A method for assessing dissolution, supersaturation and precipitation of a drug during passage through the gastro-intestinal tract

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Abstract

Purpose: To develop a method for assessing dissolution, supersaturation and precipitation of a pharmaceutical substance during passage through the gastro-intestinal (GI) tract.

Methods: A solid drug is introduced into a stirred chamber containing a buffer solution, which is initially adjusted to approximately pH 2 to represent conditions in the stomach. A fibre-optic probe connected to a UV spectrometer monitors the concentration of sample released into solution. The pH is varied with time to represent passage of the compound from the stomach to the intestine. The concentration of the sample in solution can thus be monitored over the pH range typically encountered in the GI tract.

Results: The central panel of this poster displays several GI Dissolution profiles. For example, concentration of piroxicam with time is plotted at four pH values corresponding to different regions of the GI tract. Piroxicam has pK_as at 1.9 (base) and 5.3 (acid). Hence, dissolution is relatively rapid at pH 1.85 where a significant proportion is positively charged. At pH 3.82 dissolution decreases as the piroxicam concentration tends to the solubility limit of the neutral anhydrous form. The dissolution rate increases at higher pH, where piroxicam is becoming increasingly negatively charged. Other dissolution profiles show phenazopyridine, pK_a 5.1 (base), introduced in both powder and tablet form; and diclofenac, introduced as the sodium salt, which precipitates from solution below pH 5 before re-dissolving at high pH in anionic form. The far right panel shows examples of dissolution experiments performed in simulated intestinal fluids (FaSSIF and FeSSIF).

Conclusion: A method is described for studying concentration-time profiles of drugs at different pH representing passage through the GI tract. Such experiments could be used to assess compounds' availability for oral absorption.

Apparatus

Dissolution experiments are done using Sirius GLpKa (or PCA200) and D-PAS instruments (figure 1), together with a version of Sirius RefinementPro2 software that supports dissolution experiments. Typical experiments require 2 to 10mg of compound and are performed in 10 to 15mL of dissolution medium.

To create drug tablets, a custom hydraulic pellet press was developed (see figure 2). The press is used with the tablet die shown in figure 3 to press a pellet of pure drug directly into the tablet disc, which is then pushed into the tablet disc holder (figure 4) and held in place with an "O" ring seal. The tablet disk holder is designed so that an appropriate amount of buffer solution can be introduced into the vial without wetting the drug pellet, ensuring that the tablet remains dry before the start of the experiment.

In the GI-dissolution experiment, the dissolution of a compressed tablet of drug compound is monitored by UV-absorption spectroscopy as the pH of the aqueous dissolution medium is increased, typically through four sectors, to simulate passage of the tablet through the gastrointestinal tract (see central poster panel and figure 5). The tablet is compressed under a pressure of approximately 40000 pounds per square inch and has a diameter of 3mm. Only one face of the tablet is exposed to the dissolution medium, which contains an acetate/phosphate buffer system to minimise perturbation to the experimental pH from dissolution of the drug. Stirring of the solution is continuous and at a constant rate. The absorption data is converted to an absolute sample weight using previously determined, pH-dependent, molar extinction coefficients. An appropriate wavelength range is chosen to ensure that spectroscopic data with an absorption value of < 1.25 is analyzed, avoiding erroneous dissolution results due to saturation of the UV light source. Sensitivity of the method is ~0.001 absorbance units. Dissolution rates are calculated from a fit of equation (1) to the experimental data:

(1)

$$[X]_t = S(1-e^{-k_d(t-t_o)})$$

where, $[X]_t$ is the weight of drug (g), X, in solution at experiment time, t (mins); S is the extrapolated solubility (g) of drug X; k_d is the rate constant for dissolution (mins^{-1}); and t_0 (mins) is a term allowing for a temporal offset. The dissolution rate (g/min) is reported as the product, k_dS, i.e. the dissolution rate at t_o, when the concentration of X in solution is zero.

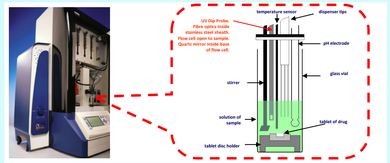


Figure 1. Sirius GLpKa and D-PAS, with expanded schematic of measurement cell

Figure 2. Pellet press

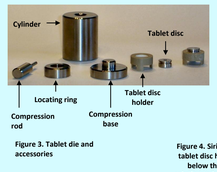


Figure 3. Tablet die and accessories

Figure 4. Sirius standard vial with tablet disc holder. The three legs below the holder allow buffer solution to be introduced without wetting the tablet surface

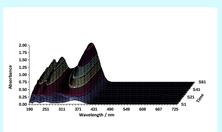


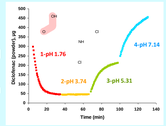
Figure 5. Example UV data obtained for piroxicam, during four consecutive pH sectors, simulating passage through the GI tract.

GI Dissolution Graphs

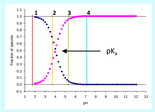
UV data is collected at 4 pH values for 30 minutes at each pH. The pH at each stage is marked on the Distribution of Species , and is colour-coded to match stages in the GI Dissolution Graph.

Diclofenac

Sample introduced as the sodium salt in powder form. Note that diclofenac was precipitating at pH 1.76, as the salt had converted to the neutral species. As expected, the dissolution rate was high at pHs above the pK_a (4.03), aided by the large surface area of the powder.



GI Dissolution Graph



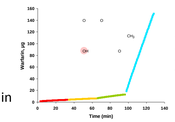
Distribution of Species vs. pH

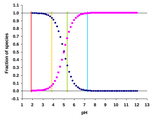
Dissolution pH	Dissolution rate, µg/min
1.76	Precipitating
3.74	No further precipitation
5.31	22.5
7.14	32.5

Warfarin

Acid with one pK_a (4.94). Sample introduced as pellet of warfarin in neutral form.

The dissolution rate was low until pH 7.27, significantly above the pK_a, where warfarin exists in 100% anionic form.



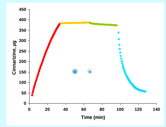


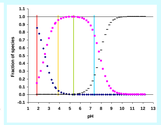
Dissolution pH	Dissolution rate, ng/min
1.86	130
3.86	128
5.34	285
7.27	4590

Cinnarizine

Base with two pK_as (2.59 and 7.88). Sample introduced as pellet of HCl-salt.

Dissolution was rapid at pH 1.85, where the drug was in highly ionized form. As the pH was increased, the sample precipitated as the concentration of the supersaturated solution exceeded the solubility limit at the new pH.





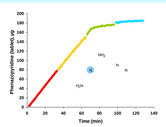
Dissolution pH	Dissolution rate, µg/min
1.85	17.3
3.87	No further dissolution
5.36	Precipitating
7.32	Precipitating

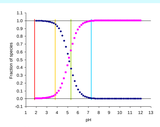
Phenazopyridine

Base with one pK_a (5.1). Introduced as HCl-salt.

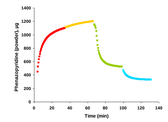
Top graph: sample introduced as pellet. Note the dissolution rate increased with a greater degree of sample neutrality. This implies that the freebase form has a higher dissolution rate than the HCl-salt.

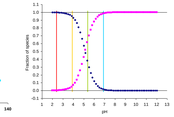
Bottom graph: sample introduced as powder. As expected, the higher surface area aids dissolution. Sample precipitation was observed at pH 5.4 and pH 6.9, reaching a final concentration similar to that reached in stage 4 with a pellet.





Dissolution pH	Dissolution rate, µg/min
1.85	2.7
3.83	2.8
5.32	26.3
7.27	11.1



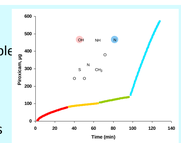


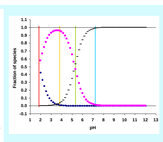
Dissolution pH	Dissolution rate, µg/min
2.38	213.8
3.89	42.3
5.38	Precipitating
6.87	Precipitating

Piroxicam

Ampholyte with two pK_as: base 1.87; acid 5.29. Sample introduced as pellet of piroxicam in neutral form.

Dissolution is relatively rapid at pH 1.85, where a significant percentage of piroxicam is positively charged. At pH 3.82 the dissolution rate decreases as piroxicam is in predominantly neutral form. Dissolution rates increase at higher pH, where piroxicam is negatively charged.





Dissolution pH	Dissolution rate, µg/min
1.85	4.0
3.82	1.5
5.32	2.2
7.23	19.0

Dissolution experiments in simulated GI fluids

UV data is collected for 120 minutes in simulated gastric fluids (FeSSIF and FaSSIF), and in aqueous solutions buffered to the same pH. Dissolution rates are calculated from data plotted in the dissolution-time profiles shown below, and solubility at the experimental pH can be estimated by projecting the curve forward to infinite time.

FeSSIF and FaSSIF buffers were prepared from reconstitutable powder supplied by EPHARES.COM. Formulae are based on published recipes [Kostewicz, E.S., Brauns, U., Becker, R., Dressman, J.B. Pharm. Res. 2002, 19(3), 345-349].

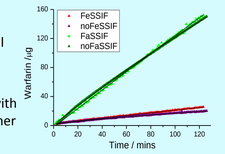
Ingredients of FeSSIF (Fed State Simulated Intestinal Fluid): pH 5.0			
Sodium taurocholate	15mM	Glacial acetic acid	8.65g
Lecithin	3.75mM	Purified water qs.	1000mL
NaOH (pellets)	4.04g		

Ingredients of FaSSIF (Fasted State Simulated Intestinal Fluid): pH 6.5			
Sodium taurocholate	3mM	$NaH_2PO_4.H_2O$	1.977g
Lecithin	0.75mM	NaCl	3.093g
NaOH (pellets)	0.174g	Purified water qs.	500mL

Warfarin

Acid with one pK_a (4.94). Sample introduced as pellet of warfarin in neutral form. Warfarin is ionized at pH 6.5. Dissolution is fastest at this pH, with equal rates with and without FaSSIF.

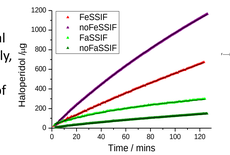
Although dissolution rates are lower at pH 5.0, a significant amount of the absorbable neutral species will be present. Equal dissolution rates are seen with and without FeSSIF. The extrapolated solubility of warfarin is significantly higher in the presence of simulated intestinal fluids (i.e. at a given pH).



Haloperidol

Base with one pK_a (8.43). Sample introduced as pellet of haloperidol in neutral form. Dissolution is fastest at pH 5.0, where haloperidol is ionized. Interestingly, rates are lower in FeSSIF compared to aqueous conditions – perhaps because the high ionic strength (0.30 M) inhibits dissolution due to the low solubility of the HCl-salt.

Dissolution rates are lower at pH 6.5, but are higher in FaSSIF relative to aqueous conditions.

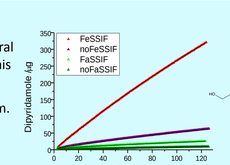


Dipyridamole

Base with one pK_a (6.12). Sample introduced as pellet of dipyridamole in neutral form. Dipyridamole is significantly ionized at pH 5.0. Dissolution is fastest at this pH, and is significantly faster in the presence of FeSSIF.

Dissolution rates are lower at pH 6.5, where most of the drug is in neutral form. FaSSIF enhances dissolution in relation to aqueous conditions.

Simulated intestinal fluids will substantially increase the dissolution rate and solubility of dipyridamole.



Extrapolated solubility

An exponential function (equation 1) was fitted to the dissolution profiles, allowing the determination of dissolution rates and extrapolated solubility at the experimental pH, as shown in the table.

Dissolution medium	Warfarin: Dissolution rate, µg/min	Warfarin: Extrapolated solubility, µg/mL	Haloperidol: Dissolution rate, µg/min	Haloperidol: Extrapolated solubility, µg/mL	Dipyridamole: Dissolution rate, µg/min	Dipyridamole: Extrapolated solubility, µg/mL
FeSSIF	0.2	14.5	6.1	180	3.04	75
no FeSSIF	0.2	3.4	12	223	0.61	12.2
FaSSIF	1.3	180	4.1	26	0.23	4.5
No FaSSIF	1.34	55	1.5	28	0.11	1.5

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