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Pharma 4.0 Ai-Integrated 3d Printing as The Future of Personalised Drug Development

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Abstract
Three-dimensional (3D) printing is a disruptive technology for pharmaceutical sciences and provides a platform on which highly complex, individualized drug delivery systems can be designed and manufactured. 3D printing allows control over dosage, geometry, and drug release properties, meeting patient-specific needs such as those of the paediatric, geriatric, and polypharmacy populations. Following the first approval of a 3D-printed product by the FDA (Spritam®), 3D printing began to be utilized to produce modified-release tablets, multi-drug dosage forms, and chewable dosage forms. Efforts to capitalize on the incorporation of Artificial Intelligence (AI) in the field have permitted the development and use of predictive modelling and real-time quality monitoring. Even with these benefits of 3D printing—rapid prototyping and a wide range of formulation capabilities—3D printing faces challenges of industrial adaptability, limits to currently available excipients, and the complexity of regulatory pathways. Future work will focus on the combination of 3D printing with AI, nanotechnology, and bioprinting to completely revolutionize the processes and practices of pharmaceutical manufacturing and to support future innovations in precision medicine.

Keywords: 3d Printing, Pharmaceutical Manufacturing, Artificial Intelligence, Personalized Medicine, Drug Delivery

1. Introduction

In accordance with the US National Human Genome Research Institute, precision medicine is an innovative approach that uses data about a person's genetic, environmental, and lifestyle characteristics to inform decisions about their medical care [1]. Traditional medicine operates under the premise that one size fits all. Personalized medicine's motto is "The right dose of the right drug for the right indication for the right patient at the right time," which emphasizes that no two people are alike [2]. More specifically, the purpose of the incorporation of 3D printing technology into drug delivery technology (pharmaceutical design) is the development of patient-centred dose forms as a function of structural design [3]. The ability to create products by 3D printing represents an important shift in the development of drugs and medicines, moving from conventional manufacturing to additive manufacturing [4]. Standard methods, including encapsulation and compression, can be expensive and struggle with the development of highly complex drugs. To overcome these limitations, a rapid and innovative method of additive products from digital patterns are utilizing additive manufacturing technology [5].

Three-dimensional printing, also known as additive manufacturing, is a process of creating a solid model by layering material on top of itself. The process takes advantage of computer-assisted design (CAD) software that communicates the necessary signals to a 3D printer. The printer converts the digital model into two-dimensional (2D) slices, which are solid layers that make up an object [6]. The 3D printing process has two major steps: (1) data is communicated from the software to the 3D printer; and (2) the print head layers material multiple times to build the object one layer at a time [7]. The US Food and Drug Administration (FDA) granted approval for Spritam on August 3, 2015 [8]. Pharmacological 4D printing refers to drug delivery systems that, through 3D printing, are created to transform shape, structure, or attributes in reaction to an external environment over time [9].

AI is known as the scientific discipline that pursues research, projects, and applications that leverage knowledge or computer-based resources as some form of assistance in decision-making, medical tasks ultimately supporting healthcare deliverables' ability to improve healthcare performance [10]. Machine learning (ML) is an influential domain of AI that serves as a key partner for drug products in three-dimensional printing (3DP) [11].

2. History

The following are significant developments in 3D printing from the early 1960s to the early 2000s, both in the medical field and in industry:

- In the 1960s, the University of Battelle Memorial Institute in Ohio investigated the use of photopolymers to produce 3D-printed items.
- The Dynell Electronics Corporation created solid photography. One of the primary 3D printing stage concepts of the 1970s was the technology's goal of cutting cross-sections according to a computer model.
- Hideo Kodoma of the Nagoya Municipal Industrial Research Institution in Japan released the guidelines for automating 3D models with photosensitive rays and resin. In 1980–1981, these were the initial methods of stereolithography.
- Stereolithography (SLA) was created in 1984. The initial patents for stereolithography were held by Alain Le Méhauté, Olivier de Witte, and Jean Claude André in France and Charles 'Chuck' Hull in the USA.
- Dr. Hideo Kodoma secured a patent for the SLA invention in 1986.
- The world's first commercial SLA printer was manufactured by 3D Systems in 1988.
- In 1989, Scott and Lisa Camp established "Stratasys" and submitted a patent for rapid prototyping, which laid the foundation for the initial principles of fused deposition modelling (FDM).
- Hans Langer founded the company electro-optical system (EOS) in late 1989, enabling the production of 3D parts directly from computer-aided design models
- Carl Deckard developed the selective laser sintering process (SLS), which involved using a laser beam to selectively solidify powder in order to fuse powdered material one layer at a time.
- By the early 1990s, the 3D-printing industry had split into two streams: one focusing on engineering complicated parts, and the other emphasizing concept generation and functional prototyping.
- By the late 1990s, only three companies existed in the 3D industry; Stratasys, 3D Systems, and EOS.
- The first production SLS printers had been made in 1992.
- In 2000 Deckard established "Sinterstation" and brought SLS into the marketplace.

- By the early 2000s, the technique of 3D printing started gaining attention and importance in the medical field. For example, oral fast-disintegration tablets from Aprecia Pharmaceuticals in Blue Ash, Ohio, USA were made using SLA printing, including Spritam (Levetiracetam) which was FDA approved. Other ME techniques were used to print scaffolds and drug-loaded implants for controlled release.
- Post-2010, applications of bioprinting and drug-loaded implants improved, such as the use of 3D-printing technology in the development of Cinnarizine gastroretentive dosage forms.
- In 2003, Dr. Thomas Boland submitted a patent for a method that was the first patent to discuss printing viable cells.
- In 2004, Gabor Forgacs patented a method for 3D-printing cells using compatible hydrogels (12).

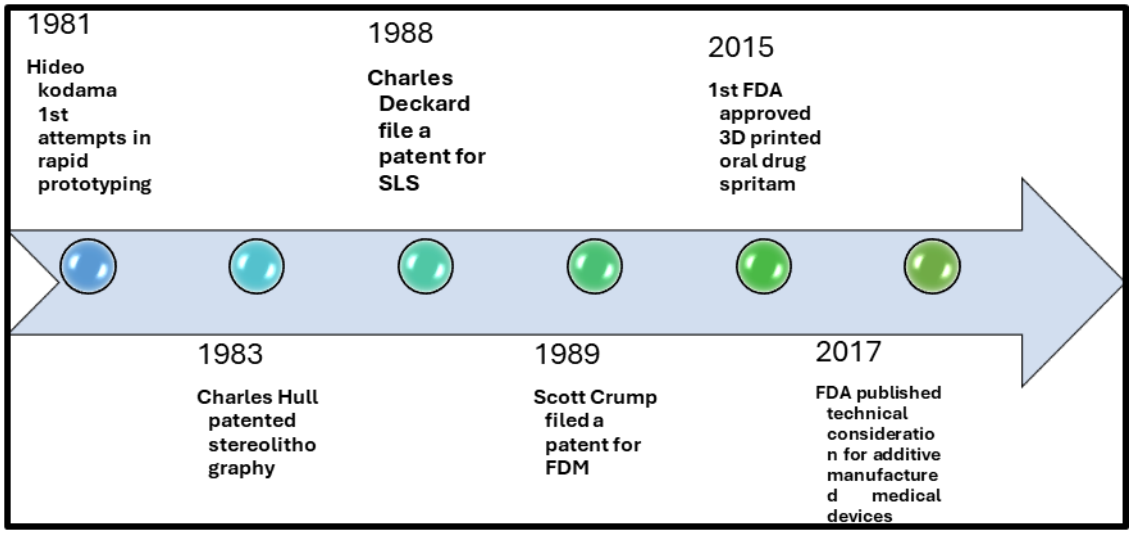

Figure 1:History of 3D Printing

3. Advantages of 3D Printing

1. Personalized Medicine for Special Population

There has long been concern regarding the safety and health of drugs for specific populations, such as children and the elderly. By modifying model parameters like size, shape, or fill rate, three-dimensional printing technology can be utilized to print specific medications. In addition to producing low-dose personalized medicat ions that are appropriate for children, 3D printing technology can also be used to enhance the taste and appearance of medications. Some 3D printed drug companies are working towards the goal of personalized medicine, such as FabRx in the UK, which prepares personalized drugs for children with maple diabetes.

2. Precise Control of Drug Release

Tablets make up over 70% of all dosage form production and are the most popular solid oral medication form. Controlled-release formulations, as opposed to traditional tablets, provide precise control of drug delivery, preventing unwanted effects and enhancing efficacy. For example, Triastek's 3D- printed product, T19, which received IND approval from the FDA in January 2021, is a controlled -release preparation designed for the circadian rhythm of rheumatoid arthritis.

3. Rapid Integration of Production

Ordinary pharmaceutical companies that produce drugs on a large scale in order to meet the demand for traditional drugs around the world typically have very high production capacities and large, comparatively single-type equipment that lacks the production flexibility needed to quickly finish cleaning and switch up the variety of drugs

produced. Contrarily, rapid manufacture can be combined with small equipment, fewer production stages, automated and digital production processes, and the ability to easily switch up the range of medications produced thanks to three-dimensional printing technology [13].

4. Complex Medication Formulations

The creation of complex drug formulations often poses challenges when utilizing conventional manufacturing methods. However, with the advent of 3D printing technology, multiple active pharmaceutical ingredients (APIs) can be accurately placed within a single dosage form, thereby facilitating the innovation of new medicinal combinations.

5. Greater Control Over Drug Particle Size, Distribution, And Formulation

Drug solubility and bioavailability may be enhanced by precise control over drug particle size, distribution, and formulation made possible by 3D printing [14].

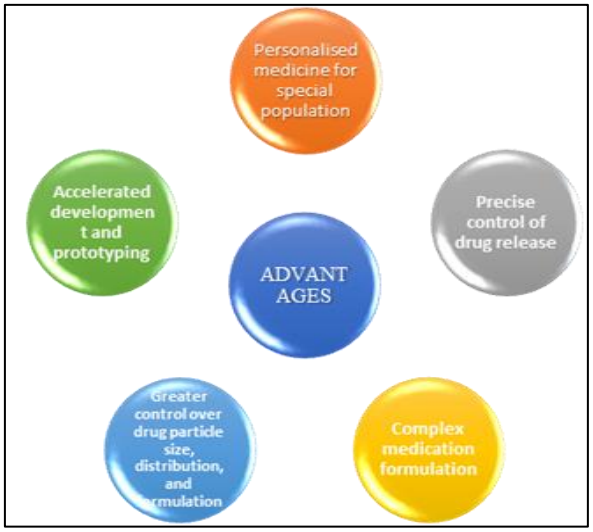

Figure 2: Advantages Of 3d Printing

4. Disadvantages of 3D Printing

a) **Limited Material Choices:** Nevertheless, some medical-grade materials are unsuitable for 3D printing or cannot be used. It is limiting the choices for specific applications, which affects the devices' intended performance.

b) **Design Limitations:** Some connected aspects, such as structural reliability, material holdings, and printing capabilities, can influence the complexity and functionality of the final product while also restricting the design constraints for 3D printing. Designing complicated structures with precise features may necessitate additional support structures or postprocessing to produce desired models.

c) **Regulatory Challenges:** Making the new model and devices remains a significant problem, complex, and time-consuming in the form of obtaining approval from the Food and Drug Administration (FDA) in the United States. Before receiving regulatory permission for the use of 3D-printed medical devices, a number of stringent testing and validation steps must be completed.

d) **Quality Control and Validation:** The quality and consistency of 3D-printed medical devices and models may be challenging due to the specific manufacturing process for required devices

e) **Cost:** Because of high-quality control and specialized designs, the cost is also a major challenge in the 3D printing models [15].

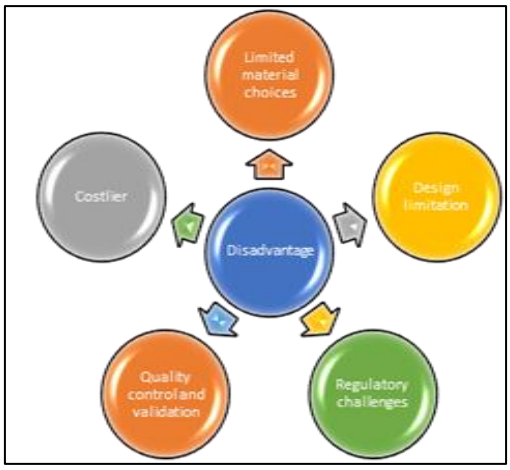

Figure 3: Disadvantages Of 3D Printing

5. Application of 3D Printing in Tablet Manufacturing

- **Manufacturing of Bespoke Combination Drug Products (Carvedilol–Simvastatin) Using FDM 3D Printing**

The dual-loaded tablets, containing spatially segregated CAR-containing and SIM-carrying layers, were 3D-printed by FDM in hollow heart-shaped dosage forms. The treatment of chronic diseases, such as cardiovascular diseases, often involves several medicines and varied doses to be changed according to the disease's course and severity, lifestyle changes, co-administration of other medication, or when a change of medicine(s) is needed. Carvedilol (CAR) is a poorly water-soluble active pharmaceutical ingredient (API) classified as a biopharmaceutics classification system (BCS) class II medication, with a water solubility of 11 lg/mL. Simvastatin (SIM) is a statin medicine that is used to treat hypercholesterolemia by lowering the liver's production of cholesterol. SIM is likewise a BCS class II medication with a low water solubility of 30 lg/mL. If the patient's symptoms persist, a beta-blocker such as CAR is indicated that the combination of SIM and CAR reduced cardiovascular death after acute myocardial infarction. The design was inspired by a single API diazepam-containing dosage form ValiumVR, which is a tablet with a hollow heart pattern, manufactured using a compaction method [16].

- **Hot-Melt Extrusion Assisted 3D-Printed Metoprolol Succinate Extended-Release Tablets**

The creation of an extended-release metoprolol succinate tablet with a 3D printable filament made with Soluplus®, citric acid as a plasticizer, and hydroxypropyl methylcellulose acetate succinate (HPMCAS) as a mixed polymeric carrier. A blend of poly (ethylene glycol) (13%), poly (vinyl acetate) (30%), and poly (vinyl caprolactam) (57%), Soluplus® is a water-soluble graft copolymer. MS is made up of substituted phenylpropanolamine, which has the necessary structural properties to selectively block β-1 adrenergic receptors. Metoprolol was approved by the FDA for use in medicine in 1978. Extrudable filaments were made easier by a well-balanced polymer-plasticizer combination, and these were then employed in fused deposition modeling (FDM) to print tablets in three dimensions (3DP) [17].

- **3D-Printed Core–Shell Tablets for Oral Delivery Of AT-MSC Secretome In IBD Therapy**

The primary goal of inflammatory bowel disease treatment is symptom relief, and for more severe cases, corticosteroids, biological therapies, or potent immune system suppressors are typically used. Mesenchymal stromal cells (MSCs) are regarded as a well-known therapeutic strategy for the treatment of IBD. Due to the drawbacks and dangers associated with MSC injection in vivo (such as tumorigenicity,

thrombosis, rejection concerns, etc.), there has been a paradigm shift toward the use of "cell-free therapies." These 3D printing techniques go beyond precision medicine and are in line with the goal of safely preserving and efficiently delivering MSCs-S. Therefore, in order to develop formulations appropriate for oral distribution, we integrated 3D printing techniques with the extremely promising therapy of adipose-tissue-derived MSCs-S (AT-S) in this study. We used the Semisolid Extrusion 3D printing (SSE) method, which is especially useful because it doesn't require high heating temperatures, protecting the growth hormones and secretome cytokines from denaturation [18].

- **3D-Printed Chewable Gummy Tablets of Amoxicillin for Pediatric Use**

Amoxicillin (AMOX), a common antibiotic for children, is often hard to swallow in tablet or capsule form. Semisolid extrusion (SSE) 3D printing, which uses a paste or gel “ink,” was employed to create bear-shaped AMOX gummy tablets. These 3D-printed gummies, made via the Pressure-Assisted Micro syringe (PAM) method, were characterized for their physical, chemical, and functional properties, offering a child-friendly design to improve compliance. [19].

6. Types of 3D Printing

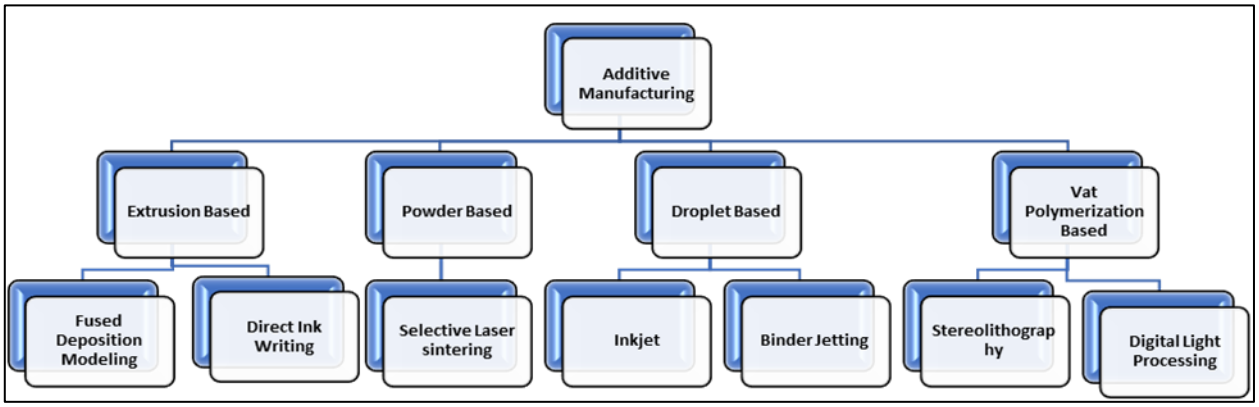

Figure 4: Types Of 3D Printing

- **Fused Deposition Modeling**

Fused deposition modeling (FDM) was invented in 1988 by Scott S. Crump, one of the founders of Stratasys Ltd. In 1989, Crump filed a U.S. patent application for a process that allowed three-dimensional objects to be iteratively constructed using a thermoplastic filament that was extruded through a heated nozzle [20]. FDM manufacturing is built upon the principle of melting raw material and forming a new shape. The material is in the form of filament that is wound on a roll, which is drawn into the FDM machine by a drive wheel and then directed into the nozzle head, whose temperature is controlled. The filament is heated in the nozzle to a semi-liquid state, where the nozzle carefully extrudes and directs the material in ultra-thin layers to create structural elements layer by layer. The filament is the primary material in FDM and typically consists of pure polymer with a low melting temperature [21]. The advantages of FDM include being cost-effective, easy to use, and performing to create dramatic geometries that may be difficult to achieve using traditional manufacturing techniques [22].

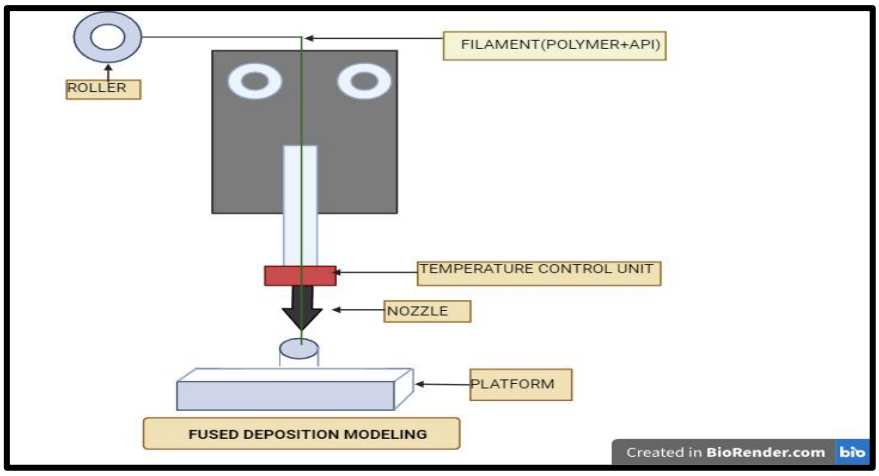

Figure 5 : Fused Deposition Modeling

- **Direct Ink Writing**

DIW (direct-ink-writing) is a printing technique in a layer-by-layer fashion, utilizing an extrusion-based process to deposit a viscoelastic ink through a small nozzle using pressure. The main development work on DIW technology goes back to the 1990s when, in 1994, Hartmann et al. introduced the concept of shape deposition with the use of robotic assistance. Cesarano and Calvert then introduced a free molding technique utilizing a low binder slurry, which was later coined as robocasting. Lewis et al. also contributed to the work on the 3D direct writing technique in 2002 and 2004, incorporating the fabrication of functional materials using DIW technology. At the time, the predominant challenge of DIW technology was to improve the 'rheological' properties of the inks [23].

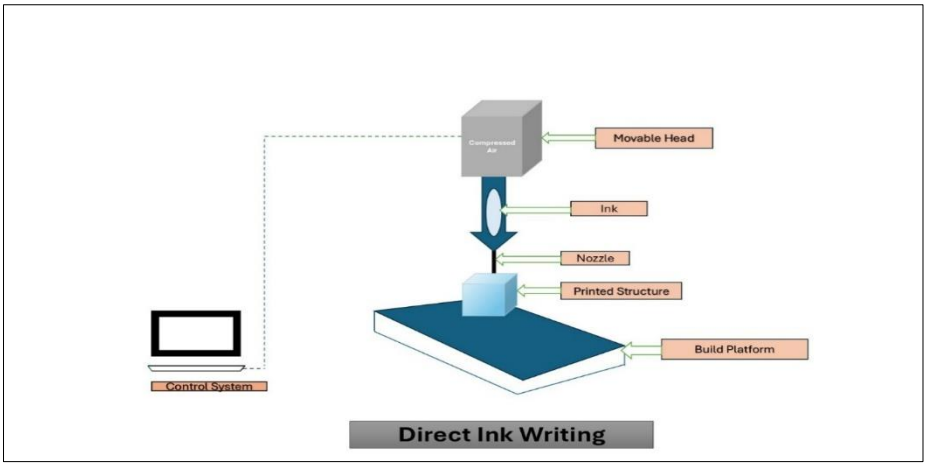

Figure 6 : Direct Ink Writing

- **Selective Laser Sintering**

Selective laser sintering (SLS) was invented and patented by Dr. Carl Deckard along with his academic advisor, Dr. Joe Beaman, at the University of Texas at Austin during the mid-1980s, with funding from DARPA [24]. Selective laser sintering (SLS), a powder bed fusion technique, fuses powder layer by layer using a laser based on a digital design. It is a solvent-free, one-step process that requires no supports and allows feedstock reuse. Various lasers, most commonly CO_2, are used depending on the material's light absorption, with CO_2 lasers preferred for pharmaceutical polymers. [25]. Gueche *et al.* conducted a study on the printing of paracetamol using blends of Kollidon VA64 and polyamide 12 to create fast-disintegrating dosage forms with an SLS printer that is equipped with a CO_2 laser printer [26].

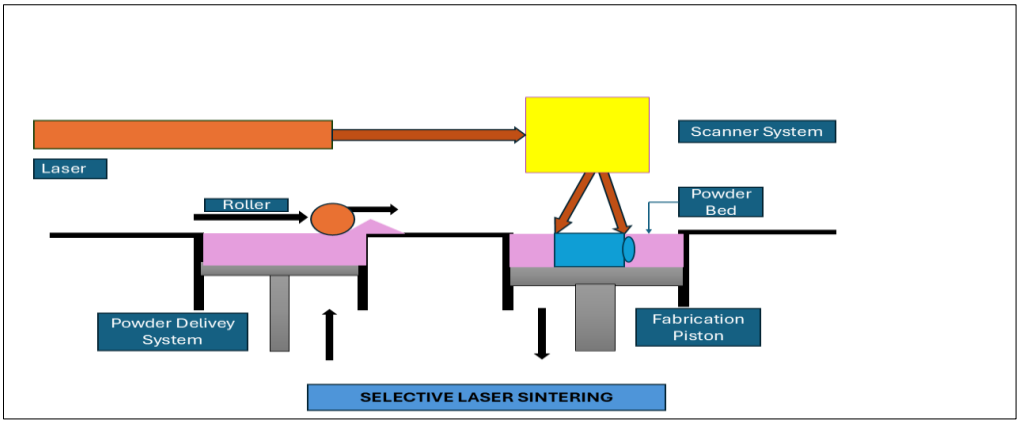

Figure 7: Selective Laser Sintering

- **Inkjet Printing**

Inkjet printing, developed in the 1960s–1970s, has evolved from simple graphic applications to advanced uses in digital fabrication and additive manufacturing. It enables 3D structure formation either by depositing binders onto powder beds or jetting photopolymers, and mainly operates in continuous inkjet (CIJ) and drop-on-demand (DOD) modes [27]. Continuous inkjet printing (CIJ) produces a constant ink stream that breaks into droplets, which are electrically charged and directed onto a substrate, while uncharged droplets are recycled. In contrast, drop-on-demand (DoD) printing ejects droplets only when triggered, using either thermal heating to form vapor bubbles or piezoelectric deformation to expel ink. Beyond drug loading, inkjet printing enables the fabrication of 3D structures such as tablets, offering greater flexibility and personalization than conventional powder-compression methods. [28].

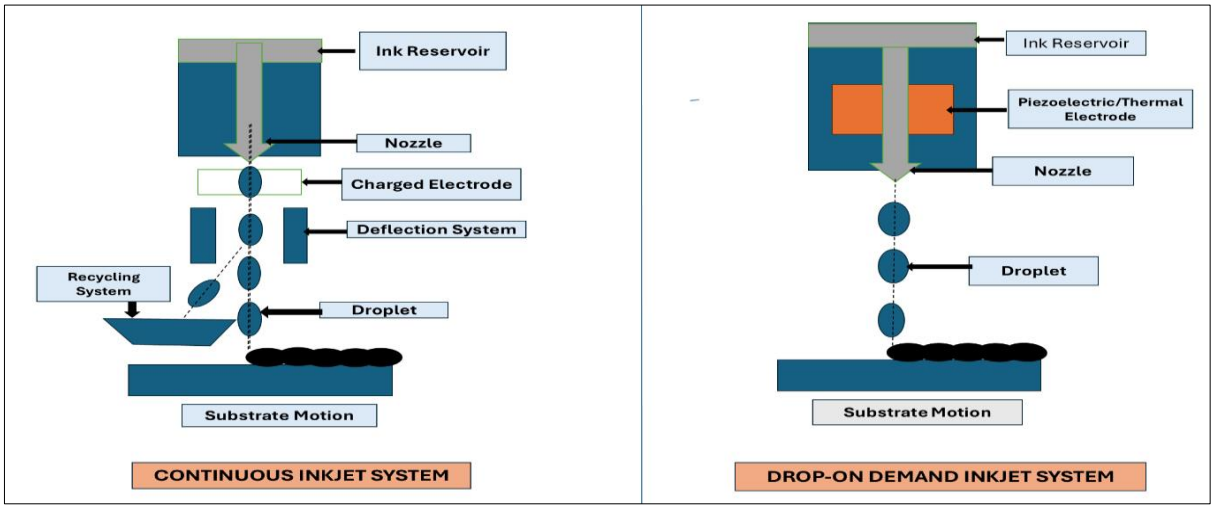

Figure 8 : Inkjet System

- **Binder Jetting**

Binder Jetting was developed at MIT in 1993 and later licensed to Z Corporation, leading to the emergence of companies such as ExOne, Voxeljet, and 3D Systems. As patents have expired, new players including Desktop Metal and HP have entered the binder jetting market. [29]. Binder jet 3D printing creates objects by selectively depositing liquid binder droplets onto a powder bed to bond particles into a 3D structure. The system includes design software, a printing nozzle, powder roller, ink cartridge, powder supply and build platforms, and a powder collection unit. The process occurs in three stages: droplet generation,

binder–powder interaction, and curing with excess powder removal. Due to its precision and flexibility, this technology is promising for personalized medicine and drugs with high toxicity or narrow therapeutic windows. [30]. A self-developed binder jet 3D printer was used to fabricate LEV–PN dispersible tablets. LEV was mixed into the powder bed, while PN was precisely jetted via ink into specific tablet regions for accurate dosing [31].

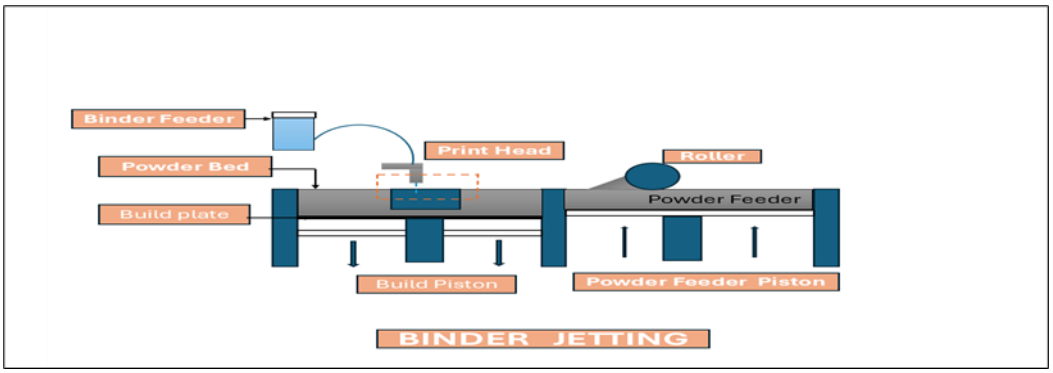

Figure 9: Binder Jetting

- **Stereolithography**

Vat photopolymerization is a 3D printing technique in which liquid photopolymers are selectively solidified by light. It includes stereolithography (SLA), digital light processing (DLP), continuous liquid interface production (CLIP), and two-photon polymerization (TPP). SLA uses a computer-controlled UV laser to cure resin layer by layer, with systems typically classified as top-down or bottom-up. SLA has been widely applied in pharmaceutical and biomedical fields, including the fabrication of tablets, microneedles, scaffolds, dental prosthetics, and medical devices. Several immediate- and modified-release tablets have been produced using SLA, such as ascorbic acid-loaded hydrogels and tablets containing paracetamol and 4-aminosalicylic acid. [32]

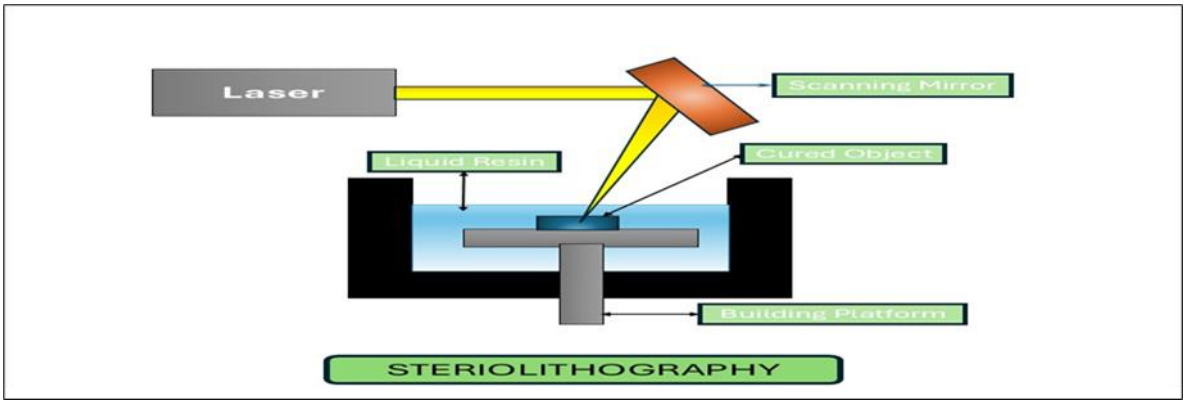

Figure 10 Stereolithography

- **Digital Light Processing**

DLP 3D printing technology originated in 1987 from digital projection technology developed by Texas Instruments. A typical DLP-based 3D printer consists of a light source, a Digital Micromirror Device (DMD), an optical system, and a movable platform. In biomedical applications, the process begins with designing a digital model using computer-aided design (CAD) software. DLP printing works by projecting patterned light onto liquid resin, curing it layer by layer to form the desired structure [33]. Hydrochlorothiazide (HCT) is a thiazide diuretic widely used as a first-line treatment for hypertension and

heart failure. To explore the potential of advanced 3D printing technologies in both laboratory and pharmacy settings, formulations were developed using semisolid extrusion (SSE) combined with UV curing and digital light processing (DLP). These techniques offer high precision, customization, complex geometries, rapid production, material flexibility, and reduced waste. SSE forms 3D structures by pressure-driven extrusion of semi-solids, while DLP uses a digital micromirror to selectively cure liquid photopolymers layer by layer using projected light [34].

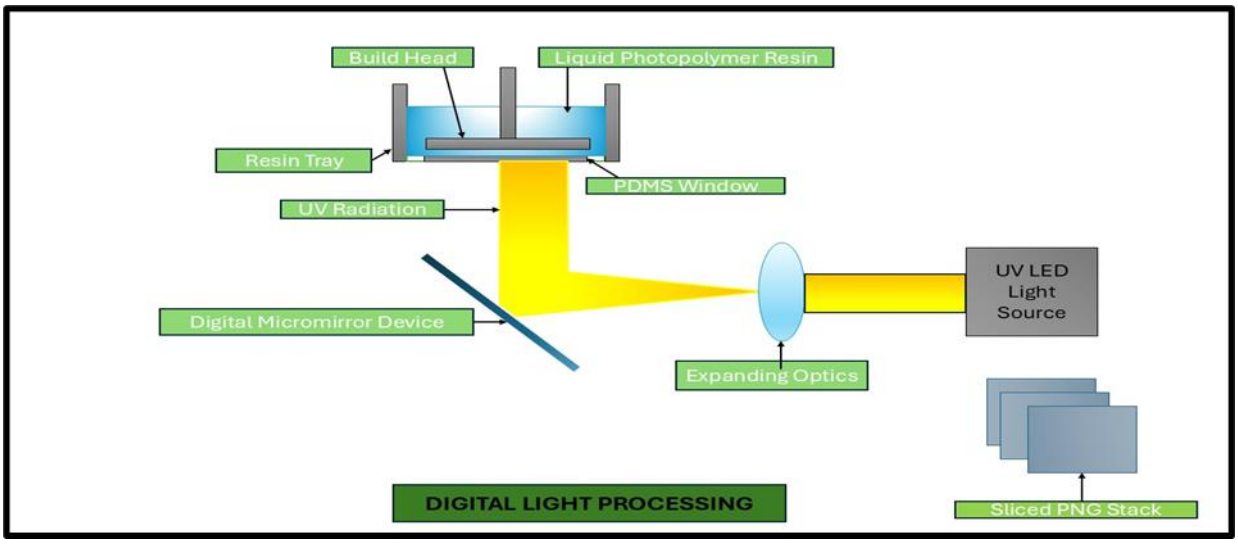

Figure 11: Digital Light Processing

7. 3D Printing Process in Tablet Manufacturing

The 3Dp Process Consists of Three Primary Stages: Pre-Printing, Printing, and Post-Printing [35].

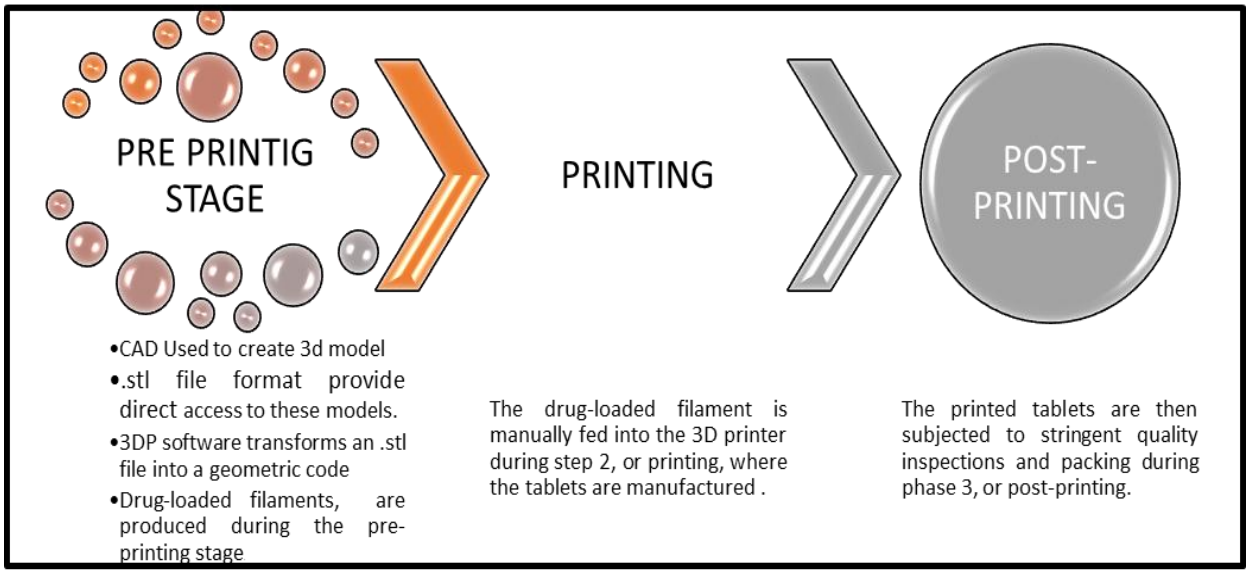

Figure 12: 3D Printing Process in Tablet Manufacturing

8. Materials Used In 3D-Printed Tablets

- **Polymers**

The most adaptable class of biomaterials is polymers, which find extensive applications in the creation of tablets. Although polymers can be created as APIs, they are primarily employed as excipients to enhance

the functionality and delivery of the APIs. The most popular polymers for tablet printing are listed below.

- Cellulose-Based Polymer
- Eudragit
- Polymer Blends/Mixtures [36].
- Soluplus® [37].
- **Binding Agents**

By enhancing the powder mixture's cohesiveness, binding agents improve its hardness and friability. The pharmaceutical business frequently uses three different kinds of binders: sugars, synthetic binders, and natural binders. Gum, acacia, and starch are a few examples of natural binders. Blends of oils, resins, and polymers make up synthetic binders. Among the often-utilized polymers are methyl cellulose, HPMC, and polyvinyl chloride (PVC). Among the sugars are sorbitol, sucrose, and glucose. Binders like polyvinylpyrrolidone K30 and Eudragit L100 are frequently utilized with BJ technology in tablet printing.

- **Fillers**

In formulations where the API is present in insufficient amounts to create a tablet, fillers are added. Binders and fillers are utilized together because fillers often have a weak binding capacity. By creating ink compositions with a variety of polymer (Eudragit EPO) to filler (TCP) ratios to 3D-print tablets using FDM printing, Sadia et al. investigated the nature of tri-calcium phosphate (TCP) as a filler. The authors demonstrated that manufactured structures exhibited poor characteristics and were deformable when Eudragit EPO filaments without TCP were employed in an FDM printer. It was discovered that 20–50% of the filament had the ideal TCP content.

- **Plasticizers**

To enhance the oral tablets' mechanical and thermal characteristics, plasticizers are added to polymer. Plasticization can be accomplished externally by mixing the polymer mixture with a plasticizer (without changing the chemistry of the polymer) or internally by chemically changing the polymer (by directly changing the backbone chemistry or adding/changing pendant chains). Triethyl citrate (TEC), tributyl citrate, and acetyl triethyl citrate are examples of citrate ester-based plasticizers.

- **Disintegrants**

Disintegrants' primary function is to speed up the release of drugs by improving dissolving and disintegration. In pharmaceutical formulations, starch, cellulose, and related derivatives are the most commonly utilized disintegrants. Desai et al. examined the effects of various disintegrants, such as croscarmellose sodium (CCS), crospovidone (CP), sodium starch glycolate (SSG), and microcrystalline cellulose (MCC), on the dissolution and tablet hardness while testing rapidly disintegrating tablets containing APIs with various solubilities, such as ascorbic acid, aspirin, and ibuprofen. 8% SSG, 7% CCS, or 8% CP disintegrant concentrations produced the quickest disintegration times for aspirin and ibuprofen tablets.

- **Lubricants**

When combining dry powders in the ink preparation process prior to printing or extruding them into 3D printable filaments, lubricants are added in tiny amounts. Hydrodynamic, electrohydrodynamic, mixed, and border lubrication are the primary lubrication mechanisms. For tables to be manufactured successfully and robustly using both traditional and additive manufacturing techniques, lubricants are necessary. A good lubricant should not be poisonous, have a low shear strength, and be unaffected by process factors.

- **APIs**

The selection of the medicine, or API, for the 3D-printed tablet typically dictates the appropriate AM technique as well as the additional tablet ingredients, such as excipients and additives. APIs that are not thermally stable within the printing temperature range, for example, should be avoided since filament and melt extrusion-based printing need for high temperatures. APIs must be stable when exposed to light since SLA uses light, typically in the UV spectrum, to cure the viscous tablet formulation. several APIs have been used in oral tablet AM, with paracetamol

and caffeine commonly selected as model drugs due to their availability, low cost, high solubility, and permeability. For instance, incorporating different grades of hypromellose acetate succinate (HPMCAS LG, MG, and HG) into paracetamol-loaded filaments enabled extended drug release. [38].

9. Ai-Integrated Quality Control In 3d-Printed Tablets

Machine Vision for Automated Defect Detection

Machine vision (MV), a subset of artificial intelligence (AI), is a promising technology that can be utilized to offer structural information. In pharmaceutics, artificial intelligence (AI) is a new technology that trains robots to carry out human-like tasks with the ultimate goal of replacing human labor. Python and Blender software were combined to create a simplified pipeline that ensured consistency, replicability, and speed in the generation of virtual images, also known as synthetic data. To automate the process of creating distinct images from the original copies, a Python script was created. A loop function was included in this script to generate 100 "Good" images for every dosage form. Images that had a flawless print were considered "good." "Over-cured," "under-cured," and "cracked" were the three subcategories that made up the "Bad" photos. MV systems can be used for real-time QC monitoring in manufacturing, enabling them to carry out identification and inspection activities. MV is contributing to increased productivity, decreased errors, and improved safety in a variety of applications by automating visual processes and delivering quick and precise outcomes [39].

Computational Intelligence in Drug Release Customization

By enhancing machines' capacities for data processing, pattern recognition, and well-informed decision-making, computational intelligence (CI) imitates human intelligence. Since 3D printing makes it possible to fabricate customized medications with exact dosages, controlled-release profiles, and intricate formulations, the combination of CI and 3D printing enhances this potential even more. Furthermore, 3D printing may be integrated with CI because of its automated and digital characteristics. Predicting material printability, maximizing drug release rates, creating intricate structures, guaranteeing quality control, and enhancing 3D printing manufacturing processes have all benefited from CI. By utilizing patient-specific data, including genetic information, disease development, and metabolic reactions, 3D printing can further enhance medicine formulations when utilized with CI. For instance, Fawzi et al. used CI in conjunction with a 3D-printed wearable insulin pump for patients with type 1 diabetes mellitus [40].

Predictive Maintenance and Process Optimization

With precise medication formulation, efficient manufacturing, and cutting-edge tailored therapy, the nexus of artificial intelligence (AI) and 3D printing is transforming the field of pharmaceutical sciences. AI-based predictive modeling reduces formulation design complexity, optimizes controlled-release dosage forms, and enhances drug-excipient compatibility. Drug formulation, optimization, and production are undergoing a revolution thanks to artificial intelligence, machine learning, and real-time analytics-based predictive modeling, which not only improves accuracy but also speeds up formulation cycles and reduces costs. To enhance print quality, mechanical characteristics, and drug release behavior in pharmaceutics 3D printing, artificial intelligence optimization of print parameters like temperature, speed, and thickness is crucial. The technique offers real-time control, reducing material usage and enhancing print quality. Maintaining 3D printers in optimal operating condition is essential to avoiding output delays. AI-powered predictive maintenance is a preventative strategy for equipment management [41].

X-Ray Microfocus Computed Tomography Technique

The Food and Drug Administration defines process analytical technology, or "PAT," as a regulatory

framework that promotes the creation and application of pharmaceutical development, production, and quality assurance techniques. Accordingly, several methods have been used as PAT for 3D printing, including thermal imaging, spectroscopy, interferometry, and ultrasonic inspection. High-resolution non-destructive 3D (volume) imaging can be used to assess porosity, check for internal defects, and confirm that formulations meet the necessary specifications. Micro-CT, also known as X-ray microfocus computed tomography, is a well-known characterization technique (μCT). μCT detects the attenuation of X-rays through an object around an axis of rotation, just like clinical CT does. The process of imaging involves putting a sample in the direction of an X-ray beam and taking a radiograph, or projection image, of it at several equally spaced angles [42].

10. Future Directions and Perspectives

With a compound annual growth rate of 17.54%, the global 3D printing in healthcare market is expected to grow from its 2021 valuation of USD 1.45 billion to USD 6.21 billion by 2030. The current 3D printing industry is experiencing significant growth due to the growing interest in personalized medicines and the growing body of research supporting 3D printing. The pharmaceutical industry has become more inclined to investigate personalized and individualized treatments, particularly since the U.S. Personalized Medication Initiative was established in 2015. Furthermore, a number of reasons are supporting the market's growth, such as the rising incidence of chronic illnesses, the increased need for affordable pharmaceuticals or drugs, and the developing applications of 3D printing in the healthcare industry [43]. According to a recent study, the development of pharmaceutical products has advanced in personalized medicine, the treatment of uncommon genetic disorders, and the creation of early-phase clinical trials thanks to 3D printing technology. Currently, Triastek and Laxxon Medical are employing 3D printing technology in pharmaceutical. Recent results from the OPERA clinical study have demonstrated that 3D-printed pharmaceutical goods are bioequivalent to generic medicines and meet pharmacopeial requirements. Despite successful initiatives, there is currently no regulatory framework for medicinal items that are 3D printed. Although regulatory bodies' initiatives, including the FDA's ETP program, have established the recognition of 3D-printed technology, there is a dearth of specific advice to promote the wider implementation of this technology in both industrial and proof-of-concept settings. There is still much uncertainty over whether or not 3D-printed pharmaceutical goods should be approved via a particular regulatory procedure [44].

11. Case Study:

3D Printed Efavirenz Tablet Since its identification in 1981, the human immunodeficiency virus (HIV) has been a public health concern. In 2022, approximately 39 million people worldwide were living with HIV, with 1.5 million of those individuals being children aged 0-14 years. For HIV-positive children, pharmacological treatment options include efavirenz (EFZ), a specific nonnucleoside reverse transcriptase inhibitor, with daily doses ranging from 100 to 600 mg, administered once or three times a day, depending on the patient's age and treatment stage. This study demonstrated for the first time the use of SLS 3D printing for the creation of dispersible EFZ printlets meant for enteral administration. Two water-soluble polymers, Parteck® MXP and Kollidon®e VA64, were effectively used to create printlets with 200 mg of medication each, weighing 500 mg and 1000 mg. Regardless of formulation, amorphous conversion of EFZ and the creation of porous printlet structures were made possible by SLS 3D printing. For P500, K500, and K1000, similar disintegration periods (<230s) were observed, but P1000 only partially

disintegrated. Parteck® MXP was discovered to be useful for quickly dissolving formulations for small dose forms; however, more polymers need to be studied in order to broaden the usage of SLS 3DP for enteral route administration [45].

12. Discussion

Three-dimensional (3D) printing has appropriately become a big emphasis in the pharmacy sector since it can do things that traditional manufacturing can't the benefits are deeply human: studies have shown success in designing tablets that are easier for children and older adults to swallow, combining multiple complex prescriptions into a single dose, and precisely controlling the drug's release rate. These concepts directly solve real-world problem with dosage and delivery.

However, the technology remains largely confined to the lab bench, with only a few examples making it to the market. The difficulty lies in translation. Scientists are currently restricted to a limited palette of materials (excipients), and many crucial drugs deteriorate when exposed to the heat or light necessary for printing. This lack of control and material choice contributes directly to the current absence of universally accepted quality standards. Furthermore, complex ethical and legal questions remain unanswered, particularly concerning point-of-care printing if a pill is printed directly at a hospital bedside, who carries the final regulatory responsibility for its safety and precision?

The critical path forward lies in integrating Artificial Intelligence (AI), which acts as the ultimate quality assurance mechanism by precisely perfecting drug formulas, modifying printing conditions, and verifying the quality of the product in real-time. While exciting developments in 4D and multi-material printing promise medications that can dynamically adapt inside the body, this future hinges on two prerequisites: a substantial increase in clinical research to prove these novel drugs are safe and effective for diverse patient populations, and the implementation of strict, harmonized regulations to guarantee the safety and consistency of every customized pill.

13. Conclusion

3D printing is steadily changing the way medicines are designed and produced, offering the chance to create tablets that match individual patient needs. Beyond simple dose adjustments, it makes possible complex drug combinations and controlled-release profiles that traditional methods struggle to achieve. Still, its use in practice is slowed down by regulatory demands, limited materials, and the challenge of scaling up production. Moving forward, clearer standards and closer integration with tools such as artificial intelligence will help improve efficiency and ensure quality. With ongoing research and collaboration between scientists, industry, and regulators, 3D printing has the potential to move from experimental use to a reliable technology that supports truly personalized medicine.

14. Abbreviation

1. 3D – Three Dimensional
2. 3DP – Three-Dimensional Printing
3. AM – Additive Manufacturing
4. API – Active Pharmaceutical Ingredient
5. FDA – U.S. Food and Drug Administration
6. AI – Artificial Intelligence
7. ML – Machine Learning

8. 4D – Four-Dimensional (Printing)
9. CAD – Computer-Aided Design
10. 2D – Two-Dimensional

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