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In-line quantification of drug and excipients in cohesive powder blends by near infrared spectroscopy

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ABSTRACT

This work was aimed at investigating the utility of near infrared (NIR) spectroscopy for simultaneous in-line quantification of drug and excipients in cohesive powder blends in a bin blender. A model formulation containing micronized chlorpheniramine maleate (μCPM), lactose, microcrystalline cellulose (MCC) and magnesium stearate (MgSt) was selected for the blending study. An optical head comprising a sapphire window mounted on the lid of the bin was used to collect in-line NIR spectral data of the powder blends. Validated partial least square (PLS) calibration models were used to quantify each component from the NIR spectra of the blends. Additionally, effects of premixing by sieving and high shear mixing and use of an internal prism fixed within the bin on the mixing performance of each component were studied. The statistical results obtained for PLS calibration models and their validation showed the sensitivity of NIR for accurate quantification of blend components. The blend prepared with high shear premixing and with prism achieved uniformity more rapidly than that with high shear premixing but without prism during blending in a bin blender. Premixing using sieving proved to be inadequate for uniform mixing of the blend components as none of the components except MgSt achieved uniform distribution after the preset blending time when blended in the bin blender. This study demonstrated that by high speed sampling and rapid spectral acquisition, distribution of individual blend components can be assessed with high accuracy during blending. Furthermore, high shear premixing facilitated rapid distribution and uniformity achievement of blend components. This technique may be used to monitor the relative distribution of individual blend components in real time and thus, to assess the performance of a bin blender for mixing of cohesive multi-component powder blends during development and production.

1. Introduction

Pharmaceutical companies are recognizing the value of excipients more than ever, particularly when it comes to the manufacture of solid dosage forms such as tablets and capsules. Besides the drug, the tableting/capsule formulations also frequently contain various excipients (fillers, binders, disintegrants, lubricants, glidants, solubilizers, etc.). These inert excipients, even in small quantities, have the potential to affect the characteristics, quality, stability, and/or performance of the final drug product. Hence, uniform mixing of drug and excipients is an essential prerequisite before proceeding to the next operation such as compression or capsule filling. However, as a standard practice, uniformity of a powder blend is determined by estimating the distribution of the drug only. Thus, the distribution of individual excipients is normally assumed to be homogeneous if the drug is uniformly distributed. The role of excipients which not only improve dosage form compliance but also affect the technological and biopharmaceutical performance of the formulation is often overlooked (Reich, 2005). Therefore, it is imperative to identify these excipients along with the drug in the formulation and to thoroughly characterize and quantify them for their uniform distribution during blending and after compression or capsule filling.

The main obstacles in the characterization of powder blends for uniform distribution of blend components (drug and excipients) lie in the collection of representative samples from the blenders and their accurate analysis. Conventionally, samples are obtained from the blender by inserting the thief probe at defined time intervals. Despite the simplicity in their operation, the detrimental effects of intrusive thief probes such as tendency to disturb the powder bed, withdrawal of non-uniform samples in terms of composition and quantity, has long been recognized. A wide array of information can be found in the literature published previously regarding the drawbacks associated with the thief probe (Berman and Planchard, 1995; Berman et al., 1996; Chang et al., 1996; Harwood and Riplay, 1977; Muzzio et al., 1999). Analytical methods usually employed for characterization of thieved samples, such as conventional HPLC, UV spectrophotometry, are often labour-intensive, tedious and require

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the use of organic solvents and reagents. Many pharmaceutical excipients, such as lactose and microcrystalline cellulose (MCC), are not sensitive to these methods or need extensive method development, and hence cannot be quantified readily. Furthermore, owing to the off-line nature of these methods, the quantitative results in terms of drug concentration only become available after some period of time. Thus, timely in-process decision making is not possible.

Several recommendations have been proposed, to replace the conventional methodologies for obtaining samples and their analysis. A special emphasis is also given by the United States Food and Drug Administration (FDA) in its Process Analytical Technology (PAT) guidelines to address these concerns wherein it has stressed the usage of at-line, on-line or in-line measurements (FDA, 2003, 2004). Therefore, development of alternative methods which enable uniformity analysis of blend components in a non-destructive, non-invasive and real time basis has become an issue of interest in both academia and industries. Several non-invasive and non-destructive methods have been investigated by researchers, such as use of radioactive tracers through the bed of non-radioactive tracers (Harwood, 1977), image analysis based on color difference of constituent particles (Lim et al., 1993), fluorescence microscopy (Staniforth and Iveson, 1986), light induced fluorescence (Lai et al., 2001; Harwood et al., 1972), light reflectance (Weinekotter and Reh, 1994), thermal effusivity (Leonard et al., 2008; Mathews et al., 2002), Raman spectroscopy (De Beer et al., 2008; Vergote et al., 2004) and near infrared (NIR) spectroscopy (Hailey et al., 1996; Sekulic et al., 1998; Wargo and Drennen, 1996; Patel et al., 2000; Ufret and Morris, 2001; Berntsson et al., 2002; Shi et al., 2008; Abatzoglou et al., 2008; Sulub et al., 2009). Among these methods, NIR spectroscopy has received considerable interest within the pharmaceutical industry and is being extensively studied owing to a multitude of merits associated with this technique. It offers the pharmaceutical analyst the ability to perform multi-component analysis in real time basis and in a fast, non-destructive manner, requiring little or no sample preparation.

Interestingly, most of the earlier studies carried out using NIR in the powder blending field were aimed at quantifying the active component in binary or multi-component blends and at determining blend uniformity end point based on the distribution of an active component within the powder bed (Hailey et al., 1996; Sekulic et al., 1998; Wargo and Drennen, 1996; Patel et al., 2000; Ufret and Morris, 2001; Berntsson et al., 2002; Sulub et al., 2009). However, some of the recent works (Abatzoglou et al., 2008; Lapointe-Garant et al., 2008; Benedetti et al., 2007; Li and Worosila, 2005; Wu et al., 2009; Shi et al., 2008) carried out in this field helped in improving our understanding of the powder blending process. Abatzoglou et al. (2008) and Lapointe-Garant et al. (2008) studied the in-line application of NIR spectroscopy for real time monitoring of a pharmaceutical blending process through multivariate analysis-derived models. Abatzoglou et al. (2008) studied the blend flow velocity and API level effect on homogeneity and NIR measurements in a 30-L v blender. Benedetti et al. (2007) successfully developed the in-line NIR technique quantifying the composition of flowing multi-component dense powder mixtures.

Li and Worosila (2005) and Wu et al. (2009) investigated the ability of NIR to quantitatively predict the individual blend components in multi-component blends. Wu et al. (2009) used the combination approach of NIR and UV spectroscopy to quantify ibuprofen, MCC, Eudragit and hydroxypropyl methyl cellulose in powder blends using a laboratory scale turbula mixer. However, in both the studies, the blender was stopped during blending and a NIR probe was inserted into the powder bed for spectral acquisition. Thus, the possibility of disturbing the powder bed was not eliminated. Moreover, off-line measurements employed were unlikely to represent the actual state of moving powder. Simultaneous in-line quantification of drug and excipients in cohesive powder blends in IBC bin blender using NIR has been reported by Shi et al. (2008) in which the characterization of the ternary powder blend based on two NIR sensors fixed in a bin blender was carried out. However, the blending study undertaken did not involve the mixing of components with a large difference in particle sizes.

The intent of this study was to investigate the mixing of a cohesive multi-component powder blend consisting of micronized drug in a modified IBC bin blender with in-line NIR sensor and to gain insights into the effect of premixing and use of prism attached at predefined position within the IBC on the mixing performance of individual blend components. A low dose cohesive blend formulation containing micronized chlorpheniramine maleate, lactose, microcrystalline cellulose and magnesium stearate was deliberately selected for the study as the movements of individual components are generally complex in cohesive blends, unlike free flowing granular blends. Moreover, inclusion of the prism further contributed to the complexity of the movements of blend components during blending in the IBC and thus enabled a more challenging process to test the developed in-line method for its accuracy.

2. Materials and methods

2.1. Materials

Chlorpheniramine maleate (Merck, Singapore), lactose (Pharmatose 100M, DMV, The Netherlands), microcrystalline cellulose (MCC; Avicel PH102, FMC Biopolymer, USA) and magnesium stearate (MgSt; Sigma–Aldrich, Germany) were used in this study. Chlorpheniramine maleate was milled in a fluidized-bed opposed jet mill (AFG 100, Hosakawa, Germany) at a pressure of 0.4 MPa with a classifying speed of 18,000 rpm to produce micronized chlorpheniramine (μCPM) particles with mean diameter of 3 μm. Lactose and MCC were sieved using sieves with aperture sizes of 90 and 180 μm vibrated at 1 mm amplitude on a mechanical sieve shaker (VS 1000, Retsch, Germany) to obtain narrow size fractions of 90–180 μm. Prior to experimentation, the materials were stored for at least 48 h at 25 °C and 50% relative humidity (RH).

2.2. Methods

2.2.1. IBC bin blender and NIR instrumentation

A newly developed intermediate bulk container (IBC) based blender (SP15, GEA Pharma Systems, UK) of 15 L working capacity with an optional prism attachment was used (Fig. 1). An optical head comprising a sapphire window was mounted on the lid of the IBC for NIR spectral acquisition (MCS 611 NIR 2.2 spectral sensor, Carl Zeiss, Germany) of 980–2100 nm wavelength range. Calibration and validation samples were scanned while the bin blender was in static position with the sapphire window facing upward.

2.2.2. NIR spectral acquisition and OLUP for in-line monitoring

Raw energy spectra were obtained from the light signals from the optical head using the MCS 611 NIR 2.2 spectral sensor (Carl Zeiss, Germany) and transferred using radio frequency to the microprocessor using the Aspect Plus (version 1.76, Carl Zeiss, Germany) and Process Explorer (version 1.1.0.6, Carl Zeiss, Germany) softwares. Unscrambler 9.8 (version 9.8, Camo Inc., India) was used off-line to build the calibration models. The calibration models for different blend components were then uploaded into the Process Explorer using the Online Unscrambler Predictor (OLUP) software. OLUP packaged Unscrambler calibration models into a dynamic link

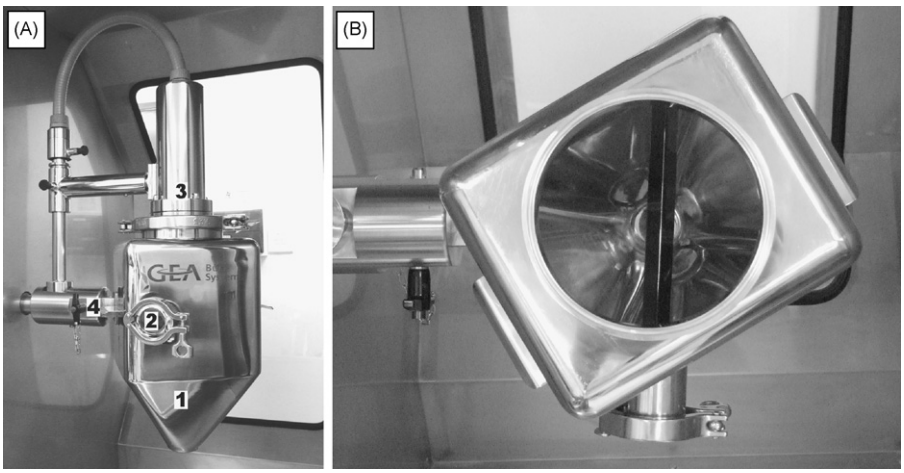

Fig. 1. (A) Laboratory IBC NIR blender (1) IBC, (2) modified IBC lid with NIR sensor and (3) axis of rotation. (B) IBC with the lid open depicting the prism.

library (DLL, 32 bit only) protocol. Through these protocols, Process Explorer was interfaced with the OLUP for obtaining in-line quantification of each of the blend components.

2.2.3. Development of NIR calibration models

A simplex lattice design of degree 5 and 21 mixture points was used to generate 126 calibration samples using a combination of each component at 6 different levels (Table 1). Mixtures with respective quantities of μCPM, lactose, MCC and MgSt for each calibration sample were prepared in a batch size of 100 g. μCPM and lactose were first premixed in a 1 L high shear mixer (Microgral, Collette NV, Belgium) at an impeller speed of 300 rpm for 3 min. Next, the premix, MCC and MgSt were mixed by tumbling in a 250 mL glass bottle for 30 min. These mixtures were then sub-divided into 8 equivalent portions (approximately 12 g) using a riffler (Retsch, Germany) and scanned by pouring onto the optical head. Each portion was scanned 5 times and thus for one calibration mixture, a total of 8×5 or 40 spectra were acquired. These 40 spectra were averaged and the resultant average spectrum was used as a representative spectrum for the respective calibration mixture. The reference values used for calibration samples were calculated gravimetrically from the actual weights of the calibration mixtures (% ingredient A = 100 × weight of ingredient A/total weight of mixture).

2.2.4. Validation of NIR calibration models

Two approaches were used to validate the respective calibration models of each of the blend components. In the first approach, leave one out full cross-validation was carried out to determine the number of principal components required to minimize the root mean squared error of cross-validation (RMSECV) and standard error of prediction (SEP). In the second approach, 22 independent validation blend samples spanning the calibration range of each component were prepared and scanned using a similar procedure to that of calibration samples. All validations were carried out using the average spectra. Prediction results obtained for each of the components using the respective calibration models were compared against the reference gravimetric values.

Table 1
Experimental design for generation of calibration samples.

Blend components	Lower bound (% w/w)	Upper bound (% w/w)	Levels (% w/w)
μCPM	0	10	0, 2, 4, 6, 8, 10
Lactose	70	80	70, 72, 74, 76, 78, 80
MCC	20	30	20, 22, 24, 26, 28, 30
MgSt[a]	0	1.25	0, 0.25, 0.5, 0.75, 1.0, 1.25

[a] MgSt was treated as a process variable owing to its lower concentrations in the blends while generating the mixture design.

2.2.5. Chemometric data preprocessing

The spectra obtained were smoothed using moving average smoothing with segment size of 3 and preprocessed with standard normal variate (SNV) followed by 1st derivative employing 9 smoothing points and 2nd polynomial order. Partial least square (PLS1) regression method was then used to build the calibration models for each component.

2.2.6. Blending study

The blending study was carried out to assess the developed NIR models for their capability to quantitatively estimate the blend components. The IBC bin blender was filled to approximately 60% fill level and rotated at 10 rpm as these conditions were reported to give better performance of bin blenders for blending cohesive blends (Sudah et al., 2002). A 5 kg powder blend comprising 4% (w/w) μCPM, 72% (w/w) lactose, 23% (w/w) MCC and 1% (w/w) MgSt was used for the blending study. In order to impart the variability in distribution of blend components within the IBC, three different sets of blending operations were carried out. For *blend A*, μCPM was premixed with the entire portion of lactose in a 10 L high shear mixer (Ultima™ Pro 10, Collette NV, Belgium) at an impeller speed 200 rpm for 3 min followed by blending in the IBC without the prism attachment. For *blend B*, μCPM was premixed with the entire portion of lactose in the high shear mixer at an impeller speed 200 rpm for 3 min followed by blending in the IBC with the prism attachment. For *blend C*, premixing of μCPM with lactose was carried out by adding them together and then passing the powders through a 355 μm aperture size sieve followed by blending in the IBC with the prism attachment. Top bottom loading pattern was used while charging the blend components into the IBC to promote dispersive mixing of the cohesive blend formulation used in the present investigation. Blend components were placed in layers: 1.9 kg drug: lactose premix, 0.575 kg MCC, 0.050 kg MgSt, 0.575 kg MCC and finally 1.9 kg drug: lactose premix. All the blending experiments in the IBC were conducted for 300 rotations and one single NIR spectrum was captured with every rotation of the IBC.

2.2.7. Determination of the extent of μCPM adhesion and agglomeration after premixing

After premixing in the high shear mixer or sieving process, drug: lactose premixed particles were gold sputter coated (JFC-1100, JEOL Ltd., Japan) and examined under a scanning electron microscope

(Phenome microscope, FEI Company, USA) to assess the extent of μCPM adhesion and agglomeration on the coarser lactose particles.

2.2.8. Determination of cohesive properties of the blends

Avalanche flow measurements (Aero-Flow powder tester, 3250, TSI, Inc., USA) were carried out for all mixed blends after the blending operation. Samples weighing about 500 g were withdrawn for determination of the dynamic flow property of the blend samples. Sample quantity of 50 mL was loaded into the disc and rotated at 7 different speeds, 110, 130, 150, 170, 190, 210 and 230 s/rev for 600 s. Resultant strange attractor plots were used to determine the mean time to avalanche (MTA) and scatter values. Avalanche flow index (AFI) and cohesive interaction index (CoI) were then subsequently calculated as described previously (Soh et al., 2006).

$$\mathrm{AFI} = \frac{1}{m},$$

where m is the slope of the graph for MTA against drum speed. A larger AFI value is indicative of better flow and vice versa.

$$\mathrm{CoI} = n,$$

where n is the slope of the graph for scatter against drum speed. A larger CoI value is indicative of higher cohesiveness.

3. Results and discussion

3.1. Calibration model development

Generally, calibration samples are prepared by assigning the reference values obtained from laboratory methods such as HPLC or UV, to the powder blend. However, similar assignments are not useful for NIR spectroscopy because the effective sample mass per unit area is not only a function of physicochemical properties of the powder sample but also of the wavelength and depth of penetration of the NIR radiation (Berntsson et al., 1998). Moreover, in multi-component mixtures, materials may be homogenous with respect to one property but heterogeneous with respect to another. There is a possibility of some variations in the composition of random samples drawn from a powder mixture. In such situation, it becomes questionable to arbitrarily assign reference values obtained by the HPLC or UV methods to the NIR spectra collected from the bulk powders. Instead, it is recognized that averaging the spectra from an appropriate number of sub-fractions of the same powder sample should be more representative of the actual reference value of the chemical content in the entire powder sample (Berntsson et al., 2000).

Therefore, in the present investigation to impart in-built variability and robustness to calibration models, a simplex lattice design which resulted in 126 different combinations of blend components was used. Each calibration data set was generated from the average of 40 subsequent spectra obtained from each of 126 samples. Averages of each sample were used to obtain the spectrum representative of the overall composition of the powder sample. Considering the differences in particle sizes of the blend components (fine μCPM, MgSt and coarse lactose, MCC), it was imperative to preprocess the spectra for removal of the scattering and baseline offsets effects (Bellamy et al., 2008). This was achieved by smoothing, followed by pretreatment with SNV and 1st derivative transformation of spectral data. The raw NIR spectra of each of the blend components in pure form are depicted in Fig. 2. The raw NIR spectra and the SNV transformed spectra of the calibration samples used for model development are shown in Fig. 3a and b, respectively.

Independent PLS1 models were calculated for all blend components from the transformed spectral data of 980–2100 nm range using Unscrambler 9.8. As calibration samples used in this study

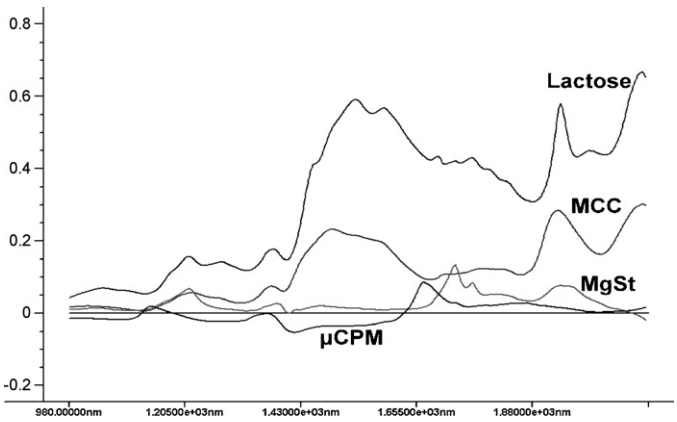

Fig. 2. Raw NIR spectra of the individual blend components. In these plots, *X* and *Y* axes represent the wavelength and absorbance, respectively.

consisted of multi-components, a further check into the efficiency of the models was carried out by comparing the corresponding scores and loadings plots (Fig. 4) obtained with each calibration model. In these plots, two principal components (PCs) were used to explain the relationship between the spectra and corresponding concentration of each blend component. The scores plots showed clear difference and separation between the spectra of the 6 different levels of calibration samples. On the other hand, loadings plots obtained for each model for PC1 and PC2 revealed that the models explained a major portion of variance (more than 90%) within the calibration samples. This indicated the NIR models were adequately accurate and sensitive for quantitative estimation of all the blend

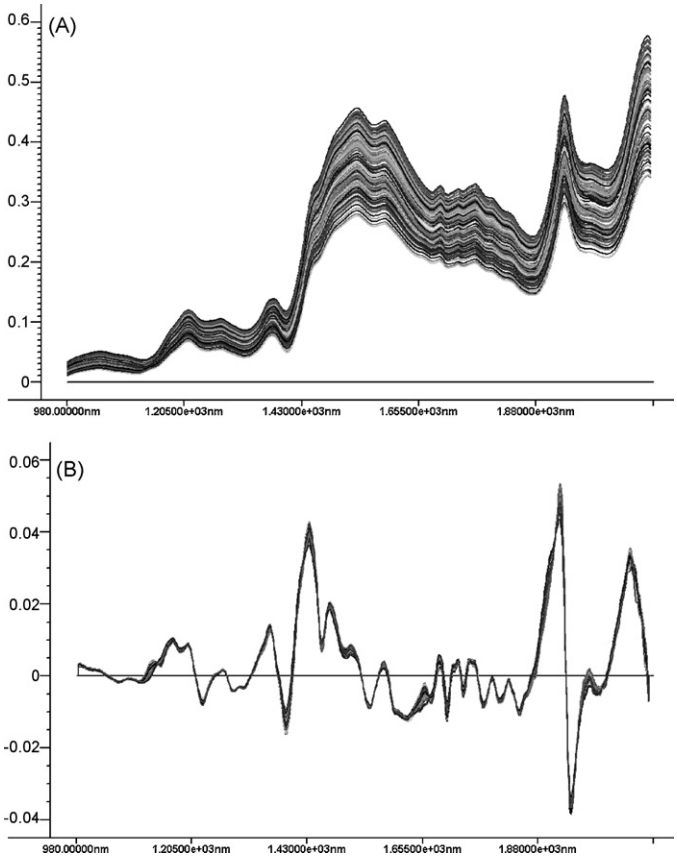

Fig. 3. NIR spectra of calibration samples used for calibration model development. (A) Raw average spectra, (B) SNV and 1st derivative pretreated spectra. In these plots, *X* and *Y* axes represent the wavelength and absorbance, respectively.

Table 2
Statistics of calibration results obtained for each calibration model with PLS1 regression method.

Blend components	No. of PC	Explained variance (%)		Calibration			Full cross-validation	
		X	*Y*	R^2	RMSEC	SEC	RMSECV	SEP
μCPM	2	97.52	97.59	0.986	0.442	0.444	0.456	0.459
Lactose	4	98.41	94.14	0.962	0.594	0.597	0.730	0.734
MCC	4	98.48	90.60	0.971	0.547	0.550	0.709	0.713
MgSt	3	97.87	90.96	0.987	0.075	0.075	0.083	0.084

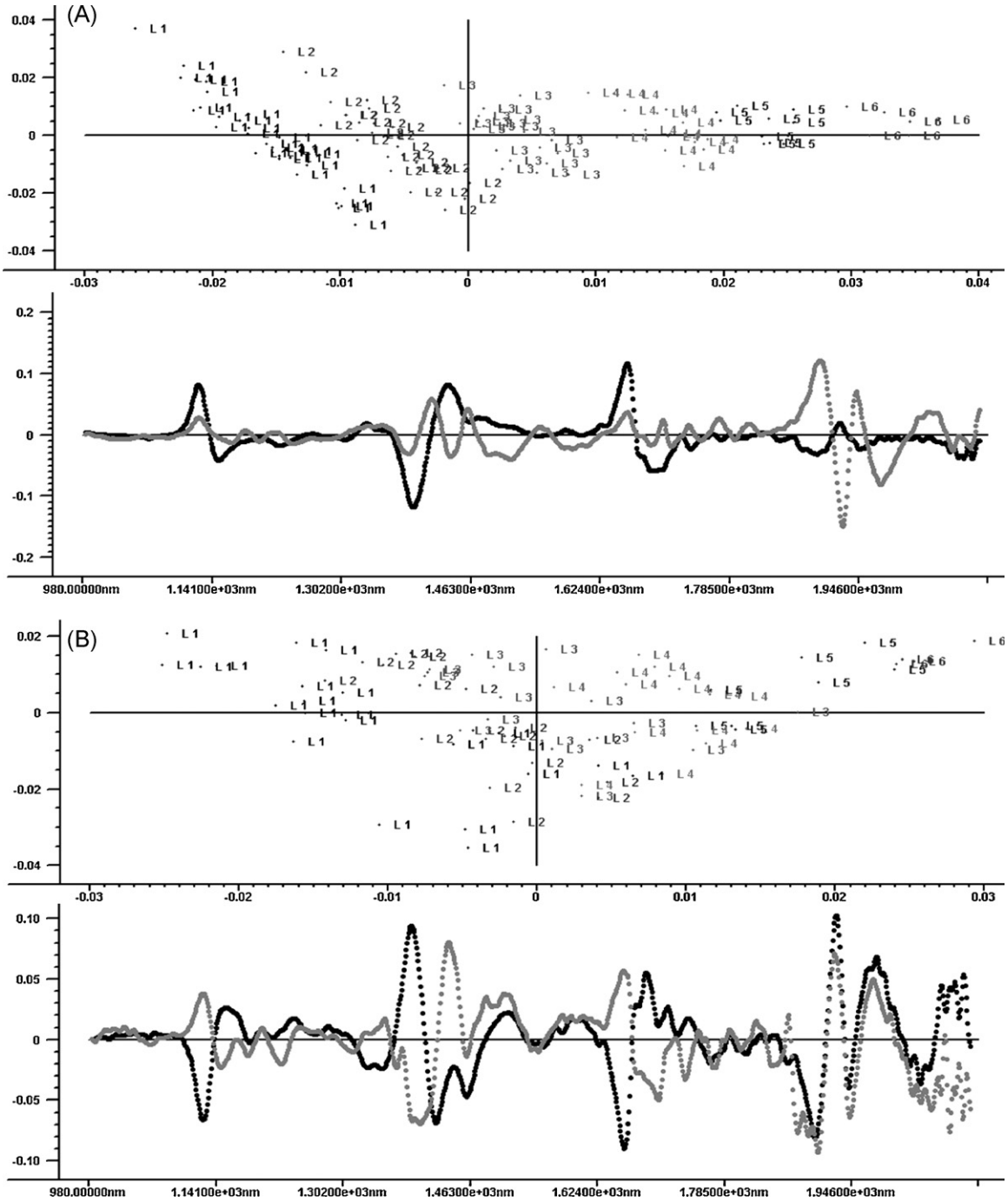

Fig. 4. 2D scatter scores and loading plots of the SNV and 1st derivative pretreated calibration spectra of (A) μCPM, (B) lactose, (C) MCC and (D) MgSt. In scores plots, Ln represents the level of the component used in preparation of calibration sample. In loadings plots, black and gray dotted curves represent the *X* loading weights for PC1 and PC2, respectively.

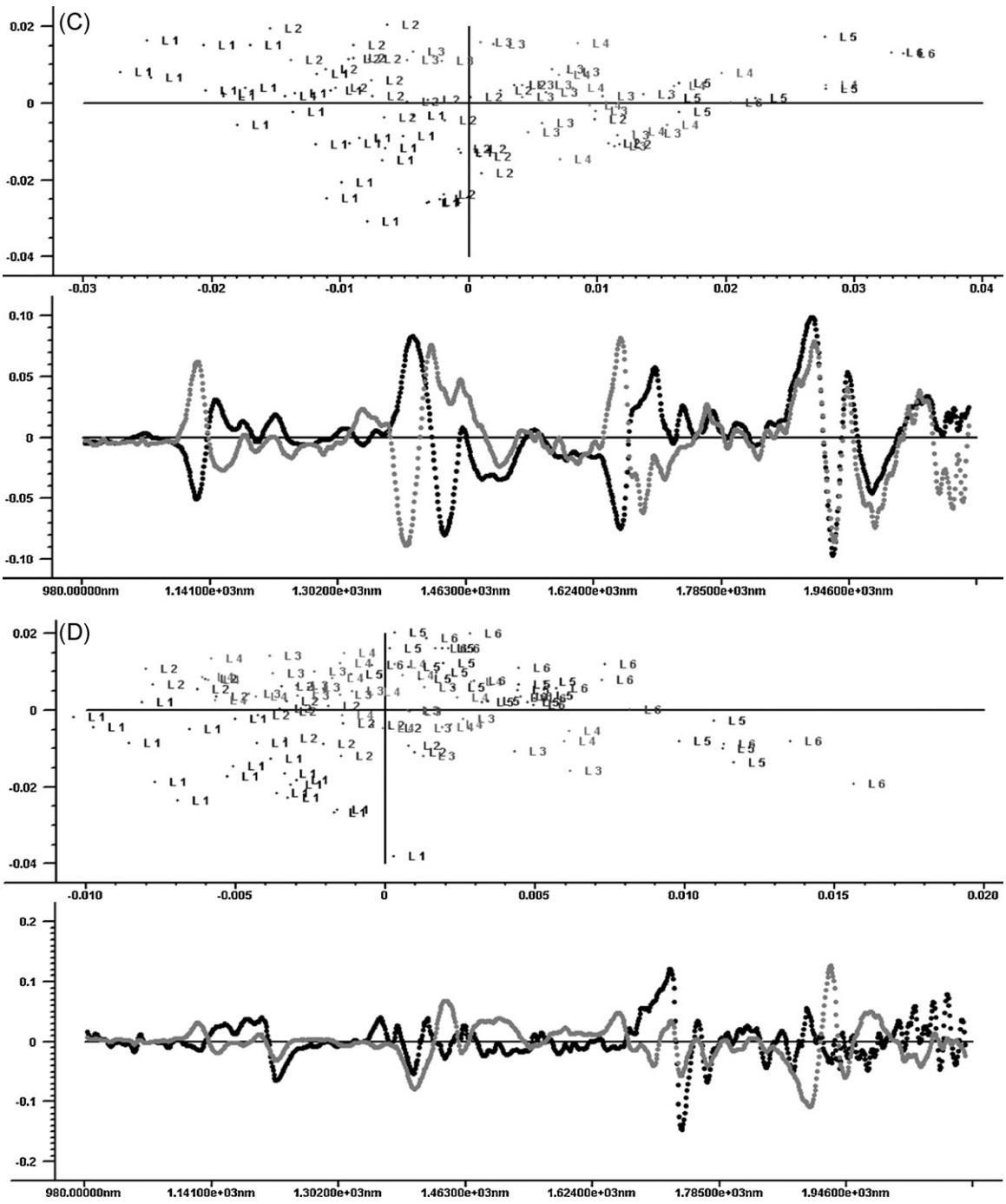

Fig. 4. (*Continued*).

components. This was further supported by the model statistics, i.e. X (NIR spectra) and Y (reference values) explained variance, root mean square error of calibration (RMSEC), standard error of calibration (SEC) and correlation coefficient (R^2) as depicted in Table 2. The root mean squared error of cross-validation (RMSECV) and standard error of prediction (SEP) values obtained from internal validation performed using full cross-validation showed the sensitivity of the calibration models in predicting the content of the blend components.

External validation results obtained with 22 independent samples are depicted in Table 3. Prediction results obtained were compared with reference gravimetric values using a paired *t*-test at the 95% confidence interval. Results obtained did not show any statistical difference between the NIR model predicted and reference values obtained gravimetrically and further confirmed the accuracy of the calibration models in predicting the contents of the blend components.

3.2. Blending study

3.2.1. In-line quantification of blend components

The NIR sensor with a diode array detector used for in-line spectral acquisition enabled quantitative characterization of the dynamic and chaotic blending process at a very fast speed, without any spectral artifacts such as spectral shifting and scattering effects due to constant movement of powder on the optical head during blending. The NIR sensor was triggered at every rotation and 10 raw energy spectra were captured and subsequently converted to

Table 3
Results of the external validation blend samples.

Batch	Blend components (% w/w)							
	μCPM		Lactose		MCC		MgSt	
	REF	NIR	REF	NIR	REF	NIR	REF	NIR
1	0.000	0.023	80.000	75.947	20.000	24.420	0.000	0.068
2	0.000	−0.401	76.000	75.307	24.000	25.260	0.000	−0.002
3	4.000	4.101	76.000	76.156	20.000	20.148	0.000	0.020
4	0.000	−0.285	74.000	73.870	26.000	26.518	0.000	−0.003
5	6.000	6.514	74.000	75.116	20.000	18.315	0.000	0.041
6	0.000	−0.655	70.000	67.580	30.000	33.128	0.000	0.012
7	4.000	3.704	70.000	69.119	26.000	28.173	0.000	−0.007
8	10.000	9.820	70.000	70.931	20.000	19.714	0.000	0.050
9	3.980	3.635	69.652	70.565	25.871	24.733	0.498	0.412
10	0.000	0.141	79.602	79.369	19.900	20.550	0.498	0.473
11	5.970	6.586	69.652	70.202	23.881	23.800	0.498	0.516
12	9.926	9.280	69.479	69.474	19.851	19.816	0.744	0.694
13	0.000	0.103	75.434	75.579	23.821	24.343	0.744	0.644
14	3.970	3.148	75.434	75.474	19.851	19.807	0.744	0.743
15	0.000	−0.181	69.479	71.382	29.777	27.662	0.744	0.692
16	9.877	9.362	69.136	67.210	19.753	20.479	1.235	1.267
17	0.000	0.293	69.136	70.352	29.630	28.830	1.235	1.133
18	0.000	0.075	73.086	75.254	25.679	23.591	1.235	1.156
19	5.926	6.353	69.136	68.242	23.704	23.564	1.235	1.255
20	5.926	6.182	73.086	72.316	19.753	19.725	1.235	1.234
21	0.000	0.152	79.012	79.403	19.753	19.182	1.235	1.182
22	3.951	4.660	69.136	70.891	25.679	25.569	1.235	1.244
Mean	3.342	3.300	72.748	72.715	23.314	23.515	0.596	0.583
SD	3.595	3.593	3.736	3.602	3.634	3.844	0.526	0.507
RMSEP	0.455		1.546		1.721		0.047	
t-value	0.458		0.105		−0.609		1.271	
p-value	0.651		0.917		0.549		0.218	

p-value greater than 0.05 indicates two means are similar. REF refers to the reference values calculated gravimetrically and NIR refers to the values predicted by NIR model. SD and RMSEP refer to the standard deviation and root mean square error of prediction.

one reflection spectrum. Hence, the individual spectrum obtained at each rotation was more representative of the actual state of powder falling on the optical head as spectral acquisition was carried out when the powder bed within the IBC was in motion. The sampling data (NIR spectra) was obtained at a very small interval (at every rotation of the bin blender) and although the sensor was fixed at one particular position, the greater volume of air available to fluidize the powder bed within the IBC (IBC was filled to approximately 60% (v/v) of total capacity) had made it possible to achieve randomness in sampling locations. Thus, with the usage of the IBC bin blender equipped with in-line NIR sensor in this study, it was possible to satisfy Allen's golden rules of sampling which state that the blend samples should be obtained at very short intervals of time from multiple locations and when the process is being carried out (Allen, 1981).

According to the recommendations in Parenteral Drug Association technical report, "Blend uniformity analysis" (Berman et al., 1997) it is essential to report the active ingredient quantity in a sample size varying between one and three unit doses. Although the aim of this study was to quantitatively estimate the distribution of all blend components, μCPM concentration equivalent to a unit dose of 500 mg was considered to determine the number of spectra to be used to calculate the average unit dose. Based on the manufacturer's recommendations and density of the powder blend, it was estimated that the 30 mm diameter optical head can measure a mass of approximately 250–300 mg (i.e. one spectrum measures the powder mass equivalent to 250–300 mg). Hence, an average of three consecutive spectra was used to assign a single data point. Thus, the mass measured by three NIR spectra (approximately 750–900 mg) was well within the standard limit recommended. The respective relative standard deviation (RSD) values for each component were calculated from the quotient of the standard deviations and the average values of each component obtained from every subsequent three spectra. Thus, a total of 100 data points (% RSD values) were calculated for preset blending of 300 rotations.

In this study, the blend components were considered uniformly mixed when their mean concentration values were in the range of $100 \pm 5\%$ of the target values and the corresponding % RSD values below 6%.

3.2.2. *Effect of premixing and prism on mixing of blend components*

The NIR spectra of the *blends A, B* and *C* collected during the preset blending time are shown in Fig. 5. Visual inspection of these spectra showed that *blend C* exhibited highly scattered spectra compared to *blends A* and *B*. On a qualitative basis, it could be said that *blend B* showed rapid attainment of uniformity of blend components followed by *blend A*. In contrast, NIR spectra of *blend C* was highly scattered indicating highly variable blend composition throughout the blending process. Thus, it was apparent that prism attachment in the IBC significantly enhanced the blending performance of the IBC bin blender after high shear premixing. However, use of the prism alone without the initial high shear premixing proved to be inefficient to uniformly blend the mixture in IBC.

The plots of % RSD versus number of rotations are shown in Fig. 6 for each of the blending experiment. The plots clearly showed that premixing and prism attachment had affected the distribution of not only the μCPM but also the excipients. As can be seen from Table 4, a large variation in number of rotations required for the blend components to attain blend uniformity was observed. Uniformity here refers to attainment of value of % RSD of respective components below 6%.

Distribution of blend components was very rapid for *blends A* and *B*. Almost all blend components achieved uniform distribution

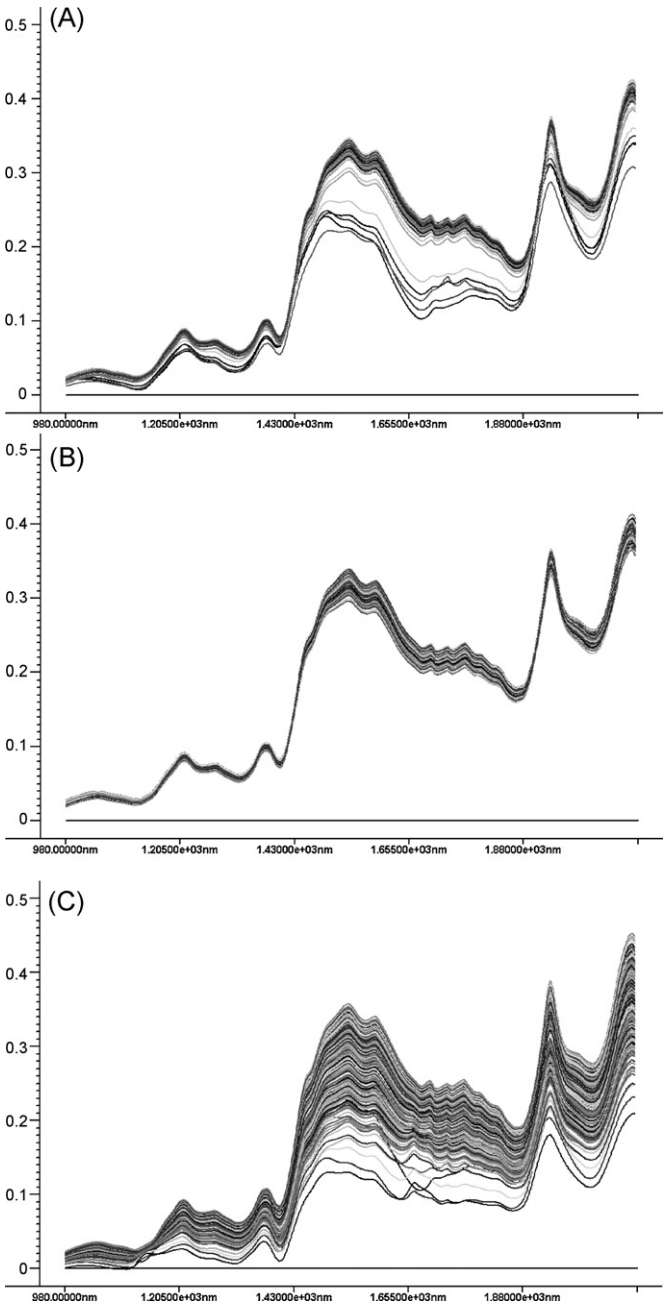

Fig. 5. Raw spectra of the blends collected during the blending process (A) *blend A*, (B) *blend B* and (C) *blend C*. In these plots *X* and *Y* axes represent the wavelength and absorbance, respectively.

Table 4
Comparative illustration of the number of rotations required for the blend components to attain uniformity.

Blend components	Number of rotations to attain uniformity		
	Blend A	*Blend B*	*Blend C*
μCPM	18	12	X
lactose	12	9	X
MCC	24	12	X
MgSt	21	15	54

X indicates the failure of components to distribute uniformly after the preset blending time. The blend components were considered uniformly mixed when their mean concentration values were in the range of 100 ± 5% of target values and the corresponding %RSD values below 6%.

after 20–40 rotations of the blender as evident from their low % RSD values. However, for *blend C*, with the exception of MgSt, none of the other blend components had distributed uniformly after the preset blending process. High shear imparted during premixing of *blends A* and *B* helped to uniformly disperse the relatively smaller size drug particles and also caused the de-agglomeration of the larger agglomerates. This could be attributed to the characteristics of high shear mixers which can impart higher kinetic energy (shear forces) during the mixing process and can thus perform better for mixing of cohesive powders regardless of total mixing time (De Villiers, 1997; Harding et al., 1989; Samyn and Murthy, 1974).

Similar findings were reported by De Villiers (1997) in a study which showed that the overall de-agglomeration of micro-fine furosemide particles in binary mixture increased with increased mixing speed and was more rapid in a higher shear turbula mixer compared to the lower speed V-blender. Thus, ordered mixing of μCPM particles was expected during premixing which would have left the lactose particles coated by the μCPM particles. This was apparent from the scanning electron photomicrographs (Fig. 7) which showed almost uniform coating of the surfaces of the lactose particles by primary μCPM particles. μCPM agglomerates were not obvious on the surfaces of the lactose particles after premixing in the high shear mixer (*blend A*) compared to those premixed using sieving (*blend C*), which showed slight coating effect of μCPM particles on the surfaces of lactose particles. Moreover, some random agglomerates as large as 1–3 mm were also observed in *blend C* when observed visually at the end of the blending process. It was postulated that the large agglomerates could be the result of opportunistic aggregation of μCPM particles during the blending process as the sieving of powders through the 355 μm aperture size sieve did not aid in dispersing the μCPM particles as efficiently as the high shear mixer during the premixing step. This was again evident from the prediction of the comparatively higher than theoretical concentration of μCPM in the blend throughout the preset blending time which could be the result of the predominant intra-reflection phenomenon exhibited by μCPM particles while in the agglomerate state. Thus, for *blend C*, NIR light had encountered a greater number of μCPM particle boundaries than that of the rest of the other blend components.

Interestingly, between *blends A* and *B*, *blend B* performed better in terms of uniformity in distribution of the blend components. All blend components from *blend B* exhibited lower % RSD throughout the blending period as compared to those from *blend A*. Improved mixing obtained for *blend B* could possibly be due to the increased rate of powder turnover and increased occurrences of failure regions with the prism attachment in the IBC (Castellanos et al., 1999). The divisive action caused by the prism enabled rapidity in uniform distribution of all the blend components in *blend B*. These results were in good agreement with the findings reported by Sudah et al. (2002) that the attachment of the prism in the IBC had positively affected the attainment of blend uniformity for cohesive powder blend formulations.

Avalanche flow experiments on the blended powders also confirmed the aforementioned trend and helped to further explain the underlying attributes for the behavior of these three powder blends. The avalanche flow properties of the blends were as depicted in the strange attractor plots (Fig. 8). The AFI values for *blends A, B* and *C* were 26.8, 30.5 and 28.1, and the CoI values for the same blends were 0.019, 0.019 and 0.020, respectively.

Blend B exhibited a rather similar but more condensed strange attractor plot than *blend C* while *blend A* exhibited the most scattered strange attractor plot. The AFI values also showed similar trend, with *blend B* exhibiting the highest AFI value, thus confirming its better flow property. The uniformity of the powder composition in terms of size and density in *blend B* had allowed better powder flow than *blend C*. A slight reduction of μCPM agglomerate size

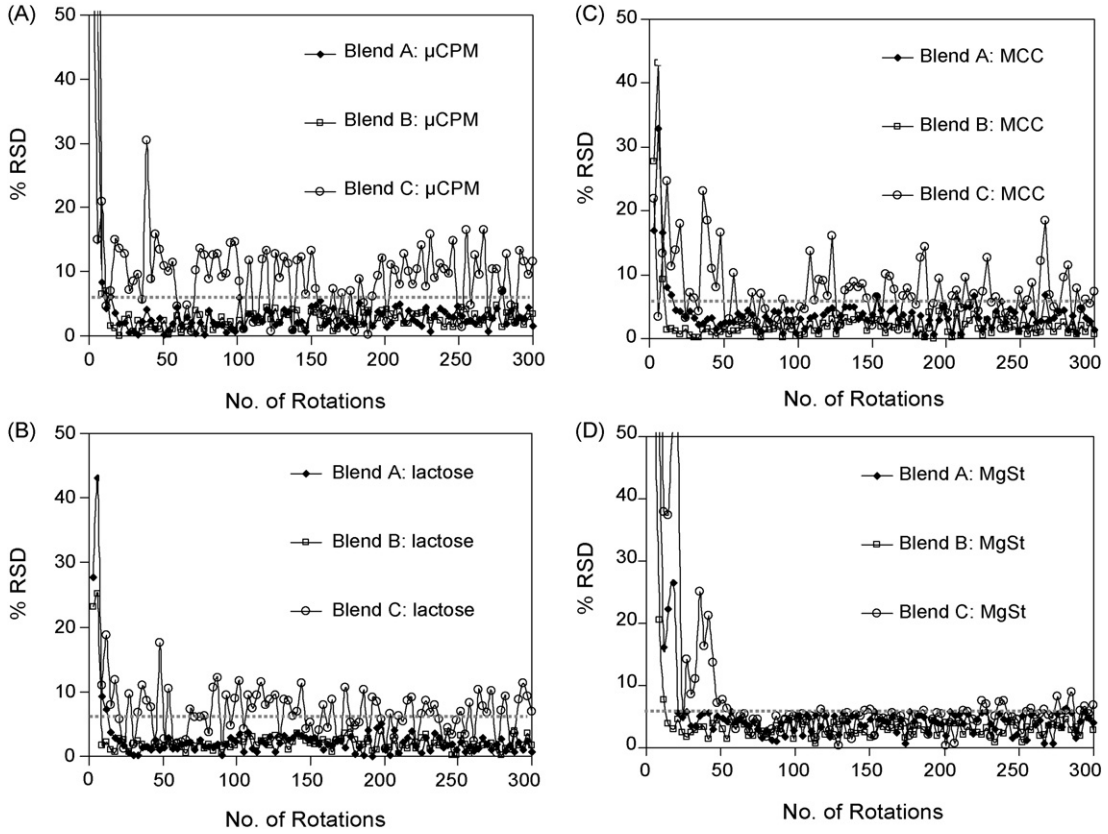

Fig. 6. Comparative assessment of uniformity of blend components (A) μCPM, (B) lactose, (C) MCC and (D) MgSt from *blends A, B* and *C*. Dotted line (- - -) represent the % RSD value of 6%. For the sake of clarity, the % RSD values above 50% for μCPM and MgSt are truncated.

by the prism during blending was anticipated, and these smaller agglomerates acted as a glidant by depositing as a fine coat over the surfaces of coarse excipients making them smooth and ultimately improving the flow property of the bulk powder.

However, in the case of *blend C*, the improved flow property compared to *blend A* could be traced to the initial presence of large μCPM agglomerates, which behaved like coarse particles and thus showed good bulk flow. This finding agreed well with the finding reported by Soh et al. (2006), where the improved flow property of finer 450 M lactose powders was attributed to the presence of transient loosely packed agglomerates within the bulk powder mass during avalanching. Despite its relatively good flow property, *blend C* showed highly variable distribution of μCPM and coarse excipients except for MgSt. As discussed previously, inadequate dispersion of μCPM particles and their opportunistic agglomeration into bigger clumps resulted in a rather highly non-uniform texture blend in terms of density and size (Sudah et al., 2002). Interestingly, it was observed that MgSt in all blends tended to distribute uniformly. Overall, premixing of μCPM and lactose using high shear mixer and further blending in the IBC with the prism

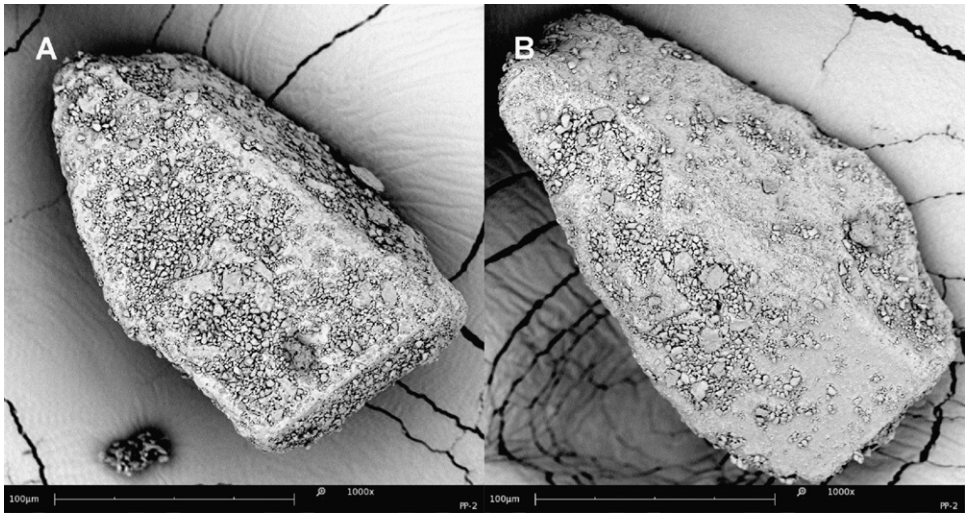

Fig. 7. Scanning electron micrographs of the lactose particles after premixing with μCPM at 1000× magnification from (A) premixing using high shear mixer and (B) premixing using sieving.

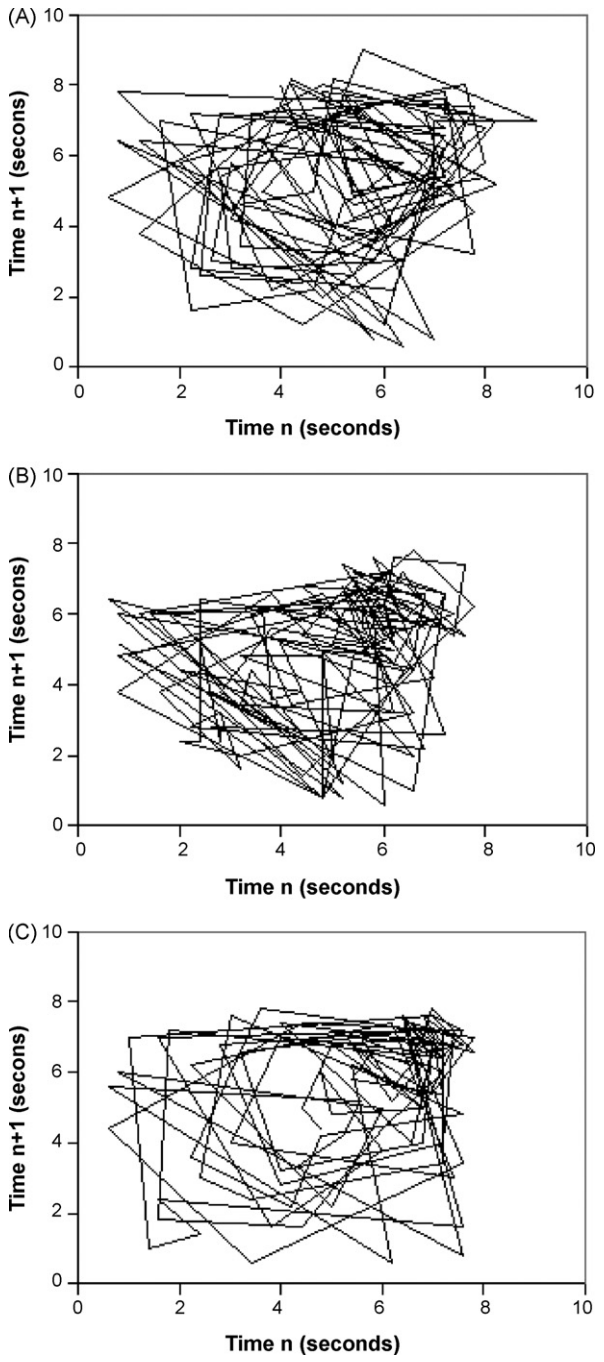

Fig. 8. Strange attractor plots (A) *blend A*, (B) *blend B* and (C) *blend C*.

attachment, helped to achieve rapid and uniform distribution of blend components.

4. Conclusion

This study demonstrated that with the unique features of NIR, i.e. high speed sampling and rapid spectral acquisition, distribution of individual blend components can be assessed with high accuracy during blending. Calibration models built using PLS and simplex lattice design spanning the appreciably wide concentration range of blend components resulted in generation of accurate and robust prediction models. Adequacy of models for in-line quantification of individual blend components was visible from the scores plots, loadings plots, RMSECV, SEP and external validation results.

In-line monitoring of the blend revealed that despite the cohesive nature of the blends, due to initial premixing using high shear mixer, uniform distribution of blend components was achieved during the early phase of the blending process in the IBC. Results obtained from the blending study explained the impact of premixing for uniform distribution of blend components. The attachment of the prism in the IBC promoted the rapid distribution of blend components after initial high shear premixing, especially that of coarse components. However, the gentle sieving process failed to disperse the micronized drug particles uniformly, and also hampered the distribution of coarse excipients even in the presence of the prism. With the ability of NIR for sample acquisition at a very fast rate and its multi-sensing property, it was possible to detect discrepancies in the mixing of MCC and MgSt, which in *blend A* took relatively longer to distribute throughout the blend compared to μCPM and lactose. This blend would be considered uniformly mixed before actual uniform distribution of all blend components if it were analyzed in the traditional sense in terms of drug only. Hence, it is imperative to monitor the distribution of excipients along with drug especially while dealing with blends similar to the one discussed in the current investigation as the rate of uniform distribution of blend component is likely to vary based on their physical properties, essentially particle size and flow.

In conclusion, spectral acquisition at high rate was possible with the in-line sensor, thereby resulting in a better understanding of the relative distribution of the excipients within the powder blend which would not have been possible with traditional blend uniformity analysis. Thus, the performance of the IBC bin blender for mixing of cohesive multi-component powder blend containing micronized drug could be improved by using high shear premixing and attachment of the prism within the IBC.

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