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Determination of the changes in surface energetics of cefditoren pivoxil as a consequence of processing induced disorder and equilibration to different relative humidities

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Abstract

The change in surface energy of cefditoren pivoxil powder as a consequence of changes in crystallinity (caused by milling duration) was studied using inverse gas chromatography (IGC) under dry conditions. The surface of the powder became more basic with decreasing crystallinity. It was suggested by considering the results of IR spectra that this resulted from exposure of the carbonyl groups, which have electron donating nature, on the particle surface. There was a direct correlation between surface energy and the % amorphous content induced during milling, giving the opportunity to use IGC to quantify amorphous content for this material. Furthermore, the changes in the acidic and basic properties on the surface of amorphous cefditoren pivoxil powder were investigated using IGC under various relative humidities (RHs). The basic nature on the surface of amorphous cefditoren pivoxil decreased with increasing RH, with a dramatic fall between 0 and 10% RH, this was attributed to water preferentially shielding the exposed carbonyl groups from acidic polar probes. Since water molecules would be adsorbed to the most hydrophilic sites at initial RH increment, it seems reasonable to suppose that the most hydrophilic adsorption sites on the surface of amorphous cefditoren pivoxil are the exposed carbonyl groups.

Keywords: Inverse gas chromatography; Surface energy; Amorphous; Milling; Cefditoren pivoxil

1. Introduction

It is clear from anecdotal reports that milled materials can give rise to variability in performance, for example, changes in wet granulation processing or variability in performance of inhalation aerosols. It is known that crystalline materials can become partially amorphous during milling and it is reasonable to believe that the changes in surface energy that accompany the conversion to the amorphous state (see, e.g., Newell et al., 2001a,b) may be critical in determining how the material behaves during product manufacture and use. Consequently, it is very important to assess the surface properties of drugs that become amorphous during milling. There are also advantages to studying the surface energy as a function of relative humidity (RH) as the physical and chemical stability of an amorphous drug can be affected by sorption of water (Andronis and Zografi, 1998; Larsen et al., 1997; Pikal and Rigsbee, 1997).

Inverse gas chromatography (IGC) is a highly sensitive technique and has been used to show that the

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dispersive surface energy (γ_S^D, which is the apolar component of surface energy) for some pharmaceutical materials decreases with increasing RH (Newell et al., 2001a,b). It has been demonstrated that not only the value of γ_S^D but also the specific energies of adsorption of polar probes, $-\Delta G_A^{SP}$ (essentially the polar component of surface energy) for crystalline drugs changes as RH is raised. The interaction sites of water molecules on powder surfaces have been identified using the combination of IGC and a molecular modeling procedure (Sunkersett et al., 2001). The basic/acidic parameter ratio, K_D/K_A, calculated from the values of $-\Delta G_A^{SP}$, can be used to describe the acidic and basic nature of the powder surface. Ahfat et al. (2000) have described that a correlation may exist between the values of K_D/K_A determined by IGC and the electrostatic charges for some pharmaceutical materials.

It has already been reported that the crystallinity of cefditoren pivoxil, a cephalosporin antibiotic, decreases with an increase in the grinding time in a vibration mill, and after 30 min grinding of the crystalline material is completely converted to the amorphous state (Ohta et al., 1999). The amounts of water adsorbed to 30 min ground cefditoren pivoxil powder at 293 K and 0, 10, 20, 30, 40, and 50% RH have also been determined from a water vapour adsorption isotherm, and the values were as follows; 0, 0.321, 0.562, 0.837, 1.125, and 1.452%, respectively (Ohta et al., 2000). Further, results of enthalpy of water sorption have demonstrated that the proportion of hydrophilic sorption sites on cefditoren pivoxil powder increases with a decrease in the crystallinity (Ohta et al., 2000). Results of infrared (IR) spectra have suggested that the increase in hydrophilicity may be due to the changes in the environment of carbonyl groups in two esters and one amide (Ohta et al., 2000). However, the hydrophilic sorption sites of cefditoren pivoxil powder, which are increasing with decreasing crystallinity, have not obviously been determined.

The aim of this study was to study the change in the values of K_D/K_A for cefditoren pivoxil as a function of crystallinity, using IGC under dry conditions, to see if it was possible to determine the nature of the exposed chemical group on the surface of the amorphous powder. A further aim was to study the impact of RH on the surface energy to see if it was possible to use such data to further understand the amorphous state.

2. Materials and methods

2.1. Materials

Cefditoren pivoxil was synthesised at Meiji Seika Kaisha Ltd. (Tokyo, Japan). Organic solvents were of analytical reagent grade.

2.2. Ground cefditoren pivoxil

Three grams of cefditoren pivoxil was ground in a vibration mill (model TI-200, CMT, Tochigi, Japan) for 1–30 min. The grinding cell was made of aluminum oxide.

The crystallinities of these samples were determined according to Ruland's (1961) method using the powder X-ray diffraction patterns as described previously by Ohta et al. (1999). The intact and 1, 3, 5, 10, 20, and 30 min ground cefditoren pivoxil had the following values of crystallinity (disorder parameter in parenthesis); 71.7% (1.3 Å^2), 53.3% (1.9 Å^2), 33.1% (2.4 Å^2), 25.8% (2.8 Å^2), 18.3% (3.2 Å^2), 10.5% (3.2 Å^2), 9.4% (3.4 Å^2), respectively (Ohta et al., 1999). The samples used in this study were the same as those used previously, and the crystallinities of the samples obtained from the powder X-ray diffraction patterns were rechecked and shown to be essentially the same as reported in the previous study (Ohta et al., 1999).

2.3. Inverse gas chromatography

Experiments were performed using an inverse gas chromatograph (Surface Measurement System Ltd.). The cefditoren pivoxil powders were passed through a 150 μm sieve prior to being packed into glass columns. Approximately, 400 mg of cefditoren pivoxil powder was packed into the silanised glass columns (Surface Measurement System Ltd.), which were 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 cefditoren pivoxil powder was carried out at 303 K and RHs varied between 0 and 50% for 3 h, and the experiment was performed at the same temperature and RHs as the conditioning.

Methane was used for the inert reference, *n*-deacane, *n*-nonane, *n*-octane, *n*-heptane and *n*-hexane were used to determine the dispersive surface energies, acetone was employed to probe the acidic nature of the surface, and the both chloroform and ethanol were employed to determine the basic nature of the surface. The gas flow rate used was 10 ml/min. Each probe was injected three times to give a measure of the reproducibility.

Using a differential scanning calorimeter (model Pyris 1, Perkin-Elmer, OH), no significant changes of the peak area due to the crystallisation were observed for the ground cefditoren pivoxil powder between before and after measurements using IGC. The DSC study was performed using a heating rate of 10 °C/min under a nitrogen gas flow using a non-hermetically sealed aluminum pan. The sample weights were about 5 mg. For the calibration of enthalpy determination, indium of 99.99% purity was used.

2.4. Determination of dispersive surface energies

The retention times for an homologous series of alkane probes were used to calculate the dispersive surface energies of cefditoren pivoxil samples. The equations for this analysis have been firmly established for some time (Condor and Young, 1979) and have been reproduced recently by Planinšek et al. (2001). Data were treated exactly as described by Columbano et al. (2003) with dispersive energies calculated from the gradient of a plot of $RT \ln V_{N^o}$ versus $a(\gamma_L^D)^{1/2}$, where R is the gas constant, T the absolute temperature, V_{N^o} the retention volume, a the surface area of the probe molecule, γ_L^D the dispersive surface energy of the probe.

2.5. Determination of acidic and basic parameters

The retention behaviour of polar probes on the $RT \ln V_{N^o}$ versus $a(\gamma_L^D)^{1/2}$ plot, results in responses that are located above the line drawn through the alkane probe results. The vertical distance between the data points of the polar probes and the alkane line gives the specific energy of adsorption, $-\Delta G^{AB}$. According to the Gutmann's (1978) acid–base concept, liquids are characterised as an electron donor or base number, DN, and an electron acceptor or acid number, AN. AN is corrected to take into account dispersive contributions by Riddle and Fowkes (1990) to give AN*. The value of $-\Delta G^{AB}$ has been related to the acidic or electron accepting parameter, K_A, and the basic or electron donating parameter, K_D, as described in Eq. (1):

$$-\Delta G^{AB} = K_A \mathrm{DN} + K_D \mathrm{AN}^* \tag{1}$$

By measuring the value of $-\Delta G^{AB}$ for polar probes, a linear plot of $-\Delta G^{AB}/\mathrm{AN}^*$ versus $\mathrm{DN}/\mathrm{AN}^*$ was obtained. The values of K_A and K_D of cefditoren pivoxil samples were determined from the gradient and intercept of the line, respectively. The selection of probe vapours was based on the fact that tetrahydrofuran is reported to damage seals in the IGC instrument and diethyl ether and ethyl acetate had previously been observed to result in broad peaks with cefditoren pivoxil (not reported in Ohta et al., 1999, but observed during that study).

3. Results and discussion

3.1. Effect of grinding on surface energy

The dispersive surface energies, γ_S^D, for intact and ground cefditoren pivoxil under dry conditions are shown in Fig. 1. The value of γ_S^D of the 1 min ground material was higher than that of the intact material, and then the values of γ_S^D of the materials ground for above 1 min gradually decreased with decreasing crystallinity. Newell et al. (2001a,b) have reported that the values of γ_S^D of partially amorphous materials are higher than that of an intact material, which is intuitive as one would expect the amorphous state to be higher energy. On the other hand, York et al. (1998) have demonstrated that as particle size of D,L-propranolol hydrochloride decreases during milling, the value of γ_S^D increases until a critical point is reached where there is a plateau followed by a small decrease for the finest powder. They have suggested that the mechanism of size reduction below the critical point is one of particle attrition rather than fragmentation. The mean particle diameters, d_{mean}, of intact and ground cefditoren pivoxil have already been determined, the value of d_{mean} of intact material is 16.5 μm and those of ground materials are not significantly changed between 8.2 and 9.4 μm regardless of the grinding time (Ohta et al., 2000). The critical size for cefditoren

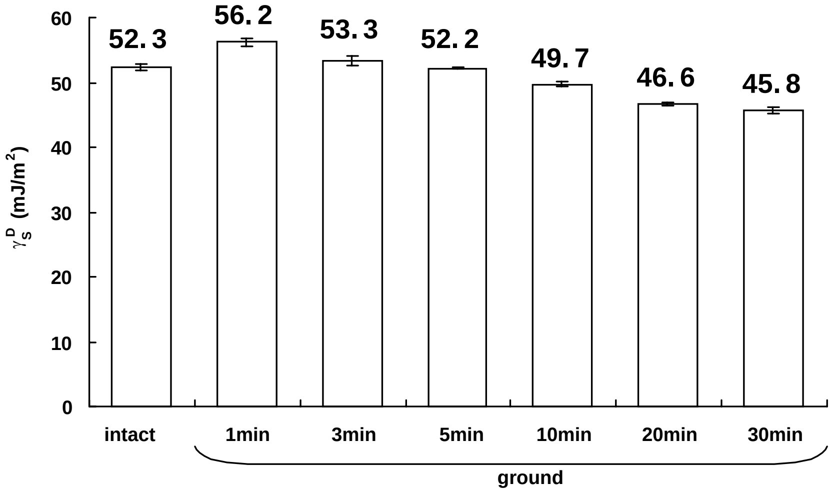

Fig. 1. The dispersive surface energies for intact and ground cefditoren pivoxil under dry conditions.

pivoxil has not been determined, but it is possible that it will link to the observed changes in surface energy.

3.2. *Effect of grinding on acidic and basic parameters*

The acidic, K_A, and basic parameters, K_D, for intact and ground cefditoren pivoxil under dry conditions are shown in Figs. 2 and 3, respectively. The value of K_A of cefditoren pivoxil gradually decreased with decreasing crystallinity, on the contrary the value of K_D gradually increased. The degree of both the acidic and basic parameters was linked to the crystallinities of the materials, with a correlation coefficient of 0.959 and −0.961, respectively. These results implied that the surface of cefditoren pivoxil particle interacted more strongly with acidic material and weakly with basic material with decreasing crystallinity. The basic to acidic parameter ratio, K_D/K_A, has been used to describe the overall acidic or basic nature of solid materials because K_A and K_D of a solid are independent of each other in most cases. The values of K_D/K_A for intact and ground cefditoren pivoxil under dry condi-

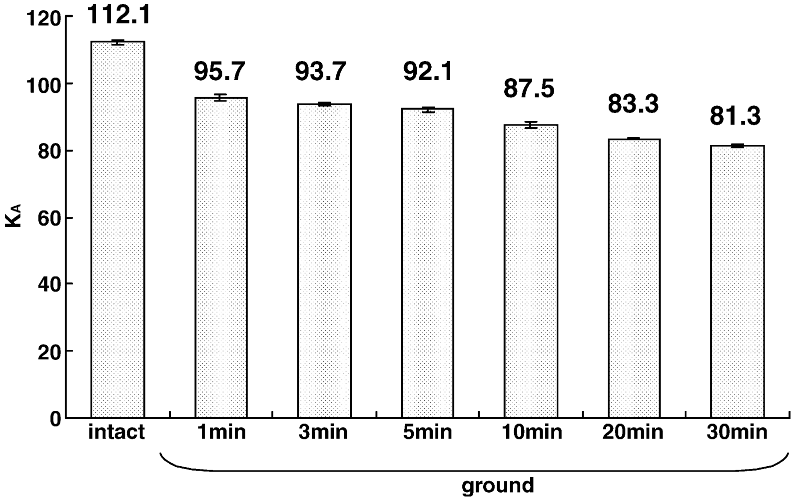

Fig. 2. The acidic parameters for intact and ground cefditoren pivoxil under dry conditions (y-axis shows $K_A \times 10^3$).

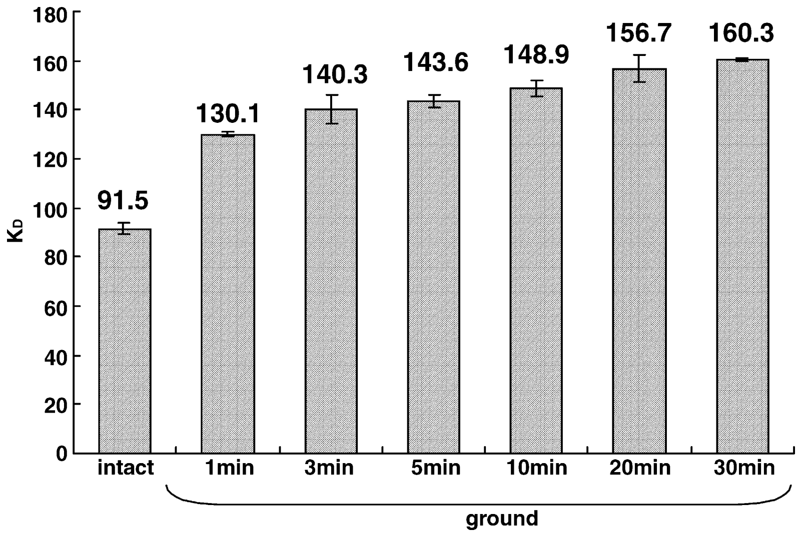

Fig. 3. The basic parameters for intact and ground cefditoren pivoxil under dry conditions (*y*-axis shows $K_D \times 10^3$).

tions are shown in Fig. 4. Values of K_D/K_A of greater than 1 mean a basic nature on the surface of a solid, and values of less than 1 mean an acidic nature. Therefore, these results implied that the surface of the intact material particle was slightly acidic since the value of K_D/K_A was approximately 0.8, the surface of the particle became more basic with decreasing crystallinity, and then the surface of the 30 min ground material particle was highly basic since the value of K_D/K_A was approximately 2.0. This indicated that the surface of cefditoren pivoxil powder became more basic, or electron donating, as the grinding proceeded. The changes in the environment of the carbonyl groups in two esters and one amide of cefditoren pivoxil with decreasing crystallinity have been reported (IR spectroscopy; Ohta et al., 2000). Consequently, the increase in the value of K_D/K_A for cefditoren pivoxil with decreasing crystallinity would result from exposing these car-

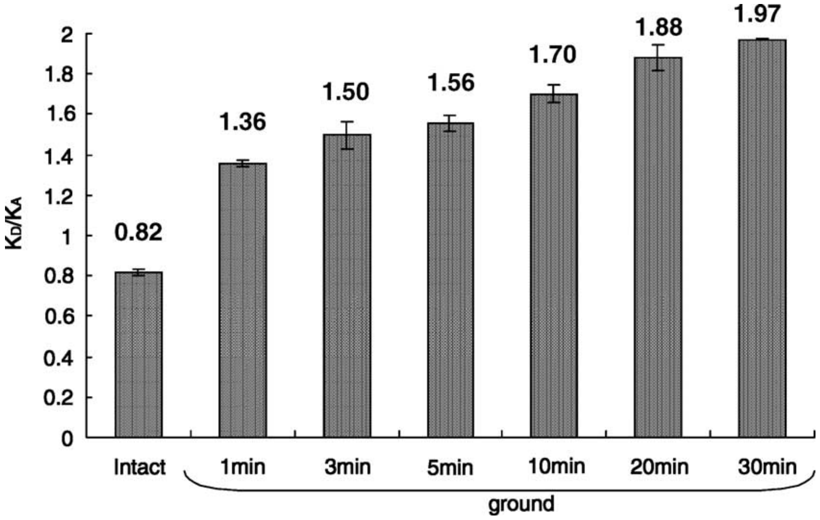

Fig. 4. The basic to acidic parameter ratios for intact and ground cefditoren pivoxil under dry conditions.

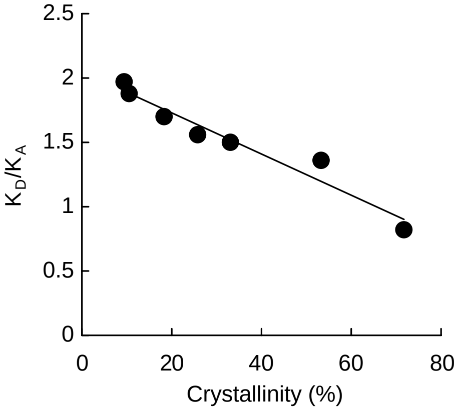

Fig. 5. The relationship between crystallinity and basic to acidic parameter ratios for cefditoren pivoxil.

bonyl groups, which have electron donating nature, on the particle surface through the grinding process. According to the result of crystal structure analysis of cefditoren pivoxil (Yasui et al., 1998), most ester and amide groups are located inside the crystal face, however the grinding process would make the surface of cefditoren pivoxil powder have the higher concentration of exposed ester and amide groups.

The relationship between crystallinity and the value of K_D/K_A for cefditoren pivoxil is shown in Fig. 5. A good linear correlation was observed between the two parameters, with a correlation coefficient of −0.972, consequently the ratio of K_D/K_A can be used to quantify the crystallinity for this material. The increase in the value of K_D/K_A for cefditoren pivoxil with decreasing crystallinity corresponded to the increase in the partial solubility parameter relating to hydrogen bonding and polar interactions, which has been previously demonstrated (Ohta et al., 1999).

3.3. Effect of humidity on surface energy

The values of γ_S^D for 30 min ground cefditoren pivoxil at a range of RHs are shown in Fig. 6. It could be seen that the value of γ_S^D for the 30 min ground cefditoren pivoxil decreased non-linearly, with the greatest fall being between 0 and 10% RH, this fall at low RH is in keeping with the shape of the sorption isotherm at 298 K (Ohta et al., 2000). Balard et al. (1997) have demonstrated that the presence of sorbed water decreases the value of γ_S^D for clays determined using IGC, and they have proposed that this is due to water shielding the high energetic interaction sites from organic probes. Therefore, the decrease in the value of γ_S^D for amorphous cefditoren pivoxil could also be caused by the blocking effect of the sorbed water, which would be expected to first accumulate at the higher energetic sites on the particle surface. IGC under various RHs could be regarded as a valuable technique by which the variation in the interaction extent between water molecules and solid surface could be evaluated.

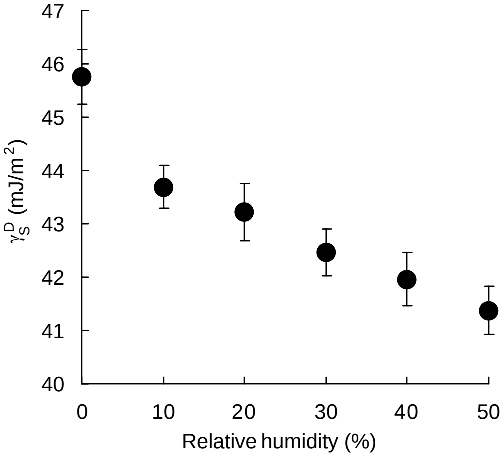

Fig. 6. The dispersive surface energies for 30 min ground cefditoren pivoxil at a range of relative humidities.

3.4. Effect of humidity on acidic and basic parameters

The values of K_A, K_D, and K_D/K_A for 30 min ground cefditoren pivoxil at a range of RHs are shown in Figs. 7–9, respectively. The value of K_A was observed to decrease gradually with an increase in RH, and the values of K_D and K_D/K_A were seen to decrease, with a dramatic fall between 0 and 10% RH. Sunkersett et al. (2001) have studied the changes in the surface energetic parameters of paracetamol under conditions of 0 and 47% RH, the value of γ_S^D remains constant and the specific energies of adsorption of polar probes, $-\Delta G_A^{SP}$, either remain constant or decrease by up to 10%, and then they have proposed that where the water molecules are adsorbing to the same sites as the polar

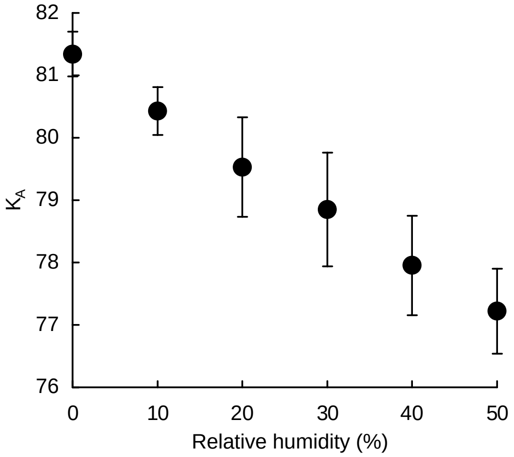

Fig. 7. The acidic parameters for 30 min ground cefditoren pivoxil at a range of relative humidities (y-axis shows $K_A \times 10^3$).

probes, the interaction of polar probes with the surface is decreased.

By considering the discussion above, the dramatic decreases in the value of K_D and K_D/K_A between 0 and 10% RH should be attributed to water preferentially shielding the carbonyl groups, which have electron donating nature. Since water molecules would be adsorbed to the most hydrophilic sites at the initial RH increment, it seems reasonable to suppose that the most hydrophilic adsorption sites on the surface of amorphous cefditoren pivoxil are the exposed carbonyl groups. The gradual decrease in the value of K_A for amorphous cefeditoren pivoxil powder as RH was raised would mean that the preferential sorption sites of water molecules were different from those of basic polar probes below 50% RH.

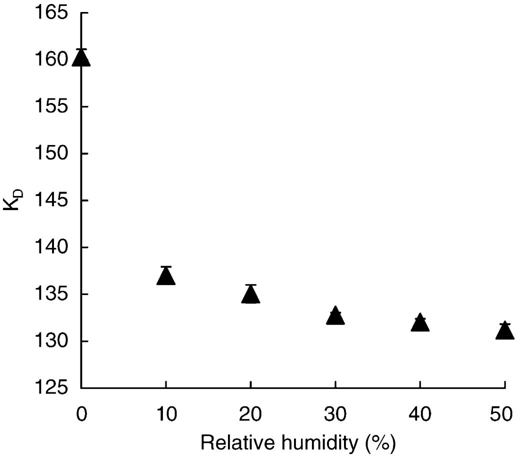

Fig. 8. The basic parameters for 30 min ground cefditoren pivoxil at a range of relative humidities (y-axis shows $K_D \times 10^3$).

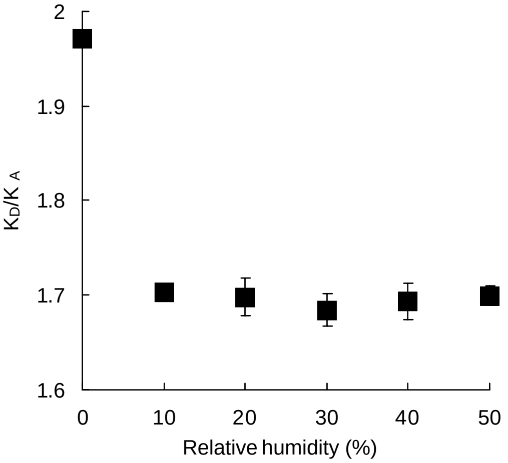

Fig. 9. The basic to acidic parameter ratios for 30 min ground cefditoren pivoxil at a range of relative humidities.

4. Conclusions

Based on the combination of K_D/K_A using IGC under dry conditions and IR spectroscopy (previously published), it is concluded that an increase in the dominance of the carbonyl groups, which have electron donating nature, exposed on the surface caused an increase in the basic nature of cefditoren pivoxil powder following processing induced reduction in crystallinity. Furthermore, the value of K_D/K_A was more suitable than the value of γ_S^D to express crystallinity of the surface of this material, i.e. the acid/base did and the dispersive surface contribution did not, change in proportion to amorphous content.

It was determined by using IGC with various RHs that the most hydrophilic sorption sites of amorphous cefditoren pivoxil powder were the carbonyl groups exposed on the surface. The determination of the value of K_D/K_A by IGC under various RHs was found to be a useful method to clarify the most hydrophilic sorption sites. The dramatic decrease in the value of K_D/K_A indicated that there was a competitive sharing of the same chemical site by organic probes and water molecules on the surface of an amorphous solid.

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