An investigation into the use of low quantities of functional additives to control drug release from hot melt extruded solid dispersions for poorly soluble drug delivery

Fahad Alqahtani[1,4], Peter Belton[2], Adam Ward[3], Kofi Asare-Addo[3], Sheng Qi[1]

[1] School of Pharmacy, University of East Anglia, Norwich, NR4 7TJ, UK

[2] School of Chemistry, University of East Anglia, Norwich, NR4 7TJ, UK

[3]Department of Pharmacy, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

[4] College of Pharmacy, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia

Corresponding author: Sheng Qi, sheng.qi@uea.ac.uk

Abstract

The motivation of this study is to demonstrate the practicality of producing slow release and fast release products in a single-step hot melt extrusion (HME) process. HPMCAS as the carrier material showed good potential in monolithic controlled release formulations for the model drug, carbamazepine (CBZ). As binary formulations, CBZ-HPMCAS extrudates showed zero-order release over 24 hours which was accompanied by the swelling of the extrudates. A range of functional excipients was used at low quantities to modulate the release rate. The release rates of the HME extrudates could be either accelerated by the incorporations of low quantities (5% w/w) of soluble additives or further sustained by adding lipid excipient, Gelucire 50/13. Clear phase separations of the soluble additives including crosscarmellose sodium, sodium starch glycolate, maltodextrin and lactose in the extrudates led to higher interior porosity and quicker erosion in comparison to the binary extrudates. The phase separated Gelucire in the extrudates led to the substantial swelling of the extrudates and resulted in further prolonged drug release. This study provided clear formulation strategies for modulating the drug release rate from controlled release formulation prepared directly by single-step HME. In addition, this research work also evaluates for the first time HME extrudates simultaneous swelling and drug release using this UV imaging technique. The whole dose cell of this instrumentation is utilised to provide insights into the dissolution process of solid dispersions prepared by HME.

Keywords: Controlled release drug delivery, amorphous solid dispersion, hot melt extrusion, phase separation, swelling, erosion, drug release kinetics, UV imaging

1. Introduction

Hot melt extruded (HME) solid dispersions have been widely used as a formulation strategy to improve the dissolution rate of poorly soluble drugs but less commonly reported for producing sustained/controlled release formulations [1, 2]. The HME extrudates traditionally have to be downstream processed into powder form to allow further tableting or capsules filling. Controlled release products can improve patient compliance by reducing the dose frequency and therapeutic outcome due to more stable plasma drug concentration in comparison to non-controlled released products [3]. This study reports the use of the single-step HME process to directly manufacture cylindrical shaped monolithic solid dispersion based extrudates as the finished product, which can be directly filled in capsules for oral controlled release of drugs. Such a shape can also allow easy control of the drug release rate when either diffusion or surface erosion are the dominate the release mechanism [4]. Therefore, from a manufacturing point of view, HME carries clear advantages as a readily scalable and a single-step method for producing amorphous solid dispersion based controlled release products.

In addition to releasing the API in a controlled manner, the challenge of developing monolithic controlled release formulations based on amorphous solid dispersions containing poorly soluble drug is that the prolonged exposure to the GI fluid could increase the risk of the recrystallization of the drug in the dispersion matrices [5]. If the drug is recrystallized instead of molecularly dispersed in the polymeric matrix, the release rate is limited by the dissolution rate of the crystalline drug particles, but not purely governed by other mechanisms such as matrix erosion and diffusion of the drug molecule through the matrix materials. In order to minimise the drug recrystallization in a solid dispersion based controlled release matrices, the polymer excipient used in the matrices should be able to not only control the release rate of the drug, but also prevent the drug crystallisation in the matrix during the course of dissolution. In

this study, the polymer, HPMCAS, which has crystallisation inhibition properties, was used to form the matrix of the extrudates [6-8]. HPMCAS is a one of a group of widely used pharmaceutical enteric polymers, which can be used in the formulation development of controlled release formulations targeting the intestines. HPMCAS can be obtained with a predetermined ratio of hydrophilic succinate groups and hydrophobic groups such as the acetyl and methoxy substituents [9]. The succinate moiety ionisation at high pH results in an increased solubility and dissolution rate compared to the un-ionised state at low pH. Furthermore, the hydrophobic groups of HPMCAS play an important role in supressing the amorphous drug mobility in a HPMCAS based solid dispersion of and inhibiting the drug recrystallisation due to the hydrophobic interaction between drug and HPMCAS [10, 11]. With such intrinsic properties, it is reasonable to predict that if HPMCAS was used to form the HME monolithic solid dispersions, it should be able to hold its structural integrity during drug dissolution and inhibiting the crystallisation of amorphous poorly soluble drugs, both in solid dispersions and in solutions [12-15]. From the processing prospective, HPMCAS–LF, the low-fine grade of HPMCAS, has been reported to be the most stable grade for HME with the lowest level of free acid released during HME even at high HME temperature and speed [16]. Therefore, LF grade was used in this study.

Carbamazepine (CBZ) was selected as the model drug. It is a well-documented, poorly water-soluble drug. used as an anticonvulsant and specific analgesic for trigeminal neuralgia in the treatment of epilepsy and neuropathic pain, [17, 18]. Clinically, controlled release CBZ products (Tegretol® prolonged release and Carbagen® SR) have demonstrated fewer side effects than immediate release CBZ products [19, 20]. However, they are manufactured by multi-step tabletting process. The motivation of this study is to demonstrate the practicality of producing slow release and fast release products in a single-step process. To modulate the CBZ

release rate of HPMCAS based extrudates, disintegrants, pore formers and lipid excipients were added to the HME extrudates. These were crosscarmellose sodium, Na starch glycolate, crosspovidone, maltodextrin, α-lactose monohydrate and Gelucire 50/13 The intention of using disintegrants and pore-formers in the extrudates was to increase the drug release rate by speeding up the water penetration and disintegration of the HPMCAS matrices; whereas adding the swellable lipid excipient, Gelucire 50/13, was intended to slow down the release rate by increasing the swelling and reducing the breakdown of the HPMCAS matrices. In order to attempt to visualise the swelling and erosion process in real time, this work also evaluates for the first time the feasibility of using a UV imaging technique that is primarily used in the determination of intrinsic dissolution rates (IDR) [21-27].

2. Materials and methods

2.1 Materials

Carbamazepine (CBZ) was purchased from (Molecula, UK). Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS-LF) with the substituent ratios of $–CH_3$, $-CH_2CH(CH_3)OH$, $-COCH_3$, and $–COCH_2CH_2COOH$ being 1.87, 0.25, 0.48, and 0.37 average number/glucose ring unit was kindly donated by Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan). Gelucire 50/13, crosscarmellose sodium (Can) and sodium starch glycolate (NaSG) were kindly donated by Gattefosse (Saint-Priest, France), IMCD UK Ltd (Sutton, UK) and Roquette (Lestrem, France), respectively. Crosspovidone (Polyplasdone-XL) (CP) was kindly donated by Ashland (Limavady, UK), maltodextrin (MD) and α-lactose monohydrate were purchased from (Sigma Aldrich, UK).

2.2 Preparation of hot-melt extruded (HME) filaments

HME filaments were prepared using a co-rotating twin screw Haake Minilab extruder (Thermo Fisher, Karlsruhe, Germany) with a 2 mm orifice die. The materials were weighed (10 g) and pre-mixed via mortar and pestle for 5 minutes. For each experiment, 7 g of the mixture was fed manually into extruder. All the formulations were extruded at 150°C for CBZ-loaded (20% w/w loading) formulations, 100 rpm screw speed and the retention time was 5 minutes. During the flushing (the exiting period of the filament from the die) period, the screw speed was decreased to 30 rpm. It is worth noting that the extrusion temperature used is above the reported dehydration temperature of lactose monohydrate [28]. The melted strands were guided onto a conveyer belt using a circular die of 1.75 mm diameter and collected continuously. CBZ containing extrudates were further used to investigate the effects of additives on the dissolution behaviour of the formulations. The HME formulations containing CBZ are summarised in **Table 1**. In all formulations the weight of CBZ was kept constant at 20% of the total weight. Excipients were added at the rate of 5% of the total weight of the formulation and Gelucire was added at the rate of 15% of the total weight of the formulation.

2.3 Attenuated total reflection-Fourier transform Infrared (ATR-FTIR) Spectroscopy

The IR spectra of the raw materials, physical mixture and extrudates were collected using an FTIR spectrometer (Vertex 70 model from Bruker Optics Limited, United Kingdom) connected with single-reflection diamond ATR accessory (MIRacl™, Pike Technologies, United States). Thirty-two scans were acquired for each sample with a resolution of 2 cm^{-1} scanning from 600-4000 cm^{-1}. All the measurements were carried out on three separate extrudates and analysed via Opus software.

2.4 Powder X-ray diffraction (PXRD)

A Thermo ARL Xtra X-ray diffractometer (Thermo Scientific, Switzerland) with a Cu Kα1 X-ray Tube was used for to study the physical form of raw materials, physical mixture and extrudates in the different formulations and the possible changes in the nature of the components due to processing. The voltage and current of the X-beam used were 45 kV and 40 mA respectively. The angular scanning range was from 5 to 60° with a (2θ) scan type, a step size of 0.01° and the scan rate was 4 s/step.

2.5 Differential scanning calorimetry (DSC)

The DSC experiments were carried out to analyse the raw materials and HME extrudates using Q-20 (TA Instrument, Newcastle, USA) at a heating rate of 10 °C/min from 25 to 210 °C. A nitrogen purge at a flow rate of 50 ml/min was used and sample weights were in range of 2-3 mg. TA standard crimped pans and lids were used for all measurements as well as universal analysis software for analysing the obtained results.

2.6 UV and visible imaging of HME extrudates

The surface imaging instrument (SDI2) is a UV dissolution imaging technique. In this study, it was used in the simultaneous determination of the swelling and drug release from a select few of the HME extrudates (placebo extrudate, H, HG, H-NaSG and HG-NaSG). These selected HME extrudates allowed the investigation of the effect of Gelucire on the HPMCAS as well as the NaSG effects on the produced extrudates. A schematic of the drug release measurements is depicted in **Fig. 1a**. **Fig. 1b** also displays how the dosage form is placed inside the whole dose cell, the direction of media flow and the measurement zone adapted for swelling evaluation. Each extrudate (placebo extrudate, H, HG, H-NaSG or HG-NaSG) was mounted using a custom designed stainless steel wire holder featuring two loops to secure the extrudate in place

(**Fig. 1c**). To perform each test the whole dosage cell with glass beads loaded (to help reduce turbulence) was inserted and connected to the fluid lines. To determine the swelling effects on the extrudates (placebo extrudate, H and HG), a 2 h flow-through assessment was conducted to determine the characteristic behaviour of each extrudate. Each experiment was conducted using both pH 1.2 and pH 6.8 at 37 °C using a flow rate of 8.2 mL/min. A 520 nm wavelength was selected for swelling measurements. Swelling is referred to as "growth" in the Figures. These measurements were taken using the data analysis software supplied with the SDI2 system and processed using Microsoft Excel™.

The first use of a dual closed loop assessment of drug loaded HME extrudate (H, HG, H-NaSG and HG-NaSG) was explored and implemented (**Fig. 2**). Two beakers containing 900 mL of each medium (pH 1.2 and pH 6.8) were placed on stirrer plates and allowed to warm to 37 °C before use. To form the first loop, the primary fluid line was connected to the pH 1.2 beaker along with the 'open loop' waste fluid line. To form the secondary closed loop, the secondary fluid line was connected to the pH 6.8 beaker along with the 'closed loop' waste fluid line. As the SDI2 has the ability to transfuse between different media *in situ* the software was set to clear 70 mL of media during change over to ensure that the pH 1.2 did not contaminate the pH 6.8 media. Each closed loop experiment was conducted for 6 h (2 h in pH 1.2 before 4 h in pH 6.8 media). Each experiment was conducted at 37 °C at a flow rate of 4.2 mL/min. A 280 nm (for CBZ release from the HME extrudate) and a 520 nm (for the HME extrudate swelling (growth) measurements) LED were selected as the light sources. Drug release and growth measurements were collected using the supplied data analysis software and processed using Microsoft Excel™. Normalisation of growth measurements was achieved by subtracting the size of the extrudate at the start of the experiment from the subsequent growth data points (Equation 1, where t_0 is initial time point and x is the subsequent time point).

$$Extrudate\ growth\ change\ (\%) = \left(\frac{Growth\ of\ extrudate\ at\ t_x - Original\ extrudate\ width}{Original\ extrudate\ width}\right) x\ 100 \quad \text{Eq. 1}$$

2.7 *In vitro* drug release studies

All *in vitro* drug release experiments were performed using the British Pharmacopeial (BP) rotating basket method (Copley CIS 8000, Copley Scientific) under sink condition for 24 hours. A 100 rpm paddle rotation speed and 900 mL of either HCl dissolution medium (pH 1.2) or pH 6.8 PBS were used for each test. The temperature of the vessel was controlled at 37 ± 0.5 °C. All dissolution tests were performed as 2-stage experiments to mimic the physiological process of gastric emptying and the transport of gastric content into the intestinal environment. Therefore after 2 hours of dissolution being performed in pH 1.2 HCl, the extrudates were removed and the dissolution media was changed to pH 6.8 PBS for the following 22 hours. Strands of extrudate containing the equivalent of 10 mg of CBZ were used in 900 ml medium to ensure the satisfaction of the sink conditions. 3 ml of the media from each vessel were filtered through 0.45 μm filters (Minisart Sartorius, Goettingen, Germany) and sampled at predetermined time intervals (0.5, 1, 2, 4, 6, 8, 12 and 24 hours) for the swellable strands and (0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 and 6.5 hours) for the rapidly erodible strands to determine the release mechanisms. The amount of CBZ in each sample was measured by an UV spectrometer (PerkinElmer Lamda XLS, USA) at 285 nm. All measurements were performed in triplicate.

3. Results and discussions

3.1 *Characterisation of binary CBZ-HPMCAS extrudates*

The DSC results of the main components of the extrudates indicate the T_g of the amorphous CBZ and HPMCAS at 48.54 ± 1.3 and 123.8 ± 0.2 ºC, respectively (**Fig. 3a**). After HME, CBZ at 20% drug loading formed clear extrudates with HPMCAS. The DSC result of the drug-

loaded extrudates displays a single T_g at 77.5 ± 1.5 ºC, confirming the formation of a molecular dispersion (**Fig. 4a**). The fully amorphous nature of the binary extrudates was further confirmed by the full halo pattern of the PXRD results. (**Fig. 4b**). The experimental T_g is higher than the Gordon-Taylor equation predicted T_g (69.7 ºC) [29, 30]. Such positive deviation has been attributed to the strong specific intermolecular interactions in the literature including hydrogen bonding, electron donor-acceptor complexes and ionic interactions [31]. ATR-FTIR confirmed the amorphous state of the binary matrix and consistency with a molecularly dispersed system but not showing strong signs of hydrogen bonding interactions. Therefore, any intermolecular interaction between HPMCAS and CBZ could be dominated by van der Waals interactions which are consistent with the hydrophobic interactions proposed by Ueda et al. [14, 15].

As seen in **Fig. 5a**, the HPMCAS-CBZ binary extrudates examined by the rotating basket method show limited release in the first hours at pH 1.2 media and a continuous zero order drug release within the 24 hours in pH 6.8. The fitting of the release data to the zero order kinetics can be found in Supplementary Material **Table S1**. Such sustained release can be explained by the over 281% swelling in weight and volume of the binary CBZ-HPMCAS extrudates (**Table S2**) after 12 hours in pH 6.8. This is in clear contrast to the HPMCAS placebo extrudates which only showed approximately 30% and 101% increases in weight and in volume, respectively, after 12 hours in pH 6.8 (Supplementary Material **Fig. S1**). A clear swelling layer of the CBZ-HPMCAS extrudates can be seen (**Fig 5a insert**).

Similar swelling behaviour of HPMCAS matrices was reported in the literature [32]. The slow erosion/dissolution of the swelled HPMCAS layer was thought to be caused by the drop in the local pH due to ionisation of the acid groups on the polymer. This resulted in the pH dropping below the threshold necessary for the dissolution of this polymer. [32]. However we would

argue that when the succinate groups ionise at pH 6.8, they release hydrogen ions and become negatively charged. This should increase electrostatic repulsion which tends to lead to polymer-polymer repulsion and disentanglement and dissolution. To counter balance this effect, the ionisation also can lead to a local increase in ionic strength and therefore an increase in shielding of the charges. Therefore the effects generated from the local ionisation of the HPMCAS acid groups may not be as large as might be expected on a simple charge model. Therefore, whilst an argument about the effect of local pH may not fully explain the slow swelling and dissolution of the polymer, the concentration of ions locally due to ionisation may reduce charge-charge repulsion and result in a reduction of the rate of swelling and dissolution.

When CBZ is added to the polymer the amount of swelling increases compared to the placebo. The most likely cause of this is the increased free volume created by the inclusion of the drug enabling polymer disentanglement to occur more easily. Evidence for this is given by the decrease in T_g of the mixed system compared to the pure polymer.

3.2 *Accelerating the drug release using low quantity additives*

In order to explore the formulation strategies for accelerating the complete drug release from the extrudates from 24 hours to 12 hours, a range of additives with 5% (w/w) loading were blended in the formulation during HME. These additives are traditionally used as either disintegrants (CNa, NaSG, and CP) or diluent/pore formers (MD and LM) in oral dosage forms. It was hypothesised that the addition of these excipients could speed up the physical disintegration process of the extrudates, subsequently the drug release rate.

Single T_gs were detected for all ternary extrudates indicating the fully amorphous nature of the drug and polymer in the extrudates (**Fig. 6a and b)** which is further confirmed by the PXRD

(**Fig. 7a**). The phase separation of the additives were not detected by the DSC, but suggested by the SEM (**Fig.8**) The ATR-FTIR data shown in **Fig. 7c** show no significant changes of CBZ peaks in comparison to the HPMCAS-CBZ binary extrudates indicating that the addition of the additives had no effect on the intermolecular interactions between CBZ and HPMCAS. The DSC results indicate slight shifts in T_g to lower temperatures in comparison to the binary HPMCAS-CBZ extrudates. This may be ascribed to the increased the relative ratio of CBZ to HPMCAS (20:75 w/w) in the ternary formulation than the binary system (20:80 w/w). From the SEM images shown in **Fig. 8**, it can be confirmed that except H-CP, all other additives are phase separated from the HPMCAS-CBZ dispersion. Significant levels of porosity were observed in the cross-section of these ternary extrudates with the exception of H-CP. The underpinning mechanisms for the formation of the internal pores is out of the scope of this study and will be discussed in a separation study.

In comparison to the binary HPMCAS-CBZ extrudates (zero order release rate K= 0.068%/min, shown in Supplementary Material Table S1), much faster drug release was achieved for all ternary extrudates. The samples H-LM, H-CNa, H-NaSG and H-MD all demonstrated first order release kinetics with very similar rate constants (average zero order release rate K= 0.395 +/-0.01 %/min, shown in Supplementary Material Table S1) approximately 6 times faster than the binary system. H-CP was exceptional in that its release profile could not be fitted to a zero order process but could be fitted to a first order process with rate constant of 0.004 %/min (Supplementary Materials Table S1). Because of the low number of data points this fit may not be unique but it does indicate a process in which the rate depends on the amount of drug available for release. Although the rate process of H-CP is different from other formulations, the half-life is similar to that for the other ternary systems at about 4 hours. With 5% (w/w) addition of CP in the binary system, the change in T_g may be too subtle to be

detected by DSC (**Fig. 6b**). Therefore it is difficult to use DSC to determine whether CP formed homogeneous molecular dispersion with HPMCAS and the drug. However it is clear in the SEM images (**Fig. 8**) that at least there is no micron scale phase separation in the H-CP extrudates. This continuous morphology of H-CP (in contrast to the highly porous interior of other formulations) may contribute to the difference in rate process. A homogeneously distributed soluble additive such as CP will enhance water absorption into the matrix and in dissolving will uniformly erode the matrix. However if the material is not homogeneously distributed its swelling or dissolution will fracture the matrix or create pores filled with water.

H-LM showed fastest release rate among all ternary extrudates. This could be caused by the local dissolution of the lactose particles which create high sugar solution in the pockets (which were previously occupied by lactose particles). This localised high sugar solution would generate high osmotic pressure which would tend to result in the faster ingress of water and consequent swelling of the lactose solution filled pockets thus contributing to the faster drug release from H-LM extrudates.

The results from the rotating basket method are confirmed by the UV imaging results. Using H-NaSG as an example, **Fig. 9** depicts the UV images obtained from the SDI2 instrumentation in both the UV and visible wavelength. The UV images in the UV region show no significant CBZ release in the pH 1.2 media for the binary extrudates. As seen in **Fig. 9**, there is an increase in the CBZ release in the pH 1.2 media with the addition of NaSG to the extrudates. This agrees well with the approximately 5% release observed in the conventional dissolution test for H-NaSG within 1 hour of dissolution in pH 1.2 (**Fig. 5a**). The red dashed lines in **Fig. 9** after the 2 h images are where the media change to pH 6.8 occurs. A change in the pH shows significant amounts of drug being released as a result of this pH shift. The results correlate well with **Fig.**

5a where the incorporation of the NaSG brought about significant increases in the CBZ release in pH 6.8.

Little erosion was observed in the binary extrudate of HPMCAS-CBZ in both media. **Fig. 10a** showed there was hardly any swelling to occur for the binary extrudate in pH 1.2. The introduction of the pH 6.8 brought about the swelling of the filament (**Fig. 10a**). This was also evident in **Fig. 10b** which is a zoomed in image of the self-same extrudate in pH 6.8 (after 60 min in the pH 6.8 media). This showed an increase in swelling to occur to due to the media ingress into the extrudate and it was also possible to visualise the gel layer. The incorporation of NaSG into the formulation brought about changes in the swelling at pH 1.2 when compared with the binary filament (**Fig. 10a**). This may be attributed to the porosity of the H-NaSG which encourage rapid water uptake into the extrudates. The extrudate continued to swell to a greater extent in pH 6.8 till after ~180 min when extrudate degradation can be observed. This continues to occur as can be visualised from **Fig. 10c** (zoomed in image after 180 min in pH 6.8 showing the gradual extrudate degradation). The filament continues to degrade past its normalised size (orange circle in **Fig. 10a**).

3.3 *Sustaining the drug release using lipid additives*

Gelucire 50/13 is one of the Gelucire group of self-emulsifying excipients often used in oral preparations. Gelucire 50/13 has been reported to exhibit significant water uptake and gel forming ability. [33] . It has been co-extruded with polymers for forming solid dispersions for taste masking and modified release applications [34-36]. It was selected to blend with HPMCAS in this study to modify the swelling behaviour of the HPMCAS matrices and allow further prolonged release of CBZ. As seen in **Fig. 6**, with a small amount of Gelucire remains phase separated as shown by the small residual melting peak in the DSC. Small amounts of

crystalline Gelucire are also evident in the PXRD results shown in **Fig. 7b**. As with the ternary extrudates, the ATR-FTIR spectra of Gelucire-containing extrudates show no shifts of the signature IR peaks of amorphous CBZ and HPMCAS indicating that the addition of Gelucire had no effect on the state of the drug and the interaction between CBZ and HPMCAS in the extrudates and that no specific interaction with Gelucire is evident.

As seen in **Fig 5b,** with the exception of the HG-LM, all the samples containing Gelucire show a much slower release profile than the samples without Gelucire. All release rates are zero order, including the CP containing sample which showed a first order rate process in the H-CP sample (Supplementary Materials **Table S1**). HG without any other additives exhibited slowest drug release rate (K=0.038 %/min, T_{50} =21 hours). This is about half the rate seen in sample H. H-CAN, H-Na SG and H-MD and HG-CP had rate constants ranging from 0.052 to 0.066 %/min which are 6 to 7 times slower than the samples without Gelucire.

HG-LM was exceptional in that its rate was very similar to that of the corresponding sample without Gelucire indicating that for this excipient the nature of the excipient itself determined the rates of release. Whereas for the remainder the presence of Gelucire was the determinant of the release rate. With the exception of the HG-LM sample, the volumes increased in linear fashion but the weight, although increasing, tended to level off at longer times indicating that some erosion may be taking place.

The slow hydration of the placebo is consistent with the results seen for the samples without Gelucire and is likely to be due to the same action of CBZ in increasing the free volume of HPMCAS thus enabling easier disentanglement.

In contrast to the ternary extrudates without Gelucire, which dissolved through surface erosion, the Gelucire-containing extrudates (except HG-LM) all show similar rates of the continuous swelling. These were up to 450-650% by 24 hours, implying that the addition of the low quantity additives had a minimal effect on the matrices. The SEM images shown in **Fig. 8** reveal the much less porosity at the surfaces of the Gelucire containing extrudates in comparison to the Gelucire-free extrudates.

HG-NaSG was used as an example to further study the impact of Gelucire 50/13 on the drug release behaviour. The UV (280 nm LED) and visible (520 nm LED) were used to simultaneously measure the CBZ release and swelling from the binary extrudates formulated with Gelucire and NaSG (HG-NaSG). The images in **Fig. 9** suggest the incorporation of Gelucire further increases CBZ release in the pH 1.2 media in comparison to H-NaSG (approximately 7% within 1 hour in pH 1.2). The order for drug release from the extrudates therefore in pH 1.2 prior to the pH shift to 6.8 was H < H-NaSG < HG-NaSG. This agrees well with the dissolution data for the first 2 hours in pH 1.2 (**Fig. 5**). In terms of the trend of the swelling behaviour of the extrudates, the trend is H < HG-NaSG < H-NaSG. The addition of Gelucire increased the swelling of the extrudates in pH 1.2 in comparison to binary extrudates, but reduced the swelling when it is compared to H-NaSG (**Fig 10a**). This agrees well with the swelling data of the extrudates tested under conventional rotational basket dissolution condition (Supplementary Materials, **Table S2 and S3**).

The change to pH 6.8 as evidenced in the UV images at 280 nm suggests much faster drug release and disintegration of the HG-NaSG extrudates when tested using SDI2 apparatus than the results obtained using the conventional dissolution test. It was interesting to note the changes to the extrudates in the visible wavelength of 520 nm: clear rapid initial swelling was

seen in HG-NaSG up to 2 hours after the pH change to 6.8. After 2 hours in pH 6.8, the rapid disintegration of the extrudates into fragments starts to occur. **Fig. 10d** shows particulates of the filaments in the media using the 520 nm LED depicting further degradation of the extrudates. This may have contributed to the significantly faster CBZ release observed in the SDI2 experiments. It is however important to note that the hydrodynamics of this miniaturised flow cell dissolution system (~70 ml volume with constant lamellar flow at 8.2 ml/min) is different to that of the standard dissolution system (900 ml with rotational basket) which may lead to differences observed with drug release behaviour. As the sample swells the polymer chains will disentangle and the mechanical strength of the sample will decrease. If the hydrodynamic regime is such that the pressure differences across the sample or the drag forces acting on it are sufficient to cause mechanical disruption, then fragmentation and erosion will follow. In the flow cell this appears to be the case but not in the rotating basket. In addition, the custom-made sample holder may also apply additional mechanical strain to the swelled extrudates and contribute to the disintegration of the integrity of the structure. These results also highlight the importance of hydrodynamic effects on the in vitro drug release results and more in depth investigation is undergoing.

4. Conclusion

This study proposed the use of HME to directly manufacture controlled release oral formulations. HPMCAS-LF showed good potential for being used as the matrix excipient for monolithic controlled release formulations. As binary formulations, CBZ-HPMCAS extrudates showed zero-order controlled release of CBZ over 24 hours. The intermolecular interactions (most likely to be either van der Waals or hydrophobic interactions which were not detected by IR) between CBZ and HPMCAS and the microenvironments are responsible for the sustained release of CBZ. The release rate of the HME extrudates could be accelerated by the

incorporation of low quantities (5% w/w) of additives and sustained further by adding lipid excipient, Gelucire 50/13. The highly water-soluble additive, lactose, led to rapid water penetration and erosion of the extrudates resulting in a faster drug release rate than the CBZ-HPMCAS binary extrudates. Clear phase separation of the disintegrants including NaSG, CNa, MD and LM in the extrudates led to higher interior porosity and quicker erosion in these matrices in comparison to the binary extrudates. The gel-forming ability of Gelucire, which is also phase separated in the extrudates, provided the substantial swelling capability of the extrudates and further prolongation of the drug release. UV imaging was also able to provide direct visualisation and further insights into the simultaneous drug release and swelling/erosion phenomena occurring. This study thus provides clear formulation strategies for modulating the drug release rate from controlled release formulation prepared directly by HME.

Acknowledgment

This project has received funding from the Interreg 2 Seas programme 2014-2020 co-funded by the European Regional Development Fund under subsidy contract 2S01-059_IMODE.

References:

[1] M.M. Crowley, F. Zhang, M.A. Repka, S. Thumma, S.B. Upadhye, S.K. Battu, J.W. McGinity, C. Martin, Pharmaceutical applications of hot-melt extrusion: part I, Drug development and industrial pharmacy, 33 (2007) 909-926.

[2] Y. Zhu, N.H. Shah, A.W. Malick, M.H. Infeld, J.W. McGinity, Controlled release of a poorly water-soluble drug from hot-melt extrudates containing acrylic polymers, Drug development and industrial pharmacy, 32 (2006) 569-583.

[3] C. Maderuelo, A. Zarzuelo, J.M. Lanao, Critical factors in the release of drugs from sustained release hydrophilic matrices, Journal of Controlled Release, 154 (2011) 2-19.

[4] A. Nokhodchi, S. Raja, P. Patel, K. Asare-Addo, The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems, BioImpacts : BI, 2 (2012) 175-187.

[5] J. Bouman, P. Belton, P. Venema, E. van der Linden, R. de Vries, S. Qi, The Development of Direct Extrusion-Injection Moulded Zein Matrices as Novel Oral Controlled Drug Delivery Systems, Pharmaceutical Research, 32 (2015) 2775-2786.

[6] J.M.O. Pinto, A.F. Leão, M.K. Riekes, M.T. França, H.K. Stulzer, HPMCAS as an effective precipitation inhibitor in amorphous solid dispersions of the poorly soluble drug candesartan cilexetil, Carbohydrate Polymers, 184 (2018) 199-206.

[7] W. Curatolo, J.A. Nightingale, S.M. Herbig, Utility of Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) for Initiation and Maintenance of Drug Supersaturation in the GI Milieu, Pharmaceutical Research, 26 (2009) 1419-1431.

[8] N.G. Solanki, K. Lam, M. Tahsin, S.G. Gumaste, A.V. Shah, A.T.M. Serajuddin, Effects of Surfactants on Itraconazole-HPMCAS Solid Dispersion Prepared by Hot-Melt Extrusion I: Miscibility and Drug Release, Journal of Pharmaceutical Sciences, 108 (2019) 1453-1465.

[9] D.T. Friesen, R. Shanker, M. Crew, D.T. Smithey, W.J. Curatolo, J.A.S. Nightingale, Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview, Molecular Pharmaceutics, 5 (2008) 1003-1019.

[10] Y. Chen, Y. Pui, H. Chen, S. Wang, P. Serno, W. Tonnis, L. Chen, F. Qian, Polymer-Mediated Drug Supersaturation Controlled by Drug–Polymer Interactions Persisting in an Aqueous Environment, Molecular pharmaceutics, 16 (2019) 205-213.

[11] Y. Fang, G. Wang, R. Zhang, Z. Liu, Z. Liu, X. Wu, D. Cao, Eudragit L/HPMCAS blend enteric-coated lansoprazole pellets: enhanced drug stability and oral bioavailability, AAPS PharmSciTech, 15 (2014) 513-521.

[12] A.C. Rumondor, L.A. Stanford, L.S. Taylor, Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions, Pharm Res, 26 (2009) 2599-2606.

[13] A.C.F. Rumondor, M.J. Jackson, L.S. Taylor, Effects of Moisture on the Growth Rate of Felodipine Crystals in the Presence and Absence of Polymers, Crystal Growth & Design, 10 (2010) 747-753.

[14] K. Ueda, K. Higashi, K. Yamamoto, K. Moribe, The effect of HPMCAS functional groups on drug crystallization from the supersaturated state and dissolution improvement, International journal of pharmaceutics, 464 (2014) 205-213.

[15] K. Ueda, K. Higashi, K. Yamamoto, K. Moribe, Inhibitory Effect of Hydroxypropyl Methylcellulose Acetate Succinate on Drug Recrystallization from a Supersaturated Solution Assessed Using Nuclear Magnetic Resonance Measurements, Molecular pharmaceutics, 10 (2013) 3801-3811.

[16] A.L. Sarode, S. Obara, F.K. Tanno, H. Sandhu, R. Iyer, N. Shah, Stability assessment of hypromellose acetate succinate (HPMCAS) NF for application in hot melt extrusion (HME), Carbohydrate Polymers, 101 (2014) 146-153.

[17] R.A. Helms, D.J. Quan, Textbook of therapeutics: drug and disease management, Lippincott Williams & Wilkins, 2006.

[18] M.A. Koda-Kimble, Koda-Kimble and Young's applied therapeutics: the clinical use of drugs, Lippincott Williams & Wilkins, 2012.

[19] R.H. Weisler, Carbamazepine extended-release capsules in bipolar disorder, Neuropsychiatric Disease and Treatment, 2 (2006) 3-11.

[20] G. Powell, M. Saunders, A. Rigby, A.G. Marson, Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy, Cochrane Database of Systematic Reviews, (2016).

[21] W.L. Hulse, J. Gray, R.T. Forbes, A discriminatory intrinsic dissolution study using UV area imaging analysis to gain additional insights into the dissolution behaviour of active pharmaceutical ingredients, International journal of pharmaceutics, 434 (2012) 133-139.

[22] A. Ward, K. Walton, K. Box, J. Ostergaard, L.J. Gillie, B.R. Conway, K. Asare-Addo, Variable-focus microscopy and UV surface dissolution imaging as complementary techniques in intrinsic dissolution rate determination, International journal of pharmaceutics, 530 (2017) 139-144.

[23] J.P. Boetker, J. Rantanen, T. Rades, A. Mullertz, J. Ostergaard, H. Jensen, A new approach to dissolution testing by UV imaging and finite element simulations, Pharm Res, 30 (2013) 1328-1337.

[24] J. Pajander, S. Baldursdottir, J. Rantanen, J. Ostergaard, Behaviour of HPMC compacts investigated using UV-imaging, International journal of pharmaceutics, 427 (2012) 345-353.

[25] K. Asare-Addo, K. Walton, A. Ward, A.M. Totea, S. Taheri, M. Alshafiee, N. Mawla, A. Bondi, W. Evans, A. Adebisi, B.R. Conway, P. Timmins, Direct imaging of the dissolution of salt forms of a carboxylic acid drug, International journal of pharmaceutics, 551 (2018) 290-299.

[26] K. Asare-Addo, M. Alshafiee, K. Walton, A. Ward, A.M. Totea, S. Taheri, N. Mawla, A.O. Adebisi, S. Elawad, C. Diza, P. Timmins, B.R. Conway, Effect of preparation method on the surface properties and UV imaging of indomethacin solid dispersions, Eur J Pharm Biopharm, 137 (2019) 148-163.

[27] A. Ward, K. Walton, N. Mawla, W. Kaialy, L. Liu, P. Timmins, B.R. Conway, K. Asare-Addo, Development of a novel method utilising dissolution imaging for the measurement of swelling behaviour in hydrophilic matrices, International Journal of Pharmaceutics: X, 1 (2019) 100013.

[28] J. Chen, J. Wang, R. Li, A. Lu, Y. Li, Thermal and X-ray Diffraction Analysis of Lactose Polymorph, Procedia Engineering, 102 (2015) 372-378.

[29] S.H. Adam, The Gordon-Taylor equation. Additivity and interaction in compatible polymer blends, Die Makromolekulare Chemie, 189 (1988) 1941-1955.

[30] P.J. Skrdla, P.D. Floyd, P.C. Dell'Orco, The amorphous state: first-principles derivation of the Gordon-Taylor equation for direct prediction of the glass transition temperature of mixtures; estimation of the crossover temperature of fragile glass formers; physical basis of the "Rule of 2/3", Physical Chemistry Chemical Physics, 19 (2017) 20523-20532.

[31] X. Lu, R.A. Weiss, Relationship between the glass transition temperature and the interaction parameter of miscible binary polymer blends, Macromolecules, 25 (1992) 3242-3246.

[32] F. Tajarobi, A. Larsson, H. Matic, S. Abrahmsen-Alami, The influence of crystallization inhibition of HPMC and HPMCAS on model substance dissolution and release in swellable matrix tablets, Eur J Pharm Biopharm, 78 (2011) 125-133.

[33] S. Qi, D. Marchaud, D.Q.M. Craig, An investigation into the mechanism of dissolution rate enhancement of poorly water-soluble drugs from spray chilled gelucire 50/13 microspheres, Journal of Pharmaceutical Sciences, 99 (2010) 262-274.

[34] M. Maniruzzaman, J.S. Boateng, B.Z. Chowdhry, M.J. Snowden, D. Douroumis, A review on the taste masking of bitter APIs: hot-melt extrusion (HME) evaluation, Drug development and industrial pharmacy, 40 (2014) 145-156.

[35] M. Maniruzzaman, M.T. Islam, S. Halsey, D. Amin, D. Douroumis, Novel Controlled Release Polymer-Lipid Formulations Processed by Hot Melt Extrusion, AAPS PharmSciTech, 17 (2016) 191-199.

[36] K.C. Panigrahi, C.N. Patra, G.K. Jena, D. Ghose, J. Jena, S.K. Panda, M. Sahu, Gelucire: A versatile polymer for modified release drug delivery system, Future Journal of Pharmaceutical Sciences, 4 (2018) 102-108.

Table 1. List of ingredients of the HME extrudates

Formulation Code	HPMCAS (% w/w)	Drug loading (% w/w)	Excipient/loading (% w/w)	Gelucire 50/13 (% w/w)
H	80	20		
H-CNa	75	20	Crosscarmellose Na/5	-
H-NaSG	75	20	Na starch glycolate/5	-
H-CP	75	20	Crosspovidone/5	-
H-MD	75	20	Maltdextrin/5	-
H-LM	75	20	α-lactose monohydrate/5	-
HG	60	20	--------	20
HG-CNa	60	20	Crosscarmellose Na/5	15
HG-NaSG	60	20	Na starch glycolate/5	15
HG-CP	60	20	Crosspovidone/5	15
HG-MD	60	20	Maltdextrin/5	15
HG-LM	60	20	α-lactose monohydrate/5	15

Figure 1. Set-up of the SDI2 for the assessment of HME filaments for the measurement of CBZ release (a), width growth (swelling) (b), custom stainless steel holder to mount HME filaments in the whole dosage cell (c).

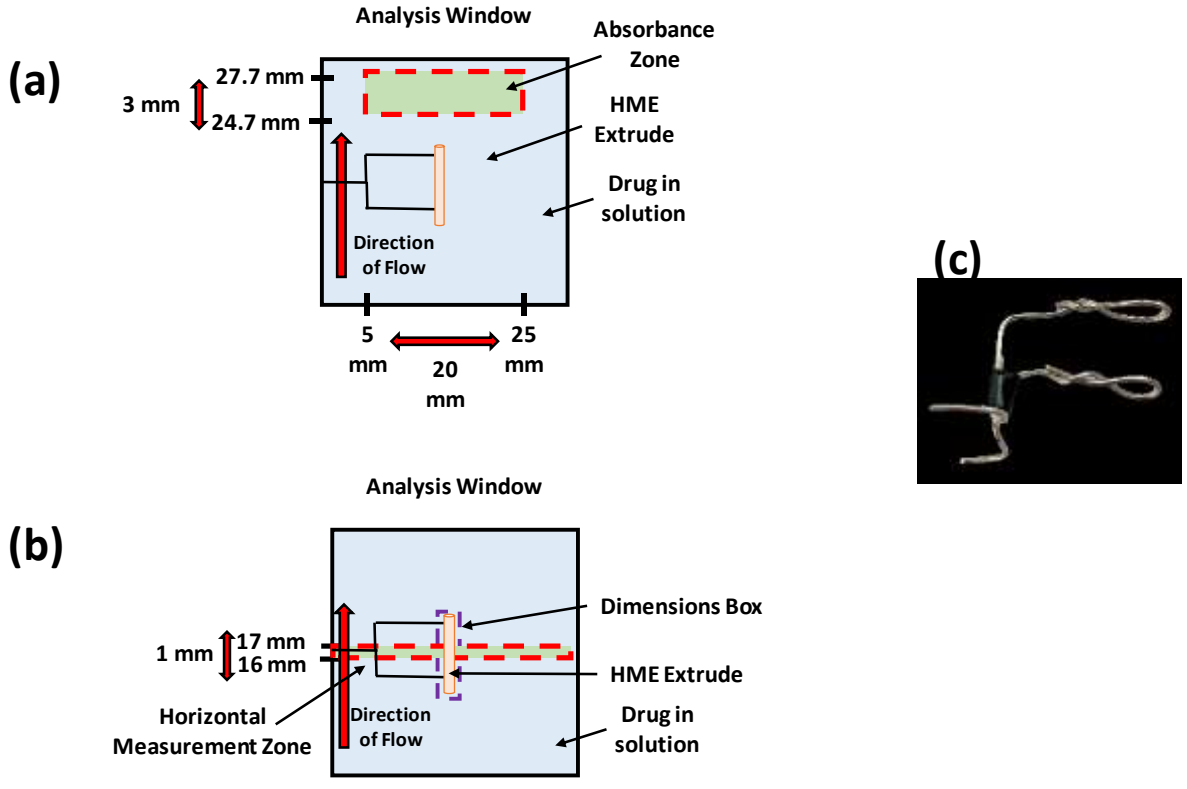

Figure 2. A schematic representation of the dual closed loop method for the assessment of the HME filaments in both pH 1.2 and pH 6.8 media.

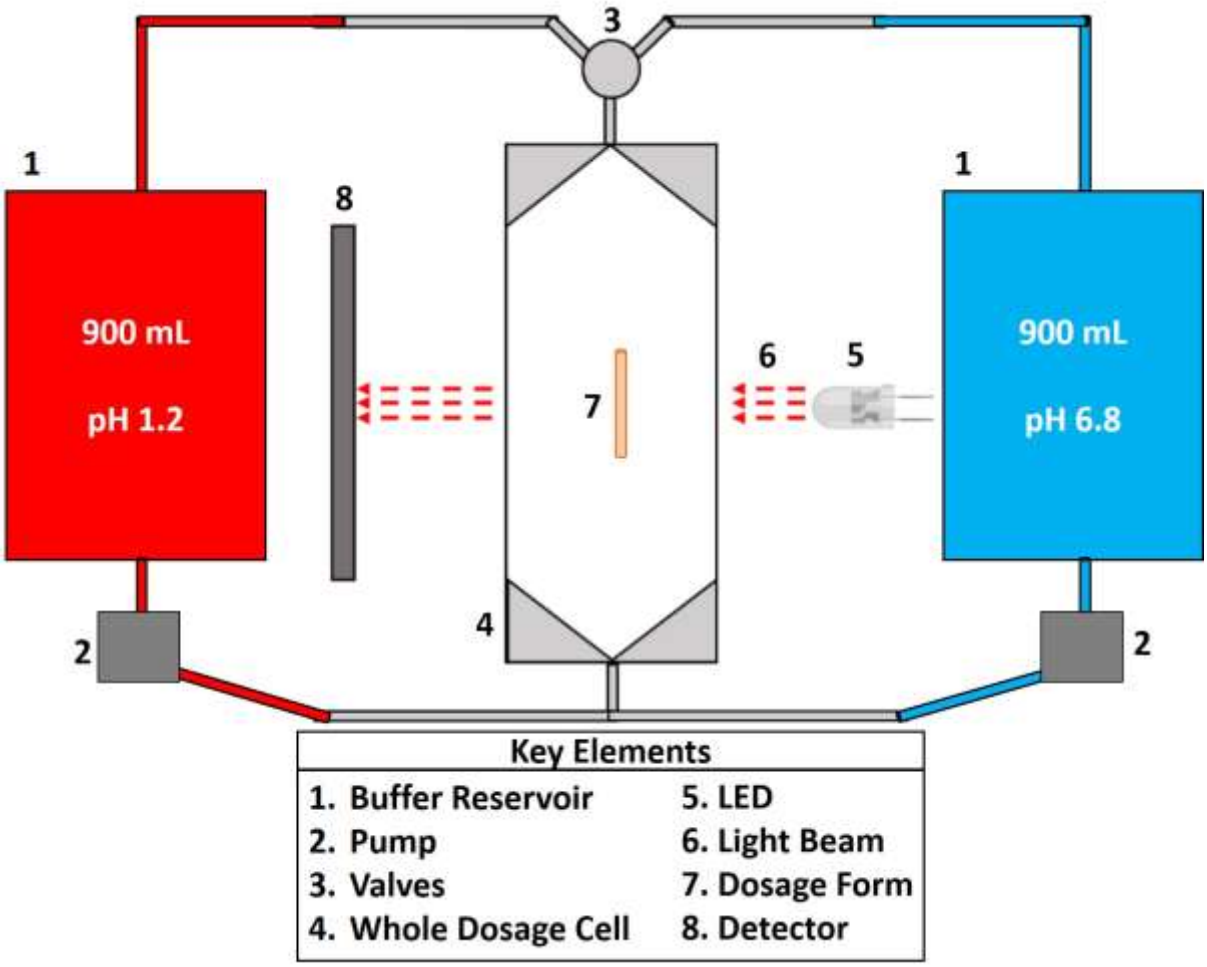

Figure 3. DSC results of (a) the main ingredients and (b) the additives

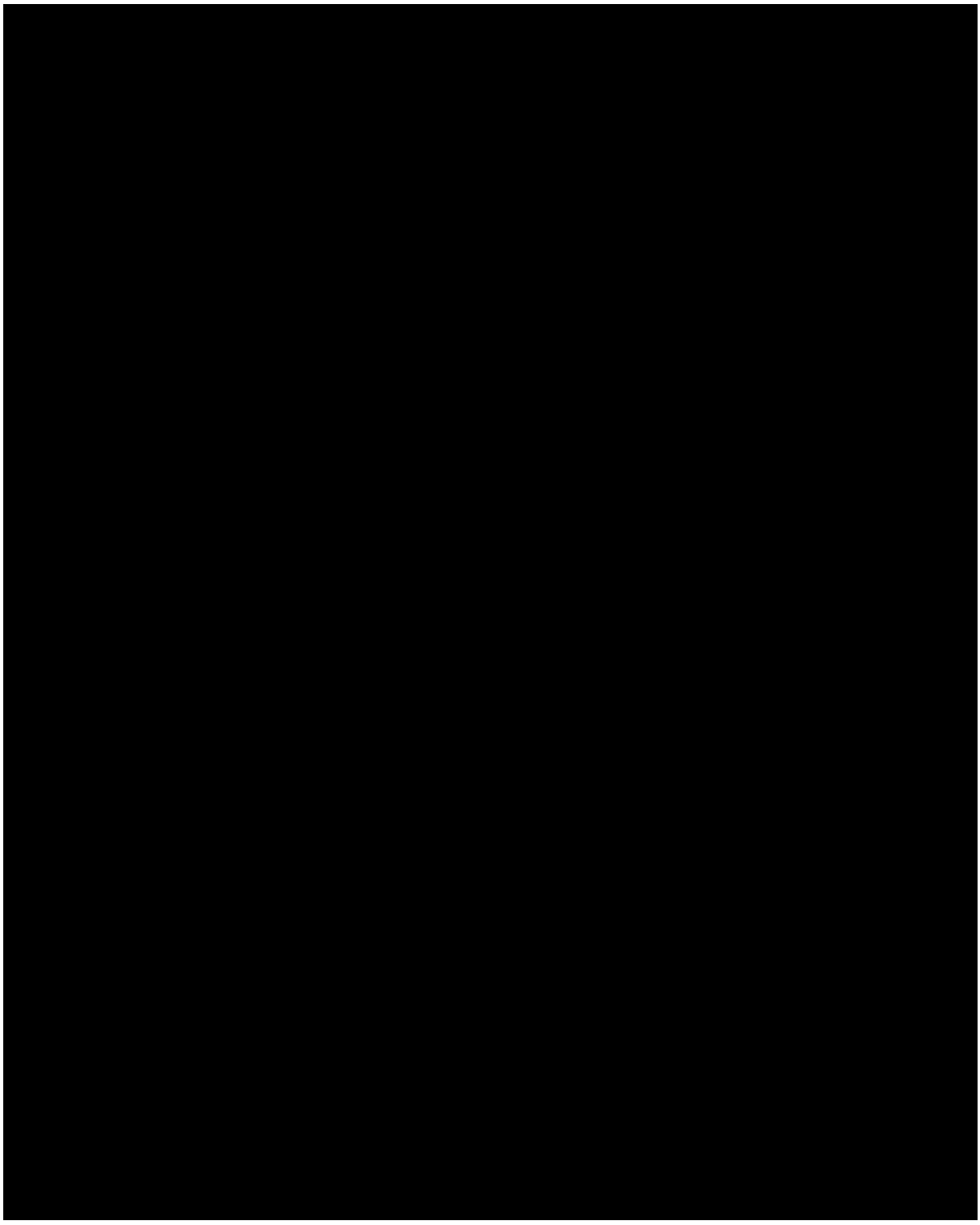

Figure 4. (a) DSC; (b) PXRD; partial ATR-FTIR data within the wavenumbers of (c) 3600-2600 cm^{-1} and (d) 1800-600 cm^{-1} of the crystalline, amorphous CBZ and extrudates of CBZ-HPMCAS binary formulation.

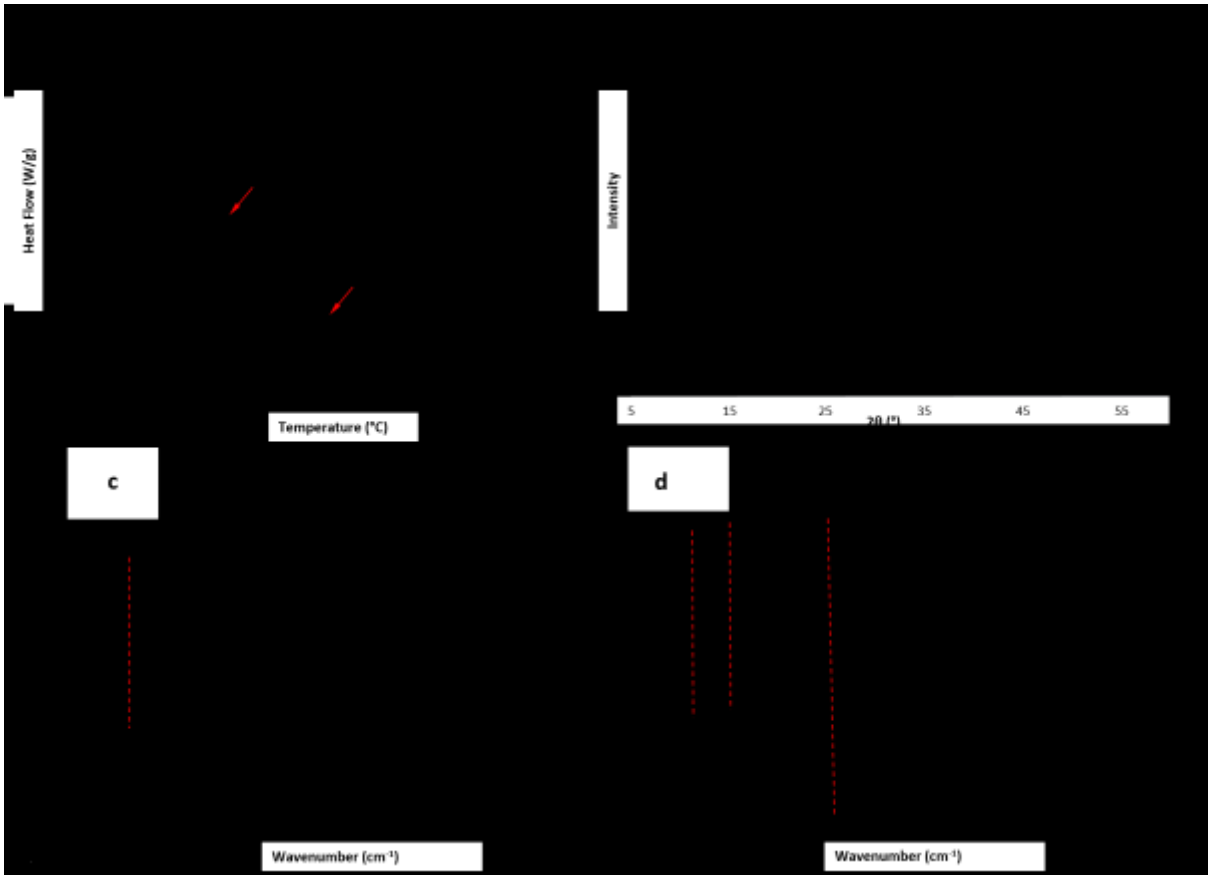

Figure 5. The 24-hour *in vitro* drug release of (a) CBZ-HPMCAS-additive ternary extrudates and (b) Gelucire-containing extrudates

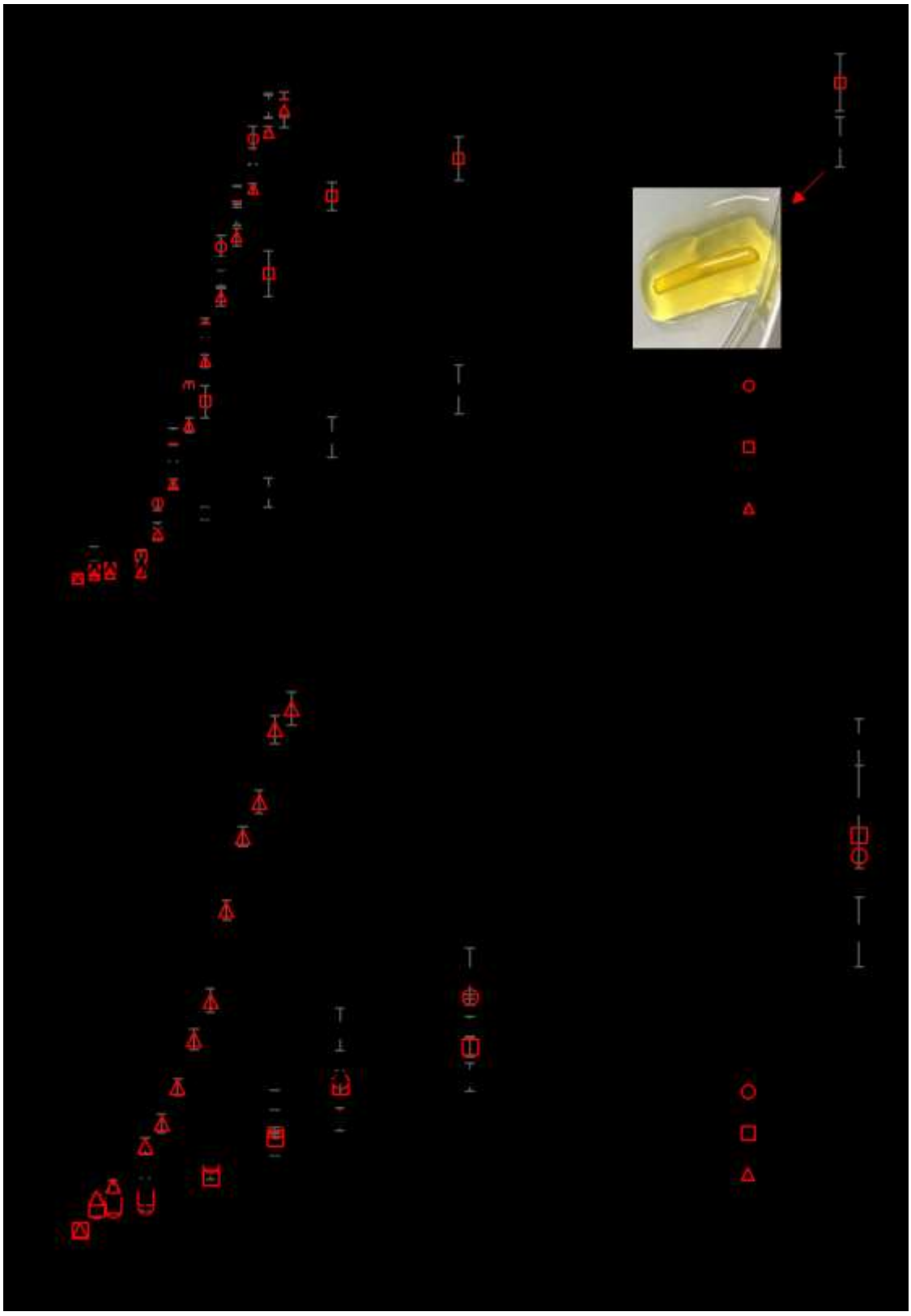

Figure 6. DSC thermograms of the (a) physical mixes and (b) HME extrudates of the CBZ-HPMCAS-additive ternary formulations; (c) physical mixtures and (d) HME extrudates of Gelucire-containing formulations

Figure 7. PXRD patterns of (a) the CBZ-HPMCAS-additive ternary extrudates and (b) the Gelucire-containing extrudates; the partial ATR-FTIR spectra of (c) the CBZ-HPMCAS-additive ternary extrudates and (d) the Gelucire-containing extrudates

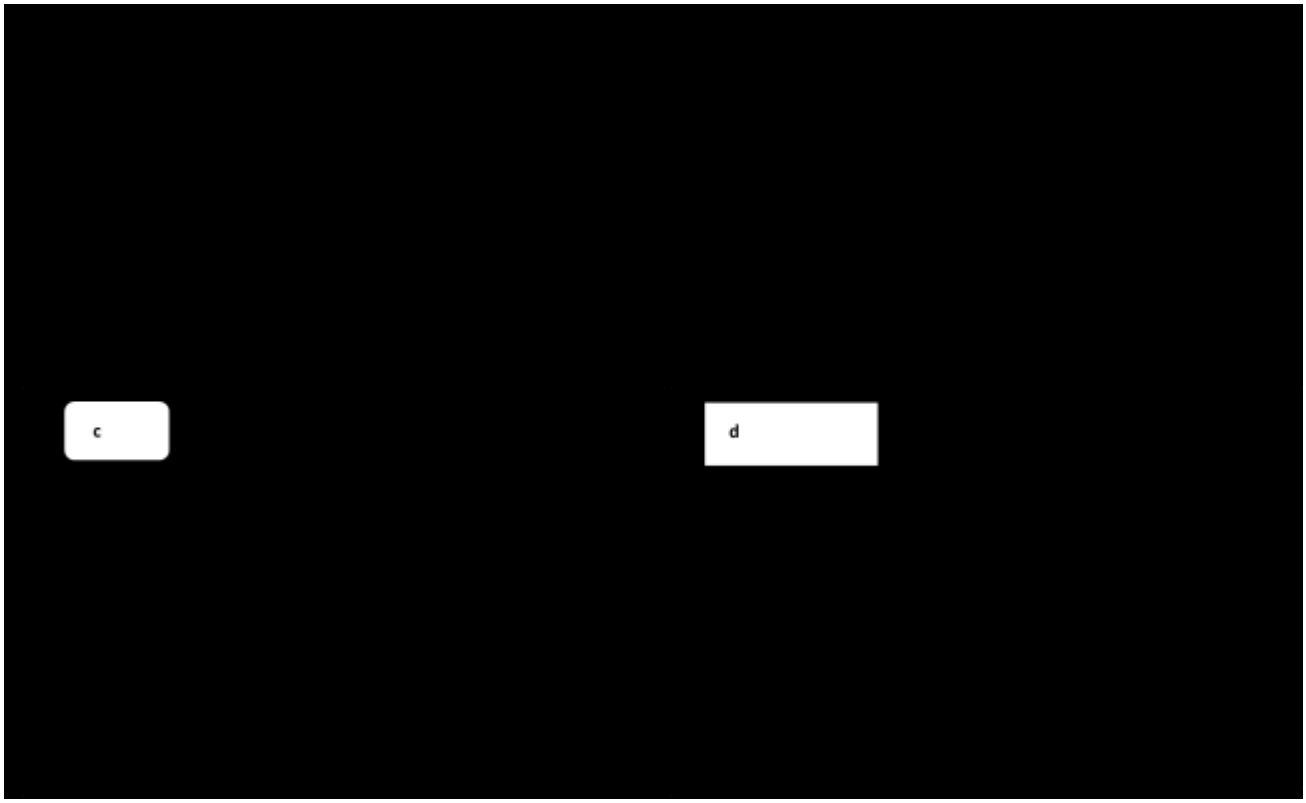

Figure 8. SEM images of the comparison of the cross-sections of the CBZ-HPMCAS-additive ternary extrudates and Gelucire-containing extrudates (freshly prepared by HME).

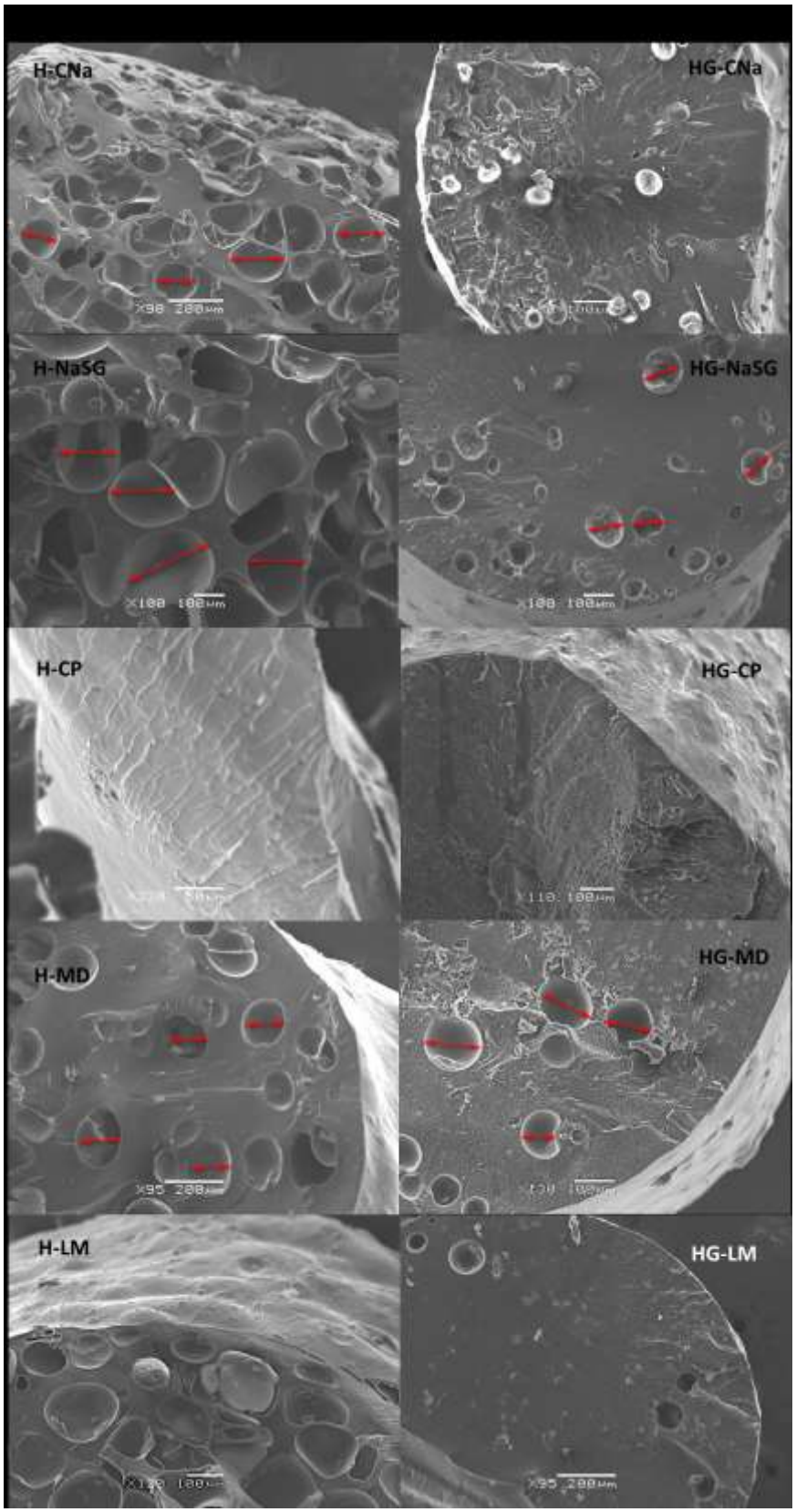

Figure 9. False coloured SDI2 images for the HME extrudates (H, H-NaSG, and HG-NaSG) obtained from the SDI2 instrument when the dissolution tests were performed in pH 1.2 for the first 2 hours and in pH 6.8 from 2-6 hours. Images depict CBZ release and swelling using UV and Vis wavelengths at 280 nm and at 520 nm, respectively.

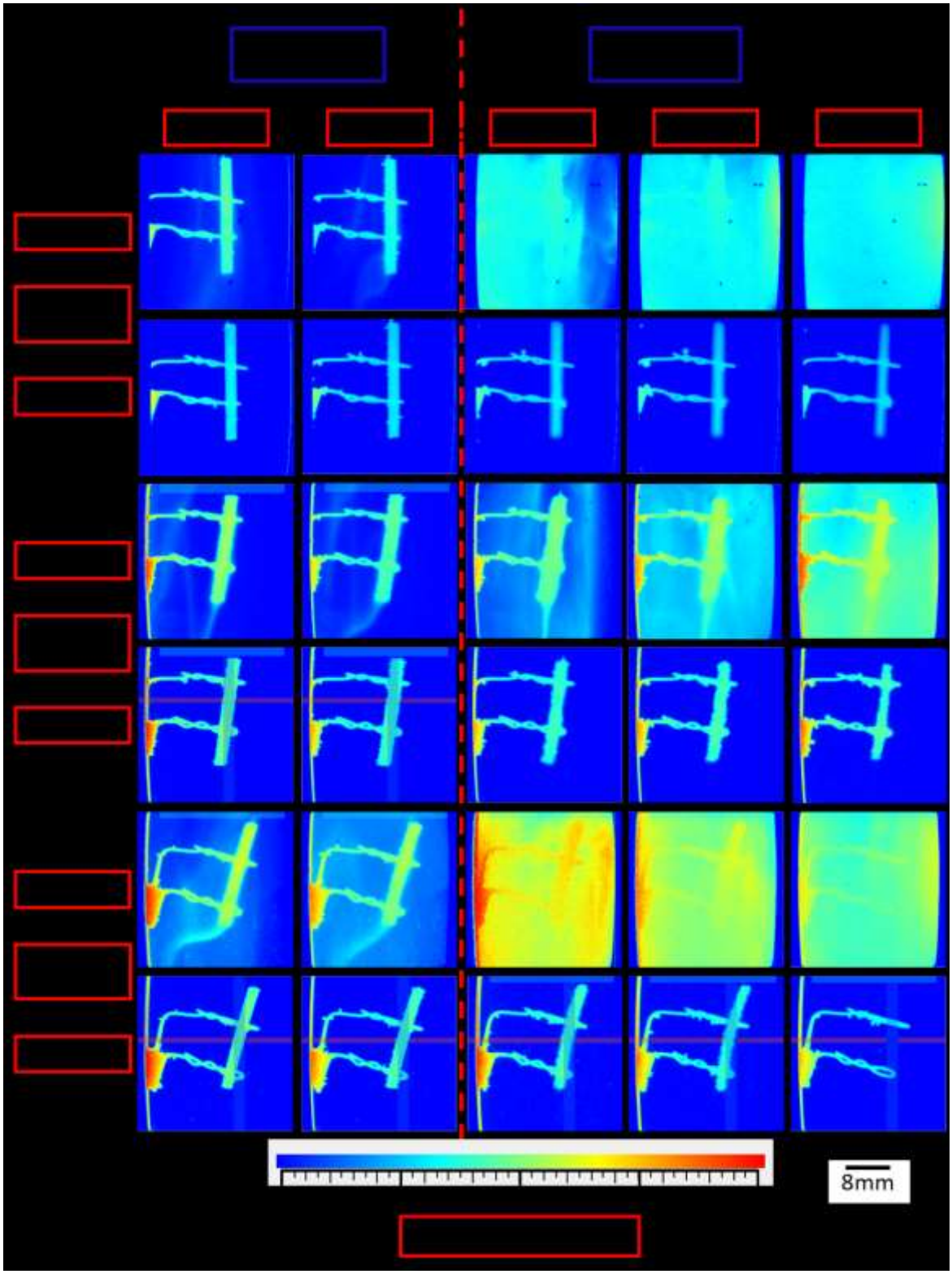

Figure 10. Normalised swelling measurements for the HME extrudates (H, H-NaSG and HG-NaSG) in (a) pH 1.2 with a pH shift to pH 6.8 obtained from the SDI instrument at 520 nm. False-coloured SDI2 swelling images for (b) the H extrudate after 60 min in pH 6.8 showing the gel layer due to media ingress; (c) the H-NaSG extrudate after 180 min in pH 6.8 showing the degradation as a result of the incorporation of NaSG; (d) the HG-NaSG extrudate after 180 min in pH 6.8. The disintegrated extrudate particulates can be visualised in the media (as highlighted by the red arrows) and may have contributed to the extended release of CBZ seen in Figure 5 (b).