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1 Research paper

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

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9 Tochukwu C Okwuosa^{1,2}, Muzna Sadia¹, Abdullah Isreb¹, Rober Habashy¹,
10 Matthew Peak³ Mohamed A Alhnan⁴

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13 ¹*School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston PR1 2HE, United Kingdom.*

14 ²*School of Life and Medical Sciences, University of Hertfordshire, AL10 9AB Hatfield, United Kingdom.*

15 ³*Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust, Liverpool, UK*

16 ⁴*Institute of Pharmaceutical Science, King's College London, London, United Kingdom.*

17

18

19

20 *Corresponding author at:

21 Institute of Pharmaceutical Sciences

22 King's College London

23 150 Stamford Street

24 London SE1 9NH. Tel.: +44 (0)20 7848 7265

25 Email: Alhnan@kcl.ac.uk

26

27 **Abstract**

28 3D printing of oral solid dosage forms is a recently introduced approach for dose personalisation. Fused
29 deposition modelling (FDM) is one of the promising and heavily researched 3D printing techniques.
30 However, the successful application of this technique relies greatly on [the](#) mass manufacturing of
31 physically and chemically stable filaments, that can be readily available as a shelf item to be 3D printed
32 on-demand. [The stability of](#) methacrylate polymers (Eudragit EPO, RL, L100-55 and S100),
33 hydroxypropyl cellulose-SSL (HPC.SSL) and polyvinyl pyrrolidone (PVP)-based filaments over 6
34 months [were investigated](#). Filaments manufactured by [hot melt](#) extrusion (HME) were stored at either
35 5 °C or 30 °C + 65 %RH with/without vacuuming. The effects of storage on their dimensions, visual
36 appearance, thermal properties, and ‘printability’ were analysed. Theophylline content, as well as *in*
37 *vitro* release from the 3D printed tablets were investigated. The filaments were analysed before storage,
38 then after 1, 3 and 6 months from the manufacturing date.

39 Storing filaments at these conditions [had](#) a significant effect on their physical properties such as shape,
40 dimensions, flexibility and hence compatibility with FDM 3D printing. The methacrylate-based
41 filaments were more physically stable and more easily printed following storage. Owing to their
42 hygroscopic nature, cellulose- and PVP-based filaments demonstrated a reduction in their glass
43 transition temperature upon storage, leading to increased flexibility and incompatibility with FDM 3D
44 [printer](#). Theophylline contents was not significantly changed during the storage.

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

48

49 **1. Introduction**

50 For many years, drug dosing [for adults were](#) based on the age and weight of the patient, with the
51 dose for children extrapolated linearly from the former. The downside of such an approach is the lack
52 of consideration of demographic, genetic, clinical and environmental factors which have been proven
53 to contribute to population's variabilities ([Cella et al. 2010](#)). Hence, varied responses to therapy and
54 susceptibility to adverse drug reactions have always been predominant issues ([Al-Metwali and Mulla](#)
55 [2017](#); [Nyboe Andersen et al. 2017](#)). Dose personalisation, therefore, offers the advantage of tailoring
56 doses to the patients' needs when required. With advancements in pharmacogenomics and wearable
57 technologies, there is a rising interest in dose personalisation, in response to tested biomarkers, to
58 achieve target pharmacodynamics and pharmacokinetics profiles.

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

66 Different approaches are currently being investigated to personalise oral dosage forms, with 3D
67 printing demonstrating significant potential ([Isreb et al. 2019](#); [Pereira et al. 2019](#); [Tagami et al. 2019](#);
68 [Sen et al. 2020](#); [Martinez et al. 2018](#)). [FDM](#) has been heavily researched as an effective and accessible
69 3D printing technique. It offers several advantages such as the absence of a post-printing processing, in
70 addition to its low-cost setup ([Pereira et al. 2019](#); [Sadia et al. 2018](#); [Okwuosa et al. 2016](#)). FDM 3D
71 printing involves the use of filaments, usually manufactured by hot melt extrusion, as a pre-product,
72 which are then fed into the heated nozzle of the FDM 3D printer ([Pereira et al. 2019](#); [Sadia et al. 2018](#);
73 [Okwuosa et al. 2016](#); [Goyanes et al., 2014](#)).

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

83 In the last six years, many studies have focused on the application of FDM 3D printing for dose
84 personalisation (Charoenying et al. 2020; Eleftheriadis et al. 2019; Jamróz et al. 2020; Wei et al. 2020;
85 Zhang et al. 2020; Fanous et al. 2020; Vo et al. 2020; Pereira et al. 2019; Sadia et al. 2018; Okwuosa et
86 al. 2016; Pietrzak et al. 2015). However, there are little to no information about the long-term stability
87 of these filaments. In fact, changes in the physicochemical properties of the filament during storage
88 might not only compromise the efficacy of the active ingredient but may also affect its printability.
89 Hence, adding more complexity to the technical challenges (Ilyés et al. 2019). For instance, a reduced
90 plasticity of the filament upon storage will result in a brittle filament that may often break under pressure
91 from the FDM 3D printer head gears (Ilyés et al. 2019, Neserreddin et al., 2018). Moreover, other
92 changes in the filament diameter and/or shape may also have an impact on the final printed product,
93 leading to variations in 3D printed tablets weights (weight uniformity) and in some cases the failure to
94 complete the 3D printing process (Ilyés et al. 2019).

95 With many researchers working towards the adaptation of FDM 3D printing in pharmaceutical
96 manufacturing, there is the need to study the stability of commonly used pharmaceutical polymers
97 adapted to suit this novel manufacturing approach. In this work, the stability of HME-based filaments
98 at 5 °C or 30 °C + 65 %RH were investigated. The impacts of the storage and packaging conditions were
99 studied using theophylline as a model drug in combination with different model polymers. As the focus
100 of this work is the impact of storage condition on physical change and the printability of different
101 polymer-based filaments, a chemically stable molecule (Serajuddin, 1986), theophylline was selected
102 as a model drug. The filaments in this study have been previously investigated to achieve immediate
103 and modified release 3D printed structures using commercially available polymers of different chemical
104 nature and hygroscopicity [PVP-based (Okwuosa et al. 2016), HPS.SSL-based (Pietrzak et al. 2015),
105 L100-55-based, S100-based, RL-based and EPO-based filaments (Okwuosa et al. 2017; Sadia et al.
106 2018; Sadia et al. 2016)]. It is important to highlight that both Eudragit L100-55 and S100-based
107 filaments were used to fabricate the shell in delayed release system and hence were made drug-free.
108 The diameter, printability, thermal properties, physical form of the API, drug content of the filament,
109 and the drug release profile of the 3D printed dosage forms were investigated before and after exposure
110 to the storage conditions.

111

112 2. Materials and Methods

113 2.1 Materials

114
115 Hydroxypropyl cellulose (HPC₂-SSL) was obtained from Nisso Chemical Europe (Dusseldorf,
116 Germany). Theophylline was purchased from ACROS Organics. Polyvinylpyrrolidone (PVP,
117 MW 40,000), triacetin and triethyl citrate (TEC) were purchased from Sigma-Aldrich (UK). Talc was
118 purchased from Fluka Analytical (UK). Eudragit L100-55, RL, EPO and S100 were donated by Evonik
119 Industries (Darmstadt, Germany).

120 2.2 Preparation of filaments

121
122 The PVP, HPC₂-SSL and Eudragit based filaments were produced by HME following
123 previously reported approach (Okwuosa et al. 2016). All filaments contained a model drug
124 (theophylline) except for Eudragit L100-55 and S100 based filaments, which were used to 3D print ~~the~~
125 enteric layers (Okwuosa et al. 2017). The mixing and processing temperatures of the HME processes
126 and nozzle sizes are detailed in **Table 1**.

127 2.3 Accelerated stability studies (storage conditions)

128 In order to determine the stability of the filaments over a long-term storage, accelerated stability
129 studies were carried out according to the International Council for Harmonisation (ICH) guidelines
130 [Q1A(R2)] (ICH, 2003). The drug loaded (PVP, HPC₂.SSL, Eudragit EPO and RL-based) and the drug
131 free (Eudragit L100-55 and S100-based) filaments were sealed in polyvinyl chloride (PVC) polybags
132 with or without vacuuming and stored in a fridge at 5 °C or in an incubator at 30 °C + 65 %RH. Vacuum
133 sealing was achieved using Andrew James VS517 Dom Sealer. The filaments were characterised when
134 freshly prepared and then after 1, 3 and 6 months of storage.

135 2.4 Filament dimension and visual appearance

136
137 In order to determine the effect of the storage conditions on the diameter of the filaments,
138 changes in the diameter of the filaments were monitored using a Draper Electronic Digital caliper (0 –
139 25 mm) with a resolution of 0.001 mm. Filaments were observed to assess change in their visual
140 appearance (change in shape, colour or presence of aggregation).

141 2.5 Printability test using FDM 3D printer

142
143 The 3D printing of the filaments that were stored under different conditions was attempted
144 using the parameters detailed in **Table 1** to determine the effect of the storage conditions on 3D printing
145 in comparison to a freshly prepared filament using Makerbot Experimental 2X 3D printer (Makerbot
146 Inc, NY, USA). 3D Printing was carried out at a standard resolution (0.2 mm layer thickness) and a 100
147 % infill with rectilinear infill pattern. Other settings were set as previously detailed (Okwuosa et al.

148 2016). A caplet (L x W x H 10 x 4 x 3.6 mm) was designed and imported into the MakerWare software
149 Version 2.4.0.17 (Makerbot Industries, LLC., USA) and used to test the printability of the filaments.
150 The printed caplets weighed approximately 110 mg, containing approximately 11, 50, 50 and 52 mg of
151 theophylline for the PVP, HPC.SSL, Eudragit RL and EPO-based caplets respectively.

152 2.6 Thermal gravimetric analysis (TGA)

153
154 TGA analysis for the extruded filaments was carried out using a TGA Q500 (TA Instruments,
155 Hertfordshire, UK). The filaments were cut into small pieces (<1mm, approximately 10 mg) were
156 accurately weighed and placed in a 40 µL aluminium pan (TA Instruments, Hertfordshire, UK), which
157 was placed on a platinum pan. Samples were then scanned from 25 to 500 °C at a heating rate of 10
158 °C/min with a nitrogen purge of 40/60 mL/min for the sample and furnace, respectively. All
159 measurements were carried out in triplicates and the data analysed using a TA Universal Analysis 2000
160 software (TA Instruments, Hertfordshire, UK)

161 2.7 Differential scanning calorimetry (DSC)

162
163 For modulated temperature differential scanning calorimetry (MTDSC) analysis, a differential
164 scanning calorimeter (DSC) Q2000 (TA Instruments, Elstree, Hertfordshire, UK) was used. PVP-based
165 filaments were subjected to a modulated heat-cool-heat scan in order to measure and exclude the effect
166 of moisture content on the plasticity of the filaments. Eudragit L100-55 and S100-based filaments were
167 also subjected to a modulated scan. The modulation scan was applied using an amplitude of 0.212 °C
168 and a period of 40 sec, scanning from -70 to 200 °C at a heating rate of 2 °C/min.

169 As moisture did not interfere with the thermographs obtained unlike the aforementioned filaments, a
170 non-modulated standard scan was used for HPC.SSL, Eudragit RL and EPO-based filaments from -50
171 to 300 °C at a heating rate of 10 °C/min. Analysis was carried out under a purge of nitrogen gas
172 (50 mL/min). All the data were analysed using a TA Universal Analysis 2000 software (TA
173 Instruments, Hertfordshire, UK). TA pin-holed standard lids and 40 µL aluminium pans (TA
174 Instruments, Hertfordshire, UK) were filled with approximately 5 mg sample and sealed. All
175 measurements were carried out in triplicates.

176

177 2.8 X-ray powder diffractometry (XRPD)

178
179 X-ray powder diffraction was carried out on the filaments over 6 months to investigate changes
180 in the physical forms of the API or excipients. This was assessed using a powder X-ray diffractometer,
181 D2 Phaser with Lynxeye (Bruker, Germany). Filaments were dipped in liquid nitrogen before crushing
182 them using a mortar and pestle. The powders were scanned from 2Theta (2θ) = 5° to 35° using 0.01

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

185 2.9 Determination of drug content (Eudragit EPO, RL, HPC.SSL and PVP-based filaments)

186
187 To determine changes in the drug contents of the filament after storage, 120 mg of the Eudragit
188 EPO and RL, HPC.SSL and PVP-based filaments containing theophylline were solubilised in 0.1 M
189 HCl and sonicated for 2h or 8 h (for Eudragit RL-based filament only). The API was measured by
190 HPLC using an Agilent UV-HPLC 1260 series (Agilent Technologies, Inc., Germany) and an XTerra
191 RP C18 column (150 × 4.6 mm, 5 µm particle size) (Waters, Ireland). A mobile phase of 10 mM solution
192 of ammonium acetate buffer, methanol and acetonitrile at volume ratio of 86:7:7. Analysis was carried
193 out at a wavelength of 272 nm, column temperature of 40 °C, flow rate of 1 mL/min, injection volume
194 was 5 µL and a run time of 7 min as reported previously (Okwuosa et al. 2016).

195 2.10 In vitro drug release studies (Eudragit EPO and RL-based filament)

196
197 In vitro drug release studies for the 3D printed tablets were carried out using a USP II
198 dissolution apparatus (AT 7 Smart, Sotax, Switzerland). The tablets were tested in 900 mL of 0.1 M
199 HCl solution for the EPO-based tablets for 2 hours. However, for the extended release formulation
200 (Eudragit RL), dissolution testing was carried out in 750 mL of HCl solution, followed by the addition
201 of 250 mL of 0.215 M tribasic phosphate buffer after 2hrs and the pH adjusted to 6.8. Samples were
202 collected for another 6 hrs. The samples were automatically collected and analysed at 5 min intervals
203 using a UV/VIS spectrophotometer (PG instruments limited, UK) at a wavelength of 272 nm. The path
204 length used was 1 mm. The data were analysed using IDIS Software version 2.0 Automated Lab
205 (Berkshire, UK).

206 2.11 Statistical analysis

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

209

210 3. Results and discussions

211

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

218 3.1 Physical and thermal properties of the stored filaments

219 Changes in the physical and thermal properties of these filaments due to storage could affect their
220 3D printing into solid dosage forms. Therefore, the impact of the storage conditions on the diameter of
221 the filaments were investigated. It was observed that a filament diameter >1.8 mm will lead to blockage
222 due to its inability to pass through the *liquifying* chamber of the FDM 3D printer's head. This is an
223 essential quality criterion of the filaments to ensure consistent flow through the pressing gears into the
224 hot nozzle. In addition, deformations in the cylindrical shape of the filament (deviation from the
225 cylindrical shape) could potentially affect the filament interaction with the gears in the 3D printer,
226 leading to inconsistency of the flow through the hot nozzle. Such effect can result in weight variation
227 of the 3D printed product (data not included). These changes could also be influenced by the changes
228 in the thermal properties of the filaments, with the TGA analysis being able to investigate water gain or
229 loss and changes in the degradation profile of the stored filaments, with reference to the freshly prepared
230 samples. Also, changes in the glass transition temperature (T_g) of the filament can significantly alter
231 the mechanical properties of the filaments, in turn, the ability to load the filaments into the *liquifying*
232 chamber of the FDM 3D printer head. Therefore, investigations into the effect of the storage conditions
233 on the T_g of the filaments were also carried out using thermal method.

234 a) *Methacrylate-based filaments*

235 Investigating the diameter of Eudragit EPO-based filaments after storage revealed *that* no change
236 *was noted* when stored at 5 °C. *However, storing the filaments at 30 °C + 65 %RH resulted in a*
237 *permanent flattening/deformation of these filaments only* when the storage bag was vacuum-sealed
238 **(Table 2)**. The resultant deformation *affected* its compatibility with the 3D printer and prevented its
239 conversion into a solid dosage form. The TGA analysis of this filament demonstrated similar
240 thermographs in the storage conditions **(Fig. 1A)** in comparison to a freshly prepared sample with
241 insignificant moisture uptake with no observed weight loss between 50-150 °C, a usual indication of
242 water evaporation due to hygroscopicity. This non-hygroscopic nature of *this* polymer was also
243 observed by Parikh *et al.* (2014) who recorded a 0.2 %w/w moisture content. On the other hand, the
244 DSC analysis revealed a slight reduction in the T_g of the filament due to storage **(Fig. 1B)**. However,

245 this did not affect the printability of the filaments stored at 5 °C and 30 °C with no vacuuming. The
246 flattening of the vacuum-sealed filament when stored at 30 °C could be attributed to the increased
247 mobility of the polymeric chains above the T_g of the Eudragit EPO matrix. In addition, the negative
248 pressure on the filaments due to the vacuuming, may have also **contributed to** the deformation of the
249 filament. This was confirmed when a protective shell placed around the filaments, resulted in no
250 alteration in shape at the same storage conditions (data not included).

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

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

265 *b) Hydroxypropyl cellulose-based filaments*

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

279 c) *Povidone-based filaments*

280 Investigating the physical properties of the PVP-based filaments revealed their stability **only** at the
281 5 °C storage condition where they retained their shape and **diameter**. The TGA of freshly prepared PVP-
282 based filaments depicted an initial weight loss of approximately 4 % at around 120 °C due to moisture
283 loss, which could be attributed to the hygroscopic nature of PVP (Gupta et al. 2014). The storage of the
284 filaments at 5 °C resulted in up to 6.5 % water uptake (**Fig. 6**). PVP has been reported to be able to take
285 moisture up to 40% of its weight (Ramineni et al. 2013). It was not possible to determine precisely the
286 Tg of these filaments due to the excessive water evaporation upon heating, which interfered with the
287 detectability of the polymer's Tg. A heat-cool-heat DSC approach could eliminate these effects of
288 moisture. However, this approach led to the removal of moisture during the first heat scan and can mask
289 the potential of storage on Tg of the filament (**Supplementary Data, Fig. S1 and S2**). Such high water-
290 uptake was reported to produce a significant drop in its Tg (Fitzpatrick et al. 2002; Xie and Taylor 2017;
291 Teng et al. 2010). Although the filaments at 5 °C remained compatible with the 3D printer, their very
292 hygroscopic nature poses a major challenge to their application. Therefore, a future product would
293 require the use a specific packaging for these filaments to provide moisture-controlled environment.
294 This might have major implications on the cost and practicality of using these filaments for on-demand
295 use in the community and hospital pharmacies.

296 **3.2 Impact of storage conditions on the physical form of theophylline**

297 Changes in the physical forms of theophylline and excipients due to storage can influence the
298 drug release profile. Due to the degradation of methacrylate polymers when thermally scanned >170
299 °C (Parikh et al., 2016), it was not possible to use DSC to assess the physical form of theophylline
300 (melting point of 272 °C) To investigate this, XRPD was used to analyse the filaments before and after
301 storage. The Eudragit EPO, RL, HPC.SSL and PVP-based filaments loaded with theophylline revealed
302 the presence of diffraction peaks at $(2\theta) = 7$ and 12° (**Fig. 7**), which corresponds to theophylline crystals.
303 Talc, which was used as the structure forming agent, demonstrated sharp peaks at $(2\theta) = 9.52, 19.54,$
304 28.87° . The drug peaks indicated that a proportion of the API remained crystalline within the filament,
305 following thermal and mechanical stress of the HME processes (Huang and Dai 2014). This proved to
306 be dependent on the model drugs as previously investigated using these matrices (Okwuosa et al. 2016;
307 Sadia et al. 2016). The intensity peaks that corresponds to theophylline were also observed after storage,
308 indicating that a proportion of the API is in its crystalline form during these storage conditions.
309 However, the peak intensity at $(2\theta) = 12^\circ$ due to theophylline was observed to increase for Eudragit
310 EPO-based filament whilst it decreased for the Eudragit RL-based filament over time (**Figs. 7A and**
311 **B**). Variations in peak intensity has been linked to crystalline concentrations (Siddiqui et al. 2015).
312 Also, it was reported that partial crystalline nature of matrices could alter due to storage (Lust et al.
313 2015; Huang and Dai 2014; Ueda et al. 2020). For filaments that did not include drug (Eudragit L100-

314 55 and S100), there were diffraction peaks at $(2\theta) = 9.52, 19.54, 28.87$, which corresponds to the crystals
315 of talc, throughout the storage (Supplementary Data, Figs. S3, S4, S5 and S6).

316 3.3 Drug integrity and *in vitro* drug release

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

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

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

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

344 In summary, we have

4. Conclusions

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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 more generally 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 conforming of produced table batches with compendial criteria. For FDM 3D printing to be successfully adopted for on-demand manufacturing, more research on this important area is required.

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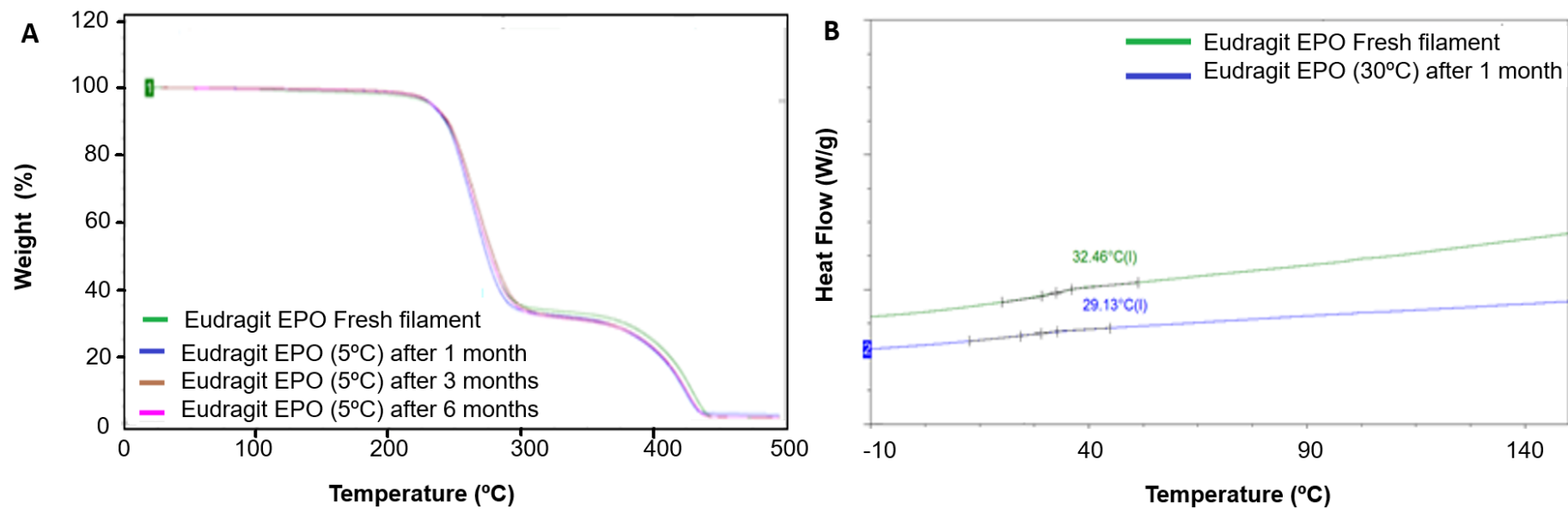


Fig. 1. TGA (A) thermographs for the impact of the storage condition (5 °C) on Eudragit EPO-based filament., (B) DSC thermographs for the impact of the storage condition (30 °C) on Eudragit EPO-based filament (filaments deformed and no further assessment was carried out after 1 month).

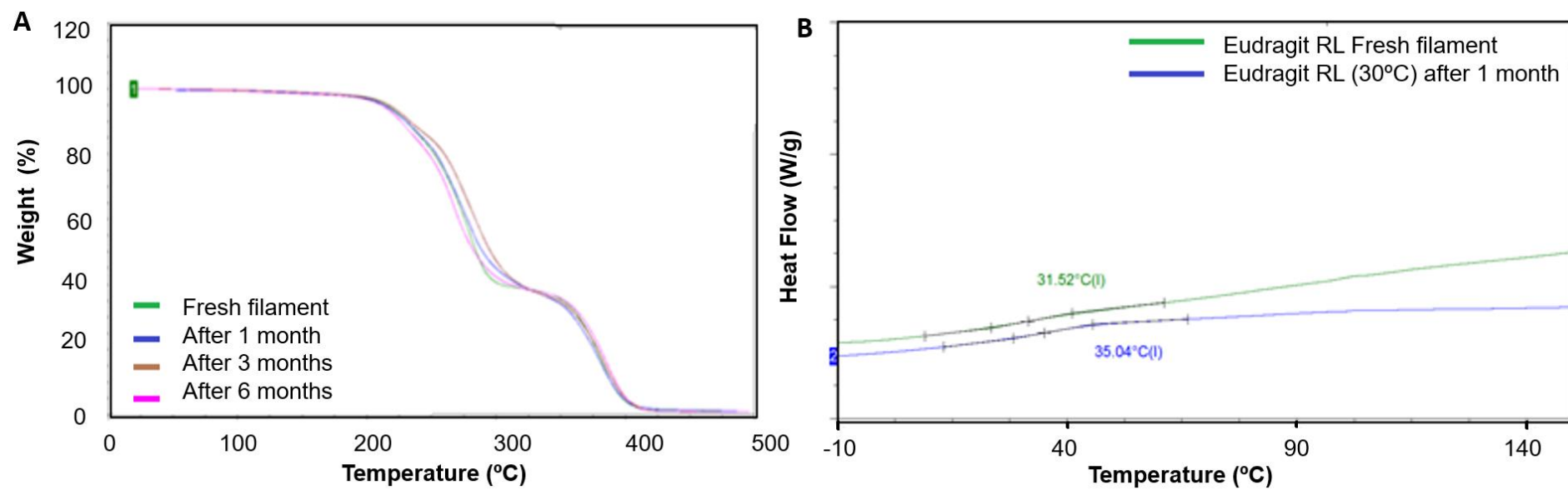


Fig. 2. TGA (A) and DSC (B) thermographs for the impact of the storage conditions on the Eudragit RL-based filament.

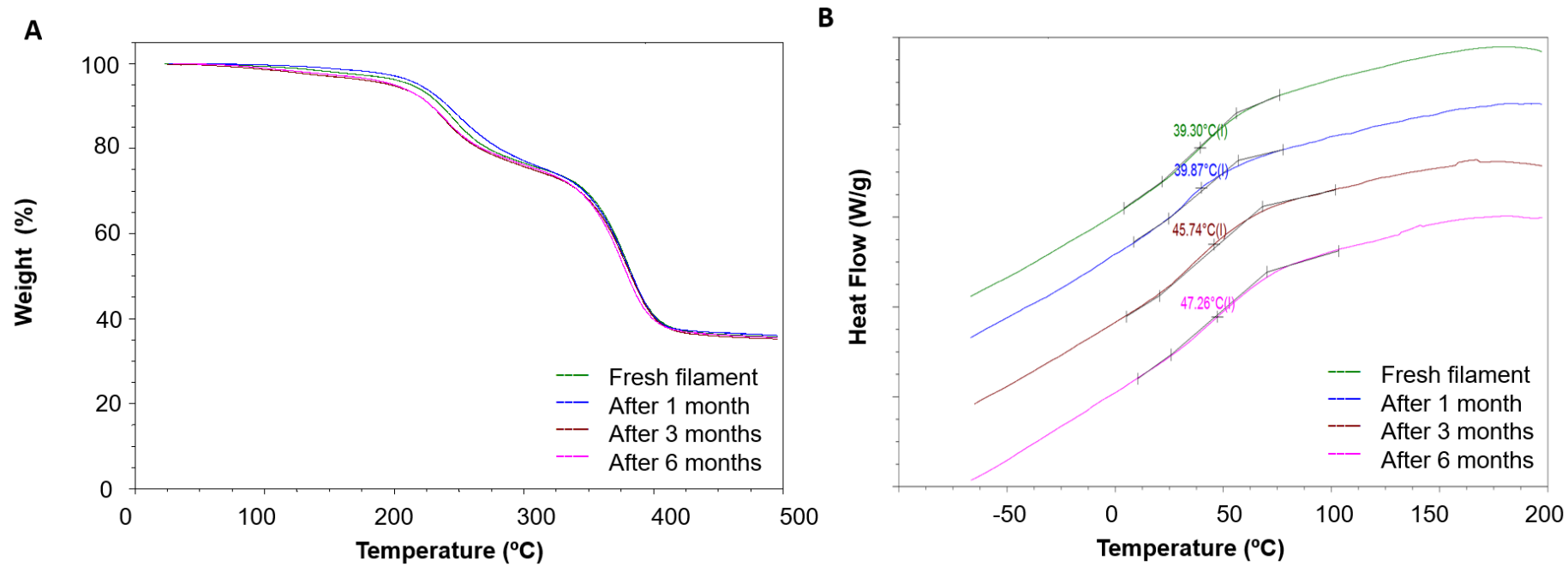


Fig. 3. TGA (A) and DSC (B) thermographs for the impact of the storage conditions (30 °C + 65% RH + Vac) on the Eudragit L100-55-based filaments.

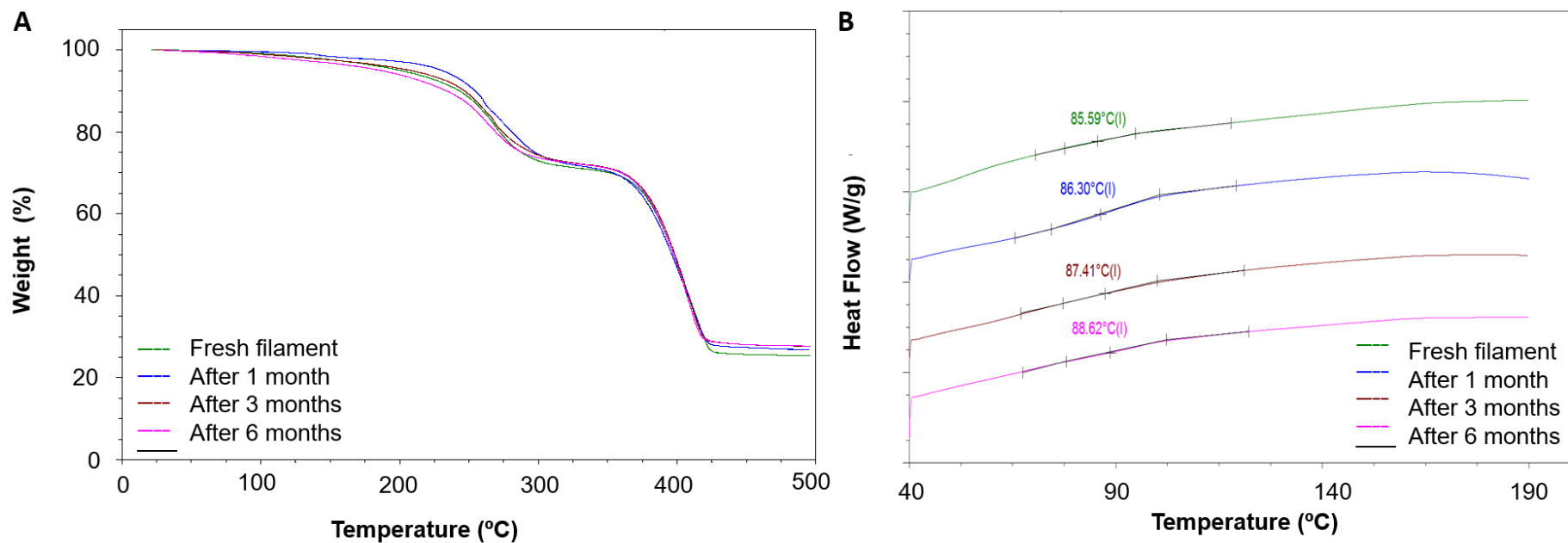


Fig. 4. Representative TGA (A) and DSC (B) thermographs for the impact of the storage conditions (30 °C + 65% RH + Vac) on the Eudragit S100-based filaments.

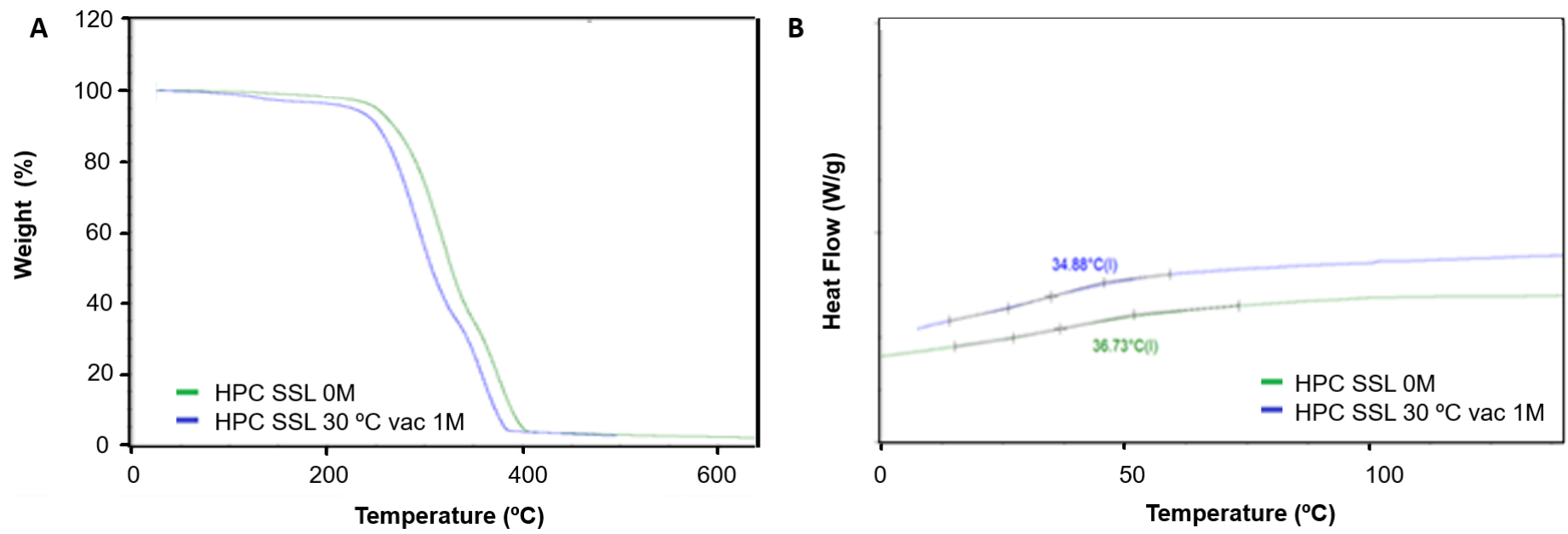


Fig. 5. TGA (A) and DSC (B) thermographs for the impact of the storage conditions on the HPC.SSL-based filaments.

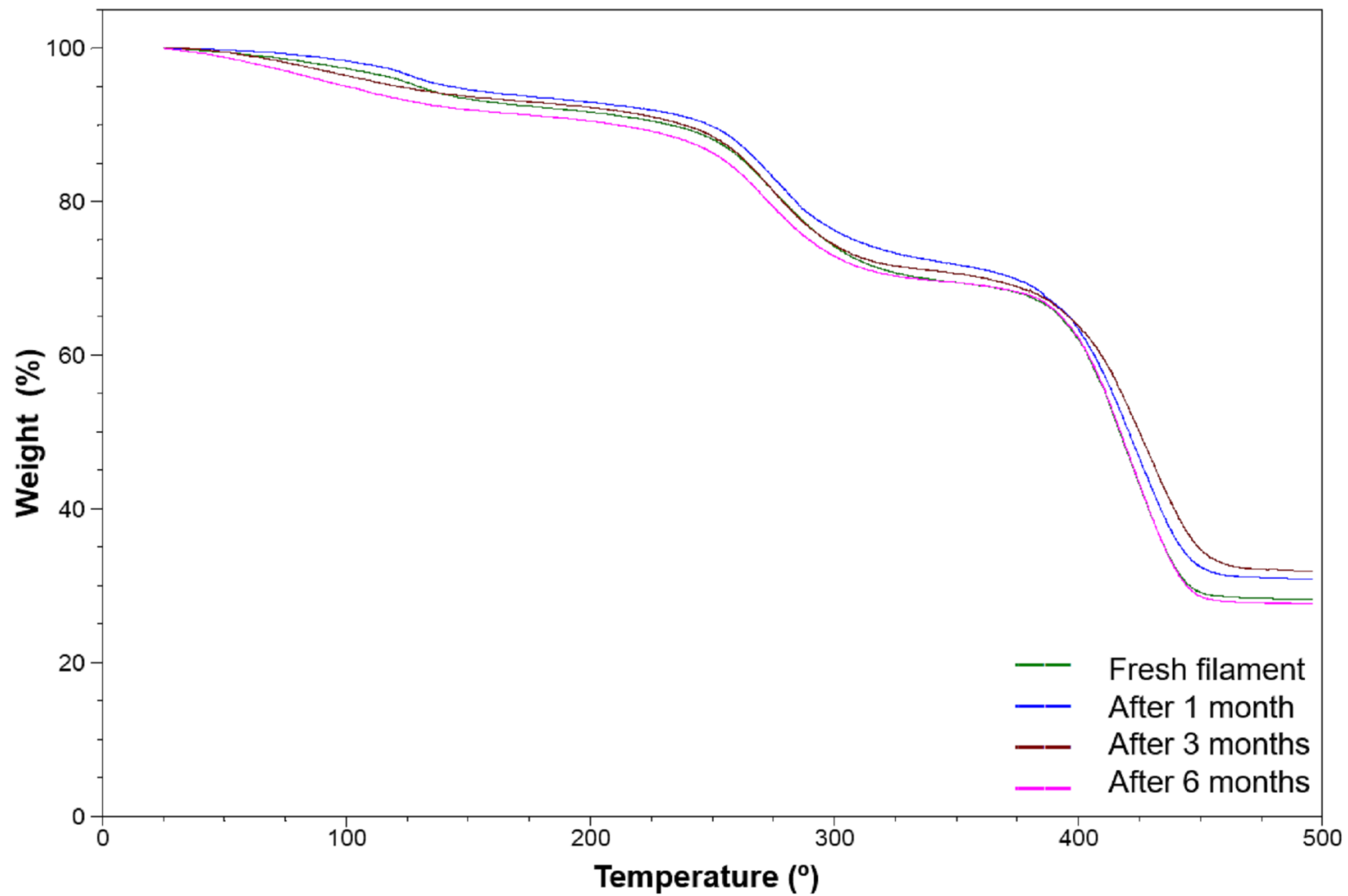


Fig. 6. TGA thermographs for the impact of the storage conditions (5 °C) on the PVP-based filaments.

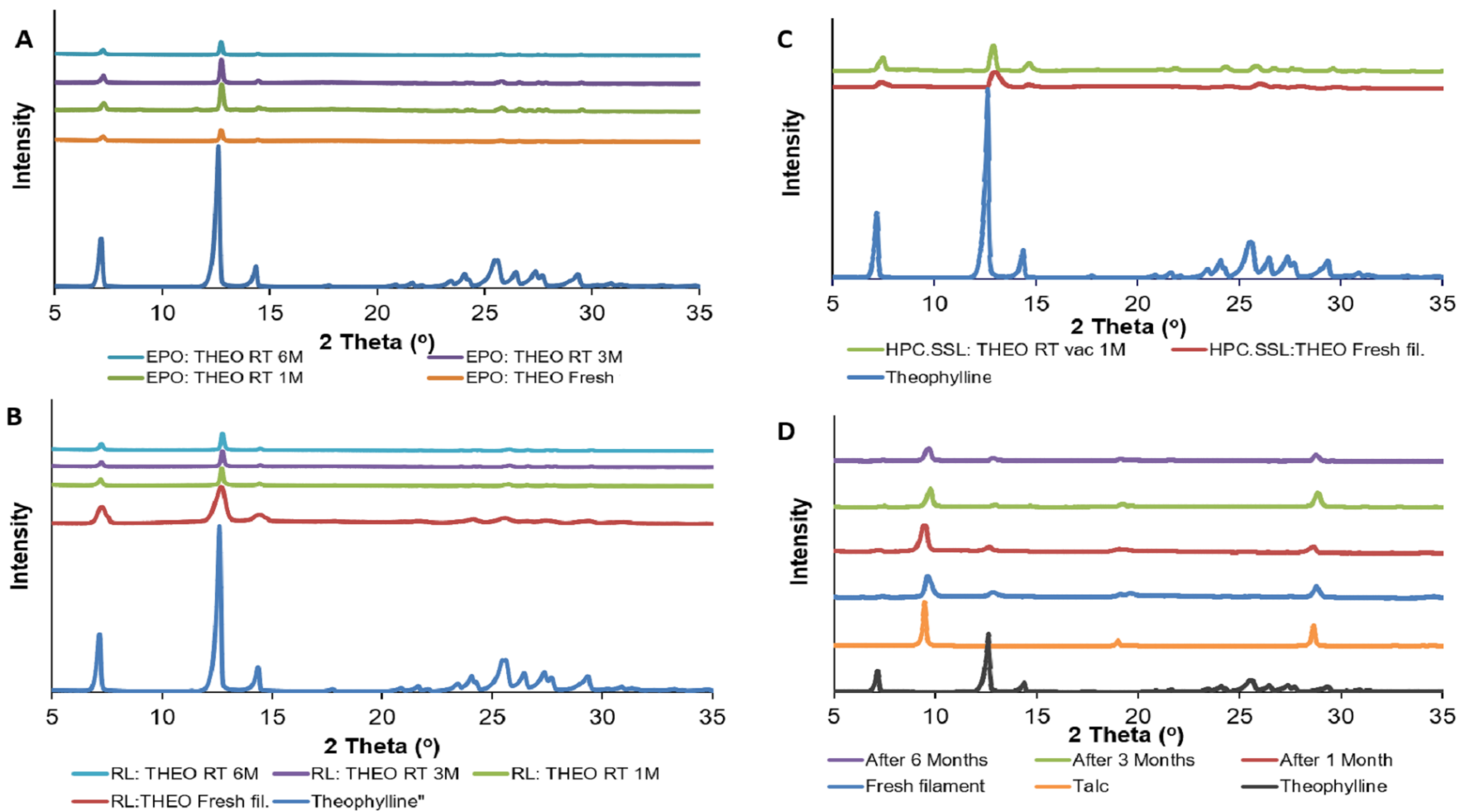


Fig. 7. XRPD data for the impact of the storage conditions on the Eudragit EPO (A), Eudragit RL (B), HPC.SSL (C) and PVP (D)-based drug loaded filament

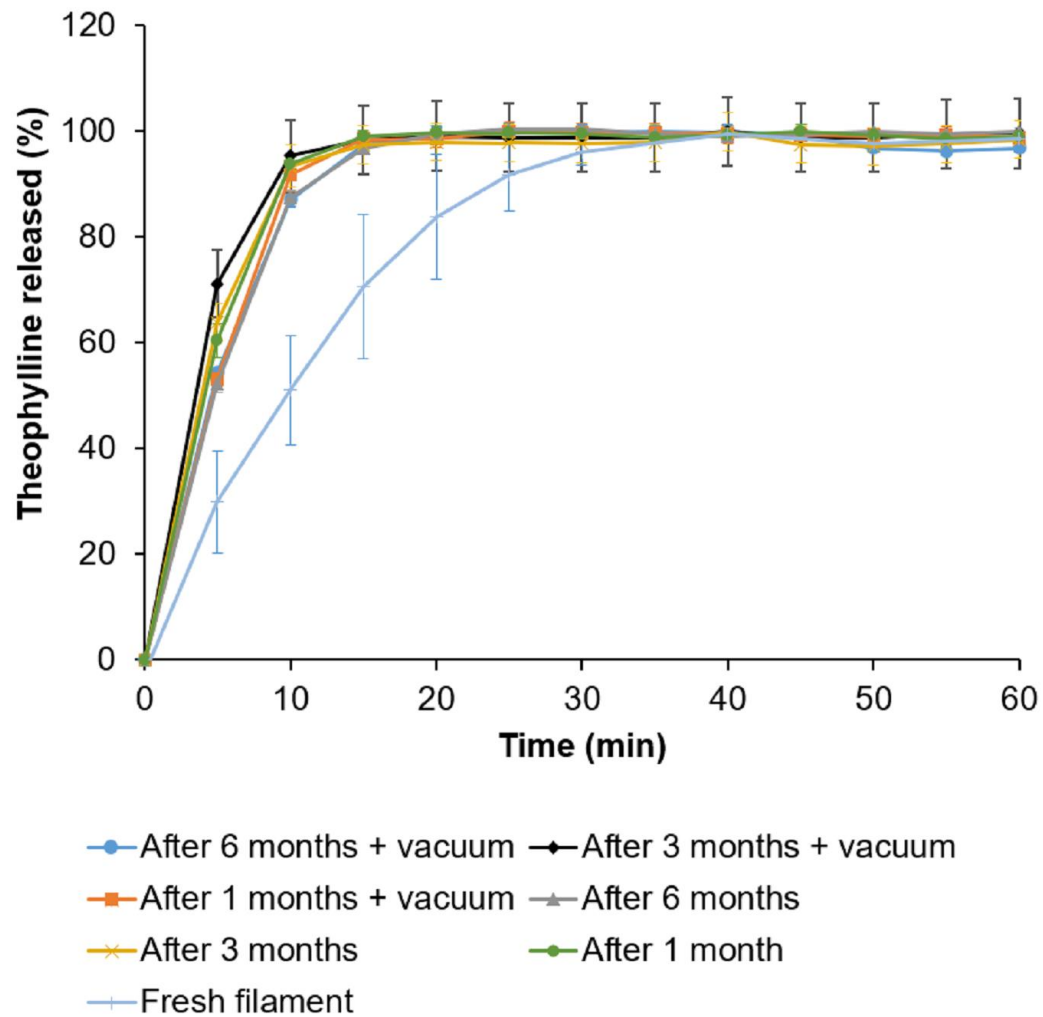


Fig. 8. The impact of storage at 5 °C on the *in-vitro* release profile of theophylline from the PVP-based product.

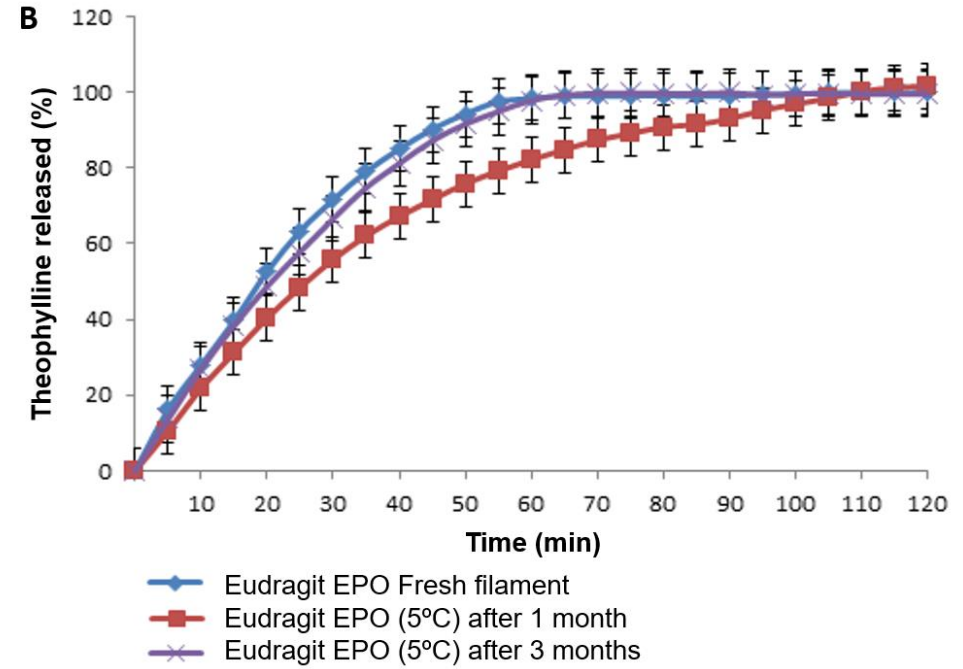
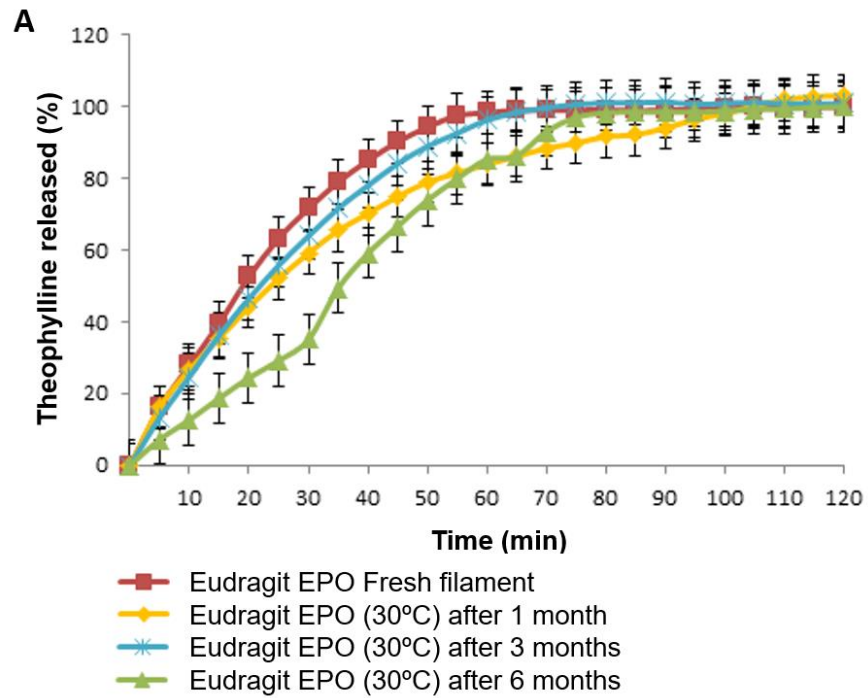


Fig. 9. The impact of the storage conditions on the *in-vitro* drug release profile of theophylline from the Eudragit EPO-based 3D printed tablets.

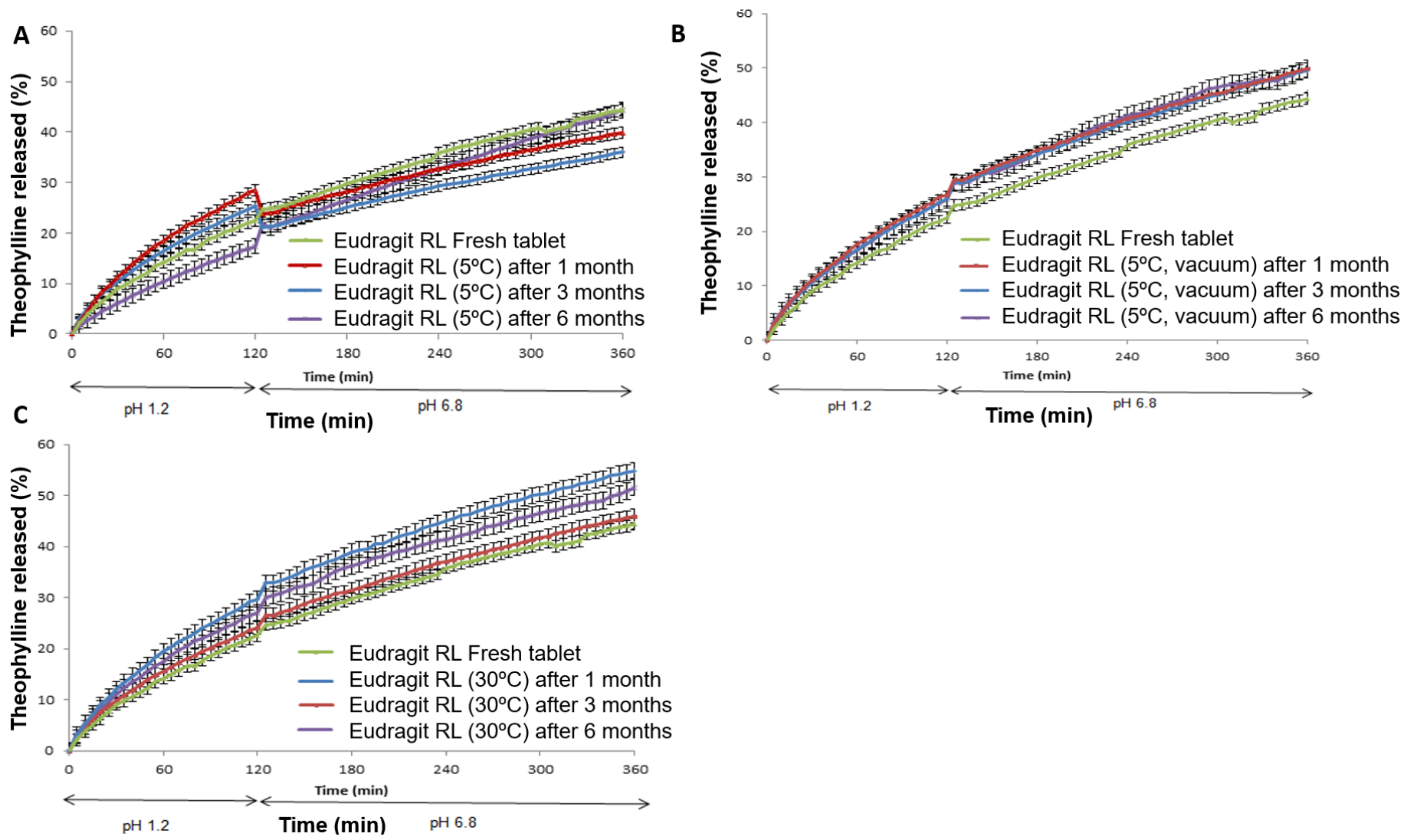


Fig. 10. The impact of the storage conditions on the *in-vitro* release profile of theophylline from the Eudragit RL-based 3D printed tablets.

