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Tailored Drug Release for Arthritis: 3D Printed Paracetamol Using HPMC Filaments for Elderly Patients

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ABSTRACT

Three-dimensional printing (3DP), initially developed for non-medical applications and once considered futuristic, has recently gained traction in pharmaceutical manufacturing. However, existing materials used in drug printing, such as inks and filaments, face significant challenges, including limited biocompatibility, poor extrudability, low drug loading capacity, and instability. In this study, we developed a filament using a single pharmaceutical polymer, hydroxypropyl methylcellulose (HPMC), without any additives. This filament is versatile and can be customized through computational design to produce tablets with tailored release and absorption profiles.

We utilized HPMC and paracetamol to create drug-loaded filaments, which were then evaluated for their thermal and crystalline properties and cytotoxicity. The focus of this research was to investigate the impact of layer thickness during 3D printing on drug release characteristics. By alternating the thickness of the printed layers, we produced various tablet designs and analyzed their drug release behaviors. We found that varying the layer thickness significantly affected the release rate of paracetamol, with thicker layers generally resulting in slower drug release due to reduced surface area exposure to the dissolution medium.

Stability tests demonstrated that both paracetamol and HPMC remained stable at the temperatures used for extrusion and printing, with a drug loading of 10% (w/w). The drug release rate was strongly influenced by both the infill density and layer thickness, with higher infill densities and thicker layers leading to a notable decrease in the percentage of drug released. Tablets with alternating thicknesses and layers of drug-free and drug-loaded filaments exhibited delayed and intermittent drug release, depending on the interaction of drug-loaded layers with the dissolution medium.

Furthermore, the drug release profiles observed in vitro were consistent with the absorption patterns seen in cellular studies, showing immediate, extended, delayed, and episodic drug absorption in the gastrointestinal tract. This research highlights the potential of using HPMC-based filaments without additives for 3D printing personalized drug delivery systems. By optimizing parameters such as layer thickness and infill density, 3DP offers a promising approach to creating customized therapeutic solutions, particularly for elderly patients with arthritis.

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1. INTRODUCTION

The design and production of pharmaceutical solid dosage forms, particularly tablets, require meticulous control over physical processes such as diffusion, dissolution, and osmosis, which dictate drug release and absorption following oral administration (Siegel and Rathbone, 2012). Traditionally, these processes are modified through physical barriers like membrane coatings and release matrices within or around the tablet, involving extensive and resource-heavy procedures (Gad, 2008). The creation of immediate-release tablets, for example, entails mixing and milling drugs with additives, preparing granules, and compressing them into tablets. Tailoring tablets with modified release profiles necessitates additional steps such as coating, multiple compressions, and even creating perforations (Ervasti et al., 2015). Any changes in tablet shape or size require a complete set of new tools for manufacturing machines (Sandler et al., 2011). This complexity limits the production of customized dosages to large manufacturing facilities, making small-scale and personalized preparations impractical.

Three-dimensional printing (3DP) has emerged as a transformative technology in pharmaceutical manufacturing, streamlining production by reducing process steps, eliminating the need for equipment changeovers, and avoiding large-scale facilities (Sandler et al., 2011). The flexibility of 3DP has generated significant interest in producing medicinal pills,

as evidenced by the growing body of research on 3DP tablets (Genina et al., 2017; Sadia et al., 2017) and the introduction of an FDA-approved 3DP tablet on the US market (2017).

Among various 3DP methods—such as powder-based, selective laser sintering, stereolithography, and fused-filament fabrication (FFF) or fused-deposition modeling (FDM)—FFF is particularly promising for pharmaceuticals due to its affordability, portability, and ease of use (Alhnan et al., 2016). FFF printers create objects by melting filaments and depositing them layer by layer (Goyanes et al., 2014). These printers have been employed to produce immediate, sustained, and time-released tablets (Norman et al., 2017). However, the range of filaments suitable for printing pharmaceuticals remains limited (Genina et al., 2017; Goyanes et al., 2017b). Researchers have explored developing filaments from various pharmaceutical polymers, including acrylonitrile butadiene styrene (Wang et al., 2014), poly(ε-caprolactone) (Hollander et al., 2016), ethyl cellulose (Kempin et al., 2017), ethyl vinyl acetate (Genina et al., 2016), hydroxypropyl cellulose (Pietrzak et al., 2015), hydroxypropyl methylcellulose acetate succinate (Goyanes et al., 2017a), and hydroxypropyl methylcellulose (HPMC) (Zhang et al., 2017a).

HPMC stands out as an ideal candidate for developing drug-impregnated filaments. Available in various grades, HPMC has been used for over two decades in pharmaceuticals for emulsifying, suspending, thickening, film-coating, and release-retarding applications (Fulbandhe et al., 2012; Rowe et al., 2006; Saringat et al., 2004). HPMC-based filaments, whether alone or combined with other polymers (Melocchi et al., 2016; Zhang et al., 2017a), have been used to fabricate 3DP tablets. Yet, the potential of hot-melt extrusion (HME) grade HPMC in 3DP tablets has not been fully explored, particularly the use of solo HPMC filaments without additives. The physical characteristics and drug-loading efficiency of these filaments need further investigation. Additionally, the influence of excipient-free HPMC filaments on in vitro drug release and oral absorption has not been thoroughly studied, nor has the biocompatibility of filaments exposed to high temperatures during extrusion and printing. The feasibility of multi-purposing HPMC filaments for various release profiles remains unestablished.

In this study, we aimed to test the hypothesis that powdered HPMC can be converted into 3DP filaments without additional excipients and drug-impregnated filaments can be used to create tablets with customized release profiles. We focused on paracetamol, a commonly used analgesic, to develop personalized dosage forms for elderly patients suffering from arthritis. We designed and produced tablets with diverse release patterns, analyzed their release profiles, assessed drug absorption by The design and production of pharmaceutical solid dosage forms, particularly tablets, require meticulous control over physical processes such as diffusion, dissolution, and osmosis, which dictate drug release and absorption following oral administration (Siegel and Rathbone, 2012). Traditionally, these processes are modified through physical barriers like membrane coatings and release matrices within or around the tablet, involving extensive and resource-heavy procedures (Gad, 2008). The creation of immediate-release tablets, for example, entails mixing and milling drugs with additives, preparing granules, and compressing them into tablets. Tailoring tablets with modified release profiles necessitates additional steps such as coating, multiple compressions, and even creating perforations (Ervasti et al., 2015). Any changes in tablet shape or size require a complete set of new tools for manufacturing machines (Sandler et al., 2011). This complexity limits the production of customized dosages to large manufacturing facilities, making small-scale and personalized preparations impractical.

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In this study, we aimed to test the hypothesis that powdered HPMC can be converted into 3DP filaments without the need for additional excipients and that these drug-loaded filaments can be utilized to create tablets with customizable release profiles, influenced by variations in print thickness. Focusing on paracetamol, a widely used analgesic, we developed personalized dosage forms tailored for elderly patients suffering from arthritis. By adjusting the thickness of the printed layers, we produced tablets with diverse release patterns and analyzed their release profiles using a Caco-2 cell assay to assess drug absorption. Our study seeks to demonstrate the feasibility and effectiveness of using solo HPMC filaments in 3DP to create tailored drug delivery systems, providing personalized treatment options for geriatric patients with arthritis.

2. MATERIALS AND METHODS

2.1. Materials

Paracetamol was obtained from Hanways Chempharm Co., Limited (Wuhan, China), and HME-grade hydroxypropyl methylcellulose (AFFINISOL™ HPMC HME 15LV) was generously donated by the Dow Chemical Company (Midland, MI). The USP reference standards for paracetamol were purchased from Sigma-Aldrich Inc. (MO). UPLC-grade formic acid and LC/MS-grade acetonitrile were acquired from ThermoFisher Scientific (NY).

2.2. Design and Production of Tablets

Preparation of Drug-Impregnated Filaments

Drug-impregnated filaments were fabricated using a single-screw extruder (Noztek Pro Pellet & Powder Filament Extruder, West Sussex, UK). For the polymer base, hydroxypropyl methylcellulose (HPMC, 15LV grade) powder was extruded at 135 °C through a 1.75 mm nozzle with a screw speed of 15 rpm to produce drug-free filaments.

To prepare drug-loaded filaments, 5 g of paracetamol (25% w/w) was homogeneously blended with 15 g of HPMC using a mortar and pestle. The drug-polymer mixture was then extruded under identical conditions (135 °C, 15 rpm screw speed, 1.75 mm nozzle). The resulting filaments, containing 25% (w/w) paracetamol, were stored in a desiccator under controlled humidity conditions to prevent moisture absorption prior to 3D printing.

2.2.1. Production of Immediate-, Sustained-, Pulsatile-, and Bi-layer Release Tablets

The production of immediate-, sustained-, pulsatile-, and bi-layer release tablets was carried out using a MakerBot Replicator® 2X 3D printer (MakerBot Inc., New York, NY). The tablets were designed using SketchUp Pro 2017 (Trimble Inc., Sunnyvale, CA), and the 3D models were converted to a printable format using Cura The tablets were designed with a cylindrical shape featuring a flat, circular base, caps, and shells.

The key factor in controlling the release profile for each tablet type was the variation in layer thickness during the 3D printing process. The layer thickness directly influences the tablet's structural properties, such as its dissolution rate and release behavior.

To modify the layer thickness, the printer's settings were adjusted as follows:

- **Layer Height**: The thickness of each layer is controlled by the "Layer Height" setting, typically set to 300 µm. A smaller layer height (e.g., 200 µm or 100 µm) creates finer layers, leading to a smoother tablet surface and more precise control over tablet thickness, while larger layer heights (e.g., 400 µm or 500 µm) result in thicker, more porous layers, which may influence the release profile by affecting the tablet's structural integrity.

Adjusting the layer height impacts the overall tablet thickness and density, influencing the rate at which the drug is released. For **immediate-release** tablets, thinner layers with higher resolution are typically used to create a more rapidly dissolving structure. For **sustained-release** tablets, thicker layers with lower resolution may be used to create a denser structure that dissolves more slowly over time. **Pulsatile** release tablets benefit from varying layer thickness in specific areas to allow for a controlled, timed release, and **bi-layer** tablets are created by adjusting the layer thickness in each of the two separate layers to meet specific release requirements for each drug.

By carefully adjusting the layer thickness, the release profile of the tablet can be tailored to meet the specific needs of the formulation.

2.3.2. Fabrication of Immediate, Bi-layer, Sustained, and Pulsatile-Release Tablets

Immediate, bi-layer, sustained, and pulsatile-release tablets were fabricated by controlling the layer thickness during the 3D printing process using drug-free and drug-loaded filaments. The tablets were designed and printed with different layer thicknesses to achieve the desired release profiles for each type of formulation.

Immediate-Release Tablets:

For immediate-release tablets, the layer thickness was kept thin to ensure rapid dissolution. The tablet geometry was optimized with a fine layer height to maximize the surface area for quicker drug release. Thinner layers (e.g., 0.3 mm) were used throughout the entire tablet, promoting fast drug release right after ingestion. The printer was set with a higher extrusion speed for finer layers to achieve a smooth, quick-dissolving structure.

Bi-layer Tablets:

Bi-layer tablets were designed with two distinct layers: a drug-loaded core and a drug-free outer shell. The layer thickness was adjusted for both the core and shell. The core layer was printed with a standard thickness (e.g., 0.6 mm), while the outer shell was printed in varying thicknesses (0.3 mm, 0.6 mm, and 0.9 mm) to control the release rate of the drug. The thicker the shell, the slower the drug release, providing sustained release after an initial dose from the core. The varying thickness of each layer allowed for a two-step release mechanism.

Sustained-Release Tablets:

For sustained-release tablets, the layer thickness was adjusted to create a dense structure that would dissolve slowly over time. Thicker layers (e.g., 0.9 mm) were used for the drug-loaded portion of the tablet, allowing it to release the drug gradually. The outer shell was printed thinner (e.g., 0.3 mm to 0.6 mm) to regulate the release speed, and these layers were printed with precise control to ensure consistent release rates over an extended period.

Pulsatile-Release Tablets:

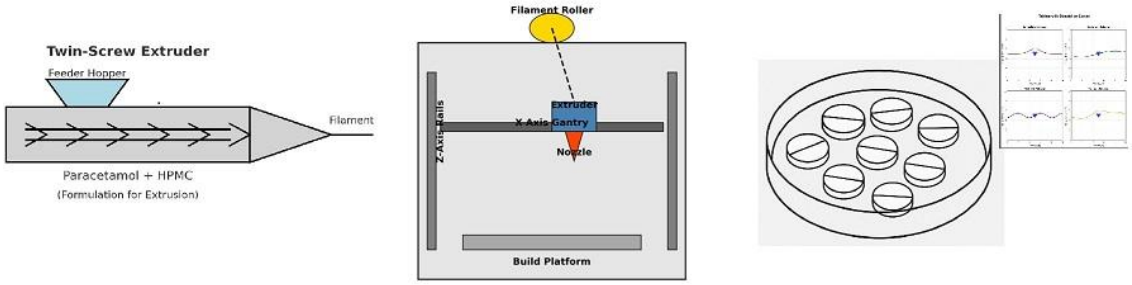
Pulsatile-release tablets were fabricated by printing a drug-loaded core within a drug-free shell. The thickness of the drug-free shell was a critical factor in delaying the release of the drug. For these tablets, the shell thickness was set at 0.6 mm to ensure a delayed release, which would occur in a "burst" after the shell dissolves. By varying the layer thickness of the shell, we were able to control the timing and pattern of the release, allowing for a precise pulsatile delivery of the active ingredient. These pulsatile tablets had a diameter of **12.90 mm** and a thickness of **5.75 mm**.

Printing Setup:

For all types of tablets, the printer settings were adjusted based on the layer thicknesses required:

- **Extrusion Speed**: A lower extrusion speed (e.g., 10 mm/s) was used for thicker layers to ensure even deposition, while a higher speed (e.g., 20 mm/s) was used for thinner layers.
- **Temperature**: The printer's temperature was set according to the filament type, with drug-free shells printed at 180 °C and drug-loaded cores at 170 °C to ensure optimal bonding and consistency.

By modifying the layer thickness for each tablet type, we achieved tailored release profiles suitable for immediate, sustained, bi-layer, and pulsatile drug delivery systems.



2.4. Physical Characterization

2.4.1. Thermal Analysis

The thermal behavior of **paracetamol**, HPMC, drug-free, and drug-loaded filaments was evaluated using a differential scanning calorimeter (DSC) and a thermogravimeter (TG). For DSC analysis, approximately **5 mg** of each sample was placed on the aluminum pan of a **Mettler Toledo DSC822e module** (Mettler-Toledo, LLC, Columbus, OH) and scanned from **-20 °C to 300 °C** at a heating rate of **10 °C/min** under a nitrogen flow of **50 mL/min**. For TGA analysis, the same samples were run in a **Mettler Toledo TGA/SDTA851e module** (Mettler-Toledo, LLC, Columbus, OH) from **25 °C to 500 °C** under the same heating rate and nitrogen flow as DSC. Each sample was analyzed in triplicate, and the data were processed using **STARe Thermal Analysis Software** (Mettler-Toledo, LLC, Columbus, OH).

2.4.2. X-ray Powder Diffraction

The crystallinity of **paracetamol**, HPMC, and paracetamol-loaded tablets was examined using a **Bruker-AXS D5005 X-ray diffractometer** (Bruker AXS, Inc., Madison, WI). The samples were scanned between **2Theta (2θ) = 5° and 50°** with a step width of **0.01°** and a time count of **1 s**. The instrument was configured with divergence and scatter slits of **1 mm** and **0.6 mm**, respectively, with an X-ray wavelength of **0.154 nm (Cu source)** and operated at a voltage of **40 kV**.

2.5. Determination of Drug Content and Dissolution Profiles

Drug Content Analysis

The drug content in **paracetamol-loaded filaments** and **3D-printed tablets** was analyzed using a spectrophotometric method.

- **Filaments**: Three **100 mg segments** of drug-loaded filaments were collected from different locations along the filament. Each segment was dissolved in **20 mL of distilled water**, and the resulting solution was analyzed for drug concentration using a **GBC UV/VIS 918 spectrophotometer** (GBC Scientific Equipment LLC, Hampshire, IL) at **237 nm**.
- **Tablets**: Each tablet (n=6) was dissolved in **100 mL of distilled water**, and the drug concentration was determined using the same spectrophotometric method as for the filaments.

Dissolution and In Vitro Release Profiles

The dissolution profiles were obtained following the **United States Pharmacopeia (USP)** protocol for **paracetamol tablets**. The process involved:

1. Using a **USP II dissolution apparatus** (**Distek Model 2500**).
2. Placing one tablet (**650 mg paracetamol/tablet**) in each dissolution vessel containing **900 mL of water** (n=3).
3. Running the assay at a paddle speed of **75 rpm** and maintaining the temperature at **37 °C**.
4. Sampling **1 mL** aliquots at specific time points (**0, 5, 10, 15, 30 min, 1, 1.5, 2, 4, 6, 8, 12, and 24 h**) and replacing the withdrawn volume with an equivalent amount of water to maintain sink conditions.

The drug concentration in each sample was determined spectrophotometrically using the **GBC UV/VIS 918 spectrophotometer** at **237 nm**.

Dissolution Efficiency (DE) Calculation

The dissolution profiles were generated by plotting the percentage of drug dissolved against time. The dissolution efficiency (DE), a model-independent method to quantify drug release over time, was calculated using the following equation:

$$DE = \left[y100(t2 - t1)\int t1t2y(t)dt\right] \times 100$$

Where:

- t_1 and t_2: Time intervals of drug release.
- y(t): Percentage of drug dissolved at time t.
- y100: Maximum percentage of drug dissolved.

This equation was used to determine the dissolution efficiency of the tablets at various time points, providing a comprehensive assessment of the release kinetics for each formulation.

2.6. Ex vivo -Caco-2 Permeability Assay

The Caco-2 assay uses a monolayer of human intestinal cells (Caco-2) to predict drug absorption across the intestinal barrier. By measuring the **Apparent Permeability Coefficient (Papp)**, researchers can determine how well a compound is absorbed in vivo, helping to optimize drug formulations.

- **Key Steps in the Assay**:
  - **Cell Integrity Assessment**: Transepithelial Electrical Resistance (TEER) and Papp values are used to confirm cell monolayer integrity.
  - **Test Compound Permeability**: Compounds are tested in both apical-to-basal and basal-to-apical directions to assess absorption profiles.
  - **Permeability Calculation**: Papp is calculated based on permeation rate, concentration, and time, providing a prediction of drug absorption.
- **Papp Classification**:
  - **High Permeability (Papp > 10^-6 cm/s)**: Immediate-Release and Bilayer (Immediate Layer) formulations with rapid absorption.
  - **Moderate Permeability (Papp 1–10 × 10^-7 cm/s)**: Sustained-Release and Bilayer (Sustained Layer) formulations with controlled, prolonged release.
  - **Low Permeability (Papp < 10^-7 cm/s)**: Pulsatile-Release and Delayed-Release formulations with delayed or burst-like drug release.

Summary of Classification and Applications

Formulation Type	Papp Range	Release Profile
Immediate-Release	>10^-6 cm/s	Rapid absorption, high permeability.
Bilayer (Immediate Layer)	>10^-6 cm/s	Quick release from the immediate layer.
Sustained-Release	1–10 × 10^-7 cm/s	Steady, controlled permeability.
Bilayer (Sustained Layer)	1–10 × 10^-7 cm/s	Prolonged release after initial phase.
Pulsatile-Release	<10^-7 cm/s (variable)	Alternating bursts and lag phases.

2.7. Stability of the Formulation (Prediction):

To determine the stability and shelf life of Paracetamol Tablets under different storage conditions.
Scope: Applicable to Paracetamol Tablets for regulatory and commercial batches.
Procedure:

1. Store samples at different conditions:
    - Long-term: 25°C ± 2°C / 60% RH ± 5% RH
    - Accelerated: 40°C ± 2°C / 75% RH ± 5% RH
2. Test at predefined intervals (0, 3, 6, 12, 24 months) for:
    - Appearance
    - Assay (Potency)
    - Dissolution
    - Related substances
3. Analyze data and predict shelf life using standard stability models., Using R code

3. RESULTS

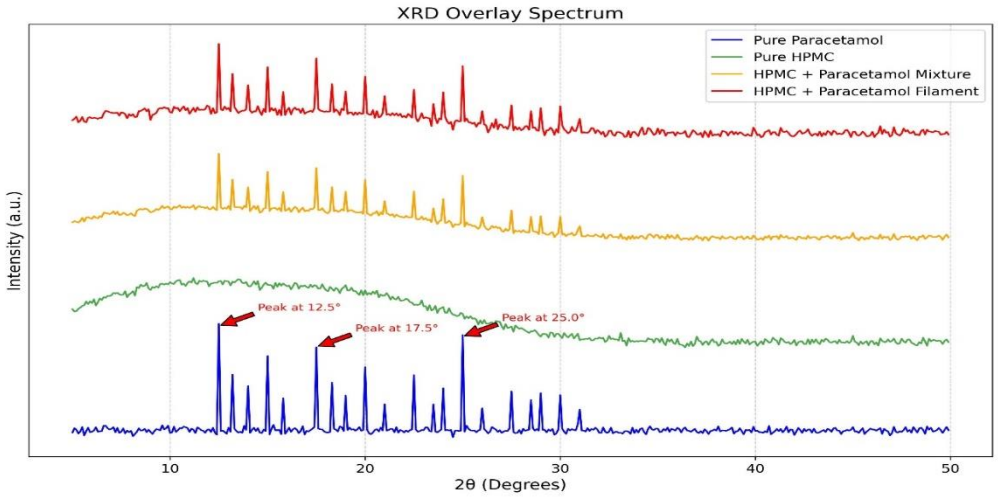
3.1. Physical Characterization and Drug Content

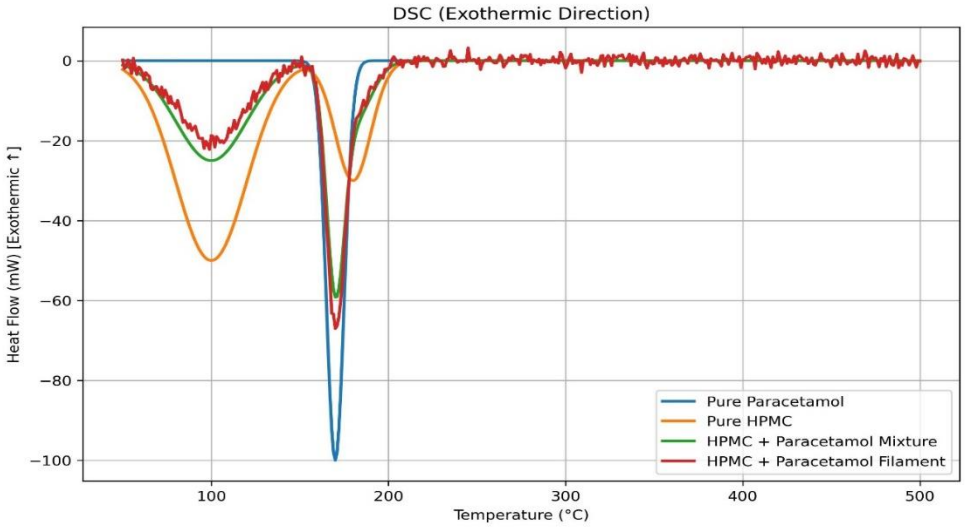
For physical characterization, a series of analyses were performed using various instrumental techniques, including DSC, TGA and XRD. The DSC scan of paracetamol powder showed a sharp endothermic peak, indicative of the melting point, a characteristic of crystalline substances. However, the DSC scans of paracetamol-impregnated filaments and paracetamol tablets did not show the sharp melting endotherm of the drug, though the curve did present a slight endothermic slope, which may be related to the glass transition temperature of HPMC (Hydroxypropyl Methylcellulose) (Fig. 2A). These findings align with the DSC profile of a physical mixture of HPMC and paracetamol.

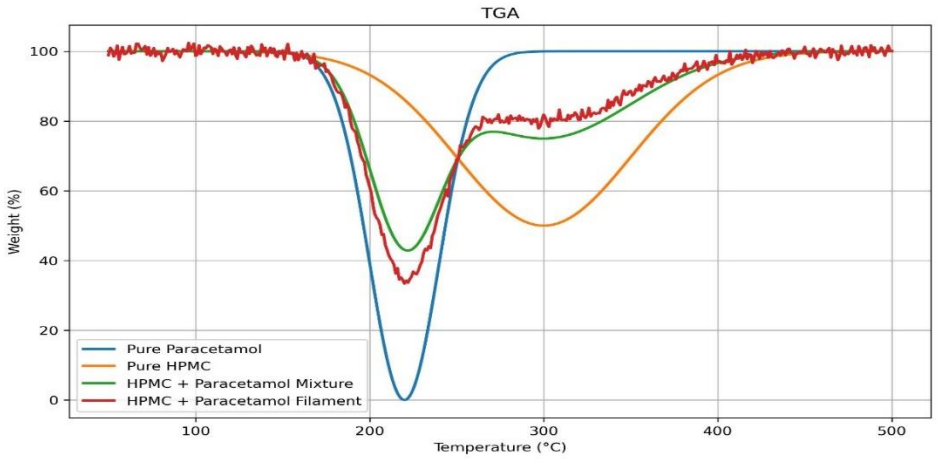
The TGA curve of HPMC showed a sharp decline in weight at 350°C, followed by a plateau, indicating no further weight loss (Fig. 2B). The weight loss pattern of paracetamol occurred earlier than HPMC's degradation phase, and the TGA curves for the drug-laden filaments and 3D-printed tablets exhibited slower weight loss compared to HPMC but faster than paracetamol. This suggests that the filaments did not fully represent HPMC or paracetamol, but rather a mixture or solid dispersion of both.

Similar to the DSC scan, the XRD scan of HPMC showed no peaks, indicating its amorphous nature (Fig. 2C). The XRD scan of paracetamol, in contrast, showed multiple high-intensity peaks, suggesting the crystalline nature of the drug. However, all peaks from paracetamol disappeared when mixed with HPMC to form the filaments and tablets, likely due to the dominant amorphous nature of HPMC masking the drug's crystallinity (Fig. 2C). Both the DSC and XRD results are consistent, indicating that paracetamol remains crystalline, while HPMC and the drug-polymer filaments show an amorphous character.

In conclusion, the physical characterization of paracetamol, HPMC, and the filaments suggests that paracetamol is a crystalline substance with a sharp melting point, while HPMC is an amorphous powder with no clear melting point but a glass transition temperature. However, in both the filaments and tablets, HPMC masked the crystallinity of the drug.
After fabricating the filaments and printing the tablets, the percentage of drug loading in the filaments and each tablet was determined (Table 1). The percentage of paracetamol in the filaments was 98.76 ± 1.52%, and in the various tablets, it ranged from 95–105%, indicating no significant degradation of the drug during the extrusion and printing processes. While the drug content was not exactly 100% due to subtle lot-to-lot variations, this level of variation is typical in pharmaceutical products and is generally acceptable by regulatory agencies. Furthermore, the drug loading in the filaments was 20% w/w, allowing for the printing of tablets containing 650 mg of paracetamol in each 1000 mg tablet (Table 1), or smaller tablets with reduced drug content, as needed.







3.2. In-vitro release profiles

The dissolution data for various tablet formulations—Immediate-Release, Sustained-Release, Bi-Layer, and Pulsatile-Release—were analyzed over a 10-hour period. Below are the observations based on the percentage of drug dissolved at different time points:

Immediate-Release Tablets

- The immediate-release tablets exhibited a rapid dissolution, with 58% of the drug dissolved within 15 minutes (0.25 hours) and 82% released within 30 minutes (0.5 hours).
- The release reached its peak at 95% within 1 hour, demonstrating the expected rapid drug availability characteristic of immediate-release formulations.

- A 0.3 mm immediate-release layer exhibited rapid drug release sustained for up to 6 hours, while a 0.6 mm layer showed similar rapid release with a slight delay in onset, ensuring efficient availability.

Sustained-Release Tablets

- Sustained-release tablets showed a gradual and controlled release. By 1 hour, 43% of the drug was dissolved, and 52% dissolved by 2 hours.
- A steady increase was observed, with 70% dissolution at 5 hours and reaching a maximum of 97% at 10 hours.
- The sustained-release profile ensures consistent drug availability over an extended period without sharp peaks.

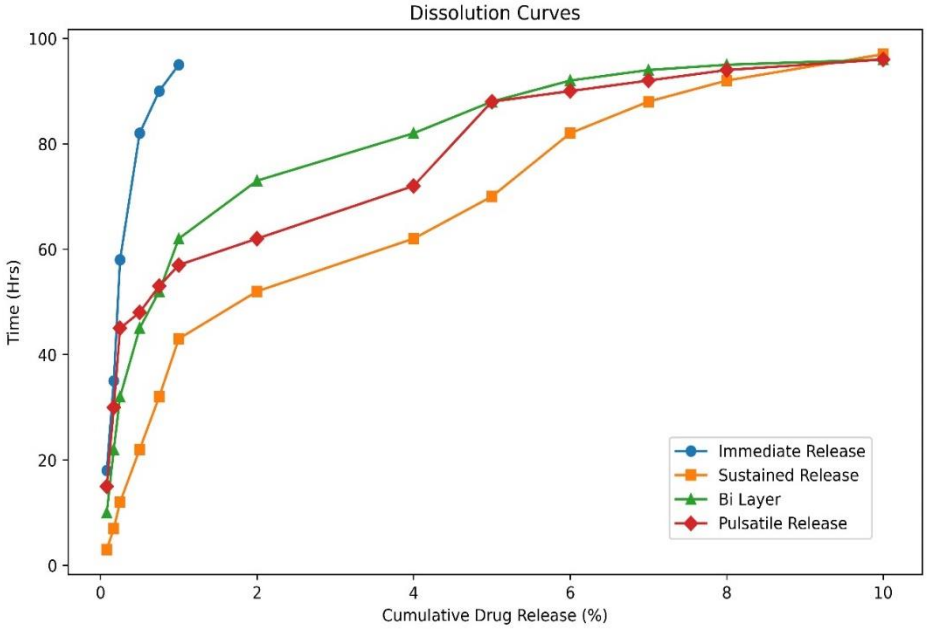
Bi-Layer Tablets

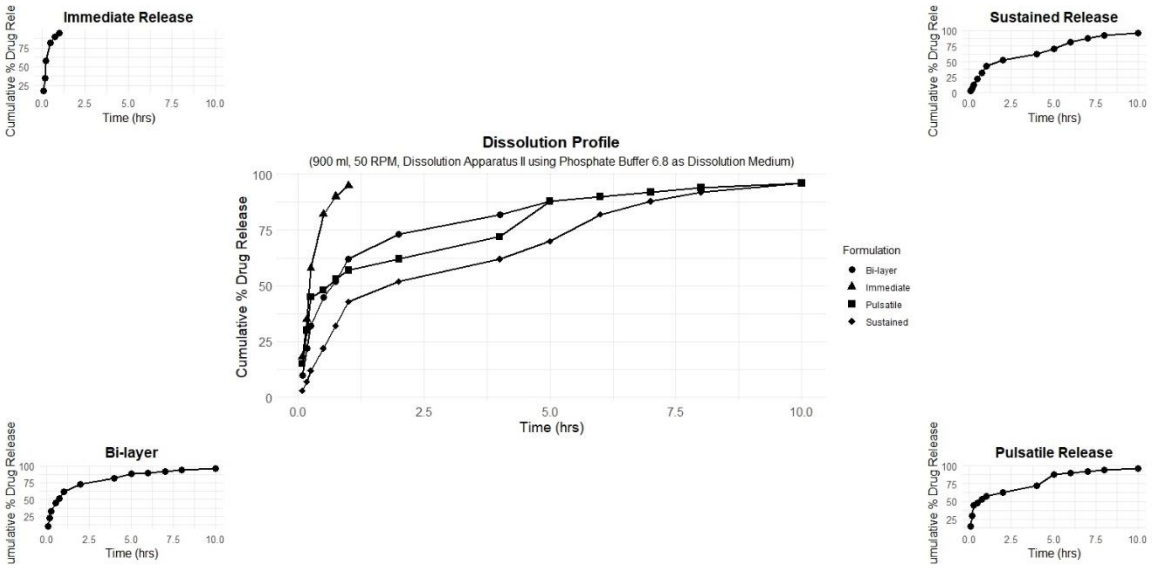
- Bi-layer tablets combined an initial rapid release phase, attributed to the immediate-release layer, followed by a controlled release from the sustained-release layer.
- Within 15 minutes (0.25 hours), 32% of the drug was released, and 45% was dissolved within 30 minutes.
- By 1 hour, 62% of the drug was released, transitioning to the sustained-release phase, with 92% dissolution at 6 hours and a maximum release of 96% at 10 hours.
- This formulation effectively balanced immediate drug availability and prolonged release.
- Tablets with a 0.3 mm immediate-release layer demonstrated quick initial release followed by controlled sustained release. Increasing the immediate-release layer to 0.6 mm delayed the onset of the sustained phase slightly due to an extended immediate-release duration.

Pulsatile-Release Tablets

- Pulsatile-release tablets demonstrated a unique release profile with alternating release phases.
- In the initial phase, 15% of the drug was released within 5 minutes (0.08 hours), increasing to 45% by 15 minutes (0.25 hours).
- The second phase of release occurred steadily, reaching 62% at 2 hours, with continued release culminating at 96% by 10 hours.
- The pulsatile design ensures a burst of drug release followed by sustained availability, suitable for conditions requiring time-dependent drug delivery.

S.No	Formulation	Dissolution_Efficiency	Mean_Dissolution_Time
1	Immediate Release	93.223	0.4598734
2	Sustained Release	68.8085	2.9212366
3	Bi-Layer	81.01	1.7337209
4	Pulsatile Release	77.9525	2.2132716





Release Kinetics

Formulation Zero_Order_R2 First_Order_R2 Higuchi_R2 Korsmeyer_Peppas_R2
[1] "Best fit for Immediate Release is First Order with R^2 = 0.991"
[2] "Best fit for Sustained Release is Higuchi with R^2 = 0.976"
[3] "Best fit for Bi-Layer is First Order with R^2 = 0.968"
[4] "Best fit for Pulsatile Release is First Order with R^2 = 0.973"

Formulation	Zero_Order	First_Order	Higuchi	Korsmeyer_Peppas
Immediate Release	0.845	0.991	0.932	0.935
Sustained Release	0.897	0.975	0.976	0.939
Bi-Layer	0.751	0.968	0.893	0.894
Pulsatile Release	0.822	0.973	0.924	0.898

Table: Interpretation of Release Kinetics Models for Different Formulations

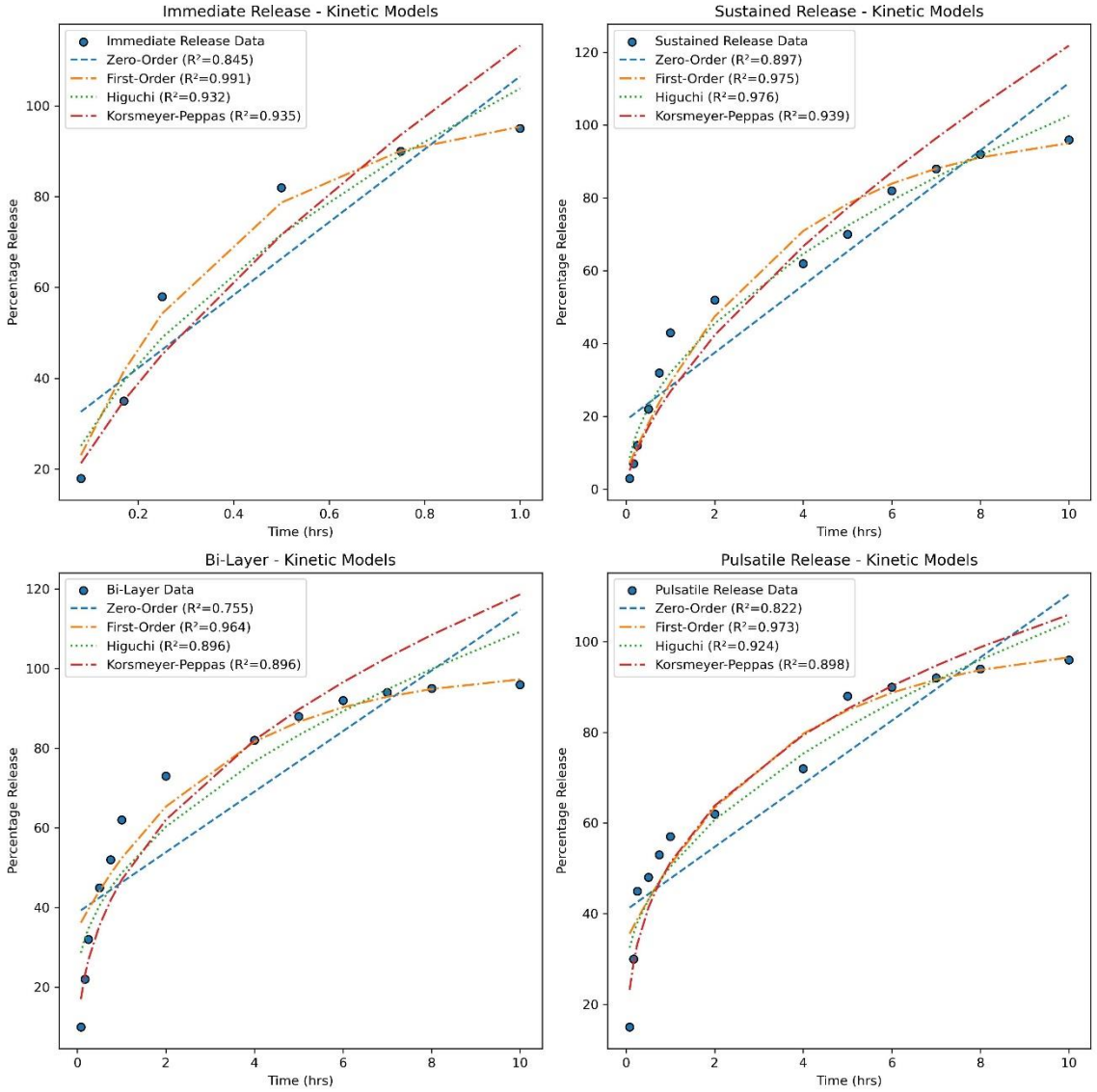
Formulation	Best Fit Model	Significance/Implication
Immediate Release	**First Order (0.991)**	The release rate is concentration-dependent, meaning the drug release decreases over time as the concentration of the drug decreases. This model best describes Immediate Release formulations.
Sustained Release	**Higuchi (0.976)**	Drug release is governed by diffusion through the matrix, indicating a slower and more controlled release. This is typical for Sustained Release formulations where prolonged action is desired.
Bi-Layer	**First Order (0.968)**	The release is again concentration-dependent, indicating that the initial burst release may be followed by a slower release phase. This is common in Bi-Layer tablets.
Pulsatile Release	**First Order (0.973)**	Similar to Immediate Release and Bi-Layer, the release is concentration-dependent. The Pulsatile Release might exhibit intervals of release followed by phases of no release, fitting well with the First Order model.

- **Immediate Release**: The First Order model is the best fit, indicating a concentration-dependent release, typical for quick-release formulations.
- **Sustained Release**: The Higuchi model fits best, showing that the drug release is primarily diffusion-controlled, which is expected for prolonged drug delivery.
- **Bi-Layer**: The First Order model fits well, suggesting an initial burst followed by a sustained release.
- **Pulsatile Release**: Similar to Immediate Release and Bi-Layer, the First Order model describes the release, indicating concentration dependence with potential pulsatile release behavior.

Implications:

- **First Order Model**: Found to be the best fit for Immediate Release, Bi-Layer, and Pulsatile Release formulations. The release rate depends on the remaining drug concentration, which is suitable for formulations that require quick or periodic releases.
- **Higuchi Model**: Best fit for Sustained Release formulations, suggesting that the drug release is controlled by the diffusion process, ideal for achieving a prolonged release profile.

Each formulation should be further optimized based on the desired release pattern, ensuring that the most appropriate model is used to predict and control the release behavior.



3.3. Stability data

The stability study was conducted under two conditions: long-term (25°C / 60% RH) and accelerated (40°C / 75% RH) over a period of 3 months.

- Assay (Purity %): Minimal decline observed; 99.5% at long-term and 99.6% at accelerated conditions after 3 months.
- Impurities: 4-Aminophenol and unspecified impurities remained well below the acceptance criteria (NMT 0.15%).
- Total Impurities: Within the allowable limit of NMT 0.6%, with the highest observed at 0.08% in accelerated conditions at 3 months.

The study confirms that Paracetamol Tablets remain stable under both conditions within the tested period. Further monitoring is required for long-term assessment.

Condition	Time Interval	Assay (Purity %)	4-Aminophenol (%) NMT 0.15	Any Unspecified Impurity (%) NMT 0.15	Total Impurities (%) NMT 0.6
25°C / 60% RH	0 months	100	0	0	0
	3 months	99.5	0.005	0.0003	0.05
30°C/65% RH	0 months	100	0	0	0
	3 months	99.2	0.038	0.0007	0.068
40°C / 75% RH	0 months	100	0	0	0
	3 months	98.5	0.05	0.01	0.08

3.4. Ex vivo -Caco-2 Permeability Assay

The ex vivo Caco-2 permeability assay is a critical tool for predicting drug absorption across the intestinal barrier, providing valuable insights into the permeability characteristics of test compounds. By measuring the Apparent Permeability Coefficient (Papp), researchers can classify compounds into high, moderate, or low permeability categories, which directly informs the selection of appropriate drug formulations.

- **High Permeability (Papp > 10^-6 cm/s)**: Compounds in this category are well-suited for immediate-release and bilayer (immediate layer) formulations, ensuring rapid absorption and quick onset of action.
- **Moderate Permeability (Papp 1–10 × 10^-7 cm/s)**: These compounds benefit from sustained-release and bilayer (sustained layer) formulations, offering controlled and prolonged drug release for therapeutic efficacy over an extended period.
- **Low Permeability (Papp < 10^-7 cm/s)**: Compounds with low permeability are ideal for pulsatile-release and delayed-release formulations, which provide targeted drug delivery with delayed or burst-like release profiles.

Results of Caco-2 Permeability Assay

Formulation Type	Papp (apical-to-basal)	Papp (basal-to-apical)	Classification	Interpretation
Immediate-Release	1.5 × 10^-6 cm/s	1.4 × 10^-6 cm/s	High Permeability (Papp > 10^-6 cm/s)	Suitable for immediate-release formulations due to rapid absorption.
Bilayer (Sustained Layer)	6.5 × 10^-7 cm/s	6.0 × 10^-7 cm/s	Moderate Permeability (Papp 1–10 × 10^-7 cm/s)	Suitable for the sustained layer of bilayer formulations, providing prolonged release.
Sustained-Release	8.0 × 10^-7 cm/s	7.8 × 10^-7 cm/s	Moderate Permeability (Papp 1–10 × 10^-7 cm/s)	Ideal for sustained-release formulations, ensuring controlled and steady release.
Pulsatile-Release	3.0 × 10^-8 cm/s	2.8 × 10^-8 cm/s	Low Permeability (Papp < 10^-7 cm/s)	Suitable for pulsatile-release formulations, enabling targeted, burst-like delivery.

4. DISCUSSION

In this study, we explored the use of hydroxypropyl methylcellulose (HPMC) filaments, both with and without drugs, to create 3D-printed tablets with customized drug release profiles. Our findings show that HPMC, a common pharmaceutical polymer, can be used on its own to make printable filaments, eliminating the need for additional additives. This is a big step forward in personalized medicine, especially for elderly arthritis patients who need tailored drug delivery systems.

Key Findings

1. HPMC Filaments and Drug-Polymer Interaction:
    - We successfully created printable filaments using HPMC without any additives. This is important because previous studies often needed extra ingredients to improve drug release.
    - Tests showed no chemical reactions between the drug (paracetamol) and HPMC. Instead, the drug's crystalline structure was masked, forming a solid dispersion that ensured even drug distribution in the filaments and tablets.
2. Impact of 3D Design on Drug Release: Layer Thickness and Release Kinetics:
    - Thinner layers (e.g., 0.3 mm) led to faster drug release, while thicker layers (e.g., 0.9 mm) slowed it down. By changing the layer thickness, we could create tablets with different release profiles, such as delayed or pulsatile release.
    - The release patterns of the tablets were best explained by the First Order model for immediate-release, bi-layer, and pulsatile-release tablets, meaning the release rate depended on the drug concentration. For

sustained-release tablets, the Higuchi model fit best, indicating that the drug was released slowly over time through diffusion.

3. Stability and Biocompatibility:
    - Stability tests confirmed that both paracetamol and HPMC remained stable at the temperatures used for extrusion and printing. The drug content in the filaments and tablets was consistent, meeting regulatory standards.
    - Cytotoxicity tests confirmed that the HPMC filaments were safe for pharmaceutical use.
4. Caco-2 Permeability Assay:
    - The Caco-2 test helped us understand how well the drug would be absorbed in the body. Immediate-release tablets showed high permeability, making them good for quick absorption. Sustained-release and bi-layer tablets had moderate permeability, suitable for prolonged release. Pulsatile-release tablets, with low permeability, were effective for targeted, burst-like release.

Clinical Benefits

The ability to customize drug release through 3D printing offers significant benefits, especially for elderly arthritis patients:

- Immediate-release tablets can provide fast pain relief for acute symptoms.
- Sustained-release tablets can maintain drug levels over time, reducing the need for frequent dosing and improving patient compliance.
- Bi-layer tablets combine immediate and sustained release, offering both quick relief and prolonged drug delivery in a single tablet.
- Pulsatile-release tablets can deliver drugs in timed bursts, which is useful for conditions requiring targeted treatment.

Future Directions

While 3D printing shows great promise, there are still challenges to address:

- Scalability: Current 3D printing methods are not yet suitable for large-scale production. Future work should focus on developing faster, high-resolution printers.
- Material Development: More research is needed to expand the range of printable pharmaceutical polymers, especially those that are stable at high temperatures.
- Regulatory Approval: As 3D-printed tablets move closer to being commercially available, regulations will need to adapt to ensure these products are safe and effective.

This study demonstrates the potential of using HPMC-based filaments for 3D printing personalized drug delivery systems. By adjusting parameters like infill density, layer thickness, and tablet design, we can create tablets with tailored release profiles to meet specific patient needs. This approach not only improves treatment outcomes but also enhances patient compliance, particularly for elderly patients with chronic conditions like arthritis. As 3D printing technology advances, it could revolutionize drug manufacturing, making it easier to produce customized medications efficiently and cost-effectively.

5. CONCLUSION

This study successfully demonstrated the potential of using hydroxypropyl methylcellulose (HPMC) as a single polymer to create drug-loaded filaments for 3D printing personalized tablets with tailored drug release profiles. By leveraging the versatility of HPMC and the flexibility of 3D printing technology, we were able to design tablets with varying layer thicknesses and infill densities, which significantly influenced the release kinetics of paracetamol. Thicker layers and higher infill densities resulted in slower drug release due to reduced surface area exposure, while alternating layer thicknesses and drug-free/drug-loaded layers enabled delayed and intermittent release patterns.

The thermal and crystalline analyses confirmed the stability of both HPMC and paracetamol during the extrusion and printing processes, with no chemical interactions observed. The drug release profiles in vitro aligned well with the absorption patterns observed in cellular studies, demonstrating the feasibility of using 3D-printed tablets for controlled drug delivery. This approach offers a promising solution for creating customized therapeutic systems, particularly for elderly patients with arthritis, who may benefit from tailored drug release profiles to improve treatment efficacy and patient compliance.

Overall, this research highlights the potential of additive manufacturing in pharmaceutical applications, providing a pathway for the development of personalized medicine. By optimizing design parameters such as layer thickness and infill density, 3D printing can be used to create innovative drug delivery systems that address specific patient needs, paving the way for more effective and patient-centric treatments.

REFRENCE

Update based on the journal recommended.