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# In-situ monitoring of pharmaceutical and specialty chemicals crystallization processes using endoscopy–stroboscopy and multivariate image analysis

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A B S T R A C T

This contribution presents the proof of concept of endoscopy–stroboscopy based in situ low-cost imaging of crystallization processes. This low-cost sensor currently is widely spread in the field of medical diagnosis of human vocal chords and this work presents its application in the context of pharmaceutical and chemical crystallization process monitoring. The model compounds used in this study are the active pharmaceutical ingredient (API) flufenamic acid and citric acid.

Since the acquired images are colored, the second aim of the paper is to evaluate the principal component (PCA) based multivariate image analysis (MIA) as a color to gray scale transformation method, and to compare it to the National Television System Committee (NTSC) standard, which uses fixed weights.

It was found that particle color, transparency, size and shape related information based on visual inspection is feasible using the endoscope–stroboscope system. The MIA results show that in the case of transparent particles the red, green, blue channels contribute equally to the total information content of color images. The acquisition price of the ATMOS endoscope is similar to that of a laboratory turbidity probe, feature which is relevant for the widespread use of this sensor.



*Keywords:* Process analytical technology; Imaging; Endoscopy; Pharmaceutical crystallization; Polymorphic transformation; Multivariate image analysis; Flufenamic acid; Citric acid

## 1. Introduction

Since the 2004 Food and Drug Administration (FDA) initiative the evaluation of in situ process analytical sensors (PAT) that focus on crystallization process monitoring and control has been significantly intensified (Nagy et al., 2008). The integration of several PAT sensors in the control loops is implemented using model free (Nagy et al., 2011; Abu Bakar et al., 2009, 2010) and model-based strategies (Nagy, 2009). In the class of PAT tools relevant for the monitoring of crystallization processes belong the spectroscopy methods, which monitor the liquid concentration; an exception is the FT-Raman spectroscopy, which is also capable to deliver information related to the crystal structure of the solids, thus to the polymorphic forms (Hu et al., 2005). The second class of PAT sensors is represented by those which monitor the solid phase. From complexity point of view the entry level representative is the turbidity probe, which gives reflective property related solid concentration information (Harner et al., 2009). More complex sensors are laser reflectance based and provide chord length information related to the crystal size in slurries, e.g. the focused beam reflectance FBRM (Kee et al., 2011) and the 3D ORM (Heinrich et al., 2011).

The in situ imaging sensors used for crystallization process monitoring have received significant attention in the last decade. An early attempt to capture the crystal characteristics during operation used a flow-through cell placed below a microscope (Matthews and Rawlings, 1998). Imaging sensor development activities have been reported by companies such as DuPont, USA (Scott et al., 2001), Lasentec/Mettler Toledo,

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