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Physiologically Based Pharmacokinetic Model To Predict Metoprolol Disposition in Healthy and Disease Populations

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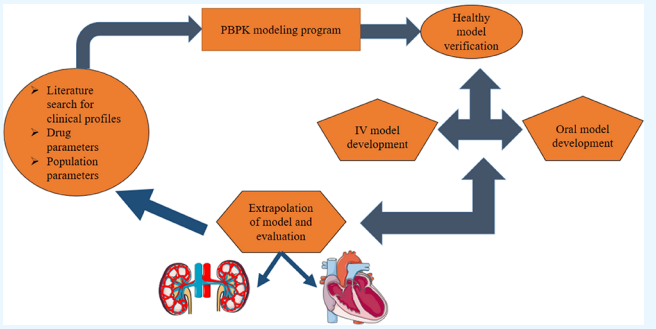
ABSTRACT: The evolution in the development of drugs has increased the popularity of physiologically based pharmacokinetic (PBPK) models. This study seeks to assess the PK of metoprolol in populations with healthy, chronic kidney disease (CKD), and acute myocardial infarction (AMI) conditions by developing and evaluating PBPK models. An extensive literature review for identifying and selecting plasma concentration vs time profile data and other drug-related parameters was undergone for their integration into the PK-Sim program followed by the development of intravenous, oral, and diseased models. The developed PBPK model of metoprolol was then evaluated using the visual predictive checks, mean observed/predicted ratios ($R_{obs/pre}$), and average fold error for all PK parameters, i.e., the area under the curve (AUC), maximal plasma concentration, and clearance. The model evaluation depicted that none of the PK parameters were out of the allowed range (2-fold error) in the case of the mean $R_{obs/pre}$ ratios. The model anticipations were executed to determine the influence of diseases on unbound and total AUC after the application of metoprolol in healthy, moderate, and severe CKD. The dosage reductions were also suggested based on differences in unbound and total AUC in different stages of CKD. The developed PBPK models have successfully elaborated the PK changes of metoprolol occurring in healthy individuals and those with renal and heart diseases (CKD & AMI), which may be fruitful for dose optimization among diseased patients.



1. INTRODUCTION

Teorell was the foremost to pioneer the notion of physiologically based pharmacokinetic (PBPK) modeling in 1937, a prime approach in the discovery and development of drug molecules. Pre-clinical data are used to anticipate the pharmacokinetics (PK) of drugs, i.e., how they are being absorbed, distributed, metabolized, and eliminated (ADME) in animals and humans.[1] As a consequence of technological advancement and the increase in computer processing power, the implementation of modeling and simulation is facile and quick now in building intricate PK models.[2] PBPK is also known as a bottom-up approach, in which the drug interacts with every organ of the human body via a common interconnecting duct in a well-consolidated way with the aim of providing understanding regarding valid extrapolations as well as the overall behavior of the system. During the process of drug development, in vitro data are used to a variable extent as inputs in structural PBPK models owing to its capability to quantitatively anticipate the PK in humans, thus the whole process is termed in vitro-in vivo extrapolation (IVIVE). The earlier empirical models are not useful concerning the description of PK variability of drugs in blood, plasma, tissues, and different organs in comparison to the physiologic models. This emerging approach being mechanistic and alluring, occasionally quoted as whole-body PBPK is efficient to narrate the PK of drugs by using equations that were difficult to answer mathematically in the past.[3]

By applying this approach, the likelihood of drug−disease, drug−drug, drug−food interactions, and dosage regimens along with the effect of diverse physiologic parameters on drug PK can be assessed in humans.[4] In the case of chronic diseases, many variations occur in pathophysiology that may affect the PK of drugs unfavorably, thus requiring an adjustment in administered medication therapy. The subsequent changes relevant to different diseases can then be integrated into the developed PBPK models for providing ease to anticipate the ADME of drugs being employed.[5] Several PBPK models on various classes of drugs have been

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Table 1. Clinical Attributes of Studies Utilized in the Model Development of Metoprolol[a]

sr. no.	population	no. of participants	administered dose (mg)	female proportion	age (years)	weight (kg)	reference
			IV Infusion				
1.	healthy	5	5	0	23−28	62−70	32
2.	healthy	6	20	0	22−28	60−88	33
3.	healthy	5	5, 10, 15, 20	0	23−28	62−70	34
4.	healthy	6	20	0	22−28	60−88	35
5.	healthy	18	15	6	20−34	43−80	36
6.	healthy	6	88.5 ± 1.1	1	23−29	N/R	37
			Oral				
7.	healthy	5	5	0	23−28	62−70	32
8.	healthy	5	20, 50, 100	0	23−28	62−70	34
9.	healthy	10	25, 50	4	71−74	53−81	38
10.	healthy	13	40	0	22−31	55−83	39
11.	healthy	6	50	0	22−28	60−88	35
12.	healthy	15	100	0	19−23	N/R	40
13.	healthy	6	50	0	22−28	60−88	33
			Diseased				
15.	AMI	27	91[b]	NR	48−84		17
			64[c]				
14.	CKD	6	20[d]	0	33−49	59−96	35
			50[e]				

[a]N/R: Not reported, No.: Number, AMI: Acute myocardial infarction, IV: Intravenous, CKD: Chronic kidney disease. [b]With ST (a section on electrocardiogram) changes. [c]Without ST changes. [d]IV dose. [e]Oral dose.

Table 2. Drug-Specific Input Variables Integrated into the Established Metoprolol Model[a]

parameters	published literature values	incorporated values for model	reference
	Physicochemical Characteristics		
molecular mass (g/mol)	267.36	267.36	23
pK_a	9.7	9.7	23
plasma protein binding	albumin	albumin	4
solubility in water (mg/mL)	171[b]	171[b]	42
log *P* (log units)	2.15	2.15	43
	Absorption		
intestinal permeability (specific) (cm/min)	1.12×10^{-5}	2×10^{-6}	23
	Distribution		
cellular permeability model		PK sim standard	
blood to plasma ratio (B:P)	1.13	1.13	28
partition coefficient model		PK sim standard	
fraction of unbound drug (f_u)	88%	88%	44
	Disposition (Metabolism & Elimination)		
clearance (CL)[c] (L/h)	5.23	5.23[e]	4
K_m[d] (uM)	26	26	28
V_{max}[d] (pmol/min/mg microsomal protein)	423	750[f]	28

[a]pK_a: dissociation constant, log *P*: Lipophilicity, CYP2D6: cytochrome P4502D6, K_m: concentration of substrate at half of maximal velocity, V_{max}: reaction's maximal velocity. [b]At pH of 6.5. [c]Clearance is renal. [d]CYP2D6 is the enzyme whose values of K_m and V_{max} are mentioned. [e]In the model, a value of 0.07 is utilized by transforming the unit from L/h to L/h/kg. [f]This value was optimized manually on grounds of observed/predicted ratio of PK-parameters and visual predictive checks.

auspiciously developed so far that are used in accordance with chronic diseases.[2,6−10]

Metoprolol being a cardio-selective β-1 blocker drug is indicated in the cure of hypertension and various cardiovascular illnesses with formulations available in intravenous (IV), per-oral (PO), immediate-release, extended-release, controlled-release, and slow-release.[11] This drug is devoid of its intrinsic sympathomimetic activity. In the heart and blood vessels, β-1 receptors are present which are competitively inhibited by metoprolol, giving rise to a decrease in the heart rate, the oxygen demand of cardiac muscles, and cardiac output, thus reducing the effects of hypertension and angina.[12] Metoprolol is almost 12% bound to human serum albumin with a bioavailability of 50% due to considerable first-pass metabolism.[13,14] It is metabolized mainly by the CYP2D6 enzyme in the liver, and only less than 5% of the administered dose is renally cleared, having a value of 5.23 L/h.[4,14]

The term acute myocardial infarction (AMI) refers to a disease whose treatment regimen involves metoprolol and is delineated by the obstruction of coronary arteries via accumulation of plaque and death of cardiac cells, thus subsequently reducing the blood flow.[15,16] As metoprolol is a drug that exhibits a greater hepatic extraction ratio, its clearance decreases in AMI when a reduction in blood flow towards the liver occurs; therefore, it will be fruitful to develop a drug-disease PK model in this case for predicting the changes

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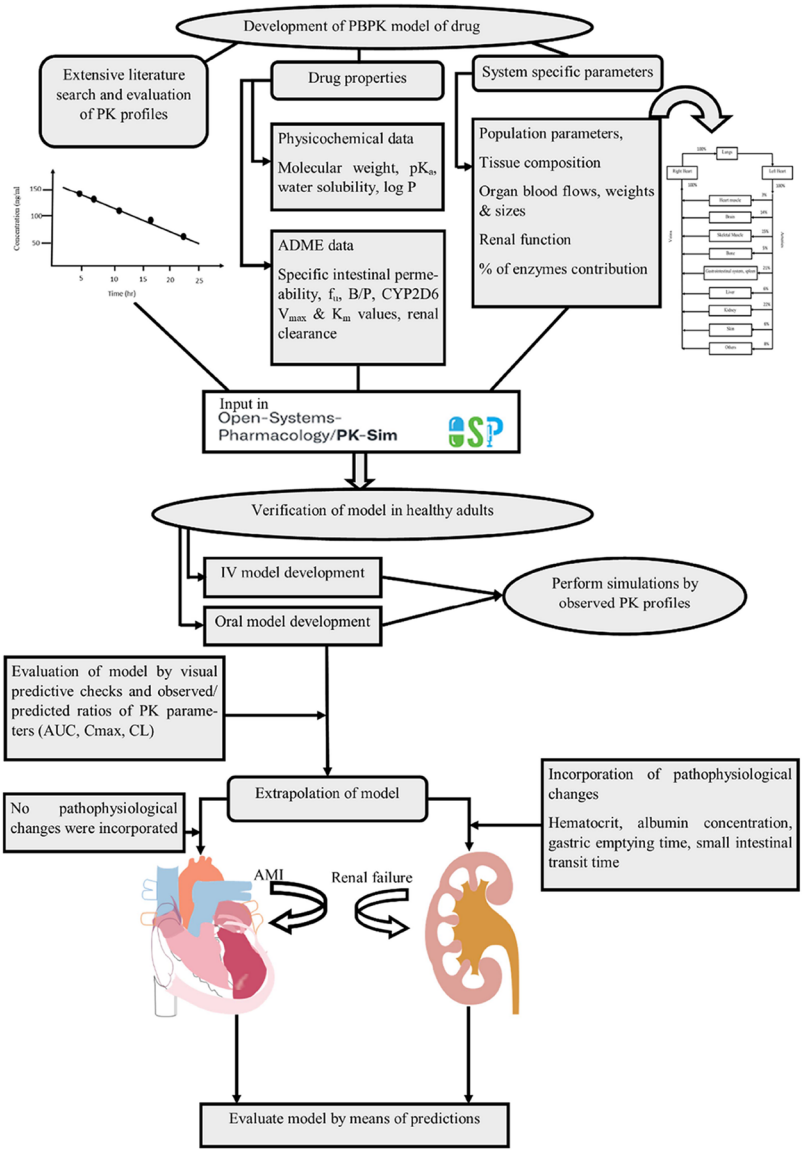

Figure 1. Workflow diagram for creating a PBPK model of metoprolol. ADME: absorption, distribution metabolism, and elimination, PBPK: Physiologically based pharmacokinetic modeling, f_u: fraction unbound, pK_a: dissociation constant, CYP2D6: cytochrome P4502D6, log *P*: Lipophilicity, V_{max}: reaction's maximal velocity, K_m: concentration of substrate at half of maximal velocity, B:P: blood to plasma ratio, AUC_{0-t}: area under the curve from time 0 to *t*, C_{max}: Maximal concentration of plasma, CL: Clearance, AMI: Acute myocardial infarction, IV: Intravenous. Parts of the figure were drawn by using pictures from Servier Medical Art (SMART). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

in its ADME.[17] Chronic kidney disease (CKD) is characterized by irregularities in the kidney structure or function and a reduction in estimated glomerular filtration rate (eGFR) to <60 mL/min.[18] Various pathophysiological changes appear in CKD that can modify the metoprolol PK and may intensify its relevant side effects.[11] The changes in albumin, hematocrit, small intestinal transit time, and gastric emptying time are reported in the previously published literature,[19,20] and upon integrating them into the PK model, it may help in optimizing the doses of metoprolol among CKD patients.

PBPK models on metoprolol have already been developed in the past, among which few put the emphasis on polymorphism, i.e., influence of different genotypes of CYP2D6 on its distribution and elimination,[21−23] some were focused on a special population (pregnant),[24−26] whereas others were concentrated on predicting PK of metoprolol following different routes of administration (IV, PO, immediate, and controlled-release).[27−29] Furthermore, the subject of a few PBPK models was related to phenotypes of CYP2D6 and various populations (including the Korean and elderly).[30,31] Our study is primarily centered on those key facets which the earlier models had not addressed so far. Up to date, no one has built up the PBPK model of metoprolol in CKD. The objective of the current study is to methodically develop and assess a PBPK model that can predict the metoprolol PK in healthy, CKD, and AMI populations that can be used for suggesting dosage adjustments.

2. METHODOLOGY

2.1. Screening of Pharmacokinetic Data. Google Scholar & PubMed databases were thoroughly searched to retrieve the articles regarding metoprolol following IV and oral

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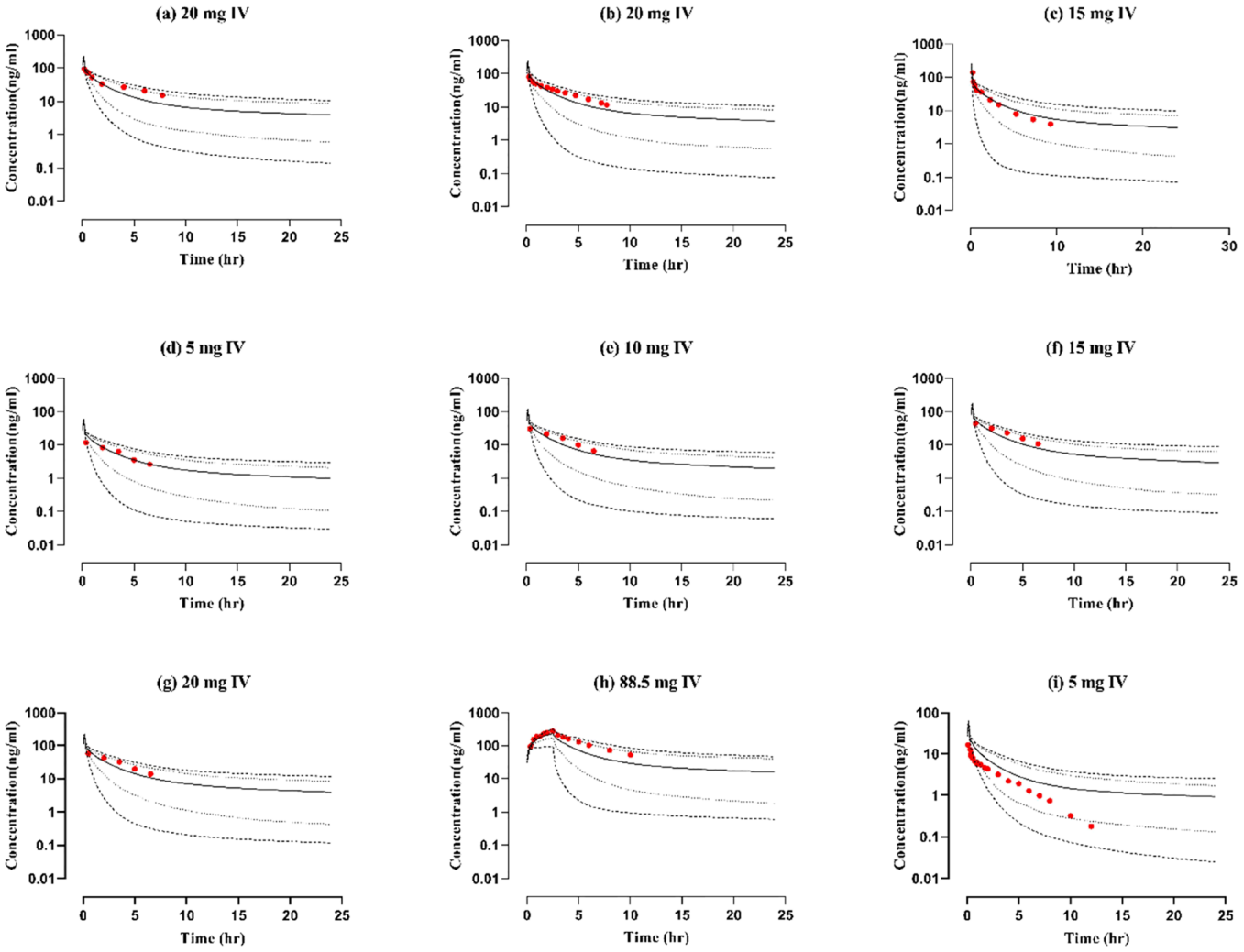

Figure 2. Comparison between observed and simulated concentration vs time profiles after IV administration of metoprolol at doses (in mg) of (a) 20,[33] (b) 20,[35] (c) 15,[36] (d) 5,[34] (e) 10,[34] (f) 15,[34] (g) 20,[34] (h) 88.5,[37] and (i) 5[32] correspondingly. Red colored dots describe the reported data values, the mean solidified line indicates the simulated data values, the dashed line represents the maximum and minimum values, and the dotted line depicts the 5th and 95th percentiles. IV: Intravenous route of administration.

routes of administration encompassing systemic concentration-time profiles among the (healthy and diseased) population. In the case of healthy individuals, 9 studies were embraced, among which 6 profiles were of IV infusions and 7 were oral, respectively. Furthermore, 2 PK studies and 3 profiles with drug concentration-time data were utilized in CKD and AMI subjects. The included CKD study consisted of profiles of 07 individuals (AO, PB, LA I, BH, IP, JZ, LA II) along with a mean profile, among which 03 individuals were categorized into moderate CKD and 04 in severe CKD based on their creatinine clearances. GetData Graph Digitizer version 2.26 software was used to digitize every graph present in the articles meeting inclusion criteria for carrying out the data extraction process. In the development and verification of a PBPK model, one-third (2 oral and 2 IV) and two-thirds (5 oral and 4 IV) studies were employed, respectively, whereas all of them were used ultimately in evaluating the model. The particular characteristics of all incorporated clinical studies are represented underneath in Table 1.

2.2. System Software for Modeling. The population-based whole-body PBPK simulator, i.e., PK-Sim version 11-build 150 (Bayer Technology Services, Biophysics, 42096 Wuppertal, Germany),[41] was adapted for the build up of model and assessment of PK of metoprolol in healthy and diseased (CKD & AMI) population.

2.3. Development of Building Blocks. Open system pharmacology suite (OSP) has made a specialized advanced form of commercial software, i.e., PK-Sim having an instinctual graphical user interface that is comprised of various building blocks. For model configuration, data related to metoprolol in different conditions (healthy and diseased) were gathered from the already published literature to create various building blocks. The drug-specific parameters that were selected in the PBPK model were created based on asserted values from the literature that are depicted in Table 2.

2.4. Strategy for Development of Model. First of all, a comprehensive online literature search was carried out to sift parameters and concentration-time profiles related to the drug (metoprolol) for initiating the development of a PBPK model. For model validation in healthy subjects, drug parameters, PK profiles, and system-related parameters were embedded into PK-Sim OSP software by creating IV and oral models that were based on previous model-building techniques.[2,45−47] The sensitivity analysis was performed for model parameters:

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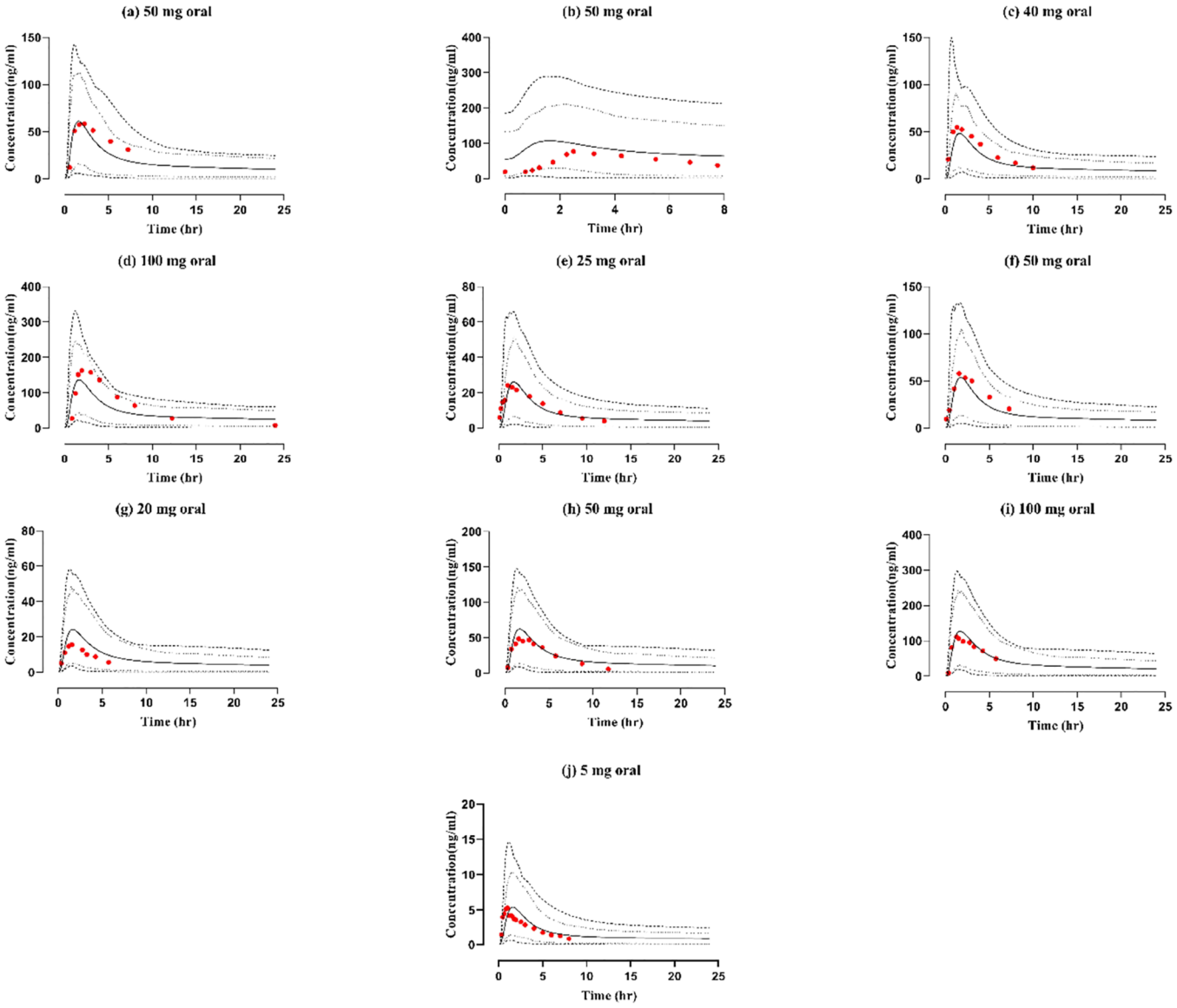

Figure 3. Comparison between observed and simulated concentration vs time profiles after oral administration of metoprolol at doses (in mg) of (a) 50,[33] (b) 50,[35] (c) 40,[39] (d) 100,[40] (e) 25,[38] (f) 50,[38] (g) 20,[34] (h) 50,[34] (i) 100,[34] and (j) 5[32] correspondingly. Red colored dots describe the reported data values, mean solidified line indicates the simulated data values, the dashed line represents the maximum and minimum values, and the dotted line depicts the 5th and 95th percentiles.

lipophilicity (log *P*), fraction unbound (f_u), values of V_{max} and K_m for CYP2D6, and specific intestinal permeability as shown in supplementary information (Figures SF1, SF2 and Table S1). The IV model was developed first to evade the complex procedure of absorption followed by generating predictions for absorption parameters (specific intestinal permeability). The oral model was afterward built up without changing the parameters that were utilized in the IV model. The model was further extended in the diseased populations (CKD and AMI) by integrating different published pathophysiological changes, thus predicting the metoprolol PK and developing the model auspiciously in healthy subjects. The diagrammatic illustration for the strategy to develop a model can be seen in Figure 1.

2.5. Model Structure. Metoprolol is a compound[4] with the molecular formula of $C_{15}H_{25}NO_3$, and a dissociation constant (pK_a) of 9.7.[23,48] Moreover, the values of lipophilicity and fraction unbound were 2.15 and 88% respectively (see Table 2). Absorption models vary concerning the software being used in the case of model building, but in the case of PK-Sim software, it is an in-built feature[47] that consists of different compartments by dividing the gastrointestinal tract.[49] The values of specific intestinal permeability vary in earlier research papers, among which one of the studies has reported it to be 1.12×10^{-5} cm/min.[23] This value was incorporated into the model first, and the simulations were done which exhibited an over-predicting behavior; thus, to establish the model in an efficient way, the reported value was adjusted to 2×10^{-6} cm/min grounded on the comparison of predicted vs reported data and visual predictive checks (VPC). Cellular permeability and partition coefficient were estimated by utilizing the method of PK-Sim standard. CYP2D6 is the major enzyme involved in the metabolism of metoprolol, and its constants K_m (concentration of substrate at half of maximal velocity) and V_{max} (reaction's maximal velocity) were employed in the prediction of the model. The remaining parameters are evident in Table 2.

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2.6. Structure of PBPK Model in Diseased Population. *2.6.1. Chronic Kidney Disease.* CKD is classified into various stages (normal, mild, moderate, severe, and end-stage) based on eGFR.[20] Different pathophysiological changes occur in the case of CKD such as plasma protein (albumin), gastric emptying time, hematocrit, and small intestinal transit time[19,20] that in turn result in changing the ADME of the drug (metoprolol). The eGFR was integrated into the model as 24.4 mL/min/1.73 m^2 in the case of mean simulation, 42.4 mL/min/1.73 m^2 in moderate and 10.9 mL/min/1.73 m^2 in severe CKD profiles respectively. The entire alterations in different parameters were then integrated into virtual populations created into the PK-Sim program with the purpose of refining the drug-disease PBPK model. Following assessment of the PBPK model with observed profiles, $AUC_{(0-t)unbound}$ and AUC_{0-t} were compared among three categories (healthy, modest, and severe) of individuals having CKD. Furthermore, box-whisker plots were employed to represent this comparison graphically to give suggestions on the dose of metoprolol.

2.6.2. Acute Myocardial Infarction. It is hereby highlighted that AMI is also linked to a variety of pathophysiological changes like a decrease in plasma clearance and blood flow towards the liver,[17] but as the effects of such parameter changes have not been demonstrated in the reported literature, they were not included in the presented model.

2.7. Model Verification. A virtual (computer-generated) population comprising 100 subjects (individuals) was constructed for all respective PK profiles and variables including the proportion of females, age, administered dose, weight, and administration method, as mentioned in the clinical PK studies above. VPC was used as a means to assess the developed model of metoprolol by overlaying the reported data from published plasma concentration−time profiles on anticipated (predicted) data which included values of 5−95th centile, arithmetic mean, minimum, and maximum. To determine PK parameters such as the area under plasma concentration-time curve from time 0 to t (AUC_{0-t}), drug clearance in plasma (CL), and maximal concentration of plasma (C_{max}), for both (reported & predicted) data, non-compartmental analysis was done by utilizing Adds-in Microsoft Excel program i.e. PK-Solver.[50] Subsequently, observed/predicted ratios ($R_{obs/pre}$) were calculated by utilizing eq 1 (presented below) for each one of the PK variables (AUC_{0-t}, C_{max}, and CL) together with a confidence interval (C.I) of 95% in studies involving healthy subjects, but data were represented as mean along with range in case of diseased (CKD and AMI) subjects due to availability of only two studies. These ratios ought to fall within an error range of 2-fold according to the PBPK models that have been developed previously.[2,5−10,47,49] Furthermore, mean $R_{obs/pre}$, average fold error (AFE), and fold error were determined to evaluate the model's certainty by employing eqs 1−3,

$$R = \frac{\text{Observed value of PK parameter}}{\text{Predicted value of PK parameter}} \quad (1)$$

$$\text{Fold} - \text{error} = \frac{\text{Observed values of parameter}}{\text{Predicted values of parameter}} \quad (2)$$

$$\text{AFE} = 10^{\sum \log(\text{fold error})/N} \quad (3)$$

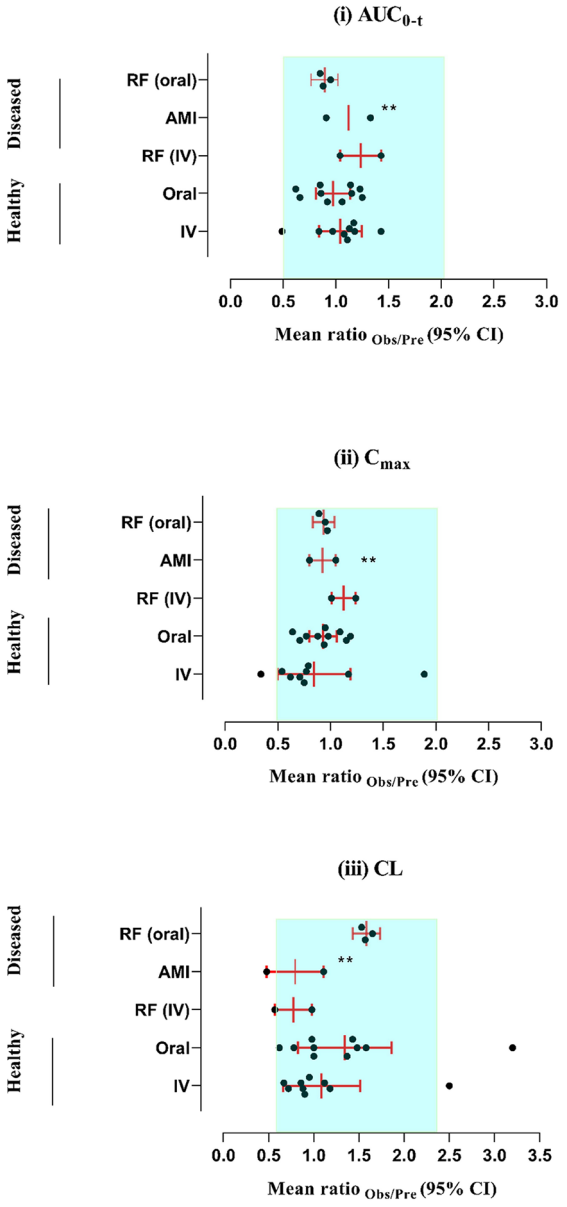

Figure 4. The comparison of the mean ($R_{obs/pre}$) for (i) maximal concentration of plasma (C_{max}) (ii) area under the curve from time 0 to t (AUC_{0-t}), and (iii) drug clearance (CL) among healthy, AMI, and renal failure patients. The outcomes are presented along with a confidence interval (C.I) of 95%. IV: Intravenous route of administration. ** In the case of renal failure IV and AMI, due to the presence of only two profiles, the results are presented as a mean with the range.

3. RESULTS

3.1. PBPK Model Evaluation in Healthy Adults. Following administration of IV (5−88.5 mg) and oral (5−100 mg) doses of metoprolol, the observed data were comparable with the predicted mean as demonstrated from both (observed & predicted) concentration-time profiles and found to be within 5−95th centile (Figures 2 and 3). These findings were additionally confirmed to assess the developed model of metoprolol by providing AFE values in which C_{max} was 0.842 and 0.933 after IV and oral route of administration, whereas the residual PK variables including CL & AUC_{0-t} were also comparable and fall within the ideal reported error

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Table 3. Comparison of of PK Parameters of Metoprolol Based on $R_{obs/pre}$ Ratios in Healthy and Diseased Subjects[a]

administered dosage	C_{max} (ng/mL)			AUC_{0-t} (ng/mL[b] h)			CL (L/h)		
	Obs	Pre	R ratio	Obs	Pre	R ratio	Obs	Pre	R ratio
IV Application Profiles									
5 mg	11.56	21.23	0.54	40.81	48.56	0.84	97	82	1.18
5 mg	16.2	46.45	0.34	27.39	55.19	0.49	178	71	2.50
10 mg	30.50	42.48	0.71	105.21	97.14	1.08	78	82	0.95
15 mg	138.83	73.34	1.89	155.11	158.63	0.97	84	75	1.12
15 mg	43.90	57.80	0.75	158.33	141.94	1.11	74	84	0.88
20 mg	94.14	151.56	0.62	243.06	205.87	1.18	58	80	0.72
20 mg	57.19	73.76	0.77	210.16	185.26	1.13	77	85	0.90
20 mg	79.86	100.36	0.79	223.97	190.37	1.17	71	82	0.86
88.5 mg	282.69	240.15	1.17	1331.2	925.18	1.43	53	79	0.67
Oral Application Profiles									
5 mg	5.29	5.39	0.98	19.68	22.69	0.86	209	146	1.43
20 mg	15.58	24.21	0.64	57.57	87.23	0.66	247	156	1.58
25 mg	24.28	25.77	0.94	142.15	133.57	1.06	151	150	1.00
40 mg	54.71	47.48	1.15	295.08	234.59	1.25	108	110	0.98
50 mg	58.05	53.17	1.09	268.92	218.29	1.23	137	174	0.78
50 mg	48.19	62.02	0.77	285.35	332.61	0.85	161	117	1.37
50 mg	76.32	107.24	0.71	389.60	620.18	0.62	77	24	3.20
50 mg	58.12	60.81	0.95	293.46	253.12	1.15	92	147	0.62
100 mg	162.57	135.82	1.19	1250.65	1088.42	1.14	74	50	1.48
100 mg	111.45	125.71	0.88	427.16	455.74	0.92	150	151	1.00
CKD (IV Study)									
20 mg	99.81	98.45	1.01	234.02	223.47	1.04	69	70	0.98
AMI (IV Profile)									
64 mg	340.16	424.52	0.8	629.75	690.33	0.91	85	76	1.11
91 mg	481.4	457.18	1.05	1204.86	899.44	1.33	40	83	0.50
CKD (Oral Study)									
50 mg[c]	89.95	91.79	0.97	493.34	557.67	0.88	63	40	1.57
50 mg (moderate)	89.95	94.21	0.95	493.34	517.9	0.95	63	38	1.65
50 mg (severe)	89.95	100.32	0.89	493.34	577.38	0.85	63	41	1.53

[a]AUC_{0-t}: area under the curve from time 0 to t, C_{max}: Maximal concentration of plasma, CL: Clearance, AMI: Acute myocardial infarction, IV: Intravenous, CKD: Chronic kidney disease, Obs: Observed value, Pre: Predicted value. [b]Mean of all individual subjects. [c]In oral concentration−time profiles, the term CL/F is used.

range of 2-fold (Table 4, Figure 4). Moreover, the calculation was conducted for AUC_{0-t}, C_{max}, and CL in terms of mean $R_{obs/pre}$ ratios (see Table 3).

3.2. PBPK Model Evaluation in Diseased Subjects. Regarding the diseased (CKD & AMI) population, observed data were consistent with simulated systemic metoprolol concentration-time profiles following IV and oral route of administration in comparison with arithmetic mean and 5−95th centile (Figure 5). In addition, these results were confirmed by the values of AFE (Table 4) and mean $R_{obs/pre}$ ratios for every single one of the PK parameters which were found to be within the error range of 2-fold (Table 3 and Figure 4) as the value for C_{max} was 0.953 following the IV route of administration.

3.3. Amendment of Metoprolol Doses in CKD Subjects. In healthy and diseased (CKD) subjects, when identical doses of the drug (metoprolol) were given via IV and oral route, the values of AUC_{0-t} and $AUC_{0-t(unbound)}$ seemed to be greater among the CKD population. Afterwards, to reach the aim of having identical exposure to metoprolol between healthy and CKD subjects, the process of dosage reduction was done in multiple steps by doing various simulations with slow tapering in which the first trial was conducted with a one-fourth lessening, i.e., 25% of 20 and 50 mg dose followed by representation with box plots in case of the IV and oral (route) in severe renal impairment. On the other hand, in moderate renal impairment, the dosage was tapered to about 12% of the doses (IV and oral), respectively, for bound AUC, i.e., (AUC_{0-t}) that depicted analogous values in comparison with those of healthy ones (population). The whole pathway of dosage modification was followed by already published research papers.[51] Apparently, no differences were noticed between AUC_{0-t} and $AUC_{0-t(unbound)}$ in the optimization of doses as exemplified below (Figures 6 and 7).

4. DISCUSSION

The presented study, for first-ever, has established a PBPK model for the drug (metoprolol) by employing a comprehensive and structured approach and consequently anticipating its ADME in healthy, AMI, and CKD populations after IV and oral (routes) administration. Firstly, in healthy subjects, the PBPK model was proficiently created and assessed in accordance with previously published investigations[2,5−10,47,49] in an attempt to ascertain the underlying variations in all PK parameters. After developing the model in healthy individuals, ADME of metoprolol was ruled out in the populations having CKD by integrating different reported pathophysiological changes. The liver is the major organ involved in the metabolism of drugs and employs the CYP2D6 enzyme to metabolize the considered drug, i.e., metoprolol, so in case of

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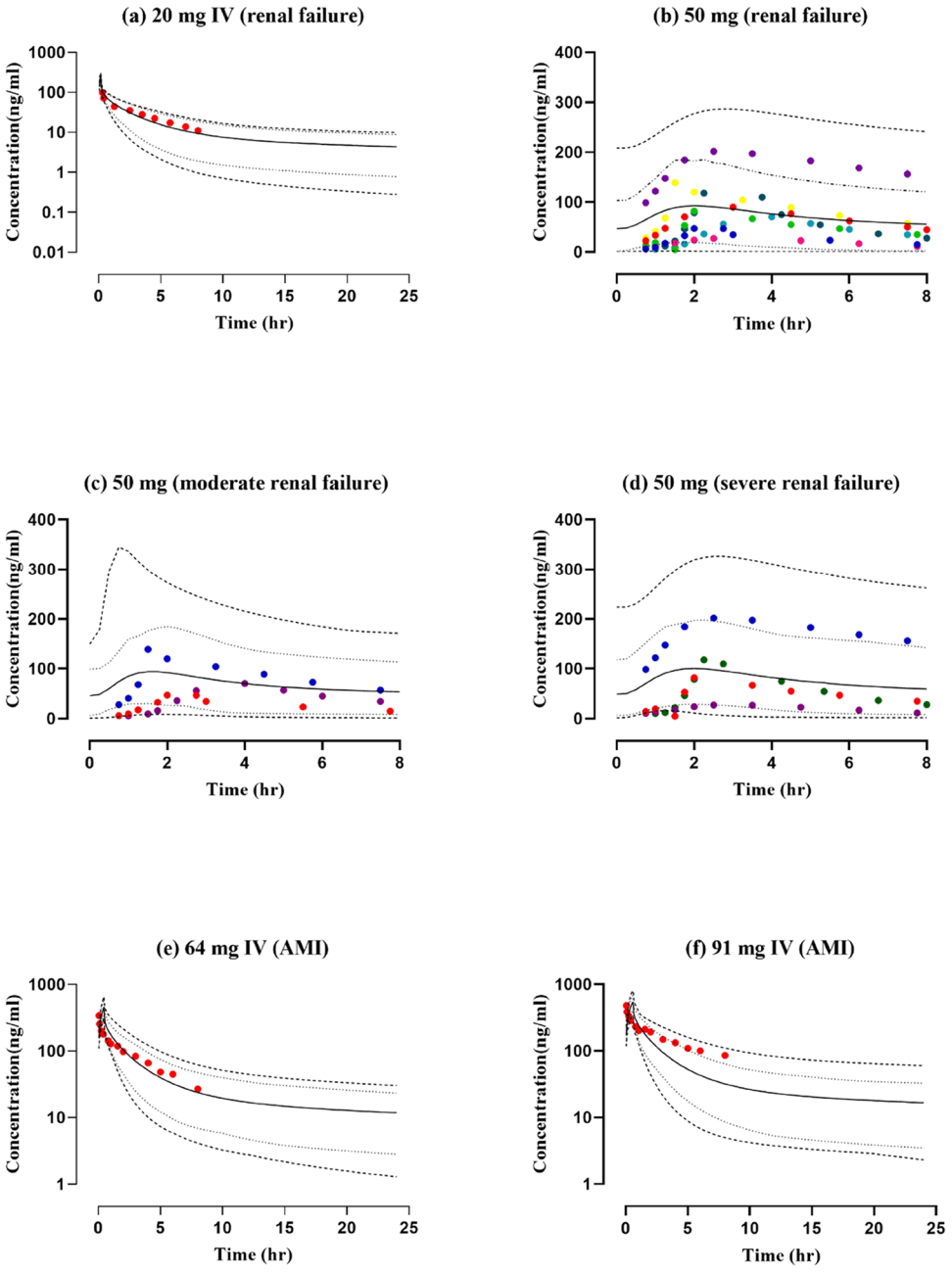

Figure 5. Comparison between observed and simulated concentration vs time profiles after IV administration of metoprolol at doses (in mg) of (a) 20,[35] and oral dose (mg) of (b) 50[35] in chronic kidney failure (CKD) containing profiles of all subjects individually and their mean, (c) 50[35] in 3 subjects with moderate CKD, (d) 50[35] in 4 subjects with severe CKD) while an IV dose (mg) of (c) 64[17] without ST-segment changes in electrocardiogram, and (e) 91[17] with ST-segment changes in AMI patients correspondingly. Red colored dots describe the reported data values, the mean solidified line indicates the simulated data values, the dashed line represents the maximum and minimum values and the dotted line depicts the 5th and 95th percentiles. In CKD, patient-specific changes such as plasma protein (albumin), gastric emptying time, hematocrit, and small intestinal transit time eGFR were incorporated. In AMI, no changes were added because of the unavailability of reported values. In (b), red dots present mean data, dark blue dots the subject AO, green dots the subject BH, purple dots the subject IP, pink dots the subject JZ, yellow dots the subject LA I, dark sea-green dots the subject LA II, and sky-blue dots the subject PB. In (c), red dots present subject AO, dark blue dots the subject LA I, purple dots the subject PB. In (d), red dots present subject BH, dark blue dots the subject IP, purple dots the subject JZ, and green dots the subject LA II. IV: Intravenous route of administration.

impaired functioning of kidney, the liver gets affected too by instigating a variety of pathological alterations such as an abundance of various included enzymes and concentration of plasma protein (albumin).[20] Taking this into consideration, the metoprolol model was generated for predicting its exposure in moderate and severe stages of CKD which could help with suggestions for dosage adjustments.

Metoprolol disposition was elaborated in a detailed way by PK-Sim software, a means of developing and evaluating the PBPK model, and all observed values were consistent with the simulated ones as depicted from the values of mean C_{max} 83.87 ng/mL vs 89.68 ng/mL following the IV route in healthy subjects. Moreover, in the case of oral administration, the observed value of mean AUC_{0-t}, i.e., 342.96 ng/mL·h was

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Table 4. Computation of AFE for each PK Variable among Healthy Individuals and those with CKD and AMII Disease[a]

PK variables	AFE
Healthy (IV)	
C_{max}	0.842
CL	1.086
AUC_{0-t}	1.043
Healthy (Oral)	
C_{max}	0.933
CL	1.344
AUC_{0-t}	0.973
CKD & AMI (IV)	
C_{max}	0.953
CL	0.856
AUC_{0-t}	1.092
CKD Oral	
C_{max}	0.936
CL	1.573
AUC_{0-t}	0.892

[a]AUC_{0-t}: area under the curve from time 0 to t, C_{max}: Maximal concentration of plasma, CL: Clearance, AMI: Acute myocardial infarction, CKD: Chronic kidney disease, IV: Intravenous.

comparable with the simulated one, i.e., 306.69 ng/mL·h. The AFE value for CL was 1.086 (2-fold error range) after administering IV metoprolol depicting that the model has accurately captured its ADME by selecting correct drug-related input parameters. In addition, the value of $R_{obs/pre}$ ratios (mean) for AUC_{0-t} in a healthy population was 0.973 after administration via the extravascular route presenting the accurate prediction of the model in terms of metoprolol PK.

Metoprolol is interpreted as a drug having high clearance after the oral route of administration;[52] therefore, alterations in the concentration of plasma protein may have an impact on its PK. According to previous studies,[19,20] changes usually occur among the CKD population regarding several variables including an abundance of enzymes, i.e., CYP2D6, gastric emptying time, the volume of kidneys, small intestinal transit time, serum albumin, and hematocrit. Regarding this CKD study, the IV profiles of 7 different individuals and their mean in both healthy and renal failure patients were too entangled to be scanned, and the same was the case with healthy oral profiles. But in the case of oral CKD, we have scanned data for all the individuals and presented all in Figure 5b. Then we categorized the individuals based on moderate and severe CKD and presented them separately in Figure 5c,d to further elaborate the results. The simulated and reported values of

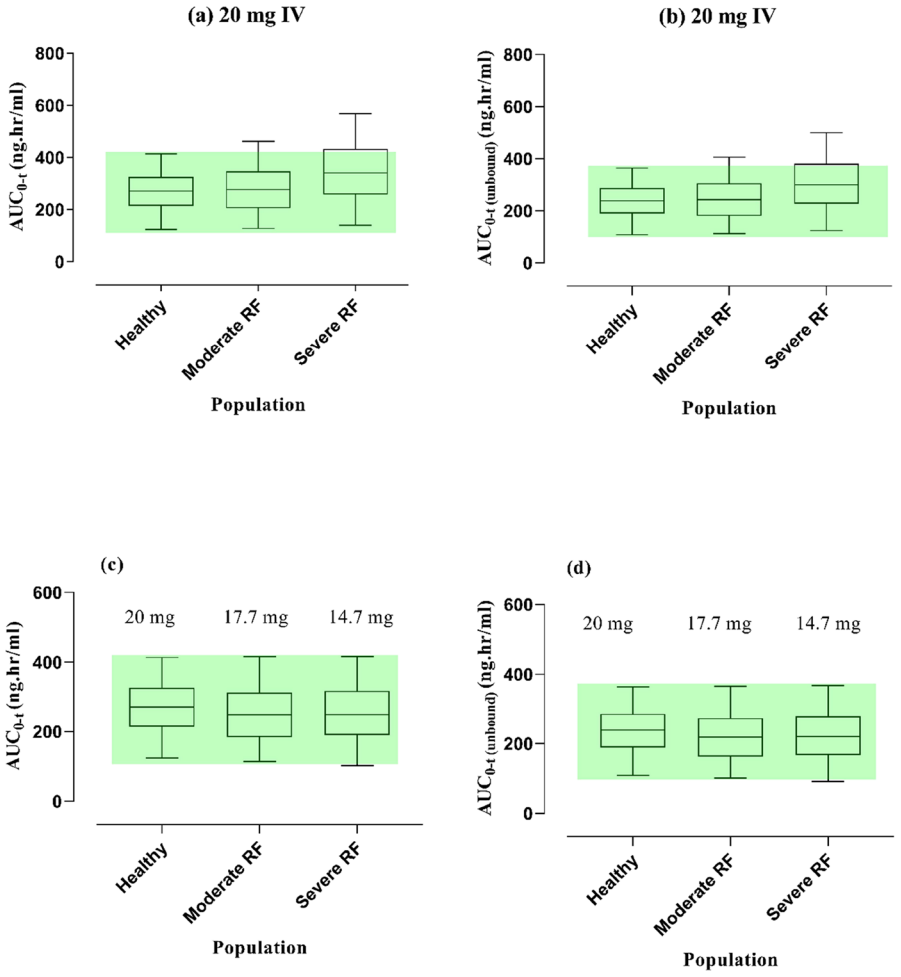

Figure 6. Graphical representation of simulated AUC_{0-t} and $AUC_{0-t(unbound)}$ as well as 5th and 95th percentiles employing box plots after administering 20 mg IV dose (a, b) in both populations (healthy and renal failure). For comparison with healthy exposure, dosage reduction in renal failure (moderate & severe) is indicated in (c, d). $AUC_{0-t(unbound)}$: area under the plasma concentration−time curve from time 0 to t unbound, AUC_{0-t}: area under the plasma concentration-time curve from time 0 to t bound, RF: Renal failure, IV: Intravenous route of administration.

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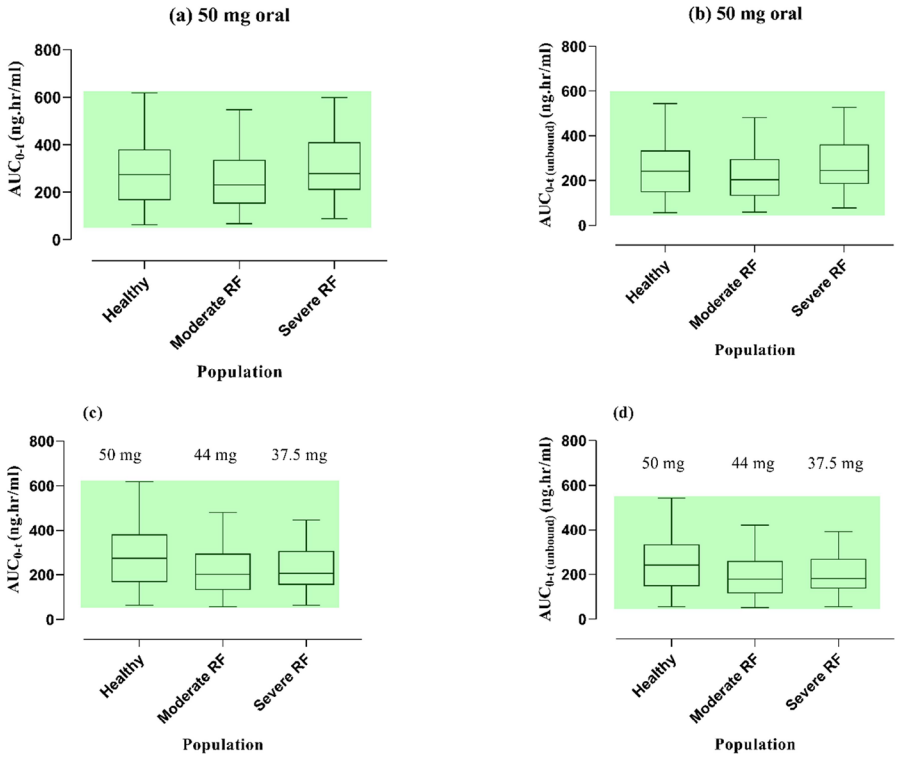

Figure 7. Graphical representation of simulated AUC_{0-t} and $AUC_{0-t(unbound)}$ as well as 5th and 95th percentiles employing box plots after administering 50 mg oral dose (a, b) in both populations (healthy and renal failure). For comparison with healthy exposure, dosage reduction in renal failure (moderate & severe) is indicated in (c, d). $AUC_{0-t(unbound)}$: area under the plasma concentration-time curve from time 0 to *t* unbound, AUC_{0-t}: area under the plasma concentration−time curve from time 0 to *t* bound, RF: Renal failure.

metoprolol AUC_{0-t} depicted an increase in patients of CKD, i.e., to 223.47 and 234.02 ng/mL·h from 190.37 and 223.97 ng/mL·h correspondingly after IV administration that was consistent with the findings of the previous study.[20] The plasma concentration-time graphs were presented in the study at the 9th dose when a steady state has achieved, and the values of maximal plasma concentration were higher in the CKD population when compared to healthy ones (subjects) after taking a 50 mg BID oral dose of metoprolol (Table 3) which may be related to the reduced concentration of serum albumin. These findings might indicate that CKD has a great impact on pathophysiological alterations by reducing the CL and raising the levels of plasma concentration.

Additionally, the metoprolol doses and their corresponding exposure after both administration routes (IV & oral) were also predicted by using the developed PBPK model as demonstrated in Figures 6 and 7. In both IV and oral (routes) cases, a comparison was done between two parameters, i.e., $AUC_{0-t(unbound)}$ and AUC_{0-0} where a 25% dose reduction was required in the case of severe and 11.5−12% in the moderate category, respectively. In contrary to the findings in the prior investigations where greater exposure in unbound was recorded,[53] the noteworthy variations were not recognized in $AUC_{0-t(unbound)}$ and AUC_{0-t}. Despite the fact that the elimination of metoprolol through kidneys is less than 10% and the diseased (CKD & AMI) population experiences only slight changes, these anticipations in metoprolol doses may help the patients with moderate to severe CKD in avoiding exacerbation of their condition.

The established healthy PBPK model was further extended to patients with AMI, and it was discerned that the predicted and observed values were relatively close (Table 3). The earlier published research study has disclosed several variations in ADME of metoprolol,[17] including altered CL in plasma and hepatic blood flow, but the estimation of these values was not given; that is why no pathophysiological alterations were accounted for in the model. The $R_{obs/pre}$ estimations for CL and C_{max} were 1.11 and 0.80 after 64 mg IV dose in patients with no alterations in ST-segment, whereas they were 0.50 and 1.05 in case of 61 mg dose among those patients who depicted changes in ST-segment correspondingly. All values of PK parameters were found to be within the error range of 2-fold which explained the correct development and evaluation of the model.

4.1. Limitations. The extraction of data from various published clinical studies containing concentration−time profiles of metoprolol was conducted by digitizing all graphs for model establishment and assessment. Different PK parameters were computed from the relevant profiles that were in harmony in comparison to the published literature but minor variations could not be evaded. To refine the model anticipations, two drug-specific parameters were adjusted carefully which were the V_{max} of CYP2D6 enzyme and specific intestinal permeability. The ultimate values entered into the model were grounded on values of $R_{obs/pre}$ and VPC. Owing to the inaccessibility of ample data in the CKD and AMI populations, we were unable to extrapolate the developed model into more profiles that may direct the findings of the study towards bias; therefore, further research will be useful in gaining plenty of data. The pathological changes were not integrated into the model of AMI due to the unavailability of scaled values in the prior reported literature that may lessen the competency of our outcomes. The clinical study of CKD that was included in the model belonged to the severe status,

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and we performed the simulations of reported profiles in a moderate degree according to accessible literature, but due to lack of documented data, we were unable to extend it in the mild group.

5. CONCLUSIONS

The ADME of metoprolol is successfully assessed by the established PBPK model in healthy subjects as well as in those having CKD and AMI diseases. Several pathological alterations in renal failure (CKD) were included for elaborating the capability of the model to forecast that may assist clinical practitioners in optimizing doses among patients having reduced kidney performance. Furthermore, the model can predict the variations of PK in patients with different degrees of severity, i.e., moderate and severe.

■ ASSOCIATED CONTENT

Data Availability Statement

All the data used for this publication is presented in the main article. Ethical approval and informed consent: Not applicable.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02673.

> Figure SF1: Sensitivity analysis of fraction unbound, lipophilicity, CYP2D6 V_{max} and K_m values, Figure SF2: Sensitivity analysis of fraction unbound, lipophilicity, CYP2D6 V_{max} and K_m values, Table S1: Output of PK parameters as a result of sensitivity analysis of fraction unbound, lipophilicity, CYP2D6 V_{max}, K_m, specific intestinal permeability, and renal plasma clearance (PDF)

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Notes

The authors declare no competing financial interest.

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