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Influence of dissolution medium buffer composition on ketoprofen release from ER products and in vitro–in vivo correlation

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Abstract

The purpose of this work was to investigate the influence of dissolution medium composition on the in vitro release of ketoprofen from a series of ER products and the impact of the different buffer media on the in vivo–in vitro (IVIV) relationship. The products investigated were coated micro bead preparations having increasing levels of coating to retard drug release. Four common dissolution media; USP phosphate buffers of pH 7.2 and 6.8, phosphate (modified isotonic) buffer pH 6.8 and a fasted state simulated intestinal fluid without lipid components (FaSSIFLF) of pH 6.5, were employed in the USP 2 apparatus. Release profiles were compared to the corresponding in vivo release profiles, obtained following deconvolution of the plasma level versus time profiles obtained from a 10-subject five-period cross-over study. Despite the relative similarity in composition of the media employed, significant differences in release profiles were observed reflecting media differences in buffer capacity, ionic strength and pH. As a consequence, the quality and shape of the IVIV relationship changed significantly, the only apparent IVIVC incorporating all four ER products, which was non-linear, was obtained using the phosphate (modified isotonic) buffer of pH 6.8. This data was fitted, using a non-linear least squares method, by the equation of Polli et al. [J. Pharm. Sci. 85 (1996) 753] and gave an alpha parameter estimate of 2, consistent with initial dissolution being more rapid in vitro than in vivo. The systematic shift in profiles, particularly with buffer capacity, underlines the sensitivity of IVIV relationship to medium composition and hence the current difficulties in making a rational choice of an appropriate single dissolution medium.

Keywords: Ketoprofen; Dissolution; Buffer capacity; In vitro–in vivo correlation

1. Introduction

An important factor in the design of a dissolution test is the composition of the dissolution medium. It is generally held that the medium should simulate that found in vivo and should provide sink conditions for the drug so as to improve the possibility of establishing a quantitative in vitro–in vivo (IVIV) correlation. While a linear relationship, with zero intercept, between the fraction of drug dissolved in vitro and the fraction dissolved in vivo is ideal (level A correlation), non-linear relationships may be obtained and quantified (Dunne et al., 1997; Polli et al., 1996).

Among the dissolution conditions often controlled, particularly for ionisable drugs, is the medium pH because of the influence of pH on the solubility and dissolution (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

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equivalent pH often varies despite evidence that buffer capacity at a given pH can substantially influence the dissolution rate of both ionisable drugs (Mooney et al., 1981; Aunins et al., 1985), excipients (Ramtoola and Corrigan, 1989) and hence formulated products. In this regard, Prasad et al. (1983) and Skelly et al. (1986) studied dissolution rates of commercial formulations of controlled release quinidine gluconate in different media. Dissolution profiles using the paddle method at 100 rpm in different media revealed large differences between the two products. The dissolution rates of the two products were widely different in water, acetate buffer of pH 5.4 and phosphate buffer of pH 5.4. The quinidine gluconate products dissolved more rapidly in acetate buffer than in phosphate buffer. The results illustrated the importance of medium buffer composition as well as pH in determining drug profiles. Dissolution medium pH and buffer capacity may not only affect the dissolution of a drug but may also substantially influence dissolution of ionisable excipients present (Ramtoola and Corrigan, 1989). The latter authors investigated the influence of buffering capacity of the medium on the dissolution of drug-excipient mixtures. It was found that the presence of acid excipients in drug-excipient compacts decreased the dissolution rate of the drug. It was also found that in the presence of the acid excipient, the enhancing effect of increasing the buffer strength on the drug dissolution rate was lowered. It was concluded that the buffering capacity of the medium is an important factor in the design of dissolution media for IVIV correlations.

Dressman et al. (1998) reported the buffer capacities in vivo, in the post ingestion 'water meal' and fed ('solid meal') states as 10.2 (pH 6.7) and 76 mEq./l per pH unit (pH 5.2), respectively, in samples recovered from mid gut samples in dogs (Greenwood, 1994). They also proposed more biologically relevant dissolution media having significantly different buffer capacities. However, media used in dissolution testing are often not fully characterised, frequently only the pH is stated. Preference has moved from pH 7.2 to 6.8 in the light of physiological data. Furthermore, some buffers are isotonic and others are not. Examples of media in use include USP phosphate buffers of pH 6.8 and 7.2 which are not isotonic and have buffer capacities 30–35 mEq./l, while the modified isotonic Sorenson's buffers of pH 6.5–7.4 (Pharmaceutical Handbook, 1980) can have greater buffer strengths than USP phosphate of similar pH.

The objective of this report is to compare the dissolution profiles of a number of test ER formulations of ketoprofen ($pK_a = 4.6$) in a range of commonly employed buffered media and compare the results to the in vivo release profiles. Nonsteroidal anti-inflammatory agents (NSAIDS) such as ketoprofen tend to have low solubilities and high permeabilities at low pH, but high solubilities and reduced effective permeabilities at higher physiological pHs (Corrigan, 1997).

2. Experimental

2.1. Buffer capacity measurements

The buffering capacity of each buffer system was measured by titrating 20 ml samples with 0.1 N HCl and with 0.2 N NaOH (Levis et al., 2003). The acid/base was added to the buffer systems in aliquots of 0.1–1 ml. The pH of the solution was recorded at each interval and a buffering capacity–pH profile was plotted. The following buffers were used in the buffer capacity measurements: USP phosphate buffers (0.05 M) of pH 7.2 and 6.8, isotonic phosphate buffer (0.067 M, NaCl: 0.082 M), pH 6.8 (Sorensen, modified, Pharmaceutical Handbook, 1980) and a fasted state simulated intestinal fluid (FaSSIF), pH 6.5 (Dressman et al., 1998), without the lipid components, hereafter referred to as FaSSIFLF.

2.2. Dissolution determinations

The dissolution tests were conducted using a six-stage dissolution apparatus (Van Kel VK7000 unit) with USP (1995) paddle (apparatus II) specifications. Dissolution medium (900 ml) was used at a temperature of 37 ± 0.5 °C and a stirring speed of 50 rpm. The dissolution medium was degassed with helium for 20 min before the dissolution began. A helical wire sinker, recommended by the USP, was used to prevent flotation of the low-density dosage form. An automated system, Icalis Data Systems (Berks, UK) fitted to a Unicam UV3 UV-Vis spectrophotometer was employed for the dissolution studies in FaSSIFLF. In these cases, withdrawal of the

sample, data acquisition and calculations are fully automated.

Samples were taken and diluted, if necessary, prior to assaying by UV spectroscopy at 260 nm in the linear range. All samples were replaced by fresh dissolution medium. The concentration of the drug in the dissolution medium was determined by comparing the absorbance of the sample with that of the reference standard solution prepared in the same medium. The percentage released was determined by taking into account the potency of the formulation, the dilution factor, dilution volume and media volume.

The ketoprofen products used were experimental multiparticulate formulations differing in the level of rate controlling polymer incorporated, the amount increasing, to retard the release rate, progressively from 'formulation A' (fastest) to 'formulation D' (slowest). The coating was ethylcellulose-based and, therefore, pH independent.

2.3. In vivo assessment

A 10-subject (fasted, healthy males), five-period cross-over (the IR formulation; Orudis 50 mg was included for deconvolution) study design was employed, following ethics committee approval. Volunteer subjects were aged between 18–40 years, were free from any clinically significant abnormality on the basis of medical history, physical examination and laboratory evaluation comprising haematology, clinical chemistry, urinalysis, ECG, virology (hepatitis B and C, HIV) and drug screen (drugs of abuse and addiction). Other exclusion criteria included history of gastritis, peptic ulcer, asthma, hypersensitivity to ketoprofen or alcohol abuse and deviation of more than 10% from ideal body weight for height.

A light supper was provided at 21:00 h on the day prior to the study treatment period. Subjects were fasted overnight (for at least 10 h prior to dosing) and remained fasted for 4 h post dosing at which time lunch was served. Administration of each formulation was accompanied by 240 ml water.

The plasma sampling times following administration of the test ER formulations, with a washout period of 1 week, were: 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36 h, while for the IR Formulation 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24 h. Ketoprofen in plasma was assayed by high performance liquid chromatography (HPLC) using a modification of the method described by Shah and Jung (1985). Mean plasma levels were deconvoluted using PCDCON to obtain apparent in vivo amount dissolved versus time profiles (Gillepsie, 1992).

3. Results and discussion

The pH and buffer capacities of the four media employed are summarised in Table 1. Significant differences in buffer capacity are evident and they are within the range of buffer capacities given by Dressman et al. (1998) to reflect fasting and fed states.

The multiparticulate formulations differed in the level of rate controlling polymer incorporated, the amount increasing progressively from 'formulation A' (fastest) to 'formulation D' (slowest) to retard the release rate. The dissolution profiles follow the expected rank order, irrespective of which medium was employed (Fig. 1). The plasma levels obtained for the four ER ketoprofen products are summarised in Fig. 2. Peak plasma level decreased and the time to peak increased with increasing level of rate controlling polymer, consistent with the release retarding nature of the coating. The deconvolution profiles are shown in Fig. 3 and indicate a similar ranking of products in terms of in vivo release. The input profiles for all four products were sigmoidal, indicating an initial delay in absorption over the first 2 h and absorption being complete after ~16 h.

The dissolution profiles obtained in vitro in USP phosphate buffer pH 7.2 are shown in Fig. 1(a) and are in rank order agreement with the in vivo trends. The relationship between the in vivo and in vitro release

Table 1
Characteristics of buffers used as dissolution media

Medium	Nominal pH	Buffer capacity (mEq./l per pH unit)
USP phosphate (0.05 M)	7.2	26
USP phosphate (0.05 M)	6.8	29
Phosphate (modified isotonic, 0.067 M)	6.8	38
FaSSIFLF	6.5	10

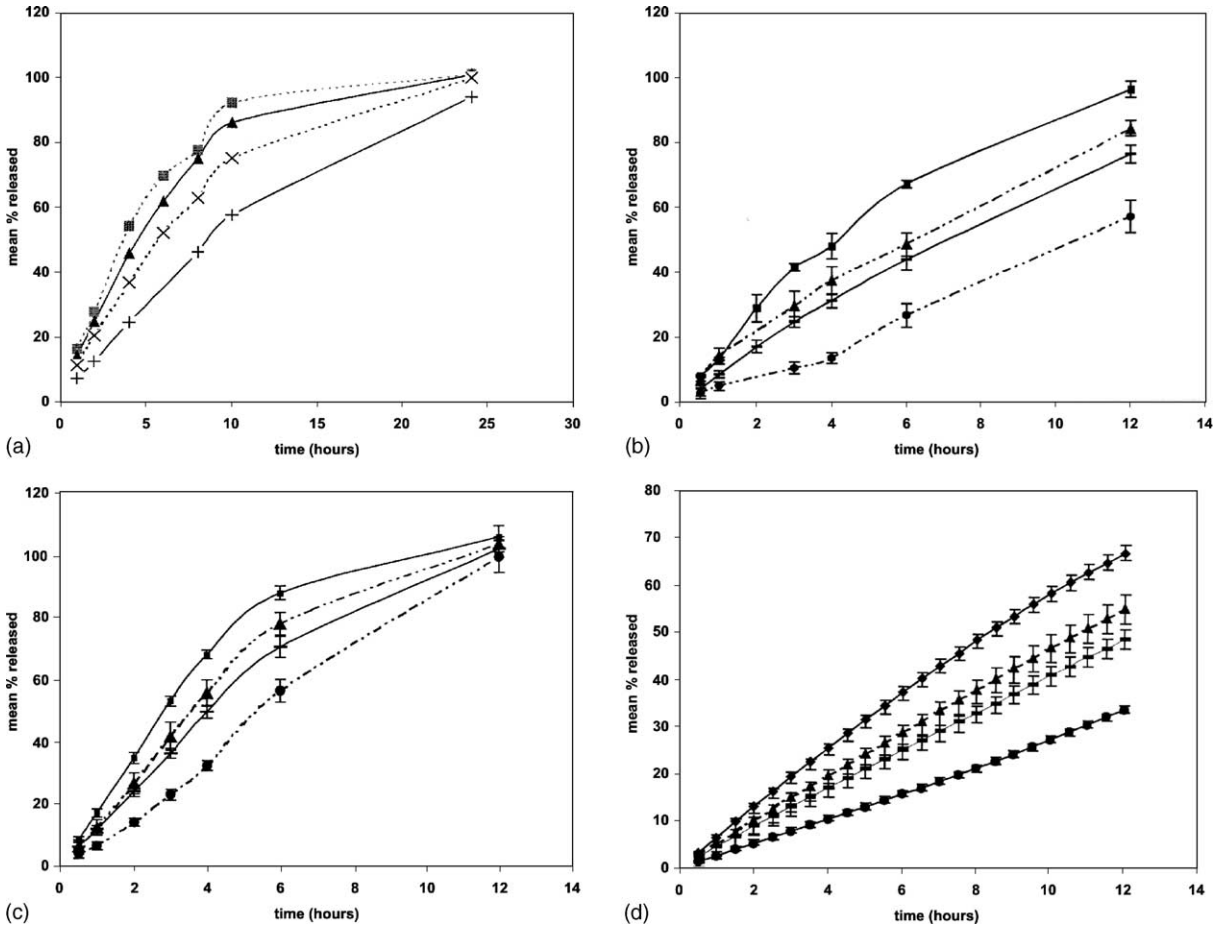

Fig. 1. Ketoprofen release (%) vs. time profiles for formulations A–D in (a) phosphate buffer, pH 7.2, key: (■) A, (▲) B, (×) C, (+) D; (b) USP phosphate buffer, pH 6.8, key: (■) A, (▲) B, (+) C, (●) D; (c) isotonic phosphate buffer, pH 6.8, key: (■) A, (▲) B, (+) C, (●) D; and (d) FaSSIF without lipids (FaSSIFLF), pH 6.5, key: (◆) A, (▲) B, (—) C, (●) D.

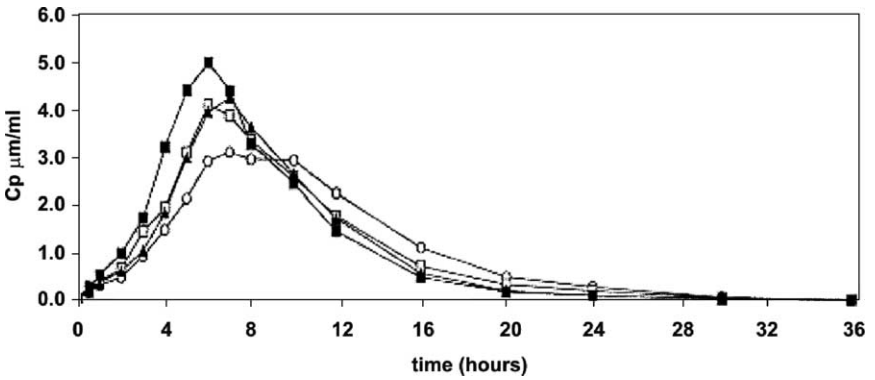

Fig. 2. Mean plasma levels vs. time profiles for ketoprofen ER formulations. Key: (■) A, (▲) B, (□) C, and (○) D.

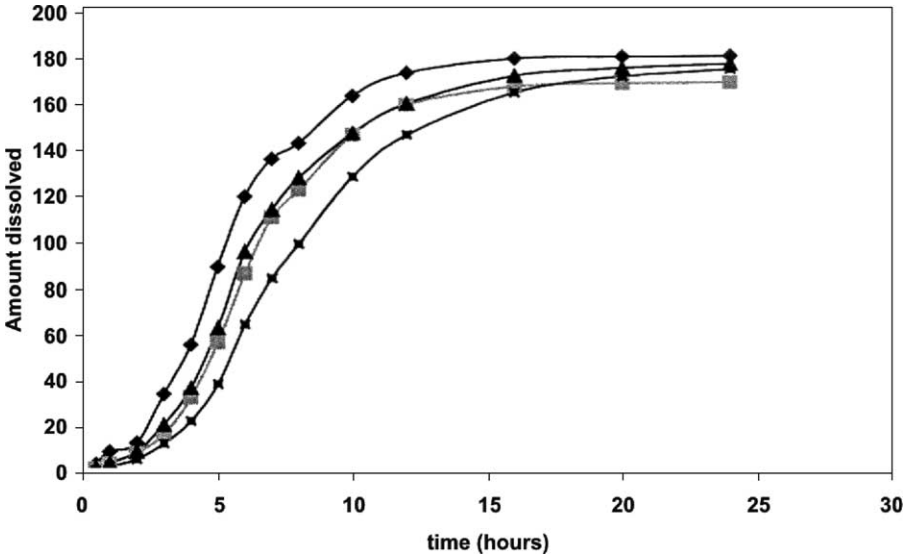

Fig. 3. Amount dissolved in vivo vs. time profiles for the four ketoprofen ER formulations obtained from data in Fig. 5 by deconvolution. Key: (◆) A, (▲) B, (■) C, and (×) D.

is shown in Fig. 4(a), where the percent dissolved in vivo at a given time is plotted against the percent dissolved at the same time in vitro. A poor level A correlation is evident, the data for each formulation being sigmoid The largest deviation from an ideal correlation (the trend line with a slope of 1.0) was evident for the faster releasing formulations. Furthermore, for all formulations much larger percentages of drug were apparently released at earlier times in vitro in USP phosphate buffer pH 7.2 than in vivo (Fig. 4a).

Altering the release medium to USP phosphate buffer of pH 6.8, maintained the same ranking of products but slowed the rate of drug release from each product Fig. 1(b). This is as expected, since the drug is an acid with a pK_a of 4.6 and solubility will decrease as the pH is reduced. The IVIV relationship for this medium is shown in Fig. 4(b). The profiles, particularly at later times, i.e. at the higher percentages released, have shifted towards the 'level A correlation' trend line when compared to the corresponding 7.2 pH medium (Fig. 4a).

In vitro release was also conducted in the phosphate buffer (modified isotonic) of pH 6.8 (Fig. 1c). Again, it is evident that as the level of rate controlling polymer is increased the dissolution rate declines. However, in this medium, having higher buffer capacity and ionic strength, the release rates are higher for all formulations when compared to those obtained in the USP buffer of equivalent pH (6.8). The IVIV relationship has also altered as shown in Fig. 4(c). Data points are all significantly below the trend line, the datasets for each formulation are closer together and the correlation is more parabolic than sigmoid or linear.

Dissolution studies were also carried out in the modified FaSSIFLF. The lipid components were omitted, as the objective of the study was to assess specifically buffer related effects. The resulting release profiles are shown in Fig. 1(d). While the ranking of formulations in terms of release rate is maintained, release is much slower than in any of the other media examined. This is not surprising in view of the lower pH and poorer buffering capacity of this medium (Table 1). The IVIV relationship obtained using this data is shown in Fig. 4(d). The profiles for each product are sigmoid, with many of the points lying above the ideal linear 'level A' correlation trend line. Since such points indicate greater apparent dissolution in vivo than in vitro, the relationship found using this medium is the least realistic of the four buffer media studied. It should be stressed that the relationship obtained is not necessarily the same as that which might result were the lipids included in the medium.

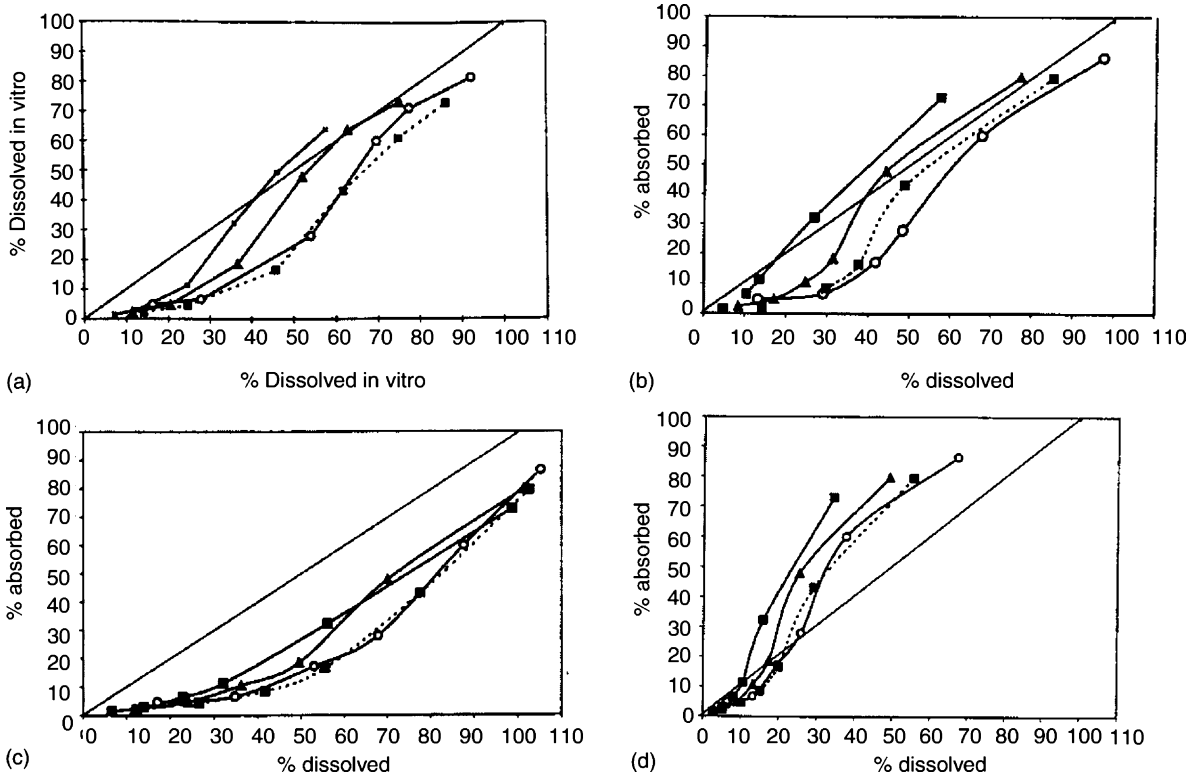

Fig. 4. Plot of ketoprofen dissolved in vivo (%) vs. drug dissolved in vitro (%) for ketoprofen ER formulations A–D. (a) Phosphate buffer pH 7.2, key: (○) A, (■) B, (▲) C, (×) D; (b) USP phosphate buffer pH 6.8, key: (○) A, (■) B, (▲) C, (×) D; (c) isotonic phosphate buffer, pH 6.8, key: (○) A, (--■--) B, (▲) C, (■) D; and (d) FaSSIFLF, key: (○) A, (--■--) B, (▲) C, (■) D.

Thus, from the point of view of IVIV correlation of the four media studied, the isotonic phosphate buffer pH 6.8 proved the most satisfactory in that the in vivo versus in vitro plots for the four products are closest together, however, the relationship is non-linear. Non-linear relationships of this shape may be interpreted in terms of the proportional odds, proportional hazards and proportional reverse hazards models described by Dunne et al., 1997 with respective equations of the form

$$\frac{A}{1-A} = a \times \frac{D}{1-D} \tag{1}$$

$$1 - A = (1 - D)^a \tag{2}$$

$$A = D^a \tag{3}$$

where A corresponds to the fraction dissolved in vivo, D the fraction dissolved in vitro and a corresponds to the constants of proportionality.

Alternatively, non-linear relationships of this form have been fitted to an equation of the form

$$A = \frac{1}{F_{\text{inf}}}\left(1 - \frac{\alpha}{\alpha - 1}(1 - D) + \frac{1}{\alpha - 1}(1 - D)^{\alpha}\right) \tag{4}$$

where α is the ratio of a first order permeation rate constant to the first order dissolution rate constant. For high values of α, absorption is controlled by dissolution and a linear level A IVIVC will be obtained. Low values of alpha give relationships of similar shape to Fig. 5 and reflect more rapid initial drug release in vitro than in vivo. Non-linear IVIV relationships of this form have been reported for IR products of drugs with low apparent permeability coefficients (Polli et al., 1996; Polli, 1997). Eqs. (1)–(4) were used to fit the data in Fig. 4(c). The best fit, as reflected by the largest coefficient of determination (CD), was obtained with Eq. (4) (CD = 0.982). The value of α in Eq. (4),

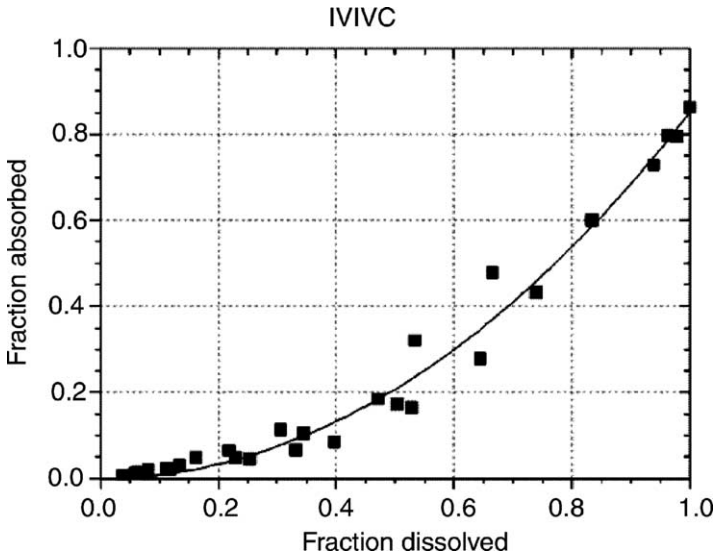

Fig. 5. Relationship between fraction released in vivo and fraction dissolved in vitro in an isotonic phosphate buffer, pH 6.8 (buffer capacity 38 mEq./l per pH unit) for four ketoprofen ER formulations. The fitted line was obtained from Eq. (4).

obtained by non-linear least squares fitting, was 1.92 (Fig. 5). Estimates of α for the individual products were in the 1.48–3.93 range, the higher values being obtained for the slower releasing products, consistent with increased dissolution control as product dissolution rate decreased. The overall shape of the IVIV relationship likely reflects delayed in vivo dissolution arising from gastric emptying and the lower drug solubility in an acidic environment. The sequential use of a range of media reflecting the H^+ change along the gastrointestinal lumen could result in a more linear correlation.

The systematic shifts in profiles observed with changes in pH and/or buffer capacity underlines the sensitivity of the IVIV relationship to medium composition and the current difficulties in making a rational choice of an appropriate dissolution medium.

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