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3D Printing for Medical Use

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CurifyLabs

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The purpose of this thesis work was to undertake a thorough investigation into the application of 3D printing technology within the medical field, with specific focus on its implementation by Curifylabs. A central point of interest in this study was custom-designed Pharma Printer developed for medical purposes. This Study endeavours to provide a comprehensive examination of the Pharma Printer, its inherent advantages, and most importantly, the existing limitations and challenges linked to 3D printing technology within the medical domain.

In the pursuit of this objective, the thesis engages in an assessment of the standards and methodologies commonly adopted in the field of medical 3D printing. Notably, this study explores data collection and analysis techniques employed to evaluate the effectiveness and safety of the technology.

Furthermore, this result of the work entails the execution of various experiments aimed at validating the performance of the Pharma Printer within the context of medical applications. By systematically addressing these key aspects, this study offers valuable insights into the dynamic and evolving landscape of 3D printing technology specifically tailored to meet unique demands of the medical sector.

Keywords: 3D-printed medicine, Personalized Medicine, 3D printing, semi-solid extrusion.

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Thesis-työn tarkoituksena oli suorittaa perusteellinen tutkimus 3D-tulostus teknologian soveltamisesta lääketieteen alalla,erityisesti Curifylabsin printterin toteuttamisessa. Tutkimuksessa keskityttiin erityisesti lääketieteellisiin tarkoituksiin kehitettyyn Pharma Printeriin. Tutkimus pyrkii tarjoamaan kattavan tarkastelun Pharma Printeristä, sen luontaisista eduista ja ennen kaikkea 3D-tulostus teknologian nykyisistä rajoituksista ja haasteista lääketieteen alalla.

Tämän tavotteen saavuttamiseksi tutkielma arvioi yleisti lääketieteen 3D-tulostuksessa käytettyjä standardeja ja menetelmiä. Erityisesti tutkimus tutkii tietojen keräämiseen ja analysointiin käytettyjä tekniikoita arvioitaessa teknologian tehokkuutta ja turvallisuutta.

Lisäksi työn tuloksena on erilaisten kokeiden suorittaminen Pharma Printterin suorituskyvyn validoimiseksi lääketieteellisissä sovelluksissa. Järjestelmällisesti käsittelemällä näitä keskeisiä näkökohtia tutkimus tarjoaa arvokkaita näkemyksiä 3D- tulostusteknologian dynaamisesta ja kehittyvästä maisemasta, joka on erityisesti tehty vastaamaan lääketieteellisen sektorin ainutlaatuisiin vaatimuksiin.

Avainsanat: 3D-printed medicine, Personalized Medicine, 3D printing, semi-solid extrusion.

Contents

Alphabetical list

3D: Three-dimensional

GMP: Good Manufacturing Practice

API: Active pharmaceutical ingredient

G-code: Code language used mostly in 3D printing.

AM: Additive Manufacturing

FDA: U.S. Food and Drug Administration

ECHA: European Chemicals Agency

SVHC: Substance of very high concern

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

RoHS: Restriction of Hazardous Substances Directive

EEE: Electrical and Electronic Equipment

EMC: Electromagnetic Compatibility

EMI: Electromagnetic interference

IEC: International Electrotechnical Commision

CE: European conformity

NIR: Near-infrared radiation

1. Introduction

In today's era of rapid technological progress, we find the convergence of innovation and healthcare reshaping the way we approach medical practice. One of the most promising innovations in this context is 3D printing, a technology that holds great potential for transforming healthcare, particularly in the field of personalised medicine.

The integration of 3D printing into medicine combines precision engineering with healthcare delivery, offering exciting possibilities for customising and optimising patient care. This thesis embarks on a detailed exploration of 3D printing, examining its applications, advantages, and the challenges it presents in healthcare, with a particular focus on its role in personalised medicine.

The impact of 3D printing on medical practices is substantial, and this study aims to shed light on its wide-ranging implications, particularly its potential to provide highly tailored medical solutions. Beyond discussing the current state of 3D printing in the medical field, this study also looks ahead to envision the exciting opportunities this technology offers in the ever-evolving landscape of personalised healthcare.

The aim of this study is to conduct a thorough examination of the application of 3D printing in the field of pharmaceuticals, specifically in the context of medical use. We will delve into its capabilities, assess its advantages and limitations, and examine the methodologies employed in research, data collection, and experiments to achieve precise measurements.

The overarching purpose of this project was to impart knowledge regarding the utilisation of 3D printers in the medical sector, with a specific focus on drug delivery applications.

2. Curifylabs Oy

CurifyLabs, a healthtech company based in Finland, is actively engaged in healthcare innovation, particularly in the realm of personalised medicine. Specialising in 3D

printing solutions, the company is dedicated to advancing pharmaceutical manufacturing techniques to cater to the dynamic landscape of personalised healthcare.

In recognition of the evolving healthcare needs of patients, CurifyLabs has undertaken the mission of modernising the drug compounding process within pharmacies and healthcare institutions. This transformative effort is centred around ensuring the sustainable, quality-controlled production of highly personalised medications. It is through this endeavour that CurifyLabs enables the creation of therapeutic options that are not just effective but also remarkably safe, meticulously designed to harmonise with the distinctive healthcare requirements of each and every patient.

At the heart of CurifyLabs' innovative approach lies its automated on-demand manufacturing concept, aptly named "the Pharma Kit." This concept, paired with the development of printable pharmaceutical inks, is the key to unlocking the potential of mass customization in medication. Furthermore, CurifyLabs customises its very own printer, known as the "Pharma Printer," designed to seamlessly integrate with the Pharma Kit, enabling the precise and efficient production of patient-specific pharmaceuticals.

The result is a paradigm shift in healthcare, where patient-specific pharmaceuticals become not only a possibility but also a cost-effective reality. With CurifyLabs at the forefront of this transformative journey, the healthcare industry is poised to provide more effective, safer, and economically sustainable treatment options for patients, ushering in a new era in personalised medicine.

3. 3D Printing in Pharmaceutical Sector

This thesis focuses on the integration of 3D printing technology within the pharmaceutical sector, emphasising its impact on drug formulation and manufacturing. The research explores the applications of 3D printing in pharmaceuticals tailored to individual patient needs and medical conditions

The investigation will assess the advantages of 3D printing in pharmaceuticals, including its potential to enhance drug manufacturing and precision. It will also address regulatory challenges and ethical considerations associated with the adoption of 3D printing in pharmaceutical production.

The primary aim of this thesis study is to explore and explain the substantial potential that 3D printing technology holds within the pharmaceutical industry. The key focus of this investigation is to present the existing standards and best practices related to 3D printing in the pharmaceutical sector. Ultimately, the purpose is to enhance patient care by redefining pharmaceutical development and delivery methodologies. This study seeks to revolutionise the pharmaceutical landscape, ultimately leading to improved healthcare quality and outcomes.[1.]

3.1. The Concept of 3D printing in Medicine

The concept of 3D printing in medicine refers to the application of cutting edge 3D printing technology within the healthcare sector. This technology is employed to create custom designed three dimensional structures and components specifically tailored for medical purposes. Such applications include the precise generation of individual droplets and the formulation of medications with an exceptional level of accuracy and adaptability.

This innovative approach involves the use of additive manufacturing(AM) and G-code programming to guide the 3D printing process. Through the careful layer-by-layer deposition of materials or the controlled dispensing of droplets at a desired weight, medical professionals can achieve an exceptional degree of precision when formulating medications.[1; 3]

Additionally, an integral part of this process is a syringe holder, which serves a dual purpose. It not only securely holds the syringe but also functions as a heating element. This heater can be finely adjusted to maintain the material at its ideal viscosity during pharmaceutical production(Figure 2).

In summary, the concept of 3D printing in medicine represents a remarkable leap forward in pharmaceutical production, allowing for the creation of highly customised and precise drug formulations. It harnesses the power of advanced AM techniques and

G-code programming to provide healthcare professionals with the tools needed to cater to the unique needs of individual patients, all while maintaining precise control over the pharmaceutical materials' temperature and viscosity.

As depicted below, the 4 by 4 print, with single waste drop on the left, has been tested using G-code to ensure the correct position, as indicated by the blue marks(Figure 1)

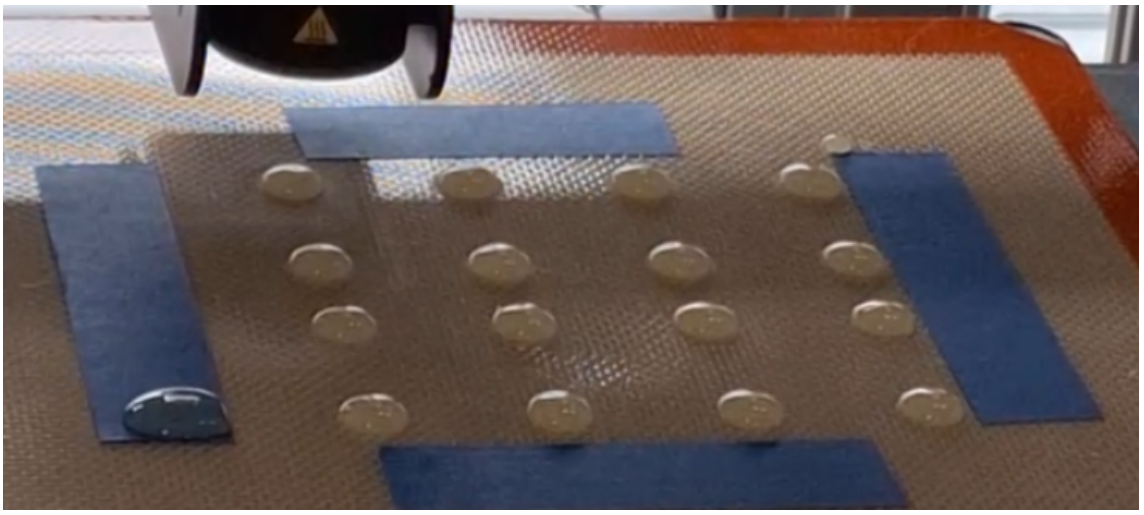

Figure 1. A preview of successful 3D printing on a test mat with blue marks.

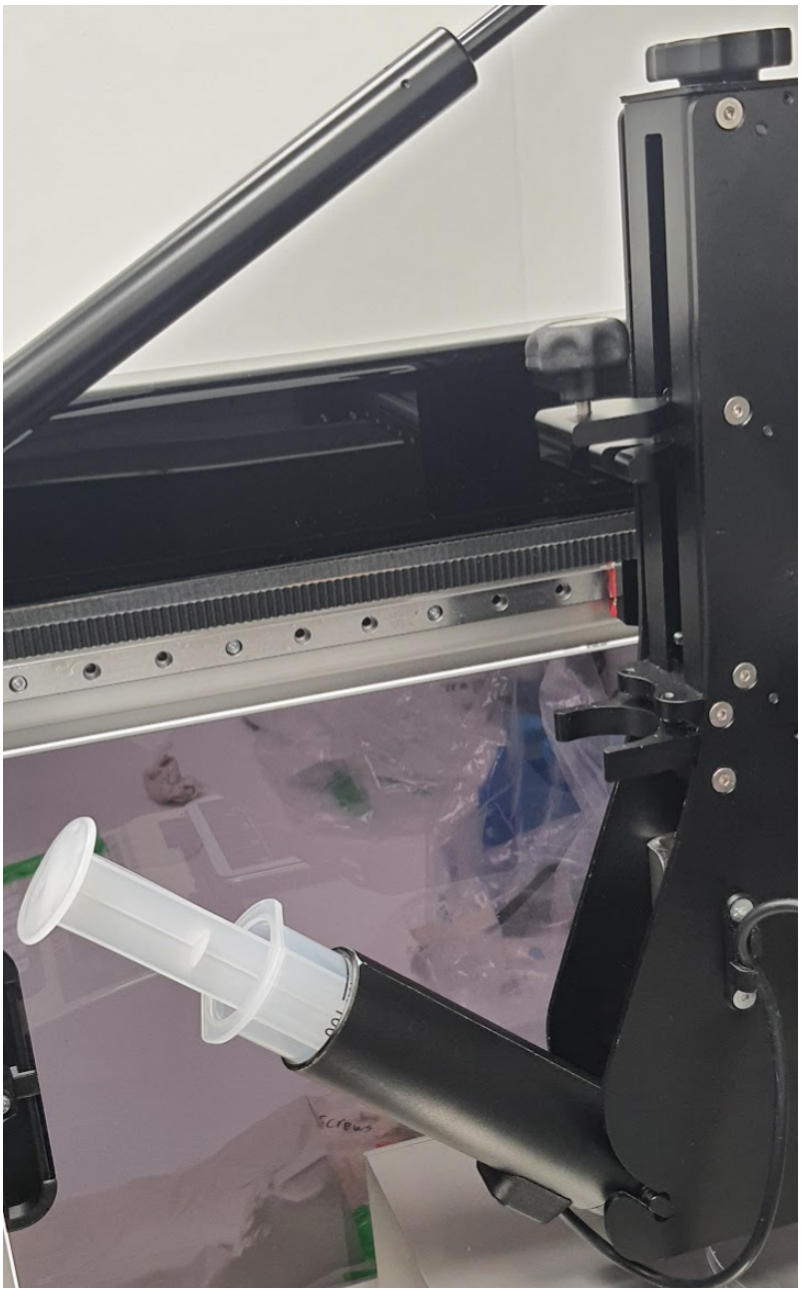

Figure 2.Printer with syringe.

3.2. The Rise and Demand of 3D Printing

The rise in demand for 3D printing in the medical drug delivery sector is considerable. This innovative technology has opened new avenues for producing precisely customised drug delivery systems. By leveraging 3D printing, healthcare professionals can create personalised medication formulation, tailored to the unique needs of each patient. This not only enhances the efficacy of treatment but also minimises adverse side effects. As the demand for more effective and patient-centric drug delivery

solutions continues to grow, 3D printing stands at the forefront of this transformative wave, promising a future where medicines are precisely tuned to the individual. Particularly within the medical field, this surge can be attributed to several key factors that underscore its growing significance.

Customization in Healthcare: 3D printing enables the creation of highly customised and patient-specific medical devices and solutions, such as gelatin based, and film based medicine to help those who have a hard time swallowing regular medicine. This capability aligns perfectly with the healthcare industry's increasing focus on personalised treatment.

Patient Compliance: Tailoring medications to individual needs with customised dosages and formats, like 3D printed tablets, holds potential to significantly improve patient compliance. When patients receive medications that align precisely with their unique requirements, they are more inclined to adhere to the prescribed treatment regimens. This, in turn, can lead to better health outcomes and a more effective management of medical conditions, as patients are more likely to consistently take their medications as directed.

Reduced Wastage: Customising drug production to match individual patient requirements is a hallmark of 3D printing technology. This approach not only minimises pharmaceutical waste but also fosters sustainable practices in the healthcare sector. Moreover, it streamlines the production process, which, in turn, reduces the time required to create personalised dosages. In this manner, 3D printing not only contributes to environmental sustainability but also enhances efficiency in drug manufacturing.

4. Overview of CurifyLabs 3D printer

4.1. Minilab Printers

The Minilab printer, which represented the alpha version, displayed significant promise with its compact design and built-in tablet. However, it required an additional box with a WiFi access point and a desktop switch to establish connections with necessary components through an Ethernet cable. These components included a scale, WiFi

access, and an iPad network, which were mainly for communication in a closed environment.(Figure 3.)

The built-in android tablet of the printer was incompatible with our software for receiving orders and controlling the printer, necessitating the use of an iPad for this purpose. Moreover, the printer lacked an integrated scale, leading us to implement an external scale to measure each tablet as it was printed on the machine.

The printer came equipped with an integrated docking system designed to accommodate as many as five distinct cartridges. Notably, this docking system boasted the capability to heat all the materials it housed, showcasing the potential for simultaneous heating and being able to print with up to five different materials.

Nevertheless, operational challenges arose during the process. There were instances where the scale experienced calibration issues, resulting in incorrect measurements during the printing procedure. Furthermore, occasional material leakage occurred from the printer’s syringe. Additionally, a notable quantity of material was expended in the pre-printing extrusion process, as quantified by an infrared sensor, contributing to material wastage.

In summary, The Minilab printer’s alpha version exhibited an innovative compact design with a built-in tablet. Despite its potential, it required additional equipment for connectivity and faced operational issues, including calibration problems and material leakage. To optimise its performance, further refinements and improvements were necessary.

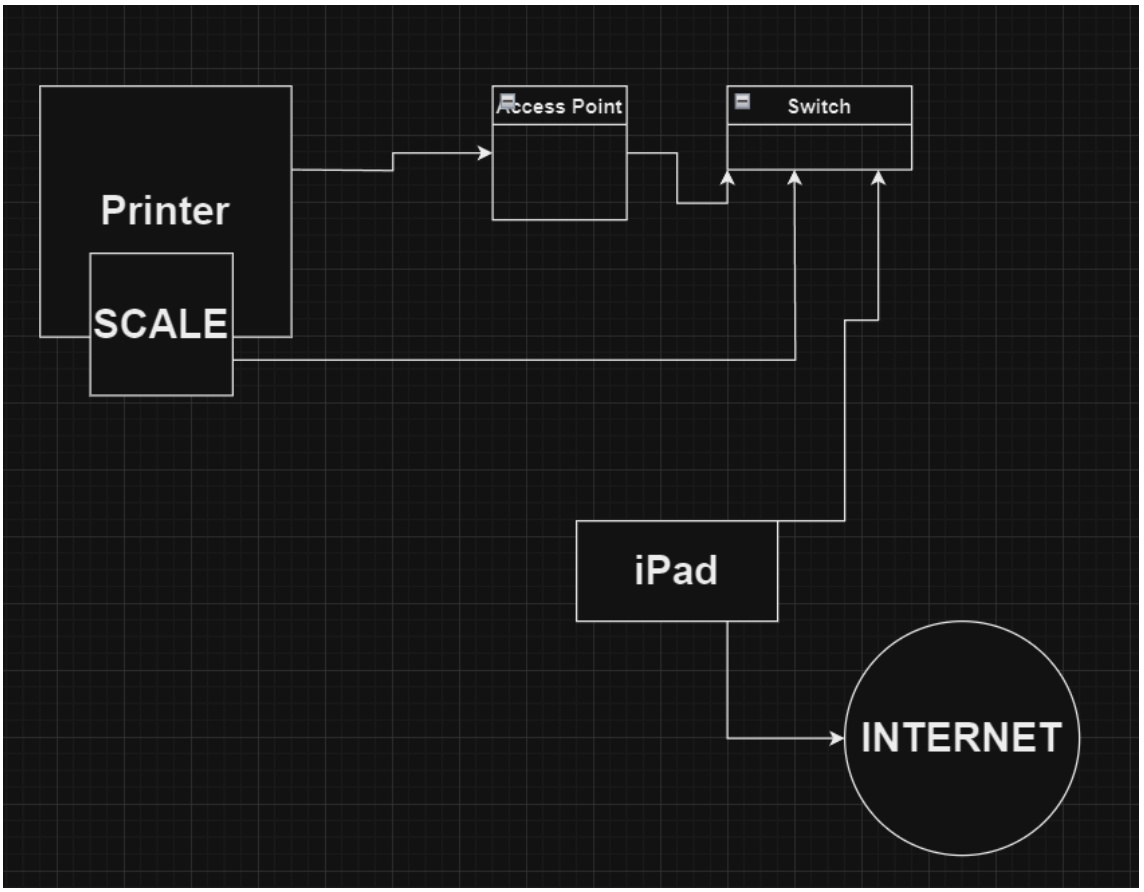

Figure 3. Connection diagram of Minilab.

Figure 4. Minilab with black box, scale and iPad attached.

4.2. Pharma Printers

The Pharma Printer is a custom-built 3D printer designed with meticulous precision for medical applications. This state-of-the-art printer operates seamlessly using CurifyLabs' exclusive software, which has been tailored for this specific design. A key feature of this innovative device is the incorporation of an integrated scale mechanism, specially designed for the medical environment. This integrated scale continuously calculates the weight of every individual droplet throughout the printing process.

The recorded data is promptly and seamlessly transmitted to a dedicated website, facilitating real-time monitoring and analysis. This capability allows to swiftly determine

whether each droplet meets the weight specifications essential for various medical applications.

In comparison to its predecessor, the alpha version, the Pharma Printer presents a series of enhancements. Notably, the black box has been eliminated, replaced by a Raspberry pi that displays all the essential information needed by pharmacists. Although the latest iteration lacks the dock designed to hold five different cartridges, it features a cutting-edge print head that keeps the material at the ideal temperature consistently.(Figure 5)

Furthermore, the waste cup component has been removed from the setup, based on extensive testing with a similar printhead and syringe system. These tests revealed that material leakage was not a concern, and the extrusion results were satisfactory. This advancement not only streamlines the printing process but also minimises material wastage.

The integration of the Pharma Printer's design with CurifyLabs' proprietary software guarantees the optimization of the printing process for medical applications. This results in enhanced efficiency, streamlined data collection, and real-time monitoring, all of which cater to the specific needs of pharmaceutical and medical professionals in their quest for precision and excellence.

Furthermore, conducted tests ensure that even in scenarios where customers do not have access to an ethernet cable at their location, an additional option of incorporating a cellular router is available. This router allows the printer to seamlessly connect to the internet using a SIM card, ensuring uninterrupted functionality.

Figure 5. Pharma printer.

4.2.1. Equipment

The Pharma Printer, incorporating cutting-edge additive manufacturing(AM) technology, has been meticulously tailored to meet the specific requirements of Curifylab. It is built upon a robust 3D printer frame, and its design incorporates a specialised printing head designed to securely house syringes. Notably, the device
features a precision heating element engineered to carefully maintain the syringe's temperature during the printing process, ensuring the integrity of the printed materials.

Additionally, the Pharma Printer is equipped with an integrated scale, offering the capability to transmit data to both the printer and a centralised database. This functionality enhances its data management capabilities, contributing to improved

efficiency and data tracking.

Recognizing that not all customers may have access to an ethernet port in their location, our team identified a solution. the option of a cellular 4G LTE router, ensuring uninterrupted connectivity, which adheres to all necessary standards and regulations. This additional equipment further augments the versatility and accessibility of the Pharma Printer.

4.2.2. Software for Medical 3D printing

Curifylab's IT team has tailored the software to ensure a seamless user experience. This user-friendly software simplifies the entire process. Users only need to log in to the website, input the necessary information, select the printer, and choose the specific print job they wish to produce. Once these selections are made they can start the printing process with a single click on the printer and then follow the step-by-step instructions provided in the appendix. (Figures 6, 7 and 8)

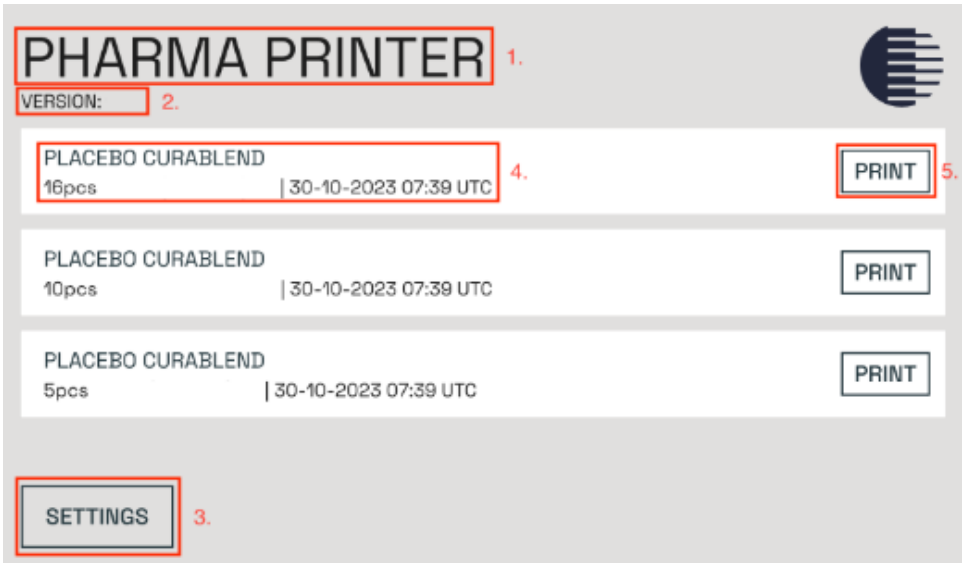

Figure 6. The individual printers' name and version number can be seen in the top left corner of the main view. (1 & 2)
The maintenance panel can be accessed from this view from the "SETTINGS" button in the bottom left corner. (3)

Order details can be seen in this view. (4)
The printing process can be started from each individual order's "PRINT" button. (5)

Figure 7. Prepare the cartridge. The "START TIMER" button will start a timer of a predetermined amount of time, during which the syringe will be heated.
During printing you will see the progress in the top-left corner of the application.
It is possible to see the weights of the tablets on the illustrated tablets themselves

A notable feature of this software is its real-time monitoring capabilities, allowing users to observe the precise weight of each droplet as it is extruded. If any droplet exceeds predetermined parameters, it is immediately highlighted in red, providing users with instant feedback and ensuring the quality and accuracy of the printed medication.

(Figure 8) This real-time feedback mechanism play a critical role in maintaining the integrity of pharmaceutical production process

5. Standards

Medical devices play an important role in the medical sector. These include healthcare equipment, supplies and software, all of which have significant impact on patient safety and risk management in healthcare. To ensure the safety and effectiveness of these devices, supplies, and software, they must meet specific requirements. Standards allow different organisations to connect with each other, enabling decentralised production of products. When requirements are harmonised, and technical barriers are removed, trading products and services becomes significantly easier. Companies involved in the manufacturing or lifecycle management of medical devices must adhere

to strict regulatory requirements set by authorities. The key requirements for this industry, including those relevant to this engineering work, are discussed in the following chapters.

Throughout our study, carefully reviewed the regulations, guidelines, and policies governing the utilisation of 3D printing in the medical field. My team's focus was assessing the compatibility of semi-solid extrusion based 3D printing technologies with existing regulations, including those established by the FDA(U.S. Food and Drug Administration) and its international equivalents. Additionally, I and the team inspected the essential standards and directives governing CurifyLabs Pharma Printer and materials associated with pharmaceuticals.

5.1. FDA (U.S. Food and Drug Administration)

The FDA plays an important role in regulating the integration of 3D printing into the field of medicine. As this technology continues to advance in healthcare, the FDA maintains an unwavering commitment to ensuring safety, efficacy, and promoting innovation. The agency conducts meticulous evaluations of 3D printed medical products, offers comprehensive guidelines to manufacturers, and addresses critical aspects, including quality control, sterility, and biocompatibility.

The FDA's dedication to the safe and effective use of 3D printing in medicine not only benefits patients by ensuring their well-being and fostering innovation but also stands as a cornerstone in the continuously expanding landscape of 3D printing in healthcare. The FDA remains an important guardian of public health. It is noteworthy that the Pharma Printer has undergone careful testing to ensure its full compliance with FDA standards, reaffirming the commitment to safety and quality in the domain of 3D printing for medical applications. It's worth highlighting that Curifylabs has diligently researched and verified the Pharma Printer's adherence to FDA standards.[1.]

5.2. Material Directive

5.2.1. The Registration, Evaluation, Authorisation, and Restriction of Chemicals. REACH

The Registration, Evaluation, Authorisation, and Restriction of Chemicals framework, established by the European Union (EU) in 2007, with a primary goal to ensure a high level of protection for both the environment and human health by regulating the production, use, and distribution of chemicals. The key components of REACH

Registration:
Manufacturers and importers of chemicals must register substances produced or imported in quantities starting at one tonne but less than 10 tonnes per year. Registration entails providing extensive information about the properties and uses of chemicals, along with conducting safety assessments.

Evaluation:
The evaluation aspect of REACH [7] is overseen by Regulatory authorities, such as the European Chemicals Agency(ECHA).During the phase, authorities accurately assess the data provided in registration documents to ensure that chemical substances are used safely and in compliance with regulatory standards. This entails a thorough review of the chemical's properties, intended applications, and safety assessments, validating that substances are handled responsibly and in line with the regulations. The evaluation phase acts as a safeguard to confirm the accuracy and completeness of the information presented during the registration process, contributing to the overall goal of protecting the environment and human health.[7.]

Authorisation:
The authorisation phase in the REACH[7]. framework is a critical and strict process. It focuses on substances of very high concern (SVHCs), recognised for their extreme hazards. Companies looking to use SVHCs must undergo strict authorisation procedure, demonstrating that the benefits of using these substances outweigh the risks. This encourages the exploration and adoption of safer alternatives, aligning with REACH's [7.] overarching mission of enhancing chemical safety, safeguarding the environment and protecting human health. By closely monitoring and assessing the

use of SVHCs, this phase aims to reduce the potential adverse impacts and promote the responsible and sustainable use of chemicals within the European Union. [7.]

Restriction:
Within the REACH Framework, regulatory authorities have the power to impose limitations or even bans on the use of certain chemicals that pose unacceptable risk to the environment or human health.
The authorisation process is a significant component of REACH as it involves careful examination of the potential risk posed by SVHCs. Companies seeking authorisation must provide compelling evidence that the benefits of using such substances outweigh the risks and that they are taking steps to minimise these risks. This encourages the industry to transition to safer alternatives and plays an important role in enhancing chemical safety within the EU. [7.]

REACH exerts a profound influence on manufacturers, importers, and users of chemicals, not only within the EU but often extending to entities exporting products to EU markets. Its goal is to promote responsible and sustainable chemical use, reduce adverse impacts on environment and health, and encourage the development of safer alternatives to hazardous substances. Compliance with REACH [7] is not only a legal requirement for businesses involved in chemical production, importation, or usage within the European market but also an ethical commitment to enhancing chemicals safety. It requires careful data collection, through assessment, and precise reporting of chemical-related information to ensure regulatory compliance.[7.]

5.2.2. RoHS Directive 2011/65/EU

The RoHS Directive 2011/65/EU, commonly known as ROHS 2, is an important piece of European Union legislation enacted in 2013. places strict restrictions on the utilisation of six hazardous substances, including lead and mercury, in electrical and electronic equipment(EEE)[8,1].
The primary goal of this directive is double: to minimise the environmental impact of EEE and promote the adoption of safer materials and manufacturing processes.

One notable feature of RoHS2 is its broader scope. Unlike its precursor, it encompasses not only EEE but also extends to cover cables and spare parts. This

expansion ensures that more products fall under its directive's strict requirements, thereby increasing its efficacy in reducing the presence of hazardous substances in the environment. To meet RoHS 2[9] compliance, manufacturers, importers, and distributors must strictly evaluate their products, involving testing and comprehensive documentation. This directive lays down rules on the restriction of the use of hazardous substances in electrical and electronics equipment (EEE) with view to contributing to ensuring the safety of the environment and human health, including the environmentally sound recovery and disposal of waste EEE [8,4].

The Impact of RoHS 2011/65/EU on the EEE industry has been substantial. It has acted as a catalyst for innovation, compelling manufacturers to explore and adopt alternative, eco-friendly materials and manufacturing methods. This not only benefits the environment but also enhances product safety and durability, providing long-term advantages for businesses and consumers alike.

The RoHS Directive 2011/65/EU is an important EU regulation that holds an important role in promoting environmental sustainability and ensuring public health. By overseeing the restriction of hazardous substances in electrical and electronic equipment, it promotes the shift toward cleaner technologies and serves the collective welfare of European citizens and the environment.[17.]

The Pharma printer will contain several components that fall under the RoHS Directive, such as the scale, along with other internal parts that adhere to the regulation.

5.3. Mechanical directives(safety)

5.3.1. Machinery Directive 2006/42/EC.

The Machinery Directive 2006/42/EC is a Key European Union regulation that was adopted in 2006 to ensure the safety of machinery and equipment placed on the European market. This directive, often referred to as the Machinery Directive, plays an important role in harmonising safety standards and requirements for machinery across EU member states.

The Primary objective of the machinery Directive is to guarantee a high level of protection of users, including workers and consumers, by specifying essential health and safety requirements that machinery must meet. It establishes a framework for the design, manufacturing, and marketing of machinery and associated components, ensuring that they are safe to use and operate.[9;18.]

Under this directive, manufacturers are responsible for assessing the risks associated with their machinery and taking measures to eliminate or mitigate them. The Machinery Directive outlines procedures for conformity assessment, including the involvement of notified bodies, to verify that machinery complies with safety requirements before it is placed on the market. One of the essential features of the Machinery Directive is its wide-ranging scope. It covers a broad spectrum of machinery, from large industrial equipment to smaller consumer products, such as power tools and 3D printers. The directive also addresses issues like the integration of safety components and the provision of clear user instructions.
The Machinery Directive 2006/42/EC has had a significant impact on the manufacturing and trade of machinery within the EU. By establishing uniform safety standards, it promotes innovation and competitiveness while safeguarding user safety. Manufacturers, importers, and distributors must comply with the directive's requirements to ensure that machinery is safe for use and free from hazards.[9.]

5.4. Electrical Directives

5.4.1. EMC Directives 2014/30/EU

The EMC Directive 2014/30/EU, an integral part of the broader European Union directive framework, was enacted in 2014 with the primary objective of standardising regulations concerning electromagnetic compatibility (EMC) for electrical and electronic equipment. This directive ensures that such equipment adheres to strict guidelines, preventing excessive electromagnetic interference and maintaining resilience against external disturbances. "Electromagnetic disturbance" means any electromagnetic phenomenon which may cause degradation performance of equipment such as electromagnetic noise, an unwanted signal or change in propagation medium itself. Manufacturers bear a significant responsibility in achieving compliance with EMC Directive. They are tasked with conducting intensive testing, careful documentation, and the application of the CE marking to indicate the conformity[10,9]. The directive's reach is extensive, encompassing a diverse spectrum of equipment types, thereby promoting uniformity in standards and encouraging technological advancements that prioritise user safety.

The impact of the EMC Directive on the electrical and electronic equipment industry within the European Union has been profound. It has played an important role in harmonising standards, fueling innovation, and promoting competitiveness while upholding the integrity and safety of equipment in the face of electromagnetic interference. This directive stands as testament to the EU's commitment to advancing technology while safeguarding its citizens.[10.]
It is worth noting that the Pharma Printer underwent thorough EMC testing, and it successfully met all the requisite standards and requirements, demonstrating its compliance with the EMC Directive.

5.4.2. **Low Voltage Directive 2014/35/EU**

The Low Voltage Directive 2014/35/EU, a key component of the European Union's directive framework, was established in 2014 to ensure the safety of electrical equipment with regards to voltage standards. This directive lays down essential requirements for electrical equipment to prevent hazards, especially those arising from low voltage usage.
Compliance with the Low Voltage Directive places a significant responsibility on manufacturers. They must ensure that their electrical equipment conforms to safety standards, carry out relevant testing, maintain comprehensive documentation, and affix the CE marking. The CE marking indicates the conformity of electrical equipment and is the visible consequence of a whole process comprising conformity assessment in a broad sense. The directive encompasses a wide array of electrical equipment, promoting consistency in safety standards and encouraging technological advancements that prioritise user safety[11.]

The Low Voltage Directive 2014/35/EU has had a substantial impact on the electrical equipment industry within the European Union. It plays an important role in harmonising safety standards, fostering innovation, and ensuring well being of users by preventing hazards associated with low voltage electrical equipment.[11.]

5.5. IEC 61010-1:2010

IEC 61010-1:2010, known as “Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 1: General requirements,” is an international standard established by the International Electrotechnical Commission (IEC). This standard,part of the broader IEC 61010 series, sets forth safety requirements for electrical equipment used in diverse settings such as laboratories, control systems, and measurement applications.
IEC 61010-1:2010 specifies comprehensive safety requirements for electrical equipment. These requirements encompass aspects like risk assessment, equipment design and construction, labelling, and documentation. The central objective is to mitigate electrical hazards and reduce the associated risks linked to the utilisation of such equipment.
Compliance with standards like IEC 61010-1 is of paramount importance for manufacturers, distributors, and users of electrical equipment in the relevant applications. It guarantees adherence to safety protocols and minimises potential risks. [12.]

5.6. ISO:13485:2016

ISO 13485:2016 stands as an important international standard within the medical device sector's domain of quality management systems. It serves the paramount purpose of establishing a sturdy and structured framework that is inherently geared towards assuring the safety, quality, and reliability of medical devices. Notably, this standard places strong emphasis on addressing the distinctive and stringent requirements of the medical device industry, which extends to innovative technologies like the Pharma Printer developed by CurifyLabs.

These encompass important aspects including regulatory compliance, risk management, and the unwavering pursuit of continuous improvement. In accordance with ISO 13485:2016, each product, including the Pharma Printer, must be accompanied by a meticulously maintained organisational folder, which serves as a comprehensive repository of documentation. This documentation serves the primary

function of substantiating compliance with ISO 13485 requirements and other pertinent regulatory standards.

At a minimum, the folder should encompass a general description of the medical device, outlining its intended purpose, labelling instructions, user manuals, and detailed product specifications. In the case of the Pharma Printer, this documentation would extend to the printer's specifications, intended applications, and guidelines for safe and effective use.[3, 1]

Additionally, the folder should provide comprehensive instructions encompassing manufacturing, packaging, storage, handling, and distribution procedures. It should also encompass protocols for device measurement and monitoring, coupled with pertinent guidelines for appropriate installation and maintenance of the Pharma Printer.

5.7. IEC 61326-1:2020

IEC 61326-1:2020, known as “Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 1: General requirements.” is an international standard developed by the Electrotechnical Commision (IEC).
This standard defines electromagnetic compatibility (EMC) requirements for electrical equipment utilised in applications related to measurement, control, and laboratory setting. EMC standards are essential to ensure that such equipment does not emit electromagnetic interference (EMI) that could disrupt other devices or systems, and to ensure that equipment itself remains resilient to external EMI.
IEC 61326-1:2020 lays out the fundamental EMC requirements, encompassing testing procedures and performance criteria. It serves as a guide for manufacturers, distributors, and users of electrical equipment in these specific applications, ensuring that equipment complies with EMC standards and does not present risks associated with electromagnetic interference[14.]

5.8. WEEE Directive 2012/19/EU

The WEEE Directive 2012/19/EU, often referred to as the “ Waste Electrical and Electronic Equipment Directive,” is a piece of legislation within the European Union aimed at addressing the environmental impact of electronics waste. This directive was established to promote the proper disposal and recycling of electrical and electronic

equipment(EEE) to minimise environmental contamination and enhance resource efficiency.

WEEE Directive 2012/19/EU places responsibility on producers, manufacturers, and distributors of EEE to manage the collection, treatment, and recycling of electronic waste generated by their products. It sets recycling targets and outlines procedures for the proper disposal and recycling of WEEE waste. The directive also encourages eco-design principles to create EEE products that are more environmentally friendly and easier to recycle.

This directive plays an important role in reducing electronic waste's impact on the environment, conserving resources, and fostering a circular economy. It ensures that electrical and electronic equipment is handled responsibly, from production to end of life disposal, and minimises the environmental and health risks associated with improper waste management.

6. Printing Materials

The materials under consideration here are active pharmaceutical ingredients (**APIs**), which possess the capability to be printed using a Pharma Printer. The list of these APIs is continually expanding, but for the time being, CurifyLabs will provide a few that are currently available:

- CuraBlend (medicine that is designed for humans)
- CuraVet (medicine that is designed for pets)

7. Advantages of 3D printers in Medical sector

The integration of 3D printing technology in medicine brings a host of transformative advantages, particularly in the field of medical drug delivery. These benefits include the ability to create personalised drug formulations tailored to individual patient needs, the development of innovative and precise drug delivery systems, improved patient adherence through customised dosages and formats, reduced side effects through precise medication placement, more efficient drug development with rapid prototyping, a focus on sustainability by reducing waste and adopting eco-friendly practices, and the capacity to swiftly respond to healthcare emergencies by producing essential

medications on-demand. Overall, 3D printing in medical drug delivery represents a pivotal advancement in healthcare, offering patient-centred care, precision, sustainability, and responsiveness to urgent healthcare needs.[4;7] Some key advantages of using 3D printers in medical drug delivery applications:

1. **Personalization**: 3D printing transforms medicine by creating patient-specific therapies, including custom drug formulations that are highly effective and convenient. This personalised approach improves patient care, addressing individual needs and anatomical variations, surpassing traditional one-size-fits-all treatments. Tailoring drug formulations to unique patient requirements accommodates variations in anatomy and metabolism, enhancing effectiveness and safety while minimising adverse effects. The precision and customization offered by 3D printing in medicine set a new patient-centered standard, resulting in superior outcomes.

2. **Customised Drug Formulations**: 3D printing technology facilitates the development of personalised drug formulations with precision-tailored dosages and controlled release profiles. This capability is particularly advantageous for patients with unique medication requirements, ensuring that treatments are optimised for individual needs.[6.]

3. **Accelerated Drug Development**: 3D Printing expedites the drug development process by facilitating the swift prototyping of drug formulation and dosage forms. This technology empowers researchers to rapidly iterate on novel drug delivery methods, effectively diminishing the time needed to introduce innovative pharmaceuticals to the market. By streamlining the development cycle, 3D printing accelerates the pace of pharmaceutical innovation, ultimately benefiting patients and healthcare outcomes.

4. **Advanced Drug Research**: 3D printing serves as a valuable tool for drug research, allowing the creation of patient-specific disease models and innovative drug testing platforms. These advancements are particularly significant in the development of targeted therapies for rare diseases and conditions.

3D printing's advantages in drug-related applications lie in its capacity to revolutionise pharmaceutical formulation, drug delivery systems, and research. These capabilities result in more effective, patient-centric, and sustainable healthcare solutions, ultimately improving patient health and treatment outcomes. As the technology continues to advance, its role in personalised drug medicine is ready to grow significantly, offering new avenues for enhancing patient care and the development of innovative pharmaceuticals.

8. Current Limitations and Hurdles

The utilisation of 3D printing in drug medicine offers substantial promise, facilitating the precise tailoring of drug formulations to enhance patient care. However, this innovative approach encounters specific challenges. These encompass navigating intricate regulatory procedures, guaranteeing the safety of material used, and grappling with scalability issues. Moreover, cost-effectiveness and intellectual property concerns demand meticulous attention. Acknowledging and overcoming these limitations stand as pivotal steps toward fully realising the potential of 3D printing in the realm of personalised drug medicine. Here are some of the known limitations and hurdles:

1. **Regulatory Compliance**: Adhering to stringent regulatory requirements in the field of pharmaceuticals is often a protracted and intricate endeavour, which can exert a profound influence on both market entry and the pace of innovation. The pharmaceutical industry is characterised by diligent oversight and stringent quality standards to safeguard public health, making it imperative for companies to navigate a complex maze of regulations, certifications, and approvals. Ensuring compliance not only requires meticulous attention to detail but also substantial time and resources. Consequently, it can significantly impact the ability of pharmaceutical innovators to introduce novel products to the market and the overall rate of progress within the industry.

2. **Material Safety**: One of the foremost challenges in the realm of 3D printed drug formulations pertains to guaranteeing the biocompatibility and enduring safety of the materials used. As delve into the innovative landscape of 3D printing for pharmaceuticals, it becomes increasingly important to address this issue comprehensively. Ensuring that the materials employed in these formulations do not provoke adverse reactions within the human body, and that they maintain

their safety and integrity over extended periods, presents a complex and pressing concern that demands careful research, testing, and regulatory inspection. This multifaceted challenge necessitates continuous exploration and development of materials that meet stringent safety standards to ensure the well-being of patients and the long-term success of 3D printed drug solutions.

3. **Cost Efficiency**: Initial setup cost and material expenses associated with 3D printing drug formulations can often be substantial, which can significantly affect the overall cost-effectiveness of this technology. These costs encompass not only the acquisition of specialised 3D printing equipment but also the procurement of high-quality printing materials. It is essential to consider these expenses when evaluating the financial viability and affordability of implementing 3D printing in pharmaceutical manufacturing.

Recognizing these limitations and actively addressing them is important for maximising the potential of 3D printing in the field of personalised drug medicine.

9. Research Methodology in Medical 3D printing

9.1. Data Collection and Analysis of Printing

In the pursuit of objectives of this study, the initial focus was on developing proficiency in G-code utilisation. aiming to identify and create efficient code suitable for the test printer, subsequently refining it to ensure compatibility with Pharma printers. The initial phase involved precise measurements of the syringe's diameter, cross-sectional area, stroke length, stroke volume, and material density. Once these calculations were finalised, it was possible to proceed to conduct a series of tests to confirm the accuracy of the obtained values, with viscosity presenting occasional challenges by occasionally deviating from my expectations.

The printing process was conducted twice, yielding two sets of 16 droplets each. This method was employed to study the printer's motor movements, particularly in relation to extrusion values and speed. Following the completion of this stage, which involved dosages ranging from 100 to 500 mg, initiating adjustments to the extrusion and retraction values, speed, and introduced a brief waiting period between the dispensing

of each droplet. However, it is noteworthy that, during this testing, the scale was not integrated into the test printer.

To account for this, after producing each set of 16 droplets, allowing them to cool within a refrigerator for a five-minute period. Subsequently, after cooling they are individually weighed, then recorded the values in our data table, and ensured that they complied with the specified standard deviation parameters. It is worth noting that during the initial printing, there were instances where the first two droplets were not dispensed due to air bubbles not being expelled beforehand. To address this, introducing a small waste print to the side to eliminate the air bubbles and ensure normal printing. Notably, this waste print also served a dual purpose as it was utilised for near-infrared radiation (NIR) analysis to confirm the wavelengths of the printed materials which is used by lab part(Figure 9).

Figure 9. NIR Spectroscopy (left side without the droplet) (right side with the droplet)

These foundational steps enabled the seamless integration of our knowledge into the G-code framework. Through a systematic process of trial and error, successfully engineered the necessary parameters for dosages from 100 to 500 mg, utilising a 4 by 4 design with the potential to adjust its size. Initially, I attempted to create circular tablets but found it inefficient, prompting us to adapt the G-code for droplet printing, which significantly improved printing speed and accuracy.

Throughout these experiments and adjustments, the keep diligently maintained

detailed records to ensure that our results closely aligned with preferred outcomes, all while closely monitoring compliance with standard deviation.

9.2. Experiments on Design and Trials

Before commencing the printing process with the placebo, the first step was to apply my newly acquired knowledge of G-code. Initially, I needed to precisely determine the location on the printer plate where our prints would be executed. After careful calculations and adjustments to the x and y axes using G-code, I marked the corners of the specified square area. To assess the necessary spacing between droplets, our initial action was to print four consecutive droplets in a row.

Following that, I designed a code that provided instructions to the printer for the sequential dispensing of a droplet, followed by a one-second pause, a lateral movement spanning a few millimetres, and the repetition of this pattern. This innovative coding technique proved instrumental in streamlining the creation of 4 by 4 designs, enhancing both efficiency and precision in our printing process.

Throughout experiments, my primary focus revolved around the dispensing of 16 droplets, each with a similar volume, with the goal of maintaining a standard deviation of no more than 5%. The most challenging aspect of this process lay in accurately determining the precise amount of medicine to be extruded.
This necessitated precise calculations for both retraction, aimed at preventing air bubbles in the syringe, and maintaining the appropriate temperature to prevent the medicine from degrading while preserving the desired viscosity, avoiding extremes of thickness or liquidity.

Furthermore, I undertook an extensive series of tests, involving the use of 28 different nozzles (as depicted in Figure 10). However, after numerous iterations and trials, it became evident that the most precise and consistent results were achieved when no nozzle was utilised.

Subsequently, I had identified the full plastic 14-gauge nozzle as the next best alternative. However, it is important to note that this option had the drawback of

frequent clogging after each print job, which in turn necessitated the regular cleaning or replacement of the nozzle.

-No Nozzle
fine printing and solves the clogging problem and cleaning during the prints
and no dripping
-Tapered (Olive 14 gauge) = passed
fine printing without dripping and cleaning is easy
have to clean after every order " when 4x4 is done"
-Rigid Tapered (Olive 14 gauge) = fail
-Tapered (Grey 16 gauge) =passed
material just passes through.
after this point material is either too thick or/and get clogged really fast
Nozzle material is thicker
-Tapered (Green 18 gauge) = too small
-Rigid Tapered (green 18 gauge) = too small
-Tapered (Pink 20 gauge) = too small
-Rigid Tapered (Pink 20 gauge) = too small
-Tapered (Blue 22 gauge) = too small
-Rigid Tapered (Blue 22 gauge) = too small
-Tapered (Red 25 gauge) = too small
-Chamfered (Red 25 gauge) = too small
-General Purpose (Red 25 gauge) = too small
-General Purpose (Clear 27 gauge 0.25 " long) = too small
-General Purpose (Clear 27 gauge 0.5 " long) = too small
-General Purpose (Lavender 30 gauge 0.25" long) = too small
-General Purpose (Lavender 30 gauge 0.5" long) = too small
-General Purpose (Yellow 32 gauge) = too small
-General Purpose (Olive 14 gauge [3sizes]) = metal nozzle gets stuck / too
long nozzle
little bit harder to print after first time because material cools down in
metal nozzle head and nozzle is too long
-General Purpose (Amber 15 gauge [3sizes]) = metal nozzle gets stuck / too
long nozzle
-General Purpose (Green 18 gauge [3sizes]) = metal nozzle gets stuck / too
long nozzle
-General Purpose (Pink 20 gauge [3sizes]) = too small metal nozzle gets stuck
/ too long nozzle
-PTFE-lined Crimped (Grey for cyanoacrylates [2sizes]) = too small
-General Purpose (Purple 21 gauge) = too small
-General Purpose (Blue 22 gauge) = too small
-General Purpose (Orange 23 gauge) = too small
-Flexible Polypro (Amber 15 gauge / Pink 20 gauge) = too small
-PTFE-lined Crimped (Pink for cyanoacrylates [2sizes]) = too small

Figure 10. Results of nozzle size testing.

Additionally, it was observed that my initial calculations did not account for the potential impact of heat on the plastic syringe, which could yield unexpected outcomes. Furthermore, the process of filling the syringe with medicine demanded a specific procedure due to the unique viscosity of the substance (Figure 11). This involved removing the piston, filling the syringe with the nozzle kept closed, reinserting the piston, rotating the syringe, and then opening the nozzle while slowly expelling any remaining air.

Following our experimentation with various nozzles, we proceeded to test the

dispensing process without a nozzle. I printed the same weight twice, and after the first print, I transferred the droplets to a designated cooling area to facilitate their cooling. Subsequently, they were individually weighed one by one, enabling the calculation of standard deviation of compliance and average values (as depicted in Figure 12).

Furthermore, conducted tests by printing droplets at 100mg intervals, commencing with 500mg and progressing down to 100mg. The results unveiled that maintaining parameters for the 100mg droplets was notably more challenging (figure 12). This issue could potentially be attributed to factors such as the medicine's viscosity or variations in the plastic syringe, which might result in differing droplet weights.

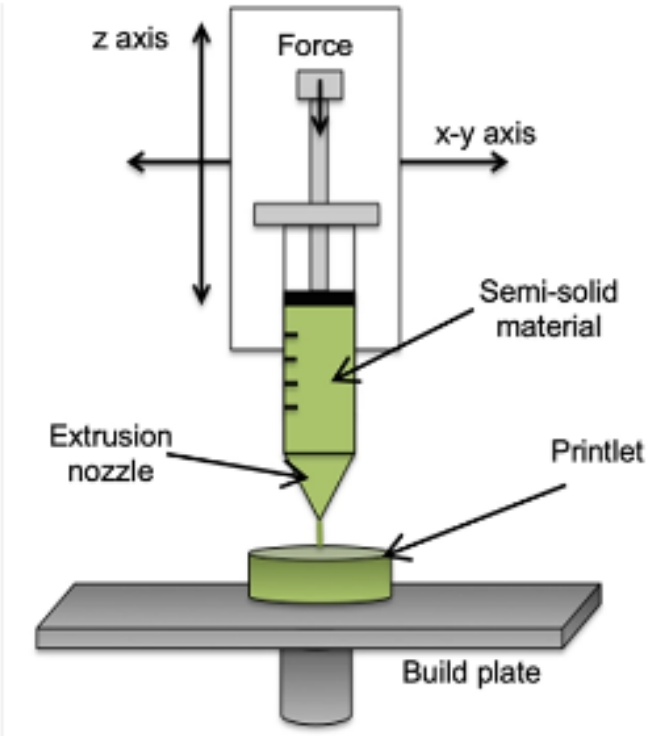

Figure 11 . Example how Semi solid extrusion would look like [2.]

	100mg	200mg	300mg	400mg	500mg
1	71	188	314	399	502
2	48	204	288	393	506
3	94	200	310	395	503
4	85	210	300	424	515
5	91	210	302	382	507
6	108	200	304	403	503
7	83	192	303	410	529
8	126	215	306	394	495
9	91	197	305	408	509
10	90	200	321	415	503
11	118	202	293	390	514
12	87	207	300	408	505
13	114	212	302	418	498
14	90	202	303	397	514
15	115	188	303	421	494
16	88	213	304	391	505
STDEV	19.35	8.45	7.52	12.34	8.64
average	93.69	202.50	303.63	403.00	506.38
2nd Print					
1	59	189	299	395	502
2	100	196	308	409	508
3	90	203	311	406	516
4	93	198	299	416	491
5	112	199	299	394	502
6	107	208	299	407	512
7	86	199	306	415	503
8	94	210	320	410	500
9	112	200	303	398	512
10	95	203	298	394	508
11	107	189	315	424	495
12	88	200	288	406	502
13	110	209	306	405	500
14	91	204	300	414	500
15	109	203	313	401	498
16	92	200	306	407	500
average	96.56	200.63	304.38	406.31	503.06
STDEV	13.55	6.03	7.92	8.54	6.60

Figure 12. Results that were in parameters.

10. Conclusion

In conclusion, the thesis study conducted at Curifylabs has yielded invaluable insights into the application of 3D printing within the medical field. My comprehensive exploration encompassed various dimensions, including a thorough understanding of the applicable standards and regulations. My investigative journey took me through the Minilab alpha version, where I diligently investigated its features and functionality.

Furthermore, during my thesis study, I meticulously examined the specifications of the Pharma Printer, and in doing so, encountered certain operational challenges. I also delved into the realm of this cutting-edge printing technology, subjecting it to a critical comparison with the Minilab alpha. This comparative analysis revealed that the Pharma Printer boasts a more compact design. Nevertheless, it is worth highlighting that, as a recent addition to the field, there is ample room for enhancements to elevate its overall performance and capabilities.

Throughout the course of thesis study, I honed my proficiency in G-code utilisation, refining my capacity to calculate syringe specifications and extrusion values through meticulous testing involving various extrusion and retraction speed settings. My work also shed light on the existing limitations and challenges that are inherent in 3D printing for medical applications. Concurrently, I've acknowledged the multifaceted advantages that 3D printing offers, particularly in terms of its speed and efficiency, which often surpass human capabilities.

My efforts have played a pivotal role in reducing human errors within the entire process. Additionally, with the introduction of the new printer, CurifyLabs team successfully resolved the need to assemble the previously problematic black box. This accomplishment is particularly noteworthy given past complications related to iPad battery regulations during shipment. Thesis study underscores the promising potential of 3D printing in revolutionising the medical field, while also underscoring the ongoing imperative for improvement and innovation in this dynamic and evolving field.

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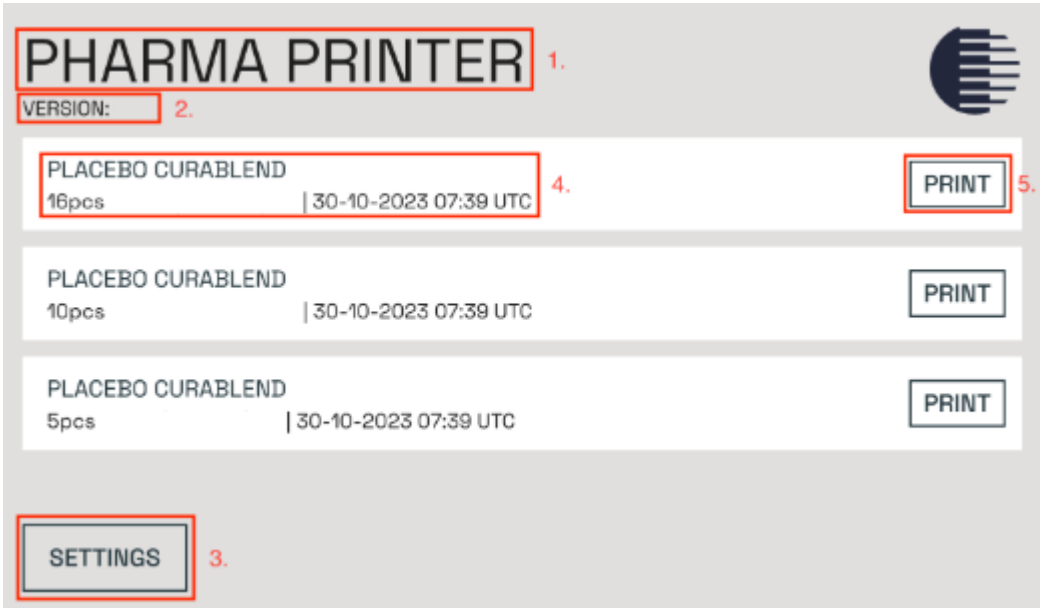
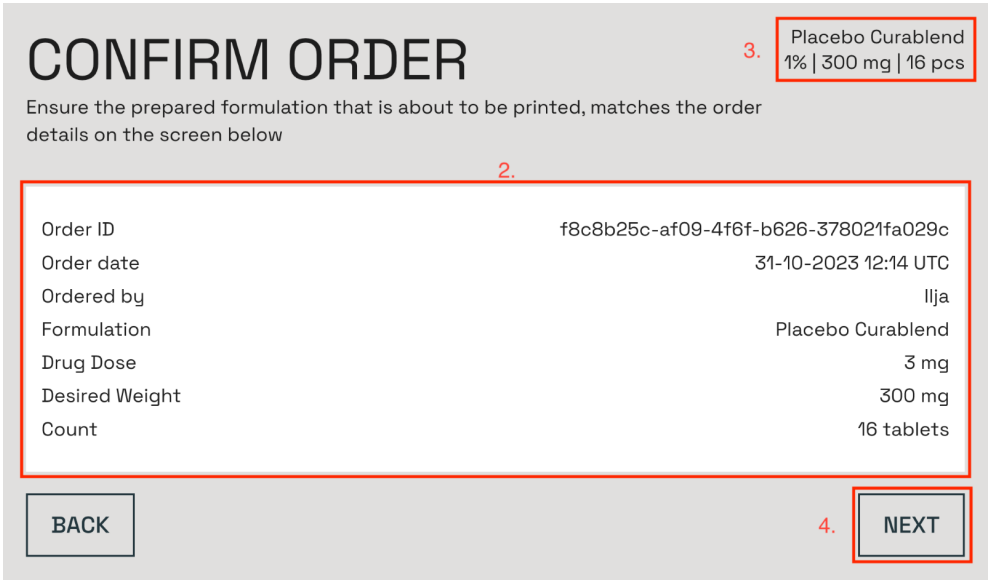
20 Printing instructions

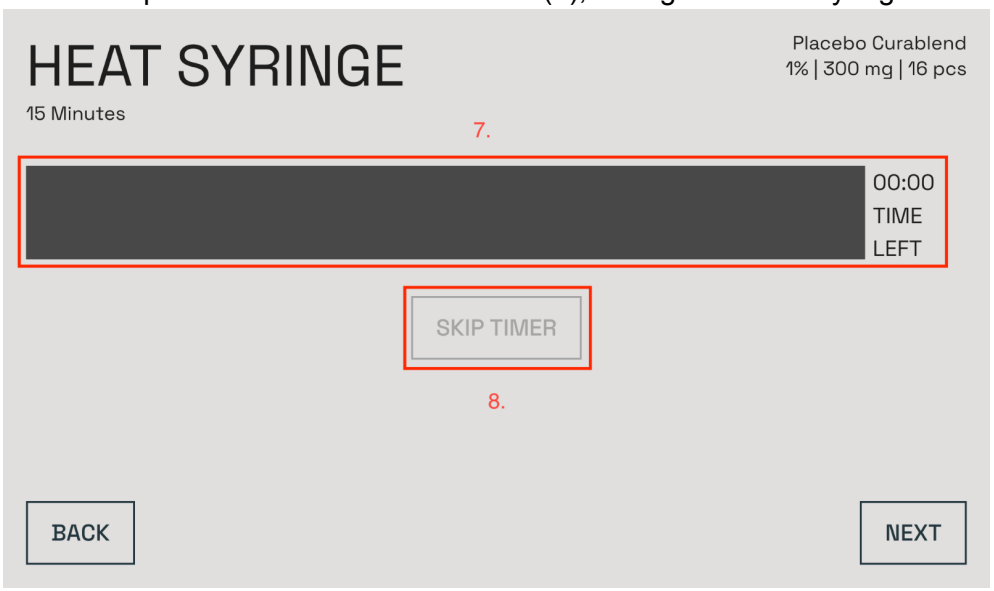


1. Begin the printing sequence by pressing the “PRINT” button on the desired order. An automatic guide will then guide you through the necessary steps to start a print (1).

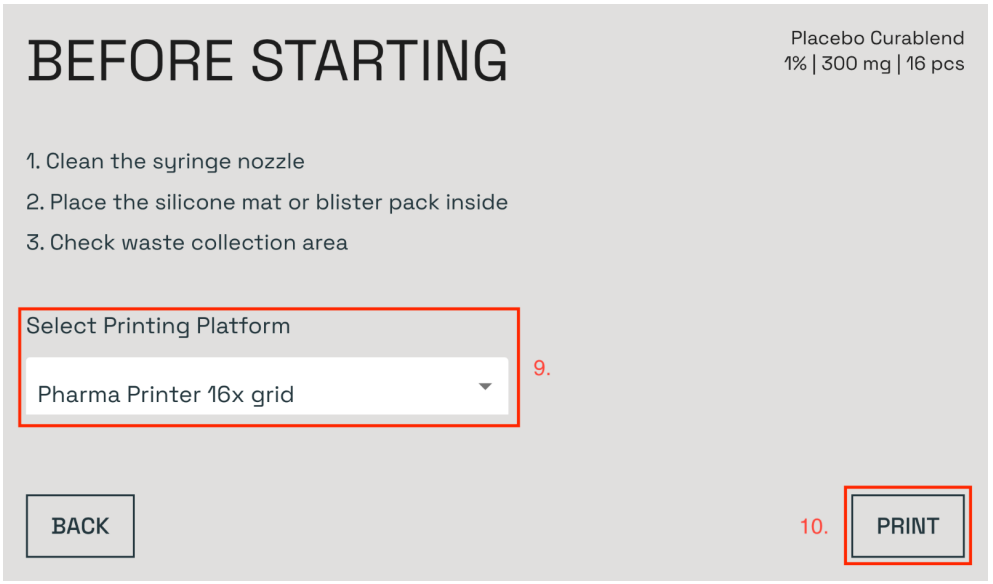


2. Confirm that the order you are about to print is correct (2). Once ready click the “NEXT” button to proceed to the next step (4).
    a. NOTE! You will see the order details in the top-right corner of the application during the guide (3).

3. Prepare the syringe (5). The “START TIMER” button will start a timer of a predetermined amount of time (6), during which the syringe will be heated.



4. Once the timer has concluded you will be able to go to the last step before printing (7).
    a. NOTE! A “SKIP TIMER” button is available if heating has already been completed outside of the automatic guide (8).



5. Final steps before printing. Select the correct platform for the print from the dropdown menu (9). Once done you will be able to start the print (10).
6. During printing you will see the progress in the top-left corner of the application (11). You will also see the weights of the tablets on the illustrated tablets themselves (12).