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3D PRINTING OF PHARMACEUTICAL DRUG DELIVERY SYSTEM: CHALLANGES AND APPLICATIONS

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ABSTRACT

Three-dimensional printing (3DP) is a unique technique for prototyping that has evolved over the past 35 years and has the tremendous potential to revolutionise the field of therapeutics with its inherent advantages of configurability and the ability to manufacture highly precise and accurate complex solid dosage types. With variable densities and diffusivity, 3DP can generate strong dosage types, complex internal symmetries, numerous drugs and excipients. Literature results reveal many benefits of 3DP technology over existing approaches in the area of innovative drug delivery systems (NDDS). The drug distribution problems of poorly water-soluble medications, peptides, potent drugs and multi-drug release, etc can be easily solved by 3DP. However, the use of 3DP in the consumer industry is limited by issues such as the selection of suitable binders, excipients and mediated gene properties of final products. Further improvement in process quality is required to solve these issues, where 3DP technology can be efficiently paired with NDDSS. Here, we present an overview of the development of emerging drug delivery technologies and the promise of 3DP.

KEYWORS: New drug delivery system, customised medicine, new drug delivery, three-dimensional printing.

INTRODUCTION

In order to ensure the high consistency of dosage formulations, innovative innovations in drug design, a better knowledge of structural properties, processing technology and processes are constantly influenced. Through each stage of product production, the variety of physicochemical and biophamaceutical characteristics of active pharmaceutical ingredients

(APIs) must be recognised and studied. To achieve the required dosage-age type, auxiliary substances must also be examined.

The patient-centered drug product development choice has been under tremendous focus over the last decade. It concentrated on novel types of dosage and technical processes. The growing demand for personalised devices coupled with the expansion of technological innovation, is driving significant progress in personal medicine, represented, For example, the creation of small series of individually selected doses and tailor-made protheses that meet patients' anatomical needs. Among the many findings in the pharmaceutical and biotechnology industry, three-dimensional printing (3DP) is considered to be the most creative and effective. This approach is known as a flexible tool for the accurate manufacturing of different devices. It acts as a technology for the development of novel dosage types, the engineering of tissues and organs and the simulation of diseases.

Nowadays, three-dimensional printing is one of the most growing branches of technology, art and science, and apps are still being expanded. The word three-dimensional printing has been defined by the International Standard Organization (ISO) as the manufacture of objects by depositing a material with a print head, nozzle or other printer technology. This technique is one of the additive manufacturing (AM) methods in which components are built from 3D model knowledge in the field of joining materials layer by layer, opposed to widely used subtractive and formative manufacturing methodologies.[1] AM's realistic approach is called rapid prototyping (RP) and its benefits include reducing the time and expense of prototyping, simple model modifications at a planned stage, the ability to manufacture small items, individual product series or structures that are difficult to shape with subtractive techniques.[2]

Since 2012, the use of 3D printing has been growing in science and engineering. The number of scientific papers containing the words B3D printing^ or B3D printed^ in the title recorded in the Web of Science Core Collection increased from 59 in 2012 to 1573 in 2017. Furthermore, in the same period, the number of citations for these papers rose from 209 to 12,411. No findings were obtained in 2012 by restricting the search results to the pharmacy/pharmacology area, but 77 documents were found until 2017, which also suggests a great interest in 3DP methods in pharmaceutical research.

This analysis focuses on the latest advances and accomplishments in pharmaceutical and biomedical research from the literature papers published in the last three years. Innovative

methods are primarily focused around how the delivery of transdermal drugs and biomedical uses of additive manufacturing technology, including implants, surgical templates, bioprinted materials and biorobotics, are also discussed in the formulation of solid dosage forms for individualised therapy. The advancement of additive manufacturing used in pharmaceutical and bioprinting technology at the same time is summarised and compared to a separate attempt made to demonstrate the evolution of bioprinting. Because of the early stage of growth and deployment of additive manufacturing pharmaceutical applications, not many regulatory issues are available, but the major issues introduced by the FDA in 2017 are listed. Today, three-dimensional printing is one of the most growing divisions of technology, art and science, and applications are being built quietly. The term three-dimensional printing was explained by the International Standard Organization as: generating objects through the deposition material using a print head, nozzle, or other printer technology.[3]

In several different areas, including the aerospace industry, architectural tissue engineering, biomedical research and pharmacy, the overview and implementation of 3D printing (DP) has facilitated enormous developments.

As an efficient system to overcome some challenges of traditional pharmaceutical unit operations, 3DP is gaining rising attention in pharmaceutical formulation growth. For example, with regard to drug loading, drug release, drug stability and pharmaceutical dosage form stability, the traditional manufacturing unit process involving milling, mixing, granulation and compression may result in disparate qualities of the final products.[4] 3D printing technology has made it possible to design and produce complex objects that can be used in customised and programmable medicine with unparalleled flexibility.[4] In different active ingredient drug formulations, 3D printing can play an important role, where the formulation can be a single mixture or multi-layer printed tablets with continuous release properties. This limits the frequency and number of dosage-type units taken on a daily basis by the patient. 3D printing technology has high promise in the individualised dose style model known as the polyp ill theory. For all the drugs needed for the treatment, this brings the likelihood of a single dose style unit.

Three-dimensional printing techniques are a modern form of rapid prototyping in which solid structures are created by depositing multiple layers of structure. Rapid prototyping requires the three-dimensional creation of physical structures using computer-aided design. Similarly, it is called additive manufacturing and the rise of solid free form. 3D printing technology has

made it possible to design and produce complex objects that can be used in customised and programmable medicine with unique versatility.[5]

Additive manufacturing is also the manufacturing of solid items by incorporating them layer by layer. "In the early 2000s, this concept was marketed and modified to a more common one called "3D printing".[6-7] All 3DP techniques depend on the 20 object structure concept by incorporating layer-by-layer materials.[8]

The terms additive manufacturing, rapid prototyping, coated production, solid freeform production, 3D fibbing, and 3D printing are used more or less synonymously in literature. Although most engineers prefer "additive manufacturing," the term "3D printing" is far more prevalent in the mass media. The words 'additive manufacturing' and 3D printing are also used in this work to explain the same general theory of manufacturing.[9]

In 3D printing, successive material layers are shaped under machine control to create an object. 3D printing has been used as an innovative drug formulation method to manufacture viable tablets capable of meeting regulatory tests and balancing the release of standard consumer tablets.[10]

3D printing is a specific technique specifically established by Charles Hull in 1986.[11] Tridimensional printing is a strong major breakthrough in a wide variety of areas, including energy, biotechnology, pharmaceutical products, and many more. The three-dimensional printing technology depends on computer-assisted designs to achieve extraordinary flexibility, time-saving and outstanding manufacturing infrastructure of pharmaceutical drug products.

It explains the 3D printing techniques used to create drug delivery systems based on natural materials, including nozzle-based deposition and printing systems based on inkjet. Furthermore, it also provides a study of 3D printing drug delivery methods containing the natural products alluded to in the literature. Prescription formulations and medication-filled scaffolds intended for tissue engineering are made from these drug delivery systems. The benefits of natural materials to 3D printing methods are explored and the potential reasons why pressure-assisted microsyringe is the most popular 3D printing process used to obtain these drug delivery systems. The 3D printing methods used to manufacture natural product-containing drug delivery systems are illustrated in Figure 1.

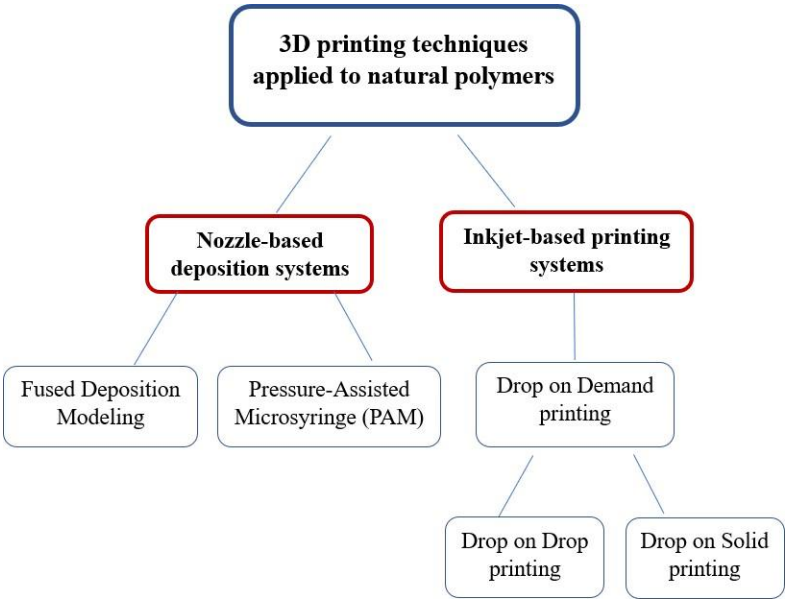

Figure 1: Classification of 3D printing technologies used for natural products.

In the last decade, the usability of 3D printers for both industrial and general public use has considerably increased. Global sales of products, supplies and facilities for commercial printers to consumer-based printers have grown by an annual average of over 33 percent over the last three years to a total of $4.1 billion in 2014.[12] A big driver of this growth is the fact that early patents related to production equipment and printing processes have expired. This opened the door for many start-up firms to develop new 3D printing machines that have powered revolutionary design practises while minimising prices, often far below $1000 for an entry-level printer. More than 400 firms currently sell comparatively affordable printing machines costing less than $5000. This rapid industry development has not only put 3D printers in enormously diverse manufacturing environments, but also in schools, public libraries, university labs, laboratories, etc.[13-15]

3D printing (3DP) is a particular technology first described by Charles Hull in 1986.[16] In its simplest configuration, 3DP uses computer-aided drafting technologies and scripting to construct a 3D model by layering content on a substratum. To establish the object's base, the material is first ejected from a target surface onto an integer track. The printer then travels along the z-axis and a liquid binder is expelled to a certain thickness onto the object's base. This method is repeated, following computer-aided drafting instructions, until the object is built layer by layer. Following therapy to eliminate the unbound layer, the item is completed.[17-18] Additive manufacturing (AM), rapid prototyping (RP) or solid free-form technology are also known as this method (SFF).[19]

A variety of 3DP technologies have been developed to manufacture novel solid dose forms, which are among the most esteemed and distinct products today.[20-22] 3D printers are often used to directly print porous scaffolds with a constructed structure, governed chemistry and interconnected porosity. They are biodegradable and have proved to be suitable for engineering bone tissue, often also with growth factor/drug delivery skills unique to the site.[23-27] 3D bioprinters have the opportunity to build extremely complex living-cell 3D architectures.[28-29] In cancer therapy, this cutting-edge approach has greatly gained acceptance and applicability.[30-31] In the area of the modern drug delivery technology, 3DP still proposes many innovative methods and techniques and is thus being of considerable importance in the pharmaceutical industry. Using 3DP, newly designed solid formulation formulations have been developed with complex inner architectures, geometries, surface texture, numerous drugs and several diverse methods of drug delivery systems. For example, devices released through oral power, microchips, capsules, implants, quickly dissolving tablets, and dosage types of multiphase release have been developed.[32-37] In addition, in developing and processing innovative drug delivery dosage formulations, 3DP technology has demonstrated numerous industrial advantages over traditional technologies. 3DP technology is expected to deliver innovative methods for the production of novel pharmaceutical dosage types.

ADVANTAGE OF 3D PRINTING

Advantages of 3D Printed Drug Delivery are as follows.

1. Tiny batch processing is feasible and the process can be completed in a single run.
2. 3D printers occupy small space and are cost-effective.
3. Eliminates batch-to-batch differences found in the processing of traditional dosage types in bulk
4. Since the modular nature and manufacture of this dosage form can mix instant and managed release layers, it helps to choose the right therapeutic regime for a person.
5. In the case of multi-drug therapy and various dosing regimens, care should be personalised to increase patient devotion.
6. Large tolerance for medication filling as opposed to predictable dosage types
7. Accurate and accurate dosing of potent medicines that are given in limited doses
8. Reduces manufacturing costs as a result of decreased resource waste.
9. For difficult to formulate active ingredients such as low water solubility, medications with, appropriate drug distribution.

10. Fine opening for therapeutics.
11. In specific, depending on genetic variants, racial distinctions, age, ethnicity and climate, medication may be personalised to a patient.
12. Facilitating dosage personalization is one of the most noticeable advantages of 3D printing.
13. For use in hospitals, mobile military bases and low-stability medications, 3D printing may be ideal.
14. In planning dosage formulations for clinical trials, 3DP can prove very useful.
15. In planning dosage formulations for clinical trials, 3DP can prove very usefu. Upgrading the dissolution of poorly soluble APIs.
16. Either through printing hollowed or extremely porous structures, disintegration and breakdown speeds may be enlarged, thereby growing the touch surface region, by through 3DP extrusion methods resulting in amorphous dispersions or also by filling loose powder inner cavities.
17. It is possible to print tremendously low API volumes, even as low as 3ng of API.
18. 3D printing is less luxurious than traditional industrial manufacturing when considering smaller batches.
19. For immediate administration, small stability APIs could be printed, although numerous studies suggest associating basic API synthesis with 3DPP.[38]

DRAWBACK OF 3D PRINTING

1. It is important to sensitively analyse the selection of raw materials: printability, physicochemical characteristics, thermal conductivity, print fluid and viscoelastic content characteristics, along with the protection of raw materials for human use.
2. 3D powder-based printing: printing requires a small or special area because powder spillage is significant and may pose an occupational hazard.
3. Mechanical resistance: friability is greater in 3D dosage forms, especially in powder-based techniques. Production technology is necessary for the dosage form to have good power.
4. In comparison to standard tablet compression methods, the material choices, colours and surface finishes currently available for 3D printing are comparatively limited.
5. Nozzle mechanism: The nozzle mechanism is used for forming the layers of the dosage type during 3D printing. Consistent printing material flow is awaited when the printer head stops and picks up during the formation of sequenced layers.

6. Suitable materials for the 3D printing of drugs are also limited.
7. In certain situations, where residual solvents need to be eliminated from the finished product, post-processing, including drying using hot air, microwaves or infrared sources, may be necessary.
8. Boundaries arise when contemplating polypills, especially when the number of APIs used and the size of the final product are taken into consideration.

PRINCIPLE OF 3D PRINTING

It is possible to assume the concept behind a 3D printer to be parallel to a standard printer. The 3D printer consists of an extrusion process that works horizontally on an axis held on top of two axes to create the object's foundation, causing it to travel back and forth in the x-y plane. The sides of the printer are joined by these two axes. The only difference is that the base of the 3D printer shifts vertically along the z axis to create the layers above the piece. Whereas the first layer is printed, the extruder stays at the top and then moves in 2D. In order to create the next layer on it the foundation that houses the substrate would decrease in height. The operation is repeated, following the computer-aided drafting instructions, until the object is assembled layer by layer. Additive processing, rapid prototyping (RP) or solid freeform technology are known as this process. To print different porous scaffolds with regulated chemistry, intertwined porosity and unique shapes, 3D printers are used. These prints are biodegradable and proven to be suitable for the potential to distribute medicines. This approach will build some of the most complex structures that incorporate living cells and has gained prominence and applicability in cancer treatment.

Using 3DP technology, various types of drug delivery systems have been developed, such as oral controlled release systems, micro pills, microchips, drug implants, quick dissolving tablets and multiphase release dosage forms.[39]

CLASSIFICATION OF 3D PRINTING

- Inkjet printing method
- Fused deposition method
- Direct inkjet writing method
- Zip dose method
- Thermal inkjet printing method
- Binder deposition method
- Material jetting method

- Extrusion method
- Powder bed fusion method
- Photo polymerisation method
- Pen based 3DP method
- Direct energy deposition method
- Sheet lamination method.[39-41]

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

Printing technology/Printer type	Dosage forms/Systems	Model drug used	Reference
3D powder direct printing technology	Microporous bioceramics	Tetracycline, Vancomycin and Ofloxacin	[42]
Fused-filament 3D printing	Tablets	Fluorescein	[43]
3D printer	Tablets	Paracetamol	[44]
3D printer	Complex oral dosage forms	Fluorescein	[45]
3D extrusion printer	Multi-active solid dosage form (polypill)	rochlorothiazide Pravastatin, Atenolol & Ramipril	[46]
Piezoelectric inkjet printer	Microparticles	Paclitaxel	[47]
Fused deposition 3D printing	Extended release tablet	Prednisolone	[48]
3D printer	Tablet implant	Isoniazide	[49]
3D printer	Doughnut-shaped multi-layered drug delivery device	Acetaminophen	[50]
3D printer	Fast-disintegrating drug delivery device	Paracetamol	[51]
Fused deposition 3D printer	Oral pulsatile capsule	Acetaminophen	[52]
3D printer	Fast disintegrating tablet	Acetaminophen	[53]
3D printer	Oral pulsatile tablet	Chlorpheniramine maleate & Diclofenac sodium	[54]
Ink-jet printer	Solid dispersion	Felodipine	[55]
Desktop 3D printer	Bi-layer matrix tablet	Guaifenesin	[56]
Laboratory scale 3-DP™ machine	Capsule with immediate release core and a release rate regulating shell	Pseudoephedrine hydrochloride	[57]
Fused deposition 3D printer	Modified-release drug loaded tablet	5-Aminosalicylic acid & 4-Aminosalicylic acid	[58]
Extrusion-based printer	Multi-active tablets (Polypill)	Captopril, Nifedipine & Glipizide	[59]
3D printer	Complex matrix tablet with ethylcellulose gradients	Acetaminophen	[60]
Inkjet printer	Implant with lactic acid polymer matrix	Levofloxacin	[61]
3D printer	Multi-layered concentric implant	Rifampicin and Isoniazid	[62]

Micro-drop Inkjet 3DP	Nanosuspension	Folic Acid	[63]
Thermal Inkjet printer	Dosing drug Solutions onto oral films	Salbutamol sulphate	[64]
Commercial inkjet printer	Nanocomposite structure	Rifampicin and Calcium phosphate	[65]
3D Extrusion printer	Drug encapsulated film of PLGA and PVA	Dexamethasone	[66]
Thermal Inkjet printer	Oral solid dosage forms	Prednisolone	[67]
3D printer	Microfluidic pump	Saline solution	[68]
Stereolithography printer	Anti-acne patch	Salicylic acid	[69]
3D printer	Biodegradable patch	5-Fluorouracil	[70]
Fused deposition 3D printer	Immediate release tablets	alicylic acid, Captopril, Theophylline & Prednisolone	[71]
Fused-deposition printer	T-shaped intrauterine systems and subcutaneous rods	Indomethacin	[72]
hydrodynamic atomization technique	Patterned micron scaled structures	Tetracycline hydrochloride	[73]
Fused deposition printer	Capsules for immediate and modified release	Acetaminophen and Furosemide	[74]
3D printer	Biofilm disk	Nitrofurantoin	[75]
Multi-nozzle 3D printer	Capsule-shaped solid devices	Acetaminophen & Caffeine	[76]
Fused-deposition printer	Capsule-shaped tablets	Budesonide	[77]
Stereolithographic 3D printer	Modified-release tablets	4-aminosalicylic acid & Paracetamol	[78]

CHALLENGES AND PERSPECTIVES OF 3D PRINTING

In the pharmaceutical sector, technical developments are continually evolving to offer numerous possibilities to satisfy the needs of customised drug therapy. As technical advancement advances, the three-dimensional (3D) printing process has infinite promise in the manufacture of patient-specific drug delivery systems (DDD) and dosage formulations. In addition, rapidly emerging 3D printing DDD research has helped us to recognise many challenges related to the development and marketing of customised drug delivery systems. 3D printing has made it easier to create DDD samples with various complications and reveals that it is possible to customise drug products. Patient-specific drug therapies in the future will be improved using printing technology. Technological developments, emerging science principles, interdisciplinary work and established regulatory guidance will continue to promote and reinforce the prospects for 3D printing as an alternative for medical device manufacturing.[79] Three-dimensional printing (3DP) is a unique technique for prototyping that has evolved over the past 35 years and has the tremendous potential to revolutionise the world of drug distribution with its intrinsic benefits of customizability and the ability to manufacture highly precise and accurate dynamic solid dosage types. With varying densities

and diffusivity, complicated internal geometries, numerous drugs and excipients, 3DP may generate solid dosage types. 3DP will effectively solve the drug delivery problems of poorly water-soluble medications, peptides, potent drugs and multi-drug release, etc. However, the use of 3DP in the commercial sector is limited by problems such as the selection of suitable binders, excipients and pharmaco-technical properties of final goods. More improvement in process efficiency is needed to address these problems where 3DP technology can be successfully combined with the latest drug delivery system (NDDS).[80]

3D printing involves a number of diverse approaches, each containing rewards and open challenges. Specifically, in the processing of drug products, powder solidification, extrusion and stereo lithography have been applied. The biggest obstacle to their exploitation of customised pharmacological treatment is likely to be linked to the regulatory challenges involved and the introduction of manufacturing models that can easily transform specific patients' clinical demands into small batches of viable medication products that satisfy predetermined quality criteria.[81]

For the pharmaceutical industry, three-dimensional printing has been a valuable and future technology, contributing to customised medicine based on the needs of patients. This has several benefits such as increasing cost savings and output speed, as it is possible to do rapid prototyping (RP) in a matter of minutes. There is still, however a major obstacle to ensuring that 3D printed drugs have the same potency, protection and durability as conventionally developed pharmaceuticals in the pharmaceutical industry. With regard to the development of standards, rules, quality processes, and the protection of the use and consumption of 3D printed medicinal products, the regulatory authorities are facing a major challenge, provided the conventional criteria of the pharmaceutical industry, which pose major barriers.[82]

The use of diverse methods of printing technology provides possible options for precision medication and optimised delivery forms to suit the needs of prospective human therapies. There are several forms of situations for the written dosage method and the definitions involve specifically deposited doses of drug compounds at the simplest level. In addition, computer architecture offers countless possibilities for constructing acceptable geometries with personalised features and differing degrees of difficulty to monitor the release properties of one or more drug substances. Since problems remain, it will take some time to translate these technical advances in printing to better therapies for patients. Printing technologies, however are increasingly evolving and have the ability to allow the use of lightweight

materials to create innovative drug delivery systems and bio-functional structures for customised therapies.[83]

PERSONALIZED PHARMACEUTICAL OF 3D PRINTING

3D drug printing is expected to have an infinite effect on drug development and customised treatment for the creation of optimum effectiveness and low toxicity drugs.[84] 3D printing is widely agreed to have three special medicinal characteristics that strengthen the effects, protection and usability of drugs: it makes it possible to manufacture complex pharmaceutical products, to personalise and to produce medications on demand.[85] Last but not least, 3D printing offers options for the manufacturing of pharmaceutical goods in different sensitive circumstances, such as natural disasters, military campaigns, emergency and operating rooms, and where time and money are scarce in healthcare units.[86]

3D printing technology offers an endless range of possibilities for manufacturing patient-specific drug delivery systems and customised drug treatment dosage forms.[87] Versatile therapeutic devices are currently being developed with tailor-made formulations of multiple active pharmaceutical compounds, in varying doses and with different kinetic profiles. The benefits of the manufacture of several separate chambers that can be filled with various compounds are 3D printed pharmaceutical forms with complex shapes and compositions, thereby modulating the bioavailability of drugs.[88]

3D PRINTING OF NEW PHARMACEUTICAL PRODUCTS

The modern medical age is discussing the issues of drug safety and effectiveness, calling for new approaches for the development and assessment of pharmaceutical forms.[89] 3D printing has gained continuous attention from the pharmaceutical industry in recent years and significant steps have been taken towards promising prospective progress in introducing new methods for developing and producing high-quality medicines through these state-of-the-art technologies.[90]

A modern revolutionary method for the manufacture of controlled release drug delivery systems is 3D Pharming (the direct printing of pharmaceutical tablets). Several examples of new pharmaceutical types produced by 3D printing are available. For the development of tailored pharmaceutical formulations based on thermoplastic polyurethane (TPU) filled with elevated pharmaceutical forms, Verstraete et al using fused deposition

modelling technology.[91]

Li et al used 3D printing to make gastro-floating tablets with a hydrophilic component made of hydroxypropyl methylcellulose. The extrusion moulding agent was microcrystalline cellulose and the active compound was dipyridamole, a drug used to prevent the production of blood clots after cardiac operations, strokes and heart attacks.[92]

For 3D printing of pharmaceutical products with hydrophilic drugs, Acosta-Vélez et al have prepared biocompatible photocurable polymeric ink. Hyaluronic acid functionalized with frozen water substituents was used to obtain the printing polymer. In the presence of Eosin Y as a photoinitiator and poly(ethylene)glycol dithiol, this compound passes through a rapid transesterification process if it is released to visible light. As an active compound for tablet formulation, Ropinirole HCL was used.[93]

In 2015, the FDA licenced the first produced 3D medication, Spritam®, which incorporates levetiracetam[94-96], an anti-epileptic drug, as an active pharmacological product. Compared with other medications of comparable pharmacological action, Levetiracetam has special properties.[96-97] For patients with childhood myoclonic epilepsy, it may be used to treat partial onset seizures, myoclonic seizures and primary generalised tonic-clonic seizures.[98] An emerging technology (ZipDose technology developed by Aprecia, a drug distribution network corporation, produces Spritam®. ZipDose technology can be used to create orodispersible drug formulations quickly disintegrating by 3D printing.

ZipDose Technology prints a porous matrix formed from several layers of aqueous fluid-fixed powder, which is further used to manufacture pre-measured orodispersible drug formulations that disintegrate with tiny amounts of liquids in the mouth. It is actually the only formulation medium for pharmaceutical drugs that quickly disintegrate and contain high concentrations of active substances.[98] The benefits of ZipDose technology focus on the gradual disintegration of the tablets even at a high dose of pharmaceutical compound (up to 1000 mg), the ability for the use of a vast range of taste masking excipients and the distribution of unit doses that improve patient compliance.[99]

"Polypill" means a prescription capsule containing a combination of many medications.

The promise of these tablets for cardiovascular therapy is great. They may also be a cheap alternative to the prescription formulations used in current practice.[100] To date, findings on the effectiveness of polypills in coronary disease outcomes and mortality are not available and are still being studied in clinical trials.[101] The CNIC-Ferrer polypill is the only substance for which a marketing permit has been issued in the EU, other European countries and Latin America.[102] The Fuster-CNIC-Ferrer CV polypill (Trinomia®, Sincronium®, Iltria®) was developed in a cost-effective manner to provide patients with access to streamlined care. Ferrer designed, developed and patented this polypill. In one single capsule, the active ingredients (atorvastatin, ramipiril and acetylsalicylic acid) are released. Properties of pharmacological substances remain unchanged and there are no physico-chemical incompatibilities (chemical incompatibility exists between atorvastatin, ramipiril and acetylsalicylic acid), 3D printing technologies that enable strict regulation of the position of active ingredients inside the polypill and drug release kinetics.[103]

Khaled et al used (3D) extrusion printing with five separate sections, each packed with a particular drug, to obtain polypills for the treatment of cardiovascular diseases. The polypill released the drugs in compliance with two pharmacokinetic release profiles. The pill contained a tank of immediate release containing aspirin and hydrochlorothiazide and three continuous release compartments containing pravastatin, atenolol and ramipril.[104] A polypill containing a bilayer guaifenesin tablet was also obtained by the same author by 3D extrusion printing, which complies with the international specifications set out in the US Pharmacopoeia.[105]

DEVELOPMENT OF NEW MEDICAL DEVICES

Cannabinoids are active in analgesia and anti-inflammatory pathways and can be used for the treatment of chronic pain[106-107] in different circumstances. 9- psychotropic tetrahydrocannabinol and cannabidiol, a non-psychotropic ingredient with anti-inflammatory properties[108-110], are the main components in cannabis.

A Tel Aviv start-up venture, Syqe Medical, developed the Syqe Inhaler®. This is the first selective pocket-sized cannabis inhaler produced using 3D printing technologies in the first class (80 percent of The Syqe inhaler was 3D printed using Stratasys MED610 biocompatible material with Stratasys Objet 350 3D Printer). The computer can be connected to a Wi-Fi network on a mobile phone or tablet. The pSyqe Inhaler Exo® is

the inhaler variant and can be used in medical units.[111-112]

Non-printed medicinal products containing cannabinoids can also be referred to, such as those obtained by 4GW Pharmaceuticals, a leading company researching and developing pharmaceutical forms of cannabinoids for the treatment of unusual cases of epilepsy syndrome.[113-114] Certain of these drugs have also been reviewed in FDA-approved trials. Epidiolex® is an oral solution derived from plants using cannabidiol (CBD). The organisation was given FDA clearance for a programme of clinical trials. Sativex® (US licenced name: nabiximols) is an oromucosal spray comprising 1:1 ratios of the main cannabinoids delta-9-tetrahydrocannabinol (THC) and CBD, as well as specific minor cannabinoids and other non-cannabinoid ingredients, of a manufactured Cannabis sativa extract. Sativex® has so far been approved in 30 countries outside the United States. In Germany, the Sativex® administration was approved in 2011. THC-containing capsules and oil have not yet been approved in this area (German Narcotic Medicines Act).[115]

Table 2: Cannabinoids approved by the U.S. Food and Drug Administration (FDA) for clinical use.[116-117]

Cannabinoid	Active substances	Formulation	Company	Indications
Cesamet®	Nabilone a dimethylheptyl analog of THC	Capsules for oral administration	Meda Pharmaceutical, Somerset, NJ, USA	Severe nausea and vomiting associated with chemotherapy neuropathic pain and pain associated with cancer and fibromyalgia
Marinol®	Dronabinol THC	Capsules for oral administration	AbbVie, Inc., North Chicago, IL, USA	Nausea and vomiting in patients receiving cancer chemotherapy who failed to respond to conventional antiemetics appetite stimulant for patients with wasting diseases such as cancer and HIV/AIDS
Sativex®	*Cannabis* extract 50:50 THC and CBD	oromucosal spray	GW Pharmaceuticals, Cambridge, United Kingdom	Treatment of chronic pain that is unresponsive to opioids

PHARMACEUTICAL APPLICATION OF 3D PRINTING

- For oral medications, implantable drug delivery systems, tissue bio printing, techniques such as prosthesis and even nutritional products, 3D painting is presently used or below.
- It was found that 3DP is capable of manufacturing moderately priced, on-demand, patient-tailored medications and/or an improved sophistication of the substance relative to conventional drug development.
- Any of the goals are to reduce side effects by printing tropical, cylindrical or perforated oral formulations or by using radial erosion gradients or diffusion-controlled excipients to achieve near-zero-order release.
- The other significant benefit of 3DP drugs may be the potential to manufacture special, individual or multi-drug and/or multi-dose formulations, as demand for customised medication grows and becomes a megatrend, according to the FDA transfers, line speed of the print head, interval time between two printing layers, distance between the nozzles and the powder layer.

MEDICAL AND CURRENT APPLICATIONS

- Wound Dressing
- Implants and Prostheses
- Models for Surgical Planning and Training, Phantoms
- Bio printing and Organs-on-Chip
- 5.4th Dimension of Printing
- Bio robotics.

CONCLUSION

For the pharmaceutical industry, 3D printing has been a valuable and future instrument, contributing to customised medicine based on the needs of patients. 3D printing technology is evolving with built-in versatility as a new avenue for automated drug distribution that is ideally positioned for personalized/customized drugs. 3D Printing technologies will revolutionise the style and formulation methods of pharmaceutical processing. There is still, however a major obstacle to ensuring that 3D printed drugs have the same potency, protection and durability as conventionally developed pharmaceuticals in the pharmaceutical industry. With regard to the development of rules, rules, compliance systems and the regulation of the use and consumption of 3D printed medicinal products, it is a significant challenge for the regulatory authorities, considering the conventional criteria of the

pharmaceutical industry, to implement major barriers.

The FDA guidance entitled "Technical Considerations for Additive Manufactured Devices" provides the initial thoughts of the FDA on process-related technical considerations and recommendations for testing and characterization of devices involving at least one stage in additive manufacturing production.

In the near future, multiple novel drug formulations will be developed and designed using the 3D printing method. While commercial manufacturing of such modern dosage forms is still difficult, the development of customised medication, optimised drug release from dosage form, compaction or avoidance of drug-drug incompatibilities, safety of biomolecules during processing, the creation of multiple drug dosage forms and multiple release dosage forms can be brought into a new era through 3D printing technology.

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