Application note 07/11

The Pion GI Dissolution Assay

An understanding of the dissolution and precipitation behaviour of active pharmaceutical ingredients is of fundamental importance in designing formulation approaches for successful drug delivery. The Pion GI Dissolution Assay has been designed as a formulation tool to conduct low volume, multi pH assays to give insight into how the dissolution of a drug is influenced by changes in pH[1]. By incorporating different excipients in the assay, methods of maintaining enhanced levels of drug in solution can be investigated to maintain supersaturation and avoid precipitation issues. Additionally, the assay can accommodate a lipid sink to further mimic drug absorption.

Experimental

The Pion GI Dissolution assay is performed on a PionT3. The assay is conducted in a single vial, typically in 15mL volumes although volumes as low as 2 mL can be used when sample quantities are limited. Based on a knowledge of the molar extinction coefficients, the concentration of the compound in solution is measured using a UV probe on the PionT3. Up to 6 different pH sectors can be accommodated and the duration of each sector can be varied according to the requirements of the assay. We use a series of pH values to mimic the GI track. Typically these are: pH2.0, 3.8, 5.5 and 7.2. The basic experiment comprises the following steps:

- Preparation of a compact of the API using a tablet die and press – this typically requires 5-10mg of compound. The sample can also be presented as a powder.
- Introduction of initial buffer solution
- Adjustment of pH for a defined period
- Monitoring of UV absorbance
- Processing of data

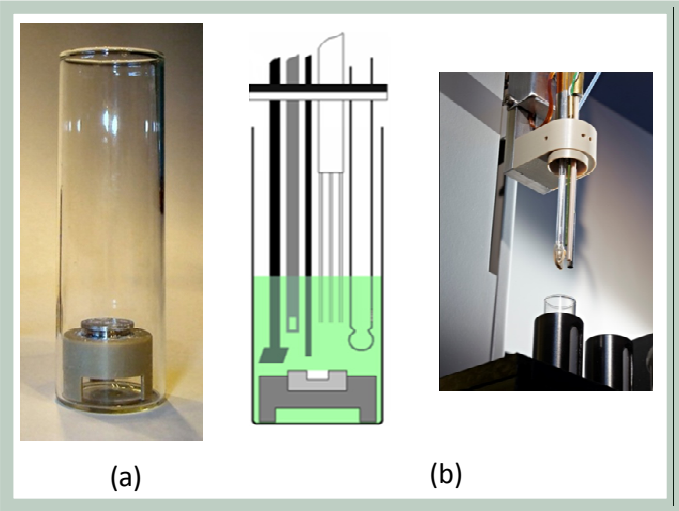

Figure 1. Assay vial detail for PionT3

(a) PionT3 vial with tablet or compact base and platform

(b) Schematic and photograph of probe assembly including stirrer, dip probe, temperature sensor, capillaries and glass pH probe

A simple dissolution experiment is presented in Figure 2 and shows the dissolution-pH dependency for clopidogrel, a base with one pK_a at 4.85. The sample was introduced as clopidogrel bisulphate.

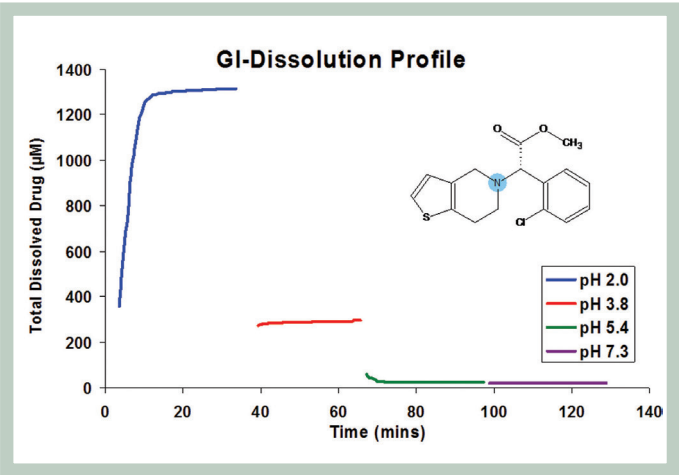

Figure 2. Simple dissolution experiment for clopidogrel in aqueous media

Dissolution: IUPAC Definition
The mixing of two phases with the formation of one new homogeneous phase (i.e. the solution).

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Discussion

Dissolution is rapid at pH2.0 where the compound is +1 charged and the tablet fully dissolves in the first pH sector. At pH3.8 some free base is generated and the solubility limit is exceeded. The sample precipitates heavily from solution in the second sector and the concentration reaches the solubility at this pH. Further precipitation occurs in sectors 3 (pH5.4) and 4 (pH7.3) as the equilibrium shifts in favour of the free base. The concentration approaches the solubility of the free base at pH7.3.

Figure 3 shows a similar assay design for the acid salt, sodium diclofenac. In this case, note the rapidly decreasing dissolution rate at pH1.76 as the salt converts to the neutral species. As expected, the dissolution rate rises significantly at pHs above the pK_a of 4.04.

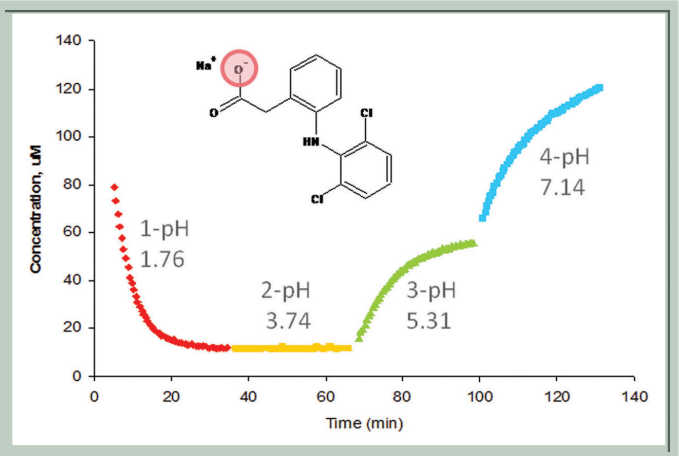

Figure 3. Dissolution profile for sodium diclofenac

A more complex study is presented in Figure 4 which shows a four sector dissolution study conducted on papaverine in the presence of povidone* and copovidone* and a lipid layer. Papaverine has a basic pK_a of 6.3. The lipid phase in this case is a mixture of nonanol and hexadecane, although other lipid phases can be used. The initial assay, conducted under aqueous conditions in the absence of lipid or excipients, shows precipitation in the fourth pH sector at pH7.2.

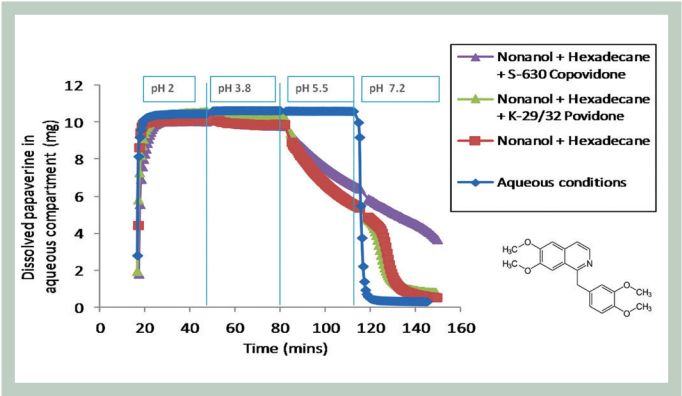

Figure 4. Dissolution studies on papaverine

Further experiments conducted in the presence of excipient and a lipid phase suggests ways of delaying precipitation at pH7.2. The addition of a lipid layer confers some advantage, but the addition of both lipid and Plasdone S-630 (copovidone) is most effective.

Conclusion

The Pion GI dissolution assay is a low volume **in vitro** technique with dynamic pH control for investigating the behaviour of pharmaceutical substances throughout the pH range of the gastrointestinal tract. Dissolution is monitored **in situ** by UV absorbance spectroscopy which allow the measurement to be automated. The flexibility of the experiment allows the addition of different excipients to study how drugs may be maintained in solution even as the neutral species. Whilst this assay does not replace existing large volume Pharmacopoeial dissolution tests, it provides an excellent tool for formulation development.

References

[1] Gravestock, T., Box, K., Comer, J., Frake, E., Judge, S., Ruiz, R., Anal. Methods, 2011, 3, 560-567

*Sourced from Ashland Speciality Ingredients