



INTRODUCTION

Bioequivalence (BE) studies compare the concentration-time (C-t) profiles of two pharmaceutical products (test (T) and reference (R)) of the same active ingredient. The C-t profiles are not compared directly but by pharmacokinetic parameters, such as area under the curve (AUC), maximum observed plasma concentration (C_{max}) and time (T_{max}) at which C_{max} is observed. Because pharmacokinetic parameters are calculated from the C-t data, the reliability of the calculations, and thus the results of a BE study, can be affected by the sampling scheme of the study. Presumably, an inadequate sampling design may lead to study inaccuracies and uncertain results, while a very dense sampling design may increase the workload and cost.

OBJECTIVES

Bioequivalence (BE) studies compare the concentration-time (C-t) profiles of two pharmaceutical products (test (T) and reference (R)) of the same active ingredient. The C-t profiles are not compared directly but by pharmacokinetic parameters, such as area under the curve (AUC), maximum observed plasma concentration (C_{max}) and time (T_{max}) at which C_{max} is observed. Because pharmacokinetic parameters are calculated from the C-t data, the reliability of the calculations, and thus the results of a BE study, can be affected by the sampling scheme of the study. Presumably, an inadequate sampling design may lead to study inaccuracies and uncertain results, while a very dense sampling design may increase the workload and cost.

The aim of the present study was to evaluate the influence of different sampling schemes on the outcome of bioequivalence studies. In this analysis, two drugs (paracetamol and irbesartan) with different pharmacokinetic properties were studied and several sampling schemes were investigated using Monte Carlo simulations of 2x2 crossover BE studies.

METHODS

A pictorial representation of the in vitro - in vivo simulations utilized in this analysis is shown in **Figure 1**.

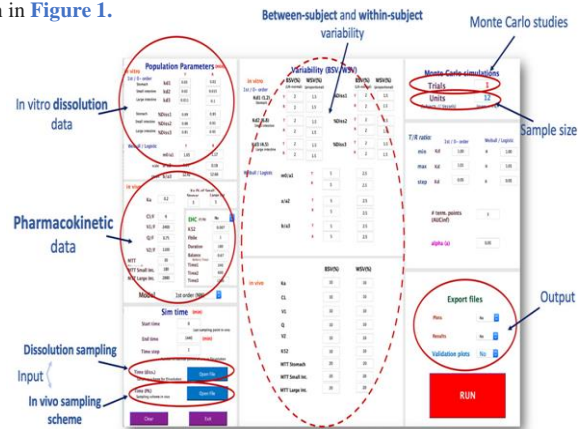


Figure 1 : A snapshot of the in-vitro-in-vivo simulations (IVIVS) of Paracetamol and Irbesartan (1)

1. Vlachou M, Karalis V. An In Vitro-In Vivo Simulation Approach for the Prediction of Bioequivalence. *Materials (Basel)*. 2021 Jan 24;14(3):555.

RESULTS

With identical release rates, the simulated C-t profiles were similar; minor differences resulted only from the applied BSV and WSV (**Table 1, Table 2**). In this case, all sampling schemes yielded 100% BE for both Paracetamol and Irbesartan. For paracetamol, a 20% difference in release rate resulted in statistical power values of 100% for C_{max} and AUC for the scenarios in which sampling was moderate to sparse or in which few points were sampled in the falling part of the C-t curve. Scenarios with sparse sampling around T_{max} had no effect on AUC power estimates, while they resulted in lower power for C_{max}, but none was below 93%. For a 40% difference in rate, the probability of declaring BE was 93% (C_{max}) and 100% (AUC) for the less sparse scenarios, but it reduced to 34% and 64% for sparse scenarios close to T_{max}. In the case of the extreme scenario with 60% difference in release rate, the statistical significance for AUC remained at high level (range 87%-100%), while it was low for C_{max} (32%, 48%, etc.). A similar trend was observed for irbesartan, but the differences were less pronounced compared to the paracetamol case. For irbesartan, the potency values were almost 10% higher compared to that of paracetamol. This suggests that irbesartan, which has slower absorption, is less affected by changes in sampling schedule. All the above results are for a sample size of 24. Higher values were taken when N=36 and lower for N=12. Additionally, as between-subject variability increases, a dispersion of the C-t curves is observed in all spaghetti plots for the two drugs (**Table 3, Table 4**).

1- Simulated C-t profiles of Paracetamol and Irbesartan

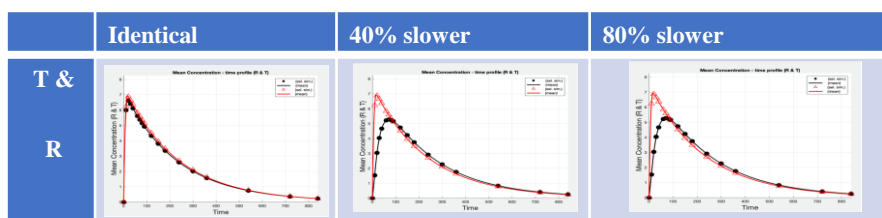


Table 1. Simulated C-t profiles for the R product, for the T product, and for both the test (T) and reference (R) products in the case of paracetamol. And with identical theoretical power and slower release rate for the T product (40%, 80%). The circles refer to the sampling points

2- Impact of between subject variability in the case of Paracetamol and Irbesartan

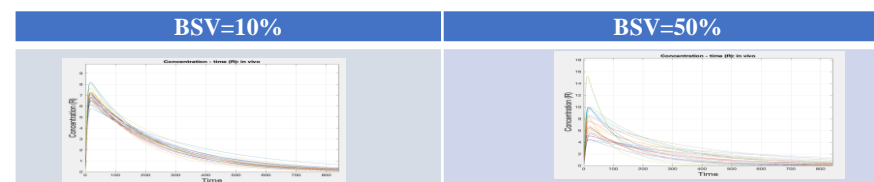


Table 3. Simulated C-t profiles for R product with BSV=10%, 50% in the case of Paracetamol

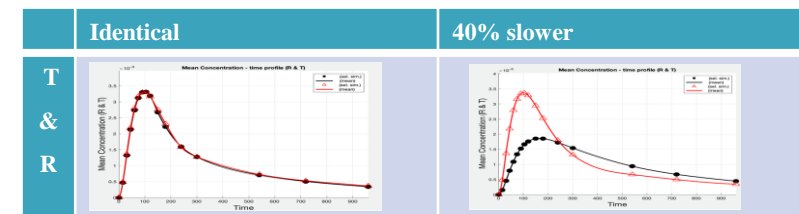


Table 2. Simulated C-t profiles for R product, for T product, and for both Test (T) and Reference (R) product in the case of irbesartan. With identical theoretical release rate and 40% slower release rate for the T product. The circles refer to the sampling points.

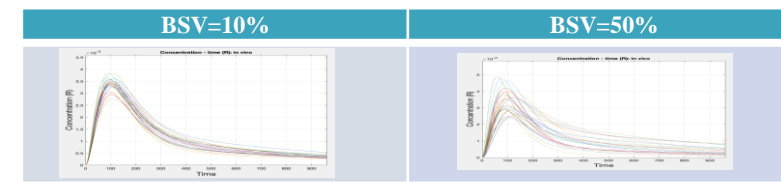


Table 4. Simulated C-t profiles for R product with BSV=10%, 50% in the case of Irbesartan

CONCLUSION

It can be concluded that the demonstration of BE is not sensitive to differences in the duration and density of sampling schedules. All applied scenarios of sampling schemes were able to show bioequivalence when the pharmacokinetic parameters of the two products were identical. AUC was affected to a lesser extent than C_{max} and only when large differences in the C-t profiles of the T and R products were present. Bioequivalence for C_{max} was sensitive to the sparse schedules only when withdrawal sites were close to T_{max} in association with large differences in drug release (greater than 20%). When the two drug products differ significantly in absorption, dense and sparse sampling schemes result in nearly similar BE acceptances.