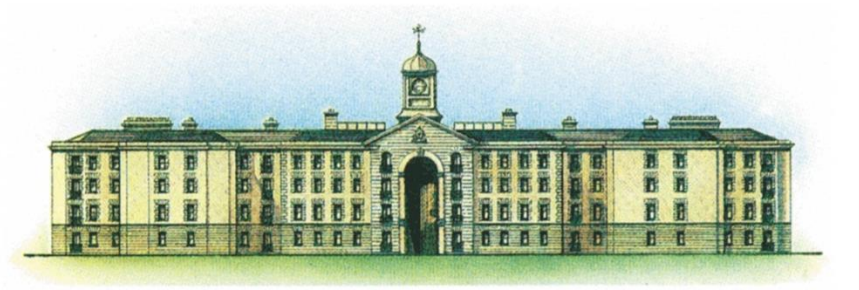

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Future of 3D Printing in commercial manufacturing of tablets in Europe

by

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A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR MSc IN PHARMCEUTICAL BUSINESS AND TECHNOLOGY (QQI)

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MAY 2023

CANDIDATE DECLARATION

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I hereby declare that the dissertation entitled "Future of 3D Printing in commercial manufacturing of tablets in Europe" submitted for the degree of MSc in

Pharmaceutical Business and Technology is a research work carried out by me, and that all sources used have been acknowledged by means of complete references.

SIGNED: MUHAMMAD RASHAD NAMBOORI KANDIYIL

DATE: 13th May 2023

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DATE: 13th May 2023

ABBREVIATIONS

3D Printing- Three-Dimensional Printing

AMCM- Additive Manufacturing Customized Machines

API- Active Pharmaceutical Ingredient

CAD- Computer Aided Design

CLIP- Continuous Liquid Interface Production

DC- Direct Compression

DoD- Drop-on-Drop

DoP- Drop-on-Powder

EU- European Union

SME- Small and Medium sized Enterprises

FDA- Food and Drug Administration

FDM- Fused Deposition Modelling

FDM- Fused Deposition Modelling

FFF- Fused Filament Fabrication

HME- Hot Melt Extrusion

IND- Investigational New Drug

MED- Melt Extrusion Deposition

PAM- Pressure Assisted Micro-syringes

SLA- Stereolithography Apparatus

SLS- Selective Layer Sintering

SODF- Solid Oral Dosage Form

PAT- Process Analytical Technology

PVA- Poly Vinyl Alcohol

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ABSTRACT

INTRODUCTION- The technology behind 3D printing has its roots in the layer-by-layer fabrication technique used to create three-dimensional (3D) structures directly from computer-aided design (CAD) drawings. 3D printing technology is extremely advanced and has recently come into its own as a flexible stage of technology. The study focuses on the future potential of 3D printing in the manufacturing of tablets. The study also focuses on the opinions and expectations of the people in the field of pharmaceutical manufacturing on the use of 3D printing in the commercial manufacturing of solid dosage forms

OBJECTIVE- To investigate the current state of 3D printing technology and its potential application in the commercial production of tablets, to evaluation of the costs, speed, scalability, quality and consistency of tablets manufactured by 3D printing technology, to identify key challenges to overcome in order to make 3D printing a viable commercial production method for tablets, to identify the advantages and disadvantages of 3D printing in commercial manufacturing of tablets, to propose a roadmap for the future of 3D printing in commercial production of tablets.

METHODOLOGY- The data was collected through surveys which collected information about the opinion and expectative of students, interns and people working on Pharma Oral Solid Dose Tablets manufacturing in Europe which was distributed through LinkedIn and other professional social networks. A structured questionnaire was prepared by means of google forms which included both open-ended and closed-ended questions and was sent to students, interns and people working in the field of pharmaceutical industry in Europe. The responses from primary research were compared with the secondary sources.

RESULTS- The result of the study was that the current state of 3D printing technology for manufacturing tablets in Europe is still in its early stages. The study also pointed out the benefits and challenges in using 3D printing technology for commercial production of tablets.

CHAPTER 1

1. Introduction

1.1. 3D Printing

The technology behind 3D printing has its roots in the layer-by-layer fabrication technique used to create three-dimensional (3D) structures directly from computer-aided design (CAD) drawings. 3D printing technology is extremely advanced and has recently come into its own as a flexible stage of technology. Companies who are aiming to increase their manufacturing efficiency can look forward to new chances and expect for many different possibilities as a result of this. The technology of 3D printing has the ability to reshape entire sectors and alter how manufacturing processes are organized. The implementation of the technology that allows for the printing of three-dimensional objects will result in an improvement in manufacturing speed while simultaneously lowering associated expenses. At the same time, there will be a greater influence of customer demand on the manufacturing of goods (Figure 1). Consumers have a bigger say in the final product, and they can ask for it to be manufactured according to their preferences and requirements. The production facilities can be positioned closer to the consumer which will make it possible for a manufacturing process that is more flexible and responsive, as well as for increased quality control (Shahrubudin *et al.*, 2019, P.1286,1287).

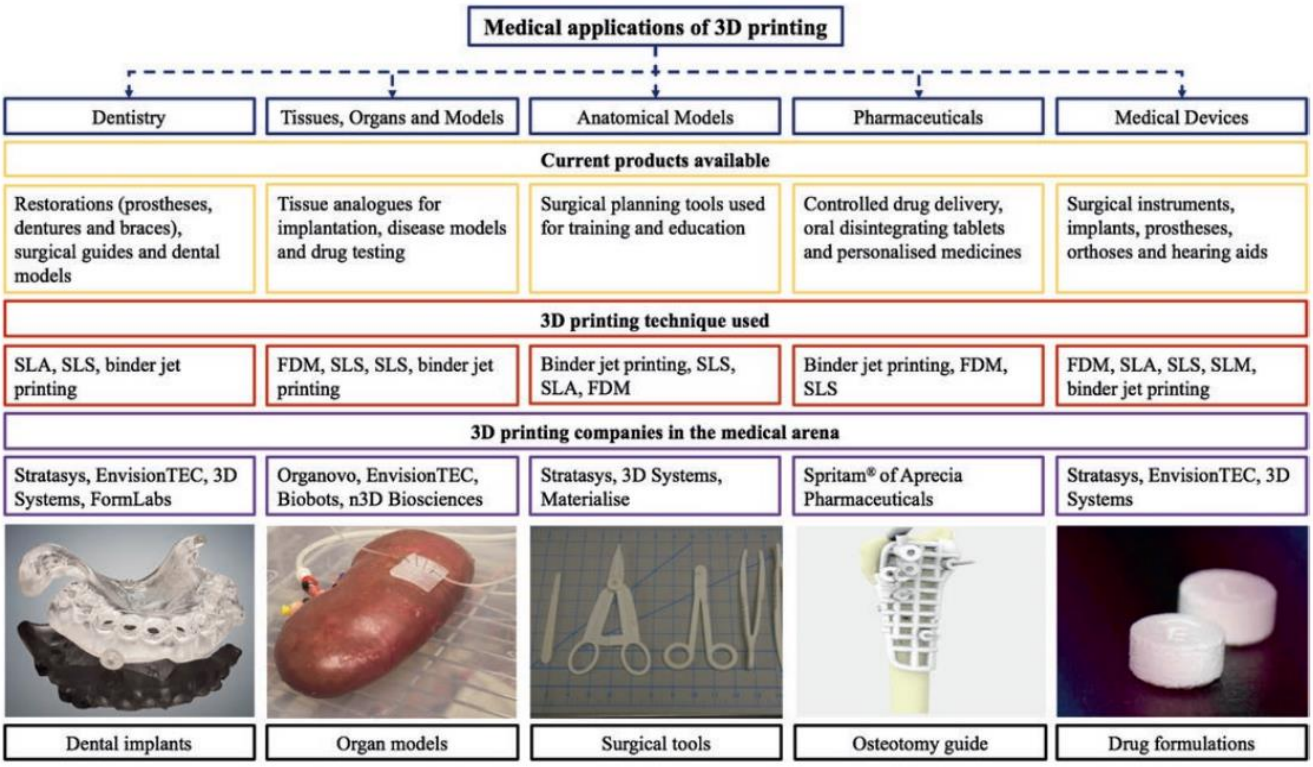

Figure 1. Applications of 3D printing in medicine, examples of products available, method of 3D printing manufacture and companies in the field (Trenfield et al.*, 2018, P. 4)*

This research is focusing on 3D printing technology because it has the potential in revolutionizing the manufacturing of tablets. It provides different design freedom as well as can reduce the time for new tablet models to reach the market. In contrast to conventional mass-manufacturing techniques like tableting and encapsulating, 3D printing allows for printing of dosage forms on demand and the personalization of pharmaceuticals to meet the needs of each patient. With 3D printing, various geometries, release properties, special dosages, and even a mixture of several medications, can be easily obtained and modified. 3D printing technology has the potential to improve the dosage accuracy and enable to create personalized medicines tailored to the needs of individual patients.

The discussion surrounding the possible future applications of 3D printing of medicines has already begun, with the primary attention being placed on the benefits and difficulties associated with each possible application. Locations where 3D printers can be installed include the patient's home, the pharmaceutical company, the community pharmacy, or the hospital pharmacy (Andreadis *et al.*, 2022, P. 1, 2).

Spritam® was the first and only FDA approved solid dosage form to be produced using the technique of 3D printing. It is a tablet containing levetiracetam, and it is prescribed to patients aged 4 years and older for the treatment of partial-onset seizures. It was produced by Aprecia Pharmaceuticals, a company based in the United States. For the creation of Spritam®, they utilized Zipdose technology, a n inkjet-based 3D printing method. It works by carefully arranging liquid drops and transferring them to a substrate. If the droplets are a binder solution, suspension, polymer, or other liquid used to bind the substrate together, the process is referred to as Drop-on-Powder (DoP) deposition. For the production of Spritam®, Aprecia Pharmaceuticals used the DoP deposition process (Souto *et al.*, 2019, P. 1044).

1.2. Personalized medicine and Orphan medications

It is also possible that 3D printing will cause a fundamental change in the production of medications. Even though they were developed more than 200 years ago, many of the production processes used in the pharmaceutical industry (such as direct compaction and encapsulation) are still in use today. In spite of the fact that these procedures save money when applied to production on a big scale, doing so might inevitably be time-consuming, labour-intensive, and restrictive in terms of dosage. It may be possible to shift away from a "one-size-fits-all" approach to allow for the personalization of medications through the use of novel creative technologies such as 3D printing, which could revolutionize the way tablets, also known as printlets (3D printed tablets) are manufactured (Trenfield *et al.*, 2018, p.3)

Orphan medications, which are intended for treatment of relatively limited number of patients but are typically not produced by the pharmaceutical companies for financial concerns also have significant promise for 3D printing technology. Traditional methods of manufacturing may be more expensive than using 3D printing to generate these pharmaceuticals on a small scale, but using this technology could help reduce overall production costs. The use of 3D printing makes it possible to create pharmaceuticals that are suited to the specific requirements of individual patients. Moreover, dosing may be more accurately calculated using this technology. The European Union has introduced the orphan drug legislation in the year 2000. When compared to US, the market exclusivity for the orphan drugs last longer in Europe, which is about 10 years compared to US which is 7 years. As the development program is being carried out, regulatory bodies will provide incentives in the form of free advice and reductions in the fees that must be paid. These incentives tend to favour small and medium-sized enterprises (also known as SMEs) in the EU, but they are periodically subject to review and revision. In US, tax credits as well as certain subsidies for clinical trials have also been provided for orphan drugs. As of 2014, there has been an approval of 78 orphan drugs in Europe. In addition to the incentives that were included in the initial legislation, there are now new regulatory channels that aid to accelerate the research and approval of medications for conditions where there is a medical need that is not currently being met (Hall and Carlson, 2014, P.1-4).dc

1.3. Comparison between 3D printing and traditional manufacturing method of tablets

When compared to the processing steps involved in traditional medicine manufacturing using direct compressions (DC) and 3D printing using fused deposition modelling (FDM) and pressure assisted micro-syringes (PAM), it is evident that direct compressions (DC) are considered to be the simplest method for the production of tablets. However, in order to make final products from raw materials like active pharmaceutical ingredients (APIs) and excipients, both FDM and PAM require the same amount of processing steps.

The additional benefits of using 3D printing include the fact that it requires a smaller footprint, that it can be managed remotely, and that it is not only suitable for use with small batches of material but also allows for the production of individual pills within a single batch of materials. This is especially helpful in the field of personalized medicine, which allows for the unique doses of pharmaceuticals to be tailored to the exact requirements of a patient. When pharmaceuticals can be manufactured on demand, there is less of a need for large-scale storage facilities, and there is also less of a chance that there will be a shortage of drugs.

However, in order for 3D printing to become a practical option for the production of pharmaceuticals, ingredients for starting formulations that are both stable and reproducible will need to be given. This is quite similar to the requirements for DC processing, in which the beginning materials need to be of a high quality and purity in order to assure that the tablet manufacturing will be consistent and reliable (Figure 2).

In addition, the utilization of 3D printing in the production of pharmaceuticals is still in its infancy, and there are a number of obstacles that need to be overcome before this method can become widely utilized. For instance, the regulatory framework that will apply to pharmaceuticals that have been created using a 3D printer needs to be developed, and the scalability of the process needs to be proved.

In general, the use of 3D printing in the pharmaceutical industry has the potential to completely transform the industry by opening the door to the development of individualized medicine, lowering the risk of drug shortages, and raising production rates. However, additional research and development will be required before the potential of this technology can be completely realized for use in the pharmaceutical industry (Azad *et al.*, 2020, P.5,6).

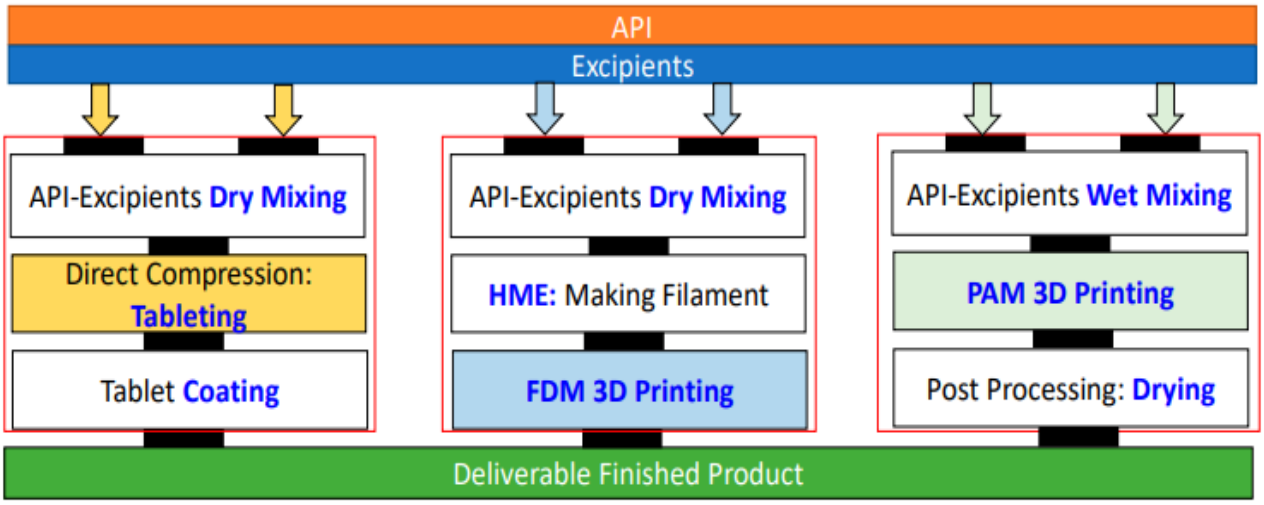

Figure 2. Comparison of direct compression and FDM/PAM (Azad et al.*, 2020, P.6)*

1.4. Research Purpose

There hasn't been a lot of research done on using 3D printing in the commercial production of tablets in Europe, which is surprising given the potential benefits of doing so. As a result, the purpose of this study is to minimise the existing knowledge gap by investigating the viability and potential of 3D printing in solid

oral dose manufacturing, as well as the challenges and possibilities that exists. The research will also improve the understanding of the possible advantages and disadvantages of using 3D printing in the manufacturing of medicines, which will help pharmaceutical companies and regulatory bodies to make better decisions. This research has the potential to pave the way for the adoption of 3D printing in the commercial production of tablets in Europe, which will ultimately lead to improved patient outcomes and cost savings for the industry.

1.5. Research Objectives

1) Investigate the current state of 3D printing technology and its potential application in the commercial production of tablets in Europe.
2) Evaluation of the costs, speed, scalability, quality and consistency of tablets manufactured by 3D printing technology.
3) Identify key challenges to overcome in order to make 3D printing a viable commercial production method for tablets.
4) Identify the advantages and disadvantages of 3D printing in commercial manufacturing of tablets.
5) Propose a roadmap for the future of 3D printing in commercial production of tablets.

CHAPTER 2

2. Literature Review

3D printing is the manufacturing of three-dimensional objects from digital designs. More than three decades ago, researchers in the fields of chemistry, optics, and robotics came together to develop this technique in order to make the process of making prototypes from ultra violet-cured resins more efficient. The automotive, aeronautical and consumer goods industries soon adapted the 3D printing technology in their manufacturing (Norman *et al.*, 2017, P.40). The overcoming of basic barriers in the interface between humans and machines will have a significant impact on the fourth industrial revolution, also known as Industry 4.0. As part of this revolution, 3D printing is anticipated to play a crucial role in the production and mass customisation of highly complicated and personalized items (Andreadis *et al.*, 2022, P.1). Despite the fact that 3D printing technology has been used to produce more than 150 FDA-approved medical devices over the past decade, the application of this technology to the production of pharmaceuticals is still in its infancy. However, with the approval of the first 3D printed pharmaceutical, Spiritam®, this is beginning to change. The United States Food and Drug Administration (USFDA) has made significant progress in the field of 3D-printed medications (Khatri *et al.*, 2018,P.154).

3D printing is widely used in the pharmaceutical industry mainly for the manufacturing of pharmaceutical products such as medical devices as well as dosage forms. Currently 3D printing has a very less impact on the tablet manufacturing. Even though lot of research is going on, not many solid oral dosage forms have been approved for marketing. Some of the possible advantages that various types of 3D printing technologies can offer have already begun to be recognized by the healthcare industry. This technology has the potential to completely transform the industry because of its capacity to produce creative solid oral dosage forms with more complicated forms and shapes that exhibit distinctive release profiles. The most intriguing component of this technology, however, is the small-scale local fabrication of personalized dosage formulations, in which pharmacists will have a crucial role (Souto *et al.*, 2019, P.1044).

2.1. 3D Printing technologies for solid oral dosage manufacturing

Different 3D printing technologies are currently available which can be used for tablet manufacturing are available such as stereolithographic, powder based, fused deposition modelling and semi-solid extrusion 3D printing technologies. With numerous patent applications and some products which are approved for marketing that has received FDA approval, powder-based 3D printing technologies have advanced. The last two years have also seen the emergence of fused deposition modelling and semi-solid extrusion, demonstrating a very good future for personalized dosing. Still these technologies are in their early stages of

research and development and they require more research to be completely understood (Alhnan *et al.*, 2016, P. 6-10, 18).

Laser-based printing**:** One of the earliest methods of three-dimensional printing, known as the Stereolithography Apparatus (SLA), is also one of the most popular (Figure. 3(A)). The formation of three-dimensional objects is accomplished through the application of radiation as a catalyst for the polymerization of photosensitive substances. A layer of solid resin is produced by scanning the surface of a photopolymerizable liquid polymer plastic resin with an ultraviolet light emitter that is controlled digitally. This results in the formation of a layer that is then lowered to the same depth as the layer that was produced earlier. While the subsequent layer is being cured, the surface of the layer that was created before it is simultaneously subjected to over-curing, which fuses the two layers together. Repeating this technique will result in the desired design being created. SLA 3D printing results in items that are accurate and precise, but the materials that are employed in the process are limited and often carcinogenic, which makes them inappropriate for use in the production of SODFs.

Continuous Liquid Interface Production (CLIP) is another laser-based printing system; it is a version of the SLA 3D printing technique. It can print at a much faster rate, has a greater resolution, and does not require any changes on the level of micrometres in the fluid height while it is being processed. This is due to the fact that polymerization occurs continuously throughout this process. As a result, it is now possible to produce structures without having to construct them one layer at a time.

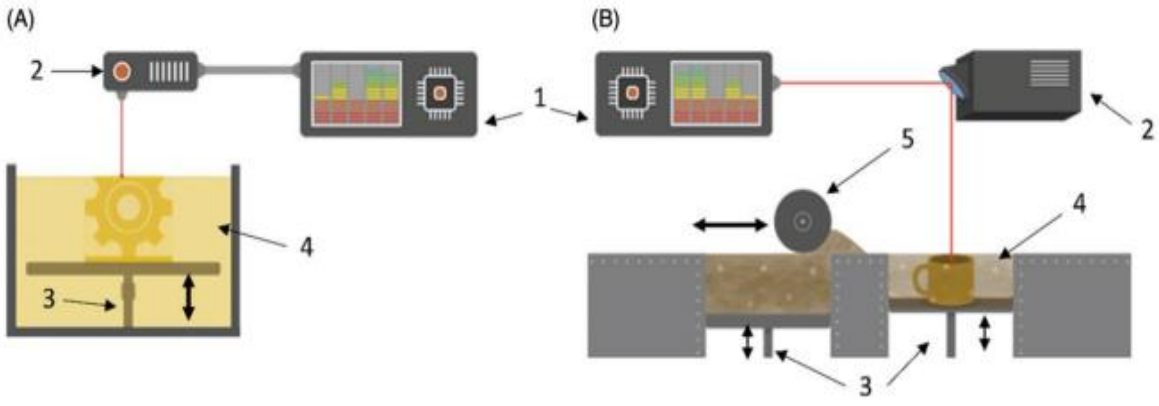

Figure 3: (A) Stereolithography apparatus (SLA) and (B) selective layer sintering 3D printing process (1, laser source; 2, scanner; 3, piston mechanism; 4, raw material (A – liquid resin; B – powder); 5, roller). (Souto et al.*, 2019,P.1045)*

In selective layer sintering, often known as SLS 3D printing, a powder bed is utilized as the starting material rather than a liquid polymer, as is the case with stereolithography additive manufacturing, or SLA (Figure. 3(B)). In order to form three-dimensional structures, these powders must first be liquefied before being fused

together with the help of a laser. Yet, this technology is utilized most frequently in the manufacturing of three-dimensional metal structures. Aside from the creation of medical equipment, the majority of pharmaceutical applications do not make use of this technology.

SLA 3D printing has been used to construct implantable devices and hydrogels, but its most potential area is in the manufacturing of micro-structures such as micro-needles, which are difficult to generate using conventional 3D printing processes. These micro-needles are employed in medical applications. SLA 3D printing, on the other hand, results in materials that are brittle and glassy due to the nature of the technique and the limited availability of materials that are acceptable for use (Melchels *et al.*, 2010, P.6124), (Souto *et al.*, 2019, P. 1045).

Inkjet-based printing: In this type of 3D printing method, the liquid droplets are placed on to a substrate in a proper way. Based on the type of droplets the system is called Drop-on-Drop deposition, DoD(if droplets are actual building material) and Drop-on-Powder deposition, DoP(if droplets are some solution or suspension or polymer which is used to adhere the substrates) (Figure. 4(A)) (Dimitrov *et al.*, 2006, P.136). DoD deposition includes putting liquid droplets onto a substrate in an orderly manner. This process is known as "drop-on-drop" (DOD) deposition (Figure. 4(B)). The droplets themselves act as the construction material, and the end product is constructed, layer by layer, from the bottom up. DoP deposition, on the other hand, requires the utilization of a binder polymer, solution or suspension which is sprayed upon a powder bed or with a powder jetting method in order to hold the substrate together. This is done in order to get the desired cohesiveness. As the technique underpinning the first FDA-approved 3D-printed solid oral dosage form, Aprecia's Spritam, DoP is widely regarded as the major 3D printing technology utilized for pharmaceutical manufacture (Norman et al., 2016, P.1046).

In most cases, the binder solution is sprayed into the powder bed using an inkjet printer, and this takes place as the substrate platform is moving downward and making space for the next layer. A levelling roller is used to add more powder to the powder bed, and this process is repeated as many times as necessary until the end product is completely created. APIs can be incorporated into the liquid that is used as a binder or into the powder that makes up the powder bed. Both of these forms are known as powder beds.

DoP is widely regarded as the principal 3D printing technique utilized in the production of pharmaceuticals. This is due to the fact that it enables pharmaceutical formulators to simply migrate from conventional production methods to 3D printing. The fact that many of these materials are currently in use in the creation

of solid oral dosage forms, this technique is one of the most significant advantages of utilizing this technology.

Items made with DoP have a high porosity and friability, both of which are physical characteristics that strongly connect to the dissolving profiles of SODF. Nevertheless, it is possible to exert some influence over these characteristics during production. For example, the thickness of each layer can be optimized, and the flow rate of the binder ink and the speed of the printer's head can be adjusted accordingly.

DoD is quite similar to DoP; however, rather than printing on a powder bed, the beginning materials that are used in the printing process are the same components that make up the structure of the building. The droplet is subjected to a thermal stimulus after it has been jetted through the print head. This causes the solvent to evaporate, which results in the droplet becoming solid and allowing it to function as a support for the subsequent droplet that will be jetted. This method of manufacturing is more difficult than DoP since it is essential to manage droplet size by regulating the rheological behaviour of the liquid, as well as the entire droplet travel pathway and ejection condition. This is done in order to achieve the best possible results.

However, due to the fact that droplets in DoD procedures have a diameter of approximately 100 millimetres, the objects that are formed using this technology have a significantly greater resolution than those that are produced by DoP processes. This results in layers that are even thinner than this as a result of surface wetting, the evaporation of the solvent, or shrinkage (Souto *et al.*, 2019,P.1045-1046), (Daly *et al.*, 2015,P.7)

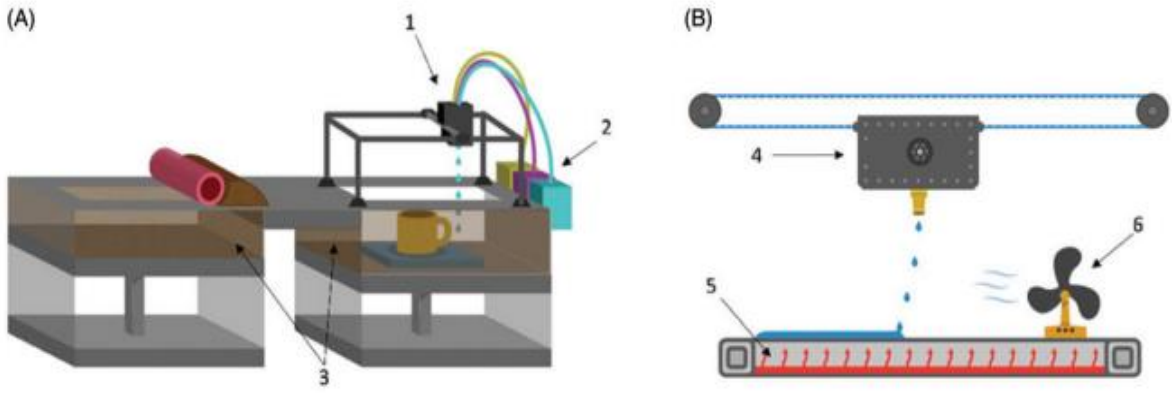

Figure 4 (A) Drop-on-powder (DoP) and (B) Drop-on-drop (DoD) (1, printer head and control; 2, inkjet feeders; 3, powder; 4, optical sensor and position adjuster; 5, heat source; 6, blower) (Souto et al.*, 2019,P.1046)*

The capacity to manufacture customised dosage forms with precise release profiles is the primary benefit that comes from using 3D printing in the pharmaceutical manufacturing industry. It is not possible to construct complicated forms and geometries using standard manufacturing methods, but 3D printing makes this

possible, enabling for more accurate dosing and more focused medication administration. (Alhnan *et al.*, 2016, P.6)

Extrusion-based printing: Because of their adaptability and ease of use, printing techniques that are based on extrusion have become the most popular approach for 3D printing. These methods make use of a nozzle from which semi-solid material is ejected, and they deposit layers of material in successive layers so that structures can be built from the bottom up. The need for a heating or melting stage in order to liquify the material that is going to be extruded classifies these systems as either Pressure-Assisted Micro syringes (PAM) Printing Systems or as Fused Filament Fabrication (FFF).

PAM printing methods utilize a pressurised air piston to extrude semi-solid materials (Figure 7). The printed object hardens upon exposure to light or drying, depending on the technology. However, this method has a poor resolution and necessitates the use of solvents to facilitate layer-to-layer adherence after evaporating. Solvents can be hazardous and may interfere with the stability of active pharmaceutical ingredients throughout the manufacturing process or after they have been dried. Also, drying temperatures in PAM printing systems are never as high as the temperatures employed in FFF procedures, which means that the risk of API degradation caused by temperature is far smaller.

The FFF printing method (also known as fused deposition modelling) is a typical type of printing technology that is based on extrusion and enables the creation of personalized oral dosage forms through the deposition of thin material layers (Figure. 5 and 6). This technique makes use of thermoplastic starting materials in the form of solid filaments. These filaments are forced into the print head by a gear system, where they melt or softens before the extrusion, and then they immediately solidify upon being deposited. The rheological characteristics of the substance that is going to be extruded are extremely important and need to be examined before the extrusion process begins. This analysis must also include other factors such as the diameter of

nozzle, feed rate, speed of print-head and nozzle temperature.

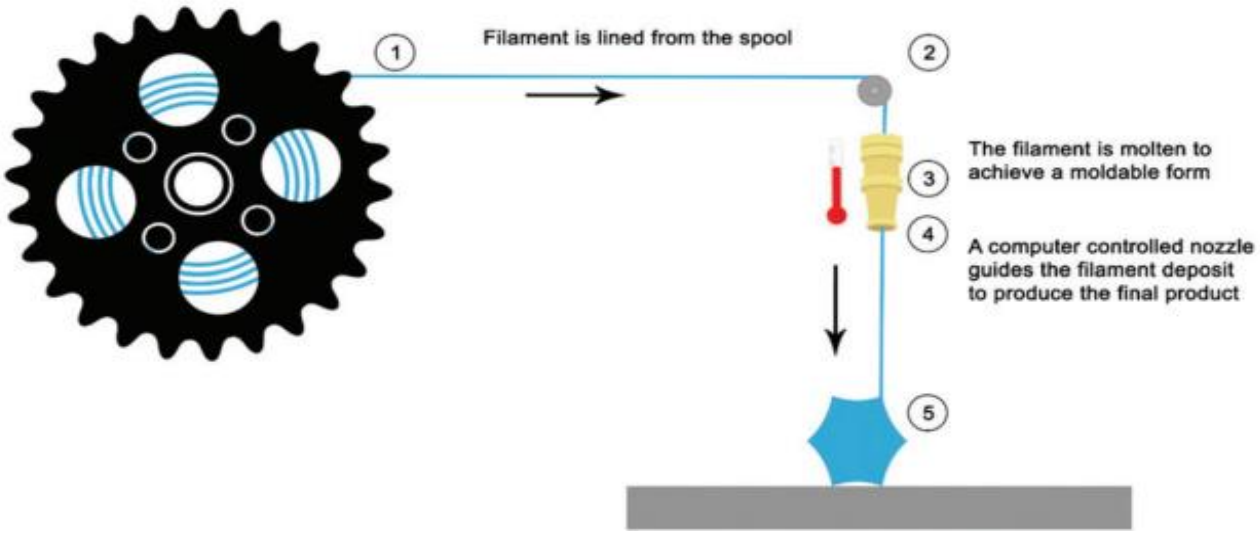

Figure 5Fused filament fabrication printing process. (1, filament; 2, roller; 3, heat extrusion head; 4, nozzle; 5, solidified final product) (Souto et al.*, 2019,P.1047)*

According to the findings of a number of studies, Fused Deposition Modelling (FDM) can be successfully utilized in the production of SODFs. For use in pharmaceutical formulations, the filaments that are chosen have to be loaded with active pharmaceutical ingredient (API) or reprocessed via hot melt extrusion (HME) in order to integrate it. However, the influence on the rheological characteristics of the filaments is magnified to the extent that the concentration of API increases. This may result in a reduction in the quality of the extrusion process. Impregnation frequently makes use of organic solvents, which can be dangerous and are notoriously difficult to eliminate. Moreover, because the rates of drug loading in impregnation techniques are often low, this method can only be used to produce low-dosage versions of the drug. Its simplicity and versatility, as well as the inexpensive cost of the equipment that is required, are three of its advantages when compared to other printing techniques. Another advantage is the greater choice of starting materials that may be used in extrusion processes (Goole and Amighi, 2016, P.23-26).

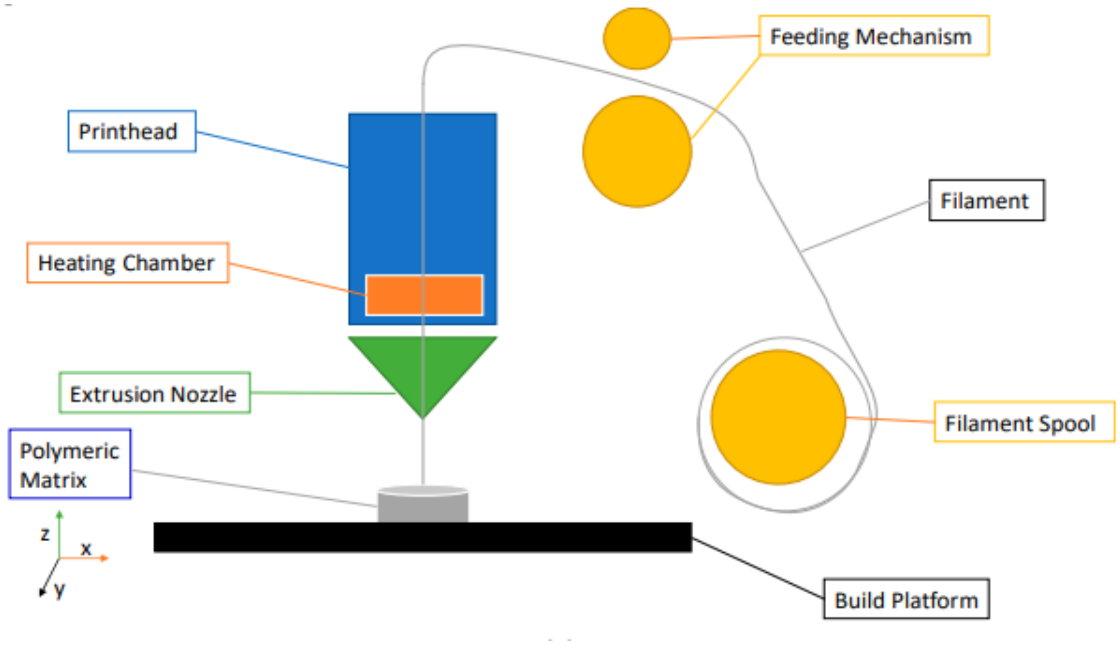

Figure 6. Fused Deposition Modelling (Azad et al.*, 2020, P. 4)*

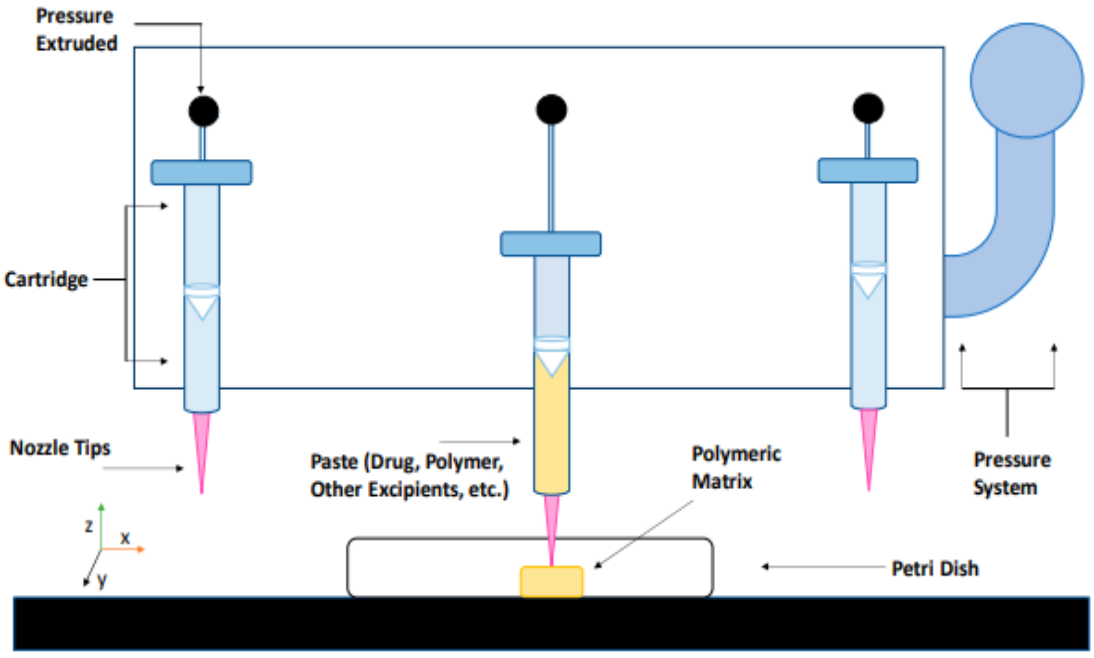

Figure 7. Pressure Assisted Micro-Syringe (Azad et al.*, 2020, P. 4)*

Technology	FDM 3D Printing	PAM 3D Printing
Advantages	• Low-cost printing technology. • No post-processing is required. • Better drug uniformity.	○ Works at room temperature. ○ High drug loading is achieved. ○ Suitable for multi-drug pill (polypill) printing.
Limitations	• High-temperature processing is required which is not suitable for thermally labile drugs. • Pre-processing steps of filament making are required. • Lack of suitable biocompatible/biodegradable thermoplastic polymers. • Active pharmaceutical ingredient (API) degradation may occur due to the high processing temperature.	○ Post-processing, drying, is required. ○ Polymer rheological properties impact on structure formation and printing process. ○ Printing resolution is depended on nozzle size. ○ Toxicity and drug instability may occur due to the usage of organic solvents.

Table 1. Comparison between FDM and PAM (Azad et al.*, 2020, P. 5)*

With the use of 3D printing, Smith et al. created polyvinyl alcohol (PVA) capsule shells, which were then either filled with a solid vehicle or a liquid vehicle containing the API (Smith *et al.*, 2018, P. 7). They were able to vary the induction time of a delayed release rate by altering the wall thicknesses of the printed capsules, which made the technology usable for diverse sections of the gastrointestinal system. In a separate line of research, a filament extruder was utilized to make PVA filaments suitable for 3D printing that contained either caffeine or paracetamol. The release profiles of the caplets, which were manufactured using the filaments and intended for oral delivery, were determined by the solubility of the drug as well as the drug loading. Because of the porous nature of the caplets, it was not possible to accurately forecast different drug release profiles (Smith *et al.*, 2018, P. 19).

In pharmaceutical uses, the success of printing systems that are based on extrusion is dependent on a number of factors. These factors include the rheological characteristics of the substance that is going to be extruded, the amount of API, and the requirement for upstream processing, in addition to the requirement for slow printing speed and the requirement for heating the filaments. Besides all of these limitations, printing systems that are based on extrusion offer a number of advantages over other printing systems. These advantages include a wider selection of starting materials that can be used in extrusion methods, as well as its simplicity, versatility, and low cost in terms of the equipment that is required (Souto *et al.*, 2019, P.1046).

2.2. Advantages and disadvantages

3D printing technology can have a lot of advantages such as manufacturing of personalized medicines and the options of adding more than one active pharmaceutical ingredient into a single tablet, etc. Apart from

these advantages, there are a number of disadvantages which has to be noted while choosing the 3D printing technology in the commercial manufacture of tablets (Pravin and Sudhir, 2018, P.147).

Advantages:

- Manufacturing of tablets on demand: Using technology such as 3D printing, it is possible to quickly and easily fabricate high-quality products in a matter of minutes. On-demand manufacturing through the use of 3D printing can be particularly helpful in circumstances in which both time and resources are in short supply, in drug research for the purpose of more rapid optimization, and in the creation of therapeutic products that have poor stability. Because desktop printers are so readily available, this is now much more feasible. Already, there are studies on the printing of low-stability pharmaceuticals using inkjet printers, and the utilization of 3D printing for the creation of low-stability drugs has been suggested.
- The idea of making medicines fit the needs, tastes, and other traits of each patient has been going on for a long time, but diagnostics have only recently made it possible. Adjusting the amount of medicine, a person takes can be especially helpful in children, where weight and age can vary a lot. Personalizing medicine with 3D printing can make it easier to manage and lower the number of people who don't take their medicine because they have more than one prescription.
- Flexibility in dosage: Polypharmacy is an everyday issue among older people, and it has been linked to harmful things like side effects, conflicts, and not taking medications as prescribed. Research has shown that people who take more than four medications are less likely to take their medicines as prescribed by 35%. Personalization and dose tweaking can make it less likely that a patient won't take their medicine as prescribed by letting doses and combinations be changed to meet the needs of each patient. With this method, things like weight, age, pharmacogenetics, and metabolism can be taken into account. People over 65 who live in their own homes have non-adherence rates that range from 43% to 100%. Complicated drug schedules are one reason for this. In such cases, mixing various active ingredients and/or dosages into just one formulation (to produce customized "polypills") may increase drug adherence and decrease administration errors (Trenfield *et al.*, 2018, P. 6).

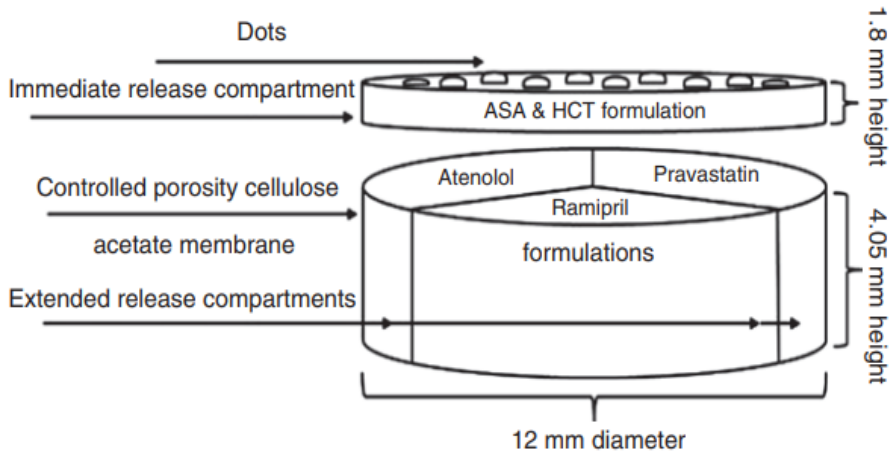

Figure 8. 3D printed polypill containing 5 different drugs with different release profiles (Trenfield et al.*, 2018, P. 6)*

- Increase in quality of dosage forms: When it comes to the 3D printing of tablets, utilizing CAD and desktop printers can help enhance control of the many factors, which in turn results in improved reproducibility. When compared to traditional processes, 3D printing requires a significantly lower number of processing steps. As a result, the chance of a batch failing owing to potential faults in many steps, such as granulating, milling, compressing, coating, and drying is significantly reduced.
- Flexibility in tablet design: Moulds are used in traditional techniques of drug manufacture, but 3D printing makes it possible to create novel product designs. Traditional drug manufacturing methods establish the shape of tablets and capsules using moulds. 3D printing makes it possible to exercise control over the distribution of active ingredients and excipients as well as the inclusion of more than one medicine. The characteristics of a dosage form can have a significant impact on the rate at which a drug is released into the body. For example, the formulation of a dosage form with a porous structure can speed up the rate at which the drug disintegrates. Additionally, 3D printing enables the customization of flavors, colors, and shapes for a variety of patient populations, such as those who have difficulty swallowing, geriatric patients, and pediatric patients (Okafor-Muo *et al.*, 2020,P.19-20)

Figure 9. Range of shapes and sizes of 3D printed tablets (Trenfield et al.*, 2018, P. 8)*

Disadvantages:

Some of the disadvantages of the implementation of 3D printing in tablet manufacturing are that the 3D printed tablets can have rough or uneven surfaces due to the removing of support materials from fused deposition modelling or the porous structure from stereolithographic printers. Patients might find these tablets less attractive which can cause decrease in patient compliance. Moreover, some of the processes for 3D printing. Such as stereolithography, entail the use of materials that may or may not pose undiscovered concerns to human health there are some probable carcinogenic concerns in the majority of authorized polymer resins and photopolymerization initiators. Also, when printing rapid dissolving tablets using the PB printing technology, the mechanical strength of the printed tablet is compromised, resulting in high friability and poor hardness (Okafor-Muo *et al.*, 2020, P.28-29). Even though, Spritam was manufactured utilizing DoP, and its high porosity offered this formulation a competitive advantage over other fast-disintegrating tablets. Powder-based technologies also have weak mechanical strength. When it comes to the potential benefits and drawbacks of bringing 3D printing technology to the pharmaceutical sector, excipients play a key role in both categories. The formulation that is selected for an excipient determines the final product's ability to develop a certain morphology, mechanical and rheological characteristics, plasticity, and a quickly dissolving dosage with a rapid release profile, all of which have an impact on the product's overall effectiveness. In order to achieve the intended result more effectively, the formulations in question can include sugar-based bulking agents, lubricants, or disintegrants (Souto *et al.*, 2019,P.1050).

Even though there have been many studies related to the types of 3D printing technologies and their use in the manufacturing of solid oral dosage forms, there has been limited researches on the comparison of quality,

cost, scalability and consistency of 3D printed solid oral dosage forms with traditionally manufactured ones. The existing 3D printing methods which are approved and are also in trial still have certain limitations which makes it difficult to implement in the manufacturing of solid oral dosage form. So, identification of certain 3D printing techniques and selection of the one with least limitation for the purpose of manufacturing tablets using 3D printing can be done. Also, identification of challenges in the implementing of 3D printing in the tablet manufacturing is an area for further research.

2.3. Studies on pharmaceutical firms personalizing treatments with 3D printing

Aprecia Pharmaceuticals: Spritam®

The first and only solid dosage form manufactured by the method of 3D printing was Spritam®. It is a levetiracetam tablet, which is intended for the treatment of partial-onset seizures in patients of 4 years and elder. Spritam® can also be prescribed in combination with other medications for treating myoclonic seizures in patients of 12 years and elder with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures in patients 6 years and older with specific kinds of generalised epilepsy (Spritam, 2022). This dosage form was manufactured by **Aprecia Pharmaceuticals** which is based in United States. 3D inkjet printing typically results in tablets which are more porous and consequently more fragile than those produced via compression. This increase in porosity is linked to insufficient contact with the printed binder solution, resulting in unbound particle regions. Aprecia Pharmaceuticals made use of this increase in porosity to develop orodispersible solid dosage forms which can dissolve in about ten seconds in extremely small quantities of water i.e., 15 ml or lesser. This is a fast-acting tablet which have a rapid dissolution and hence Tmax can be reached in about nine minutes (Prasad and Smyth, 2016, P.1024). Aprecia Pharmaceuticals used the Zipdose technology for the manufacturing of Spritam®. Zipdose technology is an inkjet- based 3D printing technology. Inkjet-based 3d printing works by properly organizing liquid drops and applying them to a substrate. The system is known as Drop-on-Powder (DoP) deposition if the droplets are a binder solution, suspension, polymer, or other liquid used to attach the substrate together. Aprecia Pharmaceuticals have used the DoP deposition method for Spritam® manufacturing (Souto *et al.*, 2019, P.1045) (Aprecia, 2022)

FabRx

FabRx is a start-up company by leading researchers from University College London who came together with a shared interest in the field of 3D printing as it relates to the creation of improved pharmaceuticals. They have invented the first 3D printer in the world, which can be used for personalised medicine called **Medimaker**. It consists of a smooth hardware system, which helps in the printing with multiple nozzles.

Special softwares controls the system which helps pharmacist to select the correct dose as prescribed by the doctor. To make sure that only qualified people are having access to the technology, a fingerprint access and data matrix is incorporated to the technology. Features of medimaker is that it is user-friendly, has multiple nozzles for printing, suitable for in0line quality control and affordable cost.

FabRx also uses the methods such as fused deposition modelling, direct powder extrusion, selective laser sintering and stereolithography for manufacturing tablets. **Fused deposition modelling** uses a nozzle to deposit melted drug and excipient mixtures onto a build plate in order to manufacture a dosage form layer by layer. **Direct powder extrusion** extrudes the powdered drug using a single screw extruder. This helps in manufacturing of delayed release dosage forms. **Selective laser sintering** converts powdered materials to solid parts. Different characteristic tablets can be manufactured using this method. **Stereolithographic** is the method of converting liquid materials into solid parts. Drugs can be incorporated into polymer network to manufacture drug-loaded tablets (FabRX, 2022). Their technology is being used to print personalized dosage forms for children with maple syrup urine disease which is a rare metabolic disorder. The treatment for this illness have to be personalized based on the age, weight and amino acid isoleucine concentration in blood. This can help to save money and time for caregivers (Ibrahim, 2022).

Triastek

Triastek, a Chinese pharmaceutical and 3D printing technology company, got IND approval from FDA for its first 3D-printed medicine product, T19. It can be produced in-house to treat rheumatoid arthritis, an inflammatory condition that causes stiff and swollen joints by attacking joint cells. They used Melt Extrusion Deposition (MED) technology for their product. Using digital design of pharmaceutical dosage form and automated intelligent manufacturing, Triastek's MED 3D printing technology platform enables the production of tablets with complex geometries and internal geometric structures. These structures permit precise control and adjustment of the onset time, duration, and mode of drug delivery, resulting in greater predictability and reproducibility of drug delivery outcomes. In order to maintain product quality and facilitate regulatory monitoring, the company has also integrated real-time PAT into the MED system. This can continuously monitor the 3D printing process (Everett, 2021).

GlaxoSmithKline

GlaxoSmithKline based in UK was another big pharmaceutical company which showed interest in manufacturing solid dosage forms using 3D printing technology. GSK collaborated with the University of Nottingham to investigate the effectiveness of 3D inkjet printing and UV curing to create solid drug forms. In

2017, researchers successfully printed tablets of the Parkinson's drug ropinirole using this method (Ibrahim, 2022).

Merck

Merck, a global pharmaceutical company has revealed plans to collaborate with AMCM (Additive Manufacturing Customized Machines), a member of the EOS Group, to create 3D printed tablets first for clinical trials and then for mass production. In the meantime, semi-solid extrusion 3D printing has been investigated as a coating method for personalizing the release rate of patient-specific medications, and 3D printing has been utilized to optimize the controlled dosage of antibiotic tablets in research settings (Harangozó, 2020)

2.4. ZipDose Technology

Aprecia's formulation technology that is associated with orodispersible dosage forms is referred to by its brand name, ZipDose technology. The name does not relate to the manufacturing method or the machines used; rather, it is aimed toward the group of formulations that are produced as a result of the manufacturing process. The ZipDose technology was first implemented in the production of a commercial product called SPRITAM. The ability of ZipDose formulations to accommodate huge quantities of their target ingredient while yet keeping the ability to disintegrate in the mouth in a matter of seconds is one of the primary points of differentiation between them and other delivery systems. To this point, a dosage loading of one thousand milligrams has been shown in commercial settings. The technology is suitable with well-established methods for masking tastes. These methods include directly masking tastes with flavours and sweeteners, creating physical barriers with coating or encapsulation, and chemically complexing tastes with ion exchange resins, cyclodextrins, or other similar substances. As accommodation of vast quantities of material is possible, there is a greater ability to use these strategies for taste-masking while yet keeping the capability of quick disintegration.

The 3D printing method developed by Aprecia makes use of both powder and liquid ingredients. It was created for the direct production of practical parts, such as oral medications, that are in accordance with cGMPs. The machine design method includes a centralized production strategy, and 3D printing is viewed as a new unit operation for creating unit doses from mass amount of beginning materials. Moreover, the machine design approach utilizes a computer-aided design (CAD) system. Aprecia designed and developed original and patented 3D printing equipment that are tailored specifically for pharmaceutical processing in order to attain a production rate that was sufficient for the company's needs. It's possible that these machines

could be useful in a variety of other fields as well. When compared to legacy systems, the throughput that can be achieved with Aprecia's machinery is significantly higher. This makes it ideal for use in the production of differentiated premium goods, for which the additional cost of manufacturing parts in a layer-by-layer fashion is justified by the additional functionality that can be achieved with 3D printing (West and Bradbury, 2019, P. 56-60)

Pharmaceutical process of 3D Printing (Zipdose Technology): Oral solid dosage medications are manufactured using a similar procedure as traditional production, with the exception that 3D printing takes the role of tableting. Powder mixtures for 3D printing can be created using a variety of techniques, such as dry blending, dry granulation, or wet granulation. Agglomerates may also need to be removed using milling and screening. In contrast to conventional tablets, 3D printed parts are generated in porous and uncompressed forms and are physically and functionally unique.

The printer prints exact positions of each layer with pre-programmed patterns of printing fluid on top of a base of dry powder layers to produce unit dosages. Until the unit dosages are built to the full height required by the product's established parameters, this process is repeated. The drying process is then applied to the wet unit dosages, with the temperature, humidity, and time parameters being set for each product. The production of "3D" unitary shapes is an end result of this process, which causes the layers of wet powder to bond together both vertically and horizontally in the printed zones.

The wet unit dosages are separated from the surrounding unprinted powder once printing and drying are finished. Then, the powder that wasn't produced is collected and put back into the powder input stream for later 3D printing. Before being blister packed, the collected pieces are first piled in trays and dedusted with filtered compressed air. Individual units are placed into blister cavities using vacuum pick-and-place capability. (West and Bradbury, 2019, P. 60-65), (Aprecia, 2022).

2.5. Regulatory environment for commercial production of 3D printed tablets

International Council for Harmonization: The International Council for Harmonization (ICH) has been working toward the goal of achieving a broader worldwide harmonization on the scientific and technical foundations of drug registration. The Multidisciplinary guideline, along with the other three ICH guidelines and their guiding principles-Quality, Safety, and Efficacy can be applied in an equivalent manner to the 3D printing technology for use with medicinal products. With regard to Quality, the ICH encourages the advancement of regulatory science and innovation in favour of a cleaner, more flexible, and more productive manufacturing of pharmaceutical products. This is achieved by promoting industries to implement

new technologies as supported by “ICH Q8 (R2), Q9, Q10, and Q11, along with science and risk-based approaches to ensure product quality”. All other CMC (chemistry, manufacturing, and control) components of a drug product that has been 3D printed, such as stability, impurities, drug substances and drug product specifications, and good manufacturing practice (GMP), can still adhere to the ICH principles that are stated in “Q1, Q2, Q3, Q6, and Q7” (Khairuzzaman, 2018, P. 217, 218).

European regulations: The European Medicines Agency (EMA) is in charge of ensuring that pharmaceutical goods in the European Union adhere to all applicable regulations. When it comes to APIs, manufacturing, impurities, specifications (analytical process and validations), excipients, packing, stability, pharmaceutical development, and special types of products as well as lifecycle management, the EMA quality guidelines provide very extensive instructions. For any medicinal products that are 3D printed, the basic principles of all of these quality characteristics can be similarly applied, along with extra features that are unique to the 3D printed products (Khairuzzaman, 2018, P. 218).

Regulatory considerations for 3D printing of oral dosage forms

It may be difficult to implement appropriate regulations for the use of 3D printers in the production of solid oral dosage forms. For instance, if the printer is located at a clinical trial site, a specialized production facility, or a ward in a hospital, the drug product may need to be classified under each of their own regulatory channels. This is because each of these locations has their own set of rules and regulations. In addition to this, thinking about quality control for the finished medication product is essential. Furthermore, in order to guarantee a constant level of product quality, each and every step of the printing process, including the hardware, the raw material suppliers, the operator training, and the quality control, would require an in-depth analysis. Good Manufacturing Practices (GMP), have not yet been incorporated into the design of any of the commercially available 3D printers at this time. Therefore, more innovations are necessary in order to ensure that these uncommon platforms are suitable for their intended use by being in compliance with such standards (Madla *et al.*, 2018, P. 35, 36).

CHAPTER 3

3. Research methodology

The pharmaceutical industry has always been a sector that is characterised by a high rate of innovation. Because of developments in technology, the pharmaceutical industry has been looking at novel and innovative approaches to the production of various drugs, including tablets. In recent years, one of these technologies known as 3D printing has attracted a lot of attention. This technology has the ability to completely alter the production process that is now used for tablets. However, prior to putting this technology into practice, it is essential to gain an understanding of the opinions and expectatives of individuals working in the pharmaceutical industry.

3.1. Research Philosophy

The term "research philosophy" is used to describe a person's fundamental assumptions about the world. Different research philosophies may have different ideas about the purpose of research and the most effective methods for achieving that purpose. These aren't always different, but the research project's focus determines the research philosophy employed (Thesismind, 2019).

3 main research philosophies are:

Ontology- It is an understanding of reality. It explains the nature of reality, what thoughts occur to mind when doing research, and what effects it has on people and the environment. The difference between reality and how you see it is made obvious by ontology. Additionally, it teaches you about how people's behaviour is affected by it. It includes objectivism, constructivism and pragmatism

Epistemology- It is frequently utilized in scientific study, and this is because it assists in identifying data that can be proven beyond a reasonable doubt. It includes positivsm, realism and interpretivism

Axiology- Axiology teaches you how views and principles affect the collection and evaluation of your research data. It helps one comprehend the influence that public opinion has on the collection and evaluation of research (Saunders *et al.*, 2009, P. 131-134).

The pragmatism research philosophy was used in this study as the focus of the study was on the practical application of 3D printing technology in the manufacturing of solid dosage forms by gathering information from people in the pharmaceutical field. Pragmatism includes the studies, which is directly applicable to real world problems. It identifies the presence of an objective reality as well as the importance of individual experience in the formation of reality (Saunders *et al.*, 2009, P. 134).

3.2. Research Approach

Based on the primary research methodology, a deductive approach was more appropriate for this research as it aims in testing the theories and hypotheses, which is based on the existing research and literature.

The research approach was both qualitative and quantitative. This integrated approach helped in collecting information through surveys which was analysed to draw conclusions about the opinions and expectations of students, interns and people working on Pharma Oral Solid Dose Tablets in Europe.

3.3. Data collection

The data was collected through surveys which allowed me to collect information about the opinion and expectative of students, interns and people working on Pharma Oral Solid Dose Tablets manufacturing in Europe which was distributed through LinkedIn and other professional social networks. A structured questionnaire was prepared by means of google forms, which included both open-ended and closed-ended questions and was sent to students, interns and people working in the field of pharmaceutical industry in Europe. This was sent through LinkedIn and other professional social networks. The questionnaire was structured with pre-defined answer choices to collect quantitative data and also it contains questions which was open-ended to collect qualitative data. This gave information on the opinion and expectation of people in the pharmaceutical industry on the implementation of 3D printing as a viable method for commercial manufacturing of tablets.

The criteria for selection of study participants were based on:

1. Individuals working in the Pharma Oral Solid Dose Tablets industry in Europe.
2. Individuals with experience in the field of tablet manufacturing.
3. Individuals with knowledge in 3D printing technology.
4. Students pursuing in the field of pharmaceutical manufacturing and innovative technologies.

To increase response rates, the questionnaire was brief, clear, and easy to complete. To ensure that the questions could be easily understood and that the survey did not take an excessive amount of time to do, a preliminary test of the questionnaire was conducted with a select few participants. In addition to this, the survey was distributed over a number of different platforms in an effort to reach the maximum number of eligible people as possible. By this method, it was possible to gain information on opinions and expectations on 3D printing in the manufacturing of tablets from a broad range of individuals in the field of solid oral dose tablet manufacturing.

3.4. Secondary Source

The secondary source of the research is literature review. I did a thorough search and study of the relevant literature that was linked to my research subject. This allowed me to read through scholarly journals, books, and other reputable sources of information in order to obtain data and information that was relevant to my research.

During this approach, I was able to identify major themes, concepts, and trends that have developed in past research in relation to the subject area that I am interested in researching. I was able to generate a critical evaluation of the current knowledge base on the subject by synthesizing this material and using it in my analysis.

3.5. Analysis of data

The data collected was analysed using Microsoft Excel, which helped to give a deeper understanding of the study. The data was then analysed using descriptive methods which were used to determine the most common opinion or expectation of the participants. This helped to provide an overall understanding of the survey results.

In addition, the collected data was represented in the form of pie charts, tables, and bar graphs. Pie charts were also used to differentiate the opinions of the participants who participated in the survey, such as students, interns, and employees in the pharmaceutical solid oral dose manufacturing field. Also, certain data, which was collected through survey were compared to the findings obtained from the literature review.

3.6. Conceptual Framework

The conceptual framework that supported the research project focused on understanding the current level of 3D printing technology and its application in the tablet manufacturing business. Several important factors and themes were considered to gain a thorough understanding of this subject. These included the current state of 3D printing technology, the challenges and limitations of this technology, the advantages and disadvantages of using 3D printing in commercial manufacturing, the necessity for the pharmaceutical industry to embrace this technology, and the potential opportunities that 3D printing presents for the future of tablet manufacturing.

One of the crucial considerations was the previous state of 3D printing technology and how it was used in the tablet manufacturing sector. While the technology of 3D printing had been known for some time, its application in the medical and pharmaceutical fields was still relatively recent. Currently, only a small

number of companies produce tablets using 3D printing technology. These businesses have had to overcome a variety of challenges and limitations associated with the use of 3D printing, including technical hurdles, problems with quality control, restrictions on the types of materials that may be used, and so on. A comprehensive understanding of these obstacles is necessary to enable the industry to fully adopt the technology.

The technical challenges presented by the 3D printing technology included the requirement for exact temperature and humidity control during the printing process, the challenge in achieving uniform distribution of the active pharmaceutical ingredient (API) in the tablet, and the need for a controlled printing environment to prevent contamination. Quality control was also a significant source of concern, as it was essential to ensure both the uniformity and precision of the finished product. There were also constraints on the materials that could be used in the 3D printing process, as not all materials could be utilized. Additionally, the choice of material could have a considerable impact on the quality of the final product.

The advantages and disadvantages of using 3D printing in commercial manufacturing were another important aspect to consider. The technology had the potential to create individualized medicines suited to the specific requirements of each patient, combine multiple APIs into a single tablet, and produce complex geometries that were difficult or impossible to achieve with standard production methods. However, there were also several drawbacks, such as the high cost of 3D printers and associated equipment, the need for skilled employees to operate the equipment, and the slow speed of the printing process.

The need for the pharmaceutical industry to adopt 3D printing technology was also a crucial issue to consider. While only one company had received marketing approval for their 3D printed oral solid dosage form at the time, there was enormous potential for this technology within the industry. Traditional tablet manufacturing methods had severe limitations in producing complicated shapes or combining different APIs. However, these limitations could be overcome with 3D printing technology. Personalized medicines tailored to the specific requirements of each patient could enhance patient outcomes while simultaneously lowering overall healthcare expenditures. The possible openings offered by 3D printing for the development of tablet production in the future should also be taken into account. The technology had the potential to completely transform the industry by enabling the production of tailored medicines, improving the means by which drugs were delivered, and lowering the price of medical treatment. However, to fully leverage these benefits, the industry would need to overcome several hurdles and restrictions related to 3D printing technology.

In conclusion, the primary purpose of the conceptual framework that was developed for this research was to gain an understanding of the current status of the 3D printing technology and how it was being applied in the tablet manufacturing industry. The challenges and limitations of this technology, the advantages and disadvantages of 3D printing in commercial manufacturing, the need for the pharmaceutical industry to embrace this technology, and the potential opportunities that 3D printing presented for the future of tablet manufacturing all influenced the development of this framework. To enable the industry to completely adopt the technology of 3D printing and realize its full potential in the field of tablet manufacture, it was essential to have an in-depth understanding of the factors and themes that were involved in this process.

CHAPTER 4

4. FINDINGS AND ANALYSIS

4.1. FINDINGS

1. Experience of study participants

The first question in the survey was to determine the experience of the participants in the pharmaceutical manufacturing sector. Out of 60 responses, 27 were by students or interns in the pharma field (45%) whereas 25 respondents had an experience of 1-5 years in the pharmaceutical manufacturing sector (41.7%) and 8 respondents had an experience of 5-10 years in the pharmaceutical manufacturing sector (13.3%). No participants with an experience of more than 10 years were found for the study.

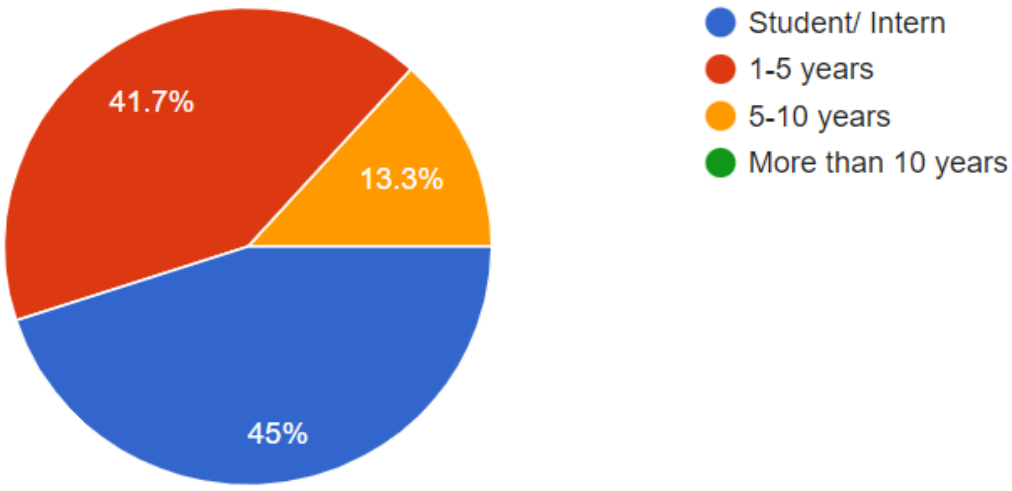

Figure 10. Pie chart representation with percentage of survey respondent's experience in the pharmaceutical manufacturing sector

2. Familiarity with 3D printing technology

The second question in the survey was to determine the familiarity of the study participants with the 3D printing technology. From the 60 responses, 27 respondents (45%) have had a basic understanding of 3D printing technology. 24 respondents (40%) have heard of the 3D printing technology but did not have much idea about it. 5 (8.3%) respondents were very familiar with 3D printing technology while 4 (6.7%) respondents were not familiar with 3D printing.

Response	Frequency	% Frequency
I am not familiar with 3D printing technology	4	6.7%
I have heard of 3D printing technology but do not know much about it	24	40%
I have a basic understanding of 3D printing technology	27	45%
I am very familiar with 3D printing technology	5	8.3%

Table 2. Familiarity with 3D printing technology

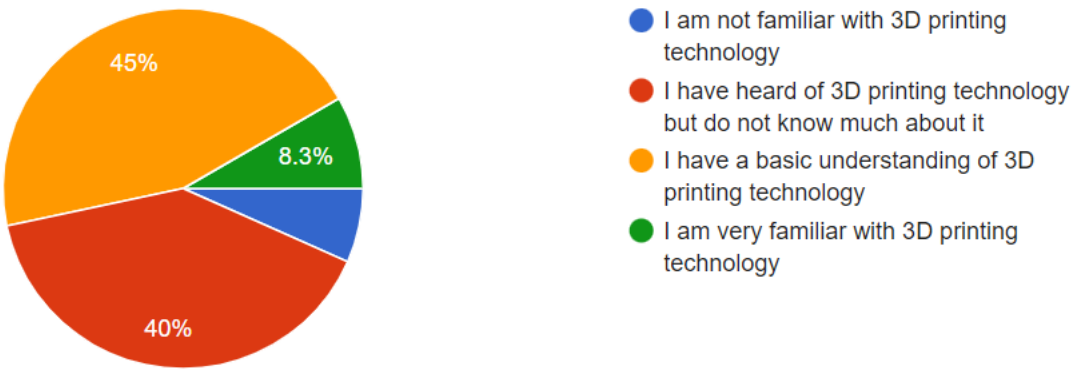

Figure 11. Pie chart representation with percentage of respondent's familiarity with 3D printing technology

2.1. Comparison between experience of study participants and familiarity on 3D printing technology and its use in solid oral dose manufacturing

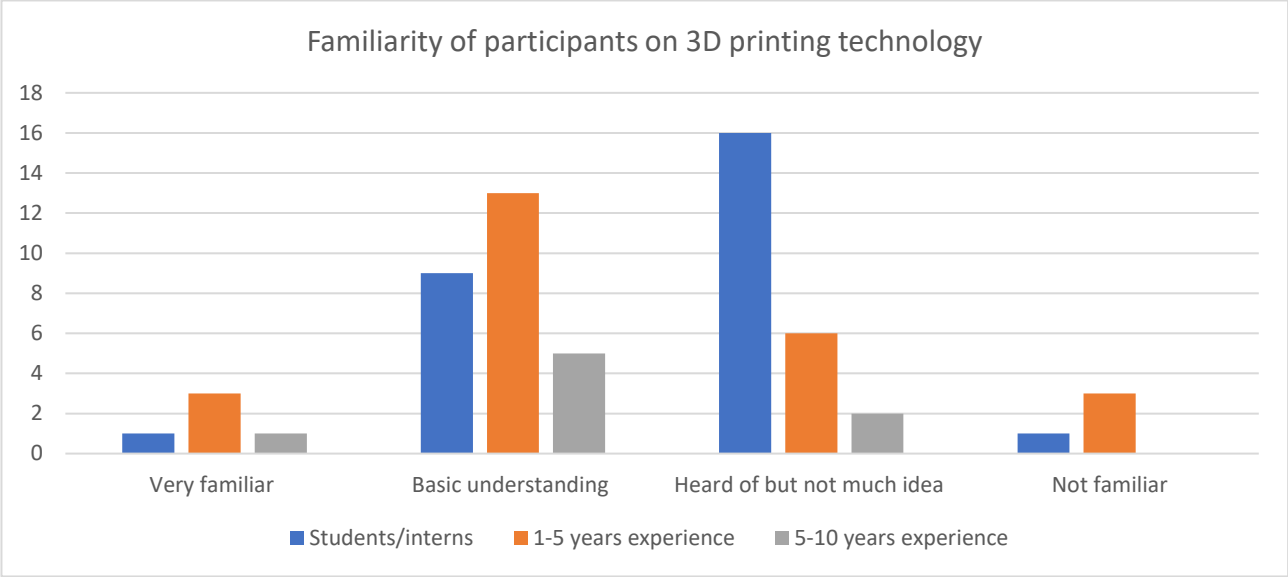

Figure 12. Comparison between experience of study participants and familiarity on 3D printing technology and its use in SOD manufacturing

Among the 27 students/interns who participated in the survey, 16 had heard of 3D printing technology but did not have much idea about it, while 9 had a basic understanding. Only one participant was very familiar, and one was not familiar with 3D printing technology. From the 25 participants with 1 to 5 years of experience in the pharmaceutical manufacturing industry, 13 had a basic understanding of 3D printing technology, while 6 had heard of it but did not know much about it. 3 participants were very familiar, and 3 were not familiar with 3D printing technology. From the eight participants with 5-10 years of experience in the pharmaceutical manufacturing industry, 5 had a basic understanding of 3D printing technology, while 2 had heard of it but did not know much about it. 1 participant was very familiar, and none were not familiar with 3D printing technology.

3. 3D printing technology in solid oral dose manufacturing

The third question in the survey was to determine if the respondents knew about the usage of 3D printing technology in the manufacturing of the solid oral dosage forms. Out of 60 responses, 43 responses (71.7%) responded “Yes” while 17 (28.3%) responded “No” to the question.

Response	Frequency	% Frequency
Yes	43	71.7%
No	17	28.3%

Table 3. Frequency for knowledge of 3D printing in SODF manufacturing

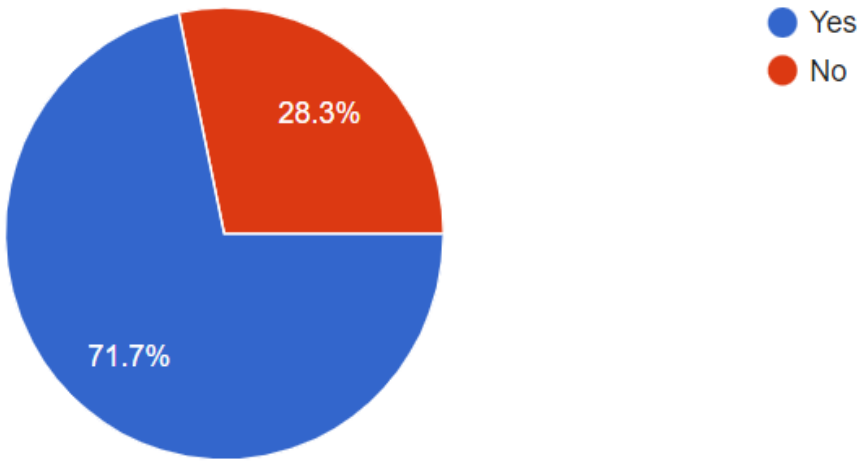

Figure 13. Pie chart representation with percentage of respondent's knowledge of usage of 3D printing technology in manufacturing of SODFs

3.1. Comparison between experience of study participants and their knowledge on use of 3D printing in SODF manufacturing

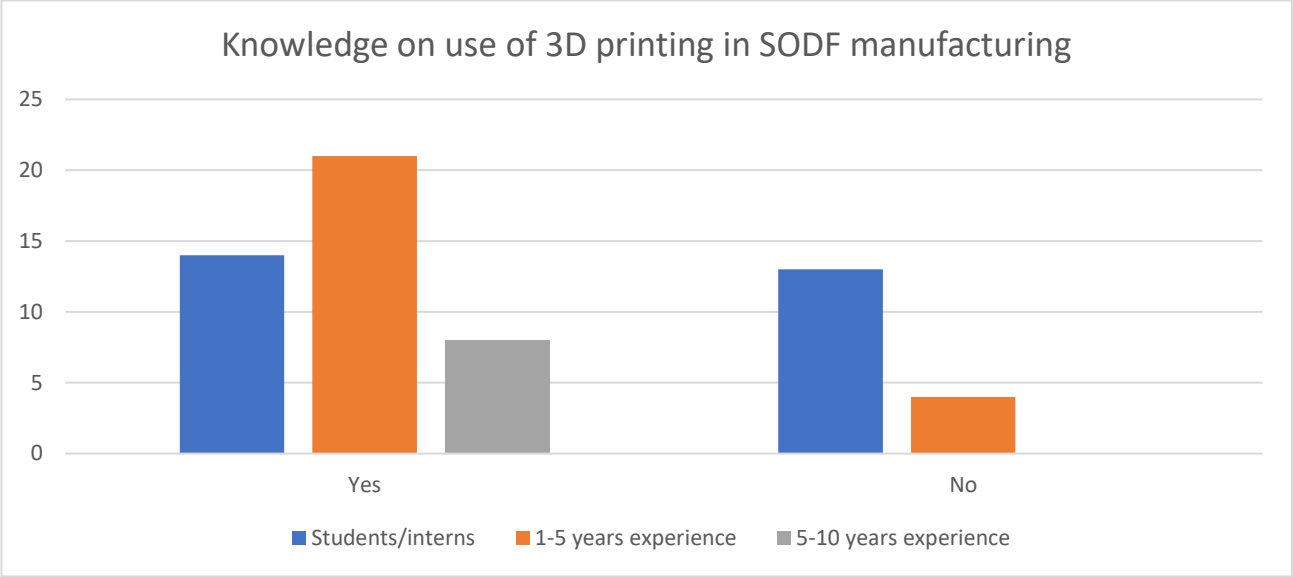

Figure 14. Comparison between experience of study participants and their knowledge on use of 3D printing in SODF manufacturing

When asked about their knowledge in the use of 3D printing in solid oral dose manufacturing, among the 27 students/interns who participated in the survey, 14 had knowledge of its use, while 13 did not know about it. Among the 25 participants with 1 to 5 years of experience in the pharmaceutical manufacturing industry, 21 had knowledge of its use, while 4 did not know about it. From the eight participants with 5-10 years of experience in the pharmaceutical manufacturing industry, all 8 participants knew about its use.

These findings suggest that while experts in the pharmaceutical manufacturing sector have a basic understanding of the 3D printing technology, there is still a lack of familiarity with the technology, particularly among students and interns. However, a significant amount of industry experts with expertise spanning from one to ten years are familiar with its possible applications in the manufacture of solid oral dosage forms. These findings show that there is a need for additional training and education on the use of 3D printing technology in the pharmaceutical sector, particularly among students and interns. This training and education should focus on the use of 3D printing technology to create medicines.

4. Advantages and Disadvantages

4.1. Advantages of usage of 3D printing technology in the tablet manufacturing

Fourth question was to identify what the respondents believed were the main advantages of use of 3D printing in the tablet manufacturing. The respondents were allowed to select multiple choices from given 5 choices. The choices given were increased speed of production, improved product quality, reduced costs, greater design flexibility and personalized medicines.

Based on the responses of 60 participants, the majority of the respondents believed that greater design flexibility (75%) and personalized medicines (68.3%) were the main advantages of using 3D printing technology in this industry. Nearly half of the respondents (46.7%) also believed that the use of 3D printing improved product quality, while 38.3% believed that it increased speed of production. Additionally, 31.7% of the respondents believed that the use of 3D printing reduced costs. One participant also mentioned that easy swallowing for pediatrics and geriatrics was an additional advantage.

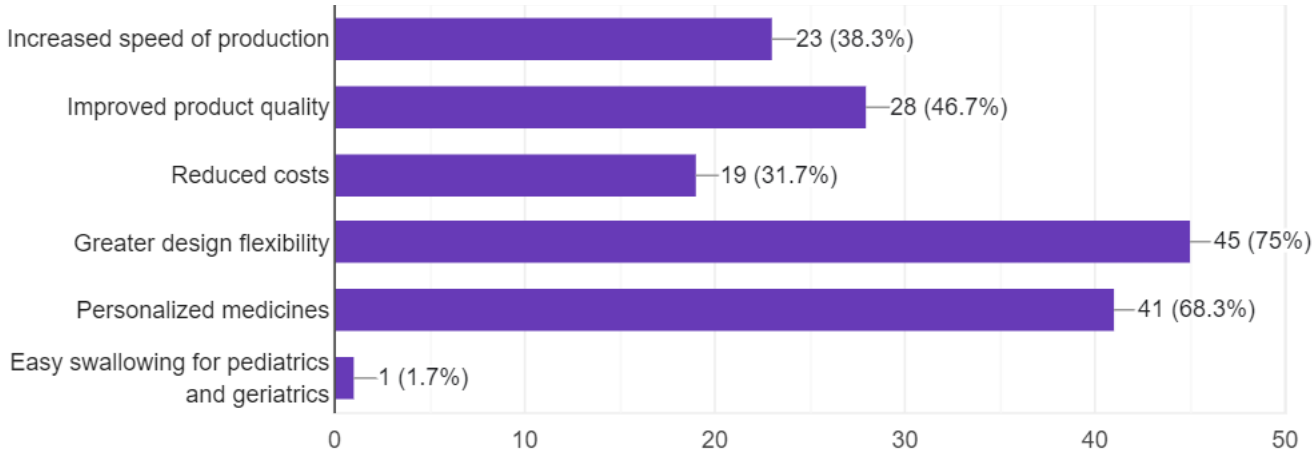

Figure 15. Bar graph representation for responses of advantages of 3D printing in tablet manufacturing

4.2. Disadvantages of usage of 3D printing technology in the tablet manufacturing

Fifth question was to identify what the respondents believed were the main disadvantages of use of 3D printing in the tablet manufacturing. The respondents were allowed to select multiple choices from given 5 choices. The choices were limited scalability, high initial investment costs, regulatory hurdles, material limitations and safety and efficacy concerns.

Based on the responses from 60 participants, the most commonly chosen disadvantage was high initial investment costs (80%), regulatory hurdles (68.3%) and material limitations (63.3%). Limited scalability was chosen by 25% of participants and a small proportion (11.7%) chose safety and efficacy concern as a disadvantage.

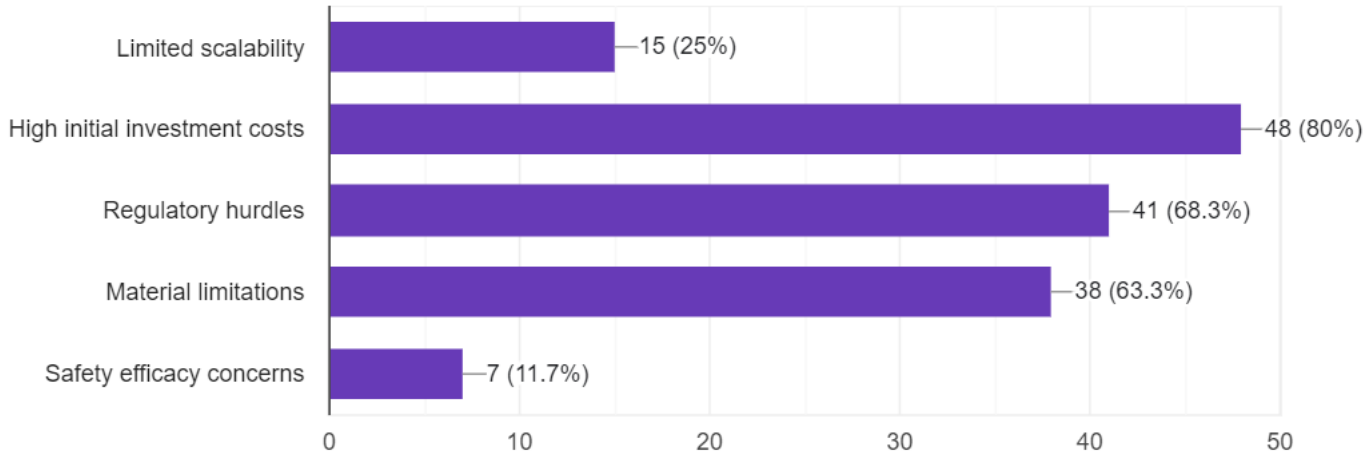

Figure 16. Bar graph representation for responses for disadvantages of 3D printing in tablet manufacturing

4.3. Comparison of advantages and disadvantages of 3D printing of tablets

The majority of respondents believed that greater design flexibility and personalized medicines were the main advantages of using 3D printing technology in this industry (Figure 13). The ability to customize the shape, size, and composition of tablets to meet specific patient needs and preferences is a key advantage of 3D printing. Participants also suggested that this technology could also improve product quality. The least selected choice among the 5 given advantages were increased speed of production and reduced costs.

From the given 5 choices of disadvantages, high initial investment costs were identified as the most commonly chosen disadvantage by 80% of participants (Figure 14). This demonstrates the importance of having large financial resources available in order to purchase and maintain 3D printing equipment. Regulatory hurdles have also been identified as a key problem; 68.3% of respondents indicated concerns over the approval of 3D printed medicine by regulatory authorities. Material restrictions were also a concern for 63.3% of participants, which indicates that there is still a problem in the industry about the availability of adequate materials for 3D printing. 25% of respondents mentioned limited scalability as a drawback, which

suggests that the existing capacity of 3D printing technology to make vast quantities of tablets is restricted. Safety and efficacy concerns were mentioned by only 11.7% of participants, suggesting that this is not a major issue in the industry related to 3D printing of tablets (Figure 14). These can also be considered as the key challenges before adopting 3D printing as a commercial production method for tablets.

Overall, the pharmaceutical industry stands to gain various potential benefits from the utilization of 3D printing technology, particularly in the areas of design flexibility and personalized medicines. However, in order to make 3D printing a viable commercial production process for tablets, there are a number of critical issues that need to be overcome. It has been determined that the primary obstacles that need to be overcome include high initial investment costs, regulatory hurdles, material limitation, and limited scalability. By addressing these challenges, the pharmaceutical industry can fully realize the potential of 3D printing technology for the production of innovative, customized, and high-quality pharmaceutical products.

4.4. Comparison of advantages and disadvantages from both primary and secondary research

The potential to create personalized medicine has been shown to be the biggest advantage of 3D printing technology in the pharmaceutical sector in both primary and secondary research. While the primary research indicated greater design flexibility as another key advantage, the secondary research also suggests that 3D printing technology can enhance product quality. This shows that 3D printing technology can aid the pharmaceutical business in a variety of ways.

High initial investment costs and regulatory hurdles were recognized as the two main issues that must be overcome in order to make 3D printing a workable commercial production technique for tablets in both primary and secondary research. Concerns about material limitations were raised in both investigations. But while limited scalability was not mentioned as a big issue in the secondary research, it was a downside in the primary research. Concerns about efficacy and safety were only brought up in the primary research.

When the benefits described in the primary and secondary research are compared, it is clear that several of the benefits mentioned overlap. According to both research studies, the two key benefits of employing 3D printing in the pharmaceutical business are design freedom and personalized medication. Given that 3D printing enables the creation of personalized, patient-specific medications that may be customized to unique requirements and tastes, this is not surprising. Another important benefit is the capability to build complex shapes and structures that are challenging or impossible to produce using conventional production methods.

Although only 46.7% chose improved product quality as an advantage in the survey, when compared to the secondary research improved product quality was seen as a major advantage of 3D printed oral solid dosage forms. This might indicate that participants did not value it on the same level with other advantages like design flexibility and personalized treatment. Also, studies implies that real-time process monitoring could be utilized on an industrial scale during the 3D printing process (Khairuzzaman, 2018, P. 227, 228). This would result in improved performance and assure that the product quality would remain uniform. It is practical to employ process analytical technology that is equipped with feedback and feed forward controls on an industrial scale when 3D printing is being done since 3D printing is a continuous process of additive manufacturing. Because of the way that additive manufacturing works, each layer of the material that is deposited makes a contribution to the overall quality as well as the specifications of the finished product. Therefore, in the absence of real-time monitoring, it would be impossible to take corrective action at the final stage of the build cycle if a single layer or several sequential layers were outside of their target specifications. This would be the case even if just one layer was affected. PAT can also be implemented on a smaller scale, either for on-demand production for personalized reasons or in the creation of drug product pilot scales for better knowledge of how the product's important quality attributes are linked to the process design and area (Khairuzzaman, 2018, P. 227, 228).

The primary and secondary research findings on the drawbacks of 3D printing technology for pharmaceutical companies show some commonalities but also some discrepancies. High initial investment costs were cited in both research studies as a key drawback of employing 3D printing for pharmaceutical manufacture. This suggests that an important entrance hurdle for businesses considering 3D printing is the financial commitment necessary to buy and maintain the necessary equipment.

However, the secondary research also discovered that most participants did not consider cost savings and faster production to be 3D printing's biggest benefits. This shows that while 3D printing has the potential to lower prices and boost manufacturing efficiency over the long run, these advantages could not be as significant as others like design flexibility and personalized therapy.

The primary research identified material limitations and regulatory hurdles as being major obstacles to the pharmaceutical industry's use of 3D printing technology. These issues were brought up in the secondary study as well, proving that they are common worries in the sector. Limited scalability, which was not noted in the primary research, was also identified in the secondary research as a drawback. This shows that some

survey respondents were concerned about the 3D printing technology's capacity to generate huge numbers of tablets, which would be a barrier to its adoption as a practical production method.

Only a small proportion of participants (11.7%) brought up safety and efficacy concerns as a disadvantage of 3D printing technology for pharmaceutical production (Figure 14), according to the primary research. This shows that the safety and effectiveness of 3D-printed pharmaceuticals were not a major worry for the majority of participants. The secondary research did not, however, specifically highlight safety and efficacy problems as a drawback of 3D printing, suggesting that this may not be a major concern in the broader sector.

While the regulatory hurdle was mentioned as a disadvantage by 68.3% (Figure 14), it has to be noted as mentioned earlier in the secondary research that according to the European regulations put forward by EMA, the oral solid dosage forms that are manufactured using 3D printing technology, should follow the basic quality characteristics as that of oral solid dosage forms manufactured using conventional method (Khairuzzaman, 2018, P. 217). But some studies suggest that it may be challenging to create adequate regulations for the use of 3D printers in the manufacturing of solid oral dosage forms (Madla *et al.*, 2018, P. 36). For instance, whether the printer is located at a clinical trial site, a specialized production facility, or a ward in a hospital, the drug product may need to be categorized under each of those locations' respective regulatory channels. This is because each of those locations has its own set of rules and regulations. This is due to the fact that each of these locations has its own distinct policies and guidelines to follow. In addition, the design of any of the currently available commercial 3D printers does not include Good Manufacturing Practices (GMP), as these standards have not yet been implemented.

Overall, the results of the primary and secondary research offer a thorough overview of the benefits and drawbacks of 3D printing technology for the pharmaceutical sector. While some of the advantages emphasized in both sets of study are similar, there are considerable variances as well, especially when it comes to the drawbacks. While secondary research offers a broader view on the benefits and drawbacks of 3D printing technology generally, the primary study findings offer a more in-depth analysis of the difficulties and problems that are particular to pharmaceutical companies.

In summary, 3D printing technology has the potential to completely transform the pharmaceutical industry by making it possible to produce personalized, patient-specific medications with more design flexibility and higher-quality end products. But before 3D printing can be used as a practical commercial production method for pharmaceuticals, a number of key challenges must be overcome, including the high initial investment

costs, regulatory challenges, material restrictions, and limited scalability. The industry may fully utilize the promise of 3d printing technology by solving these difficulties.

5. Reduction of waste and environmental impact from tablet manufacturing using 3D printing technology

The sixth question in the survey was to determine whether the respondents believed that 3D printing technology could reduce waste and environmental impact in tablet manufacturing. Out of 60 responses, 55 respondents (91.7%) believed that 3D printing can reduce waste and environmental impact in tablet manufacturing where as 5 respondents (8.3%) believed that 3D printing did not do any change in the waste management and environmental impact in tablet manufacturing.

Response	Frequency	% Frequency
Yes	55	91.7%
No	5	8.3%

Table 4. Frequency for reduction of waste and environmental impact by 3D printing

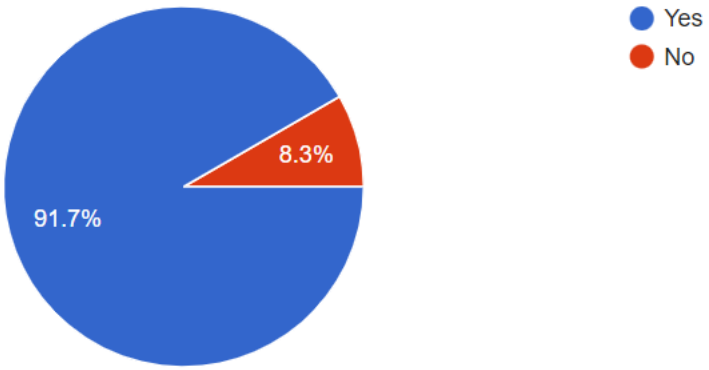

Figure 17. Pie chart representation of percentage responses for reduction of waste and environmental impact in tablet manufacturing using 3D printing

From the 60 respondents, 27 gave a reasoning to their choice. From these 27 answers, 8 respondents noted that 3D printing technology is more accurate and precise in design, which can decrease material waste and improve the production of solid dosage forms. Additionally, 4 of the respondents also mentioned on consumption of less energy. They noted that because 3D printing is automated and only produces what is required, it can use less energy and reduce carbon emissions. However, some respondents additionally stated that more research and development are required to reduce the environmental impact from tablet

manufacturing using 3D printing technology and address potential problems like choosing the material and energy consumption. It is crucial to take into account the unique circumstances and application since other technologies may also be able to reduce waste and environmental impact in tablet manufacture. The table 5 below shows some of the reasoning that the participants gave to their response

Reasoning given by participants for their choice
❖ "It has chance of reducing energy consumption and carbon emissions"
❖ "Can reduce human made environmental wastes"
❖ "When compared to the existing manufacturing methods, 3D printing have an upper hand in waste management"
❖ "It's not the only solution, other technologies can also reduce waste and environmental impact in tablet manufacturing"
❖ "Maybe, more research and practical applications are needed to determine the environmental impact of 3D printing technology"
❖ "There will be less imperfections in the produced solid dosage form, hence more chances of zero waste generation"
❖ "Traditional tablet manufacturing techniques would require more energy. 3D printing ensure production of only what's needed"
❖ "Computer aided design will help to customize the excess material and help in reducing the size to normal"
❖ "3D printing technology improves precision which can reduce waste and produce OSD more effectively"

Table 5. Reasoning given by respondents for reduction of waste and environmental impact by 3D printing

5.1. Environmental sustainability of 3D printed medicines

According to the primary research findings, the majority of respondents thought that 3D printing technology could reduce waste and the environmental impact when producing tablets (Table 4). The respondents gave a variety of explanations, including design accuracy and precision in design, decreased material waste, and decreased energy use as a result of automation. Some responders did, however, draw attention to the need for more research and development to address potential issues with waste management and consumption of energy (Table 5).

Elbadawi et al. conducted a study to investigate the environmental impact of 3D printing on the manufacturing of tablets examined the impact of printer settings on energy consumption while measuring the power utilization of printers in standby and printing modes. The findings of this study offer a framework for

creating environmental impact plans for commercial 3D printing while maintaining the quality and efficacy of pharmaceutical products.

In order to minimize the negative impacts of CO2 emissions on health and decrease the cost on healthcare institutions, the study emphasizes the necessity of carbon-neutral production. The study also demonstrates the possibility for 3D printers to offer improved and automated service quality while yet being "environmentally affordable." The study discovered that, except SLS printers, the energy consumption numbers for 3D printers were substantially lower than those needed for conventional tablet manufacture by powder compaction. According to the study, 3D printers might be fuelled by renewable sources like solar energy to reduce their carbon emission.

The fact that 3D printers are a digitalized fabrication technology and run on electricity, which is simple to decarbonize, makes it more likely that both the industrial and healthcare sectors will adopt it. Lowering the operating temperature can reduce CO2 emissions even more even though it may necessitate a modification in the composition of the material being printed. According to the study, depending on the printing method, energy demand might be lowered by 5.88% to 33.33% by lowering the printing temperature by 50 degrees Celsius (Elbadawi *et al.*, 2023, P. 5-7).

When comparing the findings from the survey and other studies on environmental impact of 3D printing on solid dosage forms manufacturing, these suggests that 3D printing technology has the potential to reduce waste and environmental impact of tablet manufacturing while simultaneously maintaining the quality and efficacy of pharmaceutical products. Varghese et al. suggested that by acceleration of additive manufacturing by the process engineers, material waste could be reduced and accuracy of the dosing could be improved (Varghese *et al.*, 2022, P. 7). This has been mentioned by 8 of the respondents in the survey.

Overall, the primary and secondary studies suggests that 3D printing could be environmentally efficient and also reduce the waste when compared to traditional manufacturing methods. Also, both of the studies also suggests that additional research is essential to understand the complete potential of environmental sustainability of 3D printed solid dosage forms.

6. Learning more about 3D printing and their potential application in tablet manufacturing

The seventh question in the survey was to know whether the participants had interest in learning more about 3D printing technology and its potential application in tablet manufacturing. Out of 60 respondents, 57

respondents (95%) responded “Yes” while 3 respondents (5%) responded “No” to the question. Respondents who responded “No” to the questioning did not gave a reasoning to their choice where as respondents who responded “Yes” for the question gave a few reasoning to their choice. Most common response was that 3D printing is an innovative technology, which could bring positive changes to the pharmaceutical industry. They think that 3D printing could be a sustainable choice that would have a significant impact on the pharmaceutical industry and enhance patient quality of life. The desire to learn more about innovative technologies applied in the sector, particularly in the area of Pharma 4.0, was another typical explanation. They believed that staying current with new developments was crucial to remain competitive and active in the industry. Some participants showed their interest in the unique opportunities that 3D printing might present, such as the capacity to design and produce tablets in custom shapes and designs that are not feasible through conventional manufacturing techniques. They viewed this as a means of improving patient compliance and producing drugs that are more effective. Overall, survey respondents considered 3D printing to be an interesting new technology with enormous potential for the pharmaceutical sector. For them to remain current and competitive in their industry, they believed that learning more about its potential and capabilities was important.

Response	Frequency	% Frequency
Yes	57	95%
No	3	5%

Table 6. Frequency for learning more about 3D printing

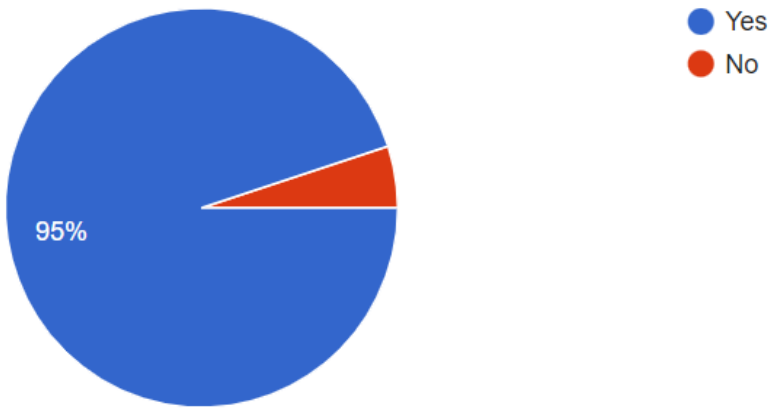

Figure 18. Pie chart representation of percentage of respondent's interest in learning more about 3D printing technology

The table 7 below shows some of the reasons that were given by the respondents for their choice

Reasoning given by respondents
❖ "I consider that it can create a great impact on the pharmaceutical sector" ❖ "New technologies can reduce the manual errors" ❖ It seems interesting to know how this works out. If it works well then maybe technology could bring us one more step closer to development" ❖ "The future production of solid dosage greatly depends on new methods of production like 3D printing technology" ❖ "I have a basic understanding only. It is better to learn more about these innovative technologies" ❖ "Since it is a sustainable option, the industry would be favouring it and hence I would like to learn more about it" ❖ "Seeking knowledge from new technology is a scoring" ❖ "Because I am a Pharmacy Graduate and new inventions and digitalisation methods in pharmacy field helps to reduce the medication errors and improve patient quality of life" ❖ "It is better to have more idea about the growing technology (Pharma 4.0)" ❖ "3D printing is an innovative technology. We have to make an idea regarding every innovative technology to be updated in the field"

Table 7. Reasoning given by respondents on their interest to learn more about 3D printing technology

7. 3D printing as a widely adopted method for tablet manufacturing in the next 10 years

The eighth question in the survey was to determine whether the participants thought that 3D printing technology could become a widely adopted method for tablet manufacturing in the next 10 years. Out of 60 respondents, 15 respondents (25%) thinks that 3D printing could very likely be adopted as a tablet manufacturing method while 41 respondents (68.3%) thinks that it is somewhat likely to happen. 3 respondents (5%) responded that it was not likely to happen and 1 was unsure about the future of 3D printing in tablet manufacturing.

Response	Frequency	% Frequency
Very Likely	15	25%
Somewhat likely	41	68.3%
Not likely	3	5%
Unsure	1	1.7%

Table 8. Frequency for future of 3D printing in the next 10 years

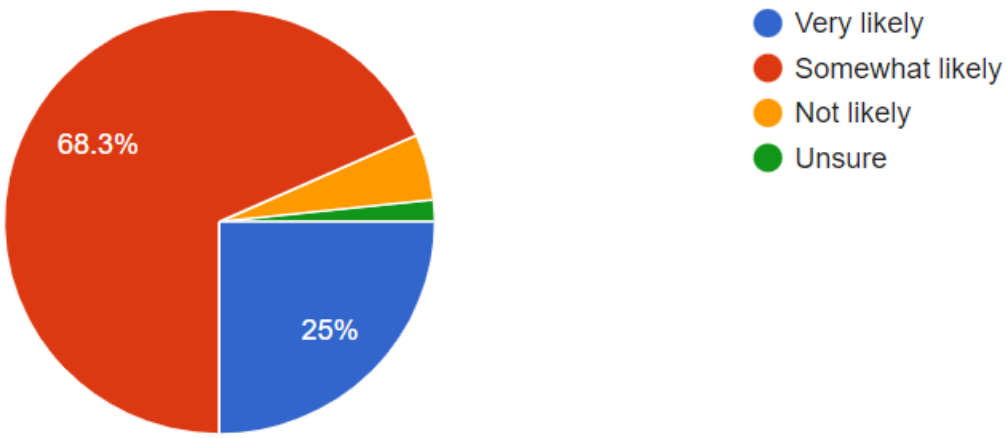

Figure 19. Pie chart representation of the responses for the chances of adoption of 3D printing in the tablet manufacturing in the next 10 years

8. Future of 3D printing technology in the commercial production of tablets

The ninth question was to gain information on what the participants thinks about the future of 3D printing technology in the commercial production of tablets. This was an open-ended question and 54 respondents responded to the question. The majority of respondents expressed support for the use of 3D printing in the production of tablets. The participants think that 3D printing technology has the power to transform the pharmaceutical sector and enhance the sustainability, quality, and productivity of tablet manufacture. There were a number of common responses including the potential for 3D printing to make it possible to produce personalized medications, the capacity to design complex tablets, the possibility of cost savings and reduced waste, and the requirement for additional study and regulatory approval.

Many respondents (18.3%) had high hopes about the possibility of 3D printing to create personalized medicines that could enhance patient outcomes by customizing medication to each patient's requirements. Participants also pointed out that complicated tablet designs that are challenging or impossible to manufacture using conventional production methods could be made possible through 3D printing technology. This might result in waste reduction and more effective, environmentally friendly manufacturing techniques.

Before 3D printing technology is widely used in the pharmaceutical sector, several participants (11.6%) highlighted the necessity for additional research and regulatory approval. Many respondents, however, were hopeful about the technology's potential for improving the effectiveness and quality of tablet manufacture and thought that it would eventually become a more widely used technique to manufacture tablets.

The table 9 below shows some of the responses given by the respondents about their opinion on future of 3D printing in the commercial manufacturing of tablets

Responses by participants on the future of 3D printing technology in the commercial production of tablets
❖ "If it gets approved by the regulations it can scale up the production of pharmaceutical products" ❖ "Since it's fast and easy manufacturing companies will adopt this method more in the future" ❖ "Different drug combinations can be made using 3D printing" ❖ "Not in the near future. But it is a very good option for personalized medicines" ❖ "On demand production and personalization can be achieved" ❖ "Very promising and sustainable mode of commercial production" ❖ "While 3D printing technology has shown promise in research and development, it remains to be seen how it will be implemented in commercial tablet production" ❖ "3D printing technology has the potential to revolutionize the commercial production of tablets, but there are still technical and regulatory hurdles to overcome" ❖ "This novel method of production will mostly replace the old production technique in the near future, which will enhance the overall quality of solid dosage form production" ❖ "The future of 3D printing technology in commercial tablet production depends on factors such as cost-effectiveness, regulatory approval, and consumer demand for customized products" ❖ "The use of 3D printing technology in commercial tablet production could lead to more efficient and sustainable manufacturing practices" ❖ "It is a great innovative technology but it is still in its initial stages. So, it needs more research and studies to be implemented as a method for tablet manufacturing" ❖ "Since personalized medicine is the next step in pharmaceutical industry, 3D printing would be very popular" ❖ "3D printing technology may play a complementary role in commercial tablet production, allowing for the creation of customized or complex designs" ❖ "The design and print of more complex designs can be easily achieved and when compared to the traditional manufacturing processes" ❖ "The scope of 3D printing technology is vast. It can be implemented to reduce time, effort and cost of manufacturing" ❖ "It has a good future in the oral dose manufacturing. As there is no much approved medications in the market, it will take quite longer to use this technology solely in tablet manufacturing"

Table 9. Responses by participants on future of 3D printing in commercial production of tablets

CHAPTER 5

2. Conclusion and Recommendation

2.1. Conclusion

In the pharmaceutical sector, the application of 3D printing technology is a relatively new field that is gaining interest from researchers, manufacturing companies and regulatory authorities. The manufacturing of complex dosage forms with customised release profiles, enhanced drug delivery and personalized medicine are some of the possible benefits that could result from the utilization of 3D printing in the pharmaceutical business. However, when compared to the US pharmaceutical companies, the adoption of 3D printing technology for manufacturing solid dosage forms are limited in European pharmaceutical is still limited.

Based on the study, it is clear that interns and students in the pharmaceutical field are unfamiliar with 3D printing technology. Few participants had a basic understanding of how 3D printing technology was used in the pharmaceutical business, despite the fact that the majority of participants had heard of it. According to this conclusion, further instruction and training are required regarding the usage of 3D printing technology in the creation of solid oral dosage forms. On the other hand, the study reveals that a significant amount of industry professionals with experience ranging from one to ten years are familiar with potential uses of 3D printing technology in the creation of solid oral dosage forms. According to the study, although there is still a lack of understanding of 3D printing technology in the pharmaceutical industry, particularly among students and interns, as more professionals in the field gain experience with the technology, 3D printing technology may become more widely used in the commercial manufacture of tablets in Europe. It is evident from the study that, the current state of 3D printing in the commercial manufacturing of solid dosage forms is such that even though 3D printing is employed in the manufacturing of several medical devices in pharmaceutical industries across Europe, its usage in the manufacturing of solid dosage forms is still in infancy.

When looking into the cost, speed, scalability, quality and consistency of 3D printed solid dosage forms, the study results shows that it can be difficult for smaller pharmaceutical companies to enter into the market due to the high expense of the equipment, materials, as well as expertise required to make 3D-printed pharmaceutical products. Also, in comparison to traditional methods of production, the production of tablets using 3D printing is a time-consuming process that is relatively slow. The rate at which a 3D printed solid dosage form is produced is determined by a number of parameters, including the complexity of the design, the size of the tablet, and the materials that are being employed. However, it is important to remember that the speed of 3D printing technology has been increasing over the past several years as a result of developments in both technology and materials. Tablets that have a quality and precision that is consistent

can be produced using 3D printing, which is vital for ensuring the drug is both safe and effective. Consistent outcomes can be difficult to achieve, however, due to factors such as differences in the characteristics of the materials that are utilized and the complexity of the designs.

Greater design freedom, personalized medicine, and the possibility of improved product quality are some of the benefits that can be realized through the use of 3D printing technology in the industrial production of tablets in Europe. The capacity to customize the shape, sizes, and composition of tablets to the requirements and preferences of individual patients is one of the most significant benefits offered by 3D printing. In addition, the technology of 3D printing can be of assistance to the pharmaceutical industry in the manufacturing of complex shapes and structures, which would be difficult or even impossible to build, using traditional production methods.

High initial investment costs and regulatory hurdles were recognized as the two main drawbacks found in the use of 3D printing technology for the manufacture of tablets. Concerns on material limitation are another challenge in 3D printing of solid dosage forms. Even though limited scalability was not noted in the primary research, it was identified as a major issue in the secondary research. Based on the studies, it is evident that in order to fully realize the possibilities of 3D printing technology for the manufacturing of innovative, customized, and high-quality pharmaceutical products, it is vital to address the challenges associated to high initial investment costs, regulatory hurdles, material limitations, and limited scalability. Only then it will be able to realize the complete potential of this technology.

In order to make 3D printing a viable method for manufacturing of solid dosage forms, further research and development is required which can enhance the capabilities of the technology. This includes the development of new materials that are suited for 3D printing as well as the improvement of the scalability as well as the speed of the manufacturing process. Since there is no much regulatory guidelines solely for 3D printed solid dosage forms, regulatory approvals must be ensured for the 3D printed tablets to make sure that they meet the safety and efficacy standards. This can be made possible by working alongside regulatory bodies to develop suitable testing techniques and to resolve any issues regarding the efficacy and safety of pharmaceuticals that have been 3D printed. Additionally, investing in necessary infrastructure to support the manufacturing of 3D printed drugs is necessary. This includes the establishment of production facilities that are equipped with the most recent technology for 3D printing, as well as the recruitment and training of skilled individuals to operate the equipment. Also, Establishing partnerships and collaborating between pharmaceutical businesses,

academic institutions, and research organizations will encourage innovation and speed up the implementation of 3D printing in the commercial manufacturing of tablets.

2.2. Recommendation and further research

3D printing for complex dosage forms, customized release profiles, better drug administration, and personalized medicine is attracting pharmaceutical companies. European pharmaceutical interns and students are found to be inexperienced with 3D printing technology for solid dosage form manufacture. There is a need for more education and training on the use of 3D printing technology in the manufacture of solid oral dosage forms. This have to be targeted among students and interns in the field of pharmaceutical sector as well as among working professionals with less than 1 year of experience. Also, as the regulatory hurdles were pointed out more as a drawback in the 3D printing of tablets, the establishment of transparent standards and guidelines for the production of 3D-printed dosage forms is an absolute necessity for the various regulatory bodies. This will serve to resolve issues relating to the safety and efficacy of the process, as well as providing clarification regarding the regulatory requirements for 3D printing.

Controlling the quality of the 3D printing process and standardizing it are both absolutely necessary to guarantee the efficacy and safety of 3D printed dosage forms. In the future, research should concentrate on developing standardized processes for 3D printing as well as quality control measures to ensure that the manufacturing process is consistent.

Pharmaceutical companies must place a significant priority on the development of new materials in order to realize the full potential of 3D printing technology. The primary focus of future researches needs to be on the development of materials that are compliant with regulatory standards, offer the essential mechanical and chemical qualities for drug delivery, and are suitable for the 3D printing process.

In order to make 3D printing a feasible option for the commercial manufacture of tablets, it is required to find solutions to the difficulties of scalability and cost-effectiveness. In the future, research should concentrate on developing 3D printing technologies that are efficient in terms of cost and can be scaled up for mass manufacturing.

2.3. Limitations and contributions of the research

The research highlights the present status of 3D printing technology in the commercial manufacturing of tablets in pharmaceutical sector, particularly in Europe, and identifies the challenges and possibilities connected with its use in the manufacturing of solid dosage forms. The findings of the study also focus on the

necessity for more research and development in the field, especially in the areas of material development, scalability, and regulatory approvals. On the other hand, there have been some limitations of the research. Because the research was limited to the pharmaceutical industries in Europe, its conclusions may not be applicable to industries in other parts of the world. Also, the study was conducted among the pharmaceutical industries mainly in UK and Ireland, but the overall study was to analyse the pharmaceutical industries in Europe. Even though the people in the pharmaceutical sector in different parts of Europe were contacted through LinkedIn and other professional social networks, most of the people responded was from Ireland and UK.

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APPENDIX

SURVEY QUESTIONNAIRE

1. Do you understand the purpose of this survey?
    - Yes
    - No

2. Are you willing to participate in this survey?
    - Yes
    - No

3. How long have you been working in a pharmaceutical manufacturing sector?
    - Student/Intern
    - 1-5 years
    - 5-10 years
    - More than 10 years

4. Which of the following best describes your familiarity with 3D printing technology?
    - I am not familiar with 3D printing technology
    - I have heard of 3D printing technology but do not know much about it
    - I have a basic understanding of 3D printing technology
    - I am very familiar with 3D printing technology

5. Have you heard of 3D printing technology being used in solid oral dose manufacturing before?
    - Yes
    - No

6. What do you believe are the main advantages of using 3D printing technology in tablet manufacturing? (Select all that apply)
    - Increased speed of production
    - Improved product quality
    - Reduced costs
    - Greater design flexibility
    - Personalized medicines

7. What do you believe are the main disadvantages of using 3D printing technology in tablet manufacturing? (Select all that apply)
    - Limited scalability
    - High initial investment costs
    - Regulatory hurdles
    - Material limitations

8. Do you believe that 3D printing technology could reduce waste and environmental impact in tablet manufacturing?
    - Yes
    - No

    Could you please explain why you chose the above option?

_____

9. Would you be interested in learning more about 3D printing technology and its potential applications in tablet manufacturing?
    - Yes
    - No

    Could you please explain why you chose the above option?

    _____

10. How likely do you think it is that 3D printing technology will become a widely adopted production method for tablets in the next 10 years?
    - Very likely
    - Somewhat likely
    - Not likely
    - Unsure

11. How do you see the future of 3D printing technology in the commercial production of tablets?
    _____

    Thank you for your time.