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Review Article

3D Printing Technology in Pharmaceutics an Overview

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There is a constant motivation towards new concepts in drug design, better understanding of material properties, manufacturing technology and processes that assures high quality of dosage forms. The diversity of physicochemical and biopharmaceutical characteristics of active pharmaceutical ingredients (APIs) have to be considered and studied through each stage of product development. Auxiliary substances need to be examined as well in order to manufacture of the desired dosage form. Within last decade the patient-centric drug product development has been under considerable attention. It was focused on novel dosage forms and technological processes. Growing demand for customized devices combined with an expansion of technological innovation drives the major progress in personalized medicine expressed e.g. by the production of small series of individually-selected doses and tailor-made prostheses meet the Anatomical needs of patients. Since long, two dimensional printing technologies (flexographic printing and inkjet technology) are being applied in the pharmaceutical sector and inclusion of three dimensional (3D) printing technology in the same field is relatively new. 3D printing technologies are already in use in many areas like fashion, construction, aerospace and many other industries. In the field of medicine, it is being used in dentistry and tissue engineering. However use of 3D printing technology in pharmaceutical field, is quite recent.

Keywords: 3D Printing Technology, active pharmaceutical ingredients (APIs).

INTRODUCTION

3DP is a form of "additive manufacturing," wherein a structure is built by depositing or binding required materials in successive layers to produce a 3D object. The 3DP term is used as an umbrella term used as coverage of more than 20 printing technologies for healthcare and other industries. 3DP is also named as rapid prototyping, solid freeform fabrication or additive manufacturing. [1] This phase of advanced "additive manufacturing" techniques are under constant advancement for the past 30 years. The earliest technique "stereolithography" was developed by Charles Hull in the early 1980s. Many other techniques, for example, fused deposition modeling (FDM), selective laser sintering (use laser as power source), inkjet-based techniques, extrusion-based FDM and fused filament fabrication (FFF), and pressure-assisted micro (PAM)-syringe technique are gaining popularity these days.[1-3] The 3DP involves the first creation of a 3D model (with the help of a computer), conversion of the model to a printer readable format and 3DP of the same by a layer by layer approach.

The "Spritiam" Revolution

Earlier 3DP was used in the manufacturing of medical devices. However, with the approval of Aprecia's SPRITAM® (levetiracetam) in August 2015, the pharmaceutical manufacturing entered into a new era, i.e., 3D era. SPRITAM® is the first drug approved by using 3DP technology, which rapidly disintegrates (1000 mg of the drug disintegrate in seconds) when

taken with a sip of water. The 3DP is done by ZipDose technology, which stitches together multiple layers of the printed drug to create a three-dimensional structure, which results in the production of a porous, water-soluble matrix. [4-6] This highly soluble form has the potential to become highly beneficial among patients with swallowing disorder or a struggling child and promote adherence to treatment. [7,8]

Three-Dimensional Printing Technologies

There are lots of technologies such as stereolithography, selective laser sintering (use laser as power source), FDM, ink-jetbased techniques, extrusion-based FDM and FFF, and PAM-syringe technique, which are there for 3DP of pharmaceuticals. [1-3]

Stereolithographic technique

It is one of the first 3DP technologies. In this technique, 3D structures are built by solidifying resins and curing it with ultraviolet rays. Photo initiators help in converting light energy to chemical energy in the process. [1,2]

Selective laser sintering

In SLS, powdered materials are sintered with the use of laser beam. With optimal control of heating, 3D structures are created, which needs to be stored in optimal storage conditions to maintain the geometry. [1-3]

Fused deposition modeling

FDM technology was invented as early as the 1990s by Scott Crump. Basically, the FDM technology uses a thermoplastic filament, and two kinds of materials: modeling material and support material. The solid polymer filaments are heated to melting temperature (predefined in the computer file) by a heating block, which is deposited onto the build platform as per predefined coordinates (as defined in the computer-based design file, usually. STL file) through a print head. A layered structure can be formed by repeating this procedure. Another similar technology is FFF. [1-3].

Steps in Three-Dimensional Printing

The first step is design, which is followed by conversion of the design into a format which is readable by the printer, processing of raw materials, printing, and removal and post processing or harvesting. The possible defect in the final product is banding and leaning, which are caused by a disturbance in printing in x-y coordinates, warping due to thermal disturbance, stringing, the collapse of the structure leading to loss of porosity, and unbound residuals. [1-3,5,8,9] The purpose of this review is to highlight the 3D printing techniques being developed for the drug delivery systems. The applications are well arranged in different sections like uses in personalized drug dosing, complex drug release profiles, personalized topical treatment devices, novel dosage forms and drug delivery devices and 3D printed polypills. This review will also summarize the range of dosage forms that have been prepared using these methods, specifically over the last 5 years, 2021 – present.

LITERATURE REVIEW

3D printing has found incredible applications in drug delivery field. Personalized drug dosing allows the flexibility of dosing which is especially useful for the pediatric population. Medications with complex release profiles can be fabricated with this niche technology very effectively since it allows precise dose control and uniformity. Different topical treatment devices were also developed successfully by different research groups with the help of 3D printing technology. Drug delivery devices with novel drug release technology have also been effectively formulated by this new technique. Many research groups have been successfully formulated Polypills with this novel technology.

Personalized Drug Dosing

Since the traditional manufacturing procedures are inappropriate for generating personalized medicines and unable to produce tailored dosage forms with modified release profile and very complex geometries, 3D printing technology has a very good future in personalized medicine [22]. This advances in personalized medicine created a demand for quick, precise and reliable manufacturing technique of tablets which can be digitally operated by healthcare staff. 3D printing technology has been exploited to

modify the dose by changing the size of the printed tablet by software command. For the pediatric population, there is a particular requirement for flexible drug delivery solutions since a wide range of doses is commonly requested. Also, the technology allows flexible in shape of the dosage form to be made to suit patients who have swallowing difficulties. 3D Printing technology brings manufacturing closer to the patient thereby achieves the adjustability of the required dosing scheme as well as offering more flexibility for treatments [23].

Pietrzak et al made a flexible dose theophylline tablet for im-mediate as well as an extended release with accurate drug loading capability and a tablet design which is easy to swallow. They used Fused Deposition Modelling 3D printing. The manufacturing method was found to be affordable and can be controlled digitally and compatible with polymers like hydroxyl propyl cellulose, Eu-dragit RS, RL and E. They obtained a dose accuracy up to 95% with a desired in vitro release pattern and weight accuracy. The method has the potential for future individualized treatment due to highly adjustable nature of the printer in addition to its small size and ease of use [24].

Nicolaos and associates employed hot melt extrusion as the core technique to produce printing filaments and subsequently coupled with a 3D printer [25]. They used hot melt extrusion coupled with fusion deposition modelling to prepare extruded filaments of indomethacin, polyethylene glycol and Hypromellose acetate succi-nate formulations to print Starmix candy like formulations for pediatrics with enhanced palatability. The team got inspired by Starmix flavor gummy sweets for the designing of their chewable tablets. By imitating these popular confectionaries, the 3D printed chewable tablets aim to improve patient compliance and palatability. The formulations were printed in the form of heart, bottle, ring, lion and bear. In vivo taste masking studies confirmed excellent masking of the drug bitterness. The effective taste masking of the Starmix de-signs suggested that 3D printed dosage forms can be successfully used in pediatric applications for enhancing palatability. Drug dis-solution studies showed immediate release regardless of the shape, within 60 min. The study also proved that the optimized printing process accomplished release patterns independent of the printed designs since it is a crucial factor for the manufacturing of oral dosage forms with several designs or shapes. Therefore, it is evi-dent that 3D printing can be successfully used for personalized drug dosing along with greater palatability, especially for the pediatric population.

Tagami and associates prepared polyvinyl alcohol-based cur-cumin tablets by fused deposition modeling 3D printer and investigated the effect of 3D printing parameters on tablet production. It was found that printing g parameters like, flow rate of polymer can affect the formation of the final tablets, printing temperature affect the color and curcumin content [26]. Clark et al. demonstrated 3D printing of ropinirole hydrochloride tablets by piezo-activated inkjet technology. This is the first published research in UV inkjet 3D printing of tablet. The drug was inside of hydrogel matrix of a cross-linked polyethylene glycol diacrylate, photoinitiated in a hypo oxygen environment [27].

Personalized 3D printed medications may mainly helpful for patients who use drugs with narrow therapeutic indices and also for patients with a pharmacogenetic polymorphism. Patient's pharma-cogenetic profile and other parameters like age, gender or race can be used to fix an optimal dosage regime. Pharmacogenetics and pharmacogenomics have been extensively accepted as fundamental steps for the development of personalized medicine. It deals with the response to drugs with individual genotypes, and holds the promise to modernize drug therapy by tailoring it as per individual genotypes. The dose can be adjusted based on the clinical response if needed [28]. Patients having multiple chronic diseases can also greatly benefited from this technology since it can provide an accu-rate, tailored dose of multiple drugs in a single tablet and thereby improved patient compliance can be achieved. In general, all the above-mentioned studies signify their potential to scale up for bulk production and likely to be marketed in future. Currently, various pharmaceutical companies have initiated the use of 3D printed personalized drug dosages in clinical research. Therefore, undoubtedly this move has reduced the bridge between research and clinical application of personalized medicines and holds promise to be an effective approach.

Personalized Topical Treatment Devices

The 3D printing technology is also practicable in the manufacture of custom-made drug-loaded devices in shape and size for the individual patient. Goyanes et al. formulated a nose-shaped mask, laden with salicylic acid, for the treatment of acne vulgaris. 3D scanning technology was used to generate a 3D model of nose of the patient. The efficiency of fused deposition modeling and stereo-lithography was also compared and it was found that stereolitho-graphy printing resulted in a higher resolution and higher drug load-ing with faster drug release without any drug degradation. Thus, the study concluded that 3D printing has a very good potential to offer solutions to produce personalized drug-loaded devices, tailored in shape and size for each patient [46].

Complex Drug-Release Profiles

Formulation of medications with complex drug release characteristics is one of the most explored or studied uses of this novel technology. Several research groups have formulated tablets with different release profiles like immediate, sustained or delayed re-lease by changing polymer type and amount, tablet filling density and tablet shape. [29-31].

Khaled et al formulated sustained release tablets of guaifenesin by 3D printing technology with an identical release profile of standard commercial tablets which are able to satisfy regulatory tests. Hydroxypropyl methylcellulose and poly acrylic acid were used as a hydrophilic matrix for making sustained release layer. Hypromellose was used as a binder and microcrystal-line cellulose and sodium starch glycolate as disintegrants for the production of immediate release layer. A comparable drug release profile was obtained as that of a commercial guaifenesin bi-layer tablet. The printed formulations evaluated for physical as well as mechanical properties and found that the values were within an acceptable range as per US Pharmacopoeia [32]. Wang and co-workers formulated and evaluated the suitability of stereolithographic 3D printing to construct drug-loaded tablets having modified-release characteristics. They used 4-aminosalicylic acid and Paracetamol as sample drugs and the tablets were successfully printed with expected loading and extended drug release profile [33].

Katstra and associates fabricated delayed-release tablets of chlorpheniramine maleate using 3D printing technique. Drug delivery studies with fluorescein proved 3D printing technology is capable of precisely constructing dosage forms with drug content as low as 10 moles per tablet. Friability and hardness of the formulations were also similar to other standard pharmaceutical products [34].

Yu and associates formulated acetaminophen tablets with zero-order drug release profile by 3D printing processes. The matrix tablets showed drug-free release-barrier layers on both bases and material gradients in the radial direction. Dissolution studies proved that drug was released by two-dimensional surface erosion mechanism. They found that through the printing of release retardation ingredients, the technology can easily fabricate tablets with high dose and desired drug release characteristics with the special design [35].

Skowyra and co-workers explored the possibility of using fused deposition modeling using 3D printer for manufacturing extended release prednisolone tablets and to control the release in the desired manner. They fabricated regular ellipse-shaped solid tablets and was able to control the mass of printed tablet by manipulating the volume of the design and obtained a good correlation between targeted and attained doses. The study concluded that fused deposition modelling based 3D printing is a promising technique to produce and control the dose of extended-release tablets, with a highly adjustable, reasonable, small sized and digitally controlled platform for producing patient-tailored medicines [36].

Goyanes and associates examined the possibility of fused-deposition 3D printing to produce modified-release tablets of 5-aminosalicylic acid and 4-aminosalicylic acid. It was found that the tablets were mechanically strong, and proved as an effective process for the manufacture of 5-aminosalicylic acid. They also suggest that the method may not be suitable for thermo degradable drugs for printing at high temperatures since major thermal degradation of the active 4-aminosalicylic acid was observed [37].

Nayan et al developed 3D printed tablets of haloperidol by hot melt extrusion tech-nique and

identified acceptability of different amorphous polymers for rapid drug release [38].

Okwuosa et al. developed dipyridamole as well as theophylline loaded tablets containing high amounts of talc as a crystalline filling agent, where the drugs also remained in the crystalline form. They aimed to bridge 3D printing process with hot melt extrusion in the presence of thermostable filler, talc, for the manufacture of immediate-release tablets at low temperature. The fabricated tablets showed outstanding mechanical properties, very low in-batch variability and an immediate release pattern [39].

Sadia and co-workers employed fused deposition 3D printing to construct immediate-release tablets with many model drugs to explore the effect of nature of filler and compatibility with the printer and polymer to filler ratio on 3D printing process. The study concluded that this unique approach offers a low-cost production technique for on-demand manufacturing of individualized dosage forms [40].

Scoutaris et al. produced a formulation which is capable of controlling the release of felodipine by inkjet printing technology and achieved a good correlation between drug release rate and loading [41].

Rattanakit and associates demonstrated the ability to con-trol the drug release rate through the spatial distribution of dexamethasone within the 3D printed structures. Drug release showed a two-stage release profile with clearly different release rates and minimum initial burst release [42].

Li and associates studied the possibility of 3D extrusion-based printing for the production of gastro-floating tablets using dipyridamole as a model drug. They prolonged the gastric residence time by this new gastric floating tablet with low-density lattice internal structure in order to improve bioavailability and efficacy. They used Hydroxypropyl methylcellulose as hydrophilic matrices and microcrystalline cellulose as an extrusion molding material. The formulated tablets were evaluated for mechanical properties, weight variation, content uniformity, floating time, re-floating ability and drug release pattern. From the study, the team concluded that 3D extrusion-based printing is a promising technique for the fabrication of gastro-floating tablets with commonly used excipients with more than 8h floating time [43].

Chai and co-workers also studied the possibility of fused deposition modeling 3D printing for the formulation of gastric floating sustained release tablets of domperidone. The drug was incorporated into Hydroxypropyl cellulose filaments by a hot melt extrusion technique. Then the drug-loaded filaments were printed as hollow structured tablets. It was found that the optimized formulation floated for about 10 h in vitro and for more than 8 h in the stomach of rabbits and showed a sustained release pattern. From the pharmacokinetic studies, it was found that the optimized formulation had a higher relative bioavailability as com-pared to commercial tablets. Hence this fused deposition modeling 3D printing can also be used for the formulation of gastric floating tablets [44].

Boetker and associates in their work describe a method to modify the release of nitrofurantoin model disk geometries printed by 3D extrusion printing for flexible dosing and precision medication. Polylactic acid and Hydroxypropyl methylcellulose with nitrofurantoin were used as feed materials. The work high-lights the potential of custom-made, feed materials loaded with drug for the production of precision drug products with personalized drug release profile by 3D printing [45]. As a whole, this technology is proved to be efficient for precise manufacturing of low dose tablets in a tailored fashion. Moreover, the promising data observed in various studies point to the fact that drugs with complex release profile and also with dual release characters will be available in the market for personalized treatment regimen using 3D printing in near future.

Novel Dosage Forms and Drug Delivery Devices

3D printing technology can be used to formulate implantable drug delivery devices with modified drug release profiles. For example, bone infection needs direct treatment with the medication on the site. Similarly, surgical treatment of osteoarticular tuberculosis needs filling of the surgical defect [47].

Zhu et al. developed an implant by 3D printing technology, which makes use the merits of osseous

regeneration as well as a local combination therapy for avoiding drug resistance and side effects. They fabricated a 3D-printed macro/mesoporous composite scaffold and loaded with high dosages of isoniazid and rifampin through 3D printing procedure. The composite scaffolds exhibited prolonged drug release time and also maintained desired drug level in peripheral tissues of defect with an extremely low level in blood [48].

3D printing technology is used to print a variety of novel dos-age forms like microcapsules, Nano suspensions, synthetic extracellular matrices, antibiotic printed micro patterns, mesoporous bioactive glass scaffolds and different types of multilayered drug delivery devices.

Lee and associates used a piezoelectric inkjet printing system as a simple and easy approach for the production of paclitaxel Microparticles with pre-defined and controlled shapes. It was found that manufacture by piezoelectric technique was accurate, reproducible, and greatly favorable for bulk production. The developed Microparticles showed a biphasic release pattern with an initial burst followed by slow release and also found that the release rate was related to the geometry and surface area [49].

By 3D printing technique, Zhou and associates developed calcium sulfate powders for using in tissue engineered bone scaffolds. High-quality printed solid and porous scaffolds were manufactured, which showed suffi-cient compressive strength and a very good printing accuracy [50].

Inzana et al., developed rifampin and vancomycin loaded calcium phosphate scaffolds using 3D printing technology for the treatment of an implant-associated Staphylococcus aureus bone infection. It was observed that the treatment considerably reduced the bacterial metabolic load [51].

Wu and co-workers fabricated slow release implant of isoniazid by 3D printing technology and found that the concentration of drug was still higher than the effective bacteriostatic concentration after 30 day's release in vitro. The study concluded that the prepared implant was an ideal drug delivery system for the antibiotics and the technique was reliable to fabricate complicated implants [52].

Huang et al. fabricated implants containing levofloxacin intended for complex drug release profiles. Levofloxacin implants with pre-defined release profile achieved a dual model release profile having both pulsatile as well as a steady-state release as intended. The evaluation results proved that 3D printing technology can be used to manufacture drug implants with complicated micro as well as macro-architecture in a single device which can be easily proto-typed and manufactured and have better advantages than conventionally fabricated implants [53].

Yu and co-workers fabricated multi-layered drug delivery de-vices in the shape of a doughnut with acetaminophen using a 3D printing system. In addition, the dosage can be adjusted. Thus, this study also concluded that 3D technique can be promisingly used for developing drug delivery devices with complex and desired drug release profiles [54].

In another attempt by Yu and associates developed fast-disintegrating drug delivery device with special inner structure characteristics by computer-aided design models and evaluated. It was observed that the devices showed satisfactory pharmacotechnical properties and hardness and a release of 98.5% within 2 min [55].

Conventional chemotherapy has limitations in achieving therapeutic concentrations at the tumor site and also accumulation in vital organs like liver and heart, which cause serious side effects. Therefore, to overcome these difficulties of conventional chemo-therapy, a local highly effective delivery system is needed.

In this context, Yi and associates developed a biodegradable patch with 5-fluorouracil to be administered at the specific tumor site with a versatile shape. The authors observed that necessary therapeutic drug concentration can be achieved by this technology with a pro-longed and controlled release. It was found that the patches were flexible, and provided drug release more than a month. The developed patch was able to control the growth of the subcutaneous pancreatic cancer xenografts in mice with fewer side effects. So the study proved that bio absorbable implants with anti-cancer drugs developed

by 3D printing technology might be a great method for the local delivery of anti-cancer agents [56].

Martinez and associates formulated ibuprofen hydrogels of cross-linked polyethylene glycol acrylate by stereolithographic printing. The prepared hydrogels could entrap 10% w/w ibuprofen and 30% w/w water and from dissolution profiles, it was observed that the drug release rates were dependent on water content, in a manner that faster drug re-lease from hydrogels with higher water content [57].

Alhijjaj and associates prepared solid dispersions of felodipine, by fused deposition 3D printing using polymer mixture of PEG, PEO and Tween 80 along with Eudragit E PO or Soluplus. It was observed that the polymer mixture showed excellent printability and apt for a commercially available fused deposition 3D printer. The rate of drug release was related to the disintegration pattern of the formulation. It was found that the drug release rate was mainly related to three factors including the miscibility of polymer blends, solubility in dissolution media and lastly the degree of fusion among printed strips during printing. The authors suggest that all these factors can be considered to manipulate or control the drug release rate [58].

Hollander and co-workers studied the printability of poly dimethyl siloxane devices for drug delivery by a semisolid extrusion printer along with the UV assisted crosslinking technology which uses UV-LED light. Using prednisolone as a model drug they developed configurations with different pore sizes and drug loading. Minimum three minutes was desirable for the required UV-curing time to achieve adequate crosslinking, yield as well as mechanical strength. It was observed that printing of structures with different release rate can be achieved by altering the surface area to volume ratio. The research team tried both the extrusion 3D print-ing as well as UV-crosslinking at room temperature and concluded that the method is an interesting alternative for manufacturing of controlled release devices with temperature-sensitive drugs [59].

Genina et al., evaluated the applicability of various model substrates including orodispersible films, water impermeable transparent films, and porous copy paper sheets for the formulation of ink-jet-printed drug-delivery systems using rasagiline mesylate. With the help of an off-the-shelf consumer thermal inkjet printer, the team developed flexible doses in a single unit by printing numerous succeeding layers on top of the previously printed ones. It was found that due to absorption of the ink on substrate matrix, no drug crystals were found after printing on the surface of the copy paper. Printing with porous copy paper showed an excellent linear correlation between the dose and the number of printing layers than the other two substrates. So the study concluded that edible substrates having absorption properties comparable to copy paper are promising substrates for the successful development of drug delivery systems by thermal inkjet printers [60].

Beck et al evaluated the coupling of 3D printing and nanotechnology, for the production of new solid dosage forms containing deflazacort loaded Nano capsules. 3D printed tablets were prepared by soaking the filaments [made of poly (ε-caprolactone) and Eudragit RL100 by fused deposition modelling] in deflazacort-loaded Nano capsules of particle size 138 nm. It was found that drug release profile was related to the polymeric material used for the preparation of tablets and also noticed that tablets made with a partially hollow core showed a higher drug loading as well as faster drug release rate. This study is a realistic approach to the conversion of Nano capsules suspensions into solid dosage forms, and also an effective method for the development of novel drug delivery systems, as personalized Nano medicines [61].

Genina and team in another study explored the printability of different grades of ethyl-ene vinyl acetate co-polymers for 3D printing by fused deposition modeling as new feedstock agents for the fabrication of custom-made subcutaneous rods and T-shaped intrauterine systems with indomethacin as a model drug. The feedstock filaments were produced below the melting point of the drug substance. The devices were efficaciously printed at a temperature higher than the melting point of the drug so that the drug in printed prototypes exhibited partly as an amorphous form, whereas in the filaments as a crystalline form. The study points out some grades of ethylene vinyl acetate copolymers which can be used as feedstock agents for fused-deposition modeling 3D printing to produce drug-loaded implants [62]. All these researches give a clear evidence of the

applicability of 3D printing of novel dosage forms including Microparticles, implants, solid dispersions, Nano capsules, patches etc. Many success-ful researches have been done for the local delivery of some anti-cancer agents in the form of patches, implants etc.

3D Printed Polypill

The concept of "polypill" means a single tablet which contains a combination of several drugs and thus potentially improves pa-tient adherence for those who take many different tablets. It also allows tailoring of a specific drug combination or drug release as per individual needs. This provides a great benefit in polymedicated patients, such as the elderly [63]. Khaled and associates formulated polypill with five compartmentalized drugs by 3D printing having two freely controlled and distinct release profiles. The developed formulation is intended for a cardiovascular treatment protocol which contains aspirin and hydrochlorothiazide as immediate re-lease compartment and ramipril, pravastatin and atenolol in three sustained release compartments. The formulation was found to be satisfactory in terms of intended release profile [64]. In another study, Khaled et al explored extrusion-based 3D printing for formulating tablets which contain an osmotic pump with captopril and two sustained release compartments for nifedipine and glipizide. The developed formulations showed satisfactory drug release and found that the captopril segment showed planned zero order release and nifedipine and glipizide followed first order release or Kors-meyer-Peppas release kinetics based on drug excipient ratio used [65].

Genina et al. developed an oral dual-compartmental dosage unit containing rifampicin and isoniazid for physically separating and controlling the release profile of this anti-tuberculosis drug combi-nation. With the help of computer-aided design, the team formulated the unit by a two-step process. Three-dimensional printing of outer structure was the first step, then drug-containing filaments were prepared and deposited by hot-melt extrusion. For modulating the drug release, the compartmentalized shells were selectively sealed. The results of this study support the manufacture of novel design controllable systems for combination therapies for achieving efficient therapeutic conversion of oral dosage forms [66].

Gioumouxouzis and associates formulated a bilayer dosage form containing metformin and glimepiride with different daily dosage regimens by fused deposition modelling 3D printing. The team investigated a number of different production methods, plasticizers and extruders, for the fabrication of Eudragit RL-metformin loaded filaments for the printing of sustained release layer. Glimepiride was incorporated in polyvinyl alcohol layer. The study gives importance to the applicability of 3D printing technology for personalized solid dosage forms with different release pro-files for combined pharmacotherapy [67]. Table 1 summarizes and classifies the different applications of 3D printing technology.

FUTURE PERSPECTIVES

The idea of tailored medication for an individual patient has been around for a while and is recognized and gained much atten-tion nowadays. However, the typical pharmaceutical manufacturing is a large batch process and generally do not support personalized therapy. In this context, 3D printing technology has proved track record in prototyping applications and has been widely used for years in various fields including bioengineering. At present, this additive manufacturing technology has also started to make a name for itself in pharmaceutical drug preparation. Being achieved the commercial status, the 3D printing technology seems to be a turning point in drug formulation and is in the process of challenging the traditional pharmaceutical manufacturing techniques. Various 3D printed formulations have signified that their unique structure can-not be achieved using conventional manufacturing methods. Extensive studies have been carried out by researchers in the past decade on various 3D printing techniques to optimize the printers in order to facilitate the manufacturing of novel drug delivery systems, which can pave the way for individualized drug therapy. Nevertheless, there is enormous scope for this promising technology in de-signing various delivery systems and provides customized patient-compatible formulations with Polypills. For instance, it is some-times necessary to administer multiple drugs in

a particular ailment for treatment, which can be achieved by this enabling technology. Therefore, to have formulations with different drugs and varying release rate are extremely important. Indeed, the 3D technology started receiving greater attention from pharmaceutical companies and is in the process of developing novel formulations to provide customized medicines by controlling drug release rate. The significant and exciting advances in technologies and development of advanced software can lead to the design of single printing device capable of producing multiple release formulations. Few research-ers have already demonstrated immediate and sustained release of different drugs from separate compartments when formulated as Polypills.

3D printing techniques have emerged as a potential alternative for producing drug delivery systems which are generally challenging in conventional methods. On the other hand, considering this niche technology as an alternative to traditional pharmaceutical manufacturing techniques is too ambitious. The feasibility of 3D technology in developing new drug formulations including micro-capsules, hyaluronic-based synthetic extracellular matrices, antibiotic printed micro patterns, mesoporous bioactive glass scaffolds, Nano suspensions, and multilayered drug delivery devices has been demonstrated. The 3D technique seems to be a promising approach to develop Mucoadhesive films or other layered structures, which was demonstrated by different research groups. Hence, this rapid prototyping tool offers the potential to create limitless dosage forms which in turn will take fabrication of drug delivery systems to a new level. Different printing techniques have been explored in formulating various delivery systems with specific geometries, al-though they are not free from one or other limitations. However, one can expect 3D printing as a routine manufacturing process once the technology is well established and the source of printing materials is easily available. The bright future of this printing technology is likely to rely on its potential to provide 3D printing systems.

Table 1. Different applications of 3D printing technology

Applications Area	Dosage Form	Method	References
Personalized Drug Dosing	A flexible-dose tablet for immediate and extended release	Fused deposition modelling 3D printing	Pietrzak et al., [24]
	Starmix candy like formulations of indomethacin	Fusion deposition modelling 3D printing	Nicolaos et al., [25]
	Ropinirole hydrochloride tablets	3D printing using inkjet with UV photo Initiation	Clark et al., [27]
Complex Drug-Release Profiles	Sustained release tablets of guaifenesin	Desktop 3D printer	Khaled et al., [32]
	Modified-release tablets of 4-aminosalicylic acid and	Stereolithographic 3D printing	Wang et al., [33]
	Delayed-release tablets of chlorpheniramine maleate	Fused deposition 3D printing	Katstra et al., [34]
	Matrix tablets of acetaminophen	Desktop 3D printer	Yu et al., [35]
	Extended-release prednisolone tablets	Fused deposition 3D printing	Skowyra et al., [36]
	Modified-release tablets of 5-aminosalicylic acid and 4-amino salicylic acid	Fused deposition 3D printing	Goyanes et al., [37]
	Rapid release tablets of haloperidol	Hot melt extrusion technique	Nayan et al., [38]
	Dipyridaole as well as theophylline loaded immediate-Release Tablets	Hot melt extrusion	Okwuosa et al., [39]
	Immediate release tablets with several model drugs	Fused deposition modelling	Sadia et al., [40]
	Controlled release tablets of felodipine	Inkjet printing technology	Scoutaris et al., [41]

	Controlled release tablets of dexamethasone	Extrusion printing	Rattanakit et al., [42]
	Gastro-floating tablets	3D extrusion-based printing	Li et al., [43]
	Gastric floating sustained release tablets of domperidone	Fused deposition modeling 3D printing	Chai et al., [44]
	Nitrofurantoin model disk geometries	3D extrusion-based printing	Boetker et al., [45]
Personalized Topical Treatment Devices	Nose-shaped mask, laden with salicylic acid, adapted to the morphology of an individual	Fused deposition modeling as well as Stereolithography	Goyanes et al., [46]
Novel dosage forms and drug delivery devices	Implant of isoniazid and rifampin for osseous regeneration as well as local Multi – Drug Therapy	3D-printed macro/meso-porous composite	Zhu et al., [48]
	Paclitaxel Microparticles with well defined and controlled shapes	Inkjet 3D printing	Lee et al., [49]
	Calcium sulfate powders for the application of tissue-engineered bone Scaffolds	Inkjet 3D printing	Zhou et al., [50]
	Rifampin and vancomycin loaded calcium phosphate Scaffolds	Inkjet 3D printing	Inzana et al., [51]
	Slow release implant of isoniazid	Inkjet 3D printing	Wu et al., [52]
	Implants containing levofloxacin for complex drug release Profiles	Inkjet 3D printing	Huang et al., [53]
	Doughnut-shaped multi-layered drug delivery devices with acetaminophen	Fusion deposition modeling 3D printing	Yu et al., [54]
	Fast-disintegrating drug delivery device with special Inner structure Characteristics	Extrusion printing	Yu et al., [55]
	A biodegradable patch with 5-fluorouracil to be administered at the exact tumor with a Versatile Shape	Extrusion printing	Yi et al., [56]
	Ibuprofen-loaded hydrogels	Stereolithographic printing	Martinez et al., [57]
	Solid dispersions of felodipine	Fused deposition modelling	Alhijjaj et al., [58]
	Rasagiline mesylate orodispersible films	Inkjet 3D printing Genina et al., [60]	Genina et al., [60]
	Solid dosage forms containing deflazacort loaded nanocapsules	Fused deposition modelling printing	Beck et al., [61]
	custom-made subcutaneous rods and T-shaped intrauterine systems with indomethacin	Fused deposition modelling	Genina et al., [60]
3D Printed Polypill	Polypill with five compartmentalized drugs namely aspirin, hydrochlorothiazide, ramipril, pravastatin and atenolol	Extrusion Printing	Beck et al., [64]
	Tablets with an osmotic pump with captopril and two sustained release compartments for nifedipine and glipizide.	Extrusion Printing	Khaled et al., [65]
	Poly dimethyl siloxane devices with prednisolone	Extrusion 3D printing with UV-crosslinking technology	Holländer et al., [59]
	Oral dual-compartmental dosage unit containing rifampicin and isoniazid	Fused deposition modelling and hot melt extrusion	Genina et al., [66]
	A bilayer dosage form containing metformin and glimepiride	Fused deposition modelling	Gioumouxouzis et al., [67

FUTURE PROSPECTIVE

The idea of tailored medication for an individual patient has been around for a while and is recognized and gained much attention nowadays. However, the typical pharmaceutical manufacturing is a large batch process and generally does not support personalized therapy. In this context, 3D printing technology has proved track record in prototyping applications and has been widely used for years in various fields including bioengineering. At present, this additive manufacturing technology has also started to make a name for itself in pharmaceutical drug preparation. Being achieved the commercial status; the 3D printing technology seems to be a turning point in drug formulation and is in the process of challenging the traditional pharmaceutical manufacturing techniques. Various 3D printed formulations have signified that their unique structure cannot be achieved using conventional manufacturing methods. Extensive studies have been carried out by researchers in the past decade on various 3D printing techniques to optimize the printers in order to facilitate the manufacturing of novel drug delivery systems, which can pave the way for individualized drug therapy. Nevertheless, there is enormous scope for this promising technology in designing various delivery systems and provides customized patient compatible formulations with Polypills. For instance, it is sometimes necessary to administer multiple drugs in a particular ailment for treatment, which can be achieved by this enabling technology. Therefore, to have formulations with different drugs and varying release rate are extremely important. Indeed, the 3D technology started receiving greater attention from pharmaceutical companies and is in the process of developing novel formulations to provide customized medicines by controlling drug release rate. The significant and exciting advances in technologies and development of advanced software can lead to the design of single printing device capable of producing multiple release formulations. Few researchers have already demonstrated immediate and sustained release of different drugs from separate compartments when formulated as polypills. 3D printing techniques have emerged as a potential alternative for producing drug delivery systems which are generally challenging in conventional methods. On the other hand, considering this niche technology as an alternative to traditional pharmaceutical manufacturing techniques is too ambitious. The feasibility of 3D technology in developing new drug formulations including microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, Nano suspensions, and multilayered drug delivery devices has been demonstrated. The 3D technique seems to be a promising approach to develop Mucoadhesive films or other layered structures, which was demonstrated by different research groups. Hence, this rapid prototyping tool offers the potential to create limitless dosage forms which in turn will take fabrication of drug delivery systems to a new level. Different printing techniques have been explored in formulating various delivery systems with specific geometries, although they are not free from one or other limitations. However, one can expect 3D printing as a routine manufacturing process once the technology is well established and the source of printing materials is easily available. The bright future of this printing technology is likely to rely on its potential to provide 3D printing systems capable of manufacturing personalized doses with real-time release based on demand in decentralized locations. In addition, the pharmaceutical industries need to address various administrative and regulatory challenges as well as need to work hard to improve scalability of the product. However, certain pharmaceutical industries have claimed to print more than thousands of tablets a day using single printer, signifying that the current technology could become part of the drug production line. The possibility of multiple print head to deposit different ingredients in 3D printers could be an effective alternative to improve production volume. One can expect the transformation of conventional pharmaceutical manufacturing to more flexible 3D printed products very soon with many more products in the market. Ultimately, the commercial success of this technology will depend on the efficiency of this unique dosage geometries to translate it into patient benefit, while considering the expense. Overall, the 3D approach is all set to revolutionize drug delivery systems and would see valid applications of the technology in near future.

CONCLUSION

The use of 3D printing in drug formulation is a new chapter in pharmaceutical manufacturing and is likely to play an integral role in developing various drug delivery systems. Indeed, this approach becomes a useful and potential tool for many patients as it brings the manufacturing close to them and offers individualized therapy. Recent advances in technology and increased research in the field definitely can provide more safe and effective therapy and also opens up the possibility for individualized medicine. Although the 3D technology is still in its infancy, this manufacturing strategy seems to be a transformative tool with more flexibility in pharmaceutical manufacturing and is likely to revolutionize drug delivery systems to a new level, though need time to evolve. The prospective of various 3D printed drug delivery systems to provide unique and/or customized release of drug moieties will certainly pave the way for tailored dosing for individualized drug therapy. The wide applications and unlimited potential of 3D printing technology in developing various drug delivery systems are briefed. 3D printing.

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