Development of *In Vitro–In Vivo* Correlation for Extended-Release Niacin After Administration of Hypromellose-Based Matrix Formulations to Healthy Volunteers

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ABSTRACT: Development of *in vitro–in vivo* correlations (IVIVCs) for extended-release (ER) products is commonly pursued during pharmaceutical development to increase product understanding, set release specifications, and support biowaivers. This manuscript details the development of Level C and Level A IVIVCs for ER formulations of niacin, a highly variable and extensively metabolized compound. Three ER formulations were screened in a cross-over study against immediate-release niacin. A Multiple Level C IVIVC was established for both niacin and its primary metabolite nicotinuric acid (NUA) as well as total niacin metabolites urinary excretion. For NUA, but not for niacin, Level A IVIVC models with acceptable prediction errors were achievable via a modified IVIVC rather than a traditional deconvolution/convolution approach. Hence, this is in contradiction with current regulatory guidelines that suggest that when a Multiple Level C IVIVC is established, Level A models should also be readily achievable. We demonstrate that for a highly variable, highly metabolized compound such as niacin, development of a Level A IVIVC model fully validated according to agency guidelines may be challenging. However, Multiple Level C models are achievable and could be used to guide release specifications and formulation/manufacturing changes. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3713–3723, 2014
Keywords: in vitro/in vivo correlations (IVIVC); controlled release; pharmacokinetics; dissolution; mathematical model

INTRODUCTION

The establishment of an in vitro–in vivo correlation (IVIVC) is considered the gold standard in linking *in vitro* dissolution data to the drug and formulation behavior in the clinic. The ability to project, via dissolution, the pharmacokinetic impact of formulation/manufacturing changes, allows for increased confidence on the reproducibility of the drug product. This facilitates formulation and/or manufacturing changes at scale up or postproduct approval and ultimately ensures patient benefit by enabling the adoption of clinically relevant specifications. Although in principle development of either immediate-release (IR) or modified-release (MR) formulations would benefit from the establishment of IVIVCs, it is most commonly pursued for the latter. As for MR formulations, the formulation allows for complete control of the rate by which the drug compound is dissolved in the intestinal lumen, and thus the subsequent absorption and appearance in the systemic circulation, the development of an IVIVC for MR formulations is considered more feasible. The benefits of IVIVCs for MR formulations are reflected in available guidances from Regulatory Agencies in which it is outlined how IVIVC data can be used to set dissolution specifications and under certain circumstances to serve as a surrogate for *in vivo* bioequivalence studies.[1–3]

Available Regulatory guidances detail the different levels of IVIVC as well as discuss methodologies for their establishment. These have also been reviewed extensively in the literature.[4–7] The establishment of point-to-point correlations (Level A) is seen as the most desirable and most informative correlation and provides the greater benefits from Regulatory perspective, including the possibility of biowaivers. However, Level C and Multiple Level C correlations can also be applicable in Regulatory discussions around dissolution specifications or supporting post-approval manufacturing changes. Level A correlations are most commonly developed using the traditional deconvolution/convolution approach that is detailed in the relevant US FDA guidance.[1] However, alternative approaches including convolution-based models have been detailed in the literature and can be considered as potential alternatives. The potential benefits of these approaches have also been extensively discussed in the literature.[8–10]

In this manuscript, we detail the efforts toward developing a validated IVIVC for extended–release (ER) niacin as part of the development of TREDAPTIVE, a niacin and laropiprant fixed dose combination formulation, focusing on Level C and

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Level A models that are commonly pursued for regulatory application. TREDAPTIVE was previously marketed (withdrawn from the market in 2013) as a bilayer tablet, with one layer containing 1000 mg ER niacin and the other containing 20 mg IR laropiprant. The pharmacokinetic profile of niacin is rather complex because of the fast and extensive first-pass metabolism, which is dose and absorption rate dependent. The parent compound can be metabolized via different pathways.[11,12] The high-affinity, low-capacity amidation pathway results in the formation of nicotinamide adenine dinucleotide and nicotinamide, which is further metabolized to predominantly N-methylnicotinamide (MNA) and to N-methyl-2-pyridone-5-carboxamide (2PY). At higher, clinically relevant doses, niacin is also conjugated with glycine to form nicotinuric acid (NUA). This is a low-affinity, high-capacity pathway. NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. IR formulations saturate the amidation pathway resulting in higher NUA levels, whereas ER formulations provide a more balanced metabolic profile along the two pathways.[13] The Niacin (nicotinic acid; NA), NUA, MNA, and 2PY are the major circulating analytes in human plasma after dosing with niacin, and all are excreted into urine. Draft FDA Guidance for Niacin recommends the measurement of niacin and NUA in plasma during conduct of bioequivalence studies.[14] Although niacin is the parent molecule for which bioequivalence should be pursued, the guidance suggests that if niacin cannot be reliably measured, bioequivalence determination based on NUA can be considered. In the manuscript, we detail our efforts to utilize both niacin and NUA as endpoints for the IVIVC. In addition, we investigate the use of total urinary excretion of niacin and its metabolites, which would reflect total niacin absorption from the dosage form, as an additional surrogate for formulation performance.

METHODS

Formulations

The excipients used in the formulation of Tredaptive are well-known excipients typically used in tablet formulations such as hypromellose (E464; HPMC), colloidal anhydrous silica (E551), sodium stearyl fumarate, hydroxypropylcellulose (E463), microcrystalline cellulose (E460), croscarmellose sodium, lactose monohydrate, and magnesium stearate. To modify the release rate of niacin in the formulations studied for the development of IVIVC, the levels of HPMC were varied. Levels of 4%, 6%, and 10% were used for the three formulations studied. The laropiprant IR layer was identical for all formulations.

Dissolution Method

For the development of the IVIVC, dissolution data for the three formulations (4%, 6%, and 10% HPMC) were obtained in a phosphate buffer pH 6.8 (USP dissolution apparatus II) method. The dissolution curves for the three formulations are shown in Figure 1. The used dissolution method represented the established release method for TREDAPTIVE. The method includes frequent sampling of dissolution points that allows for appropriate characterization of dissolution profiles for the use of IVIVC. Dissolution of the controlled release niacin component of TREDAPTIVE had been shown to be insensitive to the media pH (tested at pH 1.2, 4.0, and 6.8) and thus the use of the release method (pH 6.8 phosphate buffer) is considered appropriate for the purposes of IVIVC.

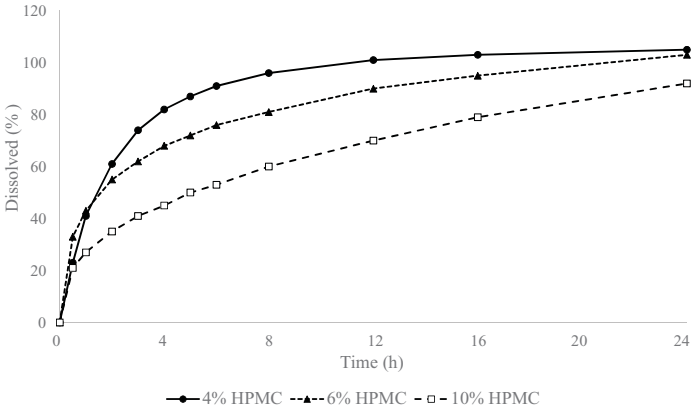

Figure 1. Dissolution profiles for tested niacin ER formulations (n = 12, USP II, phosphate buffer pH 6.8).

Clinical Evaluation of Formulations

The three formulations, along with IR Niacin (2 × 500 mg Niacor™) were evaluated in an open-label, randomized, four period, cross-over study in 36 healthy volunteers in the age range of 18–45 years old (Study MK-0524A-PN136). In each period, subjects received one of the four treatments in a randomized fashion. All randomized subjects participated in all periods. There was a minimum 5-day washout between doses in each treatment period. All treatments were administered with 240 mL of water in the fasted state at approximately the same time in each period. Water was restricted 1 h prior to and 1 h after studying drug administration while food was not allowed for 4 h postdosing. The primary objective of PN136 was to evaluate plasma concentration profiles of NUA, as well as total urinary excretion of NA and its metabolites (NUA, MNA, and 2PY) following administration of three different tablets of ER niacin 1000 mg/laropiprant 20 mg containing different ER niacin formulations designed to have different release rates that bracket the release rate of the commercial TREDAPTIVE™ formulation, and to use these data together with *in vitro* dissolution profiles of niacin from corresponding ER niacin 1000 mg/laropiprant 20 mg tablets, to establish a validated IVIVC. The plasma concentration profiles of NA were also evaluated in this study as a secondary endpoint. Study was conducted following appropriate IRB approval. Plasma samples were drawn until 24 h after dosing (collection time points of predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h). Cumulative urinary excretion of niacin and metabolites was assessed at 6, 12, 24, 48, 72, and 96 h (for simplicity, only 0–24 and 0–96 h data are presented). Samples were analyzed by a sensitive liquid chromatography–mass spectrometry method as previously described.[15] Pharmacokinetic parameters were calculated via noncompartmental analysis for all subjects/formulations and summarized via descriptive statistics. AUC_{0-24} (area under the curve to 24 h) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. C_{max} (peak concentration) and T_{max} (time to peak concentration) were obtained directly from the observed plasma concentration data.

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Level C IVIVC Analysis Methodology

Multiple Level C models for the studied ER niacin formulations were developed as follows: for each *in vitro* dissolution time point, a linear regression was performed using the corresponding *in vivo* end point. For each regression, slope and intercept terms were estimated. Five *in vivo* end points were selected for the Multiple Level C models: (1) the total urinary excretion of NA and its metabolites [i.e., NUA, MNA, and N-methyl-2-pyridone-5-carboxamide (2PY)]; (2) mean AUC_{0-24} for NA; (3) C_{max} for NA; (4) mean AUC_{0-24} for NUA; and (5) C_{max} for NUA.

At each *in vitro* dissolution time point, the Level C model was evaluated in accordance with the FDA criteria (1). The model-predicted parameters were compared to the corresponding observed values and the prediction error (%PE) was calculated according to:

$$\mathrm{PE}(\%) = 100 \times \left(\frac{\text{Predicted parameter} - \text{observed parameter}}{\text{Observed parameter}} \right).$$

Subsequently, the mean absolute percent prediction error (MAPPE) was calculated. All Level C linear regressions were performed within WinNonlin (WinNonlin Professional Edition version 5.2; Pharsight Corporation, St. Louis, MO).

Level A IVIVC Analysis Methodology

The initial Level A IVIVC analysis focused on NUA and was conducted using an individual-based deconvolution approach in three steps, following the recommendations in the respective FDA guidance.[1] This model represented a simplified approach to developing the IVIVC using only the NUA data directly, compared with a more mechanistic, physiologically representative model where niacin and NUA would be modeled simultaneously. Such more mechanistic models were attempted as discussed later in this manuscript in the compartmental model section, however with not much success. For the development of this more simplified model that is intended to link dissolution and NUA data directly (analogous to the Multiple Level C correlations for NUA), a unit impulse response (UIR) function specific to each subject was determined using the individual NUA concentration–time data following the administration of IR formulation. Subsequently, the fraction of NUA "*in vivo* release" as a function of time for each individual receiving the ER NA formulations was determined by deconvolution of the individual NUA concentration–time data for the respective formulation and finally the mean NUA "*in vivo* release" was calculated for each formulation and plotted against the *in vitro* NA release for these three ER formulations and an IVIVC relationship was fitted to the derived data.

To obtain the individual subject UIR, initially, polyexponential functions were fit to each NUA plasma concentration–time profile following administration of the IR NA formulation within the WinNonlin IVIVC ToolKit; however, a consistent bias in the fitting of the terminal phase of the concentration–time profiles was observed (data not shown). As a consequence, it was decided to fit the individual NUA plasma concentration–time data using a population-based approach as implemented in NONMEM (version 7.1.0.). A standard two compartment model was used (ADVAN4 TRANS1 subroutine with an additive plus proportional error model). Goodness-of-fit plots for each individual were generated to assess the accurate description of the UIR before incorporation in the IVIVC model. The resulting PK model parameters are shown in Table 1. The %RSE estimates for all compartmental parameters was considered acceptable for use of the model fit for UIR definition. The individual-predicted NUA plasma concentration–time profiles were subsequently used to define the UIR functions within the WinNonlin IVIVC ToolKit.

Table 1. Typical Parameter Estimates for IR Niacin Based on the popPK Model

Parameter	Final Estimate	%RSE	IIV (%)	%RSE
K (1/h)	0.899	3.49	–	
*K*23 (1/h)	0.0383	7.31	6.77	461
*K*32 (1/h)	0.137	6.86	–	
V (L)	99.9	7.36	38.9	17.8
*K*A (1/h)	1.29	7.12	27.3	37.4
ALAG (h)	0.357	3.33	–	
Residual variability (CV)	25.7	11.2		

These parameters were used to generate UIR for each subject to enable the deconvolution.

K, elimination rate constant; K23 and K32, distribution rate constants; *V*, central volume of distribution; KA, absorption rate constant; ALAG, lag time; IIV, interindividual variability estimate; RSE, relative standard error.

The initial model attempted was a traditional linear model with time scaling/shifting and with or without the inclusion of a cut-off time. However, as the *in vivo* input appears to be dependent on the *in vitro* release rate, establishment of these linear models is not straightforward. Consequently, a different approach was taken following an approach similar to that described by Balan et al.[16] This approach (termed Balan approach for the remainder of the manuscript) can be considered a convolution-based approach that allows for the model to take into account the differential bioavailability between formulations. The model is based on fitting of the dissolution data and the *in vivo* input data to empirical functions (such as the Hill function) and establishing correlations between the dissolution parameter estimates that are formulation dependent and the *in vivo* response parameters. Subsequently, a convolution step is performed to transform the *in vivo* input to the *in vivo* plasma concentration profile. Specifically for the model presented here, initially the *in vitro* release for each formulation was fit to the empirical Makoid–Banakar function (fit was empirical based on best description of *in vitro* data; equation is provided in Table 2). Subsequently, the mean *in vivo* release (i.e., fraction input) data that were obtained from deconvolution as described in the traditional Level A approach for each formulation were fit to a Hill function (equation is provided in Table 2). Models describing the relationship between the *in vitro* parameter, TMAX (time of plateau in Makoid–Banakar function), and the *in vivo* parameters, MDT (mean dissolution time), and Finf (maximum *in vivo* release), were developed. Linear models adequately described these relationships. These linear models were used as the Level A IVIVC model for NUA and were then used to obtain predicted *in vivo* Hill parameters, and from these predicted parameters, predicted fraction absorbed was obtained.

All calculations were conducted in in WinNonlin Professional Edition version 5.2 (Pharsight Corporation). To be able to more closely match the observation times in the study, convolution prediction output for model validations was set to 1-h interval.

Table 2. Parameter Estimates for *In Vitro* Niacin Release and *In Vivo* NUA Input Used in the Alternative (Balan) IVIVC Approach

Formulation	*In Vitro* Release Parameter (Makoid–Banakar Equation, Final Estimates) $x_{vitro}(t) = \text{FMAX} \times \left(\frac{t}{\text{TMAX}}\right)^b \times e^b \left(1 - \frac{t}{\text{TMAX}}\right)$ for $T \leq$ TMAX, $x_{vitro}(t) = \text{FMAX}$ for $T >$ TMAX		
	b	FMAX	TMAX
4% HPMC	0.6477	1.00	10.05
6% HPMC	0.3559	1.00	28.43
10% HPMC	0.4507	1.00	55.87
	In Vivo Input Parame (Hill Function, Final Estimate) $x_{vivo}(t) = \frac{\text{Finf} \times t^b}{\text{MDT}^b + t^b}$		
	Finf	MDT	B
4% HPMC	0.4678	1.582	2.098
6% HPMC	0.4039	1.362	1.878
10% HPMC	0.2708	1.183	1.871

An exploratory IVIVC analysis of NA was also conducted using a mean-based deconvolution approach following same procedures as described for NUA.

Compartmental Model Analysis Methodology

Over the course of the analysis, numerous PK models were evaluated to try to account for the complex PK of NA and NUA (e.g., models with incorporation of saturable first-pass metabolism) and allow for simultaneous modeling of the data. These models could allow for a more mechanistic modeling of the system compared with the simplified approach described above where NUA data were directly modeled. However, even the most promising models, based on standard diagnostic plots, failed to provide predictions of both the NA and NUA data within error that would suggest potential to be utilized for IVIVC development. The NUA data were generally better described compared with the NA data. Therefore, a simplified compartmental model was developed where the dissolution data were linked to NUA pharmacokinetic data directly. We present here only the most successful attempt to a compartmental model for NUA, which was possible only when average (geometric mean) data were used.

For the presented model, the UIR parameters are the same as described in the Level A analysis (Table 1). The method previously described by Buchwald[17] was used. Briefly, the *in vitro* dissolution profiles were first modeled via a Weibull function to calculate the *in vitro* dissolution rate (r_{diss}). The latter was subsequently linked to the *in vivo* input rate via a link function:

$$r(t) = \varphi(t)\text{SR} \times r_{\text{diss}}(T_0 + \text{S1} \times t)$$

where: $\phi(t)$, absorption cut-off (for NUA: a metabolism cut-off); SR, scaling factor; T_0, time shifting; and S1, time scaling.

All estimations were conducted in in WinNonlin Professional Edition version 5.2 (Pharsight Corporation).

RESULTS

Clinical Pharmacokinetics

Pharmacokinetic parameters AUC_{0-24}, $C_{\max}$, and $T_{\max}$ are summarized in Table 3. Observed mean plasma concentration profiles are shown in Figures 2 and 3. All controlled-release

Table 3. Mean (SD) Pharmacokinetic Parameter Values Following Administration of 1000-mg Single Oral Doses to Healthy Fasted Subjects ($n = 36$)

Formulation	Niacin		
	AUC_{0-24} (ng h/mL)	$C_{\max}$ (ng/mL)	$T_{\max}$ (h)[a]
ER 4% HPMC	2492 (1597)	1797 (1224)	1.50 (0.50, 3.00)
ER 6% HPMC	1920 (1517)	1515 (1057)	1.00 (0.50, 6.00)
ER 10% HPMC	945 (681)	878 (576)	1.25 (0.50, 3.00)
IR niacin	55,349 (22,192)	32,598 (12,838)	1.00 (0.50, 2.50)
	Nicotinuric Acid		
	AUC_{0-24} (ng h/mL)	$C_{\max}$ (ng/mL)	$T_{\max}$ (h)[a]
ER 4% HPMC	5076 (1826)	1571 (496)	2.00 (1.00, 3.00)
ER 6% HPMC	4420 (1798)	1389 (543)	1.50 (1.00, 4.00)
ER 10% HPMC	3014 (1409)	1164 (467)	1.50 (1.00, 4.00)
IR niacin	12,023 (4879)	4249 (1634)	1.50 (1.00, 2.50)
	0–24 h Total Urinary Excretion of NA, NUA, MNA, and 2PY (μmol)		
ER 4% HPMC	3494 (843)		
ER 6% HPMC	3082 (746)		
ER 10% HPMC	2320 (525)		
IR niacin	5217 (1112)		
	0–96 h Total Urinary Excretion of NA, NUA, MNA, and 2PY (μmol)		
ER 4% HPMC	5850 (1114)		
ER 6% HPMC	5479 (1070)		
ER 10% HPMC	4545 (1188)		
IR niacin	6632 (1259)		

[a]Median (minimum, maximum).

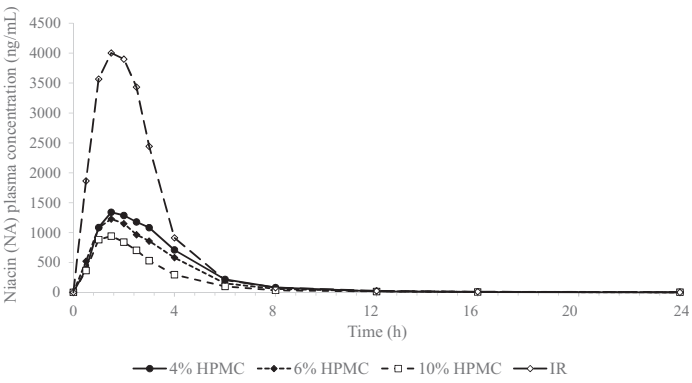

Figure 2. Mean plasma NUA) pharmacokinetic profiles following administration of three ER niacin formulations and IR niacin reference to healthy volunteers.

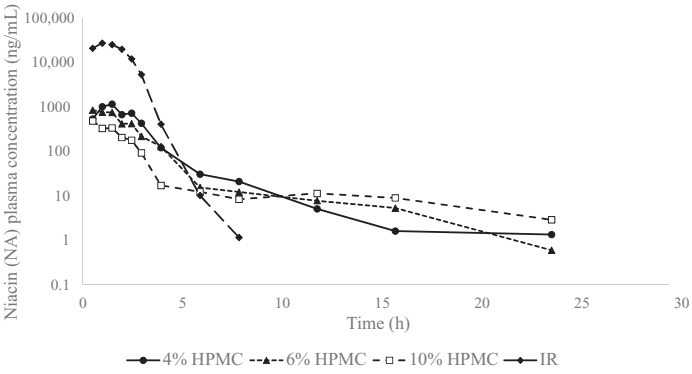

Figure 3. Mean plasma niacin (NA) pharmacokinetic profiles following administration of three ER niacin formulations and IR niacin reference to healthy volunteers.

formulations attained delayed and protracted concentration–time profiles, which were distinctly different from the IR (Niacor™) PK profile, including the 4% HPMC formulation that had a faster dissolution than the 6% HPMC formulation used in Tredaptive™. The arithmetic means for ER and IR niacin formulations have the anticipated rank order for AUC and C_{max} for NA and NUA and urinary excretion that fall in line with dissolution rates. Therefore, the data were supportive to continue evaluation of IVIVC.

Development of Multiple Level C IVIVC Models

For all *in vitro* dissolution time points, with the exception of the earliest time points, validated Multiple Level C IVIVC models were obtained. Figures 4 and 5 show the regression for select time points representing the early, middle, and late part of the dissolution. The attempted linear regression models indicated a strong correlation between summary PK and dissolution for both NA and NUA as well as the total urinary excretion of NA and its metabolites (Table 4). Specifically for the parent NA AUC, the correlation was greater than 0.9 at all time points, except for the two initial time points (0.5 and 1 h, although for 1 h the correlation was still acceptable, $r = 0.883$). For C_{max}, only the 0.5-h time point had an associated correlation less than 0.9. Similarly, strong correlations were observed for NUA. The correlation was also greater than 0.9 for the 24 and 96-h total urinary excretion parameters of NA and its metabolites at each of the *in vitro* time points, the only exception being the 0.5-h dissolution time point that showed low r values (<0.4). These Multiple Level C models were predictive for summary PK of both NA and NUA in plasma, as well as the total urinary excretion of NA and its metabolites as judged by the %PEs. The models predicted both NA and NUA C_{max} and $AUC_{0–24}$ and the total urinary excretion after 24 and 96 h with individual %PE well within the 15% criteria of internal validation for all three ER formulations and the mean %PE (MAPPE) were also well within the 10% limit defined in relevant Agency Guidances.[1–3]

Development of Level A IVIVC Models

For the traditional deconvolution-based Level A IVIVC model for NUA, a linear model with time scaling and cut-off provided the best fit to the data (Table 5). Although the model predicted $AUC_{0–24}$ well within the 15% criteria of internal validation for all three ER formulations, the model was less predictive for C_{max} of the standard ER formulation with a %PE above 15% (33.9%). Consequently, an alternative IVIVC model was attempted using the Balan approach.

To develop the alternative model, a Makoid–Banakar function (for equation see Table 2) was fit to the mean *in vitro* dissolution data (Fig. 1) for the three ER formulations where FMAX (maximum dissolution) was fixed to 1 for all three formulation. A Hill function (for equation see Table 2) was fit to the *in vivo* release data (Fig. 6) for the three ER formulations. The parameter estimates for these fits are presented in Table 2. The relationships between the *in vitro* Makoid–Banakar parameters and the *in vivo* Hill parameters were then explored (Table 5). The *in vitro* TMAX parameter was the only *in vitro* parameter that was formulation dependent following the rank order of the dissolution profiles (longer TMAX for slower formulations). Small differences were observed for the slope b term but these did not follow a trend between formulations and therefore slope b was not considered critical for inclusion in the correlation to *in vivo* data. The *in vivo* Finf and MDT parameters were, as expected, formulation dependent but the b parameter was independent of formulation suggesting a consistent absorption/release mechanism between formulations.

Models that best described the relationship between the *in vitro* parameter TMAX and the *in vivo* parameters, MDT and Finf, were developed (Table 5; Fig. 7). A linear model adequately described the relationship between *in vivo* Finf and *in vitro* TMAX:

$$\mathrm{Finf}_{in\ vivo} = 0.004343.\mathrm{TMAX}_{in\ vitro} + 0.5175.$$

Similarly, a linear model adequately described the relationship between *in vivo* MDT and *in vitro* TMAX:

$$\mathrm{MDT}_{in\ vivo} = -0.008534.\mathrm{TMAX}_{in\ vitro} + 1.644.$$

In line with the traditional model, the model predicted AUC for all formulations used in the development of the model with good precision. A reasonable prediction of the plasma concentration profile was obtained (Fig. 8). The maximum AUC %PE was 8.1% for the fast formulation, and the MAPPE was 5.9%. The model also predicted C_{max} with reasonable precision for all formulations, with the average %PE of 7.1% (Table 5).

On the contrary, a model for NA was not feasible. The mean fraction absorbed *in vivo* vs. the corresponding fraction released

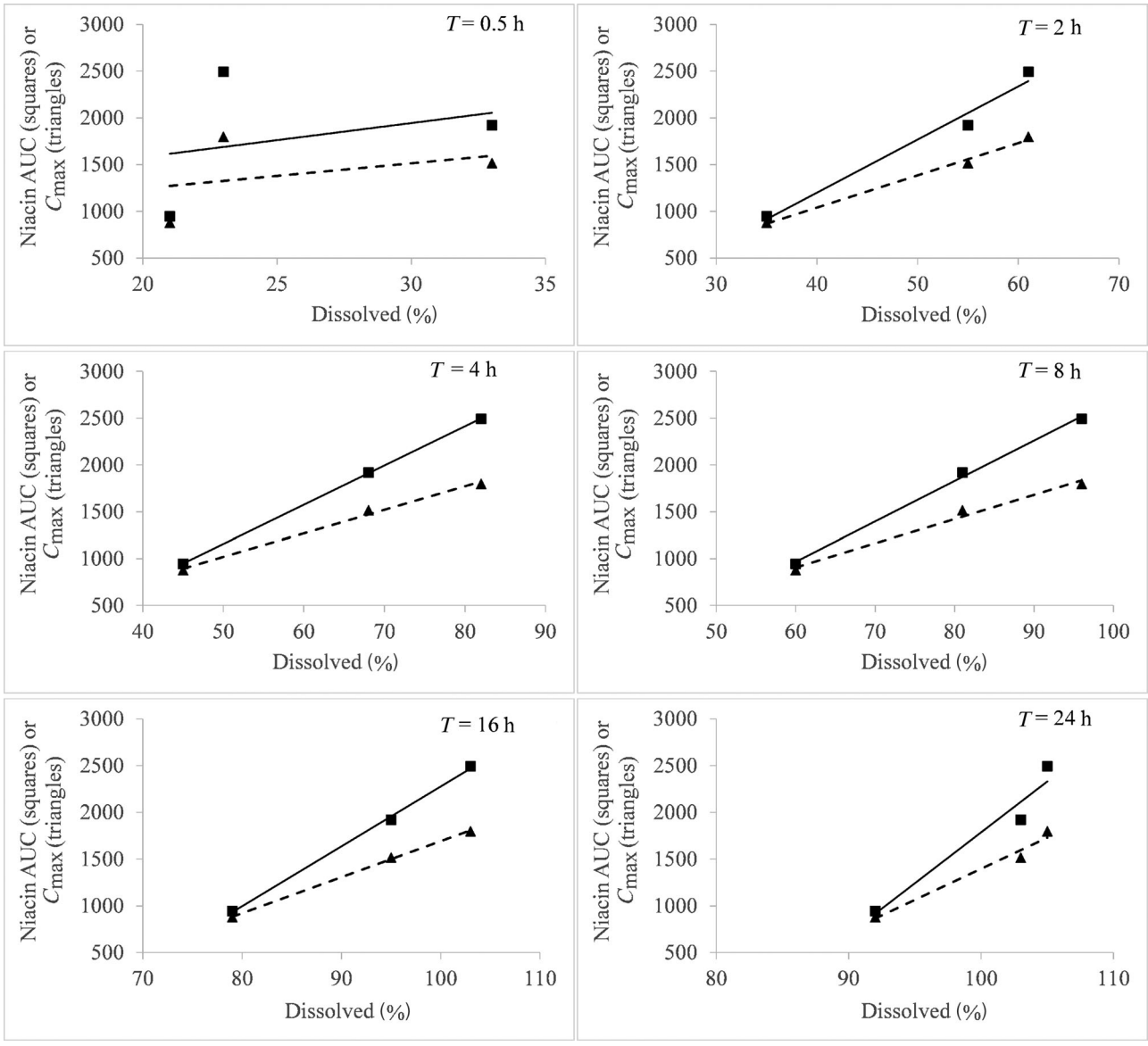

Figure 4. Multiple Level C IVIVC model for niacin (NA). Only correlations at 0.5, 2, 4, 8, 16, and 24 h are shown for both AUC (squares) and C_{max} (triangles). Regression equations and correlation coefficients are shown in Table 4.

in vitro plotted following the fast (4% HPMC), standard (6% HPMC), and slow (10% HPMC) ER formulations are presented in Figure 9. There appeared to be no more NA absorption after approximately 4 h. The overall percent fraction input for NA was very low for all ER formulations, which is indicative of likely a very significant change in the extent of metabolism relative to IR. Given the lack of a clear correlation, development of an IVIVC for NA was not pursued.

Exploration of Compartmental Population Pharmacokinetic Models for NUA

In general, the compartmental models provided a better description of the NUA data than they did for the corresponding NA data. Thus, models for NA were not pursued. For the simplified model developed, the final form of the model was:

$$r(t) = \varphi(t) * 3.00 * r_{diss}\ (0.156 + 0.196 * t) \text{ with a } T_{cutoff} \text{ of } 3.33\,\text{h}$$

The final model resulted in acceptable PEs for AUC (PEs were 2.0%, 0.6%, and 6.3% for the 4%, 6%, and 10% HPMC formulations, respectively) but failed to capture the C_{max} of the slower formulation (33.7% PE%); C_{max} PEs for the other two formulations were acceptable (6.0% and 12.4%). Although the model accurately predicted AUC, it did not provide any advantage over the alternative ("Balan") Level A IVIVC model established.

DISCUSSION

The intention of the study reported herein was to establish an IVIVC for niacin ER formulations. The first consideration in establishing an IVIVC is the suitability of the tested compound. Niacin is a highly soluble (>10 mg/mL) and highly permeable compound. The physicochemical properties make it a good candidate to formulate in hydrophilic, polymer-based

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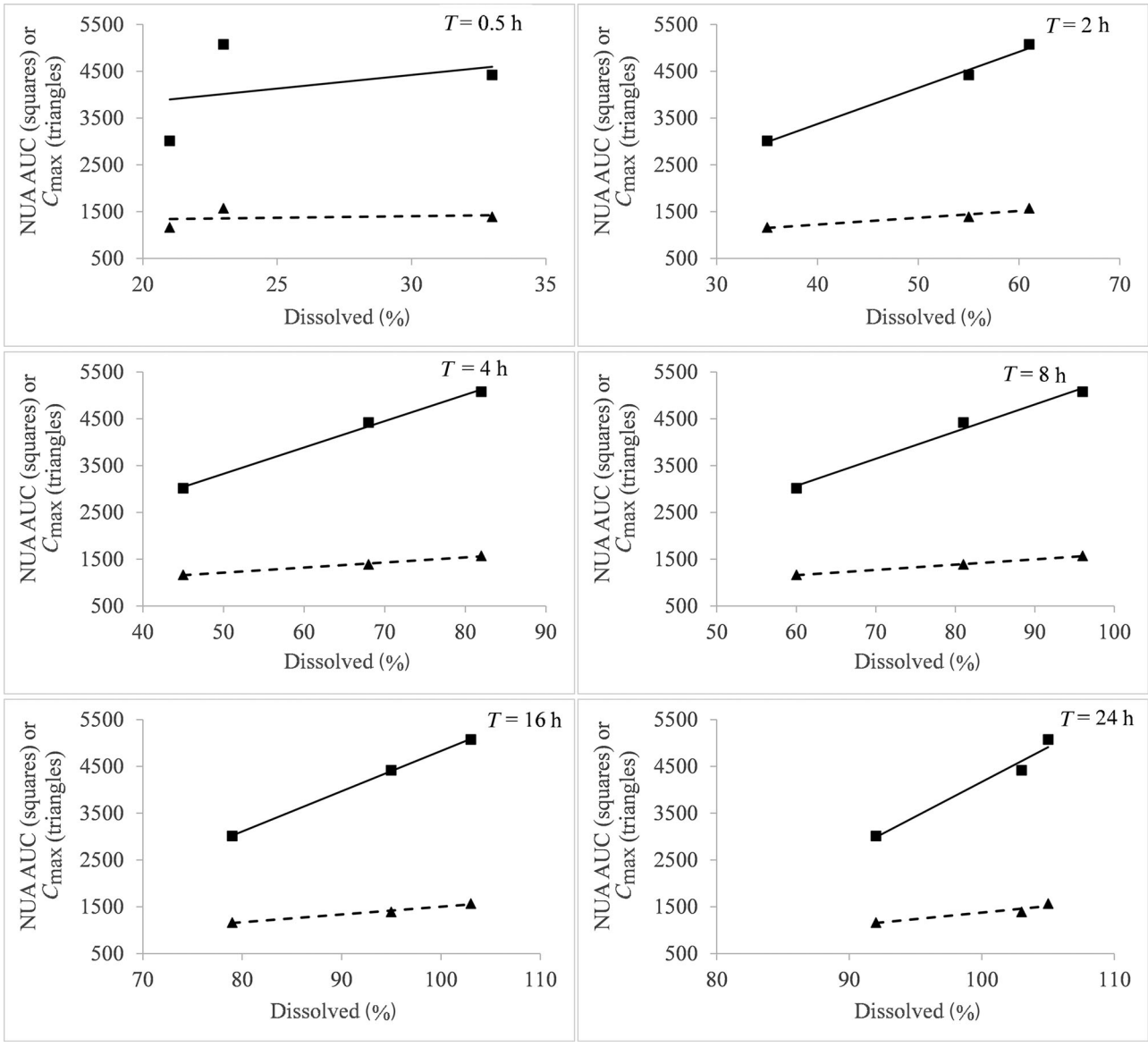

Figure 5. Multiple Level C IVIVC model for NUA. Only correlations at 0.5, 2, 4, 8, 16, and 24 h are shown for both AUC (squares) and C_{max} (triangles). Regression equations and correlation coefficients are shown in Table 4.

matrix MR dosage forms as used in this study. As a BCS Class I compound, *in vivo* absorption from the formulation in the gut lumen is solely controlled by the release from the formulation. BCS class I compounds have been suggested to possibly be good candidates for the establishment of IVIVCs if the release mechanism is maintained between tested products.[18] Thus, based on these criteria, niacin is a reasonable candidate for an IVIVC study. However, despite the BCS I classification, under the more recently established BDDCS system, BCS/BDDCS I compounds have also been shown to be subject to extensive metabolism.[19] If this extensive metabolism includes presystemic components, appearance of drug in the plasma may no longer be solely controlled by the formulation dissolution rate. Niacin is well established to undergo extensive metabolism *in vivo*, including saturable first-pass metabolism that is sensitive to the rate of absorption. The extensive metabolism results in significant variability *in vivo*, especially for the plasma levels of the parent compound niacin, both within and between subjects (typically around 80% between subjects) and in higher niacin variability for the ER formulations compared with IR. High variability and potential for differential bioavailability between formulations have been cited as one of the common limitations in establishing IVIVCs.[20] With the variability knowledge in mind, our intention was to study the feasibility of an IVIVC for such a variable and highly metabolized compound and understand the possibilities of utilizing such models either during formulation development or for regulatory application.

On the basis of the pharmacokinetic outcome of the clinical formulation study described in this manuscript, predictive Multiple Level C models were established for both niacin (NA) and its major metabolite, NUA. In addition, a validated model for total urinary excretion was developed that can be used to predict the time course of excretion for any ER formulation, based on its *in vitro* dissolution data. Following the

Table 4. Multiple Level C Correlations for NA and NUA AUC and C_{max} and Total Urinary Excretion (24 and 96 h) Versus Percent Dissolved (%Diss)

Time (h)	Regression Equation	r	MAPPE (%)	Regression Equation	Multiple R	MAPPE (%)
	NA AUC (ng h/mL)			NA C_{max} (ng/mL)		
0.5	846.5+36.6 %Diss	0.301	36.7	706.8+26.9 %Diss	0.367	25.4
2	−1074.4+56.8 %Diss	0.988	4.7	−339.1+34.5 %Diss	0.997	1.9
4	−937.2+41.9 %Diss	1.000	0.3	−237.1+25.1 %Diss	0.997	2.1
8	−1628.5+43.2 %Diss	0.999	1.9	−645.5+25.8 %Diss	0.992	3.2
12	−2546.1+49.8 %Diss	1.000	0.6	−1207.1+29.9 %Diss	0.999	1.4
24	−9098.1+108.8 %Diss	0.973	6.6	−5245.4+66.4 %Diss	0.987	3.5
	NUA AUC (ng h/mL)			NUA C_{max} (ng/mL)		
0.5	2676.9+58.2 %Diss	0.355	18.1	1199.2+6.8 %Diss	0.216	10.6
2	292.7+77.0 %Diss	0.996	1.7	642.3+14.6 %Diss	0.971	2.5
4	513.0+56.3 %Diss	0.998	1.3	667.3+10.9 %Diss	0.997	0.9
8	−403.9+57.9 %Diss	0.994	2.1	484.2+11.3 %Diss	0.999	0.4
12	−1656.6+67.0 %Diss	0.999	0.8	251.9+12.9 %Diss	0.995	1.2
24	−10,653.4+148.2 %Diss	0.985	2.9	−1391.7+27.7 %Diss	0.950	3.2
	24 h Total Urinary Excretion (μmol)			96 h Total Urinary Excretion (μmol)		
0.5	2199.6+29.8 %Diss	0.322	14.2	4246.5+40.7 %Diss	0.389	8.6
2	781.8+43.4 %Diss	0.992	1.8	2809.6+49.3 %Diss	0.998	0.5
4	894.1+31.9 %Diss	1.000	0.5	2964.6+35.8 %Diss	0.995	1.0
8	370.9+32.8 %Diss	0.997	1.2	2386.0+36.8 %Diss	0.989	1.4
12	−331.5+37.9 %Diss	1.000	0.1	1580.6+42.7 %Diss	0.997	0.7
24	−5357.7+83.2 %Diss	0.978	2.8	−4224.1+95.2 %Diss	0.991	1.2

Correlation coefficient (r) and MAPPE for each regression equation are also reported.

Table 5. Validation Statistics for the Traditional Versus Alternative (Balan) IVIVC Approach for NUA Plasma Levels

Traditional Time Scale/Time Shift Model

$x_{vivo}(t) = 0.6244 \times \text{Fdiss}(0.7099 \times t - 0.2967)$

Formulation	Parameter	Predicted	Observed	%PE
4% HPMC	AUC_{last} (ng h/mL)	5643	5296	6.4
	C_{max} (ng/mL)	1394	1340	4.0
6% HPMC	AUC_{last} (ng h/mL)	4774	4597	3.9
	C_{max} (ng/mL)	1643	1227	33.9
10% HPMC	AUC_{last} (ng h/mL)	3213	3127	2.7
	C_{max} (ng/mL)	893	941	−5.1
MAPPE	AUC_{last} (ng × h/mL)			4.3
	C_{max} (ng/mL)			14.3

Modified Level A IVIVC Model[a]

$x_{vivo}(t) = \frac{\text{Finf} \times t^b}{\text{MDT}^b + t^b}$

$\text{Finf} = -0.004343 \times \text{TMAX} + 0.5175$

$\text{MDT} = -0.008534 \times \text{TMAX} + 1.644$

Formulation	Parameter	Predicted	Observed	%PE
4% HPMC	AUC_{last} (ng h/mL)	5726	5296	8.1
	C_{max} (ng/mL)	1518	1340	13.3
6% HPMC	AUC_{last} (ng h/mL)	4761	4597	3.6
	C_{max} (ng/mL)	1308	1227	6.6
10% HPMC	AUC_{last} (ng h/mL)	3314	3127	6.0
	C_{max} (ng/mL)	954	941	1.4
MAPPE	AUC_{last} (ng h/mL)			5.9
	C_{max} (ng/mL)			7.1

[a] Parameter estimates shown in Table 2.

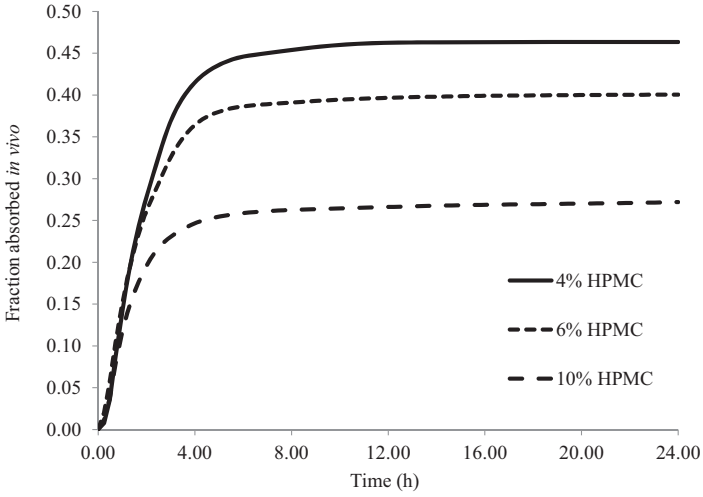

Figure 6. *In vivo* input time course for NUA for three ER niacin formulations as estimated via deconvolution.

establishment of the multiple Level C IVIVC, Level A IVIVC models were explored. On the basis of historical experience with the program, we intended to focus on NUA as that was deemed to have a higher possibility of success compared with niacin. During model development, it further became apparent that niacin models would not be successful—a correlation between dissolution and the apparent "fraction absorbed" could not be established and the overall "bioavailability" of niacin was very low, indicating the substantial first-pass metabolism that the ER formulations undergo relative to the IR, which could be a contributing factor to the inability to establish an IVIVC model. To establish a Level A model for NUA, we followed an approach similar to what was used by Balan et al.[16] for metformin. Similarly, as we demonstrate in this manuscript for niacin, in the metformin case, the authors failed to obtain acceptable Level A models via the traditional deconvolution/convolution method,

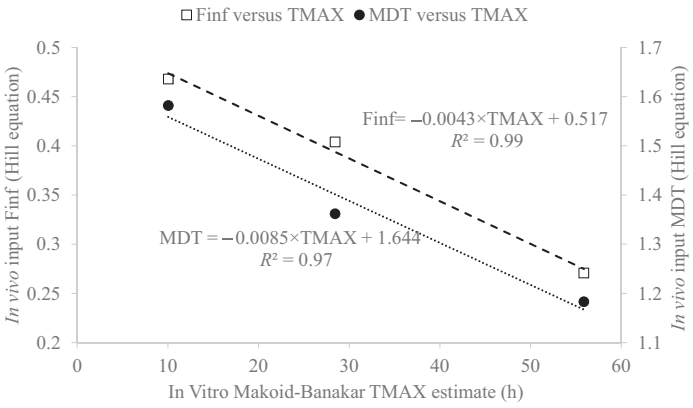

Figure 7. Correlation of *in vitro* parameter TMAX with *in vivo* Finf and MDT parameters used for the alternative (Balan) IVIVC approach. *In vitro* parameters were obtained from fit of *in vitro* dissolution data shown in Figure 1 to Makoid–Banakar equation, whereas *in vivo* parameters were obtained from fitting the NUA input plasma profiles shown in Figure 6 to a Hill equation. Parameter estimates can be found in Table 2.

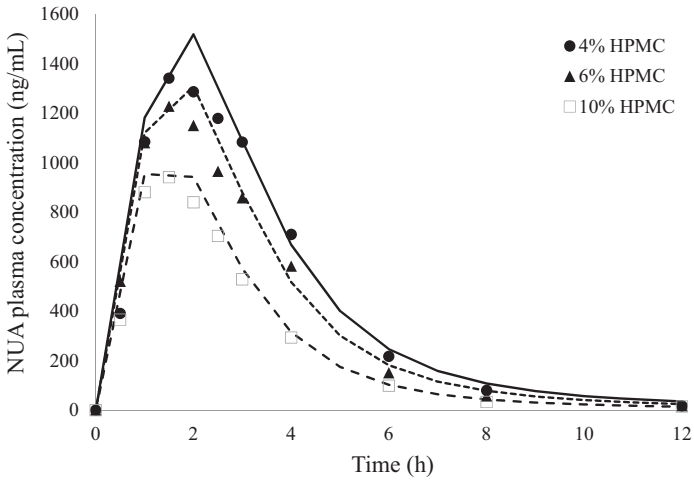

Figure 8. Validation of the alternative (Balan) Level A IVIVC model for NUA. Solid lines represent model projections against observed data (symbols).

although they had already established Level C models. The alternative correlation method allowed the authors to overcome the limitations imposed by the region-dependent absorption of metformin. In the case of niacin, this model transformation allowed us to more adequately take into account the differential bioavailability between formulations. The Level A models based on this approach provided for accurate estimation of AUC and improved estimation of C_{max}, resulting in more consistent predictions between formulations (Table 5). Recently, compartmental modeling approaches have been used for IVIVC model development.[9,10,17] Utilizing average (geometric mean data) instead of individual data, a Level A model appeared possible for NUA alone but did not provide better prediction compared with the alternative Level A model already developed. We did not attempt to establish any Level B IVIVC models. Level B models are not considered suitable for regulatory arguments, and because a Level C model was already developed, a Level B model would provide limited additional benefit even for a formulation development question.

One question that immediately comes to mind when discussing the ability to establish an IVIVC is the study design and selection of formulations. The available Agency guidelines recommend that at least two (ideally three) formulations of similar release mechanism should be tested. The formulations should exhibit sufficiently different dissolution profiles (typically defined against F2 similarity criteria). In the study described here, three formulations with different release rates (F2<50 between the formulations) were studied. The release rate was modified by only a change in the level of the polymer (HPMC)—this ensures similar release mechanism between formulations. In addition, the study needs to have sufficient subjects to allow for sufficient exploration of the pharmacokinetic differences. A strict guideline on this is not available, although recent guidance suggests at least 12 healthy volunteers should be included.[2] The sample size is of particular importance when variability is higher.[20] Niacin does exhibit high variability. In this study, a size of 36 subjects was employed. Although even with this study size significant variability is still observable, the study well covers any available guidelines on study size and allows for an exploration of the IVIVC. Thus, the difficulties to establish the IVIVC cannot be attributed to the study or formulation selection, rather this represents an inherent limitation of the compound pharmacokinetic properties.

Current Agency guidances suggest that when a Multiple Level C model is obtained, a Level A model is also typically achievable. Although this may be true for well-behaved compounds with fully linear pharmacokinetics, the case study presented here with niacin, as well as the previously described case of metformin,[16] raise important questions on the approaches for developing IVIVC for compounds with more complex pharmacokinetics, including BCS I/BDDCS I drug with significant presystemic metabolism. Specifically, what alternative methodologies may be applicable and what level of validation can be accomplished, as well as how can Multiple Level C IVIVC models be applied in the absence of a Level A model. The traditional deconvolution–convolution technique, as detailed in the FDA guidance, is inherently limited in these cases and alternative methodologies need to be considered. The establishment of Level C models that accurately predict either AUC or C_{max} (and in this case also total urinary excretion) clearly indicate that the dissolution method is of clinical relevance, despite the difficulties of the Level A model establishment. By using an alternative method, the Balan approach, acceptable prediction of the mean plasma pharmacokinetic profile was obtained for NUA. Although such a model may not exactly follow the available Regulatory guidances, it further clearly provides a link between dissolution and clinical performance within the tested formulation space.

One question that is worth considering is: what is the appropriate use of the Multiple Level C model in such case where the Level A is not established? One potential approach to this question is to consider the pharmacokinetic determinants of efficacy and safety and the intended utility of the model. Level A models are preferred as they allow for prediction of the entire pharmacokinetic time course—this may be of significant importance if this has a direct control on drug efficacy/safety. Multiple Level C models on the other hand allow for an accurate prediction of both C_{max} and total exposure (AUC). For drugs for which these parameters can be linked to pharmacodynamics end points,

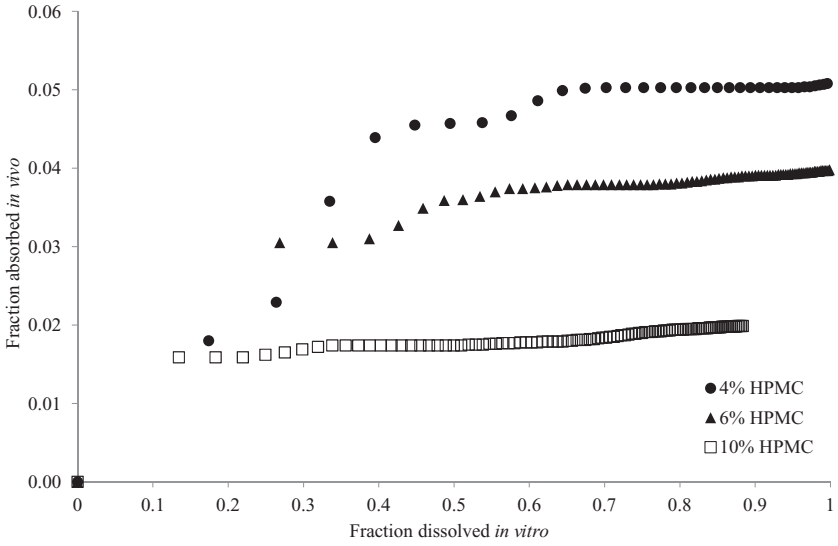

Figure 9. *In vitro* dissolution versus *in vivo* absorption for parent niacin (NA).

these models may be sufficient to inform product quality. In the case of niacin, the exact mechanism of action is not known and thus full PK/PD models cannot be established; however, it is generally believed that AUC is more relevant to efficacy compared with C_{max}. The Multiple Level C model established for parent and metabolites clearly indicated the biorelevance of the established dissolution method. The dissolution method would allow assessment of the impact on absorption on any future manufactured batch within the tested formulation space. All formulations would have adequate total exposure based on either the Multiple Level C or the Level A AUC models. Both niacin and NUA C_{max} were also adequately described by the Multiple Level C model. Thus, given the ability of the model to accurately describe the summary pharmacokinetic parameters for the parent drug (niacin), the major metabolite (NUA) and the total urinary niacin and metabolite excretion (a surrogate for total absorption), one could suggest that it may be possible to use the Level C IVIVC model to establish clinically relevant specifications as well as a surrogate of *in vivo* studies for any manufacturing changes that would be considered minor (e.g., change in manufacturing site) and do not result in a change of the release rate as that defined within standard product specifications.

One final point that needs to be addressed is the lack of correlation for the first dissolution time point (30 min) of the Multiple Level C IVIVC model and the potential impact on its application. Regulatory guidances do not specify the number of time points required to designate a Multiple Level C IVIVC correlation. In this specific case, the lack of accurate prediction at the first time point would be of no practical consequence in terms of future model application. Any new formulation within the same formulation space that has been studied and with dissolution specifications conforming to any projections out of this IVIVC model, which will be derived from the entire dissolution curve, would be inherently constrained by the formulation design at the first time point or from the proposed specifications (i.e., there will be no possibility that dissolution at that time point would be outside the studied formulation space). We would like to acknowledge that further qualification of such models may be required to fully address their applicability across wider formulation spaces than studied or when significant formulation changes are introduced.

CONCLUSIONS

Current Regulatory Agency guidelines suggest that when a Multiple Level C IVIVC is established, Level A models should also be achievable. We demonstrated in this example that for compounds such as niacin with complex *in vivo* metabolism resulting in high *in vivo* variability, this may not be the case. Multiple Level C models with acceptable PE were established for both niacin as well as its major metabolite NUA and for total urinary excretion. However, establishment of fully validated (as dictated by guidances) Level A models was not possible; although several approaches were evaluated, some limited success was obtained for NUA but not niacin. Despite the availability of a Level A model, Multiple Level C models that are more readily achievable could potentially be used to guide aspects of formulation development, clinically relevant release specifications, and potentially serve as bioequivalence surrogates for minor formulation/manufacturing changes.

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