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DEVELOPMENT OF AN ANALYTICAL METHOD FOR CRYSTALLINE CONTENT DETERMINATION IN AMORPHOUS SOLID DISPERSIONS PRODUCED BY HOT-MELT EXTRUSION USING TRANSMISSION RAMAN SPECTROSCOPY A FEASIBILITY STUDY

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ABSTRACT

The development of a quantitative method determining the crystalline percentage in an amorphous solid dispersion is of great interest in the pharmaceutical field. Indeed, the crystalline Active Pharmaceutical Ingredient transformation into its amorphous state is increasingly used as it enhances the solubility and bioavailability of Biopharmaceutical Classification System class II drugs. One way to produce amorphous solid dispersions is the Hot-Melt Extrusion (HME) process. This study reported the development and the comparison of the analytical performances of two techniques, based on backscattering and transmission Raman spectroscopy, determining the crystalline remaining content in amorphous solid dispersions produced by HME.

Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression were performed on preprocessed data and tended towards the same conclusions: for the backscattering Raman results, the use of the DuoScan™ mode improved the PCA and PLS results, due to a larger analyzed sampling volume. For the transmission Raman results, the determination of low crystalline percentages was possible and the best regression model was obtained using this technique. Indeed, the latter acquired spectra through the whole sample volume, in contrast with the previous surface analyses performed using the backscattering mode. This study consequently highlighted the importance of the analyzed sampling volume.

ABBREVIATIONS

API, active pharmaceutical ingredient ; BCS, Biopharmaceutical classification system ; DSC, differential scanning calorimetry ; EMCCD, electron multiplying charged couple device ; FTIR, Fourier transform infrared spectroscopy ; HME, hot-melt extrusion ; ITZ, itraconazole ; PCA, principal component analysis ; PCs, principal components ; PLS, partial least squares ; SEM, scanning electron microscopy ; TGA, thermogravimetric analysis

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KEYWORDS: Amorphous solid dispersions ; Crystalline content ; Analyzed sampling volume ; Confocal Raman microspectroscopy ; Transmission Raman spectroscopy ; Hot-melt-extrusion

1. Introduction

In the last decades, more and more Biopharmaceutical Classification System (BCS) class II drugs were implemented in pharmaceutical manufacturing processes. The issue of such drugs is their poor solubility and bioavailability leading to restrictive integration in conventional pharmaceutical formulations. One way to enhance this lack of solubility is to transform the crystalline Active Pharmaceutical Ingredient (API) in its amorphous state. Indeed, an amorphous drug has a higher molecular mobility inducing a higher solubility and dissolution rate but has a lower chemical and physical stability. Several techniques were developed to manufacture amorphous APIs in the pharmaceutical field such as milling, melting, quenching, spray drying, freeze drying and solid dispersions. The production of solid dispersions by a Hot-Melt Extrusion (HME) process is discussed in this work. During the HME process, the API is encompassed in a polymeric carrier and transformed in its amorphous state by manufacturing a solid dispersion. The aim of an adequate formulation is consequently to reduce the recrystallization of the amorphous API and stabilize the latter using appropriate polymers and excipients. Indeed, amorphous APIs tend to convert into the most stable form during storage, which induces solid-state changes, leading to lower dissolution rates and poorer dosage form effectiveness (Kanaujia et al., 2015, Kogermann et al., 2013, Li et al., 2014, Sarode et al., 2013a, Sarode et al., 2013b, Shah et al., 2013, Van Den Mooter, 2012).

As can be read in the literature (Agrawal et al., 2016, Bochmann et al., 2016, Engers et al., 2010, Fule and Amin, 2014, Gumaste et al., 2016, Janssens et al., 2007, Lim et al., 2017, Tian et al., 2014), more and more scientific teams explored the development of solid dispersions to solve this issue. In this context, several thermal analyses techniques such as Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TGA) were developed to characterize the solid dispersion by measuring the state of the API and thus its recrystallization that should be avoided (Agrawal et al., 2016, Bochmann et al., 2016, Engers et al., 2010, Fule and Amin, 2014, Gumaste et al., 2016, Janssens et al., 2007, Lim et al., 2017, Tian et al., 2014). The development of vibrational spectroscopic techniques spread out as it performs analyses able to distinguish the amorphous and crystalline API state (Croker et al., 2012, Hennigan and Ryder, 2013, Li et al., 2011, Mah et al., 2015, Netchacovitch et al., 2015, Nikowitz et al., 2016, Saerens et al., 2014a, Saerens et al., 2014b). Moreover, the analyses of solid dispersions by Raman microscopy are in real expansion since it also studies the spatial drug distribution inside the formulation. In this case, multivariate analyses are most often performed to extract the relevant information (Amigo, 2010; Docoslis et al., 2007; Fule et al., 2014; Gendrin et al., 2008; Sacré et al., 2014; Scoutaris et al., 2014; Vajna et al., 2011; Vigh et al., 2014; Widjaja et al., 2011). The ability to use Raman mapping and adequate chemometric tools to characterize pharmaceuticals was demonstrated by Vajna et al. (2011). They compared the spatial distribution of melt extruded and conventional Isoptin formulations by analyzing their internal structure and concluded that melt extrusion was able to manufacture sustained release products with a better

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dissolution profile than the one produced by wet granulation. Scoutaris et al. (2014) characterized paracetamol – Compritol® extrudates, as well qualitatively as quantitatively, using Energy Dispersive X-ray (EDX) and confocal Raman microscopy by means of multivariate analyses. They studied the drug distribution and concluded that a better uniformity and distribution of paracetamol in pre-mixed extruded formulations was obtained compared to direct compressed tablets. Vigh et al. (2014) developed a model to determine the drug crystallinity in extrudates. They analyzed real samples, based on a factorial design experiment, to study the relationship between process parameters and residual drug crystallinity content using confocal Raman mapping and transmission Raman spectrometry. They found that Raman spectroscopy may be a suitable tool for the prediction of drug degradation, the determination of glass transition temperature (T_g) and the determination of drug crystallinity content.

As reported in the literature, the qualitative and quantitative characterization of amorphous solid dispersions spread out during these last decades. These dispersions are of great interest in the pharmaceutical field enhancing the solubility and bioavailability of BCS class II drugs. In this context, this study reported the comparison of the analytical performances of a backscattering and a transmission Raman spectroscopic technique, analyzing tablets containing different crystalline/amorphous ITZ ratio, determining the crystalline remaining ITZ content in amorphous solid dispersions produced by HME.

2. Materials and methods

2.1. CHEMICALS

Itraconazole (ITZ) was purchased from Lee Pharma Ltd. (Andhra, Pradesh, India), Soluplus® and AcDiSol® were provided from BASF (Ludwigshaven, Germany) and FMC Biopolymer (Brussels, Belgium), respectively.

2.2. HOT-MELT EXTRUSION PROCESS

A Hot-Melt Extrusion process was performed to obtain extrudates with and without Itraconazole (ITZ). These extrudates were milled, compressed and used as validation matrix to obtain samples with different degrees of crystallinity as close as possible to the real future samples (extrudates). In this context, 12 independent batches (6 with ITZ and 6 without ITZ) were produced based on an optimized formulation containing 25% ITZ, 72.5% Soluplus® and 2.5% AcDiSol® (Thiry et al., 2016). The hot-melt extruded samples with ITZ were used to obtain amorphous solid dispersions. Indeed, the extrudates with ITZ contained 100% amorphous API and the ones without ITZ contained the polymeric matrix (Thiry et al., 2016).

For the HME process, mixtures with and without ITZ, based on the optimized formulation, were premixed in a *TURBULA*® Shaker-Mixer for 20 min and then put inside the volumetric feeder for extrusion. An 18 mm twin screw hot-melt extruder was used (L/D = 32, Scamex®, Crosne, France) with

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a common screw configuration containing two kneading zones. The temperature gradient (70–135–145–155 °C) was applied to the four heating zones of the barrel. The rotational screw speed was set at 100 rpm. A volumetric feeder was used and the feeding rate was set at 4 rpm corresponding with the formulation mixture to 6 g min^{-1}. The extrudates were collected after cooling to ambient temperature for off-line analyses. The batches were then grinded using an Ultra Centrifugal Mill, type ZM 200 (Retsch GmbH, Haan, Germany) apparatus.

2.3. TABLET PREPARATION

Based on the 12 HME productions (6 with ITZ and 6 without ITZ), tablets comprising different percentages of crystalline/amorphous ITZ ratio were prepared on three series to obtain training and test sets, as presented in Table 1. The training sets included three levels of concentration (0%, 10% and 50% crystalline ITZ) and the test sets included five levels of concentration (0%, 5%, 10%, 25% and 50% crystalline ITZ). These tablets contained crystalline ITZ powder, grinded extrudates with ITZ (amorphous samples) and grinded extrudates without ITZ (polymeric matrix) as presented in Fig. 1 and Table 2.

Table 1. Training and test sets preparation on three series.

Series 1	**Series 2**	**Series 3**
Training set 1 (production 1)	Training set 1 (production 3)	Training set 1 (production 5)
Training set 2 (production 1)	Training set 2 (production 3)	Training set 2 (production 5)
Test set 1 (production 2)	Test set 1 (production 2)	Test set 1 (production 2)
Test set 2 (production 4)	Test set 2 (production 4)	Test set 2 (production 4)
Test set 3 (production 6)	Test set 3 (production 6)	Test set 3 (production 6)

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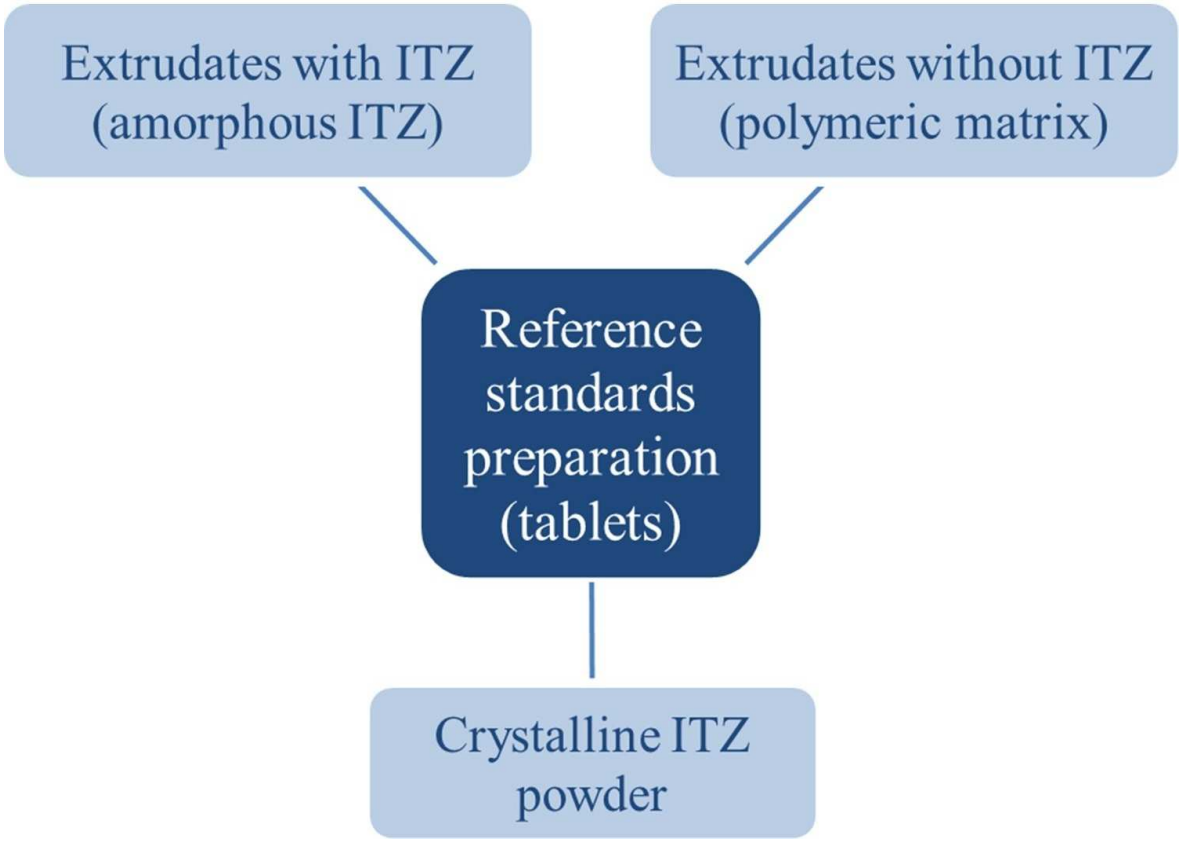

Fig. 1. Schematic representation of the reference standard preparation including crystalline ITZ powder and HME productions.

Table 2. Preparation of tablets.

Tablets (Crystalline%)	**Crystalline ITZ**	**Extrudates with ITZ**	**Extrudates without ITZ**
100%	25%	0%	75%
Weighing (mg)	50.0	0.0	150.0
50%	12.5%	50%	37.5%
Weighing (mg)	25.0	100.0	75.0
25%	6.25%	75%	18.75%
Weighing (mg)	12.5	150.0	37.5
10%	2.5%	90%	7.5%
Weighing (mg)	5.0	180.0	15.0
5%	1.25%	95%	3.75%
Weighing (mg)	2.5	190.0	7.5
0%	0%	100%	0%
Weighing (mg)	0.0	200.0	0.0

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The mixtures prepared as presented in Table 2, were homogenized in a mortar with a pestle and tablets were obtained using a tablet hydraulic press (Perkin Elmer). Tablets were then analyzed by Raman spectroscopy.

2.4. EQUIPMENT

2.4.1. BACKSCATTERING RAMAN MICROSPECTROPHOTOMETER

Tablets were analyzed using a Labram HR Evolution (Horiba scientific, Kyoto, Japan) apparatus equipped with a two-dimensional Newton 970 front-illuminated EMCCD detector (1600 × 200 pixel sensor) (Andor Technology Ltd.), a Leica 50 x Fluotar LWD objective (NA = 0.55, Wetzlar, Germany) and a 785 nm laser with a power on samples of 20 mW (XTRA II single frequence diode laser, Toptica Photonics AG). A 300 grooves/mm grating covering a spectral range from 464 cm^{-1} to 1852 cm^{-1} was used. Four accumulations of 1 s were acquired. A confocal slit-hole fixed at 200 µm, a binning factor of 1 and an Electron-Multiplying gain of 50 were applied. A point mapping mode was used to analyze the tablets surface with a laser spot size around a micrometer. The mapped area was 250 × 250 $µm^2$ covering a map of 10 × 10 pixels.

The same tablets were analyzed on the same equipment with the same acquisition parameters but using the DuoScan™ mode which enables to cover a larger surface on samples than the laser spot size by moving mirrors inside the optical path. In this study, the analyzed surface per pixel was around 20 µm. It is interesting when large areas of sample must be analyzed in a short time.

2.4.2. TRANSMISSION RAMAN SPECTROPHOTOMETER

Tablets were also analyzed using a loaned prototype of transmission Raman spectrophotometer (Horiba Scientific, Kyoto, Japan), that acquires a mean Raman spectrum of samples characterizing a large sampling volume.

It was equipped with a two-dimensional CCD detector (1024 × 256 pixels) and a 830 nm laser. The spectral range was 211–1795 cm^{-1}. Ten accumulations of 1 s were performed. A binning factor of 1 was applied. The power laser was of 1.5W and the laser spot size was of 3 mm.

2.5. MULTIVARIATE DATA ANALYSIS

The mean spectrum of each map was extracted before applying preprocessing treatments which remove artifacts and undesirable information. A Whittaker baseline correction was applied (smoothness factor $\lambda = 100{,}000$ and asymmetry factor $p = 0.001$) on spectra, followed by a normalization of the area of the ITZ specific band (1614 cm^{-1}). Finally, spectra were mean centered. These preprocessing were performed using Matlab R2016a (The Mathworks, Natick, MA, USA).

Preprocessed spectra were firstly used to compare 0% and 100% crystalline tablets aiming to highlight the critical spectral regions differentiating both spectra. A Principal Component Analysis and a Partial Least Squares regression were then applied on preprocessed data using the PLS Toolbox (EigenVector Research, Wenatchee, WA, USA).

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3. Results and discussion

The aim of this study was to compare the analytical performances of two Raman spectroscopic methods determining the percentage of crystalline API in amorphous solid dispersions. Tablets were produced with different percentages of crystalline/amorphous Itraconazole ratio and analyzed using a backscattering confocal Raman microspectrophotometer and a transmission Raman spectrophotometer. The analytical performances of the developed methods were compared using a Principal Component Analysis and a Partial Least Squares regression analysis.

The challenge of this study was to prepare validation samples, mimicking the future real ones, with known crystalline API percentages. Moreover these samples must possess the intermolecular interactions between the API and polymer to obtain spectra in adequacy with real samples. Indeed, one can not work on a mixture of powders containing crystalline and amorphous ITZ since there will be no interaction between the ITZ and the matrix powders, leading to erroneous spectra and a method that could not be used for the analysis of real samples (extrudates). The issue was thus to develop standard samples where the crystalline or amorphous ITZ has molecularly interacted with the matrix. To solve this issue, the manufacturing of 12 independent extrudates batches, 6 with ITZ and 6 without ITZ, were produced by HME according to a previously optimized formulation containing 25% ITZ, 72.5% Soluplus® and 2.5% AcDiSol®. The six batches with ITZ represented the sample at 100% amorphous ITZ and consequently the optimized formulation. The six batches produced without ITZ were used to mimic the molecular interactions inside the matrix.

3.1. IDENTIFICATION OF THE CRYSTALLINE – AMORPHOUS SPECTRAL DIFFERENCES

Before applying PCA and PLS regression on preprocessed data, tablets containing 0% and 100% crystalline API were compared to underscore the spectral differences. The major spectral differences were highlighted between tablets produced at 0% and 100% crystalline ITZ, as presented in Fig. 2, underscored using grey areas.

Several peaks were reduced, removed or broadened when the amorphous API of a tablet was compared to a crystalline one. According to these differences, it was possible to perform PCA and PLS regression analyses regarding these regions. Moreover, it was possible to note that spectral differences appeared on the entire spectrum, so, the whole spectrum was used for following treatments.

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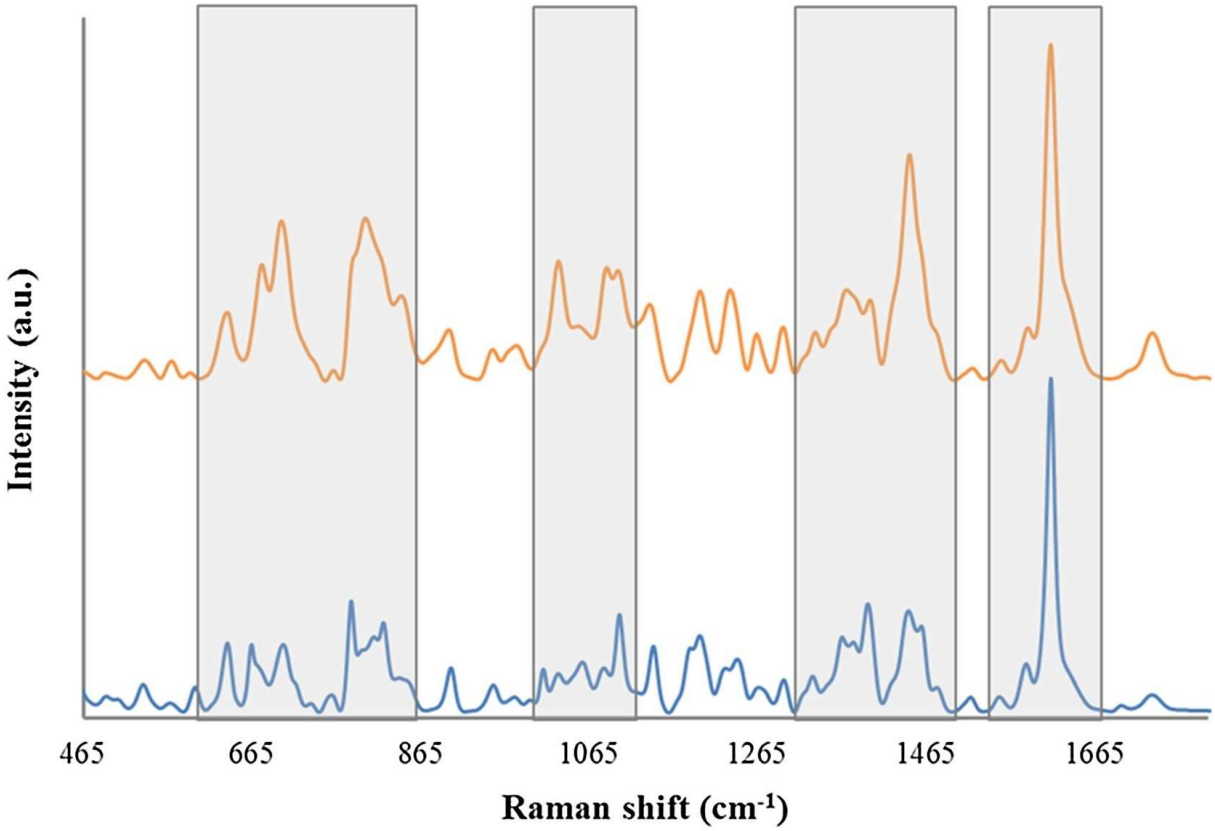

Fig. 2. Major spectral differences highlighted using grey areas for a tablet at 100% crystalline Itraconazole (blue spectrum, below spectrum) and one at 0% crystalline Itraconazole (orange spectrum, above spectrum). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. PRINCIPAL COMPONENT ANALYSIS

An exploratory study was first performed using Principal Component Analysis (PCA) on preprocessed data coming from a backscattering Raman microspectrophotometer not using and using the DuoScan™ mode and from a transmission Raman spectrophotometer. PCA is very useful for a better understanding of a system by performing linear combinations of the original variables maximizing the variance of the data. The newly obtained latent variables are called Principal Components (PCs).

For the mappings obtained with the backscattering Raman microspectrophotometer without the use of the DuoScan™ mode, each percentage of crystalline ITZ in tablets was approximately separated with some overlapping areas as shown in Fig. 3a representing the distribution of the first two PCA scores. In this figure, it was not possible to distinguish the tablets containing 0–5–10% of crystalline ITZ but they were approximately separated from the ones at 25–50%. Regarding the results acquired using the DuoScan™ mode on the same apparatus, represented in Fig. 3b, it was observed that a better clustering between the crystalline percentages was obtained. Indeed, a clear separation was highlighted between tablets at 0–5–10% of crystalline ITZ and the ones at 25–50% analyzing the first PC in function of the second one. The clustering enhancement was thus obtained using the backscattering Raman microspectrophotometer using the DuoScan™ mode, which

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analyzed larger sample volumes in contrast with the same apparatus without the use of this mode. The importance of the analyzed sampling volume was consequently highlighted.

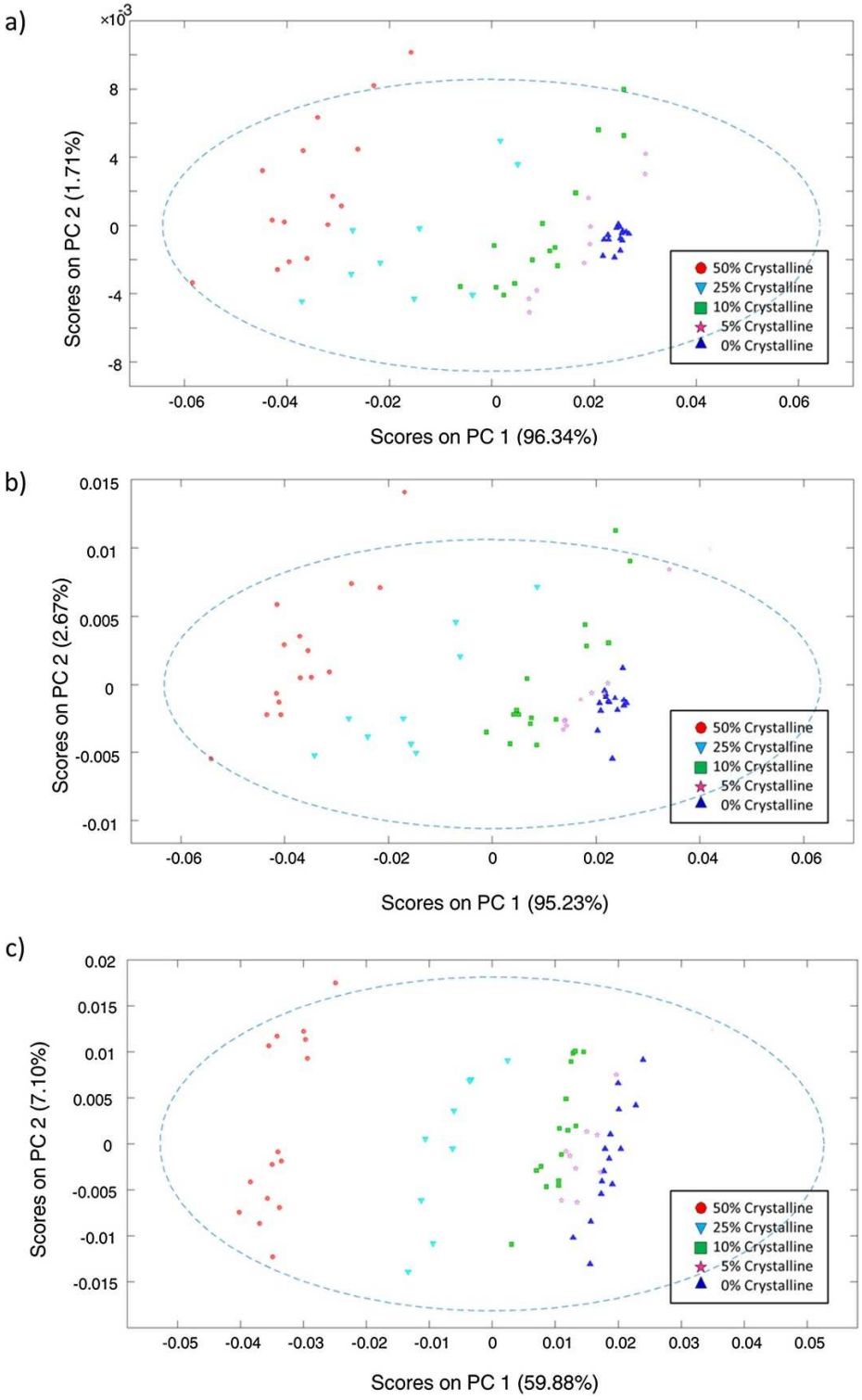

Fig. 3. Score plots of the Principal Component Analysis of tablets with different crystalline ITZ percentages analyzed by a) a confocal Raman microspectrophotometer without the use of the DuoScan™ mode, b) a confocal Raman microspectrophotometer using the DuoScan™ mode and c) a transmission Raman spectrophotometer.

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Finally, as shown in Fig. 3c, by plotting the PCA scores of the tablets analyzed by the transmission Raman spectrophotometer, a noticeable separation between the 50%, the 25% and the low concentrations of crystalline ITZ percentages was observed. Moreover, the clustering of the low ITZ crystalline percentages was distinguishable.

The PCA analyses clearly brought the analytical performances of the three techniques out for the clustering of crystalline content in amorphous solid dispersions. In third analyses the first PC may be explained by the degrees of crystallinity. The link with the second PC could not be explained. As presented in the previous paragraphs, the use of the DuoScan™ mode was of great interest in this study, when using a backscattering Raman microspectrophotometer. The class separation enhancement, for the analyses using this mode in comparison with the one without it, was due to the fact that a larger volume of sample was analyzed. Indeed, surface heterogeneities were observed using the backscattering mode due to small sampling volume. So, the use of the DuoScan™ mode, analyzing a larger sampling volume, enhanced the crystalline API percentages differentiation by reducing surface heterogeneities.

Moreover, the use of a transmission Raman spectrophotometer improved the separation of the percentages of crystalline ITZ due to the analyzed sampling volume, reducing the issues linked to the heterogeneity of the tablets. Indeed, the transmission Raman spectrophotometer advantages were clearly highlighted in this study: firstly, it acquires information on the whole volume of the sample by using the transmission mode, in contrast with surface analyses when using a backscattering mode. Secondly, if one considers the same analyzed surface, the acquisition time is reduced because it acquires a mean spectrum taking the time of one spectrum acquisition, in contrast with the time to perform a map when a backscattering spectrometer is used.

3.3. PARTIAL LEAST SQUARES REGRESSION

After the exploratory study, a Partial Least Squares (PLS) regression has been built. It constructed a quantitative predictive model by performing simultaneous modelization of the variability of the predictive matrix, X, which were the Raman spectra, and the dependent one, y, which was a vector of reference measurements representing in this study the theoretical crystalline percentages. The objective was thus to extract the link between X and y by calculating latent variables that maximized the covariance between X and y. The aim of the PLS regression was consequently to construct a model able to predict the quantitative value of a sample using its acquired spectrum.

The measured crystalline percentages were plotted against the predicted ones. The analytical performances of the three models were evaluated and compared using the analysis of the root mean squared error (RMSE) and the coefficient of determination (R^2). Indeed, the RMSE gave information on the error rate present in the model while the R^2 reported how the model fitted the data.

As presented in Fig. 4a–c, the RMSE of the model decreased from the data acquired by the backscattering Raman spectrophotometer without the use of the DuoScan™ mode to the ones using the DuoScan™ mode. The lowest RMSE were obtained from the model constructed using the

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transmission Raman data. The analysis of the coefficients of determination tended towards the same observation as illustrated in Fig. 4a–c.

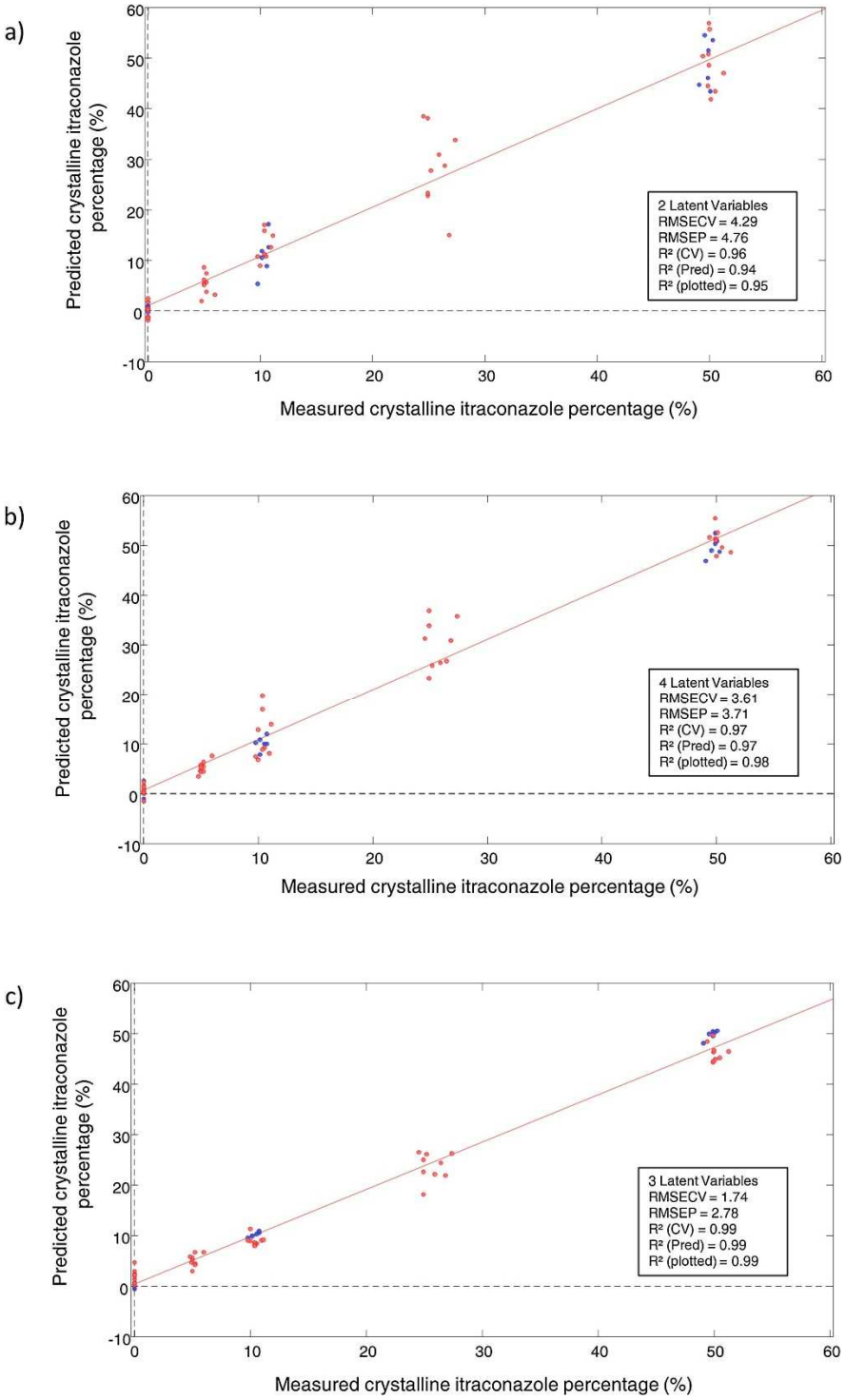

Fig. 4. Partial Least Squares regression of tablets with different crystalline ITZ percentages analyzed by a) a confocal Raman microspectrophotometer without the use of the DuoScan™ mode, b) a confocal Raman microspectrophotometer using the DuoScan™ mode and c) a transmission Raman spectrophotometer. The blue dots represent the training sets and the red ones represent the test sets. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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These findings were in adequacy with the PCA results. Firstly, if one compared results obtained with the backscattering Raman spectrophotometer without the use of the DuoScan™ mode with the ones using this mode, the results were enhanced, leading to a better predictive model for the data acquired using this mode due to a larger analyzed volume of sample. Consequently, the use of the DuoScan™ mode, enlarging the spot size, was able to enhance the performances of the model. Secondly, the predictive model was further improved when using a transmission Raman spectrophotometer. Indeed, once again the analyzed volume of sample was increased in comparison with the Raman microspectrophotometer using the DuoScan™ mode. As the spot size for the latter was a few micrometers, it was of a few millimeters for the transmission Raman spectrophotometer, enlarging consequently the analyzed sampling volume. In addition, transmission Raman spectrophotometers acquire a mean spectrum of the whole sample in one analysis. For equivalent analyzed surface areas, the time of acquisition is drastically reduced in comparison with maps performed using backscattering Raman spectrophotometers.

4. Conclusion

The Hot-Melt Extrusion process is more and more developed in the pharmaceutical field since it manufactures amorphous solid dispersions able to enhance the solubility and bioavailability of Biopharmaceutical Classification System class II drugs. The qualitative and quantitative characterizations of solid dispersions are consequently of great interest.

The development of Raman spectroscopic methods able to determine the crystalline percentage in amorphous solid dispersions produced by Hot-Melt Extrusion was performed on two Raman spectrophotometers, a backscattering and a transmission one, using Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression analyses. The issue of this work was the manufacturing of validation samples being amorphous solid dispersions including intermolecular interactions between the Active Pharmaceutical Ingredient (API) and the polymeric matrix. Tablets containing different percentages of amorphous/crystalline API ratio were produced and analyzed using a backscattering Raman microspectrophotometer, with and without a DuoScan™ mode, and a transmission Raman spectrophotometer.

The PCA and PLS analyses led to comparable conclusions. Firstly the comparison of the results obtained using a backscattering Raman microspectrophotometer without the use of the DuoScan™ mode and using this mode was performed. Indeed, the use of this mode demonstrated a better clustering, obtained by PCA, of the different crystalline percentages and an enhancement of the PLS predictive model. These results highlighted the importance of the analyzed volume of sample. Moreover, the PCA showed the best clustering between the different crystalline percentages tablets using the data acquired from the transmission Raman spectrophotometer. The lowest RMSE and the R^2 the closest to 1, carried out by PLS regression, were obtained with the same data, proving that this technique was more accurate for the determination of crystalline percentages in such tablets. The usefulness of the transmission mode was, in this case, demonstrated. Indeed, the latter

analyzed the whole sample volume, in contrast with surface analyses using backscattering spectrophotometers.

This study highlighted the importance of the analyzed sampling volume on the development of predictive models and proved the ability to determine the crystalline content in an amorphous solid dispersion using a transmission Raman spectrophotometer.

The following step of this study will be the validation of this technique to quantify the crystalline percentages in hot-melt extrudates. The optimization of the production of tablets with a better homogeneity is first necessary to reduce this variability.

In conclusion, the use of a transmission Raman spectrophotometer for the determination of the crystalline API percentage in an amorphous solid dispersion is consequently very promising.

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