CALENDERING AS A DIRECT SHAPING TOOL FOR THE CONTINUOUS PRODUCTION OF FIXED-DOSE COMBINATION PRODUCTS VIA CO-EXTRUSION.

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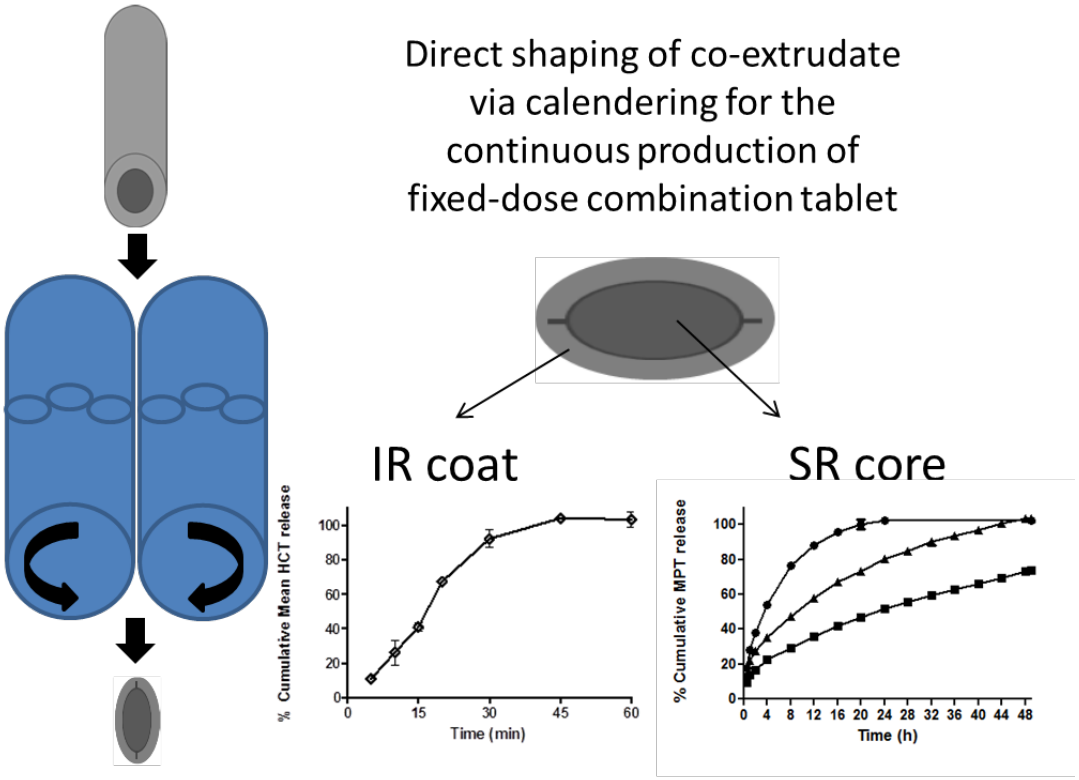
Abstract

In this study calendering is used as a downstream technique to shape monolithic co-extruded fixed-dose combination products in a continuous way. Co-extrudates with a metoprolol tartrate-loaded sustained-release core and a hydrochlorothiazide-loaded immediate-release coat were produced and immediately shaped into a monolithic drug delivery system via calendering, using chilled rolls with tablet-shaped cavities. *In vitro* metoprolol tartrate release from the ethylcellulose core of the calendered tablets was prolonged in comparison to the sustained release of a multiparticulate dosage form, prepared manually by cutting co-extrudates into mini-matrices. Analysis of the dosage forms using X-ray micro-computed tomography only detected small differences between the pore structure of the core of the calendered tablet and the mini-matrices. Diffusion path length was shown to be the main mechanism behind the release kinetics. Terahertz pulsed imaging visualized that adhesion between the core and coat of the calendered tablet was not complete and a gradient in coat thickness (varying from 200 to 600 µm) was observed. Modulated differential scanning calorimetry and X-ray diffraction indicated that the solid state properties of both drugs were not affected by the calendering procedure.

Keywords: calendering, co-extrusion, continuous production, fixed-dose combination product, sustained release, immediate release

Graphical abstract



List of abbreviations

HME	Hot-melt extrusion
FDC	Fixed-dose combination
MPT	Metoprolol tartrate
HCT	Hydrochlorothiazide
EC	Ethylcellulose
PEO	Polyethylene oxide
PEG	Polyethylene glycol
MDSC	Modulated differential scanning calorimetry
XRD	X-ray diffraction
DBS	Dibutyl sebacate
MW	Molecular weight
USP	United States Pharmacopeia
UV	Ultraviolet
Tg	Glass transition temperature
RCS	Refrigerated cooling system
TPI	Terahertz pulsed imaging
Micro-CT	Micro-computed tomography
BMP	Bitmap
ROI	Region of interest

1. INTRODUCTION

In co-extrusion two or more formulations are simultaneously processed via hot-melt extrusion (HME) through the same die. In addition to the advantages of HME, such as the continuity of the production process, not requiring the use of solvents or water and improving drug bioavailability, this technique offers the opportunity to produce fixed-dose combination (FDC) products with enhanced release characteristics, by making it possible to design multilayered dosage forms that are extruded in the same process step, in order to modulate the drug release from each layer. Although co-extrusion is used to manufacture implants [1] and vaginal rings [2], there are currently no co-extruded dosage forms for oral application on the market. In literature only a limited number of studies describe co-extrusion of dosage forms for oral drug delivery [3-6]. Recently co-extrusion has been used for the development of multiparticulate fixed-dose combination drug products for oral pharmaceutical application, consisting of a controlled release core matrix and an immediate release coat [7] and to develop sustained and dual drug release formulations for individual dosing [8]. For pharmaceutical applications of co-extrusion, one of the major challenges is the shaping of the final product in a continuous way, as a suitable downstream shaping technique is needed to ensure an efficient manufacturing line. Previously injection-molding has been used to shape extrudates into solid oral dosage forms in a semi-continuous way [9, 10] and even to prepare co-injection moulded matrices [4]. Calendering is a technique that allows in-line shaping of the extruded material in a fully continuous single-step process. Using this technique the freshly-extruded thermoplastic strand is guided through a pair of temperature-controlled rolls containing tablet- or pill-shaped cavities, yielding bands that contain single tablet-shaped cores of the desired shape. Although this technique is already widely established in the plastic and confectionary industry to produce monolithic shapes, only the Meltrex® technology [11] and the continuous extrusion process for the production of sustained release tablets developed by Knoll AG [12] report calendering as a possible shaping tool for pharmaceutical applications.

In this study the use of calendering to continuously shape a multi-layered co-extrudate into a monolithic FDC dosage form was evaluated. In the treatment of cardiovascular disease the FDC of the beta-blocker metoprolol tartrate (MPT) with the diuretic hydrochlorothiazide (HCT) is well established [13]. Therefore co-extrudates consisting of a plasticized ethylcellulose (EC) core, containing MPT and polyethylene oxide (PEO), and a coat of polyethylene oxide (PEO) / polyethylene glycol (PEG) containing HCT were previously developed [14]. After production the cylindrical co-extrudate with concentric coat layer was immediately shaped via calendering, using chilled rolls with tablet-shaped cavities. In this way monolithic dosage forms with a sustained-release core, loaded with MPT as model drug, and an immediate-release coat, loaded with HCT as model drug, were produced and evaluated for in vitro drug release, coat thickness and uniformity and pore structure. The impact of the calendering step on the physical state of the drugs in the formulations was characterized using modulated differential scanning calorimetry (MDSC) and X-ray diffraction (XRD).

2. MATERIALS AND METHODS

2.1 Materials

Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) and hydrochlorothiazide (HCT) (Utag, Amsterdam, the Netherlands) were used as sustained and immediate release model drugs, respectively. As excipients ethylcellulose (Ethocel® std 10, Colorcon, Dartford Kent, United Kingdom), dibutyl sebacate (DBS) (Sigma-Aldrich, Bornem, Belgium), polyethylene oxide (PEO) 1M (MW: 1000000 g/mol, Sentry™ Polyox® WSR N12K, Colorcon, Dartford Kent, United Kingdom), PEO 100K (MW: 100000 g/mol, Sentry™ Polyox® WSR N10, Colorcon, Dartford Kent, United Kingdom) and polyethylene glycol (PEG) 4K (MW: 4000 g/mol, Fagron, Waregem, Belgium) were used. All other chemicals were of analytical grade.

2.2 Methods

2.2.1 Co-extrusion

Co-extrusion was carried out using two co-rotating Prism Eurolab 16 mm twin-screw extruders (ThermoFisher Scientific, Karlsruhe, Germany), connected to a co-extrusion die (Guill, West Warwick, USA). In the calendering set-up the co-extrusion die was adapted to fit the diameter of the co-extrudate with the dimensions of the calender cavities, shaping a cylindrical co-extrudate consisting of a core with a diameter of 4 mm and a concentric coat with a thickness of 2 mm. To produce the multiparticulates, a cylindrical co-extrudate with an inner diameter of 3 mm and an outer diameter of 4 mm was manufactured. The heating zones of both extruders were heated to 80/90/100/100/100/100 °C from feed opening to die-end. The co-extrusion die was heated to 100 °C. Both premixes were fed separately into an extruder by a Brabender Flexwall® loss-in-weight powder feeder (Brabender, Duisburg, Germany) at a feed rate of 200 g/h for the coat and 300 g/h for the core material. A screw speed of 40 rpm and 150 rpm was used for the extruder producing the outer layer and the inner layer, respectively.

2.2.2 Downstream processing

Calendering was performed with a Collin 60 mm calender (Dr. Collin, Ebersberg, Germany), coupled to a compressed air supply and a Coolenergy chiller (Plastima, Breda, The

Netherlands), which cooled the calender rolls to a temperature within the range of 4-8 °C. The speed of the calender rolls was set at 1.5 rpm. Immediately after leaving the co-extrusion die the co-extruded strand was guided between a pair of chilled pressurized rolls that contained tablet-shaped cavities, yielding tablets with a diameter of 8 mm and a thickness of 5 mm.

To test the effect of cooling on the MPT release a core extrudate was prepared using the same process parameters as for the core in the co-extrudate. Part of this material was cooled at room temperature, while the remaining part was quench-cooled by dipping the core extrudate in liquid nitrogen immediately after extrusion.

Multiparticulates were obtained by manually cutting a cylindrical co-extrudate with an inner diameter of 3 mm and an outer diameter of 4 mm into mini-matrices of 2 mm length after cooling the co-extruded rod to room temperature.

2.2.3 In vitro drug release

In vitro dissolution was performed using United States Pharmacopeia (USP) dissolution apparatus 1 (baskets) on an Evolution 6300 dissolution system (Distek, New Brunswick, New Jersey, USA), coupled with an Evolution 4300 automatic dissolution sampler (Distek, New Brunswick, New Jersey, USA). The temperature of the dissolution medium (900 ml) was kept at 37 ± 0.5 °C and the rotational speed of the baskets was set to 100 rpm. For the first hour a 0.1 N solution of hydrochloric acid (pH 1) was used as the dissolution medium. Afterwards the baskets containing the mini-matrices or tablets were transferred to vessels filled with phosphate buffer pH 6.8 (USP) as the dissolution medium. Samples (filtered using Distek 45 µm filters) of 5 ml were withdrawn at 5, 10, 15, 20, 30, 45 and 60 minutes for the determination of HCT concentration in the first dissolution medium and at 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours for the determination of MPT concentration in the second dissolution medium. The core layer was analyzed separately to cover for the MPT release during the first hour. Samples were analyzed spectrophotometrically at 316.6 and 222.0 nm, using a UV-spectrophotometer, type UV-1800 (Shimadzu, Deurne, Belgium) and applying an appropriate calibration curve for quantification of HCT and MPT, respectively. Each experiment was performed in triplicate.

2.2.4 Modulated differential scanning calorimetry

The solubility of HCT in the coat of the tablet was studied by cyclic heating of an oversaturated sample, containing 70 % HCT, followed by annealing at a different temperature for each cycle in order to reach the maximum solubility at each temperature. After the annealing step the sample was quenched and heated again to determine the glass transition temperature (*Tg*). These cycles were performed for different annealing temperatures in between the melting point of polymer matrix and drug, and the shift in Tg was monitored using a differential scanning calorimeter Q200, equipped with a refrigerated cooling system (RCS) (TA Instruments, Leatherhead, UK). Nitrogen was used as purge gas through the DSC cell (50 ml/min) and the RCS unit (300 ml/min). Samples (± 3 mg) were run in an open aluminum pan with an underlying heating rate of 5 °C/min. The modulation period and amplitude were set at 50 s and 0.663 °C, respectively (heat-only method). Temperature and enthalpy calibration was performed with an indium standard at the same scan rate and with the same kind of pans used in the experiment. MDSC data were analyzed using the TA instruments Universal Analysis 2000 V4.7A software.

2.2.5 X-ray diffraction

Crystallinity was analyzed using X-ray diffraction (XRD) on pure compounds, physical mixtures and corresponding extrudates. X-ray diffraction was performed on a D5000 diffractor with Cu Kα radiation (λ = 1.54 Å) (Siemens, Karlsruhe, Germany) and a voltage of 40 mV in the angular range (2θ) varying from 10 to 60° using a step scan mode with a step size of 0.02° and a measuring time of 1 s/step.

2.2.6 Terahertz pulsed imaging (TPI)

The calendered tablets from different formulations were analyzed using a TPI imaga2000 coating scan system (Teraview, Cambridge, UK). The operation of this system was previously described by Zeitler et al. [15]. Images were acquired in a point-to-point mode with a step size of 200 µm. Images were analyzed using TPI View (version 3.0.3, Teraview, Cambridge, UK). A six-axis robot arm was used to produce a surface map of the calendered tablet. The

refractive index of the coating material was estimated to be 1.5, based on the surface reflectivity of the calendered tablets as well as by calibration using the X-ray micro-computed tomography. Given the very smooth texture of the surface this was deemed to represent an appropriate measurement for the refractive index as no surface scattering would contribute to the losses. Using this value histograms and maps of coating uniformity were plotted using Matlab (R2013a, The Mathworks, Natick MA, USA).

2.2.7 X-ray micro-computed tomography (Micro-CT)

The porosity of the mini-matrices and tablets was evaluated by means of micro-CT. Co-extruded mini-matrices and calendered tablets were scanned using a Skyscan 1172 high resolution X-ray micro-CT system (Bruker microCT, Kontich, Belgium), operated at 59 kV source voltage, with an image pixel size of 1.37 µm and 4.53 µm, for the mini-matrix and the tablet, respectively. The scanning system is equipped with an aluminum 0.5 mm filter and an 11 Mp CCD detector. For the scan with the image pixel size of 4.53 µm the samples were rotated over 0.4 ° steps, exposure time was 1000 ms and total scan duration was 42 min. For the high resolution offset-scan the samples were rotated over 0.2 ° steps, exposure time was 2350 ms, frame averaging was 5 and total scan duration was 9 h 17 min. The images were reconstructed with NRecon (Version 1.6.3.2, Bruker microCT, Kontich, Belgium) on a GPU-ReconServer. A Gaussian smoothing kernel of 2 pixels was applied, resulting in an 8-bit bitmap (BMP) image with a linear X-ray attenuation coefficient, displayed as a grey scale value calibrated between 0 and 255. To compare both dosage forms at the same pixel size, the images of the mini-matrix system were resized fourfold prior to analysis. Data analysis and visualization was done with CTAn software (version 1.13.5.1, Bruker microCT, Kontich, Belgium) and CTVol (version 2.2, Bruker microCT, Kontich, Belgium) for surface rendering. For image analysis the core was defined as the region of interest (ROI). To this end, applying a Gaussian blur by 2 pixels allowed separating the two peaks in the grey scale histogram with a threshold of 34. Pixels with lower intensities were assigned to the core and pixels with a

147 higher intensity were assigned to the coat layer. This ROI is applied to the original grey scale
148 images, in this way removing the coat. Greyscale images were binarised using an Otsu-
149 algorithm, one of the most popular techniques of automatic thresholding [16]. 3D objects
150 smaller than 20 voxels were considered to be noise and were filtered out of the image used
151 for porosity analysis. A distinction is made between internal pores, which are located in the
152 core of the co-extrudate, and pores at the interface between core and coat. The percentage of
153 internal pores is quantified as the ratio between the internal pore volume in the core and the
154 object volume (i.e. total volume of solid core material, excluding pores). The percentage of
155 pores at the interface between both layers is defined as the ratio between the pore volume at
156 the interface and the total core volume (i.e. region of interest volume, including pores). A size
157 distribution of the pores is illustrates the percentage of pores in a certain range of structure
158 thickness. Local structure thickness for a point in solid material is defined by Hildebrand and
159 Ruegsegger as the diameter of the largest sphere that encloses the point and is entirely
160 enclosed within the solid surfaces [17].
161

3. RESULTS AND DISCUSSION

In order to continuously shape a multi-layered co-extrudate into a final monolithic FDC tablet dosage form the co-extrusion line was extended downstream with a calender and chiller. Although calendering has been used previously to shape an extrudate into a final dosage form [11, 12], to our knowledge this study is the first to evaluate calendering as a downstream tool in a co-extrusion process, thus producing a dosage form with an outer layer that is surrounding the inner core. In order to evaluate the effect of calendering on the release profiles of two model drugs, formulations with a MPT-loaded sustained release core and a HCT-loaded immediate release coat were used (Table 1): the two core formulations A and B varied in their EC/PEO ratio while a lower MPT content was used in formulation C. This allowed to evaluate the effect of calendering as a function of the concentration of PEO (added as hydrophilic additive) and the MPT load [14]. The composition of the coat formulation was constant, except for the HCT load of formulation C that was adjusted in order to respect the same MPT/HCT ratio in each of the co-extruded formulations. The MPT-loaded plasticized EC matrix (with the addition of PEO 1M as a hydrophilic additive) was co-extruded with its HCT-loaded PEO 100K/PEG 4K coat at a temperature of 100 °C. The inserts of the co-extrusion die were adapted to match the dimensions of the co-extrudate with the dimensions of the calender cavities. The co-extruded string was guided between the chilled calender rolls to shape a string of tablets. Calendered tablets were regular in shape and had a uniform aspect as long as the calender rolls were chilled at 4 ± 1 °C. When the chiller did not succeed in adequately cooling the calender rolls (i.e. using a chill water temperature > 6°C), the calendered tablets deformed when the calendered string detached from the chill rolls. As aspect defects were found to be highly dependent on calender speed and temperature, a low calender speed was used to allow adequate cooling and perfect shaping of the calendered tablets [18]. The cooling rate of the material between the calender rolls seemed essential to obtain a dosage form with good shape and uniform dimensions (Fig. 1). Although minimized by adjusting the die dimensions to the dimensions of the calender cavities, waste material was created at the sides of the tablets when forcing the co-extruded strand in between the calender rolls. The amount of waste was

7.5 % w/w of the total weight of the co-extruded calendered material. As this waste at the edges of the tablets must be removed to obtain the final dosage forms, this is especially a disadvantage when working with highly valuable active ingredients. Based on the drug content of the waste material, it was assessed that it is mainly composed of coat material (93 % of the total waste fraction), while only a minor part of core material is lost during calendering. This should be taken into account as this yields tablets with a higher MPT/HCT ratio than theoretically anticipated based on coat and core composition. The higher MPT/HCT ratio was confirmed by quantification of the MPT and HCT concentration in the calendered tablets: a ratio of 8.58 vs. 8.00 based on the composition of coat and core layer. Since TPI was previously used for the non-destructive analysis of coated tablets [19] this technique was used to visualize the coat layer and to study the adhesion between core and coat. Especially interesting for the analysis of calendered tablets via TPI is the fact that not only the thickness of the coat layer, but also the uniformity and integrity of the coat can be analysed, since penetration depths into typical pharmaceutical formulations between 1 and 3 mm can currently be achieved [14]. The thickness of the coat layer varied between 200 and 600 µm (Fig. 2). In the false-colour images of the tablets of formulation B, a thickness gradient in the coat layer is observed (Fig. 2), which is more pronounced at the top face compared to the bottom face of the calendered tablets. This gradient can be explained by the sequenced contact of different regions of the tablet with the calender rolls. The cross section images based on the micro-CT data from a string of tablets confirmed this by revealing a recurrent pattern of the thinner area in the coating layer (Fig. 3). The analysis of the calendered tablet via TPI also clearly identified that the adhesion between core and coat was not complete as an air gap at the interface between both extruded layers was detected (Fig. 2). The incomplete adhesion was also confirmed by micro-CT (Fig. 3) and quantified as the percentage of pores at the intersection of core and coat. These pores at the intersection of core and coat for calendered tablets (2.37 %) were also found for the multiparticulates (2.06 %), indicating that the incomplete adhesion between coat and core was not linked to the calendering step in the process, but originated during the co-extrudate formation. These air pockets could become entrapped between coat and core layer when both

extrusion flows merge. The air gap between the coating and the core is unlikely to have any influence on the release characteristics for a tablet with an immediate release coat (as manufactured in this study) since the coat will rapidly dissolve and expose the core to the dissolution medium. However, the results show that calendering as a post-processing step for co-extruded formulations needs further optimization for drug delivery systems where the coat controls the release of the core, as the differences in thickness of the coating layer and incomplete adhesion between both layers observed in this study would induce significant variability in the release rate. Moreover, for those types of systems it will be challenging to obtain a coat that completely seals the core, a feat that is difficult to achieve with the calendering set-up used in this study, especially at the edges of the calendered tablets (Fig. 3).

Physico-chemical characterisation of MPT and HCT in core and coat, respectively, was performed in order to evaluate the effect of calendering on the physical state of the incorporated drug substances. The solubility of HCT in the PEO/PEG carrier was determined by monitoring the shift in Tg after annealing a supersaturated physical mixture at different temperatures and subsequent quenching. First of all the Gordon-Taylor curve was established for different mixtures of HCT in the PEO/PEG carrier. The composition dependence of the glass transition temperature was fitted by the usual Gordon-Taylor law [20, 21]:

$$Tg(X_{(HCT)}) = \frac{\left[(X_{(HCT)}.Tg_{(HCT)}) + (K(1-X_{(HCT)})Tg_{(carrier)})\right]}{\left[X_{(HCT)} + K(1-X_{(HCT)})\right]} \quad (1)$$

In equation 1 $Tg_{(HCT)}$ and $Tg_{(carrier)}$ are respectively the glass transition temperature of pure HCT and the carrier, $X_{(HCT)}$ is the HCT fraction in the mixture, and K is a fitting parameter characterizing the curvature of the evolution.

In order to determine the drug concentration dissolved in the polymer carrier at each annealing temperature the *Tg* values from the annealing experiment were plotted on the Gordon-Taylor curve. In this way the solubility curve was determined (Fig. 4). The

concentration of HCT (5.6 % w/w) in the coat layer of the tablet was far below the solubility limit (31 % w/w) of HCT in the carrier. This was confirmed by the absence of the melting endotherm of HCT in the MDSC thermogram and by the absence of any peaks representative of crystalline HCT in the X-ray diffraction pattern of the extruded coat (data not shown), demonstrating HCT was present in the coat as a solid solution in the crystalline polymer mixture. MDSC thermograms of MPT-loaded core formulations showed a melting peak at 118 °C. The enthalpy of fusion indicated that the main drug fraction remained crystalline in the calendered tablets: 82.3 and 85.0 % MPT was in a crystalline state in the core of formulations A and B, respectively. Similar values of MPT crystallinity were detected in the core of the mini-matrices (80.0 and 85.8 % for formulations A and B, respectively), indicating that the calendering step did not affect the solid state properties of MPT. The X-ray diffraction pattern of the core of the calendered tablet also revealed diffraction peaks of MPT, confirming that the crystalline state of MPT was at least partially maintained in the tablets. Moreover, the X-ray diffractogram did not reveal differences between the cores of calendered tablets and co-extruded mini-matrices (data not shown). The pore structure of the core in both dosage forms, calendered tablets and mini-matrices, was compared using micro-CT. The percentage of internal pores was 4.00 % and 1.08 % for the core of the mini-matrices and calendered tablets, respectively. The lower amount of internal pores in the calendered tablet can be attributed to the additional densification of the material during calendering. In addition, the internal pores in the calendered tablet were smaller in size: an average structure thickness of 17 ± 20 µm, in comparison to 83 ± 5 µm for the mini-matrix (Fig. 5). However, these limited differences in number and size of the internal pore structure are unlikely to have an impact on drug release. The difference in sustained release of MPT between the monolithic calendered tablets and the multiparticulates is illustrated in Figure 6. The MPT burst release was reduced by half for all calendered formulations in comparison with the mini-matrices. Moreover, the monolithic calendered tablet sustained MPT release to a larger extent than the mini-matrices, with a complete release after only 24 h instead of 8 h in case of formulation A. The lower mass transport rates from the calendered tablets were linked to the dimensions of the dosage forms:

the core of the calendered tablet had a diameter of 7 mm and a thickness of 4 mm, whereas the core of the mini-matrices had a diameter of 3 mm and a length of 2 mm. The importance of relative surface area available highlighted the importance of diffusion path length for MPT dissolution from the matrices and was confirmed by performing dissolution tests on cylindrical extrudates with a similar surface area/volume ratio to the calendered tablet and on a central part of the calendered tablet with the same dimensions as the mini-matrices. Both test set-ups indicated that the diffusion path length is the main contributor for the differences in release profiles observed between the calendered tablets and the multiparticulate formulation. Based on the release data it is evident that manufacturing an easily swallowable tablet-shaped monolithic dosage form offered an advantage over the multiparticulate formulation for sustained drug release. For the calendered formulation B, with 5 % PEO and 30 % drug content, MPT release after 48 h was only 75 %. In contrast, complete drug release from formulation C (containing 20 % PEO and 15 % MPT) was obtained after 48 h (Fig. 6). These differences in release profiles indicated that PEO was the main contributor for drug release. Because of the smaller dimensions of the mini-matrices, the matrix effect was of lesser importance for MPT release from the multiparticulates. The type of dosage form did not influence the immediate release profile of HCT, with a complete release within 45 min for all formulations (Fig. 7). To assess the impact of cooling during calendering (essential to avoid sticking of the dosage form to the rolls), the effect of the cooling rate on MPT release from the calendered tablets was determined. Cooling was performed via quench-cooling in liquid nitrogen or via cooling at room temperature. However, the MPT release profiles were independent of the cooling technique. Moreover, X-ray diffractograms of the extrudates of formulations A and B demonstrated that cooling rate did not affect crystallinity of MPT in these formulations (Fig. 8).

4. CONCLUSION

In this study we have demonstrated that calendering is a promising downstream processing step to continuously produce tablet-shaped monolithic FDC dosage forms from multi-layered matrix co-extrudates. With the calendered tablet an *in vitro* MPT release was sustained over 24 to 48 h, in combination with an immediate HCT release from the coat. The differences in diffusion path length of the final monolithic tablet-shaped dosage form mainly determined the MPT release from the core. Calendering and cooling did not affect the sustained MPT release profiles. A limited reduction of the porosity of the core after calendering indicated some additional densification of the material during calendering. The shaping technique did not alter the solid state of the drugs. Further characterization using TPI revealed a gradient in coat thickness and incomplete adhesion between core and coat, the latter being inherent to the co-extrudate and independent of the calendering step, as visualized by micro-CT. This implied that at the present stage of development calendering is promising to shape FDC dosage forms with an immediate release coat, but when a sustained or extended release coat needs to be applied the technique is not an adequate solution.

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Tables

Table 1. Composition of calendered formulations A, B and C.

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		Matrix composition (%)			Drug load (%)
Formulation A	Core	EC 53	DBS 27	PEO 1M 20	MPT 30
	Coat	PEO100K 85		PEG 4K 15	HCT 5.6
Formulation B	Core	EC 62	DBS 33	PEO 1M 5	MPT 30
	Coat	PEO100K 85		PEG 4K 15	HCT 5.6
Formulation C	Core	EC 53	DBS 27	PEO 1M 20	MPT 15
	Coat	PEO100K 85		PEG 4K 15	HCT 2.8

372

Figures

Fig. 1. Cross-section (left) and side-view (right) of a calendered tablet, with a sustained release core and an immediate release coat.

Fig. 2. False-colour images, showing spatial distribution, and histograms of coating thickness for coat layer and for the air gap between core and coating layer, of the calendered tablet formulation B, analysed both at top and bottom of the tablet.

Fig. 3. Micro-CT image of a string of calendered tablets, were the recurrent thinner part of the coat layer is indicated with an arrow, and detail of the calendered tablet for formulation B.

Fig. 4. Evolution of glass transition temperature, fitted with a Gordon-Taylor law (⬲) and solubility curve ◆ for HCT in the PEO/PEG carrier.

Fig. 5. Pore size distributions of internal pores for mini-matrix (■) and calendered tablet (●), analysed on a reconstructed micro-CT image.

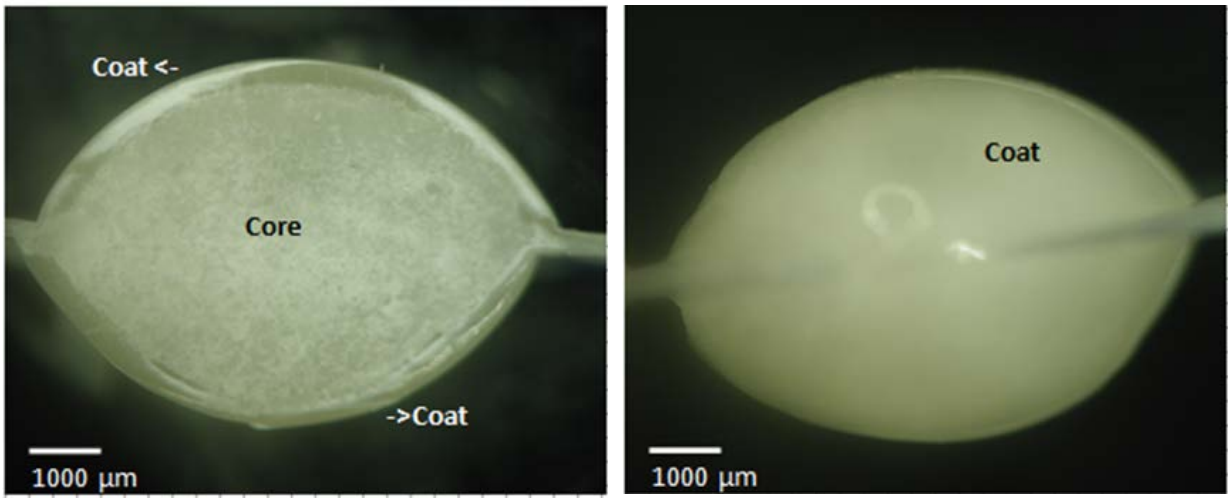
Fig. 6. *In vitro* MPT release (in phosphate buffer pH 6.8) from calendered tablets (open symbols) and mini-matrices (closed symbols) for formulation A (circle), formulation B (square), formulation C (triangle). Mean (n = 3) dissolution profiles (± SD) of co-extrudates.

Fig. 7. Mean in vitro HCT release (in HCl 0.1 N) from calendered tablets (open symbols) and mini-matrices (closed symbols) for formulations A to C. Mean (n = 3) dissolution profiles (± SD) of co-extrudates.

Fig. 8. X-ray diffraction patterns of extruded core. MPT (1), formulation B cooled at room temperature (2) or quench-cooled in liquid nitrogen (3), formulation A cooled at room temperature (4) or quench-cooled in liquid nitrogen (5).

394 **Fig. 1.** Cross-section (left) and side-view (right) of a calendered tablet, with a sustained release

395 core and an immediate release coat.



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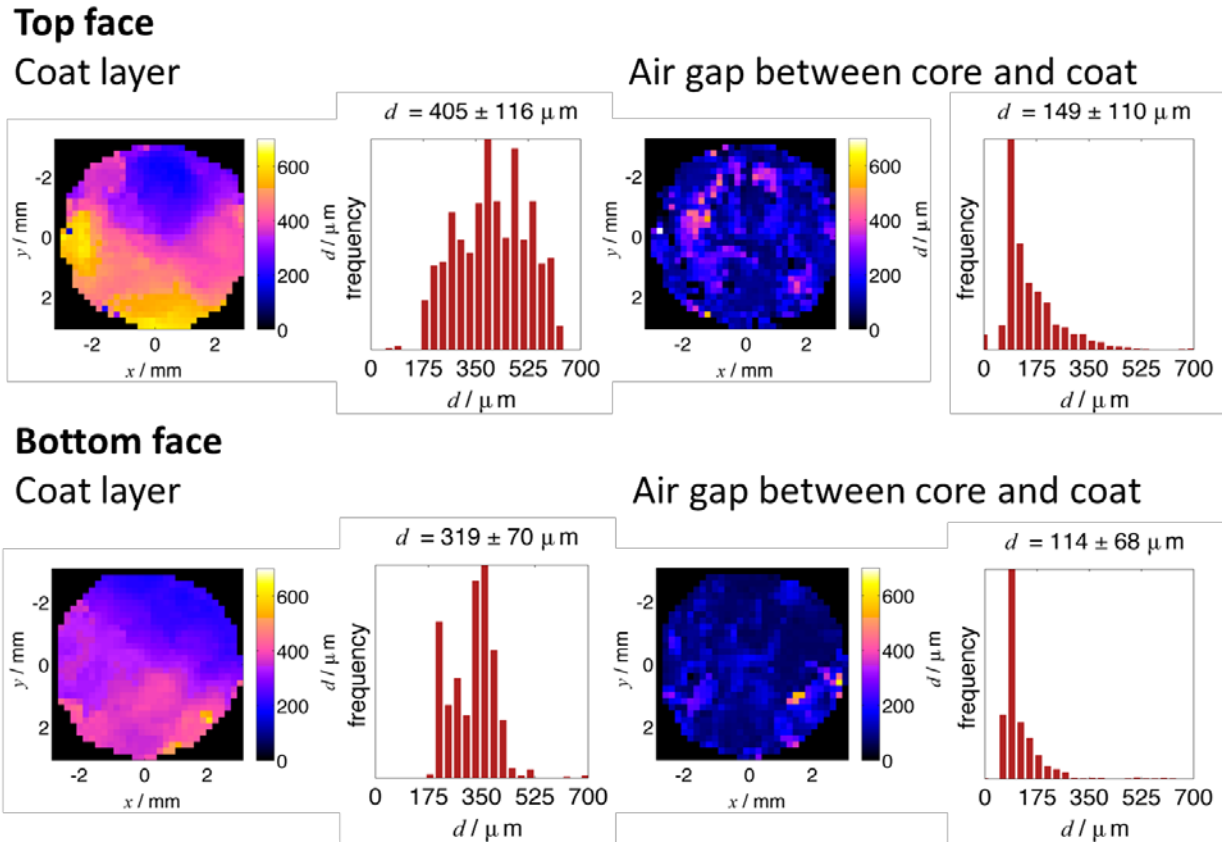

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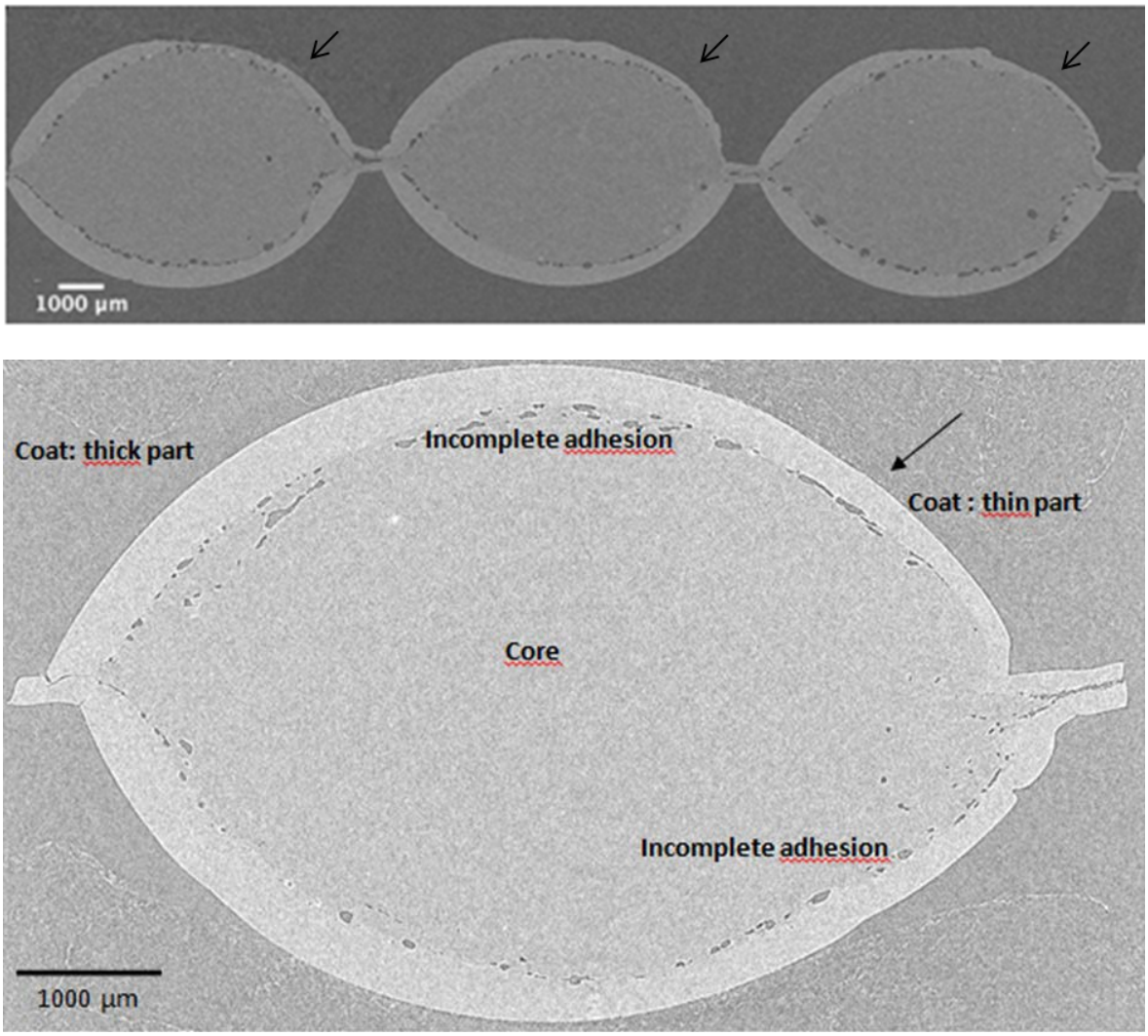

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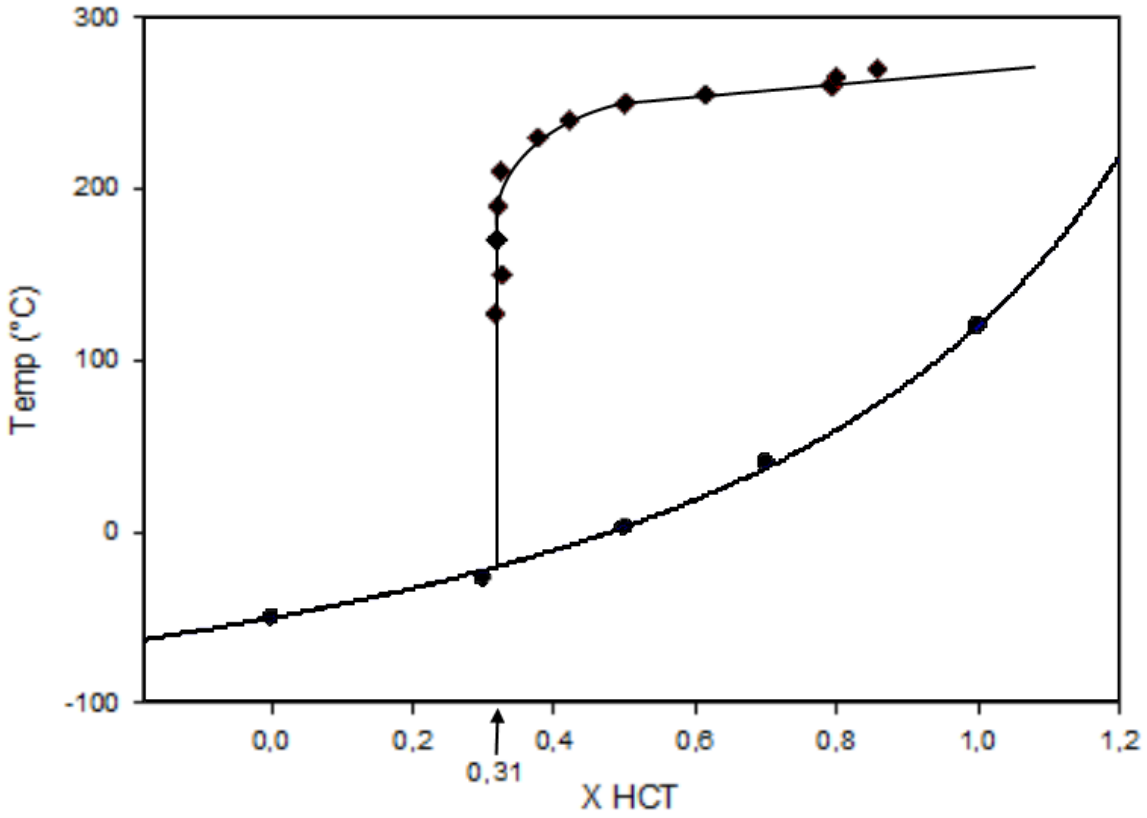

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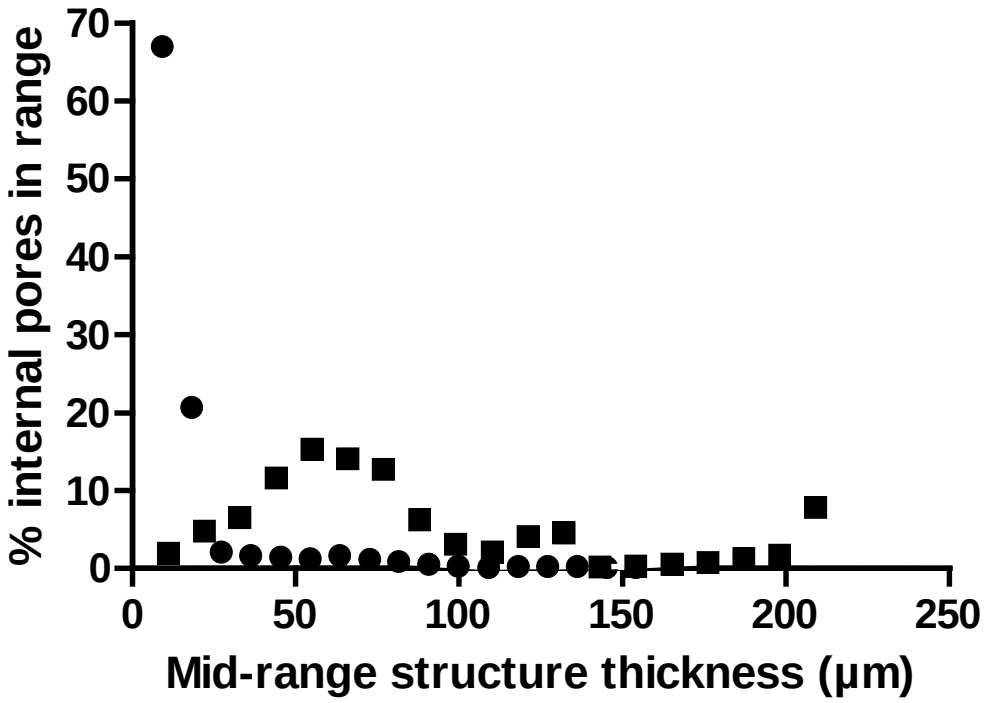

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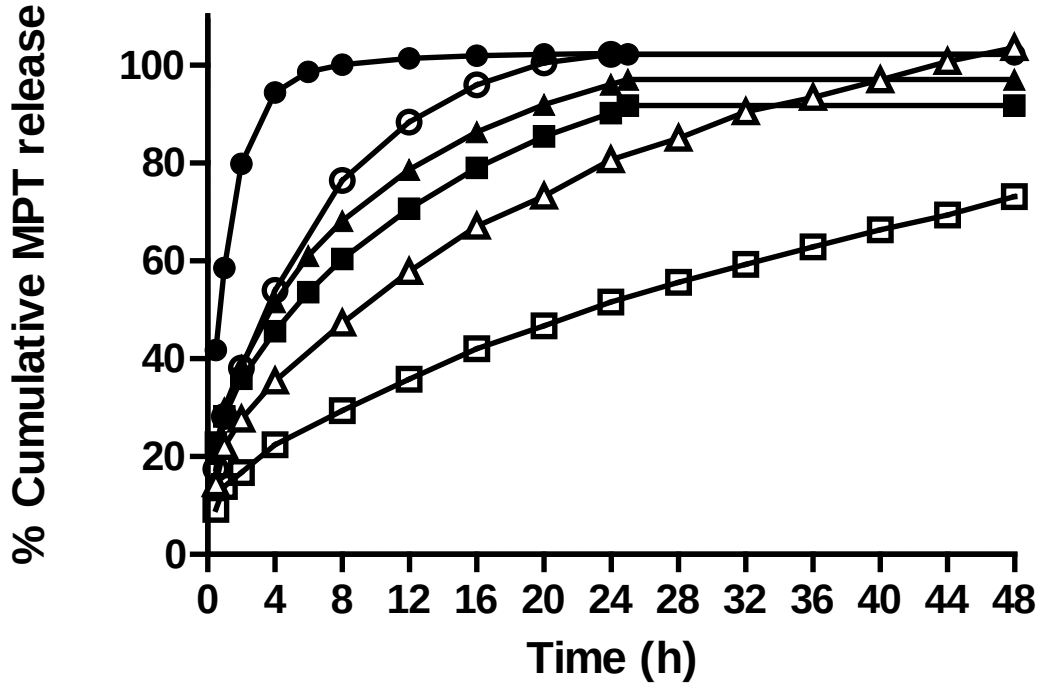

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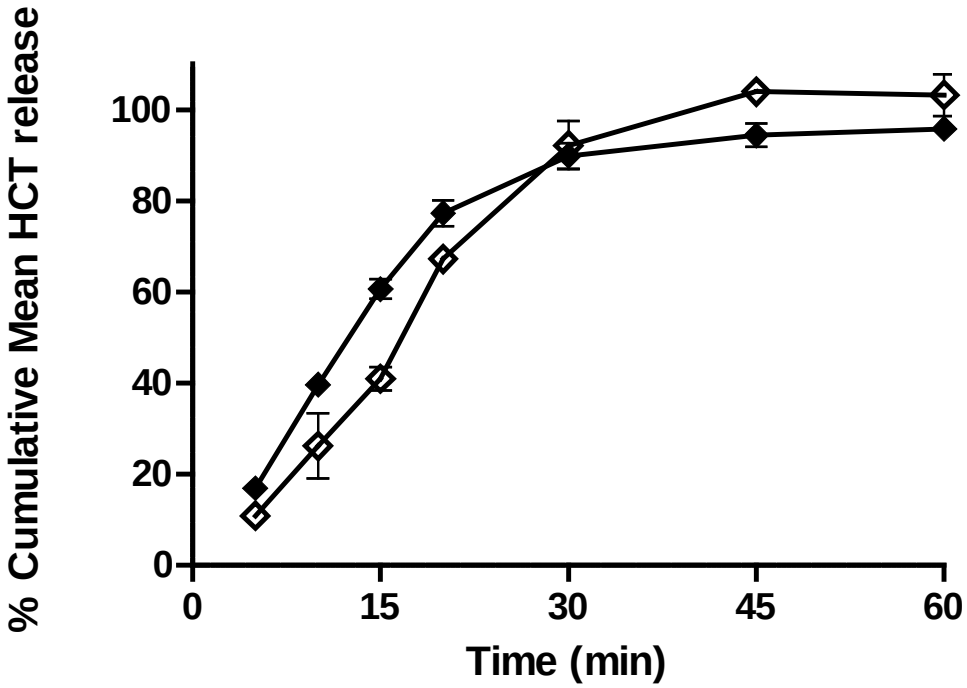

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