Possibilities of 3D & 4D Printing Technologies for Personalized Medicine

By

Fatema Tuz Zohra Moonmoon
15146021

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 here by 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.

Student's Full Name & Signature:

Fatema Tuz Zohra Moonmoon
15146021

Approval

The project titled "Possibilities of 3D & 4D Printing Technologies for Personalized Medicine" submitted by Fatema Tuz Zohra Moonmoon (15146021) of Spring, 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on August, 2019.

Examining Committee:

Supervisor:
(Member)

_____
Dr. Md Jasim Uddin
Assistant Professor, Department of Pharmacy
Brac University

Program Coordinator:
(Member)

_____
Dr. Hasina Yasmin
Associate Professor, Department of Pharmacy
Brac University

Departmental Head:
(Chair)

_____
Dr. Eva Rahman Kabir
Professor, Department of Pharmacy
Brac University

Ethics Statement

This study does not involve any human or animal trial.

Abstract

Personalized medicine is a significant achievement for modern medication as it helps to create treatment plans fixated on attributes that make each individual unique. For tailored drugs and dosage form different kinds of printing technologies exhibits immense potential to achieve this distinctive requirement of treatment. This provides 3D printing an upper hand over the conventional strategies of drug development. Despite the fact that 3D printed drug item has already been approved yet it faces some difficulties in printing complex structure. These obstacles can be overcome by 4D printing. Its additional dimension opens new possibilities for personalized medicine. In this review, the possibilities of 3D and 4D printing technology for developing personalized medicine is discussed along with future direction of this research field.

Keywords: 3D Printing; 4D Printing; Fused Deposition Modeling; Personalized Medicine; Orodispersible Film.

Dedication

Dedicated to my parents

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List of Acronyms

3DP	Three Dimensional Printing
4DP	Four Dimensional Printing
5DP	Five Dimensional Printing
6DP	Six Dimensional Printing
API	Active Pharmaceutical Ingredient
EOS	Electro Optical System
FDA	Food and Drug Administration
FDM	Fused Deposition Modeling
ODF	Orodispersible Film
ODT	Orodispersible Tablet
PLA	Polylactic Acid
PVA	Polyvinyl Alcohol
SLA	Stereolithography

Chapter 1

Introduction

Market accessible oral medications do not fulfill all needs of special patients, for example, dysphagics, pediatrics, geriatrics and patients with hypersensitivities or dietary restriction (Cilurzo, Musazzi, Franzé, Selmin, & Minghetti, 2018; Visser, Woerdenbag, Hanff, & Frijlink, 2017; Scarpa et al., 2017; Minghetti, Pantano, Gennari, & Casiraghi, 2014). In recent years, for personalizing the treatment procedure orodispersible preparations have been proposed, particularly for young age children and old because of the likelihood of combining the benefits of solid dosage form and liquid preparations (Visser et al., 2015; Orlu, Ranmal, Sheng, Tuleu, & Seddon, 2017; Slavkova & Breitkreutz, 2015). Not only orodispersible tablets but also films (ODF) are available in market now. More recently, 3D printing is generally use to design solid oral dosage forms with various geometries and release attributes. This technique was additionally explored in the preparation of orodispersible films to overcome the problems associated with other oral medicine (Awad, Trenfield, Goyanes, Gaisford, & Basit, 2018; Sadia, Arafat, Ahmed, Forbes, & Alhnan, 2018; Kadry et al., 2018; Ehtezazi et al., 2018). 3D printing enables customers to design and create their individual items without producing huge waste. Presently through development of '4D printing' it is anticipated that this technique will be able to bring socio-economic change in the following decade (Jiang, Kleer, & Piller, 2017; Tibbits, 2014).

1.1 3D printing Technologies

Three-dimensional printing (3DP) has been anticipated to reshape the pharmaceutical division. It will enable treatment to move far from a 'one-size fits-all' technique to personalization. Undeniably, this innovation grants medications to be personalized to the individual prerequisites of every patient like through changing the dosage, shape, size and

release qualities, just as by means of development of multi-drug combinations (Trenfield, Awad, Goyanes, Gaisford, & Basit, 2018). 3D printing is mainly a manufacturing process through which 3D object can be developed by depositing or merging materials in layers (Schubert, Van Langeveld, & Donoso, 2014). Any shape of object can be created by 3D printing sequential layers. A computer aided 3D design model is used to produce these objects (Kilicarslan, Ilhan, Inal, & Orhan, 2018).

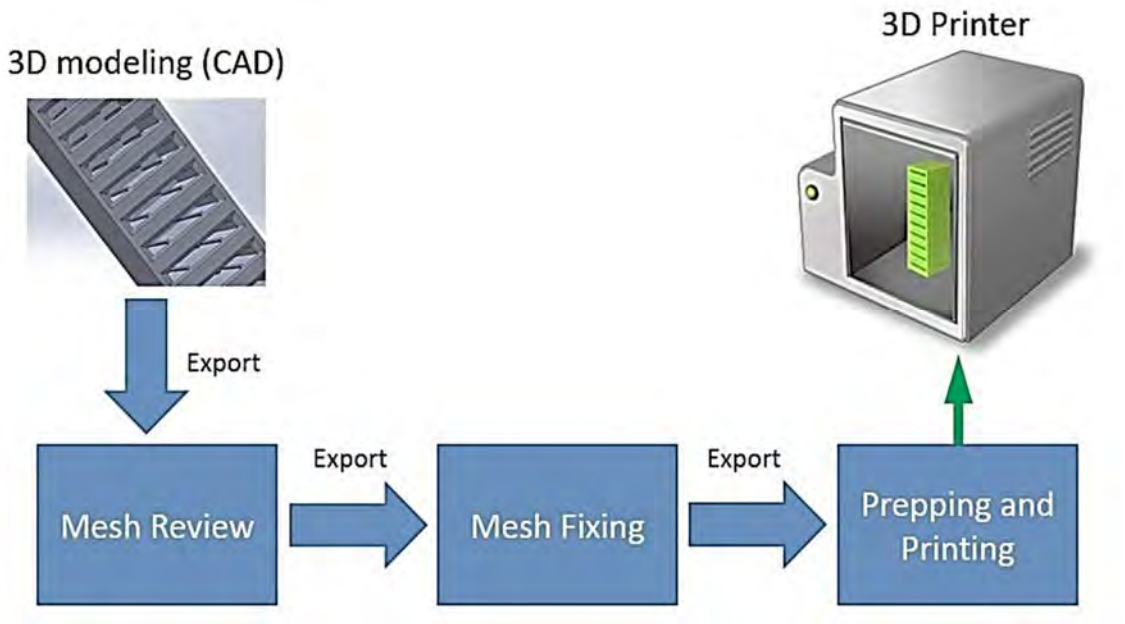

Figure 1: 3D Printing Process (Kilicarslan, Ilhan, Inal, & Orhan, 2018)

There are some 3D printing technologies present in the market like Stereolithography, sintering, melting, fused deposition modeling (FDM), inkjet printing etc. For now, more than a few extrusion-based constructions have arrived the marketplace using FDM/FFF technique. 3D printing process can be divided into 5 core elements which are (1) feedstock of material, (2) system loading, (3) liquefier, (4) head of printer and (5) the build plate. At first filament is passed via a heating block. After that melted polymer is extruded via a nozzle and then binds to prior layers when it hardens (Kwok et al., 2018).

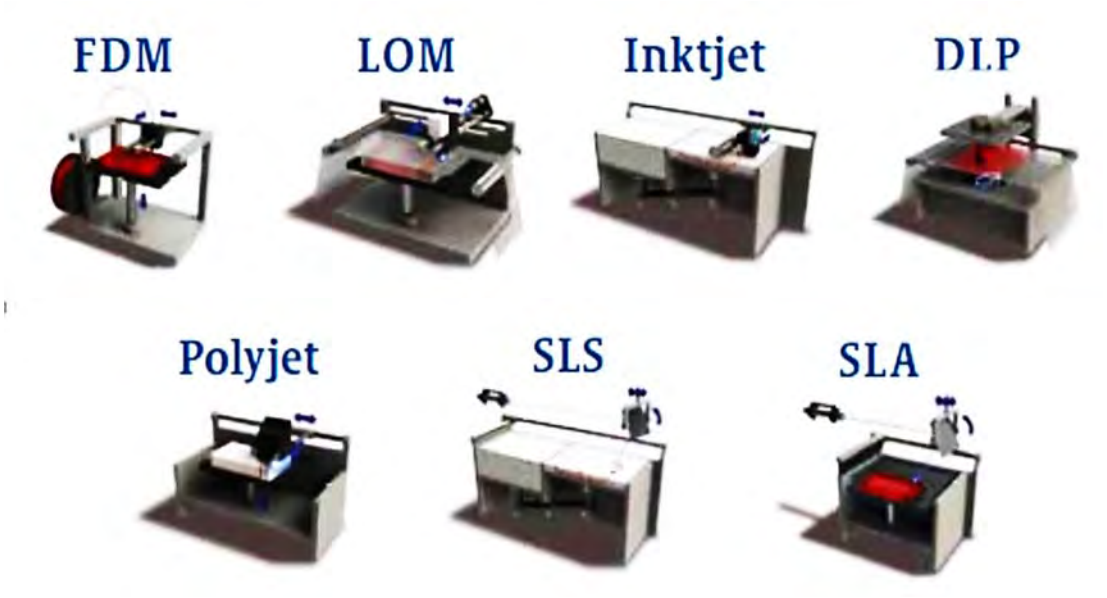

Figure 2: Different Types of 3D Printer (Turner & Gold, 2015)

After the formation of layer, the build plate lowers and after that the whole method is repeated again repeated (Turner & Gold, 2015). This technique has applied in many field including chemical, biomedical and the pharmaceutical field (Varan, Wickström, Sandler, Aktaş, & Bilensoy, 2017).

1.2 History of evolution in 3D printing technologies

The first man who developed a rapid prototyping technique or 3D printing process was Hideo Kodam. In spite of submitting a patent application in 1980, it expired without any further proceeding. After that in 1984, strelithography was invented by Charles hull. In 1988, SLA printer was first produced commercially (Bakhtiar et al., 2017). Around a similar time, Carl Deckard come with the theory of the selective laser (SLS) method. A company named Stratasys was founded by Scott and Lisa Crump in 1989 and fields a patent for fused deposition modeling (FDM). A computer guides the deposition which is based on a digital model. After that in 1989, Electro Optical Systems (EOS) was formed by Hans Langer. In this process a laser is selectively exposed to metal powder for liquid phase sintering. In 1994

EOS marketed its first stereo system. It is currently renowned as industrial prototyping (Zhang, Yang, Johnson, & Jia, 2018).

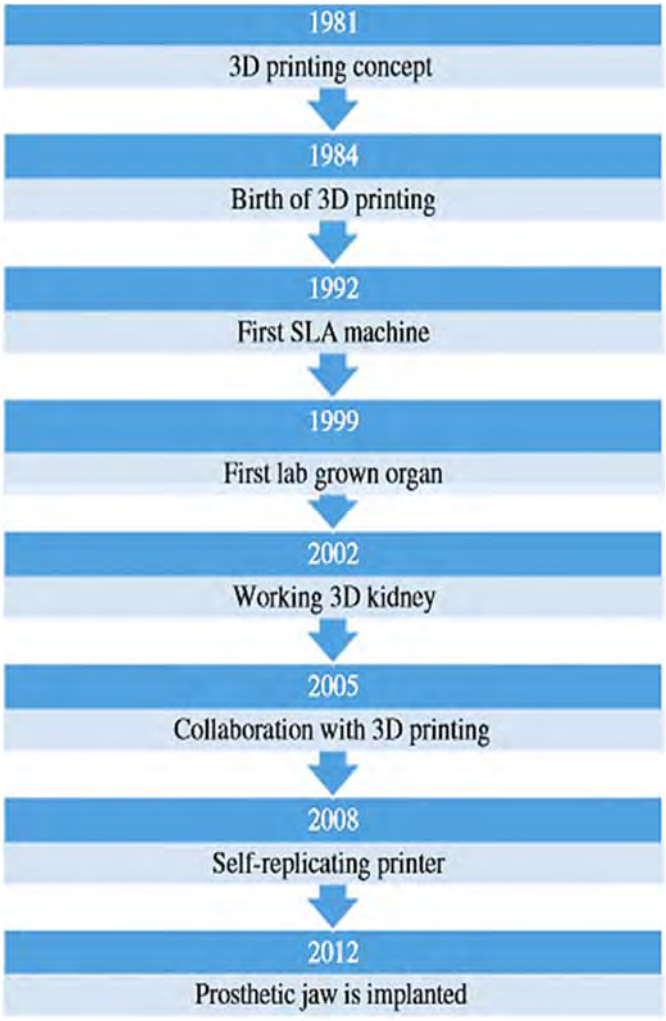

Figure 3: History of Evolution in 3D Printing Technologies (Zhang, Yang, Johnson, & Jia, 2018)

1.3 Current clinical applications

3D printing has discovered its impact in numerous businesses which is extended from rapid prototyping in designing to customize gadgets in medication. Features 3DP empower the accurate deposition of medication and excipients, conceivably results in a change in outlook in drug configuration, production and use. This process can be utilized in early stage drug

development, for example; preclinical examinations, first-in-human trials (Su & Al'Aref, 2018).

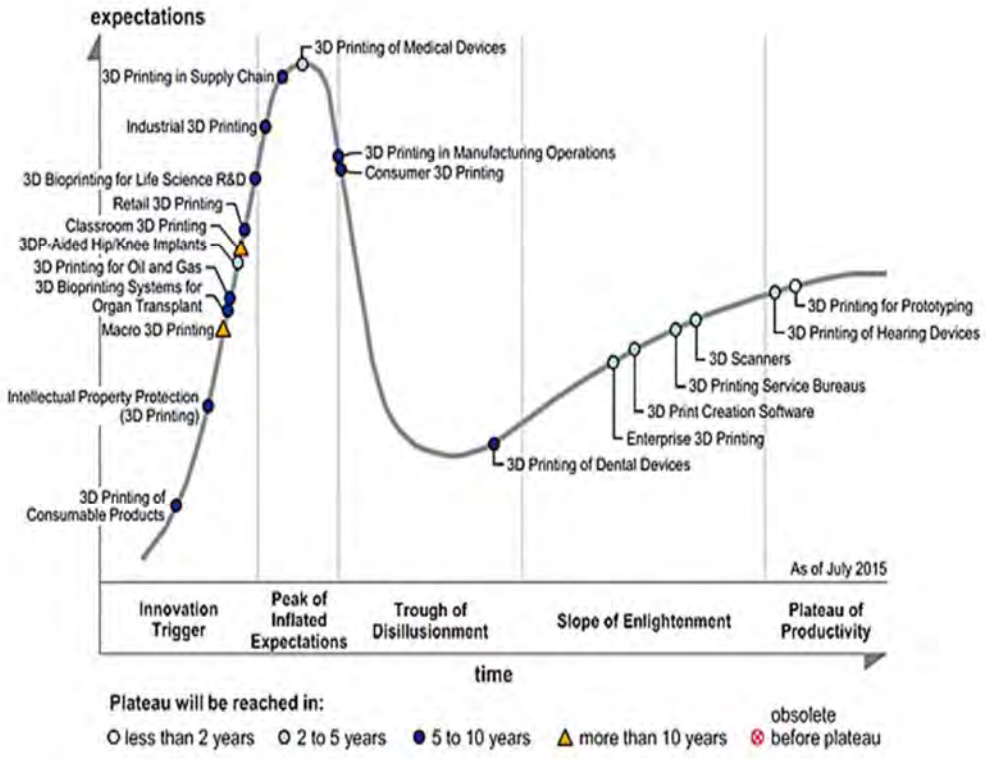

Figure 4: Gartner's 3D Printing Hype Curve (Schussler & Axhausen, 2009)

In the picture Gartner's 3D printing hyper curve is displayed. "The Hype Cycle for Emerging Technologies is the broadest aggregate Gartner Hype Cycle, including innovations that are the focal point of consideration on account of especially large amounts of interest, and those that Gartner accepts have the potential for significant effect," clarified Betsy Burton, VP and recognized analyst at Gartner. "Before, this curve was utilized to depict all innovations, with 3D printing being among them. In the most recent adaptation of this past graph, discharged in 2015, Enterprise 3D printing is as of now more distant along the natural growth curve. Consumer 3D printing is on the descending side of the hype phase. Bio-printing is moving up the hype curve. In the new examination, Hype Curve graph goes more inside and out into the

universe of 3D printing, breaking down a few unique uses of this innovation (Schussler & Axhausen, 2009).

All the more as of late, the innovation has been connected to pharmaceuticals to fabricate medicinal devices and 'printlets', which is a term that we have begat to allude to 3D-printed solid oral dosage forms. Up to this point, a scope of details have been created, including those containing various active pharmaceutical ingredients (APIs), with various geometries and release characteristics. Favorably, the innovation empowers exact portions to be stored dependent on the initial 'ink' concentration and the formulation. Moreover, in 2016, the 1st 3D-printed tablet approved by the US Food and Drug Administration (FDA) was commercialised for the treatment of epilepsy (Spritam by Aprecia Pharmaceuticalsi) (Trenfield, Goyanes, et al., 2018).

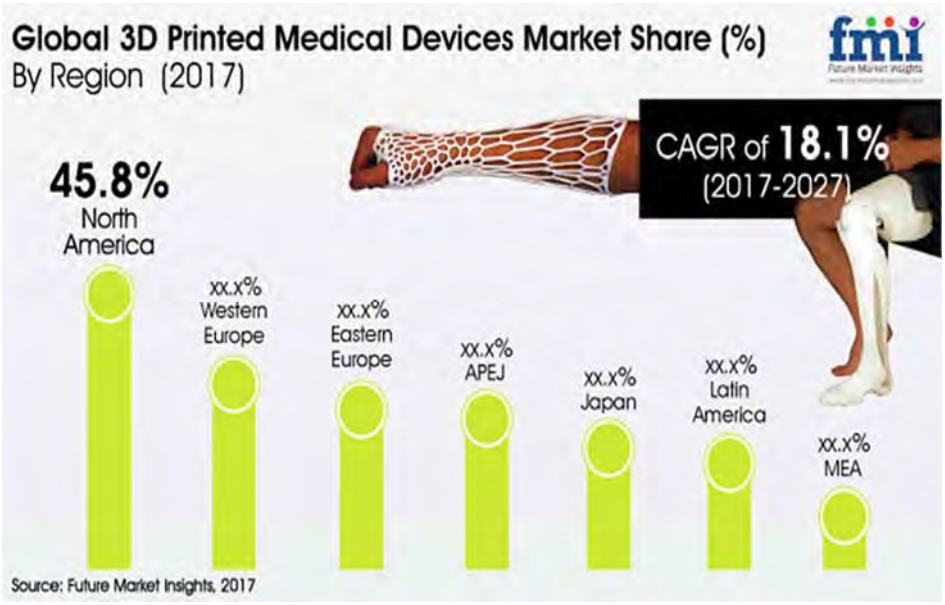

Figure 5: Global 3D Printed Medical Devices Market Share (%)(Trenfield, Goyanes, et al., 2018)

The worldwide 3D printed medicinal devices market is expected to grow at a CAGR of 18.1% during the forecast period 2017– 2027. Expanding predominance of chronic diseases and rising awareness in regards to personal care are central point that are driving the

development of the 3D printed medical devices market. Currently the medical application of 3D printing can be classified into four different levels (Phan, Sgro, Maharaj, D'Urso, & Mobbs, 2017).

1.3.1 Organ models to aid in surgical treatment analysis

High-fidelity physical organ models play a major role in clinical treatment and in medical education. Where conventional manufacturing processes, such as casting, waste so much time in preparing expensive tooling, and always ignore individual differences among patients, 3D printing has the advantage of rapidly fabricating customized medical models at a lower cost, since there are no tools involved. 3D printed organ models primarily help doctors to complete surgical analysis and preoperative training. It's possible that personalized medical models with complex shapes that are made using 3D printing can provide doctors and engineers with a medium for communication, and can assist in surgical planning and diagnosis (Yan et al., 2018).

1.3.2 Permanent non-bioactive implants

In dentistry and orthopedics where non degradable biomaterial and good biocompatibility require after surgical operation their permanent medical implants are usually used. Equated with fabricating implants by means of traditional machining technology, 3D printing can attain personalized real-time engineering of any complex implant with high dimensional accuracy and short fabrication cycles (Göke et al., 2018). During traditional bone treatments, stress- shielding phenomena can easily occur because traditional metallic implants present greater stiffness than bone, which will ultimately compromise bone integrity. Integrating topology-optimization designs with 3D printing is a new and effective technology to fabricate lightweight customized implants with adjusted stiffness. This technology is also highly compatible with digital measuring devices that have been widely used, in terms of data conversion and space docking (Ivanova, Williams, & Campbell, 2013).

1.3.3 Fabricating local bioactive and biodegradable scaffolds

Tissues and organ can be developed by two possible routes, depending on whether cells are directly manipulated throughout the formation process. Tissue engineering is the first route which is also known as indirect cell assembly. It includes forming of 3d scaffold and seeding cells. Biometric tissue like microarchitecture scaffold can be created by using living cells, biocompatible materials, growth factors, and physical factors (Razi, Nazaripoor, Sadri, Thundat, & Sadrzadeh, 2019). Direct cell assembly is the second route. It formulates both cells and materials in to fused structure. The mixture of cells and gel is encapsulated into 3D scaffolds. It can be printed directly to control the spatial distribution of cells and even *in situ* repair or composed of another gel with good mechanical strength (Lim, Kathuria, Tan, & Kang, 2018).

1.3.4 Directly printing tissue and organs

Encapsulating cells into biodegradable platforms through conventional tissue engineering can't guarantee that cells are exactly implanted into inward scaffolds, and growth factors will just influence the development and separation of surface cells. In this way, analysts have examined cell and growth factor direct-printing technology with a definitive objective of creating tissues and organs. In 2000, Professor Thomas Boland of Clemson University, USA, proposed another concept called "cell and organ printing". The beginning phase of current 3D bio-printing technology is signifies by this. Tissue structures with physiological functions can be framed by printing different materials and "biological ink" containing seed cells, growth factors, and dietary parts layer by layer, trailed by culturing the printed tissue or organ (El-Mahrouk, El-Gazayerly, Aboelwafa, & Taha, 2014).

1.4 3D printing in the biomedical field

From hydrogel implant to monitored prosthetics, Biomedical engineering comprises a wide variety of uses having its own well-matched procedures, materials, post processing techniques. The technology will be selected based on the geometrical considerations for the projected device like a twisted design could be formulated via SLS, but it would be difficult to reduce the extra powder from the interior. Due to the great cross-compatibility of materials, 3D printing can be considered as a sovereign set of choices for engineering. Many engineering problems may arrive due to the materials and tools. As biological system is very complex so the process should be chosen very wisely. For instance, Photopolymers, are normally used across all three types; pools of liquid resin can be utilized in both stereolithography and inkjet printing (Nguyen, Narayan, & Shafiee, 2018).

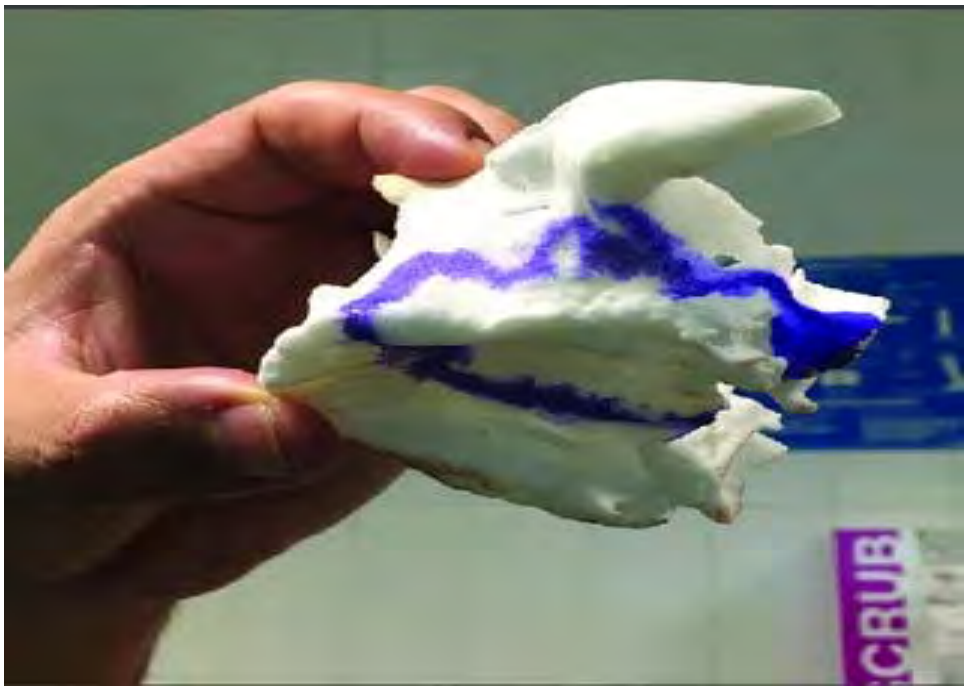

Figure 6: 3D Printed Maxillary Bone (Nguyen, Narayan, & Shafiee, 2018)

1.5 3D printing in personalized medicine

Personalized medicine is a medicine made for individual patients. The molecular basis of disease can be understood by the genomic growth or by the new information of diagnosis which eventually leads to detect patient based therapy. It includes patient's expected reaction, probability of illness in future, genetic and clinical data. Personalized medications comprise everything including the outcome of the therapy. Through molecular or cellular analysis of patient's genetic characteristics, personalized medicine selects a suitable and ideal treatment for patient. To understand which treatment will be best for patient, the diagnostic tests are used. By the help of the results of the diagnostic test combining with patient medical history, targeted treatment and prevention plan can be established. As the possibilities of 3D printed medical equipment in pharmaceutics have recently emerged, some of the personalized medicine's model has been proposed already (Song et al., 2018).

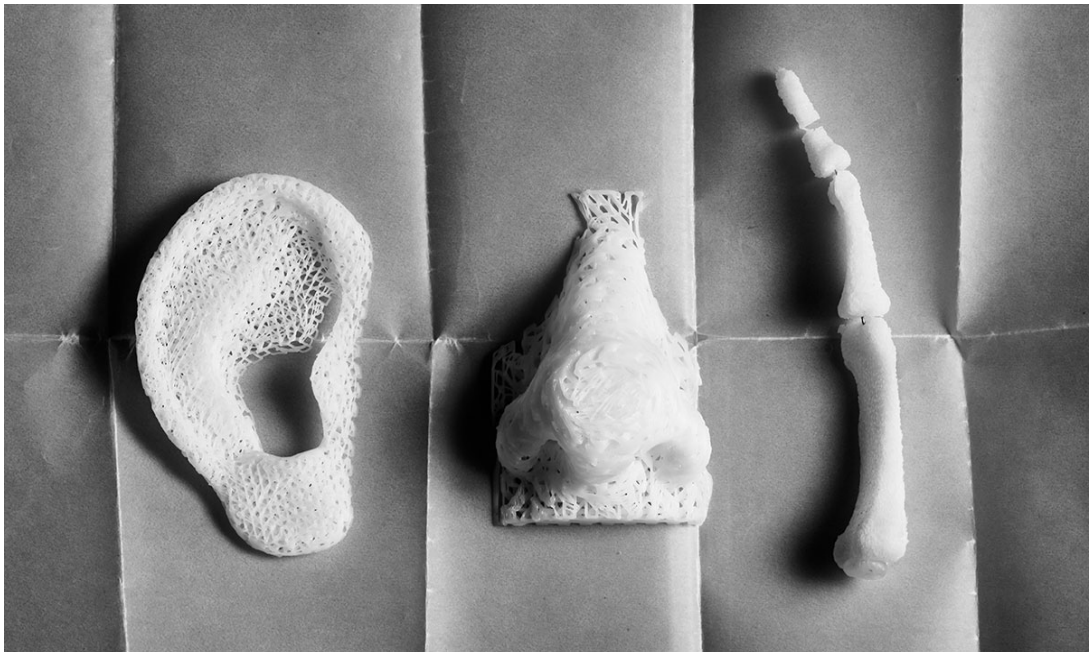

Figure 7: 3D Printed Body Parts(Song et al., 2018)

In fact, the route to customized 3D printed Dosage Forms and Medicines Delivery Devices has already been outlined to convey “the right drug at the right dose at the right time” (Hoffmann, Breitenbach, & Breitkreutz, 2011).

1.5.1 Challenges in personalized medicine

From scientific and social viewpoints, application of personalized drugs faces various problems. Economic and regulatory problems are also added to the list. The poor incentives alliance among stakeholders is responsible for the economic problem (Chen et al., 2018; Dizon, Espera, Chen, & Advincula, 2018). The old-style pharmacy compounding and galenic principle of preparing medicines is safe and effective for optimizing the absorption. Thus, customization is the main regulatory problem (Hao et al., 2019). With the help of 3D printing, the systems structure remains the same but the role changes. The main challenge is to produce unique medicine for individual patient regularly (Khaled et al., 2018). Another major challenge is to fit patient’s biological, social and economic level along with his medical condition. The precision in the selection of a drug and its dosage, reduction of adverse drug reactions, waste and prices and increasing the effectiveness of cure can be done by profound pharmacogenetic and pharmacogenomic tests. Ethical issue is present in this area (Aquino, Barile, Grasso, & Saviano, 2018).

1.6 3D printing application for transdermal delivery

The first transdermal drug delivery technique performed as pioneers of the current technique. In which they feature the use of the drug formulation directly into the skin by allowing the absorption and entrapment within the skin. After that it slowly channels the medicine into the epidermis (Pere et al., 2018). Where in conventional method the entire drug was induced in one single dosage but by the use of 3D printing the scenario is changed (Malinovskaja-Gomez, Espuelas, Garrido, Hirvonen, & Laaksonen, 2017).

1.6.1 Transdermal Film

Topical film forming techniques are emerging drug delivery systems for topical use. It adheres to the body by forming a thin transparent film. Through the film the active ingredients is delivered into the tissue. As the film is transparent, it increases the patient acceptance (Kathe & Kathpalia, 2017).

1.6.2 Patches

The 3D printing process has huge success in case of controlling shape and thickness of the pore and patches. It permits particular alteration of the discharge characteristics of drug via changing S: V ratio. 3D printing technology has the capacity to manipulate the geometry according to a particular purpose (Zheng et al., 2018). Now, Particle Replication in Non-wetting Templates (PRINT) technology can develop the anti-cancer drug loaded particles by layer-by-layer technique and can control the discharge profile by changing the particle's geometry or dimension or chemical configuration as in 3D printing innovation (Yi et al., 2016).

1.6.3 Microneedles

Microneedles have the ability to penetrate the skin in a trouble-free way and through which the drug is released into the body (Alaboodi & Sivasankaran, 2018). In the field of Transdermal Drug Delivery (TDD), Gittard et al. exhibited a photopolymerisation-based printer (DLP) to produce MNs of numerous geometries for wound curing, trailed by pulse laser deposition of silver and zinc oxide thin films (Q. L. Wang, Zhang, Chen, & Guo, 2018). Similarly, Lu et al. merged Dacarbazine (1–2%), a skin anticancer drug, into poly (propylene fumarate) / drug blends followed by photopolymerization via a microstereolithographic (DLP) apparatus that built the MN arrays (Jamkhande, Ghante, & Ajgunde, 2017).

1.7 Orodispersible Films

Film is prepared using polymers. It dissolves fast on the tongue or buccal cavity or on skin. The dug delivered to the systemic circulation through dissolution. The thin film is considered to be convenient for many reasons. It is easy to swallow, self- administrable making it a unique dosage form (Hoffmann et al., 2011).

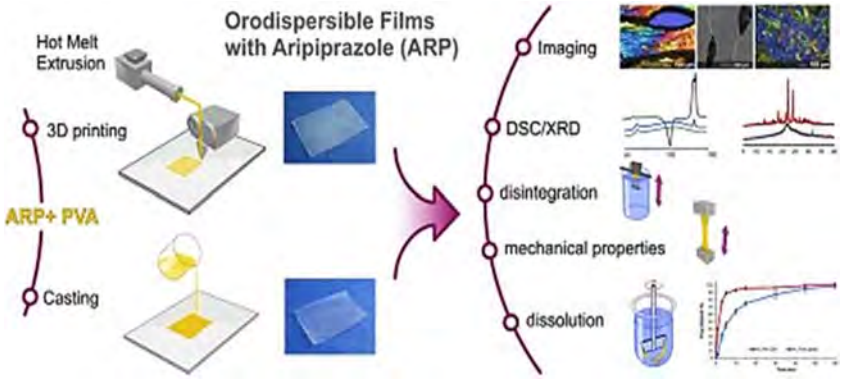

Figure 8: 3D Printed Orodispersible Film (Hoffmann et al., 2011)

1.7.1 Buccal Film

For absorption buccal film needs to be placed on cheek. Buccal delivery can be use ass alternative route to face the problem such as high hepatic first pass metabolism (Govindasamy, Kesavan, & Narasimha, 2013). This route is a highly effective one to enhance the bioavailability (Palem, Gannu, Doodipala, Yamsani, & Yamsani, 2011).

1.7.2 Sublingual Film

Sublingual film contains a hydrophilic polymer. This is responsible for the disintegration or dissolution of dosage form in the sublingual part of oral cavity. To do so , it must come to

contact with saliva without any involvement of drinking and chewing (Song et al., 2018). It allows fast absorption and increase the bioavailability. The high blood flow in the sublingual region also paves the way to rapid onset of action. IV dose can be bypassed by this method (Gomes et al., 2018).

1.7.3 Bioadhesive Film

A perfect bio-adhesive film is depends on its polymer. In ongoing decades, a few kinds of biocompatible carriers have been investigated (Karki et al., 2016). The polymer should be compatible with the film, should not have any toxic properties, should have flexibility, elasticity etc. Along with these characteristics it should be pervious to breakage. Following the progressive headways of medicinal advances over the most recent three decades, assorted bio-adhesive formulations have been produced based on various plan standards and conjugation frameworks. The meaning of bio-adhesives can be stretched out from the basic word "adhesive." Adhesive, which is the equivalent word of glue, is characterized beforehand as any substance that can polymerize (or crosslink). Such polymerization or crosslinking can hold the surfaces of two things together or fill in as a blocker to spillages. Anything conjugated by glues can be called a follower thing, for example, wood, paper, and glass. At the point when something like one of the follower things is a natural part (i.e., cell, tissue, or organ), the glue utilized is known as a bio-adhesive. Bio-adhesives, explicitly tissue cements, hemostatic operators, and tissue sealants, have been generally utilized in clinical tasks and have increased ideal results in various restorative conditions. A tissue glue alludes to a paste or fix that is utilized for restricting tissues together amid the help of wound mending (e.g., skin, muscle, and digestive system); a hemostatic operator works by specifically or in a roundabout way starting arrangement of blood clusters to quit dying, and a sealant is utilized

to seal the holes or breaks so as to avert liquid spillages (e.g., cerebrospinal liquid spillage) or air spillages (e.g., after lung medical procedures) (Zhu, Chuah, & Wang, 2018).

1.7.4 Single Layered Bioadhesive Film

This film becomes adhesive while applied on wet skin. In dry skin it does not adhere. It does not have the risk of causing skin irritation. Patches are designed to deliver a therapeutically effective amount of drug across the skin. In order to achieve a continuous and effective release of the drug to the skin, the patch must exhibit good adhesion properties. Patches can suffer from reduction in surface area of contact, falling off or lack of adhesion (Preis, 2015).

1.7.5 Multi Layered Bioadhesive Film

Multilayer bio-adhesive film have developed throughout the most recent a very long while as new polymers and handling advances have turned out to be accessible. Initially, multilayer bundling structures were delivered from single layer bio-adhesive film items which were stuck together by a few cover forms or were covered with extra polymer layers. In many cases, the polymer films, for example, cellophane, which were accessible were not dissolve extrudable and it was impractical to create multilayer items specifically as it is today by co-extrusion. Now and again, the multilayer structures were created containing non-polymer materials, for example, aluminum foil to supply the ideal bundling properties, for example, light and gas boundaries not accessible in polymer films. As polymer layers ended up slenderer, it wound up unrealistic to consolidate the layers together after they were created as movies and, now and again, the required polymer thickness fundamental for the layer was far not exactly would be down to earth to deliver and deal with as a solitary layer for consequent overlay (Cheng et al., 2018).

1.8 Marketed products

Listerine was introduced as breath fresheners. Since then ODFs have gained popularity, especially in North America. In the US market, several OTC products with APIs is available for years. In Table 1 some example of other marketed products are included (Rokaya et al., 2018).

Table 1: Examples of Marketed Products (Rokaya et al., 2018)

Products	**Manufacturer**	**Active Pharmaceutical Ingredients**
Benadryl Allergy quick dissolve strips	Mc Neil-PPC	Diphenhydramine HCl
Suboxone Sublingual Film	Reckitt Benckiser	Buprenorphine, naloxone
Sudafed PE Quick dissolve strips	McNeil-PPC	Phenylephrine HCl
Theraflu Thin Strips multi symptom	Novartis Consumer Health	Diphenhydramine HCl
Theraflu Thin Strips long acting cough	Novartis Consumer Health	Dextro methorphan HBr
Triaminic Thin Strips daytime cold & cough	Novartis Consumer Health	Dextromethorphan HBr, phenylephrine HCl
Zuplenz	Strativa Pharmaceuticals	Ondansetron
Chloraseptic Sore Throat Relief Strips	Prestige Brands	Benzocaine
Listerine Pocket Paks	Pfizer	Not mentioned
Orajel Kids Sore Throat Relief Strips	Church & Dwight Co.	Pectin
Snoreeze Oral Strips	Passion for Life Healthcare	Peppermint oil, vitamin E, sodium hyaluronate, guar gum

1.8.1 FDA Rules and regulations

FDA affirmed the primary 3D printed oral dose structure as of late. The audit has been finished by perceiving likenesses and contrast between existing innovations and proposed restorative gadgets. For added substance made gadget FDA issued a draft direction report in 2016. The reason for the record is depict the stream of the assembling procedure and to diagram the basic plan, assembling and post-handling parameters. It additionally portrays the stream of the assembling procedure and to plot the basic plan, assembling and post-handling parameters. The abuse guidelines, suitable capacity conditions and wellbeing of the computationally structured dose structures and therapeutic gadgets, just as the patient related data, must be guaranteed to dodge conceivable obligation issues identified with the abuse of the data and to limit the hazard for assembling blunders. The promoted restorative items are exposed to the Directive 2001/83/EC identified with the therapeutic items for human use in the European Union lawful system. Case by case premise assessment ought to be accomplished for the therapeutic items that don't fall under that classification. Also, it ought to be noticed that the as of late distributed European Union guidelines on medicinal gadgets that will come into power in spring 2020 will characterize the tenets and acknowledgment criteria for the therapeutic gadgets and in vitro analytic restorative gadgets. To date, there are no legitimate enactments, neither national nor global, that would cover the 3D printed DDS and DDD as a different class of therapeutic items (Minghetti et al., 2014).

1.8.2 3D printing Patents

Table 2: 3D Printing Patents

Title	Inventor	Outcome
Personalized medical model 3D printing device (2018)	Zhou Lizhen	The invention discloses a personalized medical model 3D printing device.
3D printing biomaterials compounds for medical devices (2018)	Norge Cruz Hernandez Antonio Rodriguez Delgado Ramón Gonzalez Santos	The present invention relates to the preparation of compounds nanostructured and bioactive biomaterials for 3D printing medical device formed of biocompatible polymer blends
3D-printing preparation method for tablet medicines through spraying medicines on matrix material (2016)	Wang Yanen, Wang Shuzhi, Wei Qinghua, Li Xinpei Yang Mingming	The invention provides a 3D-printing preparation method for tablet medicines through spraying medicaments on a matrix material.
Treatment for reducing the toxicity of 3D-printed parts (2015)	William H. Grover Shirin Mesbah Oskui	A method of reducing the toxicity of a 3D-printed part is provided.

1.9 4D Printing

4D printing was originally described as 4D printing = 3D printing + time. As a function of time, structure, characteristics or functionality of 3D object has the ability to change (Lal & Patralekh, 2018).

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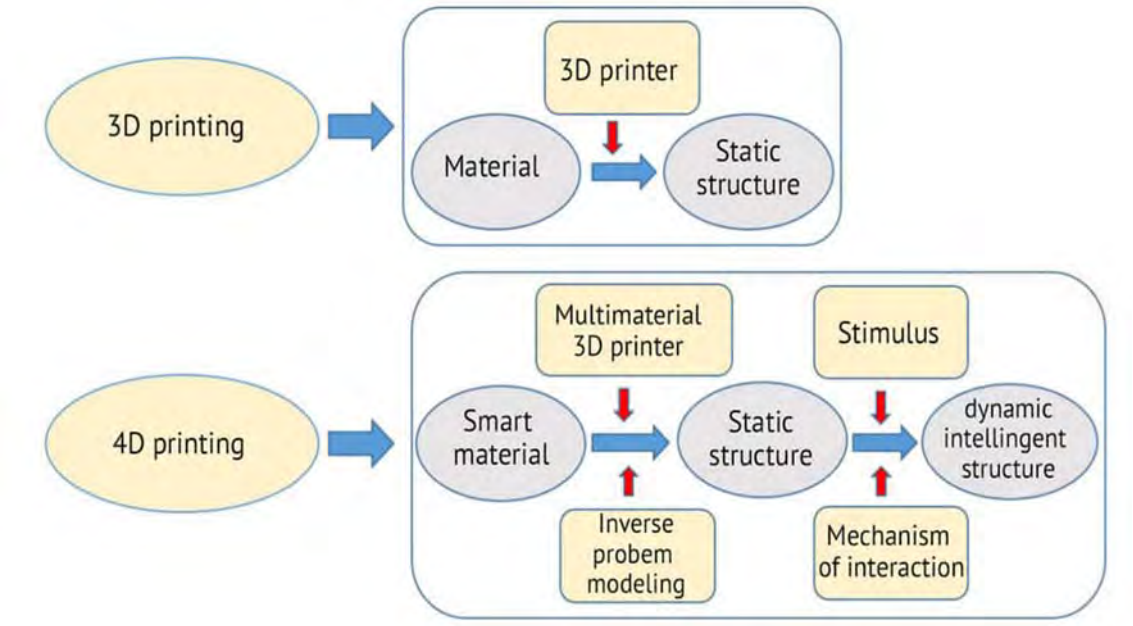

Figure 9: Diagram by Jean-Claude Andre, 2016

As the numeral amount of research on this technology increases, a more comprehensive definition of 4D printing is demonstrated here. It is a directed progression of the 3D printed structures. It has the ability to obtain; self-assembly, multi-functionality, and self-repair. It is time-dependent, printer-independent, and predictable (Momeni, M.Mehdi Hassani.N, Liu, & Ni, 2017).

1.9.1 Comparison between 3D and 4D printing

Table 3: Comparison between 3D and 4D printing

Characteristics	3D Printing	4D Printing
Building Process	Different number of 2D structure layers repeated from bottom to top.	In 4D printing 3D printing is simply extended.
Material Used	Thermoplastics, metals, biomaterial are used.	Smart and self-assembling material is used to construct an item, which alter its shape after getting fabricated.
Flexibility	No flexibility	Have flexibility
Object shape flexibility	The shape of object changed in this process	Object shape alters over time with the alteration of temperature
Programing of material	No programmable or advance material is used	programmable and advanced material is used
Applications	In medical, engineering, dentistry, automobile, jewelry, toys, fashion, entertainment etc.	Dynamically changing configuration for all applications by 3D printing

1.10 The Aim of the Project

The aim of the project is to highlight current applications of 3D & 4D printing in medical field along with the possibilities of 3D & 4D printing in personalized medicine. Lastly the future direction of this research field is discussed.

Chapter 2

Methodology

A literature search was performed for extracting all papers related to 3D Printing & 4D printing in medicine on the PubMed, Science direct and SCOPUS, utilizing appropriate key terms ("3D Printing" OR "3 dimensional printing" OR "3D printed" OR "additive manufacturing" OR "rapid prototyping") AND (''4D printing"). Pursuit was likewise performed in Web of Science, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. 190 articles were selected on the basis of title. After reading abstract 150 articles were found to be related with the project. After that all the articles are screened and 90 articles are selected for this review. These articles contain the current application of 3D and 4D printing including the future directions. No restrictions were determined to the timeframe. Titles and modified works were screened and all copy and random papers were barred.

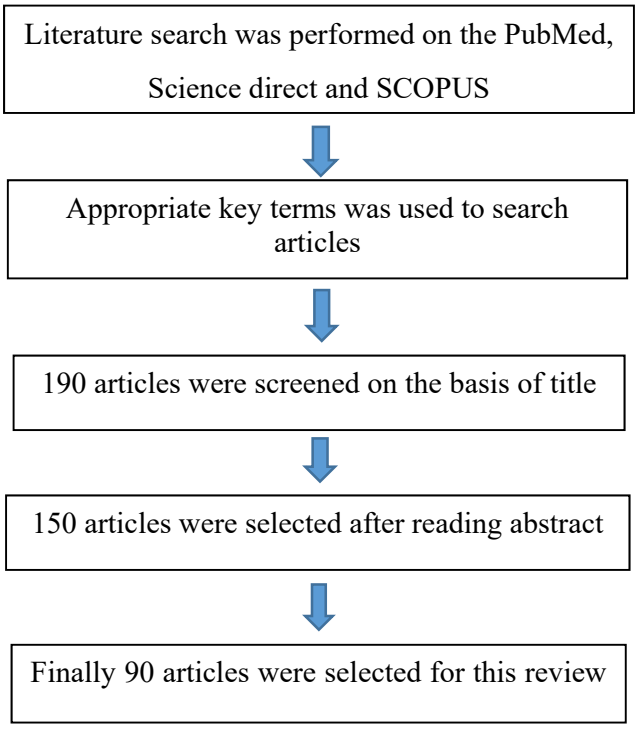

Figure 10: Flowchart of Article Search Process

Chapter 3

Discussion

Three-dimensional (3D) printing has been utilized in the improvement of complex oral dosage forms (Jamróz et al., 2017; Arafat et al., 2018; Kyobula et al., 2017). This procedure gives the likelihood of delivering a boundless selection of shapes and complex structures, its adaptability of modification for manufacturing small batch without a high opening venture, contrasted with like in injection modeling, consequently making it an alluring option for melt processed, custom-made, and personalized medication (Sadia et al., 2018). It permits an adaptable variety of the drug dose, discharge qualities, or execution of mixes of a few medications in same doses form to relate to the individual patient needs (Norman, Madurawe, Moore, Khan, & Khairuzzaman, 2017; Alhnan et al., 2016). It opens doors for progressing in more up to date and better medication (J. Z. Wang et al., 2018). Fabrication of on-demand and personalized medicine can be gained via product complexity. Further benefits are cost efficiency, freedom in designing and developing and also extended collaboration (Shende & Agrawal, 2018).

Effective printing result requires a reasonable mix of the printing strategy, excipients, and drugs, just as the suitable procedure parameters (Aho et al., 2019). Subsequently, 3D printing may turn into an alternative to create and produce desired orodispersible film by beating restrictions of current ODF fabricating strategies (Ehtezazi et al., 2018). Orodispersible films are rigid oral dose shapes which quickly dissolve in mouth what makes them suggested for patients with gulping issues (Wimmer-Teubenbacher et al., 2018). As different polymers can be utilized in film development and a significant number of them can be likewise utilized in combined statement demonstrating, this 3D printing procedure is by all accounts exceptionally encouraging strategy for ODFs development. To improve the disintegration

time of film, use of water dissolvable polymers might be helpful (Jamróz et al., 2017). The significant points of interest of this technique are wide scope of printing materials, capacity to print items with various filling and low expenses (Fina et al., 2018).

Jacob et al prepared 3DP oxcarbazepine film. The present inventors have found that a high weight percentage or mass comprises a small OXC particle diameters, sufficient hardness, showing texture of acceptable surface, and a very rapid disintegration, printed three-dimensional to produce a rapidly dispersing dosage form has been found to be very difficult. To solve this problem, the present inventors have found that without increasing the "actual particle diameter" of the drug were discovered that must increase the "effective particle size" of the OXC in the bulk powder .By doing so, it becomes possible to administer the OXC having effective particle size suitable for use in the actual particle diameter and 3DP orodispersible dosage forms of bulk powders, suitable for absorption. "Effective particle size", as the size of the drug-containing particles is greater than the natural particles OXC, the "natural grain" of small OXC, by including the "drug-containing particles" in the bulk powder increased (Jacob et al., 2013).

Jamroz et al used Noztek Pro filament extruder to prepare film with aripiprazole. The 3D printed ODFs demonstrated a rapid dissolution rate of aripiprazole where the film which was developed through solvent-casting technique exhibited slower dissolution rate (Jamróz et al., 2017).

Ehtezazi et al utilized FDM Wanhao Duplicator 4 Desktop 3D printer to develop multilayered film containing paracetamol. In 3D printed film the presence of permeable structure inside the films may add to the fast disintegration of the dosage form.3D printing enabled layers of various compositions to be included in films. It ought to be noticed that assembling of layered oral films have been accomplished before. Nonetheless, the films made

by the 3D strategy (specifically work plans) had more thickness consistency than layered films arranged by the solvent-casting method (Ehtezazi et al., 2018).

Musazzi et al utilized Cartesian FDM 3D printer for developing personalized orodispersible acetaminophen film. The breaking down period of printed ODF is increasingly like that of films with comparative composition, however arranged via hot-melt extrusion, as opposed to by solvent casting. Additionally, the printed ODF demonstrated more fragile tensile characteristics than the main casted and hot-melt extrusion ODF presumably in light of the fact that the curious testimony of liquefied material doesn't permit acquiring a uniform film in contrast with extrusion. The solvent casting method permitted to get higher attachment of the ODF matrix, since the maltodextrin chains and glycerine could adjust in a thick structure during the solvent evaporation stage, bringing about a film with reasonable mechanical properties even at slenderer thickness (Musazzi et al., 2018).

Linares et al used REGEMAT 3D V1 printer for the preparation of 3D printed colon specific drug delivery. At room temperature the medication was easily incorporated in the extruded scaffold. It helped to eliminate other intermediate processes (Linars et al., 2018).

Sjöholm et al., 2019 used semisolid extrusion 3d printer for developing warfarin ODF. The arranged warfarin films were homogenous and flexible containing a smooth surface. During handling the medication loaded films were less flexible than the unloaded films. The un-loaded films were printed with marginally higher pressure than the loaded film. That is why warfarin loaded films were bigger than the un-loaded film. The dose accuracy of the film is directly related to the uniformity of the weight. So it is very important to determine the weight uniformity. The prepared warfarin films had a suitable thickness for ODFs (Sjöholm & Sandler, 2019).

Significant knowledge of 3D printed ODF's discharge profiles can be obtained by simulation of the discharge properties of 3D printed ODF (Diaz del Consuelo, Falson, Guy, & Jacques, 2007). For 3D printed formulations such simulated tactics are predominantly required, as printing empowers an almost endless number of feasible dosage form geometries, with the same number of conceivable discharge profiles. Sun et al., 2015 represented an intriguing methodology, encouraging direct linking between one dimensional discharge from the dosage form and the drug discharge profile (Sun & Soh, 2015). This means a persistent medication release profile can be obtained by having a constant cross-sectional area of the drug loaded polymer (Scarpa et al., 2017a). On the off chance that the cross-sectional area was expanding alongside this dimension, the medication discharge would likewise rise after over time. This methodology gave an immediate and instinctive interpretation between the cross-sectional zone of the drug loaded polymer and the discharge profile and it was thus extremely straightforward to anticipate the shape required for any given desired discharge profile (Khaled et al., 2018).

3D printed orodispersible film (ODF) shows disintegration time lengthier than the marketed film or film arranged via the solvent casting technique (Cilurzo et al., 2010). Then again, 3D ODFs demonstrated both fast and expanded medication discharge profiles than films arranged by solvent casting or hot-melt extrusion techniques (Cilurzo et al., 2010; Koland, Sandeep, & Charyulu, 2010). True to form, through 3D printing, layers of different composition can be included in films. It ought to be noticed that assembling of multilayered oral films has been accomplished already via solvent casting technique (Rana & Murthy, 2013; Mukherjee & Bharath, 2013; El-Mahrouk, El-Gazayerly, Aboelwafa, & Taha, 2014). Be that as it may, the films made by the solvent casting technique had less thickness consistency than multilayered films developed by 3D strategy. Additionally, past acts have established the stability of active ingredients during FDM 3D printing (Sadia et al., 2018;

Fina et al., 2018). By and by, the stability of the taste-covering agents has to be assessed during the whole assembling procedure. The medication discharge profiles of 3D ODFs relied upon the design and presence of taste-covering layers. Plain ODFs without test-concealing layer release dug faster than ODFs with test-concealing layers. Due to the presence of test covering layers, the drug molecules are interrupted from achieving the discharge media. In contrast with the film arranged by hot-melt extrusion, 3D printed ODFs shows quicker medication release. The presence of microcrystalline cellulose in 3D ODFs prevents the glue from adhering to the extruder. Then again, plain 3D ODFs introduced slower medication discharge contrasted with ODFs arranged by the solvent casting method (Satyanarayana et al., 2012; Cilurjo et al., 2010; Koland et al., 2010). All the same, using the mesh format for printing the film might reduce this disadvantage and yet, it might be resulted in the decrease of the medication content. In this manner, this may constrain administrating large dosages as mesh design of 3D ODFs. Moreover, in contrast with the ODF arranged by hot melt extrusion, 3D printed PEO based ODF films discharge medication quicker (Prodduturi, Manek, Kolling, Stodghill, & Repka, 2005). The distinction could be because of the diverse film thicknesses. It was seen that 3D PEO film ended up delicate and lose their mechanical quality while 3D PVA film kept their quality in the course of stockpiling underneath surrounding conditions. In past days, the mechanical characteristics of PEO films were investigated based on stockpiling conditions (Mantzavinos, Hellenbrand, Livingston, & Metcalfe, 1996). In the production of film; hydroxypropyl cellulose, hydroxypropyl methyl cellulose were used. In this formulation hot-melt extrusion technique was used to develop film and FDM 3D was utilized to form disk (Melocchi et al., 2016). At that point, for the formulation of buccal film or ODF, 3D printing method might be handy for the examination of these polymers. Mostly used polymers are; PEG 400, glycerol, and propylene glycol. Nonetheless, ODF can be manufactured by 3D FDM but a specific mechanical feature

(stiffness) of the filament was essential to be utilized in the 3D printer. Hence, plasticisers were not utilized; however, 3D ODFs demonstrated a worthy adaptability appropriate as an oral film. It ought to be noticed that pharmacopeia requires 10 tests to be tried. Accordingly, 3D FDM could create ODFs that achieved the weight consistency and the consistency of substance prerequisite by pharmacopeia.

Based on the research 3D printing exhibits more than a few advantages contrasted to inkjet printing. Where 3D printing is a one-step process, the inkjet printing is a complex three-step-process. Through 3D printing the whole dosage form can be printed at once. Where in inkjet printing, first the orodispersible film need to be casted. Additionally, imprinted films need time interval for the purpose of drying. The most tedious part is to cut the film in single dose pieces. Through 3D printing whole therapeutic doses can be achieved by a single dose where with inkjet printing several films need to be ingested. The reason behind this is through inkjet printing only low amounts of drug could be imprinted into films. Through 3D printing this limitation can be overcome quite easily with the help of better correlation with design. Another benefit is printing material is free from any kind of contact with the printing equipment. That further shows 3D printing is a suitable technique for ODFs with tailored doses to fulfill patient requirement (Sjöholm & Sandler, 2019).

Because of the multifaceted nature of the human body's different elements; human genes, age, disease state and sex, different people will need different doses or dose shapes, which are not in every case promptly accessible (Alomari, Mohamed, Basit, & Gaisford, 2015; Stansbury & Idacavage, 2016; Gajdošová et al., 2016; Wimmer-Teubenbacher et al., 2018). Studies show that most drugs fail during the early stage of clinical trials increasing extensive amount of load for the pharmaceutical business. Due to this there has been a remarkable interest towards the personalization of treatment (Varan et al., 2017; Lau, Steadman, Cichero,

& Nissen, 2018). In reality, 3DP innovation enables medications to be custom-made to the personalized needs of every patient, for instance, by altering the dose, shape, size and discharge qualities, just as by means of creation of multi-drug combination (Awad et al., 2018; Venkateswaran, 2015).

In connection to the flexibility in design and formulation 3D printed ODF has potential outcomes as customized treatment. High potent drug with narrow therapeutic index are hard to personalize. Through 3D printing this limitation can be overcome by a simple adjustment in the 3D configuration. Likewise, the fixed-dose combination formulation, effectively conceivable through this method, can help accomplish improved remedial result and lessening the occurrence of adverse effect. The act of each new innovation and development accompanies a major cost. Likewise, the idea of creating 3D printed ODF innovation to customize medication in emergency clinic and network drug store is exceptionally advanced. Most remarkably, these identify with the issues of quality control (QC) and wellbeing (Trenfield et al., 2018).

Being a new and trend setting innovation, 4D printing quickly emerging through different disciplines, for example, designing, medicinal, material science, science, essential sciences, software engineering. It utilizes distinctive materials which have self-deformation ability and are well received by researchers. For quick and precise assembling of customized soft structure the technique is the most suitable. So this process might be appropriate for the formation of ODF. Utilizing 3D and 4D printing innovations, the medications will be able to customize according to the patient's need. It will enable specialists to tailor the exposure and dosage levels of drug for individual patients. According to professor Shlmo Magdassi who is also responsible for wave of prototypes, unveils that 3D printing has the potential to cause the next industrial revolution. As complex design of drug delivery system has already been fabricated through 3D printing, he believes that in the long run 3D printing will empower the

printing of customized and personalized medicine with 4D printing characteristics. He further included that what they had really done is to try to control the release of the medication from dosage form. They made a special design which has the ability to alter shape further in time. In spite of the fact that he referenced, technology isn't even now that advance however this strategy has an incredible potential to open another era in the restorative field by helping to develop shape altering dosage form or medical devices. The utmost potential of 3D and 4D printed film is that they will be able to keep up with patient's particular needs. Not only the amount of dose but also the rate of drug delivery can be controlled. Modern 3D printing methods can assemble and add improvements to ingredients but the next test is to build bespoke drugs from scratch (Walsh, Ranmal, Ernest, & Liu, 2018).

3D printing enables buyers to design and develop their own products with minimum amount of waste. Presently it is assumed that with the appearance of 4D printing the world's socio-economic condition will be changed in the following decade (Ng, He, & Rocco, 2017). A number of reviews have been written on the multi-functionality of shape memory polymers (SMP) and shape memory polymer composites (SMC) as its utilization in additive manufacturing has been extensive (Tumbleston et al., 2015). The use of thermoplastics is becoming less popular as its ability to retain shape is lost after a few cycles. Thus thermosets are replacing thermoplastics because of its firmness and durability. With the help of an external stimulus, shape memory materials (SMM) can restore their form even after twisting. Once triggered by temperature, moisture or by light enactment utilizing illumination, SMP has the ability to change their unique shape from one to several shapes (Gillaspie et al., 2016). On the other hand, the SMPs can be magnetically induced into thermoplastics by integrating nanoparticles. SMPs have revealed abundant utilizations in biomedical applications, small scale electromechanical systems and self-deployable structures. A possible weakness for SMPs is their low tensile strength and stiffness, in comparison to shape

memory alloys SMAs. Furthermore, with the multiple stimuli for triggering, SMPs can be biocompatible and biodegradable, thus custom-made depending on the requirements of application (Phan et al., 2017). The only clinically recorded application of 4D printing is personalized endo-luminal medical devices. Application include SMP made cardiovascular stent and airway stent. On the other hand, other future devices that might gain profit from this technique is pediatric rib cage and prosthetic cardiac valves. The one perception that made this process so fascinated is its ability to self-repair. In the field of regenerative medicine, this has an immense amount of application. With the help of 4D printing not only the medical procedure can be decreased but also outdated 4D printed devices and items can be disintegrated in to programmable particles for reusing (Schussler & Axhausen, 2009). In spite of the fact that the idea of 4D printing is as of now in the test stages, illustrated above are a portion of the potential advantages and application. With headway in printing innovation and further collaborative endeavors 4D printing will likely bring a paradigm shift in the near future (López-Valdeolivas, Liu, Broer, & Sánchez-Somolinos, 2018).

In this field one disagreement is noted is whether controlled degradation of 3D products can be categorized as a 4D effect or not (Small IV, Singhal, Wilson, & Maitland, 2010). 3D printing has exhibited incredible possibility in biomedical fields (Ivanova et al., 2013). Another point of the disagreement is that the 3D printed structures pointed above totally vanish in the dynamic procedures. Despite what might be expected, in shape or functional transformation through the 4D process, the majority of the 3D printed structures stay flawless (Rezaee & Ganji, 2018).

Until now biologically-inspired hierarchical morphological modifications have been generally the focus of 4D printing (Tibbits, 2014). Only the shape changing properties of 4D printing should not be focused. 4D printing is enable to cause other functional changes which also should be kept under the center of research. Until now only a few amount of research has

been done in this area. There are some possibilities which are yet to explore like 4D printed orodispersible film which are able to change shape after triggering by stimuli or materials undergoing color change due to particular wave length of light (Lee et al., 2012).

Chapter 4

Conclusion

This article prove that 3D printed medicine has already achieved the desired weight and content uniformity by pharmacopeia. 3D printing of medicine also exhibited decrease in the disintegration time. Through admiration to the vital characteristics medicinal products, medicine proposes a promising way out for effective way of drug therapy. As these small sized items minimize the risk of choking by making the administration easy, makes it one of the obvious choice for children and patient with gulping issues. The total impression of the new super vision is that the experts hold a massive interest in improving medicines by investing thoughts on how new products should be designed. Additionally, the possibility of drug polymorphism is less with 3D printed medicine. 3D printed medicine might also enable a decent chance to develop personalized solid dosage forms. The current work exhibited the ability of 3D printing to develop ODF from the correct materials that fulfil the modern USP standards. 3D printed pharmaceuticals have just been tried in vitro or in vivo animal models, with the main investigations including human subjects being an agreeableness appraisal and an assessment ponder. In any case, with the fast progression in this innovation and the present filaments being made out of by and large viewed as protected, it is just a while until 3D printed medicines might go pass clinical phase preliminaries. In any case, to accomplish this, the invention must to defeat its current exceptional problems and difficulties, empowering it to progress towards the marvel of the "perfect 3D printer" (Kilicarslan et al., 2018). 4D printing is to give advantages to medicinal specialists particularly to the areas which are not yet secured via 3D printing process. This innovation might give broad help in the medicinal area, particularly with enhanced and brilliant restorative inserts, devices and gadgets. Presently specialists and scientists can investigate by utilizing 4D printing innovation to give improved support of the patient (Javaid & Haleem, 2018).

4.1 Limitations

There are a couple of weaknesses of 3D printed ODF that would require further research and innovative improvement. These downsides incorporate surprising expenses, restricted applications in vast structures and large scale manufacturing, mediocre mechanical properties, impediment of ingredients and imperfections. Mainly the innovative work of materials and strategies have evaded a portion of these impediments. In any case, couple of hindrances still remains. A few difficulties are increasingly evident in a specific printing technique or material yet few are basic in practically all AM strategies. For example, AM of a section regularly takes additional time contrasted with customary techniques, for example, throwing, expulsion, creation or infusion shaping. Specifically, the powder bed technique and stereolithography are additional tedious contrasted with inkjet printing and intertwined affidavit displaying. What's more, 3D printing strategies, for example, powder-bed (SLS or SLM), are high in rearrangement, which consequently acquire a greater expense for materials and a higher measure of vitality for preparing. Vacant space between different layers of materials is one of the fundamental shortcomings of 3D printed ODF. The extra permeability made by 3DP can be extremely high. It might eventually diminish mechanical execution due to the reduction of interfacial holding between printed layers. The degree of void arrangement very relies upon the 3D printing strategy and the written word. PC supported plan CAD designing is the fundamental device to structure. Due to confinements the printed items can have a couple of imperfections that were not anticipated in the intended component. In any case, converting CAD into a 3D-printed items often results in mistakes and distortions especially in bended surfaces. Multilayer appearance is another test attributable to the idea of added item manufacturing. Though 3D printing technologies has been confirmed to be valid to develop different dosage forms, still the main concern is to gain the appropriate legal and technical support. There is no doubt this innovation offers the vision of the imminent future

where digital medical documents are enough to print out the drugs intended to fulfill the patient's individual therapeutic necessities. Nevertheless, before dispensing of the drug, the quality control techniques also exhibit a vital role to ensure the ability of this technology to withstand the future. It is obvious that 3D printed ODF into clinical practice could improve the digital healthcare by altering the way of designing and prescribing of medicines. Nevertheless, as with all the novel innovations arriving the digital healthcare area, acceptance is often slow and come together with a lot of obstacles. The traditional regulatory guidelines and procedures have been dwelling for so many years making the healthcare sector particularly resistance to change. Moreover, as the traditional guidelines are reasonable to preserve patient safety, it can often delay the ready approval of modern technologies. For quicker uptake of 3D printing into the practice, a rigid evidence base is necessary to verify that it will be beneficial and harmless not only for the patients but also for the practitioners. Besides different researchers have presented the abundant benefits of the 3D printed ODF, none of these records have been documented in to a single study to offer proof on the clinical benefits and consequences of personalized medications (Venkateswaran, 2015).

4.2 Future Directions

It is an era of "precision medicine" and "personalized medicine" becoming identical with high-quality patient care. 3D and 4D printing technology have exactly the same capabilities to optimize the treatment options. It previously demonstrated that it can change the surgical approach. Moreover, to expand utilization of this innovation among those thinking about patients with heart problems, a multidisciplinary technique is fundamental. It gives the idea that 3D printing will keep on being a main impetus, enabling us to all the more promptly practice customized prescription and propose the finest nature of attention for patients. Novel technique like 3D printing has already been utilized for manufacturing personalized medicine. This dosage form is beneficial to make the healthcare system personalized. In

future these technologies might be used to solve the problems which cannot be overcome the current technologies. For example:

1. This innovation has the potential to solve the problems of pharmaceutical industries to meet the demand of customized medicine.
2. Not only 3D printing but also 4D printing has contributed enormously in the medicine field. It has wider use in tissue engineering, chemotherapy and self-assembling human scale biomaterials.
3. Though 4D printed ODF is not developed yet but it has the potential to overcome the obstacles of the 3D printed ODF. As 4D printed products can change the shape. The problem with printing of bended design can be overcome.
4. Now as the technology advances; in near future 5D printed ODF might be possible too. 5D printing is another new part of additive manufacture. It differs from 3D printing in a way that its print head has the ability to move 5 degrees. It also enables to produce bended layers. So the problems with 3D printed medicine might be overcome with the 5D printing technology in the near future. This innovation might be able to satisfy this essential prerequisite. In this way there is a lesser requirement of crude material when contrasted with 3D printing for making inserts of a similar quality.
5. Scientist are now trying to develop 6D printed product. In this technology, consumer will be able to use their 6^{th} sense. With this innovation patient just have to think about the item and the data will be transferred to new 6D printing interface. Though it appears that due to the lack of exhibited work creators do not want to name it 6D printing yet.

4D, 5D printing can give more useful results in drug testing, as we'll be able to print models that reproduce aspects of human organs, such as heart muscles or parts of the liver. This is

important, because even promising animal tests don't guarantee a drug fit for human use. Other solutions include bio-printing tissue substitutes such as skin to repair burns or cartilage that protects our knees. This is why printed human body parts can be used for the drug testing of 3D and 4D printed personalized medicine.

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