Biorelevant dissolution enabling paediatric formulation selection/optimisation

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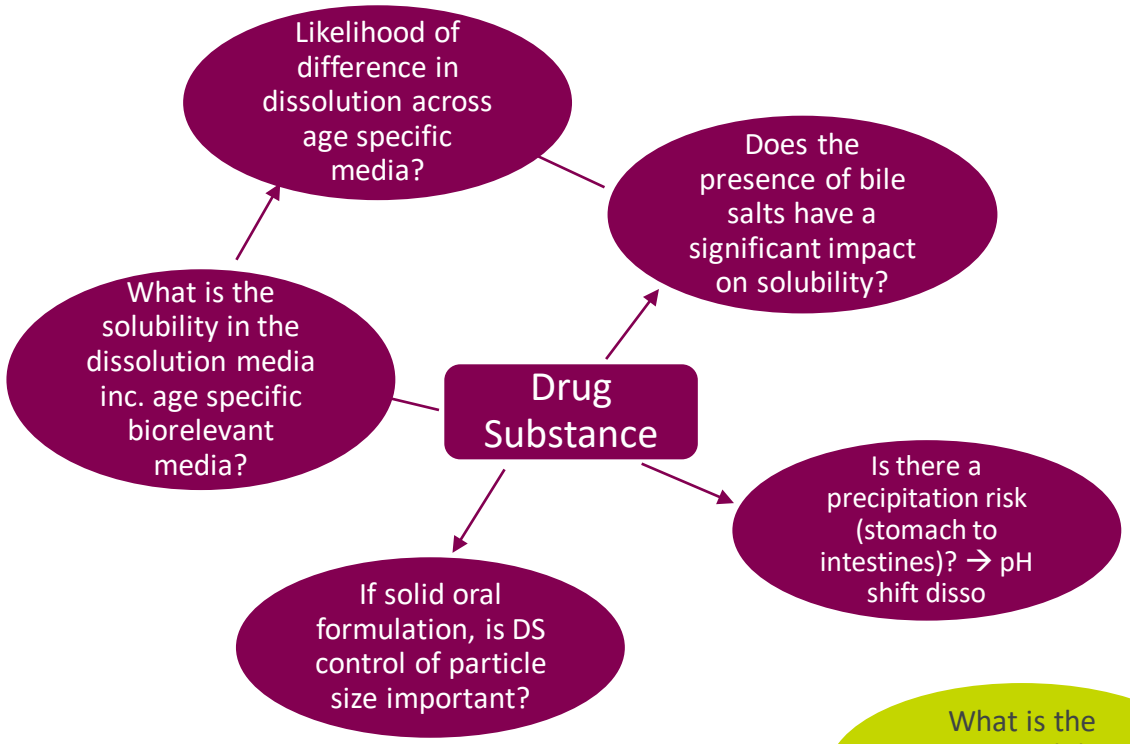
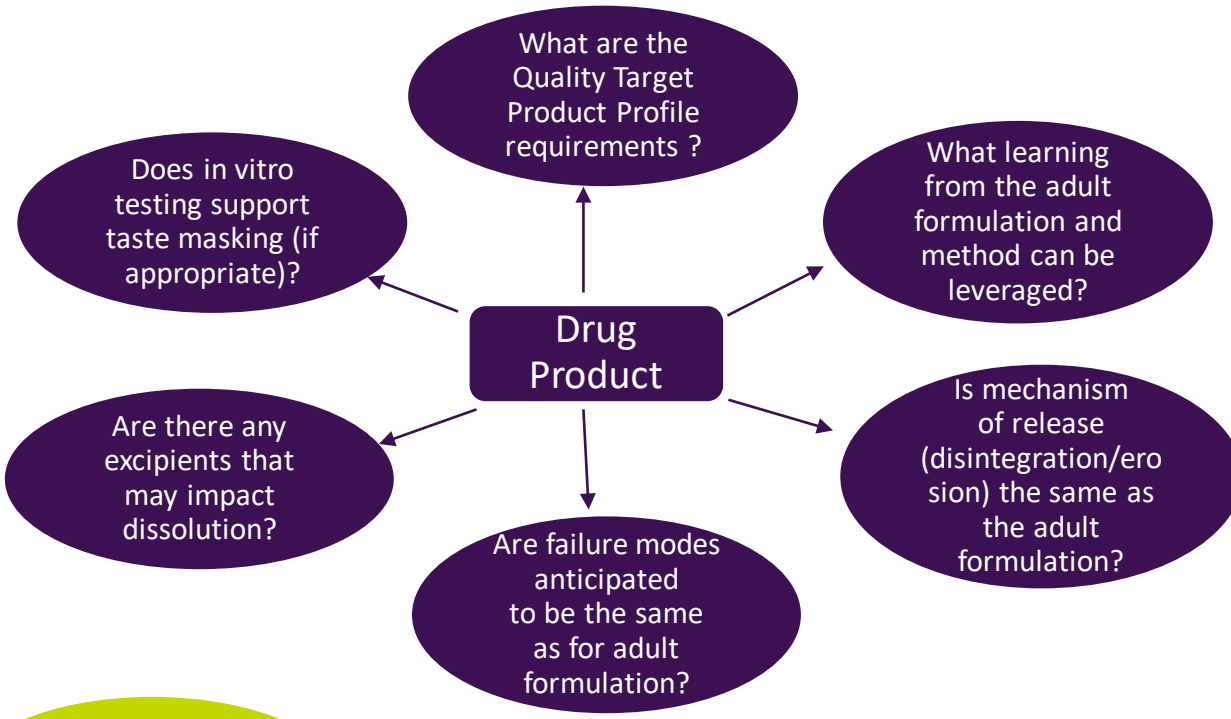
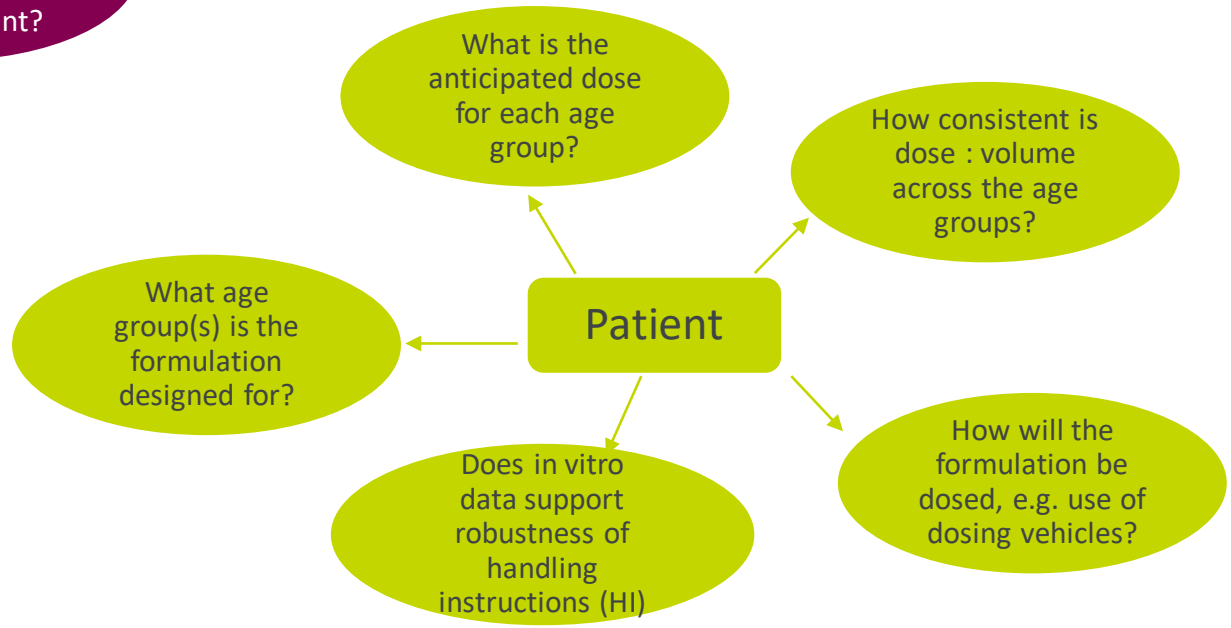
Considerations for paediatric dissolution







What is the purpose of the dissolution study?

Evaluate AAF performance across paeds age groups?

- Will age-appropriate formulation (AAF) perform consistently across age groups?
- Consider use of paediatric specific media, volumes and doses

Risk assess formulation bridging study in adults

- Rel BA studies to compare AAF to adult formulation typically performed in adults[1]
- Disso media and volumes typical of testing adult formulations may be more relevant e.g. 500 ml FaSSIF and/or release medium
- What dose - single unit vs. adult dose?

Understand impact of dosing vehicles on release?

- Disso using vehicles and biorelevant medium may be useful in predicting in vivo situation - this can be challenging analytically
- When following HI, is the formulation likely to start dissolving in the vehicle prior to dosing?[2]
- Advisable to use a well characterised vehicle with respect to pH, osmolality, viscosity etc.[3]

Establish discrimination for failure modes

Comparison of dissolution in biorelevant medium vs release medium to understand discrimination for relevant failure modes

1. Draft FDA Guidance: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (Sept 2022)
2. Draft FDA Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments (July 2018)
33. Freerks L, Sucher W, Tarnow M-J, Eckert C, Klein S. Vehicles for Drug Administration to Children: Results and Learnings from an In-Depth Screening of FDA-Recommended Liquids and Soft Foods for Product Quality Assessment. Pharm Res, Volume 39, pages 497–509, (2022)

Understanding solubility and its link to biorelevant dissolution

- Assessment of age-related changes in pediatric gastrointestinal solubility (Maharaj et. al.)[1]
  - Comparison made between solubility of the following adult media[2] and paediatric alternatives :
    - Fasted state simulated gastric medium - FaSSGF
    - Fed state simulated gastric medium - FeSSGF
    - Fasted state simulated intestinal medium - FaSSIFv2
    - Fed state simulated intestinal medium - FeSSIFv2
  - 7 BCS II compounds (absorption likely to be solubility limited)
  - For 6 of the compounds - solubility outside 80-125% of adult values in at least one of the paediatric media → potential for age-related changes in oral drug performance

1. Maharaj , AR, Edginton, AN & Fotaki, N 2016, 'Assessment of age-related changes in pediatric gastrointestinal solubility', Pharmaceutical Research, vol. 33, no. 1, pp. 52-71
2. Jantratid E, Janssen N, Reppas C, Dressman JB. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. Pharmaceutical research. 2008 Jul;25(7):1663-76.

Understanding solubility and its link to biorelevant dissolution

- Nifedipine studies measuring solubility in adult and paediatric biorelevant media in combination with dissolution studies considering clinically relevant administration (Van der Vossen et al)[1]
  - Changes in bile salt and pepsin levels had some impact on solubility → unlikely to significantly impact absorption
    - e.g. FaSSIFv2 (12.9 ug/ml), FaSSIF-50% (9.3 ug/ml) and FaSSIF-150% (15.1 ug/ml)
  - Age effects - solubility limited at each stage → no significant in vitro performance difference between neonates and infants
  - Method of admin (Intact vs pre-dispersed capsule) – unlikely to have significant impact on absorption

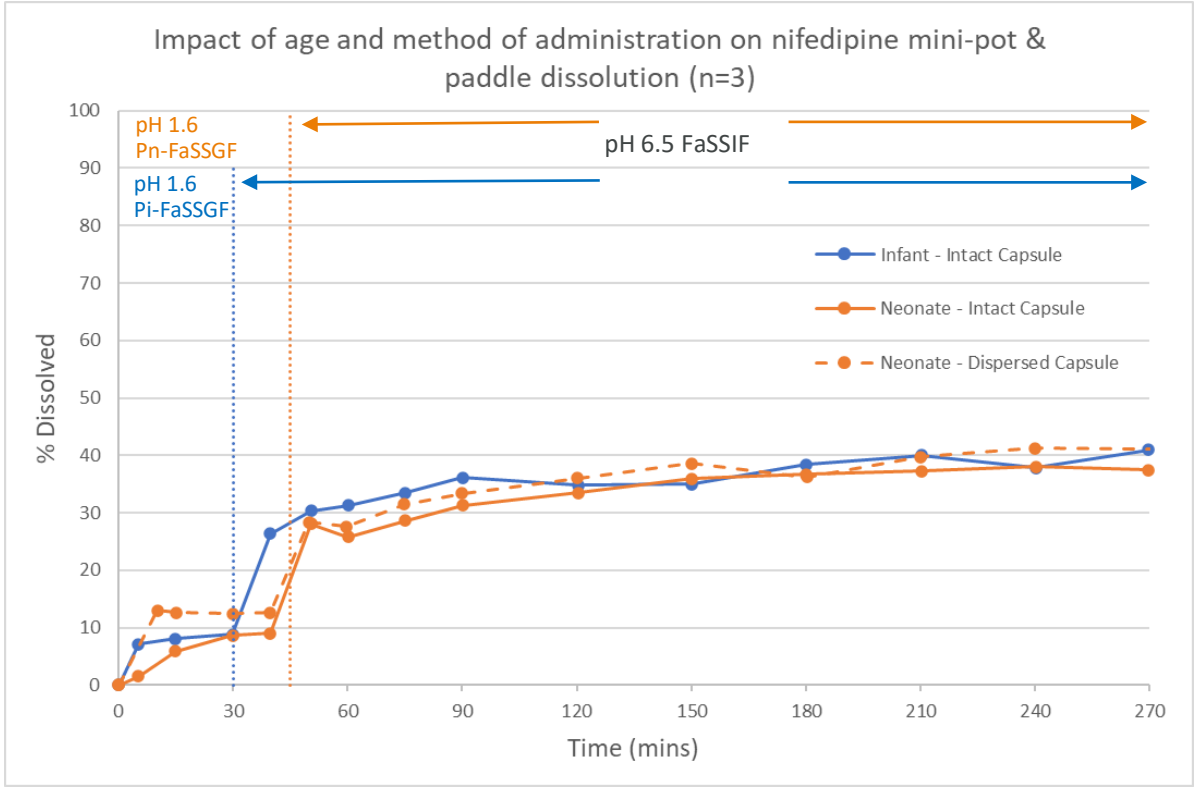


Image adapted from Van der Vossen et.al.1

1. Van der Vossen AC, Hanff LM, Vulto AG, Fotaki N, Potential prediction of formulation performance in paediatric patients using biopharmaceutical tools and simulation of clinically relevant administration scenarios of nifedipine and lorazepam. Br J Clin Pharmacol. 2019;85:1728–1739

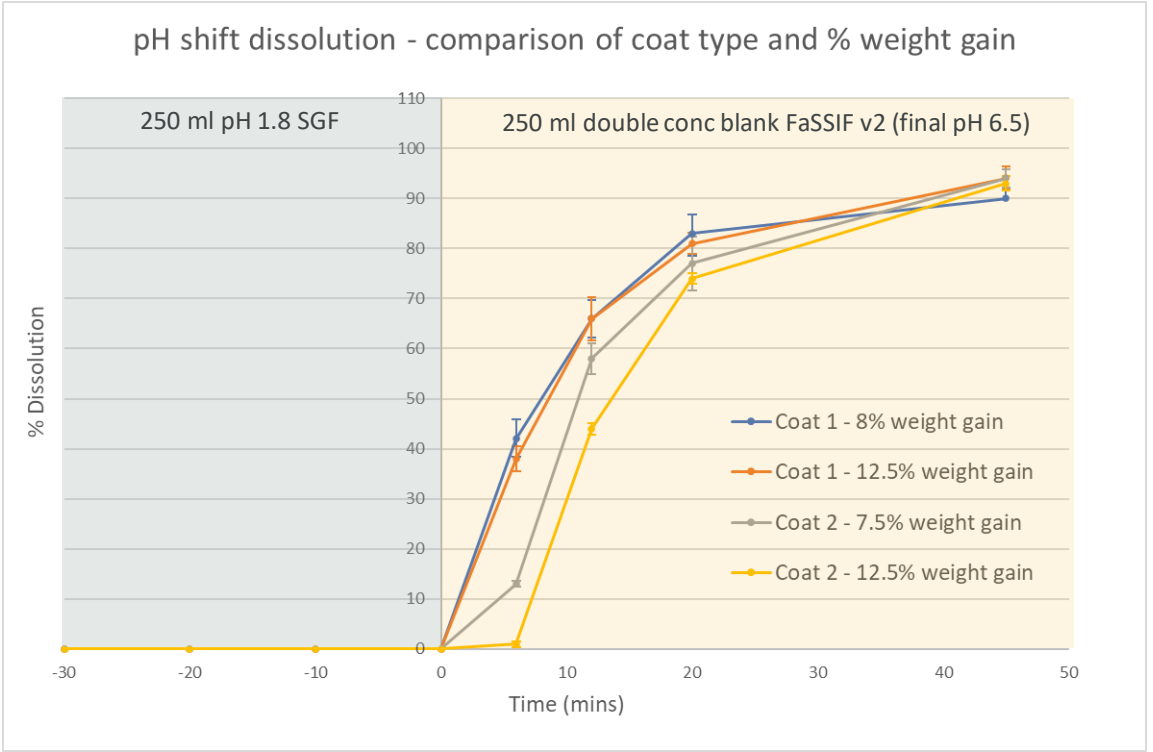
Case Study A

Compound A

- Low, pH independent solubility and moderate perm, tentative BCS 4
- Age range 6 months – 18 years
- Adult IR tablet formulations can be used for older children, but AAF required for <6 years
- IR granule formulation developed
- Taste masking achieved through selection of compatible coat and dosing vehicles to prevent drug dissolution into the vehicle during preparation and dosing
- Impact of choice of coat investigated using in vitro dissolution

pH shift dissolution to aid coat selection

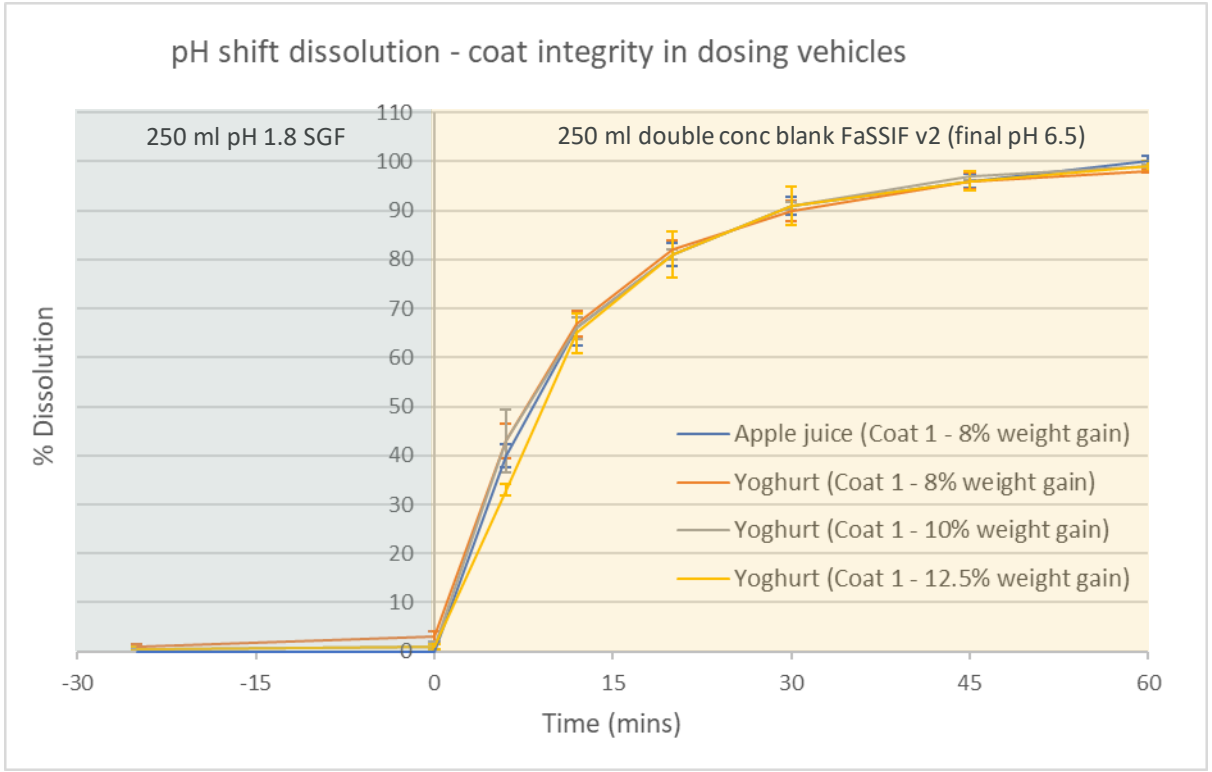
- Two pH dependent coats shortlisted
- In addition to the QC release test a more biorelevant two stage test has been used to aid selection of coat type and level
- Method maximised challenge to coat integrity in acid (agitation increased to 100 rpm) and complete release at pH 6.5 (250 ml media vols and max granule dose) compared to USP monograph <711>
- No release in 30 mins in acid – supports coat integrity in acidic dosing vehicle
- Rapid release post shift – coat not expected to limit absorption
- Coat 1 chosen as more robust to coat level



USP II apparatus @ 100 rpm stir speed
10 ml sampling volume
LC finish

pH shift dissolution to understand impact of dosing vehicles

- Acidic vehicles chosen to retain integrity of coat during in use period
- Granules with different coat levels held in dosing vehicles for 30 minutes prior to disso
- Data supports coat integrity following dosing according to handling instructions
  - Negligible release following 30 mins in apple juice and 30 mins in acid
  - ≤ 3% release following 30 mins in yogurt and 30 mins in acid.
- Complete release for all coat levels & vehicles within 60 minutes post shift (increased variability for 12.5% coat level).



TIM-1 Advanced Gastric Compartment (AGC)

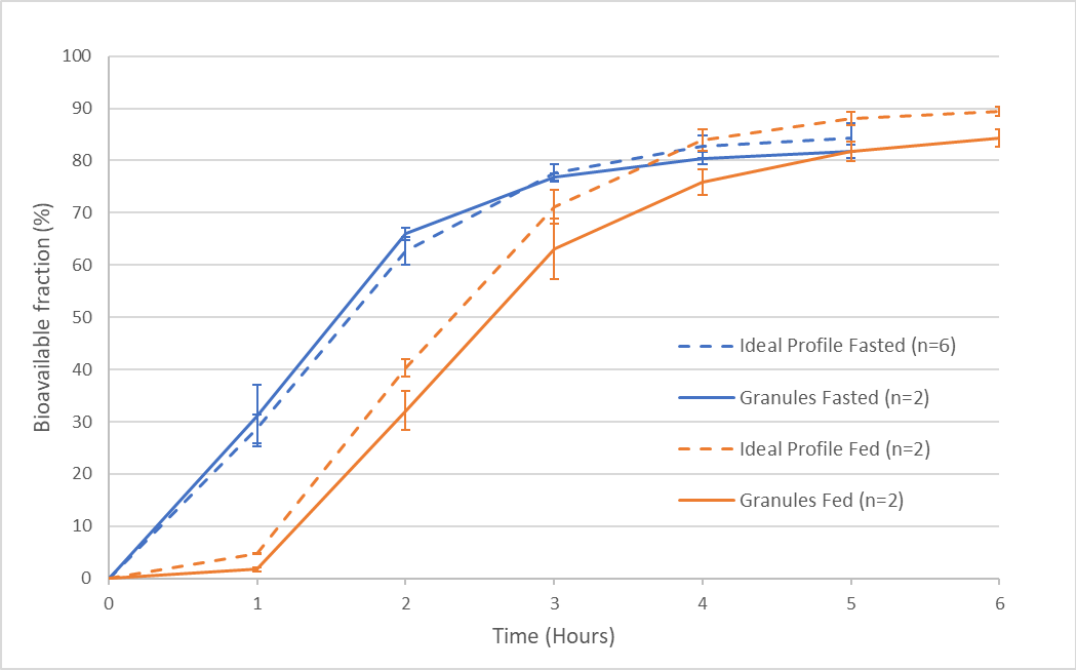
The TNO intestinal model (TIM-1) system is a multicompartmental, dynamic system that uses in vivo relevant media, volumes, and hydrodynamics to simulate the upper part of the gastrointestinal (GI) tract also including an absorptive step by hollow fibre filtration.

- The model was developed by TNO Nutrition and Food Research (Zeist, The Netherlands) and has predominantly been used for nutritional science.
- System has been modified for use with pharmaceutical products.
- The TIM-1 apparatus allows control of GI parameters, which facilitates modelling of physiological variability and disease states.
- Provides a prediction of the amount of drug in solution and thus available for absorption.

Our most in vivo relevant, advanced in vitro model - overcomes limitations of pH shift dissolution
e.g. gradual rather than bulk transfer of material/media between stomach and intestines and provides an absorptive sink

TIM-1 AGC assessment of granule formulation

- Final formulation with optimised coat type and level dosed to TIM-1 AGC
- No food restriction in clinical study for the youngest children, therefore tested under fasted and fed (FDA breakfast) conditions
  - This is not a typical meal for small children but provides data at the extremes of fasted vs fed
  - Dosing with other meal types or dosing vehicles also feasible
- TIM-1 currently set up and validated for adults, therefore dose scaled to adults rather than alteration of setup



Granule absorption profiles compared to BCS 1 solution 'ideal' profiles

Choice of formulation and coat doesn't have a detrimental impact on performance

Current and Future Approaches

- Paediatrics – within scope of Next Generation TIM development
  - 4-year development program
- Looking to develop 2-3 models/hardware to cover different age brackets
- Literature review will be used to define e.g. media composition & volumes,
- Consideration to be given to how to validate these models

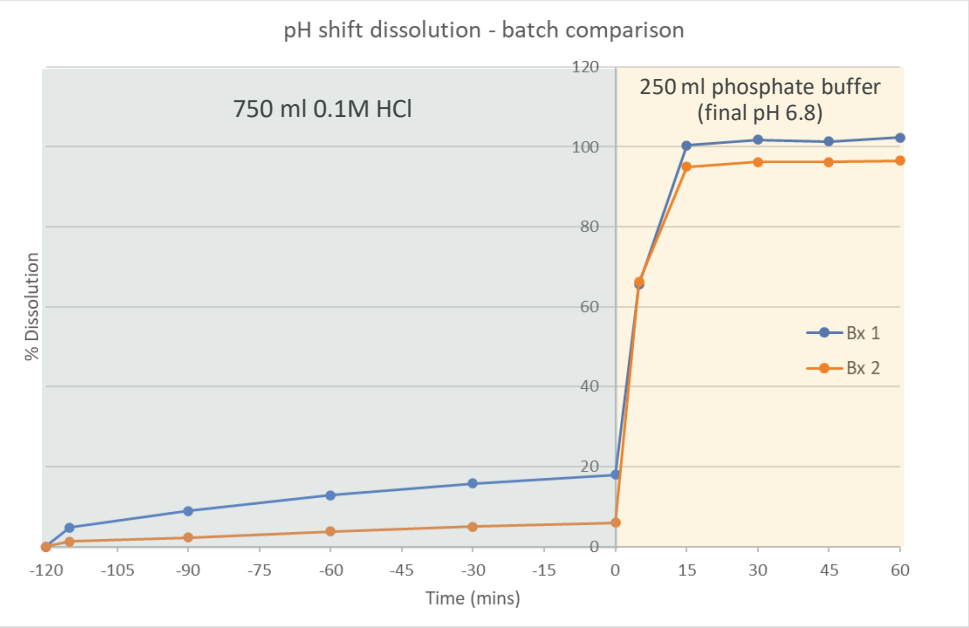
Case Study B

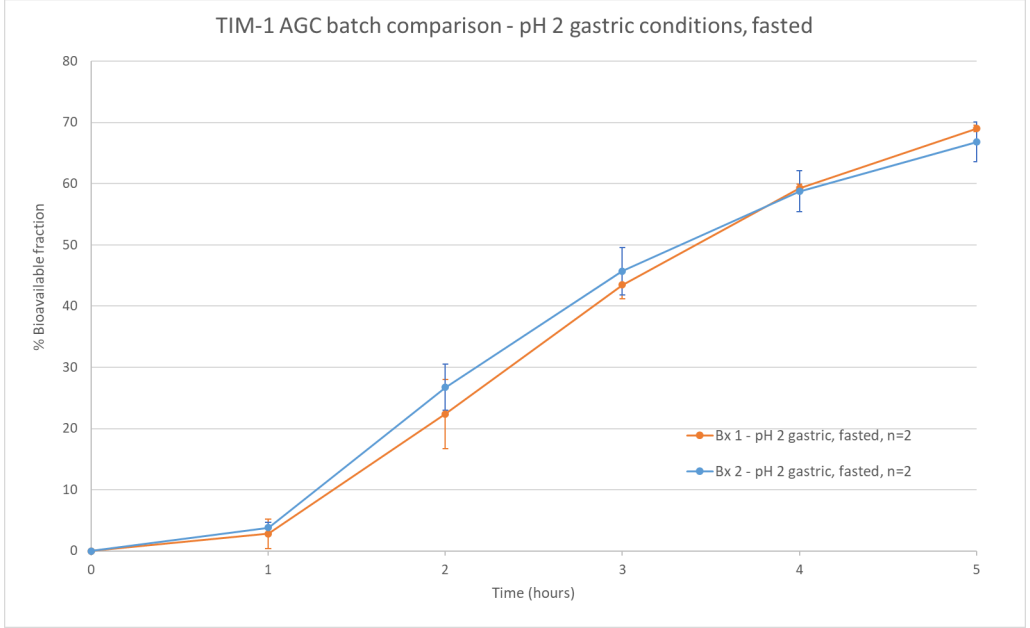
Compound B

- Low solubility and low perm, tentative BCS 4
- Age range ≥2 year
- IR capsule formulations can be used for older children but AAF required for younger children and older children who can not swallow the capsule
- Granule formulation with IR core developed
- Enteric coat used for taste masking purposes

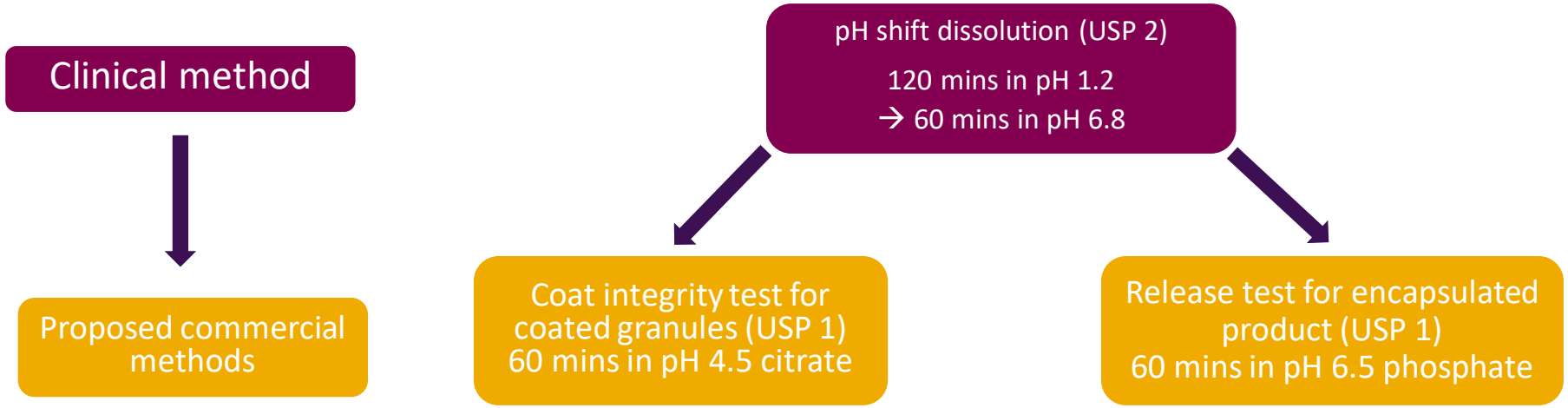
Understanding granule performance

- Clinical release test - pH-shift method using USP2 paddle apparatus according to USP <711> for DR products
  - 0.1 N HCl for two hours to assess coat integrity, followed by shift to pH 6.8 to measure drug release
- TIM-1 AGC used to understand in vivo relevance of differences in coat robustness in acid phase
- No significant difference seen between batches under more in vivo relevant conditions in TIM-1 AGC
  - 120-minute acid phase in dissolution is worst case
  - TIM-1 AGC – $t_{1/2}$ for gastric emptying is 30 mins
  - Handling instructions allow max 30 mins to add granules to acidic vehicles and dose





Clinical relevance of clinical vs commercial dissolution methods



- Proposed coat integrity method designed to be more clinically relevant to the dosing scenario compared to a traditional pH-shift
  - pH 4.5 citrate buffer - dosing vehicles include fruit-based foods, may contain citric acid and pH range 4 – 5 more likely
  - Test time of 60 mins – covers HI dosing period of 30 minutes + margin for non-compliance
- Release test with pH 6.5 - to ensure release under intestinal conditions.
  - Shown to be discriminatory for key failure mechanism
- Approach has been presented to FDA in Type B Meeting.
  - Response – ‘This seems reasonable’

Summary

- DS, DP and patient variables have the potential to impact in vitro dissolution and therefore in vivo performance
- Use of in bio-relevant media, volumes, doses can help to inform likely in vivo performance
- In vitro dissolution study design should informed by the clinical scenario that is to be understood/predicted

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