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APPLICATION OF 3D PRINTING IN PHARMACEUTICAL AND MEDICAL FIELD: A BRIEF REVIEW

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ABSTRACT

Medical, electronic, aviation and other industries can benefit from pharmaceutical additive manufacturing. With its ability to create personalized, highly customized products, 3D printing has a lot of promise for the pharmaceutical sector. We were curious about the potential applications of 3D printing in the pharmaceutical sector. The adoption of 3D printing technology by pharmaceutical businesses has created new opportunities for the development and manufacture of printed goods and devices. As pre-surgical imaging templates and tooling moulds, 3D printing has gradually advanced to make one-of-a-kind instruments, implants, tissue engineering scaffolds, testing platforms and drug delivery systems.

KEYWORDS

Medical, Electronic, Aviation and 3D printing technology.

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INTRODUCTON

The fabrication of pharmaceutical dosage forms and the 3D printing (3DP) process are both relatively new concepts in the pharmaceutical industry. 3DP is also known as additive manufacturing technology. Three-dimensional printing is one of the fields of technology, art, and science that is now advancing the fastest and its applications are continually expanding. The International Standard Organization (ISO) defined three-dimensional printing as the "fabrication of objects through the deposition of materials using a print head, nozzle, or another printer technology" that enables the creation of 3D objects from digital computer-aided design (CAD) models. This technology can be applied to the advancement of the pharmaceutical industry, where porosity has been crucial in achieving an acceptable level of biocompatibility and biodegradability with improved dosage of each ingredient for a particular purpose and makes it likely to enhance the formulation of drug delivery systems.

A subset of a collection of techniques known as 3D printing includes bio-printing, digital light processing (DLP), hot-melt extrusion (HME), inkjet-based 3DP, selective laser sintering (SLS), semi-solid extrusion (SSE) and stereo lithography (SLA). New ideas in medication design, a greater understanding of material qualities and manufacturing procedures that guarantee high-quality dosage forms are all always being pursued. Active pharmaceutical ingredients (APIs) have a variety of physicochemical and biological properties that must be taken into account and researched at every level of the product development process. To create the proper dosage form, additional chemicals must be investigated as well.

Three-dimensional printing (3DP) is thought to be the most revolutionary and potent invention among the many discoveries that have been offered to the pharmaceutical and biomedical markets. This method is acknowledged as a flexible tool for precisely constructing a variety of devices. It functions as a technology for creating novel dosage forms, engineering tissues and organs, and modelling diseases. Additionally, the 3DP methods enable on-demand printing of the pharmaceutical dosage forms and are affordable and simple to use. The 3DP technique is a layer-by-layer creation of the dosage forms using their respective digital blueprints, potentially revolutionising the healthcare industry as a result of this paradigm shift in people's perspectives on personalised medications.

In this technique, a concept is turned into a prototype with the aid of 3D computer-aided design (CAD) files, allowing for the fabrication of digitally controlled and customised products. In this technology, layers of materials, such as live cells, wood, alloy, plastics, metals, etc., are stacked on top of one another to create the necessary 3D item.

As a result, numerous names for 3D printing exist, including layered manufacturing, additive manufacturing, computer automated manufacturing, rapid prototyping and solid freeform technology.

Applications for 3DP include designing tissues, printing organs, performing diagnostics, producing biomedical devices and designing drug and delivery systems for the medical industry. Complex anatomical and medical structures can be created from data generated by a variety of techniques, such as computed tomography (CT) scans and magnetic resonance imaging (MRI), depending on the needs of the patient.

HISTORY OF PHARMACEUTICAL ADDITIVE MANUFECTURING

Manufacturing of medicinal additives began in Japan in the 1980s. In 1983, stereo-lithography was first developed. The term "stereo-lithography" is still not included in the most widely used dictionaries, like Merriam-Webster. Consequently, to put it simply, "a technique or process for creating three-dimensional objects, in which a computer-controlled moving laser beam is used to build up the necessary structure, layer by layer, from a liquid polymer that hardens on contact with laser light."

Two AM photopolymer rapid prototyping systems were created in 1981 by Hideo Kodama of the Nagoya Municipal Industrial Research Institute. In these systems, the UV exposure area is controlled by a mask pattern or the scanning fibre sent. According to Kodama's 1981 publication, A Scheme for Three-Dimensional Display by Automatic Fabrication of Three-Dimensional Model, (Kodama, 1981. Automatic method for creating a three-dimensional plastic model using photo-hardening polymer. Additionally, CAD/CAM software was used by designers and engineers, but there was no way for that software to interface with the SLA 1 initial Rapid Prototyping System. In order to complete the electronic transfer from the CAD software to the 3D printers for the purpose of producing 3D things, Chuck and 3D Systems also created the ".STL" file format, which is still in use today. When stereo-lithography was invented rapid prototyping did not exists. In 1986 a new technique was invented: selective laser sintering (SLS). First commercial SLS was in 1990. At the end of 20^{th} century, first bio-printer was developed. Using biomaterials, first kidney was 3D printed. In 1986, Charles Hull was granted a patent for this system, and his company, 3D Systems Corporation was formed and it released the first commercial the SLA-1 3D printer. Today we have large scale printers that printed large 3D objects in the pharmaceutical sector. 3D printing will be used for printing everything everywhere. The first Stereos stereo lithography equipment was sold by German company Electro Optical Systems (EOS) in 1990. The Mark 1000 SL system, which made use of visible light resin, was introduced by Quadra the same year. The visible light resin compound was introduced the following year by Imperial Chemical Industries for use with the Mail 1000. About a year later, after Quadra had dissolved because of a legal dispute with 3D Systems, ICI stopped selling its resin.

TYPE OF ADDITIVE MANUFECTURIG TECHNOLOGY

The majority of pharmaceutical and medical applications utilise additive manufacturing techniques. According to criteria including drug packing, drug release, drug stabilisation and pharmaceutical dose stability, the finishing quality produced by the typical pharmaceutical industry operations of milling, grinding, granulation and compression is frequently unpredictable. In contrast, 3DP provides strategic benefits as a potent tool technology, including improved R and D productivity, security and efficacy as well as increased accessibility to medications. The types of additive manufacturing are listed below as a result.

Stereo lithography

Stereo lithography is a sort of 3D printing method used to build models, prototypes, patterns, and production parts layer by layer. It is sometimes referred to as optical fabrication, photo-solidification, or resin printing. Pharmaceutical companies, among others, use photochemical techniques, in which light causes chemical monomers and oligomers to cross-link to form polymers. Late in the 1980s, the additive manufacturing method of stereo lithography was developed. And in the history of 3D printing, numerous approaches are currently in use. One of the most often utilised methods for creating the prototypes, production components, patterns, and models. The surface of a vat containing liquid photopolymer is the target of the concentrated ultraviolet light beam utilised in stereo lithography manufacture. By cross-linking or decomposing a polymer, the concentrated beam builds up each layer of the desired 3D design. It is a reliable fabrication technology and is based on a laser orientation print system. Laser-like ultraviolet light is focused on fluidized resin to cause photo polymerization, which gives the resin its hardness. This process keeps running until no 3D structure appears. This technique is crucial for creating the 3D structure of a reputable object.

So that this method can be used to create solid dose forms like aspirin and paracetamol tablets. The process of stereo lithography can be used to create prototypes of things that are still in development, medical equipment, computer hardware, and pharmaceutical products. Stereo lithography can be pricey even though it is a quick method for manufacturing any design. Utilising computer-aided designs of any object, stereo lithography techniques can considerably increase the capacity to build 3D structures with specified geometry.

Selective Laser Sintering (SLS)

Selective laser sintering (SLS), a powder-based 3D printing process invented by a businessman in the United States in the 1980s, uses laser light to melt and fuse powders, which are then stacked one on top of the other to create printed parts based on 3D model data. A scanning laser beam (such as a CO2 laser) is used in the selective laser sintering process to fuse the powdered materials. The process is continued until a 3D item is ready, at which point the powder bed travels downward to make room for the addition of a new layer on top.

This technique generally requires relatively long processing time and pre-heating of powders is required. SLS enables to fabricate parts with a resolution of around a few tens of microns. The most constantly used polymer in the Selective laser sintering process is polyamide, polyethene, PEEK, PCL and TPU. The persecuted material for making new object is used in Selective laser sintering printer. A laser pulls the object outline into the powder and fuses it. Then a new powder layer is formed and the process is repeated continuous and builds each layer to produce the product. With the use of SLS, numerous medication delivery methods have been created. It is the ideal technique for fully working prototypes and end-use parts. SLA technology is similar to selective laser sintering in terms of efficiency and product quality.

Fused Deposition Modeling (FDM)

This technology is employed to produce robust everyday products. Using a bottom-up construction method, the 3D printer uses industrial-grade thermoplastic filament that is melted and extruded on a tray to produce an entire part layer by layer. This method's drawback is that it needs a high processing temperature to create active thermo labile molecules.

Semi-solid extrusion (SSE)

Low temperatures are necessary. In this method, a semi-solid combination is used as the initial ingredients and is extruded using a syringe-based tool-head nozzle. For optimised mechanical qualities, processing temperature, material flow rate and printing speed should be taken into account. This method calls for post-processing activities like cooling or drying.

Thermal Inkjet (TIJ) Printing

It is a non-contact process that deposits minute ink droplets onto substrates in accordance with digital instructions using electromagnetic, thermal, or piezoelectric technologies. Resistors in this printer generate heat, which causes the ink to vaporise and form a bubble. The ink is forced out of a nozzle and onto the substrate as the bubble swells. Using a micro-resistor to heat the ink fluid, it produces a steam bubble that covers the ink and causes it to emerge from the dust after expanding. Utilising this method, exempt medication preparations or solutions are administered into 3D scaffolds.

To prevent the print head from clogging, bioink made for thermal inkjet printing is typically water based. By simply altering the bioink, this enables the printer to freely distribute cells from a single cell to several cells. Both the printed patterns and focus. It is believed to be safe to transfer biological systems because cells are always maintained and protected in an aqueous environment during the thermal printing process. Despite the fact that thermal inkjet printing technology has been used for printing cells in numerous applications, there are comparable worries that the printing process could harm or kill cells. The size of the nozzles in the print head is typically quite small in order to maintain the printing resolution.

Binder jetting 3D Printing

Various particle materials, likes and polymers, or freely selected powder materials, are used in this approach. The part's CAD data is the primary need. The loose particle ingredients are first applied to the building platform by a recorder and then the print head applies the binder selectively to the locations where the future parts must be made, joining the layers. The layer thickness lowers the building platform once the binder has been applied. Printing is done layer by layer until the required structure is achieved.

Inkjet Printing System

Three-dimensional things are created using an inkjet printing method, a type of additive manufacturing. Human cartilage can be repaired using inkjet printing technology and tissue engineering.

The ideal implanted tissue should treat lesions of varied sizes and densities and blend well with the existing native cartilage. Based on inkjet printing, bio printing technology has the attributes needed for tissue healing and can be adjusted to varied physical dimensions and properties.

In this approach, sheets of edible material are utilised in place of regular paper for pharmaceutical applications rather than medication solutions and ink. Inkjet printing is complexity agnostic, like other 3D printing technologies, which means that printing time is essentially independent of product complexity. The 3D inkjet printing technique is similar to other 3D printing processes in that it progresses by layer-by-layer deposition, meaning that the time needed to create a completely functional product only depends on the time needed to deposit the necessary amount of material and the curing time. A 3D mechanical model of your product is used to produce printing instructions for each layer, much like with well-known printing software.

Bio-Printing Technology

Artificial organs can be created using bio-ink and the bio-printing technique. For the most part, bioprinting technology uses a layer-by-layer process to deposit material known as bioink to generate tissue-like structures that are later used in many medical and tissue engineering fields. To help with medication and potential therapy studies, tissue and organ models can currently be printed using bioprinting technology.

APPLICATION OF 3D PRINTING IN PHARMACEUTICAL AND MEDICAL FIELD

The potent method employed in research in the pharmaceutical and medical fields is 3D printing technology. In this review, the following applications are mentioned.

3D printing in Oral drug delivery

The creation of solid oral dosage forms using 3D printing technology has shown to be promising. With the help of this technology, it is now possible to create innovative formulations that get around many of the drawbacks of traditional medication manufacturing techniques. To meet the demand for customised pharmaceuticals, 3D printing has the capacity to create various sizes and intricate designs with calibrated release properties. Extrusion-based 3D printing methods are the ones that are most frequently used in the creation of oral dosage forms. The methods for oral medication administration created by 3D printing Techniques have tailored the API's drug release properties to meet patients' needs, which has resulted in the creation of immediate-release and delayed-release systems, polypills that contain the entire dosage regimen for a patient with diabetes or hypertension in a single pill, and gastro-retentive drug delivery systems. Some of the most recent 3D printing methods for oral medicine delivery have been addressed in this area. The easiest way to provide API is through oral dosage forms, which also have higher patient compliance than any other method. A broad selection of excipients and significant advancements in oral dosage production provide a flexible platform for medication delivery.

The flexibility of this technology has been constrained, nevertheless, by the restricted geometry and geometries that conventional manufacturing is capable of producing. The layer-by-layer construction process that underpins 3D printing gives freedom to achieve geometric proportions that are impossible to produce using traditional techniques. Direct compression (DC), fused deposition modelling (FDM) and injection modelling (IM) were utilised to develop an oral tablet with an approach to compare the traditional manufacturing process with the 3D printing methodology.

3D printing in In Dermatology science

The science of dermatology may benefit greatly from 3D printing. The creation of 3D skin using 3D printing technology can be used to evaluate new chemical, pharmaceutical, and cosmetic items, among other things. The bio-printer that was created by researchers at the Universidad Carlos III de Madrid creates actual human skin. It has the potential to revolutionise both the medical and skin care industries. Skin is produced using a bio-printer that blends bio-inks. There is no "ink" at all in the bio-inks. Instead, they are the skin's biological constituents such keratinocytes, primary human fibroblasts, and plasma. This method can currently produce two different kinds of skin tissue. The first is simply normal skin.

This is created utilising a stock of generic human cells that are mass produced and might be used for testing novel cosmetics, perhaps replacing the need to utilise animals. The other type of skin tissue is created from a person's own cells and is employed for therapeutic purposes and in unique situations, such as as a transplant for severe burns or skin disorders.

3DPrinting in Dosage form manufacturing

Typically, tablets or capsules are used as oral solid dose forms for medications. The printing of the medications involves several procedures and sophisticated chemicals. The improvement of drug delivery methods depends on the active pharmaceutical ingredient (API).

In 2015, Aprecia Pharmaceuticals created the first Levetiracetam oral dispersible tablet using binder jet printing technology for the treatment of seizures in both adults and children. The Howard Hughes Medical Institute has developed a molecular 3D printer. The 3DP medical industry has undergone a significant shift because to this printer. Currently, The Institute of Chemical Technology and Tvasta, Mumbai, is developing a method to create tablets with controlled medication release by combining different 3D technologies. The following dosage form kinds with various compositions are created utilising 3D printing technology in the field of medicine.

Guaifenesin is a. Nifedipine, Glipizide and captopril tablets are all created using the Semi-solid extrusion (SSE) process, which is also used to create bi-layered tablets.

Selective Laser Sintering (SLS) technology is used to create drugs such as progesterone and paracetamol tablets. Fused Deposition Modelling (FDM) technique is used to create tablets such as caffeine, hydrochlorothiazide and oral film aripiprazole.

Tablets like Fluorescein, Levetiracetam and Chlorpheniramine Melate Tablets With the use of Binder jet printing technology, Methylene blue and alizarin yellow (dyes) and Cubic tabular products like pseudoephedrine are created.

The Inkjet 3DP technology is used to create implants such as Levofloxacin and Folic acid (Nanosuspension), Rifampicin and isoniazid (Multidrug Implant).

In the cancer research

The J5 Medi Jet 3D printer was used by a group of experts from the Institute of Cancer Research, London, to produce a first-of-its-kind model that precisely represents the protein that innovative medications under development are targeting within a cancer cell. The model aids scientists in developing therapeutic compounds that will bind to proteins and eradicate cancer cells in patients. Such that additive manufacturing can be used in cancer research.

Pulmonary drug delivery

By creating 3D printed medical equipment and models, respiratory disorders are treated using 3D printing, a new technology. Prototypes of lungs that were 3D printed help doctors better comprehend the diseased state and may one day be used to identify and cure disorders of the respiratory system. By utilising 3D printing processes, these strategies will help manufacture personalised inhalation medications. It is shown how 3D printing can be used to treat lung conditions.

Trachea bronchomalacia in children can be treated with 3D printed bioresorbable airway splints. By creating customised devices, the 3D printed airway splints were discovered to be a useful option to reduce patient airway collapse and provide a root map for the treatment of life-threatening disorders[1].

The development of medical devices for the management of asthma and respiratory issues has advanced thanks to the use of 3D printing technology. A group of researchers created a "sneezometer" that uses 3D printing to detect airflow and sneeze speed[2]. Additionally, the development of a lung tumour movement simulator using 3D printing technology has been used to treat lung cancer. This tool made it possible to treat lung cancer with radiotherapy and discovered how the tumour moved while the patient was breathing[3].

3D Application in traumatology and orthopedic surgery

When using 3D technology in conjunction with standard DICOM images, spine surgeons report greater anatomic understanding, increased teamwork, and improved outcomes when inserting screws and fixation material[4,5]. Pre-operative planning of the corrective reduction, choice of fixation material, and modelling of the process are all made possible by real-size 3D printed biomodels of scoliotic spines. In addition to taking less time during surgery, the precision of surgical technique employing 3D printed biomodels along with the design and 3D printing of pedicle guiders has been reported to be higher than that of freehand procedures[6].

3D printing in intrauterine drug delivery

Devices and implants for intrauterine drug delivery have been created using 3D printing techniques. The fabrication of customised size and form devices for local and systemic API delivery via the intrauterine route is made possible by the 3D printing technology. These gadgets will offer an API dose that is precise and has optimised release characteristics. Hollander *et al.* used a 3D printing process based on FDM to create a T-shaped prototype intrauterine device.

Poly-caprolactone-fabricated 3D printed devices were found to have a quicker medication release profile than extruded filament alone for the model drug indomethacin. Because the drug was discovered to be in an amorphous state in the devices as opposed to its crystalline existence in the filament, the drug release was accomplished through polymer diffusion and the efficient drug release profile was achieved through 3D printed devices[7].

The same research team also demonstrated the use of ethylene vinyl acetate (EVA) as a polymer to create subcutaneous rods (SR) and intrauterine systems (IUS) using a 3D printing technology based on FDM. For 30 days, the specially created T-shaped 3D printed prototype devices displayed a quicker medication release profile.

Ethylene vinyl acetate (EVA), a polymer suited for 3D extrudable printing, is used in this concept as a test bed to create drug-loaded implantable devices[8].

3D printing In Artificial Organ for study

Artificial Organs can be created utilizing bio printers and 3D printing technologies. Organs and body parts are being printed, with some of the parts being used as implants for real body parts. There have been printed body parts like titanium jaws, plastic tracheal splints, and titanium pelvics. The printing of human tissue for pharmaceutical testing and medical research is now possible thanks to new bio printers. The ability to create blood vessels demonstrates the amazing progress that tissue engineering has made. By vascularizing a hydrogel construct, which is possible thanks to cutting-edge 3D bio printing technology, this can be accomplished. This technique is crucial for medical student research and the testing of novel dosage forms.

The first 3D bioprinted kidney was presented in 2011 by Professor Anthony Atala, Director of the Wake Forest Institute for Regenerative Medicine. His team was able to create this 3D printed organ from stem cells in just seven hours. A team of researchers at the Politecnico di Torino's Bio-Inspired Nanomechanics Laboratory in Italy set out in 2022 to use the Poly Jet-powered Digital Anatomy Printer to print a multi-material model of specialised soft tissues like tendons and ligaments.

In 2016, University of California San Diego researchers were able to 3D print organic tissue that closely resembled real liver tissues in terms of both shape and function. The pharmaceutical industry exploited these bioengineered tissues for the development and testing of drugs. These organoid structures, which were made from human blood cells, carried out typical liver processes like protein production, vitamin storage and even bile secretion.

The Wake Forest Institute for Regenerative Medicine (WFIRM) is a research centre in the United States that specialises in tissue engineering for transplantation among other uses. A WFRIM research team asserted in 2018 that they had successfully used mouse cells to 3D bioprint functioning heart tissue.

With the first-ever fully vascularized 3D printed miniature human heart, researchers from Tel Aviv University's School of Molecular Cell Biology and Biotechnology stunned the world in 2019. This organ was created using patient-supplied human cells. The cardiac cells are now being developed and made completely functional by the TAU team.

3D printing in facial reconstruction surgery

Doctors at the Clinical University Hospital in Olsztyn, Poland, use full-scale, 3D-printed models of patients' skulls for their work in the oral and maxillofacial surgery department. These models aid in the preoperative contouring of customised implants. Over 80% of patients who have orbital injuries require orbital floor reconstruction, which affects 55% of patients admitted to the ward. Their treatment is safer and more effective thanks to 3D printing.

3D printing in organ transplantation

Cellular structures can be created using the bio-printing technique using bioinks that have stem cells added to them. The biomaterial is placed layer by layer to produce skin, tissue, or even organs. Each new bioprinting project brings us one step closer to having a completely functional and workable answer. Human livers, kidneys, and hearts are being bioprinted at laboratories and research facilities. Animal tests of WFIRM's 3D-printed living ear and muscle implants were effective. 2016 saw the successful implantation of 3D printed living muscle and ear parts into animals, according to researchers from the WFIRM.

A team led by Monica Laronda used bioprinting methods in 2017 to enable infertile mice to conceive. Ovaries were successfully created by the research team using bioprinting technology and transplanted into mice. In order to help women produce children, researchers at Northwestern University in Chicago are now totally committed to creating an artificial ovary. A brand-new bioprinting technique, called proximal tubule bioprinting, was created in 2016 by researchers from the Lewis Lab at Harvard University. The kidney's most fundamental component, nephrons, are in charge of all blood filtering in these organs. 2019 saw the successful automated manufacture of kidney organoids using the Organovo bioprinting platform, according to the American bioprinting startup the Novo Gen Organovo. These self-organizing stem cell-based structures are readily producible in huge quantities.

CONCLUSION

The development of personalised medicine that is centred on the needs of the patient is made possible by the use of 3D printing technology in the pharmaceutical industry. It is a rapidly developing technology. Medical care Professional scientists, engineers and researchers are constantly increasing its uses. It enhances manufacturing design, cuts down on lead times and lowers tooling costs for new goods. This can be used in clinical settings to create improved surgical techniques and transplants, or in educational settings to teach students and trainees more effectively. Currently, technological advancements and expanded research in the pharmaceutical and medical fields can guarantee safe and efficient therapy. The pharmaceutical business and biotech firms discussing innovative 3D printing tactics for the biotech sector.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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