The effect of in-situ pH change on a biphasic dissolution model in the presence of simulated intestinal fluids

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Purpose

A "biphasic dissolution model" has recently been developed to mimic the absorption of drugs under changing (gastrointestinal) pH conditions. This has been further developed to include simulated intestinal fluids (SIF) to better understand their effect on the uptake of orally dosed pharmaceutical drugs.

Methods

A pressed pellet of the platelet inhibitor, dipyridamole (approx 5mg), was introduced into a stirred chamber containing 45mL of solution comprising phosphate/acetate buffer plus hydrochloric acid at pH 2 to represent stomach conditions. Dissolution of the pellet was recorded for 30 minutes using a fibre-optic probe connected to a UV spectrometer. After this period, a quantity of SIF was added, immediately followed by 20mL of nonanol, during an automated addition of potassium hydroxide, to change the pH to pH 4. This was thought to mimic the gastric emptying process and enable partitioning of the drug into a pseudo lipid layer. The partitioning of the drug into the pseudo lipid layer was monitored by a second fibre-optic probe. Further pH adjustments and time periods were set to mimic transition through the intestinal tract.

Results

Under standard GI Dissolution conditions (in-situ pH change, but no SIF or lipid), dipyridamole precipitated in the final pH period (pH 7.3). The addition of SIF prevented precipitation at pH 7.3, as did the addition of a lipid, which resulted in a final partitioned mass of 3mg in the lipid. As expected, the addition of both SIF and lipid prevented precipitation. However, the final partitioned mass was down to 2mg.

Conclusion

The addition of SIF helped to maintain a solubilized state of a BCS class two drug. However, under the conditions used here, the SIF also hindered the uptake of the drug into the pseudo lipid layer. This indicated that natural bile components may further inhibit the bioavailability of some drugs.

Reference

[1] Gravestock, T. Box, K. Comer, J. Frake, E. Judge, S. Ruiz, R. *The "GI Dissolution"* method: a low volume, in vitro apparatus for assessing the dissolution/precipitation behaviour of an active pharmaceutical ingredient under biorelevant conditions. Anal. Methods, 2011, 3, 560-567

GI Dissolution Method

GI Dissolution assays were performed on a modified SiriusT3 platform (Figure 1). A schematic of the assay is shown in Figure 2.

Figure 1. SiriusT3 PhysChem Profiling platform.

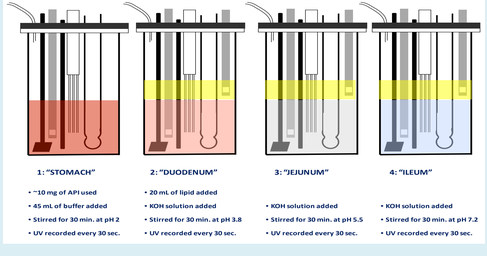

Figure 2 (right). Schematic of GI Dissolution assay. UV data are recorded during tablet dissolution at gastric pH, followed by subsequent pH adjustment to intestinal pH values. Lipid and/or simulated intestinal fluid (SIFs) can be added following the gastric stage.

Using SiriusT3 to investigate GI Dissolution in presence of lipid layer and SIFs

In the GI Dissolution method [1], a phosphate-acetate buffer system with initial pH 2 was introduced into a vial containing a compressed drug pellet and UV data were collected. Data were recorded at four pH values for 30 minutes at each pH to simulate pH in the GI tract. Lipid was introduced at the beginning of sector 2 with the option of also adding simulated intestinal fluid (SIF). UV absorption data were converted to sample weight using previously determined (pH-dependent) molar extinction coefficients (also determined on the SiriusT3) to quantitate the amount of dissolved drug in the aqueous compartment and amount of permeable drug in the lipid layer.

Dipyridamole aqueous GI Dissolution process (with and without SIF, no lipid layer)

The GI Dissolution data for dipyridamole are shown in Figure 3. Dissolution was rapid at pH 1.8 and the compound remained solubilized during pH sectors 3.9 and 5.4. Dipyridamole pK_a was 6.24, so at pH 7.3 it was predominantly in the neutral form. Under aqueous conditions, the solubility of the free base was exceeded and the concentration in solution diminished as the compound precipitated and crystallized. In the presence of Fasted State SIF (FaSSIF) the kinetic solubility was enhanced sufficiently so that no precipitation was observed at pH 7.3.

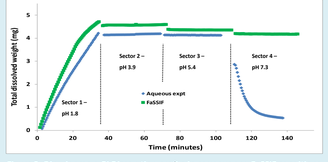

Figure 3. Dipyridamole GI Dissolution profile in aqueous and FaSSIF conditions.

Dipyridamole biphasic dissolution process

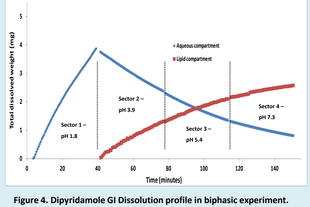

Figure 4. Dipyridamole GI Dissolution profile in biphasic experiment.

Figure 4 shows the GI Dissolution data for dipyridamole in the presence of the lipid layer. The blue trace shows the amount of dissolved drug in the aqueous compartment. The red trace directly displays the amount of drug that has been absorbed into the lipid layer (which was added at the beginning of sector 2). Dissolution into gastric solution was rapid at pH 1.8. When the lipid was added, the compound started to partition into the lipid layer (red trace increasing) whilst the dissolved concentration in the aqueous compartment decreased (blue trace decreasing), which indicated that partitioning was faster than further dissolution of the compressed drug pellet at the intestinal pH values.

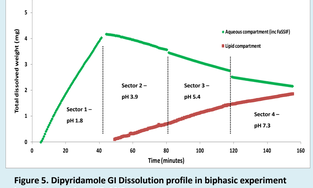

Figure 5. Dipyridamole GI Dissolution profile in biphasic experiment including addition of FaSSIF to aqueous compartment.

Figure 5 displays the GI Dissolution data for dipyridamole in the presence of the lipid layer when FaSSIF was added to the aqueous compartment. The green trace shows the amount of dissolved drug in the aqueous compartment and the red trace displays the amount of drug that has been absorbed into the lipid layer. Both FaSSIF and lipid were added at the beginning of sector 2. Dissolution into gastric solution was rapid at pH 1.8. When the FaSSIF and lipid were added, the compound started to partition into the lipid layer (red trace increasing) whilst the dissolved concentration in the aqueous compartment decreased (green trace decreasing), which indicated that partitioning was faster than further dissolution of the compressed drug pellet at the intestinal pH values. However, significantly, the rate of lipid partitioning was slower than in the absence of FaSSIF. This indicated that the SIF mixed micelles were holding onto the drug and the free drug fraction available for absorption was lower.

Niflumic acid aqueous GI Dissolution process (with and without SIF, no lipid layer)

The GI Dissolution data for niflumic acid are shown in Figure 6. Niflumic acid has a basic pK_a at 2.02 and acidic pK_a at 4.84. Dissolution in aqueous solution was slow over the first three pH sectors and increased significantly during the last pH sector (pH 7.3) where the compound was negatively charged.

The addition of FaSSIF at the beginning of the second sector resulted in a significant improvement in solubilisation of the free form of niflumic acid and an overall increase in the total amount of dissolved niflumic acid by the end of the assay.

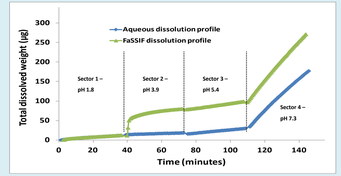

Figure 6. Niflumic acid GI Dissolution profile in aqueous and FaSSIF conditions.

Niflumic acid biphasic dissolution process

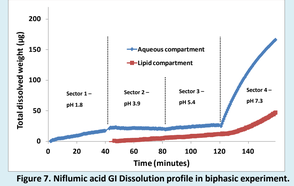

Figure 7. Niflumic acid GI Dissolution profile in biphasic experiment.

Figure 7 shows the GI Dissolution data for niflumic acid in the presence of the lipid layer. The blue trace shows the amount of dissolved drug in the aqueous compartment. The red trace directly displays the amount of drug that has been absorbed into the lipid layer (which was added at the beginning of sector 2). Dissolution into the aqueous compartment was similar to that observed in an aqueous experiment without lipid (see Figure 6). However, there was also transfer of compound into the lipid compartment when lipid was added. Significantly, the greatest transfer of niflumic acid to the lipid layer occurred in the final pH sector at pH 7.3. Increased solubilization at this pH provided a larger driving force for absorption into the lipid.

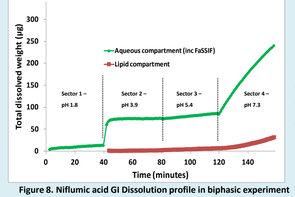

Figure 8. Niflumic acid GI Dissolution profile in biphasic experiment including addition of FaSSIF to aqueous compartment.

Figure 8 shows the GI Dissolution data for niflumic acid in the presence of the lipid layer when FaSSIF is also added to the aqueous compartment in the second sector. The green trace shows the amount of dissolved drug in the aqueous compartment. The red trace directly displays the amount of drug that was absorbed into the lipid layer (added at the beginning of sector 2). Dissolution into the aqueous compartment was similar to that observed in an experiment with FaSSIF and without lipid (see Figure 6). Transfer of compound into the lipid compartment was observed when lipid was added and the greatest transfer of niflumic acid to the lipid layer occurred in the final pH sector at pH 7.3. Increased solubilization in the last pH sector provided a larger driving force for absorption into the lipid. However, the increased solubilization capacity in the aqueous compartment for the free form of niflumic acid (in the second and third sectors) did not lead to an increase in the amount absorbed into the lipid (c.f. Figure 7). This indicated that the SIF mixed micelles were holding onto the drug and the free drug fraction available for absorption was lower.

Conclusion

In this poster we investigated the dissolution and absorption of drug compounds using a biphasic system where pH could be controlled to cover the gastrointestinal pH range. The addition of SIF helped the solubilization of poorly soluble BCS class II drugs. However, under the conditions used here, the SIF also hindered the uptake of the drugs into the lipid layer. This indicated that the drugs may have been trapped in the SIF micelles and the free drug fraction available for absorption may be lower than expected.

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