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In-line non-invasive turbidimetry as a tool to ensure content uniformity in the betamethasone filling process

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ABSTRACT

The filling process of liquid suspensions is a difficult operation,mainly due to drug settling. Small variations during the process may lead to serious deviations in the API content uniformity of the finished product, particularly if the drug settles fast. Real-time non-invasive monitoring of liquid suspensions is a useful approach to ensure an acceptable API content in the finished product. The aim of this study was to develop a method based on non-invasive turbidity measurements for in-line determinations of betamethasone content uniformity during the filling process of injections. Owing to the constructive features of the developed system, the determinations were performed in a non-destructive and non-invasive way, thus allowing the analysis of the whole batch and minimizing the risk of contaminating the product. The results obtained by the method proposed in this study demonstrated that non-invasive turbidimetry is a powerful tool for continuous monitoring of the filling process of betamethasone injections, within the Quality by Design framework (FDA, 2009).

1. Introduction

The recent promotion of the Quality by Design (QbD) approach by the FDA (2006, 2009a,b) has increased the interest of the pharmaceutical industry in ensuring the product quality through a systematic evaluation, understanding and improvement of the manufacturing process. In order to ensure that quality is built-in the products, the new approach takes advantage of the most up-to-date technologies and tools of measurement and analysis (e.g., risk assessment, design of experiments). Among these tools, the process analytical technologies focused on in-line process measurements have received a growing attention in the last few years, as it can be appreciated in several published works (Berntsson et al., 2002; Betz et al., 2003; Frake et al., 1997; Rantanen et al., 1998). These in-line measurements allow not only an improvement of process control from decisions based on real time data, but also an expansion of the knowledge and understanding of the manufacturing process from the analysis of the relationship between the process parameters and the critical quality attributes (CQA) of the product. As a consequence, several recently published works are devoted to apply in-line measurements to pharmaceutical processes (Barresi et al., 2009; Betz et al., 2004; Briens et al., 2007; De Beer et al., 2008, 2009; Knop and Kleinebudde, 2013; Hansuld et al., 2011; Moes et al., 2008; Pérez-Ramos et al., 2005; Velardiet al., 2009; Wirges et al., 2013). Nevertheless, the development and integration of innovative technologies into existing or new equipment is a difficult task because of the inherent complexity of pharmaceutical unit operations. Technologies based on the interaction between matter and electromagnetic radiation, like near infrared spectroscopy (NIRS) (Betz et al., 2004; De Beer et al., 2009; Knop and Kleinebudde, 2013; Moes et al., 2008; Pérez-Ramos et al., 2005) and Raman spectroscopy (De Beer et al., 2008, 2009; Knop and Kleinebudde, 2013; Wirges et al., 2013), are among the most frequently incorporated technologies into the pharmaceutical processes because of particular features that facilitate their integration. One of these features is the capacity of performing fast, non-invasive and non-destructive quantitative determinations, with minimal or no sample preparation. Another technique that has these characteristics and, therefore, represents a potential tool for solutions within the QbD approach (FDA, 2006, 2009a,b), is turbidimetry. Although it is often applied to crystallization processes (Brienza et al., 1995; Dorozhkina and Dorozhkin, 2002; He and Ackerson, 1997) turbidimetry has received less

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attention than other techniques with similar features. The filling process of betamethasone injections opened up a good opportunity to assess and apply this technology.

Betamethasone (BTM) is a powerful glucocorticoid used in the treatment of diverse allergic and inflammatory pathologies. Several works have been devoted to this drug owing to its properties and applications (Frears et al., 1975; Pershing et al., 1992; Schwab et al., 2001; Wang et al., 2002). Among its derivatives, BTM is available as sodium phosphate (BTM-SP), dipropionate (BTM-D), and acetate (BTM-A), in different dosage forms, e.g., tablets, drops, creams, and liquid for intramuscular, intra-articular, intrabursal or intradermal injections (not for intravenous administration). In this last form, the soluble (BTM-SP) and insoluble derivatives (BTM-D and BTM-A) can be used and combined according to the desired therapeutic effect: soluble derivatives for fast effect, and insoluble derivatives for depot effect. Unlike the BTM-SP derivative, BTM-D and BTM-A are practically insoluble in water, thus forming in this medium a white suspension that settles quickly.

The filling process of BTM suspension into vials is depicted in a recent work of Díaz et al. (2011). During this process, the suspension is delivered from a stirred tank. Owing to the features of the water-insoluble BTM floccules (e.g., speed of sedimentation, particle density, particle size), the stirrer speed is a critical process parameter (CPP). While a too low stirring speed results in an accumulation of BTM in the bottom of the tank because of settling, a too high stirring speed produces an increment in the concentration of BTM near the walls of the tank due to centrifugal forces. Moreover, if the tank stirrer comes to stop, even for a short period of time, the concentration of BTM in some vials might reach unacceptable values, and these values might not be detected in a classic quality control because of its statistical nature. Therefore, an inadequate stirring may lead to an inhomogeneous distribution of BTM in the vials that adversely affects the quality of the finished product.

Owing to the aforementioned difficulties associated with the filling process of BTM, and the high risk of producing poor quality drug products, a risk assessment was performed in a previous study (Díaz et al., 2011). In that study, different strategies were analyzed to reduce the risk of deviations in the CPPs (e.g., stirrer speed, peristaltic pump speed) that adversely affect the product CQAs (mainly, the content uniformity). A reduction in the frequency of occurrence or an increment in the detectability of the deviations in the CPPs, were among the considered strategies. Nevertheless, instead of applying these strategies, a new CPP directly related to the BTM content was devised:the suspension turbidity. As turbidity is directly related to the BTM concentration, a continuous real time measurement of this CPP would not only mitigate the risk by increasing detectability, as was previously stated (Díaz et al., 2011), but also would improve the knowledge about the filling process and its different parameters, such as the stirring speed. The aim of this work is, therefore, the development and assessment of a method capable of performing in-line and non-invasive continuous measurements of the suspension turbidity, in order to ensure content uniformity in the filling process of BTM injections.The method presented in this study is based on non-invasive turbidimetry (NIT) measurements near the filler nozzle. As it is shown in the following sections, several experiments were generated to verify the suitability of the method. The results obtained during these experiments showed a significant correlation with the reference off-line method (HPLC). Even though a thorough analysis of the filling process within the QbD framework is out of the scope of this work, different process conditions, and their influence, were also studied.

2. Materials and methods

2.1. Samples

Tests and calibrations were carried out with different generated samples, including:

- Particle size distribution: 5 mL-vial with aqueous suspensions containing a mixture of BTM-SP and BTM-A (quantity: 1 vial).
- Process analysis: 2 mL-vials with aqueous suspensions containing a mixture of BTM-SP and BTM-D (quantity: 56 vials).
- Calibration set 1: aqueous suspensions containing BTM-SP and BTM-A (quantity: five suspensions with different concentration, ranging from 93% to 155% of the label claim).
- Validation set 1: aqueous suspensions containing BTM-SP and BTM-A (quantity: 13 suspensions with different concentrations ranging from 77% to 136% of the label claim).
- Calibration set 2: aqueous suspensions containing BTM-SP and BTM-D (quantity: five suspensions with different concentration ranging from ca. 80% to 148% of the label claim).
- Validation set 2: aqueous suspensions containing BTM-SP and BTM-D (quantity: 16 suspensions with different concentrations ranging from ca. 80% to 121% of the label claim).
- Inline model validation set: aqueous suspensions containing BTM-SP and BTM-A, and aqueous suspensions containing

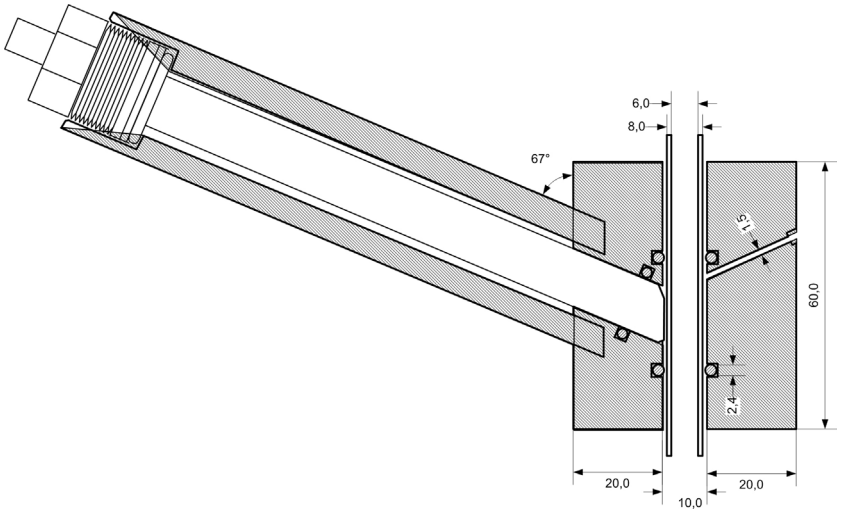

Fig. 1. Version 1 (prototype) of measurement chamber.