Pharmaceutical Research, Vol. 12, No. 7, 1995

Development of a Flow Microcalorimetry Method for the Assessment of Surface Properties of Powders

P. Louise Sheridan,[1] Graham Buckton,[1,3] and David E. Storey[2]

Received October 12, 1994; accepted January 31, 1995

Purpose. This study describes the development of a microcalorimetric flow cell which allows powder surface energetics to be probed my means of measuring their interaction with water vapour. ***Methods.*** A flow cell has been constructed and tested in an isothermal microcalorimeter to assess the interaction between water vapour and powder surfaces. The cell was constructed to mix two separate air streams (0% and 100% relative humidity respectively) to create any humidity at a standard flow rate. The powder sample was equilibrated in dry air and then exposed to sequential increments in humidity. ***Results.*** Adsorption isotherms were constructed from the cumulative heat as a function of humidity. It was possible to differentiate between different samples of α-lactose monohydrate (which appeared identical by contact angle determination). It was also possible to measure adsorption to two different alkyl p-hydroxybenzoates which were hydrophobic and of low surface area. ***Conclusions.*** This technique offers a very sensitive and versatile method of obtaining a reliable indication of powder surface energetics and as such is a major advance in the field.

KEY WORDS: isothermal microcalorimetry; adsorption; wetting; powders; lactose; batch variability.

INTRODUCTION

Surface properties of materials influence the ease of production, the physical and chemical stability and the ultimate use of many products (1). For powders there are major problems associated with contact angle techniques. Detailed criticisms of contact angle techniques for powders have been presented elsewhere (e.g. 1-6). In essence contact angles can be measured on powder systems after compaction of the material or by measuring fluid flow through a powder bed. The liquid penetration techniques are based on the Washburn equation which has been criticised (6) and have a tendency to overestimate the true contact angle (2). The use of sessile drops on compressed powders can be flawed due to the compaction process changing the surface nature (7) and because the surface must be pre-saturated with a saturated solution of the powder in the test liquid (1). The use of compacted wafer of powders as Wilhelmy plates also suffers from the fact that the powder is compacted. There is a tendency for contact angle values to be underestimates of the true wettability when studied by either of the compaction methods (4,5). Given the difficulties with contact angle methods, it is desirable to utilise other approaches to surface characterisation for powders, an alternative is to consider microcalorimetry. To date we have utilised a batch microcalorimetric approach (8,9), involving the application of a vacuum to the sample to produce a uniform defined starting point, then admitting water vapour from a remote reservoir. The interaction with a vapour is in many ways the best way to probe a surface as the first layer of adsorbed vapour molecules give the most significant information about the powder - probe interaction. The problems with the calorimetric method as used to date (e.g. 8) included the fact that vacuum treatment may affect the surface of the powder; that there were practical difficulties in maintaining the vacuum in the system; that the blank response for adding vapour into a vacuum was large in comparison with the test response; and that the system only allowed two states (dry and totally wet). The single point isotherm that was produced gave comparatively little information on the adsorption process. Furthermore, the system was unsuitable for certain materials which volatilised under vacuum, and for others which tended to exhibit deliquescence.

In this paper the development and use of a vapour flow cell is described,[4] and its suitability for use on different types of powders is investigated.

EXPERIMENTAL

A flow cell was engineered as shown in Figure 1, such that it was all housed in the water bath of the calorimeter (25 ± 0.0002 °C), with the final measuring cell being housed in the measuring site of the instrument (Thermal Activity Monitor, Thermometric). Air is passed into a dry and a wet line, the dry line is desiccated (0% RH) and the wet line is passed through 2 humidification stages within the calorimeter. These two lines are mixed to give a controlled humidity and this is then passed into the measuring cell.[5] The available space at the measuring site allows for a cylindrical cell of approximately 4 ml capacity. The flow cell was constructed from stainless steel, with tubes being secured in place with epoxy resin. All joints were sealed permanently to give air tight joints except the screw top to the powder cell, which had a O-ring fitting. Periodically the water reservoirs were emptied, flushed with alcohol then dried to minimise risk of bacterial growth.

Two variable speed peristaltic pumps (Gilson Milipuls) were used to provide the air supply for the wet and dry lines

---

[1] Centre for Materials Science, School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX.

[2] Merk, West Point, USA.

[3] To whom correspondence should be addressed.

[4] The cell as used was based on the design that was invented by Professor Bakri at University of Grenoble (10). His cell has now been commercialised by Thermometric, so other workers would not need to construct their own cell in the manner described in this work.

[5] There is a small difference between the cell here and the recent commercial product in that the vapour inlet here is at the bottom of the cell (i.e. in the powder bed), whilst the commercial cell has the inlet above the top of the powder sample. The advantage of this system is that all the powder will contact the inlet air, thus removing the risk of dead space in the cell and increasing the sample load that can be used. The advantage of the commercial system is that there will be less background noise due to the inlet air disturbing the powder bed.

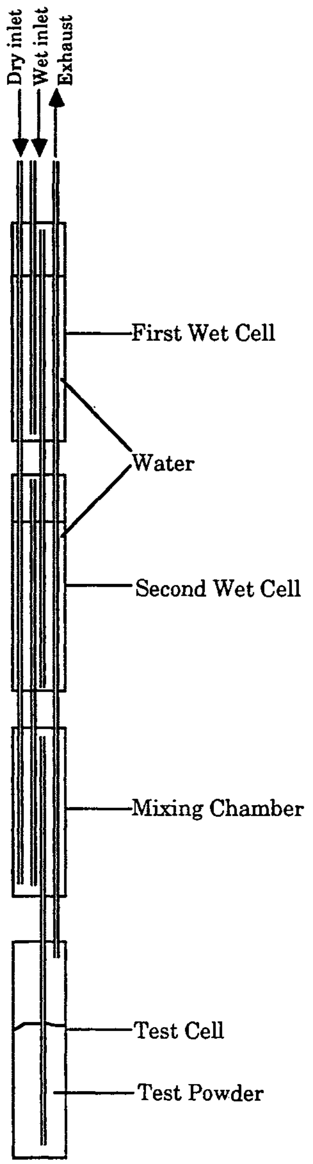

Fig. 1. Diagrammatic representation of the flow cell used. The entire unit is housed in the water bath of the calorimeter. The test cell only is housed in the measuring site of the calorimeter. The two humidification cells yield air of 100% RH which is mixed in desired proportion with air of 0% RH in the mixing chamber.

respectively. The flow rate of air through the pumps was checked by displacement of water (previously saturated with air) from an inverted measuring cylinder. The humidity of the air exhausted from the thermostated cell was monitored by use of a calibrated humidity meter (Rotronic hygroscop).

The blank response for passing air of differing humidities through the empty cell was recorded. The effect of weight of sample was checked by measuring the response for differing loads of α-lactose monohydrate (Meggle).

Standard loads (1 g accurately weighed) were used for subsequent experiments on different sources of α-lactose monohydrate (Meggle, CMV and Lactochem) and methyl p-hydroxybenzoate and propyl p-hydroxybenzoate. These samples were selected as lactose was found to be impossible to measure using the old vacuum microcalorimeter system (due to a tendency to deliquescence at 100 % RH) and methyl p-hydroxybenzoate had given problems with the old system (unpublished data) due to extreme hydrophobicity and low surface area for adsorption.

The surface areas of the powders were measured by nitrogen adsorption (Quantasorb), using a single point BET method. Results are means of duplicate samples. Whilst such single point determinations are not perfectly accurate, there use is acceptable here as the main function of the work is to demonstrate the possibilities of the calorimetric flow cell.

Contact angles were measured by use of the Wilhelmy plate approach (Cahn DCA) on rectangular compacts of powder of nominal dimensions 2 cm × 1 cm × 1 mm. Each compact contained a standard weight of powder and was prepared under a pressure of 4×10^5 kN m^{-2} for 3 minutes, using a Specac press. Two test liquids of known surface energy (analytical grade, with purity checked by measurement of surface tension) were used in order to calculate surface energy terms for the powders. The surface energy (γ) and its polar and dispersion components (γ^p and γ^d respectively) were calculated for the lactose samples using Wu's harmonic mean approach (11).

RESULTS

Pump Calibration

The air pumping capability was found to give a reproducible flow rate as a function of pump speed. The peristaltic tubing was replaced if any deviation was noted in the humidity produced. The flow rate of 600 ml h^{-1} was selected for routine use as it produced an air flow which readily resulted in 0% RH when using the dry line only. The humidity obtained at this flow rate for different combinations of the pump speed in the wet and dry pumps is shown in Figure 2, and was found to be linear over most of its range, however,

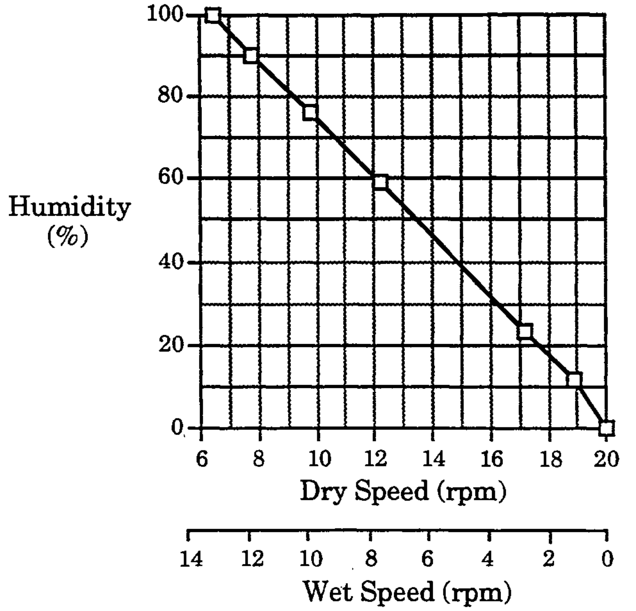

Fig. 2. The humidity produced in the flow cell by mixing air with total pump speed of 20 rpm (equivalent to 600 ml h^{-1}), from either the wet or dry lines.

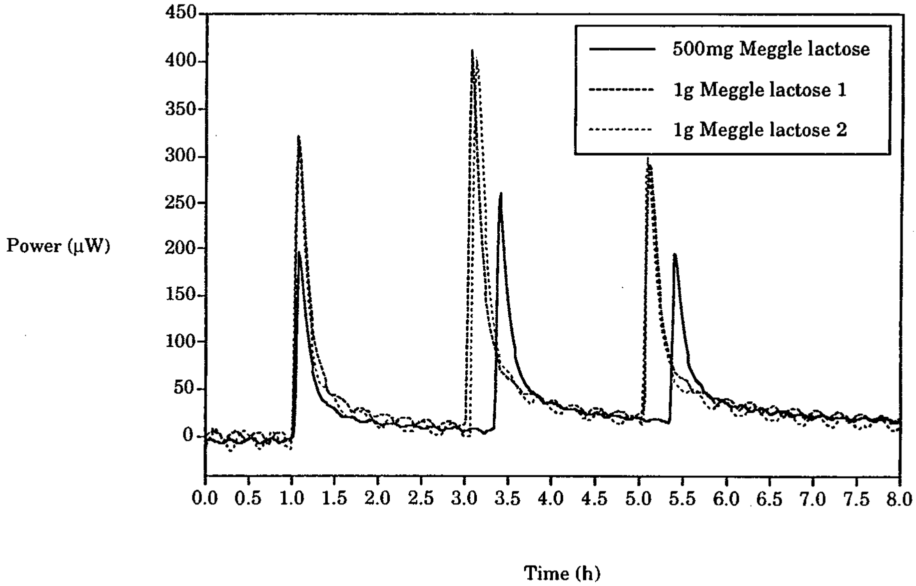

Fig. 3. Calorimetric results (power as a function of time) for three sequential changes in humidity in the flow cell (first peak from 0-24 %, second from 24-59 % and the third from 59-78 % RH) for three different samples of Meggle α-lactose monohydrate (2 of 1g weight and one of 500 mg weight).

Table I. Surface Areas of the Powders Investigated as Assessed by Nitrogen Adsorption

Sample	Surface area ($m^2 g^{-1}$)
α-lactose monohydrate (DMV)	0.567 ± 0.003
α-lactose monohydrate (Lactochem)	0.403 ± 0.001
α-lactose monohydrate (Meggle)	0.559 ± 0.002
Methyl p-hydroxybenzoate	0.292 ± 0.012
Propyl p-hydroxybenzoate	0.205 ± 0.002

the humidity obtained was not a simple mean of the wet and dry pump speeds (for example, 75 % RH was obtained if the wet and dry lines were both set to 10 rpm).

Preliminary Experiments

Effect of Weight of Sample, and Test of Reproducibility

The data in Figure 3 are responses of power as a function of time obtained for three sequential changes in humidity (0-24 %, 24-59% and 59-78% RH, respectively), for Meg-

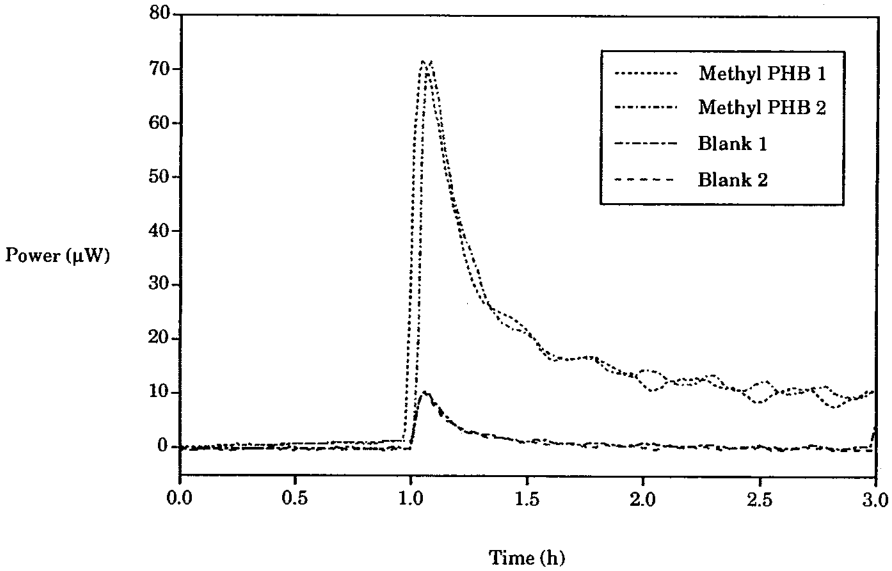

Fig. 4. Two replicate determinations for the change in humidity from 0-24% RH for 1 g of methyl p-hydroxybenzoate, with the blank response measured with an empty cell.

Table II. Areas Under the Microcalorimetric Power–Time Curves for 500 mg or 1 g of Meggle α-Lactose Monohydrate, Corrected to Unit Weight[a]

Humidity change (% RH)	Heat output for 500 mg sample (J g^{-1})	Heat output for 1 g sample (J g^{-1})
0–23.5	0.284	0.314 ± 0.012
23.5–59.0	0.302	0.308 ± 0.013
59.0–75.0	0.168	0.188 ± 0.008

[a] For 500 mg samples n = 1, for 1 g samples n = 3 results are mean ± standard deviation.

gle α-lactose monohydrate (Meggle). The peaks obtained are extremely sharp, showing an onset immediately after the humidity is changed, and then an exponential decline to (generally a new) baseline. These responses are indicative of a simple wetting process as any transition in the material (i.e. a change in crystal form) would be accompanied by a more protracted response. The heat generated is large for water interaction with lactose, despite the fact that lactose does not adsorb much water at humidities below 75 % RH (12). The baseline is seen to have a perturbation, this is thought to be due to the air flow passing through the powder bed. The reproducibility is extremely good, as can be seen for the two different data sets that are shown for 1 g of lactose (Figure 3). The areas under the curve corrected for weight for the lactose samples are given in Table II, from which it can be seen that the weight corrected areas are approximately the same for each sample loading, demonstrating that the air is penetrating the entire powder bed. Given that the areas are approximately the same when corrected for weight, and that the error will be lower when measuring the larger peak, these data were used as the basis for standardising on a 1 g sample size.

With the previous experimental set up (8) it was impossible to measure a reproducible adsorption response for water vapour onto the alkyl p-hydroxybenzoates. These powders are hydrophobic and of low surface area (Table I) and thus provide a major challenge for the technique. The essential issue is to find out the level of reproducibility that can be obtained with a sample which presents such difficulties. It is also necessary to ascertain how different the sample response will be from the blank response for the empty cell.

Some data for the adsorption of water vapour onto methyl p-hydroxybenzoate are shown in Figure 4 (for 0-24% RH change), from which it can be seen that there is a significant difference between the blank response (i.e. that for the wetting of the empty cell by the water vapour) and that for the powder. The calculation of the area under the curve is complicated by the fact that the response does not return to the initial baseline, thus areas have been calculated from the first baseline, at the point where the curve begins, to the estimated onset of the second baseline. The failure of the response to return to baseline is at present poorly understood, but may be a consequence of a different heat capacity for the wet sample. For comparison it is worth noting the difference in scales on the power axis between the lactose data (Figure 3) and that for the p-hydroxybenzoate (Figure 4).

Isotherm Data for Three Batches of α-Lactose Monohydrate

Batch to batch and supplier to supplier variation in excipient properties is a common problem in many products. One excipient which can be problematic is lactose, as it can exist in a number of crystal forms, as well as being sold as a partially amorphous form (e.g. spray dried lactose from Lactochem). This study was designed to attempt to differentiate between the surface energetics of α-lactose monohydrate from 3 different suppliers (DMV, Lactochem and Meggle). The contact angle data and calculated surface energies are given in Table 3, and the calorimetric data are presented as an isotherm in Figure 5 (with a standard state in J m^{-2}).

From the data in Table III it can be seen that the surfaces appear to be identical when assessed by contact angle analysis within experimental error. The calorimetric adsorption isotherms show that two of the samples (Lactochem and Meggle) are indistinguishable, but the other supplier (DMV) has a product with different surface energetics. The error bars on Figure 5 are within the symbols on each line, thus the difference between the DMV and the other two samples is substantial. This differentiation between different samples of lactose is indicative of a technique with enormous sensitivity to surface variation in the powders. It has recently been shown that the problems associated with different batches of materials may be attributed to small differences in the surface crystallinity of powders (e.g. 13,14,15). When studied by the batch calorimetric method (e.g. 13) the three samples of lactose used here showed no sign of recrystallisation or

Table III. Measured Contact Angles for Three Samples of Lactose, and Values for the Surface Energy Calculated Using the Method of Wu (17)

Sample	θ (°) (EG)[a]	θ (°) (DIM)[b]	γ (mJ m^{-2})	γ^p (mJ m^{-2})	γ^d (mJ m^{-2})
Meggle	9.3 ± 3.0	21.1 ± 6.7	53.9	6.9	46.9
DMV	12.5 ± 2.8	14.9 ± 6.0	54.6	6.1	48.5
Lactochem	9.3 ± 1.7	10.9 ± 2.6	55.5	6.1	49.5
Methyl p-hydroxybenzoate	17.1 ± 3.8[c]	39.0 ± 4.0[d]	56.8	29.8	27.0
Propyl p-hydroxybenzoate	33.3 ± 3.0	56.3 ± 2.3[d]	43.5	24.5	19.0

[a] EG = using ethylene glycol.
[b] DIM = using diiodomethane.
[c] Using formamide.
[d] Using water.

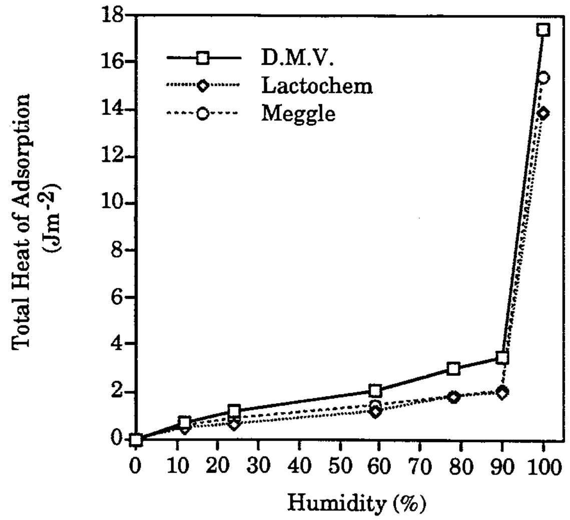

Fig. 5. Cumulative heat output (sum of areas under the curve for each humidity increase) as a function of RH for three different suppliers samples of α-lactose monohydrate. Error bars with each symbol.

transition, indicating that the surface energetic difference detected here is due to extremely small (much less than 0.5 % of total) variations on crystal form or crystallinity of the lactose samples.

Isotherm Data for Alkyl p-Hydroxybenzoates

The Wilhelmy plate technique tends to give contact angle values which underestimate the true contact angle for powdered samples (e.g. 4,5,16). It follows that the values of 39 and 56 ° measured using water (on the alkyl p-hydroxybenzoates, Table III) can be taken as being a good demonstration of a highly hydrophobic surface. The calorimetric adsorption data are shown in Figure 6. The shape of the isotherm for propyl p-hydroxybenzoate (Figure 6) tends towards Type III whereas the lactose isotherms are more like a Type II response. It is usual for adsorption isotherms to be of Type III if the interaction between the adsorbate and adsorbent is weak (such as that which exists here between water vapour and a hydrophobic powder). This kind of behaviour is in keeping with the difference in hydrophobicity for the two p-hydroxybenzoates (Table III). The calorimetric data will be a function of the number of water molecules adsorbing and the enthalpy change associated with each individual bond. It follows that the calorimetric output is directly proportional to the amount of water adsorbed, but also that the amount of water adsorbed cannot be quantified by the calorimetric data alone. As the amount of adsorption is hard to quantify (e.g. not detectable gravimetrically by weighing samples in desiccators at different humidities), the explanation of the magnitude of the calorimetric response is equally hard to develop. It will be necessary to refine gravimetric studies (or other means of quantifying the extent of vapour adsorption) to match the sensitivity of the calorimeter if further fundamental interpretation of the calorimetric adsorption data is to be obtained.

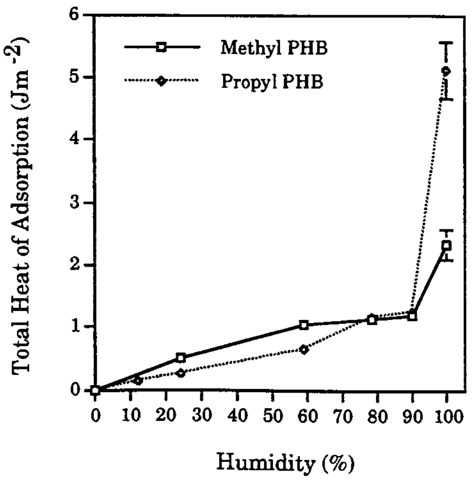

Fig. 6. Cumulative heat of adsorption as a function of RH for the two different p-hydroxybenzoates.

CONCLUSIONS

The flow vapour sorption cell has proved both versatile and valuable. A wide range of sample types can be investigated. The highly sensitive nature of the instrument means that adsorption isotherm data can be obtained for water onto hydrophobic solids of low surface area. The control of the humidity means that materials can be investigated both below and above critical moisture contents (see discussions elsewhere on critical moisture content (17,18)). The reproducibility of the experimental data is extremely good which means that small (but significant) differences in the sample surface can be investigated with comparative ease. The fact that the materials do not need to be pre-treated before measurement also means that the results relate to the real properties of the powder surface.

ACKNOWLEDGMENTS

Mr D Hunt for the engineering of the flow cell. Presented in part at the British Pharmaceutical Conference, 1993.

REFERENCES

1. G. Buckton. Assessment of the wettability of pharmaceutical powders. J. Adhesion Sci. Technol. 7:205-219 (1993).
2. G.E. Parsons, G.Buckton and S.M.Chatham. Comparison of measured wetting behaviour of material with identical surface energies presented as particles and plates. J. Adhesion Sci. Technol. 7:95-104 (1993).
3. G.E.Parsons, G.Buckton and S.M.Chatham. The extent of errors associated with contact angles obtained using liquid penetration results. Int. J. Pharm. 82:145-150 (1992).
4. P.L.Sheridan,G.Buckton and D.E.Storey. The extent of errors associated with contact angles II. Factors affecting data obtained using a Wilhelmy plate technique for powders. Int. J. Pharm. 109:155–171 (1994).
5. G.Buckton, P.Darcy and D.McCarthy. The extent of errors associated with contact angles III. The influence of surface roughness effects on angles measured using a Wilhelmy plate technique for powders. Colloids Surface. 95:27–35 (1995).
6. Y-W.Yang, G.Zografi and E.E.Miller. Capillary flow phenomena and wettability in porous media II. Dynamic flow studies. J. Colloid Interface. Sci. 28:35-46 (1988).
7. G.Buckton and J.M.Newton. Assessment of the wettability of powders by use of compressed powder discs. Powder Technol. 46:201-208 (1986).

8. G.Buckton and A.E.Beezer. A microcalorimetric study of powder surface energetics. Int. J. Pharm. **41**:139–145 (1988).
9. T.C.Blair, G.Buckton, A.E.Beezer and S.F.Bloomfield. The interaction of various types of microcrystalline cellulose and starch with water. Int. J. Pharm. **63**; 251-257.
10. A.Bakri. Design, Testing and Pharmaceutical Applications of a Gas Pressure Controller Device for Solid-Gas Microcalorimeter Titration. Thermometric Application Note 22021 (1993).
11. S.Wu. Calculation of interfacial tension in polymer systems. J. Polym. Sci. C **34**; 19-30 (1971).
12. Handbook of Pharmaceutical Excipients, 2nd Edn., Pharmaceutical Press, London, (1994).
13. L-E.Briggner, G.Buckton, K.Bystrom and P.Darcy. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. Int. J. Pharm. **63**:251-257 (1994).
14. A.Saleki-Gerhardt, C.Ahlneck and G.Zografi. Assessment of disorder in crystalline solids. Int. J. Pharm. **101**:237-247 (1994).
15. T.Sebhatu, M.Angberg and C.Ahlneck. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm. **104**:135-144 (1994).
16. A.Chawla, G.Buckton, K.M.G.Taylor, J.M.Newton and M.C.R.Johnson. Wilhelmy plate contact angle data on powder compacts: Considerations of plate perimeter. Eur J. Pharm. Sci., **2**:253–258 (1994).
17. C.Ahlneck and G.Zografi. The molecular basis of moisture effects on the physical and chemical stability of drugs. Int. J. Pharm. **62**:87-95 (1990).
18. B.Hancock and G.Zografi. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. **11**:471-477 (1994).