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## 1 NEAR INFRARED AND RAMAN SPECTROSCOPY FOR THE IN-PROCESS MONITORING OF 2 PHARMACEUTICAL PRODUCTION PROCESSES

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#### 33 Abstract

34 Within the Process Analytical Technology (PAT) framework, it is of utmost importance to obtain critical process and formulation information during pharmaceutical processing. Process analyzers are 35 36 the essential PAT tools for real-time process monitoring and control as they supply the data from 37 which relevant process and product information and conclusions are to be extracted. Since the last 38 decade, near infrared (NIR) and Raman spectroscopy have been increasingly used for real-time 39 measurements of critical process and product attributes, as these techniques allow rapid and 40 nondestructive measurements without sample preparations. Furthermore, both techniques provide 41 chemical and physical information leading to increased process understanding. Probes coupled to the 42 spectrometers by fiber optic cables can be implemented directly into the process streams allowing 43 continuous in-process measurements. This paper aims at reviewing the use of Raman and NIR spectroscopy in the PAT setting, i.e. during processing, with special emphasis in pharmaceutics and 44 45 dosage forms.

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#### 51 1. Introduction

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53 The Food and Drug Administration's (FDA) Process Analytical Technology (PAT) initiative (FDA, 2004) 54 forms the basis of the pharmaceutical Good Manufacturing Practice (GMP) rules for the 21<sup>st</sup> century (Hinz, 2006). Because the pharmaceutical industry is highly regulated, final products must meet very 55 56 stringent specifications. However, this does not mean that pharmaceutical processes are optimized. 57 Conventional pharmaceutical manufacturing is generally accomplished using batch processing with 58 off-line time-consuming and less efficient laboratory testing conducted on randomly collected 59 samples to evaluate quality. The processes themselves are not fully understood and are often 60 inefficient black-boxes. Limited relevant information is mainly obtained after the process, making 61 process control difficult which can result in batch losses. The ultimate goal of PAT is a better 62 fundamental scientific understanding of manufacturing processes (i.e., the process should not be a 63 black box system). One of the most important statements within the PAT concept is that 'quality 64 should not be tested into products; it should be built in'. PAT should therefore play a crucial role in 65 design, analysis, and control of manufacturing processes based on timely in-line, on-line and at-line measurements (i.e., during processing) of critical quality and performance attributes of raw and in-66 67 process materials, with the goal of ensuring final product quality (EUFEPS QbD and PAT Sciences 68 Network, 2010). It is thus aimed to obtain real-time information of all critical process aspects and to 69 guide processes towards their desired state, hence ensuring the quality of each end product and 70 possibly allowing real-time release. Continuous gathering of critical process information during 71 production should allow real-time process adjustments to keep product specifications within 72 predefined limits, hence avoiding batch loss. For a long time, innovations in pharmaceutical 73 manufacturing and quality assurance have been slowed down by the stringent regulatory constraints 74 within the pharmaceutical industry which allowed little room for change and which significantly 75 contributed to the aversion to bring new manufacturing technologies and quality assurance methods 76 to the attention of the regulators (in order to avoid delaying regulatory approval). The PAT initiative 77 to move towards a risk- and science based approach for pharmaceutical processing is now strongly 78 encouraged by the most important pharmaceutical regulatory authorities (e.g., FDA and the 79 European Medicines Agency, EMA).

Process analyzers are the essential PAT tools for real-time process monitoring and control as they supply the data from which relevant process and product information and conclusions are to be extracted. Available tools have evolved from those that predominantly take univariate process measurements, such as pH, temperature, and pressure, to those that provide multivariate information related to biological, physical, and chemical attributes of the materials being processed (e.g., Raman and NIR spectrometers). In a PAT environment, real-time process measurements can be

- *at-line*: measurements where the sample is removed, isolated from, and analyzed in close
   proximity to the process stream.
- on-line: measurements where the sample is diverted from the manufacturing process, and
   may be returned to the process stream.
- *in-line*: measurements (invasive or noninvasive) where the sample is not removed from the
   process stream [FDA, 2004].

- 92 The following aspects should be considered when implementing process analyzers into process 93 streams:
- 94 selection of a suitable process analyzer or combination of complementary process analyzers
   95 able to monitor the desired critical process and product information,
- 96 determination of the locations in the process streams where and how process analyzers
   97 should be and can be implemented to monitor the required information,
- 98 determination of the optimal measurement conditions for the process analyzer to obtain
   99 useful data,
- 100 validation of the performance of process stream analyzers (over time).

101 Since the last decade, near infrared (NIR) and Raman spectroscopy have been increasingly used for 102 real-time measurements of critical process and product attributes during pharmaceutical processing, 103 as these spectroscopic techniques allow rapid and nondestructive measurements without sample 104 preparations. Furthermore, probes coupled to the spectrometers by fiber optic cables can be 105 implemented directly into the process streams allowing continuous real-time in-process 106 measurements. A quick search in Web of Sciences® shows the strongly increased number of 107 publications during the last decade about the use of Raman and/or NIR for pharmaceutical in-process 108 measurements. Besides the practical advantages, an important reason for the high interest for 109 Raman and NIR spectroscopy as process analyzers is their ability to supply versatile and multivariate 110 information. One single spectrum may contain qualitative and quantitative physical and chemical 111 information.

112 This paper aims at reviewing the use of Raman and NIR spectroscopy in the PAT setting, i.e. during processing, with special emphasis in pharmaceutics and dosage forms. Hence, there will be focused 113 114 on applications where NIR and Raman spectroscopy have been used in-line, at-line and on-line to monitor and control pharmaceutical production processes in real-time. Many studies have been 115 performed using Raman and/or NIR spectroscopy as off-line tools for chemical and physical analysis 116 of pharmaceuticals (e.g., API quantification in tables, co-crystal screening, etc.). Evidently, these 117 118 studies also contribute to the increased understanding of the production of pharmaceuticals. Several 119 reviews describe and evaluate these off-line Raman and NIR applications (Aaltonen et al., 2008; 120 Aaltonen et al., 2009; Fevotte, 2007; Heinz et al., 2009; Luypaert et al., 2007; McGoverin et al., 2008; Pinzaru et al., 2004; Radtke et al., 1999; Rasanen and Sandler, 2007; Reich, 2005; Strachan et al., 121 2007; Tantipolphan et al., 2008; Tummala et al., 2005; Wen, 2007; Yu et al., 2007). 122

### 123 2. <u>NIR versus Raman spectroscopy</u>

NIR and Raman spectroscopy are both molecular vibrational spectroscopic techniques studyingvibrational transitions in molecules.

126 2.1. Raman spectroscopy

The Raman effect was first observed in 1928 by Sir C.V. Raman (Raman and Krishnan, 1928).
However, this effect was already predicted in 1923 by Smekal, based on theoretical calculations

(Smekal, 1923). The Raman effect is the inelastic scattering of electromagnetic radiation (EMR) as a
result of energy exchange between the radiation and molecular vibrations. The theoretical
background of the Raman effect is well described in literature (Gardiner, 1989; Long, 1977;
Nakamoto, 1986; Stoicheff, 1959).

133 In Raman spectroscopy, the samples are irradiated with monochromatic laser light. Typically, lasers 134 producing laser light in the visible (e.g. 532 nm) or near-infrared (e.g. 785 nm and 1064 nm) range 135 are used. The energy of this light is higher than the energy needed to bring molecules to a higher 136 vibrational state (Figure 1). Most of the incident radiation is scattered by the sample molecules at the same frequency (= energy). This identical scattered light is called Raleigh radiation. Only  $10^{-8}$  is 137 138 scattered inelastically by the sample molecules, indicating that energy exchange occurred between 139 the incident light and the sample. This inelastic scattering is called the Raman effect. This inelastic 140 scattered radiation can have a lower energy (lower frequency) than the incident radiation or a higher 141 energy (higher frequency) than the incident radiation. The first type of inelastic scattering is called 142 Stokes radiation, the latter anti-Stokes radiation (Figure 1). At room temperature, mainly Stokes 143 radiation will occur. At high temperatures (e.g., 500°C), many sample molecules are already at a 144 higher vibrational state as can be derived from the Boltzmann distribution, hence favoring anti-145 Stokes radiation.

146 The selection rule for molecules to be Raman active is that a *change in polarizability* of the molecule 147 occurs during its normal modes. The *polarizability* of a molecule is the ease with which the electron 148 cloud of a molecule can be distorted after bringing the molecule in an electromagnetic field (i.e., by light irradiation). However, molecules are no static entities, but continuously in motion by vibrations, 149 150 rotations and translations. The actual vibration of a molecule seems arbitrary, but is in fact the superposition of some simple vibration modes, called normal modes. Each of these normal modes 151 has its own frequency. An atom has 3 degrees of freedom (x, y and z direction). Hence, a molecule 152 153 containing N atoms has 3N degrees of freedom: 3 translations, 3 rotations (2 for a linear molecule) 154 and 3N-6 normal modes (3N-5 for linear molecules). For a diatomic molecule, e.g., the ease to distort 155 the electron cloud will be different for the three vibration states of its harmonic vibration having 156 frequency  $v_{v_r}$  as schematically shown in figure 2a. The larger the bond distance, the further the 157 electrons are apart from the nuclei an thus the easier they can be moved. This change in ease with 158 which the electron cloud of a molecule can be distorted (i.e.; change in polarizability) is needed for 159 Raman activity. Complicated quantum mechanics and the group theory are needed to determine for 160 which of the normal modes of complex molecules a change in polarizability occurs.

A Raman spectrum displays the frequency difference between the incident radiation and the scattered radiation, expressed as wavenumbers, versus the intensity (I) of the scattered radiation (Figure 3). Placzek developed the following equation which allows the calculation of the Raman intensity during a particular vibration:

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$$I = cte\left(\frac{v_0 + v_v}{v_v}\right)^4 \frac{NI_0}{1 - e^{(-hv_v/kT)}} \left[45(\alpha^s)^2 + 13(\alpha^a)^2\right]$$
[1]

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167	where:	$v_0$ is the frequency of the incident radiation
168		$v_{\nu}$ is the vibration frequency of the molecule
169		N is the number of irradiated Raman active molecules
170		$I_{\scriptscriptstyle 0}$ is the power of the light source
171		h is Planck's constant (= 6.6260.10 <sup>-34</sup> Js)
172		k is the Boltzman's constant
173		T is the temperature
174		$lpha^{s}$ is the polarizability from the molecules causing Stokes radiation
175		$lpha^{a}$ is the polarizability from the molecules causing anti-Stokes radiation.

However, besides these parameters the Raman intensity is also determined by instrumental (e.g., detector, length of glass fiber when using probes, etc.) and sample parameters (e.g., sampling volume, sample particle size, refractive index of sample, concentration of the considered compound, etc.). Furthermore, as scattering occurs in all directions, only a fraction is detected. When probes are implemented into process streams, only the light which is scattered into the same direction as where the incident light comes from is measured.

182 The irradiation of materials can result in different phenomena: scattering, absorption and 183 fluorescence. As the Raman effect is inherently weak, the other phenomena can interfere strongly. 184 Moreover, heating, photodecomposition and laser ablation can occur. The incident laser light can be 185 absorbed when the wavelength of this light corresponds with the absorption band in the spectrum of 186 the molecule, resulting in the transition of the molecule to the excited state (dependent of the laser 187 to the excited vibrational or electronic state). The absorbed energy is then transformed via radiationless transitions into thermic energy. This absorption interferes quite strongly with the 188 189 Raman effect as the intensity of Raman scattering is proportional to the intensity of the laser light. 190 This interference can be avoided by using another wavelength laser. Besides the absorption of the 191 laser light, absorption of the scattered light can likewise occur. Fluorescence can produce substantial 192 interferences in Raman spectroscopy when the molecule is excited to an electronic excited state. The 193 molecule decays to a lower energy level by a radiation-less transition (the vibrational ground state in 194 the electronic excited state), followed by the decay to the electronic ground state (Figure 1). During 195 this last decay, fluorescent radiation is emitted, interfering with the Raman signal. Interference by 196 fluorescence can be avoided employing lasers with other (higher) wavelengths to make sure that no 197 excitation to the electronic excited state occurs. As the intensity of the Raman signal is proportional 198 to the intensity from the laser upon the sample, it is favorable to use as high as possible laser 199 intensities. However, destructive effects can occur by high energy supply. Absorption of radiation 200 with insufficient energy transfer to the surroundings results in sample heating (and possibly 201 destruction). Laser ablation is a phenomenon where material is removed from the sample. Several 202 effects occur simultaneously: photodecomposition, thermic expansion and decomposition. 203 Furthermore, a mechanic effect occurs by a mechanic power of the laser radiation on the sample. When the energy added to the sample per time unit is larger than the bond energy and when the energy is dissipated, ablation occurs resulting in a crater (Gardiner, 1989; Long, 1977; McCreery, 2000,Nakamoto, 1986; Stoicheff, 1959);

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2.2.<u>NIR spectroscopy</u>

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The discovery of NIR energy is ascribed to Herschel in the  $19^{th}$  century (Herschel, 1800), but the first industrial applications only appeared in the 1950s. NIR spectroscopy studies the absorption of EMR in the NIR region, i.e. 700 nm - 2500 nm (14300 cm<sup>-1</sup> – 4000 cm<sup>-1</sup>). Mid infrared and Far infrared light can be situated in the 2500 nm – 10000 nm and 10  $\mu$ m – 1000  $\mu$ m range, respectively. The basic principles of NIR spectroscopy are thoroughly described in a review from Reich, 2005. The detailed theory of NIR spectroscopy can be found in Williams & Norris 1987, Osborne et al 1993, Blanco et al 1998, Chalmers & Griffiths 2002 and Ciurczak & Drennen 2002.

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218 In NIR spectroscopy, the samples are irradiated with NIR light. Some of this NIR light is absorbed by 219 the molecules, bringing them to a higher vibrational state (Figure 1). Common incandescent or quartz 220 halogen light bulbs are most often used as broadband sources of NIR radiation for analytical 221 applications. Light-emitting diodes (LEDs) are also used and offer greater lifetime and spectral 222 stability and reduced power requirements. Only vibrations resulting in changes in dipole moment of a 223 molecule can absorb NIR radiation. A dipole is the product of charge (positive and negative) and 224 distance. Figure 2b shows that there is no change in dipole moment during the stretch vibration of an 225  $X_2$  molecule. Figure 2c shows that there is a change in dipole moment during the stretch vibration of 226 an XY molecule (Visser, 1980). Two-atomic molecules require a permanent dipole to be IR active, 227 while moreatomic molecules only require a dipole induced by the vibration. R-H groups have the 228 strongest overtones as the dipole moment is high. Also O-H, N-H, C-H, S-H bonds are therefore strong 229 NIR absorbers.  $H_2$  does not absorb NIR radiation as no change in dipole moment occurs during its 230 vibrations. Molecules that absorb NIR energy vibrate in 2 modes: stretching and bending. Stretching 231 is defined as a continuous change in the interatomic distance along the axis of the bond between two 232 atoms. Bending is defined as a change in bond angle. A C-H stretch for example will have a fundamental absorption band near 2960 cm<sup>-1</sup>. The 1<sup>st</sup> and 2<sup>nd</sup> C-H stretch overtone will hence occur 233 near 5920 cm<sup>-1</sup> and 8880 cm<sup>-1</sup>, respectively. A C-H combination will occur near 4420 cm<sup>-1</sup>, which is the 234 sum of a C-H stretch (2960 cm<sup>-1</sup>) and a C-H bend (1460 cm<sup>-1</sup>). Figure 4 shows an example of an NIR 235 236 spectrum.

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238 Figure 2a shows 3 possible vibration states of a diatomic molecule. The potential energy of these 239 vibrations is dependent on the bond length as can be seen in figure 5, representing an anharmonic 240 vibration model. At equilibrium, the potential energy is low. Bringing the atoms closer to each other 241 induces repulsion, resulting in an increase in potential energy. Pulling the atoms away from each 242 other in first instance leads to attraction, resulting in an increased potential energy. However, 243 bringing the atoms far enough from each other does not result in further increase of potential 244 energy. Further displacement of the atoms will result in dissociation. However, from the quantum 245 theory, only some vibrational energy levels are allowed, respresented by the horizontal lines in figure 5. These energy levels are not equidistant in an anharmonic model. An NIR spectrum contains 246 247 overtones and combinations derived from fundamentals which appear in the IR region.

248 The low molar absorptivity of absorption bands in the NIR region permits the operation in the 249 reflection mode. Hence, spectra can be recorded with minimal or no sample preparations. In the 250 reflection mode, the light reflected by the sample surface (i.e., the non-absorbed light) is measured 251 (Räsänen et al., 2007).

#### 252 2.3. Raman and NIR spectroscopy

253 Raman and NIR spectroscopic measurements can both be done in a very fast (seconds) and non-254 destructive way, making both tools suited for real-time process monitoring. Custom made fiber optic 255 probes connected to the spectrometers can be implemented into process streams. Referring to the 256 different selection rules for Raman and NIR activity (change in polarizability and change in dipole 257 moment, respectively), both vibrational techniques can be complementary. Molecules producing 258 good signals in NIR spectra might produce weak signals in Raman spectra and vice versa. Raman and 259 NIR spectra contain qualitative and quantitative information on the chemical composition and the 260 physical properties (e.g., particle surface, particle size and shape distribution) of the measured 261 sample (Ciurczak et al., 1986; Osborne et al., 1993; Pellow-Jarman et al., 1996; Rantanen & Yliruusi, 262 1998; Wang et al., 2002; Hu et al., 2006).

263 Raman and NIR spectroscopic monitoring of pharmaceutical processes typically result in a huge 264 amount of spectral data. Chemometric techniques are obvious to explain the variation in the data 265 and to extract useful process information leading to process understanding and process conclusions. 266 Spectral pretreatment before chemometric analysis is often desired to reduce the effect of 267 interfering variance in which one is not interested, thereby increasing the part of the variance due to 268 parameters of interest (Luypaert et al., 2004). Adequate spectral preprocessing is hence very critical 269 for further chemometric data-analysis and data-interpretation (Rinnan, 2009).

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# 3. In-process monitoring using Raman and NIR spectroscopy

271 During the manufacturing process of solid dosage forms, the active pharmaceutical ingredients and 272 excipients are subjected to several consecutive process steps: synthesis, crystallization, milling, 273 blending, granulation, drying, tableting, coating and packing. Evidently, as not only tablets are 274 produced, also other widely applied unit operations will be reviewed (e.g., extrusion-sferonisation, 275 freeze-drying, etc.). Within the scope of increased process efficiency and increased production, there 276 is the intention within the pharmaceutical industry to move from traditional batch processing to 277 continuous processing (Vervaet and Remon, 2005). Continuous production processes are based on 278 the 'one-in-one-out' principle, and avoid scale-up issues, reduce cycle times, reduce production 279 costs, ensure faster product release, reduce variability, increase flexibility and efficiency, and 280 improve product quality. It is obvious that the current conventional quality control systems of 281 production processes, based on mainly off-line analyses in analytical laboratories, would annul the 282 advantages of continuous processing, and that continuous real-time quality control is indispensable 283 for continuous production. The desire within the pharmaceutical industry to shift towards continuous 284 processing strengthens the desire and need to invest in PAT. This review mainly focuses on the 285 applicability of Raman and NIR spectroscopy for in-process analysis during the production of solid 286 dosage forms. The use of Raman and NIR spectroscopy for the in-process monitoring of drug 287 synthesis processes and crystallization processes is evaluated in Rantanen (2007) and Räsänen and 288 Sandler (2007).

Process analysers are the essential PAT tools for real-time process monitoring and control (in-line, on-line or at-line) as they supply the data from which relevant process and product information and conclusions are to be extracted. The following steps should be applied to implement process analyzers in process streams:

Determination of all required critical information. In order to determine crucial and relevant information (e.g., process step endpoints, intermediate or end product quality requirements), as much as possible pharmaceutical technological knowledge should be gathered from the available literature and in-house process knowledge. It is essential to know which intermediate process step endpoints have to be reached and which required intermediate quality attributes should be obtained before the next process step can start.
 The relevant quality parameters should be defined.

- Selection of the suited process analyzer or combination of complementary process analyzers
   able to supply the required critical information.
- 302 Determination of the locations in the process streams where process analyzers should be and
   303 can be implemented.
- Determination of optimal process analyzer measurement conditions to obtain useful data.

Rantanen (2007) clearly described the challenges in process analysis with Raman spectroscopy and discussed several approaches to overcome them (Figure 6). Similar challenges and solutions are observed and valid for in-process NIR spectroscopy.

- Table 1 shows an overview of many publications in which the use of Raman and NIR spectroscopy for in-process monitoring of pharmaceutical unit operations has been evaluated. For each of these studies the in-process interfacing of the spectroscopic tool, the monitored information, the discussed
- 311 challenges and the applied spectral preprocessing and data-analysis methods are specified.

#### 312 3.1. Blending

313 Blending is a critical unit operation of the production process of many solid dosage forms. The quality 314 of products depends on the degree of mixing of their constituents, which guarantees the 315 homogeneity of the final product. Mendez et al., 2010 recently proposed a simple and practical 316 operational qualification procedure to investigate the pharmaceutical mixing operation on a large 317 scale. Compared to NIR, the use of Raman spectroscopy for the in-line monitoring of pharmaceutical 318 blending processes has been less described in literature. Vergote et al. (2004) used Raman spectroscopy for the in-line monitoring of the blending process of a binary mixture (50/50, w/w) of 319 320 diltiazem pellets and paraffinic wax beads (particle size: 800 – 1200 µm). The mixing bowl contained 321 a glass window in front of which a fiber optic non-contact probe was placed. The mean square of 322 differences (MSD) between two consecutive collected spectra was used to identify the endpoint of 323 mixing (i.e., homogeneity). Once homogeneity is obtained, the spectra remain constant resulting in 324 an MSD of zero. Wikström et al. (2005) investigated the importance of the Raman spectrometer 325 sampling optics regarding the assessment of powder mixture homogeneity. They found that large 326 spot non-contact optics (spot size 3 mm instead of 60 µm) provide significant advantages because of 327 the enhanced sampling volume and the greater robustness to fluctuations in sampling distance 328 during processing. Rantanen et al. (2005a) also found that the sample volume seriously affected the 329 performance of calibration models for the quantification of anhydrate/hydrate powder mixtures

using Raman and NIR spectroscopy. The calibrations were significantly improved using larger 330 331 sampling areas. Furthermore, the authors showed that multivariate regression not always improves 332 the predictability of the data compared to univariate analysis. As mentioned in 2.1., the detection 333 sensitivity of Raman spectroscopy is rather low. Hence, there lays an important challenge in the inline monitoring of low dose blend uniformity. Hausman et al. (2005) showed the ability of Raman 334 335 spectroscopy to determine the endpoint of the blending process of a low dose, 1%, azimilide 336 dihydrochloride formulation. However, it should be emphasized that low dose detection is very 337 formulation dependent and strongly depends on the Raman activity of API and excipients. De Beer at 338 al. (2008) presented a Soft Independent Modelling of Class Analogy (SIMCA) model allowing the determination of the homogeneity of blends in-line and real-time using Raman spectroscopy in 339 340 combination with a fiber optical immersion probe.

As water is a weak Raman scatterer, Raman spectroscopy presents itself as a suitable tool for measurements in aqueous environments. De Beer et al. (2006) showed the ability of Raman spectroscopy to monitor in-line the homogenization process of an aqueous pharmaceutical suspension. At the same, time it was possible to quantify the API concentration in the suspension.

345 NIR applications assessing powder blend homogeneity are numerous. Hailey et al. (1996) 346 demonstrated the interfacing of NIR with a blender. Complete supervisory control and data analysis 347 (SCADA) software controlled the blender and spectrometer operation and performed statistical 348 spectral data analysis in real-time. Sekulic et al. (1998) studied the effect of different preprocessing 349 approaches (detrending, standard normal variates (SNV), second derivatives, and the combination of detrending and standard normal variates) on NIR spectra collected in-line during powder blending. 350 351 Depending on the purpose of the application, the user may or may not be interested in the spectral 352 contributions originating from the physical characteristics of the sample. Where these characteristics 353 are important, the user may choose to work with the raw spectral data, otherwise some pre-354 treatment or preprocessing is usually carried out. Furthermore, the authors evaluated several 355 algorithms used to determine blend homogeneity (mean standard deviation versus blend time, 356 moving block standard deviation, dissimilarity calculations, principal component analysis (PCA) and 357 SIMCA). These blend profiling approaches did not show any appreciable differences in this study. El-358 Hagrasy et al. (2001) used NIR spectroscopy noninvasively to monitor powder blend homogeneity. 359 They showed that multiple sampling points are needed for accurate and precise estimation of mixing 360 endpoint. Therefore, six sapphire windows were mounted at different locations on the V-blender through which NIR spectra were collected. Shi et al. (2008) showed that the blending behavior at two 361 362 sensor locations demonstrated a significant difference for endpoint and blending variability. In 363 another study El-Hagrasy et al. (2006a) used a design of experiments approach to identify the critical 364 factors affecting powder blending. The effect of humidity, component concentration and blender 365 speed was evaluated on mixing endpoint, particle size and density of powder. All these variables 366 were shown to have a significant effect on the blending endpoint. Moreover, humidity and concentration had a significant effect on particle size and powder density. NIR spectroscopy showed 367 to be sensitive to changes in physicochemical properties of the mixtures. The authors found that 2<sup>nd</sup> 368 derivative spectral preprocessing was suitable to minimize the spectral variations due to changes in 369 370 physical properties, while monitoring chemical changes. In another study, El-Hagrasy et al. (2006b) 371 developed two pattern recognition models (SIMCA and Principal Component Modified Bootstrap Error-adjusted Single-sample Technique, PC-MBEST) combined with 2<sup>nd</sup> derivative preprocessing on 372

373 the spectra, allowing to predict the blend homogeneity of independent blend samples manufactured 374 under different processing conditions (humidity, blender speed, component concentration). Barajas 375 et al. (2007) developed an NIR spectroscopic method for the monitoring of flowing pharmaceutical 376 powders during their voiding and for the detection of post-blending segregation. Particle size 377 differences in powder blends are known as driver for segregation. Zhang et al. (2009) developed a 378 new blending endpoint determination method. A hidden Markov model showed to have a better 379 reliability, a higher robustness and a more transparent endpoint decision making compared to the 380 traditionally MBSD method. Ufret and Morris (2001), used NIR spectroscopy throughout blending 381 runs to obtain the mixing profile and the dynamics of the powder bed as function of the blender 382 rotations. This approach elucidated the existing relationship between the characteristic mixing 383 parameters (e.g., formulation ingredients, geometry of the mixer, batch load) and the required 384 rotations to achieve content uniformity. Bellamy et al. (2008) studied the effects of particle size and cohesive properties on mixing with non-contact NIR. They found that the magnitude of the 2<sup>nd</sup> 385 overtone NIR measurements is less affected by changes in particle size compared to the 1<sup>st</sup> overtone. 386 Furthermore, the peak-to-peak noise of the 2<sup>nd</sup> overtone NIR mixing profile increases with the 387 particle size of the added compound. Li et al. (2007) showed the importance of a large beam size on 388 389 the real-time determination of powder blend homogeneity by NIR spectroscopy.

390 Several publications describe the possibility to quantify API and excipients during blending using NIR 391 spectroscopy. El-Hagrasy et al. (2006c) developed several univariate and multivariate quantitative 392 NIR models for prediction of blending endpoint. They found that linear regression, using a single 393 wavelength, yielded optimum calibration and prediction results. Sulub et al. (2009) used a set of 21 394 off-line static calibration samples for the development of a multivariate partial least squares (PLS) 395 calibration model for in-line prediction of the API content during the blending process. Wu et al. 396 (2009) quantified the constituent concentrations of both drug and excipients in powder blends using 397 NIR spectroscopy. The authors concluded that the measurement uncertainties were higher for minor 398 components in the powder formulations. Karanda et al. (2010) studied the difference between static 399 and dynamic spectral acquisition. They found that dynamic spectral acquisition resulted in the most 400 accurate predictions for all blend components. The authors further emphasize the importance of 401 adopting appropriate and similar sampling strategies for both calibration and actual testing.

El Hagrasy et al. (2006d) reported the use of NIR spectroscopy for monitoring of adequate lubricant
(magnesium stearate, 0.5 – 9.0 %) mixing into pharmaceutical granules. Herewith, the significance of
sensor location on the blender at different fill levels was evaluated. They found that different mixing
endpoints were concluded dependent on the location of the NIR probe.

#### 406 3.2. Wet granulation

High shear granulation and fluid bed granulation are the two most applied wet granulation techniques for the production process of pharmaceutical solids. During granulation, the powder particles are mixed with a granulation liquid leading to compound particles. Granulation aims at improving the material properties for further processing: improved flow properties, less demixing, better compressibility and less dust production.

NIR and Raman spectroscopy have been mainly applied for the in-line monitoring of water content,particle size distribution, API solid state and endpoint of granulation processes. Furthermore, the

spectroscopic process fingerprints have been used to increase the understanding of the granulationprocess.

416 List and Steffens (1996) demonstrated as first the use of NIR spectroscopy for the in-line solvent 417 content determination during granulation. Rantanen et al. (2001a) showed that in-line NIR moisture 418 determination during fluid bed granulation is possible based on the simultaneous detection of only 419 four wavelengths. An entire NIR spectrum is not necessary for water determination, and often the 420 use of only a few NIR wavelengths around the water band enables reliable and high-speed detection 421 of moisture. In another study, Rantanen et al. (2000) evaluated the factors affecting in-line NIR 422 moisture measurements with the above mentioned four-wavelength sensor. They found that particle 423 size effects influence the spectral baseline and that the applied binder influences the NIR 424 measurement. Watano et al. (1996) studied the effects of operational variables on the NIR 425 measurement and found the effect of the granulation liquid flow rate and process air temperature to 426 be significant. Several authors described the simultaneous determination of moisture content and 427 particle size data using NIR spectroscopy. Frake et al. (1997) and Findlay et al. (2005) demonstrated 428 the simultaneous real-time monitoring of particle size and moisture content using NIR through a 429 window into the bed of a fluidized bed granulator. This measurement setup avoids fouling and 430 sticking of the wet material to the measurement device.

431

Luukkonen et al. (2008) predicted granule and tablet quality properties such as particle size, porosity and hardness using in-line NIR data (i.e., the first NIR overtone band for water at 1460 nm) from a high-shear granulation process. Alcala et al. (2010) acquired NIR spectra through a glass window of a fluidizer during a wet granulation process. PCA of the NIR data allowed to distinguish between the different steps of the granulation process. A PLS model was developed allowing the prediction of moisture content, particle size distribution and bulk density.

Li et al. (2005) used NIR spectroscopy for the quantitative monitoring of polymorph conversion of an active pharmaceutical ingredient during a wet granulation process. Wikström et al. (2005 and 2008) described the feasibility of Raman spectroscopy for in-line monitoring of the transformation of theophylline anhydrous to theophylline monohydrate during high shear wet granulation. Process induced transformations are important to be controlled as they can alter the API properties in the drug product, including therapeutic efficacy. They also found that process settings (e.g. mixing speed) influence the start and rate of transformation.

445 Rantanen et al. (2001b) visualized a fluid-bed granulation process based on NIR spectroscopic 446 multivariate process data. Self-organizing maps (SOMs) were used to visualize the process consisting 447 of a number of process states. In another study, Rantanen et al. (2001c) showed that in-line NIR 448 measurements provide information related to the amount of water throughout a fluid bed 449 granulation process. This information combined with trend charts of the temperature difference 450 between process inlet air and granules and the water content of process air enabled the control of 451 water during fluid bed granulation and the analysis of the different granulation processes phases. 452 Hence, in-line information on all granulation process steps was obtained. In 2005(b), Rantanen et al. 453 monitored a high shear granulation process using NIR spectroscopy. In combination with PCA 454 methods, three separate phases during the process could be elucidated. Information on the 455 homogeneity of the formulation, the amount of water in the wet mass and the granule particle size was extracted from the NIR data. Hence, NIR allowed to determine the endpoints of the three 456

457 subphases of a high shear wet granulation process. Jorgensen et al. (2004a and 2004b) described in 458 two manuscripts the visualization of a small-scale high-shear granulation process using in-line NIR 459 spectroscopy and chemometrics. Physical (impeller torque and temperature) and chemical (NIR 460 spectra) information were continuously monitored during granulation. Process vectors were created 461 combining all data and describing all relevant information. The visualization of the vectors was done 462 using PCA and SOM. None of the individual measurement techniques were able to describe the state 463 of the process alone.

464 Tok et al. (2008) analyzed and compared the responses of NIR, focused beam reflectance 465 measurements (FBRM) and acoustic emission measurements to monitor a pilot-scale fluidized bed 466 granulation process. All three process analyzers were able to detect the three granulation phases 467 (wetting and nucleation, consolidation and growth, breakage) to varying degrees of sensitivity. FBRM 468 and NIR were susceptible to fouling on probe windows. Walker et al. (2007 and 2009) proposed a 469 novel use of Raman spectroscopy, which allows in situ measurement of the composition of the 470 material within the fluidized bed in three spatial dimensions and as function of time. This was 471 achieved by recording Raman spectra from specific volumes of space using a probe positioned within 472 the fluidized bed on a long-travel x-y-z stage, hence providing 3D maps of the concentration and the 473 chemical structure of the particles in motion in a fluidized bed within 10 seconds.

#### 474 3.3. Drying

475 In 2000, Morris et al. presented a method to accelerate the fluid bed drying process relying on 476 concepts of heat and mass transfer with real-time NIR monitoring of moisture. Critical NIR readings 477 were used corresponding to the end of the evaporative cooling as temperature-independent 478 endpoint. Räsänen et al. (2003) studied the dehydration behavior of theophylline granules using a 479 novel multichamber microscale fluid bed dryer with a process air control unit and in-line NIR 480 spectroscopy. The stepwise dehydration of materials was followed by the water content difference 481 of inlet and outlet air temperature, the pressure difference over the bed, and in-line NIR 482 spectroscopy. Green et al. (2005) examined different sampling configurations to improve the 483 accuracy of the in-line residual moisture content determination during a fluid bed drying process. In-484 line NIR data were collected (i) using the probe directly inserted into the fluid bed dryer such that 485 measurements of dynamic flowing sample were collected, and (ii) using the NIR probe interfaced to a 486 home-made sheath allowing static sample collection and utilizing an air purge to clean the probe face, thereby preventing probe fouling. This latter device was (iii) further modified to allow thieving 487 488 of the actual sample being measured. They found that the latter sampling device allows collection of 489 quality spectra in process systems and eases method development as NIR and reference 490 measurements are performed on the same samples. Nieuwmeyer et al. (2007) demonstrated that NIR spectroscopy could be used for simultaneous water content determination (with errors 491 492 comparable to the reference method) and median granule size. Romer et al. (2008a) proved that in-493 line NIR measurements enable real-time monitoring of API (erythromycin dihydrate) phase 494 transformations. Kogermann et al. (2008) demonstrated the ability of Raman and NIR spectroscopy 495 for in-line quantitative solid state transformation during dehydration. Aaltonen et al. (2007) showed 496 the complementarity of Raman and NIR spectroscopy for the quantitative in-line monitoring of solid-497 state transitions during fluidization. NIR spectroscopy was particularly sensitive to water while 498 Raman spectroscopy to crystal structure changes. Märk et al. (2010) implemented a continuous NIR 499 measuring setup to rapidly gain product assay, water content and residual solvent information during 500 the fluid bed drying process in the production plant of an antibiotic substance. A bypass system 501 outside the drier combined with a robust process probe proved to provide the best sampling system 502 geometry. The spectrometer was equipped with an additional laboratory probe for simultaneous 503 offline analysis. The process probe results were in agreement with the laboratory probe results. 504 Hartung et al. (2010) showed that tablet characteristics after compression of granules are not only 505 dependent on the residual moisture content of the granules but also on the moisture profiles during 506 the entire fluid bed granulation process. The authors showed that 2 granule types with the same 507 residual moisture content but with different moisture profiles during the entire fluid bed 508 granulation/drying process are different. Granules with a low-moisture profile and a low residual 509 moisture content have little water adsorbed on the surface of the granules, while for granules with a 510 high-moisture profile and a likewise low residual moisture content the water had time to partially 511 diffuse into the structure of the solid granule particles and to form liquid bridges. Peinado et al. 512 (2010) developed a PLS model, based on NIR spectra and humidity determinations, allowing the in-513 line prediction of the drying endpoint of a fluidized bed process. The in-process method was 514 validated according to the ICHQ2(r1) guidelines. However, this guideline is not adopted to in-process 515 methods developed and validated only with in-line samples in dynamic systems. Therefore, the 516 authors propose a customized guideline addressing these challenges.

#### 517 3.4. <u>Tableting</u>

518 Raman and NIR spectroscopy have been widely used to analyze (API quantification, solid state 519 identification, process induced transformations) pharmaceutical tablets off-line in a fast, direct and 520 non-destructive way as described by Räsänen and Sandler (2007) and Rantanen (2007). Therefore, 521 there is a desire to use Raman and NIR spectroscopy in-line to evaluate tablets. The potential analysis 522 speed of Raman and NIR spectroscopy should make it possible to largely increase the number of 523 analyzed tablets (non-destructively) before release compared to the current situation where 524 traditional off-line analysis methods (e.g. HPLC) are used. However, publications describing the in-line 525 use of Raman and/or NIR spectroscopy and tool interfacing for tablet analysis are scarce. Johansson 526 and Folestad (2003) discussed the potential use of Raman spectroscopy for monitoring tableting 527 processes. Aaltonen et al. (2008) thoroughly reviewed to possibilities of using spatially offset Raman 528 spectroscopy for the analysis of tablets. For this Raman spectroscopic analysis method, the Raman 529 scattering is collected from a different sample portion than the irradiated sample fraction. Hence, 530 fluorescence interference can be reduced as there is no emission from the sampled portion. Tabasi et 531 al. (2008a) described the application of NIR spectroscopy to monitor a tablet manufacturing process. 532 NIR spectroscopy in combination with multivariate modeling was used as a rapid and nondestructive 533 technique for the prediction of content uniformity, compression force and crushing strength for 534 orbifloxacin tablets. Cogdill et al. (2004) presented the development and validation of a PAT based 535 NIR method for the on-line prediction of tablet hardness and API content.

#### 536 3.5. Coating

537 Kirsch and Drennen (1996) and Andersson et al. (1999) demonstrated the applicability of at-line NIR 538 spectroscopy as an accurate, rapid and non-destructive tool for the determination of the amount of 539 polymer film on tablets. Andersson et al. (2000) provided a first in-line study in which NIR 540 spectroscopy was used for the quantitative analysis of film coating on pellets in a fluidized bed process. Measurements were done utilizing a diffuse reflectance fiber-optic probe positioned inside a 541 542 fluidized bed process vessel. The authors thoroughly describe the probe interfacing in the fluid bed. Besides the coating thickness determination with high precision, also an estimate could be obtained 543 of the coating thickness variation. A similar study was done by Perez-Ramos et al. (2005) and Romer 544 545 et al. (2008b) in a pan coater and rotating plate coating system, respectively. These authors also 546 emphasize that a sufficiently fast sampling rate is needed and that the fiber optic probe or sensor has 547 to be optimized for the monitoring purpose. Lee et al. (2010) proposed new approaches to develop a 548 reasonable dynamic calibration model for the in-line monitoring of film thickness of pharmaceutical 549 tablets processed in a fluid-bed coater. Tabasi et al. (2008 b and c) published two papers in which the 550 applicability of NIR spectroscopy for the in-line monitoring of a coating process and its subsequent 551 curing process of a pharmaceutical sustained release product has been proven. Besides coating 552 thickness, NIR spectroscopy is able to detect polymorphic changes during coating processes (Kamada 553 et al., 2009). Raman spectroscopy has also been proved as an adequate tool for coating evaluation. 554 Romero-Torres et al. (2005) suggested the feasibility of Raman spectrometry to examine the 555 variability of tablet coatings. A Raman probe was used that can operate with a revolving laser focus 556 to average content and coating non-uniformity. Furthermore, the authors describe adequate 557 preprocessing techniques that emphasize spectral changes while minimizing the effects of 558 background light scattering and fluorescence. In another study, the same authors used Raman 559 spectroscopy to quantify tablet coating thickness in the presence of a fluorescent ingredient in the coating formulation (Romero-Torres et al., 2006). In a very recent study, Muller et al. (2010) used 560 561 Raman spectroscopy for the in-line monitoring of an active coating process. Active coating is a film 562 coating process where the API is included in the coating layer. Raman spectroscopy was able to show 563 in-line when the API quantity in the coating was as desired, hence suggesting the endpoint of the pan 564 coating process. To protect the probe against dust, compressed air was blown through an iron pipe, 565 which was attached in front of the probe.

#### 566 3.6. Pelletization

567 The number of publications describing the use of Raman and NIR spectroscopy for the in-process 568 analysis of pelletization processes is low. Sandler et al. (2005) used Raman and NIR spectroscopy at-569 line to increase the understanding of the solid-state behavior of theophylline and nitrofurantoin 570 formulations during pelletization. NIR gave valuable information on the water behavior during 571 processing, but did not allow to detect the hydrate formation in the formulations because of the 572 saturation of the water signal. However, Raman spectroscopy was able to see the hydration and 573 dehydration phenomena during the process proving the complementarity of Raman and NIR 574 spectroscopy. In another study, at-line NIR spectroscopy was applied to understand the process 575 induced transformations of erythromycin dehydrate during pellet production (Römer et al., 2007).

#### 576 3.7. Freeze-drying

Romero-Torres et al. (2007) and De Beer et al. (2007) described the use of Raman spectroscopy for
the fast, non-invasive in-line monitoring of a simple mannitol solution freeze-drying process.
Furthermore, De Beer et al. (2009a and 2009b) compared the simultaneous use of Raman and NIR
spectroscopy for the in-line monitoring of lyophilization processes. Raman spectroscopy proved to be

581 an excellent tool for crystallization and polymorphic transformation monitoring during the complete 582 freeze-drying process. As water and ice produce weak signals in Raman spectra, Raman spectroscopy 583 provides clear product solid state information during the freezing phase, primary drying phase and 584 secondary drying phase. In contrast, NIR spectroscopy is suited for the in-line monitoring of the 585 water and ice behavior during freeze-drying. As ice produces huge signals in NIR spectra, NIR 586 spectroscopy is unable to provide detailed solid state information during the freezing and primary 587 drying phase. Brülls et al. (2003) showed as first the use of NIR spectroscopy for the in-line 588 monitoring of a freeze-drying. However, measurements were done invasively in this study. The main 589 disadvantages of Raman and NIR spectroscopy for in-process freeze-drying monitoring is that only 1 590 vial can be monitored in the current set-up. Both process analyzers showed to be interesting R&D 591 tools for lab-scale freeze-dryers, but the applicability in large production scale freeze-dryers is still far 592 away. In an another study, de Waard et al. (2010) showed the applicability of in-line Raman 593 spectroscopy for controlled crystallization of the lipophilic drug fenofibrate during freeze-drying. Off-594 line studies suggest that Raman and NIR spectroscopy will be able to monitor in-line secondary 595 protein structure changes during lyophilization.

#### 596 3.8. Continuous production

597 Nowadays, there is a major interest within the pharmaceutical industry to move from traditional 598 batch processes towards continuous processes. Several production machine suppliers recently proposed their first versions of continuous production lines: e.g. the ConsiGma<sup>™</sup> system from GEA, 599 600 the EASY FLOW® system from Böhle. The challenge now is the find out if the critical process aspects from the traditional batch processes above can be monitored and controlled in-line in their 601 602 corresponding continuous production processes. We did not find publications describing the in-line 603 use of Raman and NIR spectroscopy for the in-line monitoring of continuous blending, continuous 604 granulation, continuous drying and continuous coating processes.

Saerens et al. (2010) recently showed the Raman spectroscopic in-line monitoring of a (continuous) pharmaceutical hot-melt extrusion process. Raman spectroscopy allowed the in-line API quantification as well as the polymer and API solid state characterization during processing. Solid solutions showed Raman band broadening compared to solid dispersions. Furthermore, Raman peak shifts appeared in the spectra of solid dispersions and solid solutions compared to the physical mixtures, suggesting interactions (hydrogen bonds) between polymer and API.

611

#### 612 4. Conclusions

613 Raman and NIR spectroscopy have been widely used for the in-process monitoring of several batch unit operations during the production of pharmaceutical solid dosage forms. Both PAT tools are 614 complementary and able to supply physical and chemical critical product and process information 615 616 during processing, herewith increasing the process understanding. Special attention should be paid 617 to the interfacing of probes into process streams (Figure 6). A next step within the PAT framework, is 618 the use the real-time obtained critical process and product information from the process analyzers, based on feed-forward and feed-back loops, and steer and guide processes towards their desired 619 620 state. Finally, Raman and NIR spectroscopy will certainly play a key role in the real-time monitoring 621 and control of continuous pharmaceutical production processes, which is currently of major interest 622 within the pharmaceutical industry.

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- 909 **Table 1:** Applications of Raman and/or NIR spectroscopy for the in-process monitoring of pharmaceutical production processes. Some boxes in the table are
- 910 left open as specified information was not given by the reference. The table is subdivided per described process. Within each subdivision the examples are
- 911 ordered by year of publication.

Application + formulation	Raman/NIR	In-process interfacing	Monitored critical	Evaluated challenges	Data-analyis	Spectral preprocessing	reference
1 Planding			process information		methou	methou	
In line monitoring of powder blanding	NID	Invasivo	Homogonoity	roal time control	MRCD	SNV and dotronding	Hailoy at al. 1996
		livasive	Homogeneity		ענפועו	transformation	Halley et al., 1990
In-line monitoring of powder blending	NIR	Invasive	Homogeneity	<ol> <li>Spectral preprocessing evaluation</li> <li>evaluation of different algorithms for blending endpoint detection</li> </ol>	MBSD Dissimilarity calculations Principal component analysis	Detrending SNV Second derivatives Combined detrending and SNV	Sekulic et al., 1998
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Multiple sampling points in the blender	MBSD variant	SNV MSC 2 <sup>nd</sup> derivatives	El-Hagrasy et al., 2001
In-line endpoint detection of the blending of a binary pellet mixture	Raman	Non-contact probe in front of glass window in mixing bowl	Blend homogeneity		MSD	Baseline correction Vector normalization	Vergote et al., 2004
In-line homogeneity detection	Raman	Non-contact probe	Blend homogeneity	Raman sampling optics	РСА	SNV	Wikström et al., 2005
In-line monitoring of low dose blend uniformity	Raman	an immersion probe was inserted into the V-blender through the I-bar port	Blend homogeneity	API present in low dose (1%)	<ol> <li>1. univariate: peak intensity vs. blend time</li> <li>2. Mahalanobis distance method</li> </ol>	SNV	Hausman et al., 2005
In-line monitoring a an aqueous suspension homogenization process	Raman	Invasive measurement via an immersion probe	<ol> <li>homogeneity</li> <li>API quantification</li> </ol>	aqueous environment	1. conformity index 2. PCR	Pearson's baseline correction	De Beer et al., 2006
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Evaluation of chemical and physical blend properties in NIR spectra	MBSD variant	SNV MSC 2 <sup>nd</sup> derivatives	El-Hagrasy et al., 2006a
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Prediction of blend homogeneity of independent blend samples manufactured under different processing conditions	SIMCA PC-MBEST	2 <sup>nd</sup> derivatives	El-Hagrasy et al., 2006b
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity and API content	Evaluation of univariate and multivariate quantification mehtods	1. PCR 2. PLS 3. MLR 4. Univariate	2 <sup>nd</sup> derivatives	El-Hagrasy et al., 2006c

					calibration		
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Homogeneous mixing of lubricants into granules	PLS	SNV + 2 <sup>nd</sup> derivatives	El-Hagrasy et al., 2006d
In-line monitoring of post-blending	NIR	Invasive	segregation	In-line monitoring of segregation after blending and during voiding		Spectral subtraction	Barajas et al., 2007
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Effect of beam size	PLS	Savitzky-Golay 1 <sup>st</sup> derivatives	Li et al., 2007
In-line endpoint detection of the blending of a multicomponent powder mixture	Raman	Invasive monitoring via an immersion probe	Blend homogeneity		SIMCA	Offset correction and normalization	De Beer et al., 2008
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Effect of particle size			Bellamy et al., 2008
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Multiple sampling points in the blender	PLS + root mean square from nominal value	Savitzky-Golay smoothing and 2 <sup>nd</sup> derivative	Shi et al., 2008
In-line monitoring of powder blending	NIR		Homogeneity	Accurate blending endpoint determination	Hidden Markov model		Zhang et al., 2009
In-line monitoring of powder blending	NIR	Non-invasive	In-line API quantification	In-line quantification method using an off- line external calibration approach	PLS	SNV + 2 <sup>nd</sup> derivative Savitzky-Golay	Sulub et al., 2009
In-line monitoring of powder blending	NIR	Non-invasive	In-line quantifications	In-line quantification of API and excipients simultaneously	PLS PCR MLR	Savitzky-Golay 1 <sup>st</sup> derivatives	Wu et al., 2009
In-line monitoring of powder blending	NIR	Non-invasive	Homogeneity	Static versus dynamic sampling	PLS	SNV	Karanda et al., 2010
2. granulation							
In-line monitoring of fluid bed granulation	NIR		Moisture content	Evaluation of particle size and binder effect		2 <sup>nd</sup> derivatives	Rantanen et al., 2000
In-line monitoring of fluid bed granulation	NIR		Moisture content	Moisture determination based on four wavelengths	ANN		Rantanen et al., 2001a
In-line monitoring of fluid bed granulation	NIR + other non- spectroscopic data	invasive	Visualization of fluid- bed granulation		SOM		Rantanen et al., 2001b
In-line monitoring of fluid bed	NIR + other	Invasive	Moisture		Design of	Baseline correction +	Rantanen et al., 2001c

granulation	non- spectroscopic data		determination		experiments	normalization	
In-line monitoring of high shear granulation	NIR + non- spectroscopic process information	At-line through glass vials	Visualization of a wet granulation process	SOM versus PCA	PCA + SOM	2 <sup>nd</sup> derivative spectra with Savitzky-Golay smoothing	Jorgensen et al., 2004a and 2004b
In-line monitoring of high shear granulation	NIR		Quantitative monitoring of API polymorph conversion	Solid state changes during granulation	MLR	1 <sup>st</sup> derivatives 2 <sup>nd</sup> derivatives 4 <sup>th</sup> derivatives	Li et al., 2005
In-line monitoring of fluid bed granulation	NIR	Non-invasive	Moisture + particle size	Granulation endpoint determination	Weighted linear combinations of individual reflectance values		Findlay et al., 2005
In-line monitoring of high shear granulation	Raman/NIR	Invasive measurements using immersion probe just above impeller to reduce the risk of sample adhesion	Monitoring of hydrate formation				Wikström et al., 2005
In-line monitoring of high shear granulation	NIR	through aperture in the plastic cover of the granulator. aperture was covered with glass in order to avoid coating the collection lens and light source with dust. Adhesion of powder to the glass was avoided by rotating the glass during processing.	Endpoint detection of granulation subphases		PCA	SNV	Rantanen et al., 2005b
In-line monitoring of high shear granulation	NIR	invasive	Process fingerprint	Prediction of granule and tablet properties	Univariate, PLS and multiway PLS		Luukkonen et al., 2008
In-line monitoring of fluid bed granulation	NIR + FBRM + physical acoustic	NIR + FBRM $\rightarrow$ invasive Acoustic $\rightarrow$ non-invasive	Endpoint detection of granulation subphases	FBRM and NIR susceptible to fouling	univariate		Tok et al., 2008
In-line monitoring of fluid bed granulation	Raman	Raman probe positioned in fluid bed on a long-travel x-y-z stage	3-D mapping during fluid bed granulation	Multi-point data collection at	univariate		Walker et al., 2009
In-line monitoring of fluid bed granulation	NIR	Non-invasive through glass window	Moisture content, particle size distribution and bulk		PLS	SNV 1 <sup>st</sup> derivatives 2 <sup>nd</sup> derivatives	Alcala et al.,2010

			density				
3. <u>drying</u>							
In-line monitoring of fluid bed drying	NIR	Non-invasive through window	Drying endpoint	Accelerated drying based on NIR measurements			Morris et al., 2000
In-line monitoring of fluid bed drying	NIR	Multi-channel NIR spectroscopy + non- spectroscopic data	Water content	Dehydration behavior of materials	Univariate	Normalization	Räsänen et al., 2003
In-line monitoring of fluid bed drying	NIR	invasive	Moisture content	Evaluation of sampling effects on method accuracy	PLS	SNV + Savitzky-Golay 2 <sup>nd</sup> derivatives	Green et al., 2005
In-line monitoring of fluid bed drying	NIR	invasive	Water content + median granule size		PCA PLS	SNV + Savitzky-Golay 1 <sup>st</sup> derivatives	Nieuwmeyer et al., 2007
In-line monitoring of fluid bed drying	NIR and Raman	Non-invasive	API phase transformations during drying	Raman and NIR are complementary	PLS	SNV	Aaltonen et al., 2007
In-line monitoring of fluid bed drying	NIR	Non-invasive	API phase transformations during drying		PCA	Savitzky-Golay first derivative smoothing + SNV	Romer et al., 2008a
In-line monitoring of fluid bed drying	NIR and Raman	Non-invasive	API phase transformations during drying	quantification	PLS	SNV	Kogermann et al., 2008
monitoring of fluid bed drying	NIR	On-line using bypass system	Product assay, water content, residual solvent	On-line versus off-line	univariate	SNV, MSC, 1 <sup>st</sup> and 2 <sup>nd</sup> derivatives, straight line subtraction	Märk et al., 2010
In-line monitoring of fluid bed drying	NIR	Invasive (design makes product movement cleaning the NIR window)	Drying endpoint	Difference between residual moisture and moisture profile during drying			Hartung et al., 2010
In-line monitoring of fluid bed drying	NIR	invasive	Drying endpoint	An adapted ICHQ2(r1) guideline was proposed which is suitable for in- process methods developed and validated only with in- line samples in dynamic systems.	PLS	SNV	Peinado et al., 2010
4. tablet manufacturing				1			

Monitoring of tablet manufacturing	NIR	Non-invasive	Content uniformity, compression force,	Use of rapid content NIR analyzer	PLS	SNV + MSC + Savitzky- Golay 1 <sup>st</sup> derivatives	Tabasi et al., 2008
			crushing strength	/ -		,	
5. <u>coating</u>							
Monitoring of fluid bed coating	NIR	At-line	Determination of		PCA	MSC	Kirsch and Drennen,
			amount of polymer			2 <sup>nd</sup> derivatives	1996
			coat applied to tablet				
			cores				
Monitoring of coating (rotating drum)	NIR	At-line	Determination of	Estimation of maximum	PCA	MSC	Andersson et al., 1999
			amount of tablet	depth in coating	PLS		
			coating	material			
In-line monitoring of fluidized bed	NIR	Invasive. To secure	Quantitative analysis	General aspects of in-	PLS	SNV	Andersson et al., 2000
coating		representative sampling during	of film coating	line NIR on solids and		MSC	
		processing, a sample collector		multivariate batch		2 <sup>nd</sup> derivatives	
		that was emptied by		calibration are			
		compressed air was used inside		discussed.			
		the vessel. The sapphire					
		window at the probe tip					
		constituted the interface of the					
		probe to samples in the					
		process vessel.				nd	
In-line monitoring of pan coating	NIR	Non-invasive. To avoid coating	Quantitative analysis	Real-time endpoint	Univariate	2 <sup>nd</sup> derivatives	Perez-Ramos et al.,
		droplets from damaging the	of film coating	detection of coating			2005
		sensor, the top and sides of the		process			
		sensor were protected with a					
		plexiglass box with a nitrogen					
		purge					
Monitoring of pan coating	Raman	At-line	Determination of coat	lablet-to-tablet coating	PLS	SNV	Romero-Torres et al.,
			thickness	variability			2005
						2 derivatives Savitzky-	
	Davisar	At the s	Determinetien of cost	Durante of stores	the breakets a	Golay smoothing	Develope Termine et al.
Monitoring of pan coating	Raman	At-line	Determination of coat	Presence of strong	Univariate +	SINV	Romero-Torres et al.,
			UNICKNESS	interformed	multivariate	2 <sup>nd</sup> derivetives Sovitaley	2008
				interference		2 Gelay smoothing	
In line monitoring of rotating plate	NID	Non invasivo	Prodiction of coating		DIC	SNV + Savitzky Colay	Pomor at al 2008
costing system	(NIIT)		thickness		r LJ	smoothing	NUMEL EL al., 2000
monitoring of pap coating	NID	At line	Determination of cost	curing	DCA	$SNV \pm 2^{nd}$ dorivatives	Tabaci at al. 2009a and
	INIT	Athine	thickness and curing	curing		SINV TZ UEIIVALIVES	h
	1		chickness and curing	1	1 23		~

monitoring of coating	NIR	At-line	Determination of polymorphic changes during coating	quantitative	Univariate	2 <sup>nd</sup> derivatives	Kamada et al., 2009
In-line monitoring of fluid bed coating	NIR	invasive	Prediction of film thickness	Dynamic calibration	PCA PLS	MSC	Lee et al., 2010
In-line monitoring of pan coating	Raman	Non-invasive. To protect the probe against dust, compressed air was blown through an iron pipe, which was attached in front of the probe.	Quantitative determination of API in coat + endpoint determination	Active coating process	PLS	SNV	Muller et al., 2010
6. <u>pelletisation</u>							
Monitoring of pelletisation	Raman/NIR	At-line	API solid-state changes	Complementary Raman and NIR	univariate	2 <sup>nd</sup> derivatives	Sandler et al., 2005
Monitoring of pelletisation	NIR	At-line	Process-induced transformations		univariate	2 <sup>nd</sup> derivatives + Savitzky-Golay smoothing	Römer et al., 2007
7. <u>freeze-drying</u>							
In-line monitoring of lyophilisation	Raman	Non-contact phat probe through quartz window in freeze-drier door	Mannitol phase behavior during freeze-drying		PCA		Romero-Torres et al., 2007
In-line monitoring of lyophilisation	Raman/NIR	Non-contact probes built in the freeze-drier chamber	Product monitoring and process phase endpoint determination	Raman versus NIR	PCA	Pearson's baseline correction	De Beer et al., 2007 De Beer et al., 2009a De Beer et al., 2009b
In-line monitoring of lyophilisation	Raman	Non-contact probe built in the freeze-drier chamber	In-line product behavior monitoring	Controlled crystallization of product	PCA	Pearson's baseline correction	de Waard et al., 2010
8. <u>hot-melt extrusion</u>							
In-line monitoring of hot-melt extrusion	Raman	Contact probe built in the die	In-line product behavior monitoring	API quantification + polymer/drug interactions	PCA PLS	Savitzky-Golay and SNV	Saerens et al., 2010

913	<u>Abbrev</u>	viations:		
914	-	ANN		artificial neural networks
915	-	ΑΡΙ		active pharmaceutical ingredient
916	-	MBSD		moving block standard deviation
917	-	MLR		multiple linear regression
918	-	MSC		multiplicative scatter correction
919	-	MSD		mean square of differences
920	-	NIR		near infrared
921	-	PCA		principal component analysis
922 923	-	PC-MB Technie	EST que	Principal Component Modified Bootstrap Error-adjusted Single-sample
924	-	PCR		principal component regression
925	-	PLS		partial least squares
926	-	SIMCA		Soft Independent Modelling of Class Analogy
927	-	SNV		standard normal variate
928	-	SOM		self-organizing maps
929	<u>Figures</u>	5		
930	Figure	1:	IR and	NIR absorption, the Raman effect and fluorescence.
931	Figure	2a:	Vibrati	on states of diatomic molecule
932	Figure	2b:	no cha	nge in dipole moment during the stretch vibration of an $X_2$ molecule
933	Figure	2c:	change	in dipole moment during the stretch vibration of an XY molecule
934	Figure	3:	Examp	e of a Raman spectrum (CCl <sub>4</sub> )
935	Figure	4:	Examp	e of NIR spectra
936	Figure	5:	Anharn	nonic vibration model
937 938 939	Figure	6:	Factors Reprint 177. Co	affecting the interfacing of Raman and NIR spectroscopy into process streams red with permission from Rantanen, 2007, J. Pharm. and Pharmacol. 59, 171- pyright 2007, Pharmaceutical Press.
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