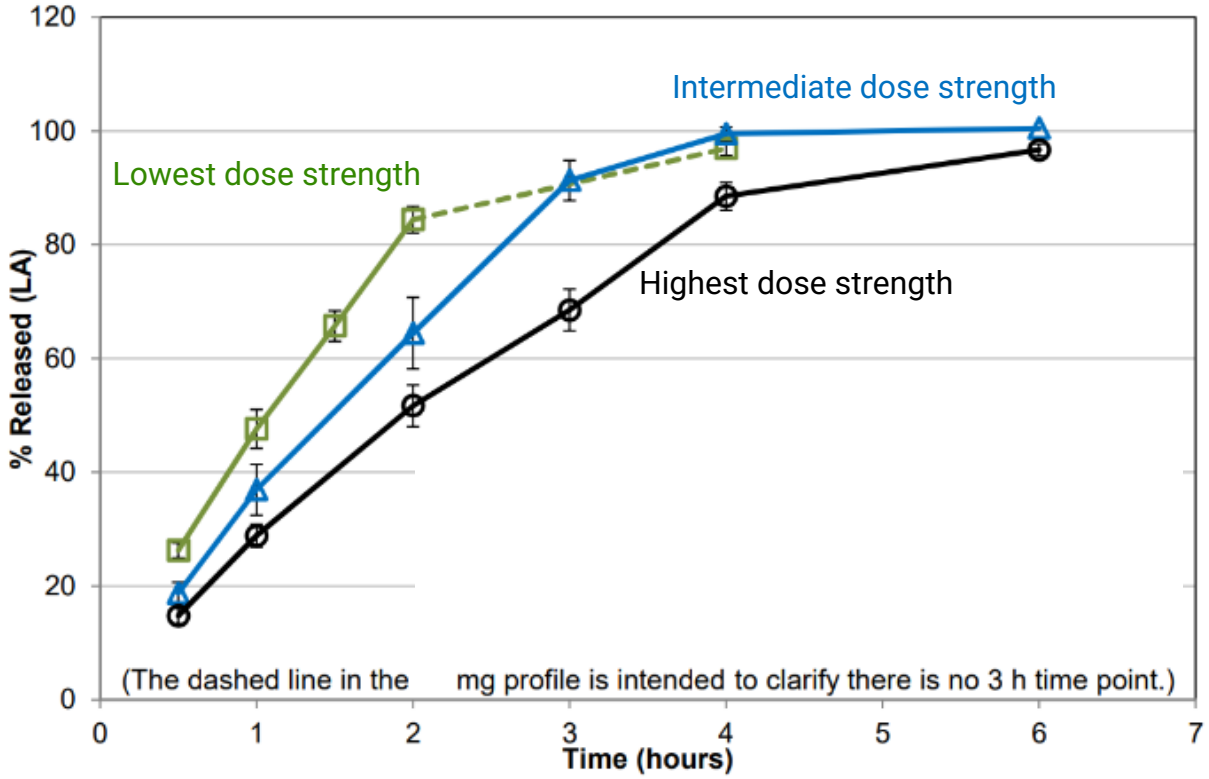
- Rapid disintegration tablets
- Similar PK results covering the entire dose strengths justify a very low biopharmaceutics risk, despite an insoluble molecule
- Disintegration in place of dissolution was granted based on the entire data package, including
  - Formulation design
  - Correlation between dissolution and disintegration
  - Similar discrimination power of both dissolution and disintegration

Case Study 2

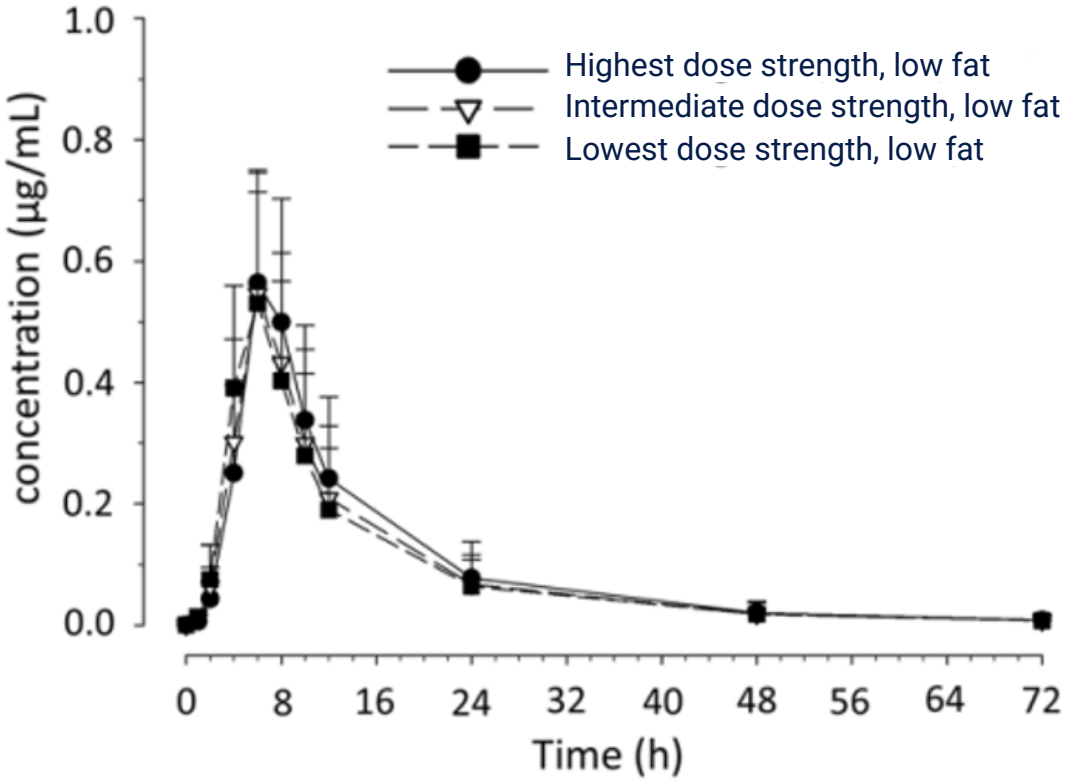
BE over a wide range of formulations (tablets and suspensions) for a BCS IV drug with long T_{max}. No discrimination for the pediatric suspensions after exhausted effort

Human BE results (AUC, Cmax and T_{max}) were observed from all three tablet strengths, despite a wide range of dissolution profiles, indicating dissolution within the range studied not critical to absorption.

In vitro release

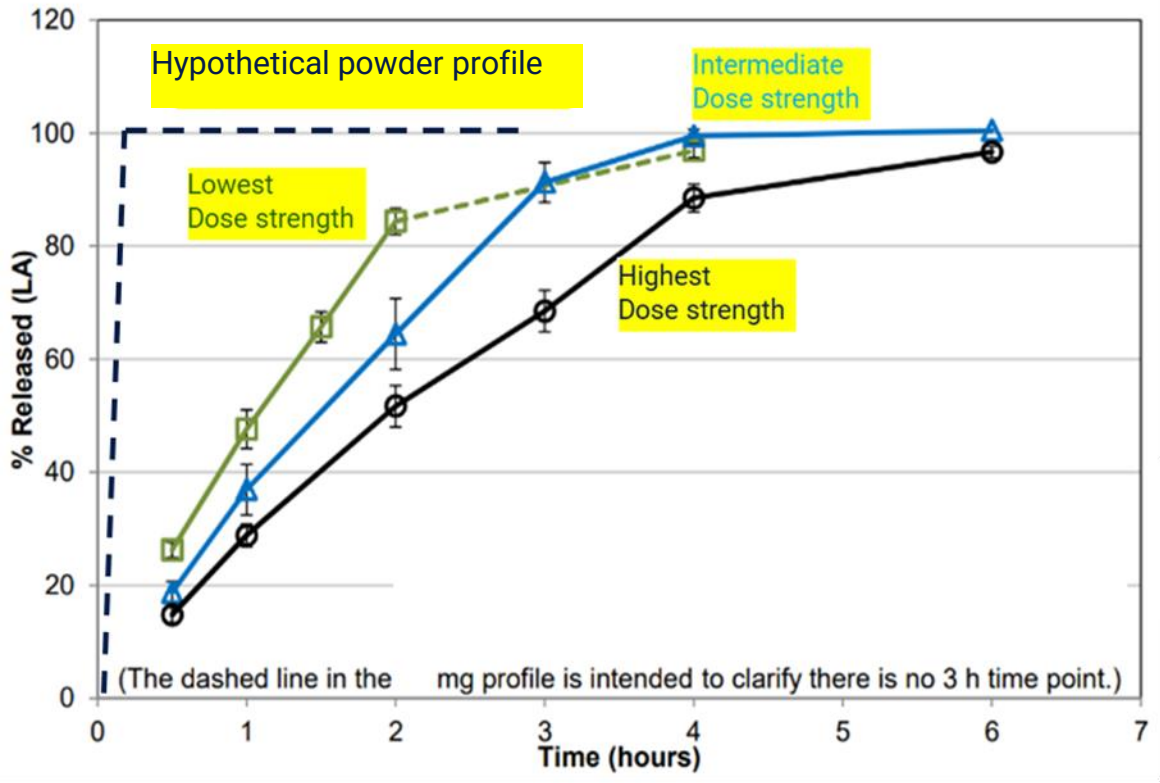


In vivo results

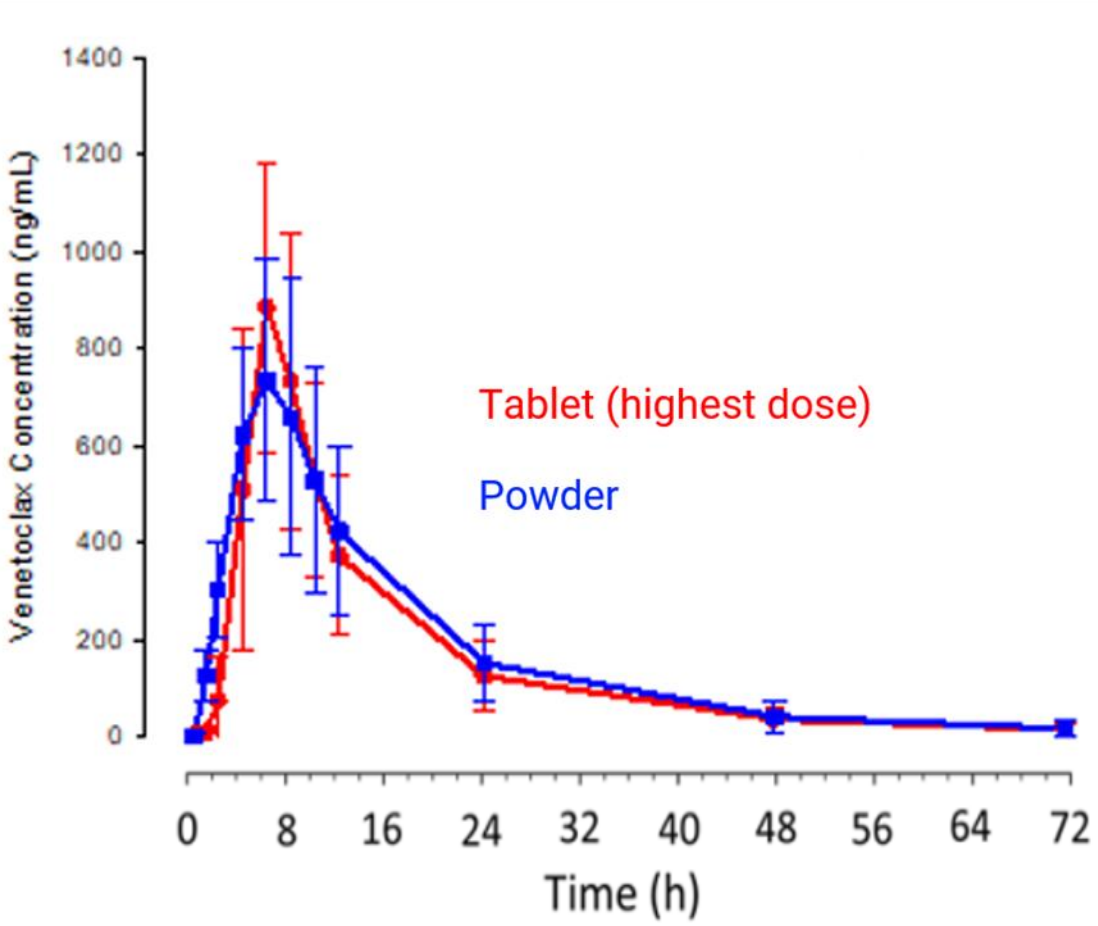


Non-criticality of dissolution over an even wider range was supported by BE results between pediatric power and tablet of the highest strength

In vitro release



In vivo results

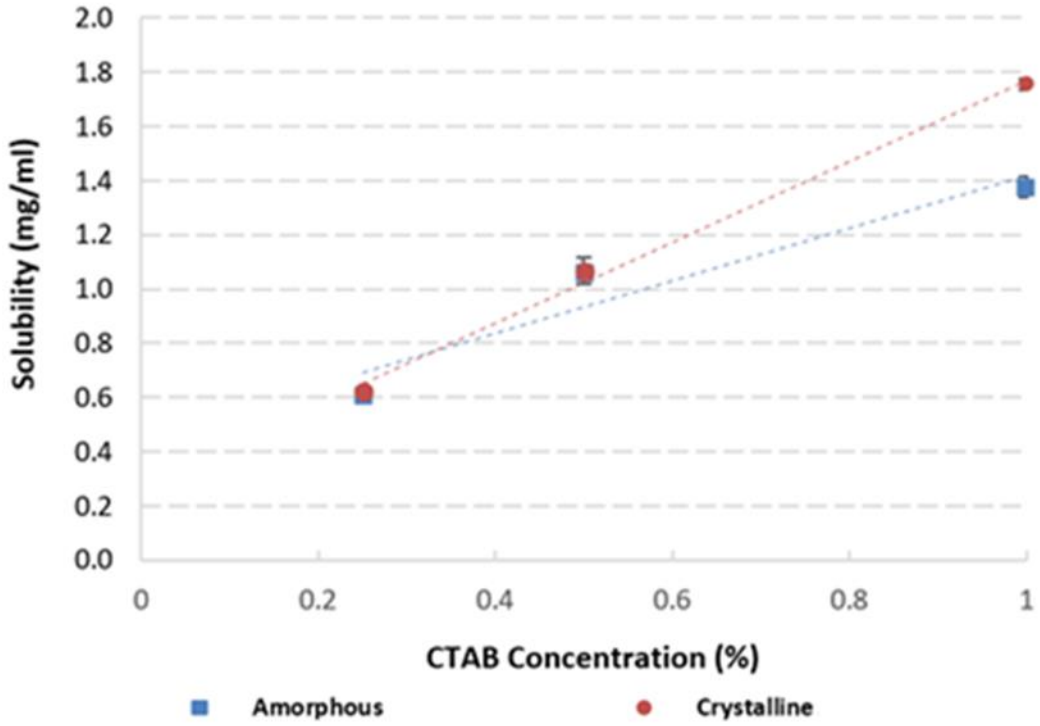


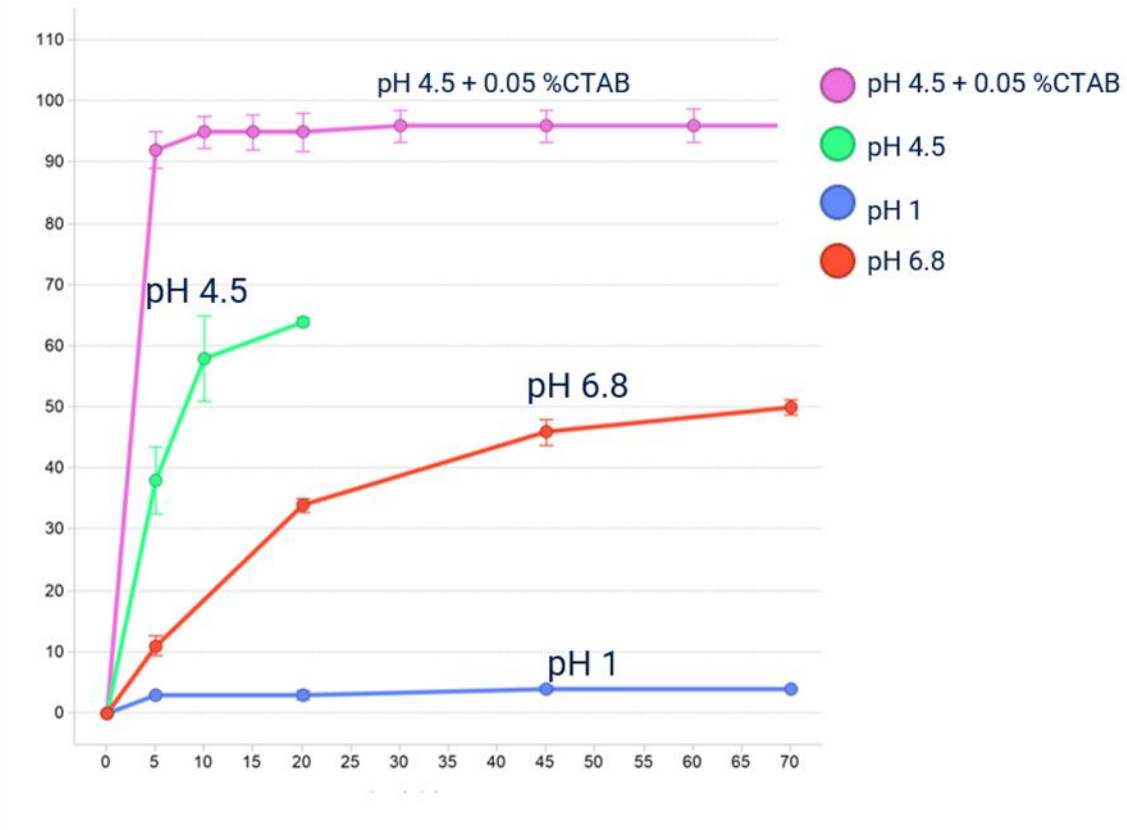
Based on the favorable BE results between tablets and power formulations, dissolution is shown not critical to absorption, and a very low biopharmaceutics risk for this family of formulations can be justified.

Discrimination for the power formulation is not necessary and unlikely. Perhaps neither dissolution nor disintegration is required. Instead, a dispersion test can be used instead.

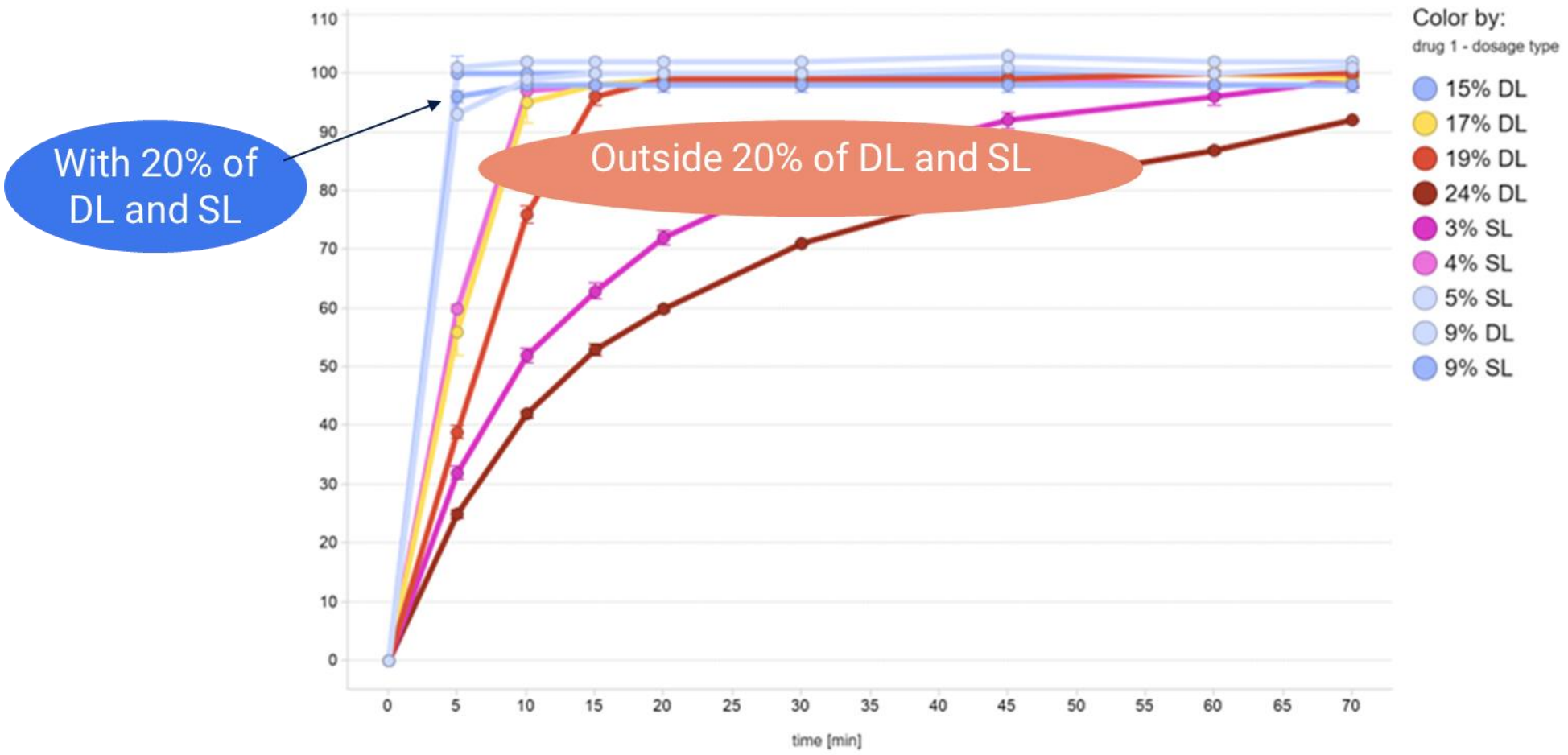
Reality: we were asked to develop a discriminating method for the pediatric powder formulation, but with no success (as expected based on the formulation design with a large surface area and supported by selected data below)

Surfactant is required to achieve complete release in all thee pHs, yet, even a very minute amount of surfactant leads to rapid dissolution primarily due to the large surface areas of the pediatric powder. Discrimination is expected unlikely. (see next slide) (App2, 25 rpm)





Effort to test two most likely variables, drug load (DL) and surfactant load (SL), failed to show discrimination withing 20% of DL (blue profiles) and SL (blue profiles)(App 2, 25 rpm). Only variations with >> 20% showed discrimination, but it's not meaningful.



Case Study 3

- PBPK modelling showed BE over a reasonably wide range of dissolution profiles for a BCS III molecule
- No discrimination observed after exhausted/excess effort.

Using PBPK modelling to widen dissolution specifications lower than pivotal/commercial batches and without a non-BE lot

Elagolix PBPK model developed for assessing DDI potential

Model validation using two BA studies where pivotal and commercial lots were tested

Dissolution profiles up to 75% slower were predicted BE to the reference

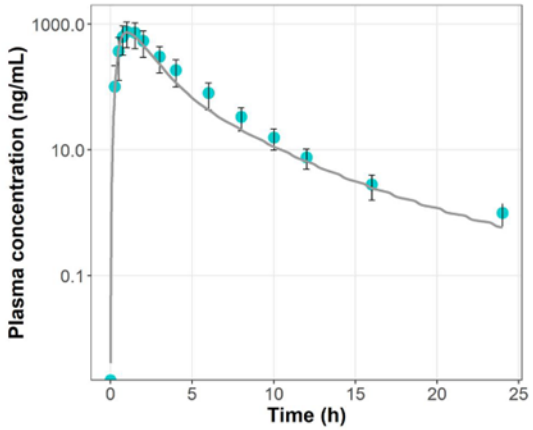
PBPK modelling supporting slower dissolution was approved by FDA without in vivo study

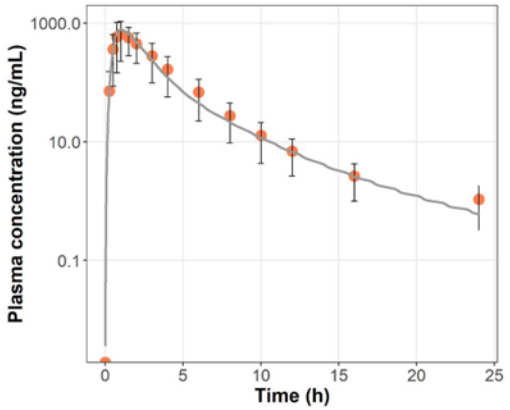
IR tablet with amorphous drug substance that is soluble throughout the physiological pH range

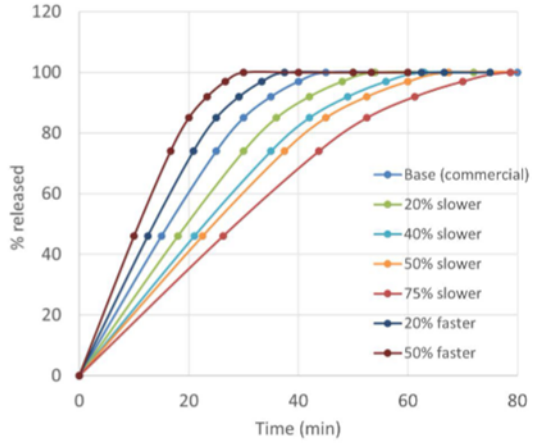
RISK: Dissolution slow down during stability could fail the approved specs

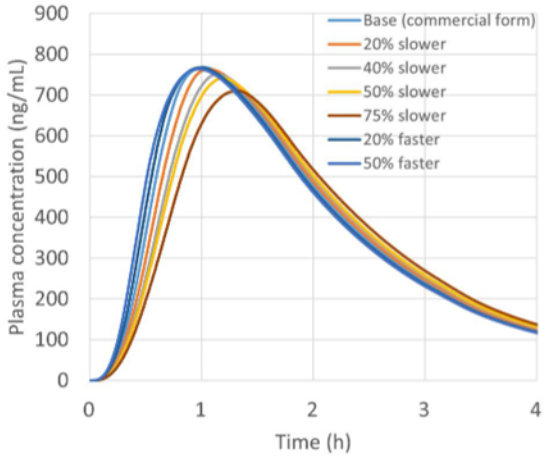
RISK level: Medium based on understanding of in vitro dissolution and biopharmaceutics failure modes.

Mitigation:PBPK modelling









The PBPK model for predicting Elagolix exposure was deemed acceptable by FDA, resulting in widened dissolution acceptance criteria of lots up to 30% slower than the commercial formulation.

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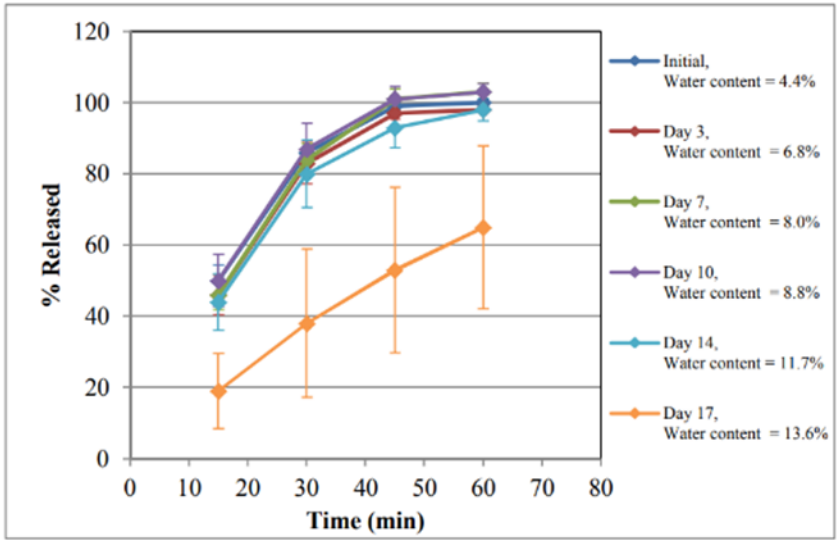
Refs:

- Biopharm Drug Dispos.2022;43:98–107.
- CDER, Application # 210450Orig1s000, Product Quality Review(s)

Summary of Discrimination Studies (Zero discrimination observed after exhaustive effort twice)

Variable Type	Variables	Level/Range	Results (Discrimination demonstrated?)
	Nominal	API specific surface area: ~34 m²/g API bulk density: 0.19 g/mL Ribbon solid fraction:~ 60% Tablet hardness: ~ 87 N	
CMAs	API specific surface area (SSA)	Low SSA ~0.3 – 43 m²/g	N
	API bulk density	Bulk density: 0.17 - 0.33 g/mL	N
CFVs	Buffer agent level	20 % less and 20% more than nominal	N
	Filler level	10% less and 10% more than nominal	N
	Lubricant level	20 % less and 20% more than nominal	N
CPPs	Ribbon solid fraction	Low ribbon solid fraction: ~58% - ~66%	N
	Tablet hardness	Tablet hardness: ~78 N, 118N, 140N	N
	Lubrication time	5 minutes more than nominal (2 minutes)	N
Moisture Content		4.3% to 13.6%	N from 4.3% - 11.7% Y at 13.6% (excessive)



Summary of Case Study 3

- A wide dissolution range covered by PBPK can be considered a safe space → biopharmaceutics risk can be reduced from medium to low, perhaps not very low due to lack of extensive in vivo studies
- A simple dissolution method can be used even if complete release is achieved in 45 minutes
- Disintegration may be a stretch given lack of extensive in vivo studies

Contents

Suggested API & formulation properties and data/evidence that can justify low to very low bio risk, but with caveats in red text indicating potential risk

	Low Permeability	Rapid Dissolution	pH independent solubility
Very low BRA	Human BE over a wide range of dissolution profiles		
Low or Very Low BRA?	In silico models support BE over a wide range of dissolution profiles Some in vivo data		
Low BRA	• BE supported by "validated" biorelevant tools • Limited in vivo data		
Risk that might need to be mitigated through additional studies	Food effect if observed (due to longer gastric emptying and/or solubilization) could elevate risk	pH dependent solubility (basic drugs) rendering precipitation in small intestines could elevate risk level for PPI users Food effect could elevate risk level, especially for DCS IIb Discrimination observed for DCS IIb such API PS	Food effect if observe could elevate risk level, especially for DCS IIb Discrimination observed for DCS IIb such API PS

Thank You