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Research paper

Phase transformations of erythromycin A dihydrate during pelletisation and drying

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Abstract

An at-line process analytical approach was applied to better understand process-induced transformations of erythromycin dihydrate during pellet manufacture (extrusion–spheronisation and drying process). The pellets contained 50% (w/w) erythromycin dihydrate and 50% (w/w) microcrystalline cellulose, with purified water used as a granulating fluid. To characterise changes in solid-state properties during processing, near infrared (NIR) spectroscopy and X-ray powder diffraction (XRPD) were applied. Samples were taken after every processing step (blending, granulation, extrusion, and spheronisation) and at predetermined intervals during drying at 30 or 60 °C. During pelletisation and drying at 30 °C no changes occurred. Partial transformation to the dehydrated form was observed for the pellets dried at 60 °C by NIR and XRPD. The variable temperature XRPD measurements of the wet pellets (from 25 to 200 °C) also confirmed the change to erythromycin dehydrate at approximately 60 °C.

Keywords: Processing induced transformation; Erythromycin; Dehydration; NIR; XRPD; Pelletisation; Drying

1. Introduction

Solid-state transformations have caused problems during manufacture of many active pharmaceutical ingredients (APIs). This has led to an increased interest in understanding the behaviour of APIs during pharmaceutical processes. One widely used process in pharmaceutical industry is extrusion and spheronisation for achieving uniformly sized and shaped spheres or pellets [1,2]. Pelletisation is a multiple-step process including four major stages: blending, granulation, extrusion, and spheronisation. According to Morris et al. [3,4], who have discussed theoretical approaches to monitor physical transformations of APIs during manufacturing processes, the process of pelletisation may result in a number of process-induced transformations (PITs). These PITs might be caused by interactions of APIs with excipients or water leading to polymorphic conversions, alteration in crystallinity or hydrate formation. Phase transformations may occur during blending of the dry mass, wetting, extrusion of the moist mass and rotation of the extrudate by spheronisation (causing mechanical stress) [3,4].

After pelletisation, the obtained pellets are commonly dried using oven tray or fluid-bed drying techniques. Oven tray drying is still commonly used though it is quite slow, labour intensive and inefficient. Slow water evaporation during tray drying leads to hard and less porous pellets. The pellets have time to shrink by capillary pressure due to the high surface tension of the water. Therefore oven-dried pellets are less deformable than pellets dried with any other drying technique. The remaining moisture has

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been found to be deeper within the pellet and strongly held [5]. Another disadvantage of oven tray drying is a static bed resulting in high differences of moisture content within the bed. Drying only takes place from the upper surface [6].

Various process analytical approaches have been applied to monitor PITs and increase understanding of process behaviour of APIs and excipients [3,4]. These approaches are often non-invasive and may also be used in-line. Near infrared (NIR) spectroscopy has been previously successfully used to monitor PITs such as pseudo-polymorphic changes of drug substances [7–9]. Advantages of using NIR are that it is fast, non-destructive and minimal or no sample preparation is required. X-ray powder diffraction (XRPD) is commonly used to confirm phase transformations. It provides a great potential for structural studies, since it can identify unknown materials and differ between polymorphic forms [10].

The transformation of erythromycin dihydrate (EM·DH) to either erythromycin anhydrate (EM·AH) or amorphous erythromycin requires a high activation energy, whereas transformation to its isomorphic dehydrate requires a much smaller activation energy and can occur at low relative humidity [11,12]. Conversion of EM·DH to these forms may influence the manufacturing process, dissolution rate, storage stability and bioavailability of the achieved product – e.g. the formation to erythromycin dehydrate (EM·DD) in a tablet containing also magnesium hydroxide leads to a slower dissolution rate [13].

The water molecules of EM·DH are incorporated in the available lattice channels and are easily removed. The loss of these water molecules due to heat or low relative humidity results in the isomorphic EM·DD with almost the same crystal structure as EM·DH. Therefore, the activation energy for dehydration to this form is quite low [14]. The resulting EM·DD is highly hygroscopic due to the existence of a driving force to satisfy the free hydrogen bonds after the loss of the water molecules. At a relative humidity of approximately 15% EM·DD has reverted to the dihydrate form. The uptake of water molecules starts instantly and at a relative humidity of less than 5% erythromycin (EM) already contains 1.8 mol of water. The desorption follows the same principle [11,12].

Such dehydration is problematic for manufacturing processes because any molecule, which is available and provides chemical groups that are able to satisfy the hydrogen bonding within the channel, e.g. magnesium hydroxide [13] or various solvents [15], may then be incorporated. Many solvents are able to associate with EM without disruption of the crystal lattice [15] but at the same time dissolution can be greatly affected. Recently, it was found that PITs of EM may be influenced by using a carrier polymer [16].

The purpose of this study was to detect the critical parameters during processing under which solid-state properties of EM may change, and in particular, study the occurrence of the problematic EM·DD. Furthermore, the aim was to check if conversion to EM·DD during processing might be avoided.

2. Materials and methods

2.1. Pelletisation

The composition of pellets was as follows: 50% [w/w] erythromycin base dihydrate (Pharmacia & Upjohn Company, Kalamazoo, MI) and 50% [w/w] microcrystalline cellulose (MCC) (Avicel PH101, FMC, Cork, Ireland). Purified water was used as a granulating fluid. The batch size was 2000 g and the amount of granulating fluid was 84% [w/w] of the dry powder mass. To distinguish any changes of MCC from those of EM during processing the same tests were performed on pure MCC pellets.

EM and MCC powders were dry mixed in a double cone mixer for 8 min. After blending, samples were taken and homogeneity analysed. Pellets were manufactured using continuous extrusion–spheronisation (Nica M6L mixer/granulator; Nica E140 radial screen extruder; Nica S320 spheroniser; Nica System AB, Sweden). The blended powder mixture was wetted with purified water in a mixer/granulator. For the EM/MCC pellets a speed of 30 rpm (1235 g/min) for the powder feeder and a liquid pump rate of 175 rpm (1035 g/min) were chosen. The size of the granule outlet was 15 rpm measured from the lower side of the gap. The extruder screen thickness was 1.2 mm and the die diameters were 1.0 mm. For spheronisation, the friction plate speed was adjusted to 900 rpm and the resulting extrudate of the EM/MCC blend was spheronised for 1.5 min. A sample (5 g) was taken at the end of each processing stage (blending, granulation, extrusion, spheronisation).

For the pure MCC pellets the parameters needed a slight change to gain comparable pellets. The granulate was achieved at a speed of 30 rpm of the powder feeder at a flow rate of 1005 g/min. The liquid pump rate had to be increased to 180 rpm (1080 g/min). The spheronisation time was 3 min for the MCC extrudate. All other conditions were retained.

2.2. Oven tray drying

The pellets were dried in a conventional oven tray dryer (Heraeus UT6760, Heraeus, Hanau, Germany) at 30 or 60 °C. The pellets dried at 30 °C were sampled at 45 min, and thereafter at 10 min intervals until 195 min. The last sample was collected after 245 min to monitor any residual moisture content changes. The pellets dried at 60 °C were sampled every 10 min until 100 min and a final sample was taken after 120 min. Before sampling the whole bed was circulated so that the sample was a representative mixture of pellets from all areas of the bed. The pellets were stored in glass vials and capped tightly. The same steps were performed on the MCC powder for the pure MCC pellets.

2.3. Variable temperature X-ray powder diffractometry

X-ray powder diffraction (XRPD) was performed using a theta-theta diffractometer (D8 Advance, Bruker axs