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Research paper

Development of a multivariate light-induced fluorescence (LIF) PAT tool for in-line quantitative analysis of pharmaceutical granules in a V-blender

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ABSTRACT

Process analytical technologies (PAT) enable process insight, process control and real-time testing. Light-induced fluorescence (LIF) spectroscopy is especially well suited for low-concentration ingredients as, in many cases, it is the most sensitive probe of the in-line PAT toolbox. This study is aimed at verifying the applicability of a multivariate LIF analyzer to monitor granulated powder blends in industrial settings. Its targets are to: (1) evaluate the critical parameters of powders to obtain robust, precise and accurate concentration predictions and (2) assess technology performance for in-line monitoring of blending operations. Varying dye properties, moisture levels and particle sizes have been shown to have the most significant impact on fluorescence emission. Reliable quantitative models can be obtained by controlling and/or mitigating these factors.

1. Introduction

The pharmaceutical manufacturing industry is currently undergoing a transition period where product portfolio diversification, cost reduction and the need to increase production efficiency are major concerns, while regulations from regulatory authorities are constantly evolving. Process analytical technologies (PAT) are part of the solution as they enable process insight, process control and proactive manufacturing, key elements of quality by design (QbD).

New trends in innovative molecules are emerging. According to Transparency Market Research, highly-potent, active pharmaceutical ingredients (HPAPIs) are among those expected to achieve the largest progress with a compound annual growth rate of 9.9% [1]. HPAPIs hold the promise of low-dose drugs and, consequently, fewer adverse effects. Still, the manufacturing challenges are significant. Blend uniformity is one of the most frequent quality issues when dealing with low-dose formulations [2].

The manufacturing process is initially validated with fixed process variables, e.g. wet massing time, screen size, blending time, intensification bar use, blender filling level, compression speed (range), etc. If every sampling point throughout the entire process meets the required quality specifications, the process is fixed as is and, then, the products are properly tested in their final form only. Critical quality attributes (CQA) are therefore rarely tested during intermediary processing stages and are mostly controlled by respecting the approved manufacturing protocols without on-line analytical tools. Monitoring should result in higher process capability, greater first-time yield and lower re-work costs.

In real-time release initiatives, it is imperative to produce in-line technologies that offer a good combination of sensitivity, specificity and acquisition speed. Ultimately, with the proper PAT toolbox, manufacturing sites would meet different quality control needs, while significantly reducing time and costs related to traditional lab analyses.

Near infrared (NIR) spectroscopy, widely employed in the past decade as a PAT solution for solid dosage manufacturing operations, has demonstrated considerable benefits, especially for blend and tablet quality assessments, such as active pharmaceutical ingredient (API) assays or blend homogeneity [3–7]. Nevertheless, there is still a need to develop/improve in-line technologies

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capable of addressing NIR's lack of sensitivity for low-concentration ingredients. Light-induced fluorescence (LIF) spectroscopy is one of these potential complementary technologies, as it can reach low detection and quantitation limit for certain pharmaceutical molecules.

1.1. Fluorescence principles

LIF consists of exposing a product to a narrow-band, UltraViolet–Visible (UV–Vis) light source with a specific energy level and collecting the light re-emitted from excited electrons during the relaxation process. The energy of a quantum of light (E), or photon, is related to wavelength according to the Planck–Einstein equation:

$$E = \frac{hc}{\lambda} \quad (1)$$

where h is the Plank constant, c the speed of light and λ is the wavelength. The Perrin–Jablonski diagram illustrates radiative and radiation-less transitions between different electronic states (Fig. 1).

The absorption of a photon of proper energy by a molecule leads to the promotion of an electron to an excited state. Transition is only possible if the absorbed energy is equivalent to the difference between the excited singlet state (S_1') and the fundamental electronic state (S_0). This value is associated with what is called excitation wavelength. The excited state lasts for a few nanoseconds, during which partial relaxation occurs through vibrational relaxation. This culminates in the lowest vibrational level of the S_1 singlet state. Then, 3 different mechanisms [8,9] can arise. One of them, called 'quenching', is non-radiative, and the other 2 are radiative and, consequently, of high interest in LIF spectroscopy:

1. The excited molecule returns to ground state by fluorescence emission. Because S_1 is of lower energy than S_1', the photons emitted with radiative relaxation are of longer wavelength. The distance between the excitation and emission maxima is called Stoke's shift.
2. The incidence of intersystem crossing is characterized by conversion of the excited electron from the singlet excited state to the triplet excited state. The latter state is defined by inverse spin of the excited electron and a relatively long lifetime (μs). The triplet state is thus regarded as energy storage with a higher probability of undergoing excited-state reactions called photobleaching.

Photobleaching is a phenomenon still not well-understood. "One reason is that some of the relevant photophysical parameters determining the photobleaching process are not known, or could not be determined in enough detail. The quantum yield of triplet formation (...) belong[s] to this category of parameters. A second reason is that these parameters tend to be sensitive to the environment, which in some cases makes it difficult to compare different investigations and also makes it difficult to precisely predict the photophysical properties specific for a certain environment." [10] Still, it has been demonstrated that anti-oxidant additives prevent triplet state molecules from oxidation and, thus, considerably reduce photobleaching [11]. While adding such additives to pharmaceutical formulations is not an option, other solutions must be considered to mitigate the photobleaching effect. Many authors have evaluated the impact of excitation parameters on the magnitude of photobleaching [12–16]. The significant ones are incident excitation power, excitation wavelength, pulse duration and time allowed for relaxation.

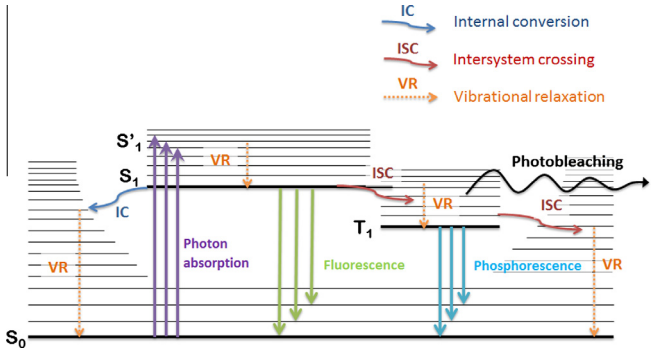

Fig. 1. Perrin–Jablonski diagram. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

1.2. LIF for powder monitoring

LIF has served the oil/petrochemical and medical sectors for many years [17–20]. However, it has not been widely exploited in the pharmaceutical industry, mainly because technologies adapted to solid-phase analysis are lacking. With increased interest in real-time, non-invasive and non-destructive analyses, new LIF systems emerged in the early 2000s. Lai et al. [21,22] worked with a filter-based univariate system. "The primary goal of [their] research is to develop a method to implement both process and product real time verification for blending of dry API with excipients" [21]. The results obtained show linearity of LIF signals with API concentration values ranging between 0 and 1 wt%. In cases tested, the API detection limit was found to be 0.1 wt%. In their second study, Lai et al. [22] evaluated an instrument version fitted with a flash lamp. They reported the potential of such a fast acquisition technique to monitor tablet surface concentration at a rate of up to 3000 tablets per minute. They also demonstrated the feasibility of this method to monitor tablet potency stability and spot segregation. Domike et al. [23] investigated tablet-monitoring capability with LIF and compared different sampling strategies (single or multiple acquisitions per tablet). Recently, Dickens et al. [12] described an in-line light emitting diodes (LED) array-based LIF sensor that carried the benefits of better control and versatility in terms of excitation parameters. They proved the suitability of such features to reduce noise due to small spot size measurements and, thus, increased both the sensitivity and limits of detection. They also showed the value of dynamic excitation control for photobleaching mitigation.

These studies have showcased, at least in some instances, the high potential of LIF probes to monitor low-concentration APIs in powder blends.

It appears that the combination of short-wavelength LEDs, and their use in novel spectroscopic probes, may prove useful in the development of accurate, precise, robust LIF sensors adapted for solid pharmaceutical products.

In previously-developed in-line LIF analyzers, one parameter has, so far, remained constant: univariate detection with a PMT (PhotoMultiplier Tube) detector. This single-channel detector typically offers high sensitivity by multiplying incident light (PMT gain) and by lowering noise (low, dark current). With a proper set of optical filters, it is possible to eliminate reflected excitation light and integrate fluorescence over a short range of wavelengths. In case multiple ingredients fluoresce in the same spectral region, this kind of detector would not offer enough specificity as integrated signals would convolute the contribution of each individual component. Even if it is not an issue for a given product, different components cannot be monitored simultaneously with a single, univariate set-up. Moreover, single fluorescence count output makes it very difficult to evaluate the impact of physicochemical parameters on the LIF response.