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A time-scaled convolution approach to construct IVIVC for enteric-coated acetylsalicylic acid tablets

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A scaled convolution-based *in vitro-in vivo* (IVIVC) model was constructed for two enteric-coated acetylsalicylic acid tablet formulations. The *in vitro* data used were the results of dissolution testing performed using three different dissolution methods: the United States Pharmacopoeia (USP) method, a method employing blank Fasted State Simulated Fluid (FaSSIF), and a new method developed in house. The *in vivo* data were obtained from a pharmacokinetic study on human subjects in the fasted state. When the new dissolution method results were used, an average prediction error less than 10% and a maximum prediction error less than 15% were obtained for the peak plasma concentration (C_{max}) and area under the curve (AUC) parameters, thus meeting the internal validation criteria of the IVIVC guidance of the US Food and Drug Administration (FDA).

1. Introduction

In vitro-in vivo correlations (IVIVCs) and relationships (IVIVRs) are used to predict *in vivo* pharmacokinetic performance of drug products based on *in vitro* dissolution testing results. The most useful ones are level A IVIVCs where a point to point correlation between *in vitro* dissolution and *in vivo* dissolution or absorption is established.

Level A correlations can be established either through a deconvolution-based approach or a convolution-based approach (Gillespie 1997; Hühn and Langguth 2013). Deconvolution-based methods are the more traditional approaches; however, convolution-based methods are considered advantageous (particularly due to their being single step methods that directly predict measured plasma concentrations) (Gillespie 1997). However, with both approaches, stretching or compressing the *in vitro* dissolution time scale to match that of the *in vivo* dissolution/absorption (i.e. performing time-scaling) is commonly needed (Gillespie 1997; Veng-Pedersen et al. 2000; Brockmeier et al. 1985). This is due to dissolution conditions (like agitation rates and dissolution media) *in vivo* being not identical to those *in vitro*.

With deconvolution-based approaches, time-scaling is traditionally done using Levy plots where the time required to achieve a certain %released/absorbed *in vivo* (obtained through deconvolution) is plotted against the time required to achieve the same % released *in vitro*. For convolution-based ones, there is no traditional approach but a few ones have been proposed (Veng-Pedersen et al. 2000; Brockmeier et al. 1985).

IVIVC's are not always easy to obtain. For instance, it is difficult to obtain an IVIVC/IVIVR for enteric-coated (EC) formulations. Indeed, such dosage forms have even been mentioned as unsuitable for IVIVC development (Cardot and Davit 2014). This is owing to mean curves misrepresenting the formulation performance (Cardot and Davit 2014), and the unsuitability of the compendial dissolution methods established in current laboratory practice (Al-Gousous et al. 2016). Therefore, attempts at IVIVC/IVIVR for EC formulations are scant in literature.

Campos et al. (2010) established a deconvolution-based IVIVR that showed the absorption of pantoprazole from EC tablets to be permeability rate-limited. Kambyashi et al. (2013, 2014) employed a physiology-based pharmacokinetic approach (PBPK) to compare the ability of different *in silico* gastric emptying models and parameters to predict the behavior of EC diclofenac sodium formulations. Al-Gousous et al. (2016) used a GastroPlus-based correlation to compare the suitability of different dissolution methods for testing EC ASA tablets. In this work, a time-scaled convolution approach coupled to the use of a new dissolution method with improved biopredictivity is going to be used to construct an IVIVC for two EC ASA single-unit formulations with prediction errors matching the FDA criteria.

2. Investigations and results

2.1. In vitro and in vivo data

The *in vitro* and *in vivo* data used were those published in a previous work (Al-Gousous et al. 2016). In short, two enteric-coated (EC) ASA products: Aspirin Protect 300 mg (Bayer AG, Germany) and Walgreens Aspirin 325 mg (LNK International, USA) were evaluated *in vitro* using three different dissolution methods: United States Pharmacopoeia (USP) method, blank Fasted State Simulated Gastric and Intestinal Fluid (FaSSGF and FaSSIF) method and a new method described in detail in the aforementioned work (Al-Gousous et al. 2016). They were also evaluated *in vivo* in a randomized fully replicated four-way, four-period, two-sequence, cross-over, open label single dose study performed on 12 healthy male volunteers (the 11 subjects who completed the study were evaluated) in the fasted state. The study protocol was approved by the Jordanian Food and Drug Administration (JFDA) (Al-Gousous et al. 2016). For a detailed description of all the methods used to obtain the data, as well as the *in vitro* dissolution and *in vivo* pharmacokinetic profiles, the reader is referred to the cited work (Al-Gousous et al. 2016).

2.2. IVIVC model

A time-scaled convolution approach was used. The convolution model is as follows:

$$C_t = f_a.(1-f_i).(1-f_h).D.(dA/dt)_t * UIR_t$$

where C_t is the plasma ASA concentration at time t, f_a is the fraction absorbed from the intestinal lumen, f_i is the fraction of the dose undergoing first-pass metabolism in the intestinal mucosa, f_h is the fraction of the dose undergoing hepatic first-pass metabolism, D is the dose, $(dA/dt)_t$ is the fractional absorption rate at time t (time *in vivo)*,* is the convolution operator, and UIR_t and is the unit impulse response at time t.

Table 1: Time-scaling factor optimization results

Dissolution method	Optimal time-scaling factor	Cmax/AUC_{0-24}					
		Product	Predicted (h^{-1})	Observed (h^{-1})	% Prediction error	Average % prediction Error	Maximum % prediction error
USP	3.55	Walgreens Aspirin	0.791	0.665	18.96	16.8	18.96
		Aspirin protect	0.542	0.635	14.66		
Blank FaSSIF	2.25	Walgreens Aspirin	0.981	0.665	47.53	36.99	47.53
		Aspirin protect	0.467	0.635	26.45		
New	2.15	Walgreens Aspirin	0.753	0.665	13.21	11.44	13.21
		Aspirin protect	0.574	0.635	9.66		

Table 2: IVIVC validation results - part I (C_{max})

Dissolution method	Cmax					
	Product	Predicted (ng/ml)	Observed (ng/ml)	% Prediction error	Average % prediction Error	Maximum % prediction error
USP	Walgreens Aspirin	1450.0	1290.7	12.34	12.35	12.35
	Aspirin protect	850.6	970.5	12.35		
Blank FaSSIF	Walgreens Aspirin	1741.4	1290.7	34.92	28.94	34.92
	Aspirin protect	747.6	970.5	22.97		
New	Walgreens Aspirin	1388.9	1290.7	7.61	9.13	10.65
	Aspirin protect	867.1	970.5	10.65		

Table 3: IVIVC validation results - part II (AUC)

Dissolution method	AUC_{0-24}					
	Product	Predicted (ng h ml^{-1})	Observed (ng h ml^{-1})	% Prediction error	Average % prediction Error	Maximum % prediction error
USP	Walgreens Aspirin	1833.0	1939.8	5.51	4.06	5.51
	Aspirin protect	1569.6	1529.5	2.62		
Blank FaSSIF	Walgreens Aspirin	1775.1	1939.8	8,49	6.57	8.49
	Aspirin protect	1600.6	1529.5	4.65		
New	Walgreens Aspirin	1844.8	1939.8	4.90	3.03	4.9
	Aspirin protect	1511.6	1529.5	1.17		

As for the time *in vivo* (t), $t=s.t_{in\ vitro}$, where s is the time-scaling factor and $t_{in\ vitro}$ is the time corresponding to a %released *in vitro* value equal to the %absorbed *in vivo* value at time t.

Using ASA pharmacokinetic data collected from literature as shown by Al-Gousous et al. (2016), f_i was set at 0.54, f_h was set at 0.5. As for the value of f_a, absorption of dissolved ASA from the intestinal lumen can be assumed to be complete (Dressman et al. 2012).

UIR (Unit impulse response) was the ASA plasma concentration profile following an intravenous (IV) bolus administration, calculated using a two-compartment open model with elimination from the central compartment. For this model, additional pharmacokinetic data collected from literature were used (Al-Gousous et al. 2016): the volume of central compartment being 0.123 L kg^{-1}, the clearance being 0.596 L h^{-1} kg^{-1}, the central to peripheral compartment transfer rate constant being 2.8 h^{-1}, the peripheral to central compartment transfer rate constant was 4.4 h^{-1}. As for body weight, the average subject weight reported for the *in vivo* study (77.4 kg) was used (Al-Gousous et al. 2016). The resulting two-compartment equation for the UIR was (assuming a 300 mg IV-bolus dose):

$$C_t=22.37e^{-9.89t}+9.14e^{-2.16t}$$

where t is the time in hours.

The dissolution profile of each tested tablet was convoluted using this approach and the peak plasma ASA concentration (C_{max}), area under the curve from zero to 24 h (AUC_{0-24}) and C_{max}/ AUC_{0-24} ratio of the resulting profiles were geometrically averaged for each dissolution set-up and compared against observed geometric mean values observed *in vivo*. The individual dissolution profiles were convoluted and then averaged instead of being averaged and then convoluted because the variability in dissolution onset lag time and in the length of an initial period of slow dissolution leads to average profiles inaccurately representing the average dissolution rates.

The convolution was performed using Kinetica 5.0 (Thermo Fischer Scientific, UK)

2.3. Determination of the time-scaling factor

The time-scaling factor, s, was determined through iterative optimization in a fashion somewhat similar to what was has been done by Veng-Pedersen et al. (2000) However, the optimization parameter proposed in this work was the C_{max}/AUC_{0-24} ratio which can be considered as a metric of the overall absorption rate (Al-Gousous et al. 2016). The time-scaling factor that gave minimal sum of

squared differences between the predicted and observed values of ln (C_{max}/AUC_{0-24}) was considered optimal. The time-scaling factor values were determined to the nearest 0.05.

2.4. Results

Table 1 shows the results of the time-scaling factor optimization. Tables 2 and 3 show the IVIVC validation results for the C_{max} and AUC parameters respectively. The new dissolution method gave the lowest scaling factor and the lowest prediction errors as well. This is in agreement with the convolution performed using physiologically-based absorption models (without any time-scaling) of the GastroPlus software in the previous work (Al-Gousous et al. 2016) where the new method also gave the best overall results. The prediction errors for the C_{max} and AUC parameters, predicted based on the new dissolution method, passed the FDA internal validation criteria (average prediction error<10% and maximum prediction error<15%) (FDA 1997).

3. Discussion

Time-scaled convolution was used to establish an IVIVC. For time-scaling, the scaling factor used to convert the *in vitro* dissolution time scale into *in vivo* absorption time scale was adjusted iteratively until a value that makes the predicted overall absorption rates fit closest to the observed ones is obtained, with the C_{max}/AUC ratio being used as the overall absorption rate metric. This way of time-scaling parameter calculation provides a way for IVIVC construction where the use of mean plasma-concentration curves is invalid, like in the case of single-unit EC ASA products (owing to the high variability in the onset of absorption and in the first-pass metabolism) (Al-Gousous et al. 2016)). It also provides a single optimization parameter, and so it allows performing the scaling factor optimization manually without the need of having an optimization algorithm programmed into the software.

Being the result of dividing two parameters (C_{max} and AUC) for which the typical measure of central tendency of choice is the geometric mean, geometric mean was also chosen as the measure of central tendency for the C_{max}/AUC ratio (since the quotient of two lognormally distributed variables is also lognormally distributed (Buszaki and Mizuseki 2014). And owing to this choice, the optimal time-scaling factor was set to be the one that gives the minimal sum of squared differences between the predicted and observed values of the natural logarithm of the geometric means of the C_{max}/AUC_{0-24} ratio. Owing to the AUC_{0-24} being deemed close to the $AUC_{0-\infty}$ in the employed dataset (Al-Gousous et al. 2016), it was used in the C_{max}/AUC ratio calculation ($AUC_{0-\infty}$ could not be calculated for some profiles owing to difficulty in fitting their terminal phases) (Al-Gousous et al. 2016).

The time-scaling factors calculated were all greater than unity indicating that the *in vitro* dissolution was faster than *in vivo* absorption. This is most probably due to a combination of two causes:

1. The *in vitro* dissolution still being somewhat faster than *in vivo* dissolution despite the considerable improvement brought by the introduction of the new method (as indicated by the results presented by Al-Gousous et al. 2016) in this regard.
2. That the overall *in vivo* absorption is also somewhat slower than the *in vivo* dissolution because of the dissolution probably not being much slower than drug permeation through the intestinal epithelium, thus making the contribution of this step not entirely negligible (since we are not dealing with a sustained release formulation with a typically much slower release in this case).

The IV pharmacokinetic data used were obtained from literature, however, because, in contrast to following oral administration, ASA pharmacokinetics are not highly variable following IV administration (Nagelschmitz et al. 2014), the resulting IVIVC is still acceptable. Moreover, the inclusion of a reference treatment is not obligatory for convolution-based IVIVC Gillespie 1997; FDA 1997). Indeed, as long two or more formulations are available, a suitable parametric function can be selected for UIR (Gillespie 1997). Had we had IV pharmacokinetic data for the subjects that volunteered in the study, then each dissolution curve could have been convoluted using the data of each individual before averaging. Another option could have been using the terminal half-lives of the individual curves, but the presence of flip-flop kinetics made this undoable (this is commonly observed even in non-sustained release ASA formulations owing to its fast elimination (Nagelschmitz et al. 2014; Mason 1984).

A valid concern is that the first-pass hydrolysis of ASA is highly variable (Al-Gousous et al. 2016). Therefore, a look on the predictions for C_{max}/AUC ratios which are far less affected by this variability is warranted, despite them not being "official" validation parameters. The C_{max}/AUC_{0-24} ratio prediction errors for each formulation, based on the new dissolution method, are both lower than the specified 15 % cut-off however the average prediction error is 11.44 % right above the 10 % criterion. This indicates that the new dissolution method results do really appreciably correlate with the *in vivo* absorption; however, including additional formulations for external validation is still recommended to conclusively establish the IVIVC despite not being a must per the FDA guidance. In addition, external validation enables full application of the IVIVC because, without it, a correlation based only on two formulations has its application limited only to Category 2a applications (FDA 1997).

All in all, using a simple time-scaled convolution approach and an improved dissolution testing method, an IVIVC could be obtained even for single unit enteric-coated formulations, which are known for being challenging in this regard. C_{max}/AUC ratio though not a bioequivalence metric could be employed to evaluate the overall degree to which the predicted absorption rate matches the observed one and to fit *in vitro* to *in vivo* absorption when a single-step convolution approach is used, and deconvoluted absorption profiles are not available. And it also provides a single optimization parameter, and thus simplifies the scaling factor optimization to a degree where it could be readily performed by hand, instead of being required to have it built into the software.

4. Experimental

The detailed experimental procedures and conditions are described in a previous work (Al-Gousous et al. 2016).

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