Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 349 (2008) 61–65
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

The impact of low-level inorganic impurities on key physicochemical properties of paracetamol

Wendy L. Hulse *, Ian M. Grimsey, Marcel De Matas

Institute of Pharmaceutical Innovation, University of Bradford, Bradford, UK

Received 5 February 2007; received in revised form 15 July 2007; accepted 20 July 2007
Available online 6 August 2007

Abstract

Trace inorganic impurities in active pharmaceutical ingredients (APIs) while having limited toxicological significance might affect the down stream processing properties of those substances. The level of impurities in paracetamol batches was quantified and mapped using inductively coupled polarization mass spectrometry (ICP-MS) and scanning electron microscopy coupled with energy dispersive X-ray microanalysis (SEM–EDX). The physical form of samples was assessed using X-ray powder diffraction (XRPD) and characterised thermally using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Surface properties were evaluated using inverse gas chromatography (IGC) and moisture sorption. Size distribution was measured using an aerosizer with dry powder dispersion. Physical analysis confirmed that the batches were of the same physical form and particle size distribution was shown to be similar. The SEM–EDX analysis however revealed the presence of aluminium on the surface of particles. This was supported by ICP-MS analysis, which showed different levels of aluminium between batches ranging from 0.1 to 5.6 ppm. IGC indicated that the batches with the highest aluminium content had the highest dispersive free energy. Differences in levels of inorganic impurities typically not considered significant in drug substance specifications correspond with differences in physical properties of APIs, with potential downstream consequences for processing and finished product performance.
© 2007 Elsevier B.V. All rights reserved.

Keywords: PAT; Inorganic impurities; Processing; Surface free energy; Physicochemical properties; Paracetamol

1. Introduction

The essential characteristics for pharmaceuticals are safety and efficacy. Permitted levels of inorganic impurities are usually defined by regulatory agencies and controlled by specification tests. Trace impurities can however still be present and often originate from different sources leading to batch-to-batch variation. Possible sources of contamination include glass packaging materials and components, catalysts, electrodes, solvents and reagents used in synthesis.

Although having few toxicological consequences at these low levels, variability in the levels of residual inorganic impurities generated during chemical manufacture could lead to batch-to-batch variation in processing characteristics. Lindberg and Lundstedt (1994) reported how impurities in prednimustine could exert influences on crystallite size and aggregate/agglomerate size as well as surface roughness and wettability. Potentially this could lead to affect on dissolution and drug release or problems with processes such as wet granulation where the spreading of binder over the substrate is required.

The US FDA guidance for industry in process analytical technologies (PAT) recognises the current lack of understanding of the impact of undetectable batch-to-batch variability in physical and mechanical characteristics of active pharmaceutical ingredients (APIs) and raw materials. In the guidance for industry it is stated (Guidance for PAT, 2004) that "the inherent, undetected variability of raw materials may be manifested in the final product".

The European medicines agency (EMEA) notes for pharmaceutical development (EMEA, 2006) identifies that "physicochemical and biological properties of a drug substance can influence the performance of the drug product and its manufacturability and that they should be identified and discussed". Differences in physical properties include particle size (Rowe et al., 2005; Steckel and Muller, 1997), surface energetics (Grimsey et al., 1999), crystal form and particle morphology.

In addition to these factors the presence of low-level inorganic impurities could also potentially affect the surface character-

* Corresponding author. Tel.: +44 7921 376485.
E-mail address: wendy.3.hulse@GSK.com (W.L. Hulse).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.07.037

istics of pharmaceutical materials and hence the processing attributes. For example, this phenomenon is particularly significant for inhaled particles where the drug-to-carrier interactions determine the drug dose released and deposition in the human lung from dry powder inhalers (De Boer et al., 2003; Iida et al., 2004). These differences in physicochemical properties have the potential to significantly influence the processability and quality of a pharmaceutical product.

The levels of inorganic contaminants and differences in the physical properties of the widely used API paracetamol (acetaminophen) have therefore been investigated using a range of analytical techniques. Inductively coupled plasma mass spectrometry (ICP-MS) has been used as a method for determining residual impurities as it can detect extremely low levels of most elements in the periodic table (Evans et al., 2001). Inverse gas chromatography (IGC) has also been extensively utilised to probe the surface energetics of pharmaceutical ingredients (Derbyshire et al., 2003; Heng et al., 2006; York et al., 1998). These techniques have therefore been used in an attempt to establish a link between the levels of trace impurities and key physical properties.

2. Materials and methods

2.1. Materials

Three batches of paracetamol (acetaminophen) were obtained from a commercial source. All three batches were obtained from the same supplier and have the same grade. The chemical structure of paracetamol is shown in Fig. 1.

All organic probes used in IGC analysis were of HPLC grade and obtained from Sigma–Aldrich, UK.

2.2. Methods

The level and nature of impurities in samples from three commercial batches (A–C) of paracetamol was determined using ICP-MS. Samples were analysed using a thermo plasma quad (Thermo Electron Corporation, UK). Samples were digested in concentrated nitric acid and diluted in de-ionised water.

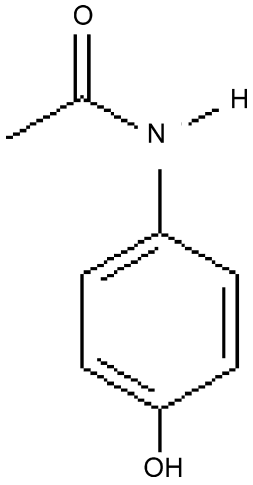

Fig. 1. Chemical structure of paracetamol.

Scanning electron microscopy coupled with energy dispersive X-ray microanalysis (SEM–EDX) was used to map the distribution of inorganic impurities on the surface of API particles. Samples were analysed using an FEI Quanta 400 (Oxford instruments, UK). Images were obtained using an accelerating voltage of 20 kV, spot size of 2 mm and a resolution of 1024×884.

The crystallinity and physical form of samples from the individual batches was assessed using X-ray powder diffraction (XRPD) using a Bruker D8 diffractometer (wavelength of X-rays 0.154 nm Cu source, voltage 40 kV, and filament emission 40 mA). Samples were scanned from 5 to 45° (2θ) using a 0.01° step width and a 1 s time count. The receiving slit was 1° and the scatter slit was 0.2°.

Thermal characteristics were determined using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) using a Perkin-Elmer series 7 thermal systems (Perkin-Elmer UK Ltd.). A scanning rate of 10 °C min^{-1} was employed between 25 and 200 °C for DSC and 25–280 °C for TGA analysis.

Moisture sorption profiles were obtained used an IGAsorp moisture sorption analyser (Hiden Isochema Ltd., UK). The sequence of isothermal steps incorporated drying the samples at 0% RH until constant weight was achieved. The RH was then increased in increments of 10% to a maximum of 95% RH. Samples were analysed at 25 °C.

Particulate surface properties were evaluated with IGC using a Perkin-Elmer gas chromatograph (Perkin-Elmer UK Ltd.). The method used in previously published by Ticehurst et al. (1994). Adsorption measurements were performed at 30 °C and 0% RH at infinite probe dilution. Hexane, heptane, octane, nonane, acetone, chloroform, ethyl acetate and THF were used as probes. The carrier gas was helium used at a flow rate of 9 ml min^{-1}. The dispersive component of the surface free energy and the specific component of the free energy of adsorption were determined using the method described by Schultz and Lavielle (1989).

Particle size distribution was measured using a time of flight analysis method with dry powder dispersing system (DDS) using a TSI aerosizer (TSI Instruments Ltd. UK). Samples were aerosolized using an aerodisperser for 300 s with a laser current of 52 mA.

3. Results

Fig. 2 shows a typical SEM photomicrograph (200×) of one of the batches highlighting the location analysed by EDX analysis and Fig. 3 shows an example of EDX spectrum.

The three batches did not differ notably in appearance, having similar irregular morphology and exhibiting a broad particle size distribution. The SEM–EDX analysis of the samples revealed differences between the surfaces content of low-level inorganic impurities and the batches. The presence of aluminium and chlorine are evident from the results along with the expected elements contained in paracetamol. The batches were therefore subjected to ICP-MS analysis to quantitatively assess the amount of alu-

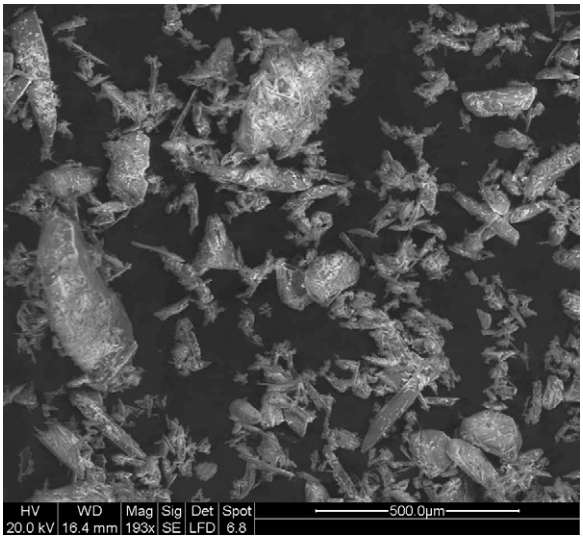

Fig. 2. SEM photomicrograph of paracetamol (200×).

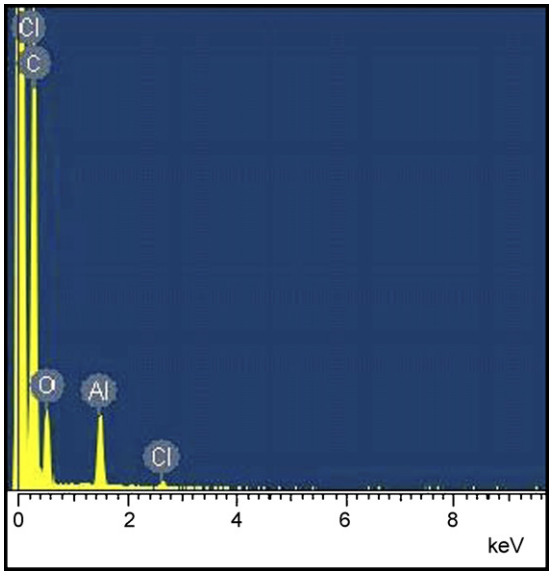

Fig. 3. SEM–EDX sample content typical result.

minium present in each of the batches. The levels of chlorine cannot be quantified as the mass difference between chlorine and argon (which is used to generate the plasma) is too close to allow peak resolution. The ICP-MS results are summarised in Table 1.

The figures in the table show markedly lower aluminium content in batch B than the other two batches. It is possible that the impurities have been introduced during the process of manufacture as previously indicated. It is however not clear if impurities at such low levels have affect on the physical properties of the samples. The physical forms of the batches were therefore determined to establish if any structure changes had occurred and if there was any notable amorphous content in the samples. Fig. 4 shows the XRPD patterns of the three batches.

Table 1
ICP-MS analysis results for paracetamol batches

Batch	Aluminium content (± relative standard deviation (R.S.D.))
A	10.8 ppm (±1.5%)
B	1.6 ppm (±1.5%)
C	8.0 ppm (±1.5%)

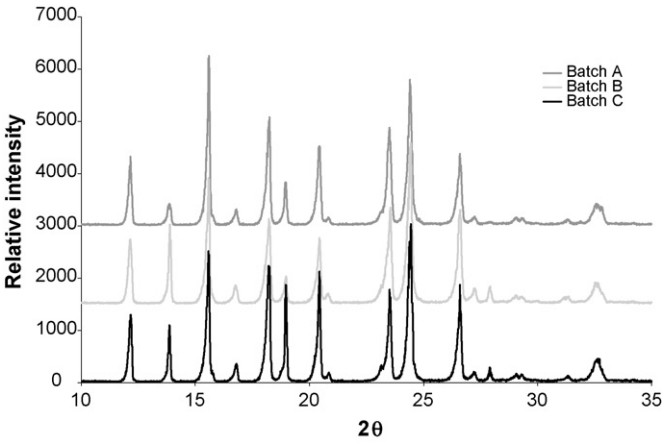

Fig. 4. XRPD patterns of paracetamol batches.

The XRPD patterns indicate that all three samples are highly crystalline and have the same monoclinic polymorphic form. This shows that the differing impurity content present has not markedly affected the physical form of the material from each of the batches. The accompanying DSC thermal profiles of the batches are shown in Fig. 5.

The results of the DSC analysis supported the XRPD results and confirmed no discernable physical differences between the samples. The average peak melting temperature showed only a 0.4 °C range between all three batches indicating again that the low level of impurity present does not affect the physical form.

Further evidence for these findings was provided by evaluation of the thermal decomposition and water content of the samples using TGA analysis. The presence of ionic surface impurities could affect the hygroscopicity of the product and hence affect the water content on storage with possible consequences for physical and chemical stability. The TGA thermal

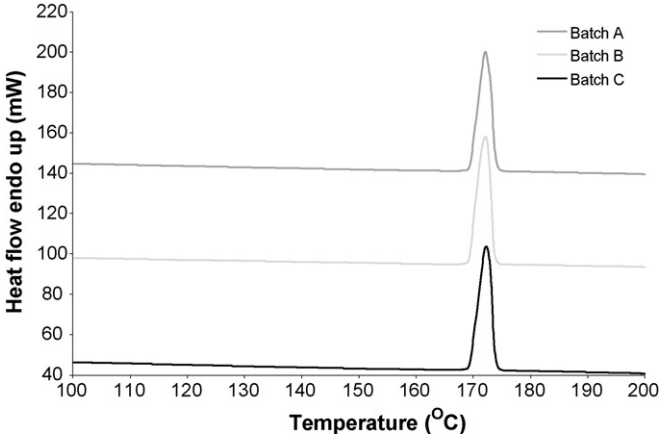

Fig. 5. DSC thermal profiles of paracetamol batches.

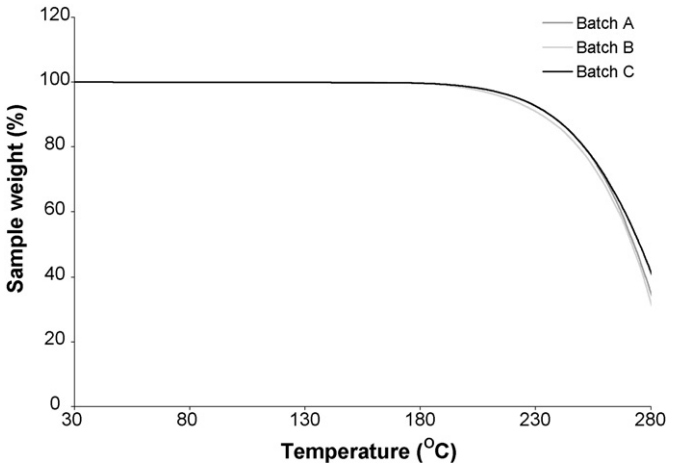

Fig. 6. TGA thermal profiles of paracetamol batches.

profiles are shown in Fig. 6 and show a single decomposition with no hydrated forms evident and no notable differences between the three batches.

The results along with the XRPD and DSC confirm that the low levels of aluminium detected during ICP-MS analysis do not affect the physical form or thermal behaviour of the batches. The use of XRPD and DSC to detect amorphous regions is however limited to lower detection limits of approximately 10% (Hogan and Buckton, 2001). Moisture sorption was therefore employed as a more sensitive method to assess the presence of any lower levels (<10%) of amorphous content in these batches. Fig. 7 shows a typical moisture sorption profile obtained from all of the batches.

The moisture sorption profiles did not differ notably in shape and showed only a small increase in weight (<0.1%) at high humidity. This suggests limited presence of amorphous material which would be characterised by a notable moisture sorption followed by a weight loss prior to adsorption of further moisture at high RH. There was a characteristic decline in weight between 200 and 1000 min before the sample started to adsorb further moisture above 1200 min. The reproducible weight loss observed between 200 and 1000 min could be related to crystallization of an extremely low level of amorphous content, probably predominating at the surface of particles (Mackin et al., 2002) or alternatively the loss of residual solvents. It is well established that exposure to elevated humidity can be used as a method of reducing the levels of residual solvents from active pharmaceutical ingredients (Dolitzky and Lifshitz, 2006). Although moisture sorption experiments were unable to detect any notable differences and it was believed that subtle changes in surface characteristics could be evaluated using IGC. This is an extremely sensitive technique to determine both the dispersive free energy and the specific free energy of samples. Sunkersett et al. (2001) have previously shown that IGC could detect differences in surface energetics of paracetamol caused by changes in the level of adsorbed moisture. Table 2 shows dispersive free energy results for the three batches.

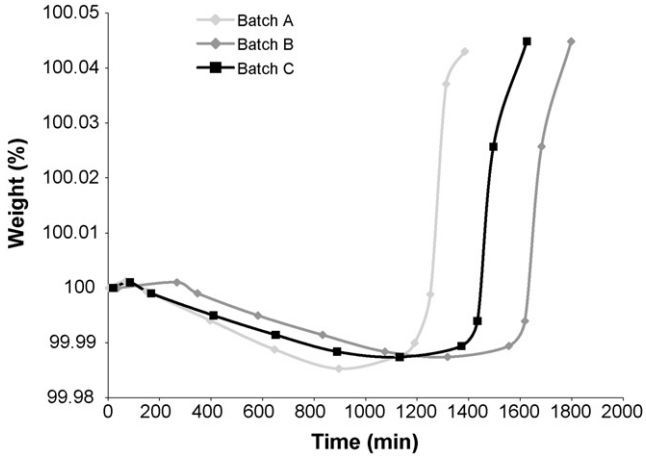

Fig. 7. Moisture sorption profiles of paracetamol batches.

Table 2
Dispersive free energy of paracetamol batches

Batch	Dispersive free energy ± range (mJ m^{-2})
A	62.06 ± 0.1
B	58.60 ± 0.4
C	62.56 ± 0.1

The results for the dispersive free energy were calculated from the retention times of the alkane probes. In each batch the regression coefficient was >0.99. These results show a difference between batch B and the other two batches with higher surface aluminium content.

The specific component of the surface free energy is calculated from the probes THF (basic), chloroform (acidic), ethylacetate (amphoteric) and acetone (amphoteric but slightly more acidic than ethylacetate). Table 3 shows the specific free energy results for the three batches.

THF is the basic probe and will therefore interact with acidic groups on the particles surface. For this probe the interaction increased in the order: C > A > B, however the results are not significantly different and therefore do not indicate a measurable change in properties between the three batches. The results for the acidic and amphoteric probes also do not show a significant difference between batches. This suggests that at such low levels of impurity, there are differences in the batches that can be correlated to the acidic/basic nature of the paracetamol but not at a significantly high enough level to attribute to true differences. Swaminathan et al. (2006) investigated the lubrication of pharmaceutical powders with magnesium stearate and showed that dispersive surface free energy was altered by differing low levels of lubricant. The reduction in dispersive free energy was attributed to coverage of some of the high-energy sites on the

Table 3
Specific free energy results for paracetamol batches

Batch	Specific free energy ± S.D. (kJ mol^{-1})			
	Chloroform	Acetone	THF	Ethylacetate
A	0.45 ± 0.04	7.56 ± 0.07	5.92 ± 0.10	6.74 ± 0.02
B	0.46 ± 0.01	7.47 ± 0.19	5.67 ± 0.02	6.59 ± 0.15
C	0.49 ± 0.02	7.58 ± 0.07	5.94 ± 0.02	6.89 ± 0.03

Table 4
Particle sizing results for paracetamol batches

Batch	Geometric mean diameter ± S.D. (μm)
A	25.92 ± 0.63
B	25.54 ± 0.76
C	24.76 ± 1.29

Table 5
Size distribution results for paracetamol batches

Batch	$D_{10\%}$ ± S.D. (μm)	$D_{50\%}$ ± S.D. (μm)	$D_{90\%}$ ± S.D. (μm)
A	11.7 ± 0.09	28.9 ± 0.57	48.9 ± 2.45
B	11.6 ± 0.31	28.2 ± 0.74	47.6 ± 0.94
C	11.3 ± 0.56	27.4 ± 2.49	46.3 ± 2.72

particles surface. It is reasonable to suggest that if aluminium (even in very low levels) interacts non-specifically with high-energy sites of paracetamol particles that a similar effect may be observed. Swaminathan et al. (2006) have suggested that the high-energy sites that are detected by IGC at infinite probe dilution may constitute only a small fraction of the energetic surfaces of the powder. Most solid surfaces are energetically heterogeneous and have a distribution of high, medium or low energy sites. It is possible therefore, that even the ppm quantities of aluminium detected by ICP-MS have the potential to preferentially interact with these high-energy sites thus causing changes to the dispersive surface energy measured by IGC. This is supported by the energy dispersive X-ray measurements which show quantifiable levels of aluminium on the surface of particles from the two batches with highest ppm levels of aluminium in the bulk powder.

Differences in surface free energy between the three batches may be attributed to other physical factors such as particle size (Heng et al., 2006). The particles size distribution was therefore established and the results are summarised in Table 4.

Comparison of geometric mean diameter for each batch suggests that there are no notable differences in the particle size of the three batches. This is supported further by the $D_{10\%}$, $D_{50\%}$ and $D_{90\%}$ results shown in Table 5.

There is no clear difference in particle size and morphology (as indicated by SEM) or crystallinity between samples taken from all three batches. Although relatively small in nature, the results suggest that the presence of the trace levels of impurities at the surface of particles could be influencing the surface properties of paracetamol. As discussed in previous publications (Mackin et al., 2002) these subtle changes in characteristics could influence the processing attributes of this active pharmaceutical ingredient as also described by (Buckton and Darcy, 1995; Forbes et al., 1998; Kaerger et al., 2004).

4. Conclusions

Initial SEM–EDX analysis revealed the presence of low-level impurities on the surface of particles within all of the batches. ICP-MS however showed that the levels of aluminium content in the bulk powder differed between batches with batch B having a notably lower aluminium content than batches A and C. IGC results revealed that batch B had a lower surface free energy than the other two batches analysed.

Differences in levels of inorganic impurities at parts per million levels, typically not considered significant in drug substance specifications correspond with differences in physical properties of an API. This may have potential down stream consequences for processing and finished product performance.

It is not known that if the variations in aluminium content are responsible for the differences in surface free energy or if the inter-batch variations had been caused by differences already inherent in the material. Further work will look to establish the underlying causes of this batch-to-batch variation and its significance for powder processing and product performance.

Acknowledgements

The authors wish to thank Mr. Richard Telford and Dr. Ben Stern for carrying out the ICP-MS analysis.

References

Buckton, G., Darcy, P., 1995. Int. J. Pharm. 123, 265–271.
De Boer, A.H., Hagenedoorn, P., Gjaltema, D., Goede, J., Kussendrager, K.D., Frijlink, H.W., 2003. Int. J. Pharm. 260, 201–216.
Derbyshire, H.M., Grimsey, I.M., Bland, C.R., Broadhead, J., Brocklehurst, K.G., Malone, N.J., Smith, G., 2003. J. Mater. Sci. 38, 57–63.
Dolitzky, B.-Z., Lifshitz, I., 2006. CODEN: PIXXD2 WO 2006011874 A1 20060202. PCT Int. Appl. 18 pp.
EMEA, 2006. Note for guidance on pharmaceutical development (EMEA/CHMP/167068/2004).
Evans, E.H., Wolff, J.-C., Eckers, C., 2001. Anal. Chem. 73, 4722–4728.
Forbes, R.T., Davis, K.G., Hindle, M., Clarke, J.G., Maas, J., 1998. J. Pharm. Sci. 87, 1316–1321.
Grimsey, I.M., Sunkersett, M., Osborn, J.C., York, P., Rowe, R.C., 1999. Int. J. Pharm. 191, 43–50.
Guidance for Industry, 2004. PAT—A framework for innovative pharmaceutical development, manufacturing, and quality assurance. http://www.fda.gov/cvm/guidance/published.html.
Heng, J.Y.Y., Thielmann, F., Williams, D.R., 2006. Pharm. Res. 23, 1918–1927.
Hogan, S.E., Buckton, G., 2001. Pharm. Res. 18, 112–116.
Iida, K., Hayakawa, Y., Okamoto, H., Danjo, K., Luenberger, H., 2004. Chem. Pharm. Bull. 52, 350–353.
Kaerger, J.S., Edge, S., Price, R., 2004. Eur. J. Pharm. Sci. 22, 173–179.
Lindberg, N.-O., Lundstedt, T., 1994. Drug Dev. Ind. Pharm. 20, 2547–3255.
Mackin, L., Sartnurak, S., Thomas, I., Moore, S., 2002. Int. J. Pharm. 231, 213–226.
Rowe, R.C., York, P., Colburn, E.A., Roskilly, S.J., 2005. Int. J. Pharm. 300, 32–37.
Schultz, J., Lavielle, L., 1989. In: Lloyd, D.R., Ward, T.C., Schreiber, H.P. (Eds.), Inverse Gas Chromatography Characterisation of Polymers and other Materials, ACS Symp. Ser. 391. American Chemical Society, Washington, DC, pp. 185–202.
Steckel, H., Muller, B.W., 1997. Int. J. Pharm. 154, 31–37.
Sunkersett, M.R., Grimsey, I.M., Doughty, S.W., Obsorn, J.C., York, P., Rowe, R.C., 2001. Eur. J. Pharm. Sci. 13, 219–225.
Swaminathan, V., Cobb, J., Saracovan, I., 2006. Int. J. Pharm. 312, 158–165.
Ticehurst, M.D., Rowe, R.C., York, P., 1994. Int. J. Pharm. 141, 93–99.
York, P., Ticehurst, M.D., Osborn, J.C., Roberts, R.J., Rowe, R.C., 1998. Int. J. Pharm. 174, 179–186.