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3D and 4D printing of personalized dosage forms

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Abstract: *Personalized dosage forms manufactured by 3D and 4D printing have brought changes in the pharmaceutical sector by helping patients with their personalized, individualized treatments. These therapies are known for their great adherence, safety, and effectiveness. It does offer the ability to formulate a personalized dosage form by controlling the dose, shape, and release characteristics. Comparatively with respect to conventional methods, they give significant benefits by tailoring dosage forms to meet patients' needs.*

This research paper gives you an idea of how 3D and 4D printing are used for formulating personalized dosage forms with the important printing techniques, smart materials, and print-friendly biomaterials used in the development of a responsive drug delivery system with the principles of additive manufacturing. There are various types of dosage forms that can be manufactured, ranging from tablets to microneedles and polypills. This paper also consists of information regarding Advantages, current challenges, and emerging trends, which do include artificial intelligence, digital healthcare manufacturing, and regulatory issues.

In short, we can see that 3d and 4D printing technologies ensure the precise enhancement of precision medicine and tailored pharmaceutical manufacturing. future advancement in smart materials, printing techniques, and laws which will enhance the growth/implantation of personalized medicine in clinical and industrial settings.

Key Word: *3D printing; 4D printing; Personalized medicine; Personalized dosage forms; Additive manufacturing*

I.INTRODUCTION

The pharmaceutical industry's traditional paradigm is going to be replaced by this new technology of personalized medicine or precision medicine, meaning a more patient-focused approach. These medicines are formulated by a method called "one size fits all". So far, for normal people, drugs were manufactured in predetermined dosage forms and release characteristics, due to which drugs are nowadays broadly available, though typically they do not match the specific needs of an individual. Factors like age, gender, weight, metabolism, genetic makeup, disease status, lifestyle, and other medications can cause a drastic change in how a drug works on an individual, its safety, and all treatment outcomes. thereby these standardized doses can lead to underdosing, overdosing, adverse effects, decreased patient adherence, and less successful treatments, mainly for pediatrics, geriatric patients, and people with medical conditions. Where precision medicine and personalized medicine are meant to seek the right medication at the right dose to the right patient at the right time, which is a revolutionary step for these problems.

Genomics, molecular biology, digital healthcare, and pharmacogenomics have contributed to the advancement of precision medicine through their significant developments. How genetic variations impact drug processing, efficacy, and possible adverse effects was better understood by scientists following the completion of the Human Genome Project; this enabled the development of individualized treatments and medicines based on a person's genetics. Then it was further enhanced with artificial intelligence. Wearable medicinal technologies, electronic health records, and predictive analytics. Yet, In order to successfully adopt personalized medicine, we need advanced manufacturing technologies that can effectively, precisely, and economically manufacture customized dosage forms. Manual compounding and traditional pharmaceutical manufacture offer very few options because they are labour-intensive, slow, and difficult to standardize for customized care.

Three-dimensional (3D) printing, also known as additive manufacturing (AM), has drawn a lot of attention as one of the most promising developments in pharmaceutical sciences among the new technologies addressing these problems. Layering materials according to computer-aided digital design, which opposes traditional manufacturing, is additive manufacturing. The layer-by-layer technique controls precisely the pharmaceutical dosage forms, dimensions, internal structure porosity, structure, drug distribution, and drug release properties. The development of complex dosage forms, which are not possible with traditional manufacturing methods, like demand production of pharmaceuticals tailored to each patient's requirements, customized doses, and modified drug release profile, is possible and enabled by 3D printing.

Additionally, additive manufacturing techniques, for example, Fused deposition modelling (FDM), Binder Jetting, stereolithography (SLA), selective laser sintering, semi-solid extrusion, and other extrusion and laser-based printing technologies are successfully modified for use in the pharmaceutical industry. These techniques have made it possible to modify numerous pharmaceutical products such as tablets, capsules, transdermal patches, vaginal and rectal dosage forms, dental devices, intravesical systems, ophthalmic formulations, wound dressings, implants, microneedles, oral films, pellets, and implantable drug delivery systems. Also, 3D printing has made it possible to formulate polypills, which reduce the hardship of taking multiple pills and have improved compliance by adding multiple active pharmaceutical ingredients into a single dosage form.

Using 3D printing and ZipDose® binder jetting technology, the first commercially produced drug named spritam® (levetiracetam) created by Aprecia Pharmaceuticals was approved by the U.S. Food and Drug Administration (FDA) in 2015, creating historic moment in pharmaceutical additive manufacturing, sparking extensive research. Since then, there is increase number of studies on 3D printing of personalized dosage forms.

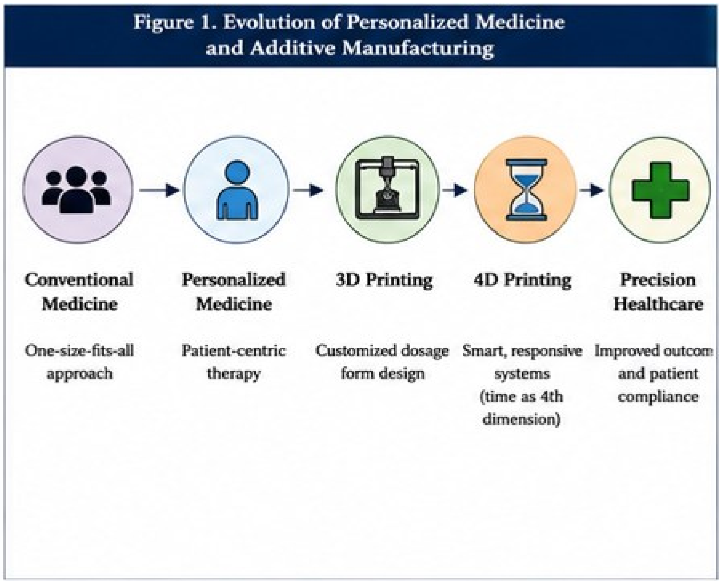

Figure 1: Evaluation of personalized medicine and additive manufacturing .

Biomedical research significantly changed when it went from pharmaceutical dosage forms to Bioprinting, a technology that sophistically enhance physiological viable tissue by depositing cells containing bioinks in a highly regulated layer-by-layer process. Bioprinting has demonstrated significant promise in drug screening, tissue engineering, disease modeling, cancer research, and regenerative medicine. Extrusion-based bioprinting is the most popular method now in use because it can print extremely viscous bioinks at high cell densities while maintaining structural integrity. However, because excessive printing pressure, poor nozzle design, or inappropriate material properties may adversely affect both structural integrity and biological function, successful bioprinting necessitates careful optimization of bioink composition, printability, mechanical strength, and cell viability.

Despite its remarkable potential, traditional 3D printing creates dosage forms that are immobile once manufactured and cannot adapt to the changing physiological conditions of the human body. Four-dimensional (4D) printing has evolved as the next phase of additive manufacturing to overcome this constraint. Time is regarded as the fourth dimension in 4D printing, allowing printed structures to experience predefined changes in shape, mechanical characteristics, or functioning after manufacturing when exposed to particular internal or external stimuli. Shape memory polymers (SMPs), hydrogels, and other intelligent biomaterials that respond to changes in temperature, pH, moisture, enzymes, light, magnetic fields, or electrical stimuli are examples of stimuli-sensitive smart materials that enable this responsive behavior.

Smart Drug Delivery Systems (SDDS) that may react dynamically to physiological situations have been made possible by the integration of smart materials into pharmaceutical formulations. 4D-printed dosage forms can provide site-specific, programmable, and stimuli-responsive drug release, increase therapeutic accuracy and minimizing undesirable side effects, in contrast to traditional drug delivery systems that release pharmaceuticals according to set schedules. Self-expanding gastro-retentive tablets, thermally activated stents, implantable drug delivery devices, and tailored formulations that release therapeutic drugs only when they reach the desired site of action are examples of these cutting-edge systems. Improved bioavailability, longer drug residence time, fewer doses, and increased patient compliance are all significant advantages of these adaptive drug delivery systems. Making them particularly helpful for managing long-term illnesses and customized treatment plans.

Despite the significant potential of 3D and 4D printing to revolutionize pharmaceutical manufacturing, there are still certain scientific, technical, and regulatory obstacles to overcome. Maintaining the stability of active pharmaceutical ingredients throughout the manufacturing process, developing printable pharmaceutical formulations with appropriate physicochemical, mechanical, and biological properties, optimizing printing parameters, attaining large-scale production, guaranteeing quality assurance, and setting regulatory standards continue to be major challenges. Maintaining cell survival while attaining sufficient printability and structural stability is still a particularly difficult task in bioprinting applications. Furthermore, before dynamic, stimuli-responsive pharmaceutical medicines may be widely used in clinical settings, more research is needed to evaluate their long-term safety and regulatory status.

Many of these constraints are anticipated to be addressed by recent developments in nanotechnology, artificial intelligence, microfluidics, computational modeling, enhanced biomaterials, and digital manufacturing. The potential for next-generation customized treatments is expanding due to the development of intelligent biomaterials, continuous manufacturing systems, and nanoprinting, which combines nanomedicine and additive manufacturing. By enabling the on-demand production of intelligent, patient-specific drug delivery systems that maximize therapeutic effectiveness, support patient compliance, and ultimately result in better healthcare outcomes, 3D and 4D printing are well-positioned to transform the future of precision medicine as pharmaceutical engineering, materials science, and regulatory frameworks continue to advance.

II.HISTORY OF 3D AND 4D PRINTING

The development of rapid prototyping methods for industrial applications in the early 1980s is where 3D printing, also known as additive manufacturing (AM), got its start. In 1981, the first photo polymerization-based layer-by-layer was developed by a Japanese researcher named Hideo Kodama. Then, in late 1986, there was Charles W. Hull, who established the first commercially viable 3D printing and invented stereolithography, signalling the contemporary additive manufacturing by creating from intricating 3d straight from CAD models.

In the 1900s and early 2000s, 3D printing started to expand from engineering origins to sectors like biomedical engineering, healthcare, automotive manufacturing, and aerospace. Researchers recognized that it does have ability of building different structures with significant accuracy, reduce material waste, and shorten production periods.

The application of 3D printing in the pharmaceutical industry attracted a lot of attention, where it was used to develop tablets of different shapes and dosages, more sophisticated dosage forms with several active ingredients, and altered drug release properties, with the growing desire for customized medicines

In 2015 , The U.S. Food and Drug Administration (FDA) approved Spritam® (levetiracetam), manufactured by Aprecia Pharmaceuticals, making it the first commercially available drug made using 3D printing and ZipDose® binder jetting technology. It was an important turning point. This inspired wide-ranging research into individualized drug delivery systems, implants, medical devices, and tissue engineering.

In 2013, Skylar Tibbit introduced the idea of 4D printing, which has time as the 4th dimension enabling the printed items to change shape, properties, and functions with respect to internal and external stimuli, including PH, temperature, moisture, light, or magnetic fields. This advancement was made possible by stimuli-responsive and smart materials such as hydrogels and shape-memory polymers.

Today, pharmaceutical sciences consider both 3D and 4D printing as key technologies as they continue to advance at a substantial rate. They are the major innovations bolstering the future of precision and personalized medicine with their ability to create patient-specific medical devices, responsive drug delivery systems, and tailored dosage forms

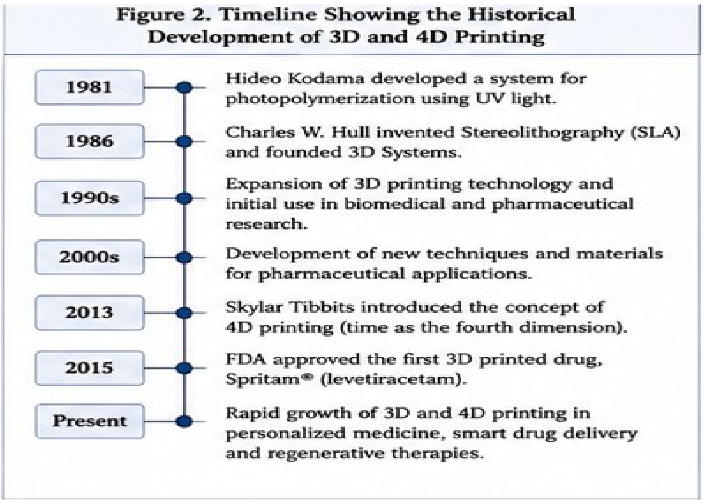

Figure 2: Timeline showing the historical development of 3D and 4D printing

Working principle of 3D printing

In 3D printing, the material is stacked on top of one another in layers. The 3D item is constructed by adhering the design from the bottom up, involving cutting and moulding of materials to achieve the desired shape, which is a different approach from typical manufacturing process. It does decrease the waste, enabling the creation of intricate, highly accurate structures.

The first step is to create a digital model using special software named computer-aided design for 3D printing. This model can also be created by a CT scan or MRI machine by utilizing photos of testes in the field of medicines can be used when medical professionals want to create medicine or an instrument for a single patient. Then it is converted into a file that the printer can read once the design is completed. Then it constructs the object by a layer-by-layer process when the printer is commanded.

As soon as the design is completed, the printer starts producing items. Material is added; one layer at a time is constructed. There are many ways to do it, for example, it can be squeezed out of a hole, or material can be dropped in little pieces and dried using specific light. Every layer adheres to the layer beneath it until the entire thing is completed. Every layer is printed according to design; therefore, the final product resembles the original product.

Sometimes, there is a little extra work for improving it, which can consist of cooling it, drying it, and sometimes removing the extra material that was used to support the creation. Then there is testing done to ensure suitable use involving the release profile and strength of the drug, as all procedures are crucial and done with accuracy, as they have to meet all the safety standards.

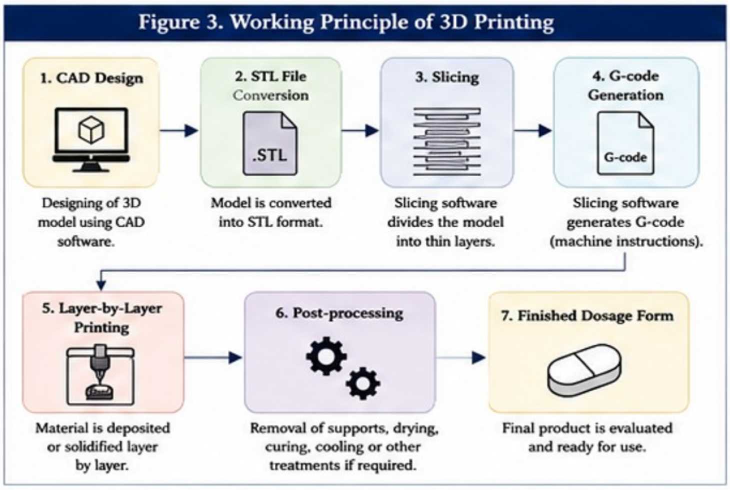

Figure 3: working principle of 3D printing

Working principle of 4D printing

4D Printing functions similarly to 3D printing. It makes use of unique materials that have the ability to alter in shape or function over time. Time is like a dimension in this technology. When the printed object is exposed to something after it is created, it is intended to alter on its own.

The first step in creating something using four printing is creating a computer model. After that, the design is converted into a printable file. Similar to 3D printing, it is printed layer by layer. The material utilized makes a significant difference. Materials such as stimuli-responsive hydrogels and shape memory polymers are used in four-dimensional printing. When these materials are created, they are programmed to do a certain action.

When something is printed with four printing, it remains unchanged until it comes into contact with anything that causes it to alter. This could be a magnetic field, water, heat, or light. When this occurs, the material undergoes controlled modifications, allowing the printed object to change in size, form, or functionality without being touched. When the device is designed, all of this is thought out so that it can logically adjust to its environment.

Four-dimensional printing is very helpful for creating medical delivery systems because of its adaptability. Four-dimensional printed objects can alter after use, which makes them ideal for customized medication, in contrast to printed objects that remain unchanged after being created. Four-dimensional printing is particularly good, for this since it can produce items that can respond to what's happening in the body.

Table 1. Comparison Between 3D Printing and 4D Printing

Parameter	3D Printing	4D Printing
Definition	Additive manufacturing of an an object layer-by-layer without change over time.	Additive manufacturing using smart materials that change over time in response to stimuli.
Principle	Static structure after printing.	Dynamic structure that adapts with time.
Fourth dimension	Not involved	Time
Materials used	Conventional polymers, ceramics, metals, excipients.	Smart materials (shape memory polymers, responsive hydrogels, SMPs, SMAs, etc.).
Stimuli required	Not applicable	Temperature, pH, moisture, light, magnetic field, electric field, enzymes etc.
Behaviour after printing	Remains unchanged.	Changes shape, size or properties.
Pharmaceutical implication	Customized dosage forms with controlled drug release.	Smart dosage systems with adaptive and on-demand drug release.

Figure 4: showing comparison of 3D and 4D printing

III.PHARMACEUTICAL DOSAGE FORMS FABRICATED USING 3D AND 4D PRINTING

- **Oral dosage forms**
- **Tablets**

One popular oral medication form is tablets. They are among the most researched applications of 3D and 4D printing in the pharmacy industry. Their simple design, usability, exact dosing, and strong patient acceptance make tablets very ideal for individualized treatment. In contrast to tablets, which are available in standard formulations and fixed strengths, 3D printing enables the creation of tablets that are customized to meet the needs of specific patients. Treatment with improved therapeutic outcomes and patient compliance can be achieved by altering the tablet's dose, size, shape, internal design, and substance. Tablets have been produced using a range of printing methods, including Fused Deposition Modeling, Semi-Solid Extrusion, Binder Jetting, Selective Laser Sintering, and Inkjet Printing. Sometimes, there is a little extra work for improving it, which can consist of cooling it, drying it, and sometimes removing the extra material that was used to support the creation. Then there is testing done to ensure suitable use involving the release profile and strength of the drug, as all procedures are crucial and done with accuracy, as they have to meet all the safety standards.

The approval of Spritam (levetiracetam) in 2015 marked a significant advancement in printing. Binder Jetting technology is used to create this FDA-approved 3D-printed tablet. The tablet is particularly beneficial for dysphagic, elderly, and pediatric patients because it dissolves rapidly with a small amount of water. 3D printing is a promising platform for precision medicine because it can create tablets with programmed drug-release properties and doses. Additionally, tablets that can alter their behavior in reaction to physiological situations may be created using 4D printing techniques.

However, the therapeutic usage of 3D-printed tablets is still limited by issues like the scarcity of printable materials, the heat sensitivity of certain medications, and large-scale production. These tablets may enhance patient care and treatment results. One advancement that could result in more individualized and efficient treatments is the use of 3D printing in pharmacies.

- **Capsules**

When taking medication orally, capsules are quite helpful. They are a means of administering precisely the right dose of medication. But due to standard manufacturing, capsules are available in a variety of sizes, but they are not suitable for everyone, as the dose must be the same for everyone, which is not compulsory to work; therefore, capsules can be altered as some people require more or less medication than found in a typical capsule

3D printing can formulate customized capsules for everyone according to their body requirements using devices that analyse the amount of drug in the capsule and its release profile, suitable for the person using methods like semisolid extrusion, binder jetting, inkjet, and fused deposition modelling. These methods do make capsules more effective, give good drug release, and also multiple medications can be combined into one capsule, reducing the burden of multiple medicines.

Well, there are some issues to be resolved regarding capsules. We must ensure that there is a uniform distribution of the drug and also use appropriate materials in manufacturing. But customized capsules can help patients recover faster and reduce their medication burden.

- **Polypills**

Polypills are capsules that contain many medications. Three-printing is used to create them. For those who must take numerous medications over an extended period of time, such as those with high blood pressure, diabetes, or heart disease, this is highly beneficial. In contrast to capsules, polypills can contain various medications in distinct sections, each of which may release the medication in a unique way.

Although formulating polypills is quite a complex procedure, patients do like that their medication is customized to their needs, and it also reduces the medication burden on patients, ensuring that multiple medications coordinate effectively and do not degrade during printing.

- **Oro dispersible Tablets (ODTs)**

Pills that do dissolve in mouth rapidly without any need of water are called orodispersible tablets, beneficial for patients who face difficulty in swallowing, such as children. Therefore, via 3D printing, these tablets are now personalized for patients with respect to their body needs, manufactured by the inkjet method, binder jetting method, and selective laser sintering method. They make tablets highly porous, which can decompose rapidly. Spritam is one tablet manufactured in this manner. It's an FDA-approved pill. Binder jetting is used to make it.

There are numerous advantages to these unique pills. They provide you with a dose of medication that is easy to take and works immediately. They must be handled cautiously because they might be delicate. Additionally, they must be properly packaged, and the printing procedure must be modified to achieve the desired results.

- **Oral Films**

Oral films are similar to oral medication strips. They. Give you the medication as soon as possible and stick to the inside of your mouth. A tablet does not need to be swallowed. Because these movies are compact and simple to use, they are excellent for both children and the elderly. 3D printing can be used to create these films. Two popular techniques are semi-solid extrusion and inkjet printing. These techniques allow you to regulate the amount and size of medication in each film. It is also possible to incorporate multiple medications into a film and control how quickly or slowly they are released.

The wonderful things about films manufactured using 3D printing are that you can receive the proper dose of medicine, they are easy to consume, and they work rapidly. Additionally, when medication is shown in a movie, people are more likely to take it. Making these movies is not without its difficulties. Getting the medication to disperse properly throughout the movie can be challenging. Additionally, the films may be brittle. It might not last very long.

- **Pellets**

Pellets resemble balls of medication. A dose of medication can be administered to you and released gradually over time. Pellets that are customized for each individual can now be produced thanks to 3D printing. They can be made in various sizes. Fill them with varying dosages of medication.

Fused Deposition Modeling and Semi-Solid Extrusion are two 3D printing techniques that allow you to create pellets that release medication quickly, slowly, or at a delayed time. You can fill these pellets into capsules or press them into tablets to get the correct dose of medication. The advantages of printing pellets are that you can get the right dose of medication, control how the medicine is released, and combine different pellets to create a customized treatment plan. Ensuring that the pellets are uniform and durable can be challenging. Making a lot of them at once might also be difficult.

- **Buccal and sublingual dosage forms**

The buccal and sublingual dose forms are oral medications. They aid in the medication's absorption through the tongue or cheek lining. In this manner, the medication begins to function more quickly and the body can use more of it because it does not need to pass through the liver. Doctors can use printing to create these medications specifically for a single patient, with the appropriate dosage and release method, particularly for medications that must act quickly or in a certain way.

Semi-solid extrusion and inkjet printing are two popular methods for producing these medications. These techniques aid in the formation of thin films of medication. While sublingual films dissolve swiftly and enter the body quickly, buccal films are often designed to release the medication in a single location. These systems are being investigated for the treatment of pain, cardiac medications, nausea medications, and emergency medications.

These systems' advantages include their ease of use and the speed at which the medication enters the body. They are more likely to be taken correctly. Additionally, the medication does not need to pass through the stomach, which occasionally breaks it down. However, there are a few issues: the films can only contain a little amount of medication; the amount of saliva in the mouth can alter them; and it can be challenging to make them strong and include the same amount of medication in each.

Feature	**Buccal Films**	**Sublingual Films**
Site of absorption	Inner cheek mucosa	Under the tongue
Drug release	Sustained/localized	Rapid/systemic
Onset of action	Moderate	Very fast
Saliva exposure	Lower	Higher
Common use	Chronic/local therapy	Emergency/acute therapy
Design focus	Mucoadhesion & retention	Fast disintegration

Table 1: Comparison of buccal films and sublingual films

- **Transdermal and microneedles**

Transdermal drug delivery systems are excellent in delivering medications to our skin and bloodstream steadily. This is an alternative to taking pills or receiving injections because it prolongs the duration of the medication, improves its effectiveness, and prevents some of the negative effects of oral medication. 3D printing is crucial when discussing medicine since it enables us to create customized patches for each patient. We can give individuals the right quantity of medication and make them feel better because we have control over how the patch is created, where the drug is, and how it exits.

Fused Deposition Modeling, Inkjet Printing, and Semi-Solid Extrusion are a few popular printing techniques for creating these patches. These techniques allow us to create layered patches, control the drug's release by placing it in a specific location, and even adjust the patch's thickness. Patches and other transdermal devices are frequently used to deliver medications to our bodies. They are effective for things like hormones, heart medication, and painkillers. A more sophisticated method of delivering medication into our skin is by microneedles. To improve the drug's penetration, they create holes in our skin. Solid microneedles are possible. Depending on what we need them to achieve, they can dissolve or have a unique covering.

Systems have the advantages of giving us a consistent and regulated dosage of medication, increasing the likelihood that people will use them, being painless, and not upsetting our stomachs. There are also some negative aspects. Because each of our skin types is unique, the medication may not always penetrate as well as it should. We may also experience skin irritation. It can be hard to get some forms of medicine to operate successfully using transdermal devices.

Feature	**Transdermal Patches**	**Microneedles**
Drug delivery mechanism	Passive diffusion through skin	Microchannel-assisted permeation
Invasiveness	Non-invasive	Minimally invasive
Onset of action	Slow to moderate	Faster
Drug types suitable	Small, lipophilic drugs	Wider range (including peptides)
Patient comfort	High	Moderate (slight skin penetration)
3D printing role	Layered patch design, drugreservoirs	Micro-needle array fabrication

Table 2: Comparison of transdermal patches and microneedles

- **Implantable Drug Delivery Systems**

Drug delivery systems are devices that doctors implant in our bodies to administer medication for extended periods of time, such as weeks or months. They assist us in getting the medication we require on a regular basis or only once to help us recover. Reduce the frequency of taking medication. With 3D printing, we can improve the implantable drug delivery system by customizing the implants according to the patient's body. We can also regulate the different doses for every patient so that the patient receives the exact dose they require. Implants can be improved by using techniques such as stereolithography, selective laser sintering, and fused deposition methods. These methods are utilized to make implants that deliver medication in a regulated manner, such as drug-eluting stents, which are the implants that help patients' hearts and stop arteries from narrowing. Also, there are drug delivery systems that are going to be used in cancer and hormonal therapies.

These drug delivery systems have advantages by taking medications for a longer time period and also in regulating, ensuring that the drug reaches the intended site while reducing side effects. The drawbacks include the need for surgery to receive the implant, the possibility of infection, and the inability to alter the dosage of medication once the implant is in place.

- **Topical Drug Delivery Systems**

Topical drug delivery systems are designed to apply medication to the skin, a particular location, or sometimes the entire body for a localized effect. These systems do not penetrate the body. They circumvent the initial stage of the body's medication breakdown. 3D printing allows us to precisely regulate the location, thickness, and release of medication, allowing us to create customized medications for each patient based on the type of wound and skin condition.

To create systems that contain medication and allow us to control the dosage, we employ 3D printing techniques such as FDM Inkjet Printing and SSE. Similar to networks, hydrogels assist release medication in a regulated manner while keeping the site wet. Wound dressings are similar to printed coverings. To improve the wound and stop infection, they have medications, antimicrobials, and wound-healing agents.

These systems have the advantages of treating the local area, improving wound healing, having fewer negative effects on the entire body, and allowing us to regulate how the medication is given. The hydrogels are not always stable, the printed dressings are not always strong enough, and the medication does not always enter the tissue.

Feature	**Hydrogels**	**Wound Dressings**
Nature	Hydrophilic polymer network	Protective layered material
Function	Moist environment + drug release	Protection + healing support
Drug release	Controlled	Sustained/antimicrobial
Use	Burns, chronic wounds	Wound management
3D printing role	Hydrogel matrix fabrication	Structured dressing design
Limitation	Weak mechanical strength	Limited deep drug delivery

Table 3: Comparison of hydrogels and wound dressings

- **Ophthalmic Drug Delivery Systems**

Ophthalmic drug delivery systems are designed to precisely and effectively administer pharmaceuticals to the eye in order to treat eye problems. The inadequate bioavailability of traditional ophthalmic eye drops is because of rapid tear drainage and limited corneal absorption, but we can improve bioavailability by 3D printing as it can formulate patient-specific devices that will have precise medication loading with controlled release, leading to improved treatment efficacy. Can be done through inkjet method, FDM, and stereolithography, which also allow the formulation of drug-loaded ocular inserts and lenses with functions as a sustained release system. They directly deliver the medicine to the ocular surface to treat conditions like glaucoma, dry eye syndrome, and infections are a significant example.

The advantages include improved ocular bioavailability, extended drug release, improved patient adherence, and fewer doses. But limits by possible visual discomfort, dose loading capacity, and difficulty in retaining optical capacity, as well as long-term stability of devices.

Feature	**Eye Drops (Conventional)**	**Drug-Eluting Contact Lenses**
Drug delivery	Surface instillation	Controlled ocular release
Bioavailability	Low	High
Duration of action	Short	Long-lasting

Dosing frequency	Frequent	Reduced
3D printing role	Limited	Lens fabrication + drug embedding
Limitation	Rapid drainage	Comfort + optical clarity issues

Table 4: Comparison of eye drops and drug-eluting contact lenses

- **Dental Drug Delivery Systems**

Dental drug delivery systems are designed to address oral health issues such as tooth decay and gum infections, as well as aid in the healing process following surgery. These medications are made better. These medications are made. Using 3D printing, we may create customized dental devices with the appropriate dosage and release method for each patient.

SLA and FDM inkjet printing are two popular methods for producing these devices. We employ these ways to manufacture assistance like scaffolding, films and inserts that have medicine in them to fight germs reduce swelling or help teeth get strong again and we can put them just where they are needed.

These systems are beneficial because they deliver medication where it is needed, they are very effective, and patients are more inclined to use them. The drawbacks include their limited capacity to hold medication, their potential for instability in the mouth, and their potential for exhaustion from chewing and saliva.

Feature	**Conventional**	**3D-Printed Dental Systems**
Delivery	Systemic/topical	Localized controlled
Targeting	Non-specific	Site-specific
Release	Short-term	Sustained
Compliance	Moderate	High
Limitation	Frequent dosing	Oral instability

Table 5: comparison of conventional and 3d printed dental systems

- **Rectal and Vaginal Drug Delivery Systems**

Rectal and vaginal drug delivery devices provide an alternative to oral medication for systemic administration. These approaches assist avoid the bodys reaction to medicine and can deliver immediate or long-lasting release depending on how the medicine is prepared. 3D printing is used in medicine to make vaginal rings, suppositories, and inserts that are customized for each patient with precise shapes, dosages, and release rates.

Common technologies used include FDM, Inkjet Printing and SSE. These are utilized to create medication forms that have structures and the capacity to administer several medications. Rectal systems are frequently utilized to treat gastrointestinal issues, fever, and pain. Hormone therapy, birth control, and infection treatment are the main uses of vaginal systems.

These systems are beneficial for individuals who are unable to take medication orally because they allow medication to be absorbed without being broken down in the stomach. However there are additional limits, such as discomfort, varied absorption rates and issues, concerning acceptability.

Feature	**Rectal**	**Vaginal**
Dosage forms	Suppositories	Rings/Inserts
Release	Local/systemic	Sustained/local
Main use	Pain, GI disorders	Hormonal therapy, infections
3D printing role	Custom suppositories	Controlled ring design
Limitation	Discomfort, variability	Acceptability, retention

Table 6: *Comparison of rectal and vaginal drug delivery systems*

- **Tissue Engineering & Bioprinted Scaffolds**

Bioprinted scaffolds are three-dimensional constructs that facilitate cell adhesion, proliferation, and tissue formation. They offer support and a healthy environment for tissue regeneration, and they resemble the tissue in which cells thrive. In the medical field, 3D bioprinting aids in the creation of scaffolds that are customized to each patient's unique requirements, taking into account the size, type, and regeneration requirements of the defect. This makes tissue to repair.

Bioprinting techniques consist of extrusion, inkjet, and laser-assisted processes that enable unique inks composed of living cells and biodegradable materials and compounds promoting cell growth. Therefore, bioprinting scaffolds can also be facilitated to release medications or growth hormones for prompting tissue growth and repair.

Bioprinted scaffolds have the advantages of being very compatible with the body, being able to be customized for a patient, and being able to provide therapy and aid in tissue regeneration. Nevertheless, maintaining cell viability for a while, encouraging the growth of blood vessels in big scaffolds, and producing them on a large scale for routine usage in clinics present difficulties.

IV.SMAT MATERIALS/TECHNOLOGIES AND INSTRUMENTS USED IN 3D AND 4D PRINTING

Materials that may alter their characteristics in response to an internal or external signal are known as smart materials. These cues can be things like temperature, light, or even biological signs. Materials utilized in medicine, on the other hand, do little more than sit there. In fact, smart materials are able to adjust to their surroundings. They can offer medicine at the appropriate kind of medicine at the right time at the right time at the right time. The transition from materials to smart materials has significantly changed the way we produce medications. Old materials were just sitting there. medication that was released gradually.

The ability of smart materials to alter their behavior in response to external events sets them apart. Smart materials are compatible with medical manufacturing techniques such as 3D printing. This enables us to create personalized medications. Additionally, it enables us to create medications that can alter their effects once administered to a patient. Smart materials are used in printing to create medications with unique shapes and dosages.

To produce the medication, they use things like light, special inks, and melted plastic. In 4D printing, this is especially crucial because the medication can vary in shape or release different amounts over time. We can do this by utilizing sophisticated materials. This may improve the medication's effectiveness and cause adverse effects. Additionally, patients can follow their treatment plan.

As research in materials and printing keeps going, these materials will be important to developing medicine that's tailored just for one person. They will contribute to the development of medications with fewer adverse effects and greater efficacy. This will improve everyone's access to more accurate healthcare.

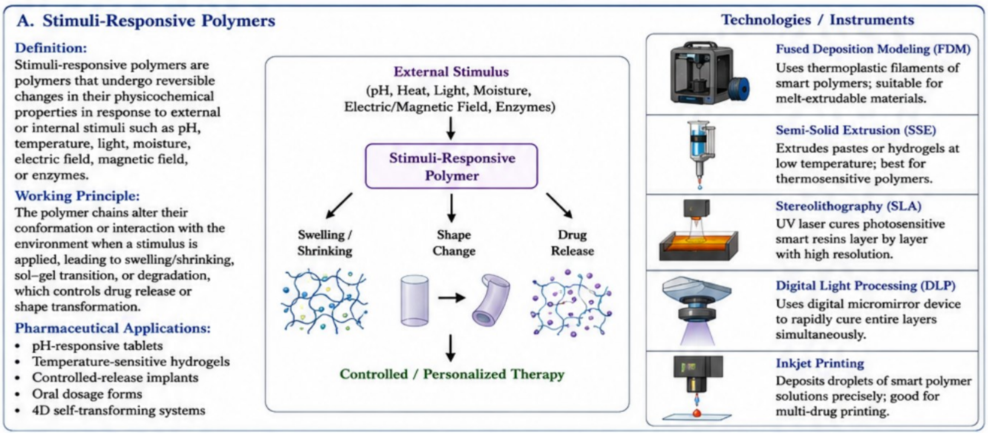

Figure 5: stimuli responsive polymers

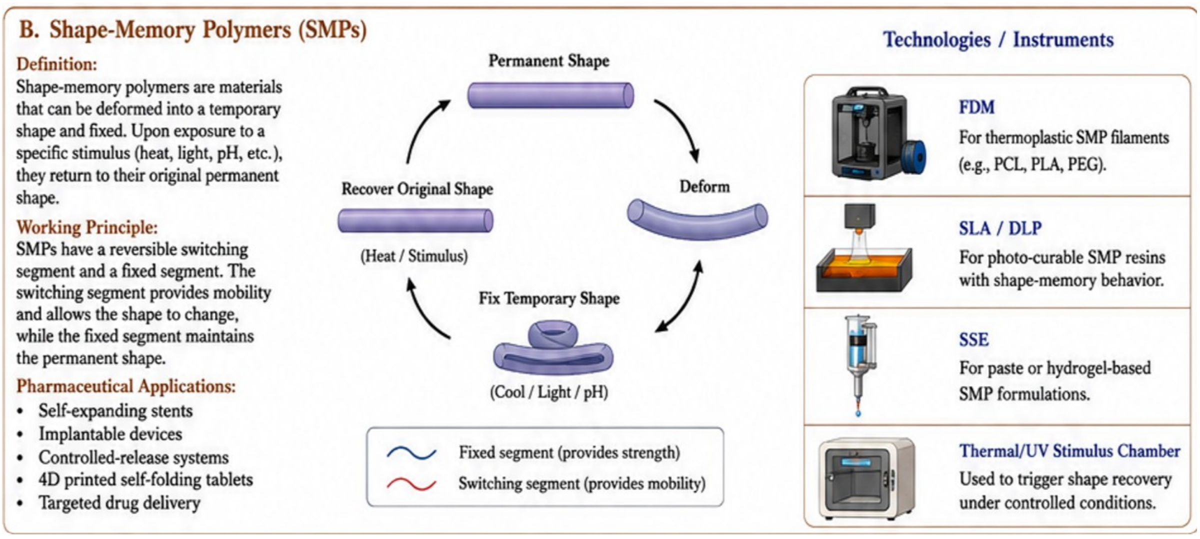

Figure 6: shape memory polymer

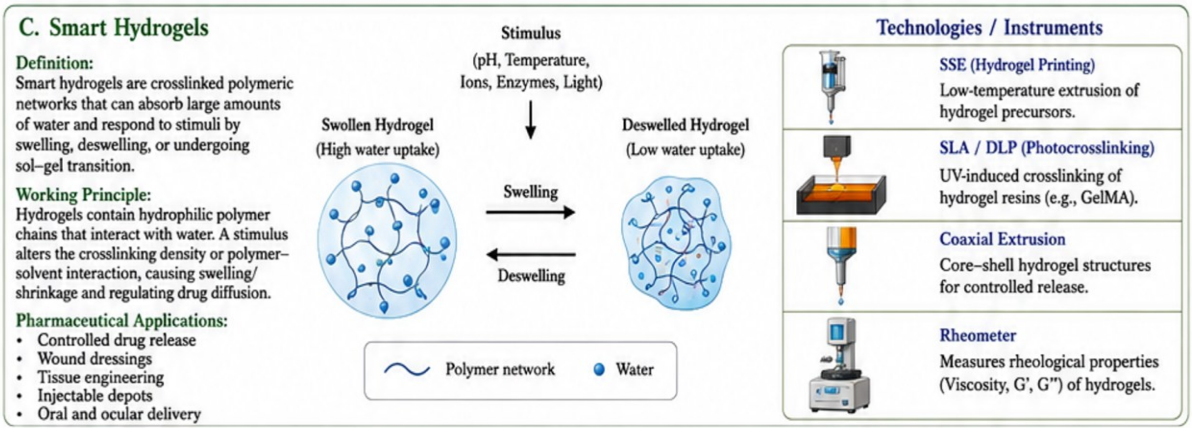

Figure 7: smart hydrogels

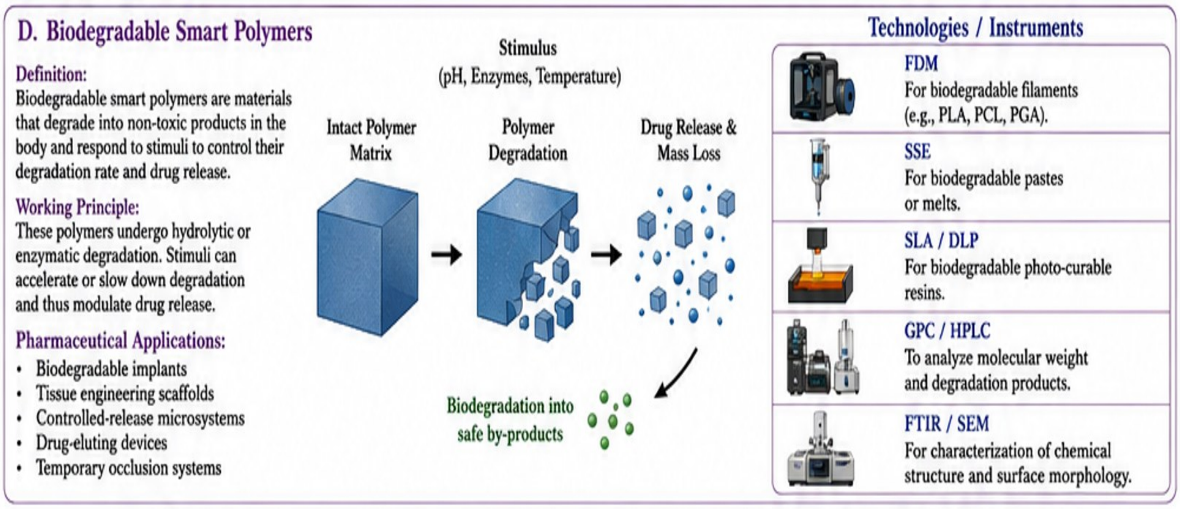

Figure 8: biodegradable smart polymers

V.ADVANTAGES OF 3D AND 4D PRINTING

3D and 4D printing have greatly revolutionized how we create medicines. There used to be a one-size-fits-all strategy. We can now customize medications to meet the needs of each patient, including their age, the type of illness they have, and the dosage they require. In contemporary pharmacies, this is a component of individualized medication.

With 3D printing, we can create medications with precise control over the dosage, form, and release mechanism of each dose. We have the ability to do not have a polypillate the ability. This makes the process easier. Particularly when they have to assist them when they take a lengthy patients.

Because 4D printing creates "smart" medications that can react to inside body processes, it is more sophisticated. Depending on factors like the body's temperature or acidity, these medications can release the drug at the right moment. This makes treatment more effective. • Another positive thing about 3D and 4D printing is that medicines may be manufactured right where the patient is being treated. Therefore, if necessary, the doses can be shifted according to patients such as pediatrics, geriatrics, and patients with uncommon illnesses .

Designs of medications are assisted by artificial intelligence and computer tools to save time and effort to ensure the formula is accurate, as well as to ensure that the release of the drug is as per schedule. Therefore, 3D and 4D printing is making medications more individualized, adaptable, and patient-centred, with the plan of dropping the traditional method of manufacturing in bulk to make medications more personalized so they meet the needs of individuals .

VI.LIMITATIONS OF 3D AND 4D PRINTED PERSONALIZED DOSAGE FORMS

1. Material Limitations

- Limited availability of pharmaceutical-grade printable polymers.
- Drug–polymer compatibility issues.
- Stability of drugs during printing.
- Limited range of stimuli-responsive biomaterials for 4D printing.

2. Manufacturing Challenges

- Slow printing speed.
- Difficulty in large-scale production.
- Batch-to-batch variability.
- High equipment and maintenance costs.

3. Regulatory Challenges
- Absence of harmonized regulatory guidelines.
- Complex quality assurance and validation.
- Good Manufacturing Practice (GMP) compliance.
- Limited pharmacopeial standards.

4. Clinical and Patient-Related Challenges
- Limited clinical evidence.
- Need for extensive safety and efficacy studies.
- Storage and shelf-life concerns.
- Acceptance of personalized printed medicines.

VII.RECENT DEVELOPMENTS

Artificial Intelligence in Pharmaceutical 3D Printing

In 3D printing the improvement of pharmaceutical designs and production it is increasingly incorporating artificial intelligence. Artificial intelligence is capable of analysing a large amount of data to determine how to produce these medications. It can decide how the drug will be released. This implies that we don't need to attempt a lot of different approaches to get it properly.

Watching the manufacturing process in real time is another benefit of artificial intelligence. It can check the quality of the medications. Look for any issues. The entire procedure becomes more effective as a result. ensures that the medications aremanufactured consistently. The employment of intelligence with 3D printing is going to help produce medicines that are personalized to each patient. Combining 3D printing with artificial intelligence allows for the creation of patient-specific intelligent medicine delivery devices.

Digital Healthcare Integration

Personalized medicine now provides more options thanks to the combination of digital healthcare technology with pharmaceutical 3D and 4D printing. Wearable technology, biosensors, telemedicine platforms, and electronic health records can all offer patient-specific clinical data that can be utilized to create dose forms that are specifically tailored to each patient's treatment need. This integrated strategy allows for continuous monitoring of treatment outcomes and timely drug modifications, resulting in more precise, data-driven healthcare.

Point-of-Care Manufacturing

Making medications in hospitals, clinics, or specialty pharmacies is known as point-of-care manufacturing. These medications are manufactured. These medications are produced as needed using 3D printers. This aids in the distribution of medications and does not depend on large manufacturing facilities. They frequently require dosages that aren't typically administered. there for point of care manufacturing must make tailored doses for an individual while ensuring the safety of the medication. Therefore, it must adhere to regulations.

Future Scope of 4D Printed Medicines

The development of smart medications that can adapt to our bodies' requirements and respond to certain signals after we take them is the future of 4D-printed pharmaceuticals. Smart materials, 3D printing of living tissues, nanoscale technology, artificial intelligence, and digital health will all contribute to the development of self-controlling and more effective medications. In the future, scientists will probably concentrate on medications that have several functions, such as sensing our needs, delivering medication to particular locations, and releasing it in a controlled manner. Although there are still certain obstacles to be solved, 4D printing has the potential to revolutionize the pharmaceutical industry.It could aid in the development of medicines that are more individualized and flexible than what we now have.4D-printed-printed-printed-printed-printed-printed-printed-printed-printed medications could improve. The advancement of 4D-printed medications will probably have an impact. 4D printing and smart materials will be important in this. The use of 4D-printed pharmaceuticals will continue to expand.

VIII.CONCLUSION

The production of pharmaceuticals is being altered by three-dimensional and four-dimensional printing. They assist in developing medications that are customized for every patient. This review examined how various printing technologies are used in the production of medications. The printing techniques, materials, and intelligent materials that react to the body were all covered. Custom oral, skin, implant, and other advanced pharmaceutical delivery methods are made possible by these technologies. Smart materials make 3D printing better. They make it possible for medications to change and react to the needs of the body. This enhances the accuracy and outcomes of treatment. There are still difficulties, though. These include locating the materials, improving the procedure, manufacturing in huge quantities, guaranteeing quality, and standardizing rules. The application of these technologies in clinics is restricted by these problems.. New breakthroughs in digital healthcare and producing medicines at the patient's bedside are propelling 3D and 4D printing forward.

Healthcare solutions are becoming more sophisticated and efficient as a result of these developments. The mix of printing technologies, smart materials, and digital breakthroughs can revolutionize the future of personalized medicine. To incorporate these advancements into clinical practice, more research, improved technology, and strict regulations are required. This will result in medical treatments that are more efficient and patient-centered.

This will involve the use of both three- and four-dimensional printing. They will contribute to the development of medications tailored to each patient's needs. Treatment outcomes will continue to be enhanced by the use of materials and cutting-edge printing technologies. Additionally, it will make it possible to develop safer and more effective medications.

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