International Journal of Pharmaceutics 361 (2008) 87–91

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effects of particle size and cohesive properties on mixing studied by non-contact NIR

Luke J. Bellamy, Alison Nordon, David Littlejohn*

WestCHEM, Department of Pure and Applied Chemistry and CPACT, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, UK

ARTICLE INFO

Article history:
Received 12 May 2008
Accepted 19 May 2008
Available online 3 June 2008

Keywords:
Near infrared spectrometry
Process analytical technologies (PAT)
Powder blending
Particle size
Cohesive powders

ABSTRACT

A scaled-down convective blender was used along with non-invasive NIR spectrometry to study the mixing of citric acid, aspirin, aspartame or povidone with microcrystalline cellulose. NIR mixing profiles were generated in real time using measurements at the 2nd overtone wavelength of the added compounds. Trends demonstrated previously for aspirin were confirmed for additions of citric acid: the magnitude of the 2nd overtone NIR measurements is less affected by changes in particle size than that of the 1st overtone; the peak-to-peak noise of the 2nd overtone NIR mixing profile increases with the particle size of the added compound. The study has demonstrated the usefulness of continuous NIR measurements for rapid evaluation of the mixing process when deciding the best particle size of microcrystalline cellulose to mix with compounds of different particle shape and cohesive properties. Smaller particle sizes of microcrystalline cellulose (53–106 μm) were better for aspirin (212–250 μm), whereas larger particles (212–250 μm) were better for aspartame (212–250 μm). The characteristics of the compounds also need to be considered when deciding the order of addition of secondary compounds when mixed with microcrystalline cellulose. The time required to achieve a uniform mixture was much less when povidone was added before aspirin, rather than vice versa.

1. Introduction

The physical properties of particles are known to have an effect on the mixing and segregation of powders. A particle size variation between individual components of powder mixtures is widely accepted as the main cause of segregation in powders; other factors include particle shape and particle density (Williams, 1976; Harnby et al., 1985; Fan et al., 1990; Rhodes, 1990; de Silva, 1997; Kaye, 1997). Another important factor that influences the mixing and segregation of powders, is the flow characteristics of the particles. Attractive forces are small between free flowing particles and this gives them a freedom of motion that facilitates movement of powder within the vessel; this can result in segregation occurring during movement. Cohesive powders exhibit stronger inter-particle forces and this restricts the movement of individual particles; movement of these powders is more difficult, although segregation is less likely (Train, 1960; de Silva, 1997; Xie, 1997; Alonso and Alguacil, 1999; Feng and Hays, 2003).

NIR spectrometry has been used *in situ* to monitor the blending (Hailey et al., 1996; Sekulic et al., 1996, 1998; Berntsson et al., 2002; Bodson et al., 2006; Ely et al., 2006; Bellamy et al., 2008) and transport (Barajas et al., 2007; Benedetti et al., 2007) of powders. If rapid NIR measurements are made during mixing, it is possible to generate a blending profile by monitoring spectral changes over time (Hailey et al., 1996; Sekulic et al., 1996, 1998; Berntsson et al., 2002; Bodson et al., 2006; Ely et al., 2006; Bellamy et al., 2008). Therefore, the point at which the mixture reaches a homogeneous state can be identified. The influence of factors such as particle size, texture, density and coefficients of friction in driving segregation in four binary mixtures has been studied *in situ* by NIR spectrometry (Ely et al., 2006). Mixtures were blended in a drum blender and axial and radial segregation was assessed; the rotation rate of the blender was found to influence axial segregation. The effects of vessel fill level, rotational speed, mixing time and the presence of baffles, on the distribution of magnesium stearate in a bin blender, were assessed by taking samples from various points throughout the vessel for analysis by off-line NIR spectrometry (Arratia et al., 2006). Segregated regions were observed at the centre of the blender when a high fill level and low rotation rate were employed. It has also been possible to detect *in situ* segregation in a lactose sample containing two different particle sizes as it flowed through a vertical pipe (Barajas et al., 2007).

In a recent study (Bellamy et al., 2008), non-invasive NIR spectrometry with a diode array detector was used to generate blending profiles for binary mixtures of microcrystalline cellulose and a second compound of pharmaceutical interest (e.g. aspirin) mixing in

* Corresponding author. Tel.: +44 141 548 2067; fax: +44 141 548 4212.
E-mail address: d.littlejohn@strath.ac.uk (D. Littlejohn).

0378-5173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2008.05.030

a scaled-down convective blender. It was shown for aspirin that in quantitative analysis, measurements made at the 2nd overtone peak in first derivative spectra are less sensitive to particle size changes than those at the 1st overtone. The peak-to-peak noise of the mixing profile obtained from the 2nd overtone of aspirin changed linearly with the particle size of aspirin (the first time this has been reported), which indicates that the mixing profile can also be used to monitor particle size changes caused by particle agglomeration or attrition during the mixing process. Hence, measurement of the mixing profile in real time with NIR spectrometry provided simultaneously the opportunity to study the dynamics of powder mixing, make quantitative measurements of an active compound and monitor changes in particle size as blending proceeds. In this study, the convective blender described previously (Bellamy et al., 2008) has been used to investigate in more detail how the mixing process is influenced by the particle size and cohesive properties of powders. Particular emphasis has been placed on evaluating the optimum choice of particle size of microcrystalline cellulose when mixed with different compounds. In addition, the order of addition of compounds with different cohesive properties and its influence on the mixing of ternary mixtures has been assessed. Studies of this type have not been reported in previous investigations of powder mixing using continuous real-time monitoring by NIR spectrometry. The study shows that analysis of mixing profiles generated by real-time non-invasive NIR spectrometry allows rapid assessment of the mixing dynamics of different powder mixtures, especially when attempting to select compatible particle size ranges and decide the order of addition of compounds in a mixture.

2. Experimental

2.1. Bench top convective mixer

The scaled-down convective mixer has been described previously (Bellamy et al., 2008). The vessel has a pot size of about 500 mL and as it is made of glass, NIR measurements of the powders can be made non-invasively during mixing. One component was placed into the vessel and the stirrer motor (IKA Eurostar, VWR International) started; agitation of the powder (at 50 rpm) was monitored for a period of time to establish a NIR baseline signal. Other compounds were added by pouring powder directly from a beaker into the centre of the vessel, without stopping the mixer; mixing was then continued for a further period of time while NIR spectra were recorded.

2.2. Powders

The microcrystalline cellulose used was Avicel (FMC, Cork, Ireland), which was sieved through 10 cm diameter brass pan sieves (Endecotts Ltd., UK) to obtain different particle size ranges; Avicel particles are granular in shape. In some experiments, unsieved Avicel PH-101 or PH-102 was used, of average particle size 50 or 90 μm, respectively, and particle size range of 20–140 or 30–259 μm, respectively. The compounds added to Avicel were aspirin (Sigma–Aldrich, A5376, Dorset, UK), citric acid (Sigma–Aldrich, C7129), aspartame (GlaxoSmithKline), or povidone K90 (GlaxoSmithKline) which have, respectively, the following particle shape: needle (low aspect ratio)/monoclinic; needle (low aspect ratio); needle (large aspect ratio); platelet. The powders were sieved to obtain specific particle size ranges to add to Avicel.

2.3. Near infrared reflectance spectrometry

A Zeiss Corona 45 NIR spectrometer (Carl Zeiss, Heidenheim, Germany) was used non-invasively. The optimum measurement distance between the mixer and spectrometer was found to be 13 mm and the spot diameter was 15 mm. Measurements were acquired, relative to a reflectance standard, using Aspect software (Carl Zeiss) and stored as $\log 1/R'$. The reflectance standard for all mixing experiments was reflective white paper placed inside the mixer vessel. The integration time for each scan was set automatically; usually, NIR spectra were acquired every 0.5 s (10 co-added scans of 32 ms). A dark current measurement was required before each set of experiments to determine the inherent noise coming from the diode array detector. Spectra were exported as tab-delimited text files into Matlab version 6.5 (Mathworks, Natick, USA) for analysis using the PLS_Toolbox version 3.0.4 (Eigenvector Research, USA). First derivative spectra were calculated using the Savitsy–Golay (Savitsky and Golay, 1964) algorithm with a filter width of 5 points and a second order polynomial. Use of second derivative spectra provided no advantage in this investigation.

Table 1
First derivative peak positions for compounds added to Avicel; 1st and 2nd overtones, respectively

Compound	Peaks in first derivative spectrum (cm^{-1})
Aspirin	6086 and 8956
Citric acid	6814 and 8669
Aspartame	6043 and 8858
Povidone 90	5960 and 8623

2.4. Real-time monitoring of mixing processes by non-invasive NIR spectrometry

Typically, 75 g of Avicel was placed in the mixing vessel and the impeller speed was set to 50 rpm. Additions of the secondary compound were made after 120 s and mixing was normally continued for a further 780 s; NIR spectra were acquired every 0.5 s. The measurements in the initial 120 s were used to establish the baseline of the mixing profile prior to addition of the second compound. The average signal during the last 99 s of the mixing profile (i.e. 801–900 s) was used for quantitative measurements at selected wavenumbers. The peaks in the first derivative spectra of the secondary components that were used to generate the mixing profiles are shown in Table 1.

3. Results and discussion

3.1. Mixing profiles based on NIR spectra

An example of a mixing profile obtained by non-invasive NIR spectrometry is shown in Fig. 1 for addition of citric acid to Avicel; the measurements were made at the C–H 2nd overtone in the 1st derivative spectrum of citric acid at 8669 cm^{-1}. The profile displays a peak at about 180 s, which results from a concentrated portion of citric acid powder moving through the NIR observation window before complete dispersion occurs and a plateau in the signal is reached.

It has been shown previously for aspirin (Bellamy et al., 2008) that the magnitude of 2nd overtone NIR signals are less affected by changes in the particle size of the aspirin added to Avicel than the 1st overtone signals, owing to the greater information depth achieved. It was also shown that the peak-to-peak noise of the signal in the plateau region of the mixing profile increased linearly with the particle size of the aspirin when 2nd overtone measurements were used. To check that these observations were applicable to other compounds, 7.5 g of citric acid particles of different sizes were added to 75 g of Avicel PH-101 and the NIR mixing profiles obtained. Fig. 2 shows that the average signals for the last 99 s of

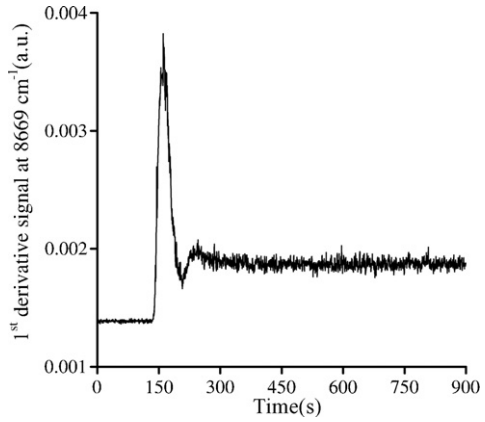

Fig. 1. Mixing profile for addition of 15 g citric acid (212–250 μm) to 75 g Avicel PH-101 mixing at 50 rpm; measurements at 8669 cm^{-1}.

each profile at 8669 cm^{-1} (2nd overtone) are much less affected by the particle size of citric acid than those at 6814 cm^{-1} (1st overtone). The mid-point of the sieve range has been used in the plots to represent each particle size fraction. Also, Fig. 3 indicates that there was an approximately linear increase in the peak-to-peak noise of the plateau signal in the 2nd overtone mixing profile as the citric acid particle size was increased, in contrast to the results obtained from the 1st overtone measurements (Fig. 4). Having confirmed the advantages identified previously for aspirin, 2nd overtone mixing profiles were used to investigate the mixing dynamics of compounds of different cohesive properties with various particle sizes of Avicel.

3.2. Effect of variation of Avicel particle size on mixing

Aspirin (212–250 and 355–425 μm) and aspartame (212–250 μm) were mixed individually with four different particle sizes of Avicel (53–106, 106–150, 150–212 and 212–250 μm). Aspirin and aspartame were selected as examples of particles that are typically classed as free-flowing and cohesive, respectively. Figs. 5 and 6 show the mixing profiles of aspirin obtained at 8956 cm^{-1} for three replicate experiments involving each combination of Avicel and the two different particle sizes of aspirin. Similar mixing profiles were obtained for measurements at 6086 cm^{-1}.

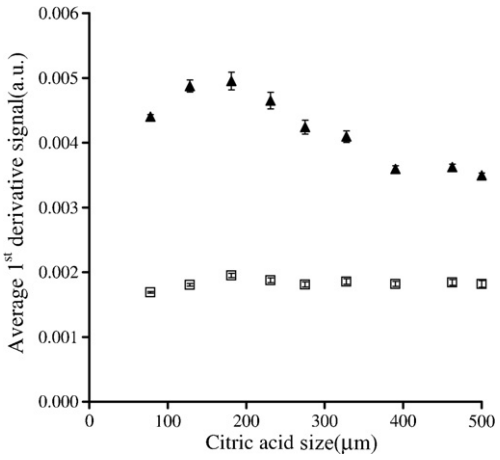

Fig. 2. Average 1st derivative $\log 1/R'$ signal at 6814 cm^{-1} (▲) and 8669 cm^{-1} (□) between 801 and 900 s, for mixtures of 7.5 g citric acid of varying particle size and 75 g Avicel PH-101, mixing at 50 rpm. The error bars are for ±one standard deviation based on measurements every 0.5 s giving $n = 199$.

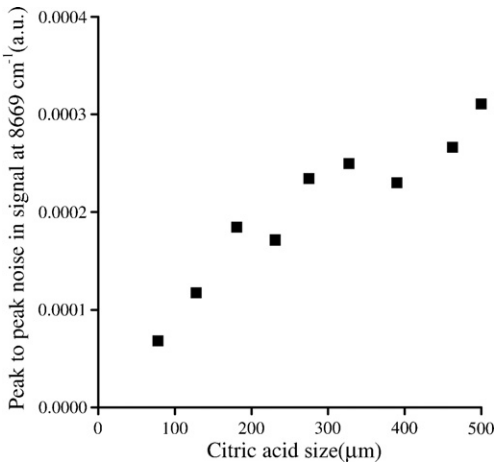

Fig. 3. Peak-to-peak noise in mixing profile based on first derivative NIR signals at 8669 cm^{-1} between 801 and 900 s, for mixtures of 7.5 g citric acid of varying particle size and 75 g Avicel PH-101, mixing at 50 rpm.

The peak-to-peak noise of the mixing profile signals tended to increase for larger sizes of Avicel and aspirin particles, in line with previous observations (Bellamy et al., 2008). Figs. 5 and 6 show that for both particle sizes of aspirin, the most repeatable mixing profiles were obtained with the smallest particle size range of Avicel. As the particle size of Avicel was increased, there was greater variability in the initial phase of mixing. Also, a different magnitude of the signal at the plateau region of the mixing profile sometimes occurred, which implies a different concentration of aspirin in the homogeneous state reached. Both features indicate poorer mixing of the aspirin particle sizes selected with larger particle sizes of Avicel. Greater inter-particle forces will exist for the smaller Avicel particles, which seem to be better at entraining and dispersing the aspirin particles; with larger Avicel particles there is a greater possibility of some of the aspirin powder remaining under the impeller, i.e. segregation, resulting in a lower NIR signal. When the particle size of Avicel is smaller, it is more likely that the Avicel particles can fill the voids between the larger aspirin particles thus reducing the amount of segregation (de Silva, 1997).

When aspartame was added to Avicel, the mixing profiles shown in Fig. 7 were obtained, based on the 2nd overtone signals at 8858 cm^{-1}. In comparison with aspirin, aspartame particles are not

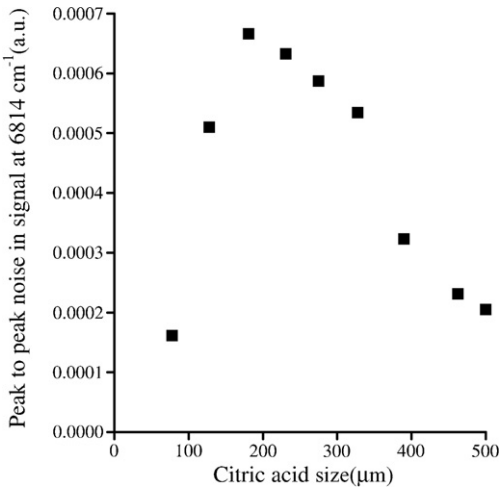

Fig. 4. Peak-to-peak noise in mixing profile based on first derivative NIR signals at 6814 cm^{-1} between 801 and 900 s, for mixtures of 7.5 g citric acid of varying particle size and 75 g Avicel PH-101, mixing at 50 rpm.

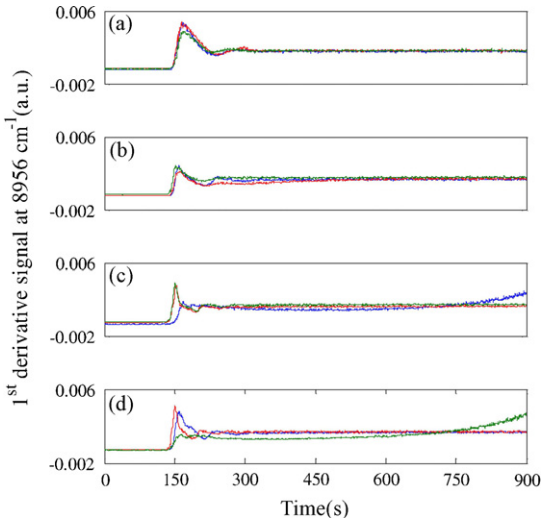

Fig. 5. First derivative $\log 1/R'$ mixing profiles at 8956 cm^{-1}, for three replicate experiments (red, blue and green) involving addition of 7.5 g aspirin (212–250 μm) to 75 g of Avicel with a particle size of: (a) 53–106 μm, (b) 106–150 μm, (c) 150–212 μm and (d) 212–250 μm, mixing at 50 rpm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

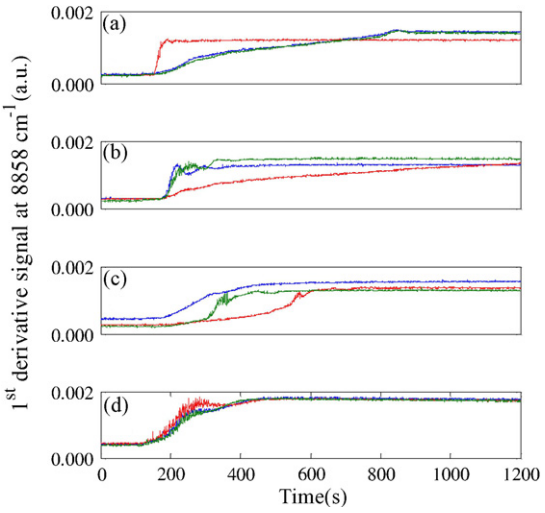

Fig. 7. First derivative $\log 1/R'$ mixing profile at 8858 cm^{-1}, for three replicate experiments (red, blue and green) involving addition of 7.5 g aspartame (212–250 μm) to 75 g of Avicel with a particle size of: (a) 53–106 μm, (b) 106–150 μm, (c) 150–212 μm and (d) 212–250 μm, mixing at 50 rpm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

drawn towards the impeller very quickly, as indicated by a slower change in the NIR signal during the initial period of mixing. The rougher particle surface and greater inter-particle spaces typical of larger Avicel particles promoted more consistent mixing of the aspartame than achieved with smaller Avicel particles. Although the nominal particle size range of the secondary powders used to generate the results in Figs. 5 and 7 were the same, the optimum particle size of Avicel for aspirin and aspartame is quite different. This demonstrates that particle shape and the cohesive properties of compounds are important factors to consider when selecting compatible particle size ranges of components in a mixture as suggested previously (de Silva, 1997) and that NIR measurements made in real time can assist the selection process.

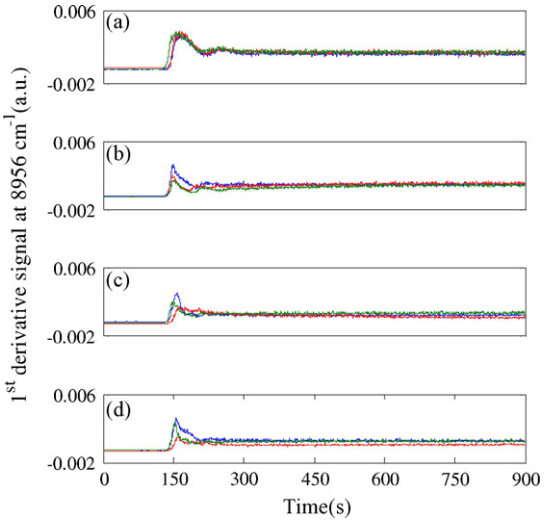

Fig. 6. First derivative $\log 1/R'$ mixing profiles at 8956 cm^{-1}, for three replicate experiments (red, blue and green) involving addition of 7.5 g aspirin (355–425 μm) to 75 g of Avicel with a particle size of: (a) 53–106 μm, (b) 106–150 μm, (c) 150–212 μm and (d) 212–250 μm, mixing at 50 rpm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.3. Multiple component powder mixtures

It is common for industrial mixing processes to contain more than two materials and the order of addition of the compounds to a blender may influence the mixing process and ease of particle dispersion, depending on the size and cohesive properties of the particles. Variations in the mixing characteristics of a three-component system were investigated for addition of 5 g aspirin and 5 g povidone 90 (both 212–250 μm) to 75 g Avicel PH-102. Mixing profiles measured at the 2nd overtone signal of povidone (8623 cm^{-1}) were obtained for addition of aspirin and then povidone, and vice versa (Fig. 8). The plot in Fig. 8a shows an increase in signal at 160 s, caused by the addition of povidone 90 and then a decrease at 460 s due to addition of aspirin. The plot in Fig. 8b shows a decrease at 140 s on addition of aspirin (the response is faster due to aspirin being free flowing and reaching the impeller more quickly) with a subsequent increase in the signal at 460 s

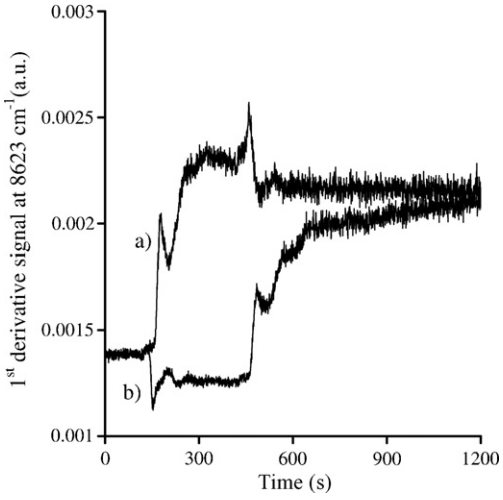

Fig. 8. First derivative $\log 1/R'$ at 8623 cm^{-1} for additions of aspirin (212–250 μm) and povidone 90 (212–250 μm) to Avicel PH-102, mixing at 50 rpm. First addition at 120 s, followed by second addition at 420 s. (a) Povidone added first; (b) aspirin added first.

following the addition of povidone 90. The plots in Fig. 8 show that the time taken to reach the plateau in the signal is much shorter if povidone is added first compared to the situation when aspirin is added first (about 700 s versus 1200 s, respectively).

These experiments illustrate that in addition to detecting when a homogeneous mixture had been achieved (the end-point of mixing), non-invasive NIR measurements can be used to optimise the order of addition of particles of different compounds and the selection of appropriate relative particle sizes. These advantages, not elucidated in previous published studies, will not only help minimise mixing times, but may also improve the stability and homogeneity of resulting mixtures. It is likely, therefore, that continuous measurement of powder mixing by NIR spectrometry offers potential advantages in process and product development as well as in control of manufacturing.

Acknowledgements

The support of EPSRC/DTI through LINK grant GR/R/19366/01 is acknowledged. AN thanks the Royal Society for a Royal Society University Research Fellowship and LJB thanks CPACT for funding.

References

Alonso, M., Alguacil, F.J., 1999. Dry mixing and coating of powders. Rev. Metal. 35, 315–328.
Arratia, P.E., Duong, N., Muzzio, F.J., Godbole, P., Lange, A., Reynolds, S., 2006. Characterizing mixing and lubrication in the Bohle Bin blender. Powder Technol. 161, 202–208.
Barajas, M.J., Cassiani, A.R., Vargas, W., Conde, C., Ropero, J., Figueroa, J., Romañach, R.J., 2007. Near-infrared spectroscopic method for real-time monitoring of pharmaceutical powders during voiding. Appl. Spectrosc. 61, 490–496.
Bellamy, L.J., Nordon, A., Littlejohn, D., 2008. Real-time monitoring of powder mixing in a convective blender using non-invasive reflectance NIR spectrometry. Analyst 133, 58–64.
Benedetti, C., Abatzoglou, N., Simard, J.-S., McDermott, L., Léonard, G., Cartilier, L., 2007. Cohesive, multicomponent, dense powder flow characterization by NIR. Int. J. Pharm. 336, 292–301.
Berntsson, O., Danielsson, L.-G., Lagerholm, B., Folestad, S., 2002. Quantitative in-line monitoring of powder blending by near infrared reflectance spectroscopy. Powder Technol. 123, 185–193.
Bodson, C., Dewé, W., Hubert, Ph., Delattre, L., 2006. Comparison of FT-NIR transmission and UV–vis spectrophotometry to follow the mixing kinetics and to assay low-dose tablets containing riboflavin. J. Pharm. Biomed. Anal. 41, 783–790.
de Silva, S.R., 1997. Mixing and segregation in industrial processes. International Fine Particle Research Institute report SAR, pp. 12–20.
Ely, D., Chamarthy, S., Carvajal, M.T., 2006. An investigation into low dose blend uniformity and segregation determination using NIR spectroscopy. Colloids Surf. A 288, 71–76.
Fan, L.T., Chen, Y.-M., Lai, F.S., 1990. Recent developments in solids mixing. Powder Technol. 61, 255–287.
Feng, J.Q., Hays, D.A., 2003. Relative importance of electrostatic forces on powder particles. Powder Technol. 135/136, 65–75.
Hailey, P.A., Doherty, P., Tapsell, P., Oliver, T., Aldridge, P.K., 1996. Automated system for the on-line monitoring of powder blending processes using near-infrared spectroscopy. Part I. System development and control. J. Pharm. Biomed. Anal. 14, 551–559.
Harnby, N., Edwards, M.F., Nienow, A.W., 1985. Mixing in the Process Industries. Butterworths, London.
Kaye, B.H., 1997. Powder Mixing. Chapman and Hall, London.
Rhodes, M.J. (Ed.), 1990. Principles of Powder Technology. John Wiley and Sons, Chichester.
Savitsky, A., Golay, M.J.E., 1964. Smoothing and differentiation of data by simplified least squares procedures. Anal. Chem. 36, 1627–1639.
Sekulic, S.S., Wakeman, J., Doherty, P., Hailey, P.A., 1998. Automated system for the on line monitoring of powder blending processes using near-infrared spectroscopy. Part II. Qualitative approaches to blend evaluation. J. Pharm. Biomed. Anal. 17, 1285–1309.
Sekulic, S.S., Ward, H.W., Brannegan, D.R., Stanley, E.D., Evans, C.L., Sciavolino, S.T., Hailey, P.A., Aldridge, P.K., 1996. On-line monitoring of powder blend homogeneity by near-infrared spectroscopy. Anal. Chem. 68, 509–513.
Train, D., 1960. Pharmaceutical aspects of mixing solids. Pharm. J. 6, 129–134.
Williams, J.C., 1976. The segregation of particulate materials. A review. Powder Technol. 15, 245–251.
Xie, H.-Y., 1997. The role of interparticle forces in the fluidisation of fine particles. Powder Technol. 94, 99–108.