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Influence of *in line* monitored fluid bed granulation process parameters on the stability of Ethinylestradiol

Katrin Roßteuscher-Carl[a,b], Sabine Fricke[a], Michael C. Hacker[b], Michaela Schulz-Siegmund[b,*]

[a] Jenapharm GmbH & Co. KG, Otto-Schott-Str. 15, 07745 Jena, Germany
[b] University of Leipzig, Pharmaceutical Technology, Institute of Pharmacy, Eilenburger Str. 15A, 04317 Leipzig, Germany

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ABSTRACT

Ethinylestradiol (EE) as a highly active and low dosed compound is prone to oxidative degradation. The stability of the drug substance is therefore a critical parameter that has to be considered during drug formulation. Beside the stability of the drug substance, granule particle size and moisture are critical quality attributes (CQA) of the fluid bed granulation process which influence the tableting ability of the resulting granules. Both CQA should therefore be monitored during the production process by process analytic technology (PAT) according to ICH Q8.

This work focusses on the effects of drying conditions on the stability of EE in a fluid-bed granulation process. We quantified EE degradation products 6-alpha-hydroxy-EE, 6-beta-hydroxy-EE, 9(11)-dehydro-EE and 6-oxo-EE during long time storage and accelerated conditions. PAT-tools that monitor granule particle size (Spatial filtering technology) and granule moisture (Microwave resonance technology) were applied and compared with off-line methods. We found a relevant influence of residual granule moisture and thermic stress applied during granulation on the storage stability of EE, whereas no degradation was found immediately after processing. Hence we conclude that drying parameters have a relevant influence on long term EE stability.

1. Introduction

Ethinylestradiol (EE) is the most commonly used estrogene substance in hormonal oral contraceptives (Ebel et al., 2012). Homogenous drug distribution and stability in the formulation must be in focus during development of formulations containing the highly active and low dosed compound. EE is prone to oxidative degradation, which is accelerated with temperature (Cotter et al., 1978) or by photocatalysis (Sedee and van Henegouwen, 1985). Autocatalysis activated by the phenyl-ring is assumed as mechanism for the oxidative degradation (Kern and Willersinn, 1955; Ph. Eur., 2001) leading to the main-degradation products 6-alpha-hydroxy-EE, 6-beta-hdroxy-EE, 9(11)-dehydro(DH)-EE, and 6-oxo-EE (Cotter et al., 1978; Li et al., 2008; Segmuller et al., 2000) (Fig. 1). To date, published data on EE stability mainly addressed environmental questions, i.e. removal from wastewater, whereas little data is available on the stability of EE in pharmaceuticals.

The most frequently used dosage forms for application of oral contraceptives are film-coated and sugar-coated tablets. Fluid-bed granulation is an important process-step in the manufacture of such dosage forms. During fluid bed granulation, EE is exposed to high temperature as well as increased humidity, both of which accelerate API degradation in general (Carstensen, 1988; Waterman et al., 2002). Particle size and humidity in the granules are critical quality attributes for the subsequent processing of the granules and drug stability. Particle size of the resulting granules is another crucial parameter influencing flow rate, blend uniformity as well as tablet properties like crushing strength, average mass, friability and dissolution (Faure et al., 2001; Kristl et al., 1993). Crushing strength and disintegration also depend on granule moisture (Dawoodbhai and Rhodes, 2008) that, on the other hand, might negatively influence API stability (Carstensen, 1988; Waterman et al., 2005). Water catalyses the oxidative degradation of API by the formation of water layers around drug crystals and particles that may increase the mobility in the solid state and result in more interactions of the API with oxidation-initiators (Mahajan et al., 2005).

Control of the key properties granule moisture and particle size during the granulation process, especially when monitored in-line,

* Corresponding author at: Pharmaceutical Technology, Institute of Pharmacy, Eilenburger Str. 15a, 04317 Leipzig, Germany. Fax: +49 341 9736609.
E-mail address: schulz@uni-leipzig.de (M. Schulz-Siegmund).

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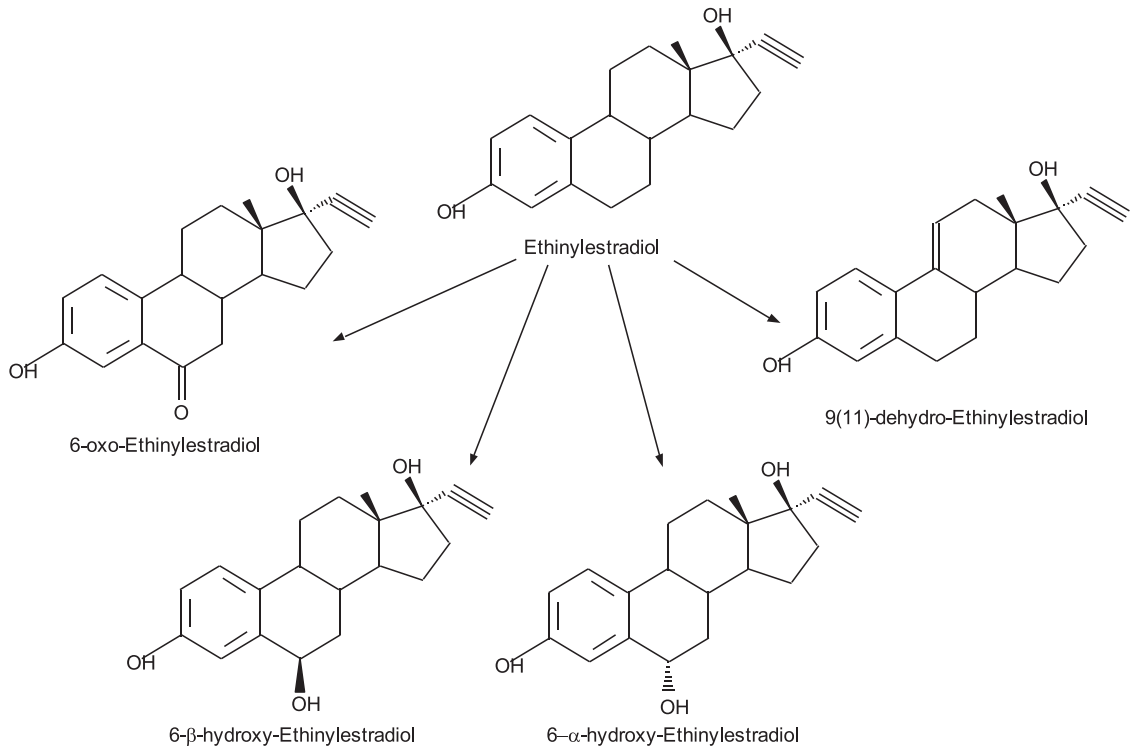

Fig. 1. Main degradation products of EE.

is therefore an important component of process development and required by the ICH guidelines (FDA, 2004; ICH, 2009). Moreover, in comparison to *off-line* or equilibrium determination of relative humidity over the granules, *in-line* process control may accelerate the granulation process considerably.

The residual moisture of the granules can be determined in different ways. Currently, a standard procedure for moisture assessment is to draw a sample to determine the loss on drying (LOD) *off-line* when a pre-defined outlet-air-temperature is reached in the granulator. In order to realize the guidelines, several publications describe the measurement of granule moisture using near-infrared (NIR)-sensors in combination with multivariate data analysis (Findlay et al., 2005; Frake et al., 1997). The advantages of the NIR-measurement (e.g. measurement independent from process variables) are accompanied by some disadvantages (e.g. complexity of particle properties to the spectrum) as discussed in several publications (Findlay et al., 2005; List and Steffens 1996; Nieuwmeyer et al., 2007; Wantano et al., 1996). An alternative *in-line* moisture-measurement technology is the microwave resonance technology (MRT). This technique has already been described for the *in-line* monitoring of the granulation (Buschmüller et al., 2009a,b) and drying process (Buschmüller et al., 2008) using this new method. The technology is based on the alignment of the water-dipole-molecules in the electromagnetic field of a resonator and the measurement of the loss in energy due to the turn-around and alignment of the water-molecules. Due to a calibration without chemometrics and a bulk-

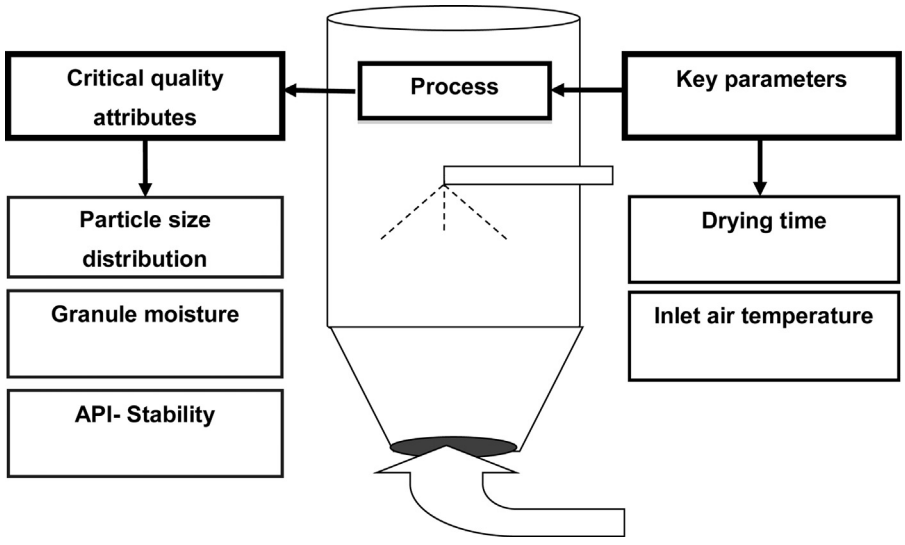

Fig. 2. Fluid bed granulation-varied key-parameters of the drying process and critical quality attributes of the product.