International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Thematic Special Issue 2022

Review Article

A REVIEW ON PRESENT AND FUTURE OUTLOOK OF 3D PRINTING IN TRANSDERMAL DRUG DELIVERY SYSTEMS

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Received: 17 Apr 2021, Revised and Accepted: 31 May 2022

ABSTRACT

The suitability of different printing processes for the direct or indirect printing of microneedle arrays, as well as the modification of their surface with drug-containing coatings, has been investigated. 3D printing refers to a group of technologies that use numerically controlled apparatus to create a physical object from a virtual representation. The transdermal route has been introduced as an alternative to the bolus system. The skin is also identified to pose a barrier to permit molecules. The loss that occurred is compensated by transdermal delivery. 3D printing has several advantages in terms of waste reduction, design flexibility, and lowering the high cost. The compatibility of 3D printing techniques with printed medicine products is a factor in their selection. The variety of printable materials that are presently being used or could be utilized for 3D printing of transdermal drug delivery (TDD) devices. 3D printing has the potential to change today's "one size fits all" production and be used across the medication development process. 3D printing technology in the field of transdermal drug development as the system can be advanced in such as way that concentration can be increased or decreased with various drugs used in the printed featuring layers to enhancement of therapeutic efficacy. The impact and limitations of using 3D printing as a production process for transdermal drug delivery devices are required to be evaluated. This review discusses the present and future overlook of 3D printing technology of transdermal drug delivery systems and some advantages and disadvantages of 3D printing technology over conventional drug delivery approach.

Keywords: History of 3D printing, 3D printing, Pharmaceutics, TDDS, Applications, Present and Future outlook, Advanced drug delivery technology

DOI: https://dx.doi.org/10.22159/ijap.2022.v14ti.15 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Since its discovery in the early 1980s, the 3DP approach has proven to be one of the most promising applications in drug delivery, particularly in the pharmaceutical area. Due to the benefits of 3D printing technology in the fabrication of drug delivery systems, their use has expanded in recent years. Three-dimensional printing is a new approach that allows transdermal medication delivery devices to be printed on demand.

Drug delivery systems are consisting of drug formulation, medical devices, or technology involved in carrying the active pharmaceutical ingredients inside the body and released at a particular region at a predetermined time to show high therapeutic efficacy with fewer side effects. In the drug delivery systems, conventional drug delivery approaches are comprised of the formulation of the active ingredients into a suitable form in a predictable as well as a predetermined rate through various routes such as orally, parenteral, rectal, etc. Due to lack of specificity, fluctuation of plasma concentration, high frequency of dosage form, low therapeutic efficacy, high toxicological as well as high adverse effects which enhance patient's compliance. This conventional drawback can be overcome through novel or new drug delivery strategies to target the active pharmaceutical ingredients to the predetermined region. A controlled and predictable rate with a low dose can excrete therapeutical efficacy. The main aim of novel drug delivery is to deliver the drug to the target region or appropriate site by maintaining the desired concentration, minimizing degradation of active ingredients, enhancing bioavailability and stable at various physiological environments with high therapeutic efficacy with fewer side effects. Novel drug delivery technology consists of several research areas: nanoparticles, liposomes, niosome, aquasomes, hydrogel technology, etc. [1, 2].

Transdermal drug delivery technology is a wonderful approach to delivering the dosage form by applied on the skin in a controlled and predictable manner and adhering dosage form through the skin by passive diffusion as the delivery mechanism. Some important criteria followed by transdermal drug delivery systems as pH of the solution must be in between 5-9 because pH of the skin is 5.5, drugs which have a low melting point as below 200°c can be used, and particle size must be less than 40 cm^2 and half-life of the drug should not exceed 2 y [3].

Several advantages can be found over conventional drug delivery technology such as avoidance of first-pass metabolism (maximum drugs degraded due to hepatic first-pass metabolism), avoidance of fluctuation of dosage form, and drugs can be released over an extended time, can be withdrawn at any time and patient compliance can be improved [4]. But it also has some drawbacks as must follow some physiological parameters to deliver the active medication into systems, low doses of drugs can be under the category of transdermal drug delivery, not achieve high plasma drug level, large molecular size is not acceptable for a transdermal patch, not suitable for ionic drugs and skin color and skin properties varies person to person which impacts on drug delivery of transdermal patches [5, 6].

3-D printing technology is started gaining too much attention to formulation development in the manufacturing units for efficiency and effective strategies and able to overcome disadvantages of traditional drug delivery systems [7, 8]. In the manufacturing of conventional drug delivery systems, various units are controlled over time being which can be updated to the quick and huge amount of production by 3D printing technology and reduction of material waste with cost-effectiveness [9, 10].

Search criteria

This review was made after reviewing approximately 80 articles from 2013-2022, which were found on electronic database systems like google scholar, PubMed, Science Direct using keywords like 3D printing technology, 3D printing on drug delivery in transdermal route and effectiveness, advancement of 3D printing technology in transdermal drug delivery, and applications, treating diseases through 3D printing technology etc. After analyzing all articles, few articles were found to be effective for the study about the Present and future outlook of 3D printing technology in transdermal drug delivery systems. Then a

comparative study is presented in this review to make it more informative and relevant.

3D Printing technology

3D printing technology or three-dimensional technology, is an enormous innovation in the field of upcoming drug development to make revolutionary changes in the health care system and is currently used in the field of tissue engineering, dentistry, aerospace engineering, and construction. 3D printing is a three-dimensional process involved in the computer-aided design (CAD) to formulate pharmaceutical dosage forms and achieve flexibility, time-saving, and decreasing patient compliance [11, 12]. Upcoming trends of 3D printing technology impact the field of treating patients as patients with pharmacogenetics, polymorphism, and chronic diseases can be resolved by enhancement of therapeutic activity and low adverse effects. 3D printing is involved in the various types of dosage forms, such as sustained-release tablets, pills, a transdermal patch which consists of multiple units of the dosage form with a single dose that can cure multiple diseases [13].

Charles Hull in 1984 first developed 3D printing technology for 3D objects from digital data and named it Stereo Lithography and patented it in 1986. Fused deposition modeling (FDM) and selectively laser sintering (SLS) was introduced at the end of the 1980s. 3D as 3-dimensional printing technology was patented by the institution of Massachusetts Institute of Technology in 1993, is similar to 2D inject technology and in 2015, Spritam® invented the first formulation (Zipdose®) based on 3D printing technology, which is approved by FDA (Food and Drug Administration) (Aprecia Pharmaceuticals, 2015) [14, 15].

3D printing technology is mainly based on the virtual design stored in Computer-Aided Design files and this file can be created using a 3D scanner and make a 3D digital copy using 3D software [16] (fig. 1).

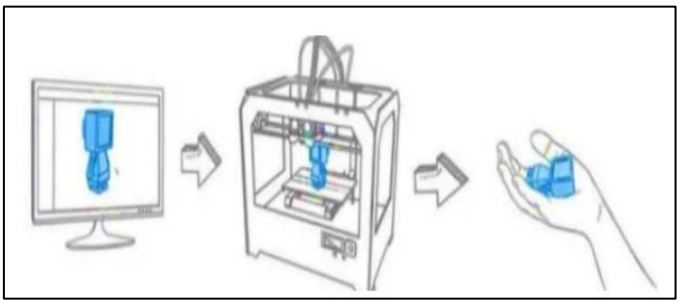

Fig. 1: Process of 3D printing technology

Advantages of 3D printing technology over conventional drug delivery systems

- Fast operating procedures lead to getting a high production yield.
- High drug loading capacity with accuracy and precision and able to make the stability of potent drugs.
- Reduction of material waste with cost-effectiveness [17].
- Poorly water-soluble peptides, proteins and drugs that have low solubility and low therapeutic index can able to formulate through 3D printing technology.
- Patience compliance reduced.
- Through 3D printing technology, drugs with carriers enhance absorption rate and although bioavailability also increases [18] (fig. 2).

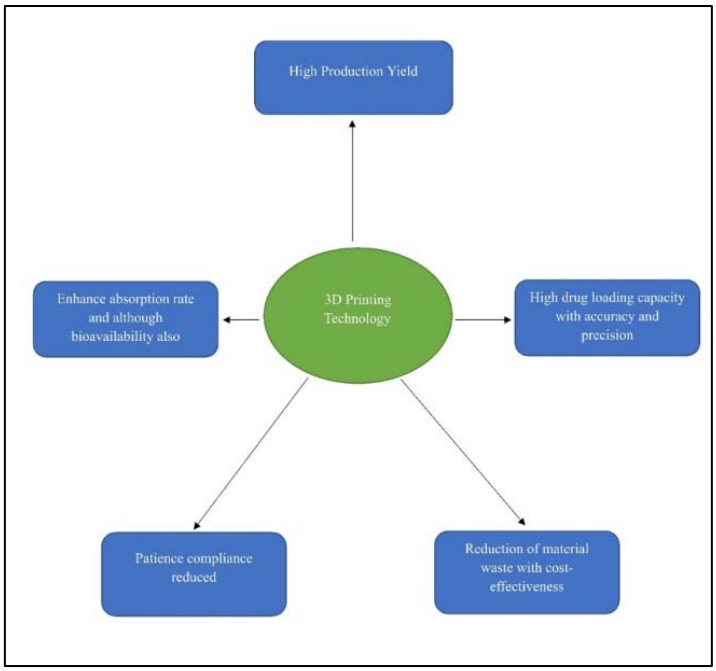

Fig. 2: Advantages of 3D printing technology in drug delivery systems

Disadvantages of 3D printing technology over conventional drug delivery systems (fig. 3)

- Machinery cost is high and maintaining those types of machinery is very difficult.
- Not suitable for large production [19].
- Skilled person required to operate machinery.
- Raw materials are limited for production [20].
- Repeated installation and moves from one end to another end are difficult.
- Toxic items are used as hazardous materials, which enhancement of serious adverse effects.
- Maintaining a therapeutic window is very difficult [21].

Fig. 3: Disadvantages of 3D printing technology in drug delivery systems

3D printing on transdermal drug delivery systems

Transdermal drug delivery is self-discrete, self-administered, painless administration, supplying the dosage form through the skin with controlled and predictable drug release at the desired location, and gaining too much interest to upcoming researchers due to whole drug amount can be administered in a single time [22]. 3D printing technology is started growing technology to the manufacturing units and exploring transdermal drug delivery systems to enhancement of effectiveness, cost reduction, and quick technology [23, 24]. 3D printing technology adopts printing facilities on transdermal patches to gain interest in children and adults. Recently 3D technology is focusing on transdermal drug delivery due to its efficiency, absorption rates, and some physicochemical characteristics that may differ from person to person, which can be overcome easily through this technology [25, 26]. In transdermal drug delivery systems, microneedles are rapidly used in third-world countries for vaccination purposes and there is no assurance for safety or contamination of microorganisms through needles with high price ranges. 3D technology may resolve this problem with high production yield with zero contamination and cost-effective technology [27] (fig. 4).

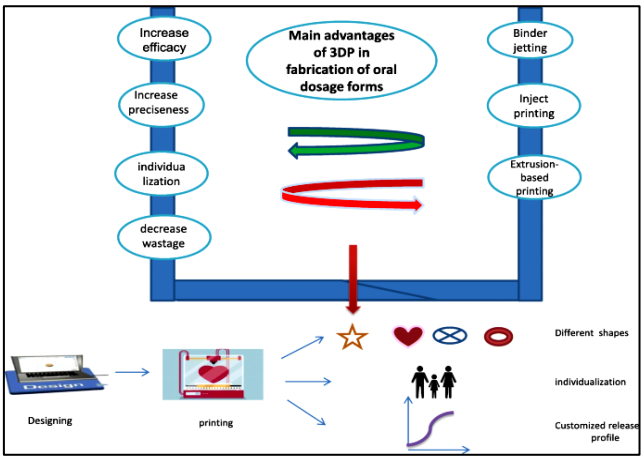

Fig. 4: Advancement of 3D technology over the conventional approach

Present aspect of 3D printing technology of transdermal drug delivery

3D printing technology is a promising approach for upcoming drug delivery systems to overcome some disadvantages of the conventional approach. Biopolymers are used in the traditional drug delivery system and are currently used in 3D printing to the reduction of adverse effects with high therapeutic efficacy [28, 29]. Bioprinting on the transdermal patches is gaining interest the

patience below 18 ages and the most important of biopolymers are compatibility and stability in the transdermal drug delivery systems [30]. Biopolymers are nontoxic, non-irritant, non-immunogenic, chemically inert, and biodegradable [31]. Some biopolymers such as chitosan, gelatin help in the enhancement of mucoadhesion properties, and polyvinyl alcohol, and polylactic acid are amazing bioprinting materials for stability in the transdermal patches [32] (fig. 5).

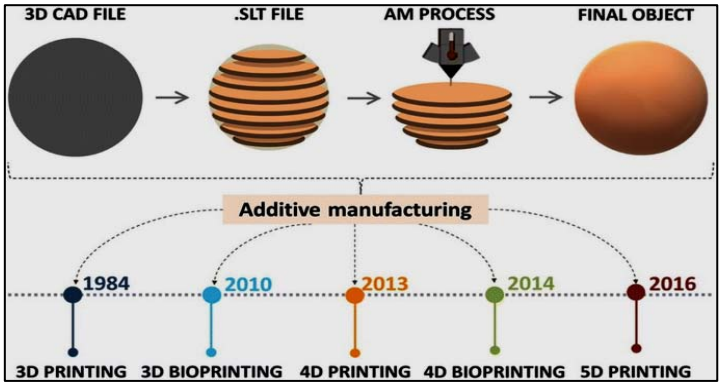

Fig. 5: Recent advancements of 3D printing technology [33]

Some recent technology comes to the markets with several benefits as follows–

Table 1: 3D printing technology applications

3D printing technology	Formulation	Tile	API	Reference
Binder jet printing	Tablets	Fabrication of fast-dissolving drug delivery device	Paracetamol and alizarin yellow (dye)	[34]
	Cubic tabular devices	Development of near zero-order release dosage forms	Pseudoephedrine	[35]
	Tablet	On-demand manufacturing of immediate release	Levetiracetam	[36]
Pressure-assisted microsyringes (PAM),	Semisolid extrusion	Controlled release oral drug delivery	Ramipril	[37]
FDM (Fused deposition modeling)	Tablet	Rapid Drug Release	Haloperidol	[38]
	Intravaginal ring	Medical devices	Clotrimazole	[39]
	Tablet	Fabrication of modified-release tablets	4-amino salicylic acid (ASA) or 5-ASA	[40]
Semi-solid extrusion	Suppositories	Self-Emulsified Drug Delivery System	Tacrolimus	[41]
	Hydrogel	Gummy drug formulations for pediatric use	Lamotrigine	[42]
Direct powder extrusion (DPE)	Tablet	Modified release	Tramadol	[43]

Future aspect of 3D printing in transdermal drug delivery

Recently 3D printing technology is rapidly used in the field of dentistry, and in-situ bioprinting is implanted or living organs are printed during surgery and through bioprinting, repairing the organ such as skin or partially damaged, malfunctioning internal organ or repairing tissues are anticipated as future aspect [44, 45]. 3D printing technology on the treatment of repairing internal organs is a very advanced technology for science and technology and robotic technology in the bioprinters can impact the surgery without having an error with convenience to upcoming medical as healthcare field [46, 47] (fig. 6).

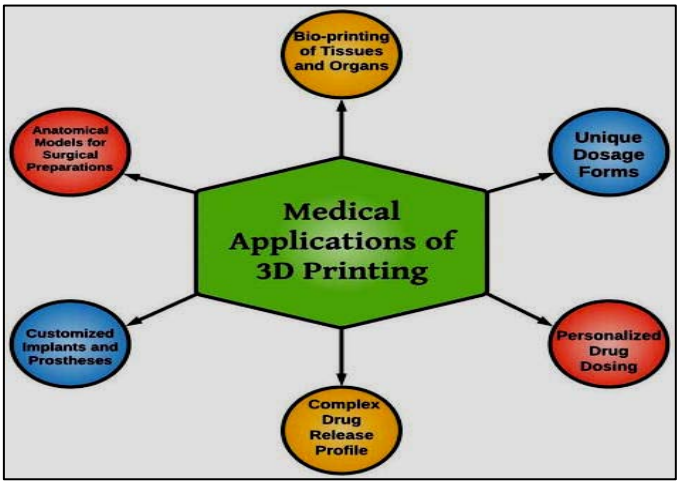

Fig. 6: Medical applications of 3D printing [48]

3D printing technology in the field of transdermal drug development as the system can be advanced in such as way that concentration can be increased or decreased with various drugs used in the printed featuring layers to the enhancement of therapeutic efficacy [49]. Systems can be developed with physiological factors that won't affect transdermal patches and can be stayed long-term with desired release rate and enhancement of therapeutic efficacy with fewer side effects [50].

Table 2: Different formulations of 3D printing

Dosage forms/Systems	Printing technology/Printer type	Drug used	Reference
Novel gastro retentive Floating Pulsatile Drug Delivery	deposition modeling (FDM)	Theophylline	[51]
Multi-active solid dosage form (polypill)	3D extrusion printer	Immediate release compartment with aspirin and hydrochlorothiazide and three sustained-release compartments containing pravastatin, atenolol, and ramipril.	[52]
Oral pulsatile capsule	Deposition modeling (FDM)	Dronedarone hydrochloride and ascorbic acid	[53]
Nanocrystals	3D Printing	Indomethacin	[54]
Nanosuspension	Micro-drop Inkjet 3DP	Folic Acid	[55]
Nanocomposite structure	Commercial inkjet printer	Rifampicin and Calcium phosphate	[56]
Nanocapsules	Fused deposition modeling	deflazacort	[57]

Table 3: Novel applications of 3D printing

Dosage form	Applications area	Method	References
A flexible-dose tablet for immediate and extended-release	Personalized Drug Dosing	Fused deposition modeling 3D printing	[58]
Effect of geometry on drug release from 3D printed tablets	Complex Drug-Release Profiles	Stereolithographic 3D printing	[59]
Nitrofurantoin model disk geometries	Complex Drug-Release Profiles	3D extrusion-based printing	[60]
Nose-shaped mask, laden with salicylic acid, adapted to the morphology of an individual	Personalized Topical Treatment Devices	Fused deposition modeling as well as stereolithography	[61]

CONCLUSION

3D printing is a potential and transformative tool in different fields and plays a very important role in drug delivery and upcoming drug development. Researchers are still focusing on improving the medical application of 3D printing technology in health care systems. Recently 3D printing technology is rapidly used in the field of dentistry, and in-situ bioprinting is implanted or living organs are printed during surgery and through bioprinting, repairing the organ such as skin or partially damaged, malfunction internal organ or repairing tissues are anticipated as future aspect. 3D printing technology in the field of transdermal drug development as the system can be advanced in such a way that concentration can be increased or decreased with various drugs used in the printed featuring layers to enhancement of therapeutic efficacy. Though 3D printing is rapidly developing in medical as health care, more revolution required in organ printing to repair the organ such as skin or partially damaged, malfunctioning internal organ or repairing tissues is anticipated as future aspects. The main motto of the review is the recent and future overlook of 3D printing of transdermal drug delivery systems and some overcome disadvantages of conventional drug delivery systems.

ABBREVIATIONS

3DP = 3D printing.

TDD = Transdermal drug delivery.

FDM = Fused deposition modeling.

PAM = Pressure-assisted microsyringes.

DPE = Direct powder extrusion.

FDA = Food and Drug Administration.

SLS = Selectively laser sintering.

CONSENT FOR PUBLICATION

Not applicable

ACKNOWLEDGEMENT

Thank you Dr. Subhabrota Majumder for supporting the work and revision the manuscript and designing the manuscript.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Soumyadip Ghosh, Debgopal Ganguly, Madhumita Banerjee, Pubali Chakraborty designed the work and revisions in the manuscript. Soumyadip Ghosh provided maximum effort in the correction, collect documents, makes proper format. Debgopal Ganguly did a proper literature survey and designed the manuscript. Madhumita Banerjee and Pubali Chakraborty did a proper review and data collection for writing this manuscript. All the authors design the final manuscript.

CONFLICT OF INTERESTS

Declared none

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