The Influence of Averaging Procedure on the Accuracy of IVIVC Predictions: Immediate Release Dosage Form Case Study

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ABSTRACT: *In vivo–in vitro* correlation (IVIVC) is an effective tool to predict absorption behavior of active substances from pharmaceutical dosage forms. The model for immediate release dosage form containing amoxicillin was used in the presented study to check if the calculation method of absorption profiles can influence final results achieved. The comparison showed that an averaging of individual absorption profiles performed by Wagner–Nelson (WN) conversion method can lead to lose the discrimination properties of the model. The approach considering individual plasma concentration versus time profiles enabled to average absorption profiles prior WN conversion. In turn, that enabled to find differences between dispersible tablets and capsules. It was concluded that in the case of immediate release dosage form, the decision to use averaging method should be based on an individual situation; however, it seems that the influence of such a procedure on the discrimination properties of the model is then more significant. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:5040–5045, 2010

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INTRODUCTION

In vivo–in vitro correlation (IVIVC) has become an effective tool to predict absorption behavior of various pharmaceutical dosage forms. The most number of described IVIVC's examples concerns prolonged release oral forms[1–3], but it is also possible to establish IVIVC for immediate release oral dosage forms[4,5] or even parenteral micospheres[6,7] or implants.[8] One of the most important issues of IVIVC for immediate release oral dosage forms is requirement to take into accounts time factor due to the relatively short dissolution time of immediate release tablet or capsule. It enables to compare *in vitro* and *in vivo* data. It is also quite difficult to achieve a good fit and FDA level A correlation between *in vivo* absorption profile and *in vitro* dissolution profile (predicted absorption). To find the best conditions of the dissolution test and best fit, it is possible to use variable hydrodynamic conditions or pH change to simulate absorption in gastrointestinal tract, but ideally a model should possess at the same time an appropriate discrimination properties for products with lower bioavailability. In IVIVC studies for prolonged release oral dosage forms, the conditions of *in vitro* test are usually constant with three formulations having different extent of absorption. On the other hand, a problem in IVIVC studies for immediate release oral dosage forms is a large number of time points on the absorption part of bioavailability curve. Applying a time factor, period between sampling during *in vitro* test becomes very short. On-line sampling systems may help to solve technical problem, but from mathematical point of view the results of dissolution test should be very close to real values of *in vivo* absorption profile. If not, T_{max} obtained from the *in vitro* data by back calculation of Wagner–Nelson (WN) method will be displaced, which makes the model less reliable.[9]

Our recent work[10] revealed that for certain group of active substances with known zero-order absorption process (e.g., amoxicillin)[11] it is possible to simplify the model for immediate release dosage form by removing points placed on linear part (positive slope) of absorption profile and bioavailability curve, what solves mathematical problems with T_{max} and makes dissolution procedure easier. It was found that our recent model established for dispersible tablets of amoxicillin showed features of level A correlation and

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possessed discrimination properties against forms of lower bioavailability (in that case—capsules).[12] In that work, WN method was used to calculate absorption profiles. However, it has some obvious limitations. On the other side, it is very useful because of no need to collect data from oral solution or parenteral injection. It can be also properly used when the active substance is known to have complete (or almost complete) absorption. IVIVC can be established on the basis of standard bioequivalence clinical trial with the use of WN method. Subsequently, the model may be applied in order to justify the lack of bioequivalence study in case of changes in production scale or formulation.

One of the latest article[13] concerning IVIVC showed that averaging procedure of *in vivo* data can possess a certain influence on results. It is claimed that averaging of data should be done after deconvolution performed on the individual subject level. Deconvolution on the averaged data can lead to lose information connected with subject variability. It means that in the case considered in the recent study[10] it should be done after calculations of absorption profiles from each of a subject by WN method instead of WN conversion made on averaged data.

The aim of the current work was to evaluate if the procedure of data averaging can possess an influence on the model prepared previously. As it was discussed above the IVIVC of immediate release dosage form has some differences in comparison to prolonged release dosage form. Especially, the concern was done to evaluate the possible changes on the level of discrimination properties of the model.

MATERIALS AND METHODS

Batches Used in the Study

Two batches of commercially available dispersible tablets (Amotaks® Dis produced by Polfa Tarchomin SA, Warsaw, Poland) containing 1000 mg of amoxicillin (as trihydrate) were used in the study (batches A and B). These batches came from the validated production process and are the same as bioavailability batch described in Ref. 11. Additionally one batch of commercially available capsules (Amotaks® produced by Polfa Tarchomin SA, Warsaw, Poland) containing 500 mg amoxicillin (as trihydrate) was used to check the change in discrimination properties of the model (batch C).

In Vitro Dissolution Testing

Dissolution testing was performed using Pharma test PTWS 3 (Pharma Test Apparatebau GmbH, Hainburg, Germany) EP apparatus 2 (paddles) operating at 25 and 95 rpm. Water ($37 \pm 0.5^{\circ}$C) was the dissolution medium. Approximately 10 mL samples were withdrawn from each dissolution vessel at 2 min 30 s, 8 min 46 s, 15 min, 25 min, 35 min, 60 min, and filtered prior to spectrophotometric analysis on Unicam UV3 (Unicam Ltd, Cambridge, United Kingdom) spectrophotometer (wavelength 272 nm). The analytical method used was a validated procedure used for routine dissolution control of production batches. Each dissolution profile was taken from 12 units. The absolute coefficient of variation (CV) for all the points was less than 10%. In the case of capsules, two dosage units were used to achieve 1000 mg dose in a dissolution vessel. To prevent floating, EP sinkers (Pharma Test Apparatebau GmbH, Hainburg, Germany) were used. Variable hydrodynamic conditions were implemented in the study to imitate a minimal absorption of the drug in a stomach. During the initial 2 min 30 s of the experiment the paddles operated at 25 rpm. After that, the rotation increased to 95 rpm simulating rapid absorption of amoxicillin in a duodenum and proximal part of small intestine.

In Vivo Study

Twenty-four adult volunteers (12 male and 12 female) were taken into a count for this study. Details are described in Ref. 11.

Pharmacokinetic Analysis

Details of the pharmacokinetics analysis are described in Ref. 11. The independent method to generate the suitable model was used. $C_{\max}$ and $T_{\max}$ were the observed values. Elimination rate constant K_e was calculated from the slope of the log-linear part of the plasma concentration–time curve using linear regression. The area under the plasma concentration–time curve from time 0 to 12 h was calculated using trapezoidal rule.

Absorption profile of amoxicillin was calculated by WN equation in the following ways:

$$\frac{A_t}{A_\infty} = \frac{C_t + K_e \times \mathrm{AUC}_{0-t}}{K_e \times \mathrm{AUC}_{0-\infty}} \tag{1}$$

In method 1 averaged bioavailability data (including averaged K_e) of all 24 subjects were converted into absorption profile as it was described in Ref. 11. In method 2 individual K_e and bioavailability data were used, individual bioavailability data were converted into absorption profiles and afterwards individual profiles were averaged.

The results were expressed as percentage of the dose absorbed. *In vitro* averaged dissolution data were converted into plasma concentration–time curve using back-calculation of WN equation:

$$C_{t+1} = \frac{2 \times \Delta F \times K_e \times \mathrm{AUC}_{0-\infty} + C_t \times (2 - K_e \times \Delta t)}{2 + K_e \times \Delta t} \tag{2}$$