https://doi.org/10.31925/farmacia.2023.3.5 **ORIGINAL ARTICLE**

3D PRINTING OF PROLONGED-RELEASE ORAL SOLID DOSAGE FORMS CONTAINING FELODIPINE

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Manuscript received: February 2023

Abstract

Coupling hot melt extrusion (HME) with 3D printing (3DP) through fused deposition modelling (FDM) allows today the manufacturing of oral solid dosage forms with desired characteristics, suitable for personalized medicine. Among the advantages of applying this combination of technologies in the manufacturing of oral solid dosage forms, one is that it enhances the solubility and bioavailability of poorly water-soluble compounds. In this context, our work aimed at the preparation of prolonged-release oral solid dosage forms containing felodipine, chosen as poorly water-soluble drug of BCS class II, by coupling HME with FDM. In a first step, the formulation and extrusion conditions for felodipine-loaded filaments were established. Regarding the formulation, filaments were prepared with felodipine loading from 5% to 50%, using polyvinyl alcohol as the main filament-forming polymer and mannitol as a plasticizer. Visual examination, mechanical and thermal characterization of filaments helped in the selection of adequate felodipine loading and extrusion conditions, which were dependent on active substance loading. The filaments with 5% and 15% felodipine were further used to 3D print tablets using FDM methodology, with tablet infill density ranging from 10% to 80%. The printed tablets were evaluated through *in vitro* drug release test, which revealed that the disintegration and dissolution behaviour is influenced by the active substance content of the dosage form, as well as by the infill density. Thus, the increase of felodipine content and of the infill percentage may be used as a strategy to prolong the release of felodipine from the 3D printed tablets.

Rezumat

Cuplarea extrudării termoplastice (ET) cu imprimarea tridimensională (3DP) folosind tehnica modelării prin depunerea topiturii (MDT) permite astăzi fabricarea unor forme farmaceutice solide de uz oral având caracteristicile dorite, adecvate terapiei personalizate. Printre avantajele aplicării acestei combinații de tehnologii în fabricarea formelor solide orale, unul este acela că oferă posibilitatea creșterii solubilității și biodisponibilității compușilor cu solubilitate redusă în apă. În acest context, acest studiu a avut ca obiectiv prepararea unor forme solide de uz oral cu felodipină, substanță cu solubilitate redusă în apă din clasa biofarmaceutică II, prin combinarea ET cu MDT. Într-o primă etapă a studiului, s-au pus la punct formularea și parametrii procesului de extrudare, pentru obținerea filamentelor cu felodipină. În ceea ce privește formularea, filamentele s-au încărcat cu substanță activă în proporție de 5% până la 50%, folosind alcool polivinilic ca polimer formator de filament și manitol ca plastifiant. Examinarea vizuală, caracterizarea mecanică și termică a filamentelor au ghidat selecția proporției adecvate de felodipină și a condițiilor de extrudare, care au fost dependente de procentul de felodipină din filament. Filamentele cu 5% și 15% felodipină au fost utilizate în continuare pentru imprimarea comprimatelor prin tehnologia MDT, variind densitatea umplerii de la 10% la 80%. Comprimatele obținute au fost evaluate prin testul de dizolvare *in vitro*, care a evidențiat că dezagregarea și dizolvarea substanței active sunt influențate de conținutul de substanță activă și de densitatea umplerii. Astfel, creșterea conținutului de felodipină și a densității umplerii poate fi utilizată ca strategie pentru prelungirea eliberării felodipinei din comprimatele obținute prin 3DP.

Keywords: 3D printing, fused deposition modelling, hot melt extrusion, prolonged release, felodipine

Introduction

3D printing (3DP) through fused deposition modelling (FDM) is extensively explored currently as a promising technology for pharmaceutical manufacturing. It is one of the many printing technologies which, along with several others (*i.e.* stereolithography (SLA), selective laser sintering (SLS), binder jetting), are applicable in the manufacturing of pharmaceutical dosage forms[1-4]. In order to prepare pharmaceutical dosage forms through FDM, a drug-loaded filament is prepared in a first step, and this filament is used to feed the printer. The printer brings the filament, with the help of feeding rollers, at a hot end, where is heated and extruded through a nozzle. The molten

material is deposited on a heated building plate, where the object of the desired design is created on a layer-by-layer basis [5-7].

To get the drug-loaded filament, two methods have been employed so far, *i.e.* impregnation and hot melt extrusion (HME). The impregnation method relies on the immersion of commercially available filaments in organic solutions of active substance, which leads to incorporation of low concentrations of active substance through passive diffusion [8]. Due to the low-efficiency active substance loading and the need to use organic solvents, the second method for filament preparation, HME, is the most used today. This involves the use of active substance-excipients combinations which are mixed, melt and pushed through a heated extrusion head, thus obtaining a filament with the desired drug loading and predetermined diameter, such as to suit the printing nozzle [9, 10].

Coupling HME with FDM allows today the manufacturing of oral solid dosage forms with desired characteristics, suitable for personalized medicine. Thus, the use of this combination of technologies has applications in the enhancement of solubility and bioavailability of poorly water-soluble compounds [11-14], in taste-masking of active substances [15, 16] and modifying or targeting the drug-release [17-21].

Despite the advantages, manufacturing dosage forms through HME coupled with FDM faces some challenges, mostly related to material properties, operation parameters and the characteristics of the 3D printer used [22]. The material attributes impacting the success of the technology are the thermal, mechanical and rheological characteristics of the filament, which are dependent on its formulation, and determine if it is extrudable/ printable or not [23]. Thus, filament formulation is an essential step, the selected materials having to meet certain critical characteristics. The polymer used as support matrix has to possess thermoplastic properties, to be of pharmaceutical grade, to melt at a temperature which ensures the stability of the active substance and to solidify rapidly upon cooling [24-26]. To ameliorate the processability of the formulation and to reduce the processing temperature, processing aids such as plasticizers are added in the polymer – active substance mixture. The most used plasticizers are mannitol [27], triethyl citrate [28], polyethylene glycol [29], sorbitol [2], but alternative plasticizing methods such as the use of water as temporary plasticizer [30] or the use of acid-base supersolubilization principles [31] have also been proposed.

In this work, the application of HME coupled with FDM was explored in the preparation of prolonged-release oral solid dosage forms containing felodipine, chosen as poorly water-soluble drug of BCS class II [32]. Felodipine is a calcium channel blocker belonging to the dihydropyridine class, with vasodilatory effects, used for the treatment of hypertension and angina pectoris [33]. It is completely absorbed from the gastrointestinal tract after oral administration, the maximum plasma concentration is reached within 2.5 - 5 hours after an oral dose, but due to first pass metabolism its bioavailability is only about 20% [34, 35]. Felodipine is usually administered as extended-release (ER) tablet formulations, and various strategies have been proposed to ameliorate its poor water solubility, among which, more recently, the preparation of HME solid dispersions [36]. In this context, the purpose of this work was to obtain felodipine-loaded filaments by HME technique and further to use these filaments to prepare prolonged release felodipine tablets using the FDM 3D printing technique.

Materials and Methods

Materials

For the preparation of filaments and 3D printed tablets, the following were used: felodipine, as active substance, from Nivedita Chemicals PVT Ltd; polyvinyl alcohol, Parteck MXP (PVA), as filament forming polymer, and mannitol, as plasticizer, from Merck, Germany. All the other reagents and solvents were of analytical grade purity and were used as supplied.

Preparation of filaments through hot melt extrusion

Felodipine-loaded filaments were prepared through hot melt extrusion, using a single-screw extruder (Noztek Pro, Noztek, UK), equipped with a 1.75 mm die, at rotational speed of 65 RPM. Briefly, a physical mixture of active substance (felodipine), polymer (PVA) and plasticizer (mannitol) was first prepared by mixing the pre-weighed components in mortar with pestle. Each obtained mixture was subsequently extruded to obtain the corresponding filaments. The feeding rate was established at 1 - 2 g/min while the extrusion temperature was varied between 170 and 190°C, in an attempt to determine the temperature at which appropriate filaments with adequate appearance are obtained.

Two formulations (F1 and F2) were proposed for extrusion, with different active substance content, 5 and 15% (w/w) respectively. Besides the active substance and the filament forming polymer, both contained mannitol as plasticizer, in a concentration of 5% (w/w). The quantitative composition of the prepared mixtures/filaments is presented in Table I.

Table I

Quantitative composition of the proposed physical mixtures/filaments with felodipine

	Felodipine (%)	Mannitol (%)	PVA (%)
F1	5	5	90%
F2	15	5	80%

HPLC method for the felodipine assay

Felodipine assay was done using a high-performance liquid chromatography (HPLC) method with UV detection (240 nm wavelength), on a HPLC Agillent 1100 series apparatus with autosampler, equipped

with a Zorbax SB-C18, 5 µm x 4.6 x 250 mm chromatographic column. The mobile phase consisted in a phosphoric acid 0.1% solution in water:acetonitrile mixture 20:80, and the flow rate used was 1.5 mL/min. In the described conditions, the retention time of felodipine was equal to 3.5 minutes.

Thermal characterization

Felodipine, the physical mixtures containing felodipine and the excipients used in F1 and F2 filaments, and MeltPrep samples having the same composition as filaments F1 and F2, were analysed using differential scanning calorimetry (DSC), to characterize the thermal properties of materials. The MeltPrep samples are disk-shape products of 5 mm diameter prepared using the MeltPrep VCM (Vacuum Compression Molding) laboratory device (MeltPrep GmbH, Austria), by melting mixtures (F1 and F2) of around 4 - 6 mg at 190°C, for 6 minutes, and subsequent cooling to room temperature. The DSC analysis was performed using a Mettler Toledo DSC 3 Stare system, in aluminium crucibles with about 2 - 6 mg of samples, under dynamic N_2 atmosphere (flow rate: 50 mL/min) at a heating rate of 10°C/min in the temperature range of 25 to 400°C.

Physico-chemical characterization of filaments

Felodipine-loaded filaments were evaluated in terms of active substance recovery and mechanical properties. To assess the impact of extrusion conditions on active substance stability, felodipine recovery in the extruded filaments loaded with 5% felodipine was evaluated, using the HPLC method for felodipine assay described above. For this purpose, filament fragments of approximately 60 mg were dissolved in a methanol: water mixture 1.5:1 (v/v), this solvent mixture being chosen to ensure felodipine solubility. After complete dissolution of the filaments, each solution was further diluted with a mixture of acetonitrile and 0,1% phosphoric acid (4:1 v/v), the resulted samples being used for felodipine quantification using the HPLC method. Felodipine recovery was calculated as the ratio between the HPLC determined felodipine content and the declared felodipine content of the filaments and were expressed as percentage (%).

Mechanical characterization was performed using a CT3 Texture Analyzer (Brookfield Ametek, USA) equipped with a 4.5 kg load cell and two different fixtures for 3-point bending test and stiffness test, known as the Repka-Zhang tests [24].

Briefly, for the flexibility testing through the 3-point bending test, 50 mm filament samples were placed horizontally over the 25 mm gap rig. The blade descended to the middle of the sample at a speed of 10 mm/s down to 15 mm distance. The maximum load, the braking distance and the load *versus* time profiles were recorded for 5 replicate measurements and analysed using TexturePro CT software (Brookfield Ametek, USA).

Stiffness test was performed on 5 mm samples placed on a flat surface and cut with a blade that descended with a 0.1 mm/s speed and down to a displacement of 5%. The maximum load, and the load *versus* time profiles were recorded for 5 replicate measurements and analysed using the same TexturePro CT software.

3D printing of felodipine-loaded tablets

Felodipine-loaded filaments (F1 and F2) were used to print tablets through FDM. The 3D printing process was performed using MakerBot Replicator 2X (MakerBot, USA). The fused layers were deposited such as to obtain tablets with three distinct infill densities, *i.e.* 10, 50 and 80%, resulting in six different tablet configurations. The printing temperature was set at the same value as the extrusion temperature, for F1 filaments, and was slightly lower than the extrusion temperature for F2 filaments. The composition and printing conditions of the felodipine-loaded tablets are depicted in Table II.

Table II

The composition and features of the printed tablets

	Felodipine (%)	**Infill (%)**	**Printing temperature** (°C)
N1	5	10	165
N2	5	50	165
N3	5	80	165
N4	15	10	180
N5	15	50	180
N6	15	80	180

Characterization of 3D printed tablets

Immediately after printing, a macroscopic evaluation of the obtained tablets was performed, in terms of appearance and size. The size of the tablets (length, width and height) was measured using a ruler, on 6 randomly selected units of each formulation. The average mass of tablets was calculated, by individually weighing six tablets for each formulation using a high-precision digital balance (OHAUS Analytical Plus, Ohaus, USA).

The felodipine-loaded printed tablets were subjected to *in vitro* dissolution test using PharmaTest PT DT 7 apparatus (Pharma Test Apparatebau AG, Germany) in USP Type II configuration (paddle). The test was performed on six tablets of each formulation. Briefly, the tablet was placed in 500 mL phosphate buffer at pH 6.5 with 1% sodium lauryl sulphate, for 5 hours, at 37 ± 0.5°C and rotation speed of 50 rpm. During the experiment, samples of 2 mL were withdrawn from the dissolution medium at pre-set time intervals,

being each time replaced with 2 mL of fresh medium. A total of 20 samples were collected and analysed for each formulation, at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105, 120, 150, 180, 240 and 300 min time points. Each sample was filtered and assayed for felodipine content using the HPLC method. The cumulative percentage of felodipine released was calculated for each sample and expressed as mean ± standard deviation, throughout the experiment.

Results and Discussion

HME of felodipine-loaded filaments

HME is a technique that has been first introduced in the plastics industry, due to its ability to produce construct of uniform shape by pumping the raw materials with a rotating screw under elevated temperature [38]). After 1995, the utility of this technique has been proven in the pharmaceutical industry as well, for the preparation of various drug delivery systems, for oral, parenteral, ocular, vaginal or transdermal administration route [39]. In the case of oral dosage forms fabrication, HME brings a great potential for poorly water-soluble drugs, for its capability to enhance the solubility and bioavailability of these compounds [40].

Increasing the solubility of compounds with low solubility in water by means of thermoplastic extrusion is attributed to the capacity of this technique to induce the formation of solid dispersions, by the interaction between the active substance with solubility problems and the hydrophilic polymer used as a support matrix. DSC was used in our study as a thermoanalytical technique to evaluate the phase transition of felodipine as a function of temperature, in raw felodipine, physical mixtures of felodipine with the excipients used in filaments F1 and F2, and in thermally treated samples, MeltPrep 1 and MeltPrep 2, obtained in conditions which mimic the thermal treatment of the samples during the extrusion process. The DSC curve for pure felodipine showed an endothermic peak at 144ºC, as shown in Figure 1. As expected, the physical mixtures showed F1 and F2 showed the same peak at around 144ºC, but with a shift of 2 - 3ºC in filaments with lower felodipine content, probably due to interactions between the active substance and the excipients. On the contrary, the thermally treated samples displayed no peaks around 140ºC, indicating the formation of an amorphous homogeneous solid dispersion of felodipine in the proposed mixture of excipients during HME.

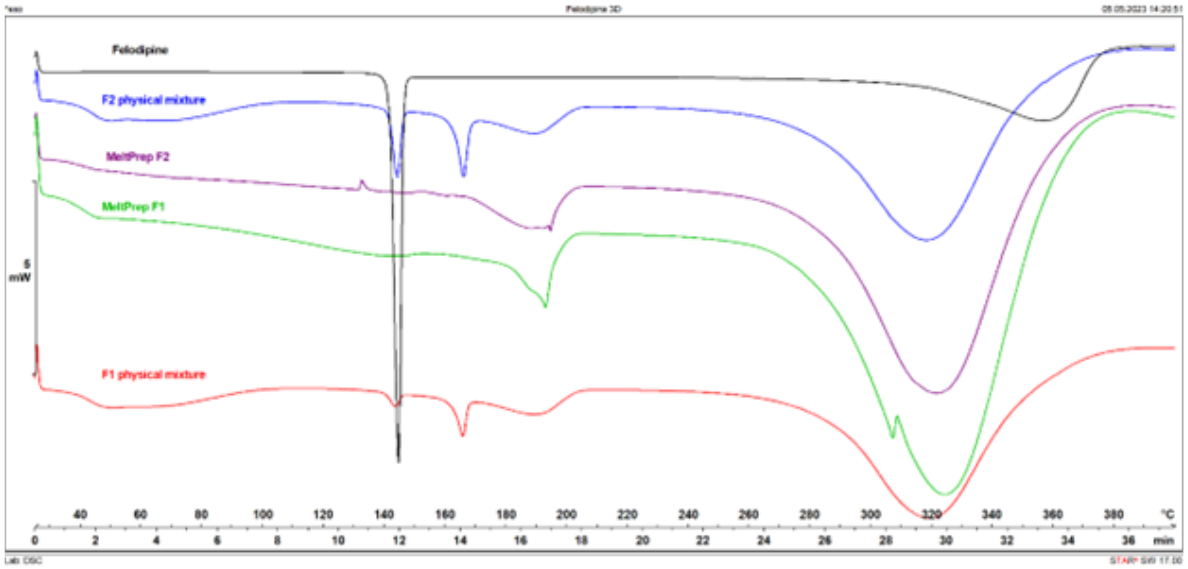
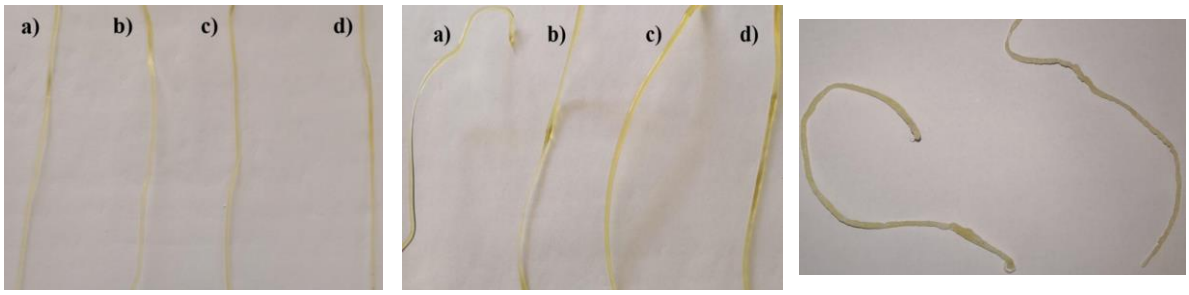


Figure 1.
The DSC thermograms of pure felodipine, physical and MeltPrep mixtures of felodipine, with the same composition as filaments F1 and F2

Despite the mentioned features and advantages of the HME technique, process and formulation development doesn't lack challenges. In terms of formulation, the mixture used should have good extrudability and the obtained filament has to possess suitable printability. Because the majority of pharmaceutical polymers blends do not possess these characteristics, adjuvants are added in the blend to correct these unfavourable properties. PVA is a slow water-soluble polymer, that is biocompatible and biodegradable and generally recognized as safe (GRAS), with a history of safety confirmed by the presence in the composition of various pharmaceutical forms. At the same time PVA is one of the classical materials used in FDM 3D printing, generally as structure material, when objects with extremely complex architectures or ones with partially enclosed cavities are printed, commercially available PVA filaments having high strength, good

durability and printability. The slow water dissolution of PVA prolongs the release of incorporated active substances, in our case felodipine, which was one desired feature of the designed pharmaceutical preparation. The printing properties of the PVA filament loaded with APIs depend on the characteristics of the active substances and the % of drug loading, and often the use of plasticizers must be considered in order to decrease the brittleness and to increase the printability. In our study, 10% mannitol has been proposed and used as plasticizer. Mannitol is a compound that has been intensively used as an adjuvant in previous studies in order to obtain API loaded filaments *via* HME, improving the processability of PVA-based blends and contributing to filaments with suitable mechanical properties for printing *via* FDM [10, 41]. The presence of the active substance in the mixture highly influences the extrudability of the filament, so mixtures containing felodipine proportions ranging from 5 to 50% were first tested for extrudability. However, mixtures with 50% felodipine content generated inadequate filaments, regardless of the processing conditions. Consequently, the highest felodipine proportion used for filaments preparation was 15%.

Regarding process development, the extrusion temperature is the most critical. The extrusion temperature is dependent on the thermal properties of the materials used. Thus, the extrusion has to be performed above the glass transition temperature (Tg) and melting point of the mixture, where the polymer is in a flexible state or melted state, but this elevated temperature has to be as low as possible, to prevent the thermal degradation of the components [23]. In this context, the first aim of our study was to explore the extrusion of felodipine-mannitol-PVA mixtures at different temperatures, between 190°C and 170°C. For F1, at 190°C, 180°C and 175°C, the obtained filaments were too soft, so the extrusion temperature was decreased to 170°C, at which suitable filaments could be formed. For F2, the same evaluation was performed, to see the effect of working temperature on the aspect of the filament. For this formulation, the temperature found as suitable was higher than for F1 (190°C), probably due to the higher active substance content of F2 compared to F1. The aspect of the extruded filaments at various working temperatures is shown in Figure 2. In the selected conditions, the filaments had uniform appearance, appropriate and uniform diameter, transparency, suitable rigidity, and lack of friability, for both formulations.



A **B** **C**

Figure 2.
The appearance of filaments with felodipine content of 5% (A), 15% (B) and 50% (C) obtained at different extrusion temperatures: 190°C (a); 180°C (b); 175°C (c); 170°C (d)

The mechanical properties of the filaments obtained at different extrusion temperatures were also tested through 3-point bending test and stiffness test. To be adequate for the printing step, the filaments must not be too fragile, they have to possess a limited degree of brittleness, so good flexibility. Too fragile filaments do not fit well between the feeding rollers of the printer, may break within the printing head and determine printing blockage. If the stiffness is not adequate, their surface is scratched and damaged by the feeding gears of the 3D printer [42, 43].

First of all, the results of the 3-point bending test were presented as load (g) *vs.* breaking distance (mm), as shown in Figure 3, the breaking load being the maximum force reached that produced sample breakage. A low breaking distance indicates that the filament lacks ductility, so it breaks without significant deformation. On the contrary, a high breaking load indicates a strong filament. According to the plot shown in Figure 3, the mechanical strength of the filaments was influenced by the composition of the filament as well as by the extrusion temperature. Thus, the mechanical strength increased with the active substance concentration, as the breaking load was higher for filaments with 15% felodipine (F2) than that of filaments with 5% felodipine (F1), at each processing temperature. Regarding the effect of the extrusion temperature, the variation of the mechanical resistance with the temperature was dependent on the composition of the filament. Thus, at 5% felodipine content, the resistance of the filaments was higher at higher temperature, while at 15% felodipine content, a reverse effect of the extrusion temperature was observed, the filament obtained at

180ºC being very flexible, it does not break, as shown by the low values of the force during the entire test. However, increasing the proportion of active substance in the filaments increased the brittleness, reflected by the lower breaking distance of F2 filaments.

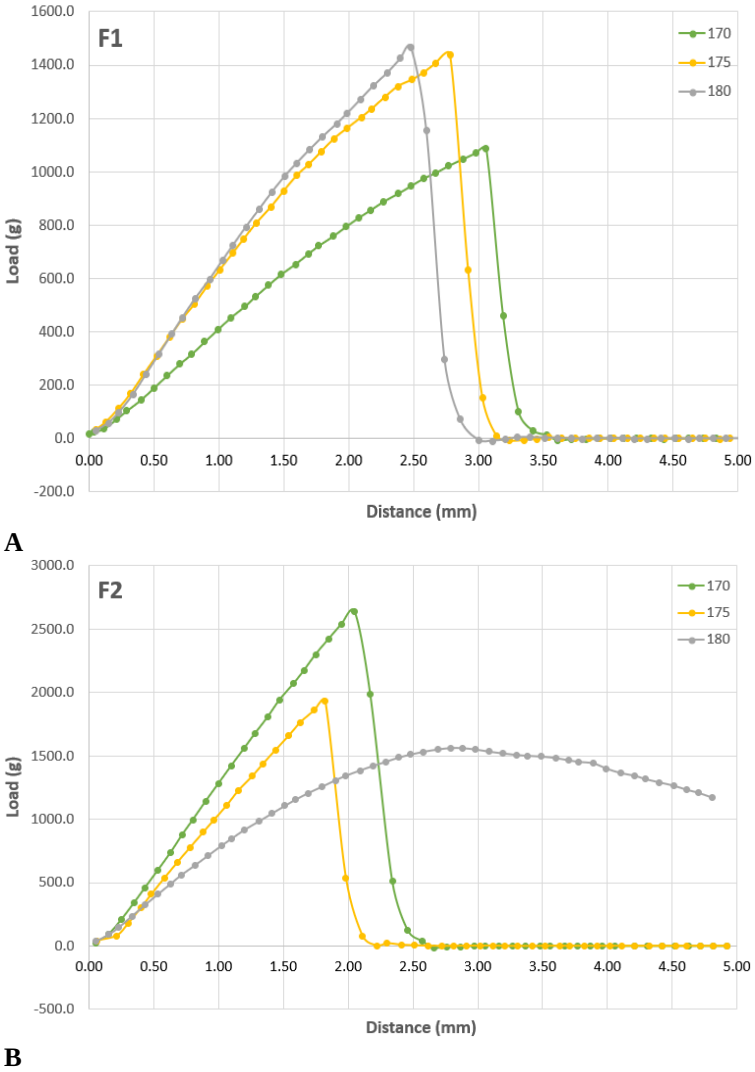


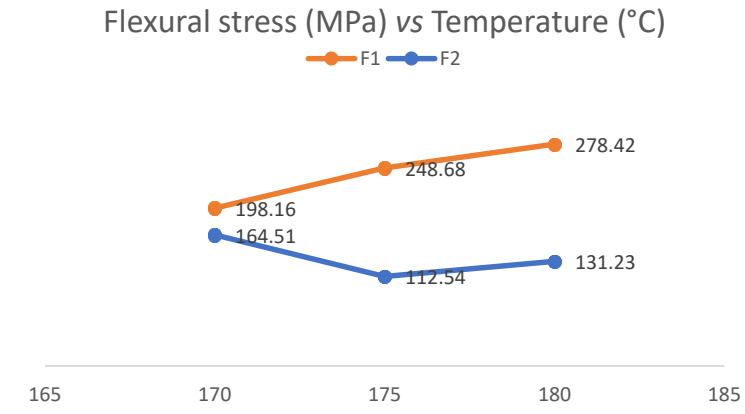
Figure 3.
The results of 3-point bend test, expressed as load *vs.* distance for filaments F1(A) and F2(B), obtained at different extrusion temperatures

Besides the plots shown in Figure 4, several parameters were calculated out of the three-point bending test. Thus, the flexural stress, strain and stiffness were determined and are displayed in Figure 4 [44, 45]. According to Figure 4A, the flexural stress values were higher for the filaments with lower active substance content (F1), regardless of the printing temperature, so the increase in substance proportion reduces the flexibility of the filaments, the same being indicated by the low breaking distance as well. Regarding the effect of the processing temperature, for F1, the flexural stress increased with the HME temperature with a simultaneous slight strain decrease. For F2 filament samples flexural stress was significantly lower than for F1 and showed an inflection point beyond 175 degrees of melting temperature.

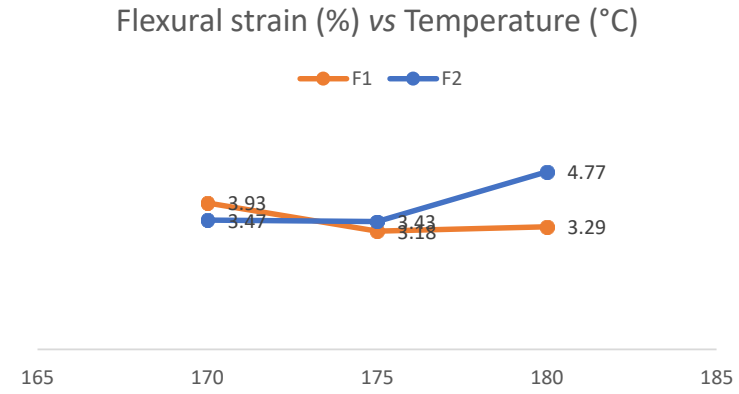
Stiffness is a feature defined for low ductility materials, that are usually hard and difficult to bend. As Figure 4C shows, stiffness was significantly related to the temperature variation. A positive influence of the temperature on the stiffness was shown on the evaluated temperature interval, for F1. For the F2 formulation, higher values were recorded compared to F1, up to 175°C. However, a further increase in temperature determined stiffness decrease.

Besides the suitability of the extrusion temperature for the preparation of filaments with adequate appearance and mechanical properties, the processing conditions must ensure the stability of the active substance. To check the adequacy of the printing temperature from this point of view, the quantitative determination of felodipine from the filaments loaded with 5% active

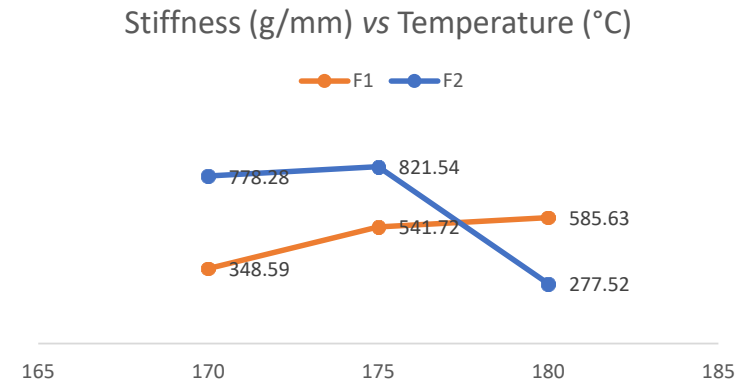
substance, obtained at all the tested extrusion temperatures, was performed. This determination showed a good recovery of felodipine in the extruded filaments. Thus, the recovered felodipine exceeded 90% in all the filaments, being 94 ± 1.1% in the filaments extruded at the proposed processing temperature, *i.e.* 170°C.



A



B



C

Figure 4.
The results of the mechanical characterization of filaments expressed as flexural stress (MPa) *vs* extrusion temperature (°C) (A); flexural strain (%) *vs* extrusion temperature (°C) (B) and stiffness (g/mm) *vs* temperature (°C) (C)

3D printing of felodipine-loaded tablets

The extruded filaments containing 5% (F1) and 15% (F2) felodipine were used to produce 3D printing tablets. For each filament, tablets were produced at three different infill percentages, resulting in six different tablet configurations. The infill represents the inner support of the printed object, whose structure includes the shell and the infill. The infill density is expressed as filling percentage and may vary from 0 to 100%, from hollow structures to full structures with no cavities. In our study, the infills used were 10%, 50% and 80%. The change in infill percentage influences the mechanical strength of the tablet, given that the density of the object is different. In the same time, the denser materials (those with higher infill) are less porous, so the surface of contact with the

aqueous medium is reduced and the release rate of the active substance is slower [23]. It has been shown that not only the infill density of the printed tablets influence the dissolution rate, but also the surface area to volume ratio [46]. Consequently, the printer was set such as to obtain tablets of the same physical dimensions (L = 12 mm, l = 5 mm, h = 2 mm), and the actual dimensions of the tablets obtained were in accordance with those set, as shown in Figure 5.

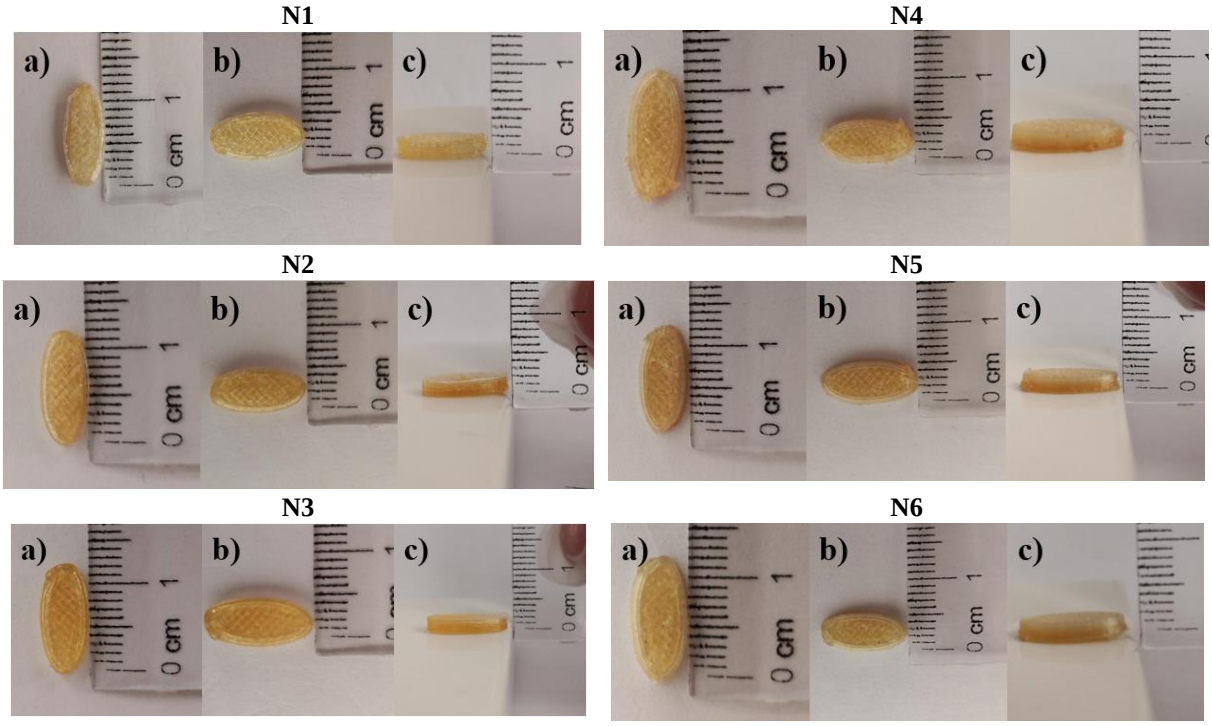


Figure 5.
Macroscopic appearance and size of printed tablets with different felodipine content and different infill percentage

The dissolution test for 3D printed tablets was performed over 300 minutes. First of all, the disintegration behaviour of the printed tablets was observed during the *in vitro* dissolution test, and an influence of the formulation and of the infill was observed on this parameter. Thus, the felodipine content had a great influence on the dosage form disintegration, because all the tablets loaded with 5% felodipine disintegrated in less than 260 minutes. On the contrary, for the tablets with 15% felodipine the disintegration process extended over 300 min, this extension being probably a consequence of the low affinity for water of the active substance. The infill had also an influence over the disintegration behaviour, the disintegration time being higher for higher infills. Thus, for filaments with lower felodipine content, the disintegration time increased from 120 minutes to 260 minutes, when the infill increased from 10 to 80%, while for tablets with higher active substance content, the disintegration time was over 300 minutes, when the infill was 50 - 80%. This behaviour is due to the lower contact surface with the release medium of tablets with higher infill.

Regarding the release of the active substance, a gradual release was observed over the period of 300 minutes of the test. The cumulative % of released felodipine was plotted *vs.* time for the six formulations, as shown in Figure 6, to allow the evaluation of the impact of the active substance content and of the infill on the release.

To evaluate the influence of active substance content on the release, tablets with the same infill but with different proportion of active substance were compared. The results show that, regardless of the infill, the release of felodipine is slower in the case of tablets with a higher percentage of felodipine. Thus, for formulations N1, N2 and N3, with 5% felodipine, the cumulative percentage of felodipine released was over 90% after 120, 150 and 240 minutes, respectively. Regarding the formulations N4 – N6, with 15% felodipine, only N4 released over 90% of felodipine content after 300 minutes, while for the other formulations the maximum released felodipine content was 80 - 90%, at the end of the test. The influence of felodipine content on the release behaviour was expected, considering its low aqueous solubility.

Regarding the effect of the infill density on drug release, regardless the active substance content, the increased infill had a negative effect on the cumulative drug release. Thus, for tablets loaded with 5% felodipine, the release profile was similar for infill densities below 50%, but for tablets with 80% infill, a delay

of 60 minutes, compared to the formulations with lower infill, was necessary to achieve over 90% active substance released. A similar observation has been reported for diazepam FDM 3D printed tablets, for which a fastest drug release was achieved for infill density below 50% [47]. For the formulations with 15% felodipine loading, the effect of the infill was similar, but the percentages released were lower, as discussed above. Thus, we may conclude that the higher the infill density the lower the release rate, because higher infill indicates a tighter 3D structure of the tablet, but the influential effect of the infill on drug release is also dependent on drug loading. As a consequence, to modulate the felodipine release from the 3D printed tablets, both the drug content and the infill may be adjusted. To extend the release of felodipine over 6 hours, a drug loading of 15% and an infill over 50% have to be used.

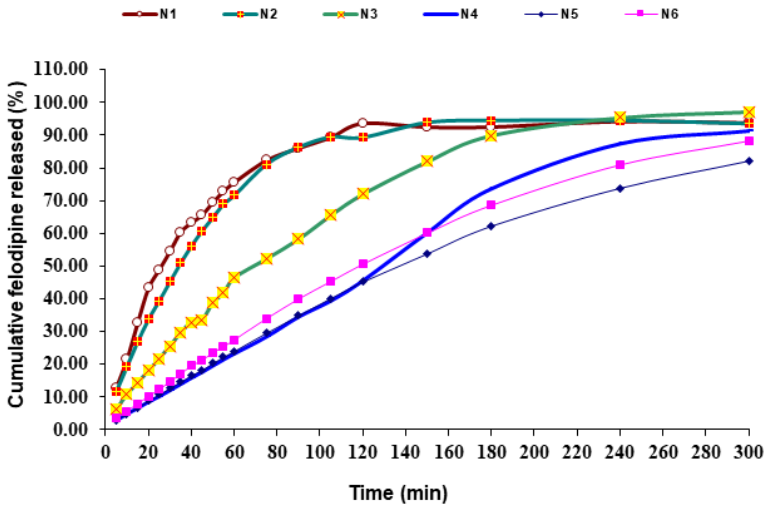


Figure 6.

The results of the *in vitro* dissolution test plotted as cumulative felodipine released (%) *vs.* time (minutes)

Conclusions

This study demonstrates the feasibility of coupling HME with 3D printing technology for the preparation of prolonged release tablets with felodipine. Filaments of felodipine-mannitol-PVA mixtures, loaded with 5 and 15% felodipine, were successfully prepared through HME, by carefully adjusting the working parameters such as to obtain filaments with adequate mechanical properties and to ensure the stability of the active substance. Further, prolonged-release tablets with both proportions of active substance were printed at infill between 10 and 80%. The *in vitro* release study has shown an interplay between the active substance content and the infill percentage, with influence on the disintegration and the cumulative percentage of felodipine release. Our results point out that the desired felodipine release profile may be obtain by modulation of both the drug content and the infill of the 3D printed tablets.

Acknowledgement

This research was financed by a grant of the Romanian UEFISCDI, project number PN-III-P4-PCE-2021-1119 (contract no. PCE41/02/07/2022).

Conflict of interest

The authors declare no conflict of interest.

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