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Review Article

Exploring metal organic frameworks for efficient drug delivery: A bibliometric review

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ABSTRACT

The biomedical application of the metal organic frameworks (MOFs) has become a field of immense interest in the last decade for worldwide research community. The present bibliometric review aims to find quantitatively the global scenario of research involving utilization of MOFs in designing new drug delivery systems. To explore the research direction of MOFs in drug delivery, the research executed in the last decade has been analyzed using sophisticated statistical tools, like, Bibliometrix-Biblioshiny package of r, and VOS viewer, a java based tool. These software packages facilitate to analyze quantitatively all the research articles published during this time frame to obtain the year wise growth, country wise distribution, mostly used keywords etc. In addition, the collaboration, as well as, the co-occurrences between keywords have been analyzed. Such detailed exploration of the present field utilizing statistical tool can be very much promising to understand the current research position and find grey areas in the research involving utilization MOFs in designing drug delivery systems.

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INTRODUCTION

The term "drug delivery system" (DDS) refers to a specialized carrier capable of transporting an active pharmaceutical ingredient (API) to a specific target within the body. DDSs serve to enhance the pharmacological effectiveness of an API by addressing factors such as solubility improvement and the optimization of pharmacokinetics and biodistribution. The concept of designing a DDS with precise control over drug release kinetics can be traced back to the 1950s when Smith, Kline, and French introduced a controlled-release formulation for delivering dextroamphetamine over a 12-hour period [1, 2]. Subsequently, an entire realm of scientific investigation has emerged, offering a multitude of exciting opportunities for enhancing drug performance, safety, and targeted distribution. Organic, inorganic, and hybrid substances like liposomes, micelles, carbon nanotubes, silica, quantum dots, and gold nanoparticles have been explored as the carrier materials in the developments of DDS in the past few decades [3]. The design of a DDS is intrinsically dependent on the specific context, necessitating a tailored selection of material composition, administration routes, and cargo release mechanisms to meet the unique biological requirements. Up to the present day, the materials employed for the synthesis

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of nanomaterials used in drug delivery encompass organic options such as liposomes, micelles, and dendrimers, inorganic materials like silica and gold nanoparticles, and hybrid materials, including metal-organic frameworks. In the diverse field of biology, these systems can be engineered to respond to external stimuli, such as changes in temperature, pH, acoustic signals, and heat. Peptides and antigens may be added to increase the precision in targeting specific cells. Additionally, they are capable of delivering small and large molecules. In light of the challenges in drug delivery, researchers are exploring alternative systems with enhanced properties and broader applications.

An intriguing option in the area of advanced materials is metal-organic frameworks (MOFs), also referred to as porous coordination polymers (PCPs). MOFs are noteworthy for their remarkable flexibility and adaptability, rendering them exceptionally well-suited for applications in drug delivery. They have characteristics like a generous pore volume, customizable pore dimensions (extending beyond 6 nanometers), substantial surface areas (reaching up to 8000 square meters per gram), and modifiable surface chemistries [4, 5]. Apart from drug delivery, MOFs have found applications in gas storage, energy conversion, chemical sensing, proton conduction, and catalysis. Industrial applications in oleo-chemicals, textiles, transportation, food packaging, and respiratory systems are also noteworthy [6]. Because of their porous structure, MOFs can absorb small molecules and gases within their structure. The application of MOFs in drug delivery was explored in pioneering studies by Horcajada and co-workers [7]. They explored the application of Chromium based MIL and MIL-101 MOFs for absorption of an anti-inflammatory drug molecule ibuprofen. MIL-101 showed unprecedently high absorption capacity of 1.4 g of ibuprofen molecule per gram of the MIL-101. Moreover, these MOFs showed excellent release capacity of the absorbed molecule in conditions similar to human body. Bermini et al. performed the Monte Carlo simulation studies and substantiated the adsorption capacity theoretically and predicted the adsorption capacity may be as high as 2 g of ibuprofen in 1 g of the adsorbent for BioMOF-100 [8], establishing strong correlation between pore volume and adsorption capacity of MOFs. These pioneering observations inspired the scientists and a huge surge of research was performed in this field in the last decades. The field expanded from Cr based to Fe based MOFs and other biocompatible metals like zirconium, zinc, and iron were explored for targeted drug delivery materials. In health care systems, application of non-toxic nano-carriers for efficient drug delivery remains a challenge. MOFs have shown remarkable advantage over conventional carriers like polymers, nanoparticles, and bacteria because of their outstanding drug loading capacity and also the ability to precisely release the adsorbed therapeutic agents. The porous structure of the MOFs allows them to encapsulate wide range of therapeutic agents, and also sparingly water soluble cancer treatment agents like curcumin. Gas transmitter molecules effective as therapeutic agents like nitric oxide (NO), carbon monoxide (CO), and hydrogen sulphide (H_2S) may also be well encapsulated by these MOFs [9-12]. Large biomolecules like nucleic acids and proteins are protected from degradation by encapsulation within MOFs [13]. It is important to have biocompatibility and minimum or no cytotoxicity and immunogenicity for successful application of drug delivery agents. But analysis of cytotoxicity may be a challenging task, because the individual component toxicity may differ in isolation and upon incorporation within MOFs [14], and cytotoxicity may differ depending on the specific cell type under investigation [15]. In addition to the MOF structure itself, it is crucial that the metal ions and ligands used in MOFs exhibit biocompatibility, as there is probability that these components may leach into biological fluids or tissues over time [16-18]

Over the past few decades, there has been much development in different carrier systems for controlled drug release, enhancing the therapeutic benefit and reducing off-target effects [19]. MOFs have been proposed as an exciting new delivery system, with properties such as high loading capacity and tunable pores making them attractive candidates for such an application [20]. There has also been some progress in the characterization of MOF toxicity, behaviour, and uptake in vitro. However, there is still a need to improve and develop an understanding of MOFs in biological systems. The evolution of methods for particle synthesis, surface functionalization techniques, and the scope for developing new composite-hybrid materials has produced nanomaterials with potential for enhanced capabilities such as stimulus-responsive drug release, imaging, cell-specific targeting, and theranostic capabilities. Combining these developments in synthesis, together with a rational selection of biological models, mechanistic characterization and appropriate selection of in vitro assays will offer exciting prospects for the future of this field [21]. In spite of huge number of publications on the utilization of MOFs in developing drug delivery systems, only one article is there to review the biomedical applications of MOFs quantitatively [22]. This computational review aims to explore different bibliometric parameters to analyse the research executed in the last decade in this avenue. The bibliometric parameters include year wise growth, country wise distribution, most cited articles, and the distribution of sources in the MOF drug delivery research. In addition, the dimensional alternation in the research themes during the ten years span can be analysed from the word dynamics and trend topics analysis. The collaborative links between countries, citation of sources, and co-occurrences of keywords can also be found in the present manuscript. As a consequence, this bibliometric review is expected to offer new researchers to understand present research status and explore novel ideas in drug delivery using metal organic frameworks.

MATERIALS AND METHODS

Retrieval of Bibliometric Data

Here, we consider the data revealed from Web of Science (WoS) database, currently administrated by Clarivate Analytics, utilizing a unique search string related to MOF drug delivery. The WoS database was chosen as it gives more relevant results as compared to the other databases available in the present time. The search string considered in the present investigation was "TS = ((MOF OR (Metal organic framework*)) AND (drug delivery))" in the advanced search, selecting the period 01-01-2014 to 31-12-2023, i.e. the last ten complete years. A total of 3384 documents were resulted in the WoS database which includes articles, reviews and other publications such as conference proceedings, book chapters etc.

Bibliometric Parameters Analysis

All the bibliometric parameters were analysed utilizing Bibiometrix-Biblishiny package of r [23]. The bibliometric data were exported into the web interface of Biblioshiny. After excluding the publications of 2024, total 3014 publications resulted. Our entire analysis was confined into these 3014 articles. The main information related to the present review can be obtained directly in tabular form from this package. The year-wise advancement in the frequency of publications and related citation parameters like, mean total citations per article (MTCPA), mean total citations per year (MTCPY) can be found from this software. Worldwide participation of research community in the MOF drug delivery research can be represented in world map using this software. In addition, most active country according to corresponding author can also be analysed by this tool. This software package also predicts most active authors, sources and related citation parameters like, h-index, average citation per article (ACPP). The most mentioned keywords, in the form of word cloud and data plot can also be generated from this tool. The growth of different words during the span of ten years can also be generated. This software tool also generates trend topics plot to explore the most mentioned topic during different period of time. All the data generated from Bibliometrix-Biblioshiny were plotted in Microsoft Excel.

Collaboration Between Countries, Interlinks Between Sources And Co-Occurrences Between Keywords

A java-based software package, VOS viewer, was utilized to find collaborative links between different countries. This software package has been used by many researchers in the last decade for finding collaborative networks between countries, authors, sources etc. [24] The research on MOF drug delivery research executed in the last decade, as retrieved from Web of Science database, was analysed with VOS viewer. To have visually detectable network paths in studying co-authorship, the minimum number of articles and minimum citations were optimized at 30. Total 84 countries were found to meet this condition, of which only 21 countries were found to possess active links.

The interlinks between the sources publishing articles on MOF drug delivery during the last decade was also analysed in terms of citation utilizing the same VOS viewer package. In this analysis the minimum number of articles and minimum citations were fixed at 40, to have well defined network structure. The VOS viewer package also facilitates the prediction of the co-occurrences of keywords during the timespan considered in this analysis. Here, all keywords, which includes both author keywords and keywords plus, were considered for analysing co-occurrences. The minimum number of occurrences was fixed at 150; only 25 keywords were found to possess interlinks with others. A similar kind of analysis has been reported to explore management science research in Turkey [25].

RESULTS AND DISCUSSION

Analysis of the Bibliometric Parameters

Year-wise growth of publication and citation parameters

The year-wise progression of number of articles published on utilization of metal organic frameworks in drug delivery and related citation parameters, such as, mean total citation per article (MTCPA), and mean total citation per year (MTCPY) has been plotted in Figure 1. As evident from the figure, the number of total publications in each year increases, suggesting growing interest of scientific community towards developing new MOFs for drug delivery. However, the pandemic occurring in 2019-2020 aggravated experimental research and thus resulted in some less article production during this time. In addition, the last five years of research on the said topic published significantly higher number of articles (2345), compared to only 969 articles in the first five years. This result strongly suggests the affinity of research community in MOF drug delivery systems in recent years. On analyzing citation parameters, an irregular trend in MTCPA and MTCPY is evident being maximized in 2016. The decrease in MTCPA and MTCPY in the recent years is very much usual and might be associated with the greater number of articles and less citation received in the last years.

Most active authors: number of publications and citation parameters

Figure 2 illustrates the top ten researchers publishing articles on MOF drug delivery research during 2013-2022 and the related citation parameters like, h-index and average citations per publication (ACPP). As can be seen, Wang Y published highest number of articles (117) on MOF drug delivery, followed by Li Y (111), Liu J (108) Zhang Y (103), and Liu Y (97). It is worthy to mention that, although Liu Z published relatively smaller number of articles (59), the ACPP tops the list, signifying greater acceptability of their findings to the worldwide scientific community. The

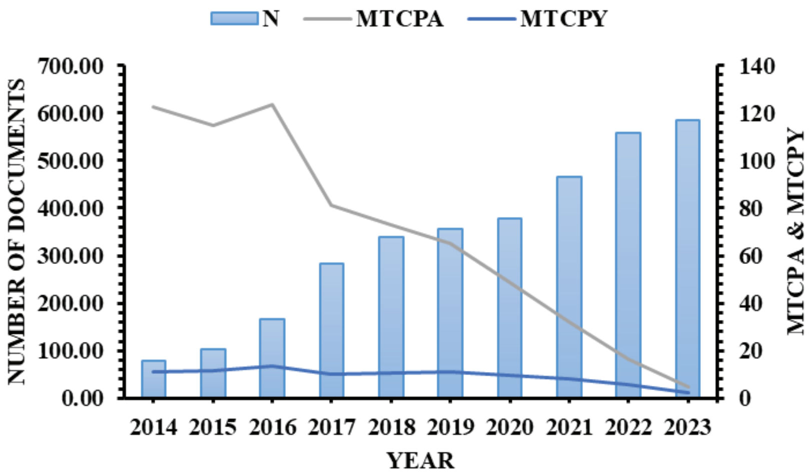

Figure 1. Year-wise growth of number of publications, MTCPA and MTCPY in the period 2014-2023.

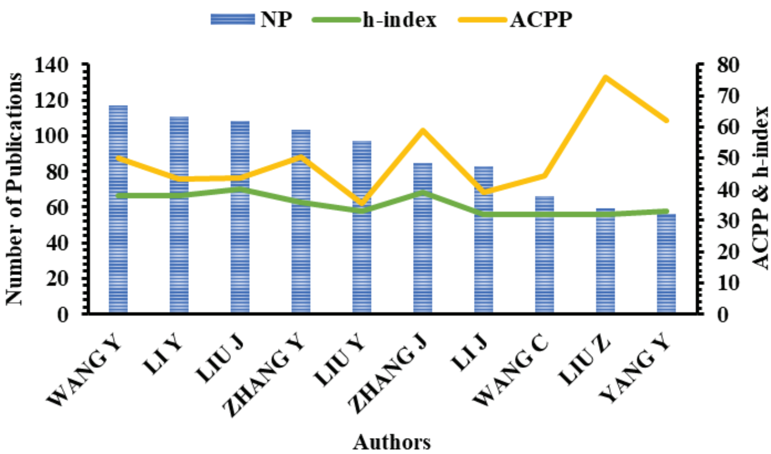

Figure 2. Number of articles, ACPP, and h-index of most active authors (top ten) publishing articles on MOF in drug delivery research in the period 2014-2023.

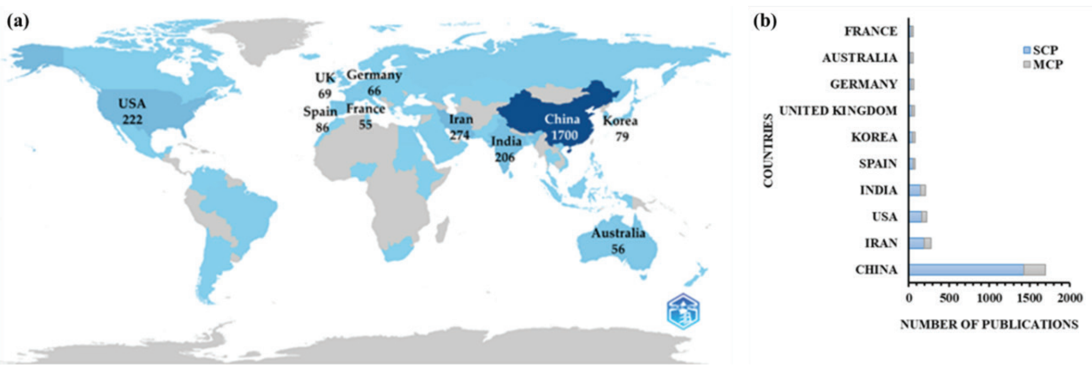

Figure 3. (a) Countries with most publications in MOF drug delivery in world map; (b) Most relevant countries by corresponding author doing research on MOF in drug delivery research in the period 2014-2023.

other authors receiving appreciably good ACPP are Yang Y, Zhang J, Wang Y, and Wang C. Additionally, h-index, another important citation parameter, appears as highest for Liu J, followed by Zhang J, Wang Y, and Li Y.

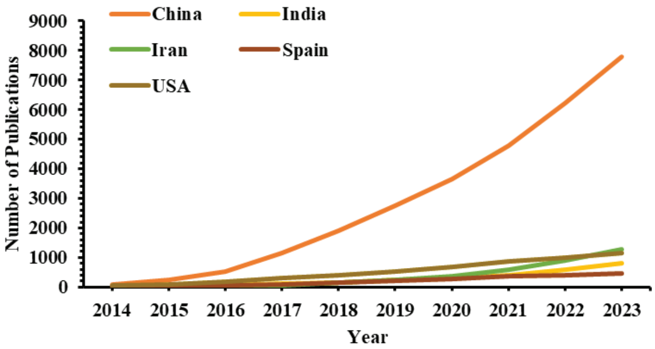

Figure 4. Growth of MOF in drug delivery research executed by top five countries in the period 2014-2023.

Most relevant countries

The most productive ten countries in MOF drug delivery research during 2014-2023 has been designated in the world map in Figure 3a. The deepening of blue colour is directly proportional with the number of publications. As evident, China published the highest number of articles on MOF drug delivery systems followed by Iran, USA, India, and Spain. The designation in the world map also suggests the worldwide participation of countries in the present research field. Figure 3b depicts the most relevant top ten countries by corresponding author in MOF drug delivery research during 2013-2022. The corresponding author data has proved itself to be the most convenient to compare the number of articles published by different countries quantitatively. The plot also predicts the SCP (single country publication) and MCP (multiple country publication), important parameters for inter-country collaboration. As evident from the plot, China published the highest number of articles (related to corresponding author) both as SCP and MCP. This was followed by Iran, USA, India, and Spain. This data analysis supports highest inter-country collaboration in case of China, followed by Iran, USA, India, and Spain.

Year-wise growth by top five countries

The advancement in the MOF drug delivery research executed by top five countries during 2014-2023 has been represented in Figure 4. As can be seen, China published the highest number of articles in the entire period under consideration. In addition, the progression of MOF drug delivery research executed by China produced highest sloped curve, indicating the greater involvement of researchers of China in the present research topic with time. This trend was followed by countries like, USA, Iran, India and Spain. Although, USA followed China during 2016-2021, in the last couple of years Iran exceeds USA and appears second after China.

Most relevant sources

Figure 5 illustrates the top ten journals and related citation parameters publishing articles on MOF drug

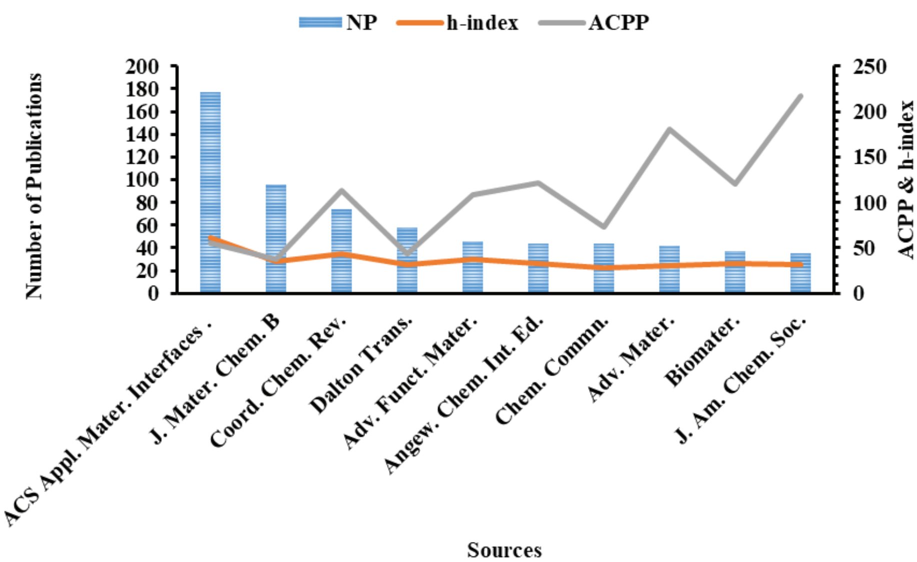

Figure 5. Total number of publications, h-index, and ACPP in the top ten journals.

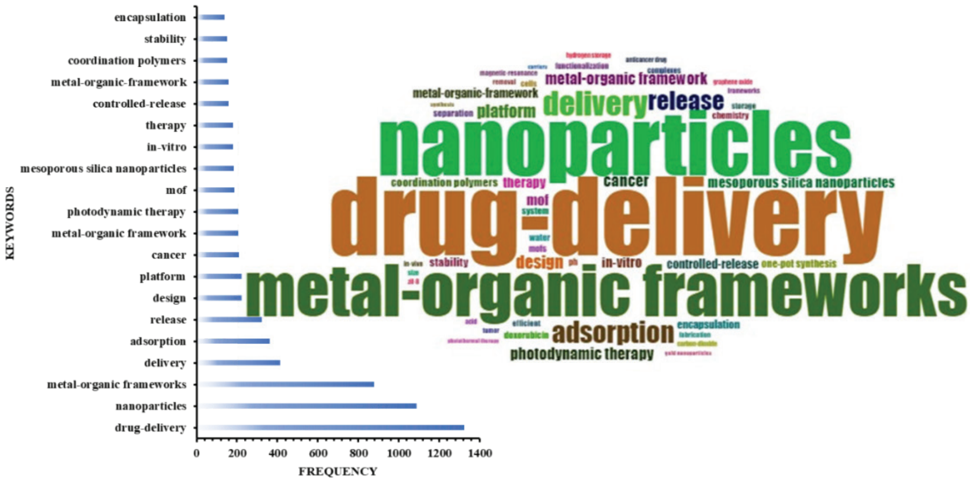

Figure 6. Mostly used keywords on MOF in drug delivery research as bar plot and keywords cloud.

delivery systems. As can be observed, the highest numbers of articles on the said topic were published in 'ACS Applied Materials and Interfaces', followed by 'Journal of Materials Chemistry B', 'Coordination Chemistry Review', and 'Dalton Transactions'. The other sources with appreciably good number of publications are, 'Advanced Functional Materials', 'Angewandte Chemie International Edition', 'Chemical Communications', 'Advanced Materials', 'Biomaterials', and 'Journal of American Chemical Society'. It is worthy to mention that, the articles on MOF drug delivery systems were published in internationally reputed high impact journals in chemical sciences published by most reputed societies of chemists. The citations of the published articles were studied in terms of ACPP and h-index. The ACPP appeared as highest for the articles published in 'Journal of American Chemical Society', suggesting greater acceptability of the research findings towards the worldwide scientific community.

Mostly mentioned keywords

Figure 6 represents the most relevant words mentioned in the articles published on MOF drug delivery systems, both as bar plot and as word cloud. The frequency of mention is directly proportional to the emphasizing of words in the word cloud. In this study our target was to find new keywords in excess to most obvious keywords, such as, 'drug delivery', 'metal organic frameworks', 'mof', 'delivery, 'release' etc. As observed, 'nanoparticles' appeared as the most mentioned word (highly emphasized in the word-cloud) in addition to the usual keywords. A huge number of nanoparticle based drug delivery systems have been produced [7,9,10-12]. where MOFs and functionalized MOFs have been used as nanocarriers for targeted drug delivery agents for specific drugs molecules, as well as, biologically important gas molecules and their efficacy have been tested in the field of intracellular delivery of drugs, nucleic acids, and proteins [26]. Recent research has also demonstrated the utilization of MOF nanocarriers for accomplishing precise drug delivery, enhancing cell absorption, and regulating drug release. This highlights the potential of MOFs as a promising category of DDSs for a wide range of therapeutic applications like anticancer drugs, antimicrobial agents, metabolic labelling compounds, antiglaucoma medications, as well as hormones [27-32]. Thus, 'nanoparticle' appears as the most dominated word in the field of

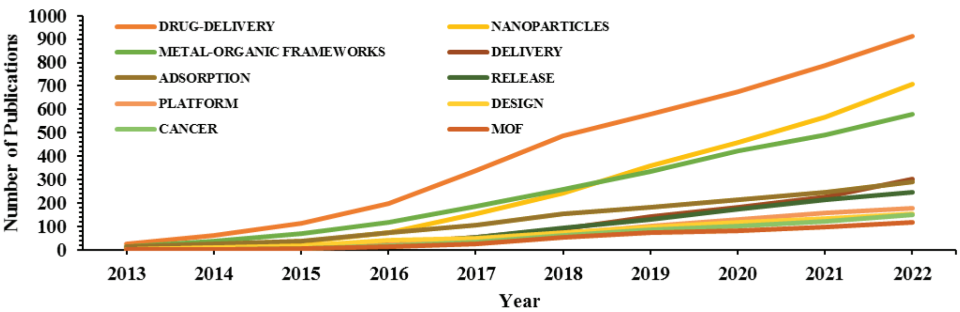

Figure 7. Growth of the most active keywords in the considered time frame.

biomedical applications of MOFs. The other new keywords, such as, 'adsorption', 'release', 'platform', 'design' was found to possess appreciable mention the articles on MOF drug delivery. This study is expected to offer new researchers to find the hot areas, as well as, grey areas of research in the MOF drug delivery systems.

Growth of most mentioned keywords

The growth in the top ten most mentioned keywords during the time frame has been represented in Figure 7. As can be seen, all the keywords considered in the study, gained a momentum after 2015, and the rally continues till the end of the period. The word 'drug delivery' tops the list in the entire period, and is obviously due to its utilization in the search string. The other very much obvious keywords in this line are, 'metal-organic frameworks', 'mof', 'delivery' etc. In addition to the usual keywords, new words like 'nanoparticles' was found to possess impressive growth in the period considered in our study. This trend was followed by 'adsorption', making itself very much growing during the entire period. Another important word 'release' appeared as important after 2016, as it has close relation with the sustained release of drug molecules. This trend was followed by keywords like, 'platform', 'design', and 'cancer'. However, to explore period-wise dominance of keywords, more sophisticated tool like analysis of 'trend topics' may come into play.

Trend topics analysis

To interpret period-wise dominance of topics, trend topics analysis was executed. Figure 8 represents the progressive trends of top twenty-five keywords related to the MOF drug delivery systems during the time frame. In the given figure, the horizontal lines represent the coverage years and the dominating year of the use of keyword is designated by the position of bubble; the size of the bubble signifies the frequency of the keyword. As can be seen, the early years of research in the MOF drug delivery systems was dominated by keywords like, 'hydrogen storage', 'crystal structure', and 'luminescence' being centralized at 2017. In the later period, 'complexes', 'co-ordination polymer', and 'storage' comes into the picture, being maximized at 2018. So, the early period of research on metal organic frameworks were dominated by applications like gas storage (specifically hydrogen), catalysis etc.

The storage and transportation of gaseous fuels is always challenging associated with their low boiling points, low densities, high diffusivity and high critical pressures. Nowadays these gases are liquefied either by compression at very high pressure (in order of several hundreds of atmosphere) or by lowering the temperature significantly (liquefied hydrogen temperature). Such kind of condition requires a specialized sophisticated facility which is difficult to achieve in ordinary laboratory. MOFs are found to be efficient in storing as well as transporting gaseous fuels at ambient condition. The porosities offered by the 3d engineering of metal and ligands make the storing and transportation of fuels feasible in a cost effective and safe way [33, 34]. The unique structural parameters of the MOFs, such as, high porosities, large surface area, tunable pore size, ease of functionalization makes them efficient as compared to the traditional materials like, zeolites, activated carbon etc. Thus, important gases like, hydrogen, acetylene, methane can easily be stored and transported utilizing MOFs.

The drug delivery utilizing metal organic frameworks gained momentum after 2017, being maximized at 2018. The topics like 'encapsulation', 'adsorption' and 'separation' during 2017-2020 supports this fact. The most extensive work on MOF DDS systems was executed in 2017-2022, being maximized in 2020. The latter period of research on MOF drug delivery was dominated by 'metal organic

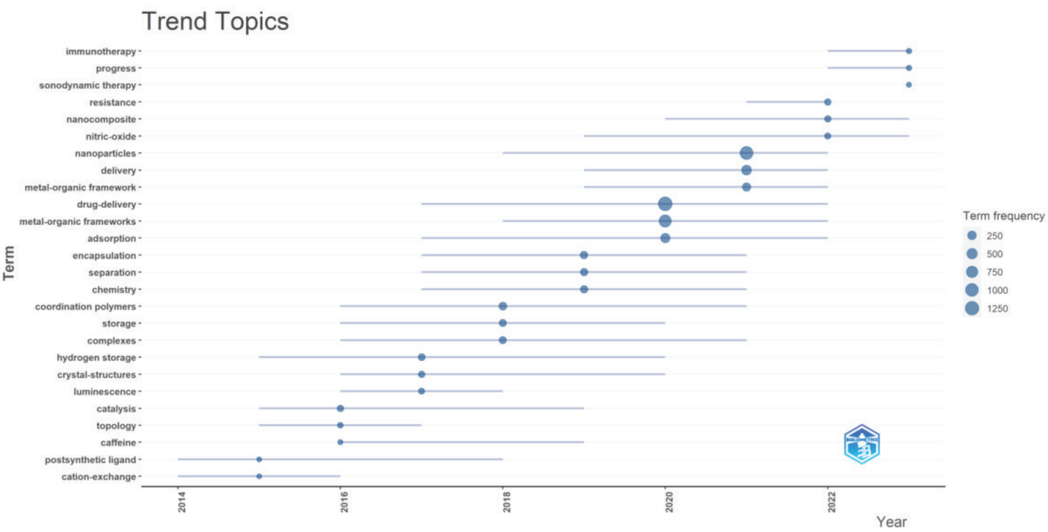

Figure 8. Trend topics analysis for the period 2014-2023.

frameworks', 'nanoparticles', and 'delivery', suggesting utilization of nanoparticles in the latter period of research for delivering of drug molecules. At the more advanced period, topics like 'immunotherapy', 'sonodynamic-therapy' were found to dominate being maximized in 2023, as modern therapeutic treatments of cancer have been inclined towards designing novel systems utilizing new MOFs different therapies were targeted utilizing the MOFs.

Sonodynamic therapy (SDT) is considered as the most advanced therapeutic treatment in cancer treatment owing to its non-invasiveness along with minimum side effects. In SDT, low intensity ultrasound is given in presence of sono-sensitizers. This sort of treatment is employed in treating deep lasions associated with its efficiency to penetrate into the deep tissues. The advantages, such as, large surface area, high porosities, good drug loading capacity and their controlled release, bio-compatibility, and precise targeting capacities make the MOFs efficient in cacncer therapeutics [35].

In recent decades, immunotherapy has emerged as a prominent treatment for cancer [36-38]. Immunotherapy involves boosting of natural defence of immune systems in contrary to inhibiting tumor growth in traditional processes of cancer treatment. By alleviating tumour-induced immunosuppression, it triggers an immune response that not only suppresses primary tumour growth but also impedes metastasis and prevents tumour recurrence. MOFs can be well utilized in cancer immunotherapy owing to their large surface area, porous structure and excellent biocompatibility.

Analysis of Collaboration Between Countries, Interlinks Between Sources and Co-Occurrences Between Keywords

Collaboration between countries

The collaboration between different countries, as obtained from VOS viewer, has been represented in Figure 9. In this figure, the frequency of keywords is indicated by the volume of the bubbles, and the intensity of the line is directly related to the number of articles published in that inter-country collaboration. In addition, the distance between the countries defines their relatedness in the present investigation. As can be seen, Peoples R China published the highest number of articles, and found to possess highest link strength (1186). The intensity of the links again suggests collaborative strength between two countries. As evident from the plot, China possesses highest number of links with highest frequency of publication. Countries like, Iran, Australia, India, Singapore are found to publish highest number of articles with Peoples R China. USA followed China in collaborating research with other countries. An appreciably good number of international collaborating articles is well evident from the plot. USA is found to yield good number of articles on collaborating with countries like, China, Iran, India, Australia, England, South Korea etc. This trend was followed by Australia, Iran, and India in publishing articles on MOF drug delivery during 2014-2023. This study reveals the extent of international collaboration by the countries worldwide in the MOF drug delivery research. China tops the list followed by, USA, Australia, Iran, and India.

The density visualization has proved itself to be more promising in evaluating inter-country collaborations. Figure 10 displays the density plot related to inter-country collaboration in MOF drug delivery research. The collaboration between China and USA is well evident from the given density visualization. The density plot also predicts good collaborations between Japan-India, India-South Korea, South Korea- Taiwan, and Australia-Iran. Additionally, a mention-worthy collaboration between USA-Saudi Arabia, Spain-England, and Poland-Brazil is evident from the density visualization.

The development of MOFs utilizing metals and ligands involve researchers from chemistry fraternity, while the

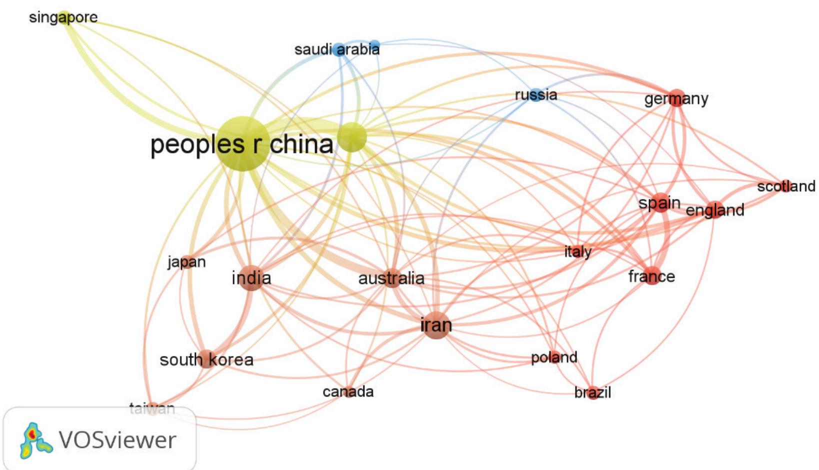

Figure 9. Collaborative networks between different countries in MOFs in drug delivery research during 2014-2023.

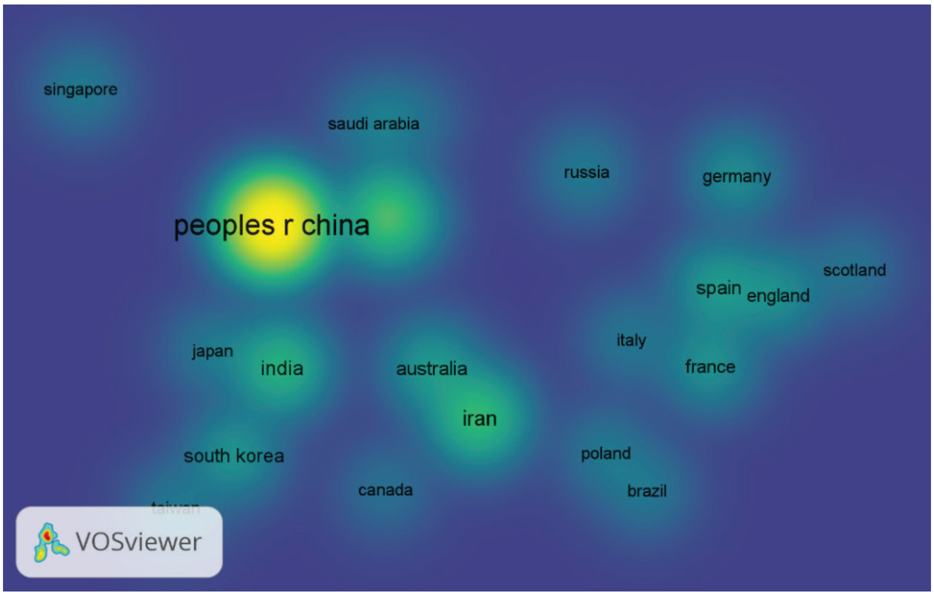

Figure 10. Density visualization of collaborations between different countries in MOFs in drug delivery research during 2014-2023.

applications of the MOFs in drug delivery requires sophisticated biology laboratory. Thus, the present research topic appears as a multidisciplinary field involving chemists, as well as, biologists. A significant number of articles has been published collaborating chemists from structural laboratory with biologists involving in biomedical research. For instance, USA-China collaboration is evident for on command cargo release of zirconium based MOF [39]. Another China-USA joint venture is evident in phototheranostic MOFs for efficient imaging-guided cancer therapy [40]. Thus, the field merges Chemistry with Biology, resulting good collaborations between structural chemists with cell biologists.

Interlinks between sources

Figure 11 depicts the interlinks between different sources publishing articles on MOF drug delivery in the considered time frame. Here, the interlinks suggests the citations by the different sources. As evident from the figure, the size of the bubble is maximum in case of 'ACS Applied Materials and Interfaces', signifying highest number of articles from

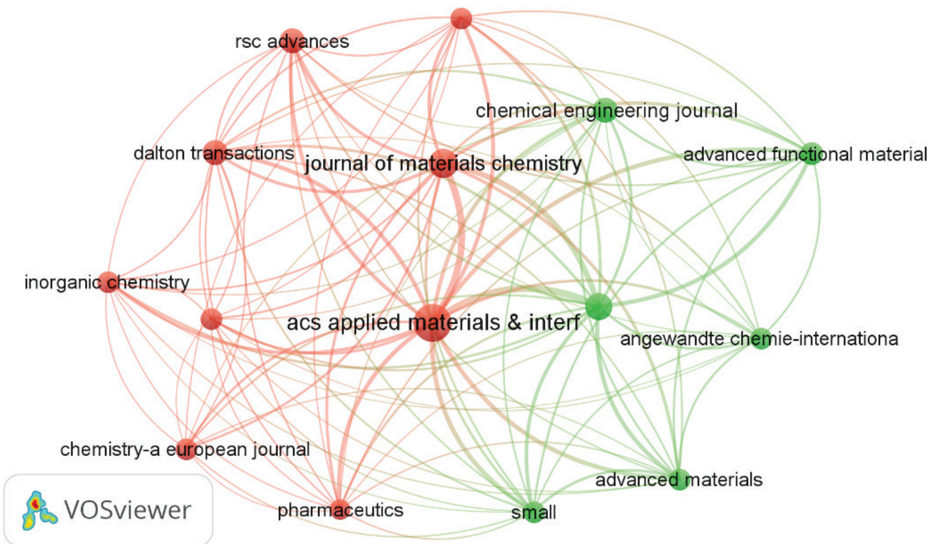

Figure 11. Interconnecting networks between sources publishing articles in MOFs in drug delivery research.

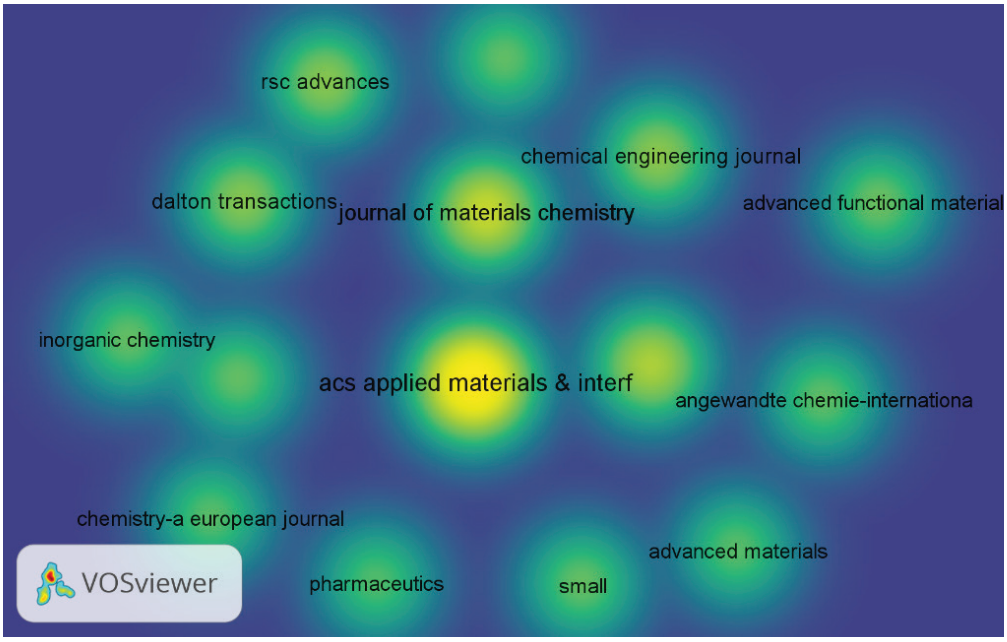

Figure 12. Density visualization between sources publishing articles in MOFs in drug delivery research.

this specific source got cited by other journals. This was followed by sources like, 'Journal of Materials Chemistry B', 'Advanced Materials', 'Advanced Functional Materials', 'Dalton Transactions', and 'Chemical Communications'. As the number of articles were greater in case of these sources the citation links were also found to be high. It is worthy to mention that, although 'Coordination Chemistry Reviews' published significantly high number of articles, the citation links are found to be less and thus has not appeared in the given plot.

Figure 12 represents the density visualization of sources publishing articles on MOF drug delivery systems. As revealed from the density visualization, no strong links between the sources is evident. However, a very weak link is observable between 'Inorganic Chemistry' and 'Microporous and Mesoporous Materials' followed by 'Dalton Transactions' and 'RSC Advances'.

Co-occurrence of keywords

The co-occurrences of different keywords associated with the present study have been plotted in Figure 13. The corresponding parameters related to the co-occurrences of keywords have been summarized in Table 1. The co-occurrences of keywords suggest its association with other keywords. As evident, keywords like, 'metal-organic frameworks', 'drug-delivery', 'nanoparticles', 'drug delivery', 'metal-organic framework', 'delivery' had the most occurrences and total link strength. As the present study involves the quantitative evolution of MOF drug delivery research in the last decade, these keywords are very much obvious and co-occurrences with other keywords. As different MOFs has been developed as the carrier of nanoparticles, as well as, different MOFs of nano-dimension has been designed for efficient drug delivery, the 'nanoparticles' keyword appears in the topline. This was followed by keywords like, 'adsorption', 'release', 'photodynamic therapy', 'cancer', 'design', 'platform', associated with their close relation with new drug delivery systems for cancer therapeutics. A few materials related keywords, such as, 'mesoporous silica nanoparticles', 'ZIF 8', 'doxorubicin', 'coordination polymers' owing to their extensive investigation in the MOF drug delivery systems. On summary, 'nanoparticles' appears as the most associated keywords in addition to the most MOF drug delivery related keywords. In addition, few materials, as well as, investigation related keywords are found to possess mention worthy occurrences and links.

Recently, there has been significant exploration into utilizing MOFs as host matrices for integrating a variety of functional materials, including nanoparticles, bio entities, and polymers. These combinations result in composites with enhanced or entirely new properties compared to their individual components. Within these MOF composite materials, both the size of the MOF hosts and the guest functional materials can be further reduced to the nanoscale, resulting in metal-organic framework nanocomposites. These MOF nanocomposites exhibit improved compatibility for bio-circulation and serve as efficient nanocarriers for delivering agents in biomedical applications. By incorporating various functional nanoparticles such as Au, Fe_3O_4, quantum dots, and up conversion nanoparticles into MOF structures, these nanocomposites retain the advantageous properties derived from the crystalline and porous structures of MOFs, while also maintaining the unique biomimetic catalytic, optical-electrical, and

Table 1. Co-occurrence of most relevant keywords and evolution in biodegradable smart and active packaging research during 2014-2023

Keyword	Occurrences	Total link strength
Metal-organic frameworks	1343	2967
Drug-delivery	1317	2862
Nanoparticles	1065	2829
Drug delivery	488	1405
Metal-organic framework	484	1084
Delivery	408	917
Adsorption	387	969
Release	327	975
Photodynamic therapy	295	826
Cancer	259	750
MOF	238	613
Design	227	581
Platform	224	671
Mesoporous silica nanoparticles	207	525
MOFs	200	474
Coordination polymers	197	491
In-vitro	182	520
Encapsulation	168	509
Metal-organic-framework	164	440
Therapy	164	476
Doxorubicin	161	501
Stability	159	466
Controlled-release	158	471
One-pot synthesis	154	476
ZIF-8	151	408

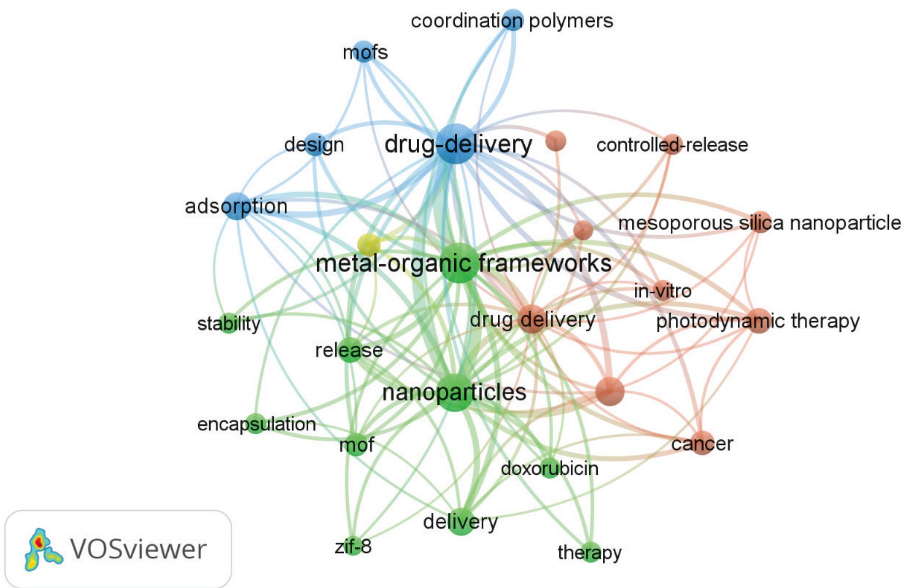

Figure 13. Network visualization of co-occurrence of keywords mentioned in the articles involving MOFs in drug delivery research.

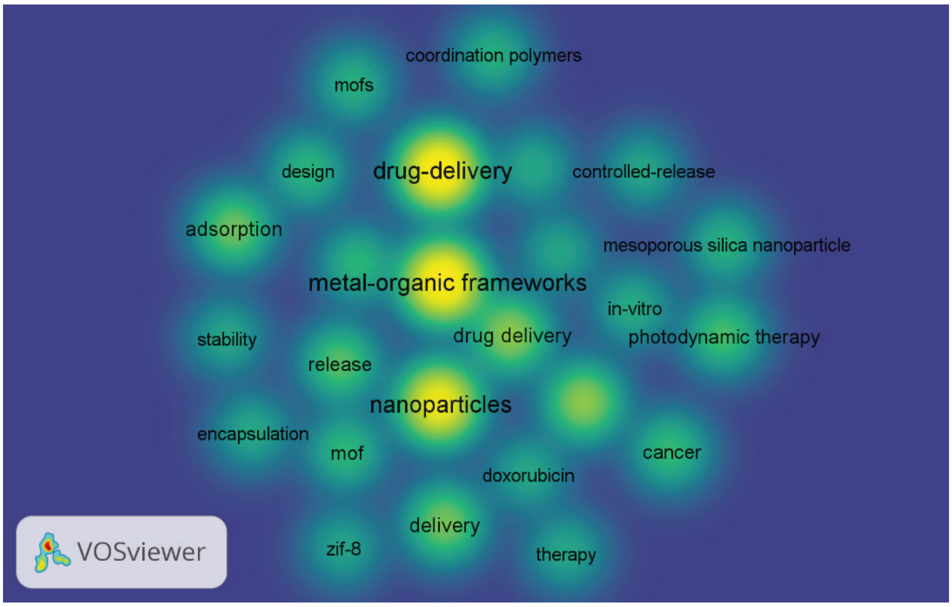

Figure 14. Density visualization of co-occurrence of keywords mentioned in the articles involving MOFs in drug delivery research.

magnetic characteristics of the nanoparticles. Furthermore, the synergistic effects resulting from the integration of these materials can lead to the emergence of novel chemical and physical properties. Many reports have also reviewed about MOF composites for bio-applications such as drug delivery, bio-imaging, and cancer therapy [40-43].

Figure 14 displays the density visualization of co-occurrences of keywords. The close association of 'metal organic framework' and 'drug delivery' is very much evident from the density plot. This result is quite obvious with the present field of investigation. In addition, 'release', 'mof', 'nanoparticles' are found to have fair overlap, suggesting the exploration of MOFs in nano-dimension, as well as, MOF bound nanoparticles for controlled release of drug molecules. To a very lesser extent, the association of 'in-vitro' and 'photodynamic therapy' might be associated with the greater in-vitro experiments involving photodynamic therapy employing MOFs.

KEY FINDINGS AND FUTURE SCOPE

On summarizing the results associated with the computational analysis the key findings can be depicted as below:

- The MOF drug delivery research lies in an inclining trend during 2014-2023, suggesting the enhanced interest of worldwide scientific communities in exploring new MOFs for efficient drug delivery
- Worldwide participation in the research involving biomedical application MOF is well evident, China being the highest publishing country with highest international collaboration.
- The country wise production of articles over time displays China being dominating the field in the entire period considered in this study, followed by USA, Iran, India and Spain
- All the research articles were mostly published on journals like, 'ACS Applied Materials and Interfaces', 'Journal of Materials Chemistry B', 'Coordination Chemistry Review', 'Dalton Transactions', 'Journal of the American Chemical Society', 'Biomaterials' etc., all highly reputed journals of chemistry.
- The keywords analysis finds 'Nanoparticles' as the most mentioned keywords in addition to MOF drug delivery related keywords. The exploration of MOFs as carrier of 'Nanoparticles' for efficient drug delivery, as well as, experiment with MOFs with nano dimension results the appearance of 'Nanoparticles' in the priority list.
- Immunotherapy, sonodynamic therapy appears as the most recent topic of investigation in the trend topics analysis
- The collaboration study reveals extensive collaboration between structural chemists and cell biologists in developing efficient MOF based drug delivery systems

For efficient drug delivery system, the effect of pH, stability of MOFs in biological medium, loading of drug molecules by controlling porosity must be taken into consideration. Although, there is extensive investigation on the exploration of MOFs in biomedical field, little stress has been given in the toxicity related parameters associated with the drug delivery systems. In addition, there is very less work on the in-vivo experiments, which are very crucial for biomedical applications. In vivo experiments assess biological responses in living organisms, providing crucial insights into drug absorption, distribution, and safety. They are essential for evaluating the efficacy of therapies before clinical trials, offering information that in vitro studies cannot provide. Moreover, environment friendly green methodologies have gained immense attention in the recent days owing to the sustainability of the environment. This approach often utilizes renewable resources and safer solvents, enhancing sustainability in MOF production. By employing techniques such as microwave-assisted synthesis and hydrothermal methods, researchers can efficiently create MOFs with reduced environmental impact while maintaining high functionality. Environment benign procedures are not much explored and thus have created a lacuna in the field of MOFs for efficient drug delivery.

The incident radiation on a participating media undergoes two phenomena: attenuation and augmentation. Radiation attenuation comes from the effects of absorption and out-scattering (the deviation of the incident radiation to a direction other than the incident direction). On the other hand, radiation augmentation includes the effects of the re-radiation (emission) and in-scattering (increasing the scattering in the direction of the incident radiation). These two phenomena (attenuation and augmentation) are explained by the radiative energy source, which indicates the absorption behavior of a participating media.

Figure 6 shows the radiative energy source which is generated in the volume of participating media (nanoparticulate media). The boundaries of the volume are specified as follows: the upper face is a radiant source (1400 W/m^2), the lower face is adiabatic and reflects the incident radiation inside the volume of the nanosuspension, the side surface is adiabatic surfaces. The main objective is to observe the effect of the nanoparticles on the radiative transfer phenomena and to clarify the effect of particle concentration on the radiative heat generation in the participating media. The generated radiative energy inside a volume of participating media is one of the thermal applications which are desired for different engineering and industrial applications. The spectral properties of the participating media play a significant role in these applications.

CONCLUSION

The utilization of metal organic frameworks in designing novel drug delivery systems has become a field of immense interest towards the worldwide research community in the last decade. This computational review has quantitatively estimated all the research works done during the span of ten years (2014-2023). A total 3014 articles were resulted from the Bibliometrix-Biblioshiny package of r with the data retrieved from Web of Science Database related to the utilization of metal organic frameworks in drug delivery. A year-wise growth in the number of articles was evident, suggesting the growing interest of the research community towards developing new drug delivery systems using metal organic frameworks. In the global participation of the present research, China was found to produce the highest number of articles, followed by, Iran, USA, India, and Spain. In addition, the year-wise growth, as well as, inter-country collaboration was found to be maximized in case of China. On analyzing the sources of articles, 'ACS Applied Materials and Interfaces' was found to publish highest number of articles, followed by, 'Journal of Materials Chemistry B', 'Coordination Chemistry Reviews' and 'Dalton Transactions', all good international journals of chemical sciences. It is worthy to mention that, although 'Journal of American Chemical Society' published a smaller number of articles on MOF drug delivery research, the citation parameters were found to be highest in the articles published in this journal, signifying greater acceptability of their results towards the world-wide scientific community. Additionally, the analysis of top twenty most cited articles revealed that these articles were published in journals like 'Advanced Materials', 'Journal of American Chemical Society', 'Angewandte Chemie International Edition', 'Chemical Communications' etc.; all are high impact journals of international repute. The analysis of the keywords was executed in terms of frequency and year-wise growth. In addition to most obvious keywords, like, 'metal organic frameworks', 'mof', 'drug delivery', 'delivery', 'release' etc., 'nanoparticle' appeared as the most frequent unique keyword in our considered time frame. The utilization MOFs as nano carriers for drug molecules, as well as, designing novel drug delivery systems utilizing the MOFs might appears to be promising to result 'nanoparticles' as highly mentioned keywords. Moreover, the analysis of trend topics revealed new topics like 'immunotherapy', 'sonodynamic therapy', signifying the enhanced interest of modern therapeutic treatments for cancer employing MOFs. On analysing collaborative networks between countries, the highest collaboration was found to be in the articles from Peoples R China was found to possess greatest number of collaborations. The collaborations of Peoples R China with countries like USA, Australia, Iran, India, Singapore etc. is well established from the network structure. ACS Applied Materials and Interfaces, a very renowned journal, was found to publish highest number of articles with mention worthy citation links. The co-occurrences of keywords revealed 'nanoparticles' to be the most mentioned and most linked keywords in addition to the most obvious keywords. In spite of extensive work, little stress has been put in the in-vivo experiments, as well as, the environmental sustainability in synthesizing the MOFs. Thus, this computational analysis is expected to offer researchers a directed path in their early carrier research on metal organic frameworks in biomedical field.

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AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in the preparation of the article.

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