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Review

Hot-melt extrusion – filament manufacturing coupled with fused deposition modeling for 3D printed pharmaceuticals - a brief review

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Abstract

3D printing, also known as additive manufacturing, is conquering many industrial fields, just as the pharmaceutical industry. While there are several types of additive manufacturing processes, the fused deposition modeling is the most outstanding in the pharmaceutical field. Fused deposition modelling uses filaments for printing. These filaments are made of polymers with diverse properties, suitable for containing active pharmaceutical ingredients for various usages. These filaments can be produced by the hot-melt extrusion (HME) process, which the pharmaceutical field already uses for several formulations. In order to get a usable filament, we require more machines than just the extruder. Through the process, the feeder, conveyor, and winder machines are necessary to get the desired homogeneity, filament diameter, and a ready-to-use filament roll to couple hot melt extrusion with fused deposition modeling easily. Polymers for pharmaceutical usage already exist, including polyethylene glycols, polylactic acids, hydroxypropyl cellulose, and many more. Finding polymers that have the appropriate rheological properties, heat, and chemical stability to apply in hot-melt extrusion and fused deposition modeling process, turned out to be a challenging, but not impossible task. In conclusion, hot melt extrusion is a reliable method to produce polymer filaments for fused deposition modeling, which is suitable for printing pharmaceuticals. However, knowledge in this field is continuously expanding, thanks to the efforts of researchers worldwide.

1. Introduction

Nowadays, 3D printing technology is one of the most significant parts for the industries and researchers to find the hidden and yet unexploited possibilities in many fields. Its history began when Dr. Hideo Kodama made the first 3D printed object in the 1980s. However, it must be noted that the first 3D printer was officially created by Charles Hull in 1984[1]. 3D printers are used to make objects that have unique properties, and would be hard to make through hands or with mass production. The manufacturing provides personalized medications in a relatively simple and cheap process. In the beginning, the 3D Systems™ and Stratasys™ companies ruled the field of additive manufacturing[2]. Later, the meaning of 3D printing evolved to a more complex and diverse field, becoming a new type of additive manufacturing process, where we can choose from numerous types of similarly unique technologies to make objects with peculiar parameters, like powder bed fusion (PBF)[3], selective laser sintering (SLS)[4], stereolitography (SLA)[5], and fused deposition modeling (FDM)[6].

FDM is one of the most famous methods among additive manufacturing processes. Most frequently, the FDM is coupled with hot-melt extrusion (HME) to manufacture the active pharmaceutical ingredients (APIs) containing polymeric filaments for FDM-type 3D printing[7,8]. This brief review will discuss the HME process, its properties, and some polymers that can be utilized.

2. Materials and methods

2.1 Importance of HME

HME has already been successfully applied in many industrial areas like rubber, food, and plastic. It also entered the pharmaceutical industry as it can be used for the manufacturing of granules and pellet formulations. It is also able to manufacture infinite filament, as detailed in the article.

There are several advantages of applying HME for making drug delivery systems. Process automation helps to reduce labor costs and capital investments. Due to the several non- or poorly water-soluble APIs, it is a challenging task to make homogeneous formulations, as poor water solubility also affects the bioavailability for gastrointestinal applications. However, HME is capable of making carrier matrixes and solid dispersions with the appropriate polymer and API combination. HME is easily

coupled with high-pressure homogenization using carbon dioxide or ethanol to produce porous extrudates, and is also a helpful method to produce filaments for 3D printing.

The main disadvantages of this technique are the high temperature and the shear stress during the extrusion process. The APIs and polymers exposed to these physical effects tend to go through degradation, amorphization and/or recrystallization. In order to avoid these destructive effects, setting the optimal temperature and choosing the appropriate polymers and excipients are crucial[9].

2.2 Quality by Design approach in HME

Quality by design is an approach that highlights the importance of all variables that affect the quality of the product. Based on Yu et al., in the case of HME, the input material attributes, also known as critical material attributes (CMAs), are the following: particle size and distribution, fines/oversize, particle shape, melting point, density, solid form or polymorphism, and moisture content. The critical process parameters (CPPs) are the following: screw design (twin/single), screw speed, screw opening diameter (mm), solid and liquid feed rates, feeder type/design, feed rate, number of zones, zone temperatures, and chilling rate. Based on these two groups, the affected quality attributes are the following: extrudate density, length, thickness, diameter, polymorphic form and transition, content uniformity, and throughput. All the above-mentioned parameters are important because the continuous process must be operated in a space of optimized parameters to ensure the targeted quality of the product[10].

2.3. Machines and properties

A lot of manufacturers can provide HME based on whether we want to produce at lab, pilot or industry level. The extruders can contain one or two screw and in case of two-screw it can be co- or reverse rotating. The machines have unique properties like the number of heating zones, whether cooling is provided, rotation speed, screw arrangement, and so on[9].

2.3.1 Quick TS12 Feeder

This machine is a twin-screw feeder. It is able to supply the powders at several grams per hour. The feeder provides continuous component flow and homogeneous screw filling, helping the solid materials to pass between the screws[11]

Figure 1.: Quick TS12 Feeder

2.3.2 Quick TS16 Extruder

After the feeder mixes the solid components, the mixed powder enters the hopper of the extruder. This twin-screw extruder is a medium-sized machine. The equipment has two segmented screws rotating in the same direction. The rotation speed (rpm) and heating parameters in five different zones can be changed and configured at any time. The screws are interpenetrating, so it contains self-cleaning parts. The polymer mixture is pressed through a heated die (zone 5), where the final or semi-final product leaves the extruder.

-Performance: 0,5-12 kg/h
-Rotation per minute: 5-900 rpm
-Twin-screws length/diameter: 400 mm / 16mm
-Zone temperature: ambient-150 °C, additional cooling option (12)

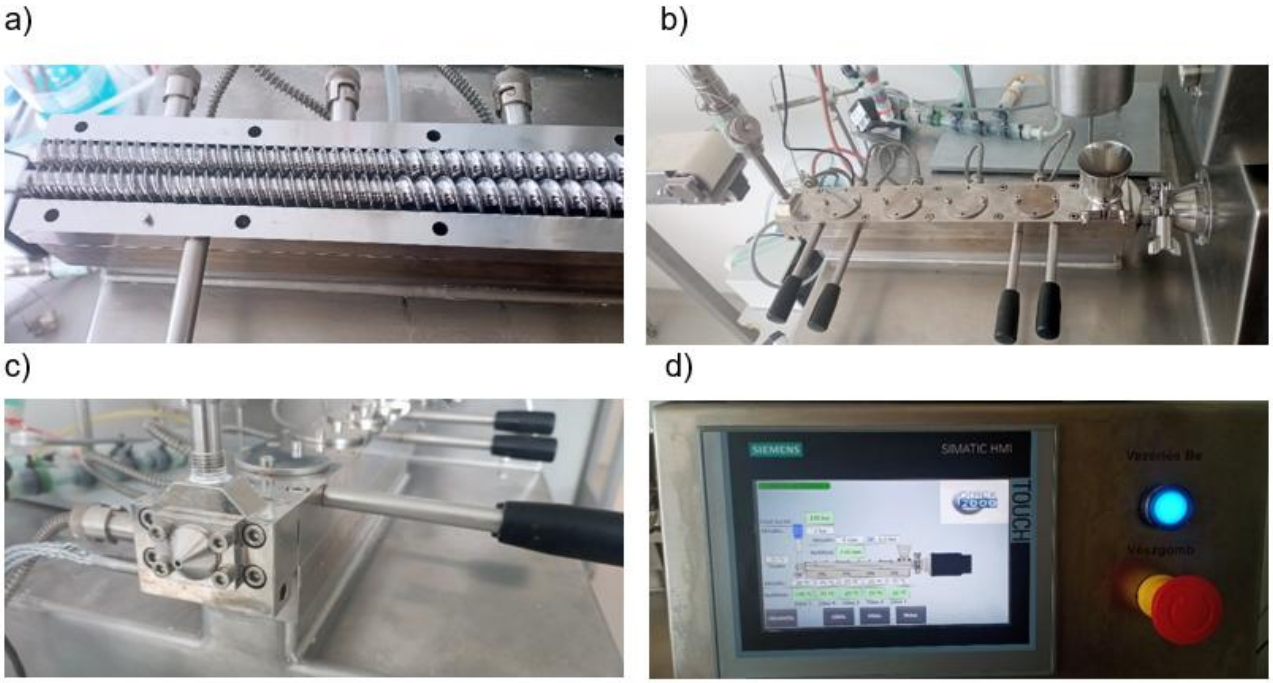

Figure 2.: Extruder parts: a) twin-screws, b) ready to use closed extruder chamber with thermometer, c) extruder nozzle, d) extruder's control touch panel

2.3.3. Quick CON1500 Conveyor Belt

After the filament is extruded, it must be conveyed from the nozzle of the extruder in order to get an optimal filament diameter. It is movable due to the four rotary-brake wheels. The height of the conveyor belt is set to match the TS16 extruder. The conveyor belt is heat-resistant (max. 170 °C) and made from FDA-approved materials, which is important to ensure mass transfer on an inert surface.

-Belt width/thickness: 100mm / 2,5mm
-Cylinder axis distance: 1500mm (13)

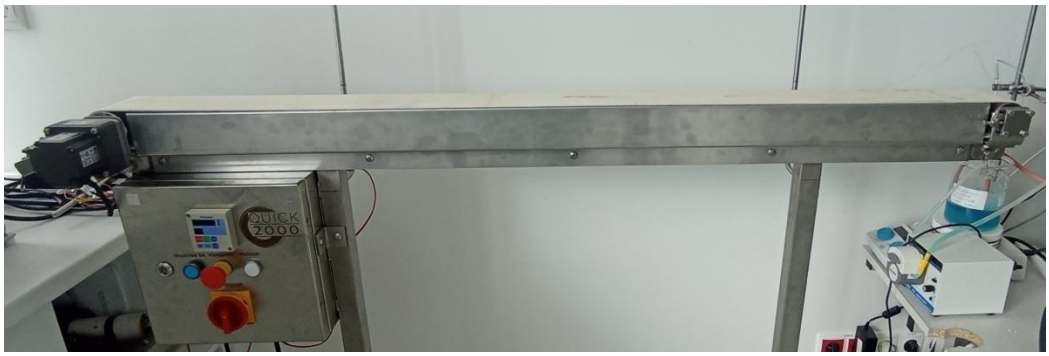

Figure 3.: Quick CON1500 Conveyor

2.3.4 Quick Wind50 Winding machine

This machine is able to wind the extruded filament products that are coming from the conveyor belt and follow the movements of the filament. When the filament is in a loose state, the winder starts, and when it gets tight, the motor stops. This mechanism helps to maintain the diameter of the produced filamentpreventing distortion and rupture. The filament diameter is measured by a digital caliper[14].

Figure 4.: Quick Wind50 Winding machine

2.4 HME process

The polymers are usually extruded with a co-rotating twin-screw hot-melt extruder (HME)[15] The twin-screws are designed to convey and mix the added materials. This design helps to produce a homogeneous mixture in the case of more than one component[16] During the process, the applied heat and the shear stress melt or soften the polymers. The temperature during extrusion must be chosen to consider the rheological and physico-chemical properties of the selected polymer. If the temperature is too low or even too high, clogging of the nozzle might occur[17,18].The temperature during the extrusion is usually above 100°C[19].

The semi-solid melted product is then pushed through a nozzle, and it solidifies on the conveyor belt. Ventilators could be used to speed up the process. The diameter of the filament is a critical material parameter as it must fit the inlet of the printing head used for the FDM 3D printer. To set the thickness, an appropriate belt speed must be maintained to achieve the desired filament diameter. During the material transfer on

the belt, the filament cools down, and then it is ready to wind onto a roll[20].Enlist and summarize the CMAs of the filaments for 3D printing!

2.5 Coupling HME and Fused Deposition Modelling (HME-FDM)

Additive manufacturing, or 3D printing, has many different technologies. However, FDM is one of the most preferred technologies for 3D printing. First, a 3D digital model should be designed with a computer-aided design (CAD) software, as numerous platforms are available, but regarding the validation, the Good Automated Manufacturing Practice (GAMP) 5th Edition is the guideline[21]. Then, after uploading the data to the 3D printer, the printing parameters should be determined, and the last step is the actual 3D printing. It applies the filament material layer by layer, building the previously designed object[22]. The filaments, as previously mentioned, can be produced with HME using a continuous filament production technique, which allows the filaments to already contain the API. Combining these two technologies, we have the opportunity to produce uniquely shaped API containing drug delivery systems. We must carefully consider the polymeric and other components to ensure they can withstand the temperature and stress from both the HME and the FDM printhead, in order to achieve the desired shape and quality. The main issue is the limited number of polymers and APIs that are fit to be involved in pharmaceutical applications made with HME-FDM[23].

2.5.1 Polymers for HME-FDM

A significant obstacle was to find polymers that can be formulated into filaments for pharmaceutical use, to apply it to FDM 3D printing[24]. In the pharmaceutical industry, they are mainly used for different purposes, such as lubricants, fillers, binders, solubility enhancers, and coating materials. As time passed, polymers became one of the key components in modified drug delivery systems and customized systems as well[25]. For HME and FDM, the thermoplastic or thermosoftening polymers are the most suitable, which have long linear chains and are only held together by weak chemical bonds[26]. Đuranovic et al. used paracetamol as model drug, while using different polymers including polycaprolactone (PLC), polyethylene oxide (PEO) 200 K, PEO 100 K, and Lauroyl PEG-32 glycerides, while others used polylactic acid (PLA), ethyl cellulose (EC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), polypropylene (PP), polyethylene terephthalate (PET), hydroxypropyl methylcellulose

acetate succinate (HPMCAS), methacrylic acid copolymer Eudragit L 100-55, polyvinyl alcohol (PVA), and polyethylene glycol (PEG) for other formulations[8,27–29].

3. Discussion

HME and FDM could complement each other when it comes to personalized medication. With the proper API concentration, polymer, and unique digital design, an adequate drug delivery system can be manufactured, ensuring the needs of the patient, and might substitute for an invasive or complex therapeutic regime. The personalization can increase patient compliance and reduce the cost of pharmaceutical production. With proper calculations, additive-manufactured medications can also help to prevent overdosing by setting the shape and size of the printed drug delivery system, thereby avoiding serious side effects and drug poisoning. The opportunity for unlimited pharmaceutical shape design also opens the door for HME-FDM to produce API-containing pharmaceutical implants providing slow release for a more extended time.

In a research, ten different polymeric components were examined. A counter-rotating twin-screw extruder was used. The Kollicoat® IR (KIR) + 12% glycerol formulation contained furosemide as the API. The others were PEO, HPMC + 5% PEG 400, HPC, PVA + 5% glycerol, Soluplus® + 10% PEG 400, HPMC acetate succinate + 5% PEG 8000, Eudragit® L + 20% triethyl citrate, Eudragit® RL + 15% triethyl citrate and EC + 10% triethyl citrate. All formulations required different printing temperatures (°C), screw speeds (rpm) and torque (N x cm). Based on the results, all of it is suitable for 3D printing, but the strict quality standard required for industrial feasibility hasto be taken into consideration for future use[8].

In a publication, polycaprolactone and different concentration of indomethacin (5%, 10%, and 15%) were used for manufacture of an implantable medical device. In this case, higher drug loading resulted in poorer quality. Lower drug content helped not only in the quality but also in on the dissolved amount in the polymer. This is the first article that states that the diameter of the extruded filament was adjusted by changing the speed of the conveyor belt[20].

In the article by Zhang et al., the most important data is that a co-rotating twin-screw extruder with 11 mm diameter screw and standard screw configuration was used. The used temperature was 180 °C for HPMC, while it ranges in all other cases 140 to160 °C accross all zones. As a reference polymer, PLA was chosen, and the API

was extruded with HPC LF, HPC EF, HPMC E5, EC N14, Soluplus, and Eudragit L100 in a 3:7 ratio, and some combination even added a disintegrant in 5%. The article mentioned that the screw speed was 50 rpm. The authors found all formulations appropriate for 3D printing, even though the 3-point bend test showed that some of them are too soft or brittle, which will not be adequate for further processing. Formulations with HPMC and EC alone, HPMC in combination with EC or HPC LF, and EC in combination with Eudragit were adequate. Based on the dissolution test, HPMC and EC together showed the fastest dissolution profile, followed by HPMC with HPC LF, then HPMC with HPC EF, and EC with Eudragit, which released only 8.9% of the API within 24 hours[7].

Another research group also highlighted that the extruded filament was adjusted by changing the speed of the conveyor belt as a fine-tuning method. In this article, thirteen different polymers were manufactured, and eight were successfully processed into tablets. A good correlation was observed between the tablet size and the mass of the tablet, indicating easy adjustment of the dose. The authors suggest the development of a software to calculate the required drug dosage form[19].

A research group intended to make two different filaments. The core filament consisted of 55% PVA, 13% mannitol, 7% sodium chloride, and 20% diltiazem. Mannitol was used as both a plasticizer and an osmotic agent, and sodium chloride was added to enhance the osmotic properties. The shell filament was made from cellulose acetate (CA) and 25 % triethyl citrate as a plasticizer. From these two filaments, three different digital designs were made to determine the effect on the 3D printing process. The first formulation has no top, the second formulation had an imported hole and one linear cavity, and the third formulation had two linear cavities. The first formulation showed an immediate release profile with a quadratic kinetic, and the other two showed delayed release, but the API dissolution started faster from the third formulation, which consisted of two linear cavities[30].

Based on previous results, it can be stated that HME should be run at temperatures 20-40 °C above the melting point of the polymer. Furthermore, the API melting point has to be taken into consideration. It can be challenging to achieve mass uniformity in the feeder of the extruder in the case of some polymers as PCL[10].

Also, 70% paracetamol containing filaments were not possible to be made, in case of PEO, a maximum of 60% API could be used, and higher amounts of API required a higher amount of extrusion temperature. Also, the type and quantity of different

surfactants require different parameters. In all cases, the chemical stability has to be examined[31].

With the combination of HME and FDM printing, a special floating preparation could be manufactured without the need for an additional technique. With the proper amount of materials, with the use of appropriate printing parameters, the STL file design and 3D printing parameters, the drug release could be adjusted as needed [17].

As the mentioned articles show, the use of FDM-HME is versatile, and multiple publications have been made in this field in the last decades. All publications have confirmed that the CMAs and the CPPs are essential because the continuous process must be operated within an optimized parameter to ensure the targeted quality of the product.

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References

1. Gokhare VG, Raut DDN. A Review paper on 3D-Printing Aspects and Various Processes Used in the 3D-Printing. Int J Eng Res. 2017;6(06).
2. Savini A, Savini GG. A short history of 3D printing, a technological revolution just started. In: 2015 ICOHTEC/IEEE International History of High-Technologies and their Socio-Cultural Contexts Conference (HISTELCON) [Internet]. Tel-Aviv, Israel: IEEE; 2015 [idézi 2025. április 14.]. o. 1–8. Elérhető: https://ieeexplore.ieee.org/document/7307314/
3. Dev Singh D, Mahender T, Raji Reddy A. Powder bed fusion process: A brief review. Mater Today Proc. 2021;46:350–5.
4. Gueche YA, Sanchez-Ballester NM, Cailleaux S, Bataille B, Soulairol I. Selective Laser Sintering (SLS), a New Chapter in the Production of Solid Oral Forms (SOFs) by 3D Printing. Pharmaceutics. 2021. augusztus 6.;13(8):1212.
5. Huang J, Qin Q, Wang J. A Review of Stereolithography: Processes and Systems. Processes. 2020. szeptember;8(9):1138.
6. Solomon IJ, Sevvel P, Gunasekaran J. A review on the various processing parameters in FDM. Mater Today Proc. 2021. január 1.;37:509–14.

7. 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. március;519(1–2):186–97.
8. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. Int J Pharm. 2016. július 25.;509(1):255–63.
9. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. Expert Opin Drug Deliv. 2016. március 3.;13(3):451–64.
10. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, és mtsai. Understanding Pharmaceutical Quality by Design. AAPS J. 2014. július;16(4):771–83.
11. QUICK 2000 Kft. TS12 Feeder Gépkönyv. Köt. 1. attachment. Tiszavasvári; 2021. 12 pages.
12. QUICK 2000 Kft. TS16 Extruder Gépkönyv. Köt. 2. attachment. Tiszavasvári; 2021. 40 pages.
13. QUICK 2000 Kft. CON1500 Conveyor Gépkönyv. Köt. 3. attachment. Tiszavasvári; 2021. 11 pages.
14. QUICK 2000 Kft. Wind50 Winding machine Gépkönyv. Köt. 4. attachment. Tiszavasvári; 2021. 9 pages.
15. Chaudhari VS, Malakar TK, Murty US, Banerjee S. Extruded filaments derived 3D printed medicated skin patch to mitigate destructive pulmonary tuberculosis: design to delivery. Expert Opin Drug Deliv. 2021. február 1.;18(2):301–13.
16. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing. J Controlled Release. 2017. december;268:40–8.
17. Zhao X, Wei W, Niu R, Li Q, Hu C, Jiang S. 3D Printed Intragastric Floating and Sustained-Release Tablets with Air Chambers. J Pharm Sci. 2022. január;111(1):116–23.
18. Reddy Dumpa N, Bandari S, A. Repka M. Novel Gastroretentive Floating Pulsatile Drug Delivery System Produced via Hot-Melt Extrusion and Fused Deposition Modeling 3D Printing. Pharmaceutics. 2020. január 8.;12(1):52.
19. Öblom H, Zhang J, Pimparade M, Speer I, Preis M, Repka M, és mtsai. 3D-Printed Isoniazid Tablets for the Treatment and Prevention of Tuberculosis—Personalized Dosing and Drug Release. AAPS PharmSciTech. 2019. február;20(2):52.
20. Holländer J, Genina N, Jukarainen H, Khajeheian M, Rosling A, Mäkilä E, és mtsai. Three-Dimensional Printed PCL-Based Implantable Prototypes of Medical Devices for Controlled Drug Delivery. J Pharm Sci. 2016. szeptember;105(9):2665–76.
21. Pedro F, Veiga F, Mascarenhas-Melo F. Impact of GAMP 5, data integrity and QbD on quality assurance in the pharmaceutical industry: How obvious is it? Drug Discov Today. 2023. november;28(11):103759.
22. Cailleaux S, Sanchez-Ballester NM, Gueche YA, Bataille B, Soulairol I. Fused Deposition Modeling (FDM), the new asset for the production of tailored medicines. J Controlled Release. 2021. február;330:821–41.
23. Tan DK, Maniruzzaman M, Nokhodchi A. Advanced Pharmaceutical Applications of Hot-Melt Extrusion Coupled with Fused Deposition Modelling

(FDM) 3D Printing for Personalised Drug Delivery. Pharmaceutics. 2018. október 24.;10(4):203.

24. Azad MA, Olawuni D, Kimbell G, Badruddoza AZM, Hossain MdS, Sultana T. Polymers for Extrusion-Based 3D Printing of Pharmaceuticals: A Holistic Materials–Process Perspective. Pharmaceutics. 2020. február 3.;12(2):124.

25. Goole J, Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. Int J Pharm. 2016. február;499(1–2):376–94.

26. Pereira GG, Figueiredo S, Fernandes AI, Pinto JF. Polymer Selection for Hot-Melt Extrusion Coupled to Fused Deposition Modelling in Pharmaceutics. Pharmaceutics. 2020. augusztus 22.;12(9):795.

27. Stanković M, Frijlink HW, Hinrichs WLJ. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. Drug Discov Today. 2015. július;20(7):812–23.

28. Sarode AL, Sandhu H, Shah N, Malick W, Zia H. Hot melt extrusion (HME) for amorphous solid dispersions: Predictive tools for processing and impact of drug–polymer interactions on supersaturation. Eur J Pharm Sci. 2013. február;48(3):371–84.

29. Maraveas C, Kyrtopoulos IV, Arvanitis KG. Evaluation of the Viability of 3D Printing in Recycling Polymers. Polymers. 2024. április 16.;16(8):1104.

30. Gioumouxouzis CI, Tzimtzimis E, Katsamenis OL, Dourou A, Markopoulou C, Bouropoulos N, és mtsai. Fabrication of an osmotic 3D printed solid dosage form for controlled release of active pharmaceutical ingredients. Eur J Pharm Sci. 2020. február;143:105176.

31. Đuranović M, Obeid S, Madžarević M, Cvijić S, Ibrić S. Paracetamol extended release FDM 3D printlets: Evaluation of formulation variables on printability and drug release. Int J Pharm. 2021. január;592:120053.