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Process analytical applications of Raman spectroscopy

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Abstract

There is an increasing demand for new approaches to understand the chemical and physical phenomena that occur during pharmaceutical unit operations. Obtaining real-time information from processes opens new perspectives for safer and more efficient manufacture of pharmaceuticals. Raman spectroscopy provides a molecular level insight into processing, and therefore it is a future process analytical tool. In this review, different applications of Raman spectroscopy in the field of process analysis of pharmaceutical solid dosage forms are summarized. In addition, pitfalls associated with interfacing to the process environment and challenges within data management are discussed.

Introduction

Achieving relevant real-time information from multicomponent systems, such as pharmaceutical formulations, is not a straightforward task. Consider a typical solid dosage form with numerous sequential processing steps. There are many possible pitfalls during processing that may critically affect the final product performance. For example, during processing, an active pharmaceutical ingredient or excipient may be stressed in an environment that is aqueous or changing in temperature. Focusing analysis on the end product will not enable the early detection of problems or the complex relations between them. Recently, the US Food and Drug Administration (FDA) introduced guidance to address this issue. Process analytical technology (PAT) is a system for developing and implementing new efficient tools for use during pharmaceutical development, manufacturing and quality assurance while maintaining or improving the current level of product quality assurance. This guidance categorizes PAT tools into four groups: multivariate tools for design, data acquisition and analysis, process analysers, process control tools and continuous improvement and knowledge management tools. All this work aims to enhance and modernize the pharmaceutical manufacturing and quality control environment according to the Current Good Manufacturing Practices (CGMPs) for the 21st century. The principles of this framework are being incorporated into the ICH guidance on Pharmaceutical Development (Q8). Future challenge will be the implementation of the right process analytical approach into each specific situation.

Near infrared (NIR) spectroscopy is a well-recognized tool for modern process analysis (Reich 2005). In some cases, NIR has been used almost as a synonym for PAT. There is, however, a wide variety of other tools available for sophisticated analysis of pharmaceutical manufacturing environment. Raman spectroscopy opens a molecular level insight into processing, and therefore it offers a new way to understand unit operations. In the case of solid dosage forms, it provides fast non-invasive information from the material stream, even in an aqueous environment.

The basic principle in Raman spectroscopy is to irradiate a substance with monochromatic light and to detect the scattered light with a different frequency to the incident beam. The differences in the frequencies between the incident and scattered radiation result in characteristic Raman shifts. The Raman effect is inherently very weak, and in addition to an intense excitation source, good filters are needed to remove the excitation line from the collected radiation. Samples in the solid, liquid and gaseous states can be analysed with only minimal (or no) sample preparation. Utilization of this phenomenon has been relatively limited in the field of pharmaceutical processing due to the high price of instrumentation and difficulties in process interfacing. Recent developments in the fields of optoelectronics, computer technology, data transfer and data analysis have enabled the real-time and non-invasive Raman analysis of pharmaceutical unit operations and, by this means, a molecular level insight into processing. This will enable process understanding for scientific, risk-managed

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pharmaceutical development, manufacture and quality assurance in accordance with the PAT ideology. In this review, different applications of Raman spectroscopy in the field of process analysis of pharmaceutical solid dosage forms are summarized together with an introduction to challenges with interfacing into a process environment.

Raman spectroscopy within pharmaceutical unit operations

There is an increasing number of published studies on the utilization of Raman spectroscopy in the process environment. Other branches of the chemical industry have also evaluated the possibilities of Raman spectroscopy (e.g., in the polymer (Hergeth et al 2003), bioprocess (von Stockar et al 2003) and food (Mills et al 2005) industries). Vankeirsbilck et al (2002) have recently reviewed the use of Raman spectroscopy in the field of pharmaceutics, and a comparison of FT-Raman and dispersive instruments was made. A recent special issue in the Journal of Raman Spectroscopy introduced pharmaceutical applications of Raman spectroscopy (Fini 2004). Threlfall (1995) and Bugay (2001) have reviewed the use of spectroscopic tools for solid-state analysis, and in these reviews they relate Raman to the other solid-state analysis tools available. Issues relating quantitative analysis with Raman are described in a tutorial by Pelletier (2003). The published work has mainly focused on the solid-state analysis of small organic compounds, but Raman spectroscopy is also capable of analysing other types of dosage forms, namely liquids and disperse systems. Drug compounds in aqueous surroundings can be analysed, which facilitates the in-situ analysis of these systems. Raman is also a useful method for probing the relationship between structure, dynamics and function of biomacromolecules (Schmitt & Popp 2006). The increasing amount of biomacromolecular drugs creates a need for process control solutions in these challenging process environments.

The following sections summarize the possibilities of Raman spectroscopy in the process analysis of pharmaceutical unit operations related to solid dosage forms. The discussion begins with the synthesis phase and finishes with the film coating process. A flow chart of unit operations related to solid dosage forms, together with a summary of potential applications of Raman spectroscopy, is illustrated in Figure 1.

Synthesis

Svensson et al (1999) used Raman spectroscopy in combination with multivariate techniques for reaction monitoring. The synthesis and hydrolysis of ethyl acetate was investigated according to an experimental design. To avoid problems related to spectral overlapping, they recommend the use of effective preprocessing (standard normal variate and derivatives) together with principal component analysis (PCA) and

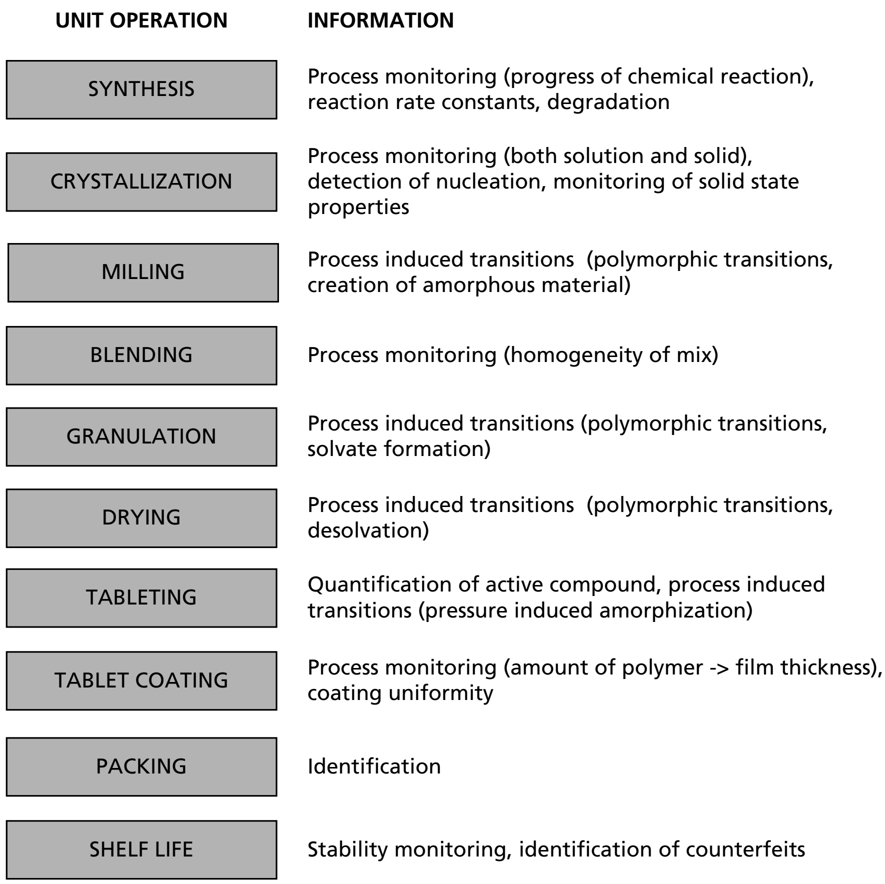

Figure 1 Flow chart of unit operations related to the manufacture of solid dosage forms with possible applications of Raman spectroscopy for process measurement.

partial least squares (PLS). Rate constants for a model system were achieved with good agreement with published values.

Crystallization

The subsequent processing step is crystallization. This critical unit operation is performed to produce material with desired purity, polymorphic composition, surface properties and particle size and shape distributions. It is crucial to have an in-depth process signature from the crystallization phase, because a failure in crystallization results in major difficulties in secondary manufacturing steps (mixing, granulation, tableting and coating). Crystallization is neither a well understood nor controlled unit operation. The recent case of ritonavir clearly underlines the need for new tools in the process analysis and control of crystallization and also in the implementation of polymorph screening (Bauer et al 2001). However, the amount of published work on real-time analysis of crystallization with pharmaceutics is relatively limited. Batch crystallizations of pharmaceutics are quite often performed in aqueous media, so Raman spectroscopy is an extremely useful tool for process control and monitoring purposes. Schwartz & Berglund (1999) monitored in-situ lysozyme concentration changes in hanging drop crystallization. Changes in polymorphic composition have been monitored and quantified with in-line Raman spectroscopy (Wang et al 2000; Starbuck et al 2002; Ferrari & Davey 2004; Ono et al 2004; Falcon & Berglund 2004; Hu et al 2005; Schöll et al 2006). Falcon & Berglund (2004) reported the use of Raman for real-time monitoring of phenomena related to antisolvent addition. Hu et al (2005) reported simultaneous monitoring of solution concentration and polymorphic outcome of the crystallization. Furthermore, solvent-mediated transformations of the model system were characterized. Raman spectroscopy can also be used to understand phase transition mechanisms (Boerrigter et al 2002; Tian et al 2005). Recently, Schöll et al (2006) reported simultaneous in-situ measurement of particle size distribution together with liquid and solid phase analysis. They analysed the liquid phase with attenuated reflection FTIR spectroscopy and the solid phase with Raman spectroscopy. This combination enabled the monitoring and modelling of fundamental phenomena governing the solvent-mediated transformation of a model compound. Raman spectroscopy can also be used to identify the mechanisms of co-crystal formation (Rodríguez-Hornedo et al 2006). These multiple component crystalline systems may show improved pharmaceutical properties compared with single component systems.

In the solid-state quantification of polymorphic form, Raman spectroscopy is an ideal candidate. Minimal sample preparation combined with sensitivity to polymorphism opens new perspectives for fast and reliable solid-state analysis (Deeley et al 1991; Langkilde et al 1997; Findlay & Bugay 1998; Campbell Roberts et al 2002; Al-Zoubi et al 2002; Auer et al 2003; Strachan et al 2004). Both univariate and multivariate methods have been used for development of quantitative models. In addition, the use of Raman spectroscopy for quantification of crystallinity has been reported (Taylor & Zografi 1998; Murphy et al 2005; Niemelä et al 2005; Nørgaard et al 2005). This may be especially useful in process monitoring of milling and spray drying, where the transitions related to crystallinity of material often occur. For inorganic materials, Raman spectroscopy has been utilized to identify solid-state transitions during milling (Štefani et al 2006). Recently, Raman has been combined with high-throughput (HTS) polymorph screening (Peterson et al 2002; Anderton 2004). There is an increasing demand for early screening of solid-state forms and also identification of the most stable form. After a case related to polymorphism of ritonavir, high-throughput crystallization experiments were carried out to explore the diversity of ritonavir solid-state forms (Morissette et al 2003).

In summary, Raman spectroscopy enables an in-depth analysis of the crystallization process and it also provides a route towards molecular level particle design. Furthermore, Raman spectroscopy can be utilized to monitor and model solid-state transformations occurring during the following unit operations. For control of solid-state phenomena within pharmaceutics, it is crucial to include crystallization as a critical unit operation in the overall development framework.

Mixing

One of the least understood unit operations within solid dosage forms is the mixing of powders. Vergote et al (2004) have reported the use of Raman spectroscopy for in-line monitoring of blending. Raman mapping in combination with near IR spectral mapping can be used to describe heterogeneous mixtures in more detail (Clarke et al 2001). Issues related to data acquisition and data processing of Raman chemical images have been recently discussed by Šašić et al (2004, 2005). Wikström et al (2005a) investigated the role of different sampling optics in the process analysis of solids. They also reported a multivariate model for monitoring powder mixing. Interpretation of loadings in a principal component space was presented on the basis of spectral features observed.

Granulation

Granulation is a unit operation needed for many products. In this process, material might undergo phase transformation after exposure to solvent, thermal stress or mechanical stress (Morris et al 2001). Possible phase transitions are polymorphic transformations, solvate formation, dehydration from solvate, production of amorphous regions and crystallization of amorphous material. The use of Raman for at-line (Jørgensen et al 2002) and in-line (Wikström et al 2005b) analysis of hydrate formation during wet granulation has been reported. Wikström et al (2005b) used the real-time information to verify a model for predicting the transformation kinetics of hydrate formation. Raman spectroscopy also opens an insight into water–solid interactions in the formulation and, furthermore, it can be used to understand the role of excipients in the early development phase. Taylor et al (2001) investigated the nature of water–polymer interactions for polymers of pharmaceutical interest. Airaksinen et al (2003) reported the use of Raman to detect hydrate formation in the presence of excipients and also the role of the excipients in the phase transformation. FT-Raman spectroscopy has been utilized in the evaluation of potential of carrageenans to protect drugs from polymorphic transformations (Schmidt et al 2003). They reported the detection of both recrystallization of the amorphous component and dehydration after the tableting process. Fechner et al (2003) utilized Raman spectroscopy in the extrusion–spheronization process environment and they explained the effect of water on the structure of cellulose during this unit operation. Wet granulation is followed by drying, in which the product is thermally stressed. In this context, Hausman et al (2005) investigated the use of Raman spectroscopy to detect solid-state changes during fluid bed drying. Raman spectroscopy can be further applied for explaining the mechanisms of thermally induced phase transitions (O'Brien et al 2004; Miroshnyk et al 2006).

Tableting

One of the most attractive possibilities of Raman spectroscopy, and other possible PAT sensors, is its use for real-time quantification of active compound in dosage forms. Moving into a situation where we can analyse, say, every tenth tablet during production, will open totally new perspectives for quality assurance and control. Widely-accepted definitions for real-time release and continuous manufacturing will be future challenges for pharmaceutical scientists. Raman has been used for quantification of components in antacid tablets (Kontoyannis 1995). Wang et al (1997) reported the use of Raman for direct assay of acetylsalicylic acid and, further, the analysis of the major degradation product, salicylic acid. Niemczyk et al (1998) utilized this technique for quantitative analysis of intact gel capsules and they reported also the analysis of capsules through blister packs. Vergote et al (2002) investigated the role of excipients in the quantification of diltiazem hydrochloride. Johansson & Folestad (2003) have recently discussed the use Raman spectroscopy for monitoring the tableting process. Another possible aspect to be considered is the use of Raman for fast analysis of possible processing induced transformation during tableting process and for fast verification of polymorphic form of a drug in final tablets (Taylor & Langkilde 2000; Auer et al 2003). Again, solid-state properties of both excipients and active pharmaceutical ingredients can be followed non-invasively. Recently, Okumura & Otsuka (2005) reported a quantitative Raman model for the crystallinity of indometacin in a model tablet formulation. They discussed also the possibility of further applying this model for identification and mapping of pressure-induced amorphization from tablet surfaces.

Coating

The subsequent unit operation in many cases is the coating process, which is usually performed using an aqueous polymer solution. Raman spectroscopy has been utilized in various other areas for analysis of film coatings, but not widely in the field of pharmaceutics. Ringqvist et al (2003) has reported the use of confocal Raman for analysis of the chemical composition in selected small areas of the coating surface. Romero-Torres et al (2005) utilized a Raman set-up with a revolving laser focus to analyse spectral features during the coating process and, further, to quantitatively characterize coating variations. The same group has developed a quantitative model for coating thickness and, further, evaluated the fluorescence-inducing role of colorants in the coating solutions to the model performance (Romero-Torres et al 2006).

Challenges in process analysis with Raman spectroscopy

There exist numerous pitfalls while applying Raman for process analysis. Figure 2 summarizes these challenges and the following discussion presents a few approaches to overcoming them.

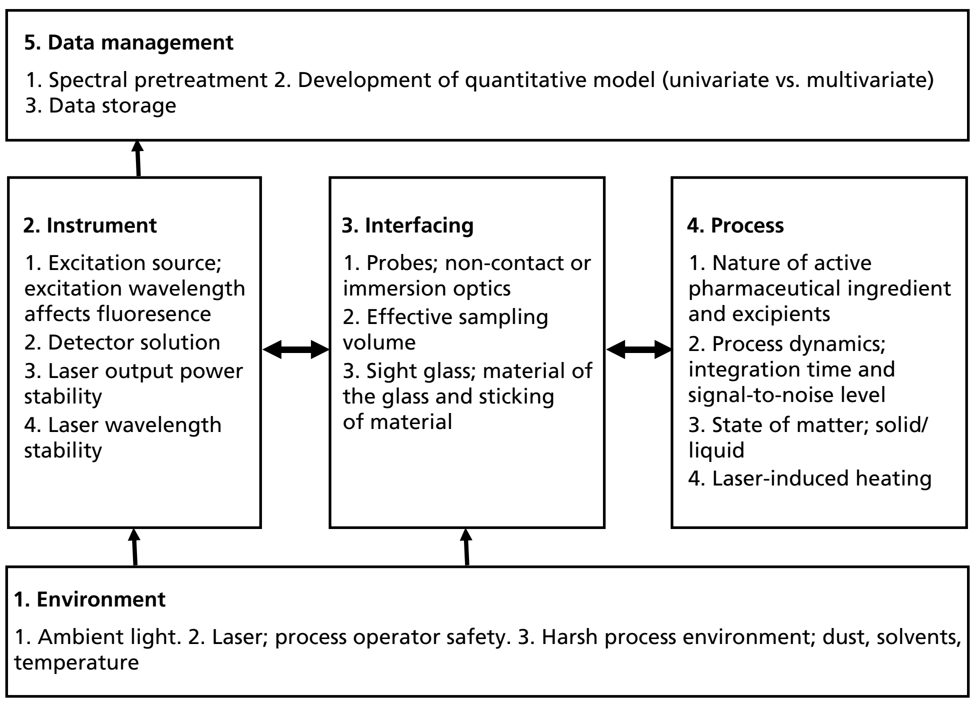

Figure 2 Factors affecting the interfacing of Raman spectroscopy to a model process environment.

First, interfacing with process results in problems due to process environment. We might expose the instrument to solvents, temperature variation or dust. A harsh process environment might also affect the laser source power stability and laser wavelength shifts. However, proper sealing and long optical fibres provide a solution for environmental stresses. Operator safety should also be considered while working with lasers. In addition, ambient light might cause some artifacts in the spectral information achieved. A fundamental question with process measurements with Raman is interfacing into process, as it is with all process analytical tools. Raman measurement can be performed invasively using immersion probe, or process monitoring can be performed non-invasively using non-contact optics. A basic problem is obviously to keep the sight glass or, in the case of immersion probe, the probe head, clean during measurements. Process interfacing is also related to two fundamental questions: are we measuring a representative part of the material and do we have the moving sample in focus. In some cases, it is useful to integrate the probe head into the sheath with sample withdrawal facility allowing static sample data collection. This has been reported previously for NIR application (Green et al 2005), but can also be easily modified for the Raman probe head. Static sample data collection should also be considered when process dynamics have a critical effect on the signal-to-noise ratio.

Another problem related to Raman is the small sampling area. The penetration depth of lasers used is relatively small, which results in a small effective sample volume. This can be altered with optics by increasing the area that is being measured (spot size of laser). Bell et al (2004) reported quantitative analysis of tablets with a special focus on possible experimental errors. By increasing the laser spot diameter and the amount of points measured from the tablet surface, they were able to find optimal measuring conditions with minimized prediction error. It is important to consider the original particle size of the components in a dosage form to optimize the experimental parameters. Wikström et al (2005a) and Johansson et al (2005) have also recently evaluated different sampling devices for in-line measurements. They evaluated the role of the laser spot size in granule and tablet samples, respectively. Wikström et al (2005a) reported measuring set-ups with laser spot sizes of 60, 150 and 3000 microns. In the crystallization environment, Schöll et al (2006) reported particle-size-related problems with quantitation of the polymorphic composition.

Sample heating is a widely recognized problem in Raman spectroscopy. Moving the sample being measured, which is the case in process analysis automatically, can minimize problems related to heating. Johansson et al (2002) investigated the sample heating of pharmaceutical materials and developed a model to predict the rotation speed needed to minimize the heating.

With some materials, a fluorescence background is observed. This can be decreased by selecting an appropriate excitation wavelength. Thorley et al (2006) have recently discussed the role of the wavelength selection on the well-described fluorescence phenomena with four model drug compounds and five excitation wavelengths at the UV, visible and NIR regions. In this study, fluorescence interference was a potential problem for the visible laser wavelengths, whereas with both UV and NIR excitation, lower fluorescence intensity was observed. However, UV excitation resulted in more degradation of samples and it was not as sensitive for identification of different polymorphic forms as visible and NIR excitation.

After a proper interfacing into the process has been performed, the most challenging part of the work is about to begin. One has to gain process understanding from the measured process information. The first step is to identify the variation in the spectral data and to explain the real source of this. Spectral pretreatment (e.g. derivatives) or internal standard is often needed to emphasize the variation and to facilitate both the band assignment and development of a quantitative model. Depending on the spectral features observed, a quantitative model can be developed as a univariate (e.g. peak ratios) or as a multivariate model (Pelletier 2003). Spectral features with Raman are typically well resolved, so univariate analysis provides a robust process model reasonably often (Rantanen et al 2005). There are several sources for experimental errors that should be evaluated when choosing multivariate modelling (Wolthuis et al 2006). Šašić et al (2004) compared univariate and multivariate modelling with Raman chemical images. They obtained better quality chemical images with a principal component (PCA)-based approach. Finally, all the monitoring applications mentioned above will result in a huge amount of data. Development of a sophisticated database solution is a crucial part of a robust process analytical solution.

Conclusions

Raman spectroscopy has matured into an effective tool for ensuring safe and efficient manufacturing of pharmaceutics. A lot has happened since Chandrasekhara Venkata Raman visited Europe in the summer of 1921 and got his first ideas related to this phenomenon while observing the blue opalescence of the Mediterranean Sea (Raman 1930). At present, we have instruments ready for non-invasive process measurements. Recent developments in the fields of optoelectronics, computer technology, data transfer and data analysis have enabled the real-time and non-invasive Raman analysis of pharmaceutical unit operations, and by this means, a molecular level insight into processing. More research is needed to understand the full potential of Raman as a process analytical tool.

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