Evaluation of hot-melt extrusion technique in the preparation of HPC matrices for prolonged release

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Abstract

The aim of the work was to explore the potential of hot-melt extrusion (HME) for preparing hydroxypropyl cellulose (HPC)-based prolonged-release matrices intended for oral administration. For this purpose, compressed and extruded systems, either composed of polymer only or containing different amounts of a model drug (theophylline or ketoprofen), were compared. The overall morphological/physical changes of the systems following interaction with water indicated that the manufacturing process would not exert a major influence on the swelling behavior of the polymeric matrices. On the other hand, the release rate was generally higher from HME systems probably due to an increase of the drug dissolution rate, which is in agreement with the relevant DSC data (loss of drug cristallinity). However, the technological characteristics of the matrices and the maximum drug load were demonstrated to depend on the mode of interaction of the active ingredient with the molten polymer. In this respect, the formation of a composite material from ketoprofen and HPC, when mixed in specific ratios, was supposed to explain the differences observed between compressed and extruded systems in terms of morphological characteristics, hydration/swelling and release. The obtained results support the possibility of exploiting the advantages offered by HME technique, above all the potential for continuous manufacturing, in the preparation of prolonged-release swellable matrices based on a cellulose derivative.

PROLONGED RELEASE MATRICES BASED ON HYDROPHYLIC-SWELLABLE CELLULOSE DERIVATIVES
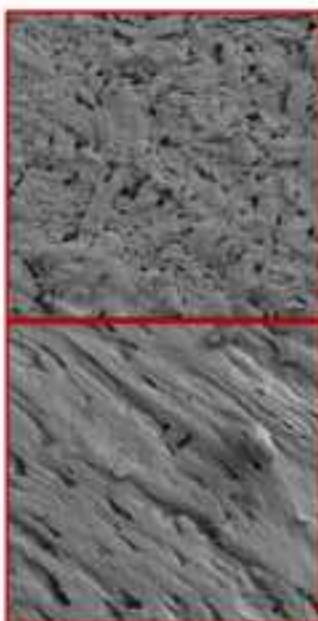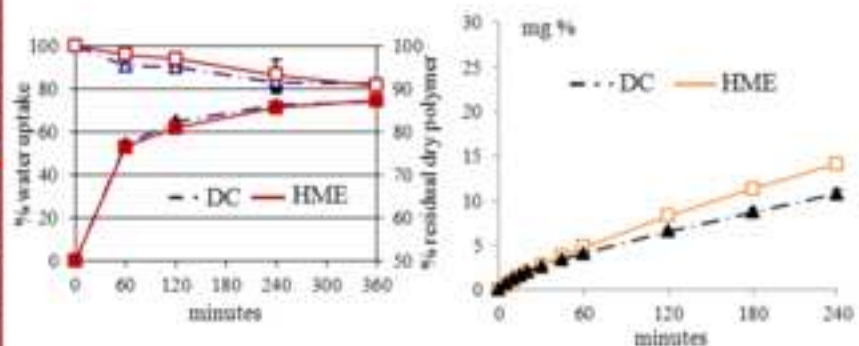
1. Introduction

Hot-melt extrusion (HME) is a processing technique widely used to convert plastic raw materials into a product of uniform shape and density by heating and forcing them through a die, generally employing a rotating screw. Despite some limitations implied by the thermal stability of drugs and formulation aids as well as the need for thermoplastic carriers, the interest in HME has grown over the last 20-30 years in the pharmaceutical field. This can be ascribed to the inherent potential of such a technology for automation and development of solvent-free manufacturing processes (Breitenbach, 2002; Crowley et al., 2007). Moreover, mixing and/or compaction problems that can be encountered with powder formulations would be overcome by HME, and the bioavailability of poorly soluble active ingredients could be enhanced due to the formation of solid phases with increased dissolution rate from molecular dispersions of the drug within the molten polymeric carrier. Further advances in the field of HME and molding techniques might be expected in the near future due to the consolidation of a continuous-manufacturing production model that could bring about significant economic benefits (Fonteyne et al., 2012; Kipping and Rein, 2013; Vervaet et al., 2005; Zema et al., 2012). In this respect, a molding process was indeed selected for the preparation of tablets in the first "drug-manufacturing prototype" built up at the Novartis-MIT (Massachusetts Institute of Technology) Center for Continuous Manufacturing, which turns raw ingredients into finished drug products through six connected units of production (Trafton, 2012).

Several research groups proposed HME for the preparation of single- and multiple-unit drug delivery systems, fast-dissolving or prolonged-release formulations, to be administered by the oral route or by the transdermal, transmucosal and transungual ones (Repka et al., 2007, 2012). In the field of oral prolonged-release systems, different kinds of polymeric materials, either insoluble/inert (such as ethylcellulose or methacrylic acid copolymers) or hydrophilic/swellable (mainly polyethylene oxide) were investigated in order to produce matrices via HME (Almeida et al., 2012; Clark et al., 2011; Crowley et al., 2004a; Fukuda et al., 2006; Özgüney et al., 2009; Verhoeven et al., 2009). As far as hydrophilic cellulose derivatives are concerned, which are broadly used to prepare tableted oral matrices owing to recognized advantages in terms of safety, versatility and low costs, their application was limited by the inherent thermal behavior. Indeed, the use of hydroxypropyl methylcellulose (HPMC), which is the most widely employed matrix-forming polymer, has proven challenging because of its narrow processing window, *i.e.* the difference between glassy-rubbery transition temperature (T_g) and degradation temperature (Coppens et al., 2005). The hydroxypropyl derivative (HPC), on the other side, was demonstrated to possess adequate thermoplastic properties and has extensively been used to prepare transdermal and transmucosal extruded systems although, at least so far, it has not been evaluated in the manufacturing of orally-administered matrices by HME (Mididoddi and Repka, 2007; Repka et al., 2005). By the way, HPC is characterized by high plastic deformation during compaction but also by high elastic recovery after tableting, which might hinder its use as a compression filler (Picker-Freyer and Dürig, 2007). Low molecular weight grades of this polymer were proposed as carriers in HME to attain solid dispersions of poorly soluble drugs (Deng et al., 2013).

Moreover, it has recently been proposed for the manufacturing of a pulsatile-delivery platform in the form of a capsular device prepared by injection molding (Gazzaniga et al., 2011; Zema et al., 2013).

Based on these premises, the aim of the work was to explore the potential of HPC as a thermoplastic carrier for monolithic matrix systems intended for oral prolonged release. In this respect, matrices prepared by HME were compared with directly compressed ones. The impact of the manufacturing process on the hydration, swelling and erosion rate of the polymer was studied by using pure polymeric systems, whereas its feasibility and the resulting release performance were evaluated taking drugs with different solubility and/or miscibility with the molten carrier into account.

2. Materials and methods

2.1 Materials

Hydroxypropylcellulose, HPC: regular and fine (X) grades, 250-300 µm and 80-100 µm average particle size, respectively (Klucel$^®$ GF and GXF; Ashland, USA; Eigenmann&Veronelli, I); theophylline (Boehringer Ingelheim, I); ketoprofen (Cosma, I); cellulose acetate propionate (CAP 482; Eastman, USA).

2.2 Methods

2.2.1 Powder characterization

Klucel$^®$ GF particle size was evaluated according to EP 7th ed. (7.6) (monograph 2.9.38 *Particle-size distribution estimation by analytical sieving*) in the 150-500 µm range; Klucel$^®$ GXF particle size was evaluated by means of an optical microscope (Axiolab, Zeiss, D). Powder d_{90} and d_{50} were calculated as reported in monograph 2.9.35 *Powder fineness*. The bulk and tapped density as well as compressibility of the powder were determined according to monograph 2.9.34 *Bulk density and tapped density of powders*, Method 1.

2.2.2 Matrix preparation

Pure-polymer and binary drug/polymer matrices with theophylline or ketoprofen content in the 5-70 % or 5-40 % range, respectively, were prepared by direct compression (DC) as well as hot-melt extrusion (HME) after mixing the powders in Turbula (type T2A-Willy A, Bachofen, CH; 10 min). Powder samples of 150 mg were manually filled in a single-punch machine (Korsch, EKO, D; flat-faced punch, ø 8 mm) and tableted at 35kN. The compression force (F_A) was measured during the process. HME was carried out in a single-screw extruder (Extrusiograph 19/25D, Brabender, D) equipped with a rod-shaped die (ø 8 mm). Process parameters, processing time and torque values recorded while manufacturing pure-polymer matrices are reported in table 1. Extruded products, stored at room temperature for 48 h, were cut into matrices with same nominal weight of the corresponding DC tablets by means of a bench-top saw.

All systems were characterized for: weight (Crystal, Gibertini, I), diameter and thickness (digital micrometer CD-C112XB, Mitutoyo, J), crushing force (F_C) (crushing tester TBH28; Erweka, D), surface wettability (contact angle test) and drug content. Cohesion index values were also calculated as (F_C/F_A) x 10^5.

2.2.3 Release test

Drug release was evaluated by a dissolution EP 7th ed. Apparatus 2 (Dissolution System 2100B, Distek, USA) using 900 ml of deionized water at 37 ± 0.5 °C and 50 rpm; throughout all tests sink conditions were maintained. Drug concentration in the release medium was determined by spectrophotometer (lambda25, Perkin Elmers, UK) at λ_{max} of 272 and 260 nm for theophylline and ketoprofen, respectively (n = 6, bars in figures indicate standard deviation). Prior to release testing, matrices were manually coated on all surfaces except for one base with an impermeable film of CAP (15 % w/v acetone solution) (Grassi et al., 2004).

2.2.4 Interaction with aqueous fluids

Water uptake and residual dry polymer of matrices immersed in unstirred water at room temperature were evaluated over 6 h (n = 3). Systems glued on a glass holder were immersed in 100 ml of deionized water, removed after predetermined time periods, gently blotted and weighed. In the case of drug-containing matrices, the amount of theophylline or ketoprofen released in the medium was spectrophotometrically determined (D_{rel}). Final dry weights were also determined after maintaining samples in an oven at 60 °C for 48 h. Two parameters were calculated, the % water uptake and the % residual dry polymer, according to the following equations:

% water uptake = $[(W_w - W_d)/W_w]$ x 100 (Eq.1)

where W_w is the weight of the wet sample on withdrawal, W_d is the weight of the sample after drying;

% residual dry polymer = $\{1 - [(W_i - W_d) - D_{rel}]/(W_i - D_{load})]\}$ x 100 (Eq.2)

where W_i is the initial weight of the sample, D_{rel} is the amount of drug released, D_{load} is the nominal drug content.

The progression of swelling and erosion fronts was determined on coated matrices maintained under the same conditions as for the release test. Samples (n = 3) were recovered from the immersion fluid at predetermined time points. The position of the fronts was determined by means of a 0.01 mm-calibrated penetrometer (Dial Thickness Gage 7305, Mitutoyo, J) provided with a 0.3 mm diameter pin.

2.2.5 Thermal analysis

Powder and extruded samples were characterized by differential scanning calorimetry (DSC 2010, TA instruments, USA) from 30 to 350 °C at 5 °C/min, N_2 purge 70 ml/min.

2.2.6 SEM analysis

Photomicrographs of gold-sputtered (10 nm) samples were collected by a scanning electron microscope (SEM; Sigma, Zeiss, D).

3. Results

3.1 Pure-polymer matrices

In order to explore the influence of the manufacturing technique on the performance of hydrophilic swellable matrices, pure polymeric systems prepared by DC and HME were preliminarily considered. A high molecular weight HPC was selected as the matrix-forming agent. Particularly, two different commercial types of the polymer were available, a regular particle size Klucel® GF (KGF) and a fine one (KGXF). Thus,

their flowability and compaction tendency were evaluated as they could have impacted on the selected manufacturing processes (table 2).

The poor flow characteristics (compressibility index in the 26-31 range; EP 7th ed. 2.9.36 *Powder flow*) of KGXF could indeed negatively influence both the tableting process, impairing the weight uniformity of the resulting matrices, and the continuous/automatic filling of the extruder. With regard to the compaction properties, coherent tablets where obtained with both polymer types by the application of relatively high compression forces (> 25 kN) only. These presented a smooth and gloss surface as well as a tendency to deformation instead of breaking when undergoing the crushing test, thereby confirming in the case of Klucel® GF the same plastic behavior shown upon tableting by other HPC grades with a different molecular weight (Picker-Freyer and Dürig, 2007). In the photomicroghaps of DC matrices, two different areas can be distinguished, an external packed layer and an internal core exhibiting a pore network (figure 1a and 1b). In both areas, and especially in the external one, partially molten aggregates of polymer particles can be observed, which are particularly evident in the KGXF system (figure 1b). Moreover, consistent with a presumably wider area exposed, the fine polymer grade displayed a higher cohesion index, and the relevant tableted products showed a lower porosity. Therefore, DC matrices were finally prepared with KGXF by manually filling the tableting machine to overcome the problems connected with the poor flowability of the powder, while the coarser material was preferred for the extrusion process. Only with KGF, by adjusting the operating parameters, continuous manufacturing of cylindrical extrudates based on pure polymer could indeed be performed, with no need for any adjuvant.

Pure-polymer matrix systems were characterized in terms of physical properties and behavior in aqueous fluids, *i.e.* water uptake/solvent penetration, swelling, dissolution/erosion and wettability. The relevant data are reported in table 3 and figure 2.

HME systems showed higher bulk density values, close to the true density of the pure polymer (1.15 g/cm^3). No particles of the coarse starting polymer could be distinguished in the photomicrograph of the extruded product, which also exhibited a lower porosity as compared with both the DC systems (figure 1c). During the crushing strength test, HME units got deformed thus hindering the evaluation of the hardness characteristics. DC and HME polymeric matrices had very similar wettability.

In the case of hydrophilic swellable matrices based on HPMC, it is well known that differences in the dry polymer particle size may only affect the initial hydration rate and thereby impact on the burst release phase, especially with very soluble drugs. Accordingly, in spite of the difference in porosity, the HPC matrices prepared by DC and HME showed an analogous behavior in contact of interaction with aqueous fluids, as pointed out by very similar water uptake, dry mass loss and solvent penetration (swelling) front profiles (figure 2).

3.2 Drug-containing matrices

In order to evaluate the release performance and the influence of drug load, DC and HME systems containing increasing amounts of an active ingredient were prepared. Theophylline and ketoprofen were

chosen as model molecules as they are characterized by melting points markedly above or below the HPC extrusion temperature, respectively (271.9 °C for theophylline and 95.8 °C for ketoprofen). The ability of ketoprofen to form solid solutions with low molecular weight grades of HPC on HME processing was already demonstrated as the drug and the polymer were found miscible (Naqvi Mohammed et al., 2012). Ketoprofen was confirmed to act like a plasticizer for KGF, progressively lowering the torque value recorded up to 1-3 N m as a function of concentration. On the other hand, a maximum load of 40 % could be achieved still maintaining an acceptable mechanical resistance of the extrudate. At the highest drug load, the operating temperatures needed to be decreased below 100 °C. Ketoprofen-containing HME matrices were all transparent with no evidence of dispersed particles, as shown by the relevant photomicrographs (figure 3a). However, while the extrudate with the 5 % load appeared quite similar to the extruded polymer as such (figure 3a$_1$), the aspect of the sample containing 40 % of drug was very different, presenting an exfoliated surface split into thin flakes (figure 3a$_2$).

With respect to the HME matrices containing the high-melting model drug, products loaded up to 70 % were obtained with no need for changing the operating conditions set for the pure polymer, thus suggesting a lesser ability of theophylline to plasticize the polymer. The matrices turned opaque already with 5 % of this drug, and the matt appearance progressively increased with the loaded amount suggesting that theophylline would remain suspended in the polymeric carrier. The presence of solid particles was confirmed by SEM analysis (figure 3b). However, as in the case of ketoprofen, a tendency of the torque value to diminish during the extrusion of drug-loaded materials was noticed, which could indicate a partial solubilization of theophylline in the molten polymer. In thermograms of HME formulations containing decreasing amounts of theophylline, from 70 to 5 %, a progressive reduction of the drug melting peak and shift towards lower temperatures was observed, pointing out a gradual loss of crystallinity possibly due to drug–polymer interactions (figure 4) (Naqvi Mohammed et al., 2012). On the other hand, the drug melting peak was evident in none of the thermograms of ketoprofen-based HME formulations With the low-melting model drug, modifications of the area and position of the peak were observed when changing the processing technique irrespective of the drug content. By way of example, thermograms relevant to formulations containing 20 % of ketoprofen processed by mixing, tableting or HME are reported (figure 5).

The drug content of HME systems was found > 97 % of the nominal load for all formulations except for those with 60 and 70 % of theophylline, for which it turned out < 95 %. This result was attributed to the poor conveying and mixing ability of single-screw extruders and might be improved by changing the using equipment (twin-screw extruder).

As far as the DC products are concerned, they needed to be manufactured manually and showed not fully satisfactory mechanical characteristics. In particular, the matrices containing theophylline exhibited lower mechanical resistance as compared with pure-polymer ones, whereas the crushing strength of ketoprofen-containing systems was not determinable because deformation occurred. In this respect, it might thus be hypothesized that the increase in the micro-environmental temperature brought about by compaction could lead to the softening/melting of ketoprofen thereby resulting in plasticization of the polymeric matrix.

Moreover, the polymer compaction was hindered by the presence of both model drugs. These findings support the need for identifying alternative manufacturing techniques for prolonged-release matrix systems based on HPC.

Subsequently, the behavior in contact with aqueous fluids (formation and evolution of a gel barrier) and the drug release performance of DC and HME matrices were comparatively evaluated. The profiles of water uptake, dry polymer loss and swelling as well as erosion fronts of systems containing the smallest and the largest amounts of drug are reported in figure 6 and 7. The position of swelling and erosion fronts was not measured for extruded products with ketoprofen loads ≥ 30 % as the relevant glassy portion did not withstand penetration of the pin device used for the experiment.

With regard to matrices with a 5 % drug load, DC and HME systems showed quite a similar behavior, which was in turn not different from that of the pure polymer. On the other hand, a faster dry polymer mass loss and a reduced gel thickness (distance between the erosion and the swelling fronts) were noticed in the case of systems with 70 % of theophylline. These results could be attributed to the formation of a less resistant and/or continuous gel barrier due to the relatively small amount of swelling polymer. Notably, the impact of polymer erosion turned out more evident for the DC systems. Ketoprofen-based HME systems with ≥ 30 % drug loads showed a very low water uptake as compared with all the other formulations and particularly with the corresponding DC matrices (maximum water content of 30 % after 6 h with 40 % drug load HME systems *vs* almost 70 % with DC ones). Moreover, no gel barrier was observed on the surface even though the position of the solvent penetration front could not be estimated as previously mentioned. Also based on the morphological aspect of ketoprofen systems with ≥ 30 % drug loads (figure 3a$_2$), the formation of a new solid phase, in which the hydrophilic nature of the cellulosic polymer was countered by the poor water solubility of the active ingredient, was supposed to take place, promoted by the interaction of the softened polymer chains with the molten drug. Such a hypothesis, however, needs to be supported by further investigation.

The release profiles of DC and HME systems containing increasing amounts of the two model drugs are reported in figures 8 and 9, respectively.

HME matrices for prolonged release are generally described as low-porosity systems able to ensure a strict control of drug release. Thus, they are used in subcutaneous, ocular or vaginal delivery where especially extended release phases are required (> 24 h). Nevertheless, the sole comparison found between HME and DC systems refers to inert ethylcellulose (EC) oral matrices for which the main factor determining the rate of release is indeed porosity (Crowley et al., 2004b). In the case of hydrophilic polymers, it was demonstrated that the entanglement of swollen macromolecular chains gives rise to meshes of relatively small size and, more importantly, independent of the initial porosity of the glassy matrix (Ju et al., 1995; Peppas et al., 2000; Sangalli et al., 2001). In this study, the drug release rate was generally higher from HME devices than from DC ones of analogous composition, practically independent of the model drug employed and the relevant content. Because hydration, swelling and erosion/dissolution processes were demonstrated only marginally influenced by the manufacturing technique, this trend was attributed to the dissolution rate of the drugs in the

microenvironment within the swollen matrix. Following extrusion, in fact, a loss of crystallinity was observed with both drugs, which could account for an increase in their dissolution rate and, therefore, in the apparent solubility gradient across the gel barrier driving drug release. On the contrary, in the case of ketoprofen-based systems containing 30 and 40 % of drug, the release profiles of DC and HME matrices were superimposable for about 1 h whereas a marked decrease in the release rate from HME systems and a reverse order of the release patterns became afterwards evident. However, such a difference could once again be ascribed to the drug that might have promoted, by melting, the previously discussed increase in hydrophobicity of the matrix system and consequent slowing down of solvent-driven processes, *i.e.* hydration/swelling of polymeric chains and dissolution of drug particles.

4. Conclusions

As HPC was demonstrated critical in terms of compaction properties, the identification of an alternative technique for the preparation of oral prolonged-release matrices based on such polymer was considered of interest. In particular, because of its thermoplasticity, the use of HME, which has recently received attention especially due to its potential for continuous manufacturing, was investigated. Promising results were obtained as regards key aspect such as process feasibility (*e.g.* continuous manufacturing with no need for adjuvants, working temperatures in the 100-150 °C range, drug loads up to 70 %) and technological characteristics (*e.g.* very low porosity, evidence of drug/polymer interaction, increase in the microenvironmental apparent solubility of the drug). The impact of the melting temperature of the active ingredient on the process conditions and the characteristics of the extruded products was highlighted. The overall results indicated that HME would be an advantageous technique for the manufacturing of swellable prolonged-release matrices, worthy of further investigation and wider application.

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FIGURE CAPTIONS

Figure 1: photomicrographs of pure polymer matrices: (a) KGF- and (b) KGXF-based DC systems, (c) KGF-based HME systems, at 100X (a_1, b_1, c_1) or 500X (a_2, b_2, c_2) magnification.

Figure 2: water uptake (■; ▲) and residual dry polymer (□; Δ) profiles (a), and swelling (■; ▲) and erosion (□; Δ) front profiles (b) of HPC matrices manufactured by DC (dotted lines) and HME (solid lines).

Figure 3: photomicrographs of HME matrices containing (a) ketoprofen, 5 (a_1) or 40 % (a_2), and (b) theophylline, 5 (b_1) or 70 % (b_2).

Figure 4: DSC thermograms of KGF, theophylline and HME matrices containing differing amounts of theophylline (5-70 %).

Figure 5: DSC thermograms of KGF, ketoprofen and formulations containing 20 % of drug processed by differing techniques.

Figure 6: water uptake (■; ▲) and residual dry polymer (□; Δ) profiles of HPC matrices manufactured by DC (dotted lines) and HME (solid lines) containing differing percentages of drug.

Figure 7: swelling (■; ▲) and erosion (□; Δ) front profiles of HPC matrices manufactured by DC (dotted lines) and HME (solid lines) containing differing percentages of drug.

Figure 8: release profiles of DC (dotted lines) and HME (solid lines) matrices containing differing percentages of theophylline.

Figure 9: release profiles of DC (dotted lines) and HME (solid lines) matrices containing differing percentages of ketoprofen.

a_1 400µm

a_2 100µm

b_1 400µm
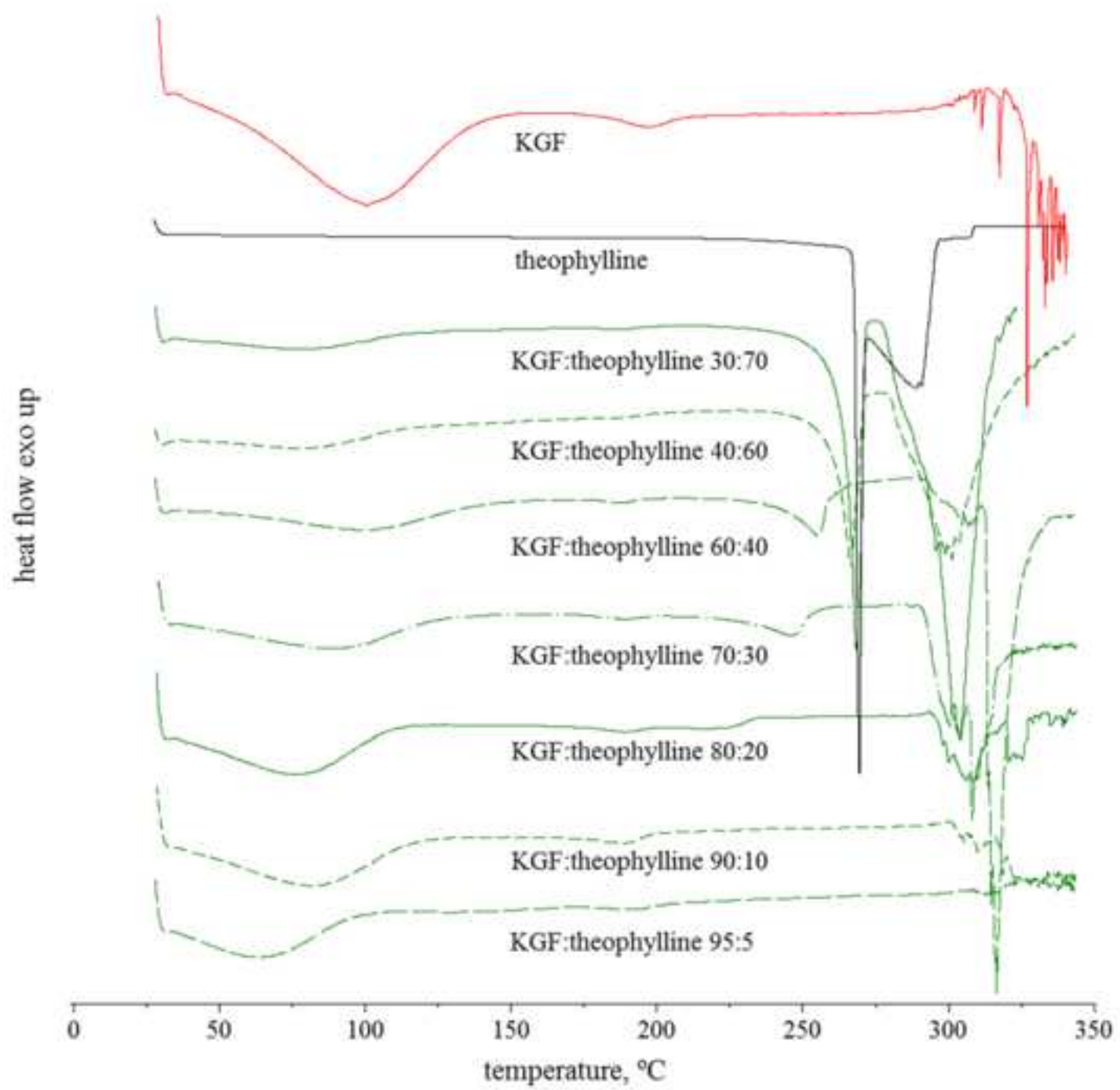
b_2 100µm

c_1 400µm

c_2 100µm
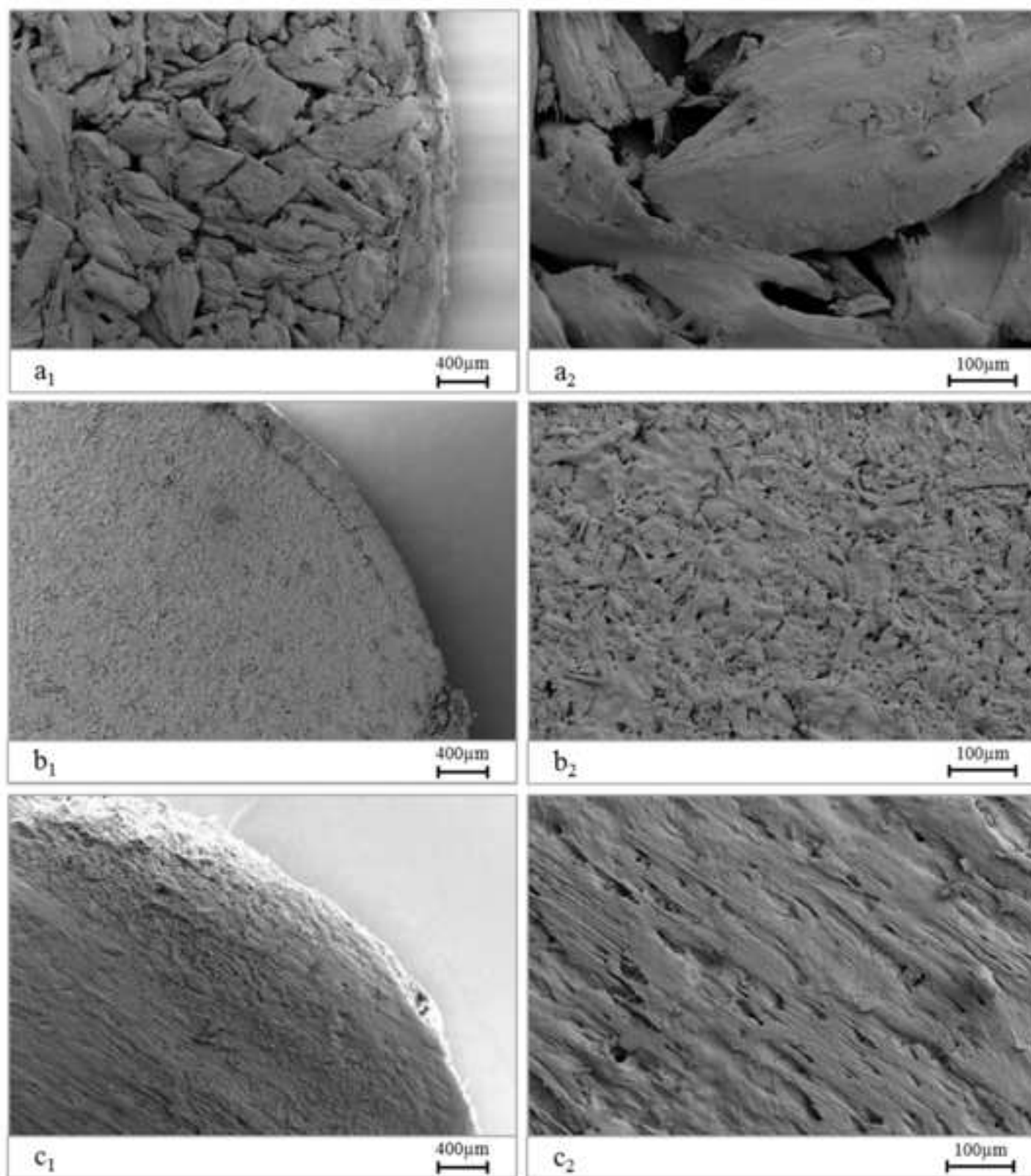
Figure 2
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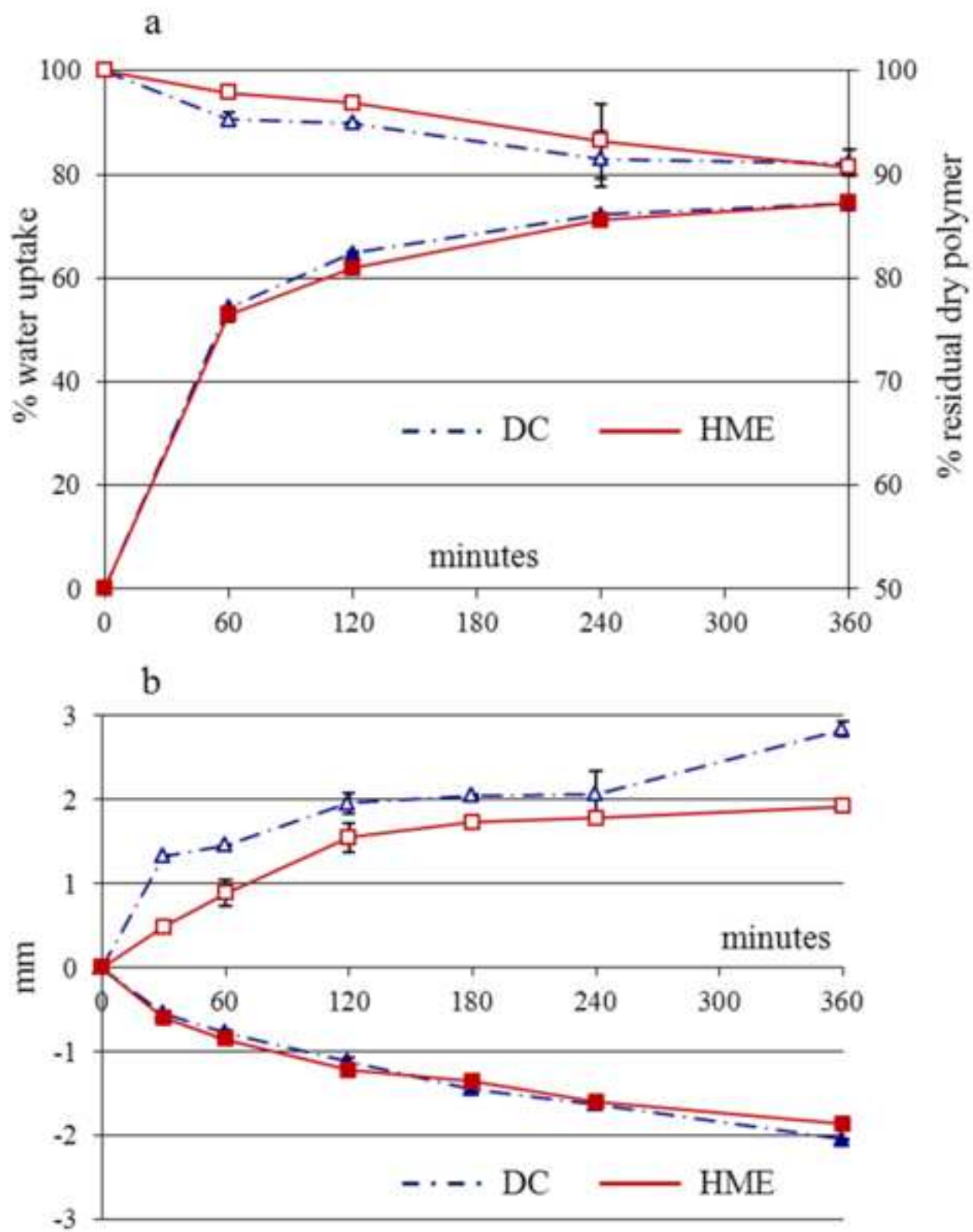
Figure 3
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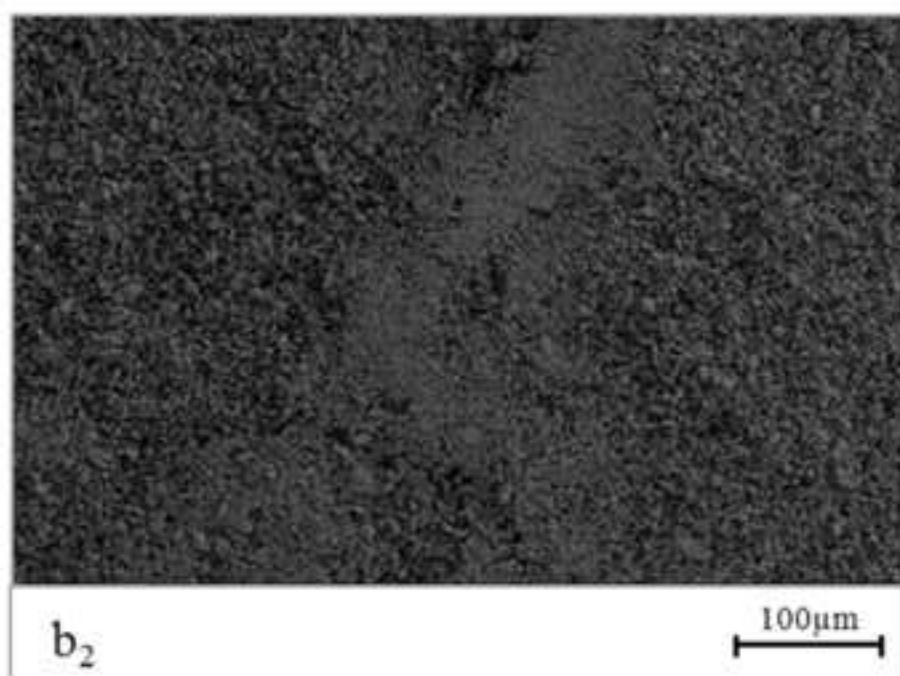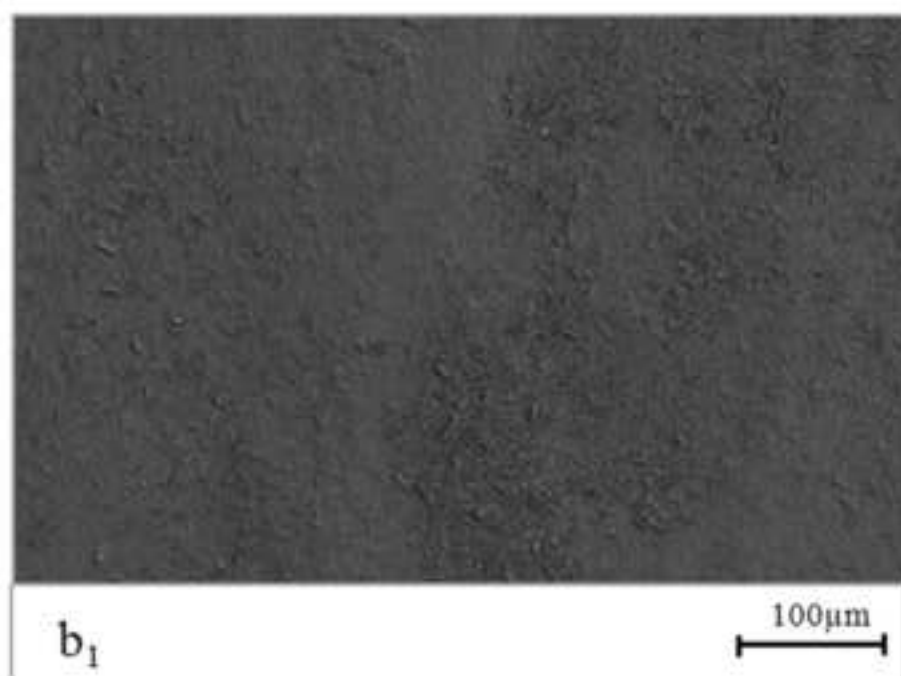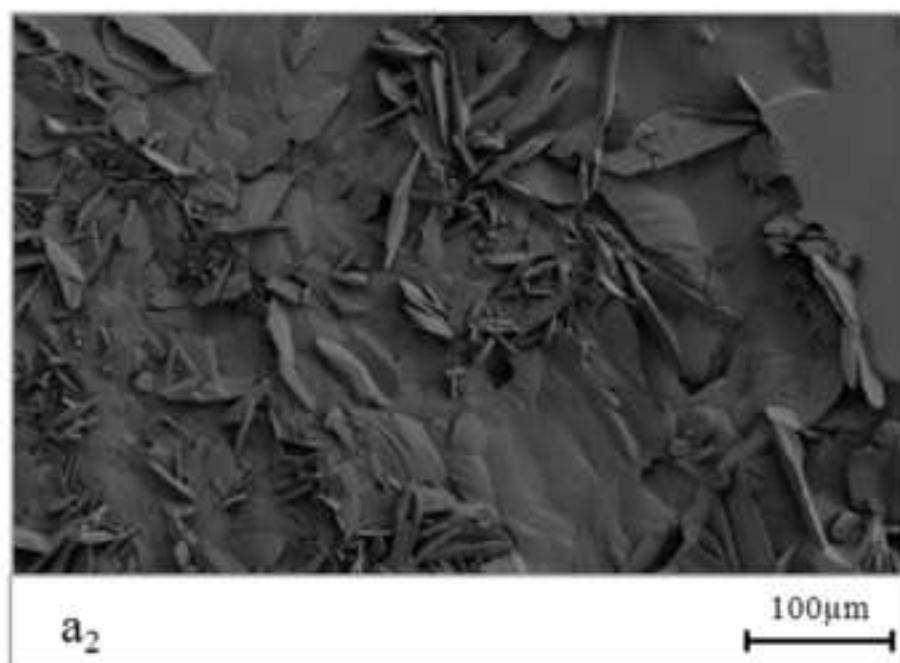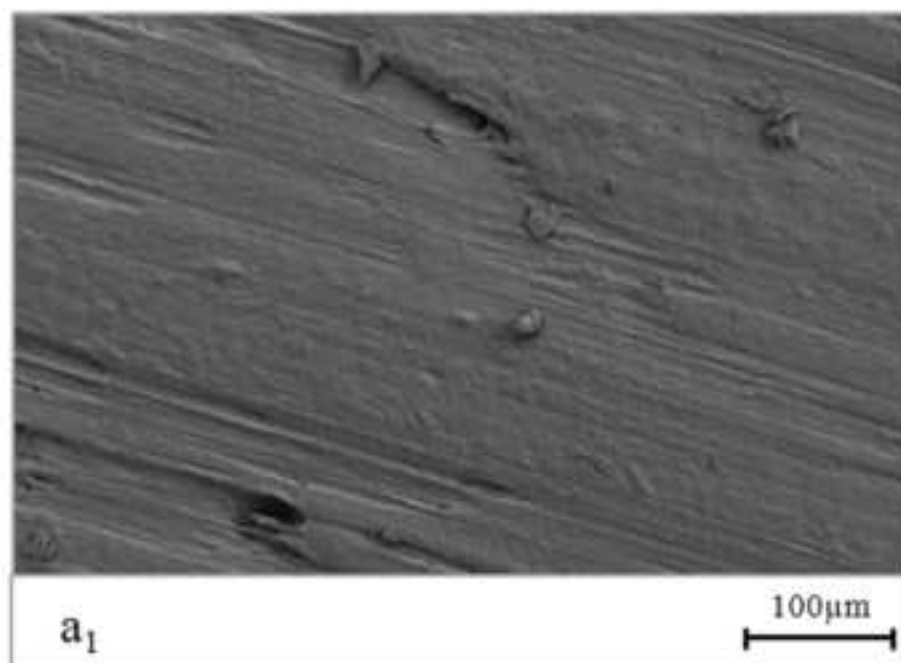
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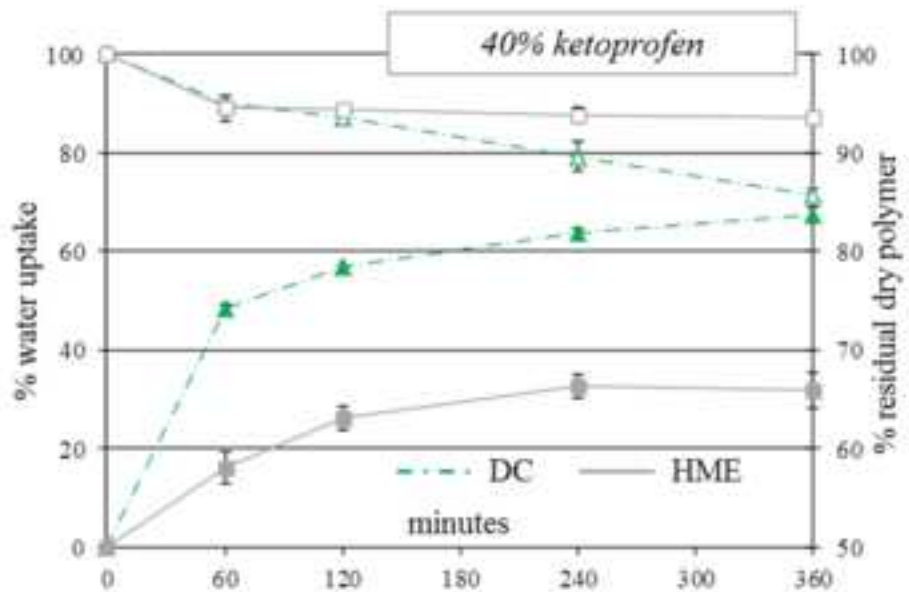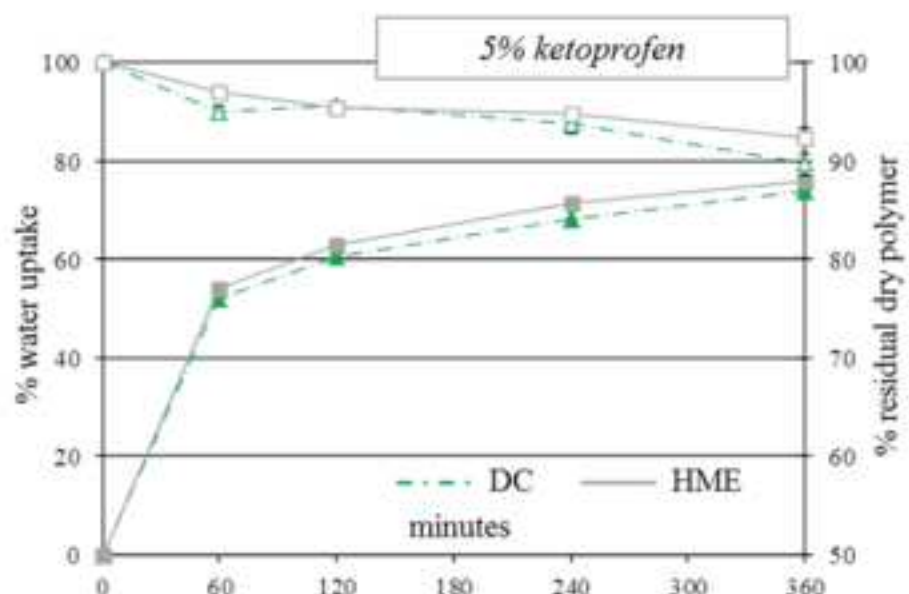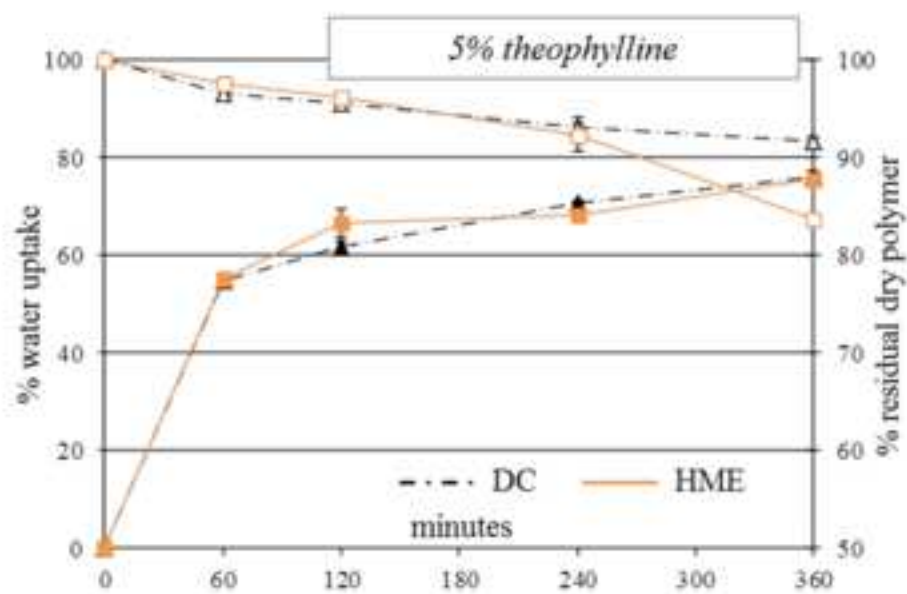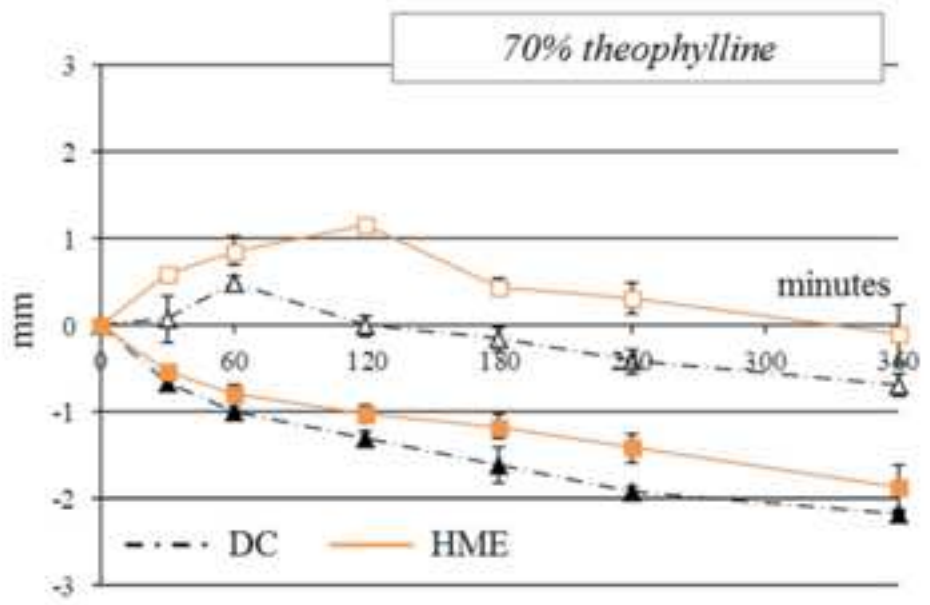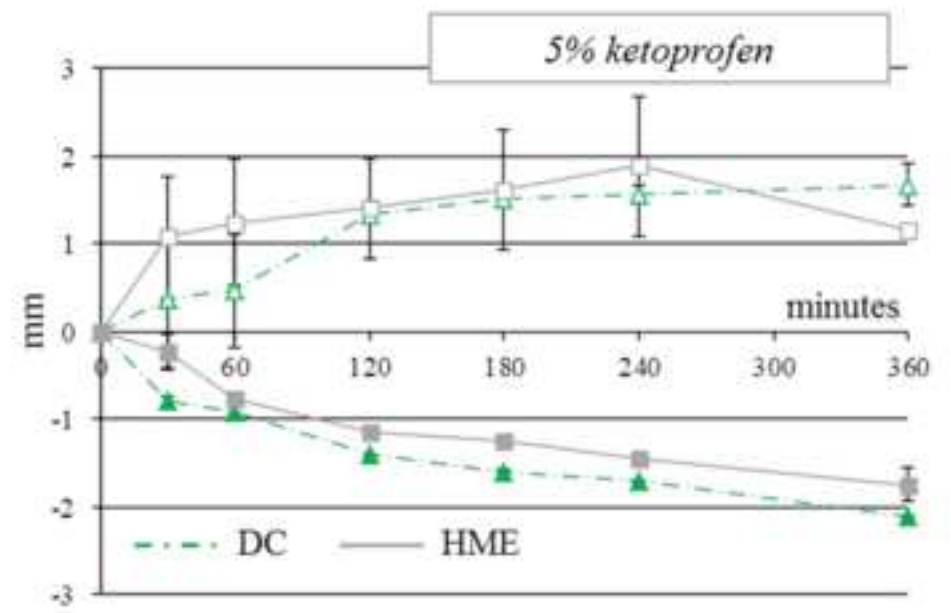**Click here to download high resolution image**

Figure 4

KGF

theophylline

KGF:theophylline 30:70

KGF:theophylline 40:60

KGF:theophylline 60:40

KGF:theophylline 70:30

KGF:theophylline 80:20

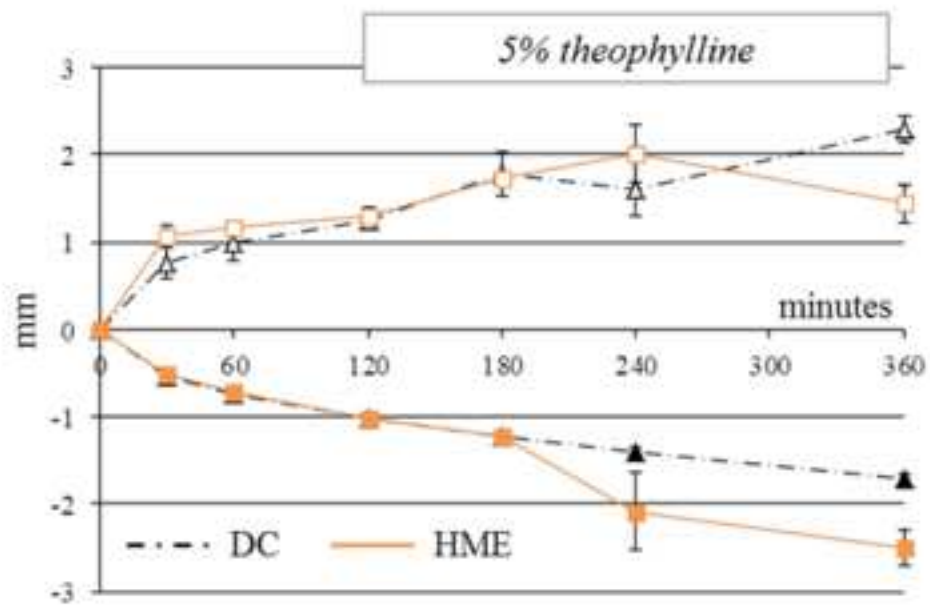KGF:theophylline 90:10

KGF:theophylline 95:5

heat flow exo up

temperature, °C

Figure 5
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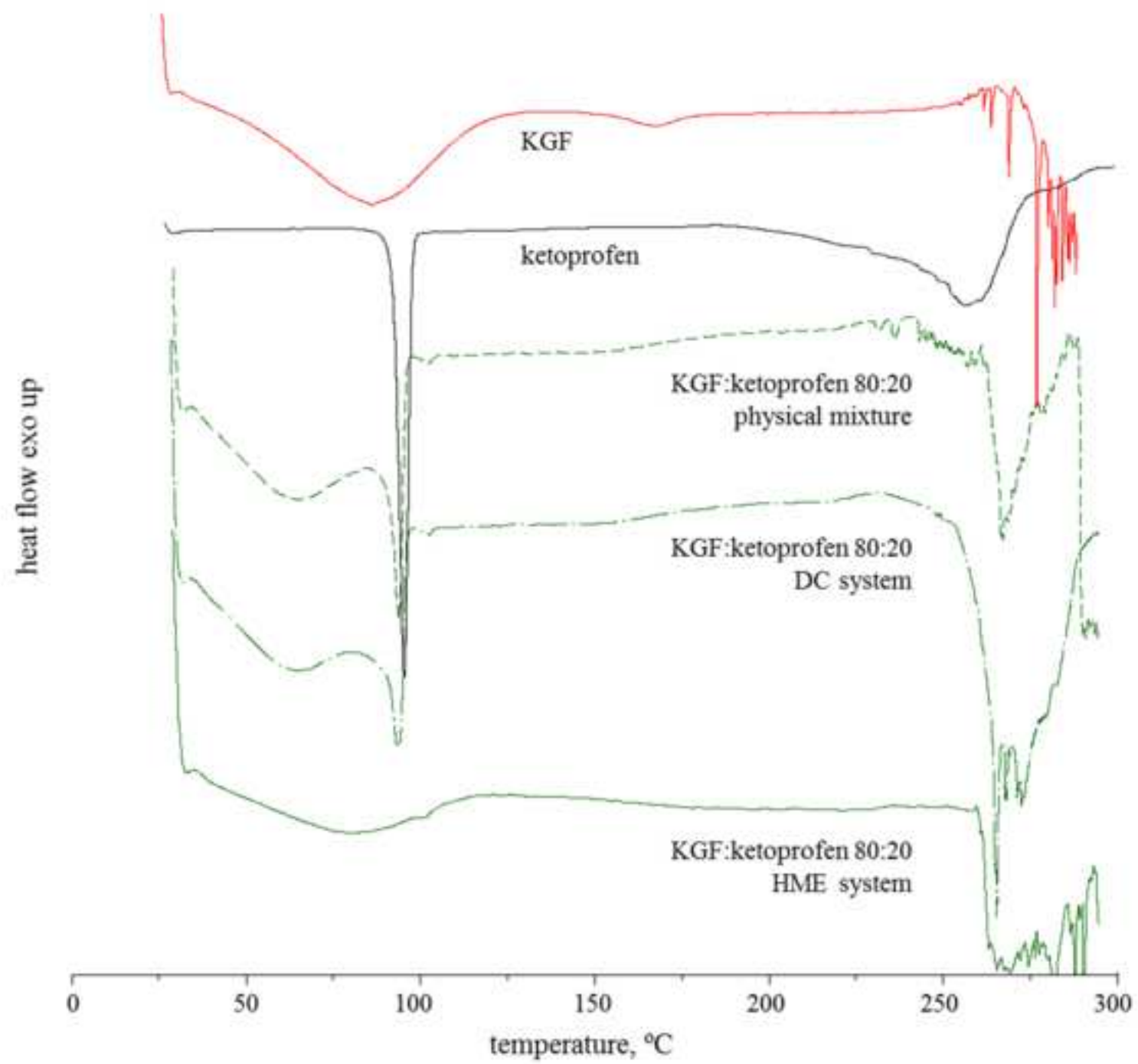
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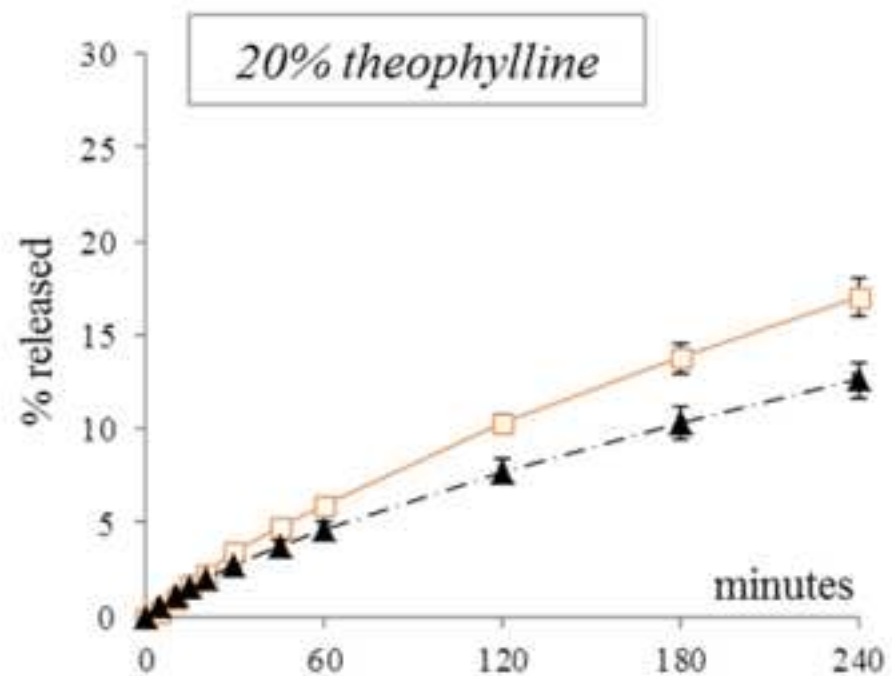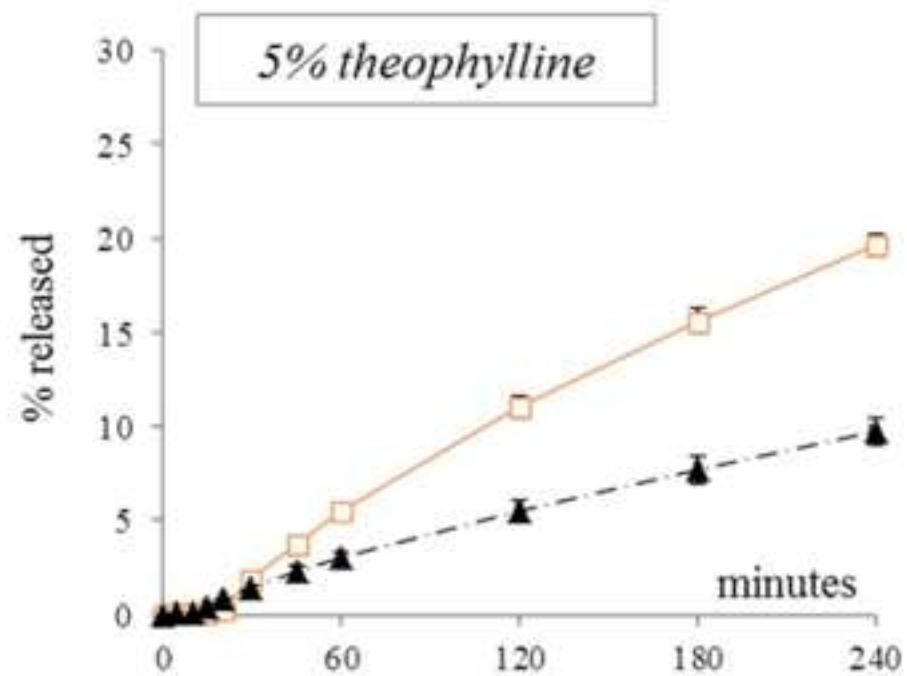**Click here to download high resolution image**
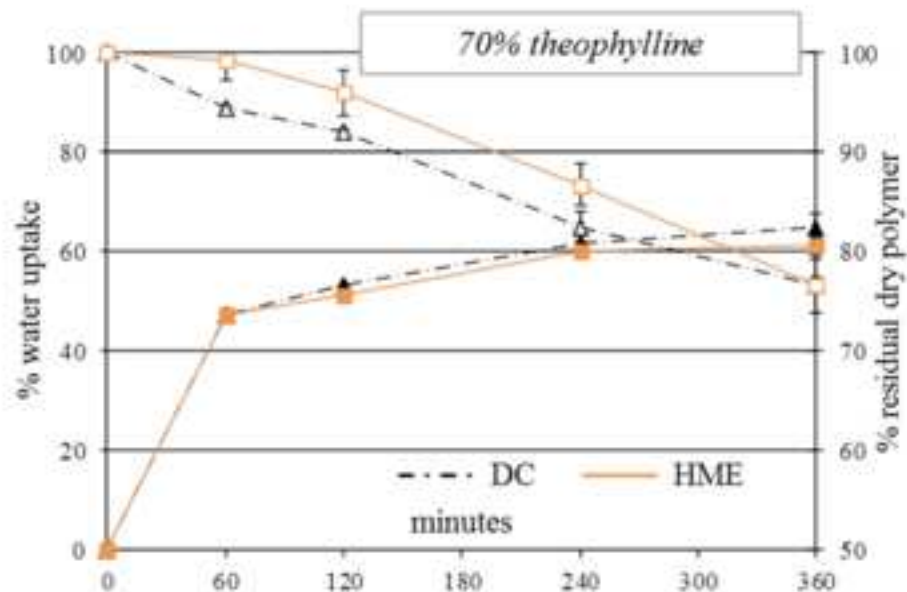
Figure 7
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Figure 8
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Figure 8. Percentage released versus time (minutes) for formulations containing 5%, 20%, 40%, and 70% theophylline.
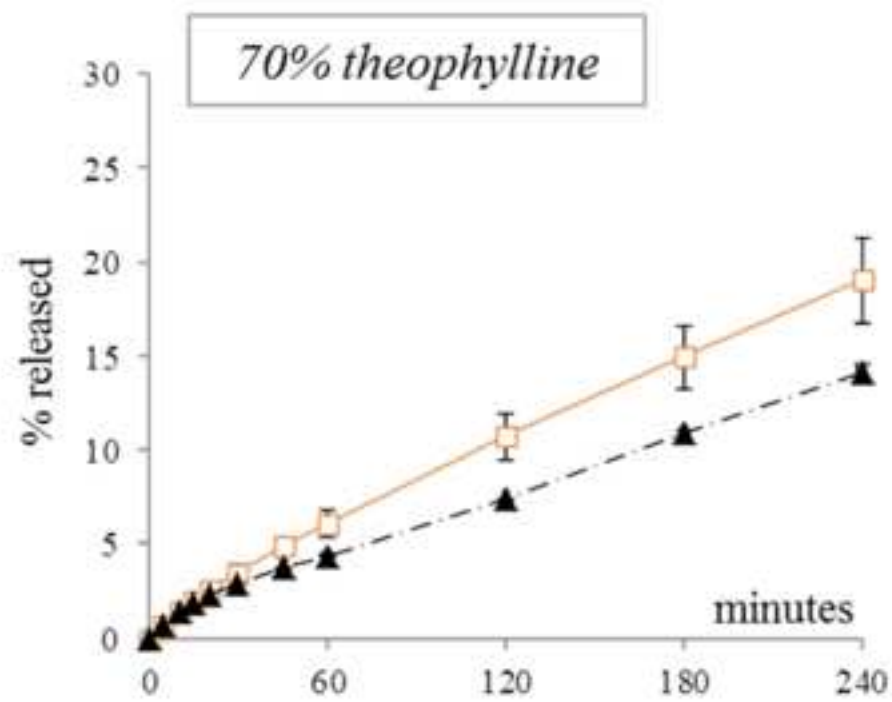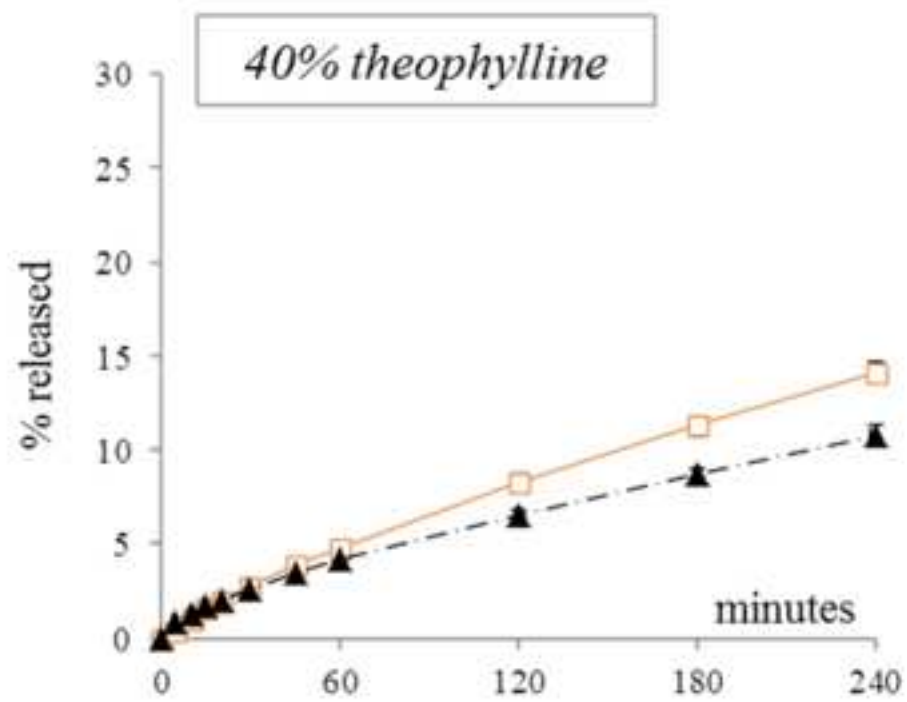
Figure 9
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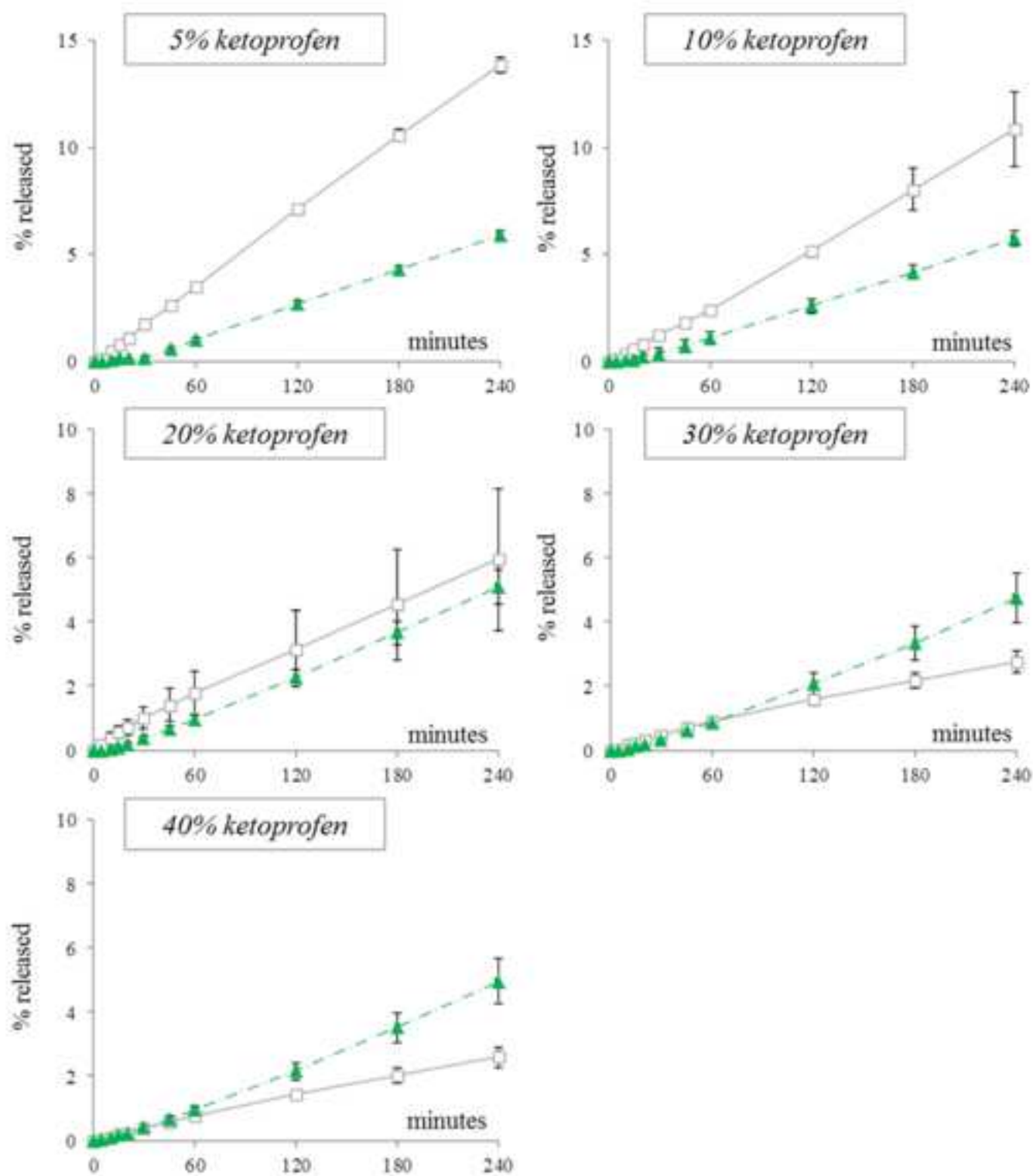
Table 1

Table 1: process and output parameters relevant to HME matrices

PROCESS PARAMETERS	barrel temperatures, $°C$	150
		155
		160
	die temperature, $°C$	150
	screw speed, *rpm*	15
OUTPUT PARAMETERS	processing time, *min*	4-6
	torque* range, *Nm*	7-10

*work of the rotating screw needed to convey the material along the heated barrel

Table 2

Table 2: physico-technological properties of HPC type KGF and KGXF (s.d. values in brackets)

	d_{50}	d_{90}	bulk density	compressibility index	cohesion index
	μm	*μm*	*g/mL*	*%*	
KGF	290	490	0.39 (0.01)	19 (1)	292 (11)
KGXF	82	164	0.22 (0.02)	29 (2)	508 (15)

Table 3

Table 3: physico-technological properties of pure polymer matrices (s.d. values in brackets)

	diameter mm	thickness mm	density g/cm^3	crushing force N	contact angle $°$
DC	7.99 (0.01)	2.92 (0.06)	0.88 (0.02)	166 (9)	47 (2)
HME	8.01 (0.06)	2.90 (0.01)	1.05 (0.10)	-	49 (3)