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Evolution of pharmaceuticals using 3D and 4D printing

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HIGHLIGHTS

- Summarise applications, Challenges and Limitations of 3D and 4D Printing.
- Discuss comparative review of 3D and 4D Printing.
- Highlight updates and current advances about 3D and 4D Printing in pharmaceutical industry.
- Significance of 3D and 4D Printing in pharmaceutical technology.
- Patents on 3D and 4D Printing.

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ABSTRACT

This overview examines the latest developments and applications of 3D and 4D printing in the health care and pharmaceutical field. The technique of creating a 3D object from a 3D model in the required size and shape is known as 3D printing. Whereas, 4D printing is the establishment of intricate three-dimensional formations that can change form in response to various external inputs. Applying 3D printing technology 3D printing, the healthcare industry has produced significant strides toward a patient-centred approach. The future of biomedical science and patient-centered care could be completely transformed by 3D printing with further advancements in research and development. 3D, 4D Technology used in printing is one of the most advanced industrial technologies available worldwide. The 3D and 4D printing pharmaceutical enterprises have completed the shift from centralised to distributed systems for the purpose of creating dosage forms. The goal of the study is to support the research goal of determining the degree to which patient-specific treatment is enhanced and healthcare outcomes are improved through the use of printing technologies in pharmaceuticals. Beyond this thorough analysis, the study highlights potential and problems from several angles and comparative aspects between 3D and 4D printing.

1. Introduction

A new technique called Pharmaceutical applications might greatly benefit from the application of three-dimensional (3D) printing. It can provide cutting-edge solutions to individuals and pharmaceutical sector.[1] Using digital data gathered with 3D printing, a three-dimensional model is, 3D printing is a process that blends multiple technologies, procedures to produce a three-dimensional object. The 3D printing is method of creating a three-dimensional structure through a digital CAD file.[2] Unprecedented adaptability in style and manufacture of numerous intricate elements for use in within tailored as well as scheduled treatment is enabled by the application of 3D printing technology. Thus an effective method in light of overcoming a few challenges associated with everyday medication unit functioning.[3] Regarded as one of the biggest

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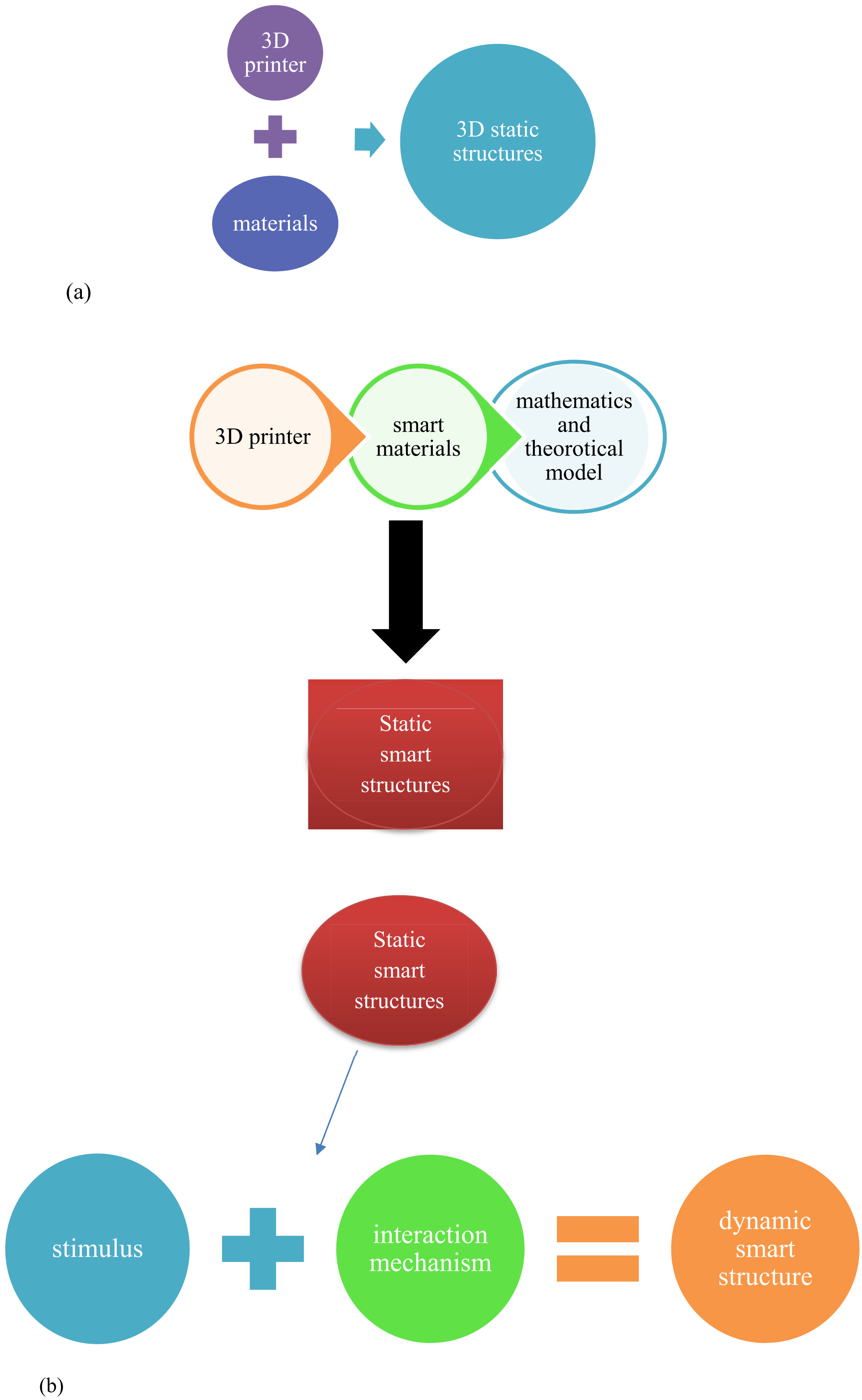

Fig. 1. 3D vs 4D Printing (a) Three-Dimensional Printing (b) Four-Dimensional Printing.

developments within the manufacturing industry is 3D printing. It possesses essentially changed the way that parts, components, and equipment are manufactured and developed in this business. Using conventional production methods, 3D printing allows researchers and producers to construct intricate structures and forms that were previously thought to be dosage forms.[4] It also aids in the creation of pharmaceutical products by providing a variety of release modalities to meet clinically impractical needs.[5] With the use of this technology, it is possible to precisely define patient demands and support patient-centric treatment, including customized dosage for the therapy of particular illness conditions or patient groups.[1] The breadth of printed materials and device research and development has increased with the arrival of three-dimensional and 4D printing technology into pharmaceutical sector.

Moreover, 4D printing (4DP) is growing. as a novel additionally difficult study.[6] Comparing 4D printing to 3D printing, one advancement is the use of materials whose shapes can alter over time.[2] The application of intelligent or wise raw components in 3D technique for printing allows for the creation of items that, when subjected to certain non-mechanical external stimuli, can change shape after they are manufactured. Smart materials possess one or more characteristics that can drastically alter in reaction to external changes, like variations in dampness, electric and magnetic fields, luminosity, warmth, pH, or ion makeup.[6] This atypical behaviour could be made possible by these properties. Compared to 4D printing, 3D printing has one extra "D". A 3D volume built a print's layers by layers route and a 2D structure are repeated from bottom to top with regard to 3D printing. Gradually converting 3D printing to 4D printing is the process. Time is then included as a fourth factor. Consequently, the capacity to alter shape throughout time is 4D Printing's finest accomplishment using 3D Printing. The process of printing a 4D digital item is identical as printing any 3D form.[7] The distinction is that cutting-edge, programmable materials that provide light, heat, or both are used in 4D printing.[5]

3D and 4D printing offer several advantages compared to conventional methods as it provides Complexity, Material Efficiency, Customization, On-demand Production, Complex Geometries. In addition, 4D printing goes one step farther by introducing materials capable of self-assemble or alter throughout time in reaction to outside stimuli like temperature, moisture, or light. This adds an extra dimension of functionality and adaptability to printed objects, opening up new possibilities in domains as robotics, architecture, and medicine.

While conventional methods still have their place, especially for high-volume production of standardized parts, 3D and 4D printing offer unique advantages in terms of flexibility, customization, and innovation. In addition to providing a comparative review of technology

And applications, obstacles, and future scope. Using 3DP technology to prepare different dosage forms and medical equipment. At the moment, this technology is being used to fabricate dosage forms (hydrogels, oral dosages, suppositories etc.) and medical devices from printouts and medicinal products.[8,9] Furthermore, a large range of dosages with unique forms and release characteristics have been devised, Certain products contain several active pharmaceutical ingredients (APIs).[10] It's interesting to note that the technique enables exact dosages to be applied depending on the formulation's structural dimensions and starting "ink" concentration.

This study begins by explaining the essential characteristics of 3D and 4D processes, emphasized regarding the advancement of 3D and 4D building capabilities and methods, with particular attention to the engineering of powders for metal, ceramic, and polymers.[10] Also includes an overview of pertinent intellectual property, industry advancements, and viewpoints on 3D and 4D technology in education. sums up the upcoming developments and trends in technology as well.

1.1. History

In the 1990s, 3D printing was proposed as feasible a stage for tailored care. With the FDA's Center for Device and Radiological Health (CDRH) evaluating and approving 3DP medical supplies, there have been notable advancements in 3D printed medical equipments. The initial use of 3D printing in the pharmaceutical industry was binding particles together by putting a powder bed and a binder solution inkjet printed on it. The procedure was carried out repeatedly up till the desired finished construction was achieved. This started at the Massachusetts Institute of Technology in the initial 1990s when Sachs et al developed and patented the method. Another Fused Deposition Modelling is a 3D printing procedure was patented in 1989 by Scott Crump. In this method, heated polymer filaments were pushed out via a hot nozzle in addition to and placed on a surface. Oral Spritam (levetiracetam) tablets were produced by inkjet printing; Aprecia Pharmaceuticals' 2016 FDA authorizes first 3D-printed medication was made feasible by this technology.[7] While field of 3D printing is very young in the pharmaceutical business, it has evolved further in the automotive, aerospace, biomedical, and tissue engineering sectors. By using risk-based strategies, the FDA promotes the advancement of cutting-edge manufacturing techniques like 3D printing.[11]

The term "4DP" was coined on a Technology, Entertainment stage, and Design (TED) Talk in February 2013. TED Talks are public conversations that are published online by a media organization under the heading "ideas worth spreading" for unrestricted access based in the United States. Skylar Tibbits, the creator and head of the Self-Assembly Lab (SAL) at the Massachusetts Institute of Technology (MIT), demonstrated what can be described as the first examples of 4D printed things capable of self-transformation over time on that occasion (Tibbits, 2013). These configurations, which were produced as a single thread, were constructed with clever materials that, when submerged in water, swelled asymmetrically and folded into the desired shape. Other research groups developed 4DP self-moving systems almost simultaneously. Ge and colleagues, for example, created and printed devices that included hinges made of a "active" composite material and "inactive" plates made of rigid plastics (Ge et al, 2013). After that, the devices were thermomechanically programmed to adopt intricate 3D shapes, with form changes occurring in response to temperature fluctuations. Following that, 3DP One-handed origami began to exist discussed in scientific journals. In this regard, the majority of applications were focused at the manufacturing of novel actuators for use in robotics (De Marco et al, 2019; Hann et al, 2020; Shiblee et al, 2019). Opportunities in the biological field were also investigated.

Making a three-dimensional building out of process of creating a digital CAD file. Layers of materials must be added until the desired form is obtained. However, because 4D printing uses materials whose properties may vary over time, it advances above 3D printing in some ways. It enables objects to be programmed to react to outside inputs and adjust form appropriately. A component of 4D printing is form programming, which is the both layout and the code of materials or structures alter their shape or arrangement in reaction to external stimulants.[12] The principle distinction among these printing methods is that 4D incorporates the use of self-transforming materials, whilst 2D does not.[10] The primary distinction among these printing methods is that 4D includes use of self-transforming materials, whereas The only thing you can do with 3D is layer by layer create static things. From its first coining in 2013 to the present day, the term "4D-printing" has seen substantial changes as scientists explore the potential of various materials and procedures to create objects with malleability, form, and texture Fig. 1.[2]

2. Technologies of 3D printing

Based on the kind of material utilized, the methods used for deposition, and the methods for solidification and fusing, 3D printing technology may be categorized into many groups. The most popular kind of 3D printing technology for use in medicine are the laser-based writing systems, nozzle-based deposition systems, and printing-based inkjet (IJ) systems.[7] These systems may be further divided into categories according to the components and sources of energy used Fig. 2.[13]

3. Printing-based- inkjet systems

Inkjet systems based on printing are categorized into four types: drop-on-demand (DOD) printing, binder jet printing, and continuous inkjet printing (IP).[14,15]

With benefits including great repeatability, droplet size control, and the capacity to create intricate and extremely permeable architectures, binder jetting (BJ) is a comparatively easier technique of producing tailored drug dose. Over a powder bed, 3DP technology ink is patterned. BJ 3DP refers to the drop on solid (DOS) method, which involves blasting a binder fluid into the printer's powder bed via the nozzle, either containing or without containing the API.[16]

The layer formed consequently of the wet powder within the powder bed combining. Powder fortification happens through the creation of binder bridges as well as particle disintegration and re-crystallization. When a layer is finished, the constructing platform goes downward.[17]

3.1. Binder jet printing

One method of additive manufacturing called binder jetting is used to produce unique and expensive components and equipment by selectively depositing a thin coating of powdered particles, such as foundry sand, ceramics, metal, or composites, and a liquid binding agent utilizing an industrial printhead. Similar to printing on paper, the process is repeated layer by layer until the desired result is achieved by using a map from a digital design file.[16,18]

3.2. DOD techniques

Are split up into two categories: drop-on-solid and drop-on-drop deposition.[11,19] Since both methods can print various sections concurrently, layer by layer, they have the benefit of employing several materials and colours, which reduces printing time. Low processing costs, speedy operation, minimal material waste, and a straightforward process with reduced contamination are some of the advantages.[14,20]

4. Nozzle based deposition

4.1. Fused Deposition Modeling (FDM)

The FDM technique was created in 1989 by Scott Crump.[14] The usage of thermoplastic polymers like poly lactic acid (PLA), acrylonitrile butadiene styrene (ABS), or polyvinyl alcohol (PVA) is known as FDM.[21]

Before being extruded via an a nozzle for an extruder that is positioned above the melting point of the substance, melted API and polymer mixtures are kept in rolls.[18] Layer by layer, the polymer-API mixture melts and deposits before hardening.[14,22,20,23] One of the easiest ways to create customized dosage forms is by 3D printing with Semi-Solid Extrusion (SSE), which eliminates the requirement for drug-loaded filaments, which is necessary for other 3D printing technologies.,[20,24,23] and.[25]

4.2. PAM technology

Within the category of extrusion-based 3DP technologies is PAM.[14] This technique uses a syringe extruder with a compressed air piston to deposit layer by layer a semi-liquid and viscous material.[20,24]. To do this, a computer-controlled microsyringe is used to extrude a semisolid material layer by layer onto a glass slide or building plate.[11,26]Smoothness, homogeneity, and adequate rheological properties are necessary for the paste to be extruded from the microsyringe without occlusion.[21] Once an appropriate paste is obtained, syringe is used to help start the printing.[26]

5. Laser-based system

Charles Hull invented this process, which is also known as Stereolithography (SLA), and its mechanism involves subjecting coating of fluid resin that is photosensitive to a UV light source. Liquid resin cures onto

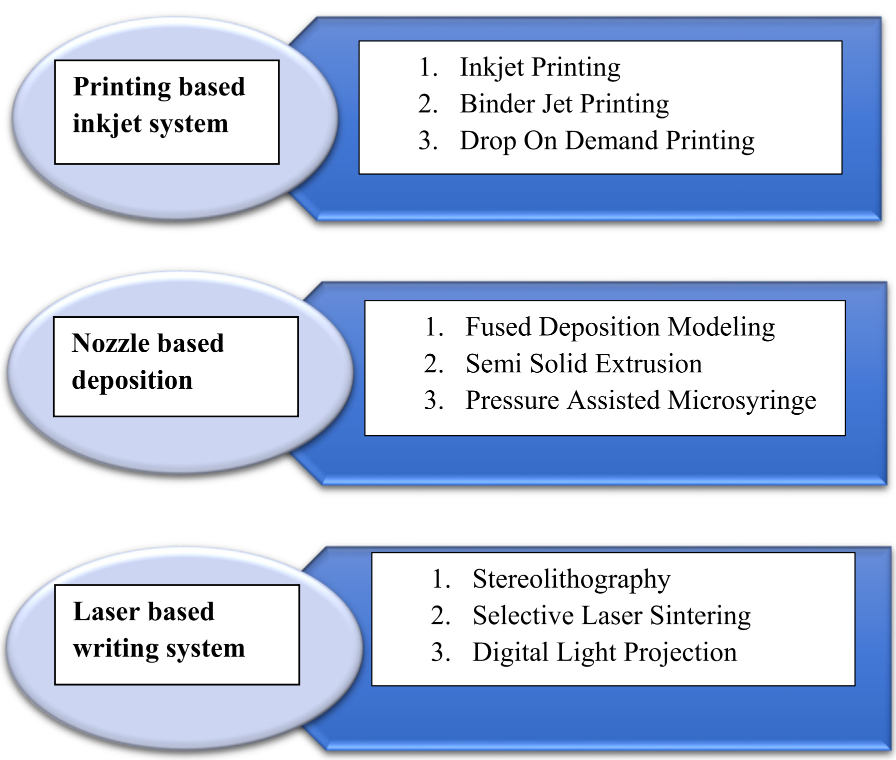

Fig. 2. Technologies of 3D printing.

the build platform in SLA technology via scanning of a resin tank through a laser(2017). One layer at a time, the item assembled once the resin hardens in the intended pattern.[25] Stereolithography (SLA) is a laser-based printing method that uses photopolymerization to control liquid's solidification resin. This method is used in production of tablets, hydrogels, and medical equipments.[9] SLA is a versatile technology that allows the medication and photopolymer to be combined prior to printing as a solid object. SLA is used for thermolabile medicines and has a high resolution. Selective laser sintering (SLS) sinters powder photopolymer using a powerful laser as a power source. SLS has the distinct advantages of great strength, chemical resistance, and quick operation. Demonstrates the use of several approaches in pharmaceutical formulations. The Google Scholar database contains around 15,900 scholarly studies and reviews pertaining to the topic of "3D printing technology in pharmaceutical domain " since 2016.,[22,24,20].

3D medication is no longer a pipe fantasy. Drugs of any type and shape can be made using innovative technology. The UK biotech startup fabrx believes that within five to 10 years, it might become a regular technique in pharmacies and hospitals for generating tailored pharmaceuticals in precise amounts. In comparison to traditional preparation technologies, A great degree of flexibility and inventiveness to customize medicines, exact control over drug release to fulfil a variety of therapeutic objectives, and a notable decrease in preparation development time are all made possible by 3D printing. It also provides adaptability in the design of complicated 3D structures within pharmaceuticals, drug dose and combination adjustments, and quick production and prototyping.[27] Many pharmaceutical products, such as dispersible films, microneedles, implants, transdermal patches, controlled-release tablets, and immediate-release tablets,[28] have been made possible by 3D printing technology.

6. Technologies of 4D printing

Over fifty AM processes have been categorized by the American Society for Testing and Materials (ASTM) into seven groups: powder bed fusion, vat photo-polymerization, material extrusion, binder jetting, direct energy deposition, and sheet lamination.[29] The following are a few of these categories' 3D technologies that use smart materials for 4D printing Fig. 3.[30]

7. Vat photo polymerization

A kind of additive manufacturing called vat photo-polymerization uses a resin-filled vat that is cured by UV radiation to solidify the material onto a hard surface. SLA and DLP are the two types of vat photo polymerization that vary in terms of their light source.[31] Due to their shared use of photo-polymers, DLP and SLA operate similarly.[32] The primary distinction between the two is the kind of light source utilized; for example, the DLP uses traditional light sources such an arc lamp and an exhibition panel made of liquid crystal. Its application is faster than SLA since it covers the entire surface in a single pass. In recent years, its increased popularity has been attributed to its quickness and capacity to instantly cure a layer of resin.

7.1. Stereo lithography (SLA)

A well-known printing method wherein resins and liquid polymers are photocrosslinked to create solid or gel-like structures using light (laser) beam emission at different frequencies. The superior surface smoothness of the constructed components and the capability to achieve high printing resolution are the primary benefits of SLA over extrusion-based printing techniques.[33] A common use of printing is to generate parts that can change shape by printing various polymeric materials, including photo-cross-linkable hydrogels and photo-curable resins.[34] Many factors, including laser energy, curing depth, polymerization shrinkage, and curing speed, are thought to affect the intricate and dynamic nature of the laser curing process.[28]

7.2. Digital light processing (DLP)

In order to cure the liquid resin in the reservoir, DLP printing employs a digital light pattern rather than the laser beam used in SLA. This allows each layer to cure in a matter of seconds. Because surface-projection-based manufacturing processes are used, it can attain faster printing rates than SLA printing. The projectors utilized in DLP printers are also reasonably priced. A projector and a Z-directional motor are the two primary functional parts of this printing method. The degree of cross-linking in this printing method is an important parameter, similar to SLA, that influences the structural design of adjustable changes, resulting in different printed item mechanical characteristics, swelling ratios, and interior stresses.[33]

7.3. Projection micro-stereo lithography (PmSL)

At micro-scale DLP, optical lens systems, often referred to as projection micro-stereolithography (PmSL), are capable of achieving high resolution.[29] PmSL is a method of microfabrication that modifies 3D printing technology. With a burst of UV light, it permits the quick photo-polymerization of an entire layer with small-scale fixation. The ability of the mask to adjust light intensity at the individual pixel level allows for the construction of a structure with the desired spatial distribution of material attributes. PmSL may be used to print a variety of substances, including polymers, biomaterials, responsive hydrogels, and shape memory polymers.[34]

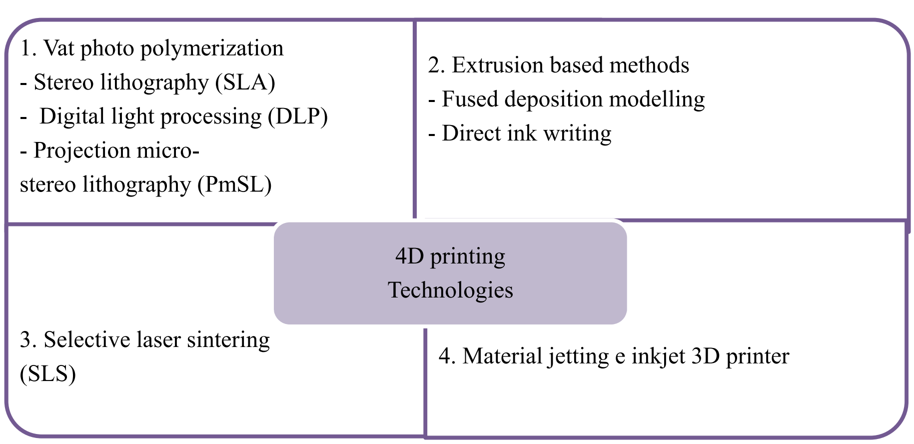

Fig. 3. 4D printing technology.

8. Extrusion based methods

Layer by layer, items are constructed by extruding materials via a nozzle and depositing them onto the printing bed. Fused Filament Fabrication (FFF)/Fused Deposition Modeling (FDM) and Direct Ink Writing (DIW) are the two most often used extrusion-based 3D printing techniques. The versatility of extrusion printing techniques is one of its most notable advantages. The resolution of both FDM and DIW is constrained by the nozzle diameter, which typically spans 100–200 mm.[32] Another drawback of extrusion-based printing techniques is their poor pace, which can be improved by employing more nozzles.

8.1. Fused deposition modelling

Within the field of extrusion-based 3D printing, fused filament fabrication, or FFF, is a widely used and researched printing technology. method has several uses in both industrial and laboratory settings since it prints at a high speed.[35,29] It loads the substance into a heating nozzle as a solid string.[36,37] Most FDM printers use a screw or piston to facilitate an extrusion process that is mechanical in nature. In addition to high temperatures, magnetic, electric, and light fields may also be used to produce a controlled and organized deposition of plastic filaments.[29] FDM, for example, can print a range of technical thermoplastics, however printing numerous materials is challenging because of their disparate printing temperatures, thermoplastics can be subpar.[38]

8.2. Direct ink writing

Direct Ink Writing (DIW), another well-liked 3D printing based on extrusion method, uses a computer to operate the print head. DIW uses the pressure to extrude Shear-thinning liquids should be extruded line by line through needles, in order to print complicated geometry-based shapes.[39] It works by melting a viscous liquid "ink" that may be post--cured.[36] This allows it to be used for printing different thermosetting polymers, and if polymer and resin are in harmony,[18] it can also be used for multi-material printing. Pneumatic,[12] mechanical,[40] and solenoid-based extrusion systems are the three different types of DIW extruders. Additionally, the DIW method provides the best interface bonding between ink filaments and permits substantial modification of mechanical characteristics upon curing, making it suitable for a range of high-viscosity resins.[22]

9. Selective laser sintering (SLS)

Support materials are not necessary for this process to manufacture the components.[6] High processing speed and manufacturing volume are further features of this technology.[41] Although a variety of materials may be used to accomplish SLS printing,[42] suitable materials for 4D printing are absent.[43] This method also comes with a lot of expenses,[44] poor health and dimensional accuracy[45] and hazards.[41] Applications for SLS that benefit include drug delivery,[46] medicinal devices,[47] magnetism-responsive grippers,[48] and aerospace.

10. Material jetting inkjet 3D printer

Using several print heads to spray various photo-curable liquid resins concurrently on the printing bed, inkjet 3D printing is one technique for polymer printing. This produces a layer that is cured with UV light (PolyJet). This allows for the reasonably high resolution fabrication of pieces composed of several materials.[33] For single-material printing, this printer's in-plane resolution usually varies between 30 and 40 mm. But when multimaterials are printed, this resolution drastically drops to 200–400 mm.[49] Inkjet technology may also be utilized for printing biocompatible materials, including as sleep apnea appliances, study model replicas, mouth guards, veneer try-ins, orthodontic bracket guides, and surgical guides for implant insertion.[50]

11. Applications of 3D printing

The data below emphasizes the most current advancements, successes related to 3D printing inside the domain of pharmaceutical and biomedical research as derived through published publications. The novel approaches in the for individualized therapy are particularly highlighted, The impressive success of additive manufacturing techniques in the biomedical field is also highlighted, encompassing implants, surgical models, bioprinted materials, and biorobotic Table 1. A new avenue for creating adaptable therapeutic formulations that take into account a person's physiology, medical history, and genetic makeup is opened up by personalized medications.[18] Various technologies such as microencapsulation also developed and characterized by 3D printing with appropriate medicinal excipients.[51] Many pharmaceuticals were developed utilizing 3D printers and technologies such powder bed extrusion, micro-extrusion printing, electrospinning, and fused deposition modelling.[34] The table that follows lists other applications for 3D printing across a wide variety of industries.[52]

Table 1
Applications of 3D printing.

Particulars	Discussion
Tailored Healthcare for Particular Groups	Personalized pharmaceuticals provide up a new field for creating tailor-made therapeutic formulations that take a person's genetic make-up, medical background, and physiology into account.
Differentiated Oral Medicine Dosage Structures	3DSP employed to research two brand-new paste formulations using 2 API and developing into a multilayered form of tablet.
Lactobacillus rhamnosus microencapsulated for oral administration by 3D printing	Technology used for safe oral delivery of probiotics to the gastrointestinal tract.
Powder bed tablet printing in 3D: Transitioning from an R&D to a scalable GMP printer	Powder bed 3D printing is used largely in laboratories to create pharmaceutical tablets. To refine the technology for commercial use, the ideas developed in the lab should be moved to good manufacturing practice (GMP) environments and confirmed.
Chewable tablets for children customized by 3D micro-extrusion printing	Chewable pediatric ibuprofen (IBU) tablets are made using a micro-extrusion printing technique, that showed powder mixtures be processed in a way is promising for the creation of customized dosage forms.
3D printing of medications to treat illnesses	study built shows how 3D used to create formulations for a variety of dosage forms, including slow releasing, buccal delivery, and localized distribution.
Targeted formulations using a multiscale strategy involving combination therapy, nanotechnology, electrospinning, and 3D printing	Collagen-based materials in particular have been recognized as promising biogenic bioinks with excellent cell-activating and biocompatible qualities for the regeneration of various tissues.
Construction of a 3D Printer	3D printing also known as desktop fabrication. This is trial method that builds structure from three-dimensional model. 3D printing is a constantly evolving and economical technology.
Creation and building of a 3D printer using fused deposition modelling	3D printer that will improve the quality of the parts produced while still being cost effective. This level of quality can be obtained by reducing the layer thickness.
Solid lipid pills are 3D printed from emulsion gels.	Numerous medications with low water solubility want more sophisticated formulations that facilitate improved oral absorption continues to provide a challenge to oral formulation development.

12. Applications of 4D printing

The information mentioned below concentrates on the most current advances and triumphs of 4D printing in pharmaceutical and biological research, as derived from published articles Table 2. Innovative methods used in the development of hydrogels for customized treatment, transdermal drug administration, and biological applications through 4D printing technology.[8] 4D printing tailors various polymers through engineering tissues, biodegradable and compatible polymers and elastomers engineered.[53] Systems like hydrogels and polymers like poly vinyl alcohol (PVA) that are temperature-sensitive and stimuli-responsive[51] were created using four-dimensional technology. The table that follows lists a few innovative uses of 4D printing in the pharmaceutical and other industries.[30,54]

13. Role of 3D printing in pharmaceuticals

Clinical pharmaceutical practice might be completely transformed by 3D printing. It has the capacity to replace traditional mass-production methods for drug manufacturing with on-demand, small-batch production of extremely dose forms that are adaptable and personalized.[55] Patients, pharmacists, and the pharmaceutical business all gain from this technology's special benefits, which include safer and more effective treatment methods.[56] In addition to being crucial in facilitating the integration of this technology, healthcare professionals—such as pharmacists, physicians, and nurses—will also be crucial in providing advice to academic institutions, the pharmaceutical industry, and biotech businesses on how to revolutionize the field through the use of 3D printing Table 3.

Table 2
Applications of 4D printing.

Particulars	Discussion
Tissue-engineered scaffold polymers that are biocompatible for use in 3D printing and 4D printing	An interconnected three-dimensional (3D) network called the extracellular matrix (ECM) gives the components of cells the necessary physical scaffolding.
4D printing: From emergence to innovation over 3D printing	4D printing can now create dynamic objects, it is essentially an advancement above 3D printing technology
Biodegradable elastomers printed in four dimensions with customizable thermal response at room temperature	The combination of new shape-memory photopolymers and digital light processing (DLP) 3D printing makes the creation of intelligent, high-resolution, 4D-printed medical devices with customizable features.
A review of new developments in hydrogel 4D printing in the biomedical area	In addition to metals, hydrogel-forming polymers such biopolymers, synthetic polymers, and nanocomposites have been widely studied.
Algal-based 3D printing as a means of achieving 4D bioprinting	Sustainable supply of different materials appropriate for 3D printing is algae. The rapidly expanding 3D printing market is pushing for innovative green materials inks with durable mechanical qualities as a step toward sustainability.
Utilizing AI and 4D printing in cardiovascular devices	4D printing and AI together function and affect the effectiveness of biomedical equipment, also emphasizes the shift in the management of infectious diseases from symptom-focused, reactive device-based therapy with a special emphasis on cardiovascular diseases (CVD)
Making use of chitosan and its byproducts in 3D/4D (bio) printing for medicinal and tissue engineering applications	Bioinks that have outstanding printability and the capacity to stimulate cell division and activity. Printing inks made from chitosan and its derivatives have proven useful in this situation.
A recent development in 3D and 4D printing technologies is the use of poly(vinyl alcohol): methods and uses	Poly(vinyl alcohol) (PVA) is a smart and stimuli-responsive polymer. PVA is becoming more interested in 3D/4D printing technologies because to a number of factors, including appropriate flowability, stimuli-responsivity, biocompatibility, affordability.
Temperature-sensitive double-layer hydrogel produced using 4D printing that exhibits rapid shape distortion	4D printing to create a bilayer structural hydrogel using a poly(NIPAM-co-DMAPMA)/clay composite hydrogel.
Using Multifunctional Polymeric Materials for 4D Printing	Using 4D printing to construct precisely specified, personalized 3D structures with the ability to reconfigure themselves in response to certain environmental cues is undoubtedly one of the current difficulties as well as an intriguing possibility.

14. Role of 4D printing in pharmaceuticals

With the use of 4D printing technology, structures that may change in form, attribute, and functioning over time can be created that are neither static nor fixed.[56] Brilliant properties of 4D printed products include multitasking, self-assembly, and self-repair capabilities. Furthermore, the technique became more sensible due to printer independence and time dependency Table 4.[53]

15. Patents on 3D and 4D printing

With its significant advancements, 3D printing might soon be indispensable in many different fields and it also produces spectacular outcomes that are patented for the concept of its development and

Table 3
Role of 3D printing in pharmaceuticals.

Role	Particulars
Personalization of Drug Dose	By adjusting the dosage form's digital design and physical size to the patient's specifications, customised manufacturing could be done with 3D printing. Additive manufacturing offers a more exact way to manufacture a wider range of dosages while tackling the issues of inaccurate dosage and dose fluctuation resulting from tablet cutting.
Polypharmacy	By presenting the idea of polypills—a single tablet containing many medications, personalized for a unique patient based on the requirement for therapy—3D printing offers a potential answer to these issues. A 3D-printed polypill containing three or more medications in discrete compartments with regulated release rates and potential advantages is included in the combination of numerous pharmaceuticals in polypills.
Regulation of Drug Release	3D printing can be used to manufacture dosage forms with variable release profiles, such as immediate, sustained, or pulsatile drug release, by changing the formulation's shape, infill, or selected polymers. Personalized suppositories are one example of a dosage form for which the release profile may be customized using 3D printing, in addition to oral dose forms.
Drug-Loaded Medical Devices	The use of 3D printing for drug-eluting implants in implantable drug delivery systems combines the benefits of longer-term, focused local medication therapy at the exact site of the disease with a manufacturing process that makes it simple to alter the implant's shape to suit each patient's unique requirements. Until recently, studies on this subject have concentrated on a range of aspects, such as 3D printing implants with unique shapes, mechanical characteristics, and release profiles utilizing different materials or printing processes.
Bioprinting	The modeling of implantable tissue benefit of 3D printing. Printed synthetic skin in three dimensions for use as a skin substitute in burn sufferers is one example. Prosthetic, chemical, and pharmaceutical product testing can also be done using it.
Customizing synthetic organs	Reducing the number of patients on the waiting list for transplants might be possible with the use of 3D printing. In the future, the pharmaceutical industry may also utilize bioprinted organs instead of animal models to assess the toxicity of novel medications.

Table 4
Role of 4D printing in pharmaceuticals.

Role	Particulars
cardiovascular stent design	Phase change material was used to create 4D printed stents with almost no structural limitations. The printed stent may initially remain flat or maintain its temporary form with smaller breadth. Certain stimuli, such as heat, are applied after the stent is transplanted into the vessel, causing it to expand into its original form and widen.
Liquid crystal elastomers	LCE extrusion/printing is used for following UV curing, this conformation technique creates shear forces that align the LCE chains and provide the polymeric network direction. For the majority of the intended applications, extrusion and TNI temperatures are frequently extremely high.
Drug delivery	To improve the tissue retentiveness of drug-delivery devices, 4D technology is also used. the practicality of printing a retentive device using 4D technology for intrusive medication administration. The apparatus relies on a form memory created by water in response of polyvinyl alcohol (PVA) and is intended to release medications into the bladder over a prolonged period of time. An FDM-based printer was used to build the gadget, and its shape-memory characteristics were noted. They discovered that the bladder could hold onto the 4D printed device and that it demonstrated good form fixity and shape retrieval. The findings imply that PVA-based retentive devices are practical for intravesical medication administration and might be a viable treatment option for bladder disorders.
Cyclodextrin formation	Cyclodextrin(CD's) and additive manufacturing make the ideal technology–material combination. The best technical platform for fully using CDs' capacity to create inclusion complexes and optimize the environment for the development of host–guest pairs is 3D printing. Numerous opportunities in 3D and 4D printing are made possible by developments in our understanding of the thermodynamic and kinetic regulation of the synthesis of drug/biomarker-CD inclusion complexes and poly(pseudo)rotaxanes using peptides and polymers is regulated both thermodynamically and kinetically.
Hydrogel formation	The high stimulus sensitivity of hydrogels makes them excellent candidates for 4D drug delivery techniques. They may also aid in the prolonged release of pharmaceuticals. A range of techniques and bio-ink formulations have been used to show the 4D printing of hydrogels in various kinds of study.
Shape memory hydrogels (SMHs)	In response to an outside input, 4D bio-constructs may be able to self-fold or unfold. These kinds of smart materials, which can react to liquid stimuli like water, have the capacity to produe a big impact on the area of 3D bio-printing of tissues. They can be used in situations where there is fluid interaction because of this feature. They have unique qualities including memory effect, self-healing, and programmable sol–gel change.
Medical devices	Using 4D printed layers that can change shape using a mathematical model to create a T-shaped vascular bifurcation. By carefully modifying parameters, it is possible to create tubular constructions with varying diameters with effectiveness. Immersion in water causes the 4D printed films to self-transform into a T-junction with a diameter in the millimeter range. In a simulated aqueous medium, little leakage and a maximum flow velocity of 0.11 m/s are demonstrated with perfusion of the tubular T-junction imitating blood flow. Furthermore, the T-junction's inner surface, containing human umbilical vein endothelial cells as seed, shows remarkable growth characteristics and elevated cell survival.

implementation Table 5.

16. Challenges in 3D and 4D printing

Although 3D printing has a lot of potential for customized medicine, there are a number numerous important issues Something has to be fixed before using technology be widely adopted. One of the most common issues is ensuring the quality of the products that are 3D printed. Innovative non-destructive techniques and process analytical technologies (PAT) are essential for confirming the medication's safety and quality without tampering with the sample. When customized medications made with 3D printing are distributed in non-cgmp facilities, quality control becomes a problem. These concerns ensure that the drug product is physically intact, that the correct amount of drug is printed, that the correct quantity of tablets printed. —especially If the medication product is printed at the patient's personal home —and other factors, among others. Due to the lack of a structured process in place to ensure certain critical quality criteria are met, as occurs in cgmp bulk manufacturing, these challenges assume further significance. Furthermore, studies are needed to find out how presently used excipients and medications behave under the pressures and circumstances imposed by 3D printing technology, such as the appropriate temperature ranges for processing thermolabile materials. For this reason, techniques like thermogravimetric analysis (TGA) that evaluate the materials' heat stability must be a crucial component of the pharmaceutical 3D printing assessment process. As briefly stated the regulatory bodies listed below in the section on regulatory difficulties are creating a structure for advice in these domains to assist with using a few of results and solutions.

Table 5
Patents on 3D and 4D printing.

Patent No	Country	Name of Patent	Description
CN105687153A	China	Method for preparing tablets for 3D printing by spraying medication into a matrix	The invention outlines a process for spraying drugs into a matrix material to 3D print pharmaceutical tablets.
CN105534713A	China	Prescription-applied drug 3D printing system and method	The 3D printing system for prescription pharmaceuticals combines hardware and software development for 3D printing with materials (such as chemical and biological drugs), drug preparation sterilizing, and fast detection., and packaging into a whole
KR20200006106A	South Korea	System and method for producing pharmaceutical objects through 3D printing	The system for 3D printing pharmaceutical items like tablets, granules, and capsules is the subject of the current invention.
US20220339857A1	United States	3D printing device and method	Research focuses on the advancement of printing technology and methods.
EP3505163B1	Europe	Solid dosage form production	The invention of solid dosage forms by 3D printing is covered in the patent.
EP4065083B1	Europe	Composition for the 3D printing of semisolid drugs	Printing produces semisolid formation of the hydrogel type.
WO2017183893A2	–	4D printing assembly structure	In one case, research is given on a 4D printing assembly structure whose shape changes over time.

17. Future scope of 3D and 4D printing

The background of 3D printing drugs has previously been covered, with a focus on the advantages and disadvantages of each possible site. There are several locations where 3D printers might be put, including community pharmacies, hospitals, pharmaceutical businesses, and patient homes. Nowadays, the benefits and drawbacks of any potential configuration are the main topics of discussion when it comes to potential drug production settings.[27] Recently, there has been increased awareness of the potential applications of 4D printing outside of the biomedical domain, such as in manufacturing, robotics, and aerospace. This method appears to have countless possibilities in the future, especially as efforts to speed up printing, reduce structural degradation, and discover new, high-performing smart materials continue. In the case that production costs are reduced via additional advancements, 4D printed objects may ultimately be used in homes.[57] Furthermore, the creation of smart textiles, such as orthopedic casts, appears to be a promising use for 4D printing. Homes may utilize 4D printed products if further developments are made to reduce production costs.[57]

18. Limitations of 3D and 4D printing

The small number of smart materials that are acceptable for printing—especially those that are suitable for biomedical applications because they are biocompatible—is one of the primary disadvantages of this technology is one of the main drawbacks of this technology.[58] As previously mentioned, liquid photopolymerisable resins, which may solidify when exposed to UV light, are necessary for light-curable printing processes, but low glass transition temperature SMPs are challenging to extrude using powder-solidification procedures. Research and Cost Restraints Commercial FDM printers are currently available for as little as $150 USD, demonstrating the dramatic decline in cost of 3D printing technology in recent years.[59] Since 4D printing is a relatively new and developing field of technology, significant research expenditure is necessary before 4D printed buildings can be implemented in the market, even if advancements have lowered the cost of AM printers.[55] It has been demonstrated that continuous actuation between configurations degrades printed structures; hence, further research and development is needed to increase these structures' resilience and lifespan.[58]

19. Conclusion

The progress of 3D and 4D printing technologies in the pharmaceutical industry was emphasized in the revised review. When 3D and 4D technologies are utilized, the creation of various dosage forms for pharmaceuticals only requires a few time-consuming, multi-step procedures. More promising uses for 3D and 4D printing are found in the pharmaceutical and biological sciences sectors. The revolutionary potential of 3D and 4D printing in medicine delivery and chronic illness treatment might result in better patient outcomes and life quality. Notably, though, a lot of problems still need to be investigated and resolved in the area of 3D printing for medical delivery.

Disclosure of interest

The authors affirm that they have no competing interests.

CRediT authorship contribution statement

Afiya Baig: Writing – review & editing, Conceptualization. **Rohan Barse:** Writing – original draft. **Asawari Paryekar:** Conceptualization. **Vijay Jagtap:** Dr.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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