A model-informed drug development (MIDD) approach to designing modified release formulations for a BCS Class I drug

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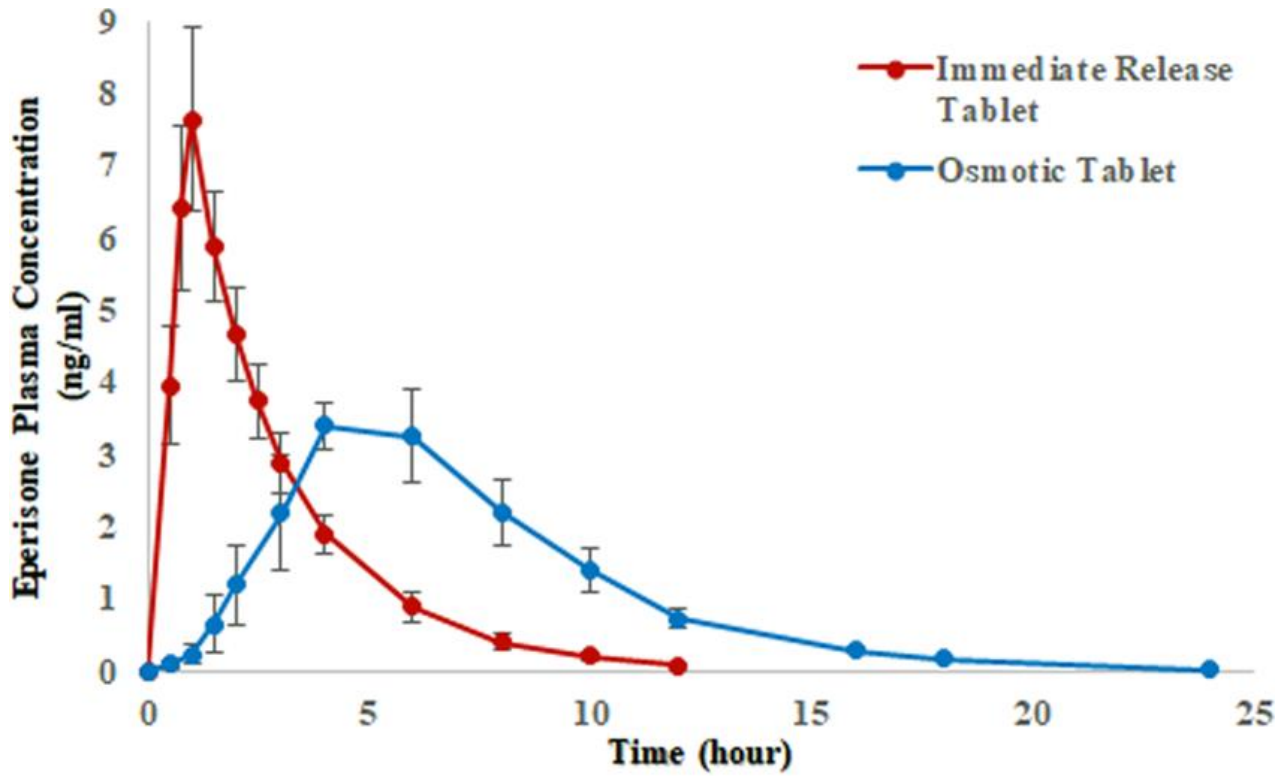
Types of controlled-release oral dosage formulations

Common formulation approaches:

- Matrix tablet
- Multiparticulates
- Osmotic tablet

Non-conventional formulations

- Gastric retentive
- Colonic specific delivery
- Bilayer formulation (IR & MR combined)



Ahmed et al. *Scientific Reports.* **2020**.

https://www.nature.com/articles/s41598-020-58801-1

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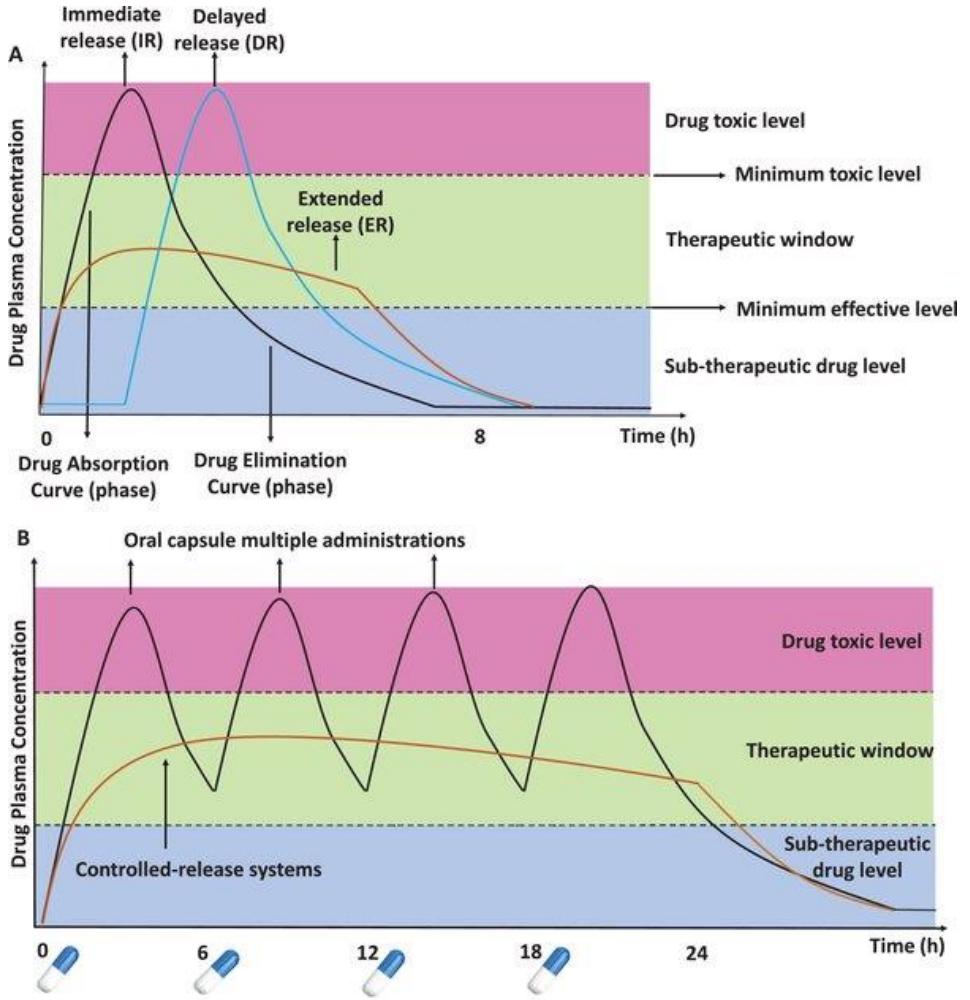
Controlled-release formulations provide benefits to patients

- Improved patient compliance e.g. QD or once daily vs BID or more
- Reduce side effects e.g. blunting C_{max} can reduce risk of adverse events (AEs)
- Enhanced therapeutic effect
- Suitable for short $t_{1/2}$ drugs
- Targeted delivery to lower GI



Gerali et al. *View*. **2021**.

https://onlinelibrary.wiley.com/doi/10.1002/VIW.20200126

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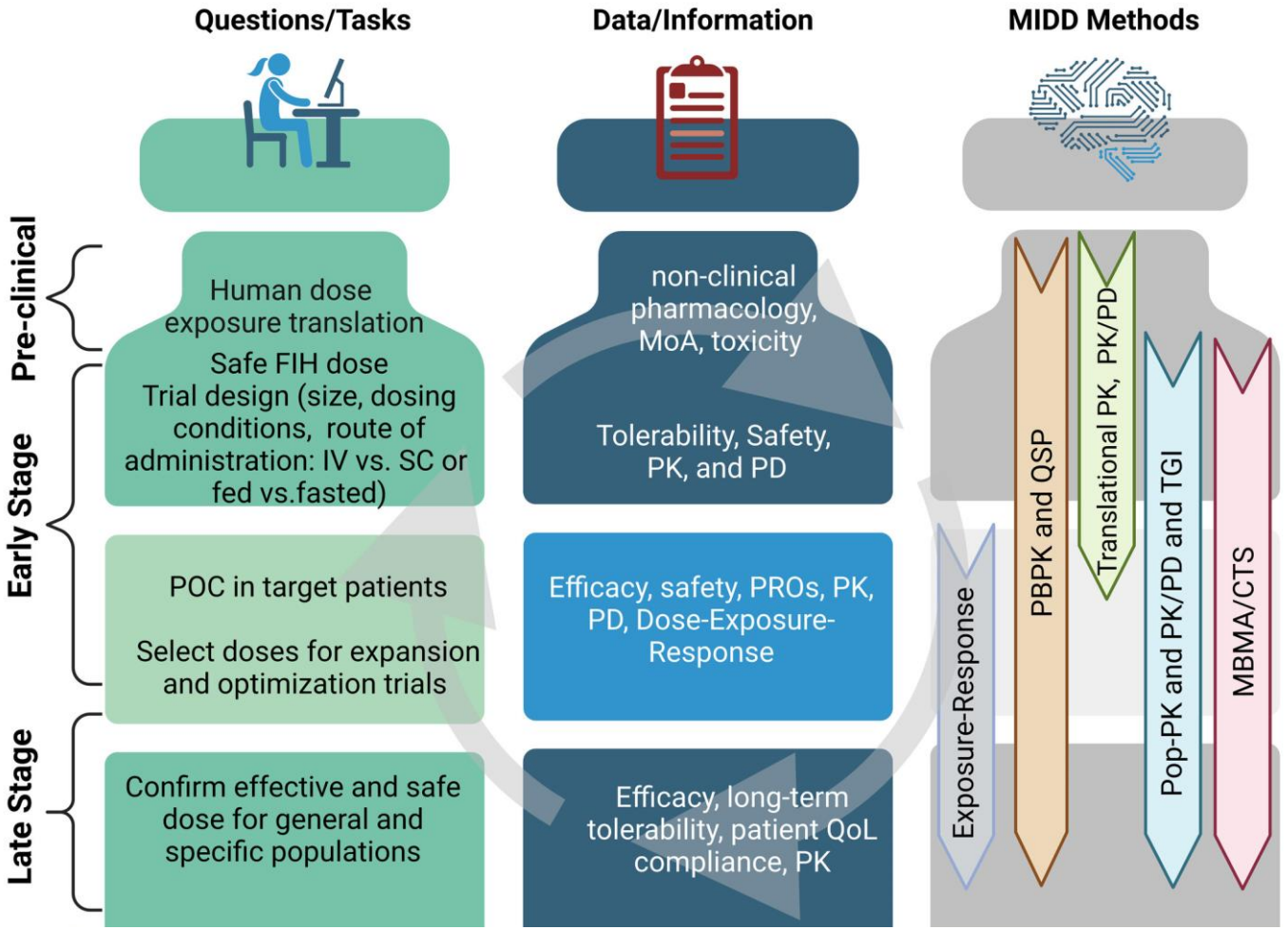
Model-informed drug development (MIDD)



Gao et al. *CPT Pharmacometrics Syst Pharmacol*. **2024**.

10.1002/psp4.13079

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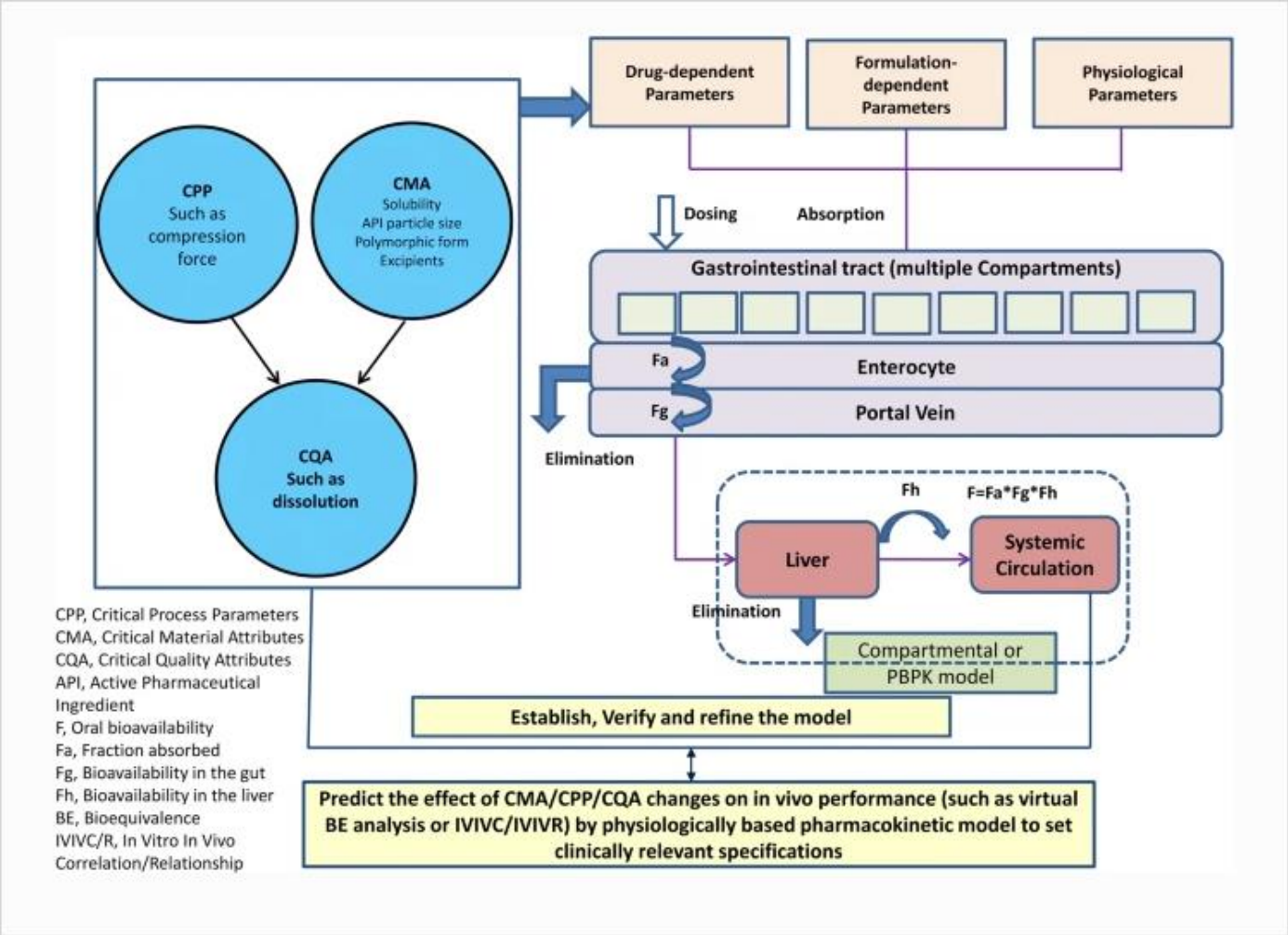
Physiological-based pharmacokinetic modeling (PBPK)



Gao et al. *CPT Pharmacometrics Syst Pharmacol*. **2024**.

10.1002/psp4.13079

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Drug and Formulation parameters

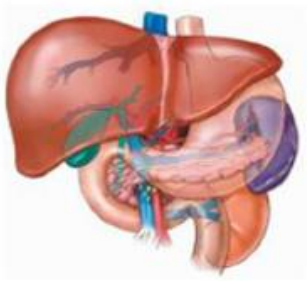
Molecular weight
pKa
LogD/LogP
pH-solubility profile
Dissolution profile
Particle size
Dosage form
Dosing regimen
Permeability
K_M, V_{max}
fup, B:P, fu_{inc}

System-specific parameters

Demographic and genetic factors

Age
Weight
Height
Sex
Genetics
Race
Disease

Physiological factors



Gastrointestinal transit time
Gastric pH
Bile salt concentration
Organ size and the associated tissue types
Blood flow
Drug metabolizing enzymes
Drug transporters
Plasma protein
Hematocrit

Pharm Research 2022 – W. Lin et.al. The most frequently used system- and drug-specific factors in a PBPK/PBBM Model. Modified after Jamei M et al 2009
pKa: $-\log_{10}$ dissociation constant; B:P: blood to plasma partition ratio; fu: free fraction of drug in plasma; K_M : Michaelis constant; V_{max}: velocity of enzyme-catalyzed reaction at infinite concentration of substrate; fuinc: Incubational binding or the fraction of drug unbound in an in vitro incubation

Clinical development of a BCS I drug through MIDD

Case study – BCS I Drug, Compound X a great candidate for MR

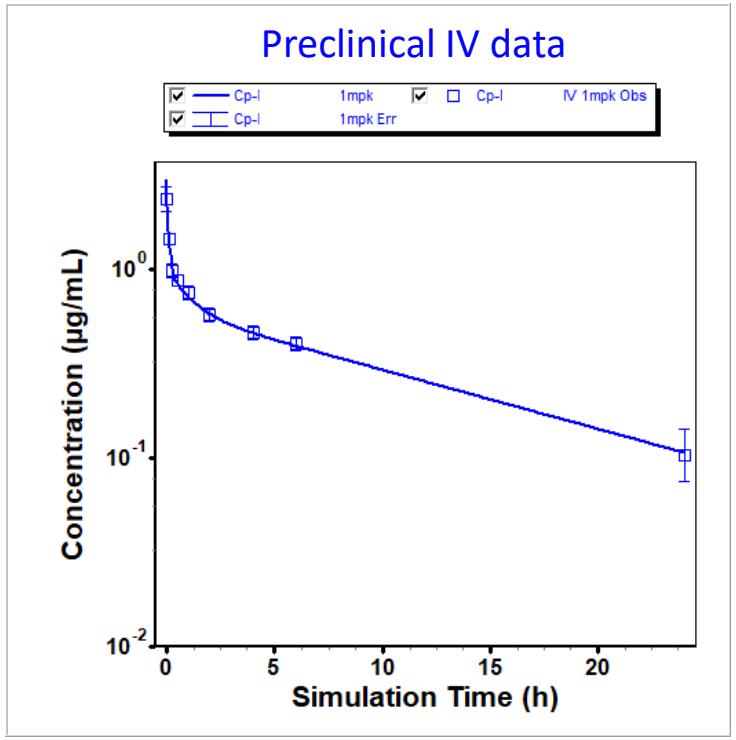
Characteristics of Compound X

- High solubility including FaSSIF/FeSSIF
- High permeability
- Small molecule (<400 Da)
- Unknown half-life at time of pre-clinical development
- Therapeutic indication – Narcolepsy
- Dose regularity – QD or BID

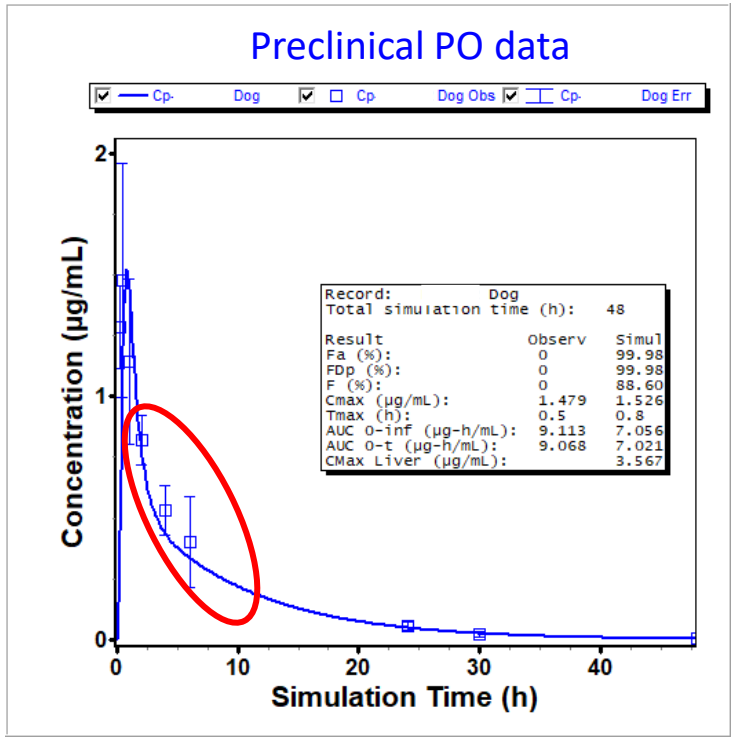
Applying PBPK approach to formulation design

1. Establish baseline preclinical PBPK model
2. Explore dissolution profiles to PK prediction
3. Refine formulation design + clinical PBPK model
4. Clinical assessment of MR formulation

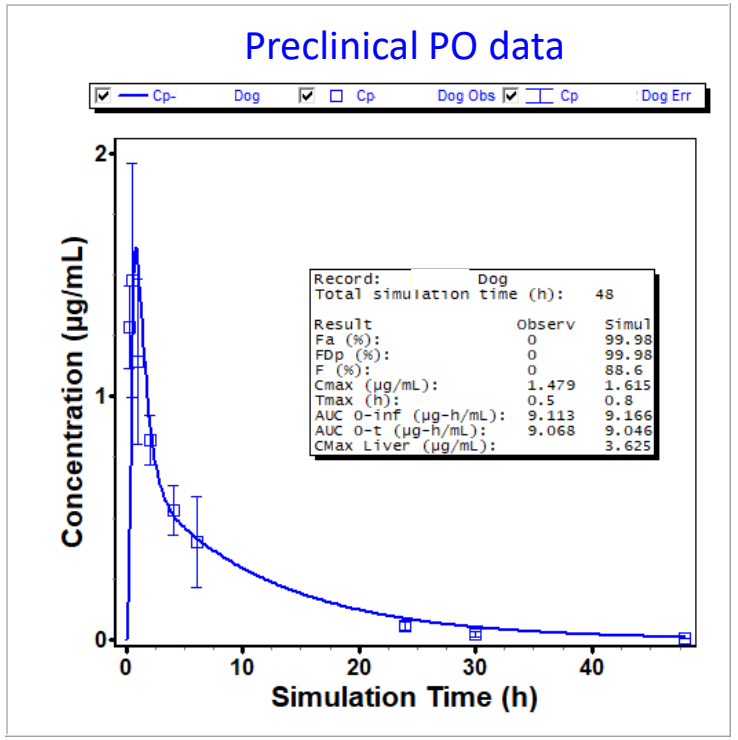
Establishing a baseline preclinical PBPK model



Use IV data to determine CL



PO data shows moderate data fit with CL 0.37



Refinement of CL to 0.29 shows a perfect fit of PO data

Abbreviations – CL: clearance; PBPK: Physiological-based pharmacokinetic model

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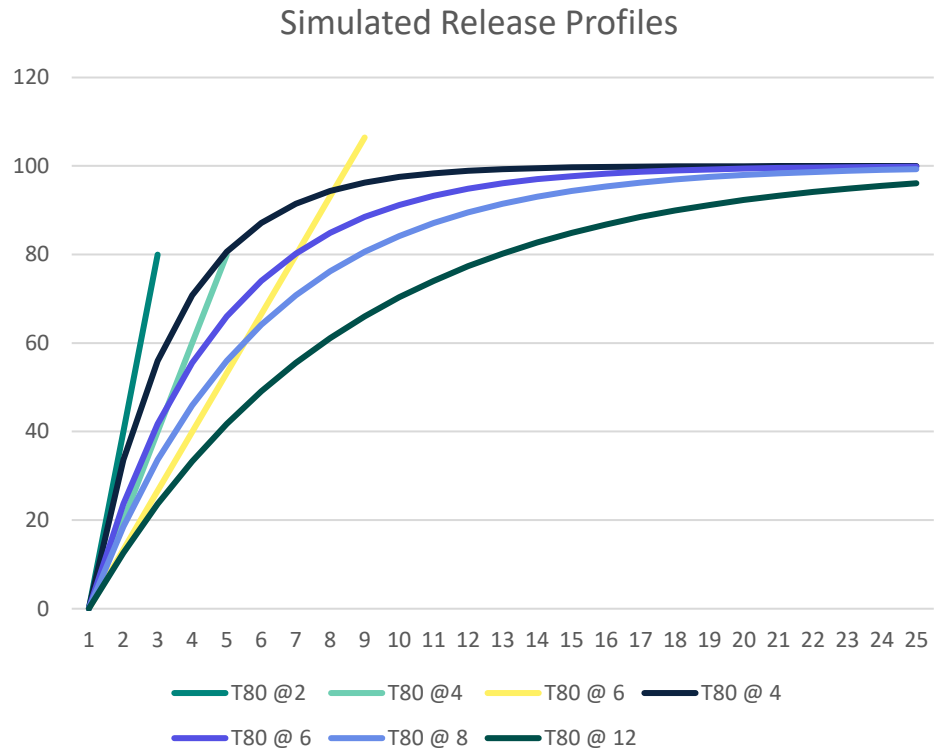
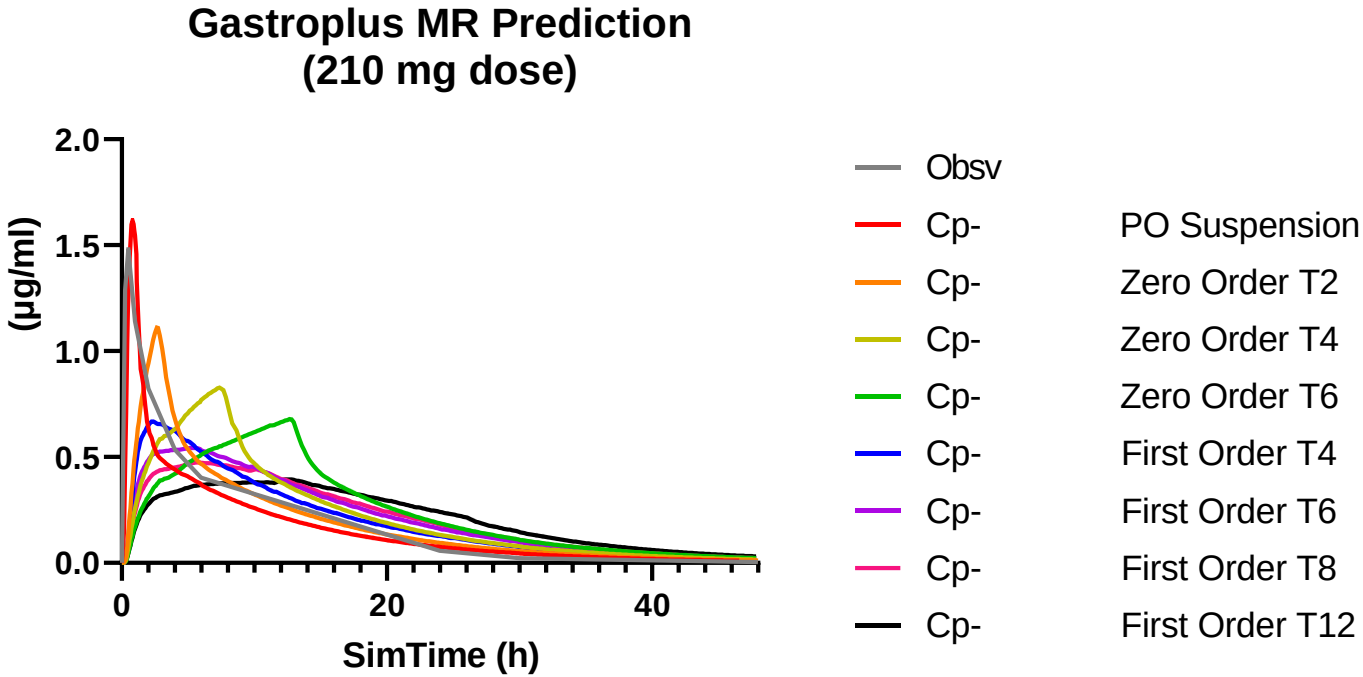
Exploring **simulated** MR profiles to guide formulation design





Zero order kinetics resulted in a delayed Cmax but IR like profile.
Whereas, first order kinetics results it a blunted Cmax, equal AUC, and longer target engagement

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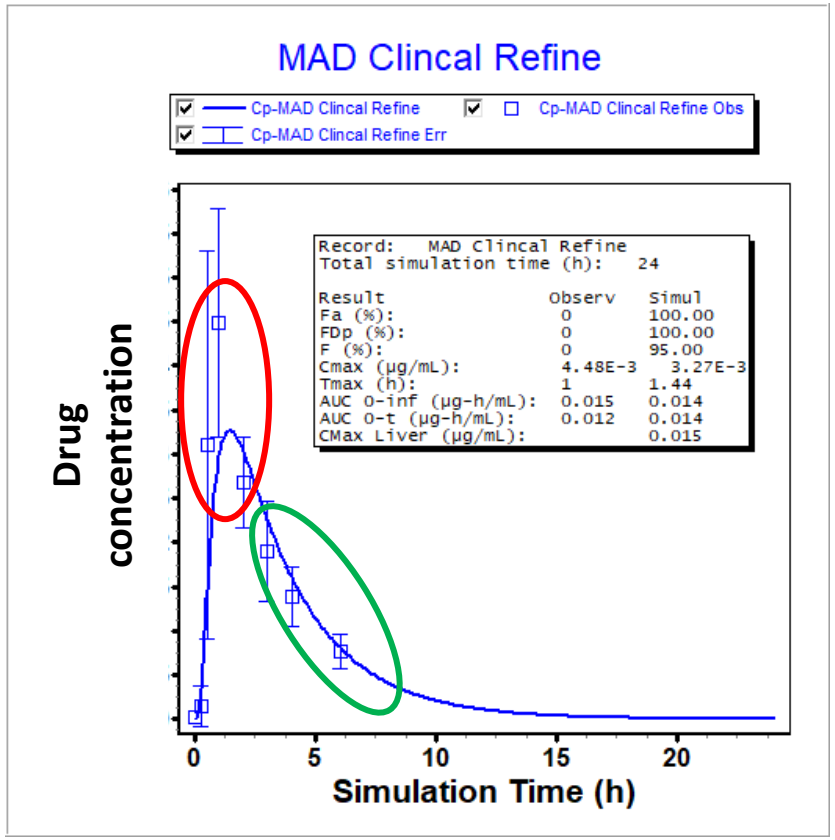
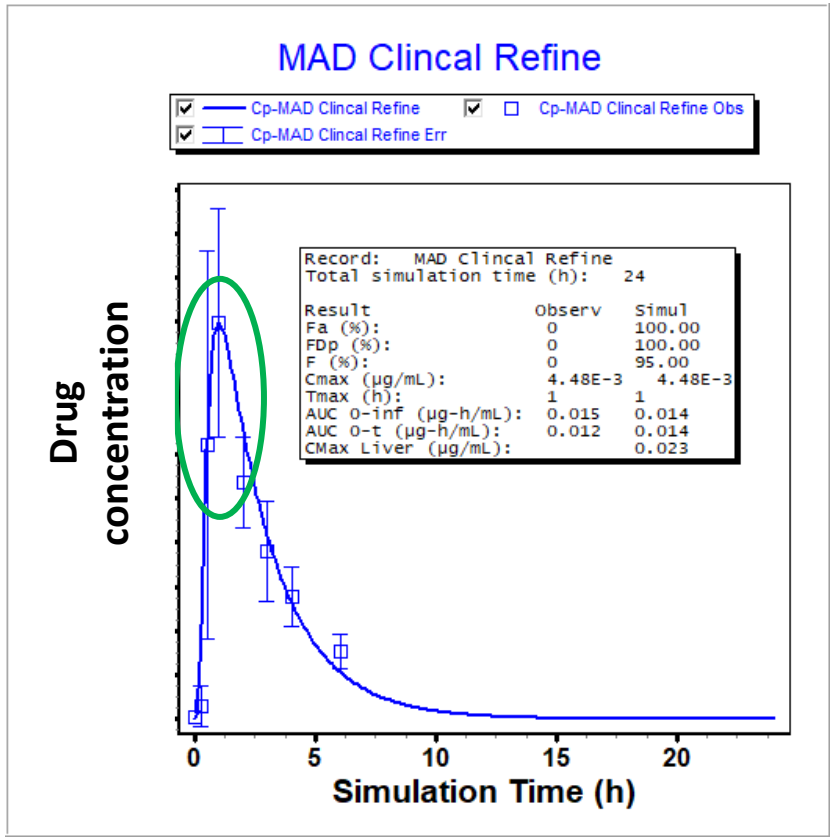
Refining PBPK model based on SAD/MAD data





SAD/MAD data was incorporated into the model but under predicted Cmax and Tmax
Refinement of permeability co-efficient resolved disconnect in model

Abbreviations – SAD: Single ascending dose; MAD: multiple ascending dose

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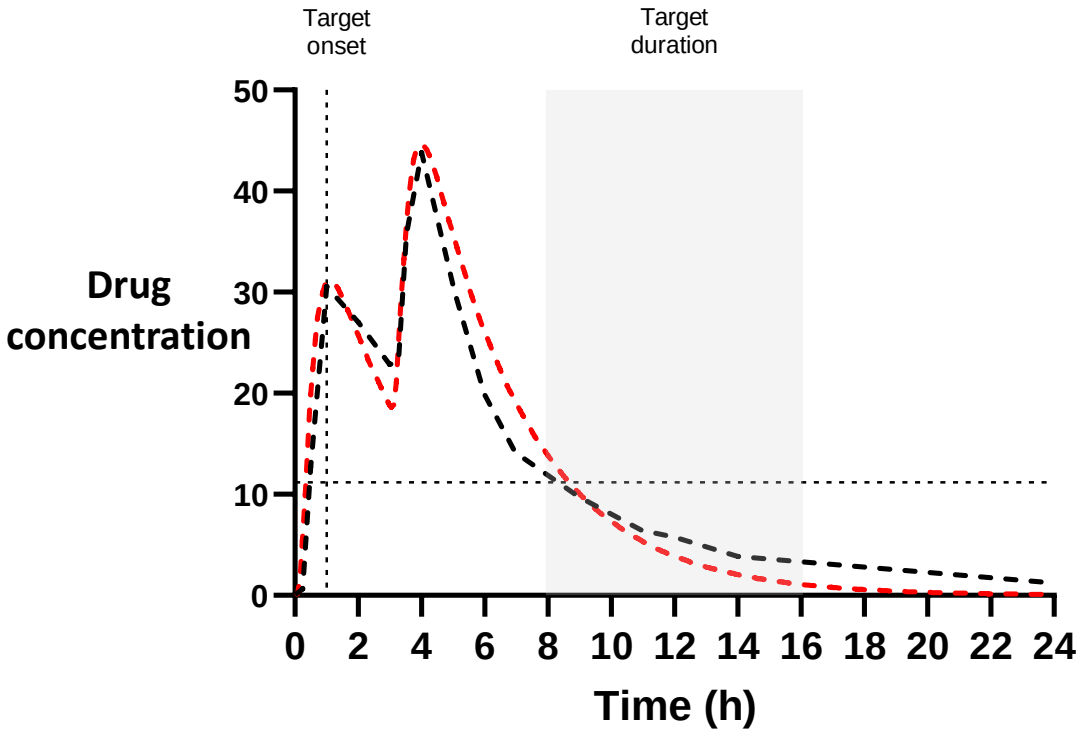
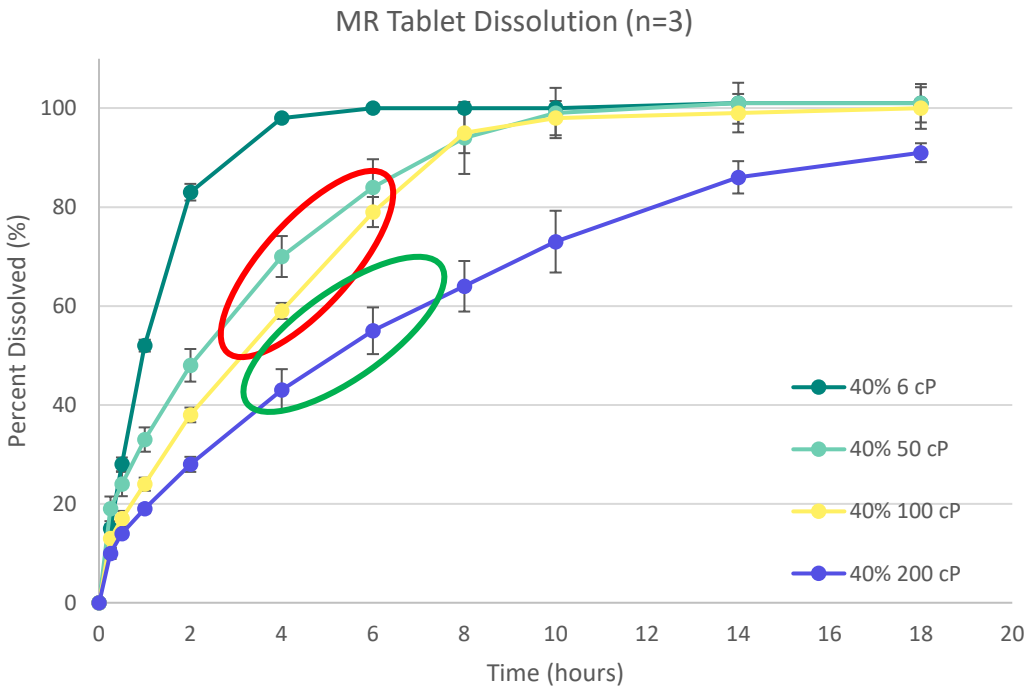
Fitting PBPK (GastroPlus) model to clinical observations



Clinical
G+
4 mg BID q3h

	Clinical	G+
Time (h)	Concentration	
1	30.5	30.9
4	43.8	44.5
9	9.7	10.1
14	3.8	2.1

Formulation design based on PBPK approach



Rotation Speed	100 rpm
Apparatus	USP I (40-mesh baskets)
Sampling Device	Autosampler (with offline HPLC analysis)
Sampling Times	15 min, 30 min, 1, 2, 4, 6, 8, 10, 14, 18 h
Medium	50 mM Phosphate Buffer, pH 6.8
Volume	500 mL
Bath Temperature	37°C

50cP formulation was borderline f2 dissimilar from 100cP formulation
50cP and 200cP showed sufficient dissimilarity in release profile

Abbreviations – MR: Modified release formulation; f2: *in vitro* dissolution similarity factor

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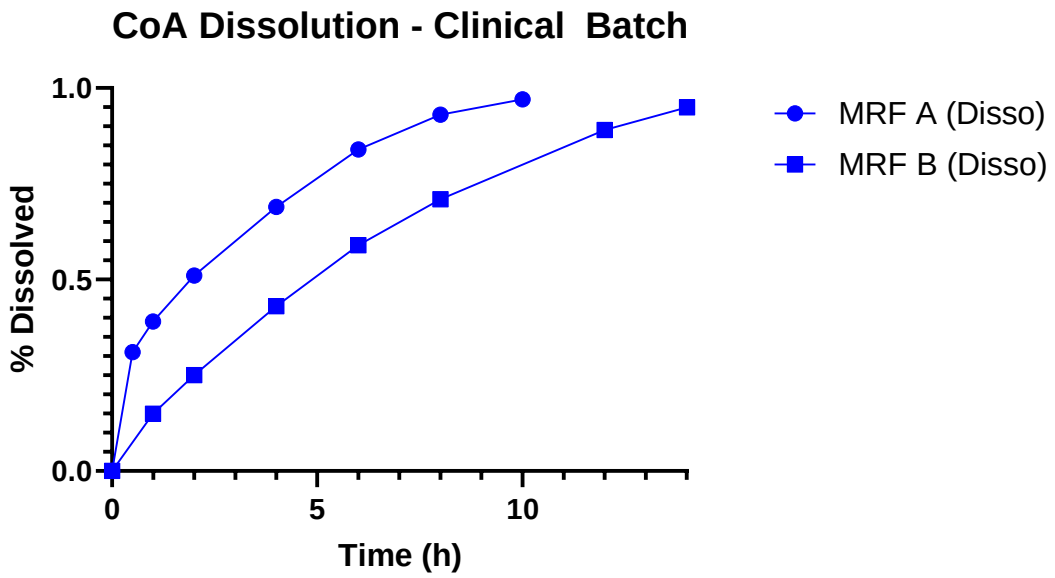
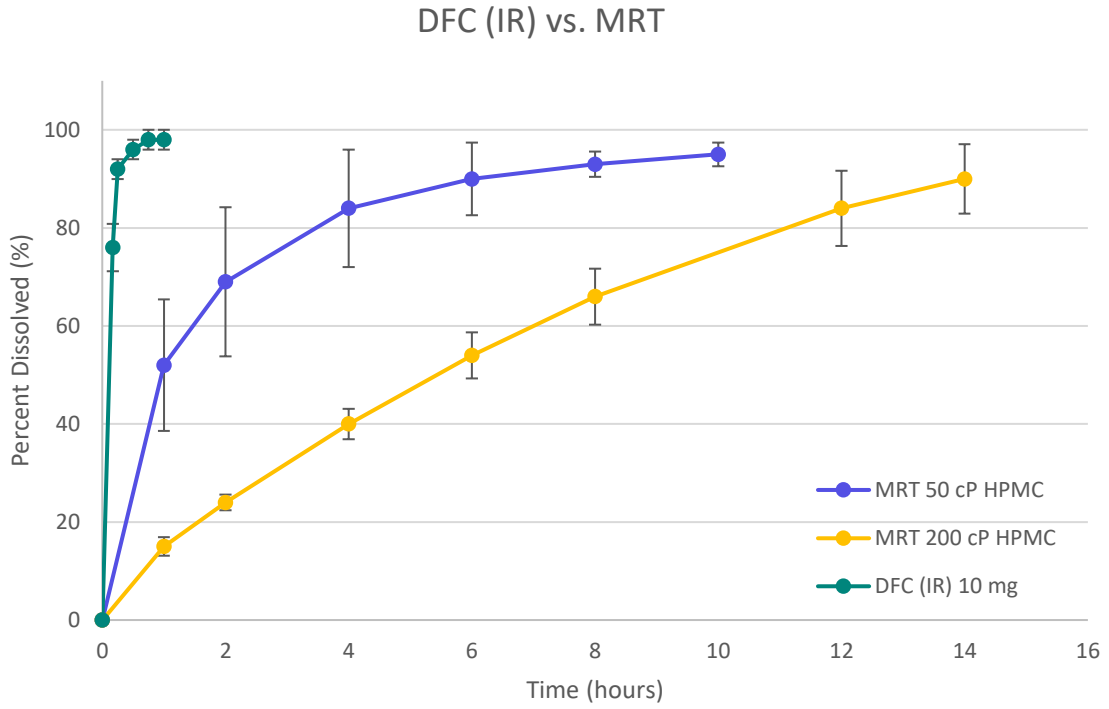
Formulation design based on PBPK approach



Rotation Speed	75 rpm
Apparatus	USP II (paddle with basket sinker)
Sampling Device	Autosampler
Sampling Times	1, 2, 4, 6, 8, 10, 14, 18 hours
Medium	50 mM Phosphate Buffer, pH 6.8
Volume	500 mL
Bath Temperature	37°C



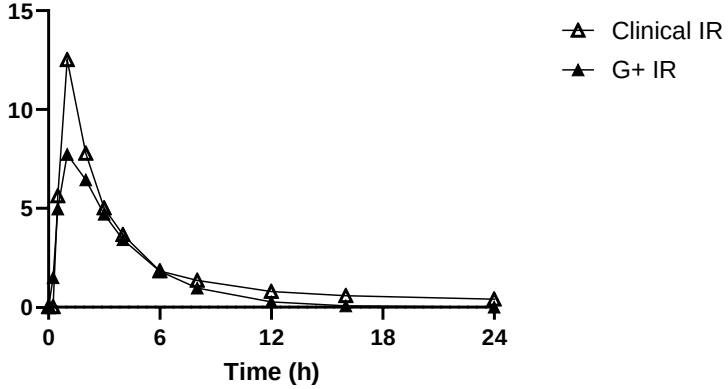
Clinical formulations showed dissimilarity in release profile between IR and MR

Abbreviations – MRF/MRT: Modified release formulation; DFC: dry filled capsule; IR: immediate release; CoA: Certificate of analysis

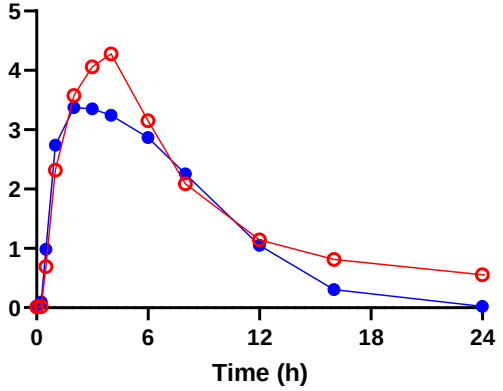
GastroPlus projections prior to study

Phoenix Deconvolution of Clinical PK data

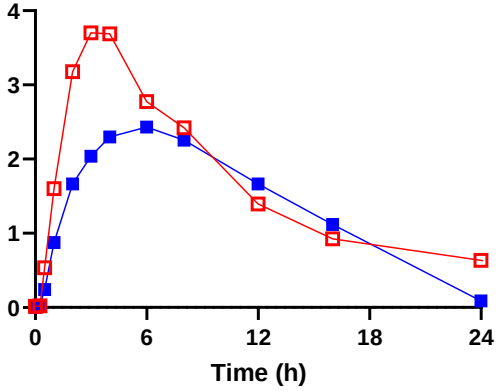
Drug concentration

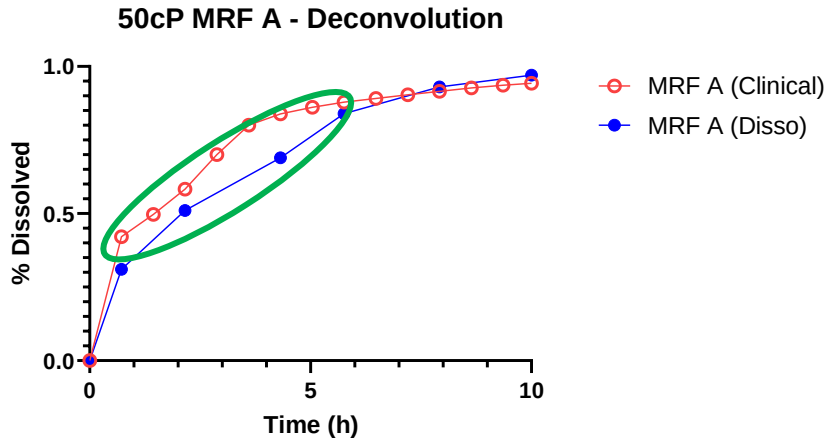


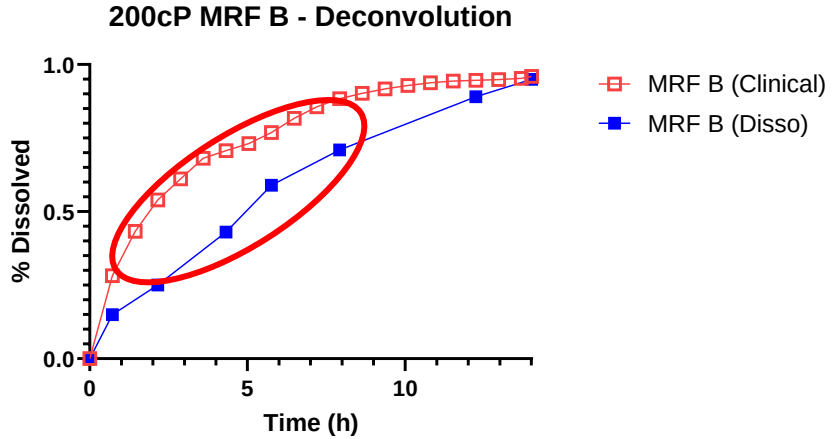
Drug concentration



Drug concentration







Abbreviations – MRF/MR: Modified release formulation; G+: GastroPlus;

Conclusions

- A MIDD approach can be used to successfully guide and design an MR formulation
- The success of a model approach is dependent on input parameters e.g. dissolution data should be interrogated appropriately
- 3Rs – MIDD can replace heavy reliance on *in vivo* models by supplementing with *in silico*

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Thank you