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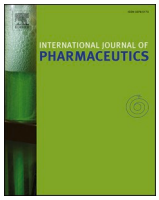

Tailoring drug release in bilayer tablets through droplet deposition modeling and injection molding

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ABSTRACT

This study explores the innovative production of personalized bilayer tablets, integrating two advanced manufacturing techniques: Droplet Deposition Modeling (DDM) and Injection Molding (IM). Unlike traditional methods limited to customizing dense bilayer medicines, our approach uses Additive Manufacturing (AM) to effectively adjust drug release profiles. Focusing on Caffeine and Paracetamol, we found successful processing for both DDM and IM using Caffeine formulation. The high viscosity of Paracetamol formulation posed challenges during DDM processing. Integrating Paracetamol formulation for the over-molding process proved effective, demonstrating IM's versatility in handling complex formulations. Varying infill percentages in DDM tablets led to distinct porosities affecting diverse drug release profiles in DDM-fabricated tablets. In contrast, tablets with high-density structures formed through the over-molding process displayed slower and more uniform release patterns. Combining DDM and IM techniques allows for overcoming the inherent limitations of each technique independently, enabling the production of bilayer tablets with customizable drug release profiles. The study's results offer promising insights into the future of personalized medicine, suggesting new pathways for the development of customized oral dosage forms.

1. Introduction

The traditional approach to medicine administration, using separate dosage forms, poses challenges in terms of inconvenience, potential medication errors, and issues with patient compliance (Khaled et al., 2015; Pereira et al., 2020; Robles-Martinez et al., 2019). In recent decades the emergence of polypharmacy propelled by the aging demographic and the surge in chronic health conditions, underscores the urgent need for innovative solutions in medication administration (Molokhia and Majeed, 2017). The concept of a customized polypill, incorporating numerous layers and compositions, offers a potential avenue for personalized drug administration (McDonagh et al., 2023b, Auriemma et al., 2022; Fuenmayor, O'Donnell, et al., 2019; Goh et al., 2021, 2021; Ullah et al., 2023; Xu et al., 2023).

Despite the technological advancements and extensive research on personalized medicine, the pharmaceutical manufacturing industry continues to rely on mass-production models due to their cost-effectiveness (Andreadis et al., 2022). Mass customization aims to produce individually designed products for the patients while maintaining production cost-effectiveness (Fuenmayor, O'Donnell, et al., 2019). Three-dimensional printing (3DP) or additive manufacturing (AM) plays a pivotal role in revolutionizing the pharmaceutical manufacturing landscape, offering the ability to create customized medication forms with distinct shapes and drug release patterns not easily achievable with traditional methods (Ebrahimi et al., 2023; Ebrahimi and Ramezani Dana, 2022; Fuenmayor et al., 2018a; Fuenmayor, O'Donnell, et al., 2019; Ramezani Dana and Ebrahimi, 2023).

Droplet Deposition Modeling (DDM), a type of AM, requires feedstock material in granulate form, offering increased versatility in material options compared to conventional fused filament fabrication. This advantage can allow broader applications for DDM, making it a valuable and adaptable technology. Our earlier study assessed the drug release properties of oral dosage forms containing Hydrochlorothiazide using two AM techniques of DDM and FFF (Ebrahimi et al., 2023). The results

Abbreviations: AM, additive manufacturing; 3D, three dimensional; 3DP, three-dimensional printing; FFF, fused filament fabrication; ME, Material extrusion; APF, Arburg Plastic Freeforming; DDM, droplet deposition modelling; CAD, computer aid design; API, active pharmaceutical ingredient; HME, hot-melt extrusion; IM, injection moulding; T_g, glass transition temperature; T_m, melting temperature; IVR, *In Vitro* drug release; MFI, melt flow index; PCL, polycaprolactone; PVP/VA, Kollidon VA64; DSC, Differential scanning calorimetry; FTIR, Fourier transform infrared spectroscopy; SEM, scanning electron microscopy.

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indicated that due to the filament nature of FFF and droplet deposition nature of the DDM technique, fabricated tablets with identical infill densities had distinct microstructures, resulting in variable drug release profiles. DDM technique demonstrated satisfactory reproducibility compared to pharmacopoeia specification (McDonagh et al., 2023a). Earlier, DDM application has been explored as a novel approach to enhance the release of poorly water-soluble compounds and to achieve desired dosage levels by requiring lower drug loadings compared to conventional thermoplastic processing techniques (Welsh et al., 2019). DDM has been used for the fabrication of multiple medications using different dual-drug designs for achieving simultaneous, delayed, and pulsatile drug release regimes (McDonagh et al., 2023a, B. Zhang et al., 2021).

DDM's layer-by-layer deposition of molten plastic allows for the customization of drug release profiles. However, challenges such as material adhesion and viscosity affect its applicability. On the other hand, injection molding (IM) is a high-production method widely used for tablet manufacturing, offering notable advantages such as time and cost savings, as well as increased efficiency (Ebrahimi et al., 2023; Fuenmayor et al., 2018a; Fuenmayor, Forde, et al., 2019; Fuenmayor, O'Donnell, et al., 2019; Walsh et al., 2022; Welsh et al., 2019; Wirth et al., 2023; Xu et al., 2023). IM is a sophisticated, solvent-free manufacturing process, allowing for the production of complex shapes with high precision and repeatability widely utilized in various industries. This method begins with the feeding of raw materials, typically in pellet or granule form, into a high-temperature chamber. Here, the material melts to form a viscous liquid and is then injected under high pressure into precisely designed molds.

Combining AM and IM techniques provides opportunities for modifying and controlling drug release profiles from a single tablet. The dosage forms manufactured through the IM method typically possess a dense structure, resulting in a slower drug release kinetic compared to tablets fabricated using AM techniques (Ebrahimi et al., 2023; Fuenmayor, O'Donnell, et al., 2019; Qi and Craig, 2016; Tambe et al., 2021; Xu et al., 2023). Recently, researchers have investigated combining FFF and IM techniques for the fabrication of multiple drugs from a single tablet (Fuenmayor, O'Donnell, et al., 2019), and achieve the modified and controlled drug release profile through the use of bilayer solid dosage form tablets (Xu et al., 2023).

In our study, the DDM technique is employed to address the limitation in conventional tablet manufacturing pertains to the challenge of adjusting drug release properties by modifying the processing parameters, such as infill percentage. DDM's versatility in modifying these parameters allows precise control over the drug release characteristics, a crucial aspect of personalized medicine. However, the incorporation of high-viscosity material as feedstock in DDM presents particular challenges. These challenges stem from the material properties affecting the printing process, notably the high adhesion between layers and the nozzle, and reduced adhesion to the printing platform. Addressing these challenges, our primary objective was to develop a comprehensive manufacturing platform capable of customizing polypill fabrication. This platform leverages the strengths of both DDM and IM techniques. While DDM offers the flexibility of altering infill percentages to alter the drug release properties, IM is utilized to counteract the limitations associated with DDM's handling of incompatible feedstock viscoelastic properties. This combined approach enables the fabrication of tablets with varied structural properties, denser tablets using IM, and those with higher porosity through DDM allowing us to tailor drug release characteristics to individual patient needs. To evaluate the effectiveness of this mass customization approach, we prepared two formulations consisting of Caffeine and Paracetamol as model drugs using the HME technique. These formulations were then processed using both DDM printing and IM, adopting an over-molding methodology. Our comprehensive evaluation includes analyzing structural composition, thermal properties, melt-flow characteristics, internal structure, friability, and drug-release properties. Through these assessments, we aim to provide valuable insights into advanced pharmaceutical manufacturing techniques.

2. Materials and methods

2.1. Materials

Polycaprolactone (PCL) in powder form (Capa 6506, average Mw = 50,000) was purchased from Perstop (Cheshire, UK). Kollidon® VA64 (PVP/VA) was obtained from BASF Ireland (Cork, Ireland). Caffeine was purchased from VWR International (Dublin, Ireland). Both Paracetamol (acetaminophen, Batch number: MKCD6375) and Phosphoric acid were supplied from Sigma Aldrich, Wicklow, Ireland). Potassium chloride (KCL) and Hydrochloric acid (HCL) 37 % were obtained from Merck KGaA, (Darmstadt, Germany). Methanol (99.99 %, HPLC grade) was ordered from Honeywell (Seetze, Germany). Deionized water was used throughout the experiment. All chemicals and solvents were analytical grade. The formulations were prepared as outlined in Table 1.

2.2. HME

The formulations were accurately weighed, mixed, and dried under a vacuum overnight at 50 °C before the extrusion process. The prepared formulations were extruded using lab-scale the PRISM TSE 16 TC -screw compounders twin (diameter: 25 mm, length: 1 mm) wired with a manual control panel (Thermo Electron stone, UK). HME was equipped with a conical-shaped cavity dye and a circular orifice. Following the extrusion process, the extruded filaments were passed through a conveyor air-cooled belt system (covered by Teflon film). In this process, the flange temperature, and barrel temperature were adjusted to 100 °C and 150 °C, respectively. The screw speed was set at 50 RPM and the feeding rate was adjusted to 2.5 kg/min. The compounded formulation was palletized using Rapid Granulator (Bredaryd, Sweden), size 5 mm.

2.3. DDM

The computer-aided design (CAD) software SolidWorks was used for designing the oral tablets with specific dimensions of 1.8 mm (thickness) and 10 mm (diameter). The CAD model was exported in the standard tessellation language (STL) file. The STL file was loaded in an Arburg freeformer 300-3X (ARBURG GmbH, Lossburg, Germany) for additive manufacturing fabrication. The processing parameters were adjusted considering the material surface tension, viscosity, and thermal properties. The initial printing condition was objected to: Layer height of 0.2 mm, nozzle diameter of 0.2 mm, nozzle temperature of 190 °C, barrel (zone 2) 180 °C, barrel (zone 1) 170 °C, and the droplet aspect ratio of 1.7. In addition, the printing angle was adjusted at 0/90°, and the number of contours was constant (1). Upon the HME process, the compounded formulation in pellet form was dried at 50 °C overnight and the granulates were fed via a hopper. The moisture content during the DDM process was controlled by operating the dryer with an adjusted temperature of 50 °C. Throughout the process, the fed material was followed by the hopper, heated, and melted through the cylinder. Following by reciprocating screw the melted formulation was passed into the material reservoir and towards the nozzle. The molten material in droplet form was deposited on the build plate, attached to a platform moving along the XY axis. Upn material deposition in the chamber with

Table 1
The drug and the polymer content used in the formulation.

Formulation number	Composition (w/w %)			
	PCL	PVP/VA	Caffeine	Paracetamol
1	38	57	–	5
2	38	57	5	–

a temperature lower than the material melting point, the deposited droplets were solidified and the 3D printed part was formed. In the DDM printing stage, the tablets were subjected to be manufactured with variable infill percentages (50 %, 75 %, and 100 %).

2.4. Injection moulding (IM)

BabyPlast 6/10P, Cronoplast S.L.; Rambaldi S.r.L., Lecco, Italy equipped with a 14 mm diameter piston was used for the fabrication of the tablets via IM. Each formulation was formerly dried overnight at 50 °C, loaded through the hopper into the plasticating chamber, and conveyed to the injection chamber. The plasticizing zone temperature, the chamber temperature, the nozzle temperature, the mold temperature, and the shot size were adjusted to control the reservoir filling and solidification of the tablets. The fabricated tablets via DDM were inserted into the full stainless steel mold cavity with the dimensions of 1.8 mm (thickness) and 10 mm (diameter) and pushed until the bottom of the orifice was reached (Xu et al., 2023). The overprinting process was conducted according to the processing parameters presented in Table 2. The IM stages were conducted for the tablet manufacturing of Caffeine and Paracetamol formulations.

Fig. 1 illustrates the mass-customized tablet design using DDM for the fabrication of the bottom layer and IM for the top layer. This design is subjected to distinct formulations: Paracetamol and Caffeine.

2.5. Melt flow index (MFI)

The melt flow index (MFI) was conducted using a Zwick Roell Cflow extrusion plastometer equipped with a 2 mm orifice die and following the guidelines of the ASTM standard D1238-13 using a fixed weight of 2.16 kg. MFI test has been determined with adjusted variable temperatures as 150 °C, 170 °C, and 190 °C. The melt flow test was conducted for 5 replicates per formulation and the average results were reported in g/10 min.

2.6. Rheology measurements

Rheology measurements were performed employing an oscillatory rheometer, TA Discovery Hybrid Rheometer HR30 (New Castle, PA, USA). The instrument was operated in parallel circular plate geometry with a plate of diameter 25 mm and a gap of 1 mm at 190 °C. The frequency sweep measurement was carried out under the angular frequency range of 0.1 to 100 rad/s at a steady strain amplitude of 1 %.

2.7. Differential scanning calorimetry (DSC)

DSC analysis was performed using Pyris 1 equipped with Intracooler II, Perkin Elmer 7, CT, USA. This test has been performed aiming to analyze the thermal characterization of pure drugs (Paracetamol and Caffeine), drug excipients (PVP/VA and PCL), as well as formulations upon each process (HME, DDM, and IM). The samples were dried in a vacuum oven at 50 °C overnight prior to the DSC test. A precisely weighed amount of sample (6–10 mg) was placed in a hermetically sealed DSC aluminum pan and subjected to: Heat scanning from 15.00 °C to 260.00 °C at 20.00 °C/min, Isothermal at 260.00 °C for 3 min, Cool from 260.00 °C to 15.00 °C at 5.00 °C/min, Isothermal at 15.00 °C for 5 min, Heat scanning from 15.00 °C to 260.00 °C at 5.00 °C/min. In addition, during this test Nitrogen gas with a flow rate of 50 ml/min was used as a purge gas. The DSC results were analyzed using OriginPro 2021 software (OriginLab Corp., Northampton, MA, USA).

Table 2
IM process parameters and their values employed for tablet fabrication using Paracetamol and Caffeine formulations.

Process parameters	Value
Shot size [mm]	15
Cooling time [sec]	30
1st injection pressure [bar]	70
1st injection pressure time [sec]	2
2nd injection pressure [bar]	60
2nd injection pressure time [sec]	6
H1-Plastification [°C]	160
H2-Chamber [°C]	150
H3-Nozzle [°C]	120

2.8. Fourier transform infrared spectroscopy (FTIR)

The FTIR analysis was conducted using a Perkin Elmer Spectrum One fitted with a universal ATR (Perkin Elmer, USA) with a wavelength range of 4000–600 cm^{-1}. FTIR test was used to provide information about the compatibility between the drug and polymer used for fabricated tablets. FTIR was conducted for Paracetamol, Caffeine, PVP/VA, and PCL, as well as formulations upon each process (HME, DDM, and IM). OriginPro 2021 software (OriginLab Corp., Northampton, MA, USA) was used for analyzing FTIR results.

2.9. Friability test

The friability test was required to evaluate the mechanical strength of the tablets due to abrasion, friction, or mechanical shock. The friability test has been carried out for each batch upon DDM fabrication as well as the over-molding process. Thus, the number of tablets randomly selected to afford a total weight of at least 6.5 g, dusted and weighted. The specimens were located in an auto-friability tester PTF E/ER (Pharma Test Apparatebau GmbH, Hainburg, Germany) and rotated at 25 rpm for 4 min. Afterward, the samples were dusted and the weights were recorded. The percentage of weight loss was calculated using Eq. (1).

$$\text{Friability}\,\% = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100 \quad (1)$$

2.10. In Vitro drug release (IVR)

The IVR test was carried out to investigate the drug release properties of oral tablets using the USP basket apparatus (Erweka® DT700LH dissolution system, Heusenstamm, Germany), applied on Distek dissolution system 2100B with a Distek temperature control system TCS 0200B (Distek Inc., USA). The fabricated tablets were submerged in 900 ml dissolution media with the pH:1.2 (HCL0.2 M) presented in each vessel with a controlled temperature of 37 ± 5 °C, and the basket rotation speed was set at 50 rpm. At predetermined time intervals, 5 ml was withdrawn, and 5 pre-heated media was added to each vessel to maintain the sink condition. The withdrawn samples were filtered through a 0.2 μm filter and analyzed via HPLC for drug quantification over time. The dissolution profile performed for the study was carried out by performing the subsequent activities (n = 6) over a 72-hour time point. Drug release quantification was conducted using the high-performance liquid chromatography (HPLC) method described in the following section.

2.11. HPLC assay of oral tablets

The drug contents in relevant aliquots were quantified using the HPLC Waters Alliance e2695 separations module equipped with a Waters 2487 dual absorbance detector (Waters Chromatography Ireland Ltd., Dublin, Ireland). The HPLC assay consisted of a stationary phase of an Eclipse 5 μm C18 column, 4.6 mm × 150 mm (Agilent, Santa Clara, CA, USA), and a mobile phase constituted of *ortho*-phosphoric acid, adjusted to pH 2.7 (A) and acetonitrile (B) at 25 °C according to the method validated previously (Robles-Martinez et al., 2019). The gradient system consisted of; A–B (87:13 v/v) until 2 mins, at this time

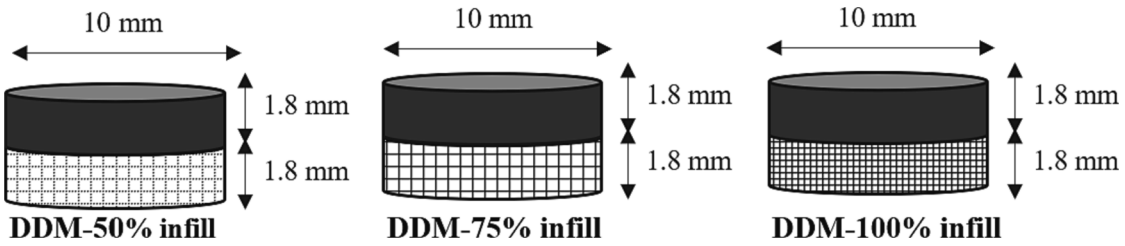

Fig. 1. A visual design of overprinting oral tablets using Paracetamol and Caffeine formulations. The bottom layer was fabricated via the DDM method. IM technique used for the overprinting stage (top layer). DDM and IM manufacturing stages have been conducted for both Paracetamol and Caffeine formulations.

point the proportion was changed to A–B (50:50 v/v) and kept for 1 min, then the condition was changed to the initial state, A–B (87:13 v/v) for 2 mins. Analysis was carried out at a wavelength of 263 nm, temperature of 25 °C, flow rate of 1.5 ml/min, injection volume was 10 μL, and a run time of 5 min. The retention times for Paracetamol, and Caffeine were 2 min and 3 min accordingly. Further analyses were performed using Empower ® Version 2.0 software.

2.12. Statistical analysis

Statistical analysis was performed on the rheological characteristic of the placebo and drug-contained formulations as well as IVR results of the Caffeine tablets fabricated via DDM, and over-molded tablets containing Caffeine and Paracetamol. This analysis utilized a two-way analysis of variance (ANOVA) performed using GraphPad Prism version 9 for macOS, GraphPad Software, San Diego, CA. In all the experiments, $p < 0.05$ was considered the acceptable value for intercepting the statistician's results. To differentiate drug release curves between subgroups, multiple comparisons were made using the Bonferroni post-hot test.

2.13. Scanning electron microscopy (SEM)

The morphology of the tablets fabricated with DDM and over-molding techniques was evaluated using SEM (Tescan Oxford Instruments, UK). To determine the degree of melt penetration, tablets were crashed under Nitrogen gas and the cross-sectional area of bilayer tablets was examined via SEM imaging. Before the SEM test, the samples were placed on an aluminum stub and the gold coating was applied using Baltec SCD 005 sputter coater (BAL-TEC GmbH, Germany) for 110 sec at 0.1 mBar vacuum. SEM observation has been conducted for the tablets before (upon manufacturing) and after the IVR assay.

3. Results and discussion

3.1. Manufacturing observation

In DDM, the careful adjustment of material properties and processing parameters is crucial in defining the characteristics of the deposited droplet chain, which in turn significantly influences the quality of the final printed product. Our previous research has shown that alterations in processing temperature can markedly affect the morphology of the deposited droplets (Ebrahimi et al., 2023). Specifically, lower processing temperatures result in the formation of spherical droplets, while higher temperatures produce filament-like droplets, highlighting DDM's sensitivity to thermal conditions.

Furthermore, modifications in the formulation composition and material content have been noted to change droplet properties, particularly in terms of adhesion to the substrate (Chu et al., 2017; S. Li et al., 2020). A major challenge in DDM is the high adhesion nature of some materials, which can hinder material flowability, disrupt droplet adhesion to the print bed, and lead to poor bonding with the printer bed surface. These issues compromise not only the structural integrity of the printed object but also the mechanical properties of the fabricated parts, as low bonding adhesion and layer distortion can substantially impact the final product (Zou et al., 2016).

A detailed analysis of feedstock material properties, especially viscosity, is essential for successful DDM fabrication to ensure optimal material flow. Caffeine and Paracetamol have high melting points of around 240 °C and 170.5 °C, respectively (Fuenmayor et al., 2018a; Healy et al., 2019). In accordance with prior research findings, these drugs are well-suited for hot melt-based processes such as IM, AM, and HME (Fuenmayor et al., 2018a; Krueger et al., 2023; Zhang et al., 2021). In this study, the ideal operating temperature for a placebo formulation containing 60 % PVP/VA and 40 % PCL was around 190 °C. Our study encountered that the addition of 5 % Paracetamol to the formulation has introduced a challenge related to viscosity. The increased viscosity of Paracetamol formulations could potentially hinder the printing process via the DDM technique at a similar temperature range (190 ± 10 °C), leading to poor adhesion between the material and the printing bed. This resulted in material adherence to the nozzle and uneven material deposition.

To overcome this issue, adjusting the formulation, like increasing PCL content to modify adhesiveness, was considered but not pursued due to potential increases in the formulation's hydrophobic properties and reduced drug solubility. In addition, during AM process, higher processing and nozzle temperatures are known to enhance the mobility of amorphous thermoplastic polymer chains. However, high operating temperatures require longer diffusion times between layers, leading to the 'elephant foot' deformity in printed parts. This deformation, characterized by material spreading at the base of a structure, creating a wider, flatter layer, is a common issue in AM when hot droplets are deposited too closely or when a high bed temperature prevents immediate layer solidification. The 'elephant foot' effect can also be exacerbated by the weight of the object compressing partially cooled lower layers, or by a nozzle positioned too close to the printing bed (Del Rosario et al., 2022). Moreover, considering Paracetamol's decomposition temperature (above 160 °C), increased processing temperatures can accelerate drug degradation (Calvino et al., 2023). Therefore, increasing the temperature to address high material adhesiveness was not a viable solution in DDM, given the risk of drug degradation.

Despite the limited application of DDM for processing Paracetamol formulation, the same formulation was successfully processed using IM, demonstrating the method's ability to handle high-viscosity materials efficiently. In addition, the formulation containing 57 % PVP/VA, 38 % PCL, and 5 % Caffeine exhibited favorable processing characteristics in both DDM and IM. Caffeine tablets were thus prepared using DDM, while both Caffeine and Paracetamol were used as feedstock for overprinting tablets via IM. Hence, considering the drug properties is crucial to fabricating effective and stable dosage forms and optimizing drug delivery. The manufacturing times for each tablet were determined to be approximately 1.6 min for DDM and 1 min for IM, highlighting the efficiency of both methods.

3.2. MFI

The MFI test, a crucial measure in assessing the flowability of thermoplastic materials, was conducted to determine the mass of the formulation (in grams) that passed through a capillary of a specific length and diameter over ten minutes. As depicted in Fig. 2, MFI tests were carried out on a placebo formulation (60 % PVP/VA-40 % PCL) and two drug-encapsulated formulations containing 57 % PVP/VA-38 % PCL-5 % Caffeine and 57 % PVP/VA-38 % PCL-5 % Paracetamol at varying temperatures of 150 °C, 170 °C, and 190 °C. The results showed that higher MFI values directly correlate with increased material flowability and decreased melt viscosity.

For a consistent material flow in the DDM technique, the minimum MFI value should be approximately 22 g/10 min (Ebrahimi et al., 2023). It is important to note that MFI values can vary among different blend formulations due to changes in the properties of the formulation itself (Fuenmayor et al., 2018a). At 190 °C, the average MFI value for the Caffeine-containing formulation was higher (23.4 ± 10 % g/10 min) compared to the placebo (20.9 ± 10 % g/10 min) and Paracetamol (11.58 ± 8 % g/10 min) formulations. Hence, at 190 °C Paracetamol formulation with the average melt viscosity value of 11.58 ± 8 % g/10 min decreased below the minimum required MFI value of approximately 22 g/10 min (Ebrahimi et al., 2023).

This higher MFI value, indicative of lower viscosity, suggests that Caffeine acts as a plasticizer, increasing chain mobility and overall formulation flowability. Conversely, the lower MFI value observed in the Paracetamol-encapsulated formulation indicates an anti-plasticization effect, reducing material flowability upon the addition of Paracetamol. High-viscous formulations can lead to poor adhesion between the bed surface and the material, resulting in material adhering to the nozzle and uneven material deposition during the printing process. The Caffeine formulation showed consistent droplet deposition at 190 °C, with no issues observed during tablet fabrication. This observation indicates that the Caffeine formulation has the necessary flowability for consistent material deposition, ensuring high-quality tablet production via DDM. Interestingly, both Paracetamol and Caffeine formulations were successfully used in the over-injection process.

3.3. Rheology measurements

Polymer viscosity plays a pivotal role in determining polymer chain mobility, bond formation, and the strength of bonds between layers in additive manufacturing processes. A decrease in material viscosity leads to increased mobility of polymer chains and more effective intermingling between material layers. This enhanced mobility facilitates stronger adhesion between printed layers, which is critical for the structural integrity of the final product (Shahriar et al., 2017). In the context of DDM, selecting a feedstock formulation with the right viscosity characteristics is essential for consistent material deposition, sufficient material adhesion, and achieving high-quality printed parts. Lower-viscosity materials can improve wetting between layers, creating a more substantial interface and stronger bonds between them (Golbang et al., 2020). However, it is important to note that excessively low viscosity can lead to over-deposition of material, which can hinder proper adhesion between layers and the printing platform (Fuenmayor et al., 2018b).

To understand the rheological properties of various formulations, rheology measurements were conducted. These measurements included formulations of 57 % PVP/VA-38 % PCL-5 % Paracetamol, a placebo consisting of 60 % PVP/VA-40 % PCL, and 57 % PVP/VA-38 % PCL-5 % Caffeine. The results, illustrated in Fig. 3, revealed clear viscosity differences among these formulations. Each of them exhibited distinct characteristics; while the difference between Caffeine and the placebo was less pronounced compared to Paracetamol. The statistical analysis

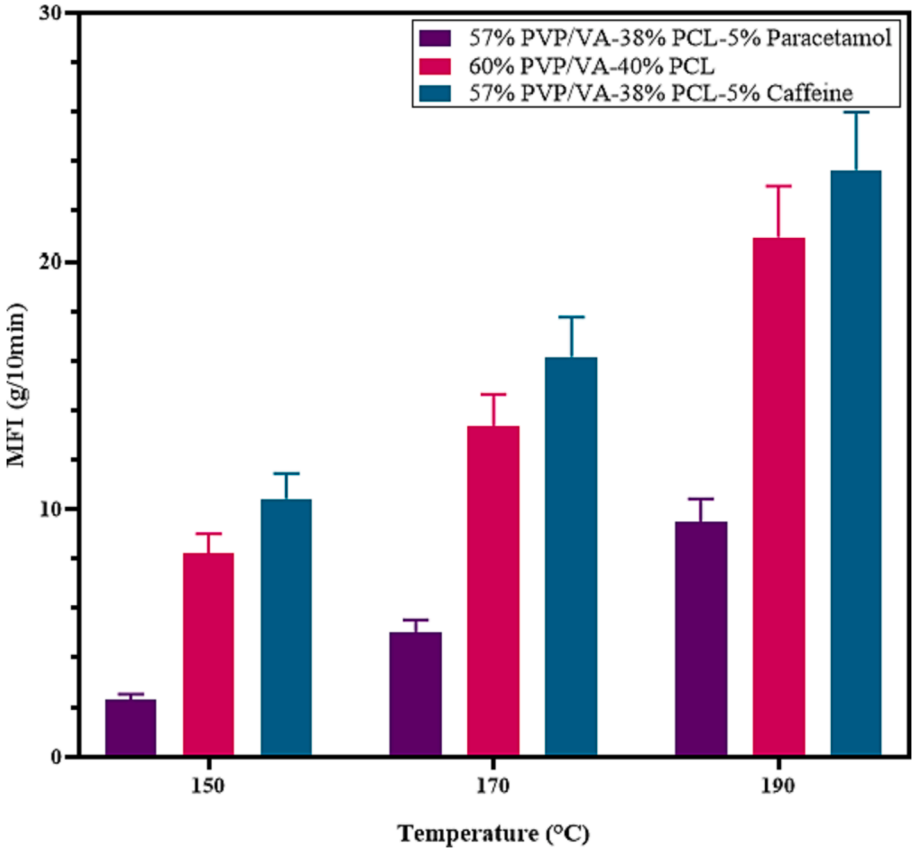

Fig. 2. MFI measurements of encapsulated Paracetamol, Caffeine, and placebo formulations were carried out at 150 °C, 170 °C, and 190 °C.

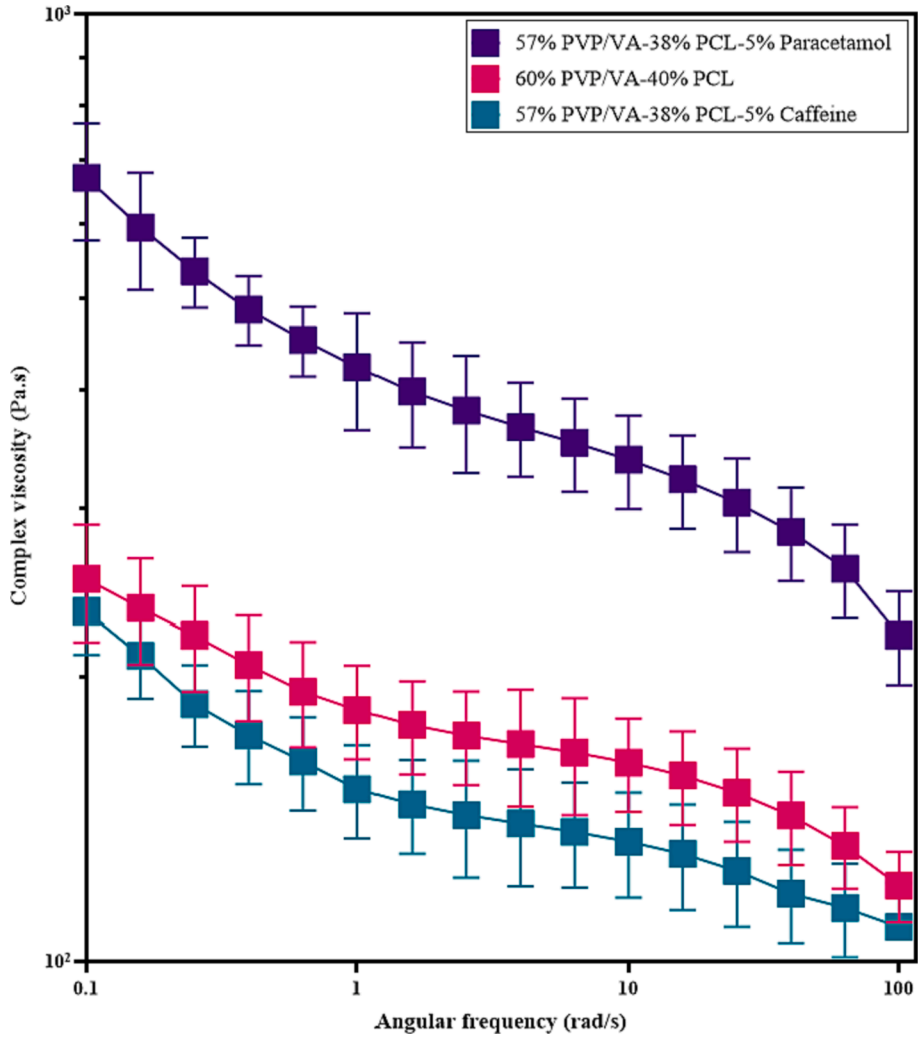

Fig. 3. Complex viscosity as a function of the angular frequency of the formulations consisting of 57% PVP/VA-38% PCL-5% Paracetamol, 60% PVP/VA-40% PCL, and 57% PVP/VA-38% PCL-5% Caffeine.

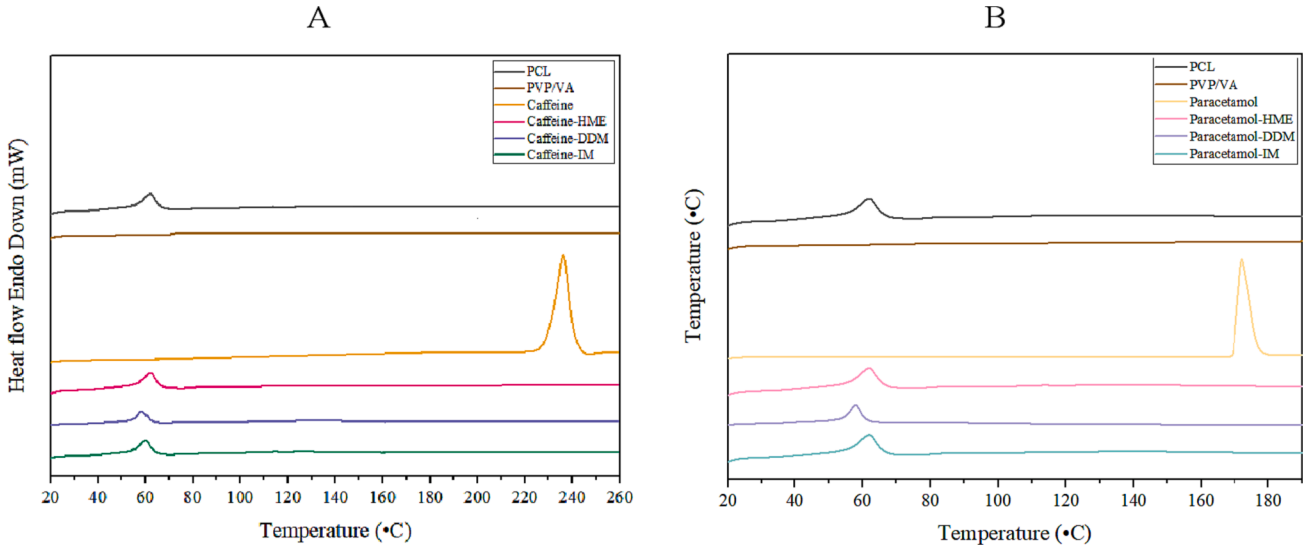

Fig. 4. Overlaid DSC thermograms of neat material and encapsulated (A) Caffeine and (B) Paracetamol upon HME, DDM, and IM processing.

showed that the viscosity behavior of the placebo and Caffeine formulations exhibited fewer variations (P value = 0.0001), while the rheological characteristics of the Paracetamol formulation were notably different (P value < 0.0001). As the frequency of measurement increased from 0.1 rad/s to 100 rad/s, a significant decrease in viscosity was observed across all formulations, consistent with the shear-thinning behavior of PVP/VA, where the viscosity decreases with increasing shear frequency. At a frequency of 0.1 rad/s, the average complex viscosity of the Paracetamol formulation was measured at 671.99 Pa.s. In comparison, at the same frequency, the placebo and Caffeine formulations exhibited average viscosities of 253.09 Pa.s and 233.94 Pa.s, respectively. At the maximum frequency of 100 rad/s, the average viscosity values for the formulations containing Paracetamol, placebo, and Caffeine were recorded as 220.81 Pa.s, 120.27 Pa.s, and 108.77 Pa.s, respectively. These findings indicate that the formulations containing 60 % PVP/VA-40 % PCL and 57 % PVP/VA-38 % PCL-5 % Caffeine meet the critical viscosity threshold necessary for processing via AM, unlike the Paracetamol formulation (57 % PVP/VA-38 % PCL-5 % Paracetamol), which exhibited higher viscosity values beyond the optimal range for AM processing.

3.4. DSC

Fig. 4 presents the DSC thermograms (heating cycles) of PCL and PVP/VA, alongside the thermograms of each formulation following HME, DDM, and IM processing. Fig. 4 (A) depicts the thermogram for the Caffeine formulation, while Fig. 4 (B) shows the results for the Paracetamol formulation. It was observed that PCL exhibits a distinct melting peak at around 60 °C, consistent with its semi-crystalline nature (Dalton et al., 2023). Conversely, the PVP/VA material did not exhibit a melting peak, reflecting its amorphous character as demonstrated in previous experimental findings (Ebrahimi et al., 2023; Xu et al., 2023).

For the formulation containing Caffeine, a sharp melting peak was identified at approximately 240 °C, which corresponds to the melting temperature of Caffeine (Ebrahimi et al., 2023; Krueger et al., 2023). In the case of the Paracetamol formulation, a pronounced melting peak was noted at around 170 °C, indicative of Paracetamol's presence (Healy et al., 2019; Patel et al., 2023). Interestingly, melt-blended formulations containing both Caffeine and Paracetamol exhibited a single transition peak around 60 °C, aligning with the melting temperature of PCL (Fuenmayor, O'Donnell, et al., 2019). The absence of distinct peaks for Caffeine and Paracetamol in the DSC thermograms of the processed formulations could be attributed to the molecular dispersion of the drugs within the polymer matrix during the HME process. Alternatively, this observation may be due to the relatively low drug content within the formulations, which might not generate a significant thermal response in DSC analysis (Ebrahimi et al., 2023).

3.5. FTIR

In the FTIR analysis, the spectra of raw materials and the processed formulations containing Caffeine and Paracetamol are depicted in Fig. 5-A and Fig. 5-B, respectively. PCL displayed characteristic absorption bands at various wavenumbers: two peaks at 2946 cm^{-1} and 2865 cm^{-1}, indicative of stretched methylene groups, a peak at 1722 cm^{-1} corresponding to the carbonyl (C═O) group, and another peak at 1160 cm^{-1} signifying symmetric stretching of the COC bonds (Dalton et al., 2023). In the PVP/VA spectrum, the peak observed at 1729 cm^{-1} is associated with the vinyl acetate group, while the peak at 1663 cm^{-1} relates to the C = O group of the pyrrolidone ring (Ebrahimi et al., 2023). Additionally, the stretching vibration of the C-N bond is represented by the peak at 1231 cm^{-1}.

Caffeine's spectrum exhibits distinct peaks at 3107 and 2968 cm^{-1}, corresponding to aromatic C–H stretching (Hasan and Alharthi, 2022). Vibrational peaks observed at 1653 and 1695 cm^{-1} are attributed to the stretching vibrations of carbonyl groups (C═O), C═C bonds, and C═N bonds present in caffeine. The peak at 740 cm^{-1} is indicative of the stretching of the C–C bond of caffeine (Paradkar and Irudayaraj, 2002). For Paracetamol, characteristic vibrational peaks were detected for N–H stretching of the amide group at 3328 cm^{-1} (Patel et al., 2023). The peak at 1644 cm^{-1} corresponds to the C═O stretching of the amide group, while the peak at 1602 cm^{-1} is assigned to C═C stretching. The absorption peak at 1256 cm^{-1} is attributed to symmetrical bending in C-N stretching, and the vibrational peak at 837 cm^{-1} signifies the *para*-disubstituted aromatic ring.

Upon analyzing the processed formulations, all primary vibrations observed in the raw materials were present, and no new peaks were detected. This indicates that there was no evidence of interaction between the ingredients in the different samples, suggesting that the processing methods (HME, DDM, and IM) did not induce any chemical changes in the formulations.

3.6. Friability test

The friability of the tablets was assessed following the guidelines set forth by the United States Pharmacopeia (USP). Previous studies have

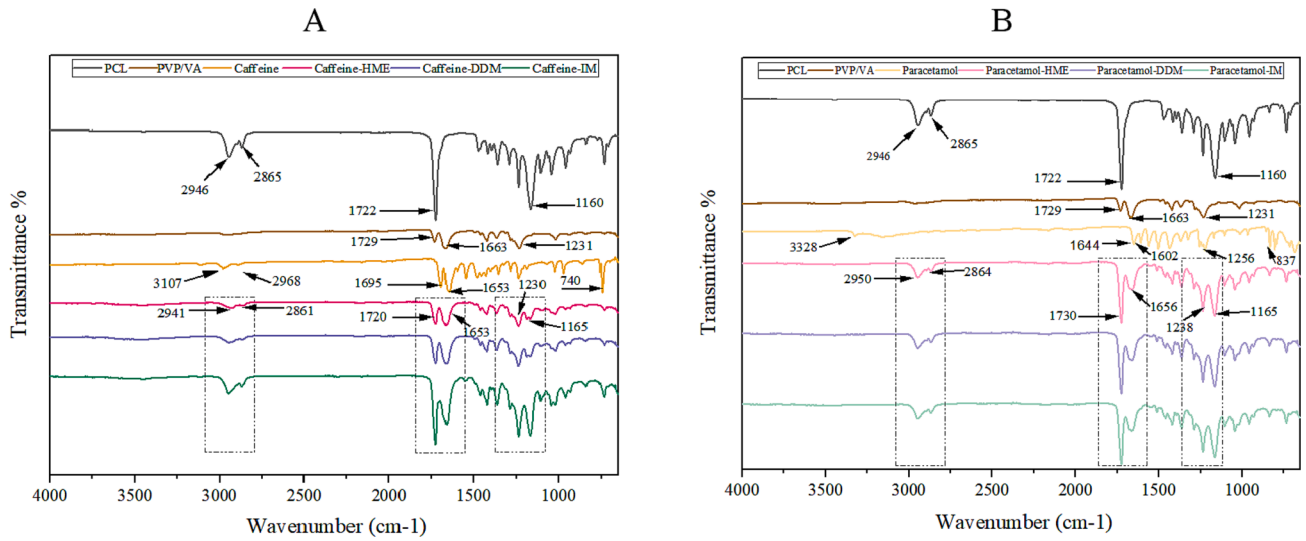

Fig. 5. FTIR spectra of neat material and encapsulated (A) Caffeine and (B) Paracetamol upon HME, DDM, and IM processing.

shown that tablets fabricated using both DDM and IM possess appropriate physical integrity, as evidenced by the absence of weight loss during friability testing (Ebrahimi et al., 2023). Additionally, the properties of the materials used in the formulation are pivotal in determining the internal structure of the tablet, which in turn significantly impacts the quality of the final product (Zhang et al., 2021). The test was applied to batches of Caffeine additive manufactured tablets with varying infill percentages, as well as over-molded tablets made using Caffeine and Paracetamol formulations. In considering the composition of these formulations, both Caffeine and Paracetamol contained 38 % PCL, a material known for its significant flexibility and elasticity (Ebrahimi et al., 2023). After undergoing the friability test, no signs of cracks, cleavage, or breakage were observed on the surface of any of the tablets. As a result, the Caffeine additive manufactured tablets, irrespective of their infill percentages, and the over-molded tablets comprising Caffeine and Paracetamol formulations demonstrated no weight loss, maintained their physical integrity, and met the required standards. This outcome can be attributed to the robust adhesion between layers achieved during the DDM and over-molding manufacturing stages, confirming the resilience of these tablets to handling and transportation stresses.

3.7. IVR

The physical properties of the drugs, particularly their solubility characteristics significantly affect the IVR results. As such, for the tablet manufacturing and optimization Caffeine and Paracetamol release profile considering the drug thermal stability during manufacturing processes and the drug solubility characteristics are necessary as they affect the IVR results. In addition, the design of pharmaceutical products, particularly in terms of their physical structure, plays a crucial role in modifying drug release properties (Goyanes et al., 2015; Robles-Martinez et al., 2019). Specifically, the mechanism of drug dispersion can be influenced by altering the porosity of the tablet matrix, which in turn affects diffusion and dissolution rates. In this context, tablets fabricated using the IM technique have been observed to exhibit slower drug release profiles compared to those produced via DDM. This difference is hypothesized to result from the lower tortuosity of the matrix created during IM, where molten material is injected under high pressure (Van Der Merwe et al., 2020). To further investigate this phenomenon, studies were conducted to assess the impact of different infill percentages of Caffeine on the drug release profiles of Caffeine and Paracetamol in over-molded tablets. IVR studies were carried out for Caffeine-printed dosage forms with varying infill percentages, as well as for tablets containing printed Caffeine with over-molded Paracetamol. The results of these studies are presented in Fig. 6 and Fig. 7.

Fig. 6 illustrates the IVR results for over-molded tablets; specifically, Fig. 6-A shows the drug release profiles of DDM-printed tablets containing Caffeine, and Fig. 6-B presents the release percentages of over-molded Paracetamol tablets. Based on the IVR results, it was observed that increasing the infill percentage of Caffeine tablets during the printing process resulted in a decreased drug release rate for Caffeine, a trend commonly seen in melt-based AM solid dosage forms. For instance, over 72 h, the Caffeine release profile from over-molded tablets containing a printed Caffeine formulation with 100 % infill density exhibited the slowest drug release rate compared to tablets with 75 % and 50 % infill percentages. Within the same batch, the tablets with 100 % infill density demonstrated a 42 % drug release rate. In contrast, the fastest Caffeine release rate was observed in tablets with a 50 % infill density, achieving 82 % release over 72 h.

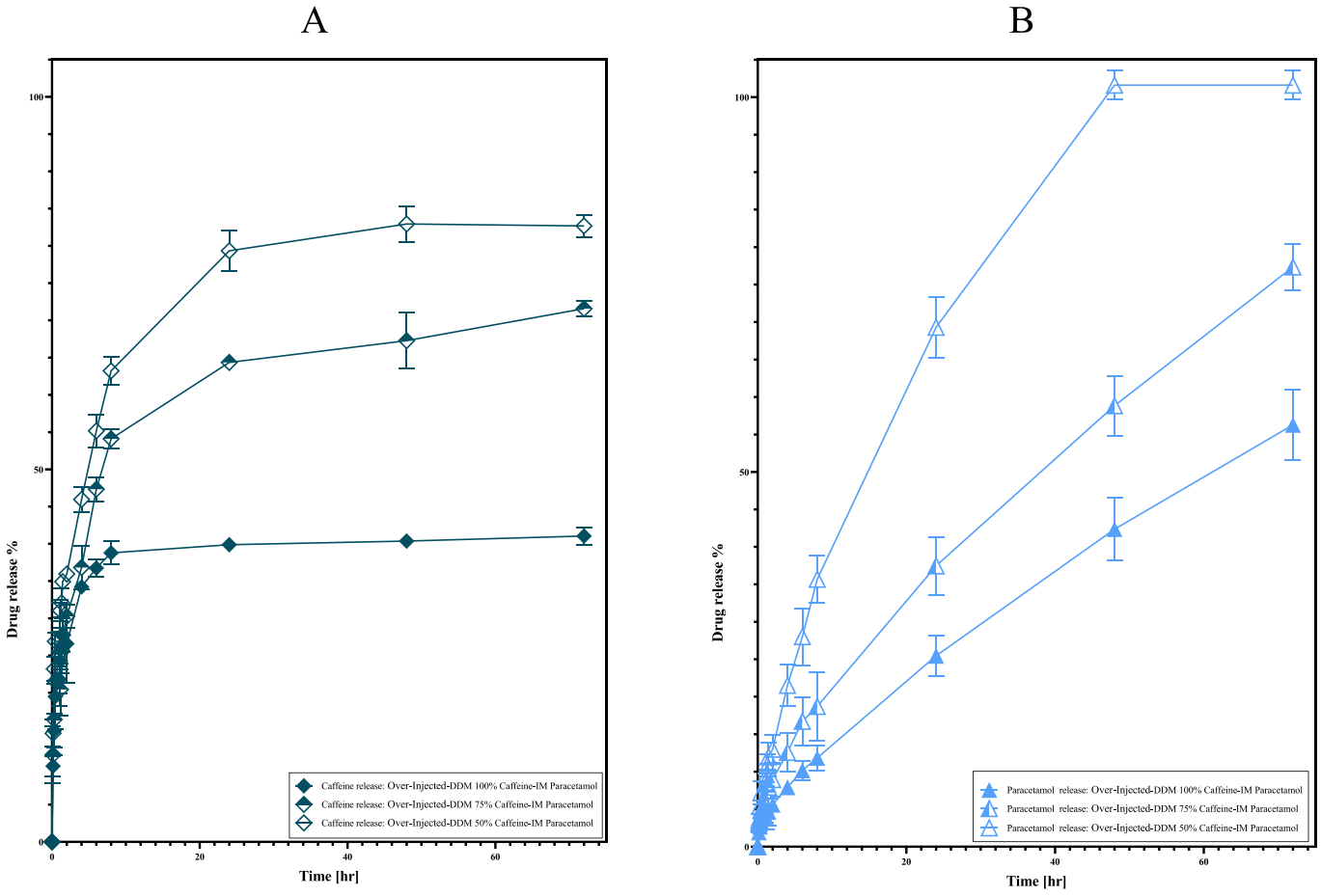

Fig. 6. Release profiles of additive-manufactured Caffeine (A) and over-molded Paracetamol (B).

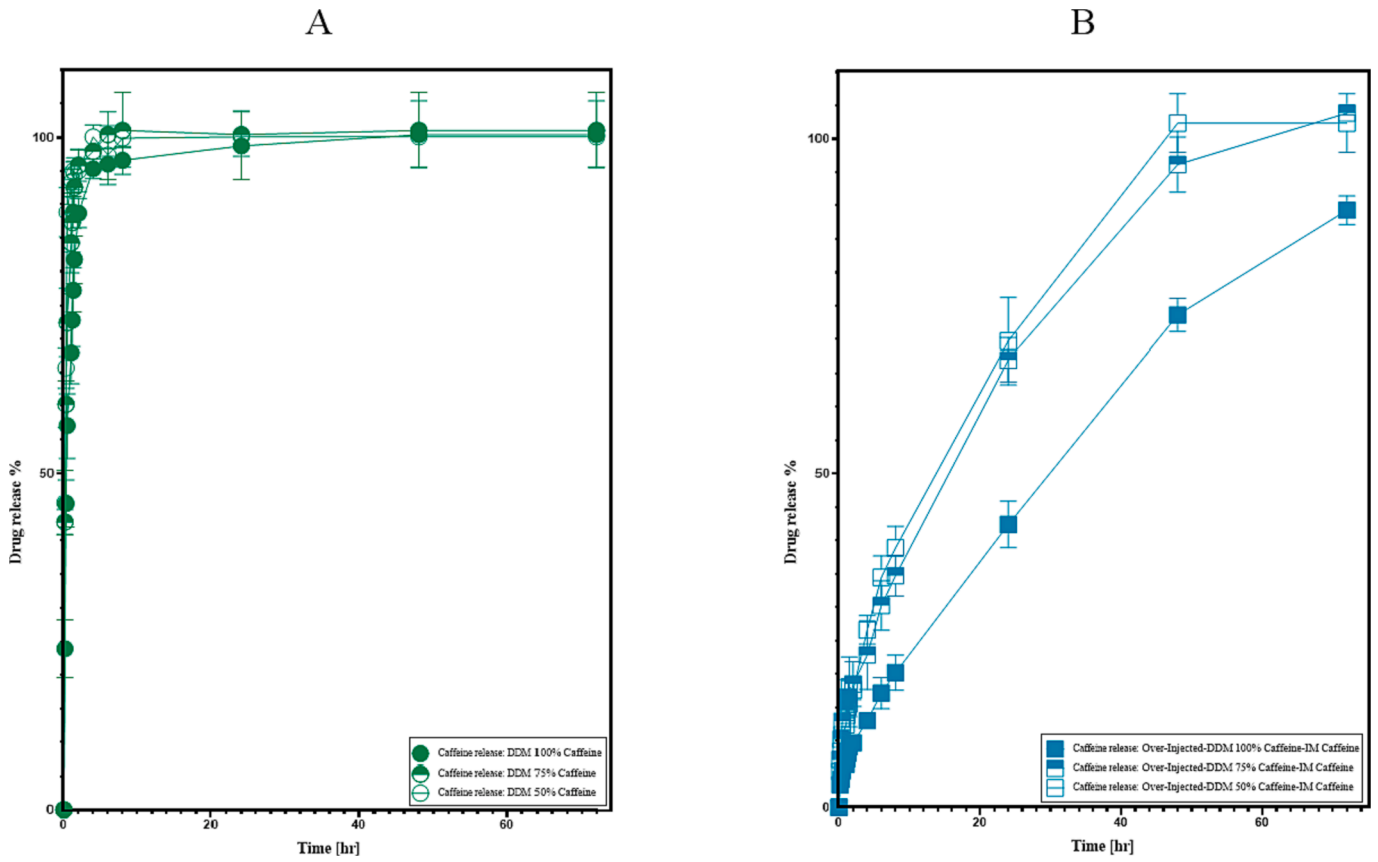

Fig. 7. Caffeine release profile of fabricated tablets using A); DDM technique (single layer) and B) IM (over-molded).

In the over-molded batch combining DDM Caffeine and IM Paracetamol tablets, as illustrated in Fig. 6-A and Fig. 6-B, the drug release profiles of printed Caffeine tablets with varying infill densities (50 %, 75 %, and 100 %) were observed to be more sustained compared to the release profile of over-molded Paracetamol. DSC testing has confirmed the thermal stability of both drugs during each processing stage (Fig. 4). Observed differences in dissolution rates between Paracetamol and Caffeine (Fig. 6-A and Fig. 6-B) can be due to the variation in the drug water solubility aspect. Since Paracetamol is sparingly soluble in water and more soluble in certain organic solvents, has a lower tendency for drug dissolution and exhibits a slower dissolution rate compared to Caffeine in the same conditions. So, the relatively higher solubility of Caffeine in water and organic solvents can contribute to a faster dissolution rate. This difference in drug release rates can be also attributed to the high density of the Paracetamol tablets formed during the IM process, which limits the pathways available for the drug molecules to escape from the tablet matrix into the surrounding medium, thereby reducing the contact area and slowing the drug release over time (Ebrahimi et al., 2023).

Among the over-molded batches, the slowest drug release rate was found in the Paracetamol tablets, particularly those combined with Caffeine tablets at 100 % infill density. Conversely, the fastest drug release rate for Paracetamol was observed in the batch with a 50 % infill density of Caffeine. It was also noted that at some study time points, the Paracetamol release profiles exceeded those of Caffeine. This may be due to the decreasing thickness of the Caffeine tablet's outer layer as the diffusion process progresses, thereby enhancing the contact between the tablet core and the surrounding liquid, leading to increased drug release (Alzahrani et al., 2022; R. Li et al., 2022a).

Over 24 h, the drug release from over-molded Paracetamol tablets in the batch with 100 % Caffeine infill was lower (25 %) than the Caffeine release from the same batch (40 %). However, by 48 h, the drug release percentages of Caffeine and Paracetamol became similar, at approximately 40 %. After 72 h, these percentages increased to 42 % for Caffeine and 58 % for Paracetamol, respectively. For the over-molded Paracetamol tablets containing Caffeine with 75 % infill density, the drug release rate over 72 h was slightly higher at 78 %, compared to the Caffeine tablets with the same infill density (71 %).

The drug release profile of over-molded Paracetamol tablets containing Caffeine with 100 % infill density displayed a 55 % release over 72 h, while the corresponding Caffeine tablets showed a 42 % release rate. Similarly, over-molded Paracetamol and Caffeine tablets with 75 % infill density exhibited drug release percentages of 77 % and 71 %, respectively. The fastest drug release profile was seen in over-molded Paracetamol tablets containing Caffeine with 50 % infill density, achieving 100 % release within 48 h.

Fig. 7-A presents the IVR results for Caffeine tablets fabricated with 100 %, 75 %, and 50 % infill densities. Fig. 7-B shows the drug release characteristics from over-molded batches containing Caffeine-Caffeine. Notably, the IVR results for Caffeine release varied significantly among the different batches of printed Caffeine, over-molded Caffeine-Paracetamol, and over-molded Caffeine-Caffeine ($p < 0.0001$), as evident in Fig. 6 (A and B) and Fig. 7 (A and B). A decrease in tablet infill density led to a faster drug release profile, attributed to the increased diffusion and dissolution mechanisms (Ebrahimi et al., 2023; Van Der Merwe et al., 2020). Caffeine tablets fabricated using DDM exhibited quicker drug release compared to over-molded Caffeine tablets, likely due to higher porosity, enhanced contact with aqueous environments, and accelerated dissolution mechanisms (Ebrahimi et al., 2023; R. Li et al., 2022b; Zhang et al., 2021). In the first 4, 6, and 8 h, 100 % of the initially introduced Caffeine was released for the additive manufactured Caffeine tablets with 50 %, 75 %, and 100 % infill percentages, respectively. When comparing Caffeine release profiles among the over-molded tablets, the release profile from the Caffeine-Paracetamol

batches was found to be more sustained compared to the Caffeine-Caffeine over-molded batches. Over-molded Caffeine tablets with 50 %, 75 %, and 100 % infill densities showed drug releases of 100 % (over 48 h), 100 % (over 72 h), and 90 % (over 72 h), respectively.

These IVR findings underscore the versatility and efficacy of mass customization in pharmaceutical manufacturing. By adjusting the infill densities in the DDM process and combining them with the IM technique, the drug release profiles of the fabricated bilayer tablets can be precisely tailored to meet specific requirements. This adaptability is crucial, especially in the context of personalized medicine, where drug release rates need to be customized according to individual patient needs or specific population characteristics. The observed variations in drug release profiles demonstrate that a slow-release profile can be achieved through the IM technique, while the DDM technique offers tunability in drug release by incorporating variable infill percentages. Thus, these results confirm that applying a single technique like DDM or combining processing techniques like DDM and IM allows for the customization of drug release profiles, enhancing the potential for personalized pharmaceutical therapies from fast to modified drug release.

The IVR results broadcast the importance of the mass-customization strategy in determining personalized drug release profiles. The application of this strategy emphasizes the requirements for careful selection of manufacturing techniques and adjusting the processing parameters to establish individual, clinically relevant drug dissolution profiles. Such customization holds promise for tailoring drug delivery through the utilization of both DDM and IM techniques, the feasibility of observing distinct release profiles ranging from fast to modified drug release profiles.

3.8. SEM

SEM was utilized to investigate the internal morphology of over-molded tablets with high precision. Fig. 8 displays SEM images that reveal the internal structure of over-molded tablets containing Caffeine-Paracetamol both before and after the IVR assay, specifically in Fig. 8 (A, B, C) before IVR and Fig. 8 (A′, B′, C′) for after IVR. The SEM analysis showed a uniform mixture in the formulation without any agglomeration, highlighting the effectiveness of the manufacturing process in achieving a homogenous distribution. The images revealed the impact of the manufacturing process on the internal structure: the distinguishable DDM printed patterns with an internal filament and tortuosity structure are evident in the bottom section of the tablets (Fig. 8 A, B, C, and Fig. 9 A, B, C), while the denser and smoother top layer reflects the nature of the IM process. Additionally, it was observed that lower infill densities in DDM tablets allow for greater penetration of molten polymer during the injection cycle, while higher infill densities reduce this penetration (Fuenmayor, O'Donnell, et al., 2019).

Comparing the internal structures of the over-molded tablets before and after IVR (Fig. 8 A, B, C, and A′, B′, C′), significant differences were noted in the IM section (Paracetamol). This observation aligns with the IVR profiles indicated in Fig. 6, where up to 24 h, DDM tablets (Caffeine) had a faster drug release rate than those produced with IM

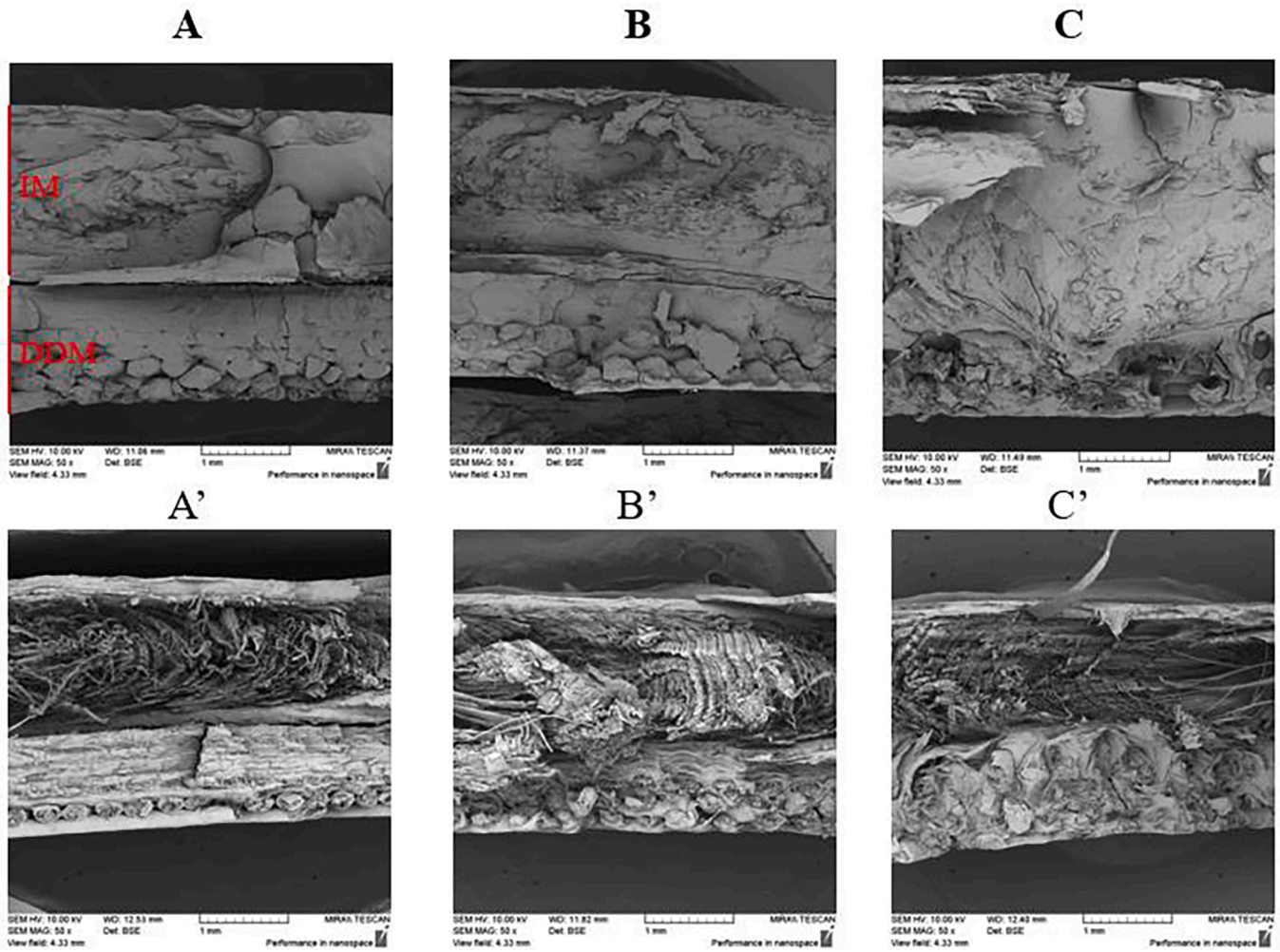

Fig. 8. SEM images of over-molded tablets (cross-section) before IVR; A: DDM-100% Caffeine-IM Paracetamol, B: DDM-75% Caffeine-IM Paracetamol, C: DDM-50% Caffeine-IM Paracetamol; and after IVR, A′: DDM-100% Caffeine-IM Paracetamol, B′: DDM-75% Caffeine-IM Paracetamol, C′: DDM-50% Caffeine-IM Paracetamol.

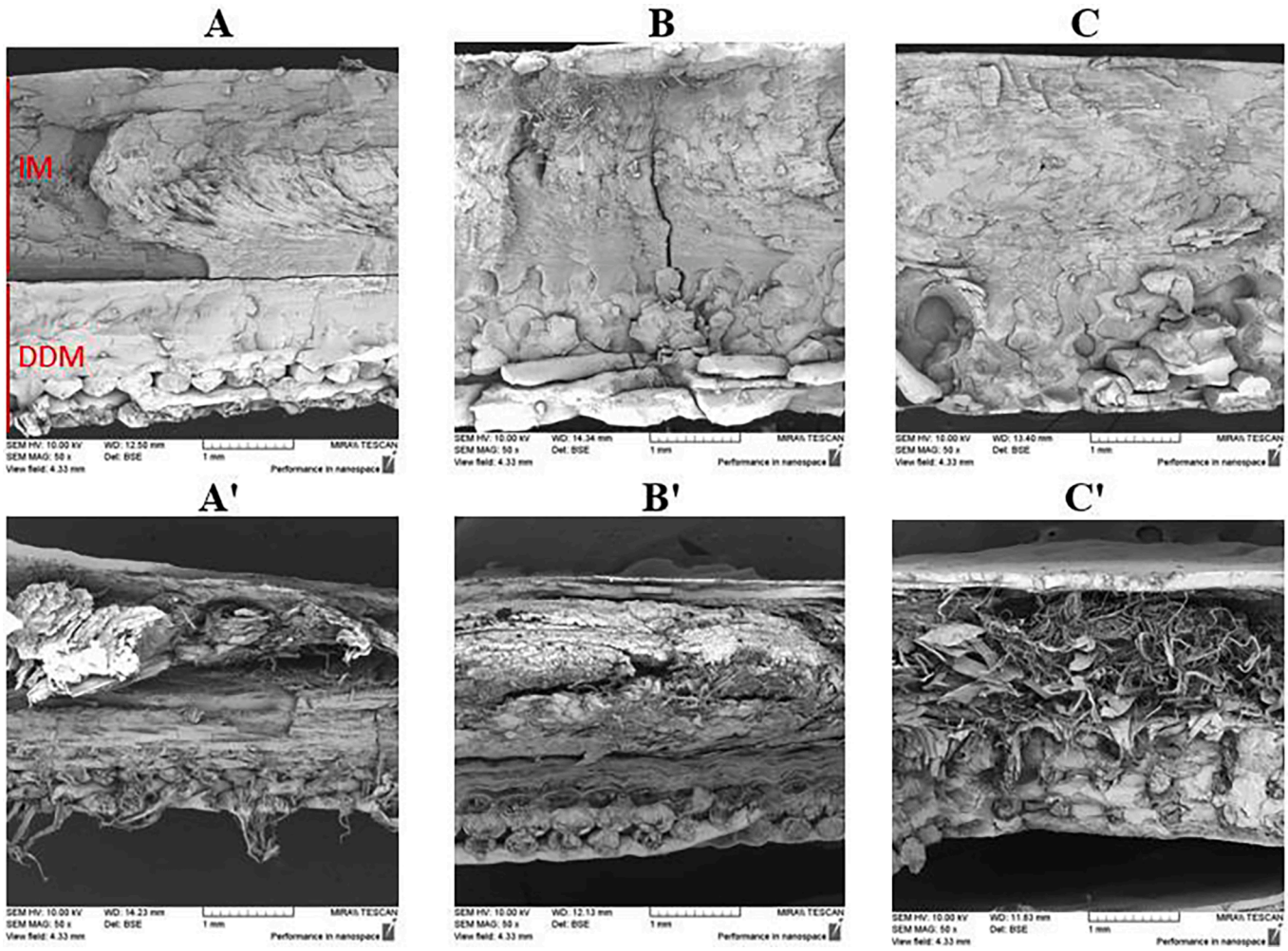

Fig. 9. SEM images of over-molded tablets (cross-section) before IVR; A: DDM-100% Caffeine-IM Caffeine, B: DDM-75% Caffeine-IM Caffeine, C: DDM-50% Caffeine-IM Caffeine; and after IVR, A′: DDM-100% Caffeine-IM Caffeine, B′: DDM-75% Caffeine-IM Caffeine, C′: DDM-50% Caffeine-IM Caffeine.

(Paracetamol), attributed to the higher density of the IM tablets. The lower infill density in DDM tablets results in a quicker drug release profile due to enhanced diffusion and dissolution mechanisms (Ebrahimi et al., 2023).

Furthermore, Fig. 8-A shows the distinct DDM printed patterns with 100 % infill density in tablets fabricated using IM. In contrast, for tablets with a 50 % infill percentage (Fig. 8-C), the penetration of the molten formulation appears higher than in DDM tablets with 100 % infill density. Slight structural differences observed in DDM samples before and after IVR studies suggest a correlation with the sustained release profile of Caffeine-fabricated tablets using this technique. Thus, these morphological differences can influence the drug release profiles of the fabricated tablets.

Fig. 9 captures the morphological structures of over-molded Caffeine-Caffeine tablets in their initial state and after 72 h of IVR assessment. The distinct structures of over-molded tablets, particularly in the injection-molded Caffeine section, are highlighted before (Fig. 9 A, B, C) and after (Fig. 9 A′, B′, C′) the IVR study, mirroring the results observed in Fig. 7. Additionally, the IVR results for over-molded Paracetamol (Fig. 6-B) and Caffeine (Fig. 7-B) tablets showed similar drug release profiles, slower than those of DDM tablets up to 24 h. Post this period, the drug release rates of IM tablets increased, while the release profiles of DDM tablets (Caffeine) remained consistent. The marked structural changes observed before and after IVR in over-molded tablets can be attributed to the drug release characteristics of the IM tablets.

The mechanism of drug release from bilayer tablets is intricately influenced by the interplay of tablet design and manufacturing techniques, as evidenced by the IVR and SEM results. The physical structure of pharmaceutical products emerges as a critical factor in adjusting the drug release properties, where the alteration of tablet matrix porosity directly affects diffusion and dissolution rates.

The IVR profiles (Fig. 6 and Fig. 7) align with SEM observations (Fig. 8 and Fig. 9), showing that over-molded tablets exhibit a slower drug release profile compared to those fabricated via the DDM procedure. The higher density of tablets formed through the IM process during over-molding restricts pathways for drug molecules, leading to a reduction in the contact area and a gradual slowing of drug release over time. In contrast, the DDM technique presents a distinctive advantage in adjusting the tablet infill percentages to alter drug release profiles. (Fig. 6 and Fig. 7) indicates that lower infill densities in DDM tablets result in a quicker drug release profile, attributed to enhanced diffusion and dissolution mechanisms. SEM images in Fig. 8 and Fig. 9 further support this observation, illustrating that lower infill densities in DDM tablets contribute to an augmentation of diffusion and dissolution mechanisms, enabling quicker drug release profiles. The combined findings from IVR and SEM investigations underscore the pivotal role of tablet design and manufacturing techniques in tailoring drug release profiles. Offering a valuable avenue for achieving personalized pharmaceutical therapies with precise control over drug release properties.

4. Conclusions

This study explored the innovative manufacturing of bilayer tablets with personalized drug release characteristics, utilizing the synergistic capabilities of Droplet Deposition Modeling (DDM) and Injection Molding (IM). Focusing on Caffeine and Paracetamol, which exhibit distinct rheological properties, the study offered a detailed investigation into the unique aspects of each manufacturing method. The results revealed that the Paracetamol formulation encountered challenges in the DDM process due to its high viscosity, leading to unsatisfactory tablet fabrication. In contrast, the Caffeine formulation met the essential processing criteria for DDM and demonstrated varied release rates based on tablet infill percentages. Despite DDM challenges, IM successfully processed the viscous Paracetamol formulation, resulting in bilayer tablets with customizable drug release. DDM, as a rapid prototyping proved effective in creating tablets with variable porosities and tailored release characteristics, contingent on material factors. Integrating DDM and IM techniques emerges as a promising strategy to address the limitations inherent in each technique. This approach provides a significant advancement in the field of pharmaceutical manufacturing, particularly for the creation of personalized oral dosage forms. The findings of this research contribute valuable insights and methodologies that could shape future developments in the production of customized medications, aligning with the evolving needs of personalized medicine.

CRediT authorship contribution statement

Farnoosh Ebrahimi: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Han Xu:** Methodology, Investigation, Formal analysis, Conceptualization. **Evert Fuenmayor:** Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Ian Major:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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