Oral PBPK to Support BE Evaluation for Pediatric Drugs

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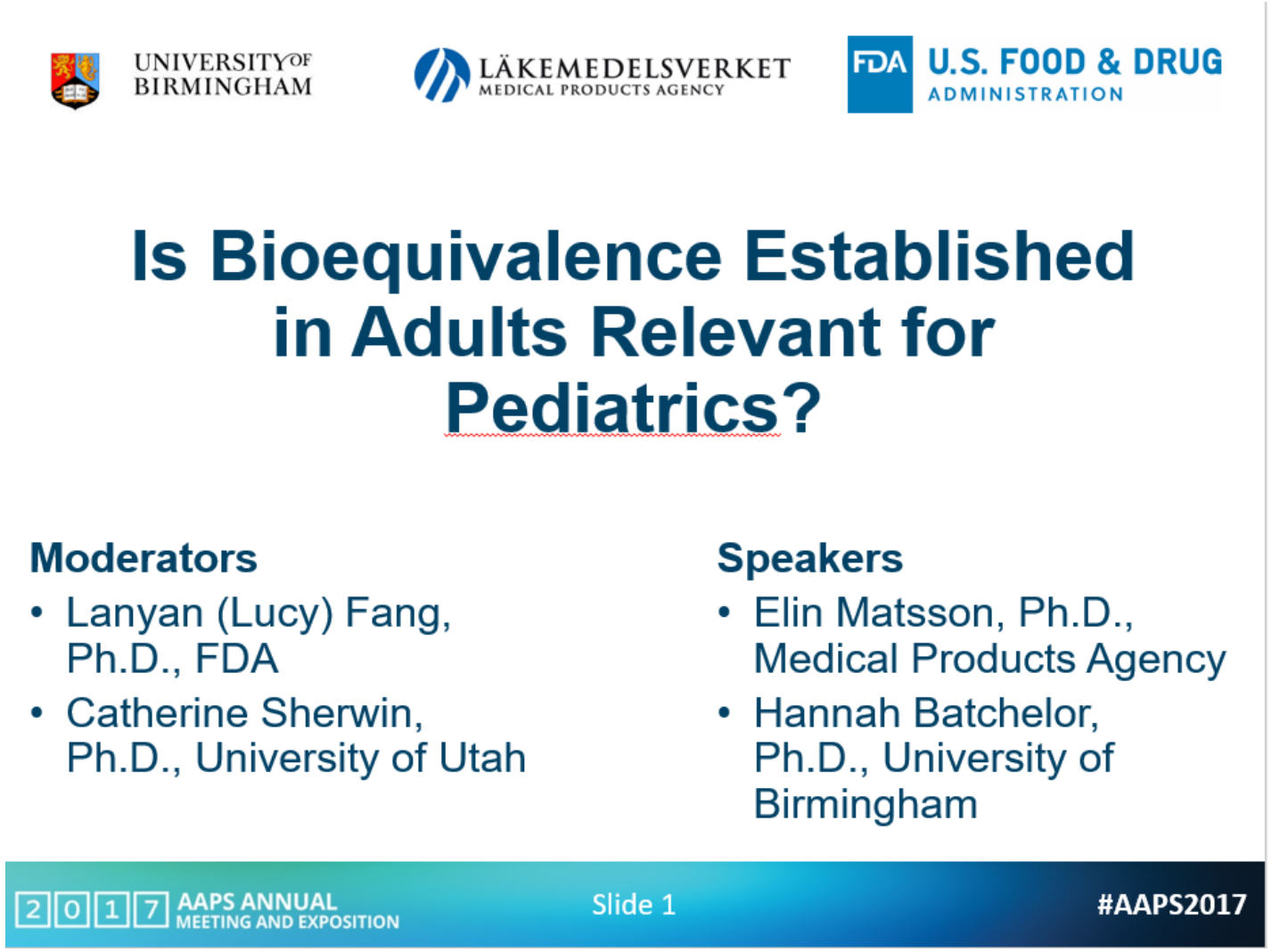


Project initiated in 2017…

Are there any ways to predict “at risk” pediatric drug products?

- Usually BCS is used as a tool for risk management
- Assessment of risk
  - Likelihood of occurrence and the severity of the consequences?
- Regulatory Decision
  - whether or not the risks are such that the project can continue with or without additional arrangements to mitigate the risk
- Acceptability of the Decision
  - is the decision acceptable to society?

Key goals of project

Identify generic pharmaceutical products most at risk of suboptimal efficacy in pediatric patients

Use literature to scope evidence

Use *in vitro* and *in silico* models to generate additional evidence

Objectives

Part 1: A data mining exercise to bring together all available information on the bioinequivalence of pediatric formulations (both innovator and generic products will be included). This aspect will allow interrogation to determine which products/drugs are likely to be “high risk” for bioinequivalence.

Part 2: A practical component where *in vitro* dissolution models and physiologically based pharmacokinetic modelling will be used to conduct sensitivity analysis of active ingredient and formulation variables related to *in vitro* dissolution and *in vivo* bioequivalence.

Part 1

DEVELOPMENT OF A DATABASE CONTAINING CLINICAL DATA ON BIOEQUIVALENCE AND RELATIVE BIOAVAILABILITY STUDIES CONDUCTED IN PEDIATRIC POPULATIONS

Overview

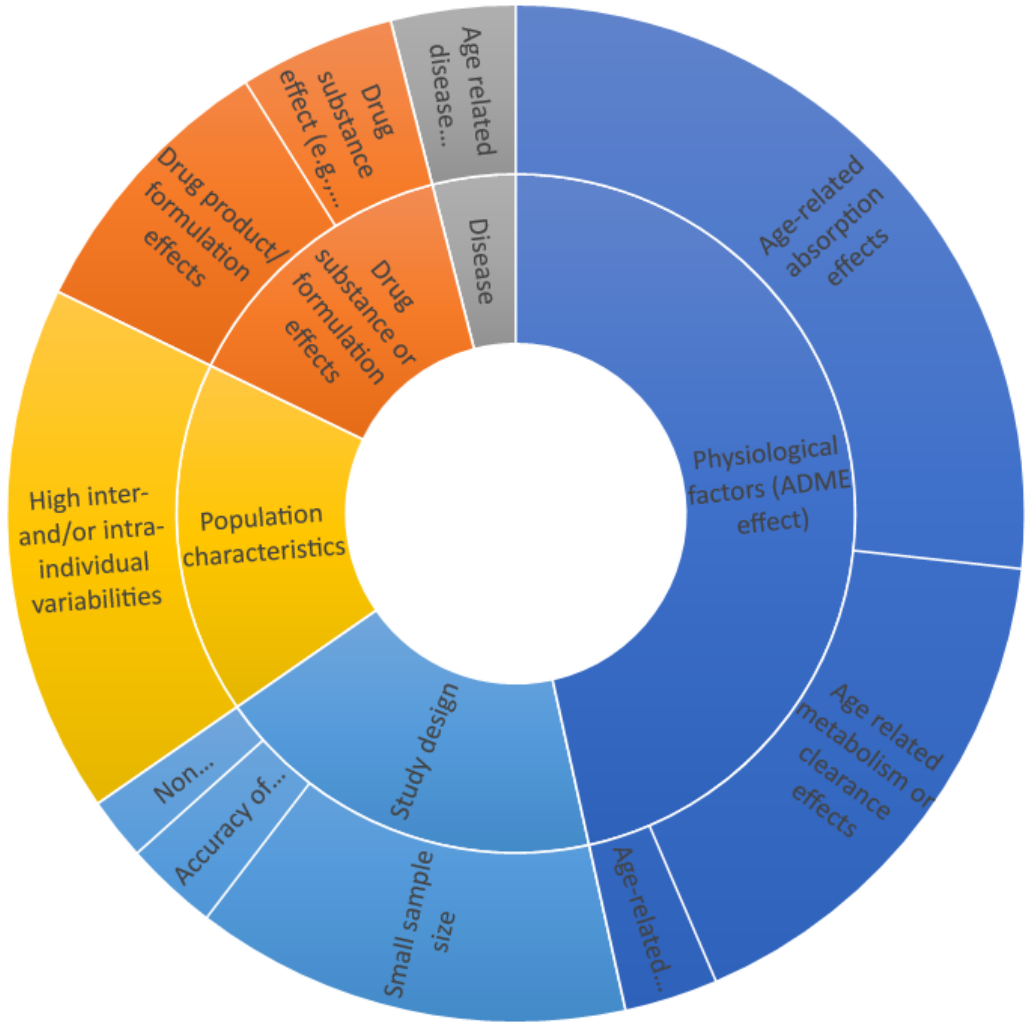
78 clinical studies containing data from pediatric populations were identified – search terms and inclusion/exclusion criteria listed

A total of **40 studies** with **bioinequivalence** results or different relative bioavailability between test and reference products remained for further analysis

To identify relevant studies	**"Bioequivalence" OR "Relative Bioavailability" OR "Non-Bioequivalent" OR "Failed Bioequivalence" OR "Lack of Bioequivalence" OR "Bioinequivalence"**
	AND
To limit to a pediatric population	"Infant" OR "Child" OR "Children" OR "Adolescent" OR "Pediatrics"
	AND
To limit to orally administered products	"Oral drug"

Inclusion Criteria	• Studies conducted on US FDA or European Medicines Agency (EMA) approved drugs for oral administration only. • Studies must include data from pediatric populations. • The studies must provide information on study design (e.g., randomized controlled, cross-over design, parallel design), subjects information (age, weight, height, sex, origin, inclusion or exclusion criteria), sample size, dose of the drugs (single or multiple), washout period, study conditions (fasting or fed state) and clinical trials registration ID. • BE studies must report the statistical analysis containing the 90% CIs (80-125%) or geometric mean ratios (0.8-1.25) for both the test and reference medicines for the PK endpoints AUC and Cmax. Studies should also state whether they met the BE criteria according to US FDA or EMA guidelines. • In case of relative BA studies PK endpoints such as AUC, Cmax data are required for tested and reference products.
Exclusion Criteria	• Studies on drugs not administered orally • Studies reporting bioinequivalence due to the presence of food or drinks or herb-drug interactions or drug-drug interactions.

Overview of risk factors identified



	Putative risk factors	Number of studies identified
Physiological factors (ADME effect)	Age-related absorption effects (e.g., Gastrointestinal (GI) motility, GI fluid volume or composition, GI transit time)	28
	Age-related distribution effects (e.g., protein binding)	2
	Age related metabolism or clearance effects	15
Drug substance or formulation effects	Drug substance effect (e.g., alternative salt or polymorphic form of drug substance)	5
	Drug product/formulation effects	12
Disease	Age related disease manifestation	4
Population characteristics	High inter- and/or intra-individual variabilities	18
Study design	Non-equivalent dose effects	2
	Accuracy of administered dose	2
	Poor study design including small sample size	11

Pawar, G., Wu, F., Zhao, L. *et al.* Development of a Pediatric Relative Bioavailability/Bioequivalence Database and Identification of Putative Risk Factors Associated With Evaluation of Pediatric Oral Products. *AAPS J* **23,** 57 (2021). https://doi.org/10.1208/s12248-021-00592-y

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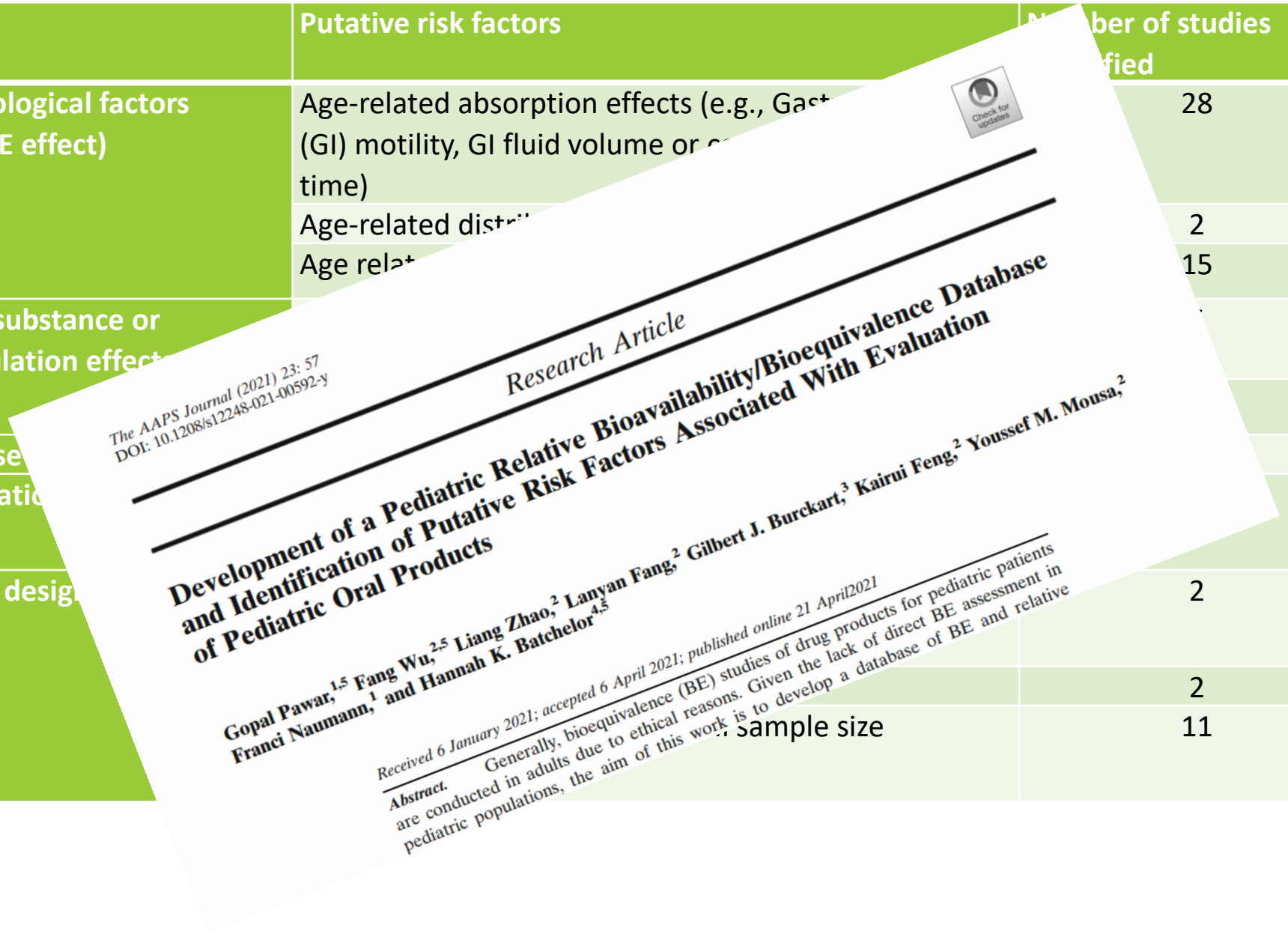
Drug substance or formulation effect…		
Disease…		
Populati…		
Study desig…		2
		2
	…l sample size	11



The AAPS Journal (2021) 23: 57
DOI: 10.1208/s12248-021-00592-y

Research Article

Development of a Pediatric Relative Bioavailability/Bioequivalence Database and Identification of Putative Risk Factors Associated With Evaluation of Pediatric Oral Products

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Abstract. Generally, bioequivalence (BE) studies of drug products for pediatric patients are conducted in adults due to ethical reasons. Given the lack of direct BE assessment in pediatric populations, the aim of this work is to develop a database of BE and relative

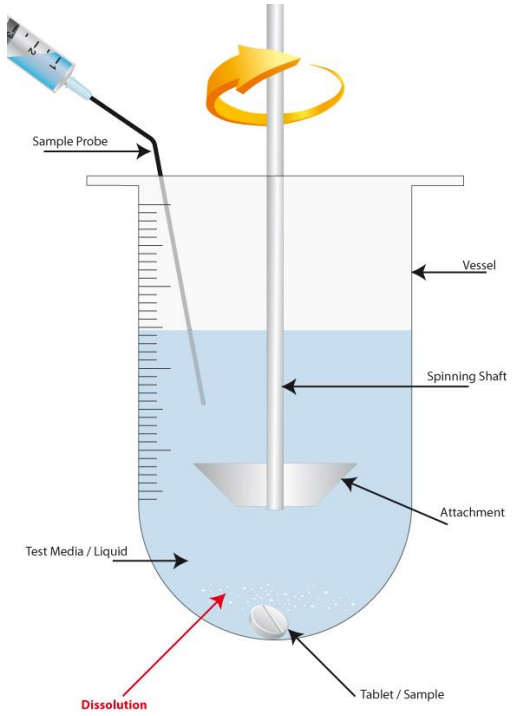
Part 2

DEVELOPMENT OF IN VITRO AND IN SILICO METHODS TO PROVIDE MECHANISTIC UNDERSTANDING OF RISKS OF BIOINEQUIVALENCE

Dissolution and risks of bioinequivalence

There is known variability in GI fluids in children compared to adults

There is a known difference in fluid volume in children compared to adults



Can we use dissolution testing integrated into PBPK modelling to mimic these differences and better predict a risk of bioinequvialence?

Prototype Pediatric simulated intestinal fluid

Composition	FaSSGF	Pediatric FaSSGF	FaSSIF	Pediatric FaSSIF
Bile (Taurocholate) mM	0.08	0.04-0.3	3	0.1-0.6
pH	1.6	2-3	6.5	2-3
Osmolality (mOsm/kg)	120	90-300	180	250-300
Buffer capacity (mmole/L/pH)	-	12-40	10	12-20

Literature data shows much lower levels of bile salts in pediatric GI fluids
Glycocholic acid; taurocholic acid; glycochenodeoxycholic acid and taurochenodeoxycholic acid are the most commonly identified bile salts in pediatric intestinal fluids

Gopal Pawar, Eleni Papadatou-Soulou, Julie Mason, Rafeeq Muhammed, Alison Watson, Catherine Cotter, Mohamed Abdallah, Stuart Harrad, Claire Mackie, Tina Arien, Sabine Inghelbrecht, Hannah Batchelor, Characterisation of fasted state gastric and intestinal fluids collected from children, European Journal of Pharmaceutics and Biopharmaceutics, Volume 158, 2021, Pages 156-165, ISSN 0939-6411, https://doi.org/10.1016/j.ejpb.2020.11.010.

Products selected (all BCS 2 and NTI drug products):

Carbamazepine

- 100 mg Tegretol tablets (Novartis)
- 100 mg generic Carbamazepine tablets – either Mylan, Medreich PlC

Ciclosporin

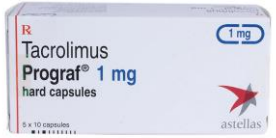
- 50mg Neoral Soft Gelatin Capsules (Novartis)
- 50mg Sandimmun Soft Gelatin Capsules (Novartis)
- 25mg Neoral Soft Gelatin Capsules (Novartis)
- 25mg Sandimmun Soft Gelatin Capsules (Novartis)
-

Phenytoin

- 100mg Phenytoin Sodium Flynn Hard Capsules 100mg (Flynn Pharma Ltd)
- 100mg Phenytoin Sodium Hard Capsules – either Accord-UK; AAH Pharmaceuticals; Actavis; Alliance Healthcare; DE Pharmaceuticals; Ennogen Healthcare; Sigma Pharmaceuticals
- 50mg Phenytoin Sodium Flynn Hard Capsules 100mg (Flynn Pharma Ltd)
- 50mg Phenytoin Sodium Hard Capsules – either Accord-UK; AAH Pharmaceuticals; Actavis; Alliance Healthcare; DE Pharmaceuticals; Ennogen Healthcare; Sigma Pharmaceuticals

Tacrolimus

- 1mg Prograf hard capsules (Astella pharma)
- 1mg Adoport hard capsules (Sandoz ltd)
- 0.5mg Prograf hard capsules (Astella pharma)
- 0.5 mg Adoport hard capsules (Sandoz ltd)



Dissolution plans

Determine differences:

USP – adult FaSSGF and FaSSIF

Then compare adult FaSSGF and FaSSIF to pediatric FaSSGF and FaSSIF

- However, no accurate recipe is available for pFaSSGF and pFaSSIF thus using reduced bile levels compared to adult FaSSGF and FaSSIF
- Also need to consider how to best capture the dose:volume likely to be observed in children
  - Paediatric Fasted State Intestinal Media formulated with bile salt concentrations 25% (0.75mM) of adult levels (P-FaGF and P-FaSSIF-25%)
  - Paediatric Fasted State Intestinal Media formulated with bile salt concentrations 50% (1.5mM) of adult levels (P-FaGF and FaSSIF-50%).

Impact of volume from 900, 500, 200, 100, 50 mL

Impact of composition
All media compared at 200mL volume

Media	FaSSGF	FaSSIF	pFaSSGF (14BS)	pFaSSIF (14BS)	pFaSSGF (50% 14BS)	pFaSSIF (50% 14BS)	pFaSSGF (TCA only)	pFaSSIF (TCA only)
FaSSGF								
FaSSIF								
pFaSSGF (14BS)								
pFaSSIF (14BS)								
pFaSSGF (50% 14BS)								
pFaSSIF (50% 14BS)								
pFaSSGF (TCA only)								
pFaSSIF (TCA only)								

PBPK Plans

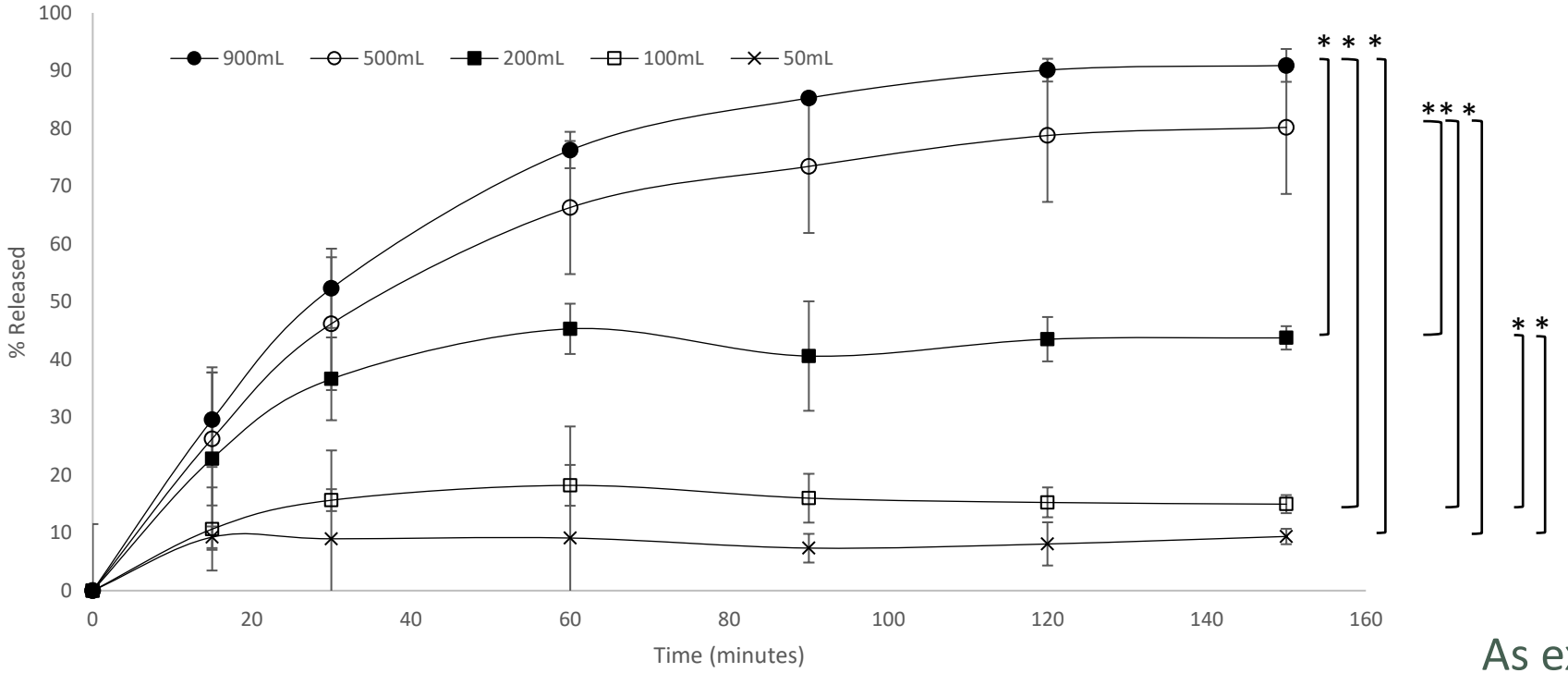
Use PBPK in conjunction with published clinical data to determine which in vitro dissolution conditions best predict performance in

(i) Adults

(ii) Children

Propose suitable dissolution methodology for prediction of exposure in pediatric populations

Impact of Ad-FaSSGF dissolution media volume on dissolution of 100mg carbamazepine tablet



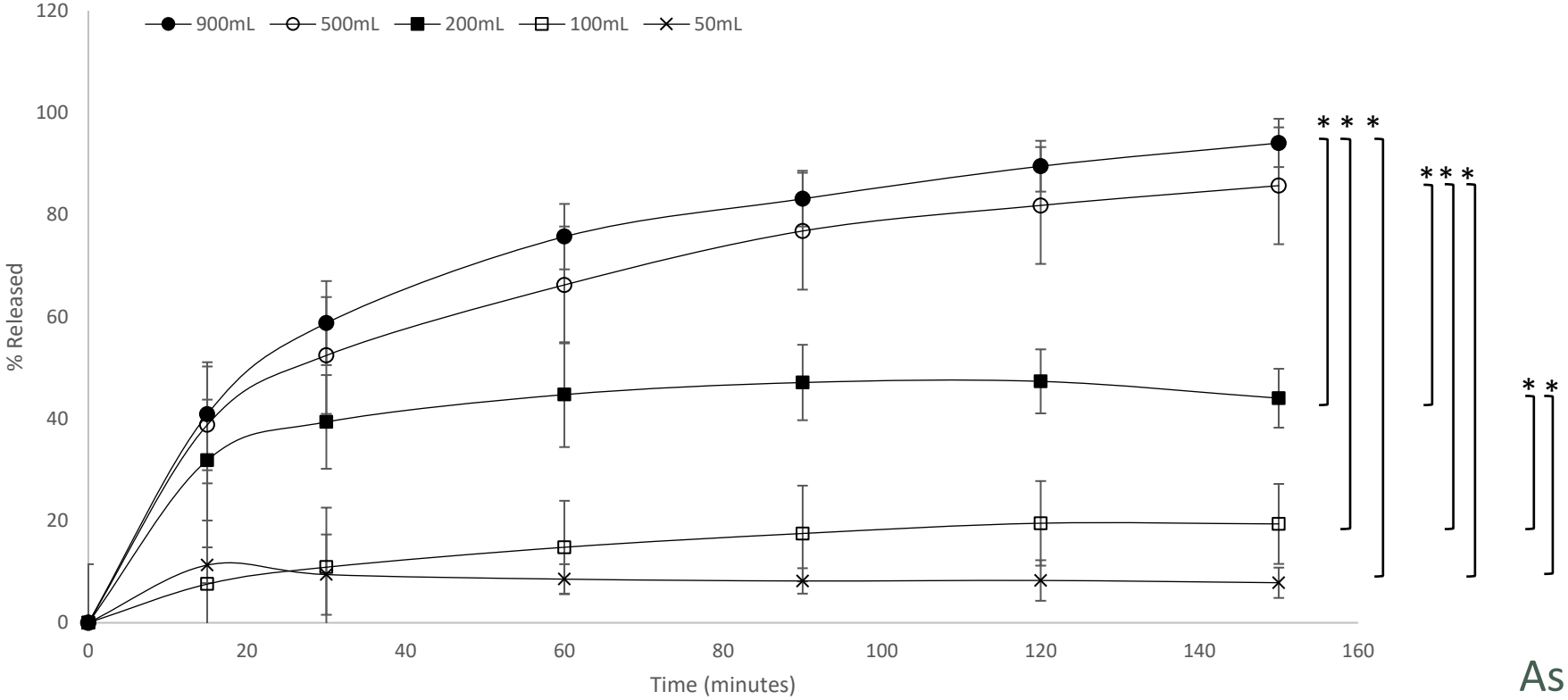
		500mL	200mL	100mL	50mL
900mL	F1	9.1	42.4	79.7	87.1
	F2	58.8	25	12.6	10.4
500mL	F1		36.6	77.7	85.8
	F2		29.8	15.3	12.7
200mL	F1			64.8	77.6
	F2			29.6	25.4
100mL	F1				45.1
	F2				57.6

F1<15 and F2>50 indicates similarity

Comparison of the dissolution where * indicates dis-similar profiles
Data points are mean of n=6 and error bars show %CV

As expected media volume affects dissolution for carbamazepine as a poorly soluble drug

Impact of Ad-FaSSIF dissolution media volume on dissolution of 100mg carbamazepine tablet



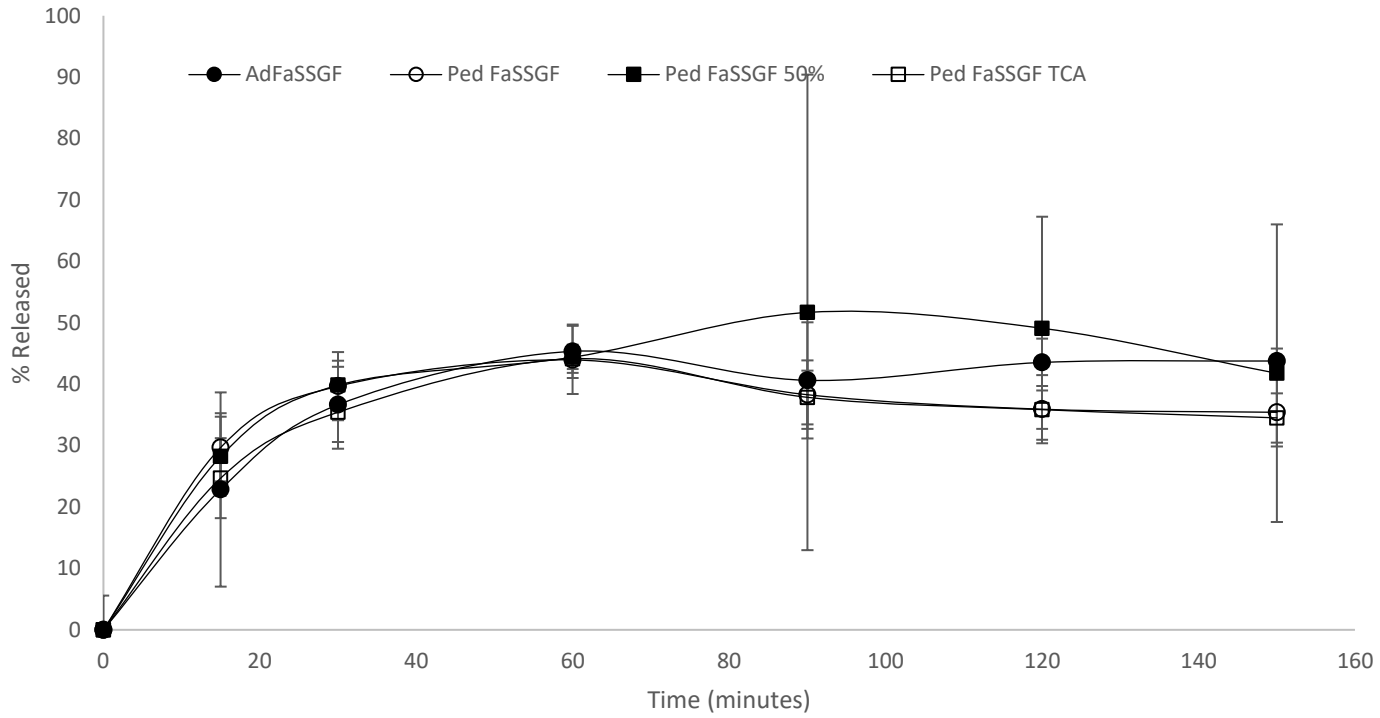
		500mL	200mL	100mL	50mL
900mL	F1	12.5	45.2	78.6	87.7
	F2	52.9	24	12.9	10.7
500mL	F1		37.3	75.5	85.9
	F2		30.5	16.7	14
200mL	F1			61	77.5
	F2			32.3	27
100mL	F1				42.4
	F2				59.4

F1<15 and F2>50 indicates similarity

Comparison of the dissolution where * indicates dis-similar profiles
Data points are mean of n=6 and error bars show %CV

As expected media volume affects dissolution for carbamazepine as a poorly soluble drug

Impact of gastric dissolution media composition on dissolution of 100mg carbamazepine tablet in 200mL volume



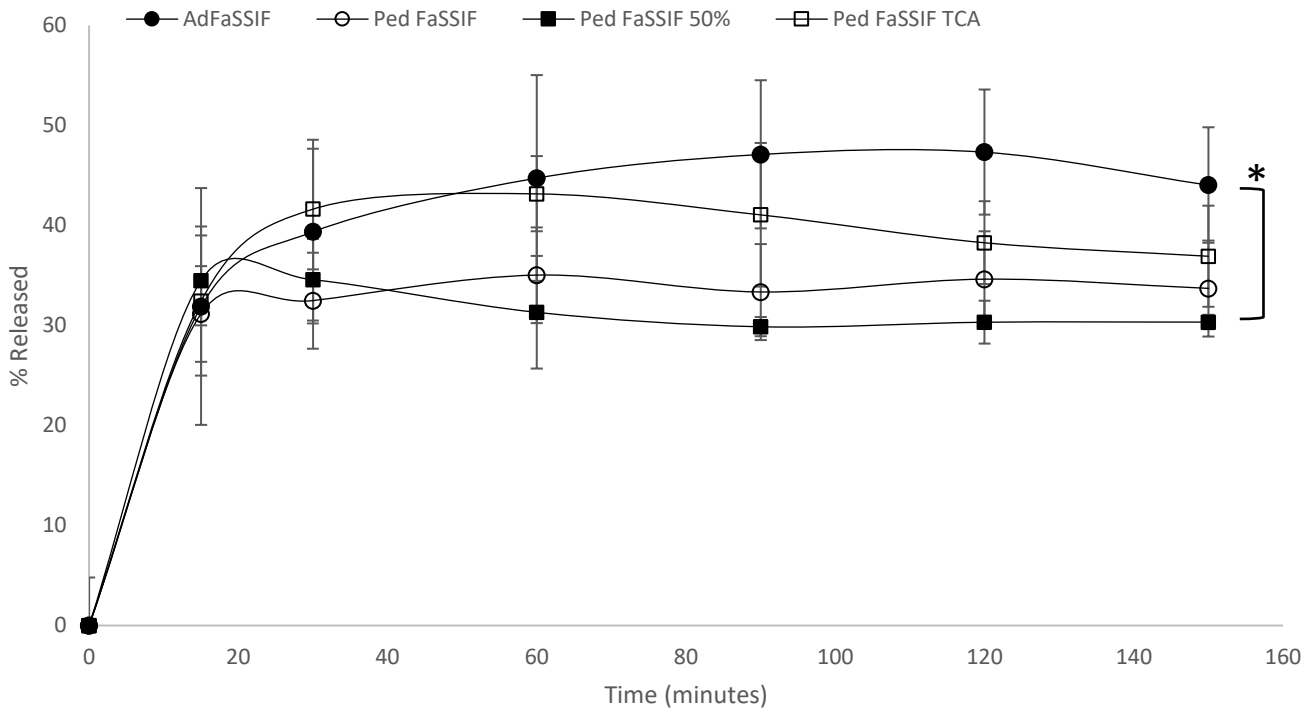
Media	[bile salt] µM
AdFaSSGF	80
Ped FaSSGF	16.62
Ped FaSSGF 50%	8.31
Ped FaSSGF (TCA)	16.62

		Ped FaSSGF	Ped FaSSGF 50%	Ped FaSSGF TCA
AdFaSSGF	F1	9.1	12.1	10.3
	F2	58.8	63.3	65.6
Ped FaGF	F1		9.2	4.9
	F2		75.9	78.4
Ped FaGF 50%	F1			16.7
	F2			54.6

Comparison of the dissolution where * indicates dis-similar profiles
Data points are mean of n=6 and error bars show %CV

Bile salt concentration does not affect dissolution of carbamazepine in simulated gastric media

Impact of intestinal dissolution media composition on dissolution of 100mg carbamazepine tablet in 200mL volume



Media	[bile salt] µM
AdFaSSIF	3000
Ped FaSSIF	178
Ped FaSSIF 50%	89
Ped FaSSIF (TCA)	178

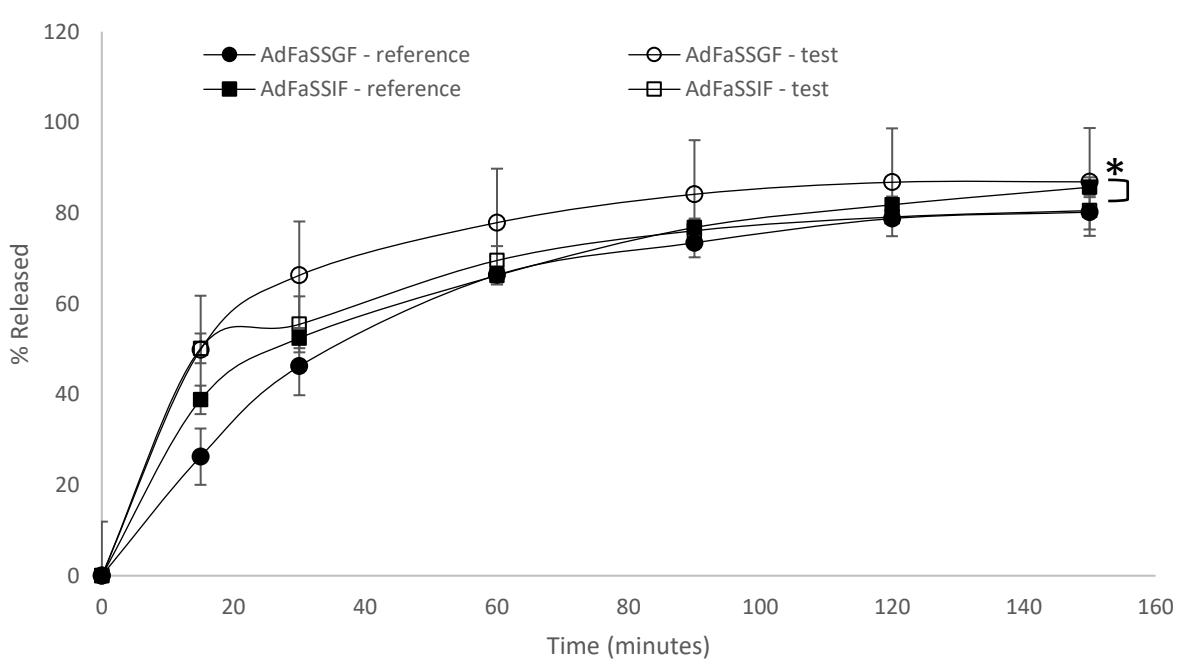
		Ped FaSSIF	Ped FaSSIF 50%	Ped FaSSIF TCA
AdFaSSIF	F1	21.3	27	10.5
	F2	51.5	46.2	64.5
Ped FaSSIF	F1		11.4	17.8
	F2		61.7	60.7
Ped FaSSIF 50%	F1			24.5
	F2			55.2

Comparison of the dissolution where * indicates dis-similar profiles
Data points are mean of n=6 and error bars show %CV

Bile salt concentration affected dissolution of carbamazepine in simulated intestinal media

Comparison of equivalence of a test and innovator carbamazepine product using biorelevant dissolution testing

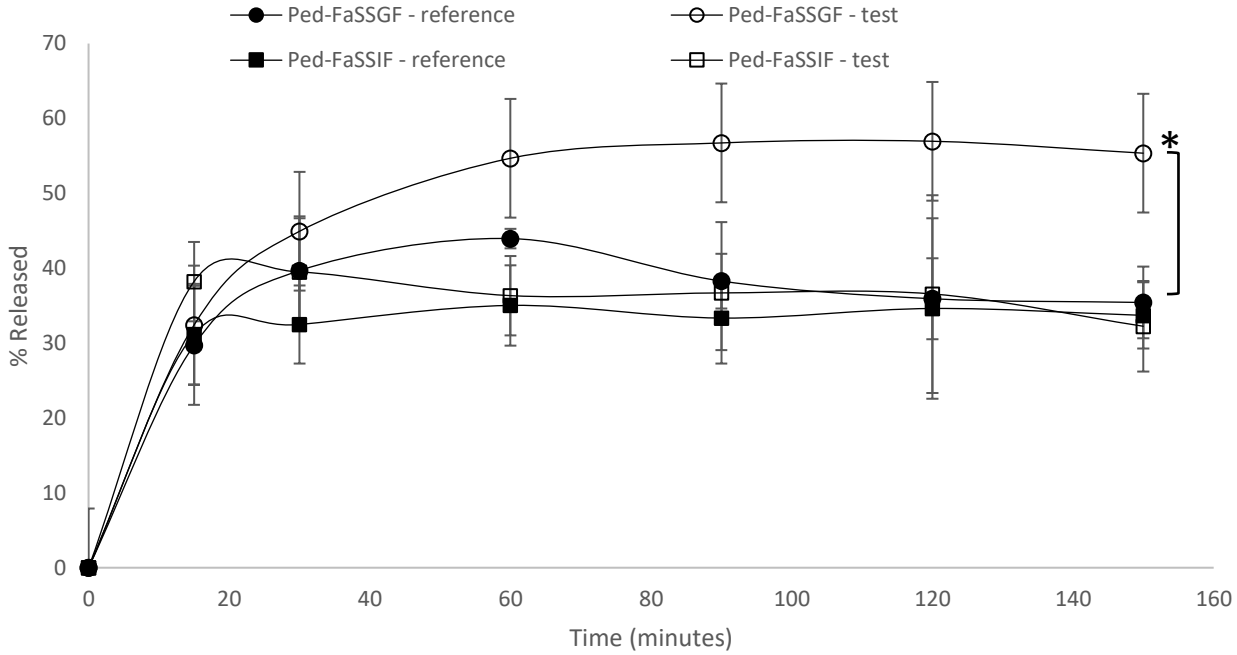
ADULT BIOPREDICTIVE TEST USES 500ML MEDIA



		AdFaSSGF - reference
AdFaSSGF - test	F1	17.8
	F2	43.1

		AdFaSSIF - reference
AdFaSSIF - test	F1	6.4
	F2	64.2

PEDIATRIC BIOPREDICTIVE TEST USES 200ML MEDIA



		Ped-FaSSGF - reference
Ped-FaSSGF - test	F1	25.9
	F2	43

		Ped-FaSSIF - reference
Ped-FaSSIF - test	F1	11
	F2	68.7

PBPK: carbamazepine

A PBPK model for CBZ was developed in SimCyp® Simulator (Version 19, Release 1; Certara UK Limited, Sheffield, UK)

The in vitro data sets were incorporated into the PBPK simulator Advanced Dissolution Absorption and Metabolism (ADAM) model

Model prediction accuracy was compared to published clinical PK data in both adult and pediatric populations

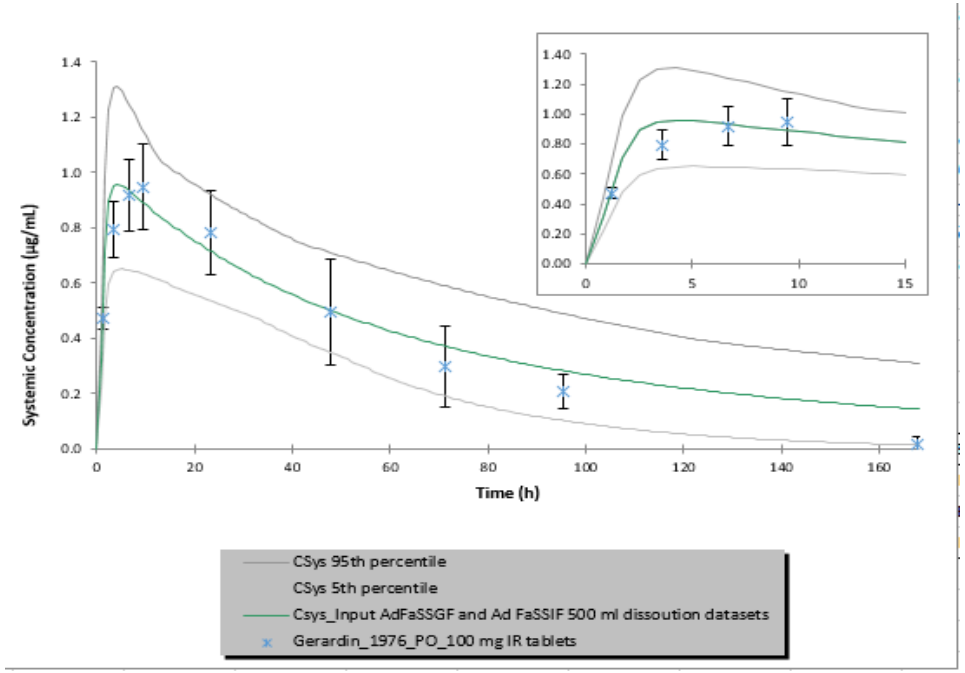
PBPK model inputs

Parameter	Adult Values	Reference	Pediatric Values
Mol. wt (g/mol)	236.2	DrugBank	
Log P o:w	2.2	Almond 2016	
Compound type	Neutral		
Blood: Plasma Ratio (B/P)	1.21	de Groot 1984; Bonneton 1992	
Unbound fraction (Fu)	0.25	Almond 2016	
Human jejunal permeability (Peff)	4.3 X 10^{-4} cm/s	Lennernäs 1992	
Vss (L/kg)	0.78-1.9	Rawlins 1975; Ramsay 1990; EMC	0.3 (value used based on the parameter estimation within SIMCYP)
Invitro metabolic system (recombinant) Pathway	10,11- epoxidation		
Enzyme	CYP3A4	Cazali 2003; Huang 2004	The ontogeny of these enzymes was incorporated into the pediatric population
Vmax (pmol/min/pmol); Km (µM)	0.72; 180.2		
Enzyme	CYP3A5	Huang 2004	
Vmax (pmol/min/pmol); Km (µM)	1.44; 332.3		
Enzyme	CYP2C8	Cazali 2003	
Vmax (pmol/min/pmol); Km (µM)	0.03; 741.74		

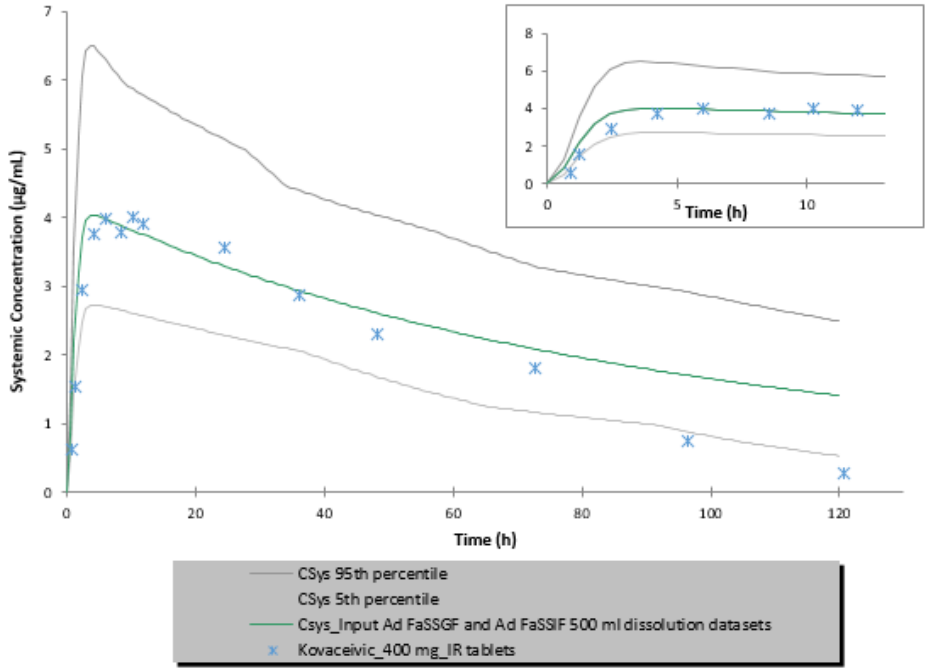
Note: SimCyp V19; Advanced Dissolution Absorption Model (ADAM); minimal PBPK model was used

Adult: Carbamazepine PBPK model verification

Observed and simulated CBZ plasma concentration-time profiles in adult populations using input dissolution from 500mL FaSSGF and FaSSIF data



Clinical data from Gerardin 1976
(n=6 Healthy; oral PK study; 100 mg IR Tegretol).



Clinical data from Kovacevic 2009
(n=18 healthy; 29-37 years; relative BA study; 400 mg (2X 200 mg) IR (Tegretol) tablets SD).

Géradin AP, Abadie FV, Campestrini JA, Theobald W. Pharmacokinetics of carbamazepine in normal humans after single and repeated oral doses. J Pharmacokinet Biopharm. 1976;4(6):521-35. doi: 10.1007/bf01064556.

Kovacević I, Parojcić J, Homsek I, Tubić-Grozdanis M, Langguth P. Justification of biowaiver for carbamazepine, a low soluble high permeable compound, in solid dosage forms based on IVIVC and gastrointestinal simulation. Mol Pharm. 2009;6(1):40-7. doi: 10.1021/mp800128y.

Using adult dissolution data to predict exposure in adults

Clinical study	Details of the study	PK parameter	Mean Predicted	Mean observed	PPE
Gerardin 1976	PK study; Healthy fasting volunteers n=6; Single oral dose 100 mg;	AUC_{0-t} (µg/mL.h)	66.16	58	14.06
		Cmax (µg/mL)	0.96	0.95	1.07
Gerardin 1976	PK study; Healthy fasting volunteers n=6; Single oral dose 200 mg;	AUC_{0-t} (µg/mL.h)	126.7	113	12.13
		Cmax (µg/mL)	1.71	1.65	3.57
Kohlman 2017	Meta-analysis (mean-weighted profiles); n=76; 200 mg	AUC_{0-t} (µg/mL.h)	122.26	121	1.04
		Cmax (µg/mL)	2.16	1.99	8.54
Kohlman 2017	Meta-analysis (mean-weighted profiles); n=94; 400 mg	AUC_{0-t} (µg/mL.h)	206.277	207	-0.35
		Cmax (µg/mL)	4.322	4.01	7.78
Kovacevic 2009	Relative bioavailability; Healthy fasting volunteers (n=18; 29-37 years); 400 mg (2 IR tablets);	AUC_{0-t} (µg/mL.h)	294.5	224	31.47
		Cmax (µg/mL)	4.036	3.78	6.79
Olling 1999	Relative bioavailability; Healthy fasting volunteers (n=18; 20-38 years); 200 mg; 150 mL water;	AUC_{0-t} (mg/L.h)	318.88	317.0	0.59
		Cmax (mg/L)	5.63	5.0	12.69

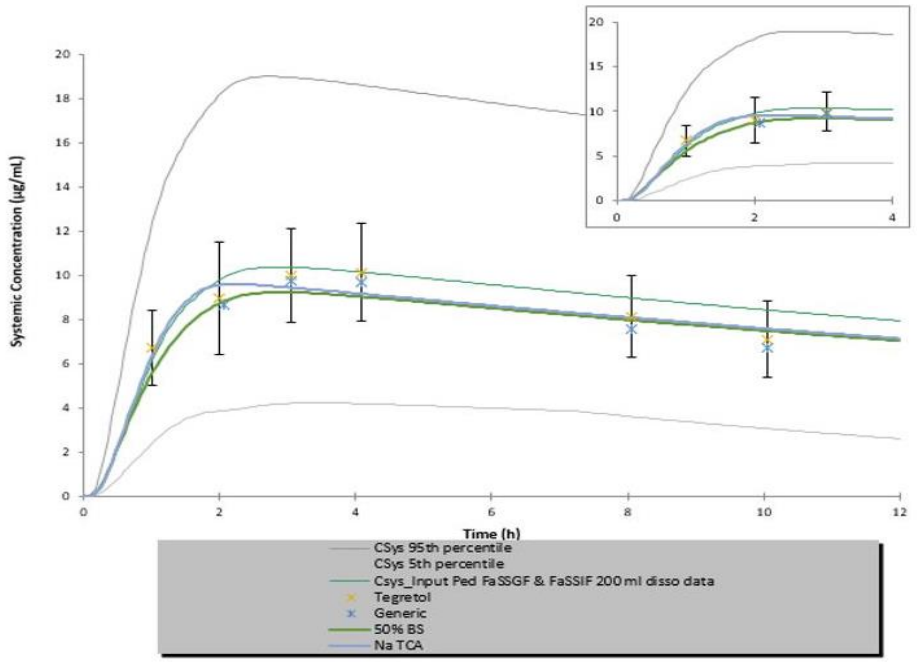
The input dissolution (500mL Ad FaSSGF/FaSSIF)provides a good fit to the clinical data

Target is PPE<20%

Kohlmann P, Stillhart C, Kuentz M, Parrott N. Investigating Oral Absorption of Carbamazepine in Pediatric Populations. The AAPS Journal. 2017;19(6):1864-77. doi: 10.1208/s12248-017-0149-6
Olling M, Mensinga TT, Barends DM, Groen C, Lake OA, Meulenbelt J. Bioavailability of carbamazepine from four different products and the occurrence of side effects. Biopharm Drug Dispos. 1999;20(1):19-28. doi: 10.1002/

Pediatric: Carbamazepine PBPK model verification

Observed and simulated CBZ plasma concentration-time profiles in pediatric populations using input dissolution from 200mL volumes of pediatric media



Clinical data from Hartley 1991
(n=12 children aged 6.5-15 years taking CBZ as either 100 or 200mg tablets twice daily).

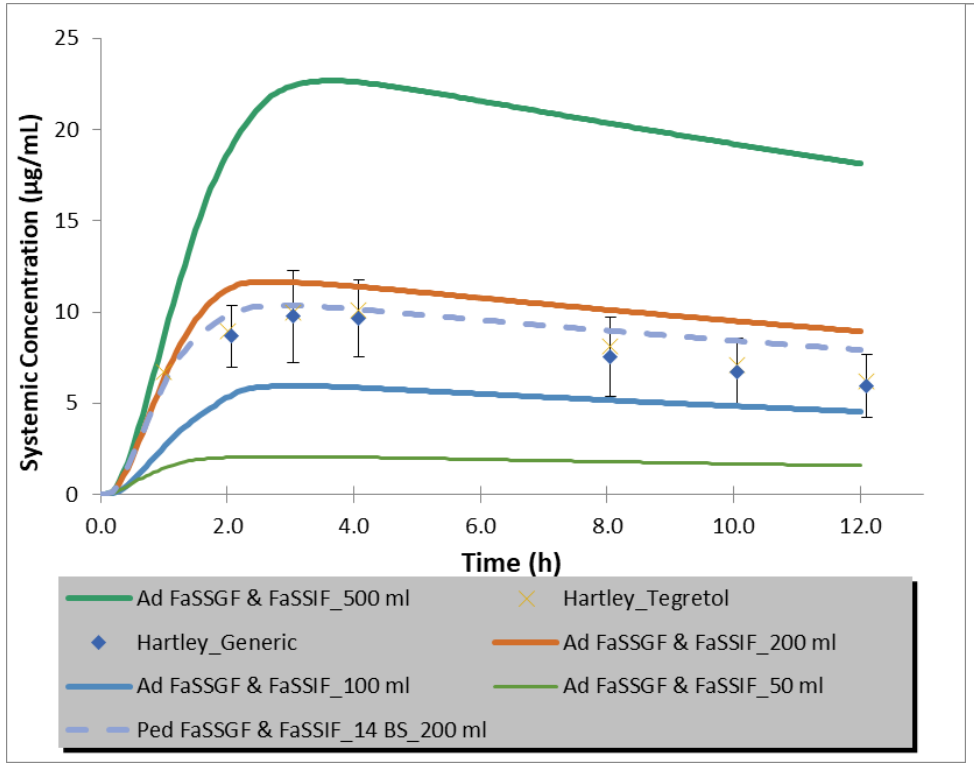
Input dissolution datasets	PK parameter	Mean Predicted	Mean observed	PPE
Ped-FaSSGF/FaSSIF 14 BS 200 mL	AUC_{0-t} (µg/mL.h)	103.24	99	4.29
	Cmax (µg/mL)	10.35	8.2	26.3
Ped-FaSSGF/FaSSIF 50% 14 BS 200 mL	AUC_{0-t} (µg/mL.h)	92.0	99	-7.07
	Cmax (µg/mL)	9.23	8.2	12.5
Ped-FaSSGF/FaSSIF Na TCA 200 mL	AUC_{0-t} (µg/mL.h)	94.70	99	-4.34
	Cmax (µg/mL)	9.588	8.2	16.92

Target is PPE<20%

Dissolution data from 200mL pediatric media mapped well to clinical data.

Hartley R, Aleksandrowicz J, Bowmer CJ, Cawood A, Forsythe WI. Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy. Journal of Pharmacy and Pharmacology. 1991;43(2):117-9. doi: https://doi.org/10.1111/j.2042-7158.1991.tb06644.x.

Using adult dissolution data to predict exposure in pediatric populations



Input dissolution datasets	PK parameter	Mean Predicted	Mean observed	PPE
Ad-FaSSGF/FaSSIF 500 mL	AUC (µg/mL.h)	224	99	126.3
	Cmax (µg/mL)	23	8.2	180.5
Ad-FaSSGF/FaSSIF 200 mL	AUC (µg/mL.h)	116	99	17.2
	Cmax (µg/mL)	12	8.2	46.3
Ad-FaSSGF/FaSSIF 100 mL	AUC (µg/mL.h)	58.2	99	-41.2
	Cmax (µg/mL)	6.0	8.2	-26.8
Ad-FaSSGF/FaSSIF 50 mL	AUC (µg/mL.h)	21	99	-78.8
	Cmax (µg/mL)	2.1	8.2	-74.4
Ped-FaSSGF/FaSSIF NaTCA 200 mL	AUC (µg/mL.h)	103.25	99	-4.34
	Cmax (µg/mL)	10.35	8.2	16.92

Target is PPE<20%

Dissolution data from 200mL Ped FaSSGF/FaSSIF Na TCA media was closest to the clinical data although a slightly lower volume may have provided a more accurate prediction

Clinical data from Hartley 1991
(n=12 children aged 6.5-15 years taking CBZ as either 100 or 200mg tablets twice daily).

Hartley R, Aleksandrowicz J, Bowmer CJ, Cawood A, Forsythe WI. Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy. Journal of Pharmacy and Pharmacology. 1991;43(2):117-9. doi: https://doi.org/10.1111/j.2042-7158.1991.tb06644.x.

Virtual bioequivalence studies: Population 100 mg dose-Tegretol and generic CBZ; Simulation run time-24 hrs

	Cross-over design	Input dissolution datasets	(GMR-90% CIs) AUC (µg/mL.h)	GMR-90% CIs) Cmax (µg/mL)	Bioequivalence Yes, or No?
Adult	N=12 10 Trials	Only adult FaSSIF 500 ml	94.81 (92.60-97.01)	94.47 (92.13-96.81)	Yes
	N=12 10 Trials	Ad-FaSSGF & FaSSIF 500 ml	105.29 (101.04-109.53)	104.78 (100.49-109.07)	Yes
	N=16 10 trials	Ad-FaSSGF & FaSSIF 500 ml	105.45 (101.53-109.38)	104.96 (100.98-108.94)	Yes
	N=24 10 trials	Ad-FaSSGF & FaSSIF 500 ml	105.23(101.06-109.39)	104.73 (100.5-108.97)	Yes
	N=48 10 trials	Only adult FaSSIF 500 ml	94.81 (92.47-97.15)	94.48 (92.00-96.96)	Yes
	N=48 10 trials	Ad-FaSSGF & FaSSIF 500 ml	105.59 (98.06-113.3)	104.91 (100.3-109.51)	Yes
Pediatrics	N=12 10 Trials	Only Ped- FaSSIF 200 ml_14 BS	98.93 (90.78-107.08)	101.34 (93.08-109.61)	Yes
	N=12 10 Trials	Ped-FaSSGF & FaSSIF 200 ml_14 BS	112.30 (98.16-126.43)	112.65 (100.12-125.16)	For both AUC & Cmax Higher bound of 90% CI slightly beyond 125% or on a borderline
	N=16 10 trials	Ped-FaSSGF & FaSSIF 200 ml_14 BS	112.78 (98.0-127.56)	112.92 (99.80-126.04)	For both AUC & Cmax Higher bound of 90% CI slightly beyond 125% or on a borderline
	N=24 10 trials	Ped-FaSSGF & FaSSIF 200 ml_14 BS	112.28 (97.93-126.24)	112.52 (99.94-125.0)	For AUC only- Higher bound of 90% CI slightly beyond 125% or on a borderline
	N=48 10 trials	Only Ped- FaSSIF 200 ml_14 BS	98.92 (90.30-107.54)	101.28 (92.57-109.99)	Yes
	N=48 10 trials	Ped-FaSSGF & FaSSIF 200 ml_14 BS	112.04 (98.13-125.94)	112.311 (100.40-124.22)	For AUC only- Higher bound of 90% CI slightly beyond 125% or on a borderline

VBE simulations were performed with a sample size of 12, 16, 24, 36 and 48 healthy adults (18-45 years) and a single dose of CBZ IR tablets 100 mg administered with **240 mL of fluids**.

For VBE simulation, the dissolution profiles generated in Ad-FaSSGF/FaSSIF 500 mL were incorporated into the adult PBPK model.

For pediatrics, VBE simulations were performed with a sample size of 12, 16, 24, 36 and 48 healthy subjects (6.5-15 years) and a single dose of CBZ IR tablets 100 mg administered with **120 mL of fluids**.

For VBE simulation, the dissolution profiles generated in Ped-FaSSGF/FaSSIF 200 mL were incorporated into the pediatric PBPK model.

Conclusions: Carbamazepine case study

Carbamazepine dissolution is more sensitive to volume compared to bile salt concentration

Dissolution input for adults of 500mL Ad FaSSGF or Ad FaSSIF media gave a good match to the existing clinical data

Dissolution input for pediatric populations using 200 mL Ped FaSSIF media gave a good match to the existing clinical data

Using adult dissolution media to predict exposure in pediatric populations was strongly influenced by volume with 200mL providing the closest approximation. However a volume of ~150-200 may be superior.

The VBE showed equivalence based on dissolution inputs. As the dissolution profiles were similar this is unsurprising

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Questions