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The Effect of Selected Water-Soluble Excipients on the Dissolution of Paracetamol and Ibuprofen

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ABSTRACT The purpose of this investigation was to study the dissolution behavior of paracetamol and ibuprofen in the presence of a range of selected potential excipients. First, a pH-solubility profile was generated for both drugs, and the effect of changing hydrodynamic conditions on the intrinsic dissolution rate was investigated. It was established that both drugs dissolved according to the diffusion-layer model. Paracetamol solubility (approximately 20.3 mg mL^{-1}) did not vary from pH 1.2–8.0, corresponding to the in vivo range in the gastrointestinal tract. Ibuprofen had an intrinsic solubility of approximately 0.06 mg mL^{-1}, and pK_a was calculated as 4.4. Second, the effects of selected potential excipients (lactose, potassium bicarbonate, sodium bicarbonate, sodium chloride, and tartaric acid) were evaluated by measuring the effect of the inclusion of each additive in the dissolution medium on drug solubility, drug intrinsic dissolution rate, and solution viscosity. The results were evaluated using the diffusion-layer model, and it was determined that for paracetamol, the collected data fitted the model for all the excipients studied. For ibuprofen, it was found that there were differences between the excipients that raised the solution pH above the pK_a to those that did not. For the excipients raising the pH above the pK_a, the effect on intrinsic dissolution rate was not as high as that expected from the change in drug solubility. It was postulated that this might be due to lack of penetration of the excipient into the drug boundary layer microenvironment. Formulators may calculate the effect of adding an excipient based on solubility increases but may not find the dissolution rate improvement expected.

KEYWORDS Paracetamol, Ibuprofen, Dissolution, Solubility, Excipient, Diffusion-layer model

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INTRODUCTION

Immediate-release products are generally formulated so that the drug is rapidly released from the formulation, enabling the fast onset of the therapeutic action of the drug. This may apply particularly to analgesic drugs,

where the therapeutic action is the relief of acute pain in conditions such as dysmenorrhea, migraine, postoperative pain, and dental pain. It is generally accepted that the pharmacokinetics of the drug, e.g., the C_{max} and t_{max}, can be correlated to the pharmacodynamic effect induced by the drug, and a shorter t_{max} correlates with a faster onset of action. Although enjoying enormous commercial success, conventional tablet formulations of paracetamol and ibuprofen were observed to have t_{max} values of approximately 1 h (Ameer et al., 1983; Petring et al., 1986; Sack-Walter et al., 1989) and 2 h (El-Sayed et al., 1995; Jamali et al., 1988; Stead et al., 1983), respectively. For conventional paracetamol tablets, the rate of gastric emptying controls the rate of absorption (Heading et al., 1973), but a recently developed formulation, Panadol Actifast®, marketed in the United Kingdom, improves the absorption rate through a combination of accelerated dissolution and gastric emptying (Kelly et al., 2003). Rapid and consistent dissolution behavior is, therefore, desirable to ensure reduced variability in the onset of action. Due to its poor solubility in the stomach, there are opportunities for formulation improvement through more rapid dissolution and, therefore, more rapid absorption of ibuprofen. There have been many reports of attempts to enhance the dissolution of ibuprofen. For example, an effervescent tablet formulation was designed that was more rapidly absorbed than a sugar-coated tablet with a t_{max} of 0.5 h compared to 1.1 h for the standard preparation (Altomare et al., 1997). A patent describing an ibuprofen formulation containing arginine and sodium bicarbonate claims a t_{max} of 15 min (Gazzaniga et al., 1988). The water-soluble lysine salt of ibuprofen was developed to enhance the speed of dissolution of ibuprofen, thereby reducing the time to onset of therapeutic effect (Geisslinger et al., 1989). In a previous study (Shaw et al., 2002), we evaluated the role of common tablet excipients as dissolution enhancers for ibuprofen and paracetamol in 1:1 powder mixtures. It was observed that the results were caused by physical factors, e.g., effervescence that had an enhancing effect on dissolution or "shielding," resulting in an inhibition of dissolution. Increasing the solubility of ibuprofen by modifying the pH in both the bulk and diffusion layers above the pK_a of the drug was also observed.

The excipients used in the current study are all water soluble and include sodium bicarbonate, which is often used as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. The other excipients are potassium bicarbonate, sodium chloride, lactose, and tartaric acid. These excipients, therefore, include a neutral nonionic, two basic, a neutral ionic, and an acidic compound covering the range of inhibition of dissolution of paracetamol through to promotion of dissolution. In order to understand the effect of the presence of codissolving excipients on the solubility and dissolution rate of the drugs, we measured the solubility and dissolution of paracetamol and ibuprofen over a range of pH using buffered solutions or in aqueous solutions containing the predissolved excipients. The concentration range for the excipients was selected to reflect the sodium bicarbonate quantity in the marketed Panadol Actifast® (75 mmol dm^{-3}) when diluted in gastric contents), and under dissolution conditions, the microenvironment around the tablet could have a higher concentration due to localized effects, hence, the increase of one order of magnitude. The buffer solutions were chosen to simulate the primary dissolution site for each drug, i.e., the stomach for paracetamol and the intestine for ibuprofen. As the instrinsic dissolution rate is a rate phenomenon rather than an equilibrium phenomenon, it was suggested that it may correlate more with in vivo dissolution dynamics than solubility (Yu et al., 2004). Therefore, disks containing the drugs were formed, and the intrinsic dissolution was examined using a fixed surface area.

MATERIALS AND METHODS

Materials

Paracetamol, ibuprofen, lactose (Pharmatose DCL11), and sodium bicarbonate (extra fine grade) were obtained from GSK Consumer Healthcare (Weybridge, UK). Hydrochloric acid, sodium hydroxide, tartaric acid, potassium bicarbonate, sodium chloride, potassium chloride, boric acid, disodium phosphate, citric acid, methanol, acetic acid, acetonitrile, orthophosphoric acid, and monobasic potassium phosphate were purchased from Aldrich (Poole, UK). All materials were of pharmaceutical or analytical grade as appropriate. Double-distilled water was generated in-house using a Fisons Fi-Streem still (Loughborough, UK).

Methods

Solubility and pH Profiles

The saturated solubilities of paracetamol and ibuprofen at 37°C, over the pH ranges of 1–11 and 1–7, respectively, were determined. The compositions of the buffers used are detailed in Table 1. Approximately 1 g of drug was added to 30 mL of buffer, each experiment being performed in triplicate. The suspensions were well shaken manually and then agitated in a water bath at 37°C for 4 days, ensuring that the solutions remained saturated throughout. On the fifth day, and after a minimum of 96 h, sampling was undertaken. For paracetamol, 1.0 mL was withdrawn, ensuring no solid was collected (supernatant was clear), using a micropipette. Four 1.0 mL aliquots of warm (40–50°C) water were used to wash out the pipette tip. The aliquot and washings were combined in a single vial, and 10.0 mL of solvent mixture (95:5/methanol:acetic acid) was added to give a total volume of 15.0 mL. A 5.0 mL aliquot was taken, and 2.0 mL, of an internal standard was added (details below). The samples were analyzed using reversed-phase high-performance liquid chromatography (HPLC). For ibuprofen, 10 mL was withdrawn and filtered through a 0.45 μm cellulose filter into a prewarmed beaker, the first 5 mL being discarded. An aliquot of between 0.1–1.0 mL was sampled to a volumetric flask (10.0–50.0 mL), and four aliquots of warm (40–50°C) water were used to wash out the pipette tip. An internal standard quantity between 0.2 and 1.0 mL was added, before dilution to volume. The samples were analyzed using reversed-phase HPLC.

The actual pH values used to derive the pH/solubility profiles were obtained by measuring the pH of the drug saturated buffer solutions, post sampling.

Reversed-Phase HPLC Analysis of Paracetamol and Ibuprofen

The HPLC system was composed of a Wisp 712 autoinjector, Waters 484 variable wavelength ultraviolet detector, and Waters 600E system controller (Milford, MA, USA) using a Techsphere ODS-2 5 μM 150 × 4.6 mm column (Welwyn Garden City, UK). For paracetamol, the mobile phase was methanol:

TABLE 1 Composition of Buffers Used in Drug Solubility Experiment (*q.s.* 1000 mL)

Buffer	Component 1	Component 2
pH 1.2	250.0 mL 0.2 M potassium chloride	425.0 mL 0.2 M hydrochloric acid
pH 2.0	250.0 mL 0.2 M potassium chloride	65.0 mL 0.2 M hydrochloric acid
pH 3.0	401.5 mL 0.1 M citric acid	98.5 mL 0.2 M disodium phosphate
pH 4.0	620.0 mL 0.1 M citric acid	380.0 mL 0.2 M disodium phosphate
pH 5.0	49.0 0.1 M citric acid	510.0 mL 0.2 M disodium phosphate
pH 6.0	250.0 mL 0.2 M monobasic potassium phosphate	28.0 mL 0.2 M sodium hydroxide
pH 7.0	250.0 mL 0.2 M monobasic potassium phosphate	145.5 mL 0.2 M sodium hydroxide
pH 8.0	250.0 mL 0.2 M boric acid and potassium chloride	19.5 mL 0.2 M sodium hydroxide
pH 9.0	250.0 mL 0.2 M boric acid and potassium chloride	104.0 mL 0.2 M sodium hydroxide
pH 9.7	250.0 mL 0.2 M boric acid	104.0 mL 0.5 M sodium hydroxide
pH 11.0	250.0 mL 0.2 M boric acid and potassium chloride	Adjusted to pH 11.0 with concentrated sodium hydroxide

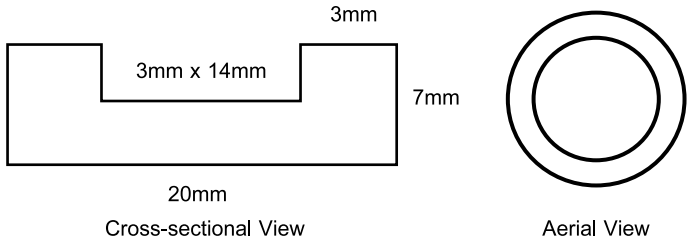

FIGURE 1 Diagram of Poly Tetra-Fluoroethylene (PTFE) Pellet Holders.

0.75% acetic acid (1:3), the injection volume was 20 μL, the wavelength used was 280 mm, and the flow rate was 1.0 mL min^{-1}. Caffeine was employed as an internal standard.

For ibuprofen, the mobile phase consisted of acetonitrile:water:orthophosphoric acid (500:500:10), the injection volume was 100 μL, wavelength was 225 nm, and the flow rate was 1.0 mL min^{-1}. Fenoprofen was the internal standard.

Solubility of Paracetamol and Ibuprofen in Excipient-Containing Solutions

The samples were prepared as detailed in the previous section, except the dissolution testing liquids used were 0.05 M HCl for paracetamol and USP buffer pH 6.8 for ibuprofen with the following additives: sodium chloride, tartaric acid, sodium bicarbonate, and potassium bicarbonate, at concentrations of 75, 375, and 750 mmol dm^{-3} and lactose at 75 and 375 mmol dm^{-3} only due to the relatively high viscosity of lactose solutions. The excipient-containing solutions were used "as is," i.e., without readjustment of pH to the nominal value after addition of drug, and the pH of the final solution was recorded. Samples were taken after 4 days, and paracetamol and ibuprofen were analyzed by HPLC according to stated methods.

Viscosity of Excipient-Containing Solutions

Kinematic viscosity was measured using a U-tube viscometer. Experiments were conducted in triplicate at 37°C. U-tubes were calibrated in-house using double-distilled water.

Dissolution-Rate Model Determination

Pellets of pure drug were compressed using a 13 mm punch and dye set using a force of 7000 kg with a pellet weight of 300±3 mg, 6 min dwell time for paracetamol, 3 min dwell time for ibuprofen, and a minimum 24 h elastic recovery period before use. The pellets were fixed, using molten paraffin, into cup-shaped pellet holders,

TABLE 2 Summarizing the Solubility/pH Relationship for Ibuprofen and Paracetamol in Buffer Solutions

Ibuprofen buffer pH final/nominal	Ibuprofen solubility (mg mL^{-1} ±SD)	Paracetamol buffer pH final/nominal	Paracetamol solubility (mg mL^{-1} ±SD)
1.51/1.2	0.058±0.001	1.46/1.2	21.0±0.3
1.83/2.0	0.053±0.004	1.92/2.0	20.9±0.5
2.82/3.0	0.062±0.017	2.93/3.0	20.5±0.3
3.85/4.0	0.058±0.007	4.00/4.0	19.5±0.1
4.77/5.0	0.166±0.027	5.06/5.0	18.7±0.2
5.45/6.0	0.713±0.018	6.09/6.0	20.4±0.1
5.55/8.0	0.938±0.008	7.14/7.0	20.9±0.8
6.16/9.0	4.20±0.23	7.93/8.0	22.4±0.2
6.28/7.0	3.89±0.46	9.32/9.0	24.8±0.3
6.52/9.7	10.3±1.59	9.82/13.0	40.8±0.3
7.02/11.0	27.5±3.3	10.80/13.5	120.5±7.8

Note: Results are the mean of three replicates ±SD.

TABLE 3 Summary of Paracetamol and Ibuprofen IDR with Changing Hydrodynamic Conditions

Paddle stirrer speed (rpm)	Paracetamol IDR (mg min^{-1} cm^{-2})	Ibuprofen IDR (mg min^{-1} cm^{-2})
10	0.73	0.0952
30	1.28	0.1872
40	1.76	0.2189
50	1.94	0.2844
60	2.18	0.2817
70	2.62	0.3537

as illustrated in Fig. 1. Paraffin was also used to seal the edges around the circumference of the pellet. Replicate intrinsic dissolution rate (IDR) assays were performed at paddle speeds of 10, 30, 40, 50, 60, and 70 rpm using 900 mL of 0.05 M HCl and USP buffer pH 6.8, controlled at 37±0.5°C, as the dissolution media for paracetamol and ibuprofen, respectively. The dissolution equipment consisted of a Caleva Model 7ST dissolution bath (Sturminster Newton, UK) equipped with 1 L round-bottomed flasks and paddles. For paracetamol, data were collected at 5 min intervals for 90 min and analyzed at 295–298 nm using a LKB Biochrom Ultospec II multicell ultraviolet/visible (UV/Vis) spectrometer (Cambridge, UK), using a continuous loop with a Watson-Marlow 5025 peristaltic pump (Falmouth, UK). For ibuprofen, data were collected at 6 min intervals for 120 min, and absorbances were obtained at 233 nm. For both drugs and for all IDR studies, the mass of drug dissolved (mg) versus dissolution time was calculated by comparison with a linear equation derived from the six-point calibration data. Standards were matrix-matched for pH and dissolution media.

TABLE 4 Summary of Measured Factors Contributing to the Dissolution of Paracetamol from Pellets Using the IDR Paddle Method

Excipient concentration (mmol dm^{-3})	Buffer pH^1 (initial/final)	IDR (mg min^{-1} cm^{-2} ±SD)	Viscosity (cm^2 min^{-1})	Buffer pH^2 (initial/final)	Saturated solubility (mg mL^{-1} ±SD)	$\frac{IDR \times \eta}{Cs}$ (k_2) min^{-2} cm^{-3} ±SD
Lactose-75	1.50/1.49	1.66±0.06	0.4524	1.61/1.50	19.2±1.4	0.03999±0.003
Lactose-375	1.54/1.35	1.21±0.04	0.5448	1.57/1.50	19.2±0.3	0.0336±0.001
Sodium bicarbonate-75	7.01/7.05	1.98±0.21	0.4308	6.60/6.78	18.5±0.2	0.0455±0.005
Sodium bicarbonate-375	7.45/7.50	1.79±0.18	0.444	7.99/7.82	16.5±0.2	0.0467±0.004
Sodium bicarbonate-750	8.33/8.35	1.42±0.18	0.4632	8.07/8.33	14.1±0.3	0.0438±0.005
Sodium chloride-75	1.40/1.30	1.89±0.29	0.4278	1.49/1.50	18.7±0.4	0.0434±0.006
Sodium chloride-375	1.29/1.06	1.74±0.09	0.4272	1.37/1.36	16.5±0.1	0.0452±0.002
Sodium chloride-750	0.87/0.90	1.35±0.09	0.4344	1.26/1.22	14.2±0.3	0.0413±0.003
Tartaric acid-75	1.62/1.60	2.01±0.03	0.4362	1.57/1.56	19.4±0.8	0.0452±0.002
Tartaric acid-375	1.55/1.56	1.87±0.20	0.4572	1.57/1.56	19.8±0.8	0.0431±0.005
Tartaric acid-750	1.60/1.59	1.61±0.07	0.4872	1.51/1.53	22.0±0.7	0.0338±0.002
Potassium bicarbonate-75	8.50/8.52	1.92±0.145	0.4242	8.63/8.55	20.5±0.8	0.0405±0.003
Potassium bicarbonate-375	8.70/8.74	1.94±0.22	0.4302	8.90/8.80	20.3±0.3	0.0426±0.006
Potassium bicarbonate-750	8.62/8.70	1.53±0.15	0.4344	8.73/8.70	16.4±0.6	0.0447±0.004

Note: k_2 values were calculated using factorial design and cannot be directly calculated for the presented data. Buffer pH^1 is the pH of the buffers in dissolution studies, and buffer pH^2 is the pH of the buffers in solubility measurements.

Dissolution in Solution Containing Dissolved Excipients

Replicate IDR assays were performed at a paddle speed of 50 rpm. For paracetamol studies, 0.05 M HCl was used as the dissolution medium, and for ibuprofen, USP buffer pH 6.8 was used. The IDR of each drug was obtained in dissolution buffer containing each excipient/concentration from the experimental series and was analyzed using a UV/Vis spectrometer.

RESULTS

Solubility/pH Profiles for Paracetamol and Ibuprofen

The solubilities of paracetamol and ibuprofen were determined over the pH ranges of 1–11 and 1–7, respectively, as summarized in Table 2. For paracetamol, literature values were summarized as 19 and 20 mg mL^{-1} in distilled water and 23.8 mg mL^{-1} in buffer pH 6.0, all at 37°C (Fairbrother, 1974). As paracetamol is a weak acid, the measured solubility over the pH range 1.2–8.0 in this study was determined to be 20.3 mg mL^{-1}, with a small standard deviation of 0.8 mg mL^{-1}. As the pK_a was approached, variously reported as between 9.0–9.5 and also 10.15 (Fairbrother, 1974), a rapid increase in solubility was detected. The pK_a was not determined for paracetamol due to a limited number of data points at higher pH.

For ibuprofen, solubility over the pH range 1–4 was determined as 0.058 ± 0.004 mg mL^{-1}, i.e., sparingly soluble in the stomach. A rapid and continual increase in solubility was recorded as the pK_a [summarized from the literature as 4.4 and 5.2 (Moffat, 1986) and 5.3 (Lund, 1994)] was approached and thereafter. A plot of solubility versus reciprocal hydrogen ion concentration was linear ($r^2 = 0.994$), and the pK_a was calculated as 4.4 using an intrinsic solubility determined from the intercept of 0.0664 mg mL^{-1}.

Drug Solubility in Buffers Containing Dissolved Potential Excipients

The range chosen for excipient concentration was 75–750 mmol of excipient per dm^{-3}, and the buffer

TABLE 5 Summary of Measured Factors Contributing to the Dissolution of Ibuprofen from Pellets Using the IDR Paddle Method

Excipient concentration (mmol dm^{-3})	Buffer pH^1 (initial/final)	IDR (mg min^{-1} cm^{-2} ±SD)	Viscosity (cm^2 min^{-1})	Buffer pH^2 (initial/final)	Saturated solubility (mg mL^{-1} ±SD)	$\frac{IDR \times \eta}{Cs}$ (k_2) (min^{-2} cm^{-3} ±SD)
Lactose-75	6.83/6.81	0.232±0.013	0.4523	6.80/6.80	3.11±0.00	0.0344±0.001
Lactose-375	6.77/6.80	0.182±0.013	0.5599	6.82/6.30	2.90±0.15	0.0355±0.003
Sodium bicarbonate-75	7.68/7.68	0.423±0.002	0.4396	7.71/6.90	11.3±0.01	0.0165±0.008
Sodium bicarbonate-375	8.27/8.41	0.845±0.019	0.4441	8.30/7.10	49.9±3.0	0.0076±0.000
Sodium bicarbonate-750	8.34/8.34	2.56±0.21	0.4961	8.33/7.10	109±11.4	0.0117±0.002
Sodium chloride-75	6.67/6.71	0.235±0.007	0.4342	6.68/6.10	3.08±0.21	0.0335±0.003
Sodium chloride-375	6.34/6.36	0.238±0.006	0.4256	6.36/6.10	2.35±0.27	0.0447±0.003
Sodium chloride-750	6.16/6.20	0.132±0.011	0.4297	6.12/6.00	1.77±0.25	0.0330±0.006
Potassium bicarbonate-75	7.58/7.70	0.455±0.037	0.4330	7.62/6.90	9.75±1.50	0.0208±0.002
Potassium bicarbonate-375	8.76/8.76	0.912±0.065	0.4334	8.67/7.10	59.5±2.8	0.0096±0.008
Potassium bicarbonate-750	8.34/8.50	1.76±0.665	0.4339	8.40/7.10	205.6±9.4	0.0042±0.001

Note: k_2 values were calculated using factorial design and cannot be calculated directly from the presented data. Buffer pH^1 is the pH of the buffers in dissolution studies, and buffer pH^2 is the pH of the buffers in solubility measurements.

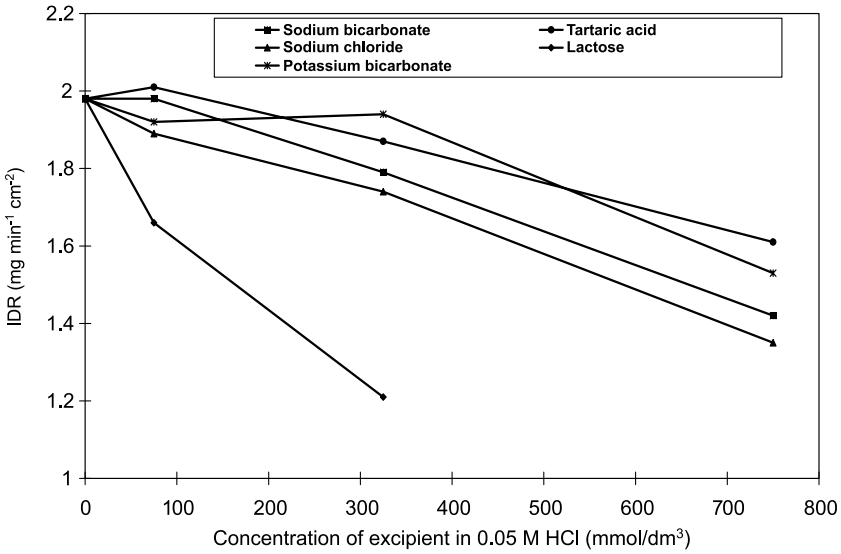

FIGURE 2 **IDR of Paracetamol in 0.05 M HCl Containing Dissolved Excipients. Results are the Mean of at Least Five Replicates at 50 rpm.**

solutions were chosen to simulate the primary dissolution site for each drug, i.e., simulated gastric fluid for paracetamol and simulated intestinal fluid for ibuprofen. With reference to Table 4 for paracetamol, the results demonstrate that potassium bicarbonate, sodium bicarbonate, and sodium chloride reduce the solubility of paracetamol by up to 20–30% compared to the intrinsic solubility. This is concentration dependent for the latter two. Lactose does not affect the solubility of paracetamol, and tartaric acid increases the solubility with increasing concentration. With reference to Table 5 for ibuprofen, both sodium bicarbonate and potassium bicarbonate enormously increase the solubility of the drug. The measured final pH increased from approximately pH 6.9 to 7.1 as the concentration of these excipients was increased (Table 5). This change in pH above the pK_a value can be attributed to the cause of the dramatic increase and the dominant factor. Lactose does not have a major effect on the solubility of ibuprofen, and sodium chloride decreases it proportionally with increasing concentration.

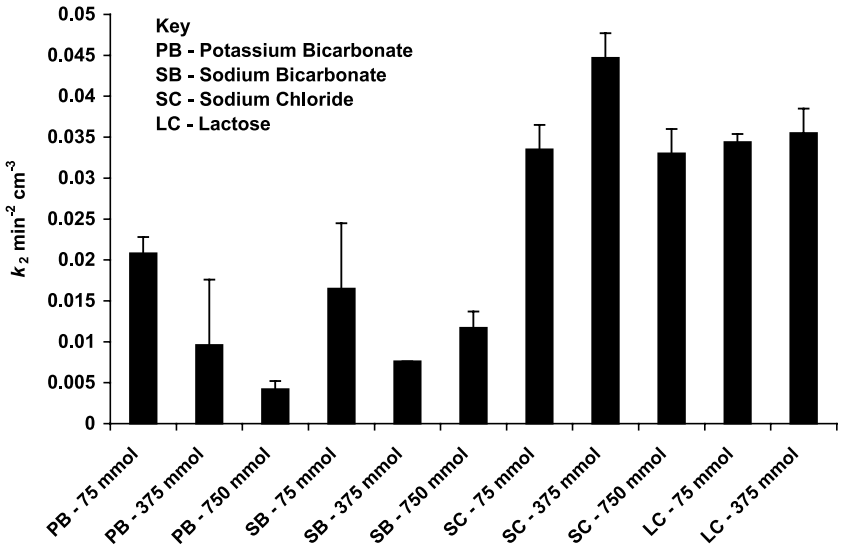

FIGURE 3 **Calculated Values of k_2 Constant for Dissolution of Ibuprofen in Excipient-Containing Solutions. Results are the Mean ± SD (n = 6) Derived Using Cross-over Analysis. Excipient Concentrations Expressed as mmol dm^{-3}.**

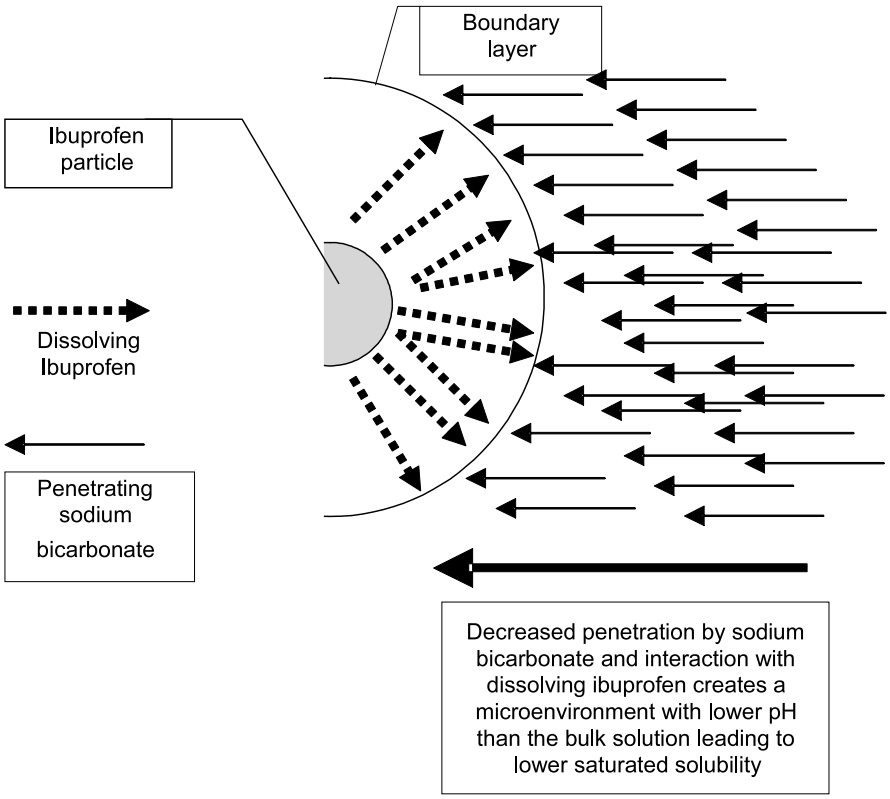

FIGURE 4 **Representation of the Dissolution Process Illustrating How the Incomplete Penetration of Sodium Bicarbonate into the Boundary Layer May Alter the Saturated Solubility of Drug Compared to that Within the Bulk Solution.**

Determination of Intrinsic Dissolution Rates

The IDRs of both drugs at each paddle speed were calculated by dividing the gradient obtained from each linear profile by the surface area (1.327 cm^2) of the exposed drug. The data are summarized in Table 3. The calculated correlation coefficients demonstrated excellent linearity for the IDR over the whole speed range of the paddles. Also, IDR versus hydrodynamics expressed as paddle speed showed a very strong linear relationship, i.e., for paracetamol $R^2 = 0.9887$ and ibuprofen $R^2 = 0.9734$. From this, it can be concluded that for both drugs, the rate constant k is proportional to the stirrer speed, and the dissolution process for both drugs can be described by the diffusion-layer model (Macheras et al., 1995).

Drug Dissolution in Excipient-Containing Solutions

First, for paracetamol, it was observed that all the excipients inhibited the dissolution at higher concentrations with lactose demonstrating the largest effect (Fig. 2). For ibuprofen, it was observed that at higher concentrations, both sodium chloride and lactose inhibit the IDR. Both sodium bicarbonate and potassium bicarbonate are demonstrated to massively increase the dissolution rate. The results are detailed in Tables 4 and 5.

DISCUSSION

The results demonstrate that over the pH range 1–8, which is the range found in vivo in the gastrointestinal (GI) tract, the solubility of paracetamol will not be affected by the environmental pH. A recent study examining the solubility of ibuprofen in a selection of buffers with pH ranging from 5.01 to 8.22, gave an estimated intrinsic solubility of 0.068 mg mL^{-1} using a pK_a of 4.57 (Levis et al., 2003). These estimations are slightly higher than measured here but included data from a number of buffers that include sodium taurocholate, such as FeSSIF (fed-state simulated intestinal fluid). An average solubility of 0.02 mg mL^{-1} over the pH range 1–4 was reported with the profile changing as recorded in this study in terms of

the effect of pH on solubility but not in terms of magnitude (Herzfeldt & Kummel, 1983). They conducted the experiment at room temperature with only a 48 h dissolution time, possibly explaining the lower absolute solubility values obtained.

Considering the diffusion-layer model to describe dissolution, if the surface area of the dissolving drug remains constant, as in the IDR method used in this study, the following equations apply (Macheras et al., 1995; Marriott, 2002):

$$IDR = kCs \tag{1}$$

and

$$k = \frac{D}{h} \tag{2}$$

where

$$D = \frac{RT}{6Nr\pi\eta} \tag{3}$$

where k is the intrinsic dissolution rate constant, Cs is the saturated solubility, D is the diffusion coefficient of the drug, h is the thickness of the diffusion layer, R is the Boltzmann constant, T is the absolute temperature, and r is the radius of the molecule in solution. As η is the kinematic viscosity, it is apparent that the dissolution rate constant is inversely proportional to the viscosity of the dissolution medium (Macheras et al., 1995). It was shown that the IDR of paracetamol decreases with increasing viscosity, for solutions containing mixtures of taurine, glycine, and sorbitol (Mahmud & Li Wan Po, 1991). However, this work did not take into account changes in saturated concentration of drug in the various solutions (C_s).

By rearranging, it can be shown that

$$\frac{IDR}{Cs} \times \eta = \frac{RT}{6Nr\pi h} \tag{4}$$

R, T, N, and π are constants, assuming that the radius of the molecule in solution r is unchanged or not measurably changed (a fair assumption on the basis that most carboxylic acids are dimeric in nature in neutral solutions, any drug–excipient interactions would form simple salts, and the parameter is based on the cube root of the size) and that the hydrodynamic effect is consistent, it can be deduced that

$$\frac{IDR \times \eta}{Cs} = k_2 \tag{5}$$

where k_2 is a constant. The experimental data obtained for IDR, C_s, and viscosity (η) were processed using this equation. Factorial design was used to calculate k_2. The results for paracetamol and ibuprofen are summarized in Tables 4 and 5.

Reviewing the data for paracetamol in Table 4, the average k_2 value is 0.042 min^{-2} cm^{-3} with a %RSD of 9.6%. The sampling data followed a normal distribution (results not shown) and the data were considered as being from the same population. From these data, it may be concluded that the dissolution of the drug can be satisfactorily explained by the relationship between IDR, viscosity, saturated solubility, and k_2 as encompassed in the stated equations. For example, it is shown that sodium bicarbonate in solution inhibits dissolution of paracetamol by reducing the saturated solubility and by increasing the viscosity of the solution, with a consequential decrease in IDR. The low IDR observed for lactose at 375 mmol dm^{-3} (0.0336 ± 0.001 min^{-2} cm^{-3}) can be explained by its relatively high solution viscosity (0.55 cm^2 min^{-1}) compared to other solutions in the series (0.43–0.48 cm^2 min^{-1}). The increase in viscosity with lactose solutions could result in deviations from the diffusion-layer model. For tartaric acid, although the IDR decreases as expected with increasing viscosity, the saturated solubility remains constant and even increases slightly at high concentrations (Table 4), although the k_2 value still concurs with the current model.

Reviewing the data for ibuprofen in Table 5, the average k_2 value is 0.023 min^{-2} cm^{-3} with a %RSD of 60.5%. The large %RSD indicates that the data do not fit the model, and the data can be divided into two distinct groups, one containing the pH-altering sodium and potassium bicarbonate solutions and the other containing the sodium chloride and lactose solutions as illustrated in Fig. 3.

This infers that the model proposed in Eq. 5 does not completely describe the dissolution process for ibuprofen in the excipient-containing solutions under investigation. Further, the pH-modifying and solubility-enhancing excipients, i.e., sodium bicarbonate and potassium bicarbonate, have much lower k_2 values than sodium chloride and lactose-containing solutions. It is known that surface dissolution of weak acids may buffer the boundary layer to a value near the pK_a of the drug, and this is one reason why USP

buffers, which are capable of overcoming this effect, are used in dissolution studies (Macheras et al., 1995). It is, therefore, postulated that the experimental values of saturated solubility do not represent the situation within the boundary layer. The saturated solubilities were measured on bulk solutions, allowed to equilibrate over several days; however, the actual saturated solubility in the boundary layer may be lower due to lower excipient concentrations in the microenvironment. This hypothesis is illustrated in Fig. 4, where a lower concentration of dissolved excipient in the boundary layer is represented. To ascertain the magnitude of this effect, the average k_2 value for the lactose and sodium chloride experiments was calculated as 0.0036 min^{-2} cm^{-3}. Using the IDR and viscosity values for each experiment, the "apparent saturated solubility" within the boundary layer was calculated. For sodium bicarbonate (750 mmol dm^{-3}), the apparent saturated solubility in the microenvironment was calculated as 35 mg mL^{-1} versus a concentration of 109 mg mL^{-1} measured in the bulk solution. Similarly, for potassium bicarbonate at the same strength, the calculated apparent saturated solubility was 21 mg mL^{-1} versus a concentration of 205.6 mg mL^{-1} measured in the bulk solution. For these two excipients, the overall apparent saturated solubility was in the range of 10–56% of that predicted, over the measured concentration range. It was demonstrated that for these examples, the excipient was far less efficient in promoting dissolution than would be expected from the drug pH/solubility profile and the solubility of ibuprofen in excipient bulk solutions.

CONCLUSIONS

This work evaluated the effects of soluble excipients on the solubility and intrinsic dissolution rate of two analgesic drugs. The weakly acidic drugs and neutral and basic excipients were selected so that the alkalyzing effect of certain excipients would be expected to increase the saturated solubility and intrinsic dissolution rate of ibuprofen but not paracetamol. Experiments were conducted to measure specific parameters of the diffusion-layer model for drug dissolution, which was shown to be the appropriate mechanism. Both viscosity and pH were found to have modifying effects on dissolution, and it was found that for paracetamol, the dissolution model adequately described the observed results. For ibuprofen, this was not the case, as it was found that the data did not fit the model. For experiments where the alkalyzing excipients altered the pH near to or above the drug pK_a and, hence, increased drug solubility, the resultant IDR increase was lower than expected. It was postulated that this was because the measured drug solubility in bulk solution was higher than that actually present in the boundary layer microenvironment. A reason for this could be the lack of penetration of the pH-modifying excipient. The use of alkalyzing excipients to increase the rate and extent of dissolution of weakly acidic drugs is a strategy for improving drug delivery. However, the theoretical improvement may not be observed in practice.

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