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HIGHLIGHTS

# Raman and near-infrared spectroscopy for in-line sensors

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In-line sensors based on spectroscopic techniques have been used in various industrial processes. Here, Raman and near-infrared (NIR) spectroscopy are highlighted as in-line sensors for manufacturing process monitoring. Especially, in pharmaceutical industry, science and risk-based quality control approaches are recommended, and the guideline is prepared by ICH [1]. The point of the approach is to understand the mechanisms of each process with scientific basis. Spectroscopic techniques are widely used to investigate manufacturing processes as process analytical tools (PATs) such as Raman [2, 3] and NIR spectroscopy [4]. Since these spectroscopic measurements do not require sample pretreatments, the in situ collection of spectra in the manufacturing lines without sampling action.

In the beginning of the twenty-first century, these spectroscopic in-line sensors were developed to investigate manufacturing process of solid dosages [5] and for quantification of active pharmaceutical ingredients (APIs) in a dosage form [6, 7]. Today, these techniques are utilized as PATs not only for batch manufacturing but also for continuous manufacturing [8]. On another front, continuous synthesis and manufacturing of APIs and biopharmaceuticals are innovative processes and expected to be cost-effective and time-efficient production processes. In these processes, the crucial functions are detecting impurities and removing them from the process line. These functions are necessary for the utilization of continuous manufacturing. Therefore, highly sensitive and high-throughput PATs are desired to detect the low level of impurities.

Synthesized peptide drugs are prepared by the iteration of condensation reaction between peptides and/or amino acids and the deprotection reaction [9]. These iterative routine processes can be developed into the automated synthesis process as the continuous-flow peptide synthesis system. Raman and NIR spectroscopy are possible as the essential PAT tools for the system. When using Raman spectroscopy for monitoring peptide synthesis, the difficulty is the fluorescence background due to the protection group. Ryttersgaard et al. demonstrated monitoring of peptide synthesis by FT-Raman spectroscopy [10]. They utilized a Nd/YAG laser as the excitation source ($\lambda = 1064$ nm) to avoid the fluorescent emission from the sample. However, highly sensitive and high-throughput performance is remaining as the problems for Raman spectroscopy.

Recently, surface-enhanced Raman spectroscopy (SERS) is a potential candidate, and many researchers reported about the applications for detecting low level of samples [11, 12]. Han et al. studied rapid detection of dezocine in biological fluids using silver nanoparticles as the substrate of SERS [13]. Zhang et al. developed SERS coupled with dispersive solid-phase extraction [14]. Gao et al. reported highly sensitive detection of sulfate ion using SERS chip of silver nanoparticles [15]. The SERS chip enabled to improve the selectivity and sensitivity down to 10 nM. Subaihi et al. developed the system of liquid chromatography-SERS for the online quantification of methotrexate and its metabolites [16]. SERS technology provides not only high sensitivity but also high selectivity of a target compound. Thus, the substrates of a SERS chip have to be exclusively prepared for the target. In addition, it is considered have to be improve the lifetime of SERS substrates for the utilization of SERS as an in-line sensor.

NIR spectroscopy is another candidate for an in-line sensor of the continuous-flow peptide synthesis system. Mid-infrared (IR) spectroscopy usually required utilizing an ATR probe to collect in-line spectra caused by the high molar absorption coefficient. The remarkable feature of NIR spectroscopy is the lower molar absorption coefficient than IR spectroscopy. Due to the feature of NIR, transmittance NIR spectra can be collected in-line of a manufacturing process. Thus, absorbance of transmittance spectra can be controlled to be the adequate level by the optical path length, and transmittance spectra resulted in higher sensitive than ATR-IR spectra for the in-line sensor. Ishigaki et al. reported

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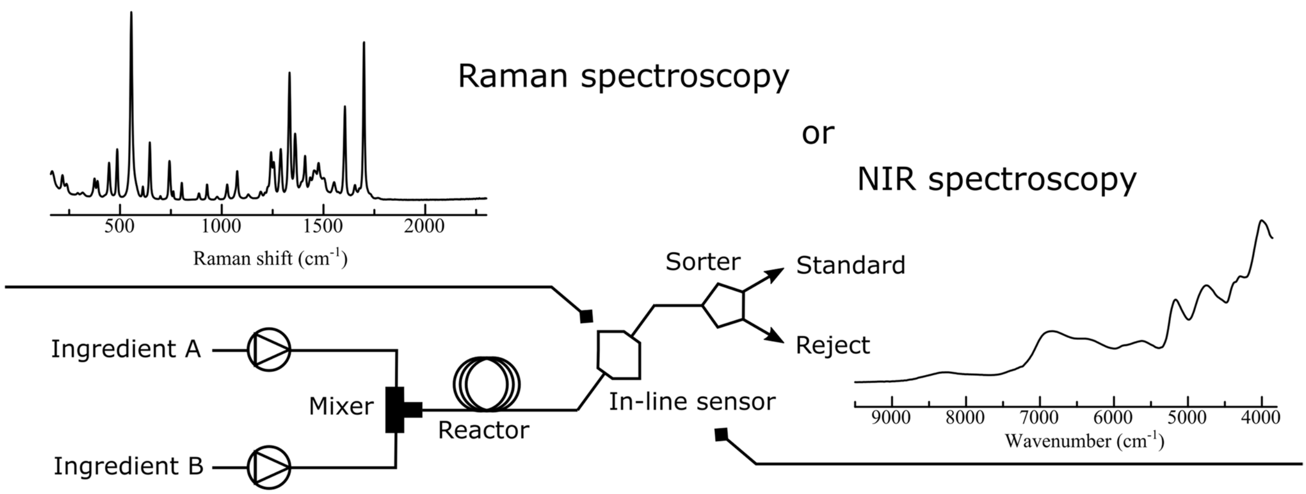
the quantitative evaluation of the number of amide bonds using NIR spectroscopy and partial least squares regression (PLSR) method [17]. The combination modes due to amide bonds are less represented in the NIR spectra; however, adequate processing of spectra such as derivations makes the bands of amide bonds clear. Determining the optimal wavenumber range for PLSR is also critical for quantification.

In other cases, Koga et al. reported the analysis results of rheo-optical NIR spectroscopic data of polymer films [18]. They applied two-trace two-dimensional correlation analysis for the rheo-optical NIR spectra. The result suggests the possibility for these techniques testing mechanical properties of polymer films. NIR spectroscopy can be applied to obtain spectral imaging [19]. In addition, a variety of NIR devices are developed [20]. When NIR spectroscopy is utilized as an in-line sensor, it is important to use an adequate device and proper analysis method for the target process.

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