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Original article

Trend of pharmaceuticals 3D printing in the Middle East and North Africa (MENA) region: An overview, regulatory perspective and future outlook

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ABSTRACT

The traditional method of producing medicine using the "one-size fits all" model is becoming a major issue for pharmaceutical manufacturers due to its inability to produce customizable medicines for individuals' needs. Three-dimensional (3D) printing is a new disruptive technology that offers many benefits to the pharmaceutical industry by revolutionizing the way pharmaceuticals are developed and manufactured. 3D printing technology enables the on-demand production of personalized medicine with tailored dosage, shape and release characteristics. Despite the lack of clear regulatory guidance, there is substantial interest in adopting 3D printing technology in the large-scale manufacturing of medicine. This review aims to evaluate the research efforts of 3D printing technology in the Middle East and North Africa (MENA) region, with a particular emphasis on pharmaceutical research and development. Our analysis indicates an upsurge in the overall research activity of 3D printing technology but there is limited progress in pharmaceuticals research and development. While the MENA region still lags, there is evidence of the regional interest in expanding the 3D printing technology applications in different sectors including pharmaceuticals. 3D printing holds great promise for pharmaceutical development within the MENA region and its advancement will require a strong collaboration between academic researchers and industry partners in parallel with drafting detailed guidelines from regulatory authorities.

1. Introduction

Pharmaceutical mass manufacturing has been a long-standing practice for producing medicines. The primary goal of the mass manufacturing process is the production of large volumes of medicine with less variability in dose, shape and geometry, in a concept commonly known as "one-size-fits-all". With the latest advancements in genomics and diagnostics, this process has become non-practical and does not meet the need for personalized medicine (Rantanen and Khinast, 2015; Giacomini, 2012). In clinical practice, healthcare providers recommend patients split the dose, i.e., breaking tablets, or prescribing compounded medicines to obtain a specific therapeutic dose. This often leads to a suboptimal therapeutic dose or overdose and may put the patient at risk for unwanted side effects (Cohen, 1999; Quinzler, 2006). In addition, this scenario becomes even more challenging in the pediatric and geriatric populations where medicine dosage form, dose and/or shape are frequently tailored to meet their special need (Giacomini, 2012). On the other hand, the disruption of the pharmaceutical supply chain remains an unresolved issue for pharmaceutical manufacturers and often results in a significant shortage of essential medicines. This was recently experienced following the stress of the Coronavirus disease (COVID-19) pandemic on the global supply chain, which made even

Abbreviations: 3D, three-dimensional; API, active pharmaceutical ingredients; AM, additive manufacturing; ASTM, American Society for Testing and Materials; AI, artificial intelligence; CAGR, compound annual growth rate; CAD, computer-aided design; CIJ, continuous inkjet printing; COVID-19, Coronavirus disease; DOD, drop-on-demand; FDA, Food and Drug Administration; FDM, Fused deposition modeling; GCV, Ganciclovir; HPMC, Hydroxypropyl methylcellulose; LPV, lopinavir; ML, machine learning; MENA, Middle East and North Africa; PEG, Polyethylene glycol; PEO, Polyethylene oxide; PLA, Polylactic acid; PVP, Polyvinyl pyrrolidone; SLS, Selective laser sintering; SNEDDS, self-nanoemulsifying drug delivery systems; SSE, Semi-solid extrusion; SLA, stereolithography; TCP, tri-calcium phosphate; UAE, United Arab Emirates.

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generic medicines hard to reach in various countries (Dey, 2021; Badreldin and Atallah, 2021). Furthermore, the pharmaceutical manufacturing process is very complex, costly and time-consuming (Awad, 2018). Therefore, there is an urgent need for a viable approach to overcome some of the hurdles associated with the conventional pharmaceutical manufacturing process while also meeting the need for personalized medicine.

Additive manufacturing (AM) is a new disruptive technology that has received considerable attention in the pharmaceutical industry. In addition, AM technology is widely adopted in several other industries including aerospace, automobile and healthcare (Khorasani, 2022). It is estimated that the current AM size is valued at $17 billion, and it is projected to reach $44 billion by 2027, representing a compound annual growth rate (CAGR) of 27% (The Worldwide Additive Manufacturing Industry is Expected to Reach $44 Billion by, 2027). Due to the rapid progress of digital technology, e.g., artificial intelligence (AI) and machine learning (ML), the AM is expected to play a pivotal role in the production of countless customized products (Andreadis, 2022; Hunde and Woldeyohannes, 2022). There are seven AM technologies recognized by the American Society for Testing and Materials (ASTM), including binder jetting, vat photopolymerization, material jetting, material extrusion, powder bed fusion, sheet lamination, and directed energy deposition (Pérez, 2020). Three-dimensional (3D) printing is an additive manufacturing technique that relies on building a 3D object in a layer-by-layer fashion. The successful adoption of 3D printing technology in the healthcare sector led to the development of patient-specific prosthetics, surgical tools and medical implants (Arefin, 2021). Additionally, there has been a tremendous interest in extending the applications of 3D printing technology in the manufacturing of medicines on demand (Seoane-Viaño, 2021; Wang, 2023; Pawar and Pawar, 2022; Seoane-Viaño, 2023). Indeed, 3D printing technology meets the need for personalized medicine by producing medicine with customized doses, geometries, colors, drug combinations and tailored release characteristics (Awad, 2018; Seoane-Viaño, 2021). In 2015, the United States Food and Drug Administration (FDA) granted full approval for the first 3D-printed oral tablet, SPRITAM®, for the treatment of epilepsy (West and Bradbury, 2019), highlighting the potential applications of 3D printing in the large-scale manufacturing of pharmaceuticals. Unlike the conventional manufacturing process, 3D printing technology requires a limited amount of materials and fewer steps for production (Moldenhauer, 2021). The high flexibility in formulation design and dosing may lower the cost associated with the production of medicine at phase I clinical trials by utilizing a small quantity of active pharmaceutical ingredients (API) and excipients (Tracy, 2023). Not only does this represent a cost-effective method of producing medicine but it also lowers the burden on the supply chain (Mohr and Khan, 2015; Using Additive Manufacturing to Improve Supply Chain Resilience and Bolster Small and Mid-Size Firms., 2022; Chan, 2018). The 3D printing technology is recognized today in many countries as a critical strategy to enhance the resilience of the supply chain (Using Additive Manufacturing to Improve Supply Chain Resilience and Bolster Small and Mid-Size Firms., 2022).

The global trend of research and development in 3D printing has grown slowly partially due to the right protection of several earlier versions of the 3D printers. However, there was recent interest from various countries in the advancement of 3D printing technology, reflected by the high number of publications, from 59 to 1573, in 2012 and 2017, respectively (Hunde and Woldeyohannes, 2022; Jamróz, 2018). This translated to several marketed products in countries, such as the United States and China, which had the initiative to invest heavily in the early development of 3D printing and its applications. Due to the widespread of 3D printing technology across a wide range of sectors, it is expected to have a major impact on the translation of many pharmaceuticals around the world and in the Middle East and North Africa (MENA) region, particularly with the remarkable transformation in the regional healthcare sector and the emphasis on transferring and localizing drug manufacturing (Tawfik, 2022). Thus, it's very critical to explore the ongoing research activity of 3D printing technology in the MENA region and predict its impact on the pharmaceutical industry.

This review gives an overview of the current trend of the 3D printing technology research in the MENA region, discusses the most commonly used 3D printing technology in pharmaceutical development and highlights some of the published papers in the MENA region. It also provides insight into the regulatory perspective and future outlook of 3D printing technology in the pharmaceutical industry. To the best of our knowledge, this is the first analysis to assess the research efforts of the 3D printing technology in the MENA region.

2. Publication of 3D printing technology in the MENA region

A literature search was conducted mainly using the search engine of the MEDLINE database *PubMed*. To obtain the number of 3D publications in Fig. 1, the following search terms "3D printing [All Fields] AND MENA countries [Affiliation]" were used for the publication year from 2012 to 2022. Different search terms "3D-printing OR 3D-printed [Title] AND MENA countries [Affiliation] NOT review [Publication Type]" were employed to generate the data presented in Table 1. The MENA countries included were Algeria, Bahrain, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Malta, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, United Arab Emirates and Yemen. All the data was imported to EndNote™ software and further processed with Microsoft Excel. Duplicated publications were checked and removed.

A total number of 745 publications were collected (Fig. 1) for authors from twenty MENA countries from 2012 to 2022. Before 2017, there was a limited number of publications in the 3D printing technology (6% of the total publications). Nevertheless, there was a substantial upsurge in the number of 3D printing publications after 2017, marking the beginning of the research activity in 3D printing technology within the region. The data in Fig. 1 represent all the publication types, such as original articles, systemic reviews, clinical trials and *meta*-analyses. To compare the total number of publications in the MENA countries to the United States, the same search terms "3D printing [All fields] AND USA [Affiliation]" for the year 2021. The results showed that the countries in the MENA region accounted for 26% of the total number of 3D printing technology publications in the United States ($n = 605$).

A sub-analysis study of the twenty MENA countries showed that 36%, 24% and 17% of the total publications were from authors located in Iran, Saudi Arabia, and Egypt, respectively. The search criteria were subsequently narrowed down to obtain original articles, not reviews, for

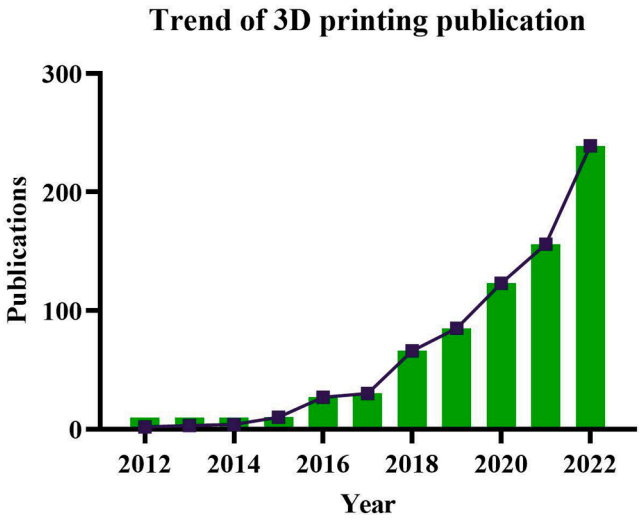

Fig. 1. The trend of 3D printing publications in the MENA countries (2012–2022). Data were obtained from *PubMed* using the search terms "3D printing AND MENA country".

Table 1
The top 5 MENA countries in 3D printing publications (2018–2022). Data were obtained from *PubMed* using the search terms "3D printing OR 3D printed AND MENA country".

Country	2018	2019	2020	2021	2022	Total
Iran	8	9	12	23	30	**82**
Saudi Arabia	4	4	9	18	42	**77**
Egypt	2	2	4	10	12	**30**
Lebanon	3	1	0	2	3	**9**
Jordan	2	2	0	4	0	**8**

authors from the top five MENA countries in 3D printing technology publications including Iran, Saudi Arabia, Egypt, Lebanon and Jordan (Table 1). Several original research articles were the result of a collaboration between authors from different MENA countries. Thus, we classified the articles for each country based on the affiliation of the first author, the corresponding author, or the other authors, i.e., 2nd and 3rd.

There was a steady increase in the number of 3D printing technology original articles for all the countries from 2018 to 2022, except for Lebanon and Jordan (Table 1). It is worth noticing that the number of original articles on 3D printing technology has been doubling in Iran and Saudi Arabia in the period from 2020 to 2022. 70% of the original articles in the MENA region were published by authors from Iran and Saudi Arabia, suggesting a high level of 3D printing technology research activity. In a further analysis of the type of 3D printing technology research in 2022, 50% of the original articles found in Iran were related to applications of 3D printing technology in tissue engineering whereas 33% of the original articles in Saudi Arabia were related to dental applications (Table 2). The pharmaceuticals-related 3D printing original articles were 19% and 10%, in Saudi Arabia and Iran, respectively. These articles were focused primarily on developing pharmaceutical dosage forms using 3D printing technology.

The data shown in this study indicates that Iran and Saudi Arabia are leading the region in establishing a solid research infrastructure for 3D printing technology, particularly in the bioengineering and dentistry fields. There is some research activity on the 3D applications in the pharmaceutical field but it accounts for only a small fraction (20%).

3. 3D printing of pharmaceuticals in the MENA region

3D printing is an emerging technology that has the potential to revolutionize drug design, development and manufacturing (Seoane-Viaño, 2021; Kotta et al., 2018). Several 3D printing techniques have been discovered but only a few techniques have gained attention in pharmaceutical research and development. These techniques can be broadly classified into three categories: extrusion-based, inkjet-based and laser-based systems (Fig. 2). In the MENA region, the extrusion-based and laser-based systems are the most commonly used 3D printing techniques for the development of pharmaceutical forms including tablets (Mohamed, 2020; Arafat, 2018; Arafat, 2018; Algahtani, 2021; Hu, 2023), inserts (Naguib et al., 2021); polypills (El-Say, 2022) discs (Alhijjaj et al., 2016) and printlets (Hamed, 2021) (Table 3).

All 3D printing techniques operate in two basic stages. The first stage is creating the 3D object using computer-aided design (CAD) which will then be subsequently sliced and converted to readable files by 3D printers. Various parameters such as the distance between the printed layer and infill percentage are usually optimized at this stage. The second stage is the printing stage, which involves the fabrication of a 3D object with the required shape and size. The mechanism of constructing the 3D object layer-by-layer varies from one technique to another (Jamróz, 2018). 3D printing techniques are discussed briefly herein but an in-depth description of 3D printing techniques and/or their applications can be found in other previous studies (Wang, 2023; Pawar and Pawar, 2022; Jamróz, 2018). Fig. 2 displays an illustration of the various techniques outlined in the subsequent sections.

Table 2
Distribution of 3D printing applications in 2022 for original articles in Saudi Arabia in Iran.

Field	Saudi Arabia	Iran
Dentistry	33 %	3 %
Tissue Engineering	2 %	50 %
Pharmaceuticals	19 %	10 %
Others	45 %	37 %

3.1. Extrusion-based 3D printing

Extrusion-based 3D printing is the most explored type due to the simplicity of the technique and the variety of materials that can be used to formulate dosage forms using this technique. In this technique, the materials are extruded through a small nozzle to the building stage (Algahtani et al., 2018). Based on the extrusion process, extrusion-based printing is divided into two types: Semi-solid extrusion (SSE) and Fused deposition modelling (FDM).

3.1.1. Semi-solid extrusion (SSE)

SSE-based 3D printing is an additive manufacturing technique that uses a syringe extruder to deposit material onto a printing platform layer-by-layer to create a 3D object (Seoane-Viaño, 2021). It is commonly used to deposit semi-solid preparations and create 3D structures at room temperature. The SSE-based 3D printer hardware consists of two main parts: the syringe extruder and the printing platform. The syringe is loaded with the printing material, which is typically semi-solid or molten (Algahtani et al., 2018; Seoane-Viaño, 2021). The extruder is controlled by robotic arms to move the syringe vertically and horizontally to deposit the material onto the printing platform in a controlled manner. The material in the syringe is extruded using screw-driven systems, piston-driven systems or pneumatic systems (Algahtani et al., 2018; Seoane-Viaño, 2021).

This type of printing is one of the most suitable techniques for implementation in bioengineering and the development of pharmaceuticals. It is characterized by the ability to use pharmaceutical-grade excipients to improve the quality of the printed dosage form, in addition to the ability of the 3D printer to print multiple APIs in the same dosage form. This technique has also been used to print dosage forms with thermolabile drugs and biomaterials. However, it has some limitations, such as it is not suitable for moisture-sensitive drugs due to the use of solvents and could sometimes face printing defects such as layer separation, collapse of the printed structure, and the need for a drying step after printing (Algahtani et al., 2018; Seoane-Viaño, 2021).

Khaled *et al* were among the first to evaluate the advantages of this technique with a set of works, including the ability to produce a polypill (Khaled, 2015). Polypill is a solid dosage form that contains multiple drugs for the management of chronic diseases such as diabetes and hypertension. By using the SSE-based 3D printing, the authors were able to fabricate a polypill that has two controlled-released profiles: an osmotic pump for the captopril and sustained release for a combination of nifedipine and glipizide. Due to the versatility of 3D printing technology to produce personalized medicines with multiple drug combinations, the patient's adherence is expected to improve leading to better clinical outcomes (Khaled, 2015). In another study by Hu et al., SSE-based 3D printing was utilized to formulate pediatric orodispersible mini-tablets of carbamazepine, an anti-epileptic drug. By employing a Design of Experiments (DoE) approach, the study optimized the formulation by adjusting the printing parameters, as well as the concentrations of super disintegrant and binder, to achieve optimal tablet properties (Hu, 2023).

The application of this 3D printing technique can be also extended to fabricate new pharmaceutical forms incorporated with advanced drug delivery systems including nanoparticles, liposomes and self-nanoemulsifying drug delivery systems (SNEDDS) (Seoane-Viaño, 2021; Kulkarni, 2022). For example, Algahtani *et al* used SSE-based 3D

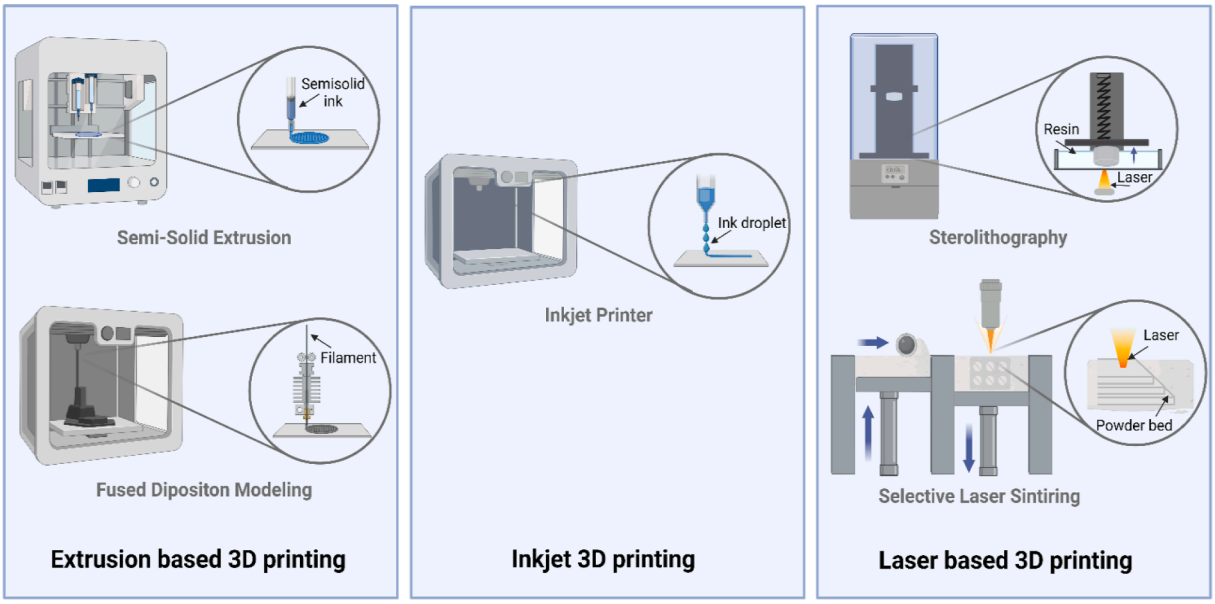

Fig. 2. Illustration of 3D printing techniques. Created by Biorender.com.

Table 3
Example studies of the most commonly used 3D printing techniques in the MENA region.

3D Printing Technique	Dosage Form	API	Printing Material	Country	Reference
SSE	Polypills	Glimepiride	HPMC, Microcrystalline cellulose, Croscarmellose sodium	Saudi Arabia	(El-Say, 2022)
	Tablet	Dapagliflozin	Poloxamer 188, Capryol 90, PEG 400, PEG 6000	Saudi Arabia	(Algahtani, 2021)
	Hydrogel		Gelatine, Methacrylic anhydride, Lithium phenyl-2,4,6-trimethylbenzoylphosphinate	Kuwait	(Mirek, 2023)
FDM	Tablets	Lopinavir/ritonavir	Hypromellose Acetate Succcinate, PEG 4000, magensim stearate	Saudi Arabia	(Malebari, 2022)
	Tablets	Theophylline	Hydroxypropyl cellulose, Sodium starch glycolate, Triacetin	Jordan	(Arafat, 2018)
	Tablets	Warfarin	Eudragit® EPO, Triethyl citrate, tri-calcium phosphate (TCP)	Jordan	(Arafat, 2018)
	Solid Dispersion/ Disc	Felodipine	Eudragit®-EPO, PEG, PEO, Polysorbate	Iraq	(Alhijjaj et al., 2016)
	Ocusert	Ganciclovir	Polylactic acid, phosphatidylcholine, Sodium taurocholate, edge activator	Egypt	(Naguib et al., 2021)
SLS	Tablets	Clindamycin palmitate	Kollidon®-VA64, Microcrystalline cellulose, Lactose monohydrate, Aluminum Lake, Iron (III) Oxide	Egypt	(Mohamed, 2020)
	Printlets	Lopinavir	Candurin®, Kollicoat IR, Lactose Monohydrate, talc	Jordan	(Hamed, 2021)

API, active pharmaceutical ingredients; FDM, Fused deposition modeling; HPMC, Hydroxypropyl methylcellulose; PEG, Polyethylene glycol; PEO, Polyethylene oxide; SLS, Selective laser sintering; SSE, Semi-solid extrusion; TCP, tri-calcium phosphate.

printing to improve the solubility of the anti-diabetic drug dapagliflozin by loading the drugs into SENDDS systems, which were printed as oral tablets (Algahtani, 2021).

3.1.2. *Fused deposition modeling (FDM)*

FDM-based 3D printing is one of the most researched 3D printing techniques due to its low cost, easy handling and the strength of the printed dosage forms. The drug is incorporated in a thermoplastic filament before it's loaded into the printer. The filament is then melted by heat and extruded through a nozzle onto a printing platform to form a layer (Rahim et al., 2019; Parulski, 2021). The printed layer solidifies in a short time, and the platform then lowers to allow for the creation of a new layer. This process is repeated until the 3D design is complete. Despite the simplicity and reliability of this method, it is limited by the low drug loading and the limited range of thermoplastic materials that can be used as ink for 3D printing(Rahim et al., 2019; Parulski, 2021).

Justyna *et al* employed FDM-based 3D printing to produce a tailored-release tablet dosage form. They impregnated a methanolic solution of prednisolone (drug model) into a Polyvinylpyrrolidone (PVP) polymer filament, which allowed the prednisolone to diffuse into the filament. They then extruded the filament to fabricate different tablet sizes (Skowyra et al., 2015). FDM enabled the printing of tablets with different sizes, shapes and release profiles.

In another study, 3D-printed ocular inserts were fabricated and loaded with nanovesicles. The nanovesicles were incorporated with Ganciclovir (GCV) and provided a sustained drug release over 24 h. When the nanovesicles were loaded into the 3D-printed Polylactic acid (PLA) ocusert laden, it extended the release of the GCV for more than five days and improved its ocular bioavailability *in vivo* (Naguib et al., 2021). The application of 3D printing, in this work, led to the development of a non-invasive, sustained drug delivery system that can be utilized for several drugs with short half-lives.

3.2. *Inkjet-based 3D printing*

Inkjet-based 3D printing is a very promising technique with many pharmaceutical applications. SPRITAM®, the first 3D FDA-approved product was fabricated using this technique (West and Bradbury,

2019). The inkjet principle is based on the ability to jet and digitally control the deposition of small liquid droplets. 3D inkjet printers are classified into two types: continuous inkjet printing (CIJ) and drop-on-demand (DOD) printing (Scoutaris et al., 2016). CIJ printing maintains a continuous stream of ink flowing through the printhead, which is then selectively ejected onto the build platform. This type of printing is faster than DOD printing, but it has lower resolution and precision. DOD printing ejects droplets of ink onto the build platform one at a time, controlled by a computer. This type of printing is slower than CIJ printing, but it has higher resolution and precision (Scoutaris et al., 2016; Shirazi, 2015).

Mary *et al* demonstrated for the first time the use of hot-melt inkjet printing to fabricate tablets with complex geometries for controlled drug release. The antilipemic fenofibrate was added to melted beeswax to fabricate honeycomb-like shape tablets with different geometries using a piezoelectric inkjet printer. The authors suggested that the honeycomb geometry is an optimal shape for personalized dosing tablets because it provides a high degree of freedom to vary the geometries based on the required drug release profile. This work demonstrated the feasibility of using inkjet-based 3D printing to fabricate tablets with complex geometries for controlled drug release (Kyobula, 2017).

Despite the ability of inkjet-based 3D printing to fabricate complex structures, the whole formulation must comply with the printing method and obtain a suitable viscosity to prevent nozzle blockage. Additionally, the drug loading and hardness of the printed products may be insufficient (Scoutaris et al., 2016; Shirazi, 2015).

3.3. Laser-based 3D printing

This technique employs a focused laser to solidify the top surface of the material to form layers that produce the 3D structure. There are two types of this technique: stereolithography (SLA), which uses a focused laser to solidify a specific area of the top layer of liquid resin. The reservoir then descends so that the laser can solidify a new layer of the liquid resin until the 3D shape is completed. SLA can fabricate complex and challenging structures with high resolution including microneedles, tissue scaffolds and dental devices(Shirazi, 2015; Lakkala, 2023).

The other type of this technique is selective laser sintering (SLS), which directs the laser to a specific area at the top layer of polymeric powder, causing this layer to melt and solidify. Then, the powder platform descends, and a new layer of powder is passed over the previous layer. The laser is then directed again to the specified area and the process is repeated to form the 3D structure. The printing accuracy and hardness depend on the accuracy and intensity of the laser, in addition to the particle size of the powder. In comparison with the SLA, the SLS does not require the use of toxic excipients such as photocurable polymers and photoinitiators. There is also no need for post-printing processing for the 3D structure (Lakkala, 2023; Awad, 2020).

Printlets^{TM} is a 3D-printed oral tablets that offer great dose flexibility and has been tested clinically in patients born with a metabolic disorder (Goyanes, 2019). Owing to their potential applications in personalized medicine, they have been vigorously investigated with SSE and FDM-based 3D printing techniques. In a recent study, Hamed *et al* evaluated the feasibility of using SLS to improve the solubility of lopinavir (LPV). The 3D-produced printlets have demonstrated a high percentage of the LPV in amorphous forms, i.e., more than 90% of the drug dissolved in less than 30 min. Increasing the LPV content has increased the printlet porosity, suggesting faster dissolution. It also found that the laser speed has a major impact on the crystallinity of the LPV (Hamed, 2021).

Although laser-based 3D printing has gained a lot of attention in biomedical engineering (Ho et al., 2015; Xu, 2021), due to primarily its ability to produce patient-tailored devices with high resolution, its translation in the pharmaceuticals is hampered by many challenges such as drug incompatibility with resin and the lack of safe photocurable polymers and drug degradation following laser exposure.

4. Regulatory perspective

In the highly regulated pharmaceutical industry, the adoption of 3D printing technology presents both technical and regulatory challenges. The stringent quality and risk management systems mandated by regulatory bodies mean that pharmaceutical manufacturers are often hesitant to adopt new technologies without extensive validation data. This cautious approach is compounded by the industry's reliance on proven manufacturing processes and the lack of a robust regulatory framework, particularly addressing the unique aspects of 3D printing. The existing regulations were developed with conventional manufacturing processes in mind, concentrating on manufacturing process validation rather than specific components of the production line. This approach ensures that as long as the end product meets the required standards, the specific technologies employed in the production are given less scrutiny (Norman, 2017). However, this paradigm is challenged by the introduction of 3D printing technology, which requires a component-focused regulatory review due to the technology's distinct characteristics. The existing documentation and experience of reference regulatory bodies with new manufacturing technologies such as 3D printing are not sufficiently detailed, leading to a gap in clear regulatory guidance. This lack of detailed guidance can result in a delay in the technology adoption as manufacturers await clearer regulatory expectations and fear the risk of non-compliance.

As technology advances, there is a growing need for regulatory developments that keep pace with technological advancements. This includes establishing standards for 3D printing equipment qualification, process validation, and quality control measures specific to the technology's application in pharmaceutical production. To address these challenges, regulatory bodies are beginning to develop frameworks that consider the specificities of 3D printing. For instance, the FDA has issued guidance on technical considerations for additive-manufactured medical devices, which may serve as a precursor to more detailed guidelines for 3D printing in pharmaceutical manufacturing. The future of 3D printing in pharmaceuticals will depend on the industry's ability to navigate these regulatory landscapes, ensuring patient safety while fostering technological innovation. As such, collaboration between regulatory bodies, manufacturers, and technology experts will be crucial in developing a regulatory ecosystem that supports the safe and effective integration of 3D printing into pharmaceutical research, development and manufacturing processes.

The encouragement of emerging technologies by regulatory bodies is crucial for fostering innovation in the pharmaceutical industry (Junker, 2017). Regulatory support for technologies like 3D printing not only catalyzes their development but also ensures that their integration into the market is aligned with public health interests. By providing clear guidelines and frameworks, regulators can mitigate potential risks associated with new technologies, thereby protecting patient safety while promoting scientific advancement. Such regulatory endorsement is essential for maintaining the integrity and efficacy of the pharmaceutical manufacturing process. Moreover, proactive regulatory engagement with technology developers can accelerate the translation of research into therapeutic solutions that address unmet medical needs. This symbiotic relationship between regulation and technological progress is vital for the evolution of personalized medicine and the optimization of healthcare delivery. In the context of 3D printed pharmaceuticals, for example, physical quality defects are anticipated (e.g. z-layer separation, bending, layer shifting …etc.) and present quality control challenges. The current quality control measures as well as the current technology state may not be sufficient to prevent such defects, this underscores the indispensable role of the regulatory bodies in mandating regulations that balance the limited nature of the technology, technology performance, and the safety-and-efficacy of the pharmaceutical product. Regulatory oversight is essential for the pharmaceutical industry to fully harness innovative technologies such as 3D printing and ultimately improve healthcare outcomes (Cui, 2021;

Mancilla-De-la-Cruz, 2022; Wu and Chen, 2018).

5. Future outlook

Three-dimensional printing is increasingly recognized as a transformative technology in pharmaceutical development and manufacturing (Awad, 2018; Elbadawi, 2021). Its versatility extends beyond the development of medical devices and tissue engineering, heralding a new era in the production of personalized medicine. The 3D printing technology offers unparalleled precision in clinical trial dose optimization, enabling researchers to produce dosage forms with exact specifications. This precision extends to the customization of drug release profiles, allowing for the controlled release of APIs and the potential to improve therapeutic outcomes. The cited works of (Kotta et al., 2018; Lepowsky and Tasoglu, 2018; Araújo, 2019; Alruwaili, 2018) underscore the breadth of research supporting the integration of 3D printing technology into various pharmaceutical processes, reflecting a growing consensus on its value within the industry.

Despite the potential of 3D printing technology, the MENA region faces challenges characterized by limited research activity, primarily in academia, and a cautious approach to adopting new technologies by local pharmaceutical manufacturers. This hesitancy is reflected in the lower volume of 3D printing research compared to that in developed economies. However, there is an anticipated gradual increase of 3D printing research in the MENA region, driven by a slow but steady influx of investments, increasing interest in the technology's potential, and increasing scientific collaborations with other scholars.

Current economic constraints and limited research funding pools in the region present significant barriers, yet there is optimism as certain countries within the region are making strategic efforts to overcome these hurdles. For instance, Saudi Arabia's INVEST SAUDI program under the Ministry of Investment is a pivotal initiative aimed at enhancing the nation's manufacturing capabilities across various sectors, including healthcare. This program is an overarching strategy that fosters industrial innovations and attempts to attract specialized 3D printing enterprises to the region, positioning the healthcare sector and pharmaceutical manufacturers to benefit from the advanced manufacturing techniques that 3D printing offers (Badreldin and Atallah, 2021). Another initiative in MENA is the Dubai 3D Printing Strategy, where the United Arab Emirates (UAE) is envisioning and working toward positioning itself as a leader in 3D printing by 2030, with a particular focus on construction, consumer products, and medical and pharmaceutical products (Dubai 3D Printing Strategy., 2023).

These strategic initiatives undertaken by Saudi Arabia and the United Arab Emirates are anticipated to catalyze an upsurge in scholarly publications focused on the medical applications of 3D printing technology, ranging from prosthetics and orthopedic implants to complex drug formulations, potentially transforming patient care and treatment modalities in the region and around the globe.

The outlook for 3D printing in pharmaceutical research and development is exceptionally promising, with the potential to fundamentally alter the landscape of drug development and personalized medicine. As the technology matures, we anticipate more sophisticated drug dosage forms, enabling precise control over release kinetics and the ability to combine multiple drugs in a single pill tailored to individual patient profiles. The recent approval of the first 3D-printed tablet on a commercial scale demonstrated the capability of 3D printing technology to be a major player in the pharmaceutical industry. Moreover, the ability of 3D printing to produce medicine on demand could revolutionize supply chains, ensuring medication availability even in remote regions. As regulatory bodies adapt to this innovation, we can expect a surge in 3D printing applications within the pharmaceutical industry, ultimately enhancing patient outcomes and ushering in a new era of medical treatment customization.

6. Conclusion

The integration of 3D printing technology into pharmaceutical research and development indicates a significant shift towards more personalized and flexible medicine production on-demand. The early adoption of 3D printing technology in large-scale manufacturing has the potential to save time and reduce the costs associated with medicine manufacturing. Our data provide evidence for the limited research activity in the MENA region, particularly in pharmaceutical research and development. This can be explained by the lack of resources (e.g., funding, 3D printer devices, 3D printers' inks, 3D printing expertise, etc.), which is expected with the birth of this innovative technology. While the MENA region currently lags in the overall 3D printing research and its applications, initiatives such as Saudi Arabia's INVEST SAUDI and the UAE's Dubai 3D Printing Strategy are indicative of a growing recognition of the technology's potential. These efforts are expected to foster innovations, attract investment and ultimately enhance the healthcare sector's capabilities with better outcomes. Despite some inherent technical limitations of 3D printing technology that make it require careful consideration before its use in medicine manufacturing (e.g., limited pool of pharmaceutical-grade compatible material, slow fabrication process, and the exposure of materials to high-energy that might affect sensitive components of the formulation), the 3D printing technology has the potential to solve many challenging issues in the pharmaceutical industry (Shahrubudin, 2020). The 3D printing technology holds a promising future for the MENA region and its advancement will require ongoing collaboration between academic institutions, industry stakeholders and regulatory bodies to fully realize its potential in translating pharmaceutical research findings into products that will ultimately reshape patient care.

7. Institutional review board Statement

Not applicable.

8. Informed consent Statement

Not applicable.

CRediT authorship contribution statement

Riyad F. Alzhrani: Conceptualization, Investigation, Writing – original draft. **Mohammed Y. Alyahya:** Investigation, Writing – original draft. **Mohammed S. Algahtani:** Investigation, Writing – original draft. **Rawan A. Fitaihi:** Investigation, Writing – original draft. **Essam A. Tawfik:** Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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