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International Journal of Pharmaceutics 345 (2007) 108–115

INTERNATIONAL JOURNAL OF PHARMACEUTICS

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Uniformity of poorly miscible powders determined by near infrared spectroscopy

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Received 4 April 2007; accepted 23 May 2007
Available online 25 May 2007

Abstract

The objective of this work was to study with near infrared spectrometry (NIRS) the degree of mixing of poorly miscible binary mixtures of carbamazepine (CBZ) and α-lactose monohydrate (LMH). CBZ was cohesive and the particle size difference between CBZ (0.3 μm) and LMH (75 μm) was substantial. Mixed batches were measured directly in the mixing container with a fiber-optic probe. The spectral data were filtered by applying a novel automated selection technique during the NIRS measurement. The data analyses were performed with partial least squares modeling. Reference measurements were carried out with ultraviolet spectrophotometry. The results describe the degree of homogeneity at various depths. Some of the mixtures densified when the mixing speed increased. The densification of the batches was a source of error because it caused changes in the measuring geometry. The automated selection technique for the spectra reduced this problem. NIRS detected differences in the mixing degrees of mixtures and the method is suitable for mixing studies. However, the difference in the particle size of the materials and the densification caused problems to the measuring geometry. NIRS can be used *at line*, but the method requires accurate operation and method developing before it is useable.

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Keywords: Powder mixing; Uniformity of powders; Near infrared spectroscopy; Particle size; Partial least squares modeling

1. Introduction

Mixing is a crucial process for manufacturing solid dosage forms. Mixing is also a complex process and many variables can influence the degree of mixing. Such variables can include, for example, the characteristics of the solid or of the mixer and the operation conditions (Fan et al., 1970). This explains why optimum operation conditions are unique to every product (Sindel et al., 1998).

Mixing has been the target of many previous studies. Poux et al. (1991) studied various kinds of mixers. Johnson (1975) researched the influence of powder characteristics such as particle size and size distribution on the segregation of mixtures. Speiser and Tawashi (1962) attempted to determine how various types of mixers influence the mixing time and the homogeneity of a mixture.

The uniformity of pharmaceutical dosage forms has been controlled by assembling samples from the processing mass at different stages. Sampling has been major problem in the mixing studies. It has been challenging to obtain representative sample from the container. When any kind of probe or thief sampler is pushed in the mass it will affect the mass. The active ingredient content of these samples has been determined with chromatographic or ultraviolet–visible (UV–vis) spectroscopic method (Wargo and Drennen, 1996). Conventional operations are time consuming and laborious. Near infrared spectroscopy (NIRS) is overtaking previous methods because of its advantages. The biggest benefits of NIRS are that the samples require no pre-processing and real time information is gained from the process. Unlike conventional methods of analysis, NIRS is fast, non-invasive, provides information about physical and chemical properties of the sample and it can be used *in line*, *at line* and *on line* measurements. NIR spectroscopy can be used for the qualitative analysis as well as for the quantitative analysis of powders (Siesler et al., 2002).

Quite recently, process analytical technology (PAT) has been developed to improve our understanding of the pharmaceu-

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doi:10.1016/j.ijpharm.2007.05.044

tical process and to monitor and to control critical process parameters (FDA, 2004). NIRS could be one of the major PAT tools because its aforesaid benefits. NIR spectroscopy has been used as a process analytical technology tool (Cogdill et al., 2004). Cogdill et al. (2005a,b,c) developed and validated a PAT method using NIR spectroscopy for the *on line* prediction of intact tablet hardness and active pharmaceutical ingredient (API) content.

A chemical reference measurement from liquid bulk cannot be compared with measurements made with a fiber-optic probe from a solid because a powder mixture is always heterogeneous (Berntsson et al., 2000). When measuring solids, it would be favorable to spin the sample and to measure from different sides of the sample. In this way, sample error can be avoided. Usually, the average concentration of the powder mixture serves as a reference for all the spectra to increase the signal-to-noise ratio (Siesler et al., 2002). At least some of the samples must be analysed with a reference technique such as high performance liquid chromatography (HPLC) or UV spectroscopy. The real concentrations can be found with these methods, which can be used in a calibration model or validation process (Berntsson et al., 2000).

Recently, NIRS has been attached to many kinds of mixing systems. Ciurczak (1991) investigated the homogeneity of mixtures *off line*. Sekulic et al. (1996) and El-Hagrasy et al. (2001) studied powder blend homogeneity. Blanco et al. (2004) and Filho et al. (2004) acquainted themselves with strategies for constructing a calibration set for quantitative NIRS measurements. Berntsson et al. (2002) monitored *in line* powder blending by near infrared reflection spectroscopy and Patel et al. (2000) quantitated polymorphs in mixtures. Rantanen et al. (2005) used chemometrics in order to specify the factors influencing the quantification of anhydrate/hydrate powder mixtures. Chemometrics has also been used in a study conducted by Li and Worosila (2005) when they studied the quantitation of ingredients in powder mixtures using *at line* NIRS. Other studies have used NIRS with a fiber-optic probe. The first reported study on powder mixtures with a fiber-optic probe was conducted by Kaye et al. (1969). More recently, for example, Li et al. (2006) studied the mass-balanced blend uniformity of pharmaceutical powders with a fiber-optic probe. Benedetti's study concerning powder flow characterisation with *in line* NIRS also used a probe (Benedetti et al., 2007).

The purpose of this work was to study whether NIR spectroscopy is suitable for measuring the degree of mixing in poorly miscible powder mixtures. The mixtures were measured *at line* with a fiber-optic probe using a novel automated selection technique during the NIRS measurement. This filtering technique decreased influence of chances in the measuring geometry. To obtain an analysis, the content of the powder mixture was determined for each acquired NIR spectrum by means of a multivariate calibration model. Special attention was paid to the particle size differences between carbamazepine (CBZ) and α-lactose monohydrate (LMH), the triboelectricity of CBZ and the effect of these factors on the process.

2. Experimental

2.1. Materials

The experiments were prepared on carbamazepine (CBZ) (USP, CAS 298-46-4, Hawkins Inc. Pharmaceutical Group, Minneapolis, USA) and α-lactose monohydrate (LMH) (Pharmatose, DMV International, Veghel, The Netherlands). CBZ was identified as a polymorph III by NIR spectroscopy and X-ray powder diffraction (XRPD). CBZ was micronised and its particle size was around 300 nm measured with Zetasizer 3000 HAS (Malvern Instruments, Worcestershire, UK) based on intensity measurement. The particle shape seemed spherical. The particle size and shape appear in the SEM micrographs (Fig. 1a1, a2). In addition to the 300 nm particles, the powder also contained larger particles. The small particles aggregate in the CBZ powder. The particle size of used LMH was, according to the manufacturer, 200 mesh (i.e. 75 μm). According to the SEM micrographs (Fig. 1b1, b2) the LMH powder also contained smaller particles. The CBZ particles were about 250 times smaller than LMH particles.

2.2. Methods

2.2.1. Mixtures

The batch size was 25.0 g and the filling rate was approximately 80% (v/v). The dominant substance was first weighed right in the jar, followed by the residual substance. The CBZ percentages for the calibration model were 0, 1, 5, 10, 15, 20, 25, 30, 40, 45, 50, 60, 70, 75, 80, 85, 90 and 100%. The powders for the calibration model were mixed in a Turbula mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) until the mixtures were mixed homogenously according to the UV analysis. The experimental batches were mixed at varying speeds and concentrations, and the experiment includes nine replicates according to the experiment chart (Fig. 2). The mixing time was 14 min for all of the experimental batches. The experiment chart was created with MODDE software (Umetrics, Umeå, Sweden). All of the powders were stored in 45% relative humidity (RH) to reduce the electrostatic forces at least 72 h before the mixing.

2.2.2. Near infrared spectroscopy

The near-infrared spectroscopy setup consisted of a NIRS spectrometer with an InGaAs diode array detector, tungsten light source, and six 400-μm collecting optical fibers around one collection fiber (Control Development Inc., South Bend, USA). The white teflon served as a reference (99% reflective Spectralon, Labsphere Inc., North Sutton, USA). Spec32 software (version 4.0, Control Development Inc., South Bend, USA) was used to control the NIR spectrometer. The batches were measured at the spectral region from 1100 to 2200 nm in the same jars where they were mixed using the fiber-optic probe. Consequently, removal of the sample was unnecessary. Measurements were made at three different depths in the batch: at the surface, in the middle and at the bottom, according to Fig. 3. The NIR measurement data were filtered as described afterwards.

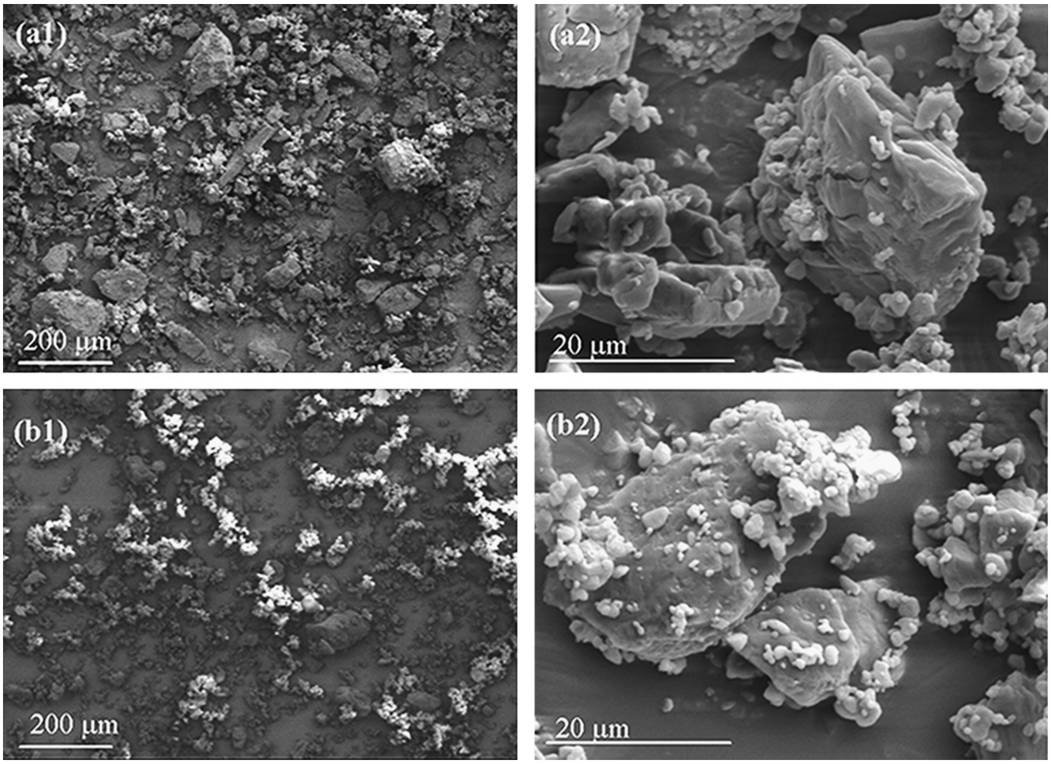

Fig. 1. SEM micrographs (a1 and a2) CBZ; (b1 and b2) LMH.

2.2.3. *Filtering of NIRS-measurement data*

In NIRS reflectance measurement, the bulk density (i.e. geometry changes in the NIR measurement) of the mass affects among other things the intensity of the reflected signal. Because of this phenomenon, the level of the measured absorption spectrum fluctuates during measurement. This variation in the intensity of the spectra results from the fact that the probe can densify the batch. The density of some batches is also higher at the edges of the batch jar due to centrifugal forces during the mixing process. Total computational correction of the fluctuation phenomenon is impossible today.

NIR equipment is capable of measuring over 10 spectra per second. This makes it possible to choose and use those spectra in which the intensity is about the same. At this moment, the bulk density of the batch is, within certain limits, the same. The filtering programme was coded using Matlab software (Ver-

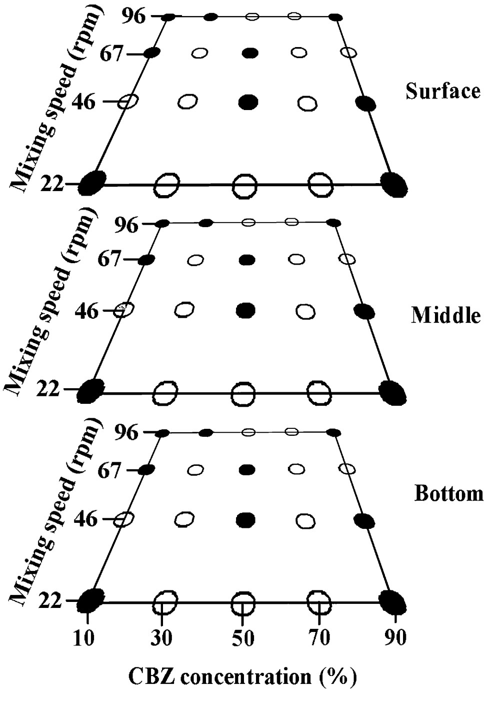

Fig. 2. The experiment chart. Batches from 1 to 29 (S1–S29). The replicates marked with black.

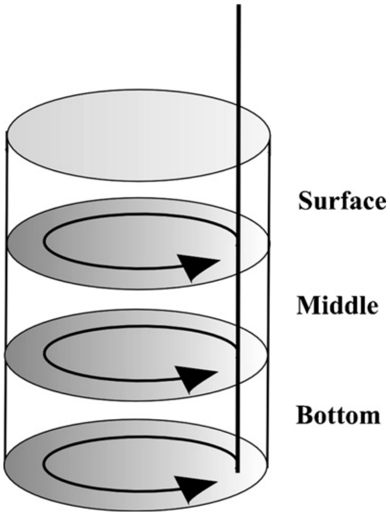

Fig. 3. A schematic picture of the batch jar. The batches were measured at the surface, in the middle and at the bottom of the batch using a fiber-optic probe.

sion 7.0, The MathWorks Inc., Natick, USA). The programme examined the inactive part of the spectrum and defined those spectra for which NIR reflectance ranges from 95 to 100% as the same as identical to the background (white teflon). The filtering accepted pure substances and all the mixtures between them. The measurement was carried out using counts as intensity so that the inactive part in the spectra was similar in all the mixtures. In this study, at least 36 spectra from each experimental batch were accepted within the limits of 95–100% of the background reflection. This means that from each measuring point on the bottom, in the middle and on the surface of the batch, at least 12 spectra were gathered. The filtering made it possible to remove nearly completely any fluctuation in the measured absorption spectrum.

2.2.4. *CBZ assay*

The calibration curve for the UV assay was prepared for the CBZ solutions. The sample size was 60.0 mg of CBZ dissolved with 25.0 ml of ethanol (96%) in the 100% CBZ sample. An assay for CBZ powder mixtures was made for the calibration set batches in concentrations of 1, 10, 30, 60, 70 and 100%. CBZ concentrations were determined with a UV-vis spectrophotometer (Ultrospec II, LKB Biochrom Ltd., Cambridge, UK) at 285 nm.

2.2.5. *Data analysis*

Diffuse reflection NIR spectra of powders typically display a scattering variation, due to, for instance, variation in the powder density or in particle size or shape. This scattering variation is approximately proportional to the pseudo-absorbance value ($\log(1/R)$) (Norris and Williams, 1984). The influence of scattering can be diminished by the data pre-treatment method standard normal variate (SNV) transform (Barnes et al., 1989; Guo et al., 1999). SNV is a preprocessing method that corrects for differences in spectroscopic path lengths or multiplicative variations. SNV corrections were performed for the data matrix with self-made m-script using the Matlab software. SNV correction is necessary even if the NIR measurement data were already filtered.

The multivariate calibration model was used to define the degree of mixing. The model provided relationships between concentrations of components and measured pseudo-absorbencies ($\log(1/R)$) to those batches with at least two wavelengths (Berntsson et al., 2000). In this study, Partial Least Squares (PLS) modeling served as a multivariate calibration model. The PLS modeling was performed with SIMCA-P software (Umetrics, Umeå, Sweden).

Before PLS modeling, the data were mean centered (i.e. each data point was subtracted by the average value of that variable). Such matrix normalisation is usually recommended to improve the predictability and interpretation of the PLS regression model (Eriksson et al., 2001). The batches of the calibration model were used to create a PLS model. The actual measurements were fitted to this calibration model with SIMCA-P software. Over 500 spectra were used to the calibration set and over 930 spectra were set against this calibration by PLS modeling.

3. Results and discussion

CBZ was difficult to mix because of its electrostatic nature and small particle size. Moreover, the size difference between CBZ and LMH presented a problem in mixing and in the NIR measurement. Increasing the relative humidity of the air decreased, but did not eliminate, the problem. CBZ particles adsorbed to the surface of LMH particles which affected to the mixing behavior of the mixtures (Bell et al., 1971; Malcolmson and Embleton, 1998). The coating of the LMH by CBZ particles appears in the SEM micrographs (Fig. 4). The results are divided into two sections: Mixing results and the NIR measurement.

3.1. *Mixing results*

The principal component analysis (PCA) was created from SNV-corrected calibration data with SIMCA-P software (Fig. 5). The three most important components are described in the PCA score scatter 3D plot. They explained 99.5% of the X-variance after mean centering. The distribution of batches in the PCA plot indicated that the spectra contain logically changing sections. The averages were calculated from each calibration point. The average calibration model was used to create a PLS model for the experimental batches. Calibration curve gave a good linearity (Fig. 6).

PLS model from SNV-corrected data was completed using five components. The first PLS component explained 85.1% of the X-variance after mean centering. All five components explain 97.1% of the X-variance. In addition, the X-residuals were small and non-systematic (data not shown). This means that the model is adequate to describe the systematic variation in the NIR spectra of the powder mixtures. No exact quantitative results are introduced here because SNV correction can alter intensities of spectra (Barnes et al., 1989).

The RMSEM (root mean square in mixing) value was created for this study to describe the degree of mixing. The equation was similar to the RMSEP (root mean square in prediction) equation. The RMSEP equation was used to assess the predictive ability of multivariate models by comparing predictions with reference values for a test set (Faber and Kowalski, 1997). In this study, the RMSEM equation (Eq. (1)) described the deviation of a measured concentration at every measuring point at every level in every batch:

$$\mathrm{RMSEM} = \sqrt{\frac{\sum_{i=1}^{n}(\hat{y}_i - y_i)^2}{n}} \tag{1}$$

In Eq. (1), $\hat{y}_i$ denotes the predicted CBZ concentration and y_i the actual CBZ concentration, and n is the number of values or spectra measured at every measuring point at every level in every batch, respectively. Thus, the RMSEM value was calculated for every measuring point from three different locations: (a) at the surface, (b) in the middle and (c) at the bottom. RMSEM values were calculated with Microsoft Office Excel 2003 software (Microsoft, Redmond, USA). RMSEM values were used

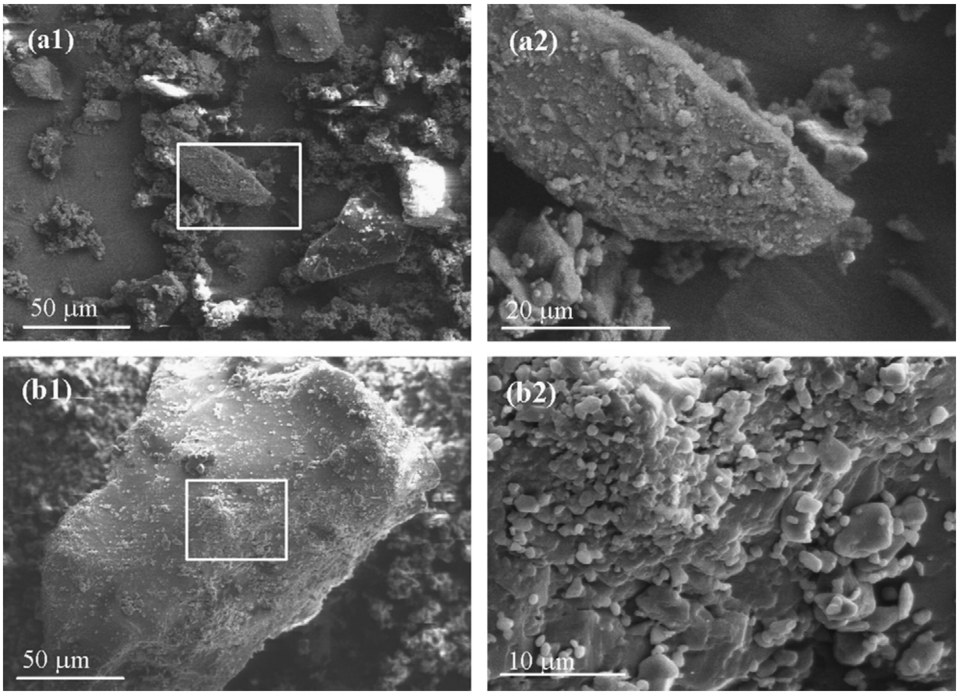

Fig. 4. SEM micrographs (a1 and a2) 50% CBZ and 50% LMH; (b1 and b2) 90% CBZ and 10% LMH.

to create contour plots with SigmaPlot 2000 software (Systat Software Inc., Erkrath, Germany) (Fig. 7). The contour plot was created for every depth level to describe the degree of mixing for every batch. The contour plots of the different levels expressed the degree of mixing in the experimental domain. The mixing degrees varied substantially according to Fig. 7. No coherent pattern was observed.

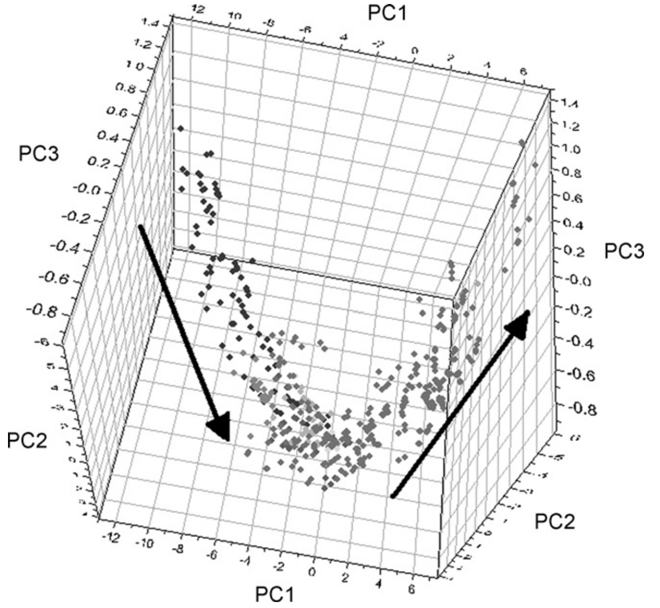

Fig. 5. PCA score scatter 3D plot. The PCA plot provides a graphical presentation of the spectra in the calibration set. The data have been mean centered and SNV corrected. The arrows point towards increasing CBZ concentration. The first PC explained 86.3% of the X-variance, the second PC, 98.5% (cumulative with the first PC), and the third, 99.5% (cumulative with the first and the second PC).

The data acquired was also analysed with MODDE software (Umetrics, Umeå, Sweden)(data not shown). The model provided relations to the data based on the experimental chart. The contour plots from the different levels were independent of each other. However, all the models provided relatively similar results. The model obtained was not predictive (Q^2 value was only 0.27 and its R^2 value was 0.39). The inability of the model to predict degree of mixing was due to, among other things, the wide dispersion in predicted CBZ concentrations.

Differences in the degree of mixing were great. Most of the batches were mixed well (RMSEM value 5 or less) or moderately well (RMSEM value over 5 but under 15), but some of the batches hardly mixed at all (RMSEM value over 15). This was desirable because one purpose of this study was to measure differences in mixing degrees of the batches to enable analysis of the degree of mixing.

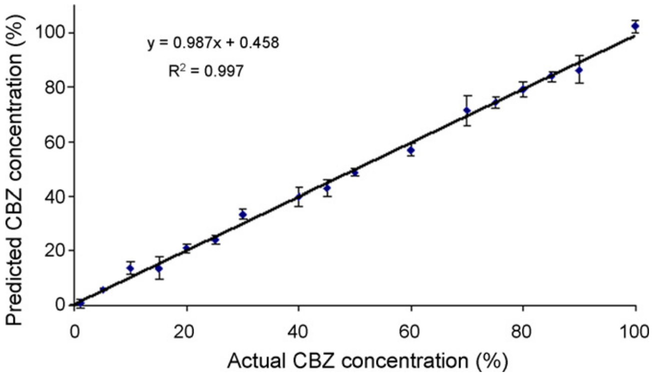

Fig. 6. Calibration curve, SNV-corrected data. The averages with standard deviation, of the spectra from each data point.

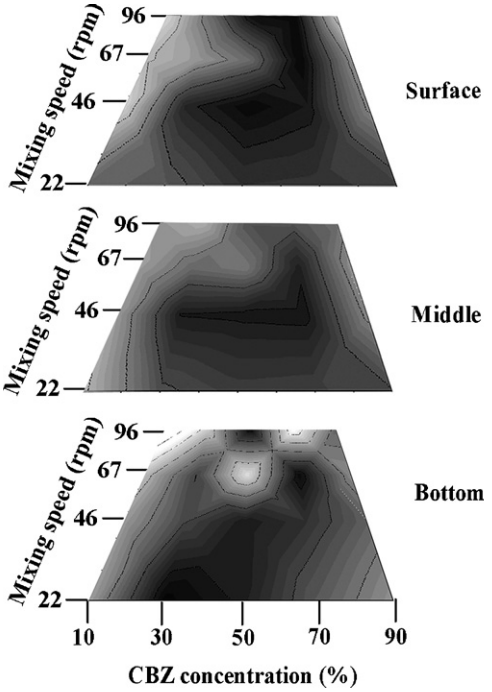

Fig. 7. The concentration difference in the different layers described with the help of RMSEM values. The RMSEM value increases when the concentration difference (heterogeneity of the batch) increases. The darker colour indicates a higher degree of mixing.

The experiment involved nine replicates (Fig. 2). All of these replicates were mixed similarly among each replicate. The replicates control the repeatability of the experiment. The greatest difference in concentration between the predicted and the actual values was about 3% (w/w). This difference occurred between replicate batches which mixing speed was 22 rpm and CBZ concentration 10%. The concentration difference between other replicates was near 1% (w/w). These results suggest that the experiment was repeatable.

UV spectroscopy is considered a standard method for the determination of the content uniformity of powder mixtures (El-Hagrasy et al., 2001). Most of the batches in the calibration set were measured with a UV spectrophotometer. According to the UV analysis, the batches used to create the calibration model were very well mixed. The R^2 value of the equation was 0.9998 (data not shown).

3.2. NIR measurement

The coating of the LMH particles with the CBZ particles caused changes also in the NIR signal when the mixing process proceeded. The small CBZ particles formed clusters between bigger LMH particles in the early phase of the mixing (Fig. 8A). The CBZ particles covered the LMH particles when the mixing proceeded (Fig. 8B). The NIRS detected the situation differently in these two circumstances. In the early stage of the mixing, NIR radiation reflected from one CBZ particle to another CBZ particle before it reflected back to the detector (Fig. 8A). In that case, NIRS detected more CBZ than the mixture contains according to the calibration. When CBZ covered LMH, NIRS radiation reflected straight form the LMH particles (Fig. 8B). The calibration had to be done with as homogeneous a mixture as possible which in this context meant a long mixing time. When the powders were mixed for a long time, the charging of the CBZ particles and the coating increased. This caused dispersion between batches and also the measured CBZ concentration of 10 and 30% were higher than the corresponding values in the

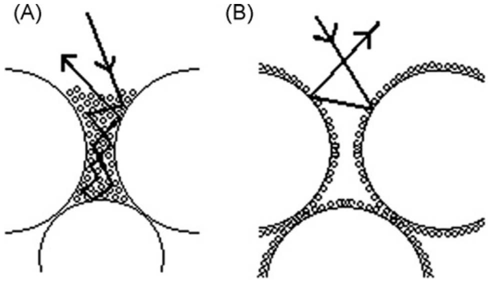

Fig. 8. Behavior of the NIR signal in the mixture. (A) The small CBZ particles form clusters between larger LMH particles in the early phase of the mixing. NIR light reflects from CBZ particle to CBZ particle before it reflects back to the detector in the early stage of the mixing. (B) The CBZ particles cover the LMH particles as the mixing proceeds. NIR radiation reflects from the LMH particles.

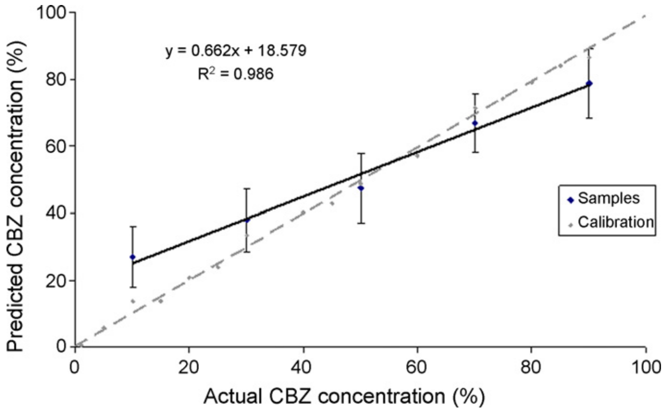

Fig. 9. The calibration curve (grey) and the predicted concentrations of all measured spectra (black).

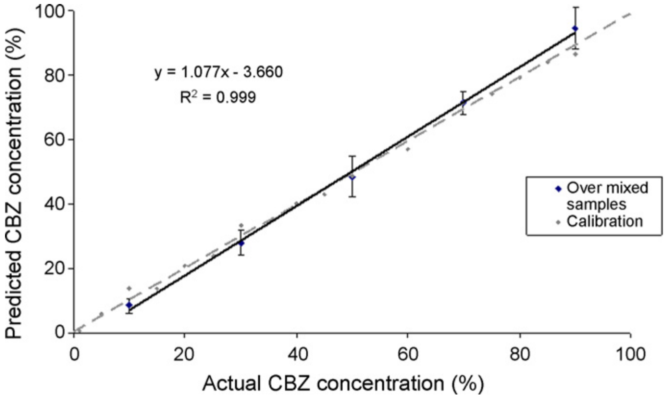

Fig. 10. The calibration curve (grey) and the predicted concentrations of every measured spectrum (black) after extra 45 min. mixing. The lower CBZ concentrations (10 and 30%) have descended to the level of the calibration curve.

Table 1
The decrease in standard deviation with increased mixing time

Mixing time (min)	CBZ concentration level % (w/w)				
	10%	30%	50%	70%	90%
14	9.2	9.4	10.5	8.6	10.4
59	2.3	3.8	6.3	3.5	6.4

calibration curve (Fig. 9). This phenomenon was explained by mixing 12 batches extra 45 min (mixing speed 46 rpm), until the predicted CBZ concentrations decreased to the same level as with the calibration curve (Fig. 10). The increase in homogeneity could also be seen as a decrease in the standard deviation of the predicted CBZ concentrations with different concentration levels (Table 1).

When the CBZ concentration was high (70 or 90% depending on mixing speed), the batch may have densified. The densification of the mixtures was greater when the mixing speed increased. This phenomenon was related to the centrifugal force. In addition, CBZ stuck to the walls, bottom and cap of the mixing jar. The densification of the batches was usually a generator of error because the geometry of measurement changes (Fig. 11). The intensity of the NIRS measurement increased, and thus the predicted CBZ value also increased if the powder was very tight. The distance of the batch from the probe was also crucial for the geometry of the measurement. The geometry of the measurement changed when the distance from the receiver changes. According to Fig. 11, only very little reflection could reach the receiver if the batch lied at distance A from the receiver. If the batch was moved further away from the receiver, to distance B the batch reflected more radiation that could reach the receiver and the intensity increased. The intensity also changed if the distance between the batch and the probe was too high. The distance between the batch and the probe was very important. The filtering of the spectra decreased the densification and the distance problems in this study. Without this filtering the NIR analysis could not be done reliably.

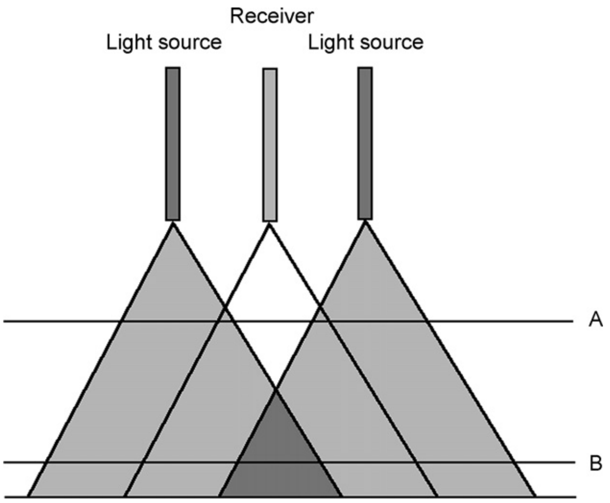

Fig. 11. The influence of geometry on the NIRS measurement.

4. Conclusions

The PCA of the NIR spectra was able to distinguish batches with different CBZ concentrations, which suggests that NIRS detected differences in the mixing degrees of poorly miscible powders. However, the difference in particle size of the materials and the densification due to the electrostatic nature of CBZ caused problems in the NIR measurement. A new filtering technique was used to decrease this problem. The *at-line* NIRS method requires accurate operation and method development before it will be suitable for measuring poorly miscible powders.

Acknowledgement

Orion is acknowledged for the support of this research.

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