International Journal of Pharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Optimization of a pharmaceutical tablet formulation based on a design space approach and using vibrational spectroscopy as PAT tool

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ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form 10 March 2015
Accepted 13 March 2015
Available online xxx

Keywords:
Design space
Quality by design
Process analytical technology
Vibrational spectroscopy
Optimization
Pharmaceutical tablet formulation

ABSTRACT

The aim of the present study was to optimize a tablet formulation using a quality by design approach. The selected methodology was based on the variation of the filler grade, taking into account the particle size distribution (PSD) of active pharmaceutical ingredient (API) in order to improve five critical quality attributes (CQAs). Thus, a mixture design of experiments (DoE) was performed at pilot scale. The blending step was monitored using near infrared (NIR) spectroscopy as process analytical technology tool enabling real-time qualitative process monitoring. Furthermore, some tablets were analyzed by Raman imaging to evaluate the API distribution within the samples. Based on the DoE results, design spaces were computed using a risk-based Bayesian predictive approach to provide for each point of the experimental domain the expected probability to get the five CQAs jointly within the specifications in the future. Finally, the optimal conditions of the identified design space were successfully validated. In conclusion, a design space approach supported by NIR and Raman spectroscopy was able to define a blend that complies with the target product profile with a quantified guarantee or risk.

1. Introduction

In the last few years, the pharmaceutical industries were encouraged by authorities to enhance knowledge and understanding of their products and manufacturing processes. In order to help industries in this task, the International Conference on Harmonization (ICH) has published several guidelines, as the ICH Q8 guideline on pharmaceutical development, which insists on the concept of Quality by design (QbD). In this guideline, QbD is described as a science- and risk-based approach for which the quality should not be tested into products but should be built in by design. Moreover, this QbD approach contributes to a continuous improvement of the product quality by a systematic assessment, understanding and refining of the formulation and processes throughout the product lifecycle (ICH, 2008, 2009). ICH Q8 also defines the design space as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." (ICH, 2009). It is also mentioned that modifying the operating conditions while staying within the limits of the design space is not considered as a change and does not require a regulatory post approval change. Q2

Process analytical technology (PAT) is described by the Food and Drug Administration (FDA) as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." (FDA, 2004). Consequently, PAT fits thoroughly with the QbD concept.

Near infrared (NIR) spectroscopy is an analytical method that allows acquiring real-time data from manufacturing process without sample preparation or alteration using probes enabling

Abbreviations: AA, average assay; API, active pharmaceutical ingredient; AV, acceptance value; CI, Carr index; CMA, critical material attribute; CQA, critical quality attribute; CU, content uniformity; DHI, distributional homogeneity index; DoE, design of experiments; HR, Hausner ratio; ICH, International Conference on Harmonization; NIR, near infrared; PAT, process analytical technology; PC, principal component; PCA, principal component analysis; PSD, particle size distribution; QbD, quality by design; RSD, relative standard deviation; TPP, target product profile.

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http://dx.doi.org/10.1016/j.ijpharm.2015.03.025
0378-5173/

in-line measurements (Luypaert et al., 2007). Taking into account its advantages, NIR spectroscopy is a significant tool for the implementation of PAT and has already been described for various applications such as blend homogeneity and coating monitoring or moisture and active content determination (Blanco et al., 2008; Bodson et al., 2007; Grohganz et al., 2010; Krier et al., 2013; Mantanus et al., 2011, 2010; Moes et al., 2008). When considering a tablet manufacturing process, one of the more critical steps is the mixing of the raw materials that should lead to a homogeneous powder blend. Thus, the in-line monitoring of the blending kinetic, using NIR as suitable tool, allows ensuring the quality of the final powder blend.

Based on Raman spectroscopy, Raman imaging is an hyperspectral technique providing spectral and spatial information, simultaneously (Gendrin et al., 2008; Sacré et al., 2014b). Therefore, it can be used to obtain distribution maps of compounds of interest (Krier et al., 2013; Mantanus et al., 2011). In this study, the distributional homogeneity index (DHI) developed by Sacré et al. (2014a) has been applied to assess the distributional homogeneity of the active pharmaceutical ingredient (API) in tablets without calibration model.

The aim of the present study was to optimize the formulation of a pharmaceutical tablet form which was already manufactured at production scale. Indeed, this tablet has exhibited a high content variation (measured by API content uniformity) with a mean acceptance value (AV) above 10 and an average API assay of 97.8%, biased below the target value of 100%. Thus, it was essential to improve average assay, individual batch Relative standard deviation (RSD) for content uniformity (CU) and AV. In order to stay as close as possible to the current approved registration file, the proposed methodology was based upon the variation of the filler grade, taking into account API particle size distribution (PSD), using a mixture design of experiments (DoE) and a design space approach. Based on the DoE results, design spaces were computed using a risk-based Bayesian predictive approach to provide for each point of the experimental domain the expected probability to get the responses jointly within the specifications in the future runs. This Bayesian predictive approach enables taking into account uncertainties and interactions of the model and is therefore an efficient tool for ensuring the quality as required by ICH Q8 (Castagnoli et al., 2010; Lebrun et al., 2012; Peterson, 2008). As a result, within the framework of a formulation optimization, determining the type and quantity of excipients using a design space approach is fully compliant with the QbD concept.

2. Material and methods

2.1. Tablet formulation

The studied formulation was a powder blend of API and excipients for direct compression with a final API concentration of 7.14% (w/w). The main excipient was a filler that was present in the blend at a final concentration of 61.8% (w/w). The remaining excipients had various functions as binding agent to improve the compatibility of the blend, disintegrant, lubricant and glidant. For confidentiality reasons, no more qualitative or quantitative information about the formulation can be disclosed.

2.2. Particle size distribution measurements

PSD measurements of API batches were achieved by laser diffraction using a Mastersizer 2000 particle size analyzer (Malvern Instruments, Malvern, UK) equipped with a Scirocco 2000 dry powder dispersion unit (Malvern Instruments). Measurements were realized in triplicates with a dispersion air pressure of 2 bar.

2.3. Tablets manufacturing

Tablets were manufactured at pilot scale with a batch size of 7 kg corresponding to 1/10 of the production scale and following the same current instructions of fabrication.

The blending process was carried out using a planetary mixer Collette MP20 (GEA Pharma Systems-Collette, Wommelgem, Belgium) and was split into three successive steps. First, the pre-blend was mixed in a 6 L bowl during 15 min afterwards it was mixed with the rest of excipients in a 20 L bowl during 20 min. Finally, the lubricant was added and mixed during 4 min. The mixing speed was set to 69 rpm for all the blending steps.

Next, the powder blends were directly compressed using a rotary tablet press R090-F (GEA Pharma Systems-Courtoy, Halle, Belgium) equipped with 18 round punches of 6 mm of diameter and performing a pre-compression before the final compression. The target weight and hardness of tablets were 70 mg and 40 N, respectively. The production output was set to 650 tablets per minute and about 84,000 tablets were produced per batch.

2.4. Flowability assessment

The flowability assessment of powder was carried out using the tapped density test of the European Pharmacopoeia 2.9.34 to obtain the bulk and the tapped densities (Europe, 2012a). This test was carried out with 100 g samples of each final powder blend introduced in a 250 mL graduated cylinder placed in a tapped density device Stampfvolumeter (JEL, Ludwigshafen, Germany).

2.5. PAT tools

2.5.1. FT-NIR equipment

The blending processes were monitored with a Multi Purpose Analyzer Fourier Transform near infrared spectrometer (Bruker Optics, Ettlingen, Germany) equipped with a thermoelectrically cooled semiconductor Indium Gallium Arsenide (TE-InGaAs) detector.

The spectra were collected with a NIR reflectance probe for solids (Bruker Optics) non-invasively interfaced with the blending bowl. Each spectrum was the average of 4 scans and the resolution was set at 16 cm^{-1} over the range from 12,500 to 4000 cm^{-1}. The time required for a NIR measurement was 1.7 s and time interval between two measures was 1 s. The spectra were collected with the Opus 6.5 software (Bruker Optics).

2.5.2. Raman equipment

Raman maps were collected with a dispersive Raman spectrometer RamanStation 400 F (PerkinElmer, Waltham, MA, USA) equipped with a two-dimensional CCD detector (1024 × 256 pixel sensor). The laser excitation wavelength used was 785 nm with a power of 100 mW.

An area of 16 mm^2 corresponding to the largest square possible was analyzed per tablet with a step size of 100 μm and a map size of 40 × 40 pixels. Each measure consisted of 1 scan with an exposure time of 1 s and a resolution of 2 cm^{-1} over the spectral range from 90 to 1622 cm^{-1}. Background measure was repeated each 20 min during mapping. Spectra were collected with Spectrum 6.3.2.0151 software (PerkinElmer).

Before analyzing, tablets were prepared to obtain a flat surface with a Leica EM Rapid milling system equipped with a tungsten carbide miller (Leica Microsystems GmbH, Wetzlar, Germany).

2.5.3. Multivariate data treatment

NIR spectra were preprocessed using a standard normal variate and a mean centering over the spectral range from 9056 to 4312 cm^{-1} before being analyzed by principal component analysis (PCA).

Please cite this article in press as: Chavez, P.-F., et al., Optimization of a pharmaceutical tablet formulation based on a design space approach and using vibrational spectroscopy as PAT tool. Int J Pharmaceut (2015), http://dx.doi.org/10.1016/j.ijpharm.2015.03.025