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Determining particle size and water content by near-infrared spectroscopy in the granulation of naproxen sodium

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ABSTRACT

Near-infrared spectroscopy is frequently used by the pharmaceutical industry to monitor and optimize several production processes. In combination with chemometrics, a mathematical-statistical technique, the following advantages of near-infrared spectroscopy can be applied: It is a fast, non-destructive, non-invasive, and economical analytical method. One of the most advanced and popular chemometric technique is the partial least square algorithm with its best applicability in routine and its results.

The required reference analytic enables the analysis of various parameters of interest, for example, moisture content, particle size, and many others. Parameters like the correlation coefficient, root mean square error of prediction, root mean square error of calibration, and root mean square error of validation have been used for evaluating the applicability and robustness of these analytical methods developed. This study deals with investigating a Naproxen Sodium granulation process using near-infrared spectroscopy and the development of water content and particle-size methods.

For the water content method, one should consider a maximum water content of about 21% in the granulation process, which must be confirmed by the loss on drying. Further influences to be considered are the constantly changing product temperature, rising to about 54 °C, the creation of hydrated states of Naproxen Sodium when using a maximum of about 21% water content, and the large quantity of about 87% Naproxen Sodium in the formulation. It was considered to use a combination of these influences in developing the near-infrared spectroscopy method for the water content of Naproxen Sodium granules. The "Root Mean Square Error" was 0.25% for calibration dataset and 0.30% for the validation dataset, which was obtained after different stages of optimization by multiplicative scatter correction and the first derivative.

Using laser diffraction, the granules have been analyzed for particle sizes and obtaining the summary sieve sizes of >63 μm and >100 μm. The following influences should be considered for application in routine production: constant changes in water content up to 21% and a product temperature up to 54 °C. The different stages of optimization result in a "Root Mean Square Error" of 2.54% for the calibration data set and 3.53% for the validation set by using the Kubelka-Munk conversion and first derivative for the near-infrared spectroscopy method for a particle size >63 μm. For the near-infrared spectroscopy method using a particle size >100 μm, the "Root Mean Square Error" was 3.47% for the calibration data set and 4.51% for the validation set, while using the same pre-treatments. – The robustness and suitability of this methodology has already been demonstrated by its recent successful implementation in a routine granulate production process.

Abbreviations: NIR, Near-infrared; EMA, European Medicines Agency; GMP, Good Manufacturing Practice; ICH, International Council for Harmonization; API, Active Pharmaceutical Ingredients; NapSo, Naproxen Sodium; PLS, Partial Least Square; Cellulose, Microcrystalline Cellulose 102; PVP, Polyvinylpyrrolidone K30; XRD, X-ray diffraction; NapSo*0*H_2O, Naproxen Sodium Anhydrate; NapSo*1*H_2O, Naproxen Sodium Monohydrate; Amorphous NapSo*2*H_2O, Amorphous Naproxen Sodium Dihydrate; Chrystalline NapSo*2*H_2O, Crystalline Naproxen Sodium Dihydrate; NapSo*4*H_2O, Naproxen Sodium Tetrahydrat; LOD, Loss on drying; FT, Fourier-Transformation; MPA, Multi-Purpose-Analyzer; PbS, Lead sulfide; HeNe, Helium Neon; LES, Light-emitting Diode; R^2, Correlation Coefficient; RMSE, Root Mean Square Error; RMSEC, Root Mean Square Error of Calibration; RMSEV, Root Mean Square Error of Validation; MSC, Multiplicative scatter correction; 1st derivative, First derivative; KM, Kubelka-Munk.

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1. Introduction

Near-infrared (NIR) spectroscopy is a fast spectroscopic method for analyzing various aggregation states. Macroscopic parameters can be measured and determined within a few seconds only. It is non-destructive and non-invasive [1,2].

At-line, on-line or in-line methods improve process efficiency and provide consistent product quality [3–5]. This facilitates the immediate release of intermediates as well as finished goods [6,7] with better supply to market and reduced analysis and storage costs. The pharmaceutical industry often uses NIR technology to control various production processes due to the impact of the "Note for Guidance on the Use of Near Infrared Spectroscopy by the pharmaceutical Industry and the Data Requirements for new Submissions and Variations" by the European Medicines Agency (EMA 2003) [8]. With the publication of Annex 15 of the GMP Guide and its coming into effect in 2015, NIR spectroscopy has become still more important in the pharmaceutical industry. Annex 15 expands the ongoing process verification with a new process verification procedure [9]. This future mandatory continuous process verification was described by the "International Council for Harmonization (ICH) in its quality guideline Q8, "Pharmaceutical Development", and allows a combined attempt of standard validation and continuous process verification to replace the hitherto mandatory re-validation [10]. Together with Continued Process Verification it becomes crucial to define critical process parameters and permanently collect data for evaluation of the process [11]. The tracking and review of critical process parameters will tell whether the process is under control or not, so the process can be immediately and constantly adjusted [12].

Processes like mixing, granulation, compression and coating can be controlled by NIR spectroscopy to ensure real-time release of finished goods [13–16]. NIR spectroscopy can also indicate physicochemical attributes of the analyzed goods [13]. To develop a NIR method, specific properties or parameters of a particular process need to be found, including water content, particle size, the quantity of active pharmaceutical ingredients (API), the hardness of tablets [13–18].

Many publications have dealt with the use of NIR spectroscopy in Naproxen Sodium (NapSo) tablet production, typically powder blend uniformity, particle size and content uniformity [20,21]. The water content of a NapSo granulation process has not been examined by NIR spectroscopy yet. Published studies simply focus on particle size determination using dried materials or materials with a constant water content [19,20]; [22,23]. When variable water content during the process is considered, the analysis becomes more challenging [1,15,19]. The spectral information for particle size is actually hidden beneath that of different water contents and is therefore not directly accessible [24]. NIR spectroscopy determination of particle size therefore needs standardized sample pretreatment, but it will be impossible to factor out the influence of moisture completely. Particle size and water content caused by granulation need to be taken into consideration jointly when developing a NIR method [19,25,26].

Apart from the intricacies of water content and particle size, the quantity of NapSo in the granules represents another challenge. This is because NapSo forms several hydrates which influence the shape of the spectra and complicate the creation and interpretation creation of a water content method [20,27–30]. These NapSo hydrates can be obtained at different water contents during granulation and show polymorphic and pseudopolymorphic properties [28,29]. The spectral information of each hydrate changes with different product temperatures caused by granulation [28,31].

The scope of the study was the development of two at-line NIR methods to determine the water content and the particle size during the whole granulation process of NapSo at different product temperatures up to 54 °C, with different water contents up to 20%, different particle sizes and an amount of NapSo of about 87%. Attempts were made at developing methods using partial least square (PLS) algorithms and internal test set validation, which should make these methods more robust and suitable for routine. Even more importantly, NIR spectroscopy validation parameters were optimized by a test set validation.

2. Materials & methods

2.1. Materials

NapSo, microcrystalline cellulose 102 (cellulose), and polyvinylpyrrolidone K30 (PVP) were provided by Bayer Bitterfeld GmbH (Greppin, Germany). They were mixed in a ratio of 87.3% NapSo, 8.7% cellulose, and 4.0% PVP to produce the PREMIX. The PREMIX was granulated with purified water in a top-spray fluid bed granulator GPCG 15/30 by Glatt GmbH (Binzen, Germany).

The NapSo used for granulation was anhydrous (NapSo*0*H_2O), evidenced by the identity of NapSo*0*H_2O and NapSo*0*H_2O dried over phosphorous pentoxide (Merck Chemicals GmbH, Darmstadt, Germany). Identity was proven by the NIR spectra and x-ray diffraction (XRD) pattern (Data not shown). NapSo forms four different hydrated forms which were compared by NIR spectroscopy and XRD: NapSo monohydrate (NapSo*1*H_2O), crystalline NapSo dihydrate (NapSo*2*H_2O), amorphous NapSo dihydrate (NapSo*2*H_2O), and NapSo tetrahydrate (NapSo*4*H_2O) with different polymorphic and pseudopolymorphic properties.

According to a procedure in the literature [28], the hydrates were prepared in laboratory scale. However, some minor adjustments were necessary to actually get the hydrates [33]

2.2. Methods

2.2.1. Blending process

The PREMIX of NapSo*0*H_2O, cellulose and PVP was blended in a drum by Müller GmbH (Rheinfelden, Germany) with a volume of 100 L and the dimensions of 56.0 cm diameter and 44.9 cm height. It was closed with a lid and rubber seal. The PREMIX was mixed with at a mixing speed of 20 rpm for 8 min.

2.2.2. Granulation

Granulation was performed in the GPCG 15/30 by Glatt GmbH (Binzen, Germany), a pilot scale top spray fluid bed granulator with one spray nozzle and partially conditioned air processing. The settings of the spray nozzle were: diameter 1.5 mm, 4.7 mm distance from the nozzle to the air cap, spray lance in slot 2. The product container included a sieve bottom of 100 μm mesh size. The filter stockings automatically vibrate every 30 s for 10 s. An electric peristaltic pump 504 U IP55 with a pump head 505 L (both Watson-Marlow GmbH, Rommerskirchen, Germany) was put next to the granulator and used a tube system of two Marpene pieces, each with a diameter of 4.8 mm. The spraying rate and direction of the spraying liquid were separately adjusted.

Granulation recipe:

The batch size was 17 kg and needed approximately 7.5 kg of purified water and an air temperature of 70 °C to achieve a maximum water content of about 20% after the third spraying phase. A loss on drying (LOD) of approx. 20–22% was required to obtain NapSo*4*H_2O in the granulation process [28]. During drying, the moisture of the granules was decreased to 4–6%, achieving a product temperature of about 57 °C at the end of the drying process.

2.2.3. Sample preparation for NIR spectroscopy

The granules (5 g) were filled into each sample vessel, an injection bottle with mirrored bottom (20 mm neck, Fiolax, clear