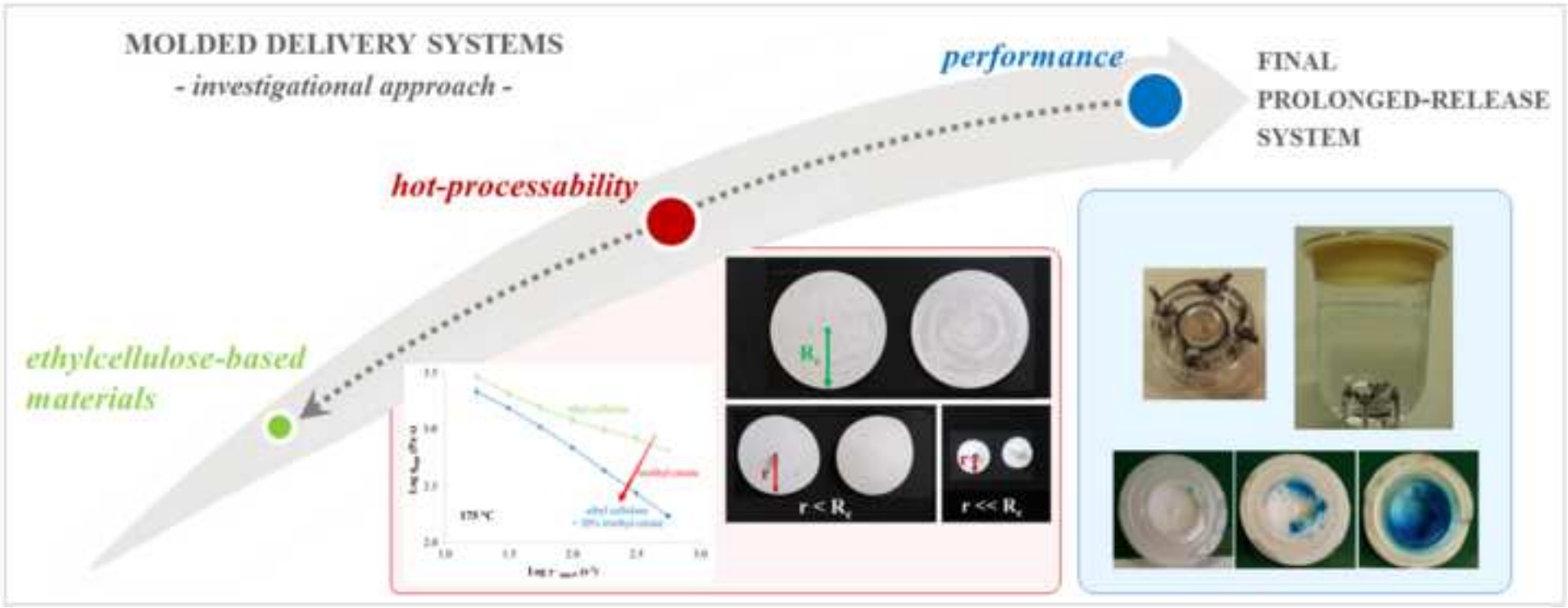
*Graphical Abstract (for review)



Assessment of hot-processability and performance of ethylcellulose-based materials for injection-molded prolonged-release systems: an investigational approach

F. Casati[a,b,1], F. Briatico-Vangosa[c,1], F. Baldi[d], A. Melocchi[a], A. Maroni[a], A. Gazzaniga[a], L. Zema[a*]

[a]Dipartimento di Scienze Farmaceutiche, Sezione di Tecnologia e Legislazione Farmaceutiche "Maria Edvige Sangalli", Università degli Studi di Milano, Milano, Italy;

[b]Current address: IMA S.p.a. - IMA Active division, Ozzano dell'Emilia, Bologna, Italy;

[c]Dipartimento di Chimica, Materiali e Ingegneria Chimica "G. Natta", Politecnico di Milano, Milano, Italy;

[d]Dipartimento di Ingegneria Meccanica e Industriale, Università degli Studi di Brescia, Brescia, Italy.

[1]These authors contributed equally to the work.

[*]Corresponding author: Lucia Zema, Telephone: +390250324654, E-mail: lucia.zema@unimi.it

Abstract

The present work focuses on application of an investigational approach to assess the hot-processability of pharmaceutical-grade polymers with a potential for use in the manufacturing of reservoir drug-delivery systems *via* micromolding, and the performance of resulting molded barriers. An inert thermoplastic polymer, ethylcellulose (EC), widely exploited for preparation of prolonged-release systems, was employed as a model component of the release-controlling barriers. Moldability studies were performed with plasticized EC, as such or in admixture with release modifiers, by the use of disk-shaped specimens ≥ 200 μm in thickness. The disks turned out to be a suitable tool for evaluation of the dimensional stability and diffusional barrier performance of the investigated materials after demolding. The effect of the amount of triethyl citrate, used as a plasticizer, on hot-processability of EC was assessed. The rate of a model drug diffusion across the polymeric barriers was shown to be influenced by the extent of porosity from the incorporated additives. The investigational approach proposed, of simple and rapid execution, holds potential for streamlining the development of prolonged-release systems produced by micromolding in the form of drug reservoirs, with no need for molds and molding processes to be set up on a case-by-case basis.

Keywords: ethylcellulose; micromolding; drug delivery; prolonged release; melt rheology; microcompounder.

1. Introduction

The exploitation of hot-processing techniques, based on the extrusion and molding of polymeric materials, is currently one of the most appealing goals of the pharmaceutical industry, especially with respect to its potential for improving the bioavailability of poorly-soluble drugs, achieving new drug delivery targets and enabling continuous manufacturing (Melocchi et al., 2015; Tiwari et al., 2016; Vynckier et al, 2015; Zema et al., 2012). Moreover, 3D printing of dosage forms, which is supporting the advent of personalized therapy, can also be performed by extrusion, as in the case of fused deposition modeling (FDM) (Genina et al., 2016; Goyanes et al. 2015; Melocchi et al., 2016; Norman et al., 2017). In this respect, injection molding (IM) and 3D printing by FDM were recently proposed for the manufacturing of new drug delivery systems (DDSs) in the form of capsular devices, which may represent an advantageous alternative to traditional reservoir systems, *i.e.* drug-containing cores surrounded by a release-controlling barrier, generally applied by film-coating (Gazzaniga et al., 2011; Macchi et al., 2015; Melocchi et al., 2015; Zema et al., 2013a,b). In fact, capsule shells can be manufactured separately and then filled with different types of drugs/drug formulations, governing the release performance mainly on the basis of the design and composition of the shell itself (*e.g.* gastric resistance, delayed/pulsatile or prolonged release, colon targeting). One of the main reasons that still limits the use of hot-processing techniques in the drug delivery area is the lack of information about the thermal, rheological and stability characteristics of melts resulting from pharmaceutical formulations and of methods for the evaluation of their processability (Aho et al., 2015).

Ethylcellulose (EC) is a non-toxic insoluble polymer that has widely been used for the production of prolonged-release dosage forms, both as reservoir systems and monolithic devices, where the active ingredient is dispersed within the polymer. It is well known that slowing down the release of drugs, thus sustaining their plasma concentrations over time, may be related to major improvements in the therapy efficacy and patient compliance (*e.g.* avoidance of peak-trough concentration profiles and of multiple administrations, reduction of the overall drug dose) (Lin and Chien, 2013).

Depending on the duration of release, these systems can be suitable for different routes of administration. For instance, parenteral implants/inserts (*e.g.* injectable, auricular, ocular, vaginal) are able to deliver their contents for days up to several months, whereas formulations intended for the oral route release the drug conveyed within 12/24 h, consistent with the gastrointestinal transit. EC has shown to be extrudable, and several monolithic DDSs based on this polymer have been manufactured by hot melt extrusion (HME) and FDM as well as IM, the latter techniques allowing finished 3D-shaped items to be fabricated with greater detail precision and versatility in terms of size (miniaturization) and geometry (Bar-Shalom et al., 2003; Feng et al., 2016; Kempin et al., 2017; Mehuys et al., 2004; Quinten et al., 2009,2011; Verhoeven et al., 2006,2009; Vynckier et al., 2014; Zema et al., 2012) More recently, the possibility of attaining EC filaments intended for 3D printing by FDM was also demonstrated (Melocchi et al., 2016; Yang et al., 2018). In the present work, an investigational approach was proposed for time- and cost-effective assessment of the micromolding (µIM) processability of EC-based materials and prediction of behavior of the relevant molded barriers. For this purpose, screening specimens in the form of disks were employed. Indeed, the simple geometry of such a model, which was conceived and exploited for previous rheological, mechanical and barrier performance studies of polymeric materials of pharmaceutical interest, would make the analysis of the process and of its effects on the final product easier and faster to carry out (Melocchi et al., 2016; Zema et al., 2013b; Treffer et al., 2015). Demonstration of EC processability by µIM and its in-depth understanding may ultimately promote development of new DDSs fabricated by this technique. Particularly, the polymeric materials under investigation would be intended for the manufacturing of insoluble barriers, such as the capsule shell or the coating of a dosage form. Such barriers would allow biological fluids to permeate, thus bringing the drug contained within an inner compartment into solution, and the dissolved drug molecules to diffuse through.

2. Materials and Methods

2.1 Materials

Ethylcellulose, EC (Ethocel™ Std. 100 FP premium; Dow, US-MA): particle size ≤ 150 µm, mean particle size 30-60 µm; ethoxyl content 48.0-49.5 %wt; the viscosity of 5% solution in 80% toluene and 20% alcohol (25 °C; Ubbelohde viscometer) 90-110 mPa·s; molecular weight not provided by the producer. Triethyl citrate, TEC (Aldrich, D). Polyvinyl alcohol-polyethylene glycol graft copolymer, KIR (Kollicoat® IR; BASF, D): MW ≈ 45.000 Da; d_{50} = 23 µm and d_{90} = 55 µm. Low-substituted hydroxypropylcellulose, LHPC (L-HPC NBD 020; Shin-Etsu, J): d_{50} = 42.6 µm and d_{90} = 91.1 µm; hydroxypropoxy content 14%. Blue dye-containing preparation (Kollicoat® IR Brilliant Blue, BASF, D), acetaminophen (Rhodia, I).

2.2. Methods

2.2.1 Preparation of materials

Plasticized EC - Plasticized EC mixtures (ECTEC) containing 10, 20 and 25% by weight (% wt) of TEC (ECTEC10, ECTEC20 and ECTEC25, respectively), calculated on the dry polymer, were prepared by kneading (Baldi et al., 2016). EC powder was placed in a mortar and the liquid plasticizer was added dropwise under continuous mixing. The resulting mixture was left 12 h at room conditions (21 ± 5 °C, 55 ± 5% RH). Afterwards, aggregates were ground by means of a blade mill and the < 250 µm fraction was recovered.

Plasticized materials - Release modifies, KIR or LHPC, previously dried in an oven (40 °C for 24 h), were added as powders to milled ECTEC20 in a 70:30, 50:50 and 40:60 weight ratio. Formulations ECTEC20:KIR (70:30), ECTEC20:LHPC (70:30), ECTEC20:KIR (50:50) and ECTEC20:KIR (40:60) were thus obtained, respectively ECTEC20 and the release modifier were mixed in a mortar for less than 1 min; physical mixtures were stored in plastic bags under vacuum and used within 1 or 2 days.

2.2.2 Rheological study

The flow behavior of neat and plasticized EC was evaluated by resorting to a slit capillary die (width 10 mm, height 1.5 mm, length 75 mm) integrated in the recirculation channel of Haake™ MiniLab II (Thermo Scientific™, US-MA) microcompounder, equipped with 2 conical screws (diameter 5/14 mm, length 109.5 mm) in counter-rotating configuration. Samples of 10 g were manually fed into the microcompounder. Data were collected at 165 °C and 175 °C. At each extrusion temperature, a series of measurements was carried out at screw rotation speeds from 10 to 200 rpm, acquiring data at 15 logarithmically-spaced points. For each speed, the difference in pressure between the exit and the entrance of the channel, ΔP, was monitored and recorded when a stable constant value was reached. The ΔP values *vs* revolution speed were then processed according to Yousfi et al., 2014, in order to obtain apparent viscosity curves. In Figure 1 the results obtained by this procedure applied to ECTEC20 are compared with those from standard capillary viscosimetry tests performed on the same material (Baldi et al., 2016). Even if the overlapping of apparent shear rate ranges investigated by the two techniques is limited to one point, the overall trend seems to confirm the reliability of the measurements carried out in this work.

2.2.3 Moldability study

Micromolding (μIM) trials were carried out by a bench-top hydraulic press (BabyPlast 6/10P; Cronoplast S.L., S; Rambaldi S.r.l., I), equipped with a 10 mm piston and cooling circuit. 50 g samples were loaded into the μIM press hopper and extruded from the injecting unit as during a purge operation (air shot test) (Rosato and Rosato, 2000); the test was repeated under different operating temperatures.

Short shot test - ECTEC materials were processed by the μIM press equipped with a disk-shaped mold (diameter 30 mm) provided with a central gate and allowing to set different values of cavity thickness, *i.e.* 1000, 600, 400 and 200 μm. The molding process is pressure-controlled and based on two stages: the first-stage pressure (P_1) supports the filling of the mold cavity, while the second-

stage one (P_2) leads to proper packing of the material until it solidifies (Rosato and Rosato, 2000). During short shot tests, the influence of the filling step on the melt progression throughout the mold was only considered, while P_2 was kept constant at the lowest setting conditions (Table 1). Several injection tests at different P_1 values (10-100 bar, 10 bar increments) and fill time of 1.0 s were initially performed. When incomplete disks were obtained, the fill time was increased up to 2.5 s (0.5 s increments), while keeping all the other settings constant.

Digital photographs of disks, both complete and incomplete, were taken (Nikon D70, Nikon, J) and analyzed by ImageJ. As the image processing software requires a sharp contrast between the scanned object and the background, transparent EC-based disks were coated with a white acrylic paint and laid on a black background. Aspect ratio (AR) (eq. 1) and effective radius (R_{eff}) (eq. 2) of disks were calculated using the major axis (R_{max}) and minor axis (R_{min}) of the best fitting ellipses:

$$AR = R_{max}/R_{min} \qquad (1)$$

$$R_{eff} = (R_{max} + R_{min})/2 \qquad (2)$$

2.2.4 Evaluation of molded products

Dimensional stability - To investigate the tendency to shrinkage and warpage of the molded products, 400 μm screening disks were molded at P_1 values of 40 (ECTEC10) or 30 (ECTEC20 and ECTEC25) bar and a fixed fill time of 1 s, followed by a 1 s packing phase carried out at such P_2 values that the difference between packing and filling pressures, $\Delta P(= P_2 - P_1)$, turned out equal to -20, 0, 30 and 60 bar. Images of the disks were taken by a digital camera (Nikon D70, Nikon, J) immediately after molding and after storage at ambient conditions (t = 1 h, 24 h, 48 h, 72 h and 10 days) or exposure to a 15 min thermal treatment inside the heating chamber of a thermal balance (Mettler PM100 equipped with Mettler LP 15, Mettler-Toledo, I) at 40, 50, 60, 70, 80 and 120 °C. A deformation score, based on an arbitrarily defined scale (ranging from 0 to 5), was attributed comparing samples of the same composition maintained under different storage conditions.

Barrier performance - 600 µm thick disks were evaluated in terms of water uptake, mass loss and permeability to aqueous fluids. When ECTEC materials containing release modifiers were employed, the influence of the method of preparation on the characteristics of the molded barriers was first considered. The mixtures obtained as described above were extruded by a single-screw extruder (Extrusiograph 19/25D, Brabender, D) equipped with a 4 mm rod-shaped die (processing temperatures in the 125 - 140 °C range and rotational speed 15 rpm). 50 g samples of pellets obtained by manually cutting the extruded rods were then used to fill the µIM press. ECTEC materials prepared via the two methods underwent an air shot test, *i.e.* a flow test through the injection nozzle of the molding machine, and showed similar aspect and comparable resistance to manual rupture immediately after ejection and after cooling, independent of the method by which the material was obtained. Moreover, few disks based on the ECTEC20:KIR (70:30) and ECTEC20:LHPC (70:30) formulations were prepared starting from both physical mixtures and extruded pellets. As after processing under the same conditions the hand-made mixtures and the extruded pellets led to disks that showed comparable physical characteristics and permeability behavior, the preparation of ECTEC materials by hand-mixing of powders was preferred for simplicity.

Water uptake and mass loss tests - The test was carried out by adapting a method described in the literature to the shape and dimensions of samples (Karrout et al., 2009). Cylindrical samples (diameter 11 mm; n = 3), die cut from molded disks dried in an oven at 40 °C (24 h), were hung up on a purposely-designed support through a hole that was manually punched on each of them by means of a needle of 0.8 mm in diameter. The support was immersed in 125 mL of distilled water at 37 ± 0.5 °C stirred at 120 rpm (magnetic stirrer). At pre-determined time points, *i.e.* 1, 2, 4, 8 and 24 h, samples were withdrawn, blotted and weighed (m_{wet}). After this procedure, they were dried in an oven at 40 °C for 24 h and weighed (m_{dry}). Water uptake (WU) and dry mass loss (DML) were calculated according to equations 3 and 4, respectively.

$$WU\%\ (t) = [m_{wet}\ (t) - m_{dry}(t)]/\ m_{wet}\ (t)*100 \qquad (3)$$

$$DML\%\ (t) = [m_{dry}(0) - m_{dry}(t)]/\ m_{dry}(0)*100 \qquad (4)$$

Permeability test - The test was carried out with EC disks employing manually-assembled cells (area exposed to the medium = 177 mm^2) modified from the extraction cells used for the dissolution test for transdermal patches (2.9.4 Dissolution test for transdermal patches - Cell method, Ph. Eur. 9.1) (Melocchi et al., 2016; Zema et al., 2013b). Molded disks were mounted to close the cell cavity, which was filled with approximately 50 mg of acetaminophen powder or a blue dye-containing preparation as the tracer (Figure 2). The test (n = 3) was performed by a USP 38 dissolution apparatus 2 (Dissolution System 2100B, Distek, US-MA) in 500 mL of distilled water at 37 ± 0.5 °C, paddle rotating speed 100 rpm.

When cells were loaded with the drug tracer, fluid samples were withdrawn from dissolution vessels at fixed time points over 24 h and assayed spectrophotometrically at 244 nm (spectrophotometer Lambda25, Perkin Elmer, US-MA). Cells filled with the dye-containing formulation were visually inspected over 30 days. By employing a dye tracer, the time taken by the solvent to permeate the polymeric barrier was assessed through the blue coloring inside the cell cavity resulting from the dye dissolution. At the end of the test, disks were collected from the cells and photographed.

Scanning Electron Microscopy, SEM - SEM analysis of disks was carried out before and after immersion in water at 37 °C, under magnetic stirring, for 7 days, followed by drying in a ventilated oven at 40 °C for 24 h. The disks were then broken under liquid nitrogen, in such a way as to obtain a fracture surface almost perpendicular to the direction of the material flow during mold filling, and the cryo-fractured surface was studied by SEM (model Zeiss Evo 50 EP, D) operating in high vacuum mode. The surface, prior to be analyzed, was sputtered with a thin layer of gold.

Release test - The test was carried out on capsular devices. ECTEC materials were processed by the µIM press equipped with a capsular mold having two interchangeable inserts for the manufacturing

of matching cap and body items of 600 µm nominal thickness (Zema et al., 2013a). The process conditions are reported in Table 2. In order to evaluate the release performance of capsular devices (n = 3), each body was filled with 40 mg of acetaminophen (cv ≤ 2) and then closed with the matching cap. The test was carried out in pharmacopoeial apparatus 2 (Dissolution System 2100B, Distek, New Jersey) at 100 rpm, 900 mL of distilled water, 37 ± 0.5 °C . Fluid samples were withdrawn at fixed time points and assayed spectrophotometrically (λ = 244 nm) over a time period of 12 h.

3. Results and Discussion

3.1. Evaluation of material processability

3.1.1 Rheological studies

Rheological characterization of materials was first approached, in order to assess the effect of the amount of TEC and select the temperature conditions for the µIM trials. The need for a plasticizer to enable processing of EC below its decomposition temperature (≈ 180 °C), *i.e.* in the 170-175 °C range, was already demonstrated by capillary rheometry (Baldi et al., 2016). In particular, the addition of 20 % wt of TEC was shown to lower the viscosity at any fixed shear rate and, more interestingly, to give a pronounced shear thinning characteristic to the viscosity curve. Rheological measurements of EC-based materials containing different amounts of the plasticizer were carried out under a compounding step, which would have yielded more easily available and strictly process-related information. The use of this technique was supported by demonstration of agreement of the data collected from ECTEC20 with those previously obtained by standard capillary viscosimetry, as reported in Figure 1.

At all the amounts of plasticizer investigated, a shear thinning behavior was confirmed, and the temperature increase was shown to lower the apparent viscosity (Figure 3). The effect of plasticizer content was more evident at high temperature and low apparent shear rates, while the effects of both temperature and TEC content tended to decrease at high shear rates. It can thus be assumed that

under µIM processing, where shear rates are expected to be higher, also above the maximum value explored in the slit capillary die rheometer, differences in the behavior of the various formulations would be relatively limited. However, during injection into the disk-shaped mold, the flow of the material was neither isothermal nor stationary, as in the rheometer. Thus, fundamental rheological data supply information useful for the screening of materials to be processed. In order to investigate the rheological behavior under processing conditions more in-depth, a series of molding experiments were performed.

3.1.2 Moldability studies

An investigation protocol based on the evaluation of short shots was used to assess the effect of TEC on EC moldability and determine appropriate molding conditions for the resulting mixtures. From preliminary tests, the mold cavity that could completely be filled to give the thinnest disks turned out to be the 400 µm thick one. Using this mold cavity, a wide range of filling conditions was investigated, including injection pressure (10 - 100 bar), fill time (1 - 2.5 s) and plasticizer amount (10 - 25 % wt). All the other process parameters were kept constant (see Table 1).

In each experiment, irrespective of whether the mold cavity was partly or completely filled, the aspect ratio (AR) of resulting disks, either complete or incomplete, turned out very close to 1. The base of screening specimens was thus circular, and the measured radius (R_{eff}) was observed to increase up to 15 mm, *i.e.* the nominal radius of a complete disk, by raising the injection pressure (setting the fill time at 1 s) (Figure 4a). The ECTEC material containing the lowest amount of plasticizer, and therefore characterized by the highest viscosity at each shear rate, required the greatest pressure to entirely fill the mold, while almost complete disks were obtained with ECTEC25 already at the lowest P_1 value. The effect of fill time at a pressure of 20 bar was also investigated. Figure 4b shows that, with ECTEC20, complete cavity filling could be attained provided that enough time was allowed. However, this was not observed with all the formulations and process conditions. Indeed, during other tests performed at lower pressure values, complete

filling was never achieved, even in a longer time, due to the early freezing of the material inside the mold.

3.1.3 Dimensional stability

The tendency of disks to shrinkage and warpage was evaluated, in order to finally select the most adequate material composition and process parameters for the relevant production. Starting from the minimum P_1 value required to have a complete mold filling with each mixture (see Figure 4a), a set of disks were molded at increasing $\Delta P (= P_2 - P_1)$ levels, from -20 to 60 bar. The deformation of such items stored at ambient conditions and after exposure to high temperatures (up to 120 °C) was investigated over time (10 days after demolding). No deformation was shown by disks stored at room temperature, regardless of the amount of plasticizer and of pressures applied during the molding process. In the case of samples exposed to heating treatments, changes in shape (bending and twisting) and diameter (reduction) were observed, which turned out dependent on the amount of plasticizer in the polymeric mixture, on the temperature and on the ΔP applied. Figure 5 and 6 report the minimum temperature at which warpage was observed (T_{start}) and the extent of deformation of disks maintained for 15 min at the highest temperature of 120 °C (Deformation level @ 120 °C) as a function of TEC content and process pressures.

The minimum temperature after exposure to which disks showed warpage seemed almost independent of the pressures applied during the molding process. On the other hand, such a temperature decreased with the increase of plasticizer content in the material. This can be explained by the increase in molecular mobility (at a given temperature) promoted by TEC, which is reflected in the reduction of the glass transition temperature of ECTEC mixtures at increasing TEC content, from 127 °C for neat EC to 80, 60 and 45 °C for ECTEC10, ECTEC20 and ECTEC25, respectively. Glass transition temperature (T_g) was estimated by Dynamical Mechanical Analysis, carrying out heating ramps at the rate of 10 °C/min.

As for maximum deformation at 120 °C, the expected beneficial effect of applying a packing pressure was observed only in the case of disks made of ECTEC20 and, to a lower extent, of ECTEC10.

Therefore, the overall results indicated that 20 % wt of plasticizer would offer the best balance of moldability of the polymeric mixture and dimensional stability of the molded object, also taking possible changes in the composition of the material into account. In fact, while the addition of solid release modifiers, potentially useful to improve the permeability of the polymeric barrier thus increasing the release rate, should enhance the dimensional stability, the presence of polyvinyl alcohol-polyethylene glycol graft copolymer (KIR) and low-substituted hydroxypropyl cellulose (LHPC) particles was already shown to be responsible for an increase in the melt viscosity without affecting the shear-thinning behavior of the material (Baldi et al., 2016).

3.2 Evaluation of molded disk performance

Molded disks were used as a model for release controlling barriers of reservoir delivery systems and advantageously exploited for assessing the potential of materials under investigation as the relevant components. In particular, the ability to take up water, the mass loss resulting from dissolution of soluble components and erosion phenomena as well as the rate of diffusion of tracers through the molded barrier were investigated. The addition of solid KIR and LHPC, a water-soluble and -insoluble additive, respectively, which may act as release modifiers by modulating the permeability of the molded barrier, was also considered (Häbel et al., 2016). The channeling action of such additives in molded barriers was already demonstrated and attributed to particle dissolution in the case of KIR, and formation of cracks as a consequence of swelling in that of LHPC (Zema et al., 2013b).

Disks based on the selected ECTEC20 formulation and containing increasing amounts of the solid additives (charges) were prepared. KIR and LHPC confirmed the tendency to increase the viscosity of melts, as dynamically measured by rotational rheometry (Baldi et al., 2016). Therefore, a mold

cavity having thickness of 600 μm, which was deemed less challenging than 400 μm, was employed, and process parameters were accordingly adjusted (Table 3). In particular, the shot size was increased and the injection pressure was decreased. Due to some limitations in the processability of EC-based materials, the influence of the amount of release modifier added to ECTEC20 was investigated up to 60 % wt only with those containing KIR. The increase in the amount of solid particles in the melt, in fact, involved the use of higher pressures and pointed out some criticalities in the mechanical resistance of disks during automatic ejection.

Water uptake (WU) and dry mass loss (DML) profiles over 24 h relevant to molded disks containing different type and amount of release modifiers are shown in Figure 7.

In all cases, the highest rate of water uptake was observed at the beginning of the test and turned out to strongly be influenced by the composition of EC-based materials. Indeed, the water content of samples after 1 h increased from about 12% in the case of ECTEC20 to 60% of the disks with maximum KIR load, *i.e.* those based on ECTEC20:KIR (40:60) formulation. During the next several hours, water uptake tended to slow down considerably: the water content of disks never increased more than 10% from 8 to 24 h. The ability of materials with the same load of adjuvant to take up water was higher when soluble KIR was used as the release modifier. As regards mass loss, the highest rate was observed for all samples in the first hour of the test. The values reached, generally maintained over 24 h, slightly decreased with increasing amounts of KIR in the material. This suggests that the mass loss of molded disks should be attributed to the release of soluble components. Although very limited, the mass loss of ECTEC20 disks was probably due to the leaching of the plasticizer. Indeed, TEC is known to have < 10% miscibility with water (Snejdrova and Dittrich, 2012). Dry mass loss profiles of disks containing the water-insoluble release modifier LHPC were almost superimposed to those obtained without any adjuvant in the disk (ECTEC20), ruling out a major impact of the polymer swelling on the molded barrier integrity. The mass loss after 24 h in aqueous fluids did not even exceed 20% in samples containing 50% of release modifier; only with ECTEC20:KIR (40:60) the initial weight of disks was nearly halved. In all

cases, polymeric barriers showed practically unchanged dimensions and surface aspect after 24 h of test.

SEM photomicrographs of ECTEC20 disks containing 30 % wt of KIR, analyzed before and after being in contact with distilled water for 7 days (followed by drying), seemed to confirm the hypothesis of KIR leaching out of the disk barrier by dissolving in the aqueous fluid (Figure 8). As a matter of fact, KIR particles can clearly be observed in the "as produced" sample (Figure 8a), while no inclusion having the same aspect can be identified after immersion in water (Figure 8b). In the latter case, isolated voids can be distinguished that do not appear interconnected to form a network, which may represent a critical issue in molded systems intended for drug release, as already highlighted with scaffolds (Kramshuster and Turng, 2012; Mi et al., 2014).

Finally, the barrier performance of molded disks was studied by positioning them to close the cavity of permeability cells filled with acetaminophen as a tracer and immersed in stirred distilled water (dissolution apparatus). Independent of the composition of the molded barrier, acetaminophen was not detected in the medium over 24 h because water was not able to penetrate into the cell cavity within the considered period of time, thus failing to bring the tracer into solution. Indeed, the drug tracer powder was found dry at the end of the test. Therefore, a longer experiment (30 days) was carried out using a dye tracer, enabling visual inspection. The appearance of an intense blue coloration inside the cell cavity was used to define the time for the solvent front to permeate the polymeric barrier, and the morphological characteristics of molded disks withdrawn from the cells after 30 days were evaluated. The obtained results are reported in Table 4.

ECTEC20 disks were confirmed to be very slowly permeable to aqueous fluids. In fact, after 30 days, no coloration was observed inside the cell cavities yet. Moreover, the cavity-exposed face of the disks withdrawn appeared practically uncolored and the powder loaded into the cell was found dry. The presence of release modifiers in the polymeric barrier generally improved the solvent penetration rate, more markedly in the case of KIR as a function of the relevant amount. The time for solvent permeation, highlighted by blue coloration inside the cell cavity, was reduced to 5 days.

However, disks containing 60% of KIR, when withdrawn from the cell after 30 days of testing, showed some little cracks on the surface suggesting a possible threshold of particle load that may still be compatible with maintenance of the barrier resistance. Such results are in good agreement with the hypothesized effect of LHPC and KIR as release modifiers. Based on these findings, the permeability characteristics of the EC barriers would be consistent with systems having very low release rate, such as implantable devices/inserts. EC might also be exploited for the manufacturing of capsular devices for the oral route, which is known to require a faster release behavior (*i.e.* complete release within 12/24 h), through appropriate formulation strategies aimed at enhancing the diffusion rate across the relevant barriers.

The polymeric materials considered in this study were also used to produce capsular devices. The capsules were successfully molded but failed to release the drug tracer (acetaminophen) over a time frame of 12 h (Table 2, Figure 9 and 10). In the case of the formulation containing 60% of KIR, such results seemed to contrast with water uptake and dry mass loss data from disks having same composition. Although the experimental conditions adopted for capsule release testing were different in terms of hydrodynamics, fluid volume and area exposed, this could indicate that water taken up by the molded material, leading to dissolution of barrier components, failed to bring about formation of a porosity network within the entire thickness of capsule shells.

The possibility of obtaining molded capsules with the desired physico-technological properties and the relevant release performance were generally predicted through the investigational approach proposed and implemented, thus proving its effectiveness.

4. Conclusions

In the present work, an approach to simple and rapid evaluation of the processability of pharmaceutical-grade polymers by µIM was proposed, involving rheological studies of material candidates and manufacturing as well as characterization of molded screening specimens. Such an

approach allowed to assess the effect of the amount of plasticizer on the moldability of EC, an insoluble polymer largely employed for the formulation of prolonged-release drug delivery systems. The use of disk-shaped specimens enabled collection of useful data about IM processability of EC-based materials. Moreover, when used as a model for diffusion barriers, such disks helped highlight technological features and performance of molded structures composed of this polymer. Since permeation of aqueous fluids through the molded disks was found very slow, the addition of permeability modifiers was also explored and successfully accomplished, in spite of some limitations encountered when processing the EC-based materials. Interesting results were obtained in terms of improved drug permeation rate across EC barriers. Future studies will be required for the evaluation of new release modifiers that may promote formation of an effective interconnected pore structure acting as a continuous path for diffusion, thus allowing release rates suitable for orally-administered systems such as capsular devices to be attained.

The investigational approach proposed holds the potential for streamlining the R&D phases for drug delivery systems produced by µIM in the form of reservoirs by yielding fundamental knowledge on processability and performance of polymeric materials of different composition through the use of a single versatile and economic tool (*i.e.* the disk-shaped specimen) with no need for having molds and molding processes specially developed on a case-by-case basis.

References

Aho JM, Boetker JP, Baldursdottir S, Rantanen J. Rheology as a tool for evaluation of melt processability of innovative dosage forms. Int. J. Pharm. 2015; 494, 623-642.

Baldi F, Ragnoli J, Zinesi D, Bignotti F, Briatico-Vangosa F, Casati F, Loreti G, Melocchi A, Zema L. Rheological characterization of ethylcellulose-based melts for pharmaceutical applications. AAPS PharmSciTech. 2016; 18, 855-866.

Bar-Shalom D, Slot L, Wang Lee W, Wilson CG. Development of the Egalet® technology. In Rathbone, M. J., Hadgraft, J., & Roberts, M. S. (Eds.), Modified-release drug delivery technology (2003) (pp. 263-271). New York: Marcel Dekker.

Feng X, Vo A, Patil H, Tiwar RV, Alshetaili AS, Pimparade MB, Repka MA. The effects of polymer carrier, hot melt extrusion process and downstream processing parameters on the moisture sorption properties of amorphous solid dispersions. J. Pharm. Pharmacol. 2016; 68, 692-704.

Gazzaniga A, Cerea M, Cozzi A, Foppoli A, Maroni A, Zema L.. A novel injection-molded capsular device for oral pulsatile delivery based on swellable/erodible polymers. AAPS PharmSciTech, 2011; 12, 295-303.

Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. Eur. J. Pharm. Sci. 2016; 90, 53-63.

Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, Basit AW. 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics. Mol. Pharm. 2015; 12, 4077-4084.

Häbel H, Andersson H, Olsson A, Olsson E, Larsson A, Särkkä A. Characterization of pore structure of polymer blended films used for controlled drug release. J. Control. Rel. 2016; 222, 151-158.

Karrout Y, Neut C, Wils D, Siepmann F, Desreumaux P, Siepmann J. Novel polymeric film coatings for colon targeting: How to adjust desired membrane properties. Int. J. Pharm. 2009; 371, 64-70.

Kempin W, Franz C, Koster L-C, Schneider F, Bogdahn M, Weitschies W, Seidlitz A. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. Eur. J. Pharm. Biopharm. 2017; 115, 84-93.

Kramschuster A, Turng LS. An injection molding process for manufacturing highly porous and interconnected biodegradable polymer matrices for use as tissue engineering scaffolds. J. Bio. Mat. Res. B: Appl. Biomaterials, 2010; 92, 366-376.

Lin S, Chien YW. Drug Delivery: Controlled Release. In Encyclopedia of Pharmaceutical Science and Technology Fourth Edition (2013) (pp. 955-984). New York: Taylor and Francis.

Macchi E, Zema L, Maroni A, Gazzaniga A, Felton LA. Enteric-coating of pulsatile-release HPC capsules prepared by injection molding. Eur. J. Pharm. Sci. 2015; 70, 1-11.

Melocchi A, Loreti G, Del Curto MD, Maroni A, Gazzaniga A, Zema L. Evaluation of hot melt extrusion and injection molding for continuous manufacturing of immediate release tablets. J. Pharm. Sci. 2015; 104, 1971-1980.

Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. Int. J. Pharm. 2016; 509, 255-263.

Mehuys E, Vervaet C, Remon JP. Hot-melt extruded ethylcellulose cylinders containing a HPMC-Gelucire® core for sustained drug delivery. J. Control. Rel. 2004; 94, 273-280.

Mi HY, Jing X, Salick MR, Turng LS, Peng XF. Fabrication of thermoplastic polyurethane tissue engineering scaffold by combining microcellular injection molding and particle leaching. J. Mat. Res. 2014; 29, 911-922.

Norman J, Madurawe RD, Moore CMV, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Adv. Drug Del. Rev. 2017; 108, 39-50.

Quinten T, Gonnissen Y, Adriaens E, De Beer T, Cnudde V, Masschaele B, Van Hoorebeke L, Siepmann J, Remon JP, Vervaet C. Development of injection moulded matrix tablets based on mixtures of ethylcellulose and low-substituted hydroxypropylcellulose. Eur. J. Pharm. Sci. 2009; 37, 207-216.

Quinten T, De Beer T, Almeida A, Vlassenbroeck J, Van Hoorebeke L, Remon JP, Vervaet C. Development and evaluation of injection-molded sustained-release tablets containing ethylcellulose and polyethylene oxide. Drug Develop. Ind. Pharm. 2011; 37, 149-159.

Rosato DV, Rosato MG. Injection Molding Handbook. Springer Science & Business Media, 3rd Ed. (2000) Kluwer Academic Publishers.

Snejdrova E, Dittrich M. Pharmaceutically used plasticizers. In Mohammad Luqman (Ed.), Recent advances in plasticizers (2012) (pp. 45-68). Rijeka, Croatia: InTech.

Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert Opinion on Drug Delivery 2016; 13, 451-464.

Treffer D, Troiss A, Khinast J. A novel tool to standardize rheology testing of molten polymers for pharmaceutical applications. Int. J. Pharm. 2015; 495, 474-481.

Verhoeven E, Vervaet C, Remon JP. Xanthan gum to tailor drug release of sustained-release ethylcellulose mini-matrices prepared via hot-melt extrusion: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 2006; 63, 320-330.

Verhoeven E, De Beer TRM, Schacht E, Van den Mooter G, Remon JP, Vervaet C. Influence of polyethylene glycol/polyethylene oxide on the release characteristics of sustained-release ethylcellulose mini-matrices produced by hot-melt extrusion: in vitro and in vivo evaluations. Eur. J. Pharm. Biopharm. 2009; 72, 463-470.

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

Vynckier A-K, Lin H, Zeitler JA, Willart J-F, Bongaers E, Voorspoels J, Remon JP, Vervaet C. Calendering as a direct shaping tool for the continuous production of fixed-dose combination products via co-extrusion. Eur. J. Pharm. Biopharm. 2015, 96, 125-131.

Yang Y., Wang H, Li H, Ou Z, Yang G. 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release. Eur. J. Pharm. Sci. 2018, 115, 11-18.

Yousfi M, Alix S, Lebeau M, Soulestin J, Lacrampe MF, Krawczak P. Evaluation of rheological properties of non-Newtonian fluids in micro rheology compounder: Experimental procedures for a reliable polymer melt viscosity measurement. 2014; Pol. Testing, 40, 207-217.

Zema L, Loreti G, Melocchi A, Maroni A, Gazzaniga A. Injection Molding and its application to drug delivery. J. Control. Rel. 2012; 159, 324-331.

Zema L, Loreti G, Macchi E, Foppoli A, Maroni A, Gazzaniga A. Injection-molded capsular device for oral pulsatile release: development of a novel mold. J. Pharm. Sci. 2013a; 102, 489-499.

Zema L, Loreti G, Melocchi A, Maroni A, Palugan L, Gazzaniga A. Gastroresistant capsular device prepared by injection molding. Int. J. Pharm. 2013b; 440, 264-272.

Table(s)

Table 1: µM conditions for the manufacturing of screening disks based on ECTEC materials.

Process parameter		
compression zone temperature; *°C*		170
metering zone temperature; *°C*		175
nozzle temperature; *°C*		175
1st injection	pressure (P_1); *bar*	varied from 10 to 100
	time (t_1); *s*	varied from 1.0 to 2.5
2nd injection	pressure (P_2); *bar*	10
	time (t_2); *s*	0.0
cooling time; *s*		2.5

Table(s)

Table 2: µIM conditions for the manufacturing of 600 µm thick capsule parts containing different types and amounts of release modifiers.

		Polymeric formulation				
Process parameter		**ECTEC20**	**ECTEC20: LHPC (70:30)**	**ECTEC20: KIR (70:30)**	**ECTEC20: KIR (50:50)**	**ECTEC20: KIR (40:60)**
compression zone temperature; *°C*		145			150	155
metering zone temperature; *°C*		155			160	165
nozzle temperature; *°C*		165			165	170
hot runner temperature; °C		180			175	180
1st injection	pressure (P_1); *bar*	50			60	60
	time (t_1); *s*	0.4			0.7	0.7
2nd injection	pressure (P_2); *bar*	40			50	50
	time (t_2); *s*	0.3			0.6	0.6
cooling time; *s*		2.5			2.5	3.5

Table(s)

Table 3: µIM conditions for the manufacturing of 600 µm thick disks containing different type and amount of release modifiers.

		Polymeric formulation				
Process parameter		**ECTEC20**	**ECTEC20: LHPC (70:30)**	**ECTEC20: KIR (70:30)**	**ECTEC20: KIR (50:50)**	**ECTEC20: KIR (40:60)**
compression zone temperature; *°C*		170			170	180
metering zone temperature; *°C*		175			175	185
nozzle temperature; *°C*		175			175	185
1^{st} injection	pressure (P_1); *bar*	20			30	30
	time (t_1); *s*	1.0			2.0	2.0
2^{nd} injection	pressure (P_2); *bar*	80			90	90
	time (t_2); *s*	1.0			1.0	1.0
cooling time; *s*		2.5			2.5	10

Table(s)

Table 4: data relevant to permeability tests of 600 μm thick disks.

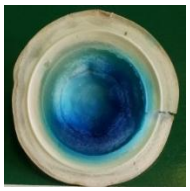
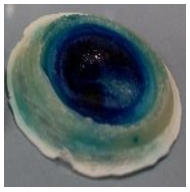
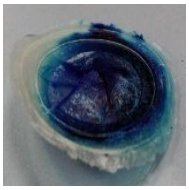
Polymeric formulation	**Appearance of blue color inside the cell cavity**	**Aspect of disks after 30 days**		
		Color intensity	Integrity	
ECTEC20	no	-	yes	
ECTEC20:LHPC (70:30)	after 30 days	-/+	yes	
ECTEC20:KIR (70:30)	after 20 days	+	yes	
ECTEC20:KIR (50:50)	after 8 days	++	yes	
ECTEC20:KIR (40:60)	after 3-5 days	++	no (evidence of cracks)	

Figure captions

Figure 1: apparent viscosity *vs* shear rate curves at 175 °C for ECTEC20, measured through capillary rheometry (adapted from Baldi et al., 2016) and slit rheometry in the Haake™ MiniLab II microcompounder.

Figure 2: cell for the evaluation of molded disk permeability: (a) partially assembled, with the cell cavity filled with a dye tracer; (b) assembled for the test and (c) positioned into a vessel of the dissolution apparatus.

Figure 3: apparent viscosity *vs* apparent shear rate curves of ECTEC mixtures as a function of temperature and TEC content.

Figure 4: effective radius (R_{eff}) of (a) disks with different TEC content produced at increasing injection pressure (P_1) and fixed fill time of 1.0 s; (b) ECTEC20 disks produced at increasing fill time (t_1) and fixed P_1 of 20 bar (n = 6; bars in figures represent standard deviation).

Figure 5: minimum temperature of warpage (T_{start}) *vs* ΔP (= P_2 - P_1) applied during the molding process as a function of TEC content in the material.

Figure 6: extent of deformation after a 120 °C treatment of disks (Deformation level @ 120°C) *vs* ΔP (= P_2 - P_1) applied during the molding process as a function of TEC content in the material. Selected experimental points are coupled with photographs of deformed disks.

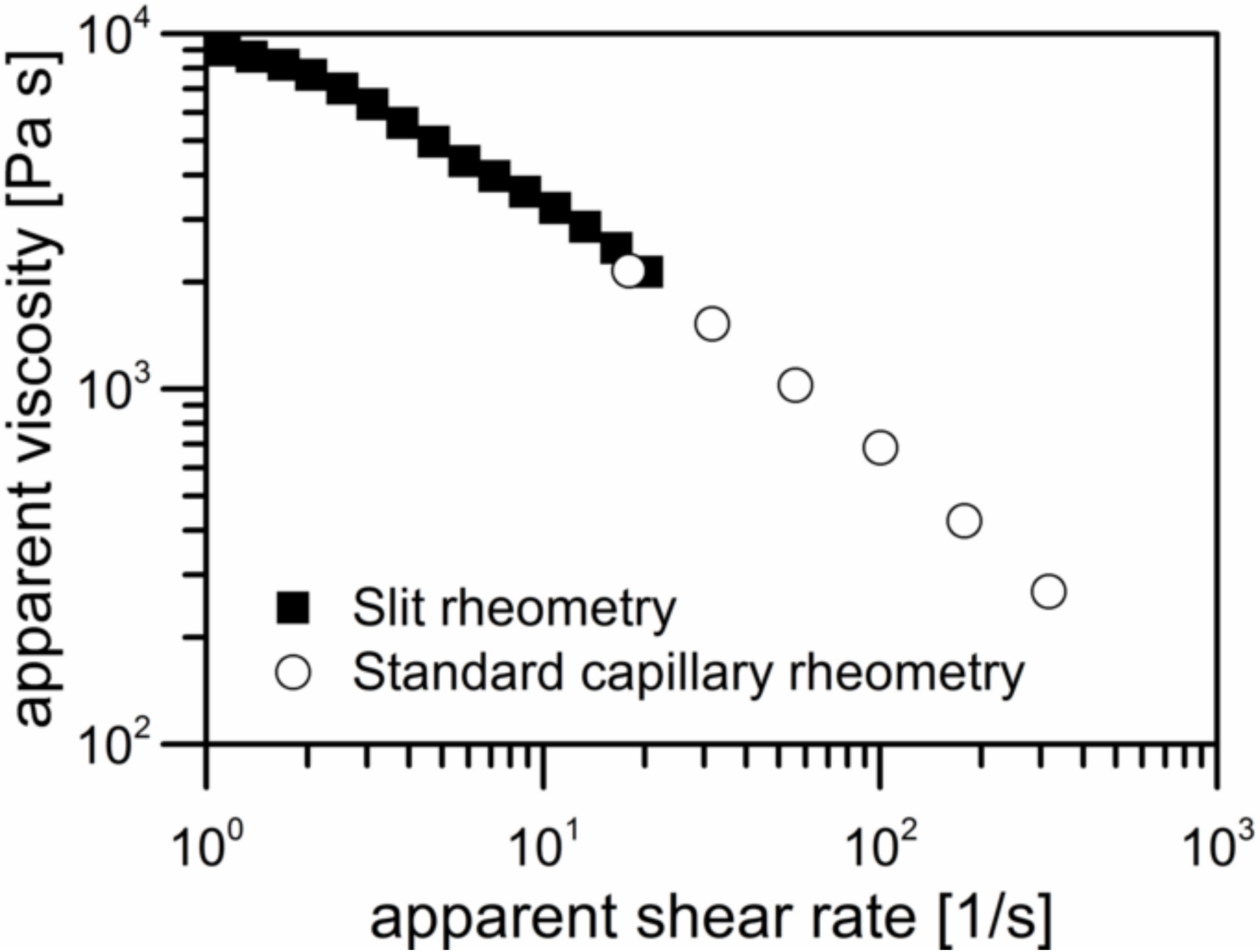
Figure 7: (a) WU and (b) DML profiles of molded disks based on ECTEC20 containing different type and amount of release modifiers.

Figure 8: SEM photomicrographs of the cross section of 600 µm thick ECTEC20 disks containing 30 % wt of KIR (a) immediately after molding and (b) after immersion in stirred water for 7 days.

Figure 9: Photographs of capsule bodies and caps molded from different formulations.

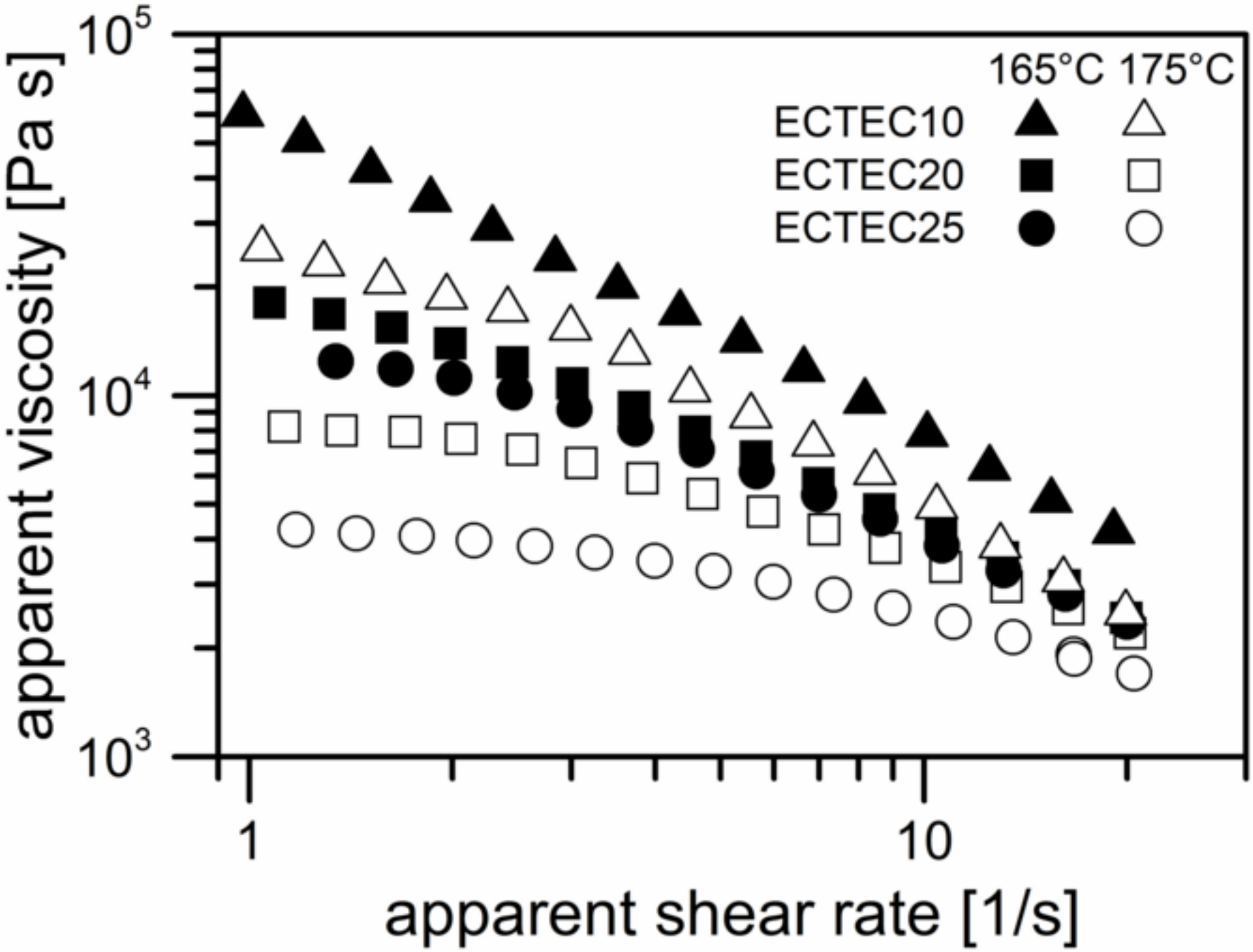
Figure 10: Release profiles of 600 µm thick capsules molded from different formulations.

Figure(s)

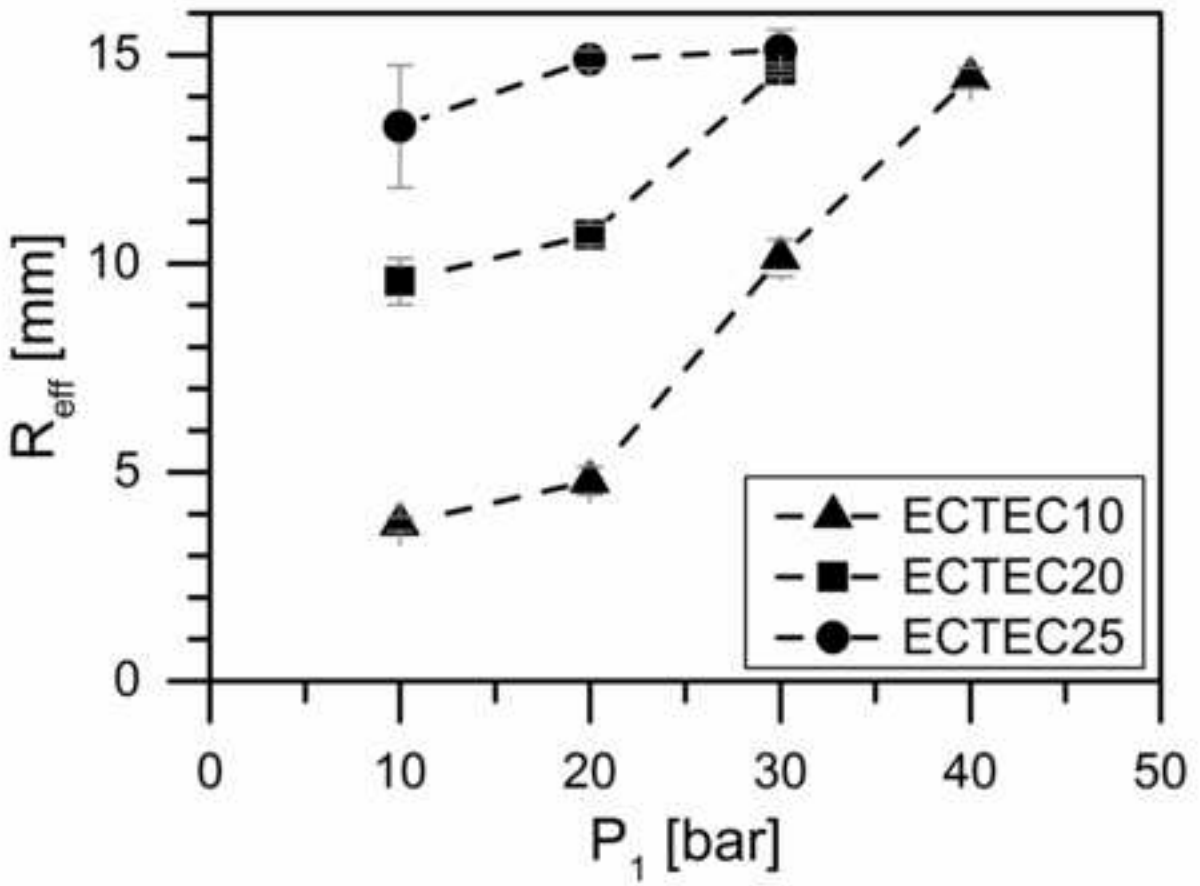

apparent viscosity [Pa s]
10^4
10^3
10^2
Slit rheometry
Standard capillary rheometry
10^0
10^1
10^2
10^3
apparent shear rate [1/s]

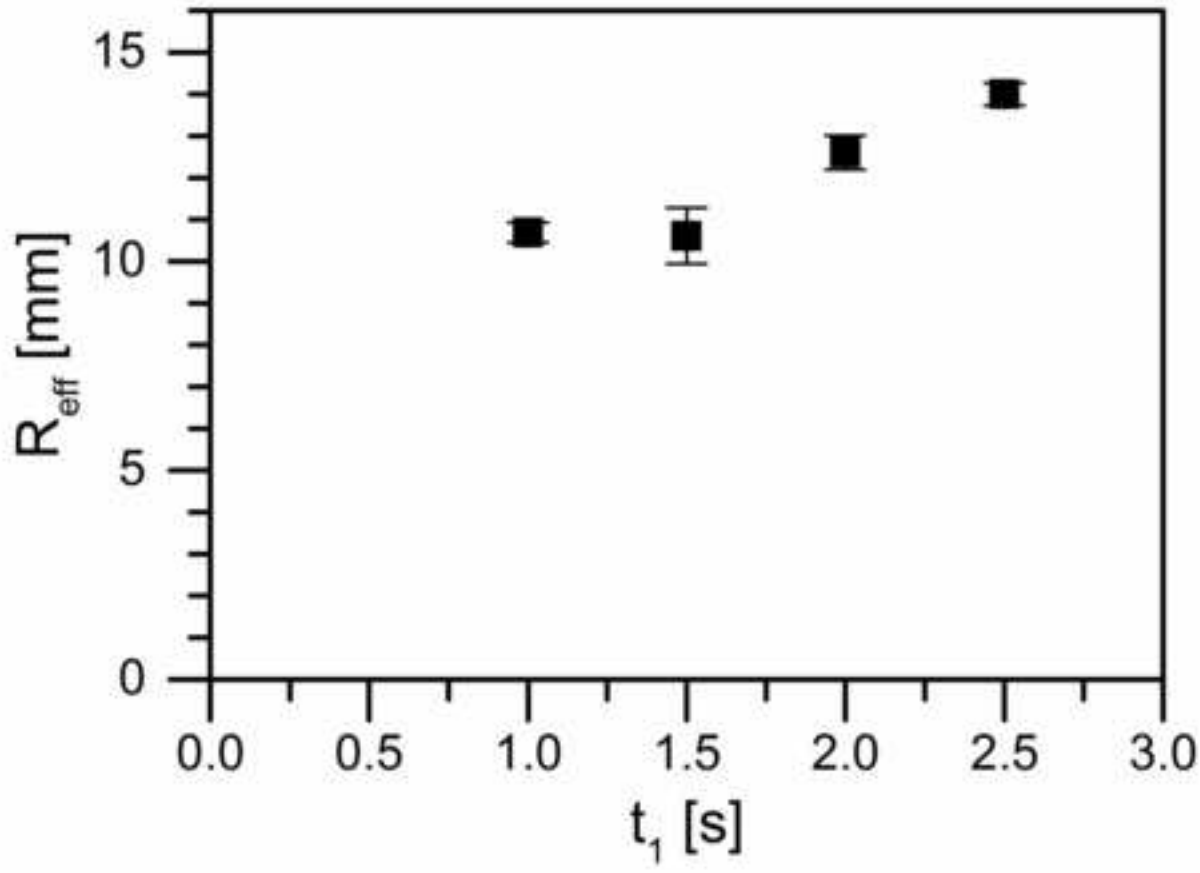
Figure(s)

Figure(s)

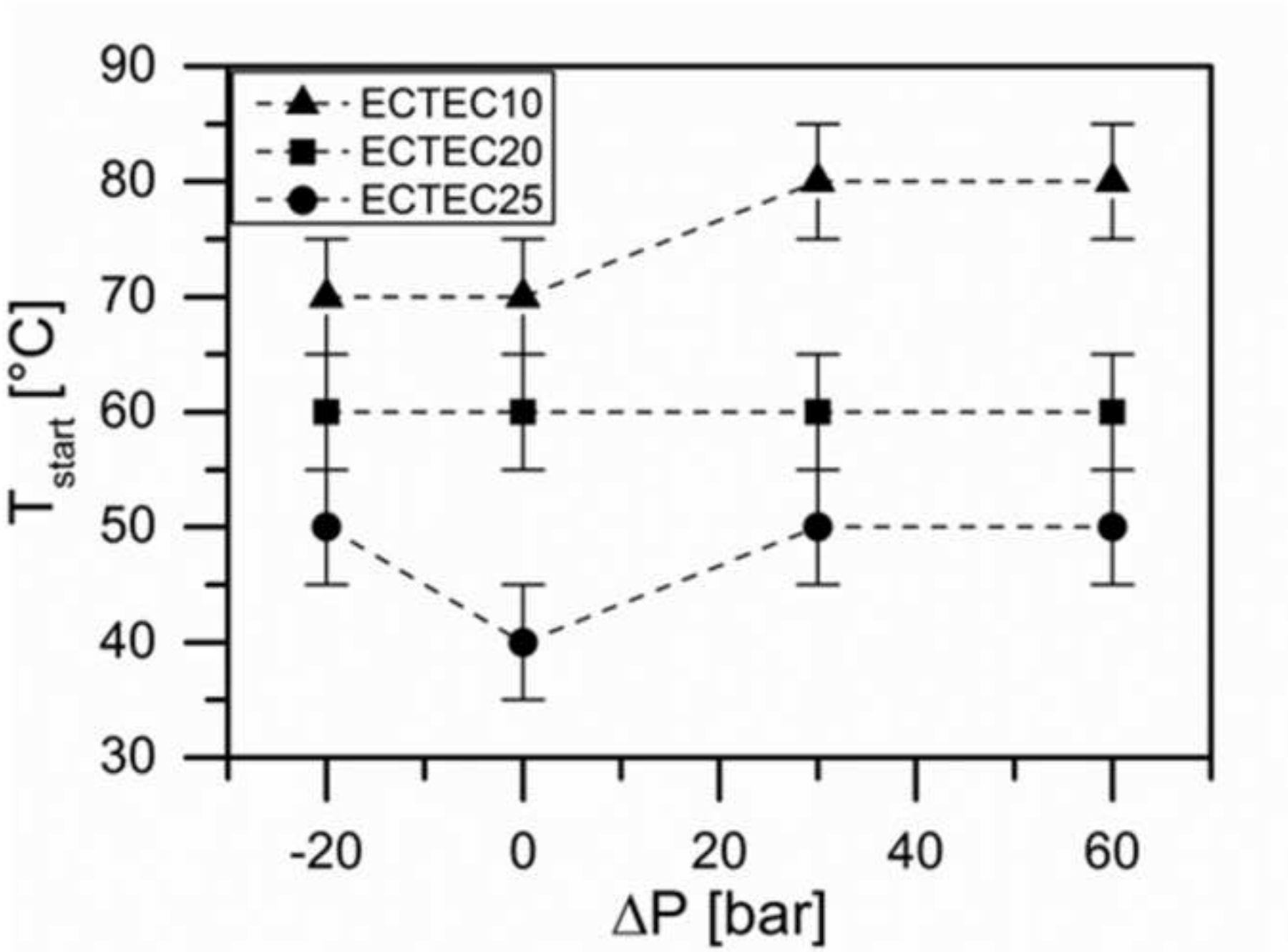

apparent viscosity [Pa s]
10^5
10^4
10^3
1
10
apparent shear rate [1/s]
165°C 175°C
ECTEC10
ECTEC20
ECTEC25

Figure(s)

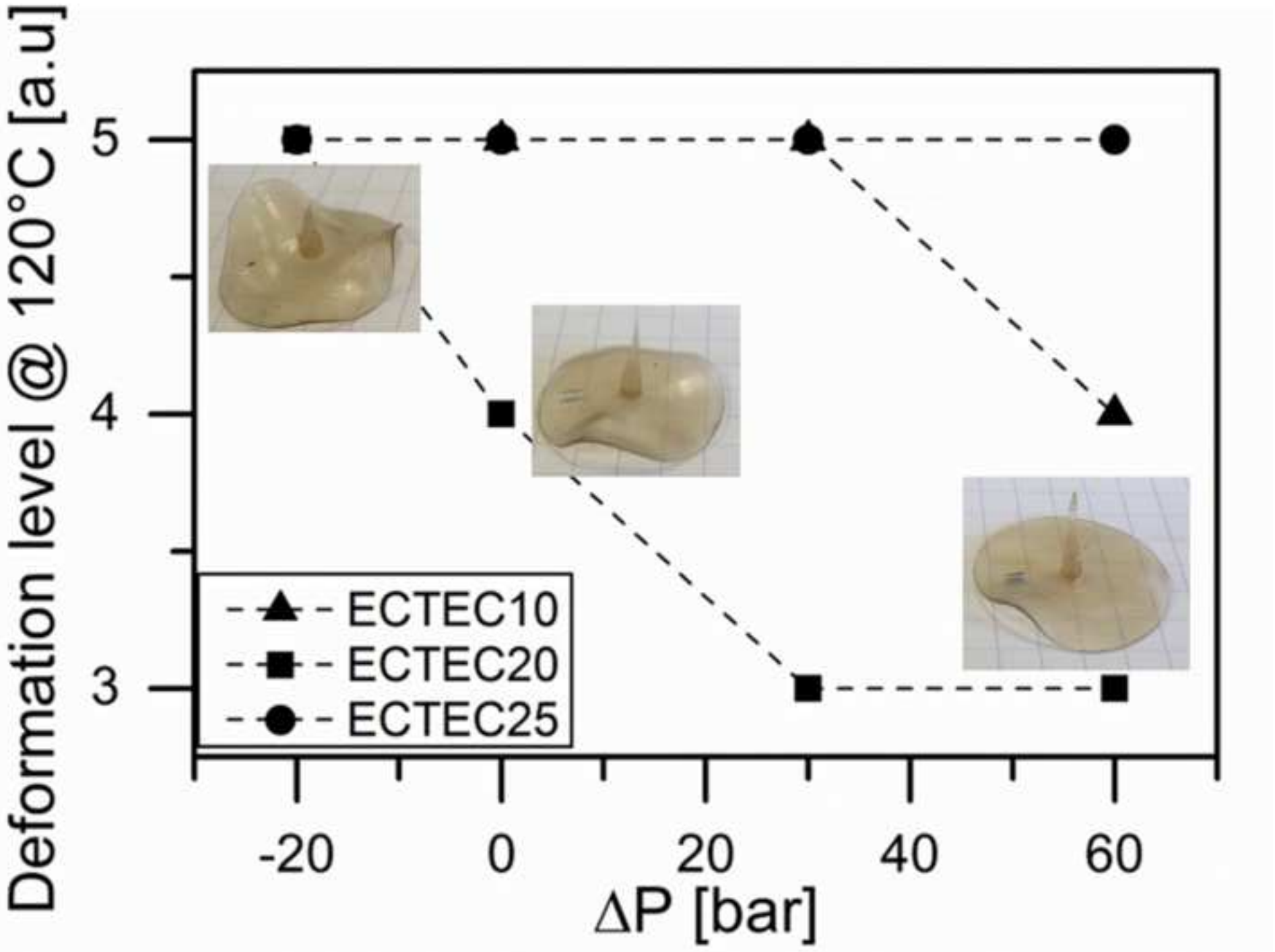

15
10
5
0
R_{eff} [mm]
0
10
20
30
40
50
P_1 [bar]
ECTEC10
ECTEC20
ECTEC25


15
10
5
0
R_{eff} [mm]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
t_1 [s]

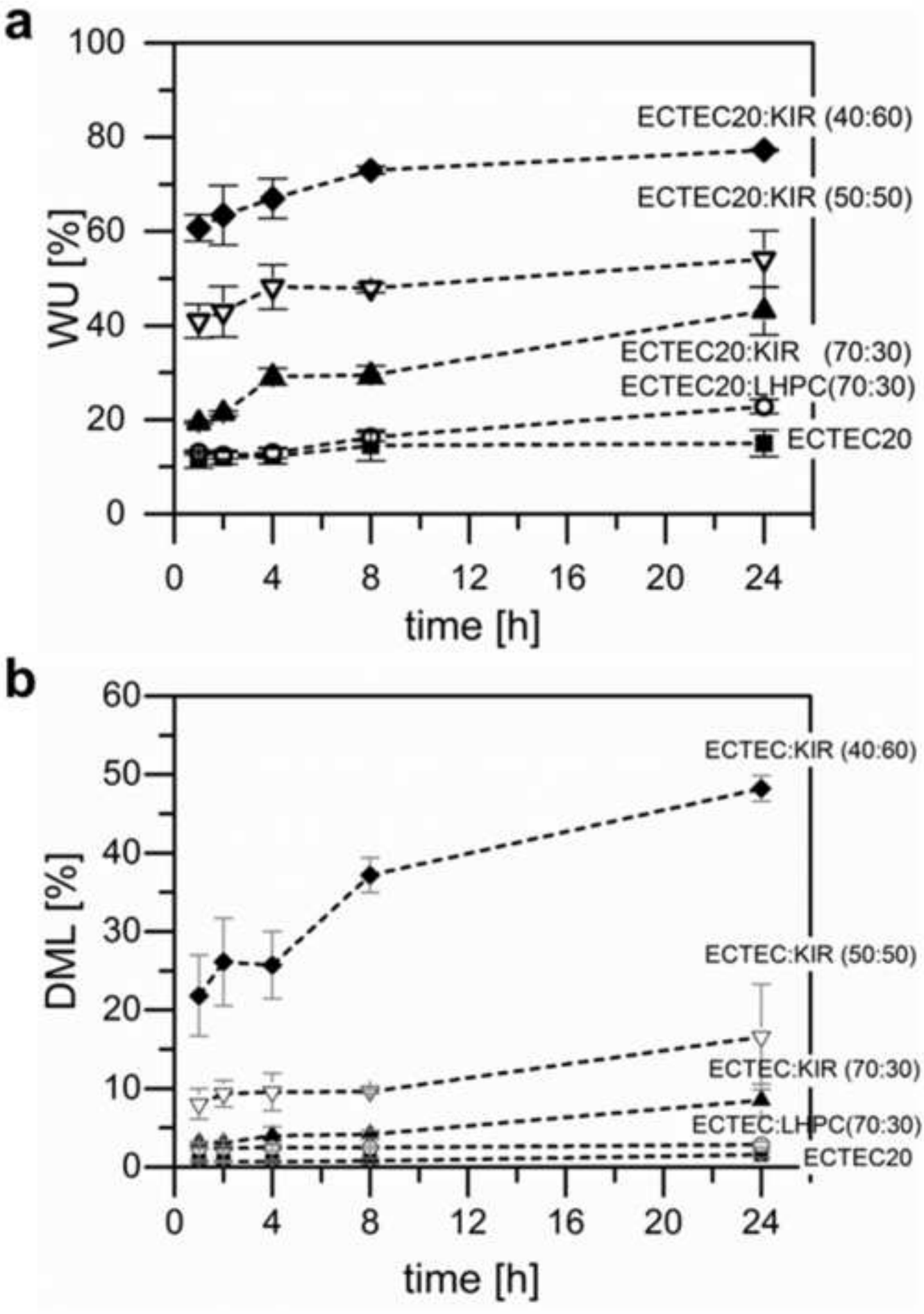
Figure(s)


ECTEC10
ECTEC20
ECTEC25
90
80
70
60
50
40
30
T start [°C]
-20
0
20
40
60
ΔP [bar]

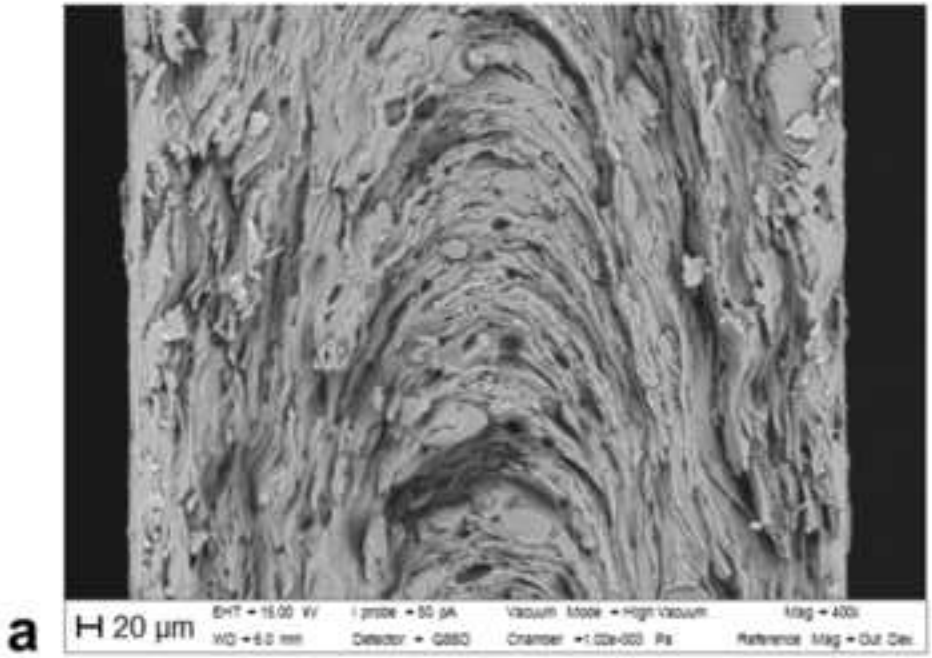
Figure(s)

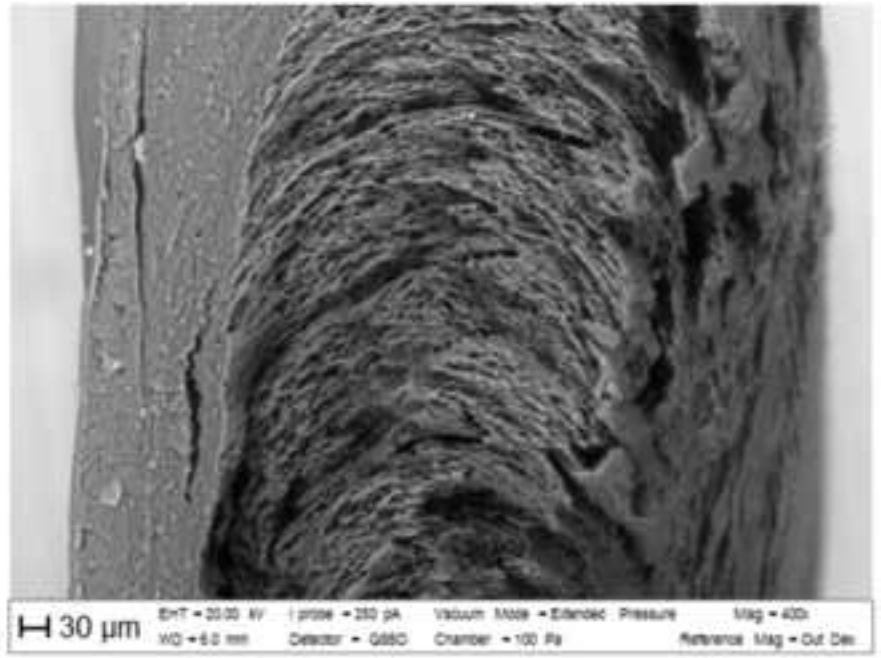

Deformation level @ 120°C [a.u]
5
4
3
-20
0
20
40
60
ΔP [bar]
ECTEC10
ECTEC20
ECTEC25

Figure(s)

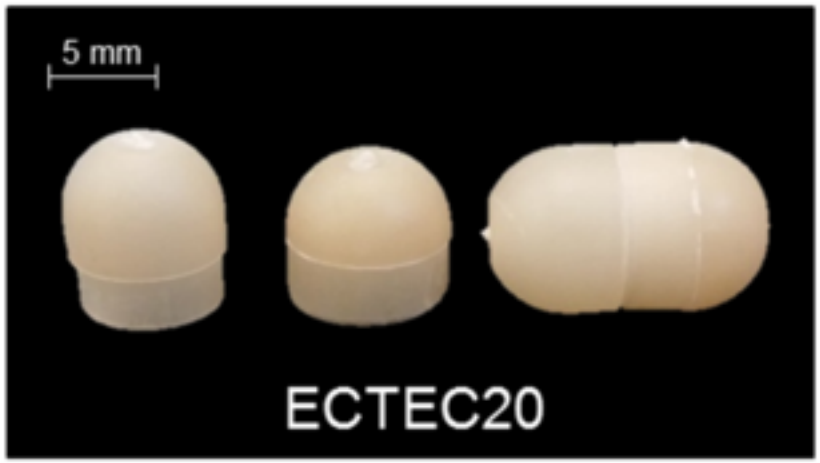

a
100
80
60
40
20
0
WU [%]
ECTEC20:KIR (40:60)
ECTEC20:KIR (50:50)
ECTEC20:KIR (70:30)
ECTEC20:LHPC(70:30)
ECTEC20
0
4
8
12
16
20
24
time [h]
b
60
50
40
30
20
10
0
DML [%]
ECTEC:KIR (40:60)
ECTEC:KIR (50:50)
ECTEC:KIR (70:30)
ECTEC:LHPC(70:30)
ECTEC20
0
4
8
12
16
20
24
time [h]

Figure(s)

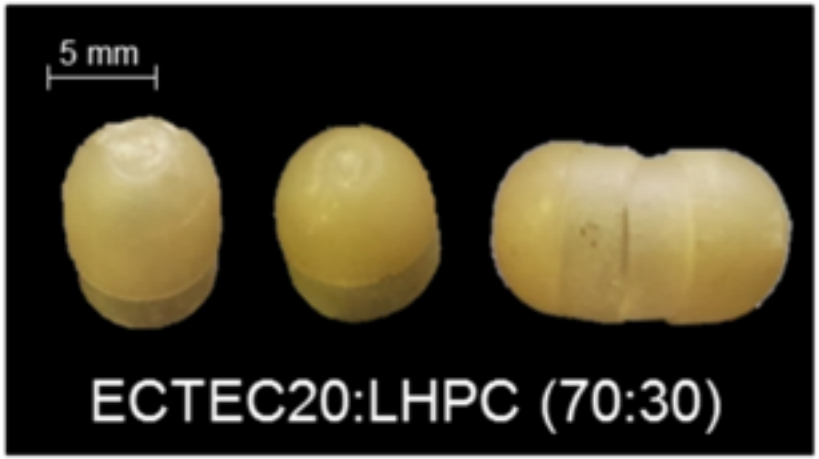


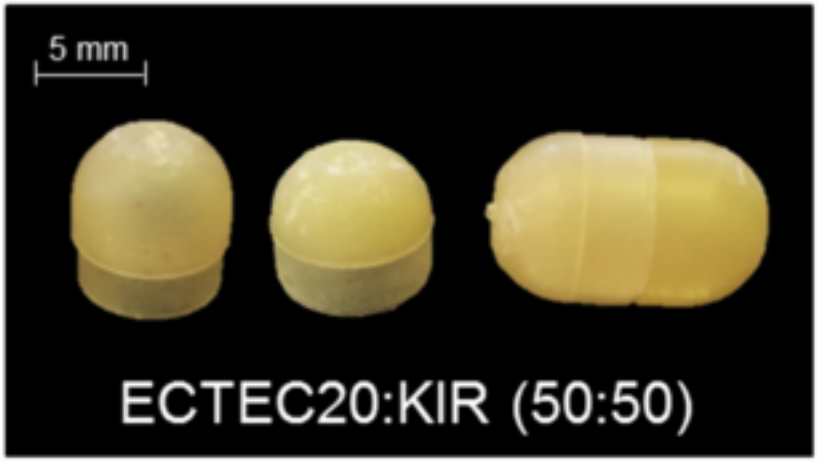


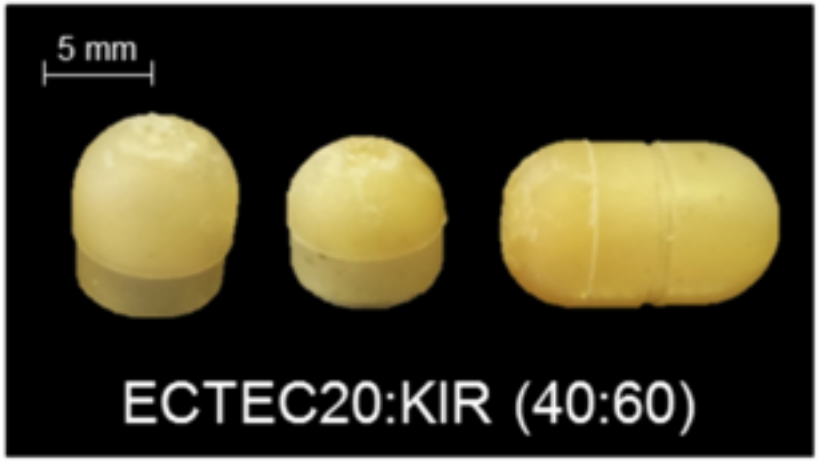
Figure(s)


5 mm
ECTEC20

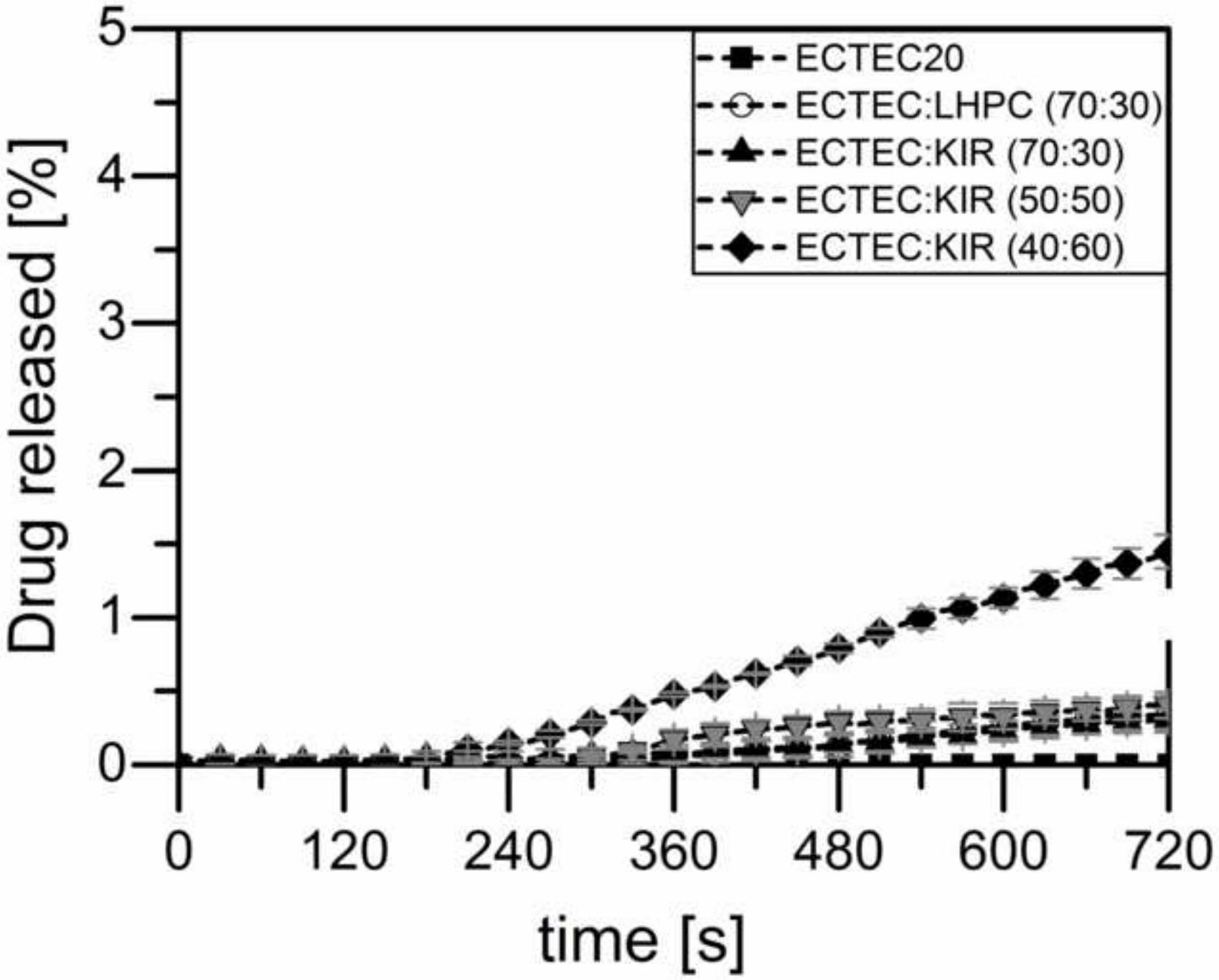

5 mm
ECTEC20:KIR (70:30)


5 mm
ECTEC20:LHPC (70:30)


5 mm
ECTEC20:KIR (50:50)


5 mm
ECTEC20:KIR (40:60)

Figure(s)


Drug released [%]
time [s]
0
1
2
3
4
5
0
120
240
360
480
600
720
ECTEC20
ECTEC:LHPC (70:30)
ECTEC:KIR (70:30)
ECTEC:KIR (50:50)
ECTEC:KIR (40:60)