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NIR based approach to evaluate anhydrate-hydrate transformations

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Abstract: The spectroscopic techniques are widely used as Process Analytical Technology (PAT) tools supporting the Quality by Design (QbD) concept. The present study focuses on evaluating the feasibility of NIR spectroscopy as a PAT tool to understand phase transformations of anhydrate and hydrate forms of naproxen sodium (NS) during pharmaceutical development. Four solid forms of NS *i.e.* anhydrate (AH), monohydrate (MH), dihydrate (DH) and tetrahydrate (TH) forms were used in the study. The identity and phase purity of the solid forms were confirmed by TGA and PXRD measurements. The NIR and FTIR spectra were also distinct among the four solid forms. Moreover, the chemical information offered by NIR spectroscopy was better understood by comparison with corresponding fundamental bands in FTIR spectroscopy. The NIR spectra were analysed using Principal Component Analysis (PCA). Scores plot of PCA from NIR spectral data depicted good separation among the four solid forms. The loadings plots indicated that the C-H and O-H spectral regions were mainly contributing to the separation observed in the scores plot. Thus, the present study indicates the feasibility of NIR spectroscopy to efficiently monitor phase transformation of NS. Future studies will focus on development of NIR based quantitative model that can be applied for online monitoring of hydrate formation and dehydration behaviour of the NS solid forms during processing and storage.

Key words: Hydrates, Phase transformation, Principal Component Analysis, NIR spectroscopy, Naproxen Sodium

1. Introduction

Solid dosage form is probably the most attractive for the pharmaceutical product development. Therefore, understanding on the solid forms of an API is one of the key requirements to obtain quality pharmaceutical products. The changes in the solid form, known as phase transformations, can have a great impact on the final product performance[1,2]. The phase transformations can occur during various stages of product development such as wet granulation[3], drying[4] and compression[5] and also during storage[6]. Therefore, it is important to identify suitable technique that can monitor process induced phase transformation during early stages of the drug product life cycle[7]. Moreover, the recent trend is shifting towards use of online monitoring tools with advancements in the Quality by Design (QbD) and Process Analytical Technology concepts[8].

Naproxen sodium (NS, Figure 1) is a widely used non-steroidal anti-inflammatory drug, marketed as

anhydrate form. NS is known to exist as anhydrate, various hydrate and solvate forms [9-11]. Alteration in physicochemical properties of NS, attributed to the anhydrate to hydrate transformation during processing, has been reported [12, 13].

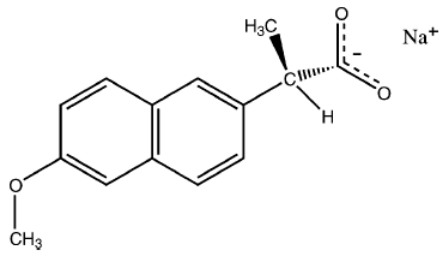

Figure 1: Chemical structure of Naproxen sodium

Real time monitoring of the phase transformations using spectroscopic techniques can provide better process understanding and control[3]. In the present study, feasibility of NIR spectroscopy as an online monitoring tool was evaluated. Due to the fast, noninvasive and real time data acquisition possibilities of NIR makes it an ideal PAT tool. Furthermore, the significance of principal component analysis was also evaluated as a simple and fascinating multivariate data analysis approach to extract information from the NIR data.

2. Experimental Section

2.1. Materials

Naproxen sodium (Batch no. RPSN-0010708, USP grade) was received as gratis sample from Divi's Laboratories Limited, India. It was identified as the anhydrate (AH) form of NS (CSD refcode: ASUBUL) and was used as received for preparation of other solid forms. Methanol (HPLC grade) and Milli-Q water (generated using a Milli-Q plus system, Millipore, Milford, USA) were used for the preparation of monohydrate (MH) form.

2.2. Generation of NS hydrate forms

The MH form was generated by recrystallization from supersaturated solution in methanol-water mixture (64 mol% methanol)[14]. Dihydrate (DH) and tetrahydrate forms (TH) were generated by exposing AH form in desiccators for more than 20 days at 53% and 94% RH, respectively.

2.3. Thermogravimetric Analysis (TGA)

TGA thermograms were recorded using TGA 7 (Perkin Elmer, Norwich, CT, USA). The temperature was calibrated using a ferromagnetic standard, and weight calibration was performed using a 100 mg standard. Samples (5-6 mg) of NS hydrate forms were analyzed in a flame-cleansed platinum pan under open conditions at a heating rate of 10 °C/min from with a dry nitrogen purge of 40 ml/min.

2.4. Powder X-Ray Diffraction (PXRD)

Diffraction patterns were recorded at room temperature using PANalytical X'Pert Pro powder diffractometer (PANalytical B.V., Almelo, The Netherlands), consisting of a θ/θ goniometer and a solid-state PIXcel detector. The radiation was CuK_α (λ = 1.5418 Å), generated at tube voltage and a current of 45 kV and 40 mA, respectively. A continuous 2θ scan was performed in the range of 2º to 40° 2θ with a step size of 0.026° 2θ and at a speed of 96.39 sec/step. Measurements were performed at ambient conditions using zero-background silicon plates. Sample spinning was employed at the speed of 2 sec/revolution during measurements to minimize preferred orientation effects. Data were collected using X'Pert data collector version 2.2 and were analyzed with X'Pert highscore plus version 2.2.4 (both from PANalaytical B.V., Almelo, The Netherlands).

2.5. Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra were recorded between 400 to 4000 cm^{-1} using Nicolet 380 FTIR, SmartiTR (Thermo Fischer Scientific Inc.), fitted with ATR accessory (Thermo Smart Omni-Sampler). Each spectrum was an average of 32 scans with spectral resolution of 2 cm^{-1}. Samples were mounted on

the ATR crystals and compressed. The data were collected and analysed using OMNIC 8.1.11 software (Thermoscientific).

2.6. Near Infrared (NIR) spectroscopy

Spectra were collected using NIR spectrometer (NIR-256L-2.2T2, Control Development Inc., South Bend, IN, USA) having a thermoelectrically cooled 256 element InGaAs array detector, a tungsten light source and a fiber optic probe (six illuminating optical fibers around one signal-collecting fiber). The spectra were recorded in a reflectance mode from 1090 to 2223 nm (equal to 9174 to 4498 cm^{-1}) with 10 milisec integration time, and each spectrum was an average of 32 scans. The resolution of the NIR system was approximately 8 nm. The samples were measured on glass slide. The spectra were collected using CDI Spec32 software (Control Development Inc.).

2.7. Multivariate data analysis

The spectroscopic data were evaluated using Matlab version 7.11.0 (MathWorks Inc., Natick, MA, USA) installed with PLS Toolbox version 6.0.1 (Eigenvector Research Inc., Manson, WA, USA). Principal component analysis (PCA) was used to visualize the clustering of the samples, and to understand the scores and loadings. To overcome the scattering and baseline effects, various spectral pre-processing methods, such as standard normal variate (SNV), multiplicative scatter correction (MSC) and first and second derivatives, were attempted. The data were mean centered before calculating the PCA model.

3. Results and Discussion

3.1. Thermogravimetric analysis (TGA)

TGA thermograms of AH, MH, DH and TH forms are shown in Figure 2. Water loss depicted by TGA was found to be 6.59%, 12.03% and 21.67% for MH, DH and TH forms, respectively. The experimental water content was in well agreement with the theoretical water content of MH (6.66%), DH (12.49%) and TH (22.21%) forms.

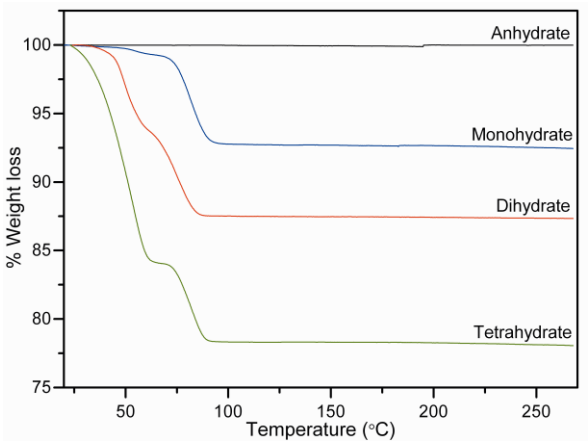

Figure 2: TGA of NS solid forms

3.2. Powder X-ray diffraction (PXRD)

PXRD patterns of AH, MH, DH and TH forms are shown in Figure 3. The experimental patterns of AH and MH forms were super-imposable with the patterns calculated from the respective crystal structures with CSD Refcode of ASUBUL for AH form[15] and IVIDEW for MH form[16]. The characteristic peaks for the NS solid forms were found to be at 2θ values of 8.6° for AH, 4.0° and 7.9° for DH, 4.2° and 8.4° for MH, 13.8° and 14.2° for TH forms. This was found to be matched with the reported PXRD patterns[10, 17].

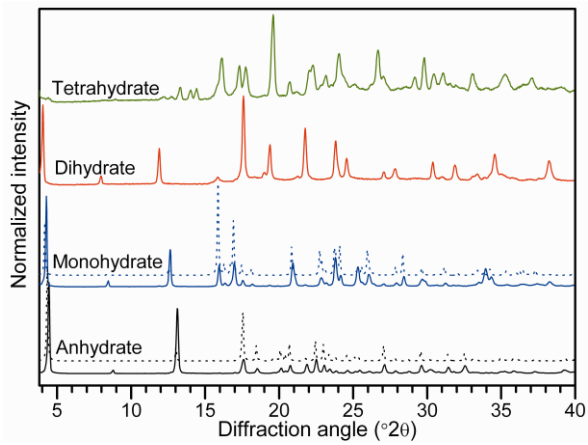

Figure 3: PXRD patterns of NS solid forms
(The dotted diffractograms are the calculated patterns for AH and MH forms from their crystal structures)

3.3. FTIR spectroscopy

As depicted in Figure 4, FTIR spectra of the four solid forms of NS were found to be distinct. The O-H stretching region (3700-3000 cm^{-1}) revealed

characteristic differences among the solid forms. Hydrate forms showed band associated with water of crystallization, while no O-H peak was observed for the AH form. Moreover, the broader O-H peak in case of DH and TH as compared to the sharp peak in MH indicates weaker hydrogen bonding interaction between molecules of water and drug molecule in DH and TH forms as compared to that in the MH form. Moreover, the differences among the four solid forms were also observed in the fingerprint region. Characteristic peaks were found to be at 1585 and 1574 cm^{-1} for the AH form; 1671 cm^{-1} for the MH form, and 1229 cm^{-1} for the DH form.

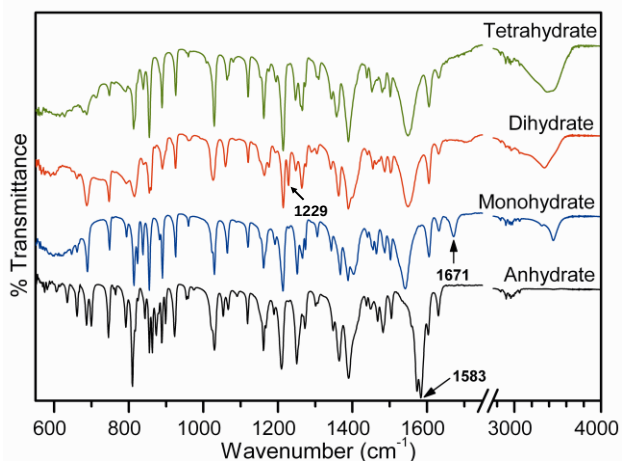

Figure 4: FTIR spectra of NS solid forms

3.4. NIR spectroscopy

NIR spectra are shown in Figure 5. SNV was found to be the most suitable preprocessing method for the current spectral dataset. All the four solid forms exhibit different NIR spectral profile. The major differences between AH and hydrate (MH, DH, TH) forms were found to be the presence of absorbance maxima at ~2000 nm (O-H combination bands) and ~1450 nm (first O-H overtone bands) in the latter, which can be attributed to the water of crystallization in the hydrate forms. All the solid forms were showing distinct features in the regions of C-H overtone bands (~1650 nm). Moreover, the three hydrate forms were also showing distinct features in the regions of O-H combination bands and first O-H overtone bands. The correlation between fundamental O-H stretching bands in IR spectra and corresponding first O-H overtone bands in NIR spectra is depicted in Table 1. It was difficult to assign such correlation for C-H stretching vibrations and O-H bending vibrations due to complex nature of the peaks in these regions in FTIR spectra.

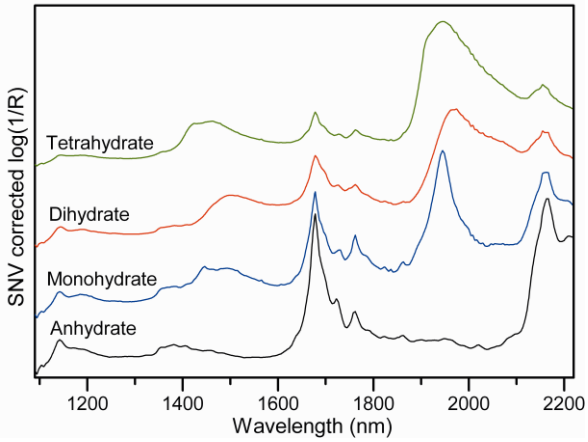

Figure 5: SNV corrected NIR spectra of NS solid forms

Table 1: Correlation of FTIR and NIR vibrations

Solid form	O-H stretching (FTIR)	1st O-H Overtone (theoretical*)	1st O-H Overtone (experimental#)
MH	3450 cm^{-1}	6900 cm^{-1} (1449 nm)	1446 nm
DH	3350 cm^{-1}	6700 cm^{-1} (1492 nm)	1496 nm
TH	3450-3380 cm^{-1}	6900-6760 cm^{-1} (1449-1479 nm)	1447-1465 nm

*calculated by multiplying the wave-number values for fundamental vibrations in FTIR spectra by 2; #observed by NIR spectroscopy

3.5. Multivariate data analysis

Principal component analysis (PCA) is one of the most widely used methods for analysis of spectral data, where large number of variables (*viz.* spectral data points) is correlated[18]. For the current dataset, PCA model with 2 principal components (PC) were able to explain 95.3% variation in the NIR spectra of NS solid forms. Scores plot of PCA model is depicted in Figure 6. PC1 was mainly separating AH form from the hydrate forms as well as MH form from the TH form, while PC2 was separating DH form from the other three solid forms. Thus, PC1 together

with PC2 was adequate for distinguishing the four solid forms of NS.

The differences in the NIR spectra contributing to the separation of the four solid forms can be interpreted by the loadings plot (Figure 7). Loadings in PC1 (Figure 7a) indicates that C-H absorption band at 1650 nm and O-H absorption band at 2000 nm are the most important variation among the spectral data of the NS solid forms; while separation by PC2 was mainly due to O-H overtone (1450 nm) and combination bands (1950 nm) as depicted by loadings in PC2 (Figure 7b).

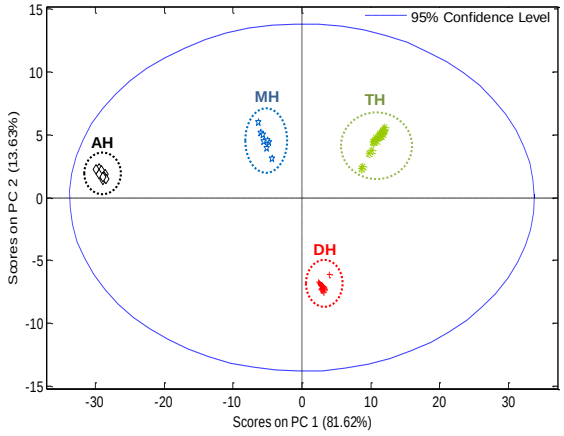

Figure 6: PCA Scores plot (PC1 *vs.* PC2) for the NIR data of NS solid forms

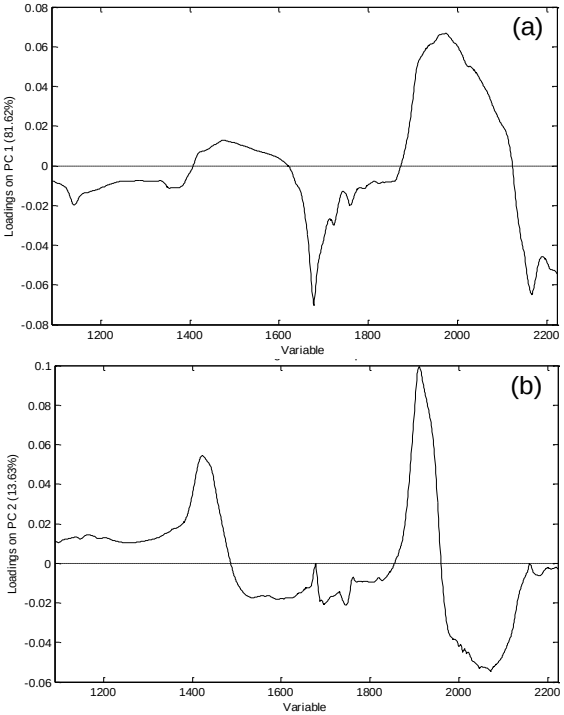

Figure 7: PCA loadings plot (a) loadings on PC1, (b) loadings on PC2 for the NIR data of NS solid forms

4. Conclusions

The present study dictates ability of NIR spectroscopy coupled with multivariate data analysis to distinguish the NS solid forms. Thus, NIR can be considered as a potential technique to monitor phase transformations. Further studies will focus on development of NIR based quantitative model that can be applied for real time monitoring of hydrate formation and dehydration behaviour of the NS solid forms during processing and storage.

5. References

1. Bauer, J.; Spanton, S.; Henry, R.; Quick, J.; Dziki, W.; Porter, W.; Morris, J. Ritonavir: An extraordinary example of conformational polymorphism. *Pharm. Res.* **2001**, 18, 859-867.
2. Zakrzewski, A.; Zakrzewski, M., Solid state chracterization of pharmaceuticals. ASSA International Inc.: Danbury, CT, **2006**; pp. 11.
3. Rasanen, E.; Rantanen, J.; Jérgensen, A.; Karjalainen, M.; Paakkari, T.; Yliruusi, J. Novel identication of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. *J. Pharm. Sci.* **2001**, 90, 389-396.
4. Romer, M.; Heinamaki, J.; Miroshnyk, I.; Kivikero, N.; Sandler, N.; Rantanen, J.; Yliruusi, J. Phase transformation of erythromycin A dihydrate during fluid bed drying. *J. Pharm. Sci.* **2008**, 97, 4020-4029.
5. Chan, H.K.; Doelker, E. Polymorphic transformation of some drugs under compression. *Drug Dev. Ind. Pharm.* **1985**, 11, 315-332.
6. Raijada, D.K.; Singh, S.; Bansal, A.K. Influence of microenvironment pH, humidity, and temperature on the stability of polymorphic and amorphous forms of clopidogrel bisulfate. *AAPS PharmSciTech* **2010**, 11, 197-203.
7. Morris, K.R.; Griesser, U.J.; Eckhardt, C.J.; Stowell, J.G., Theoretical approaches to physical transformations of active

pharmaceutical ingredients during manufacturing processes. *Adv. Drug Deliv. Rev.* **2001**, 41, 91-114.

8. Jørgensen, A.; Rantanen, J.; Karjalainen, M.; Khriachtchev, L.; Räsänen, E.; Yliruusi, J., Hydrate formation during wet granulation studied by spectroscopic methods and multivariate analysis. *Pharm. Res.* **2002**, 19, 1285-1291.
9. Chavez, K.J.; Rousseau, R.W., Solubility and pseudopolymorphic transitions in mixed solvents: Sodium naproxen in methanol-water and ethanol-water solutions. *Cryst. Growth Des.* **2010**, 10, 3802-3807.
10. Kim, Y.; Rousseau, R.W., Characterization and solid-state transformations of the pseudopolymorphic forms of sodium naproxen. *Cryst. Growth Des.* **2004**, 4, 1211-1216.
11. Martino, P.D.; Barthelemy, C.; Joiris, E.; Capsoni, D.; Masic, A.; Massarotti, V.; Gobetto, R.; Bini, M.; Martelli, S., A new tetrahydrated form of sodium naproxen. *J. Pharm. Sci.* **2007**, 96, 156-167.
12. Bansal, P.; Haribhakti, K.; Subramanian, V.; Plakogiannis, F., Effect of formulation and process variables on the dissolution profile of naproxen sodium from tablets. *Drug Dev. Ind. Pharm.* **1994**, 20, 2151-2156.
13. Martino, P.D.; Malaj, L.; Censi, R.; Martelli, S., Physico-chemical and technological properties of sodium naproxen granules prepared in a high-shear mixer-granulator. *J. Pharm. Sci.* **2008**, 97, 5263-5273.
14. Kim, Y.; Paskow, H.C.; Rousseau, R.W., Propagation of solid-state transformations by dehydration and stabilization of pseudopolymorphic crystals of sodium naproxen. *Cryst. Growth Des.* **2005**, 5, 1623-1632.
15. Kim, Y.S.; VanDerveer, D.; Rousseau, R.W.; Wilkinson, A. P., Anhydrous sodium naproxen. *Acta Cryst.* **2004**, E60, m419-m420.
16. Kim, Y.B.; Park, I.Y.; Lah, W.R., The crystal structure of naproxen sodium, (Cl4H1303Na), a non-steroidal antiinflammatory agent. *Arch. Pharm. Res.* **1990**, 13, 166-173.
17. Malaj, L.; Censi, R.; Martino, P.D., Mechanisms for dehydration of three sodium naproxen hydrates. *Cryst. Growth Des.* **2009**, 9, 2128–2136.
18. Jorgensen, A.C.; Miroshnyk, I.; Karjalainen, M.; Jouppila, K.; Siiria, S.; Antikainen, O.; Rantanen, J., Multivariate data analysis as a fast tool in evaluation of solid state phenomena. *J. Pharm. Sci.* **2006**, 95, 906-916.