Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 246–252
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Phase transformations of erythromycin A dihydrate during pelletisation and drying

Meike Römer [a,*], Jyrki Heinämäki [a], Inna Miroshnyk [a], Niklas Sandler [a], Jukka Rantanen [b], Jouko Yliruusi [a]

[a] Division of Pharmaceutical Technology, University of Helsinki, Helsinki, Finland
[b] Department of Pharmaceutics and Analytical Chemistry, The Danish University of Pharmaceutical Sciences, Copenhagen, Denmark

Received 2 November 2006; accepted in revised form 13 December 2006
Available online 21 December 2006

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

* Corresponding author. Division of Pharmaceutical Technology, Faculty of Pharmacy, P.O. Box 56, FI-00014 University of Helsinki, Helsinki, Finland. Tel.: +358 9 191 59672; fax: +358 9 191 59144.
E-mail address: meike.romer@helsinki.fi (M. Römer).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.12.008

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

GmbH, Karlsruhe, Germany), operating in symmetrical reflection mode with CuK_α radiation (1.54 Å) and Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured using a scintillation counter. Measurements were performed from 5° to 40° (2θ) with steps of 0.1° and a measuring time of 1 s/step using a voltage of 40 kV and a current of 40 mA. All samples were analysed at room temperature and ambient humidity approximately 10 min after sampling.

Wet pellet samples were additionally measured with variable temperature XRPD. Measurements started at 25 °C and continued from 30 to 200 °C at 10 °C intervals, with a final measurement after the samples were cooled down to 25 °C.

2.4. Near infrared (NIR) spectroscopy

NIR measurements were performed in reflectance mode with a Fourier-Transform- (FT-) NIR spectrometer (Bomem MD-160 DX, Hartmann & Braun, Quebec, Canada) using Bomem-GRAMS software (v.4.04, Galactic Industries Inc., Salem, NH) with Teflon serving as reference (99% reflective Spectralon, Labsphere Inc., North Sutton, NH). The pellets were presented to the NIR probe on a petri dish. The spectra were recorded at-line within the range of 1100–2200 nm with a resolution of 8 cm^{-1} and 32 scans were averaged for each spectrum. Second derivative transformations of absorbance (1/R) were achieved with 11-point Savitzky-Golay smoothing using Matlab software (v.7.0 MathWorks Inc., Natick, MA). All measurements were made approximately 2 min after sampling.

2.5. Moisture content analysis

All samples were measured with a moisture content analyser (Sartorius moisture analyser MA 100 Sartorius GmbH, Götting, Germany). During this measurement, the sample is rapidly heated to 100 °C, and the time required for the water loss to stabilise below 0.1% (w/w) in 24 s is determined.

3. Results and discussion

3.1. Solid-state characterisation of active substances and excipients

The XRPD patterns of EM·DH, EM·AH, EM·DD and amorphous EM are different, making it possible to distinguish the various forms (Fig. 1). Miroshnyk et al. [17] have described characteristic features of XRPD patterns for the different forms of EM. The NIR spectral information of the different forms is illustrated in Fig. 2.

EM·AH and EM·DH have a substantially different solid-state structure [9,11,12] and therefore contain different reflections in their XRPD patterns (Fig. 1). In contrast, EM·DH and EM·DD are isomorphic and therefore both

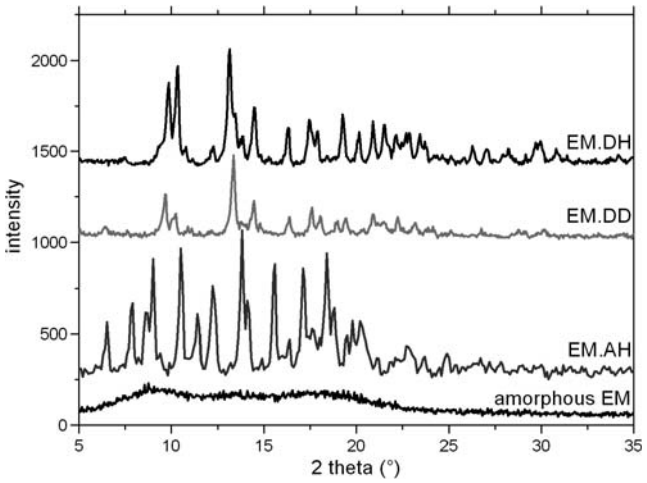

Fig. 1. X-ray powder diffraction patterns of the different EM forms used as references.

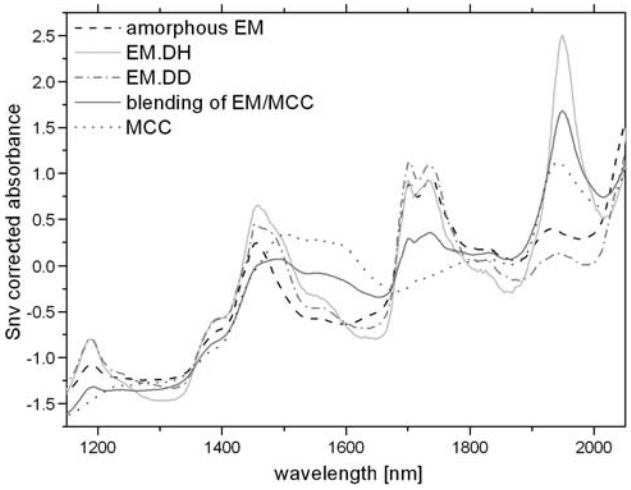

Fig. 2. Near infrared absorbance spectra of the reference substances.

diffractograms closely match each other. According to Miroshnyk et al. [17], there are small but clear changes detectable in XRPD pattern between EM·DH and EM·DD. To distinguish EM·DD from EM·DH one may observe the shift for the reflections at 9.9° (2θ) and 10.3° (2θ) (EM·DH) to 9.6° (2θ) and 10.1° (2θ) (EM·DD), respectively. Furthermore, the first reflection of EM·DH at 9.9° (2θ) is significantly less intense than that at 10.3° (2θ), whereas for EM·DD the first reflection is more intense than the second at 10.1° (2θ). Another significant shift in reflection can be found in a reflection at 13.1° (2θ) for EM·DH that moves to 13.3° (2θ) for EM·DD.

The NIR absorbance spectra of reference materials used (EM·DH, EM·DD, EM amorphous, MCC) as well as the NIR spectra of the blends of EM·DH and pure MCC are presented in Fig. 2. The spectrum of EM·DH exhibits large differences to the samples of the blend and to EM·DD in the region of 1935 nm, where the combination band of water occurs. EM·DD and amorphous EM are harder to distinguish from each other. Both forms do not contain

water and no band occurs at 1935 nm. There are subtle differences between the two forms throughout the whole spectrum.

3.2. Pelletisation phase (blending, granulation extrusion, and spheronisation)

The XRPD patterns taken after blending, granulation extrusion, and spheronisation of MCC samples do not indicate any phase transitions. The patterns for all wet samples show less pronounced reflections resulting again from the large amount of water added to the system. The XRPD patterns for the pelletisation process of EM/MCC samples present no considerable differences (Fig. 3). Peaks are absent in all diffractograms during the granulation phases, giving the appearance of amorphous material, but these patterns result from the high amount of water. During extrusion water evaporates due to pressure and heat exposure (45.8% [w/w] moisture content) and therefore the main reflections of EM·DH become visible again. The pure MCC pellets show a generally lower moisture content during the whole process than the EM/MCC pellets (Table 1). Changes to EM·DD were not expected in this part of the study due to the high amount of water in the system. Nevertheless, it had to be assured that no transformation to any of the other forms of EM occurred during pelletisation.

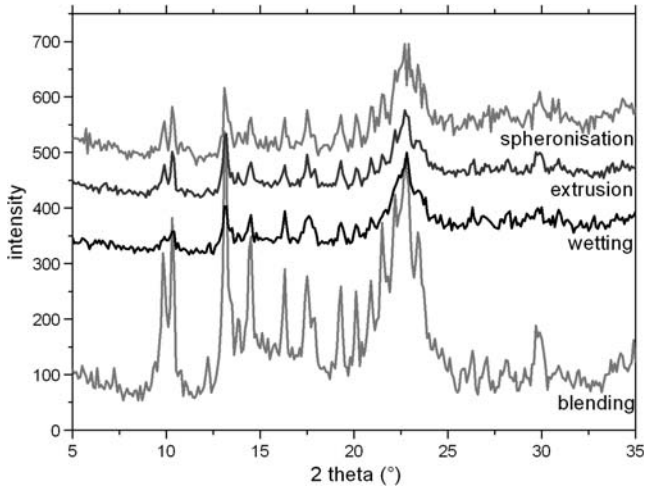

Fig. 3. X-ray powder diffraction patterns for the EM/MCC reference pellets, samples obtained at different stages of the pelletisation process.

According to Sandler et al. [18], saturation of the water signal limits the application of NIR for monitoring PITs in high moisture content systems such as pelletisation by extrusion–spheronisation. In the present study it was also not possible to obtain any data except the water signal after adding water during the granulation step.

3.3. Drying phase

The drying behaviour of both MCC reference pellets and EM/MCC pellets is illustrated in Fig. 4. The initial phase for the pellets dried at 60 °C is significantly shorter compared to the pellets dried at 30 °C. During the heat-transfer limited drying step, both MCC reference pellets and EM/MCC pellets showed equal drying behaviour (90–150 min) at 30 °C whereas the MCC pellets dried at 60 °C contained more moisture than the EM/MCC pellets. Further drying was limited due to diffusion. During this process the drying behaviour between the pure MCC reference pellets and the EM/MCC pellets started to differ at both drying temperatures. Water seems to diffuse more easily to the surface of the pure MCC pellets than of those with EM, which obviously is able to retain water more strongly. Therefore the final moisture content of the MCC reference batches is lower (though starting at a higher value) than that of the EM/MCC pellets.

The reflections of the pure MCC pellets that got less intense during pelletisation reappear during drying, and the patterns of the dried MCC (245 min at 30 °C and 120 min at 60 °C) equal those of the reference. This simplifies the identification of the actual solid state of EM after drying.

During drying at 30 °C there are no changes detectable in the XRPD patterns. As the transformation of EM·DD occurs at rather low relative humidity this is not unexpected. The moisture content of the blend was 4.5% [w/w] on average and after drying it was 3.9% [w/w].

No phase transformation is evident from the NIR spectra during drying; nevertheless the water loss is clearly shown. The two characteristic peaks for the ketone stretching become detectable after 135 min of drying, when the water signals have decreased. The spectra of the final pellets (245 min) are nearly identical to those of the EM/MCC dry blending.

Table 1
Moisture content analysis of the pelletisation and drying process of MCC reference pellets and erythromycin/MCC pellets ($n = 2$)

Preparation	Moisture content (%) (mean ± SD)					
	Dry blend	Wet granulate	Extrudate	Wet pellets (spheronised)	Pellets (dried at 30 °C)	Pellets (dried at 60 °C)
Micro-crystalline cellulose (MCC) ref. pellets	4.0 ± 0.1	51.9 ± 0.7	51.5 ± 0.3	48.2 ± 0.1	2.6 ± 1.1	2.1 ± 1.9
Erythromycin/MCC pellets						
Batch 1	4.1	45.6	45.4	44.6	4.2	1.3
Batch 2	4.8	46.1	46.1	44.8	3.5	2.1

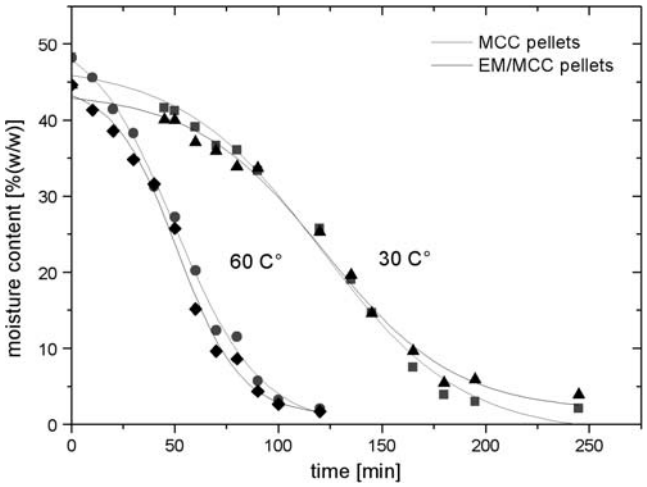

Fig. 4. Moisture content analysis of the different batches of MCC and EM/MCC pellets dried at 30 °C and at 60 °C.

The sufficiency of the drying process is determined by moisture content analysis. Although all batches (MCC and EM/MCC) initially contained similar moisture contents, they differ slightly during the intermediate drying (135–165 min). This may be due to the manually circulated bed. The disadvantage of tray drying is, as mentioned before, the static bed and different drying abilities in different parts of the bed. So the sample may contain more pellets from the lower bed, which are less sufficiently dried, after circulating the bed before sampling.

The XRPD patterns of the samples taken during drying at 60 °C (Fig. 5) indicate a change to EM·DD after 120 min in the first batch of EM/MCC pellets. There is a small reflection appearing at 9.7° (2θ) in addition to the one characteristic for EM·DH at 9.9° (2θ). There are other characteristics in the XRPD patterns indicating the appearance of EM·DD, e.g., a distinct reflection at 10.2° (2θ), shifted from 10.3° (2θ) for EM·DH, and one at 13.3° (2θ), which appears at 13.1° (2θ) for EM·DH. Generally, the reflections

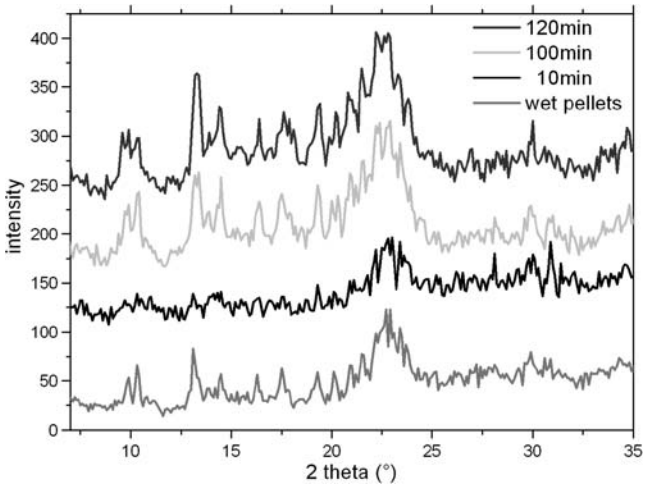

Fig. 5. X-ray powder diffraction patterns for the EM/MCC pellets obtained at different steps during oven tray drying at 60 °C.

are less pronounced due to the amorphous excipient. It seems unlikely that EM·DD occurs in the second batch, though the moisture content is considerably lower (2.1% [w/w]) than after drying at 30 °C (3.9% [w/w]).

In the NIR spectra, the water signals at 1450 and 1940 nm and the bands at 1680 and 1775 nm clearly change. The water band overlays all other spectral information (Figs. 6a and b) in the samples taken after 10 min drying at 60 °C. After 80 min drying the spectrum of the first batch (Fig. 6a) is already comparable with that of the EM/MCC dry mixture while the pattern of the second batch (Fig. 6b) is still mainly dominated by the water signal.

The spectrum of the first batch changes at the final stage of drying (120 min), indicating a phase transformation to amorphous EM, EM·DD, or probably both. The 2nd derivative spectra illustrate the differences more clearly (Fig. 6c). Transformation towards EM·DD is indicated when comparing the spectrum of the sample dried at 120 min at 60 °C (1st batch) to the EM·DD reference. The two batches of EM/MCC pellets dried at 60 °C exhibit greater differences in drying behaviour than those dried at 30 °C, and these differences occur throughout the whole process.

The final moisture content of the parallel EM/MCC pellet batches was 1.3% and 2.1%. However, XRPD and NIR show that transformation of EM·DH to EM·DD only occurred in the first batch. Between 0% and 5% relative humidity EM loses or takes up 1.8 mol of water [12]. Therefore, it is possible that transformation to EM·DD starts at moisture contents between 2.1% [w/w] (second batch without changes to EM·DD) and 1.3% [w/w] (first batch) considering also the 50% [w/w] MCC in the pellets.

3.4. Variable temperature XRPD

The results of the variable temperature XRPD measurements (Fig. 7) show that after heating to 70 °C the first signs of transformation to EM·DD appeared with the distinct reflections at 9.7° (2θ), 10.1° (2θ) and 13.3° (2θ). The process of dehydration continues up to 100 °C. This is in accordance with the findings of Mirza et al. [15,16]. For the pellets containing 50% [w/w] MCC and 50% [w/w] EM·DH the same changes in solid-state performance at similar temperatures were detected when performing the variable temperature XRPD with the pure, powdered EM·DH.

4. Conclusions

Process-induced transformations (PITs) are evident with EM·DH during oven tray drying at higher temperatures (60 °C). Transformations to the isomorphic dehydrate form of the drug are partly induced under this condition. No dehydration or phase transformations of EM occurred during pelletisation and when dried at the lower drying temperature of 30 °C. These findings suggest that EM does

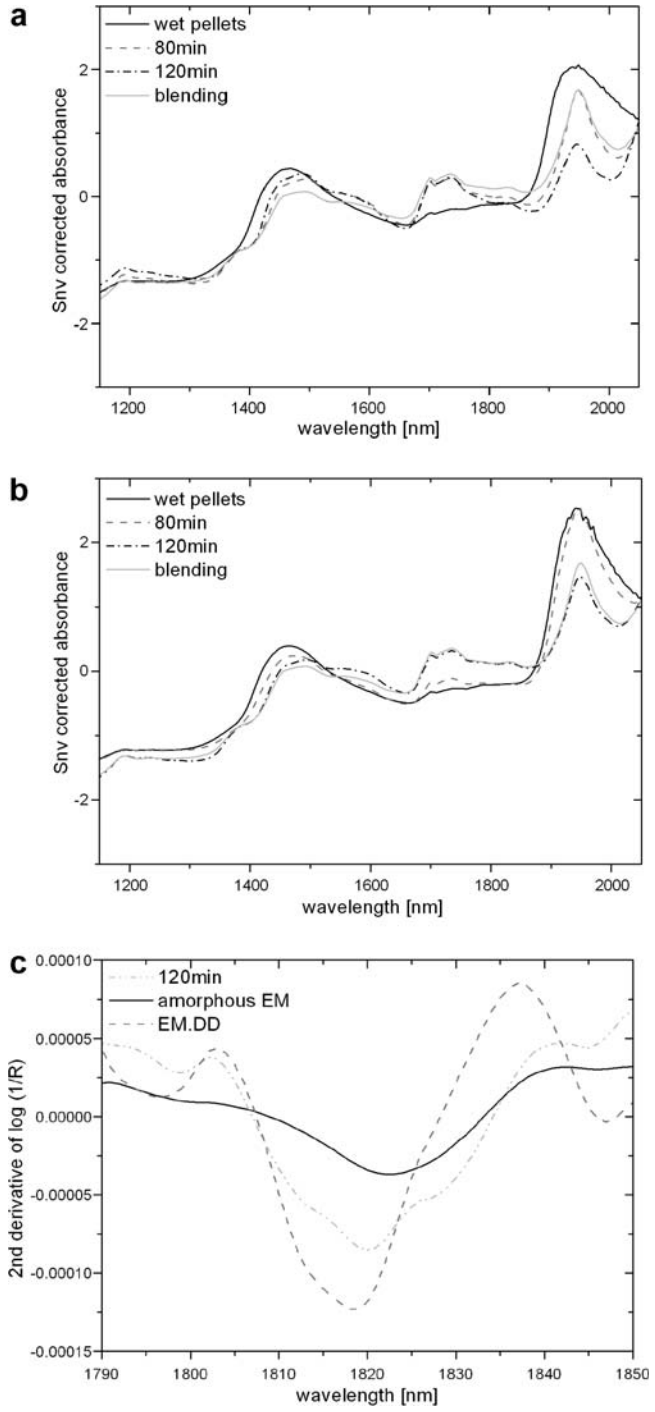

Fig. 6. Near infrared spectra for the first batch (a) and the second batch (b) of the EM/MCC pellets presenting the changes during drying at 60 °C. Second derivative of $1/R$ (c) of the final pellets and EM references.

not tend to transform easily during processing. If no severe conditions are applied such as high temperatures which lead to a low moisture content (less than 2% [w/w]) EM·DH remains stable throughout the whole process. The combined use of XRPD and NIR is adequate because the two methods confirmed the results of one another and provided insight into solid-state transformations in a complex system. Furthermore XRPD is able to give information about the solid state of the drug during pelletisation when the use of NIR is limited due to the high amount of water in the samples. Since NIR spectroscopy, being a rapid method, proved able to detect changes in phase transition during tray drying it is possible, unlike with XRPD, to apply it as an in-line approach on further drying studies using a fluid bed dryer.

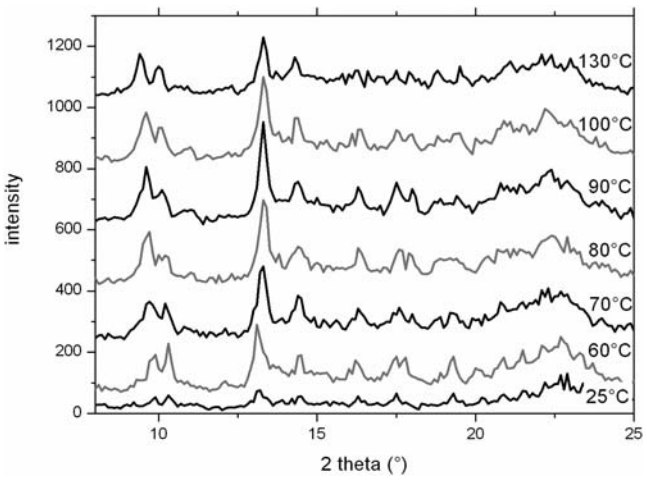

Fig. 7. Variable temperature X-ray diffraction patterns for the EM/MCC pellets.

References

[1] L. Hasznos, I. Langener, M. Gyarmathy, Some factors influencing pellet characteristics made by an extrusion/spheronization process. Part I. Effects on size characteristics and moisture content decrease of pellets, Drug Dev. Ind. Pharm. 18 (1992) 409–437.
[2] C. Vervaet, L. Baert, J.P. Remon, Extrusion-spheronization A literature review, Int. J. Pharm. 116 (1995) 131–146.
[3] K.R. Morris, U.J. Griesser, C.J. Eckhardt, J.G. Stowell, Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes, Adv. Drug Deliv. Rev. 48 (2001) 91–114.
[4] K.R. Morris, S.L. Nail, G.E. Peck, S.R. Byrn, U.J. Griesser, J.G. Stowell, S.-J. Hwang, K. Park, Advances in pharmaceutical materials and processing, Pharm. Sci. Technol. Today (PSTT) 1 (1998) 235–245.
[5] A.B. Bashaiwoldu, F. Podczeck, J.M. Newton, A study on the effect of drying techniques on the mechanical properties of pellets and compacted pellets, Eur. J. Pharm. Sci. 21 (2004) 119–129.
[6] A.J. Hlinak, B.A. Clark, Drying and driers. Encyclopedia of Pharmaceutical Technology, Marcel-Dekker, New York, 2002, 1018–1032.
[7] EMEA, Note for guidance on the use of near infrared spectroscopy by the pharmaceutical industry, 2003, <http://www.emea.eu.int/pdfs/human/qwp/330901en.pdf/>.
[8] M. Blanco, D. Valdes, I. Llorente, M. Bayod, Application of NIR spectroscopy in polymorphic analysis: Study of pseudo-polymorphs stability, J. Pharm. Sci. 94 (2005) 1336–1342.
[9] J. Haleblain, W. McCrone, Pharmaceutical applications of polymorphism, J. Pharm. Sci. 58 (1969) 8, 911–929.
[10] M. Karjalainen, S. Airaksinen, J. Rantanen, J. Aaltonen, J. Yliruusi, Characterization of polymorphic solid-state changes using variable temperature X-ray powder diffraction, J. Pharm. Biomed. Anal. 39 (2005) 27–32.
[11] G.A. Stephenson, J.G. Stowell, P.H. Toma, R.R. Pfeiffer, S.R. Byrn, Solid state investigations of erythromycin A dihydrate: structure, NMR spectroscopy, and hygroscopicity, J. Pharm. Sci. 86 (1997) 1239–1244.

[12] G.A. Stephenson, E.G. Groleau, R.L. Kleemann, W. Xu, D.R. Rigsbee, Formation of isomorphic desolvates: creating a molecular vacuum, J. Pharm. Sci. 87 (1998) 536–542.
[13] J.F. Bauer, W. Dziki, J.E. Quick, Role of an isomorphic desolvate in dissolution failures of an erythromycin tablet formulation, J. Pharm. Sci. 88 (1999) 1222–1227.
[14] Z. Wang, J. Wang, L. Dang, Thermal, phase transition and spectral studies in erythromycin pseudopolymorphs: dihydrate and acetone solvate, Cryst. Res. Technol. 41 (2006) 1219–1225.
[15] S. Mirza, I. Miroshynk, J. Heinämäki, L. Christiansen, M. Karjalainen, J. Yliruusi, Influence of solvents on the variety of crystalline forms of erythromycin, AAPS Pharm. Sci. 5 (2003) 12.
[16] S. Mirza, J. Heinämäki, I. Miroshnyk, J. Rantanen, L. Christiansen, M. Karjalainen, J. Yliruusi, Understanding processing-induced phase transformations in erythromycin-PEG 6000 solid dispersions, J. Pharm. Sci. 95 (2006) 1723–1732.
[17] I. Miroshnyk, L. Khriachtchev, S. Mirza, J. Rantanen, J. Heinämäki, J. Yliruusi, Insight into thermally induced phase transformations of erythromycin A dihydrate, Cryst. Growth Des. 6 (2006) 369–374.
[18] N. Sandler, J. Rantanen, J. Heinämäki, M. Römer, M. Marvola, J. Yliruusi, Pellet Manufacturing by Extrusion-Spheronization Using Process Analytical Technology, AAPS, PharmSciTech 6 (2005) E174–E183.