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3D printing of scaffolds with fluoxetine hydrochloride for personalized depression therapy

Marcos dos Reis Casarim
Nupics, Faculdade de Farmácia
Universidade Federal de Juiz de Fora
Juiz de Fora, Brazil
marcosreiscasarim22@gmail.com

Nádia Rezende Barbosa Raposo
Nupics, Faculdade de Farmácia
Universidade Federal de Juiz de Fora
Juiz de Fora, Brazil

Francisco José Raposo
Nupics, Faculdade de Farmácia
Universidade Federal de Juiz de Fora
Juiz de Fora, Brazil

Urias Pardócimo Vaz
Nupics, Faculdade de Farmácia
Universidade Federal de Juiz de Fora
Juiz de Fora, Brazil

Marcos Antônio Fernandes Brandão
Nupics, Faculdade de Farmácia
Universidade Federal de Juiz de Fora
Juiz de Fora, Brazil

***Abstract* — Depression is a mental disorder affecting millions of people worldwide, with an impact on function, particularly in the elderly, a group in which physiological and clinical factors can alter the response to conventional treatment. Given the wide inter-individual variability of antidepressants observed in pharmacokinetics and pharmacodynamics, it has become clear there is a need for approaches that allow for personalization of therapy, taking into account the clinical, genetic and social peculiarities of each patient. Individualized treatment for depression has emerged as a proposal for treating each patient in a unique way, and is a fundamental strategy for optimizing the effectiveness and safety of treatment. However, the traditional industrial processes still impose limitations on the production of pharmaceutical forms with individualized dosage. In this context, 3D printing has surfaced as a promising emerging technology to fill this void, permitting the development of tailored medication in a precise and reproducible way. The aim of this study was to develop and evaluate scaffolds containing fluoxetine hydrochloride produced through 3D printing via fused deposition modelling (FDM), aimed at personalizing doses for elderly patients. The polymers polylactic acid (PLA) and polyvinyl acid (PVA) were used as the base materials for the scaffolds, which were subsequently impregnated with the ethanol solution of the drug. The evaluation of the scaffolds included the following tests: printing reproducibility, friability, content, uniformity of content, and dissolution profile, based on Brazilian Pharmacopoeia (FB7). The results showed that the PVA scaffolds performed adequately regarding the physicochemical tests conducted, but the dissolution profile was found to be inadequate for the pharmacopoeia determination of fluoxetine hydrochloride tablets (74.38 ± 3.85% in 45 minutes), while the scaffolds prepared with PLA were discontinued due to problems in the impregnation stage. The study points to 3D printing being a promising tool for the personalized production of solid medication, with potential for application in complex clinical scenarios such as geriatric care.**

Keywords* — *Three-dimensional printing; fluoxetine; drug delivery systems; personalized treatment.

I. INTRODUCTION

Depression is a recurring, chronic mental disorder characterized by depressive moods, anhedonia and fatigue, which may evolve into severe conditions with cognitive, autonomic and functional impairment [1]. International estimates point to a significant prevalence of the disease, with a marked increase following the COVID-19 pandemic. In Brazil, the depressive disorder affects around 5% of the population, rising to 15% among the elderly, a group which is particularly vulnerable due to higher comorbidity loads and concomitant use of multiple medication [2].

Among the drugs used in the treatment, fluoxetine (Prozac) has remained one of the most commonly prescribed selective serotonin reuptake inhibitors since its clinical introduction in 1988 [3] [4]. Mainly available in solid form, the drug has a prolonged half-life and a metabolism dependent on the CYP450 enzymatic system, which may be compromised by physiological changes due to ageing, hepatic diseases or genetic variability [5] [6]. These conditions reinforce the importance of individualized adjustments

to the dosage in order to ensure the effectiveness and safety of treatment [7] [8].

However, traditional industrial processes make it difficult to produce multiple dosages and formats, often resulting in fractioning of tablets, a practice that compromises dosage precision, physicochemical stability and the predictability of the clinical effects [7] [9]. This scenario is particularly critical in elderly patients, subject to polypharmacy, drug interactions and a higher risk of adverse events [10].

In this context, additive manufacturing has emerged as a promising technological alternative. 3D printing permits the fabrication of personalized pharmaceutical forms, by adjusting volume, geometry, dosage and delivery profile depending on individual needs [11]. In the pharmaceutical area, this technology has already been applied in the production of *printlets*®, gastro-retentive systems, implants and other controlled delivery devices, the highlight being their potential to modulate pharmacokinetics and enable production on demand [12] [13] [14] [15] [16] [17].

Given these prospects, the present study proposed the use of 3D printing through fused deposition modelling (FDM) in order to manufacture scaffolds designed to be impregnated with fluoxetine hydrochloride. The approach seeks to provide a personalized alternative for elderly patients, by evaluating techno-pharmaceutical viability and the physicochemical characteristics of printed tablets, focusing on dosage precision and the potential for individualized treatment.

II. Material and Methods

A. 3D printing of scaffolds

The scaffolds were designed using 3D CAD software (SolidWorks® 2015), using the model described by Junqueira as a reference [16]. The adopted design consisted of a disk 12 mm in diameter and 4 mm high, containing a central concavity with a diameter of 10 mm and depth of 2 mm, designed to house the drug.

After modelling, the file was exported to a stereolithographic format (.stl) for the printer software, where the slicing took place. The fabrication of the scaffolds was carried out on a Bambu Lab A1 printer equipped with a 0.4 mm extruder nozzle using PLA and PVA filaments, both of which were 1.75 mm in diameter.

The PVA was subjected to an extrusion temperature of 220 °C, platform at 60 °C and filling of 100%. The first layer was printed at 50 mm/s, with a subsequent filling at 105 mm/s; the outer and inner walls were printed at 200 mm/s and 300 mm/s, respectively. The PLA, meanwhile, underwent an extrusion temperature of 220 °C, platform at 65 °C and filling of 20%. The first layer was also printed at 50 mm/s, followed by filling at 105 mm/s, while the outer and inner walls were printed at 50 mm/s.

B. Evaluation of 3D printing reproducibility

The reproducibility of 3D prints was evaluated via a dimensional analysis of the scaffolds (n = 10 per type of polymer) — height, width and depth — using a digital pachymeter, as well as the measurement of individual weights on analytical scales. The results were expressed as mean, standard deviation (SD) and relative standard deviation (RSD).

C. Impregnation of the ethanol solution of fluoxetine hydrochloride

To produce the scaffolds containing fluoxetine hydrochloride, 150 µL of ethanol solution of fluoxetine hydrochloride (100 mg/mL) were administered by pipette into the concavity of the PLA and PVA scaffolds, totalling 15 mg of drug per unit. The scaffolds were then placed in an oven at 40 °C until the solvent had fully evaporated, giving rise to the end product, the tablet.

D. Friability

The friability test was conducted in accordance with the FB7 [18]. Scaffolds impregnated with fluoxetine hydrochloride (n = 10) were initially weighed and subjected to a friability tester, programmed at 25 rpm for 4 minutes. The tablets were then reweighed. Friability was calculated from the percentage variance between the initial and end weights, as per Equation 1, where F represents the friability, W_i the initial weight of the tablets and W_f the weight of the tablets post-test.

$$F = \left(\frac{W_i - W_i}{W_f}\right) \times 100 \quad (1)$$

E. Analytical curve

Initially, 37.5 mg of fluoxetine hydrochloride were dissolved in hydrochloric acid (HCl) 0.1 M in a 50 mL volumetric flask and sonicated for 30 minutes, obtaining the stock solution at 0.075% (w/v). From this, a variety of dilutions (7.5; 11.25; 15; 18.75 and 22.5 µg/mL) were prepared to construct the analytical curve. The samples were analysed spectrophotometrically using a fixed wavelength of 225 nm and using HCl 0.1 M as a blank. Knowing the absorbance values and concentrations, the analytical curve was obtained via linear regression, the resulting equation being employed for all the remaining calculations.

F. Fluoxetina Hydrochloride content

To determine the content of the fluoxetine, tablets (n = 10) were dissolved in HCl 0.1 M (500 mL), sonicated and filtered. A 1 mL aliquot was diluted to 15 µg/mL and analysed spectrophotometrically, employing a fixed wavelength of 225 nm. The blank was prepared from a scaffold without the drug, subjected to the same dilutions [18]. The quantification was carried out using the analytical curve equation.

G. Uniformity of content

The uniformity of content was evaluated individually for 10 tablets. Each unit was sonicated for 30 minutes in HCl 0.1 M, filtered, and topped up to 100 mL; 5 mL of this solution were then diluted to 50 mL, arriving at a final concentration of 15 µg/mL. The samples were analysed in UV-VIS, using as a blank a scaffold without any drugs, subjected to identical dilutions. The individual concentrations were calculated from the analytical curve equation and, from these values the acceptance value (AV) was computed, as per Equation 2, where *AV* is the acceptance value, *M* is a reference value which depends on the value of $\bar{x}$, $\bar{x}$ is the mean of the individual contents, *k* is the constant of acceptability, and *s* is the standard deviation of the sample [18].

$$AV = |M - \bar{x}| \times ks \quad (2)$$

H. Dissolution profile

The dissolution profile of the impregnated tablets was carried out in accordance with the FB7 [18] for fluoxetine hydrochloride. Three tablets (n = 3) were evaluated individually in a dissolution tester, using paddles, with 900 mL of HCl 0.1 M/cup, stirred at 50 rpm for 63 minutes. Aliquots were collected at 9, 18, 27, 36, 45, 54 and 63 minutes. Simultaneously, scaffolds without drugs (n = 3) were analysed as an analytical blank, under the same experimental conditions. The collected aliquots were filtered and analysed in UV-VIS, using HCl 0.1 M as the reference solution, enabling the computation of the concentration of drug released over time.

III. Results

The scaffolds were printed by FDM using PLA and PVA, in a standard format 12 mm in diameter, 4 mm in height, and a central concavity 10 × 2 mm. The dimensions adopted follow the recommendations of the Food and Drugs Administration (FDA) in the USA, that tablets and capsules should not exceed 22 mm, and that they should comply with the patients' preferences for heights between 2 and 6 mm, as observed by Kabeya, ensuring ease of handling and swallowing [19] [20]. The PLA was chosen on account of its performance during printing, the absence of odour, good cost/benefit ratio and superior mechanical properties. It is a bioplastic that has been widely studied, biodegradable, biocompatible, insoluble in water, and approved by the FDA and the European Medicines Agency (EMA). It is not metabolized in toxic subproducts and does not possess carcinogenic side effects, underlining its safety for biomedical applications. As for PVA, this is a biocompatible polymer, intumescent, soluble in water and mildly soluble in ethanol, also approved by the FDA. Extensively used in FDM, it dissolves quickly in hydrochloric acid, making it adequate for forms of immediate release, though it also allows for controlled delivery when associated with certain printing models [16] [20].

It was also possible to impregnate the scaffolds with an ethanol solution of fluoxetine hydrochloride, obtaining a personalized dosage of 15 mg, representing a viable alternative in solid pharmaceutical form for the treatment of depression. The impregnation technique, based on the solubility of the drug, controlled application of the solution and evaporation of the solvent, enables the active ingredient to be easily, accurately and reproducibly incorporated. The choice of solvent is crucial, requiring good solubility of the drug, adequate volatility and low toxicity. This approach can be easily integrated into complementary technologies such as inkjet printers, thereby increasing the precision of the dosage and scalability of the process [16]. In this way, production can be adapted for both local pharmacies and specialized services, including hospital environments, strengthening the potential for personalized treatment and decentralized manufacture.

Analysis of the reproducibility of the scaffold printing is an important factor in the standardization and reproducibility of the stipulated measures. As displayed in Figure 1, each printed scaffold must strictly follow the dimensional model defined in the design, and its weight depends directly on the volume of polymer extruded and the density of the material. Table 1 exhibits the parameters analysed in the PLA and PVA scaffolds. Collegiate Directorate Resolution RDC 166/2017 does not define numeric limits for the Relative Percent Difference (RPD), therefore, the RPD < 5% criterion was adopted in accordance with the technical reference of ANVISA's earlier special resolution RE 899/2003, in which this value is considered indicative of good precision [22] [23]. All the parameters evaluated had an RPD below this limit for both polymers, demonstrating high reproducibility of the 3D printing process. The largest variance occurred in the dimension of depth — 1.47% for the PLA and 3.25% for the PVA — possibly due to it being the smallest dimension of the model, rendering it more susceptible to operating variations. Nonetheless, the mean values remained very close to the values projected in the CAD, with low dispersion, reinforcing the dimensional consistency of the scaffolds produced.

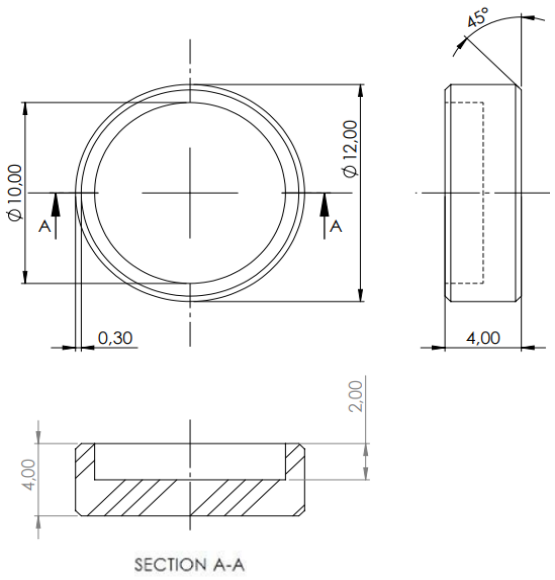

Fig. 1. *3D design of the scaffold tablet with the dimensions in mm.*

TABLE I. DIMENSIONAL EVALUATION OF THE POLYMERIC SCAFFOLDS.

Scaffold	Width (mm)	Height (mm)	Depth (mm)	Weight (mm)
1	11,93	4,16	2,00	351,00
2	11,89	4,14	1,98	350,50
3	12,05	4,14	1,97	351,00
4	11,93	4,13	2,02	351,50
5	11,98	4,18	2,05	351,70
6	11,99	4,16	1,98	354,10
7	12,01	4,17	1,96	352,20
8	11,94	4,13	1,97	352,10
9	12,01	4,13	1,97	351,80
10	11,92	4,14	2,02	352,40
Mean	11,96	4,15	1,99	351,83
SD	0,05	0,02	0,03	1,00
RSD	0,42	0,44	1,47	0,28

The results of the mass before and after impregnation (Table 2) show that the PLA tablets exhibited an average increase of 15.65 mg, a value close to that expected for a dose of 15 mg, consistent with the complete evaporation of the solvent due to the water-insoluble nature of the polymer. For the PVA, the increment of 25.96 mg was significantly higher, probably a result of the partial retention of solvent and the hygroscopicity of the material, which can absorb humidity from the environment. Although the average masses before and after impregnation may have exhibited a low variation (reduced RPD), the difference in mass between the units resulted in an elevated RPD for both polymers (9.10% for PLA and 13.34% for PVA). However, this metric is not adequate for estimating the drug content, the appropriate method for evaluating the variance in dosage between the tablets being the uniformity of content.

As for the visual aspect following impregnation, the PVA, being water-insoluble, permitted a better absorption of the solution, resulting in little or no visible crystallization on the surface. In contrast, for the PLA, impregnation was inadequate: the drug was concentrated mainly on the upper edge of the scaffold, with minimal internal penetration, as illustrated in Figure 2. Given the external, superficial deposition, which could lead to the loss of dosage through attrition, a risk of contamination during manipulation and its inadequate appearance, the study of the tablets produced using PLA was discontinued.

Fig. 2. *PLA and PVA tablets impregnated with fluoxetine hydrochloride (a) and detail of the PLA tablet (b) showing the deposition of the drug on the outer edge.*

The mechanical resistance of the tablets was evaluated via the friability test, which simulated the attrition and impact suffered during the entire trajectory of the production chain through to administration. Tablets with high friability cannot endure this kind of stress and suffer progressive abrasion of the matrix, which could compromise the contents of the drug. According to the FB7, the loss of mass should not exceed 1.0%. The PVA tablets met fully with this criterion, resulting in a friability of 0.36%, deemed to be an acceptable value.

The quantification of fluoxetine hydrochloride was carried out via UV-VIS spectrophotometry. The drug exhibited a maximum absorption of 225 nm, the wavelength selected for the analyses. The constructed analytical curve showed adequate linearity ($R^2 > 0.99$), resulting in the regression equation $y = 0.0298x + 0.0592$, employed in the calculation of concentrations in the other assays. As the drug content is fundamental for ensuring effectiveness of treatment, and avoiding toxic effects, the content test — mandatory according to the FB7 — was conducted using this method [24]. Complete solubilization was possible with just 10 tablets, and the resulting solution was analysed by UV-VIS. Absorption of the PVA was observed in the same wavelength, it being necessary to use a blank

containing the polymer in the same concentration as the sample. The content obtained was 96.26 ± 0.07%, a value within the range required by the FB7 for fluoxetine (90%–110%), indicating conformity and adequate incorporation of the drug into the tablets.

The results of uniformity of content indicated an average content of 103.31 ± 4.41%, with an RPD of 4.27%, an adequate value and representative of good consistency between the units evaluated. All the tablets came within the range of 85% to 115% established by the United States Pharmacopeia Convention (USP), evidencing the efficiency of the impregnation process in the uniform incorporation of the drug [25]. Following the recommendations of the FB7, the data obtained were used for the calculation of the AV. Considering an average content of 103.31%, the value M was adjusted to 101.5%, with k = 2.4, given that n = 10 and s = 4.41, resulting in an AV of 12.38. In the absence of specification in the monograph, the criterion requires an AV < 15. Thus, the tablets were approved per the uniformity of content test, demonstrating low variation between the samples analysed.

TABLE II. WEIGHT OF THE SCAFFOLD BEFORE AND AFTER IMREGNTION.

Scaffold	PLA			PVA		
	Before (mg)	***After (mg)***	***Difference (mg)***	***Before (mg)***	***After (mg)***	***Difference (mg)***
1	351,00	367,90	16,90	334,50	356,30	21,80
2	350,50	365,80	15,30	335,20	361,30	26,10
3	351,00	367,70	16,70	332,20	359,10	26,90
4	351,50	369,20	17,70	335,30	359,50	24,20
5	351,70	367,20	15,50	332,20	361,70	29,50
6	354,10	367,30	13,20	329,40	357,20	27,80
7	352,20	365,60	13,40	333,80	359,10	25,30
8	352,10	366,90	14,80	337,50	356,30	18,80
9	351,80	368,40	16,60	331,60	359,70	28,10
10	352,40	368,80	16,40	331,20	362,30	31,10
Mean	351,83	367,48	15,65	333,29	359,25	25,96
SD	0,95	1,12	1,42	2,28	2,04	3,46
RSD	0,27	0,31	9,10	0,68	0,57	13,34

The dissolution test, widely used in the development and control of formulation quality, evaluates the fraction of the drug released over a period of time and presents a good correlation in vitro/in vivo, which is particularly essential in the development of generic drugs [26]. Dissolution, a critical element of the pharmaceutical phase, has a direct influence on gastrointestinal absorption and, consequently, the pharmacological effect [3]. In the present study, the dissolution profile indicated a rapid delivery in the first 18 minutes, plateauing between 18 and 36 minutes, and a further increase until it reaches 85.38 ± 3.85%, at 63 minutes, as shown in Figure 3. This behaviour suggests there are two delivery phases: initial, related to the drug adhering to the surface following impregnation, and another, later on, corresponding to the release of the drug into the polymer as the structure dissolves.

The FB7 requires that fluoxetine hydrochloride tablets undergo ≥ 75% dissolution within 45 minutes. However, the tablets analysed exhibited a mean percentage of 74.38 ± 11.17%, a value influenced by the inferior performance of Cup 6, as reported in Table 3. Slower dissolution is consistent with partial incorporation of the drug in the polymer matrix, particularly considering that PVA is a slow-release polymer. The profile presented an RPD of 15.02% at 45 minutes, above the limit stipulated by resolution RDC 31/2010, which requires < 20% at the first points and < 10% for the others. Divergences were observed at 9, 27, 36 and 45 minutes, possibly resulting from the variation in the fraction of the drug trapped in the polymer and the tablets' adherence to the base of the

cup, a phenomenon which reduces surface contact with the medium and compromises the delivery of the drug, as shown in Figure 4.

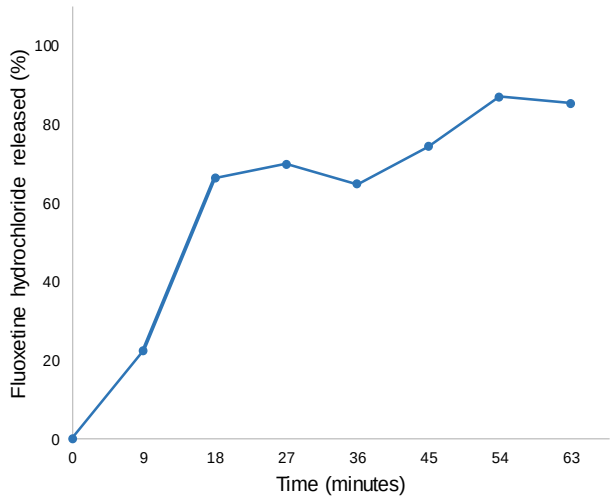

Fig. 3. *Dissolution profile of the fluoxetine hydrochloride tablet.*

TABLE III. FLUOXETINE CONTENT AS A FUNCION OF TIME, IN THE DISSOLUTION PROFILE TEST.

		Time (minutes)						
		9	***18***	***27***	***36***	***45***	***54***	***63***
Content (%)	Cup 2	30,03	62,66	63,46	71,35	83,74	89,34	88,34
	Cup 4	5,43	71,95	78,66	68,19	77,40	90,64	81,03
	Cup 6	31,93	64,90	67,54	54,78	62,01	81,40	86,79
	Mean	22,46	66,50	69,89	64,77	74,38	87,13	85,38
	SD	14,78	4,84	7,87	8,80	11,17	5,00	3,85
	RSD	65,80	7,28	11,26	13,58	15,02	5,74	4,51

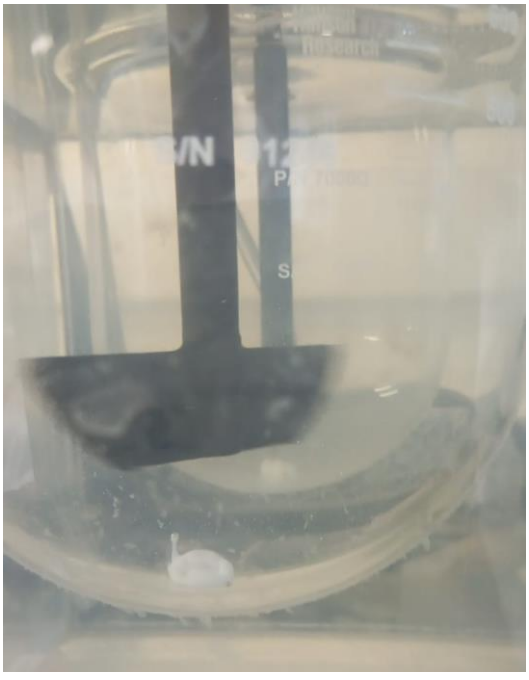

Fig. 4. *Tablet with fluoxetine hydrochloride adhering to the base of the cup.*

The unimpregnated scaffolds demonstrated a wide variability of absorbance over time, ranging from 116.27% to 82.75% around the mean, evidence of a non-linear, heterogeneous behaviour between the cups, as illustrated in Figure 5. This irregularity indicates that the dissolution of the polymer takes place in an unstable fashion, regardless of any adherence to the base of the cup.

This variation in the blank compromises the adequate interpretation of the drug's dissolution profile as it interferes directly in the spectrophotometric readings. As the tablets share the same polymer in their matrix, this irregular delivery also contributed to the variability observed in the dissolution of the drug, thereby limiting the precision of the method employed.

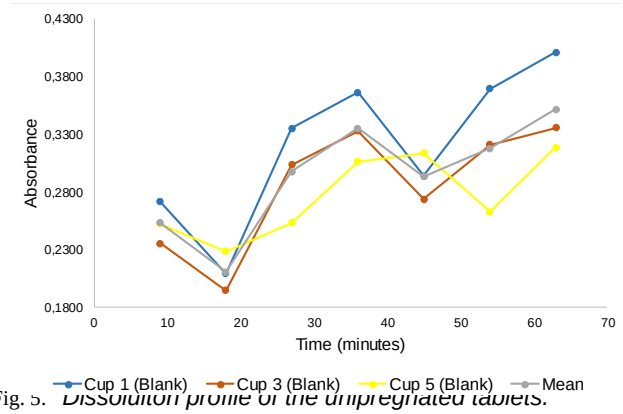

Fig. 5. *Dissolution profile of the unimpregnated tablets.*

IV. Conclusion

The results reinforce the applicability of 3D printing via FDM as an emerging platform for personalized pharmacotherapy. Scaffolds were produced through this technique which were impregnated with 15 mg of fluoxetine hydrochloride. The tablets obtained complied with pharmacopoeia quality control parameters, confirming the robustness and reproducibility of the process and highlighting its potential for individualized treatment in the management of depression. However, a lack of compatibility was observed between the PLA and the ethanol solution used in the impregnation stage, indicating that the PVA exhibited superior performance and greater compatibility to this end.

For subsequent studies, it is recommended that alternative methods be adopted for the dissolution assays, including the use of different apparatus — like the apparatus II modified with a paddle anchor, and quantification using chromatographic methods in order to obtain more robust profiles, less prone to polymer interference.

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For papers published in translation journals, please give the English citation first, followed by the original foreign-language citation [6].

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