TAMPEREEN TEKNILLINEN YLIOPISTO
TAMPERE UNIVERSITY OF TECHNOLOGY

VALTTERI VIRTANEN

3D PRINTING OF A PERSONALIZED DOSAGE FORM

Master of Science Thesis

Examiners: Asst. Prof. Sampo Tuukkanen and Assoc. Prof. Timo Laaksonen
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ABSTRACT

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The purpose of this thesis was to study the possibilities of 3D printing of a personalized dosage form from biocompatible and biodegradable PLA (polylactic acid) polymer. In this thesis multiple sets of capsules with different settings were designed and printed with a 3D printer. The chosen designs and printed capsules were evaluated first with leakage tests with a blue dye and then with release tests with Nadolol-nanocellulose mixture. 3D printing turned out to be effective with fast prototyping. The release tests showed that a dosage form printed from PLA polymer with a wine bottle shaped inner cavity provides a stable release profile during long time tests. This can be utilized as a 3D printed personalized implantation device.

TIIVISTELMÄ

VALTTERI VIRTANEN: Personoidun lääkkeen 3D-printtaus
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Tässä diplomityössä tutkittiin personoidun lääkekapselin 3D-tulostusta PLA-polymeeristä. PLA-polymeeri on biohajoava ja bioyhteensopiva yleisesti 3D-tulostuksessa käytetty niin kutsuttu biopolymeeri. Työ suoritettiin tulostamalla kapseleita erilaisilla asetuksilla. Kapseleiden muotoilu ja 3D-tulostimen tulostusjälki testattiin vapautuskokeissa, joista saadun datan perusteella iteroitiin tulostusasetuksia. 3D-tulostus osoittautui nopeaksi ja käteväksi nopeassa prototypoinnissa (fast prototyping). 3D-tulostettu PLA-kapseli sopii muotoilunsa ja materiaalinsa puolesta todennäköisesti implantoitavaksi kapseliksi paremmin kuin perinteiseksi ns. kertavaikutteiseksi lääkkeeksi.

PREFACE

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Tampere, 30.6.2018

Valtteri Virtanen

CONTENTS

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LIST OF SYMBOLS AND ABBREVIATIONS

3D Printing	Fabrication of a three-dimensional objects with a specialized printer. Also referred as 3DP in literature
AM	Additive Manufacturing, building objects adding material layer by layer
ANFC	Anionic Nanofibrillar Cellulose, a nanocellulose hydrogel
API	Active pharmaceutical ingredient, for example medicine used to test application such as controlled drug release
ASTM	American Society for Testing and Materials
CAD	Computer Aided Design, a software to create shapes and objects *in silico*
CLIP	Continuous Liquid Interface Production
CT	Computerized Tomography, a medical imaging method using X-ray imaging with computer to analyze results
DLP	Digital Light Processing
DMLS	Direct Metal Laser Sintering
DPBS	Dulbecco's Phosphate-Buffered Saline, a balanced salt buffer solution
FDA	Food and Drug Administration
FDM	Fused Deposit Modeling, a method of 3D printing involving pushing filament through a hot extruder nozzle
FFF	Fused Filament Fabrication, alternative, non-patented name for FDM
G-code	A numerical control programming language used to control automated machinery such as 3D printer
G-file	G-coded file containing the information of object shape for printer
HME	Hot Melt Extrusion, process where heat and pressure is used to push (a mixture of) material through a gap, nozzle or an orifice
HPLC	High Performance Liquid Chromatography, an analyzing method
LCD	Liquid Crystal Display, a common electronic lightweight display
MRI	Magnetic Resonance Imaging, a method of medical imaging using magnetic field
SD Card	Secure Digital Card, a small portable memory card commonly used in digital cameras and mobile phones
SEM	Scanning Electrode Microscopy, an imaging method
SLA	Stereolitography
SLS	Selective Laser Sintering
.STL	Standard Tesselation Language, CAD format for 3D printing
PLA	Polylactic Acid, a type of polymer commonly used for 3D printing
PVA	Polyvinyl Alcohol,
TUT	Tampere University of Technology
URL	Uniform Resource Locator
UV	Ultraviolet radiation (also UV light), electromagnetic radiation with a wavelength range of 10 nm to 400 nm
XRPD	X-ray Powder Diffraction

1. INTRODUCTION

3D printing (three-dimensional printing), also known as 3DP, has been a growing trend since its invention in the mid 1980's [1, 2]. The development of materials and software have made the 3D printing technology readily available to the public. These days, the price of a moderate desktop 3D printer on the market can be compared to the price of a moderate desktop PC, ranging from a few hundred euros to a few thousand euros depending on the quality and profession of use. The development, the ease and the endless ways of designing things makes 3D printing interesting. The 3D printing allows fast prototyping and designs that can be tested and evaluated right after printing. This is fast, efficient and time saving.

The diversity of opportunities makes 3D printing also intriguing from the biomedical application point of view. First FDA (Food and Drug Administration) approved medicine fabricated using 3D printing technology, Spiritam, was approved in 2016 [3].

When designing and fabricating biomedical equipment, the biocompatibility of the material is vital. The most common printing polymer PLA (Polylactic Acid) is a biocompatible and biodegradable polymer. In this thesis I studied the possibilities of 3D printing applied to medicinal capsule fabrication. Capsules were fabricated with a common type 3D printer, which is an example of affordable and home use-oriented RepRap project where some or nearly all of the 3D printer components are printed with a 3D printer. The printing method was FDM or Fused-Deposition Modeling (or FFF, Fused Filament Fabrication, used without patent permission), a type of extruding material through a hot nozzle, which is considered as "perhaps the most immediate potential to unit dose fabrication" because of the low cost, speed and options to alternate the printing settings [4].

Challenges of 3D printed medicinal capsules include the size and the shape of the capsule. Capsule must be smooth and relatively small to be easy to swallow. Other crucial factors are material thickness or porosity depending on the application [5], surface area/ratio of the formulations [4, 6] and the shape of inner cavity. In this case thick FDM-printed PLA capsules were used. The form of the inner cavity is the factor that dictates the release profile by regulating the diffusion and the flow of medical content that is loaded separately.

Alternative popular fabrication method for passive diffusion is Hot-Melt Extrusion or HME processing, which is used to incorporate medicine into polymer filaments using a rotating screw to pump materials through a die in hot temperatures [4]. So-called drug

loading can also be done to a ready filament such as PVA (Poly(vinyl alcohol)) by diffusing it to a filament using solvents such as ethanol. [6]

In this study, the release profile of the designed capsules turned out to be stable in time of dozens of hours. Therefore, the printed and API loaded capsules could serve as an implant type of application where a constant release profile is desired, better than a traditional swallowable single dose medicinal tablet which usually exits the body within a day.

In this thesis work the second chapter elaborates the history of 3D printing and theoretical background of additional manufacturing in general. The third chapter explains the materials and methods related to the work in this study. The fourth chapter includes discussion of the results of this study along with the future aspects of printing PLA personalized dosage form with FDM-type 3D printer followed by the fifth chapter that concludes this thesis.

2. THEORETICAL BACKGROUND

2.1 3D printing and printing from a file

The actual idea and invention of three-dimensional printing - or 3D printing - of material was developed by Charles Hull from University of Colorado [1,2,7]. Hull was studying liquid photopolymers that turned into solid piece of plastic after exposed to UV light at Ultra Violet Products in California. [1,2,8] After patenting his invention, Hull founded 3D Systems which is a company now providing 3D printers and tools for digital designing of 3D printed objects [8]. Hull has received numerous awards from his work as a pioneer of 3D printing. [1, 7, 8]

3D printing is a process which can be described as additive manufacturing (AM) [9,10,11]. It is a so-called umbrella term and means that the objects are made adding more material after material and building objects rather than molding, casting or cutting objects with machinery. This removes the need of expensive machinery and allows *rapid prototyping*. 3D printing is applied in various applications ranging from automotive and airplane industries to bioprinting. Rapid prototyping is especially useful in tool prototype manufacturing [1].

Bioprinting is quite new application of 3D printing. It is used to print biological material with 3D printer. The printed material can be biomaterial or so called "bioink" which consists of biological matter such as cell tissue or medium used for cell growth. [10] Bioprinting can be applied in regenerative medicine where tissue or organs are replaced with so-called bioartificial tissues.

The CAD drawn .STL (Standard Tesselation Language) file system was developed by Hull and 3D Systems in 1986 [1]. In this thesis work, .STL files were created *in silico* using OnShape, free cloud-storing CAD software. The .STL file contains the coordinates for triangulated forms which are the information of the surfaces of 3D model. Increasing the number of surface defining triangles results to better printing resolution. The increased amount of vertices increase the resolution of printed object. Illustration of this can be seen in Figure 1.

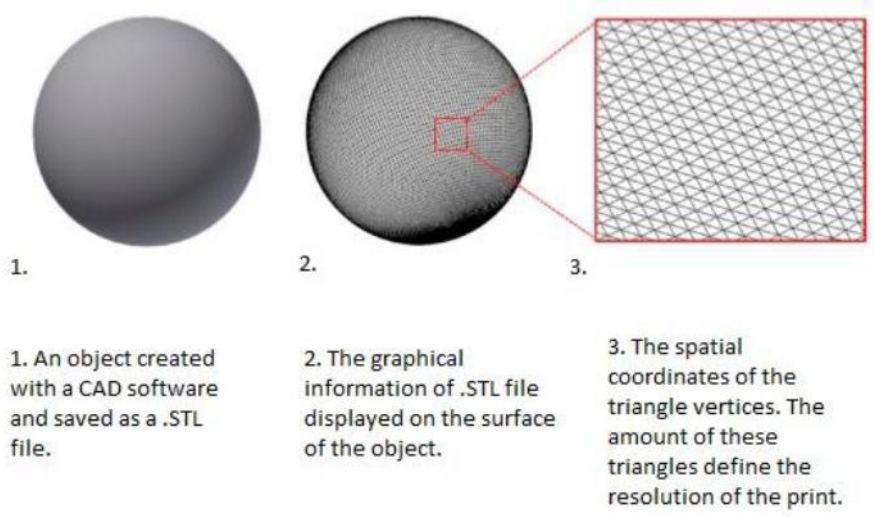

Figure 1. *The Illustration of a .STL file to be printed. Modified from source [1].*

With a slicer software, the digital three dimensional object coordinates from .STL are "sliced" into horizontal slices and converted into G-code or G-files. For example in this study, the software is Prusa Slic3r provided by 3D printer manufacturer Prusa. G-code dictates the three-dimensional .STL file into a sequence of two-dimensional horizontal cross sections which are in the range of 25-250 micrometers depending on the printing method. The three-dimensional object is then printed starting at the base, layer by layer to be constructed as a series of two-dimensional layers according to original .STL file drawn with CAD software. The result is controlled and dependent on the printing algorithms and printing settings of the printer. Of course, the material and even the printing environment affects the results. [1]

.STL format has become the standard format and nearly every CAD system can output .STL files. CAD image must be 3D representation of a surface in order to print 3D objects. [11]

There are numerous other methods in the medical field that are used to render 3D objects, for example laser scanning [1, 11], computerized tomography (CT) and magnetic resonance imaging (MRI) of which data can be used to create .STL files. With software added to printing it is possible to make nearly exact copy from the original scanned object. It can be applied in biomedical engineering for example in organ tissue scaffolding. [1]

Most of the 3D printer (AM machine) build processes contains the 8 steps represented in Figure 2. The first step is the designing with a CAD software, second step is the file conversion. Third step is STL file manipulation where the STL file is translated to language that the machine understands. For example G-code. Fourth step is the machine

setup: printer must be set up to print. Necessary parameters such as setup for specific material, setup for infill and settings for machine speed are crucial. Fifth step is the actual building which can be automated. Usually supervision is only required for errors. Sixth step is the safe removal of object. Seventh step is post processing of objects. This may contain special care such as coating or simply cleaning the object. Eighth step is the application which means the actual use of an object after necessary treatments. [11]

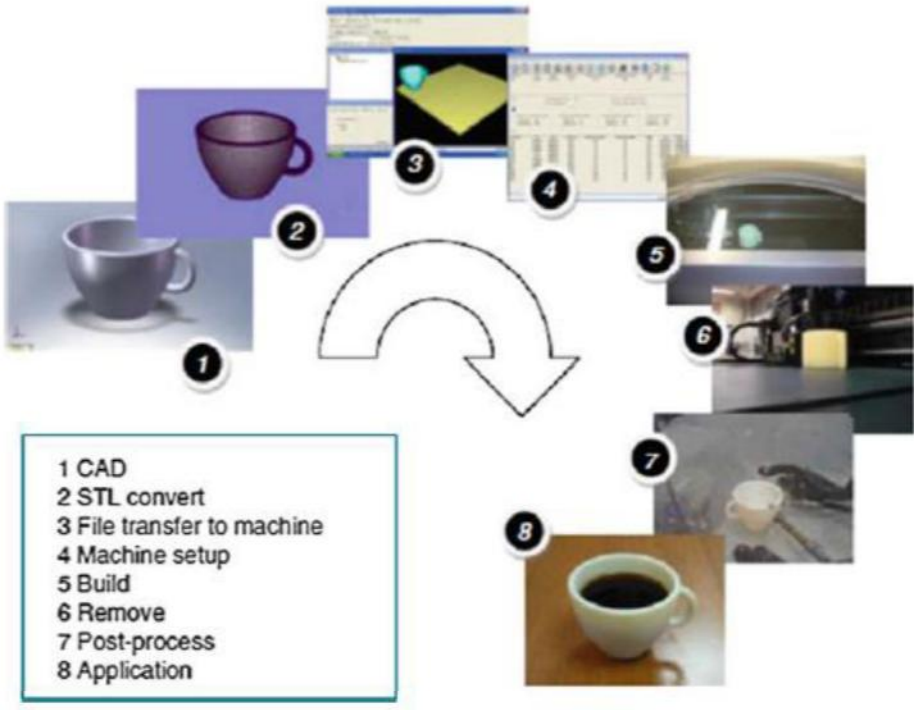

Figure 2. *A typical 3D printing process from designed CAD model to an actual applicable object. These eight steps are typically involved in every additive manufacturing processes. Source: [11].*

3D printers vary in ways to print material. American Society for Testing and Materials (ASTM) group ASTM F42 Additive Manufacturing has set categories for different additive technologies. [11, 12, 13, 14, 15]

These are

1. VAT Photopolymerisation
   a. Continuous Liquid Interface Production (CLIP)
   b. Digital Light Processing (DLP)
   c. Stereolitography (SLA)

2. Material Jetting
3. Binder Jetting
4. Material Extrusion
   a. Fused Deposition Modeling (FDM)
   b. Fused Filament Fabrication (FFF)
   c. Contour Crafting
5. Powder Bed Fusion
   a. Selective Laser Sintering (SLS)
   b. Direct Metal Laser Sintering (DMLS)
6. Sheet Lamination
7. Direct Energy Deposition

1. **VAT Photopolymerisation** uses a vat of liquid photopolymer resin. The model is fabricated layer by layer and an UV light is used to harden the resin in specific places while a platform moves down layer by layer after a layer is done. [12, 13]

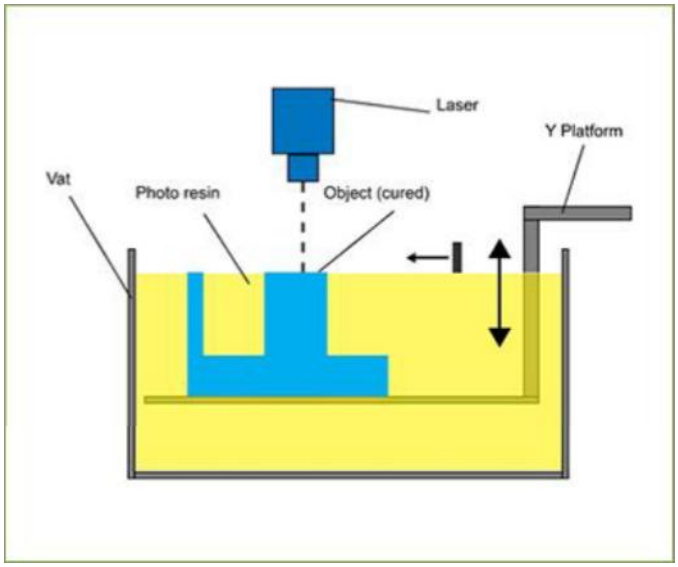

Figure 3. *Principle of VAT Photopolymerisation. Source: [13].*

Typical VAT photopolymerization methods are Stereolitography (SLA) Continuous Liquid Interface Production (CLIP), Digital Light Processing (DLP). [12]

2. **Material Jetting** works like a traditional ink jet printer: material is jetted trough a horizontally moving nozzle to a platform and it is solidified layer by layer and

cured with UV light. The jetting can be continuous jet or so-called Drop on Demand approach in which dots are dispensed to print the object with further droplets added until the object is complete. [13, 15]

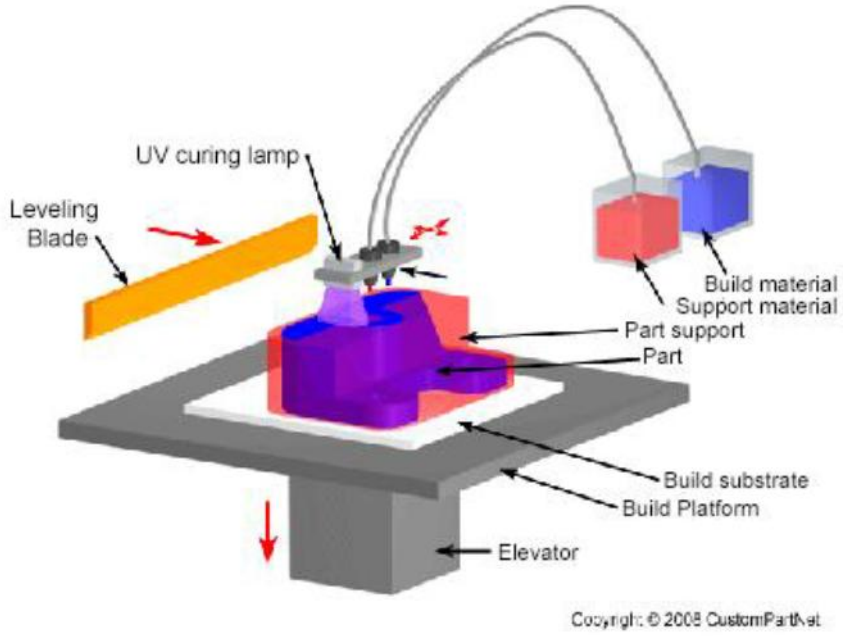

Figure 4. *Material jetting. Source: [13].*

3. **Binder Jetting** is a two material approach. The materials are powder formed material and binder which is typically liquid. Printer head moves horizontally and deposits material and binding material in alternating fashion. The excess material is cleaned and recycled to be used in fabrication of next object. Post processing of object can increase total time of fabrication. [12, 13, 15]

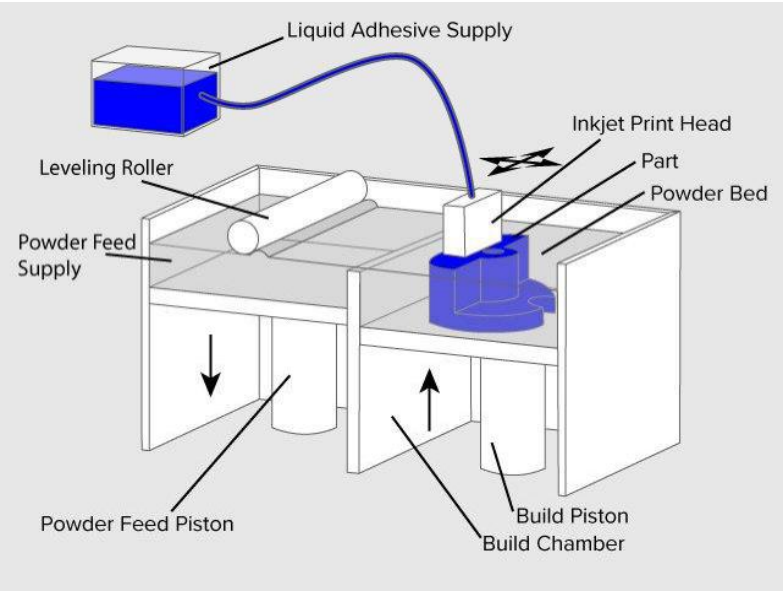

Figure 5. *Binder Jetting. Source: [12].*

4. **The Material Extrusion** is the most common method of 3D printing. It is used in most common household 3D printers. Material extruders consist of a nozzle, coil of filament and supportive material holding the printer together. The hot nozzle melts and extrudes filament (usually PLA, PVA or ABS) which is unwound through the nozzle powered by electric motor. In this thesis work, the Prusa i3 Mk2 printer represents this technology. [12, 13]

   The benefits are cheap relatively low cost of material and printers, ability to easily optimize the printing settings such as infill and speed of the extrusion. The speed and the resolution of the printer dictates the results of the printings. Methods are Fused Deposition Modeling (FDM) which is a trademark, (other organizations use FFF, Fused Filament Fabrication) [12, 15]. Methods include also Contour Crafting. [12, 13]

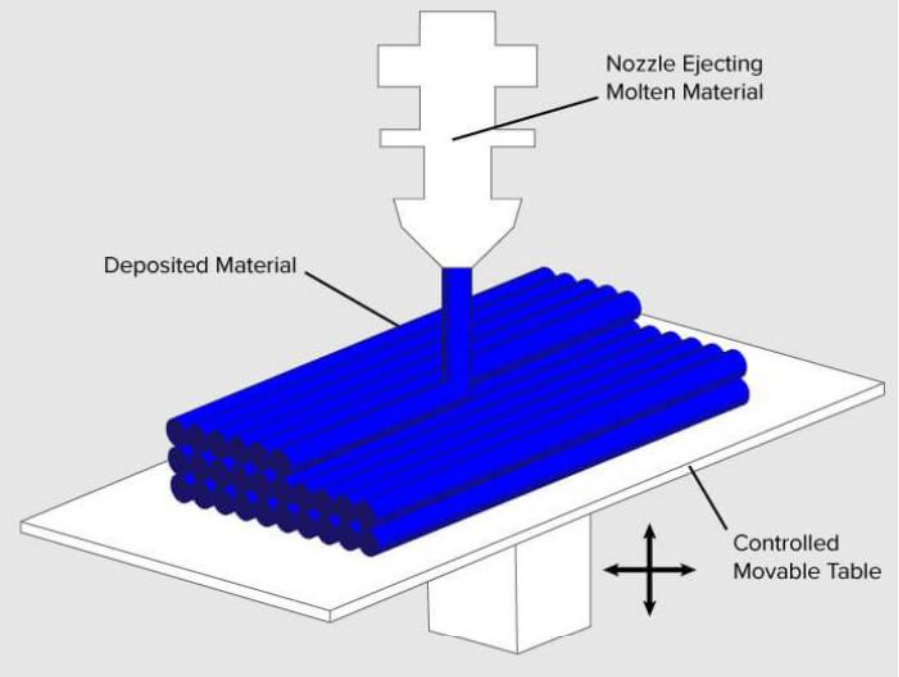

Figure 6. *Material Extrusion: Fused Deposition Modeling. Source: [12].*

5. In **Powder Bed Fusion** technology laser or electron beam is used to melt and fuse material together. A common application is Selective Laser Sintering (SLS), in which a high power laser is utilized to fuse powdered small particles of plastic, glass or ceramic into three dimensional shape. The laser scans cross-sections and selectively fuses material. After each scan the powder bed is lowered a thickness of one layer. After that, a new layer is formed until completion of object. Another method in Powder Bed Fusion is Direct Metal Laser Sintering. [12, 13]

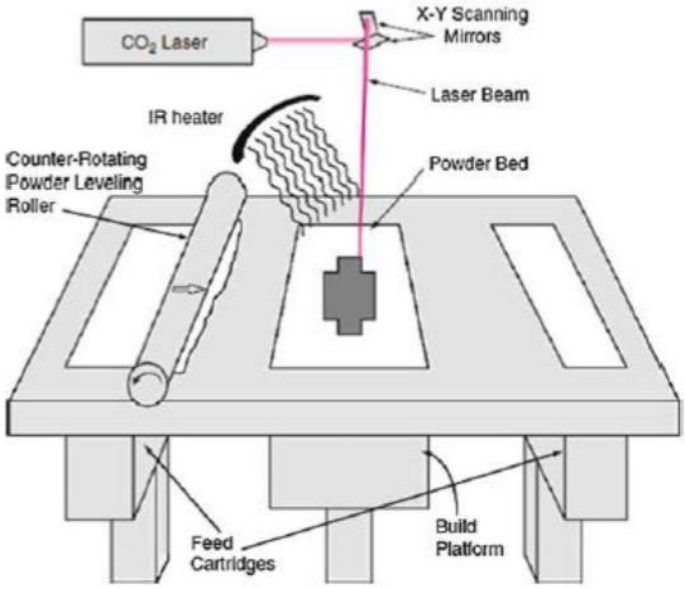

Figure 7. *Selective Laser Sintering, a common application of powder bed fusion. Source: [11].*

6. **Sheet lamination** is a process of laminating sheets together with force. The lamination can be used with paper, polymer and metal. With paper, sheets are glued together with adhesive glue and then cut into shapes. With metal sheets, a rotating cylindrical sonotrode uses ultrasonic oscillation and welds (ultrasonic welding) metal layers together, using clamping force from sonotrode and reaction force from anvil and base plate as counter. After welding the sheets are CNC milled into desired shape. [12, 13]

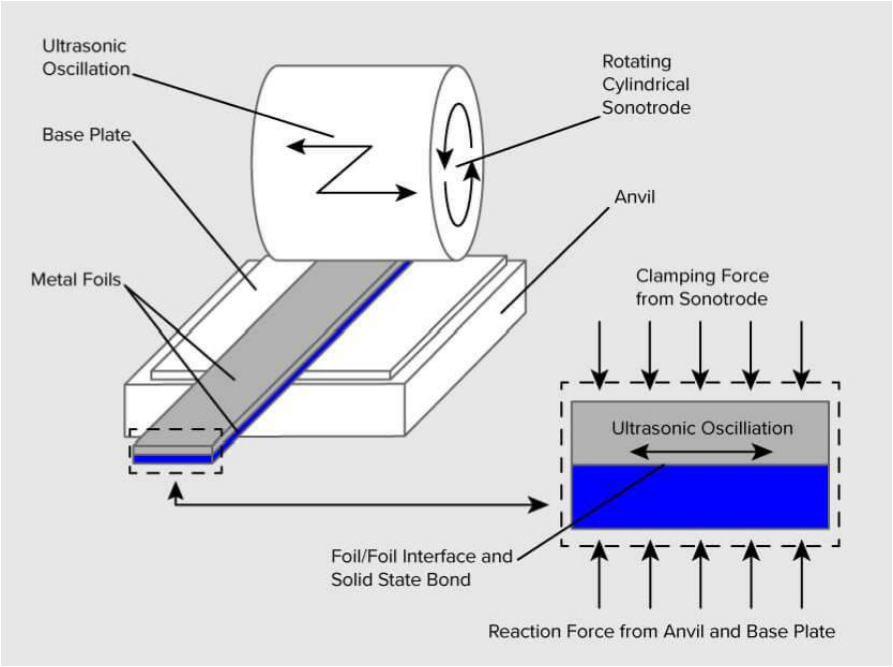

Figure 8. *Ultrasonic sheet metal 3D printing. Source: [12].*

7. **Directed Energy Deposition**, also known as 3D laser cladding, directed light fabrication or laser engineered net shaping, is a process where usually a robotic arm with multiple axis and a nozzle or nozzles deposits metal in powder form or a metal wire and melts it on a surface with an energy source such as laser, plasma arc or electron beam. The result is a solid object. [12, 13]

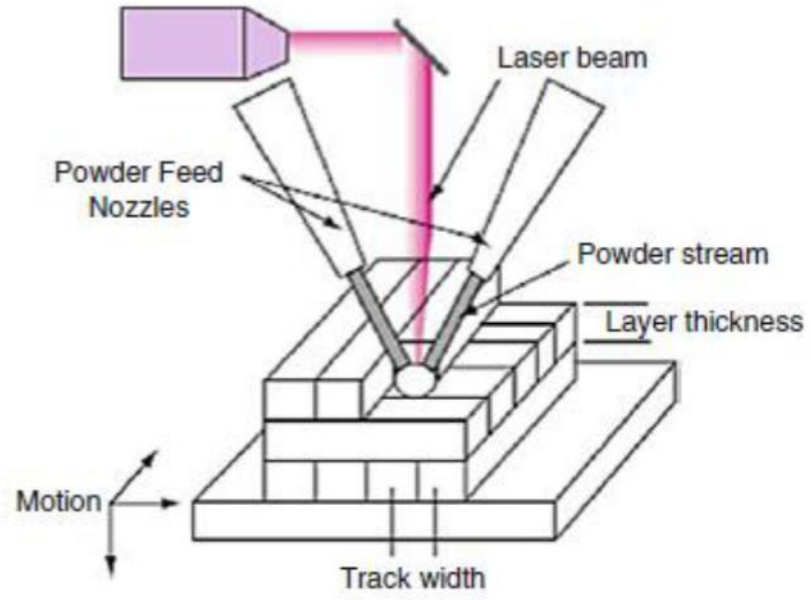

Figure 9. *Directed Energy Deposition with metal powder and melting with laser. Source: [11].*

2.2 Personalized medicine

Most medical treatments such as drugs have been designed for "average patients" [16]. Same medicine can be described for example for a patient with mass of 50 kilograms or 150 kilograms that are both considered just as a patient. This leads to that the treatment can be more successful with some patients than others. The idea of personalized medicine is a growing trend to give patients tailored, individualized care. [15, 16, 17, 18, 19]

Also known as precision medicine, personalized medicine takes in account patients size, weight, metabolism [15] and genetic and genomic information to tailor disease diagnosis, prevention and treatment. In other words, personalized medicine offers new

treatments that are tailored for example diseases such as cancer which can vary a lot depending on patient's individual traits and the case and condition of disease. [15, 16, 17, 19]

In 2015 former President Barack Obama announced that he is launching the Precision Medicine Initiative which was declared to be a new research effort to revolutionize health and disease treating. The stated long-term goals of the Precision Medicine Initiative are utilizing precision medicine and health care. [18, 19, 20]

National Institute of Health (NIH) is planning a program called All of Us Research Program which will involve a cohort group of "at least 1 million volunteering individuals who will provide genetic data, biological samples and health information" as an open data sharing with personal open access to each individual's own personal health information. The data is being used to study diseases and disease risk to find improved diagnosis and treatments. [20]

In personalized medicine, the amount of medicine and release profile are the key points that can be affected. In this study the material is thick and not porous so the shape of the inner cavity regulates the release profile of the drug.

3D printed personalized dosage forms could be especially beneficial for growing children to optimize the dosage. Also tailored dosage forms could provide accurate dosing of potent drugs such as theophylline or prednizolone. [15]

2.3 Similar studies

In paper *3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles* [21] Khaled et al. used 3D extrusion printing to fabricate a dosage form of many API's, so called polypill as they refer to it. The aim of their study was to tailor and manufacture a combination drug a personal medicine tablet with different medicines for complex medications, eliminating the need for multiple different drugs. The polypill was designed using 3D drawing software BioCAD. [21]

The powders were manually mixed using mortar and pestle for 15 minutes, pastes were mixed. Printable paste for barrier of sustained release was mixed of cellulose acetate (shell), d-mannitol (filler) and polyethylene glycol as a plasticizer with acetone and dimethyl sulfoxide. Paste was mixed to a homogenous paste. They also mixed powders of atenolol, pravastatin and ramipril with ultra-pure water to make a homogenous paste. The pastes were loaded to printer (Figure 10) ink cartridges. Extrusion was through 500 μm tip. [21]

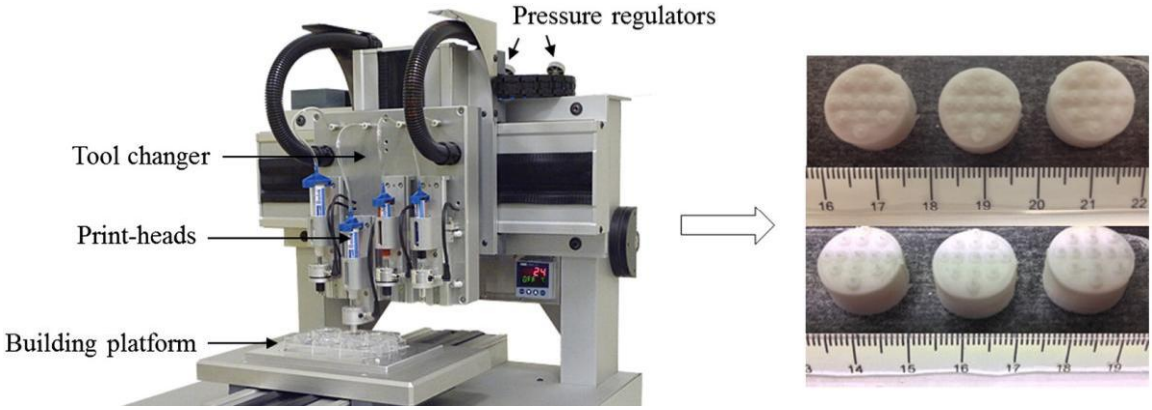

Figure 10. *3D extruder used to make 5-in-one polypill and the results of the printings. Source: [21].*

At the conclusions Khaled et. al state that they "successfully demonstrated 3D extrusion printing of a novel complex geometry five-in-one polypill" and proved that the polypill is able to deliver five actives via well-defined two release mechanisms: immediate and sustained release. In paper they also state that application of 3D printing pharmaceutics could offer a solution for children and elderly people with difficulties of swallowing multiple tablets. Also special tailored tablets could help patients with allergies. [21]

In paper *Fused-filament 3D printing (3DP) for fabrication of tablets* [22], the printing material was other biocompatible and more water soluble commercial ready PVA (PolyVinyl Alcohol) filament. PVA filaments were loaded with drug: filaments were placed in an solution containing ethanol and fluorescein, and stirred for 24 h. Ethanol turned out to be better than aqueous solvent because the polymer filament did not dissolve even after 24 h. Fluorescence offered UV chromophore to be used for analysis. [22]

The CAD software used to design the PVA tablets was MakerWare Software. The tablets were printed with FDM method using Makerbot Replicator 2x Desktop printer. Tablet dimensions were 10 mm x 10 mm x 3.6 mm (Figure 11). The infills varied as seen in Figure 12 A. [22]

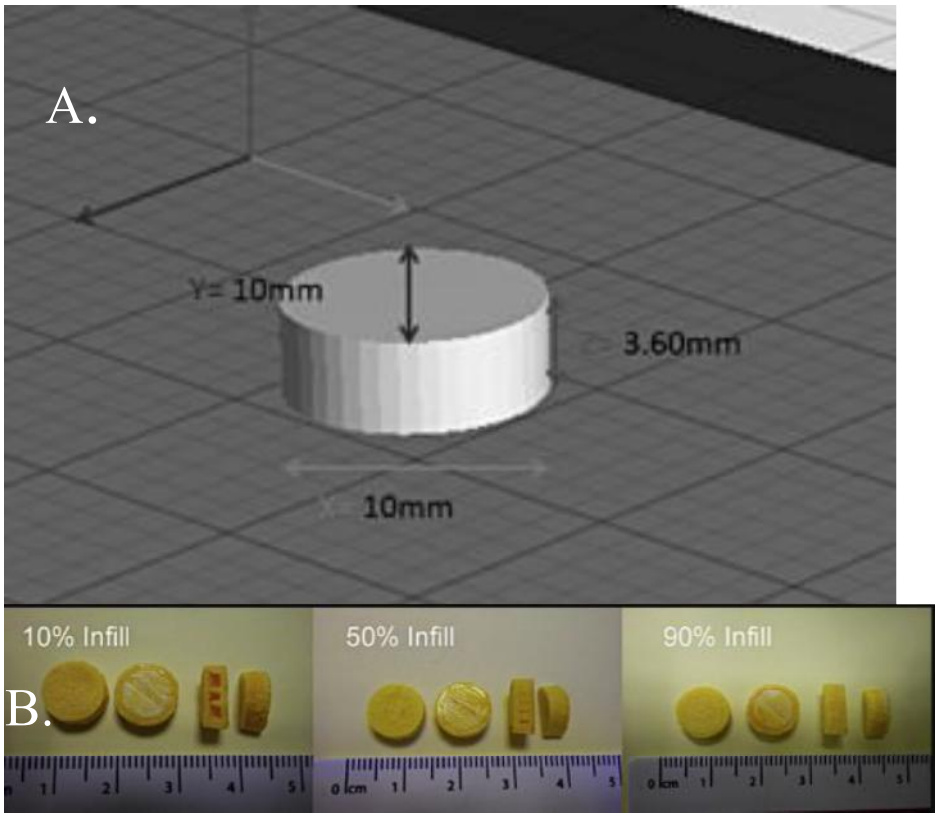

Figure 11. A. *A CAD image of PVA tablet dimensions by Goyanes et. al* ***B.*** *Printed fluorescein tablets by Goyanes et. al. Modified from source [22].*

PVA tablets were mechanically strong and *Goyanes et. al.* describe that "the tablets were produced with a high degree of repeatability of weight and physical dimension". The fluorescein drug parts in the filaments were revealed under UV light and the fluorescein seemed to have distributed evenly (Figure 11). 10%, 50% and 90% infill tablets were tested in dissolution tests using modified Hank's Buffer which mimics the fluids in human small intestine with pH 6.8. [22]

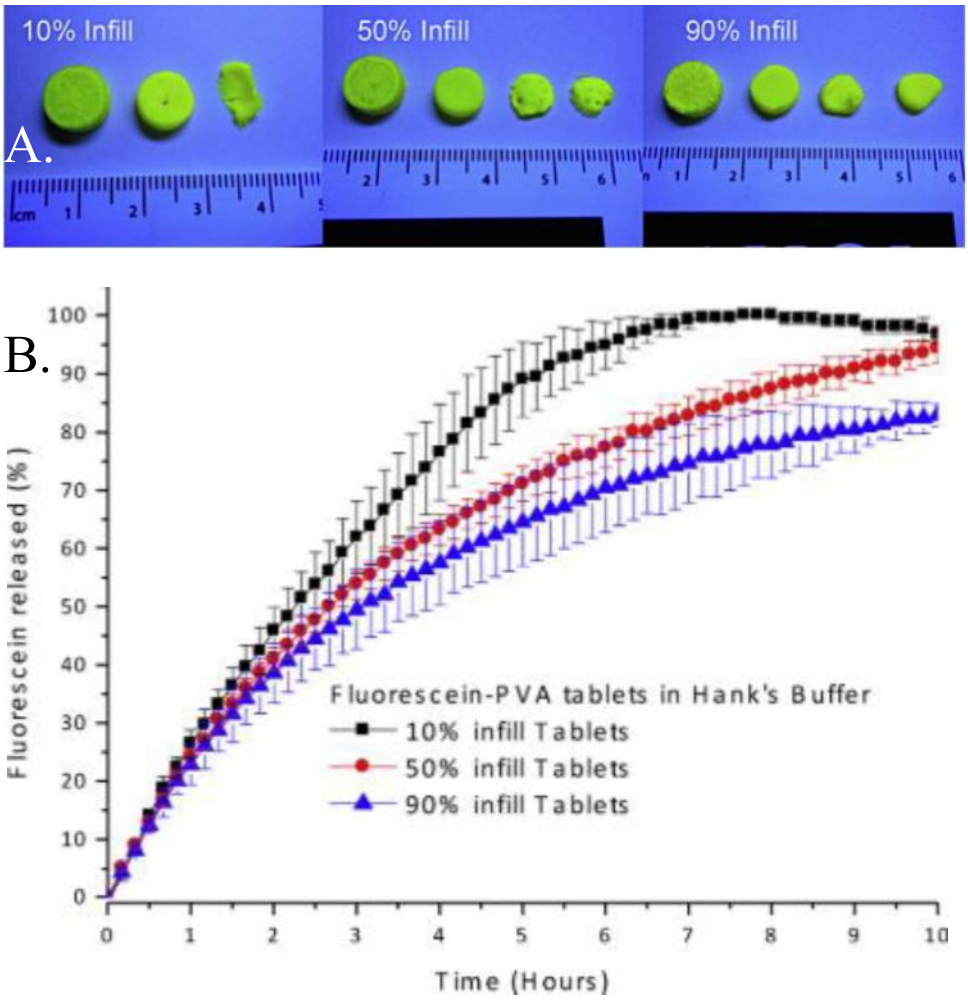

Figure 12. A. *Fluorescein-PVA tablets under UV light.* ***B.*** *The dissolution profile of the tablets in Hank's Buffer. Modified from source [22].*

Goyanes et. al. state that Fused Filament Fabrication release profiles can be modified by changing the printing settings and the infill percentage modulates the dissolution profile. The release profile for 10%, 50% and 90% infills can be seen in Figure 12 B. [22]

Study *Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing* [23] involved also FDM printing with drug loaded commercial PVA filament. PVA was cut into tiny cylindrical pellets with a dedicated pelletizer and then grinded into powder with a grinder. The drug, which was budesonide, a glucocortical steroid for treating asthma and for example noninfectious rhinitis [24] was manually mixed to PVA powder with mortar and pestle. The mixture was extruded with HME method by a single screw extruder and pushed through a 1.75 mm nozzle to make filaments ready to be printed with a FDM 3D-printer. Before printing, the filaments were analyzed with

HPLC (High Performance Liquid Chromatography) method to determine the budesonide content. Filaments were also analyzed with scanning electron microscopy (SEM), X-ray Powder Diffraction (XRPD) and Thermal analysis. [23]

The dosage forms were designed with AutoCaD and processed with MakerWare software. Dosage forms were capsule shaped tablets or “caplets". [23]

Figure 13. A. *Printed PVA caplet, coated printed PVA caplet and a cross-section of a coated caplet.* ***B.,C.*** *SEM images of the coated caplet cross-section surface. Image source: [23].*

The filaments were loaded to MakerBot Replicator 2X Desktop FDM printer, and the tablets (or caplets as they refer the tablets in the paper) were printed with layer height of 0.2 mm and set to 100% infill. Caplets (Figure 13) were coated with isopropanol, water and L100 powder mix. [23]

In the paper they state that the coating is resistant to acidic conditions of the stomach and after the coat has dissolved the drug release is sustained through small intestine and the core continues to colon (Figure 14). The surface erosion and diffusion are the release mechanisms. [23]

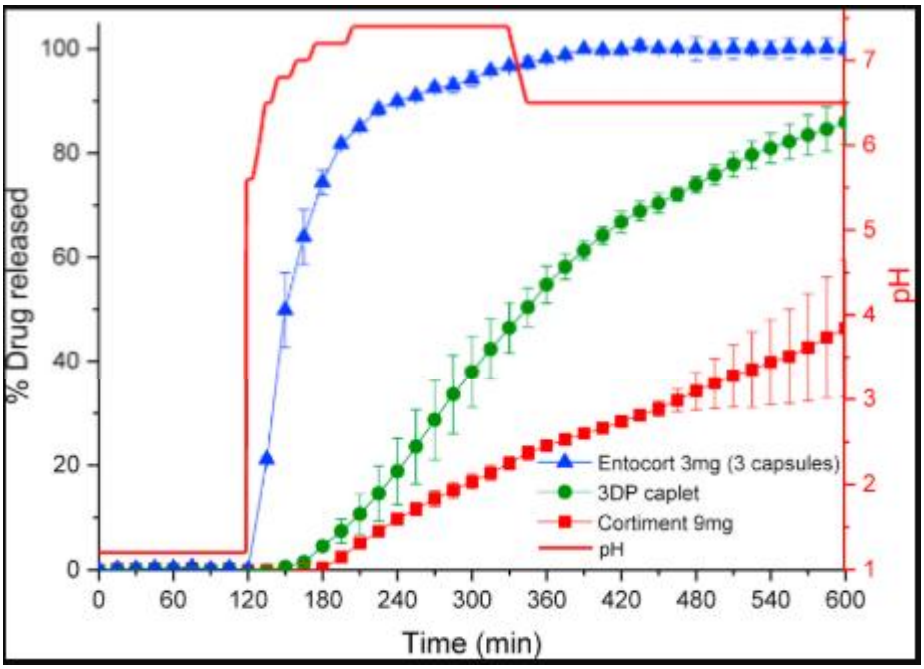

Figure 14. *Release profile of the PVA caplets by Goyanes et. al. Source: [23].*

In paper *Hot-melt extruded filaments based on pharmaceutical grade polymers* [25] *Melocchi et al.* evaluated different polymers and conducted a series of tests with them. [25]

In study, *Melocchi et. al.* used fused deposition modeling (FDM) with 1.75-diameter PLA (L-PLA by company MakerBot). The HME extruder used in the study to prepare the filaments was a twin screw extruder Haake Minilab II which utilizes counter-rotating screws and a custom-made aluminum rod-shaped die with a diameter of 1.80 mm. Extruded rods were manually pulled and after that forced through a caliper. [25]

The designing of the FDM printing was done with an adapted MakerBot Replicator 2 by MakerBot industries. *Melocchi et. al.* produced successfully pharmaceutical grade polymers which suited for FDM fabrication. [25]

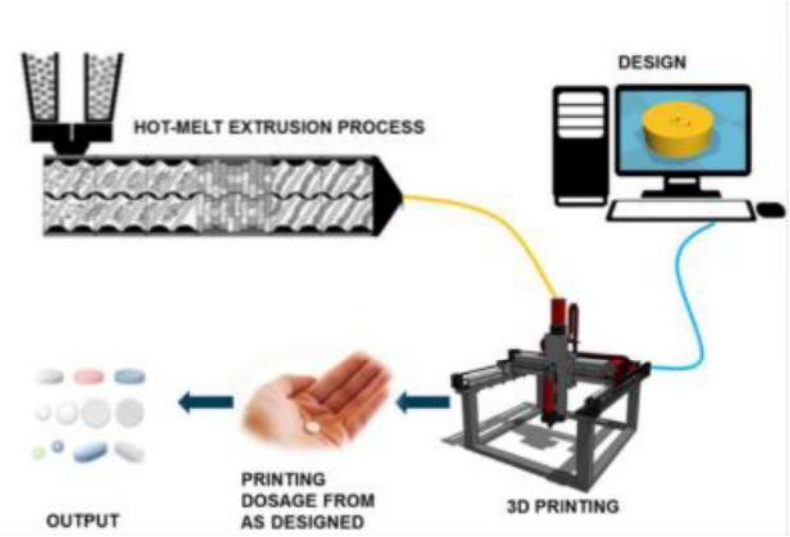

Figure 15. *Typical from HME to 3DP tablets process. Source: [26].*

In paper *Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets* a research successfully team fabricated solid-dispersion filaments with API extruded in a polymer matrix using HME technology. The (typical) process from HME to 3DP tablets process is represented in Figure 15. They also tested their printings with three-point bending tests with a control. [26]

As they state in the paper, their main objectives were "to study coupling fused deposition modeling (FDM-) based 3D printing with HME technology to print controlled-release tablets, to screen different grades of pharmaceutical polymers suitable for 3D printing based on the HME-fused filaments' physical and chemical properties, and to study the drug release profiles of 3DP tablets in comparison to those of directly-compressed milled extruded and physical-mixture tablets." The used API was Acetaminophen (APAP). [26]

In paper *Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing (Genina et. al)* in Journal of Controlled Release, the team created a PLA capsule with PVA cap. [27] This study is probably the closest to this thesis as it contains printing of capsules and testing controlled release. However the structure is different and the inner cavity design is simpler and is not in such a big role.

The fillings were separated into two departments A and B. (Figure 16 A and B.) The "oral dual-compartmental dosage units" (capsules) were designed by CAD software

Comsol Multiphysics and then fabricated with Ultimaker 3 Extended printer (fused deposition modeling technique) in two steps; first 3D-printing of the capsule and then hot-melt extrusion of the API (drug-containing filaments). The capsules were inspected with scanning electron microscopy. [27]

The capsules were sealed with PVA cap to regulate drug release (Figure 16). The drug release profile of the capsule was characterized by pH-transfer dissolution *in vitro.* Pharmacokinetics studies were conducted *in vivo* in rats. Postmortem studies of the rats revealed that the capsule was decapped or biofluids dissolute the sealing cap more aggressively than thought, which of course affected the results and the function of the sealing cap couldn't be fully proven. Tests resulted in modified release of the APIs from the capsule were compared to the free control filaments. [27]

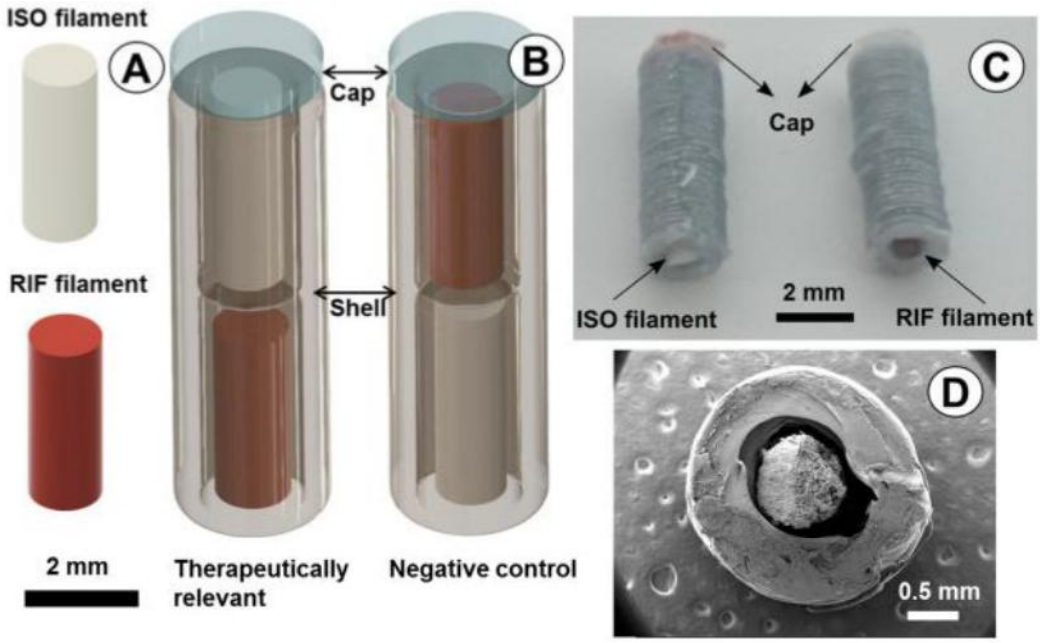

Figure 16. A. *Therapeutically relevant capsule and* ***B.*** *Negative control capsule.* ***C.*** *Ready PLA capsules with PVA cap.* ***D.*** *SEM image of the capsule filled with drug filament without a cap. Image source: [27].*

3. MATERIALS AND METHODS

3.1 Properties of PLA

In this study, polymer PLA also known as polylactic acid (CAS name: poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]; 1,4-dioxane-2,5-dione, 3,6-dimethyl-, homopolymer) was used. PLA is a common thermoplastic polymer material used in 3D printers. First synthesized by DuPont Scientists in the presence of p-toluenesulfonic acid. [28]

PLA is commonly known to be biodegradable, biocompatible, economical and user-friendly material with good tensile strength after extrusion and a high stiffness ratio. Its complete fragmentation in compost is 15 days and total degradation approximately 4,8 years at 25 Celsius-degrees [28]. [29, 30, 31] The biocompatible properties are used vastly in biomedical engineering. The diversity of PLA applications is demonstrated in Figure 17.

The long degradation time reduces its potential as a biodegradable polymer. However, the degradation time and other properties of the PLA can be modified by chemical modification, cross-linking or for example surface modification, combining the PLA with other degradable polymers or with radiation [31, 32]. PLA is so-called

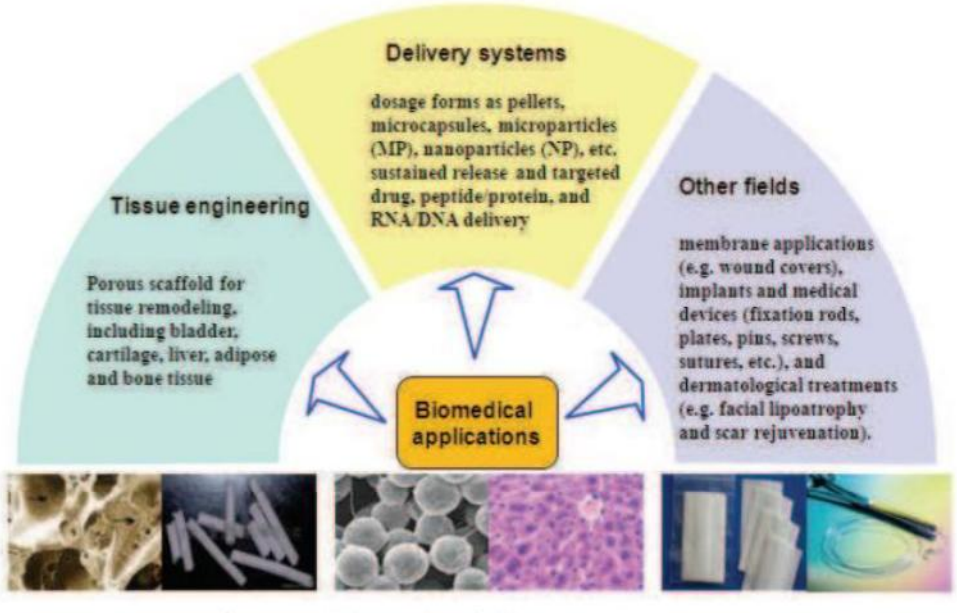

Figure 17. *A graph demonstrating the diversity of biomedical applications of PLA. Image source: [30].*

bioplastic; plastics derived from sources of renewable biomass such as wheat, sugar beets sugar cane, and corn unlike traditional plastics which are derived from petroleum

sources are called bioplastics [29]. The economical features and relatively inexpensive price has grown its popularity among home users and industrial sector. [30]

The cycle of PLA from natural agricultural products to a processed polymer which degrades over time back to nature with the synthesis can be seen in Figure 18.

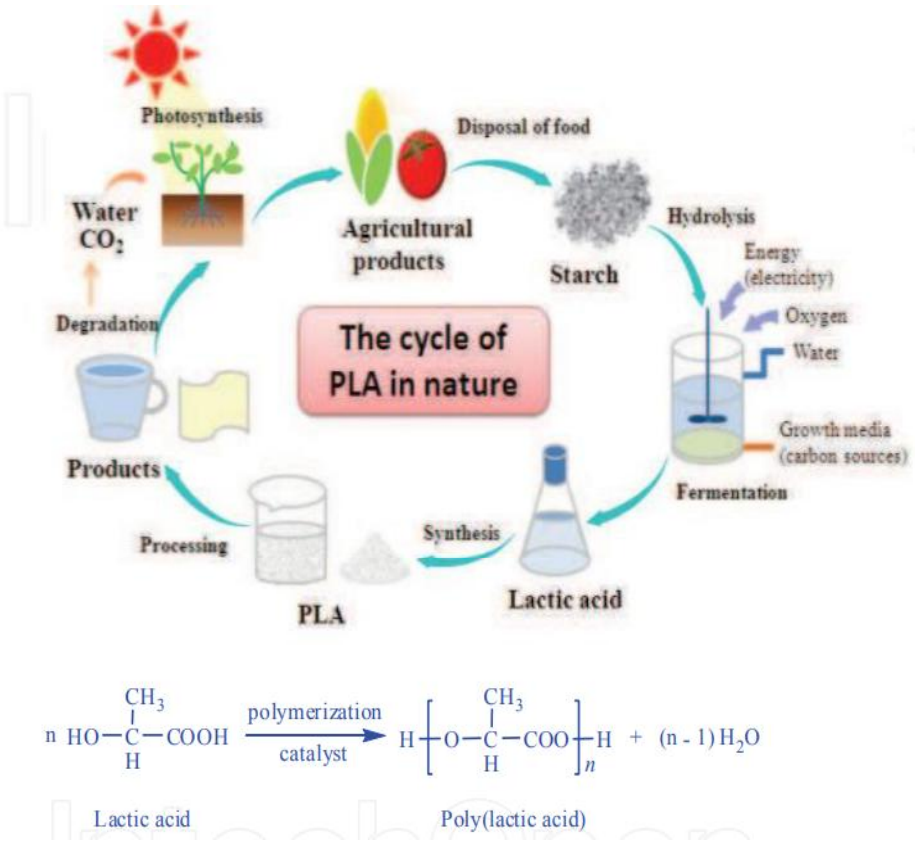

Figure 18. *The cycle of PLA in the nature and PLA polymerization synthesis from lactic acid to poly(lactic acid). Source: [30].*

3.2 Properties of nanocellulose hydrogel

Nanocelluloses which are cellulose nanocrystals (CNCs) or cellulose nanofibrilis (CNFs) are quite new material widely investigated in pharmaceutical studies and biomedical engineering It is sustainable material that has potential in many industrial sectors alongside with biomedical industry for example construction and chemical industries [33].

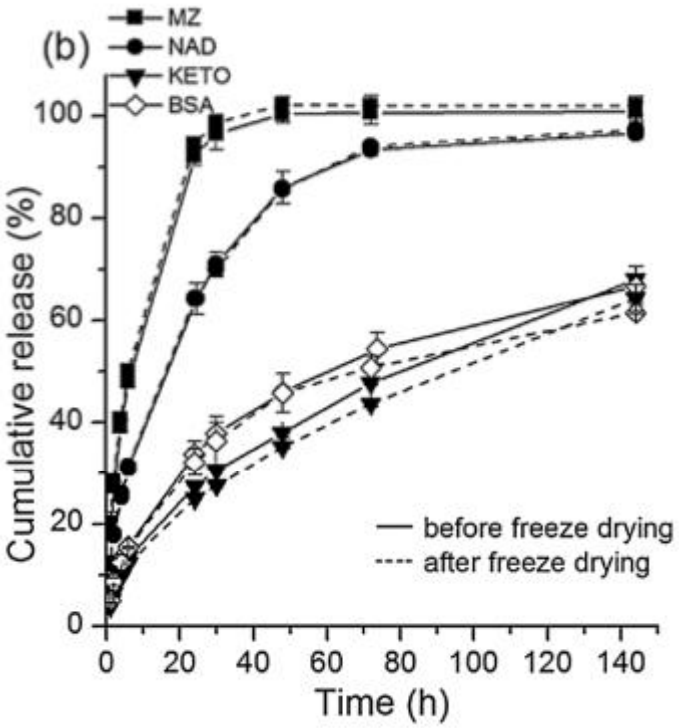

Figure 19. *Nanocellulose release profile. MZ is Metronidatzol, NAD is Nadolol, a heart medicine, KETO is Ketoprotein, BSA is Bovine Serum Album. Modified from source [34].*

Nanocellulose is interesting material because the aerogels and hydrogels are practically inert and according to in vitro studies, biocompatible [34]. It is a biopolymer made from natural cellulose, typically wood pulp [33, 34].

In biomedical and pharmaceutical applications nanocellulose hydrogel is freeze-dried to aerogels which can be utilized in drug delivery as a carrier structure. The release profile of nanocellulose is presented in Figure 19. [34]

3.3 3D printer

The 3D printer used in the work of this thesis was Prusa i3 (iteration 3) Mk2 Multi Material manufactured by start-up company Prusa Research by Josef Prusa. Printer (Figure 20) itself was assembled at TUT. Prusa MK2 is considered as a pioneer of RepRap project, a philosophy of 3D printing where some or nearly all parts of the printer are printed with the 3D printer itself [35], and the Multi Material technology it utilizes with multiple extruders offer significant vantage while printing multi material prints. The heat bed is clear and the frame structure is sturdy as seen in Figure 20.

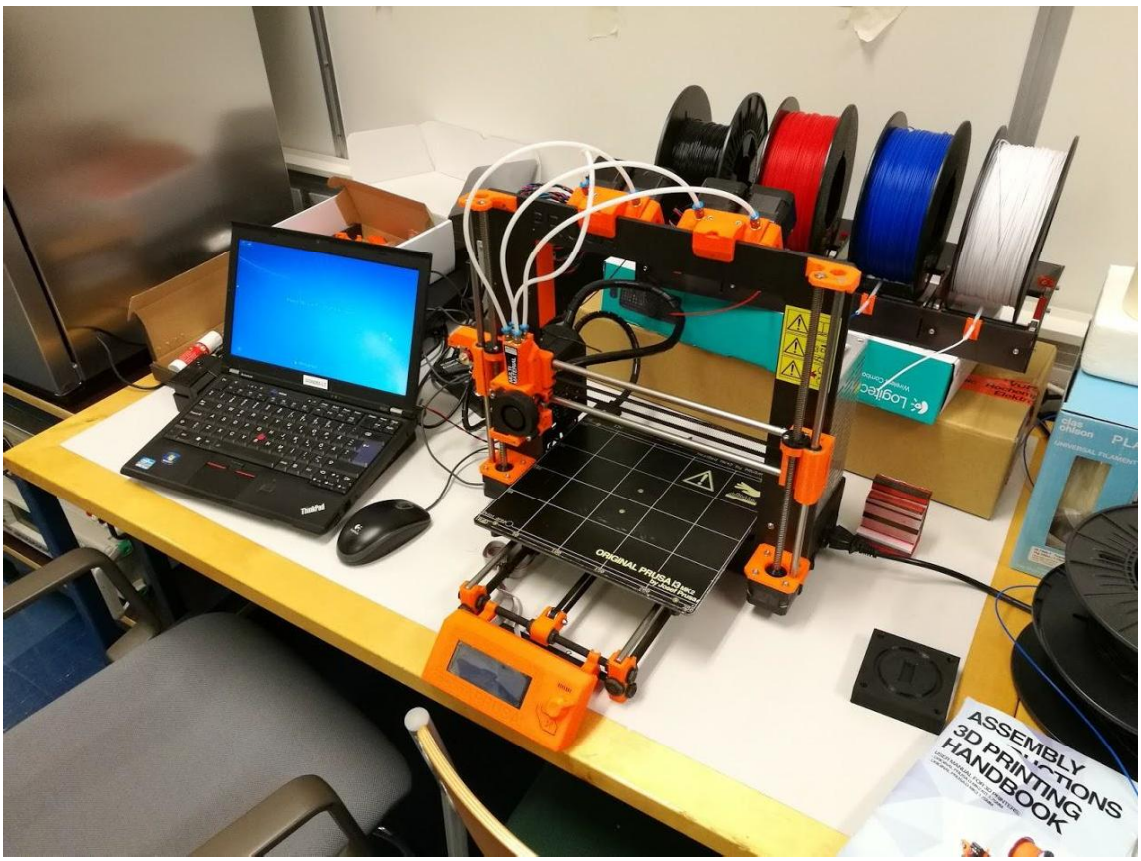

Figure 20. *The Prusa i3 Mk2 multi material 3D printer connected to a dedicated workstation to run the printer Slic3r software.*

the filament rolls have their own stand and roll smoothly when the printer prints.

The slicer software Slic3r Prusa Edition (Figure 21) which can be downloaded from manufacturer's website [36] is clear to beginners yet suitable for professionals. The UI itself is very understandable and it makes the slicing easy. There are two options to control the printer: either from dedicated workstation connected to printer via USB connector (Figure 20) or straight from the printer interface (Figure 24).

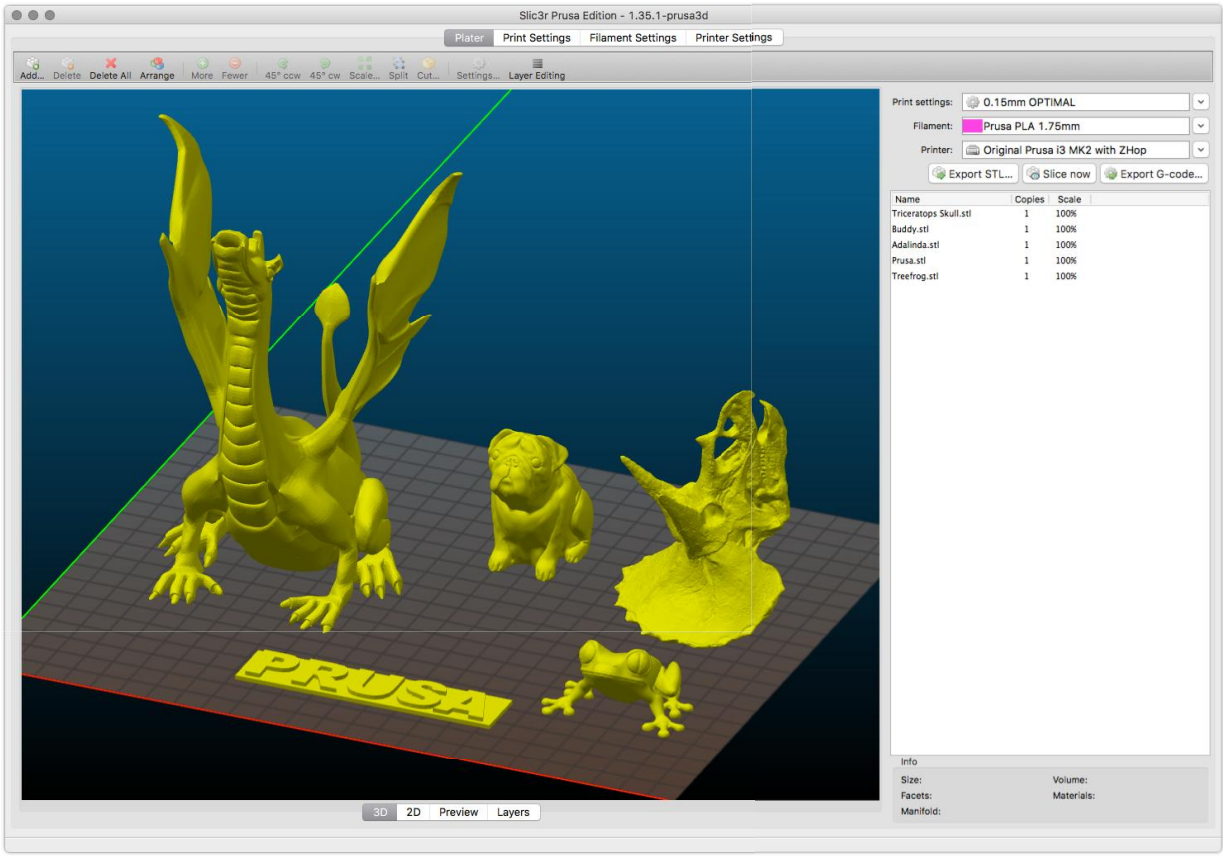

Figure 21. *Prusa Slic3r interface including clear preview pictures of the designed objects to be printed. Different materials which can be printed with different extruders are color coded. Image source: [36].*

Slic3r software is a tool that converts or "slices" 3D models into horizontal layers which are the G-code printing instructions for 3D printers. It is a non-profit open source project within the RepRap community. It is based on GitHub where tens of thousands of people contribute material to keep 3D printing free. [37]

Printer needs room to move its axis and extruders for safety and functionality. Some materials like ABS polymer can release hazardous fumes when printed so a proper ventilation and fume extractor arm is needed. Nozzle is hot (typically 215-210 Celsius degrees when printing PLA), so touching it should be avoided.

The electric actuator powered movement of the extruder and heat bed is explained in Figure 21. The X-axis is the move of the extruder sideways on metallic rails. The metallic double railing makes extruder more stable than the single-railed options. Y-axis controls the heat bed forward and backward from the user point of view. The movement

of the heat bed causes minor stability issues especially with objects with narrow standing point or base. This can be compensated with proper adhesion. Prusa recommends a normal office supply glue stick mixed with distilled (or de-ionized) water. The Z-axis is the vertical movement of the extruder nozzle head, motivated by metallic screws at the sides of the printer.

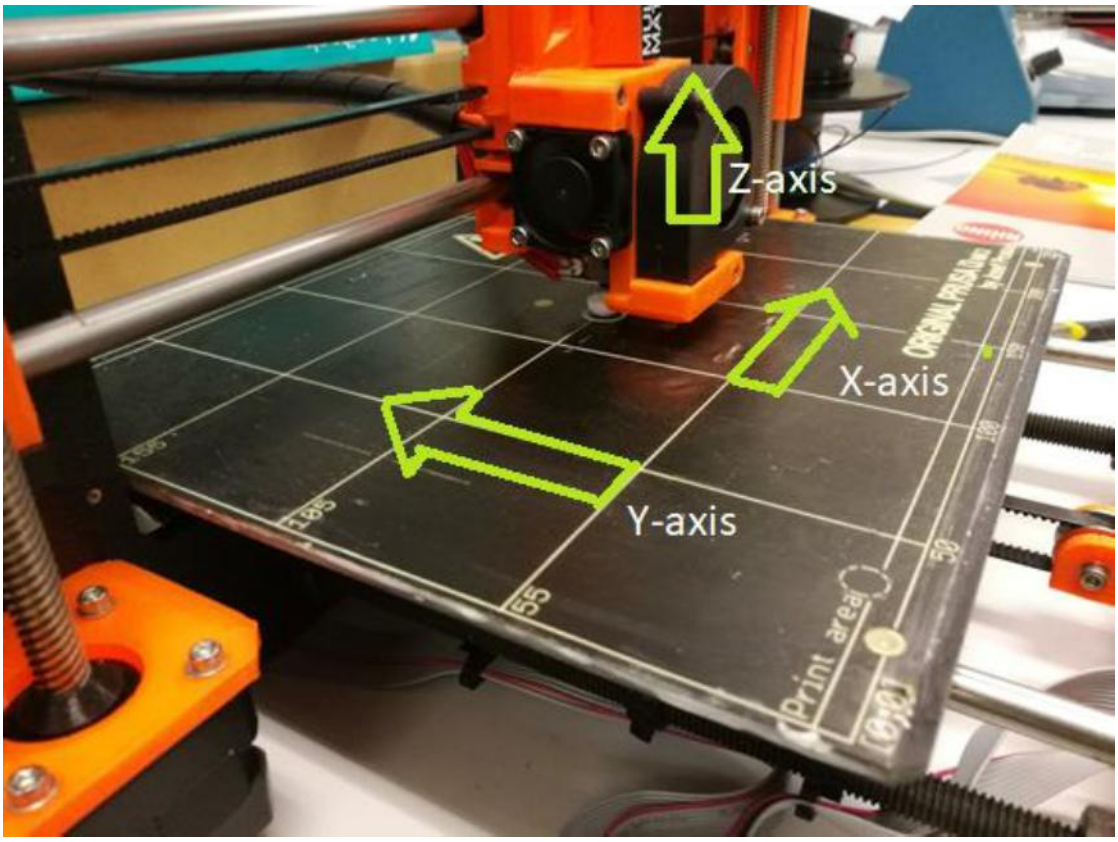

Figure 22. *Printer working on capsule base. The Z-axis is the vertical axis, the extruder height. The Y-axis is the forward-backward moving heat bed. The X-axis is the extrude moving sideways, left and right from operator's point of view.*

Prusa i3 Mk2 calibrates its extruders and axis movement automatically which makes the operating of the printer easier for the user.

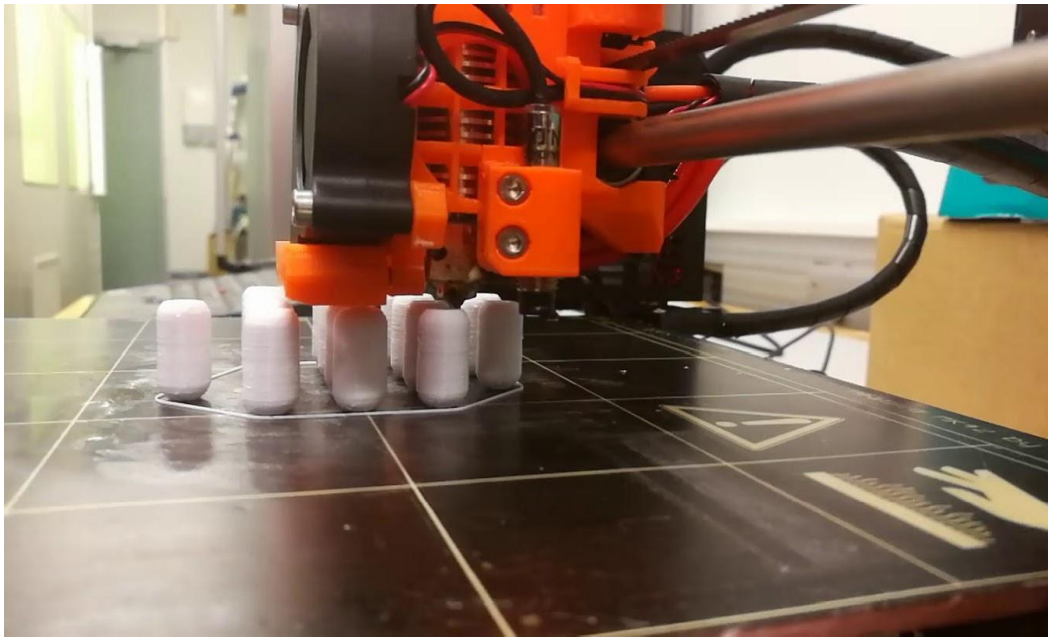

Figure 23. *A detail of printings and the printer nozzle on a nearly finished batch of capsules. Notice the cooling fan next to heated nozzle to keep the nozzle temperature stable.*

As mentioned earlier, the printer has its own interface with LCD display and an operating knob (Figure 24). With the interface,

Figure 24. *Printer user interface, power off. Note the control knob on the right side of the LCD panel.*

filaments can be loaded to extruder or unloaded from extruder. The printer can be preheated according to built-in ready temperature settings. Printer can function without a computer as it has a SD card slot from where user can load G-code files directly to printer. All the axis can be moved separately from interface and even the extruder can push filament through the nozzle with turn of a knob. Printer can be also manually calibrated with the built-in interface.

Tables including the full exact printer settings can be found in the appendix A section along with the PRUSA mk2 manual. The interface and status screen can be seen in picture below. Nozzle temperature is set to 210 Celsius degrees (first layers are printed at 215 Celsius degrees) and the heat bed temperature is set to 55 Celsius degrees. These values are the standard default Prusa Slic3r temperature settings for PLA. As seen in the picture, the temperature varies with a degree dynamically as the thermostats set the temperature as close to optimal.

The first printings were printed with completely default settings where the infill was 20 %. Printing time was around 10 minutes. Later the settings were iterated since 20% infill turned out to be too porous in release tests. The capsules with 20% infill had random leaking pixels that affected the results. Porous capsules could be good for some application but when testing and studying the optimal inner cavity shape, porosity wasn't a desired trait.

The layer height was 0.25 mm (0.2 mm the first layer height, default). After the infill set to 100 % the printing time per capsule was doubled to about 20 minutes. The filament usage for one capsule was about 400 millimeters.

One of the most critical factors during the printing process is the adhesion of the heat bed. If a capsule tilts, falls or moves during the printing the whole printing or batch is likely ruined. This not only wastes time but also filament especially when printing large batches. The printing can be paused but the printing process has to be started all over again because it is practically impossible to put a failed print back to its original position. When one capsule/print is moved the extruder doesn't know it and extrudes filament which doesn't attach to the object being printed but curls around the hot nozzle ruining the extrusion of filament to every capsule. To avoid unnecessary material loss or waste of time the batch size should not be very large. The greatest amount of capsules printed in one printing was 20 pieces. One finished batch can be seen in Figure 25.

The necessary adhesion was ensured with a common office supply glue stick combined to de-ionized water. The use of a common glue stick is also a recommendation in Prusa i3 Mk2 manual.

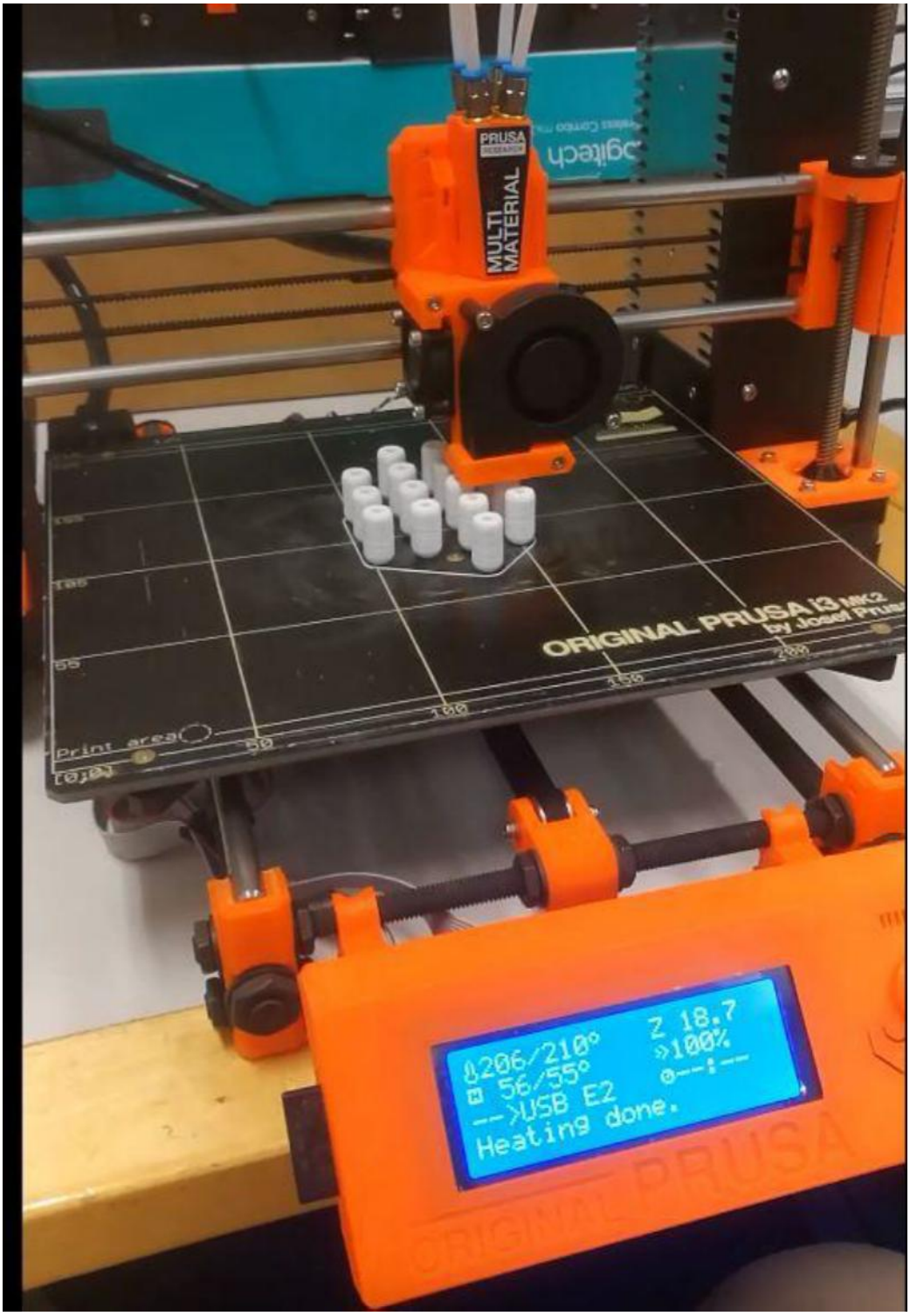

Figure 25. *Printer interface with power on. Nozzle temperature and heatbed temperature can be clearly seen from the LCD display panel. This batch of capsules is nearly finished.*

3.4 The CAD software

As mentioned earlier the CAD software used to design the capsules *in silico* was cloud based CAD software OnShape with a student license. OnShape allows user to create and manipulate 3D objects and the changes to work in progress is saved in the cloud in real time.

OnShape is an easy and well-designed software. The options and possibility to create own scripts makes the design possibilities diverse. The created files are saved straightly to .sls files although there are other CAD file options also such as .dwg. .SLS files are loaded directly to Prusa Slic3r software and are ready to be printed.

The user interface of OnShape is presented in Figure 26. In addition to ready built-in tools user is able to make, save and share own scripts and tools. There is also a large and helpful community and user forum from where user can get help and self-made scripts from other users and community members.

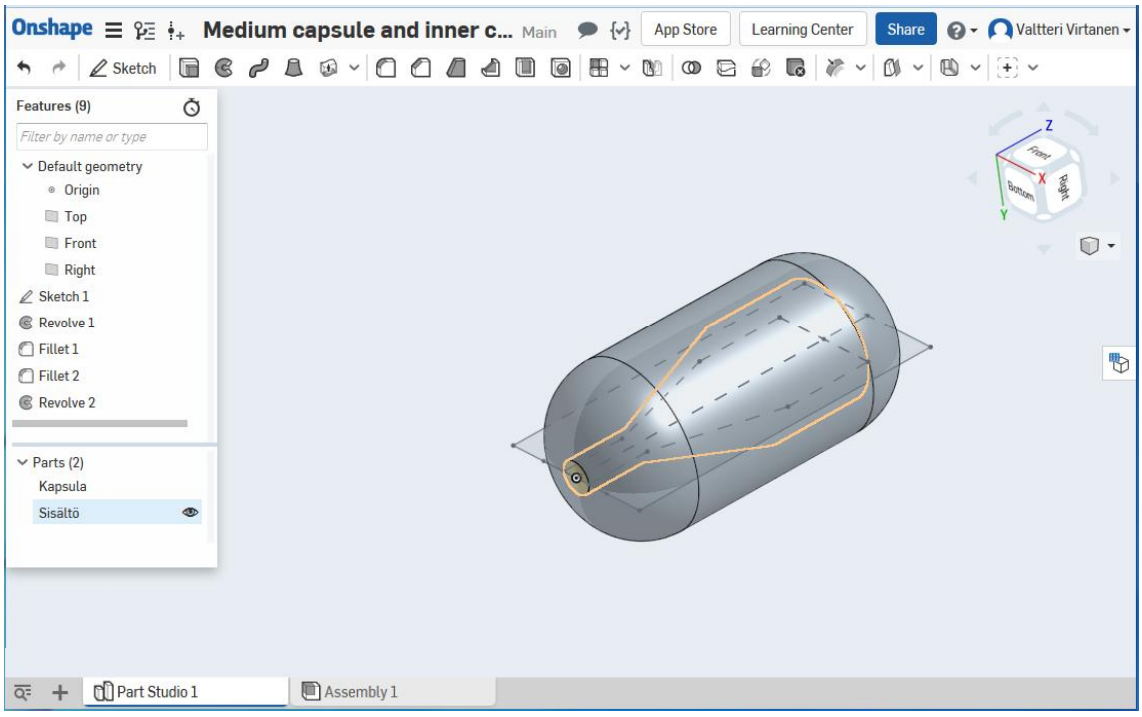

Figure 26. *A screenshot of OnShape user interface. Symbols are logical and clear. Manipulation of object is easy. Note the dashed line sketch on the background and also the visible inner structure ("wine bottle shaped cavity", highlighted as "Sisältö" at Parts menu).*

4. RESULTS AND DISCUSSION

4.1 The first printings and leakage tests

The first sketches were simple cylinder with a bottom wall and open head and the cylinder with previously brainstormed “wine bottle shaped” inner cavity. This sketch was iterated with outer edge fillets 3 mm steeper and more round 4 mm radius (of which the one with the 4 mm radius was rounder and therefore chosen later) to gain the traditional distinctive and easy to swallow “pill shape”. Both of these options can be seen in Figure 27.

The first test print, a cylinder with one head open. This cylinder shaped prototype is presented in Figure 27 B. It was printed with Prusa Slic3r default PLA settings and it printed out so well that I decided to try to print the best prototype drawing (Figure 27 A, the third capsule from the left). The early prototype capsule was also visually inspected and it looked adequate. Printing time of the first print was about ten minutes with default settings which included 20 percent infill setup.

After printing the adequate-looking capsules they were also printed into half to

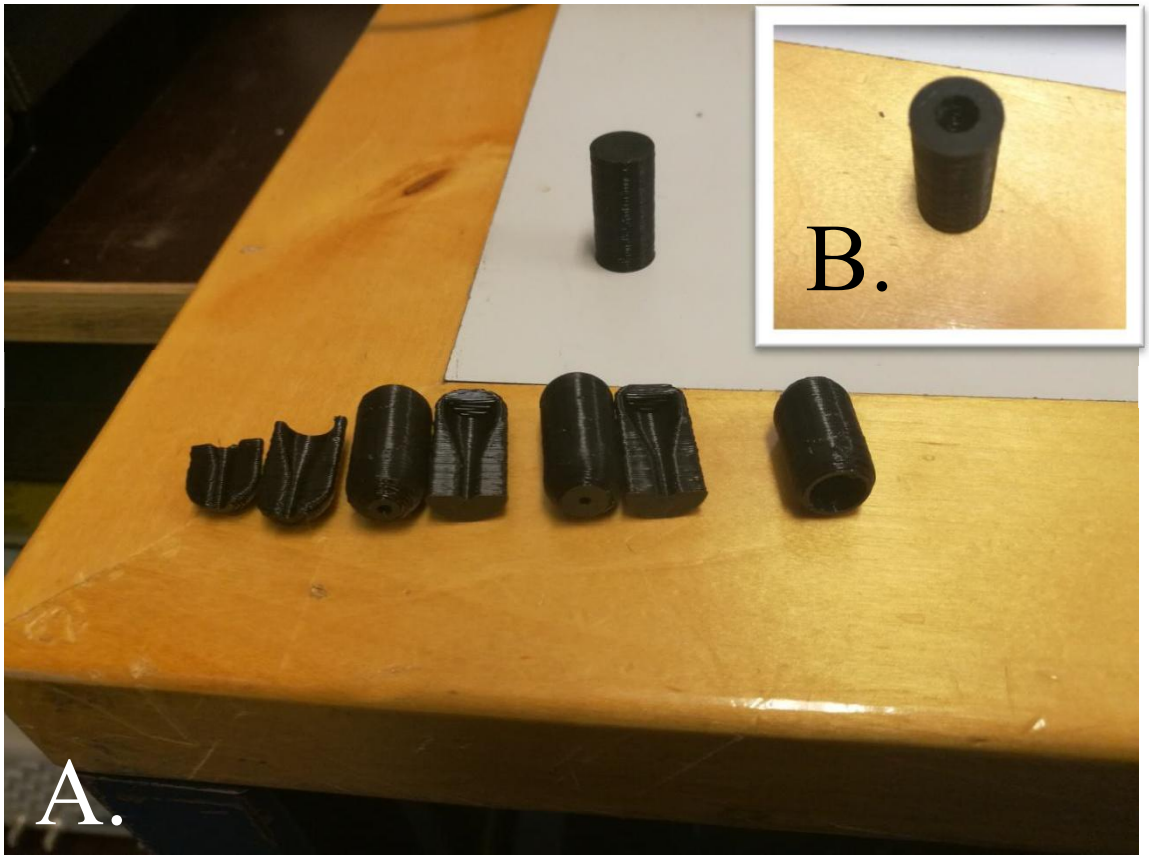

Figure 27. A. *First set of printings. Capsules printed into half show the wine bottle shape inside the capsules.* ***B.*** *The first prototype capsule cylinder with an open head.*

demonstrate the inner cavity of the capsules. These printings can be seen in Figure 27.

The surfaces of the printings were adequate: not very smooth but not too jagged. The grainy surface could be for example sandpapered to reduce or remove excess grains. The resolution and printing speed determines the quality of the printing as mentioned earlier.

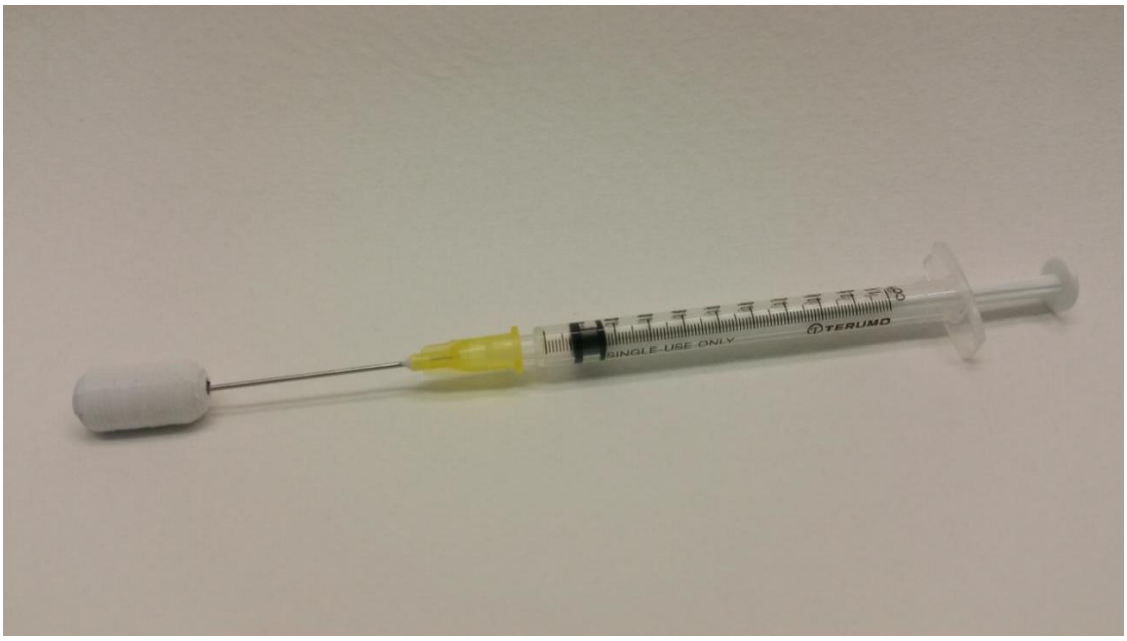

Figure 28. *A capsule is injected with blue-colored dye for a leakage test.*

Next thing to do was to evaluate their leakage. For clarity the color of the PLA was changed to white. The capsules were filled with blue colored dye which is blue food coloring (Figures 28 and 29). In the leakage tests the white capsules were strapped to a magnetic stir bar and spun with magnetic stirrer in clear dish containing clear water. A digital video camera was set to film the leakage test and the video could be later reviewed and analyzed. A capture image of the video is presented in Figure 30. The finished test can be seen in Figure 31.

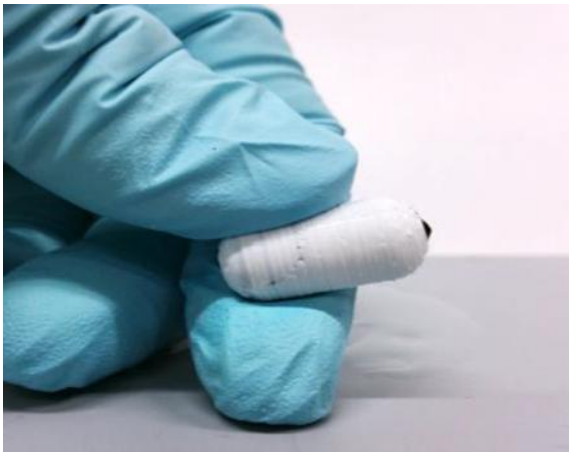

Figure 29. *A capsule filled with blue-colored dye.*

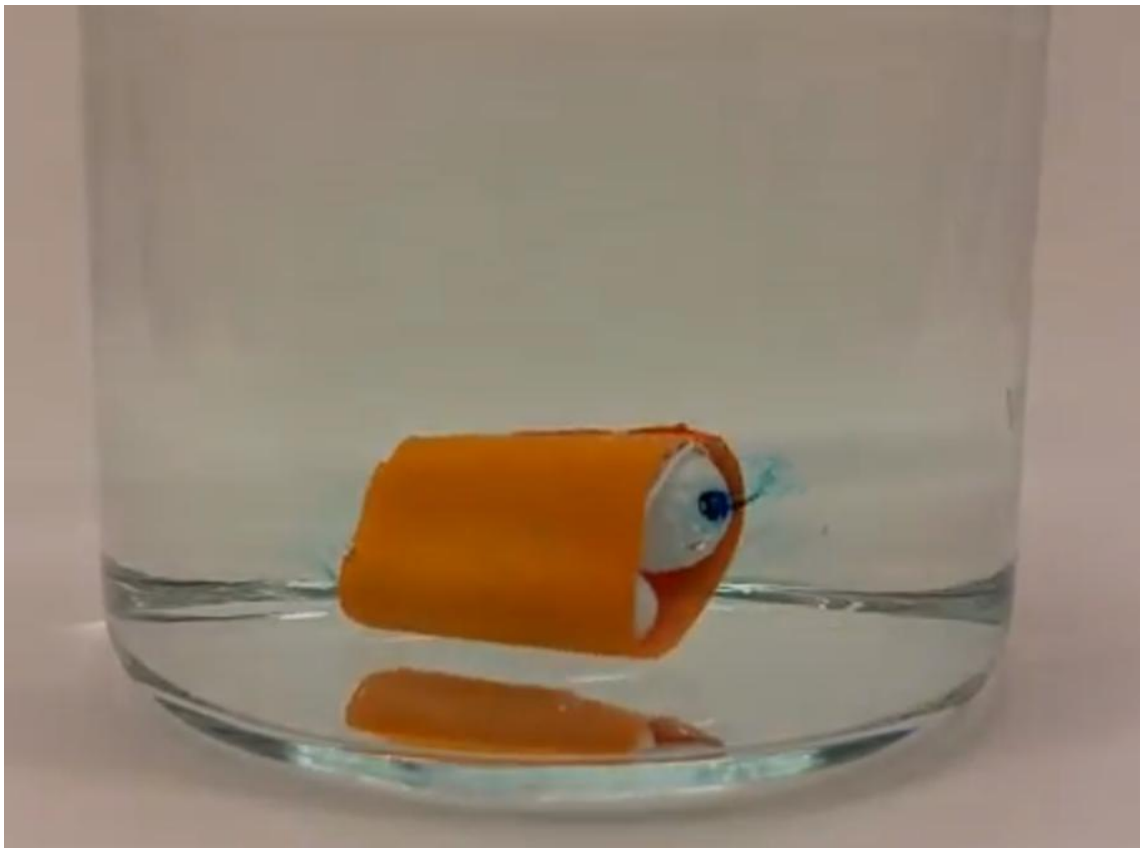

Figure 30. *A dye filled capsule attached to a flea (stir bar) spins in magnetic mixer and releases blue colored dye during first leakage tests. Some undesired leakage can be seen behind the other end of the capsule.*

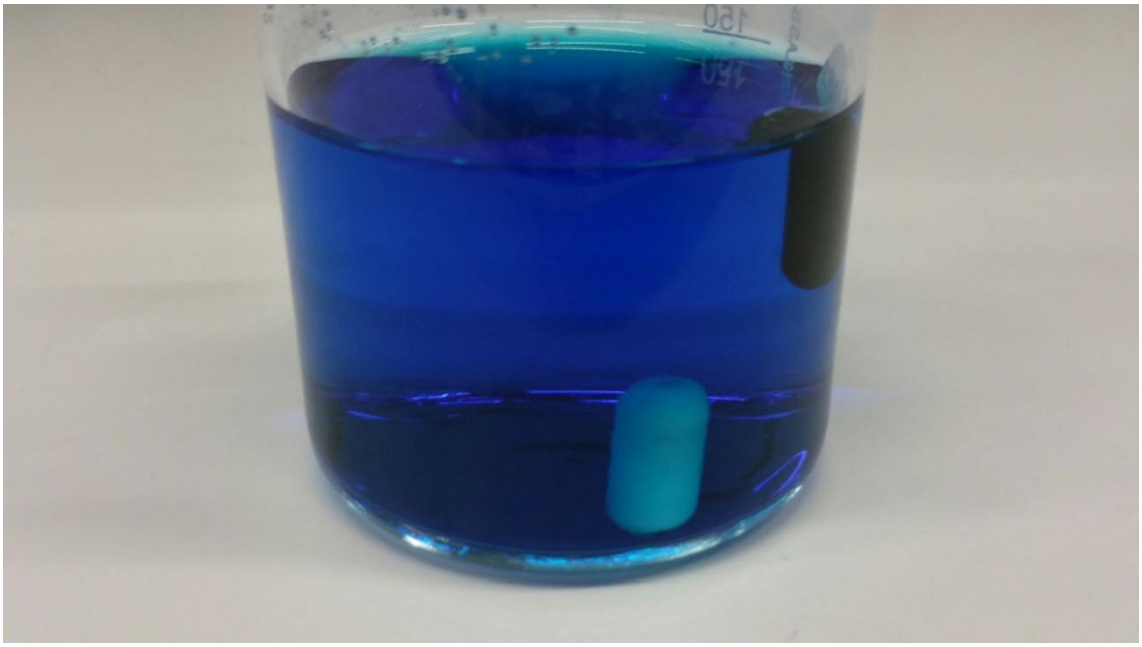

Figure 31. *A finished leakage test.*

In the first leakage tests the capsules that were printed leaked (Figures 29, 30 and 31). The pinpointing of the reason for leakage was done by changing the infill thickness and redesigning the capsule walls increasing thickness and inside corner fillets. After making new prototypes they were also tested in leakage tests. The proposed design changes were:

1. 1 millimeter raise to the bottom wall (which was 2 mm from bottom to bottom of the cavity to) 3 mm.
2. Changing the filled radius from 4 mm to 3 mm which raised the thickness between inner cavity and slope of the fillet
3. Designs 1 and 2 combined: a 1 mm raise to bottom wall and change to the fillet radius from 4 mm to 3 mm.
4. 1 mm rounding to the inner corners of the “inside bottom of the bottle” cavity design
5. 2 mm rounding to the inner corners of the “inside bottom of the bottle” cavity design
6. Original design with 100 % infill with printer settings (others were default 20 %)
7. Original design with 100 % infill and 1 mm raise to the bottom wall
8. 2 mm rounding to the inner corners of the “inside bottom of the bottle” cavity design with 100 % infill

These proposed design changes are presented in Figure 32 and Figure 33 along with their dimensions which can be seen among the rendered shell structure. Of each of these designs a prototype was printed and tested for leakage. The results and the designs are presented in Table 1.

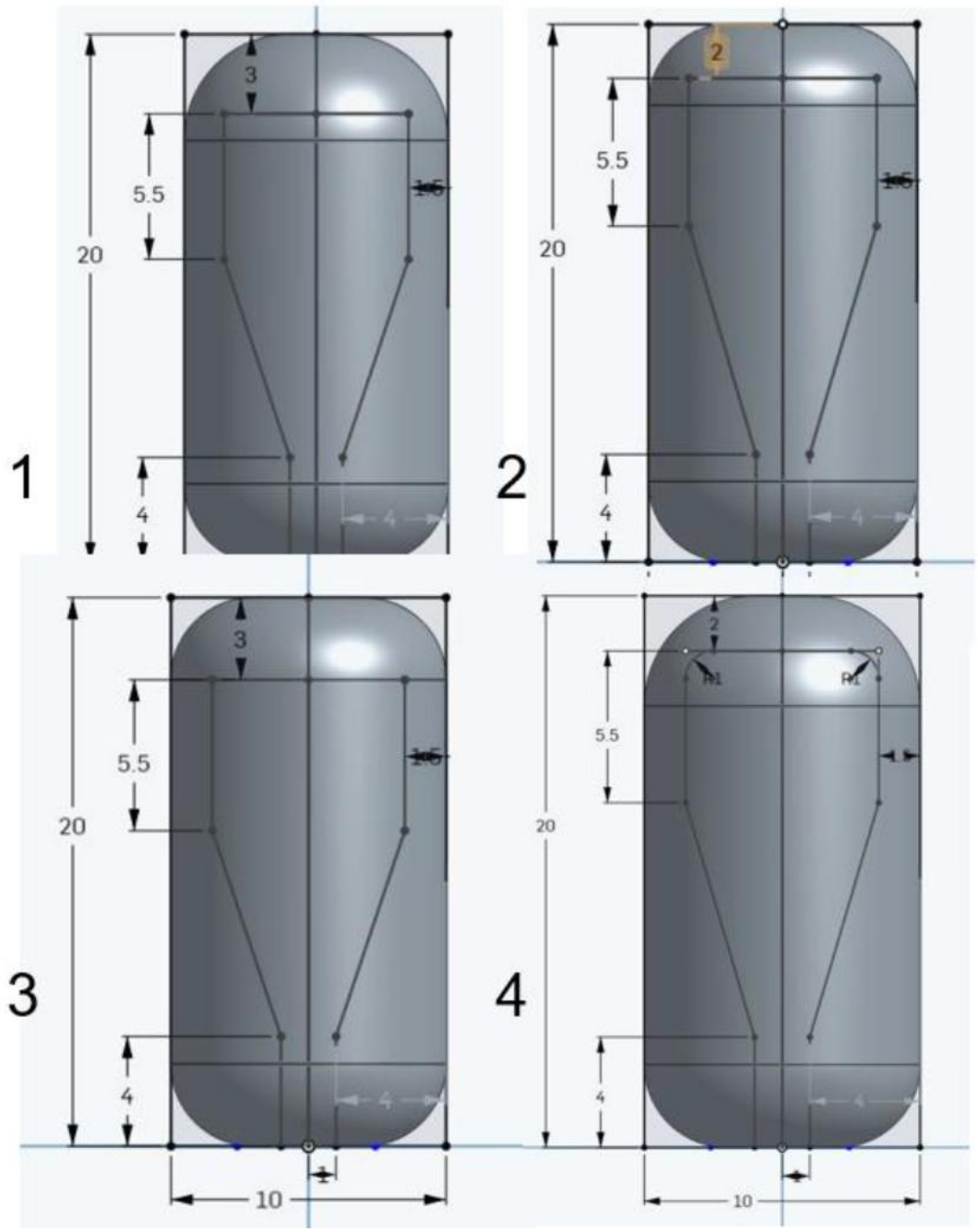

Figure 32. *Designs 1-4 with original 20 % infill. Note the rendered shape of 2 and 3 which are less round than 1 and 4 because their fillet radius is 3 mm instead of 4 mm.*

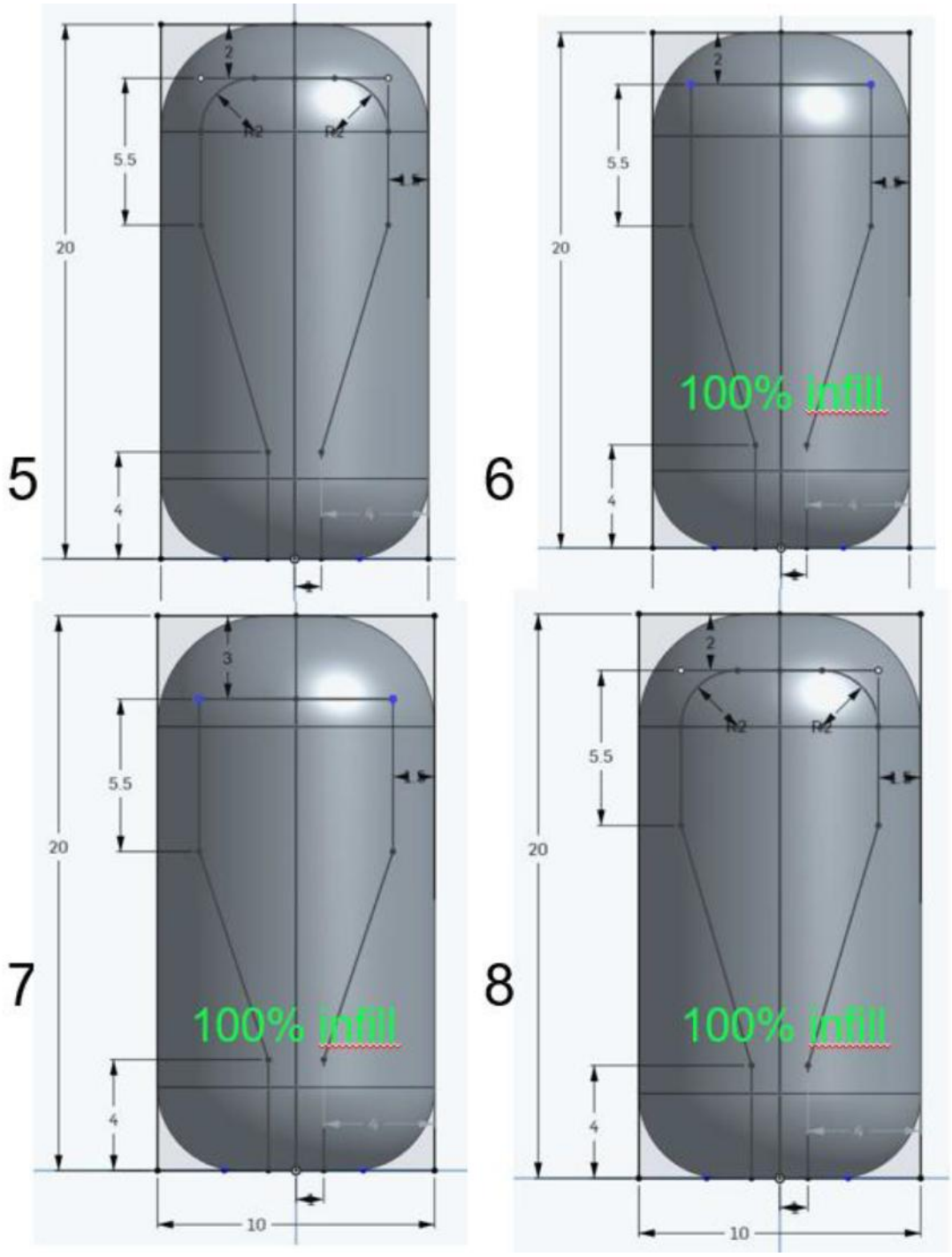

Figure 33. *Designs 5-8 of which 6-8 have the iterated 100% infill.*

Table 1 *Results of the leakage tests and evaluation of the design of the capsule.*

Nr/ name	Design of the capsule	20% infill	100% infill	Mass (grams)	Leakage?	Comments
1	1 mm raise to bottom wall (from 2 mm → 3 mm)	x		1.1299	x	Leakage at the bottom
2	Fillet radius smaller, therefore steeper capsule endings	x		1.1269	x	Leakage at the bottom
3	Designs 1 and 2 combined: raise and fillet	x		1.1870	x	1 tiny "leaking pixel" at the bottom
4	1 mm rounding to inner corners of the design	x		1.0614	x	Leakage at the middle and the bottom
5	2 mm rounding to inner corners of the design	x		1.0623	x	Overall leakage
6	Original design with 100% infill		x	1.2426		
7	1 mm raise of the bottom wall with 100% infill		x	1.2060		CHOSEN FOR RELEASE TESTS
8	2 mm rounding to inner corners of the design with 100% fill		x	1.2522	x	Leaking holes at the middle suture... picture
”Ranska”	Original design, capsule tricolored	x		1.1088	x	Heavy leakage trough red plastic
”Suomi100”	Original design with 20% infill, capsule with blue and white color	x		1.2068	x	Leakage at the bottom

As seen on Table 1. there were two designs (highlighted with green background color) that were not leaking: the design number 6 and the design number 7. The design number 7 (highlighted with orange background) looked the most promising option with a few design changes (raise of the bottom wall with 1 mm just to be sure) and infill settings were changed to 100 % infill. The complete list of printer settings, printing settings and filament settings for successful capsules can be seen in Appendix A.

The chosen design was tested in a series of release tests to evaluate the release profile of the capsule. This also tested the function of the i$_2$nner form of the capsule. The test series consisted of three 20-piece batches of chosen capsules. Each batches got their own bottle hole area multiplier: 1 for “small capsule”, 3 for “medium capsule” and 10 for “large capsule”. These names are later used to refer those designs. The radiuses and other dimensions for the capsules were calculated and drawn with CAD. The designs can be seen in Figure 34. The formulas for the dimensions of the capsules are:

$1\ A = \pi {r_1}^2,\ 3\ A = \pi {r_3}^2\ ,\ 10\ A = \pi {r_{10}}^2,$

where

$A = 1\ A = 1.047\ mm^2,\ r_1 = 0.577\ mm,\ V_1 = 330.536\ mm^3$

$B = 3\ A = 3{,}142\ mm^2,\ r_3 = 1.00\ mm,\ V_3 = 355.785 mm^3$

$C = 10\ A = 1.047\ mm^2,\ r_{10} = 1.823\ mm,\ V_{10} = 426.567 mm^3$

These designs and their dimensions are illustrated in Figure 33.

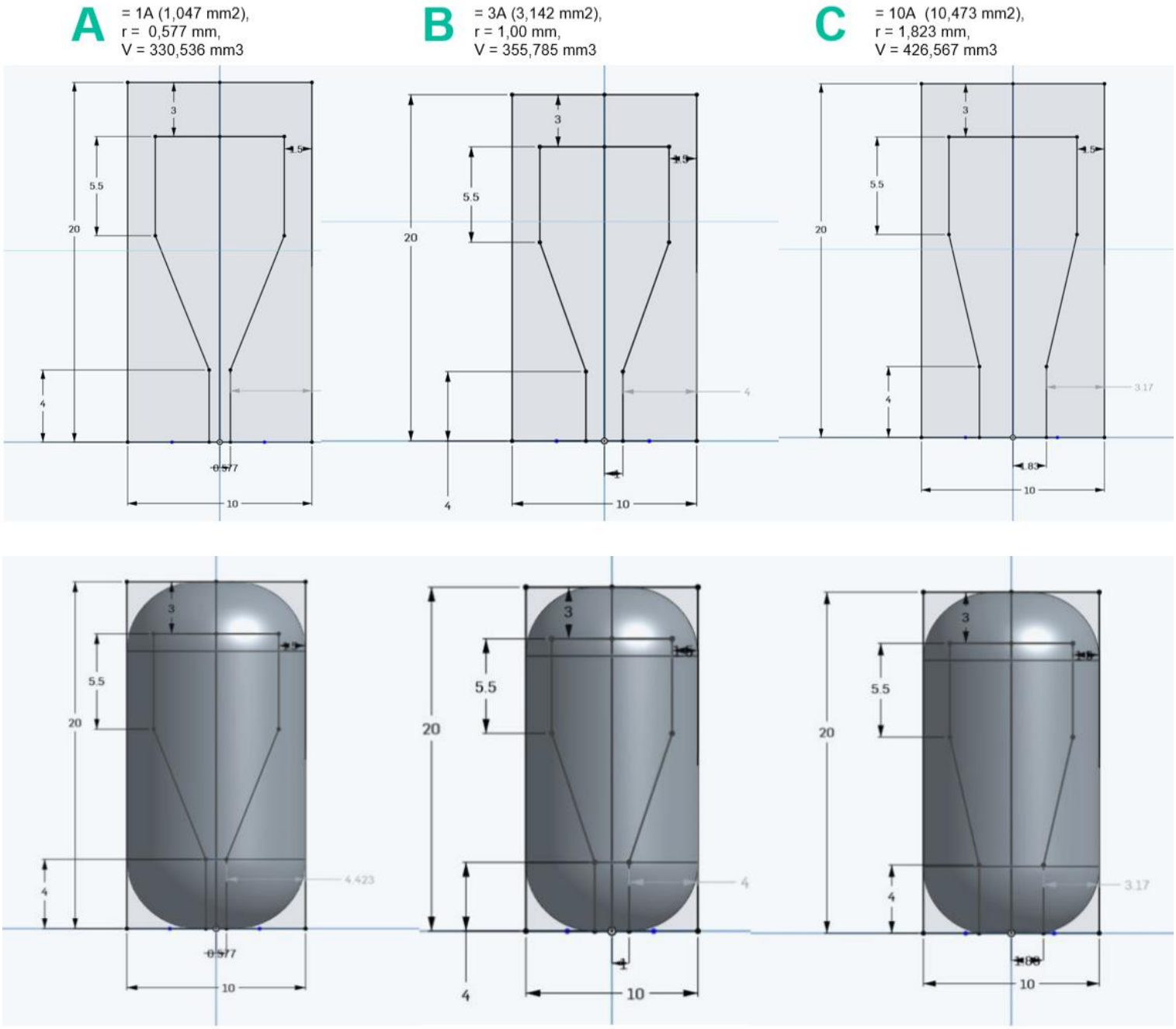

Figure 34. *Capsule designs to be evaluated in release studies. A is "small capsule", B is "medium capsule" and C is "large capsule".*

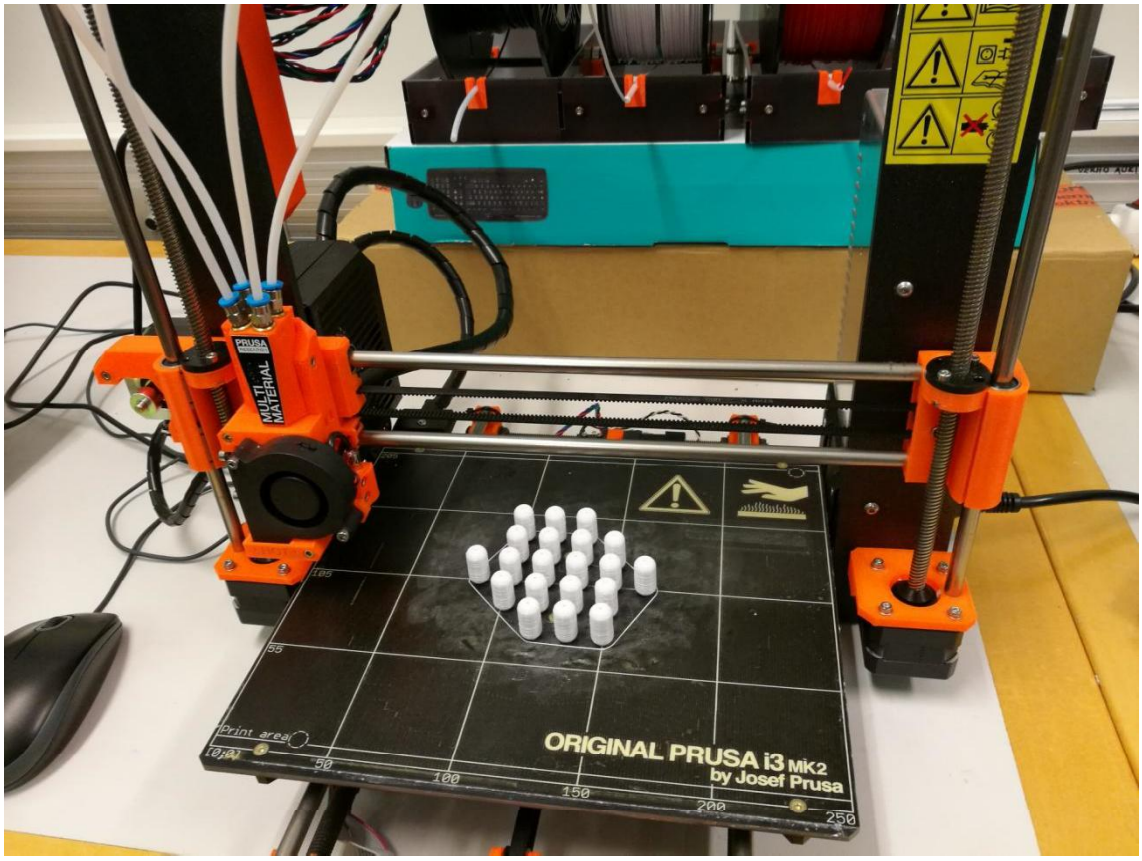

Figure 35. *A finished 20-piece batch of capsules ready to be bagged for release tests.*

A total of 60 capsules were made for the first release studies. 20 pieces of each with different batch sizes to determine if printing time/batch size has an effect to release tests. The batch sizes were 5, 10, 15 and 20. Finished batch of 20 capsules can be seen in Figure 35. Note the excessive adhesion needed to keep the capsules in standing position.

The time, extruder used, date, name of the printer and filament consume was measured. The capsules were packed in Minigrip bags made by Finnish company Amerplast. The measurement recordings were written on bags as seen in Figure 36.

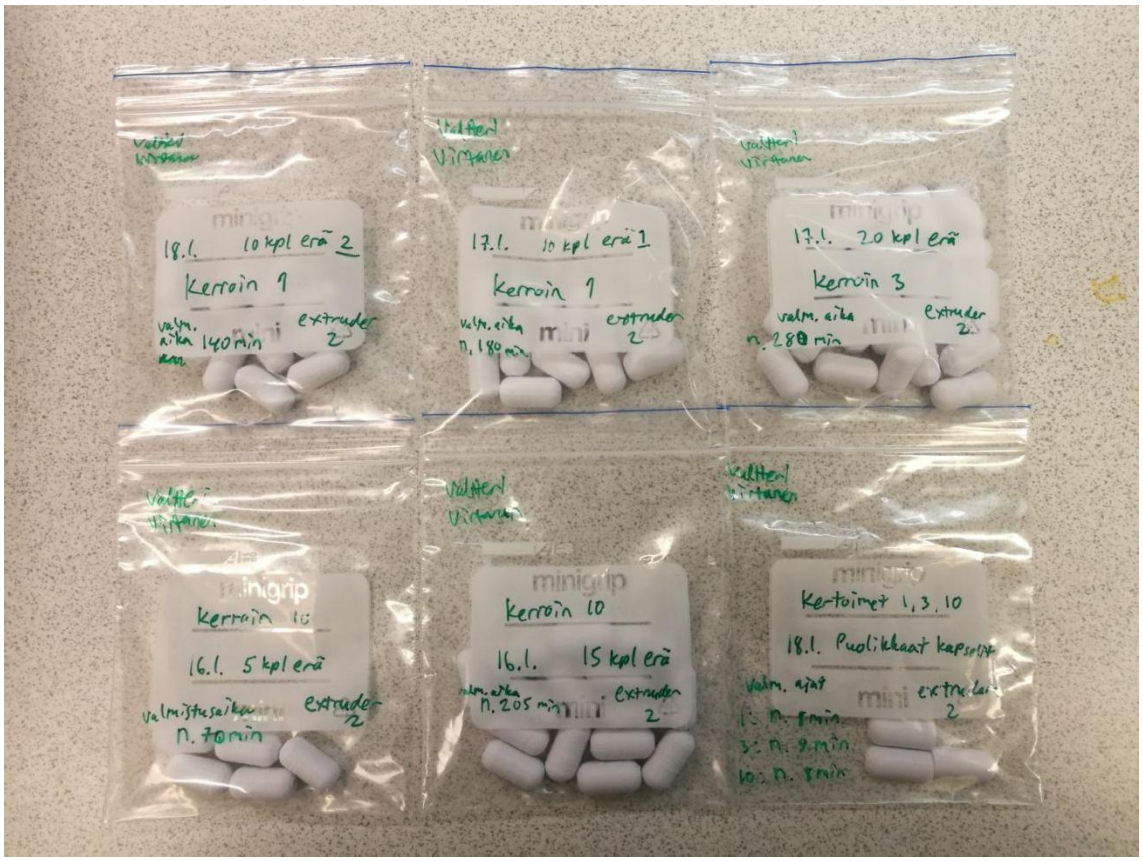

Figure 36. *The capsule series printed with different batch sizes to study its relation to success of the tests. The area multiplier, date, number of batch, printing time, number of extruder that was used and the name of the person operating printer are mentioned on the capsule bags.*

4.2 Release tests

In this study we decided to leave the small capsule completely out of release tests because not only the filling with injection needles or pipettes was hard, the release profile would have been useless for any medical application. We decided to exclude the small capsule out of the tests. Medium and large capsules were tested with equipment.

In both test capsules, there are burst phases at the beginning. About 2 milligrams are released during first hours of release tests. After that the release profile is linear. Larger holed capsule releases Nadolol more aggressively than medium (Figure 37).

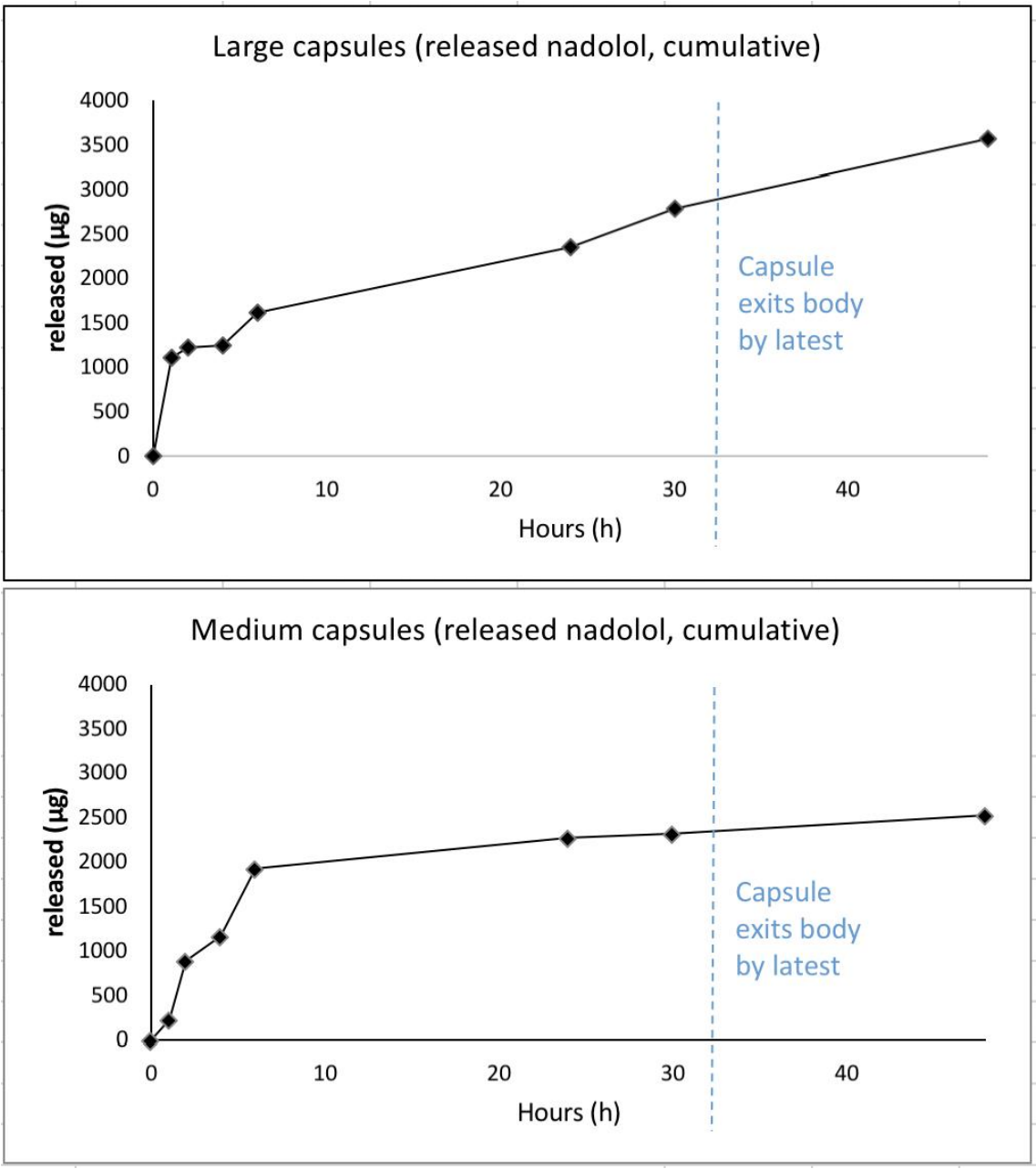

Figure 37. *Large and medium capsule (micrograms) release profiles with function of time (in hours).*

The release tests were conducted using digital magnetic hotplate stirrer RT 10 P made by IKA. The large capsules were completely filled (426 mm^3) with gel which included 110 mg of Nadolol (a heart medicine) and the rest (3%) ANFC (Anionic Nanofibrillar Cellulose) hydrogel.

Each test dish contained 70 ml of DPBS (Dulbecco's Phosphate-Buffered Saline, a balanced salt solution with pH 7 and the temperature was kept constant 37 Celsius degrees). During the tests 1.5 ml of DPBS-solution was taken to Eppendorf tubes and measured with UPLC (Ultra/High Performance Liquid Chromatography) at every test

point. To compensate the loss of DPBS, 1.5 ml of pure DPBS was added to dishes. The added DPBS was backwards calculated to get the exact results.

As seen from the release profile curve seen in Figure 38. the capsule appears to be more suitable for implant use than as a medicine. In real life situation, the mass of food typically moves through large intestine in approximately 18 hours. In normal medicine use the maximum amount of 3 mg dose released during that time is not enough for normal medical use. However, the results show that the wine bottle shape actually works as a retardant for water soluble substances.

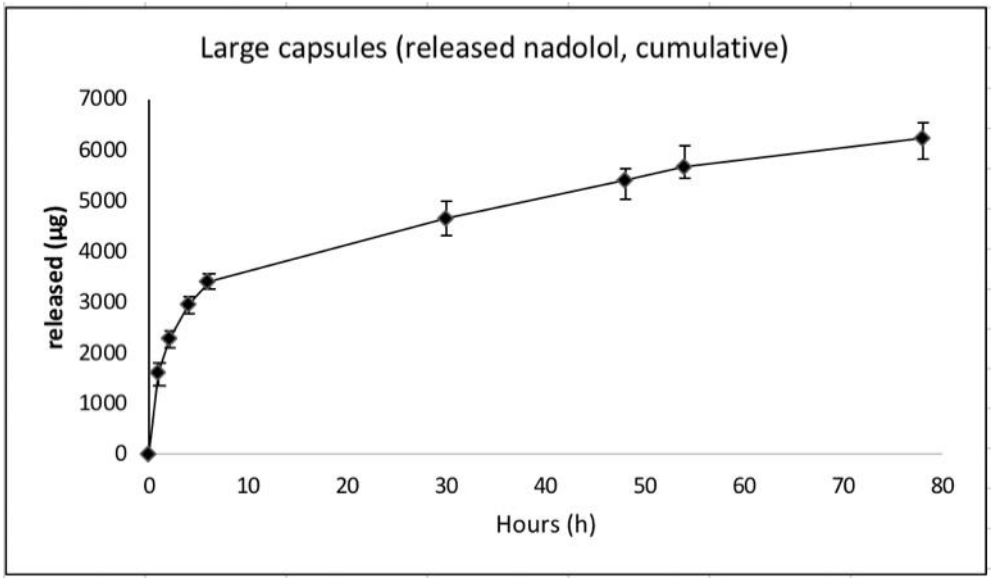

Figure 38. *API long time release profile with error margins.*

In future designs the text can be printed on the surface of the capsule. This makes the surface unnecessarily rough at this point with equipment used during this thesis work.

4.3 Future aspects

In near future and with more advanced equipment, the surface text option may be good for clarity. The amount of medicine or the name of the implant can be printed directly on the surface of the capsule. This makes the laser crafting or other methods unnecessary when everything can be done with one printing. The CAD design of the surface text is presented in Figure 39 and a printed prototype can be seen in Figure 40. Note the rough but clearly readable surface text of the capsule.

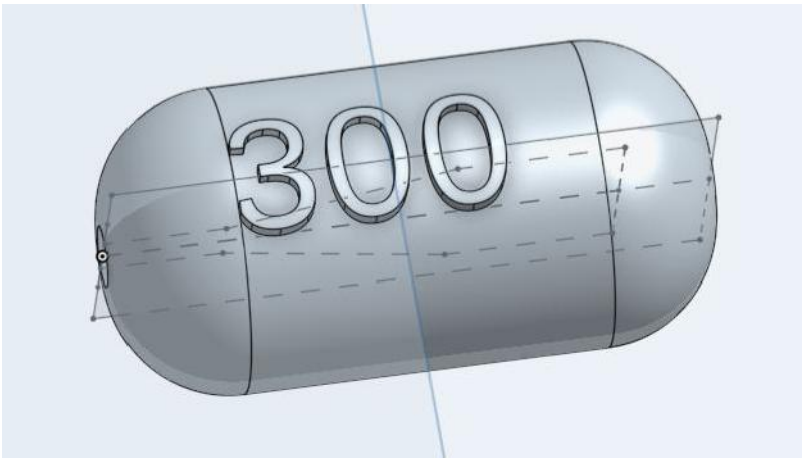

Figure 39. *A CAD design of a capsule with a surface text on its side.*

Figure 40. *A printed prototype of a surface text capsule.*

Multi material possibility can be also utilized in capsule printing as seen in Figure 41. With Prusa mk2 i3 MultiMaterial capsule can be printed with up to four different colors during one printing session. However this wastes filaments because the extruder has to create a so-called wiping tower to completely discard the previous filaments from extruder. This is also time consuming and the new l layers are cooled between the layers printing when extruder is busy discarding the previous filaments into wiping tower.

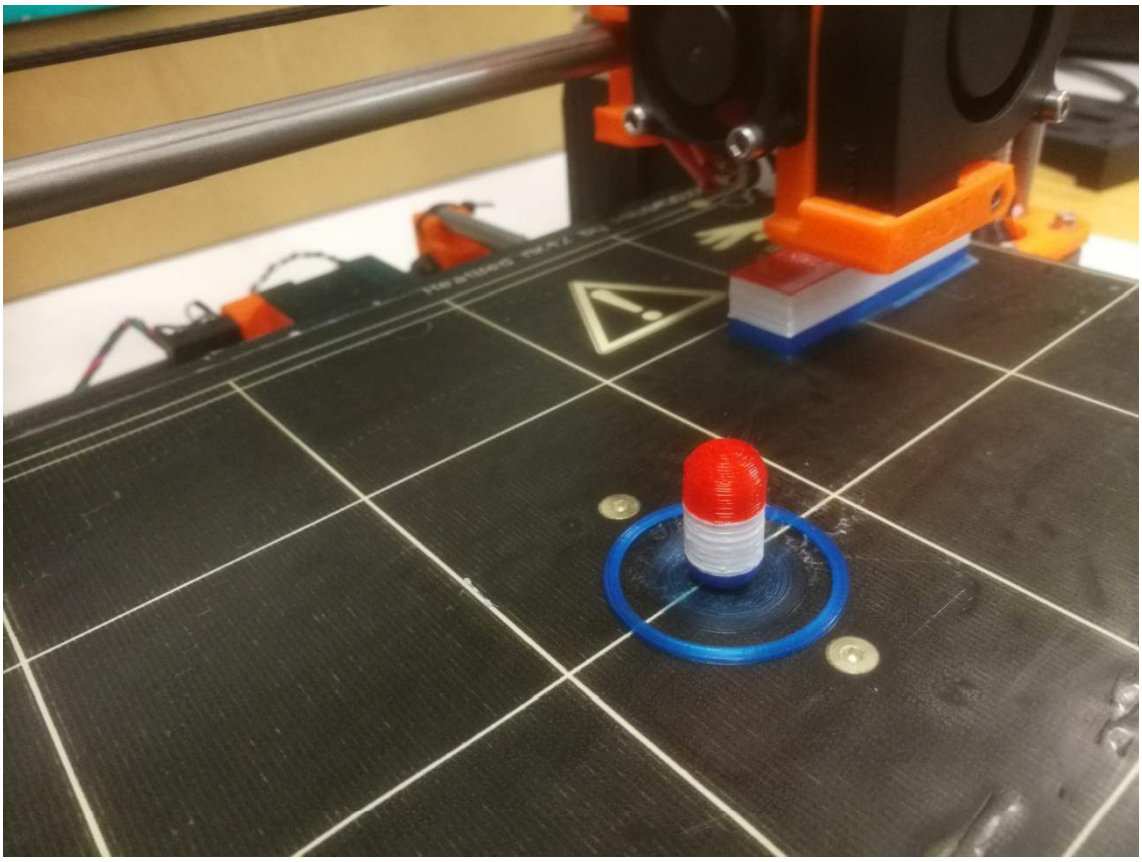

Figure 41. *Multi color/multi material printing of a capsule. Note the wiping tower block next to capsule. This is used to ensure clean layers of new material between different materials. The Color coding of the capsules is one of the future aspects along with surface text.*

Future studies include the long time release tests of medium capsules and comparison between the large capsules. Application of freeze drying which is used to make hydrogels aerogels and therefore affect the release profile of the medicine [12] is also studied in the near future.

The material studies are also needed to determine the biocompatibility of this application. PLA and its copolymers are applied for years now and are known to be safe and completely biocompatible, however there is a recent (2016) study that puts the biocompatibility of PLA combined to medicine into doubt (Ramot et. al). Some of the possible symptoms include for example common foreign body reaction or inflammation. [38]

Foreign body reactions may occur with any foreign biomaterial in body [39]. To tackle this kind of questions the application of PLA as an implant and its biocompatibility and toxicology must be studied well. As mentioned earlier, properties of the PLA can be modified. The negative effects can be modified for example surface coating and

blending PLA with other biocompatible polymers. In future, the biocompatibility PLA can be optimized with material engineering [31].

The capsule releases its contents in about a couple of days according to release tests (Figure 38) so long term harmfulness is out of question if the capsule is removed from the body soon after the dosage.

5. CONCLUSION

The aim of this thesis was to print PLA capsules and study the possibilities to utilize 3D printing for pharmaceutical purposes. The application as a traditional swallowed drug of the PLA capsule studied in this thesis seems very unlikely because the time the capsule spends inside the digestive tract is simply too short as the possible dosage is about 1% of the volume of the drug (Figure 38). However, the capsule studied in this thesis solves the problem of long term stable delivery of medicinal compounds to bloodstream at a constant rate without need of any external connections to medical systems. The printed capsules are in the prototype phase and the shape of the inner cavity of the capsule is crucial according to the tests.

The invention report for a long and stable release implant device was recently accepted.

The capsules can be used both as an implant and an oral capsule. The capsule is filled with a drug-nanocellulose hydrogel. The future improvements could be multicolored capsule, polishing the surface and the text surface. In future, the definition and the quality of printings will be improved. It is important that the capsule is easy to swallow and the smoother the surface of the capsule is the easier it is to swallow. Also smoother surface is better for implant applications too. The toxicology and actual biocompatibility of the capsule is necessary to be studied before application.

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APPENDIX A: PRUSA I3 MK2 SETTINGS AND MANUAL

LAYERS AND PERIMETERS	
Parameter	*Value/setting*
LAYER HEIGHT	
Layer height	0.25 mm
First layer height	0.2 mm
VERTICAL SHELLS	
Perimeters	2 (minimum)
Spiral vase	disable
HORIZONTAL SHELLS	
Solid layers	Top: 6, Bottom: 5
QUALITY (SLOWER SLICING)	
Extra perimeters	disabled
Ensure vertical thickness	enabled
Avoid crossing perimeters	disabled
Detect thin walls	disabled
Detect bridging perimeters	disabled
ADVANCED	
Seam position	Nearest
External perimeters first	disabled

INFILL	
Parameter	*Value/setting*
INFILL	
Fill density	100 %
Fill pattern	Rectilinear
Top/bottom fill pattern	Rectilinear
REDUCING PRINTING TIME	
Combine infill every	1 layers
Only infill where needed	disabled
ADVANCED	
Solid infill every	0 layers
Fill angle	45°
Solid infill treshold area	70 mm²
Only retract when crossing perimeters	enabled
Infill before perimeters	disabled

SKIRT AND BRIM	
Parameter	*Value/setting*
SKIRT	
Loops (minimum)	1
Distance from object	2 mm
Skirt height	3 layers
Minimum extrusion length	4 mm
BRIM	
Brim width	0 mm

SUPPORT MATERIAL	
Parameter	*Value/setting*
SUPPORT MATERIAL	
Generate support material	disabled
Overhang treshold	0°
Enforce support for the first	0 layers
RAFT	
Raft layers	0 layers
OPTIONS FOR SUPPORT MATERIAL AND RAFT	
Contact Z distance	0.2 (detachtable) r
Pattern	Pillars
With sheath around the support	enabled
Pattern spacing	2.5 mm
Interface layers	3 layers
Interface pattern spacing	0 mm
Interface loops	disabled
Support on build plate only	disabled
XY separation between an object and its support	50 %
Don't support bridges	enabled
Synchronize with object layers	disabled

SPEED	
Parameter	*Value/setting*
SPEED FOR PRINT MOVES	
Perimeters	60 mm/s
Small perimeters	15 mm/s
External perimeters	50 %
Infill	80 mm/s
Solid infill	20 mm/s
Top solid infill	15 mm/s
Support material	60 mm/s
Support material interface	100 %
Bridges	60 mm/s
Gap fill	20 mm/s
SPEED FOR NON-PRINT MOVES	
Travel	130 mm/s
MODIFIERS	
First layer speed	30 mm/s
ACCELERATION CONTROL (ADVANCED)	
Perimeters	0 mm/s²
Infill	0 mm/s²
Bridge	0 mm/s²
First layer	0 mm/s²
Default	0 mm/s²
AUTOSPEED (ADVANCED)	
Max print speed	80 mm/s
Max volumetric speed	0 mm³/s
Max volumetric slope positive	0 mm³/s
Max volumetric slope negative	0 mm³/s

MULTIPLE EXTRUDERS	
Parameter	*Value/setting*
EXTRUDERS	
Perimeter extruder	1
Infill extruder	1
Solid infill extruder	1
Support material/raft/skirt extruder	1
Support material/raft interface extruder	1
OOZE PREVENTION	
Enable	disabled
Temperature variations	-5 A°C
WIPE TOWER	
Enable	disabled
Position X	180 mm
Position Y	140 mm
Width	60 mm
Per color change depth	15 mm
ADVANCED	
Interface shells	disabled

ADVANCED	
Parameter	*Value/setting*
EXTRUSION WIDTH	
Default extrusion width	0 (auto)
First layer	200 %
Perimeters	0 (default)
External perimeters	0 (default)
Infill	0 (default)
Solid infill	0 (default)
Top solid infill	0 (default)
Support material	0 (default)
OVERLAP	
Infill/perimeters overlap	25 %
FLOW	
Bridge flow ratio	1
OTHER	
Clip multi-part objects	disabled
Elephant foot compensation	0 mm
XY Size Compensation	0 mm
Threads	4
Resolution	0 mm

OUTPUT OPTIONS	
Parameter	*Value/Setting*
SEQUENTIAL PRINTING	
Complete individual objects	disabled
Extruder clearance (mm)	Radius 20 mm Height 20 mm
OUTPUT FILE	
Verbose G-code	disabled
Output filename format	[input_filename_base].gcode
Post-processing scripts	-

GENERAL		CUSTOM G-CODE
Parameter	*Value/setting*	*Function and code*
BED SHAPE		**START G-CODE**
Z offset	0 mm	M115 U3.0.12 ; tell printer latest fw version
CAPABILITIES		Start G-Code sequence START
Extruders	4	T[initial_tool]
Single Extruder Multi Material	enabled	M109 S[first_layer_temperature]
USB/SERIAL CONNECTION		G21 ; set units to millimeters
Serial port	COM7 Speed: 115200	G90 ; use absolute coordinates
OCTOPRINT UPLOAD		M83 ; use relative distances for extrusions
Host or IP	-	G28 W
API Key	-	G80
FIRMWARE		**END G-CODE**
G-code flavor	RepRap (Marlin/Sprinter)	M107 ; fan off
ADVANCED		M104 S0 ; turn off temperature
Use relative E distances	enabled	M140 S0 ; turn off heatbed
Use firmware retractions	disabled	G28 X0 ; home X axis
Use volumetric E	disabled	M84 ; disable motors
Enable variable layer height feature	disabled	**BEFORE LAYER CHANGE G-CODE**
		;BEFORE_LAYER CHANGE
		;[layer_z]
		AFTER LAYER CHANGE G-CODE
		;AFTER_LAYER_CHANGE
		;[layer_z]
		Tool change G-code

EXTRUDER 1-4 (THESE SETUPS APPLY ALL EXTRUDERS)	
NOZZLE DIAMETER	0.4 mm
LAYER HEIGHT LIMITS	
Min	0.07 mm
Max	0.25 mm
POSITION (FOR MULTI-EXTRUDER PRINTERS)	
Extruder offset	x: 0 mm y: 0 mm
RETRACTION	
Length	5 mm
Lift Z	0.5 mm
Only lift Z	Above Z: 0 mm Belovw Z: 199 mm
Retraction Speed	50 mm/s
Deretraction Speed	0 mm/s
Extra legnth on restart	0 mm/s
Minimum travel after retraction	3 mm
Retract on layer change	disabled
Wipe while retracting	enabled
Retract amount before wipe	0 %
RETRACTION WHEN TOOL IS DISABLED (ADVANCED SETTINGS FOR MULTI-EXTRUDER SETUPS	
Length	7 mm
Extra length on restart	0.1 mm

FILAMENT			**COOLING**	
Parameter	*Value/setting*		*Parameter*	*Value/setting*
FILAMENT			**ENABLE**	
Color	user defines		Keep fan always on	enabled
Diameter	1.75 mm		Enable auto cooling	enabled
Extrusion multiplier	1		**FAN SETTINGS**	
Density	0 g/cm³		Fan speed	Min: 85 % Max: 100 %
Cost	0 money/kg		Bridges fan speed	100 %
TEMPERATURE (°C)			Disable fan for the first	1 layers
Extruder	First layer: 215 Other layers: 210		**COOLING TRESHOLDS**	
Bed	First layer: 55 Other layers: 55		Enable fan if layer print time is below	100 approximate seconds
			Slow down if layer print time is below	25 approximate seconds
			Min print speed	15 mm/s
ADVANCED			**CUSTOM G-CODE**	
FILAMENT PROPERTIES			*Function/code*	
Filament type	PLA		**START G-CODE**	
Soluble material	disabled		; Filament gcode	
PRINT SPEED OVERRIDE			**END G-CODE**	
Max volumetric speed	0 mm³/s		; Filament- specific end gcode	
			; END gcode for filament	
NOTES				
LIST OF MATERIALS TESTED WITH STANDARD PLA PRINT SETTINGS FOR MK2				
Das Filament				
Esun PLA				
EUMAKERS PLA				
Fiberlogy HD-PLA				
Fillamentum PLA				
Floreon3D				
Hatchbox PLA				
Plasty Mladec PLA				
Primavalue PLA				
Proto pasta Matte Fiber				
Verbatim PLA				
Verbatim BVOH				

MULTI MATERIAL HANDBOOK

USER MANUAL FOR 3D PRINTERS:
- ORIGINAL PRUSA I3 MK2/MK2S WITH MULTIMATERIAL UPGRADE

V1.00

PRUSA RESEARCH
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Please always refer to the http://www.prusa3d.com/drivers/ for an updated version of this Multi Material handbook (PDF download).

QUICK GUIDE TO THE FIRST PRINT

1. Carefully follow upgrade steps (page 13)
2. Read about different filaments and print quality (page 11)
3. Learn how to load/unload filament - **it's different from MK2/S** (page 12)
4. Stopping the print is critical operation - read about it (page 17)
5. Learn about smart wipe tower (page 19)

About the author

Josef Prusa (born Feb 23rd, 1990) became interested in the 3D printing phenomenon before joining the Prague's University of Economics in 2009 - at first it was a hobby, a new technology open to changes and improvements. The hobby soon became a passion and Josef grew into one of the leading developers of Adrien Bowyer's international, open source, RepRap project. Today, you can see the Prusa design in different versions all around the world, it is one of the most popular printers and thanks to it, knowledge about the 3D printing technology significantly increased among public.

Jo's work on self-replicating printers (you can print the other printer parts with your printer) are still ongoing and currently there is Prusa i3 - the third iteration of the original 3D printer. It is constantly updated with the latest innovations and you've just purchased its latest version. In addition to printer hardware upgrades, the main goal is to make the technology more accessible and understandable for all users.

Josef Prusa also organizes workshops for the public, participates in professional conferences dedicated to the popularization of 3D printing. For example, he lectured at the TEDx conference in Prague and Vienna, at World Maker Faire in New York, Maker Faire in Rome or at the Open Hardware Summit hosted by MIT. Josef also teaches Arduino at Charles University and was also a lecturer at the Academy of Arts in Prague.

In his own words, he imagines 3D printers will be available in every home in a not too distant future. If anything is needed, you can simply print it. In this field, you just push the boundaries every day... We're glad you're part of it with us!

Table of contents

Important notice, tip, hint or information that helps you print with ease.

Read carefully! This part of text has uppermost importance - either for user safety of for a proper printer service.

This symbol indicates text related to printer kit only.

2 Product details

Title: Multi Material Upgrade for Original Prusa i3 MK2/S
Manufacturer: Prusa Research s.r.o., Partyzánská 188/7a, Prague, 170 00, Czech Republic
Contacts: phone +420 222 263 718, e-mail: info@prusa3d.com
EEE group: 3 (IT and/or telecommunication equipment), Device use: indoor only
Power supply: 90-135 VAC, 2 A / 180-264 VAC, 1 A (50-60 Hz)
Working temperature range: 18 °C (PLA)-38 °C, indoor use only
Working humidity: 85 % or less

CE

3 Multi Material Upgrade introduction

Multi Material Upgrade (MMU) is an addition to the Original Prusa i3 MK2/MK2S 3D printer which enables printing with up to 4 different materials in one single print.

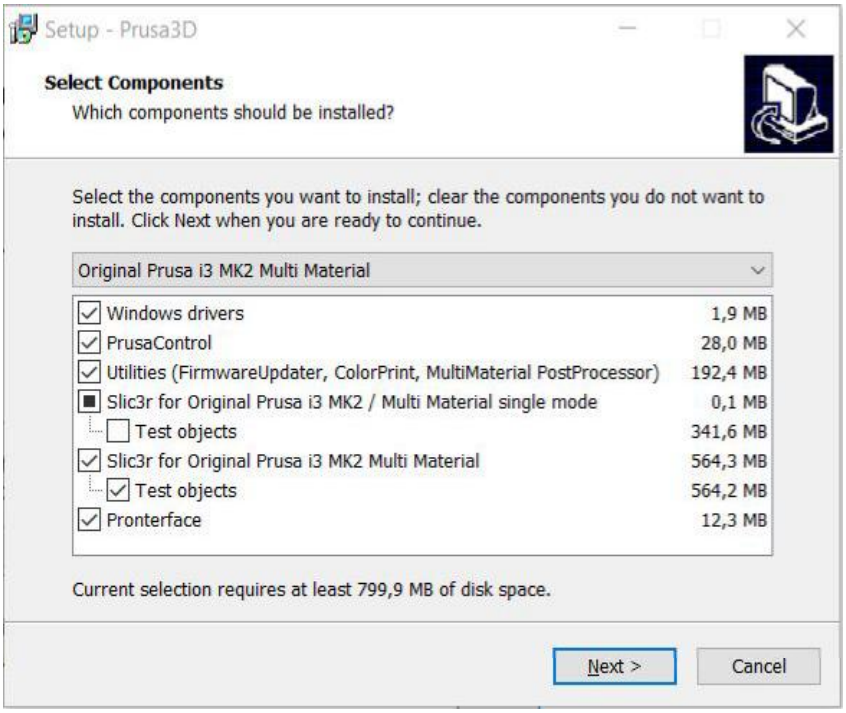
3.1 How it functions

Instead of traditional use of multiple independent extruders which is considered industry standard, MMU uses only one hotend with 4 extruder motors and Y splitter. When the material use is finished during the layer, it is pulled out of the hotend and next one is inserted back in.

This removes any need to calibrate the position of the nozzle tips and eliminates oozing from unused extruder or artifacts as only one nozzle is present. It is the first commercial solution like this.

4 Software

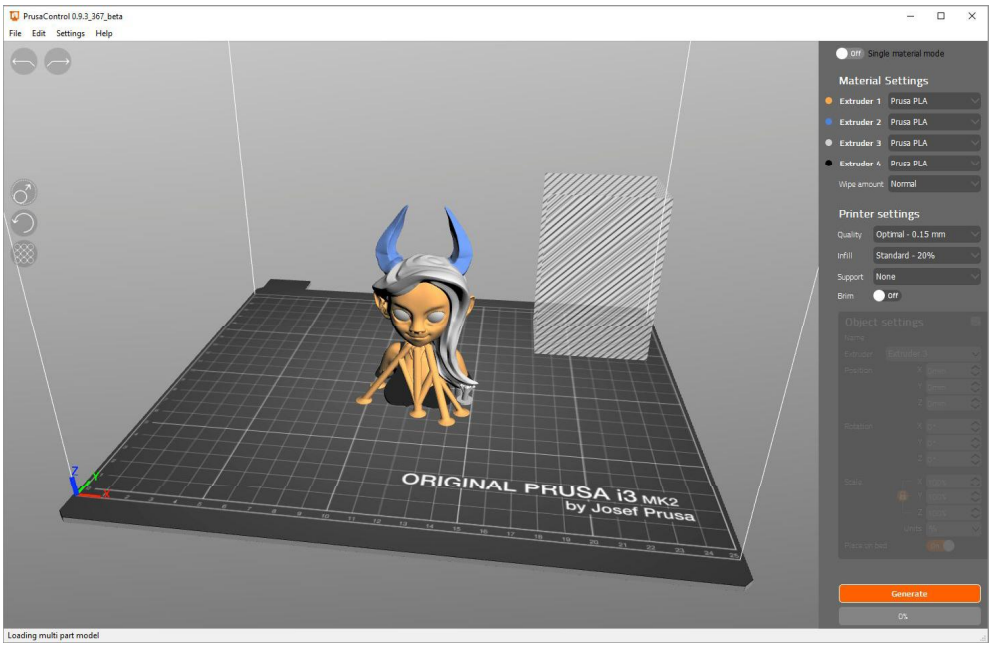
Install the driver package version 1.9.0 or the latest from http://www.prusa3d.com/drivers/ and during installation, select **Original Prusa i3 MK2 Multi Material** as one of the installed printers. Two additional programs will be installed compared to the standard MK2/S installation.



4.1 PrusaControl

PrusaControl is the easiest way how to dive into Multi Material printing with MK2. Open settings and choose “Original Prusa i3 MK2 MM” as your printer. Menu on the right will extend to accommodate more extruders.

Wipe tower is also shown, you can see and adjust the position of it (more info about how Smart Wipe Tower works can be found in 9.1 Smart Wipe Tower size and additional print time).



4.1.1 Slicing profiles

Print profiles for 150 um, 200 um and 300 um are preconfigured in the PrusaControl. Lower layer heights are not available yet, only when using single mode discussed in chapter 8 Printing in Single mode with one extruder. **Single material mode** can be easily enabled by toggling a switch at the top of the right menu.

Additional print settings and materials can be used on the **Multi Material in single extruder mode.** The printer is as capable as regular MK2/MK2S in this mode so it can print flexible materials etc. without problems.

4.1.2 Basics

Materials
Assign materials to used extruders. By clicking on the color dot you can set filament color and see it on the final model. When one extruder contains soluble material, soluble supports options appear in support menu. All assigned extruders are displayed in bold.

Wipe amount
Sets the amount of wiping done on filament change. Increase the amount if your colors bleed into each other.

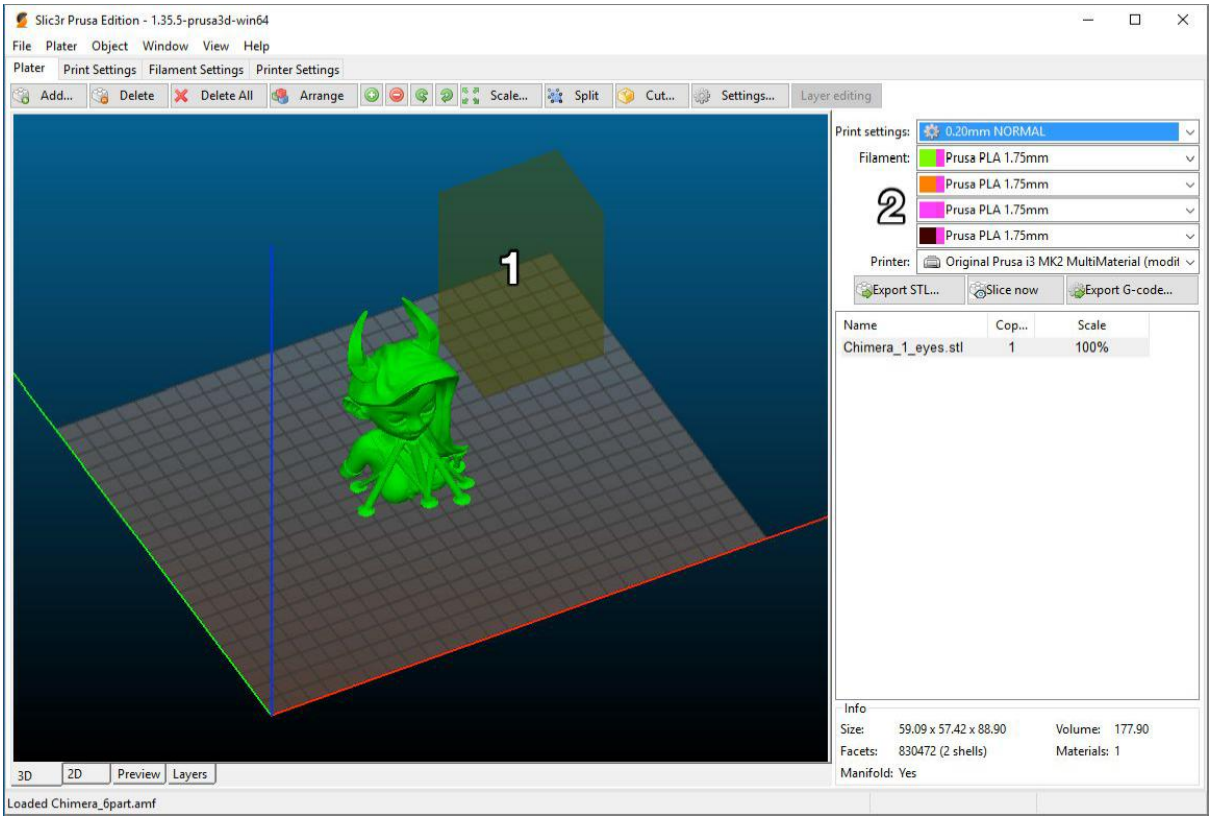
Printer settings
Select the print quality and infill you want to use. Soluble supports are enabled when one extruder contains soluble material.

Object settings
You can assign extruders/filaments to the object parts. Either click on the part and select extruder. Or select the part by name if the part is hard to select by mouse.

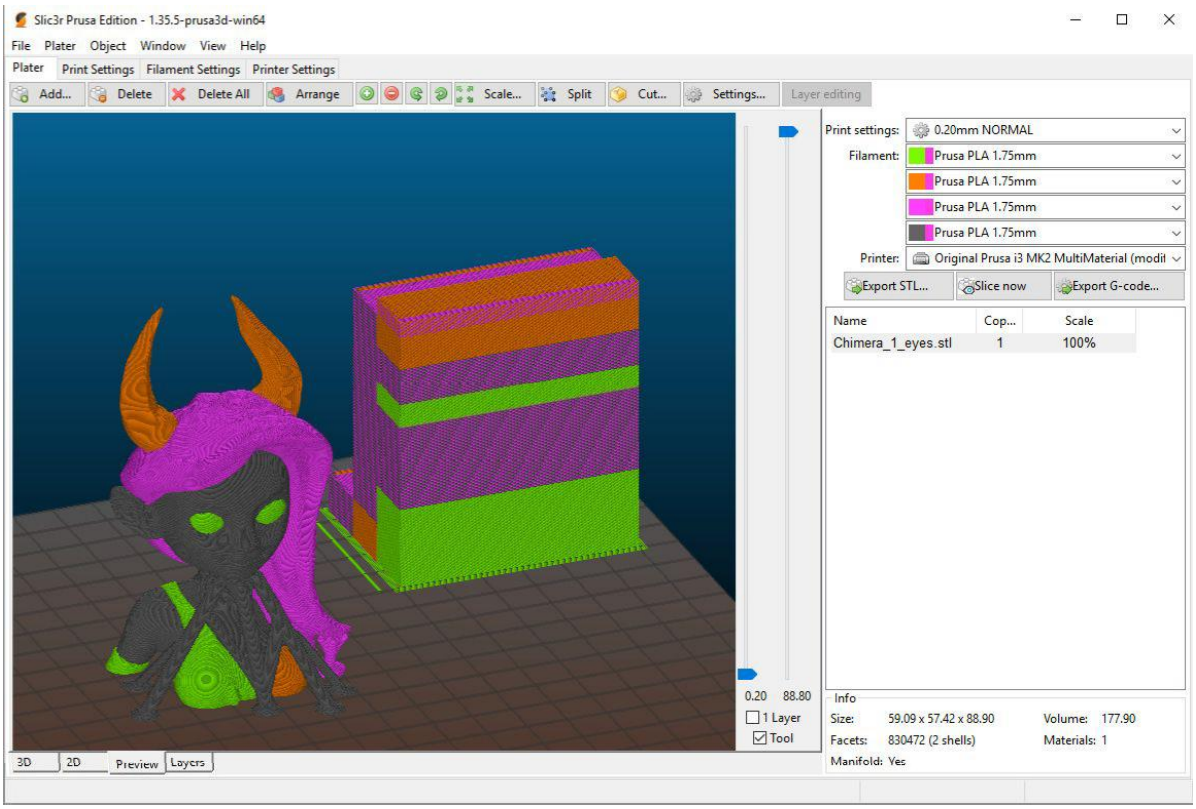
Single material mode
Single material mode can be enabled by switch at the top of the right menu.

4.2 Prusa3D Slic3r Multi Material

Slic3r enables more advanced control over the generated G-code. When you open the Prusa3D Slic3r Multi Material you can immediately see few differences. First you can see and adjust the position of Smart Wipe Tower (more info about how Smart Wipe Tower works can be found in 9.1 Smart Wipe Tower size and additional print time) marked as **1** on the picture and you can see 4 material select boxes marked as **2.**



Material selectors have colored boxed on the left, by clicking on them you can assign color to each extruder and preview the model in final colors when the model is sliced in **Preview** tab.



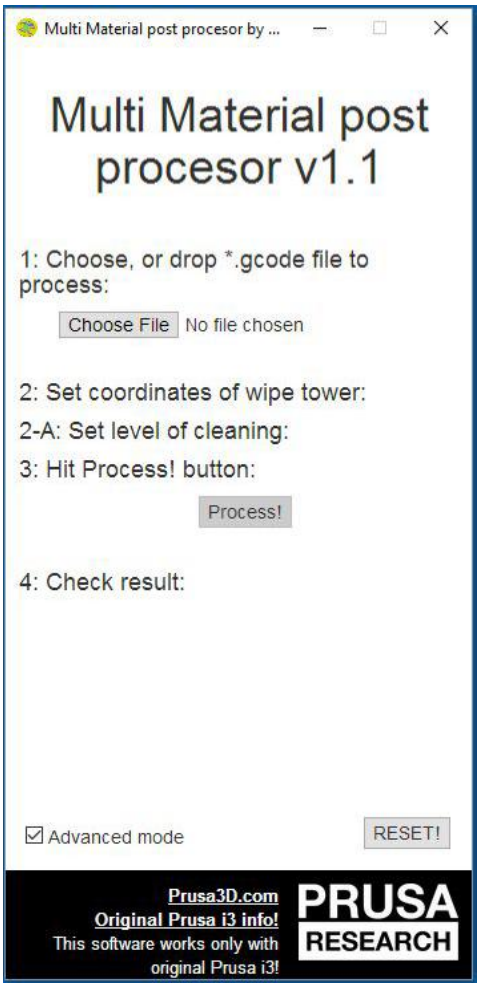
4.2.1 Slicing profiles

Print profiles for 150 um, 200 um and 350 um are preconfigured in the Slic3r PE for Multi Material. Lower layer heights are not available yet, only when using single mode discussed in chapter **8 Printing in Single mode with one extruder.**

Additional print settings and materials can be used on the **Multi Material in single extruder mode.** Just install normal MK2 from Drivers package (when selection Original Prusa i3 MK2 Multi Material, everything is automatically pre selected) and select Multi Material Single Mode from printer options. This will allow you to use Variable Layer Height and 100 um and lower layer heights. The printer is as capable as regular MK2/MK2S in this mode so it can print flexible materials etc without problems.

4.3 Multi Material post processor

Multi Material post processor is an application installed with Drivers package to generate Smart Wipe Tower and filament switching into the g-code file for the MMU equipped printer. G-code generated with Multi Material Slic3r and PrusaControl already has those since drivers release v1.7.8 so post processor is not needed, however **when using ColorPrint, G-code needs to be processed**. Post Processor will also be needed in the future to process G-codes from other slicing engines like Simplify3D. Official support for 3rd party slicers hasn't been released yet. More information about ColorPrint can be found in 8.3 Using web Color Print app.



5 Supported materials

Currently only PLA, ABS and PVA/BVOH (Primaselect PVA or Verbatim BVOH works reliably) are supported in the Multi Material mode. Normal range of filaments can be used in single mode discussed at chapter 8 Printing in Single mode with one extruder. We're testing and preparing settings for more. Combinations of different temperature materials are possible, hotend can change temperature during the printing of Smart Wipe Tower.

Filaments which tend to be extremely stringy can however increase the chance of clogging the Y splitter and require cleaning.

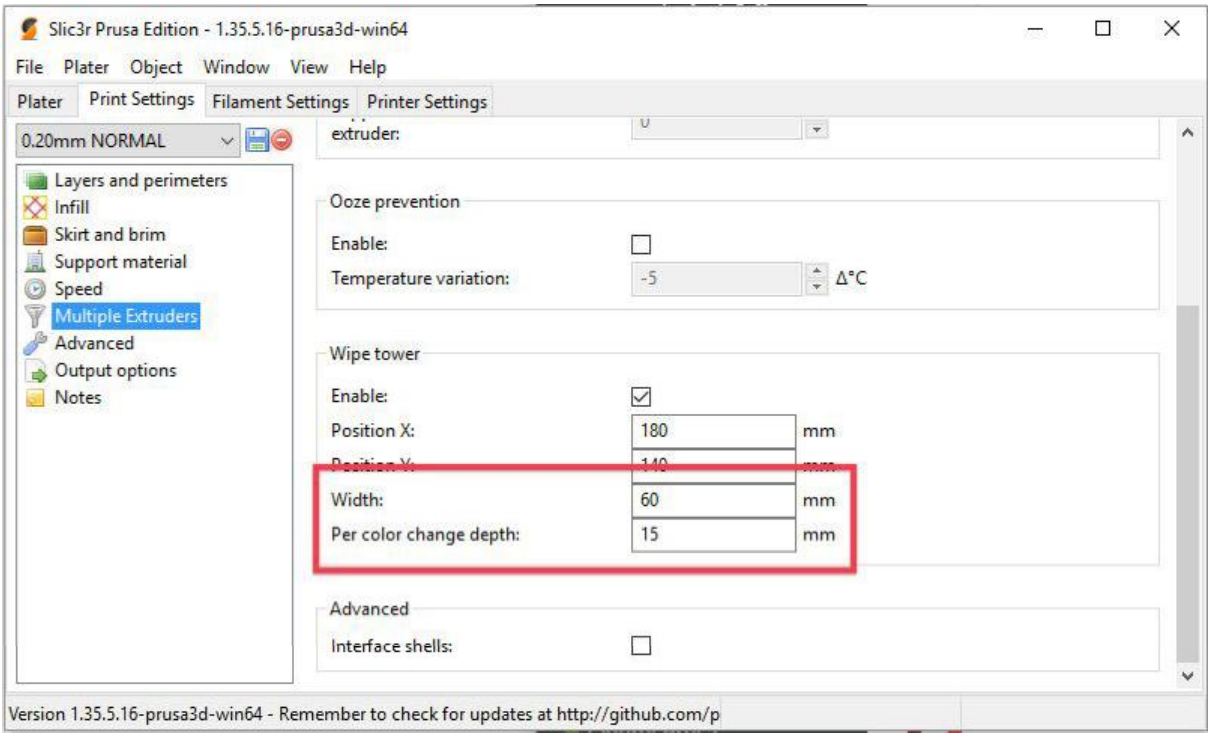
5.1 Filaments and print quality

Some filaments are harder to print with than others. If you are having troubles, try a different brand or color. From our experience chalky feeling filaments with mineral filler are not as aesthetically pleasing. Same applies on MK2 but the effect is multiplied with multi material upgrade. Smooth and shiny looking filaments will produce the best results. See chapter 11 List of tested filament.

For some filaments or color combinations (such as black color together with white color) additional wipe area might be needed. In **Slic3r** that can be set up in Multiple Extruders menu under the Print Settings tab. Default value works with most materials and color combinations. In **PrusaControl** under the **Wipe amount** option.

Presets are:

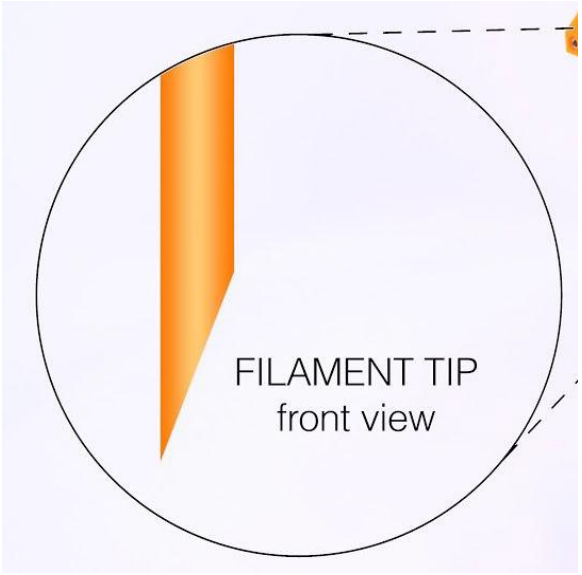
- **Decreased** 60 mm / 7.5 mm
- **Normal** 60 mm / 15 mm
- **Increased/Soluble** 60 mm / 20 mm



A better quality filament will yield much better results than a low cost filament from ebay. Good and well working brands are Prusa, ColorFabb, Fillamentum …

5.2 Loading/Unloading the filament

Always check the filament before the print for potential damage, cut off all of the damaged part to be sure that filament can pass extruder pulleys and cooling tubes properly. **Pay special attention to this after every aborted print**.



Loading filament now has slightly changed behaviour compared to regular MK2 and always load/unload it from menu.

When opening the Load or Unload menu, you have an option to Load/Unload all 4 automatically or each extruder separately.

First phase of automatic loading is slow feed (In this phase you just push the filament to the entry hole of the extruder and as soon as you feel that the extruder grabs it, press the knob).

Second phase is fast feed (This phase just loads the filament to the cooling tube and prepare it for the operation).

Printer tests all used extruders prior to the print on the first layer at the front of the print bed to **verify proper filament insertion** (for G-codes generated from Slic3r/PrusaControl from Drivers 1.9 package). After all the filaments are primed, the printer beeps and waits for 10 seconds for the user to verify that all the filaments are primed properly. If the priming regions interfere with the print, the printer is paused indefinitely for the user to remove the priming material before the print starts.

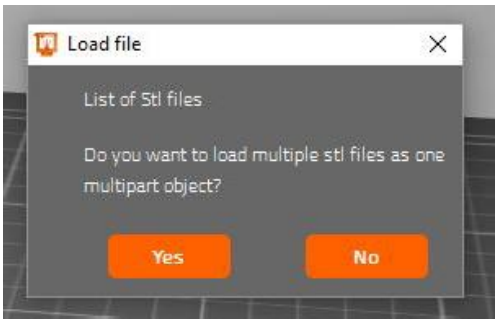
6 Upgrade and first print

1. Assemble the upgrade according to http://manual.prusa3d.com/c/Original_Prusa_i3_MK2_to_Multi_Material_upgrade
2. **Upgrade firmware to 3.0.12** or the newer from www.prusa3d.com/drivers. Use the **Multi Material versio**n placed in folder "MK2-MultiMaterial".
3. Run **Calibrate XYZ** before continuing. It is not mandatory but can save some troubleshooting later. (Described in *3D Printing Handbook - chapter 6.3.5 Calibrate XYZ*)
4. Install **1.9.0 drivers** or newer with Prusa3D Slic3r MK2 Multi Material and Multi Material postprocessor from www.prusa3d.com/drivers
5. **Delete all files** from your printer SD card. They are no longer compatible.
6. Copy all sample G-codes from our driver package **Objects/MK2MM** folder to the SD card. You can check out the models at www.prusa3d.com/printable-3d-models/.
7. **Load filament**. See the section 5.2 Loading/Unloading the filament
8. Run **V2MM Calibration** from SD card and run Live Adjust Z like on a regular MK2/S. Described in chapter *6.3.9 First layer calibration* in our *3D Printing Handbook*.
9. Print a sample G-code. Gear Bearing is a good start model.

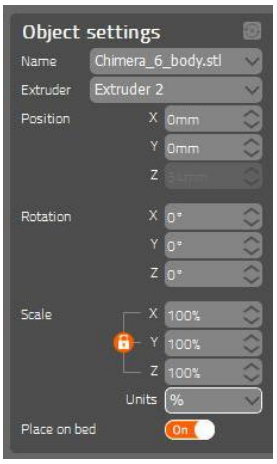
7 Printing in Multi Material mode

7.1 Loading the model in PrusaControl

Select all parts of the multipart object and drag and drop them on the PrusaControl, it will be automatically recognized as multipart object. Click **Yes** to finish the import.

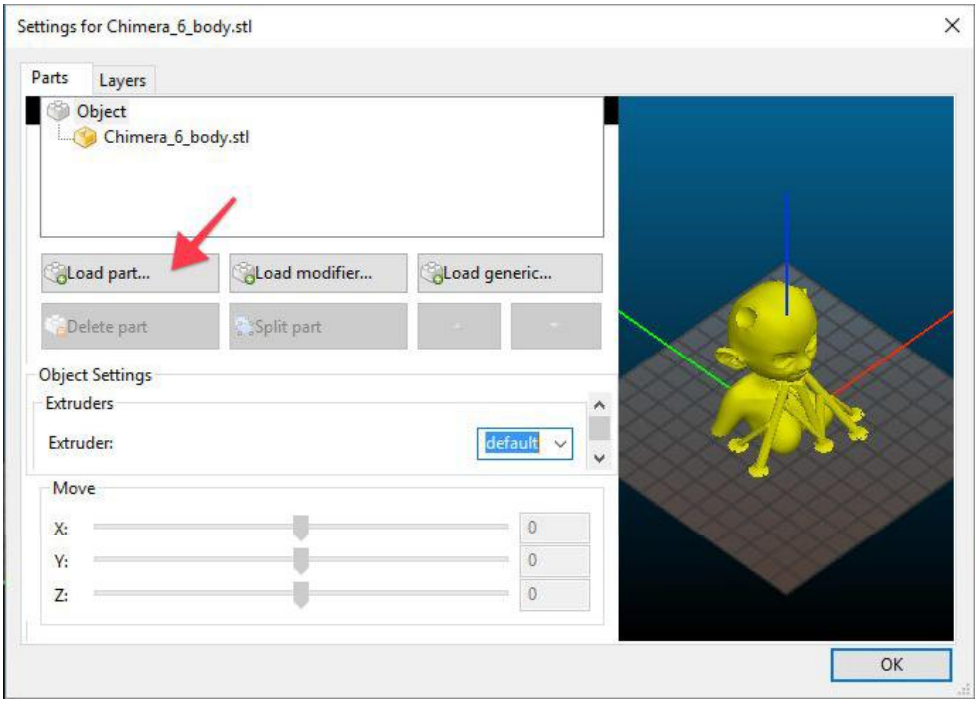


Select the parts of the object by clicking on them and assign **extruder** under **Object settings**. Hard to reach objects can be selected in the drop down menu by their **name**.

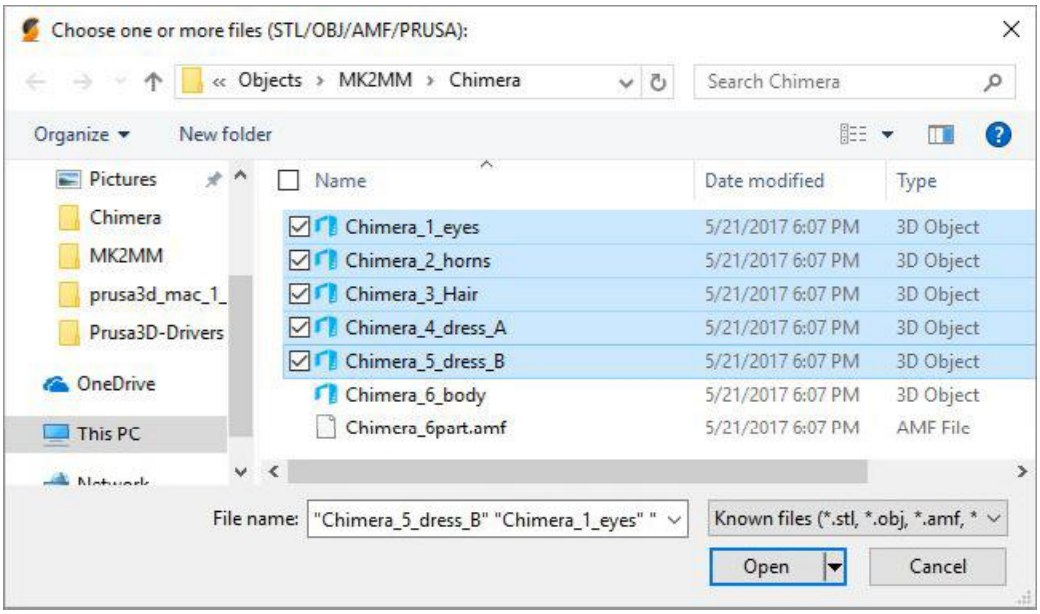


7.2 Loading the model in Slic3r Multi Material

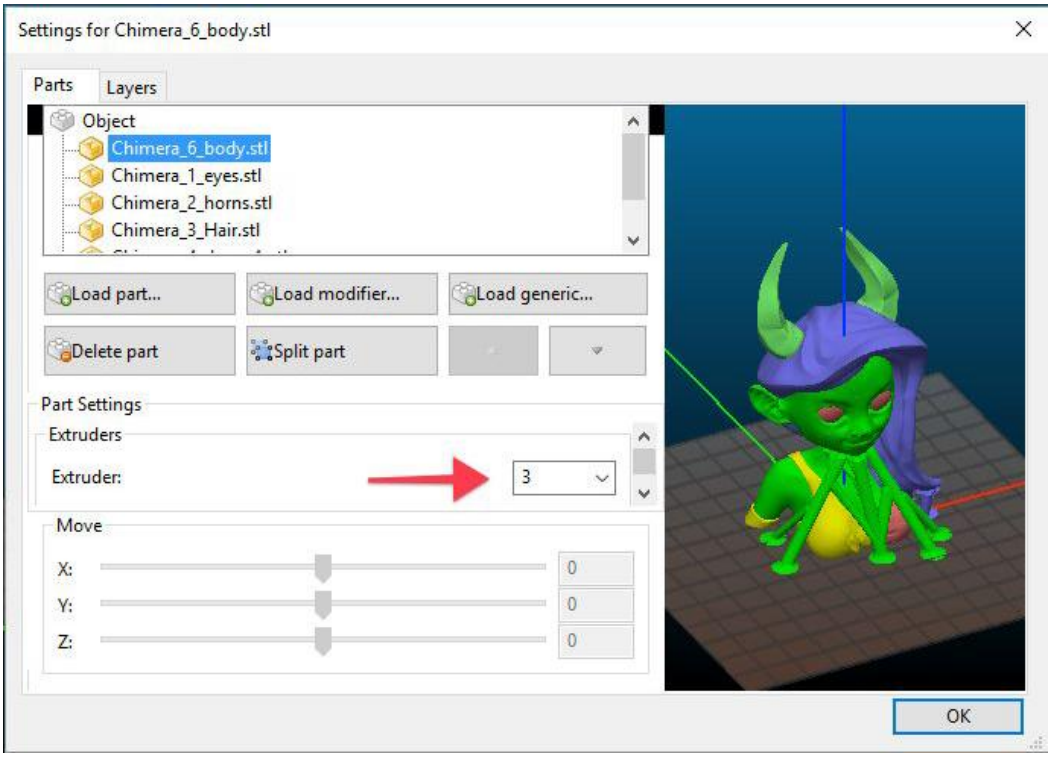
Start by opening the main part of the model. In our example we use Chimera (it is copied to your hard drive during the Drivers installation) and **Chimera_6_body.stl.** Load the file as if printing with normal MK2 and double click the object afterwards. New dialog will open where you can load additional parts.



Click **Load parts...**, select all additional files and **Open**.



Now you can easily highlight every part and set the extruder with which it should be printed.



Easier to follow video guide how to prepare the g-code files is available at

http://www.prusa3d.com/MMUVIDEO

Note: You can use the same system as used in PrusaControl with drag and dropping all the parts at the same time.

7.2 Printing with soluble supports

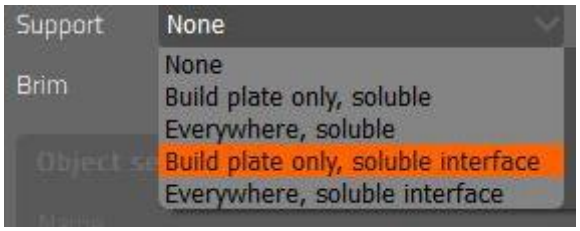
We strongly suggest to use Verbatim BVOH support material. It is available on our eshop http://shop.prusa3d.com/en/special/161-verbatim-bvoh-soluble-support-05kg.html or as a second best option Prima Select PVA also available http://shop.prusa3d.com/en/special/169-primaselect-pva-soluble-support-500g.html. Unfortunately quality of different PVA brands vary greatly and we cannot guarantee anything from other soluble support brands :-/

When cleaning soluble supports up, try to break away as much material as possibly while dry. Then continue peeling the material under running warm water. The last bits can be removed by letting the print soak in warm water. Water soluble supports **always** need to be stored in dry conditions.

7.2.1 Soluble supports in PrusaControl

Soluble material must be selected in one of the extruders first. Then two new options are available under the support menu:

1) **Everywhere, soluble** - soluble material is used everywhere
2) **Build plate only, soluble interface** - supports only starting from printbed from main material and with soluble interface
3) **Everywhere, soluble interface** - regular supports with soluble interface



7.2.2 Soluble supports in Slic3r

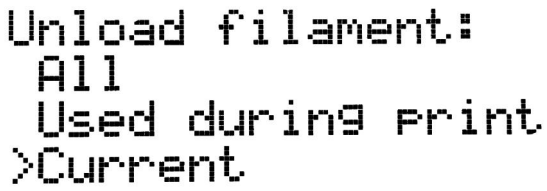
Soluble support material always needs to be selected in the extruder number 4 (the rightmost one) and selected in **Prusa3D Slic3r MK2 Multi Material** as the fourth filament.

Special print setting with **"Soluble Supports"** appended to the name needs to be used. Apart from this change printing works as with regular multi material printer. Extruder 1 to 3 can be used as usual.

7.3 Stopping the print

Three options will be presented how to unload the filaments. For successful printing, **all filament ends must be nice and clean**, so printer will ask which

filaments to unload so you can check. Check out the chapter 5.2 Loading/Unloading the filament to see how the filament end should look.



1) **All** - All filaments will be unloaded to check the ends and user has to load all of them back.
2) **Used during print** - Only the filaments used in the print being stopped will be unloaded assuming the ones unused maintain perfect condition from the last loading
3) **Current** - The filament currently in use is unloaded. This should be used only when the print was running nicely and something else was problem, like a wrong color filament used.

8 Printing in Single mode with one extruder

Features like Smooth Variable Layer Height or finer print settings are not yet available in Multi Material mode yet. But they can be used in Single mode with just one extruder enabled. It makes the printer basically bowden version of MK2.

WARNING: The G-codes generated for normal MK2/MK2S will either not work at all or produce very poor results. They need to be generated again.

Single material mode testing G-codes are present in the objects folder from the installation.

8.1 Single mode with PrusaControl

Enable Single material mode switch at the top of the right menu. New materials and print settings will load automatically.

8.2 Single mode with Slic3r

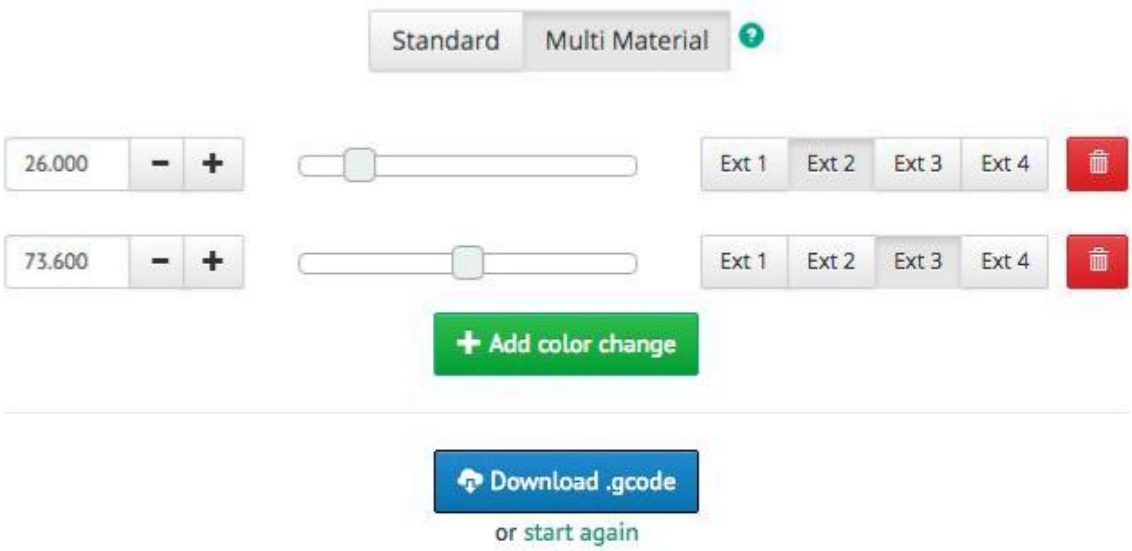
Simply launch **Prusa3D Slic3r MK2** where additional printer config is available as **"MK2 MultiMaterial single mode"**.

When printing G-code generated like this, printer will ask you which extruder should be used to print the object.

8.3 Using web Color Print app

Slice the object as you are used to in **Multi Material Single mode.** Load the G-code into http://www.prusaprinters.org/color-print/ and select Multi Material.

You can add color changes as you are used to, but you will be able to select to which extruder printer will switch.



After downloading the .gcode, you need to use Multi Material Post Processor app to generate wipe tower as described in 4.3 Multi Material post processor

Please note, all used colors need to be the same material.

9 Frequently asked questions

9.1 Smart Wipe Tower size and additional print time

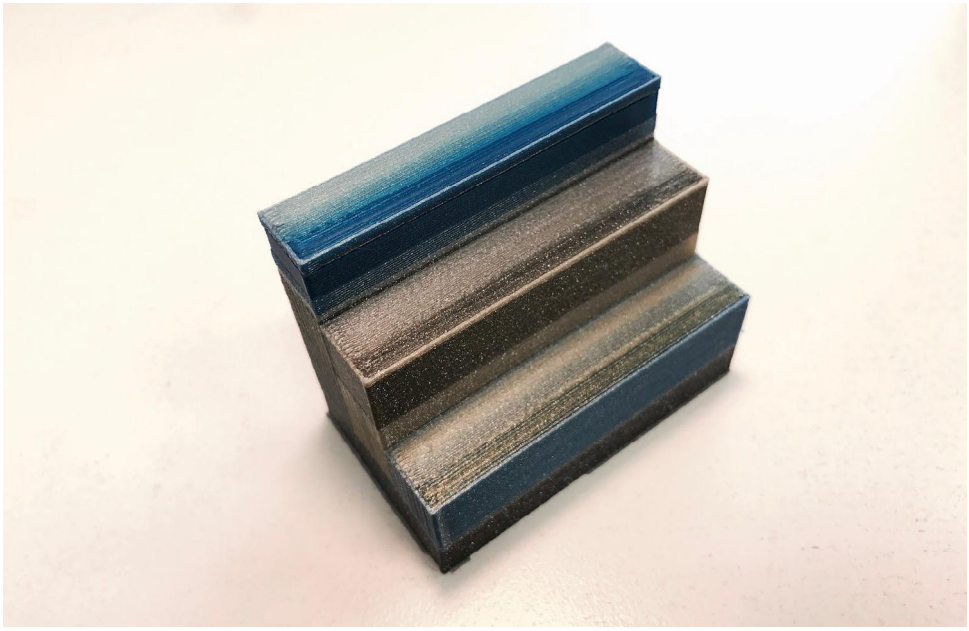
How big is the smart wipe tower?

Wipe tower is always 60 mm wide and contain between one and three by default 15 mm slots based on the model you are printing. If you only two materials are printed at one layer, one slot is used. Each additional material will add one slot and increase the size by another 15 mm. One slots takes approximately 1 minute per layer. The size of slots in the wipe tower can be changed, see chapter 5.1 Filaments and print quality.

In some prints, multiple materials during single layer are used later, but print starts with only one. In this case the smart wipe tower is still being printed with number of slots from the

most complex part of the model. However, before those slots are actually used, they are printed with sparse infill to save material. When slots are not needed anymore later in the print, the number is automatically reduced. This is the reason it is called “smart”. The wipe ower is smaller than from all the competing technologies.

When filament change is not needed, smart wipe tower is hollow.

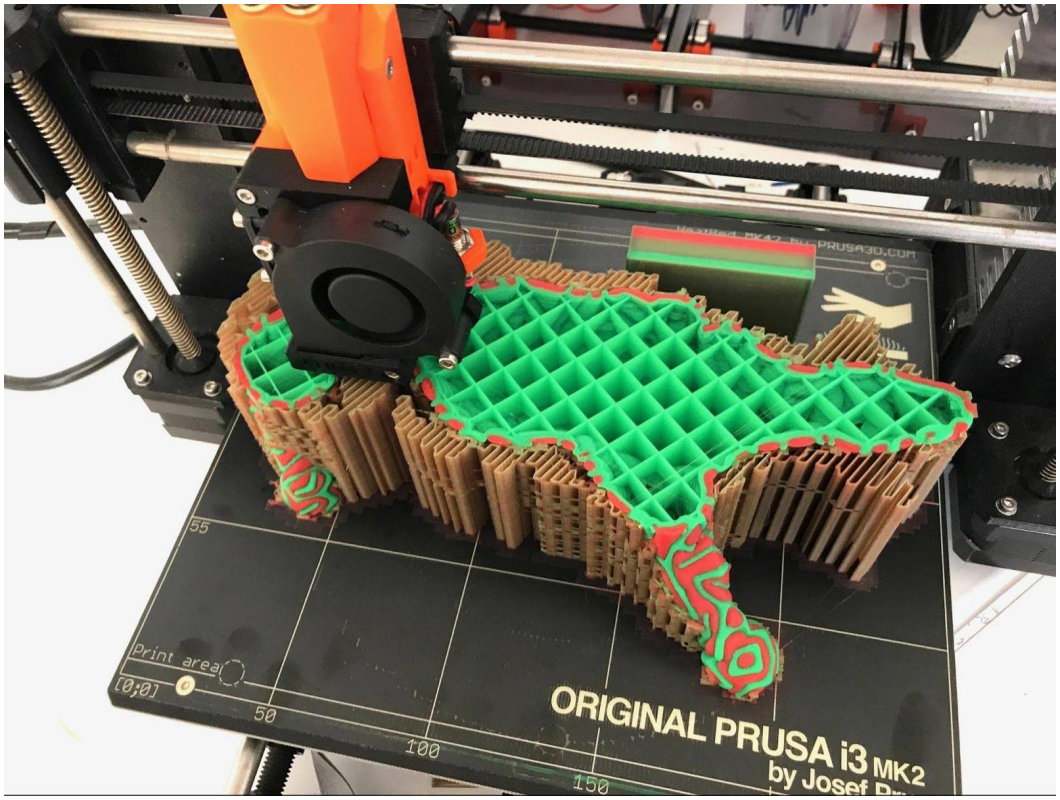


When number of filament changes needed decreases, tower will shrink.

Smart wipe tower prevents the need to use any sort of ooze shields as in traditional multi extruder systems! The size also remains constant, no matter how many copies of the objects you print or how big the object is.

We suggest to print more copies of the same object, if printing small parts as the Smart Wipe Tower will remain the same size.

Multiple objects with 4 materials wipe tower



Large object with 3 materials wipe tower

10 Troubleshooting

In case of any problems, please first look here - http://manual.prusa3d.com/c/Troubleshooting

10.1 Extruder jammed

The best way to diagnose a jammed extruder is to follow this checklist based on amazing work of our forum member **PJR**.

1. Check the filament diameter. It can't exceed 1.85mm, however, close the filament is to 1.75 mm the better it will work.
2. Check the spool is moving freely and the filament is **not tangled**.
3. **Ensure that the filament moves through the PTFE feeder tube with little resistance.**
4. Ensure that the drive pulleys are aligned perfectly with the filament path.
5. The grub screw on the motor pulley should be tight and held in place.
6. Check that the tensioner pulley moves freely and also make sure the "door" holding this pulley also moves easily.
7. Ensure that both filament drive pulleys are free from any debris.
8. **Ensure that the tension screws are not too tight** for the filament being used (this will cause filament damage and prevent proper feeding).
9. Check to make sure the cooling tubes are in place.
10. Take out the PTFE tube and remove any burr that may be present at the bottom end.
11. Insert the PTFE tube fully so that it makes a good seal with the heat break.
12. Remove all festos from the top of the MUX and **ensure filament passes through to the heat break easily**.

When you still experience jamming, try decreasing the hotend temperature by 5°C (can be done only in Slic3r).

Also try different spools of filament as the filament quality can vary.

10.2 Colour bleeding

If colours bleed into each other, increase the wipe amount according to 5.1 Filaments and print quality chapter.

11 List of tested filaments

We've tested all the filaments from our shop.prusa3d.com for Multi Material print quality and prepared recommended wipe tower settings. See chapter 5.1 Filaments and print quality for how to change the smart wipe tower size. An updated list of materials can be found at help.prusa3d.com.

	Print quality	Wipe Tower
PLA Silver	Good	Normal
PLA Transparent/Clear	Good	Increased
PLA White	Not optimal	Normal
PLA Beige/Ivory	Not optimal	Normal
PLA Orange	Good	Normal
PLA Pink	Good	Normal
PLA Blue	Good	Increased
PLA Yellowgreen/Lime Green	Good	Increased
PLA Brass	Good	Normal
PLA Copper	Good	Normal
PLA Black	Good	Increased
PLA Glow in the Dark	Good	Normal
PLA Metalic Violet	Good	Normal
PLA Metallic Green	Good	Normal
PLA Green	Good	Normal
PLA Pearl White with Glitter	Good	Normal
PLA Yellow	Good	Normal
PLA Flourescent Orange	Good	Normal
PLA Red	Good	Normal
PLA Lila	Not optimal	Normal
PLA Brown	Good	Increased
PLA Orangebrown	Good	Normal
PLA Extrafill Purple Red	Good	Normal
PLA Extrafill Melon Yellow	Good	Increased
PLA Extrafill Luminous Orange	Good	Normal
PLA Extrafill Rapunzel Silver	Good	Normal
PLA Extrafill Metallic Grey	Good	Normal
PLA Extrafill Noble Blue	Good	Increased
PLA Extrafill Luminous Green	Good	Normal

PLA Extrafill Luminous Yellow	Good	Normal
PLA Extrafill Pearl Ruby Red	Good	Increased
PLA Extrafill Vertigo Grey	Good	Normal
PLA Extrafill Traffic Black	Good	Increased
PLA Extrafill Chocolate Brown	Good	Normal
PLA Extrafill Signal Brown	Good	Normal
PLA Extrafill Gold Happens	Good	Normal
Flexfill Signal Red	In works	
Flexfill Luminous Green	In works	
Flexfill Metallic Grey	In works	
Flexfill Signal Yellow	In works	
Flexfill Skyblue	In works	
Flexfill Black	In works	
Flexfill Natural	In works	
ABS-T White	Not optimal	Normal
ABS-T Orange	Good	Normal
ABS-T Transparent Red	Good	Normal
ABS-T Transparent Blue	Good	Normal
ABS-T Silver	Good	Normal
ABS-T Black	Good	Normal
ABS-T Pearl White with Glitter	Good	Normal
ABS-T Clear	Good	Normal
ABS-T Copper	Good	Normal
ABS-T Transparent Glitter	Good	Normal
ABS-T Blue with Glitter	Good	Normal
ABS-T Yellowgreen/Lime	Good	Normal
ABS-T Brass	Good	Normal
ABS-T Brown	Good	Normal
PETG Transparent	Good	Normal
PETG Black	Good	Increased
PETG Transparent Violet	Good	Normal
PETG Transparent Green	Good	Normal
PETG Transparent Yellow	Good	Normal
PETG Transparent Brown	Good	Normal
PETG Transparent Blue	Good	Normal
PETG Transparent Red	Good	Normal
PETG Orange	Good	Normal

PETG White	Good	Normal
XT CF20	In works	
XT Yellow	In works	
XT Black	In works	
XT Light Green	In works	
XT White	In works	
XT Pink	In works	
XT Light Blue	In works	
XT Purple	In works	
XT Orange	In works	
XT Red	Good	Normal
XT Dark Gray	In works	
Corkfill	In works	
Woodfill	In works	
Bronzefill	In works	
Copperfill	In works	
Brassfill	In works	
Steelfill	In works	
PLA/PHA Ultramarine Blue	Not optimal	Normal
PLA Green Transparent	Good	Normal
PLA/PHA Pale Gold	Good	Normal
PLA/PHA Sky Blue	Not optimal	Increased
PLA Red Transparent	Good	Increased
PLA/PHA Navy Blue	Not optimal	Normal

Print and share!

Do not forget to tag your prints with *#prusai3mk2* and *#mk2mm* while sharing so we can find, pin and showcase them with our

Pinterest

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Happy Printing :)