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Fabrication Of Oral Low-Dose Minoxidil Printlets Using A Novel Single-Step Process

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***Abstract* — The application of the three dimensional printing (3DP) in the pharmaceutical industry can lead to a paradigm shift in this area, enabling the development of personalized medicines, as well as an increase in the medicines complexity. In pharmaceutics, the fused deposition modelling (FDM) is the most commonly used 3DP technology, in which the drug can be incorporated through hot melt extrusion (HME) or impregnation. Although HME is the best option it requires high-cost equipment, while impregnation presents problems such as: it is a time-consuming process, the drug should be highly thermostable and the drug waste. As such, the objective of this work was to explore the use of a novel direct method of impregnation of drugs using 3D printed tablets as scaffolds. For this, scaffold tablets in the disk geometry were printed by FDM and the print reproducibility was evaluated. Then, minoxidil printlets (1 mg) were produced through the application of an minoxidil ethanolic solution on top of the scaffold tablet. The printles were evaluated for their drug content, drug content uniformity, friability and dissolution. The scaffold tablets produced showed low printing variability for the parameters: width, height, depth and weight. The drug content and drug content uniformity of the printlets were 109.09% and 103.28% respectively. The minoxidil printlets showed rapid drug release, with 99.15% of the drug released in 5 minutes, this can be attributed to the way minoxidil was incorporated into the scaffold tablet. All the tested printlets were approved on friability (weight loss = 0.063%). Our results show a quick and cost-effective method to 3D drug printing.**

Keywords — 3D printing; FDM; Minoxidil.

I. INTRODUCTION

Three dimensional printing (3DP) was defined by the International Standard Organization as the fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology [1]. Its introduction and application have promoted innovations in several areas, such as aerospace industry, architecture, tissue engineer, biomedical research and pharmacy [2]. In the pharmaceutical industry 3DP can lead to a paradigm shift in the design, production and use of medicines [3].

Traditional drug manufacturing processes were introduced about 200 years and despite the advances, many of them are still used today. Even though these processes are profitable for the large batches production, they can be time-consuming, laborious, and dose inflexible. The introduction of 3DP can transform drug production, enabling a change from a "one size fits all approach" toward personalized medicines [4]. This is because the modification of digital designs is easier to perform than physical equipment. Thus, 3DP can produce several small, individualized batches economically feasible, allowing the personalization of doses and products [5]. Personalized medicines are especially relevant for pediatrics [6] and geriatric [7] populations, as well as for the drugs with a narrow therapeutic index [8]. Another advantage of three dimensional drug printing is the control over the spatial distribution of drugs and excipients in the dosage form, which allows an increase in the medicines complexity [9].

In pharmaceutics, the fused deposition modelling (FDM) is perhaps the most commonly used 3DP technology, owing to its versatility, simplicity and cost [10]. It was used, for example, in the production of: oral dosage forms [11] [12], orodispersible films [13], implants [14], vaginal rings [15] and microneedles [16]. This technology is based on extrusion of molten thermoplastic material, the filaments. They pass through a heated nozzle which melts the polymer and it is then deposited on a build plate, creating the layers of the object to be printed [10] [7].

In FDM the drug can be incorporated through two different processes, hot melt extrusion (HME) or impregnation. The first uses an extruder which provides heat and homogenization to produce a drug-loaded filament. Although this method is the best option to incorporate drugs, it requires high-cost equipment [17] [18]. Impregnation is based on the passive diffusion of a drug, present in a concentrated solution, to the filament. However, this process is expensive due to the use of highly-concentrated solutions, necessary to incorporate small amounts of drug. Furthermore, it is a time-consuming process and

the drug should be highly thermostable [19]. As such, the objective of this work was to explore the use of a novel direct method of impregnation of drugs using 3D printed tablets as scaffolds. For this, minoxidil was used as a model drug. Recently, the use of oral minoxidil in low doses has been studied for the treatment of alopecias [20] [21] [22].

II. Material And Methods

A. Material

Minoxidil sulphate (Fagron, Brazil) was used as a model drug. Polylactic Acid (PLA, Oderço Distribuidora, FlashForge, China) was used to produce the scaffold tablets. Organic solvents, buffering reagents and all other substances used were of analytical grade and obtained from Sigma Aldrich, Germany.

B. 3D printing of scaffold tablets

Scaffold tablets in the disk geometry were designed using the software 3D CAD SolidWorks® 2015 (Dassault Systèmes SolidWorks Corporation, France), then the design was exported as a stereolithography file (.stl) into the 3D printer software (Flashprint, FlashForge, China). A Dreamer NX (Oderço Distribuidora, FlashForge, China) printer was used to fabricate the tablets, with the following printing parameters: extrusion temperature (205 °C), platform temperature (50 °C), infill percentage (100%), extruding speed (50 mm/s).

C. Evaluation of print reproducibility

The print reproducibility was evaluated by measurements of the scaffold tablets dimensions and weight. The width, height and depth of 36 tablets were measured using a digital caliper (Mitutoyo Sul América Ltda, Suzano, SP, Brazil), and the tablets were individually weighed on analytical balance (Y220, Shimadzu, Japan), the results are expressed as mean, standard deviation (SD) and relative standard deviation (RSD).

D. Impregnation of the scaffold tablets with minoxidil (printlets)

Minoxidil printlets (1 mg) were produced through the application of an minoxidil ethanolic solution (10 mg mL-1) on top of the scaffold tablet, using an electronic micropipette (Thermo Fisher Scientific, USA). Then, the printlets were placed in an oven at 40 °C for the ethanol evaporation.

E. Ultraviolet–visible (UV–VIS) spectroscopy analysis

The amount of minoxidil into the samples was quantified using a UV-VIS spectrophotometer (Multiskan GO, Thermo Fisher Scientific, USA) at the wavelength of maximum absorption (λmax = 227 nm). For the dissolution studies, a calibration curve was plotted using five different minoxidil concentrations (0.707; 0.859; 1.010; 1.162; 1.313 µg mL-1). For the other tests, the quantification was performed by direct comparison with the standard at the same concentration.

F. Determination of minoxidil

The drug content and the drug content uniformity of the printlets were carried out. For the drug content determination, five printlets were placed together in absolute ethanol and sonicated for 30 minutes. Then, the sample was diluted (final concentration = 1 µg mL^{-1}) and quantified. The evaluation of the drug content uniformity was similar, however, 10 printlets were individually evaluated.

G. Dissolution study

Printlets (n=3) were immersed in phosphate buffer pH 7.2 (10 mL) and kept under stirring (300 rpm). Samples (0.1 mL) were withdrawn at 5, 10, 15, 20, 25 and 30 minutes, diluted in the same buffer (10 mL) and then analyzed by UV–VIS spectroscopy.

H. Friability

Ten (n=10) printlets were weighed, and placed carefully in an Ethik 300 (Ethik Technology, São Paulo, Brazil) friability apparatus. The tester rotated with 25 rpm for 4 min. Afterwards the tablets were dedusted and weighed again. The relative weight loss was calculated.

III. Results And Discussion

In this work, we applied 100 µL of an minoxidil ethanolic solution (10 mg mL^{-1}) in each tablet, producing minoxidil printlets (1 mg). The design used is shown in Fig. 1, as well as the 3D printed scaffold tablet.

PLA is the front-runner in the biodegradable plastics market, with the best availability and the most attractive cost versus mechanical properties ratio [23] [24]. The use of neat PLA in FDM 3D printing increases every year. It does not emit any unpleasant smell during the printing process and allows us to obtain components with reasonable tolerance [25]. PLA was chosen as raw material for the tablet manufacture due to some characteristics: a) it is a pharmaceutical grade polymer which can be made into filaments; b) it is the most used bioplastic for 3D printing by FDM and has been approved by the Food and Drug Administration and European Medicines Agency; c) this polymer is biocompatible, biodegradable and has high mechanical strength [26] [27]. An important feature is its ability of not producing toxicity or carcinogenic effects on the human body and not be metabolized into toxic products [28].

The results for the evaluation of print reproducibility can be seen in Table 1. For all the parameters the print variability was low (RSD < 5), indicating good print reproducibility. However, among the parameters, the depth showed the greatest variability, which may be due to its smaller dimension than others. The data of the dimension parameters are complied with the values defined in the CAD file.

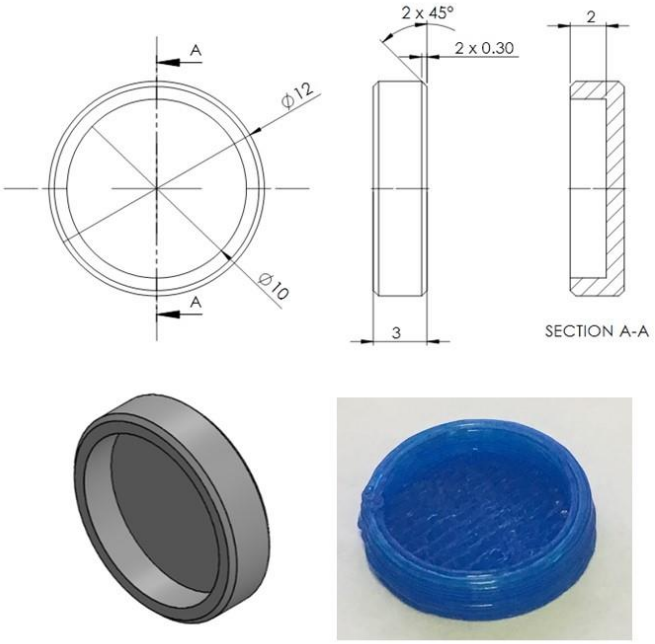

Fig. 1. *3D design (with the dimensions in cm) and photographic image of the scaffold tablet.*

The result of drug content was 109.09% and drug content uniformity was 103.28% (SD = 4.98; RSD = 4.85). Minoxidil is the most used drug in the topical treatment for female pattern hair loss [29] [30]. This pathology is the main cause of hair loss in clinical practice and has social and psychological impacts on people's quality of life [31]. However, if topical minoxidil therapy is discontinued, clinical regression may be observed for the balding stage before treatment. Thus, its continued use is necessary, which can cause rejection of patients [32]. Recently, the use of oral minoxidil in low doses has been studied for the treatment of alopecias [20] [21] [22]. 3D printing of low dose minoxidil printlets, performed in this work, allows dose customization according to the need of each patient, which could increase adherence to therapy and minimize potential adverse effects.

Dissolution data from the minoxidil printlets show that all the drug (mean= 99.15 %, SD= 7.47) was released within the first five minutes (Fig. 2). This rapid drug release can be attributed to the way minoxidil was incorporated into the scaffold tablet. Ethanol was used to solubilize the drug during impregnation. However, PLA is not soluble in ethanol [33]. Thus, after applying the ethanolic solution of minoxidil on the tablet surface,

TABLE I. SUMMARY OF WEIGHT AND THE DIMENSIONS OF THE 3D PRINTED SCAFFOLDS (N=36).

Parameter	Width (cm)	Height (cm)	Depth (cm)	Weight (mg)
Mean	12.13	2.73	1.58	203.27
SD	0.14	0.04	0.05	1.09
RSD	1.19	1.60	3.44	0.54

SD: standard deviation; RSD: relative standard deviation.

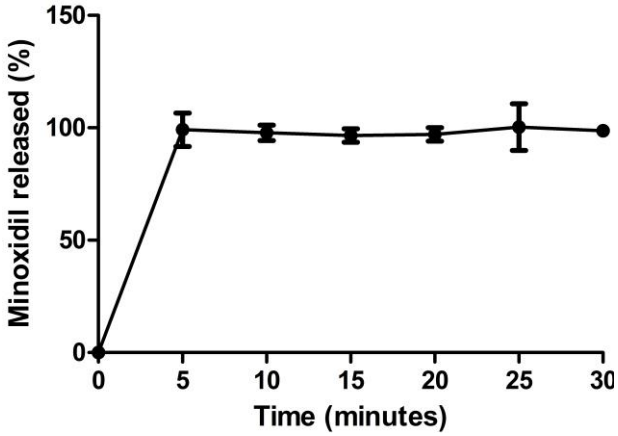

Fig. 2. *In vitro release of minoxidil from the minoxidil printlets (n=3).*

the solvent was not able to penetrate into its structure (due to solubility) and evaporated. Thus, the drug remained only on the surface of the tablet, causing the rapid drug release. Most conventional (immediate release) oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. Immediate-release products generally result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects [34].

According to the dissolution test, the minoxidil remained on the surface of the tablet. As a consequence, a problem that could occur is the loss of drug during handling/packaging. To evaluate this, the friability test was performed. To friability, which demonstrate the printlet mechanic resistance wear, are considered acceptable printlets with loss equal or lower than 1% of its weight according to USP Pharmacopeia [35]. All the tested printlets were approved on friability (weight loss = 0.063%).

The method developed in this work of manufacturing scaffold tablets has some advantages over the traditional impregnation. Firstly, the time required to carry out the process; the filament is usually left for 24 to 48 hours in a concentrated solution of the drug for the impregnation, while in our method the drug solution is rapidly applied/ evaporated. Secondly, the amount of drug wasted; in the impregnation large quantities of drugs are necessary to incorporate small amounts of it, while in our work the exact amount of the drug is applied to the scaffold tablet, without waste. Thirdly, the possibility of drug degradation due to high temperature; with the use of scaffold tablets, the drug is not subjected to high extrusion temperatures, as occurs in the filament impregnation. Then, the developed method is a quick and cost-effective alternative to 3D drug printing.

The approach presented involving FDM 3D printing offers several advantages for developing personalised dose on demand; these include: a) use of low cost printer and widely available, b) suitability of different drug molecules, and c) significant improvement on mechanical resistance (friability).

IV. Conclusion

In this work, we produced oral low-dose minoxidil printlets using a novel single-step process. This method allows customization of treatment for alopecia, which can decrease the chances of side effects and may increase adherence to therapy. In addition, the use of scaffold tablets enables the production of thermolabile medicines through FDM.

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Conflicts Of Interest

The authors declare that they have no conflicts of interest to disclose.

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