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Original Article

Application of Mechanistic Pharmacokinetic Model for the Optimization of Metformin Delayed Release Dosage Form for Intestinal Targeting

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ABSTRACT

Background: Metformin (MET) is a widely prescribed drug for managing Type 2 Diabetes Mellitus (T2DM). Despite the rich clinical experience and advantages, the clinical utility of MET in renal failure patients is limited because of the treatment-related side effects. A novel colon-targeted MET Delayed-Release (DR) dosage form could be a lucrative option for managing T2DM in renal failure patients. MET DR tablets have minimum systemic exposure and are believed to have the same efficacy as other formulations. Physiologically Based Pharmacokinetic (PBPK) modelling can be useful for drug product development, especially for new dosage forms for improving the safety, efficacy, and clinical applicability of off-patented generic drugs. **Objectives:** The current study aims to develop a PBPK model for Proto-type (PT) screening of MET DR tablets. **Materials and Methods:** MET PBPK model was developed based on the available literature data. Firstly, Intravenous (IV) and oral PBPK models of MET are developed and validated. The developed model was then used to predict the Bioavailability (BA) of PT MET DR tablets using Virtual Bioequivalence (VBE) trials. **Results:** The relative bioavailability of the MET DR tablet was about 20% when compared with other MET formulations. The results indicate that the DR formulation could be effective for reducing the BA and systemic exposure of the drug in chronic renal failure patients. **Conclusion:** PBPK modelling and VBE trials can successfully demonstrate the Pharmacokinetic (PK) parameters of PK formulations and the lower systemic exposure and site targeting of MET DR tablets could be useful for the management of T2DM in renal failure patients.

Keywords: Metformin, Delayed release, Renal failure, PBPK, Pharmacokinetics, Optimization.

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INTRODUCTION

MET, an oral hypoglycaemic agent belonging to the class of biguanides is the first-line agent for managing T2DM. According to the American Diabetes Association, MET can be given alone or in combination with other agents for the management of T2DM along with lifestyle modification and diet.[1] MET is historically connected to *Galega officinalis*, a guanidine-rich herb used to treat diabetic symptoms in Europe in the 1700s. MET was first synthesized in 1922 and approved for treating T2DM in Europe in 1958. In 1995, MET was introduced into the US market and is still the most prescribed drug for T2DM worldwide.[2] The anti-diabetic effect of MET is achieved by inhibiting hepatic glucose production, increasing peripheral glucose utilization, and increasing insulin-mediated glucose uptake. Additional benefits of MET therapy include cost-effectiveness, no weight gain, and non-hypoglycaemic effect.[3] MET has several other pharmacological actions aside from glucose reduction, including cardioprotective effects, antitumor activity, immunosuppressive effects, and anti-aging properties, and it also reduces the hyperandrogenic symptoms of polycystic ovarian syndrome.[4]

The currently available MET oral solid dosage forms are in the form of Immediate-Release (IR) and Extended-Release (XR) tablets. IR tablets of MET are available in various doses like 500, 850, and 1000 mg, whereas XR tablets are in 500, 750, and 1000 mg doses. The dosage regimen for the management of T2DM is not fixed and can be individualized based on effectiveness and tolerance level without exceeding the maximum daily dose of 2000 mg.[5] Even though the significance of MET therapy is known, patients are showing poor adherence and compliance to the dosing regimens and treatment. The major barriers to patient

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compliance are swallowing difficulty (dysphagia) due to the large tablet size and rough coatings; and Gastrointestinal (GI) side effects such as abdominal discomfort, diarrhoea, cramps, nausea, and vomiting.[6] MET use is limited in conditions characterized by high plasma concentrations, such as renal and hepatic impairment, because of higher plasma drug concentration; it leads to MET-associated Lactic Acidosis (LA) (a condition of elevated blood lactate level). The United States Food and Drug Administration (USFDA) recommends that before starting MET therapy, the glomerular filtration rate should be estimated and MET will contraindicate in patients with a glomerular filtration rate below 30 mL/min/1.73 m^2. The maximum feasible dose in such patients is between 250 to 500 mg.[7]

IV MET administration has no direct effect on the fasting blood glucose level, insulin, and glucagon production in healthy individuals compared to oral administration. This could be linked with the hypothesis of local GI action of MET rather than systemic drug concentration.[8] In a study on T2DM patients with MET on and off therapy, it was shown that withdrawal of MET is associated with reductions in gut hormones such as Glucagon-Like Peptide-1 (GLP-1), gastric inhibitory polypeptide, and peptide tyrosine-tyrosine, which confirms that MET has a gut-based local effect and could be used as a novel approach for the treatment of T2DM.[9] The ileum part of the intestine predominantly contains L cells, which are responsible for the secretion of incretin hormones. These hormones play an important role in blood sugar regulation by increasing insulin secretion and decreasing glucagon release.[10] MET improves GLP-1 concentration in the gut either by a direct effect on L cells or by reducing dipeptidyl peptidase-4 activity, an enzyme responsible for the degradation of GLP-1. MET-associated alteration of the bile acid pool also results in GLP-1 secretion by stimulating bile acid receptors in the L cells.[11] The absorption of MET is mainly taking place from the duodenum and jejunum. Targeting the drug release onto the ileum is achieved by formulating DR MET tablets. Site targeting can elevate its glucose-lowering efficacy with less systemic intolerance and GI side effects when compared with MET IR and XR formulations. Another important objective of delaying MET release is minimizing the systemic exposure, thereby reducing the incidence of LA in renal-impaired patients, and providing a diabetic treatment option for chronic kidney failure patients.[12]

The formulation and manufacturing of MET DR tablets are reported in the literature. The primary objective of MET DR is to reduce BA without compromising the therapeutic efficacy, thereby reducing GI intolerance and LA.[13] MET DR is studied in several clinical trials, including phases 1 and 2 studies. The phase 1 study consists of a comparative BA of MET DR with currently marketed formulations of IR and XR tablets in healthy volunteers. The results of the study proved that MET DR had a lower BA than IR and XR MET formulations. The phase 2 clinical trial was a placebo-controlled, dose-ranging study in patients with T2DM over 12 weeks. In this study, the patients were randomly assigned to receive either MET DR (600, 800, or 1000 mg Once Daily), or placebo, or MET XR (1000 or 2000 mg Once Daily). The treatment with MET DR produced a clinically significant reduction in the blood glucose level and was well tolerated when compared with MET XR tablets.[14] Currently, a pivotal phase 3 clinical trial of MET DR is ongoing on T2DM patients with normal renal function and stage 3 chronic kidney disease to ensure the safety and efficacy of the product.[15]

PBPK models are mechanistic mathematical models, which describe the PK properties of drug substances and drug products.[16] The main advantage of this model is that, by using physiologically integrated mathematical equations, it can predict the *in vivo* PK of the drug, which, subsequently minimizes the preclinical and clinical studies and is also useful for life cycle management and regulatory requirements. Other widely used applications of PBPK models are the prediction of drug-drug interactions, dose and dosage regimen, and human PK from preclinical PK data.[17] PBPK models are composed of several compartments that represent the various organs and tissues of the body that are connected by circulating blood systems. The tissue volume and blood flow rate define each compartment. The drug's PK in these compartments is described by a series of differential equations.[18] PBPK modelling for MET was developed to predict the PK profiles in diabetic patients, pregnant women, geriatrics, and impaired renal populations.[19,20] The present study aims to develop a PBPK model for MET DR tablets for predicting the BA of the dosage form for managing T2DM in renal failure patients.

MATERIALS AND METHODS

Software and Data Source

The PBPK model for MET was developed using the commercially available GastroPlus™ version 9.8.3 (Simulation Plus Inc.), with the Advanced Compartmental Absorption Transit (ACAT™) module, and the PBPKPlus™ module. The physicochemical properties of drug substances and clinical PK data were collected from literature using search engines such as Google, Web of Science, and PubMed and the keywords used are "Metformin", "Biopharmaceutics", "Chronic kidney failure", "Lactic acidosis", "PBPK", and "Clinical pharmacokinetics". The *in silico* physicochemical properties of the drug were predicted using the ADMET Predictor™ module of GastroPlus™. Clinical PK study data were digitized using WebPlotDigitizer version 4.6.

Physicochemical Properties of the Drug Substance

MET is a basic drug that exists as a salt of hydrochloric acid. It is an odourless, white, crystalline, hygroscopic powder with the molecular formula $C_4H_{11}N_5 \cdot HCl$.[21] The physicochemical properties of a drug substance are the important input parameters to build the PBPK modelling of the drug. Lipophilicity and molecular weight are the major parameters that determine the

Table 1: Physicochemical and biopharmaceutical characteristics of the drug.

Sl. No.	Parameters	Values
1	Molecular weight	129.17 (free base)
2	Log P	-0.82
3	pKa	10.39
4	Protein binding (%unbound)	0.04% (negligible)
5	Solubility	Exceeds 100 mg/mL in water, 0.1 N HCl, pH 4.5, pH 6.8, and pH 9.5 phosphate buffers
6	Particle size (micron)	100 µ
7	Blood-to-plasma ratio	1.36
8	Mean precipitation time	900 s
9	Drug particle density	1.2 g/mL (ADMET Predictor)
10	Diffusion coefficient	$0.75x10^{-5}$ cm^2/s (ADMET Predictor)
11	Permeability	Caco2 Papp-$5x10^{-4}$ cm/s (optimized) Papp-$6.67x10^{-6}$ cm/s (optimized)
12	ASF model	Opt log D Model SA/V 6.1(ADMET Predictor)
13	First-pass effect	No
14	Enterohepatic circulation	No
15	Biliary excretion	No
16	PK linearity	No
17	Oral BA (%)	50-60

membrane permeability of the compound. In contrast, aqueous solubility determines the compound's absorption from the GI tract, which in turn depends on the pKa of the compound.[22] The physicochemical parameters of the drug were summarised in Table 1.[23,24]

Biopharmaceutics and PK

MET has a high pH-independent aqueous solubility of >100 mg/mL at room temperature. The highest single dose of 1000 mg is soluble in 250 mL of aqueous media over the physiological pH range. The maximum therapeutic dose of 3000 mg is also soluble across the physiological pH range of 1.2 to 7.2. Hence, it is designated as a highly soluble drug in accordance with the Biopharmaceutical Classification System (BCS). The predicted pKa value of MET is 10.39 and experimental data demonstrates two acid dissociation constants at pH 2.8 and 11.5. *In silico* and experimental pKa values indicate that the drug has a greater extent of ionization and hence high solubility across the physiological pH range. The log *p* value of MET is -1.83, which indicates that the drug has poor compound lipophilicity and passive diffusion across the biological membrane. The delayed Tmax of 3 hr after oral IR formulation implies that the drug has a slow absorption rate constant and this could be correlated with its physicochemical properties. MET is poorly absorbed from the stomach. The drug has an absolute oral BA of 50-60% and the rest of the drug is excreted as an unchanged drug in faeces. MET has a longer urinary excretion rate and a long terminal half-life of about 20 hr. MET shows dose-dependent absorption and hence lacks dose proportionality from 500 to 1500 mg. The lack of dose proportionality could be lined with carrier-mediated absorption process and saturation kinetics of the transporter systems, which results in less extent of absorption with high dose. The Caco2 cell permeability data of MET implies that the drug has poor permeability (i.e., lower than metoprolol). Food reduces the rate and extent of MET absorption, with 40% and 25% reductions in C_{max} and AUC, respectively. MET is a substrate for the organic cation transporters, plasma membrane monoamine transporter, thiamine transporter-2, serotonin transporter, and high-affinity choline transporter. The organic cation transport system plays an important role in the absorption, distribution, and elimination of MET.[25,26] The biopharmaceutical and PK characteristics of MET were summarised in Table 1.

PBPK Modelling

Sixteen clinical PK studies published in the literature were collected and eleven were used for the development and validation of the PBPK model for MET. Four IV PK studies were considered for model development from the reported literature. Oral PK data were extracted from different pharmaceutical dosage forms such as IR, XR, and DR dosage forms. The patient demographics of all the clinical studies were summarised in Table 2.[14,27-39]

IV PK Model Development and Validation

IV PK data were used to understand the distribution and elimination parameters. Demographic information such as age, body weight, sampling times, and methodology were obtained from the literature. IV PK data were used to select the suitable PK and PBPK models using Gastroplus 9.8.3 software. Based on the best fit and prediction errors, the optimized model was selected. The selected model was then used for the development of the oral absorption model.

Oral Absorption Model Development and Validation

The oral PK absorption model was built based on the PK data reported in the literature. Numerical data were obtained from the published graph using WebPlotDigitizer. The study demographic parameters such as age, sex, and body weight were incorporated

Table 2: Pharmacokinetic studies used for MET PBPK model development and validation.

Sl. No.	Formulations	Dose and Dosage	Subjects	Age (Y)	B W (kg)	Sex ratio	Condition
1	IV infusion	500 mg	16	22-29		5 M, 11 F	Fasting
2	IV infusion	500 mg	3	37.6	60.3	1 M, 2 F	Fasting
3	IV infusion	250 mg	4	32.5	70.25	4 M	
4	IV bolus	1000 mg	5	44.8	72	4 M, 1 F	Fasting
5	Oral IR tablet	250 mg	10	20-45		10 M	Fasting
		1000 mg	10	20-45		10 M	Fasting
6	Oral IR tablet	500 mg T	28	28	63.31	28 M	Fasting
		500 mg R	28	30	63.31	28 M	Fasting
7	Oral tablet	500 mg GR-6	14	37	74.48	7 M, 8 F	Fed
		500 mg GR-9	14	37	74.48	7 M, 8 F	Fed
		500 mg T	15	37	74.48	7 M, 8 F	Fed
8	Oral tablet	500 mg XR OD	16	27	71	9 M, 7 F	Fed
		1000 mg XR OD	16	27	71	9 M, 7 F	Fed
		1500 mg XR OD	16	27	71	9 M, 7 F	Fed
		2000 mg XR OD	14	27	71		Fed
		1000 mg IR BID	15	27	71		Fed
9	Oral IR tablet	250 mg IR T	21	21-55		21 M	Fed
		250 mg IR R	21	21-55		21 M	Fed
10	Oral IR tablet	850 mg T	24	21.2	60.5	10 M, 14 F	Fasting
		850 mg R	24	21.2	60.5	10 M, 14 F	Fasting
11	Oral IR tablet	500 mg IR	5	42	63.4	2 M, 3 F	Fasting
12	Oral IR tablet	1000 mg	16	22-29		5 M, 11 F	Fasting
13	Prandimet	2/500 mg	55				Fasting
		1/500 mg	55				Fasting
		2+500 mg	55				Fasting
14	Actoplus met	15/500 mg	62	18-55			Fasting
		15+500 mg	62	18-56			Fasting
		15/850 mg	62	18-56			Fasting
		15+850 mg	62	18-56			Fasting
15	Janumet	50/500 mg	24			8 M, 16 F	Fasting
		50+500 mg	24			8 M, 16 F	Fasting
		50/1000 mg	24			8 M, 16 F	Fasting
		50+1000 mg	24			8 M, 16 F	Fasting
16	Oral tablet	1000 mg IR BID	20	32.2	89	14 M, 6 F	Fed
		1000 mg DR BID	20	32.2	89	14 M, 6 F	Fed
		500 mg DR BID	20	32.2	89	14 M, 6 F	Fed
		2000 mg XR OD	20	32.2	89	14 M, 6 F	Fed

OD: Once daily; BID: Twice daily; T: Test; R: Reference; GR-6: Gastro-retentive 90 % drug release in 6 hours; GR-9: Gastro-retentive 90 % drug release in 9 hours.

for model building. MET is generally administered with food; hence, a high-fat, high-calorie meal menu was chosen to build the model. PK rate constants obtained from the validated IV PK model were used to predict the oral profile of MET dosage forms. Opt log D Model SA/V 6.1 was used as an absorption scale factor for human-fed state physiologies. The developed oral PK model was fine-tuned with pharmaceutical characterization data such as mean particle size of active pharmaceutical ingredient, particle

density, and drug solubility. Population PK simulations with 55 subjects were carried out for MET IR tablets 500 mg once daily (IR 1 and IR 2) and 16 and 20 subjects' simulations for MET IR tablets 1000 mg once daily and 1000 mg twice daily, respectively. The developed model was applied to predict the XR and DR dosage forms for MET. The plasma profiles were mechanistically convoluted to get *in vivo* dissolution profiles. The obtained *in vivo* release profiles were used as dissolution profiles for modelling and simulations. Dissolution profiles were generated for 500 mg and 1000 mg for XR tablets and 500 mg for DR tablets. The dissolution profiles were fitted to the Weibull model and modelled data were used for PK modelling and simulations. Population simulation studies were carried out with MET XR tablets 1000 mg (twice daily; 30 subjects), MET XR tablets 500 mg (twice daily; 30 subjects), MET DR tablets 1000 mg (twice daily; 20 subjects), and MET DR tablets 500 mg (twice daily; 20 subjects). Further, the predicted PK parameters (C_{max}, T_{max}, and AUC) were compared with the observed parameters from respective PK studies. All developed models were validated.

VBE trials for the proposed MET DR tablets

The developed PBPK model was then applied to predict the PK parameters of the proposed DR MET tablets for the management of T2DM in chronic renal failure patients. The dissolution data obtained from the literature were integrated with oral PBPK model data and used to build the PBPK model for DR tablets. The patient demographics and other input parameters for these models were taken from the published phase 2 clinical data. The developed model was then validated by using PK data reported in phase 2 clinical studies. Four VBE trials were conducted to estimate the *in vivo* PK and BE of the MET DR tablets. MET 1000 mg IR tablets (twice daily) were used as a reference product, and three PT MET 900 DR tablets with different drug release profiles were used as test products. The description of the test and reference group is given in Table 3. Each trial was designed in two period, two sequence, two treatments, randomized, single-dose, cross-over, VBE simulations with PK endpoints in healthy subjects under fed conditions.

Another VBE trial was conducted using PT 3 (Target profile) MET DR tablets as the test group and MET 500 mg IR tablets as the reference group. The objective of this study is to compare the PK of PT 3 MET DR tablets vs MET 500 mg IR tablets. The maximum daily dose of MET for the management of T2DM in chronic renal failure patients is 500 mg. The dose of 500 mg in the reference group was chosen based on the recommendations of the American Diabetes Association (i.e., a maximum dose of 500 mg MET for renal failure patients). The number and demographics of virtual subjects were taken similarly to the *in vivo* Bioequivalence (BE) studies. Average BE analysis was performed for the two sequence, two treatment, cross-over, VBE simulation. The sensitivity for determining the formulation differences was accessed by comparing the PK parameters such as C_{max}, $AUC_{0-t,}$ and $AUC_{0-\infty.}$ The 90% confidence intervals for the geometric mean ratios of test and reference are between 80% and 125%.

RESULTS AND DISCUSSION

IV PK Model Development and Validation

MET IV PBPK model was developed using the reported plasma concentration-time profile from the literature. The model was optimized and validated for better predictability. The PK data after 250 mg, 500 mg, and 1000 mg of MET IV dose was screened for various models. Two compartment models was selected as the best-fitted model. The predicted and observed PK parameters of various MET IV doses after simulation were reported in Table 4. Table 5 summarizes the PK parameters of the validated model. Figure 1 represents the predicted PK data along with the observed data of MET IV after population simulation.

Oral Absorption Model Development and Validation

The oral PBPK model was developed using IR dosage forms. 500 mg and 1000 mg IR tablets were chosen as dosage forms. Both once-daily and twice-daily dosage regimens were modelled to understand the effect of the residual unabsorbed drug on subsequent dosage administration. All four oral data were validated using the oral absorption model and IV disposition kinetics model. Table 6 illustrates the PK parameters of all oral IR absorption models and Figure 2 (a-d) shows the plasma concentration profile of all IR doses after simulation. Population PK trials were performed between two 500 mg IR tablets (Sr

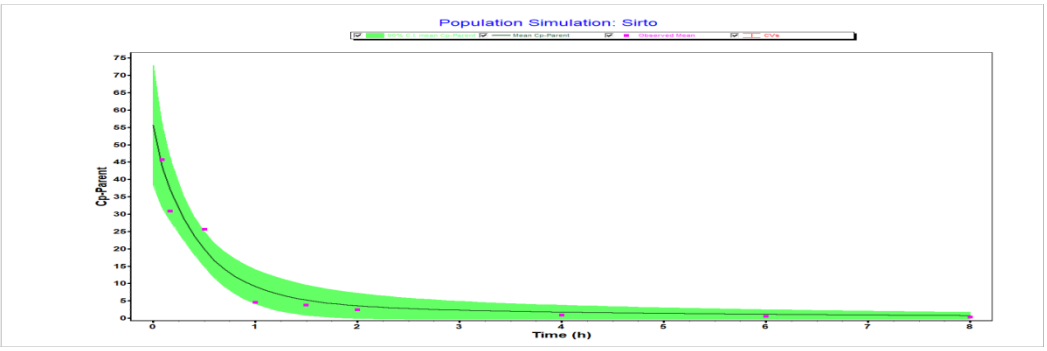

Figure 1: Plasma concentration time profile of MET IV infusion after population simulation.

Table 3: VBE trials of MET DR tablets.

Sl. No.	Trial objective	Formulations	Test	References	Sample size	Study design
1	PT 1 (Fast profile)	PT 1 and IR	PT 1	MET IR	20	Cross-over
2	PT 2(Slow profile)	PT 2 and IR	PT 2	MET IR	20	Cross-over
3	PT 3(Target profile)	PT 3 and IR	PT 3	MET IR	20	Cross-over

Table 4: IV PK parameters after PBPK simulation.

IV Dose	C_{max} (ng/mL)				$AUC_{0-\infty}$ (ng.h/mL)				AUC_{0-t} (ng.h/mL)			
	OBS	DIG	PRE	% PE	OBS	DIG	PRE	% PE	OBS	DIG	PRE	% PE
250 mg, infusion	-	7.7	6.7	13	-	5.7	5.3	7	-	5.5	5.2	5.4
500 mg, infusion	-	15.4	13.1	15	-	13.6	12.3	9.5	17.6	13.7	12.6	8.0
1000 mg, bolus	-	-	53.7	-	-	35.1	38.3	9.1	-	33.9	35.8	5.6

OBS: Observed data; DIG: Digitized data; PRE: Predicted error; % PE: % Prediction error.

Table 5: PK parameters of validated IV PK model.

PK parameters	Model output	PK parameters	Model output
Model	2 Compartmental	Vc (L/kg)	0.19721
B/P ratio	1.36	$T_{1/2}$ (hr)	2.48
Plasma %Fup	99.6	K_{12} (1/hr)	0.47143
Adj. Plasma % Fup	99.59	K_{21} (1/hr)	0.37749
Cl; (L/h/kg)	22.925	V_2 (1/kg)	0.24629

B/P ratio: Blood to plasma ratio; Cl: Clearance; $T_{1/2}$: Biological half-life; K_{12} and K_{21}: Elimination rate constants; Vc and V_2: Volume of distribution.

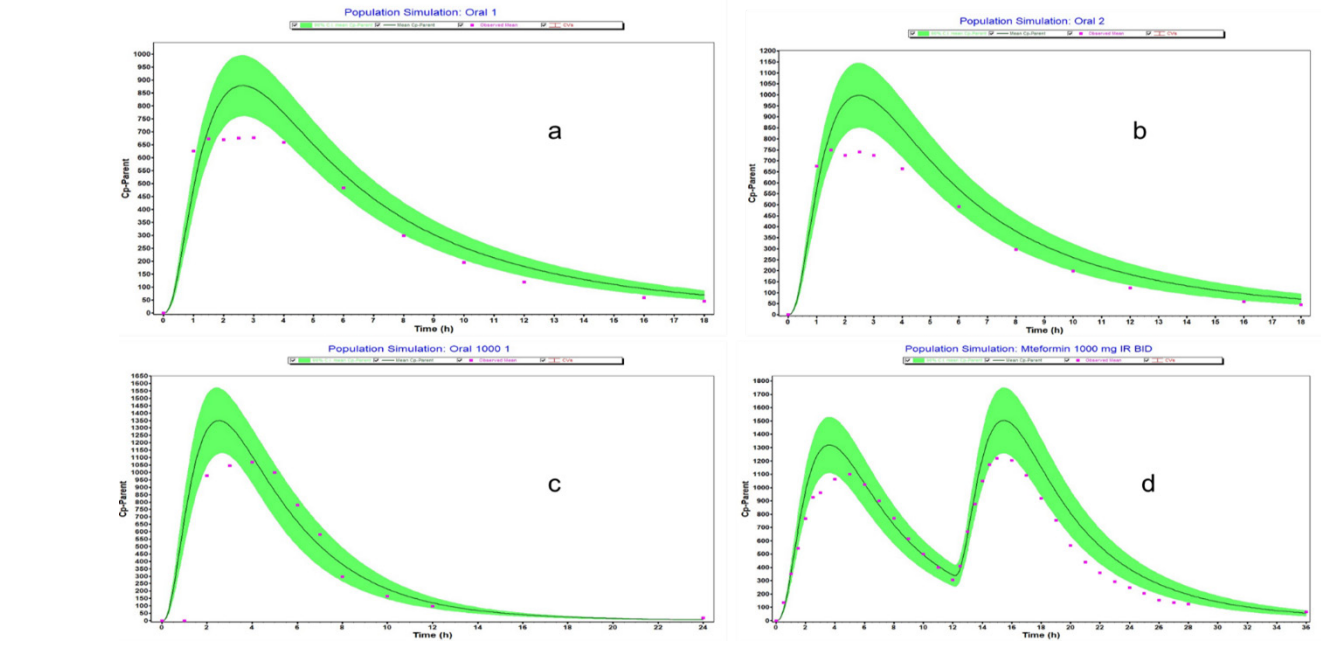

Figure 2: (a) Plasma concentration time profile of MET 500 mg IR tablet after population simulation, (b) Plasma concentration time profile of MET 500 mg IR tablet after population simulation, (c) Plasma concentration time profile of MET 1000 mg IR tablets after population simulation, (d) Plasma concentration time profile of MET 1000 mg IR BID tablets after population simulation

No: 1 and 2 of Table 6). The population simulation results were compared with reported values and summarized in Table 7. The %T/R ratios for all PK parameters are well within the limit. The predictive outcomes of the oral PK model reveal that the model is robust and prediction errors are well within the regulatory limit.

Dissolution data obtained from the mechanical convolution method was used to predict the PK properties of XR and DR formulations. All other model parameters are fixed, except the dissolution profiles. Figure 3a and 3b show the convoluted % *in vitro* drug release of both MET XR and DR, respectively.

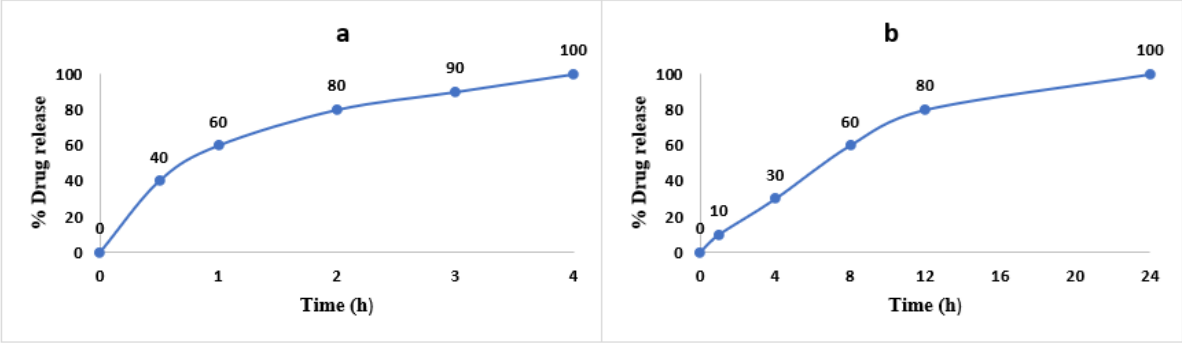

Figure 3: (a) *In vitro* dissolution profile of 500 mg MET XR tablets, (b) *In vitro* dissolution profile of 500 mg MET DR tablets

Table 6: Oral IR, XR, and DR PK parameters after PBPK simulation.

Sl. No.	Oral IR, XR, DR Dose and Dosage	C_{max} (ng/mL)				$AUC_{0-\infty}$ (ng.h/mL)				AUC_{0-t} (ng. h/mL)			
		OBS	DIG	PRE	% PE	OBS	DIG	PRE	% PE	OBS	DIG	PRE	% PE
1	500 mg OD IR (*n*=55)	792	678	771	2.6	5741	5869	5520	3.8	5633	5511	5244	4.7
2	500 mg OD IR (*n*=55)	816	748	849	-4.0	5877	6070	5787	1.5	5756	5712	5534	3.8
3	1000 mg OD IR (*n*=16)	1180	1070	1314	-11.3	8300	7169	7453	10.2	-	7028	7416	-
4	1000 mg BID IR (*n*=20)	1328	1220	1364	-2.7	-	19700	19660	-	18710	18880	19390	-3.6
5	1000 mg XR (*n*=30)	1301	1247	1529	-17.5	-	15660	12270	-	14182	14730	12060	14.96
6	500 mg XR (*n*=30)	812	769	868	-6.8	-	15760	12430	-	15260	15320	12000	21.36
7	500 mg DR (*n*=20)	607	436	551	9.2	-	6741	6957	-	6160	6539	6821	-10.7
8	1000 mg DR (*n*=20)	905	742	817	9.7	-	12880	10350	-	9010	9367	10150	-12.65

OBS: Observed data; DIG: Digitized data; PRE: Predicted error; % PE: % Prediction error; OD: Once daily; BID: Twice daily.

Table 6 represents the PK parameters of developed models of XR and DR tablets, and the plasma concentration profile of XR and DR tablets after population simulation is given in Figure 4 (a-d). The model validation data demonstrates oral PK models for all the dosage forms (IR, XR, and DR) could be used for predicting the BA of new PT formulations using pharmaceutical and dissolution data.

VBE Trials for the Proposed MET DR Tablets

MET DR 900 mg tablets are designed to target the drug release in the ileum for localized therapeutic activity in the GI tract. The localized therapy reduces the systemic exposure of the drug with a targeted relative BA of 20% when compared with MET IR tablets. The dosage form with reduced BA shall be used as an alternative therapeutic option for the management of T2DM in chronic renal failure patients. The hypothetical dissolution data was integrated with the validated oral PK model. MET being a pH-independent high soluble drug, the minimum influence of pH on drug dissolution shall be anticipated. However, DR formulations are usually fabricated with pH-dependent polymers. Hence, the influence of pH on drug release from DR formulation is based on the buffer species, buffering capacity, and pH of the dissolution medium. The proposed dissolution method for hypothetical dissolution data is derived from product-specific guidance documents from the Office of Generic Drugs, USFDA.[40] Table 8 shows the dissolution profiles of three PT formulations. Population simulations were carried out using 20 healthy subjects and Table 9 shows the results of the population simulation. The PK profiles of three MET DR PT formulations were predicted using the validated PK model reported in the above-mentioned section. Figure 5 (a-c) shows the plasma concentration-time profile of all the 3 PT MET DR tablets after population simulation. PT 3 was targeted to get 20% of the relative BA. The simulation results demonstrate that the relative predicted BA of 19.9% when compared with MET IR 1000 mg tablets administered twice daily. The results indicate that the DR formulation could be effective for reducing the BA and systemic exposure of the drug in chronic renal failure patients. Clinical trials are required to demonstrate the safety and efficacy of the DR formulation in the management of T2DM in renal failure patients

The second VBE trials were conducted to establish the comparative PK between the 500 mg IR tablets once daily vs 900

Table 7: Population simulation results of MET IR tablets.

PK metric	LCI 90% CI			%T/R			UCI 90% CI		
	OBS	PRE	%Error	OBS	PRE	%Error	OBS	PRE	%Error
C_{max}	98.49	95.9	2.6	103.11	110	-6.6	107.96	126	-16.7
AUC_{∞}	98.53	89.54	9.1	102.39	104.8	-2.3	106.40	122.7	-15.3
AUC_{t}	98.22	90.7	7.6	102.19	105.5	-3.2	106.31	122.8	-15.5

OBS: Observed data; PRE: Predicted data.

Table 8: *In vitro* dissolution data of proposed DR tablets.

Time (hr)	PT 1(Fast)	PT 2 (Slow)	PT 3 (Target)
0.0	0.0	0.0	0.0
1.0	10.0	10.0	10.0
4.0	40.0	30.0	30.0
8.0	80.0	50.0	60.0
12.0	100.0	70.0	80.0
24	-	100.0	100.0

Table 9: PK parameters of IR tablets and proposed DR tablets after population simulation *(n=20).*

Sl. No.	Formulations	C_{max} (ng/mL)	AUC_{0-t} (ng. h/mL)	% T/R C_{max}	% T/R AUC_{0-t}	% T/R AUC_{0-t} (Dose normalized)
1	1000 mg IR BID	1328	18710	-	-	-
2	PT 1 (900 mg DR BID)	302	4151	22.7	22.2	24.6
3	PT 2 (900 mg DR BID)	166	2340	12.5	12.5	13.90
4	PT 3 (900 mg DR BID)	243	3718	18.3	19.9	22.07

BID: twice daily.

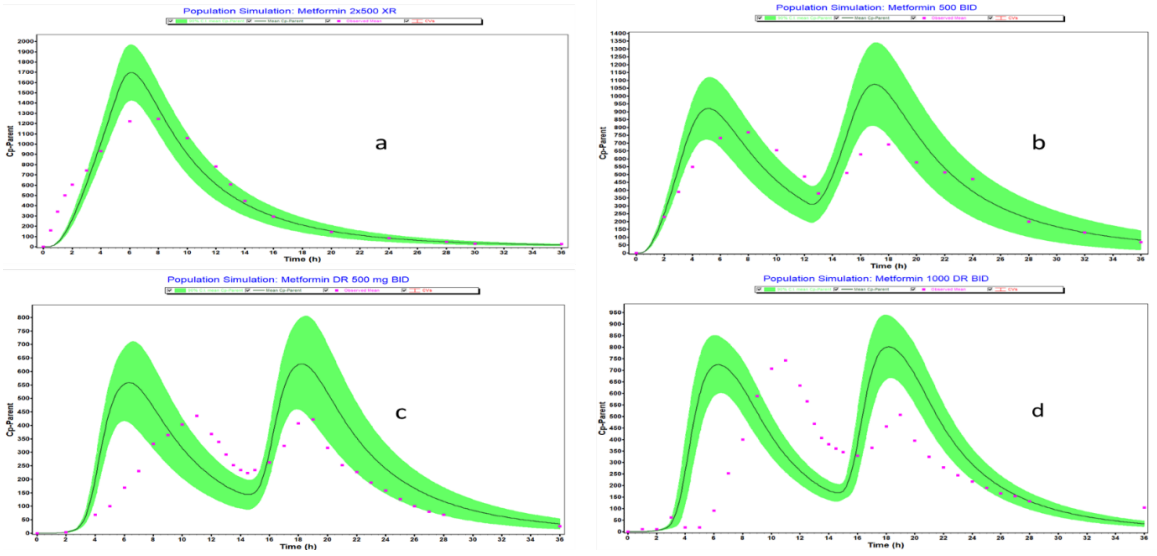

Figure 4: (a) Plasma concentration time profile of MET1000 mg XR tablet after population simulation, (b) Plasma concentration time profile of MET 500 mg XR BID tablet after population simulation, (c) Plasma concentration time profile of MET 500 mg DR tablet after population simulation, (d) Plasma concentration time profile of MET 1000 mg DR tablet after population simulation

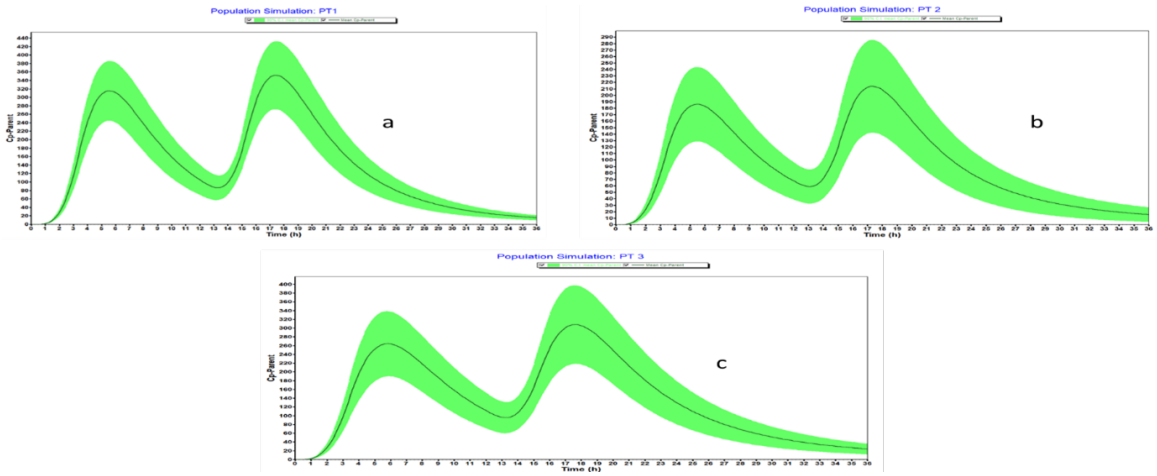

Figure 5: (a) Plasma concentration time profile of PT 1 after population simulation, (b) Plasma concentration time profile of PT 2 after population simulation, (c) Plasma concentration time profile of PT 3 after population simulation.

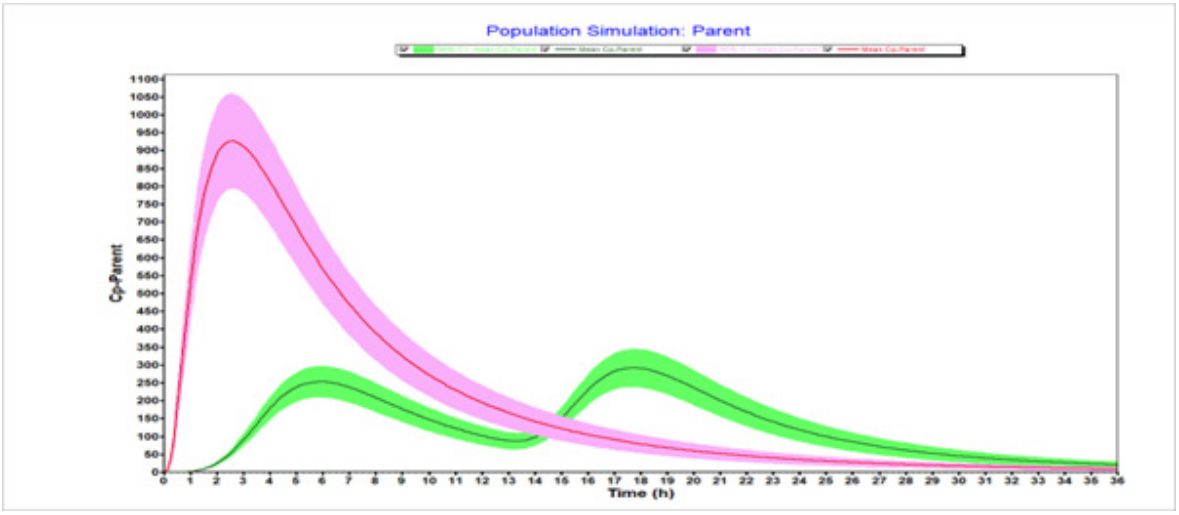

Figure 6: Plasma concentration time profile of PT 3 and IR after virtual BE trial.

Table 10: PK parameters of IR tablets and PT 3 DR tablets after VBE trials.

Sl. No.	Formulations	C_{max} (ng/mL)	AUC_{0-t} (ng. h/mL)	AUC_{0-I} (ng. h/mL)	% T/R C_{max} (CI-90%)	% T/R AUC_{0-t}	% T/R AUC_{0-i}
1	500 mg IR OD (*n*=55)	789	5733	5863	29.3 (25-34)	57.6 (48-69)	58.5 (49-70)
2	PT 3 (900 mg DR BID) (*n*=55)	231	3302	3428			

OD: Once daily; BID: Twice daily.

mg DR tablets twice daily. The 500 mg IR once daily was chosen based on the maximum daily recommendation dose for type 2 diabetic patients with renal failure. The results of VBE studies are illustrated in Figure 6 and Table 10. MET 900 mg DR tablets twice daily have 58.5% relative BA when compared with MET 500 mg IR tablets once daily. The results obtained from the VBE study demonstrate that the MET DR tablets, even with an 1800 mg daily dose have significantly lower BA than the dose of 500 mg IR formulation. Lower systemic exposure could be beneficial for renal failure patients in real-time clinical settings. However, Phase 3 pivotal clinical studies are required to prove the efficacy and local action of MET DR tablets. The positive phase 3 clinical outcomes in the near future change the therapeutic strategy for diabetic management not only in renal failure patients but also in other diabetic subjects.

CONCLUSION

MET DR tablets could be an important attempt for the management of T2DM in renal failure patients. This dosage form was designed to offer minimum systemic exposure and associated side effects. The PBPK model is the lucrative *in silico* tool in pharmaceutical product development, which minimizes the cost and time of development and improves the quality of the products being developed. The PBPK model for MET DR tablets was developed and validated to facilitate the PT selection. Three PT formulations of MET DR 900 mg tablets with hypothetical dissolution data were subjected to VBE trials against MET IR 1000 mg as a reference product. The relative BA of PT formulations was close to the targeted theoretical BA of 20%. Furthermore, these formulations were subjected to VBE using 500 mg once daily IR tablets as reference product, based on the current standard of care therapy, and were found to be suitable for the management of T2DM in renal failure patients. PBPK modeling and VBE trials demonstrate that the current PT formulations meet the desired PK profiles and future clinical trial outcomes validate the PK outcomes of VBE trials.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Rajkumar Malayandi: Conceptualization, design, supervision, writing original draft preparation, and editing; Anu Mol C J: Data acquisition, writing original draft preparation, and editing; Sideequl Akbar: Data acquisition, writing original draft preparation, and editing; Subramanian Natesan: Conceptualization, review and supervision; Ravichandiran V: Supervision and conceptualization. All authors have read and agreed to the published version of the manuscript.

ABBREVIATIONS

MET: Metformin; **T2DM:** Type-2 Diabetes Mellitus; **DR:** Delayed-Release; **PBPK:** Physiologically Based Pharmacokinetic ; **IV:** Intravenous; **VBE:** Virtual Bioequivalence; **IR:** Immediate-release; **XR:** Extended-Release; **GI:** Gastrointestinal; **LA:** Lactic Acidosis; **GLP-1:** Glucagon-Like Peptide-1; **BA:** Bioavailability; **PT:** Proto-type; **BE:** Bioequivalence.

SUMMARY

The use of the commonly prescribed oral hypoglycaemic drug MET is limited in T2DM patients with renal failure due to its dose-related side effects. A new colon-targeted, DR formulation of MET might be beneficial for these patients, offering similar efficacy with reduced plasma drug concentration. The PBPK modelling technique was useful in drug product development stages for predicting the drug's PK properties in vivo. Firstly, the MET PBPK model was developed and validated for IV and oral IR and XR dosage forms. The developed model was then used to predict the BA and efficacy of the new MET DR tablets. The VBE trials of the PT formulations also confirmed the DR profile and approximately 20% relative BA, suggesting that they may be effective for managing T2DM in renal failure patients with reduced side effects.

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