Review Article

3D Printing in Capsule

Abstract

The 3D printing technique is a 3D fabricating technique, which involves numerous working operations and manufacturing techniques. Nowadays, the technique is mostly used in the healthcare and pharmaceutical industries. This is not very new while the seed of this technique originated in the 1980s. The article contains background, historical development, types, global market, and examples of 3D-printed marketed preparations. This paper gives a focus in particular on 3D printing in capsules. In 3D printing, capsules will be a defining moment in capsule development and capsule applications for customized and personalized medications.

Keywords: *3D printing, additive manufacturing, capsule, fused deposition modeling, stereo lithography*

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Introduction

3D printing is a manufacturing process that requires stacking a succession of layers on top of one another to produce a variety of geometric forms.[1] 3D printing, also referred to as additive manufacturing (AM), is a production method that involves building an object layer by layer.[2] It also involves numerous operating procedures.[3]

Certain Aided Manufacturing technologies may produce highly accurate products, such as digital lightning process (DLP) and stereo lithography apparatus (SLA), that allow for the production of micro-scale medication delivery systems such as micro-needles.[4] Three-dimensional (3D) printing became a reality as a result of the technological revolution. 3D printing is transforming the globe, based on reports from the Financial Times and some other publications (3D experts are included).[5] 3D printing applications are rapidly growing, and this technology is infiltrating a wide range of industrial sectors, a trend that is only expected to accelerate. The pharmaceutical business is also seeing the benefits of implementing this technology. According to pharmaceutical and 3D printing technology experts, pharmaceutical R&D can be transformed by 3D printing solutions that allow for the fabrication of bespoke one-off batches with adjustable doses, chemicals, shapes, sizes, and delivery rates.[6] So far, in dentistry, 3D printing has been widely employed for a range of applications, varying from the creation of ortho operation models to the production of tooth replacement.[7,8] According to results, through 2022, 3D printing is expected to be a $3.1 billion market in this sector.[9]

Limitations and disadvantages

- The proliferation of counterfeit pharmaceuticals is likely to be the most serious problem for the pharmaceutical business when it comes to 3D printing. Inkjet is much more vulnerable to hacking than traditional production, and the incredibly fast turnaround time increases the likelihood of forgery.
- A hacker who gains access to a pharmaceutical company's private layout, for example, could send the instructions to a manufacturing plant in another country to mass create the drug. This form of copyright exploitation has the potential to have a significant impact on a business's success.
- Furthermore, poorly produced pharmaceuticals may reach the market and cause harm to patients, resulting in financial and reputational damage to the company.[10]
- Pharma businesses should assess whether 3D printing can add value to their operations and determine how to put their plans into action as soon as possible (e.g., by collaboration with researchers). It is called a disruptive technology for a

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reason: by the time it catches on in a certain industry, it may be too late to jump on board.[11]

- Two 3D printing technologies utilized in the pharmaceutical sector are SLA and fused deposition modeling (FDM). The layered 3D constructions are created using the SLA technique, which entails depositing a thin coating of liquid resin on the mobile platform and curing the polymer with an ultraviolet light ray at a specified depth over the liquid surface.
- SLA is an appealing approach for fabricating components with complicated 3D interior structures due to its great accuracy and resolution. However, the availability of biocompatible photopolymerizable oligomers limits SLA's use in the pharmaceutical business.[12]
- Another issue is that SLA typically uses individual ingredients, making it difficult to create complex preparations such as polymer mixtures and substance structures.[13]
- FDM, in contrast, has low performance, and higher processing heat causes severe deterioration of heat-sensitive pharmaceutical active ingredients, according to a thermal investigation of FDM formulations.[14]

Historical context

The notion of 3D printing dates back to the early 1970s when Pierre A. L. Giraud invented the technology of layering powdered substances and then cementing them with a strong laser. In this situation, melted materials such as plastics or metals could be utilized to prepare the object.[15]

In a patent, "Ross Householder" proposed the notion of sand binding with various materials entitled "A molding technique for creating a three-dimensional product in layers in the early 1980s," and "Carl Deckard invented the selective laser sintering (SLS) method of solidifying powdered beds using a laser." "Chuck Hull's earliest innovation that is available commercially was Stereo Lithography Apparatus (SLA)." This approach relied on UV light to photopolymerize liquid resin. Near the end of the 1980s, FDM is a patent submitted by Scott Crump, a process for producing shapes out of thermoplastic material. Emanuel Sachs, an MIT scientist, and coworkers patented three-dimensional printing techniques based on merging defined parts of powder by binding material in the 1990s.[15] "However, in the last 30 years, AM technology has advanced to the point where it now plays a significant part in the production process." [Table 1][17]

Types of 3D Printing

Fused deposition modeling (FDM)

FDM is a popular 3D printing technique that uses heat to soften or melt materials during the printing process to create items [Table 2].[18] The production of delayed-release printlets using FDM 3D printing is possible without the use of an external enteric-coated, as well as the delivery of customized therapeutic dosages. This 3D printing highlights various system limitations, including a lack of appropriate polymers.[19] Drug and additive miscibility with the polymers used were not appreciated, resulting in the slow and frequent partial release of a drug because the drug was entrapped in the polymers.[20]

Stereo lithography apparatus (SLA)

SLA is a method of solidifying a liquid polymer or resin using a desktop laser beam, resulting in a three-dimensional design.[21] The most noteworthy advantage of stereo lithography over prior methods of 3DP is its remarkable resolution and avoidance of heat procedures that can be dangerous to particular medication molecules.[22]

Selective laser sintering (SLS)

SLS is a technology for binding particles in a powder bed. The laser is meant to generate a precise pattern on the powdery bed's surface throughout the printing process, resulting in a 3D structure. Paracetamol, for example, is an oro-dispersible tablet created in this manner. In the industrial sector, it is now used to make plastic, metal, and ceramic items.[23]

Inkjet printing

Inkjet printing represents a variety of printing methods that include the generation and arrangement of droplets on a substrate that are remotely controlled. Inkjet printing can be classified into two types: continuous and drop-on-demand.[24] Drop-on-demand can be categorized as thermal inkjet or piezoelectric inkjet based on the kind of print-head use. Drop-on-drop or drop-on-solid is based on the material.[12]

Vat polymerization

Photo-polymers, radiation-curable resins, and liquids are accumulated in vats and cured one layer at a time with a source of light, resulting in a layer of 2D patterned. The SLA, continuous DLP, and DLP are examples of these processes. SLA is categorized into two sorts of configurations based on the location the light-absorbing resin polymerizes on the surface of the light source:

✓ Bath set-up (a strategy based on free space)
✓ Bat set-up (surface—a restricted strategy).[25]

Holt melt extrusion (HME)

HME is a technique of combining polymers and medicines at high temperatures while gradually increasing pressure in the instrument.[26] It is a continuous manufacturing procedure that includes feeding, cooking, blending, and sculpting.[27] In the last few years, it has been demonstrated that HME can improve the solubility and bioavailability of moderately soluble medications [Figure 1].[28]

Table 1: Historical development of the 3D printing field[16]

S. no.	Year	Development of 3D printing technology
1.	1980	The person who was the first to file a patent for "RP technology" was "Dr. Hideo Kodama."
2.	1984	The "Stereo lithography apparatus (SLA)" was devised by "Charles Hull."
3.	1986	"Carl Deckard" created a method for selectively "sintering components."
4.	1989	"Carl Deckard" received a patent for his "SLA" invention.
5.	1990	"Fused deposition modeling (FDM)"
6.	1992	The "3D system" was used to create the first "SLA machine."
7.	1993	"E.M. Sachs" was given a patent for "3D printing."
8.	1996	"Biomaterials" in clinical practice for "tissue regeneration."
9.	1999	"Luke Massella" was the very first person to receive a "3D printed bladder" comprising 3D printed polymers and his cells.
10.	2000	The "Selective Laser Technology (SLM)" was introduced by "Multiple Laser Beam (MCB)" technologies.
11.	2002	A "miniature working kidney" was created.
12.	2003	"Organ printing" is a term that was coined.
13.	2004	The "RepRap notion" of a completely open, auto-replicating 3D printer was created through "Dr. Bowyer."
14.	2005	"Z Corporation" introduced the "first color 3D printer."
15.	2007	On-demand manufacturing of industrial machinery parts with extremely selective layer modification.
16.	2009	The first completely "bio-printed blood vessels" data have been released by "Organovo," Inc.
17.	2011	In gold and silver, 3D printing was used. The "robotic aircraft," the first "3D printed automobile," in the world was unveiled.
18.	2012	Using "Extrusion-based bio-printing," a "3D printed prosthetic jaw" was placed into an artificial liver.
19.	2013	Solid concepts created a "metal gun" that was 3D printed.
20.	2014	Using a multi-arm bioprinter, integrate tissue synthesis with printed vasculature.
21.	2015	The first "3D printed pill" has been authorized by the "US FDA." The first entirely bioprinted kidney has been released by Organovo.

Table 2: List of 3D-printed pharmaceuticals

Formulation	Drug	3DP technology	Target	Ref.
Capsule	Lamivudine	Fused deposition modeling (FDM)	Capsules of various thicknesses were made to control the release of the drug and evaluate regional absorption of the drug in dogs' gastrointestinal tracts.	Arafat *et al.*[35]
Tablet	Sodium warfarin	FDM	As an alternative to breaking marketed pills, manufacture tablets with varied dosages of anticoagulant medication.	Arafat and Qinna[36]
Capsule	Octreotide, paracetamol	FDM	Making a force-sensitive capsule for local medicine delivery in the upper GI tract.	Berg *et al.*[37]
Suppository	Tacrolimus	Semi-solid extrusion (SSE)	The therapeutic efficiency of liposome tacrolimus suppositories was evaluated using an animal experimental model of colitis.	Seoane-Viaño *et al.*[38]
Printlets	None	FDM	The influence of varied placebo printlets shape, size, and color on end-user acceptance was explored.	Goyanes *et al.*[39]
Rapidly disintegrating tablets	Levetiracetam	Binder jetting	A clinical study was undertaken on healthy volunteers to quantify and analyze drug plasma concentrations following oral administration of a 3D-printed tablet and the standard formulation, as well as to analyze the effect of meal intake on the 3D-printed tablet's PK profile.	Boudriau *et al.*[40]
Controlled release tablet	Fenofibrate	MJP (Dimatix DMP 2800 inkjet printer)	More than a long period, a drug is released in a controlled manner.	Kyobula *et al.*[41]
Immediate release tablet	Paracetamol	SLS (Sintratec Kit)	The action takes place quickly.	Fina *et al.*[42]
Nano-suspensions	Folic acid	Inkjet-type printing technique	When compared with folic acid suspension, the breakdown rate of folic acid nanosuspension was substantially higher.	Pardeike *et al.*[43]
Bioresorbable nanocomposites	Rifampicin, biphasic calcium phosphate	Inkjet printer	The RFP-containing micro-patterns efficiently prevented *Staphylococcus epidermidis* biofilm colonies from forming and growing.	Gu *et al.*[44]

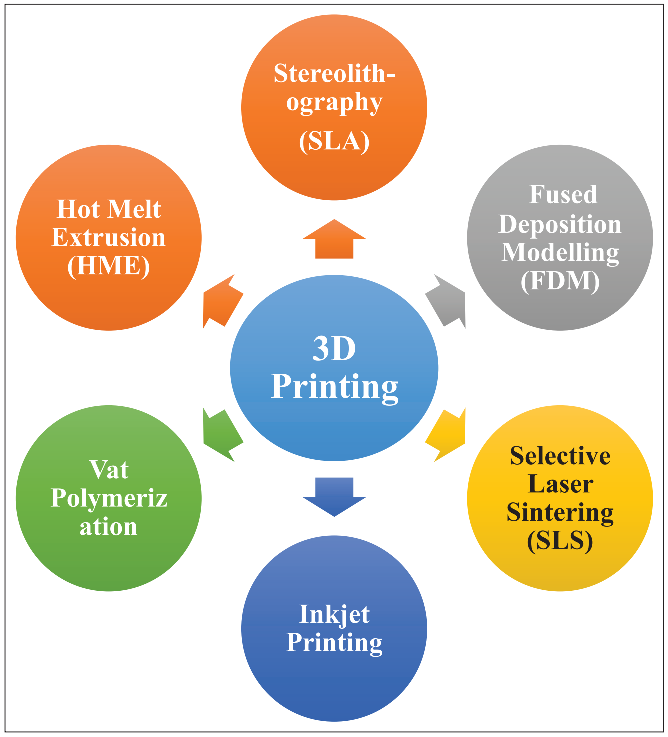

Figure 1: 3D printing technology comes in a variety of forms

Figure 2: 3D printing applications in the pharmaceutical field[29]

3D Printing Applications

Application of 3D printing technology is mentioned in [Figure 2].

3D Printing in Market and Industries

3D printing in industries

- Aprecia Pharmaceuticals was the first company to receive in 2015 the Food and Drug Administration (FDA)-granted permission for a 3D-printed pill. Two years later, GlaxoSmithKline conducted a trial in which inkjet 3D printing and UV curing were used to create Parkinson's disease tablets. With applications in sustained release, quick medicines, and sometimes even on-site printing at pharmacies, the 3D printing technique offers great ability to transform the pharmaceutical industry.[30]
- In February 2020, Merck KGaA and Additive Manufacturing Customized Machine have formed a partnership to improve and manufacture 3D-printed pharmaceuticals for the trials of clinical research and, eventually, clinical manufacturing.
- In April 2020, FabRx, a company based in the UK, released the first available commercially 3D printer for customized medicine manufacturing.[31]
- Pharmaceutical 3D printing for personalized dosing and drug compositions will probably become the standard procedure for a few more demanding treatment courses around the world in the next 10 years, according to forecasts.[32]

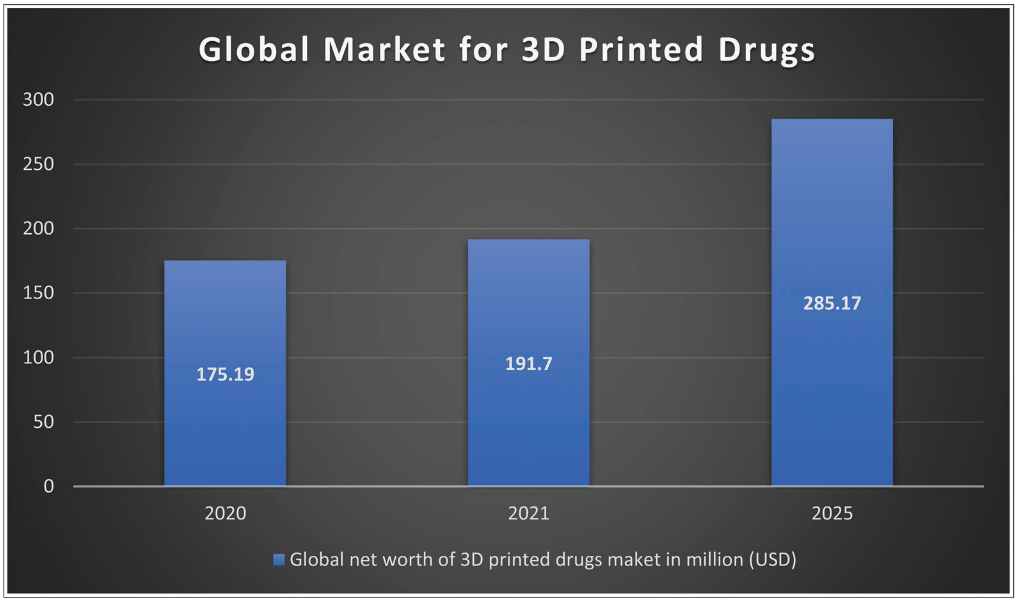

Figure 3: Global net worth chart of 3D printing technology

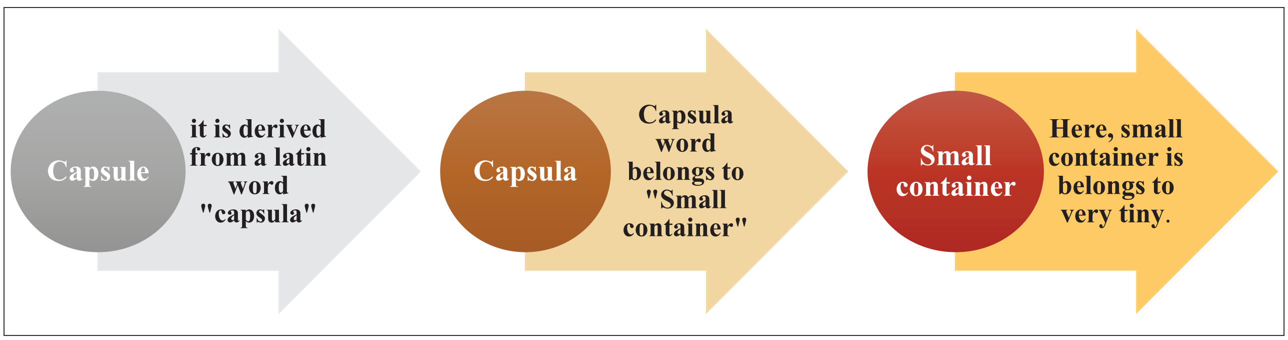

Figure 4: Explanation of the word "Capsules"

3D printing in market

According to the latest study, the worldwide economy for 3D printing components will be worth more than USD 18.4 billion in 2030 as the technology evolves into larger-scale manufacturing. As per the IDTechEx report, 3D printing in both home and industrial settings has exploded because the fused deposition printing technology moved off-patent in 2009, and professional 3D printing in factories and by 3D-printed agencies is now an established industry vertical. While these end users initially created primarily models or items for product development, their scope has broadened significantly in recent years, But we now see "3D printing expanding into popular manufacturing and on to the production lines," the report states. According to the study, small, local businesses used 3D printing to make bespoke masks, swabs, and ventilation machine valves at the start of the COVID-19 outbreak, when health care was in critical need of effective personal protective equipment and medical supplies.[33]

The worldwide economy for 3D-printed medicines was worth USD 175.19 million in 2020 and is predicted to grow to USD 191.70 million in 2021 and USD 285.17 million by 2025, with a compound annual growth rate of 10.23% [Figure 3].[34]

3D-printed Market Preparations

There are a few examples of 3D-printed drugs or market preparations.

3D Printing in Capsules

- Capsules are a solid unit oral dosage form that can be used to complement life-saving drugs, minerals, vitamins, and other therapeutic substances. These handy packagings allow for accurate dosing, mobility, and excellent consumer compliance. More onerous liquid, powder, or paste formulations are available as alternatives.[45]
- The word capsule comes from the Latin word Capsula, which means "little container" [Figure 4].[46]
- Two types of capsules are used to distribute medications and pharmaceuticals [Figure 5].

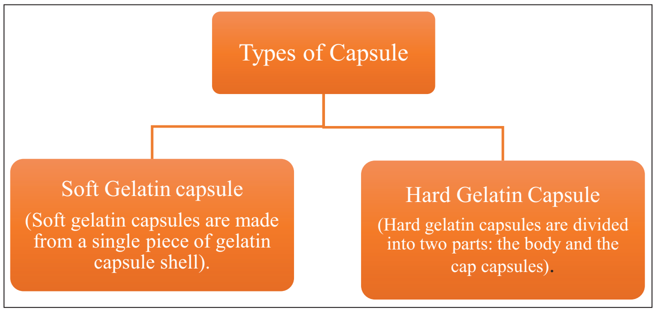

Figure 5: A different form of "Capsule"[47]

In the pharmaceutical sector, new strategies for medicine delivery are being studied; one of the most significant is 3D printing technology.[48] 3D printing is currently being employed in the fabrication of capsules, and research on the design of capsules and 3D printing of a multi-compartmental polyvinyl alcohol (PVA) capsule for progressive medicine release has just been completed. PVA capsules come in three different compartment sizes: solo, double, and triple compartments.[45] 3D printer N2 FFF (Raise 3D Inc., Irvine, CA, USA) was utilized to create capsules in two stages: first the reservoir and then the cap.[49]

Manufacturing method of a 3D-printed capsule

The 3D printing capsule goes through several steps in its manufacturing process, as discussed subsequently:

- The hot-melt extrusion technique was used to produce customized 3D-printed filaments, which have been the feedstock for 3D-printed capsules.
- Preparing PVA powder, combining hydroxy-propyl-methyl-cellulose (HPMC) and PVA powders with a specific composition, and extrusion using an extruder are the three procedures in this technique (EX2, Filabot, Barre, VT, USA).
- The PVA had been in the form of a 3.00 mm diameter filament, which is suitable for manufacturing control capsules. PVA filament was crushed into powder using a SHARDOR CG628B grinder.
- Following its acquisition of the PVA powders, three powder compositions were constructed having 5%, 15%, and 25% hydroxy-propyl-methyl-cellulose in PVA by weight.
- The powder mixtures were then fed into an extruder with an extrusion process of 190°C near the nozzle to produce 1.75 mm diameter 3D printing filaments in a non-oxygen environment.
- All of the filaments were kept in a dry box to avoid any contact with the surrounding environment's moisture content.
- After creating customized 3D printing filaments, tailored capsules were printed using an FDM printer with a 0.25 mm nozzle.
- To simplify the FDM 3D printing process easier, digitally capsule models with a certain layer thickness were developed using Autodesk Fusion 360.
- The intended capsules did not have any support or brim structures. A coating of glue was placed on the build plate to aid in the bonding of the early print layers.
- After the printing was completed, the capsules were examined for adhesive residue and any residue was cleaned using a soft cloth. Before moving on to the next step, we double-checked that the capsules were free of glue residue.
- To create capsules with superior dimensional accuracies and surface textures, the customized filaments were optimized for 3D printing process characteristics such as nozzle heat, temperature difference, nozzle size, printing speed, and structural components.
- The dimensional accuracy of 3D-printed capsules was tested. Only authorized capsules were sent for testing. Figure 6 depicts the detailed workflow of the aforementioned processes.[50]

Role of HPMC (hydroxy-propyl-methyl-cellulose) in 3D printing capsule composition

- The hydrophilic matrix material HPMC is utilized as a thickening agent, binder, and film-forming in 3D printing capsule manufacturing, and there are several viscosity grades of HPMC polymers for making hydrophilic matrix systems, ranging from 4000 to 100,000 mPa s.[51]
- Another cellulose-based bioinspired polymer is HPMC. It has been the preferred option for extended-release trials because, like HPC, the gel barrier it forms when in contact with aqueous liquids can be used to extend drug release.[52]

Future Prospects of 3D Printing in Capsule

- When a delayed release or the distribution of two separate active components is necessary, 3D-printed capsules can be employed as modular devices for medication administration.[53]
- The slow breakdown of PVA reservoirs has been established to provide a simple technique for a prolonged supply. Multi-compartmental capsules were developed and studied as a viable method for adjusting medication release timing.
- Because of the aging population and the daily increase in the number of chronic conditions, patients are taking more medicines at different times throughout the day. Taking the proper medicines at the right time is a huge difficulty, especially for dementia and other comparable conditions; polypills are being used to treat various chronic diseases. A polypill is a pill that contains two or more active pharmacological substances and is accessible in pill form (i.e., tablet or capsule). They are

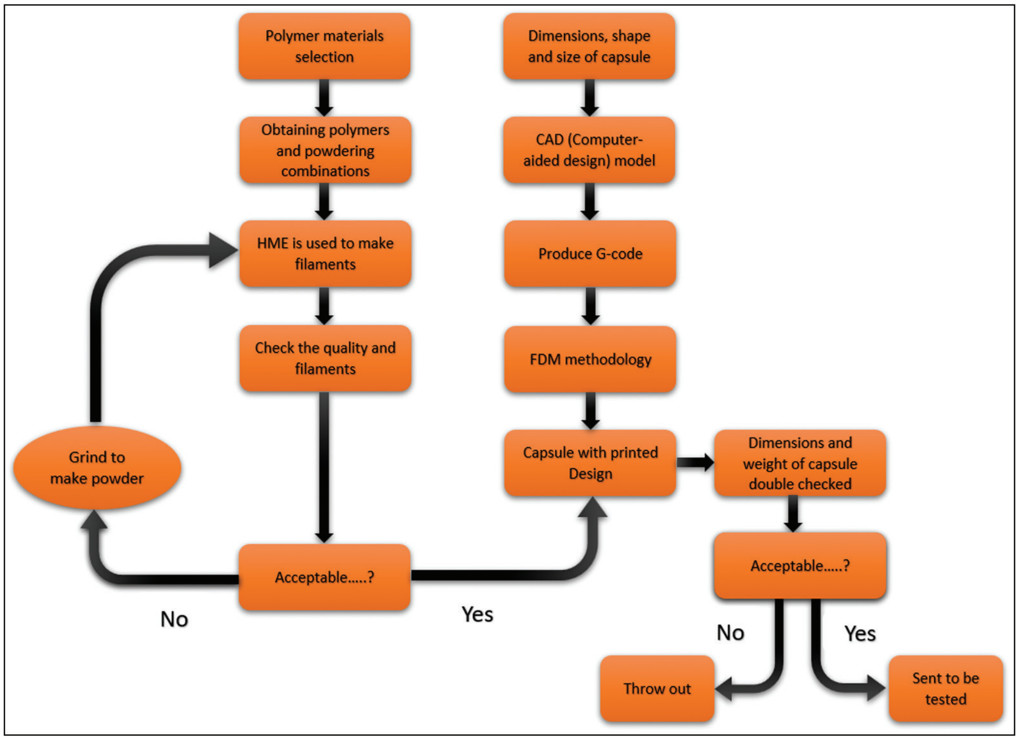

Figure 6: Fabrication of filaments and capsules workflow[50]

inexpensive, have various targets, and are simple to manufacture in big quantities; nevertheless, one problem is that they may not necessarily help all patients. As a result, the potential for 3D-printed pharmaceuticals presents itself. These are small-batch personalized medicines having sizes, forms, dose formats, and drug release characteristics that are precisely adjusted to the needs of particular patients. This has the potential to drastically alter the future therapeutic landscape for a variety of diseases. The 3D printing method also enables the masking of the pharmaceutical ingredient's taste by including flavor into the pill itself rather than using a film covering.[54]

Conclusion

The application of 3D printing is rapidly growing in all the fields for the betterment of healthcare services but also it is a financially growing segment for the country. As the trend and application of personalized medicines increase, the 3d printing techniques become useful in the formulation sector also. The creation and manufacturing of 3D-printed pharmaceutical formulations, as well as 3D-printed capsules, are being researched.

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Conflicts of interest

There are no conflicts of interest.

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