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Effect of buffer media composition on the solubility and effective permeability coefficient of ibuprofen

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Abstract

The effect of perfusion medium composition on the two important biopharmaceutical parameters drug solubility and permeability was determined for ibuprofen. Eight commonly used buffers were examined. Equilibrium solubility, buffer capacity profiles and permeability coefficients, using the in situ rat gut perfusion model, were determined for each medium at 37 °C. The solubility of ibuprofen differed sixfold over the range of buffer systems studied. The differences in solubility were associated with different pHs of the buffers when saturated with drug and also the presence of micelles and divalent ions. The solubility of ibuprofen in FeSSIF was significantly higher than predicted from the pH due to micellisation, while that in Krebs was significantly lower due to ibuprofen-calcium salt formation. Buffer capacities varied over a 40-fold range. The pK_a values of the buffer components were determined from the buffer capacity versus pH profiles and were in good agreement with the thermodynamic values when corrected for temperature and ionic strength. Smaller, but statistically significant differences in P_{app} values for ibuprofen were also observed between some of the buffers. During perfusion, pHs of the perfusate samples gradually changed over time towards a median value of approximately 6.5. HBSS gave a P_{app} ~50% greater than that observed in PBS 7.4. Physicochemical factors such as medium pH, buffer capacity and osmolarity should be considered when determining the P_{app} values of ionisable compounds. Care needs to be exercised when comparing P_{app} values from different laboratories as buffer composition can have a significant effect on both solubility and permeability of a drug, whose ionisation is substantially changed over the pH range of the buffers. Despite the high amount ionised, ibuprofen appears to be well absorbed and it can be classified as a highly permeable drug.

Keywords: Ibuprofen; Solubility; Permeability coefficient; Buffers; Buffer capacity

1. Introduction

The key biopharmaceutical characteristics impacting on bioavailability and on the likelihood of obtaining a good in vitro in vivo correlation (IVIVC) are the drugs solubility (C_s) and permeability (P_{app}) (Amidon et al., 1995). However, these properties may be sensitive to experimental medium composition, particularly if the drug is ionisable in the medium in which the parameters are determined.

Particularly for ionisable drugs, the dissolution medium pH is important because of the influence of pH on solubility, dissolution and the level of sink conditions (Mooney et al., 1981; Aunins et al., 1985). Thus media containing HCl, acetate, citrate, phosphate or Tris in the pH range 1–7.6 are often used. However, the buffer capacity of such media of equivalent pH often varies despite evidence that buffer

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capacity at a given pH can substantially influence the dissolution rate of ionisable drugs and excipients (Mooney et al., 1981; Aunins et al., 1985; Ramtoola and Corrigan, 1989). In this regard, both Prasad et al. (1983) and Skelly et al. (1986) studied dissolution rates of quinidine gluconate products. The dissolution rates of products were widely different in water, acetate buffer of pH 5.4 and phosphate buffer of pH 5.4. The results highlighted the importance of buffer composition as well as pH on the dissolution results.

A variety of in vitro and in vivo models for studying drug absorption have been developed. These include Ussing chambers, everted gut sac techniques, cell culture models, in situ perfusions and intestinal perfusions in man (Stewart et al., 1997). Using these methods, researchers have employed a variety of different buffer solutions to assess the absorption properties of drug substances. These range from simple phosphate based systems (PBS) at pH 7.4 (Iwanaga et al., 1999) to more complex systems containing lipids and surfactants to simulate intestinal contents, i.e., the fasted (FaSSIF) and fed (FeSSIF) state simulated intestinal fluids (Galia et al., 1998). Xiang et al. (2002) used McIlvaine citrate-phosphate buffer to study transbuccal drug delivery, while Hanks' balanced salt solution (HBSS, Crowe and Lemaire, 1998) and Krebs buffer (Leone-Bay et al., 1996; Kim et al., 1994) have been employed for intestinal absorption studies.

Fagerholm et al. (1996) used a phosphate based buffer system (pH 6.5) to compare the permeability coefficients of a range of drugs between rat and human jejunum. They obtained a high correlation between perfused rat and human jejunum P_{app} estimates, and therefore concluded that the perfused rat model can be used with precision to predict in vivo oral absorption in man.

In this work we examine the influence of a range of commonly used 'physiological' media on ibuprofen C_s and P_{app}, the latter obtained using the in situ perfused rat model.

2. Experimental

2.1. Materials

Acetic acid (analytical grade) (Merck, Germany), calcium chloride (Riedel-de-Haen, Germany), citric acid (Merck), D-glucose (Riedel-de-Haen), ibuprofen acid (Sigma Chemical Co., Germany), magnesium sulphate (BDH Chemicals Ltd., UK), potassium acid phosphate (BDH Chemicals Ltd.), potassium chloride (BDH Chemicals Ltd.), sodium acid phosphate (Merck), sodium bicarbonate (BDH Chemicals Ltd.), sodium chloride (Merck), sodium hydroxide (Sigma), sodium phosphate (Merck) and taurocholic acid (sodium salt) (Sigma) were used in the preparation of the buffers in the quantities shown in Table 1. Lipoid E PC phosphatidylcholine (lecithin) (Lipoid GMBH, Germany) was a gift from the manufacturer and was used as received.

2.2. Buffer systems

The buffer systems examined were: Sorensens phosphate buffer pH 7.4 (Iwanaga et al., 1999; Wade, 1980), sodium phosphate perfusion solution (Fagerholm et al., 1996), McIlvaine buffer (Xiang et al., 2002; Wade, 1980) pH 6.0, HBSS (Crowe and Lemaire, 1998), Krebs buffer (Leone-Bay et al., 1996; Lund, 1994), Sorensens phosphate buffer pH 6.8 (Wade, 1980), FaSSIF (Galia et al., 1998), FeSSIF (Galia et al., 1998).

2.3. Solubility determination

The solubility of ibuprofen acid in a particular buffer was determined by the method of Chiou and Kyle (1979). Excess drug was added to 50 ml of the buffer at 37 °C in a jacketed water vessel connected to a circulating water bath and the mixture was stirred at a rate of 300 rpm. A total of 3 ml samples were removed at regular intervals over a 2-h time period. After filtration and dilution, the samples were assayed spectrophotometrically at 222 nm. All syringes, pipettes, filters, vials and needles used were preheated to 37 °C in an oven. The solubilities quoted at each time point are an average of two determinations.

2.4. Identification of ibuprofen-Ca^{2+} salt

The precipitate obtained on addition of ibuprofen sodium to 25 ml of Krebs buffer was isolated by filtration, rinsed with deionised water, dried at 37 °C and analysed by energy dispersive X-ray analysis. The

Table 1
Composition of the individual buffer systems

Buffer component	Sorensen PBS pH 7.4	Sorensen PBS pH 6.8	Fagerholm's buffer (in mM)	McIlvaine buffer (in mM)	Krebs buffer (in mM)	Hanks' balanced salt solution (in mM)
$NaH_2PO_4 \cdot 2H_2O$	13.46 mM	33.33 mM	43.00			
$Na_2HPO_4 \cdot 12H_2O$	53.31 mM	33.23 mM	28.00	126.21		0.34
NaCl	75.28 mM	82.14 mM	48.00		118.07	136.89
	FaSSIF pH 6.5	FeSSIF pH 5.0				
KCl	103.29 mM	203.22 mM	5.40		4.69	5.37
KH_2PO_4	28.66 mM					
Sodium taurocholate	3.0 mM	15.00 mM				
Lecithin	0.75 mM	3.75 mM				
NaOH	13.85 mM and q.s. pH 6.5	101.00 mM and q.s. pH 5.0				
Acetic acid		144.11 mM				
D-Glucose			10.00		10.09	5.05
Citric acid				36.64		
$MgSO_4 \cdot 7H_2O$					1.18	0.81
KH_2PO_4					1.18	0.44
$NaHCO_3$					24.97	4.17
$CaCl_2 \cdot 2H_2O$					2.52	1.26

amount of ibuprofen in the precipitate was quantified by HPLC analysis.

2.5. Buffer capacity profiles

Buffer capacity, the ability of a solution to resist attempts to change its pH (Butler, 1998), can be expressed numerically as the number of equivalents of strong base needed to change the pH value by 1 unit (Van Slyke, 1922). The buffer capacities of the systems were measured by titrating 25 ml samples of buffer with 0.2 M HCl or 0.2 M NaOH in aliquots of 100 μl using an auto-titrator, while continuously stirring. The titration with both acid and base was performed in duplicate. The pH of the solution was recorded after the addition of each aliquot and the buffering capacity (β) at each pH value was calculated using Eq. (1):

$$\beta = \frac{\Delta AB}{\Delta pH} \quad (1)$$

where AB is the amount of acid or base added. Buffer capacity, expressed as equivalents/litre/pH unit, was plotted versus pH and best-fit profiles were generated by fitting the experimental data to a suitable model using a curve fitting programme (Micromath® Scientist™ version 1.0). The buffer capacity for a monoprotic acid system is given by Eq. (2):

$$\beta = 2.303\left(\left(\frac{K_W}{[H^+]}\right) + [H^+] + \left(C \times K_a \times \frac{[H^+]}{(K_a + [H^+])^2}\right)\right) \quad (2)$$

where C is the concentration of buffer salt in moles and K_a is the dissociation constant of the buffer salt. The data was fitted to variations of Eq. (2) depending on whether the buffer concerned contained salts that were mono-, di-, or triprotic, and on the number of buffer species present.

2.6. Osmolarity

Osmolarity was determined from the molar concentrations of buffer components.

2.7. In situ absorption studies

In situ absorption studies were carried out on male Wistar rats (280–320 g) that had been fasted for 24 h prior to the experiment and were anaesthetised by intraperitoneal (i.p.) injection of pentobarbital sodium (50 mg/kg). The studies were conducted according to the rat gut perfusion method described by Komiya et al. (1980) using a 33.3 cm length of intestine and a

flow rate of 0.2 ml/min. Perfusate samples were collected every 10 min for a period of 120 min and were assayed for drug content by HPLC. Blood samples were taken at 30-min intervals, centrifuged to separate the plasma and the plasma was then frozen until analysis. The intestines were kept moist throughout the experiment by gently applying buffer using cotton wool balls saturated with warm saline and body temperature was maintained at 37 °C using an overhead work-light and a heating mat. Sample vials were weighed prior to use and after perfusate collection in order to check the flow rate and to determine any variation in the volume of liquid collected. Perfusate samples were filtered and analysed by HPLC using a method based on that used by Lalande et al. (1986).

The fraction of ibuprofen unabsorbed was calculated for each perfusate sample and at each time point for a particular buffer these values were averaged over the number of rats studied ($n \geq 5$). This allowed us to plot a fraction unabsorbed against time profile for each buffer. The fraction unabsorbed values were converted to permeability coefficients using steady-state data and Eq. (3). The steady-state was determined to be between 100 and 120 min as, for a particular buffer, there was no significant difference between the individual time points in this range:

$$P_{app} = \frac{-Q}{2\pi rl} \times \ln\left(\frac{C_1}{C_0}\right) \quad (3)$$

where C_0 is the input perfusate drug concentration, C_1 is the outlet perfusate drug concentration, r is the effective lumen radius (cm), Q is the perfusate flow rate (ml/s), and l is the length of intestinal segment (33.3 cm).

The permeability coefficient (P_{app}) for ibuprofen was obtained by averaging the permeability coefficients over 100–120 min for each perfusion experiment. For a particular buffer, the P_{app} values for each rat were averaged and a standard deviation calculated. Pair-wise comparisons were performed using a one-way ANOVA using Minitab^{TM} Statistical Software (version 13.1).

3. Results and discussion

3.1. Buffer composition and ibuprofen solubility studies

Fig. 1 shows the solubility profiles of ibuprofen in each of the eight buffer systems. The solubility of ibuprofen varied significantly with the buffer, with a sixfold difference between HBSS and PBS 7.4. The solubility profiles in Fig. 1 were fitted to Eq. (4):

$$C = C_s(1 - e^{-kt}) \quad (4)$$

where C is the concentration at a particular time point 't', C_s is the saturated solubility and k is the rate constant. Saturation appeared to be reached within 1 h. There were slight differences in the rate of attainment of steady state. The "k" values in Table 2 indicate that ibuprofen in FaSSIF and FeSSIF attained a steady state 3–4 times faster than the simple buffer systems. FaSSIF and FeSSIF differ from the other systems as they contain sodium taurocholate, which has surfactant properties thus promoting better wetting of the ibuprofen particles which would explain the higher solubility rate.

The eight buffers studied varied in pH over a range of 3.21 pH units from 5.01 to 8.22. The final pH values of the saturated solutions of ibuprofen in each of the

Table 2
Solubility of ibuprofen in each of the buffers at 37 °C, ionic strengths (IS), pH values of the saturated solutions and buffer osmolarities

Buffer system	Solubility C_s (mg/ml)	S.D.	k (min^{-1})	IS	Initial pH of buffer	Final pH	Osmolarity (mOsm/l)
PBS 7.4	6.02	0.10	0.12	0.21	7.21	6.35	337.5
PBS 6.8	4.55	0.04	0.11	0.20	6.72	6.25	330.6
Fagerholm (pH 6.5)	3.65	0.09	0.18	0.17	6.56	6.15	286.8
Krebs	3.45	0.09	0.16	0.16	8.22	6.93	317.8
McIlvaine (pH 6.0)	2.99	0.03	0.17	0.37	6.19	6.05	415.3
FaSSIF (pH 6.5)	1.56	0.04	0.61	0.15	6.38	5.85	270.0
FeSSIF (pH 5.0)	1.16	0.05	0.74	0.32	5.01	4.98	635.0
HBSS	0.97	0.05	0.18	0.15	7.56	5.52	310.7

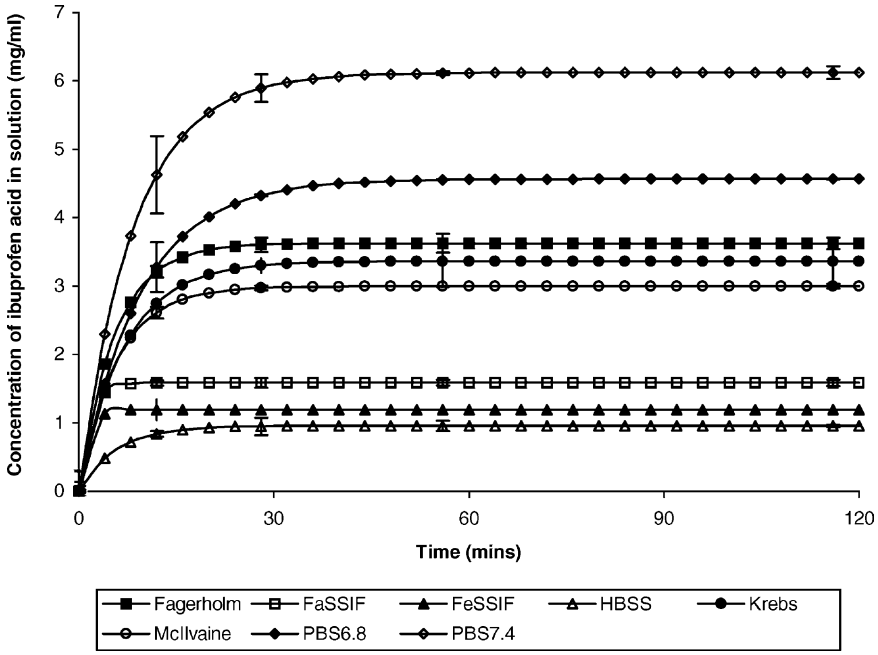

Fig. 1. Ibuprofen concentration vs. time profiles in each of the buffer solutions.

systems and the corresponding solubility values were fitted to Eq. (5) to generate the pH-solubility profile (Fig. 2):

$$C_s = C_0(1 + 10^{(pH - pK_a)}) \quad (5)$$

where C_0 is the intrinsic solubility. The best-fit values for C_0 and the pK_a of ibuprofen are 0.068 mg/ml (0.33 mM) and 4.43 at 37 °C, respectively, which when corrected for ionic strength gives a pK_a of 4.57. These agree closely with previously reported values

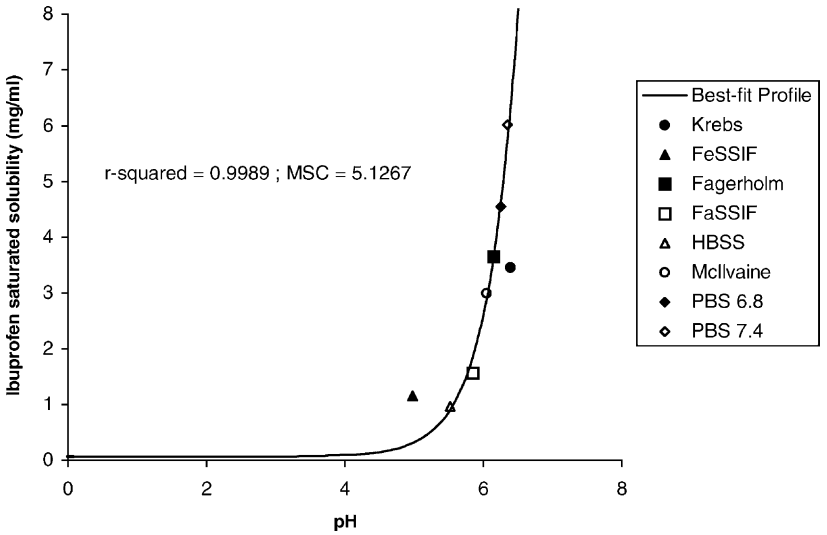

Fig. 2. pH-solubility profile of ibuprofen acid.

of 0.078 mg/ml (0.38 mM) and 4.55 at room temperature by Fini et al. (1995). The slightly higher intrinsic solubility determined by Fini et al. may be due to ionic strength. Fini et al. (1995) have also shown that in an aqueous medium containing 0.5 M NaCl (ionic strength 0.5), the solubility of the sodium salt of ibuprofen is 42.23 mg/ml (185 mM) at 25 °C. The ionic strength, Na^+ concentration and solubility are all significantly higher than in any of the systems used in this study (Table 2), indicating that the solubility of ibuprofen in the systems studied is not limited by the solubility of the ibuprofen sodium salt.

The solubility of ibuprofen in FeSSIF is significantly higher than predicted from Eq. (5) even when the pK_a is corrected (to 4.43) to account for ionic strength. The higher solubility is likely due to the presence of sodium taurocholate (15 mM) which is above its critical micellar concentration (CMC, Poelma et al., 1990; Staggers et al., 1990) leading to aggregation and micelle formation. The hydrophobic nature of the micelle centre allows a higher than expected amount of ibuprofen to dissolve in the buffer at pH 4.98 as the ibuprofen partitions into the micelle.

The solubility of ibuprofen in Krebs is significantly lower than predicted at pH 6.39 from Eq. (5), again using a pK_a of 4.43 to account for ionic strength. The presence of divalent ions in Krebs buffer was investigated as a possible cause. Addition of excess ibuprofen sodium to Krebs buffer resulted in a visible precipitate, which on collection and examination by energy dispersive X-ray analysis showed two major peaks corresponding to carbon (0.3 keV) and calcium (3.6 keV). From the results of the energy dispersive X-ray analysis and HPLC determination of the ibuprofen present, it was concluded that the precipitate was an ibuprofen-Ca^{2+} salt having a stoichiometric ratio of 2:1. Fini et al. (2001) have shown that indomethacin forms a sparingly soluble salt with Ca^{2+} when the molar ratio of indomethacin/Ca^{2+} reaches the stoichiometric value (2:1). This supports our view that the solubility of ibuprofen acid in Krebs buffer is limited by the relatively insoluble salt that it forms with Ca^{2+}.

The osmolarities of six of the eight buffers lie within the physiological range (280–320 mOsm/l), the exceptions being FeSSIF and McIlvaine buffers (Table 2).

3.2. Buffer capacity

The experimental buffer capacity versus pH profiles for FaSSIF, FeSSIF, Krebs buffer and PBS 7.4, together with the best-fit curves are shown in Fig. 3. The best-fit profiles for all eight buffers are compared in Fig. 4 and the initial pH and buffer capacity values are annotated on each profile with the standard deviations at the maximum buffer capacities. Table 3 shows the buffer capacities of each of the buffers at

Table 3
Buffer capacity (β) results

Buffer system	Buffer type	Concentration (mM)[a]	pH	β[b]	β_{max}[c]	pK_a[d]	pK_a[e]	Best-fit pK_a[f]
Fagerholm	H_3PO_4	71.00	6.63	0.0381	0.0408	7.21	6.84	6.86
FaSSIF	H_3PO_4	29.00	6.53	0.0146	0.0164	7.21	6.85	6.82
FeSSIF	CH_3COOH	144.00	5.06	0.0647	0.0742	4.76	4.61	4.74
HBSS	H_3PO_4	0.80	7.35	0.0016	0.0035	7.21	6.84	6.56
	H_2CO_3	4.20			0.0035	6.40	6.25	6.52
Krebs	H_3PO_4	1.20	8.36	0.0025	0.0201	7.21	6.85	6.29
	H_2CO_3	4.20			0.0201	6.40	6.25	6.29
McIlvaine	H_3PO_4	126.00	6.17	0.0608	0.0807	7.21	6.77	6.72
	$C_6H_8O_7$	37.00			0.0326	6.40*	5.65	5.40
PBS 6.8	H_3PO_4	66.56	6.79	0.0366	0.0368	7.21	6.82	6.85
PBS 7.4	H_3PO_4	66.79	7.37	0.0219	0.0328	7.21	6.80	6.80

[a] Concentration of each buffer salt (mM).
[b] Buffer capacity at the initial pH of the buffer (mEq/l per pH unit).
[c] Maximum buffer capacity (mEq/l per pH unit).
[d] Thermodynamic pK_a at 25 °C (Beynon and Easterby, 1996; *Wade, 1977).
[e] pK_a corrected for ionic strength and temperature.
[f] Best-fit pK_a using Scientist® curve fitting programme.

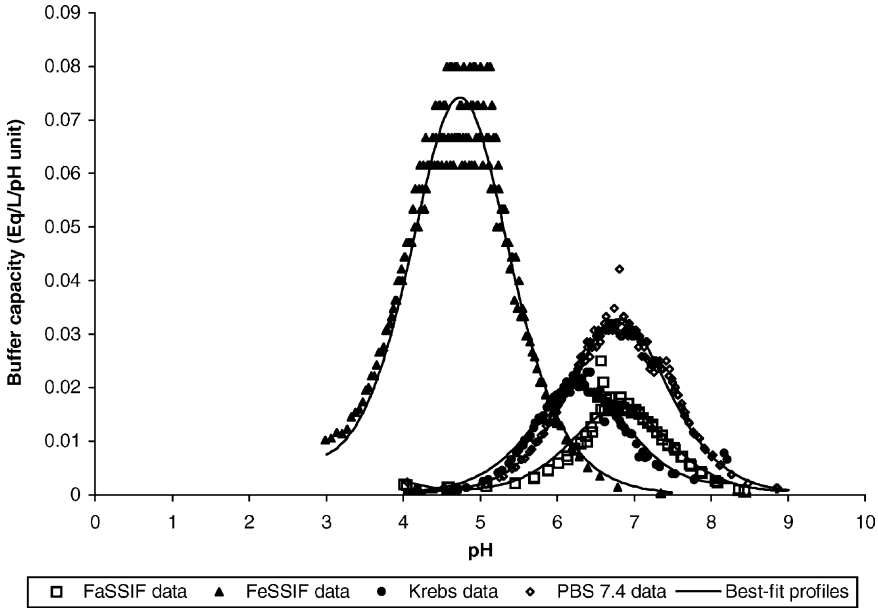

Fig. 3. Buffer capacity vs. pH profiles showing experimental data and lines of best-fit for FaSSIF, FeSSIF, Krebs and PBS 7.4 buffers.

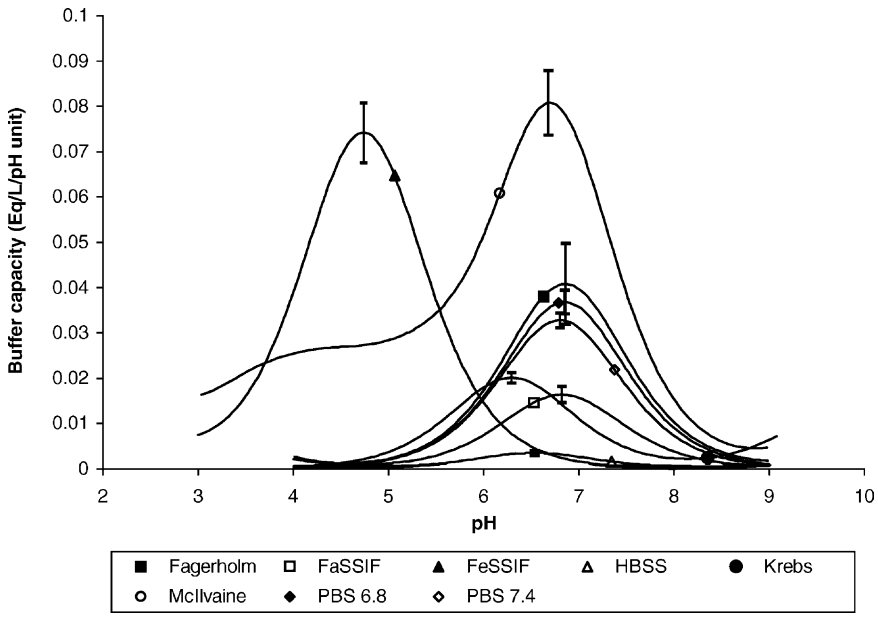

Fig. 4. Best-fit buffer capacity vs. pH profiles of each of the eight buffers, their initial pH and buffer capacities, and standard deviations at maximum buffer capacity.

their initial pHs (β). There is a 40-fold difference between the lowest (HBSS) and the highest (FeSSIF). Also indicated in the table are the maximum buffer capacities (β_{max}) and, with the exception of PBS 6.8, it is apparent that all of the buffers are used at their suboptimal pH (Fig. 4). This is of significance as similar buffer capacities were observed at the initial pH values for FeSSIF and McIlvaine. However, for FeSSIF the initial pH is on the downward slope of its profile, while for McIlvaine the initial pH is on its upward slope (Fig. 4). Consequently, it takes a greater amount of base to shift the pH of 1 l of McIlvaine by 1 pH unit (1.84 mM NaOH) than for FeSSIF (0.94 mM NaOH).

When the thermodynamic value for the pK_a of the buffer component is corrected for temperature and ionic strength there is good agreement with the experimental data (Table 3).

3.3. In situ permeability studies using ibuprofen

The permeability coefficients (P_{app}) for ibuprofen in each of the buffers are given in Table 4 and ranged from 1.40×10^{-4} to 0.93×10^{-4} cm/s.

The P_{app} for HBSS was significantly different from six other buffers (FaSSIF, FeSSIF, Krebs, McIlvaine, PBS 6.8 and 7.4). Fagerholm's buffer was different from McIlvaine buffer and PBS 7.4, and PBS 6.8 was different from PBS 7.4. The critical F-value from the ANOVA results is 4.21 with a P-value of 0.002.

The concentration of ibuprofen in the perfusion solution (prior to entry into the gut) before and at the end of each experiment was, on analysis, the same in all systems indicating that precipitation of ibuprofen salts of low solubility (e.g., calcium salt) over the course of the experiment did not occur.

Table 4
Permeability coefficients (P_{app}) of ibuprofen in each buffer

Buffer system	$P_{app} \times 10^{-4}$ (cm/s)	S.D.
HBSS pH 7.4[a]	1.40	0.10
PBS (Fagerholm et al., 1996) pH 6.5[a]	1.20	0.14
PBS 6.8 (Sorensen)[a]	1.15	0.12
FaSSIF pH 6.5	1.10	0.19
FeSSIF pH 5.0	1.05	0.17
Krebs pH 8.1	1.01	0.09
McIlvaine pH 6.0	0.97	0.13
PBS 7.4 (Sorensen)	0.93	0.11

[a] Buffers that are significantly different based on ANOVA ($P = 0.002$) using pair-wise comparisons.

Komiya et al. (1980) investigated the intestinal permeability in the rat of a range of steroids using varying flow rates and intestinal lengths. When using a flow rate of 0.247 ml/min and an intestinal length of 33.3 cm, the permeability of hydrocortisone in phosphate buffer (pH 6.0) was found to be membrane controlled with a permeability coefficient of 0.30×10^{-4} cm/s. In contrast, the corresponding permeability coefficient for progesterone was 1.08×10^{-4} cm/s and its transport was aqueous boundary layer controlled. From our studies, the permeability coefficient of ibuprofen in a similar buffer (citrate-phosphate pH 6.0) was 0.97×10^{-4} cm/s. This suggests that the absorption of ibuprofen in the rat is aqueous boundary layer controlled due to its relatively high permeability coefficient.

A compound is considered to be completely absorbed in the rat if its P_{app} is greater than approximately 0.2×10^{-4} cm/s (Fagerholm et al., 1996). The values reported in the present work are all greater than this and when they are converted to human fraction absorbed values (Fagerholm et al., 1996), they show 99.9% absorption with no statistically significant differences observed.

The pHs of the perfusate samples were monitored over the course of each experiment and the pH versus time profiles are shown in Fig. 5. Over the time course of the perfusion experiments, the pH of the samples gradually change from their initial values towards a median value of approximately 6.5, with some of the systems being shifted upwards and others shifted downwards from their initial values. The extent of these pH changes is significant in four of the buffers: FaSSIF, FeSSIF, HBSS and PBS 7.4. This would be expected from the buffer capacity profiles as FaSSIF, HBSS, PBS 7.4 and Krebs correspond to the four lowest buffer capacity values of the perfusion solutions. However, despite its low buffer capacity, the pH change for Krebs is not significant as it shows no definite trend in its pH values. This may be due to carbon dioxide dissolving into the perfusate samples. Despite its high buffer capacity, FeSSIF shows a significant change in pH during the perfusion which may be due to its relatively low pH (compared to the microclimate pH) that may stimulate the intrinsic intestinal buffering system to produce the pH change observed. In the

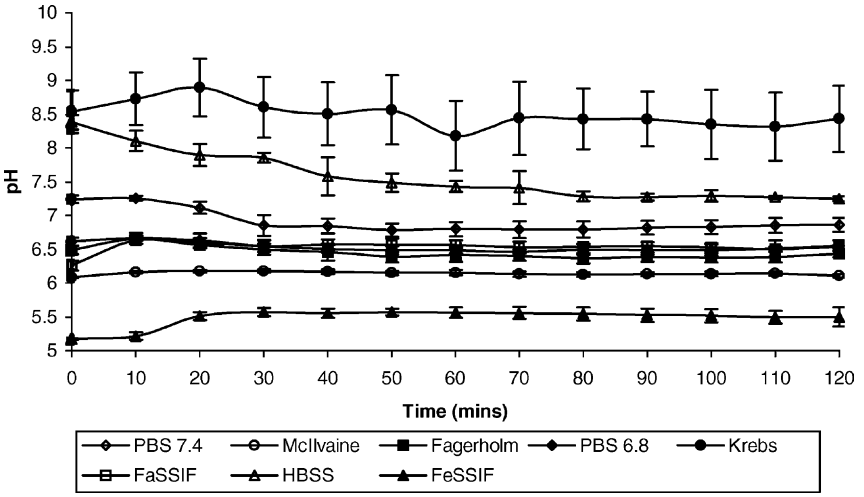

Fig. 5. pH vs. time profiles of perfusate samples.

case of most of the buffers, the change in pH occurs over ~50 min. Desai (1977) reported that the pH of buffered solutions, initially pH 9.5 and 4.5, respectively, of low buffer capacity tended rapidly towards a pH of 6.5 when placed in the rat intestine and Ikuma et al. (1996) have shown that the jejunal microclimate pH in young adult rats is 6.12 ± 0.04. It is well established that the cell surface of the rat jejunum has an acidic microclimate in vitro (Iwatsubo et al., 1989) and this microclimate appears to be maintained by a dynamic equilibrium of H^+ secretion and absorption across the luminal membrane and the diffusion from the microclimate towards the luminal fluid (Shimada, 1987). The reduction in the change in pH of the perfusate samples after 50 min suggests that there is some exhaustion of this microclimate pH-maintenance system. Several studies have shown that the absorption processes of some drugs and nutrients are influenced by the microclimate pH (Lister et al., 1997).

The changes in the pHs of the perfusate samples produce changes in the percentage of drug ionised. Despite some of the pH changes being significant, the corresponding change in fraction of ibuprofen ionised is negligible for all buffers except FeSSIF. The starting pH of the FeSSIF perfusion solution (5.17) corresponds to 84.6% ionised and its pH at the steady-state (5.51) corresponds to 92.3% ionised. At the steady-state, the remaining seven buffers give 98–99.9% of drug ionised. Compounds with molecular weights less than 200 are able to pass through the aqueous pores (Lennernas, 1995), but transcellular transport of the unionised fraction can occur simultaneously (Chan and Stewart, 1996). The high permeability of ibuprofen, along with its molecular weight (206) and degree of ionisation, implies that the drug may be absorbed principally by the paracellular route. Alternatively, the proton/monocarboxylate transporter, MCT1, (Tamai et al., 1995) may be involved.

4. Conclusions

Within the range of the eight buffers studied, the solubility of ibuprofen acid differed sixfold from the lowest (HBSS) to the highest (PBS 7.4). These differences reflected the pHs of the buffers when saturated with drug. The results were consistent with Eq. (5) with two exceptions, FeSSIF and Krebs buffers, due to the presence of micelles and divalent ions, respectively.

Significant differences were also observed in the buffer capacities of the buffers. When reporting buffer capacity values it is important to specify the pH of the buffer and whether an acid or a base was used to measure it, as each may produce different results unless the pH is at the pK_a.

Significant differences in the apparent permeability coefficients were observed between HBSS and six other buffers (FaSSIF, FeSSIF, Krebs, McIlvaine,

PBS 6.8 and 7.4). Fagerholm's buffer was significantly different from McIlvaine and PBS 7.4 buffers. PBS 6.8 was observed to be significantly different from PBS 7.4. Physicochemical factors such as pH and buffer capacity should be considered for determining the P_{app} values of ionisable compounds. Care needs to be exercised when comparing P_{app} values from different laboratories as buffer composition can have a significant effect on the permeability of an acidic drug which is substantially ionised over the pH range of the buffers. The absorption of ibuprofen is aqueous boundary layer controlled and the degree of ionisation suggests it is absorbed paracellularly or by the MCT1 transporter. The intestinal microclimate buffering system appears to maintain the pH of the rat small intestinal contents somewhere in the range of 6.13–7.27 and it seems to be exhaustable.

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