Comparison of in-line active content determination of polymeric implant by near infrared spectroscopy and Raman spectroscopy

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INTRODUCTION

In recent years, various approaches have been implemented in an attempt to develop devices to effectively control the release of drugs. These controlled delivery systems can be localized in specific regions of the body, such as vaginal, intrauterine, subcutaneous, or corneal sites. Although some degree of systemic absorption is inevitable, with its associated side effects, local delivery appears to be a more efficient alternative, with limited adverse effects and increased patient compliance, particularly during long-term treatment. The quantification of the Active Pharmaceutical Ingredient (API) content in such device is very time-consuming. According to the Process Analytical Technology (PAT) concept, the aim of this study is to compare a near infrared (NIR) and a Raman methods able to quantify the API of implant during the manufacturing process.

MATERIALS AND METHODS

Polymeric Implant Preparation

The model formulation consists in pharmaceutical implants manufactured by co-extrusion technique with an equipment from Scamex (Crosne, France). The co-extruder uses two small single screws. The first (12mm) is responsible for the mixing between the API and Ethyl-Vinyl-Acetate (EVA) from Celanese (Dallas, USA) forming the implant core, while the second (8mm) adds a membrane around the core. The implant diameter is adjusted in real time during the manufacturing process by means of a laser measurement. Figure 1 shows the extruder during these experiments.

Near Infrared and Raman Spectrometer settings

The extruder die was non invasively interfaced with a multipurpose analyzer Fourier transform near infrared spectrometer (MPA, Bruker Optics, Ettlingen, Germany) equipped with a semiconductor room temperature sulfide lead (RT-PbS) detector and with a dispersive spectrometer RamanStation 400F (Perkin Elmer, MA, USA) equipped with a two-dimensional CCD detector (1024 × 256 pixel sensor) (Fig.2). The NIR spectra were collected with a NIR reflectance probe for solids. The spectra were collected with the Opus Software 6.5 (Bruker Optics). Each spectrum was the average of 10 scans and the resolution was 8 cm^{-1} over the range from 12500 to 3600 cm^{-1}. The Raman spectra were collected with a Raman reflectance probe for solids and liquids. The spectra were collected with the Spectrum Software 6.3.2.0151 (Perkin Elmer). The laser excitation wavelength used was 785 nm. The spectral coverage was 250–3400 cm^{-1} and the spectral resolution was equal to 4cm^{-1}. A cosmic ray filter was applied. The time necessary for a NIR or a Raman measurement was 5 seconds.

Calibration Samples

5 implants production batches were included in the calibration of the NIR and Raman methods with respectively 35, 40, 50, 60, 65 % (w/w) of API. 6 implants for each concentration were used for calibration.

External Validation Samples

3 implants production batches were included in the calibration of the NIR and Raman methods with 50 % (w/w) of API. 6 implants per production were used for external validation.

Figure 1: Co-extruder equipment.

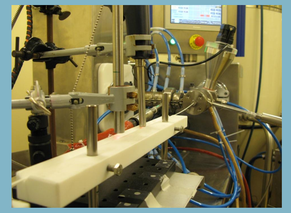

Figure 2: Interfacing of the extruder by NIR and Raman fiber optic probe.

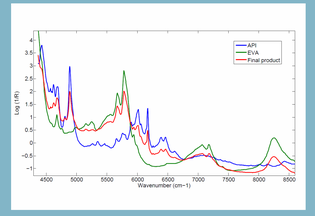

Figure 3: NIR spectra of API, EVA and Final Product.

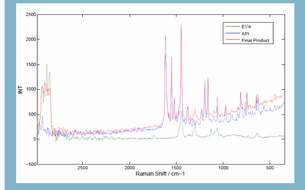

Figure 4: Raman spectra of API, EVA and Final Product.

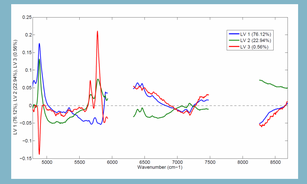

Figure 5: Loading factors of the NIR PLS model.

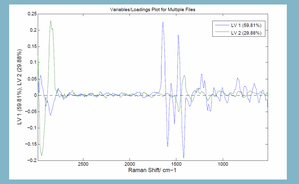

Figure 6: Loading factors of the NIR PLS model.

Reference Method

Each implant was cut in 20 pieces and was put into a flask with 100 mL of methanol. The flask was heat to reflux during 2 hours. Then, 1mL of the methanol solution was withdraw and put into a volumetric flask of 250 mL of phosphate buffer. The solution was analyzed with HPLC method which was validated using the accuracy profile approach (β-expectation tolerance limits: 95% and α risk: 5%).

Multivariate Data Analysis

Standard Normal Variate (SNV) and mean center using cross-validation random subsets was performed on the calibration set to build the prediction NIR model with PLS Toolbox 5.0 for Matlab version 7.6 (Eigenvector Research Inc, Wenatchee, USA). First derivative and mean center using cross-validation random subsets was performed on the calibration set to build the prediction Raman model. The random subsets cross-validation was performed with 5 data splits, on 30 samples and with 11 iterations. The model ability to predict the API content was further tested with the external validation set.

RESULTS

Raw Materials Spectra and Loading Factor

As can be seen on Figures 3 and 4, a spectral range linked to the API and EVA was manually selected for the calibration of the NIR model and all spectral range were selected for the Raman model calibration. To check its adequacy, the loading factors (Figures 5 and 6) were compared with the raw materials spectra displayed in Figures 3 and 4. It was found that the loading factors highlighted spectral bands belonging to the API and the EVA. Indeed, it is the ratio between both ingredients that mainly defines the 5 different API content formulations. Consequently, the selected spectral range was found to be adequate regarding the purpose of the NIR and Raman models: to quantify accurately the API content of the implant.

Cross-validation based on random subsets was carried out to select the optimal number of PLS factors. For the random subsets cross-validation, 3 PLS factors were selected for the NIR model and 2 PLS factors were selected for the Raman model as the Root Mean Squared Error of Calibration (RMSEC) was the lowest from this number of factors.

NIR and Raman Models

Considering the Root Mean Squared Error of Calibration (RMSEC) and the Root Mean Squared Error of Prediction (RMSEP) of the NIR model, their values are 1.92 and 1.66 respectively, indicating the robustness and the global accuracy of the NIR model. For the Raman model, the RMSEC and the RMSEP are 1.96 and 2.64 respectively.

NIR and Raman Predictions

Figures 7 and 8 show the agreement observed between the NIR and the Raman predictions and the reference method results for both calibration and validation sets (in green).

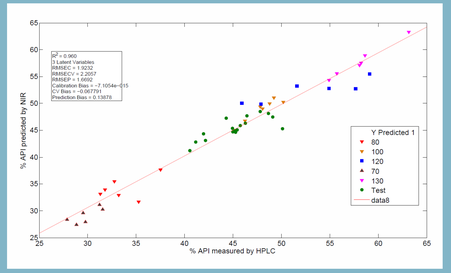

Figure 7: NIR predictions versus reference method results for calibration and validation sets.

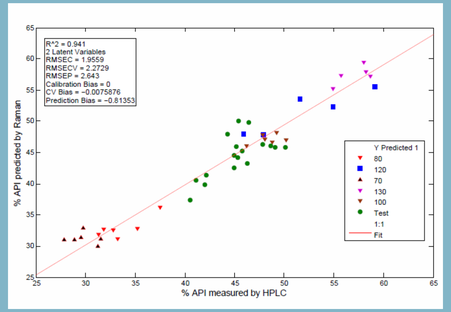

Figure 8: Raman predictions versus reference method results for calibration and validation sets.

CONCLUSIONS

NIR and Raman spectroscopy were found to be suitable techniques to determine the API content within implants during the process. Theses techniques are very fast (only 5 seconds) compared with the reference method (min. 4 hours). In-line process measurement allows to adapt some critical parameters during the process in order to ensure the right amount of API in this specific pharmaceutical formulation. Theses two different techniques provide comparable results. In fact, the RMSEC and RMSECV are very close in each PAT techniques. Predictions seem to be better for the NIR that for the Raman but the validation set is only composed with 50% (w/w) of API samples.

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