



Application of 3D Printing Technology in the Development of Novel Drug Delivery Systems

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Abstract

Three-dimensional printing (3DP) is a unique prototyping technology that has advanced over the past 35 years and has the great potential to revolutionize the field of drug delivery with its inherent advantages of customizability and the ability to fabricate complex solid dosage forms with high accuracy and precision. 3DP can fabricate solid dosage forms with variable densities and diffusivities, complex internal geometries, multiple drugs and excipients. Literature data suggest many benefits of the 3DP technology over the conventional technologies in the field of novel drug delivery system (NDDS). 3DP can successfully address the issues relating to the drug delivery of poorly water-soluble drugs, peptides, potent drugs and the release of multi-drugs, etc. However, there are some problems that restrict the applications of 3DP in commercial market, such as the selections of suitable binders, excipients and the pharmaco-technical properties of final products. Further advancement in process performance is required to overcome these issues where 3DP technology can be successfully combined with NDDS. Here we present an overview and the potential of 3DP in the progress of new drug delivery systems.

Keywords: Three dimensional printing; Novel drug delivery system; Challenges; Drug delivery

Introduction

The accessibility of 3D printers for both industrial and general public use has grown dramatically in the past decade. Global sales that include the devices, materials and services for industrial-scale to consumer-based printers have grown by an annual average of more than 33% over the last three years to a total of \$4.1 billion in 2014 [1]. A significant driver of this growth is the fact that the early patents related to the manufacturing devices and printer processes have expired. This has opened the door for many start-up companies to develop new 3D printer devices that have pushed innovative design approaches while driving down the cost, in some cases well below \$1000 for an entry-level printer. There are now more than 400 companies selling relatively inexpensive printer devices, which cost less than \$5000. This rapid evolution of the market has placed 3D printers not just in tremendously varied industrial settings but also in schools, public libraries, university classrooms, laboratories, etc. [2-4].

3D printing (3DP) is unique technology that was first described by Charles Hull in 1986 [5]. In its most basic setup, 3DP uses computer-aided drafting technology and programming to produce a 3D object by layering material onto a substrate. The material is first ejected from a printer head onto an x-y plane to create the foundation of the object. The printer then moves along the z-axis, and a liquid binder is ejected onto the base of the object to a certain thickness. This process is repeated following the computer-aided drafting instructions until the object is built layer by layer. After treatment to remove the unbound substrate, the object is complete [6,7]. This process is also referred to as additive manufacturing (AM), rapid prototyping (RP), or solid free-form technology (SFF) [8].

A variety of 3DP technologies have been developed to fabricate novel solid dosage forms, which are among the most renowned and distinct products today [9-11]. 3D printers are also used to directly

print porous scaffolds with designed shape, controlled chemistry and interconnected porosity. They are biodegradable and have proven ideal for bone tissue engineering, sometimes even with site specific growth factor/drug delivery abilities [12-16]. 3D bioprinters offers the capability to create highly complex 3D architectures with living cells [17,18]. This cutting edge technique has significantly gained popularity and applicability in cancer treatment [19,20]. 3DP also offer many novel strategies and approaches in the field of novel drug delivery system and so is becoming of much interest in pharmaceutical industry. Recently engineered solid dosage forms with complex inner structures, geometries, surface texture, multiple drugs and many different types of drug delivery systems have been developed using 3DP. For example oral control released systems, microchip, pills, implants, rapidly dissolving tablets, and multiphase release dosage forms have been developed [21-26]. Moreover, 3DP technology showed many industrial benefits over conventional technologies in designing and fabricating novel drug delivery dosage forms. It is expected that 3DP technology could offer new approaches for developing novel pharmaceutical dosage forms.

Fabrication of various novel drug delivery systems using 3D printers

Drug delivery refers to delivery of a pharmaceutical active ingredient (API) in the body or at the site of action to achieve its desired therapeutic effect. The idea of drug delivery has greatly progressed over the years from conventional dosage forms to novel target drug delivery systems [27]. Therefore, the conventional method like direct tableting are now progressively evolved towards multi-step manufacturing technologies, including granulation, extrusion or coating processes, to allow the development of controlled-release systems. Now-a-days novel concepts of formulation have emerged (e.g., nano-scale medicines, biomimetic particles, functionalized liposomes) as well as more sophisticated manufacturing methods [28-30]. Thus, 3D printing process naturally appeared to be an essential tool in research and development area to fit with actual industrial directions of reducing both time and costs in the early stage of a novel manufacturing concept, reducing the inherent

risk of new development to fail at later stages [31-33]. 3D printing in pharmaceutical industry represents a well-designed tool for designing simple, accurate, cheap, structured and tailored drug delivery systems [34-36]. This flexibility can offer many novel strategic approaches for the research and development of controlled-release drug delivery systems [37,38]. In the last 15 years (Table 1), a large variety of 3D printing techniques have been introduced into the rapid prototyping (RP) industry [39].

Gbureck et al. investigated the adsorption and desorption kinetics of antibiotics from microporous bioceramics (hydroxyapatite, brushite and monetite) fabricated by a novel low temperature 3D powder direct printing process as a drug delivery system. Vancomycin and ofloxacin were rapidly released into buffer media within 24-48 h, while tetracycline showed a sustained release for 5 days. Additional polymer impregnation of the drug loaded matrix with polylactic acid/polyglycolic acid polymer solutions showed improved drug release kinetics [40]. Alvaro et al. demonstrated the feasibility of using fused-filament 3D printer to fabricate drug-loaded tablets which showed

sustained drug release profiles, which can be modified by careful selection of the printing parameters. Their results suggest that the 3D printer could offer a new potential method for manufacturing personalised-dose medicines [41]. They also formulated and developed modified-release drug loaded tablets containing 5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA) via a fused-deposition 3-dimensional printing (FDM 3DP) method with varying infill percentages, which demonstrate the feasibility of using 3D printer to fabricate drug-loaded tablets [42]. In another approach, they explored the feasibility of combining hot melt extrusion with 3D printing technology to formulate different shaped (cube, pyramid, cylinder, sphere and torus) paracetamol-loaded tablets which would be otherwise difficult to produce using conventional traditional methods [43]. Weidong et al. developed levofloxacin implants using a novel 3D printing technique based on a lactic acid polymer matrix with a predefined microstructure that is amenable to rapid prototyping and fabrication. The implant showed bi-modal profile displaying both pulsatile (day 5 to 25) and steady state drug release (day 25 to 50) from a single implant, the next pulse release phase then began at the 50th day

Printing technology/Printer type	Dosage forms/Systems	Model drug used	Reference
3D powder direct printing technology	Microporous bioceramics	Tetracycline, Vancomycin and Ofloxacin	[40]
Fused-filament 3D printing	Tablets	Fluorescein	[41]
3D printer	Tablets	Paracetamol	[43]
3D printer	Complex oral dosage forms	Fluorescein	[45]
3D extrusion printer	Multi-active solid dosage form (polypill)	Aspirin, Hydrochlorothiazide Pravastatin, Atenolol & Ramipril	[47]
Piezoelectric inkjet printer	Microparticles	Paclitaxel	[48]
Fused deposition 3D printing	Extended release tablet	Prednisolone	[49]
3D printer	Tablet implant	Isoniazide	[51]
3D printer	Doughnut-shaped multi-layered drug delivery device	Acetaminophen	[52]
3D printer	Fast-disintegrating drug delivery device	Paracetamol	[53]
Fused deposition 3D printer	Oral pulsatile capsule	Acetaminophen	[54]
3D printer	Fast disintegrating tablet	Acetaminophen	[56]
3D printer	Oral pulsatile tablet	Chlorpheniramine maleate & Diclofenac sodium	[22]
Ink-jet printer	Solid dispersion	Felodipine	[59]
Desktop 3D printer	Bi-layer matrix tablet	Guaifenesin	[46]
Laboratory scale 3-DP™ machine	Capsule with immediate release core and a release rate regulating shell	Pseudoephedrine hydrochloride	[50]
Fused deposition 3D printer	Modified-release drug loaded tablet	5-Aminosalicylic acid & 4-Aminosalicylic acid	[42]
Extrusion-based printer	Multi-active tablets (Polypill)	Captopril, Nifedipine & Glipizide	[65]
3D printer	Complex matrix tablet with ethylcellulose gradients	Acetaminophen	[57]
Inkjet printer	Implant with lactic acid polymer matrix	Levofloxacin	[44]
3D printer	Multi-layered concentric implant	Rifampicin and Isoniazid	[55]
Micro-drop Inkjet 3DP	Nanosuspension	Folic Acid	[70]
Thermal Inkjet printer	Dosing drug Solutions onto oral films	Salbutamol sulphate	[71]
Commercial inkjet printer	Nanocomposite structure	Rifampicin and Calcium phosphate	[72]
3D Extrusion printer	Drug encapsulated film of PLGA and PVA	Dexamethasone	[61]
Thermal Inkjet printer	Oral solid dosage forms	Prednisolone	[73]
3D printer	Microfluidic pump	Saline solution	[74]
Stereolithography printer	Anti-acne patch	Salicylic acid	[66]
3D printer	Biodegradable patch	5-Fluorouracil	[67]
Fused deposition 3D printer	Immediate release tablets	5-Aminosalicylic acid, Captopril, Theophylline & Prednisolone	[68]
Fused-deposition printer	T-shaped intrauterine systems and subcutaneous rods	Indomethacin	[69]
Electro hydrodynamic atomization technique	Patterned micron scaled structures	Tetracycline hydrochloride	[75]
Fused deposition printer	Capsules for immediate and modified release	Acetaminophen and Furosemide	[76]
3D printer	Biofilm disk	Nitrofurantoin	[77]
Multi-nozzle 3D printer	Capsule-shaped solid devices	Acetaminophen & Caffeine	[62]
Fused-deposition printer	Capsule-shaped tablets	Budesonide	[63]
Stereolithographic 3D printer	Modified-release tablets	4-aminosalicylic acid & Paracetamol	[64]

Table 1: Summary of 3-Dimensional printing technologies applied in the development of pharmaceutical drug delivery systems.

and ended up to 80th day [44].

Katstra et al. manufactured oral dosage forms by 3D printing technology which showed excellent content uniformity and dosage control than conventional mixing and pressing techniques [45]. Shaban et al. developed guaifenesin bi-layer tablets using 3D printing technology, which satisfied the requirements of regulatory standards and matches with the release of standard commercial tablets [46]. They also used 3D extrusion printer to manufacture a multi-active solid dosage form (polypill), where the complex medication regimes can be combined in a single personalised tablet. The polypill contain an immediate release compartment for aspirin and hydrochlorothiazide and three sustained release compartments containing pravastatin, atenolol, and ramipril [47]. Byung et al. used a piezoelectric inkjet printing system to fabricate paclitaxel-loaded poly (lactic-co-glycolic acid) polymer microparticles with well-defined and controlled shapes. The microparticles showed a biphasic release profile with an initial burst due to diffusion and subsequent sustained release due to degradation of polymer. The release rate was dependent on the geometry, mainly the surface area, with a descending rate order of honeycomb>grid, ring>circle [48].

Skowyra et al. investigated the feasibility of using a fused deposition modelling based 3D printer to fabricate extended release tablet using prednisolone loaded poly (vinyl alcohol) filaments. The methodology showed highly adjustable, affordable, minimally sized, digitally controlled platform for producing patient-tailored medicines [49]. Wang et al. developed zero-order controlled-release pseudoephedrine hydrochloride formulations using 3-D technology. Mixtures of Kollidon SR and hydroxypropylmethyl cellulose were used as drug carriers [50]. Gui et al. fabricated sustained released isoniazide NH/ Poly-L-lactic acid tablet implant via 3D printing technique for topical drug delivery [51]. Deng et al. developed novel doughnut-shaped multi-layered acetaminophen delivery devices by varying drug and release-retardant material to provide linear release profiles. Based on computer-aided design models, different devices containing acetaminophen, hydroxypropyl methylcellulose as matrix and ethyl cellulose (EC) as a release-retardant material were prepared automatically using a three-dimensional printing (3DP) system [52]. They also fabricated novel fast-disintegrating drug delivery devices with special inner structure characteristics using 3D printers [53]. Melocchi et al. fabricated capsular device for oral pulsatile release based on an erodible hydroxypropyl cellulose using fused deposition modeling 3D printer [54].

Weigang et al. fabricated a programmed release multi-drug implant for bone tuberculosis therapy using 3D printers. The drug implant was a multi-layered concentric cylinder divided into four layers from the center to the periphery. Isoniazid and rifampicin were distributed individually into the different layers in a specific sequence of isoniazid-rifampicin-isoniazid-rifampicin. The *in-vitro* and *in-vivo* release data showed that the isoniazid and rifampicin were released orderly from outside to the center to form a multi-drug therapeutic alliance [55]. Deng et al. fabricated a novel fast disintegrating tablet using computer-aided models (3D printer) to have control over the material composition, microstructure, and surface texture [56]. They also fabricated complex tablets with zero-order drug release characteristics using 3D printer. The matrix tablets with 68% drug weight exhibited material gradients in radial direction with drug-free release-barrier layers on both the sides. *In vitro* results showed linear release up to 12 h, through two-dimensional surface erosion mechanism [57].

Rowe et al. fabricated many different types of complex oral

drug delivery devices using 3D printers, including pulsed release of chlorpheniramine maleate which occurred after a lag time of 10 min, followed by extended release up to 7 h. Breakaway erodible tablets composed of three sections, an interior fast-eroding section separated by two drug-releasing sub-units which erode in 30-45 min in simulated gastric fluid. An enteric dual pulsatory tablet composed of diclofenac sodium was printed into two separated areas. All formulations showed promising results in *in-vitro* drug release studies [58]. To control the release of drug, Nikolaos et al. fabricated felodipine solid dispersion using polyvinyl pyrrolidone by inkjet printer [59]. Natalja et al. fabricated controlled-release oral dosage forms by printing drugs on porous model carriers using inkjet printing technology with flexographic printers. The technology added the advantage of accurate dosing and tailored drug delivery according to dosage requirements [60]. To control the drug release profile, Parawee et al. used a novel extrusion printing system to encapsulate dexamethasone salt within a biodegradable polymer (PLGA) and water soluble poly (vinyl alcohol) (PVA). The *in vitro* studies showed minor burst release with sustained release up to 4 months [61].

Alvaro et al. used multi-nozzle 3D printer to fabricate capsule-shaped solid devices loaded with multiple drugs (Acetaminophen and Caffeine) [62]. They also used fused deposition printing technology with hot melt extrusion and fluid bed coating to develop modified-release budesonide dosage forms [63]. The team also showed the use of stereolithographic 3D printer to fabricate 4-aminosalicylic acid and paracetamol-loaded tablets to tailor the drug release profiles [64]. Shaban et al. used extrusion-based printing technology to fabricate multi-active tablets (Polypill) containing 3 drugs molecules (Captopril, Nifedipine and Glipizide) to treat patients suffering from diabetics and hypertension [65]. Deng et al. developed complex matrix tablet with ethylcellulose gradients to achieve zero-order acetaminophen release using 3D printing processes. The tablet showed linear drug release via a two-dimensional surface erosion mechanism up to 12 h [57]. Alvaro et al. developed salicylic acid patches to treat acne using stereolithography printer. The patch showed high drug loading with release rate of 291 µg/cm² for 3 h, without drug degradation [66]. Gyeong et al. introduced novel 3D-printed patches which composed of a blend of poly (lactide-co-glycolide), polycaprolactone, and 5-fluorouracil to deliver the anti-cancer drug in a sustained manner for 4 weeks. The 3D printing technique provides a versatile shape to the biodegradable patch to be administered at the exact tumor site [67]. Muzna et al. demonstrated a reproducible approach based on pharmaceutical grade non-melting filler which allowed a consistent flow from printer's nozzle to facilitate 3D printed tablets using Eudragit as a polymer filament with four different physiological drugs entrapped. The fabricated immediate release tablets possessed excellent mechanical strength and acceptable in-batch variations [68]. Natalja et al. investigated the printability of different grades of ethylene vinyl acetate copolymers for fused-deposition modeling based 3D printing technology to fabricate T-shaped intrauterine systems and subcutaneous rods to deliver drugs up to 30 days [69].

Challenges in 3D printing technology

Although 3D printing technology showed promising results in drug delivery applications, the technology is still under the developing stage. The challenges include optimization of the process, improving performance of device for versatile use, selection of appropriate excipients, post treatment method, etc., need to be addressed to improve the 3D printed products' performance and to expand the application range in novel drug delivery systems.

Drop-on-demand (DoD) printer heads which are most commonly used in 3D printing technology showed major limitation of nozzle clogging. The binder gets dried up if not frequently used (or improper washing). Also in case of ballistic ejection, agglomeration of fine powder restricts the application in drug delivery [70-78]. The use of electrostatic and acoustic (DoD) print head designs are still in the developing stage [79]. Fluid handling systems are quite complex in continuous jet (CJ) printer, although it allows freedom from nozzle clogging and the use of volatile solvents [32]. To achieve quality 3DP products, the chemistry of binder and formulation need to be addressed. The selected binder in 3DP process should be compatible with the printer head components. Also control over surface tension and viscosity of binder solution is important to achieve stable droplet formation [9]. To apply 3DP for drug delivery, it is mandatory to study the rheological properties of binder solution, especially when high-molecular-weight polymers are involved in dosage forms [80]. In powder deposition technique, polymers must be present in fine particles for 3DP process. Thus the polymer which can be processed in fine particles can only be used in 3DP technology [39]. Stair stepping problem need to be addressed in powder deposition technique [81].

To achieve quality 3DP products, many important parameters need to be optimized like printing rate, printing passes, line velocity of the print head, interval time between two printing layer, distance between the nozzles and the powder layer, etc. [82,83]. It is also important to consider post process after prototyping like drying (hot air heat, microwaves and infrared) methods, as it has major impact on the quality of the finished 3DP products [84-86]. To increase the drug loading capacity in 3DP processed tablet, uniaxial compression and suspension dispersed methodologies are adopted, but this technique suffer from increased complexity and clogging of spray nozzle [87,88]. To achieve precise 3D configuration, high spatial resolution and desirable drug release profile, bleeding must be controlled in printing process. Thus a thorough understanding of powder binder interaction, powder dissolution, re-solidification and evaporation rate of binder liquid is required to control bleeding [57,89-91].

Conclusion

The versatility of 3DP technology sketched in this review clearly shows the benefits in the field of development of novel drug delivery systems. The development of 3DP processes in the field of pharmacy is only in its infancy, but in the near future 3DP approach will be utilized to fabricate and engineer various novel dosage forms, to achieve optimized drug release profiles, developed personalized medicines, avoid incompatibilities between multiple drugs, design multiple-release dosage forms, limit degradation of biological molecules, etc. Although commercial production of such novel dosage forms is still challenging. The scientists are certain that modern pharmaceutical industry is seeing a turning point and that the 3DP of solid dosage forms are set to revolutionize drug delivery.

Declaration of Interest

The authors report no conflicts of interest and have no proprietary or commercial interests in any concept or product or material discussed in this paper.

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