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Review

Recent advancements in additive manufacturing techniques employed in the pharmaceutical industry: A bird's eye view

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ABSTRACT

The 3–dimensional printing process (3DP) was patented in the 1980s, but the utilization of this process has expanded substantially over the past decade, to which the pharmaceutical industry is a major contributor. With increasing interest, researchers across the globe are striving for the fabrication of novel pharmaceutical dosage forms, especially tailored ones, which can cater to the specific needs of the patient. These dosage forms intend to cater for on–demand manufacturing, personalized medications, enhanced geometry, size, and dosage, and increased bioavailability of the medicinal active. With the emergence of precision medicine in healthcare, the inclusion of additive manufacturing (AM) technologies is deemed imperative for the fabrication of oral dosage forms and polypills, which opens new horizons for the administration of drug combinations and formulations tailored to individual needs. Although the extensive commercialization and acceptance of the AM techniques may disrupt the current healthcare supply chain, it has the potential to curtail the waste produced by expired and unused medications. This article attempts to outline these additive manufacturing techniques of great interest in the pharmaceutical industry while underscoring the current innovative trends pertaining to the 3D printing of pharmaceutical dosage forms, as well as their advantages, limitations, and prospects in the field of research and development. The article also showcases the viability of various 3D printing techniques by citing numerous papers in which said techniques have been successfully exploited to deliver unique pharmaceutical formulations.

Introduction

At the outset, the pharmaceutical industry is growing by leaps and bounds, and recent innovations have certainly facilitated the development of novel dosage forms for targeted therapy. Nonetheless, manufacturing these pharmaceutical dosage forms on an industrial level is still limited and continues to rely on traditional drug delivery systems, primarily in modified tablets. The inception of 3–dimensional printing (3DP) technology has pushed the boundaries of the research and development of novel dosage forms, especially in personalized and modified tablets [1]. Although traditional dosage form manufacturing is meant for mass production, it has certain shortcomings, namely high capital expenditure for acquiring the major equipment, the requirement of a large operating space, a well–trained and adept workforce, and lack of flexibility in dose adjustment. Additionally, it lacks the flexibility in bringing tailored medicine to reality, owing to the lack of flexibility and multifarious process [2].

In the cases of solid unit dosage forms, dose modifications are achieved by dispensing several low–dose tablets that would produce a greater dose or via breaking or dividing high–dose tablets [2]. In the United States, approximately 3000 compounding pharmacies fill over 30 million prescriptions a year, in an effort to personalize the medications for individual patients [2,3]. The splitting of tablets is mainly achieved by means of tablet splitters, hands, or knives, resulting in varying doses, due to dissimilar weight distribution post splitting [4–6]. Tablet splitting could also have a profound effect on the drug release profiles, especially in the extended or controlled release formulations [7,8]. Furthermore, its fractionation has a direct effect on the integrity of the tablet coating, thereby promoting premature drug release [2].

Conventional treatment of patients with a standard dose of a drug can sometimes lead to trial–and–error, suboptimal treatment, and prolong time to establish the optimal dose. This not only leads to a higher treatment cost to the patients but also substantially increases

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the morbidity and mortality of the patients [9]. This problem can be settled by the individualization of the treatment regimen, which significantly reduces the risk of Adverse Drug Reactions (ADRs) [10]. The Personalized Medication (PM) can potentially tailor the treatment therapy to deliver the best response with the highest margin of safety, to ensure better care of the patients, with lower incurred costs [11]. Although the extemporaneous compounding of personalized medicine is important, compounded preparations pose a multitude of drawbacks, including lack of quality control, variable drug absorption across biological membranes, and unknown stability parameters [12].

3D Printing (3DP) or Additive Manufacturing (AM) has become one of the most innovative technologies in the pharmaceutical sector, with the last decade witnessing a significant expansion in the manufacture of drug delivery models. 3DP or AM technologies include a plethora of processes in which a solid object is created in a layer−by−layer process [13]. The AM facilitates the creation of pharmaceutical dosage forms by means of computer−aided designing (CAD), which in turn generates a computer−designed model that fabricates the desired product using layer upon layer feed deposition. Additionally, AM also provides an innovative platform to overcome the limitations attributed to the conventional 'one−size−fits−all' concept. The most commonly used 3DP technologies employed in pharmaceutical companies include electron beam melting (EBM), extrusion−based 3D printing, inkjet printing, multijet fusion (MJF), powder bed deposition, selective laser melting, selective laser sintering (SLS), and direct metal laser sintering (SLM/DMLS), and stereolithography (SLA). Owing to the multitude of desirable features like flexibility with the design and polymers used, wide availability, and low operational charges, extrusion−based 3DP has portrayed immense potential and interest among researchers [3,14,15]. Extrusion−based 3DP technologies are classified as direct powder extrusion (DPE), pressure−assisted microsyringe (PAM) and fused deposition modeling (FDM) technologies, based on variations in process parameters, as well as the nature and type of polymers used [16]. Direct powder extrusion (DPE) technique involves the use of a single−screw direct powder extruder 3D printer which was fabricated for printing with polylactic acid (PLA) or acrylonitrile butadiene styrene (ABS). In this technique, a small spatula is employed to add the mixture into the hopper of the printer and to push the material inside the single−screw extruder. The extruder is placed vertically that facilitates the flow of powder into the screw and also decreases the presence of air bubbles. Furthermore, pressure−assisted microsyringe is used to produce hybrid film structures while circumventing the problem of blending immiscible polymers. This technique is useful in determining the chemical structure, morphology, mechanical properties and disintegration [17]. Lastly, Fused deposition modeling (FDM) is an additive or anabolic process that involves building components by addition of material [18]. The next part of the review will briefly underscore the various 3DP−based technologies, that precede the development and manufacture of personalized dosage forms.

The inception of 3DP as a drug−delivery modality

The 3DP technology, or AM, was first put forth by the engineer Charles Hull in the early 1980s [19]. The recent approval of SPRITAM® (anti−epileptic drug, Levetiracetam), the World's first 3DP oro−dispersible tablet, has tremendously increased the interest in fabricating 3DP dosage forms [20]. 3DP technology is a manufacturing process in which an entity is fabricated using layer−by−layer deposition of the substance [21,22]. Researchers, pharmacists, or doctors make use of computer−aided design (CAD) to design the directives that guide the printing trajectory of the nozzle. The printer nozzle stacks the ink, including the APIs (Active Pharmaceutical Ingredients) and the binder, one layer at a time, using this command to yield a 3DP product or dosage form, according to a pre−designed 3D model [15]. 3DP technology possesses tremendous potential in personalized medicine, owing to its flexibility in creating tablets with different sizes, shapes, and percentages of APIs. Additionally, by regulating the outward shape and internal structure of the tablets, 3DP allows for the micro−controlling and production of various drug release profiles [23]. The flexibility of 3DP allows local control of the material composition and microstructure. 3DP also provides significant advantages over conventional processes in terms of generating byzantine, intricate, and customized objects, making it more time−saving and cost−effective [22,24]. Fig. 1-7 classifies the various AM techniques, following which each AM techniques employed in the pharmaceutical sector would be concisely described.

Fused deposition modeling (FDM) or fused filament fabrication (FFF)

Since its introduction in 2014, the fused deposition modeling (FDM) 3DP of the Fused Filament Fabrication (FFF) 3DP, is one of the most used and efficient technologies used for fabrication of drugs in pharmaceutical industries. This technique employs a filament, usually obtained from a thermoplastic polymer by hot−melt extrusion (HME) [25]. The pharmaceutical−grade polymers commonly used in the FDM 3DP include cellulosic derivatives, polylactic acid (PLA), polymethacrylates, polyurethanes, polyvinyl alcohol (PVA), and polyvinyl pyrrolidine (PVP). However, plasticizers like glycerol, oleic acid, and polyethylene glycol (PEG) 400, are occasionally added, in order to create and extrude the filaments evenly [3]. These filaments are driven into the heated block of the polymer via a geared system, for melting or softening. Additionally, this facilitates the deposition of multiple layers of material via the nozzle onto the 3D−printer build plate. After cooling, these overlaid layers bond and fuse with each other, thus yielding the finished 3D object. Since FDM includes the deposition of subsequent layers obtained by molten/softened formulation extrusions, they bear strong similarities with other hot−processing techniques like HME, which have already made their way into the pharmaceutical sector [25]. As a measure to control drug release profiles, several process parameters [16] like nozzle temperature, layer height, print speed, infill density, and building platform along with changes in geometry [2] and non−melting inert fillers [26] have been widely used.

The FDM technology is a promising yet common 3DP technique in which the thermoplastic feedstock materials, usually containing a drug [26,27] are plasticized and extruded through a thin nozzle, followed by its deposition on the 3DP build platform, thereby facilitating the layer−by−layer fabrication of 3D geometries or tablets [28]. FDM technology has recently been extended to yield various types of tablets with various compartments and adjustable release kinetic profiles [29,30], drug−eluting implants [27,31], and functional medical devices [32,33], among several other examples. The studies by Goyanes et al. explored the outcomes of geometry on the drug release parameters [34], while Alhnan et al. investigated the effects of drug dosage forms other than tablets, such as porous matrices and capsular devices [2]. Despite its gargantuan popularity, FDM has a number of significant flaws. Firstly, FDM necessitates the use of HME in the preparation of the drug−loaded filaments. The medicine is commonly incorporated with the powdered excipients, and further blended during the preparation of filaments, via extrusion, for use in the 3D printers. Subsequently, the excipients and API are subjected to repeated heat stress as a result of this multifarious process, which may enhance the chances of degradation. Additionally, initial blending and the HME process limit the utility of API and excipients that lack the desired physical and mechanical properties for extrusion and therefore 3DP [35]. Secondly, the absence of any regulatory structures for the consent of dosage forms printed using 3DP technology currently limits the accessibility of these applications [19,36]. Moreover, the determination of the mechanical strength of filaments, the chemical stability of thermolabile components, and the total shelf life

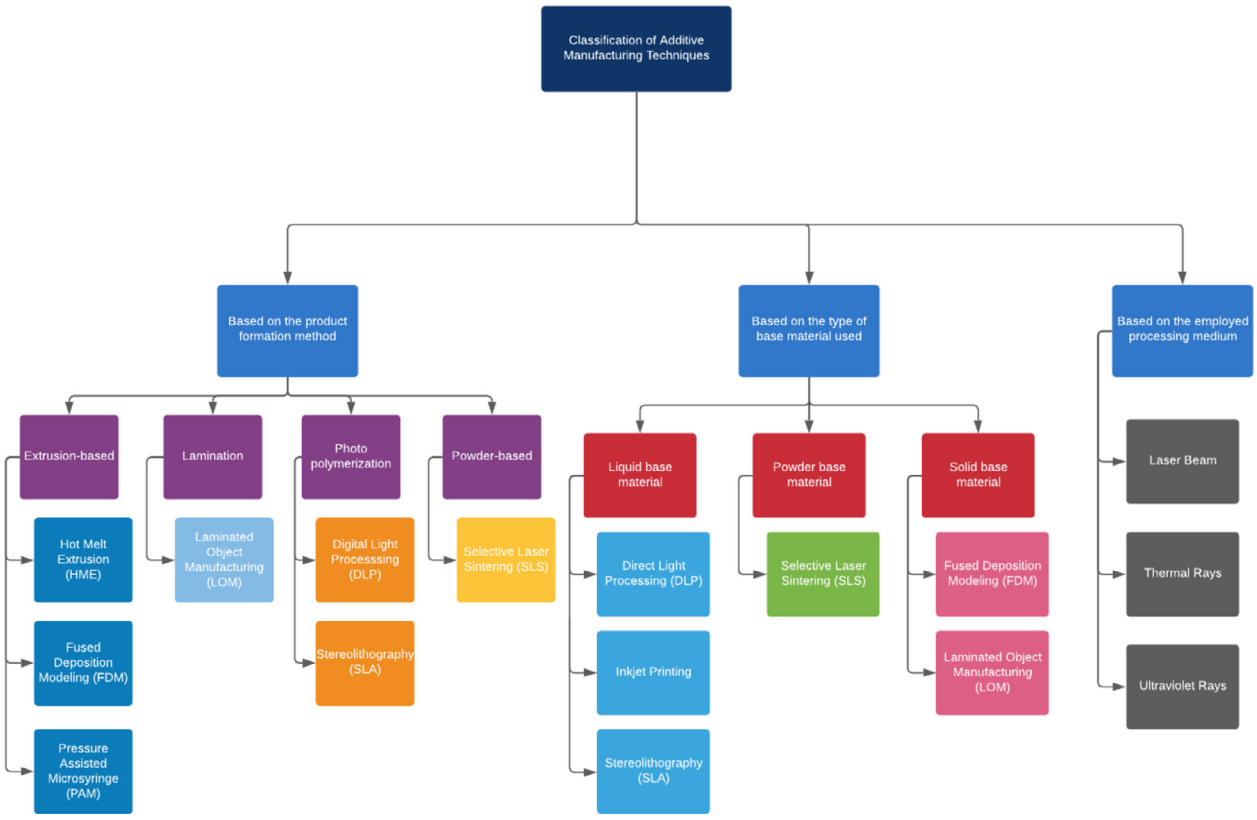

Figure 1. . Classification of Additive Manufacturing Techniques

of the final product must be carefully addressed. The excipients must be carefully chosen, and the complete process of filament manufacture utilizing HME must be optimized, as well as the reproducibility of drug loading and release profiles. Furthermore, multi−phase production requires an investment in time and manpower, along with uncertainty about the acceptability and stability of the end product. However, the limitation of poor drug loading onto the filaments could be addressed by incubating the filament in a drug−loaded organic solvent by passive diffusion [15], but in most cases may necessitate the use of a very concentrated solution to load even a small amount of drug [37,38]. Additionally, proving the printer's capacity to satisfy the production criteria reproducibly, an equipment certification for 3D printers as a part of a confirmation procedure can potentially facilitate and also hasten the approval process. Furthermore, knowledge of the characteristics of the 3D printer would also allow the validation of the adequacy of multiple 3D printers for a particular product, as well as the comparison of different printers among themselves [39]. Nonetheless, the direct extrusion of drug and polymer using HME is an alternate method to produce a homogenous mixture of polymer and drug, that renders an increased amount of drug loading [37,38], along with uniformity in the shape and density of the dosage form [40]. The combination of FDM 3DP with HME

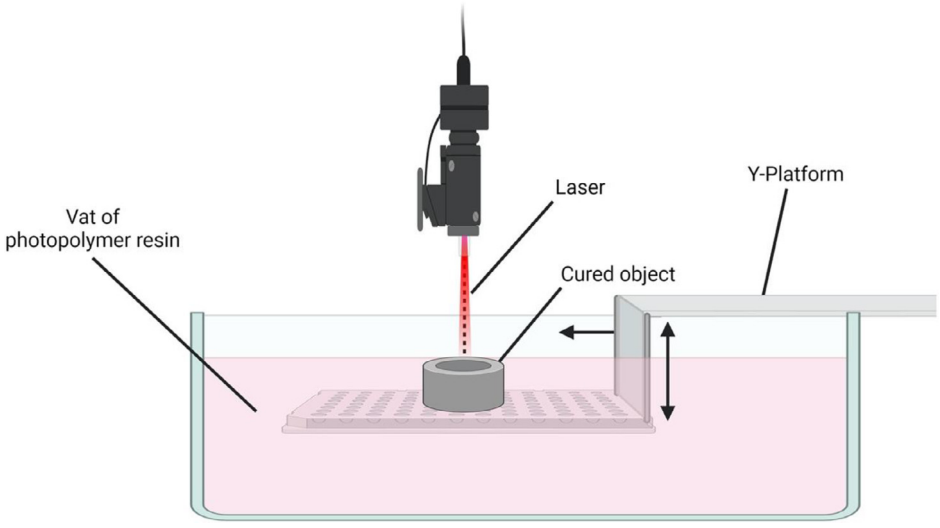

Figure 2. Stereolithography Technique

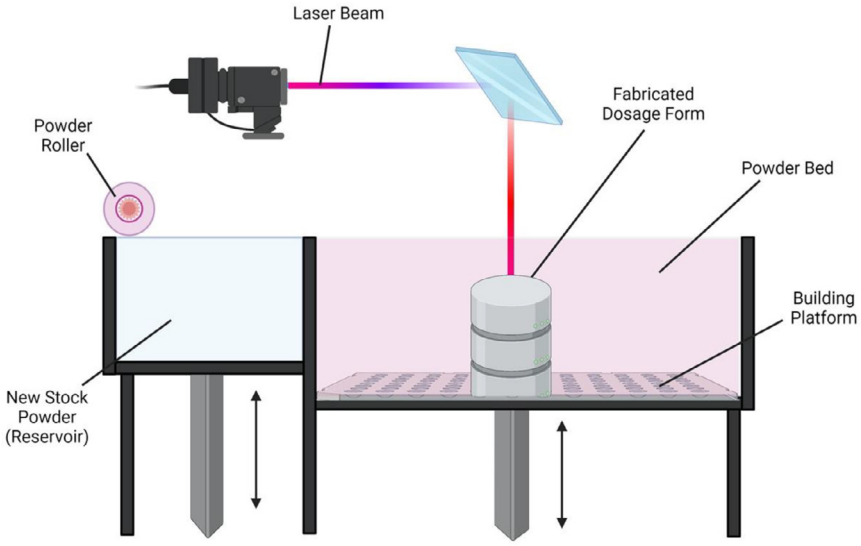

Figure 3. Selective Laser Sintering Technique

facilitates the possibility of manufacturing various dosage forms at the point of care for instant consumption by the patient [41]. As an example, the linking of HME with the FDM 3D printer has been used by Fu et al. to create customized progesterone–loaded PLA/PCL implants (vaginal rings) for long–term medication delivery. Drug –loaded filaments were fabricated into several vaginal ring forms (M, Y, and O), which demonstrated progesterone release with each lasting more than seven days. Because of its design and greater surface area/volume ratio, the 'O'–shaped vaginal ring disintegrated faster than the others. In addition, these implants cater to customization, which is absent in the conventional preparations marketed [42]. Furthermore, the HME used in adjunct with the FDM 3DP technology was used for making instant release pills containing pantoprazole API, which is a thermolabile drug, using PVP K12, which showed a faster release time of <10 min. Additionally, this process needed a lesser processing temperature of <100 °C, thereby facilitating the easy processing of thermolabile medicaments [41].

Stereolithography (SLA)

The Rapid Prototyping (RP) technology has a brief history dating not more than 30 years. This technology was a giant breakthrough in the manufacturing sector, due to the latter being the predecessor to the generation of 3D objects, by adding materials rather than fabricating a part by removing the material. Therefore, this is the ultimate reason that these techniques are referred to as additive manufacturing (AM) processes [43,44]. Stereolithography (SLA), a subset of liquid material–based RP techniques invented and patented by Charles W. Hull in 1986, was the first RP method to be introduced [45]. Additionally, it is characterized as a method for fabricating 3D objects by stacking narrow layers of ultraviolet (UV)–curable substances on top of each other. Subsequently, the substance was subjected to UV irradiation, which provided the necessary power to start a chemical reaction (curing process) that solidifies the material by bonding numerous tiny molecules, thereby fabricating a highly cross–linked polymer. Moreover, in the nascent stages of its development, UV laser sources combined with galvanometers were employed in the process to guide the beam to the required location for solidification [43,46]. Over recent years, various guiding systems and laser sources (IR, UV, visible light) have been presented, that have borne a multitude of alternative processes (like galvanometers, mask projection, and x–y –z driving). SLA demonstrates several desirable and salient features over other RP methods, such as the capability to produce finalized samples relatively quickly. Moreover, the fabricated models have

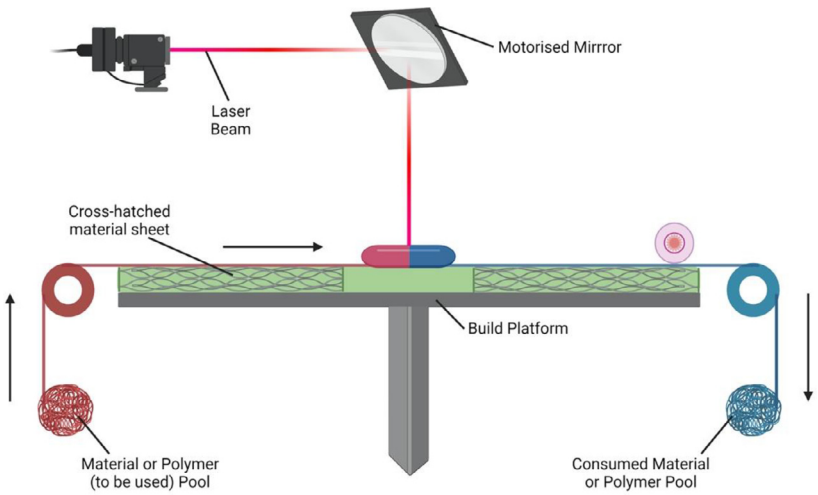

Figure 4. Laminated Object Modelling Technique

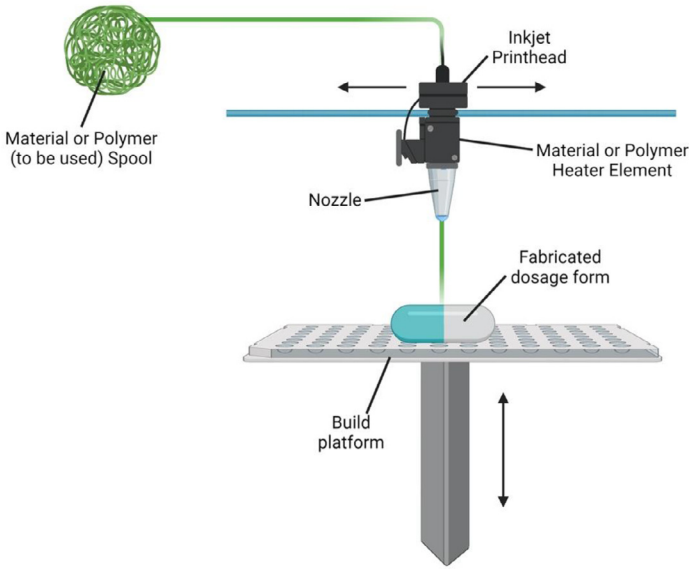

Figure 5. Fused Deposition Modelling Technique

significant resistances and are strong enough to be tested for friability. Furthermore, these procedures could be utilized to produce small batch quantities as a cost–effective alternative to injection molding. Moreover, SLA may also be employed in the manufacturing of investment casting patterns for any type of material or polymer [43].

In addition, the limitations that have been posed by the FDM technologies are not observed in the Vat Photopolymerization (VP) techniques like SLA and Digital Light Processing (DLP), because their modus operandi neither require powders nor relies on the heat for the fabrication process. Instead, each layer is manufactured either by a digital processor screen (in DLP) or a laser beam (in SLA) that induces the polymerization of the drug–loaded resin [47]. These methods are highly accurate, especially with high printing resolution, thereby allowing the manufacture of solid dosage forms with higher patient acceptance in comparison to techniques like Selective Laser Sintering (SLS) and FDM [48,49]. The studies by Robles–Martinez et al. elucidated a novel SLA printing technology that facilitated the manufacture of polypills (multi–layered tablets), with variable shapes and drug contents. Several APIs such as aspirin, caffeine, chloramphenicol, naproxen, paracetamol, and prednisolone were utilized in the study. The tablets were fabricated into different shapes like a ring, cylinder, and a ring with a soluble filler. The analysis by Raman microscopy validated the spatial separation of medications, but also revealed that owing to their solid–state properties, medications like aspirin, naproxen, and paracetamol, were able to permeate between the layers. Furthermore, dissolution studies demonstrated that the type of excipients and geometry of polypills exert a significant effect on the release of each of the six drugs. This study also demonstrates the utility of SLA 3DP in the production of personalized patient–centered tablets or dosage forms [50]. Healy et al. employed the SLA technique to fabricate oral dosage forms of aspirin and paracetamol with concentrations of 2.5% and 5%, utilizing a novel photopolymerizable

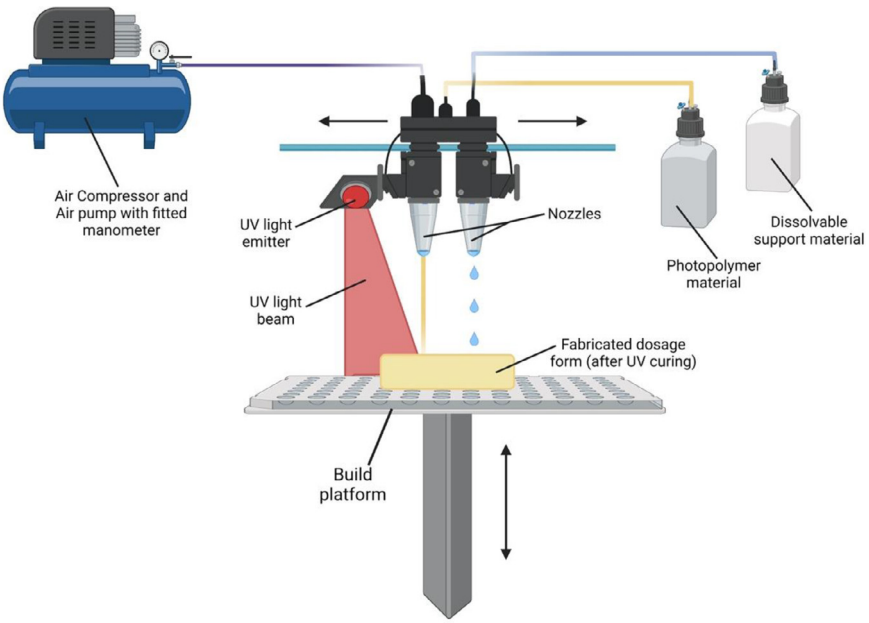

Figure 6. Pressure Assisted Microsyringe Technique

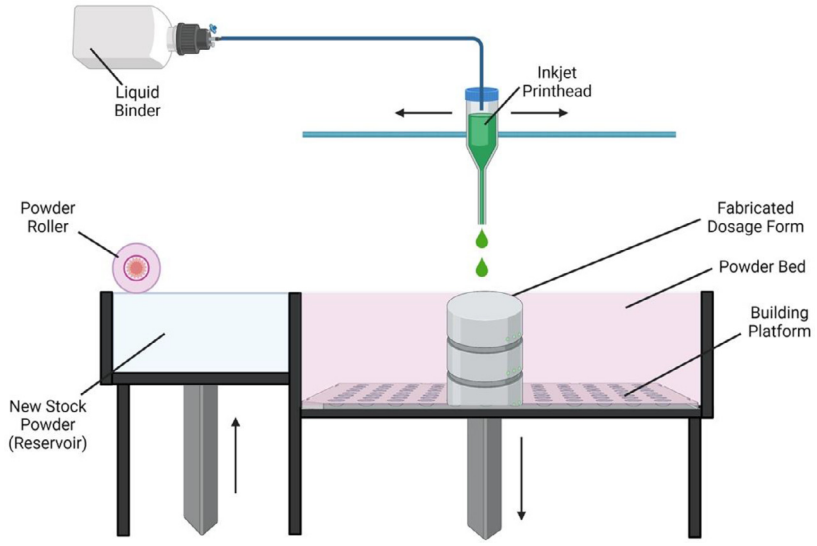

Figure 7. Inkjet Printing Technique

resin. They were also able to print 28 pharmaceutical dosage forms in one print cycle, demonstrating the utility of SLA in the mass production of oral dosage forms. This study also underscored the effect of drug incorporation on the dimensions of printed dosage forms, with the dimensions of the printed form being different from the design. The results from release studies demonstrated an increased drug release with increment in the drug loading, implying the development of patient−specific drugs with the ability to modulate drug release profiles. This study unravels potential areas in AM techniques, where substantial studies could be conducted on the influence of drugs on the printed product, formulation, or dosage form. Additionally, this study also elucidated the future potential in creating solid dosage forms using SLA printing technology, indicating the potential research in the ability to create personalized medication and also to modulate drug release profiles from the formulations [51]. Nevertheless, solid dosage form is considered as the most popular and standard form of administration of drugs but with the advancements in 3DP technologies, many other formulations are being developed. A recent study elucidated by Xu et al. highlighted 3DP plugs for controlled ocular drug delivery. These 3D printed plugs were fabricated using polyethylene glycol diacrylate (PEGDA), polyethylene glycol 400 (PEG 400) and a semi−interpenetrating network (semi−IPN) was developed. Furthermore, a clinical study was conducted in which the release of Dexamethasone form the Punctal plugs was measured. The results of this study reported sustained release of Dexamethasone for 7 days from Punctal plugs made with 20% w/w PEG 400 and 80% w/w PEGDA, while punctal plugs prepared with 100% PEGDA exhibited prolonged release for more than 21 days thus proving the efficient action of PEGDA to attain longer action of drug [52]. Furthermore, by looking into the advantages SLA has brought in the drug delivery system, different dosage forms are being explored. One such exploration is elucidated by Yadav et al. in which 3DP hollow microneedles (HMN) array were fabricated using SLA for efficient transdermal delivery of Rifampicin. These transdermal patches contained sub−apical holes present in each quarter of the needle tip that improved or enhanced the physical strength and integration of HMNs array. Conclusively, in the ex−vivo permeation study it was reported that HMNS array system had greater penetration and improved bioavailability [53].

However, the pharmaceutical utility of VP technologies, especially SLA only account for a minor portion of the market and are still in their nascent stages, owing to certain constraints that limit their utility [16,47]. The restraints include the inability to print concomitantly using low volumes of various resins [54], thereby rendering formulation development operations arduous, onerous, and inept. Even though several discontinuous methods have been proposed to tackle these hurdles to enhance the overall process [50]. Furthermore, there are restrictions due to the paucity of suitable materials for VP; Commercially obtainable photopolymer resins are mostly created for engineering applications wherein robust and sturdy structures are required [55,56]. However, such mechanical characteristics are undesirable from a pharmaceutical standpoint, as dosage forms taken by mouth must break fully to liberate their inner content and then be removed without the possibility of depositing tablet pieces in the GIT [57]. However, despite the availability of commercial biocompatible resins [58], hardly a small amount of photopolymer formulations have been studied for use in pharmaceutical applications [50,59−61]. Therefore, such constraints establish the groundwork for a thorough examination of the photopolymers and their various evaluation parameters. The various commercially available SLA 3D printers are designed to use huge quantities of a single resin at once [54], further allowing for enormous prints, which find extensive use in pharmaceutical prototyping. However, this is not necessary nor advantageous in the evolution of novel pharmaceutical formulations and, as a result, their production cost would increase drastically, which further decrease the acceptance of the formulation due to economic reasons [62].

Laminated object modeling/laminated object manufacturing (LOM)

The Laminated Object Modeling or Laminated Object Manufacturing (LOM) technology, developed by Feygin and Pak in 1988 [63] is a hybrid of additive and subtractive manufacturing techniques [64]. It is a technique that feeds the adhesive−coated thin−film material, followed by the integration of the cutting and laminating processes to render the final product [64].

The layer fabrication commences with a sheet of paper, metal [65], or a synthetic polymer being bonded to the substrate with the laminated roller. Subsequently, post the spreading−out of the layer onto the building platform, the blades [66], or the carbon dioxide laser [67], attached to the print head, trace the contours of the layer, based on the input given as the CAD file [64]. The adhesive−coated films are then bonded together between the layers, post which the film is sliced to the desired pattern using the laser beam [64]. Furthermore, the platform is then lowered, thereby facilitating the distribution of a new sheet of construction material [64]. After the coating

of the previous layer with the film, the second cross−section pattern is cut and laminated [68]. Following this, the cutting operation is repeated layer−by−layer, based on the total number of desired sheets in the final product or dosage form [64]. When compared to other AM processes, LOM provides a quick way to print products with larger dimensions quickly [69], but the material within each layer must be maintained constant [64]. In addition to the faster building of prototypes [64,69−71], the LOM renders tensile strength in the laminate direction [64,72] with sufficient quality characteristics [44,64]. Additionally, owing to the use of a pre−fabricated film sheet as the raw material, this technique is most versatile, highly adaptable, and could be suited for various materials, including the majority of composite reinforcement, particularly the long fibers [68,73]. Furthermore, a support material is not required because the building material is retained in place and does not migrate outside the model's contour during the process of lamination [64]. Moreover, the LOM technique also demonstrates sufficient anisotropic performance to generate things with intricate patterns and complex 3D geometries [73,74].

LOM processes find substantial utility, as they do not require a heating step during production that ensures the adhesive bonding of the sheets. In comparison to its shortcomings that arise in other techniques like FDM, the impact of this step on the non−uniformities in the manufactured part is minimal [75]. However, a drawback of the LOM is that the materials that could be utilized in the procedure are limited by their capacity to be shaped into sheets and then further merged with adhesive [76]. Additionally, the LOM process poses sheet−bonding problems, that cause weak bonding, process failure, and problematic disengagement between the supporting frame and the part [64]. Furthermore, an additional limitation of LOM is that if the local temperature of either the stage or the roller is not adequately regulated, the part may also become delaminated owing to ineffective heating of the adhesive or even account for structural damage if the temperature is high enough to destroy the adhesive [77].

Kechagias also opines that the vertical surface is one of the most imperative quality factors of parts fabricated using LOM. This factor could be improved by the process optimization, minimization of post −process time, easier decubing, less finishing, and facilitating the disengagement between the part and the supporting frame [64]. For the LOM process, Kechagias investigated the effect of print settings on surface roughness. Further studies have determined that the heater temperature, laser speed, and layer thickness have a conspicuous effect on the surface roughness parameters, and the latter could be optimized by fine−tuning these variables [64]. A number of researchers have provided substantial research that attempts to analyze and improve the quality of LOM parts by presenting both statistical and analytical mathematical models for good bonding of the laminates [77−80] and/or mathematical models for prediction of the surface roughness [81,82].

Hot melt extrusion (HME)

Over the last 12 years, the interest in the pharmaceutical applications of the hot−melt extrusion (HME) techniques has grown tremendously [83].

In the mid−nineteenth century, HME was introduced in the plastics industry to manufacture polymeric insulation that was used in wire cover and then later used in the production of all plastic bags, pipes, and sheets [83,84]. HME has long served as a popular method for the plastics and polymers industry but has proven to be a feasible way for the manufacture of a multitude of pharmaceutical dosage forms and drug transporting systems. HME fabricated dosage forms are formed by intricate combinations of APIs, excipients, and other processing aids [83]. The studies by Egakey et al. examined HME as a pharmaceutical manufacturing process, thereby marking its utility in the fabrication of pharmaceutical dosage forms. The polymeric carrier employed in the previous study included poly−(vinyl acetate−co −methacrylic acid) and an epoxy resin containing a secondary amine [85]. HME also proves to be of great importance over conventional pharmaceutical processing procedures, including fewer processing stages, continuous operations, lack of solvents, increased bioavailability, and the ability to generate solid dispersions [83].

The extrusion can be defined as a process of driving a substance between an aperture or die, under regulated conditions, that account for the change in its physical properties [84,86]. In addition, the feed material is forced forward towards the die by the rotation of the screws, following which they are relaxed by the heat generated by the barrel wall via friction. The feed is viscous when it reaches the other end of the screw and can be driven through the aperture or die, and later be cast into the required structure [87]. The three primary types of extrusion equipment include radial screen, ram, and roll & screw extruders [84,86]. Screw extruders are the most imperative in the manufacturing sector due to their ability to convert feed material into a completed shape, such as a film, rod, or tube, on a continuous basis [87]. The HME is regarded as a continuous procedure that consists of the pumping of several polymeric substances at temperatures exceeding their glass transition temperature (Tg), and at times even exceeding their melting temperature (Tm), with a rotating screw that facilitates the admixing of active compounds (Polymers, thermoplastic binders or both), at a molecular level [84,88,89]. The HME technique pumps the raw materials through a die at raised temperatures, utilizing a rotating screw that yields a product of uniform shape. Additionally, the HME technique also poses an attractive alternative to conventional manufacturing methods. The utility of HME as a technique has been made concrete by the numerous advantages it poses over other conventional pharmaceutical processing techniques. The primary reason is that, during the extrusion process, the molten polymers act as thermal binders, but on solidification after cooling, they possess enormous potential as drug depositories and/or drug release retardants. Additionally, the number of processing steps is substantially reduced, as water and other solvents are not required, thereby eliminating the time−consuming and onerous drying steps. Furthermore, polymer dispersity and particle aggregation issues are circumvented by the agitation and vigorous mixing brought about by the revolving screw, thereby making the process more continuous and efficient [83].

One of the most herculean and challenging tasks for formulation scientists is the formulation of such chemicals as oral dosage forms. Owing to its low water solubility, more than 40% of all novel molecular entities demonstrate low bioavailability. Additionally, owing to the importance of lipophilic receptors and the introduction of combinatorial chemistry, these numbers are expected to rise even further. By forming molecular dispersions, the utility of HME has been employed for substantially increasing the bioavailability of medicinal compounds, particularly in cases of those with poor aqueous solubility and hydrophobicity [90−94]. Additionally, this molecular blending transforms the constituents into an amorphous form, portraying homogeneity in their density and shape, thereby improving the drug dissolution profile of poorly water−soluble APIs.

Furthermore, as numerous APIs are thermolabile in nature, the HME utilizes a pharmaceutical−grade polymer that can be treated at low temperatures.

This condition may limit the applicability of the API, in being processed as the HME in some cases [84,88,89]. However, over the last decade, the newer equipment specifications and procedures have substantially increased the number of actives that were previously thought to be ineligible for this burgeoning technology [83].

Moreover, the HME has also been used in the administration of water−soluble and hydrophilic medicaments for a spectrum of applications, including taste−making [84,88,89].

Furthermore, to improve the understanding of process and product, several regulatory agencies continue to encourage investment in quality by design (QbD) and process analytical technology (PAT) that are crucial elements in the HME process. Moreover, several PAT procedures, such as near−infrared (NIR) and Raman spectroscopy, have set the precedent for real−time quality monitoring and knowledge of extrusion processes, primarily HME, in the manufacture and characterization of pharmaceutical dosage forms [84].

The Food and Drug Administration (FDA) in August 2015 granted the use extrusion technology for the production of first commercial 3DP tablet Spritam (Levetiracetam). It is a complex, pyramid shaped and immediate release 3DP tablet produced by Aprecia Pharmaceuticals. The critical factors that were kept in consideration while fabricating the tablet included− type of polymer, molecular weight, viscosity, glass transition temperature, strength, toughness, filament diameter, etc. The development of Spritam led to increase of trust and confidence towards the new extrusion−based technologies and that resulted in development of many 3DP drugs like − Acetaminophen controlled release tablet, warfarin fast disintegrating tablet, Ritonavir 3DP tablet and many more [95].

Since the early 1980s, the total number of patents filed using HME in the production of pharmaceutical systems has increased exponentially. Over recent years, several researches have substantiated the utility of HME processes as a potential method for the formulation of pharmaceutical drug transporting methods, including pellets [96−101], granules [102−104], transmucosal and transdermal [105−113], implants [114−119] and sustained release [101,120−127] pharmaceutical dosage forms as well as the matrices and film coatings of these dosage forms [128−132].

Selective laser sintering (SLS)

Of the various 3DP technologies employed for pharmaceutical manufacture, Selective Laser Sintering (SLS) is the one that has gained tremendous attention among researchers. In the early 1980s, Joe Beaman and Carl Deckard devised the SLS technique. In recent years, implants, metal parts, and tissue scaffolds were found to be the most prevalent applications of this technique [2,27,133].

The SLS creates three−dimensional things by using laser energy to selectively heat the powdered particles, which ultimately facilitate their fusion. Subsequently, these fused particles solidify to make a three−dimensional model. Using FDA−approved excipients, the SLS printing method facilitates the personalization of medications for various cohorts, including geriatric, pediatric, or special populations. The three major constituents of the SLS printer (scanner and laser) system comprise a powder bed, a spreading platform, and a laser system. The scanning patterns of these vectors are predesigned based on the characteristics of the finished products. By the laser melting/sintering of the particles, the substance is heated to a temperature that is enough to promote the fusion. The scanner facilitates the laser movement in a 2D plane, and concurrently, the height of the powder bed is altered in order to concentrate the laser beam on the freshly produced surface. Additional support is provided by the loose powder particles. Subsequently, the surface of the powder bed is reduced by a thickness of 1 layer, following which the laser fuses and deposits another layer of the powder. This method is repeated over and over again until the desired formulation is fabricated, following which the product is allowed to cool within the printer [134,135]. The major pre−requisite of this method is the thermal stability and thermoplasticity of the formulation [136,137]. However, only the Food and Drug Administration (FDA)−approved thermoplastic excipients and polymers, used nowadays in the HME method, can only be extrapolated for use in the SLS process [138].

To ensure that the products are produced within a range of specified quality parameters, the SLS process necessitates the management of process parameters. Over the years, the characteristics of the SLS process have been widely investigated in the pharmaceutical sector, where information about related procedural parameters from the engineering department can be utilized for the manufacture of dosage forms and medical devices [139−144]. The SLS method is optimized to increase the mechanical characteristics, dimensional accuracy, subsurface/surface quality, and other critical quality attributes (CQAs) of the fabricated dosage forms. Additionally, these CQAs are primarily determined by the precision of the STL (stereolithography) file conversion, from the CAD software. However, other factors like beam offset, bed temperature, hatch distance, layer slicing, layer thickness, laser beam speed, laser beam spot size, laser power, machine resolution, material shrinkage, and working platform distance could also have a profound effect on the CQAs [1,135,144−146]. Furthermore, the density of the laser beam has a significant impact on the density and mechanical strength of the 3DP dosage form [1,136,137,145−148]. With continuous improvement in the SLS printing process, the most used printer employed for the printing of pharmaceutical formulations is the SLS printer that employs a diode laser [136,137,146,148]. The energy density is in turn controlled by the velocity of the laser across the powder bed, laser energy, and distance between scan lines (hatch distance) [134,135,149]. However, the competence of laser sintering is greatly affected by the particle size of the powder. The particle size also exerts its influence on the content uniformity, physical and chemical stability, solubility, and bioavailability of dosage formulations owing to its effect on the surface area [134,135]. For the first time, Gueche et al. demonstrated the production of solid oral dosage forms (SODFs) with paracetamol and copovidone, using the SLS and employing a CO2 laser. The ability of the KVA64 in the formulation to absorb the laser's wavelength (10.6 m) makes it ideal for the SLS, eliminating the addition of an absorbance enhancer. Furthermore, the UHPLC analysis confirmed the absence of the occurrence of drug degradation, despite the relatively high power of the laser beam. Additionally, this opens new horizons in the utility and research of this printing technology for the preparation and characterization of SODFs. However, they also opined that more thermolabile drugs could be affected by the CO2 laser and their degradation should be critically evaluated in further studies [150]. In addition, several oral formulations [1,136,140,145,151−154], implants [155,156] and controlled release formulations [137,157] have been manufactured and characterized in different areas of the globe.

This approach poses a multitude of advantages over the currently existing printing technologies that have been employed within the pharmaceutical sector. An additional benefit it provides is that the process is solvent−free, relatively fast, and does not need post−processing, polymerizable monomer/polymer liquid binder, or any filament form of raw material. The solvent−free nature of this technique makes it quintessential for the manufacturing and characterization of pharmaceutical dosage forms, where API is sensitive to water and other organic solvents. Furthermore, this eliminates the need for processes like curing or drying (except harvesting printlets from the loose powder), therefore making them readily available for dispensing and consumption after printing. Moreover, by modifying this process and the material features, the printlets containing several medicines with varying drug release profiles and mechanical properties can also be manufactured using this method [145,151]. The various advantages that SLS demonstrates set it apart in the pharmaceutical sector. For instance, the capacity of SLS techniques to construct the free−from 3D structures without taking aid from the external support materials further expands the spectrum of dosage forms that can be manufactured from the latter. SLS also enables the creation of objects with high pore connectivity (the average volume of pores within an object) and high porosity (the proportion of void spaces in the overall volume of the object) [158]. Additionally, compared to other printing techniques (like the SLA or FDM), the SLS eliminates the need to pre−process the starting material or the

addition of potentially harmful excipients that impart desirable characteristics in the formulation. Furthermore, the lack of solvents in the process ensures the stability and protection of APIs susceptible to hydrolysis. Previous studies have substantially demonstrated the cost−effectiveness of SLS for the production of custom parts or dosage forms, compared to traditional manufacturing methods such as injection molding and 3DP technologies such as FDM and SLA [145,147]. The printed products can also be stacked on top of one another, boosting the efficiency and capability of the platform, thereby deeming it ideal for the mass production and scaling−up of the process. Concurrently, it also opens up avenues for the reprocessing and recycling of the feed content, which may be imperative in reducing the waste whilst promoting green pharmaceuticals [14,145]. Additionally, this technique also expedites the development of specialized dosage forms like the abuse−deterrent formulations, amorphous solid dispersions, orally disintegrating tablets among several applications. The commercially available SLS 3DP is primarily developed for engineering and polymer purposes, but have now found their utility in the manufacture and fabrication of several pharmaceutical dosage forms. With continuous improvement in the SLS technology, several versions of the printers will be made commercially available for pharmaceutical applications in the near future, with cGMP−compliant attributes that may be employed in resource−constrained environments like, hospitals and retail pharmacies. Although existing regulatory procedures may be used in the submission seeking regulatory approvals, the submitted document must comprise required information according to the various modules of the common technical documents. However, FDA approval may not be necessary while manufacturing the individualized dosage forms in a hospital, retail pharmacy, or therapeutic setting [134,135].

However, the shortcomings of the SLS techniques include issues in the in−process monitoring/testing, reuse/recycling of the materials, and finding a current Good Manufacturing Practice (cGMP)−compliant printers [138]. However, the SLS also has several limitations, including its effect on laser−sensitive compounds, especially natural polymers, pharmaceutical APIs, and excipients. Furthermore, printing huge amounts of powder is quintessential in terms of technical elements to ensure proper powder flow characteristics and consistent height of the powder layer, which is not feasible in small−scale applications, especially in expensive, drugs for orphan diseases, or limited quantity drugs [145]. Nevertheless, while the unsintered powder can be recycled, this process can only be used for a limited number of prints, owing to numerous concerns pertaining to the physical changes and chemical consistency of the powder used. Therefore, when significant amounts of powder are employed, always a percentage of the raw material may be squandered, thereby plummeting the capability and optimization of the process. Moreover, the process necessitates post−treatment (like the sieving and brushing of the printed dosage forms), it accounts for the expenditure of more cost and time [145,147].

Pressure−assisted microsyringe (PAM) / semi−solid extrusion (SSE)

Another 3DP process which facilitates the use of viscous and semisolid substances for microsyringe extrusion is the pressure−assisted microsyringe (PAM) or the semisolid extrusion (SSE) [159]. Recent decades have witnessed a paradigm shift in the demands and manufacture of pharmaceutical dosage forms. New findings in the pharmacogenomic field have played an essential role in this shift towards catering to customized or personalized dosage forms [160,161]. This 3DP technology has gained tremendous acceptance and is being extensively researched on a global platform [159]. This approach employs a semisolid formulation as the preliminary material, which possesses the ability to build the 3D object without crumpling during the process. In comparison with the rest of the 3DP technologies such as FFF or FDM, PAM eliminates the need to manufacture solid filaments using HME. An added benefit of PAM is that the semisolid formulation is extruded by pressurized air via the nozzle during the printing process, in contrast to being strained by a gear system, as in the case of the FFF or FFDM technique. Additionally, the printing can be carried out below or at room temperatures, because the printing material need not be molten, but instead be just deformable plastically, thereby making it ideal in processing formulations containing thermolabile or thermally unstable APIs and/or excipients. Furthermore, viscosity is known to have a profound effect on the printability of the medicines, as a higher viscosity may possibly clog the nozzles, thus impeding the printing process. However, even if the viscosity is too low, it will not sustain the construction of a 3D scaffold or pharmaceutical dosage forms. Furthermore, because most of the fabricated formulations for the PAM process are solvent−based, drying is an imperative step in the manufacturing process [162]. Depending on the materials and the master formula used, the required drying time varies significantly. Although some fabrications harden within minutes after printing, others may require dedicated post−printing drying steps to achieve proper solidification of the printlet [163]. Though the feedstock material has been prepped with solvents, a solvent evaporation step may be deemed necessary to assure complete removal of the solvent. However, the viscosity of the materials may be a major determinant of whether or not a drying state is required, as less viscous feedstocks may demand a prolonged drying time and may be linked with a higher risk of material collapse and loss of orientation [164,165]. Although SSE outperforms competing technologies in terms of its printing speed, the resolution obtained is consistently low [166]. Additionally, while employing nozzles with narrower orifices may enhance the resolution, this may not hold strong for extremely viscous materials, which may require a larger nozzle diameter. Furthermore, the lesser resolution may only affect the precision with which the printlets may be printed and exerts no influence on the faster speed of printing [161].

Khaled et al. published their findings in 2014, which described the production of bilayer guaifenesin tablets based on hypromellose (HPMC) possessing sustained−release characteristics using PAM [167]. They later used PAM to make multi−drug tablets with various drug release profiles [163], as well as a polypill comprising of 5 separate APIs with variable release kinetics [30]. A publication on the manufacturing of high drug−loaded paracetamol with instant release characteristics was also released by the same research group [168]. These studies demonstrated the capability of PAM printing technology as a potential manufacturing process for oral solid dosage forms. Nonetheless, to avoid clogging of the printing nozzle, a solvent mixture of Acetone/DMSO was utilized in these studies [163]. However, the usage of these organic solvents poses some limitations, owing to which the utility of drug delivery systems, such as DMSO, is restricted to specific patient populations, like the pediatric cohort. According to the European Pharmacopoeia, the utilization of organic solvents results in a residual solvent determination [162]. Another limitation of the aforementioned works is the long manufacturing time of 24 h in printing the formulation. The tablets must also be desiccated for about 24 h [163] or 48 h [167].

The studies by Siyawamwaya et al. describe the treatment of HIV utilizing fixed−dose combinations produced by the PAM technique, by producing a matrix composed of 3 different medications [169]. However, the printed object in this work has a low resolution. Furthermore, organic solvents (Methanol/Acetone) were employed in the fabrication process, to create the printing formulation in this study, yielding results similar to those previously reported. Interestingly, only one investigation on PAM printing techniques, without the use of organic solvents, has been reported to date [168].

The study by El−Aita et al. demonstrates that employing PAM printing, on−demand manufacturing of levetiracetam tablets with a rapid release profile is possible. To circumvent the nozzle clogging, semisolid printing 16 formulations were designed and printed

without employing organic solvents. These formulations were capable of creating a 3D object that did not crumple during the printing process. Differential scanning colorimetry (DSC) and X−Ray Powder Diffraction (XRPD) measurements have shown that the amorphous form of the drug within the tablet is stable for at least three months. Additionally, the drying time has been substantially reduced to half, compared to the earlier efforts, taking only 3 h in total. These pills demonstrated adequate mechanical qualities to be consumed on a daily basis and can be utilized in the fabrication of personalized medicine and drug transporting systems. Additionally, the consistency of the content and mass attained via the adopted 3D printer demonstrates the usefulness of this production method [162].

Studies by Tartarisco et al. demonstrated the possibility of fabricating polyurethane−based microactuators by using the PAM method, which employed the mixing of carbon black with a polyurethane matrix, blended with a suitable dispersant agent, that yielded a suspension with viscosity optimal for processing using the PAM system. Additionally, this composite approach aided them in ensuring a perfect adhesion between the electroactive and the conductive layers, thereby reducing the stress shielding between the various layers. The proposed physical model of the microsyringe system demonstrated adequate agreement with the experimental deposition data within the upper and lower pressure limits. A quintessential parameter that is considered to be imperative for the quality assessment of the products fabricated using this technology includes uniformity of the film thickness and a substantial control on the waviness or edge roughness [170]. The SSE is attributed to be the most appropriate technology, in addition to FDM and direct powder extrusion (DPE), for the fabrication of various pharmaceutical formulations like polypills, oral dosage forms, chewable printlets, orodispersible films, etc. in a plethora of flavors, shapes and drug release profiles [30,164,171−173]. The prime advantage of this technology is its simplicity, which promotes the direct mixing of the excipients, following which it is loaded into a cartridge or syringe for printing [174]. The use of SSE is deemed ideal for the production of patient −friendly formulations, to improve patient compliance, as it enables the production of chewable formulations, in the geriatric and pediatric cohorts. While pediatric preference for the chewable dosage forms is deep−rooted, this technique expedites the printing of necessary medications that cater to the preferences and needs of the patient populations [49]. SSE also finds remarkable utility in drug formulations formulated for consumption in preclinical and clinical applications. In the preclinical scenario, the SSE permits flexibility of producing devices and dosage forms that are personalized to meet some particular study requirements, circumventing the shortcomings that would arise due to the absence of specially designed equipment-sequipment that aid in preparing formulations for animal testing [164,175]. Additionally, this technology could be used in the formulation of soft materials, like rectal forms [171]. This method prevents drug and excipient degradation by utilizing high temperatures, owing to the fact that these materials have a comparatively low melting point, which is corroborated by their semi−solid physical state at room temperature. Thus, the maintenance of lower temperature conditions during the printing procedure enhances its utility in manufacturing of implants and live cell−loaded patches, as well as for biomacromolecules, proteins, enzymes, and several other thermosensitive and thermolabile excipients and drug moieties [176,177]. Although the advantages of this technique far outweigh its limitations, these issues need to be addressed for ensuring optimum printing processes. However, the viscosity of the material could be modulated by fine−tuning the temperature, pH, or quantity of excipient to acquire a printable feedstock. However, these changes could alter the physical state of the drug, which may additionally necessitate further optimization processes [174]. In addition, several other aspects of this technology need to be underscored here, primarily including regulatory, clinical, stability, and storage parameters, which could exert a profound influence over the characteristics of the printed formulation or dosage forms. Although the printlets could be fabricated right before administration, which further eliminates the need for long−term stability testing, although it may be highly advantageous to store syringes loaded with the formulation, to be printed on−demand or for filling into pharmaceutical packaging [164,178]. In a study undertaken by Algahtani et al., the fabrication of a self−nanoemulsifying tablet dosage form with an immediate −release drug profile for poorly water−soluble drug was successfully carried out. The drug of interest was dapagliflozin propanediol monohydrate, which was fabricated into a formulation which contained oils and co−surfactants as a liquid phase and surfactants and solid matrix as a solid phase. This formulation possesses the capacity to self−nanoemulsify on contact with GIT fluid or water. These tablet formulations were subjected to multiple tests and evaluation parameters, from which it could be concluded that the study signified the capability of the PAM technique to print a dosage form characterized by an immediate−release drug profile for poorly water−soluble drugs [179]. Moreover, in a similar study conducted by the same author, a coating system of encapsulating cellulose acetate was printed through extrusion−based 3D printing technology. An immediate−release propranolol HCl tablet was coated to obtain a sustained drug release profile. Various excipients were used in the making of the shell as well as various sizes were experimented on to successfully achieve a modified drug release profile. After undergoing a series of evaluations, it could be concluded that this approach is suitable for altering and customizing the drug release profile of BCS Class 1 drugs.

Inkjet printing

Inkjet printing is a scalable method that has been employed for the preparation of pharmaceutical agents. The process involves the selective settling of liquid droplets onto a substrate followed by their solidification [180]. This process is deemed responsible for the placement and digital control of the formation of small liquid droplets and also the beginning of the processing of ∼1−100 pl liquid droplets into the 2D or 3D structures. The drops are generally created by either heating the liquid to a temperature greater than its boiling temperature or by passing a voltage to a piezoelectric transducer which further causes the vibrational movement of the material [181]. This technology is classified on the basis of the physical properties by which droplets are prepared; into either continuous inkjet printing (CIJ) or drop−on−demand (DoD) printing. The CIJ employs a continuous stream of water, ejected from a nozzle, which accelerates its breaking up into a stream of drops due to surface tension forces. This breakdown can be enhanced by using a piezoelectric transducer behind the nozzle, which optimizes flow, at desired frequencies, and is effective only when individual drops are guided to a specific landing site to produce a printing pattern. However, in DoD printing, the liquid drop is formed as response to a trigger and is ejected only when the drop is required. The liquid ejected from the printer heads is in the form of a jet, which under forces of surface tension, separates and falls from the nozzle, thereby forming droplets. The main drop contains the highest amount of water and is generally followed by a set of few satellite drops. The number of satellite drops can be reduced by altering the rheology and ejection conditions of the liquid. Additionally, the DoD printer consists of various nozzles (about 100 −1000, some may also contain only 1 nozzle). Unlike the CIJ printers that have external fluid pressure that facilitates the drop ejection, in DoD the kinetic energy of the drop itself leads to its ejection. Furthermore, the drops formed by DoD fall in a size range of ∼10 to 50 μm and drop volume of ∼1 to 70 pl while the drops formed in CIJ have an optimal size of ∼10 μm. Moreover, while the piezoelectric ceramic element is equipped with multiple designs, few (thermal inkjet) heads comprise a small electric heating element in the liquid itself

that leads to the expansion of a small bubble, thereby facilitating the formation of drops. Nonetheless, there are several pros and cons associated with both these techniques which include: a greater range of the liquids can be used by printer heads of piezoelectric technology as compared to thermal inkjet heads as these include volatile liquids that vaporize. Moreover, DoD can be employed with a minimal amount of liquid, while, on the other hand, CIJ requires a higher amount of liquid for proper recirculation [182]. A major application of Inkjet printing is the High Throughput Screening (HTS), which incorporates the evaluation and collection of samples followed by their analysis and is utilized for discovering ligands for enzymes, ion channels, receptors, or other pharmacological targets. Studies by Silzel et al. in 1998 demonstrates the utility of inkjet printers in the development of microarrays for antibodies and specific ligands, where the Inkjet printers were used to locate the monoclonal antibodies which retained specificity and affinity for their targets against four human immunoglobulins, IgG1, IgG2, IgG3 and IgG4 followed by further recognition of the human myeloma proteins [183]. Another study by Hughes et al. reported the use of inkjet printing methods employing the phosphoramidite chemistry standard for the in−situ synthesis of a large number of oligonucleotides [184]. Additionally, Melindez et al. illustrated the use of thermal inkjet printing for preparing solid dosage forms having hydrophobic API. The 3D Printed solid dosage forms consisting of successive layers can be prepared by the use of Inkjet printers [185]. Furthermore, for the construction of these dosage forms, support materials like waxes are used to fill the voids or other free−standing parts while a flattener smoothened each printed layer [186]. Inkjet printing also leads to the incorporation of data−enriched edible pharmaceuticals (DEEP) of medical cannabis [187] and evaluation of different substrates of rasagiline mesylate [188]. Although of paramount importance in the pharmaceutical industry, inkjet printing poses few limitations. These shortcomings include a lack of research in areas like fluid formation and supply, ancillary fluid−delivery equipment, drop formation and impact/collection, phase change/drying/fixing/absorption, stability, and characterization [182]. The future perspectives of the inkjet printing technology facilitate an extensive construction of multi −layer 3D solid dosage forms that have the ability of controlled drug release rate, thereby decreasing the dosing frequencies. In conclusion, advanced printing technologies such as inkjet printing can be considered a powerful tool for pattern processing and the manufacture of pharmaceuticals and pharmaceutical dosage forms [189].

Direct powder extrusion (DPE)

Direct powder extrusion (DPE) is a relatively new, revolutionary, and innovative 3D printing method used for preparing amorphous printlets/tablets. It is a novel technology that consists of just a single step, which not only aids in ease of operations but also overcomes one of the major drawbacks of fused deposition modeling (FDM). In FDM, since the preparation of filaments using hot melt extrusion (HME) is necessary, the drugs undergo thermal stress which could possibly result in discoloration and sometimes even degradation via oxidation. After the filament is manufactured, the drug is fed into the 3D printer and heated once again. However, the most significant drawback is the limited availability of options of excipients and drugs to make filaments with the appropriate physical and mechanical properties for 3D printing. In a study conducted by Duranovic et al. [190], paracetamol loaded filaments were processed using poly ether oxide (PEO) and poly(ε−caprolactone) (PCL) polymers, and printed at 130 °C. Even though the extrusion of the filaments and printing was successful, the final products had a yellowish coloration, which indicated a slight degradation. The DPE method circumvents this issue by completely skipping past the filament preparation process, and directly printing the active pharmaceutical ingredient (API) and excipient in powder form. DPE could also potentially authorize the extrusion of mixtures which were previously not feasible to be printed by the traditional FDM process, because of the filaments being too flexible or too brittle, or having insufficient mechanical properties. For example, Goyanes et al. [191], 3D printed directly from the powder form using an FDM modified printer, thus avoiding the need of preparing drug loaded filaments. Different molecular weights of Hydroxypropyl Cellulose (HPCs) were loaded with 35% itraconazole and the pills were successfully printed, processing the blends at 170 °C. This research was expanded upon by Ong et al. [192], who also evaluated the direct printing of powders at 170 °C using various HPC grades loaded with poly ether oxides (PEO) and tramadol as API. In this way, using modified 3D printers, it is feasible to directly print the excipients and drugs in powder form, consequently reducing the thermal stress on the API, thereby reducing the chances of degradation. For tablet production, direct compression is the most popular and widely used process [193]. However, some of the APIs used display poor compression characteristics, which limits the drug loading capacity of the process. For instance, when it comes to paracetamol tablets, only about 30 to 40% weight of the active ingredient can be contained, in turn leading to an increase in the size of the tablet, which can cause patient non−compliance. Additionally, the paracetamol crystals are known to exhibit poor flowability and low compressibility. When these crystals undergo direct compression, they show considerable elastic deformation along with other issues like tablet capping, cracking, chipping, lamination, etc. under pressure [168]. A study performed by Mendibil et al. [194] evaluated the suitability of different formulations on the basis of starch and HPC with varying amounts of paracetamol using the HME process. The various drug excipient mixtures were thermally processed, along with different proportions of Guar gum, via HME. Parameters like drug release curves and dissolution rates of each combination ratio were measured, and the samples were characterized thermally to ensure minimal thermal degradation. A total of 12 mixture combinations were evaluated, with the amount of HPC remaining constant at 25% of the total weight for all combinations. The total weight of all the formulations was fixed at 15 gs, while the paracetamol quantities were 5%, 20%, 35% and 50% of the total weight, while the Guar gum quantities were decided to be 0%, 5% and 10% by weight. The amount of starch added in each sample was decided on the basis of the paracetamol and Guar gum proportions in each combination. Ultrapure water was also added in the ratio of 3% by weight according to the amount of starch present. All of these formulations, even those containing 50% paracetamol by weight, were easily extruded at 85 °C. Looking at the results of the various parametric tests performed, it could be concluded that the presence of Guar gum in small quantities did not hinder the recovery rate and, since the samples were a bit stickier, eased the extrusion process. However, in the samples containing 10% Guar gum, the recovery percentage was found to be significantly affected, possibly because of adsorption phenomenon [195]. In comparison to the traditional paracetamol tablet, which completely dissolved in under ten minutes, the extruded stripes exhibited a steady and slow dissolution over sixty minutes to completely release the API. The samples were aged for 6 weeks and their recovery values were found to be dependent on the amount of paracetamol present, with the samples having higher API content showing lower recovery values. In contrast, the fresh samples gave opposite results, with the recovery values being higher for samples with a higher API concentration. In conclusion, this innovative, single −step method can circumvent a significant number of roadblocks of FDM 3D printing via nullifying a need of filament fabrication via HME, and could totally revolutionize the fabrication of amorphous solids as final formulations. Furthermore, since the HME step is omitted, the shelf life of the formulation could be potentially prolonged, as thermal stress is applied only once, that is, right before tablet production. This technique might be especially useful in preclinical trials and studies, where the quantity of API is usually limited [194].

Advantages of AM techniques

Several comorbidities add to the pill burden and financial costs for both the patients and insurance parties, especially for individuals belonging to an elderly age group suffering from several comorbidities [202]. Additionally, non−compliance with the prescribed therapeutic regimen generally advances into a progressed disease state, with a higher risk of acute disease−related events. Here, the pharmaceutical dosage forms manufactured from AM facilitates increased patient quality of life (QoL), with long−term health advantages, when concurrently supported with pharmacometabolomics and pharmacogenomics [203,204].

The pharmaceutical AM technique allows customization of unique therapeutic regimens, with polypills having the potential to promote patient compliance, provide flexibility in dosing in medication adjustment and precision medicine [30,167]. The AM also gives the patients and healthcare providers a spectrum of options, when it comes to dosage forms, such as fabrication of readily−dispersible or controlled−release tablets for patients with special needs [30,167,203,205].

Furthermore, the advantage of allowing the community and hospital pharmacies to tailor the therapeutic regimen for the incoming patients using the appropriate AM technique facilitates in improving the overall patient health, thereby substantially lowering the total burden of acute conditions on the already burdened healthcare system. Moreover, the utilization of AM techniques in community and hospital pharmacies enables to expand the current practice of compounding pharmacy, with a keen focus on precision medicine on a much larger and accessible gage [30,203]. Table 1 summarizes the advantages and disadvantages of the various AM techniques employed in the pharmaceutical sector.

Limitations of AM techniques

While there are many advantages to incorporating AM techniques into healthcare, there are also some caveats associated with the latter. Some of these roadblocks are mentioned below. The first major hurdle is the licensing of the APIs in several currently available medicines. The second hurdle is the economic feasibility of the printed polypills compared to the mass−manufactured medications currently used. The third hurdle is the need for newly established clinical guidelines to enable the provider prescriptions for diseased states. For instance, in the case of the lack of a legal license from the innovator company, the intellectual property protection of the therapeutic benefit of APIs in current medications and the chemical structure would legally prohibit the sales. Usually, generic companies fabricate comparable varieties of a brand name drug and sell them at a lower price once the patent on the composition and molecular structure of the brand name drug expires [203,204]. This causes the patients as well as insurance companies to prefer the cost−reduced generic medication over brand medications. This method adopted by generic manufacturers could potentially be followed by the polypills manufactured for generic medications. Additive manufacturing technology should be able to exhibit a stable and consistent reproduction of pharmaceutical formulations which are bioequivalent to mass−manufactured tablets, in order to comply with the existing Unites States Food & Drug Administration (FDA) existing regulations and guidelines [206,207]. Integrating additive manufacturing tools into ambulatory care or community pharmacies could help with the economic aspects of manufacturing a singular polypill for every patient. Current compounding pharmacy costs are based on the prices of the ingredients used, along with a small fee for compounding expenses, which reduces the total cost to be much lower than what is usually available in the market [203]. Following the same principle, the creation of personalized polypills could be economically feasible for compounding pharmacies. Furthermore, this not only allows for better monitoring and management of the patients but also improves personalization via facilitation of tailoring therapeutic care based on the patient, as opposed to the current guidelines which follow the "one−size−fits−all" concept [203,207,208]. Table 2 elucidates the recent advances of employing these AM techniques in fabrication of drug dosage and delivery modalities, while Table 3 enlists the most recent patents filed in the latter.

Conclusions and outlook

Although there is a multitude of 3DP technologies, not all of them are amenable for utility in the pharmaceutical manufacturing sector. However, these technologies may be promising technologies for the future and can be employed in specialized manufacturing technologies, like in the case of fabricating intrauterine devices, implants, microparticles, printlets, orodispersible films, etc. that demand a high level of quality, purity, and precision.

Even in the COVID−19 pandemic, with the medical fraternity, healthcare professionals, researchers, and investigators constantly striving to reduce the infection rate, AM technologies have emerged

Table 1
Summary of the Advantages and Disadvantages of various AM Techniques employed in the pharmaceutical sector.

Techniques	Advantages	Disadvantages	References
Stereolithography (SLA)	High−resolution Nozzle free Eliminates layer connection problems Immediate results Good surface finishing	DNA damage High cost of raw materials Few distortions are prone on prints Care should be taken for good handling of resins	[196]
Inkjet Printing	A wide range of liquids can be used. Great resolution Microarray printing applications Potency to combine polymers	A large amount of water is required in continuous inkjet printing (CIP) Wastage of material Slow process High cost Care should be taken for good handling of resins	[182]
Fused Deposition Modelling	Low cost Easy Use A wide range of materials can be used	Ripped and rough surface Low resolution Fragile along the Z−axis	[197]
Laminated Object Modelling	High surface finish Low cost No support structure required 3D structure is formed by cutting, laminating and bonding	Decubing issue Slow Delamination	[198,199]
Hot Melt Extrusion	Anhydrous process Few steps required No compression of the active compound required Easy to use	High equipment cost Unsatisfactory surface finish High temperature needs to be achieved Low resolution	[83,200]
Selective Laser Sintering	Connect powder particles together Wide selection of particles Produces drugs with sustained release ability High−accuracy	Weak and more porous objects can be formed High temperature required Complex system High cost Laser damage	[147,198]
Pressure−Assisted Microsyringe	It does not depend on intermediate products. No effect of the mixing efficiency of powder High−accuracy Good surface finish	Expensive process Drying is required Complex system Pressure should be maintained	[201]
Direct Powder Extrusion	The prepared products show good mechanical and physical properties. Avoids preparation of filaments High−resolution Single−step process	Ripped and rough surface High cost Limited option of excipients	[190,191]

Table 2
Recent advancements of the AM Techniques in formulating various pharmaceutical dosage forms.

Techniques	AM Study	API	Excipients	Remarks	Reference
Stereolithography (SLA)	Multilayer 3D printed oral dosage form (polyprintlet)	Irbesartan, atenolol, hydrochlorothiazide, and amlodipine	Polyethylene glycol diacrylate (PEGDA), Diphenyl (2, 4, 6−trimethyl−benzoyl) phosphine oxide (TPO), Polyethylene glycol (PEG 300), Acetonitrile	A multilayered antihypertensive polypill was successfully fabricated to deliver low−dose combination therapy.	[209]
	Tablets loaded with drugs with modified drug release profiles	4−aminosalicylic acid (4 −ASA) and Paracetamol (acetaminophen)	Diphenyl (2,4,6−trimethyl benzoyl) phosphine oxide (DPPO), Poly (ethylene glycol) diacrylate (PEGDA), Poly (ethylene glycol) (PEG 300)	Varying the percentage of cross−linkable polymers in the tablets modulates the drug dissolution profiles. Higher ratios of PEGDA reduce the dissolution rate, while a higher concentration of PEG 300 promotes drug release.	[210]
	Ascorbic acid−loaded solid dosage Hydrogels	Ascorbic acid, Riboflavin	Poly (ethylene glycol) dimethacrylate (PEGDMA), triethanolamine, phosphate buffer (pH 6.8), phosphoric acid, methanol, hydrochloric acid	This work showed the ability of SLA 3D printing to successfully release a bioactive molecule from a single formulation in a controlled manner.	[211]
	Ibuprofen−loaded cross −linked polyethylene glycol diacrylate (PEGDA) hydrogels	Ibuprofen	Polyethylene glycol diacrylate (PEGDA), polyethylene glycol (PEG 300), riboflavin, triethanolamine (TEA), diphenyl (2,4,6− trimethyl benzoyl) phosphine oxide (DPPO)	SLA is a suitable technique that can be used to prepare pharmaceutical hydrogels.	[212]
	3DP of a multilayer polypill containing 6 drugs	Paracetamol, Caffeine, Naproxen, Chloramphenicol, Prednisolone, Aspirin	Polyethylene glycol diacrylate (PEGda) and diphenyl (2,4,6−trimethyl benzoyl) phosphine oxide (TPO)	Cylindrical and ring−shaped polypills with and without a soluble filler were made that showed acceptable physicochemical characteristics and various combinations of the physicochemical properties. Drug Release Profiles	[50]
	Riboflavin and ibuprofen hydrogels	Riboflavin, Ibuprofen	Polyethylene glycol diacrylate, polyethylene glycol (PEG300)	Prepared drugs have a controlled release capacity.	[212]
Inkjet Printing	Controlled release acetaminophen tablets	Acetaminophen	Hydroxypropyl methylcellulose E100, Ethyl cellulose, Polyvinylpyrrolidone K30 (PVP K30), colloidal silicon dioxide	The release efficiency of poorly water−soluble drugs was enhanced by combining them with hydrophilic polymers.	[213]
	Controlled release rates of two types of Chlorpheniramine maleate tablets. One with Eudragit E−100 as polymer and another with Eudragit RLPO as polymer.	Chlorpheniramine maleate	Eudragit E−100, ethanol, Eudragit RLPO,	The release rate varied for both the tablets and was based on the quantity of polymer used.	[214]
	Controlled release of Chlorpheniramine maleate, diclofenac tablets	Chlorpheniramine maleate, diclofenac	Eudragit E−100, ethanol, Eudragit RLPO, Avicel PH301, DCL11 spray −dried lactose, Kollidon K −25, methanol	Prepared tablets contained a quick dissolve region to break the tablet into controlled regions and the release rate was measured.	[215]
	The rapid release rate of levetiracetam tablets	Levetiracetam	Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyethylene glycol 3350, polyethylene glycol 6000, polyvinyl alcohol, talc, titanium dioxide.	Prepared tablets disperse in less than 15 s in the mouth and exhibit high release rates.	[216]
	Zero−order controlled release Pseudoephedrine HCl formulation	Pseudoephedrine HCl	Kollidon SR, Hydroxypropylmethylcellulose (HPMC)	Zero−order controlled release pseudoephedrine HCl formulations were prepared, and the drug release rate was altered by modulating the number of polymers used.	[217]
Fused Deposition Modeling		Progesterone.		A seven−day controlled release was observed	[42]

(*continued*)

Table 2 (*Continued*)

Techniques	AM Study	API	Excipients	Remarks	Reference
	Controlled release of progesterone by vaginal rings of different shapes.		Polyethylene glycol (PEG), polycaprolactone (PCL), and polylactic acid (PLA).		
	Controlled release Acetaminophen tabs	Acetaminophen	Polylactic acid (PLA), Cellulose (EC/HPC/HPMC)/ Eudragit L100.	The printed tabs had a consistent appearance with the extended drug release property.	[218]
	Controlled Indomethacin Release Tabs	Indomethacin	Ethylene−vinyl acetate, Sodium chloride, Absolute ethanol, Purified water	The burst release of the drug was followed by a slow diffusion in the matrix.	[219]
	Controlled Deflazacort Release Tabs	Deflazacort	Poly(e−caprolactone) (PCL), Eudragit RL100 (ERL), mannitol (Channelling agent)	The prepared tablets had a partially hollow core (50%), a high drug loading (0.27% w/w) & faster drug release	[220]
	Controlled Paracetamol release tabs	Paracetamol	Hypromellose acetate succinate, Methylparaben, magnesium stearate	Prepared tablets had 20% infill capacity and different drug release rates were observed in different phases.	[221]
	Controlled Theophylline release tabs	Theophylline	Methacrylic polymers (Eudragit RL, RS, and E)/ HPC, Hydroxypropyl cellulose, Triethyl 110 citrate (TEC), Triacetin	The thermal analysis reported crystalline structure of theophylline and drug release rate was determined	[222]
	Thermal non−degradable and controlled release potent fluorescein tabs	Fluorescein	Polyvinyl alcohol (PVA), Absolute ethanol,	The prepared tablets were mechanically strong and no thermal degradation was reported. The controlled release profile was also reported.	[15]
	Controlled release Budesonide tablets	Budesonide	Polyvinyl alcohol, Eudragit L100, Cortiment, Entocort1 CR	The drug began its release in the middle of the small intestine and continued until the distal intestine and colon. Therefore, it has a controlled release ability.	[223]
	Controlled release Prednisolone tablets	Prednisolone	Polyvinyl alcohol, glycerol, acetonitrile, and methanol	The precision control of the drug ranged between 88.7% and 107%. Prednisone is present in amorphous form and the release could increase up to 24 h with the use of 3d printing.	[222]
	Modified release, 4 ASA and 5 ASA tablets	5−aminosalicylic acid (5 −ASA, mesalazine), 4 −aminosalicylic acid (4 −ASA)	Polyvinyl alcohol (PVA)	4 ASA tablets were degraded about 50% during the process, while on the other hand 5 ASA tablets were not degraded and were mechanically stable.	[224]
Laminated Object Modelling	Pelvis model manufacturing	−−−	Polyethylene tubercle	Pelvis model was prepared with equal proportion (1:1) to the patient's pelvis	[225]
Hot Melt Extrusion	Glass solution formation of poorly water−soluble drugs	Indomethacin, nifedipine, tolbutamide.	Polyvinylpyrrolidone (PVP), Vinyl acetate (VA)	A crystalline structure was detected, which indicated an incomplete melting point of the drug.	[226]
	Preparation of Nifedipine tablets by kneading the paddle element.	Nifedipine	Hydroxypropylmethylcellulose phthalate (HPMCP)	Kneading paddle elements of twin−screw extruders play a significant role in the transformation of the crystalline form to the amorphous form.	[227]
	Stability of Polyethylene oxide (PEO)in Chlorpheniramine Maleate tablets.	Chlorpheniramine Maleate	Polyethylene oxide (PEO).	The prepared tablets were sensitive to both temperature and screw speed.	[124]
	A starch−based formulation for preparation of Theophylline tablets	Theophylline	Starches and sugar alcohols	Sustained drug release was observed and no significant effect on water content and porosity was reported.	[228]
		17β−estradiol hemihydrate			[230]

(*continued*)

Table 2 (*Continued*)

Techniques	AM Study	API	Excipients	Remarks	Reference
	Stability determination of 17β−estradiol hemihydrate Tablets prepared by extrusion.		Estradiol, Polyvinylpyrrolidone (PVP), Sucroester WE15, magnesium stearate	The study was based on the preparation of 17β−estradiol hemihydrate tablets that do not recrystallize after extrusion as stability could decrease due to the recrystallization process.	
	On−demand warfarin release tablets	Warfarin	Eudragit E, triethyl citrate (TEC), acetonitrile, tricalcium phosphate (TCP)	Prepared tablets were dynamic and responses could be set according to patients' profile	[231]
	Non−destructive dose verification paracetamol tablets	Paracetamol	L−HPC, mannitol, magnesium stearate	The prepared drug has non−destructive property and rapid release property	[146]
	Controlled release Guaifenesin tablets	Guaifenesin	Hydroxypropyl methylcellulose, Polyacrylic acid, Carbopol NF, hydroxypropyl methylcellulose (HPMC)	The release rate of all formulations had an n−value between 0.27 and 0.44 thereby indicating the Fickian diffusion drug release pattern.	[167]
	Controlled release Acetaminophen tablets	Acetaminophen	Polyethylene glycol, polyvinyl acetate, and polyvinyl caprolactam, hydroxypropyl methylcellulose	The prepared drug showed a steady release rate (Zero order)	[232]
	Dapivirine releasing vaginal rings	Dapivirine	Thermoplastic polyurethanes PY−PT87AE (T87) and PY−PT60DE (T60), e isopropyl alcohol (IPA), acetonitrile (ACN), methanol, and acetone	Drug loading in the vaginal rings was convenient and the dose could be altered depending on the patients	[233]
Selective Laser Sintering	Oral disintegrated Ondansetron tablets	Ondansetron, cyclodextrin	Mannitol, Kollidon VA64, Candurin, Gold Sheen	Prepared tablets were formulated in cyclodextrin complexes and high conc. mannitol and possessed fast disintegration (15 s) and 90% of the drug was disintegrated in about 5 mins.	[151]
	pH dependent, Sustained release Paracetamol tablets	Paracetamol	Kollicoat IR, polyvinyl alcohol, polyethylene glycol copolymer, and Eudragit L100−55	The prepared drug was pH. dependent and with a complete release of approximately 12 h.	[147]
	Diclofenac sodium solid dosage 3d printed drug	Diclofenac sodium	Kollidon VA64, Lactose monohydrate, Candurin NXT Ruby Red	Prepared tablets possessed good mechanical stability, a high rate of integration and dissolution rates. No chemical reactions between components and crystalline structure were reported	[1]
	The drug release pattern of Progesterone tabs formulated with PCL	Progesterone	Polycaprolactone (PCL)	The drug release pattern was linear and possessed zero−order kinetics.	[234]
	Miniprintlet preparation consisting of Paracetamol & Ibuprofen	Paracetamol, Ibuprofen	Ethyl cellulose, Kollicoat Instant release (IR)	The prepared drug was very flexible and the drug content and release properties could be modified.	[145]
	Fabrication of polymeric drug delivery devices (DDD)	Methylene blue	Polyamide (PA), phosphate buffer solution (PBS)	The devices could retard and release the drug in a sustained manner.	[235]
Pressure−Assisted Microsyringe	Immediate release Levetiracetam tablets	Levetiracetam	Polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone−vinyl acetate	The prepared tablet had an API in the amorphous form which exhibited stability for 3 months.	[162]
	Pediatric dose Levetiracetam tablets	Levetiracetam	Polyvinyl alcohol−polyethylene glycol, Di−sodium hydrogen phosphate dihydrate, potassium dihydrogen orthophosphate	The prepared dosage form disintegrated quickly, facilitating use as a pediatric dose. Splitting the tablet into multiple layers led to less API concentration for pediatric patients.	[201]
	Sustained release of levetiracetam tablets	Levetiracetam	Polyvinyl acetate/polyvinyl pyrrolidone (PVAc−PVP), hydroxypropyl	The release rate could be controlled by the amount of polymer used and the	[178]

(*continued*)

Table 2 (*Continued*)

Techniques	AM Study	API	Excipients	Remarks	Reference
			methylcellulose (HPMC), silicon dioxide (SiO2)	drugs exhibited great mechanical stability.	
Direct Powder Extrusion	Fabrication of amorphous solid itraconazole dispersions	Itraconazole	HPC−UL (MW 20,000), HPC −SSL (MW 40,000), HPC −SL (MW 1,00,000) and HPC−L (MW 1,40,000).	Dispersions fabricated using HPC−UL (ultra−low MW) showed drug release faster than those of the other HPC grades.	[191]
	Preparation of 3DP tablets of amorphous solid dispersions for pediatric use	Praziquantel	Kollidon (KOL), Kolliphor SLS Fine, Acetonitrile.	Printlets showed improved performance in performance studies, along with acceptable taste thresholds.	[236]
	DPE of paracetamol−loaded mixtures via low thermal processing	Paracetamol (acetaminophen 98%)	Potato starch, Hydroxypropyl cellulose, Guar gum, Hydrochloric acid, Acetonitrile	The applicability of this mix for customized drug development at low temperatures and without the requirement for specific equipment was demonstrated.	[194]

as a promising solution for the latter. These AM techniques not only aid in rapid printing of medical devices and Personal Protective Equipments (PPEs), but also in monitoring and diagnosis of the pandemic and case fatality rates. These AM techniques thus aided a helping hand in overcoming the COVID−19 crisis by making these 3DP dosage forms, PPE kits, medical devices, theranostics, readily available to healthcare professionals across the globe within a short span. However, the downsides to the latter include the lack of thorough guidelines, approvals, and process designing challenges associated with the 3DP technique [237].

Nonetheless, these technologies may be exempted from the regulatory restraints in a hospital or a community pharmacy setting,

Table 3
Recent patents filed for formulating various pharmaceutical dosage forms utilizing AM Techniques.

Sr. No.	Patent Title	Organization, Country	Year	Patent ID
1	Encased tamper resistant controlled release dosage forms	Purdue Pharma L.P., USA	2021	US−10,966,932−B2
2	Oral drug dosage form comprising drug in the form of nanoparticles	Triastek Inc., USA	2021	US−10,973,767−B2
3	Abuse−resistant drug formulations with built−in overdose protection	Kashiv Biosciences, LLC, USA	2020	US−10,632,113−B2
4	Chewable gelled emulsions	Vitux Group As, USA	2020	US−10,668,013−B2
5	Lipid nanoparticle compositions and methods as carriers of cannabinoids in standardized precision−metered dosage forms	Nanosphere Health Sciences Inc., Australia	2020	AU−2,019,201,792−B2
6	Tofacitinib oral sustained release dosage forms	Pfizer Inc., USA	2020	US−10,639,309−B2
7	Apparatus and process for encapsulating capsules or other solid dosage forms within capsules	Procaps S.A., USA	2019	US−10,383,826−B2
8	Gastric reflux resistant dosage forms	Patheon Softgels Inc., USA	2019	US−10,182,990−B2
9	Multi−phase soft gel capsules, apparatus and method thereof	Catalent Ontario Limited, Australia	2019	AU−2,018,275,028−B2
10	Oxidation−stabilized tamper−resistant dosage form	Grünenthal GmbH, USA	2019	US−10,493,033−B2
11	Small volume oral transmucosal dosage forms containing sufentanil for treatment of pain	Acelrx Pharmaceuticals Inc., USA	2019	US−10,507,180−B2
12	Small−volume oral transmucosal dosage forms	Acelrx Pharmaceuticals Inc., USA	2019	US−2,020,022,918−A1
13	Zero−order modified release solid dosage forms	SpecGx LLC, USA	2019	US−2,019,358,164−A1
14	Capsule pharmaceutical dosage form comprising a suspension formulation of an indolinone derivative	Boehringer Ingelheim International Gmbh, USA	2018	US−9,907,756−B2
15	Coated particles and pharmaceutical dosage forms	Lek Pharmaceuticals D.D., USA	2018	US−9,907,757−B2
16	Dosage form containing oxycodone and naloxone	Purdue Pharma L.P., USA	2018	US−2,018,008,593−A1
17	Gastric retentive pharmaceutical compositions for treatment and prevention of CNS disorders	Depomed, Inc., USA	2018	US−9,937,142−B2
18	Modified release dosage forms of xanthine oxidoreductase inhibitor or xanthine oxidase inhibitors	Takeda Pharmaceuticals U.S.A., Inc., USA	2018	US−9,937,157−B2
19	Process for manufacturing chewable dosage forms for drug delivery and products thereof	Bayer B.V., Australia	2018	AU−2,015,203,843−B2
20	Uniform films for rapid dissolve dosage form incorporating taste−masking compositions	Monosol Rx, LLC, USA	2018	US−9,931,305−B2
21	Dosage forms for administering combinations of drugs	Pozen Inc., USA	2017	US−9,801,827−B2
22	Dosage forms for oral administration of zoledronic acid or related compounds for treating disease	Antecip Bioventures Ii LLC, USA	2017	US−9,616,078−B2
23	Dual drug dosage forms with improved separation of drugs	Depomed, Inc., USA	2017	US−9,572,780−B2
24	Pharmaceutically acceptable solubilizing composition and pharmaceutical dosage form containing same	AbbVie Deutschland Gmbh & Co Kg, USA	2017	US−9,616,130−B2
25	Amphipathic lipid−based sustained release compositions	Pegasus Laboratories, Inc., USA	2016	US−9,248,096−B2
26	Immediate release composition resistant to abuse by intake of alcohol	Egalet Ltd., USA	2016	US−9,358,295−B2
27	Modified release dosage forms of skeletal muscle relaxants	Adare Pharmaceuticals, Inc., USA	2016	US−9,399,025−B2
28	Oral dosage form comprising a therapeutic agent and an adverse−effect agent	Purdue Pharma L.P., USA	2015	US−RE45822−E
29	Pharmaceutical composition simultaneously having rapid−acting property and long−acting property	Yungjin Pharm Co., Ltd., USA	2015	US−9,180,101−B2
30	Abuse−resistant oral dosage forms and method of use thereof	Elite Laboratories, Inc., USA	2014	US−8,703,186−B2

where these prescriptions are compounded on demand for special patient cohorts including, geriatric, pediatric or patients with special prescription requirements, like those allergic or intolerant to the certain APIs or excipients (e.g. Lactose intolerance). These 3DP techniques also find utility in the on−demand manufacture of personalized dosage formulations in both pre−clinical and clinical settings. Although these impediments limit the applicability and acceptance of these 3DP techniques, addressing these issues ensures the future implementation of these novel techniques [138].

Additionally, when it exerts a profound effect on the health of patients, there are several regulatory, quality control, and technical facets that need to be addressed, before the bulk manufacturing of these dosage forms. These may also include the addressing of a pandora box that may include a thorough understanding of the variables and controls in the process, the unavailability of cGMP compliant 3D printers, the unavailability and/or affordability of the cleaning techniques, a quality assurance team with prior knowledge of the analysis and quality control of 3DP variables, and an expert formulation team for the formulation and characterization of pharmaceutical dosage forms.

Therefore, while 3DP is opined to have a bright future, a substantial amount of groundwork may be needed to assist patient care and meet the therapeutic targets linked with personalized medicine.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

CRediT authorship contribution statement

Ryan Varghese: Conceptualization, Resources, Data curation, Writing − original draft, Writing − review & editing, Visualization, Project administration. **Sahil Salvi:** Writing − original draft, Writing − review & editing, Visualization. **Purab Sood:** Writing − original draft, Writing − review & editing, Visualization. **Jainam Karsiya:** Writing − original draft, Writing − review & editing, Visualization. **Dileep Kumar:** Resources, Supervision, Project administration.

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