W0930-13-89

Exploring Clinical Relevance of Dissolution Testing by Physiologically Based Biopharmaceutics Modeling (PBBM)

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PURPOSE

In vitro dissolution testing, if reflective of *in vivo* drug release/absorption, is considered a surrogate for *in vivo* drug performance. Establishing *in vitro-in vivo* link to ensure clinical performance is feasible by implementing PBBM to guide product development and regulatory submissions [1].

OBJECTIVE(S)

This work provides insights into PBBM - based methodologies for:

- Development of IVIVC and its utilization to waive biostudies and establish clinically relevant dissolution specifications;
- Evaluation of dissolution differences and establishment of dissolution safe space by incorporating mechanistic absorption modeling (MAM).

Applicability of PBBM-based approaches (with or without Level A IVIVC) to ensure clinical performance is illustrated by the examples of a BCS class 3 drug formulated as modified-release (MR) tablet (Example 1) and a BCS class 2 drug formulated as immediate-release (IR) formulation.

METHOD(S)

Example 1: PBBM with Level A IVIVC

PBBM-based methodology to establish Level A IVIVC using GastroPlus® software tool equipped with IVIVC module (Simulations Plus, Inc.) is illustrated using a BCS 3 class drug formulated as MR matrix-based tablets.

METHOD(S), CONT'D

For this drug, due to its absorption characteristics (i.e. saturable, dose-dependent and transporter mediated uptake) [2], a conventional Level A IVIVC is found non-applicable.

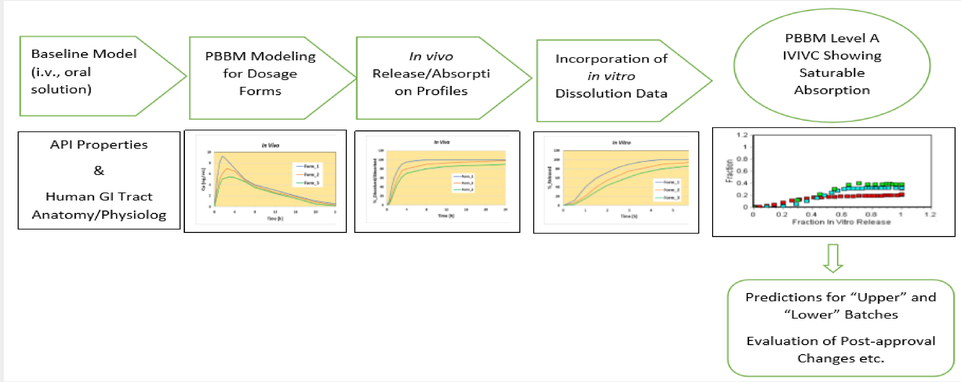
To develop and validate PBBM-based Level A IVIVC clinical data and the corresponding dissolution data from multiple biostudies are employed. The validated PBBM-based Level A IVIVC is further applied to waive biostudies for post-approval changes (formulation/process/additional strengths) and define clinically relevant acceptance criteria for dissolution testing.

Example 2: PBBM (without Level A IVIVC)

PBBM- based approach is applied on a BCS Class 2 drug with a molecular weight of 475, no permeability limited absorption, the pKa (dibasic) of 9.41 and 5.2, and a low solubility at pH above 6. For this drug, formulated as the 300 mg IR tablet with target *in vitro* performance, to assess clinical quality risk, the batches with the variables (i.e. process, formulation, particle size) potentially critical for the *in vitro* dissolution rates, are also manufactured and subjected to biostudies [3]. Note that all variants are shown to be bioequivalent with the target product as well as with the oral solution, suggesting irrelevance of the dissolution differences observed in the media of physiological relevance, on the product clinical performance [4]. As per the authors [3], mechanistic modeling is recommended as a future tool to understand the link between dissolution and bioavailability/clinical performance.

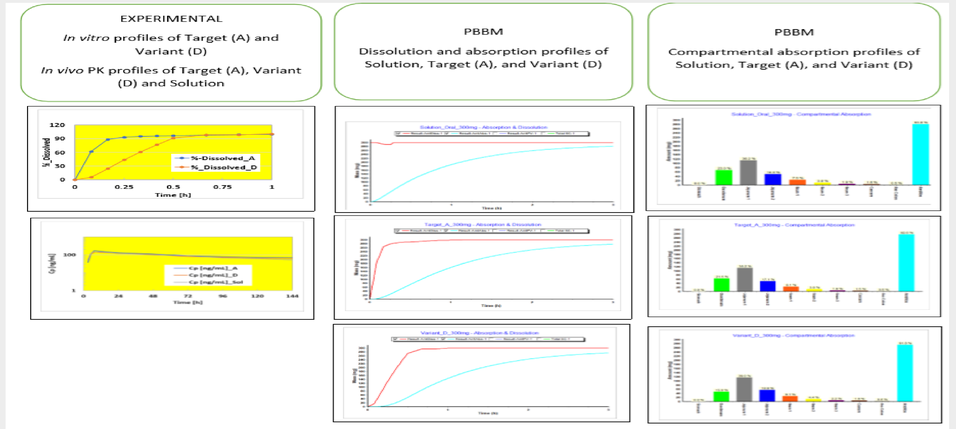
RESULT(S)

Example 1: PBBM-based Level A IVIVCs is developed and validated for the BCS Class 3 drug with no metabolism, transporter (OTC) mediated and saturable absorption. The *in vitro-in vivo* correlation plot exhibiting plateau is in the agreement with saturable absorption. The approach is applied to define clinically relevant dissolution limits and waive bio-studies for post-approval changes **(Scheme 1).**



Scheme 1. Level A IVIVC for BCS Class 3 drug with saturable absorption formulated as MR tablet

Example 2: PBBM (without IVIVC) approach, applied on the BCS Class 2 drug, is verified using the *in vitro* and *in vivo* literature data [3]. The *in vitro* dissolution differences at early time points are shown to somewhat impact regional extent of absorption without affecting the overall extent of absorption and *in vivo* performance **(Scheme 2).**



Scheme 2. Dissolution safe space for the BCS 2 class drug evaluated by PBBM-based approach

CONCLUSION(S)

Clinical relevance of dissolution testing and clinically meaningful dissolution acceptance criteria/dissolution safe space may be evaluated/established *via* PBBM.

PBBM-based Level A IVIVC approach was successfully applied to establish clinically relevant *in vitro* dissolution acceptance criteria for a BCS Class 3 drug formulated as a matrix-based MR tablet formulation.

PBBM without IVIVC provides insights into *in vivo* release/absorption characteristics that are further linked with *in vitro* dissolution, as illustrated using a BCS Class 2 drug formulated as an IR dosage form. This approach is applicable to define dissolution safe space and assess virtual BE to a broader range of BCS 2 class drugs exhibiting insignificant metabolism, long elimination half-life, and prolonged (i.e. late time to C_{max}), no site-specific, no permeability limited and practically complete absorption.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

References

1. Heimbach et al, AAPS J, 2019; 21-29 https://www.ncbi.nlm.nih.gov/pubmed/?term=heimbach+T+AAPS+J+2019
2. McCraight et al, Diabetologia, 2016; 59: 426–435. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4742508/
3. Dickinson et al. AAPS J. (2008) 10: 380 https://www.ncbi.nlm.nih.gov/pubmed/?term=dickinson+AAPS+J+2008
4. NDA 22-405, Clinical Pharmacology Review https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022405Orig1s000ClinPharmR.pdf

Note: Example 1 was presented in the GastroPlus User Group webinar (https://www.simulations-plus.com/assets/2018-10-29-Applying-GastroPlus-Modeling-Establish-Level-A-IVIVCs-Waive-Biostudies.mp4)

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