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Uncovering advances in final end-user applications, user acceptability, quality assurance, and digital technologies for 3D-printed oral drug delivery systems

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Abstract

The increasing demand for innovative drugs and personalized treatment is radically changing the pharmaceutical industry, where significant efforts in research and development (R&D) are taking place. Three-dimensional (3D) printing offers interesting solutions for these demands, solving some of the limitations of current manufacturing processes. 3D-printed oral drug delivery systems can improve the delivery of pharmaceutical substances in the body, and the dynamic interaction between pharmaceutical ingredients, while providing personalized formulations, geometries, sizes, controlled release rates, and increasing time in the gastrointestinal tract. Advances in 3D printing for oral drug delivery systems have been investigated in terms of processes, materials, and effects. However, it is important to also consider other topics, such as the specific needs of the users to enhance drugs acceptability, the quality control processes due to the absence of approved guidelines, and the digitalization of the industry to respond to future challenges of the digital era; nevertheless, there are no studies that comprise these elements. To fill this gap, the aim of this research is to identify advances in terms of final end-user applications, quality assurance, user acceptability, and digital technologies for 3D-printed oral drug delivery systems. To accomplish this, a competitive technology intelligence (CTI) methodology was applied, where scientific literature was retrieved from the Web of Science covering the period from January 1, 1900, to May 1, 2023. For this task, a scientometric analysis was performed, and the main trends involving the previously mentioned elements were identified. In the first case, 3D-printed oral drug delivery systems are being designed for different purposes, including as anti-deterrent formulations to decrease the global problem of opioid abuse. For quality assurance, the results demonstrated the implementation of approaches like quality by design to increase the quality of the 3D-printed dosage forms. In the case of user acceptability, the interest in creating more attractive formulations was identified; for this, innovative technologies such as ColorJet 3D printing are being used. Lastly, regarding digital technologies, the importance of cyberattacks while sending the 3D-printed dosage form file to the 3D printer is highlighted; for this, cybersecurity systems are being studied. The outcomes of this study can add value to researchers, organizations, and investment firms interested in the R&D of novel and personalized treatments, and the areas of 3D printing, pharmaceutical, medical, and health.

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Keywords: 3D Printing; Oral drug delivery; Quality; Acceptability; Digital technologies

1. Introduction

Drug delivery systems (DDS) are characterized by technologies that enhance the delivery of pharmaceutical products (drugs, vitamins, health supplements, or diagnostic substances) into the body. Innovations in drug delivery technologies can help meet their unique delivery needs[1] and mitigate treatment side effects. According to the United States National Institute of Biomedical Imaging and Bioengineering (NIBIB)[2], DDS can be described in two broad-ranging categories: routes of delivery and delivery vehicles. The first one refers to the routes of administration of pharmaceutical compounds, with the most common being oral, parenteral (intravenous, intramuscular, subcutaneous, intra-arterial), sublingual, topical, nasal, intraosseous, ocular, rectal, and vaginal[3]. On the other hand, delivery vehicles concern the various ways in which pharmaceutical compounds can be encapsulated or packaged so they can safely travel through the body; some examples are liposomes, polymeric nanoparticles, microbubbles, hydrogels, micelles[4], scaffolds[5,6], and microneedles[7].

In October 2022, Euromonitor International, a global leading company in business intelligence and market research, analyzed four trends that will impact the pharmaceutical and medical industry, with "Rising investment in research and development (R&D) and innovation" being one of them[8]. This trend points to the rising demands for high-value innovative treatments, driving investment in R&D and personalized treatment. For this, the versatility of three-dimensional (3D) printing and its diverse processes can be utilized in various areas, including the medical and pharmaceutical industry, reducing high production costs, and limitations of traditional processes, as well as allowing personalized manufacturing according to individual needs. The introduction of 3D printing technology into the pharmaceutical field can revolutionize the medical industry, as it enables varying dosage batch sizes, novel dosage forms, and drug distribution.

Under this context, 3D printing of oral DDS concerns the development of technologies and dosage forms using 3D printing processes to improve the delivery of pharmaceutical products, the dynamic interaction between pharmaceutical ingredients, and the user safety. They can offer personalized formulations, geometries, sizes, release rates, and increased time in the gastrointestinal tract, making 3D printing more attractive than traditional procedures. For instance, one of the most used methods to manufacture tablets and pills is direct compression, which has advantages such as short operation time and use of fewer resources[9]. However, some active pharmaceutical ingredients (APIs) demonstrate low compressibility[10], directly affecting the mechanical properties of the tablet and pill. On the other hand, this process requires a compression press, in which the punch and die can cause other defects like sticking, picking, double impression[11], and edging. Another inconvenience is that changing the appearance of the tablet and pill is not an immediate operation, as it requires the fabrication of a new die based on the desired geometry.

Hard capsules and softgels are not exempt from manufacturing defects, problems related to body caps (differences in length or improperly sealed), and incorrect rotary die pressure, which can occur during their production. 3D printing techniques offer solutions to these issues. From a general perspective, they operate through a 3D printer that reads a computer-aided design (CAD) file, which was created to produce a physical model according to the dosage form desired. The printhead moves in the x–y plane to create the foundation of the object, then the printhead moves along the z-axis, resulting in layer-by-layer formation of the dosage form[12]. As each 3D printing technique has different process parameters, the applied technique can be selected based on which is more suitable for the specific active pharmaceutical ingredients (APIs) and the type of dosage form.

3D-printed oral DDS encompass various types of films, tablets, capsules, pills, and fibrous dosage forms. Figure 1 illustrates some examples of the types of 3D-printed oral dosage forms, with the most common materials alongside the API being polymers and hydrogels, as shown in Table 1.

There are different studies on 3D-printed oral DDS, including one that reveals the advances and current state in terms of processes and applications. For instance, Mancilla-De-la-Cruz and Rodriguez-Salvador studied the available technologies for 3D printing of oral drug delivery in 2022[27]; during the same year, Mancilla-De-la-Cruz *et al.* investigated the process, materials, and effects of 3D printing for DDS, where oral administration was studied[14]; however, the user has specific needs that need be attended to promote drugs acceptability; moreover, considering the novelty of 3D-printed DDS and the lack of standardization, quality control represents a crucial topic to be analyzed. In addition, to cope with the challenges of the digital era, it is necessary to study efforts toward digitalization. Despite the importance of these topics so far, there are no studies that discuss them; to fill this gap, the purpose of this research

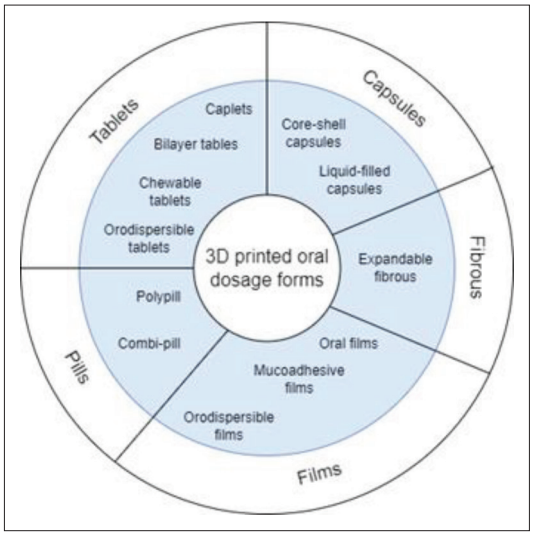

Figure 1. Types of 3D printing oral dosage forms.

is to uncover advances in the following categories: end-user applications, quality assurance, user acceptability, and digital technologies for 3D printing of oral DDS. To this end, a competitive technology intelligence (CTI) methodology was applied to reveal the current scientific and technological advances in the field.

In this research, end-user applications refer to the use of 3D-printed oral DDS to meet the specific end-user needs, such as designing dosage forms that are user-friendly to visually-impaired patients, creating non-commercially available formulations for pediatric patients, and conceiving novel solutions to target global problems, such as drug abuse.

Quality assurance focuses on methods, protocols, and tools to guarantee quality during the preparation and fabrication of 3D-printed dosage forms. It is a common concern in 3D-printed oral DDS, but unfortunately there is no specific US Food and Drug Administration (FDA) guideline for 3D-printed medicines, which are usually fabricated according to chemistry, manufacturing, and control (CMC) standards, Good Manufacturing Practices (GMP), and regulatory processes for pharmaceutical drug product applications from the US FDA Center for Drug Evaluation and Research (CDER)[28].

On the other hand, user acceptability analyzes user-centered needs, exploring the real demands of the user, including preferences and palatability. This can facilitate the introduction of 3D-printed orally administered drugs to the market and increase the acceptability of these novel treatments. For this reason, user acceptability should be considered.

Digital technologies examine advances in this field. Currently, the most innovative industries are rapidly migrating toward digitalization. In the pharmaceutical industry, important efforts for the implementation of digital technologies throughout 3D printing processes are growing. In this study, a category focused on digital technologies is examined.

CTI is a strategic and systematic process that focuses on monitoring the technical and competitive environment of an organization at different levels, with the purpose of providing actionable information for decision making in the areas of technology, innovation, product design, R&D, and markets (global, national, and local)[29].

Through CTI, it is possible to identify available opportunities that can be used to predict future trends, generating competitive advantages. Its continuous process is assisted by a diversity of tools and qualitative and quantitative methods that facilitate the acquisition, extraction, collection, visualization, and interpretation of the information.

2. Methodology

In this research, the methodology applied is that proposed by Rodriguez-Salvador and Castillo-Valdez in 2021, which consists of an eight-step process with interdependent phases and continuous feedback: (i) project planning, (ii) identification of data sources, (iii) search strategy design, (iv) data collection, (v) information analysis, (vi) expert feedback, (vii) validation and final results, and (viii) decision making[30].

Primary and secondary sources were determined to gather information. The primary sources were international experts in the field of 3D printing. The secondary source was scientific literature from Web of Science (WoS), which includes more than 21,000 peer-reviewed journals and 17.2 million open access records[31].

Terms and keywords related to 3D printing of oral DDS and data subjects were identified and manually validated. These terms include words related to 3D printing, delivery systems, type of dosage forms, and pharmaceutical area. In addition, exclusion terms were identified manually to exclude irrelevant documents. These terms were integrated into a query with a period corresponding to January 1, 1900, to May 1, 2023. The document types were limited to articles, proceeding papers, and early-access articles. The query was validated by international experts in 3D printing. Figure 2 illustrates the generated query.

A total of 621 publications were retrieved from the query; after the manual inspection, the total number of papers was reduced to 512. These documents were classified

Table 1. Excipients utilized in various 3D printing techniques

Process	Technique	Material (excipients)	Reference
Binder jetting	Binder jetting	– Polyvinylpyrrolidone (PVP) – Kollidon® SR – Hydroxypropyl methylcellulose (HPMC) – Polyvinylpyrroldine-vinyl (PVPV) – Hydroxypropyl cellulose (HPC) – Ethylcellulose (EC) – Mycrocrystalline cellulose (MCC) – Lactose monohydrate – Methyl cellulose (MC)	[13]
Material extrusion	Fused deposition modeling	– Polylactic acid (PLA) – Polyvinyl alcohol (PVA) – Soluplus – Ethylcellulose (EC) – Eudragit® – Hydroxymethyl cellulose (HMPC) – Hydroxypropyl cellulose (HPC) – Polycaprolactone (PCL) – Polyethylene glycol (PEG) – Hydroxypropyl methylcellulose (HPMC) – Polyethylene oxides (PEOs) – Polyvinylpyrrolidone (PVP)	[14]
	Pressure-assisted microsyringe	– Hydroxymethyl cellulose (HMPC) – Mycrocrystalline cellulose (MCC) – Polyvinylpyrrolidone (PVP) – Lactose – Hydroxypropyl cellulose (HPC) – Hydroxypropyl methylcellulose (HPMC) – Polyvinyl alcohol (PVA) – Kollicoat® – Ethylcellulose (EC) – Hydroxypropyl methylcellulose (HPMC)	[15] [16] [17]
Material jetting or inkjet printing	Drop-on-demand	– Polycaprolactone (PCL) – Polyvinylpyrrolidone (PVP) – Poly (N-isopropylacrylamind-co-acrylamide) (PNIPAM) – Hydroxypropyl methylcellulose (HPMC) – Hydroxypropyl cellulose (HPC)	[18] [19]
	Continuous inkjet printing	– Hydroxypropyl methylcellulose (HPMC) – Hydroxypropyl cellulose (HPC) – Polyethylene glycol (PEG)	[20]
Powder bed fusion	Selective laser sintering	– Polycaprolactone (PCL) – Eudragit® – Kollicoat® IR – Hydroxymethyl cellulose (HMPC) – Poly-I-lactic acid (PLLA) – Kollidon® – Mycrocrystalline cellulose (MCC) – Ethylcellulose (EC) – Polyethylene oxide (PEO) – Methylcellulose (MC)	[21]
Vat photopolymerization	Stereolithography	– Polycaprolactone (PCL) – Polyethylene glycol diacrylate (PEGDA) – Polyethylene glycol dimethacrylate (PEGDMA) – Poly (2-hydroxyethyl methacrylate) (pHEMA) – Polypropylene fumarate (PPF) – Diphenyl (2,4,6-trimethylbenzoyl) (TPO) – Polyethylene glycol (PEG) – Triol	[22] [23] [24]
	Digital light processing	– Polyethylene glycol diacrylate (PEGDA) – Polyethylene glycol (PEG) – Acrylated hyperbranched polyester (AHBPE) – Polyethylene glycol dimethacrylate (PEGDMA) – Polycaprolactone (PCL) – Polypropylene fumarate (PPF) – Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (TPO)	[22] [25] [26] [24]

(TS=((("3D" OR "3-D" OR "3 D" OR "Three-d" OR "Three d" OR "Three-dimensional" OR "Three dimensional") NEAR/0 print*) OR ("additive" NEAR/1 manufact*) OR ("pharmaco" NEAR/0 print*) OR ("on-demand" NEAR/0 manufactur*) OR ("3DP"))) AND (TS=(((tablet* OR capsule* OR "buccal" OR ("soft" NEAR/0 tablet*)) AND ("oral" OR pharma* OR "drug" OR "delivery" OR "ODD" OR "dosage" OR "release" OR health* OR medic*)) OR (caplet* OR ("bilayer" NEAR/0 tablet*) OR "polypill" OR printlet* OR ("orodispersible" NEAR/0 tablet*) OR ("oral" NEAR/1 film*) OR ("solid" NEAR/0 "oral" NEAR/0 form*) OR ("orodispersible" NEAR/0 film*) OR ("solid" NEAR/0 "dosage" NEAR/0 form*) OR ("mucoadhesive" NEAR/0 film*) OR ("tailored" NEAR/0 "dosage" NEAR/0 form*) OR ("mucoadhesive" NEAR/0 "patch")) OR ((("pill" OR "pills" OR "pellet") AND ("oral" OR pharma* OR "drug" OR "delivery" OR "ODD" OR "dosage" OR "release" OR health* OR medic*)) NOT (image* OR "sensor" OR "ultrasound" OR "bottle" OR "culture")))) NOT (TS=("wastewater" OR "artwork" OR "concrete" OR ("user" NEAR/0 interface*) OR "Puccinia triticina" OR ("robot" OR "robots") OR "image reconstruction" OR "gastric resident electronic" OR endoscop* OR "antenna" OR "oximeter" OR voltammetri* OR "synovial" OR "digital anatomy" OR "acoustic" OR "pedagogical capabilities" OR "electromechanical switches" OR "powder inhaler" OR "metallic clay" OR "flexible electronics" OR "running shoes" OR "electrochemical pestle" OR "dentures" OR "tabletop" OR "educational technology" OR "optical sensor" OR endodo* OR "orthopedic" OR "suppository moulds" OR "bone models" OR ("tissue" NEAR/0 ("reconstruction" OR "formation" OR "production" OR "implant")) OR "mouth sticks" OR "radiotherapy" OR "face mask" OR "anatomical structure" OR "total body irradiation" OR "hotel" OR "nasal absorption" OR "dental models" OR "abs beam" OR "sport equipment" OR ("bioabsorbable medical" NEAR/0 device*) OR "heart models" OR ("topical" NEAR/0 application*) OR "delivery implant" OR "ophthalmologic patches" OR "implantation" OR "bladder device" OR "bone tissue engineering" OR "molds" OR "transdermal" OR "scandium" OR "subcutaneous" OR "implant")))

Figure 2. Query for 3D printing of oral drug delivery systems.

into different categories, but only the four categories relevant to the objective of this study were analyzed, which are end-user applications, quality assurance, user acceptability, and digital technologies, representing a total of 149 research documents. A scientometric analysis was carried out to determine publication trends in the scientific literature, provide statistics about the publication output rate[32], and uncover key players, innovation activities, and main technology trends[33]. Expert feedback was used as support at all stages of the CTI methodology to validate the results obtained.

3. Results and discussion

In this section, the results of the analysis are presented. As previously mentioned, a total of 149 publications were analyzed based on the categories end-user applications, quality assurance, user acceptability, and digital technologies; the distribution of publications is shown in Figure 3.

Through the scientometric analysis, the number of publications per country, number of publications per country and key players, number of publications per year, number of publications per research area, and number of publications per journal were determined. In addition, technological trends were determined in each category.

In terms of number of publications per country, a total of 35 countries were identified, the top 5 countries with most publications being England, with a total of 30, followed by China with 18, the United States with 15, Germany with 11, and lastly South Korea with 8. By identifying some of the key players in 3D-printed pharmaceuticals by country (Figure 4), the level of technological and industrial development in 3D-printed pharmaceuticals of a country is a factor that influences the number of publications per country. As shown in Figure 4, regarding the top three countries, England has many companies and universities working with 3D printing of DDS; FabRx and the University College London (UCL) have a large repository of published research papers. In the case of China, Triastek (located in Nanjing) accounts for 20% of 3D-printed pharmaceutical applications, while in the United States, companies include Aprecia Pharmaceuticals and Merck.

The number of publications related to the 3D printing of oral DDS demonstrated a significant increase after 2017, creating a positive trend over the past 7 years. During this time, aside from partnerships within companies, technologies like M3DIMAKER™, MED®, CraftMake™, and MakerBot® were introduced, facilitating investigation and product development. For the year 2023, the number of publications has declined; however, since the data was

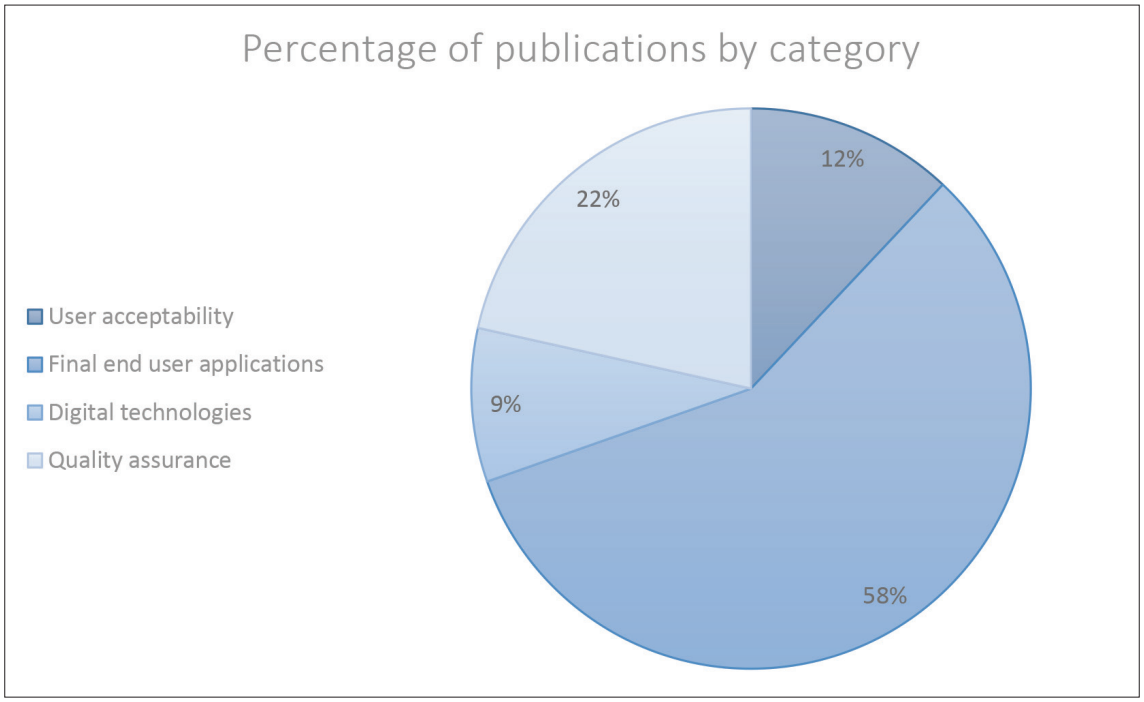

Figure 3. Percentage of publications by category.

retrieved only until the first of May 2023, the total number of publications for 2023 is not complete (Figure 5).

The results were also analyzed in terms of the area of research according to the Web of Science categories, with some papers belonging to more than one; from the 149 results, 126 (72.83%) are classed in "Pharmacology & Pharmacy," 15 (8.67%) publications in "Chemistry," and 6 (3.47%) publications in "Material Science." According to our results, the top three journals with the most publications are *The International Journal of Pharmaceutics* (INT J PHARMACEUT), which had the highest number of published articles with 38, *Pharmaceutics* (PHARMACEUTICS) close behind with 35, followed by *AAPS PharmSciTech* (AAPS PHARMSCITECH) with 9.

With regard to the most used 3D printing techniques, the analysis of the 149 publications revealed some of the techniques already presented in Table 1 as well as some new ones. There are many 3D printing techniques and many names too. For convenience, the names used in the figures are extracted directly from the publications without regrouping, and some may refer to the same technique due to name variations (see Table 2). Fused deposition modeling was the most used technique, followed by pressure-assisted microsyringe and selective laser sintering (Figure 6). Fused deposition modeling was used for the creation of tablets, solid dosage forms (various geometries), capsules, polypills, orodispersible films, gummies, mucoadhesive films, and others; while pressure-assisted microsyringe was utilized to produce mucoadhesive films, orodispersible films, polypills, tablets, and soft dosages (Figure 7). Lastly, selective laser sintering was applied to fabricate tablets (and printlets) and polyprintlets. On the other hand, some of the least used 3D printing techniques were stereolithography, thermal inkjet printing, and drop-on-powder (Figure 6). For the development of the outer shell of the capsules, the predominant materials are polyvinyl acetate (PVA) and polylactic acid (PLA).

Table 2. Identified 3D printing techniques

Process	Technique
Binder jetting	– Binder jetting – Color jet printing – Drop-on-powder
Material extrusion	Extrusion-based 3D printing/micro-extrusion – Fused deposition modeling – Direct ink writing • Pressure-assisted microsyringe • Pneumatic-based extrusion • Syringe extrusion – Direct powder extrusion
Material jetting or inkjet printing	– Thermal inkjet printing
Powder bed fusion	– Selective laser sintering
Vat photopolymerization	– Stereolithography – Digital light processing – Micro 3D printing

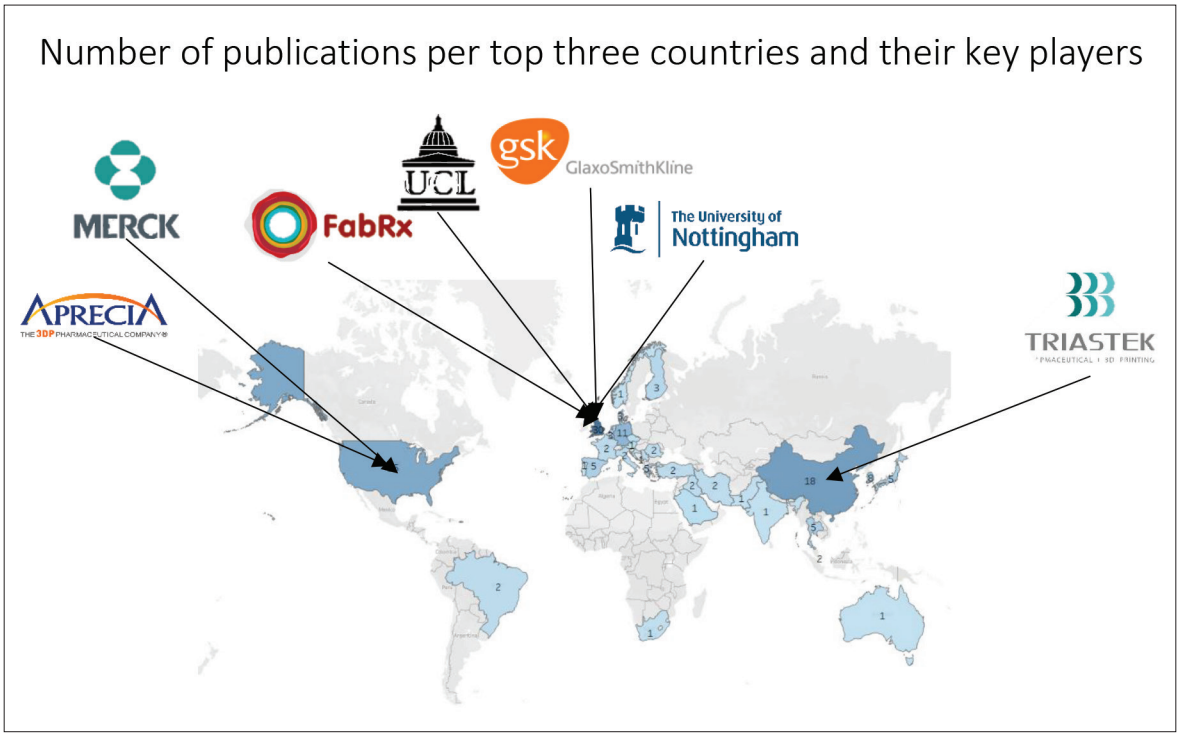

Figure 4. Number of publications per top three countries of the categories "end-user applications," "quality assurance," "user acceptability," and "digital technologies," and their key players.

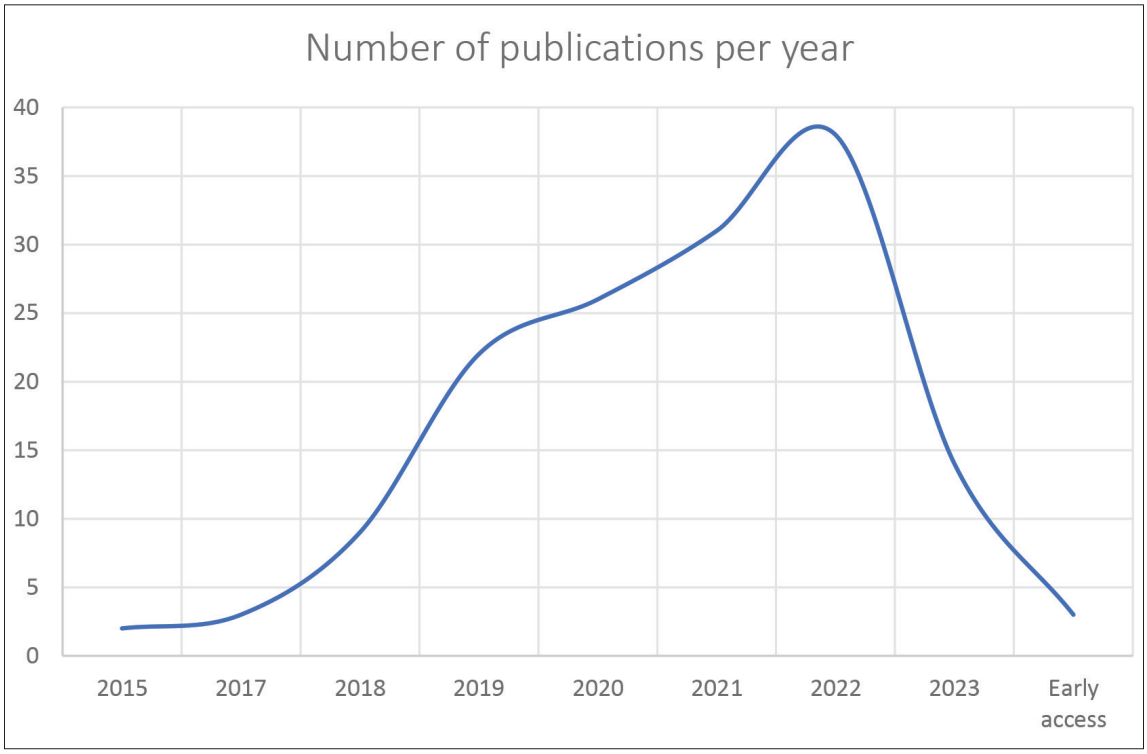

Figure 5. Number of publications per year of the categories "end-user applications," "quality assurance," "user acceptability," and "digital technologies."

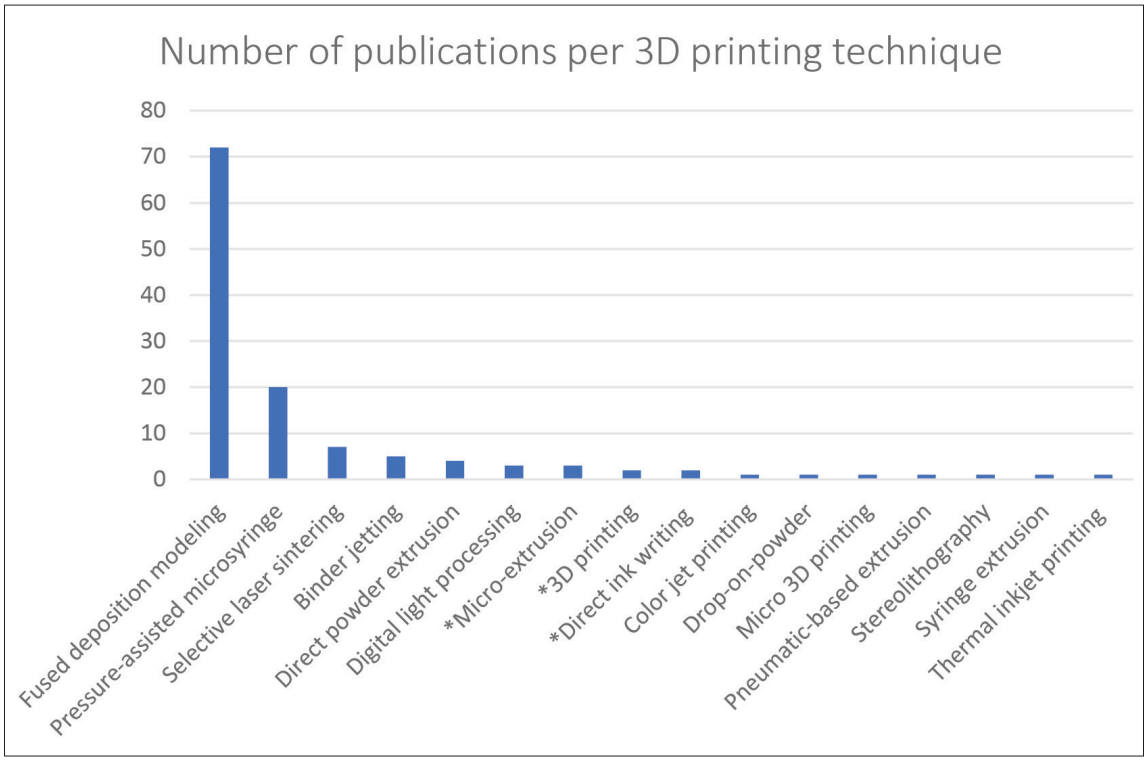

Figure 6. Number of publications per 3D printing technique of the categories "end-user applications," "quality assurance," "user acceptability," and "digital technologies." *Specific technique not available.

The technological trends of the categories are presented based on the total number of publications of each category previously established:

3.1. Final end-user application

There are 92 publications in the final end-user application category. This category targets specific applications of 3D-printed oral DDS including "disease treatment," "pediatrics," "gastrointestinal," "patients with limitations (visual impairment)," and "abuse deterrent."

3.1.1. Disease treatment

This sub-section describes the advances of 3D-printed oral DDS for specific diseases, as well as solutions for negative interactions between active pharmaceutical ingredients and alternatives for multiple medication intake.

The combination of the anti-tuberculosis drugs, rifampicin (RIF) and isoniazid (ISO), has a negative interaction upon simultaneous release in an acidic environment. Genina *et al.* designed a 3D-printed multi-compartment dosage unit with fused deposition modeling where the APIs were loaded in the filaments via hot melt extrusion[34]. The multi-compartment dosage unit demonstrated a delayed release and absorption of the drugs, avoiding the interaction of rifampicin and isoniazid[34]. In 2021, Tabriz *et al.* also tackled this problem, except that the result was a fused deposition modeling-printed bilayer tablet; the design of the tablet enabled a reduction in the degradation of rifampicin in acidic environments, avoiding interactions between rifampicin and isoniazid[35].

Parkinson's disease should be controlled symptomatically as it cannot be cured, and its treatment requires the intake of various medications such as levodopa, benserazide, and pramipexole. Windolf *et al.* used fused deposition modeling to create a series of easy-to-swallow mini-polypills with different dosages, layers, and geometries. As a result, they improved the design of the formulation and the floating property, and prolonged the API absorption of levodopa in the upper gastrointestinal tract. The fabricated polypills allowed individualized dosing, reducing the amount of different medicine intake, and improved patient adherence to their therapy[36].

Hydrocortisone, a medicine for the treatment of adrenal insufficiency, if taken three times daily, can produce negative side effects due to plasma cortisol fluctuations. To reduce the daily dosage intake, Ayyoubi *et al.* created a 24-h release 3D-printed hydrocortisone tablet using M3DICORT[37]. The tablets demonstrated a 24-h dissolution profile and unique quality attributes. On the other hand, some impurities within the tablet were

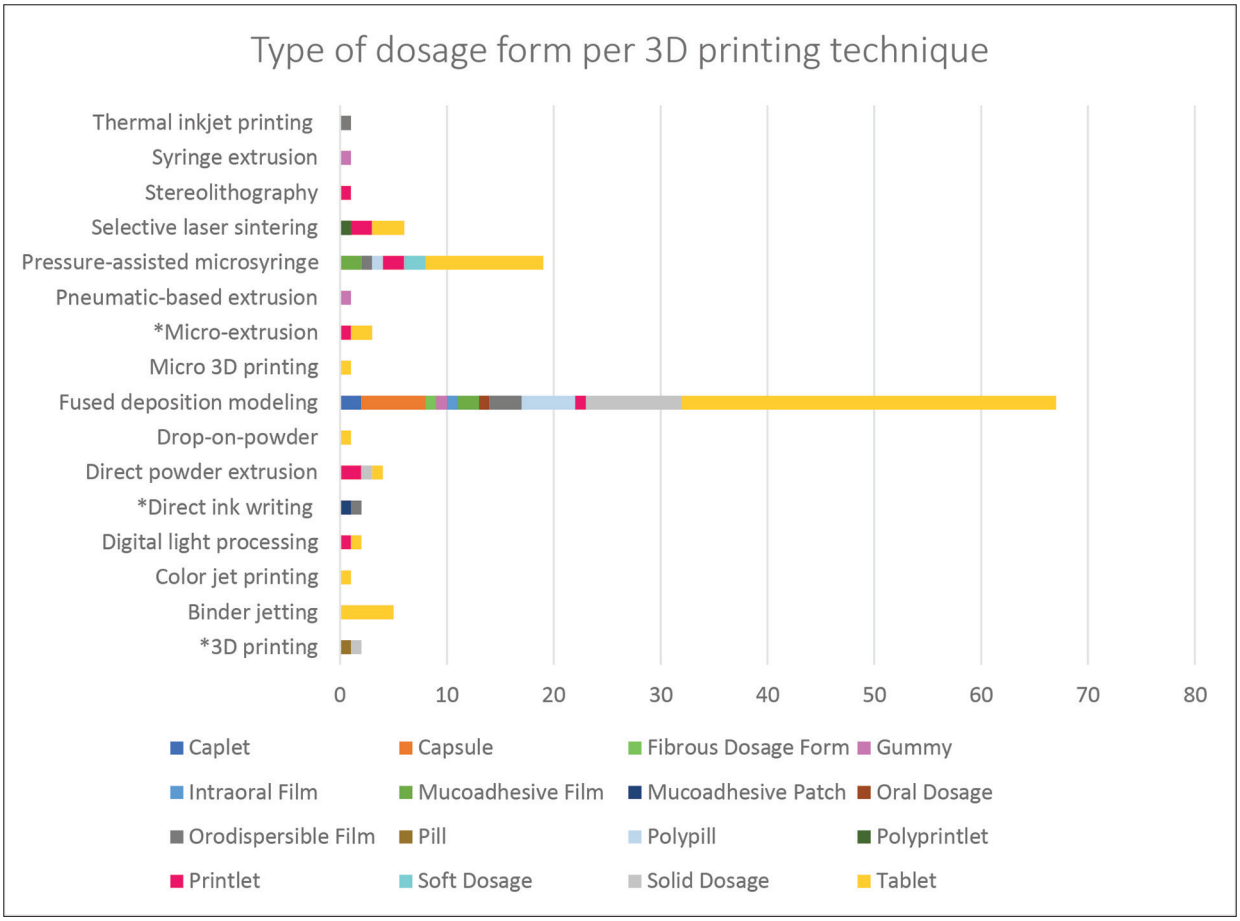

Figure 7. Type of dosage form per 3D printing technique of the categories "end-user applications," "quality assurance," "user acceptability," and "digital technologies." *Specific technique not available.

identified, which should be reduced or eliminated before clinical assessment[37].

To improve antitumor activity, tumor targetability, and safety for the treatment of colon cancer, Mirdamadian *et al.* merged fused deposition modeling and nanotechnology to produce a 3D-printed tablet loaded with oxaliplatin alginate nanoparticles[38]. The 3D-printed tablets had a remarkable antitumor effect and safety profile[38].

Intestinal alkaline phosphatase can regulate intestinal inflammation and treat ulcerative colitis, an inflammatory bowel disease; nonetheless, its intraduodenal administration is not convenient. Nguyen *et al.* fabricated powder bed-printed coated tablets loaded with alkaline phosphatase and a coating of PEG 1500[39]. The results showed a controlled release profile and ileocolonic targeted activity. The 3D-printed tablets help avoid the degradation of alkaline phosphatase and help selective delivery to the colon[39]. In 2023, due to the limits of commercial formulations for the treatment of inflammatory bowel disease, Ou *et al.* produced an adjustable and controlled release 3D-printed budesonide tablet. The tablets were printed using semi-solid extrusion with a CraftMake™ 3D printer. The results revealed excellent and significant dose accuracy and quality[40].

Oral premalignant lesions can lead to oral cancer. Liu *et al.* developed non-invasive 3D-printed mucoadhesive patches loaded with oxaliplatin and mycophenolate. The patch exhibited sustained release, significant ablation to dysplastic lesions, and minimal side effects[41]. Tagami *et al.* also created a mucoadhesive film using a pressure-assisted microsyringe. The film was loaded with ibuprofen/lidocaine ionic liquid to treat oral mucositis caused by radiation therapy and chemotherapy[42]. During the same year, alternatives for the treatment of oral leukoplakia were evaluated. Here, Takashima *et al.* developed an apigenin-loaded mucoadhesive oral film, but with a different 3D printing process, in this case semi-solid extrusion, and it was designed to avoid surgical removal. The film demonstrated a remarkable chemopreventive effect, which may be of great help to prevent oral carcinogenesis[43].

3.1.2. Pediatric

Compared with drugs for adults, drugs for children have very different pharmacokinetics in terms of absorption, distribution, metabolism, and excretion[44]; consequently, it is not recommended to provide children with adult medication at a lower dose. The lack of age-appropriate and commercially available pediatric formulations forces pharmacists or caregivers to manipulate adult formulations[45]. In normal practice, approximately one-tenth of the medicines that are prescribed for children are unlicensed or off-label[46]. Given this, the 3D printing of dosage forms can create age-appropriate formulations for pediatrics.

Using fused deposition, modeled minicaplets loaded with baclofen for pediatrics were produced by Palekar *et al.*[47] The authors decided to fabricate this product since a child formulation based on baclofen was not available yet on the market. The results revealed that the minicaplets were successful, and the size had a greater influence on the API release than the infill percentage[47].

Due to the lack of praziquantel formulations for children, Boniatti *et al.* produced pediatric Printlets™ with praziquantel, using direct powder extrusion and a M3DIMAKER™ printer. While the tablets demonstrated better performance in the dissolution tests and an acceptable formulation taste, the drug loading still needed optimization. The resulting tablets are a promising solution for the lack of a suitable a praziquantel formulation for children[48].

Suárez-González *et al.* printed orodispersible dosage forms (printlets™) for pediatrics with a semi-solid extrusion process and a M3DIMAKER™ printer[49]. The active ingredient for the formulation was hydrochlorothiazide (not commercially available for pediatrics), the excipients were selected based on the possible toxicity by age, maximum daily dose, and route of administration, and databases including Safety and Toxicity of Excipients for Paediatrics (STEP database), Aggregated Computational Toxicology Resource (ACTor), Toxicology Data Network (TOXNET), and Vitic were used for the excipient selection. The results showed that semi-solid extruded printlets passed all the recommended pharmacopoeia tests[49].

To increase the safety and efficiency of the drug administration of 3D-printed levetiracetam tablets in Chinese children, Li *et al.* used physiological pharmacokinetic modeling to guide drug development and drug selection[50]. The 3D-printed tablets were developed with binder jetting technology[50].

To reduce the possible therapeutic ineffectiveness of the poor solubility, low absorption, and unavailability of budesonide in pediatric treatment, Pistone *et al.* generated a powder bed extruded (PBE) minitablet for pediatrics with suitable swallowing, palatability, and dose flexibility control requirements[51].

3.1.3. Gastrointestinal tract

Drug absorption can be affected by the environmental pH and the drug pKa (acid dissociation constant) [52], and the complexity, heterogeneity, and differences in luminal pH of the gastrointestinal tract can lead to inferior pharmacokinetics and inefficient drug release. This sub-section focuses on the enhancement of oral DDS to boost drug release and residence time in the gastrointestinal tract.

Giri *et al.* used a hot melt extrusion process as well as fused deposition modeling to create controlled release 3D-printed theophylline tablets with different infill percentages and shell thickness[53]. The fabricated tablets had the characteristic of floating for 10 h and exhibited zero-order release kinetics[53].

In the same year, Reddy Dumpa *et al.* developed a core-shell gastroretentive floating pulsatile delivery system. The hollow tablets were fabricated using fused deposition modeling and had the ability to remain in the stomach gastric fluid until the pulse release of the dosage took place. The tablets demonstrated successful results as they were able to deliver the dosage when high residence time in the stomach was needed[54].

Oladeji *et al.* applied fused deposition modeling to produce robust 3D-printed tablets using a sandwich model design with voids[55]. The tablets were designed to support floatability and prolonged gastric residence time and reduce the influence of process and formulation variables[55].

To obtain an intragastric floating and sustained release DDS, Zhao *et al.* used hot melt extrusion and dual fused deposition modeling[56]. The manufactured tablets were designed with air chambers to improve floatability and the release behavior of the drug. The 3D-printed tablets manifested closer zero-order drug release for 24 h, and reduced density due to the hollow air chambers[56].

Mora-Castaño *et al.* prepared 3D-printed gastroretentive floating tablets loaded with metformin as the API[57]. The main aim was to maintain robust release kinetics when varying the dose formulations with a controlled release. The tablets were created with fused deposition modeling, and the design allowed buoyancy of the tablets and a sustained release of more than 8 h[57].

Gastroretentive fibrous expandable dosage forms are also being investigated as an alternative to improve residence in the stomach and release time. Blaesi and

Saka developed an expandable fibrous dosage form with 3D micropatterning, which was formulated with acetaminophen and hydroxypropyl methyl cellulose (HPMC)[58]. The normalized axial expansion was up to 100% in 15 min, making a 10 mm diameter disk into a 20 mm viscous gel; the disks also had delayed dose release (80% in 2.0–8.4 h)[58]. Blaesi and Saka continued their investigation with expandable dual-excipient fibrous dosage forms of sparingly-soluble drugs[59].

3.1.4. Patients with limitations (visual impairment)

The benefits of 3D printing oral DDS go further than being a solution to correct incorrect dosage administration and lack of controlled release, or to prevent negative interactions between different active pharmaceutical ingredients. 3D printing can also be used to satisfy other patient needs. This sub-section incorporates the latest findings related to visual impairment patients.

Using selective laser sintering, Awad *et al.* produced orally disintegrating paracetamol printlets with Braille and Moon patterns on their surface. The various shapes of the printlets were intended to provide additional information like dosing regimen and medication indication. The tablets had good mechanical properties and a disintegration time of 5 s, avoiding water intake and facilitating self-administration. The readability was tested by a blind participant[60].

Ketoprofen intraoral films with braille characters on the surface were developed by Eleftheriadis and Fatouros[61] using fused deposition modeling. The haptic identifiers on the surface of the dosage forms helped patients with visual impairment to recognize the correct treatment regimen. The Braille characters on the 3D-printed film complied with the Marburg Medium spacing convention for Braille. The intraoral films were tested by participants with visual impairments, who reported excellent readability[61].

3.1.5. Abuse deterrent

Opioids are pain-reliving drugs; when attached to receptors in brain cells, the cells release signals that subdue pain perception and magnify the feeling of pleasure[62]. On a global scale, about 0.5 million deaths are related to drug abuse, and more than 70% of those deaths are linked to opioids, with 30% caused by overdose[63]. In order to solve this problem and reduce abuse, abuse-deterrent formulations are created to target the expected routes of opioid abuse, such as injecting and snorting[64].

In 2019, Nukala *et al.* used fused deposition modeling and a MakerBot® printer to develop a 3D-printed methamphetamine loaded egg-shaped tablet[65]. These egglets had different sizes and infill densities for varying the drug dose. The optimized tablets passed most of the US FDA tests. The hardness of the egglets confirmed its snort-resistant potential, making it a promising tool to avoid opioid abuse[65].

Ong *et al.* produced tramadol printlets with alcohol-resistant and abuse-deterrent properties[66]. The tablets were fabricated with a powder bed extrusion process and a M3DIMAKER™ printer. The results revealed strong ethanol-resistance and moderate abuse-deterrent properties. By adding polyethylene oxide (PEO) to the formulations, its dissolution in solvent extraction tests was delayed, and the resistance to physical tampering improved[66].

Palekar *et al.* developed a novel 3D-printed capsule shell filled with an aversion liquid[67]. The filaments were loaded with metformin hydrochloride and had higher mechanical strength compared to other drug loadings. The 3D-printed capsule was filled with an aversion liquid composed of Sudan Black B and sodium polyacrylamide starch. By making the manipulable formulation less attractive, the 3D-printed capsule has the potential to visually discourage opioid abusers[67].

3.2. User acceptability

This classification includes 19 publications, with information related to improving the palatability of 3D-printed dosage forms and the general perception of end users. The sub-categories are "pediatric acceptability," "healthcare professionals," "patients," and "palatability methods."

3.2.1. Pediatric acceptability

Medicine taste can be an important factor in children compliance and treatment adherence since their taste buds are more sensitive to bitter tastes[68]. An article stated that giving children more choices can help overcome their aversion to medicine[69]. At the same time, masking the taste profiles of medicines can make pediatric patients more willing to take them[68]. This sub-category focuses on various advances in 3D-printed dosage form to improve the pediatric compliance.

Rycerz *et al.* produced a novel form that consisted of a chewable dosage form with dual loading in the form of a Lego™, using embedded 3D printing (e-3DP) and a M2 MakerGear FDM 3D printer[70]. The brick-like dosage form was composed of an internal paracetamol and ibuprofen powder suspension in a model drug ink (embedded phase) and a gelatin-based matrix (embedding phase). The created gelatin-based LEGO™ had a soft consistency and a sweet taste, making it easier for patients with swallowing problems[70].

Herrada-Manchón *et al.* developed children-tailored medicinal gummies with an attractive appearance

(bear- and heart-shaped) using syringe-based extrusion 3D printing[71]. The formulation contained ranitidine hydrochloride, xanthan gum, strawberry essence, gelatin, Maizena®, liquid sweetener, deionized water, and food coloring. The structured features of the 3D-printed gummies permitted easy handling and intake, improving treatment adherence[71].

Karavasili *et al.* fabricated chewable chocolate-based 3D-printed dosage forms with paracetamol and ibuprofen as active ingredients using an extrusion-based process[72].

In 2021, Wang *et al.* used an innovative ColorJet 3D printing (CJ-3DP) technology to create colorful cartoon tablets[73]. The tablets were loaded with a pediatric formulation of levetiracetam and had the design of rabbits, bears, hearts, and candy. Spearmint flavor and sucralose were used to improve the taste. Through the CJ-3DP process, the tablets were conferred friendly physical appearance and good mechanical properties[73].

Tabriz *et al.* masked the bitter taste of diphenhydramine hydrochloride (DPH)-fused deposition modeling tablets with sweetener (sucralose) and strawberry flavor, which exhibited a good aftertaste perception and synergy between the sweetener, strawberry flavor, and the DPH[74].

Bracken *et al.* evaluated the acceptability of 3D-printed placebo solid dosage forms in children and youths aged 4–12 years[75]. The participants rated the swallowability, acceptability, mouthfeel, volume of water consumed, and taste of the sample. Seventy-seven percent of the participants reported that there would be no inconvenience in taking the tablet every day as medicine[75].

3.2.2. Healthcare professionals

With the latest advances in 3D-printed oral DDS, their adoption in hospitals and pharmacies is becoming a near reality; therefore, it is also relevant to know the perspective of healthcare professionals in the adoption and perception of the different types of 3D-printed dosage forms.

Goh *et al.* studied the preferences of healthcare professionals at Tan Tock Seng Hospital in Singapore; the results of the pilot study revealed that more than 70% of the respondents agreed with the benefits of 3D-printed tablets and more than 60% of the participants were willing to be prescribed 3D-printed tablets[76]. On the other hand, there were still concerns regarding the formulation considerations, manufacturing processes, and administrative issues[76].

In 2020, Rautamo *et al.* explored the perception of healthcare professionals of oral 3D-printed dosage forms in pediatric treatments[77]. The study was made in a tertiary university hospital (HUS Helsinki University Hospital) that specializes in health care of neonates to children aged 15. The results showed a positive perception toward the 3D printing of oral medicines with the participants considering that there were many positive aspects and opportunities. Nevertheless, the respondents also demonstrated uneasiness associated with quality control, dosage accuracy, stability, and shelf life of formulations[77].

3.2.3. Patient

For a product to be successful, it should be aligned with the preferences of the users. This sub-category covers studies related to the preferences and perceptions of patients on the shapes, colors, and sizes of 3D-printed dosage forms.

Since 2017, Goyanes *et al.* have started exploring the influence of shape, size, and color of various placebo Printlets™; in addition, the acceptability with regard to picking and swallow was also investigated[78]. The tablets were manufactured using fused deposition modeling and had different geometries, including disc, torus, sphere, capsule, title diamond, pentagon, heart, diamond, triangle, and cube. The overall results indicate that torus-shaped tablets had the top score for ease to swallow and pick, followed by capsule and disc shape; the familiarity with the geometry of the dosage form is a relevant factor influencing acceptability of the end user. The color also affected the perception of the printlets[78].

The perceptions and preferences of 3D-printed medicines of polypharmacy patients in Zealand, Denmark, were studied by Fastø *et al.* who concluded that there was a preference for shapes similar to conventional formulations; there was also an inclination to different colors[79]. The overall patient acceptability was affected by the following factors: appeal (appealing), physiological (swallowing), practical (handling), pedagogical (understanding), and psychological (relate to)[79].

Kabeya *et al.* researched patient preferences of the size of 3D-printed tablets and capsules[80]. The study was carried out in a pharmacy in Japan. The results demonstrated that age, gender, disease status, number of drugs usually taken, and ingestion problems did not have a big impact on the evaluation outcome. Larger capsules and tablets (thickness above 6 mm) had the highest swallowing difficulty score, and smaller formulations (thickness below 2 mm) had the worst picking difficulty score[80].

3.2.4. Palatability methods

To determine the palatability of 3D-printed oral DDS, focus groups and interviews are needed; this requires gathering people, which can be inconvenient. Two methods to analyze the palatability of 3D-printed DDS that do not require the user *in situ* are presented.

In 2021, Wang *et al.* employed the ASTREE electronic tongue to design the additives of binder jetting 3D-printed levetiracetam instant dissolving tablets[81]. Different formulations were created, and their palatability was examined using ASTREE and design of experiment (DoE). The oral dispersion time and *in vitro* drug release were predicted with a texture analyzer and a dissolution apparatus. The results showed that the electronic tongue had an excellent ability for taste discrimination. The credibility of the results of the electronic tongue was evaluated with human gustatory sensation tests[81].

Using a toolbox of modern techniques, Desai *et al.* assessed 3D-printed orodispersible films in terms of disintegration, taste, texture, and mouthfeel, as they affect the sensory perception. Three *in vitro* methods were applied: Petri dish (disintegration), oral cavity model (disintegration), and bio-tribology (disintegration and oral perception). The findings suggested good oral palatability and mouthfeel with higher molecular weight (MW). The toolbox can be used during the design process to raise the positive perception of orodispersible films when consumed, improving overall treatment acceptability[82].

3.3. Quality assurance

This category includes a total of 34 papers and focuses on the quality of 3D-printed dosage forms at different levels: design, processing, and repeatability. The sub-categories are "quality by design," "control verification," "protocols and standardization," and "influence factors."

3.3.1. Quality by design

Products that do not meet their specifications or fail during performance increase compliance costs and workload and reduce efficiency. Quality should be controlled at all development stages. Quality by design (QbD) aims to ensure the quality of medicines in their design, development, and manufacturing, by applying statistical, analytical, and risk-management tools[83].

Nukala *et al.* applied multifactorial design to optimize 3D-printed egglets for solvent extraction and drug release[65]. The mechanical manipulation of the egglets was evaluated and optimized considering: household equipment, milling, particle size distribution, solvent extraction, and drug release. For the response surface design, drug loading, infill density, and dimensions were defined as critical quality attributes (CQA), while time for 85% of cumulative drug release (D85) and percentage of drug extracted using water in 5 min (%S) were defined as the dependent variables. The technique was validated with a good correlation between the optimized response model and the generated data[65].

In order to evaluate the structure–function relationship of various fused deposition 3D-printed tablets, Zhang *et al.* used Box–Behnken design, with the experimental design based on the effect of design parameters and responses (drug loading, mechanical properties, and *in vitro* drug release performance)[84]. Shell thickness, infill density, and layer height were chosen as the independent variables. The results of this research revealed a favorable future of patient-focused drug production and on-demand manufacturing, with inputs from experts (doctors, pharmacists, formulation scientists, and pharmaceutical engineers) throughout the fabrication process. Design of experiments can contribute to robust guidance for formulation and optimization of 3D-printed dosage forms[84].

The printability parameters of selective laser sintering in 3D-printed solid dosage forms loaded with copovidone and paracetamol were evaluated by Gueche *et al.*[85]. The influence of the heating temperature was verified individually, while Box–Behnken design was applied to identify the effects of laser power, scan speed, and layer thickness in the printability. Printing yield, height, weight, hardness, disintegration time, and percentage of drug release were established as the measured responses. The significance of three process parameters was determined with an analysis of variance (ANOVA). With a QbD approach, this study demonstrated that the process parameters are critical for printability[85].

Wang *et al.* explored the factors affecting fabrication of binder jetting 3D-printed dosage forms using a two-level full factorial design[86]. Disintegration time, tensile strength, friability, dimensions (diameter and height accuracies), residual water content, weight, and drug loading were selected as the critical quality attributes based on the quality target product profile (QTPP). The authors concluded that QbD is a systematic and effective approach for efficient product design[86].

In 2022, Crișan *et al.* implemented a QbD approach to guide the development of fused deposition modeling 3D-printed diclofenac tablets[87]. Risk management strategies, design space definition, and DoE were employed to reveal the effects that tablet design, tablet size, and layer height had on drug release and on the API content. The design strategy and appropriate formulation lead to rapid release of the active pharmaceutical ingredient. Consequently, the model was accurate and can be employed for the optimization of selected parameters[87].

3.3.2. Control verification

3D-printed oral DDS are usually created in small batches due to equipment limitations, as they are smaller than a manufacturing plant. Nondestructive quality verification

methods are needed to characterize the 3D-printed dosage forms without total loss of all the samples.

To ensure final product quality of paracetamol printlets, non-destructive characterization techniques like process analytical technologies, near-infrared spectroscopy (NIR), and Raman confocal microscopy can be applied. Trenfield *et al.* evaluated cylindrical 3D-printed tablets[88]. A calibration model was created using an NIR spectrometer, and it successfully predicted the drug concentration. The model also demonstrated excellent linearity and accuracy with dosage forms of different geometries and formulations. The drug distribution was observed with a Raman confocal microscopy[88].

Trenfield *et al.* verified the dosage of multiple drugs in polyprintlets and 3D-printed films at the point of dispensing[89]. The dosage forms were loaded with amlodipine and lisinopril. The analysis and verification were made using a portable NIR spectrometer and validated calibration models (partial least squares regression). The results demonstrated an excellent linearity, accuracy, and specificity for amlodipine and lisinopril. The microstructure was observed with x-ray powder diffraction (XRPD) and thermogravimetric analysis (TGA)[89].

Gioumouxouzis *et al.* investigated the structural and functional characterization of 3D-printed dosage forms with x-ray microfocus computed tomography (μCT) to verify if the formulations complied with the required specifications (quality assurance)[90]. The results demonstrated that the use of μCT can perform a qualitative inspection of the products, a 3D image of the dosage form structure for dimensional metrology, and the functional performance of the formulation overtime. The authors believe that μCT can help accelerate the adoption of 3D printing technology in the pharmaceutical technology sector[90].

Lima *et al.* employed oscillatory shear rheology and mechanical evaluation as a control tool for fused deposition modeling 3D-printed medicines. Hot melt extrusion filaments were assessed in terms of viscoelastic behavior, definition of printing parameters, and the prediction of their repercussions on the 3D tablets. The outcome of this research was the validation of oscillatory shear rheology as a tool to identify significantly sensitive viscoelastic alterations and quality control parameters, and as a method to predict rheological changes and their effects on the printed dosage forms[91].

Quality control of 3D-printed dosage forms can also be done on hot melt extrusion API-loaded filaments. Chamberlain *et al.* investigated the possible use of colorimetric evaluations for direct and indirect determination of extruded filaments with API and/or coloring agents[92]. The results showed that colorimetry can be used as a quality control tool to detect differences in drug loading[92].

3.3.3. Protocol and standardization

Standards and protocols are guidelines for production that ensure consistent quality and safety. In this sub-section, protocols developed for 3D-printed dosage forms are presented.

Silva *et al.* proposed a new protocol for preformulation studies simulating thermal processing and aging of the fused deposition modeling printed medicines. The protocol included tests related to morphology and thermal, crystallographic, and spectroscopic profiles. In the study, the protocol simulated the combined thermal stresses of formulations with four different polymers and two model drugs and obtained stable pharmaceutical dosage forms[93].

Pressure-assisted microsyringe (PAM) was selected by Callede *et al.* to develop zolpidem printlets[94]. The design process included the integration of protocols to standardize compounding procedures (mixing, preparation, and printing) related to the dosage amount of zolpidem in the tablets. The printing parameters were evaluated and optimized, and some of them were fixed at certain values. One of the outcomes of the research was a decision tree model that allows the compounding pharmacists to ensure quality control of the zolpidem printlets at industry level immediately after printing[94].

3.3.4. Factors of influence

High-quality products can be obtained by optimizing process or formulation parameters. This sub-section contains publications related to the effects of a factor of influence (selected by the author of each article) on the properties of the 3D-printed oral DDS.

Zhang *et al.* studied the influence of process temperature on the quality and crystallinity of fused deposition modeling-printed phenytoin dosage forms[95]. Comparative studies such as morphology, solid-state analysis, and *in vitro* drug release between the printlets and filaments were carried out. The results showed that the printing process and product qualities are affected by the printing temperature and slicing[95].

The quality of binder jetting paracetamol orodispersible films was improved by adding a thin layer of polyvinylpyrrolidone (PVP) coating to the matrix particles. Wang *et al.* concluded that coated particles improved the resistance to crushing and decreased the disintegration time[96].

3.4. Digital technologies

This classification includes a total of 14 publications and is characterized by the use of digital technologies to improve and enhance processes and dosage formulations with machine learning, decreasing the risk of frauds with cybersecurity and novel ways of adding information to the printed forms by quick response (QR).

3.4.1 Machine learning

Machine learning (ML) can be used as a predictive method for formulation and release profiles in 3D-printed dosage forms, making it a possible quality control tool. ML can automate and reduce development times while maintaining a good accuracy of the design parameters.

ML was employed alongside 3D printing to provide on-demand manufacturing and quality control of orodispersible films. O'Reilley *et al.* developed orodispersible films with direct ink writing (DIW) and complex geometries. These films were classified by active ingredient using ML algorithms and NIR spectrums. Based on the results of the subsequent partial least square algorithm, it was stated that ML, 3D printing, and NIR have the potential to automate orodispersible film workflows and enable rapid drug and dose verification[97].

In 2021, Obeid *et al.* also tried to predict the diazepam release of tablets with artificial neutral networks[98]. Tablets of different shapes were printed using fused deposition modeling. Self-organizing maps and multi-layer perceptron were applied to model the influence of tablet surface area to volume (SA/V) ratio and printing parameters (infill density and infill pattern) on the release of diazepam. The results showed the ability of the multi-layer perceptron network to predict drug release behavior as a function of infill density and SA/V ratio[98].

Ong *et al.* created a balanced database of 1594 formulations with in-house and literature data of hot melt extrusion and fused deposition modeling to predict formulation outcomes using ML. The models were able to predict hot melt extrusion and fused deposition modeling processing temperatures with a mean absolute error of 5.5°C and 8.4°C, and the printability and mechanical characteristics of the filaments with an accuracy of 84%. The optimized models were added to the FabRx web-application software M3DISEEN[66].

Mazur *et al.* obtained specific dosage and release profile using fused deposition modeling dosage forms employing artificial neural networks (ANN) to predict appropriate geometries. With the *in vitro* dissolution results and the mathematical description of the API release profiles, ANN architectures were created to predict the most suitable geometry. The results demonstrated that it was not possible to predict a geometry with the required length, width, height, and underlying geometry, with ANN[99].

3.4.2. Cybersecurity

Cybersecurity involves protecting systems, networks, and programs to reduce or avoid the risk of cyberattacks. The most common target of cyberattacks is accessing, changing, or destroying sensitive information[100]. The supporting software and systems for the formulation or production of 3D-printed dosage could be a target to cyberattacks as they might contain sensitive information related to the patient or the dosage form.

Due to the possible cyber risks of remote digital transfer of an electronic prescription to the 3D printer while printing dosage forms, Kok *et al.* explored the application of DEFEND3D, a technology to enhance cybersecurity and intellectual property protection[101]. DEFEND3D is a patented secure streaming transfer protocol (SSTP) and a virtual inventory communication interface with controlled reproduction. Different shapes were created using remote fused deposition modeling. The authors concluded that DEFEND3D can remotely 3D-print various designs at various infill densities[101].

3.4.3. Quick response and binary digits (bits)

Quick response (QR) codes allow the storage of information in small surface areas; the information is easy to access as the QR code just needs to be scanned with a smartphone or QR scanner.

In 2019, Trenfield *et al.* printed QR codes and data matrices on the surface of paracetamol printlets to generate a unique track-and-trace measure for product authenticity[102]. The QR code can be scanned with a smartphone, and the encoded information can be personalized to illustrate data related to the drug product (batch, expiration date, active ingredient, etc.), patient (age, birth, and gender), and prescriber (name). The results demonstrated a novel anti-counterfeit mechanism[102].

Oh *et al.* developed a 3D-printed QR-coded orodispersible film (QRODF) in a one-step process using a hot melt pneumatic process. The QRODF was loaded with aripiprazole and can be read with a smartphone in a QR scanning application to obtain additional information about the film. QRODF may be a promising approach for tailored drug formulations as they are easy to scan and are not easily broken due to their flexibility[103].

Two years later, Windolf *et al.* used a different approach using QR codes to store information on 3D-printed geometries and ensure batch traceability[104]. The dosage forms were fabricated with fused deposition modeling, a

3D Printer Prusa i3MK3, and had different formulations. The blind-watermarking bits were printed as a pattern on the flat sides of the oblong tablets; the bits were distributed across the layers, and the interaction between the layers created a code. Even though this is a novel approach, not all polymers are suitable for this method, and QR codes can store more information than bits encoded in the tablet[104].

3.4.4. Mobile health technologies

Smartphone-enabled 3D printers can be an innovative option to patients that have non-complex dosage formulations; they can be located at the patient's home, and given their accessibility, they can be printed at any moment.

Xu *et al.* created a smartphone-enabled 3D printer for dosage forms. The compact printer used the light from the smartphone to photopolymerize liquid resins and created solid structures, and it worked under stereolithography principles. Warfarin printlets were produced based on the shape determined on the smartphone app. The printlets obtained high resolutions and outstanding dimensional precision. The developed printer can be an alternative to produce tablets in resource-limited settings, in emergencies, or at the patient's home[105].

4. Conclusion

According to the main objective of this research, a CTI methodology was applied to analyze 3D-printed oral DDS, specifically to reveal the current trends and advances in R&D in terms of end-user applications, quality assurance, user acceptability, and digital technologies. The research period was from January 1, 1900, to May 1, 2023. Some of the most important insights are:

(i) There is a tendency toward digitalization in the industry that foresees the migration of clinical trials to digital solutions. Machine learning is being used to optimize and predict process parameters and formulation behaviors, with some of the optimized models already available for general use, which is the case of M3DISEEN, a web-application predicting tool based on artificial intelligence. Applications like DEFEND3D are being assessed to avoid cyber risks stemming from the remote digital transfer of electronic prescriptions to the 3D printer. Digital technologies are also used as facilitators; QR codes are being tested as a traceability method to increase security and obtain additional information about the dosage form. Light from smartphones was used to enable 3D printing of dosage forms on a medium-sized 3D printer.

(ii) Quality assurance is one of the main concerns of developing 3D-printed oral DDS due to the regulatory challenges. The QbD approach is being used to improve efficiency in the design of a product, by identifying the parameter effects with the selected responses. Tools like DoE, ANOVA, and Box–Behnken design are implemented to ensure quality. At the same time, protocols to standardize compounding procedures (mixing, preparation, and printing) as well as decision maps to facilitate decision-making are being developed. The integration of all these methods can lead to quality assurance in the different types of dosage forms.

(iii) Trends related to the final end-user application included abuse-deterrent 3D-printed oral dosage forms that are being designed to limit the accessibility to non-prescribed opioids, as a solution to the global opioid abuse crisis. 3D-printed pediatric formulations taking into consideration the age, maximum daily dose, route of administration, and toxicity of the active ingredients are also being developed. Tailored 3D-printed pediatric oral dosage forms are an opportunity to adapt formulations that are not commercially available for children. For disease treatment, 3D-printed capsules that allow the intake of multiple drugs and avoid negative interactions between active pharmaceutical ingredients are also being studied.

(iv) For user acceptability, 3D-printed oral DDS have a general positive impact on children, healthcare professionals, and general patients, and understanding the user preferences can facilitate the emergence of these types of dosage forms in the market. Aside from the processes, materials, and functionality of these dosage forms, researchers are now taking into consideration the physical appearance and taste to increase their appeal, making them more user-centered.

The results of this study can be helpful for researchers, organizations, and investment firms interested in novel treatments, R&D in areas of 3D printing, medicine, healthcare, and pharmaceutics.

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Conflict of interest

The authors declare no conflicts of interests.

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