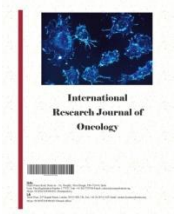

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3D Printing in Drug Delivery; Future of Cancer Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. A designed and directed the project. Author BOA, RTO, GCN, VCU, PCA and NOO contributed to the implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Numerous advances have been made in the treatment of cancer, but there have also been a number of drawbacks as a result of the drugs' inability to reach the affected organs with sufficient precision. As a result, cancer is still listed as the leading cause of fatalities, meanwhile, the treatment itself has many side effects. In cancer therapy, tumor diverseness and inter-patient's diffrences are seen to be the major issue during the course of therapy, consequently, each patient reacts differently to medication regimens. Dose modifications are usually based on empirical techniques, increasing the likelihood of unfavorable side effects and traditional methods of drug

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formulation does not allow for customing the dose to specific patient so as to keep costs down, which leaves a glaring unmet need. As a result, improved drug delivery system and a deeper scientific understanding of how pharmaceutical administration affects safety and efficacy are required.

Three-dimensional printing (3DP) has recently been regarded as the most groundbreaking and promising technology in the pharmaceutical and healthcare industry. The technology mentioned above focuses on novel approaches in the design of solid dosage forms for personalized therapy, transdermal medication, and biomedical applications of additive manufacturing techniques such as implants, surgical models, bio-printed materials, and bio-robotics, among other things. Because of its multiple intrinsic benefits over traditional delivery systems, 3DP technology has received increased attention in recent years in novel drug delivery approaches. As a result, this review's objective is to provide a thorough overview of the potential and actual applications of 3D printing in cancer chemotherapy drug delivery.

Keywords: 3D printing; drug delivery; cancer; chemotherapy.

1. INTRODUCTION

Cancer is still a significant source of human pain and mortality worldwide [1]. Cancer cells that have metastasized from the original organ and migrated to other parts of the body, known as secondary organs, are responsible for most misery and mortality [1]. However, a better solution for cancer can be found in additive manufacturing technologies, also called 3D printing [2]. Additive manufacturing is essential for creating patient-specific implants that may be utilized for surgical planning [3,4]. This technology uses a layer-by-layer method from a computer-assisted design model to generate 3D objects, which aids the understanding of the disease behaviour of a patient [5]. The benefits of this technology include education, research, and patient care; hence, 3D printing has found a new home in the targeted drug delivery industry [6]. Diverse therapeutic strategies that can produce individualized medication combinations, drug doses, and release kinetics have attracted high acclaim in the drug delivery industry, mainly because of the benefits personalized pharmaceutical therapies can provide [7]. Personalized medicine dosage aids in dosing flexibility, particularly beneficial in the juvenile population [8]. This advanced technology can quickly produce medications with complex release patterns, allowing precise dosage control and homogeneity [9]. This article reviews 3D printing's applications in Drug Delivery and its future in cancer chemotherapy.

1.1 What is Cancer?

In its simplest form, cancer could be referred as an uncontrolled cell growth. It is characterized by the uncontrolled division of aberrant cells in the body, commonly referred to as a tumour. Cancer is a neoplasm, defined as new and abnormal tissue development in a specific portion of the body [10]. Medically, cancer is a genetic illness produced by accumulating harmful mutations in the genome throughout a lifetime. They can be categorized into four distinct forms based on the tissue they emerged from. Carcinomas form in epithelial tissue that lines the inside and outside of the body. The most frequent type of cancer is adenocarcinoma, which is the cancer of an organ or gland; for example, prostate, breast, and liver cancer. Skin, bladder, oesophagus, and lung squamous cell carcinomas arise in the squamous epithelium. Sarcomas develop from connective tissue in bones, tendons, cartilage, muscle, and fat and account for fewer than 10% of all malignancies [11]. Leukaemias, cancers of the blood, originate from the bone marrow, while Lymphoma refers to cancers that develop in the lymph system. Chemotherapy, surgery, radiation therapy, medication therapy, and stem cell transplantation are the most common treatments for this illness [12].

1.2 Pathophysiology of Cancer

Cancer has a complex pathophysiology, and this begin with alterations in multiple normal genes (oncogenes and tumour suppressor genes), which then progress through genomic amplification (gaining many copies of a small chromosomal locus), acquisition of further mutations (such as point mutation and translocation) to tumour growth. A cancerous tumour can proliferate and spread to other tissues. Some tumours, such as leukaemias grow as cell suspensions, although most grow as solid masses of tissue. The progeny of that cell acquires as it divides [13]. A malignant tumour's

formation leads to anti-tumour immunity suppression, damaging the genomic cell's genetic system. It is worth noting that suppressing anti-tumour immunity is a natural physiological reaction of the body, and when this reaction becomes a pathological state, cancer results [14].

1.3 Conventional Cancer Therapy and Its Limitation

Conventional cancer treatments are treatment modalities generally recognized and utilized by healthcare professionals to treat cancer [15]. They are also known as the traditional cancer treatment methods, especially since the influx of novel methods in this new era [16]. The three main techniques used in conventional cancer treatment are surgery, chemotherapy and radiotherapy. Additionally,there are a number of considerably less common techniques, including immunotherapy and hormone therapy [17].

1.3.1 Chemotherapy

This conventional treatment procedure involves using chemicals in the form of drugs to inhibit the growth of cancerous cells without affecting the host cells. Chemotherapeutic drugs can be used for curative purposes or to prolong life, and it is also possible to use them with other conventional cancer therapies, especially surgery [18]. Some known chemotherapeutic agents include: alkylating agents like nitrogen mustards and triazenes, anti-metabolites such as folic acid analogs, purine analogs, pyrimidine analogs, antibiotics, enzymes [19].

1.3.2 Limitations

Studies have shown that chemotherapy has a cancerous effect and likely induces secondary tumours. Most drugs used in chemotherapy have rapid drug metabolism and a cytotoxic effect [17]. In addition, most chemotherapeutics suffer limited aqueous solubility because of their hydrophobic nature; they require solvents to formulate dosages which increase their toxicity. The inability of chemotherapeutics to accurately select cancer cells results in significant damage to normal non-cancerous cells in the host. They also develop multi-resistance over time due to increased efflux pumps in the host [20].

1.3.3 Radiotherapy

This cancer treatment employs exceptionally high doses of ionizing radiation to shrink tumours and kill malignant cells. It is the second most commonly used conventional cancer therapy after surgery. Cancer cells generally have increased sensitivity to radiation because they are in a constant state of proliferation and cannot withstand radiation damage more than normal cells [21]. After prolonged exposure to radiation, there is considerable damage to the cancer cells' DNA which causes them to stop proliferating and die, from which the body removes the dead cancer cells. Radiation therapy is divided into external and internal beam radiation (Brachytherapy). External radiation beam emanates from an external machine aiming radiation at cancerous cells and tumours at different angles outside the host. However, in an internal radiation beam, the radiation source, which may be liquid or solid, is put inside the body [15].

1.3.4 Limitations

Like chemotherapy, radiation therapy also affects nearby healthy cells. Because radiation is focused on a particular body area, it does not help treat cancer spread throughout the body [15,22].

1.3.5 Surgery

The development of new treatment modalities has minimized the extent of surgical interventions in cancer. Notwithstanding, surgery remains the oldest type of cancer treatment. Surgical cancer interventions can be curative or palliative (to reduce pain intensity, for instance) [21]. Curative surgery is usually used as the first line of treatment for localized tumours. Other forms of surgical interventions in cancer are;

- Preventive surgery removes non-malignant cells, which may develop into a malignant tumour.
- Diagnostic surgery is used in the removal of tissue samples from the body for evaluation to verify a diagnosis
- Staging surgery is employed to reveal the extent of cancer in the patient [23].

1.3.6 Limitations

In the early stages of cancer, it is widely popular public opinion that surgical removal of the tumour makes it possible for a long remission. Unfortunately, cancer is a disease that affects the entire organism, and mere removal of the symptom in the form of the localized tumour does not translate to curing the disease [17].

Furthermore, surgical treatment is associated with pain, post-surgical infection, bleeding, damage to nearby tissues and even death. All conventional cancer treatments are also expensive [15].

1.4 Complementary Therapies

1.4.1 Immunotherapy

The lymphatic system and white blood cells that make up immune system, aid in the body's defense against diseases. Immunotherapy strenghten the immune system of a cancer patient to fight cancer. Immunotherapy is of different types: Immune checkpoint inhibitors, monoclonal antibodies, T-cell transfer therapy, treatment vaccines etc. produce an effect by blocking immune checkpoints, increasing the visibility of cancer cells to the immune system and boosting the fighting ability of the t-cells to enhance the body's immune response to malignant cells [15]. This therapy stimulates the body's natural defences to work smarter. Damyanov et al. [17] have shown that immunotherapy is not as commonly used as conventional cancer treatments.

1.4.2 Limitations

The following are some of the most common side effects experienced by men receiving hormone therapy for prostate cancer: hot flashes, loss of interest in or ability to have sex, weakened bones, diarrhoea, nausea, enlarged and tender breasts, and fatigue. The following are some of the most common side effects experienced by women receiving hormone therapy for breast cancer: hot flashes, vaginal dryness, if you have not entered menopause yet, you may notice changes in your periods., loss of interest in sex, nausea, mood changes, fatigue.

1.4.3 Hormonal Therapy

Hormone therapy as a cancer treatment works by slowing or stopping the growth of tumours that secrete hormones. Hormones are required for the growth of several malignancies. As a result, hormone-blocking or -altering medications can occasionally help delay or stop the progression of certain tumours. This is commonly used to treat breast and prostate cancers and as well as other malignancies that rely on sex hormones to thrive. Because the hormones they target circulate throughout the body, it is also considered a systemic treatment. This distinguishes it from treatments that target a single bodily component, such as most types of surgery and radiation therapy [15].

1.4.4 Limitations

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2. 3D PRINTING

According to the International Organization for Standardization (ISO), three-dimensional printing is defined as "the manufacturing of objects by depositing a substance using a print head, nozzle, or other printer technology". Tissue and organ engineering, diagnostics, disease modelling, biomedical device production and the design and development of novel dosage forms are just a few applications [24,25]. It is used as a process innovation technology in the pharmaceutical industry to build digitally controlled and individualized products by converting a concept into a prototype (additive manufacturing (AM)) utilizing 3D computer-aided design (CAD) or a Magnetic Resonance Image (MRI) [26,27]. 3D printinghas existed for approximately 30 years, and its novel applications will continue to emerge in the coming years [28].

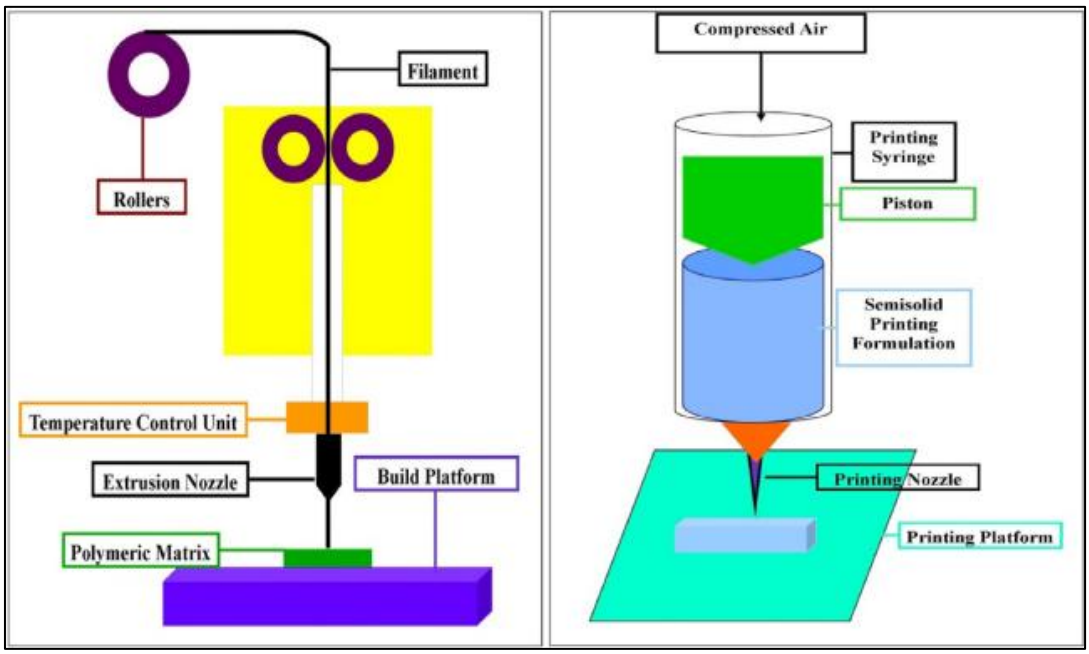
The rapid growth of 3DP technology and the development of flexible and biocompatible materials have facilitated widespread use in the pharmaceutical industry [27,25]. Early 1990's, Massachusetts Institute of Technology, Cambridge, USA pioneered 3D printing innovation in the pharmaceutical business with a rapid prototyping strategy called "three-dimensional printing technologies," which Sachs et al. invented and patented [26]. Printing a range of pharmaceutical formulations of poorly water-soluble medicines and proteins has shown 3D printing to be a potential method [29]. The technology mentioned above focuses on novel approaches in solid dosage forms for tailored therapy, transdermal medication, and biomedical

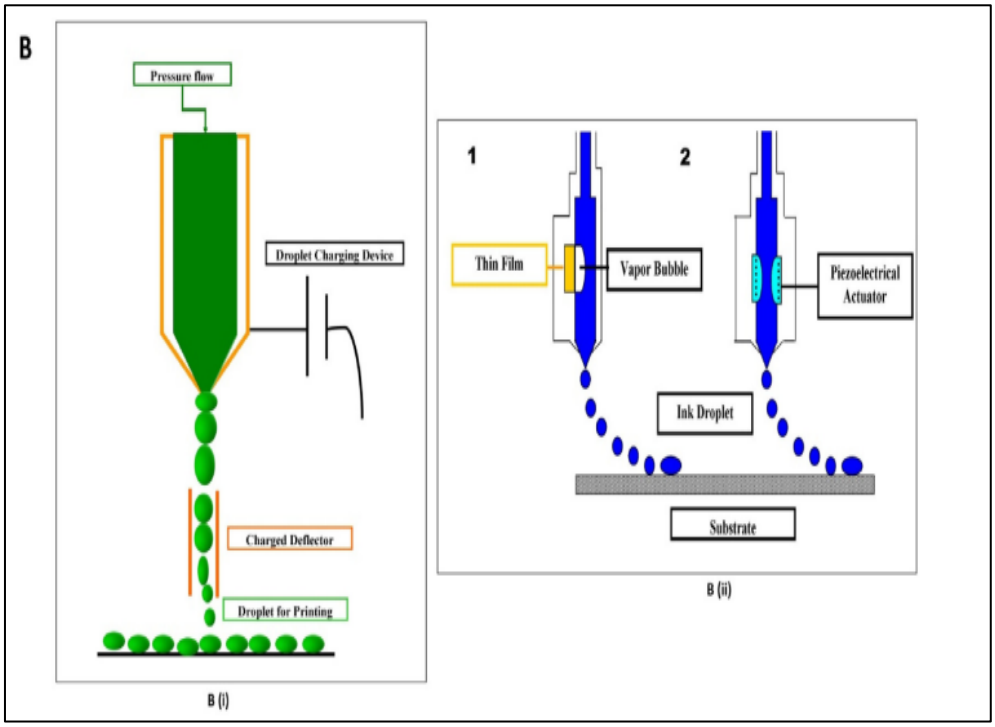
applications of additive manufacturing techniques, including implants, surgical models, bio-printed materials, and bio-robotics. Furthermore, because this technology can be utilized to construct more predictable drug screening platforms at a lower cost than standard drug product and device screening approaches, it can reduce the likelihood of failure at later stages of the new medicine improvement process. Due to its numerous innate benefits over the conventional technologies like a customized and individualized formulation with adjusted dose, fabrication of highly accurate solid dosage forms on-demand manufacturing, more mechanized, fast and straightforward to utilize and cost-effectiveness, the 3DP technology has gained greater attention in recent years in novel drug delivery approaches, which is evidenced from various scientific databases such as Scopus, MEDLINE, EMBASE, Pub Med, Science [30].

The method involves laying down thin layers of material, such as liquid or powdered metal, plastic, or cement, and then merging the layers. According to Horvath [28], instead of cutting away layers of an object, it creates an object up layer by layer. Additive Manufacturing (AM) is the opposite of subtractive manufacturing, which involves removing material from an object to produce it [31], and it is frequently linked with machines that are inexpensive and/or have limited capabilities [32]. Some forms of cancer can be treated with this approach. The tumour's exact location in the patient's body is shown in a 3D printed representation of the tumour [33]. Additionally, 3D printers can quickly create drugs in disaster zones, emergency rooms, quick response units, and military missions, and they can make 3D drug goods from digital blueprints [34]. Medicines, components, medical implants, and gadgets are created via 3D printing by layering material until the desired Computer-Aided Design file is physical acquired [25].

2.1 Principles of Operation

In their piece "3D Printing Principles: General Principles Involved in Additive Manufacturing", Robots and Android summarized 3D printing into three principles: modelling, printing, and finishing. The principle of 3D bioprinting include the layer by layer accurate positioning of biological components, biochemical, and living cells as well as spatial control offuntional components of the generated 3D structure. It is built on three basic approaches, which are as follows: biomimicry or biomimetics, autonomous self-assembly, lastly mini-tissue building blocks [35].





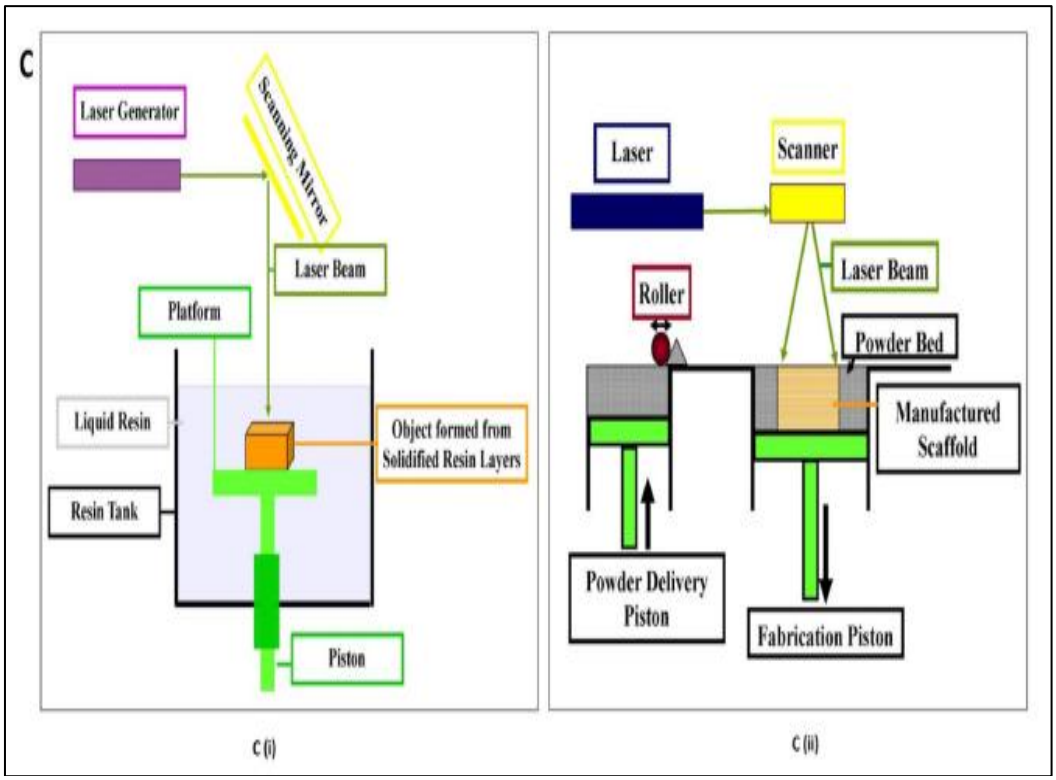


Fig. 1. Different 3D printing techniques;[37] A. Nozzle Based Deposition System: A(i) Fused Deposition Modeling (FDM), A(ii) Pressure-Assisted Micro syringes (PAM), B. Printing Based Inkjet System: B(i) Continuous Inkjet Printing (CIJ), B(ii) Drop-on-Demand Printing (DOD): 1. Drop-on-Solid Deposition, 2. Drop-on-Drop Deposition (Piezoelectric Technology), C. Laser-Based Writing System: C(i) Stereolithography (SLA), C(ii) Selective laser sintering (SLS)

2.2 Technique

According to Srinivasan et al.[36]' 3D printing does not require expensive moulds or instruments for machining, construction, or punches, and it is a cost-effective method. The production methods for 3D printing rely on various sources. They include (i) Powder-Based Systems (ii) Direct Metal Laser Sintering (DMLS) (iii) Selective Laser Melting (SLM) (iv) Laser Metal Deposition (LMD) (v) Electron Beam Melting (EBM) (vi) Solid-Based Systems (vii) Fused Deposition Modeling (FDM) (viii) Electron Beam Freeform Fabrication (EBFF) (ix) Wire Pulse Arc Additive Manufacturing (WPAAM) (x) Liquid-Based Systems (xi) Stereolithography (SLA) (xii) Direct Light Processing (DLP).

2.2.1 3DP techniques in pharmaceutical formulations

Based on the energy source, material source and other mechanical characteristics, various 3DP methods have been designed. Printing-based inkjet (IJ), nozzle-based deposition, and laser-based writing systems are the most prevalent 3DP technologies for pharmaceutical applications, which are additionally parted into subtypes dependent on materials and energy sources Fig.1 [37].

3. 3D PRINTING IN THE PHARMACEUTICAL INDUSTRY

3D printing to create drug items has piqued the pharmaceutical industry's and academics' interest. The assembly of medication conveyance frameworks with refined architectures and customized medication are two standard bearings of drug usage of 3D printing to transport drug item development to unfamiliar locations. 3DP has seen widespread use in the pharmaceutical industry due to its potential benefits, including increased productivity, a complicated drug release profile, multiple doses, a single-step method with minimal cost, and drug delivery customization/personalization. This advanced technology is a valuable tool for more precise drug dispensing and personalized drug release to meet each patient's specific needs. Furthermore, personalized medicine is a once-in-a-lifetime chance for 3D printing to address the obstacles to treating diverse ailments. Oral solid dose forms, implants, microneedles, and hydrogels are among the many formulations available.

3.1 Oral Solid Dosage Forms

Tablets have been thoroughly examined for 3DP breakthroughs in medicine manufacturing. Tablets delivered using 3DP techniques can generally be divided into single API and numerous API tablets. Individual examples of each type are depicted in the following two sections.

3.2 Implants

An implant can be a drug delivery system that contains effective drugs within a sustained release delivery matrix, benefiting patients who demand long-term medication treatment. An embed is a dosing structure containing dynamic medications inside a supported delivery conveyance grid, giving advantages to patients who need long haul treatment of medications.

3.3 Microneedles

A new inkjet printing technology for transdermal drug administration coats metal microneedle arrays with three anticancer components: curcumin, cisplatin, and 5-fluorouracil [38]. Farias et al. [39] used stereo lithography to design a cell-hydrogel having 3D printed methacrylate-based custom hollow microneedle assembly (circular array of 13 conical frusta) to evaluate the potentiality of cells named human hepatocellular carcinoma (HepG2) cells [39]. Economidou et al. [40] designed 3D printed microneedle arrays by stereo lithography (SLA) using a biocompatible resin for transdermal insulin delivery.

4. DRUG DELIVERY

Drug delivery describes methods and approaches to deliver drugs, pharmaceutical products, and other xenobiotics to the organism's place of action to achieve a therapeutic outcome or effect. It also involves technologies designed to improve therapeutics' specificity by stabilizing them in vivo, controlling their release, and localizing their effect [41].

Medicine relies on the use of pharmacologically active agents (therapeutics or drugs) to manage or reverse the course of the disease. The global pharmaceutical market is worth $980 billion annually, and, in the US, nearly 50% of the population has used at least one prescription medication in the past 30 days [42]. Notably, pharmacologically active agents are not

inherently effective; their benefit is directly coupled to how they are administered. Drug pharmacokinetics (PK), absorption, distribution, metabolism, duration of therapeutic effect, excretion, and toxicity are all affected by administration [43]. The discovery of new therapeutic compounds comes the need for enhanced delivery methods and a better scientific knowledge of how medication administration impacts safety and efficacy. The diagram below shows that traditional drug delivery techniques have several drawbacks, including nonspecific side effects from unspecified targeting, low therapeutic indices, and poor water solubility. As a result, approaches in delivery of drug have changed dramatically in the past few decades, and even more significant changes are expected in the future [44].

4.1 3D Printing in Cancer Drug Delivery

According to a study by Shafiee (as cited by Li et al. [45]), Since the first 3D-printed tablet was reported in 1996, 3D printing technologies have become increasingly used in pharmaceutical manufacturing, first FDA-approved 3D-printed medicine, SPRITAM®, was released in August 2015. However, other studies are ongoing, and several previously completed studies are currently undergoing clinical trials, all intending to determine anticancer dosage formulations and routes of administration. The use of 3D printing technology to convey API in various dosage forms as seen in immediate-release tablets, sustained-release tablets, modified-release tablets, immediate-release films, pulsatile release capsular devices, controlled-release implants, and controlled-release transdermal patches is gaining traction. Hydrophilic and lipophilic drugs have been delivered using 3D printing technology [46].

4.1.1 3D Printing for oral delivery of targeted cancer therapy

3D printing technology has shown to be promising in creating solid oral dosage forms. This approach enables the development of innovative formulations that overcome many drawbacks of traditional medication manufacturing processes. To fulfill requirements for tailored pharmaceuticals, 3D printing offers the capacity to generate diverse sizes and intricate shapes with tuned release properties. Extrusion-based 3D printing techniques are the most often used in the production of oral dosage forms [46].

Since this technology is up-and-coming, it is presently being explored for use in cancer therapy. Although some works have had considerable success, none have been used in clinical settings. The first oral tablets (diameters of 10 mm and 13 mm) filled with the anticancer model medicine 5-fluorouracil (FLU) were created using an innovative drop-on-powder (DoP) three-dimensional (3D) printing process. This tablet can be loaded with a personalized 5-FU unit dose with excellent accuracy and shape integrity [47].

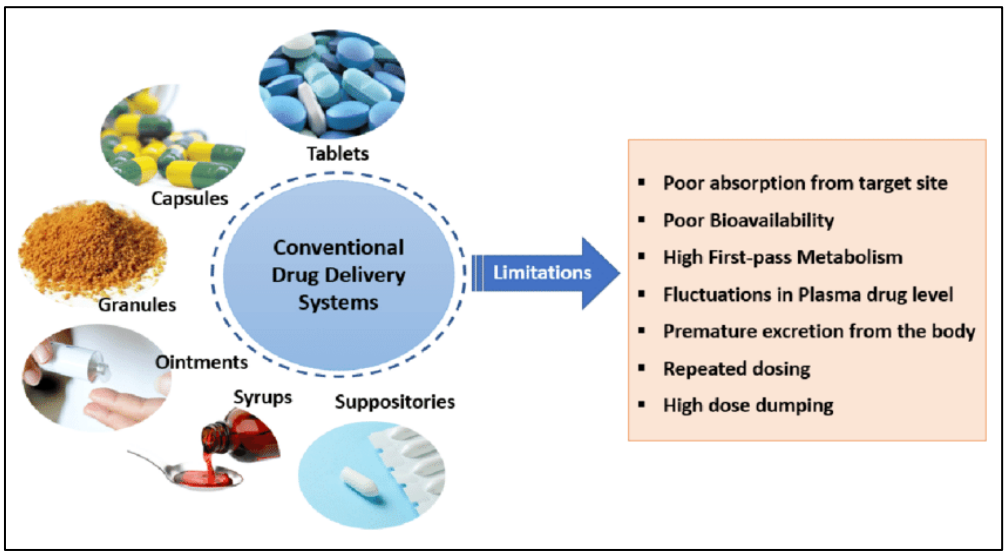


Fig. 2. Limitations of conventional drug delivery system [44]

Mirdamadian et al. [48] employed a mix of nanotechnology and fused deposition modelling (FDM) 3D printing to create colon-targeted oxaliplatin (OP) tablet with improved anticancer activity, tumour target ability, and safety profile. In CT-26 tumour-bearing mice, the anticancer efficacy of 3D printed tablets containing Oxaliplatin Nanoparticles (OP-NPs) was compared to intravenous and oral administration of OP solution and compressed tablets containing OP-NPs prepared by direct compression method with the same formulation. The antitumor effect of 3D printed tablets containing OP-NPs was remarkable and comparable to intravenous OP solution (p 0.05) with a better safety profile. In contrast, compressed tablets had no significant antitumor effect, most likely due to non-selective drug release in the stomach and upper intestine environments. The research demonstrates the promise of 3D printing in developing colon-specific drug delivery systems for chemotherapeutic medicines with good antitumor efficacy, tumour target ability, and safety profile for the treatment of colorectal cancer [48].

4.1.2 3D Printing for transdermal delivery of cancer drugs

Researchers have looked into 3D printing for complex transdermal drug delivery systems. Oikonomidou [49] conducted research on the ability of solid and hollow microneedles to be printed in three dimensions using photopolymerization-based 3D printing in order to create reliable production techniques for reproducible, mechanically strong, and versatile micro needles. The produced micro needles were used as drug delivery systems for treating diabetes through insulin administration. The hollow micro needles were discovered to pierce porcine skin without causing anatomical damage, and it was also possible to distribute the liquid across porcine skin tissue without creating depots that would hinder absorption. In comparison to subcutaneous injections, the device is reported to offer a quicker onset of action and a better therapeutic impact.

Furthermore, Uddin et al.[50] looked into constructing innovative three dimensional(3D) printed polymeric microneedle arrays for increased cisplatin delivery to A-431 epidermal skin tumours for treatment. The study's findings verified tumour regression and a high inhibitory effect, demonstrating the possibility for in-vivo anticancer medication delivery via transdermal application.

4.1.3 3D printing implant for cancer therapy

Drug-loaded implants,due to its ability to deliver drugs precisely to cancerous organs, have gotten much attention in cancer treatment due to their precise delivery of medications into cancer tissues. In contrast to injectable drug administration, the application of drug-loaded implants is underutilized due to the need for a surgical procedure. On the other hand, drug-loaded implants provide various advantages, including reduced drug administration frequency, low systemic toxicity, and improved delivery efficacy [51].

A unique, precise drug delivery device for orthotropic breast cancer therapy capable of suppressing breast tumour development and reducing pulmonary metastasis utilizing combination chemotherapy was developed by Yang et al. [51]. 3-D printed poly-lactic-co-glycolic acid scaffolds were used to immobilize 5-fluorouracil and NVP-BEZ235. The implanted scaffolds considerably reduced drug dosages and ensured curative drug levels near tumour locations for extended periods while minimizing drug exposure to normal tissues. Besides, long-term drug release was established, potentially allowing for one-time implantation and, as a result, a significant reduction in medication delivery frequency. This demonstrates that the drug-loaded scaffold has promising anticancer potential, leading to cancer therapy that is selective, effective, and non-toxic.

4.1.4 3D printing for pulmonary drug delivery

Pulmonary diseases are the third most common cause of death; around 3.23 million people died in 2019 [52]. However, treatment and conclusion of these infections proceed due to the lungs' complicated anatomical structure and physiological forms, which is a problematic task [53]. With computer-aided drug design and different options of printing materials, as varied anatomies, ages, genders, and pathological states must be considered, 3D printing has introduced unique ways for creating such devices when personalization is necessary, says Lim et al. [54].

Inhaled therapies are often regarded as adequate for respiratory problems since this

mode of delivery allows medicines to be delivered directly to the affected location [55]. Pathology arises non-uniformly in the airways in patients with lung cancer and chronic obstructive pulmonary disease (COPD), resulting in lobe-specific localized consequences [56].

Inhaled drug molecules are generally insufficient in these diseased regions' airways. In tumours obstructing airways, airflow can be directed toward healthy tissue and away from unhealthy tissue areas, taking the treatment with it. As a result, intravenous (IV) and oral medicines are increasingly used to treat various respiratory disorders, such as Lung cancer and pneumonia. Inhalable cancer clinical trial therapies such as doxorubicin have begun because using inhalable therapeutics instead oral or intravenous might lessen. Improve delivery to the illness location and reduce systemic effects [57,58].

Researchers have 3D printing models of lungs generated from computed tomography (CT) images for quantifying aerosol dispersal in the last decade [59]. Without clinical investigations, 3D-printed models of human airways broaden the scope of measurable data in aerosol research, allowing for thorough examination of particle deposition and assessing regional aerosol transport.

Emily et al. [60] evaluated a 3D-Printed *in-vitro* lung model using a computational fluid-particle dynamic (CFPD) model to realize the lungs' lobe-specific aerosol targets. That study concluded that aerosol targeting of a particular lobe is conceivable in vitro under ideal conditions, and manipulating inlet locations could be a valuable strategy for treating lobe-specific illnesses. This study is the first example of lobe-specific particle collection in a physical lung model, highlighting several issues that will need to be addressed as this technology is applied in clinical settings.

Additionally, in treating lung cancer, a 3D-printed lung tumour movement stimulator for radiotherapy by Quinone et al. [61] was studied to establish its characteristic movement equation, a hysteresis loop of human lung movement. At the same time, breathing was used to efficiently detect a tumour and minimize target irradiation margins to lessen the adverse effects of radiotherapy. This device helped in Procedures to ensure the quality of radiation is being improved in lung cancer.

4.1.5 3D printing for intrauterine drug delivery

Recent advancements in gynaecological cancer treatment, such as 3D printing and Image-guided adaptive brachytherapy, have improved the procedure's quality and results.

Laan et al. [62] have developed 3D-printed brachytherapy applicators precisely adjusted based on MRI scans of cervical cancer patients, potentially enhancing access to lesions during treatment. This is one of the most often used therapies for cervical cancer, and its success is dependent on the exact radioactive sources delivered to tumours. This approach can provide advantages for accurate positioning of the applicator during and between fractionated (brachytherapy) treatments that target lesions near or behind tissue folds, reducing the number of needles needed and allowing individuals with lesions in low-incidence areas receive effective therapy [61]. Even for months, vaginal medication delivery devices can provide consistent and long-term liberation of the active medicinal ingredient.

Zhao et al. [63] developed an implantable, personalized cervical implant in 3D printing technology focused on low-temperature deposition manufacturing (LTDM) to make the polyurethane, which was then lyophilized for rapid solidification. cervical implants made with 3D printing in the study were beneficial in meeting the requirements for gynaecological products regarding their mechanical properties, and they have much promise as tissue implants useful for preventing HPV infection following cervical conization.

Salmoria et al. [64] fabricated an intrauterine drug delivery system using the selective laser sintering (SLS) technique loaded with progesterone and fluorouracil, two medications used to treat endometrial and ovarian cancers. Two laser strengths made available (3 W and 5 W) were prepared, and the laser with the higher power (fluorouracil, 5 W) resulted in devices with improved mechanical characteristics. The release profile demonstrated the influence of drug hydrophilicity on the elution rate. The prepared IUD showed good potential for future cancer treatment applications in this study.

5. FUTURE APPLICATION/GAP IN KNOWLEDGE OF 3D PRINTING

With the current developments in the world and the evolving change in science and technology,

3D printed techniques might have some risk factors that could cause drug degradation leading to serious safety concerns [65]. Standardizing these 3D-printed drugs should be of great concern to pharmaceutical industries for regulatory approvals and increased turnout of clinical trials. Although 3D- printed are known to be performed in an aseptic environment, due to the different 3D printed materials needed for its production, such as polymers, some Standardization methods should be considered for the safety, efficacy, and quality of the drugs [54].

3D printing is the future of the healthcare sector shifting away from traditional mass production, triggering a paradigm shift in pharmaceuticals and clinical pharmacy practice of drugs towards personalizing and customizing certain medications or pharmacological combinations based on a person's needs preference in order to make it more effective and safer to use, and not the regular one-size-fits-all model. However, because many 3D-printed items are customized for particular patients, meeting FDA requirements through the traditional clearance method has hampered the introduction of 3D-printed pharmaceutics [66].

For cancer applications, it could bring about newer drug discoveries from conventional 3D-printed personal organs, cancer and surgery models, and other biocompatible and functional products that have the potential to benefit pharmaceutical enterprises and present medical systems. Customized Multifunctional medicine has the potential to reduce R&D costs and time by delivering immediate feedback from specific patients and attaining the ultimate objective of personalization. The capacity to truly customize 3D printed medicines is a massive benefit of personalized treatment based on a patient's therapeutic or individual needs. This technology attracts attention during crisis periods due to its commitment to the fight against the epidemic and to creating a greener, more environmentally friendly future [67]. The potential of 3D printing is an untapped source of knowledge to be exploited. In an interview, Laura Dormer, Editor-in-Chief of Future Medicine, which publishes the Journal of 3D Printing in Medicine, says, "It is exciting to see the ways 3D printing is being used in the medical environment". This 3D printing technology has great potential and proves to be time-saving, and helps avoid time-consuming processes that play significant roles in developing different treatments.

Table 1. Advantages and disadvantages of 3 DP In drug delivery for cancer therapy

Adavatages	Ref
Rapid prototyping and optimisation of oncology drug discovery and development	[45]
3D technology Improves bioavailability of cancer drugs	[70]
Better personalisation to meet patient's specific needs	[71]
Customizing release profile and retention time according to patient's need	[71]
3D technology is suitable for making polypill. Which is suitable to combine incompatible API's in a different compartment within a single pill thereby reducing drug interactions	[45]
Ability to achieve both immediate and sustain release through same pill	[45]
Helps design and tailor medications to individual patient's need taking into account biological genetic and environmental factors	[72]
3D bioprinting human models, useful for drug development and increase surgery success rate	[72]

6. DISCUSSION

Cancer is a condition characterized by the uncontrolled division of cells in the body [10]. It has remained a significant source of pain and mortality worldwide [1]. The adverse outcomes of cancer necessitated the introduction of various treatment modalities which aim to achieve a cure, prolong life or relief patients of suffering [68]. These treatment modalities, which include chemotherapy, radiotherapy, surgery etc., are known as the conventional and contemporary therapy options and are generally recognized and utilized by healthcare officials while handling cancer patients. They possess several side effects, including cytotoxicity [20]. Due to emerging research worldwide, new treatment options for cancer using 3D printing are being developed. 3D printing is manufacturing objects by depositing a substance using a print head, nozzle or other printing technology (ISO). 3D printing has proven to be promising, especially in creating solid oral dosage drug forms and is being explored extensively for use in cancer therapy [47]. This technique has developed specific innovative formulations which serve as a solution to the many drawbacks of the conventional and contemporary cancer treatment

options. Studies by Shi et al. [47] and Mirdamadian et al. [48] have shown that the use of 3D techniques such as drop-on powder (DoP) and Fused Deposition Modelling (FDM) in oral delivery of targeted cancer therapy produced remarkable results accompanied by good safety profile. Compared to compressed tablets, this resulted from a good selection drug release and tumor target ability of 3D printed drugs.

Similarly, 3D printing techniques have also been used in other research works for transdermal and printing implant drug delivery systems. Yang et al. [51] developed a drug delivery device which utilized scaffolds in breast cancer therapy. The implanted drugs significantly reduced drug dosages while ensuring curative drug levels near the tumour sites for extended periods. This mechanism considerably minimized drug exposure to normal tissues, reducing toxicity associated with conventional cancer therapies. 3D printing has improved pulmonary drug delivery in lung cancer and intrauterine drug delivery in gynaecological cancer treatments [61,62].

Although most of these works have produced considerable success, none have been used in clinical settings [47]. This could be because not all printable materials are biocompatible to meet the safety requirements that must be in place before human usage. Unlike traditional clinical trials, which require many subjects, 3D printed medicines are limited to individual clinical trials because each 3D medicine is tailored for individual use. As a result, the effect on many people cannot readily be established. This has impeded the introduction to clinical settings as they find it challenging to meet the FDA requirements. Sterilization of 3D printed materials is also a significant challenge as the materials, and drug efficacy may not withstand heat as a sterilization mode [69]. Therefore, there is a need for continuous work and research to tackle the limitations of 3D printing in cancer therapy and further make it friendly for human use [70-72].

7. CONCLUSION

Research on 3D printing in drug delivery; in application to cancer is an emerging area of research and can increase due to 3D printing's potential advantages over tailoring medications in individually tailored doses," according to this evaluation. Much research is being done in this area, and the findings are being tested in clinical trials to improve drug delivery in cancer treatment. This method has much potential for generating chemotherapeutic medicines that are effective and safe for cancer treatment. 3D printing made possible, the precise delivery of pharmaceuticals and excipients, leading to a shift in medication design, manufacture, and use. It can cover the full spectrum of drug improvement, from preclinical events and clinical preliminaries through frontline medical care. Despite the therapeutic and commercial benefits of 3DP technology, numerous specialized and administrative hurdles limit its use in pharmaceutical products. As a result, continuous research and improvement of 3DP approaches must be used to get over current constraints and utilize patients' tailored medical services in the future using personalized medications. Numerous studies are ongoing, and a number of those that have been completed are currently undergoing clinical trials, all intending to determine anticancer dosage formulations and routes of administration, however, there is no FDA approved 3D printed drug for cancer therapy.

COSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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