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From Solubility to In-Vivo Predictability: Dissolution as a Low-Risk Parameter in Oral Suspensions

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Bioequivalence risk assessment

Regulatory requirements

Multiple studies: FAST/FED/Steady-State/PPI
BE study at multiple strengths

Additional BE criteria (AUC t_{max}; $AUC_{0\text{-}1,5h}$)

Alternative dosing: e.g., without water, beverages, sprinkle.

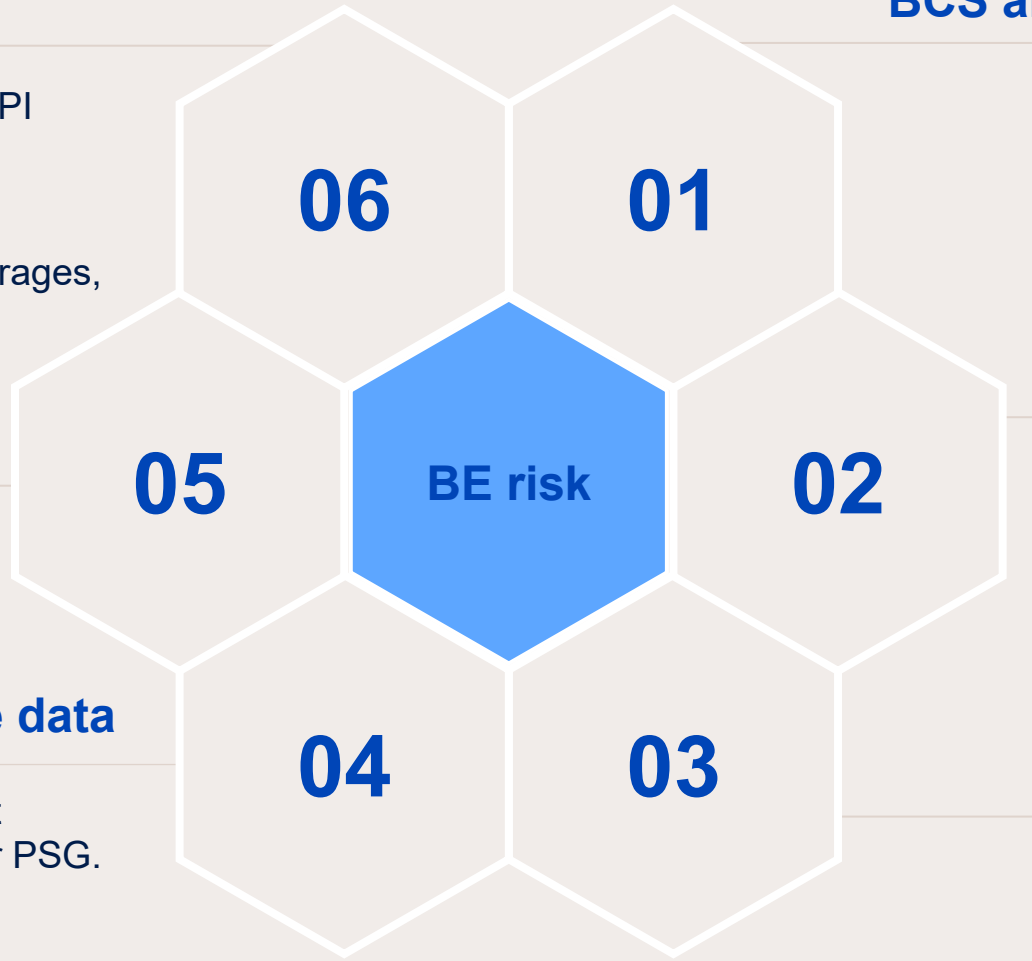
Dosage design

Modified release > Immediate release

Fixed dose combination
Design around > Brand similar

Availability of RLD and literature data

Limited literature or internal data, insufficient experience in BE design, and lack of RLD or PSG.



BCS and Phys-Chem API properties

Complexity of API (CDER)

BCS II & IV > BCS I & III

Stability of API

Pharmacokinetic properties

Absorption window/Metabolism

Locally acting API

Elimination and Distribution rate

ISCV

Pharmacodynamic properties

Narrow therapeutic window

Non-standard dosing at BE study

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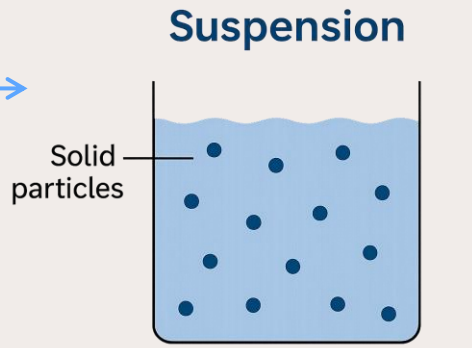
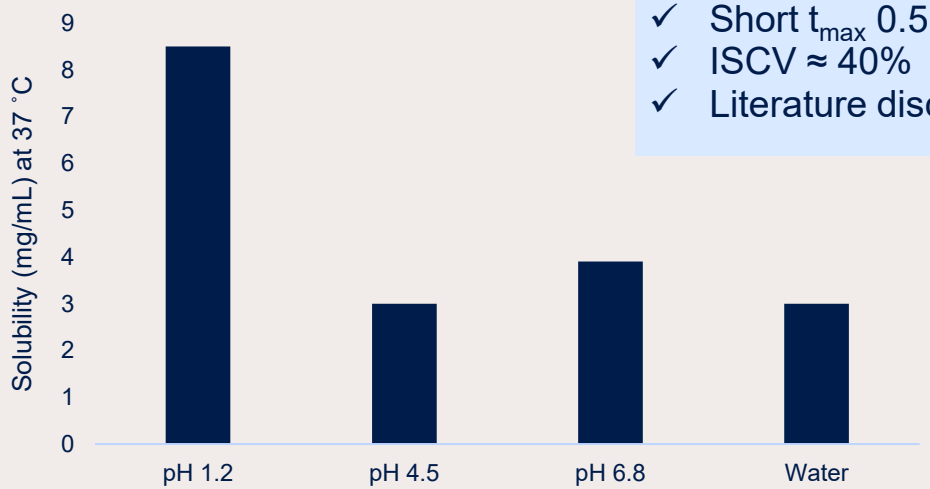
Generic oral suspension – Bioequivalence risk

Weak acid, pKa 7.5 & 1.3
Dose/solubility ratio: 35 ml
High solubility



Polymeric solution (ionic)



Factors decreasing BE risk:

- ✓ I.V. formulation and oral suspension demonstrated bioequivalent exposure
- ✓ High solubility
- ✓ Good intestinal absorption (urinary excretion data showed that ≥77% of orally administered drug substance is absorbed)

Factors increasing BE risk:

- ✓ Short t_{max} 0.5 h (0.25-0.75)
- ✓ ISCV ≈ 40%
- ✓ Literature discrepancy in solubility data – BCS IV

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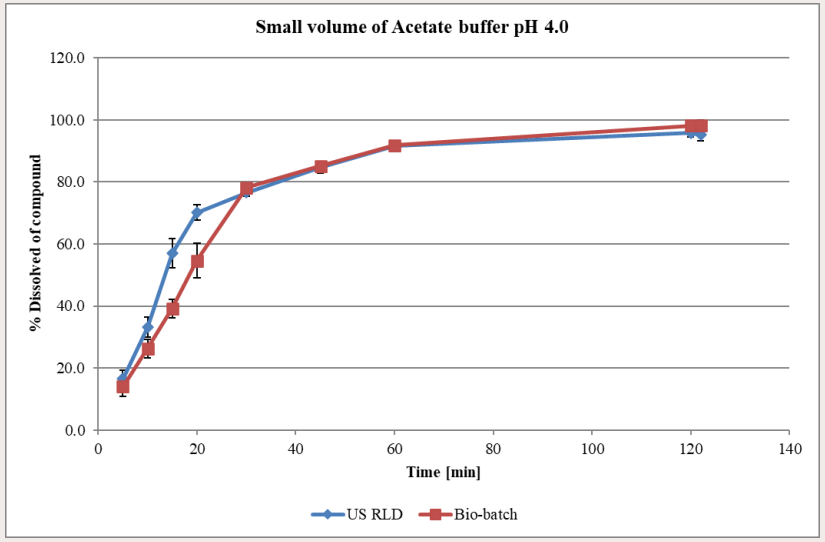
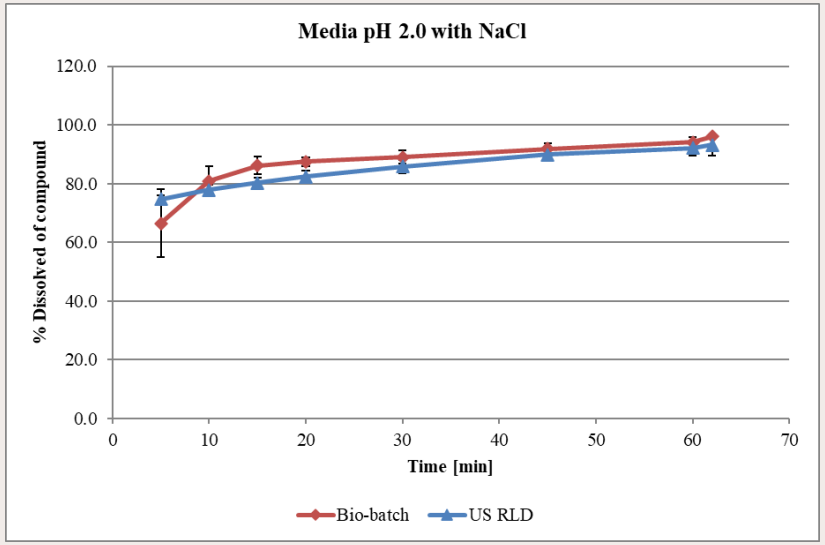
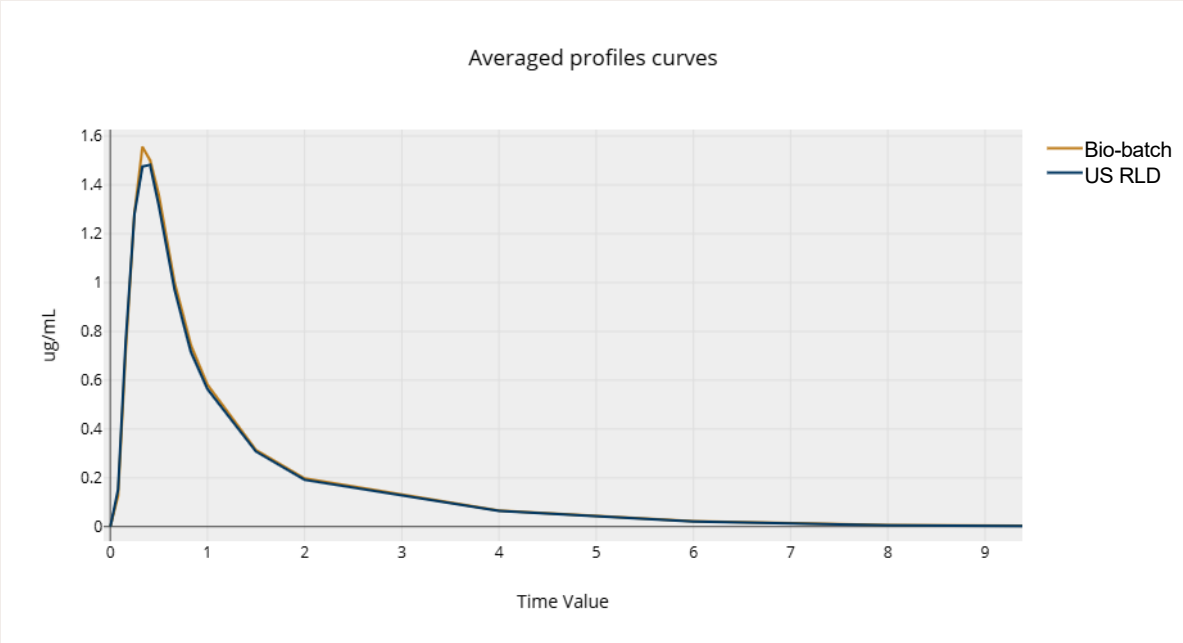
Biorelevant dissolution conditions

Biorelevant conditions were selected based on biopharmaceutical properties of API and machine learning model (MODIS)







- ✓ PSD of the API was reflected under pH 4.0, while viscosity was captured using the pH 2.0 + NaCl medium.
- ✓ Rapid dissolution was observed with both methods.
- ✓ Neurofuzzy model integrating both dissolution datasets showed good predictability (error < 10%).
- ✓ Bioequivalence confirmed:
  - C_{max}: 101.8% (90% CI: 94.9–109.1)
  - AUC_t: 103.8% (90% CI: 99.5–108.2)

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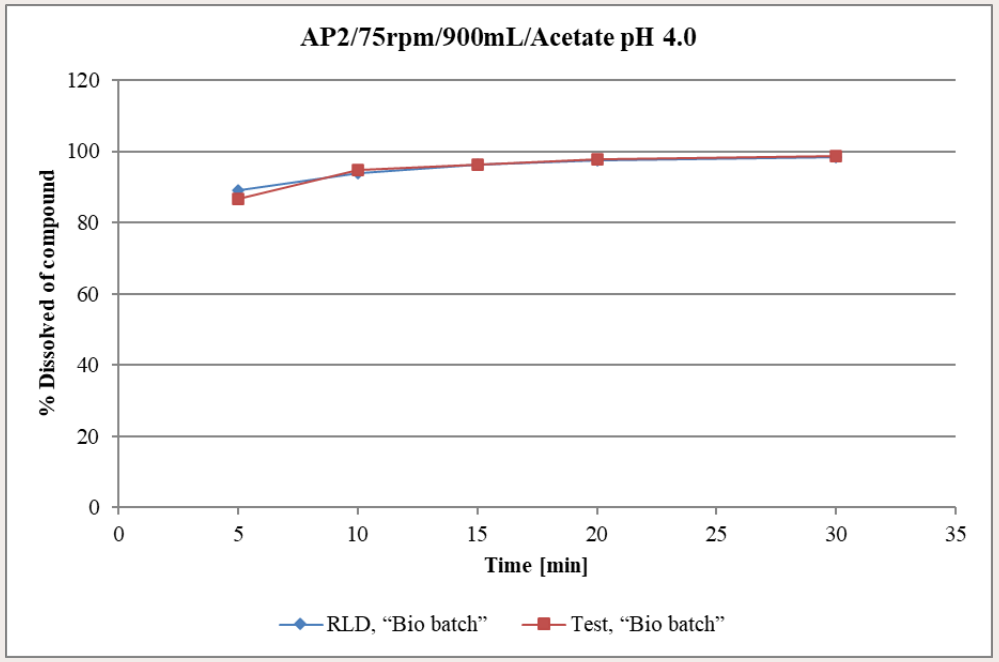
QC dissolution method

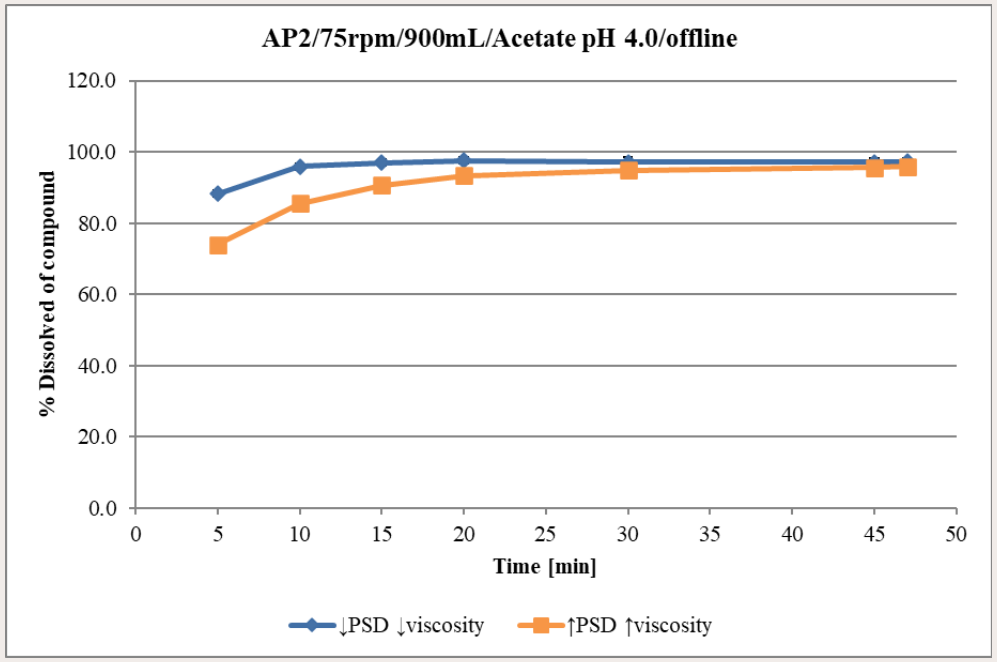
FDA dissolution method

Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)
Suspension	II (Paddle)	75	pH 4.0 Acetate Buffer	900	5, 10, 15, 20 and 30



Discriminatory power of dissolution method:

✓ Very limited to PSD and viscosity



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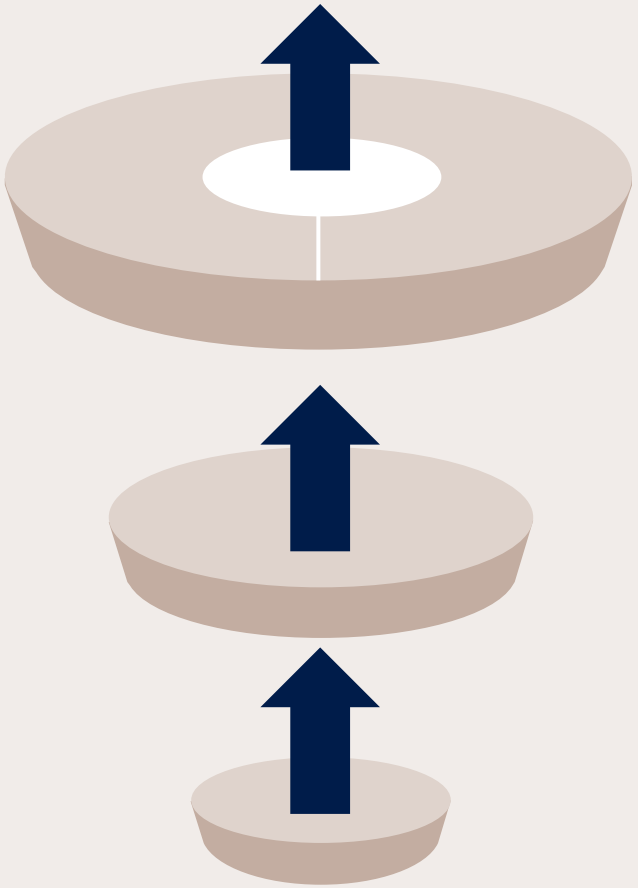
Approaches for setting dissolution method (i)

USP Dissolution Test
Not Available;
Dissolution Test for RLD
Not Available

USP Dissolution Test
Not Available;
Dissolution Test for RLD
Available

USP Dissolution Test
Available



Product specific dissolution method

- **Multiple dissolution conditions evaluated (pH, hydrodynamics, apparatus; Section 3.2.P.2)**
  - ✓ FDA method is robust, sufficiently discriminatory. Specification point set up at 15 min.
- **FDA-requested conditions:**
  - ✓ **DRL**: 500 mL 0.1 N HCl, A2, 25-50 rpms
  - ✓ **IRL:** 900 mL Acetate pH 4.0, A2, 50 rpm

FDA Dissolution Methods (A2, 75 rpms, Acetate pH 4.0, 900 mL)

For the generic oral suspension, **FDA dissolution method was available**.

- ✓ Limited discrimination for PSD and viscosity, consistent with high API solubility/permeability;
- ✓ Method validated with confirmed robustness.

Quality control dissolution test is the test described in the USP.

For the generic oral suspension, QC dissolution method **was not available in USP.**

Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, CDER 1997

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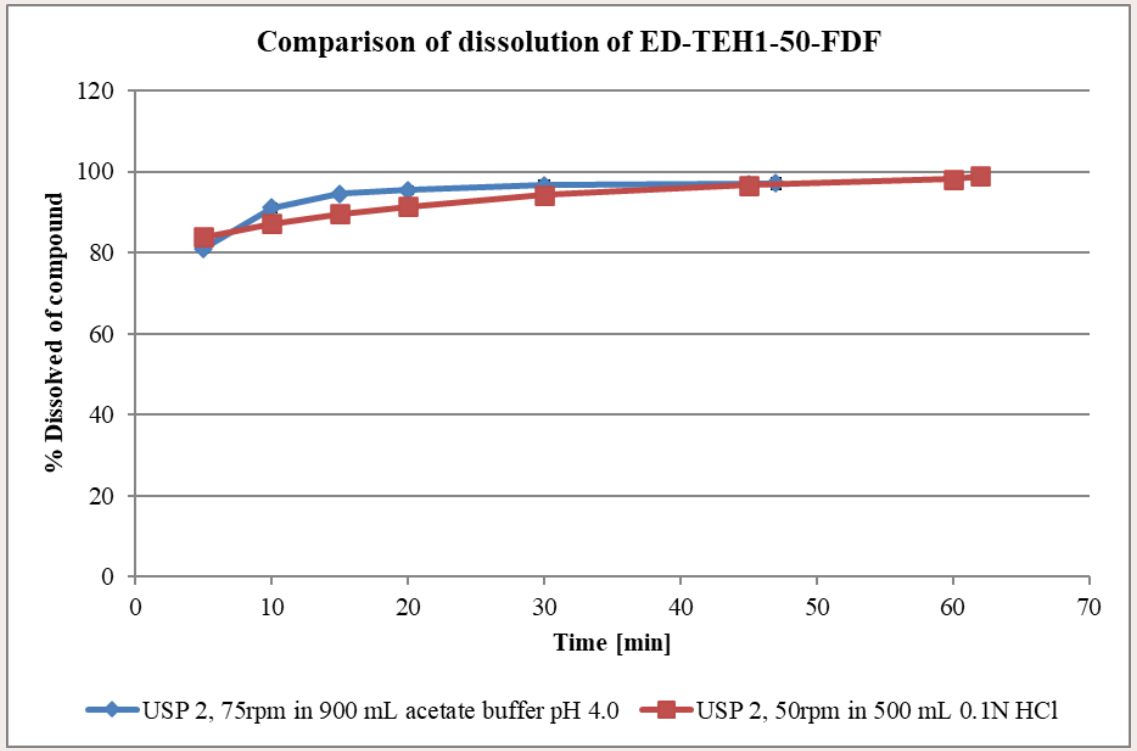
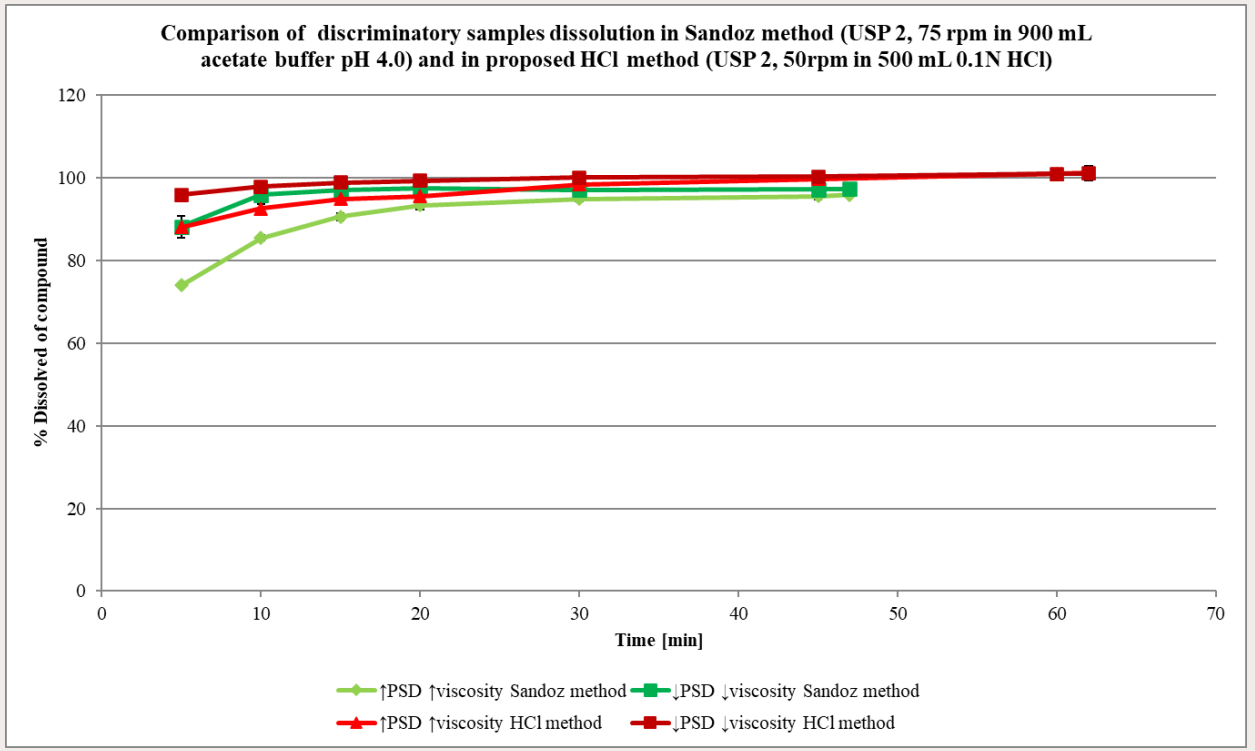
Approaches for setting dissolution method (ii)

FDA vs. DRL proposal



FDA vs. DRL proposal – discriminatory power



Conclusions:

- ✓ Both dissolution methods are rapid; drug release profiling is more clearly differentiated using the FDA method
- ✓ Both methods show limited discrimination for PSD and viscosity; the FDA method demonstrates greater sensitivity
- ✓ FDA-recommended conditions: Apparatus 2, 50 rpm, 500 mL of 0.1 N HCl
  - as recommended in FDA guidance for **highly soluble oral solids => applicability to suspensions remains to be assessed.**

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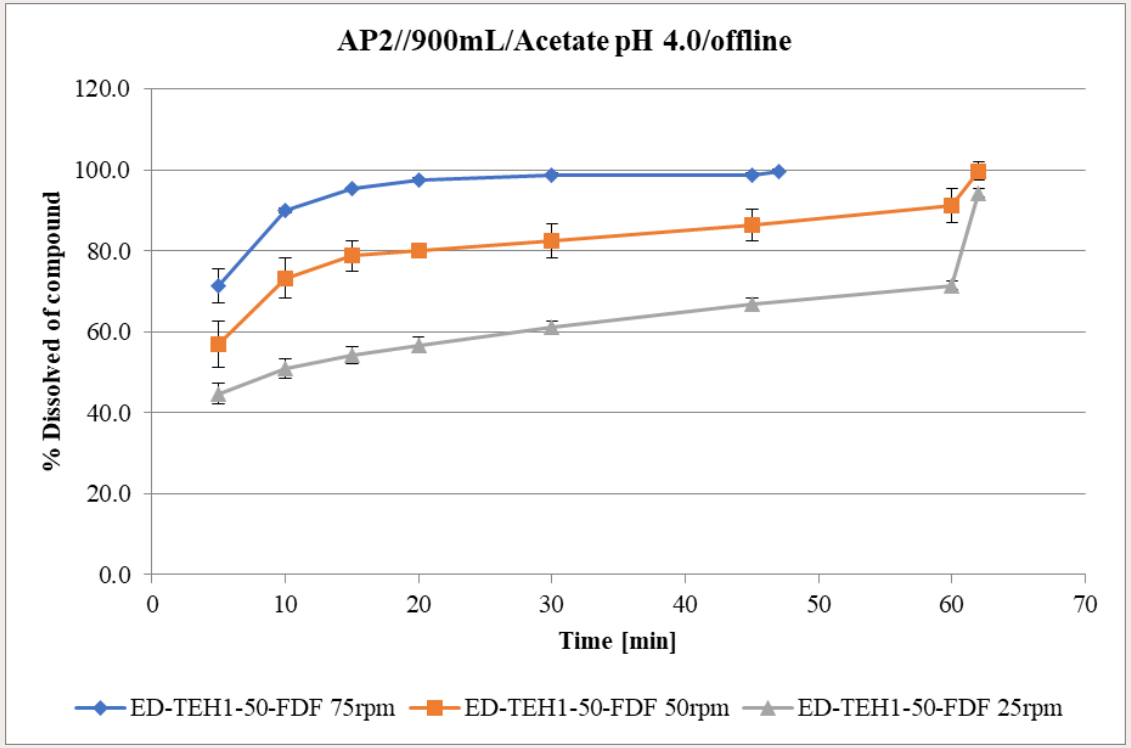
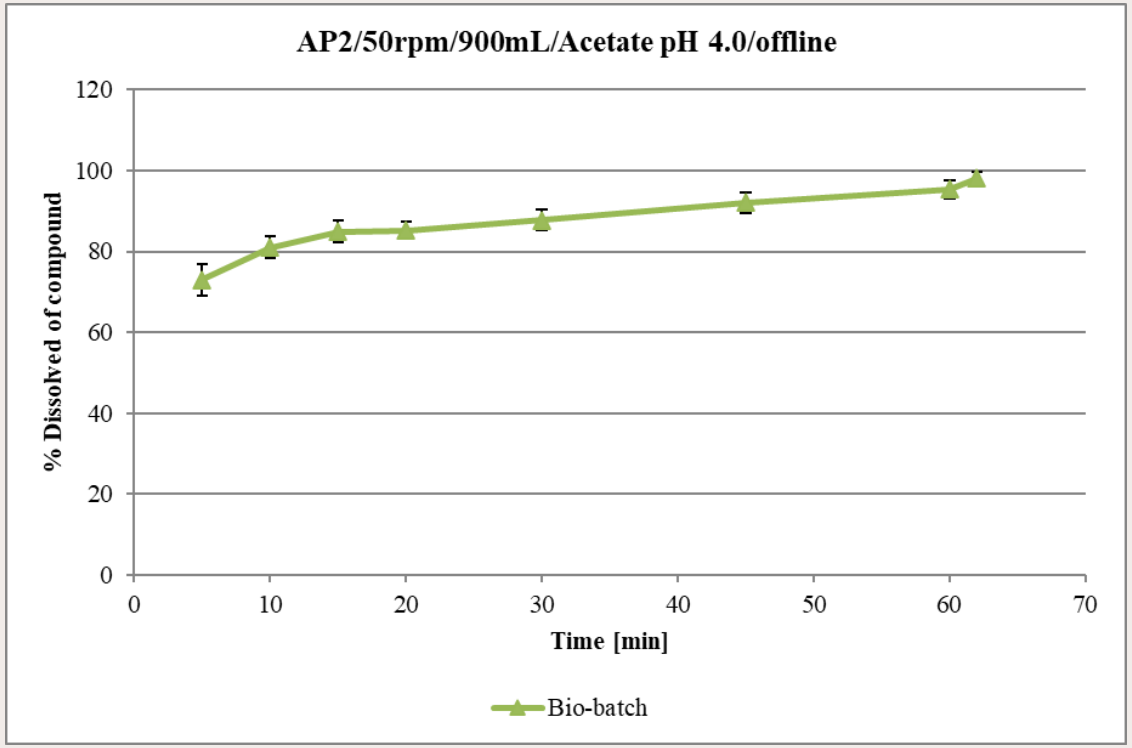
Approaches for setting dissolution method (iii)

FDA vs. IRL proposal



FDA vs. IRL proposal – bio-batch



Conclusions:

- ✓ Coning evident at 25 rpms (recommended rpms for suspensions) and 50 rpms. 75 rpms represents adequate hydrodynamics.
- ✓ The bio-batch achieved approximately 85% drug release at 15 minutes (Stage S2), representing a borderline specification from a lifecycle perspective.
- ✓ FDA approved method is still suggested as adequate for generic oral suspension:
  - It is aligned with recommendations from USP <1092>.
  - The method is undoubtedly proven to be **robust** and **biorelevant** while simultaneously achieving **sufficient discriminatory power**.

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Summary

BCS category

Highly soluble drugs

Dissolution is unlikely to be the rate-limiting step for absorption – **LOW BE** risk

Intrinsically less sensitive to formulation and manufacturing variables, which lowers the likelihood of BE failure

Dissolution profiles should be rapid

DISSOLUTION-RELATED VARIABILITY IS UNDER CONTROL

Pharmacokinetic properties

Absorption-related PK factors

Short t_{max} (0.25-0.75)

High ISCV => 40%

Clinical study design is crucial for assessing of PK behavior and BE

PK-VARIABILITY COULD BE STILL CLINICALLY RELEVANT

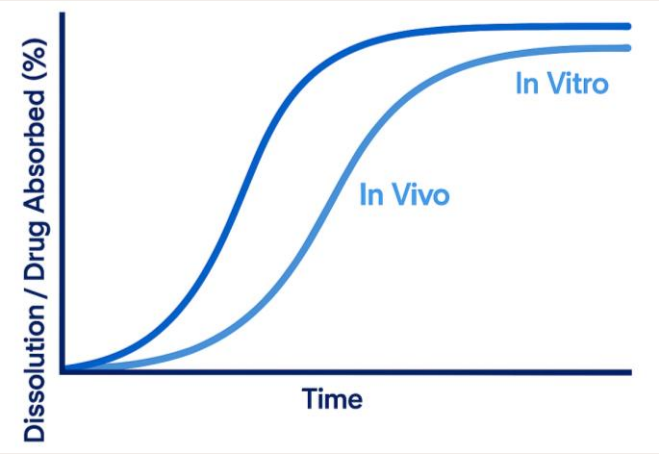
QC Dissolution method

Industry guidelines

I. FDA approved method

II. Guideline for dissolution of highly soluble oral solids = is applicable to suspension

DISSOLUTION METHOD SHOULD BE SIMPLE AS HIGH SOLUBILITY SUPPORTS SAFE RELIANCE ON IN-VITRO DATA



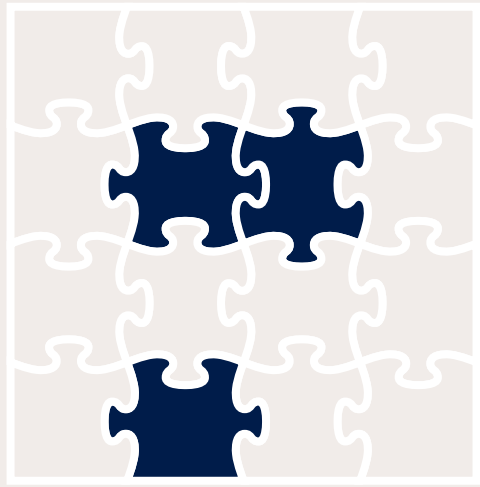
PBPK MODELS

Lifecycle tool

Impact of PSD – CMA for suspensions

Validated model

PBPK MODELING MAY SUPPORT THE ASSESSMENT OF PSD-RELATED LIFECYCLE CHANGES IN HIGHLY SOLUBLE ORAL SUSPENSIONS AS AN ALTERNATIVE TO COMPARATIVE DISSOLUTION STUDIES



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