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Assessment of extrusion process of drug-loaded filaments for 3D printing: metformin and Affinisol™

Mora Castaño Gloria[1], Millán Jiménez Mónica *[1], Caraballo Isidoro[1]

[1] Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla.
*Correspondencia: momillan@us.es

1. Introduction

3D printing technology enables the design of new drug delivery systems using polymers which can be molten. Most studies dealing with drug-loaded filaments report two main situations: in the first one, drugs and excipients melting points are similar [1], whereas in the second one drug melting point is much higher than excipient melting point. For this second case, we have studied some parameters of blends related with the extrusion process. Moreover, some parameters of drug-loaded filaments, containing metformin as model drug and a HPMC as main carrier, were also studied to know their printability.

2. Materials and methods

2.1. Materials

The filaments were made with HPMC (Affinisol™ 15 cP), donated by The Dow Chemical Company (Midland, MI); metformin (MF) was donated by Pharmhispania S.A. Pharmaceuticals (Barcelona, Spain); magnesium stearate (ES) and polyethylene glycol 6000 (PEG 6000). Affinisol™ is a cellulose derivative which can be molten (melting point 135 ºC-200 ºC). Metformin's melting point is 270 ºC. ES was used as a lubricant. PEG 6000 was used as plasticizer [2].

2.2. Methods

2.2.1. Extrusion process

A single-screw filament extruder (Noztek Pro Desktop Filament Extruder, Noztec, UK) was employed to obtain the drug loaded filaments (extrusion temperature 150 ºC). Filaments with varying drug load (10 %, 20 %, 30 %, 40 %, 50 % and 60 % w/w) were performed with a percentage of PEG 6000 and ES 5 % w/w each one. Residence time and flow speed were parameters employed to evaluate the behaviour of the blends in the extrusion process.

2.2.2. Mechanical and physical properties testing of filaments

Three-point bend test was applied to measure the brittleness of filaments using a Texture Analyser TA-XT (Stable Micro Systems, Godalming, UK).

The irregularity degree of the filaments surface could be highly abstracted into a fractal dimensional value (Df). Images of filaments surface were captured with Nikon SMZ800N. Matlab R2020a was employed to perform the box counting fractal analysis.

2.2.3. Homogeneity studies

Samples of filaments were dissolved in 200 ml of dissolution medium (pH=1.2) at 37 ± 0.5 ºC, under magnetic stirring until complete dissolution. Aliquots (5 ml) were then filtered (0.45 mm membrane filters) and diluted (1:10). Absorbance of these solutions was measured at 230 nm using UV Visible spectrophotometry (Agilent 8453).

3. Results and Discussion

Behaviour of blends in the extrusion process and final filaments (diameter 1.71 ± 0.04 mm) were

Table 1. Extrusion process parameters and final filament parameters of blends containing 5 % of ES and PEG 6000 from 10 % to 60 % MF.

Blend	MF (%)	AFF (%)	Residence time (min)	Flow speed (cm/min)	Brittleness (kg/mm^2*%)	Fractal dimension	Drug content (%)
60A	60	30	12.00±0.00	2.71±0.00	5.70±0.65	1.035±0.006	65.99±4.39
50A	50	40	7.00±0.00	6.63±2.28	10.15±1.89	1.029±0.004	51.22±4.66
40A	40	50	5.75±0.96	6.87±4.77	15.93±3.55	1.028±0.006	38.44±1.74
30A	30	60	6.40±1.52	5.07±3.75	44.03±5.22	1.023±0.006	30.88±2.07
20A	20	70	7.83±2.32	4.77±4.14	57.63±11.36	1.022±0.008	22.23±0.27
10A	10	80	7.00±1.73	1.65±1.32	65.81±11.35	1.032±0.005	9.76±0.04

evaluated. As we can observe in Table 1, blend 10A shows one of the lowest flow speeds. This suggests 10 % of drug is insufficient to make the extrusion properly due to low viscosity of the blend. Blend 60A shows the longest residence time and one of the lowest flow speeds. This might be due to the high amount of not molten drug contained in these blends which was hindering the extrusion process. The results suggest a threshold for the extrusion of blends containing not molten drugs and AFF at 60 % drug load with percentages of 5 % of ES and PEG 6000. This result is analogous

to the previously observed in the granulation process. The mean torque intensity of a mixer torque rheometer follows a curve as a function of the liquid/solid ratio, which describes the mechanism of rheological variations during the sample wetting process [3]. Belem & Ferraz, 2020 [4] reported rheological profiles showing a curve with the maximum peak at 0.4 mL/g binder ratio. This curve decreased after this maximum. This agrees with our results as 60A contains 40 % of the main carrier together with ES and PEG 6000 and it is the blend which resists more the extrusion process and complicates it.

Regarding to the brittleness of filaments, the higher the value showing in the table, the lower the brittleness. From 10A to 30A, brittleness is lower than filaments from 40A to 60A. That suggests the more AFF in blends, the lower brittleness.

The surface roughness, using Df parameter, shows a turning point given that it decreases from 10 % to 30 % of drug but increases from 30 % to 60 %. Thus, the not molten drug seems to contribute to the stiffness and consistency of the filament. Therefore, it would be needed over 10 % of drug to obtain a uniform texture on the surface of filament. Prasad et al., 2019 [5] has also reported that filaments above 25 % concentration of paracetamol (which did not melt at extrusion temperature) with Affinisol 15cP as carrier polymer were much softer than those with lower drug load. However, the smoothness of filaments decreased while the drug load increased.

The uniformity of filaments is one of the key parameters for the further development of successful 3D printed systems. Table 1 shows the concentrations of MF in the filaments. Filaments showed good agreement with the theoretical value. Thus, demonstrating that homogeneous mixtures were processed.

4. Conclusions

Summarizing parameters assessed in this study we could conclude blends containing more than 50 % of not molten drug and less than 40 % of Affinisol are not suitable for extrusion process neither to obtain drug-loaded filaments with physical and mechanical characteristics to be used in 3D printing.

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References

1. Huang S, et al. Processing thermally labile drugs by hot-melt extrusion: The lesson with gliclazide. Eur J Pharm Biopharm. 2017;119:56-67.

2. Goyanes A, et al. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. Int J Pharm. 2017;527:21-30.

3. Hancock BC, York P, Rowe RC. An assessment of substrate-binder interactions in model wet masses. 1: Mixer torque rheometry. Int J Pharm. 1994;102(1–3):167–76.

4. Belem, BR, Ferraz, HG. Rheological profile in mixer torque rheometer of samples containing furazolidone and different binders. Chem Eng Res Des. 2020;160:533–9.

5. Prasad E, et al. Development of a hot-melt extrusion (HME) process to produce drug loaded AffinisolTM 15LV filaments for fused filament fabrication (FFF) 3D printing. Addit Manuf. 2018;29:100776.

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