FARMACIA, 2024, Vol. 72, 6

https://doi.org/10.31925/farmacia.2024.6.15

ORIGINAL ARTICLE

MECHANICAL CHARACTERIZATION AS A TOOL FOR PREDICTING THE PROCESSABILITY OF FELODIPINE-LOADED FILAMENTS DURING FUSED DEPOSITION MODELLING

RAREȘ IULIU IOVANOV, ALINA SILVIA PORFIRE *, ANDREA GABRIELA CRISAN, NADINE COUȚI, SONIA MEDA IURIAN, TIBOR CASIAN, ANAMARIA-ALEXANDRA CĂLIN, OANA-BIANCA FARCĂU, GRAȚIELA-VICTORIA CUMURCIUC, MONICA-REKA GASPAR, DIANA-ROXANA DRAGOȚEL, IOAN TOMUȚĂ

Pharmaceutical Technology and Biopharmacy, Department 1, Faculty of Pharmacy, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

**corresponding author: aporfire@umfcluj.ro*

Manuscript received: September 2024

Abstract

Nowadays, 3D printing (3DP) is gaining momentum to prepare customized solid pharmaceutical forms. This additive manufacturing technique is versatile, flexible, cost effective and easy to use. Among various 3DP techniques, fused deposition modelling (FDM) is the most applied for manufacturing of pharmaceutical dosage forms. For this purpose, the 3D printers are fed with filaments of pre-defined diameter, loaded with active pharmaceutical ingredients (APIs), usually obtained through the hot melt extrusion (HME) technique. The filament quality is essential for the success of the printing step and for the quality of the drug product, good mechanical properties of the filament being mandatory for smooth processability through FDM. In this context, our work aimed to evaluate the mechanical properties and printability of filaments obtained through HME, and to establish mechanical parameters that might be used to predict their processability through FDM. Filaments were extruded using polyvinyl alcohol as filament-forming polymer and mannitol as plasticizer, while felodipine was the selected active substance. The impact of the formulation on the quality of the filaments has been evaluated and their processability was evaluated using mechanical characterization. Our results have shown the impact of the formulation on the processability of the filaments through FDM and led to the establishment of target values for several mechanical characteristics of felodipine-loaded filaments that warrant obtaining processable filaments in the 3D printing step.

Rezumat

În ultimii ani, imprimarea tridimensională (3DP) a câștigat importanță în domeniul preparării formelor farmaceutice solide personalizate. Această tehnică de fabricație aditivă este versatilă, flexibilă, rentabilă și ușor de utilizat. Dintre diferitele tehnici de 3DP, modelarea prin depunerea topiturii (FDM) este cea mai aplicată pentru fabricarea formelor farmaceutice. Pentru această aplicație, imprimantele 3D sunt alimentate cu filamente de diametru predefinit, încărcate cu substanțe active (API), obținute de obicei prin tehnica extruderii termoplastice (HME). Calitatea filamentului este esențială pentru succesul etapei de imprimare și pentru calitatea produsului medicamentos, proprietățile mecanice bune ale filamentului fiind obligatorii pentru o procesabilitate facilă prin FDM. În acest context, studiul nostru și-a propus evaluarea proprietăților mecanice și imprimabilității filamentelor obținute prin HME, precum și stabilirea unor parametri mecanici care ar putea fi utilizați pentru a prezice procesabilitatea filamentelor prin FDM. Filamentele au fost extrudate folosind alcool polivinilic ca polimer formator de filamente și manitol ca plastifiant, în timp ce felodipina a fost substanța activă selectată. S-au evaluat impactul formulării asupra calității filamentelor și procesabilitatea acestora prin caracterizare mecanică. Rezultatele obținute au demonstrat impactul formulării asupra procesabilității filamentelor prin FDM și au condus la stabilirea unor valori țintă pentru mai multe caracteristici mecanice ale filamentelor încărcate cu felodipină, care pot garanta obținerea de filamente procesabile în etapa de imprimare 3D.

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

Introduction

Nowadays, 3D printing (3DP) is gaining momentum to prepare customized solid pharmaceutical dosage forms, due to its versatility, flexibility, reduced cost and easy to use [1]. Among the 3DP techniques, the most common are fused deposition modelling (FDM), stereolithography, selective laser sintering and binder jet on powder bed [2]. In the pharmaceutical field, the most applied and accessible is FDM, especially to produce pharmaceutical solid dosage forms for oral use, either with immediate [3, 4] or modified release profile [5]. This technique is based on the extrusion of a molten material through the nozzle of the 3D printer and the subsequent deposition of successive layers of material on a build platform, in the desired shape, controlled by a computer [6-8].

To obtain pharmaceutical dosage forms through FDM, the 3D printers are fed with filaments of pre-defined diameter, loaded with active pharmaceutical ingredients (APIs). The most common method to obtain the API loaded filaments is the hot melt extrusion (HME) technique, that uses a powder blend of API, thermoplastic polymers and other additives, most common being the plasticizer [9]. Due to the requirement to use only pharmaceutical grade materials in dosage forms manufacturing, and the specific need to use thermoplastic materials in FDM through HME, the number of adequate filaments forming polymers is limited. The most popular are polyvinyl alcohol (PVA), cellulose derivatives, methacrylic polymers, polyvinylpyrrolidone, polycaprolactone [10-14]. On the other hand, several material, process and equipment attributes are critical for the performance of the HME process [15]. The filament quality is essential for the success of the printing step but also for the quality of the final drug product, good mechanical properties of the filament being mandatory for smooth processability in the 3D printing step [16]. During the preparation of the API-loaded filaments *via* FDM, homogeneous API distribution, uniform diameter, smooth aspect, adequate thermal, mechanical and rheological properties are critical quality attributes of the filament, that must be ensured [3, 17]. In general, filaments that could not be printed were classified as too brittle, too soft, or insufficiently stiff [18]. If the filaments have uneven diameter that is larger than the maximum printing diameter or they have a sharkskin-like surface, they can clog the printing head or if they are too narrow, the feeding gears can't grip enough the filament or extruder backflow phenomenon can appear. When the filament is fed in the 3D printer, it must preserve his shape, to resist the frictional forces from the driving wheels, and withstand buckling between the wheels and the printing head where it will be liquefied. To meet these requirements, a sufficient strength is needed, that will prevent filament rupture, and an adequate degree of stiffness, that will prevent buckling [19].

The objective of the study was to evaluate the mechanical properties and printability of PVA-based felodipine-loaded filaments obtained through HME, and to establish the mechanical parameters that might be used to predict the processability of filaments through FDM. Filaments were prepared based on a full experimental design with two variables and three levels of variation, to link the filament formulation with its mechanical characteristics and finally to predict the ability to use them as feedstock material for FDM 3D printing. Felodipine, an antihypertensive agent, has been selected as model active substance for this study because it is a BCS Class II, low solubility and high permeability drug, for which FDM 3D printing has been proposed as adequate for the formulation of solid dispersions [20, 21]. This formulation strategy has been shown to considerably improve the solubility of the low solubility drugs, including felodipine [10, 22].

Materials and Methods

Materials

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

Preparation of the filaments

The powder mixture for filament preparation was homogenized with Alphie 3 3D mixer (Hexagon Product Development Pvt. Ltd., India) for 30 minutes at 50 rpm. For the filament preparation, a twin-screws extruder with five heating zones – QUICK TS16 (Quick 2000, Hungary) has been used. The screw speed varied between 40 and 75 rpm, while heating level was set for each heating sector, as follows: T1: 98 - 108°C; T2: 115 - 138°C; T3: 140 - 155°C; T4: 168 - 173°C; T5: 168 - 172°C. The operation of twin-screw the extruder used to obtain the filaments is schematically shown in Figure 1.

Design of experiments

To explore the effect of the composition on the mechanical characteristics of the filament, 11 filament mixtures were prepared and extruded in the conditions detailed above, according to a full factorial experimental design, with two variables (felodipine % w/w/; mannitol % w/w) and three levels of variation (Table I). The experimental design and data analysis were done using the Modde 13 software (Sartorius, Germany).

Mechanical characterization of the filaments

Filaments were evaluated in terms of mechanical characteristics using the CT3 Texture Analyzer (Brookfield Engineering Laboratories, MA, USA) in two different set-ups for three-point bending test (3P-BT) and stiffness test (ST), as displayed in Figure 2. Briefly, the flexibility was evaluated through the 3P-BT, on 50 mm samples of each extruded filament placed horizontally over the 25 mm gap rig, by descending the blade to the middle of the sample at a speed of 10 mm/s down to 15 mm distance. Stiffness test was performed on 50 mm filament samples of each formulation 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 mechanical parameters were recorded each time for 5 replicate measurements and analysed using TexturePro CT software (Brookfield Ametek, USA) [23].

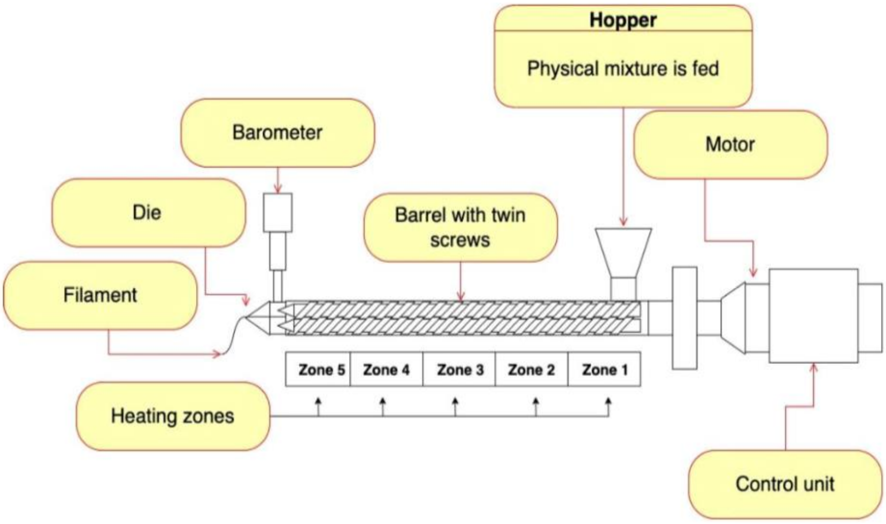


Figure 1.
Twin screw extruder schematics for filament preparation *via* HME

Table I
The factors included in the DoE and the evaluated responses

Factors		Levels		
		-1	0	+1
API %	X_1	5	15	25
Plasticizer %	X_2	0	7.5	15
Responses				
3PB test				
Hardness (g)		Y_1	Flexural stress (N/mm^2)	Y_6
Deformation at hardness (mm)		Y_2	Flexural strain (%)	Y_7
Total work (mJ)		Y_3	Breaking distance (mm)	Y_8
Maximum force (N)		Y_4	Stiffness (N/mm)	Y_9
Peak stress (N/mp)		Y_5		
Stiffness test - derived parameters				
Hardness (g)		Y_{10}	Rigidity at 4% deformation (g)	Y_{12}
Rigidity at 2% deformation (g)		Y_{11}	Peak stress (N/m^2)	Y_{13}

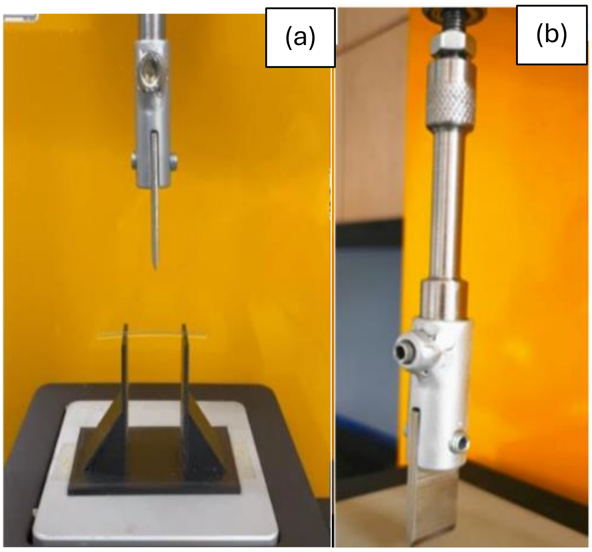


Figure 2.
CT3 Texture Analyzer set-up for the mechanical characterization of filaments:
(a) three-point bending test (3P-BT); (b) buckling test (BT) and (c) stiffness test (ST)

Printability evaluation

For this test the CraftBot Flow Idex (CraftBot, USA) printing head was disassembled and only the feeding mechanism was active. Felodipine loaded filaments of appropriate diameter (≈ 1.75 mm) were selected and fed manually through the printing head, as shown in Figure 3, to check their ability to overcome the mechanical stress exerted by the driving gears of the printer during FDM. The filaments were divided into 5 categories depending on their behaviour, as follows: score 1 – impossible to print; score 2 – unlikely to print; score 3 – possibly can be used for printing; score 4 – printable and score 5 – very suitable for printing.

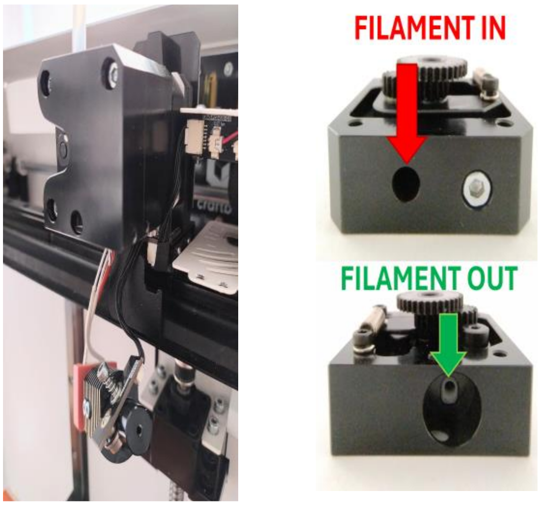


Figure 3.
The setup used to test filament feeding through the printing head

3D printing based on FDM technique

All the filaments evaluated for printability were further used to print tablets *via* FDM technique. The printing step was done using the CraftBot Flow Idex 3D Printer (CraftBot, Hungary), the cylindrical prints being previously designed using a CAD software, Tinkercad (Autodesk, USA). CraftWare Pro software (CraftBot, Hungary) was used to generate the required file (.gcode) for the 3D printer. The dimensions of the printed tablets were as follows: width – 10 mm and height – 2 mm. The FDM printing conditions were: printing head temperature varied between 175 - 185°C, printing bed temperature was 60°C and printing speed was 1X.

Data analysis

The statistical analysis of the DoE was performed using Modde 13 software (Sartorius Stedim Data Analytics AB, Umea, Sweden). To correlate the mechanical parameters of the filaments with the printability score, the results of the mechanical tests were plotted *vs.* printability score, and statistical analysis was performed using one-way ANOVA (α=0.05) with Tukey's post-hoc test for normally distributed data. Data analysis was performed in GraphPad (GraphPad Software, USA).

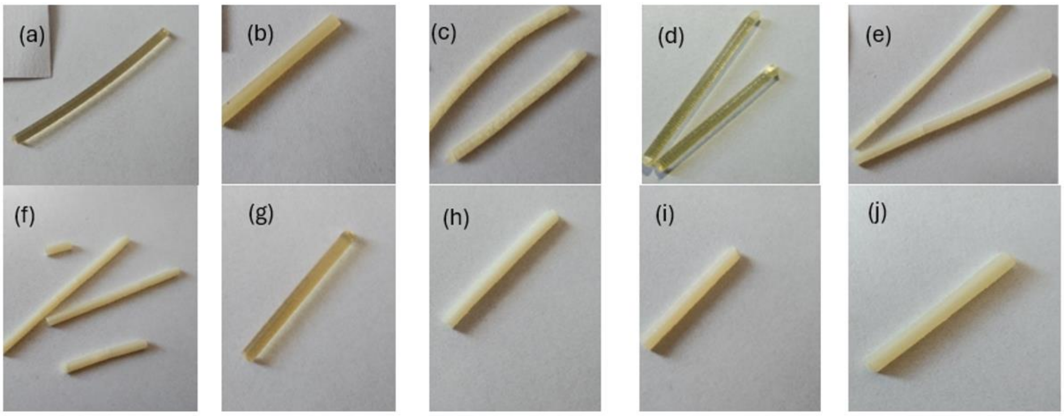
Results and Discussion

Filament aspect and printability

HME has been shown as a suitable technique to convert mixtures of active substances and hydrophilic polymers into solid dispersions, through thermal treatment. This capacity makes it recommended especially for poorly water-soluble compounds for which the interaction with the matrix-forming hydrophilic polymer increases the solubility and consequently the bioavailability. In the case of felodipine, we have demonstrated in a previous study the ability to convert the active substance mixed with PVA and mannitol and thermally treated through HME into an amorphous homogeneous solid dispersion [24].

In the current study, the extrusion temperatures of ≈ 170°C in the final heating zone, along with the continuous monitoring of the diameter and screw speeds, enabled the production of uniform, good quality felodipine-loaded filaments, whatever the API or mannitol content, as shown in Figure 4. However, when the printability score was determined, the values were between 2 and 5, depending on the composition. To better understand the influence of active substance and plasticizer content on this score, the values were graphically plotted, as shown in Figure 5. This plot clearly reveals the influence of the presence and concentration of the plasticizer, but also of the concentration of the active substance, on the printability score. Thus, the filaments without plasticizer were all included in the unlikely to print category, the printability score being 2. For the plasticized filaments, a concentration of 7.5% of mannitol was enough to get very suitable for printing filaments loaded with 5% felodipine. However, when the concentration of active substance increased, the printability decreased, at 15% felodipine a percentage of 15% mannitol being required to obtain filaments that were very suitable for printing.

Further, to confirm that the filaments with a high printability score can practically be used in FDM, all the filaments were used to obtain three-dimensionally printed tablets. During the FDM printing step, only 8 of the 11 felodipine filament formulations were suitable for 3D printing. The filaments that were successfully printed into tablets were: N1, N4, N5, N7, N8, N9, N10 and N1. The success of the printing was linked to the printing score of the used filament. Filaments N4, N5, N7, N8 and N9 that got a printability score (4 or 5) were easily used for tablet printing. Filaments N1, N10 and N11 that got a printability score (2 or 3) were used for tablet printing, but with great difficulty because of clogging problems due to filament breakage during printing. On the other hand, filaments N2, N3 and N6 that were graded a score of 1 or 2, weren't suitable at all for printing purposes. The macroscopic aspect of the 3D printed felodipine tablets, is presented in Figure 6.



	(a) N1	(b) N2	(c) N3	(d) N4	(e) N5	(f) N6	(g) N7	(h) N8	(i) N9	(j) N10/11
API (%)	5	15	25	5	15	25	5	15	25	15
Man (%)	0	0	0	7.5	7.5	7.5	15	15	15	7.5

Figure 4.
The aspect and composition of the filaments prepared through HME. The API and mannitol (Man) contents are expressed as % w/w of the mixtures used for the extrusion of the filaments

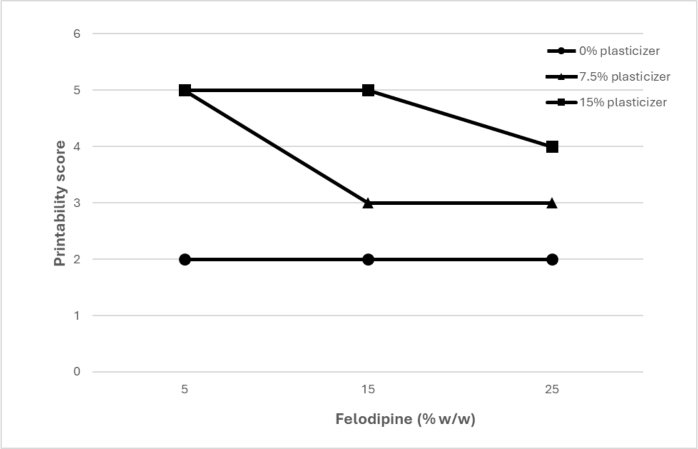


Figure 5.
The variation of the printability score depending on the composition of the filament

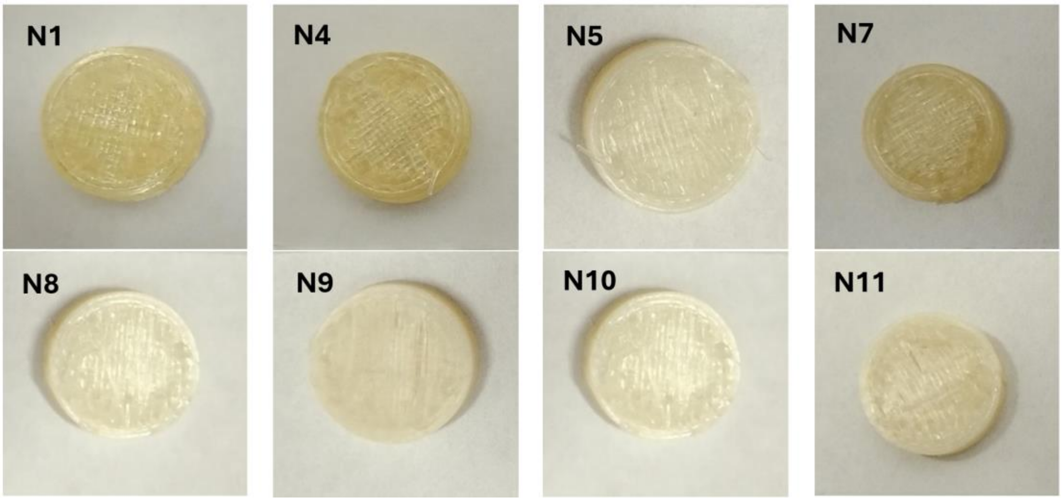


Figure 6.
3D printed tablets containing felodipine, prepared *via* FDM - macroscopic aspect

The 3D printed felodipine tablets had a uniform appearance, in terms of diameter and height. The deposited layers did not present any delaminations, empty spaces or other obvious defects in their structure.

Mechanical characterization of filaments

The mechanical properties of all the filaments prepared according to the experimental design were tested through 3P-BT and stiffness test. The mechanical tests are in-process control methods used after HME step and before FDM 3D printing, in order to evaluate the filaments in terms of adequacy for the printing step. For successful FDM 3D printing, the filaments must not be too fragile, but they must possess good flexibility and a limited degree of brittleness [25, 26]. If the filament is too fragile, printing may be blocked as the filament will not fit well in the feeding system or may even break. Filaments inappropriate in terms of stiffness are damaged by the feeding gears of the printer, their surface being scratched during the feeding step.

In our study, all the mechanical parameters determined for the filaments were evaluated as responses of the experimental design, and the results are displayed in Table II. The experimental data was fitted with multi-linear regression model, and the quality of fitting was evaluated through summary of fit parameters and Analysis of Variance (ANOVA).

Table II

The mechanical characteristics of the filaments (responses of the experimental design)

	N1	**N2**	**N3**	**N4**	**N5**	**N6**	**N7**	**N8**	**N9**	**N10**	**N11**
Y1	827.5	1175.0	1107.5	1160.0	1011.0	759.0	1198.5	933.5	736.0	1081.5	1058.5
Y2	1.9	2.2	2.1	2.9	1.5	2.5	3.6	3.7	3.1	2.6	3.0
Y3	7.5	12.5	9.9	18.5	8.9	10.3	21.6	20.0	10.3	15.6	15.6
Y4	8.1	11.5	10.9	11.4	9.9	7.4	11.7	9.1	7.2	10.6	10.4
Y5	4.1E+06	4.3E+06	4.3E+06	5.7E+06	4.2E+06	3.8E+06	4.6E+06	4.0E+06	3.3E+06	4.9E+06	3.7E+06
Y6	128.5	117.7	118.5	180.1	119.8	120.1	128.3	118.6	98.6	147.6	97.9
Y7	2.9	3.9	3.6	4.4	2.5	3.8	6.2	6.0	4.9	4.1	5.5
Y8	1.9	2.2	2.1	2.9	1.5	2.5	3.6	3.7	3.1	2.6	3.0
Y9	4.2	5.2	5.2	4.0	6.7	2.9	3.3	2.5	2.4	4.1	3.4
Y10	8680.0	7695.0	10640.0	8760.0	7370.0	5335.0	9095.0	6635.0	6205.0	8105.0	7865.0
Y11	1560.0	991.0	1741.0	2844.0	815.0	505.0	2797.0	1357.0	2106.0	1255.0	1655.0
Y12	3613.8	2231.0	4099.0	6879.0	2195.0	1742.0	6884.0	3528.0	5086.0	2739.2	4808.0
Y13	2.8E+07	1.8E+07	3.3E+07	4.1E+07	1.8E+07	2.5E+07	5.1E+07	2.4E+07	3.3E+07	4.4E+07	5.2E+07

Y1: Hardness (g); Y2: Deformation at hardness (mm); Y3: Total work (mJ) Y4: Maximum force (N); Y5: Peak stress (N/mp); Y6: Flexural stress (g/mmp); Y7: Flexural strain (%); Y8: Breaking distance (mm); Y9: Stiffness (N/mm); Y10: Hardness (g); Y11: Rigidity at 2% deformation (g); Y12: Rigidity at 4% deformation (g); Y13: Peak stress (N/mp); R^2 : The model fit ; Q^2 : The prediction precision. * p-value < 0.001

Table III

Model performance parameters of the DoE

Response		**Summary of fit**					**ANOVA**		
		R^2	Q^2	Model validity	Reproducibility		Regression model	Lack of fit	
Y_1		0.9780	0.8435	0.9325	0.9328		0.0014	0.7636	
Y_2		0.8704	0.7313	0.9283	0.7510		0.0008	0.7511	
Y_3		0.6410	0.3855	0.9100	0.3853		0.0277	0.6980	
Y_4		0.8284	0.5654	0.4714	0.9612		0.0021	0.1211	
Y_5		0.3108	-0.6803	0.8621	0.2734		0.3274	0.5765	
Y_6		0.3586	-0.2766	0.9291	-0.1960		0.1692	0.7535	
Y_7		0.7070	0.5499	0.9649	0.2219		0.0023	0.8694	
Y_8		0.8704	0.7892	0.9409	0.7510		0.0001	0.7896	
Y_9		0.7722	0.6377	0.8685	0.7962		0.0008	0.5915	
Y_{10}		0.8400	0.5007	0.9232	0.6206		0.0196	0.7359	
Y_{11}		0.6003	-0.0933	0.7354	0.6862		0.0779	0.3476	
Y_{12}		0.8605	0.4792	0.6978	0.9544		0.0141	0.2991	
Y_{13}		0.4057	-0.7085	0.7314	0.7735		0.3401	0.3420	

Y_1: Hardness (g); **Y_2**: Deformation at hardness (mm); **Y_3**: Total work (mJ) **Y_4**: Maximum force (N); **Y_5**: Peak stress (N/mp); **Y_6**: Flexural stress (g/mmp); **Y_7**: Flexural strain (%); **Y_8**: Breaking distance (mm); **Y_9**: Stiffness (N/mm); **Y_{10}**: Hardness (g); **Y_{11}**: Rigidity at 2% deformation (g); **Y_{12}**: Rigidity at 4% deformation (g); **Y_{13}**: Peak stress (N/mp); **R^2** : The model fit ; **Q^2** : The prediction precision. * p-value < 0.001

Further, for each mechanical characteristic a regression model was established using Modde 13 software. For most of the responses, the results fit well with the proposed models, as indicated by the values of the R^2 and Q^2, which were over 0.5 and 0.3, respectively, as shown in Table III. However, three of the evaluated responses did not fit well with the proposed models, as reflected by the low R^2 and Q^2 values for peak stress, determined both by 3PB-T and stiffness test, and flexural stress. Additionally, ANOVA analysis evidenced that the investigated factors, *i.e.* the concentration of felodipine and mannitol, have a significant impact on the same mechanical characteristics of the filaments for which the quality of fit was good (p-values < 0.05), and there is no lack of fit those (p-values > 0.05).

The influence of the formulation factors on the mechanical characteristics of the filaments was further evaluated using the plots of the polynomial equations' coefficients for each response, illustrated in Figure 7.

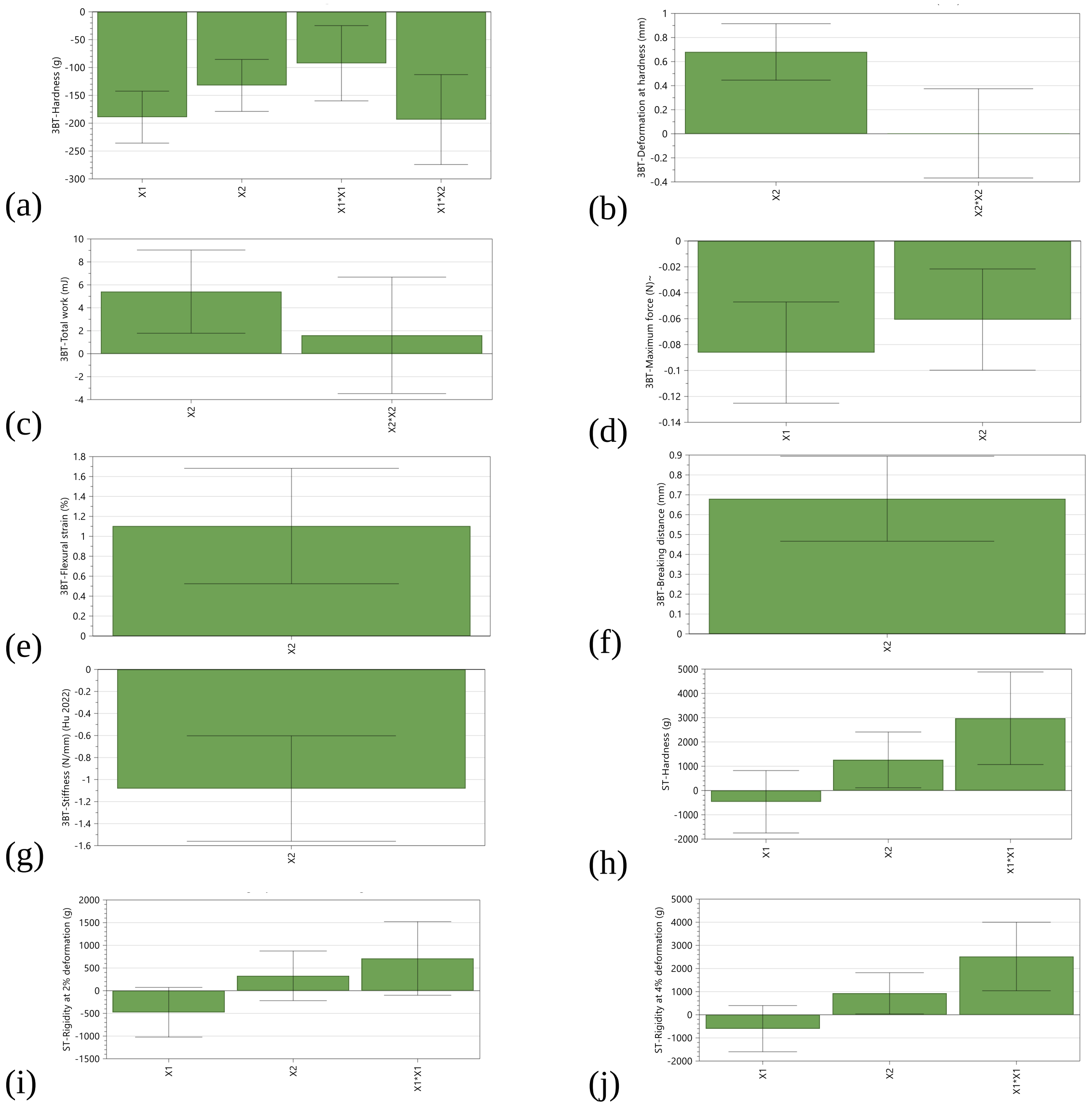


Figure 7.

Coefficient plots showing the influence of formulation on the mechanical characteristics of filaments with felodipine. (a) 3BT – hardness (g); (b) 3BT – deformation at hardness; (c) 3BT – total work; (d) 3BT – maximum force; (e) 3BT – flexural strain; (f) 3BT – breaking distance; (g) 3BT – stiffness (N/mm); (h) ST – Hardness; (i) ST – rigidity at 2% deformation; (j) ST – rigidity at 4% deformation

The concentration of felodipine had a significant negative effect on hardness (determined by 3BT), maximum force, rigidity at 2% and rigidity at 4%, meaning that the values of the mentioned parameters are significantly reduced when the concentration of felodipine is higher. This indicates that filaments with felodipine are less tough and may easily break using a lower force when the concentration of felodipine is higher. The concentration of felodipine did not positively influence any of the determined mechanical parameters, but a nonlinear influence was observed on the parameters determined by ST, *i.e.* the hardness, rigidity at 2% deformation and rigidity at 4% deformation, meaning that the force needed to achieve a certain deformation of the filaments is higher when felodipine concentration increases from 5 to 15%, but these parameters lower at higher felodipine contents. Additionally, the mechanical properties of felodipine-loaded filaments were significantly influenced by the concentration of mannitol, used as plasticizer. Thus, the concentration of plasticizer had a positive influence on deformation at hardness, total work, flexural strain, breaking distance, hardness (ST test) and rigidity at 4% deformation, showing that the increased concentration of plasticizer determines the decrease of brittleness, increased flexibility and toughness, and a higher capacity of the filament to absorb the energy before fracturing. The same observations are reflected by the negative impact of this factor on hardness (3BT test), maximum force and stiffness, indicating that the filament is less stiff when the concentration of plasticizer is higher. An interaction between the concentration of felodipine and plasticizer has been evidenced to have a significant, negative effect on hardness. Thus, at high felodipine concentration, a low mannitol ratio is needed to achieve high values (over 1100 g) of hardness (3P-BT), while to reduce this parameter to the lowest values for filaments loaded with high concentration of active substance, the concentration of plasticizer has to increase to maximum as well. When the concentration of felodipine is below 10%, the values of hardness are high, independent of mannitol concentration.

Correlation between printability and mechanical characteristics

The ultimate objective of the study was to establish a relationship between the mechanical characteristics of the filaments and their printability, being generally accepted that there is a correlation between them. To be processable through FDM, filaments should be neither too brittle nor too rigid, so that they are able to withstand the stress induced by the 3D printer driving gears during the printing step, but they must not be too soft, because they have to possess a piston-like function for the molten mass [3]. Despite the recognized relevance of the mechanical behaviour for printability, reference values of mechanical parameters that would guarantee the printability of the filaments are missing [27]. In this context, the development of predictive models is needed, to guide material selection in order to succeed in the FDM step, not only in terms of processability, but only regarding the uniformity of dosage forms characteristics [9].

For the felodipine-loaded filaments developed in this study, the variation of the mechanical parameters in function of the printability scores was evaluated through Box and Whisker Plot. To identify which mechanical parameters have a significant influence on printability score, one-way ANOVA (α = 0.05) with Tukey's post-hoc test for normally distributed data was performed. The mechanical characteristics for which a statistically significant influence on the printability score was found were deformation at hardness (mm), flexural strain (%) and breaking distance (mm). For those characteristics, the Box and Whisker Plot are displayed in Figure 8.

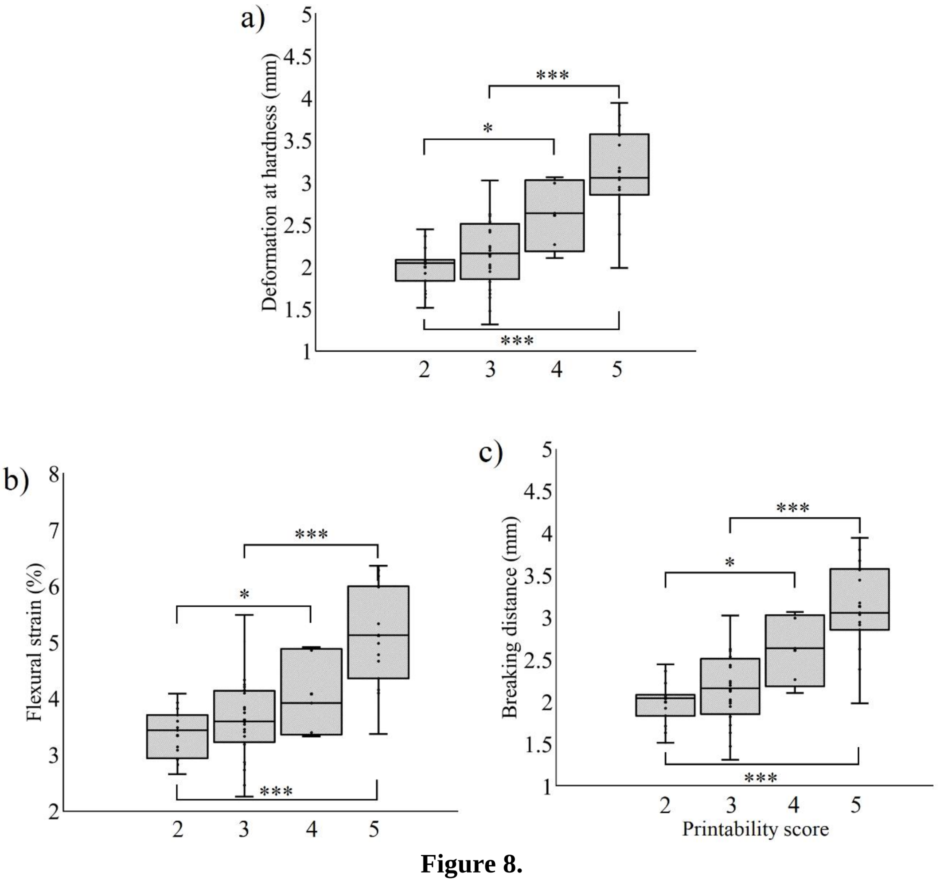


Figure 8.

Variation of mechanical properties for filaments presenting different printability scores

a) Deformation at hardness (mm); b) Flexural strain (%); Breaking distance (mm); * $p < 0.05$; *** $p < 0.001$

As seen in this figure, the values of the mechanical parameters were positively correlated with the printability score, this indicating that higher values of deformation at hardness, flexural strain and breaking distance make the filaments more suitable for printing. Another important observation is that there were significant differences in the values of the mentioned parameters for filaments belonging to different classes of printability. The most significative difference was observed between scores 2 *vs.* 5; and 3 *vs.* 5, which denotes that, based on the values of the evaluated parameters, one would be able to clearly differentiate between the filaments that “possibly can be used”/are “unlikely to print” on one hand and “very suitable for printing” filaments, on the other hand.

Table IV

Target values for deformation at hardness, flexural stress and breaking distance, to have FDM-processable filament-loaded filaments

Mechanical parameter	Determination test	Target interval
Deformation at hardness (mm)	3P-BT	2.26 – 3.94
Flexural strain (%)	3P-BT	3.39 – 6.36
Breaking distance (mm)	3P-BT	2.26 – 3.94

The plot in Figure 8 and the statistical significance of the plotted data allowed us to establish target values for the relevant mechanical parameters that would be predictive for a good processability of the filaments during FDM 3D printing, these values being presented in Table IV. This finding brings an important contribution to the field, highlighting the importance of mechanical characterization of the filaments as a tool for the selection of filaments that can be successfully processed in the three-dimensional printing stage. Other authors highlighted the importance of stiffness test for the prediction of printability [18, 28]. Stiffness and brittleness were identified in the work of Zhang *et al.* as parameters determined by stiffness test that define the printability. Our results indicate that 3P-BT is more useful than the previously mentioned test for predicting processability through 3D printing. The same test has been found as suitable predictor of printing ability for filaments with paracetamol, extruded using a mixture of polymers. For those filaments, the maximum displacement and the maximum force were reported as parameters that were correlated with the printing behaviour, while the maximum stress was not [18]. Correlating our findings with those reported in the literature, we can observe that breaking distance is frequently reported as indicator of printability, as brittleness or maximum displacement indicate the same characteristic, the flexibility of the filament. Taking into account that the data analysis in our study revealed that only the concentration of the plasticizer had a significant impact on the breaking distance, we may say that all filaments that are well plasticized will display high breaking distance and will be very suitable for printing, explaining thus the importance of this parameter for printability prediction.

However, there is a need for further investigation and standardization in the field of mechanical tests applied and relevant parameters, for more accuracy in printability prediction.

Conclusions

This study brings an important contribution to the development of three-dimensional printing through FDM as drug manufacturing technology, a technique that allows obtaining pharmaceutical dosage forms for which there are no official quality standards and control methods. Due to the complexity of this manufacturing technology, combining HME and FDM, the success is guarantee by appropriate selection of the materials and working conditions, but in process controls are essential for the success of the process and the quality of the product. Our study demonstrated the impact of the formulation on the processability of the filaments through FDM. Finally, this work led to the establishment of target values for several mechanical characteristics of felodipine-loaded filaments that can guarantee that the filaments will be processable in the 3D printing step and shows that the 3P-BT can be used as screening test to predict further printing ability of felodipine-loaded filaments.

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.

References

1. Sultana N, Ali A, Waheed A, Aqil M, 3D Printing in pharmaceutical manufacturing: Current status and future prospects. Mater. *Today Commun.*, 2024; 38: 107987.
2. Kozakiewicz-Latała M, Junak A, Złocińska A, Pudło W, Prusik K, Szymczyk-Ziółkowska P, Karolewicz B, Nartowski KP, Adjusting the melting point of an Active Pharmaceutical Ingredient (API) via cocrystal formation enables processing of high melting drugs

via combined hot melt and materials extrusion (HME and ME). *Addit Manuf.*, 2022; 60A: 103196.

3. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, Alhnan MA. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. *Int J Pharm.*, 2016; 513(1-2): 659-668.
4. Solanki NG, Tahsin M, Shah AV, Serajuddin ATM, Formulation of 3D printed tablet for rapid drug release by fused deposition modeling: Screening polymers for drug release, drug-polymer miscibility and printability. *J Pharm Sci.*, 2018; 107(1): 390-401.
5. Feng S, Bandari S, Repka MA. Investigation of poly (2-ethyl-2-oxazoline) as a novel extended release polymer for hot-melt extrusion paired with fused deposition modeling 3D printing. *J Drug Deliv Sci Technol.*, 2022; 74: 103558.
6. Mohamed OA, Masood SH, Bhowmik JL, Optimization of fused deposition modeling process parameters: a review of current research and future prospects. *Adv Manuf.*, 2015; 3(1): 42
7. Goole J, Amighi K, 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. *Int J Pharm.*, 2016; 499: 376-394.
8. Parulski C, Jennotte O, Lechanteur A, Evrard B, Challenges of fused deposition modeling 3D printing in pharmaceutical applications: Where are we now? *Adv Drug Deliv Rev.*, 2021; 175: 113810.
9. Censi R, Gigliobianco MR, Casadidio C, Di Martino P, Hot Melt Extrusion: Highlighting Physicochemical Factors to Be Investigated While Designing and Optimizing a Hot Melt Extrusion Process. *Pharmaceutics*, 2018; 10(3): 89.
10. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, Alhnan MA, Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. *Int J Pharm.*, 2016; 513: 659-668.
11. Kempin W, Franz C, Koster LC, Schneider F, Bogdahn F, Weitschies W, Seidlitz A. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. *Eur J Pharm Biopharm.*, 2017; 115: 84-93.
12. Prasad E, Islam MT, Goodwin DJ, Megarry AJ, Halbert GW, Florence AJ, Robertson J, Development of a hot-melt extrusion (HME) process to produce drug loaded Affinisol™ 15LV filaments for fused filament fabrication (FFF) 3D printing. *Adv Manuf.*, 2019; 29: 100776.
13. Palekar S, Nukala PK, Mishra SM, Kipping T, Patel K, Application of 3D printing technology and quality by design approach for development of age-appropriate pediatric formulation of baclofen. *Int J Pharm.*, 2019; 556: 106-116.
14. Azad MA, Olawuni D, Kimbell G, Badruddoza AZM, Hossain MS, Sultana T, Polymers for Extrusion-Based 3D Printing of Pharmaceuticals: A Holistic Materials-Process Perspective. *Pharmaceutics*, 2020; 12: 12020124.
15. Bandari S, Nyavanandi D, Dumpa N, Repka MA, Coupling hot melt extrusion and fused deposition modeling: Critical properties for successful performance. *Adv Drug Deliv Rev.*, 2021; 172: 52-63.
16. Kreft K,Lavric Z, Centa UG, Mihelcic M , Peres LS, Dreu R. Correlating mechanical and rheological filament properties to processability and quality of 3D printed tablets using multiple linear regression. *Int J Pharm.*, 2024; 651: 123719.
17. Ponsar H, Wiedey R, Quodbach J, Hot-Melt Extrusion Process Fluctuations and Their Impact on Critical Quality Attributes of Filaments and 3D-Printed Dosage Forms. *Pharmaceutics*, 2020; 12(6): 511.
18. Xu P, Li J, Meda A, Osei-Yeboah F, Peterson ML, Repka M, Zhan X, Development of a quantitative method to evaluate the printability of filaments for fused deposition modeling 3D printing. *Int J Pharm.*, 2020; 588: 119760.
19. Spoerk M, Savandaiah C, Arbeiter F, Sapkota J, Holzer C, Optimization of mechanical properties of glass-spheres-filled polypropylene composites for extrusion-based additive manufacturing. *Polym Compos.*, 2017; 40(2): 638-651.
20. Alhijjaj M, Belton P, Qi S, An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing. *Eur J Pharm Biopharm.*, 2016; 108: 111-125.
21. Iovanov RI, Porfire AS, Crisan AG, Dobre AA, Iurian SM, Rus LM, Casian T, Tomuta I, 3D printing of prolonged-release oral solid dosage forms containing felodipine. *Farmacia*, 2023; 71(3): 480-490.
22. Parulski C, Gresse E, Jennotte O, Felten A, Ziemons E, Lechanteur A, Evrard B, Fused Deposition Modeling 3D Printing of Solid Oral Dosage Forms Containing Amorphous Solid Dispersions: How to Elucidate Drug Dissolution Mechanisms through Surface Spectral Analysis Techniques?. *Int J Pharm.*, 2022; 626: 122157.
23. Zhang J, Xu P, Vo AQ, et al. Development and evaluation of pharmaceutical 3D printability for hot melt extruded cellulose-based filaments. *J Drug Deliv Sci Technol.*, 2019; 52: 292-302.
24. Iovanov RI, Porfire AS, Crisan AG, Dobre AA, Iurian SM, Rus LM, Casian T, Tomuta I, 3D printing of prolonged-release oral solid dosage forms containing felodipine. *Farmacia*, 2023; 71(3): 480-490.
25. Lamprou A, Mora-Castaño G, Millán-Jiménez M, Linares V, Caraballo I, Assessment of the Extrusion Process and Printability of Suspension-Type Drug-Loaded Affinisol TM Filaments for 3D Printing. *Pharmaceutics*, 2022; 14: 871.
26. Crișan AG, Iurian S, Porfire A, Rus LM, Bogdan C, Casian T, Lucacel RC, Turza A, Porav S, Tomuță I, QbD guided development of immediate release FDM-3D printed tablets with customizable API doses. *Int J Pharm.*, 2022; 613: 121411.
27. Fuenmayor E, Forde M, Healy A, Devine DM, Lyons JG, McConville C, Major I, Material considerations for fused-filament fabrication of solid dosage forms. *Pharmaceutics*, 2018; 10: 10020044.
28. Zhang J, Feng X, Patil H, Tiwari RV, Repka MA, Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. *Int J Pharm.*, 2017; 519: 186-197.