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PAPER

The "GI dissolution" method: a low volume, *in vitro* apparatus for assessing the dissolution/precipitation behaviour of an active pharmaceutical ingredient under biorelevant conditions

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This paper describes a low volume, *in vitro* apparatus for investigating the dissolution and precipitation behaviour of active pharmaceutical ingredients (APIs) under a wide range of experimental conditions and dissolution media. The apparatus has automated and dynamic pH control, allowing the simulated passage of drugs through the gastrointestinal tract (GIT). Experiments can be performed in the presence of biorelevant media and excipients, providing information related to the predicted behaviour of APIs under physiological conditions. The technique is described in detail and results are presented for a number of neutral, basic, acidic and ampholytic drug compounds.

Introduction

Dissolution testing[1–6] plays an increasingly important role in the formulation, development and regulatory approval of pharmaceutical products.[7–11] For many drug molecules, dissolution testing shows good *in vivo–in vitro* correlation and dissolution data are often accepted by regulatory bodies in lieu of clinical studies.[12–18] This can greatly reduce the time-to-market for new drug products. Dissolution testing is also used to assess the product stability and batch-to-batch reproducibility, making it a valuable tool for the product development and quality control. Continual development of dissolution testing is needed as scientific and regulatory requirements change.

The solubility and dissolution behaviour of ionizable compounds are strongly dependent on the pH environment. Many APIs have ionization constants which lie within the pH range of the GIT (gastrointestinal tract).[19] This can result in complex dissolution and precipitation behaviour as the API moves through the GIT, which is not adequately modelled by experiments at fixed pH. Some weakly basic drugs, for example dipyridamole, are soluble at gastric pH and have the ability to remain in supersaturated solution at intestinal pH, where they are otherwise highly insoluble, for some time before precipitating. This illustrates the need for dynamic pH control. It is also essential to be able to perform experiments in the presence of excipients and biorelevant media, which can both have a significant impact on the supersaturation behaviour.[20]

Traditional dissolution methods have high sample weight requirements, typically 150–700 mg.[21] Consequently, the use of dissolution testing is presently limited to compounds in the later stages of development where larger sample quantities are available. There is growing interest in the development of low-volume, API-sparing techniques to allow the characterisation of compounds earlier in their development cycles. Miniaturised dissolution techniques using *ca.* 5 mg of API have been described previously and good correlation with traditional methods has been obtained.[22] However, these methods have thus far been limited to fixed pH.

This paper presents the novel *GI dissolution* method, a low volume *in vitro* technique with dynamic pH control for investigating the behaviour of pharmaceutical substances throughout the GIT. Dissolution is monitored *in situ* by UV absorbance spectroscopy, allowing a high level of automation. The method is easily adaptable and experiments can be carried out in the presence of excipients. Disk intrinsic dissolution rates (DIDRs) obtained at fixed pH show excellent agreement with published values. Dynamic pH experiments allow dissolution and precipitation events over the physiological pH range to be investigated. Results are presented for a diverse range of drug molecules, illustrating the applicability of the technique and its implications for use in the pharmaceutical industry.

Experimental

Molar extinction coefficients and pK_as

Molar extinction coefficients and pK_as of all of the compounds investigated were determined in advance by UV-metric titration using the SiriusT3 or GLpKa (Sirius Analytical Instruments, East Sussex, UK). The SiriusT3 and its predecessor GLpKa are automated titration systems specifically designed for the measurement of various physiochemical properties, for example pK_a, log P and solubility. The UV-metric method allowed the determination of the molar extinction coefficients for both the neutral and ionised forms of a particular compound from a single

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experiment. Samples were typically prepared as 5 mM stock solutions in DMSO and titrated between pH 2 and pH 12 in 1.5 mL of 0.15 M aqueous KCl. Sample concentrations were optimized in order to obtain a peak UV absorbance of approximately 1 absorbance unit. Where possible, titrations were carried out under aqueous conditions; however, it was necessary to investigate some compounds in the presence of methanol cosolvent due to their poor aqueous solubilities.

Tablet production

Tablets of 3 mm diameter comprising 5–40 mg of pure API were created inside a tablet disc using a manual hydraulic tablet press (Specac Ltd, Orpington, UK). The tablet disc is made from stainless steel (grade 316) and the compression rod (3 mm diameter) is certified up to a compression weight of 0.5 tonnes. Tablets were typically produced under a weight of 0.4 tonnes (approximately 900 lb) applied for 120 s. All tablets were visually examined to ensure their surfaces were smooth and free of visible defects.

The tablet discs were placed in tablet disc holders and held *in situ* by an O-ring seal, as shown in Fig. 1. This prevented exposure of the reverse side of the tablet to the dissolution medium, giving a total exposed surface area of 0.07 cm^2. The tablet disc holder was then inserted into an appropriate-sized vial. The tablet disc holder raises the tablet approximately 7 mm above the base of the vial, allowing the introduction of up to 2 mL of liquid to the vial without wetting the surface of the tablet prior to the start of the dissolution experiment.

Initial calibration and disk intrinsic dissolution rates

Dissolution rates are strongly dependent on the nature of the dissolution medium and on experimental conditions such as stirring speed.[23] Initial calibration experiments were carried out using 30 mg tablets of pure salicylic acid in a 50 mM sodium phosphate solution at pH 7.4. Salicylic acid is an accepted reference standard for the calibration of the existing dissolution apparatus.[23,24] All experiments were carried out at room temperature in 15 mL of the relevant dissolution medium. Reproducibility was assessed by repeating the experiments on a number of SiriusT3 and GLpKa instruments.

To compare the performance of the apparatus with other miniaturized dissolution systems, the disk intrinsic dissolution rates of atenolol, haloperidol, hydrochlorothiazide, ketoprofen, naproxen, piroxicam and propranolol were subsequently determined in 0.1 M HCl, 0.2 M acetate buffer at pH 4.5 and 0.2 M phosphate buffer at pH 6.8. Labetalol was investigated in 0.1 M HCl. The dissolution of ketoprofen was also investigated in FeSSIF and FaSSIF, to illustrate the applicability of the technique to biorelevant media. The simulated intestinal fluids were prepared from Phares SIF powders (http://www.ephares.com). The FaSSIF contained 3 mM of sodium taurocholate and 0.75 mM of lecithin adjusted to pH 6.44. The FeSSIF contained 15 mM of sodium taurocholate and 3.75 mM of lecithin at pH 4.92.

GI dissolution

A concentrated buffer solution, typically 1.5 mL of a 0.125 M phosphate/acetate buffer at pH 1.5, is introduced into the sample vial below the surface of the tablet. The instrument then automatically adds the dissolution medium, typically 13.5 mL of 0.15 M aqueous KCl solution. The buffer ensures that the start pH of the experiment is close to pH 2, modeling gastric conditions, without the need for an initial pH adjustment. This allows data collection to be started as soon as the dissolution medium has been added. The buffer solution also serves to prevent changes in the pH of the medium due to dissolution of the sample.

The medium is stirred at a constant rate throughout the GI dissolution experiment. UV-visible absorption spectra are recorded *via* a fibre optic dip probe with a diode array spectrometer at fixed intervals for a specified period. Spectra are typically recorded every 30 seconds for 30 minutes. Examples of UV spectra are displayed in Fig. 2a, which show the increase in the concentration of the drug in solution as the tablet dissolves and the UV absorbance increases. Low sample concentrations can be detected (<1 μM) giving a wide dynamic range to the measurement of dissolution rates, 1×10^{-9} to 1×10^{-3} g s^{-1} cm^{-2}.

When the specified time at the initial pH has elapsed, a titrant (*e.g.* 0.5 M KOH solution) is automatically dispensed to adjust to the next pH and UV spectra are again recorded for a specified period. This process is repeated for all the pH zones investigated. The GI dissolution experiment normally consists of four zones

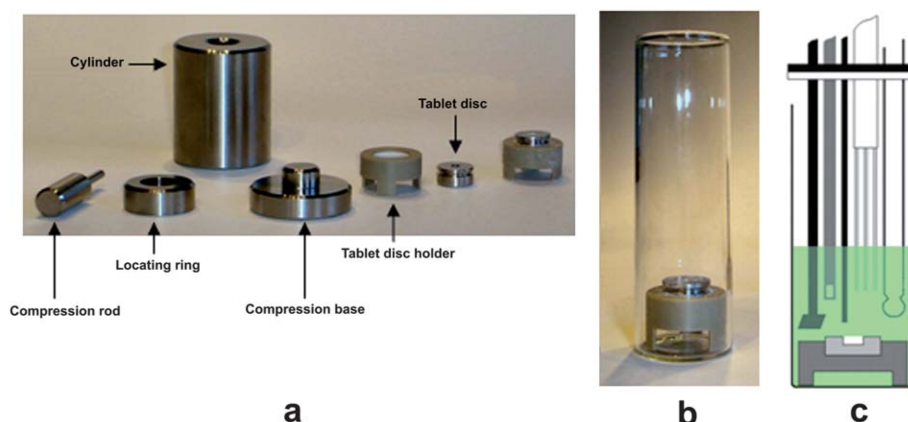

Fig. 1 Apparatus required for the GI dissolution experiment.

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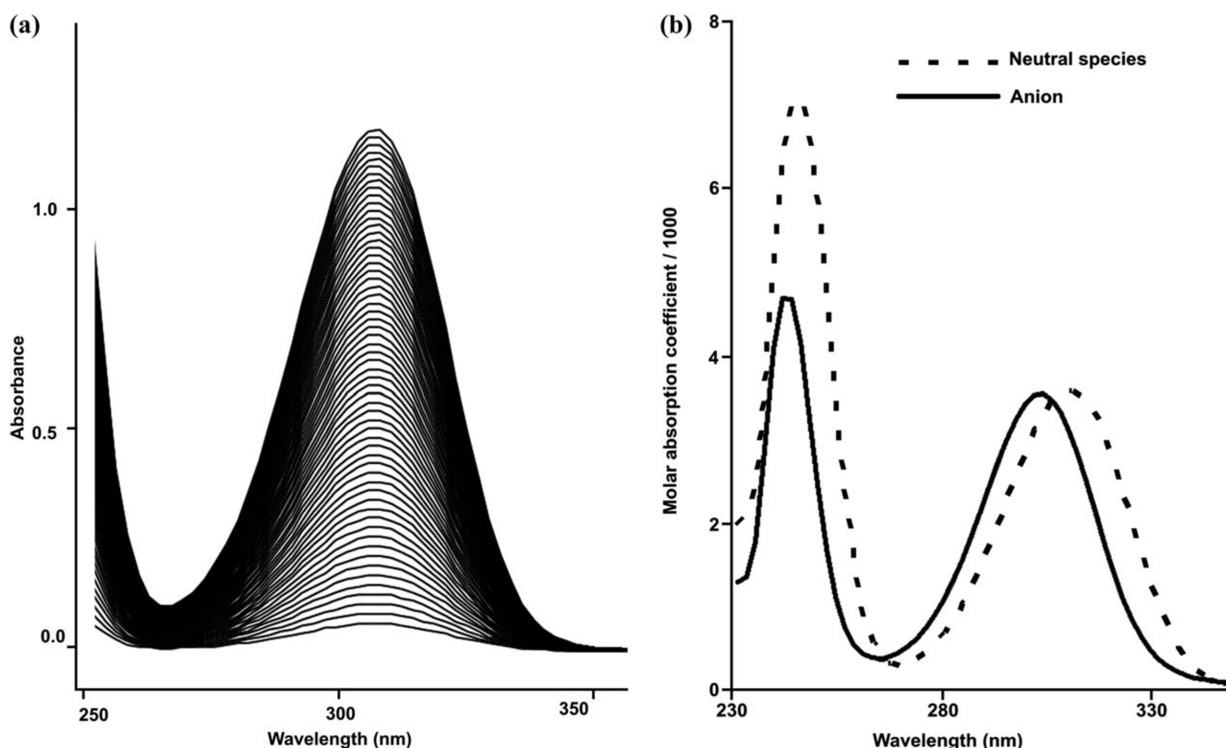

Fig. 2 (a) UV absorption spectra collected at pH 1.77 during a GI dissolution experiment of salicylic acid.(b) Molar absorptivities of salicylic acid (dashed line) and salicylate anion (solid line), obtained from an experiment to measure salicylic acid pK_a value using a solution with a known concentration of salicylic acid.

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(pH 1.9, pH 3.8, pH 5.3 and pH 7.2) so that dissolution of the drug compound is monitored over the entire pH range typically encountered in the GIT. The desired pH zones, frequency of point collection and duration of time in each zone can be easily modified to suit the needs of the experimenter. A range of basic, acidic, ampholytic and neutral compounds were investigated to illustrate the applicability of this technique.

Results and discussion

Calculation of dissolution rates

The concentration of sample in solution at each time point is determined from the spectroscopic data by applying the Beer–Lambert law, using previously determined molar extinction coefficients. Fig. 2b shows the molar extinction coefficient profile for salicylic acid. Analytical wavelength ranges are selected by the software; any data corresponding to the saturation of the UV light source are automatically excluded from the calculation. The concentration data are converted into absolute sample quantities and used to generate a graph showing the sample quantity in solution *vs.* time. The software then attempts to fit a first order exponential eqn (1) to the data to obtain the dissolution rate and an extrapolated solubility value.

$$[\mathrm{X}]_t = S\left(1 - \mathrm{e}^{-k_\mathrm{d}(t-t_0)}\right) \quad (1)$$

Here $[\mathrm{X}]_t$ is the weight in grams of drug X in solution at experiment time t (min); S is the extrapolated solubility (g) of the drug; k_d is the rate constant for dissolution (min^{-1}); and t_0 (min) is a term allowing for a temporal offset. Results are calculated using a refinement process in which S, k_d and t_0 are varied in order to minimize the root mean square deviation between the modeled concentrations and the measured concentrations. The dissolution rate (g min^{-1}) is given by the product $k_\mathrm{d}S$, *i.e.* the dissolution rate at t_0, when the concentration of X in solution is zero. The dissolution rate can be normalized for the surface area to give the intrinsic dissolution rate (IDR) with units of g s^{-1} cm^{-2}. The half-life for dissolution, $t_{\mathrm{d}1/2}$, can be expressed by

$$t_{d1/2} = \frac{\ln(2)}{k_\mathrm{d}} \quad (2)$$

In some cases, data obtained when samples precipitate can be analysed with eqn (3) to yield an initial precipitation rate and extrapolated solubility value.

$$[\mathrm{X}]_t = C_0\mathrm{e}^{\left(-k_\mathrm{p}(t-t_0)\right)+S_\mathrm{f}} \quad (3)$$

Here $[\mathrm{X}]_t$ is the weight in grams of drug X in solution at experiment time t (min); C_0 is the initial concentration of the drug in solution before the precipitation event (g); k_p is the rate constant for precipitation (min^{-1}); t_0 (min) is a term allowing for a temporal offset; and S_f is the extrapolated solubility of the drug after the precipitation event is complete. In cases where the initial concentration C_0 is well defined and the precipitation data can be approximated by first-order kinetics, the precipitation rate (g min^{-1}) is determined as the product $k_\mathrm{p}C_0$, *i.e.* the precipitation rate at t_0 when precipitate first appears in the supersaturated solution. The half-life for precipitation, $t_{\mathrm{p}1/2}$, can be determined by substitution of k_p for k_d in eqn (2). It should be noted that the

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accurate treatment of dissolution data obtained under turbid conditions relies on a wavelength-independent contribution to the absorbance from particulate scattering of light. This is not always observed, particularly when the suspension consists of particles of variable size.

Calibration and disk intrinsic dissolution rates at fixed pH

Initial calibration experiments were performed on a GLpKa instrument using salicylic acid as a reference standard. The dissolution of a tablet of salicylic acid in a 50 mM aqueous solution of $NaH_2PO_4 \cdot H_2O$ adjusted to pH 7.4 was measured at room temperature in three identical experiments. Each tablet contained approximately 30 mg of pure salicylic acid. The average dissolution rate was determined as 86.1 ± 1.4 μg min^{-1} and demonstrated good repeatability. The disk intrinsic dissolution rate is thus 2.03 ± 0.03 × 10^{-5} g s^{-1} cm^{-2}, which is in reasonable agreement with the USP (1.84 × 10^{-5} g s^{-1} cm^{-2} in a 50 mM phosphate buffer at pH 7.4 and 37 °C, at a 100 rpm paddle speed).[25]

Repeatability and reproducibility were investigated for the SiriusT3 instrument. Initially, two sets of dissolution experiments (each consisting of three experiments) were performed on the same instrument at stirrer speeds of 4800 rpm and 2700 rpm. As with the GLpKa, good repeatability was observed and the dissolution rate was found to be dependent on the stirrer speed, with results of 116.8 ± 2.6 μg min^{-1} and 71.2 ± 1.9 μg min^{-1} determined at 4800 rpm and 2700 rpm respectively. At 2700 rpm the average dissolution rate was determined as 1.68 × 10^{-5} g s^{-1} cm^{-2}, which is in reasonable agreement with the USP. To investigate the reproducibility, single dissolution experiments were performed at a 2700 rpm stirrer speed on four SiriusT3 instruments. A mean result of 1.5 ± 0.2 × 10^{-5} g s^{-1} cm^{-2} was obtained, showing a reasonable level of reproducibility.

Disk intrinsic dissolution rates (DIDRs) for a selection of compounds at pH 1.2 (0.1 M HCl), pH 4.5 (0.2 M acetate buffer) and pH 6.8 (0.2 M phosphate buffer) at room temperature are shown in Table 1. All measurements were carried out on the SiriusT3. Tablets typically consisted of *ca.* 5 mg of pure compound and all experiments were carried out in 15 mL of the relevant medium. DIDRs in the table were measured in order to compare with values reported in the literature.[22,26] No literature DIDRs were reported for atenolol and haloperidol at pH 1.2, or for labetalol HCl at pH 4.5 and 6.8, so these DIDRs were not measured in this study. Excellent correlation with literature values was obtained, with a coefficient of determination (r^2) of 0.98.

It must be stressed that the GI dissolution apparatus is not intended to replace the existing large volume dissolution apparatus for the measurement of intrinsic dissolution rates. The primary purpose of the apparatus is to investigate the dissolution and precipitation behaviour of APIs under experimental conditions that are relevant to the GIT using low sample weights and small volumes. However, it is useful that the measured intrinsic dissolution rates compare well with published values.

Ketoprofen at a single pH in FaSSIF and FeSSIF

Fig. 3 shows the dissolution profiles of ketoprofen obtained in FaSSIF (fasted state simulated intestinal fluid) and FeSSIF (fed state simulated intestinal fluid).[27] Ketoprofen is an acidic molecule with a pK_a of 4.2. It is predominantly ionised at pH above 4.2 and becomes increasingly soluble as the pH increases. The dissolution experiments were performed in 15 mL of the dissolution medium at 25.7 °C and pH 6.44 (FaSSIF) and at 26.3 °C and pH 4.92 (FeSSIF). Dissolution rates of 31.6 μg min^{-1} (FaSSIF) and 8.4 μg min^{-1} (FeSSIF) were calculated. Note that

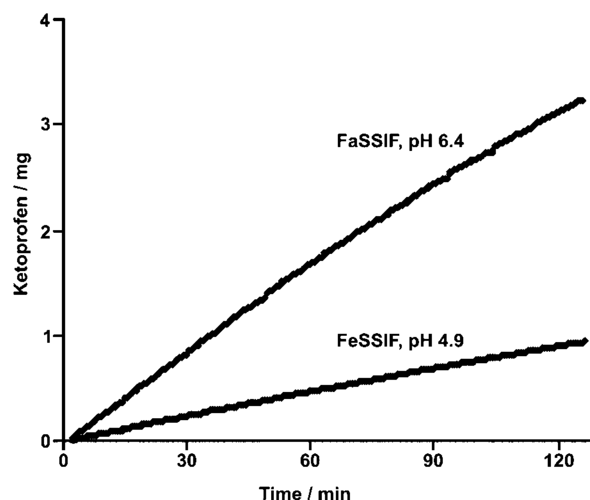

Fig. 3 Ketoprofen dissolution profiles obtained in FaSSIF and FeSSIF.

Table 1 Disk intrinsic dissolution rates (DIDRs) of acidic (A), basic (B), and ampholytic compounds (A and B), at pH 1.2 (0.1 M HCl), pH 4.5 (0.2 M acetate buffer) and pH 6.8 (0.2 M phosphate buffer). Tablet weights were in the range 4.93–21.94 mg. All experiments were performed at room temperature (21.2–25.1 °C)

		Disk intrinsic dissolution rate (DIDR)/μg min^{-1} cm^{-2}		
Compound	pK_a	pH 1.2	pH 4.5	pH 6.8
Ketoprofen	5.08 (A)	15.1	56.6	1939.6
Naproxen	4.32 (A)	n/a[a]	16.3	314.1
Hydrochlorothiazide	8.66 (A), 9.88 (A)	207.7	96.4	120.5
Atenolol	9.43 (B)		6649.1	3775.9
Haloperidol	8.42 (B)		427.2	n/a[a]
Propranolol HCl	9.54 (B)	7908.2	19013.7	10451.9
Labetalol HCl	7.19 (A), 7.84 (B)	980.4		
Piroxicam	1.89(B), 5.34 (A)	19.2	4.6	80.6

[a] UV change not sufficient to allow determination of the dissolution rate.

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the dissolution rate of ketoprofen in FeSSIF is lower than in FaSSIF despite FaSSIF's lower taurocholate and lecithin contents, largely because more of the ketoprofen is in the soluble ionised form at the higher pH of FaSSIF.

Salicylic acid GI dissolution

Salicylic acid is a weak acid with a pK_a of 2.8. The GI dissolution profile of salicylic acid is displayed in Fig. 4. In this experiment, the pellet was made from 34 mg of salicylic acid; 1.5 mL of mixed phosphate/acetate buffer (0.125 M) was introduced beneath the pellet and 13.5 mL of 0.15 M KCl was introduced automatically to give an initial pH of 1.77. By applying eqn (1), the dissolution rates at pH 1.8, pH 3.7, pH 5.2 and pH 7.1 were found to be 26.2 μg min^{-1}, 39.2 μg min^{-1}, 51.1 μg min^{-1} and 64.8 μg min^{-1} respectively. The dissolution rate of salicylic acid is approximately 2.5 times greater at pH 7.1 than that at pH 1.8. An increase in the dissolution rate with pH is to be expected as salicylic acid is in fully anionic form at pH 7.1 but in predominantly neutral form at pH 1.8.

According to the Henderson–Hasselbalch equation,[28] the solubility of salicylic acid is several orders of magnitude higher at pH 7.1 than at pH 1.8. A similar increase in the dissolution rate might therefore be expected. This, however, is not the case. The diffusion of the drug compound across the aqueous boundary layer (ABL) at the tablet surface is thought to be the rate-determining step in the dissolution process.[26] This establishes a microclimate at the surface of the tablet, wherein the local concentration of the drug is considerably higher than in the bulk medium, assuming that sink conditions are in effect. For ionisable drugs, this has the consequence of creating a localised pH environment at the tablet surface. In this example, the high concentration of salicylic acid in the diffusion layer lowers the local pH at the tablet surface, lowering the observed dissolution rate considerably, relative to what might be expected based on its equilibrium solubility. The magnitude of the difference between the interfacial pH and the bulk solution, and consequently the impact on the dissolution rate, is strongly dependent on the solubility of the drug and its ionization state.[26]

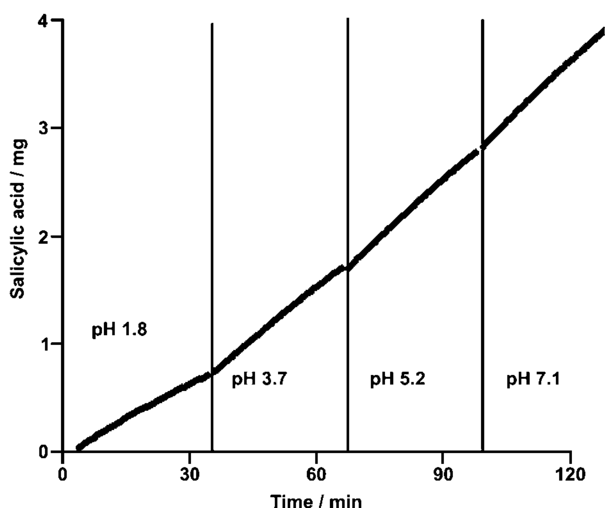

Fig. 4 GI dissolution profile for salicylic acid in 0.15 M aqueous KCl at 25.4 °C.

GI dissolution experiments with dipyridamole

Fig. 5a shows the GI dissolution profile of dipyridamole in 0.15 M aqueous KCl. Dipyridamole has two basic pK_as, 6.2 and approximately 0.8. The whole tablet rapidly dissolves in the first zone at pH 1.8, with an initial rate of 329 μg min^{-1}. In the second zone, at pH 3.8, no change to the concentration of the drug in solution is observed. Precipitation of dipyridamole is observed in both the third (pH 5.2) and fourth (pH 7.2) pH zones. At the end of the experiment the concentration of dipyridamole in solution is 7.9 μg mL^{-1} which approaches the measured intrinsic solubility of dipyridamole, 3.6 μg mL^{-1}.[20] In Fig. 5b, eqn (3) is fitted to the dipyridamole precipitation data. The data obtained at pH 5.2 during precipitation of the sample from solution do not approximate well to first-order kinetics. This is not surprising as the precipitation rate will depend on a number of dynamic factors such as particle size and surface area. In such cases, fitting of the precipitation data cannot provide reliable quantitative results. The data obtained at pH 7.2 approximate well to first-order kinetics. In this zone the precipitate has already been present in solution for 30 minutes and the physicochemical properties of the particles are likely to be well defined. Eqn (3) should therefore provide accurate quantitative information about the precipitation event. In the refinement of the pH 7.2 data, all parameters were varied with the exception of C_0 which was constrained to the final dipyridamole concentration at the end of the pH 5.2 zone. It is a requirement that either C_0 or t_0 is constrained to an appropriate value in the fitting procedure, since these two parameters are highly interdependent. The following results were obtained: $k_p = 0.453$ min^{-1} ($t_{p1/2} = 1.53$ min); $t_0 = 97.4$ min; $S_f = 0.139$ mg. These results correspond to an initial precipitation rate (k_pC_0) of 602 μg min^{-1} and an extrapolated solubility of 8.5 μg mL^{-1}.

The dipyridamole GI dissolution profile obtained in 0.15 M aqueous KCl containing 1.5% v/v Triton X-100 surfactant is shown in Fig. 6. The whole tablet dissolves in the first pH zone (pH 2.0), at a similar rate (250 μg min^{-1}) to that of the aqueous experiment. No precipitation is observed as the pH is increased through the subsequent three zones, highlighting the stabilizing effect of Triton X-100 on supersaturated solutions of dipyridamole. This is consistent with the results of earlier studies,[20] which indicated that some formulation excipients have the ability to stabilize supersaturated solutions, and illustrates the importance of dynamic pH control to dissolution experiments.

GI dissolution experiments with well known drugs

Table 2 shows the GI dissolution results obtained for a number of well known drugs. All experiments were performed on the same GLpKa instrument and under similar experimental conditions. All samples were measured in 0.15 M aqueous KCl in the presence of a mixed acetate/phosphate buffer.

Neutral compounds. The dissolution rates of the neutral compounds chloramphenicol and dexamethasone were found to remain constant across the four pH zones. This is to be expected because these molecules remain in the same ionisation state throughout the experiments.

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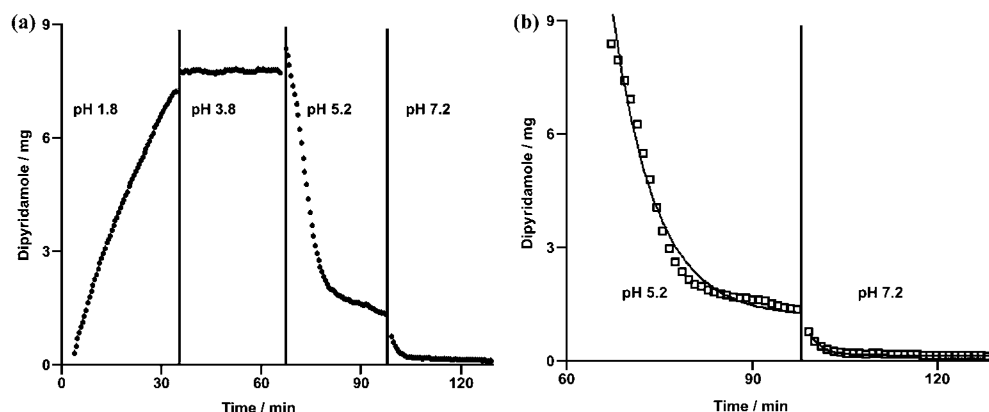

Fig. 5 (a) Dipyridamole GI dissolution profile in 0.15 M aqueous KCl at 26.7 °C.(b) Analysis using eqn (3) of the dipyridamole precipitation data obtained at pH 5.2 and pH 7.2 in the GI dissolution experiment shown in Fig. 7a.

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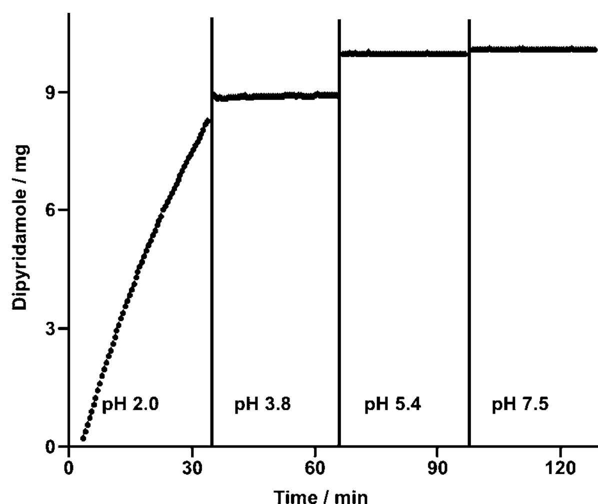

Fig. 6 Dipyridamole GI dissolution profile in 0.15 M aqueous KCl containing 1.5% v/v Triton X-100 at 26.0 °C.

Basic compounds. For the basic compounds carvedilol, chlorpromazine HCl, clopidogrel bisulfate, dipyridamole, haloperidol, maprotiline and propranolol several types of behaviour were observed. In general, dissolution rates were found to decrease with increasing pH and precipitation was commonly observed in the latter pH zones of the GI dissolution experiments. This is expected because basic drugs become more neutral, and consequently less soluble, as pH is increased.

Haloperidol, maprotiline and propranolol continued to dissolve in the higher pH zones in 0.15 M KCl, though propranolol dissolved more slowly at higher pH. For chlorpromazine HCl, clopidogrel bisulfate and dipyridamole, precipitation was observed in one or more pH zones in 0.15 M aqueous KCl dissolution media. This illustrates the importance of an experiment that simulates the changing pH conditions of the GIT, which can be of great relevance for basic drugs where supersaturation effects can occur.

Acidic compounds. Dissolution rates of the acidic compounds carprofen, ibuprofen, tolmetin and warfarin were generally observed to increase with increasing pH. This is expected because acidic compounds become more ionised as the pH increases. Warfarin appeared to behave anomalously, dissolving at a slightly higher rate at pH 1.9 than at pH 3.8 and 5.3; this observation may be due to experimental uncertainty. Perhaps the most interesting results for the acidic compounds were obtained in the GI dissolution experiments of the sodium salts of ibuprofen and tolmetin in 0.15 M aqueous KCl. In the case of ibuprofen (Fig. 7), the free acid initially dissolves slowly in the neutral form before the dissolution rate increases at high pH where ibuprofen becomes increasingly anionic. The sodium salt, which might be considered to be considerably more soluble than the free acid at low pH, rapidly dissolves at pH 1.9. Once in solution, the anionic ibuprofen released from the salt converts to the less soluble neutral form, which precipitates from solution. Precipitation of the neutral ibuprofen occurs while the salt is still dissolving, resulting in the complex behaviour shown in Fig. 7. Later, the precipitate rapidly dissolves at pH 5.2 and pH 7.0, presumably due to the large surface area available for dissolution. These results suggest that the amount of an acidic drug available for absorption in the GIT can in some cases be increased by administering the drug in the salt form, thus allowing it to dissolve at low pH where it would otherwise be insoluble, forming a supersaturated solution.

Ampholytic compounds. As with other ionizable compounds, the pK_as of ampholytes are likely to have a significant impact on their dissolution behaviour under aqueous conditions. Luminol has a basic pK_a of 1.4 and an acidic pK_a of 6.2. It was found to dissolve at an initial rate of 0.70 μg min^{-1} at pH 1.9, where a significant proportion of the compound was in the cationic form. The dissolution rate was lower at pH 3.8, where the compound was predominantly neutral. The dissolution rate then increased at higher pH, due to the presence of increasing amounts of the anionic form of the molecule. Piroxicam, which has similar pK_as, displays similar behaviour.

Conclusions

An automated *in vitro* method has been described for measuring the dissolution and precipitation rates of pharmaceutical substances, using low sample weights and low volumes in a variety of dissolution media. The apparatus is designed to

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Table 2 Dissolution rates of neutral, acidic (A), basic (B), and ampholytic compounds (A and B), obtained from GI dissolution experiments in 0.15 M aqueous KCl. Tablet weights were in the range of 6.3–24.3 mg and all experiments were conducted at room temperature (25.0–27.8 °C). The four pH values correspond to the average pH values of the four zones of the GI dissolution experiments. Dissolution was monitored for 30 minutes at each pH zone, with the collection of UV absorbance spectra every 30 seconds

		Absolute dissolution rate/μg min^{-1}			
Compound	pK_a	pH 1.9	pH 3.8	pH 5.3	pH 7.2
Chloramphenicol	Neutral	46.4	48.9	52.8	52.0
Dexamethasone	Neutral	1.00	0.77	0.85	0.77
Carprofen	4.25 (A)	0.07	0.64	0.95	11.8
Ibuprofen	4.35 (A)	2.9	3.6	5.4	23.0
Ibuprofen Na	4.35 (A)	n/a[b]	n/a[b]	1972	3666
Tolmetin	3.50 (A)	0.46	1.5	9.6	23.2
Tolmetin Na	3.50 (A)	n/a[b]	n/a[b]	163.1	973.2
Warfarin	4.94 (A)	1.3	1.1	1.2	2.9
Carvedilol	8.0 (B)	9.8	8.5	8.9	n/a[b]
Chlorpromazine HCl	9.24 (B)	1105	n/a[c]	n/a[c]	n/a[b]
Clopidogrel bisulfate	4.74 (B)	1282	n/a[b]	n/a[b]	n/a[b]
Dipyridamole	0.8 (B), 6.2 (B)	329.0	n/a[c]	n/a[b]	n/a[b]
Haloperidol	8.42 (B)	3.0	3.1	6.7	n/a[a]
Maprotiline HCl	10.33 (B)	16.0	13.8	12.4	19.2
Propranolol HCl	9.54 (B)	41.4	16.3	14.1	17.4
Luminol	1.4 (B), 6.2 (A)	0.70	0.47	2.1	3.2
Piroxicam	1.9 (B), 5.3 (A)	0.71	0.45	0.86	4.5

[a] Dissolution result could not be obtained due to insufficient change in the sample concentration with time. [b] Dissolution result could not be obtained due to sample precipitation. [c] Dissolution result could not be obtained due to dissolution of the entire tablet.

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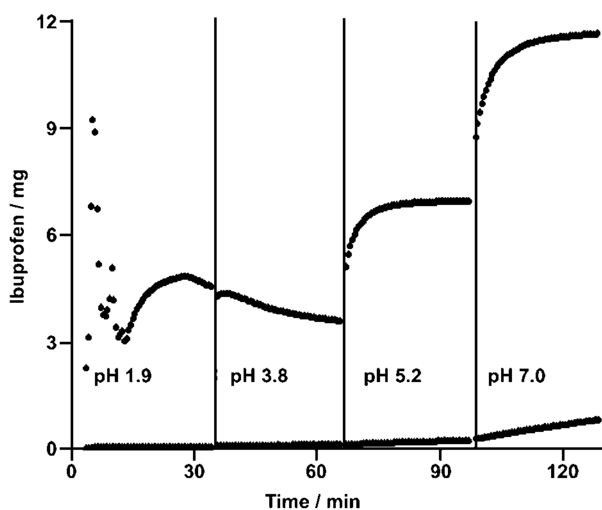

Fig. 7 GI dissolution profiles of ibuprofen free acid (lower profile) and ibuprofen sodium salt (upper profile) obtained in 0.15 M aqueous KCl at 27 °C.

measure the dissolution of API tablets but could also be used to investigate the dissolution of other drug formulations, such as suspensions of powders. Whilst the apparatus does not conform to the USP, disk intrinsic dissolution rates show excellent correlation ($r^2 = 0.98$) with published results obtained using similar miniaturized systems. Measured dissolution rates show good repeatability (CV ≈ 2%) and are suitable for looking at batch-to-batch reproducibility. The dissolution apparatus has automated pH control and can be used in the novel GI dissolution experiment to simulate passage of an API through the pH zones of the GIT. Formulation excipients can be added to the dissolution medium to investigate dissolution under a wide range of conditions relevant to physiological conditions and formulation strategies. Information regarding supersaturation and precipitation can be obtained, providing data for comparison with *in vivo* drug behaviour that cannot be obtained by traditional dissolution methods.

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