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Utilization of PVP-PLA Combination in Fabricating Theophylline-loaded Filament for 3D Printing with Immediate Release Behavior

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ABSTRACT

Fused deposition modeling (FDM), known as a highly effective 3D printing technique, holds promise as an alternative approach to tablet manufacturing. While commonly employing thermoplastic polymers as starting materials, the integration of established pharmaceutical excipients remains unexplored. Polyvinyl pyrrolidone (PVP) is a frequently used excipient known for its potential to confer immediate-release properties to drugs. However, its suitability for extrusion is hindered by its thermal and melt-rheological properties. In contrast, polylactic acid (PLA), which has robust mechanical strength and thermal plasticity, was expected to overcome PVP's limitations. This study aims to obtain drug-loaded filaments using the combination of PVP and PLA through a hot-melt extrusion process, aiming for favorable mechanical properties and immediate-release behavior. Utilizing a twin-screw extruder, and theophylline was used as the model drug, three formulations were optimized –FP1, FP2, and FP3– containing 0%, 10%, and 20% theophylline, respectively. Subsequent evaluation including filament morphology, mechanical properties, drug content, and drug release profile, were performed to each filament. FP2 emerged as the most promising formulation, with 10.35% (w/w) drug load and over 95% drug released in an hour. All formulations exhibited slightly rough filament surfaces with diameters averaging 1.4-1.6 mm. Notably, an increase in the theophylline content correlates with the diminished filament strength, evident in reduced hardness and a rise in brittleness. This study emphasized the potential of PVP-PLA-based filaments for future pharmaceutical 3D printing formulations, providing immediate drug release characteristics.

Keywords: *3d printing; drug-loaded filament; fused deposition modeling; polylactic acid; polyvinyl pyrrolidone.*

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INTRODUCTION

Three-dimensional printing (3D printing) technology involves a series of processes that can print a 3D object layer by layer using a computer-aided design (CAD). This technology has been utilized for producing many types of products in various fields considering the ease and effectiveness of the process (Goole & Amighi, 2016; Tan et al., 2018). The application of 3D printing in producing pharmaceutical products is very interesting since it allows the manufacture of various designs with certain shapes, sizes, dosages, and drug release profiles based on the needs of each patient (Patrizia et al., 2018). Among all the 3D printing methods that have been developed, fused deposition modeling (FDM) is one of the most used techniques for producing drug products (Norman et al., 2017; Shende & Agrawal, 2018).

Thermoplastic polymers are generally applied for this method since they can melt while being heated and then immediately back to solid when the temperature is down so they can form each layer firmly (Goole & Amighi, 2016). Several studies have been carried out using many kinds of polymers that are usually used in pharmaceutical formulations such as cellulose derivatives (Boetker et al., 2016; Chai et al., 2017), acrylate derivatives (Gioumouxouzis et al., 2018; Sadia et al., 2018), as well as polyvinyl pyrrolidone (Ilyés et al., 2019; Okwuosa et al., 2016), containing single active pharmaceutical ingredient (API) (Fu et al., 2018; Jamróz et al., 2018) or combination of two or more APIs (Gioumouxouzis et al., 2018; Sadia et al., 2018).

PVP, a water-soluble polymer, has been widely used in pharmaceutical applications since it has good solubility-enhancing properties (Okwuosa et al., 2016). Using this hydrophilic polymer in fabricating tablets brings a great benefit, specifically to obtain the immediate release profile of drug substances. Although this polymer has been used in several studies (Ilyés et al., 2019; Solanki et al., 2018), our preliminary trial showed that the use of PVP alone did not flow well while being extruded. It has been explained in several reports that PVP is difficult to be extruded related to its thermal and rheological

behavior (Dedroog et al., 2019; LaFountaine et al., 2016). Another study reported that the melt viscosity of PVP is too high (>10.000 Pa.s) so it becomes unable to be extruded (Gupta et al., 2014).

PLA has been known for its numerous advantages such as high mechanical strength, good biodegradability, and thermal plasticity (Singla et al., 2017). The melt viscosity of PLA pellets, which is relatively low, was expected to improve the melt rheology of PVP. There has been no similar study that used the combination of these two polymers in fabricating filament for 3D printing. However, the superiorities of PLA are expected to outweigh PVP's limitations by combining them, mainly to get better mechanical strength and thermal plasticity to facilitate the extrusion process. PEG 4000 was added as the plasticizer due to the high melt viscosity of PVP during the heating process. The addition of PEG 4000 was intended to reduce the melt viscosity and lower the process temperature (Gupta et al., 2014; Li et al., 2014). Theophylline was chosen as the model drug since it is thermo-stable and has a relatively high melting temperature ranging from 270°-274°C, so it is predicted to be stable during the hot-melt extrusion (HME) process (Pietrzak et al., 2015).

In this study, the combination of PVP and PLA was used as filament forming material in fabrication of filaments with good mechanical strength and provide immediate drug release profile. The obtained theophylline-loaded filaments were characterized, including measurement of size (diameter), mechanical properties, observation of surface morphology, as well as the analysis of drug content and drug release profiles. Accelerated and long-term stability studies were also performed to determine the stability profile of the filaments and they were evaluated for physical characteristics, analysis of drug content and drug release profiles.

MATERIALS AND METHODS

The materials used were theophylline anhydrous (Shandong, China) which is donated by PT Dexa Medica, povidone K30S from BASF (Shanghai, China), PEG 4000 from PACC (Taiwan, China), PLA pellets from Suntran (Anhui, China), the standard reference of theophylline (BPOM, Indonesia), PLA filament (Shenzen, China), and distilled water (Brataco, Indonesia).

Preparation of PVP-PLA Mixture

PVP and PLA were weighed by the ratio 1:1 and PEG 4000 was added as much as 10% of the total polymer weight. Each batch which consists of 55 g of the mixture was mixed using Rheomixer® OS Polylab (Thermo Scientific, USA). The mixing process was performed at 160°C for 10 minutes with the rotor speed at 40 rpm. The torque of the rotor was monitored as the control parameter during the process, with the maximum value set at 80 Nm. All the solidified molten mixtures were ground thus resulting in a powdered polymeric mixture. The powdered mixtures were stored in a sealed plastic bag equipped with silica gel.

Preparation of Theophylline-loaded Filaments

Three formulations of filament namely FP1, FP2, and FP3 which vary in theophylline concentration were prepared through a hot-melt extrusion process using a twin-screw extruder PTW16 HAAKE Polylab (Thermo Scientific, USA). Each of the three filaments contains 0%, 10%, and 20% of theophylline, respectively. The required amount of API for each formulation was weighed and then pre-mixed with the previously prepared PVP-PLA mixture. Furthermore, the pre-mixed mixtures were extruded at a range of temperature between 135 – 180°C divided into 10 heating zones, with a screw speed of 50 rpm. The torque value of the extruder was monitored as the control parameter during the process, with a maximum value of 80 Nm. A 1.75 mm die was used to produce a controlled-size filament. To prevent water absorption, the obtained filaments were stored in a sealed plastic bag equipped with silica gel.

Physical Appearance and Diameter

The physical appearance of each filament was observed for the color and surface roughness. To confirm the effect of moisture content on the surface morphology, a moisture content analysis was performed for each formulation using a Moisture Balance (AMB 50, USA). The mean diameter of each filament was observed using a vernier caliper (Tricle Brand, China) at three points of measurement, which are in the middle, and both ends of the filament strands.

Morphology

The morphology of the filament was observed using a scanning electron microscope (SEM). The samples were coated using gold (Au) under vacuum and then examined using SEM microscope (JEOL ITO-200, Japan) at 15 kV to observe the outer surface and the cross-section of each filament.

Mechanical Properties

Samples from each of the extruded filaments were collected and cut into 5 cm length segments. The hardness and brittleness of each extruded filament were tested using a texture analyzer (TAXT.Plus Stable Micro System, Japan) with a three-point bend probe set. Each sample was placed on the sample holder with a 25 mm gap and the speed of the blades was set at 10 mm/s until they reached 15 mm below the samples (Zhang et al., 2017). The observed parameters were maximum force (g) to describe hardness and maximum displacement

distance (mm) to describe the brittleness of the filaments. The test was performed on three samples of each formulation.

Determination of Drug Content

The filaments were cut into 5 cm segments, each from the middle and both end parts of the filament and then ground into powder. The powder was weighed equal to ±14 mg of theophylline and solubilized in a 100 mL flask using distilled water. The flask was placed in an ultrasonic bath to help the solubilizing process for 30 minutes. The filtration step was performed using a Whatman filter with a pore size of 0.45 µm to separate the remaining undissolved polymer. The filtrate was then analyzed using UV-Vis spectrophotometer (Shimadzu, Japan) at 267 nm.

***In vitro* Drug Release Study**

Drug release from the filaments was determined using a USP-I dissolution apparatus (Erweka, Germany). Dissolution tests were conducted following the USP method for theophylline tablets with some modifications, using water as the dissolution medium. The samples were gathered from the middle part, and both ends of the filament, then they were weighed for an amount equivalent to 20 mg of theophylline and placed in the basket. Each test was performed in triplicate using 900 mL distilled water at 37°C ± 0,5°C with the speed set at 50 rpm. Samples were taken after 5, 10, 15, 30, 45, 60, 120, 180, and 240 minutes and then analyzed. The amount of theophylline released from the filaments was determined using UV-Vis spectrophotometer (Shimadzu, Japan) at 267 nm.

Stability Study

All formulated filaments were stored in a sealed plastic container at 40°C±2°C for 6 months for accelerated stability study, and the samples were taken at 0, 3, and 6 months after storage (ACCSQ-PPWG, 2018). The long-term stability study was performed by storing the samples at room temperature (±30°C) for 12 months. In this study, the samples were taken at 0, 6, and 12 months after storage and all samples were then evaluated for physical appearance, drug content, and drug release profiles.

RESULTS AND DISCUSSION

The filament manufacturing process was strated with a pre-extrusion phase, involving the production of a PVP-PLA polymeric blend using the Rheomixer®. This was essential due to the distinct physical states of PVP and PLA –PVP in powder form and PLA in pellet form– posing a potential challenge for extrusion. This step was also aimed to homogenize the polymers with PEG 4000 which is used as the plasticizer. The outcome was a yellowish-white powdered polymer mixture (depicted in Figure 1), ensuring a seamless transition to subsequent extrusion steps. This polymer blend could be directly mixed with the active ingredient, tailored to the desired concentration for further processes.

Figure 1. The powdered polymer mixture of PVP and PLA obtained from the mixing process using the Rheomixer®

During the mixing phase, the torque value was monitored as an indicator of material melting ease, influencing extrudability. Lower torque is preferable in pharmaceutical HME applications for enhanced throughput and better mixing (Alshahrani et al., 2015). In this study, a maximum torque of 80 Nm was set to control the filament extrusion. Initially, the torque steeply rose and then stabilized during the formulation's outset, with values noted for each formulation were 22 Nm for FP1, 29 Nm for FP2, and 35 Nm for FP3 (Table 1). The sharp rise at the beginning was associated with the rotor's response to partially melted materials, and it gradually decreased as the material melted (Fazli & Rodrigue, 2021). The addition of theophylline as a non-melting ingredient increased the torque value, and the same effect was observed as the concentration of theophylline increased. This might be related to the impact of non-melting particles added to the mixture seemed to augment the composite melt resistance and lead to a higher torque value (Barczewski et al., 2020).

The solidified molten mixtures were blended into powder using a standard blender. This powder was directly employed in the subsequent filament formulations steps, utilizing a twin-screw extruder with temperature ranging from 135° to 180°C across 10 heating zones along the extruder barrel. The lowest temperature was set for the

Table 1. Several data observed during the extrusion of the filaments

Formulation	Torque (Nm)	Yield (% w/w)	Moisture Content (%)
FP1 (0% API)	22	75.60	5.29±0.12
FP2 (10% API)	29	71.16	4.10±0.40
FP3 (20% API)	35	69.24	3.17±0.30

*The moisture content data were presented as the mean±standard deviation (n=3)

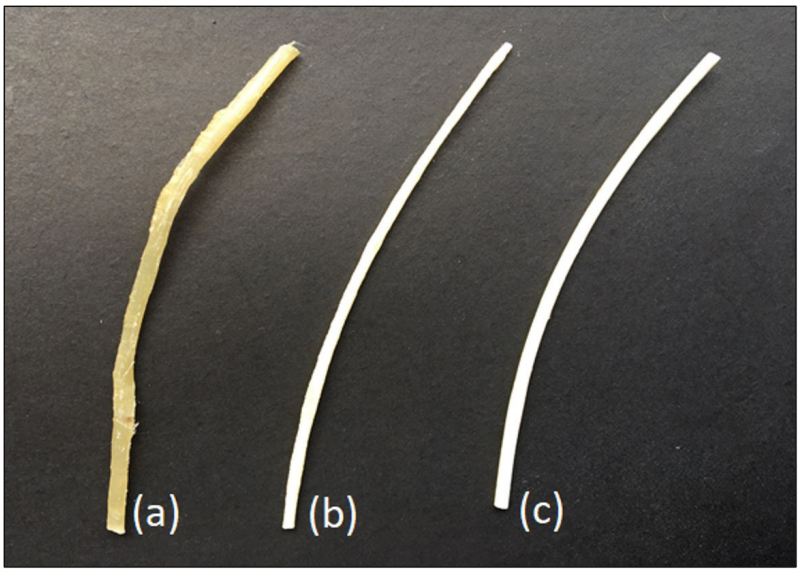

Figure 2. Images of filaments prepared by the HME process using a twin-screw extruder: (a)FP1 (no API), (b)FP2 (10% theophylline), and (c)FP3 (20% theophylline)

first zone, then it was increased up to the end of the extruder barrel. However, extruder die's temperature was lowered near the polymer's melting point (around 160°C) to facilitate rapid material solidification. Filament diameter was controlled by balancing extruder output rate with the conveyor speed.

Three formulations of yellowish-white filament with rough surfaces were successfully prepared using this method. It was observed that theophylline concentration influenced filament color, with FP3 exhibiting the whitest color, followed by FP2 and FP1 due to the greater theophylline content (Figure 2). The white color of theophylline, as a non-melting ingredient, impacted filament coloration. Higher API levels contributed to better filament appearance. Figure 2 showed that FP3 had a smoother surface than FP2, while FP1, devoid of API, displayed the roughest surface. Improved physical appearance, according to Alshahrani et al. (2015), might be linked to reduced moisture content. FP3, containing less PVP, displayed lower hygroscopicity, resulting in the lowest moisture content among formulations (Table 1).

SEM images were captured to observe both the external surface and cross-section of the filaments, illustrated in Figure 3. As depicted in Figure 3(a), the FP1 filament has a rough surface with internal voids. Additionally, elongated fiber-like textures were noted along the FP1 filament. Contrastingly, the presence of theophylline as a non-melting API, represented by FP2 and FP3, resulted in smoother surfaces (Figure 3(b) and 3(c)). This phenomenon aligns with a study employing metformin as a model drug and Affinisol™ 15LV as the polymer matrix, where drug concentration elevation correlated with enhanced surface smoothness (Mora-Castaño et al., 2022). Another study observed a similar trend, as theophylline addition up to 30% led to smoother filaments (Than & Titapiwatanakun, 2021). Those SEM images in Figure 3 also highlighted denser filaments with increased API content.

Overall, the extrusion process was relatively smooth, yielding values of 75.60%, 71.16%, and 69.24 for FP1, FP2, and FP3, respectively. The yield of extrusion process was calculated as the percentage of extruded materials to the total material fed into the extruder. These

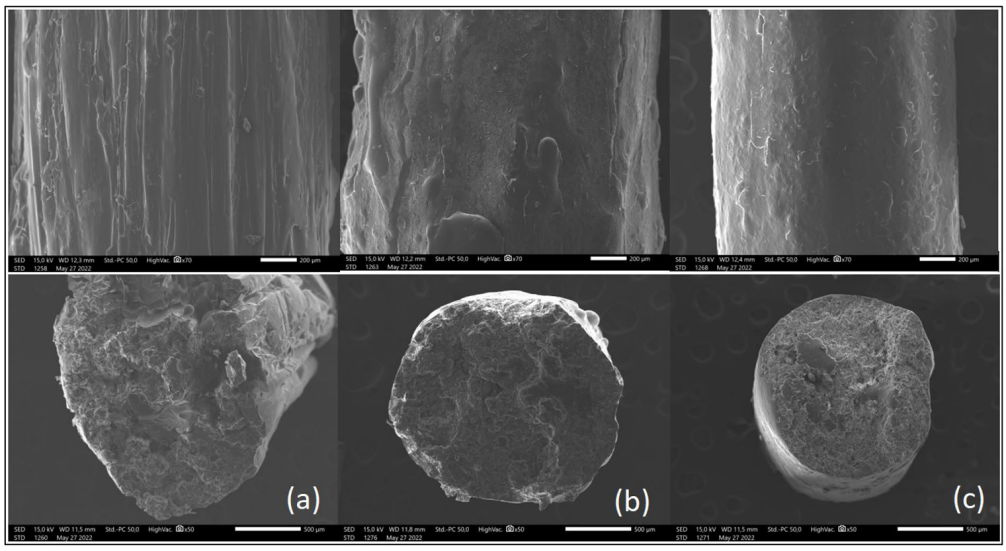

Figure 3. SEM images, with 70x magnification, of the surface (top row) and cross-section (bottom row) of filaments: (a)FP1, (b)FP2, and (c)FP3

yield values were not showing the best result, but it is understandable due to the limitation of the feeder to push the materials related to the amount of material fed into the extruder. In this study, each batch of the extrusion process only consisted of 55 g of the mixture which was considered low compared to the extruder's capacity (0.2-10 kg/h) and caused a lower extrusion force during the process. Unfortunately, technical constraints prevented the use of larger batches.

Another study reported that increased non-melting material content led to decreased process yields for two reasons. Firstly, the yield might be influenced by the quantity of material that can be processed by the extruder; less material led to lower yield. Second, insufficiently plasticized formulation with high solid levels presented higher material resistance during flow through the extruder barrel, especially if small-size dies are utilized (Schilling et al., 2010). Additionally, some extrudates from the initial extrusion couldn't be classified as viable product and were deemed process waste, thereby reducing the yield. Nonetheless, the result indicated that combining PVP with PLA enhanced PVP's extrudability compared to using the polymer alone.

The primary challenge during extrusion process was maintaining the intended filament diameter. Despite employing dies with a 1.75 mm diameter, the obtained filament diameter consistently fell below this size on average. Table 2 shows the results from the filaments' characterization including diameter, drug content, as well as the mechanical strength which is represented by the breaking force and breaking distance. This discrepancy might be attributed to imbalances between extrusion and conveyor speeds. If extrudate speed decreased suddenly while conveyor speed remained constant, the molten filaments could elongate, leading to reduced diameter. Geng et al. (2019) stated that a high extrusion speed might cause an uneven fluctuation in filament diameter, so it is important to find an optimized speed for the extrusion since it is highly associated with the extrusion force that occurs during the process. Feed rate also plays a huge impact on the extrusion force along the extruder barrel. Processing small batches resulted in feed rate instability, impacting the pressure. Unstable pressure directly affected the process, potentially altering filament morphology and diameter (Geng et al., 2019). The dies temperature also played a crucial role, impacting molten extrudates solidification time (Cardona et al., 2016; Yu et al., 2022). Failure to cool immediately could lead to filament elongation and diameter reduction due to its pliability.

However, there is still a range of tolerance set for filament diameter which is around 0.05 mm from the expected size (Cardona et al., 2016). Even so, this problem should be resolved because the inconsistency of diameter may cause a serious problem during 3D printing. A sudden diameter decrease could impede gear gripping while feeding to the 3D printer's nozzle and lead to printing failure. Otherwise, an unexpected diameter increase could render the filament incompatible with the printer nozzle, causing a sudden stop in the 3D printing process. Still, this diameter inconsistency problem can be mitigated by adjusting temperature and dies diameter or implementing automatic pulling while extruding. The extruder's orientation, whether horizontal or vertical, could also impact the filament outcomes (Cardona et al., 2016).

Table 2. Physical, mechanical, and chemical characteristics of the filaments prepared by HME

Formulation	Diameter (mm)	Drug content (% w/w)	Mechanical Strength	
			Force* (g)	Distance* (mm)
FP1 (0% API)	1.60 ± 0.16	-	2477.76 ± 134.78	7.17 ± 0.05
FP2 (10% API)	1.51 ± 0.17	10.35 ± 0.09	864.96 ± 18.08	7.67 ± 0.22
FP3 (20% API)	1.55 ± 0.16	18.25 ± 0.29	611.21 ± 43.96	8.31 ± 0.20

Data presented as the mean±standard deviation (n=3).
*Force value represents the hardness and displacement distance shows the brittleness of the filaments

Mechanical properties of the filament which are determined as hardness and brittleness were analyzed using a texture analyzer. These properties are considered important and related to the ability of the filament to be printed. The filament may get stuck in the nozzle or gripping gear if it is too flexible, so an adequate hardness value is needed. However, excessive brittleness could lead to breakage during printing. Thus, these problems may lead to printing failure (Đuranović et al., 2021). Hardness is represented by the maximum force value required for a specific deformation point, while brittleness corresponds to the maximum blade displacement during testing.

Results indicated that heightened theophylline content correlated with decreased breaking force, signifying reduced filament hardness and increased brittleness, evidenced in Table 2. Filament forces ranged from 611.21±43.96 g to 2477.76±137.78 g, with displacement values varying from 7.17±0.05 to 8.31±0.20 mm. FP1 exhibited the best mechanical strength, possibly due to the absence of active ingredients emphasizing the inherent polymer properties. Meanwhile, FP3, with the highest API concentration, demonstrated the weakest mechanical attributes. Theophylline, which is not melting within the extrusion temperature range, seemingly lowered filament mechanical strength, inducing brittleness and inhibiting printability (Katsiotis et al., 2023). This could arise from disrupted theophylline crystals altering the matrix, transitioning it from being elastic to becoming more rigid and friable (Tidau et al., 2019).

Commercial PLA filament, a preferred 3D printing material, was also evaluated for its mechanical properties. It exhibited a maximum force of 10,685.22±149.98 g and a maximum displacement of 7.94±0.04 mm. Compared to those results, the stiffness and brittleness of the formulated PVP-PLA-based filaments are good enough in terms of mechanical strength and are predicted to be suitable for 3D printing. Other studies noted that filaments with breaking distance exceeding 1 mm should possess sufficient stiffness and optimal feeding conditions (Zhang et al., 2017), while those with maximum displacement over 1.09 mm are deemed printable (Đuranović et al., 2021).

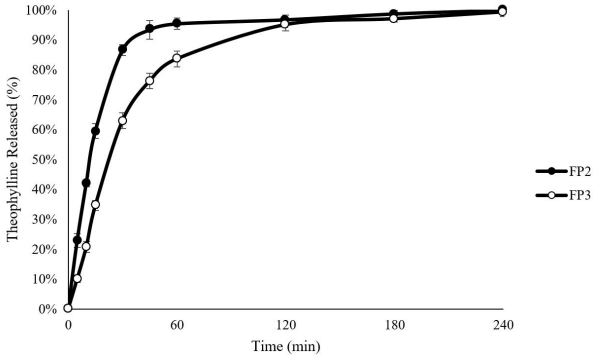

Figure 4. The release profile of theophylline from the FP2 and FP3 filaments determined using the type 1 dissolution apparatus in distilled water at 37°C ± 0,5°C; data presented as mean± SD(n=3)

The drug content in the filaments was determined through analysis of segmented filament sections taken from the middle and both ends of the strand. FP1, which contains no API, was excluded. Table 2 demonstrates that FP2 formulation contained 10.35±0.09% theophylline, yielding the closest result to the intended amount. Conversely, FP3, with 20% API, exhibited unexpectedly lower drug content at 18.25±0.29%. This discrepancy likely stemmed from extrusion problems; some theophylline powder remained in the feeding area, unable to be extruded and was discarded as waste. This is attributed to a significant portion of non-melting API, theophylline, supported by the data that shows that FP3 was the lowest yield among formulations. This indicates more residue in FP3's process compared to others. Nonetheless, with over 90% drug content relative to theoretical amount, it remains acceptable.

Both FP2 and FP3 filaments underwent drug release profile analysis, displayed in Figure 4. Employing an adapted method for theophylline tablet dissolution, theophylline release from the filaments was observed. As expected, all the filaments exhibited rapid release of the active ingredient, suggesting their potential in generating immediate-release 3D printed tablets. FP2 filament showed excellent release of theophylline, with over 90% of drug released within 45 minutes. On the

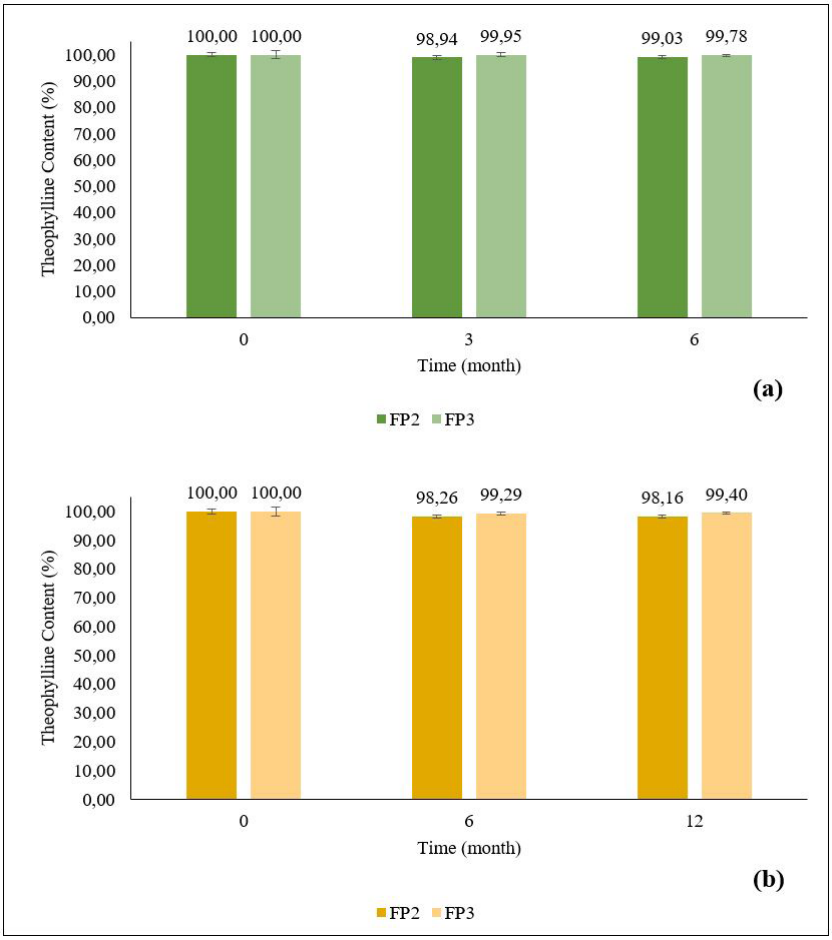

Figure 5. Theophylline content in each filament during the stability study after being stored at 40°C for 6 months (a) and at room temperature (30°C) for 12 months (b); Data presented as mean±SD (n=3)

other hand, FP3 exhibited a somewhat slower release profile, with around 75% drug released in 45 minutes, gradually increasing to 95% in 2 hours and reached 100% after 4 hours. This variation could stem from difference in PVP concentration in the formulations, as PVP has been employed to enhance dissolution for poorly soluble drugs (LaFountaine et al., 2016; Martinez-Marcos et al., 2016; Okwuosa et al., 2016). As the FP2 formulation has a bigger proportion of polymer compared to FP3, the surplus PVP offered a more pronounced dissolution-enhancing effect, resulting in a swifter initial release (Fu et al., 2018; Martinez-Marcos et al., 2016; Okwuosa et al., 2016).

To assure filaments' stability, an accelerated stability study was conducted. Three samples of each filament formulation were stored in an oven at 40°C ± 2°C for 6 months, with one of each sample examined at the initial, 3-month, and 6-month marks. Additionally, another three samples were stored at room temperature (±30°C), with one from each set evaluated at the initial, 6-month, and 12-month intervals. Figure 5 illustrates that the theophylline content within each filament exhibited minimal variation during storage, with a decrease of no more than 2% in the drug content for both accelerated and long-term stability studies. Figure 6 and Figure 7 show that the drug release profiles remained largely unchanged during stability assessments.

No substantial alterations were observed in the samples' physical attributes, except for a slight increase in surface stickiness, possibly associated with PVP's hygroscopic nature (Martinez-Marcos et al., 2016). According to the ASEAN Guideline on Stability Study of Drug Products, parameters indicative of significant changes during stability studies include alteration in physical attributes and functionality, formation of certain degradation products, and over 5% change in the drug assay from its initial value. The data indicate a decrease in drug content of less than 2%, and no noteworthy shifts in physical attributes throughout both accelerated stability (40°C±2°C for 6 months) and long-term stability (±30°C for 12 months) tests. Overall, all the filaments exhibit stability and fulfil the requirement for storage at room temperature for at least 2 years.

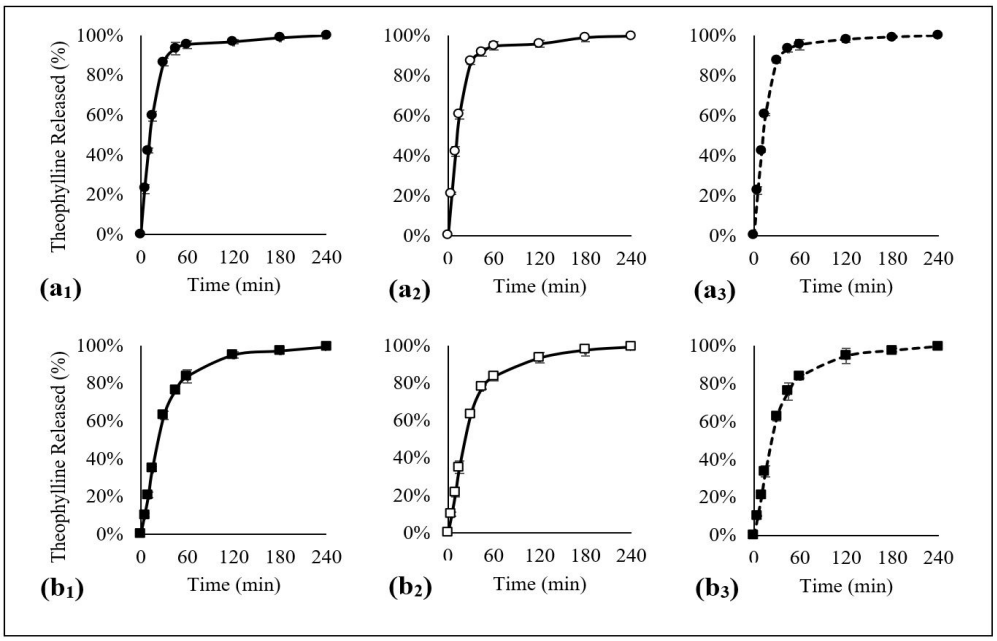

Figure 6. The drug release profile from the filaments during accelerated stability study at 40°C±2°C: (a1) FP2 at initial, (a2) FP2 after 3 months, (a3) FP2 after 6 months, (b1) FP3 at initial, (b2) FP3 after 3 months, and (b3) FP3 after 6 months. Data presented as mean±SD (n=3)

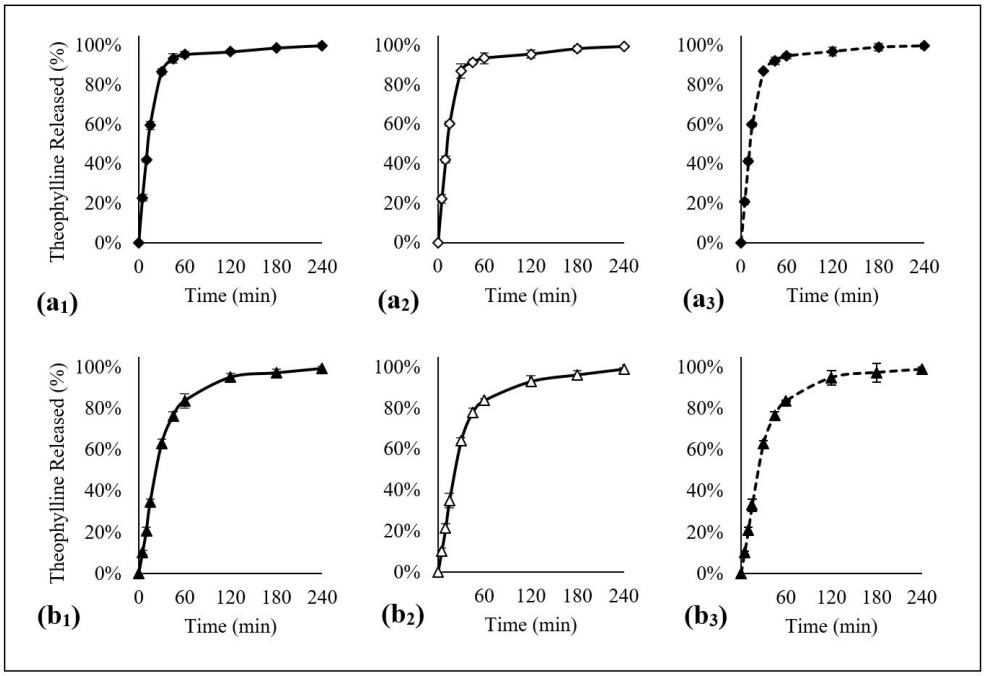

Figure 7. The drug release profile from the filaments during a long-term stability study at room temperature (±30°C): (a1)FP2 at initial, (a2)FP2 after 6 months, (a3)FP2 after 12 months, (b1)FP3 at initial, (b2)FP3 after 6 months, and (b3)FP3 after 12 months. Data presented as mean±SD (n=3)

CONCLUSION

In this study, three filament formulations were successfully produced using the combination of PVP and PLA, where two of these formulations integrated theophylline as the active ingredient. The combination of PVP with PLA effectively overcomes PVP's limitations related to challenging extrusion due to its melt-viscosity. The resulting filaments exhibited commendable mechanical properties, rendering them well-suited for 3D printing, albeit with room for enhancement in terms of diameter consistency. Notably, the integration of a hydrophilic polymer such as PVP within filament composition facilitated rapid drug release. Moreover, comprehensive accelerated and long-term stability studies affirmed the durability of the formulated filaments when stored at room temperature over a span of at least 2 years.

Looking ahead, there are exciting opportunities for further investigation. Improving filament diameter consistency is crucial for a smooth 3D printing process. This can be achieved by refining extrusion settings and exploring innovative methods. Additionally, exploring these filament formulations with various active pharmaceutical ingredients can expand their application in tailored drug delivery systems. Modifying drug release rates through polymer adjustments or using new additives is also worth exploring. Overall, this study forms the basis for developing drug-loaded filaments that are potentially used in production of pharmaceutical preparations using FDM 3D printing technique.

AUTHOR CONTRIBUTION

AK contributed to the study conception and design, literature search, data acquisition, data analysis, manuscript preparation, and editing. Meanwhile, SS contributed to conceiving the concept, supervised the work and data analysis, and gave the provision of final approval to the manuscript.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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