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Monitoring of high-load dose formulations based on co-processed and non co-processed excipients

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ABSTRACT

This work presents the evaluation of a co-processed material for high-load dose formulations and its real-time monitoring by near-infrared (NIR) spectroscopy at the tablet press feed frame. The powder and tableting properties of co-processed material blends were evaluated and compared to the blend of the individual excipients. The formulations with the co-processed material showed excellent flow properties and were superior to the physical blend of individual excipients. Two NIR spectroscopic methods were developed to monitor ibuprofen concentration between 40.0 and 60.0% w/w, one method using a co-processed material as the main excipient and the other using the blend of the individual excipients. The NIR spectra were obtained while the powder blends flowed within a three-chamber feed frame from a Fette 3090 tablet press. The NIR spectroscopic method with the co-processed material presented better performance with significantly lower prediction error. Variographic analysis demonstrated that using the co-processed material considerably reduces the sampling and analytical errors in the in-line determination of ibuprofen. The authors understand that this is the first study where the sampling errors are evaluated as a function of the excipients used in the pharmaceutical formulation. This study demonstrated that selecting a suitable excipient for the formulation helps optimize the manufacturing process, reducing the magnitude of the total measurement error.

1. Introduction

Pharmaceutical tablets are worldwide the most common solid drug dosage forms. Tablets offer an easy administration, simplicity of manufacture, accurate doses, and physicochemical and microbial stability compared to liquid and semisolid dosage forms (Gohel and Jogani, 2005; Natoli et al., 2017). There are three commonly followed approaches for tablet manufacturing: direct compaction, wet granulation, and dry granulation. Direct compaction is the most straightforward manufacturing route where the active pharmaceutical ingredient (API) and suitable excipients are blended and fed directly into the tablet press, eliminating the heat and moisture effects typical of wet granulation (Carlin, 2008; Jivraj et al., 2000). However, the direct compaction approach requires excipients with good flowability, high bulk density, and good compactability to achieve a consistent die-filling process and tablets with proper properties (Augsburger and Hoag, 2008; Carlin, 2008; Jivraj et al., 2000). These properties are not present simultaneously in most current excipients and play an important role in the success or failure of this manufacturing process (Chen et al., 2018b). Direct compression could be further enhanced through the development of new excipients or the improvement of commercial excipients.

Co-processing is one of the methods most used in the pharmaceutical industry to produce new and high functional excipients for direct compaction. Co-processing combines two or more established excipients at the sub-particle level by an adequate process to increase functional performance and decrease the unfavorable properties of individual ingredients, such as low flowability and poor compactability (Rojas et al., 2012; Saha and Shahiwala, 2009). **Supplementary Material** **Table S-1** shows a list of commercially available co-processed excipients. These materials present good compactability and excellent flowability, two essential characteristics of excipients for tablet manufacturing. The use of co-processed excipients facilitates the development of pharmaceutical formulations because typically, only three ingredients need to be mixed: API, lubricant, and the co-processed excipient (Heinz et al., 2000), decreasing the number of feeders required in the continuous process. Pharmaceutical formulations for direct compaction with cohesive API

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such as ibuprofen, acetaminophen and metformin are limited to 30% API or less to ensure adequate properties in the tablet (Chen et al., 2019; Jivraj et al., 2000; Mangal et al., 2015). The use of a co-processed excipient could overcome the expected decrease in flowability and compactability, which usually arises with the inclusion of a high-load of cohesive API in the formulations.

Numerous studies have been performed to develop co-processed excipients and compare their properties with the physical blend of individual excipients (Bowles et al., 2018; Chen et al., 2018a, 2018b; Gohel and Jogani, 2005; Rojas et al., 2012; Schmidt and Rubensdörfer, 1994a, 1994b). Nevertheless, previous studies do not compare the performance of a co-processed excipient and its non co-processed excipients to develop real-time near-infrared (NIR) spectroscopic methods for blend uniformity analysis of a cohesive API. Blend uniformity depends directly on the properties of the materials, and the challenges to develop a multivariate model increase with the number of ingredients in the formulation (Esbensen and Swarbrick, 2018). The determination of blend uniformity is a requirement of the current Good Manufacturing Practices to ensure that patients receive an adequate amount of the drug from each tablet (U.S Department of Health and Human Services, 2014). Blend uniformity can be monitored at the feed frame without interrupting the manufacturing process, regardless of whether a continuous or batch mixing process is performed. The feed frame is now recognized as a viable option for monitoring blend uniformity in tablet manufacturing (Harms et al., 2019; Hetrick et al., 2017; Sierra-Vega et al., 2019). The feed frame provides the closest point to the final product for monitoring, while the entire powder blend has the same opportunity of being analyzed (Sierra-Vega et al., 2019). The in-line evaluation of blend uniformity allows the estimation of the sampling errors associated with the measurement system. The material properties affect the sampling errors in a system (Sierra-Vega et al., 2020); thus, they should be considered when optimizing a formulation.

The first objective of this paper was to compare the performance of two NIR calibration models to quantify high ibuprofen concentrations in flowing powder blends. The first model was developed using a co-processed material as the main excipient, and the second model was developed using a formulation with the individual excipients of the co-processed material. The NIR spectra were acquired in-line with the powder blends flowing through a three-chamber feed frame. The second objective was to deepen the understanding of the powder flow and tableting properties of high-load dose formulations based on a co-processed excipient and their differences with the properties of the physical blend of individual excipients. Ludipress® was the co-processed excipient selected for this study. Ludipress® has been reported as an appropriate excipient for direct compaction of low-dose formulations (Abouzaid et al., 2017; Baykara et al., 1991; Heinz et al., 2000; Schmidt and Rubensdörfer, 1994a). However, the use of this co-processed excipient has not been explored in high-load API formulations (>30%), where the powder blend properties tend to be dominated by the API, presenting high cohesion and poor properties for direct compaction. An in-depth assessment of the properties of powder blends based on Ludipress® with a high concentration of a cohesive drug is necessary to determine its suitability for these formulations. The last objective of this study was to estimate the sampling errors associated with the in-line determination of high ibuprofen concentration when co-processed and non co-processed excipients are employed.

This paper aims to answer the following three questions regarding the use of a co-processed excipient in high-load dose formulations: (1) Does it lead to powder blends with properties suitable for direct compaction? (2) Does it lead to a NIR calibration model with high accuracy and precision compared to blends of individual excipients? (3) Does it lead to lower sampling errors?

2. Materials and methods

2.1. Materials

Ibuprofen powder (Ibuprofen 50, Ph.Eur./USP/JP/IP, BASF Corporation/Bishop, Texas, USA) was selected as a representative cohesive and agglomerated active pharmaceutical ingredient (API). Ludipress® (BASF AG, Ludwigshafen, Germany), crospovidone (Kollidon CL-F, BASF Corporation), povidone (Kollidon 30, BASF Corporation), and lactose monohydrate (Tablettose 70, Agglomerated, Ph.Eur., USP/NF, JP, Molkerei MEGGLE Wasserburg GMBH & Co.) were selected as excipients. Magnesium stearate (MgSt, N.F. non-Bovine, Tyco Healthcare/Mallinckrodt, St. Louis, Missouri, USA) was used as a lubricant in all powder blends.

2.2. Preparation of the powder blends

Table 1 shows the concentration of the calibration and test set blends prepared for this study. Two NIR calibration models were developed spanning an API concentration range between 40.0 and 60.0% w/w but changing the main excipients. The first NIR calibration model was developed using the co-processed excipient (Ludipress®), while the second NIR calibration model was developed by changing the co-processed excipient by its base components: α-lactose monohydrate, crospovidone, and povidone. For a fair comparison, a free-flowing α-lactose-monohydrate agglomerated, Tablettose 70, was used instead of the fine lactose used in the production of Ludipress®. All powder blends used in the model with non co-processed excipients have the same proportions of the base components in Ludipress®: 93.0% w/w lactose, 3.5% w/w povidone, and 3.5% w/w crospovidone (Schmidt and Rubensdörfer, 1994a). The MgSt was added at a level of 1.0% w/w for all powder blends.

Each powder blend was prepared with a total batch size of 6 kg in a 16-quart stainless-steel V-blender (Patterson-Kelley, Pennsylvania, USA). The materials were first blended without lubricant for 60 min at 15 revolutions per minute (RPM). MgSt was then added to the blender and mixed for an additional four minutes at 15 RPM to avoid over-lubrication of the powder blend. The ibuprofen was passed through standard testing sieve No. 60 before the mixing process. Two additional powder blends with an ibuprofen concentration of 50% w/w were prepared for each model. These blends were used to evaluate the effect of paddle wheel speed on the flow properties.

2.3. Characterization of powder properties

2.3.1. Particle size distribution

A total of 15 g of powder were analyzed using dry laser diffraction with a Malvern Insitec Analyzer Model IDC2000 (Malvern Instruments Ltd, Worcestershire, United Kingdom) to determine the particle size distribution. This equipment was controlled using the RTSizer software version 5.6 (Malvern Instruments Ltd, Worcestershire, United Kingdom). The cumulative volume versus particle diameter and the values of d_{10}, d_{50}, and d_{90} were obtained with the RTSizer software. The d_{50} represents the diameter where 50% of the particles have a larger diameter, and the other 50% have a smaller diameter.

2.3.2. True, bulk and tap density

The bulk and tap densities were determined in a 100-mL graduated cylinder mounted on an automatic tapping machine (Vankel Variance Tap Density Tester, Quantachrome Instruments, Florida, USA). Approximately 30 g of the material were placed in the graduated cylinder, and the first volume was recorded (V_0). A total of 1250 taps were then applied, and a second volume (V_{Tap}) was recorded. Bulk and tap densities were calculated by dividing the powder mass by V_0 and V_{Tap}, respectively.

True density was determined in a helium pycnometer (AccuPyc II

Table 1
Composition of calibration (Cal) and test set (Test) blends for the model with the co-processed excipient and model with non co-processed excipients. All values are reported in (%w/w).

Material	Cal_1	Cal_2	Cal_3	Cal_4	Cal_5	Test_1	Test_2	Test_3
Co-processed excipient								
Ibuprofen	40.0	45.0	50.0	55.0	60.0	42.5	50.0	57.5
Ludipress®	59.0	54.0	49.0	44.0	39.0	56.5	49.0	41.5
MgSt	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Non co-processed excipients								
Ibuprofen	40.0	45.0	50.0	55.0	60.0	42.5	50.0	57.5
Tablettose 70	54.9	50.2	45.6	40.9	36.3	52.5	45.6	38.6
Povidone	2.07	1.89	1.72	1.54	1.37	1.98	1.72	1.45
Crospovidone	2.07	1.89	1.72	1.54	1.37	1.98	1.72	1.45
MgSt	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

1340 Micromeritics Instrument, Norcross, GA). The pycnometer was operated using a sample chamber of 10 cm^3. Approximately 2.0 g of sample were placed in the pycnometer chamber. The analysis included ten gas purges to clean up and remove air and moisture from the sample. After purges cycles, ten density readings were performed. The temperature was kept at approximately 21.5 °C.

2.3.3. Compressibility, cohesion, and flow factor

The compressibility, cohesion, and flow factor of each material and formulation were characterized using an FT4 powder rheometer (Freeman Technology Inc., Worcestershire, UK) through the compressibility shear cell test. The measurements were carried out using the 50 mm × 85 mL cell and approximately 60 g of powder. The compressibility was measured by slowly applying increasing normal stress from 0.5 to 15 kPa on the powder bed using a vented piston. The change in volume was measured for each applied normal stress, and the compressibility was automatically calculated as a percentage change in volume after consolidation at 15 kPa. Additional information on the FT4 rheometer compressibility test can be found in the literature (Freeman, 2007; Freeman et al., 2009).

Cohesion and flow factor were obtained from the shear cell test at 9 kPa. The powder samples were conditioned, consolidated, pre-sheared, and sheared using the established FT4 protocols (Freeman, 2007). The shear head applied a normal stress (σ) while rotating to induce a rotational stress (τ) until the powder bed fails. The point (σ, τ) was recorded, and the cycle was repeated five times at lower normal stress. The Mohr circle analysis was performed automatically using the σ versus τ plot. The cohesion parameter is the τ value when σ = 0 kPa, which may be understood as the shear stress required to deform the powder bed when no normal stress is applied. The flow factor is defined as the relationship between the major principal stress and unconfined yield strength and indicates how well a powder flow (Freeman, 2007).

2.4. Three-chamber feed frame and experiments

The system used in this study consists of a hopper, a feed frame from a Fette 3090 tablet press (Fill-O-Matic®, Fette Compacting, Schwarzenbek, Germany) mounted on a table, and a high-density polyethylene disc (12.5 mm of thickness, with 36 holes of 10 mm in diameter) employed to simulate the tablet press turret. This system allows the replication of the powder flow dynamics within a tablet press while representative spectral data is acquired. The hopper delivers the powder to the feed frame using gravity as a driving force. The feed frame consists of three chambers in two levels and two inspection windows on the top of the bottom chambers, as shown in Fig. 1. The distributing chamber receives the powder from the hopper and transports it, using a paddle wheel, to filling and dosing chambers through two orifices in the partition plate. The paddle wheel in the dosing chamber rotates counterclockwise, transferring the powder to the dies. In contrast, the paddle wheel in the filling chamber removes the powder accumulated on the dies rotating clockwise. Additional information on the feed frame and die disc can be found in the literature (Méndez et al., 2012).

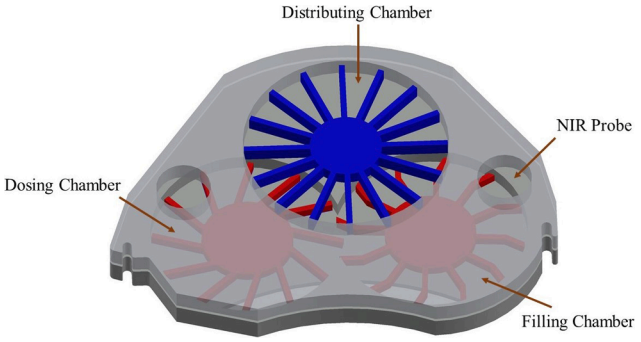

Fig. 1. Schematic top-view representation of the feed frame.

The feed frame experiments were started by adjusting the paddle wheel speed and die disc speed using Traceable® Photo/Contact Tachometer (Fisher Scientific, Pittsburgh, PA, USA). The paddle wheel speed and die disc speed used during the calibration and test set experiments were 40 and 30 RPM, respectively. The powder blend was then added to the hopper whilst the paddle wheel and die disc were stationary. The paddle wheel and die disc were turned on, and the feed frame transported the powders to the dies while a NIR probe installed over the left sapphire window acquire spectra of the flowing powder. The NIR spectra were obtained for approximately 6 min after reaching the steady-state. The feed frame was prepared for the next experiment using a vacuum cleaner to entirely remove the remaining powder within the feed frame and avoid cross-contamination between calibration and test set samples.

2.5. Effect of paddle wheel speed on the powder flow properties and tablet hardness

Additional experiments were performed to evaluate the effect of paddle wheel speed on the flow properties of powder blends with co-processed and non co-processed excipients. Powder blends with the same composition of test set 2 described in Table 1 were used for these experiments. Two paddle wheel speeds were defined for these experiments: 40 and 80 RPM, while the die disc speed remained constant at 30 RPM. The powder blend was added to the hopper whilst the paddle wheel and die disc were static. The paddle wheel was turned on as well as the die disc. At three minutes of operation, a powder blend sample was taken at the exit of the feed frame to evaluate its physical properties.

Powder blend samples from experiments were also used to prepare pharmaceutical tablets under a compaction force of 3.0 metric tons. A total of ten tablets were obtained from each powder blend sample employing a Carver laboratory press (Model C, Carver, Inc., USA). Tablets were prepared using approximately 700 mg powder sample and a stainless-steel die of 13 mm inner diameter with a flat-faced round

punch. Alcohol wipes cleaned the die and punches before each compression. The hardness or breaking force was measured with a hardness tester VK200 (Varian, Inc., Weston Parkway, North Carolina, USA) immediately after preparing the tablet.

2.6. NIR spectral acquisition

All NIR spectra were collected using a Bruker Matrix-FE Fourier transform near-infrared spectrometer (Bruker Optics GmBH, Ettlingen, Germany) with the powder blend flowing within the feed frame. The Q412 diffuse reflectance probe for non-contact analysis of this spectrometer includes two tungsten NIR light sources for the 12,000–4000 cm^{-1} spectral range. A resolution of 16 cm^{-1} and 16 averaged scans were used for the NIR spectral acquisition, while 64 scans were used to collect the background. The acquisition time for 16 scans was 1.5 s. The OPUS® software package version 7.2 (Build: 7,2, Bruker Optics, GmbH Ettlingen, Germany) was used to control the spectrometer.

2.7. Development and evaluation of the NIR calibration models

All NIR spectra were acquired with the powder blend flowing through the feed frame. Quantitative multivariate models were developed and evaluated in Unscrambler® software Version 11 (Camo Analytics, Aspen Technology Company, Oslo, Norway) employing Partial Least Square (PLS) regression, based on non-linear iterative partial least square (NIPALS) algorithm. The calibration set consisted of 1250 and 750 spectra for the model with the co-processed excipient and model with non co-processed excipients, respectively.

The root mean square error of prediction (RMSEP), Relative Standard Error of Prediction (%RSEP), and the bias were employed to evaluate the predictive model performance using three test set blends (independent from the calibration blends) with ibuprofen concentration of 42.5, 50.0 and 57.5% w/w, as shown in Table 1. The RMSEP, %RSEP and bias were calculated using the following mathematical relationships:

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{N}\left(\hat{y}_i - y_i\right)^2}{N}} \tag{2}$$

$$\%RSEP = \sqrt{\frac{\sum_{i=1}^{N}\left(\hat{y}_i - y_i\right)^2}{\sum_{i=1}^{N} y_i{}^2}} \times 100\% \tag{3}$$

$$Bias = \frac{1}{N}\sum_{i=1}^{N}\left(\hat{y}_i - y_i\right) \tag{4}$$

where $\hat{y}_i$ is the predicted concentration, y_i is the reference concentration, and N is the total number of predicted concentrations. The number of latent variables was determined by the ability of the model to predict the test set blends, the cumulative **Y**-variance explained by the model, and the correlation between API spectrum and loading of the first latent variable.

2.8. Variographic analysis

The variograms were calculated to estimate the sampling error associated with in-line ibuprofen determination within the feed frame when co-processed and non co-processed excipients are used. A MATLAB (version 2013b, MathWorks®, Natick, MA) code was used to calculate the variogram using **Equation (5)**. Where *V(j)* is a function of the distance between extracted increments; Q_{total} is the total number of spectra; *j* is the lag (distance between pairs of ibuprofen concentration); and $h_{(q+j)} - h_q$ represents the heterogeneity contribution.

$$V(j) = \frac{1}{2(Q_{total} - j)}\sum_{q=1}^{Q_{total}-j}\left(h_{(q+j)} - h_q\right)^2 \tag{5}$$

3. Results and discussion

3.1. Characterization of the material properties

Fig. 2 shows the characterization of the physical properties of ibuprofen, Ludipress®, Tablettose 70, povidone, and crospovidone. The results show that ibuprofen has the lowest flow properties, with average compressibility of 21.2% v/v, average cohesion of 0.9 kPa, and a flow factor ~ 81% lower than Ludipress®. The co-processed excipient has an average cohesion of 0.15 kPa and an average flow factor of 28. These flow properties explain the expected decrease in flow properties, which usually arises with the addition of API in the formulation. Albeit the compressibility values of Ludipress® and Tablettose 70 are similar, Tablettose 70 has a flow factor 75% lower than Ludipress®. Tablettose 70 is an agglomerated lactose derived from the same α-lactose-monohydrate used in the production of Ludipress®. Fig. 2**(b)** also displays an average cohesion less than 0.2 kPa and an average flow factor greater than 25 for crospovidone and povidone. Crospovidone and povidone are the disintegrant and binder co-processed in Ludipress®.

The ranges of true density, bulk density, and tap density for the raw materials were 1.127–1.560, 0.224–0.546, and 0.324–0.625 g/mL, respectively, as shown in Fig. 2**(c)**. Tablettose 70 is the densest raw material, while crospovidone is the excipient with the lowest density. Fig. 2**(d)** also shows the d_{10}, d_{50}, d_{90}, and the span of the particle size distributions. Ibuprofen has the smallest particle size with an average d_{50} = 51 μm, while Ludipress® and Tablettose 70 were the largest excipients with d_{50} of 206 and 188 μm, respectively. The particle size distributions expressed in span are in the range of 1.44 to 2.44. Tablettose 70 presents a span value of 1.44, while Ludipress® has a span of 2.07. A lower span value indicates a narrow particle size distribution.

3.2. Flow properties at different operating conditions

The properties of two powder blends of 50 %w/w ibuprofen, one with the co-processed material and the other with non co-processed excipients, were compared at different paddle wheel speeds in the feed frame. Fig. 3 shows the particle size distribution for these formulations before and after the feed frame experiments at 40 and 80 RPM. Both formulations have similar particle size distribution with a d_{50} of approximately 130 μm. A two-sample *t*-test at 95% of confidence level demonstrated that there is no significant difference between the d_{50} of the particle size distributions before and after the experiments, showing no evidence of breakage or particle attrition within the feed frame under the evaluated conditions. This is an essential feature for the materials because attrition and breakage affect the properties of both the powder blend and tablets.

Fig. 4**(a)** shows the changes in compressibility at different paddle wheel speeds. Both formulations show a decrease in compressibility as the paddle wheel speed increases. However, the formulation with the co-processed material presented lower compressibility. Powder blends with lower compressibility tend to have lower cohesion and a more stable flow behavior within the process units (Osorio and Muzzio, 2013), and require a lower compaction pressure to obtain hard tablets with low friability (Heinz et al., 2000). Fig. 4**(b)** displays the cohesion as a function of paddle wheel speed. The formulation with the co-processed excipient has lower cohesion at all paddle wheel speeds. This powder blend has a cohesion of 0.34 kPa before the experiments, and afterward, it is reduced by 41% in the 40 RPM experiment. However, there are no significant differences between the cohesion at 40 RPM and 80 RPM. The formulation with non co-processed excipients starts with an average cohesion of 0.52 kPa and then reduces by 5.8% at 40 RPM and 8.2% at

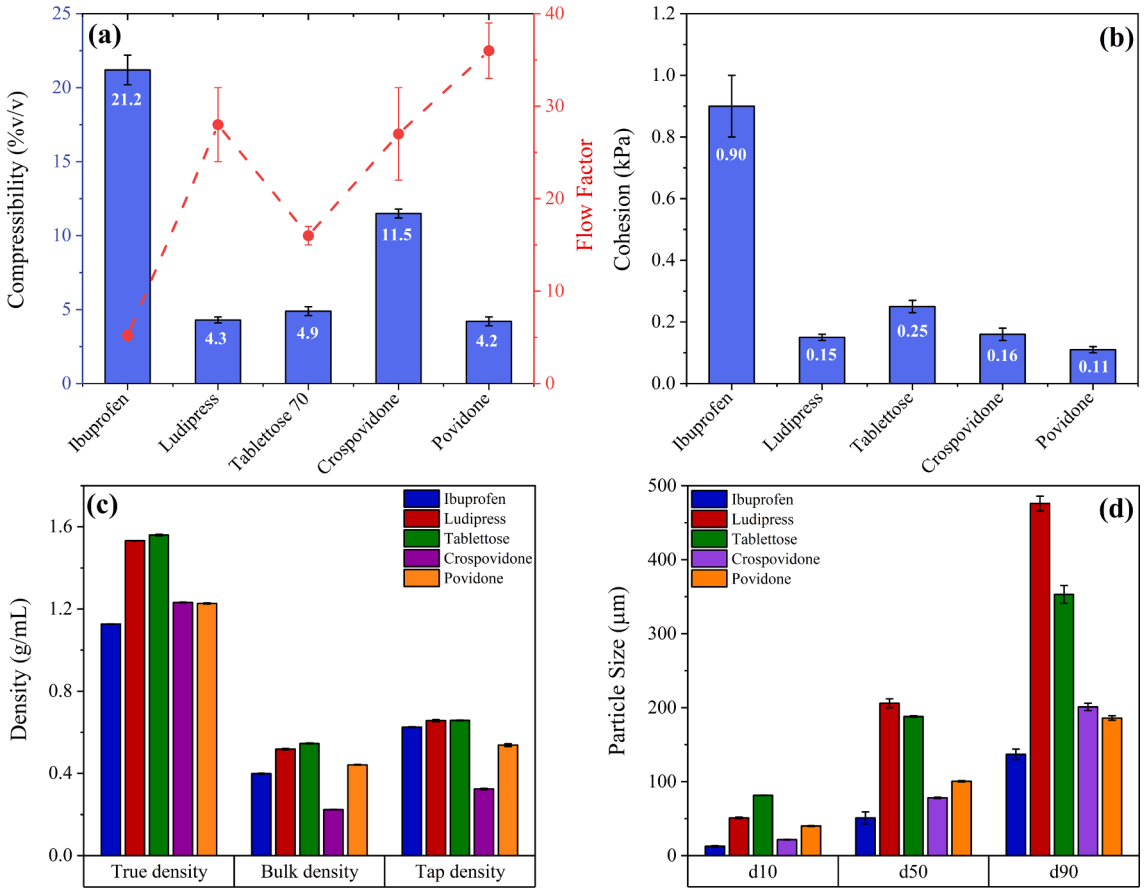

Fig. 2. Raw materials characterization: (a) Compressibility and flow factor (b) cohesion (c) true density, bulk density, and tap density (d) Particle size distribution. Each column represents mean value and the interval on each column represents one standard deviation for three determinations.

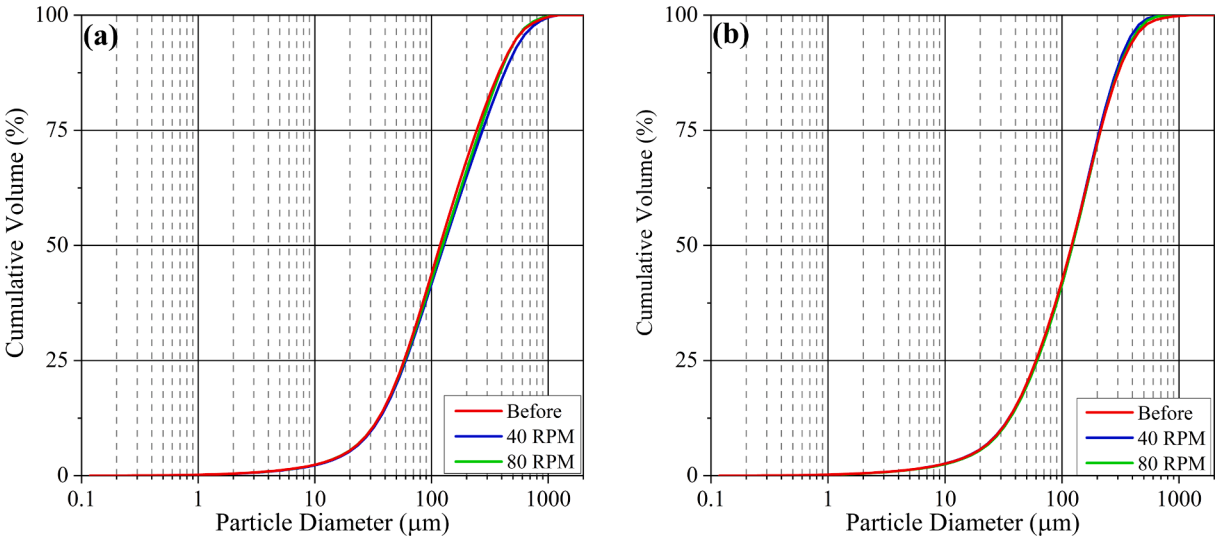

Fig. 3. Particle size distribution for (a) formulation with the co-processed excipient and (b) formulation with non co-processed excipients before and after flowing through the feed frame.

80 RPM. The powder blend cohesions behavior was consistent with the compressibility behavior.

Fig. 4**(c)** demonstrates that a decrease in cohesion led to an increase in the flow factor of the powder blends. The powder blend with the co-processed excipient presents flow factors greater than 12, while the formulation with non co-processed excipients had a flow factor less than 10. The flow factor is usually utilized to classify the material flow properties numerically using the categories proposed by Jenike (Leturia et al., 2014). The very cohesive materials have flow factors less than 2; cohesive materials present flow factors between 2 and 4; easy-flowing materials have a flow factor between 4 and 10, and the free-flowing materials present a flow factor greater than 10 (Megarry et al., 2019).

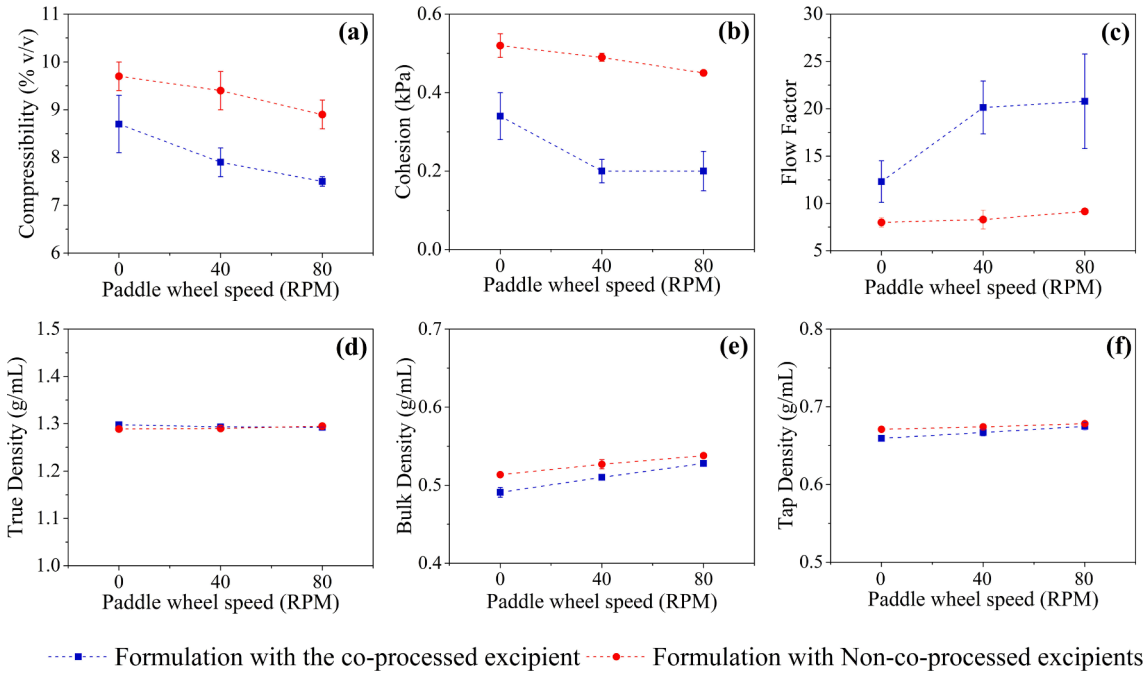

Fig. 4. Characterization of powder blends (a) Compressibility (b) Cohesion (c) Flow factor (d) True density (e) Bulk density (f) Tap density. The reported values are the average of three measurements. The interval in each measurement represents one standard deviation. Paddle wheel speed of 0 RPM represents the characterizations of powder blends before the experiments.

Surprisingly, the 50% w/w ibuprofen powder blends with the co-processed material were classified as free-flowing according to the Jenike scale due to the excellent flow properties of the co-processed excipient, whilst the blends with non co-processed excipients were classified as easy-flowing. These results demonstrated that pharmaceutical formulations based on Ludipress® could be used for direct compaction at high ibuprofen loading (50% w/w), where flow factors greater than approximately 7.0 are generally expected for the formulations (Chen et al., 2019). Even though Ludipress® and Tablettose 70 are excipients currently available for direct compaction, Ludipress® is a material that combines three functionalities: filler, binder, and disintegrant, while Tablettose 70 only have one of these functions.

The changes in compressibility, cohesion, and flow factor after the experiments may be linked to a better distribution of lubricant in powder blends due to applied shear to formulations by the paddle wheels within the feed frame. Previous studies have demonstrated that powder blends containing MgSt are shear sensitive; therefore, large amounts of applied strain significantly improve the flow properties (Mendez et al., 2010; Peeters et al., 2016). An improvement in the flow properties of the powder blends can increase the performance of the die filling process.

Fig. 4**(d), 4(e), and 4(f)** show the true, bulk, and tap density for the formulations. These properties affect the compression behavior of materials, particularly in formulations with high-dose drugs (Dai et al., 2019). The two formulations have true densities of approximately 1.30 g/mL. Even though there are no statistically significant differences between the true densities, a slight increase was observed in bulk and tap densities after passing through the tablet press feed frame due to the reduction in cohesion. Powder blends with the non co-processed excipients had a higher bulk and tap density than the blend with the co-processed excipient. This finding was expected since formulations with non co-processed excipients have smaller particles that promote more significant particle rearrangement, mainly when taps are applied.

3.3. Effect of excipients on tablet hardness

Fig. 5 shows the hardness profiles at different paddle wheel speeds of the tablets prepared with the powder blend samples of the two

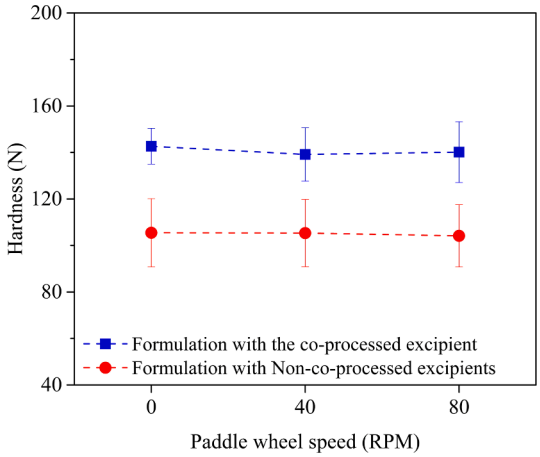

Fig. 5. The hardness of the tablets as a function of paddle wheel speed. The interval on each measurement point represents one standard deviation. Paddle wheel speed of 0 RPM represents the characterizations of powder blends before the experiments.

formulations of 50% w/w ibuprofen. Tablets with the co-processed excipient present a higher hardness than tablets with non co-processed excipients. These results agreed with the evaluations of the flow properties, where the formulation with the co-processed excipient showed better flow factor and lower compressibility. Schmidt and Rubensdörfer reported that Ludipress® presents a higher compactability than a powder blend of Tablettose 70, povidone, and crospovidone, linking this behavior to the irregular surface structure of Ludipress®, which causes strong interlocking of the compacted granules, and the presence of the binder (povidone) that contributes to the hardness (Schmidt and Rubensdörfer, 1994b).

Fig. 5 shows an average hardness of 142.7, 139.2, and 140.1 N for the tablets with the co-processed material, while the tablets with non co-processed excipients presented hardness of 105.5, 105.3, and 104.2 N

for the blend samples from 0, 40, and 80 RPM experiments in the feed frame, respectively. There are no significant differences between the hardness of the tablets from each formulation (p-value >0.05). These results demonstrate that changes in flow properties caused by powder processing within the tablet press feed frame due to the increase in the distribution of the lubricant do not affect the compactability of the formulation and the mechanical properties of the tablets.

3.4. Overview of spectral data

Fig. 6 displays the NIR diffuse reflectance spectra after the SNV normalization between 12000 and 4000 cm^{-1} for the ibuprofen and the excipients used in this study. The NIR spectra for raw materials were acquired off-line; however, all NIR spectra for calibration and test set blends were acquired with powder blends flowing through the tablet press feed frame. The ibuprofen spectrum showed pronounced differences over the entire spectral range compared with Ludipress® and Tablettose 70. The most intense ibuprofen absorption bands were observed in the following spectral range: 9000–6750, 6200–5200, and 4700–4150 cm^{-1}. Likewise, povidone and crospovidone present absorption bands between 9000–8000, 7500–6200, 5700–5500, 5300–4900, and 4400–4150 cm^{-1}. The spectral differences between the API and excipients are essential to quantify drug concentrations using NIR spectroscopy. Fig. 6 also shows that Ludipress® and Tablettose 70 have very similar NIR spectra with a correlation of 99.9% in the 12,000–4000 cm^{-1} spectral range. This is because Ludipress® is a co-processed excipient containing 93% lactose, and the individual excipients preserve their chemical structure and stability after co-processing (Chow et al., 2008; Rojas et al., 2012).

3.5. Quantitative NIR calibration models

The NIR spectra used to develop the NIR calibration models were acquired with the powder blend flowing through the tablet press feed frame while the paddle wheel speed operated at 40 RPM and the die disc speed at 30 RPM. Seven preprocessing approaches were investigated for each spectral region: SNV, first derivative, second derivative, SNV followed by the first derivative, SNV followed by the second derivative, first derivative followed by SNV, and second derivative followed by SNV. The derivatives were determined using the Savitzky-Golay algorithm with 15 points segment size. The RMSEP, RSEP (%), and bias of predicted concentrations from test set blends were used as figures of merit to evaluate the performance of the NIR calibration models. The quantitative model using the co-processed excipient was developed using 250 spectra per concentration level, while the model that includes the non co-processed excipients was calculated using 150 spectra per concentration level.

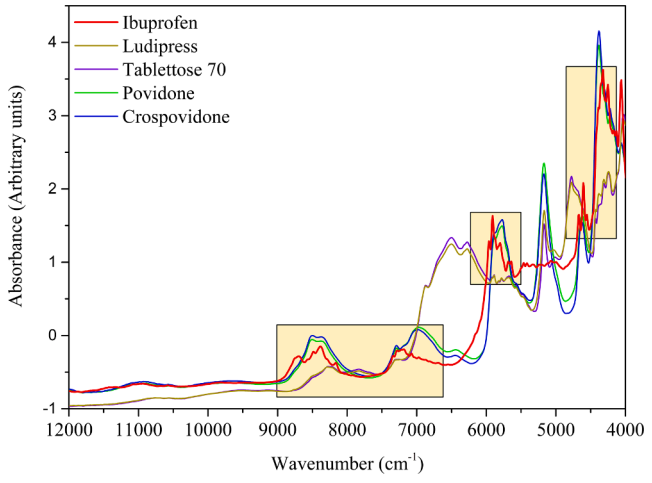

Fig. 6. NIR spectra for ibuprofen, Ludipress®, Tablettose 70, povidone, and crospovidone after SNV preprocessing. The shaded area corresponds to the spectral region associated with ibuprofen spectral bands.

Table 2 summarizes the figures of merit for the NIR calibration models. The NIR calibration model that delivers the best performance in predicting test set blends using the co-processed excipient was calculated using a spectral range of 6200–5500 cm^{-1} (Model 1), while the model for the powder blends using the non co-processed excipients was developed in 9402–6100 cm^{-1} spectral range (Model 4). Both models with the second derivative (second polynomial order and Savitzky–Golay algorithm with 15 points segment size) as data preprocessing and one latent variable. The explained **Y**-variance of the two models is greater than 95%. The selected NIR calibration model for the co-processed material and non co-processed excipients present an RMSEP of 0.95 and 1.67% w/w, respectively. The RSEP (%) of the model for the co-processed material was 1.89%, and 3.31% for non co-processed excipients model. Nevertheless, the NIR model with non co-processed excipients has a lower bias with a value of −0.16% w/w. The RMSEP, RSEP (%), and bias obtained demonstrated the excellent performance of the quantitative models when predicting the test set blends. Table 2 also shows an increase in RMSEP and RSEP (%) when the NIR calibration model for the co-processed excipient is developed in 9402–6100 cm^{-1} spectral range (Model 2), and when the NIR calibration model for the non co-processed excipients is developed in 6200–5500 cm^{-1} spectral range (Model 3).

Fig. 7**(a)** shows the PLS score plot for the selected NIR calibration model with the co-processed excipient. Well-defined clusters for the five concentration levels are observed along the first latent variable. As the first latent variable (LV1) increases, the ibuprofen concentration increases. The LV1 and LV2 (second latent variable) explained 98.6% and 0.42% of the variation in the ibuprofen concentration (**Y**-variance), respectively. Fig. 7**(b)** shows the loading plot for the first latent variable and the preprocessed ibuprofen spectrum within the same spectral region of the model. The main absorption bands of ibuprofen were observed in the loading weight vector. An evaluation of the correlation between these two vectors was performed, yielding a value of 95.6%. This high correlation demonstrated the ability of the NIR calibration model to explain the variability associated with the ibuprofen concentration. Loading-weights represent the covariance among the individual **X**-variables (wavenumbers) and the response variable for each latent variable. The higher the loading value for the **X**-variable, the more critical that variable is for the prediction of the **Y**-variable (Esbensen and Swarbrick, 2018).

The PLS score plot for the selected NIR calibration model with non co-processed excipients is shown in Fig. 8**(a)**. Well-defined clusters can be observed along the first latent variable. The first latent variable explained 96.33% of the ibuprofen concentration variability, while the second latent variable explained 0.99%. Fig. 8**(b)** shows the loading plot for the model and the pre-processed ibuprofen NIR spectrum within the chosen spectral range. The ibuprofen absorption bands were present in the loading of the first latent variable. The coefficient of correlation between these two vectors is approximately 0.74. The agreement between the ibuprofen spectrum and the loading vector demonstrated that the variability explained by the model is related to ibuprofen concentration. The loading-weight of the NIR calibration model with non co-processed excipients correlates with the ibuprofen spectrum in a lower percentage than the loading of the NIR model with the co-processed excipient, demonstrating that the model using Ludipress® was more specific to ibuprofen. Although there is a direct correlation between the API and the main excipient of the formulation (Ludipress® or Tablettose 70) as shown in Table 1, the models show a high specificity towards ibuprofen due to the strong absorption bands of this API in the spectral ranges used in the development of the models.

Table 2
Global Figures of merit of the NIR calibration models.

Model ID	Spectral region (cm^{-1})	Data preprocessing	No. Latent variables	Explained **Y**-variance (%)	No. samples – Test set	RMSEP (%w/w)	RSEP (%)	Bias (%w/w)
	Co-processed excipient							
1	6200–5500	2 Der (15)	1	98.6	600	0.95	1.89	0.56
2	9402–6100	2 Der (15)	1	93.6		1.82	3.64	−0.22
	Non co-processed excipients							
3	6200–5500	2 Der (15)	1	94.9	570	3.22	6.28	−1.04
4	9402–6100	2 Der (15)	1	96.3		1.67	3.31	−0.16

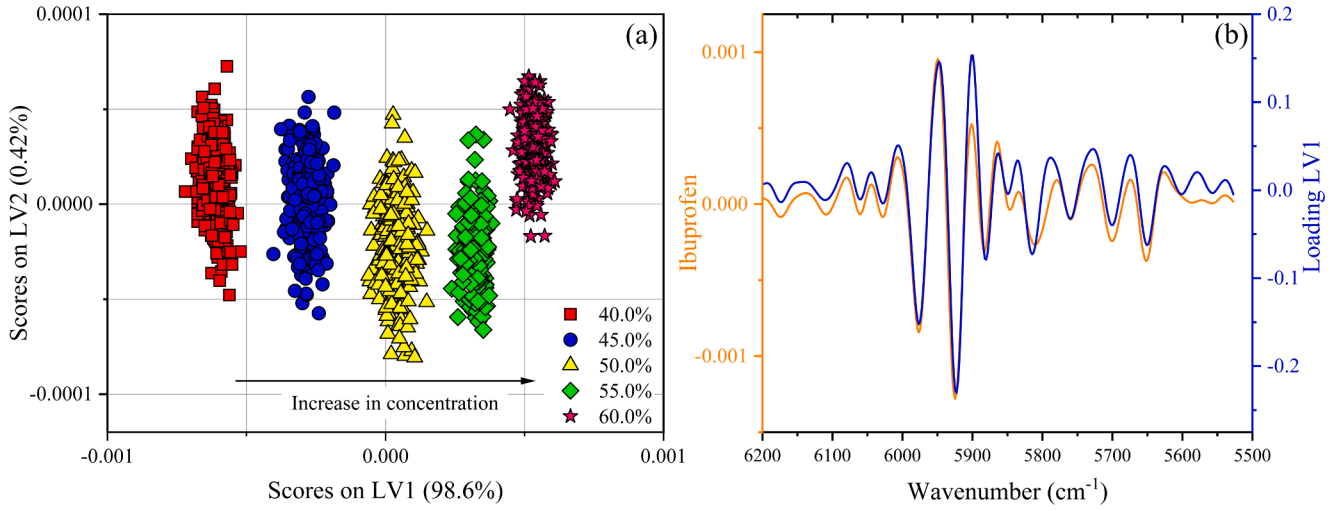

Fig. 7. (a) PLS score plot and (b) Loading weight vector for the first latent variable and the ibuprofen NIR spectrum with the same data preprocessing used in the selected NIR model using the co-processed excipient.

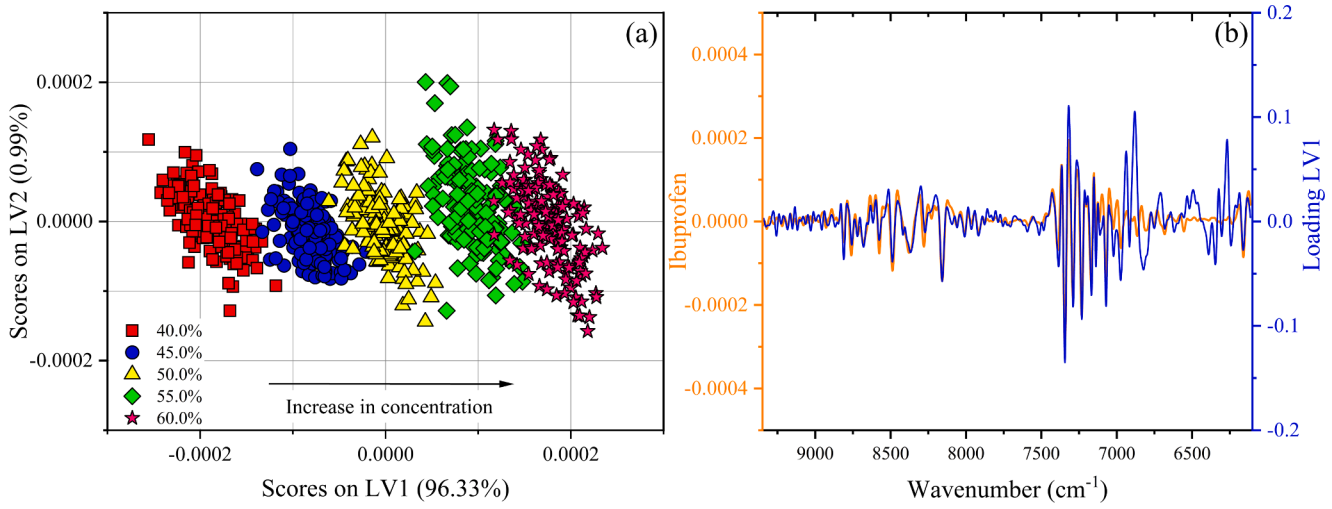

Fig. 8. (a) PLS score plot and (b) Loading weight vector for the first latent variable and the ibuprofen NIR spectrum with the same data preprocessing used in the selected NIR model using non co-processed excipients.

3.6. Quantitative process monitoring

Fig. 9 shows the concentration versus time profiles obtained from the test set blends of the two optimized NIR calibration models. The solid blue lines represent the target concentration of the test blends, and the dash-dot lines represent ± 5% of the target concentration in the test blends. Fig. 9**(a)** shows the NIR predictions for the test set blends of the NIR model with the co-processed excipient. All the individual predictions were within the ± 5% of the target concentration, showing a narrow variation between them. Likewise, the test blend of 57.5% w/w ibuprofen presents a slight positive deviation from the target concentration. Fig. 9**(b)** shows the NIR predictions for the test set blends of the NIR model with non co-processed excipients. Some individual predictions were outside the 95–105% of the target concentration but within ± 10% of the target concentration. The NIR predictions of the model with non co-processed excipients were more dispersed around the target concentrations, which lead to high standard deviations. These concentration profiles also demonstrate no evidence of segregation by

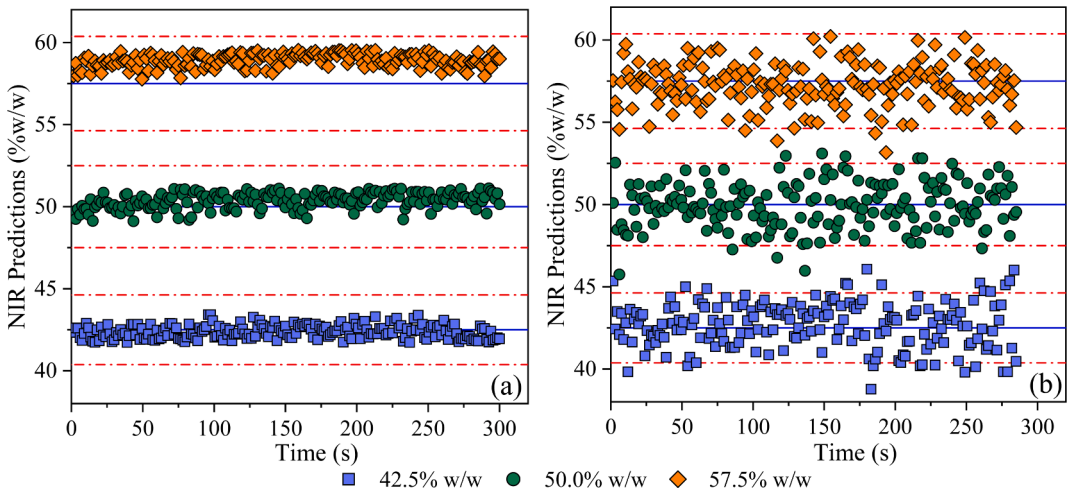

Fig. 9. Concentration profiles for the test blends ***(a)*** NIR model using the co-processed excipient ***(b)*** NIR model using non co-processed excipients. The solid blue lines represent the target concentration of the test blends. Dash dot lines represent ±5% of the target concentration in the test blends.

percolation within the feed frame despite the differences in particle size between ibuprofen and the main excipients: Ludipress® and Tablettose 70.

Table 3 shows the figures of merit of the NIR predictions for each test set blend. The average concentrations for the test set blends of the NIR model using the co-processed excipient were 42.4, 50.4, and 58.9% w/w, while for the model with non co-processed excipients were 42.7, 49.9, and 57.3% w/w. All average values were very close to the respective reference concentration. The RSD values obtained for the predictions of the NIR model using the co-processed excipient were significantly low, less than 1.00%, while the RSD values of the other model varied between 2.30 and 3.24%. These results demonstrated that the NIR calibration model with the co-processed excipient delivers the most precise results.

3.7. Variographic analysis

A variographic analysis was performed to estimate the total sampling and total analytical error associated with the in-line determination of high ibuprofen concentration when a co-processed excipient or non co-processed excipients are used in a pharmaceutical formulation. The authors understand that this is the first study where the sampling errors are evaluated as a function of the excipients used in the pharmaceutical formulation. Sampling errors can be affected by the material properties (Sierra-Vega et al., 2020); thus, the sampling strategy must be adjusted to contributes to its reduction. Fig. 10 shows the computed variograms for the test set blends. This analysis was completed using the predictions of the test blends from the optimized NIR calibration models. A flat variogram was obtained for all test set blends, indicating that the residual variance of the powder blend does not change with the lags (Esbensen and Julius, 2010). *V(j)* values were lower for the model with the co-processed excipient than for the model with non co-processed excipients. Low *V(j)* values are synonyms of a higher serial correlation between ibuprofen concentrations.

The sill, minimum practical error (MPE), and the correct sill were calculated from the variograms and are shown in Table 4. The sill provides information about the maximum observable process variance and is calculated by averaging the *V(j)* values for all lags (Esbensen et al., 2016; Esbensen and Paasch-Mortensen, 2010). Sill values less than 0.23 $(\%w/w)^2$ were obtained for the model with the co-processed excipient and between 1.7 and 2.1 $(\%w/w)^2$ for the model with non co-processed excipients. These sill values show that including the Ludipress® in the formulation leads to a more stable process with low sample-to-sample variations. Table 4 also shows the MPE values. MPE provides an estimate of the sum of the total sampling error and the total analytical error associated with the measurement system (Esbensen and Julius, 2010). The variogram is not defined for lag = 0, since it would correspond to analyzing the same sample twice, which is not physically possible in the flowing blend. However, lag = 0 would be an estimate of the sum of the total sampling and analytical errors associated with the measurement system, when all incorrect sampling errors have maximally reduced (Esbensen and Julius, 2010). Thus, the variance at lag = 0 is estimated through the MPE determined by back-extrapolating the first five *V(j)* values, as shown in the insert in Fig. 10**(a)**. MPE values varied from 0.136 to 0.166 and 1.74 to 1.88 $(\%w/w)^2$ for the model with the co-processed material and non co-processed excipients, respectively. The significantly low MPE values in the variograms for the powder blend with Ludipress® confirm higher process stability during the experiment with the co-processed material. Similarly, the correct sill also is shown in Table 4. This parameter delivers information on the residual heterogeneity of the blend (calculated by subtracting the MPE form sill). Low corrected sill values were obtained for the two models due to the similarity between the MPE and sill values, indicating that the process can only be optimized by decreasing the MPE (Esbensen et al., 2016).

Table 4 also shows the results of the repeatability study. The repeatability evaluates the short-term precision of the quantitative models. Six consecutive spectra were collected for test set blends with the powder flow stopped, and the standard deviations of its predictions were calculated. The standard deviations obtained varied between 0.13–0.30 and 0.35–0.47%(w/w) for the NIR model with the co-processed material and with non co-processed excipients, respectively. These values represent the minimum expected variation in the analysis of blend uniformity and demonstrate the superiority of the short-term precision of the model with the co-processed material. The variance of the repeatability study was determined to estimate the analytical error.

Table 3
Average predicted concentration, standard deviations, and RSD (%) per concentration level of the test set blends.

NIR model	Reference concentration (% w/w)	Number of samples	Average NIR predictions (% w/w) [a]	RSD (%)
Co-processed excipient	42.5	200	42.4 (0.4)	0.96
	50.0	200	50.4 (0.5)	0.96
	57.5	200	58.9 (0.4)	0.68
Non co-processed excipients	42.5	190	42.7 (1.4)	3.24
	50.0	190	49.9 (1.4)	2.82
	57.5	190	57.3 (1.3)	2.30

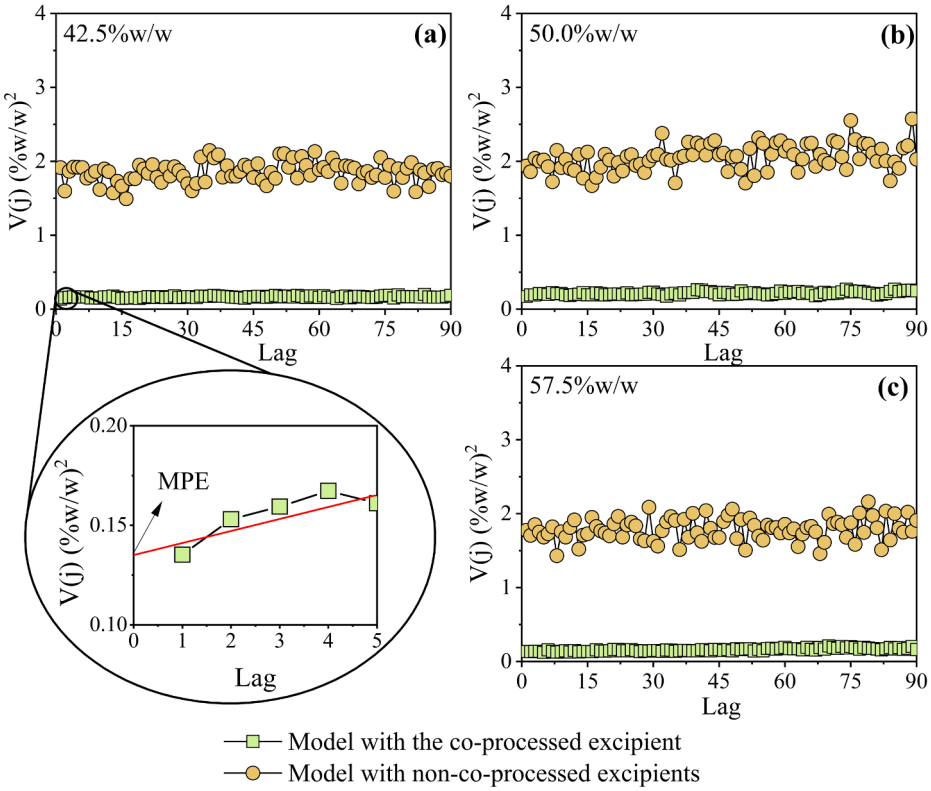

Fig. 10. Variograms for the test set blends.

Table 4
Summary of the results obtained from variographic analysis.

Parameter	NIR model with co-processed excipient			NIR model with non co-processed excipients		
Reference Concentration (%w/w)	**42.5**	**50.0**	**57.5**	**42.5**	**50.0**	**57.5**
Sill $(\%w/w)^2$	0.167	0.217	0.161	1.85	2.04	1.78
MPE $(\%w/w)^2$	0.136	0.166	0.138	1.74	1.88	1.76
Corrected sill $(\%w/w)^2$	0.0315	0.0507	0.0229	0.108	0.165	0.0225
Repeatability study (%w/w)	0.191	0.127	0.281	0.356	0.464	0.374
Repeatability: variance $(\%w/w)^2$	0.0365	0.0160	0.0788	0.127	0.215	0.148
Estimated Sampling error $(\%w/w)^2$	0.262	0.400	0.194	1.61	1.66	1.61

These variances were significantly lower than MPE since MPE represents the sum of the total analytical error and the total sampling error. Finally, an evaluation of the sampling errors was performed by subtracting the analytical variance from the MPE values. The sampling errors ranged from 0.19 to 0.40 and 1.61 to 1.66 $(\%w/w)^2$ for the model with the co-processed excipient and with non co-processed excipients, respectively. The in-line ibuprofen determination in the powder blend with 50% w/w ibuprofen and non co-processed excipients had a sampling error of approximately 315% greater than the powder blend based on the co-processed excipient. These results demonstrated that the use of the co-processed material (Ludipress®) in the high-load dose formulations reduced the sampling errors.

4. Conclusions

This work shows how PAT can help in the development of a pharmaceutical formulation. This study presented the assessment of the suitability of a co-processed excipient for formulations with high ibuprofen concentrations. Compared with the powder blend of individual ingredients, the formulations with the co-processed excipient showed significant advantages: lower compressibility, lower cohesion, and higher flow factor. The tablet press feed frame improved the flow properties of the powder blends; however, these changes did not affect the particle size distribution of the formulations or the hardness of the tablets. This study demonstrated that high-load dose formulations with Ludipress® have suitable properties for a direct compaction tablet manufacturing process.

Two in-line NIR spectroscopic methods were developed spanning an ibuprofen concentration range from 40 to 60% w/w. A NIR spectroscopic model was developed using the co-processed excipient, while the second NIR spectroscopic model was developed, changing the co-processed excipient by its base components. The NIR calibration models determined the ibuprofen concentration in the test set blends with RSEP (%) below 3.4%. Nevertheless, the NIR model with the co-processed excipient presented better performance with lower prediction error and greater specificity to ibuprofen. The concentration profiles of test set blends from the NIR model with the co-processed excipient demonstrated that all the individual predictions were within the ± 5% of the target concentration, while some predictions for the test set blends of the NIR model with non co-processed excipients were outside the 95–105% of the target concentration. The concentration profiles do not show segregation within the feed frame during the quantification of ibuprofen.

The variographic analysis performed from the NIR predictions of test

set blends showed that the use of the co-processed excipient in the formulations significantly reduces the sampling and analytical errors in the in-line determination of ibuprofen. MPE values from the NIR model with the co-processed excipient were extremely low, confirming the higher process stability during the experiment with the co-processed material. These results demonstrate that selecting a suitable excipient for the formulation reduces the magnitude of the total measurement error.

CRediT authorship contribution statement

Nobel O. Sierra-Vega: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Krizia M. Karry:** Conceptualization, Methodology, Formal analysis, Resources. **Rodolfo J. Romañach:** Conceptualization, Validation, Formal analysis, Resources, Writing – review & editing, Visualization, Funding acquisition. **Rafael Méndez:** Conceptualization, Validation, Formal analysis, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2021.120910.

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