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Research paper

The influence of measurement conditions on the Hammett acidity function of solid pharmaceutical excipients

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Abstract

In this work the Hammett acidity function has been measured to assess the *relative acidity* of excipients used in the preparation of pharmaceutical solid dosage forms. A systematic series of experiments is reported which illustrates how the selection of the measurement conditions can influence the results of such determinations. Although the technique is somewhat empirical and relies on several key assumptions it is shown that very consistent results can be achieved by carefully controlling the measurement conditions. It is also shown that by taking this approach laboratory-to-laboratory variation can be reduced to a negligible level and the influences of subtle changes in the acidity of pharmaceutical excipients due to intrinsic variations in their physical properties or due to different processing histories can be detected and quantified.

Keywords: Excipient; Hammett acidity function; Equivalent pH

1. Introduction

The micro-environmental acidity within pharmaceutical dosage forms is of great interest to pharmaceutical scientists, primarily because of its links to performance and the chemical stability of the active pharmaceutical components [1–8]. The acidity of aqueous solutions is conventionally measured in terms of the relative concentration of hydrogen ions present and is expressed using the well-known logarithmic pH scale [9]. However, the pH scale is only appropriate for use with dilute aqueous solutions. To extend the pH and pKa concepts to highly concentrated aqueous solutions, Hammett proposed an acidity function based on the use of dye indicator molecules that change color as their protonation changes [10]. The Hammett acidity function, H, was defined in terms of the ionization of a neutral acidic indicator ($HA \leftrightarrow A^- + H^+$) as:

$$H = \log\left[\frac{c_{A-}}{c_{HA}}\right] + pK_a = -\log a_{H+}\left[\frac{f_{A-}}{f_{HA}}\right] \quad (1)$$

where c, f and a_H are the indicator concentration, indicator activity coefficient and proton activity, respectively. Subsequently, the derivation and use of the Hammett acidity function has been extended to non-aqueous solutions [9,11,12], solid surfaces [13,14], and amorphous solids [15,16]. Even so, for solid samples the concept of acidity is still very complex, mainly because of their limited water content, and the quantification of acidity is correspondingly difficult.

In the pharmaceutical literature the concept of a 'solid state pH' or 'pH equivalent' has been widely described, primarily as a means of pragmatically ranking the relative acidity of solid samples [15,17]. In the work of Glombitza and co-workers [18,19] colored indicators were deposited on the surface of solid samples and the degree of indicator ionization in the environment of the solid sample was measured using diffuse reflectance UV-visible spectrophotometry. The equivalent pH of the system was then calculated from a calibration curve constructed using

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buffered aqueous solutions of the same indicator. This method of assessing acidity is analogous to the Hammett acidity approach and the values obtained using these two approaches can be shown to be equivalent, provided that the ratio of the extinction coefficients of protonated and unprotonated indicator species in the solid state is similar to that in solution [15]. This has been proven to be a reasonable assumption for several different indicators [15].

Prior to adopting measurements of the equivalent pH or the Hammett acidity function for assessing the acidity of solid pharmaceutical samples it is important to understand the influences of the measurement conditions on the experimental results obtained. This is necessary in order to achieve a robust analytical method and to be confident of achieving consistent and reliable data. The work described in this article is aimed at investigating the effects of measurement conditions on the Hammett acidity function of some common pharmaceutical excipient powders, specifically the influences of the sample presentation method, operator-to-operator variations, across instrument differences, sample lot-to-lot differences, day-to-day experimental variability, and different sample preparation methods.

2. Materials and methods

2.1. Materials

Sodium salts of bromocresol green (BG), phenol red (PR) and thymol blue (TB) were selected as indicators which could cover a wide range of pH values (Table 1). High purity samples of each were obtained from Sigma-Aldrich Co. (St. Louis, MO, USA). The materials selected for this study were common solid dosage formulation excipients (Table 2). Microcrystalline cellulose (Avicel PH105; Avicel PH101) and croscarmellose sodium (Ac-Di-Sol) were obtained from FMC Corporation (Philadelphia, PA, USA), calcium carbonate (GCC 300) from Particle Dynamics Inc. (St. Louis, MO, USA), dibasic calcium phosphate (A-TAB) from Rhodia Inc. (Cranbury, NJ, USA), magnesium stearate from Mallinkrodt (Hazelwood, MO, USA), sodium bicarbonate USP powder from EM Science Inc. (Gibbstown, NJ, USA) and pre-gelatinized starch (Starch 1500) from Colorcon (West Point, PA, USA). They were used as received from the suppliers and stored at controlled laboratory conditions (22±2 °C and 40±5% RH). Pure methanol (HPLC grade) was used as solvent for the indicators and was obtained from J.T. Baker (Phillipsburg,z NJ, USA).

2.2. Methods

The relationship between the pH and visible spectra of aqueous indicator solutions that had been buffered to various pH values was used to quantify the indicator ionization state in solution and as deposited onto excipient powder surfaces. This approach is analogous to that used by Glombitza et al. [18]. The following techniques were used to prepare all of the samples unless otherwise specified.

2.2.1. Indicator solutions

Solutions of the indicators for deposition onto the solid samples were prepared by dissolving them in pure methanol at a concentration of 1 mg per ml. These conditions were selected to ensure that sufficient indicator could be deposited on the sample whilst minimizing any potential for dissolution of the sample.

2.2.2. Indicator treated excipients

The excipient-indicator combinations and the final indicator concentrations used are shown in Table 2. The indicator concentrations were selected to obtain less than one hundred percent theoretical coverage of the excipient surface with indicator (Table 3) and thus minimize any potential for aggregation of the indicator molecules upon deposition.

The excipient samples were approximately ten grams in weight and were prepared by addition of the methanol-indicator solutions using a 3-ml volumetric syringe (Becton Dickinson and Co., Franklin Lakes, NJ, USA). The materials were mixed gently with a pestle and mortar to ensure uniform distribution of the indicator. The mixtures were then dried in a vacuum oven (Model 1410, VWR Scientific Products, Boston, MA) at 40±2 °C for 48 h to remove any residual methanol from the excipient surface. After drying, the materials were gently mixed again using the pestle and mortar to eliminate any large aggregates that may have formed during sample preparation. Prior to and in-between measurements the indicator treated samples were

Table 1
pH calibration data for the various indicators (in solution)

Indicator and concentration	pK_a	Buffer	pH range[a]	Regression equation[b]	R^2
Thymol blue (acidic range) (20 μg/ml)	1.6 [27]	Hydrochloric acid	1.64–2.73	$y=-0.91x+1.82$	0.997
Thymol blue (alkaline range) (20 μg/ml)	9.0 [28]	Phosphate (50 mM)	7.76–8.74	$y=0.92x-7.89$	0.995
Bromocresol green (20 μg/ml)	4.7 [29]	Citrate (20 mM)	3.38–4.84	$y=0.92x-4.05$	0.999
Chlorophenol red (10 μg/ml)	6.0 [30]	Citrate (20 mM)	3.98–6.08	$y=1.01x-5.59$	0.992
Phenol red (8 μg/ml)	7.9 [30]	Phosphate (50 mM)	6.04–7.92	$y=0.94x-6.97$	0.996

[a] The pH range represents the range over which the equation was generated.
[b] y = log 10 (signal ratio), x = solution pH.

Table 2
Excipient samples and their preparation

Excipient name (abbreviation)	Grade	Indicator	Solvent	Indicator concentrations	
				Solution[a] (mg/ml)	Excipient[b] (mg/g)
Microcrystalline cellulose (MCC)	Avicel PH 101	Bromocresol green	Methanol	1.0	0.2
	Avicel PH 105	Bromocresol green	Methanol	1.0	0.2
Croscarmellose sodium (CS)	Ac-Di-Sol	Bromocresol green	Methanol	1.0	0.2
Calcium carbonate (CC)	GCC-300	Phenol red	Methanol	1.0	0.2
Dibasic calcium phosphate anhydrous (DCP)	A-TAB	Thymol blue	Methanol	1.0	0.1 and 0.2
Magnesium stearate (M)	Vegetable derived	Phenol red	Methanol	1.0	0.2
Sodium bicarbonate (SB)	USP, powder	Thymol blue	Methanol	1.0	0.1
Pre-gelatinized starch (S)	Starch 1500	Bromocresol green	Methanol	1.0	0.2

[a] Weight of indicator (mg) per volume of solution in methanol (ml).
[b] Weight of indicator (mg) per weight of excipient (g) in solid state.

stored under controlled laboratory conditions (22 ± 2 °C and 40 ± 5% RH).

To correct the measured reflectance spectra of the indicator treated materials for any potential color changes of the excipient alone during preparation, blank samples of each of the excipients were prepared as described above, with the use of pure methanol in place of the indicator solution.

2.2.3. Instrumentation

The visible spectra for all samples were recorded using a Cary 100 Bio Spectrophotometer (Varian Inc., Mulgrave, Victoria, Australia) equipped with an integrating sphere diffuse reflectance accessory (Model DRA-CA-301, Labsphere, North Sutton, NH, USA). Measurements for liquid and solid materials were conducted over a wavelength range of 400–800 nm with a scan frequency of 600 nm per minute and wavelength step interval of 1 nm. The lower limit of detection for the instrument ($F(R) = 10^{-5}$) was determined by measuring a Spectralon® reflectance standard (Labsphere®, North Sutton, NH, USA).

2.2.4. Calibration

The spectra of pH adjusted dilute aqueous indicator solutions were measured using a 10 mm path length quartz cuvette (Labsphere®, North Sutton, NH, USA) (Table 1). A Specralon® reflectance standard was placed at the back of the reflectance port to ensure that no absorption of light occurred outside of the cuvette during measurements. A cell containing pure solvent was used as a reference (blank). All measurements were conducted in duplicate. The reflectance was recorded using the log (1/R) transformation, where R is the fraction of incident light reflected by the sample. The correlation between the solution pH (measured using a calibrated pH meter) and the log of the peak height ratio between the higher and lower wavelength peaks was determined (Table 1). The peak heights at low and high wavelengths were determined as the maximum values of the log (1/R) function of the reflectance spectra.

2.2.5. Measurement of indicator treated excipients

A packed powder sample holder (Model PCH-010, Labsphere, North Sutton, NH, USA), was used for the measurements of the reflectance spectra of the indicator treated excipient powders. To help reduce specular reflection a flat stainless steel punch was used to lightly compress powder into the holder, making the sample surface as flat and as perpendicular to the incident light beam as possible. A quartz window was used to cover the sample, the approximate fill weight was 800 mg and the powder bed depth was 6–9 mm. The reflectance data obtained was transformed using the Kubelka–Munk model

Table 3
Example estimates of extent of excipient surface coverage by various indicators

Excipient	Grade	SSA mm^2/g[a]	Indicator type	Cross sectional area of indicator Ä^2 [b]	Indicator deposition level mg/g of substrate[c]	Excipient surface coverage (%)[d]
Microcrystalline cellulose	Avicel PH 101	1.3 [31]	Bromocresol green	88	0.2	11
Croscarmellose sodium	Ac-Di-Sol	0.8 [32]	Bromocresol green	88	0.2	18
Dibasic calcium phosphate anhydrous	A-TAB	17.0	Thymol blue	90	0.4	3
Magnesium stearate	Vegetable derived	5.7	Thymol blue	90	0.4	8

[a] Mean specific surface area values, measured via N_2 BET adsorption.
[b] Value calculated from molecular weight and absolute density of indicator molecule.
[c] Amount of indicator deposited on substrate.
[d] Percent surface coverage = 100 × (((number of molecules of indicator per gram of substrate) × (cross sectional area of indicator molecule))/(specific surface area of substrate)).

(Eq. (2)) [20]:

$$F(R_\infty) = \frac{(1 - R_\infty)^2}{2R_\infty} \quad (2)$$

where R_∞ is the fraction of incident light reflected by the sample. The reflectance spectra of the excipient powders treated with methanol were used for base-line correction.

2.3. Measurement conditions

The experimental variables investigated in this work and the materials used for each evaluation are summarized in Table 4. The following sections describe any special sample preparation techniques, materials, or measurement approaches not described above.

2.3.1. Operator-to-operator variation

To evaluate potential errors due to operator-to-operator variability three different operators measured the reflectance spectra of microcrystalline cellulose (Avicel PH105) and croscarmellose sodium (Ac-Di-Sol) in duplicate. Each sample evaluated was from the same lot of material and the samples were all measured on the same day. The measurement procedure included loading powder into the sample holder, generating the reflectance spectra, and analyzing the raw data.

2.3.2. Day-to-day variation

Reflectance spectra measurements for microcrystalline cellulose (Avicel PH101) ($n=5$) and croscarmellose sodium ($n=4$) were repeated after 4 days and 2 months, respectively. Samples were from the same lot in each case. Measurements included loading powder into the sample holder, obtaining reflectance spectra and analyzing the raw data.

2.3.3. Instrument-to-instrument variation

One operator measured the reflectance spectra for microcrystalline cellulose (Avicel PH105), calcium carbonate and dibasic calcium phosphate anhydrous in duplicate using two equivalent instruments (same model and manufacturer). Samples were taken from the same lots, but due to differences in the physical locations of the two instruments the measurements were conducted on different days.

2.3.4. Lot-to-lot variation

Two different lots of three excipients, microcrystalline cellulose (Avicel PH105), croscarmellose sodium and dibasic calcium phosphate anhydrous, were used to assess the effect of lot-to-lot differences on the Hammett acidity determinations. In addition to using different lots, different operators prepared (i.e. indicator deposition, drying etc.) and conducted the measurements on different days. In addition, lot-1 of the dibasic calcium phosphate anhydrous contained fifty percent less indicator than lot-2.

2.3.5. Sample holder type

Two different sample holders obtained from Labsphere® (North Sutton, NH, USA) were used to evaluate the influence of sample holder design on the results. The standard sample holder (Model PCH-010) required powder

Table 4
Measurement variables studied in this work

Effect studied	Range	Excipient(s)	Grade(s)
Operator-to-operator variation	4 operators	Microcrystalline cellulose	Avicel PH 105
		Croscarmellose sodium	Ac-Di-Sol
Day-to-day variation	0 and 4 days	Microcrystalline cellulose	Avicel PH 101
	2 months	Croscarmellose sodium	Ac-Di-Sol
Instrument-to-instrument variation	2 instruments	Microcrystalline cellulose	Avicel PH 105
		Calcium carbonate	GCC 300
		Dibasic calcium phosphate anhydrous	A-TAB
Lot-to-lot variation	2 lots	Microcrystalline cellulose	Avicel PH 105
		Croscarmellose sodium	Ac-Di-Sol
		Dibasic calcium phosphate anhydrous	A-TAB
Sample holder type	Front packing	Microcrystalline cellulose	Avicel PH 101
	Rear packing		
Indicator deposition technique	Mortar and pestle	Microcrystalline cellulose	Avicel PH 101
	High-shear mixer		
Sample density (solid fraction)	3 solid fractions (0.30, 0.47 and 0.85)	Microcrystalline cellulose	Avicel PH 101
Lubrication effects	0 and 1% lubricant	Microcrystalline cellulose	Avicel PH 101
	0, 2, 5, 10, 20, 50, and 100 min mixing	Magnesium stearate	Vegetable derived
Comparison to literature	2 publications	Microcrystalline cellulose	Avicel PH 101
		Croscarmellose sodium	Ac-Di-Sol
		Pregelatinized starch	Starch 1500
		Dibasic calcium phosphate anhydrous	A-TAB
		Sodium bicarbonate	–
		Magnesium stearate	Vegetable derived

introduction from the front of the holder, with some slight 'head space' between the powder surface and the quartz window. The alternate sample holder (Model AS 02240) permitted powder introduction from the rear of the holder and this ensured intimate contact between the powder and the quartz window. This results in a very flat powder surface that is perpendicular to the light source. Reflectance spectra of microcrystalline cellulose (Avicel PH101) samples were measured ($n=5$) in each sample holder and compared.

2.3.6. Material densification effects

Microcrystalline cellulose (Avicel PH101) powder treated with bromocresol green was prepared using a high-shear mixing process (see Section 2.3.7) and compacts were produced using flat-faced, one inch diameter tooling and an eccentric single station tablet press (F-press, Manesty, Knowsley, Merseyside, UK). The compacts were manufactured at solid fractions of 0.47 and 0.85 (± 0.01) (solid fraction = 1 − Porosity/100 [21]). The reflectance spectra of the powder (SF ~ 0.30) and compacts were measured using the standard front-loading sample holder ($n=5$).

2.3.7. Indicator deposition technique

For one indicator-excipient combination two different methods were used to deposit the indicator on the excipient powder. In the standard approach bromocresol green was deposited onto microcrystalline cellulose (Avicel PH101) by mixing using a mortar and pestle (Section 2.2.2). In the alternate method a high-shear mixer (Mi-Pro mixer-granulator, Pro-C-ept®, Zezlate, Belgium) equipped with a 1700 ml bowl and operated with impeller and chopper speeds of 600 and 2000 rpm, respectively, was used to deposit the indicator onto the excipient surface. All other aspects of sample preparation (e.g. indicator concentration, solvent, drying etc.) were identical. The high-shear mixer was also used to prepare the blank powder samples required for baseline correction.

2.3.8. Lubrication effects

To probe the potential effects of a manufacturing unit operation on the measured Hammett acidity value of a sample the reflectance spectra of microcrystalline cellulose (Avicel PH101) treated with bromocresol green were measured in the presence and absence of a lubricant as a function of mixing time. The high-shear mixing procedure outlined above (Section 2.3.7) was used to deposit the indicator onto the excipient. The material was then subdivided into two equal parts, one percent by weight of magnesium stearate was added to one of the containers, and both were then blended using a Turbula® T2C mixer (Glen Mills Inc., Maywood, NJ, USA) operated at 45 rpm. Powder aliquots from each container were collected at 2, 5, 10, 20, 50 and 100 min intervals and the Hammett acidity values determined. Blank powder samples underwent identical processing with the use of pure methanol instead of the indicator solution.

3. Results and discussion

3.1. Materials

The range of excipients selected for study is typical of that used in immediate release tablet formulations [22] and represents a diverse range of chemical structures and types. Several different grades of the most common excipients were evaluated and a few materials were chosen so that the results of this work could be directly compared with previous reports [17–19]. Because of the wide range of physical and chemical properties of the samples it was a significant challenge to identify suitable solvents for the indicators that did not either dissolve or markedly change the substrate materials. It was noted that some types of materials (e.g. film coating and wet granulation polymers) could not be studied because of their interactions (e.g. gelling) with the most likely carrier solvents. For the materials studied the amount of solvent used was minimized and care was taken during the mixing and drying operations to avoid grinding or aggregation of the powders. As a result of these precautions there were no obvious changes in appearance of samples (apart from their color) before, during, or after the deposition of the indicators.

3.2. Calibration plots

For each indicator the UV-visible transmission spectra were collected over a range of solution pH values. An example spectra is shown in Fig. 1. pH vs. peak ratio calibration curves were constructed and linear regression analysis was used to determine the best-fit function that most accurately described the data for each system (Fig. 1 and Table 1). As expected the linearity and reproducibility of these plots was very high. The regression relationships were used to calculate the corresponding Hammett function for the solid samples from their measured peak ratios (for example see Fig. 2), assuming that the ratio of the extinction coefficients of protonated and unprotonated indicator species in the solid state was similar to that in solution. Based on theoretical calculations the indicator coverage on the solid samples was significantly less than one-hundred percent (Table 3) indicating that there should have been no significant bias due to agglomeration or association of the indicator molecules on the solid surfaces.

3.3. Typical measurement variation

Variations in the results from one operator to another, from one day to the next, and from one instrument to another are each important potential sources of error in measurements of this type. The magnitude of these sources of error has not been reported by previous workers and thus it has been difficult to assess the significance of small differences in the Hammett functions of different samples up

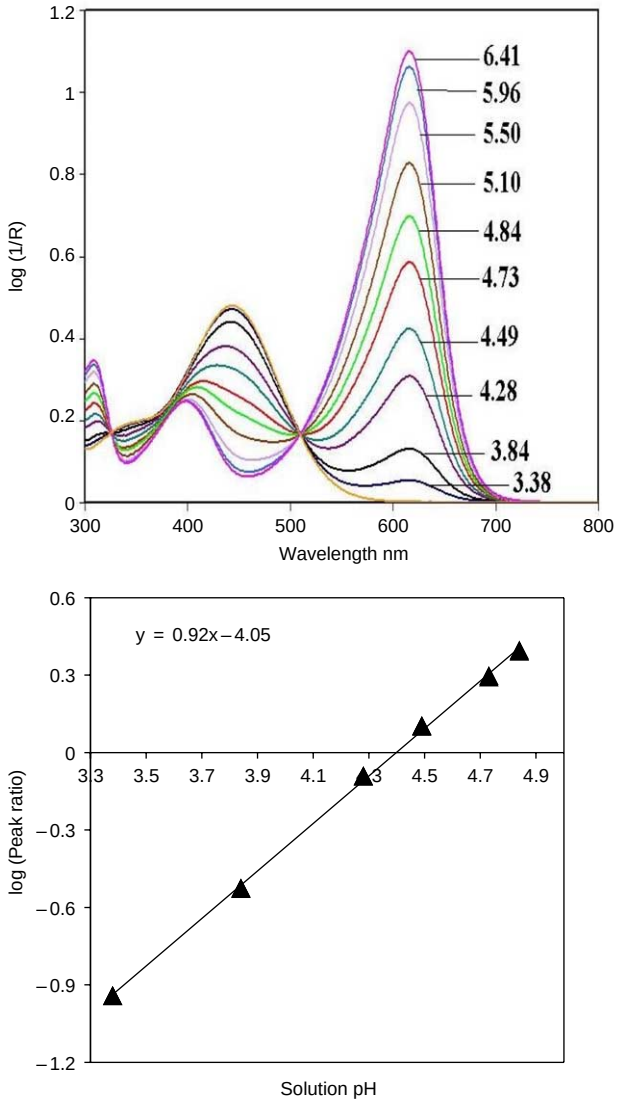

Fig. 1. UV-visible spectra of bromocresol green solutions at different solution pH values (top), and log (peak ratio) vs. solution pH plot for bromocresol green (bottom).

to this point. As part of this work, measurements of the Hammett function for several materials were repeated several times to probe the normal variation in results from day-to-day, from operator-to operator, and between different instruments.

Fig. 3 indicates that there was some operator induced variation in the absolute $F(R)$ values for the different spectra, however, the peak ratios remained very stable. This resulted in Hammett acidity values recorded by the different operators being only a few hundredths of a unit apart. It was, therefore, concluded that the magnitude of the operator-to-operator error in this work was quite small. Likewise, the intrinsic variation in the Hammett values from one day to another with a given sample and instrument was very small even over a two month period (Fig. 4). In addition, the variation in the Hammett values obtained from two different instruments operated at two separate locations

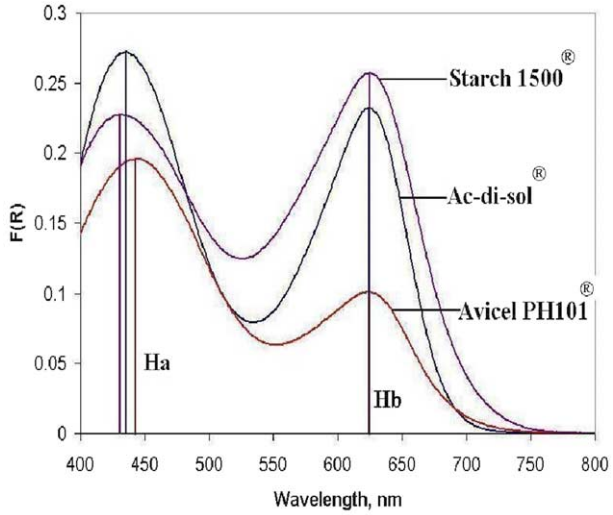

Fig. 2. Diffuse reflectance visible spectra of bromocresol green deposited on three different excipients.

by independent operators was insignificant (Fig. 5). It can be concluded, therefore, that the measurement procedures used in this work are quite robust and should be able to distinguish small differences ($\geq$0.1 units) in the Hammett acidity function of different samples.

3.4. Comparison to literature

A significant concern with this type of measurement is in the ability to reproduce data from one laboratory to another. Whilst the results described in Section 3.3 go a long way to addressing this concern, this effect can also be probed by comparing the results from this work to data previously published for analogous materials. From the current studies and the work of Glombitza et al. and Scheef et al. [17,18], there are a total of six materials in common and data for these were selected for direct comparison. Fig. 6 shows the 'equivalent pH' values previously reported plotted alongside to the data obtained in this work. The range of values covered by these materials is between two and eight pH units, and for five of the six materials the agreement between the two sets of data is within half a unit. This is very good correspondence considering that the data were generated with different sample lots, indicator lots, operators and instruments. Reassuringly there is no systematic bias, with the data from one laboratory being slightly higher than the other for exactly 50% of the materials. For one material, magnesium stearate, there is nearly a two unit discrepancy between the values reported by the different laboratories. Given the well known variability in the physical and chemical properties of this excipient it can reasonably be concluded that this difference is probably real and reflects true differences in the acidity of the lots of this material that were tested by the two groups. The magnitude of such lot-to-lot variability for other excipients is explored further in the next section.

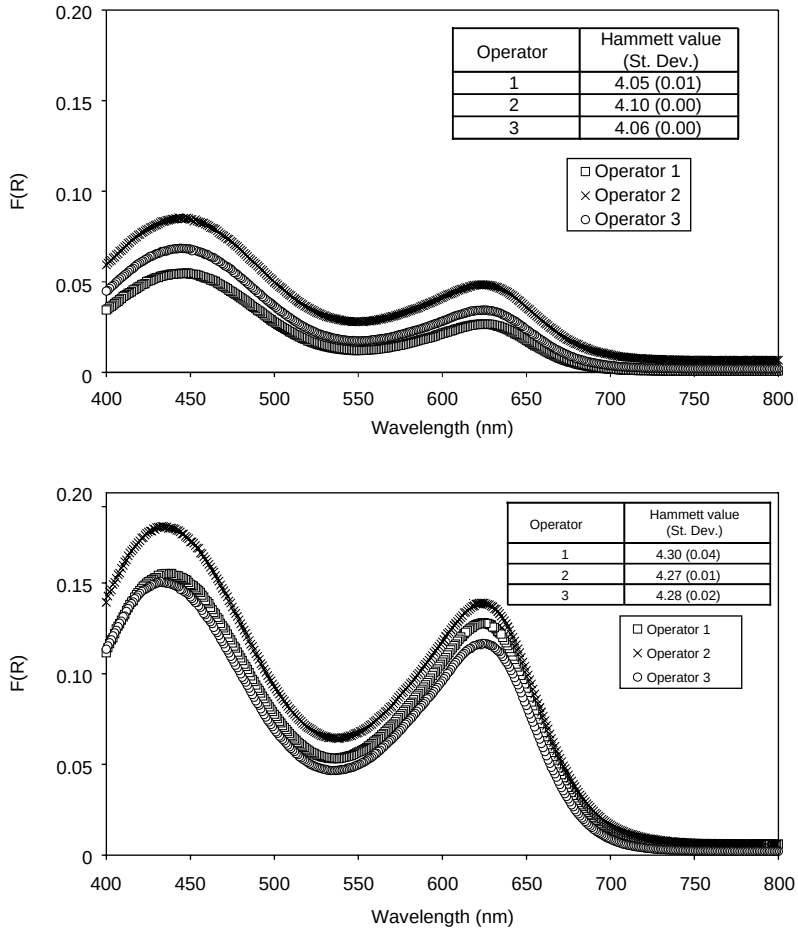

Fig. 3. Operator-to-operator variation of measured solid state spectra and Hammett values of microcrystalline cellulose (Avicel PH 105) (top) and croscarmellose sodium (Ac-Di-Sol) (bottom) (mean of $n=2$) (square—operator 1, cross—operator 2, circle—operator 3).

3.5. Lot-to-lot variation

Having established that errors that are introduced due to normal experimental variations are quite small, a study was conducted to quantify the magnitude of lot-to-lot differences in several additional excipients of interest. Two different lots of microcrystalline cellulose, of croscarmellose sodium and of dibasic calcium phosphate anhydrous were examined and the results are shown in Fig. 7. The variation in response from lot-to-lot of each of these excipients ($F(R)$ vs. wavelength plots) translated into small but significant differences in the calculated Hammett function values for the different lots. Because variations of a similar magnitude were observed for all three materials it can be concluded that variations of a few tenths of a unit are probably typical when comparing different sources of such raw materials. Consequently, if control of the micro-environmental acidity in a solid dosage formulation is critical, then acidity modifying systems (e.g. buffers, acidifiers) will need to be designed to allow for, say, at least half of a unit of variation from formulation-to-formulation.

3.6. Sample holder type

An important experimental consideration in a work of this type is the presentation of the sample to the measurement system. This is because with solid powders being considered there are particle size and sample surface roughness variations that can potentially bias the response of the measuring system. Preferred particle orientation and packing effects can be quite pronounced in other spectroscopic approaches (e.g. X-ray powder diffraction) and thus it was considered important to determine the magnitude of such effects in this work and establish if an optimal sample presentation procedure could be identified. Previous workers have not considered this experimental parameter in detail and it may offer an opportunity to markedly improve the reproducibility of these types of determinations.

For the measurement system used in this work there were two types of sample holders available. With the standard sample holder powder is introduced from the front of the holder and a quartz window is placed in front of the powder. With the alternate sample holder powder is introduced from the rear of the holder and held in place by a spring loaded

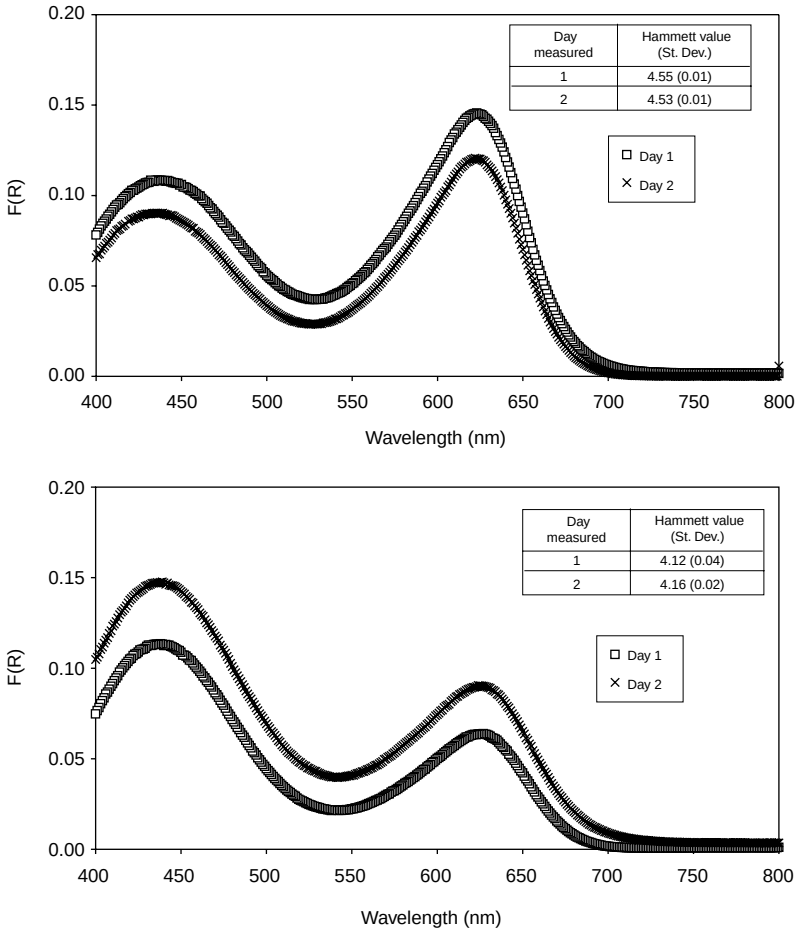

Fig. 4. Day-to-day variation of the measured solid state spectra and Hammett acidity values of microcrystalline cellulose (Avicel PH 101) (top) and croscarmellose sodium (Ac-Di-Sol) (bottom) (mean of $n \geq 4$) (square—day 1, cross—day 2).

back-plate. This ensures a more intimate contact between the powder and the quartz window. To probe the differences in performance of these two types of sample holders an excipient sample with a large particle size and irregular particles was selected vis. microcrystalline cellulose (Avicel PH101 [23]). The results of five replicate determinations using the two different sample holders are shown in Fig. 8. It is quite clear that a significant improvement in the reproducibility of the reflectance spectra can be obtained by using the alternate sample holder which permits sample

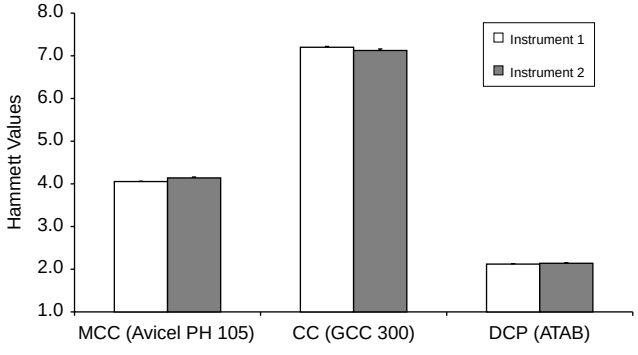

Fig. 5. Instrument-to-instrument variation of Hammett values for microcrystalline cellulose (Avicel PH 105), calcium carbonate (GCC 300) and dibasic calcium phosphate anhydrous (A-TAB) (mean of $n \geq 2$) (white bar—instrument 1, shaded bar—instrument 2).

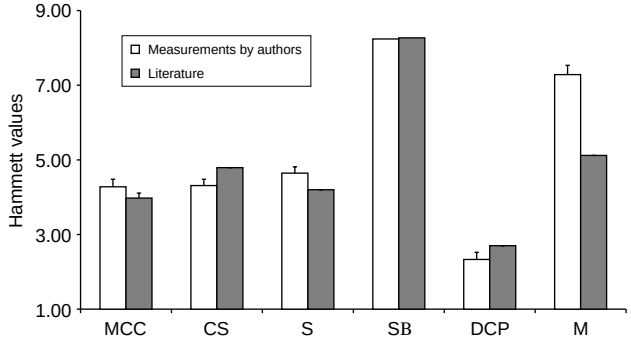

Fig. 6. Comparison of pH equivalent values for various excipients to literature data () (MCC, microcrystalline cellulose [Avicel PH 101]; CS, croscarmellose sodium: croscarmellose sodium [Ac-Di-Sol]; SB, sodium bicarbonate; S, starch pre-gelatinized [Starch 1500]; DCP, dibasic calcium phosphate anhydrous [A-TAB and DICAFOS AN (59% RH)]; M, magnesium stearate [vegetable source and unknown]) (mean ± standard deviation) (white bar—this work, shaded bar—literature values).

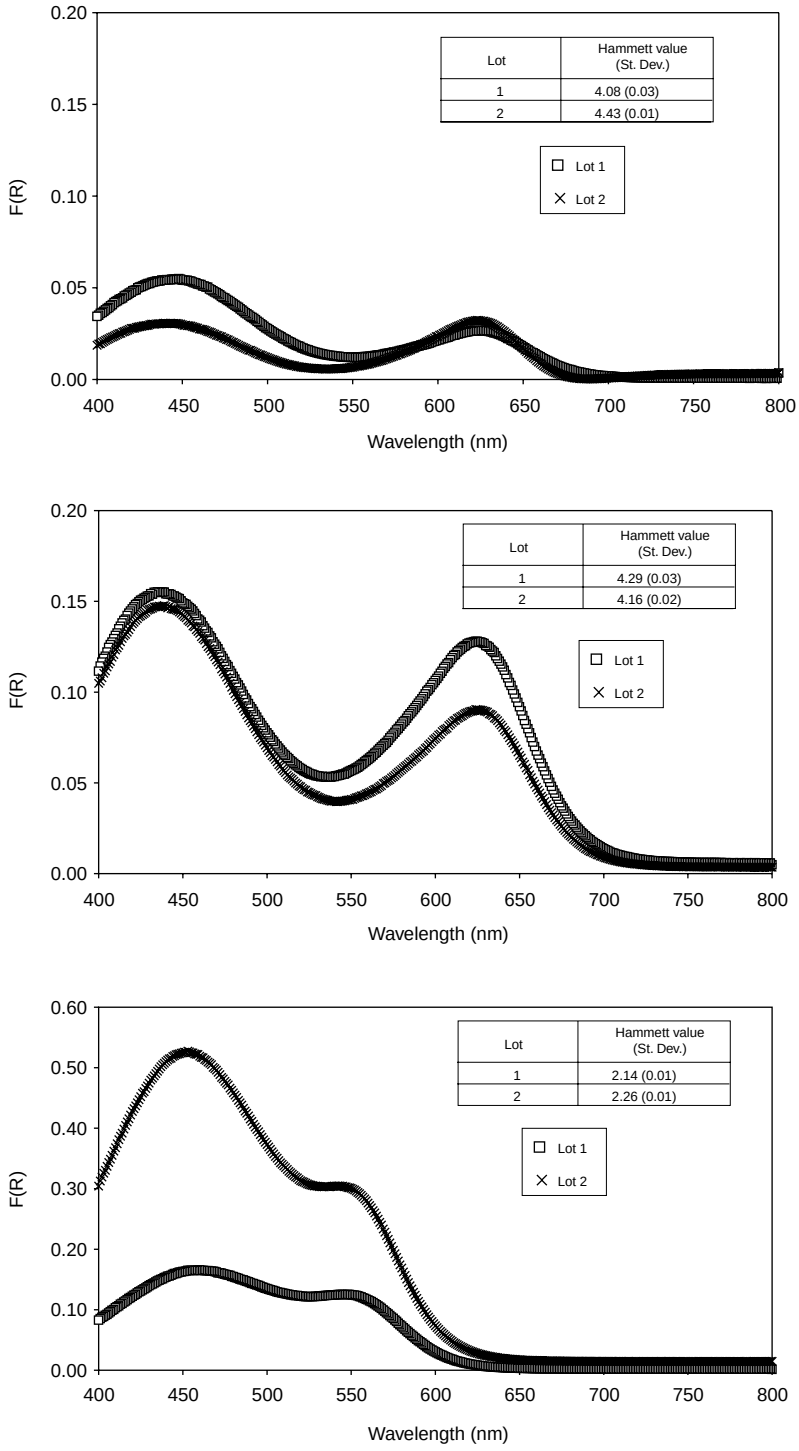

Fig. 7. Lot-to-lot variability of measured solid state spectra for microcrystalline cellulose (Avicel PH 105) (top), croscarmellose sodium (Ac-Di-Sol) (middle), dibasic calcium phosphate anhydrous (A-TAB) (bottom) (mean of $n \geq 3$) (square—lot 1, cross—lot 2).

loading from the rear. Although the calculated mean Hammett function is very similar for both sample holders the variation in the absolute value of $F(R)$ is much smaller for the alternate sample holder, and its use could significantly improve the quality of the data obtained, especially for materials with large or irregular particles, such as the Avicel PH101.

3.7. Sample density

In other spectroscopic techniques (e.g. near infra-red spectroscopy) samples are often prepared by compaction to form a regular, reproducible 'pellet' specimen. An analogous approach was investigated in this work in an attempt to further improve method robustness and

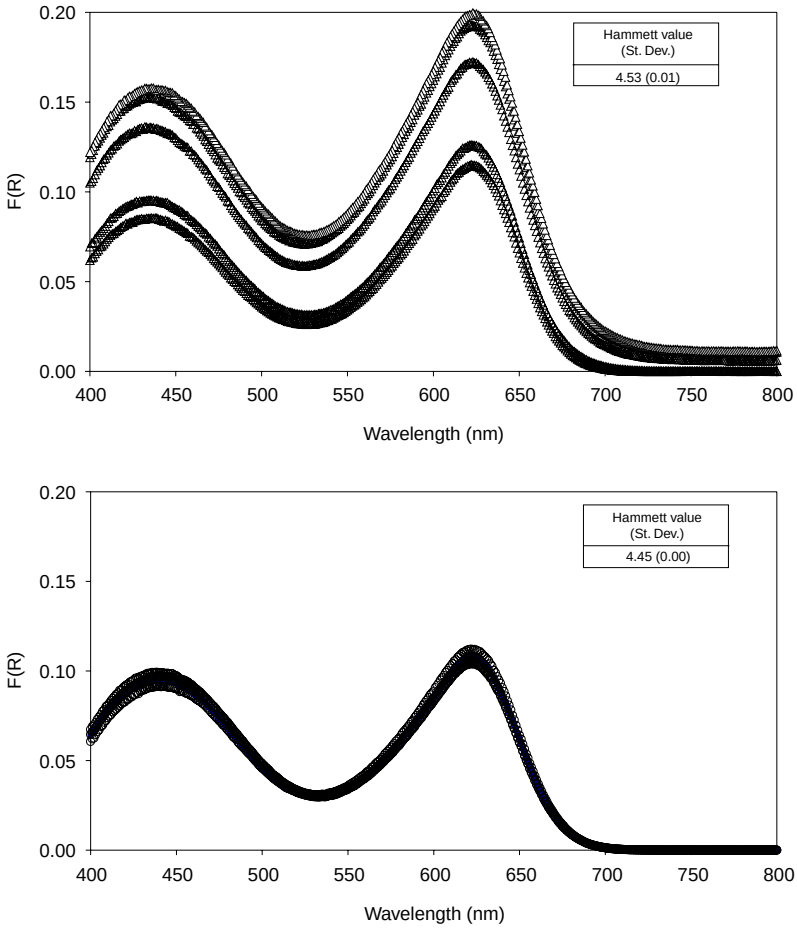

Fig. 8. Sample holder type effects on the measured solid state spectra of microcrystalline cellulose (Avicel PH 101) (front loading type (top), rear loading type(bottom)) (individual spectra of $n=5$).

reproducibility. In addition to probing the effect on data quality it was also of interest to determine if the Hammett function of compacts could be directly determined using this method because, if successful, this might indicate that the micro-environmental acidity of compressed dosage forms could be monitored in the future.

The degree of densification of a compact is described by its solid fraction (SF) (solid fraction = 1 − Porosity/100 [21]) and this is an important parameter to control in studies of this type [24]. Compressing powders into pellets or compacts creates a sample with a higher density and more regular surface texture. These features should increase the signal to noise ratio by increasing the effective surface concentration of indicator molecules and reducing specular reflectance. However, if particle fracture occurs a surface which is not covered in indicator molecules could, theoretically, be exposed.

Microcrystalline cellulose was selected for this assessment because it is very commonly compressed to form tablet dosage forms and it forms elegant compacts. Fig. 9 shows a comparison of data for a loosely packed powder sample ($SF = \sim 0.30$), and for a 'soft' and a 'hard' compact ($SF = 0.47$ and 0.85, respectively). The mean Hammett function values for each of these sample types were effectively identical and measurement variability was low in all cases. The absolute reflectance was slightly lower for the sample compressed to the highest extent, but, although not readily apparent from Fig. 9, the consistency of the measurements was greatest for this sample. Overall, it appears that compressing microcrystalline cellulose into compacts did not compromise the assessment of the sample's acidity in any significant way and this suggests that this measurement approach could be attempted with actual dosage forms in the future provided their manufacturing conditions were adequately controlled.

3.8. Indicator deposition technique

It is likely that the method by which the indicator is deposited on the surface of a solid substrate could have a significant impact upon the measured Hammett acidity function of the material. To probe this potentially important experimental variable a comparison of indicator deposition methods was conducted. The standard method,

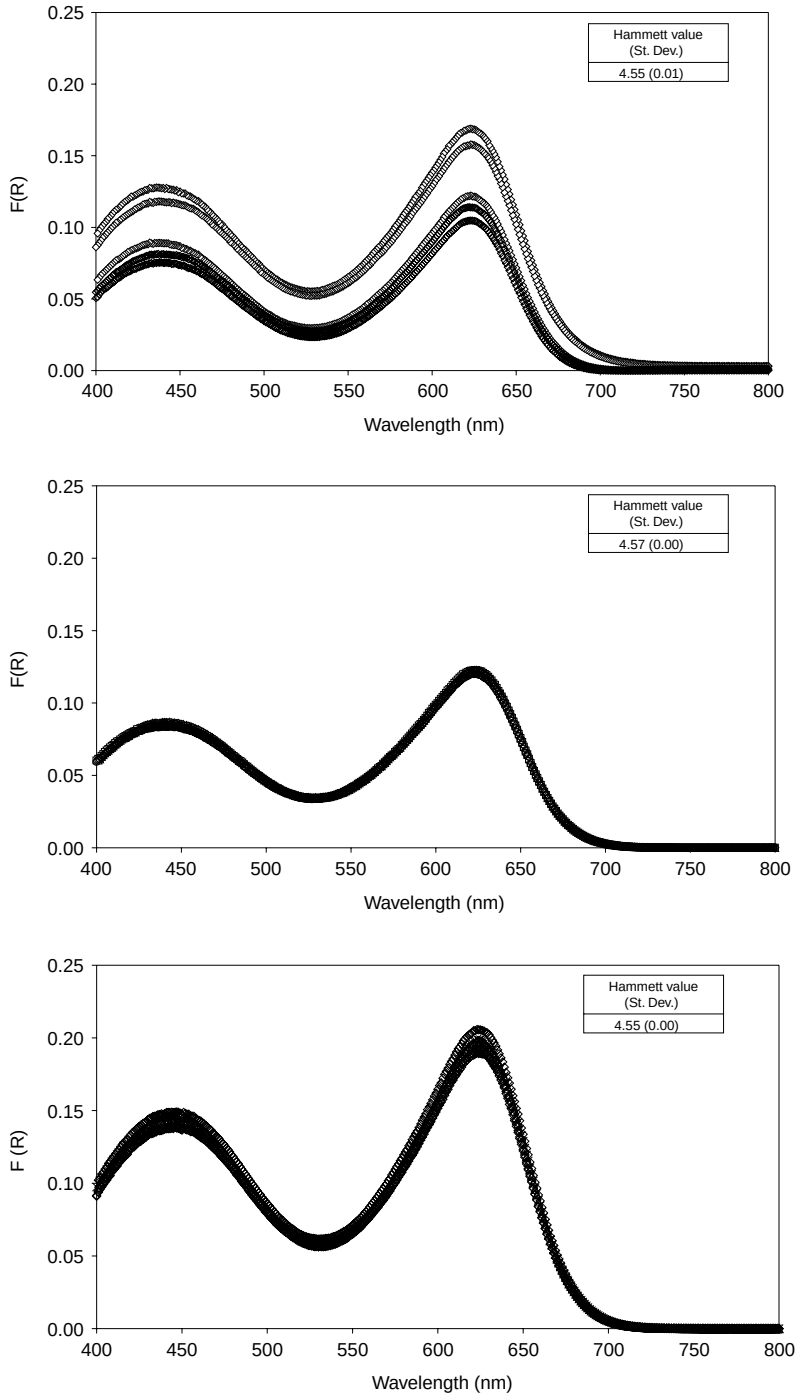

Fig. 9. Sample solid fraction (SF) effects on the measured solid state spectra ($n=5$) of microcrystalline cellulose (Avicel PH 101) (SF of ~0.30 (top), SF of 0.47 (middle), SF of 0.85 (bottom)) (individual spectra of $n=5$).

conducted at the gram scale, employed a conventional mortar and pestle and was analogous to that reported by previous workers [18,19]. An alternate method was also used and was designed to minimize the operator dependence and duration of the mixing process. It employed a small scale high-shear mixer granulator with a capacity of several hundred grams of material. Apart from the scale and mixing technique all the other variables (e.g. indicator concentration, solvent identity) were kept constant for this experiment.

The results of this indicator deposition technique comparison, which was conducted with a microcrystalline cellulose (Avicel PH 101) sample, are shown in Fig. 10. Whilst the values of the Hammett functions measured under each set of conditions are similar (4.31 vs. 4.54) they can be said to be appreciably different based on the known

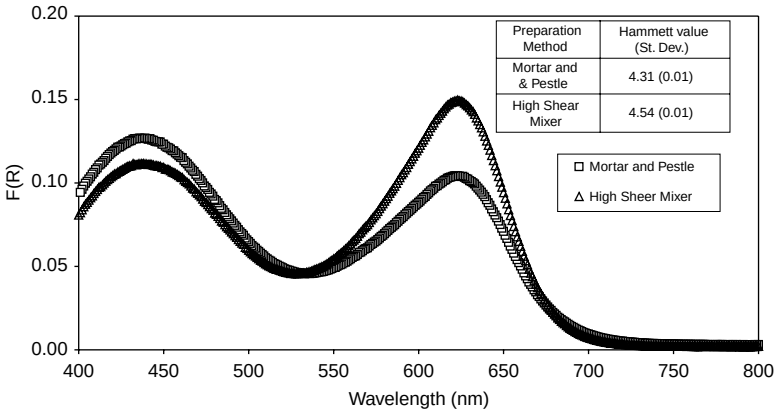

Fig. 10. Effect of indicator deposition technique on the measured solid state spectra of indicator treated microcrystalline cellulose (Avicel PH 101) (mean of $n=3$) (square—mortar and pestle, triangle—high-shear mixer).

reproducibility of the measurement technique (see Section 3.3) and the standard deviation of the measurements. It is not possible to know exactly what caused this small difference in the measured acidity of the material when the indicator was deposited in two different ways, but there are several plausible explanations. Firstly, the higher intensity mixer may have created a more intimate contact between the indicator molecules and the substrate. Secondly, it may have distributed the indicator onto locations on the surface of the material that are normally inaccessible. Thirdly, it is possible that the high shear mixing actually altered the surface properties of the microcrystalline cellulose causing it to be slightly less acidic than otherwise. A similar result has previously been reported for dibasic calcium phosphate where the surface of this excipient became more acidic as it was milled [25,26]. The effect of the mixing conditions on the measured Hammett function is clearly important when conducting precise work of this type; more detailed studies will be required before it is possible to fully understand the subtle effects of different processing operations (e.g. mechanical activation, tribo-electrification) on the acidity of excipients and their formulations.

3.9. Lubrication effects

An additional investigation into the effects of sample history on the measured Hammett acidity function was designed to determine the effect of adding a lubricant on the surface properties of microcrystalline cellulose (Avicel PH 101). The indicator was first deposited on the surface of the substrate using a high shear mixer and then the lubricant was added and mixed for a prolonged period to accentuate any effects that might be observed.

The use of the high-shear mixer to deposit the indicator resulted in a higher than normal Hammett acidity value at the start of the experiment, in agreement with earlier findings (see Section 3.8). Upon addition of the magnesium stearate the Hammett function increased by almost 0.2 units compared to the control over the first 40 min of mixing and then became approximately constant (Fig. 11). The Hammett function for this lot of magnesium stearate had been measured to be about seven (much higher than that of the microcrystalline cellulose) (Fig. 6) and it appears that even at a low concentration ($\sim$1% w/w) this material was able to modify the surface properties of this substrate.

From this result it is clear that changes in the acidity of a material during normal pharmaceutical processing operations may be significant and can potentially be monitored using this measurement technique, with the indicators being sensitive to the changes in the system as it is processed. Further work is required to investigate processing and formulation effects in detail and to probe the physical reasons for the changes that are observed.

4. Conclusions

It can be concluded that with sufficient care and experimental controls the assessment of the Hammett acidity function of solid pharmaceutical excipients using

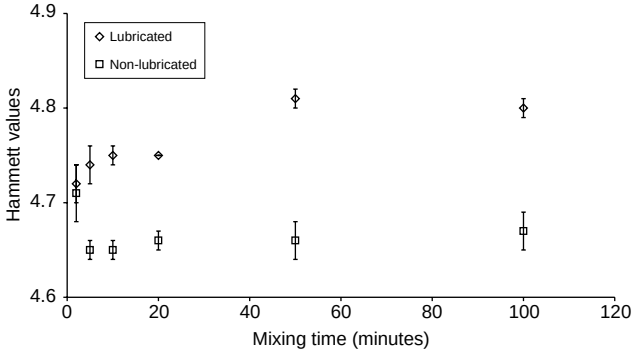

Fig. 11. Lubrication effects upon the measured Hammett values of microcrystalline cellulose (Avicel PH 101) (mean $\pm$ standard deviation) (diamond—lubricant added, square—no lubricant).

the method described in this work can be considered to be a robust and reliable technique. Whilst the method is empirical it indicates that there are differences in the solid state acidities of different excipients, and that common formulation and processing operations, such as blending and lubrication, can influence the surface properties of these materials. As a consequence of this, care should be taken when formulating active pharmaceutical ingredients that are sensitive to their micro-environmental surroundings and the potential effects of process and formulation changes should be carefully considered and studied.

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