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Manufacturing of solid dosage forms using pressure-assisted microsyringe 3D-printing

Inaugural-Dissertation

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultät

der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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Düsseldorf, Januar 2021

aus dem Institut für Pharmazeutische Technologie und Biopharmazie

der Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der
Mathematisch-Naturwissenschaftlichen Fakultät der
Heinrich-Heine-Universität Düsseldorf

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Tag der mündlichen Prüfung:

26.03.2021

Only a life lived for others is a life worthwhile.

Albert Einstein

-For my beloved Family-

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List of abbreviations

Three-dimensional printing	3DP
Active pharmaceutical ingredient	API
Binder jetting	BJ
Computer-aided design	CAD
Direct metal laser sintering	DMLS
Dimethyl sulfoxide	DMSO
European pharmacopoeia	Ph. Eur.
Et alii	Et al.
Food and Drug Administration	FDA
Fused deposition modeling	FDM™
Fused filament fabrication	FFF
Good manufacturing practice	GMP
Government Accountability Office	GAO
Human epidermal growth factor receptor-2	HER-2
Hot melt extrusion	HME
Hydroxypropyl methylcellulose, Hypromellose	HPMC
In-process control	IPC
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Humans Use	ICH
Immediate release	IR
Inkjet printing	IJP
Minitablet	MT
Numerical control	NC
Liquid dosage forms	LDF
Office of Science and Engineering Laboratories	OSEL
Orodispersible film	ODF
Orodispersible minitablet	ODMT
Polyethylene glycol, Macrogol	PEG
Pressure-assisted microsyringe	PAM
Powder-bed fusion	PBF
Polylactic acid	PLA
Polyvinyl alcohol	PVA
Polyvinylpyrrolidone, Povidone	PVP
Polyvinylalcohol-polyethylene glycol	PVA-PEG

Polyvinylpyrrolidone-vinyl acetate copolymer	PVP-PVAc
Stereolithography	SLA
Selective laser melting	SLM
Selective laser sintering	SLS
Stereolithography file	STL
Surface area/volume	SA/V
Sustained release	SR
Synaptic vesicle glycoprotein 2A	SV2A
Ultraviolet	UV

Chapter I - Introduction

1 Introduction

1.1 3D-printing

1.1.1 Introduction to 3D-printing

For years, patients were viewed as a homogeneous group and selected drug treatment was based on experience from clinical studies. Consequently, individual factors such as age, physiological condition and especially genetic pattern were ignored during the selection of appropriate drug treatment. Scientific breakthroughs in molecular medicine and human genome research triggered a paradigm shift in health care systems away from the traditional “one size fits all” concept towards a more personalized approach [1]. The concept of personalized medicine intends to provide the right drug with the appropriate dose at the right time to the right patient [2]. Especially, improved understanding of a person´s unique molecular and genetic profile enables to individualize the treatment of patients [3]. By individualizing the drug therapy, the response rate of an applied drug treatment might increase while minimizing the occurrence of adverse effects [4].

Besides the individualized treatment of patients, novel diagnostic methods enable the identification of certain predisposition for a specific disease [5]. An early recognition allows the initiation of preventive measures much sooner, which promotes a shift of emphasis in medicine from reaction to prevention.

Currently, individualized drug treatment has been implemented successfully in many examples. The introduction of the individualized concept has fundamentally changed the strategies in breast cancer treatment. Through the above mentioned newly available genetic diagnostic possibilities, breast tumor cells can be analyzed regarding a possible overproduction of human epidermal growth factor receptor 2 (HER-2) protein. A positive test outcome (HER-2-positive breast cancer) for this specific protein helps the physician to individualize the treatment by selecting drugs which target the HER-2-protein [6] specifically. By individualizing the treatment, the survival rate of patients might increase significantly, while the risk of adverse effects might decrease.

Besides breast cancer, individualized medicine is expanded for other cancer types like colorectal cancer, lung cancer or melanoma. The concept is currently also being tested further for Alzheimer´s disease [7], Parkinson´s disease [8] or multiple sclerosis [9].

Alongside with enhancements in diagnostic procedures and drug treatment selection, changes in drug manufacturing are mandatory to ensure successful implementation of individualized medicine into existing health care structures.

For decades, solid dosage forms like tablets or capsules are manufactured at large scales. Pharmaceutical equipment has been designed and optimized to increase the overall throughput and therefore to maximize the revenues of the pharmaceutical industry. This profit-oriented strategy does not allow research and development activities on individualizing the manufactured product in order to fulfil patient's needs. Besides the economical view, there is also a lack of suitable equipment that enable a fast adapting manufacturing of tailored dosage forms in smaller batch sizes.

One of the oldest approaches to individualize the administered dose are liquid dosage forms (LDF). Especially for the treatment of special patient groups with swallowing difficulties, for example pediatrics or geriatrics, LDF were utilized as first choice treatment for individualized drug therapy. LDF are delivered to the patient with a dosing device, which helps to achieve the right dose [10]. Thereby, the dose can be varied easily and precise by changing the administered volume [11]. The LDF show a high patient acceptability and compliance since flavor can be added to achieve a taste masking and LDFs are also easy to swallow. Nevertheless, most of the available active pharmaceutical ingredients (APIs) are not processable due to their solubility. Further, LDF face stability issues and microbiological instability, which limit the storage of LDFs.

The academic research community introduced various new manufacturing technologies as well as new dosage forms to individualize the dispensed dose. The research was often combined with the development of child-appropriate dosage forms. Multiparticulate dosage forms like minitablets (MT) [12-14] or orodispersible minitablets (ODMT) [15, 16] were found as promising to adjust the required dose according to the needs of the patients. Combined with the development of dispensing devices, MT and/or ODMT dispensed accurate by ensuring the required amount of dose. The use of these dosage forms is limited to high potent drugs since the processing of low potency drugs require the daily intake of a high number of units. Furthermore, academic studies revealed challenges in achieving an acceptable dosage uniformity according to the European Pharmacopoeia (Ph. Eur.). Currently, test methods for MT and ODMT are lacking and need further research and guidance by health authorities.

Academic research further demonstrated the potential of implementing orodispersible films (ODFs) in regard to individualizing the dispensed dose [17, 18]. According to the literature, ODFs are single- or multilayer sheets consisting of suitable polymers, which are intended to be placed into the oral cavity where they dissolve rapidly without the need of beverages [19]. Due to the rapid disintegration in the oral cavity, ODFs are highly suitable for patients with swallowing difficulties especially pediatrics and geriatrics [17]. ODFs have the advantage that they can be cut into different sizes after production, which enables an individual dose adaption [20]. Alongside with the advantages provided by ODFs there are some challenges limiting the

commercial use of ODFs. Currently, manufacturing of larger batches is not applicable. Furthermore, the maximum possible drug-load is limited making the dosage forms currently only suitable for high-potent APIs, which are dispended in a low dose.

A recent approach that has been studied intensively to individualize drug therapy is the inkjet printing (IJP) of drug-loaded inks onto substrates like ODFs [21-23]. In this application, a pre-formulated drug-loaded ink is printed dropwise with a print head (thermal or piezoelectric print heads) onto a substrate [21]. The interesting point about IJP is that the dose can be precisely controlled by varying the number of printed layers. Also, the number of printed drugs can be varied to achieve fixed dose combinations [24-26]. Nevertheless, besides the provided advantages of IJP, the preparation of suitable drug-loaded inks for printing purposes appears to be challenging [27].

In regard to suitable manufacturing processes for individualization purposes, three-dimensional printing (3DP) has been explored as a new potential manufacturing technology. The healthcare system already recognized 3DP as a promising approach [28-30] for the production of customized prosthetics, required surgical instruments, bone replacement and implants [31], whereas the use of 3DP for manufacturing pharmaceutical dosage forms is in its infancy.

According to the Government Accountability Office (GAO) of the United States, 3DP is defined as a layer-by-layer process of producing 3D objects directly from a digital model [32]. The digital model is created using a computer-aided design (CAD) software. Since the designed digital model can be adapted relatively easily and fast to changing requirements, a high variability of possible structures is given. Furthermore, it is also possible to design complex structures, which are rather challenging to obtain by conventional processes [33].

Due to these possibilities, 3DP has been recognized as a highly potent manufacturing process for individualized dosage forms. Aside from this, dosage forms with customized drug release characteristics can be manufactured using 3DP [34].

With the approval of the first printed tablet, Spritam® by Aprecia, by the Food and Drug Administration (FDA) in 2015, 3DP technology made its way into the pharmaceutical market [35]. By this milestone, the technology was taken out of its niche existence and placed into the spotlight as future manufacturing process for individualized dosage forms.

1.1.2 Technologies in 3D-printing

The term 3DP is an umbrella term encompassing several technologies, which differ in the printing style and/or used material. Nevertheless, these technologies have the same starting point in common as illustrated in Figure 1. All 3DP technologies share the same procedure of fabricating solid objects from a digital model. The procedure is divided into 5 subsections which are described in detail below.

1. **Creation of a CAD model & conversion to a STL file**

   The 3DP process always starts with designing a digital model. CAD software is commonly used to create digital models in the first step. After designing the desired model with the CAD software, it is converted into a stereo lithography file format (STL file). The STL file contains information about the external surface of the model. This STL file serves as basis for the sequential processes in the printing process.

2. **Transfer to slicing software**

   After the design phase, the STL file is imported within the next step into a slicing software. The slicing software converts the STL file into a G-code, numerical control (NC) programming language. Through the G-code, the action of the used 3D-printer can be controlled. Furthermore, changes of building parameters like supporting material, layer height or the orientation of the object are possible in this stage of process.

3. **Transfer to the machine & machine setup**

   Once the G-code has been created, it will be provided to the respective 3D-printer. At this stage of process, relevant printing parameters can be set to control the process.

4. **Printing phase & removal**

   At this stage, the desired object is printed layer-wise. The building step is completely automated and needs therefore no supervision by the operator. Most 3D-printers have a built-in control unit that controls the process and in the event of a deviation, aborts the process and displays an error message.

   As soon as the printing process is finished, the object can be removed from the building platform. Depending on the used printing technology safety aspects must be considered during removal of the finished object from the platform.

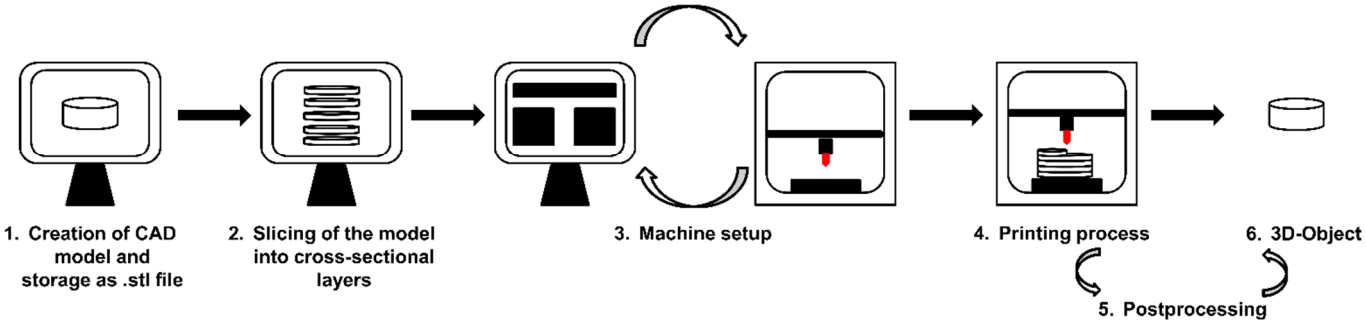

Figure 1. Scheme of the general 3DP process.

5. Post-processing

Depending on the used printing technology, post-processing procedures are essential to achieve a certain product quality. Some printing technologies require for example a post-thermal treatment to increase the mechanical strength.

The relevant printing technologies covered by the term 3DP are indicated in Figure 2.

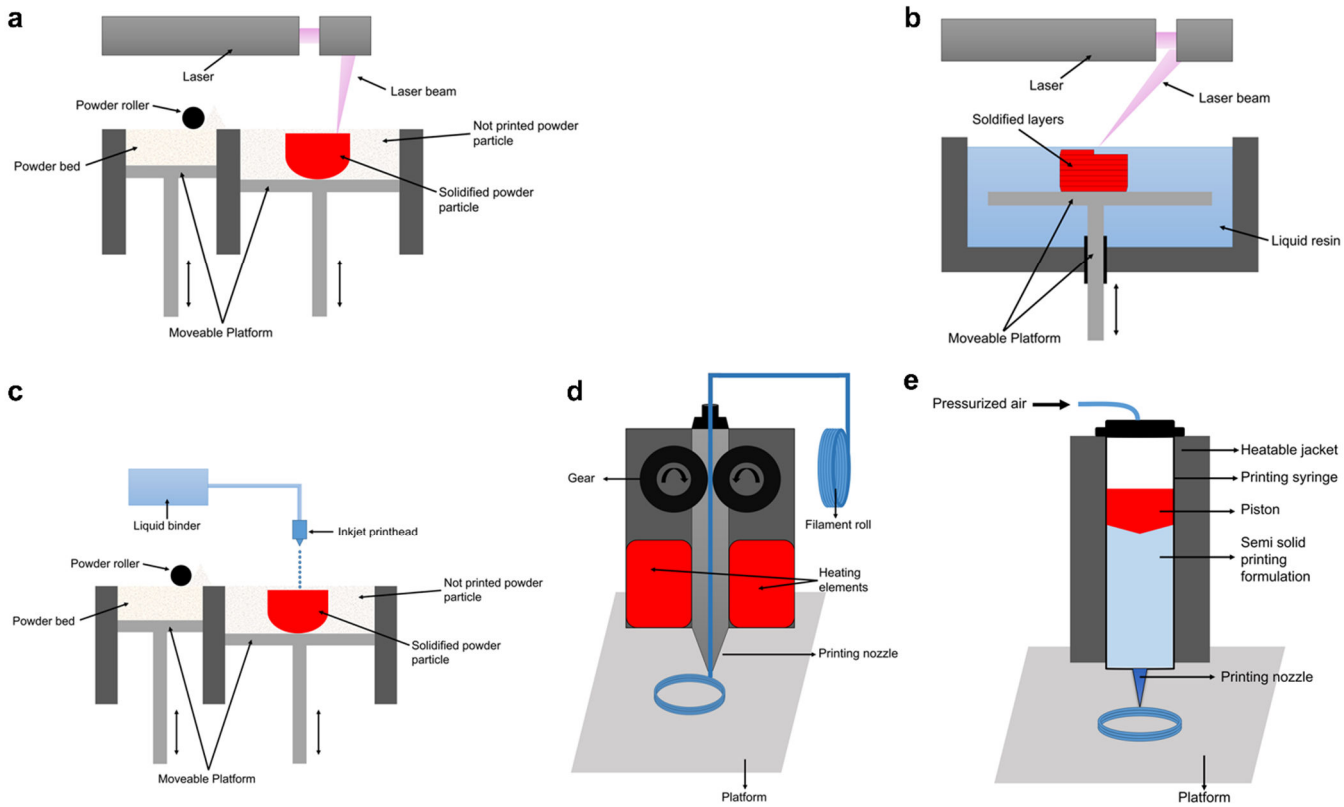

Figure 2. 3DP technologies: (a) powder-bed fusion, (b) stereo lithography, (c) binder jetting, (d) fused filament fabrication (also fused deposition modeling), (e) pressure-assisted microsyringe printing

The printing technology powder bed fusion (PBF) comprises three different printing techniques: selective laser sintering (SLS), direct metal laser sintering (DMLS) and selective laser melting

(SLM). These printing technologies share the same working principle and differ from each other in the used printing material and therefore the required energy input (Figure 2a).

DMLS and SLM are predominantly used in the aerospace and automotive industry [36, 37]. SLS printing gained recently increasing interest as manufacturing process for pharmaceutical products [38-43] as well as for the production of bone scaffolds [44-46] and implants [47]. During the printing process, a polymer powder layer of the starting material is spread onto a building platform using a roller. The spread polymer powder layer is then preheated inside the printer to temperatures just below the respective melting point of the polymer [48, 49]. Subsequently, a laser scans the surface of the polymer powder layer, sintering selective parts of a cross section of the object to be printed. The absorbed laser heat energy causes a melting of the powder particles, which leads to a fusion of neighbored particles [50]. After scanning the entire cross section, the building platform is lowered by the thickness of one layer and a further powder layer is spread over the previous layer using the roller. The sintering process is repeated until the complete object is formed. After finishing the printing process non-sintered powder must be removed [51].

SLS has been studied recently as manufacturing process for oral solid dosage forms [41-43]. Depending on the used polymer, different dissolution profiles were achieved. Further, adjustment of laser scanning speed affected the resulting disintegration of printed tablets [42]. SLS has been further utilized to manufacture orodispersible printlets containing ondansetron [52]. A recently published study introduced the ability of producing dosage forms with unique surface pattern which allows visually impaired patients to differentiate their medication [53]. During the printing process, the used powder bed acts as support material for the printed object, so no further additional supporting material is needed. Nevertheless, the accumulation of non-sintered powder material represents a major drawback of the technology. For pharmaceutical applications, a verification must be performed, whether the non-sintered powder must be classified as drug containing waste or might be recycled. Since high-performance lasers are applied during the PBF printing process, degradation of API as well as of excipients might occur, which would represent a further problem for any re-use [43].

The stereo lithography (SLA) printing is based on the selective photo-polymerization of a liquid resin via an ultraviolet (UV) laser beam (Figure 2b) [54]. In comparison to the other 3DP technologies the resulting resolution of printed products is clearly superior. The use of other printing technologies provides objects with a resolution of 50 – 200 µm, whereas with SLA printing a resolution of up to 20 µm can be achieved [55]. The printing process starts with filling the liquid into a basin, which has an integrated movable building platform [56]. The platform is then adjusted to the height of a single layer to the surface. In the next process step, the UV laser beam traces a cross-section of the object to be printed on the surface of the liquid resin.

Through the exposure of the liquid resin to the UV laser beam, the monomer carbon chains of the resin are activated forming a coherent layer through solidification. After the first layer is manufactured, the building platform moves down automatically by the thickness of a single layer. The scanning and solidification processes then start again from the beginning and are repeated until the complete object is manufactured [54]. Post processing is necessary either to remove excessive resin with solvents like isopropanol or to increase the mechanical properties of the printed object by UV light exposure [55].

The application of SLA technology is still in the initial development stage and needs to overcome some major hurdles and challenges to be recognized as suitable manufacturing process for pharmaceutical use. Especially the hazardous properties of the used resins cause SLA not being applied in manufacturing of pharmaceutical dosage forms currently [34]. During the printing process, residual monomers and photo-initiator molecules might be entrapped into the structure of the photo-polymerized structure. These can be cytotoxic upon leaching out of the structure and lead to undesirable effects when the printed structure is used for humans. Furthermore, the used resins are photosensitive, which also might lead to stability issues during storage of produced dosage forms. The occurrence of chemical reaction between a photopolymer and an API has to be taken into consideration during the selection process, since a chemical reaction might affect the product quality negatively [57]. Nevertheless, there are some scientific studies available adapting SLA printing for the manufacturing of pharmaceutical dosage forms [58-60]. Further, SLA has been used recently to print a bladder device containing lidocaine enabling an intravesical drug delivery [61]. Depending on the printed shape (hollow or solid), a sustained drug release up to 14 days was achieved [61].

With regard to commercial sales in pharmaceutics, binder jetting (BJ) is currently the most successfully applied 3DP technology (Figure 2c). Until now, it is the only 3DP technology that resulted in a commercialized product [62]. The drug approval of the 3D-printed product Spritam® (Aprecia® Pharmaceuticals) by the FDA represents a significant milestone in the development and establishment of 3DP processes as manufacturing processes for solid dosage forms. Commercialization of a printed product increase the interest of manufactures in printing technologies as manufacturing process and thus financial resources could be generated for research and development of 3D-printers as well as for printable materials.

The printing process of BJ starts with spreading a thin powder layer onto the building platform using a recoating blade [63]. Subsequently, an inkjet printer head is moved over the powder bed depositing droplets of a binder solution onto the powder bed. The movement of the print head is controlled via the G-code. Through the printed solution the powder particles are wetted causing a local hardening and therefore layer solidification. After the first layer solidifies, the building platform is lowered by the thickness of a single layer and a new powder layer is spread

over the previous solidified layer. The printer head is moved to the initial position and the deposition process of droplets onto the powder layer is repeated. The printing steps are repeated until the desired object is printed completely. After finishing the printing process, the printed object needs to be removed from the powder bed and loose powder discarded carefully [63, 64]. Execution of post processing like thermal sintering is often necessary to improve the mechanical properties of printed objects [63]. In pharmaceutical application, BJ process can be carried out in two different variants. The API can be present in the powder mixture as well as dissolved in the binder solution. For both variants, the printing process is the same as described above. For pharmaceutical application, feasibility of implementing BJ as manufacturing process for oral solid dosage forms has been demonstrated in various scientific studies [65-71]. These studies revealed the opportunity of manipulating the drug release by either using polymers with different characteristic like basic butylated methacrylate copolymer (Ph. Eur.) (Eudragit® E 100) and ammonio methacrylate copolymer type A (Ph. Eur.) (Eudragit® RL PO) as binder material or by designing complex geometries.

Due to the low thermal stress during the printing process, BJ printing enables the processing of thermo-sensitive APIs. Additionally, colored additives can be added to the printing inks, improving the patient´s compliance. Objects printed with BJ printing display a fragile structure with high friability and inferior mechanical properties, which make them rather unsuitable for further handling and packaging processes [34]. Further, post-processing step is required to remove residual powder after the printing process which increase the manufacturing time.

A further 3DP technology of interest is the fused filament fabrication (FFF) printing technology, in the printing community also called fused deposition modeling (FDM™) (Figure 2d) [72]. In most areas of scientific research and development, FFF is the widely used printing technology. Thereby, the number of scientific research articles using FFF as manufacturing process for pharmaceutical dosage forms increased significantly in the last years compared to the other printing technologies. Reasons for this might be that after the expiration of the original patent in 2009 [72], the number of available FFF printers has risen tremendously, causing a significant drop in the acquisition costs of FFF printers. FFF printing technology requires the pre-manufacturing of filaments using for example hot melt extrusion (HME) [73, 74] or incubation of commercially available filaments like polyvinyl alcohol (PVA) or polylactic acid (PLA) filaments in drug-loaded solutions [75-78]. Since the achievable drug load via incubation is low, the incubation in drug-loaded solutions is not of interest for pharmaceutical purposes. During the printing process the premanufactured filament is loaded into the printer using a gear system [75]. The applied filament is mechanically stressed by the gear system, which therefore must provide a certain mechanical resilience to ensure printability [73]. During the FFF printing, the printing nozzle is heated causing the filament to melt within the nozzle. The molten

filament is then extruded through the heated tip of the nozzle onto a building platform, where solidification of printed material takes place. The movement of the print head is repeated layer-wise until the object is printed completely. The approach of FFF printing as manufacturing process has been carried out to manufacture for example patient-tailored tablets [30, 78, 79], tablets with combined different drug release mechanisms [79, 80] or to print network structures with predictable drug release kinetic [81]. Especially, modulating the resulting drug release behavior of printed drug delivery systems has been explored utilizing FFF printing either achieving an immediate drug release [82] or a sustained drug release [83-85]. Furthermore, general requirements to ensure printability has been investigated intensively [73, 86-89]. The exploration of FFF printing technology is already advanced compared to the other 3DP technologies.

Objects printed by FFF technology do not necessarily need a post-process treatment, by which the overall manufacturing time might be reduced compared to other printing technologies like BJ or SLA. FFF printing provides objects with sufficient mechanical properties, which do not need further post treatment, and which allow packaging by the manufacturer as well as safe handling by the patients. Besides the mentioned advantages, there are some disadvantages to consider regarding the use as pharmaceutical manufacturing process. Especially the thermal stress during the filament preparation via HME as well as during the printing process might limit the number of processable APIs due to possible thermal degradation of the ingredients (API and excipients) [76, 90]. Insufficient temperature adjustment of the printing nozzle might lead to nozzle clogging caused by solidification of the polymer within the printing nozzle.

For the present thesis, pressure-assisted microsyringe (PAM) printing technology was selected as preferred manufacturing process (Figure 2e). PAM printing technology was invented in 2002 by Vozzi and colleagues as an alternative manufacturing process in the field of tissue engineering and bioprinting [91]. In the first version of the invention, the printer was equipped with a glass syringe, an electronic pressure controller and a computer as a control unit for the process parameters [91, 92]. Over the last years, the invention has been further elucidated resulting in a fully automated and controllable printing process [93, 94].

The PAM printing technology requires semi-solid formulations as printing material. Semi-solid formulations are achieved usually by gelling of polymers [95-97] or by dissolving gel-formers into either water or organic solvents [98]. In the first stage of the process, the prepared printing formulation is transferred into a printing syringe and closed with a piston or plunger at the top. The printing process is carried out by applying pressurized air to initiate the extrusion of the semi-solid formulation from the syringe through the adapted printing nozzle [91-94]. The printing pressure must be sufficient enough to enable a constant flow of the material out of the

printing nozzle. Usually printing pressures ranging from 3 – 5 bar are used during the PAM printing process [95-99].

To ensure a successful process, the selected material should provide the ability to form a stable object without collapsing during the printing process. Since the printing formulations are based on solvents (organic and inorganic), a drying step is essential to achieve a solid 3D-object [95, 100]. Due to the necessary drying process shrinkage of the printed object is expected [34].

The choice of the nozzle diameter mainly depends on the rheologic properties of the used printing material. Materials with high viscosities are not processable with a small nozzle diameter due to the occurrence of nozzle clogging. Since the solidification of the printed material does not occur directly after being extruded onto the building platform, the printing temperature and building platform temperature are of great importance for the PAM technology. The printing process is determined by the dynamic viscosity of the material, which is also determined by the temperature as well as by the applied shear stress. A high printing temperature would decrease the viscosity of the printing material, which would lose its semi-solid nature and become too liquid for the execution of the printing process. Printing of these formulations would lead to the complete spreading of the formulation on the building platform without the ability of forming a stable structure. On the other side, a low printing temperature would result in a high viscosity which might not be suitable anymore for the PAM printing process, since the printing pressure would not ensure a constant flow of material through the printing nozzle. The applied printing pressure mainly depends on the viscosity of the printing material. Materials with a high viscosity require high printing pressure to enable a constant material flow, while low viscosity materials require rather low printing pressure to achieve a suitable extrusion through the applied nozzle. Additionally, the viscosity of the printing material determines the applicable printing speed. During the printing process, a constant material flow should be realized to avoid printing errors, which might result in dose variations for pharmaceutical application. For printing materials with a high viscosity, a high printing speed would result in an irregular extrusion of the material, which would result in significant fluctuations in the dose. For materials with a low viscosity, a lower applied printing speed might result in regional over extrusion, which would result in an overdosing of API.

Although until today this technology is mainly used in the field of tissue engineering and bioprinting, it has great potential to be implemented as manufacturing process for individualized dosage forms with unique dissolution characteristics [101-104] as well as for the manufacturing of fixed dose combinations [95, 96, 105]. Shaban et al. utilized PAM printing to manufacture a fixed-dose combination product named polypill [97]. The printed polypill consisted of five different APIs with different release profiles [97]. Acetylsalicylic acid and

hydrochlorothiazide were printed into one immediate release (IR) compartment, while atenolol, pravastatin and ramipril were embedded in a sustained release (SR) compartment. The IR compartment was printed on top of the SR compartment and consisted of sodium starch glycolate as disintegrants and polyvinylpyrrolidone (PVP) K30 as binder (Figure 3).

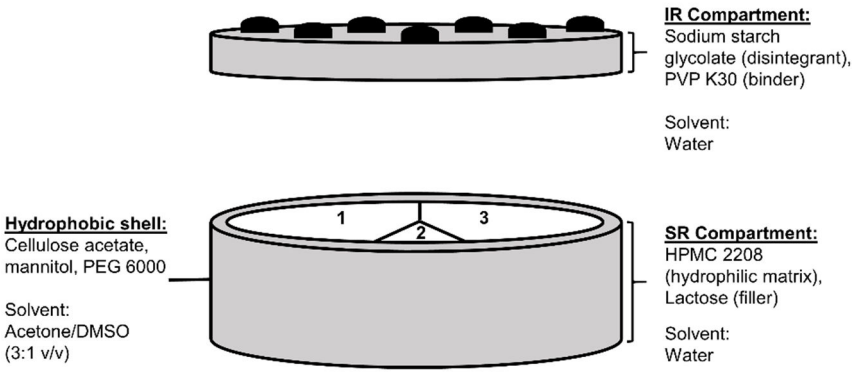

Figure 3. Scheme of the polypill concept (adapted and modified from [97], used with courtesy of the International Journal of Pharmaceutics, Elsevier).

A powder mixture of cellulose acetate, mannitol, and polyethylene glycol (PEG) 6000 was suspended in a solution of acetone/dimethyl sulfoxide (DMSO) (3:1 v/v) to prepare the printing formulation for the hydrophobic shell of the SR compartment. Drug loaded printing formulations for the SR compartment were obtained by mixing the respective API with hydroxypropyl methylcellulose (HPMC), lactose and water. Dissolution testing revealed that 75 % of the incorporated drug of the IR compartment was released within 30 min. In comparison, sustained drug release from the SR compartment could be demonstrated over the course of 720 min for all three incorporated APIs. In future, the availability of dosage forms with more than one API might have a distinct influence on the compliance of patients, since the frequency of daily drug intakes might be reduced significantly.

PAM printing technology enables the execution of the printing process at room temperature. Hence, PAM is a promising technology for the processing of thermo-sensitive API even at ambient conditions. In addition, printing of pharmaceutical pastes with this technology appears to be feasible, which enables a high drug-load for pharmaceutical application [99]. Beside manufacturing of tablets, PAM printing was utilized to print ODFs [105]. ODFs were printed directly into their final size by which a further cutting step is not required anymore [105].

For the execution of printing processes, plastic syringes as well as plastic nozzles are used. Besides the plunger to close the syringe at the top, these parts are the only ones that are in direct contact to the printing formulation. Since the acquisition cost of these components are negligible, they might be used as disposable item to avoid cross-contamination. Therefore, complex cleaning concepts for PAM printing are redundant, compared to other 3DP

technologies like FFF printing where the starting material is in direct contact to the equipment. The use of disposable printing components makes it further possible to switch easily to other APIs, since there is no necessity to remove not printed powder material between the printing processes as it is the case for printing technologies like BJ or SLA.

Besides the advantages, the use of PAM technology as pharmaceutical manufacturing process shows some limitations. Especially, the use of organic solvents in the preparation of the printing formulations like acetone or DMSO must be considered as critical. According to the ICH guideline for residual solvents, acetone and DMSO are listed as a class 3 solvents, meaning that the daily intake for humans is limited to 50 mg [106]. Especially dosage forms intended for paediatric use should not contain the mentioned solvents to avoid possible harm of paediatric patients. Thus, for printing formulations containing organic solvents, a determination of the residual solvent according to the Ph. Eur. is required [107]. Furthermore, the usually required drying process should also be considered as a critical step in the manufacturing cascade. Drying processes are often long-term processes utilizing often high drying temperatures [34]. Due to the thermal stress, the stability of APIs and excipients might be influenced because of their possible thermal degradation. Nevertheless, the overall thermal stress is lower compared to printing technologies like FFF printing. Another issue to consider is that the achievable resolution is limited by the applied nozzle size. For pharmaceutical applications, nozzles of 400 – 800 µm diameter are available, which is clearly inferior compared to other printing technologies [34, 95, 96, 99, 100].

1.1.3 Advantages and challenges of pharmaceutical 3DP

The utilization of 3DP as manufacturing process might provide some potential benefits for the pharmaceutical industry as well as for patients. In regard to customization and tailoring of pharmaceutical dosage forms, 3DP appears to have a high potential as on-demand manufacturing process. Compared to conventional manufacturing processes, 3DP technology seems to be rapidly adapting and flexible. Besides the possibility of printing customized and complex structures, 3DP might further be used to adjust the drug release characteristics of a dosage form as needed.

The implementation of 3DP might shorten the overall manufacturing chain significantly since manufacturing steps like granulation, milling, sieving, tableting, and coating would become redundant [34]. Further, 3DP provides the opportunity to be set up as an on-demand manufacturing process in community and hospital pharmacies. The on-demand manufacturing might shorten lead times as well as decrease the amount of wasted material, since only small batches with the required amount of dosage forms would be printed [108]. Furthermore, 3D-printers generally have a small footprint, which results in only a small percentage of the production area being occupied by the equipment. Therefore, 3D-printers are particularly

suitable as stationary manufacturing equipment in community and hospital pharmacies. Recently published studies demonstrated the ability of printing tablets with Braille and Moon patterns, allowing visually impaired patients to identify the medication and therefore reducing the risk of medication errors [53].

Alongside with the advantages and opportunities provided, 3DP has to overcome major challenges [109]. These challenges can be classified into three categories: 1. Technical challenges; 2. Regulatory challenges; 3. Good manufacturing practice (GMP) challenges.

1. Technical challenges:

Depending on the applied printing technology, printed objects might have insufficient mechanical properties and possess a high friability, which makes the further processing of these dosage forms rather difficult. Especially during packaging of printed tablets defects might occur, which might lead to rejection of complete batches. For some of the 3DP technologies like BJ or SLA, a lot of unprinted material accumulates after the printing process. On the one hand, technical solution must be found to avoid excessive amount of unprinted material and on the other hand clarification is needed whether unprocessed material might be reused for further printing.

Compared to established pharmaceutical manufacturing processes, 3DP is lacking in process control strategies. During conventional production of tablets, in-process control (IPC) is carried out to monitor the production intensively. For 3DP processes, IPC technologies are currently not commonly implemented, by which printed tablets are assessed analytical after being printed. Further, 3DP is a time-consuming process, whereas conventional tableting equipment is able to manufacture several hundred thousand tablets per hour (depending on the scale of tablet press).

2. Regulatory:

From a regulatory perspective, 3D-printed dosage forms have to meet the same requirements as conventionally manufactured dosage forms. However, at this point a big gap is existing in the regulatory framework. While for established processes guidelines are well implemented and standardized, the process of 3DP is lacking any guidelines from regulatory authorities. Health authorities around the world recognized the lack of guidance and initiated the process of developing standards and defining practical guidelines. The FDA designated two internal laboratories, the Laboratory for Solid Mechanics as well as the Functional Performance and Device Use Laboratory within the FDA´s Office of Science and Engineering Laboratories (OSEL), to explore the future potential of 3DP in pharmaceutics [110]. The work of these two units should help to gain knowledge in the first step and to help developing standards as well as identifying critical aspects affecting the product safety. Nevertheless, health authorities must

put more effort into defining standard processes and providing guidance for pharmaceutical manufacturers.

Furthermore, liability as well as responsibility must be discussed in case of occurred incidents. If it is intended to use 3DP as on-demand manufacturing process in community and hospital pharmacies, different scenarios for supply chain are possible. Regarding FFF technology, drug-loaded filaments must be provided by external chemical or pharmaceutical companies and the printing process executed in the pharmacy itself. The scenario raises the question of how incoming goods should be tested with the equipment at the pharmacy and who would be responsible for the release of the starting material for manufacturing [111].

3. GMP challenges

Moreover, qualification standards for 3D-printer manufacturers must be defined to meet GMP requirements. Especially, the topic of cleaning validation should be addressed to avoid cross-contamination. As long as cleaning concepts are not in place and validated, pharmaceutical manufacturers are obliged to use 3D-printers as dedicated equipment.

The mentioned regulatory and GMP challenges must be tackled together by health authorities and pharmaceutical manufacturers to establish 3DP as manufacturing process for pharmaceutical dosage forms.

1.1.4 3D-Bioplotter

The 3D-Bioplotter of EnvisionTec GmbH (Gladbeck, Germany), equipped with a pneumatic extrusion system, was used to manufacture oral solid dosage forms for the research performed in the scope of this thesis. An image of the used 3D-Bioplotter is depicted in Figure 4.

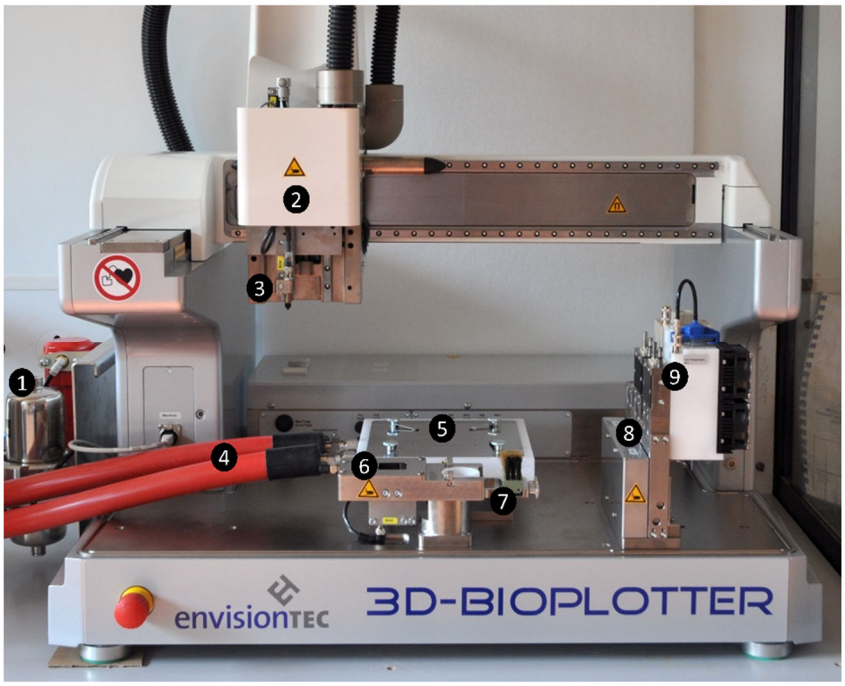

Figure 4. 3D-Bioplotter of EnvisionTec GmbH.

The 3D-Bioplotter is composed of the following components:

1. Sterile and particle filters
2. Print head carrier
3. Platform height control sensor
4. Connection to the temperature controlling system
5. Temperature controlled building platform (-10 – 80 °C)
6. Photo calibration station for needle tip
7. Cleaning station for needle tip
8. Parking station of print heads
9. Print heads (white: low temperature print head; beige: high temperature print head)

The above-mentioned components ensure that the printing process itself is controlled to a high degree. For example, it is always guaranteed by the platform height control sensor that the height of the used substrate is measured and fixed during the printing process. At the calibration station the geometry of the needle tip is detected by a photo sensor and the information thereof transferred to the software of the printer. In general, the printer can operate with two different print heads:

- Low temperature print head: Disposable polyethylene cartridges with a volume of 30 ml and a temperature working range of 0 – 70 °C
- High temperature print head: Reusable stainless-steel cartridges with a volume of 10 ml and a temperature working range of 30 – 250 °C

The availability of print heads for different temperature ranges allows processing of a broad variety of materials with different physicochemical properties. Printing formulations with a low melting point or semi-solid/liquid characteristics are well suited for the low temperature print head [112], while materials with high melting points can be processed utilizing the high temperature print head. With regard to these options, a broad field of applications is covered. In addition, the building platform offers an active cooling and heating option. This feature further increases the possible number of processable materials.

1.2 Levetiracetam as model drug

Levetiracetam [IUPAC: (2S)-2-(2-oxopyrrolidin-1-yl)butanamide] is an anti-epileptic drug that was first approved in 1999 by the FDA. The molecular formula of levetiracetam is $C_8H_{14}N_2O_2$ with a molecular weight of 170.209 g/mol. The chemical structure of levetiracetam is depicted in Figure 5.

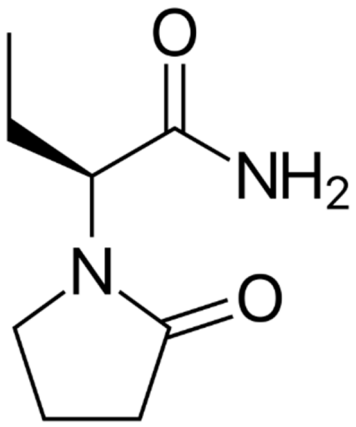

Figure 5. Chemical structure of levetiracetam.

The external appearance of levetiracetam is a white crystalline powder, which is characterized by its high-water solubility (104 g/100 ml). Levetiracetam is freely soluble in chloroform (65.3 g/100 ml) and practically insoluble in n-hexane and is reported as a drug with a bitter taste.

The pharmacological mechanism of action of levetiracetam has not been finally clarified yet, however, there are already hypotheses introduced in scientific studies [113, 114]. It has been proven that levetiracetam achieves its antiepileptic effect by binding to the synaptic vesicle glycoprotein 2A (SV2A). SV2A is a membrane protein located in synaptic vesicles. SV2A is known as a key protein in the release of neurotransmitters from the vesicles into the synaptic

gap. The binding of levetiracetam to SV2A results in a reduction of the release of neurotransmitter. Furthermore, binding of levetiracetam influences the calcium concentration in the neurons.

Levetiracetam is used in the treatment of partial and generalized epilepsy. The recommended applications and related doses are listed in Table 1. Levetiracetam tablets with doses of 250, 500, 750 and 1000 mg [115] are available for oral administration.

Table 1. Recommended doses of levetiracetam for therapy of epilepsy.

Application	Recommended dose
Partial onset seizures in patient 4 years of age and older with epilepsy	• 4 years to < 16 years: 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily • Adults 16 years and older: 500 mg twice daily, increase as needed and tolerated in increments of 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily
Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy	• 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily
Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy	• 6 years to < 16 years: 10 mg/kg twice daily, increase in increments of 10 mg/kg twice daily every 2 weeks to recommended dose of 30 mg/kg twice daily • Adults 16 years and older: 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily

Spritam®, the first licensed 3D-printed drug, contains levetiracetam as API. However, the production of Spritam® doses is only performed in discrete steps

(doses from 250 – 1000 mg), without the possibility of tailoring the dose to individual conditions of patients [62]. The PAM printing technology seems to be a promising approach in this context, with the ability of manufacturing dosage forms with individualized doses.

Levetiracetam´s high-water solubility makes this API highly suitable especially for water-based printing formulations.

As shown in Table 1, the dosage of levetiracetam for paediatrics is based on the respective body weight. Since the physical conditions of paediatrics change significantly during the first years of life, a fast adapting treatment regime for levetiracetam is necessary. Due to the fact that only tablets with higher doses are available, splitting of tablets is used to achieve the desired dose. In most cases, medical dividing devices are utilized by patients to control the splitting process of tablets [116]. Even though the splitting of tablets is a well-established technique for many years, it owns major risks for the patients. It has been shown that splitting of tablets results in inhomogeneous fragments and therefore to a high content variation within these fragments [116-118]. Furthermore, tablets with a functional coating cannot be divided since it would destroy the coating. Therefore, coated tablets are mostly excluded from the practice of individualizing the dose manually by splitting. For coated tablets consisting of multiparticulate units, splitting of these tablets is feasible (e.g. Nexium® MUPS). The implementation of 3DP as manufacturing process for individualized dosage forms might close a gap and promote the development of individualized medicine.

Preliminary studies of this thesis revealed that levetiracetam tends to form needle-shaped particles under heat influence (Figure 6), which may make an extrusion process for manufacturing of drug-loaded filaments rather difficult [119]. Since the processing of the API via HME is rather difficult, execution of FFF printing is not a suitable manufacturing option for levetiracetam. However, since PAM printing processes can be conducted at room temperature, it appears to be a highly promising option for manufacturing solid dosage forms containing levetiracetam.

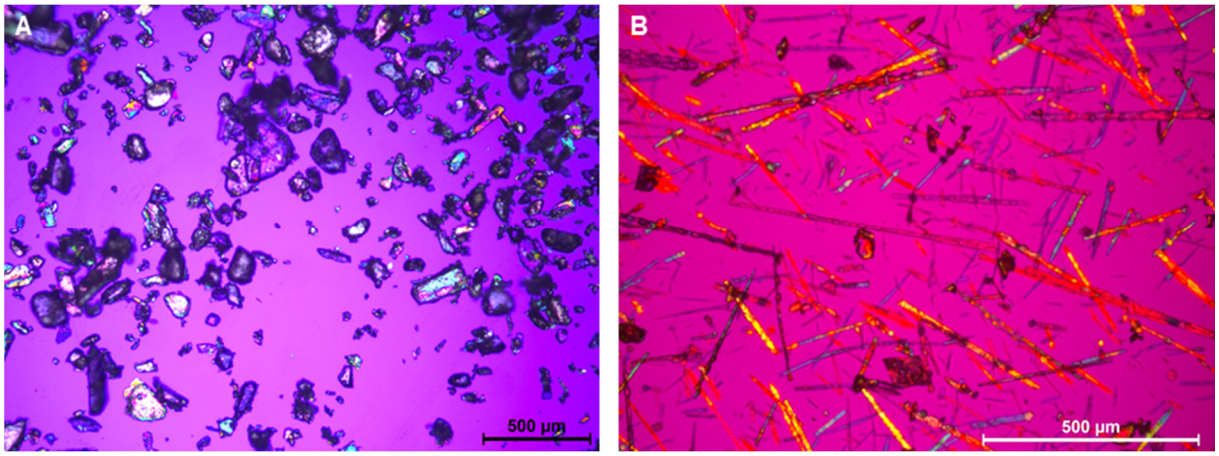

Figure 6. Polarization microscopy images of levetiracetam. A: Before thermal treatment; B: After thermal treatment.

1.3 Selection of polymers suitable for the development of printing formulation for PAM printing technology

As described in chapter 1.1.2, semi-solid formulations are utilized as starting material for the selected PAM printing technology. In order to be suitable for the printing process, the printing formulation must meet predefined criteria. The most important criterion for the success of the process is that the formulation is capable of maintaining the printed structure during the printing process, i.e. in a moist state, without collapsing. Maintaining the structure during the printing process is enabled by increasing for example the solid content of the formulation (referred as molding agent). After evaporation of the used solvent during the drying process, the suspended solid components are able to form a coherent structure. Most of the published scientific studies used the combination of different grades of HPMC as hydrophilic matrices and microcrystalline cellulose as extrusion molding agent [95-97, 120]. Depending on the desired disintegration and dissolution properties of the printed tablets, additional binder material or disintegration agents might be added to the printing formulation [95-97].

After a screening phase, polyvinyl alcohol polyethylene glycol graft copolymer (PVA-PEG) was identified as promising polymer. Unlike other polymers, PVA-PEG exhibit water solubility even at concentration of up to 40 %. Thereby, a high solid content might be achieved, which might impact the printing process positively.

The selected polymer consists of 75 % PVA, 25 % PEG and approximately 0.3 % of colloidal silica. Colloidal silica is added to improve the flowability of the polymer. The structure of PVA-PEG is displayed in Figure 7. PVA-PEG is produced by grafting of vinyl acetate onto polyethylene glycol followed by saponification of the polyethylene-polyvinyl acetate graft copolymers. The synthesis is finished by solvent exchange against water and spray drying to a powder.

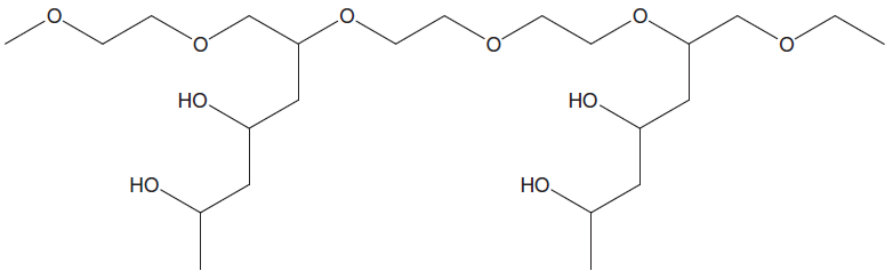

Figure 7. Chemical structure of PVA-PEG.

PVA-PEG has been developed as coating agent for immediate release. Due to the physicochemical properties, PVA-PEG already demonstrated its ability as excipient for further pharmaceutical applications such as binding agent in wet granulation processes or as carrier for solid dispersions manufactured by hot melt extrusion. In regard to the physicochemical properties of PVA-PEG, an immediate drug release was expected.

With polyvinyl acetate polyvinylpyrrolidone copolymer (PVAc-PVP) a second polymer was identified as promising polymer for PAM printing purposes. PVAc-PVP consists of 80 % polyvinyl acetate, 19 % polyvinylpyrrolidone, 0.8 % sodium lauryl sulfate and 0.2 % colloidal silica. The structure of PVAc-PVP is illustrated in Figure 8.

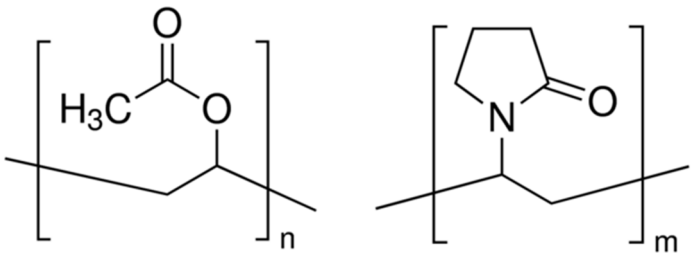

Figure 8. Chemical structure of PVAc-PVP.

Compared to PVA-PEG, PVAc-PVP is not soluble in water (only the polyvinylpyrrolidone component). Generally, PVAc-PVP is used as pH-independent sustained release matrix for dosage forms manufactured by direct compression.

In combination with HPMC and silicon dioxide, PVAc-PVP appeared to form a highly suitable printing formulation with expectable sustained release characteristic.

1.4 Aim of the thesis

3DP has been recognized as potentially revolutionary manufacturing process for individualized pharmaceutical dosage forms. In particular, specific patient populations like paediatric and geriatric patients might significantly benefit from new opportunities to individualize dosage forms. By implementing 3DP as manufacturing process for pharmaceutical dosage forms, a broad range of APIs might be processed in future regardless of their physicochemical properties (e.g. low solubility) and thus made available for patients.

The aim of this thesis was to investigate the ability of manufacturing oral solid dosage forms containing levetiracetam as API using PAM printing technology. Formulation development as well as process development should be performed to achieve the opportunity of manufacturing dosage forms with either an immediate or sustained drug release. Further, a concept of individualizing the dispensed dose should be implemented for the utilized printing technology.

More detailed aims of the presented studies were:

- To provide a detailed overview about the current state of research and to evaluate the use of 3DP for individualizing the dosage forms critically (Chapter II)

- To develop a printing formulation for PAM printing technology as well as characterize the printing process and required drying process (Chapter III)

- To transfer the gained knowledge of PAM printing to develop and establish an individualization concept for paediatric patients (Chapter IV)

- To develop a storable printing formulation with adjustable sustained drug release (Chapter V)

1.5 Outline of the thesis

The current state of research in the field of manufacturing pharmaceutical dosage forms with 3DP is provided in chapter II of this thesis in the form of a review article. An overview of the different 3DP technologies including the description of the printing processes, relevant process parameters as well as advantages and disadvantages for the pharmaceutical use are presented. Further, a critical evaluation about the impact of 3DP on individualization drug dosage forms is provided by the authors. For PAM printing technology in particular, oral dosage forms and especially fixed-dose combinations are producible. Nevertheless, concepts for individualizing the dispensed dose are still lacking. Compared to PAM printing, several concepts have already been presented and successfully implemented in academic studies for the FFF printing technology.

Chapter III deals with the development of a printing formulation for PAM printing purposes as well as with the optimization of the printing process. In order to ensure that the printed tablets might also be suitable for paediatric patients, a water-based printing formulation was developed. Furthermore, in comparison to other academic studies, additional solvents such as DMSO to avoid nozzle clogging during the printing execution were completely avoided. The required drying process has been studied intensively, with the focus of defining the shortest drying time possible. Thereby, the overall thermal load on the API and excipients should be minimized while the overall production time should be decreased significantly compared to other academic studies.

The experience and insights gained in Chapter III have been used to implement a novel individualization concept for paediatric patients, which is depicted in chapter IV. The concept should enable the fast adaption of the required amount of levetiracetam based on the body weight of the respective paediatric sub-population. The printed tablets should further meet the requirements set by the pharmacopoeia.

Chapter V describes the development of a storable printing formulation without reduced loss of printability, by which the preparation of stock formulation as intermediate at a local manufacturing site might be feasible. The storage time and storage condition should not have a negative impact on the printability or properties of the printed tablets. Furthermore, the influence of HPMC as well as influence of different printed infill design on the drug release behavior of printed tablets should be investigated intensively.

In chapter VI, a conclusion of the presented thesis is provided as well as a statement about the future perspective of 3DP as manufacturing process of pharmaceutical dosage forms.

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Chapter II – A critical review on 3D-printed dosage forms

Pretext

Since the successful approval of the first printed tablet by the FDA, 3DP as manufacturing process for pharmaceutical purposes has gained increased interest. The increased interest can be recognized in particular in the strongly increased number of scientific articles published. Enormous expectations were placed in the 3DP technology as a game changer for individualized medicine. Especially the possibility to adapt and change the desired dose in a fast manner is praised in the existing literature as one of the most important advantages of the technology compared to conventional manufacturing processes. The following review article evaluates the current state of research and provides a critical evaluation regarding the implementation of 3DP as manufacturing process as well as the realizability of individualizing the dispended dose.

Evaluation of authorship

The following review article has been written on invitation by the journal Current Pharmaceutical Design (impact factor 2018: 2.412) and has been accepted in 2018. The first author Ilias El Aita was responsible for the design, the literature evaluation, and the writing of the manuscript. The second author Hanna Ponsar was involved in the design, the literature evaluation, and the writing of the manuscript. Dr. Julian Quodbach as senior author was responsible for the idea, the design, writing as well as revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Ilias El Aita	30	35	-	60	40
Hanna Ponsar	30	35	-	40	40
Julian Quodbach	40	30	-	-	20

A critical review on 3D-printed dosage forms

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Cur. Pharm. Des. 2018, doi.org.-10.2174/1381612825666181206124206

Abstract

Background: In the last decades, 3D-printing has been investigated and used intensively in the field of tissue engineering, automotive and aerospace. With the first FDA approved printed medicinal product in 2015, the research on 3D-printing for pharmaceutical application has attracted attention of pharmaceutical scientists. Due to its potential of fabricating complex structures and geometrics, it is a highly promising technology for manufacturing individualized dosage forms. In addition, it enables the fabrication of dosage forms with tailored drug release profiles.

Objective: The aim of this review article is to give a comprehensive overview of the used 3D-printing techniques for pharmaceutical applications, including information about the required material, advantages, and disadvantages of the respective technique.

Methods: For the literature research, relevant key words were identified, and the literature was then thoroughly researched.

Conclusion: The current status of 3D-printing as a manufacturing process for pharmaceutical dosage forms was highlighted in this review article. Moreover, this article presents a critical evaluation of 3D-printing to control the dose and drug release of printed dosage forms.

Chapter III – On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing

Pretext

Evaluation of the review article reported in chapter II showed that PAM printing is lacking in process knowledge as well as concepts for individualizing the dispensed dosed. The literature research demonstrated that PAM processes are carried out mostly with the use of organic solvents during formulation development and further to avoid nozzle clogging during the printing process. Since solvents of class 3 (according to the ICH guideline Q3C) are used in most studies, the use of these printing formulations for paediatric dosage forms is limited. Further, characterization of the required drying process and its influence on the manufactured dosage form are not fully examined. The following research study aims to develop a suitable printing formulation based on water, which should be processable at room temperature. Besides the formulation development, an intensive examination of the drying process is aimed to achieve a low and efficient drying time to keep the overall thermal load on the API and excipients low. The developed printing formulation should display an immediate drug release of the incorporated levetiracetam.

Evaluation of authorship

The following research paper has been published by the European Journal of Pharmaceutics and Biopharmaceutics in 2019 (impact factor 2019: 4.604). The first author of the published manuscript Ilias El Aita is responsible for the idea and study design as well as for the execution of experimental work. Data evaluation as well as the writing of the manuscript was performed by Ilias El Aita. Prof. Dr. Jörg Breitkreutz and Dr. Julian Quodbach as senior authors were responsible for the idea and the study design as well as for the revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Ilias El Aita	40	80	100	80	80
Jörg Breitkreutz	10	10	-	-	10
Julian Quodbach	50	10	-	20	10

On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing

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Eur. J Pharm. Biopharm. 2019, 134: 29 – 36; doi.org. 10.1016/j.ejpb.2018.11.008

Abstract

Fast and accurate manufacturing of individually tailored solid dosage forms is one of the main challenges for personalized medicine. The use of 3D printers has recently been studied to determine their suitability for personalized drug manufacturing.

In the current work, formulations free of organic solvents were developed for a pressure-assisted microsyringe printing method (PAM). The water-soluble polymer polyvinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG) was used as matrix, while levetiracetam (LEV) was used as model drug. Furthermore, the influence of a second polymer, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-PVAc) on the properties of the printed tablets was investigated. Tablets were printed using a 3D-Bioplotter. The printed formulations were analyzed regarding mass variation, friability, and thickness. Furthermore, the disintegration behavior and dissolution profile were analyzed. Investigations of the dissolution profiles of printed tablets show that an immediate release of the API could be achieved. For tablets with PVA-PEG the drug is released completely within 10 min while the additional use of PVP-PVAc leads to a slightly delay with a complete release within 20 min. The same trend is observed regarding the disintegration time of printed tablets. Tablets with PVA-PEG disintegrated within 95 ± 10 s while tablets with additional PVP-PVAc disintegrated within 130 ± 20 s.

Friability of <0.5% indicate that the used PAM printing method provides tablets without loss of structural integrity during handling. Furthermore, it could be shown that the production of tablets with a good content uniformity using a 3D Bioplotter is suitable.

Chapter IV – 3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing

Pretext

In the previous research paper, PAM printing was established successfully as an on-demand manufacturing process for oral dosage forms. In the subsequent research paper, the developed PAM printing process should be used to explore the potential of PAM printing to individualizing dosage forms and to manufacture age-appropriate dosage forms. PAM printing has been so far utilized successfully to print fixed-dose combinations but is lacking in practical approaches for individualizing the desired dose. The following research article aims to investigate the existing gap in dose individualization using PAM printing. The individualization method should ensure a flexible and fast adapting dose dispensing of levetiracetam to allow the manufacturing of age-appropriate dosage forms.

Evaluation of authorship

The following research paper has been published by the European Journal of Pharmaceutics and Biopharmaceutics in 2020 (impact factor 2019: 4.604). The first author of the published manuscript Ilias El Aita is responsible for the idea and study design as well as for the execution of experimental work. Data evaluation as well as the writing of the manuscript was performed by Ilias El Aita. Prof. The second author Jhinuk Rahman was involved in the execution of experimental work, data evaluation and writing of the manuscript. Prof. Dr. Jörg Breitkreutz and Dr. Julian Quodbach as senior authors were responsible for the idea and the study design as well as for the revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Ilias El Aita	70	70	80	70	60
Jhinuk Rahman	10	10	20	20	20
Jörg Breitkreutz	10	10	-	-	10
Julian Quodbach	10	10	-	10	10

3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing

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Eur. J Pharm. Biopharm. 2020, 157: 59 – 65; doi. 10.1016/j.ejpb.2020.09.012

Abstract

The establishment of 3D-printing as manufacturing process for oral solid dosage forms enables new options for the individualized medicine.

The aim of this work was to develop a novel drug-printing model using pressure-assisted microsyringe (PAM) technology, which allows the precise dispensing of drug substances.

Printed tablets with different numbers of layers, mimicking different doses for paediatric subgroups, were analyzed regarding mass variation, friability, thickness, and disintegration time. Furthermore, the uniformity of dosage units and the dissolution behavior were investigated.

Friability was < 0.3 % in all cases, which demonstrates the ability of PAM printing to manufacture robust solid dosage. Disintegration results showed the dependency of the disintegration on the number of layers and therefore on the compact mass of polymer. However, all tablets disintegrated within 3 min and fulfilled the requirements of immediate release tablets of the USP and orodispersible tablets according to the Ph. Eur. Results of uniformity dosage units confirmed the successful manufacturing of the intended individualized doses. Drug dissolution appeared to be dependent on the number of layers. An increase of layers resulted in a decrease of the drug release rate. Further, the drug release could be correlated to the surface area/volume (SA/V) ratio.

Chapter V – Investigation of semi-solid formulations for 3D printing of drugs after prolonged storage to mimic real-life applications

Pretext

The previous paper demonstrated the ability of implementing a concept to individualize the manufactured dose. However, these studies also revealed that there are still some technical hurdles to overcome.

While for other 3DP technologies, the required printing material might be produced as well as stored as a stock formulation, this has yet not been implemented for PAM printing technology. Since the evaporation of the contained solvent led to a change of viscosity, the printing process might need therefore some adjustment. Further, the use of respective polymers as well as introduction of different infill designs might influence the drug release of the incorporated API. The following research article aims to investigate the development of a storable printing formulation for PAM printing purposes. The printability of the developed printing formulation should not be impacted negatively by the storage. Storage of printing formulation might reduce the preparation time as well as the drug containing waste.

Evaluation of authorship

The following research paper has been published by the European Journal of Pharmaceutical Sciences in 2020 (impact factor 2019: 3.616). The first author of the published manuscript Ilias El Aita is responsible for the idea and study design as well as for the execution of experimental work. Data evaluation as well as the writing of the manuscript was performed by Ilias El Aita. Prof. Dr. Jörg Breitkreutz and Dr. Julian Quodbach as senior authors were responsible for the idea and the study design as well as for the revision of the manuscript.

author/co-author	Idea [%]	Study design [%]	Experimental [%]	Evaluation [%]	Manuscript [%]
Ilias El Aita	40	80	100	80	80
Jörg Breitkreutz	10	10	-	-	10
Julian Quodbach	50	10	-	20	10

Investigation of semi-solid formulations for 3D printing of drugs after prolonged storage to mimic real-life applications

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Eur. J Pharm. Sci. 2020, 146: 105266; doi.org/10.1016/j.ejps.2020.105266

Abstract

The implementation of tailor-made dosage forms is currently one of the biggest challenges in the health sector. Over the last years, different approaches have been introduced to provide an individual and precise dispensing of the appropriate dose of an active pharmaceutical ingredient (API). A more recent approach, which has been intensively researched in the last years, is 3D-printing of medicines.

The aim of this work was to develop printing formulations free of organic solvents for a pressure-assisted microsyringe printing method (PAM), which should also be printable over several days of storage. Furthermore, the printed dosage forms should provide a sustained release of the incorporated API. A mixture of polyvinyl acetate/polyvinylpyrrolidone copolymer (PVAc-PVP), hydroxypropyl methylcellulose (HPMC) and highly dispersed silicon dioxide (SiO2) was found to be a feasible polymer matrix to achieve a sustained drug release. Levetiracetam (LEV) was used as model drug.

The printed formulations were analyzed regarding mass variation, friability, and thickness. Furthermore, the dissolution behavior of freshly printed tablets and tablets printed from stored printing formulations were investigated. The dissolution profiles indicate that the dissolution of LEV could be modified by varying the amount of HPMC and by changing the infill design of tablets. Tablet-like geometries with an infill design of 0.35 mm and 5 % HPMC released 50 % of the incorporated drug after 4 h, while for tablets with a higher HPMC amount the release was decreased (10 % HPMC: 5.5 h; 15 % HPMC: 8 h). All printed tablets exhibit a friability < 0.5 %, indicating that PAM printing is suitable for the manufacturing of tablets with a high structural integrity. Furthermore, this study demonstrates the ability of producing tablets with a uniform content and mass using PAM printing.

Chapter VI – Conclusion and future perspective

3DP technology has been considered as revolutionary for the manufacturing of pharmaceutical dosage forms. Published academic studies already indicate the potential of 3DP and its beneficial impact on health care systems. Patients, regardless whether young or old, might further benefit from the newly acquired opportunities to individualize dosage forms. Nevertheless, the technology of printing pharmaceutical dosage forms is still in its infancy and must overcome some major challenges. The presented thesis might contribute to the further understanding and progression of PAM printing technology. In the following section of the thesis, a conclusion of the presented chapters is provided and a perspective about future application of 3DP is given.

1. A critical review on 3D-printed dosage forms

The published review article provides a detailed overview of the various existing 3DP technologies as well as the application of 3DP for the manufacturing of pharmaceutical dosage forms. The literature-based research demonstrated the ability of manufacturing simple and complex geometries and structures, by which new treatments options arise for patients. In particular, the potential for individualizing dosage forms has been emphasized in the existing literature.

Beside the demonstrated abilities and advantages of 3DP, the review article provides further a critical evaluation of the 3DP as suitable manufacturing process. In regard of the batch size and the maximal possible throughput, 3DP is clearly inferior compared to conventional manufacturing processes. Further, deeper insights into the literature revealed that most of the published studies do not deliver a concept of individualizing the dispensed dose. Instead of this, dosage forms were printed without knowing the resulting dose strengths. The review further displays that most of the academic studies aimed to modify the drug release rate either by changing the formulation or by modifying the surface area of the respective dosage form.

Especially for PAM printing technology, concepts for individualizing the dispensed dose are currently not being introduced. Published studies are focused mainly on the manufacturing of fixed-dose combinations with different release kinetics, which should decrease the number of tablets to be taken daily and therefore improve the patient compliance.

2. On-demand manufacturing of immediate release levetiracetam tablets using pressure assisted microsyringe printing

Although studies about manufacturing dosage forms with PAM printing technology are already available, the process itself is still lacking know-how and knowledge. The PAM printing technology appears to be a versatile technology, whose success depends on both the characteristics of the developed printing formulation and the selected settings of the 3D printer. Further the success of the printing process relies on the ability of the developed formulation to maintain the form during the process as well as during the drying without collapsing.

The results of the present study revealed the successful development of a suitable printing formulation for PAM use. After a polymer screening phase, a formulation was developed, which consists of a polymer, polyvinyl alcohol-polyethylene glycol graft copolymer, an API, levetiracetam, and only water as solvent. The introduction of a water-based printing formulation with such a small number of components is a novelty in the field of PAM printing technology. It was feasible to set up a printing process, which was executed at room temperature. Furthermore, the drying process as well as the shrinkage of tablets caused by the evaporation of solvent has been successfully investigated. Compared to existing studies, the drying time could be reduced significantly without affecting the mechanical properties of tablets. Due to the plastic properties of the used polymer, tablets with a low friability were manufactured, which is unusual for products made by PAM printing. Data obtained for the uniformity of mass and content displayed the suitability of the 3D printer to manufacture reproducible dosage forms, which is mandatory for a pharmaceutical process.

3. 3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing

The implementation of PAM printing as manufacturing process for pharmaceutical dosage forms was demonstrated successfully in previously introduced studies of this thesis as well in existing literature. As pointed out in the review article, concepts to individualize the dispensed dose are currently not presented. Even for the FDA approved product Spritam®, the printing technology was used to manufacture dosage forms with discrete doses.

The present study revealed the opportunity of individualizing the dose of levetiracetam based on a calibration model. Based on the developed individualization model, the required amount of levetiracetam could be adjusted according to the body weight of the respective patient. Especially for paediatric patient, the developed model might be promising, since for the paediatric population physiological conditions are proceeding rapidly in the first months and years. Therefore, it can be assumed that the implementation of such an individualization concept increases the treatment options for paediatric patients. In particular, it should be

further emphasized that printed tablets demonstrated in this study fulfilled the necessary pharmacopoeial requirements. Beside the provided advantages, the size of printed tablets must be recognized as a major drawback. Infants and especially neonates might face severe swallowing issues in case of tablets with a diameter of 10 mm.

4. **Investigation of semi-solid formulations for 3D printing of drugs after prolonged storage to mimic real-life applications**

The patient compliance is a crucial aspect for the success of an exerted drug therapy. Clinical studies have demonstrated that the compliance of patient correlates with the number of dosage forms to be taken daily. With increase number of dosage forms per day, the compliance might decrease significantly. A preventive action might be the administration of sustained-release dosage forms.

Scientific studies demonstrated the ability of manufacturing sustained-release dosage forms using 3DP. Interestingly a sustained-release mechanism was achieved by either using polymers such as EC or HPMC or by changing the design of the structure. Especially, variation of infills appeared to be a feasible option to slow down the release rate.

For this study, sustained drug release of levetiracetam was successfully accomplished by varying the infill design as well as varying the amount of incorporated HPMC within the developed printing formulation. Beside the achievement of a sustained drug release, the study revealed further the development of a printing formulation, which might be stored up to five days. The storage time and conditions did not affect properties of the printed tablets as well as the printability of the stored printing formulation. The development of a storable printing formulation was first introduced in this study. Thereby, the possibility is given to produce a stock formulation, which can be stored until needed for printing processes.

Future perspective

With regards to the pharmaceutical industry, 3DP is an emerging technology with a potentially significant impact on current health care systems and patients. Several polymers in pharmaceutical quality are available for PAM and offer sufficient stability for practical use in community pharmacies. Numerous published scientific studies revealed the tremendous potential of 3DP as manufacturing process for both simple and complex structures and geometries. 3DP provides the opportunity of tailoring products to the needs of customers. Especially for individualized medicine, this platform technology might be highly suitable. Since 3DP includes different printing technologies, a large number of materials can be processed.

However, the broad application of the technology is currently limited both by technical hurdles and by the lack of regulatory guidance. Fundamental concepts as for example cleaning

procedure, which are standard processes for conventional processes, are completely missing for 3DP.

The future fields for application of the technology are defined mainly by its strengths and provided advantages. 3DP allows the effective and time-saving manufacturing of small batches. Therefore, 3DP might be especially applicable for the manufacturing of clinical samples. Furthermore, 3DP might be further implemented as an on-demand manufacturing process in community and hospital pharmacies. Studies presented in this thesis revealed the potential of a 3DP technology as on-demand manufacturing process.

In the recent years, the development of the technology itself has been rapid. Keeping up the same pace in the development phase, 3DP might achieve its breakthrough in the pharmaceutical industry within the next years. As a result of the breakthrough, further drug approvals from health authorities are expected.

Summary

With the first drug approval by the FDA in 2015, 3DP has finally arrived in the pharmaceutical industry as manufacturing process for pharmaceutical dosage forms. Due to the new arising opportunities provided by 3DP, the technology is considered revolutionary for the pharmaceutical industry. As described in chapter 1.1, 3DP is an umbrella term, which covers several different printing technologies. Among all the different 3DP technologies, the PAM printing technology emerges as the technology with the biggest potential as local manufacturing process for pharmacies and hospital pharmacies. Compared to other printing technologies, PAM printing does not rely on industrially pre-manufactured intermediate products such as filaments for FFF printing. Neither is the technology dependent on powder mixing processes, which are mandatory for powder-based printing technologies. Further, the use of a semi-solid formulations as printing formulation is advantageous due to several aspects. Semi-solid formulations can be produced relatively quickly and in any desired batch size. Furthermore, numerous polymers are already established in the production of semi-solid formulations. In addition, pharmacists are intensively trained in the production of semi-solid formulations during their vocational training. This intensive training enables the possibility of the in-house production of high-quality 3D-printed dosage forms.

The review of existing literature demonstrated that 3DP has mostly been claimed as highly promising manufacturing process for individualized manufacturing process. However, the provided review article revealed the lack of introduced concepts to individualize the dispensed dose. The thesis aims to close the existing gaps in process knowledge as well as in terms of individualizing the dispensed dose of printed dosage forms.

The establishment of a printing platform requires first the screening of suitable polymers. After identifying a suitable polymer, a formulation platform was developed. A printing formulation consisting of a polymer, levetiracetam as API and water as solvent was successfully developed. The printing formulation was able to maintain the printed structure without collapsing during the printing process. Further, the drying process as well as its influence on the dimension of the final object were characterized intensively. The success of the printing process was displayed by the analytical results. The low variation of the mass as well as the content uniformity and obtained friability demonstrated that the printing process is reproducible and robust. In regard of the chemical properties of the utilized polymer, PVA-PVP, and levetiracetam, an immediate drug release was achieved, as expected. The incorporation of a second polymer, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-PVAc), into the developed printing formulation indicated the ability of manipulating the properties of printed tablets. The feasibility of delaying the disintegration and drug release could be achieved by the addition of PVP-PVAc.

As mentioned before, most scientific studies did not introduce concepts for individualizing the dose of dosage forms. Dosage forms were printed without knowing the resulting dose. In order to close the existing gap, a calibration model was established, which should enable the individualization of dose according to the needs of paediatric patients. Tablets with different desired doses were printed according to the calibration model. The success of the calibration model was displayed especially by the accomplished acceptance value (AV). For all tablets, an AV far below 15 % was achieved, which indicated the consistency of the API content within a batch of printed tablets. Beside the establishment of an individualization concept for the levetiracetam dose, the dependency of the drug release on the surface area-to-volume ratio of printed tablets was demonstrated. By increasing the surface area-to-volume ratio, the drug release rate of the dosage forms was also increased. Based on the correlation, the drug release might be manipulated as needed.

In order to reduce the production time as well as the production costs, the development of a storable formulation would be advantageous. Through storable formulations, manufacturer would be able to manufacture a stock formulation, which might be used to print dosage forms when needed. However, since the most PAM printing formulations contain solvents, the printability is directly linked to the evaporation of solvents. The thesis presented the opportunity of developing storable printing formulations. The printability of the printing formulation as well as the properties of printed tablets were not affected by the storage. Furthermore, the drug release rate of printed tablets could be manipulated successfully by varying the amount of incorporated HMPC as well as changing the infill design of printed tablets.

The present thesis demonstrated the ability of manufacturing oral solid dosage forms using PAM printing. Pharmaceutical finished products with either an immediate or sustained drug release of levetiracetam have been printed successfully. In particular, the manufacturing of individualized dosage forms based on a calibration model was introduced successfully in this thesis. PAM printing appeared to be feasible for the reproducible manufacturing of tablets. The results of the thesis contribute to the further process understanding and opportunities of PAM printing as manufacturing process. Nevertheless, drawbacks of the current state of the technology are recognized as well. For the process, control strategy concepts are still lacking. Therefore, dosage forms are printed without knowing the resulting API content per single dosage form. Furthermore, inline process controls are also not introduced yet. Especially, control of the diameter of the single printed strands as well as the printed mass during the printing process would be highly interesting as process control strategy.

Original publications

Ilias El Aita, Jörg Breitkreutz, Julian Quodbach; On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing. Eur. J. Pharm. Biopharm.134, 29-36 (2019).

DOI: 10.1016/j.ejpb.2018.11.008

Ilias El Aita, Hanna Ponsar, Julian Quodbach; A Critical Review on 3D-printed Dosage Forms. Cur. Pharm. Des. 24 (42), 4957-4978 (2018).

DOI: 10.2174/1381612825666181206124206

Ilias El Aita, Jörg Breitkreutz, Julian Quodbach; Investigation of semi-solid formulations for 3D printing of drugs after prolonged storage to mimic real-life applications. Eur. J. Pharm. Sci. 146: 105266 (2020).

DOI: 10.1016/j.ejps.2020.105266

Ilias El Aita, Jhinuk Rahman, Jörg Breitkreutz, Julian Quodbach; 3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing, Eur. J. Pharm. Biopharm. 157: 59-65 (2020).

DOI: 10.1016/j.ejpb.2020.09.012

Contributions to meetings

Oral presentations

Ilias El Aita, Jörg Breitkreutz, Julian Quodbach; *Extrusion based 3D printing of immediate release levetiracetam tablet*s. 11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2018 Granada.

Ilias El Aita, Jhinuk Rahman, Jörg Breitkreutz, Julian Quodbach; Printing *Paediatric Dosage Forms Precisely: Layer by Layer*. 10th European Paediatric Formulation Initiative, 2018 London.

Ilias El Aita, Emrah Yildir, Jörg Breitkreutz, Julian Quodbach; *Production of Highly Drug-Loaded Orodispersible Films using Extrusion Based 3D printing.* 12th Central European Symposium on Pharmaceutical Technology and Regulatory Affairs, 2018 Szeged.

Poster presentations

Ilias El Aita, Bastian Hahn, Jörg Breitkreutz; *Extrusion of natural waxes: A new way for green and sustainable pharmacy.* 2th European Conference on Pharmaceutics, 2017 Krakow.

Ilias El Aita, Jörg Breitkreutz; *Development of 3D printable extrudates containing levetiracetam for paediatrics.* 9th European Paediatric Formulation Initiative, 2017 Warsaw.

Danksagung

Die vorliegende Arbeit entstand während meiner Zeit als wissenschaftlicher Mitarbeiter am Institut für Pharmazeutische Technologie und Biopharmazie der Heinrich-Heine-Universität Düsseldorf.

Meinem Doktorvater Prof. Jörg Breitkreutz danke ich herzlich für die Aufnahme in seinen Arbeitskreis, die Vergabe eines innovativen Promotionsthemas und seine Unterstützung und stete Diskussionsbereitschaft. Insbesondere Ihre kreative Herangehensweise an Fragestellungen hat mich persönlich geprägt. Zutiefst dankbar bin ich zu dem für die Ermöglichung zur Teilnahme an vielen verschiedenen Konferenzen, Symposien und Seminaren, welche sowohl fachlich als auch persönlich lehrreich waren.

Prof. Peter Kleinebudde danke ich sehr für die Übernahme des Korreferats sowie für kritischen Fragen und Denkanstöße während der Fokusgruppen und Doktoranden-vorträge, welche zum Gelingen der Arbeit beigetragen haben. Für Ihr stets offene Ohr möchte ich Ihnen ebenfalls danken.

Mein besonderer Dank gilt Dr. Julian Quodbach für die intensive und lehrreiche Betreuung während meiner Zeit am Institut. Deine stete Unterstützung und Ansprechbarkeit in allen Situationen haben wesentlich zum Gelingen der Arbeit beigetragen. Ich wünsche dir für deinen weiteren Weg maximalen Erfolg.

Bei Karin Matthée bedanke ich mich herzlichst für die Durchführung von unzähligen DSC Messungen und der Aufarbeitung der Ergebnisse. Genies deinen wohlverdienten Ruhestand.

Meine Zeit am Institut wird mir vor allem durch meine Weggefährten besonders in Erinnerung bleiben:

Bei Dr. Isabell Immohr, meiner ersten Bürokollegin, möchte ich mich für die schöne Zeit zu meiner Anfangsphase bedanken. Insbesondere für die Jogurt Pausen mit musikalischer Begleitung durch Andreas Gabalier. Dr. Haress Mangal, Dr. Simon Grote, Dr. Raphael Wiedey und Dr. Oscar Arndt danke ich für die Kulturreise nach Prag und die Unterstützung bei schweren Angelegenheiten.

Bei Ard Lura, Martin Müller, Bastian Hahn, Jhinuk Rahman, Dina Kottke und der gesamten U1-Truppe möchte ich mich für die schöne Zeit am Institut bedanken. Sowohl die wissenschaftlichen als auch insbesondere nicht-wissenschaftlichen Diskussionen werden mir immer in Erinnerung bleiben.

Mein besonderer Dank gilt Dr. Shirin Barimani und Dr. Roc Šibanc für die fortwährende Unterstützung und guten Ratschläge. Es freut mich sehr, dass all unsere Pläne bisher in Erfüllung gegangen sind.

Ala Fadel, Dr. Emrah Yildir und Muhammed Aybey, möchte ich für all die Reisen, lustigen Abende und der besonderen Freundschaft danken. Bei der Projects Truppe, Ala Fadel, Philip Kirstein, Mussa Aghili und Paul Baude, möchte ich mich für den Austausch und Diskussionen bedanken. Ich freue mich sehr auf unsere weiteren Projects.

Peter Limmer danke ich von ganzem Herzen für unsere jahrelange Freundschaft und der fortwährenden Unterstützung in allen Situationen.

Meiner Mutter Jamila El Gourari danke ich für ihr Vertrauen, Hilfsbereitschaft und stete Unterstützung. Mama, ohne dich wären Studium und Promotion nicht möglich gewesen. Danke für alles, ich liebe dich!

Meinen Geschwistern Mouhamed und Badr El Aita danke ich für die Unterstützung und Ablenkung während all der stressigen Zeit.

Zuletzt möchte ich meiner Ehefrau Souad El Machichi von ganzem Herzen danken. Du hast während der Promotionszeit meine Launen mit viel Geduld ertragen und mich immer unterstützt. Ich freue mich sehr auf die weiteren Herausforderungen des Lebens.

Eidesstattliche Versicherung

Ich versichere an Eides Statt, dass die vorliegende Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität in Düsseldorf“ verfasst worden ist.

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Ilias El Aita