Challenges & OPPORTUNITIES

for the adoption of 3D printing technologies in Pharmaceutical Industry: An overview of additive manufacturing techniques, the case for Fixed-Dose Combinations.

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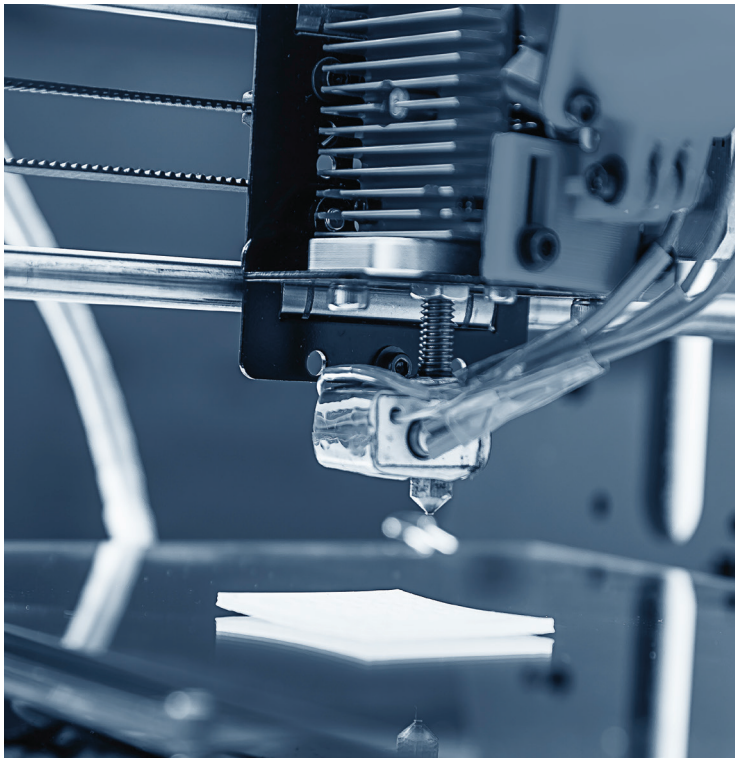


Non-adherence of chronic patients to medication regimens is a highly prevalent and critical issue that results in an unsustainable economic burden to health systems worldwide **[1].** For instance, it has been proven that the higher the patient adherence to medication, the lower the health spending in type 2 Diabetes Mellitus (T2DM) patients, decrease the total health spending by 1074 USD per patient **[1],** which could lower the burden on public healthcare systems due to the high prevalence for T2DM. However, The National Council on Patient Information and Education estimates an approximate compliance rate of just over 30% for Diabetes and Cardiovascular diseases **[2].** While several factors influence medication adherence, treatment complexity is directly related to adherence in chronic conditions like Hypertension and Diabetes **[3].** These pathologies are often treated with combination therapies, and it is not uncommon for individuals to be prescribed over five different types of medicines daily due to their chronic conditions **[4].**

Fixed-dose combinations are the preferred approach to simplify the disease management for chronic diseases (e.g., HIV, asthma, diabetes, lipid regulation, hypertension) by reducing the number of dosage intake and improving efficacy through the synergistic effect of active compound's mechanisms of action **[5]–[7].** Conversely, fixed-dose combinations can offer a more cost-effective therapeutic option than monotherapy by reducing manufacturing, packaging, and distribution costs and may serve as a viable strategy for patent life cycle management **[8].** Although there are some approaches for the design and manufacturing of Fixed-Dose combinations, multilayer tablets are the most common dosage design for administering incompatible pharmaceutical compounds in a single dosage due to the inherent flexibility in terms of release profiles and dissolution modes that can be incorporated into the tablet layers **[9].** However, the fabrication of multilayered tablets introduces various adhesion

integrity **[10]** is a clear example of such issues during different value chain stages. It is generally caused by capping or delamination at the interface of the two layers **[11].** Depending on formulation design and process control, weak interfacial planes are formed during tablet compression, leading to an increase in fracture susceptibility in specific tablet mechanical stress conditions during fabrication, packaging, or transport **[12], [13].** Product recalls might result in financial losses to pharmaceutical companies, and product defects could also significantly affect patient adherence to medication. Besides, current process technologies for multilayer tablet manufacturing demand for additional controls (independent weight and force control, quality defects) to ensure high-quality final product, whereas final yields are closer to 85% in contrast to state-of-the-art tablet presses equipment where reported efficiencies are higher than 99% for conventional single-layer tablets **[14]–[16].** In addition to manufacturing issues, the inherent lack of dosing flexibility of multilayered tablets for Fixed-Dose combinations could affect patient adherence, as for increasing such dose flexibility demands a larger number of presentations to maintain, for cases in which the prescriber requires to adjust dosing in one of the active compounds **[17].** Hence, product design in Fixed-Dose combinations is focused on covering the requirements general population, rather than adjusting to personalized requirements for specific patients **[5].**

Additive Manufacturing or 3D-Printing includes a wide range of process technologies that enable creating three-dimensional structures layerwise from 3D digital designs **[18], [19].** Pharmaceutical Additive Manufacturing technologies emerge as a promissory and effective solution to address some of the issues related to Polytherapies in chronic patients since it allows manufacturing advanced drug delivery systems and complex/sophisticated three-dimensional dosages in a single operation that achieve personalization in terms of release profiles and dosage strengths without further machine adjustments **[20], [21].** Spritam® from Aprecia Pharmaceuticals is the first 3D-printed FDA-approved pharmaceutical product, a significant milestone for additive manufacturing technologies adoption in the pharmaceutical industry. As reported by **[22],** Spiritam® is based on the ZipDose® technology platform, allowing fabricating tablets with a total disintegration time between 4 to 11 seconds. Other advantages of additive manufacturing technology adoption in the pharmaceutical industry include patient-centric therapy/personalized medicine **[20], [23],** on-demand manufacturing **[20], [21],** and low capital/operation costs compared to traditional processes **[23].** Nevertheless, widespread adoption of Additive Manufacturing technologies in the Pharmaceutical Industry remains to be seen.

This work aims to show an overview of recent academic works regarding the implementation of Additive Manufacturing to develop Pharmaceutical Products, particularly the design and manufacturing of dose combinations products for chronic patients. At first, a brief review of research works for Pharmaceutical Additive Manufacturing according to the standard proposed by ASTM is presented, with special emphasis on the fabrication of oral dosage, focusing on their benefits and suitability for Dose-combination product's manufacturing. Additional comments related to technical issues facing different 3D printing technologies for Dose combinations manufacturing will be provided.

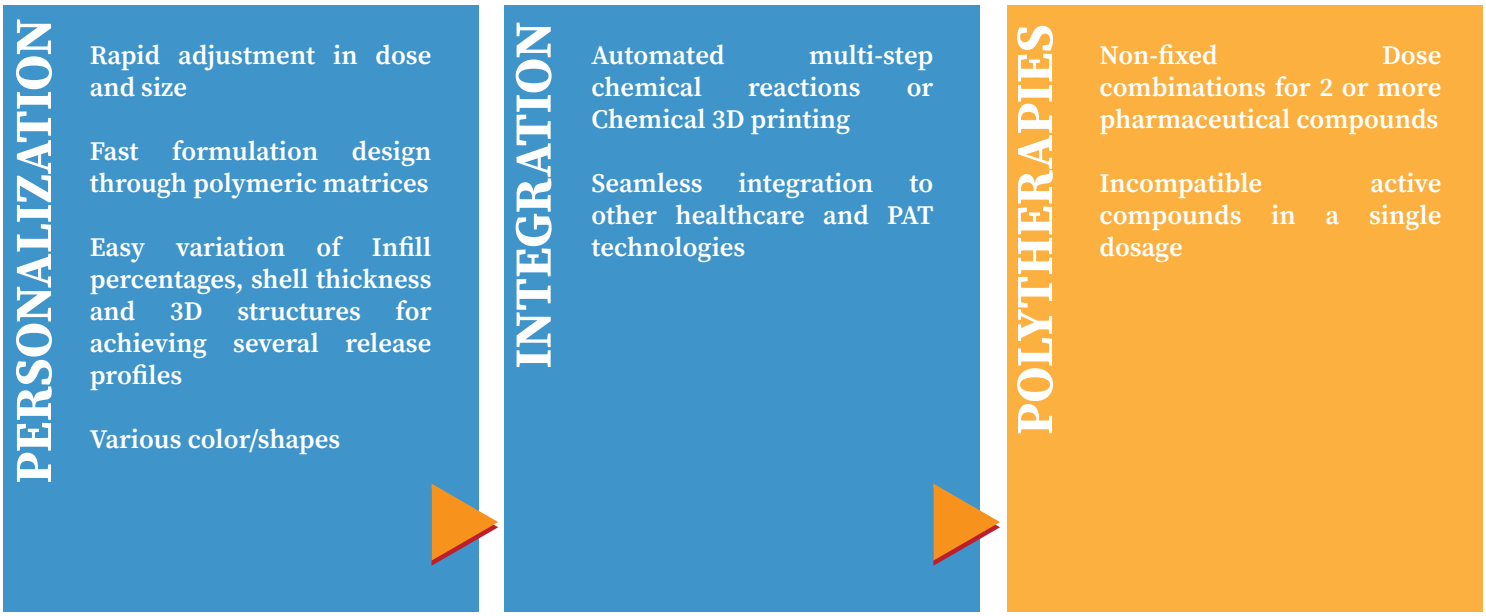
2. Additive Manufacturing as an ALTERNATIVE TECHNOLOGY

for oral dosage fabrication in the Pharmaceutical Industry

While the AM technology adoption in the Pharmaceutical Industry for manufacturing oral dosages is still in its infancy, the current use of 3D printing techniques in medicine is quite diverse, going from drug delivery implant devices to tissue regeneration. Medicine applications for 3D printing with higher technology adoption levels include personalized hearing aids and dentistry [24]. Despite its slow introduction to the market, there are primary incentives for AM in the pharmaceutical industry. At first glance, the personalization of dosing and shape appears as an attractive technical feature that could offer feasible solutions to the personalized medicine

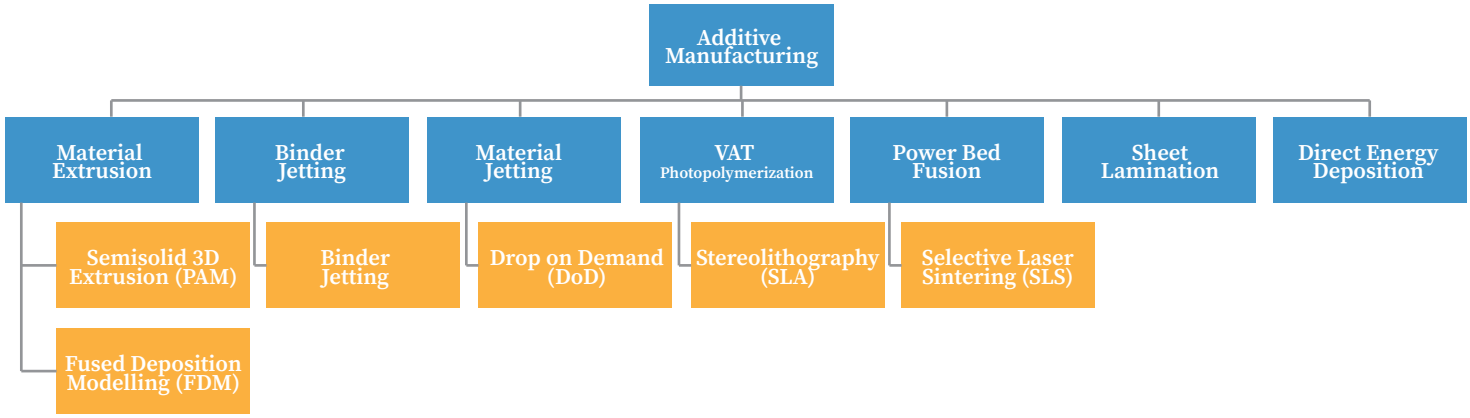
field [25]. Nevertheless, the level of personalization for 3D printed oral dosages goes beyond if it is considered that these technologies enable the fabrication of complex three-dimensional structures and the fine-tuning of polymeric matrix composition; thus, providing a simple and elegant solution to composite and tailored release profiles. Further benefits are shown in Figure 1.

Figure 1: Benefits derived from the adoption of AM Technologies in the Pharmaceutical Industry.



Stereolithography was the first Additive Manufacturing technology developed for generating solids layer by layer from instructions generated by Computer-Aided-Design. The main application was Rapid Prototyping, as disclosed in the patent titled "Apparatus for production of three-dimensional objects by stereolithography" [26]. This patent disclosed a "new and improved system for generating a three-dimensional object by forming a successive, adjacent, cross-sectional lamina of that object at the surface of a fluid medium capable of altering its physical state in response to appropriate synergistic stimulation, the successive laminae being automatically integrated as they are formed to define the three-dimensional object." By applying the layerwise construction principle, several technologies have been developed in the last 30 years. In 2010 the ASTM F42 Committee suggested a standard for the classification of Additive Manufacturing processes depending on the materials and machine technologies [27], AM technologies can be grouped in 7 technology families shown in Figure 2. In this section, a review of Additive Manufacturing technologies for oral dosage fabrication in the Pharmaceutical context, according to ASTM F2792 Standard, is presented.

Figure 2: Benefits derived from the adoption of AM Technologies in the Pharmaceutical Industry.



2.1 MATERIAL EXTRUSION

Semisolid 3D Extrusion

Semisolid 3D extrusion

The process uses a semisolid (paste) formulation composed of multiple materials such as polymers and hydrogels. Feed rate, line spacing, layer thickness, and extrusion pressure distance between the nozzle tip and substrate are critical process parameters that can be adjusted to settle the design space for pharmaceutical formulation printing. Proof of concept for manufacturing bi-layer guaifenesin tablets for immediate and extended-release profiles in a single dosage was reported by [28], demonstrating the process capabilities for release profile control achieving weight variation, thickness, hardness, and friability within the limits of USP specification. Hydroxypropyl methylcellulose and poly-acrylic acid were the hydrophilic matrix materials in the sustained release layer, using hypromellose as a binder while microcrystalline cellulose and sodium starch glycolate were the disintegrants for the immediate release layer. Further advances focused on incorporating multiple active compounds in a single dosage were reported by [29], achieving compliance in weight variation and content uniformity for the combination of captopril osmotic drug delivery and nifedipine/glipizide sustained release multi-compartment tablets. Intermediate layers in tablet design avoided physicochemical interactions between the active compounds. This technology feature was exploited in later research where the fabrication process of a 3D printed polypill (atenolol, pravastatin, ramipril, ASA, and hydrochlorothiazide) was disclosed having sustained and immediate release profiles with no interaction between drug-loaded compartments. Printed dosages achieved content uniformity and weight variation within USP Pharmacopeia limits [30].

c3. Filament incubation on alcoholic solutions [42]–[45], single screw hot-melt filament extrusion [32], [33], [36], [39], [46]–[50] and twin screw hot-melt filament extrusion [35], [37], [56], [57], [38], [40], [41], [51]–[55] the main filament fabrication processes. Drug loading by incubation is a process governed incubation is a process governed by the mass diffusion from the ethanolic solution to the polymer filament external surface, and therefore larger incubation times and low drug-loading have been reported. Table 1 shows a summary of research publications using this filament fabrication technology, where drug loadings between 0.06 %w/w to 1.9 %w/w are achieved, and the use of FDM-printable polyvinyl alcohol is predominant.

Figure 3: Schematic representation of Hot Melt Extrusion + Fused Deposition Extrusion based printing process.

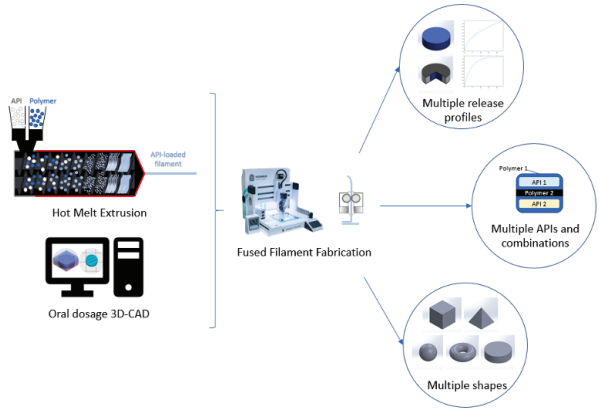


Table 1 Drug loading by incubation on alcoholic solution FDM 3DP-based process related publications.

Ref	API	BCS CLASS	POLYMER	DRUG LOADING	RELEASE PROFILE
[43]	Fluorescein	I	PVA	0.29 %/w/w	Sust. Release
[42]	4-ASA	I	PVA	0.29 %/w/w	Sust. Release
	5-ASA	IV	PVA	0.29 %/w/w	Sust. Release
[44]	Prednisolone	I	PVA	0.29 %/w/w	Sust. Release
[45]	Curcumin	II	PVA	0.29 %/w/w	Sust. Release

A report for materials and drug concentrations in printed tablets in research output related to filaments fabricated by Single-Screw Extrusion is shown in table 2. While a significant improvement is observed (drug-loadings between 4.3%w/w – 9.5%w/w), low concentrations are reported for pharmaceutical filaments manufactured by Single Screw Extrusion technology, mainly attributed to poor mixing capabilities [32]. Various insights such as thermal

degradation due to high printing temperatures [58], and CPP effect on 3D-printed tablet properties [39] have been disclosed in Single-Screw Extrusion related publications; nonetheless, the development of controlled-release tailored drug delivery systems is also reported, including enteric gastro-resistant tablets [33], orodispersible dosage forms [50], [59], near-zero order release systems [47], and extended-release "DuoTablet" designs [46].

Table 2. Summary of FDM-3D printing research output with filament fabrication by Single-Screw Extrusion technology.

REFERENCES	ACTIVE COMPOUNDS	BCS CLASS	POLYMERS	DRUG-LOADING	RELEASE PROFILES
[33]	Budesonide	II	PVA	4.1%w/w	Delayed - Release
[38]	Paracetamol	III	PVA	3.95%w/w	Sustained - Release
[39]	Paracetamol	III	PVA	4.7%w/w	Controlled - Release
	Caffeine	I	PVA	9.5%w/w	Controlled - Release
[47]	Hydrochlorothiazide	II	PVA	2.79%w/w	Near-Zero Order Release
[49]	Paracetamol	III	HPMCAS	50%w/w	Delayed - Release
[46]	Glipizide	II	PVA	4.8%w/w	Sustained - Release

A wide range of pharmaceutical polymers (Eudragit, HPC, HPMC, Soluplus, Kollidon, Ethyl Cellulose) has been explored as polymer matrices in FDM 3D printed tablets using twin-screw extruding for filament fabrication [60]. The use of Twin Screw Extrusion (TSE) technology for filament fabrication can improve the mixing efficiency and the extrudate homogeneity due to the intense mixing related to short inter-screw mass transfer distances, and small residence times can reduce thermal degradation in heat/shear sensitive formulations due to the low time of exposure to high temperatures [61]. Both co-rotating and counter-rotating intermeshed TSE are reported in the stated of the art for filament fabrication [35], [62]–[66].

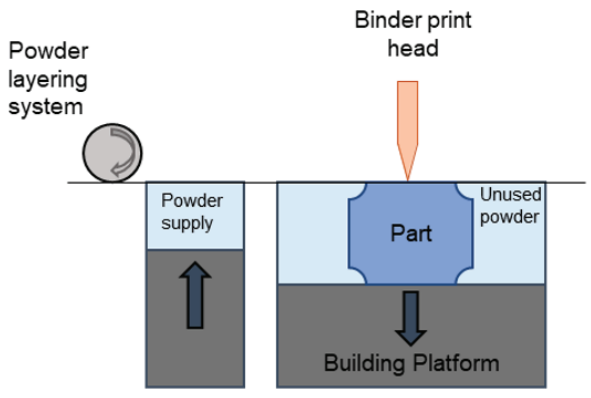
Table 3. Summary of FDM-3D printing research output with filament fabrication by Twin-Screw Extrusion technology.

REFERENCES	ACTIVE COMPOUNDS	POLYMERS	MAXIMUM DRUG-LOADING	RELEASE PROFILES
[51]	Theophylline	Eudragit RL, RS, and E Hydroxypropyl cellulose	40%	Extended-Release
[40]	Indomethacin	EVA Copolymers	15%	Extended - Release
[37]	Felodipine	Eudragit EPO Soluplus	10%	Immediate - Release Extended - Release
[35]	Acetaminophen	Kollicoat PEO HPC HPMC PVA	30%	Immediate Release Extended - Release
	Furosemide	Soluplus Ethyl Cellulose Eudragit R and L		Delayed - Release
[38]		HPMCAS Eudragit	12.5%	Immediate - Release
[67]	5-ASA Captropil Prednisolone Theophylline		20%	Immediate - Release
[68]	Haloperidol	Kollidon HPMC	60%	Extended - Release
	Theophylline	Thermoplastic Polyurethane		
[57]	Metformon HCl		24%	Extended - Release
[69]	Ibuprofen	Ethyl Cellulose	9.4%	Extended - Release
	Domperidone	HPC		
[41]		HPC - BaSO4	30%	Delayed - Release
[54]	Acetaminophen	Eudragit and PVP	10%	Zero - Order Release
	Acetaminophen	HPMC Soluplus		

2.2 BINDER JETTING

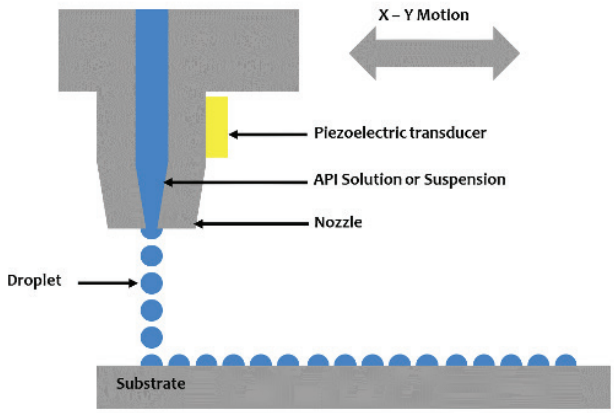
Binder Jetting 3D-printing is a technology in which a drug-loaded formulation in solution is dispensed onto a powder material layer. In some cases, the solution is used to bind particles inside the powder bed; another possible use is to carry the active compound in a liquid solution, suspension, or slurry form [70]. Binding solution solidification, particle joining through solvent evaporation, and adhesive substance action are the main particle binding mechanisms present in the powder bed [71]. The three-dimensional structure is generated by selectively binding specific portions in the powder layer and repeating this process in new powder layers generated when the piston, powder bed, and part are lowered [70], [72]. This sequence is shown in Figure 4. The TheriForm® technology is a licensed application from the original Binder Jetting 3D printing MIT patent [73]. The license covers various aspects associated with applying 3D printing technology to the development and manufacturing of drug delivery devices. While there is an important volume of research related to Binder Jetting technology in pharmaceutical applications [71], [74]–[76], the main milestone for Binder Jetting and Additive Manufacturing technologies in general for Pharmaceutical applications came with the launch of Spiritam® from Aprecia Pharmaceuticals, which was the first 3D-printed FDA-approved pharmaceutical product. As reported by Aprecia [22], Spiritam® is based on the ZipDose® technology platform, which allows fabricating tablets with a total disintegration time between 4 to 11 seconds up to 1000 mg/dose.

Figure 4. Schematic representation of the Binder Jetting 3D printing process.



Spatial dosing control capabilities have been exploited to develop controlled-release zero-order kinetic drug delivery systems with Binder Jetting 3D printing technology. [71] fabricated oral dosage forms composed of an immediate release core of pseudoephedrine hydrochloride and a release regulating shell. A similar approach was implemented to design a Paracetamol drug delivery device with a linear release profile in [75], introducing variations on dimensional characteristic and local material drug concentrations to doughnut-shaped tablets. The method reported by [76] utilizes a similar approach for achieving near zero-order release profiles, restraining the erosion mechanism into the radial direction by building the top and the drug-free bottom sections, but dispensing the active compound inside the powder bed mixture for achieving higher drug loadings. The zero-order release profile was attempted by gradually decreasing the concentration of release-modulated materials from the periphery to the center of the tablet dispensing the binder liquid a prescribed number of times onto certain annular regions in the powder layers.

Figure 5. Schematic representation of the material Jetting printing process.



2.3 MATERIAL JETTING

Drop on solid inkjet printing or Material Jetting allows for an accurate drug dosing and release profile control through solid-state surface microstructure adjustment. Similar to the binder jetting process, this technology uses an inkjet

printhead for controlling the API-based ink solution ejection towards an edible porous solid substrate, as shown in Figure 6. While several works focused on proof of concept technology development stages [77]–[82], some reported attempts to increase the technology readiness level for launching a drop on solid-manufactured products into the market. Such is the case of Glaxo Smith Kline [83], whose efforts for launching pharmaceutical products based on Material Jetting technology platform (LDT – Low Dose Technology) includes a complete manufacturing platform for different production scales and several compounds in development up to phase IIb, including the successful development for over 15 compounds [83]. Earlier stage developments include orodispersible drug delivery systems based on the drop on solid technology, as reported by [84], [85] for Rasagiline Mesylate, and Sodium Picosulfate model drugs respectively. Also, the application of piezoelectric inkjet printing for manufacturing microparticles containing the anticancer drug Paclitaxel and PLGA polymer; with different geometries (circles, grids, honeycombs, and rings) was reported by [86].

2.4 PHOTOPOLYMERIZATION

The synergistic stimulate referred in the original patent for Stereolithography or VAT Photopolymerization process referred into the patent of Charles Hull [26] is laser energy of a specific frequency, and the "fluid medium capable of altering its physical state" is a photo-polymeric resin that is cured during the printing process. In Stereolithography, laser energy is influenced by the exposure time, polymer and photoinitiator concentration, and the printing speed. The lack of GRAS photocrosslinkable polymers has directed authors towards improving the SLA manufacturing process using non-pharmaceutical materials. The drug content effect was significant on Paracetamol, and 4-ASA SLA printed tablets release profile reported by [87]. Tablet formulation was composed of PEG 300 and polyethylene glycol diacrylate (PEGDA) as monomers and diphenyl (2,4,6-trimethyl benzoyl) phosphine oxide as the photoinitiator. This effect is associated with the rise in molecular mobility generated by the increased proportion of the polymer PEGDA in the core formulation. A different approach for controlling the release profile was followed by [88], adjusting water concentration on ibuprofen-loaded hydrogels of crosslinked PEGDA, and using Riboflavin and Thioethanolamine as photoinitiator and co-initiator respectively. Besides release controlling techniques through material formulation approaches, additional methods for reducing photopolymer consumption has been implemented, usually by integrating SLA to other additive manufacturing techniques. For example, [89] developed a 3D inkjet-based resin dosing method that uses UV photoinitiation in a low oxygen concentration environment for fabricating extended-release Ropinirole HCl tablets. During in vitro dissolution test, the dosage forms remain intact, indicating a diffusion transport mechanism for drug release, achieving 89% of Ropinirole HCl released in four hours. An important remark of this study is the evidence of drug degradation with a 3% mass loss in the printing process, which could be attributed to drug exposure to UV light, free-radicals, or water, as stated by the authors. [90] developed a process that integrates a semisolid 3D extrusion technique to the SLA process to overcome this issue. The Prednisolone/Polydimethylsiloxane/Platinum Catalyst formulation was fed into the syringe of a desktop extrusion-based 3D printing, and crosslinking of PDMS was achieved by exposing the 3D printed dosage to UV light. The drug release rate was controlled by altering the dosage geometric configuration.

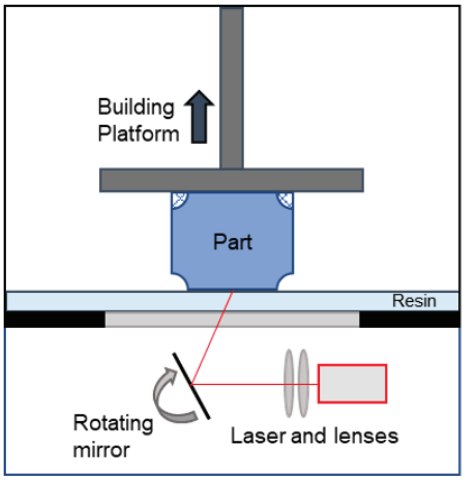
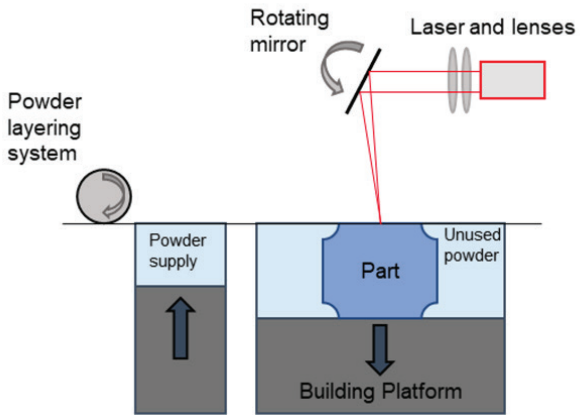


Figure 6. Representative scheme of Stereolithography Printing process

2.5 POWER BED FUSION

Selective Laser Sintering is a Laser-Based Additive Manufacturing technique that employs a high-power laser beam for selectively sinter two-dimensional zones in multiple layer configurations for generating a 3-dimensional object. This process is similar to the Binder Jetting technique, with the main difference that the particle bonding mechanism between them comes from the laser energy selectively directed to the powder bed. SLS is a solvent-free process; therefore, it does not require an additional drying stage. Figure 7 shows a schematic of the tablet SLS 3DP process. [91] investigated the potential application of the technology for fabricating Paracetamol tablets with where two pharmaceutical-grade polymers, Kollicoat® IR and Eudragit® L. As preliminary tests indicated that no sintering effect was achieved in Kollicoat/Eudragit/Paracetamol formulations, 3% candurin® gold sheen, an approved pharmaceutical excipient used for tablet coating processes, was added to improve the formulation absorbance at the specified wavelength increasing powder printability. A significant effect of API concentration on internal and external porosity was found by X-ray micro-computed tomography analysis. Further research for SLS manufacturing of Paracetamol fast dissolving tablets was reported by [91], achieving a 4 second disintegration time for a formulation composed of 92% Kollidon, 3% Candurin®, 5% paracetamol with 80°C chamber temperature, 100°C surface temperature, 300 mm/s laser scanning speed.

Figure 7. Representative scheme of Selective Laser Sintering Printing process



2.4 DRAWBACKS AND ADV FOR ADDITIVE MANUFACTURING TECHNOLOGIES IN THE PHARMACEUTICAL SECTOR

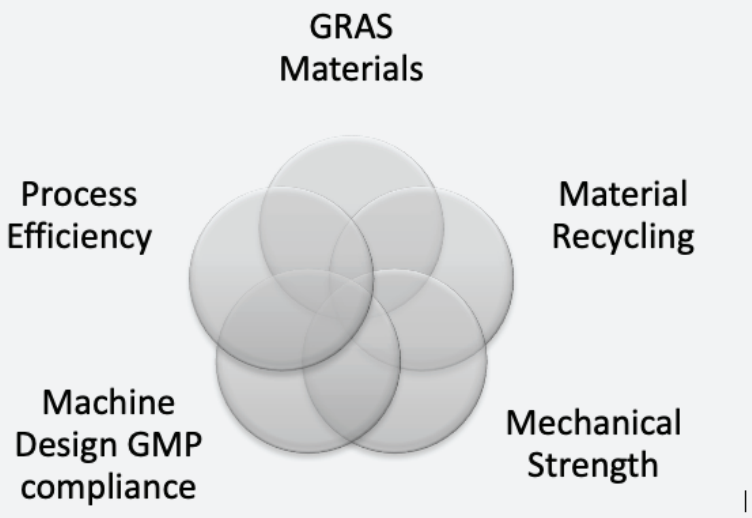
While several competitive advantages can be related to AM technologies in Pharmaceutical Industry, some regulatory and technical challenges need to be addressed for widespread technology adoption, some of which are shown in Figure 8.

The pharmaceutical processes require the use of safe materials approved for human consumption. Despite the need for pharmaceutically-suitable materials was satisfied by formulating traditional polymers for increasing their processability in different AM processes, there is still a requirement for developing new GRAS materials with optimum thermophysical properties that allow to formulation scientist to develop new value propositions for patients. For instance, in the Stereolithography process, most currently used photopolymers are potentially carcinogenic. The photochemical layer formation process is highly susceptible to producing free radicals, introducing product stability issues due to potential interactions between the active compound and the photopolymer [92]. On the other hand, thermo-labile active compounds can be challenging in the Fused-Deposition Modeling process as many of the polymeric matrices requires processing temperatures higher than the active compound degradation temperature [93], exhibiting a reduction in printed tablets drug-loading. Also, there is a requirement non-degradable polymeric materials in the Selective Laser Sintering process, due to potential degradation issues derived from thermal effect laser directed energy or bed warming [94].
Technologies such as Stereolithography, Selective Laser Sintering, and Binder Jetting have an unbounded material excess derived from the layer formation process, which requires

strategies to minimize material consumption that includes material recycling and material dosing. Nevertheless, the reuse of non-processed material in the Pharmaceutical Industry context can be challenging because of the quality compliance requirements. It can significantly affect the dosage form mechanical properties, degradation products, and release profiles of printed dosages considering that changes are introduced in particle size distribution when the coalescence effect is presented in the unbounded bed material for the Selective Laser Sintering and the Binder Jetting processes. Besides, preheating the bed material in the SLS process for avoiding quality defects on printed parts can exert a negative effect on its physicochemical properties and solid-state microstructure [94]. On the other hand, potential interaction with active compounds and photopolymer reaction intermediates could be present in non-used resins for the Stereolithography process [95][96]. As an attempt to circumvent these issues, Aprecia Pharmaceuticals presented a patent application for a Binder Jetting 3D printing process in which the binding solution is printed within a portion of the packaging, thus eliminating the presence of unbound powder from the bed and integrating fabrication and packaging in one single step [97]. Besides, printing directly on the package alveolate prevents printed tablets from being subjected to dynamic mechanical loads during the primary packaging process, a feasible alternative for Binder Jetting and SLS processes. Hardness and mechanical resistance are inferior to direct compression and material extrusion printing processes [96].

The biggest hurdles to widespread Additive Manufacturing adoption in Pharmaceuticals are related to Throughput and GMP equipment compliance. The production efficiency in the state of the art tableting equipment cannot be compared to pilot scale 3D printing pharmaceutical equipment. Even though AM technologies are suitable for personalized medicine applications taking distance from the one-size-fit-all traditional approach, further research is required to increase manufacturing process speed. 3D printing machinery was not initially intended for the GMP environment, in which special considerations must be taken into account for pharmaceutical product compliance. First, establishing suitable criteria and mechanisms for product collection, individual and whole batch product rejection must be established in a pharmaceutical process line to ensure the desired product quality profile. Also, the definition of standard operating procedures and process controls for deviation management must be established to identify batch sections impacted during deviation events. The integration of failure detection techniques through inline Process Analytical Technologies should be the object of further research. The integration of cleaning and maintenance considerations to pharmaceutical equipment design is clear in CFR 21 Part 211 Section 63. Product design must facilitate such cleaning and maintenance operations, and product contact surface materials must ensure product compliance in terms of Critical Quality Attributes.

Figure 8. Technical and regulatory challenges to widespread adoption of Additive Manufacturing technologies in Pharmaceuticals



While there are several technical challenges in GMP compliance for pharmaceutical additive manufacturing equipment, a process innovation trend can be observed in the last ten years. Figure 9 shows the growth trend in the number of cumulative patent documents and main assignees related to patents for machinery or apparatus related to additive manufacturing. Aprecia Pharmaceutical leads the ranking for Organizations with most patent documents in the B33Y30/00 IPC category holding 56% of patent documents in the top 9, with an arrangement of 3D printing technologies based on binder jetting technique designed for a pharmaceutical environment. Triastek Inc owns 9% of patent documents in the ranking with material extrusion-based 3D printing technologies that allow fabricating flexible-design controlled-release oral dosage forms, integrating filament fabrication and tablet printing in a single process stage. Despite showing signs of declining in recent years, there is a rise in the number of patent documents related to pharmaceutical AM machinery from 2015 to date, which shows tech companies' efforts to provide diverse technical solutions.

Figure 9. Growth trend and Top Patent Assignee for Pharmaceutical 3D printing patent documents related to apparatus for a dditive manufacturing (or B33Y30/00)

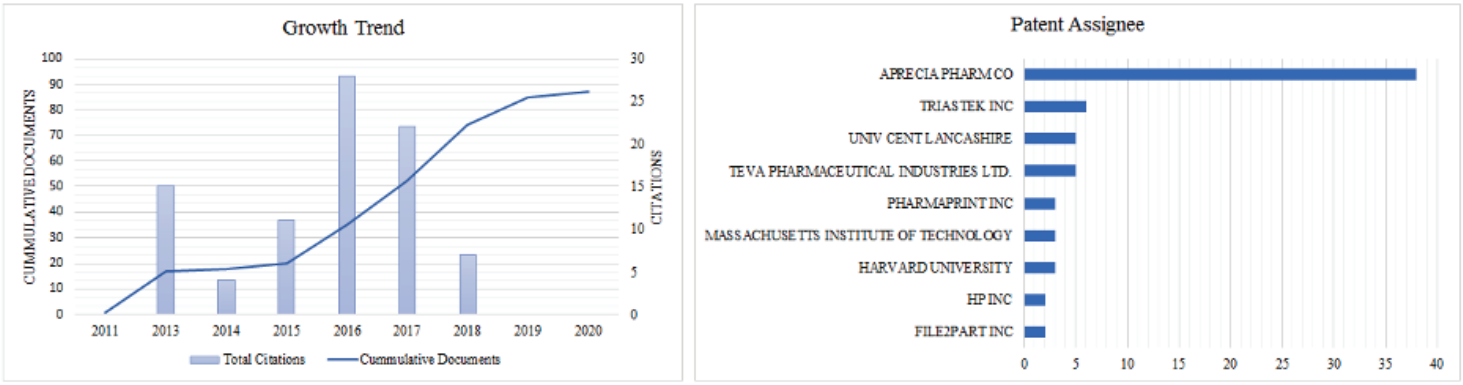
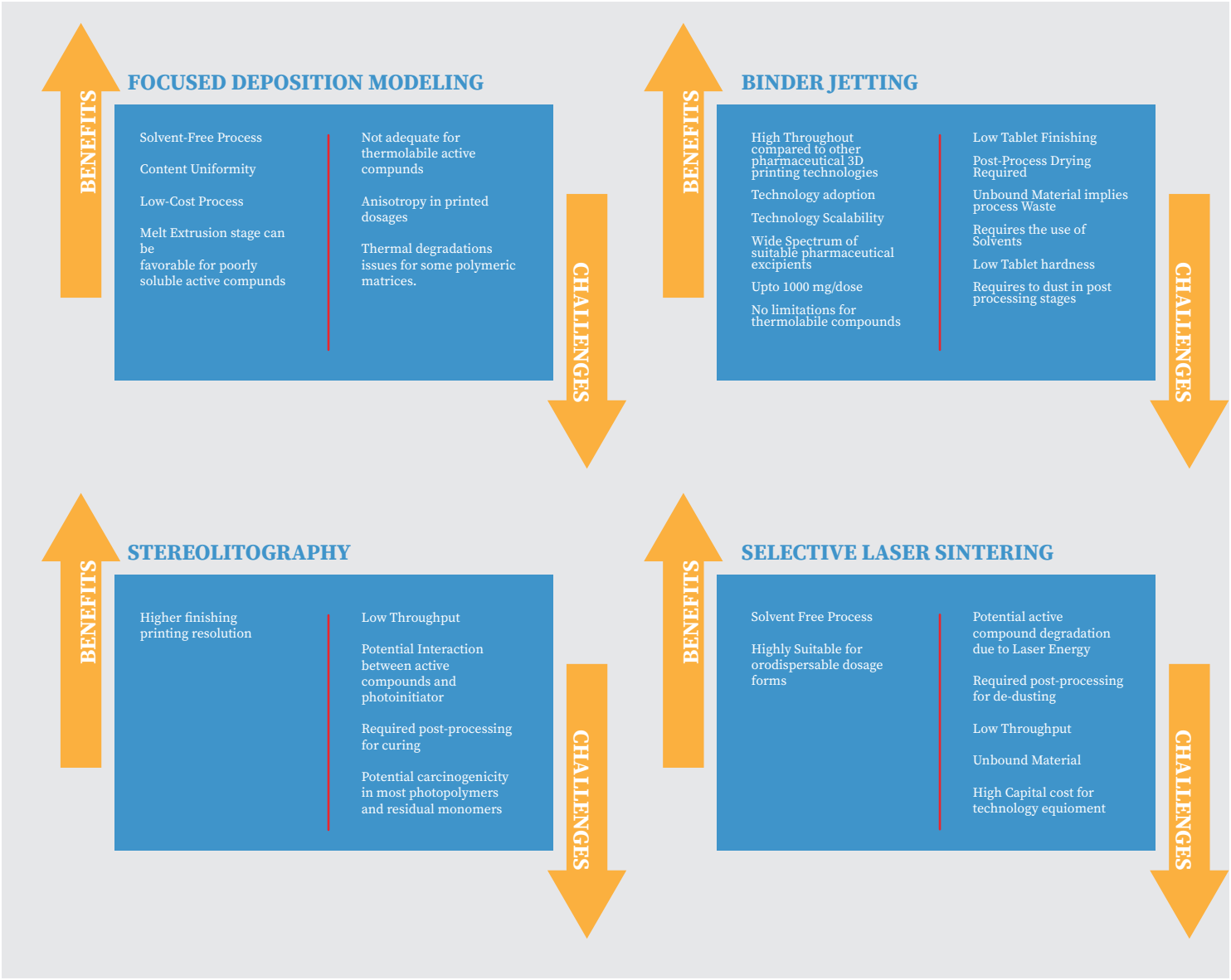


Figure 10 shows a comparative analysis showing benefits and challenges for Material extrusion (Fused Deposition Modeling), Binder Jetting, Vat Photopolymerization (Stereolithography), and Powder bed fusion (Selective Laser Sintering) additive manufacturing technologies. Fused Deposition Modeling and Binder Jetting technologies are frequently encountered in academic research and patent documents, respectively, mainly due to the low cost for FDM machinery and the wave of process innovation introduced by Aprecia Pharmaceuticals in Binder Jetting-based technologies related to higher process scalability and productivity. Also, the FDM technology allows the formulation of amorphous solid dispersions in the melt extrusion stage, which could be convenient for improving shelf stability, enhancing the dissolution and oral bioavailability of poorly soluble active compound solvent-free drug formulations [98]. Nonetheless, the high temperatures required for the extrusion process and the low manufacturing speed are the most challenging barriers.

The Stereolithography technique produces the best finishing for AM technologies available in pharmaceutical applications. Nevertheless, potential issues related to resins' carcinogenic nature and potential interactions between active compounds and photoinitiator need to be addressed in future investigations. On the other hand, Selective Laser Sintering offers the possibility to develop orodispersible dosage forms as internal porosity can be controlled with printing settings. The potential for effectuating multiple printing operations in parallel could represent an opportunity for increasing process throughput. However, problems related to potential degradation due to Laser Energy and excess of unbound powder need further research.

Figure 10. Comparative analysis for pharmaceutical additive manufacturing techniques.)



Fixed-Dose Combination fabrication by Additive Manufacturing technologies could be possible, but the appropriate technique must be selected to achieve product compliance, flexibility, and process scalability. In state of the art, Pressure Assisted Microsyringe (or semi-solid 3D extrusion), Fused Deposition Modeling, and Stereolithography have been used for fabricating lab-scale dose combinations. As previously stated, the potential use of carcinogenic excipients and reported interactions with active compounds demands the exploration of new biocompatible photopolymer materials in the Stereolithography process. Despite successful experiences in lab-scale polypill fabrication, the use of solvents, the need for a drying post-printing stage, and a high tablet friability are some of the drawbacks of Pressure assisted Microsyringe process implementation that could represent significant problems at pilot scale manufacturing. Dual or Multi nozzle Fused Deposition Modeling offers a simple solution for non-thermolabile active compound dose combinations. The wide array of extrudable polymers grant flexibility in release profiles and active compounds that could be processed in the technology platform, guaranteeing product integrity through packaging, minimum cross-contamination, and product stability. It must be considered that there is a trade-off between manufacturing speed and product look and feel, as higher processing throughput increase the layer thickness in printed tablets, thus increasing the dosage form surface roughness.

CONCUSION

The sustained growth in publications and patent documents related to the implementation of additive manufacturing technologies to manufacture pharmaceutical oral dosages is an indicator of the technology potential for transforming the pharmaceutical value chain. More efforts are required to develop new value propositions for patients, specifically in the context of chronic therapies, where the potential for improving medication adherence in patients could represent an enormous relief to the health systems worldwide. The peak of inflated expectations has been surpassed, and new technology developments that exploit the potential of AM technologies such as personalized oral dosages, smart drug delivery systems, dosage design for narrow therapeutic drugs, and polypharmacy solutions are expected in the near future. For dose combination products, several technologies have been tested, however Material extrusion AM technologies, more specifically, Fused Deposition Modeling harness the potential for achieving dose and release profile flexibility by using multi-material technologies in the printer's extruding device, minimizing the potential for cross-contamination and reaching suitable finished product properties such as hardness and friability. Nevertheless, several technical and regulatory challenges must be addressed, including cGMP machine design, process throughput, and new polymer excipients for thermos-labile compounds. These strategic areas constitute future (or actual) research areas that will accelerate the technology adoption in the pharmaceutical market.

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