Method comparison for bioequivalence prediction through the example of aripiprazole

Szabina Kádár[1], Andrew Kennedy[2], Samuel Lee[2], Rebeca Ruiz[2], Zsombor K. Nagy[1], Enikő Borbás[1], Balint Sinko[3,4]

[1]Budapest University of Technology and Economics, Budapest, Hungary

[2]Pion Inc., Forest Row Business Park, Forest Row RH18 5DW, UK

[3]Pion Inc., 10 Cook Street, Billerica, MA 01821, USA

[4]Semmelweis University, Budapest, Hungary

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PURPOSE

One of the biggest challenges of generic formulation development is to ensure appropriate performance during in vivo human comparison studies. In silico models supported by various in vitro assays are utilized to give suitable predictions, but the success rate of bioequivalence studies is still far from 100%. In recent years, dissolution-permeation systems have been utilized extensively to improve the accuracy of predictions. The purpose of this study was to compare small and larger volume flux studies with biphasic dissolution experiments to see their prediction potential on the bioequivalence of marketed generic formulations. Aripiprazole (ARI) was selected as a model compound, and the original formulation (Abilify) along with four marketed generic formulations were studied. The flux and biphasic dissolution data were compared to in vivo human data published in the public assessment reports.

METHOD(S)

Small volume flux assay on µFlux

The formulations were tested using MicroFLUX™ apparatus. Concentration in both chambers was monitored in real-time using in situ fiber optic dip probes connected to the Rainbow instrument (Pion Inc.). A PVDF membrane was impregnated with 25µL n-dodecane to form a lipophilic barrier between the donor and the acceptor chamber.

Large volume flux assay on BioFlux

Final dosage forms of ARI were measured using BioFLUX™ apparatus. The schematic of the experiments is shown on Figure 1. Concentration in both chambers were monitored in real time using in situ fiber optic dip probes connected to the Rainbow instrument (Pion Inc.).

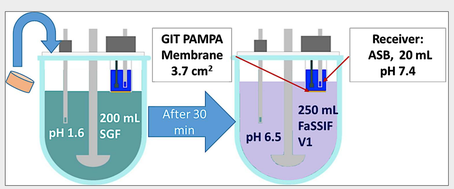

Figure 1. A dosage form was added to 200 mL of SGF and dissolution profile was monitored. After 30 min, the medium was converted to 250 mL of FaSSIF continuing the concentration monitoring in both dissolution and receiver chambers.

Biphasic dissolution assay on InForm

In a fully automated procedure, final dosage forms and formulation powders at a scaled dose of ARI were assayed using the biphasic dissolution protocol on the Pion inForm instrument. Samples were introduced to a pH 1.6 HCl medium at 37°C, spectra were then collected using an in-situ UV dip-probe. After 30 minutes, the media was converted to pH 6.50 FaSSIF by the addition of a concentrate, along with 40mL of 1-decanol for the secondary phase. A secondary UV-dip probe was used to monitor partitioning to the 1-decanol phase.

RESULT(S)

Modelling Approach

Flux through the membrane was calculated based on concentration – time profiles in the acceptor chamber

$$J_{invitro} = \frac{1}{A} \cdot \frac{dm}{dt} \quad (1)$$

where A is the area of the membrane and dm/dt (µg/min) is the rate of absorption into receiver chamber.

Fraction of dose absorbed ratio (Fa ratio) for the prediction of bioequivalence was calculated using Eq.2.

$$F_a \text{ ratio} \approx \frac{J_{test}}{J_{reference}} \quad (2)$$

where test and reference are related to the flux measured for the test and reference drug product correspondingly.

Biphasic dissolution results (InForm)

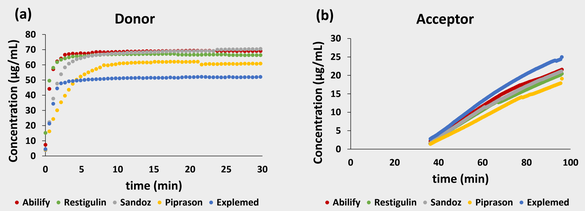

Figure 2. Dissolution in pH 1.60 HCl (a), partitioning to decanol (b) of ARI formulations in the biphasic assay at a scaled dose (1.2 mg API load)

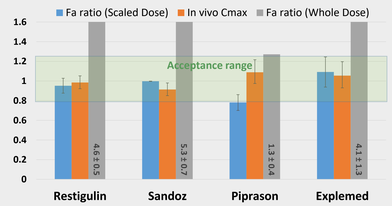

Figure 3. Comparison of *in vitro* Fa ratios for each dose level and *in vivo* c_{max} ratios (test/reference)

Runs of the biphasic assay carried out on the final dosage forms produced a poor estimation of bioequivalence, with flux ratios ranging from 1.3 – 5.3; though when performed with a scaled dose, the equivalence prediction was found to improve substantially (flux ratios 0.8 – 1.09). However, the lowest and highest flux ratios did not correlate to the lowest and highest C_{max} ratios as per the in vivo data. The flux ratio of Piprason fell marginally below the acceptance range; this can be attributed to powder loss in the sample addition step resulting in underestimated flux, as the mass of Piprason powder required for a 1.2 mg load of API exceeds the effective capacity of the cradle utilised for delivery.

Small volume flux results (MicroFLUX)

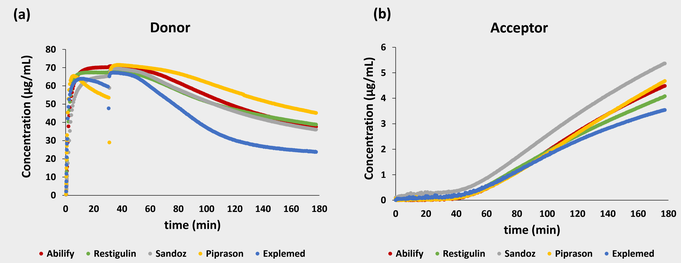

Figure 4. Dissolution in SGF (a) and appearance profile (b) of ARI formulations in the small volume flux (MicroFLUX) assays.

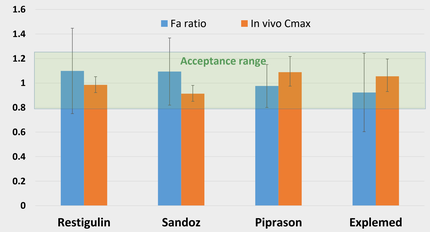

Figure 5. Comparison of *in vitro* Fa ratios and *in vivo* c_{max} ratios (test/reference)

The small volume flux assay provided a reasonable prediction of bioequivalence, with the flux ratios ranging from 0.92 – 1.10. However, the formulation with the lowest and highest flux ratio did not match with the lowest and highest C_{max} ratio of the in vivo study. Also, due to extensive precipitation, the flux data had a relatively high variation, about 20-30%.

Large volume flux results (BioFLUX)

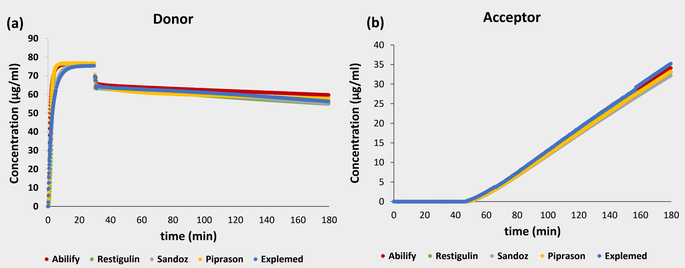

Figure 6. Dissolution in SGF (a) and appearance profile (b) of ARI formulations in the large volume flux (BioFLUX) assay

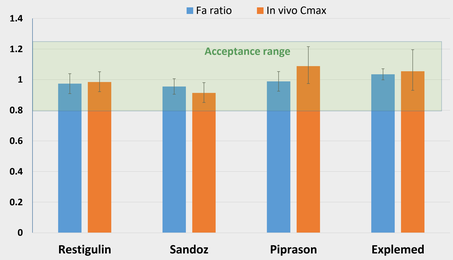

Figure 7. Comparison of *in vitro* F_a ratios and *in vivo* c_{max} ratios (test/reference)

The large volume flux assay also provided a good match to bioequivalence study outcome with flux ratios 0.95-1.03. In this case, the formulation with the lowest flux ratio matches the in vivo results and the variation of the data was below 10%.

CONCLUSION(S)

Five aripiprazole commercial formulations were investigated with three different methods to evaluate their bioequivalence prediction potential. The biphasic dissolution assay protocol proved unsuitable for bioequivalence prediction using a whole dosage form, while applying a scaled dose improved the predictions significantly and provided results relatively close to in vivo human data.

Small volume flux assays were also run with a scaled dose and results were found to provide a reasonable prediction.

Large volume flux assays were performed with whole dosages and provided the best match to in vivo data, presumably due to the ability to study tablet disintegration and dissolution and their effects on flux more precisely.

In conclusion, all three methods were found to be suitable for formulation comparison, although BioFlux was the only method that was able to study the whole dosage forms and provide a reasonable prediction of the ranking of the formulations.

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