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Advancing medication compounding: Use of a pharmaceutical 3D printer to auto-fill minoxidil capsules for dispensing to patients in a community pharmacy

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ABSTRACT

Compounding medications in pharmacies is a common practice for patients with prescriptions that are not available commercially, but it is a laborious and error-prone task. The incorporation of emerging technologies to prepare personalised medication, such as 3D printing, has been delayed in smaller pharmacies due to concerns about potential workflow disruptions and learning curves associated with novel technologies. This study examines the use in a community pharmacy of a pharmaceutical 3D printer to auto-fill capsules and blisters using semisolid extrusion, incorporating an integrated quality control system. This retains the customisation and automation advantages of 3D printing, speeding up the manufacturing process while increasing familiarity for pharmacists. Minoxidil capsules (2.5 mg and 5 mg doses) were prepared using a pharmaceutical 3D printer and dispensed to 9 patients in a community compounding pharmacy setting in Spain. This innovative production method was compared to the conventional manual capsule filling. All capsules met the European Pharmacopeia standards for mass uniformity, drug content and dissolution, and demonstrated stability at 25 °C and 65 % relative humidity for three months, matching the typical treatment duration. The 3D printer offers greater precision and efficiency and reduced operator involvement by more than half compared to manual capsule filling, making the process faster and more cost-effective. This study offers for the first time a clear roadmap for implementing a pharmaceutical 3D printer in a community pharmacy for automated compounding to prepare reliable and precise personalised medication for patients, marking a valuable step forward in precision medicine.

1. Introduction

Most treatments adhere to a standardised approach, prescribing the same medication to different patients without considering their individual needs. This "one-size-fits-all" approach overlooks the impact of relevant patient characteristics (e.g. age, co-morbidities, genetics, metabolism, etc) on the effectiveness of treatments, and frequently results in the appearance of side effects (Litman, 2019; Goetz and Schork, 2018). Therefore, a shift towards personalised therapies with tailored doses or alternative dosage forms is required (Pravin and Sudhir, 2018; Englezos et al., 2023).

The personalisation of treatments for patients with special medical needs and at doses not available commercially is currently done by compounding in pharmacies within hospitals and the community. In this small-scale approach, medicines are prepared manually by combining and mixing different pharmaceutical products (drugs and excipients) in

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precise amounts, based on a medical prescription (AEMPS, 2023a; FDA, 2024). This approach enables the personalisation of doses (Sinclair, 2018), the preparation of alternative dosage forms, the avoidance of allergens, the adaptation of treatments to paediatric patients (Heitman et al., 2019; Rouaz-El-Hajoui et al., 2024) and addressing the shortage of commercial medicines (Torrado-Salmeron et al., 2022), making compounding an essential element of healthcare systems worldwide.

Compounded formulations represent a small percentage of all prescribed medications, so compounding is normally subject to more relaxed regulations than mass manufactured medication (FDA, 2024; Allen, 2020). The commercialisation of compounded medicines does not require approval from regulatory authorities, such as the Food and Drug Administration (FDA) in the US or the European Medicines Agency (EMA) in Europe, and in most countries, it does not require Good Manufacturing Practices (GMP) (FDA, 2024; Donovan et al., 2018; The European Parliament, 2001; European Commission, 2025). Compounding errors are common and can result in serious side effects or even the death of a patient. In 2012, contaminated steroid injections prepared by a Compounding Centre in the US resulted in 64 reported deaths, due to fungal meningitis (Abbas et al., 2016). Moreover, a FDA report analysing 29 medicinal products from 12 compounding pharmacies concluded that, while the analytical testing failure rate for commercially manufactured medicines was under 2 %, this rate rose to 34 % for compounded formulations, mostly due to potency-related issues (FDA, 2018). More recently, multiple US states have reported quality testing failure rates of 11–53 % for compounded medicines with many listing potencies ranging from 0-450 % from the actual prescription (Gudeman et al., 2013).

Automation technologies such as three dimensional (3D) printing, computer vision and internet of things could improve compounding precision, efficiency and medicines quality (Batson et al., 2020; Yoon et al., 2024; Beer et al., 2023). Among those technologies, pharmaceutical 3D printing (3DP), also known as additive manufacturing, is an innovative manufacturing method allowing personalisation in terms of dose, shape, flavour, colour, release profile and drug combination, all while performing quality control monitoring to guarantee safety (Beer et al., 2023; Jandyal et al., 2022; Awad et al., 2018). 3DP allows to produce medicines automatically and can be coupled with non-destructive quality control technologies. Examples of these quality control technologies or Process Analytical Technologies (PATs) include an inbuilt analytical balance for mass uniformity control, a near-infrared (NIR) or RAMAN spectroscopy sensor for content uniformity and pressure sensors (Bendicho-Lavilla et al., 2024; Díaz-Torres et al., 2022; Jørgensen et al., 2023; Herrada-Manchón et al., 2020; Díaz-Torres et al., 2023). These PATs could ensure a better process performance and produce higher quality medicines (Khairuzzaman et al., 2018).

3DP has been used in multiple clinical studies in hospitals around the world, (Rodríguez-Pombo et al., 2024; Goyanes et al., 2019; Denis et al., 2024) demonstrating its value for treatment compliance in diverse patient populations (paediatrics, geriatrics and patients with dysphagia). However, its widespread use for treating patients has yet to be observed (Seoane-Viaño et al., 2021). Uncertainty surrounding regulatory, ethical and social aspects hinder the implementation of 3D-printed medicines in clinical settings (Seoane-Viaño et al., 2021; Lind et al., 2017). Some reasons include prescribers' unfamiliarity with the technology, pharmacists' limited training or expertise in operating 3D printers and an unclear regulatory framework. This extends to aspects such as required equipment, classification of 3D-printed medicines (e.g., tablets, "printlets" (3D-printed tablets), troches, gummies, orodispersible films, etc.), and the implementation of quality standards for point-of-care manufacturing (Herrada-Manchón et al., 2020; Wang et al., 2023; FDA, 2022; MHRA, 2023; Goyanes et al., 2017; Musazzi et al., 2018; Goyanes et al., 2014). An easier alternative for quick implementation in a clinical setting is using a pharmaceutical 3D printer to fill capsules as an automatic material dispenser (Denis et al., 2024). With this approach, the final dosage form is a capsule, even though a 3D printer is used for the filling process. This method allows for automated personalised dosing and quality control while avoiding the unfamiliarity surrounding 3DP.

A drug commonly used in compounding that could benefit from this technology is minoxidil, an active ingredient effective in the treatment of many forms of alopecia (androgenic alopecia, telogen effluvium, chemotherapy, etc.). Although the oral treatment of minoxidil is not commercially authorised in some countries, small batches of hard capsules containing minoxidil at low dose (0.25–5 mg) are commonly prescribed by doctors and compounded in pharmacies as extemporaneous (compounded) formulations (Torrado-Salmeron et al., 2022; Randolph and Tosti, 2021; Watson et al., 2021). Dose accuracy is important to avoid the occurrence of side effects associated with this drug such as facial hypertrichosis, postural hypotension or tachycardia (Suchonwanit et al., 2019).

The aim of this study was to pioneer and demystify the implementation of a pharmaceutical 3D printer as a capsule filling platform for medication production in a community compounding pharmacy. Minoxidil capsules with two different dose strengths (2.5 mg and 5 mg) were prepared through conventional compounding methods and by using a pharmaceutical 3D printer equipped with an in-line quality control system alongside specialised software. In the study, both preparation methods were compared in terms of characteristics of the batches, resources, cost and production time. Additionally, a comprehensive evaluation of the regulatory framework was performed to assess the legal feasibility of using a pharmaceutical 3D printer to manufacture medicines and give them to patients.

2. Materials and methods

2.1. Materials

Minoxidil, polyethylene glycol 4000 (PEG 4000), xanthan gum, size 3 capsules red colour, riboflavin and microcrystalline cellulose (Capsucel®) were purchased from Guinama (Valencia, Spain). Techna 20 SF^{TM} troche base with bitter-bloc technology was obtained from SpecializedRx (Minnesota, US). All materials used are widely utilised in pharmaceutical compounding and were of pharmaceutical grade, suitable for human consumption.

2.2. Preparation of minoxidil capsules using a pharmaceutical 3D printer

2.2.1. Preparation of the pharma-ink

Pharma-inks, consisting of a mixture of drug and excipients, were prepared following a Standard Operating Procedure (SOP) designed for easy implementation in a compounding pharmacy. Briefly, Techna and PEG pharma-inks were prepared by heating 19.66 g of Techna 20 SF^{TM} or 19.56 g of PEG 4000 and 0.1 g of xanthan gum at 70 °C on a heating plate while stirring at 500 rpm (Table 1). Once melted, minoxidil was dispersed into the molten mixture using a homogeniser (T10 basic ULTRA-TURRAX, IKA, US) at 20,000 rpm for 3 min. The resulting pharma-inks were then transferred into disposable syringes (Injekt 20 mL Luer Lock solo, B. Braun, Germany) and allowed to cool down at room temperature until solidification. The pharma-inks were subsequently used to fill size 3 gelatine capsules containing 2.5 mg and 5 mg doses of minoxidil. The same pharma-ink can be used to prepare multiple doses, as the 3D printer precisely controls the amount extruded to

Table 1
Composition of pharma-inks used for filling capsules prepared using a pharmaceutical 3D printer.

Pharma-ink	PEG 4000 (% w/w)	Techna 20 SF^{TM} (% w/w)	Xanthan gum (% w/w)	Minoxidil (% w/w)
Techna	–	98.3	–	1.7
PEG	97.8	–	0.5	1.7

achieve the desired dose.

2.2.2. Capsule filling process

A M3DIMAKER 1 pharmaceutical 3D printer (FABRX Ltd., UK) equipped with an exchangeable Semi-Solid Extrusion (SSE) Laguna printhead, an inbuilt analytical balance, and a capsule holder (Fig. 1) was used for the filling process. The M3DIMAKER 3D printer was controlled by M3DIMAKER Studio software (FABRX AI, Spain) to automatically dispense 2.5 mg and 5 mg doses of minoxidil in size 3 gelatine capsules and perform in-line quality control using the inbuilt quality control equipment. The rheological behaviour of the pharma-inks was obtained using the SSE Laguna's integrated pressure sensor and analysed using M3DIMAKER Studio software. This process enabled the determination and optimisation of the printing parameters, as described in previous studies (Díaz-Torres et al., 2022; Díaz-Torres et al., 2023).

To fill the capsules, the pre-filled syringes of minoxidil pharma-ink were preheated to 70 °C in the SSE Laguna printhead and fitted with a 1.6 mm tip (Fisnar, US). 90 or 100 capsules were placed in a commercial capsule holder inside the printer and filled after selecting the dose to dispense using M3DIMAKER Studio software, which also recorded critical process data (Fabrx, 2024). In-line quality control of each capsule was automatically carried out using M3DIMAKER Studio software with the integrated balance and pressure sensor (Section 2.6.3). Finally, the capsules were closed and stored in a hermetically sealed topaz glass bottle before being analysed and dispensed to patients.

2.3. Compounding minoxidil capsules using the conventional method

The conventional minoxidil capsules were prepared following the PN/L/FF/001/00 SOP from the Spanish National Formulary for the preparation of hard capsules (AEMPS, 2025a). Two different blends were prepared (Table 2). Capsucel®, riboflavin and minoxidil were weighed (SOP code PN/L/OF/001/00) (AEMPS, 2025b) and mixed (SOP code PN/L/OF/002/00) (AEMPS, 2025c) using a homogeniser (SAMIX® BR200, Guinama, Spain). Size 3 gelatine capsules were filled with minoxidil doses of 2.5 mg or 5 mg, as shown in Table 2. In this method, each capsule dose required a different blend. A manual capsule filling machine (Capsunorm, Guinama, Spain) was used to dispense the powder blend into the capsules and to close them. To ensure accurate dosing of minoxidil, the blend was repeatedly compacted inside the capsules until they were fully filled. Finally, the capsules were visually analysed, stored in hermetically sealed topaz glass bottles and dispensed to patients.

Table 2
Composition of capsules prepared using the conventional method.

	Capsucel® (% w/w)	Riboflavin (% w/w)	Minoxidil (% w/w)
Conventional 5 mg capsules	96.6	0.3	3.1
Conventional 2.5 mg capsules	97.8	0.4	1.8

2.4. Manual quality control

Although only the inspection of organoleptic characteristics is mandatory (Decreto, 2003), mass uniformity was evaluated as an extra quality control measure. For the capsules prepared with the M3DIMAKER 3D printer, this was in addition to the automatic weighing carried out by the inbuilt balance in the printer. The European Pharmacopeia (Ph. Eur. 2.9.5) monograph was followed for mass uniformity control with minor modifications (EDQM Council of Europe, 2023a) and 20 capsules of 2.5 mg or 5 mg of minoxidil were randomly sampled. The mass of the capsule contents was determined as the difference between the intact capsules weight and the average weight of the empty capsules. The capsule contents weight was determined using this methodology due to the propensity of PEG to adhere to the gelatine capsule walls, which hinders complete capsule emptying as described in the European Pharmacopeia. A 10 % deviation was established as the acceptable threshold for passing the test in line with standard practice.

2.5. Physicochemical characterisation

2.5.1. Thermal analysis

The content of the capsules prepared by both methods, conventional and with the pharmaceutical 3D printer, were characterised using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

For DSC analysis, 3–6 mg samples were analysed using a Q2000 DSC (TA Instruments, Waters LLC, USA) at temperatures ranging from 20 °C to 240 °C at a rate of 10 °C/min. Nitrogen served as the purge gas at a flow rate of 50 mL/min. GraphPad Prism software (version 9.5.0) was

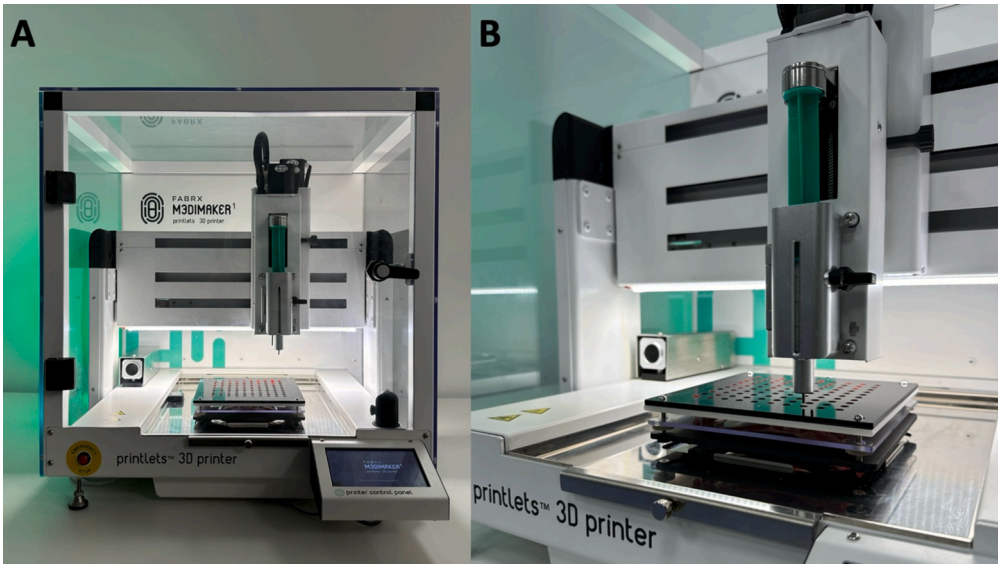

Fig. 1. M3DIMAKER 1 pharmaceutical 3D printer with the capsule holder on top of the integrated balance: (A) Full view of the capsule holder- pharmaceutical 3D printer system in a community compounding pharmacy laboratory, (B) Magnified view of the capsule holder within the printer.

used to analyse the data.

For TGA analysis, 3–6 mg samples were placed in open aluminium pans and analysed with a Discovery TGA (TA Instruments, Waters LLC, USA). Samples were first equilibrated at 30 °C and then heated to 320 °C, at a heating rate of 10 °C/min. Nitrogen was used as the purge gas at a flow rate of 25 mL/min. Data collection and analysis were performed using TA Instrument's Trios software.

2.5.2. X-ray diffraction

The X-ray diffraction (XRD) patterns of minoxidil, pharma-inks, capsules content, and excipients were assessed using an X-ray diffractometer (Rigaku MiniFlex 600, Rigaku, USA) with a Cu Kα X-ray source (λ = 1.5418 Å) and Miniflex Guidance software. Samples were evenly spread on a disc with a diameter of 23 mm and a height of 1 mm for the analysis. The intensity and voltage applied were 15 mA and 40 kV, respectively. The angular range of data acquisition was 2-40° 2θ, with a stepwise size of 0.02° at a speed of 5°/min.

2.5.3. Fourier transform-infrared spectroscopy (FTIR)

The infrared spectra of minoxidil, pharma-inks, capsules content, and excipients were collected using a Spectrum 100 FTIR spectrometer (PerkinElmer, Waltham, MA, USA). All samples were scanned over a range of 4000–650 cm^{-1} at a resolution of 4 cm^{-1} for 6 scans.

2.5.4. High performance liquid chromatography (HPLC)

The minoxidil content in samples was determined using a stability-indicating high-performance liquid chromatography-ultraviolet (HPLC-UV) method (Polonini and Silva, 2023). A 1100 Series HPLC system (Agilent Technologies, Cheadle, UK) was used. The stationary phase was a Symmetry C18 5 μm, 250 x 4.6 μm column (Waters, Spain) and the mobile phase was a combination of methanol, water and acetic acid at a ratio of 70:30:1 *v/v/v*. The flow rate was set to 0.5 mL/min with a column temperature of 25 °C and an injection volume of 20 μL. The UV wavelength was 254 nm, and the runtime was 10 min. The retention time of minoxidil was approximately 3.4 min.

2.5.5. Determination of drug content

The minoxidil content of PEG and Techna capsules was determined by HPLC using the method described in Section 2.5.4 and following the European Pharmacopeia monograph '*2.9.6. Uniformity of content of single-dose preparations*' (EDQM Council of Europe, 2024). Ten capsules from each batch were randomly selected and dissolved in a 70:30 methanol:water solution to obtain a theoretical minoxidil concentration of 5 μg/mL. The solution was then filtered through a 0.22 μm nylon filter (Chmlab Group, Barcelona, Spain) and drug content (%) was calculated using equation (1).

$$\text{Drug content}\,(\%) = \frac{\text{Measured amount of minoxidil in capsule}\,(\text{mg})}{\text{Theoretical dose of minoxidil in capsule}\,(\text{mg})}\text{x}100 \quad (1)$$

2.5.6. In vitro dissolution

The drug release profiles of the capsules were obtained using a Plus Dissolution Test Station USP Type I apparatus (Hanson Research, Chatsworth, CA, USA). The dissolution conditions were set in accordance with the United States Pharmacopeia and National Formulary (USP-NF) minoxidil tablets monograph (USP, 2021). Capsules were placed in apparatus baskets and introduced into 900 mL of phosphate buffer pH 7.2 medium at 37 ± 0.5 °C. The rotation speed was set at 75 rpm. Within the dissolution process, 5 mL of each sample solution (n = 6) was collected at 5-minute intervals for 20 min, and then at 10-minute intervals up to 50 min. After each sample collection, 5 mL of fresh medium was added. The solutions were diluted in a 70:30 methanol:sample ratio and filtered through 0.22 μm nylon filters. Minoxidil concentration was determined with HPLC, using the method described in Section 2.5.4.

2.5.7. Stability study

A 3-month stability study was conducted on conventional, PEG and Techna capsules in accordance with the ICH guideline '*Q1A(R2) Stability Testing of New Drug Substances And Products*' (Harmonization ICo, 2003). The capsules (n = 3 per batch) were placed in hermetically sealed topaz glass bottles inside a climate chamber (Ineltec, Barcelona, Spain) at a temperature of 25 ± 2 °C and a relative humidity (RH) of 60 ± 5 %. At 15, 30, and 90 days, the capsules were dissolved in a 70:30 methanol: water solution to achieve a theoretical concentration of 5 μg/ml minoxidil, filtered through 0.22 μm nylon filters and were analysed using the stability-indicating HPLC method described in Section 2.5.4.

2.6. Clinical implementation

2.6.1. Legal assessment of compounding minoxidil capsules using a pharmaceutical 3D printer

The Spanish National Formulary, the official compendium of the standardised compounded medicines, was thoroughly examined to determine whether minoxidil hard capsules for oral use are classified as a standardised formula and if they are subject to any specific SOP for their preparation or quality control (AEMPS, 2023b).

Additionally, the Official College of Pharmacists of Madrid (Colegio Oficial de Farmacéuticos de Madrid, COFM), a local public law corporation that represents and groups all licensed pharmacists in Madrid, was contacted to evaluate the legal feasibility of preparing minoxidil capsules using a pharmaceutical 3D printer as a capsule filling platform instead of the conventional manufacturing method.

The companies FABRX Ltd. and FABRX Artificial Intelligence S.L (FABRX AI) provided documents and support related to regulatory requirements and quality aspects of the manufacturing process, including the compliance of the equipment and software with existing compounding regulations, user manuals and SOPs for the pharmaceutical 3D printer and software, batch records, cleaning SOP, and quality control of the resulting medicines.

SOPs were written for both the preparation of the pharma-ink and the filling of capsules with the 3D printer. The SOP for the minoxidil capsules was written based on the COFM's SOP for Non-standardised Compounded Formulas of Minoxidil Capsules. The SOP included the denomination and/or qualitative composition, pharmaceutical dosage form, pharma-ink components, preparation method, quality controls, packaging, storage conditions, expiration date and information for patients.

2.6.2. Preparation and dispensing of minoxidil capsules using a pharmaceutical 3D printer as a capsule filling platform in a pharmacy setting

The pharmaceutical 3D printer was installed in the compounding laboratory of the community pharmacy Ángel Orive Pharmacy (Madrid, Spain). The pharmacists responsible for compounding were trained in using the equipment and software, as well as in preparing the minoxidil pharma-inks. Minoxidil capsules with doses of 2.5 mg or 5 mg were prepared for a treatment duration of 3 months (90 or 100 capsules) and were dispensed to patients in accordance with the requirements of their

specific medical prescription.

Additionally, a preparation report and a patient information leaflet were created for each treatment using ATENFARMA software (MICOF, Valencia). The elaboration report included the report number, dispensing state, formulation name, dosage form, number of capsules, elaboration and expiration date, prescriber, prescription number, composition in grams per treatment and per capsule with batch ID of the components, equipment, elaboration procedure, quality control and selling price. The leaflet included information relative to the prescription, elaboration report, composition of the capsules, activity and indication of minoxidil, posology, regimen of administration, contraindications, treatment precautions and warnings, side effects, intoxication and overdose instructions, storage conditions and relevant additional information.

2.6.3. *In-line quality control*

In-line quality control of each capsule was carried out using M3DIMAKER Studio software, the integrated balance (Bendicho-Lavilla et al., 2024) and pressure sensor (Díaz-Torres et al., 2022; Díaz-Torres et al., 2023). Mass uniformity was assessed by recording the weight of each capsule's content after filling. A stabilisation time of 3 s per capsule was set on the analytical balance to ensure accurate measurement. A colour-coded system in the M3DIMAKER Studio software indicated whether the weight was within (green) or outside (red) the acceptable limits of a 10 % deviation from the target, in line with deviation requirements of the European Pharmacopeia (EDQM Council of Europe, 2023a). The pressure sensor measured the mechanical force required to extrude the molten material through the tip. The extrudability profile, which tracks the force applied over time, was analysed to identify potential blockages, lumps, or inconsistencies during the printing process.

2.6.4. *Cleaning Standard Operating Procedure (SOP)*

A cleaning SOP supplied by FABRX Ltd. was followed to verify the cleanliness of the pharmaceutical 3D printer after preparing the minoxidil capsules in the compounding pharmacy. After completing the preparation of a batch of minoxidil capsules, the printer was turned off, and the SSE printhead was detached according to the manufacturer's instructions. The printer surfaces and printhead were then wiped with a disposable cellulose paper moistened with water. Finally, any remaining residue was removed using a disposable cellulose paper moistened with 70–80 % alcohol.

Possible residues of minoxidil were collected from the printer using a cotton swab before preparation of the capsules and after cleaning the 3D printer. Samples were taken from various areas of the 3D printer, including the capsule holder surface, the bottom, top, left and right sides of the 3D printer surface, inside the printhead, the Z calibration button, and inside the heating chamber (Fig. 2). The cotton swabs were introduced in 2 mL of a 70:30 methanol:water solution, and the samples were analysed by HPLC with the method described in Section 2.5.4.

2.6.5. *Cost-time comparison between conventional compounding and automated capsule filling using a 3D printer*

A comparison of conventional methods versus pharmaceutical 3D printing for preparing minoxidil capsules was conducted based on cost and time efficiency. The preparation time for a 3-month treatment was determined for both the conventional and the minoxidil capsules filled using the M3DIMAKER 3D printer. Additionally, the selling price in euros (EUR) for a three-month treatment with 2.5 mg and 5 mg doses of minoxidil capsules produced with both methods was calculated. This calculation included the cost of raw materials (drug and excipients) and consumables (disposable cartridge and dispensing tip) as well as the operatoŕs active involvement time in the elaboration process of the

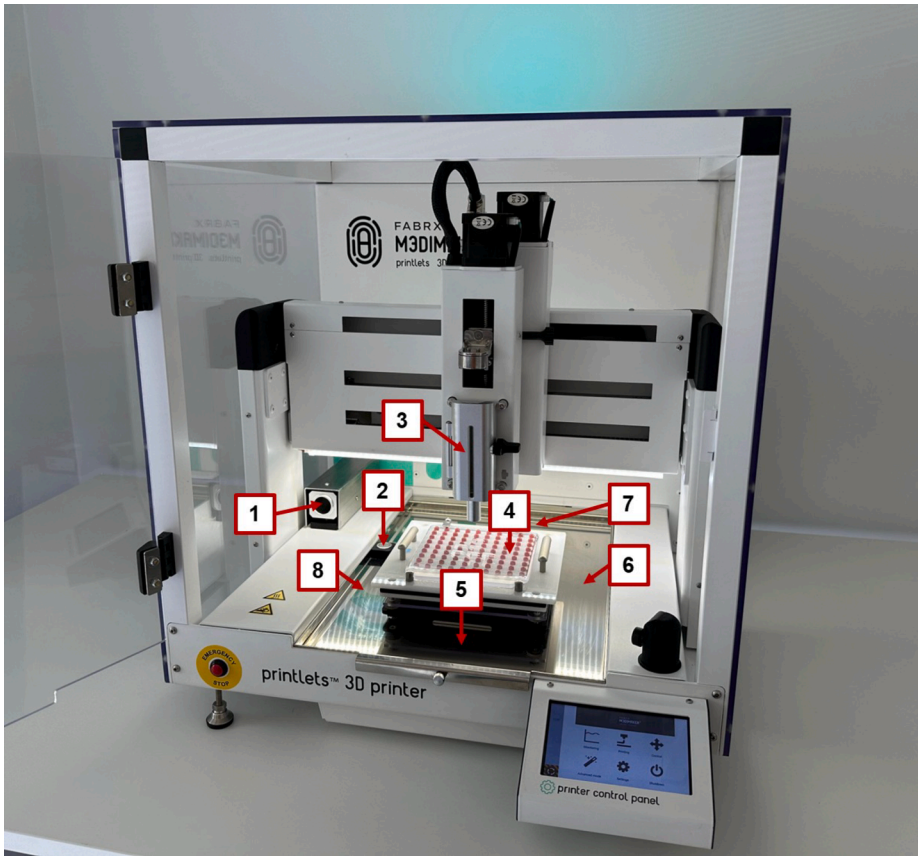

Fig. 2. Sampling points during the cleaning SOP:1. Inside the heating chamber, 2. Z calibration button, 3. Inside SSE printhead, 4. Capsule holder surface, and 5. Top, 6. Right, 7. Bottom and 8. Left sides of the 3D printer.

capsules, which was different in both methods, and excluded fixed costs such as packaging, pharmacist fees and the 4 % Spanish Value Added Tax (VAT) for medicines. Pharmacist fees are professional fees included in the cost of all compounded medicines in Spain. These fees are standardised and determined based on the type of formulation, such as sterile or non-sterile preparations (oral, rectal, vaginal or topical) (COFC, 2024).

3. Results and discussion

In this study, the M3DIMAKER pharmaceutical 3D printer equipped with an integrated in-line quality control system was employed for the first time in a community compounding pharmacy to automatically fill capsules with two different doses of minoxidil (2.5 mg and 5 mg) for actual patient use. This innovative method was compared with the conventional preparation of minoxidil capsules in terms of formulation physicochemical characterisation, quality control, cost, and preparation time.

The excipients of the pharma-ink were selected for their safety profile and general use in compounding worldwide (GUINAMA, 2022; GUINAMA, 2024; SpecializedRx, 2020). SSE technology, unlike the conventional capsule preparation method that requires powder, utilises semi-solid pharma-inks that need to be extruded into capsules. This reduces pharmacist exposure risk as harmful powders are contained in a semi-solid (Hannah Echt and Colleen ÓConnor, 2023). PEG pharma-ink (Table 1) used PEG 4000 as main excipient, which melts around 60 °C, making it suitable for extruding into capsules with a SSE printhead (GUINAMA, 2022; Secretan et al., 2023). Additionally, xanthan gum was used as a suspending agent for enhancing the stability of poorly soluble drugs (Nsengiyumva and Alexandridis, 2022). As an alternative composition, Techna pharma-ink was used, a pre-mixed marketed base composed of different grades of PEG and suspending agents, such as xanthan gum. Pre-mixed bases such as this are FDA-approved and widely used in compounding hospitals and pharmacies in US, although not so widely adopted in Europe. The availability of these pre-formulated bases simplifies the pharma-ink preparation process for pharmacists. Pharmacists only need to mix the drug into the molten base and fill the syringes, allowing the 3D printer to produce the medication tailored to each patient's needs. They are available from a wide range of pharmaceutical excipient suppliers around the world.

The optimisation of the 3D printing parameters for the specific pharma-inks used in this study took under 30 min, characterised by the rapid filling of capsules in a reliable way with minimal errors, displaying the fast turnaround time of new protocols. The pressure sensor in the SSE Laguna printhead, along with the M3DIMAKER Studio software, was used to optimise the printing parameters. The extrudability profile of the pharma-inks was studied to determine the appropriate printing temperature and extrusion rate (Díaz-Torres et al., 2022; Díaz-Torres et al., 2023) (Fig. 3). The optimal conditions were set at a temperature of 70 °C and an extrusion rate of 50 mm/min to maintain constant pressure during the capsule preparation process. Under these conditions, PEG pharma-ink exhibited slightly thixotropic behaviour, requiring a certain pressure to initiate flow through the tip, after which a steady flow was achieved. When the applied pressure was released during the hold period, the recorded pressure dropped abruptly, indicating a low percentage of stress recovery, as the flow of ink through the tip ceased quickly after pressure release.

The extruded PEG and Techna pharma-inks solidified immediately upon contact with the capsule shell. Moreover, the capsule was visually inspected, and its structure remained intact, without melting or softening during the process.

For the preparation of the conventional capsules, the existing pharmacy SOPs were followed. Riboflavin was added as a colour indicator to ensure proper mixing of the excipients and drug (Torrado-Salmeron et al., 2022).

Mass uniformity results showed that conventional capsules fell within the ± 10 % tolerance range established by the European Pharmacopeia, with total weights of 135.90 ± 2.79 mg and 146.85 ± 3.98 mg for 2.5 mg and 5 mg respectively. The same test was performed on capsules filled using 3D printing, which also fell within the ± 10 % tolerance range in all cases, with weights of 145.10 ± 2.73 mg and 291.45 ± 2.46 mg for 2.5 mg and 5 mg PEG capsules, and 146.25 ± 1.93 mg and 294.05 ± 2.98 mg for 2.5 mg and 5 mg Techna capsules, respectively.

3.1. Physicochemical characterisation

TGA analysis was conducted to assess the thermal stability of minoxidil, as temperature is involved in both the preparation of the pharma-ink and the filling of capsules. The TGA thermogram (Fig. 4A) shows the weight loss of minoxidil with temperature, displaying an intense weight decrease at 280 °C due to degradation. Thus, the TGA data suggest that minoxidil remains stable at 70 °C, which was the maximum temperature the drug was exposed to during the preparation of pharma-inks and filling process of the capsules.

DSC analysis was conducted to study the solid state of minoxidil in

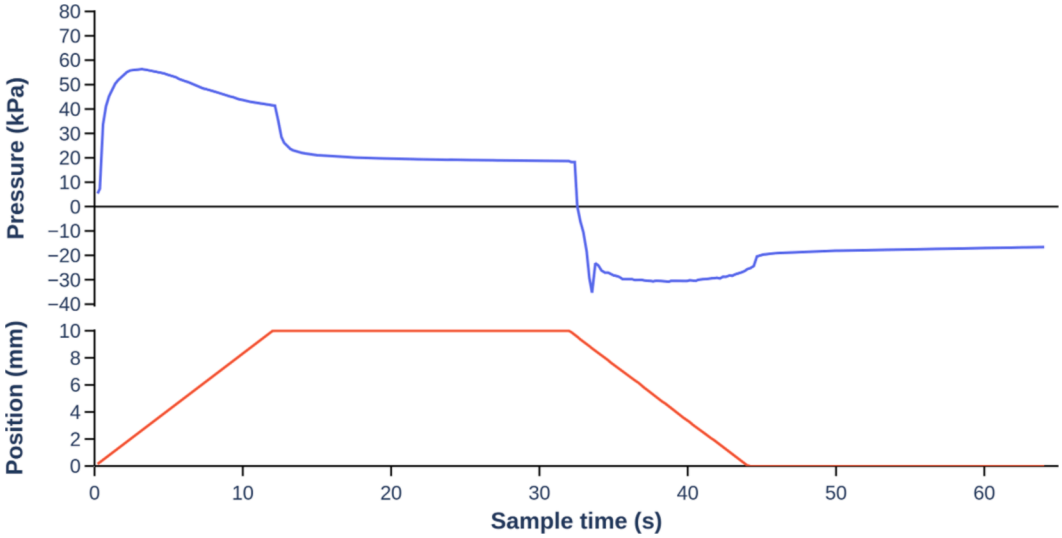

Fig. 3. Graphical representation of the extrudability profile of PEG pharma-ink.

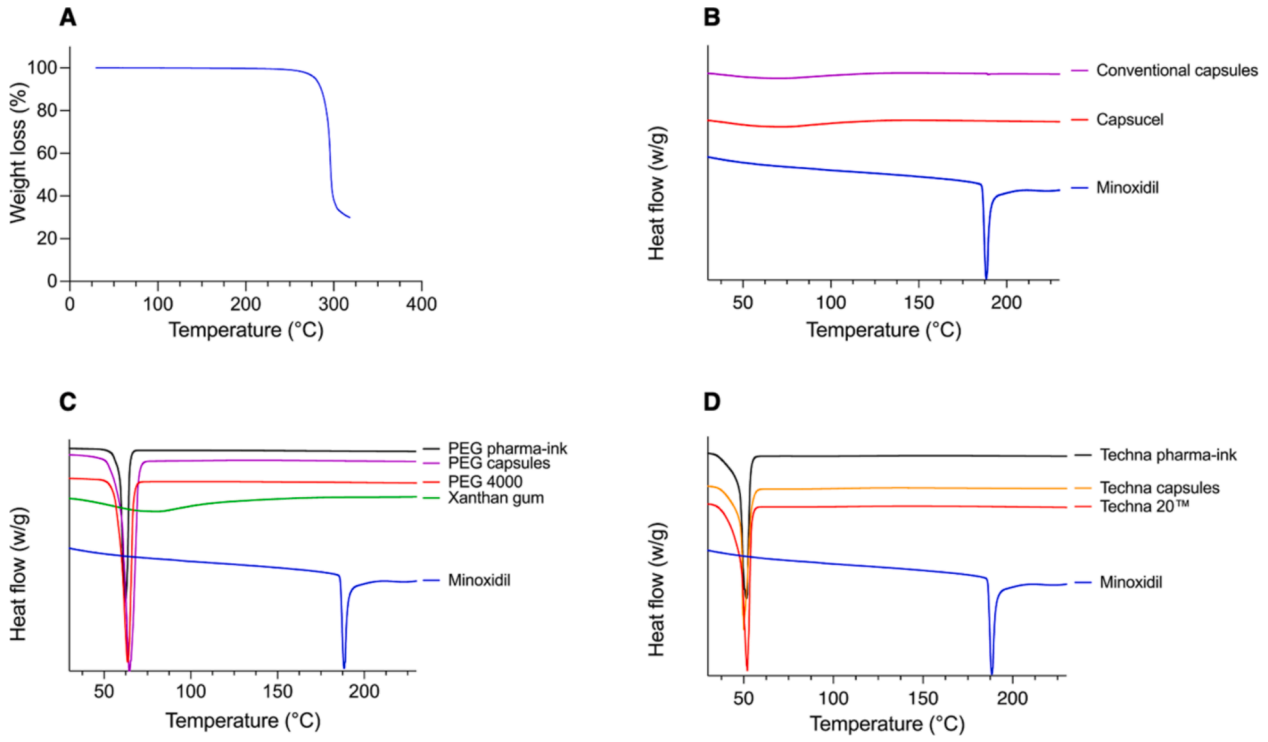

Fig. 4. (A) TGA thermal profile of minoxidil raw material. (B) DSC curve of minoxidil raw material and conventional capsules. (C) DSC curve of PEG pharma-ink and capsules. (D) DSC curve of Techna pharma-ink and capsules. (Exo up).

the conventional capsules and the capsules prepared with the pharmaceutical 3D printer. Minoxidil showed a melting endotherm around 190.39 °C, PEG 4000 and Techna 20 SF^{TM} showed melting endotherms at 61.15 °C and 49.70 °C, respectively. The rest of the excipients did not show any endothermic peaks indicative of their amorphous state (Fig. 4B-D). The DSC data of the conventional capsules showed a small endothermic peak as seen in the pure minoxidil, indicative of its crystalline state in the conventional powder blend (Fig. 4B). On the other hand, the DSC results for Techna and PEG pharma-inks and capsules revealed the endothermic peaks seen in pure Techna 20 SF^{TM} and PEG 4000 (Fig. 4C-D), but there was no evidence of melting around 190 °C for the pure minoxidil. This suggests that the drug is molecularly dispersed within the polymer matrix as a solid dispersion or not detectable due to the low concentration.

The XRD pattern of the pure minoxidil showed sharp peaks at 2θ values of 12.40°, 15.50°, 16.38°, 19.50°, 22.57°, and 29.74°, confirming its crystalline form (Abdel-Raouf et al., 2021) (Fig. 5). In contrast, Techna and PEG pharma-inks and capsules exhibited broad halos, characteristic of semi-crystalline PEG in Techna 20 SF™ and PEG 4000 samples. The absence of the characteristic diffraction peaks for minoxidil in the diffractograms of the pharma-inks and capsules suggests the drug is in an amorphous form, or that any remaining crystalline fraction is below the detection limit of $\leq$ 5 % w/w. The XRD pattern of conventional capsules shows very low-intensity minoxidil peaks. These results are consistent with the DSC results.

The IR spectrum of pure minoxidil shows stretching bands corresponding to NH_2 at 3453 and 3409 cm^{-1}, =N–H at 3277 cm^{-1}, aromatic C = C and C = N at 1644, 1615, and 1554 cm^{-1}, and pyrimidine N-oxide at 1236 cm^{-1} (Fig. 6A). These results are in accordance with those reported in the literature (Abdel-Raouf et al., 2021; Mura et al., 2013). In the spectra of Techna and PEG pharma-inks and capsules, the stretching bands corresponding to NH_2 and = N–H diminished due to the low concentration of minoxidil (1.7 % w/w) (Fig. 6B). The aromatic C = C and C = N, and pyrimidine N-oxide stretching bands appeared with minor shifts and lower intensity relative to the pure minoxidil. Similarly, diminished band intensities are also evidence for the conventional capsules.

The IR spectra of Techna and PEG capsules were dominated by PEG 4000 (97.8 % w/w), as seen in the pure PEG 4000 spectrum (Fig. 6A), indicating no interactions between the drug and excipients. Additionally, the spectra of the capsules were superimposable with that of their corresponding pharma-inks indicative that the filling process of the capsules did not alter the pharma-ink composition.

3.1.1. *Determination of drug content*

The results of the drug content of the capsules prepared with the pharmaceutical 3D printer show that all the capsules have a drug content between 99.3–101.9 % (Table 3). The capsules met the European Pharmacopeia's content uniformity criteria, requiring 85 % to 115 % content for each unit, with no more than one unit outside this range or beyond 75 % to 125 % (EDQM Council of Europe, 2024).

3.1.2. *In vitro dissolution*

The dissolution test indicated that both the conventional and the capsules filled via 3D printing exhibited an immediate release profile for minoxidil (Fig. 7). All capsules released over 80 % of minoxidil within 45 min, complying with the "5.17.1. Recommendations On Dissolution Testing" monograph of the European Pharmacopeia (EDQM Council of Europe, 2023b).

Some differences were observed between the conventional and 3D printer-filled capsules. Conventional capsules showed a higher release rate of minoxidil, reaching 80 % release in under 5 min and 100 % release in under 10 min. This was likely because conventional capsules, containing a powdered blend of drug and excipients, opened in the apparatus basket, causing rapid release. In this case, the capsule shell limited the drug release into the dissolution medium.

In contrast, the capsules prepared with the 3D printer showed a more gradual release of minoxidil over time, although still within the immediate release standards. In these capsules, the erosion effect of water-soluble PEGs, along with the capsule shell remaining closed,

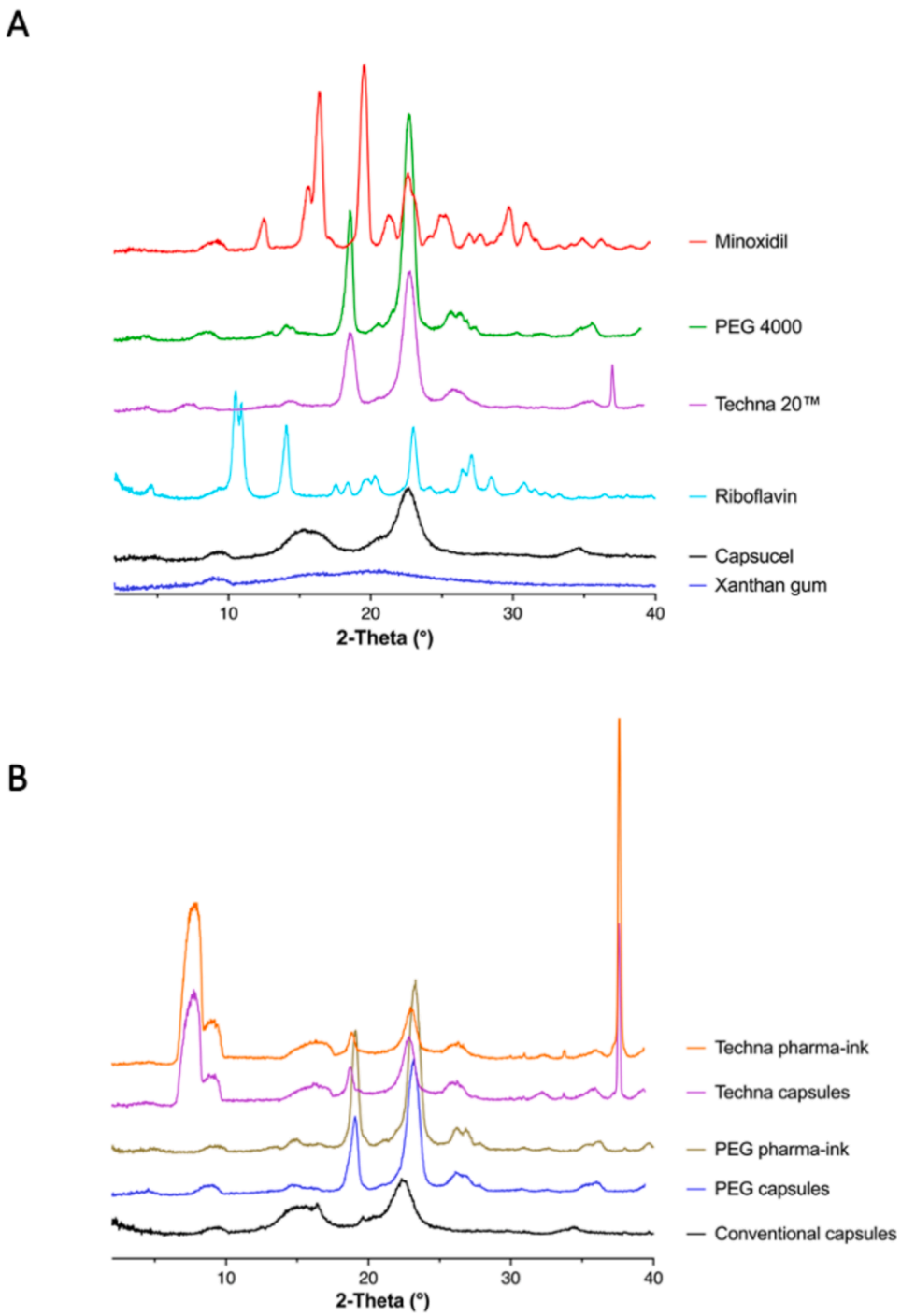

Fig. 5. (A) X-ray diffraction patterns of pure minoxidil and excipients. (B) X-ray diffraction patterns of Techna and PEG pharma-inks and capsules and conventional capsules.

contributed to greater control of drug release (Tajiri et al., 2010).

3.1.3. Stability studies

In this study, a three-month stability study was conducted to align with the typical prescribed oral treatment duration for alopecia with minoxidil capsules. All capsules remained stable throughout the studied period (Table 4), with no degradation peaks observed in the HPLC chromatograms, confirming that no significant chemical changes occurred. The stability of the conventional compounded minoxidil capsules over time has not been studied to date as such studies are typically reserved for marketed medicines (The European Parliament, 2001).

3.2. Clinical implementation

3.2.1. Legal assessment

The legal feasibility of preparing minoxidil capsules using a pharmaceutical 3D printer in a Spanish compounding pharmacy was assessed to ensure compliance with the European and Spanish compounding regulations. The preparation of medicinal products in pharmacies is not harmonised across Europe, with compounding falling under the national regulations of individual countries (The European Parliament, 2001; Minghetti et al., 2014). In Spain, the Spanish National Formulary (Formulario Nacional) includes standardised compounded formulas, their categories, indications, raw materials used in their preparation, and

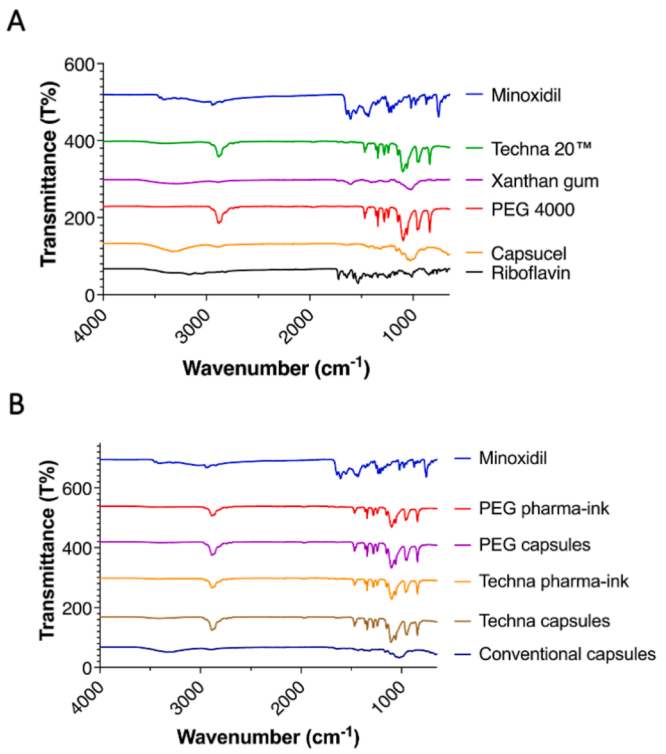

Fig. 6. (A) FTIR spectra of pure minoxidil and excipients. (B) FTIR spectra of Techna and PEG pharma-inks and capsules and conventional capsules.

Table 3
Drug content of minoxidil capsules (n = 10).

	2.5 mg	5 mg
PEG capsules	99.3 ± 3.4 %	100.9 ± 2.1 %
Techna capsules	101.9 ± 1.9 %	101.3 ± 2.2 %

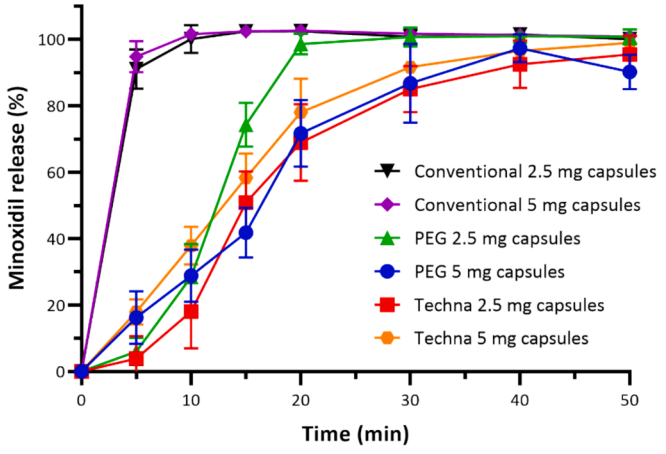

Fig. 7. Dissolution profiles of conventional capsules and capsules prepared with a 3D printer containing 2.5 mg and 5 mg doses of minoxidil (n = 6).

guidelines for proper preparation and control. While the National Formulary includes a 2 % minoxidil solution for topical administration, no monographs specifically address minoxidil hard capsules for oral administration (AEMPS, 2023b).

Compounded formulas not listed in the National Formulary but commonly prescribed are prepared based on medical prescriptions and supported by scientific evidence, literature, and clinical trials. In addition, when a prescription lacks specific details on composition or preparation, the pharmacist may select the most appropriate excipients and methods, while ensuring compliance with the prescription requirements, as confirmed by the COFM. Furthermore, while the National Formulary sets minimum quality controls for standardised formulas, non-standardised formulas only require organoleptic control (Decreto, 2003).

Both PEG and Techna pharma-inks have proven stability and suitable physicochemical and printability properties. PEG pharma-ink was selected for clinical implementation because it uses pharmaceutical-grade raw materials approved in Europe from qualified suppliers. The pre-mixed base Techna 20 SF™ is not accessible in the European market, however, it would be a good alternative for the US market.

3.2.2. *Implementation in a pharmacy setting*

The M3DIMAKER 1 was chosen as an easy-to-implement medication manufacturing kit for automating the preparation and quality control of compounded medicines, such as filled capsules. The M3DIMAKER 1 3D printer integrates a pressure sensor, a mass quality control system, exchangeable printheads for technology versatility and easy cleaning, as well as various printing platforms, including a capsule holder for preparing capsules, for additional flexibility. Hence, the capsule holder could be easily replaced by a blister filling system, moulds or a flat 3D printing surface. The 3D printer ensures higher safety standards and significantly reduces the manual effort required for capsule preparation compared to conventional methods, while also meeting the diverse requirements of medical prescriptions for patients (e.g., varying doses or quantities of capsules). Additionally, the M3DIMAKER Studio software securely records the entire printing process, providing a reliable log for audits or future reference.

The 3D printer was installed in Orive Mayor pharmacy, a medium-sized community pharmacy with a compounding license and a conditioned laboratory located in Madrid, Spain. Over the past year, this pharmacy prepared minoxidil capsules, containing only minoxidil (88 %) or minoxidil in combination with other active ingredients (12 %) such as dutasteride, finasteride, methionine, or melatonin. Among the treatments containing minoxidil alone, the 2.5 mg and 5 mg doses were commonly prescribed, accounting for 13 % and 25 % of all prescriptions, respectively.

FABRX executed the Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) for M3DIMAKER 3D printer and M3DIMAKER Studio to guarantee that all the processes complied with the requirements of a GMP environment, although this is not a legal requirement in Spain for compounding pharmacies, which solely must comply with specific national legislation (Decreto, 2003). The pharmacy staff received training on using the pharmaceutical 3D printer and software. User manuals and SOPs for operating and cleaning the 3D printer and software were also provided.

Minoxidil capsules of 2.5 mg and 5 mg doses were prepared in the laboratory of Orive Mayor compounding pharmacy, meticulously following the established SOPs for PEG pharma-ink preparation and capsule elaboration. These SOPs provided a detailed, step-by-step outline of the entire process, ensuring consistency and adherence to quality standards. A three-month treatment was prepared for 9 patients, who received either 90 or 100 capsules of 2.5 mg or 5 mg of minoxidil, depending on their medical prescriptions. In total, 870 capsules of minoxidil were successfully prepared with the pharmaceutical 3D printer in one working day.

During the preparation of the capsules, quality controls were conducted on all the capsules for each treatment. All data, including protocols, users, pharma-ink and quality control analysis were stored in M3DIMAKER Studio software as batch records for consultation and auditing purposes.

The pharma-ink syringes were labelled with a QR code to maintain traceability (Fig. 8A). The QR code was scanned by a QR reader connected to M3DIMAKER Studio software. This security measure was

Table 4
Stability study data for conventional capsules and capsules filled with a 3D printer.

Condition	Month	Average drug content (%) (n = 3)					
		Conventional 2.5 mg capsules	Conventional 5 mg capsules	Techna 2.5 mg capsules	Techna 5 mg capsules	PEG 2.5 mg capsules	PEG 5 mg capsules
T = 25 ± 2°C	0	94.1 ± 0.1	96.8 ± 1.6	101.7 ± 1.5	102.3 ± 0.9	100.6 ± 0.7	94.2 ± 1.2
RH = 60 ± 5	0.5	98.7 ± 2.2	96.5 ± 1.7	101.7 ± 0.5	101.0 ± 1.7	101.0 ± 0.4	95.0 ± 2.0
%	1	101.9 ± 2.3	97.4 ± 0.6	99.2 ± 1.8	94.8 ± 5.7	100.2 ± 0.3	96.7 ± 1.8
	3	101.2 ± 2.5	92.6 ± 3.7	101.8 ± 4.2	92.9 ± 1.4	100.1 ± 1.2	98.3 ± 3.9

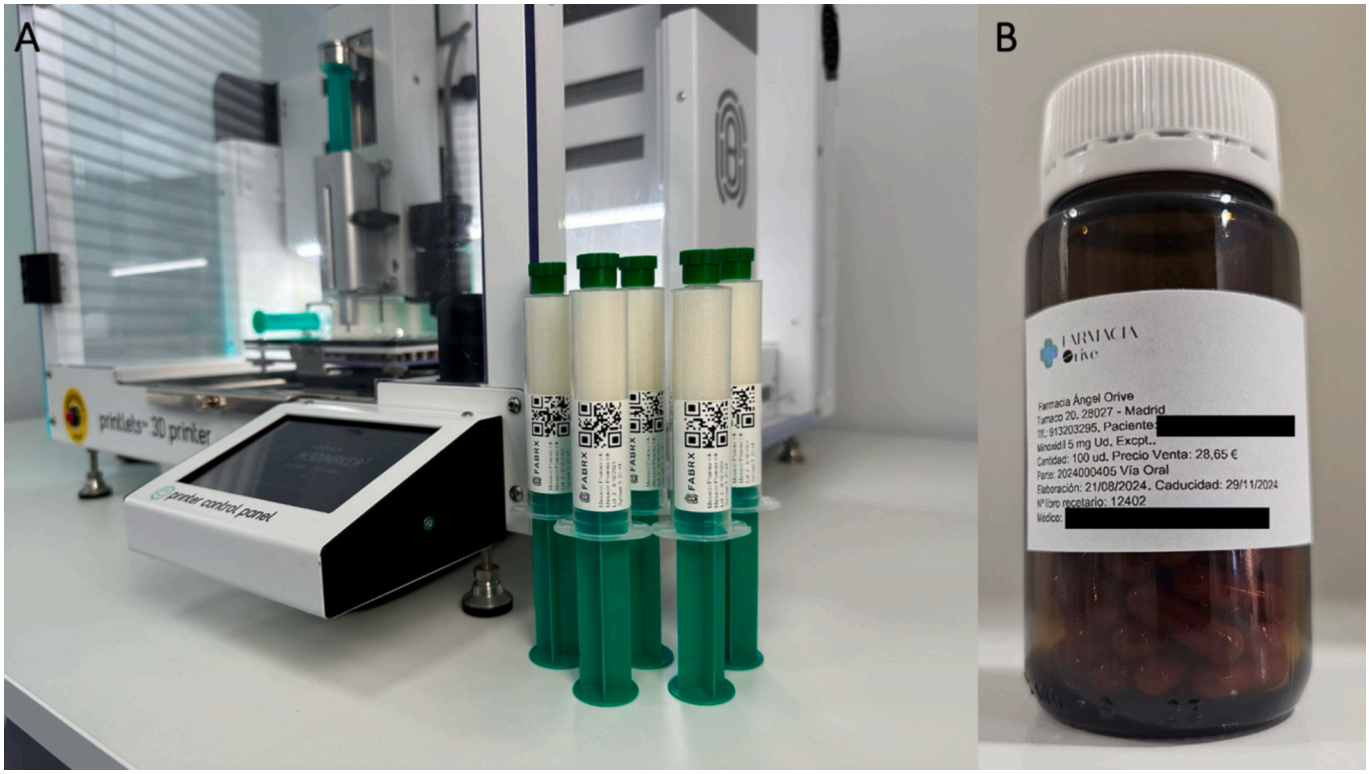

Fig. 8. (A) PEG pharma-inks labelled with a QR code for traceability. (B) Hermetically sealed topaz flask containing 100 capsules with a 5 mg dose of minoxidil prepared with the M3DIMAKER pharmaceutical 3D printer and ready to be dispensed. Patient and prescriber information not disclosed for confidentiality reasons.

implemented to record critical information regarding the preparation of the pharma-inks in the software and auto-load the printing protocol. The critical information included description of the pharma-ink (components with their respective quantities), the operator, the date and time of preparation, and the filled volume of the syringes. The treatments were dispensed at the pharmacy in a hermetically sealed topaz flask, labelled with information about the pharmacy, the treatment (type of treatment, dose, number of capsules, expiration date, selling price, etc.) and the prescriber (Fig. 8B). Along with the flask, patients were provided with a leaflet containing relevant information about the treatment.

3.2.3. *In-line quality control*

The preparation process was monitored using the in-line pressure quality control utility of the M3DIMAKER Studio software, which confirmed that the pressure of the printhead remained constant, and no obstructions or inconsistencies were detected.

During the printing process the content of each capsule was weighed using the integrated balance and the in-line uniformity of mass analysis function in the M3DIMAKER Studio software. The auto-tare function of the integrated balance was activated at the beginning of the printing process. After filling each capsule with the required amount of pharma-ink, the balance was re-tared before filling the next capsule. The software displayed both the measured capsule weight and the target weight for the desired dose (Fig. 9).

The target weights were 294 mg for a 5 mg dose and 147 mg for a 2.5 mg dose of minoxidil. The software can be set to either a target dose or weight and reports the percentage of deviation from the target for each capsule. The European Pharmacopeia specifies a maximum deviation limit of ± 10 % for capsules weighing less than 300 mg (EDQM Council of Europe, 2023a). Although this was the selected limit due to the characteristics of the dosage form (capsules weighing less than 300 mg), the software allows to set more restrictive limits if necessary and can be set depending on the requirements of the individual pharmacy or local regulation. Capsules meeting the ± 10 % deviation limits were marked in green, while those exceeding the 10 % deviation were marked in red, discarded and replaced with capsules that met the requirements (Fig. 9). Alongside the complementary data reported by the pressure sensor, capsules outside limits could be discarded. This mass control system enabled the automatic detection of capsules that met or failed the established standards, thus enhancing the safety of compounded medicines while reducing pharmacist workload.

3.2.4. *Cleaning Standard Operating Procedure (SOP)*

Following the capsule filling process, surface samples from the 3D printer were collected to verify its cleanliness and analysed using HPLC. According to the World Health Organizatioń s (WHO) Annex 3, which

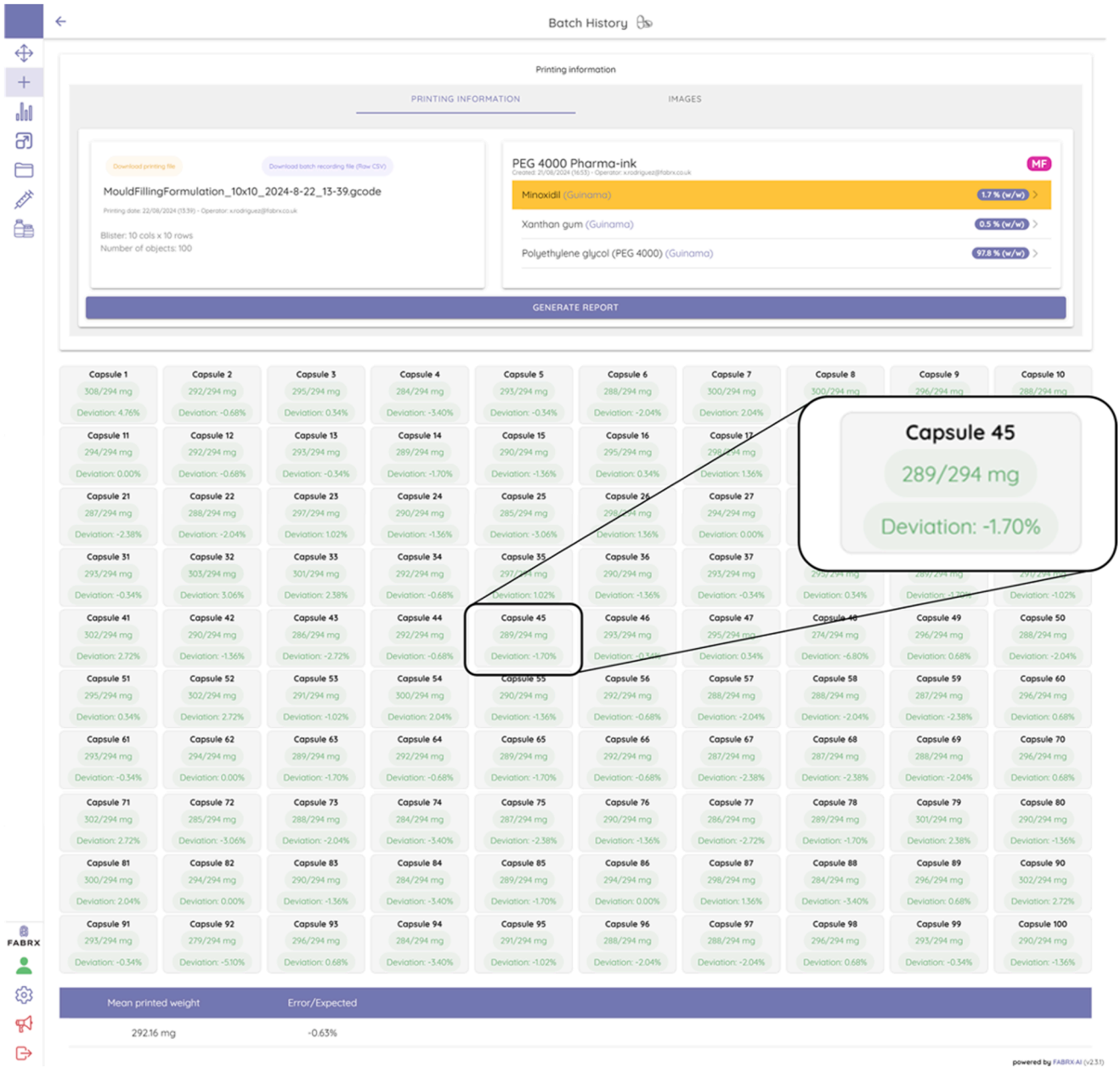

Fig. 9. In-line uniformity of mass test of PEG 5 mg capsules for a three-month treatment, recorded by M3DIMAKER Studio software. The reported and target weight as well as the deviation percentage are displayed for each capsule.

provides guidelines on cleaning validation, one of the most commonly used criteria for establishing acceptable limits is that residue should not exceed specific thresholds, often set at no more than 10 ppm (WHO, 2019). The results confirmed the absence of minoxidil in the post-cleaning samples (Fig. 10) in comparison with a minoxidil solution at 5 ppm, demonstrating that the cleaning SOP was highly effective in removing all traces of the drug. This shows that the pharmaceutical 3D printer can be thoroughly and easily cleaned between uses, preventing cross-contamination and maintaining compliance with GMP standards in a compounding pharmacy setting.

3.2.5. *Automation and cost effectiveness analysis*

The use of a 3D printer for capsule filling has demonstrated several advantages in terms of time, cost, operator exposure, quality control and patient safety over the conventional way of manufacturing using a manual capsule filler. In terms of time efficiency, the use of the M3DIMAKER pharmaceutical 3D printer for the preparation of minoxidil capsules demonstrated a reduction in preparation time and operator involvement (Fig. 11). Current compounding practices pose a high risk of causing repetitive strain injuries and work-related musculoskeletal disorders, even if reasonable ergonomic conditions are implemented and the staff involved have a low risk of back pain (Castilho Lopes et al., 2023). Furthermore, the increased use of powders in activities such as capsule filling is well known to increase pharmacists' exposure risk to drugs through higher air dust levels (Hannah Echt and Colleen ÓConnor, 2023). It is also well documented that compounded medicines sometimes fail to meet specifications and basic safety levels at a higher rate than regulatory-approved drugs, leading to increased insurance claims and exposing the pharmacist provider to liability (Gudeman et al., 2013). All these points can be improved through automation, reducing the workload of the pharmacist, for example with a pharmaceutical 3D printer.

The preparation of pharma-ink for each of the 9 patients took approximately 8 min. However, the 3D printing workflow also enables

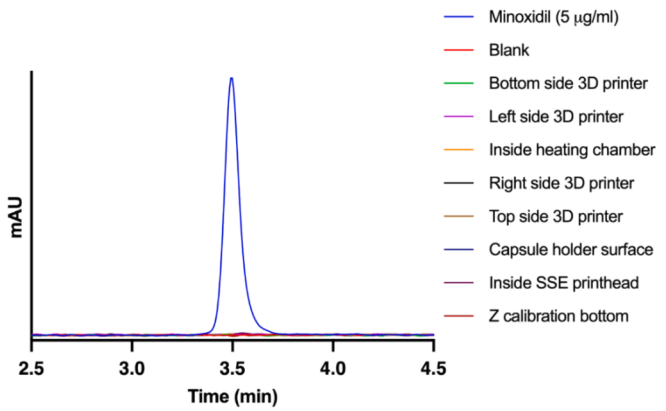

Fig. 10. HPLC chromatograms of the samples taken after cleaning the 3D printer following the cleaning SOP. A 5 µg/mL minoxidil solution (blue) and a blank sample of 70:30 v/v methanol:water (red) were used as references. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

batch production of pharma-ink for all treatments, regardless of the minoxidil dose. This could contribute to the overall efficiency of the process. For 2.5 mg and 5 mg minoxidil capsules, the filling time per capsule was 5 and 5.4 s, respectively, including the weighting time. The slight increase in time for the 5 mg capsules was due to the higher dose. Therefore, the total preparation time for 9 treatments (a total of 870 capsules), including pharma-ink mixing, syringe filling and using the M3DIMAKER 3D printer, was approximately 3 h (Fig. 11). Notably, only 50 % (1.5 h) of this time required active operator involvement.

In the conventional method, the preparation time for a single treatment was approximately 22 min. For 9 treatments, this time increased to 3.3 h. With this method, the operator is actively involved for the entire duration. The 3D-printer-driven approach also included an integrated, automatic quality control system, minimising the necessity for supplementary post-production quality verification of the capsules and increasing quality assurance and safety. The conventional method did not include a quality control system, and any additional time required for quality controls would extend beyond the 3.3-hour estimate, potentially delaying the availability of the treatments. Therefore, the 3D printing workflows reduced total treatment preparation time by approximately 10 % (20 min) and reduced manual labour by approximately 55 % (1 h and 50 min) while also incorporating fully automated quality control analyses to enhance safety.

The automation of the process reduced manual labour, allowing the operator to focus on other tasks and thereby decreasing workload, reducing exposure to the drug, and alleviating physical fatigue. This also minimises the risk of repetitive strain injuries and work-related musculoskeletal disorders. Importantly, the 3D printer takes over during one of the most critical stages for potential exposure and human error—filling capsules by handling fine powder mixtures, which poses a risk of creating particle clouds and inhalation (Hannah Echt and Colleen ÓConnor, 2023). In comparison, the 3D printing method utilises a semi-solid mixture and operates within a closed environment, effectively preventing exposure risks. The M3DIMAKER 1 is also small enough to fit inside a safety cabinet or fume hood if required for added safety. These advantages position this method as a significant improvement for producing hard capsules of potentially hazardous drugs with low therapeutic indices.

Regarding costs, in Spain, the selling price of minoxidil capsules is flexible and includes the cost of raw materials (active ingredients and excipients), packaging, a 4 % VAT and pharmacist fees. For this analysis, only the cost of raw materials was compared between conventional treatment and treatment prepared with a 3D printer, as VAT, pharmacist fees and packaging costs are the same for both treatments. In Spain, pharmacist fees are standardised professional fees, which are included in the cost of all compounded formulations (COFC, 2024).

The cost of the raw materials for the capsules filled with the 3D printer was comparable to that of the conventional treatment, depending on the material suppliers. Moreover, the use of a 3D printer offered several advantages that offset the increased expense associated with consumables, including a reduction of more than 50 % of the operatoŕs involvement time, from 22 min to 10 min. It also provided integrated quality control, process recording and enhanced personalisation capabilities with higher precision. Taking into account the 2024 remuneration table from the Pharmacy Offices Agreement (de Trabajo, 2022), the elaboration of minoxidil capsules is more economical using the proposed innovative method due to the reduced operatoŕs involvement time. The 3D printer produces 2.5 mg and 5 mg minoxidil capsules at a price per capsule that is 35 % and 20 % lower than the conventional method, respectively, while providing the numerous advantages outlined above, making it a cost-effective approach. In this short-term evaluation, the cost of the equipment (hardware and software), its validation and its maintenance over time were not evaluated. A more comprehensive economic study would require a long-term analysis involving a larger number of patients, a wider range of minoxidil doses, and additional drugs. The increased utilisation of the equipment is a key aspect for understanding the cost impact of implementing this innovative preparation method in the clinic, as highlighted in a recent study using a similar 3D printing equipment with a different extrusion technology (Ayyoubi et al., 2024).

The developed PEG pharma-ink has the potential for industrial-scale production, with the pharmaceutical industry supplying pre-filled syringes directly to compounding pharmacies under incoming point-of-care/distributed/modular manufacturing regulation (MHRA, 2023). Pharmacies would then simply scan and insert these syringes into the 3D printer and select the required dose based on a medical prescription, which could also be sent electronically. This approach may significantly reduce the risk of errors associated with manual preparation or material contamination, while also reducing operator exposure (Abbas et al., 2016; FDA, 2018), and reducing the costs of pharmaceutical compounding by integrating large-scale manufacturing. The end outcome would be a fully end-to-end automated process, promoting the production of safe, high-quality personalised medication in a cost-effective and efficient manner.

4. Conclusions

Minoxidil capsules (2.5 mg and 5 mg doses) were successfully prepared using a pharmaceutical 3D printer equipped with an advanced automatic quality control system and specialist software in a community compounding pharmacy setting and dispensed to patients without legal or regulatory obstacles. The integrated mass and pressure quality control systems in the printer allowed for real-time monitoring of the elaboration process, accomplishing significant improvements in capsule preparation by enhancing dose accuracy, consistency and overall production efficiency.

Although two different pharma-inks comprised either by Techna 20 SF^{TF}, a marketed base in US, or PEG 4000, were tested, PEG pharma-ink was chosen for implementation in the community pharmacy due to its pharmaceutical-grade materials approved in Spain from qualified suppliers, meeting regional standards. However, Techna pharma-ink showed potential as a suitable option for US compounding pharmacies. A content and mass uniformity test following European Pharmacopeia requirements and a three-month stability study further confirmed the reliability of minoxidil capsules prepared with the 3D printer, ensuring efficacy of the treatment. Moreover, an in-vitro dissolution test confirmed the immediate release profile of capsules regarding European Pharmacopeia standards.

In terms of cost-efficiency analysis versus conventional compounding workflows, the 3D printer demonstrated a significant reduction in active operator time by more than 50 % and overall time by

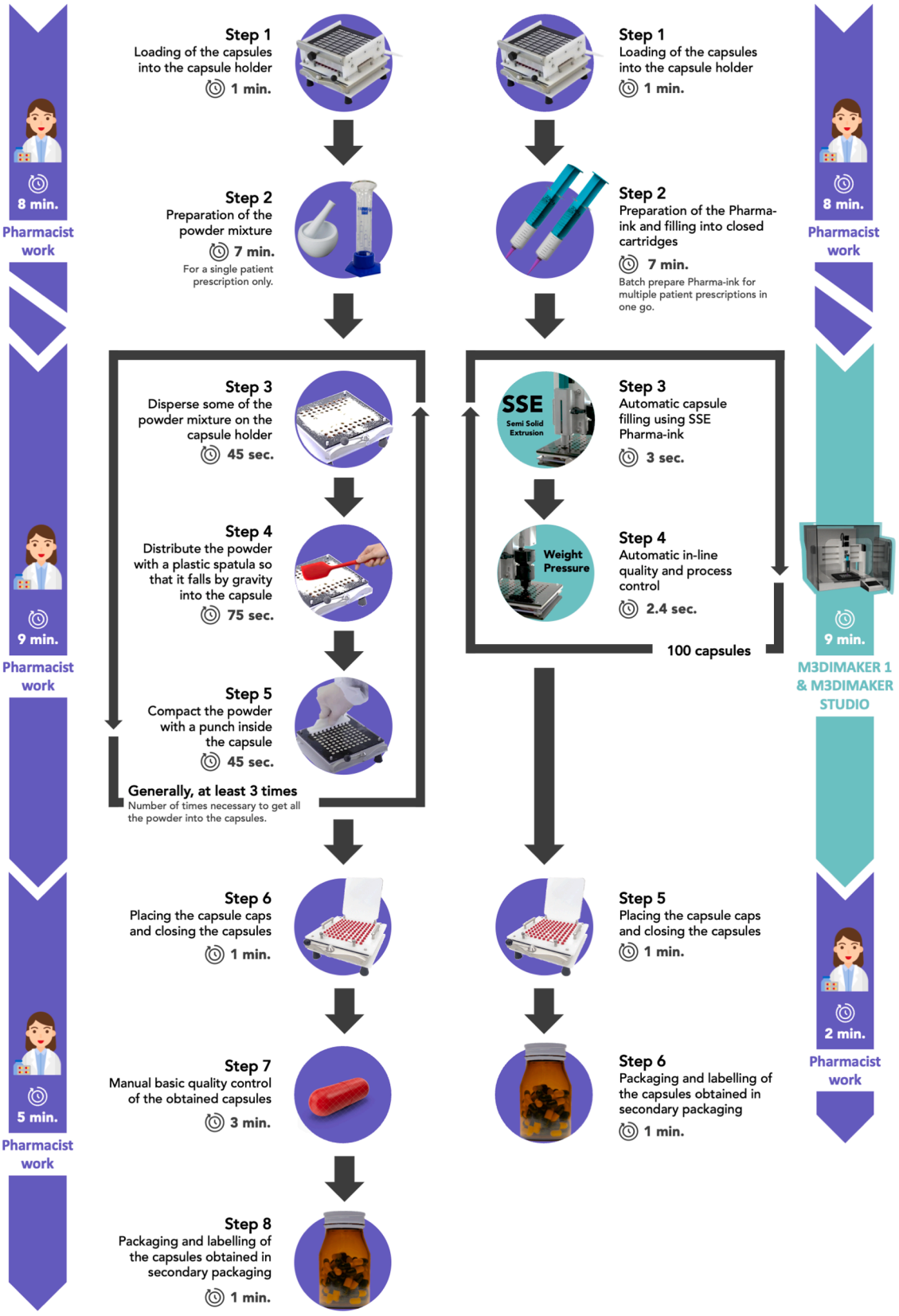

Fig. 11. Workflow for each of the proposed methods, time distribution in the production of 2.5 mg and 5 mg minoxidil capsules. Conventional manual filling, on the left, and 3D printer filling, on the right.

approximately 10 %, directly lowering production costs, making the treatment more affordable. Indirect costs could also be reduced in the longer term through human error and work-place injury rate reductions in relation to the increased automation.

Overall, this study highlighted the feasibility of integrating a pharmaceutical 3D printer in the workflows of a community compounding pharmacy for preparing minoxidil capsules, balancing cost with substantial improvements in safety and efficiency. This innovative approach paves the way for future applications of this technology for patient care and medication safety, particularly for critical treatments, such as chemotherapy or narrow therapeutic index medicines, where precision and accuracy are paramount, not only in compounding pharmacies but also in hospital pharmacy services worldwide.

CRediT authorship contribution statement

Xela Rodríguez-Maciñeiras: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carlos Bendicho-Lavilla:** Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Carlos Rial:** Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Khalid Garba-Mohammed:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Anna Worsley:** Writing – review & editing, Visualization, Validation. **Eduardo Díaz-Torres:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Celia Orive-Martínez:** Validation, Resources, Project administration, Conceptualization. **Ángel Orive-Mayor:** Validation, Resources, Project administration, Conceptualization. **Abdul W. Basit:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Carmen Alvarez-Lorenzo:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization. **Alvaro Goyanes:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alvaro Goyanes and Abdul W. Basit are cofounders of FABRX Ltd. Abdul W. Basit and Carmen Alvarez-Lorenzo are part of the editorial board in International Journal of Pharmaceutics.

All other 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2025.125251.

Data availability

Data will be made available on request.

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