3D Printing Technology for Visually Impaired Patients- A Review

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "3D Printing Technology for Visually Impaired Patients- A Review" submitted by Ayesha Kabir Shanta (17146015) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on January, 2022.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

285 million individuals worldwide are visually impaired or blind, resulting in a significant public health burden. Every day is a struggle for a person who is blind or visually impaired. As it turns out, the utilization of 3D printing to manufacture orally dissolving printlets (ODPs) and Braille-encoded Intraoral Films, designed for patients with visual impairment, can be an excellent solution to this problem. In addition, SLS and FDM 3D printing technologies were used to create printlets and intraoral films with Braille and Moon patterns on their surfaces, permitting patients to identify drugs once they were removed from their original packaging. There is also more information, like medication's indication or dose regimen, was provided through printlets with a wide variety of shapes. There was only a slight alteration in the mechanical properties of intraoral films due to the patterns, but printlets preserved their authentic mechanical properties and dissolving properties despite the patterns' existence. Furthermore, blind volunteers verified the printlets' and intraoral films' readability. Therefore, individuals with visual impairments should benefit from this unique and practical strategy, which is expected to reduce medication errors and enhance medication adherence.

Keywords: Three-dimensional printing (3DP); Fused deposition modeling (FDM); Selective laser sintering (SLS); Visual impairment; Braille and Moon patterns (Printlet);

Dedication

Dedicated to my beloved parents.

Acknowledgement

First and foremost, I want to express my thankfulness to Almighty Allah for providing me with an abundance of strength during this time of study. I would want to express my gratitude and appreciation to my esteemed supervisor Namara Mariam Chowdhury (Lecturer, Department of Pharmacy, Brac University) for her helpful suggestions and instructions that made my thesis more acceptable. I am sincerely grateful for the support she has given me, with her time, expertise, and important advice. Finally, I would want to express my gratitude to my family and friends for their constant support and encouragement throughout my life.

Table of Contents

List of Figures

List of Acronyms

3DP	Three Dimensional Printing
CAD	Computer Aided Design
3D	Three Dimensional
ISO	International Standard Organization
FDA	Food and Drug Administration
ODTs	Orally Disintegrating Tablets
UV	Ultraviolet
SLS	Selective Laser Sintering
FDM	Fused Deposition Modeling
ODPs	Orally Disintegrating Printlets
Nd:YAG	Neodymium-Doped Yttrium Aluminum Garnet
ABS	Acrylonitrile Butadiene Styrene
CO_2	Carbon Di-Oxide
APIs	Active pharmaceutical ingredient(s)
RNIB	Royal National Institute of Blind People
USP	United States Pharmacopeia
PLA	Polylactide/ Polylactic Acid
HPMC	Hydroxy Propyl Methyl Cellulose

IH	Indentation Hardness
EM	Elastic Modulus
DDS	Drug Delivery Systems
GMP	Good Manufacturing Practice
QC	Quality Control

Chapter 1: Introduction

1.1 What is braille?

Braille is a raised-dot pattern that blind or low-vision persons can read with their fingertips. The Braille writing and reading system is the most widely used tactile reading and writing method in the world. Louis Braille invented it, and it consists of a series of raised dots that form the letters and punctuation (*World Braille Day - United Rehabilitation Services of Greater Dayton*, n.d.). There is no such thing as a language in Braille. Instead, it's a system for writing and reading a wide variety of languages, including English, Spanish, Arabic, Chinese, and dozens more. Thousands of people throughout the world utilize Braille in their native languages, making it a viable option for universal literacy (*What Is Braille?| American Foundation for the Blind*, n.d.).

1.2 History of Braille

Louis Braille, a young Frenchman, invented the raised-dot system commonly known as "braille". A childhood accident caused Louis to lose his sight. When he was ten, he was admitted to the Royal Institution for Blind Youth. Using raised dots as a coding scheme was originally discussed at the Institute in 1821, when Louis was there for the first time. Captain Charles Barbier of Napoleon's army came to school to show his "night writing". Military code-named "night writing" was originally used to develop Braille. To enable soldiers to converse at night without the use of candles or speaking, the French military designed this technique (*World Braille Day - United Rehabilitation Services of Greater Dayton*, n.d.).This was a tactile technology developed to allow soldiers to communicate without speaking. Instead of letters, it employed raised dots and dashes. Louis Braille, a young schoolboy, discovered the code and later produced the more useful, simplified form of the braille alphabet that we are all familiar with today. Louis saw the value of Barbier's system but thought it was very complex. He spent the next few years perfecting his own version of the code, utilizing six dots instead of Barbier's 12. By 1824, Louis, aged 15, had discovered 63 uses for a six-dot cell the size of a fingertip. On his "planchette," or writing slate, he perfected the pattern of raised dots used in braille (*Invention of Braille - RNIB - See Differently*, n.d.). Because braille requires more space than the standard alphabet, braille books are substantially bigger than printed books. Braille is divided into two types: contracted and uncontracted.

Each word is spelled out in uncontracted braille. Contracted braille is a "shorthand" form of braille that abbreviates popular words, similar to how the word "don't" is a shortened version of "do" and "not". The uncontracted version of braille is learned first, followed by the contracted version (*World Braille Day - United Rehabilitation Services of Greater Dayton*, n.d.).

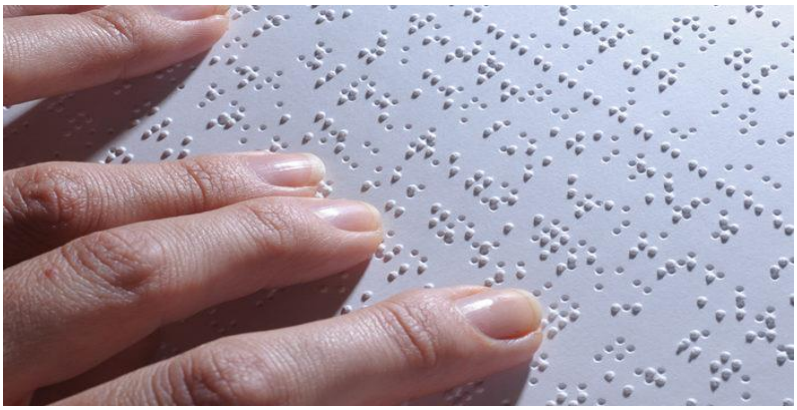

Figure 01: The embossed letters and numbers in Braille system (*BRAILLE UNDER COPYRIGHT LAW - Talwar Advocates*, n.d.)

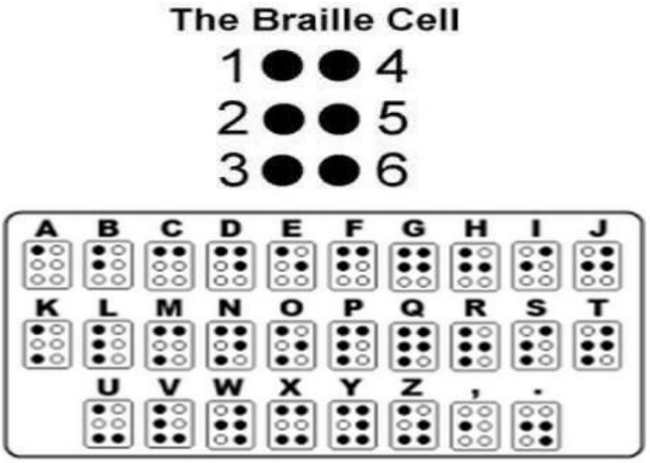

Figure 02: The Braille Cell (Zerin, 2016).

1.3 Why is Incorporating Braille Necessary?

Visual impairment is a widespread health issue that has serious implications for a person's personal, professional, and social well-being. An estimated 1.3 billion individuals on the planet are blind or partially blind. In accordance with the International Classification of Diseases, those with visual acuity less than 6 out of 60 have extreme distant vision problems, while those with visual acuity less than 3 out of 60 are officially classified as legally blind

(WHO, 2017). Approximately 217 million individuals worldwide suffer from mild to moderate visual impairments, and around 36 million are completely blind (WHO, 2017). Patients who are blind or visually challenged have numerous difficulties, such as taking the wrong medication, forgetting to take a dose, or mistaking one container for another. The majority of visually impaired people struggle to read pharmaceutical labels even with low-vision aids and equipment (Awad, Yao, et al., 2020). These people have unique requirements that can't be overlooked. The visual impairments that have an impact on their day-to-day activities can also have an impact on the safety and efficacy of their medications. As a result of their impairment, members of this group cannot tell the difference between drug names and colors. People with visual impairments can't understand the normal drug pamphlets that list dosages, expiration dates, and storage requirements. Unintended medication errors are therefore expected, particularly amongst polypharmacy practitioners (Zhi-Han et al., 2017).

According to a latest Malaysian research including 100 people with visual impairments aiming to uncover frequent concerns visually impaired people have when utilizing their medications (Zhi-Han et al., 2017), researchers found out that 89% of people couldn't read prescription labels, 75% didn't know when their drugs were about to expire, and 58% didn't even know what their medications were called. Researchers believe that Braille labeling for visually impaired patients' drugs could alleviate some of the challenges these patients face and help them correctly self-administer their medications (Almukainzi et al., 2020). Moreover, in another study a total of 121 people took part where, researchers discovered that the most prevalent obstacles faced by the blind patients were related to medicine determination (75 percent), recognition of dose (82 percent), and identification expiration date (92%). A significant proportion of patients would then have to depend on sighted caregivers to appropriately administer their prescriptions, according to the study findings (Kentab et al., 2015).

Importance of incorporating braille in pharmaceuticals:

- Reducing medication errors
- Improving medication adherence
- Facilitating self-administration of medications
- Improving independence
- Overcoming depression and emotional stress
- Reducing morbidity & improving quality of life

1.4 What is 3D printing?

Digital fabrication technology, often known as 3D printing or additive manufacturing, builds physical items from a geometrical representation by successively adding suitable materials. In 3D printing, a design of an object is created straight from a (CAD) computer-aided design model, and the three-dimensional printer creates the object by layering material until the desired shape is achieved. Range of different printing materials, including polymers, powders, filaments, and paper, can be used for creating the object. 3DP allows us to create complicated shapes with less material than conventional methods. 3D printing is a rapidly developing technology. 3D printing is already widely used around the world. 3D printing technology is increasingly being used for mass customization and manufacture of any form of open source design in agriculture, healthcare, automobile, locomotive, and aviation industries (Shahrubudin et al., 2019). The International Standard Organization (ISO) defines three-dimensional printing as "the production of objects through the deposition of a substance utilizing a print head, nozzle, or another printer technology" (Jamróz et al., 2018).

3D Printing Technology in Pharmaceuticals

The pharmaceutical industry has just newly discovered three-dimensional (3D) printing technology, which offers a wide range of uses for individualized dosing and complex formulation designs (Eleftheriadis & Fatouros, 2021). Pharmaceutical 3DP is a revolutionary fabrication technology that has the ability to make customized pharmaceutical items in almost any form or size from a CAD model (Awad, Fina, et al., 2020). In recent years, the increased need for customized pharmaceutics and medical devices has boosted additive manufacturing's significance. 3DP has emerged as a novel and powerful technique for the exact fabrication of specifically customized dosage forms, tissue engineering, and disease modeling. 3DP is widely regarded as the most groundbreaking and potent of the several advancements introduced into the pharmaceutical and biomedical markets. This method is well-known as a potential tool for producing precise devices. It’s a technology that can be used to create innovative dosage forms, tissues and organs engineering, and disease modeling (Jamróz et al., 2018). Because of the ability to rapidly prepare tailor-made things for use in personalized therapy or medicine, 3DP processes are growing rapidly in the pharmaceutical and medical fields. The incorporation of 3DP into pharmaceutical technology is aimed specifically on the development of patient-centered dose forms depending on structure design (Jamróz et al., 2018).

Figure 03: FDA approved of 3D printed tablet (Spritam®) (Aprecia Pharmaceuticals, 2018)

1.5 Significance of 3D Printing Technology in Pharmaceuticals

- 3D printing enables the individualization of medicine to the patient's body mass and style of living through dose and dosage form adjustments, such as for active or noncompliant individuals, orodispersible tablets may be used in place of conventional tablets.
- This manufacturing process appears to be particularly advantageous for the development of orphan drugs for limited groups of patients.
- Dosage form manufacture at a minimal cost.
- Preparation of orally disintegrating formulations. The production of orally disintegrating tablets (ODTs) has gotten more attention as the benefits of ODTs have grown. Because 3D printing uses a layer-by-layer preparation method rather than compression, the formulation has a higher permeability and disintegration rate.
- 3D printing opens up previously unimagined possibilities for the creation and preparation of tailored medications on a pharmaceutic or industrial scale.
- 3DP enables the creation of tablets containing a variety of active ingredients, each with unique characteristics and disintegration profiles.
- This promising approach allows for formulation flexibility that is difficult to attain using traditional technological processes.
- To prepare formulations with a high drug loading. The use of 3DP technology has shown to improve the preparation's drug load capabilities. 3D printing technology may considerably minimize the quantity of excipients used in the formulation and make high-drug loading tablets, easing the preparation of high-dose pharmaceuticals to some level (Arafat et al., 2018).

- 3D printing can also be used to build multipurpose drug delivery systems, multidrug devices, and medication formulas for customized, rapid release therapy.
- Preparation of special and customized geometric shapes. 3D printing offers greater flexibility and precision in spatial positioning, and it may be used to create a variety of unique geometric shapes. The drug's release may be tailored by printing these geometric shapes. By simply adjusting the 3D model, this technique may truly adapt the drug release behavior for the patient (Fina et al., 2018).
- Finally, the benefits to patients and the broader healthcare system enabled by 3DP adoption make the number of research necessary to build the process of customized product production affordable (Annaji et al., 2020).

1.6 Other Suggested Ways of Incorporating Braille into Pharmaceuticals

Embossing

In the process of embossing, a male and female die are used in combination. The Braille dots are made by pressing the pharmaceutical label or carton between two dies and applying pressure. Use of tooling that simultaneously embosses the Braille and cuts/creases the packaging substrate is a typical practice that is both cost-effective and efficient in the manufacturing process. This is a one-step procedure. As another option, the Braille can be applied and cut/creased at the same time using separate Braille and cut/crease tools (two pass process) (*Introduction to Pharmaceutical Braille – PharmaBraille*, n.d.).

Screen-printing

Paper, carton board, and polymers are among substrates that can benefit from this procedure. When Braille fonts are printed on packaging, they are usually handled as an additional color and produced with screen technology. The dots are normally made of transparent material so that they don't interfere with the legibility of the illustrations underneath (Introduction to Pharmaceutical Braille – PharmaBraille, n.d.).

Adhesive labels

Adhesive labels can be printed in Braille and then placed to the product's packaging during production (Introduction to Pharmaceutical Braille – PharmaBraille, n.d.).

UV inkjet technology

Numerous studies have established that braille may be printed using UV inkjet technology. The appropriate height of braille dots can be achieved by applying many coats of UV varnish, the quantity of which varies according to the machine and type of UV varnish used. UV inkjet printed braille has a promising future, and studies have proven that by applying UV varnish in a few layers, it is possible to achieve the required height of braille dots as per the standards, and that as the number of layers increases, the height of braille dots increases as well (Vujčić et al., 2021).

Compression, Engraving, Grinding & Etching:

These methods are used for embedding encoded identification directly onto pharmaceutical products (Eleftheriadis & Fatouros, 2021).

1.7 Aims and Objectives

To address the issue with visually challenged individuals incorrectly identifying pharmaceutical labels or doses, it's indeed critical to establish a simple, standardized, yet cost-effective technique of putting Braille or Moon patterns directly onto drug items. 3DP may provide an attractive and effective answer in this instance. Therefore, the aim & objective of this review is to demonstrate an innovative and feasible technique for developing dosage forms that are suitable for individuals having vision disability. SLS 3D printing, FDM technology and PBF 3D printing, are all examples of this. ODPs, intraoral films with the patterns of moon and braille are made using these procedures. Once the medications had been removed from their original packing, patients could then use the tactile patterns to identify them. Furthermore, it's not necessary to take these printlets with water because they breakdown fast in the mouth. As a result, self-administration of medications enhances patient compliance and treatment effectiveness while also promoting drug safety and independence for visually impaired people.

Chapter 2: Research Methodology

After deciding on a topic for the thesis project, academic journals, research papers, and review articles from reputable websites and databases were explored in an effort to learn as much as possible about 3D printing. As part of this investigation, a thorough evaluation of the existing literature was conducted by searching for relevant publications using keywords and then examining them on several online databases, including Google Scholar, PubMed, Elsevier's ResearchGate, ScienceDirect, etc. Useful information on 3D printing technology for visually impaired patients was found and compiled using these well-known and trustworthy database resources. To construct this review study, roughly 150 papers were meticulously analyzed, and important information was gathered from them. In addition to the previously indicated secondary approach, a qualitative method was used to conduct this review. A variety of decisions, selections, and analyses were made based on the filtered articles and journals that were used for this study. Lastly, Mendeley software was utilized to ensure that the citations are accurate and respectful of the original authors' work.

Chapter 3: Techniques Used for Fabrication

3.1 Selective Laser Sintering (SLS) 3D Printing Technology

SLS is a powder based 3DP technique that uses a laser beam to precisely combine the powdered particles together to generate three-dimensional items. In 1984, Carl Deckard invented the SLS technique. In the realm of drug delivery, SLS 3DP is used to generate printlets with a number of various release properties, which includes various dosage forms (orally disintegrating, immediate release, and modified release). Owing to the excellent resolution of the laser, novel structures such as three-dimensional gyroid lattices, bi-layer printlets, and dual miniprintlets may be easily created and modified to have various drug release patterns to fulfill the demands of individual patients (Awad, Yao, et al., 2020). Moreover, while a clear trend toward customized doses continues to be the primary emphasis of the majority of 3DP technology, a variety of other potential remains untapped. For instance, the unique laser characteristics of SLS 3D printing enable a novel and advanced approach to developing dose forms tailored to certain patient populations, such as individuals who are visually impaired. Orally disintegrating printlets (ODPs), for example, having braille and moon patterns on their surface have been developed in order to assist patients in identifying prescriptions once they are removed from their original package. Due to the fact that all Printlets disintegrate within five seconds, they minimize the requirement for water and thereby ease medication self-administration (Awad et al., 2020). Additionally, Printlets of various designs, including a moon, sun, caplet, heart, pentagon, and square, were successfully created utilizing SLS 3DP technology. Indication and/or dose regimen are included in these shapes. For example, several commercialized paracetamol medications come in caplet form. A heart shape could also signify cardiovascular drugs due to the organ's similarities. The sun and moon designs may indicate morning and evening dosage. The quantity of edges in pentagon or square forms might also be utilized to correlate to the time of medication intake (Awad et al., 2020).

3.2 Properties of Selective Laser Sintering (SLS) 3D Printing Technology

- It was primarily centered on a 100 W neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (Beaman and Deckard, 1990). The feedstock material for the printer was a powder of acrylonitrile butadiene styrene (ABS), a thermoplastic polymer that was utilized in numerous prototypes (Shellabear and Nyrhilä, 2004).

- Presently**,** most of the SLS printers that are commercially accessible utilize CO_2 lasers, which delivers increased power at a cheaper price, opening the door for the application of a broad range of powdered thermoplastic materials (Di Giacomo et al., 2016). SLS printing mostly utilizes thermoplastic polymers as a feedstock source.

- When compared to other 3DP technologies, SLS printing uses a feedstock material that is most similar to that used in traditional tabletting. Such as, it was believed that SLS would be more suitable for pharmaceutical applications. Since SLS is capable of sintering **pharmaceutical-grade powders**, it is ideal for application in pharmaceutical research. Thus, it represents a novel and adaptable method for rapidly modifying medications (Kruth et al., 2003).

- The SLS equipment is composed of **six components**: (i) A building platform, where 3D item fabrication is carried out; (ii) A laser, used for sintering; (iii) Galvano mirrors, for projecting and directing the laser beam to the desired positions for printing; (iv) A reservoir platform, stores and distributes new powder on to the building platform; (v) A mechanical roller, for spreading and flattening fresh powder on the building platform; (vi) A material vat, for recovering powder materials which are unsintered; (Akande et al., 2016; Ma et al., 2018; Tiwari et al., 2015).

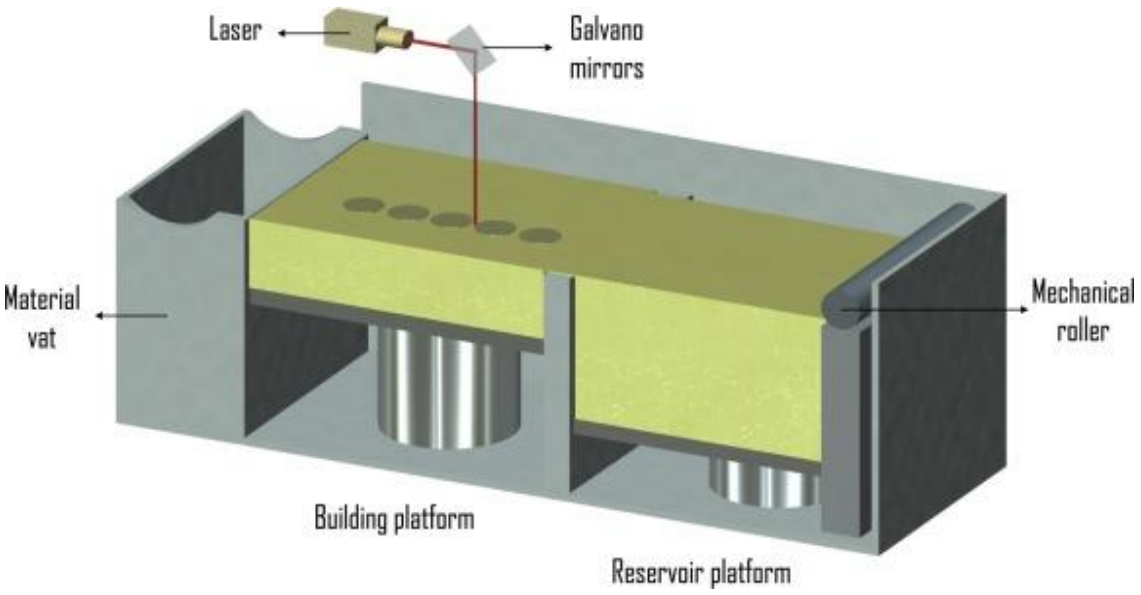

Figure 4: A graphical representation of Selective laser sintering (SLS) 3D printer (Awad et al., 2020)

Table 1: Examples of pharmaceutical products fabricated utilizing SLS 3DP technology

Pharmaceutical applications	**Active pharmaceutical ingredient(s) (APIs)**	**Polymer(s)**	**Other Excipients**	**Reference**
Orally disintegrating Printlets	• Ondansetron • Paracetamol • Diclofenac-sodium	Kollidon VA64 Kollidon VA64 Kollidon VA64	β-Cyclodextrin, Candurin® Gold Sheen, Mannitol Candurin® Gold Sheen Candurin® NXT Ruby Red, Lactose monohydrate	(Allahham et al., 2020) (Fina et al., 2018c) (Barakh Ali et al., 2019)
Immediate-release Printlets	• Paracetamol • Paracetamol	Kollicoat IR HPMC	Candurin® Gold Sheen Candurin® Gold Sheen	(Fina et al., 2017) (Fina et al., 2018c)
Controlled-release Printlets	• Paracetamol • Progesterone • --	Eudragit L100-55 PCL PCL, PLLA	Candurin® Gold Sheen -- --	(Fina et al., 2017) (Salmoria et al.,2017a) (Leong et al., 2006)
Printlets for the visually impaired**	• **Paracetamol**	**Kollidon VA64**	**Candurin® Gold Sheen**	(Awad et al., 2020)
Miniprintlets	• Paracetamol, ibuprofen	Kollicoat IR, EC	Candurin® Gold Sheen	(Awad et al., 2019)
Gyroid lattices and bi-layered Printlets	• Paracetamol	PEO, Eudragit L100-55, Eudragit RL and EC	Candurin® Gold Sheen	(Fina et al., 2018b)

Multi-reservoir drug delivery system	• Progesterone	PCL	--	(Salmoria et al., 2012c)
Tissue and bone regeneration implants	• 5-fluorouracil • Ibuprofen • 5-fluorouracil	PE PCL PCL	-- -- --	(Salmoria et al., 2017b) (Salmoria et al., 2016) (Salmoria et al., 2017c)
Intrauterine devices	• Progesterone, • 5-fluorouracil	HDPE	--	(Salmoria et al., 2018)

3.3 Printlets for the Visually-Impaired by SLS 3D Printing Technology

With the goal of generating individualized solid oral medication forms which are especially addressed to individuals who seem to be blind or visually challenged, the SLS 3DP process was satisfactorily employed to imprint patterns like braille and moon on the cylindrical printlets' surface. As seen in the Figures, all 26 alphabets were printed in braille and moon alphabets. Most crucially, the readability of the printlets was confirmed by a blind staff member at the (RNIB) (Fina et al., 2018).

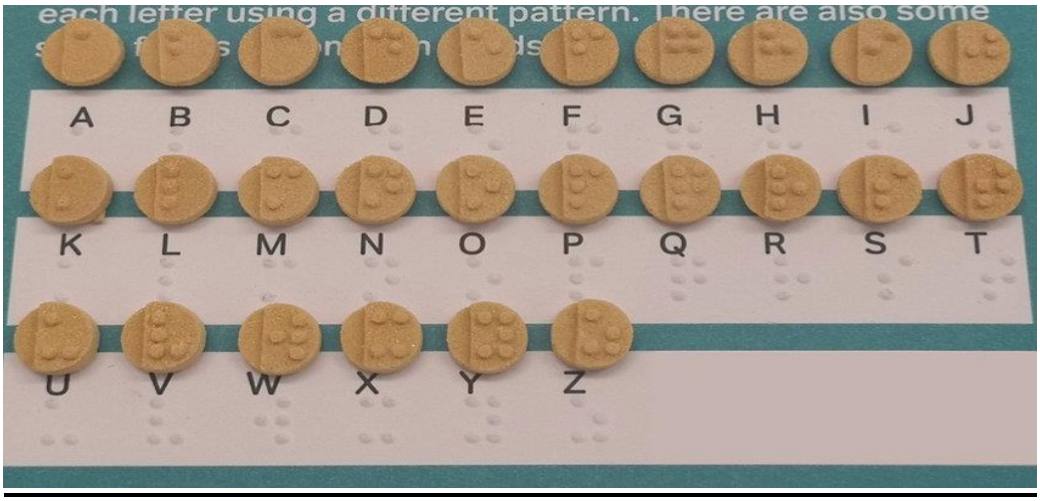

Figure 5: Illustration of cylindrical printlets comprising the 26 Braille alphabets (Awad et al., 2020)

According to the RNIB, the goal with this property was to let the patients know in which way to read the braille and moon alphabets (e.g., from left to right) properly, thus stopping people from mistaking different letters with alike patterns (Awad et al., 2020).

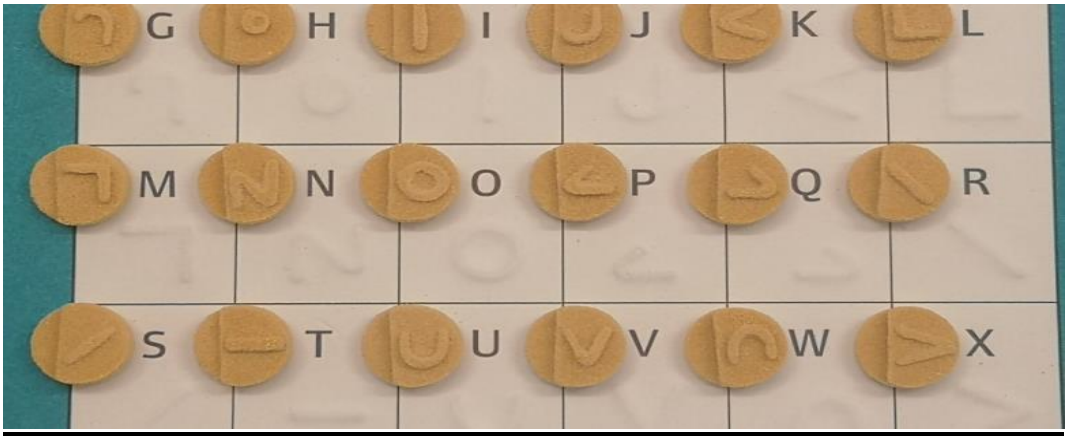

Figure 6: Illustration of cylindrical printlets comprising the 26 Moon alphabets (Awad et al., 2020)

SLS 3DP was also utilized effectively to create printlets having novel shapes, including a sun, a moon, a heart, a caplet, a pentagon, and a square. The purpose of these shapes was to provide patients with low eyesight with additional pharmaceutical information (for example, dosing regimen and/or medicine indication). There were a lot of different shapes used with braille or moon patterns to share more details in this case. As model alphabets, the Braille and Moon letters for "M" (for example, morning), "N" (for example, night), "C" (for example, cardiovascular), and "P" (for example, paracetamol) were chosen (UKAAF, 2020). In addition, the heart shape was chosen for "cardiovascular" products because it is a clear representation of the damaged organ. Shapes like the sun and moon were selected to symbolize "morning" and "evening" dosing, respectively. Finally, due to the difference in the amount of edges between the shapes of pentagon and square, they were chosen to separate the medication ingestion time (for instance, the time of intake can be linked to the amount of edges). In contrast to the other patterns, the heart and the moon shapes didn't need the addition of a step-down. Most of it is owing to their differing structures, in which by finding the heart's curved top and pointed bottom, the right and left sides can be determined. When given the appropriate instructions, the inner and outer curves of the moon shape may readily be recognized as left and right directions by the patients. Lastly, owing to the fact that all Printlets dissolve within five seconds**,** they reduce the requirement for water and thereby enable self-administration of medications (Awad et al., 2020).

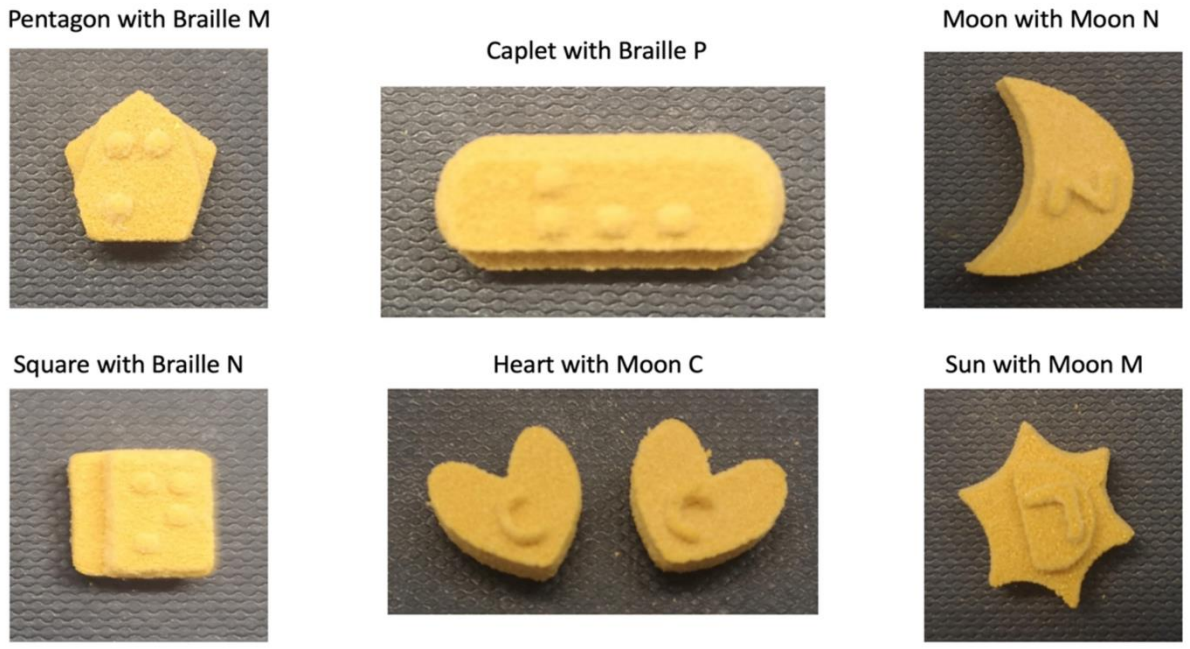

Figure 7: Printlets of various shapes with Braille and Moon patterns on them (Awad et al., 2020)

3.4 Materials Used for Printlets

1) As a model drug, paracetamol of the United States Pharmacopeia (USP) grade was chosen.
2) For SLS printing, Kollidon VA64, a vinylpyrrolidone-vinyl acetate copolymer with a molecular weight of approximately 45,000 Da and **immediate release qualities**, was utilized.
3) A pharmaceutical pigment called Candurin® Gold Sheen was applied.
4) The (RNIB) in the United Kingdom produced cards as a reference containing the Braille and Moon alphabet on them.

3.4.1 Specifications of Printed Braille

The Braille printlets weighed an average of 171.3 mg each. Weights of Braille printlets ranged from 164.1 ± 1.6 mg (average weight of printlets with one Braille dot) to 178.1 ± 5.6 mg (average weight of Braille printlets with two Braille dots) (Awad et al., 2020).

3.5 Advantages of SLS 3D Printing

- Uniquely, SLS can be used to make 3D structures that are very slight and very precise which can't be made with traditional manufacturing methods (Awad et al., 2020).

- The key benefit of the SLS 3D printer is the convenience of batch printing and the elimination of the requirement for supports, 3D printing is extremely rapid.

- Precision and capability are combined in SLS 3DP to produce medicines with distinct engineering and functional properties. SLS is a flexible technique that enables the printing of a wide variety of dosage forms with distinctive features. (Awad et al., 2020).

- SLS provides a diverse range of materials with a variety of intrinsic qualities. A variety of drug release patterns could be achieved by selecting the appropriate polymer and fine-tuning the processing parameters

- At the moment, CO2 lasers are used in a large number of commercially available SLS printers that give more power at a cheaper price, allowing for the usage of a broad variety of powdered thermoplastic materials (Awad et al., 2020).

- SLS is expected to be more suitable for pharmaceutical applications. While other 3DP processes, such as binder jetting, also use powdered materials, the fact that SLS is a solvent-free process minimizes necessity for additional drying steps to remove any remaining binder (Awad et al., 2020).

- SLS has been used to create implants that are patient-specific (Williams and Revington, 2010) and surgical tooling (George et al., 2017). SLS has demonstrated significant utility in tissue engineering for the repair and regeneration of tissues (Chua et al., 2004; Eosoly et al., 2010; Partee et al., 2006; Tan et al., 2003; Tan et al., 2005a). Also, SLS has been investigated in dentistry for its potential use in the fabrication of prosthetics (Di Giacomo et al., 2016) and dental appliances (Revilla-León and Özcan, 2017).

3.6 Disadvantages of SLS 3D Printing

- SLS has progressed slowly in pharmaceutical development. It is primarily because of the initial concerns about laser-induced degradation of drugs and excipients (Alhnan et al., 2016) and the lack of pharmaceutically authorized materials commercialized for SLS application.

- SLS has a number of significant disadvantages, one of which is its effect on laser-sensitive materials, most importantly natural polymers including pharmaceuticals. Thus, imposing limitations on the compatibility of materials and drugs (Vail et al., 1996; Walker and Santoro, 2017).

- Additionally, from a technical standpoint, printing requires a substantial quantity of powder to achieve regular layer height and proper powder flow and in some cases, it may not be possible (Telenko and Seepersad, 2010).

- Moreover, while unsintered powders are recyclable, they are only suitable for a selected amount of prints due to the issues about chemical stability and physical changes (Dotchev and Yusoff, 2009). As a result, when vast quantities of powder are required, if the process is not optimized, some of the material may go to waste. Thus, recycling of materials is not possible.

- Due to the fact that the method may occasionally require post-treatment (e.g., sieving and brushing printed dosage forms), as a result additional charges and time may be involved in this process. Thus, post-processing operations might be challenging. (Thomas and Gilbert, 2014).

- Biocompatible and biodegradable polymers must be FDA-approved (i.e. generally recognized as safe, GRAS). Irrespective of the eventual usage, the chosen polymer must also fulfill printing criteria, which include adequate flow properties and particle shape and size (Awad et al., 2020).

3.7 Fused Deposition Modeling (FDM) 3D Printing Technology

FDM is an additive material extrusion technology that builds items out of thermoplastic polymers. The platform's unique architecture enables the use of 3DP in sectors such as engineering and medicine, significantly expanding the possibilities. FDM has a straightforward fundamental aspect but is capable of producing complex shapes (Khamkar & Mahapatra, 2021). It involves printing items by depositing layers of material from a computer-controlled moving nozzle. Typically, the printing material is a plastic filament [Acrylonitrile butadiene styrene (ABS) or polylactide (PLA)] that is melted inside the printing nozzle and extruded as a thinner filament. The molten filament adheres to the printed layers below and cools to ambient temperature, generating a new printed layer (Loconsole et al., 2016). In addition, fused deposition modeling (FDM) is the most frequently researched 3D printing technology for the production of customized medications (Kollamaram et al., 2018). FDM is a 3D printing technique that has gained widespread adoption in both professional-grade and low-cost consumer 3D printers.

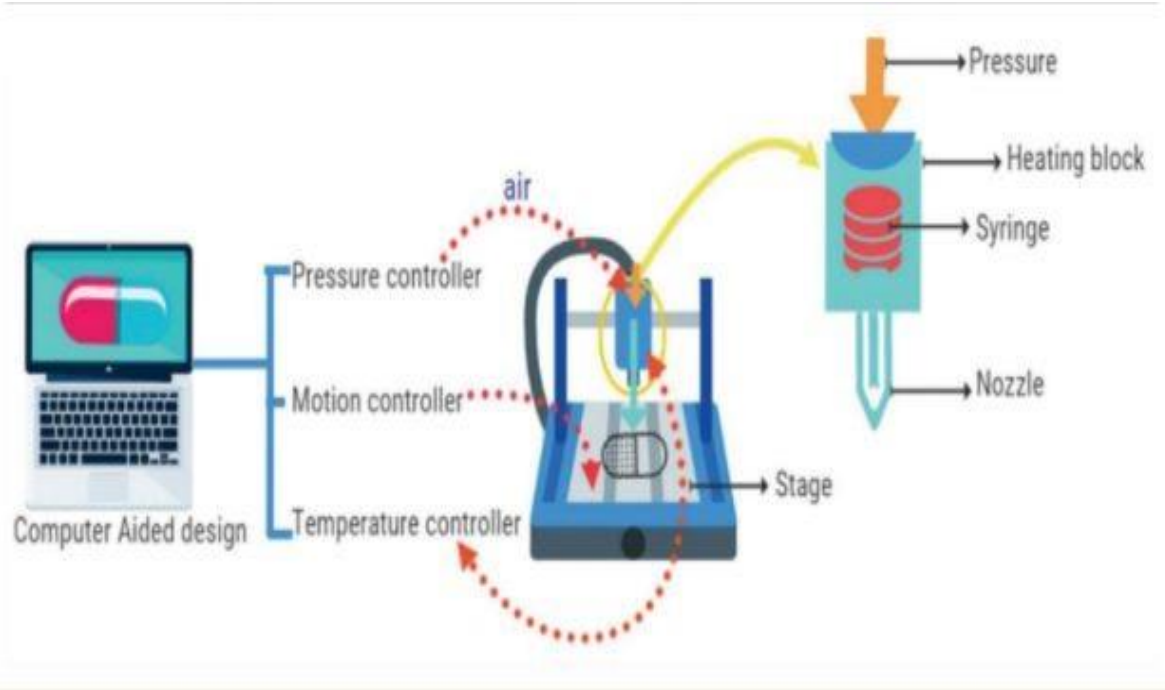

Figure 8: Schematic representation of fused-deposition modelling (FDM) process (Khamkar & Mahapatra, 2021).

3.7.1 Properties of Fused Deposition Modeling (FDM) 3D printing technology

- FDM is a method of melt extrusion in which a feedstock filament is provided by an electric motor-driven device (Khamkar & Mahapatra, 2021).

- A heated liquefier is used to melt the filament. Stepper motors are used to transport the liquefier/print head unit across a platform. The melted filament is then pushed through the liquefier to the nozzle, where it is deposited in the XY plane (fixtureless worktable) (Khamkar & Mahapatra, 2021).

- After the of deposition at each new cross-section, the platform or print head moves down or up on the Z-axis by the thickness of one layer at a time. There are many layers that make up the 3D structure, so it is built one at a time. This process is repeated until the component is done. Moreover, FDM starts with a lot of material on the part's edges and then moves inside the outline. A certain number of outlines is required to pack the component according to the reaction required (Khamkar & Mahapatra, 2021).

- Physical and chemical quality of the filament are two of the most important things to think about before printing. They check to see if the print process is possible. Printing temperature and the density of the infill, for example, are factors that are specific to each operation. These things influence the final quality and dissolving behavior of the objects (Khamkar & Mahapatra, 2021).

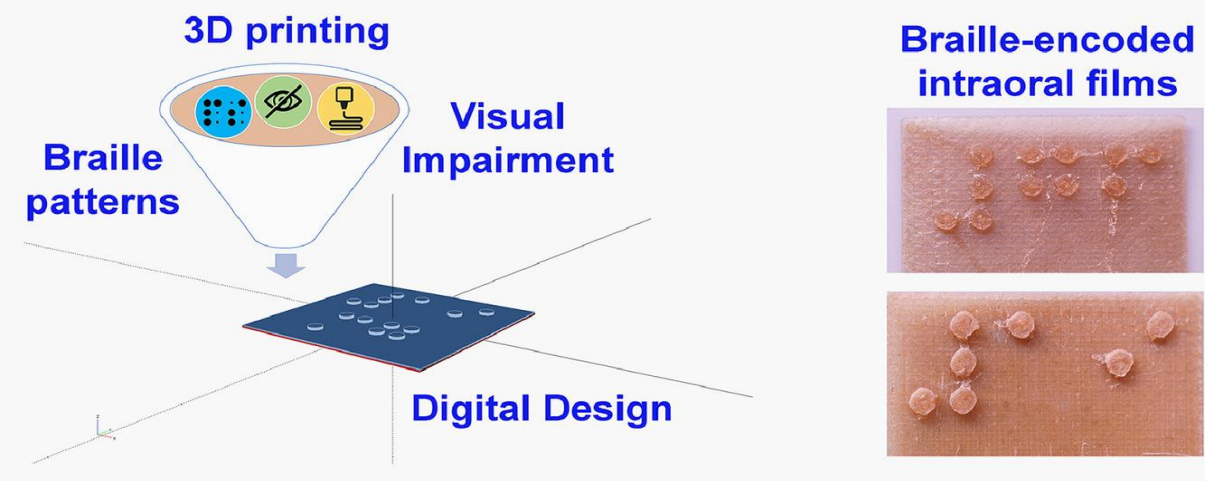

Figure 9: Graphical representation of Braille-encoded Intraoral Films by FDM 3D printing technology (Eleftheriadis & Fatouros, 2020).

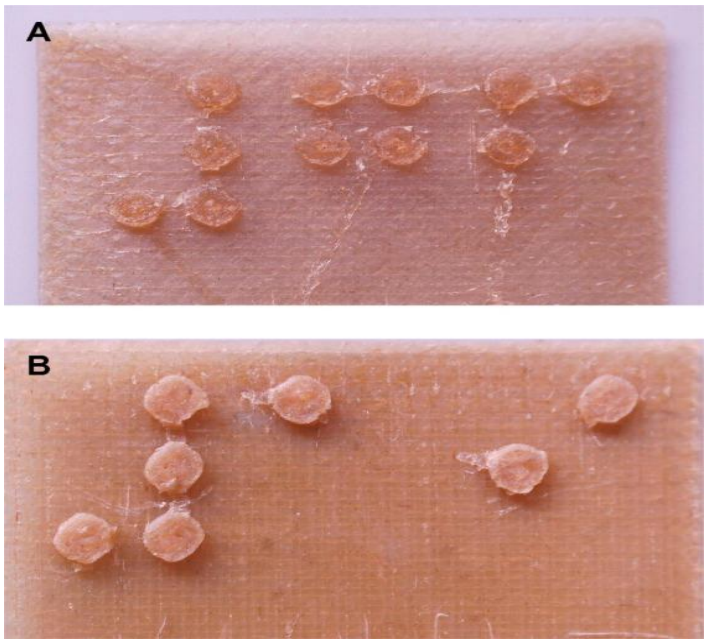

Figure 10: Illustration of the Braille dots onto the surface of formulation developed by the FDM 3D printing technology (Eleftheriadis & Fatouros, 2020).

Table 2: Drug delivery systems fabricated using Fused deposition modeling (FDM) 3DP technology

Drug	Drug Delivery System	References
Calcein	3D printed composite tablets having drug-loaded polyvinylalcohol (PVA) as the drug component	Tagami et al.,2018
Deflazacort	3D printed tablets loaded with polymeric drug-loaded nanocapsules	Beck et al.,2017
Progesterone	3D printed biodegradable projectile	Long et al., 2018
Lamivudine	3D printed polyvinyl alcohol (PVA) capsule shells, wherein the shells were filled with either solid or liquid vehicle containing the API	Smith et al., 2018
Riboflavin	TiD (tablet-in-device) system was formed where the riboflavin tablets were filled into the device (whose cap and body were 3D printed by FDM)	Fu et al.,2018
Haloperidol	3D printed tablets for rapid release of drug	Solanki et al.,2018
Indomethacin	3D printed drug-containing T-shaped prototypes of the intrauterine system (IUS) having controlled drug delivery	Holländer et al.,2016
Paracetamol	Single layered fast dissolving oral films (FDFs), and multi-layered FDFs	Ehtezazi et al.,2018
Metformin, Glimepiride	3D printed bilayer oral solid dosage form having metformin (for prolonged drug delivery) and glimepiride (for immediate drug delivery)	Gioumouxouzis et al.,2018
Gentamicin sulfate	Antibiotic-laden catheters were constructed which showed sustained drug release	Weisman et al.,2018
Hydrochlorothiazide	Caplets with perforated channels were used to accelerate drug release from the 3D printed tablets	Sadia et al.,2018

3.7.2 Braille-encoded 3D Printed Intraoral Films by FDM 3D Printing Technology

The FDM process is utilized to create Braille-encoded intraoral films for visually challenged individuals, particularly for treatments that requires repeated dose modifications. In addition, as for the Braille dots, they had to meet the "Marburg Medium spacing" rule for pharmaceutical packaging braille, which stipulates that dots must be at least 0.2 millimeters tall (ISO 17351, 2014). Pharmaceutical-grade hot melt extruded filaments were used to fabricate the films. Due to the high resolution of the three-dimensional printer, it was feasible to generate these identifiers in cylindrical forms *(Eleftheriadis & Fatouros,2020).* Moreover, the films have a drug-loaded portion and a backing layer with architectural properties that are comparable to those used for buccal delivery**.** The model API was ketoprofen, and the polymer matrix for both portions was hydroxypropyl methylcellulose (HPMC), a hydrophilic polymer because of its mucoadhesive characteristics, it was employed as the core polymer. *(Eleftheriadis & Fatouros,2020).* Furthermore, the formulation allowed for the insertion of five Braille characters on the films' top surface, arranged in two rows, to denote the amount of API included *(Eleftheriadis & Fatouros,2020).*

Table 3: Advantages & Disadvantages of FDM In A Nutshell (Pal & Rajpoot, 2021)

S.No.	Advantages	Disadvantages
1.	Budget-Friendly	Rough Surface Finishing
2.	Filament Reusable	Warping is common, Complex structures require support
3.	Ease of use	Nozzle Clogging
4.	Easy Ergonomics	Longer Printing Time, relatively low resolution
5.	Variety of Material Choice	Layer Adhesion Problem (Layer Shift)
6.	High equipment diversity	Weak in Strength, not suitable for heat-labile molecules
7.	High uniformity, excellent mechanical properties	Low drug loading, Difficult to scale up

Chapter 4: Results & Discussion

4.1 SLS 3D Printing

Printlets with Braille and Moon patterns were successfully printed using the SLS 3D printing technique, with the goal of generating personalized solid oral dosage forms for blind or visually impaired patients. It was possible to print all 26 different alphabets, including the Braille and Moon patterns. The Braille printlets had an average weight of 171.3 mg, whereas the average weight of the Moon printlets was 165.8 milligrams. Whereas, the average weight of the Moon printlets was 165.8 mg, weights ranging from 162 ±1.7 mg (average weight of printlets with the letter H) to 171.1 ±5.9 mg (average weight of printlets with the letter N). The addition of a single Braille dot increased the printlet's average weight by 3.8% and for the inclusion of the Moon patterns, the printlets' average weight increased by 4.9%. The patterns were perceptible to the naked eye and could be recognized by touch. A (RNIB) staff member who is blind has confirmed the recognition.

Table 4: Mechanical properties and disintegration times of the printlets with or without the addition of the Braille patterns (Awad et al.,2020)

Printlet Type	Breaking Force (N ± SD)	Disintegration Time (s ± SD)
Printlets without pattern	14.5 ± 1.8	4.0 ± 1.3
Printlets with Braille A	13.9 ± 1.4	4.3 ± 1.5
Printlets with Braille Q	14.3 ± 2.1	5.2 ± 1.2

The mechanical characteristics of the printlets were determined with and without Braille patterns. This demonstrates that the patterns had no effect on the printlets' mechanical properties and similar breaking forces had been exhibited by all the printlets (Fina et al.,2018). In addition, the printlets' disintegration time was determined. The results indicate that all printlets disintegrated similarly, with no statistically significant variations between the groups. Due to the fact that these printlets disintegrate in less than five seconds, they should dissolve in the mouth prior to drinking the formulation (Fina et al.,2018).

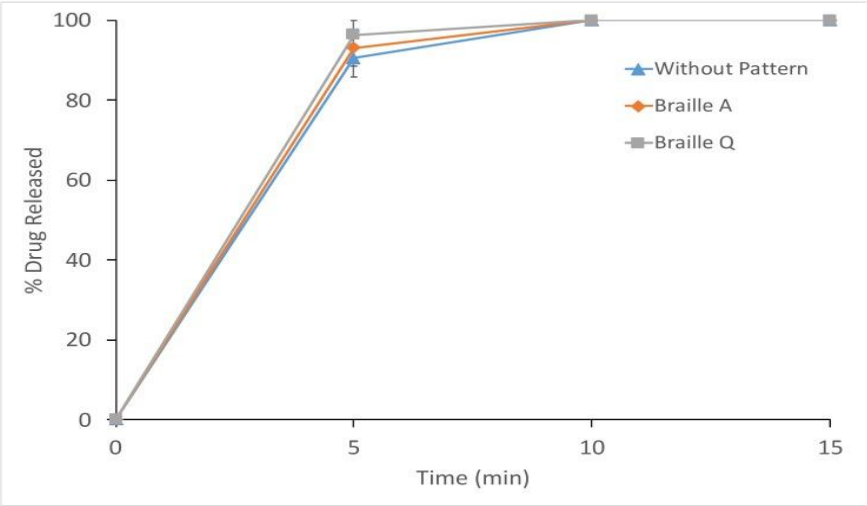

Figure 11: Drug dissolution profiles of the printlets without pattern, with Braille A, or with Braille Q in a 0.1 M HCl (pH = 1.2) dissolution medium (Awad et al.,2020)

Dissolution tests were also done with printlets containing braille letters A and Q and also printlets that didn't have a pattern. Result shows, there were no significant changes on the release rates of the printlets when Braille patterns were added to them. Printlets with Braille patterns were assumed to have a comparable drug release profile to printlets without any Braille patterns (Awad et al.,2020).

4.2 FDM 3D Printing

According to the data collected, the mechanical properties of the films revealed, the IH and EM values for Keto and polyethylene glycol-containing HPMC-based objects were significantly different ($p < 0.05$). This resulted from the differing nature of each compound or its concentration in the polymer matrix, indicating that Keto had a greater plasticizing effect than polyethylene glycol. Most notably, local differences in IH and EM were minor ($p>0.05$) for both the HPMC-polyethylene glycol plain surface and Braille dots (Eleftheriadis & Fatouros, 2020). In addition, a haptic evaluation was undertaken in vivo, with fifteen participants with vision impairment chosen to participate. Six distinct films from the study were sent to participants, and they were politely asked to assess the number of Braille text on the surface. After that, participants were requested to continue analyzing the Braille text, ensuring that the whole haptic assessment process took not less than five minutes for every specimen. **The participants claimed** that the Braille-encoded text on all films was excellently readable, regardless of the criteria used to design the Braille dots; hence, the rating technique was heavily concentrated toward participant preference.

Table 5: The (IH) indentation hardness and (EM) elastic modulus of the specimens (n=3) (Eleftheriadis & Fatouros,2020).

Sample	IH (MPa)	EM (MPa)
HPMC:Keto	18.29 ± 2.64	104.23 ± 3.54
HPMC:polyethylene glycol (surface)	47.59 ± 6.37	226.43 ± 26.58
HPMC:polyethylene glycol (Braille dot)	48.32 ± 5.89	240.24 ± 24.64

Finally, the participants were asked to express their views on the upcoming capability and convenience of fabricating braille encoded instructive messages directly into the surface of formulations. It was noted that the provided solution is found favorable to the existing state braille text on pharmaceutical packaging.

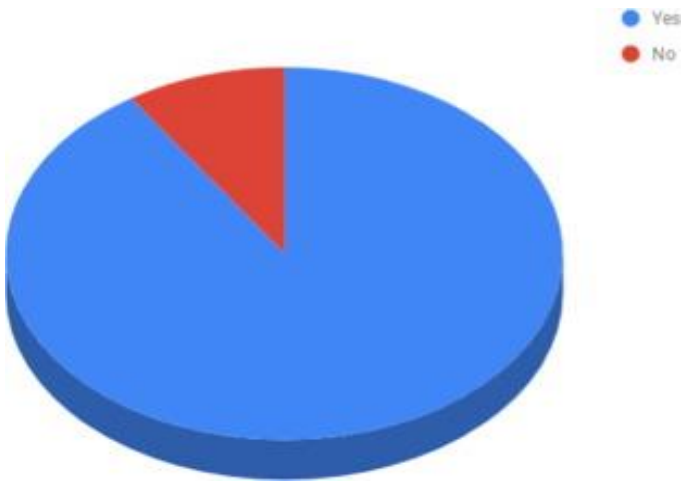

Figure 12: According to a survey of 215 blind people over the age of 18 in Saudi Arabia, were asked whether braille labels may increase the efficiency of therapy and eliminate the problems they had taking their medications, 91 percent agreed (9 percent disapproved) that braille labeling may enhance the effectiveness of the therapy (Almukainzi et al.,2020).

Chapter 5: Future Perspectives & Challenges

5.1 Future perspectives

Many technical and regulatory issues remain with 3D printing, but these are expected to be resolved in the near future. The correct use of braille in pharmaceuticals will alleviate a number of difficulties faced by patients who are blind or visually impaired, such as mistaking one dose for another, forgetting to take a medication, and mistaking one container for another. In addition, 3D printing will open up new opportunities for the creation of medications and speed up the advent of individualized and intelligent drug distribution, which will benefit both patients and manufacturers.

5.2 Challenges

Despite the benefits of 3D printing technology, several technical challenges and impediments must be overcome promptly in order to expand the use of DDSs (Drug Delivery Systems). 3DP has a number of obstacles which includes;

- **Regulatory landscape:** The fragile nature of printed materials, particularly cell-based objects, combined with the complexity of manufactured structures demands a well-thought-out approach. Concerning design, manufacturing process, and quality testing factors, there are **no valid regulations** (Jamróz et al., 2018). Many questions have been raised about how 3D-printed products are supervised and evaluated before and after they are sold. There are currently no regulations or norms in place for 3D-printed medications (Cui et al., 2021).
- **The 3DP devices' scalability** is a disadvantage, since the existing 3D printers other than binder jetting are not scalable and flexible.
- **Mechanical properties**: Due to their poor mechanical strength, 3DP items have restricted packaging, administration, and general handling operations (Khan et al., 2019). In addition, because of the unique printing approach used in 3DP, different polymers or powders are piled on top of one other, resulting in a rough surface and products with low mechanical strength (Zheng et al., 2016).
- **Excipients:** Due to their distinct printing principles, all types of 3D printing technologies have specific requirements on the qualities of excipients throughout the preparation process. As a result, the presence of residual solvents in some of the final 3D printed

tablets is a significant limitation. In comparison to traditional pharmaceutical methods, the excipients available for 3D printing technology are quite limited. Selecting the correct excipients may be crucial, especially for specific dosage forms of individual administration. Furthermore, many of the materials used in the printing process are non-pharmaceutical grade, which makes their use in pharmaceutical formulations difficult due to compatibility issues and hazardous side effects (Cui et al., 2021).

- Drug release is affected by the geometry of 3DP's drug delivery method. **Thermolabile pharmaceuticals** may be incompatible with 3D printing technology. The use of high processing temperatures can cause thermally labile pharmaceuticals to degrade considerably (Palo M et al., 2017).
- Drug delivery systems (DDS) made with printing-based inkjet systems **must go through a drying process,** which can be quite severe (high temperatures) in order to eliminate any remaining solvent (Wang C-C et al., 2006).
- **High maintenance**: Cleaning 3D-printed devices after each usage is necessary, independent of the 3DP technique used, because it eliminates the support material and leftover monomers. Additionally, finishing treatments such as tumblers or sandblasting may be required for some techniques. To preserve the physical stability of the finished product, technical parameters such as laser beam energy density, scanning speed, deposition velocity, and humidity have to be considered (Khan et al., 2019).
- **The technical challenges** of using 3D printers to prepare pharmaceutical formulations continue to suppress the advancement of 3DP technology; additionally, 3D printers used in medicine do not meet the good manufacturing practice (GMP) standard, necessitating validation of the process and products to ensure that they are safe for human health (Cui et al., 2021). In addition, commercialized SLS printers presently don't really adhere to Good Manufacturing Practice (GMP) standards, making it impossible to create dosage forms in a clinical setting. This creates technical and logistical issues, making it more difficult to assure batch-to-batch consistency and end-product consistency, which necessitates the use of in-process quality control (QC) measures (Awad et al., 2020).

Chapter 6: Conclusion

Blind or visually impaired individuals confront numerous obstacles while attempting to self-administer medications. For the visually challenged, the need for braille on dosage forms, manufacturing packaging and drug labeling prescriptions is growing significantly. SLS and FDM 3D printing technologies could be used to produce individualized dosage forms for blind or visually impaired individuals. These approaches may be used to create Braille- or Moon-patterned printlets that blind individuals could read, as well as Braille-encoded intraoral films. This novel concept is likely to revolutionize the way visually impaired patients are treated, increasing independence, medication adherence, and lowering medication errors. This could eventually result in the rethinking of the regulatory or standards framework for pharmaceutical Braille, given the recent rise of 3D printing technologies and their enormous potential for pharmaceutical manufacture and patient well-being.

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