The Tale of Truqap Dissolution: The Apex of Science vs. Compliance

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Role of In Vitro Dissolution Studies for Predictive Insight into In Vivo Performance and Biopharmaceutics Risk Mitigation
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Truqap (Capivasertib) – General Properties

- First in class AKT inhibitor for treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations
- Dibasic compound
- Solubility > 10 mg/mL in SGF
- Solubility ~0.3 mg/mL in FaSSIF-V2
- BCS Class 4 compound

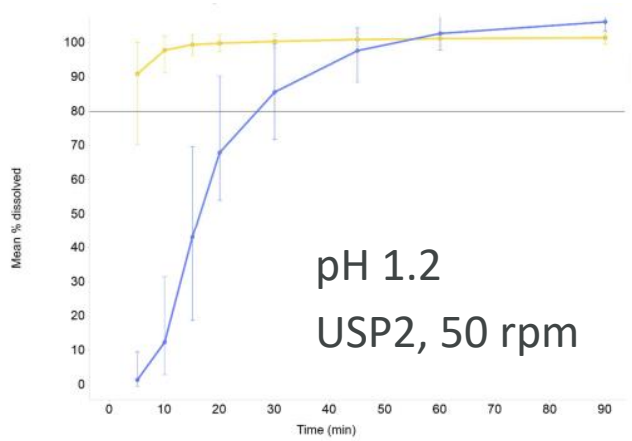
- Presented as a 160 or 200 mg film-coated tablet
  - US blister presentation PVC to allow child resistant packaging
  - US HPDE bottle
  - ROW blister presentation Alu/Alu
- Formulation contained MCC/DCPA = Coning!

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics Limited (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

Data from NDA 218197 P2 Pharmaceutical Development

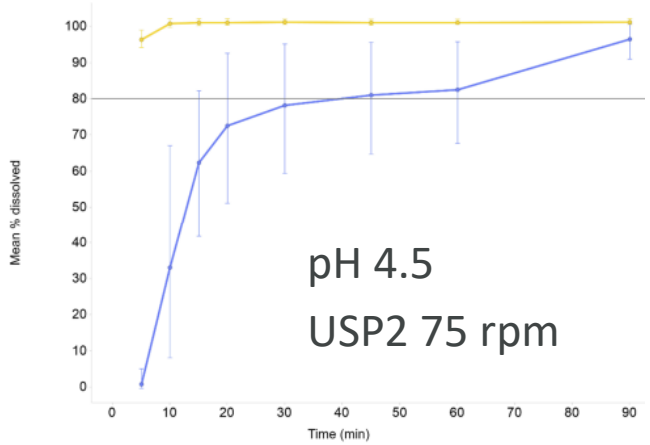
The Anchor – An *In Vivo* Reference (Ph1 to Ph2)

- Bridging between the phase 1 capsule and the phase 2 tablet was demonstrated in a Rel BA study.
- The formulations exhibited markedly different in vitro dissolution behaviour across the pH range.



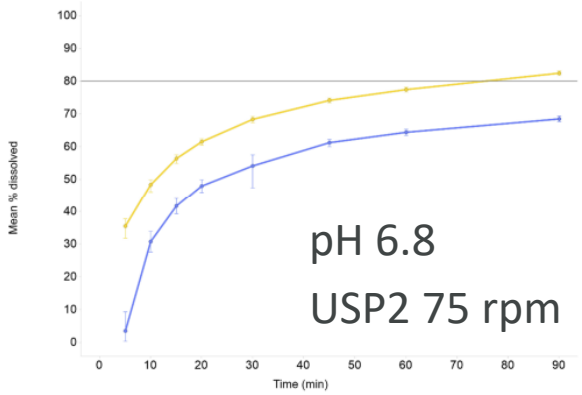
pH 1.2

USP2, 50 rpm



pH 4.5

USP2 75 rpm

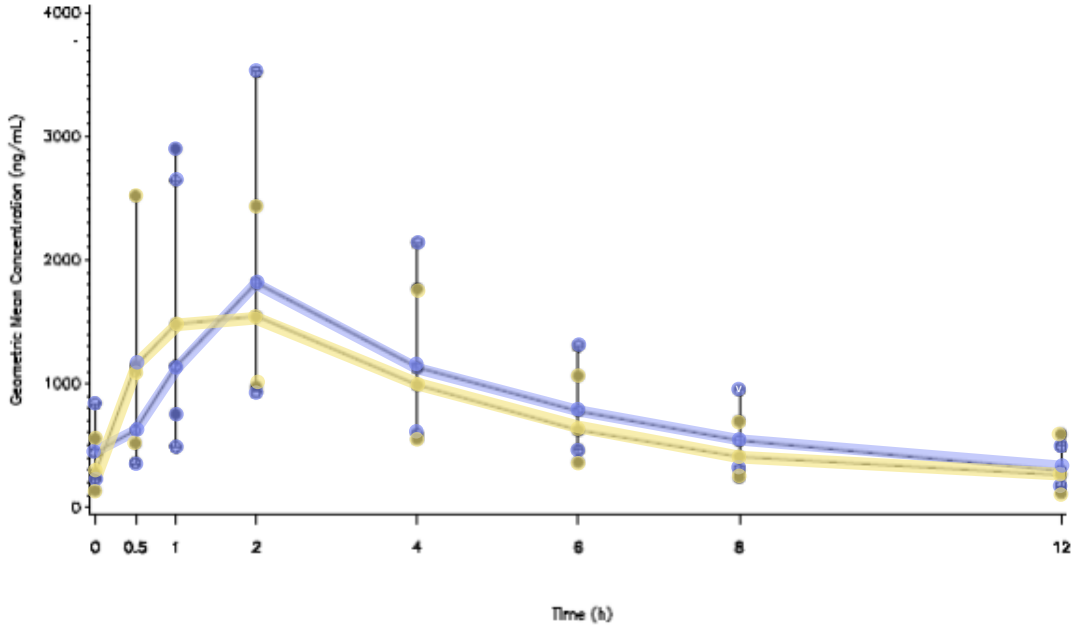


pH 6.8

USP2 75 rpm

Ph 1 Capsule

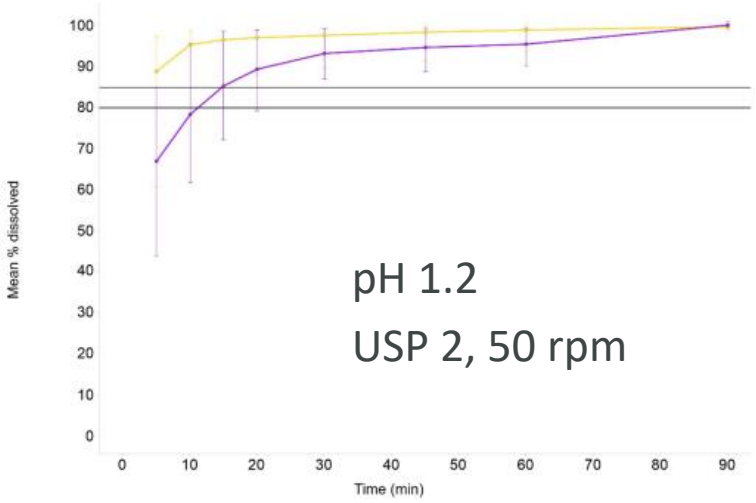
Ph 2 Tablet

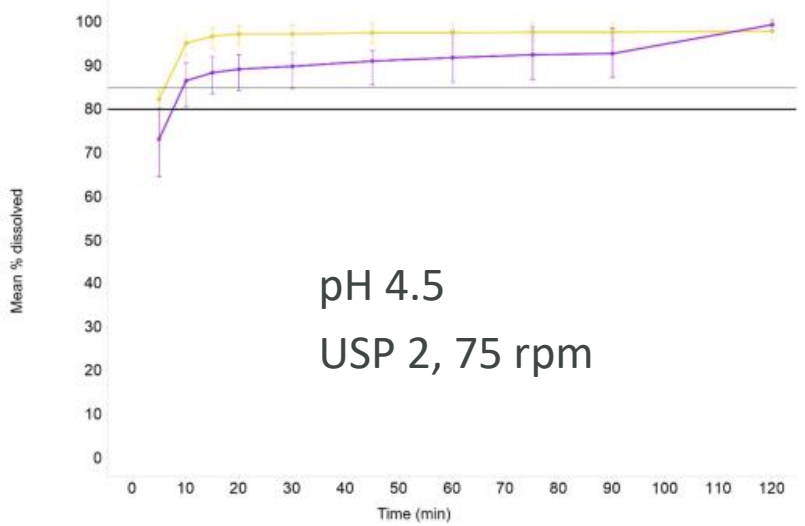


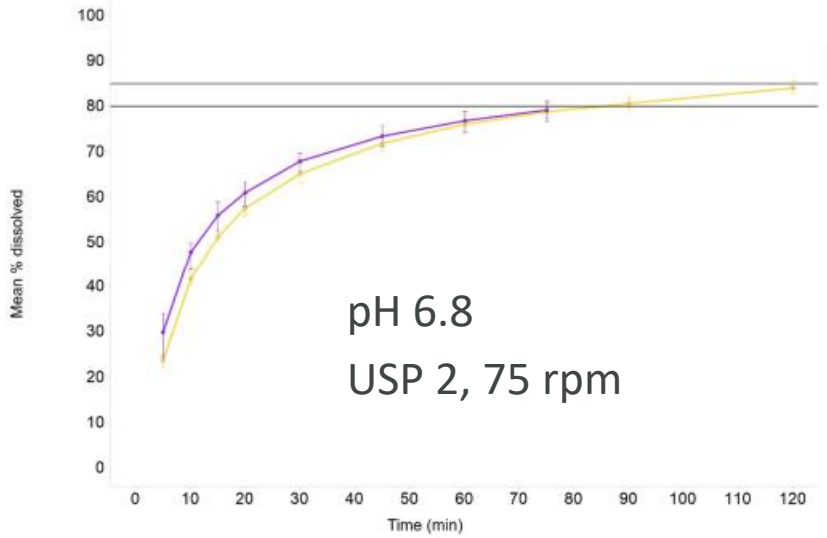
Pharmacokinetic parameter	Tablet		Capsule		Point estimate of geometric mean ratio of tablet to capsule	90% CI of geometric mean ratio of tablet to capsule	Intra-patient variability (%)
	n	LS Mean	n	LS Mean			
AUC_{ss} (h*ng/mL)	11	8535.68	11	9444.53	0.90	0.77, 1.06	20.29
$C_{ss,max}$ (ng/mL)	11	1779.37	11	1745.23	1.02	0.86, 1.20	21.75

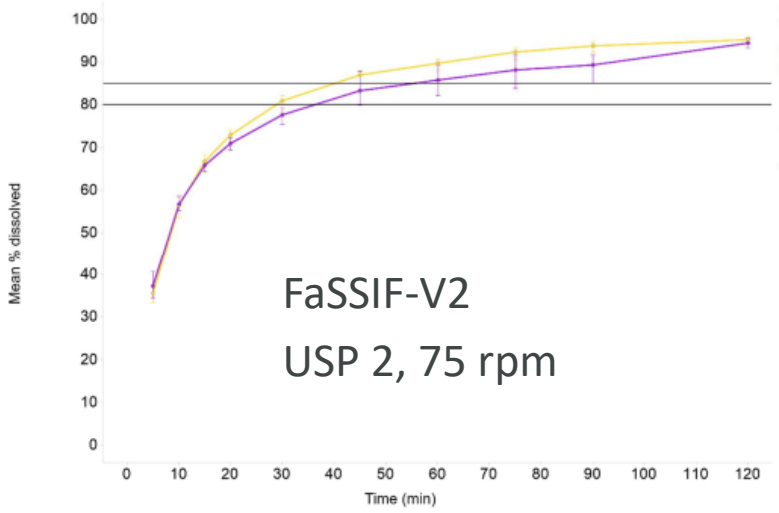
Data from NDA 218197 P2 Pharmaceutical Development

Bridging Ph2 Tablets to Ph3 Tablets – In Vitro









Ph 2 Tablet

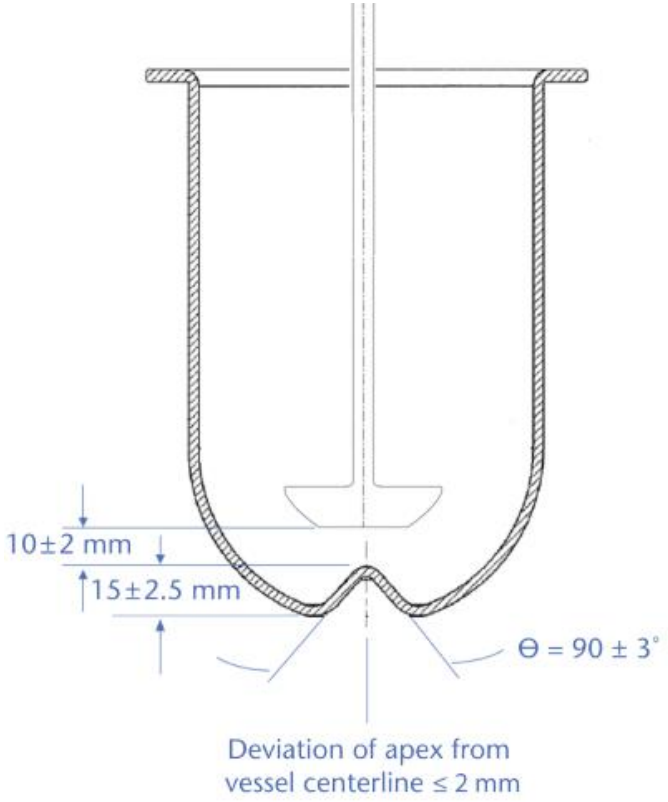
Ph 3 Tablet

- A change in formulation was required due to impact of compression speed on tensile strength – strain rate sensitivity.
- Improved manufacturability and product robustness was introduced in the Ph 3 tablet formulation.
- Bridging between the phase 2 tablet and the phase 3 tablet was performed using only in vitro dissolution.
- All comparisons showed >85% in 15 minutes or f2 >50.

Data from NDA 218197 P2 Pharmaceutical Development

Principles for Selecting a QC Method

- Simple aqueous buffers evaluated
- FaSSIF-V2 used as a biorelevant reference medium
- Surfactants explored at pH 6.8 due to incomplete release at pH 6.8
- Selected media which provided sink conditions for the 200 mg tablet in 900 mL
- Discrimination assessed against Ph 1 capsule, formulation & process variants & stability samples.
- Apparatus limited to paddle (50 and 75 rpm) and basket (100 rpm)
- Apex vessels explored to overcome incomplete release and variability related to coning



Criteria

- *Complete release within 60 min*
- *Appropriate level of discrimination*
- *Low method variability*
- *Robust method free of in vitro artefacts*

Formulation & Process Variants

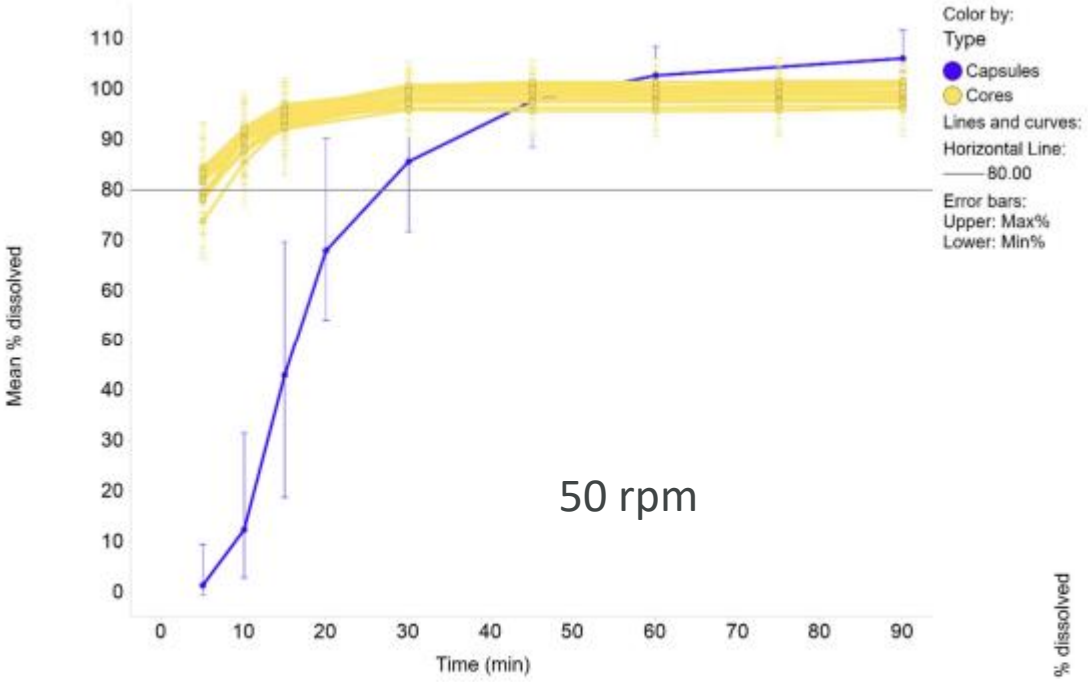
- Designed several variants to explore the discrimination of the dissolution methods.
  - Worst case variant as cores and coated tablets
    - Over lubricated in both level and blend time
    - Reduced disintegrant level by 20%
    - High roll force – low porosity
    - High compression force – low porosity
  - Un-milled API variant as cores and coated tablets
  - Un-milled API variant and extended process parameters film coated tablets
    - High roll force and high compression force
  - 0% Disintegrant variant film coated tablets
  - Film-coated variant
    - Film-coat level increased

Methods Screened

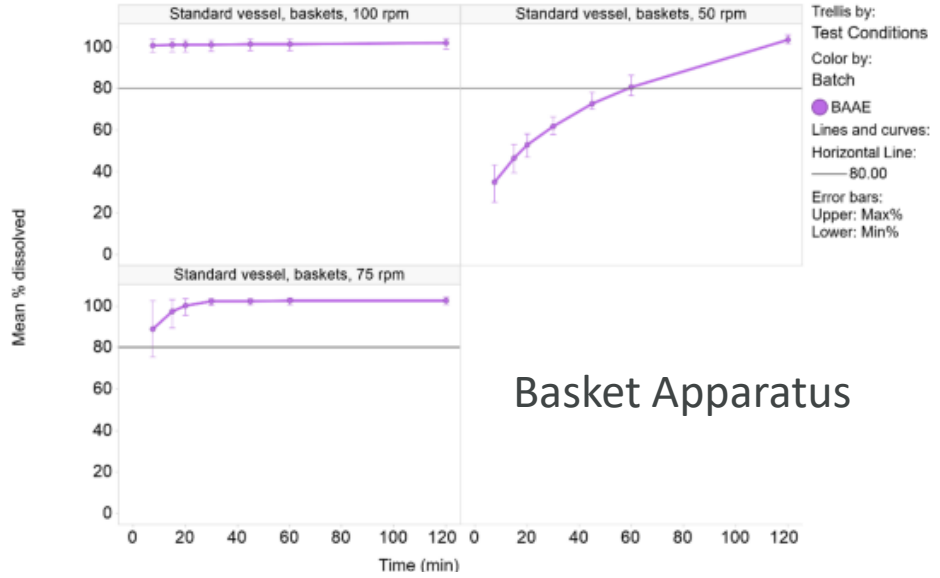
- pH 1.2 SGF, paddle apparatus, 50 rpm (early clinical), std vessel
- pH 1.2 SGF, paddle apparatus, 60 rpm (clinical), std vessel
- pH 4.5 acetate, paddle apparatus, 75 rpm, std vessel
- pH 6.8 phosphate, paddle apparatus, 75 rpm, std vessel
- FaSSIF-V2, paddle apparatus, 75 rpm, std vessel
- pH 6.8 phosphate + 0.5% SLS – various apparatus/stirring conditions
- pH 6.8 phosphate + Tween80 – instability observed
- pH 6.8 phosphate + 0.1% CTAB – various apparatus/stirring conditions

We screened a lot!

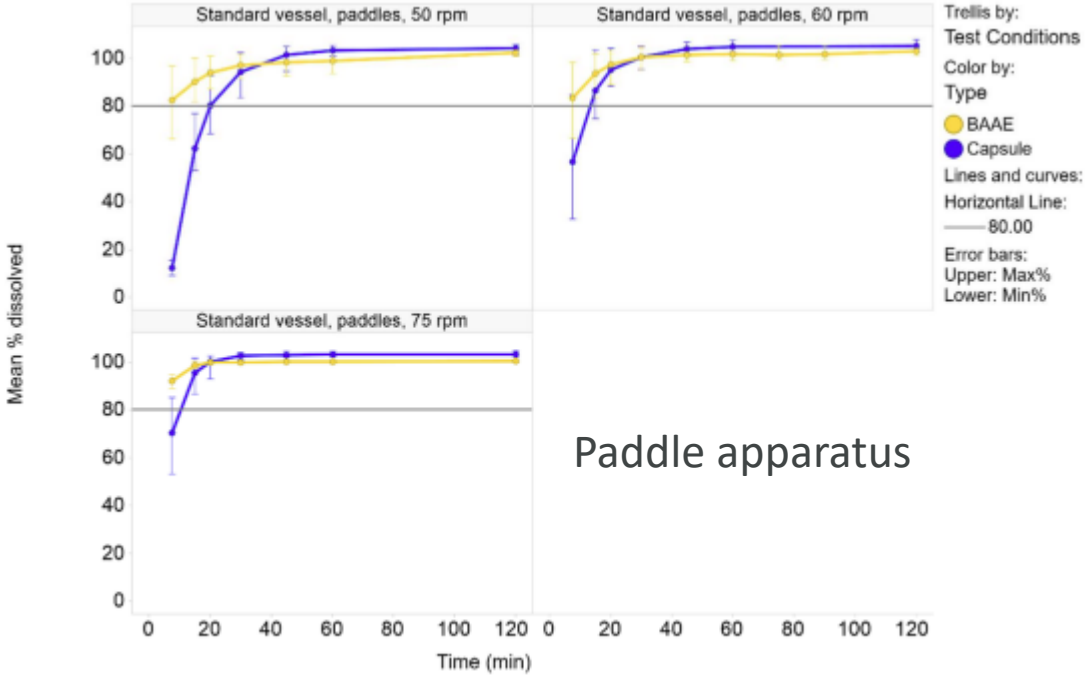
Low pH Methodology



50 rpm



Basket Apparatus



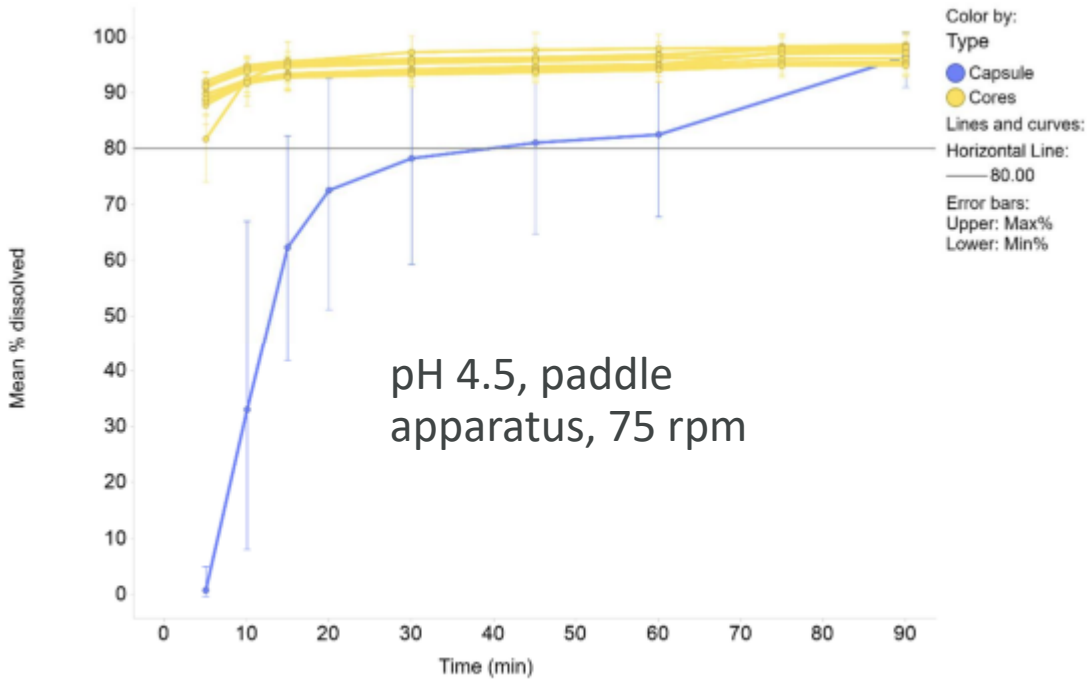
Paddle apparatus

- Discrimination between capsule and tablet
- No discrimination between tablet variants
- 50 rpm early clinical method was not successfully transferred to ICH stability site due to high variability associated with coning at 50 rpm

- 60 rpm selected as clinical method as compromise between discrimination and variability

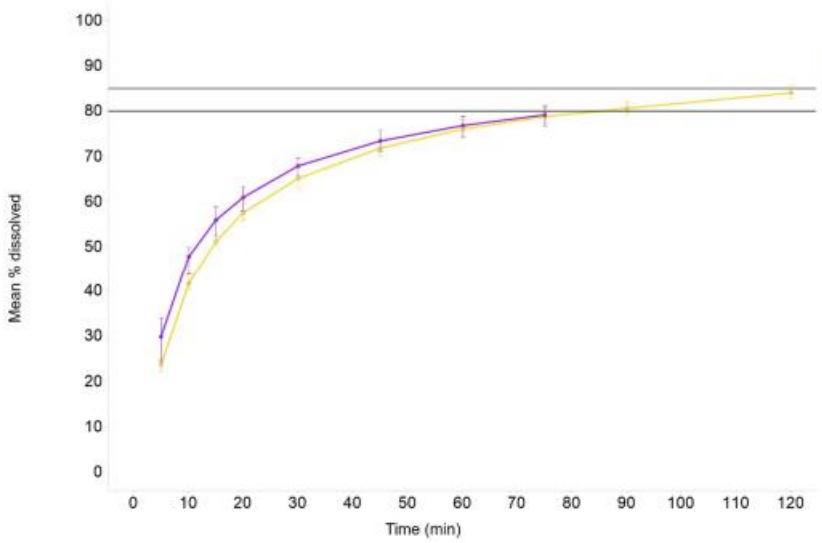
Data from NDA 218197 P2 Pharmaceutical Development

pH 4.5 and pH 6.8



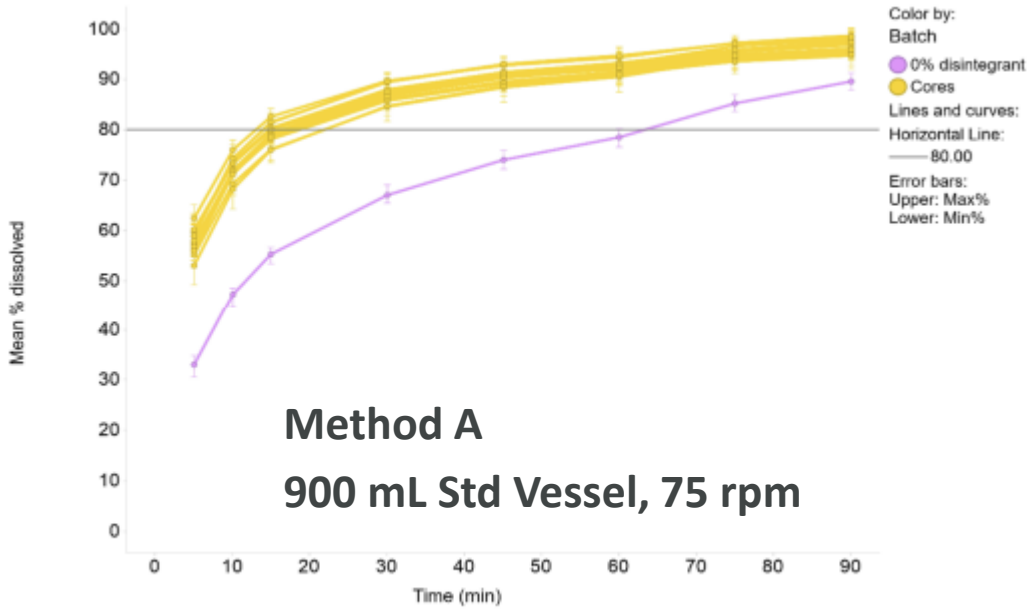
- 75 rpm required to reduce coning for tablets
- Discrimination between capsule and tablet
- No discrimination between tablet variants
- Capsule dissolution looked non-optimal

- pH 6.8 gives incomplete release due to low solubility and non-sink conditions
- Employed during in vitro bridging at 75 rpm to reduce impact of coning

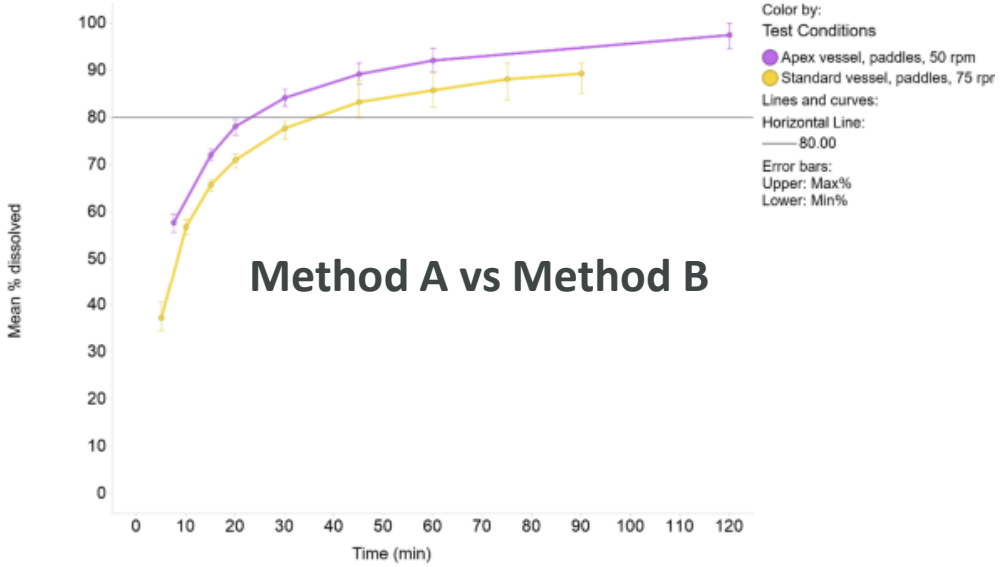


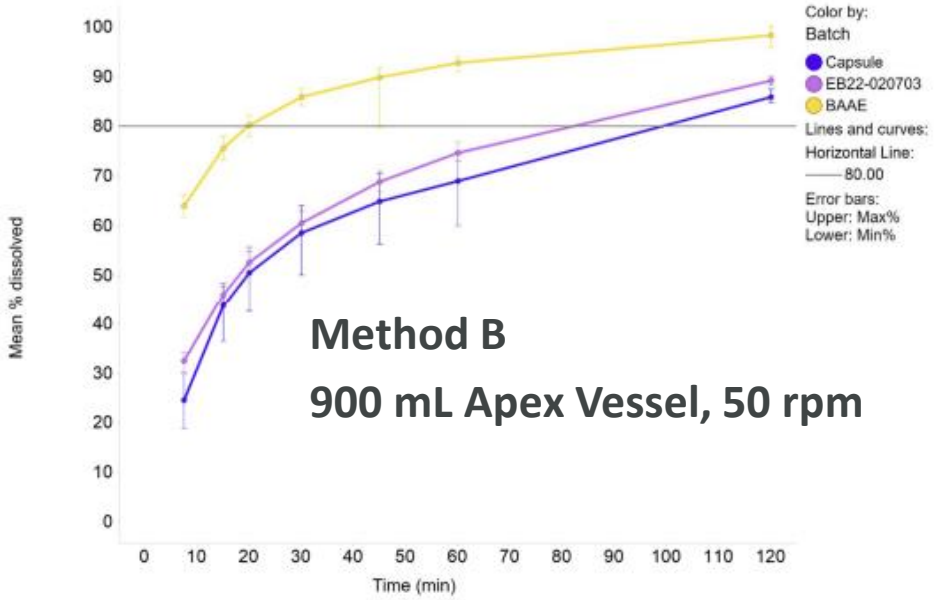
Data from NDA 218197 P2 Pharmaceutical Development

FaSSIF-V2



- Biorelevant method used during development
- Solubility in FaSSIF-V2 > pH 6.8 but sink conditions are not achieved for 200 mg strength
- Coning is observed even at 75 rpm
- Method used in in vitro bridging studies
- Discrimination achieved for 0% disintegrant variant

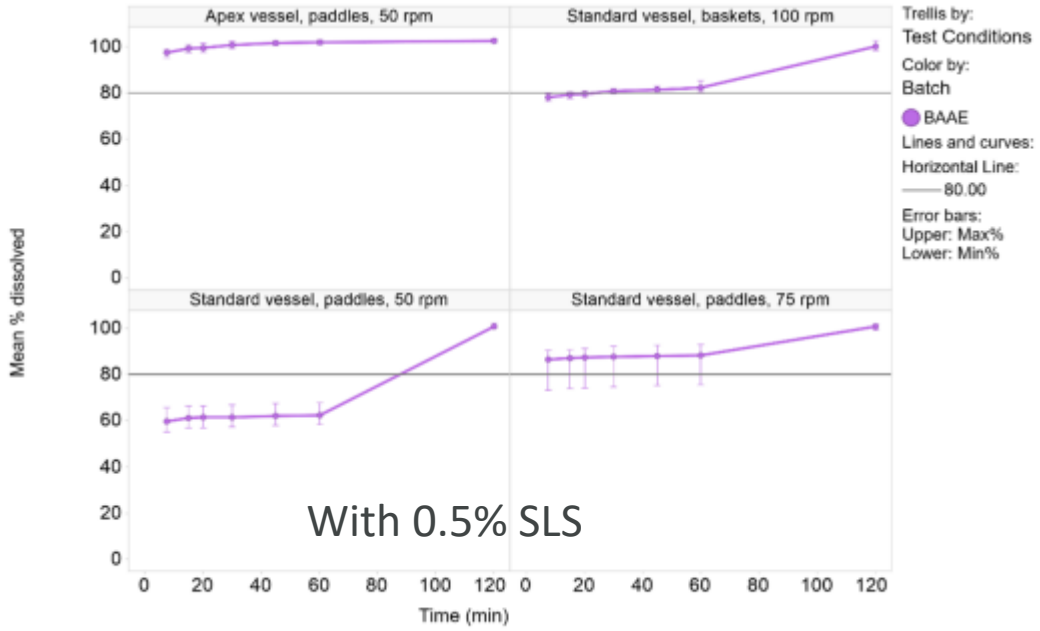




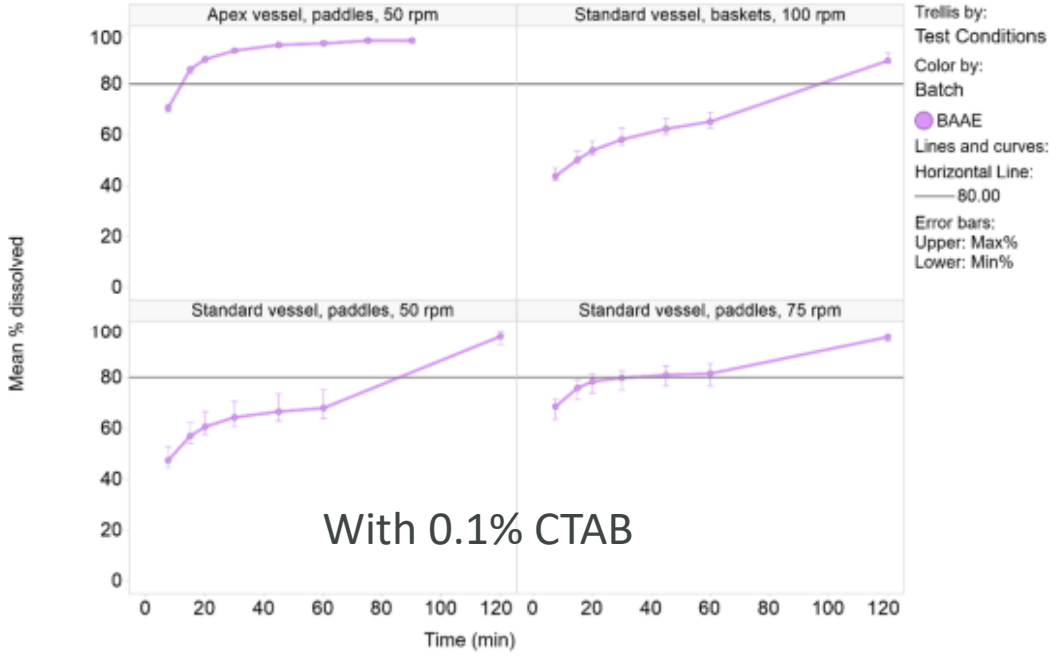
- FaSSIF-V2 method optimized to remove influence of coning by use of apex vessel and reduced paddle speed
- Discrimination was maintained

Data from NDA 218197 P2 Pharmaceutical Development

pH 6.8 with SLS or CTAB



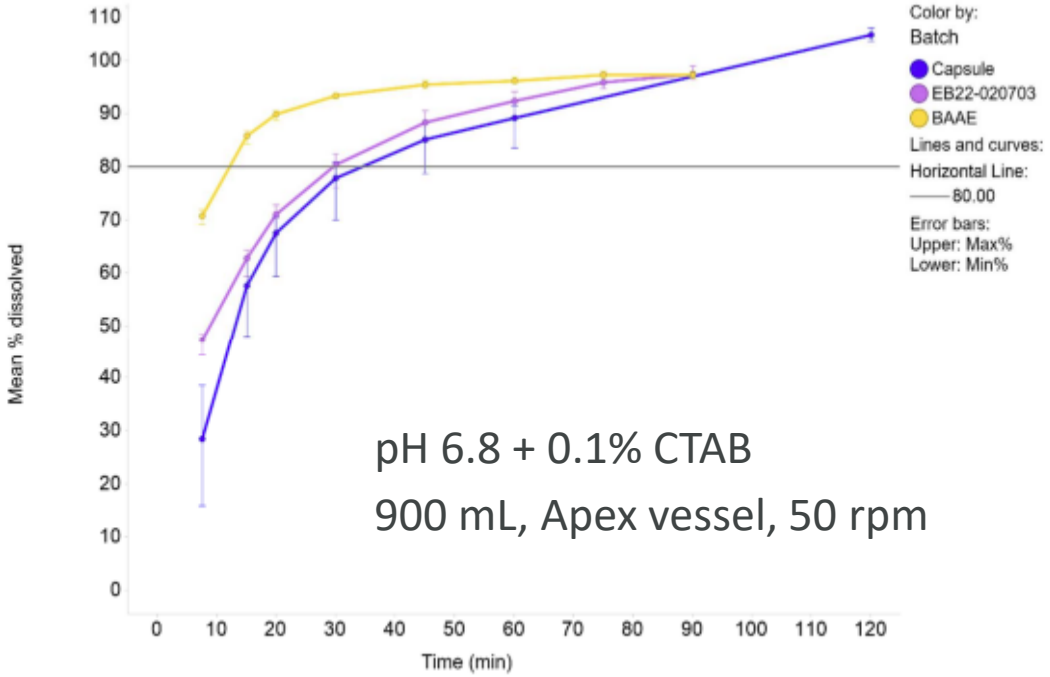
- 0.5% SLS chosen to provide sink condition for 200 mg
- Coning present in std vessels and stirring speeds for basket and paddle
- Very rapid dissolution in apex vessels



- 0.1% CTAB chosen to provide sink condition for 200 mg
- Coning present in std vessels and stirring speeds for basket and paddle
- Profile present in apex vessel at 50 rpm, potential discrimination
- Taken forward for further screening

Data from NDA 218197 P2 Pharmaceutical Development

pH 6.8 + 0.1% CTAB



pH 6.8 + 0.1% CTAB

900 mL, Apex vessel, 50 rpm

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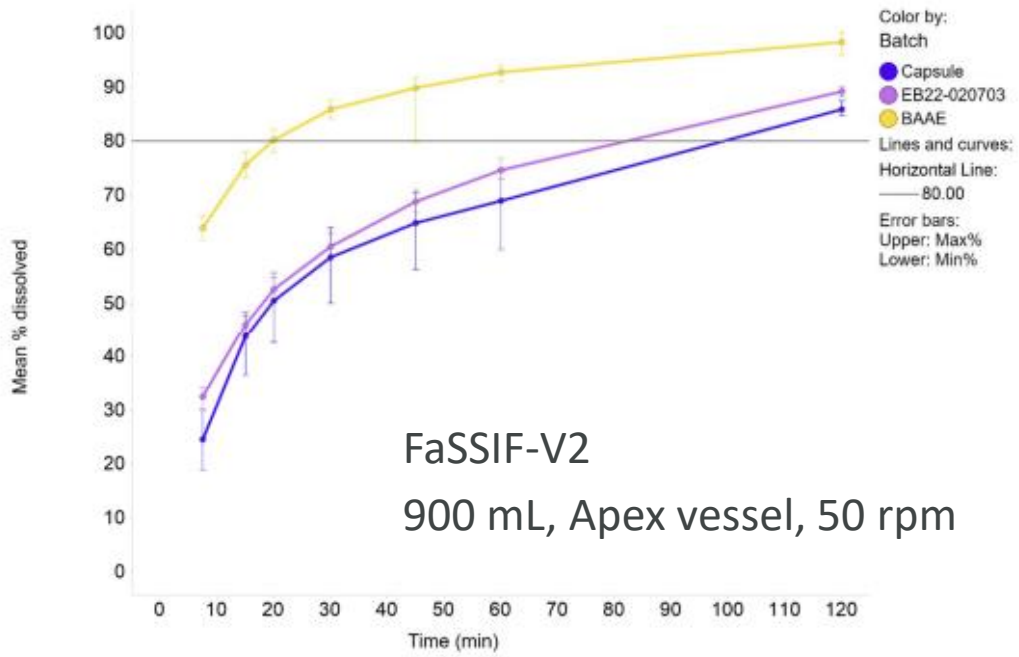


FaSSIF-V2

900 mL, Apex vessel, 50 rpm

- Discrimination observed for both **capsule** and **0% disintegrant**
- Similar level of discrimination to biorelevant FaSSIF-V2 method
- Coning overcome with use of apex vessels and near complete release achieved within 60 minutes
- Apex vessels show superiority with regard to overcome coning relative to standard vessels and at lower paddle speeds.

Data from NDA 218197 P2 Pharmaceutical Development

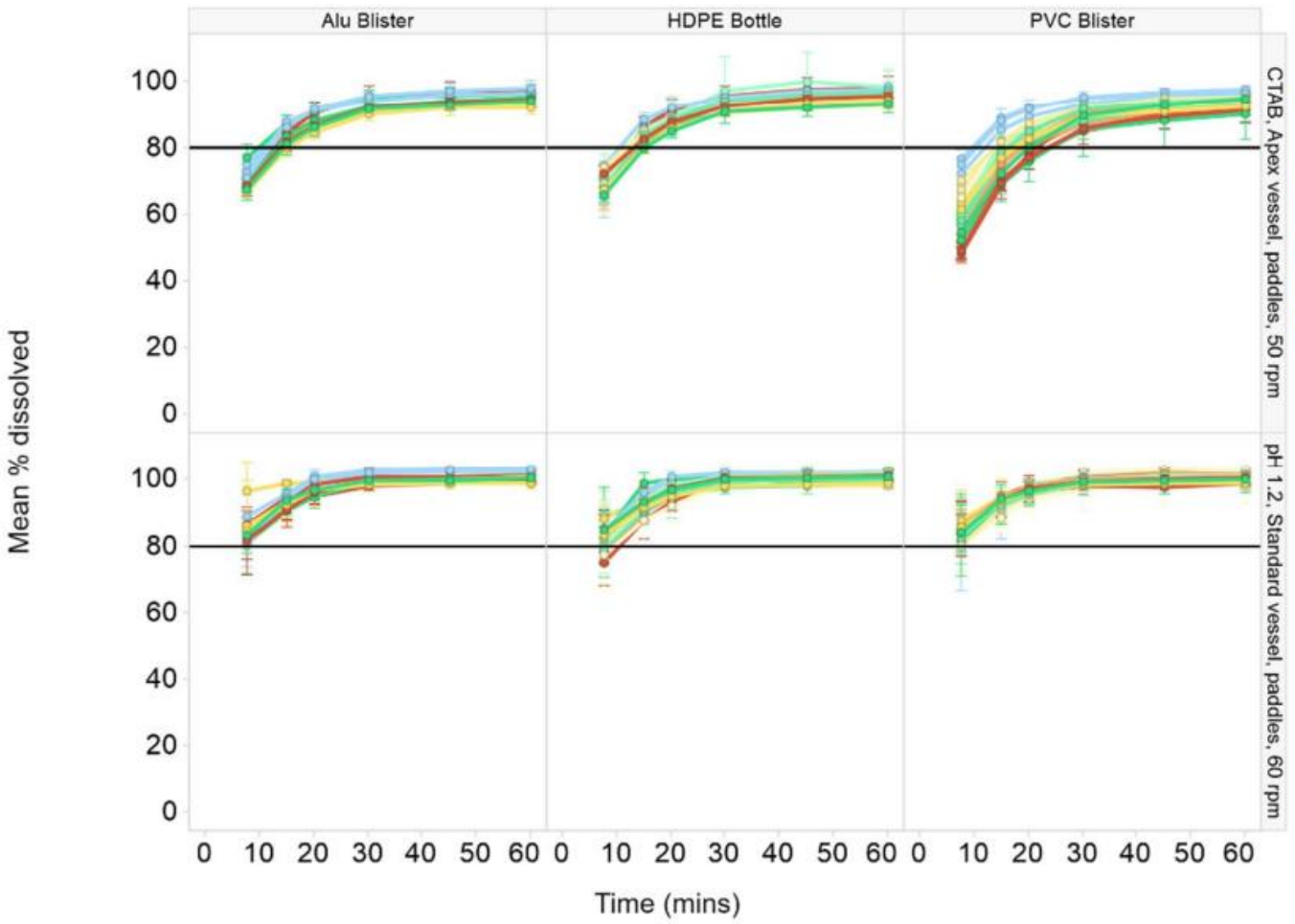
pH 1.2 (60 rpm) vs pH 6.8 + 0.1% CTAB (Apex 50 rpm)

Failure Mode	pH 1.2 SGF 60 rpm Std Vessel	pH 6.8 + 0.1% CTAB 50 rpm Apex Vessel	FaSSIF-V2 50 rpm Apex Vessel
Tablet vs Capsule	✓ (<15 min)	✓ (< 45 min)	✓(All timepoints)
Disintegrant Level	✗	✓	✓
Over lubrication	✗	✗	✗
Particle Size	✗	✗	✗
Film Coat Level	✗	✗	✗
Compression Force	✗	✗	✗
Stability	✗	✓	Not tested

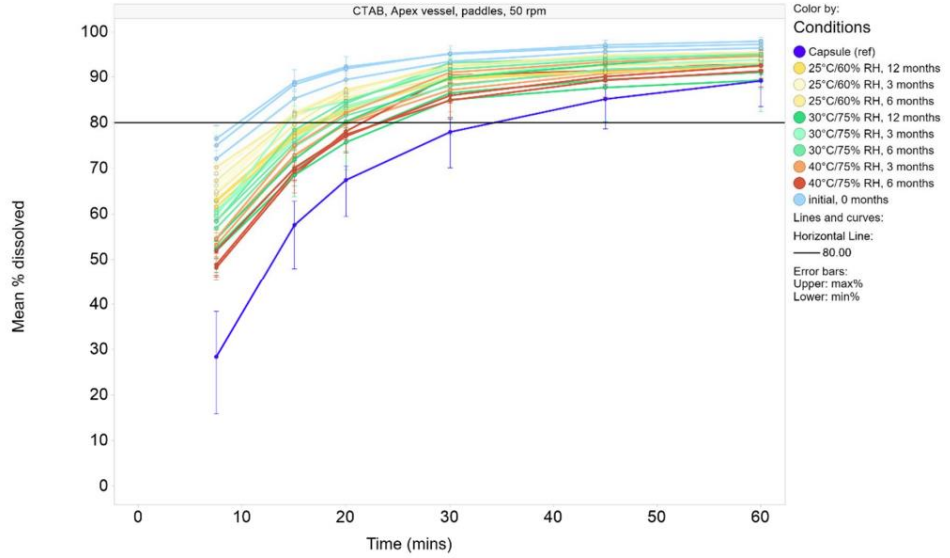
All variants faster than *in vivo* reference of capsule

= Ability to discriminate

Stability Results by Pack Type

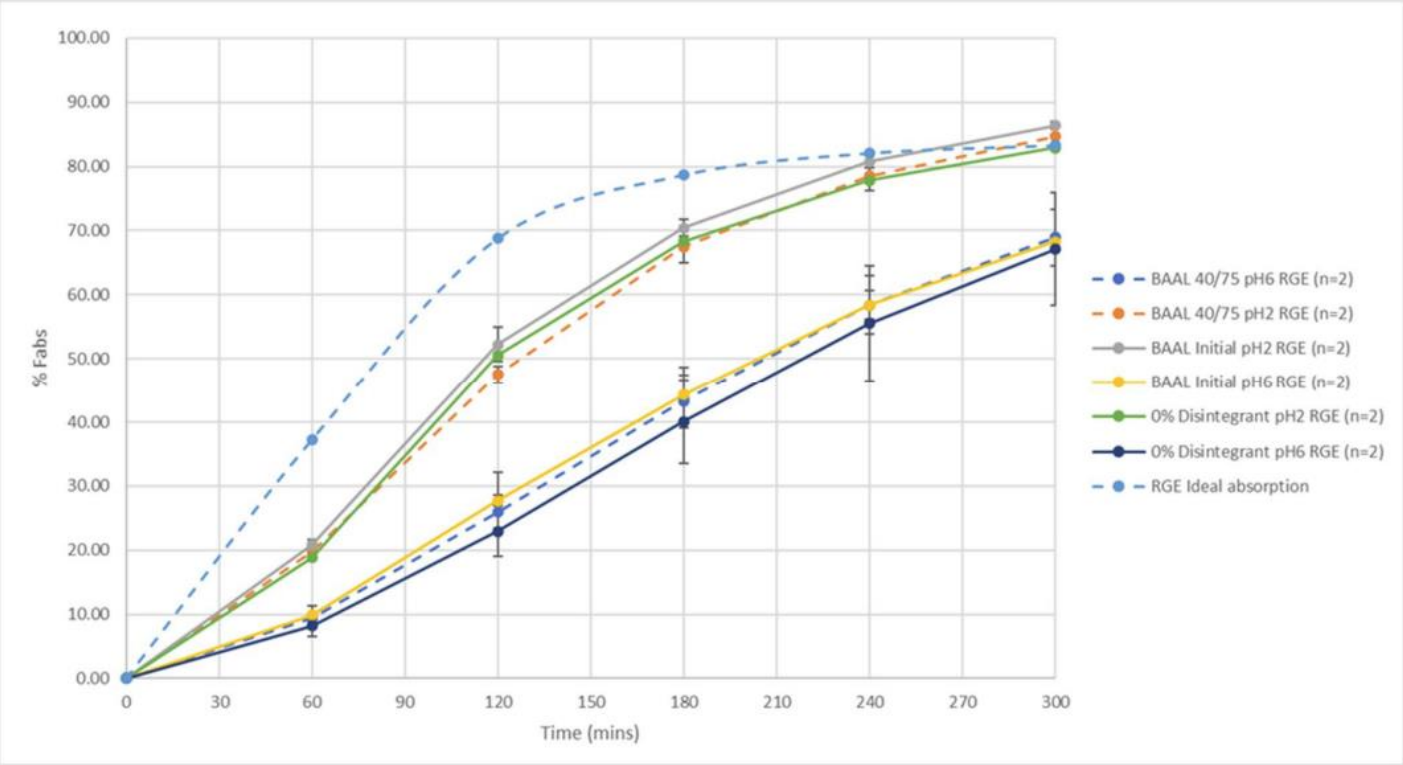


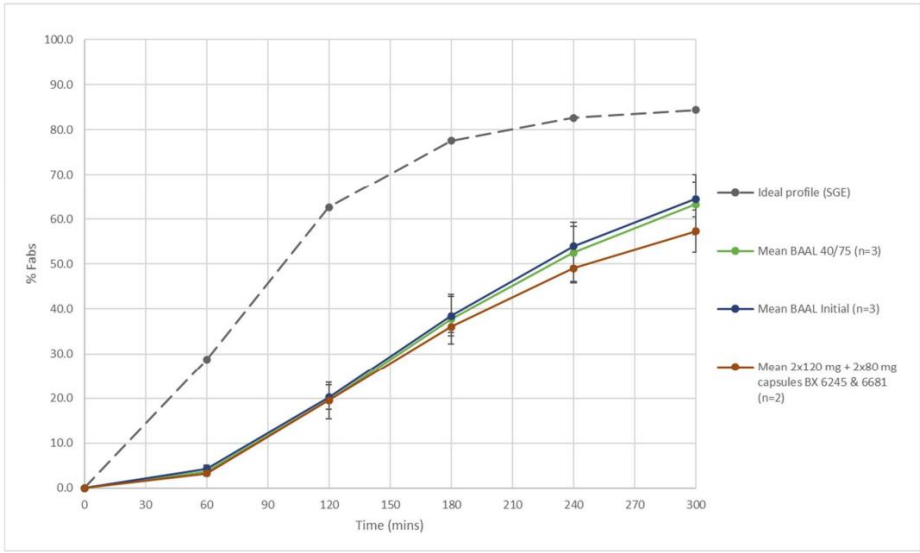
- Dissolution decrease seen on stability for PVC blister for high temp and high humidity conditions but only in CTAB method
- All profiles are still faster than capsule reference
- Stability in PVC blister drove the choice of method ultimately



Data from NDA 218197 P2 Pharmaceutical Development

Supporting TIM-1 Data





- In TIM-1 no difference between 0% disintegrant and 6M 40°C/75% RH sample and Ph 3 tablet reference at both pH 2 and 6
- Capsule performance at pH 6 was identical to Ph 3 reference and stability
- CTAB method over discriminating relative to in vivo but capable of seeing change in product performance

Data from NDA 218197 P2 Pharmaceutical Development

Proposed Method & Specification

Method Criteria	pH 1.2 SGF 60 rpm Std Vessel	pH 6.8 + 0.1% CTAB 50 rpm Apex Vessel
Complete release within 60 minutes	Yes	Yes
Appropriate level of discrimination	Yes	Yes
Low method variability	Yes	Yes
Method robustness	Yes	Yes
Additional discrimination for disintegrant and stability	No	Yes

Proposed QC method: 900 mL pH 6.8 phosphate buffer + 0.1% CTAB, paddle apparatus with apex vessel at 50 rpm

Proposed Specification: Q=80% at 45 minutes

Regulatory Challenge

- FDA challenged the method during the review period.
  - Asked for more information on pH 4.5 methods.
    - Issue: No discriminatory power and evidence of coning.
  - Asked for a specification tightened to Q=80% at 20 min in CTAB method
    - Issue: Overly tight specification that would unnecessarily limit shelf life and lead to high level of failures for batches with acceptable in vivo performance.
  - Asked for a low pH method in either paddles (50 rpm) or baskets (100 rpm) in standard vessel with Q=80% at 30 min
    - Issue (paddles): 50 rpm low pH method had coning as an issue.
    - Issue (baskets): No data or validation available for the project using baskets.

Regulatory Resolution

- 3 Alternatives were proposed:
  1. Preferred CTAB method with Q=80% at 30 min - **REJECTED**
  2. Disintegration in lieu of dissolution (NMT 10 min) - **REJECTED**
     - Low biopharm risk due to high solubility in gastric pH
     - Full ICH disintegration data available
     - Pharmacopeial test so no delay on establishment of method at commercial site.
     - Suitable dissolution test would be available for post approval change
  3. Clinical Dissolution Method (900 mL pH 1.2 SGF, paddle apparatus at 60 rpm with Std vessels with Q=80% at 30 min) - **ACCEPTED**
     - Method validation & robustness data available
     - ICH stability data available
     - Required establishment at commercial site and testing of PV batches

Summary of Other HA Opinions

- EMA accepted AZ proposal at Day 120 but with request for 30 min specification

- Japan accepted AZ proposal but with request for 30 min specification

- Canada (who are part of Project Orbis) waited on outcome of US discussions and then requested AZ proposal with request for 30 min specification.

- UK appeared to ask for same approach as US but after 1 round of questions accepted AZ proposal at 30 minutes.

- No other health authority has requested the low pH method.

Conclusions

- A discriminatory method was developed as per current regulatory guidance.
- Stability signal in PVC blister and 40°C/75% RH drove the selection of the CTAB method for commercial QC as it gave an assurance that we could monitor our product and assess any drift in performance.
- Other health authorities actively saw US position and still went with discriminatory method even when they were not receiving the PVC blister.