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Validation of an in-line Raman spectroscopic method for continuous active pharmaceutical ingredient quantification during pharmaceutical hot-melt extrusion

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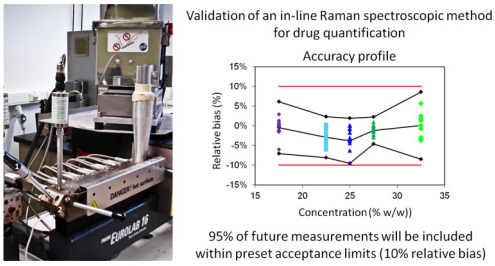
HIGHLIGHTS

- Creation of an API calibration model with Raman spectra gathered during extrusion.
- 95% of future measurements will be included within 10% relative bias limits.
- The unknown true value is found at a maximum of ±7.00% around the measured result.
- Small fluctuations in process settings do not affect API concentration predictions.

GRAPHICAL ABSTRACT



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ABSTRACT

A calibration model for in-line API determination was developed based on Raman spectra collected during hot-melt extrusion. This predictive model was validated by calculating the accuracy profile based on the analysis results of validation experiments. Furthermore, based on the data of the accuracy profile, the measurement uncertainty was determined. Finally, the robustness of the model was evaluated.

A Raman probe was implemented in the die of a twin-screw extruder, to monitor the drug concentration during extrusion of physical mixtures containing 15, 20, 25, 30 and 35% (w/w) metoprolol tartrate (MPT) in Eudragit® RS PO, an amorphous copolymer of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts. Several different calibration models for the prediction of the MPT content were developed, based on the use of single spectra or averaged spectra, and using partial least squares (PLS) regression or multivariate curve resolution (MCR). These predictive models were validated by extruding and monitoring mixtures containing 17.5, 22.5, 25.0, 27.5 and 32.5% (w/w) MPT. Each validated concentration was monitored on three different days, by two different operators. The β-expectation tolerance intervals were calculated for each model and for each of the validated MPT concentration levels (β was set at 95%), and acceptance limits were set at 10% (relative bias), indicating that at least 95% of future measurements should not deviate more than 10% from the true value. The only model where these acceptance limits were not exceeded was the MCR model based on averaged Raman spectra. The uncertainty measurements for this model showed that the unknown true value can be found at a maximum of ±7.00% around the measured result, with a confidence level of 95%. The robustness of this model was evaluated via an experimental design varying throughput, screw speed and barrel temperature. The robustness designs showed no significant influence of any of the process settings on the predicted concentration values.

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Raman spectroscopy proved to be a fast, non-destructive and reliable method for the quantification of MPT during hot-melt extrusion. From the accuracy profile of the MCR model based on averaged spectra, it was concluded that for each MPT concentration in the validated concentration range, 95 out 100 future routine measurements will be included within the acceptance limits (10%).

1. Introduction

Raman spectroscopy is a molecular vibrational spectroscopic technique, allowing fast and non-destructive measurements which do not require any sample pretreatment. The use of custom made fibre optic probes connected to the spectrometers allows the implementation into the process stream [1–5]. A Raman spectrum is an overlay of the fingerprints (i.e., a combination of spectral bands) of the individual components in a mixture, making Raman spectroscopy a suitable tool for quantification purposes. Hence, Raman spectroscopy can be applied as a process analytical tool to monitor and predict the concentration of an active pharmaceutical ingredient (API) during hot-melt extrusion.

So far, only two quantitative applications of Raman spectroscopy during hot-melt extrusion have been reported. In a first application [6] the API concentration was monitored behind the extrusion die, where a Raman probe was clamped above an extruded film. In the second application [7], the Raman probe was implemented in the extrusion die to monitor the API content of the extrudates. In both applications, a partial least squares (PLS) regression model was developed for the prediction of the API concentration, and a traditional chemometric validation approach [8] was used to validate the predictive models. First, the root mean square error of calibration (RMSEC) and the root mean square error of the cross validation (RMSECV) are calculated, and then an external validation dataset is used to validate the predictive model. The quantitative performance of the Raman spectroscopic models is evaluated by calculating the root mean square error of prediction (RMSEP) based on the prediction results of the validation experiments. Small values of RMSEC, RMSECV and RMSEP indicate a good quantitative performance of the models. However, this validation approach does not fulfil the regulatory requirements in the ICH Q2 [9] and FDA [10] guidelines for validation of analytical procedures.

Official documents such as the ICH Q2 and FDA guidelines [9,10] describe the validation criteria which should be assessed, but no experimental protocols are provided. The ICH Q2 guideline [9] requires the assessment of accuracy, precision (repeatability and intermediate precision), specificity, linearity and range to validate an analytical quantification method for the active pharmaceutical ingredient in a drug product. The same validation characteristics are entailed by the FDA guidelines for validation [10], with addition of the robustness of the method. However, the validation guidelines are most often limited to these general concepts [11]. The determination of the validation parameters and the chemometric values (RMSEC, RMSECV, RMSEP) does not suffice to evaluate the risk that every future measurement will be close enough to the unknown true value of the sample. These statistics only provide information concerning previously performed experiments. Statistics allowing to make a decision concerning the validity of a method for future analyses are necessary.

The Société Française des Sciences et Techniques Pharmaceutiques (SFSTP) has developed a validation strategy based on the total error of the procedure (bias + standard deviation). Each analytical measurement reflects its true value, the bias of the method and its precision [12]. This approach minimizes the risk to accept an inaccurate calibration method or to reject a capable method. The objective of validation is to guarantee that every measurement performed in future analysis is close enough to the unknown true value [11], and that the difference will be lower than an preset acceptance limit. In this paper, a Raman spectroscopic method for the quantification of metoprolol tartrate (MPT) in a polymer matrix during a hot-melt extrusion process was developed and validated by calculating the accuracy profile based on the analysis results of validation experiments.

2. Materials and methods

2.1. Materials

Physical mixtures containing MPT (Esteve Quimica, Spain), Eudragit® RS PO (Evonik, Germany) and magnesium stearate (Mg St) (Fagron, Belgium) were blended for 20 min in subbatches of 300 g in a Turbula mixer before extrusion. The Mg St was added to the formulation to improve feeding behaviour of the mixtures in the extruder. Preparation of the validation mixtures was performed in triplicate, to allow extrusion on three different days, by two different operators.

2.2. Hot-melt extrusion

All physical mixtures were extruded on a 16 mm twin-screw extruder (Prism Eurolab 16, Thermo Fisher Scientific, Germany). The hot-melt extruder was equipped with a DD Flexwall® 18 gravimetric feeder (Brabender Technologie, Germany), which was set in its gravimetric feeding mode and supplied the physical mixtures with a throughput of 0.3 kg h^{-1}. The applied screw speed was 80 rpm for all experiments, and the barrel temperature from feeding area to die was set at 70–142–142–142–142–120 °C.

2.3. Raman spectroscopy

In-line Raman spectra were collected with a Raman Rxn1 spectrometer (Kaiser Optical Systems, Ann Arbor, MI, USA). For in-line measurements, a fibre-optic Raman Dynisco probe was implemented into the die head (Fig. 1) [7], to monitor the MPT concentration of the melt before it is forced through the die. The laser wavelength employed was 785 nm from a Invictus NIR diode laser (Kaiser Optical Systems). All in-line collected spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of three seconds, using a laser power of 400 mW. Spectra were collected every 15 s. Data collection and data transfer were automated using the HoloGRAMS™ data collection software, and the Matlab software (version 7.1, The MathWorks Inc., Natick, MA). Once an experiment was started, 15 min process stabilization time was applied before starting the collection of the spectra. After this, the experiments were continued for another 15 min, during which 60 in-line spectra were collected.

2.4. Development of the Raman calibration models

Four different calibration models based on the Raman spectra collected during extrusion of the calibration mixtures (Table 1) were developed and evaluated. First, a PLS model was developed using the SIMCA P+ software (Version 12.0.1.0, Umetrics, Umeå, Sweden) (Model 1). Prior to modelling, SNV pre-processing and Savitzky-Golay smoothing were applied on the spectral range of 0–1800 cm^{-1} to eliminate differences in the slope of the baseline