Assessing the Bioequivalence of Tacrolimus Amorphous Formulations with Varying Degrees of Crystallinity using Mechanistic Dissolution Models in a Population Physiologically-based Pharmacokinetic (PBPK) Modelling Framework

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Introduction

Amorphous drug products are susceptible to drug crystallization during their manufacture and shelf life which may result in altered pharmacokinetics and potentially bioinequivalence compared to the completely amorphous formulation.[1]

A Particle Population Balance (PPB) model implemented in Simcyp V18 provides mechanistic models for simultaneous handling of two solid states within the dosage, thereby enabling the evaluation of the effect of various degrees of drug crystallinity on the pharmacokinetics (PK) and bioequivalence (BE) of amorphous tacrolimus dosage forms. In addition, interplay of tacrolimus product quality and individual subject characteristics such as CYP3A4/5 expression levels and small intestinal transit time on PK and BE are explored.

Methods

A tacrolimus intravenous profile is used to obtain distribution parameters of a minimal PBPK model.[2] Intrinsic clearance values (CYP3A4/5-mediated) were obtained from the literature.[3] Table 1 shows the compound and formulation related parameters used for the development of the PBPK model. The oral absorption model was verified using PK data from literature.[2]

A series of population (50 individuals) simulations varying proportions of crystalline drug from 0 – 100% in the drug product were conducted and the resulting data analyzed for BE with the completely amorphous reference product. The simulations were set to mimic crossover (virtual) BE trials.

Table 1 Parameters Values used for Tacrolimus simulations

Parameter	Value
Physiochemical Properties	
MW	804.031
LogP	3.3
Neutral	-
Blood Binding Properties	
B:P Ratio	35
f_u, plasma	0.013
Plasma Binding Protein	Human Serum Albumin
Absorption	
P_{eff},man (10-4 cm/s)	6.327
Formulation	Immediate Release
Dissolution Model	Diffusion Layer (DLM)
DLM Model	Particle Population Balance
Intrinsic Solubility – Amorphous (Solid State 1)	50 µg/mL
Intrinsic Solubility – Crystalline (Solid State 2)	1.8 µg/mL
Particle Radius (µm)	10
Particle H_{eff} Model	Hintz Johnson
Bile Micelle Partition Coefficient	
$logK_{m:w,\ neutral}$	4.732
$logK_{m:w,\ ion}$	2.732
Precipitation Model	Model 1
CSC	100000
PRC (1/h)	0.0001
Distribution Parameters	
V_{ss} (L/kg) (Minimal PBPK)	17.1
Volume [V_{sac}] (L/kg)	1.43
SAC k_{in} (1/h)	0.314
SAC k_{out} (1/h)	0.048
Elimination Parameters	
CL(CYP3A5) – 12-HT	
V_{max}	0.476
K_m	0.35
CL(CYP3A4) – 12-HT	
V_{max}	0.204
K_m	0.29
CL(CYP3A5) – 13-DMT	
V_{max}	5.78
K_m	0.21
CL(CYP3A5) – 13-DMT	
V_{max}	2.72
K_m	0.21
Renal CL (L/kg)	0.048

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Results

The PBPK model was able to capture plasma concentration time profiles of tacrolimus following intravenous and oral administration (Figure 1). Overprediction of elimination phase of tacrolimus can be captured by inclusion of concentration dependent B:P ratio exhibited by tacrolimus. Exposure to orally administered tacrolimus was found to reduce with an increase in % drug crystallinity in the drug product (Figure 2). The predicted PK metrics (C_{max} and AUC_{0-t}) for different proportions of crystalline and amorphous tacrolimus drug product were assessed for virtual BE. Drug product with crystallinity 20% or more is found bioinequivalent to the completely amorphous product (Figure 2). In addition, two of fifty virtual individuals dosed with the 10% crystalline (i.e. 90% amorphous) formulation were at the edge of being bioinequivalent. These individuals expressed very high levels of CYP3A4/CYP3A5 leading to faster metabolism of tacrolimus potentiating the discrimination between the two products as compared to other subjects.

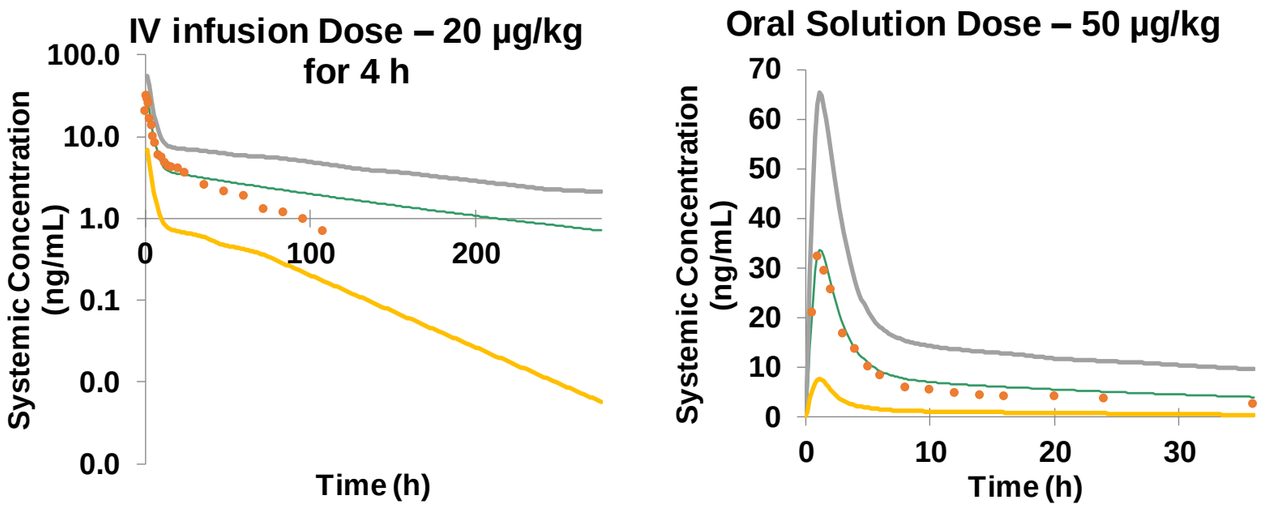

Figure 1 Observed (dots) and simulated (lines) exposure data of tacrolimus from Moller et all 1999 following (A) intravenous infusion Dose 20µg/kg for 4 h (B) single dose oral administration Dose 50µg/kg

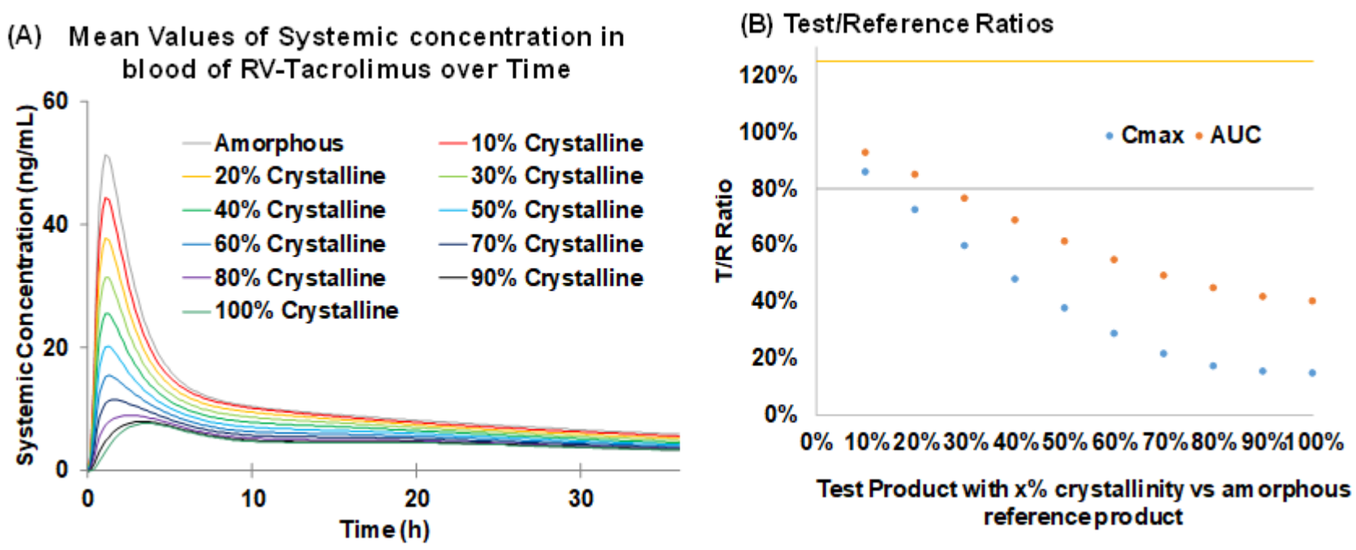

Figure 2 Simulated systemic exposure for tacrolimus with varying proportions of amorphous and crystalline drug in the dosage form (B) Virtual BE simulations (2-way Crossover) evaluating the pharmacokinetic metrics (C_{max} and AUC_{0-t}) of 50 healthy volunteers comparing 100% amorphous product (reference) with varying proportions of crystalline drug (10-100%) in the test drug product

Conclusions

- Crystallization within the tacrolimus drug product could lead to potential bioinequivalence. PBPK models can be a good tool in identifying formulation design space
- The simulation results demonstrated that the gastrointestinal site dependent Fa and Fg can play a role in determining BE for tacrolimus formulations
- Simulated individuals expressing very high levels of CYP3A4/5 levels were found to be at the risk of bioinequivalence. Virtual Bioequivalence can help to identify individuals which could exhibit failure of therapy or at risk of failure of therapy (bioinequivalence)

References

1. Purohit et al, J Pharm Sci 107 (2018) 1330-1341
2. Moller, A. et al. Drug Metab. Dispos. 27, 633–636 (1999)
3. Dai, Y. et al. Drug Metab. Dispos. 34, 836–847 (2006)