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Chemotherapeutic Drug Delivery from 3D-Printed Biodegradable Polymer for Breast Cancer Treatment

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Abstract: The controlled delivery of chemotherapeutic agents is critical for enhancing therapeutic efficiency and minimizing side effects in cancer treatment. This study investigates the drug release, thermal stability, and mechanical performance of polylactic acid (PLA) resin doped with boric acid (H_3BO_3) and 5-fluorouracil (5-FU), fabricated through digital light processing (DLP) 3D printing technology. Samples with various concentrations of 5-FU (0-30 wt.%) and 1 wt.% boric acid were prepared and characterized structurally, mechanically, thermally, and biologically. Incorporation of 1% H_3BO_3 improved compressive strength significantly by approximately 13%, reaching 55.04 MPa compared to 48.86 MPa in pure PLA, and enhanced elongation at break from 5.75% to 7.24%. Thermally, boric acid slightly increased the glass transition temperature from 58°C to 61°C and melting temperature from 179°C to 184°C, indicating improved polymer stability. Swelling behavior peaked around day 9 with up to 50% water uptake for some formulations. Moreover, drug release profiles exhibited sustained release over 15 days, reaching a maximum release amount of 4.24% on day 9 at low drug loadings. Cytotoxicity tests against MCF-7 breast cancer cells demonstrated significant reductions in viability, notably achieving 33.39% after 15 days at the highest 5-FU concentration (30%). These findings suggest that boric acid and 5-FU-doped PLA composites produced via 3D printing offer promising mechanical and controlled-release drug delivery characteristics suitable for developing advanced biomedical applications, particularly in targeted cancer therapy.

Keywords: Controlled drug release, cancer, 5-fluorouracil, boric acid, polylactic acid (PLA).

Meme Kanseri Tedavisi için 3D Baskılı Biyobozunur Polimerden Kemoterapötik İlaç Salınımı

Öz: Kemoterapötik ajanların kontrollü dağıtımı, kanser tedavisinde terapötik etkinliği artırmak ve yan etkileri en aza indirmek için kritik öneme sahiptir. Bu çalışma, dijital ışık işleme (DLP) 3D baskı teknolojisiyle üretilen borik asit (H_3BO_3) ve 5-florourasil (5-FU) ile katkılanmış polilaktik asit (PLA) reçinesinin ilaç salımını, termal kararlılığını ve mekanik performansını araştırmaktadır. Çeşitli 5-FU (%0-%30 ağırlıkça) ve %1 ağırlıkça borik asit konsantrasyonlarına sahip numuneler hazırlandı ve yapısal, mekanik, termal ve biyolojik olarak karakterize edildi. %1 H_3BO_3 eklenmesi, basınç dayanımını yaklaşık %13 oranında önemli ölçüde iyileştirerek saf PLA'daki 48,86 MPa'ya kıyasla 55,04 MPa'ya ulaştı ve kopma anındaki uzamayı %5,75'ten %7,24'e çıkardı. Termal olarak, borik asit cam geçiş sıcaklığını 58°C'den 61°C'ye ve erime sıcaklığını 179°C'den 184°C'ye hafifçe artırarak polimer kararlılığında iyileşme gösterdi. Şişme davranışı, bazı formülasyonlar için %50'ye kadar su alımıyla 9. gün civarında zirveye ulaştı. Aynı zamanda, ilaç salım profilleri 15 gün boyunca sürekli salım sergiledi ve düşük ilaç yüklemelerinde 9. günde %4,24'lük maksimum salım miktarına ulaştı. MCF-7 meme kanseri hücrelerine karşı sitotoksisite testleri önemli canlılık azalmaları gösterdi, özellikle en yüksek 5-FU konsantrasyonunda (%30) 15 gün sonra %33,39 canlılığa ulaşıldı. Bu bulgular, 3B baskı yoluyla üretilen borik asit ve 5-FU katkılı PLA kompozitlerinin, özellikle hedefli kanser tedavisinde ileri biyomedikal uygulamalar geliştirmek için uygun, umut verici mekanik ve kontrollü salımlı ilaç verme özellikleri sunduğunu göstermektedir.

Anahtar kelimeler: Kontrollü ilaç salınımı, kanser, 5-florourasil, borik asit, polilaktik asit (PLA).

1. Introduction

Cancer continues to pose a significant global health challenge, remaining one of the leading causes of morbidity and mortality worldwide. This underscores the urgent need for continuous advancements in cancer treatments aimed at improving patient outcomes (Wu et al., 2024). A highly effective cancer treatment strategy involves accurately targeting therapeutic agents to tumor sites to maximize drug efficacy while minimizing systemic toxicity. Controlled drug delivery systems have emerged as essential tools in achieving this objective, significantly enhancing the safety and effectiveness of cancer therapies (Chavoshi et al., 2019). These systems ensure therapeutic drugs reach their intended targets, thereby reducing adverse effects commonly associated with systemic drug administration.

Among the materials used extensively for controlled drug delivery, polylactic acid (PLA) stands out due to its excellent biodegradability, biocompatibility, and versatile mechanical properties. PLA's suitability for biomedical applications, particularly drug delivery systems, is well-established in the scientific literature, which documents its favorable degradation kinetics and tissue compatibility (Balla et al., 2021; Pirkani et al., 2024). Leveraging these advantageous characteristics, researchers continue to develop advanced polymer-based systems designed to enhance therapeutic efficacy while minimizing associated side effects.

Recent advances in additive manufacturing technologies, particularly digital light processing (DLP)

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3D printing, have opened new avenues for fabricating customized polymer scaffolds with intricate geometries and precise internal architectures (Yuan et al., 2024; Wang et al., 2023). This technology facilitates the direct integration of bioactive agents within polymer scaffolds, enabling controlled and targeted drug delivery directly to tumor sites. One prominent chemotherapeutic agent extensively utilized in these systems is 5-fluorouracil (5-FU), known for its effective anticancer properties against cancers such as breast and colorectal cancer (Jubeen et al., 2022; Hu et al., 2023). Studies demonstrate that embedding 5-FU within PLA scaffolds significantly enhances localized therapeutic effects and reduces systemic chemotherapy-associated side effects, highlighting the critical role of localized drug delivery approaches (Yun et al., 2017; Carotenuto et al., 2023).

Additionally, recent research has explored the benefits of incorporating additives such as boric acid (H_3BO_3) into polymer matrices. Boric acid has been shown to enhance key polymer properties, including thermal stability, mechanical strength, and controlled degradation behavior, which are essential for biomedical applications (Avci et al., 2024). These improvements directly impact drug release profiles and scaffold performance, potentially leading to better therapeutic outcomes and enhanced patient safety.

This study aims to investigate the effects of incorporating 1% boric acid and various concentrations of 5-FU into PLA scaffolds fabricated through DLP 3D printing. The innovative approach presented systematically evaluates how these additives influence the scaffolds' structural, thermal, mechanical, swelling, degradation, drug release, and cytotoxic properties. Understanding these interactions is crucial for advancing targeted drug delivery technologies, improving therapeutic effectiveness, and offering substantial clinical advantages in cancer treatment (Croitoru et al., 2021). Through such approaches, this research aims to facilitate the development of efficient drug delivery scaffolds capable of providing effective localized treatment while significantly reducing systemic chemotherapy-related adverse effects.

2. Material and Methods

2.1. Sample Preparation

In this study, polylactic acid (PLA) resin (PH100 eResin-PLA Pro, eSUN, China) was used as the primary material, while boric acid (H_3BO_3, 99% purity, Sigma-Aldrich, St. Louis, MO, USA, Cat. No: B0394) and 5-fluorouracil (5-FU, $C_4H_3FN_2O_2$, Sigma-Aldrich, St. Louis, MO, USA, Cat. No: F6627) served as additives. Specifically, 5-FU was incorporated into the PLA resin as a chemotherapeutic agent to enable controlled drug release with the exact compositions detailed in Table 1. The H_3BO_3 powder and 5-FU drug, weighed according to the compositions specified in Table 1, were gradually added into the UV-curable PLA resin. Eight different sample formulations were prepared for this purpose: B0F0 contained pure PLA without any additives; B0F10, B0F20, and B0F30 included 10, 20, and 30 wt.% 5-FU respectively without boric acid; B1F0 contained 1 wt.% H_3BO_3 alone; and B1F10, B1F20, and B1F30 included both 1 wt.% H_3BO_3 and 10, 20, and 30 wt.% 5-FU, respectively. The resulting mixture was homogenized using a magnetic stirrer at 500 rpm for 30 minutes at room temperature. Subsequently, this prepared resin mixture was employed to fabricate samples using a digital light processing (DLP) 3D printer (Elegoo, China) intended for characterization, mechanical testing, cytotoxicity evaluation, and drug release analyses. After the 3D printing process was completed, residual resin on the sample surfaces was removed by immersion in an ethanol-filled ultrasonic bath for 30 seconds. Following this cleaning procedure, the printed parts were fully cured and hardened by exposure to UV light in a curing device for 1 minute (Aktas et al., 2024).

Table 1. Compositions and densities of prepared samples.

Sample code	Polylactic acid (PLA), wt.%	Boric acid (H_3BO_3), wt.%	5-Fluorouracil (5-FU), wt.%	Density (g/cm³)
B0F0	100	0	0	1.153
B0F10	90	0	10	1.171
B0F20	80	0	20	1.098
B0F30	70	0	30	1.175
B1F0	99	1	0	1.162
B1F10	89	1	10	1.189
B1F20	79	1	20	1.064
B1F30	69	1	30	1.104

2.2. Structural, Thermal, and Mechanical Characterization

M_t denotes the drug mass measured at time t (mg), while M_0 represents the initially loaded drug mass (mg). Structural analysis of the samples was performed using a Bruker Hyperion 3000 Fourier Transform Infrared Spectroscopy (FTIR) system, covering a wavenumber range of 400–4000 cm^{-1} (Aktas et al., 2019). The thermal properties of the produced samples were investigated via differential thermal analysis (DTA/TG). Approximately 10 mg of powdered pure PLA and H_3BO_3-doped PLA were placed in a platinum crucible and heated to 600°C at a rate of 10°C/min under a nitrogen atmosphere (Rasul et al., 2025). The tensile and compressive strengths of the produced samples were measured using a computer-controlled universal testing machine equipped with a 10 kN load cell. The tensile and compressive strength values were obtained by averaging the results from five individual samples (Demircan et al., 2020; Alkabbanie et al., 2024).

2.3. Physical Characterization: Density, Swelling, and Degradation

The densities of the samples fabricated by 3D printing were measured using the Archimedes method as described previously (Aktas et al., 2024).

Swelling tests were conducted by immersing the samples in phosphate-buffered saline (PBS) (pH: 7.4) for durations of 1, 5, 9, and 15 days and the swelling rates were determined according to Eq. 1 (Mamidi et al., 2019).

$$Swelling\ Rate\ (\%) = 100 \times (W_w - W_d)/W_d \quad (1)$$

Where W_d represents dry weight, W_w is measured at the end of the specified periods.

Biodegradation tests were performed by placing

samples in PBS for 1, 5, 9, and 15 days, after which their masses were recorded, and biodegradation amounts were calculated as weight loss (%) using Eq. 2 (Chu et al., 2018).

$$Weight\ Loss\ (\%) = 100 \times (W_0 - W_t)/W_0 \quad (2)$$

W_0 is the sample's initial weight (mg) and W_t is the weight measured after drying the samples at various time intervals (mg).

2.4. Drug Release Study

The concentration of 5-fluorouracil (5-FU) released from the samples was determined using UV spectrophotometry at a wavelength of 266 nm (MultiSkan, Thermo Scientific, USA). A stock solution of 5-FU was initially prepared in phosphate-buffered saline (PBS) at a concentration of 1 mg/mL. From this stock, a series of standard solutions were prepared at concentrations of 2, 4, 6, 8, 10, 12 and 14 µg/mL to generate a calibration curve (Samy et al., 2022). For the release study, the samples were immersed in equal volumes of PBS and incubated at predetermined time intervals (1, 5, 9, and 15 days). At each time point, the absorbance of the PBS solutions was recorded at 266 nm and the corresponding 5-FU concentrations were determined using the calibration curve. The percentage of drug release was then calculated using Equation (3) as described by Mamidi et al. (2019).

$$Released\ drug\ amount\ (\%) = 100 \times (M_t/M_0) \quad (3)$$

M_t represents the amount of drug released (mg/mL), while M_0 denotes the initial amount of drug loaded (mg/mL).

2.5. Cytotoxicity Analysis

Cytotoxicity analyses were conducted on MCF-7 breast cancer cells. Initially, the samples were incubated in a complete cell culture medium (DMEM/F12 supplemented with 10% FBS and 1% Penicillin/Streptomycin, Gibco, Thermo Fisher Scientific Inc., Waltham, MA USA, Cat. Numbers: 11320033, A5670201, 15140122) at 37°C for 1, 5, 9, and 15 days. After the incubation period, the collected media were applied to the cells and cell viability was assessed using the MTT assay (Sigma-Aldrich, St. Louis, MO, USA, Cat. No: M5655) following the method described previously (Gumushan Aktas & Altun, 2016; Gumushan Aktas & Akgun, 2018). 5-FU (25µM) was used as positive control. The concentration was chosen according to the literature (Azimi et al., 2022) and our preliminary studies. Absorbance measurements, reflecting the density of viable cells, were taken at 570 and 690 nm. Cell viability (%) was calculated based on the absorbance values. All experiments were performed in triplicate to ensure reproducibility. Differences between groups were statistically evaluated with One-Way ANOVA and Student's *t*-test using the GraphPad Prism 10 software.

3. Results and Discussion

3.1. Structural, Thermal, and Mechanical Characterization

The FT-IR spectrums of $H3BO_3$ and 5FU-doped PLA are shown in Figure 1. The bands observed between 3800-3600 cm^{-1} are due to OH groups. The main component PLA in this study shows characteristic stretching frequencies for C=O, $-CH_3$ asymmetric, $-CH_3$ symmetric, and C–O at 1719, 2994, 2900, and 1062 cm^{-1} respectively (Chieng et al., 2014). The characteristic bands at 1615 cm^{-1} and 1515 cm^{-1} are associated with amide I due to the asymmetric coupling of C=O stretching vibration of the peptide bond and amide II (N–H bending/C–N Stretching) (Rani et al., 2018). The band seen at 1444 cm^{-1} is due to C=C vibration. The C—O—C bond has been seen at around 1021 cm^{-1}. The peak at around 1367 cm^{-1} refers to the vibration of the pyrimidine compound confirming 5-fluorouracil. Further, the peak at around 1235, 1515, and 2353 cm^{-1} belong to C—F stretching or C—N stretching and N—H in plane bending, CH3–N and N—H stretch in 5FU (Mngadi et al., 2021; Olukman et al., 2012). The vibration, which is the presence of Amide IV, has been seen at 675 cm^{-1} and assigned to N–C=O in plane bending (Rani et al., 2018).

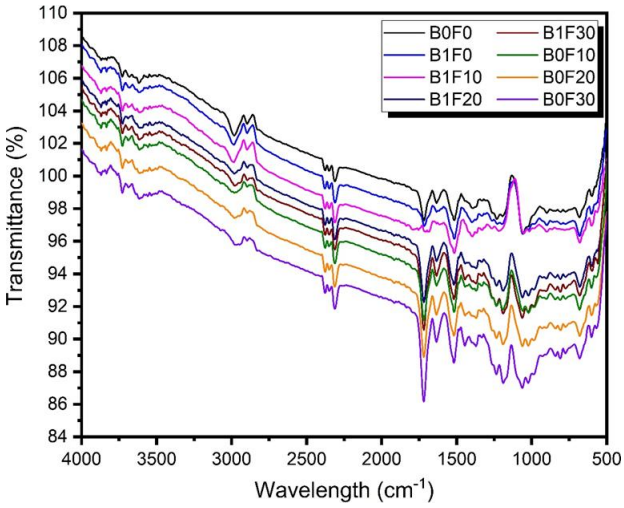

Figure 1. The FT-IR Spectra of PLA samples.

The results obtained from DTA/TG analyses (Fig. 2) demonstrate that incorporating 1% H_3BO_3 into PLA slightly influences the polymer's thermal properties. Specifically, the glass transition temperature (T_g) increased from 58°C to 61°C, indicating improved thermal stability and reduced chain mobility within the polymer structure due to the presence of boric acid. This finding aligns well with previous studies that reported similar enhancements in T_g upon the addition of fillers or additives that restrict polymer chain mobility (Nofar et al., 2019; Rasal et al., 2010). Moreover, the melting temperature (T_m) also rose from 179°C to 184°C with the addition of H_3BO_3, confirming enhanced crystalline stability in the polymer matrix. This observation is consistent with the existing literature where boron-based additives were shown to enhance crystallinity and overall thermal performance in biodegradable polymers (Avci et al., 2024). Such improved crystallinity is beneficial for drug delivery applications as it can facilitate more controlled and sustained drug release by decreasing polymer erosion rates under physiological conditions (Middleton & Tipton, 2000).

The tensile and compressive strength properties of 3D-printed pure PLA (B0F0) and PLA samples containing 1 wt% H_3BO_3 additive (B1F0) were performed to assess the effect of H_3BO_3 incorporation on mechanical performance. The results, presented in Table 2 and Figure 3, clearly demonstrate how the addition of H_3BO_3 influences the tensile and compressive behavior of PLA. The tensile strength of the pure PLA sample (B0F0) was measured as 24.45 MPa, while the H_3BO_3-added PLA sample (B1F0) exhibited a slightly improved tensile strength of 25.30

MPa. This increase in tensile strength can be attributed to the dispersion of H_3BO_3 particles within the PLA matrix that likely enhances interfacial bonding and stress transfer. Studies in the literature have shown that adding ceramic or inorganic fillers can enhance the mechanical properties of polymer matrices by reinforcing the polymer structure and restricting molecular mobility (Kangallı et al., 2022).

Table 2. Tensile and compressive strength data of PLA samples with and without H_3BO_3 additive.

Sample code	Tensile strength (MPa)	% Elongation at break	Elastic modulus (GPa)	Compressive strength (MPa)
B0F0	24.45 ± 1.07	5.75 ± 0.55	0.71 ± 0.068	48.86 ± 0.85
B1F0	25.30 ± 1.85	7.24 ± 2.47	0.69 ± 0.047	55.04 ± 5.68

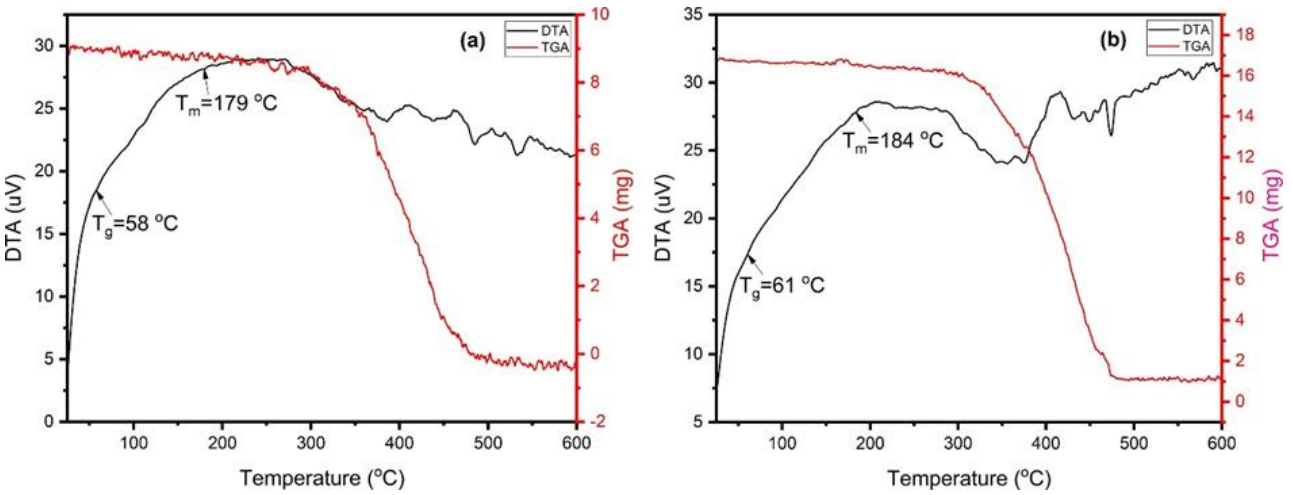

Figure 2. DTA/TG analyses of samples; (a) PLA, (b) 1 wt% H_3BO_3-doped PLA

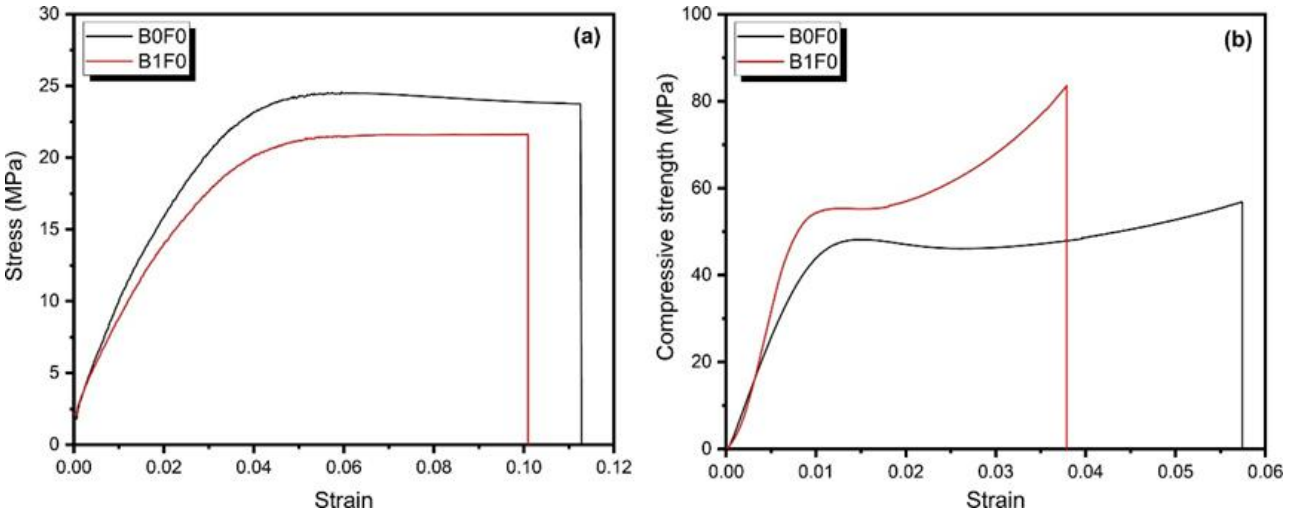

Figure 3. Mechanical properties of the samples: (a) Tensile strength, (b) Compressive strength.

The elongation at break significantly increased from 5.75% in pure PLA to 7.24% in the H_3BO_3-added sample. This improvement suggests that the presence of H_3BO_3 contributes to a more flexible polymer network possibly due to the plasticizing effect or the formation of a composite structure that allows more deformation before fracture. Similar findings have been reported by Avci et al. (2024) who observed increased elongation in PLA composites reinforced with boron-containing compounds. However, the elastic modulus of the PLA sample slightly decreased from 0.71 GPa in pure PLA to 0.69 GPa in the H_3BO_3-added PLA. This reduction indicates that the incorporation of H_3BO_3 might reduce the stiffness of the composite possibly due to the formation of softer interphases within the polymer matrix. Regarding compressive strength, the pure PLA sample demonstrated a value of 48.86 MPa, while the H_3BO_3-added sample showed a notable improvement to 55.04 MPa. This increase of approximately 13% indicates that the presence of H_3BO_3 enhances the material's resistance to compressive forces potentially due to the filler-induced densification and improved load distribution.

In conclusion, the incorporation of H_3BO_3 into PLA via 3D printing demonstrates a positive impact on compressive strength and elongation at break while maintaining tensile strength at an acceptable level.

3.2. Swelling and Degradation

Figure 4 provides quantitative swelling data, revealing notable differences among samples over time. Initial observations (day 1) indicated that PLA samples without additives (B0F0) exhibit relatively low swelling ratios,

around 12.98%, whereas the addition of 5-FU alone (B0F10, B0F20, and B0F30) significantly enhances water absorption capabilities (up to 35.00%). Remarkably, PLA samples containing only 1% H_3BO_3 without 5-FU (B1F0) showed elevated swelling ratios (29.20%), inherent hydrophilic properties of boric acid. The swelling ratios varied dynamically over time, peaking around day 9 for several formulations, such as B0F10 and B0F20, with values reaching up to 50.00% and 39.24%, respectively. This temporal fluctuation is characteristic of polymeric drug delivery systems and is influenced by the continuous interplay between water uptake and the structural integrity of the polymer matrix (Dash & Konkimalla, 2012). Interestingly, samples combining both H_3BO_3 and varying amounts of 5-FU (B1F10, B1F20, B1F30) exhibited inconsistent swelling behaviors over time, suggesting complex interactions between the polymer, drug, and additive. For instance, sample B1F20 demonstrated an unusually low initial swelling ratio (7.60% on day 1), slightly increasing to 15.93% by day 15. Such variations may result from competition between drug-polymer interactions and H_3BO_3-induced structural alterations affecting water diffusion pathways (Byun et al., 2008).

Figure 5 illustrates the degradation behavior of PLA samples incorporating various concentrations of 5-FU, with or without boric acid. On day 1, the most pronounced degradation (27.69%) was observed in PLA samples containing 10% 5-FU but no boric acid (B0F10), implying that the absence of boric acid may facilitate more extensive water infiltration and initial hydrolytic activity. In contrast, the 1% H_3BO_3 (e.g., B1F0, at 6.70%) might stabilize the polymer against early-phase degradation (Tawiah et al., 2018; Byun et al., 2008). Over the 15-day study period, the progression of degradation might be influenced by multiple factors, including water penetration, polymer hydrolysis, and concurrent drug release. By day 15, samples with 5-FU content, such as B0F10 (28.46%) and B0F30 (18.22%), show markedly greater breakdown, reinforcing the notion that drug loading can enhance the hydrophilicity and susceptibility to hydrolysis of polymer (Singh, & Lillard, 2009; Liechty et al., 2010). Meanwhile, formulations that combine 1% H_3BO_3 and increased levels of 5-FU (e.g., B1F20 and B1F30) have exhibited unique degradation patterns, pointing to potential synergistic or antagonistic interactions between the additive and the drug.

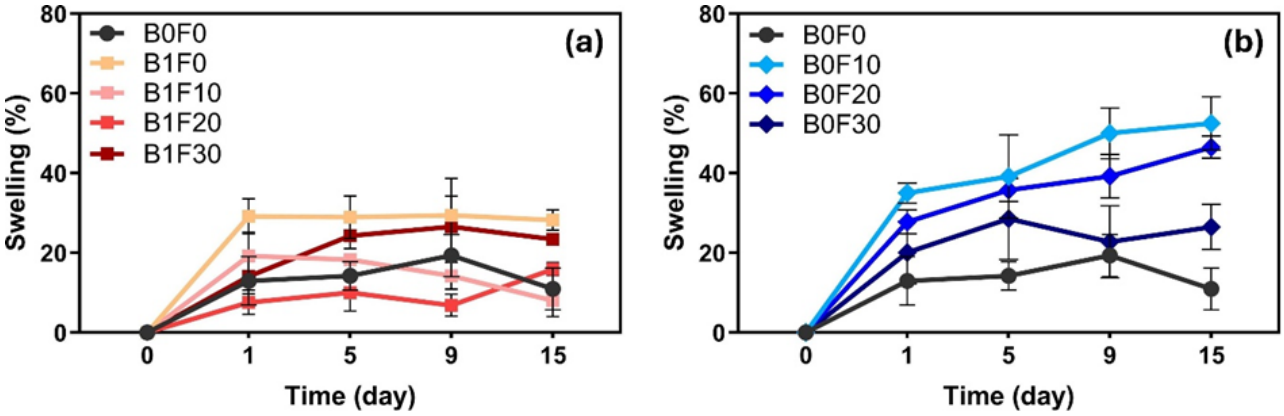

Figure 4. Time-dependent swelling ratios of the samples: (a) PLA samples containing 1% H_3BO_3 and varying concentrations of 5-FU (10, 20, 30 wt%), (b) PLA samples containing varying concentrations of 5-FU (10, 20, 30 wt%).

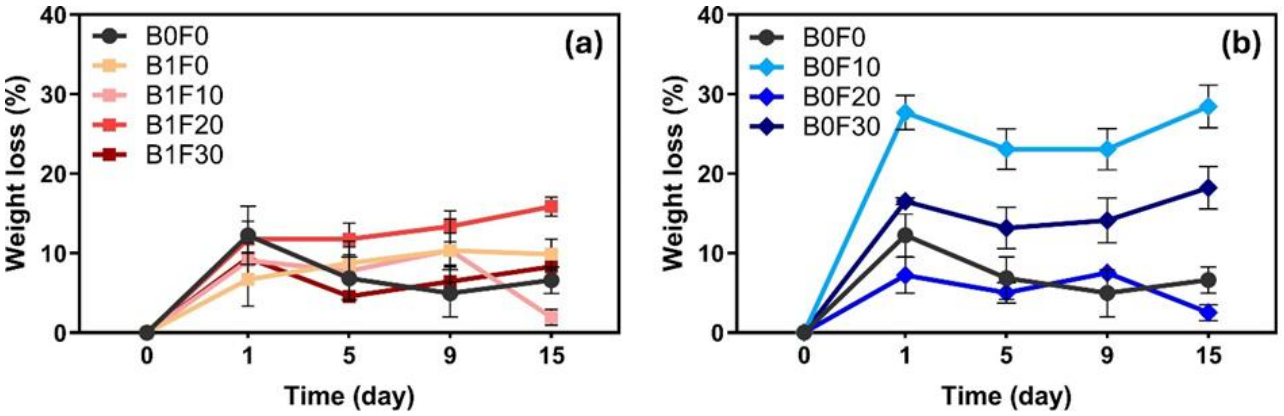

Figure 5. Degradation profiles over time of PLA samples loaded (a) with (b) without 1% H_3BO_3, and varying amounts of 5-FU.

3.3. Drug Release Profile

The drug release profiles reveal that the rate of 5-FU release from the samples is significantly influenced by both the concentration of 5-FU and the presence of H_3BO_3 (Fig. 6). PLA samples containing 1% H_3BO_3 (B1F10, B1F20, B1F30) consistently showed higher drug release rates compared to their counterparts without H_3BO_3 (Fig. 6a-c). This increment likely may result from reducing polymer matrix rigidity induced by boric acid. On the first day, sample B1F20 exhibited the highest initial drug release percentage (2.32%). Interestingly, increasing the concentration of 5-FU to 30% (samples B1F30 and B0F30) did not enhance the initial drug release. This suggests a possible saturation effect or altered polymer-drug interactions at higher concentrations as supported by previous findings on PLA-based systems (Proikakis et al., 2006; Lasprilla et al., 2012). Between days 5 and 9, drug

release steadily increased for all formulations (Fig. 6d-e) with samples containing H_3BO_3 consistently showing slightly higher release percentages than their counterparts lacking boric acid (Fig. 6a-c). For instance, after 9 days, sample B1F10 demonstrated the highest release amount (4.24%) compared to 3.30% observed for sample B0F10 without H_3BO_3. Such findings align with the literature indicating that incorporating additives such as boric acid can modify polymer matrix interactions, potentially enhancing drug diffusion by altering polymer hydrophilicity or network structure (Makadia & Siegel, 2011; Gagliardi et al., 2021). Among the samples without H_3BO_3 (B0F10, B0F20, B0F30), the B0F10 sample showed the highest release amount (3.30%) after 9 days, while the B0F30 sample exhibited a significantly lower release of 2.33% at the same time point (Fig. 6e). This pattern is consistent with other polymeric drug delivery systems where the encapsulated drug diffuses gradually through the polymer matrix over time (Lee & Yeo, 2015). Such behavior aligns with previous reports indicating that higher drug loading can reduce initial release rates due to denser packing or agglomeration of drug particles within the polymer matrix which limits the diffusion of the drug (Herdiana et al., 2022; Vlachopoulos et al., 2022).

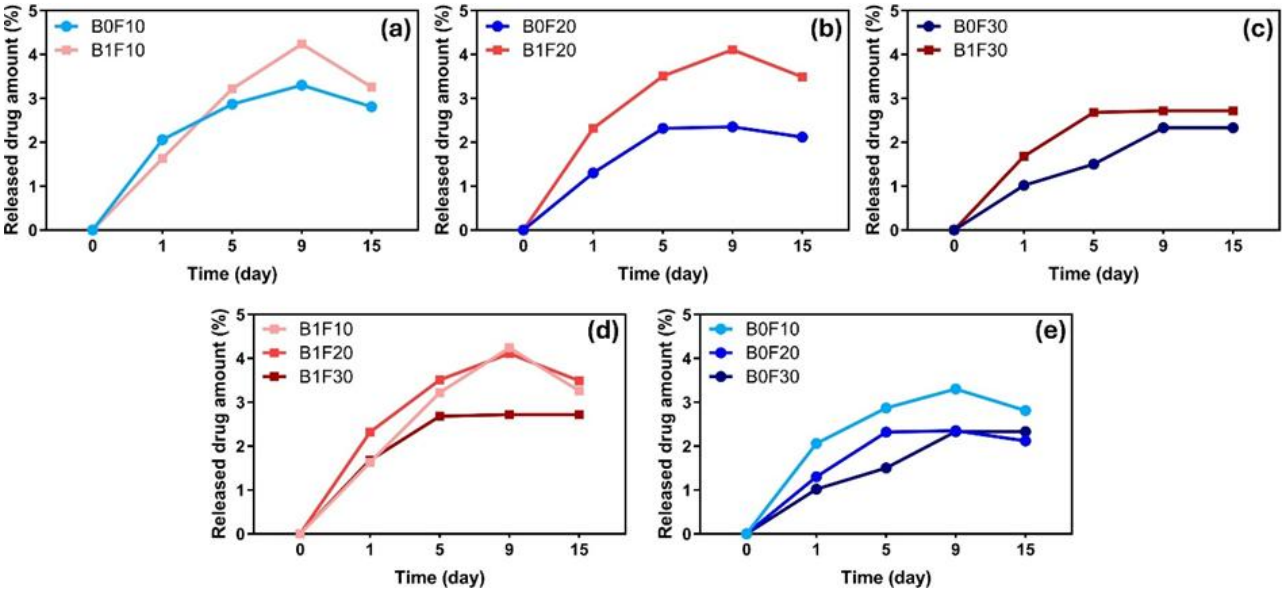

Figure 6. Drug release profiles over time for PLA samples doped with 5-FU.

3.4. Cytotoxic Activity

In this part of the study, the cytotoxic effects and drug release performance of polylactic acid (PLA) scaffolds containing different concentrations of 5-fluorouracil (5-FU) and boric acid (H_3BO_3) were evaluated using MCF-7 breast cancer cells. Cell viability was assessed at four time points (days 1, 5, 9, and 15) using the MTT assay and the results are presented in Figure 7.

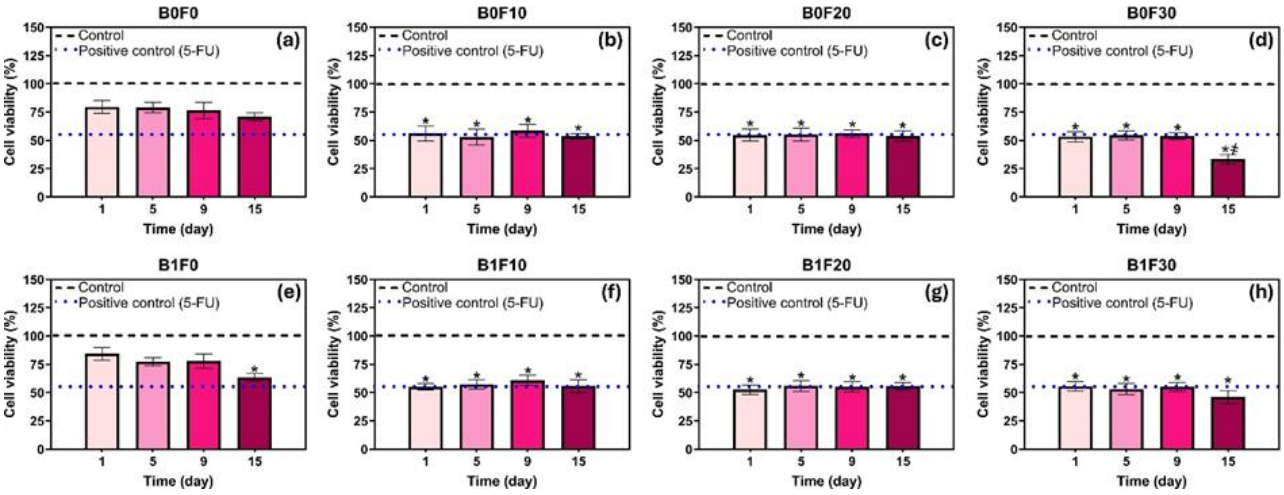

Fig. 7. Cell viability (%) measured on MCF-7 breast cancer cells exposed to samples (a) undoped PLA, (b)-(d) different ratios (10%, 20%, 30%) of 5-FU; (e)-(h) H_3BO_3 (1%) and different ratios (10%, 20%, 30%) of 5-FU for different periods of time (1, 5, 9, 15 days).

*: Statistically significant difference between test and control groups ($p<0.05$).

≠: Statistically significant difference between test and positive control (5-FU) groups ($p<0.05$)

Undoped PLA (B0F0) exhibited consistently high cell viability across all time points, maintaining 79.60% viability on day 1 and 70.96% on day 15 (Fig. 7a, Fig. 8a), confirming its excellent biocompatibility. This observation is consistent with previous findings that PLA is well-tolerated in vivo and degrades gradually into non-toxic by-products. For instance, Majola et al. (1991) observed that PLA scaffolds implanted in rat femurs were

biocompatible and slowly absorbed over 1 to 48 weeks. Similarly, Robert et al. (1993) demonstrated that PLA membranes implanted subcutaneously in rats maintained biodegradability and compatibility. Middleton and Tipton (2000) further emphasized that PLA's slow hydrolysis kinetics and inert degradation products make it an ideal matrix for drug delivery systems.

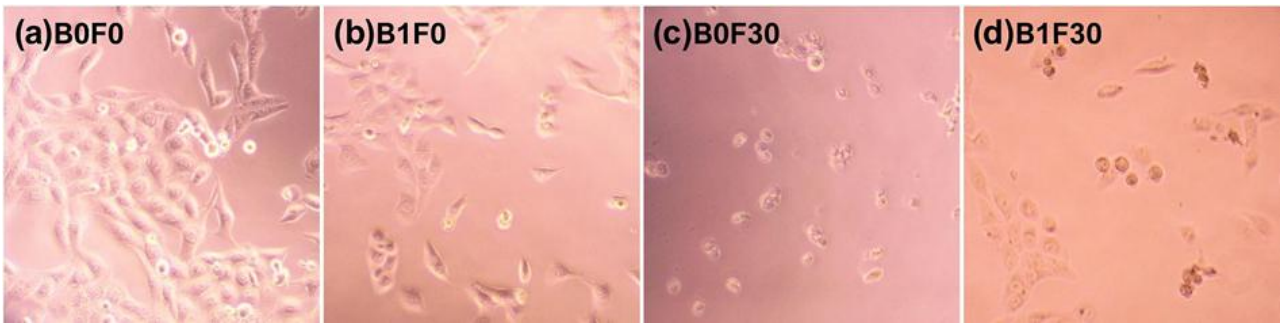

Fig. 8. Cell morphology after treatment with PLA samples doped with different amounts of boric acid and 5-FU by day 15. (Olympus CKX41 invert microscope, Magnification: 20×)

In the present study, upon incorporation of 5-FU, a significant ($p<0.05$) and concentration-dependent decrease in cell viability was observed. In all samples doped with 5FU addition (with or without boric acid), cell viability decreased significantly ($p<0.05$) compared to the control group at all time intervals (1, 5, 9, and 15 days). For instance, the B0F30 sample (30 wt% 5-FU, no boric acid) showed a reduction in cell viability from 53.47% on day 1 to 33.39% on day 15 (Fig 7d, Fig 8c). This progressive cytotoxicity is attributed to the sustained release of 5-FU from the PLA matrix. The release behavior of PLA is known to be influenced by its molecular weight and hydrophilicity. Makadia and Siegel (2011) reported that low molecular weight PLA releases drugs more rapidly, while modifications to the polymer composition can tailor its hydrophilic character and control the release rate. In a related study, Ocal et al. (2014) demonstrated that 5-FU-loaded low molecular weight PLA microspheres significantly suppressed Caco-2 cell viability by approximately 50%. Similarly, Karavelidis and Bikiaris (2012) observed 50% viability in HepG2 and 20% in HeLa cells using paclitaxel-loaded PLA systems.

The addition of 1 wt% H_3BO_3 notably influenced cytotoxicity profiles. Interestingly, the B1F30 sample (containing both boric acid and 30 wt% 5-FU) exhibited higher viability (46.12% at day 15) compared to B0F30 (33.39%) (Fig. 7h vs. Fig. 7d, Fig. 8d vs. Fig. 8c). This suggests that boric acid may modulate drug release behavior, leading to a more controlled and gradual release of 5-FU. Previous studies report that boron-containing additives can form secondary interactions with polymer chains, thus influencing polymer network density or hydrophilicity, altering degradation kinetics, and drug diffusion pathways (Ailincai et al., 2020). For instance, Aliasgharlou et al. (2020) demonstrated that incorporating boric acid into ethyl cellulose and polyvinyl alcohol films altered their degradation and drug release profiles. Vedelago et al. (2021) also showed that boric acid crosslinking in polymer networks significantly impacted mechanical performance and enabled the design of controlled release systems.

Moreover, boric acid itself displayed anticancer activity. The B1F0 sample (1% H_3BO_3 only) showed a noticeable reduction in cell viability after 15 days compared to undoped PLA (B0F0), indicating its bioactive potential (Fig. 7e, Fig. 8b). Prior studies have shown that boric acid can induce oxidative stress, cause cell cycle arrest, and promote apoptosis in various cancer cell lines, including those derived from breast, liver, and prostate tumors (Khaliq et al., 2018; Scorei & Popa, 2010).

Samples containing lower concentrations of 5-FU (10% and 20%) along with H_3BO_3 (B1F10 and B1F20) exhibited moderate and stable cytotoxic responses (~55–60% viability), indicating a balanced profile of sustained drug release and material biocompatibility (Fig. 7f, Fig. 7g). Such steady responses are beneficial for long-term therapeutic applications where continuous drug delivery at sub-cytotoxic levels is desired to inhibit tumor progression without inducing acute toxicity (Musumeci et al., 2006; Kumar et al., 2017).

Overall, the combined use of H_3BO_3 and 5-FU in DLP 3D-printed PLA scaffolds demonstrates a synergistic potential for localized cancer therapy. Boric acid not only enhances structural and thermal scaffold properties but also contributes to the modulation of drug release and may exhibit independent anticancer activity. These multifunctional properties position the scaffold system as a promising platform for sustained, site-specific chemotherapeutic delivery.

4. Conclusions

In this study, PLA-based scaffolds incorporating 5-fluorouracil (5-FU) and boric acid (H_3BO_3) were successfully fabricated via digital light processing (DLP) 3D printing to achieve controlled drug release for cancer treatment. Comprehensive characterization revealed that introducing 1% H_3BO_3 moderately affected drug release kinetics, slightly lowering early-stage release rates and influencing overall drug efficacy. Meanwhile, the addition of 1% H_3BO_3 markedly enhanced PLA's thermal properties, elevating the glass transition temperature (Tg) from 58 °C to 61 °C and the melting temperature (Tm) from 179 °C to 184 °C. Mechanical testing indicated an increase in tensile strength from 24.45 MPa (pure PLA) to 25.30 MPa alongside a significant rise in elongation at break from 5.75% to 7.24%, suggesting improved flexibility. Compressive strength also increased from 48.86 MPa to 55.04 MPa with 1% H_3BO_3. Swelling analyses showed that scaffolds containing 10% 5-FU without boric acid reached a maximum swelling ratio of about 50.00% by day 9, while degradation tests revealed the highest mass

loss (28.46%) at day 15 in these same formulations. In contrast, boric acid-containing samples (B1F10, B1F20, B1F30) exhibited higher or more controlled 5-FU release compared to samples without boric acid. For instance, by day 9, B1F10 released 4.24% of 5-FU versus 3.30% in B0F10. At higher drug loads (30% 5-FU), the initial release was somewhat lower yet more sustained, possibly due to denser drug packing within the polymer matrix. In terms of cytotoxicity, undoped PLA (B0F0) displayed good biocompatibility (>70% cell viability at day 15). However, the introduction of 5-FU significantly reduced cell viability, particularly in the 30% 5-FU sample (B0F30), which dropped from about 53.47% on day 1 to 33.39% by day 15. Combining 1% boric acid with 5-FU (B1F30) resulted in 46.12% cell viability at day 15, indicating boric acid's modulatory effect on 5-FU cytotoxicity. Additionally, the B1F0 sample (1% boric acid without 5-FU) also lowered viability relative to undoped PLA due to probable anticancer or antiproliferative properties of boric acid itself.

In conclusion, the findings demonstrate that DLP 3D-printed PLA scaffolds co-loaded with H_3BO_3 and 5-FU possess desirable structural, mechanical, and biological properties for localized chemotherapeutic delivery platforms. The synergistic integration of PLA, boric acid, and 5-fluorouracil offers a promising strategy for enhancing the therapeutic efficacy and safety of cancer treatments through localized and sustained drug release. Further in vivo investigations are warranted to validate the clinical applicability of this system.

Ethics committee approval: Ethics committee approval is not required for this study.

Conflict of interest: The author declares that there is no conflict of interest.

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