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Automated extrusion-based dispensing: Personalized dosing and quality control of clopidogrel tablets for pediatric care

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ABSTRACT

The exploration of three-dimensional (3D) printing inspired technologies in pharmaceutical compounding reveals a promising frontier in personalized medicine manufacture. This study focuses on the development of clopidogrel bisulphate tablets, with doses ranging from 2 mg to 20 mg per tablet, suitable for pediatric use. The study explored a semi-solid extrusion-based deposition technology already being used in compounding pharmacies across several European locations. The investigation explored various properties of two formulations of 1 % and 2 % clopidogrel gel tablets, with a specific focus on mass variation, drug content uniformity, *in vitro* drug release profiles, disintegration time, and stability.

The mean weights of the smallest printed 200 mg tablets with 1 % and 2 % clopidogrel concentrations were 199.1 ± 4.6 mg and 201.0 ± 3.2 mg, respectively. For the largest printed 500 mg tablets with 1 % and 2 % concentrations, the mean weights were 499.3 ± 7.7 mg and 501.7 ± 6.5 mg, respectively. The mean clopidogrel content uniformity for 1 % clopidogrel 200 mg and 500 mg tablets were 102.0 ± 1.8 %and 96.6 ± 2.6 %, respectively, and for 2 % clopidogrel 200 mg and 500 mg were 102.6 ± 3.9 % and 101.2 ± 1.6 %, respectively, well within the acceptable acceptance value (AV) range of 3 to 12. Both 1 % and 2 % formulations of clopidogrel tablets exhibited rapid drug release, meeting the USP pharmacopeial target of 85 % release in 15 min. All tablet sizes formulated at 1 % and 2 % concentrations met specified disintegration specifications. The stability assessment over three months revealed consistent pH values and assay results within target specifications for both clopidogrel formulations (93.5 % for 1 % formulation and 93.6 % for 2 % formulation). At three months, X-ray Diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FTIR) results demonstrated stability in clopidogrel tablets.

In conclusion, a comprehensive evaluation of our developed clopidogrel tablets demonstrate their suitability for clinical use in an extemporaneous setting using the presented semi-solid extrusion-based automation technology.

1. Introduction

Novel pharmaceutical dosing technologies and drug delivery systems hold significant promise for revolutionizing the manufacture of medicines and enhancing personalized drug delivery. This offers a shift from conventional "one-size-fits-all" approach towards personalized medicine, wherein drug treatment and dosage forms are tailored to meet the specific needs of individual patients (Maroni et al., 2017; Sandler & Preis, 2016; Vaz & Kumar, 2021). This paradigm shift has led to the development of pharmaceutical 3D printing approaches, enabling the formulation of medications with diverse dosage levels, shapes, flavors, colors, drug combinations, and release profiles that can be customized

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for each patient or disease condition (Alhnan et al., 2016; Norman et al., 2017).

Different techniques are available for extrusion oral solid dosage forms, including fused deposition modelling, direct powder extrusion, selective laser sintering, vat photopolymerization, and semi-solid extrusion (SSE) (Alhnan et al., 2016; Goyanes et al., 2017; Zheng et al., 2022). Among these, SSE stands out for its suitability in clinical settings due to its versatility in accommodating a wide range of active pharmaceutical ingredients (APIs), including chemically unstable drugs (Sandler & Preis, 2016). SSE typically involves the extrusion of a paste or gel, either formed through solvents or heat, through a nozzle onto a printing bed (Alhnan et al., 2016; Goyanes et al., 2017). This method's adaptability and ability to handle various drug formulations make it particularly promising for personalized medicine applications. SSE 3D printing has emerged as a promising technology due to its ability to operate at low temperatures and its relative simplicity compared to other methods (Sandler & Preis, 2016). For instance, SSE-based manufacturing has successfully produced orodispersible films, facilitating on-demand production of patient-specific doses (Awad et al., 2018). Compared to traditional compressing technologies, 3D printed drug delivery systems offer possibilities for dosage form flexibility and precise control over release profiles (Yu et al., 2008).

While 3D printing holds promises as a technology, its application to manufacturing simple dosage forms often complicates the process. The layer-by-layer deposition approach tends to result in slow production, offering little additional value compared to traditional manufacturing methods for conventional dosage forms. Despite the advancements, establishing quality requirements for 3D printed tablets also remains a challenge according to some authors (Arafat et al., 2018; Sadia et al., 2018). The authors continue by stating that while the European Pharmacopoeia (pH. Eur.) outlines quality tests for conventional tablets, their applicability to 3D printed tablets is uncertain (Arafat et al., 2018; Sadia et al., 2018). This is partially due to the overly complex structures that are typically created by 3D printing without any functional benefit, especially in the case of immediate release tablets. In contrast, an automated extrusion-based material deposition technology offers a more efficient solution. It streamlines the manufacturing process, allowing for faster production times and produces conventional pharmacopeial dosage forms while maintaining the necessary quality standards. This method mitigates the challenges associated with 3D printing, making it a superior alternative for producing immediate release tablets.

One population that particularly stands out to benefit from personalized medicine is pediatric patients, who often require dosage adjustments based on their body weight (Van Riet-Nales et al., 2011). However, commercially available solid dosage forms may be unsuitable for children due to their size and inappropriate excipients (Van Der Zanden et al., 2021). Clopidogrel, commonly used in adults as an antiplatelet agent, is also occasionally prescribed for children. However, pediatric patients require individualized dosing based on e.g. body weight, and suitable formulation is not currently commercially available (Finkelstein et al., 2005; Li et al., 2008). Even though there are no approved pediatric indications for clopidogrel, it is used off-label in children with certain type of heart disease to prevent thrombotic events. Studies such as those by Finkelstein et al. (2005), Li et al. (2008), and Mertens et al. (2008) have demonstrated its potential benefits in reducing platelet aggregation. However, concerns persist regarding the drug's safety profile, particularly its association with bleeding complications, as highlighted by Soman et al. (2006) and Wessel et al. (2013). These studies underscore the need for cautious monitoring and individualized dosing strategies when administering clopidogrel to pediatric patients, emphasizing ongoing research efforts to optimize its clinical use.

This study introduces an SSE dispensing technology, inspired by 3D printing, that allows precise deposition of materials to create solid dosage forms with accurate dosing. We applied this technology to evaluate the quality of low-dosage (2 mg - 10 mg) immediate-release clopidogrel bisulphate tablets, intended as extemporaneous products for pediatric patients. Although such products are not subject to U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) approval, improving the quality and consistency of compounded medications is crucial due to reports of inconsistent quality (Eileen Kairuz et al., 2007; Mohiuddin, 2020).

The study evaluated mass variation, dissolution, content uniformity, disintegration, and stability, emphasizing the role of modern technologies in improving the safety and reliability of personalized medications for vulnerable populations, as per U.S. and EMA regulations.

2. Materials and methods

2.1. Materials

Clopidogrel bisulphate (later in the article named as clopidogrel) pharmaceutical secondary standard was obtained from Merck (New Jersey, United States). Clopidogrel API pH. Eur. grade obtained from Dr. Reddy's Laboratories Ltd (Hyderabad, India), polysorbate 80 (Caesar & Lorez GmbH, Hilden, Germany), citric acid (Caesar & Lorez GmbH, Hilden, Germany) and pharmaceutical excipient base, CuraBlend® with ingredients of purified water, xylitol, gelatin, cocoa butter, glycerol, maltodextrin, citric acid, sodium citrate, potassium sorbate, and flavors (CurifyLabs Oy, Helsinki, Finland) were used for the preparation of extrudable API -excipient base mixtures and tablets (Sandler Topelius et al., 2024). Solvents and buffering chemicals used in this study were of reagent grade. Plavix® 75 mg clopidogrel tablet contain 87.875 mg Clopidogrel bisulphate corresponding to 75 mg pure Clopidigrel with molecular weight 321.82 (Sanofi, Paris, France) was used as a reference tablet for comparison in the dissolution release studies.

Mini Medi-Cap® Plus™ Blisters (MD425, from MediDose Group, Pennsylvania, USA) with 3/16″ size were selected for blister packaging. Additionally, LaserLabel™ "25″ Lid-Label® Cover Sheets, also from MediDose Group, were utilized for sealing the blister lids.

2.2. Methods

2.2.1. Formulation of clopidogrel pharmaceutical ink

The 1 % clopidogrel formulation consisted of 94.6 % w/w gelatin based CuraBlend® as the main component, 2 % w/w polysorbate 80 (PS 80) as a surfactant, 2.4 % w/w citric acid for pH regulation, and 1 % w/w clopidogrel bisulphate (molecular weight 419.90) as API.

Similarly, the 2 % clopidogrel formulation included 94.8 % w/w CuraBlend® as the core ingredient, 2 % w/w PS 80, 1.2 % w/w citric acid for pH regulation, and 2 % w/w clopidogrel bisulphate as API.

The process involved melting CuraBlend® in a water bath at +45 °C (within a temperature range of ±3 °C) for 30 min until it transitioned from a solid to a liquid state. Clopidogrel and PS 80 were measured in a metal mortar and mixed until forming a white paste. In incremental steps, warm CuraBlend® was introduced to the mortar while mixing. As the final step for pH adjustment, citric acid was incorporated. The formulation was thoroughly mixed for 3–4 min. Subsequently, the covered mortar was immersed in a warm water bath for 5 min and mixed once again to ensure consistent distribution of the API in the formulation.

To eliminate air bubbles generated during mixing and to ensure a successful deposition outcome, the freshly prepared formulation was left undisturbed and securely covered in a water bath (+42–45 °C) for 10–15 min before dispensing.

The warm formulation was then transferred to a disposable sterile syringe (100 mL), expelling excess air until the first drops emerged from the nozzle. Capped syringe was placed in the printer's holder and left to stand for 15 min at +41 °C before commencing the extrusion process. Formulation preparations were carried out in a dark room to protect clopidogrel bisulphate from light exposure.

2.3. Deposition by semi solid extrusion

The tablet production process utilized extrusion-based dosing equipment, Pharma Printer (CurifyLabs Oy, Helsinki, Finland) which features a dispensing head specifically designed for compatibility with semi-solid extrusion. To design the tablets, the user can choose flexibly the weight of the tablets to be dispensed using the dedicated software (Sandler Topelius et al., 2024).

The integration of the Pharma Printer involved linking it with an analytical balance (Kern PES-620–3 M, Balingen Germany) and the latest CurifyLabs control software 2.0. Orders were initiated through the Pharma Kit Software (CurifyLabs Oy, Helsinki, Finland). Accurate blueprint parameters were verified by CurifyLabs and integrated into the software blueprint.

To meet diverse dosing needs, tablet sizes were varied, resulting in different strengths of the formulation. For example, 1, 2, 3, 4, and 5 mg of clopidogrel per tablet for the 1 % formulation, and 2, 4, 6, 8, and 10 mg of clopidogrel per tablet for the clopidogrel 2 % formulation were prepared, providing a wide range of therapeutic options. The printing process was carried out in a dark room to avoid exposing clopidogrel bisulphate to light.

2.4. Mass variation test and dose accuracy

All tablets had their mass uniformity, as outlined in European Pharmacopoeia (pH. Eur.) 2.9.5, evaluated. Also, the relative standard deviation (RSD) quality criteria were set at 7.5 % for 200 mg tablets and 5.0 % for 300, 400 and 500 mg tablets.

Dosing accuracy is defined as the percentage of dosage units within a batch that adhere to the specified criteria or tolerances for mass variation. To determine dosing accuracy, calculate the percentage of tablets that meet the mass variation criteria by dividing the number of compliant tablets by the total number of tablets and then multiplying by 100:

$$\text{Dosing Accuracy} = (\text{number of tablets within specification} / \text{ total number of tablets}) \times 100$$

2.5. Drug content by high-performance liquid chromatography

The clopidogrel content was measured using a validated high-performance liquid chromatography (HPLC) method, aligned with the International Council for Harmonisation (ICH) Guideline Q2. The HPLC system used was a Waters Corporation instrument (Milford, Massachusetts, USA) with a Photodiode Array (PDA) detector and an XBridge Premier BEH C18 column (2.5 μm particle size, 4.6 mm x 100 mm dimensions). The mobile phase consisted of 10 mM potassium phosphate monobasic, adjusted to pH 2.9 using phosphoric acid, and acetonitrile (35:65). The column was maintained at room temperature with a flow rate of 1 mL/min, a detection wavelength of 225 nm, a run time of 8 min, and an injection volume of 15 μL. To create analytical stock reference standard solutions, 50 mg of clopidogrel from Dr. Reddy's was dissolved in 500.0 mL of a diluent composed of a 50:50 volume-to-volume ratio (v/v) mixture of methanol and water. From this diluent, 5.0 mL of the solution was further diluted to 10.0 mL with diluent. Clopidogrel tablet samples of various doses were prepared to achieve a concentration of 50 ppm.

For tablet content calculations, Waters Empower software (version 3.6.1) was used. Tablet assay sample preparation (50 ppm) involved dissolving 500 mg of a tablet containing 1 % clopidogrel in 50 mL of mobile phase, heating in a 50 °C water bath, vortexing, and filtering through a 0.2 μm filter. The final concentration was 50 ppm.

For each preparation, the content homogeneity of each dose was evaluated by analyzing 10 dosage units within the batch. These batches needed to meet the content uniformity criteria specified in pH. Eur. 2.9.40.

The acceptance value (AV), as per the methodology outlined in pH. Eur. chapter 2.9.40 ("Uniformity of dosage units"), is computed based on the average of specified content limits in the relevant monograph. This reflects the arithmetic mean of uniformity results across unit doses. The calculation, which involves the acceptability constant (coverage factor) and the standard deviation of the samples, is derived from the analysis of 10 units. The AV should not exceed the acceptance limit set at AV = 15.

The AV is determined by the formula $AV = |M - X| + ks$, where M represents the target value, which equals X if $98.5 \leq X \leq 101.5$. M is set to 98.5 if X is <98.5, and 101.5 if X exceeds 101.5. The constant k is assigned a value of 2.4, and S denotes the standard deviation (Sandler Topelius et al., 2024).

2.6. In vitro drug release measurements

A hydrochloric acid buffer solution with a pH of 2 was utilized as a test medium. The test volumes for the clopidogrel tablet samples were set at 500 ml and maintained at a temperature of 37 °C for 400 mg tablet sizes. Analysis was conducted using a Waters Acuity 2998 PDA HPLC system (Milford, Massachusetts, USA) and an ERWEKA GmbH (Langen, Germany) dissolution paddle apparatus.

Samples were collected at specific time intervals: 0, 5, 10, 15, 20 and 30 min, while the paddles were stirred at a constant speed of 50 rpm. Six tablets were assessed for each dosage.

The solution needed to adhere to the requirements outlined in pH. Eur. 2.9.3 and pH. Eur. 5.17.1 for conventional-release solid dosage forms. Sample analysis was carried out following the method described in Section 2.5. The tolerance criteria were set such that no <80 % (Q) of the labeled amount of clopidogrel should be dissolved within 30 min in stage 1 with six tablets.

2.7. Disintegration time

The disintegration time of the clopidogrel tablets was assessed using a Sotax DT2 tablet disintegrator (Sotax, Allschwil, Switzerland) according to the procedure outlined in pH. Eur. chapter 2.9.1 for uncoated tablets, which specifies a disintegration time of no >15 min. The test was conducted using purified water at 37 °C in 1-liter beakers. Six tablets (400 mg each) were tested ($n = 6$), and the time was recorded until complete disintegration of each tablet was observed.

2.8. Fourier-transform infrared spectroscopy

Infrared spectra of raw materials and extruded gel tablets were taken by using FTIR spectrophotometer Shimadzu IRPrestige-21 (Kyoto, Japan), equipped with a Golden Gate ATR crystal, Specac Ltd., (Orpington, United Kingdom) at three different locations on the tablet.

2.9. Scanning electron microscopy

The surface morphology was investigated with a high-resolution scanning electron microscope (SEM; Zeiss EVO® 15 MA, Oberkochen, Germany). The samples were mounted on aluminium stubs with a conductive carbon film and were magnetron-sputter coated with a 3-nm platinum layer in an argon atmosphere before microscopy.

2.10. X-Ray diffraction analysis

X-ray powder diffraction (XRPD) patterns of raw materials and extruded gel tablets were obtained by using an X-ray diffractometer (D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany). The XRPD experiments were carried out in a symmetrical reflection mode (Bragg-Brentano geometry) with CuK_α radiation (1.54 Å). The angular range was from 5° 2-theta to 35°2-theta with steps of 0.2° 2-theta. The scattered intensities were measured with the LynxEye 1-dimensional detector with 165 channels. The operating voltage and current were 40 kV and 40 mA, respectively.

XRD analysis was conducted on the semi-solid CuraBlend base and the solid powder components outlined in the CuraBlend mixture materials subsection, including cocoa butter, citric acid, and clopidogrel. To prepare the sample for XRD, the CuraBlend mixture was dried in an XRD mold for 24 h at room temperature (20 °C) and 20 % relative humidity. This preparation method was selected to ensure the visibility of distinct peaks in the resulting spectrum. In addition, gel tablets containing the API were analyzed immediately after removal from their packaging, without undergoing any further drying process.

2.11. pH determination

The pH of the clopidogrel tablets was assessed at room temperature using an Edge pH meter from HANNA Instruments, Inc. (Woonsocket, USA). Three 400 mg clopidogrel tablets ($n = 3$) were placed in glass vials and melted at 45 °C. After a 30 s interval, the pH electrode was immersed in the melted formulation, and readings were taken after allowing the system to equilibrate for 1 min.

2.12. Preparation of gel tablets for stability study: packaging in Medi-Cup blisters®

The tablets were packed in Medi-Cup green Blisters® (Medi Dose, USA), selected as the primary packaging material for its reliability and suitability for this specific application.

The final step in this packaging process involves the application of a sealing lid using the Roll-E-ZY Press (Medi-Dose, USA). This sealing mechanism ensures a robust and tamper-evident closure, providing an additional layer of protection against environmental factors. The Roll-E-ZY Press is employed to firmly seal the lids onto the Medi-Cup Blisters, guaranteeing the tablets' containment within a controlled and secure environment.

In order to assess the stability of 1 % clopidogrel and 2 % clopidogrel formulations, a stability study was conducted at specified time points (0, 1, and 3 months) under room temperature conditions (21–25 °C) and refrigerated conditions (2–8 °C), with all samples kept in the dark.

3. Results

3.1. Mass variation test for tablets

The acceptance limits for mass variation were consistently narrow across the various strengths. Instances where tablets fell outside the acceptable range were noted, particularly at the 300 mg strength for both the 1 % and 2 % formulations (Table 1). The 2 % formulations exhibited slightly lower standard deviations compared to the 1 % formulations. The majority of tablets complied with quality standards.

3.2. Drug content and dose accuracy by HPLC

The content uniformity of the produced tablets with varying concentrations of clopidogrel (1 % and 2 %) across four different tablet sizes (500 mg, 400 mg, 300 mg, and 200 mg) is presented in Table 2. Key statistical parameters include the minimum, maximum, mean, and AV, which is a critical indicator for content uniformity.

The acceptance criteria for content uniformity were set at 85.0 % to 115.0 % with an AV <15, ensuring the reliability and consistency of the pharmaceutical product. Across all concentrations and tablet sizes, the mean values consistently fell within the acceptable range. For instance, the mean clopidogrel content for 1 % clopidogrel 500 mg tablets was 96.6 %, well within the specified range. Examining the AV for each

Table 2
Comparative analysis of content uniformity: 1 % and 2 % clopidogrel formulations at various strengths.

Product Name	N	Minimum (%)	Maximum (%)	Mean (%)	Acceptance Value (AV)
1 % Clopidogrel _200 mg	10	99.3	104.1	102.0	5
1 % Clopidogrel _300 mg	10	96.7	104.8	99.7	4
1 % Clopidogrel _400 mg	10	97.5	104.8	101.7	5
1 % Clopidogrel _500 mg	10	89.5	98.7	96.6	8
2 % Clopidogrel _200 mg	10	92.3	106.0	102.6	10
2 % Clopidogrel _300 mg	10	97.6	106.0	103.7	9
2 % Clopidogrel _400 mg	10	89.5	105.8	101.5	12
2 % Clopidogrel _500 mg	10	98.1	103.7	101.2	3

Table 1
Comparative analysis of mass variation: 1 % and 2 % clopidogrel formulations at various strengths.

Target Weight	No of tablets	Acceptance limit (mg)	Minimum (mg)	Maximum (mg)	Mean (mg)	Standard deviation (SD) (± mg)	No of out-of-range tablets	Dose Accuracy (%)
1 % clopidogrel _200 mg	32	185.0 - 215.0	187.0	208.0	199.1	4.6	0	100 %
1 % clopidogrel _300 mg	128	285.0 - 315.0	280.0	315.0	300.4	6.8	2	98 %
1 % clopidogrel _400 mg	224	380.0 - 420.0	383.0	443.0	402.4	7.1	2	99 %
1 % clopidogrel _500 mg	144	475.0 - 525.0	480.0	518.0	499.3	7.7	0	100 %
2 % clopidogrel _200 mg	48	185.0 - 215.0	195.0	207.0	201.0	3.2	0	100 %
2 % clopidogrel _300 mg	48	285.0 - 315.0	274.0	316.0	299.2	7.2	3	93 %
2 % clopidogrel _400 mg	48	380.0 - 420.0	385.0	415.0	400.5	6.9	0	100 %
2 % clopidogrel _500 mg	48	475.0 - 525.0	489.0	519.0	501.7	6.5	0	100 %

tablet size and concentration, all values remained below the threshold of 15. Notably, 2 % clopidogrel 500 mg exhibited the lowest AV of 3. The minimum and maximum values further supported the consistency observed in the mean and AV values. Referring to Table 2, the narrow range between the minimum and maximum values for each tablet size and concentration showed consistent clopidogrel content, supporting the reliability of the manufacturing process across different tablet sizes.

3.3. In vitro drug release profile

The *in vitro* drug release profiles for three formulations, namely 400 mg 1 % clopidogrel, 400 mg 2 % clopidogrel, and the branded version were assessed at various time points (0, 5, 10, 15, 20, and 30 min). The percentage of drug release was measured for each formulation at these time intervals.

Fig. 1 presents the comparative dissolution profiles of the 1 % clopidogrel 400 mg and 2 % clopidogrel 400 mg dispensed tablets versus the branded product.

3.4. Disintegration time

Analyzing the disintegration time for both the 1 % and 2 % formulations of clopidogrel tablets across various sizes revealed positive outcomes. The gathered statistics consistently demonstrated that the disintegration time for all tablet sizes was under 10 min, highlighting a rapid and efficient breakdown when exposed to water.

Immediate-release tablets are expected to disintegrate within 15 min, as per the requirements of the pH. Eur. The clopidogrel tablets, formulated at 1 % and 2 % concentrations, met the specified disintegration standards outlined in the pharmacopoeias.

3.5. Fourier-transform infrared spectroscopy

Infrared spectra of CuraBlend as excipient mixture, clopidogrel bisulphate as API, and clopidogrel extruded tablets were taken using an FTIR spectrophotometer. The objective of the analysis was to compare FTIR spectra of clopidogrel in powder and tablet forms to discern differences in peak characteristics for formulation and quality control insights.

Fig. 2 presents the FTIR spectra of clopidogrel bisulphate powder, extruded tablets (CuraBlend tbl – pure CuraBlend mixture extruded tablet without API; Clopidogrel tbl – extruded tablet with 2 % clopidogrel content), and some components of the CuraBlend mixture.

3.6. Scanning electron microscopy

The surface morphology of the samples was examined during the stability study, employing high-resolution SEM. Fig. 4 presents SEM images of clopidogrel bisulphate powder crystals (A; B), 1 % (C) and 2 % (D) Clopidogrel extruded tablets cross section after 3-month storage in a fridge. Magnification: (A, C, D) 1000 × (scale bar 10 μm) and (B) 500 × (scale bar 20 μm).

3.7. X-Ray diffraction analysis

X-ray diffraction (XRD) analyses were conducted immediately after the SSE printing of tablets (zero point) and after the storage of tablets in a refrigerator (2 to 8 °C) for approximately 3 months. Fig. 4 presents the XRD patterns for clopidogrel bisulphate powder, CuraBlend excipients mixture, some components of the mixture, and the extruded tablets with 1 % and 2 % of clopidogrel.

The XRD pattern of pure clopidogrel powder showed 2-theta values at 9.2°, 10.9°, 11.5°, 14.8°, 18.5°, 20.6°, and 23.2° (±0.2°), corresponding to peaks of form I (Koradia et al., 2004). The CuraBlend excipient mixture without API was measured after heating (45 °C) and smoothing the mixture into the XRP mold, showing a completely amorphous state (amorphous halo). The same measurement after three months resulted in the same amorphous halo. The CuraBlend mixture as an API-free extruded tablet showed identical results to the blend with API (not shown in Fig. 4). Clopidogrel peaks could not be detected in the mixture with API.

The visible peaks in the extruded tablets were related to changes in the physical solid state of some excipients, such as the rapid solidification of the extruded tablets occurring at fridge conditions (2 to 8 °C). These peaks were mainly due to the crystal modifications of cocoa butter and the interaction of different sugars. To confirm this hypothesis, we

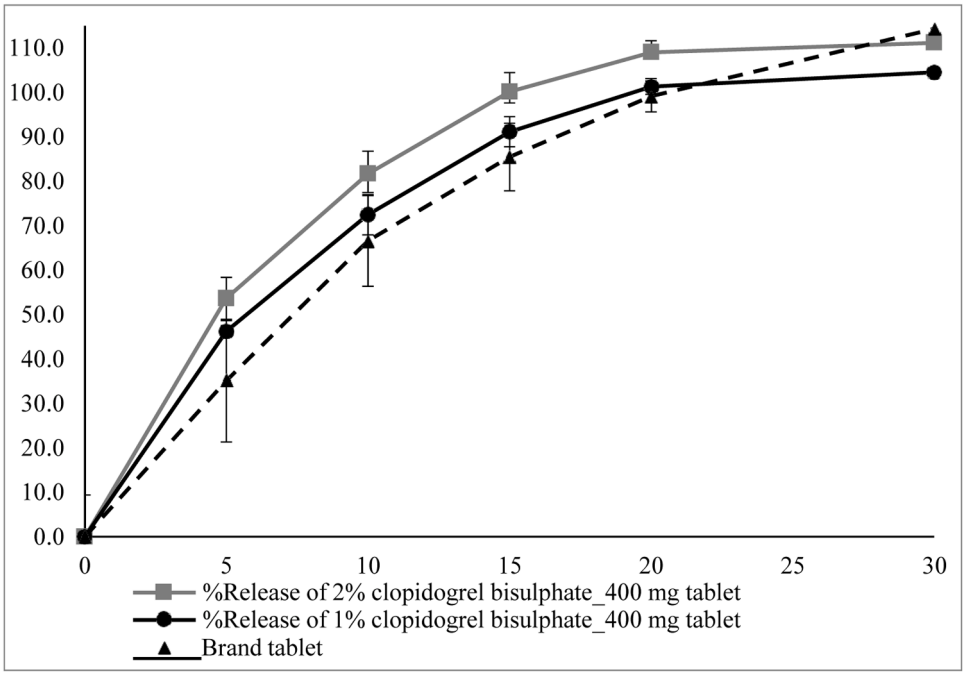

Fig. 1. Comparative dissolution profiles of 1 % clopidogrel 400 mg and 2 % clopidogrel 400 mg dispensed tablets versus brand product in hydrochloric acid buffer solution with a pH of 2 medium. Six tablets were used for each formulation.

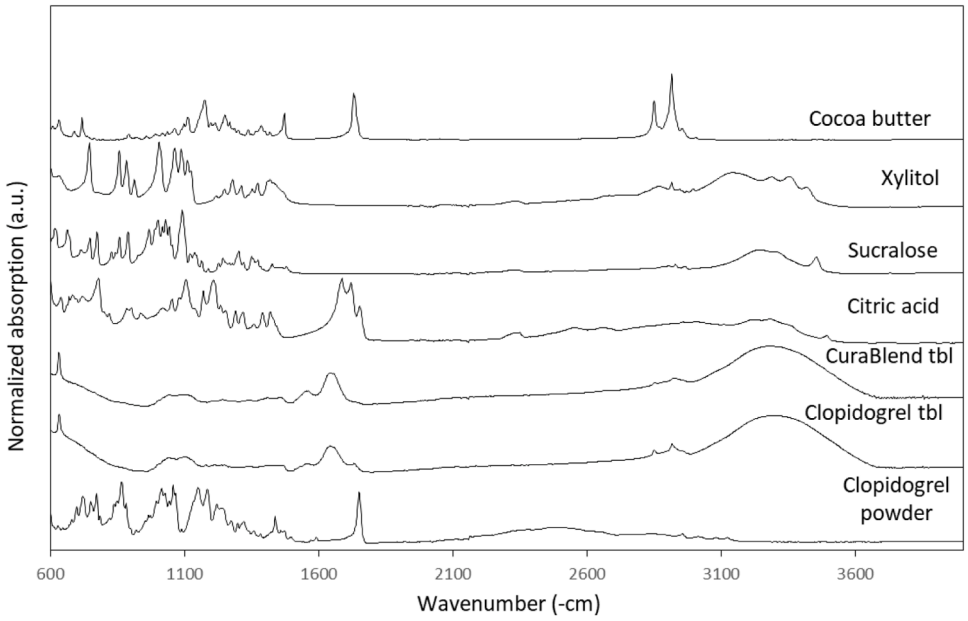

Fig. 2. Fourier-transform infrared spectroscopy spectra (FTIR) of clopidogrel bisulphate powder (Clopidogrel powder), extruded tablets (CuraBlend tbl – pure CuraBlend® mixture extruded tablet without API; Clopidogrel tbl – extruded tablet with 2 % clopidogrel content) and some components of the CuraBlend® mixture.

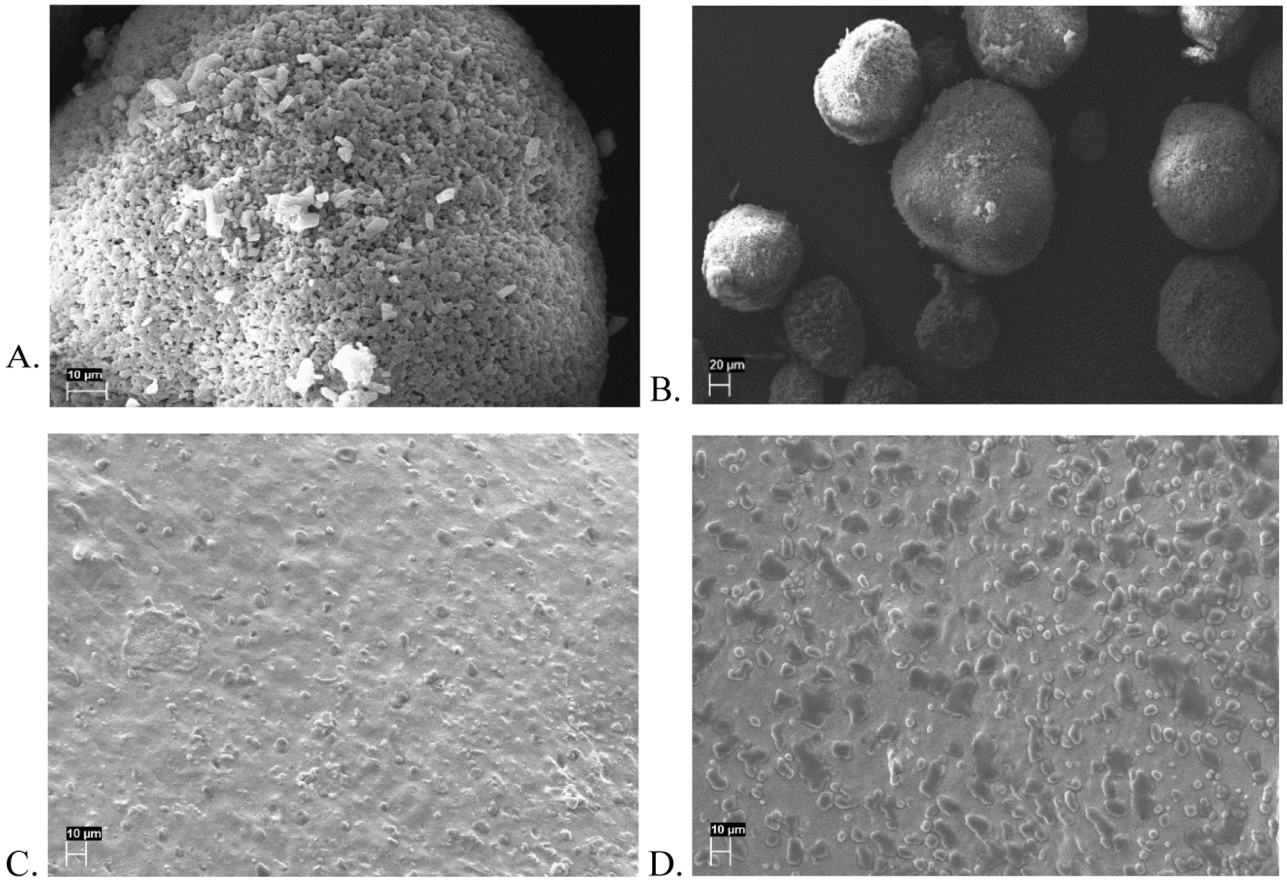

Fig. 3. Scanning electron microscopy (SEM) images of clopidogrel bisulphate powder crystals (A; B), 1 % (C) and 2 % (D) Clopidogrel extruded tablets cross section after 3-month storage in fridge. Magnification: (A, C, D) 1000 × (scale bar 10 µm) and (B) 500 × (scale bar 20 µm).

allowed the CuraBlend mixture to dry for 24 h at room temperature (22 ±2 °C) and 20 % relative humidity (RH) to accelerate the crystallization process by reducing the moisture in the tablet. The obtained result confirmed that the resulting peaks are due to excipients, mainly cocoa butter and sugars. This emphasizes the importance of air-tight blistering of the tablets after preparation. Additionally, the X-ray diffraction (XRD) patterns of the tablets stored in the blister pack did not change for three months, indicating that the extruded tablets maintained their solid-state

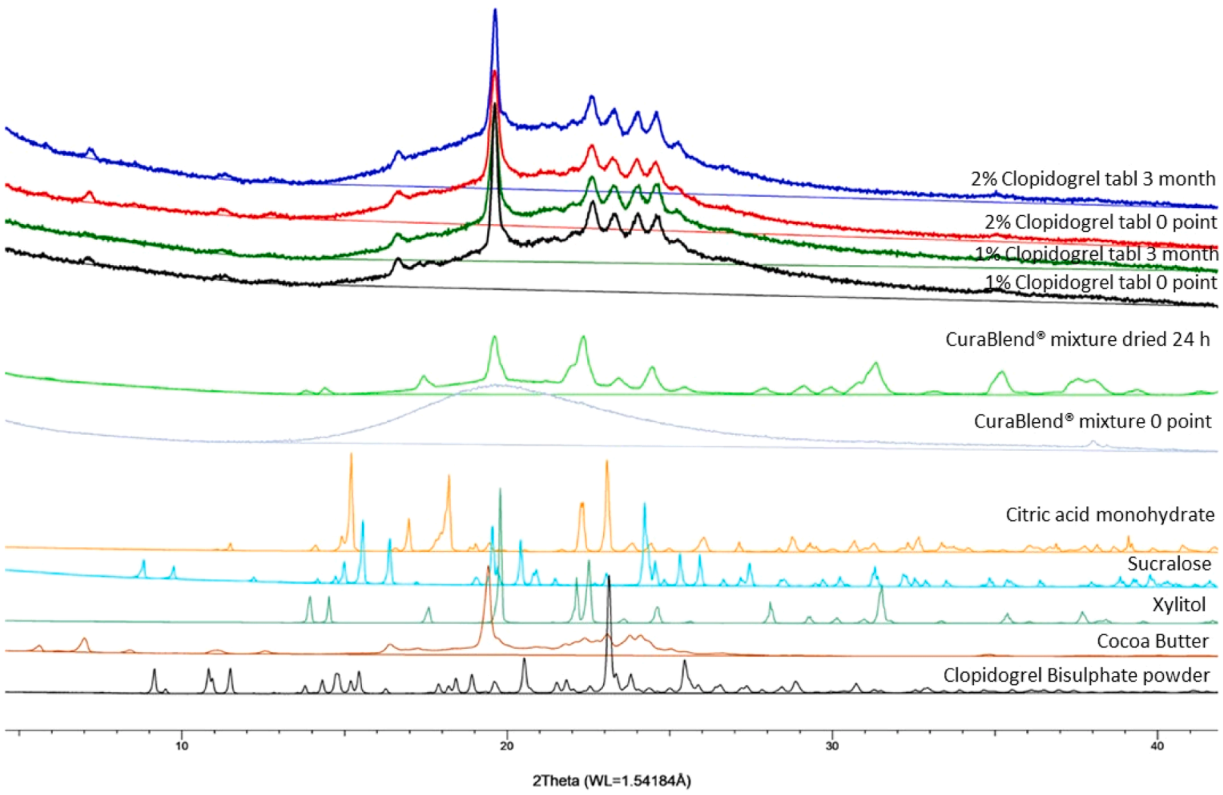

Fig. 4. X-ray diffraction (XRD) patterns for clopidogrel bisulphate powder and extruded tablets with 1 % and 2 % clopidogrel content. CuraBlend® excipient mixture (0 point) without API and citric acid (added to printing mixture). Sucralose, Xylitol and Cocoa Butter are some components of the CuraBlend® mixture.

quality for at least three months.

3.8. Stability study

The stability study conducted on two formulations of clopidogrel, 1 % and 2 % 400 mg tablets, offered insights into the effects of different storage conditions with light protection ensured by using green blisters and storing in a dark condition over a three-month period.

Both formulations exhibited satisfactory appearance characteristics throughout the study duration, meeting the specifications of off-white, soft chewable tablets with vanilla flavour at all time points and under both room temperature (RT) and refrigeration (Fridge) conditions.

Fig. 5 illustrates the appearance of 1 % and 2 % clopidogrel tablets after three months of stability testing. Throughout this period, the tablets maintained their shape and appearance, with no visible changes such as spotting, discoloration, or deformation under either room temperature and refrigerated conditions was observed. After six months of storage at room temperature, the tablets exhibited a dried appearance, though no significant alterations in color or physical integrity were noted during the earlier three-month evaluations.In terms of pH stability, refrigeration emerged as the superior storage condition for maintaining pH levels close to initial values. For the 1 % formulation, pH remained stable at 3.1 under refrigeration, while a slight increase to 3.3 was observed at RT over the three-month period. Similarly, the pH of the 2 % formulation showed minimal variation under refrigeration, increasing from 2.9 to 3.1, compared to an increase from 2.9 to 3.2 at RT (Table 3).

The pH specifications during the stability test were determined according to manufacturing procedures and the solubility characteristics of clopidogrel bisulphate. Clopidogrel bisulphate is freely soluble in lower pH values but practically insoluble in water. By adding citric acid during the formulation preparation, the target pH was set at 3, as values above 3.5 could lead to reduced dissolution. The dissolution medium

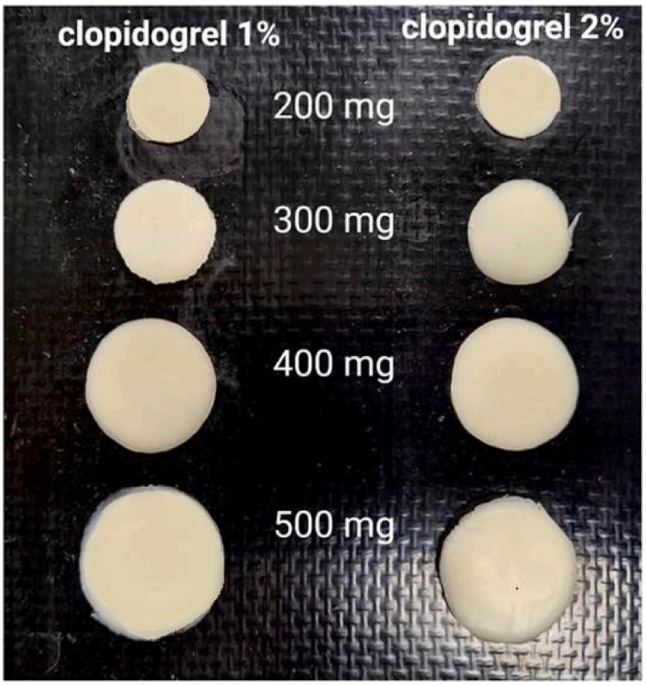

Fig. 5. 1 % and 2 % Clopidogrel tablets appearance after three months stability.

was also maintained at pH 2, and for the mobile phase, the buffer was set at pH 2.9 to ensure optimal solubility and stability.

Assay results provide crucial insights into the potency and stability of the formulations. Both formulations experienced a decline in assay percentage over time, indicative of degradation. However, refrigeration

Table 3
Stability report for extruded gel tablets – 1 % clopidogrel and 2 % clopidogrel.

Test	Specification	Zero Time	First Month	Third Month
1 % Clopidogrel				
Appearance	Off-white, soft chewable tablet with vanilla flavour	Conforms	RT: Conforms Fridge: Conforms	RT: Conforms Fridge: Conforms
pH	2.5–3.5	3.1	RT: 3.1 Fridge: 3.1	RT: 3.3 Fridge: 3.1
Assay *N* = 5 tablets	90.0–110.0 % of clopidogrel bisulphate	94.9 %	RT: 95.2 %	RT: 84.7 % Fridge: 93.5 %
Dissolution (mean ± SD) *N* = 6 tablets	Q=80 % of clopidogrel bisulphate in 30 min	104 % ± 0.70	___	Fridge:103 % ± 2.3
2 % Clopidogrel				
Appearance	Off-white, soft chewable tablet with vanilla flavour	Conforms	RT: Conforms Fridge: Conforms	RT: Conforms Fridge: Conforms
pH	2.5–3.5	2.9	RT: 2.9 Fridge: 2.9	RT: 3.2 Fridge: 3.1
Assay *N* = 5 tablets	90.0–110.0 % of clopidogrel bisulphate	95.1 %	RT: 91.8 %	RT: 88.2 % Fridge:93.6 %
Dissolution *N* = 6 tablets	*Q*=80 of clopidogrel bisulphate in 30 min	111.2 % ± 1.3	___	Fridge: 102 % ± 2.1

RT: room temperature, Fridge: fridge condition, N: number.

significantly mitigated this degradation compared to RT storage. The 1 % formulation demonstrated a decrease from 94.9 % ± 0.02 to 93.5 % ± 0.03 under refrigeration, contrasting with a more substantial decline from 94.9 % ± 0.02 to 84.7 % ± 0.02 at RT. Similarly, the 2 % formulation displayed better stability under refrigeration, with assay percentages declining from 95.1 % ± 0.05 to 93.6 % ± 0.02, compared to a decrease to 88.2 % ± 0.08 at RT.

These variations are within the acceptable range of 90.0–110.0 %, ensuring the tablets' continued efficacy. The findings in fridge condition stability regarding clopidogrel assay closely mirrored the initial results and adhered to the guidelines outlined in ICH Q1A (R2), demonstrating consistency and compliance with regulatory standards.

In fridge condition, 1 % clopidogrel demonstrated a dissolution of 103 % ± 2.3 at the third month, meeting the target of 80 % in 30 min. 2 % clopidogrel displayed a dissolution of 102 % ± 2.1 at the third month, again meeting the target.

4. Discussion

This study aimed to evaluate the application of semi-solid extrusion (SSE) technology for producing personalized immediate-release clopidogrel tablets. The primary focus was on assessing mass variation, content uniformity, *in vitro* drug release profiles, disintegration times, and stability. Findings showed reliable content uniformity and rapid drug release, with both SSE-produced and branded tablets releasing over 85 % of the drug within 15 min, meeting pH. Eur. standards. The tablets disintegrated in under 10 min and maintained stability over three months when stored in refrigerated conditions, highlighting the importance of proper storage for product efficacy.

The findings from the mass variation test for the clopidogrel tablets highlight the importance of robust quality control measures during the manufacturing process. The consistently narrow acceptance limits across the various strengths suggest that the manufacturer has implemented effective in-process controls to ensure consistent tablet masses. However, instances where tablets fell outside the acceptable range, particularly at 300 mg strength, indicate the need for further optimization of the manufacturing process or formulation. This could involve adjustments to the formulation and printing parameters to improve the uniformity of the tablet masses aligning with previous research highlighting the impact of formulation on tablet characteristics and in process controls (Kovács et al., 2024). Additionally, for out-of-specification weight results, it is worth noting that non-compliant tablets can easily be replaced, ensuring that all released tablets are 100 % quality-controlled.

The observation that the 2 % formulations generally exhibited lower standard deviations compared to the 1 % formulations suggests that higher concentrations of the active ingredient may contribute to more uniform tablet masses (Jakubowska and Ciepluch, 2021; Xiang et al., 2009).

The results from the content uniformity analysis of the clopidogrel tablets demonstrate a reliable and precise manufacturing process. The mean values consistently fell within the acceptable range, indicating that the tablets meet the specified content uniformity standards. The AV for each tablet size and concentration remained below the threshold of 15, further supporting the adherence to content uniformity standards. The exceptional uniformity and reliability in the tablet's clopidogrel content, particularly for 2 % clopidogrel 500 mg, highlights the effectiveness of the manufacturing process. The narrow range between the minimum and maximum values for each tablet size and concentration reinforces the consistency observed in the mean and AV values, ensuring the reliability of the pharmaceutical product.

The *in vitro* drug release profile results indicate that, at the 15 min mark, both the dispensed tablet strengths and the branded version release over 85 % of the drug, thus meeting United States Pharmacopeia standard of Q 80 % within 30 min. This means the tablets released the drug quickly, similar to the branded ones within the expected time of 30 min. The extruded tablets met the criteria in 15 min, so there was no need to calculate similarity factors. This finding is consistent with prior research. For instance, Tagami et al. (2021) developed a 3D-printed gummy drug formulation comprising gelatin, hydroxypropyl methylcellulose, syrup, water, and lamotrigine, achieving an 85 % drug release within 15 min. The rapid disintegration times observed for the 1 % and 2 % clopidogrel tablets, regardless of the concentration or tablet size, indicate that the formulation and manufacturing process are suitable to achieve the desired immediate-release characteristics. The consistent disintegration times of under 10 min for all the tablet sizes tested that the formulation has been designed to facilitate efficient breakdown and drug release when the tablets come into contact with water or gastrointestinal fluids. Meeting the pH. Eur. standard of disintegration within 15 min is an important quality attribute for immediate-release tablets, as it ensures the timely availability of the active pharmaceutical ingredient for absorption and therapeutic effect.

Each spectrum from the FTIR analysis provided insights into the molecular composition and potential interactions within the samples. Peaks in the FTIR spectra correspond to various functional groups, indicating the presence of specific chemical bonds. Differences between the tablet and powder forms of clopidogrel highlighted the impact of formulation processes on the FTIR spectrum. Notable differences in peak characteristics were observed around 1700 cm^{-1}, 1500 cm^{-1}, and 1250 cm^{-1}. Around 1700 cm^{-1}, the clopidogrel powder showed a sharper and more pronounced peak, typically indicative of C=O stretching vibrations in carbonyl groups. The clopidogrel tablet had a broader and less intense peak, suggesting possible interactions or dilution effects with excipients that alter the vibrational characteristics of the carbonyl group. Around 1500 cm^{-1}, the clopidogrel powder displayed a distinct peak, likely associated with ring vibrations or C-N stretching in aromatic compounds. This peak appeared reduced and slightly shifted for the clopidogrel tablet, which could be due to the presence of other components in the tablet formulation that affect the vibrational environment of the aromatic ring structures. Around 1250 cm^{-1}, a clear peak was visible in the clopidogrel powder spectrum, possibly related to C-O

stretching or C-N stretching. In the clopidogrel tablet, this peak was less distinct and appeared as a shoulder or part of a broader peak complex, indicating the influence of tablet excipients. These differences highlighted how the physical form (powder vs. tablet) and the presence of excipients in the tablet can influence the FTIR spectral characteristics of the pharmaceutical compound. This analysis was crucial for understanding the formulation properties and ensuring the quality and efficacy of the final pharmaceutical product. The assessment of excipient-drug compatibility involves observing shifts in peak positions and changes in peak intensities, indicating potential interactions between the drug and excipients. While retaining principal peaks may suggest compatibility, modifications in their characteristics hint at possible interactions, aligning with previously published research (Rao & Lakshmi, 2014).

The SEM images show the surface morphology of the samples, highlighting the differences in particle size and shape between the powder and the extruded tablets. The clopidogrel bisulphate powder obtained from the manufacturer was in Form I, and the particles were spherical. This is important because the production of spherical particles is difficult but necessary due to the poor compressibility, flowability, and high surface tension of the powder. Therefore, clopidogrel Form I spherical agglomerates with a uniform particle size distribution are usually produced. The SEM images of the extruded tablets show cross-section morphology after 3-month storage in a fridge. The images indicate that the tablets maintained their shape and structure over time, with no significant changes in particle size or shape. The SEM analysis provides valuable insights into the surface morphology of the samples, which is crucial for understanding the physical properties and behaviour of the pharmaceutical compounds.

The XRD analysis of the extruded tablets containing 1 % and 2 % clopidogrel demonstrated that these tablets maintained their solid-state quality for at least three months when stored in a refrigerator. The absence of clopidogrel peaks in the mixture with the API suggests that the API did not interact with the excipients in a manner that would alter the XRD pattern. Additionally, the amorphous state of the CuraBlend mixture without the API indicates that it exists in a non-crystalline form, and the consistent results after three months imply that this state remains stable over time.

A comparison of the CuraBlend mixture at 0 h (light gray line) and after 24 h of drying (light green line) reveals clear differences. The 0 h mixture displays a relatively flat profile with few distinct peaks, indicating a more amorphous structure. In contrast, the 24 h dried sample shows more pronounced peaks, particularly in the 10–25° 2θ range, with significant peaks at 12°, 19°, and 23° 2θ. This suggests that crystallization occurred during the drying process, leading to a more ordered structure.

In the extruded tablets, the visible peaks are attributed to changes in the physical solid state of certain excipients, such as the rapid solidification of the extruded tablets under refrigeration. These peaks primarily reflect the crystal modifications of cocoa butter and the interactions among different sugars. The XRD analysis thus provides assurance that the extruded tablets maintain their solid-state quality for at least three months when stored under these conditions, which is essential for ensuring the stability and efficacy of the product. For the clopidogrel formulations, both 1 % and 2 % concentrations exhibit consistent XRD patterns over time. At 0 h and after three months, the 1 % clopidogrel samples (black and green lines) show similar profiles, with a prominent peak around 23° 2θ and only minor variations in peak intensity. The 2 % samples (red and blue lines) also demonstrate high similarity, maintaining the same peak around 23° 2θ with minimal changes after three months. This stability indicates that the crystalline structure of both concentrations remains unchanged over time. While the CuraBlend mixture exhibits crystallization upon drying, the clopidogrel formulations (both 1 % and 2 %) retain their crystalline structure over a three-month period, with no significant structural differences observed. Overall, the XRD analysis enhances our understanding of both the characteristics of the CuraBlend mixture and the stability of the clopidogrel formulations, highlighting the importance of solid-state quality in ensuring the efficacy of the final product.

The stability study underscores the importance of refrigeration as a favourable storage condition for clopidogrel formulations. Refrigeration not only preserves appearance and pH stability but also mitigates degradation, as evidenced by superior assay results compared to room temperature storage. The findings highlight the need for careful storage and handling of clopidogrel formulations to maintain their potency and stability. Refrigeration is recommended for long-term storage to prevent degradation and ensure the continued efficacy of the tablets. The study demonstrates the importance of monitoring pH stability and assay results to ensure the quality and efficacy of the formulations. The drying process inherent to this printing technique may lead to shrinkage of the printed object (Alhnan et al., 2016). In this study the primary packing prevented drying and shrinking of the tablets.

In pediatric personalized medicine, using semi-solid extrusion (SSE) based automated dispensing technology to create clopidogrel tablets represents a significant advancement. This approach ensures precise dosing, which is crucial for tailoring treatments to individual pediatric patients based on factors like age, weight, and medical condition. Compared to current practices, where compounded oral suspensions or capsules are manually prepared for pediatric patients (Nahata & Allen, 2008), SSE offers enhanced precision and uniformity in dosing. Pharmacists often rely on extemporaneous methods to prepare clopidogrel suspensions, but these formulations are limited by short beyond-use dates (United States Pharmacopeia) and potential variability in dose accuracy (Li et al., 2008). SSE technology facilitates the creation of customized drug delivery systems with precise control over drug release and dosage (Zhu et al., 2022). Studies further demonstrate SSE's capacity to produce tablets with high uniformity in mass and drug content, adhering to pharmacopoeial standards (Johannesson et al., 2023). This precision in dosing highlights the critical role SSE plays in personalized pediatric treatments (Roche et al., 2023). While extemporaneous preparation may be faster for short-term, patient-specific needs, SSE offers superior quality control and dosing accuracy, which can be especially beneficial for chronic treatments requiring sustained precision. Thus, SSE holds promise for optimizing therapeutic efficacy and safety, reflecting the growing importance of personalized healthcare in pediatric medicine.

5. Conclusion

This study underscores the potential of semi-solid extrusion (SSE) technology in producing personalized immediate-release clopidogrel tablets, demonstrating its suitability for pediatric applications. SSE-produced tablets exhibited consistent mass variation, content uniformity, and rapid drug release profiles, releasing over 85 % of the drug within 15 min, comparable to branded counterparts. Disintegration times under 10 min further highlight the technology's capability to meet pH. Eur. standards for immediate-release formulations.The stability results confirmed that tablets stored under refrigerated conditions maintained their physical integrity and drug content over three months, emphasizing the importance of proper storage to preserve product efficacy. FTIR and XRD analyses supported the chemical stability of the clopidogrel-excipient mixtures, showing no significant interactions or changes in the solid-state properties of the drug. SEM analysis revealed that the tablets maintained their structural integrity without significant changes in particle size over time, confirming the robustness of the manufacturing process.These findings validate the precision, reliability, and stability of SSE technology as a promising method for producing personalized medications. The ability to achieve accurate dosing, especially in pediatric patients, and the rapid, consistent release of clopidogrel enhances the therapeutic potential of SSE, offering a viable alternative to traditional compounding methods in hospital settings.

Supplementary material

All data relevant to this study are included in the main text. No supplementary materials are available.

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CRediT authorship contribution statement

Farnaz Shokraneh: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anne M. Filppula:** Writing – review & editing, Supervision. **Aleksi Tornio:** Writing – review & editing, Supervision. **Jaan Aruväli:** Writing – review & editing, Methodology. **Urve Paaver:** Writing – review & editing, Writing – original draft, Methodology. **Niklas Sandler Topelius:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. CurifyLabs provided the materials, equipment, and PharmaPrinter for this study. Additionally, F.S. and N.S.T. are employed by CurifyLabs, and their roles influenced the research outcomes and manuscript preparation as follows:

- Role in Planning Tests: CurifyLabs contributed to the planning and design of the experiments, ensuring that the methodologies employed were robust and aligned with industry standards.
- Interpretation of Data: CurifyLabs provided expertise in the interpretation of data, offering insights into the results based on their extensive experience in pharmaceutical development.

We acknowledge that the work utilizes commercialized technology, and the founders of this technology were involved in financing and conducting the research, as well as interpreting the results. We believe this collaboration enhances the rigor and relevance of the findings.

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Data availability

Data will be made available on request.

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