Small Scale Biphasic Dissolution testing of Dipyridamole Suspension

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Introduction

Precipitation *in vivo* can occur for a multitude of reasons, including the shift of pH from the acidic gastric environment to the more neutral intestinal environment. Predicting *in vivo* supersaturation and precipitation is key to understanding variability in oral bioavailability.

Biphasic dissolution tests use an organic layer, which is immiscible with the dissolution media, to act as an "absorptive sink". This absorptive sink is intended to mimic drug uptake as it passes through the biological membrane in the intestine. This could be particularly advantageous for BCS class II drugs (low solubility, high permeability) as sink conditions can be generated as drug is removed by uptake into the organic layer.

In this experiment, the effect of a pH shift from an acidic gastric environment to the more neutral intestinal environment on the dissolution profile of dipyridamole suspension (BCS class II, basic pKa 6.24 at 25°C) was examined using a small-scale biphasic dissolution test using Sirius-Analytical's inform platform (Figure 1).

Methods and Materials

- 1mL of a Dipyridamole 10mg/mL aqueous suspension was introduced into the aqueous compartment using an automatic aqueous handler needle.
- Stirring speed was 100rpm.
- Drug concentrations were determined by multi-wavelength UV-absorption spectroscopy using two in-situ fibre-optic UV probes

Table 1. Overview of Experimental Conditions.

	pH2		pH 6.8	
Experiment	**Duration (mins)**	**Media**	**Duration (mins)**	**Media**
Simple Media with pH Shift	30	40 mL Acetate Phosphate Buffer	240	40 mL Acetate Phosphate Buffer + Decanol
Simple Media Single pH	-	-	240	40 mL Acetate Phosphate Buffer + Decanol
Biorelevant Media with pH Shift	30	36 mL Acetate Phosphate Buffer	240	40 mL FaSSIF V2 + Decanol
Biorelevant Media Single pH	-	-	240	40 mL FaSSIF V2 + Decanol

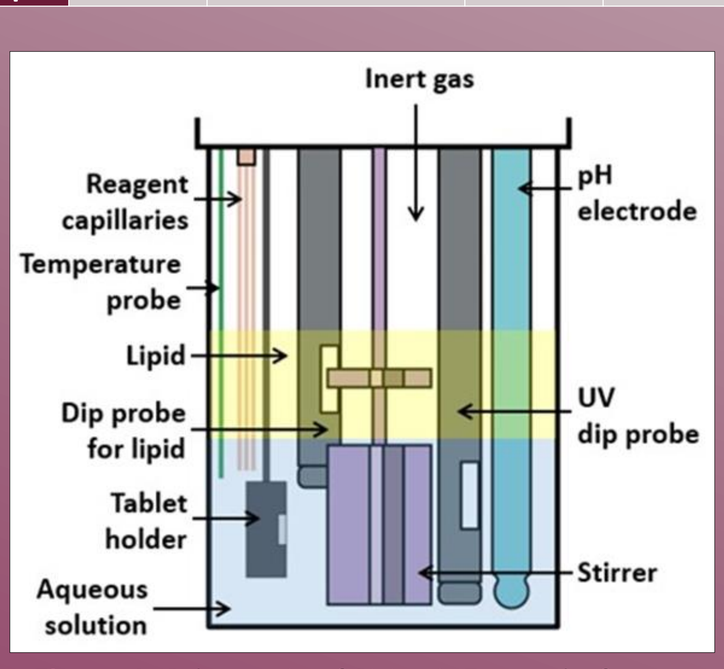

Figure 1. Schematic of Sirius inForm platform used for biphasic dissolution testing.

Results

Incorporating an initial gastric sector resulted in a significant increase in dipyridamole concentrations in the organic layer (two tailed t-test $P<0.05$). Using biorelevant media, such as FaSSIF, significantly increased the concentration of dipyridamole in the organic layer (two tailed t-test $P<0.05$). When using biorelevant media with a pH shift, dipyridamole did not appear to significantly precipitate out of solution upon transition to pH 6.8, which correlated well with previous *in vivo* studies.[1] Dipyridamole seemed to rapidly and readily partition from the aqueous phase into the organic phase.

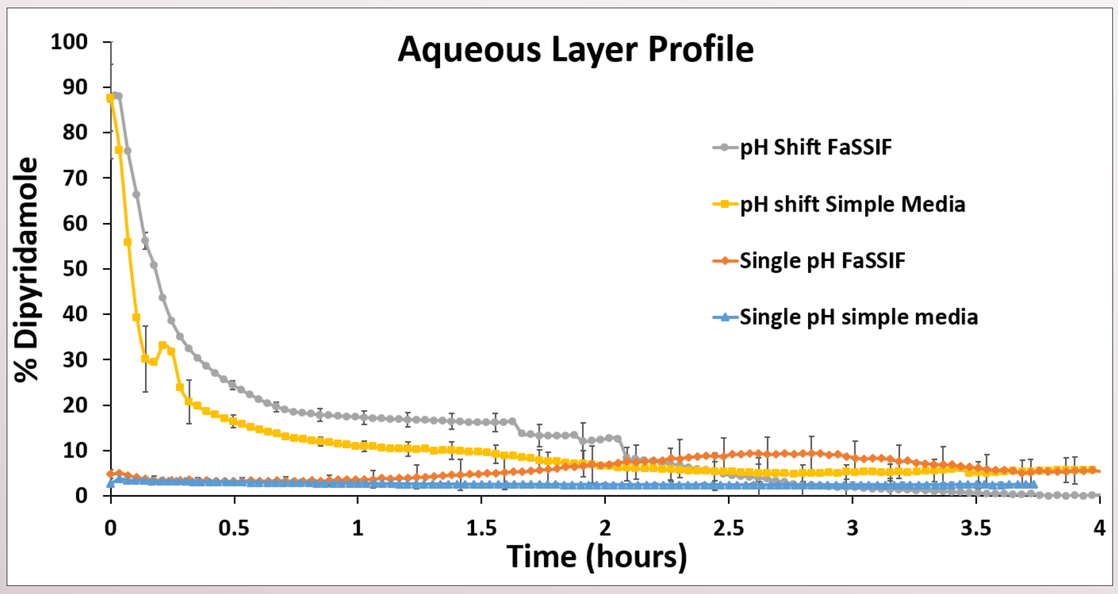

Figure 2. Drug concentration time profiles of Dipyridamole in the aqueous media at pH 6.8. Each data point represents mean ± SD (n=3).

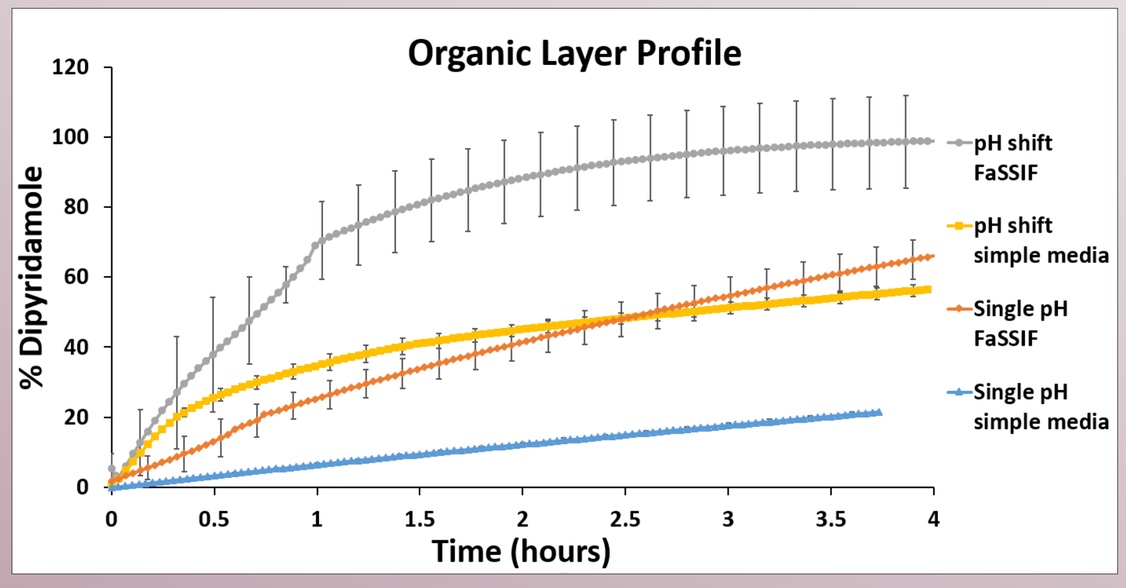

Figure 3. Drug concentration time profiles of Dipyridamole in the organic phase. Each data point represents mean ± SD (n=3).

Conclusion

This experiment highlights the need to incorporate a pH shift from acidic to intestinal pH when analysing weakly basic drugs. Carrying out dissolution experiments at a single pH could lead to a large underestimation of oral bioavailability of weakly basic drugs, such as dipyridamole. In addition, the use of biorelevant media appears to be justified when testing a BCS class II weakly basic drug.

The disadvantage of biphasic experiments is the organic layer is in direct contact with the aqueous layer. Some of the organic layer may be solubilized and an emulsification could occur. Nevertheless, no model of the drug absorption comes without disadvantages, and biphasic dissolution experiments are a simple and convenient method to incorporate an absorption step. Also, visually, there is an aqueous boundary layer across which precipitated drug particles do not appear to cross. Consequently, only dissolved drug particles are absorbed into the lipid. Further research is ongoing to investigate the utility of biphasic dissolution tests among a wide range of drugs and novel formulations.

References

1. Psachoulias D, Vertzoni M, Goumas K, Kalioras V, Beato S, Butler J, et al. Precipitation in and supersaturation of contents of the upper small intestine after administration of two weak bases to fasted adults. Pharm Res. 2011;28(12):3145–58.

PEARRL Consortium

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