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Use of in-die powder densification parameters in the implementation of process analytical technologies for tablet production on industrial scale

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ABSTRACT

The use of process analytical technologies (PAT) to ensure final product quality is by now a well established practice in pharmaceutical industry. To date, most of the efforts in this field have focused on development of analytical methods using spectroscopic techniques (i.e., NIR, Raman, etc.). This work evaluated the possibility of using the parameters derived from the processing of in-line raw compaction data (the forces and displacement of the punches) as a PAT tool for controlling the tableting process. To reach this goal, two commercially available formulations were used, changing the quantitative composition and compressing them on a fully instrumented rotary pressing machine. The Heckel yield pressure and the compaction energies, together with the tablets hardness and compaction pressure, were selected and evaluated as discriminating parameters in all the prepared formulations.

The apparent yield pressure, as shown in the obtained results, has the necessary sensitivity to be effectively included in a PAT strategy to monitor the tableting process. Additional investigations were performed to understand the criticalities and the mechanisms beyond this performing parameter and the associated implications.

Specifically, it was discovered that the efficiency of the apparent yield pressure depends on the nominal drug title, the drug densification mechanism and the error in pycnometric density.

In this study, the potential of using some parameters derived from the compaction raw data has been demonstrated to be an attractive alternative and complementary method to the well established spectroscopic techniques to monitor and control the tableting process. The compaction data monitoring method is also easy to set up and very cost effective.

1. Introduction

The term “process analytical technologies (PAT)” describes a system for designing and controlling manufacturing through timely measurements (during processing) of critical quality and performance attributes of raw and in-process materials, as well as of processes, with the goal of ensuring final product quality. Thus, PAT focuses on building quality into the product and manufacturing processes. In fact, Quality by Design (QbD) is an established concept in the pharmaceutical industry. Even before the introduction of the Common Technical Document (CTD), the regulatory systems required information on the pharmaceutical development of the medicinal products. For this reason, during the last decade many studies have been devoted to analytical technologies for improving product quality through control of the manufacturing process, in accordance with the fundamental principle that quality cannot be tested into products, but instead should be built-in or should be designed with the production process. In most cases, spectroscopic techniques, including Raman spectroscopy, UV–vis spectroscopy, nuclear magnetic resonance (NMR), and especially near infrared spectroscopy (NIR) have been proposed for monitoring the process (Bakeev, 2010). Examples of the application of such techniques on pharmaceutical process include reaction monitoring (Cue et al., 2009; Streefland et al., 2013), crystallization (Schaefer et al., 2013; Yu et al., 2004), powder blending (De Beer et al., 2008; El-Hagrasy et al., 2006a,b;

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El-Hagrasy and Drennen Iii, 2006), hot-melt extrusion (Saerens et al., 2011; Saerens et al., 2012), granulation (Burggraeve et al., 2013; Fonteyne et al., 2013), compression (Blanco and Alcalá, 2006; Blanco et al., 2006; Shah et al., 2007; Sulub et al., 2008), coating (Knop and Kleinebudde, 2013; Ozawa et al., 2013; Wirges et al., 2013), cleaning validation (Hellings and Vanbaelen, 2008), and freeze-drying (De Beer et al., 2007; Patel et al., 2010). A detailed description of the use of spectroscopic techniques in pharmaceutical PAT can be found in the literature (Bakeev, 2010).

Among these processes, compression is particularly challenging in term of PAT due to the difficulty in establishing sensible methods for monitoring the production of tablets.

Currently, the production of tablets is monitored by continuous recording of the compression force and by measuring tablet hardness and weight. Although these methods are time-tested and useful, they present some limits, as for instance in detecting variations in the composition of the powder mixture.

Most of the efforts to develop analytical methods capable to monitor tablet on-line quality concern the use of Raman and, especially, NIR spectroscopy. Although the NIR-based methods performed quite well for PAT purposes on tablet production, they also present some drawbacks. Particularly, the spectra interpretation are not straightforward, as the signals recorded depend not only on the concentration of the active ingredient, but also on excipients, when these absorb in the NIR region (1100–2500 nm) (Ozawa et al., 2013), and on the compaction pressure (Blanco et al., 2006). Moreover, these parameters change during tablet production when demixing of the powder blend occurs. In fact, due to the different tabletability of the different materials, a change in the blend composition will also be accompanied by a change of compaction pressure. To overcome this drawback it is necessary to apply chemometric methods, a particularly time-consuming and costly approach because these require a robust calibration curve through the manufacturing, testing several series of tablets at different operative conditions to validate the method.

So far, compression pressure is the only available in-line (sample is not removed from the process stream) parameter able to give information about tablets production in real time and while the tablet is processed and formed in the die cavity. Unfortunately, this parameter is not very sensitive to changes in the composition of the powder mixture unless they are significant. Development of more appropriate and sensitive in-line methods, capable to immediately reveal any demixing of the powder blend, could be very advantageous.

Compaction analysis makes use of several measuring devices to monitor process parameters in tablet machines before, during, and after the compaction event. The ability to screen the complete process in term of force and punch penetration, obtaining and recording real-time data, makes it possible to carry out several kinds of analyses to identify the mechanisms whereby a particulate mass is turned into a tablet (Ridgway Watt and Armstrong, 2008). The compaction analysis approach, using force–displacement (or porosity) data, could be very effective for PAT implementation in tablet production. In fact, the mechanical properties of the powder mixture depend mainly on the composition of the mixture itself and on the porosity of the powder bed. Thus, parameters derived from compaction could be very sensitive to the variation of powder composition and compression pressure even when they occur at the same time. As a matter of fact, with the exception of inconstant and inaccurate die filling, variation of the powder composition (such as in de-mixing during compression) and compression pressure are very often linked.

The goal of this work was to assess the sensitivity of some methodologies for investigating the densification mechanism, especially those based on force–displacement data, such as Heckel and energy analysis, in view of their potential use as PAT tool for tablet production.

To this end, the authors selected two commercial formulations, the first containing a high strength of drug substance and the second containing two drug substances in very different amounts. The two original formulations were then changed by varying the percentage of the active ingredients. All the blends were finally compressed in a rotary tablet machine equipped to monitor compression force and punch displacement. The hardness of the tablets, the yield pressure (Py) derived from Heckel analysis, the plastic and elastic energies derived from energy analysis and the compaction pressure were recovered, and their ability to discriminate between different powder compositions was evaluated and the statistical significance assessed.

2. Materials and methods

2.1. Materials

Powdered Cellulose (PC) (Vitacel, JRS Pharma GmbH & Co., Rosenberg, German), microcrystalline cellulose (MCC) (Avicel PH-102, FMC BioPolymer, Brussels, Belgium), maize starch (MaS) (Acef, Fiorenzuola D'Arda, Italy), pregelatinized starch (PreS), starch 1500 (Colorcon, Dartford England), sodium starch glycolate (EXP) (Explotab, JRS Pharma GmbH & Co., Rosenberg, Germany), polyvinylpyrrolidone (PVP) (Kollidon K30, Basf SE, Ludwigshafen, Germany), and magnesium stearate (MgSt) (Acef, Fiorenzuola D'Arda, Italy) were all used as received.

Powdered acetaminophen (Acet), tramadol hydrochloride (TraHCl), and roller compacted ibuprofen lysine salt (IbuLys) were provided by Janssen–Cilag SpA (Borgo San Michele, Italy).

2.2. Methods

2.2.1. Formulations

The work was performed selecting as model formulations two commercially available compositions, named formulations A and B, respectively.

Formulation A contained IbuLys as active compound in a percentage of 86.07% and PVP, MCC, and MgSt as excipients. A series of variations on formulation A was prepared with varying amounts of IbuLys ranging from 50 to 115% of the commercially available amount. Any increase or reduction of the drug title was accompanied by a concomitant reduction or increase of the other ingredients in proportion to their initial amount, except for the lubricant, kept constant at 0.6% as in the reference formulation A. The maximum achievable concentration of drug substance in the formulation A was 115%, corresponding to a mixture containing only active ingredient and lubricant. Table 1 reports the composition of all the formulations tested, being 100% the commercially available one.

Table 1
Composition of all the formulations A prepared. The formulation with a drug title equal to 100% is the original formulation.

Formulation	Ibulys title (%)	Composition (%)			
		IbuLys	PVP	MCC	MgSt
A-115	115	99.4	–	–	0.6
A-105	105	90.4	2.8	6.2	0.6
A-100	100	86.1	4.3	9.1	0.6
A-95	95	81.8	5.6	12.0	0.6
A-90	90	77.4	7.2	14.8	0.6
A-75	75	64.6	11.4	23.4	0.6
A-50	50	43.0	18.6	37.8	0.6