ejpmr, 2020,7(3), 473-483

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

3D PRINTING TECHNOLOGY FOR TABLETS: OPPORTUNITIES & CHALLENGES

Rameesha N. K.*, Sirajudheen M. K.[1], Shiji Kumar P. S.[2] and Sherin A.

[1]Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Malappuram, India-673637.
[2]Department of Pharmaceutical Analysis, Jamia Salafiya Pharmacy College, Malappuram, India 673637.

***Corresponding Author: Rameesha N. K.**

Department of Pharmaceutics, Jamia Salafiya Pharmacy College, Malappuram, India-673637.

Article Received on 20/01/2020 **Article Revised on 10/02/2020** **Article Accepted on 02/03/2020**

ABSTRACT

The 3D printing has a role in medical devices industry & pharmaceutical industry due to its application on various channels of health care industry. It has become one of the most revolutionary & powerful tool serving as a technology of precise manufacturing of individually developed dosage forms, tissue engineering & disease modeling. This technology exist for a long time it is of public interest highly now due to the approval of 3D printed tablet, other medical devices & also with the arrival of USFDA's guidance on technical considerations specific to devices using additive manufacturing with possess 3D printing has triggered many thoughts about this technology which needs to be considered for successful delivery of intended product. This review summarizes the newest achievement & challengers of additive manufacturing in the field of pharmaceutical & biomedical research that have been published since 2015. Currently developed techniques of 3D printing are briefly described while extensive analysis of extrusion – based methods as the most intensively investigated is provided. And also this paper presents regulatory agencies expectations, limitations, problems in establishing such setups in production of drug products, advantages, disadvantages, applications, methods and associated risks involved in manufacturing. The issue of printlets attributes,I.e. shape & size is described with regard to personalized dosage forms and medical devices manufacturing. The undeniable benefit of 3D printing are highlighted, however a critical view resulting from the limitation & challenges of the additive manufacturing is also included. It provides the extensive review of the current status of research and development on this platform. As well as the regulatory issue is pointed.

KEYWORD: 3d printing, FDM method, Spritam.

INTRODUCTION

The oral drug administration of drug is the most common route of delivery due to patient's preference. Numerous solid dosage form allows a medication to be administrated by swallowing with tablets and capsules are mostly used. Tablets have lot of advantages over capsule due to low cost in less time. Tablets are solid dosage form obtained by mechanical compression of granules or mixtures of powders with one or more active pharmaceutical ingredients with the addition of excipients. The size, shape and weight of tablet may vary and are derived from the use of punches and matrices. Due to this type of dosage form does not allow for considerable changes in the geometry of the tablet, much less achieving individual dose adjustment for patients.

Based on above mentioned issue, there are two little explored aspects of pharmaceutical technology. The use of geometric design can be used to modify the release of APIs after administration. Such as modifying the buoyancy of the tablet in the stomach. On the other hand it is very difficult to achieve solid dosage form with individual dose adjustment for each patients, taking into account current trends referring to customized medicines. These two features can be overcome using additive manufacturing or 3D printing. An increase or opportunity of this technology is foreseen in the coming years. 3D printers allows to making objects from a digital model. Where the material is added layer by layer to form the final product piece, which can have an unlimited variety of geometries.[1]

3D printing recently explored in the biomedical and pharmaceutical field. It is attractive to scientists and manufacture in the pharmaceutical field that currently are bound to conventional manufacturing method that produce fixed – dose tablets with limited possibilities of customization[2][3] small batches manufacturing or single dose utilizing 3D printing is considered cost effective[4][5][6] when compared to traditional method of manufacturing. Small scale production plays a vital role in personalized drug therapies.[2][7]

In pharmaceutical field 3D printing mainly involved printing of drug - loaded commercially available filaments that were developed for the fused deposition modeling(FDM) 3D printers (eg: poly lactic acid, acrylonitrile butadiene styrene etc.) The oral route of

administration of drug is one of the favored choice for patients.[8][9] Various polymer – drug combination have been hot melt extruded (HME) and other suitability for FDM printing of oral tablets has been explored.[10][11] The recent FDA approval of a 3DP powder layered tablet SPRITAM in 2015[12] and the recent advance in the printing of medicines with multiple API[13][14][15] have already proven 3DP as a basic technology in the manufacturing of solid dosage form.[16]

On the basis of hot extrusion FDM technique the materials used for printings are prepared before printing in the form of paste and then extruded layer by layer without the need of melting the material by nozzle.[17] The materials used for 3D printing are viscoelastic materials that are homogenous and suitable for extrusion under certain conditions and have good shape retain capacity.[18]

Liu et al (2017) established the precision printing of extrusion based materials by studying the importance of edible inks using inks used in 3DP for extrusion based printers, it is an important think to understand the rheological properties of the materials to be printed.[19]

A BIT OF HISTORY

In early 70's of the twentieth century when Pierre A.L.Ciruad described the method of application of powdered material and subsequent solidification of each layer through the action of high energy beam. Meltable materials such as plastics or metals can be theoretically used for the object preparation. In early 80's in a patent entitles :"A molding process for forming a 3D article in layers", Ross Housholder described an idea of sand binding by different materials and Carl Deckard established a method of solidification of powdered bed by laser beam called selective laser sintering (SLS).

Commercially available technology first created by Chuck Hull was stereo lithography (SLA). It was based on photo polymerization of liquid resin by ultraviolet light. At the end of 80's Scott Crump field a patent for fused deposition modelling (FDM) – this technique is used thermoplastic material for object preparation. In 90's Emanuel Sachs – MIT scientist with co - workers patented "3D printing techniques" based on joining the selected regions of powder by binding material.

HOW IT WORKS

Among almost 40 years of 3DP history many several techniques were developed and evolved with the technological progress.

The main methods are based on

- Powder solidification,
- Extrusion
- Liquid solidification,

Fig 2 3DP methods applied for drug formulation.

Despite of the diversity of 3DP methods, preparation of 3D-printed object includes several stages: & the design of 3D object geometry according to printer specification, and the export of 3D model to a common and printer identifiable file format e.g. STL which includes only 3D geometry in form of each vertex position data or OBJ in which additionally information about polygonal faces or color texture are coded, and the import of the file to the software and generation of layers which will be printed. the height of the printed layer essentially influences the quality of the printed object as well as printing time, and the fabrication of the object by subsequent application (or solidification) of the material layers dedicated to the adequate printing method.

The 3D printing methods earn an importance in the field of pharmaceutical and medical applications because of the possibility of rapid preparation of tailor-made objects which can be applied in customized therapy or medicine. The introduction of 3D printing into the pharmaceutical technology particularly goals at the development of patient-centered dosage forms based on structure design. It is still a new research direction with possible to create the targeted release drug delivery systems in freeform geometries. Large scale research are conducted for oral dosage forms because that route of administration still remains the major and the favorite one. Some investigations are also concentrated on dosage forms for topical administration.

3D printing basics

The term 3D printing protect a host of processes and technologies that offer a full spectrum of capabilities for the production of parts and products in different materials. Essentially, what all of the procedure and technologies have in common is the manner in which production is carried out- layer by layer in an additive process which is in different to traditional methods of

production involving subtractive methods or moulding/casting processes. Applications of 3D printing are appearing almost by the day, and, as this technology continues to penetrate more widely and deeply across industrial, maker and consumer sectors, this is only set to increase.

Most esteemed commentators on this technology sector agree that, as of today, we are only just beginning to see the true potential of 3D printing. 3DPI, a reliable media source for 3D printing, brings you all of the latest news, views, process developments and applications as they emerge in this rousing field. This overview article aims to provide the 3DPI audience with a attested backgrounder on 3D printing in terms of what it is (technologies, processes and materials), its history, application areas and benefits. All fronts, more and more systems, materials, applications, services and ancillaries are appearing. History of 3D Printing. The advance 3D printing technologies first became visible in the late 1980's, at which time they were called Rapid Prototyping (RP) technologies. This is because the processes were originally conceived as a fast and more gainful method for creating prototypes for product development within the industry. As an interesting aside, the first patent application for RP technology was filed by a Dr. Kodama, in Japan, in May 1980. Unfortunately for Dr. Kodama, the full patent specification was ensuing not filed before the one-year deadline after the application, which is particularly disastrous considering that he was a patent lawyer. In real terms, however, the origins of 3D printing can be find back to 1986, when the first patent was issued for stereo lithography apparatus (S.L.A).

This patent belonged to one Charles (Chuck) Hull, who first discovered his SLA machine in 1983. Hull went on to co-found 3D Systems Corporation-one of the biggest and most prolific organizations operating in the 3D printing sector today. 3D System's first commercial RP system, the SLA-1, was introduced in 1987 and following severe testing the first of these systems was sold in 1988. As is fairly typical with new technology, while SLA can claim to be the first past the starting post, it was not the only RP technology in evolution at this time, for, in 1987, Carl Deckard, who was employed at the University of Texas, filed a patent in the US for the Selective Laser Sintering (SLS) RP process. This patent was provide in 1989 and later SLS was licensed to DTM Inc., which was later acquired by 3D Systems. 1989 was also the year that Scott Crump, a co- scientist of Stratasys Inc. filed a patent for Fused Deposition Modelling (F.D.M)-the proprietary technology is still held by the company today, but is also the process used by many of the entry-level machines, on the basis of open source RepRap model, that are prolific today. The F.D.M, patent was provide to Stratasys in 1992.

The technology used for printing physical 3D objects from digital data was first developed by Charles Hull in 1984. He named the technique as Stereo lithography and acquired a patent for the technique in 1986. While Stereo lithography systems had become wellliked by the end of 1980s, other similar technologies such as Fused Deposition Modelling (F.D.M) and Selective Laser Sintering (S.L.S) were introduced. In 1993, Massachusetts Institute of Technology (M.I.T) patented another technology, named "3 Dimensional Printing techniques", which is alike to the inkjet technology used in 2D Printers. In 1996, there are three major products, "Genisys" from Stratasys, "Actua 2100" from 3D Systems and "Z402" from Z Corporation, were introduced. In 2005, Z Corp. introduced a breakthrough product, named Spectrum Z510, which was the first high definition color 3D Printer in the market. Another breakthrough in 3D Printing obtained in 2006 with the initiation of an open source project, named Reprap, which was goal at developing a self- replicating 3D printer.

3D printing is now enabling much more innovation in this area, with many researchers investigating the kinetic properties of shapes that were once very hard to produce. 3D printed pyramid-shaped tablets, for instance, may gain vogue as a format for fast-acting remedies because they have been found to release drugs more quickly than standard cylinder-shaped pills. The US Food and Drug Administration (F.D.A) has given the go-ahead to the world's first 3D-printed drug, Spritam, which is intended to treat seizures brought on by epilepsy in adults and children. The drug was developed using Pennsylvania-based Aprecia Pharmaceuticals's proprietary ZipDose technology, which made upon existing 3DP research carried out by M.I.T into creating fast- melting materials. In addition to authorizing the production of more effective dose formats, the technology is likely to play a key part in the pharmaceutical industry's move towards low-volume production and personalised medicine. Going a step further, on-demand drug-printing facilities at clinics and pharmacies, or even in patient's homes, could allow doctors to surpass treatment by creating tailored dosing regimens. In addition to this, doses could be personalised with individual colours, flavours and shapes to retrial to individual patient which will boost their adherence.

Types of 3D printing Hot-Melt Extrusion

A total of 13 formulations which containing 30% (w/w) isoniazid and varying polymers and plasticizers were prepared in 50 g batches (Table I). The powder blends were assorted in a closed plastic container on a Maxiblend (GlobePharma, New Brunswick, NJ, USA) at 25 rpm for a minimum of 20 min before being extruded as cylindrical filaments employ a Thermo Fisher Process 11 mm co-rotating twin-screw extruder (Waltham, MA, USA). A standard screw assembly with three mixing zones are used. Barrel temperatures between 100 to 155°C and a screw speed of 50 rpm were used to extrude the different formulations. Polymer melts were extruded through a circular die (⌀ 2 mm) and guided onto the conveyor belt for cooling and fine-tuning of the filament

diameter. The diameter of the extruded filament is adjusted by changing the speed of the conveyor belt. The hotmelt extruded filaments were coiled and stored in sealed zip lock bags protected from the light, and subsequently used as feedstock material for the FDM 3D printing.

FDM Fused Deposition Modeling

Fused Deposition Modelling, is an additive manufacturing technology frequently used for modelling, prototyping, and production applications. F.D.M, works in an "additive" principle by laying down material in layers. A plastic filament or metal wire is unwound from a coil and provides material to an extrusion nozzle which can turn the flow on and off. Nozzle is heated to melt the material and can be moved in both horizontal and vertical directions by a numerically controlled mechanism, directly controlled by a computer-aided manufacturing (C.A.M) software package. The model or part is produced by extruding small beads of thermoplastic material to form layers as the material solidify immediately after extrusion from the nozzle. Stepper motors or servo motors are typically engage to move the extrusion head. FDM, a prominent form of quick prototyping, is used for prototyping and quick manufacturing. Rapid prototyping facilitates iterative testing, and for very short runs, quick manufacturing can be a relatively inexpensive alternative.

Advantages: Cheaper since uses plastic, more expensive models use a different (water soluble) material to detach supports completely. Even cheap 3D printers have enough resolve for many applications.

Disadvantages: Supports leave streaks that require removing and sanding. Warping, limited testing permitted due to Thermo plastic material.

SLA-Stereolithography

Stereolithography is an additive manufacturing process which recruit a vat of liquid ultraviolet curable photopolymer "resin" and an ultraviolet laser to build part's layers one at a time. For each layer, the laser beam traces a cross-section of the part pattern in the surface of the liquid resin. Exposure to the ultraviolet laser light cures and solidifies the pattern traced on the resin and joins it to the below of layer. After the pattern has been traced, the SLA's elevator platform descends by a distance equal to the thickness of single layer, typically 0.05 mm to 0.15 mm (0.002" to 0.006"). Then, a resin-filled blade is sweeps across the cross section of the part, re-coating it with fresh material. On this new liquid surface, the subsequent layer pattern is draw up, joining the previous layer.

A complete 3-D part is devise by this process. After being built, parts are immersed in a chemical bath in order to be cleaned of excess resin and are later cured in an ultraviolet oven. Stereolithography need the use of supporting structures which serve to attach the part to the elevator platform, prevent deflection due to gravity and hold the cross sections in place so that they withstand lateral pressure from the re-coater blade. Supports are produced automatically during the preparation of 3D Computer Aided Design models for use on the stereolithography machine, although they may be manipulated manually. Supports must be cleared from the finished product manually, unlike in other, less costly, rapid prototyping technologies.

Advantages and Disadvantages: One of the advantages of stereo lithography is its speed; functional parts can be produced within a day. The length of time it takes to manufacture one particular part depends on the size and complexity of the project and can last from a few hours to more than a day. Most stereo lithography machines can produce parts with a maximum size of almost 50×50×60 cm (20"×20"×24") and some, like the Mammoth stereo lithography machine (which has a build platform of 210×70×80 cm), are capable of developing single parts of more than 2m in length. Prototypes made by stereo lithography are strong sufficient to be machined and can be used as master patterns for injection molding, thermoforming, blow molding, and various metal casting processes. Although stereo lithography can produce a wide variety of shapes, it has often been expensive; the cost of photo-curable resin has long ranged from $80 to $210 per liter, and the cost of stereo lithography machines has ranged from $100,000 to more than $500,000. Cheaper S.L.A, 3D printers have been created recently and one can only assume that in the future more will be generated that are within the price range of individuals. SLS-Selective laser sintering: Selective laser sintering is an additive producing technique that uses a high power laser (for example, a carbon dioxide laser) to fuse small particles of plastic, metal (direct metal laser sintering), ceramic, or glass powders into a mass that has wanted three-dimensional shape.

The laser selectively fuses powdered material by scanning cross-sections created from a 3-D digital description of the part (for example from a C.A.D, file or scan data) on the surface of a powder bed. After each cross-section is scanned, the powder bed is lowered by one-layer thickness, a new layer of material is applied on top, and the process is frequent until the part is completed. Because finished part density hang on peak laser power, rather than laser duration, a S.L.S, machine typically uses a pulsed laser. The S.L.S, machine preheats the bulk powder material in the powder bed relatively below its melting point, to make it easier for the laser to increase the temperature of the selected regions the rest of the way to the melting point. Some S.L.S, machines use single-component powder, like direct metal laser sintering. However, most S.L.S, machines use two-component powders, commonly either coated powder or a powder mixture. In single-component powders, the laser melts only the outer surface of the particles (surface melting), fusing the solid non- melted cores to every’

2other and to the previous layer. Compared with usual other methods of additive manufacturing, SLS can make parts from a relatively wide range of commercially available powder materials.

3D Printing Materials

Metals an enlarge number of metals and metal composites are used for industrial grade 3D printing. Two of the most ordinary are aluminium and cobalt derivatives. One of the strongest & therefore most commonly used metals for 3D printing, it is Stainless Steel in powder form for the sintering/ melting/E.B.M processes.

It is naturally silver, but can be plated with other materials to allow a gold or bronze effect. In the last couple of years Gold and Silver have been added to the range of metal materials that can be 3D printed directly, with clear applications across the jewellery sector. These are both very strong materials and are deal with in powder form. Titanium is one of the strongest conceivable metal materials and has been used for 3D printing industrial applications for some time. It is supplied in powder form, it can be used for the sintering/melting/E.B.M processes. Ceramics are a relatively new group of materials that can be used for 3D printing with different levels of success. The particular thing to note with these materials is that, post printing, the ceramic parts need to undergo the same processes as any ceramic part produce using traditional methods of production-namely firing and glazing.

The Printing Cycle

The 3D printing process is clean and highly automated. All the steps involved here take place without any input from you. Preparation-once you click on "3D Print" from ZPrint, the printer initiates a prebuild routine. First, it warms the air inside the printer to generate the optimum operating environment for 3D printing. In the same time, the machine fills the build chamber with a 1/8th inch (3.18 mm) layer of powder so that the parts, when finished, rest on this powder for easy cleared.

The machine may also sprint an automatic head alignment routine. It routine involved printing a pattern onto the powder, reading the pattern with an electronic eye, and aligning its own print heads accordingly. Printing-once the pre-build routine is complete, the printer immediately begins printing the layers produced in the Z Print software. The machine deposits powder from the hopper in the hind of the machine, spreading a thin 0.004 inch (0.1 mm) layer forward across the build platform. This print carriage then moves across this layer, depositing binder (and various inks for a color model) in the pattern of the first slice that was sent from Z Print. The binder solidifies the powder in that cross-section of the model, leaving the rest of the powder dry for recycling the process. At this point, the piston below the build chamber lowers the powder bed 0.004 inch (0.1 mm), make ready for the next layer (see figure 4.1 on page 9).

The cycle repeats itself until the model is completed.

Depowering/recycling-when finished, the model is swing in powder to cure. At the end of the curing time, the machine automatically cleares most of the powder from around the model by applying vacuum pressure and vibration to the bottom of the build chamber. It loose powder is pneumatically conveyed through the system, filtered, & returned to the hopper for use in subsequent builds. Next, you open the front of the machine and displace the part to the fine- depowering chamber. Here you spray the part with compressed air to clear any last traces of powder (this material, too, is automatically vacuumed back into the Z Printer and recycled for future use). All of the powder which enters a Z Printer in the end becomes a model. None is wasted or lost. All powder loading, removal and recycling is part of a closed- loop system supported by persistent negative pressure for involving airborne particles within the machine.

How 3D Printing works when the user clicks "3D Print," the Printer warms up, fills the make chamber with build material, and, if necessary, automatically realigns its print heads. The Printer begins to producing the model, depositing a layer of powder. The print carriage moves across that layer dumping binder (and inks for a color model) in the pattern of the first slice. Steps 3.2 and 3.3 will be repeated until the model is completed. The binder harden the powder in the cross-section of the model, leaving the rest of the powder dry for recycling the process. After each layer, the piston below the made chamber lowers the powder bed, manufacturing for the next layer. The cycle is continues until the model is completed. When finished, the model is suspended in powder for cure. At the end of curing time, the machine simultaneously vacuums most of the powder from around the model and recycles it for use in subsequent builds.

Designing for 3D printing

All the parts developed using a 3D printer need to be designed using some kind of C.A.D, software. This type of manufacture depends mostly on the quality of the C.A.D, design and also the precision of the printer. There are many types of C.A.D, software are available, some are free others require you to buy the software or have a subscription. Deciding what type of C.A.D, software is good for you will depends on the requirements of what you are designing. However, for beginners, that easily want to learn C.A.D, and create basic shapes and features, any of the free C.A.D, software packages will do.

The part needs to be a solid, that is, not just a surface; it requires to have a real volume. Producing very small, or delicate features may not be printed properly, this depends greatly on the type of 3D printer that is going to be used. The Parts with overhanging features will need supports to be printed properly. This should be taken into account since after the model requires to be cleaned by removing the supports.

It may not be an issue unless the part is very delicate, since it might break. Be sure to calibrate the 3D printer before using it, this is essential to ensure that the part sticks properly to the build plate. If it does not, at some point the part may come ruin and loose the entire print job. Some thought should be given to the orientation of the part, since some printers are more precise on the X and Y axes, then followed the Z axis. 3D printing set to revolutionize pharma by Zuzanna Fimińska on Jul 15, 2014. 3D printing is revolutionizing pharma by allowing new substances to be tested directly on human tissues, and by changing the economies of scale, whereby any drug can be more economic.

In 2012, Lee Cronin from the University of Glasgow shared his vision in a T.E.D, talk. In the future, he said, doctors will no longer write prescriptions, but it will provide patients with algorithms that will allow them to print their own medication at home. "With a printer, it should be hopefully that with a relatively small number of inks we can make any organic molecule", then he told the Guardian. If he were right, somewhere down the line, Cronin suggested, the technology would possibly enable a greater range of drugs to be produced, changing the economies of scale, and creating any drug cost effective. Two years ago, Cronin admitted that his vision was in the "science fiction stage," but dream – if in a somewhat altered form – might be turning into reality anticipated than sooner.

Printing drugs

We expect the technology to supplies new chances for specialty products". But printed organs are only one piece of a larger revolution brought upon medicine by 3D printing. Slightly converted version of Cronin's vision is already becoming reality at Aprecia Pharmaceuticals, a company built upon a 3D printing technology platform. They are the first and only company in the world to utilize this technology for the commercial and development scale manufacture of pharmaceutical products.

"We expect the technology which to provide new opportunities for specialty products," said Don Wetherhold, Chief Executive Officer at Aprecia Pharmaceuticals, in an interview with eye for pharma. "We expect it to happen in the high-dose for short time, fast-melt products, which we're focusing on first through our product line. Over time, we believe there will be equal opportunities in controlled release products, for example, to meet the need for a specific release profile for a certain drug," he added.

At Aprecia, they believe that getting medicine into the human body reliably and accurately is both a challenge and a huge opportunity. While the most common method of taking medicines is to swallow tablets, capsules, or liquids, swallowing poses a significant hardens for some people. The elderly, children, and special patient groups (such as stroke, neurological and cancer patients) are all more prone to having difficulty to swallowing tablets and capsules, and while liquids might be perceived as a useful different, they come with their own set of challenges. Overcoming those obstacles translates into real commercial & clinical value by improving patient compliance and accuracy of dosing.

The technology

Founded in 2003, the company has focused on applying 3D printing to a new "fastmelt" formulation platform technology, which brings easy-to-consume functionality to high dose products that remain unaddressed by prior technologies. How does it work - "This technology is a formulation platform for high-dose quickly dispersing dosage forms", Wetherhold explained. "The platform is a result of a good material science and layer-by-layer control of 3DP, earn highly- porous structures even at high loading, and high doses of the drug. Accordingly, our products have more 'headroom' to accommodate taste-masking techniques that go beyond inclusion of flavors and sweeteners, and may contain coating, complexation, or other particle engineering techniques." He goes on: "We chose ingredients from surviving pharmaceutically acceptable materials (e.g.G.R.A.S, food additives, etc.), but employ them somewhat differently – and with very specific process settings to made the porous network of each product.

The end result is a high dose product that still disintegrates very quickly, and we can do this for a wide range of substances." Industry-wide, Wetherhold echoed Cronin's belief, 3D printing will help enable specialized approaches for delivering certain molecules or therapies, or both, offering a "best fit" solution for patients whose requires are not fully met by other technologies. He is enthusiastic about the opportunities to design unique structural or compositional features into each "slice" of the product, but cautions that commercializing the technology might be very difficult than anticipated in a highly regulated industry. Although "We expect to address this challenge as we work through our first N.D.A, demonstrate the commercial path for products like that," Wetherhold asserted.

Regulatory challenges

Aprecia's first product will be a high-dose, fast-melt drug offered in multiple strengths, up to 800 mg, aimed at improving the dosing experience for patients, especially younger and older individuals, who would otherwise have to recieve a very large tablet or a liquid preparation. "We do not expect to announce any additional details until the product is filed," Wetherhold stated, adding that what gives the company a ruthless edge is the fact that they will produce O.D.Ts, [orally disintegrating tablets] with higher strengths than currently available in the market. They expect to file their first N.D.A, in the second half of 2014, and expect approval by the end of the second half of the 2015. According to Stephen King from the C.D.E.R, Trade Press Office at the Food and Drug Administration, Centre for Drug Evaluation and Research, there is a

"clear potential" for 3D printing to allow entirely new formulation types, such as new geometries, complex multi-later or multi-reservoir tablets, to turn 3D printing into large-scale manufacturing the "regulatory requirements could be a hurdle to be removed." "The technology is still in development & has many drawbacks."

Manufacturing a model with the 3D printer

The model to be produced is built up a layer at a time. A layer of powder is simultaneously deposited in the model tray. The print head is then applies resin in the shape of the model. The layer is dries solid almost immediately. The model tray is moves down the distance of a layer and another layer of power is deposited in position, in the model tray. The print head again applies resin in the shape of the model, linking it to the first layer. This sequence occurs one layer at a time until the model, which is complete.

Very recently Engineers at the University of Southampton in the UK have designed, printed, and sent skyward the world's first aircraft created almost entirely via 3-D printing technology. UAV dubbed S.U.L.S.A, is powered by an electric motor that is pretty much the only part of the aircraft not produced via additive manufacturing methods.

World's First 3D Printed Plane Takes Flight Created on an EOS EOSINT P730 nylon laser sintering machine, its wings, hatches and control surfaces basically everything that creates up its structure and aerodynamic controls was custom printed to break together.

We can now use 3D printing to make items using a wide range of filaments, and not just plastics. Metals, edibles, bio and construction materials are just some of the examples that are being produced for 3D printing. So it shouldn't come as a surprise when the U.S. Food and Drug Administration (F.D.A) approved Spritam, is an epilepsy medication develop using 3D printers. This makes Spritam the first 3D printed product approved by the F.D.A for use inside the human body. The company that produced it, Aprecia Pharmaceuticals, used powder-liquid three- dimensional printing (3DP) technology, which was developed by the Massachusetts Institute of Technology (M.I.T) in the late 1980s as a rapid-prototyping technique. In 3Dprinting, rapid prototyping is the same technique used. According to the company, this defenite process was expanded into tissue engineering and pharmaceutical use from 1993 to 2003.

After acquiring exclusive license to M.I.T's 3DP process, Aprecia produced the ZipDose Technology platform. The medication delivery process allows high doses of up to 1,000 mg, rapidly disintegrate to contact with liquid. This is attained by breaking the bonds that were created during the 3DP process. If you advance the technology a decade or more, having the medication you require printed at home is not that implausible. While big-pharma may have something to say about it, new business opportunities will be produce that will be able to monetize the technology.

As impressive as that sounds, there are many more medical applications are in the pipeline. National Institute of Health (N.I.H) has a website with an large scale database of 3D printing applications in the medical field. Which includes the N.I.H, 3D Print Exchange special collection for prosthetics, which lets you print next generation prosthetics at a fraction of the cost of the ones now being sold in the marketplace. The coming next evolution in the field of medicine is printing complex living tissues.

Which also known as bio-printing, the potential applications in regenerative medicine is incredible. In conjunction with the stem cell research, printing human organs is not as far-fetched as it sounds. Currently various body parts have been printed, and the days of long transplant waiting lists will eventually become a thing of the past. It's important to remember that a lot goes into the creation of a medication or other medical break-through than just being able to "print" drugs. Other costs include intensive development and research, then exhaustive testing. So there's no reason to believe the 3D printing alone will allow smaller drug firms to more effectively compete with huge pharmaceutical firms. But the breakthrough will certainly make more opportunities in the medical industry for companies of all sizes.

Outside of medicine, the 3D printing has been used to print cars, clothes and even guns, which goes to prove the only limitation of this technology is your imagination. Many of the technologies we use today were produced many years ago, but they take some time before they are ready for the marketplace. 3D printing is one of the great example. It was founded in 1984, but its full potential is just now being realized. In 2012, The Economist labelled this technology as, "The Third Industrial Revolution," and that sentiment has been echoed by many since then. This has developed unrealistic expectations, even though it is evolving at an impressive rate.

Printing Applications

The origins of 3D printing in 'Rapid Prototyping' were identified on the principles of industrial prototyping as a means of speeding up the earliest stages of product development with a quick and straightforward way of manufacturing prototypes that allows for multiple iterations of a product to arrive more quickly and efficiently at an optimum solution. This saves time and money at the outset of the entire product manufacturing process and ensures confidence ahead of production tooling. Prototyping is still probably the largest and even though sometimes overlooked, application of 3D printing today. The improvements and development of the process and the materials, since the emergence of 3D printing for prototyping, saw the processes being taken

up for applications further down the product development process chain.

Tooling and casting applications were developed utilizing the advantages of the various processes. Again, these applications are increasingly being adopted and used across industrial sectors. Similarly, for final manufacturing operations, the development are continuing to facilitate uptake. In terms of the industrial vertical markets which are benefitting greatly from industrial 3D printing across all of these broad spectrum applications, the following is a basic breakdown: 3D Printing Applications The medical sector is viewed as being one that was an early adopter of 3D printing, but also a sector with big potential for growth, due to the personalization and customization capabilities of the technologies and the ability to improve people's lives as the processes improve and materials are developed that meet medical grade standards. 3D printing technologies are being used for a host of various applications. In addition to creating prototypes to support new product development for the medical and dental industries, the technologies are also utilized to make patterns for the downstream metal casting of dental crowns and in the manufacture of tools over which plastic is being vacuum formed to produce dental aligners. The technology is also taken advantage of directly to develope both stock items, such as hip and knee implants, and bespoke patient-specific Medical and Dental products, such as hearing aids, orthotic insoles for shoes, personalised prosthetics and one-off implants for patients suffering from diseases such as osteoarthritis, osteoporosis and cancer, along with accident and trauma victims.

3D printed surgical guides for specific operations are also an entering application that is aiding surgeons in their work and patients in their recovery. Technology is also being produced for the 3D printing of skin, bone, tissue, pharmaceuticals and even human organs. However, these technologies are remain largely decades away from commercialisation. Like the medical sector, the aerospace sector was an early adopter of 3D printing technologies in their earliest forms for product prototyping and development. These companies, typically working in partnership with academic and research institutes, have been at the sharp end in terms or pushing the boundaries of the technologies for producing applications. Because of the critical nature of aircraft manufacture, the R&D is demanding and strenuous, standards are critical and industrial grade 3D printing systems are put through their paces. Materials development and process have seen a number of key applications developed for the aerospace sector-and some non-critical parts are all-ready flying on aircraft.

Biomedical Engineering in recent year's scientists and engineers have already been able to use the 3D printing technology to create body parts and parts of organs. The first entire organ created through the 3D Printing is expected to be done in the coming years. The process of making the organ or body part is exactly the same as if you were to create a plastic or metal part, however, instead the raw material used are biological cells created in a lab. By making the cells specifically for a particular patient, one can be certain that the patient's body will not reject the organ.

Another application of 3D printing in the biomedical field is that of producing limbs and other body parts out of metal or other materials to replace lost or damaged limbs. Prosthetic limbs are needed in many parts of the world due to injuries sustained during war or by disease. Currently prosthetic limbs are very different and generally are not customized for the patient's needs. The 3D printing is being used to design and produce custom prosthetic limbs to meet the patient's exact requirements. By scanning the patient's body and existing bone structure, designers and engineers are able to re-create the lost part of the limb.

High technology companies such as aerospace and automobile manufacturers have been using now 3D printing as a prototyping tool for some time. However, in recently years, with further advancement in 3D printing technology, they have been able to make functional parts that can be used for testing. This process of design and 3D printing has allowed these companies to advance their designs faster than ever before due to the large reduction in the design cycle. From what used to take months between design and the physical prototype, now within hours the design team can have a prototype in their hands for testing and checking. The future of 3D printing in these industries lies with making working parts directly from a 3D printer for use in the final product, not just for testing purposes. This process is already underway for future aircraft and cars. The way in which the 3D printing works (creating a part layer by layer).

FDA approved the first 3D printed drug product

Aprecia Introduced their First Product Using the ZipDose® Formulation Platform for the Treatment of Epilepsy BLUE ASH, Ohio, August 3, 2015 Aprecia Pharmaceuticals Company today announced that the U.S. Food and Drug Administration (F.D.A) has approved SPRITAM® levetiracetam for oral use as a prescription adjunctive therapy in the treatment of partial onset seizures, myoclonic seizures and primary generalized tonic-clonic seizures in adults and children having epilepsy. SPRITAM utilizes Aprecia's proprietary ZipDose® Technology platform, a ground breaking advance that uses three-dimensional printing (3DP) to generate a porous formulation that rapidly disintegrates with a sip of liquid.

While 3DP has been used previously to produce medical devices, this approval marks the first time a drug product manufactured with this technology has been approved by the F.D.A "By combining 3DP technology with a highly-prescribed epilepsy treatment, SPRITAM is designed to

fill a require for patients who struggle with their current medication experience," said Don Wetherhold, Chief Executive Officer of Aprecia. "This is the first in a line of central nervous system (CNS) products Aprecia plans to introduce as part of our commitment to transform the way patients experience taking medication." ZipDose Technology sanction the delivery of a high drug load, up to 1,000 mg in a single dose. As a result, SPRITAM enhances the patient experience - administration of even the largest strengths of levetiracetam with just a sip of liquid or water. In addition, with SPRITAM there is no measuring required as each dose is individually packaged, creating it easy to carry this treatment on the go. SPRITAM is the expected to be available in the first quarter of 2016. "In my experience, patients and caregivers often have difficulty to following a treatment regimen. Whether they are dealing with a swallowing disorder or the daily struggle of getting a to child take his or her medication, adherence can be a challenge," said Marvin H. Rorick III, M.D, neurologist at Riverhills Neuroscience in Cincinnati, Ohio. "Especially for children and seniors, with an option for the patients to take their medication as prescribed is important to managing that disease." Nearly three million people in the United States have been diagnosed with active epilepsy, with an estimated 460,000 of those cases obtaining in children. Additionally, in a recent survey of people age 65 and older living in an independent living facility, 15 percent reported difficulty to swallowing.

Other chronic conditions can impair the ability to administer, further exacerbating the problem. While there are many reasons, including swallowing difficulties, for which patients may not take their medication as prescribed, missed doses of medication can be undermine treatment outcomes for conditions like epilepsy. Patient's having poor adherence to epilepsy drugs are more likely to have a breakthrough seizure. In one survey completed by the patients, 71 percent of acknowledged having forgotten, missed or skipped a dose of seizure medication at some time, and almost half reported having had a seizure after a missed dose at some time during treatment. About ZipDose®.

Technology ZipDose Technology combines with formulation science, the unique manufacturing capabilities of 3DP. Aprecia developed its ZipDose Technology platform using the 3DP technology that originated to Massachusetts Institute of Technology (M.I.T.). Using 3DP as a catalyst and Aprecia is developing formulations of medicines that rapidly disintegrate with a sip of liquid, even at high dose loads. The company intends to produce them on Aprecia's proprietary equipment. Aprecia holds an exclusive, worldwide license for the pharmaceutical applications of this 3DP technology.

Spritam Indications For Use Spritam

Levetiracetam is a prescription medicine taken by mouth that is used with the other medicines to treat primary generalized tonic-clonic seizures in people 6 years of age and older with certain types of generalized epilepsy, myoclonic seizures in people 12 years of age and older with juvenile myoclonic epilepsy, and partial onset seizures in people 4 years of age and older with epilepsy. Swallow whole SPRITAM along with a sip of liquid, SPRITAM is recommended for use in patients weighing 20 kg (44 lbs) or more. IMPORTANT SAFETY INFORMATION SPRITAM may not be for everyone. Ask your healthcare provider if the SPRITAM is right for you.

Warnings and Precautions for Antiepileptic drugs, including SPRITAM, may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call your healthcare provider right away if you have new or worsening symptoms of depression, any unusual changes in mood or behaviour, or suicidal thoughts, or thoughts about self-harm, behaviour that you have never had before or may be worse than before. SPRITAM may cause extreme sleepiness, tiredness, weakness, and problems with muscle coordination. We should not drive, operate machinery or do other dangerous activities until you know how the SPRITAM affects you. Call your healthcare provider right away if you have any skin rash. Serious skin rashes can obtain after you start taking SPRITAM. There is no way to tell that, if a mild rash will become a serious reaction. Do not stop taking SPRITAM unless instructed by your healthcare provider or physician. Stopping a seizure medication all at once can cause seizures that will not stop, if it stop a very serious problem.

In clinical trials, the most common side effects (incidence ≥5% more than placebo) seen in people who take SPRITAM include sleepiness, dizziness, weakness and infection. In addition to those previously listed, the most common side effects seen in children who take SPRITAM include tiredness, acting aggressive, nasal congestion, irritability and decreased appetite. Talk to your healthcare provider or physician about other possible side effects with SPRITAM. You are supported to report the negative side effects of prescription drugs to the F.D.A. Visit the website www.fda.gov/medwatch or call 1-800-F.D.A,-1088. For additional safety information, please visit

U.S. Full Prescribing Information and Medication Guide at www.SPRITAM.com. This information does not take the place of talking with your healthcare provider or physician about your condition or your treatment. SPRITAM® is one of the registered trademark of Aprecia Pharmaceuticals Company. About Aprecia Aprecia is an entering pharmaceutical company that uses proprietary ZipDose Technology to transform the way people take medicine. Aprecia is the first and only company in the world to utilize three-dimensional printing (3DP) technology to develop and produce pharmaceutical products at commercial scale. Aprecia plans to launch multiple new products utilizing ZipDose

Technology in the coming years, focusing first on the central nervous system therapeutic area, where there is a need for medicines that are easy to take. The company is privately owned, with Prasco Laboratories and its parent company, Scion Companies, holding controlling interest.

CONCLUSION

The present study of 3D printing of oral tablet is relatively low cost and the production of dosage forms with different doses is one of the major advantages in term of short series of medicinal products. The 3D printing brings unequalled opportunities for the development and preparation of personalized medicines at pharmaceutical and industrial scale. 3D printed drugs having the properties like high dose loading, a wide range of taste masking capacities and rapid disintegration in seconds when taken with a sip of water.

3D printing can produce innovative nano medicines through this method. It is mainly produced by FDM and HEM methods. Materials for FDM 3D printing was prepared utilizing HEM. 3D printing become an even more attractive manufacturing method. E.g: Hospital pharmaceutics so that patient sooner could benefit for dosage form adapt according to their needs.

This concluded the newest achievement & challengers of additive manufacturing in the field of pharmaceutical & biomedical research that have been published since 2015. Currently developed techniques of 3D printing are briefly described while extensive analysis of extrusion – based methods as the most intensively investigated is provided.

REFERENCES

1. Marson N, Diaz Nocera A, Real JP, Palma SD. Las impresoras 3D y el dise˜no de medicamentos. Bit´acora Digital, Revista Electr´onica de la Facultad de Ciencias Qu´ımicas – UNC, 2016; (3).
2. Zema L, Melocchi A, Maroni A, Gazzaniga A. Threedimensional printing of medicinal products and the challenge of personalized therapy. J Pharm Sci., 2017; 106(7): 1697–705.
3. Yu DG, Branford-White C, Ma ZH, Zhu LM, Li XY, Yang XL Novel drug delivery devices for providing linear release profilesfabricated by 3DP. Int J Pharm., 2009; 370(1–2): 160–6.
4. Jamróz W, Kurek M, Łyszczarz E, Brniak W, Jachowicz R. Printing techniques: recent developments in pharmaceutical technology. Acta Pol Pharm - Drug Res., 2017; 74(3): 753–63.
5. Lim SH, Kathuria H, Tan JJY, Kang L. 3D printed drug delivery and testing systems—a passing fad or the future? Advanced drug delivery reviews, 2018; 132: 139–168.
6. Palo M, Holländer J, Suominen J, Yliruusi J, Sandler N. Expert review of medical devices 3D printed drug delivery devices: perspectives and technical challenges 3D printed drug delivery devices: perspectives and technical challenges. Expert Rev Med Devices, 2017; 14(9): 685–96.
7. Sandler N, Preis M. Printed drug-delivery systems for improved patient treatment. Trends Pharmacol Sci., 2016; 37(12): 1070–80.
8. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm., 2014; 461(1–2): 105–11.
9. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: opportunities and challenges. Pharm Res., 2016; 33(8): 1817–32.
10. Chai X, Chai H, Wang X, Yang J, Li J, Zhao Y, et al. Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone. Sci Rep., 2017; 7(1): 2829.
11. Goyanes A, Robles Martinez P, Basit AW. Effect of geometry on drug release from 3D printed tablets. Int J Pharm., 2015; 494(2): 657–63.
12. Y.F. He, R.D. Wildman, C.J. Tuck, S.D.R. Christie, S. Edmondson, An investigation of the behavior of solvent based polycaprolactone ink for material jetting, Sci Rep., 2016; 208(6).
13. S.A. Khaled, J.C. Burley, M.R. Alexander, J. Yang, C.J. Roberts, 3D printing of fivein- one dose combination polypill with defined immediate and sustained release profiles, J. Control. Release, 2015; 217(5): 308–314.
14. A. Goyanes, J. Wang, A. Buanz, R. Martinez-Pacheco, R. Telford, S. Gaisford, A.W. Basit, 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics, Mol. Pharm., 2015; 12: 4077–4084.
15. S.A. Khaled, J.C. Burley, M.R. Alexander, C.J. Roberts, Desktop 3D printing of controlled release pharmaceutical bilayer tablets, Int. J. Pharm, 2014; 461: 105–11.
16. I.C.K. Wong, M.A. Ghaleb, B.D. Franklin, N. Barber, Incidence and nature of dosing errors in paediatric medications: a systematic review, Drug Saf., 2004; 661-670.2: 20862.
17. Wegrzyn, Teresa F., Matt Golding, and Richard H. Archer. Food Layered Manufacture: A New Process for Constructing Solid Foods. Trends in Food Science and Technology, 2012.
18. Liu, Z., Zhang, M., Bhandari, B., & Yang, C. Impact of rheological properties of mashed potatoes on 3D printing. Journal of Food Engineering, 2018; 220: 76–82.
19. Liu, Z., Zhang, M., Bhandari, B., & Wang, Y. 3D printing: Printing precision and application in food sector. Trends in Food Science & Technology, 2017; 69: 83-94.5
20. SPRITAM [package insert]. East Windsor, N. J. Aprecia Pharmaceuticals Company 2015. Data on file. Aprecia Pharmaceuticals Company, 2015.
21. Centers for Disease Control and Prevention. Epilepsy Fast Facts. March 12, 2015. Available: http://www.cdc.gov/epilepsy/basics/fast-facts.htm, 2015.

22. Chen P. H, et al., Prevalence of Perceived Dysphagia and Quality-of-Life Impairment in a Geriatric Population. Dysphagia, 2009; 24(1): 1-6.
23. Ekberg O. et al., Social and psychological burden of dysphagia; its impact on diagnosis and treatment. Dysphagia, 2002; 17: 139-146.
24. Davis K. L, Candrilli S. D, Edin H. M. Prevalence and Cost of Nonadherence with Antiepileptic Drugs in an Adult Managed Care Population. Epilepsia, 2008; 49.
25. Stegemann S, Gosch M, Breitkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. International Journal of Pharmaceutics, 2012; 430: 197-206.
26. Cramer J. A, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy and Behavior, 2002; 3(4): 338-342.