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The use of inverse gas chromatography to assess the acid–base contributions to surface energies of cefditoren pivoxil and methacrylate copolymers and possible links to instability

Masato Ohta [a,b], Graham Buckton [a,*]

[a] *Department of Pharmaceutics, School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK*
[b] *Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan*

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Abstract

It is known that acids and bases when mixed together have the potential to react, however, there is complexity when materials are in the solid state, as the surface of the solids may not have all functional groups of the molecule expressed in equal proportions. Conceptually a drug that is acidic when in solution could have a crystal surface that is largely basic (if the acid groups are aligned away from the surface). The interaction of cefditoren pivoxil (a basic drug when dissolved) and various Eudragit polymers was studied. The drug was chemically unstable with Eudragit EPO (basic) and stable with Eudragit L100 or S100 (both acidic). Thus, the hypothesis of this work was that the surface of these materials had a different nature to the dissolved molecules, such that solid state reactions do not proceed in line with the expectation from the solution state. Inverse phase gas chromatography (IGC) was used to investigate the cefditoren pivoxil and the Eudragits. The basic to acidic parameter ratios (K_D/K_A) on the powder surface of the samples by IGC revealed that surface nature was in keeping with the tendency to react, such that the incompatibility could be due to the acid–base interaction between any carbonyl groups having an amphoteric nature on the surface of cefditoren pivoxil crystal and dimethylaminoethyl groups having a basic nature on the powder surface of Eudragit EPO. This study indicated that IGC would be suitable to elucidate the cause of incompatibility between two different solids.

Keywords: Cefditoren pivoxil; Eudragit; Inverse gas chromatography; Surface energy; Stability

1. Introduction

Surface energies of drug substances and excipients provide a means of predicting the interaction between different solid materials. Surface energy data, obtained using contact angle measurements, have been used to predict various physico-chemical interactions, such as that between a drug and a dry powder inhaler carrier (Chawla et al., 1993), and binder–drug interactions, which yielded good correlations with properties of granules and tablets (Rowe, 1989).

However, since contact angle measurement for powders have some limitations (Buckton et al., 1995), there is a continuing need to develop new methodologies with which to probe powder surface properties. It is accepted that contact angle methods for powders are flawed (e.g. Buckton et al., 1995), so vapour sorption approaches offer a potential benefit. As there can be

* Corresponding author. Tel.: +44-20-7753-5858; fax: +44-20-7753-5858.
E-mail address: graham.buckton@ulsop.ac.uk (G. Buckton).

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no great confidence in contact angle data for powdered systems, there is no obvious reason why correlations should exist between contact angle and inverse gas chromatography (IGC) data, however, there is some comfort in knowing that IGC can give similar results to some contact angle results. Dove et al. (1996) have compared the values of the dispersive surface energies of theophylline and caffeine using IGC and two contact angle measurement techniques (powder adhered to a glass slide and powder compacts in the Whilhelmy plate method). Good agreement was found between IGC and the glass slide method, whereas the powder compact method gave different results. Ahfat et al. (2000) have compared the values of the dispersive surface energies of pharmaceutical powders by IGC and the dynamic angle tester (DAT) (by which contact angles are determined on the basis of the sessile drop technique). The IGC values yielded higher surface energy values than those obtained through the DAT. Planinšek et al. (2001) have demonstrated that the values of the dispersive surface energies of pharmaceutical powders by IGC correspond with those by the Wilhelmy plate method when surface energies were calculated using only an apolar liquid such as diiodomethane or 1-bromonaphthalene. Thus, as might be expected, comparisons between contact angle measurement techniques and IGC provide some similarities, but have usually yielded different results, reflecting the difference in the measurement principle between the two techniques.

One potential limitation of IGC is that it is usually operated by injecting very small amounts of probe vapour (infinite dilution of the probe). It is argued that at infinite dilution the probe will preferentially interact with the higher energy sites on the powder surface and thus yield data for just these sites rather than the mean surface energy of all available sites on the powder surface. Since many interactions would occur at high-energy sites on the solid surface, this may even be an advantage for this technique.

This study was based on a preliminary observation that cefditoren pivoxil (essentially a basic drug) showed a chemical interaction with a basic Eudragit, which was contrary to expectation. The hypothesis was that the surface properties of the drug and excipient in the solid state dominated the interaction, making the solution state properties irrelevant. Consequently, the aim of the work was to measure the chemical stability of cefditoren pivoxil with a series of metacrylate-based polymers and to see if any correlation existed with the surface energy data as assessed using IGC.

2. Materials and methods

2.1. Materials

Cefditoren pivoxil (crystalline) was synthesised at Meiji Seika Kaisha Ltd. (Japan). Three different methacrylate copolymers were employed throughout the study, these were Eudragit EPO, L100 and S100 (Röhm Pharma, Germany). Organic solvents, ammonium formate, formic acid, *n*-propyl *p*-hydroxybenzoate, hydrochloric acid, sodium hydroxide, distilled water, potassium chloride, phosphoric acid, acetic acid and boric acid were analytical reagent grade.

2.2. Preparation of physical mixtures

A physical mixture was prepared by bottle tumbling cefdioren pivoxil crystal (50%) with either Eudragit EPO, L100 and S100 (50%). The samples (400 mg) were put into a 3 ml glass bottle and tumbled using a Rotamixer Deluxe (Hook & Tucker Zenyx Ltd., UK) set at maximum speed for 5 min.

2.3. Differential scanning calorimetry (DSC)

The DSC study was performed using model DSC 7 (Perkin-Elmer, USA) under a nitrogen gas flow using an aluminum pan with a non-hermetically sealed lid and a heating rate of 10 °C/min. The sample weights in the study were about 5 mg of drug. For the calibration of enthalpy determination, indium of 99.99% purity was used.

2.4. Chemical stability study

About 800 mg of cefditoren pivoxil alone and the binary physical mixtures consisting of cefditoren pivoxil and Eudragit EPO, L100 and S100 were stored in glass jars at 60 °C for 2 weeks. The content of cefditoren pivoxil in the samples was determined using high per-

formance liquid chromatography (HPLC) as described below.

2.5. Determination of apparent solubility of cefditoren pivoxil

Ten grams of cefditoren pivoxil was suspended in 10 ml of aqueous solution of various pH values at 25 °C. Clark–Lubs buffer solution was used as pH 1.5, and the Britton–Robinson buffer solutions were employed as pH 2.0, 3.0, 4.0, 5.0, 6.0 and 7.0 (Clark and Lubs, 1917; Britton and Robinson, 1931). The suspensions were shaken for 30 s during every 5 min period until 30 min had passed. The aliquots were filtered through a membrane filter (Millipore, 0.45 μm). The concentrations of cefditoren pivoxil were determined by HPLC as described below.

2.6. Determination of cefditoren pivoxil content

The content of cefditoren pivoxil in powders was determined by HPLC (Hitachi, Japan). The HPLC conditions were as follows: a pre-filled column (model ChemcoPak, packing material chemcosorb 5-ODS-H, 4.6 mm × 250 mm, Chemco, Japan) was used. The column temperature was kept at 25 °C. The composition of the mobile phase was 0.025 M ammonium formate solution (pH 6.0), acetonitrile and methanol (18:11:11). The flow rate of the mobile phase was 1.0 ml/min. The wave number detected by ultraviolet was 230 nm. *n*-Propyl *p*-hydroxybezoate was used as an internal standard.

2.7. Inverse gas chromatography (IGC)

Experiments were performed using IGC (Surface Measurement System Ltd., UK). Approximately 400 mg of cefditoren pivoxil crystal and approximately 300 mg of each Eudragit were packed into the silanised glass column (Surface Measurement System Ltd., UK) of size 6 mm o.d., 3 mm i.d. and 300 mm long, by vertical tapping. Progress was monitored visually while tapping for at least 15 min. Tapping continued until there were no visible cracks, hollows or channels in the body of the powder. Both ends of the columns were loosely stoppered with silanised glass wool. The conditioning of the column packed with the sample powder was carried out at 303 K and 0% RH for 3 h, and the experiment was performed at the same conditions. Methane was used for the inert reference, *n*-decane, *n*-nonane, *n*-octane, *n*-heptane and *n*-hexane were used to determine the alkane line, and acetone, chloroform and ethanol were employed as polar probes. The gas flow rate used was 10 ml/min. Each probe was injected three times to give a measure of the reproducibility.

2.8. Determination of acidic–basic parameters

The retention times for a homologous series of alkane probes and polar probes were used to calculate the acidic–basic parameters of cefditoren pivoxil and Eudragits. The retention behaviour of polar probes on the $RT\ln V_n^\circ$ versus $a(\gamma_L^D)^{1/2}$ plot, results in responses that are located above the line drawn through the alkane probe results, and the vertical distance between the data points of polar probes and the alkane line gives the specific energy of adsorption of a polar probe with a solid material ($-\Delta G^{AB}$), where R = gas constant, T = absolute temperature, V_n° = net retention volume, a = surface area of the probe molecule, γ_L^D = the dispersive surface energy of the probe. The values of V_n° were obtained from the retention times of probes as described by Planinšek and Buckton (2003), and the values of a and γ_L^D were obtained from the literature (Schultz et al., 1987; Nardin and Papirer, 1990). The value of $-\Delta G^{AB}$ was related to the acidic or electron accepting parameter (K_A) and the basic or electron donating parameter (K_D) as described in Eq. (1):

$$-\Delta G^{AB} = K_A\,DN + K_D\,AN^* \quad (1)$$

where DN is an electron donor or base number characterised according to Gutmann (1978), and AN* is an electron acceptor or acid number (Riddle and Fowkes, 1990).

By measuring the value of $-\Delta G^{AB}$ for polar probes, a linear plot of $-\Delta G^{AB}/AN^*$ versus DN/AN^* was obtained. The values of K_A and K_D of sample powders were determined from the gradient and intercept of the line, respectively. The values of DN and AN* were obtained from the literature (Gutmann, 1978; Riddle and Fowkes, 1990).

3. Results and discussion

3.1. Characterisation of acidic or basic nature

For certain solid materials (such as ibuprofen and Eudragits, see discussion below), the chemical groups on the solid surface, which are likely to interact with other materials, might simply be predicted from the chemical structural features. Eudragit EPO has dimethylaminoethyl groups and dissolves at pH of less than 5, so clearly is a basic material. Eudragit L100 and S100 have carboxylic acid groups having an acidic nature, and all Eudragits have some carbonyl groups having an amphoteric nature in the chemical structures as shown in Fig. 1(a). Eudragit L100 and S100 are soluble at pH of greater than 6.0 and 7.0, respectively, due to the ratio of carboxylic acid groups in their chemical structures (Bauer et al., 1998) and thus behave as typical acids.

Cefditoren pivoxil has characteristic basic groups and some carbonyl groups having an amphoteric nature as shown in Fig. 1(b), and consequently would be expected to be basic. The apparent solubilities of cefditoren pivoxil crystal in aqueous solutions of various pH values at 25 °C are shown in Fig. 2, the results showed a typical behaviour for a basic material.

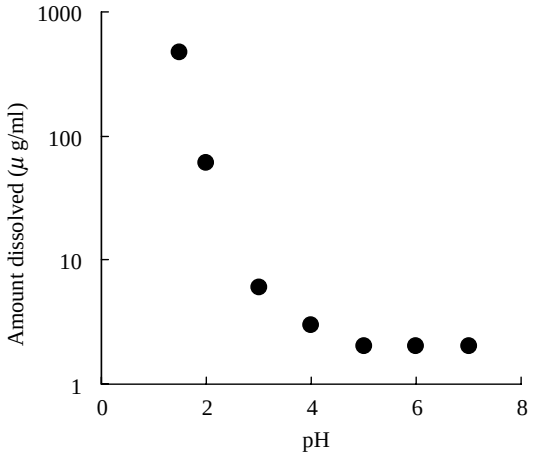

Fig. 2. The apparent solubilities of cefditoren pivoxil crystal in aqueous solutions of various pH values at 25 °C (error bars, $n = 3$).

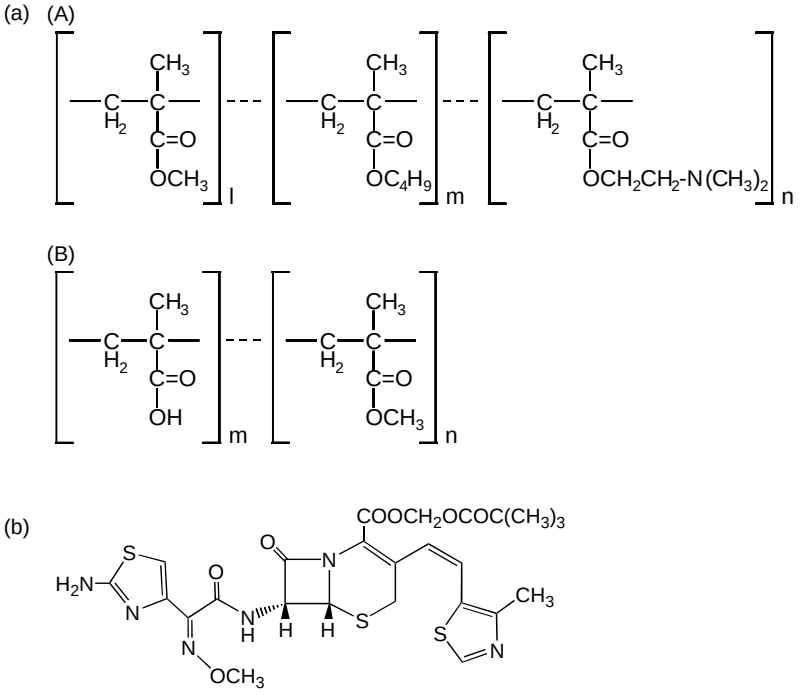

Fig. 1. (a) Chemical structures of Eudragits. (A) Eudragit EPO (l:*m*:*n* 1:1:2), (B) Eudragit L100 (*m*:*n* 1:1) and S100 (*m*:*n* 1:2). (b) Chemical structure of cefditoren pivoxil.

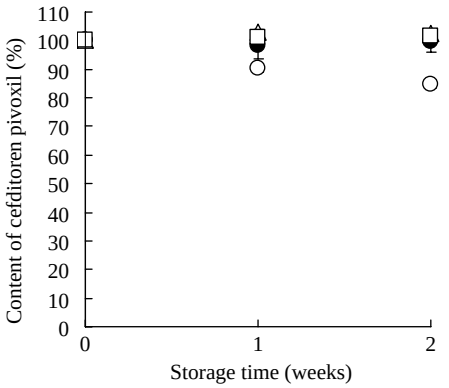

Fig. 3. Changes in the content of cefditoren pivoxil in the crystal alone and the binary physical mixture with Eudragit stored at 60 °C. Filled circle, cefditoren pivoxil crystal alone, open circle, physical mixture (cefditoren pivoxil crystal:Eudragit EPO 1:1 (w/w)), triangle, physical mixture (cefditoren pivoxil crystal:Eudragit L100 1:1 (w/w)), square, physical mixture (cefditoren pivoxil crystal:Eudragit S100 1:1 (w/w)) (in all cases $n = 3$).

The above results of the acidic or basic nature, obtained from the chemical structures and solubility behaviours, would lead to the expectation that cefditoren pivoxil (basic) would be compatible with Eudragit EPO (basic) and incompatibility with Eudragit L100 or S100 (acidic).

3.2. Compatibility study

Changes in the content of cefditoren pivoxil and the binary physical mixture with Eudragit EPO, L100 and S100, which were stored in glass jars at 60 °C, are shown in Fig. 3. The content of cefditoren pivoxil in the physical mixture with Eudragit L100 or S100 remained approximately 100% for 2 weeks as did the cefditoren pivoxil control, whereas the content of cefditoren pivoxil in the physical mixture with Eudragit EPO gradually decreased with time, being 84.7% after storage for 2 weeks. From these results, cefditoren pivoxil was apparently compatible with Eudragit L100 or S100 and incompatible with Eudragit EPO.

The DSC traces of cefditoren pivoxil alone and the binary physical mixtures consisting of cefditoren pivoxil crystal Eudragit EPO, L100 and S100 are shown in Fig. 4. An endothermic event at 210 °C followed by an exothermic peak was observed for the physical mixture including Eudragit L100 or S100 as well as cefditoren pivoxil alone. In the previous paper (Ohta et al., 1999), it has been described that the endothermic peak is due to fusion and the exothermic peak is due to decomposition for cefditoren pivoxil. These data demonstrated that the drug was in the crystalline state. For the physical mixtures of drug and Eudragit EPO, an endothermic event was observed at

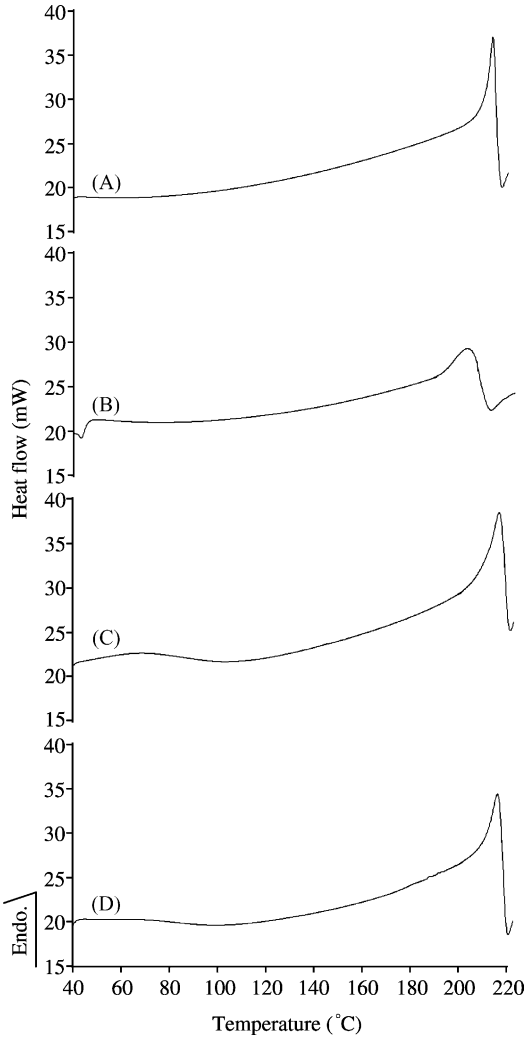

Fig. 4. DSC traces of cefditoren pivoxil crystal alone and the binary physical mixture consisted of cefditoren pivoxil crystal and Eudragit. (A) Cefditoren pivoxil crystal alone, (B) physical mixture (cefditoren pivoxil crystal:Eudragit EPO 1:1 (w/w)), (C) physical mixture (cefditoren pivoxil crystal:Eudragit L100 1:1 (w/w)), (D) physical mixture (cefditoren pivoxil crystal:Eudragit S100 1:1 (w/w)).

200 °C, followed by an exothermic peak. This depression of melting point is in keeping with the presence of an interaction and is similar to literature (Petereit and Weisbrod, 1999 reported the melting of ibuprofen, an anionic drug, with Eudragit E100, a cationic polymer, being decreased in comparison with that of ibuprofen crystal alone). Eudragit EPO is a fine powder made from Eudragit E100, both are chemically identical. The shift to lower temperature of the melt of cefditoren pivoxil in the presence of Eudragit EPO therefore suggested an interaction between these two materials and the absence of a shift in melting point indicates an absence of reaction with Eudragit L100 and S100.

The glass transition temperature (T_g) of Eudragit EPO with cefditoren pivoxil immediately after mixing was 46.1 °C by DSC, and the value of T_g of the same sample stored in a dry glass jar at 60 °C for 2 weeks was 40.6 °C (not shown). Petereit and Weisbrod (1999) have reported that a significant reduction in T_g for Eudragit E100 following storage with ibuprofen, probably due to the formation of a salt between amino groups of Eudragit E100 and carboxylic acid groups of ibuprofen. The reduction in T_g for Eudragit EPO with cefditoren pivoxil hence suggested that an acid–base interaction between either acidic or amphoteric groups of cefditoren pivoxil and amino groups of Eudragit EPO, which is contrary to expectations based on the solution state properties of this drug.

3.3. Determination of acidic–basic parameters

The specific surface energies of adsorption of polar probes ($-\Delta G^{AB}$) for cefditoren pivoxil crystal and Eudragits are shown in Table 1, and the acidic (K_A) and basic (K_D) parameters of the samples, which were obtained from the values shown in Table 1, are shown in Figs. 5 and 6, respectively. The surfaces of samples used in this study had similar values of K_A, and the results would be obtained because all samples had some carbonyl groups having an amphoteric nature.

Table 1
Specific surface energies of adsorption of polar probes for crystal and Eudragits at 303 K ($n = 3$)

	Specific surface energy of adsorption (kJ/mol)		
	Chloroform	Acetone	Ethanol
Cefditoren pivoxil	2.21–0.03	8.96 (0.08)	12.98 (0.22)
Eudragit EPO	12.06–0.15	14.37 (0.09)	16.18 (0.06)
Eudragit L100	1.76–0.01	9.52 (0.05)	7.30 (0.02)
Eudragit S100	2.75–0.01	9.26 (0.01)	7.06 (0.08)

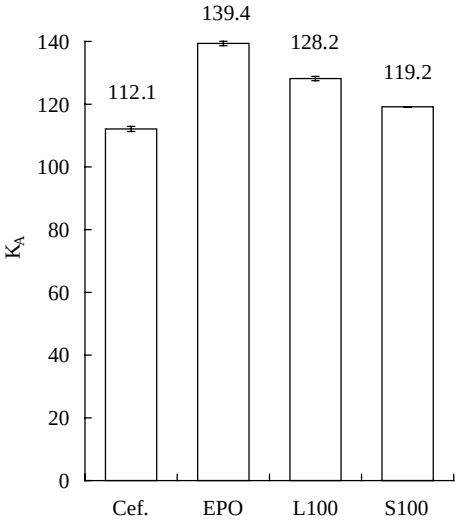

Fig. 5. The acidic parameters of cefditoren pivoxil crystal and Eudragits by IGC. Cef., cefditoren pivoxil crystal, EPO, Eudragit EPO, L100, Eudragit L100, S100, Eudragit S100 ($n = 3$) (y-axis is $\times 10^{-3}$).

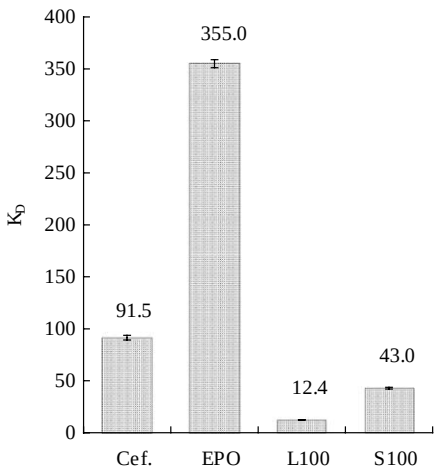

Fig. 6. The basic parameters of cefditoren pivoxil crystal and Eudragits by IGC. Cef., cefditoren pivoxil crystal, EPO, Eudragit EPO, L100, Eudragit L100, S100, Eudragit S100 ($n = 3$) (y-axis is $\times 10^{-3}$).

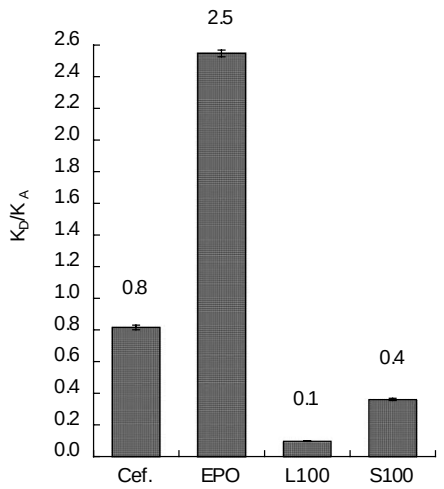

Fig. 7. The basic to acidic parameter ratios of cefditoren pivoxil crystal and Eudragits by IGC. Cef., cefditoren pivoxil crystal, EPO, Eudragit EPO, L100, Eudragit L100, S100, Eudragit S100 ($n = 3$).

The surface of Eudragit EPO had a remarkably greater value of K_D than those of the other samples. The results of $-\Delta G^{AB}$ of the three polar probes indicated that these probes had the stronger acid–base interaction with Eudragit EPO than the other samples, suggesting that the greater value of K_D was caused by dimethylaminoethyl groups having a basic nature.

The basic to acidic parameter ratios (K_D/K_A) of cefditoren pivoxil crystal and Eudragits are shown in Fig. 7. Values of K_D/K_A of greater than 1 mean a basic nature on a solid surface, and values of less than 1 imply an acidic nature. Accordingly, the surface of cefditoren pivoxil crystal was slightly acidic, and the surface of Eudragit EPO was obviously basic, and the surfaces of Eudragit L100 and S100 were definitely acidic. The results of Eudragits all corresponded to an acidic or a basic nature obtained from the solubility behaviours, but the result of cefditoren pivoxil was different from that predicted. The values of K_D/K_A of cefditoren pivoxil and Eudragits demonstrated that any acid–base incompatibility would be due to the acid–base interaction between carbonyl groups having an amphoteric nature on the surface of cefditoren pivoxil and dimethylaminoethyl groups having a basic nature on the surface of Eudragit EPO. The observed compatibility with the acidic Eudragit L100 and S100 was due to the absence of the basic groups from the surface of cefditoren pivoxil.

4. Conclusions

It has been shown that it is possible to use acid–base contributions to evaluate incompatibility due to acid–base interaction at the interface between solids, which could not be predicted from the chemical structural features or solution state properties. For this reason, IGC is a valuable tool in preformulation, not just for vital physical information, but also to make rational excipient selections.

Acknowledgements

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