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The potential of natural products use in fused deposition modeling 3D printing of pharmaceutical dosage forms

Jelena Čanji Panić[1], Nemanja Todorović[1], Ana Stjepanović[1], Mladena Lalić-Popović[1,2*]

[1]University of Novi Sad - Faculty of Medicine, Department of Pharmacy, Hajduk Veljkova 3, 21000 Novi Sad, Serbia
[2]University of Novi Sad - Faculty of Medicine, Centre for Medical and Pharmaceutical Investigations and Quality Control (CEMPhIC), Hajduk Veljkova 3, 21000 Novi Sad, Serbia

*Corresponding author: Mladena Lalić-Popović, E-mail: mladena.lalic-popovic@mf.uns.ac.rs

Abstract

In recent years, the interest in 3D printing of medicines has increased due to many advantages of this technology, such as flexibility of the dose and dosage form of the printed product. Fused deposition modeling (FDM) is one of the most popular 3D printing technologies in the pharmaceutical field, due to its low cost and simplicity. The subject of this review is the potential use of natural products as biodegradable and biocompatible materials with good safety profiles in FDM 3D printing of pharmaceuticals. Natural products such as alginate, chitosan and starch have already been employed as excipients in FDM 3D printed pharmaceutical dosage forms, while others like shellac and zein show the potential, but haven't yet been part of 3D printed pharmaceutical formulations. These excipients have different roles in the formulation of filaments for FDM 3D printing, for example as fillers, matrix carriers or drug-release modifiers. In addition, the possibility of incorporating active pharmaceutical ingredients of natural origin in filaments for FDM 3D printing was reviewed. High printing temperatures limit the use of natural products in FDM 3D printing. However, adequate selection of thermoplastic material and printing parameters can widen the use of natural products in FDM 3D printing of pharmaceutical dosage forms.

Key words: biopolymers, natural fillers, natural plasticizers, FDM, three-dimensional printing

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Introduction

Three-dimensional (3D) printing is an additive manufacturing method that involves stacking layers of material to form different 3D shapes. This technology enables rapid production of prototypes using computer-aided design (1). 3D printing technology is applied in a variety of fields, including the consumer goods industry, the automotive and aerospace industry, and also the development of medical devices and medicines (1, 2). The interest in 3D printing of pharmaceutical products has been growing since the US Food and Drug Administration (FDA) approved the first 3D printed drug Spritam® in 2015 (2).

One of the major advantages of 3D printing of pharmaceutical dosage forms is the high adaptability of drug dose and dosage form. 3D printed medicines can be customized for the individual, which can lead to the transformation of extemporaneous compounding in pharmacy practice. This can be of particular importance for the pediatric and geriatric populations, patients suffering from rare diseases, as well as for veterinary patients, for whom there are generally no adequate doses and drug dosage forms available on the market (2, 3). The adoption of 3D printing as an alternative method of tablet production can be used in both preclinical and clinical research, as it enables cheap and fast printing of a small series of products, and at the same time highly dose-flexible formulations (3).

3D printing is a term that encompasses several technologies. The most commonly used 3D printing technologies for the development of pharmaceutical products are binder jetting, vat polymerisation, powder bed fusion, material jetting and material extrusion. Material extrusion includes semi-solid extrusion and fused deposition modeling (FDM) (3, 4).

FDM is an extrusion-based 3D printing technology. The printed material is melted and softened, then extruded through the printer nozzle and finally deposited on the printer build plate layer by layer in order to form a 3D structure. Each layer bonds to the previous layer, becoming solid after cooling. There are a few important parameters for FDM 3D printing: the printing temperature, build plate temperature, printing speed, infill density, shell thickness, top/bottom thickness and layer height. Modifying these parameters affects product characteristics (5). In FDM 3D printing of pharmaceutical dosage forms, printing parameters such as layer thickness and infill density modification gives the opportunity to alter pharmaceutical dosage forms' geometry, complexity and inner structure, which can affect the release of the active pharmaceutical ingredient (API) from a 3D printed dosage form (6, 7). Therefore, one of the advantages of FDM 3D printing is the easy modification of the drug release profile. Additional advantages are the possibility of printing pharmaceutical dosage forms with multiple APIs, and the fact that no post-processing is needed after printing. Another important advantage of FDM 3D printing technology is its low cost (6). On the other hand, FDM 3D printing has its limitations, a major one being the high printing temperature, which can lead to degradation of the API and other thermosensitive components (3). Another limitation is the lack of thermoplastic materials suitable for formulation of pharmaceutical dosage forms (8).

Feedstock material for FDM 3D printing are thermoplastic polymers in the form of filaments (9). The currently available commercial filaments for FDM 3D printing are not suitable for pharmaceutical application, which is why in-house preparation of filaments is needed prior to the printing process. Hot-melt extrusion (HME) is the most frequently used method for the preparation of filaments with pharmaceutical-grade polymers (10, 11). Commonly used thermoplastic polymers for this purpose are polyvinyl alcohol (PVA), polylactic acid (PLA), polyvinylpyrrolidone (PVP), cellulose ethers, derivates of acrylates, polyethylene glycol (PEG), polyethylene oxide (PEO). Other excipients and APIs can also be added to the powder mixture for HME (10). Excipients often used to improve physical and rheological properties of the filament are plasticizers and fillers. Plasticizers are substances that can reduce the glass transition temperature of the polymers, lowering the extrusion temperature and thus broadening the range of thermosensitive APIs and other substances that can be incorporated into filament formulation (10, 12). Plasticizers most commonly used for FDM 3D printing of pharmaceuticals are glycerol, polyethylene derivatives, triacetin, triethylene citrate. Immiscible fillers such as talc, lactose, starch, microcrystalline cellulose, magnesium stearate and tricalcium phosphate can also be added to filament formulation along with disintegrants, solubilizers and modifiers of the drug release (10).

Natural products in FDM 3D printing

Due to biocompatibility, biodegradability and a good safety profile, natural products are increasingly used as pharmaceutical excipients. The growing interest in sustainability is shifting the focus on utilization of biopolymers obtained from renewable sources (unlike petroleum derived polymers, which are exhaustible in nature) (13). In 3D printed pharmaceutical dosage forms made by the FDM 3D printing technology, polymers make up more than 50% of the dosage form. As sometimes partial or complete degradation of polymers can occur in the gastrointestinal tract, with this relatively high intake of these excipients, their safety is of great importance, especially for pediatric patients (14).

The requirements that natural products for 3D printing in medical and pharmaceutical field should fulfil in general are biocompatibility, biodegradability, appropriate mechanical properties and printability (13). Natural products can have various roles in formulation of filaments for FDM 3D printing, such as thermoplastic matrix carriers, fillers, and drug-release modifiers, as will be shown in this review. For example, with the use of plasticizers, biopolymers such as starch and proteins can be processed as thermoplastics. Some natural products can be used as APIs in 3D printing of pharmaceutical dosage forms, which will also be a subject of this review. Because they are biocompatible, some also edible, and available directly from plant or animal sources, they represent good candidates for FDM 3D printing of natural products in the food sector, biomedical and pharmaceutical field (15).

Natural fibers from vegetables such as rice or coconut husks, hemp fibers, flax fibers and others are mainly waste products coming from industry or local agriculture.

Using natural fibers as fillers in filament formulations for FDM 3D printing has numerous advantages, because they are environmentally friendly and economical. These fillers are pulverized cheap materials, which can be added to the filament formulation to lessen the use of expensive plastic materials and consequently reduce the overall cost of the 3D printing process. Fillers can increase flexural stiffness of the filaments and increase dimensional stability after solidification, but also reduce filament tensile strength and increase filament density (16).

However, there are certain limitations to using natural products in filament formulations for FDM 3D printing. In the pharmaceutical field, filaments produced by HME are exposed to temperatures ranging from 47 ˚C to 200 ˚C (17). The temperature used for the 3D printing of filaments is usually even higher than the HME temperature, because nozzle diameters of 3D printer and extruder differ, the printer nozzle diameter being smaller, which is why a higher temperature is needed to achieve adequate viscosity of the filament and avoid blockage of the nozzle (17, 18). When natural fillers are exposed to high temperatures (above 200 ˚C) for more than a few minutes, thermo-oxidative degradation is expected to occur. For example, Domingues-Robles et al. used FDM 3D printing to create objects from PLA composites containing lignin as a natural filler. The printing temperature ranged from 185 ˚C to 205 ˚C and the thermogravimetric analyses showed that thermal degradation of the lignin started to occur (a small amount, ca. 3%) (19). This is why the choice of thermoplastic polymer has to be limited to those polymers with a rather low melting temperature when natural fillers are added to the filament formulation. Moreover, natural fillers are highly hydrophilic. The accumulation of water in these materials can lead to water evaporation during filament formation and printing processes, or even hydrolysis of the polymeric material susceptible to this type of degradation (16). Therefore, careful drying of natural fillers is of great importance prior to the filament forming process.

Because excipients of natural origin cannot withstand high temperatures used in FDM process, FDM technology is not the most suitable one for 3D printing of natural products. Natural products are more often employed as excipients in semi-solid extrusion 3D printing, because this type of technology doesn't require high temperatures (14). Nevertheless, utilization of natural products is certainly possible in FDM 3D printing in various fields, including pharmacy, as will be discussed in this review.

Excipients of natural origin utilized in 3D printing

Alginate is a naturally occurring anionic polysaccharide, derived mainly from brown algae cell walls (*Laminaria hyperborea, Macrocystis pyrifera, Ascophyllum nodosum)* and several strains of bacteria (*Azotobacter, Pseudomonas*). Sodium alginate is the most widely used form of alginate in the pharmaceutical industry and biomedicinal field (20). A few studies have reported on using alginate in FDM 3D printing for the formulation of pharmaceutical dosage forms. Mirtamadian et al. used FDM 3D printing combined with HME to produce tablets containing alginate nanoparticles loaded with oxaliplatin for colon cancer targeted delivery. Oxaliplatin loaded alginate nanoparticles

were prepared using the ionic gelation method with calcium chloride as a cross-linking agent. Eudragit® L 100-55 was used as the main polymer for the formulation of the filaments, with PEG 6000 and triethyl citrate as plasticizers and freeze-dried alginate nanoparticles containing API. By combining nanotechnology and FDM 3D printing, they successfully prepared colon-specific oral tablets for targeted drug delivery to colorectal cancer tissue (21). Yang et al. mixed ibuprofen as an API, ethylcellulose as a thermoplastic polymer and sodium alginate as a drug release modifier. This mixture was extruded in a twin-screw extruder at 100-120 ˚C. The obtained HME filaments were used for FDM 3D printing of controlled-release ibuprofen tablets (22). In another study, the authors reported printing a pH-responsive tablet using FDM 3D printing technology with a filament made of Eudragit® L100-55 and Eudragit® S100 and PLA filament. Before completion, the printing process was paused, the previously made non-coated or chitosan-coated alginate beads containing 5-fluorouracil were placed in the hollow part of the print, and the printing process was resumed. In this formulation, alginate and chitosan are technically part of the 3D printed tablet; however, neither of these natural products is employed in either HME during filament forming, or FDM during the 3D printing of the dosage form (23).

Chitosan is a natural polycationic polysaccharide derived from chitin, found in the exoskeleton of insects, cell walls of fungi and crustaceans (crabs and shrimps mainly) (24). Eleftheriadis et al. utilized the mucoadhesive properties of chitosan, adding it to the PVA filament formulation, plasticized with xylitol and with diclofenac sodium as the API. The HME temperature was 169 ˚C and the filaments with and without chitosan were prepared. FDM 3D printing technology was used to obtain mucoadhesive buccal films from the previously prepared filaments. Filaments with and without 1% w/w of chitosan were printed at 200 ˚C, and better mucoadhesion and permeation properties were confirmed in the presence of chitosan in the 3D printed buccal film (25). Yang et al. reported FDM 3D printing of drug delivery implants, consisting of polycaprolactone (PCL) as a drug delivery carrier, ibuprofen as an API and chitosan as an agent for controlled drug release. The filaments were made via a two-step HME process. The first step was granulation in a twin-screw extruder, and in the second step extrudates were placed in a single-screw extruder in which the filaments were formed. The implants were 3D printed on an FDM 3D printer from the previously produced filaments. Controlled drug release was adjusted by changing the API and chitosan content and the structure of the printed product (26). Chitosan was also used in a hollow tablet formulation with 5-fluorouracil as the API, along with alginate in the study mentioned previously, though not as part of the HME or FDM 3D printing process itself (23).

Pectin is an anionic polysaccharide found in the cell wall of plants. Among other uses, it is used as a thickening agent in the food industry and an encapsulating agent in pharmaceutical formulations (27, 28). Apples and citrus fruits are sources of commercial pectin. Other possibilities for the extraction of pectin are being investigated, such as various agro-industrial residues (28). Hwan Lee et al. have successfully produced 3D printed gastro-retentive tablet formulations containing sarpogrelate, prepared by FDM 3D

printing, coupled with the HME of the filaments with different amounts of polymers Eudragit® L 100-55, PEO and pectin. They were able to develop a 3D printed gastro-retentive tablet with the ability to float for over 10 hours. Moreover, they have shown that the interaction between Eudragit® L 100-55 and pectin has a significant effect on the dissolution rate of sarpogrelate from this dosage form (29).

Starch is a versatile biopolymer that can be extracted from agricultural plants, such as rice, corn, sugarcane, sugar beets, and wheat (30, 31). It is an excipient widely used in the pharmaceutical industry, mainly in oral solid dosage forms as a disintegrant, binder and diluent (filler) (32). Ehtezazi et al. reported successful FDM 3D printing of multilayered fast dissolving oral films with ibuprofen and paracetamol as APIs. The layer containing ibuprofen was extruded from PEO filaments with sodium lauryl sulphate and starch. In this formulation, starch was used as a disintegrant. The HME process was conducted at 60 ˚C on a single-screw extruder, while the FDM 3D printing process of the obtained filaments was performed at 165 ˚C (33). In addition to this, unmodified starch can be processed as thermoplastic in the presence of a highly viscous plasticizer (e.g. glycerol). Starch contains many hydroxylic groups, available for interaction with the plasticizer. The result of this interaction is the formation of an amorphous structure and the viscous starch melt (31). Mendibil et al. performed a direct powder extrusion of paracetamol tablets on an FDM 3D printer with an added powder-extrusion head, which allowed a 3D printing process without previous preparation of the filaments. Mixtures containing hydroxypropyl cellulose and starch with different proportions of paracetamol and guar gum were extruded with a twin-screw extruder at 85 ˚C, only to determine the thermal processability of the formulations. The obtained filaments were later not used for 3D printing. Instead, direct powder FDM 3D printing was used make the tablets and explore possibilities of reducing the API thermal stress, because it meant skipping one thermal process – HME. Hydroxypropyl cellulose and potato starch were used as matrix carriers and, because of the low printing temperature (90 ˚C), water was used as a plasticizer. **Guar gum** is another natural product added to this formulation (34). Guar gum is a non-ionic polysaccharide found in the seeds of *Cyamopsis tetragonolobus* (35). It is an excipient used in pharmaceutical dosage forms as a disintegrant and binder (32). Mendibil et al. concluded that the addition of 5% w/w of guar gum eased the extrusion process. (34).

There are a few studies showing the possibility of employing thermoplastic starch as a filament forming material in combination with other thermoplastics. Ju et al. obtained filaments of starch plasticized with glycerol (70:30 % w/w) in a twin-screw extruder at 135-150 ˚C. Filaments were then cut to pellets and mixed with PLA and poly(butylene adipate-co-terephthalate) and extruded again at 165-180 ˚C. In this filament formulation, thermoplastic starch made up 50% w/w and was used as a matrix material. These filaments were later successfully used for FDM 3D printing of various shapes at 180 ˚C (36). Kuo et al. made filaments consisting of thermoplastic starch and acrylonitrile-butadiene-styrene copolymers, with the addition of pigments and compatibilizers and impact modifiers, to improve mixing of thermoplastic polymers and physical properties

of the filaments (37). Zhao et al. reported obtaining PCL/starch filaments for low-temperature FDM 3D printing (38). These studies show promise that thermoplastic starch composites can be used in 3D printing of pharmaceuticals. It should also be mentioned that natural starch is a starting material for the synthesis of PLA, one of the most commonly used biodegradable synthetic thermoplastics for FDM 3D printing (30).

Cellulose, being one of the principal plant components, is a ubiquitous, biodegradable and almost inexhaustible natural polymer. Chemically, it is an unbranched, linear polysaccharide. Cellulose and its derivates are well known pharmaceutical excipients used in formulations with controlled drug release, mucoadhesive and bio-adhesive formulations, osmotic drug delivery systems and others (39). Natural cellulose possesses a strong hydrogen bonding network, which is why it degrades before melting (40). This is why natural cellulose cannot be used in HME and FDM 3D printing as matrix polymer. However, it is a source material for numerous cellulose derivates, highly employed in FDM 3D printing of pharmaceuticals. In addition to synthetic thermoplastic polymers like PLA, PVA and PVP, cellulose derivates are the most commonly used thermoplastics for filament formulation in pharmaceutical field. The use of hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), ethylcellulose (EC), hydroxypropyl methylcellulose acetate succinate (HPMCAS) was reported for the formulation of filaments loaded with APIs for FDM 3D printing of dosage forms in various studies (8, 10, 18, 22, 41-50), examples of which are shown in the Table I. Table II gives an overview of the selected excipients of natural origin (other than cellulose and its derivates) and their specific roles in FDM 3D printed pharmaceutical dosage forms.

Table I FDM 3D printed pharmaceutical dosage forms containing cellulose-derivates

Tabela I Farmaceutski oblici lekova sa derivatima celuloze štampani FDM tehnologijom

Cellulose-derived polymer	API	Dosage form	Reference
EC	Ibuprofen	Controlled release tablet	(22)
	Quinine	Implant	(18)
	Paracetamol	Controlled release tablet	(41, 42)
HPC	Theophylline	Immediate release tablet	(43, 44)
	Paracetamol	Controlled release tablet	(41, 42)
	Domperidon	Intragastric floating controlled release tablet	(45)
	Itraconazole	Controlled release floating tablet	(46)
HPMC	Paracetamol	Controlled release tablet	(41, 42, 47)
	Haloperidol	Immediate release tablet	(48)
	Carvedilol	Gastro-retentive floating tablet	(49)
HPMCAS	Paracetamol	Controlled release tablet	(42, 50)

Table II Selected excipients of natural origin and their specific roles in 3D printed pharmaceutical dosage forms

Tabela II Odabrani ekscipijensi prirodnog porekla i njihove specifične uloge u 3D štampanim farmaceutskim oblicima lekova

Excipient of natural origin	FDM 3D printed pharmaceutical dosage form	API	Role of excipient	Reference
Alginate	oral tablet for targeted drug delivery	oxaliplatin	carrier	(21)
	controlled release tablet	ibuprofen	drug release modifier	(22)
Chitosan	mucoadhesive buccal film	diclofenac sodium	mucoadhesive agent	(25)
	implant	ibuprofen	agent for controlled drug release	(26)
Pectin	gastro-retentive tablet	sarpogrelate	release modifier	(29)
Starch	fast dissolving oral films	ibuprofen; paracetamol	disintegrant	(33)
	tablet	paracetamol	matrix carrier	(34)
Guar gum	tablet	paracetamol	plasticizer	(34)

Excipients of natural origin with the potential to be utilized in 3D printing

There are some natural products not yet used in the formulation of FDM 3D printed pharmaceutical dosage forms, but with the potential to be applied in this field. **Shellac** is a natural resin secreted by insects and a known pharmaceutical excipient. In pharmaceutical dosage forms it is mostly used as moisture barrier, usually in the form of an aqueous or alcoholic solution (32). It has also found its use in the food industry, for example as the shiny shell on candies (17). Chansatidkosol et al. managed to prepare filaments based on shellac by HME, and reached the conclusion that shellac might have suitable properties, such as decomposition temperature, melting temperature and melting enthalpy, for the formulation of filaments for FDM 3D printing (51). **Zein** is a plant protein obtained from corn. In the pharmaceutical industry it is used as a binder and coating agent (32, 52). Chaunier et al. used zein from maize with glycerol as a plasticizer to produce filaments via a single-screw extruder at 130 ˚C. Afterwards they used these filaments to print a ring geometry model by the FDM 3D printing technology at the same temperature at which the HME process was done. The authors suggest the possibility of zein filament application in the biomedical and pharmaceutical field (52).

Many studies have been conducted to examine the possibility of adding natural fillers to thermoplastic biocomposites in order to lower the cost of filaments and excess use of thermoplastics such as PLA (30). For example, Domínguez-Robles et al. prepared printable antioxidant PLA filaments with **lignin** as a biofiller (19). Lignin is a plant-based polymer and a by-product of the pulp and paper industries (30). The authors suggested a possible application in healthcare products for wound healing (19). Cali et al. made two types of PLA filaments containing either **hemp** or waste powder of hemp inflorescences as fillers. This study acknowledged the effect of filler particle size and moisture content on the compatibility with the matrix polymer. The authors successfully used an FDM 3D printer to make neck orthosis from these filaments, and point to further usage possibilities in the cosmetic, biomedical and pharmaceutical fields (53). Many more agricultural-waste products have been investigated as natural fillers for FDM 3D printing filaments, like soybean hull fiber (54, 55), cocoa shell (56), sugarcane (57), etc. However, the possibility of their usage in the formulation of pharmaceutical dosage forms is still to be evaluated.

Apis of natural origin in HME and FMD 3D printing

To the authors' knowledge, only a few studies have reported using a naturally occurring substance as an API in FDM 3D printed formulations. Quinine is an antimalarial drug naturally occurring in the bark of the cinchona tree (58). Kempin et al. 3D printed implants with quinine as the API. Different types of filaments were produced, with either PLA, PCL, EC or Eudragit® as matrix carriers. Quinine was incorporated into polymer matrixes by a solvent casting method. Ethanolic solutions of quinine and a solution of polymers in either methylene chloride (PCL, PLA) or acetone (EC, Eudragit®) were mixed and poured as a thin layer on a glass plate. After solvent evaporation, the created films were broken into small pieces, which were afterwards extruded into filaments. The created filaments were then 3D printed into implant shapes, with the

printing temperature depending on the polymer (164 ˚C, 155 ˚C, 145 ˚C and 53 ˚C for PLA, Eudragit®, EC and PCL respectively). The authors showed that the quinine release rate greatly depended on the polymer used and the amount of drug loaded into the filament (18). Tagami et al. used FDM 3D printing technology to print **curcumin** tablets (9). In this study, curcumin, a polyphenol with antioxidant and anti-inflammatory effects, naturally occurring in *Curcuma longa* (59), was incorporated into PVA filaments by the soaking method (avoiding HME of the filaments with API). These filaments were later successfully used for 3D printing of the tablets (9). On the other hand, Chuah et al. prepared an amorphous solid dispersion of curcumin by HME. HPMC, lecithin and isomalt were used as excipients in this formulation. It should be mentioned that in this study the authors did not aim to produce filaments for FDM 3D printing, but rather to formulate a dosage form with improved bioavailability of curcumin (60).

A few other studies have investigated the possibility of forming extrudates with plant extracts by HME. Pinho et al. used HME to produce filaments with **cocoa extracts** from *Theobroma cacao.* Cocoa extract contains high amounts of flavonoid theobromine, with cardioprotective and anti-inflammatory potential. Different polymers were used as matrix carriers (Soluplus®, Plasdone® S630, and Eudragit® E), and the authors reported that the stability of the natural product was preserved (61). ***Ginkgo biloba* extract** is widely used in cardiovascular and neurodegenerative diseases (13). Extrudates containing a 25% extract of *Ginkgo biloba* were obtained by the HME process, with a Kollidon® VA64 and Kolliphor® RH40 mixture (85:15) as the matrix carrier, by Wang et al. (62). ***Angelica gigas Nakai*** (AGN), a medicinal plant with anticancer, antiamnestic and antiallergic effect, has also been employed in the HME process. Jiang et al. (63) and Kalam Azad et al. (64) obtained extrudates of Angelica gigas Nakai dry root, in Soloplus® and HPMC as a polymer matrix, respectively. Piperin (65), artemisinin (66), paclitaxel (67) and quercetin (68) are additional examples of natural extracts successfully loaded into polymeric matrix formulations, either pellets or powders, by HME. The aim of these studies was to increase the dissolution rate and bioavailability of the abovementioned compounds by formulation of solid dispersions. The likelihood of loading these ingredients into filaments for FDM 3D printing is yet to be researched. However, the very possibility of processing these natural products using the HME technology shows promise for their utilization in FDM 3D printing.

Conclusion

Based on this review, we can conclude that many natural products have a lot of potential to be employed as either excipients or APIs in FDM 3D printing of pharmaceuticals. As excipients, they can have various roles in filament formulations, such as matrix carriers, fillers, disintegrants, modifiers of drug release and many others. Most of the used natural excipients in FDM 3D technology can be described as multifunctional, and their functional categories should be determined in the future. A major obstacle of employing natural products in FDM 3D printing and HME are the high temperatures often used in these technologies. By selection of appropriate polymers (with low melting

temperatures), plasticizers and other excipients, HME and FDM 3D printing parameters, the temperatures used in these technologies can be reduced. With lower extrusion and printing temperatures, the use of natural products in FDM 3D printing of pharmaceutical dosage forms can be broadened. This review provides a comprehensive overview of natural excipients with the potential to be used in FDM 3D printing in order to leverage this technology for application in the pharmaceutical industry and drug production.

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References

1. Jose PA, GV PC. 3D printing of pharmaceuticals–a potential technology in developing personalized medicine. Asian J Pharm Res Dev. 2018;6(3):46-54.
2. Norman J, Madurawe RD, Moore CM, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Adv Drug Deliver Rev. 2017;108:39-50.
3. Seoane-Viaño I, Trenfield SJ, Basit AW, Goyanes Á. Translating 3D printed pharmaceuticals: from hype to real-world clinical applications. Adv Drug Deliver Rev. 2021;174:553-75.
4. Kim JH, Kim K, Jin, HE. Three-Dimensional Printing for Oral Pharmaceutical Dosage Forms. J Pharm Investig. 2022;52:293–317.
5. Dumpa N, Butreddy A, Wang H, Komanduri N, Bandari S, Repka MA. 3D printing in personalized drug delivery: An overview of hot-melt extrusion-based fused deposition modeling. Int J Pharm. 2021;600:120501.
6. Pitzanti G, Mathew E, Andrews GP, Jones DS, Lamprou DA. 3D Printing: an appealing technology for the manufacturing of solid oral dosage forms. J Pharm Pharmacol. 2022;20:1-22.
7. Brambilla CRM, Okafor-Muo OL, Hassanin H, ElShaer A. 3DP printing of oral solid formulations: a systematic review. Pharmaceutics. 2021;13:1–25.
8. Azad MA, Olawuni D, Kimbell G, Badruddoza A, Hossain MS, Sultana T. Polymers for Extrusion-Based 3D Printing of Pharmaceuticals: A Holistic Materials-Process Perspective. Pharmaceutics, 2020;12(2):124.
9. Tagami T, Kuwata E, Sakai N, Ozeki T. Drug Incorporation into Polymer Filament Using Simple Soaking Method for Tablet Preparation Using Fused Deposition Modeling. Biol Pharm Bull. 2019;42(10):1753-60.
10. Pereira GG, Figueiredo S, Fernandes AI, Pinto JF. Polymer Selection for Hot-Melt Extrusion Coupled to Fused Deposition Modelling in Pharmaceutics. Pharmaceutics 2020;12(9):795.
11. 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;509(1-2):255–63.

12. Prasad LK, Smyth H. 3D Printing technologies for drug delivery: A review. Drug Dev Ind Pharm. 2016;42(7):1019-31.
13. Aguilar-de-Leyva Á, Linares V, Casas M, Caraballo I. 3D Printed Drug Delivery Systems Based on Natural Products. Pharmaceutics. 2020;12(7):620.
14. Quodbach J, Bogdahn M, Breitkreutz J, Chamberlain R, Eggenreich K, Elia AG, et al. Quality of FDM 3D Printed Medicines for Pediatrics: Considerations for Formulation Development, Filament Extrusion, Printing Process and Printer Design. The Innov Regul Sci. 2022;56(6):910-28.
15. Chaunier L, Guessasma S, Belhabib S, Della Valle G, Lourdin D, Leroy E. Material extrusion of plant biopolymers: Opportunities & challenges for 3D printing. Addit Manuf. 2018;21:220-33.
16. Mazzanti V, Malagutti L, Mollica F. FDM 3D printing of polymers containing natural fillers: A review of their mechanical properties. Polymers. 2019;11(7):1094.
17. Ehtezazi T, Sarker SD. The Use of natural Products in 3D Printing of Pharmaceutical Dosage Forms. J Nat Prod Disc. doi: 10.24377/jnpd.article654.
18. Kempin W, Franz C, Koster LC, Schneider F, Bogdahn M, Weitschies W, et al. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. Eur J Pharm Biopharm. 2017;115:84-93.
19. Domínguez-Robles J, Martin N, Fong M, Stewart S, Irwin N, Rial-Hermida M, et al. Antioxidant PLA composites containing lignin for 3d printing applications: a potential material for healthcare applications. Pharmaceutics. 2019;11(4):165.
20. Szekalska M, Puciłowska A, Szymańska E, Ciosek P, Winnicka K. Alginate: Current Use and Future Perspectives in Pharmaceutical and Biomedical Applications. Int J Polym Sci. 2016;8:1–17.
21. Mirdamadian SZ, Varshosaz J, Minaiyan M, Taheri A. 3D printed tablets containing oxaliplatin loaded alginate nanoparticles for colon cancer targeted delivery. An in vitro/in vivo study. Int J Biol Macromol. 2022;205:90-109.
22. Yang Y, Wang H, Li H, Ou Z, Yang G. 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release. Eur J Pharm Sci. 2018;115:11-8.
23. Gioumouxouzis CI, Chatzitaki AT, Karavasili C, Katsamenis OL, Tzetzis D, Mystiridou E, et al. Controlled release of 5-fluorouracil from alginate beads encapsulated in 3D printed pH-responsive solid dosage forms. AAPS Pharm Sci Tech. 2018;19(8):3362-75.
24. Cheung RC, Ng TB, Wong JH, Chan WY. Chitosan: an update on potential biomedical and pharmaceutical applications. Mar Drugs. 2015;13(8):5156-86.
25. Eleftheriadis GK, Ritzoulis C, Bouropoulos N, Tzetzis D, Andreadis DA, Boetker J, et al. Unidirectional drug release from 3D printed mucoadhesive buccal films using FDM technology: In vitro and ex vivo evaluation. Eur J Pharm Biopharm. 2019;144:180-92.
26. Yang Y, Wu H, Fu Q, Xie X, Song Y, Xu M, Li J. 3D-Printed Polycaprolactone-Chitosan based drug delivery implants for personalized administration. Mater Des. 2022;214:110394.
27. Zamboulis A, Michailidou G, Koumentakou I, Bikiaris DN. Polysaccharide 3D Printing for Drug Delivery Applications. Pharmaceutics. 2022;14(1):145.
28. Freitas CM, Coimbra JS, Souza VG, Sousa RC. Structure and applications of pectin in food, biomedical, and pharmaceutical industry: A review. Coatings. 2021;11(8):922.
29. Lee SH, Cho YH, Lee GW. The Development of Gastro-Retentive Tablet using Hot Melt Extrusion and 3D Printing Technology. J Pharm Soc Korea. 2022;66(2):76-89.

30. Wasti S, Adhikari S. Use of biomaterials for 3D printing by fused deposition modeling technique: a review. Front Chem. 2020;8:315.
31. Aida HJ, Nadlene R, Mastura MT, Yusriah L, Sivakumar D, Ilyas RA. Natural fibre filament for Fused Deposition Modelling (FDM): A review. Int J Sustain Eng. 2021;14(6):1988-2008.
32. Rowe CR, Sheskey JP, Quinn EM. Handbook of Pharmaceutical Excipients. 6th ed. Grayslake: Pharmaceutical Press and Washington, DC: American Pharmacists Association; 2009.
33. Ehtezazi T, Algellay M, Islam Y, Roberts M, Dempster NM, Sarker SD. The application of 3D printing in the formulation of multilayered fast dissolving oral films. J Pharm Sci. 2018;107(4):1076-85.
34. Mendibil X, Tena G, Duque A, Uranga N, Campanero MÁ, Alonso J. Direct powder extrusion of paracetamol loaded mixtures for 3D printed pharmaceutics for personalized medicine via low temperature thermal processing. Pharmaceutics. 2021;13(6):907.
35. George A, Shah PA, Shrivastav PS. Guar gum: Versatile natural polymer for drug delivery applications. Eur Polym J. 2019;112:722-35.
36. Ju Q, Tang Z, Shi H, Zhu Y, Shen Y, Wang T. Thermoplastic starch based blends as a highly renewable filament for fused deposition modeling 3D printing. Int J Biol Macromol. 2022;219:175-84.
37. Kuo CC, Liu LC, Teng WF, Chang HY, Chien FM, Liao SJ, et al. Preparation of starch/acrylonitrile-butadiene-styrene copolymers (ABS) biomass alloys and their feasible evaluation for 3D printing applications. Compos Part B Eng. 2016;86:36-9.
38. Zhao YQ, Yang JH, Ding X, Ding X, Duan S, Xu FJ. Polycaprolactone/polysaccharide functional composites for low-temperature fused deposition modelling. Bioact Mater. 2020;5(2):185-91.
39. Giri BR, Poudel S, Kim DW. Cellulose and its derivatives for application in 3D printing of pharmaceuticals. J Pharm Investig. 2021;51(1):1-22.
40. Chen Z, Zhang J, Xiao P, Tian W, Zhang J. Novel thermoplastic cellulose esters containing bulky moieties and soft segments. ACS Sustain Chem Eng. 2018;6(4):4931-9.
41. 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(1-2):186–97.
42. Zhang J, Xu P, Vo AQ, Bandari S, Yang F, Durig T, Repka MA. Development and evaluation of pharmaceutical 3D printability for hot melt extruded cellulose-based filaments. J Drug Deliv Sci Technol. 2019;52:292–302.
43. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. Eur J Pharm Biopharm. 2015;96:380–7.
44. Arafat B, Wojsz M, Isreb A, Forbes RT, Isreb M, Ahmed W, et al. Tablet fragmentation without a disintegrant: A novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. Eur J Pharm Sci. 2018;118:191–9.
45. Chai X, Chai H, Wang X, Yang J, Li J, Zhao Y, et al. Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone. Sci Rep. 2017;7(1):1–9.
46. Kimura SI, Ishikawa T, Iwao Y, Itai S, Kondo H. Fabrication of zero-order sustained-release floating tablets via fused depositing modeling 3D printer. Chem Pharm Bull. 2019;67(9):992–9.
47. Zhang AJ, Yang W, Vo AQ, Feng X. Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. Carbohydr Polym. 2017;177:49–57.

48. 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.
49. Ilyés K, Balogh A, Casian T, Igricz T, Borbás E, Démuth B, et al. 3D floating tablets: Appropriate 3D design from the perspective of different in vitro dissolution testing methodologies. Int J Pharm. 2019;567:118433.
50. Goyanes A, Fina F, Martorana A, Sedough D, Gaisford S, Basit AW. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. Int J Pharm. 2017;527(1-2):21–30.
51. Chansatidkosol S, Limmatvapirat C, Piriyaprasarth S, Patomchaiviwat V, Limmatvapirat S. Assessment of Shellac as Alternative Material for Preparation of Fused Deposition Modeling (FDM) 3D Printing Filaments. Key Eng Mater. 2022;914:53–62.
52. Chaunier L, Leroy E, Valle GD, Dalgalarrondo M, Bakan B, Marion D, Madec B, Lourdin D. 3D printing of maize protein by fused deposition modeling. AIP Conf Proc. 2017;1914:190003.
53. Calì M, Pascoletti G, Gaeta M, Milazzo G, Ambu R. New filaments with natural fillers for FDM 3D printing and their applications in biomedical field. Procedia Manuf. 2020;51:698-703.
54. Balla VK, Tadimeti JG, Sudan K, Satyavolu J, Kate KH. First report on fabrication and characterization of soybean hull fiber: polymer composite filaments for fused filament fabrication. Prog Addit Manuf. 2021;6(1):39-52.
55. Balla VK, Tadimeti JG, Kate KH, Satyavolu J. 3D printing of modified soybean hull fiber/polymer composites. Mater Chem Phys. 2020;254:123452.
56. Tran TN, Bayer IS, Heredia-Guerrero JA, Frugone M, Lagomarsino M, Maggio F, et al. Cocoa shell waste biofilaments for 3D printing applications. Macromol Mater Eng. 2017;302(11):1700219.
57. Liu H, He H, Peng X, Huang B, Li J. Three-dimensional printing of poly (lactic acid) bio-based composites with sugarcane bagasse fiber: Effect of printing orientation on tensile performance. Poly Advan Technol. 2019;30(4):910-22.
58. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria J. 2011;10(1):1-2.
59. Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. Foods. 2017;6(10):92.
60. Chuah AM, Jacob B, Jie Z, Ramesh S, Mandal S, Puthan JK, et al. Enhanced bioavailability and bioefficacy of an amorphous solid dispersion of curcumin. Food Chem. 2014;156:227–33.
61. Pinho LAG, Souza SG, Marreto RN, Sa-Barreto LL, Gratieri T, Gelfuso GM, et al. Dissolution enhancement in cocoa extract, combining hydrophilic polymers through hot-melt extrusion. Pharmaceutics 2018;10(3):135.
62. Wang W, Kang Q, Liu N, Zhang Q, Zhang Y, Li H, et al. Enhanced dissolution rate and oral bioavailability of Ginkgo biloba extract by preparing solid dispersion via hot-melt extrusion. Fitoterapia. 2015;102:189–97.
63. Jiang Y, Piao J, Cho HJ, Kang WS, Kim HY. Improvement in antiproliferative activity of Angelica gigas Nakai by solid dispersion formation via hot-melt extrusion and induction of cell cycle arrest and apoptosis in HeLa cells. Biosci Biotechnol Biochem. 2015;79(10):1635-43.

64. Azad MOK, Kang WS, Lim JD, Park CH. Bio-Fortification of Angelica gigas Nakai Nano-Powder Using Bio-Polymer by Hot Melt Extrusion to Enhance the Bioaccessibility and Functionality of Nutraceutical Compounds. Pharmaceuticals. 2020;13(1):3.
65. Ashour EA, Majumdar S, Alsheteli A, Alshehri S, Alsulays B, Feng X, et al. Hot melt extrusion as an approach to improve solubility, permeability and oral absorption of a psychoactive natural product, piperine. J Pharm Pharmacol. 2016;68(8):989–98.
66. Kulkarni C, Kelly AL, Gough T, Jadhav V, Singh KK, Paradkar A. Application of hot melt extrusion for improving bioavailability of artemisinin a thermolabile drug. Drug Dev Ind Pharm. 2018;44(2):206–14.
67. Oh KS, Song JY, Cho SH, Lee BS, Kim SY, Kim K, et al. Paclitaxel-loaded pluronic nanoparticles formed by a temperature-induced phase transition for cancer therapy. J Control Release. 2010;148(3):344–50.
68. Khor CM, Ng WK, Kanaujia P, Chan KP, Dong Y. Hot-melt extrusion microencapsulation of quercetin for taste-masking. J Microencapsul. 2017;34(1):29

Potencijal upotrebe prirodnih proizvoda za 3D štampu farmaceutskih oblika lekova primenom fused deposition modeling tehnologije

Jelena Čanji Panić[1], Nemanja Todorović[1], Ana Stjepanović[1], Mladena Lalić-Popović[1,2*]

[1]Univerzitet u Novom Sadu - Medicinski fakultet, Katedra za farmaciju, Hajduk Veljkova 3, 21000 Novi Sad, Srbija

[2]Univerzitet u Novom Sadu - Medicinski fakultet, Centar za medicinska - farmaceutska istraživanja i kontrolu kvaliteta (CEMFIK), Hajduk Veljkova 3, 21000 Novi Sad, Srbija

*Autor za korespondenciju: Mladena Lalić-Popović, E-mail:mladena.lalic-popovic@mf.uns.ac.rs

Kratak sadržaj

Poslednjih godina interesovanje za 3D štampanje lekova je u porastu usled mnogih prednosti ove tehnologije, kao što su visoka fleksibilnost u pogledu doze i farmaceutskog oblika štampanog farmaceutskog proizvoda. *Fused deposition modeling* (FDM) je jedna od najpopularnijih tehnologija 3D štampanja u farmaciji, zbog svoje niske cene i jednostavnosti. Predmet ovog preglednog rada je upotreba prirodnih proizvoda kao biorazgradivih i biokompatibilnih materijala sa dobrim bezbednosnim profilima u FDM 3D štampanju farmaceutskih proizvoda. Prirodni proizvodi kao što su alginat, hitozan i skrob već su primenjivani kao ekscipijenti u FDM 3D štampanim farmaceutskim oblicima lekova, dok drugi, poput šelaka i zeina, pokazuju potencijal, ali još uvek nisu korišćeni za 3D štampu farmaceutskih oblika lekova. Uloge ovih ekscipijenasa u formulaciji filamenata za FDM 3D štampu mogu biti različite, npr. punioci, nosači matriksa ili modifikatori oslobađanja. Takođe je razmatrana mogućnost inkorporacije aktivnih farmaceutskih sastojaka prirodnog porekla u filamente. Visoke temperature štampanja ograničavaju upotrebu prirodnih proizvoda u FDM 3D štampanju. Međutim, adekvatan izbor termoplastičnog materijala i parametara štampanja može proširiti upotrebu prirodnih proizvoda u FDM 3D štampanju farmaceutskih proizvoda.

Ključne reči: biopolimeri, prirodna sredstva za dopunjavanje, prirodni plastifikatori, FDM, trodimenzionalno štampanje