World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

3 D PRINTING TECHNOLOGY: A NEW ERA IN MEDICINE

Sachin M. More*[2], U. N. Mahajan[1] and Nitin H. Indurwade[2]

[1]Asst. Professor, Dadasaheb Balpande College of Pharmacy, Nagpur [MS].
[2]Manoharbhai Patel Institute Of Pharmacy, Gondia, India[MS].

***Corresponding Author: Sachin M. More**
Asst. Professor, Manoharbhai Patel Institute of Pharmacy, Gondia, India [MS].

Article Received on 23/01/2018 **Article Revised on 13/02/2018** **Article Accepted on 06/03/2018**

ABSTRACT

Three dimensional printing may open up a whole new chapter of opportunities for pharmaceutical research and bio-technology applications. Three dimensional printing (3D) is a method to make three dimensional objects by fusing or depositing materials including plastic, metal, ceramics, powders, liquids or living cells in layers .There are a number of ways it could be used for manufacturing of drug dosage forms, supporting delivery, or helping to research cures. Several 3D printing technologies, including stereo lithography, deposition modelling, inkjet-based printing and selective laser sintering have been developed. Medical applications for 3D printing are expanding rapidly and are expected to revolutionize healt care. Medical uses for 3D printing, both actual and potential, can be organized into several broad categories, including: tissue and organ fabrication; creation of customized prosthetics, implants, and anatomical models; and pharmaceutical research regarding drug dosage forms, delivery, and discovery. The application of 3D printing in medicine can provide many benefits, including: the customization and personalization of medical products, drugs, and equipment; cost-effectiveness; increased productivity; the democratization of design and manufacturing; and enhanced collaboration. From above information we can conclude that, use of 3 D printing technology is new approach in Medicine. It has potential to change research dimensions of Medical Sciences.

KEYWORDS: 3D printing, Additive Manufacturing, Rapid Prototyping, Stereo Lithography.

INTRODUCTION

Three Dimensional Printing (3D) is a method to make three dimensional objects by fusing or depositing materials including plastic, metal, ceramics, powders, liquids or living cells in layers. This manufacturing process of 3D objects is also referred as Additive Manufacturing (AM), Rapid Prototyping (RP), Solid Free-Form Technology (SFF). 3D printers are similar to traditional inkjet printers. 3 D printing technology is used in several streams of science including metallurgy, mechanical engineering, chemical engineering, energy technologies, and medicine.[1]

Its application in medicine is expected to revolutionalise medical field. "3 D printing is a revolution" said Procopio. "Once I saw 3D printers in action, I saw the light about what they could do for drug production in the future." Additive technology can design a high-surface-area device that maintains the same surface area when shrunk to production size, said Procopio. This can't be done with traditional means. "You can design something by supplying criteria and using software to build to specs," Procopio continued. Just come up with an optimized geometry, then 3D print it. "Complexity is free in 3D printing," he noted. "You don't have to think about how to make it—the printer creates the complexity." 3D printing is 2D printing—several thousand times," Procopio explained. The printers stack layers to generate parts. Currently, there are two modes of 3D printing. Thermal phase transition—"a glorified hot glue gun"—uses laser sintering to weld polyamide particles together, or fused deposition modeling (FDM), which works with a limited set of materials, most of them not relevant to the pharma industry.[2]

3D printing is gaining increasing attention in pharmaceutical formulation development as an effective strategy to overcome some challenges of conventional pharmaceutical unit operations. 3D printing could change the way you are healed. It could help doctors create personalised treatments, unique to each patient. For instance, the conventional manufacturing unit operation involving milling, mixing, granulation and compression can result in disparate qualities of the final products with respect to drug loading, drug release, drug stability and pharmaceutical dosage form stability. The efforts in developing 3DP in pharmaceutical product development resulted in a landmark FDA approval (August, 2015) o

Levetiracetam (SPRITAM®) tablets (www.accessdata.fda.go v). The porous structure of the tablets means they dissolve more readily when introduced to water, making them easier to swallow. This attribute is especially important for children and elderly patients.[2]

Figure 1: Spritam 750 mg (foreground) and 1,000 mg tablets.

The term 3D printing covers a host of processes and technologies that over a full spectrum of capabilities for the production of parts and products in different materials. Essentially, what all of the processes and technologies have in common is the manner in which production is carried out-layer by layer in an additive process-which is in contrast to traditional methods of production involving subtractive methods or moulding/casting processes. Applications of 3D printing are emerging almost by the day, and, as this technology continue to penetrate more widely and deeply across industrial, maker and consumer sectors. Most reputable commentators on this technology sector agree that, as of today, we are only just beginning to see the true potential of 3D printing.[3]

THE HISTORY OF 3D PRINTING

- The earliest 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 cost-effective method for creating prototypes for product development within industry. As an interesting aside, the very first patent application for RP technology was filed by a Dr Kodama, in Japan, in May 1980.
- In real terms, however, the origins of 3D printing can be traced back to 1986, when the first patent was issued for stereolithography apparatus (SLA). This patent belonged to one Charles (Chuck) Hull, who first invented his SLA machine in 1983.
- 3D Systems' first commercial RP system, the SLA-1, was introduced in 1987 and following rigorous testing the first of these system was sold in 1988. Carl Deckard, who was working at the University of Texas, filed a patent in the US for the Selective Laser Sintering (SLS) RP process. This patent was issued in 1989 and SLS was later licensed to DTM Inc, which was later acquired by 3D Systems.
- 1989 was also the year that Scott Crump, a co-founder of Stratasys Inc. filed a patent for Fused Deposition Modelling (FDM) .The FDM patent was issued to Stratasys in 1992.
- In Europe, 1989 also saw the formation of EOS. Today, the EOS systems are recognized around the world for their quality output for industrial prototyping and production applications of 3D printing. EOS sold its first 'Stereos' system in 1990.
- Other 3D printing technologies and processes were also emerging during these years, namely Ballistic Particle Manufacturing (BPM) originally patented by William Masters, Laminated Object Manufacturing (LOM) originally patented by Michael Feygin, Solid Ground Curing (SGC) originally patented by Itzchak Pomerantz et al and 'three dimensional printing' (3DP) originally patented by Emanuel Sachs et al. And so the early nineties witnessed a growing number of competing companies in the RP market but only three of the originals remain today 3D Systems, EOS and Stratasys.
- In terms of commercial operations, Sanders Prototype (later Solidscape) and Corporation were set up in 1996, Arcam was established in 1997, Objet Geometries launched in 1998, MCP Technologies (an established vacuum casting OEM) introduced the SLM technology in 2000, Envision Tec was founded in 2002. Notably, there were many parallel developments taking place in the Eastern hemisphere. However, these technologies, while significant in themselves and enjoying some local success, did not really impact the global market at that time.
- Specifically, these were 3D printers that kept the focus on improving concept development and functional prototyping, that were being developed specifically as office and user-friendly, cost-effective systems. The prelude to today's desktop machines. However, these systems were all still very much for industrial applications.
- 2012 was the year that alternative 3D printing processes were introduced at the entry level of the market. The B9Creator (utilising DLP technology) came first in June, followed by the Form 1 (utilising

stereolithography) in December. Both were launched via the funding site Kickstarter and both enjoyed huge success.

- As a result of the market divergence, significant advances at the industrial level with capabilities and applications, dramatic increase in awareness and uptake across a growing maker movement, 2012 was also the year that many different mainstream media channel spicked up on the technology.[4,5]

METHODS OF 3D PRINTING

A. Stereo Lithography

Stereo lithography allows you to create a solid, plastic, three dimensional objects from CAD drawings in a matter of hours. It is an Additive manufacturing process which uses a vat of liquid UV curable photopolymer resin and a UV laser to build parts a layer at a time. On each layer, the laser beam traces a part cross-section pattern on the surface of the liquid resin. Most SLA machines can produce parts with a maximum size of 20" x 20" x 24". Prototypes made by SLA can be very beneficial as they are strong enough to be machined and can be used as master patterns for injection moulding, thermoforming, blow moulding, and also in various metal casting processes. Although there are no limitations when it comes to the shape of the parts that it can be created, the process is expensive. An SLA machine can cost up to $100,100 to $400,000.[6,7,8]

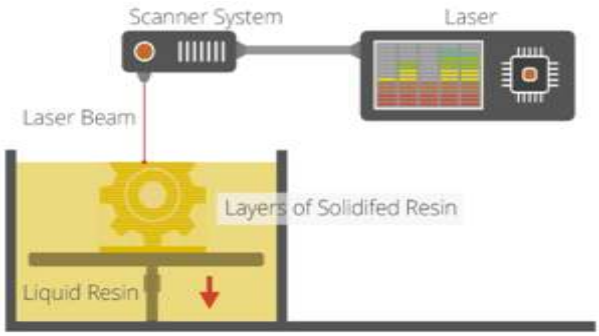

Figure 2: Stereolithography technique of 3D printing.

B. Fused deposition modelling (FDM)

Fused deposition modelling (FDM) is a solid-based rapid prototyping method that extrudes material, layer-by-layer, to build a model. In this method, a thread of plastic is fed into an extrusion head, where it is heated into a semi-liquid state and extruded through a very small hole onto the previous layer of the material. Support material is also laid down in a similar manner. It builds parts with a size of 10" x 10" x 10", by using materials like ABS, Casting Wax. Advantages of this method are High Strength, Water Proof, Cost effective, multiple material colours.

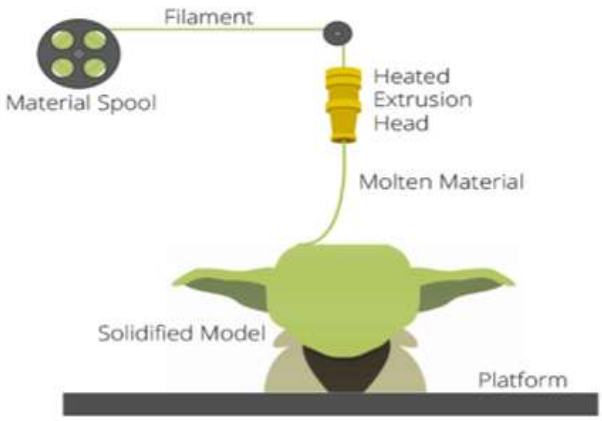

Figure 3: Fused deposition modelling technique of 3D printing.

C. Selective laser sintering (SLS)

Selective laser sintering is an additive rapid prototyping technique that uses a high power laser to fuse small particles of thermoplastic, metal, polyamide (nylon), ceramic, or glass filled nylon. SLS offers the key advantage of making functional parts in essentially final materials, depending on use of the part. Size of SLS single made parts are generally 13.3" x 13.3" x 12". The thickness of an individual SLS layer is 0.15 to 0.2 mm layer thickness, depending upon the material used. The process of SLS is quite simple. The entire internal system is heated to below the melting point of whatever substance is being used. So that when heat is applied by the high energy CO_2 laser melts and sinters the substance. To do this two piston-like platforms, a roller, an optical sensor, and whatever material is being used to form a part are used in co-ordination with the laser. The first piston contains most of the substance. When this piston is raised it makes the substance available to the roller. The roller moves the material over the second position to cover the part being constructed. The material which has been moved to the second piston will then be sintered by the laser, to form an additional layer on the part.

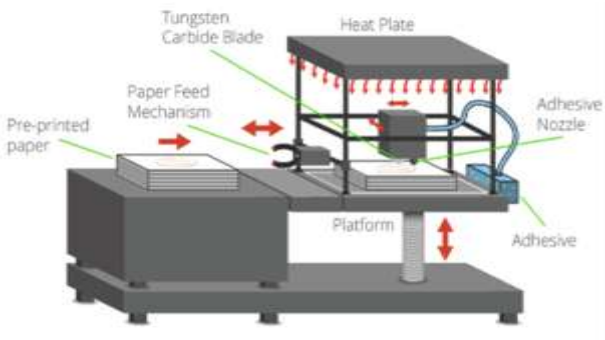

Figure 4: Selective laser sintering technique of 3D printing.

D. Laminated object manufacturing (LOM)

As the name implies the process laminates thin sheets of film. The laser has only to cut the periphery of each layer. In this process the build material is stretched from

a supply roller across a platform to a take-up roller on the other side. A heated roller passes over the paper bonding it to the platform. A laser, focused to penetrate through one thickness of paper cuts the profile of that layer. The excess around and inside the model is etched into small squares to facilitate its removal. The objects created using LOM technique are durable, multilayered structures which can be machined, sanded, polished, coated and painted. It is used as visual models and for limiting testing.[6,7,8]

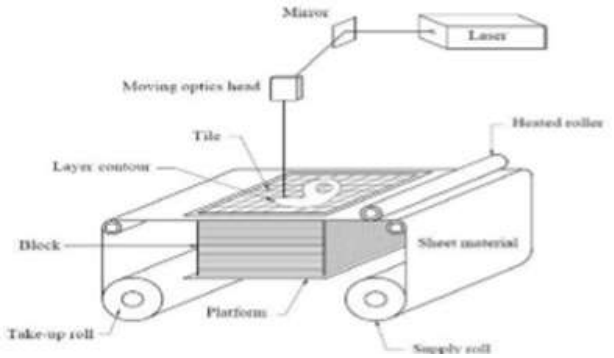

Figure 5: Laminated object manufacturing technique of 3D printing.

3D PRINTING WORKING

The working of 3D printing involves three stages.

- Preparation: Once you click "3D print" from Z-print, the printer initiates the pre build routine. First it warms the air inside the printer and creates optimum operating environment. At the same time, it fills the Build Chamber with 1/8th inch layer powder.
- Printing: Once the pre build is complete, the printer begins printing the layers created in the Z-print software. The machine deposits 0.1mm thick layer of powder from the Hopper. The Print Carriage then moves across this layer depositing the binder. The binder solidifies the powder in that cross section of the model. The piston below the Build Carriage lowers the powdered bed by 0.1mm, preparing the next layer. The process repeats until the model is complete.
- Recycling: When finished the model, it is suspended in the powder to cure. At the end of curing time, the machine then automatically removes most of the powder around the model by vacuum pressure. The loose powder is pneumatically conveyed through the system for reuse.[9]

Table 1: Current 3D printing technologies in pharmaceutical drug delivery.

Type of 3DP Technology	Details
Inkjet Printing	In the technique, different combinations of active ingredients and excipients (ink) are precisely sprayed in small droplets (via drug on demand) or continuous jet method) in varying sizes layer by layer into a non-powder substrate. The technique Silicone is non-degradable, remarkably flexible, and easily generated by mixing a curing agent with an elastomer base. It is extensively used for biomedical instruments (e.g., tubes, catheters, and gaskets) and implants (breast implants and drains).encompasses powder-based 3D printing that uses a powder foundation (powder substrate) for the sprayed ink where it solidifies into a solid dosage form.
Direct-write	Uses a computer-controlled translational stage that moves a pattern-generating device in order to achieve, layer-by-layer, 3D microstructure.
Zip Dose	Provides a personalized dose in addition to the delivery of a high drug-load with high disintegration and dissolution levels by manufacturing highly porous material.
Thermal Inkjet (TIJ) printing	TIJ system consists of a micro-resistor that heats a thin film of ink fluid (located in the ink reservoir) forming a vapor bubble that nucleates and expands to push the ink drop out of a nozzle. TIJ affords the opportunity of dispensing extemporaneous preparation/solution of drug onto 3D scaffolds (drug carriers/films).
Fused deposition modelling (FDM)	The process can be applied to multiple dosage forms that apply polymers as part of the framework such as implants, zero-order release tablets, multi-layered tablets and fast-dissolving devices. In the process the polymer of interest is melted and extruded through a movable heated nozzle. The layer by layer ejection of the polymer is repeated along x-y-z stage, followed by solidification to create a shape previously defined by the computer aided design models.

Table 2: Examples of pharmaceutical formulations that were developed by 3DP technology.

3DP Technology	Dosage Forms	Active Ingredients
Desktop 3D printer	Tablet	Guaifenesin
A laboratory-scale 3DP machine	Capsule	Pseudoephedrine hydrochloride
Fused Deposition Modelling (FDM)	Tablet	5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA)
3DP extrusion-based printing	Tablet	Captopril with Nifedipine and Glipizide
3DP technology	Tablet	Acetaminophen
Inkjet 3DP	Implant	Levofloxacin
3DP machine	Multi-drug implant	Rifampicin and Isoniazid
Inkjet 3DP	Nanosuspension	Folic Acid
Thermal Inkjet (TIJ) Printing	Solution	Salbutamol sulphate
Inkjet 3DP	Nanoparticles	Rifampicin
3D Extrusion Printing	Encapsulated within a polymer (PLGA) poly(vinyl alcohol) (PVA)	Dexamethasone-21-phosphate disodium salt
Thermal Inkjet (TIJ) Printing	Solid dosage forms	Prednisolone

3D PRINTING MATERIALS

In 3Dprinting of an organ-on-a-chip, the printing ink can be any biocompatible material, depending on the purposes and functions of the chip components. Printing inks can be broadly divided into two categories, natural and synthetic. The biological, chemical, and mechanical characteristics differ between the two categories.

A. NATURAL MATERIAL

Natural materials originate from various living organisms and exhibit highly biocompatible characteristics. These materials—such as Alginate, Gellan gum, Collagen, Fibrin, and Gelatin form hydrogels, called Bioinks, and are used to encapsulate cells in 3D cell printing.

- Bioinks have a viscoelastic property and high water content, and protect the cells during the printing process. The cells encapsulated in the hydrogels are insulated from exogenous risk factors such as mechanical stress when passing through the printing nozzle, drying, and potential contaminating factors from the printing space.
- Natural materials from marine algae (e.g., alginate and agarose) and plants (e.g., gellan gum and cellulose) are gel-forming polysaccharides. Because these materials can be massively synthesized from the engineered bacteria.
- Alginate and cellulose can be chemically cross-linked by adding cations such as calcium chloride or other metal salt solutions.
- Agarose and gellan gum show thermos-reversible gelation kinetics. However, these materials inherently have no site that interacts with mammalian cell membrane proteins. Thus, there are many studies on the modification of materials, such as immobilization of arginyl glycylaspartic acid, on the polysaccharide chain.
- Fibrin is a fibrous protein with a crucial role in blood clotting and hemostasis. It is generated by the action of thrombin on monomer fibrinogen. When thrombin releases fibrinopeptides fibrinogen, the remnant fibrin monomers aggregate into insoluble fibrin. Because this reaction proceeds rapidly, fibrin is used extensively as a sealant in clinical treatments.
- Gelatin is mass produced by denaturation of collagen from animal skin and bone. Because gelatine is abundant, low-cost, and easy to handle, it is widely applied in in vitro experiments. The thermal cross-linking mechanism of gelatin is opposite to that of collagen.

The cross-linking mechanism of bioinks made of heart, cartilage, and adipose tissue dECMs is similar to that of collagen, with rheological characteristics that enable 3D printing. Moreover, in each of these bioinks, the stem cells differentiate into a tissue-specific lineage, demonstrated that muscle dECM bioink produces tunable and complex shapes, and generates more matured and functional muscles than single-collagen bioink.[10,11]

B. SYNTHETIC MATERIAL

Synthetic materials are tailorable for a particular purpose and are consistent from batch to batch. The biocompatible synthetic polymers exhibit low cytotoxicity and bioinert property. Since most of these materials show higher stiffness and rigidity than natural hydrogels, they are able to serve as a cell-supporting framework for 3D Cell printing.

- Polycaprolactone (PCL) is an FDA-approved thermoplastic polymer that is widely used in sutures, implantable devices, and other biomedical applications. Although this polymer has biodegradable characteristics, the total degradation period exceeds one year, and it maintains its shape over the usual test period of in vitro experiments.
- Silicone is non-degradable, remarkably flexible, and easily generated by mixing a curing agent with an elastomer base. It is extensively used for biomedical instruments (e.g., tubes, catheters, and gaskets) and implants (breast implants and drains).

- Pluronic F127 is a triblock copolymer consisting of two hydrophilic poly(ethylene oxide) (PEO) blocks and a hydrophobic poly(propylene oxide) (PPO) block, which is arranged in a PEO-PPO-PEO configuration. Above the critical temperature (4 ^{0}C), Pluronic F127 forms micelles in water and exhibits a gel-like viscoelastic property.[11]

PRINTING APPLICATIONS

1) Medicinal application

- **Costumization and personalization**

The greatest advantage that 3D printers provide in medical applications is the freedom to produce custom-made medical products and equipment.3 For example, the use of 3D printing to customize prosthetics and implants can provide great value for both patients and physicians.[12]

- **Personalize drug dosing**

The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalized medications.Oral tablets are the most popular drug dosage form because of ease of manufacture, pain avoidance, accurate dosing, and good patient compliance.1However, no viable method is available that could routinely be used to make personalized solid dosage forms, such as tablets.[12]

- **Increased cost efficiency**

Another important benefit offered by 3D printing is the ability to produce items cheaply.Traditional manufacturing methods remain less expensive for large-scale production; however, the cost of 3D printing is becoming more and more competitive for small production runs. 3D printing can also reduce manufacturing costs by decreasing the use of unnecessary resources. For example, a pharmaceutical tablet weighing 10 mg could potentially be custom-fabricated on demand as a 1-mg tablet. Some drugs may also be printed in dosage forms that are easier and more cost effective to deliever the patients.[13]

- **Implants and prosthesis**

Implants and prostheses can be made in nearly any imaginable geometry through the translation of x-ray, MRI, or CT scans into digital. 3D print files. In this way, 3D printing has been used successfully in the health care sector to make both standard and complex customized prosthetic limbs and surgical implants, sometimes within 24 hours. This approach has been used to fabricate dental, spinal, and hip implants. Previously, before implants could be used clinically, they had to be validated, which is very time-consuming.

2) Medical application

- **Biomedical engineearing**

The process of creating the organ or body parts is exactly the same as if you were to create a plastic or metal parts, however, instead the raw material used are biological cells created in lab. By creating the cell specificity for a particular patients, one can be certain that the patients body will not reject the organ. Another application of 3DP in the biomedical field is that of creating limb or other body parts out of other material to repace lost or damaged limbs. Proshtetic limbs are required in many parts of the world due to injuries sustained during war or by disease. By scanning the patients body and existing bone structure, designers and engineers are able to create the lost parts of that limbs.[14]

- **Organ and tissue bioprinting**

Tissue or organ failure due to aging, diseases, accidents, and birth defects is a critical medical problem. Current treatment for organ failure relies mostly on organ transplants from living or deceased donors. However, there is a chronic shortage of human organs available for transplant.

- **Building vascular organ**

It can use a 3D printer to create an exact replica of a medical model or device, allowing the precise sharing of designs. Toward this end, the National Institutes of Health established the 3D Print Exchange (3dprint.nih.gov) in 2014 to promote open-source sharing of 3D print files for medical and anatomical models, custom labware, and replicas of proteins, viruses, and bacteria.[14]

- **Model for surgical preparation**

The individual variances and complexities of the human body make the use of 3D-printed models ideal for surgical preparation. The use of 3D-printed models for surgical training is also preferable to training on cadavers, which present problems with respect to availability and cost.

3) Commercial application

- **Aerospace**

High technology companies such as aerospace and automobile manufacturers have been using 3D printing as a prototyping tool for some time now. They have been able to create an 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 decrease in the design cycles. The way in which 3D printing works allow the designer to create the part exactly the way is needs to be accomplish the the task at hands. Extremly complex geometry can be easily created by using a 3D printer allowing the parts to be lighter, more stronger than there machined counter parts.[14]

- **Consruction and architecture**

Architects and city planners have been using 3D printers to create a model of the layout or shape of a building for many years. There are already prototype printets that used printer system that use concrete and other more specialized material to create a structure similar to small

house. The goal is the replace many cranes and even construction workers with these printing systems.

- **Product prototype**

The creation of new product is always one of that involve many changes in the same design. 3D printing revolutionized the industry by allows designers to create their new design. Plastic parts for ex., required molds and tooling to be created, these customs parts are expensive to create, therefore one must be certain the designed meets the requirements. With the 3D printing you can create a part that will look and feel exactly like the finished product.[14]

Challenges, Prospects and Our Perspectives

3DP technology has many anticipated advantages that are not yet proven; as such continuous clinical development of 3DP will require vision, money, and time. We envisage that activities to develop 3DP from a broader appeal clinically will include (i) optimization and improvement of software performance, (ii) development of new excipients or assessment of old excipients for application in 3D formulations; and (iii) development and optimization of manufacturing process for a wide range of drug products, and (iv) clinical studies to assess efficacy, safety and stability of new 3D-based formulations.

Apart from the cost of developing new formulations or re-designing existing formulations through 3DP, the built-in flexibility may be a major source of liability from safety point of view. It is important to rule out tampering of the dose or drug through the process to ensure there is no adulteration or mix-up of treatment regimens among patients. It is also anticipated that regulatory stipulations for 3DP formulations will be stringent in order to rule out illegal printing of drug products. Thus, depending on the drug product, it is expected that a broad-based application of 3DP in pharmaceutical drug delivery will be greatly impacted by regulatory concerns and the need to have built-in tamper-proof strategies. Although, 3DP is an adaptable technique for a broad range of pharmaceutical active ingredients, it is important to note that the impact of 3DP on physicochemical properties of a drug and excipients must be established on a case by case basis. This is because it is widely known that the therapeutic efficacy of any drug is affected by properties like drug-excipient interaction, polymorphic changes and stability in the dosage form.

It can be anticipated that a faster way to broaden areas of application of 3DP in pharmaceutical drug delivery is to combine 3DP with conventional pharmaceutical technologies. Such hybrid systems will apply the proven effectiveness of conventional pharmaceutical technologies as well as exploit all the benefits of 3DP with respect to customization, precision and reduction of material wastage.[15]

CONCLUSION

In conclusion, 3DP technology opens the door to a new era of advanced drug delivery with built-in flexibility that is well suited for personalized/customized medicines. We believe that with patience and perseverance, 3DP will continue to revolutionize the development of new generations of pharmaceutical formulations that are safe and effective. 3D Printing technology could revolutionize and re-shape the world. Advances in 3D printing technology can significantly change and improve the way we manufacture products and produce goods worldwide. It has a lot of possible benefits to the society and there will be a significant decrease in the product development cycle and costs. The digital 3D printing revolution could bring mass manufacturing back a full circle to an era of mass personalization, and a return to individual craftsmanship.

REFERENCES

1. Schubert C, van Langeveld MC, Donoso LA. Innovations in 3D printing: a 3D overview from optics to organs. Br J Ophthalmol, 2014; 98(2): 159–161.
2. Klein GT, Lu Y, Wang MY. 3D printing and neurosurgery—ready for prime time? World Neurosurg, 2013; 80(3-4): 233–235.
3. Ursan ID, Chiu L, Pierce A. Three-dimensional drug printing: a structured review. J Am Pharm Assoc, 2013; 53: 136-144.
4. Yu DG, Zhu LM, Branford-White CJ, Yang XL.Three-dimensional printing in pharmaceutics: promises and problems. J Pharm Sci, 2008; 97: 3666-3690.
5. Wang CC, Tejwani Motwani MR, Roach WJ, Kay JL, Yoo J, et al. Development of near zero-order release dosage forms using three-dimensional printing (3-DP) technology. Drug Dev Ind Pharm, 2006; 32: 367-376.
6. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, et al. Multimechanism oral dosage forms fabricated by three dimensional printing. J Control Release, 2000; 66: 11-17.
7. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, et al. Top-Down and Bottom-Up Approaches in 3D Printing Technologies for Drug Delivery Challenges. Crit Rev Ther Drug Carrier Syst, 2015; 32: 61-87.
8. Bertassoni L, Cecconi M, Manoharan V, et al. Hydrogel bioprinted microchannel networks for vascularization of tissue engineering constructs. Lab on a Chip, 2014; 14(13): 2202.
9. Gross, BC, Erkal JL, Lockwood SY, et al. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. Anal Chem, 2014; 86(7): 3240–3253.
10. Ozbolat IT, Yu Y. Bioprinting toward organ fabrication: challenges and future trends. IEEE Trans Biomed Eng, 2013; 60(3): 691–699.

11. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm, 2014; 461(1–2): 105–111.
12. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, et al. Top-Down and Bottom-Up Approaches in 3D Printing Technologies for Drug Delivery Challenges. Crit Rev Ther Drug Carrier Syst, 2015; 32: 61-87.
13. Yu DG, Yang XL, Huang WD, Liu J, Wang YG, et al. Tablets with material gradients fabricated by three-dimensional printing. J Pharm Sci, 2007; 96: 2446-2456.
14. Banks J. Adding value in additive manufacturing: Researchers in the United Kingdom and Europe look to 3D printing for customization. IEEE Pulse, 2013; 4(6): 22–26.
15. Yu DG, Zhu LM, Branford-White CJ, Yang XL. Three-dimensional printing in pharmaceutics: promises and problems. J Pharm Sci, 2008; 97: 3666-3690.