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Biphasic Dissolution Studies of Poorly Water Soluble Drugs

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PURPOSE

An automated biphasic dissolution assay was used to study the lipid absorption of poorly water soluble drugs and covering a range of acidic, basic and neutral compounds. The pH of the aqueous phase was adjusted to pH 6.5 to represent intestinal pH and decanol was selected as the lipid layer. The passage of drug into the lipid phase simulates the absorption into the gut wall. The protocols used take advantage of robotics and automation to ensure well-designed, reproducible and successful experiments.

METHODS

Biphasic experiments were performed using the Sirius inForm platform (figure 1). The Sirius inForm contains dispensers for volumetrically dispensing reagents via capillaries into the measurement cell. For this study, 40 mL of an aqueous acetate-phosphate buffer was dispensed and adjusted to pH 6.5, after which 30 mL of decanol was added as a lipid phase. Stirring of the solution was continuous and at a constant rate of 100 rpm.

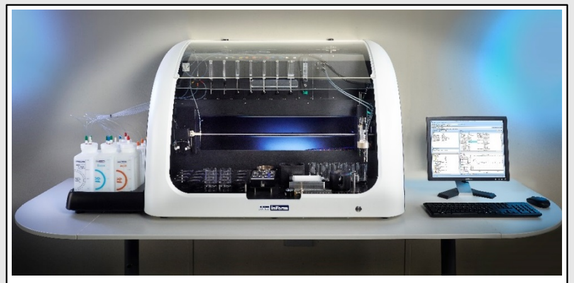

Figure 1: **Sirius inForm** platform used for biphasic dissolution testing

Pre-solubilised compound, prepared as a DMSO stock solution, was then automatically injected into the aqueous compartment using a liquid handling needle, such that a total weight of 10mg of drug was introduced. DMSO content was kept below 1% for all samples. Drug concentrations were determined by multi-wavelength UV-absorption spectroscopy using two in-situ fibre-optic UV probes and converting the UV absorption data to an absolute sample weight using molar extinction coefficients previously measured automatically on the inForm platform. Experiments were conducted over one hour.

RESULTS

Although classed as poorly water soluble drugs, **carvedilol, ibuprofen, indomethacin, sertraline** and **valsartan** all remained soluble at pH6.5 with recorded aqueous concentrations starting at 100% (figures 2 – 6). Over the one hour timeframe, the drugs partitioned into the lipid layer to different extents, with **carvedilol** (95%), **ibuprofen** (82%), **indomethacin** (96%) and **sertraline** (82%) all displaying good lipid uptake. **Carvedilol** (pKa 8.0) and **sertraline** (pKa 9.5) are weak bases and will be positively charged at pH 6.5. **Ibuprofen** (pKa 4.4) and **indomethacin** (pKa 4.2) are weak acids and have negative charges at pH 6.5. It is generally the case that only the neutral forms of ionisable drugs will be absorbed by passive diffusion. Nevertheless, there is sufficient driving force to remove the neutral forms of these four drugs from the aqueous compartment.

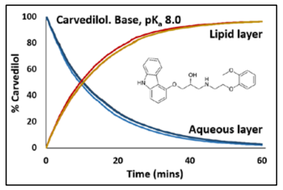

Figure 2: **Carvedilol**

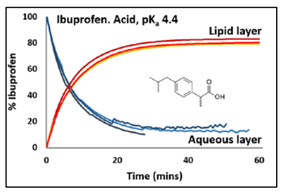

Figure 3: **Ibuprofen**

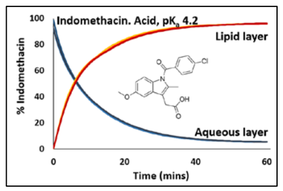

Figure 4: **Indomethacin**

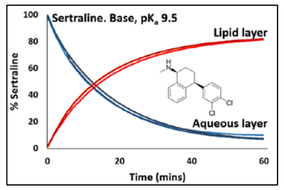

Figure 5: **Sertraline**

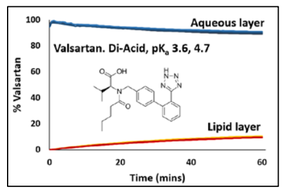

Figure 6: **Valsartan**

Valsartan has two acidic groups (pKas 3.6, 4.7) and will have a multiple negative charge at pH 6.5. Even so, some 10% of **Valsartan** partitioned into the lipid layer at pH 6.5, presumably in neutral form.

Felodipine, fenofibrate and tadalafil are neutral compounds. They precipitated in the aqueous phase when injected at the 10mg dose level. For **felodipine** and **tadalafil** it was possible to measure aqueous concentrations, whilst for **fenofibrate,** the aqueous compartments were too turbid to reliably read UV spectra. Over the one hour timeframe, the drugs partitioned (figures 7 – 9) into the lipid layer to modest extents: **felodipine** (32%), **Fenofibrate** (10%), and **tadalafil** (37%). In the case of **fenofibrate**, it was additionally studied at a 5 mg dose and showed the same extent of lipid absorption as the 10 mg dose. This shows that it is only molecularly dissolved drug species that are able to partition across the interface and that the overall lipid absorption is dictated by the compound's aqueous solubility.

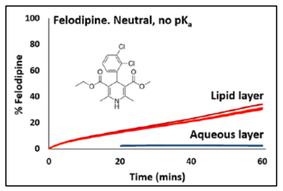

Figure 7: **Felodipine**

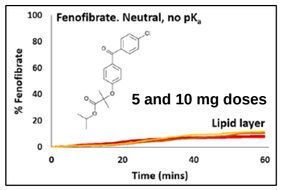

Figure 8: **Fenofibrate**

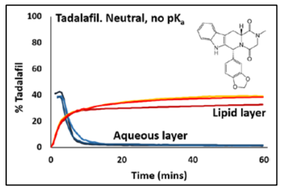

Figure 9: **Tadalafil**

RESULTS

The other drugs in this study also all precipitated in the aqueous phase when injected at the 10mg dose level. For **aprepitant, bromocriptine, and ketoconazole,** it was possible to measure aqueous concentrations. It is often commented that precipitated particles will dissolve directly into the lipid. However, there is a boundary or unstirred water layer that prevents particles from reaching the interface and so only molecularly dissolved species are free to diffuse into the lipid. Over the one hour timeframe, these three drugs partitioned into the lipid layer to different extents: **aprepitant** 60%, **bromocriptine** 92%, and **ketoconazole** 84% (figures 10 – 12). **Bromocriptine** (pKa 6.2) and **ketoconazole** (pKa 3.3 and 6.3) are weak bases with partial positive charges; both are extracted into the lipid. **Aprepitant** is an ampholyte and is predominantly neutral at pH 6.5.

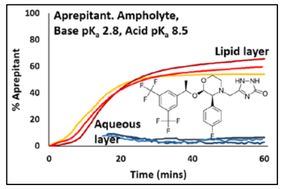

Figure 10: **Aprepitant**

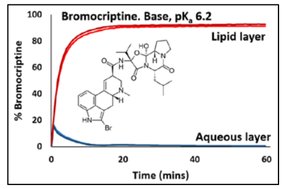

Figure 11: **Bromocriptine**

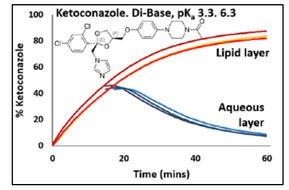

Figure 12: **Ketoconazole**

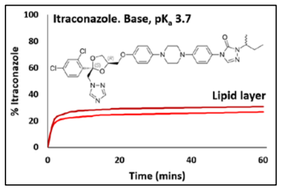

Figure 13: **Itraconazole**

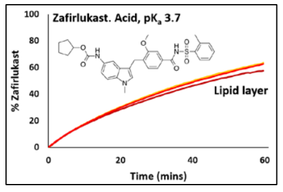

Figure 14: **Zafirlukast**

For **itraconazole** and **zafirlukast,** the aqueous compartments were too turbid to reliably read UV spectra. Both were absorbed by the lipid: **Itraconazole** 29% and **Zafirlukast** 61% (figures 13 – 14). **Itraconazole** is a base (pKa 3.7) that is neutral at pH 6.5 and **Zafirlukast** is an acid (pKa 3.7) that is negatively charged at pH 6.5.

CONCLUSION

Biphasic dissolution studies were performed using the Sirius inForm and were used to assess compound uptake into a lipid layer. Results suggest that only molecularly dissolved drug is able to diffuse into the decanol. Hence, biphasic dissolution can help indicate when solubility-limited oral absorption may become an issue.

ACKNOWLEDGEMENTS

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