ENTERIC PROTECTION OF NAPROXEN IN A FIXED-DOSE COMBINATION PRODUCT PRODUCED BY HOT-MELT CO-EXTRUSION.

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Abstract

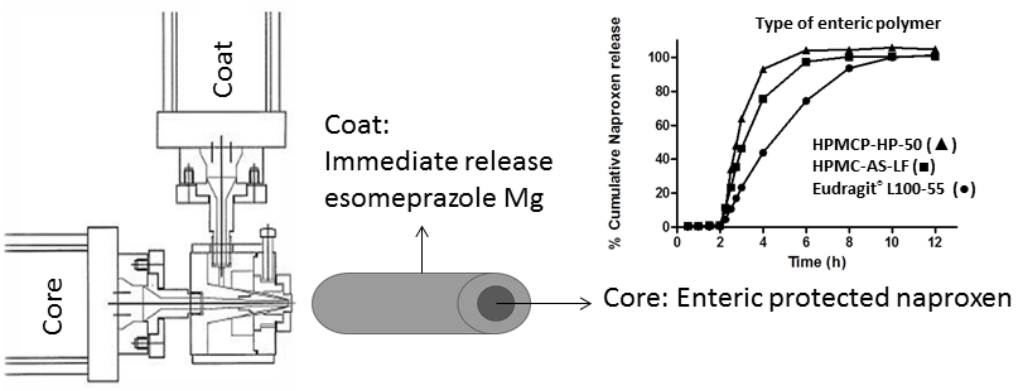
In this study hot-melt co-extrusion is used as processing technique to manufacture a fixed-dose combination product providing enteric protection to naproxen incorporated in the core and immediate release to esomeprazole magnesium embedded in the coat. The plasticizing effect of naproxen and triethyl citrate (TEC) was tested on the enteric polymers investigated (Eudragit® L100-55, HPMC-AS-LF and HPMCP-HP-50). Core matrix formulations containing HPMC-AS-LF, TEC and a naproxen load of 15, 30 and 50% were processed and characterized. The *in vitro* naproxen release in 0.1N HCl was prevented for 2h for all formulations. The physicochemical state of the drug in the extrudates was determined and a stability study was performed. Intermolecular interactions between naproxen and polymer were identified using attenuated total reflection Fourier-transform infrared (ATR FT-IR) spectroscopy. When esomeprazole magnesium was formulated in a polyethylene oxide 100K:polyethylene glycol 4K (1:1) matrix, separated from the naproxen-containing layer, the formulation could be easily processed and complete *in vitro* drug release was observed after 45min. When co-extruding the core/coat dosage form it was observed that a third layer of polymer, separating the naproxen loaded enteric formulation in the core from the coat, is required to prevent degradation of the acid-labile esomeprazole magnesium at the core/coat interface.

Keywords: enteric protection, hot-melt co-extrusion, continuous production, fixed-dose combination product, matrix formulation

Chemical compounds studied in this article:

Naproxen (PubChem CID: 156391); EsomeprazoleMg (PubChem CID: 130564)

54 **Graphical abstract**



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1. INTRODUCTION

Hot-melt co-extrusion is defined as the simultaneous hot-melt extrusion of two or more materials creating a multi-layered extrudate (Vynckier et al., 2014a). This continuous manufacturing technique still has to break through in pharmaceutical production, although several literature reports are already available on the use of co-extrusion for oral drug delivery. Quintavalle et al. (Quintavalle et al., 2007, 2008) were the first to produce cylindrical co-extrudates with controlled drug release via hot-melt extrusion, using polyethylene glycol as hydrophilic matrix and stearic acid or microcrystalline wax as hydrophobic matrix. Co-extruded mini-matrices have recently been formulated using core/coat technology with drugs incorporated in different polymer matrices in order to steer the release of different drugs (Dierickx et al., 2012; Vynckier et al., 2014b) or to provide a dual release of a single drug (Dierickx et al., 2013). Although co-extrusion offers the potential to formulate fixed-dose combination products containing two chemically incompatible drugs in separate layers, this application has not yet been reported.

The present study investigated if hot-melt co-extrusion allowed to manufacture a fixed-dose combination product providing enteric protection to the active pharmaceutical ingredient (API) incorporated in the core and immediate release to the API embedded in the coat. Several enteric polymers were tested as core matrix former in combination with naproxen. This non-steroidal anti-inflammatory drug (NSAID) was used as a model drug. Since gastro-protective co-therapy using a proton pump inhibitor is recommended to decrease the incidence of NSAID-related adverse events, esomeprazole magnesium was incorporated in the coat (Cryer et al., 2011; Wang-Smith et al., 2012). Esomeprazole magnesium was formulated in a separate non-enteric polymer layer providing immediate drug release, which is essential to achieve rapid absorption of esomeprazole (Howden, 2005). For both the core and coat layers different polymers were tested and their influence on release, physicochemical state characteristics and stability was monitored. Finally it was evaluated if co-extrusion as an innovative processing technique of core/coat dosage forms allowed to formulate the two chemically incompatible

API’s in a bilayer fixed-dose combination and still offered the desired release profile for both API’s, as obtained by Wang-Smith et al. (2012).

2. MATERIALS AND METHODS

2.1 Materials

Naproxen (pKa 4.15) (Fagron, Waregem, Belgium) and esomeprazole magnesium trihydrate (Nifty labs, Hyderabad, India) were chosen as model drugs. Vimovo® (AstraZeneca, Brussels, Belgium), containing 500 mg enteric-coated naproxen and 20 mg non-enteric coated esomeprazole Mg, was used as a commercially available reference. The following enteric polymers were used: methacrylic acid – ethyl acrylate copolymer (1:1) Type A (Eudragit® L100-55, Evonik, Darmstadt, Germany), hydroxypropyl methylcellulose acetate succinate (HPMC-AS-LF, Aqoat® AS-LF, Shin-Etsu, Tokyo, Japan) and hydroxypropyl methylcellulose phthalate (HPMCP-HP-50, Shin-Etsu, Tokyo, Japan). Triethyl citrate (TEC, Sigma-aldrich, Bornem, Belgium) and talc (Luzenac® Pharma, Imerys Talc, Gent, Belgium) were used as excipients in the core formulation. The polymers used in the coat formulation were polyethylene oxide 100K (PEO 100K, Mw: 100000 g/mol, SentryTM Polyox® WSR N10, Colorcon, Dartford Kent, United Kingdom), polyvinylpyrrolidone (Kollidon®12 PF, Mw: 2500 g/mol, BASF, Ludwigshafen, Germany), hydroxypropyl methylcellulose (Methocel® E3, viscosity: 3 mPa.s, Colorcon, Dartford Kent, United Kingdom), hydroxypropyl cellulose (Klucel® EF, Mw: 80000, Ashland, Covington, USA) and polyethylene glycol 4K (PEG 4K, Mw: 4000 g/mol, Fagron, Waregem, Belgium). All other chemicals were of analytical grade.

2.2 Methods

2.2.1 Hot-melt extrusion and co-extrusion

In a first step hot-melt extrusion was performed to select an appropriate polymer matrix for core and coat separately, using a co-rotating Prism Eurolab 16 mm fully intermeshing twin-screw extruder (ThermoFisher Scientific, Karlsruhe, Germany) connected to a co-extrusion die having a core and coat insert with a diameter of 4 and 6 mm, respectively (Guill, West Warwick, USA). For the core formulations the processing temperatures are given in Table 1. The coat formulation was processed at a temperature of 100 °C in all zones of the extruder and the die. Premixes of drug, polymer and additives were fed into the extruder using a Brabender

Flexwall® loss-in-weight powder feeder (Brabender, Duisburg, Germany) at a feed rate of 375 g/h for the coat and 300 g/h for the core material. A screw speed of 120 rpm was used for each of the extruders.

In a second phase co-extrusion was carried out using two co-rotating Prism Eurolab 16 mm twin-screw extruders (ThermoFisher Scientific, Karlsruhe, Germany), both connected to the co-extrusion die (Guill, West Warwick, USA). A cylindrical co-extrudate with a core diameter of 4 mm and a concentric coat with a thickness of 1 mm (total co-extrudate diameter: 6 mm) was manufactured. After cooling to room temperature the cylindrical co-extrudate was manually cut into cylinders of 10 mm length, which were used for further analysis.

2.2.2 *In vitro* drug release

In vitro dissolution was performed using United States Pharmacopeia (USP) dissolution apparatus 2 (paddles) 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 was kept at 37 ± 0.5 °C and the rotational speed of the paddles was set to 100 rpm. To characterize the release of naproxen from the core of the extrudates 750 ml of a 0.1 N solution of HCl was used as the dissolution medium for the first 2 h. After collecting the 2 h sample, 250 ml $Na_3PO_4.12H_2O$ 0.2 M was added to the dissolution vessel to adjust the pH of the medium to 6.8. Samples (filtered using Distek 45 µm filters) of 5 ml were withdrawn after 0.5, 1, 1.5 and 2 h in the acid stage and consequently after 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h and 10 h in the pH 6.8 buffer stage. To assess the esomeprazole magnesium release from drug-loaded coat of the extrudates a dissolution test in demineralized water was performed for 2 h. For this *in vitro* dissolution test samples of 5 ml were withdrawn after 5, 10, 15, 20, 30, 45, 60, 90 and 120 min. Each experiment was performed in triplicate.

2.2.3 Ultra high performance liquid chromatography (UHPLC) analysis

For the determination of both active compounds in the dissolution samples an ultra high performance liquid chromatography (UHPLC) analysis was performed using a reversed-phase

C_{18} column with a gradient system (10 min) based on aqueous 10 mM ammonium acetate (A) and acetonitrile (B). The gradient used was: a linear ramp from 0 to 5 min going from 85 % A + 15 % B to 50 % A + 50 % B, changing over to 5 % A + 95 % B at 5.1 min, maintained for 1.8 min and afterwards changing over to chromatographic start conditions 85 % A + 15 % B from 6.9 min to 7 min, followed by an equilibration of 3 min preceding the next injection. An Acquity CSH C_{18} column (1.7 µm particle size, 2.1 x 100 mm) (Waters, Brussels, Belgium) was used in an oven set at 40 °C. The flow rate was set at 0.35 ml/min, injection volume was 0.3 µl. A photo-diode array detector (Acquity, Waters, Brussels, Belgium) was used. For the quantification of esomeprazole a detection wavelength of 290 nm was used, whereas for naproxen the detection wavelength was set at 260 nm. An appropriate calibration curve was applied for quantification of esomeprazole and naproxen, respectively.

For the quantification and purity determination of esomeprazole in the solid dosage forms a verified UHPLC method was developed, using an Acquity CSH C_{18} column (1.7 µm particle size, 2.1 x 100 mm) (Waters, Brussels, Belgium) in an oven set at 40 °C, with a gradient system (30 min) based on the same two-component mobile phase system: aqueous 10 mM ammonium acetate (A) and acetonitrile (B). The gradient used here was: a linear ramp from 2 to 20 min going from 90 % A + 10 % B to 5 % A + 95 % B, holding this condition for 5 min and afterwards changing over to chromatographic start conditions 90 % A + 10 % B from 25 to 25.1 min, maintaining this condition for 4.9 min as an equilibration step preceding a next injection. The flow rate was set at 0.35 ml/min, an injection volume of 1.2 µl was used. For the quantification of esomeprazole a photo-diode array detector (Acquity, Waters, Brussels, Belgium), with a detection wavelength set at 301 nm, was used. Sample preparation was performed by stirring the extrudates in a 10 ml flask filled with demineralized water : acetonitrile in a 1 : 1 ratio. An appropriate calibration curve was applied for quantification of esomeprazole.

The UHPLC system consisted of an isocratic solvent pump, an automatic autosampler and a column oven (Acquity, Waters, Brussels, Belgium). Peak integration and data acquisition was performed using the software package Empower® (Waters, Brussels, Belgium).

166 2.2.4 Modulated differential scanning calorimetry (MDSC)

167 The crystallinity of naproxen in the enteric core matrix and the thermal behavior of pure
168 compounds, physical mixtures and corresponding extrudates were studied using a differential
169 scanning calorimeter Q2000 V24.8 equipped with a refrigerated cooling system (TA
170 Instruments, Leatherhead, UK). Nitrogen was used as purge gas through the DSC cell (50
171 ml/min) and the RCS unit (300 ml/min). Samples (± 8 mg) were run in hermetically closed
172 Tzero pans with perforated lid, supplied by TA Instruments, with an underlying heating rate of
173 2 °C/min. The modulation period and amplitude were set at 60 s and 0.318 °C, respectively.
174 After a first heating cycle to 175 °C, samples were cooled to -30 °C using a linear cooling rate
175 of 10 °C/min. Finally, a second modulated heating cycle was applied. Mass of sample pan and
176 empty reference pan were taken into account. Temperature and enthalpy calibration were
177 performed using an indium standard, whereas calibration of the heat capacity was performed
178 using a sapphire standard. MDSC data were analyzed using the TA Instruments Universal
179 Analysis 2000 V4.7A software. Melting enthalpies and glass transition temperatures were
180 determined in the total heat flow signal and reversing heat flow signal, respectively. Reported
181 glass transition temperatures of the physical mixtures were determined in the second heating
182 cycle to ensure maximal interaction between the compounds and to simulate a thermal history
183 comparable to the extrudates when analyzed during the first heating cycle in MDSC. The
184 degree of crystallinity was calculated comparing the melting enthalpy of the naproxen melting
185 peak in the analyzed sample to that of pure naproxen (147.2 J/g).

186 2.2.5 X-ray diffraction

187 Crystallinity was analyzed using X-ray diffraction (XRD) on pure compounds, physical
188 mixtures and corresponding extrudates. X-ray diffraction was performed on a D5000
189 diffractometer with Cu Kα radiation (λ = 1.54 Å) (Siemens, Karlsruhe, Germany) and a voltage
190 of 40 mV in the angular range (2θ) varying from 4 to 60 ° using a step scan mode with a step
191 size of 0.02 ° and a measuring time of 1 s/step.

192 2.2.6 Attenuated total reflection Fourier-transform infrared analysis

193 Attenuated total reflection Fourier-transform infrared (ATR FT-IR) spectroscopy was
194 performed on the pure substances, physical mixtures and extrudates to identify molecular
195 interactions formed between naproxen and the enteric polymers during extrusion. Spectra
196 were recorded in absorbance mode using a Nicolet iS5 ATR FT-IR spectrometer
197 (ThermoFisher Scientific, Karlsruhe, Germany). A diamond ATR crystal was pressed against
198 the samples in order to obtain the ATR FT-IR spectra in the 4000 – 550 cm^{-1} range, with a
199 resolution of 4 cm^{-1}, averaged over 32 scans.

200 2.2.7 Stability study

201 Clear core extrudates formulated with different polymer matrices and 30 % naproxen
202 (Table 1), and core extrudates containing 50 % naproxen and 50 % HPMC-AS-LF were
203 manufactured to perform a stability study. Immediately after extrusion, the formulations were
204 filled in an amber glass container and stored in closed condition at 25 °C / 60 %RH and in open
205 and closed condition at 40 °C / 75 %RH. To investigate the influence of storage MDSC, XRD,
206 and *in vitro* drug release tests were performed on the extrudates immediately after
207 manufacturing (T0), after 1 week (T1w), 2 weeks (T2w), 1 month (T1m) or 6 weeks (T6w), 3
208 months (T3m) and 6 months (T6m) storage.

209

3. RESULTS AND DISCUSSION

In order to formulate a core/coat fixed-dose combination product via co-extrusion both layers were first independently developed. Afterwards the compatibility of the core and coat matrices was checked. Finally it was evaluated if the final drug-loaded formulations were compatible and if a fixed-dose combination product with the desired release characteristics could be manufactured via co-extrusion.

3.1. Core formulation

To develop a core matrix formulation providing enteric protection for naproxen, using hot-melt extrusion (HME) as production technology, three enteric polymers were compared: methacrylic acid - ethylacrylate copolymer (Eudragit® L100-55), hypromellose acetate succinate (HPMC-AS-LF) and hypromellose phthalate (HPMCP-HP-50). Hot-melt extrusion of these polymers in combination with 15% naproxen required a plasticizer as without plasticizer the torque values during extrusion were too high. Although naproxen (with a melting point at 156.1 °C and a glass transition temperature (*Tg*) of 6.2 °C) (Alleso et al., 2009) had a concentration-dependent plasticizing effect on these polymers (Table 2), the effect of this polymer/drug interaction on the process temperature and/or torque during extrusion cannot be exploited to its full extent as the plasticizing effect was only evident during the second heating cycle of the MDSC analysis of a physical mixture. Hence, these drug/polymer interactions were only established after intense intermolecular contact following the 1st heating phase of the MDSC experiment.

TEC was an efficient plasticizer for Eudragit® L100-55, reducing its *Tg* from 117.7 °C to 108.5 and 90.2 °C after the 1st and 2nd heating cycle, respectively, at a concentration of 10 % TEC. For this formulation a screw speed of 120 rpm and a higher processing temperature at the die-end of the barrel was required to reduce die swell. The addition of 10 % talc to the formulation was critical as it improved the flow properties of the powder, ensuring consistent feeding of the powder into the extruder. When 10 % TEC was added to HPMC-AS-LF the *Tg* lowered from 122.8 °C to 97.5 and 91.1 °C after the 1st and 2nd heating cycle respectively. This

237 formulation, containing 15 % naproxen, yielded an extrudate with a smooth appearance and
238 without die swell when processed at 150 °C. The addition of 10 % TEC to HPMCP-HP-50 as
239 enteric polymer reduced *Tg* from 142.1 °C to 126.6 and 95.7 °C after the 1st and 2nd heating
240 cycle, respectively. The 15 % drug-loaded formulation yielded extrudates that were
241 processable at 145 °C, but had an irregular surface.

242 At a 15 % naproxen content hot-melt extrusion of all polymer formulations resulted in clear
243 extrudates with the entire drug content molecularly dispersed in the polymer matrix. A higher
244 drug load (30 %) resulted in opaque formulations with a significant degree of crystallinity.
245 However, the extrusion temperature was critical to the physicochemical state of the drug in the
246 extrudates as nearly the entire naproxen content was molecularly dispersed in the polymer
247 matrices when processed at a higher temperature (Table 1), e.g. HPMC-AS-LF mixtures with
248 30 % drug processed at 100 and 120 °C contained 29.0 and 2.6 % crystalline drug,
249 respectively. This was also reflected in the X-ray diffractogram of the Eudragit® L100-55
250 extrudates processed at different extrusion temperatures (Fig. 1). Interestingly the
251 hypromellose-based polymers containing a higher naproxen content could be extruded at a
252 lower temperature, even when they contained a significant crystalline drug fraction. This can
253 be linked to the plasticizing effect of naproxen on these polymers: thermal processing of
254 mixtures with a higher drug content induced more interaction between drug and polymer in the
255 extrusion barrel. Hence, a lower extrusion temperature could be employed, without risking too
256 high torque values. This plasticizing effect of naproxen was even more evident for a HPMC-
257 AS-LF formulation containing 50 % naproxen which could be processed without plasticizer at
258 an extrusion temperature of 120/120/120/110/110/100/100 °C from feed opening to die-end,
259 despite its high percentage of crystalline drug.

260 The *in-vitro* naproxen release profiles of the different polymer formulations containing 10
261 % TEC as a plasticizer and loaded with 15 % naproxen are shown in Fig. 2. For all formulations
262 naproxen release in 0.1 N HCl was prevented for 2 h. In pH 6.8 buffer HPMCP-HP-50 matrices
263 showed a faster release rate compared to HPMC-AS-LF and Eudragit® L100-55 formulations.
264 Although the process temperature did affect the API's physicochemical state for the 30 %

naproxen formulations, it did not have a significant effect on the release profiles. The enteric protection of naproxen during a 2 h period was not impaired in formulations containing 30 and 50 % drug. However, naproxen release in pH 6.8 buffer was determined by drug concentration: after 2 h HPMC-AS-LF matrices containing 30 and 50 % naproxen released 58 and 81 % of their drug content, respectively (Fig. 3). Drug release form the core matrix was diffusion and erosion controlled as it was observed that the core slowly eroded during dissolution testing.

A stability study was performed on the transparent extrudates containing 30 % naproxen and 10 % TEC. Independent of the matrix polymer, naproxen completely recrystallized after two weeks storage at 40 °C / 75 %RH, while XRD analysis detected no recrystallization over a 6 month period in a hypromellose matrix stored at 25 °C / 60 %RH. For the 50 % naproxen formulation in HPMC-AS-LF the physicochemical state nor the dissolution profiles of the drug had changed after 6 months storage at the different storage conditions (data not shown).

To identify intermolecular interactions between naproxen and polymer (Eudragit® L100-55, HPMC-AS-LF), Fourier-transform infrared (FT-IR) spectra were collected of transparent extrudates, containing 30 % drug and plasticized with 10 % TEC, immediately after manufacturing and after 2 weeks storage at 40 °C / 75 %RH in open condition (i.e. after recrystallization of the drug). From the FT-IR spectra of the Eudragit® L100-55 formulation shown in Fig. 4 and Fig. 5 it is suggested that naproxen is mainly molecularly dispersed in the formulation immediately after processing, since some of the peaks characteristic for naproxen completely disappeared, e.g. peaks at 1347 cm^{-1} (rocking of OH of the carboxyl group (Balci, 2014)) and 642 cm^{-1} (wagging of OH of the carboxyl group (Balci, 2014)), while others broadened, e.g. peaks at 1416 cm^{-1} (in-plane bending of CH of the naphthalene ring (Balci, 2014)) and 1628 cm^{-1} (bond stretching of the naphthalene ring (Balci, 2014)), confirming the loss of crystalline material (1.3 %). After storage for 2 weeks at 40 °C / 75 %RH the visual recrystallization in the extrudate was confirmed by the appearance of characteristic naproxen peaks in the FT-IR spectra (Fig. 5). The changing ratio between the peaks at 1727 cm^{-1} and 1686 cm^{-1} (attributed to non-hydrogen and hydrogen bonded –C=O stretching of the crystal structure (Paudel and Van den Mooter, 2012)) before and after storage implied that the amount

of hydrogen bonds formed during processing between the drug and the matrix decreased over time (Fig. 6). While the interaction between drug and polymer is maximal immediately after processing, the reduction of the peak at 1686 cm^{-1} after storage clearly indicated that the amount of hydrogen bonds decreased. The peak shifts observed in the extrudates for the naproxen peaks at 1227 cm^{-1} (stretching of CO of the methoxy group (Balci, 2014)) and 1603 cm^{-1} (bond stretching of the naphthalene ring (Balci, 2014)) are another indication of the hydrogen bond interaction between drug and matrix (Fig. 4). Also the HPMC-AS-LF formulations showed a partial recrystallization over time. The characteristic naproxen peaks were more pronounced in the FT-IR spectra of the extrudates after storage. Moreover after storage the characteristic naproxen peaks in the FT-IR spectra of the extrudate were not different from those of pure naproxen (Fig. 7). Also at 1727 and 1686 cm^{-1} (Fig. 8) the FT-IR spectrum of the stored extrudate has the same profile as pure drug. This indicated that there is no permanent interaction between HPMC-AS-LF and naproxen.

3.2. Coat formulation

Formulation of esomeprazole magnesium presents a challenge since degradation of the drug can occur due to a high process temperature and in acidic environment (Razzaq et al., 2012). When formulating esomeprazole magnesium in the enteric polymers Eudragit® L100-55, HPMC-AS-LF and HPMCP-HP-50 complete degradation of the drug occurred, most likely due to the presence of acidic groups in the polymers. Therefore esomeprazole magnesium was formulated in an immediate release polymer, separated from the naproxen-containing enteric layer. A similar approach was used in a commercially available combination product of naproxen and esomeprazole magnesium (Vimovo®) which is formulated as an enteric-coated naproxen tablet with a non-enteric-coated esomeprazole magnesium layer on top (both layers are physically separated via a barrier coat). The immediate release polymers tested were PEO 100K, Kollidon®12 PF, Klucel® EF and Methocel® E3. While extrusion of the PEO 100K formulation was feasible at a process temperature of 100 °C, the other polymers required a processing temperature of 130 °C, even with the addition of a plasticizer, and as a result more

esomeprazole magnesium degradation occurred: only 40 to 75 % of the drug content was recovered after extrusion, vs. 94 % drug recovery in the PEO 100K formulation. As drug release from the PEO 100K polymer was limited to 70 % after 45 min, PEG 4K was added to the mixtures: complete drug release was observed after 45 min in combination with smooth processing (lower torque) for a 2 % esomeprazole magnesium loaded PEO 100K : PEG 4K (1 : 1) formulation (Fig. 9). The coat layer rapidly and completely dissolved during dissolution testing.

Thermal analysis of the physical mixture and the extruded formulation only revealed a melting endotherm of PEO 100K and PEG 4K, due to dissolution of the esomeprazole magnesium crystals in molten polymer. While two distinct melting endotherms were detected for the physical mixture, only a single endotherm was visible in the extruded sample, indicating the formation of a single phase system.

3.3. Co-extrudate formulation

After evaluating the naproxen-containing enteric layer and the esomeprazole magnesium-containing immediate release layer separately, co-extrusion of 50 % naproxen in the HPMC-AS-LF core and 2 % esomeprazole magnesium in the PEO 100K : PEG 4K 1:1 coat yielded an opaque co-extrudate with a smooth surface. However, after cooling of the co-extrudate discoloration was observed at the interface of core and coat (Fig. 10), and *in vitro* dissolution revealed that only 72 % of the esomeprazole content could be recovered, despite the fast and complete dissolution of the PEO / PEG layer. Since this was not seen when processing the co-extrudate with a placebo HPMC-AS-LF + 10 % TEC core, the discoloration is most probably due to an interaction between the naproxen fraction at the core surface and esomeprazole magnesium in the coat, leading to degradation of the acid-labile esomeprazole magnesium. A possible solution to this problem could be the extrusion of a barrier layer between core and coat. This technique is already applied for the production of multi-layer films in packaging applications (Thellen et al., 2009, 2012), but could not be evaluated at this stage as it implies the use of a third extruder.

4. CONCLUSION

Hot-melt extrusion was a suitable technique to manufacture an enteric 50 % naproxen-loaded dosage form. Producing a fixed-dose combination product also containing esomeprazole magnesium in a separate immediate releasing coat was not an adequate solution to prevent interaction between both chemically incompatible API's. Co-extrusion as a continuous one-step manufacturing process for the production of a fixed-dose combination product providing enteric release to naproxen and immediate release to esomeprazole only would be feasible when a third layer of polymer, separating the naproxen loaded enteric formulation in the core from the coat, would be applied to prevent interaction between both API's.

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References

Alleso, M., Chieng, N., Rehder, S., Rantanen, J., Rades, T., Aaltonen, J., 2009. Enhanced dissolution rate and synchronized release of drugs in binary systems through formulation: amorphous naproxen-cimetidine mixtures prepared by mechanical activation. J. Control. Release 136, 45-53.

Balci, K., 2014. The effects of conformation and intermolecular hydrogen bonding on the structural and vibrational spectral data of naproxen molecule. Vib. Spectrosc. 70, 168-186.

Cryer, B.L., Sostek, M.B., Fort, J.G., Svensson, O., Hwang, C., Hochberg, M.C., 2011. A fixed-dose combination of naproxen and esomeprazole magnesium has comparable upper gastrointestinal tolerability to celecoxib in patients with osteoarthritis of the knee: results from two randomized, parallel-group, placebo-controlled trials. Ann. Med. 43, 594-605.

Dierickx, L., Saerens, L., Almeida, A., De Beer, T., Remon, J.P., Vervaet, C., 2012. Co-extrusion as manufacturing technique for fixed-dose combination mini-matrices. Eur. J. Pharm. Biopharm. 81, 683-689.

Dierickx, L., Remon, J.P., Vervaet, C., 2013. Co-extrusion as manufacturing technique for multilayer mini-matrices with dual drug release. Eur. J. Pharm. Biopharm. 85, 1157-1163.

Howden, C.W., 2005. Review article: immediate-release proton-pump inhibitor therapy - potential advantages, Aliment. Pharmacol. Ther. 22, 25-30.

Paudel, A., Van den Mooter, G., 2012. Influence of solvent composition on the miscibility and physical stability of naproxen/PVP K 25 solid dispersions prepared by cosolvent spray-drying. Pharm. Res. 29, 251-270.

Quintavalle, U., Voinovich, D., Perissutti, B., Serdoz, F., Grassi, M., 2007. Theoretical and experimental characterization of stearic acid-based sustained release devices obtained by hot melt co-extrusion. J. Drug Del. Sci. and Tech. 17, 415-420.

Quintavalle, U., Voinovich, D., Perissutti, B., Serdoz, E., Grassi, G., Dal Col, A., Grassi, M., 2008. Preparation of sustained release co-extrudates by hot-melt extrusion and mathematical modelling of in vitro/in vivo drug release profiles. Eur. J. Pharm. Sci. 33, 282-293.

Razzaq, S. N., Ashfaq, M., Khan, I.U., Mariam, I., 2012. Development and validation of liquid chromatographic method for naproxen and esomeprazole in binary combination. J. Chil. Chem. Soc. 57, 1456-1459.

Thellen, C., Schirmer, S., Ratto, J.A., Finnigan, B., Schmidt, D., 2009. Co-extrusion of multilayer poly(m-xylylene adipimide) nanocomposite films for high oxygen barrier packaging applications. J. Membr. Sci. 340, 45-51.

Thellen, C., Cheney, S., Ratto, J.A., 2012. Melt processing and characterization of polyvinyl alcohol and polyhydroxyalkanoate multilayer films. J. Appl. Polym. Sci. 127, 2314-2324.

Vynckier, A.-K., Dierickx, L., Voorspoels, J., Gonnissen, Y., Remon, J.P., Vervaet, C., 2014a. Hot-melt co-extrusion: requirements, challenges and opportunities for pharmaceutical applications. J. Pharm. Pharmacol. 66, 167-179.

Vynckier, A.-K., Dierickx, L., Saerens, L., Voorspoels, J., Gonnissen, Y., De Beer, T., Vervaet, C., Remon, J.P., 2014b. Hot-melt co-extrusion for the production of fixed-dose combination products with a controlled release ethylcellulose matrix core. Int. J. Pharm. 464, 65-74.

Wang-Smith, L., Fort, J., Zhang, Y., Sostek, M., 2012. Pharmacokinetics and relative bioavailability of a fixed-dose combination of enteric-coated naproxen and non-enteric-coated esomeprazole magnesium. J. Clin. Pharmacol. 52, 670-680.

Tables

420 **Table 1.** Extrusion temperature, degree of crystallinity and extrudate appearance of 15, 30 and
421 50 % naproxen loaded core extrudates, with different matrices.

422 **Table 2.** Glass transition temperatures (*Tg*) of placebo and drug-loaded (15 and 30 %) physical
423 mixtures measured by MDSC in a 2nd heating cycle.

424

Tables

Table 1. Extrusion temperature, degree of crystallinity and extrudate appearance of 15, 30 and 50 % naproxen loaded core extrudates, with different matrices.

Matrix polymer	TEC conc.*	Naproxen load	Processing temperature(°C) (from feed opening to die-end)	Appearance	Degree of crystallinity
Eudragit® L100-55	10 %	15 %	100/100/100/100/120/120/120	clear	/
HPMC-AS-LF	10 %	15 %	150/150/150/150/150/150/150	clear	/
HPMCP-HP-50	10 %	15 %	145/145/145/145/145/145/145	clear	/
Eudragit® L100-55	10 %	30 %	110/110/110/110/125/125/125	clear	1.3 %
			100/100/100/100/110/110/110	opaque	37.3 %
HPMC-AS-LF	10 %	30 %	120/120/120/120/120/120/120	clear	2.6 %
			100/100/100/100/100/100/100	opaque	29.0 %
HPMCP-HP-50	10 %	30 %	130/130/130/130/130/130/130	clear	0.7 %
			115/115/115/115/115/115/115	opaque spots	1.5 %
HPMC-AS-LF	/	50 %	120/120/120/110/110/100/100	opaque	70.8 %

*The concentration of plasticizer is expressed in relation to the matrix polymer

433 **Table 2.** Glass transition temperatures (*Tg*) of placebo and drug-loaded (15 and 30 %) physical

434 mixtures measured by MDSC in a 2nd heating cycle.

Formulation	*Tg* (° C)		
	Eudragit®L100-55 + 10%TEC	HPMC-AS-LF + 10%TEC	HPMCP-HP-50 + 10%TEC
100% matrix	90.2	91.1	95.7
85% matrix + 15% naproxen	61.4	63.4	59.0
70% matrix + 30% naproxen	24.9	24.2	26.9

435

436

Figures

Fig. 1. X-ray diffraction patterns of (from bottom to top): naproxen (A), Eudragit® L100-55 (B), the formulation containing 30 % naproxen in a 70 % (Eudragit® L100-55 : TEC 9:1) matrix, processed at, from feed opening to die-end, 110/110/110/110/125/125/125 °C (C) and 100/100/100/100/110/110/110 °C (D).

Fig. 2. *In-vitro* naproxen release profile of formulations containing 15 % naproxen and an enteric polymer, plasticized with 10 % TEC: Eudragit® L100-55 (●), HPMC-AS-LF (■), HPMCP-HP-50 (▲). Dissolution in 0.1 N HCl (2 h) and pH 6.8 buffer (10 h) at 37 °C using paddle dissolution system at 100 rpm (Mean ± SD; n=3).

Fig. 3. *In-vitro* naproxen release profile of two extruded HPMC-AS-LF formulations with 30 (●) and 50 (■) % drug load. Dissolution in 0.1 N HCl (2 h) and pH 6.8 buffer (10 h) at 37 °C using paddle dissolution system at 100 rpm (Mean ± SD; n=3).

Fig. 4. ATR FT-IR spectra of naproxen (blue), Eudragit® L100-55 (green), physical mixture of Eudragit® L100-55 plasticized with 10 % TEC and a drug load of 30 % naproxen (red) and the extrudate of the same formulation immediately after processing (yellow).

Fig. 5. ATR FT-IR spectra of naproxen (blue), physical mixture of Eudragit® L100-55 plasticized with 10 % TEC and a drug load of 30 % naproxen (red) and the extrudate of the same formulation immediately after processing (yellow) and after storage for 2 weeks at 40 °C / 75 %RH (grey).

Fig. 6. ATR FT-IR spectra of naproxen (blue), physical mixture of Eudragit® L100-55 plasticized with 10 % TEC and a drug load of 30 % naproxen (red), the extrudate of the same formulation immediately after processing (yellow) and after storage for 2 weeks at 40 °C / 75 %RH (grey).

Fig. 7. ATR FT-IR spectra of naproxen (blue), HPMC-AS-LF (green), the physical mixture of HPMC-AS-LF plasticized with 10 % TEC and a drug load of 30% naproxen (red), the extrudate

462 of the same formulation immediately after processing (yellow) and after storage for 2 weeks at
463 40 °C / 75 %RH (grey).

464 **Fig. 8.** ATR FT-IR spectra of naproxen (blue), physical mixture of HPMC-AS-LF plasticized
465 with 10 % TEC and a drug load of 30 % naproxen (red), the extrudate of the same formulation
466 immediately after processing (yellow) and after storage for 2 weeks at 40 °C / 75 %RH (grey).

467 **Fig. 9.** *In-vitro* esomeprazole Mg release from the coat extrudate containing 2 % esomeprazole
468 Mg formulated in PEO 100K : PEG 4K 1 : 1 (▲) and pure esomeprazole Mg powder (●).
469 Dissolution in demineralized water for 2 h at 37 °C using paddle dissolution system at 100 rpm
470 (Mean ± SD; n=3).

471 **Fig. 10.** Top view and detail of separated core and coat layer from final co-extrudate,
472 containing 50 % naproxen in the HPMC-AS-LF core and 2 % esomeprazole magnesium in
473 the PEO 100K : PEG 4K 1:1 coat, showing a discoloration at the core surface.

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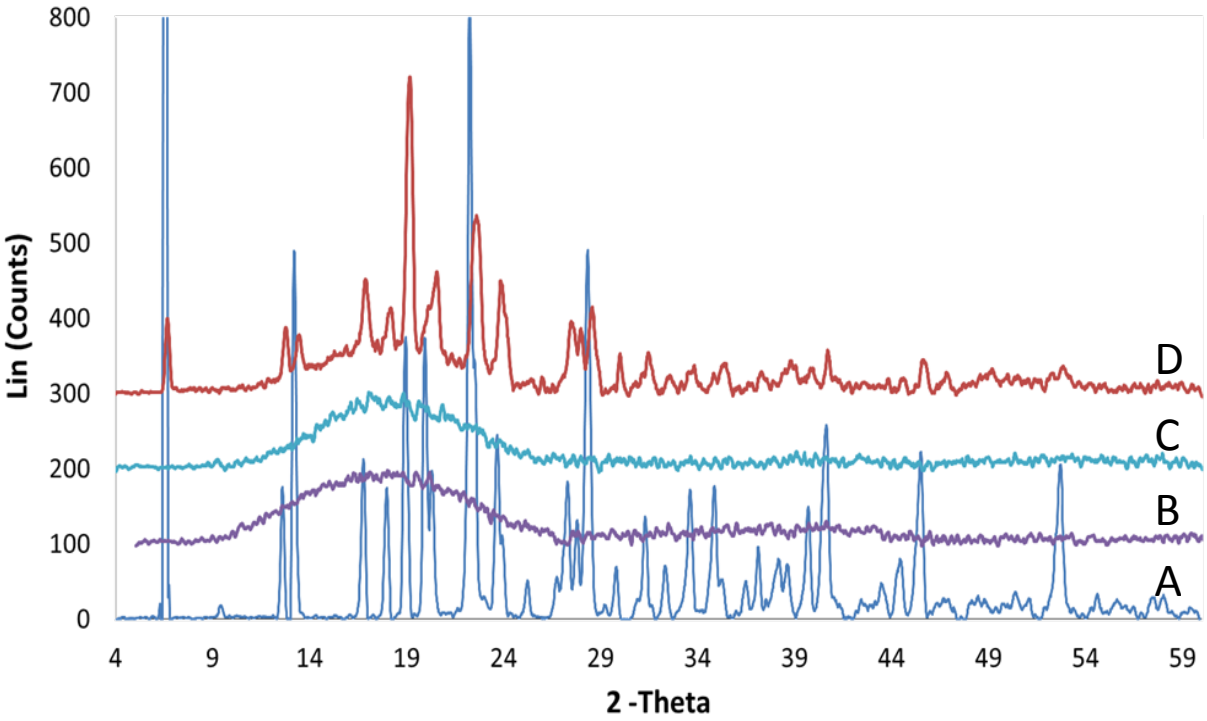
Fig. 1. X-ray diffraction patterns of (from bottom to top): naproxen (A), Eudragit® L100-55 (B), the formulation containing 30 % naproxen in a 70 % (Eudragit® L100-55 : TEC 9:1) matrix, processed at, from feed opening to die-end, 110/110/110/110/125/125/125 °C (C) and 100/100/100/100/110/110/110 °C (D).



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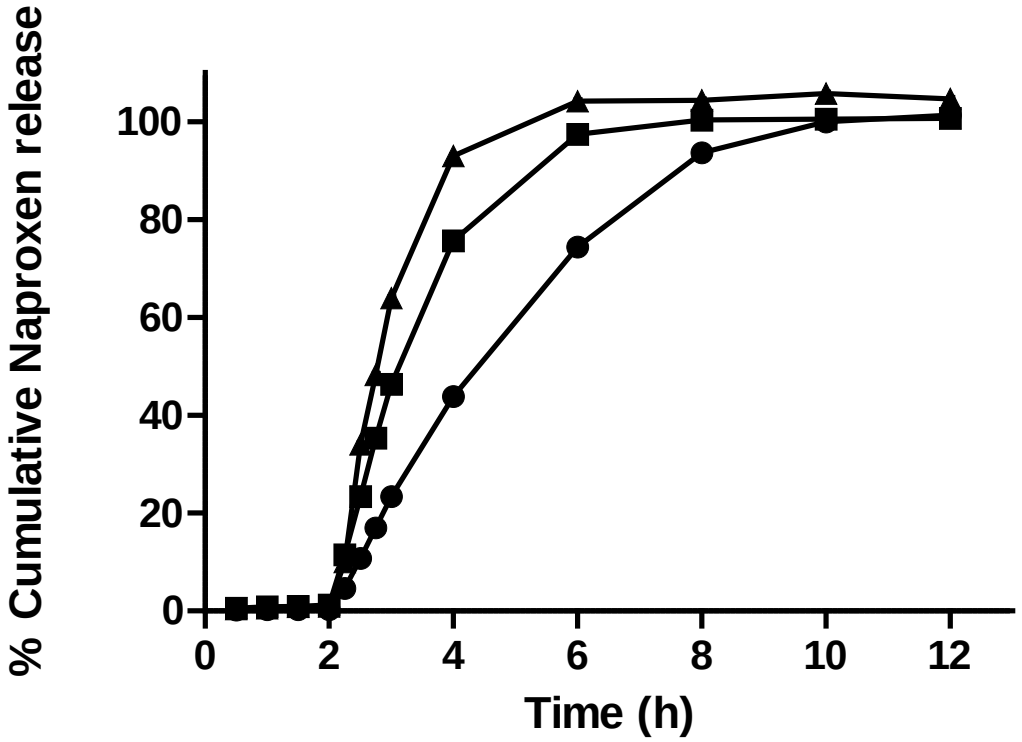

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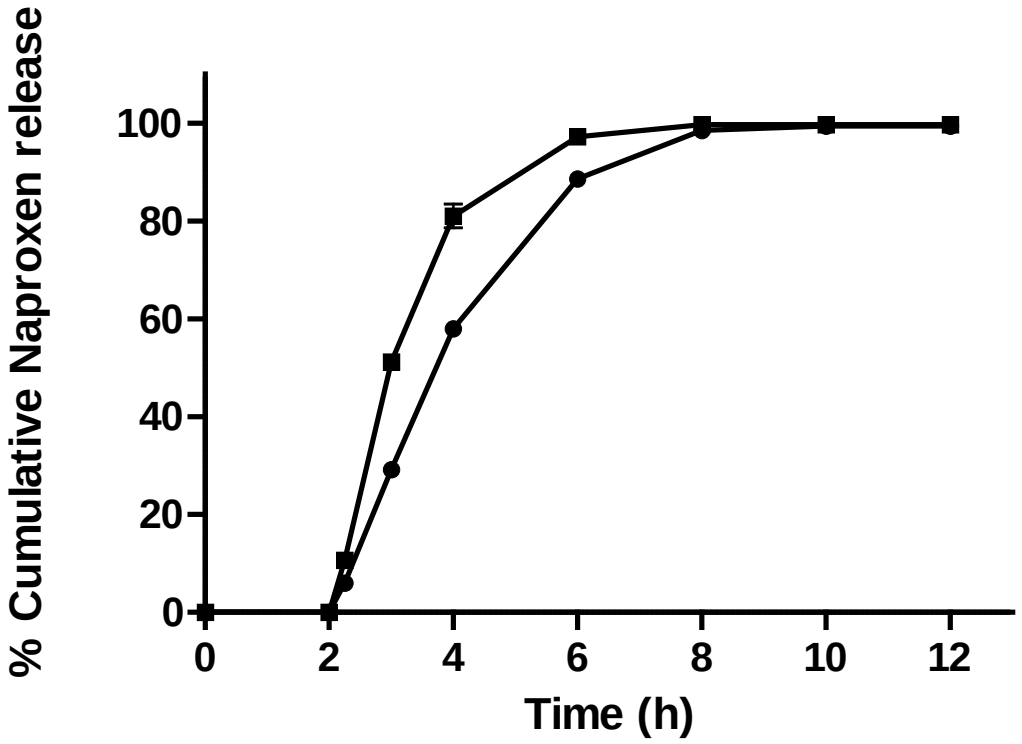
495 paddle dissolution system at 100 rpm (Mean ± SD; n=3).



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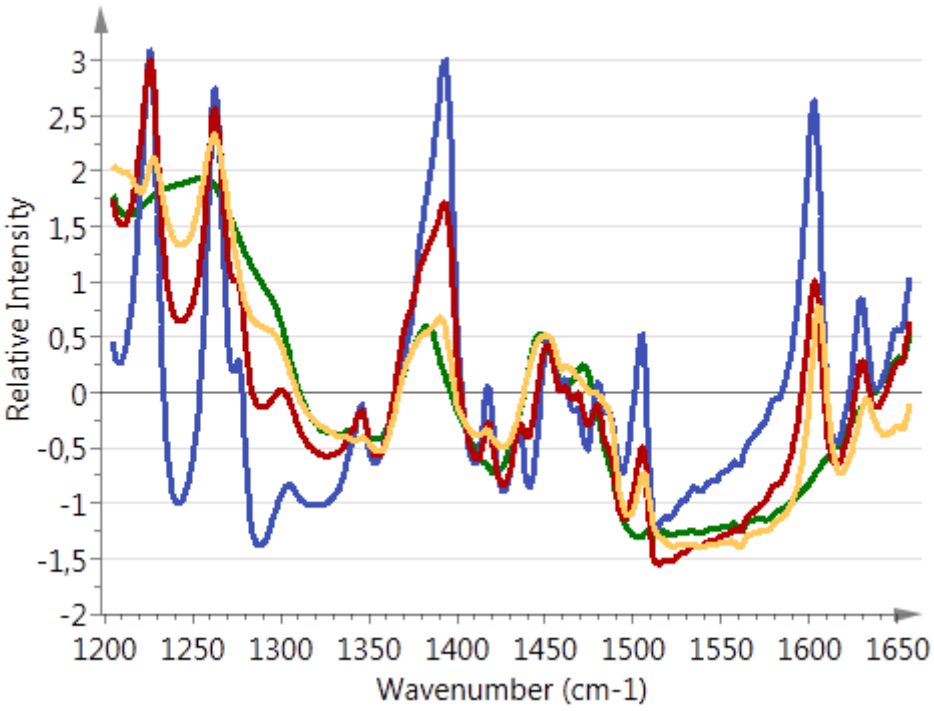

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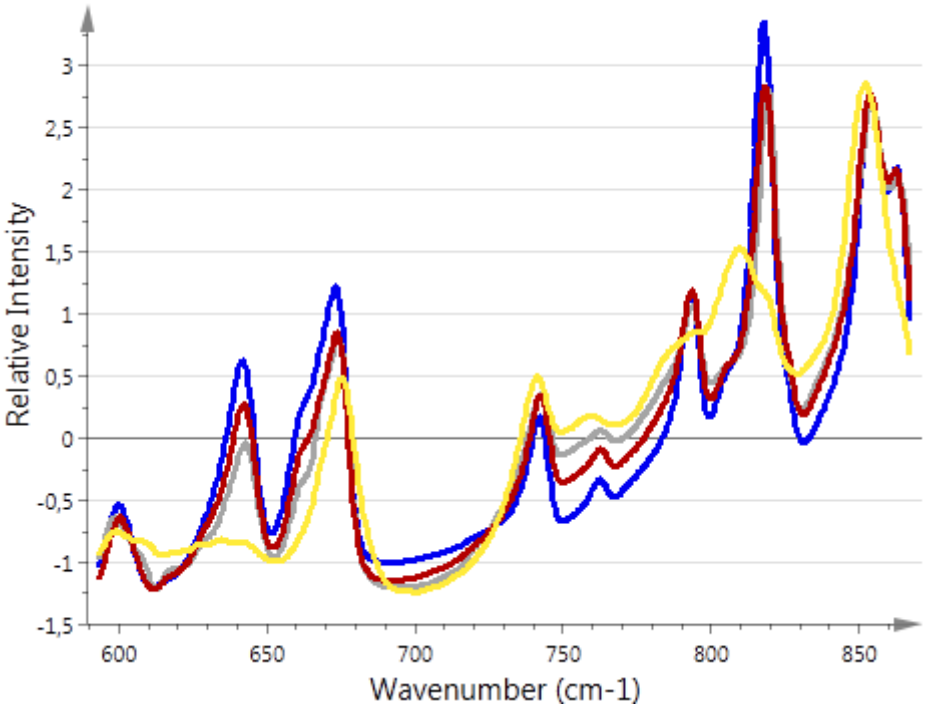

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512 %RH (grey).

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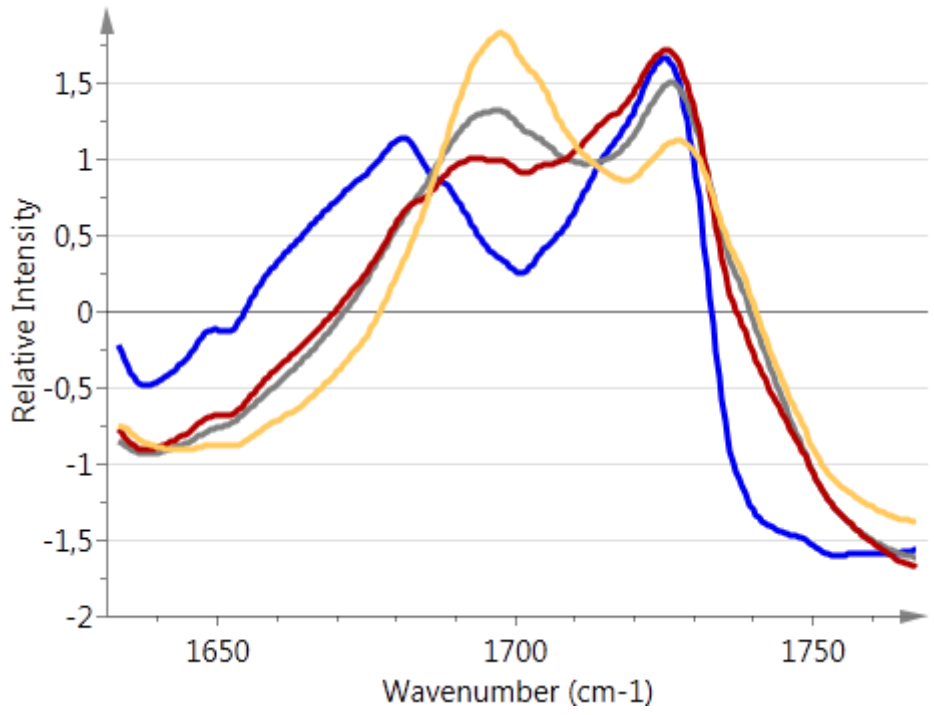

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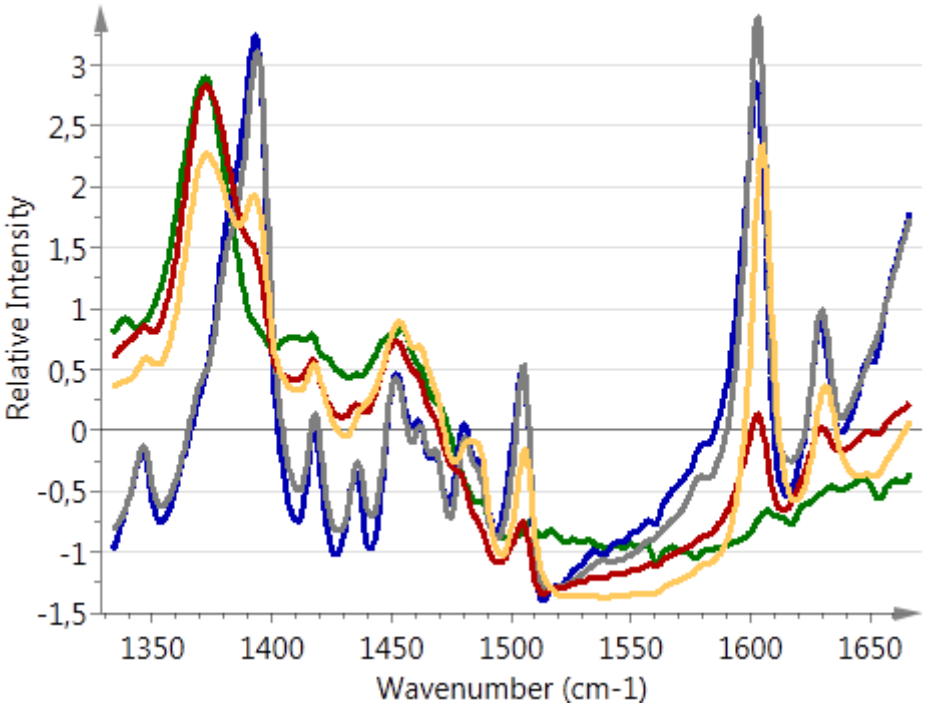

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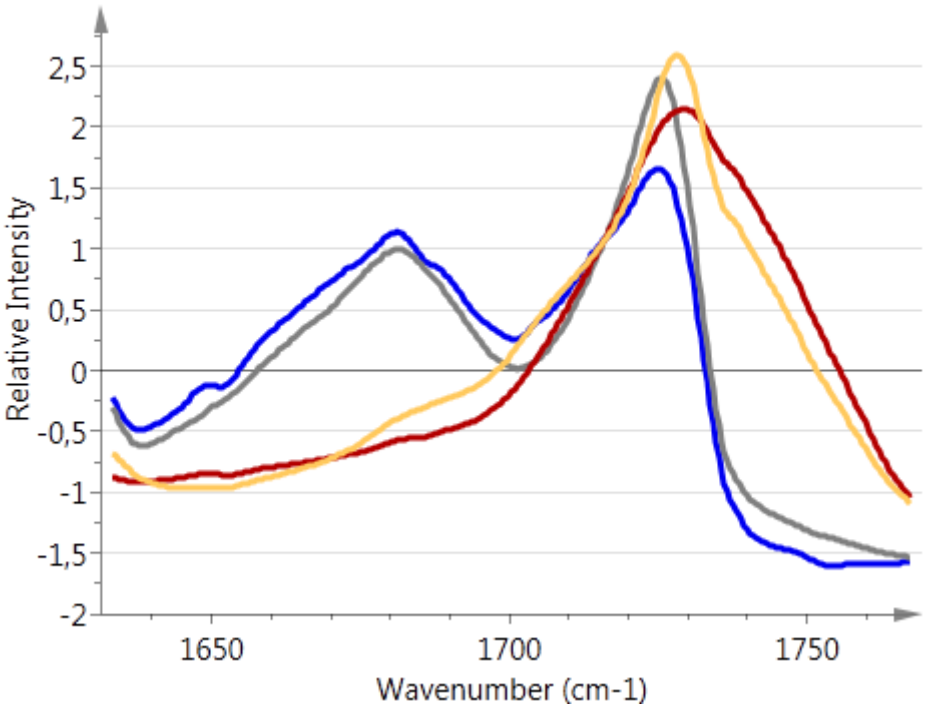

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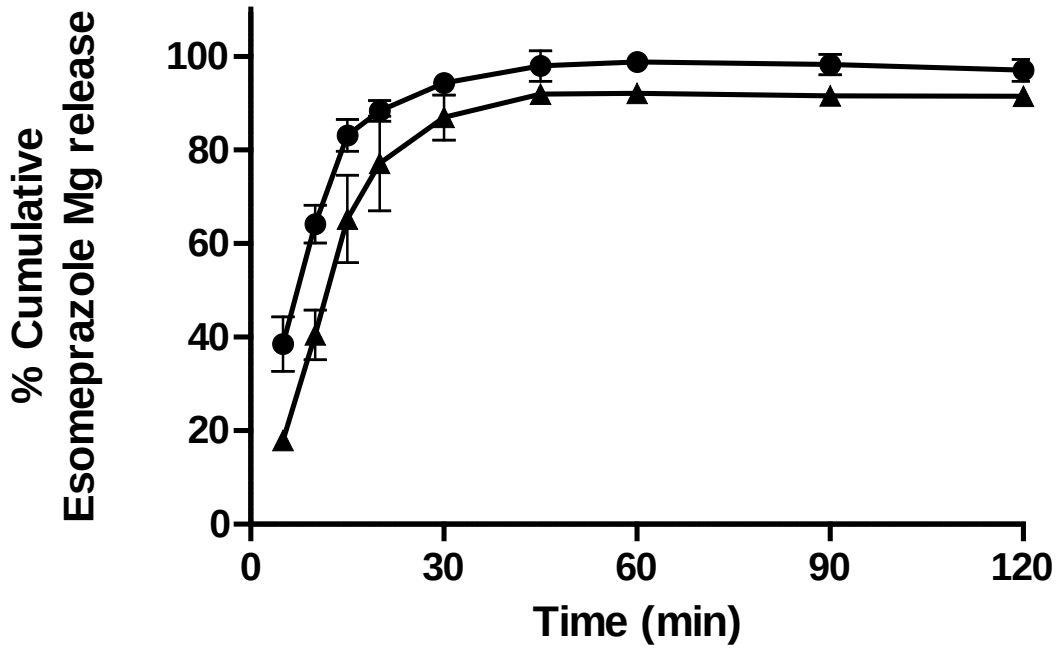

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