Level A IVIVC Using a Comprehensive Absorption/PBPK Model for Metoprolol

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Introduction

Wagner-Nelson, Loo-Riegelman, numerical deconvolution, and convolution-based methods are conventional ways to form an *in vitro-in vivo* correlation (IVIVC). The ultimate goal for forming an IVIVC is to develop a correlation or relationship between the *in vitro* release and *in vivo* release of a formulation so that an *in vivo* release profile can be predicted from a given *in vitro* release profile. The Wagner-Nelson and Loo-Riegelman methods form a correlation between *in vitro* release and bioavailability, which is not truly representative of a correlation between *in vitro* release and *in vivo* release, because bioavailability is affected by a combination of factors such as *in vivo* release, precipitation, permeability (carrier-mediated and passive transport), and first pass metabolism. Numerical deconvolution and convolution-based methods can be used to develop a correlation between *in vitro* release and *in vivo* release; however, these methods require the assumption of linear kinetics, which may not be appropriate for drugs that exhibit nonlinear pharmacokinetics.

Physiologically based pharmacokinetic (PBPK) models offer an alternative approach in which a direct correlation between *in vitro* release and *in vivo* release can be made without requiring a linear system. Such a correlation provides more useful information for formulation scientists than a correlation between bioavailability and *in vitro* dissolution. PBPK models provide a framework for the integration of physiological and *in vitro* data to construct mechanistic models that better represent the absorption, distribution, metabolism and excretion processes occurring *in vivo* than an empirical model that lumps these processes into one, two, or three compartments. Futhermore, PBPK models do not require intravenous data to calculate pharmacokinetic (PK) parameters. These advantages render PBPK modeling an appealing method to form an IVIVC.

Metoprolol is a widely used $beta_1$-selective blocking agent indicated for treatment of hypertension, angina pectoris and stable, symptomatic heart failure [1]. Under the Biopharmaceutics Classification System (BCS), it is classified as a Class I compound. Metoprolol is a weak base with a pKa of 9.7 [2] and is metabolized predominantly by CYP2D6 [1].

Objective

Form a Level A IVIVC using a comprehensive absorption/PBPK model for metoprolol.

Methods

- Construct a comprehensive metoprolol absorption/PBPK model for a typical 30-year-old male [3] using the PBPKPlus™ module in GastroPlus™ (Simulations Plus, Inc.). Estimate tissue:plasma partition coefficients (Kp) using a modification of a method described by Rodgers and Rowland [4]. Use *in vitro* metabolic measurements in human liver and intestinal microsomes as estimates for metabolic clearance parameters (Km, Vmax) [5], along with enzyme expression levels in the liver and gut [5]. Calibrate the absorption model using plasma concentration-time data obtained by injecting a metoprolol solution directly into the jejunum and colon [6].

- Obtain *in vitro* dissolution-time and plasma concentration-time profiles for three hydrophilic 100 mg metoprolol tartrate extended release (ER) tablet formulations (fast, moderate, slow) from the literature [7, 8].

- Use the IVIVCPlus™ module in GastroPlus to:
  - ✓Deconvolute *in vivo* release-time profiles for the moderate and fast formulations using separate Weibull functions for each *in vivo* release profile
  - ✓Form an IVIVC by fitting a single best average polynomial to the two resulting *in vivo* vs. *in vitro* release curves
  - ✓ Convolute all three formulations (slow, moderate, & fast) using the fitted polynomial
  - ✓Use the same two hydrophilic 100 mg metoprolol tartrate ER tablet formulations to form an IVIVC with the Loo-Riegelman method (pharmacokinetic parameters for a 2-compartment model calculated from intravenous data [2])
  - ✓ Evaluate the internal predictability for the moderate and fast formulations and external predictability for the slow formulation using both PBPK and Loo-Riegelman methods.

Results

PBPK Model

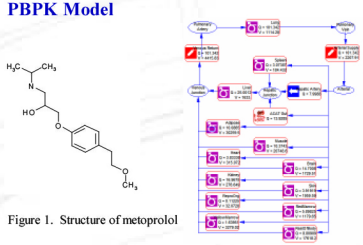

Figure 1. Structure of metoprolol

Figure 2. Schematic of PBPK model

Tissue	Kp
Hepatic Artery	0.00
Lung	7.52
Arterial Supply	0.00
Venous Return	0.00
Adipose	0.85
Muscle	3.95
Liver	8.66
ACAT Gut	0.00
Spleen	6.50
Heart	4.84
Brain	2.15
Kidney	9.32
Skin	3.18
ReproOrg	9.32
RedMarrow	1.92
YellowMarrow	0.85
RestOfBody	6.50

Figure 3. Kp values for each organ

Metoprolol Exhibits Nonlinear Pharmacokinetics

Simulation

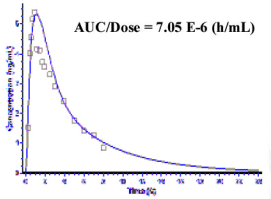

Figure 4. Simulated and observed [2] plasma concentration-time profile for 5 mg metoprolol tartrate solution.

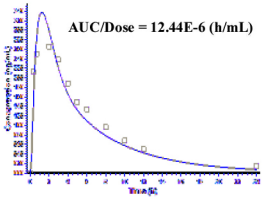

Figure 5. Simulated and observed [9] plasma concentration-time profile for single dosing of conventional metoprolol tartrate tablets 2 x 100 mg.

Deconvolution using moderate and fast formulations

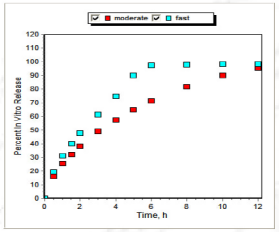

Figure 6. Observed *in vitro* dissolution-time profiles [8]. Apparatus II, pH 6.8, 50 rpm

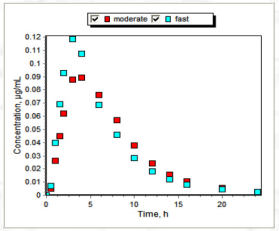

Figure 7. Observed plasma concentration-time profiles for metoprolol tartrate ER tablets [7]

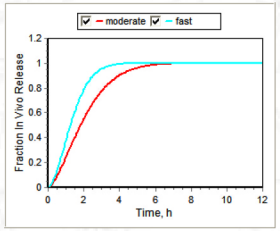

Figure 8. PBPK model deconvoluted *in vivo* release profiles

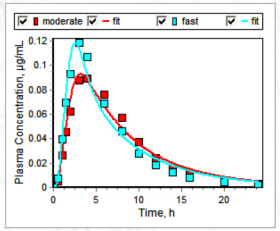

Figure 9. PBPK reconstructed plasma concentration-time profiles with observed data .

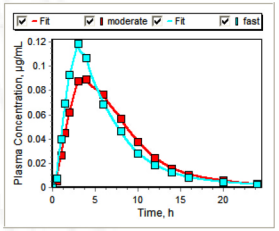

Figure 10. Loo-Riegelman reconstructed plasma concentration-time profiles with observed data .

Convolution and Evaluation of Internal (moderate and fast) and External (slow) Predictability

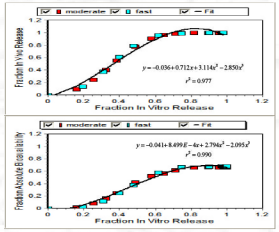

Figure 11. Third order polynomial IVIVC. Top: PBPK Bottom: Loo-Riegelman

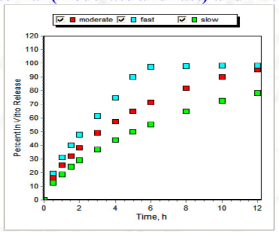

Figure 12. *In vitro* dissolution-time profiles for all three formulations (8). Apparatus II, pH 6.8, 50 rpm

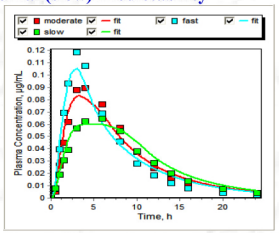

Figure 13. PBPK convoluted plasma concentration-time profiles with observed values.

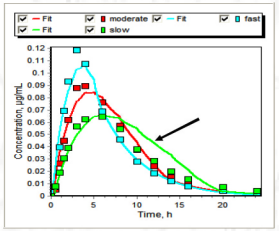

Figure 14. Loo-Riegelman convoluted plasma concentration-time profiles with observed values shows poor external validation for slow release.

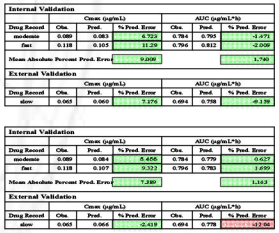

Figure 15. Internal and external validation of convoluted plasma concentration-time profiles. Top: PBPK Bottom: Loo-Riegelman

Conclusions

- A correlation between *in vitro* release and *in vivo* release for metoprolol ER formulations was developed using a mechanistic PBPK model. The model incorporated physiological and *in vitro* data to simulate the pharmacokinetic profile of metoprolol, did not require a linear system, and did not require pharmacokinetic parameters to be calculated from intravenous data.
- The comprehensive absorption/PBPK model met the criteria for internal and external predictability.
- The Loo-Riegelman method met the criteria for internal predictability, but not external predictability.

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