



Analysis of the literature on 3D printing in healthcare with reference to pharmaceuticals using a bibliometric approach

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ABSTRACT

3D printing is an emerging digital technology. Approximately 30 years since its introduction, 3DP technology is set to revolutionize research and teaching laboratories. The said technology has revolutionized the development of modified dosage formulations and regenerative medicine. The aim of the present study is to analyze the trends in research publications in 3DP in pharmaceuticals using the bibliometric method. A literature search was carried out to extract all publications related to 3DP in pharmaceuticals using the PubMed database. The data were extracted for the years 2010–2020. Insights were categorized based on year of publications, document types, authors, publication source titles, country, citations, research areas, and keyword analysis. An upward trend in the growth of publications is witnessed for the years 2020 and 2019 with 23.21% and 22.81% of records, respectively. Our retrieved publications indicated that the United States was the leading country in the literature with 203 publications (20.13%). In 3DP research publication trends, researchers from USA received the highest number of citations. Words such as “printing,” “3D printing,” “drug,” “hydrogels,” “tablets,” “tissue,” “bioprinting,” “drug delivery,” and “pharmaceutical” were found as high-frequency keywords. Alvaro Goyanes was found to be most productive author with $n = 42$ (4.16%) publications. Currently, 3DP is in a primitive stage in the field of pharmaceuticals. There has been an upsurge in interests in 3DP in pharmaceuticals. It is evident by an increasing number of research publications in recent years. Researchers and various authors had expressed the positive aspect of 3DP. The research publication trends may continue and increase with robust studies in the field of 3DP in pharmaceuticals.

INTRODUCTION

The last few decades have witnessed enormous advancements in the field of pharmaceutical drug, design, and delivery. One of the recent developments is the advent of 3DP technology (Mirza and Iqbal, 2018). The global market of pharmaceuticals has recently witnessed a new revolution in the form of 3DP technology (Chandekar *et al.*, 2019). 3DP technology continues to push the boundaries of cost-efficiency, convenience, and customization (Banks, 2013). Approximately 30 years since its introduction, 3DP technology is set to revolutionize research and teaching laboratories. With regard to research settings, 3DP has been

limited to biomedical applications and engineering, although it has shown tremendous potential in the chemical sciences (Gross *et al.*, 2014). 3D printing is forecast to revolutionize drug delivery, moving away from mass manufacture toward small-batch personalized medicines. For the first time, personalized 3D-printed medicines have been evaluated in a clinical study in pediatrics to treat a rare metabolic disease (Trenfield *et al.*, 2019). Recent approval of Spritam® and publication of United States Food and Drug Administration technical guidance on additive manufacturing related to medical devices has led to an extensive research in various fields of drug delivery systems and bioengineering (Jacob *et al.*, 2020), identifying the key progress points that have been made on the use of 3D printing to manufacture microneedles (MNs) in the past 3 years. The study revealed that the printing resolution and the material properties are the two critical parameters that have the most influential effect on the outcome of every MN-printing endeavor (Economidou and Douroumis, 2021). MN technology shows excellent potential in controlled drug delivery, which has received much attention from investigators and clinics.

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Recently, three-dimensional (3D) printing has given the prototyping and manufacturing methods the flexibility to produce MN patches in a one-step manner with high levels of shape complexity and duplicability (Elahpour *et al.*, 2021).

A large number of original articles, systematic reviews, short articles, etc. have been published in recent years on 3DP in pharmaceuticals. To date, little work has been devoted to summarizing worldwide trends in 3DP in pharmaceutical research publications. To the best of our understanding, this is the first article on the publishing patterns in 3DP in pharmaceuticals. The aim of the present study is to analyze the research publication trends in 3DP in pharmaceuticals using the bibliometric method. Bibliometrics is a statistical discipline investigating the publication patterns and trends in a certain academic field (Senel and Bas, 2020). The findings of the study can provide an overall scenario of what types of research work are more common around the world and where the focus lies.

MATERIALS AND METHODS

Search tool and strategy

We used PubMed as the search engine. PubMed was chosen because it is widely used and is recognized as the primary tool for scholars. This database is freely accessible for researchers throughout world. It covers the maximum number of quality research articles in the medical field. PubMed was chosen because it is recognized as the primary tool for scholars in the medical field (Islamaj Dogan *et al.*, 2009; Lu, 2011; Ma *et al.*, 2016) and it remains the optimal tool in biomedical electronic research (Falagas *et al.*, 2008). Almost 5 million queries are issued to PubMed each day by users around the world (Islamaj Dogan *et al.*, 2009), who rely on frequent access to be updated on biomedicine and make discoveries in their own fields (Lu, 2011). A literature search was carried out to extract all papers related to 3DP in pharmaceuticals. Keywords used for the study were “3D printing,” “pharma,” and “pharmaceuticals”. Various publications from PubMed were collected for an 11-year period from January 1, 2010, to December 31, 2020, and then data were entered in Microsoft Office Excel sheets manually.

Data analysis

Secondary data were collected in Microsoft Office Excel sheets based on the findings from PubMed to conduct the data analysis. A total of 1,600 publications were retrieved the PubMed database. The information was processed using applications such as Microsoft Office Excel and Word. The analysis consists primarily of descriptive data that are analyzed, interpreted, and expressed in tables and percentages. Insights are categorized based on year of publication, document type, authors, publication source titles, country, research areas, etc. The keyword occurrences and country citations were visualized with help of Tableau software (<http://www.tableau.com>, Tableau 2021.1), a visual analytics platform. It is a tool for exploring, analyzing, and presenting data in a visual, interactive format.

RESULTS

Number of publications, study types, and research areas

An increasing trend in research publications involving applications of 3DP in pharmaceuticals was observed. Analyses

Table 1. Year-wise distribution of publications.

Publication year	Number of publications	% of publication
2020	234	23.21
2019	229	22.81
2018	189	18.75
2017	122	12.00
2016	90	9.02
2015	85	8.33
2014	32	3.37
2013	5	0.49
2012	5	0.49
2011	9	0.89
2010	6	0.59

Table 2. Document types in the scientific literature.

Document types in the scientific literature	Total number	% of publication
Original article	673	66.89
Review article	175	17.36
Editorial	17	1.68
Comparative study	16	1.58
Evaluation study	9	0.89
Communication	6	0.59
Validation study	3	0.29
Technical note	2	0.19
Case report	3	0.29
Comment	1	0.09
Other	101	10.01

Table 3. Top 10 topics of research areas in the scientific literature.

Research areas	Total number	% of publication
Dosage forms	518	51.38
Tissue engineering	253	25.09
Bioprinting	136	13.49
Implants	39	3.86
Wound healing	10	0.99
Dental	9	0.89
Orthology	7	0.69
COVID-19	7	0.69
Oncology	4	0.39
Cardiology	2	0.19

showed that the number of research publications increased significantly. An upward trend in the growth of publications is witnessed for the years 2020 and 2019 with 23.21% and 22.81% of records, respectively. The least active years were 2012 and 2013 with 0.49% of records, respectively (Table 1). Among the studies conducted, original articles, reviews, comparative study, and editorials contributed to 66.89%, 17.36%, 1.68%, and 1.58% of the records, respectively (Table 2).

Table 4. Top 10 countries with the highest research publications.

Top 10 countries	Total number	% of publication
USA	203	20.13
China	153	15.17
UK	153	15.17
Germany	69	6.84
Republic of Korea	48	4.76
Italy	41	4.06
India	35	3.47
Canada	23	2.28
Japan	21	2.08
Switzerland	20	1.98

Table 5. Top 10 journals with the highest research publications.

Journals	Total number	% of publication
International Journal of Pharmaceutics	107	10.61
Biofabrication	69	6.84
Journal of Pharmaceutical Sciences	57	5.65
Acta Biomaterialia	48	4.76
Pharmaceutics	42	4.16
Advanced Healthcare Materials	30	2.97
Biomedical Materials	27	2.67
Materials Science and Engineering	25	2.48
Scientific Reports	23	2.28
AAPS PharmSciTech	23	2.28

The major topics of the research area found in the literature are presented in Table 3. It was observed that dosage form in 3DP pharmaceuticals was the key studied topic. Other key areas of focus include tissue engineering, bioprinting, implants, wound healing, dental, and orthology (Table 3). This is also evident and is reflected in the occurrence of keywords analysis (Fig. 2).

Countries from which publications originated, citations, and top journal sources

Our retrieved publications indicated that the United States was the leading country in the literature with 203 publications (20.13%), followed by the China, United Kingdom, and Germany ($n = 153$, 15.17%; $n = 153$, 15.17%; and $n = 69$, 6.8%, respectively). Other countries with research publications were Republic of Korea, Italy, India, Canada, Japan, and Switzerland with 4.76%, 4.06%, 3.47%, 2.28%, 2.08%, and 1.98%, respectively (Table 4). Name of journal sources was recorded for all manuscripts. Among the leading journals, the top contributions in said areas were in the International Journal of Pharmaceutics, Biofabrication, Journal of Pharmaceutical Sciences, Acta Biomaterialia, and Pharmaceutics with 10.61%, 6.84%, 5.65%, 4.76%, and 4.16%, respectively (Table 5).

The quality of scientific works of researchers is judged through citations received. The more citations received by individual researchers, the more favorable the growth and image of those countries in the scientific discipline. In 3DP research publication trends, researchers from USA received the highest number of citations ($n = 2,105$), followed by few leading countries, namely UK ($n = 2,090$), China ($n = 1,711$), India ($n = 848$), Germany ($n = 707$), Spain ($n = 656$), Italy ($n = 452$), Republic of Korea ($n = 376$), Poland ($n = 316$), and Japan ($n = 302$). The density world map of the top countries in terms of research publication citations is shown in Figure 1.

Country citations



Map based on Longitude (generated) and Latitude (generated). Size shows sum of No. of Counts. Details are shown for Countries.

Figure 1. Density world map of the top countries in terms of research publication citations.

Table 6. Top 10 authors with the highest research publications.

Authors	Total number of articles	% of publication
Alvaro Goyanes	42	4.16
Sarah J. Trenfield	14	1.38
Niklas Sandler	13	1.28
Atheer Awad	12	1.19
Tatsuaki Tagami	8	0.79
Fabrizio Fina	8	0.79
Georgios K. Eleftheriadis	7	0.69
Yan Yang	6	0.59
Alice Melocchi	6	0.59
Jiaxiang Zhang	6	0.59

Top authors and highly cited manuscripts

Alvaro Goyanes is found to be the most productive author with $n = 42$ (4.16%) publications, followed by Sarah J Trenfield, Niklas Sandler, Atheer Awad, Tatsuaki Tagami, Fabrizio Fina, Georgios K Eleftheriadis, Yan Yang, Alice Melocchi, and Jiaxiang Zhang with 1.38%, 1.28%, 1.19%, 0.79%, 0.79%, 0.69%, 0.59%, 0.59%, and 0.59% of the records, respectively (Table 6). The most cited publication in this field was entitled “A 3D bioprinting system to produce human-scale tissue constructs with structural

integrity,” with 369 citations published in the journal Nature Biotechnology. Another publication entitled “Medical applications for 3D printing: Current and projected uses” received 193 citations and was published in Pharmacy and Therapeutics. Publications that received more than 100 citations are presented in Table 7.

Keyword frequency analysis

Some features of the study on 3DP in pharmaceuticals could be reflected by the occurrence of keywords. Words such as “printing,” “3D printing,” “drug,” “hydrogels,” “tablets,” “tissue,” “bioprinting,” “drug delivery,” and “pharmaceutical” were found as high-frequency keywords in the present study with 45.13%, 22.42%, 20.43%, 28.76%, 13.98%, 12.30%, 12.20%, 7.83%, and 7.14%, respectively. Table 8 presents the top 20 keywords that are related to the objective of the study. The density visualization map of the top 20 keywords is shown in Figure 2.

Discussion

Our bibliometric study on 3DP in pharmaceuticals from the year 2010 to 2020 indicates an exponential growth in the number of research publications. Every year, 3DP expands its uses in the pharmaceutical sector, saving and improving lives in ways that were previously unimaginable. Indeed, 3DP technology has been used widely in the healthcare and pharmaceutical sectors. With regard to the trends of field, most of the research publications were focused on advantages of 3DP technology, oral dosage forms, hydrogels, tablets, bioprinting, drug delivery, and pharmaceuticals. A

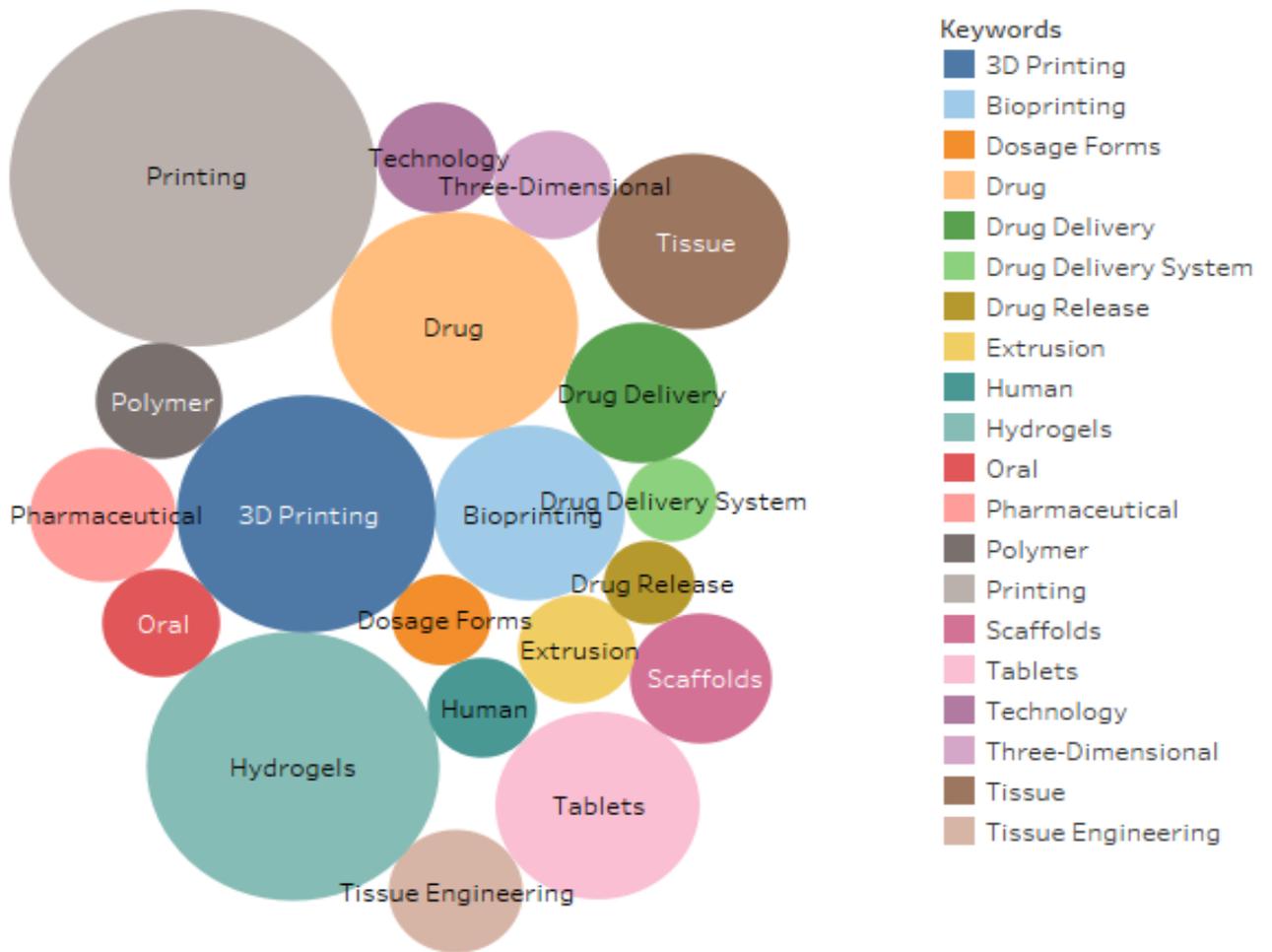
Table 7. Most cited research publications.

Title of publication	Research area	year	Journal name	Total number of citations
A 3D bioprinting system to produce human-scale tissue constructs with structural integrity	Bioprinting	2016	Nature Biotechnology	369
Medical applications for 3D printing: current and projected uses	Dosage forms	2014	Pharmacy and Therapeutics	193
3D bioprinting for engineering complex tissues	Tissue engineering	2016	Biotechnology Advances	185
3D bioprinting human chondrocytes with nanocellulose-alginate bioink for cartilage tissue engineering applications	Bioprinting	2015	Biomacromoles	167
Microfluidic bioprinting of heterogeneous 3D tissue constructs using low-viscosity bioink	Bioprinting	2016	Advanced Materials	131
Omnidirectional printing of 3D microvascular networks.	Tissue engineering	2011	Advanced Materials	124
Bioprinting 3D microfibrinous scaffolds for engineering endothelialized myocardium and heart-on-a-chip	Bioprinting	2016	Biomaterials	124
Direct 3D printing of shear-thinning hydrogels into self-healing hydrogels	Tissue engineering	2015	Advanced Materials	121
3D printing of scaffolds for tissue regeneration applications	Tissue engineering	2015	Advanced Healthcare Materials	110
Direct human cartilage repair using three-dimensional bioprinting technology	Bioprinting	2012	Tissue engineering	110

Table 8. Top 20 keywords' frequency analysis

Keyword	Co-occurrence times	% of total	Keyword	Co-occurrence times	% of total
Printing	455	45.13	Tissue engineering	61	6.05
3D Printing	226	22.42	Polymer	54	5.35
Drug	206	20.43	Technology	49	4.86
Hydrogels	290	28.76	Three-dimensional	47	4.66
Tablets	141	13.98	Extrusion	46	4.56
Tissue	124	12.30	Oral	46	4.56
Bioprinting	123	12.20	Human	40	3.96
Drug delivery	79	7.83	Dosage forms	33	3.27
Pharmaceutical	72	7.14	Drug release	28	2.77
Scaffolds	68	6.74	Drug delivery system	28	2.77

Sheet 3



Keywords. Colour shows details about Keywords. Size shows sum of No.of Counts. The marks are labelled by Keywords.

Figure 2. Density visualization map of the top 20 keywords.

significant number of authors have discussed about 3DP technology, its applications, and challenges ahead. In the pharmaceutical industry, 3DP is a cutting-edge manufacturing technology and it may overcome the traditional manufacturing regime of one-size-fits-all (Azad *et al.*, 2020). Although being in its infancy, when compared with the other sectors, year 2005 marked the rapid progression of 3DP technologies in the pharma sector (Wadher *et al.*, 2021). This progress is also evident in terms of growth of research publications from year 2015, as shown in Table 1.

The 3DP technology is expected to transform drug delivery systems through customization of pharmaceutical formulations (Elkasabgy *et al.*, 2020) and favorable applications in the medical sectors (Trenfield *et al.*, 2019). Technology seems a rational approach to realize the quest for personalized drug delivery (Khan *et al.*, 2018) and recent improvement in oral drug delivery (Pandey *et al.*, 2020). The literature indicates the role of technology in sophisticated transdermal drug delivery systems and the range of printable materials that are presently used (Economidou *et al.*, 2018). Various authors have highlighted the advances in technologies toward producing formulations with intended drug release (Kotta *et al.*, 2018; Sadia *et al.*, 2018). The application of 3DP technology for generating tablets is attracting the attention of the pharmaceutical industry (Tagami *et al.*, 2020). Technology also favors flexible-dose drug products, polypills (polyprintlets) (Trenfield *et al.*, 2020), and precision in dose adjustment (Karavasili *et al.*, 2020). In addition to these advantages, extrusion-based 3DP technology is a relatively new technique (Panraksa *et al.*, 2020). Drop-on-demand 3D bioprinting technologies currently hold the greatest potential for generating functional tissues for clinical use and for drug development (Grottkau *et al.*, 2020). Hydrogels have been widely used as extracellular matrix materials in various 3D bioprinting applications (Krishnamoorthy *et al.*, 2019). Authors have also deliberated on hot-melt extrusion, a technology which mixes the advantages of solid dispersion technology and mechanical preparation and is recognized in various applications in pharmaceutical formulations (Ren *et al.*, 2019). However, issues and challenges related to 3DP are also debated in the literature. Biofabrication with various hydrogel systems allows the production of tissue or organ constructs *in vitro* to address various challenges in healthcare and medicine (Han *et al.*, 2019). Technology has transformed conventional pharmaceutical operations and has focused on the design and production of dosage forms according to the patient's needs (Pereira *et al.*, 2020).

Katakam *et al.* (2015) discussed about 3DP technology, its broader applications, merits, demerits, and intellectual property rights challenges. There are some regulatory challenges faced by the pharmaceutical sector and common myths surrounding the technology (Stones and Jewell, 2017). Authors in the literature have focused on many technical difficulties for 3DP of pharmaceutical products; technologies can help to overcome these challenges, in relation to marketing and lack of regulatory standards (Liang *et al.*, 2019).

There were some limitations to our study. There was no study to compare our results within the literature. Since not all publications are indexed in PubMed, the total number of papers retrieved could be smaller than the actual number. We did a manual search and tried our best to analyze the database related to our subject, but there might have been some errors. We used only one database, PubMed, to create the rankings. However, certain

authors seem to have several profiles due to the various spellings of author names or institution names.

CONCLUSION

There has been an upsurge in interests in 3DP in pharmaceuticals, as evident by an increasing trend in research publication in recent years. USA is the leading country in terms of research publications and citations. Currently, 3DP is in the primitive stage in the field of pharmaceuticals. 3DP technology has the ability to open doors in product development, manufacturing, and delivery. It has the potential to help fulfill the idea of personalized medicine, a trend that is growing rapidly in the industry. The research publication trends may continue and increase with robust studied in the field of 3DP in pharmaceuticals.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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