Advances in Science and Technology Research Journal

Advances in Science and Technology Research Journal 2023, 17(6), 116–126
https://doi.org/10.12913/22998624/174079
ISSN 2299-8624, License CC-BY 4.0

Received: 2023.09.25
Accepted: 2023.10.12
Published: 2023.11.21

Geometrical Accuracy and Strength of Micro-Needles Made of Polylactide by Fused Filament Fabrication Method

Radosław Wichniarek[1*], Wiesław Kuczko[1], Dorota Tomczak[2], Ariadna B. Nowicka[3], Monika Wojtyłko[4], Anna Froelich[4], Tomasz Osmałek[4]

[1] Institute of Materials Technology, Faculty of Mechanical Engineering, Poznan University of Technology, 5 M. Skłodowska-Curie Square, 60-965 Poznan, Poland

[2] Institute of Chemical Technology and Engineering, Faculty of Chemical Technology, Poznan University of Technology, Berdychowo 4, 60-965 Poznan, Poland

[3] Faculty of Materials Engineering and Technical Physics, Poznan University of Technology, Piotrowo 3, 60-965 Poznan, Poland

[4] Chair and Department of Pharmaceutical Technology, Poznan University of Medical Sciences, 6 Grunwaldzka Street, 60-780 Poznań, Poland

* Corresponding author's e-mail: radoslaw.wichniarek@put.poznan.pl

ABSTRACT

Additive manufacturing is a technology that can be successfully used in pharmacy and medicine. One of the examples of products that can be additively manufactured are microneedle systems. The specificity of these products, which are used for transdermal drug delivery, makes additive manufacturing a perfect choice for related research. However, the dimensions of microneedles usually do not exceed 2 mm, which means that manufacturing them using the most widely available additive manufacturing method, Fused Deposition Modelling (FDM), is problematic. In this study, the authors decided to investigate the possibilities of manufacturing microneedle systems using the FDM method in such a way as to minimize or exclude the need for post-processing. Five types of microneedle geometries were tested in four sizes, examining how changing the values of FDM process parameters would affect the accuracy of reproducing the digital geometry of the microneedles. From the point of view of the application of microneedle systems, it is not only necessary to obtain the designed shape of the microneedles, but also to maintain their appropriate strength. The study presents the results of the bending and compression strength of microneedles made of polylactic acid.

Keywords: additive manufacturing; microneedle; 3D printing; transdermal drug delivery; polylactic acid.

INTRODUCTION

In medicine, microneedles, and often entire microneedle systems, are a type of medical devices with the potential to be used for topical delivery of drugs. This approach has several advantages, including being less painful, minimally invasive, and can be self-administered by the patient. The dosage and rate of drug release can be controlled through the appropriate design of the microneedle and concentration of the active substance [12, 13]. The typical size of microneedles is significantly smaller in every dimension compared to typical needles used for intravenous or subcutaneous injections. To enable the diffusion of the active substance (drug) through the skin, the microneedle only needs to create a channel with a diameter of one hundredth of a millimeter. The literature categorizes microneedles into several basic types based on their structure: solid microneedles (SMNs), hollow microneedles (HMNs), dissolving microneedles (DMNs), and coated microneedles (CMNs) [14].

The first ideas and research related to the use of microneedles took place in the 1950s. Due to technological limitations, production

possibilities, and limited applications, their use was severely restricted. It was not until the end of the century that microneedles became a more frequent subject of research, with the aim of replacing traditional injections [1]. Since the beginning of the second decade of the 21st century, there has been a significant increase in interest in the use of additive manufacturing methods for the production of microneedles. Recent years have shown that many researchers are interested in developing methods for producing microneedle systems that already contain a therapeutic agent and are capable of releasing it at a designed rate. Such microneedle manufacturing systems could be used directly by doctors or pharmacists to produce patient-specific drug doses directly in the hospital or pharmacy.

Microneedle systems, as single-use tools, should be relatively inexpensive to enable their widespread use [5]. However, in the case of additive manufacturing, there are significant differences in production costs between different manufacturing methods. These differences also extend to technical coefficients related to the strength of the manufactured components, process time, and the type of required post-processing. The most widely used and accessible method of additive manufacturing is Fused Deposition Modelling (FDM), developed by Stratasys company. In the case of machines from other manufacturers, it is most commonly referred to as Fused Filament Fabrication (FFF) or, more generally, as material extrusion method (MEX), although with less precision. FDM devices can operate in office conditions and process thermoplastic polymers, with their operation requiring minimal qualifications from the operator. Products obtained using the FDM method have numerous applications in machinery construction, but can also come into contact with food and human skin [4], and even have potential uses as biocompatible implants [2] or customized prosthetics [3].

The potential use of the FDM method for the production of minitablet as a drug delivery platform tailored to age, without the need for tablet splitting while maintaining consistent release profiles was examined by Yang et al. [7]. Their research showed that the FDM method provides great flexibility in drug delivery and eliminates many issues associated with traditional tablet production. However, in the case of applying FDM to the production of microneedles, the authors of study [6] identified several challenges and limitations. Due to the relatively high processing temperature (>200 °C) of the FDM method, (for materials that allow skin penetration and are suitable for microneedles), processing may result in crystalline drug amorphization or even degradation. As a result, some active substances may not be present inside the native material of the microneedle, but only on its surface, requiring an additional coating operation, thus limiting the control over drug release rate. The research presented in study [10] indicates that the dip coating is the best coating method for FDM-printed microneedles. The authors of the study highlight the simplicity and ability to achieve uniform coating on printed microneedles as the major advantages of this method. Another issue is the insufficient accuracy and slow production speed of microneedles using the FDM method.

The authors of the study [8] investigated the influence of various FDM process parameters on the ability to produce microneedle systems using polylactic acid (PLA) material. Surface finish and dimensional accuracy of microneedles were adopted as measures of product quality. Only one type of needle geometry was used, consisting of truncated cones with a height of 4.5 mm, a base diameter of 1.5 mm, and a peak diameter of 0.5 mm. In addition to changing the values of FDM process parameters, the distances between the manufactured micro-needles were also altered. It was demonstrated that a smaller nozzle diameter and larger distances between microneedles resulted in better surface quality of the components, but not their accuracy. The problematic issue was the disruption of material extrusion flow, which led to swelling and distortion of the geometry. The authors suggest that this phenomenon can be alleviated by increasing the extrusion temperature, reducing the width of the fill paths, and adjusting the extrusion speed. On the other hand, the same authors discovered that the increase in temperature caused a change in the molecular weight of the polymers, indicating thermal degradation of the material from which the microneedles were manufactured.

The limited and insufficient accuracy of FDM manufacturing machines hinders the direct creation of precise microneedle systems. If it is not possible to increase the precision of FDM manufacturing, it is possible to use additional technological operations in the form of chemical etching. However, according to the authors of [9], while it is possible to achieve a tip size of

microprinted needles as small as 1 μm, this significantly increases the cost and time of manufacturing microneedle systems. This would be particularly troublesome if the geometry of the microneedles had to be individually tailored to the patient's needs. The problems arising during the chemical etching of microneedle systems have also prompted research described in [11]. The authors indicate that it is necessary to optimize the microneedle system and the manufacturing process in order to reduce or prevent detachment of the needles and collapse of carrier surfaces during etching. The main reasons for the degradation of microneedle systems during etching are discontinuities in the material structure and weak bonding force between individual layers. The authors suggest using a higher degree of filler content and higher processing temperature as a method of improvement.

Polylactic acid is likely the most commonly processed material using the Fused Deposition Modeling (FDM) method, particularly in the area of hobbyist applications. PLA is also widely used in traditional processing of polymer materials. However, despite being a plant-based, biocompatible and biodegradable material with properties that enable relatively trouble-free processing using FDM, its mechanical properties do not rank it among the best available materials. Nonetheless, PLA can serve as a good foundation for other materials, resulting in the development of many composites based on PLA. In recent years, there has been significant interest among scientists in various additives for PLA, aiming to improve or completely alter its specific properties [15]. This applies to a large extent to medical applications, such as the production of composite scaffolds consisting of PLA and nano-hydroxyapatite (n-HA) [16].

Fused Deposition Modeling (FDM) processed materials, including PLA, exhibit significant differences in strength parameters. This is particularly evident in the orientation parameter of the product in the build chamber, which can pose a challenge when manufacturing micro-needle systems [17]. On the other hand, other studies have shown that the tensile strength of PLA material produced by FDM increases with a decrease in layer thickness at the same printing angles [18]. In the case of manufacturing micro-needles, the layer thickness should be as small as possible to best replicate the digital geometry.

As noted by the authors [19], methods based on light-induced polymerization can produce micro-needles with greater accuracy, making them more suitable for further use. On the other hand, they also note the problem of transitioning from the research phase to mass production, due to the limited prevalence of these methods and the toxicity of the materials. FDM machines are much more common, and with further research and the use of additional tools such as artificial intelligence models, it will be possible to shorten the time for designing and producing micro-needles, as well as significantly reducing costs, which will translate into faster adaptation for medical applications [20]. Based on a literature review and their own scientific experience, the authors of this paper believe that it is reasonable to conduct further research on designing and manufacturing micro-needles using the widely available and easy-to-use manufacturing method of FDM and PLA material.

MATERIALS AND METHODS

Research concept and plan

The aim of this study was to investigate the accuracy of reproducing digital geometry and the compressive and shear strength of incrementally manufactured microneedle systems made from PLA using the FDM method. Determining these assessment indicators for microneedle systems allows for the preliminary verification of their suitability for transdermal drug delivery procedures.

The first step in the study was to examine the geometries of microneedles and the parameter values of the FDM method that would allow for the production of microneedles of sufficiently good quality. Subsequently, the mechanical properties of the microneedle systems were investigated for the best configurations. Since determining the values of several different parameters is necessary when designing the FDM process, it was decided to limit the variability to three parameters: the material's extrusion temperature, the layer height, and the angle of inclination of the base of the micro-needle system relative to the working table (the orientation of the product in the workspace), based once again on literature and authors own experience.

A separate issue is the selection of the FDM machine for research purposes. There are

numerous machines available on the market for additive manufacturing using the FDM method. They differ significantly in their construction and the range of parameter values with which the manufacturing process can be initiated. This implies that some machines are better suited than others for producing products such as microneedles. Based on a literature analysis and authors' experience, five characteristics that an FDM machine should possess in order to be most useful for manufacturing micro-needle systems were identified.

The first characteristic is the possibility of producing with the thinnest possible layer thickness. This depends on both the mechanical structure of the FDM machine and the ability to adjust this parameter in the machine's control software. The thinner the layer thickness that can be used, the better the strength properties should be, particularly at the layer interfaces.

The second characteristic is the ability to use nozzles with a smaller diameter than those found in standard office-type FDM machines. The smaller the nozzle diameter, the better the replication of the digital geometry of the product should be.

The third characteristic is the machine's direct feeding of material to the extrusion nozzle (direct extruder). This FDM machine design allows for better control of retraction, which can be critical when extruding individual paths with very small amounts of material.

The fourth characteristic is the use of deeply grooved wheels in the extruder for material movement. The small nozzle diameter requires greater force for pushing the softened material, compared to filaments of the same diameter.

The final characteristic of the FDM machine, which can be very useful for producing a large number of microneedle systems, is the automation of the process of leveling the machine's work table. In the case of repeated heating and cooling of the machine, including the use of removable magnetic tables, automated leveling ensures greater production repeatability and, consequently, consistent results.

Design of micro-needles

In the study, five types of microneedle geometries were employed. The first one was a cylinder with a diameter of 0.5 mm, used as a reference simply geometry. The second type, commonly found in scientific literature, was a cone with a diameter of 0.5 mm. The third type was a cylinder terminated with a cone, with a cylinder diameter of 0.5 mm. The fourth geometry was a pyramid, with a square base of dimensions 0.5 mm. The final type of geometry was a cylinder terminated with a cone, where the base had a flange with a diameter of 0.7 mm. According to the authors,

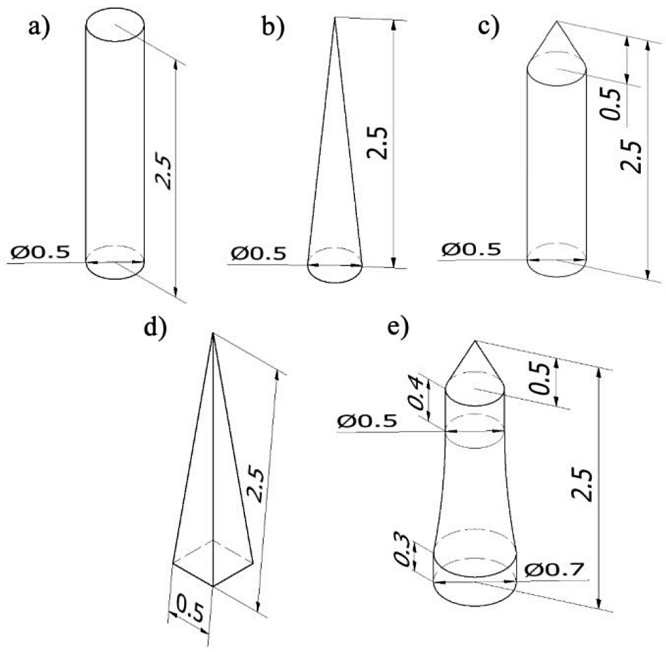

Fig. 1. Types of microneedle geometry: a) cylinder, b) cone, c) cylinder with a cone, d) pyramid, e) cylinder with a cone and a flange at the base

the flange was intended to enhance the adhesion force of the microneedle to the base of the microneedle system.

Each of the geometrical types was prepared for four different microneedle heights: 1.0, 1.5, 2.0, and 2.5 mm. The literature usually mentions microneedles no longer than 2 mm [21], however, the authors wanted to investigate the possibility of producing slightly larger micro-needles. A longer microneedle represents a larger surface area, which can be covered with medication, allowing for the application of a higher dose of the drug, in addition to deeper skin penetration. The visualization of the microneedle geometry with maximum height is presented in Figure 1. A total of 20 microneedles with differing digital geometries were prepared. All geometries were designed using Autodesk's Inventor 2023 software. Each experimental sample (microneedle system) consisted of a square base measuring 10x10x1 mm and a microneedle array of 5x5. Hence, each experimental sample contained 25 microneedles, all of the same type.

Manufacturing

The device used for the production of research samples was a Prusa MK3S+ manufactured by Prusa Research, operating according to the FDM method. The material used for producing the samples was a thermoplastic PLA filament with a nominal diameter of 1.75, in white color, manufactured by Spectrum Filaments. The choice of colored filament rather than transparent was motivated by the possibility of better visual control over the produced elements.

To prepare the control codes for the FDM machine, PrusaSlicer software version 2.5 was utilized. The values of the technological process parameters, which were altered for each research series, were chosen based on the recommendations of the machine and material producers, as well as authors own experience. The material extrusion temperatures were varied by five degrees Celsius, ranging from 190 to 205. The layer heights were set at two different values: 0.05 and 0.1 mm. In the case of the inclination angle of the microneedle system base relative to the worktable, two values were applied: 0° (flat) and 45° (inclined). The exemplary visualization of the setup is presented in Figure 2.

In order to reduce stringing, the retraction length parameter was set to 1.5 mm (compared to the standard value of 0.8 mm). The retraction speed was changed from 35 mm/s to 40 mm/s. The path width was 0.15 mm, determined by the diameter of the extruder nozzle used. The standard diameter of the extruder nozzle is 0.4 mm, which is 166% larger than the diameter used in the study.

When producing small FDM parts with low layer heights, it is also necessary to reduce the material deposition speed. In this study, the default extrusion speed was changed to 15 mm/s. Additionally, a z-hop of 0.15 mm was set for all technological processes. The technological parameters of FDM that were not mentioned above were set to their standard values.

In the first part of the research, which aimed to determine the capabilities and quality of digitally reproducing geometry in the FDM process, batches of 3 samples were used. A total of 960 microneedle systems were produced. Subsequently, for the process settings and microneedle geometry that provided the best shape and surface quality, production of experimental batches consisting of 10 samples was repeated. At this stage of the research, 80 microneedle systems were produced and subjected to further strength testing.

Samples from each batch were produced in a single technological process, but not layer by layer. Instead, the FDM device's extrusion head would produce the entire sample before moving

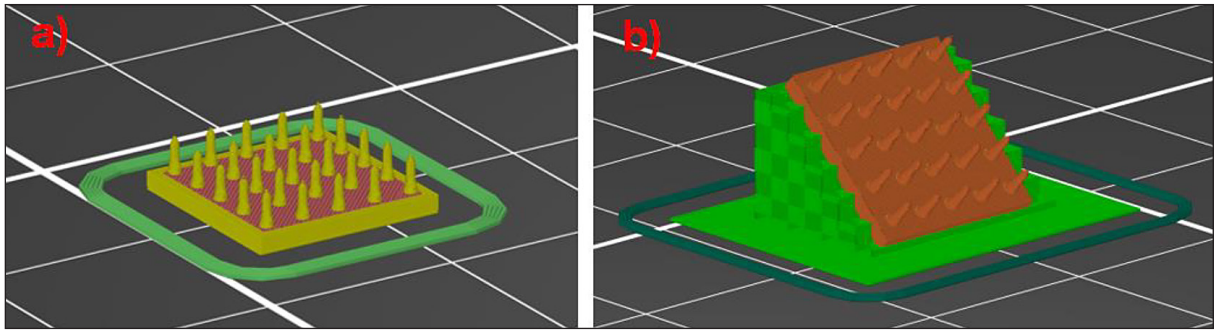

Fig. 2. Sample orientation relative to the FDM machine worktable: a) flat - 0°, b) inclined - 45°

on to the next. The production of a single sample took approximately 20 minutes for the largest layer thickness and smallest geometric volume of microneedles, up to approximately 60 minutes for the smallest layer thickness and largest geometric volume of microneedles. To improve adhesion between the manufactured element and the FDM machine's build plate, Dimafix adhesive was utilized.

Testing procedure

In the first part of the study, the quality of manufactured microneedles was examined using an InSize ISM-PM200SB microscope at a magnification of x200. If a sample exhibited visible significant signs of stringing, the geometry of the microneedles was not examined and the sample was rejected. For samples without excessive stringing, height and width measurements at the base level were taken for five random microneedles. If significant differences in microneedles geometries were observed for a particular sample, it was rejected. If two samples were rejected in a series, the process parameters and sample geometry were considered inappropriate. In the case of one rejected sample in a series, the entire series underwent the technological process again. The height and width measurements for the series were determined as the arithmetic mean of all measurements in the series.

In the second part of the study, the strength of the samples was determined using the Sunpoc WDW-5D-HS universal strength testing machine. The test was repeated on 5 samples for each series. The bending test involved applying a load at the middle of the height of the microneedles and near the end of the microneedles (Fig. 3). At one time, the force was applied to the entire row of microneedles (five pieces). Each of the five rows could be tested consecutively. In order to properly secure the sample and apply the load force, a holder was designed and manufactured for the strength testing machine. The purpose of both of the above-mentioned strength tests was to simulate a situation in which the microneedle system is partially embedded in the epidermal layer and a patient tries to move or remove it, resulting in a similar tearing force as with a standard plaster. In such a situation, the detaching force is not perpendicular to the skin surface and induces bending load on the microneedles.

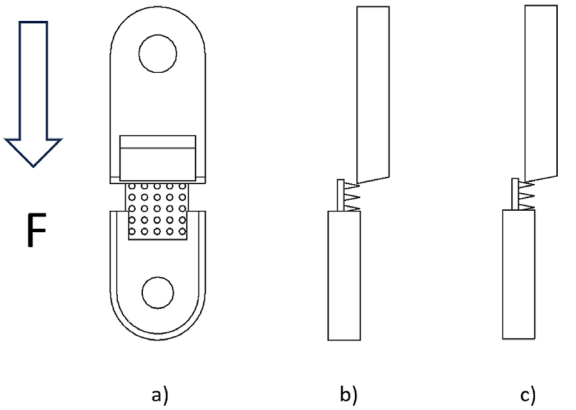

Fig. 3. Scheme of loading microneedles in a bending test: a) front view of the sample in the holder, b) force applied near the end of the microneedles, c) force applied halfway up the microneedles

The compressive strength test was performed using standard equipment of the machine. The entire sample was subjected to compression, which means that 25 micro-needles were simultaneously loaded. A compressive force equal to 50 N was adopted as the reference value. This is the upper range of the force value that an adult can exert while gripping a microneedle system of the size of the applied test specimen. This value was determined experimentally using the FB500 dynamometer from AXIS company and a slice of artificial skin made of Smooth-On Ecoflex 00-30 elastomer with a Shore 00 hardness of 30.

RESULTS AND DISCUSSION

For most samples in the first part of the study, the combination of the FDM process technological parameter values and the microneedle geometry did not allow obtaining samples without excessive stringing or visible deformations of geometry visible to the naked eye. It turned out that no sample manufactured with a flat orientation relative to the worktable was qualified for the second part of the study. The best results in reducing stringing, when manufacturing samples with a flat orientation, were obtained using the lowest extrusion temperature and the highest layer thickness value. On the other hand, when using the lowest temperatures, some microneedles broke when detaching the samples from the worktable. This occurred at the layer boundaries, indicating that the temperature of the extruded material was too low to ensure sufficient diffusion time of polymer chain between consecutive layers.

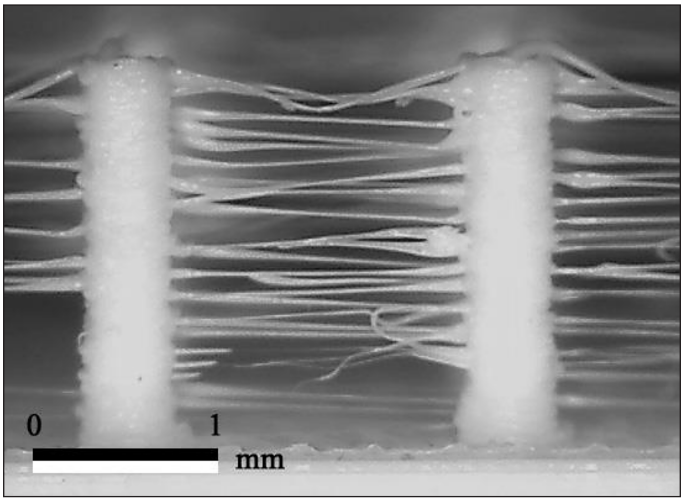

Fig. 4. Cylindrical microneedles (2 mm height) with extensive stringing, flat manufacturing orientation

In general, the greatest problem during the extrusion of small volumes of PLA material through a nozzle with a small diameter (0.15 mm) was stringing (Fig. 4). It should be noted that practically for each of the applied geometries, the stringing was greater with higher microneedles. The slimmer the microneedles, the smaller the volume of material extruded for a single layer of the microneedle tip. Due to excessive stringing, in the case of some samples, the machine operator would not even be able to determine the type of microneedle being manufactured.

The most problematic type of microneedle in the manufacturing process was the pyramid shape. Although it did not pose significantly greater threading problems compared to other types of microneedles, due to the very small dimensions of its geometry, the FDM machine was unable to reproduce the shapes of the pyramid cross-sections in individual layers. This means that for very small geometries and manufacturing processes used in this study, it was not possible to extrude paths in the form of corners. This situation occurred both in the manufacturing of flat samples and at a 45° angle.

Among all geometries, the microneedle samples constructed with a cylinder terminated to a cone with a flange at the base showed the best reproduction of shape and dimensions. The thinner layer thickness allowed for better shape reproduction. For many samples, there was a phenomenon of constriction at the base of the microneedle (Fig. 5), especially in the case of manufacturing flat samples. The constrictions reached a value of up to 70% of the nominal diameter of the microneedle. For samples manufactured without defects, while using a 0.05 mm layer, the stepped effect was very difficult to notice with the naked eye.

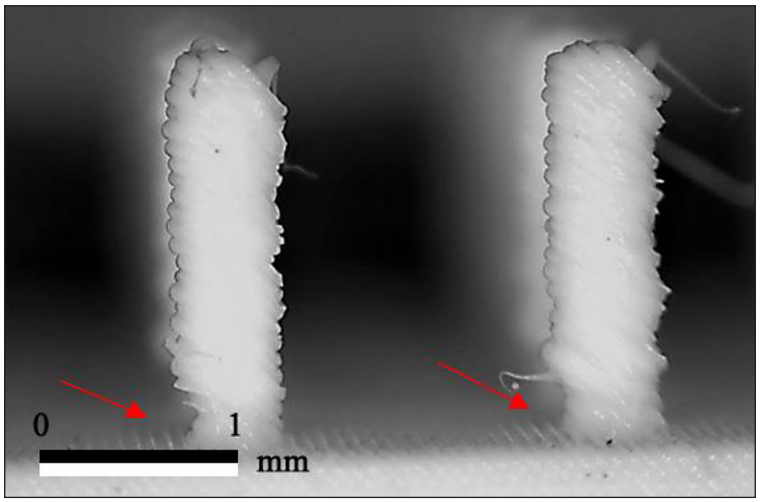

Fig. 5. Constriction at the base of a cylindrical microneedle (2 mm height), inclined manufacturing orientation - place marked with an arrow

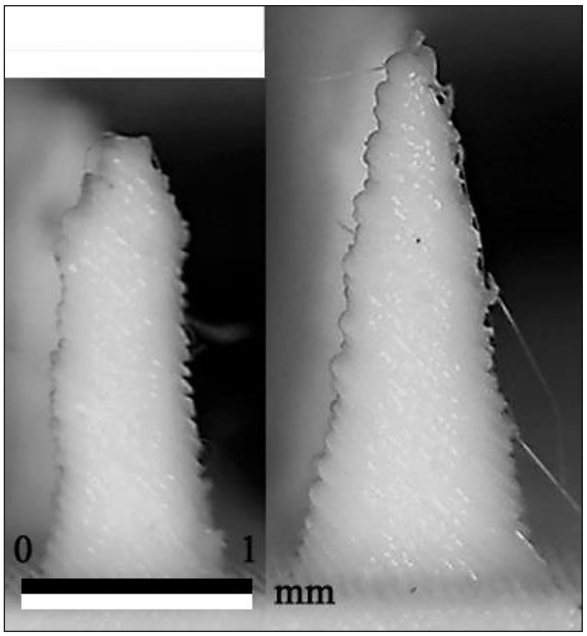

Fig. 6. Examples of microneedles manufactured at an angle of 45°. On the left, a 2 mm high microneedle of the cylinder type with a cone and a flange. On the right, a 2.5 mm high cone-type microneedle

The production of samples at a 45° angle resulted in significantly better outcomes. Not only was the stringing noticeably smaller or practically nonexistent (Fig. 6), but also the durability of the microneedles improved, as they did not crack when removed from the table, despite using the same manufacturing parameter values as flat samples.

From all the settings and process geometries investigated in the first part, the authors selected the top eight, which were further examined to determine their strength. The results of the nominal height of the microneedles for these series and the FDM process settings were presented in Table 1. All specified series were manufactured at a 45° angle. Table 2 presents the results of the arithmetic mean of the maximum force required to bend the entire row of microneedles when the load was applied at the middle of their height.

Table 2. Bending strength test results of a row of microneedles, load applied at the center of the height of the microneedles

Series	Arithmetic mean of the maximum bending force [N]	Standard deviation [N]
S1	25.05	2.92
S2	26.84	2.41
S3	23.01	1.35
S4	22.03	1.14
S5	24.3	1.28
S6	24.07	1.37
S7	37.37	1.92
S8	41.34	2.24

The microneedle systems made using a cylindrical-shaped microneedle with a cone and flange demonstrated the highest durability. Due to their design, the same bending load was distributed over a larger surface area of the microneedle. Furthermore, the microneedles in the form of a cone and those with a cone and flange cracked near the point of load application. On the other hand, the cylindrical microneedles were damaged at the contact point with the base. It was not material cracking, as observed in other types of microneedles, but rather delamination along the layer boundary (Fig. 7). This indicates that the additional flange (reinforcement) at the base is effective.

The maximum bending force of cone-shaped microneedles was slightly lower than that of cylindrical microneedles, which can also be attributed to the difference in cross-sectional area. However, the cones exhibited the highest repeatability of results, while the cylinders performed the worst in this regard.

Table 1. Series of samples of the second part of the study, which in the studies of the first part had the smallest stringing and the best reproduction of the digital representation of microneedle systems

Series	Type	Extrusion temperature [°C]	Layer height [mm]	Nominal height of the microneedle [mm]	Average real height of the microneedle [mm]
S1	cylinder	195	0.1	2.0	1.99
S2	cylinder	200	0.05	2.0	2.01
S3	cone	195	0.1	2.0	1.93
S4	cone	195	0.05	2.5	2.42
S5	cone	200	0.05	2.0	1.90
S6	cone	200	0.05	2.5	2.38
S7	cylinder with a cone and a flange	195	0.05	2.5	2.43
S8	cylinder with a cone and a flange	190	0.05	2.0	1.97

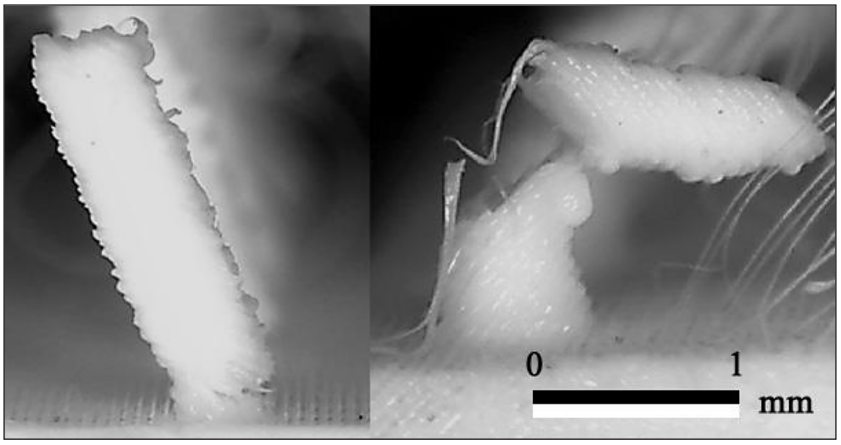

Fig. 7. Characteristics of failure of a microneedle in a bending test - on the left for 2 mm high cylinder-type microneedles, on the right for 2 mm high microneedles in the form of a cylinder with a cone and a flange

The results of the strength test on the microneedles' tip are presented in Table 3. The longer arm on which the force acted caused a significantly lower maximum load that the microneedles could bear - 60% for cylindrical microneedles, 70% for conical micro-needles, and 40% for cylindrical microneedles with a conical tip and flange. The manner in which the microneedles were damaged was the same as in the test with the load applied at the center of the microneedle. It can be concluded that the microneedles in the form of cylinders with a conical tip and flange are best suited for bearing the loads proposed in this study. The reported results relate to one row consisting of 5 microneedles. When simultaneously loading the entire microneedle system, the maximum force would be up to 5 times greater for a 5x5 arrangement. According to the authors, for all tested series, these are load values that are unlikely to be exceeded with careful use of microneedle systems.

The results obtained from the bending test confirm that a smaller thickness of the layer results in greater strength, especially at the layer boundaries. Additionally, a higher extrusion temperature increases the ability of the microneedles to bear loads.

The last strength test involved compressing the entire microneedle systems. The average deformation values of the microneedles are presented in Table 4. None of the microneedles, even the cylindrical type, suffered distortion or damage in a location other than the tip. The damage to the microneedles was minimal and practically the same for samples terminated with a cone (S3-S8), and slightly smaller for samples with cylindrical microneedles (S1 and S2).

Since the results are close to the sensitivity limit of the tensile strength machine, it is not possible to determine whether factors other than microneedle geometry have influenced the compressive strength. However, the authors believe this is not particularly significant because during the strength test, the tips of the microneedles come into contact with a hard surface, which causes their deformation (Fig. 8). In the case of using them on the skin, before the microneedles deform, the skin layer undergoes penetration.

Table 3. Microneedle row bending strength test results, load applied at the end of the microneedles

Series	Arithmetic mean of the maximum bending force [N]	Standard deviation [N]
S1	10.10	2.35
S2	10.21	2.17
S3	7.03	1.38
S4	6.92	1.69
S5	7.05	1.73
S6	6.90	1.47
S7	15.48	1.90
S8	17.51	2.21

Table 4. Compressive strength test results of the entire microneedle system

Series	Average deformation at a load of 50 N [mm]	Standard deviation [mm]
S1	0.062	0.0040
S2	0.064	0.0049
S3	0.086	0.0049
S4	0.078	0.0040
S5	0.080	0.0063
S6	0.082	0.0075
S7	0.090	0.0063
S8	0.096	0.0049

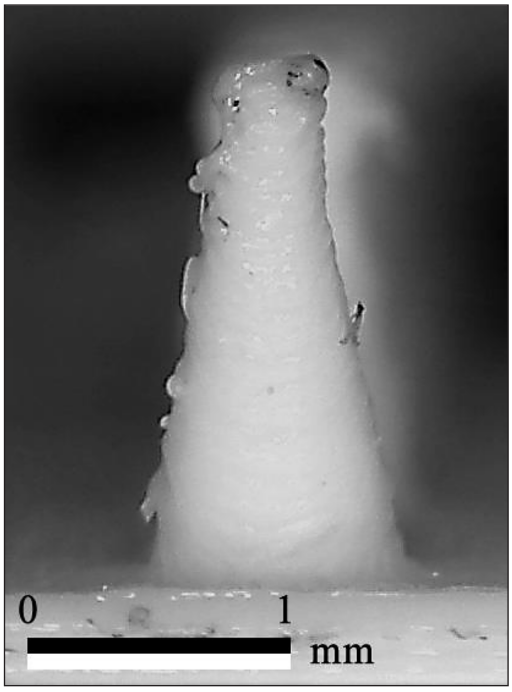

Fig. 8. A 2 mm high cone-shaped microneedle deformed under a compressive force of 50 N

Furthermore, the load will be distributed over a much larger area of intact skin, which will deform on the surface of the microneedle. In the case of incorrect application of the microneedle system, such as in the area around the elbow joint, the micro-needles may come into contact with the patient's bone, resulting in conditions similar to those presented in this study. It is worth noting that during deformation under compression, none of the samples fragmented, thereby reducing the risk that even in such an unlikely situation as permanent deformation of the microneedle in the human body, a part of it would remain after detachment of the microneedle system, which is even less probable.

CONCLUSIONS

The conducted research has shown that it is possible to design microneedle geometry and a technological process in such a way that the resulting product does not require complicated post-processing. However, manufacturing microneedle systems from PLA material using FDM method is not easy or even possible with every device available on the market. As the results indicate, obtaining the correct microneedle geometry requires the use of the smallest possible nozzle diameters, which are not used in standard office FDM machines. It is also necessary to significantly decrease the manufacturing speed, which can be even ten times slower than the maximum speed recommended by the device manufacturer. Additionally, considering that using a thinner layer thickness also results in better mechanical strength properties of microneedles, the time required to manufacture a single microneedle system is approximately one hour. Therefore, using FDM machines is possible and justified in the case of conducting research related to transdermal drug delivery using microneedle systems. However, applying the same solutions in production conditions, e.g., directly by medical personnel in hospitals, would be highly problematic due to the low production efficiency or the need to multiply the machine park.

Analyzing the strength results of microneedle systems, it can be concluded that production using the FDM method allows for the creation of safe-to-use microneedle systems. Particularly promising is the microneedle geometry in the form of a cylinder with a flanged ended with cone. Of course, these are only preliminary studies of microneedles that were not coated with a therapeutic agent. Selected active substances that will be applied to the microneedles may affect their mechanical properties, which requires appropriate research for each material combination.

According to the authors, further research related directly to the production of microneedle systems should focus on mechanical changes in the FDM machine's construction in order to better adapt it to the production of this type of geometry. On one hand, the extruder itself should be the object of research, better adjusted for extruding smaller amounts of material. It would also be reasonable to introduce filaments with smaller cross-sections. Finally, in the case of manufacturing microneedle systems dedicated to a specific patient, with the same geometry, it would be justifiable to introduce FDM devices with multiple extruders into production to perform the manufacturing process synchronously.

Acknowledgements

This study was supported by the National Science Centre (Poland) project no. 2021/42/E/NZ7/00125 (ID: 526262) and statutory activity financed by Polish Ministry of Science and Higher Education (0613/SBAD/4821).

REFERENCES

1. N. Roxhed, B. Samel, L. Nordquist, P. Griss and G. Stemme, Painless drug delivery through microneedle-based transdermal patches featuring active infusion. In: *IEEE Transactions on Biomedical Engineering*, 2008, 55, 3, 1063-1071. doi: 10.1109/TBME.2007.906492.
2. Cano-Vicent, A.; Tambuwala, M.M.; Hassan, S.S.; Barh, D.; Aljabali, A.A.A.; Birkett, M.; Arjunan, A.; Serrano-Aroca, Á. Fused deposition modelling: Current status, methodology, applications and future prospects. Addit. Manuf. 2021, 47, 102378.
3. Górski, F.; Wichniarek, R.; Kuczko, W.; Żukowska, M. Study on Properties of Automatically Designed 3D-Printed Customized Prosthetic Sockets. *Materials* 2021, *14*, 5240. https://doi.org/10.3390/ma14185240
4. Górski F., Kuczko W., Weiss W., Wichniarek R., Żukowska M. Prototyping of an Individualized Multi-Material Wrist Orthosis using Fused Deposition Modelling. Advances in Science and Technology Research Journal. 2019;13(4):39-47. doi:10.12913/22998624/113543.
5. Lima, A.L., et al. Extrusion-based systems for topical and transdermal drug delivery. Expert Opinion on Drug Delivery (2023): 1-14.
6. Yang, Q., Zhong, W., Xu, L., Li, H., Yan, Q., She, Y., & Yang, G. Recent progress of 3D-printed microneedles for transdermal drug delivery. International Journal of Pharmaceutics, 2021, 593, 120106.
7. Gorkem Buyukgoz, G., Kossor, C.G., Ji, S., Guvendiren, M., & Davé, R.N. Dose titration of solid dosage forms via FDM 3D-printed mini-tablets. Pharmaceutics, 2022, 14(11), 2305.
8. Tang, T.O., Holmes, S., Dean, K., & Simon, G.P. Design and fabrication of transdermal drug delivery patch with milliprojections using material extrusion 3D printing. Journal of Applied Polymer Science, 2020, 137(23), 48777.
9. Luzuriaga, M.A., Berry, D.R., Reagan, J.C., Smaldone, R.A., & Gassensmith, J.J. Biodegradable 3D printed polymer microneedles for transdermal drug delivery. Lab on a Chip, 2018, 18(8), 1223-1230.
10. Camović, M., Biščević, A., Brčić, I., Borčak, K., Bušatlić, S., Ćenanović, N., ... & Vranić, E. (). Coated 3d printed PLA microneedles as transdermal drug delivery systems. In: CMBEBIH 2019: Proceedings of the International Conference on Medical and Biological Engineering, 16−18 May 2019, Banja Luka, Bosnia and Herzegovina, Springer International Publishing, 2020, pp. 735-742.
11. Wu, L., Park, J., Kamaki, Y., & Kim, B. Optimization of the fused deposition modeling-based fabrication process for polylactic acid microneedles. Microsystems & Nanoengineering, 2021, 7(1), 58.
12. He X., Sun J., Zhuang J., Xu H., Liu Y., Wu D. Microneedle System for Transdermal Drug and Vaccine Delivery: Devices, Safety, and Prospects. Dose Response. 2019, 17(4), 1559325819878585. doi: 10.1177/1559325819878585.
13. Jung J.H., Jin S.G. Microneedle for transdermal drug delivery: current trends and fabrication. J Pharm Investig. 2021;51(5):503-517. doi: 10.1007/s40005-021-00512-4.
14. Zhao, Z., Chen, Y., & Shi, Y. (2020). Microneedles: A potential strategy in transdermal delivery and application in the management of psoriasis. Rsc Advances, 10(24), 14040-14049.
15. Subramaniam, S.R., Samykano, M., Selvamani, S.K., Ngui, W.K., Kadirgama, K., Sudhakar, K., & Idris, M. S. (2019, January). 3D printing: Overview of PLA progress. In: AIP conference proceedings. AIP Publishing, Vol. 2059, No. 1.
16. Wang, W., Zhang, B., Li, M., Li, J., Zhang, C., Han, Y., ... & Zhang, X. 3D printing of PLA/n-HA composite scaffolds with customized mechanical properties and biological functions for bone tissue engineering. Composites Part B: Engineering, 2021, 224, 109192.
17. Yao, T., Deng, Z., Zhang, K., & Li, S. A method to predict the ultimate tensile strength of 3D printing polylactic acid (PLA) materials with different printing orientations. Composites Part B: Engineering, 2019, 163, 393-402.
18. Yao, T., Ye, J., Deng, Z., Zhang, K., Ma, Y., & Ouyang, H. Tensile failure strength and separation angle of FDM 3D printing PLA material: Experimental and theoretical analyses. Composites Part B: Engineering, 2020, 188, 107894.
19. Detamornrat, U., McAlister, E., Hutton, A.R., Larrañeta, E., & Donnelly, R.F. The role of 3D printing technology in microengineering of microneedles. Small, 2022, 18(18), 2106392.
20. Rezapour Sarabi, M., Alseed, M.M., Karagoz, A.A., & Tasoglu, S. Machine learning-enabled prediction of 3D-printed microneedle features. Biosensors, 2022, 12(7), 491.
21. Mdanda, S., Ubanako, P., Kondiah, P.P., Kumar, P., & Choonara, Y.E. Recent advances in microneedle platforms for transdermal drug delivery technologies. Polymers, 2021, 13(15), 2405.