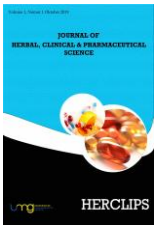

HERCLIPS *(Journal of Herbal, Clinical and Pharmaceutical Sciences)* , Vol. 06 No.02
PRODI DIII FARMASI UNIVERSITAS MUHAMMADIYAH GRESIK
E-ISSN : 2715-0518 P-ISSN : 2715-3053
Open Access at http://journal.umg.ac.id/index.php/herclips/index
DOI. 10.30587/herclips.v6i02.9608

A Bibliometric Study of 3D Printing In Pharmaceutical Technology For Tablet Dosage Form

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Info artikel:
Diterima:
03/03/25
Direview:
02/04/25
Diterbitkan:
30/04/25

Abstract
Three-dimensional printing (3DP) is the process of producing 3D items layer by layer using computer-generated designs. 3DP has been utilized to manufacture numerous drug dosage forms. The goal of 3D printing products is to create personalized medicine so it can enhance medication compliance and obtain better treatment outcomes. There are a lot of publications about fabricated tablets using 3DP. However, the results of analyses based on previous research in this field are lower. We conducted a bibliometric study using RStudio and VOSviewer software to summarize tabletting using 3DP research from 2014-2024. This study was based on the Scopus Database, and 405 suitable publications were evaluated. The most productive authors are Basit, A.W, Goyanes, A., and Gaisford, S., from the Department of Pharmaceutics, UCL School of Pharmacy, University College London, United Kingdom. Its affiliations and its country are also ranked the highest in producing articles in this field. In the future, 3DP will be an attractive alternative for tablet printing. Pharmacists in hospitals and drugstores can produce personalized tablets to improve treatment outcomes.

Keyword : Bibliometric; 3D-printed; Tablet; VOSviewer; rstudio

I. INTRODUCTION

Three-dimensional printing (3DP) in drug production is an additive manufacturing [1], [2]. 3DP is a revolutionary technology that converts 3D computer models into physical products. It refers to the process of creating 3D objects layer by layer using digital drawings [3]. Using 3DP techniques, the Massachusetts Institute of Technology (MIT) unveiled the first powder-based free-form fabrication in 1993. SPRITAM® is the first 3D-printed medication approved by the FDA, and it is available in tablet form based on powder bed [4]. This novel product serves as an example of the potential applications of 3DP technology for both point-of-use personalized therapy and large-scale pharmaceutical manufacturing. 3DP technology reveals the prospects for using 3DP technology to personalize medication at the time of application [5].

Personalized medication is treatment by medicine that customizes prevention and treatment plans for each patient [6]. It provides treatment for patients that considers the characterization of individuals' phenotype and genotype, as well as anatomical and physiological particulars. Pharmacists are able to immediately create customized pills and give them to patients [7]. It reflects a significant shift from "one size fits all" techniques of treating individuals with diseases or predispositions to new approaches, such as targeted medicines, which can yield the best results in treating patients' conditions [6]. 3D-printed drugs can produce custom strength of dose and dosage

combinations, so they can enhance medication compliance and obtain better treatment outcomes [8], [9].

In recent years, 3DP has been utilized to manufacture numerous drug dosage forms. There have been many recent publications on 3DP in fabricating tablets [10]. Oral administration of drugs to patients is preferred because it is easy to take, resulting in high patient compliance and acceptance [4]. Tablets initially enter through the mouth and will enter the gastrointestinal tract before circulating systemically. Conventional tablets consist of a mixture of active pharmaceutical ingredients (API) and excipients. There are various methods of conventional tablet production, such as wet granulation, dry granulation, and direct compression. Direct compression as a manufacturing process for tablet production offers several advantages as fewer steps and tools are required [11], [12]. However, there are some disadvantages of conventional tablet production, such as several steps, large batch sizes, and costly production equipment [5].

3DP technology has advantages, including fabricating structures of precise geometries, inexpensive cost, reducing the number of production steps, being able to deposit different materials concurrently, easily creating a complex product, and customizing the shaped tablets [13], [14], [15]. 3DP technology also offers flexibility in terms of dosage modification and control, feasibility of the development of unique and complicated inner structures and geometries, simplifying the printing process, and high use of resources throughout the entire printing process [16]. Bibliometric analysis is a systematic approach for describing and cartographically representing regions of scientific knowledge based on unstructured data from diverse scientific investigations [17]. In addition, the proposed methodology can assess the quality of the research, research the main domains of inquiry, and forecast the path of future research [18].

There has been no comprehensive bibliometric analysis of articles on tablet manufacturing using 3D printing technology from 2014 to 2024. Bibliometric publication articles that currently exist are A Bibliometric Analysis of 3D Printing in Personalized Medicine Research from 2012 to 2022 [4] and Analysis of the Literature on 3D Printing in Healthcare with reference to pharmaceuticals using a Bibliometric Approach 2010 to 2022 [10]. Both publications have gaps in analysis with our study, which do not discuss articles in 2023 and 2024 and are not specific to screening articles that are only for tablet dosage forms. In this study, we used updated articles from 2014-2024 for bibliometric analysis, especially for tablet dosage forms. The findings of this study can provide information about previous research and identify gap analysis for new ideas for future research.

. II.METHOD

2.1. Data source and search strategy

The article data in this study was obtained from the Scopus database (https://www.scopus.com) on 19 May 2024. The Scopus searches used keywords: “3D”, AND “print” AND “formula*” AND “drug”. We used the inclusion criteriain searching documents, only articles, and in English. We are limited to time framing, which is from 2014 up to 2024 (Figure 1).

E-ISSN : 2715-0518
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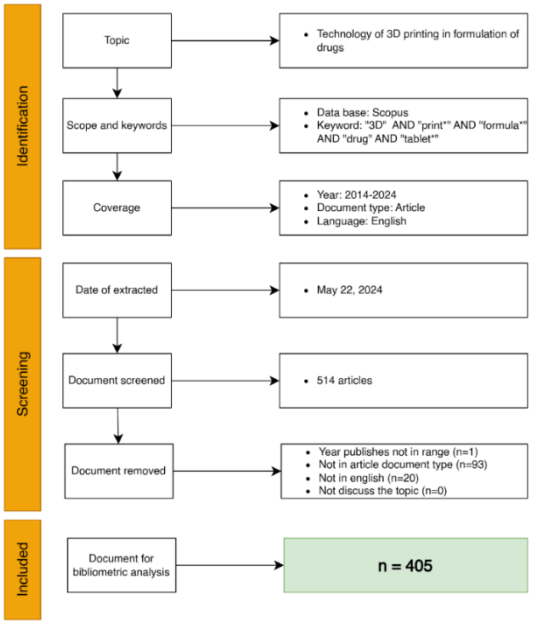

Figure 1. Flow diagram of the steps of article search

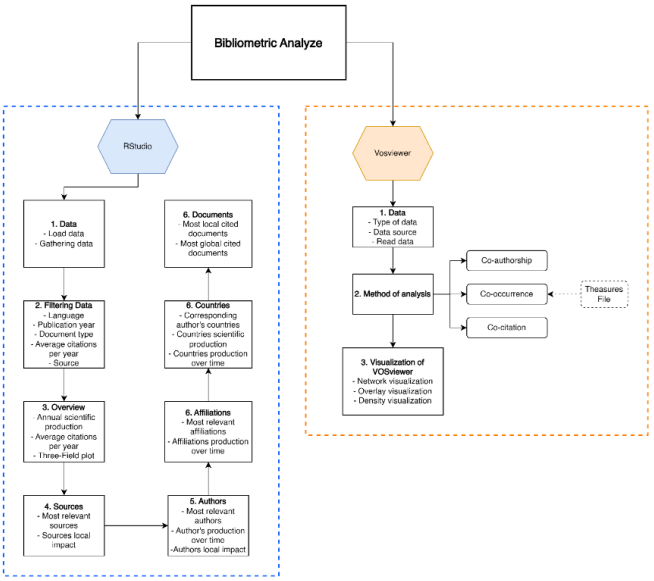

Figure 2. Frameworks of bibliometric analysis

2.2. Data analysis

The VOSviewer version 1.6.19 was created by the Centre for Science and Technology Studies at Leiden University in the Netherlands. It can be downloaded for free at https://www.VOSviewer.com/download. The type of analysis and counting method by co-occurrence, citation, and co-citation. The thesaurus tools can be used to avoid duplicate words. The data analysis was performed using the RStudio program version 2024.04.1 Build 748 from the Department of Economics and Statistics, University of Naples Federico II, Italy. We used the R version 4.4.0 of the Bibliometrix package, specifically Biblioshiny, which is a shiny app for bibliometric analysis. It can be downloaded for free at https://www.rstudio.com/products/rstudio/download. The program is used to analyze the parameters of sources, authors, affiliations, countries, and documents. Frameworks of Bibliometric Analysis are shown in Figure 2.

III. RESULT AND DISCUSSION

3.1 Country

We analyzed the country with 405 documents using VOSviewer and RStudio software. The result of this study was 54 countries. Figure 3 shows the article production of countries in the world represented through the world map. It can be interpreted that the more intense the blue colour is, the more articles are produced. The highest frequency was in the United Kingdom, China, USA, and Germany, which amounted to 439, 348, 339, and 137, respectively. Article production has increased over time in almost every country. The most significant increases were in the United Kingdom, China, and the USA (Figure 4).

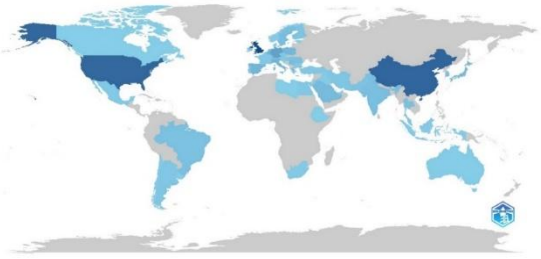

Figure 3. Country Scientific Production of Articles by RStudio

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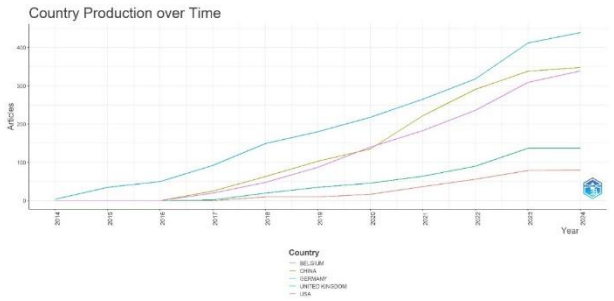

Figure 4. *Country Production of Articles by RStudio*

The countries collaborate with other countries, and the collaboration network between countries is present in Figure 5. The countries that collaborate the most with other countries are the United Kingdom (20 links), the USA (13 links) and Germany (13 links). In contrast, China has only four links.

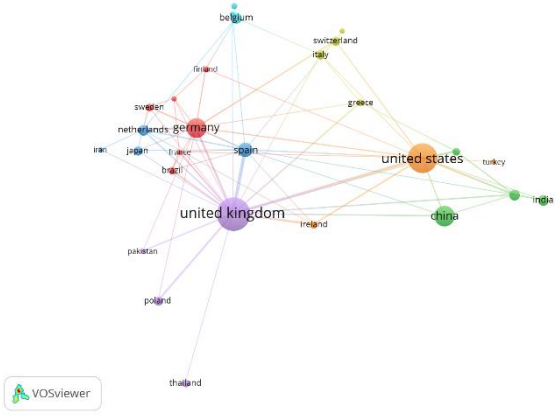

Figure 5. Network visualization of the co-authorship country by VOSviewer

The low number of collaboration links is also proportional to the number of Chinese corresponding authors who do not collaborate with authors from other countries, with a percentage value of 95% (Figure 6). In contrast, corresponding authors from Spain, the United Kingdom, and the Netherlands collaborate with other countries with a percentage value of more than 50%.

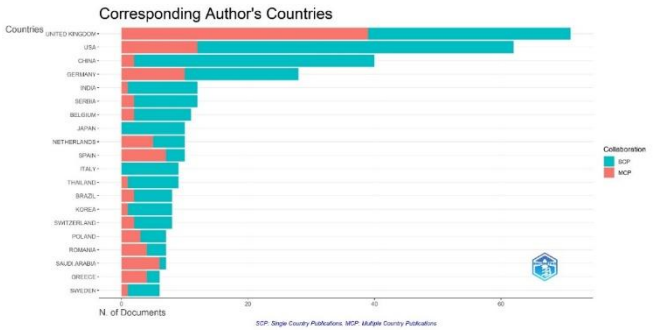

Figure 6. Top 20 corresponding author's countries by Rstudio. SCP: Single Country Publication. MCP: Multiple Country Publication.

3.2 Author

We analyzed the author using VOSviewer and RStudio software, which used 405 documents. The total number of authors is 1457 people. The most relevant authors with the most documents are Basit, A.W, Goyanes, A., and Gaisford, S. with 32, 31, and 30 documents, respectively (Table 1). They are from the same institution, namely the Department of Pharmaceutics, UCL School of Pharmacy, University College London, United Kingdom.

Table 1. Most relevant authors and author's H-index by RStudio

Author	Number of documents	H-Index
Basit, A.W	32	26
Goyanes, A.	31	26
Gaisford, S.	30	25
Repka, M.A.	18	10
Quodbach, J.	16	9
Alhnan, M.A.	13	10
Maniruzzaman, M.	12	8
Roberts, C.J.	12	11
Zhang, J.	12	9
Ibric, S.	11	9

Co-authorship analysis was conducted to see the network visualization of co-authorship with a minimum number of 5 documents (Figure 7). The VOSviewer visual analysis produced circles

E-ISSN : 2715-0518
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demonstrating the quantity of publications. The bigger the circle, the more publications there are. The lines between circles show the collaboration between authors. The top 3 authors who collaborate the most with other authors are Basit, A.W, Goyanes, A., and Gaisford, S., with a total of 19 links. They are in line with the number of co-citations that are also dominated by them (Figure 8), with a network visualization of co-citations in Figure 9.

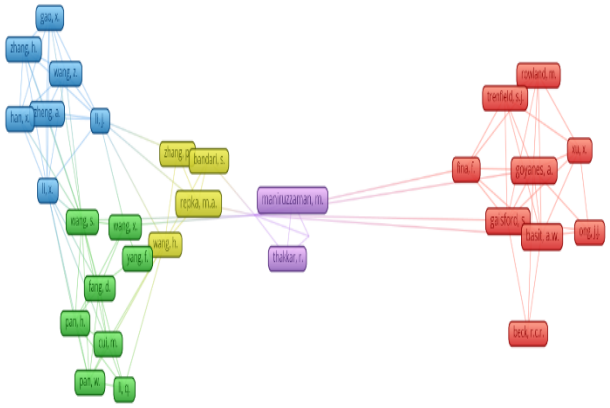

Figure 7. *Network visualization of Co-authorship by VOSviewer*

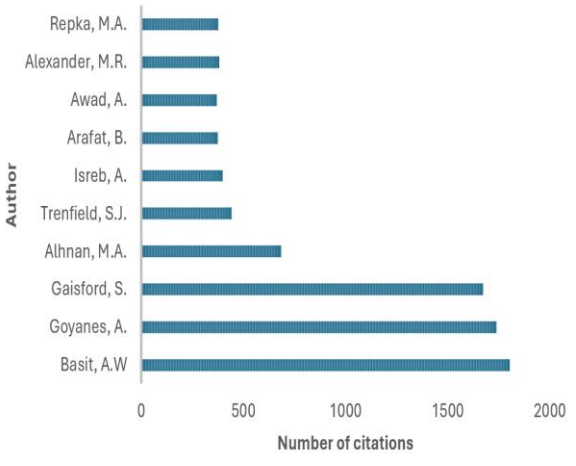

Figure 8. Number of co-citations from authorship by RStudio

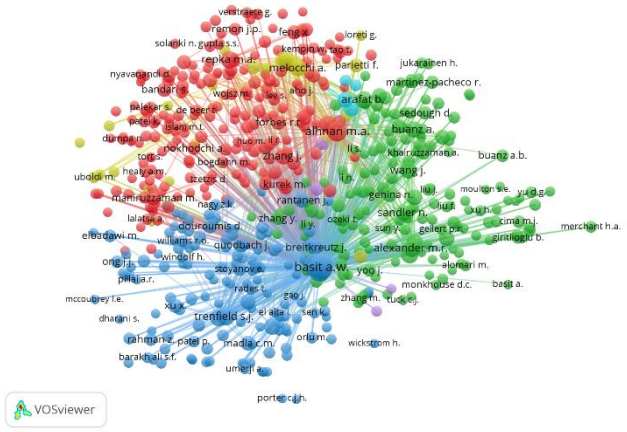

Figure 9. *Network visualization of co-citation of the author by VOSviewer*

3.3 Affiliation

We analyzed the affiliation using RStudio software, which used 405 documents. The total of affiliations is 353 affiliations. Author affiliation analysis was conducted using RStudio. The top 5 most relevant affiliations that produce articles, the more the year, the more it increases (Figure 10).

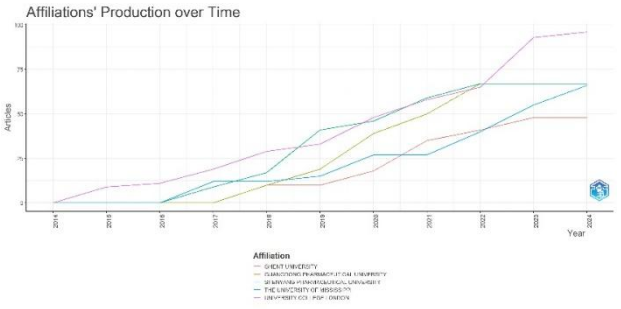

Figure 10. Affiliations production overtime by RStudio

The most relevant affiliations can be seen in Table 2. The affiliation that produces the most articles is University College London from the United Kingdom. Besides, there are two other universities in the country, the University of Nottingham and the University of Central Lancashire, so it is not surprising that the United Kingdom produces the most articles.

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Table 2. The most relevant affiliation by RStudio

Affiliation	Country	Number of Documents
University College London	United Kingdom	96
Guangdong Pharmaceutical University	China	67
Shenyang Pharmaceutical University	China	67
The University of Mississippi	USA	66
Ghent University	Belgium	48
University of Nottingham	United Kingdom	42
Beijing Institute of Pharmacology And Toxicology	China	41
Nagoya City University	Japan	40
University of Belgrade	Serbia	39
University Of Central Lancashire	United Kingdom	37

3.4 Source

Source analysis of 405 documents using a combination of VOSviewer, RStudio, and Microsoft Excel software. The total of sources is 67 sources. The most relevant source in the top 10 can be seen in Table 3. The top rank is the International Journal of Pharmaceutics, which has 137 documents, which is 44.77% of the total most relevant source articles. The H-Index value of the journal is 44, which indicates that the journal has a strong influence on related disciplines. The total number of citations for the International Journal of Pharmaceutics is the highest number of citations, which is 7880 citations.

Table 3. The most relevant source by RStudio

Source	Number of Documents	Citation	H-Index
International Journal of Pharmaceutics	137	7880	44
Pharmaceutics	57	1543	21
AAPS Pharm SciTech	22	728	14
European Journal of Pharmaceutics and Biopharmaceutics	20	1562	12
Journal of Drug Delivery Science and Technology	19	230	12
European Journal of Pharmaceutical Sciences	18	1192	8
Journal of Pharmaceutical Sciences	11	444	7
Pharmaceuticals	9	112	6
International Journal of Pharmaceutics: X	7	66	6
Pharmaceutical Research	6	579	5

3.5 Documents

Extracted data from the Scopus database was used to analyze documents. The most cited documents from 2014 to 2024 can be seen in Table 4. Starting in 2013, the era of articles about 3D printing began to emerge. Articles from 2014 to 2016 discussed modified-release tablets, where optimization of the use of polymers was carried out to produce drug release with sustained or controlled release. Articles in 2017-2020 discussed the modification of methods for making 3D-printed tablets. Then, from 2021 to 2024, we discussed advanced technology for performing evaluations of 3D-printed tablets.

Table 4. Documents most cited year by year using scopus database

Title	Year	Cited by	Reference
Visualizing disintegration of 3D printed tablets in humans using MRI and comparison with in vitro data	2024	7	[19]
Releasing fast and slow: Non-destructive prediction of density and drug release from SLS 3D printed tablets using NIR spectroscopy	2023	18	[20]
Volumetric 3D printing for rapid production of medicines	2022	32	[21]
Machine learning predicts 3D	2021	84	[22]

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printing performance of over 900 drug delivery systems			
Selective laser sintering 3D printing of orally disintegrating printlets containing ondansetron	2020	12	[23]
Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process	2019	567	[12]
Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs	2018	545	[24]
Selective laser sintering (SLS) 3D printing of medicines	2017	529	[25]
Stereolithographic (SLA) 3D printing of oral modified-release dosage forms	2016	503	[26]
3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets	2015	89	[5]
Desktop 3D printing of controlled-release pharmaceutical bilayer tablets	2014	461	[27]

3.6 Keyword

A co-occurrence analysis of 405 documents was conducted using VOSviewer and RStudio software, with the unit of analysis being all keywords. The all-keywords category consists of author keywords and indexed keywords. The total number of keywords obtained was 3131 keywords; by setting the minimum number of occurrences of a keyword to 10, 181 met the threshold. We use filtering by uploading a thesaurus to remove irrelevant words and replace words that are synonymous or have similarities. Ten words were removed, namely article, review, procedures, priority journal, concentration (parameter), concentration, clinical article, case report, fff, and comparative study. For word synonyms, 160 words are replaced with synonym data so that they become one meaning for different words. The visualization results can be seen in Figure 11. The results of this analysis can be used to find out the topic of research that has been done before. The most occurrences of keywords are “3D printing” (394 occurrences), “tablet” (323 occurrences), “drug release” (291 occurrences), “controlled release” (233 occurrences), and “solubility” (227 occurrences). The following data interpretation of the results of the keyword was analyzed with VOSviewer refer to Table 5.

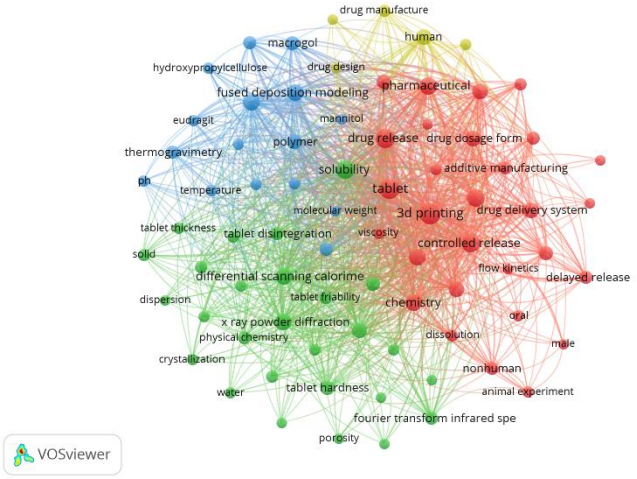

Figure 11. Network visualization of all keywords by VOSviewer

Table 5. Theme interpretation of keywords in each cluster by VOSviewer

Cluster	Number of items	Top 5 Keyword	Theme Interpretation
1 (red nodes)	29	3d printing, controlled release, delayed release, sustained release, personalized medicines, targeted drug delivery,	This cluster describes the development of modified release using 3D printed tablet
2 (green nodes)	27	Tablet compression, tablet disintegration, tablet friability,	This cluster describes the characterization and testing of the final drug product.

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		tablet hardness, tablet thickness, tablet weight, DSC, XRD, SEM, FT-IR	
3 (blue nodes)	16	Fused deposition modeling (FDM), hot melt extrusion (HME), eudagrit, macrogol, mannitol, hydroxypropyl cellulose, polymer, polyvinyl alcohol	This cluster describes the method and excipient to fabrication of a 3D printed tablet.
4 (yellow nodes)	5	Drug design, drug manufacture, human, child, stereolithography	This cluster describes the production of 3D printed tablets using the stereolithography (SLA) technique for personalized medicine of children

Trend topics were analyzed using RStudio software from 2014 to 2024 (Figure 12). The results of trend topics were based on keywords plus articles with a frequency of 100-400. Trends of active drug substances used for 3D printed tablets are atenolol, captopril, mesalazine, glipizide, aminosalicylic acid, caffeine, and celecoxib. The trend method used for fabricating 3D-printed tablets is fused deposition modelling (FDM). The trend polymer in 2024 is carrageenan.

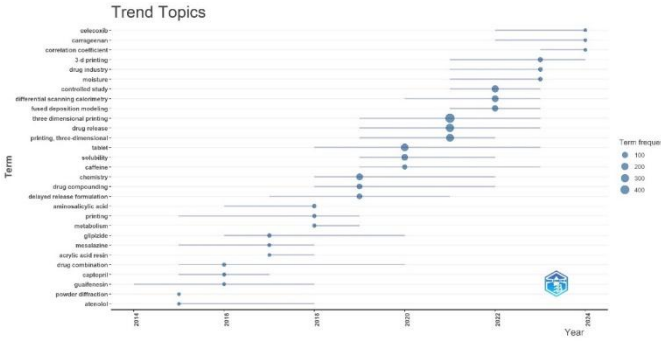

Figure 12. Trend Topics by RStudio

The three-field plot analysis was conducted using RStudio software. The correlation between source (SO), author (AU), and author country (AU_SO) in a plot of three fields is presented in Figure 13. In this study, we focus on the top 20 sources, top 20 authors, and top 20 countries that publish articles about 3D printing tablets. The grey line connects the three fields. The thickness of the line indicates the size of the connection between the fields; the thicker the line, the greater the number of articles associated with the fields.

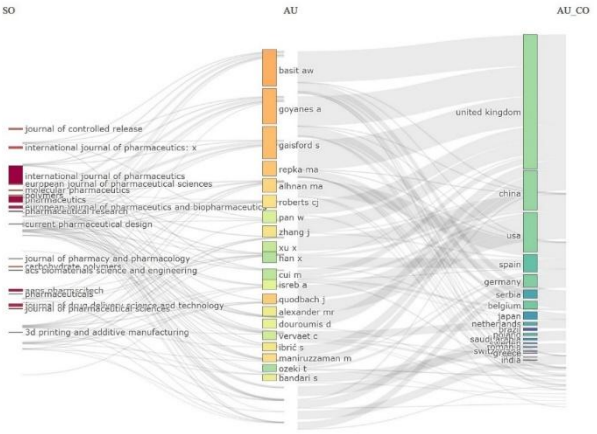

Figure 13. Three-field plot between the name of the source (SO), author (AU), and author country (AU_SO) by RStudio

3.7. Discussion

Manufacturing of tablets utilizing 3D printing technology is an intriguing topic for the development of drug delivery systems. 3D printing allows for the creation and modification of complicated shapes through simple adjustments to the CAD model, as well as the ability to swiftly alter formulation. It is especially crucial in personalized medicine, where specific doses or formulations may be required in small quantities with quick production periods [28]. There are various types of tablets that 3d printing produces. Furthermore, controlled-release tablets, immediate-release tablets, sustained-release tablets, orally disintegrating tablets, solid

E-ISSN : 2715-0518
P-ISSN : 2715-3053

lipid tablets, chewable tablets, and gastric retention tablets have been investigated [4].

Fused Deposition Modelling (FDM) is a widely used and affordable bench-top 3D printing technique [29], relatively low cost [29], higher resolution compared with powder-bed printing, good mechanical strength [26], and small-scale batch size [30]. The process of FDM is extruded polymer filaments that are sent through a heated nozzle, and they melt into a semi-liquid condition. The softened filaments are subsequently applied layer by layer to form a 3D structure onto a build plate to harden [8], [30], [31]. This technique cannot be used for drugs that are not heat-resistant because the manufacturing process passes through high temperatures (185-220^{0}C) so that drugs that are not heat-resistant can be degraded. Examples of drugs that can be produced using this technique are theophylline [8], glipizide [32], budesonide [5], domperidone [33], etc. To overcome this problem, Kollamaram found a way for the FDM technique to be performed at low temperatures by using two immediate-release polymers, Kollidon VA64 and Kollidon 12PF. Thus, thermolabile drugs such as Ramipril can be produced using the low-temperature FDM technique (Kollamaram, 2018). FDM also has shortcomings related to low drug loading, which is only about <2%, so it is combined with the hot melt extrusion (HME) technique to produce better drug-loaded strands [34]. However, this HME method also uses high temperatures, making it unsuitable for thermostable drugs due to HME need high temperature, so the active pharmaceutical ingredient (API) will be damaged. Linares, et al used Injection Volume Filling (IVF) combined with FDM to overcome the problem of using high-temperature and low-loading drugs [34]. The direct powder extrusion (DPE) technique can be used as an alternative to the FDM technique by avoiding the preparation of filaments by hot melt extrusion [12].

The stereolithography (SLA) technique produces highly accurate prints with high resolution that have higher patient acceptance compared to the FDM method [35]. However, the issue with SLA is the limitation of photopolymer materials that are biocompatible, non-toxic, and carcinogenic [25], [36], longer time, and not cost-efficient [35]. Semi-solid extrusion technology (SSE) technology can produce a combination of multiple actives into a single table with an immediate and sustained release [37], [38], [39]. The drawback is the drying process, and the resulting tablets have high friability [37]. Selective laser sintering (SLS) techniques use lasers to bond powder particles together, resulting in product objects with high resolution due to the precision of the laser [25], [40]. However, the materials used require high temperatures and high laser energy [25].

Based on the articles that have been published, we can conclude that it has only been utilized in laboratories and has not yet been released on the market. The possible causes are a shortage of printing materials and no established criteria for the regulation of 3D-printed medicinal dosage forms. As a result, 3D printing is not currently available for large-scale medication development and manufacture. However, we are expecting that these issues will be resolved in the future.

IV. CONCLUSSION

E-ISSN : 2715-0518
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In this study, we have conducted a bibliometric study using VOSviewer and RStudio software. This study was based on the Scopus Database having 405 suitable publications were evaluated. The result from analyzing the data of the most frequent countries that published articles, the most relevant authors, affiliation producing the most articles, the total number of citations, and the most occurrences of keywords. The findings of this study can provide information about previous research and identify gap analysis for new ideas for future research. In the future, 3DP will be an attractive alternative for tablet printing. Pharmacists in hospitals and drugstores can print more personalized tablets so that treatment outcomes will improve because they are tailored to the individual's phenotype and genotype, as well as anatomical and physiological particulars.

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