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Can Filaments be stored as a shelf-item for on-demand manufacturing of oral 3D printed tablets? An initial stability assessment

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Abstract

3D printing of oral solid dosage forms is a recently introduced approach for dose personalisation. Fused deposition modelling (FDM) is one of the promising and heavily researched 3D printing techniques in the pharmaceutical field. However, the successful application of this technique relies greatly on the mass manufacturing of physically and chemically stable filaments, that can be readily available as a shelf item to be 3D printed on-demand. In this work, the stability of methacrylate polymers (Eudragit EPO, RL, L100-55 and S100), hydroxypropyl cellulose (HPC SSL) and polyvinyl pyrrolidone (PVP)-based filaments over 6 months were investigated. Filaments manufactured by hot melt extrusion (HME) were stored at either 5 ºC or 30 ºC + 65 %RH with/without vacuuming. The effects of storage on their dimensions, visual appearance, thermal properties, and 'printability' were analysed. Theophylline content, as well as *in vitro* release from the 3D printed tablets were also investigated. The filaments were analysed before storage, then after 1, 3 and 6 months from the manufacturing date.

Storing filaments at these conditions had a significant effect on their physical properties such as shape, dimensions, flexibility and hence compatibility with FDM 3D printing. In general, the methacrylate-based filaments were more physically stable and compatible with FDM 3D printing following storage. Owing to their hygroscopic nature, cellulose- and PVP-based filaments demonstrated a reduction in their glass transition temperature upon storage, leading to increased flexibility and incompatibility with FDM 3D printer. Theophylline contents was not significantly changed during the storage.

This work provides preliminary data for the impact of polymer species on the long-term stability of the filaments. In general, storage and packaging conditions have major impact on the potential of on-demand manufacturing of 3D printed tablets using hot melt extruded filaments.

1. Introduction

For many years, drug dosing for adults were based on the age and weight of the patient, with the dose for children extrapolated linearly from the former. The downside of such approach is the lack of consideration of demographic, genetic, clinical and environmental factors, which proved to contribute to population variabilities (Cella et al. 2010). Hence, varied responses to therapy and susceptibility to adverse drug reactions have always been predominant issues (Al-Metwali and Mulla 2017; Nyboe Andersen et al. 2017). Dose personalisation, therefore, offers the advantage of tailoring doses to the patients' needs when required. With advancements in pharmacogenomics and wearable technologies, there is a rising interest in dose personalisation, in response to tested biomarkers, to achieve target pharmacodynamics and pharmacokinetics profiles.

A readily available dosing system will ensure efficient and safe dosing with minimal adverse effects when administered to patients. However, such an approach is mostly applicable currently for injectables, which allows easy dose adjustments (Patel et al. 2014). For this approach to be widely applied, a digital personalisation solution for commonly used dosage forms e.g. tablets should be developed. For tablets, dose adjustments are frequently achieved through the practice of splitting. This approach is reported to introduce dosing inaccuracies (Habib et al. 2014), which could lead to underdosing, overdosing and severe toxicities with certain active pharmaceutical ingredients (APIs).

Different approaches are currently being investigated to personalise oral dosage forms, with 3D printing demonstrating significant potential (Isreb et al. 2019; Pereira et al. 2019; Tagami et al. 2019; Sen et al. 2020; Martinez et al. 2018). FDM has been heavily researched as an effective and accessible 3D printing technique. It offers several advantages such as the absence of a post-printing processing, in addition to its low-cost setup (Pereira et al. 2019; Sadia et al. 2018; Okwuosa et al. 2016). FDM 3D printing involves the use of filaments, usually manufactured by hot melt extrusion (HME), as a pre-product, which are then fed into the heated nozzle of the FDM 3D printer (Pereira et al. 2019; Sadia et al. 2018; Okwuosa et al. 2016;Goyanes et al., 2014).

The potential of FDM 3D printing for on-demand manufacturing relies on producing stable, reproducible, dose-consistent and ready-to-use filaments. In order to effectively utilise this technique, these filaments should be easily mass-produced, packaged and stored before shipping to the printing sites, including hospitals and community pharmacies. This will enable the vision of producing 3D printed dosage forms that are intended to be dispensed shortly after being fabricated to match patients' needs in small batches to be achieved, and should maintain at least the stability standards for extemporaneous preparations. Therefore, the long-term stability of the filament, as a pre-product on the shelves of manufacturing units or compounding pharmacies, is of paramount importance for the success of this approach.

In the last six years, many studies have focused on the application of FDM 3D printing for dose personalisation (Charoenying et al. 2020; Eleftheriadis et al. 2019; Jamróz et al. 2020; Wei et al. 2020; Zhang et al. 2020; Fanous et al. 2020; Vo et al. 2020; Pereira et al. 2019; Sadia et al. 2018; Okwuosa et al. 2016; Pietrzak et al. 2015). However, there are limited information about the long-term stability of these filaments. In fact, changes in the physicochemical properties of the filament during storage might not only compromise the efficacy of the active ingredient but may also affect its printability. Hence, adding more complexity to the technical challenges (Ilyés et al. 2019). For instance, a reduced plasticity of the filament upon storage will result in a brittle filament that may often break under pressure from the FDM 3D printer head gears (Ilyés et al. 2019, Nesereddin et al., 2018). Moreover, other changes in the filament diameter and/or shape may also have an impact on the final printed product, leading to variations in 3D printed tablets weights (weight uniformity) and in some cases the failure to complete the 3D printing process (Ilyés et al. 2019).

With many researchers working towards the adaptation of FDM 3D printing in pharmaceutical manufacturing, there is the need to study the stability of commonly used pharmaceutical polymers adapted to suit this novel manufacturing approach. In this work, the stability of HME-based filaments at 5 ^{o}C or 30 ^{o}C + 65 %RH were investigated. The impacts of the storage and packaging conditions were studied using theophylline as a model drug in combination with different model polymers. As the focus of this work is the impact of storage condition on physical change and the printability of different polymer-based filaments, a chemically stable molecule (Serajuddin, 1986), theophylline was selected as a model drug. The filaments in this study have been previously investigated to achieve immediate and modified release 3D printed structures using commercially available polymers of different chemical nature and hygroscopicity [PVP-based (Okwuosa et al. 2016), HPS.SSL-based (Pietrzak et al. 2015), L100-55-based, S100-based, RL-based and EPO-based filaments (Okwuosa et al. 2017; Sadia et al. 2018; Sadia et al. 2016)]. It is important to highlight that both Eudragit L100-55 and S100-based filaments were used to fabricate the shell in delayed release system and hence were made drug-free. The diameter, printability, thermal properties, physical form of the API, drug content of the filament, and the drug release profile of the 3D printed dosage forms were investigated before and after exposure to the storage conditions.

2. Materials and Methods

2.1 Materials

Hydroxypropyl cellulose (HPC.SSL) was obtained from Nisso Chemical Europe (Dusseldorf, Germany). Theophylline was purchased from ACROS Organics. Polyvinylpyrrolidone (PVP, MW 40,000), triacetin and triethyl citrate (TEC) were purchased from Sigma-Aldrich (UK). Talc was purchased from Fluka Analytical (UK). Eudragit L100-55, RL, EPO and S100 were donated by Evonik Industries (Darmstadt, Germany).

2.2 *Preparation of filaments*

The PVP, HPC SSL and Eudragit based filaments were produced by HME following previously reported approach (Okwuosa et al. 2016). All filaments contained a model drug (theophylline) except for Eudragit L100-55 and S100 based filaments, which were used to 3D print enteric layers (Okwuosa et al. 2017). The composition, processing temperatures of the HME processes and nozzle sizes are detailed in **Table 1**.

2.3 Accelerated stability studies (storage conditions)

In order to determine the stability of the filaments over a long-term storage, accelerated stability studies were carried out according to the International Council for Harmonisation (ICH) guidelines [Q1A(R2)] (ICH, 2003). The drug-loaded (PVP, HPC.SSL, Eudragit EPO and RL-based) and the drug-free (Eudragit L100-55 and S100-based) filaments were sealed in polyvinyl chloride (PVC) polybags with or without vacuuming and stored in a fridge at 5 ºC or in an incubator at 30 ºC + 65 %RH. Vacuum sealing was achieved using Andrew James VS517 Dom Sealer. The filaments were characterised when freshly prepared and then after 1, 3 and 6 months of storage.

2.4 Filament dimension and visual appearance

In order to determine the effect of the storage conditions on the diameter of the filaments, changes in the diameter of the filaments were monitored using a Draper Electronic Digital caliper (0 – 25 mm) with a resolution of 0.01 mm. Filaments were observed to assess change in their visual appearance (change in shape, colour or presence of aggregation).

2.5 *Printability test using FDM 3D printer*

The 3D printing of the filaments that were stored under different conditions was attempted using the parameters detailed in **Table 1** to determine the effect of the storage conditions on 3D printing in comparison to a freshly prepared filament using Makerbot Experimental 2X 3D printer (Makerbot Inc, NY, USA). 3D Printing was carried out at a standard resolution (0.2 mm layer thickness) and a 100 % infill with rectilinear infill pattern. Other settings were set as previously detailed (Okwuosa et al.

2016). A caplet (L x W x H 10 x 4 x 3.6 mm) was designed and imported into the MakerWare software Version 2.4.0.17 (Makerbot Industries, LLC., USA) and used to test the printability of the filaments. The printed caplets weighed approximately 110 mg, containing approximately 11, 50, 50 and 52 mg of theophylline for the PVP, HPC SSL, Eudragit RL and EPO-based caplets respectively.

2.6 Thermal gravimetric analysis (TGA)

TGA analysis for the extruded filaments was carried out using a TGA Q500 (TA Instruments, Hertfordshire, UK). The filaments were cut into small pieces (<1mm, approximately 10 mg) were accurately weighed and placed in a 40 µL aluminium pan (TA Instruments, Hertfordshire, UK), which was placed on a platinum pan. Samples were then scanned from 25 to 500 ^{o}C at a heating rate of 10 ^{o}C/min with a nitrogen purge of 40/60 mL/min for the sample and furnace, respectively. All measurements were carried out in triplicates and the data analysed using a TA Universal Analysis 2000 software (TA Instruments, Hertfordshire, UK)

2.7 Differential scanning calorimetry (DSC)

For modulated temperature differential scanning calorimetry (MTDSC) analysis, a differential scanning calorimeter (DSC) Q2000 (TA Instruments, Elstree, Hertfordshire, UK) was used. PVP-based filaments were subjected to a modulated heat-cool-heat scan in order to measure and exclude the effect of moisture content on the plasticity of the filaments. Eudragit L100-55 and S100-based filaments were also subjected to a modulated scan. The modulation scan was applied using an amplitude of 0.212 °C and a period of 40 sec, scanning from -70 to 200 °C at a heating rate of 2 °C/min.

As moisture did not interfere with the thermographs obtained unlike the aforementioned filaments, a non-modulated standard scan was used for HPC SSL, Eudragit RL and EPO-based filaments from -50 to 200 °C at a heating rate of 10 °C/min. Analysis was carried out under a purge of nitrogen gas (50 mL/min). All the data were analysed using a TA Universal Analysis 2000 software (TA Instruments, Hertfordshire, UK). TA pin-holed standard lids and 40 µL aluminium pans (TA Instruments, Hertfordshire, UK) were filled with approximately 5 mg sample and sealed. All measurements were carried out in triplicates.

2.8 X-ray powder diffractometry (XRPD)

X-ray powder diffraction was carried out on the filaments over 6 months to investigate changes in the physical forms of the API or excipients. This was assessed using a powder X-ray diffractometer, D2 Phaser with Lynxeye (Bruker, Germany). Filaments were dipped in liquid nitrogen before crushing them using a mortar and pestle. The powders were scanned from 2Theta (2θ) = 5° to 35° using 0.01

step and 1.25 sec count. The divergence slit was 1 mm and the scatter slit 0.6 mm. The wavelength of the X-ray was 0.154 nm using Cu source and a voltage of 30 kV and a current of 10 mA.

2.9 Determination of drug content (Eudragit EPO, RL, HPC.SSL and PVP-based filaments)

To determine changes in the drug contents of the filament after storage, 120 mg of the Eudragit EPO and RL, HPC.SSL and PVP-based filaments containing theophylline were solubilised in 0.1 M HCl and sonicated for 2h or 8 h (for Eudragit RL-based filament only). The API was measured by HPLC using an Agilent UV-HPLC 1260 series (Agilent Technologies, Inc., Germany) and an XTerra RP C18 column (150 × 4.6 mm, 5 µm particle size) (Waters, Ireland). A mobile phase of 10 mM solution of ammonium acetate buffer, methanol and acetonitrile at volume ratio of 86:7:7. Analysis was carried out at a wavelength of 272 nm, column temperature of 40 ^{o}C, flow rate of 1 mL/min, injection volume was 5 µL and a run time of 7 min as reported previously (Okwuosa et al. 2016).

2.10 In vitro drug release studies (Eudragit EPO and RL-based filament)

I*n vitro* drug release studies for the 3D printed tablets were carried out using a USP II dissolution apparatus (AT 7 Smart, Sotax, Switzerland). The tablets were tested in 900 mL of 0.1 M HCl solution for the EPO-based tablets for 2 hours. However, for the extended release formulation (Eudragit RL), dissolution testing was carried out in 750 mL of HCl solution, followed by the addition of 250 mL of 0.215 M tribasic phosphate buffer after 2hrs and the pH adjusted to 6.8. Samples were collected for another 6 hrs. The samples were automatically collected and analysed at 5 min intervals using a UV/VIS spectrophotometer (PG instruments limited, UK) at a wavelength of 272 nm. The path length used was 1 mm. The data were analysed using IDIS Software version 3 Automated Lab (Berkshire, UK).

2.11 Statistical analysis

One-way ANOVA was employed using SPSS Software (22.0.0.2) to analyse the results. the level of statistical significance was set at (p <0.05).

3. Results and discussions

The use of FDM 3D printing for on-demand dose personalisation relies greatly on the manufacturing of stable filaments that will be able to withstand storage and transportation. This ensures compatibility with the FDM 3D printer at the point of use, whilst maintaining the integrity of the loaded APIs and meeting the individual needs of patients. Therefore, the goal of this research was to investigate stability-related challenges that could be faced in the use of methacrylate, cellulose and polyvinyl pyrrolidone-based filaments for FDM 3D printing.

3.1 Physical and thermal properties of the stored filaments

Changes in the physical and thermal properties of these filaments following storage could affect their 3D printing into solid dosage forms. Therefore, the impact of the storage conditions on the diameter of the filaments were investigated. It was observed that a filament diameter >1.8 mm will lead to blockage due to its inability to pass through the liquifying chamber of the FDM 3D printer's head. This is an essential quality criterion of the filaments to ensure consistent flow through the pressing gears into the hot nozzle. In addition, deformations in the cylindrical shape of the filament (deviation from the cylindrical shape) could potentially affect the filament interaction with the gears in the 3D printer, leading to inconsistency of the flow through the hot nozzle. Such effect can result in weight variation of the 3D printed product (data not included). These changes could also be influenced by the changes in the thermal properties of the filaments, with the TGA analysis being able to investigate water gain or loss and changes in the degradation profile of the stored filaments, with reference to the freshly prepared samples. Also, changes in the glass transition temperature (Tg) of the filament can significantly alter the mechanical properties of the filaments, in turn, the ability to load the filaments into the liquifying chamber of the FDM 3D printer head. Therefore, investigations into the effect of the storage conditions on the Tg of the filaments were also carried out using DSC.

a) Methacrylate-based filaments

Investigating the diameter of Eudragit EPO-based filaments after storage revealed that no change was noted when stored at 5 ^{o}C. However, storing the filaments at 30 ^{o}C + 65 %RH resulted in a permanent flattening/deformation of these filaments only when the storage bag was vacuum-sealed **(Table 2, Supplementary Data Fig. S1).** The resultant deformation affected its compatibility with the 3D printer and prevented its conversion into a solid dosage form. The TGA analysis of this filament demonstrated similar thermographs in the storage conditions (**Fig. 1A**) in comparison to a freshly prepared sample with insignificant moisture uptake with no observed wright loss between 50-150 ^{o}C. The non-hygroscopic nature of this polymer was also observed by Parikh et al. (2014), who recorded a 0.2 %w/w moisture content. On the other hand, the DSC analysis revealed a slight reduction in the Tg of the filament due to storage (**Fig. 1B**). However, this did not affect the printability of the filaments

stored at 5 ºC and 30 ºC with no vacuuming. The flattening of the vacuum-sealed filament when stored at 30 ºC could be attributed to the increased mobility of the polymeric chains above the Tg of the Eudragit EPO matrix. In addition, the negative pressure on the filaments due to the vacuuming, may have contributed to the deformation of the filament. This was confirmed when a protective shell placed around the filaments, resulted in no alteration in shape at the same storage conditions (data not included).

The Eudragit RL-based filament also lost its original cylindrical shape when stored in a vacuumed PVC bag at 30 ºC and 65 % RH, and hence was incompatible with the FDM 3D printer only at this storage condition (**Table 2**). This was also the case for Eudragit L100-55-based filaments. Both Eudragit based filaments demonstrated no changes in their weight loss TGA patterns due to storage as well as no indication of water uptake (**Figs. 2A and 3A**). The filaments stored at 5 ºC (with or without vacuuming) and in a non-vacuumed bag at 30 ºC + 65% RH were easily printed, demonstrating desirable filament properties. An increase in Tg was observed, however, this had no effect on the filament printability (**Figs. 2B and 3B**) (Melocchi et al. 2020).

The dimensions of Eudragit S100-based filaments did not incur any significant changes due to storage and maintained compatibility with the FDM 3D printer, irrespective of the storage condition (**Table 2**). Their TGA thermographs remained similar during storage, demonstrating no water uptake during the storage period (**Fig. 4A**). Unlike the previously discussed filaments, the S100-based filaments demonstrated a higher Tg value (85-89 ºC) (**Fig. 4B**), hence were unaffected by the storage at 30 ºC and the vacuuming pressure.

b) Hydroxypropyl cellulose-based filaments

The HPC-based filament deformed when stored in a vacuumed bag at 30 ºC and 65% RH. In addition, the filaments from other storage conditions were also incompatible with the FDM 3D printer. The TGA analysis of the stored filaments showed weight gain values of 2.25 % and 2 %w/w for filaments stored at 5 and 30 ºC + 65% RH, respectively (**Fig. 5A**). This demonstrated the hygroscopic nature of the cellulose-based matrix (Rowe et al. 2006). Water has often been reported to have a plasticising effect on polymeric matrices (Teng et al. 2010), leading to a drop in the Tg of these filaments from 36.7 to 34.9 ºC after storage as demonstrated by DSC thermograph (**Fig. 5B**). This confirms the potential role of water uptake as a major disruptor for compatibility with FDM 3D printing process, due to increased flexibility. Such an increase will obstruct feeding into the liquifying chamber of the FDM head, resulting in a poor grip of the gears on the filament and subsequently, the folding of the filaments around the gears (Ilyés et al. 2019). This effect of high plasticity on the printability of the filaments was also observed by Tan *et al.* (2020). As a result of these initial negative findings following one-month storage, the HPC-based filaments were withdrawn from further studies.

c) Povidone-based filaments

Investigating the physical properties of the PVP-based filaments revealed their stability only at the 5 °C storage condition where they retained their shape and diameter. The TGA of freshly prepared PVP-based filaments depicted an initial weight loss of approximately 4 % at around 120 °C due to moisture loss, which could be attributed to the hygroscopic nature of PVP (Gupta et al. 2014). The storage of the filaments at 5 °C resulted in up to 6.5 % water uptake (**Fig. 6**). PVP has been reported to be able to take moisture up to 40% of its weight (Ramineni et al. 2013). It was not possible to determine precisely the Tg of these filaments due to the excessive water evaporation upon heating, which interfered with the detectability of the polymer's Tg. A heat-cool-heat DSC approach could eliminate these effects of moisture. However, this approach led to the removal of moisture during the first heat scan and can mask the potential of storage on Tg of the filament (**Supplementary Data, Figs. S2 and S3).** Such high water-uptake was reported to produce a significant drop in its Tg (Fitzpatrick et al. 2002; Xie and Taylor 2017; Teng et al. 2010). Although the filaments at 5 °C remained compatible with the 3D printer, their very hygroscopic nature poses a major challenge to their application. Therefore, a future product would require the use a specific packaging for these filaments to provide moisture-controlled environment. This might have major implications on the cost and practicality of using these filaments for on-demand use in the community and hospital pharmacies.

3.2 Impact of storage conditions on the physical form of theophylline

Changes in the physical forms of theophylline and excipients due to storage can influence the drug release profile. Due to the degradation of methacrylate polymers when thermally scanned >170 °C (Parikh et al., 2016), it was not possible to use DSC to assess the physical form of theophylline (melting point of 272.8 °C) (Kuzminska et al., 2021). To investigate this, XRPD was used to analyse the filaments before and after storage. The Eudragit EPO, RL, HPC.SSL and PVP-based filaments loaded with theophylline revealed the presence of diffraction peaks at (2θ) = 7 and 12° (**Fig. 7**), which correspond to theophylline crystals. Talc, which was used as the structure forming agent, demonstrated sharp peaks at (2θ) = 9.52°, 19.54°, 28.87°. The intensity peaks indicated that a proportion of the API remained crystalline within the filament, following thermal and mechanical stress of the HME processes (Huang and Dai 2014). This proved to be dependent on the model APIs as previously investigated using these matrices (Okwuosa et al. 2016; Sadia et al. 2016). The intensity peaks that corresponds to theophylline were also observed after storage, indicating that a proportion of the API is in its crystalline form during these storage conditions. However, the peak intensity at (2θ) = 12° due to theophylline was observed to increase for Eudragit EPO-based filament whilst it decreased for the Eudragit RL-based filament over time (**Figs. 7A and B**). Variations in peak intensity has been linked to crystalline concentrations (Siddiqui et al. 2015). Also, it was reported that partial crystalline nature of matrices could alter due to storage (Lust et al. 2015; Huang and Dai 2014; Ueda et al. 2020). For filaments that

did not include drug (Eudragit L100-55 and S100), there were diffraction peaks at (2θ) = 9.52, 19.54, 28.87, which correspond to the crystals of talc, throughout the storage (**Supplementary Data, Figs. S4-S7).**

3.3 Drug integrity and *in vitro* drug release

It was important that the integrity of the API-loaded in the filaments (Eudragit EPO, RL, HPC and PVP-based) remains intact throughout the stability trial. This was important to ensure dosing accuracy towards meeting the individual needs of patients using this novel manufacturing approach. HPLC analysis showed no significant changes in API contents (**Supplementary Data, Table S1),** confirming the stability of theophylline in the matrix.

Cellulose and the PVP-based filaments were deemed unstable and the L100-55 and S100-based filaments were drugs-free, therefore, the dissolution testing for the tablets printed from these filaments was not investigated. *In vitro* release study on the PVP-based matrices demonstrated an increase in the rate of drug release with the aging of the filament (**Fig. 8**), which was not as expected (Tian et al. 2014). It is possible that the highly hygroscopic nature of PVP led to an increase in moisture contents within the polymeric matrix. Drug mobility may also increase leading to phase separation and further drug crystallisation (Chen et al. 2018).

Eudragit EPO is an immediate release polymer and as expected, the caplets from a freshly prepared filament achieved more than 75 % theophylline release at 45 min. However, the rate of release slowed down over time due to storage at 5 and 30 ºC + 65 %RH (**Fig. 9**). This could be due to crystalline growth during storage at high temperature and humidity (Tian et al. 2014). This was observed in the XRPD analysis of the filament with peak intensity due to theophylline increasing as the filament ages. It is also possible that during storage, polymer relaxation led to the formation of denser matrix, leading to reduced dissolution rate. Phase separation was observed in a solid dispersion of indometacin and Eudragit EPO produced by HME, which decreased the dissolution rate of the API (Sarode et al. 2013).

On the other hand, Eudragit RL-based tablets showed a faster drug release after storage at 5 ºC in comparison to the fresh sample (**Fig. 10**). A depression in peak intensity with aging was observed from the XRPD studies, suggesting that more of the API became dissolved in the polymer over time. Filaments stored at 30 ºC did not show a significant change in drug release compared to a freshly prepared product. A solid dispersion containing Eudragit RL and indometacin demonstrated no alteration in drug release after exposure to 40 and 50 ºC for a short period of time (5 h) (Azarmi et al. 2002).

In summary, the presented data suggested that filaments based on methacrylate polymers are less prone to physical changes and remains compatible with FDM 3D printer following storage. Such findings are

particularly important to future efforts of engineering ‘a pharmaceutical ink’ based on HME drug-loaded filaments to be used as a shelf-item for on demand manufacturing.

4. Conclusions

This work highlights some of the stability challenges facing HME based-filaments as a pre-product shelf item for on-demand use via FDM 3D printing. Storage conditions had a major impact on the physical properties of the filaments such as shape, dimensions, flexibility and hence compatibility with the FDM 3D printing. In comparison to the cellulose- and povidone-based filaments, methacrylate-based filaments (Eudragit EPO, RL, S100 and L100-55) were generally more physically stable and continued to be printable following storage. Polymers of lower Tg required specific storage conditions such as the use of a vacuumed container or fridge temperature. Filaments based on hygroscopic polymers (HPC and PVP) were more sensitive to Tg alterations due to water uptake, leading to 3D printing failures, and hence they were deemed less suitable to be used as a shelf-item product for on-demand printing. Overall, the integrity of the API in the drug loaded filaments was maintained. This research provides a pioneering preview on the long-term stability consideration of pharmaceutical filaments. Further research is needed to confirm this trend with a wider range of polymers and to assess the impact of filament storage on the compliance of 3D printed tablets with compendial criteria.

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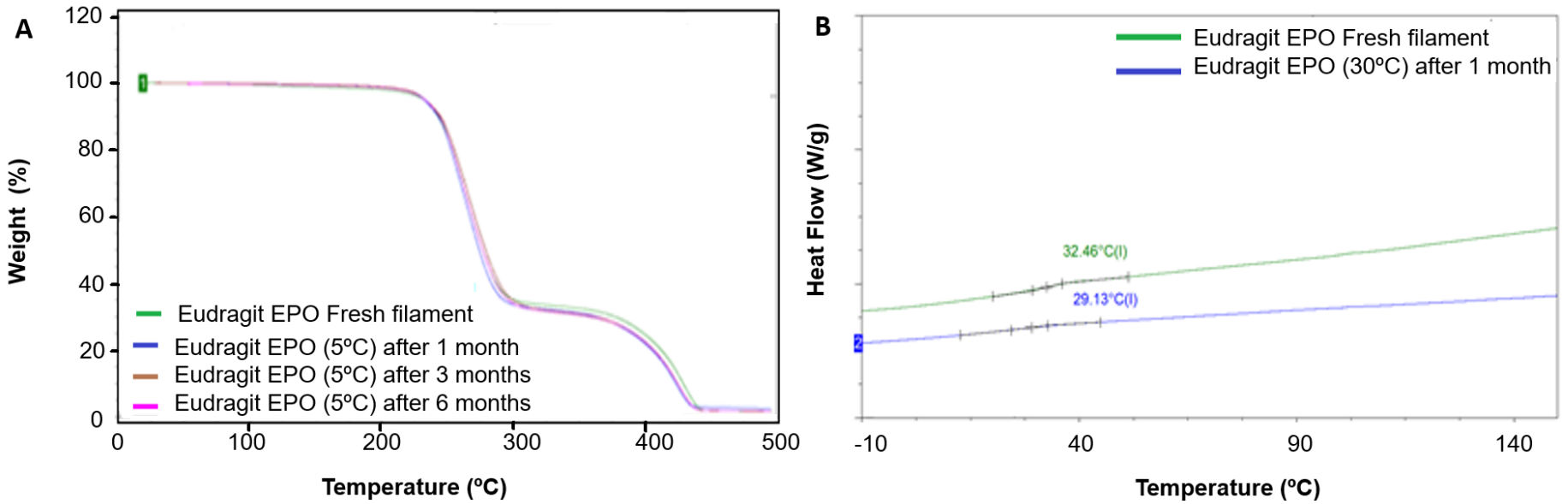

Fig. 1. (A) TGA thermographs for the impact of the storage condition (5 ºC) on Eudragit EPO-based filament, (B) DSC thermographs for the impact of the storage condition (30 ºC+ 65% RH+ vacuum) on Eudragit EPO-based filament (filaments deformed and no further assessment was carried out after 1 month).

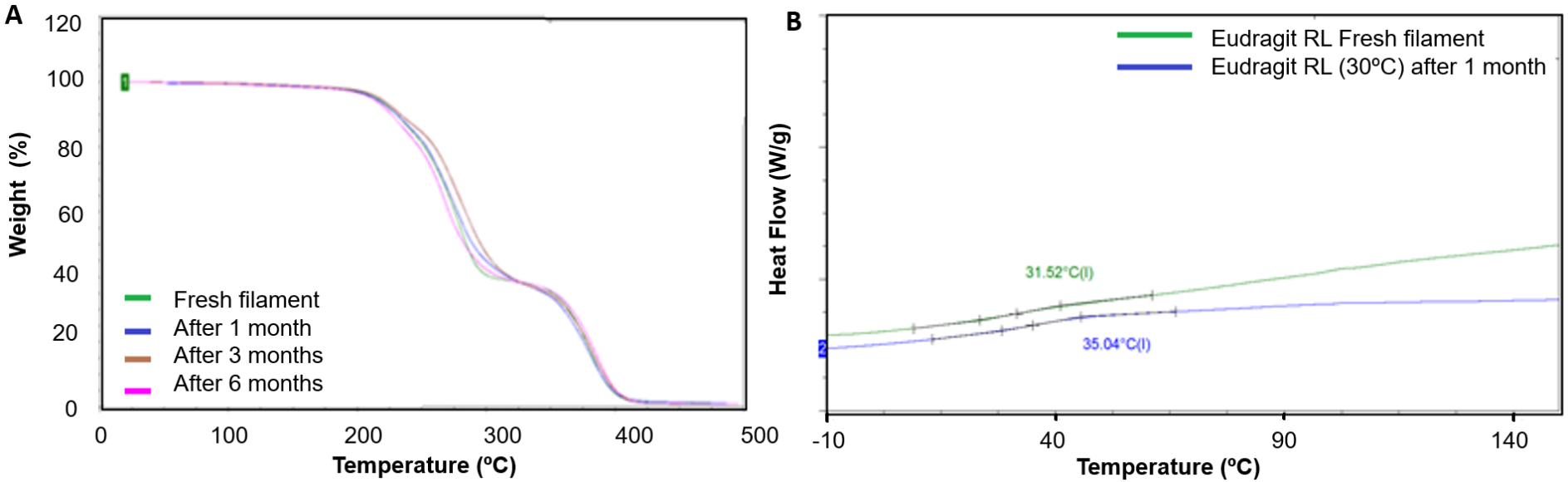

Fig. 2. TGA (A) thermographs for the impact of the storage condition (30 ºC + vacuum) on Eudragit RL-based filament, (B) DSC thermographs for the impact of the storage condition (30 ºC+ 65% RH+ vacuum) on Eudragit RL-based filament (filaments deformed and no further assessment was carried out after 1 month).

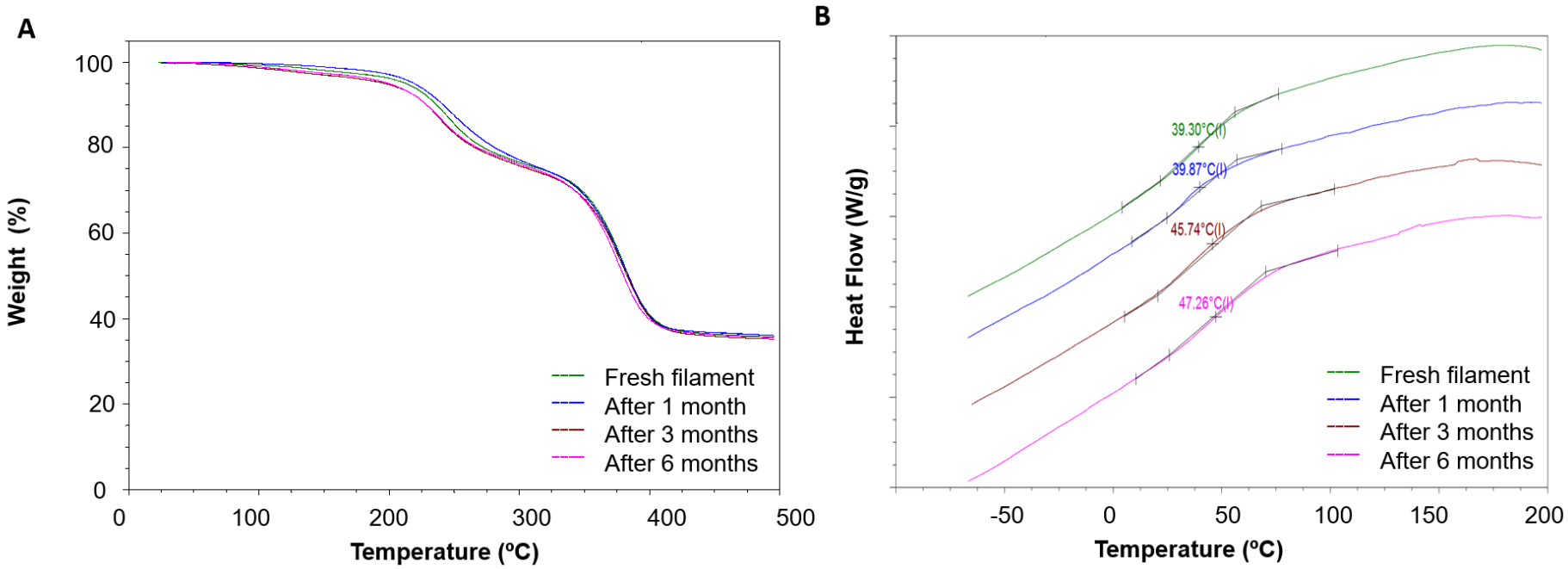

Fig. 3. TGA (A) and DSC (B) thermographs for the impact of the storage conditions (30 °C + 65% RH + vaccum) on the Eudragit L100-55-based filaments.

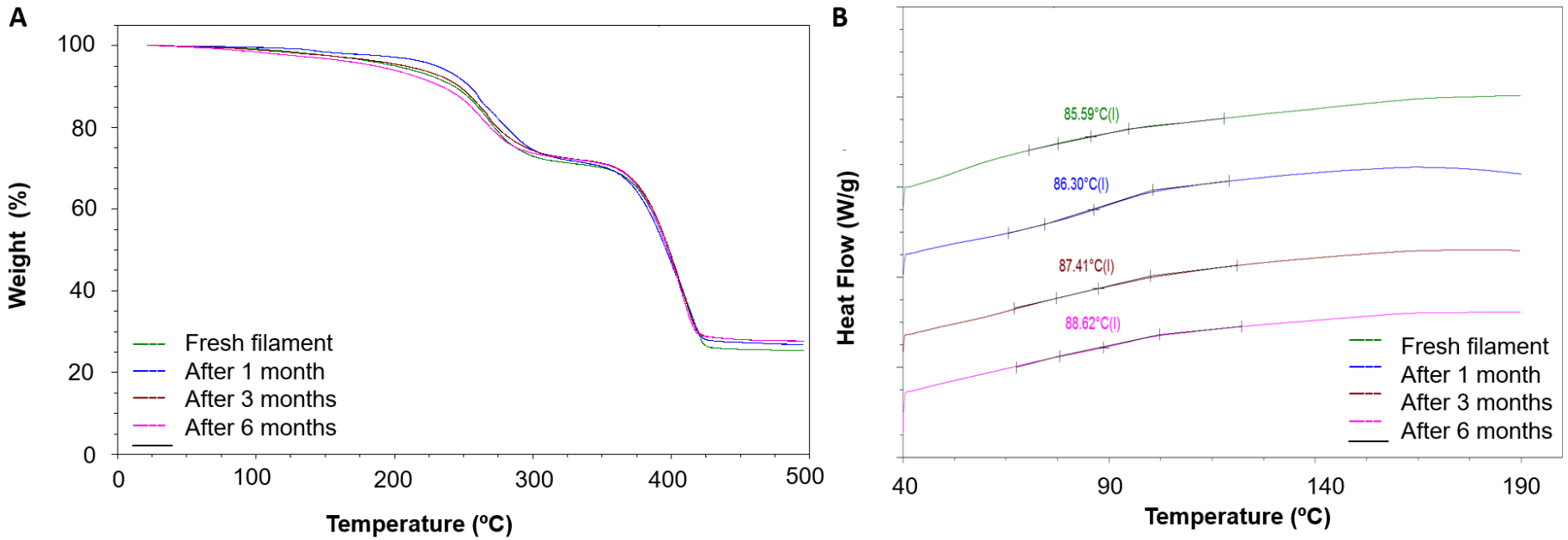

Fig. 4. Representative TGA (A) and DSC (B) thermographs for the impact of the storage conditions (30 °C + 65% RH + Vac) on the Eudragit S100-based filaments.

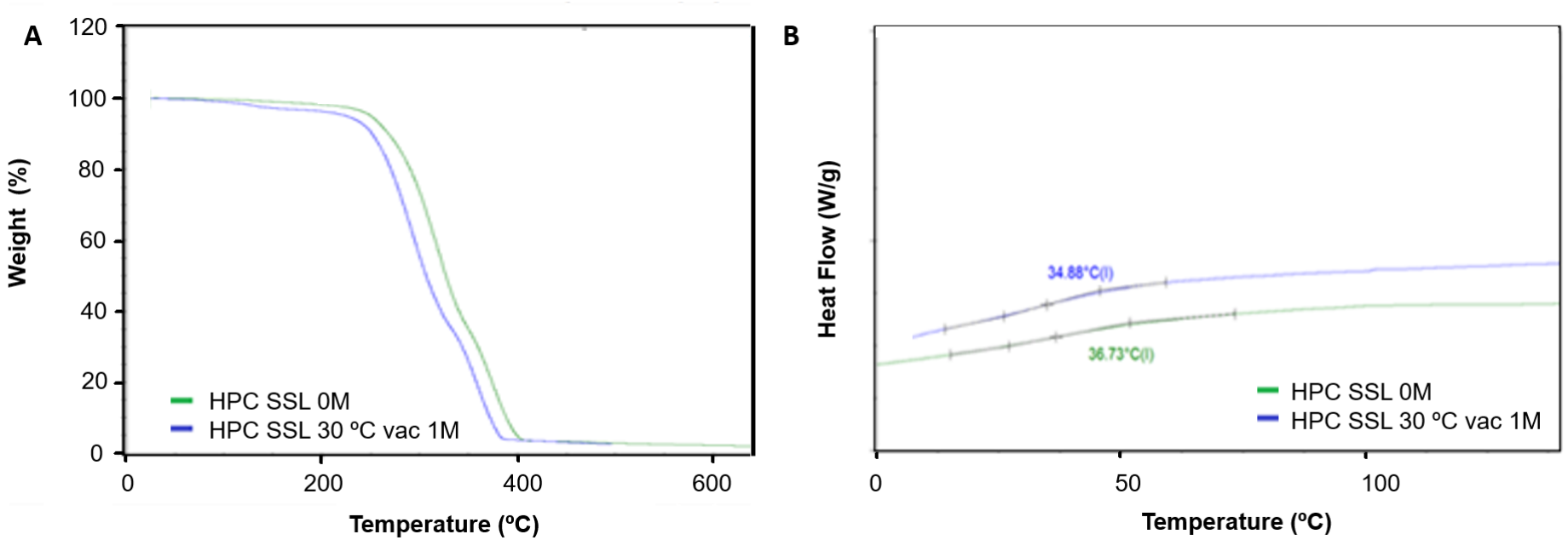

Fig. 5. TGA (A) and DSC (B) thermographs for the impact of the storage conditions on the HPC.SSL-based filaments.

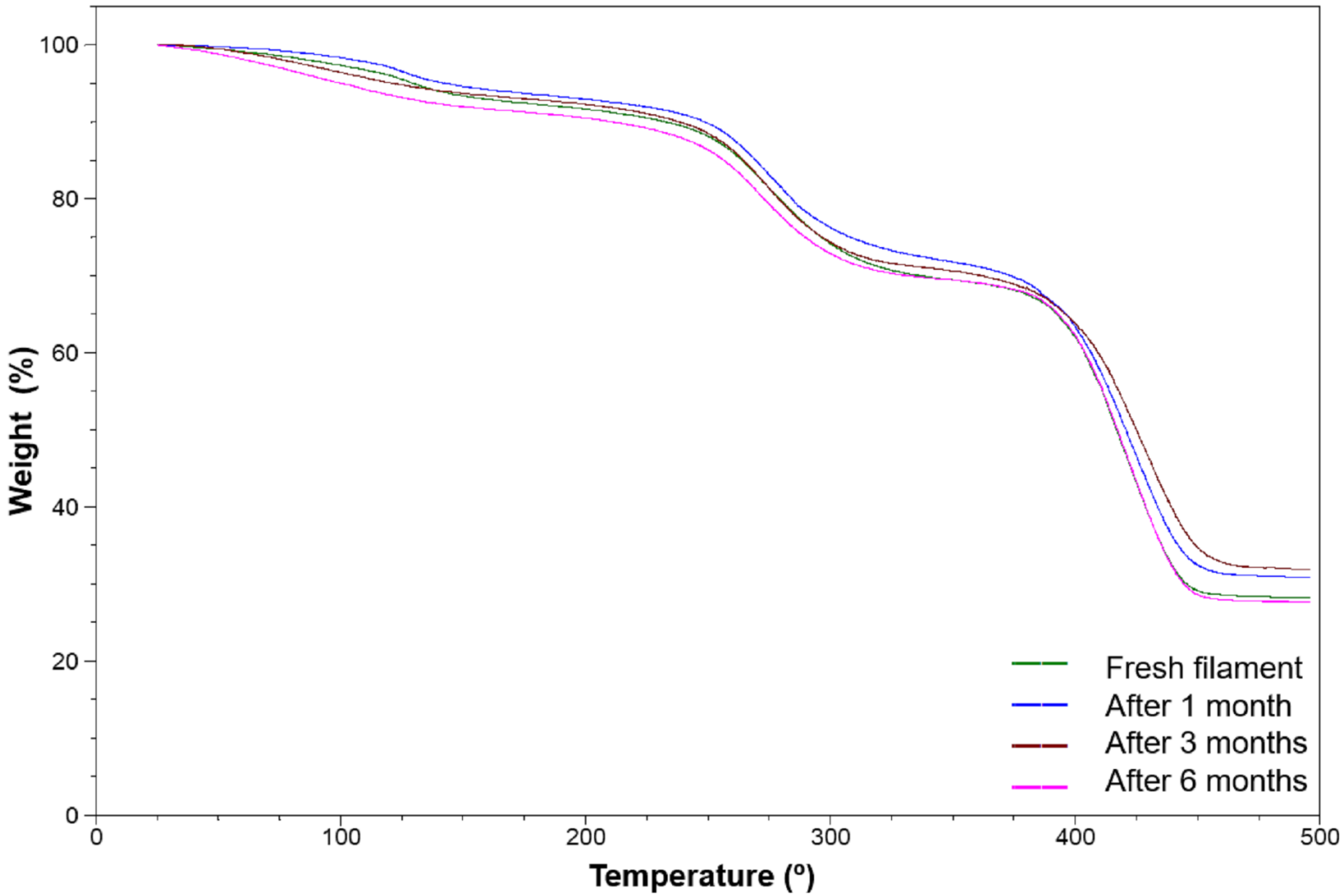

Fig. 6. TGA thermographs for the impact of the storage conditions (5 ℃) on the PVP-based filaments.

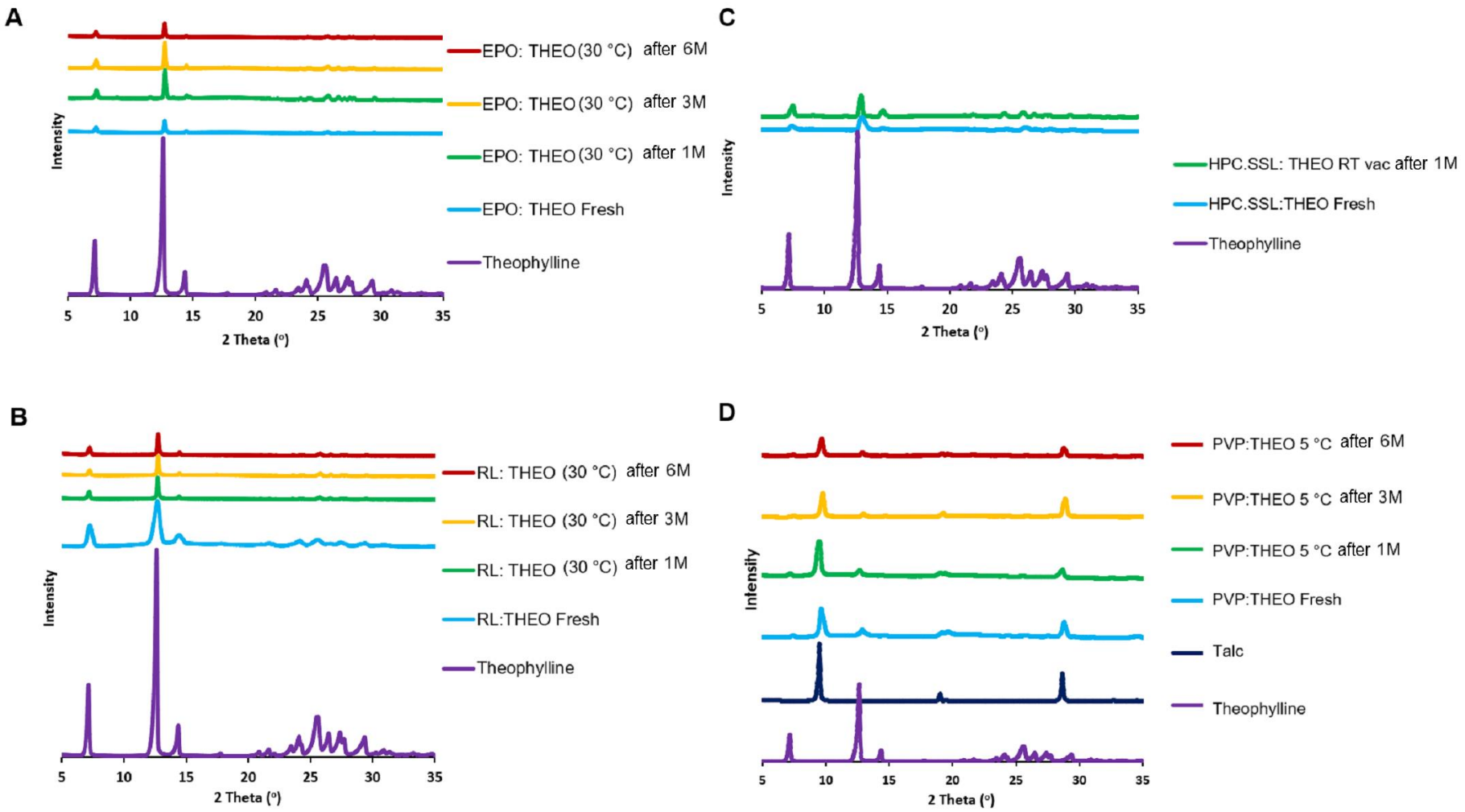

Fig. 7. XRPD data for the impact of the storage conditions on the Eudragit EPO (A), Eudragit RL (B), HPC.SSL (C) and PVP (D)-based drug loaded filament

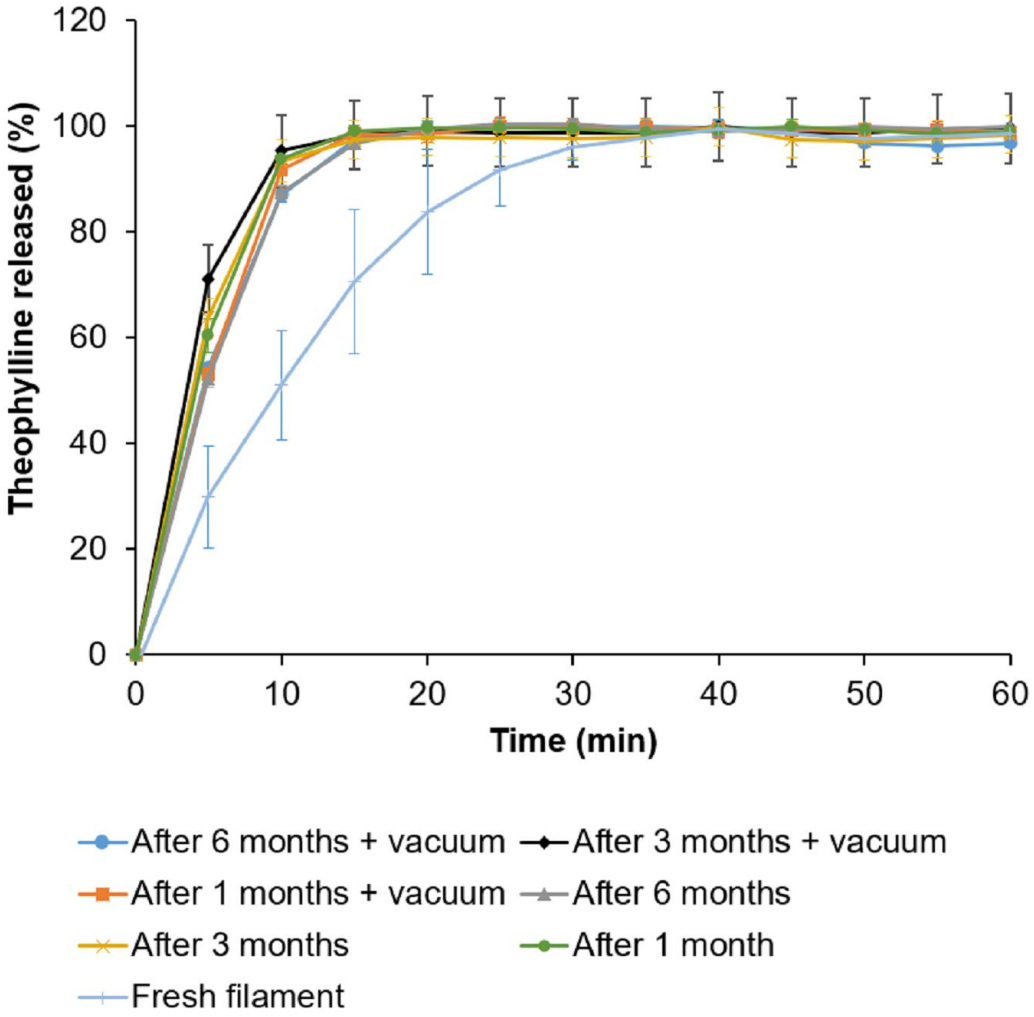

Fig. 8. The impact of storage at 5 ^{O}C on the *in-vitro* release profile of theophylline from the PVP-based product.

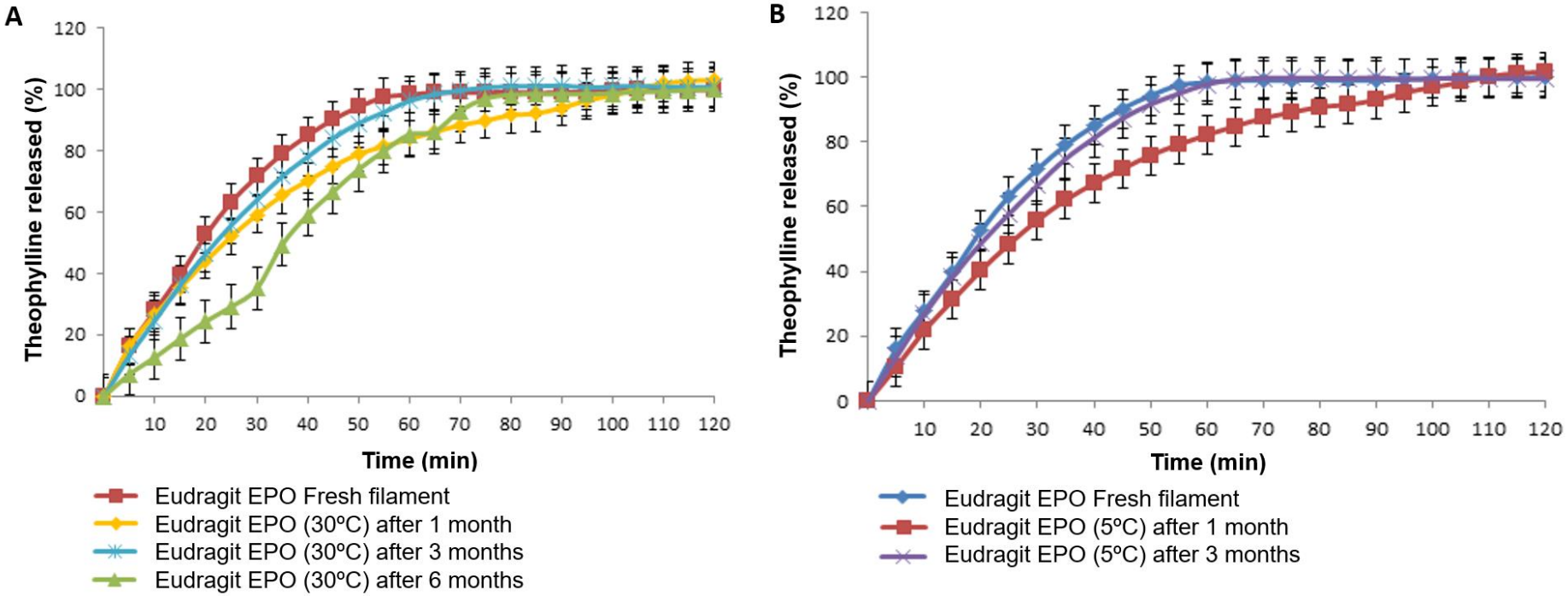

Fig. 9. The impact of the storage conditions on the *in-vitro* drug release profile of theophylline from the Eudragit EPO-based 3D printed tablets.

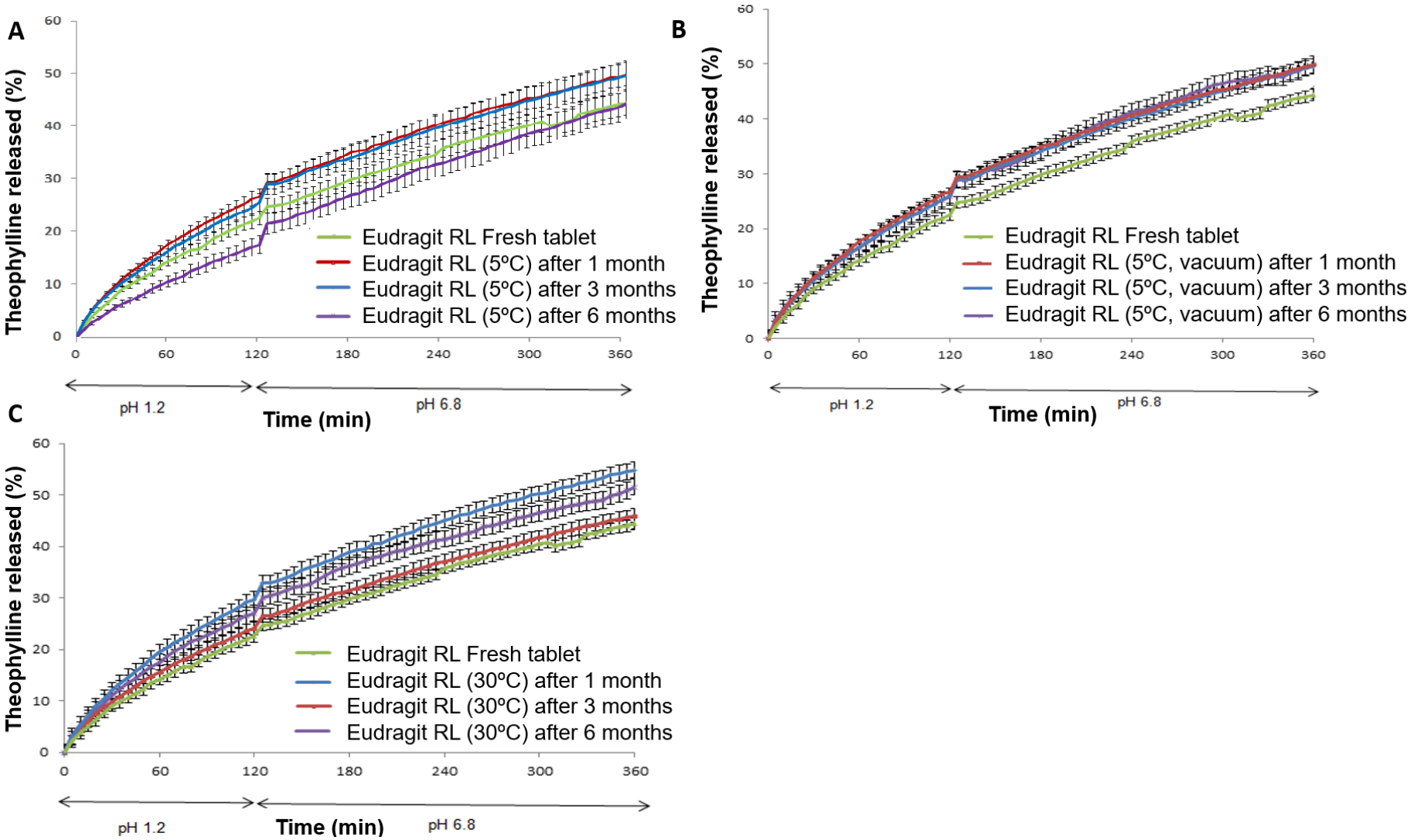

Fig. 10. The impact of the storage conditions on the *in-vitro* release profile of theophylline from the Eudragit RL-based 3D printed tablets.

printing temperatures).

Formulation/ Ratio (%)	HME Processing temp (ºC)	HME Extrusion temp (ºC)	Nozzle size (mm)	3D printing temp (ºC)	Platform temp (ºC)
PVP: TEC: Talc: Theo 50: 12.5: 27.5: 10	100	90	1.25	110	40
HPC.SSL: Triacetin: Theo 50: 5: 45	125	115	1.7	160	40
Eudragit L100-55: TEC: Talc 50: 16.67: 33.33	135	125	1	185	40
Eudragit S100: TEC: Talc 52.5: 22.5: 25	130	120	1.5	190	40
Eudragit RL: TEC: Theo 50: 5: 45	130	120	1.5	160	40
Eudragit EPO: TEC: Theo 50: 3.25: 46.75	100	90	1.25	135	45

Table 2. Impact of storage conditions on filament diameters, visual appearance and compatibility with printing process.

Filament	Filament/ Storage condition	Filament diameter (mm)		Compatibility with FDM 3D printing	Visual appearance after storage
		Before storage	After 6 months		
PVP-based	5 ºC	1.50 ±0.04	1.53 ±0.03	✓ too flexible	No Change
	5 ºC + Vac	1.50 ±0.01	1.48 ±0.02	✓ too flexible	No Change
	30 ºC + 65% RH	1.37±0.09	N/A*	X Deformed	flattened
	30 ºC + 65% RH + Vac	1.49±0.01	N/A*	X Deformed	flattened
HPC.SSL-based	5 ºC	1.64 ± 0.04	1.63 ± 0.04	X too flexible	No Change
	5 ºC + Vac	1.79 ± 0.01	1.69 ± 0.04	X too flexible	No Change
	30 ºC/65% RH	1.58 ± 0.10	1.59 ± 0.13	X too flexible	No Change
	30 ºC/65% RH + Vac	1.69 ± 0.05	N/A*	X Deformed	flattened
Eudragit L100-55-based	5 ºC	1.67 ±0.03	1.67 ±0.04	✓	No Change
	5 ºC + Vac	1.67 ±0.14	1.65 ±0.14	✓	No Change
	30 ºC + 65% RH	1.61 ±0.05	1.77 ±0.06	✓	No Change
	30 ºC + 65% RH + Vac	1.73 ±0.06	N/A*	X Deformed	flattened
Eudragit S100-based	5 ºC	1.53 ±0.02	1.54 ±0.02	✓	No Change
	5 ºC + Vac	1.61 ±0.08	1.62 ±0.05	✓	No Change

	30 ºC + 65% RH	1.63 ±0.02	1.63 ±0.02	✓	No Change
	30 ºC + 65% RH + Vac	1.62 ±0.03	1.62 ±0.03	✓	No Change
Eudragit RL-based	5 ºC	1.59 ± 0.05	1.57 ± 0.03	✓	No Change
	5 ºC + Vac	1.57 ± 0.01	1.59 ± 0.04	✓	No Change
	30 ºC/65% RH	1.57 ± 0.01	1.55 ± 0.03	✓	No Change
	30 ºC/65% RH + Vac	1.57 ± 0.04	N/A*	X Deformed	Flattened
Eudragit EPO-based	5 ºC	1.59 ± 0.05	1.58 ± 0.03	✓	No Change
	5 ºC + Vac	1.59 ± 0.01	1.61 ± 0.04	X Too flexible	No Change
	30 ºC/65% RH	1.68 ± 0.04	1.66 ± 0.03	✓	No Change
	30 ºC/65% RH + Vac	1.62 ± 0.04	N/A*	X Deformed	Flattened