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3D PRINTING IN PHARMACEUTICS

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ABSTRACT

Three-dimensional (3D) printing is a type of additive manufacturing technology. It is a layer by layer process capable of producing 3D products from digital designs. It has the potential to be the "next great step" in pharmaceutical manufacturing, enabling fabrication of specialty drugs and medical devices. 3D printing could be used for personalized or unique dosage forms, more complex drug-release profiles, and printing living tissue. Spitram is the first 3D printed tablet. For years, these methods were extensively used in the field of biomanufacturing (especially for bone and tissue engineering) to produce sophisticated and tailor-made scaffolds from patient scans. There's no question that 3D printing is going to change the world. From manufacturing to design, medicine to electronics, the technology has made significant leaps in terms of production - making what was once expensive and inaccessible now cost-efficient and available to many.

KEYWORDS: Additive manufacturing, computer-aided design, stereolithography, fused deposit modeling, personalized medicine.

INTRODUCTION

3D printing is a form of additive manufacturing technology where a three dimensional object is created by laying down successive layers of material. 3D printing is also known as Rapid prototyping. 3D printing in pharmaceuticals represents an elegant tool for designing simple, accurate, cheap, structured and tailored drug delivery systems.[1]

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. It may involve scientific site-targeting within the body, or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products. Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the target area of the body. Due to recent advances in biotherapy and personalized medicine, novel concepts of formulation have emerged.[2]

Rapid prototyping is a group of techniques used to quickly fabricate a scale model of a physical part or assembly using three-dimensional computer aided design (CAD) data. Construction of the part or assembly is usually done using 3D printing or "additive layer manufacturing" technology. The first methods for rapid prototyping became available in the late 1980s and were used to produce models and prototype parts. Today, they are used for a wide range of applications and are used to manufacture production-quality parts in relatively small numbers if desired without the typical unfavorable short-run economics.[3] Rapid Prototyping has also been referred to as solid free-form manufacturing, computer automated manufacturing, and layered manufacturing.[4]

3D printing refers to processes in which material is joined or solidified under computer control to create a three-dimensional object, with material being added together (such as liquid molecules or powder grains being fused together). 3D printing is used in both rapid prototyping and additive manufacturing (AM). Objects can be of almost any shape or geometry and typically are produced using digital model data from a 3D model or another electronic data source such as an Additive Manufacturing File (AMF) file (usually in sequential layers). There are many different technologies, like stereolithography (STL) or fused deposit modeling (FDM). Thus, unlike material removed from a stock in the conventional machining process, 3D printing or AM builds a three-dimensional object from computer-aided design (CAD) model or AMF file, usually by successively adding material layer by layer.

3D printable models may be created with a computer-aided design (CAD) package, via a 3D scanner, or by a plain digital camera and photogrammetry software. 3D printed models created with CAD result in reduced errors and can be corrected before printing, allowing verification in the design of the object before it is printed. The manual modeling process of preparing geometric data for 3D computer graphics is similar to plastic arts such as sculpting. 3D scanning is a process of collecting digital data on the shape and appearance of a real object, creating a digital model based on it.

Before printing a 3D model from an STL file, it must first be examined for errors. Most CAD applications produce errors in output STL files. A step in the STL generation known as "repair" fixes such problems in the original model. Generally STLs that have been produced from a model obtained through 3D scanning often have more of these errors. This is due to how 3D scanning works-as it is often by point to point acquisition, reconstruction will include errors in most cases. Once completed, the STL file needs to be processed by a piece of software called a "slicer," which converts the model into a series of thin layers and produces a G-code file containing instructions tailored to a specific type of 3D printer. This G-code file can then be printed with 3D printing client software (which loads the G-code, and uses it to instruct the 3D printer during the 3D printing process).

Construction of a model with contemporary methods can take anywhere from several hours to several days, depending on the method used and the size and complexity of the model. Additive systems can typically reduce this time to a few hours, although it varies widely depending on the type of machine used and the size and number of models being produced simultaneously. Traditional techniques like injection moulding can be less expensive for manufacturing polymer products in high quantities, but additive manufacturing can be faster, more flexible and less expensive when producing relatively small quantities of parts. 3D printers give designers and concept development teams the ability to produce parts and concept models using a desktop size printer.

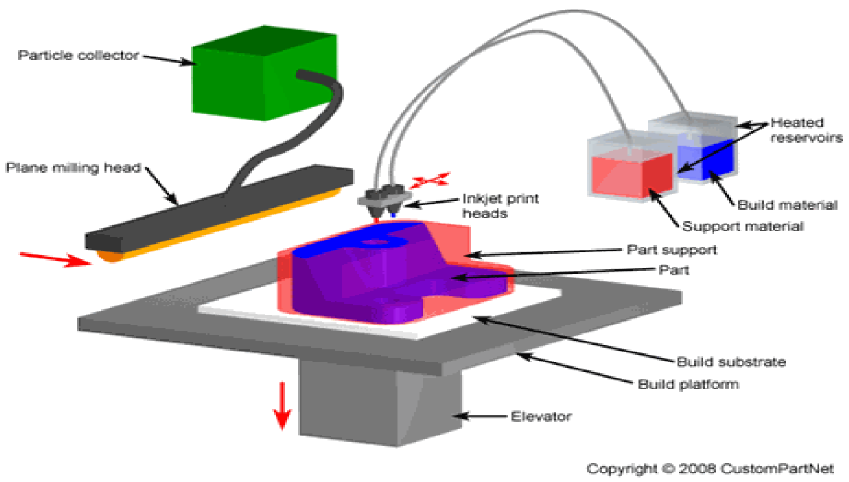
A large number of additive processes are available. The main differences between processes are in the way layers are deposited to create parts and in the materials that are used. Each method has its own advantages and drawbacks, which is why some companies offer a choice of powder and polymer for the material used to build the object. Others sometimes use standard, off-the-shelf business paper as the build material to produce a durable prototype. The main considerations in choosing a machine are generally speed, costs of the 3D printer, of the printed prototype, choice and cost of the materials, and color capabilities. Printers that work directly with metals are generally expensive. However less expensive printers can be used to make a mold, which is then used to make metal parts.[5]

TYPE OF 3D PRINTING TECHNOLOGY

Inkjet Printing: As in many other additive manufacturing processes the part to be printed is built up from many thin cross sections of the 3D model. An inkjet print head moves across a bed of powder, selectively depositing a liquid binding material. A thin layer of powder is spread across the completed section and the process is repeated with each layer adhering to the last. When the model is complete, unbound powder is automatically and/or manually removed in a process called "de-powdering" and may be reused to some extent. The de-powdered part could optionally be subjected to various infiltrants or other treatments to produce properties desired in the final part.[6]

The additive fabrication technique of inkjet printing uses a jet to deposit tiny drops of ink onto paper. When printed, liquid drops of these materials instantly cool and solidify to form a layer of the part. For this reason, the process if often referred to as thermal phase change inkjet printing. Inkjet printing offers the advantages of excellent accuracy and surface finishes. However, the limitations include slow build speeds, few material options, and fragile parts. As a result, the most common application of inkjet printing is prototypes used for form and fit testing.[7]

Inkjet three-dimensional (3D) Printing is a fast, flexible and costeffective technology which enables the construction of both simpleand complicated 3D objects directly from Computer-Aided Design(CAD) data without the need for tooling. Inkjet 3D Printing belongsto a broader family of manufacturing technologies known as SolidFreeform Fabrication (SFF).[8]



Direct-write: The term “Direct Write” (DW) in its broadest sense can mean any technology which can create two- or three-dimensional functional structures directly onto flat or conformal surfaces in complex shapes, without any tooling or masks. Direct Ink Writing (DIW) is an additive manufacturing technique in which a filament of a paste (known as an 'ink', as per the analogy with conventional printing) is extruded from a small nozzle while the nozzle is moved across a platform. The object is thus built by 'writing' the required shape layer by layer.[9]

The process begins with a software process which slices an STL file (stereolithography file format) into layers of similar thickness to the nozzle diameter. The part is produced by extruding a continuous filament of ink material in the shape required to fill the first layer. Next, either the stage is moved down or the nozzle is moved up and the next layer is deposited in the required pattern. This is repeated until the 3d part is complete.[10]

Zip Dose: The first 3D printed pill, an anti-epilepsy drug called Spritam, was recently approved by the FDA. Created by Ohio-based Aprecia Pharmaceuticals, Spritam is made with Aprecia’s proprietary 3D printing technology, ZipDose. ZipDose creates pills that instantly dissolve on the tongue with a sip of liquid, a potential boon to those who have trouble swallowing traditional medications. The ZipDose printer is about 6 feet by 12 feet. Using a small nozzle, it lays down a thin disc-shaped layer of powder. The printer then deposits tiny droplets of liquid on the powder, to bind it together at a microscopic level. These two steps are repeated until the pill reaches its proper height. The final product looks more or less like any regular pill, just slightly taller and with a rougher exterior. While most medications use inert filler material to create the body of the tablet, ZipDose technology allows the active ingredients to be squeezed into a smaller space. So one small pill can have a relatively high dose of medication, meaning patients have to take far fewer tablets.[11]

Fused deposition modelling (FDM): the most widely used is a process known as Fused Deposition Modeling (FDM). FDM printers use a thermoplastic filament, which is heated to its melting point and then extruded, layer by layer, to create a three dimensional object. Objects created with an FDM printer start out as computer-aided design (CAD) files. Before an object can be printed, its CAD file must be converted to a format that a 3D printer can understand — usually. STL format.

FDM printers use two kinds of materials, a modeling material, which constitutes the finished object, and a support material, which acts as a scaffolding to support the object as it's being printed. During printing, these materials take the form of plastic threads, or filaments, which are unwound from a coil and fed through an extrusion nozzle. The nozzle melts the filaments and extrudes them onto a base, sometimes called a build platform or table. Both the nozzle and the base are controlled by a computer that translates the dimensions of an object into X, Y and Z coordinates for the nozzle and base to follow during printing.

In a typical FDM system, the extrusion nozzle moves over the build platform horizontally and vertically, "drawing" a cross section of an object onto the platform. This thin layer of plastic cools and hardens, immediately binding to the layer beneath it. Once a layer is completed, the base is lowered — usually by about one-sixteenth of an inch — to make room for the next layer of plastic. Printing time depends on the size of the object being manufactured. Small objects — just a few cubic inches — and tall, thin objects print quickly, while larger, more geometrically complex objects take longer to print. Compared to other 3D printing methods, such as stereolithography (SLA) or selective laser sintering (SLS), FDM is a fairly slow process.

Once an object comes off the FDM printer, its support materials are removed either by soaking the object in a water and detergent solution or, in the case of thermoplastic supports, snapping the support material off by hand. Objects may also be sanded, milled, painted or plated to improve their function and appearance.[12]

APPLICATION OF 3D PRINTING

3D printing has been around for many years; predominantly been used in manufacturing. This type of printing, also called stereolithography, can create almost any object by fusing different materials, layer by layer, to form a physical version of a digital 3D image. Over the past 15 years, 3D printing has expanded into the healthcare industry, where it's used to create custom prosthetics and dental implants. Now, there may be an opportunity to use it for personalized healthcare as well.[12]

IN HEALTH CARE: It is recognized that medical uses for 3D printing, both actual and potential, will bring revolutionary changes. They can be organized into several broad categories, including: creation of customized prosthetics, implants, and anatomical models, tissue and organ fabrication; manufacturing of specialty surgical instruments, pharmaceutical research regarding drug fabrication, dosage forms, delivery, and discovery as well as manufacturing medical devices. Benefits provided by application of 3D printing in medicine include not only the customization and personalization of medical products, drugs, and equipment, but also cost-effectiveness, increased productivity, the democratization of design and manufacturing, and enhanced collaboration.

It seems that the applications in healthcare can be divided into at least three categories: mainstream or close to them (hearing aids and dental devices), those that are widely used but still are not in the mainstream (including the greater part of the prosthesis market or manufacturing medical devices such as stethoscopes or books for blind, and those in an early stage of development but capable of entering the mainstream (such as bioprinting with cells or 4D printing, that is 3D printing in which the printed object changes its shape after being made, and which are hoped to revolutionize medical 3DP applications in future. Still another area is 3DP of drugs.[13]

PERSONALIZED DRUG DOSING: 3D printing could add a whole new dimension of possibilities to personalized medicine. In its most simplistic form, the idea of experts and researchers is to produce personalized 3D printed oral tablets.

Additionally, a doctor or a pharmacist would be able to use each patient's individual information — such as age, race and gender — to produce their optimal medication dose, rather than relying on a standard set of dosages. 3D printing may also allow pills to be printed in a complex construct of layers, using a combination of drugs to treat multiple ailments at once. The idea is to give patients one single pill that offers treatment for everything they need.

IN HEARING AIDS: 3DP transformed the manual, labor-intensive industry into an automated one that is fast and patient-oriented. Before introducing 3DP into this domain, manufacturing of hearing aids looked like a kind of artisanal production; it took more than a week. Today the 3DP process that involves scanning, modeling and printing can take less than a day. Interestingly, the application of 3DP has not driven the cost of the hearing aids down, probably because few companies dominate the market. It should be stressed that the applications of 3DP in hearing aids manufacturing was analyzed as an example of its disruptive effect on established companies. In Poland, the Institute of Physiology and Pathology of Hearing in Kajetany uses 3DP not to produce implants but for modeling and teaching purposes.[12]

PRINTING LIVING TISSUE: While it's not likely that this will possible on a full scale anytime soon, experts project that science is less than 20 years away from a fully functioning 3D printed heart. But for now, 3D is still challenged by intricate nature of vascular networks. Each organ presents a different level of complexity. So while some tissue would be much easier to print — such as flat structures, like human skin — the most difficult areas in organ printing are the heart, liver and kidneys.[12]

IN DENTISTRY: The first industrial applications of 3DP were in the fields of rapid tooling and rapid prototyping. Thus, its use in dentistry, where single, personalized objects were manufactured, was an obvious next step. Today, by combining oral scanning, CAD/CAM design and 3D printing, dental labs can accurately and rapidly produce crowns, bridges, plaster/stone models, and a range of orthodontic appliances such as surgical guides and aligners. Instead of uncomfortable impressions, a 3D scan is taken, which is later transformed into a 3D model and sent to be 3D printed. The printed model can be used to create a full range of orthodontic appliances, delivery and positioning trays, clear aligners and retainers. Moreover, the models can be conveniently stored digitally as 3D CAD (Computer Assisted Design) files. 3DP allows one to digitize the whole workflow, dramatically accelerating production times and significantly increasing production capacity. In addition, they allow one to eliminate physical impressions and the storage of models.[13]

CONCLUSION

3D printing is a relatively new, rapidly expanding method of manufacturing that found numerous applications in healthcare, automotive, aerospace and defense industries and in many other areas. Today, it is rapidly expanding: almost every week new printers and printing materials offering novel possibilities as well as new exciting applications appear. 3DP applications in medicine are booming. They include customized implants and prosthetics, medical models and medical devices that revolutionize healthcare and may even disrupt many areas of traditional medicine.[13] 3DP technology relies on computer aided designs to achieve unparalleled flexibility, time-saving, and exceptional manufacturing capability of pharmaceutical drug products.[14]

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