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RESEARCH PAPER

Unraveling the pulmonary drug delivery carriers in inhalable nanostructures

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Abstract Nano-systems (size range: 1 ~ 1000 nm) have been widely investigated as pulmonary drug delivery carriers, and the safety of inhaled nano-systems has aroused general interests. In this work, bibliometric analysis was performed to describe the current situation of related literature, figure out the revolutionary trends, and eventually forecast the possible future directions. The relevant articles and reviews from 2001 to 2020 were retrieved from the Web of Science Core Collection. The documents were processed by Clarivate Analytic associated with Web of Science database, Statistical Analysis Toolkit for Informetric, bibliometric online platform and VOSviewer, and the data were visualized. The bibliometric overview of the literature was described, citation analysis was performed, and research hotspots were showcased. The bibliometric analysis of 3362 documents of interest indicated that most of the relevant source titles were in the fields of toxicology, pharmacy, and materials science. The three research hotspots were the biological process of inhalable nano-systems in vivo, the manufacture of inhalable nano-systems, and the impact of nano-systems on human health in the environment. Toxicity and safety have always been the keywords. The USA was the major contributing country, and international collaboration and co-authorship were common phenomena. The general situation and development trend of literature of inhalable nano-systems were summarized. It was anticipated that bibliometrics analysis could provide new ideas for the future research of inhalable nano-systems.

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Introduction

Since the emergence of nanoscience and nanotechnology, various kinds of nano-systems have been designed and developed in the academy and industry, including but not limited to nanospheres (Ganganboina et al. 2021), nanomicelles (Rezaeisadat et al. 2021), nanotubes (Wu et al. 2021), nanowires (Dai et al. 2021), and nanosheets (Yang et al. 2021). Nowadays, it has become a consensus that there is an interplay between nano-systems and human health. This inference is supported by two facts: (I) nano-systems have been employed as versatile drug delivery carriers to treat different diseases (Alavi and Varma 2021) and (II) nano-systems of non-biomedical use in the environment can enter human bodies (Kong et al. 2021).

For drug delivery, nano-systems possessed the advantages of enhanced solubility (Telange et al. 2021), improved stability (Hasanovic et al. 2010), and controlled release (Qiu et al. 2021) of the loaded drugs. They are widely reported in the literature for the therapy of local and systemic diseases, with encouraging in vitro and in vivo outcomes (Zhao and Liu 2018). For non-biomedical use, nano-systems have been utilized in various trades of industries, e.g., chemical industry (Zhu et al. 2016), food industry (Sun et al. 2018), and electronic industry (Tan et al. 2019). During the manufacture, distribution, and use of the relevant products, nano-systems will inevitably release into the environment and finally enter the human body. No matter what functions they possess, nano-systems will be regarded as xenobiotics by the body (Ruzycka-Ayoush et al. 2021), and interactions will take place between nano-systems and biomolecules, organelles, cells, tissues, and even organs (Muraca et al. 2020). Therefore, the impact of nano-systems on human health should be scrutinized, and it has attracted increasing attention from the science community.

It should be noted that there were many approaches for nano-systems (both for drug delivery and non-biomedical use) to enter the human body, for instance, oral, injection, transdermal, etc. (Delshadi et al. 2021). In recent decades, inhalation as an intake approach for nano-systems has turned to be a research hotspot. On the one hand, nano-systems for inhalation can augment the accumulation of the drug in the lesion site, which is favorable for the treatment of pulmonary diseases (Kaur et al. 2021). On the other hand, the inhaled nano-systems in the environment may cause severe pulmonary diseases like lung fibrosis (Wang et al. 2017) and silicosis (Liu et al. 2012), particularly for the less degradable ones. It is of great significance to further investigate the inhalable nano-systems for their applicability of drug delivery and safety aspects.

There are many studies reporting the drug delivery and safety aspects of inhalable nano-systems. Their main research topics lie in (I) functional drug-loaded nanocarriers for inhalation were developed, for the therapy of respiratory diseases and systemic diseases (Muralidharan et al. 2015), and (II) toxicities of inhaled nanoparticles, both for drug delivery and non-biomedical use, were intensively assessed (Bakand and Hayes 2016). These two topics may be associated with many disciplines, like pharmaceutical, toxicological, material, and environmental sciences. Relevant researches have advanced the understanding of inhalable nano-systems and paved the way to the better manipulation of nanotechnologies.

In order to summarize the current status of the researches on inhalable nano-systems in the last two decades (2001 ~ 2020), figure out the revolutionary trends, and finally indicate the possible directions for future studies, this work performed bibliometric analysis to describe the overall bibliometric profiles and refine the publication trends. It was anticipated that this paper could present the whole framework of the researches on inhalable nano-systems from a bibliometric perspective and might provoke new ideas in this field.

Methods

Documents retrieving

Document retrieving was performed at 12 a.m., May 14, 2021 (UST + 8 time zone). The documents of interest were retrieved from the Science Citation Index-Expanded collection in Web of Science Core Collection, with the search set of "topic = nanoparticl*" AND "topic = inhal*." The type of documents was restricted to "article" and "review" and the publication time 2001 ~ 2020. The duplicates were precluded. The retrieved documents were exported in the form of "full record and cited references" as plain text or tab delimited (Win, UTF-8) files.

Bibliometric analysis

The documents were processed by Clarivate Analytic associated with Web of Science database, Statistical Analysis Toolkit for Informetric (SATI, version 4.0), bibliometric online platform (https://bibliometric.com/), and VOSviewer (version 1.6.16, https://www.vosviewer.com). The data were visualized by the embedded module of the tool or graphing software (GraphPad Prism).

(1) Publication years, organizations, funding agencies, authors, source titles, countries/regions, languages and research areas of the documents, and the citing papers thereof were analyzed by Clarivate Analytic.
(2) The word cloud figures and time evolution of keywords were obtained from SATI (Liu et al. 2012).
(3) The number of documents from top 10 countries/regions over time and cooperation relationship between countries/regions was visualized by bibliometric online platform.
(4) Co-authorship, co-citation, bibliographic coupling, and co-occurrence were analyzed by VOSviewer. In order to ensure the concise visualization outcome, the filtration thresholds were set with relatively high criteria, and only the most relevant results (30 ~ 60 items) were involved in these analyses (Chen et al. 2021). Full counting was used as the counting method.

Results

Totally, 3362 documents with the topic of inhalable nano-systems were retrieved from the Science Citation Index-Expanded collection in Web of Science Core Collection, which were analyzed in detail to discover the publication tendencies; demographics: open access, 1411; subscription, 1951; article, 2861; review, 501.

Bibliometric profiles

The word cloud figures were shown in Section 1 of Supplementary data, which intriguingly described the 3362 documents. Quantitative bibliometric analyses were further launched. The number of publications over the year was depicted in Fig. 1. In 2001, the first two papers were published. Within 2002 ~ 2004, the number of publications was lower than 10 per year. After 2005, the number substantially increased, and a continuous growing trend was shown. The number reached 400 in 2020 and was believed to raise afterwards.

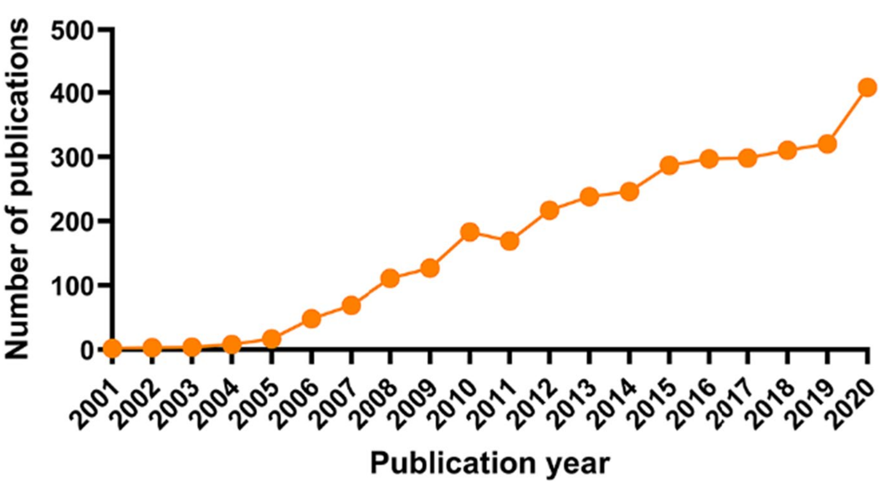

Fig. 1 The number of publications over a year of the retrieved 3362 documents

The top 10 research areas of the documents were shown in Fig. 2, viz. toxicology, pharmacology & pharmacy, science & technology: other topics, chemistry, environmental sciences & ecology, materials science, engineering, public environmental & occupational health, physics, and biochemistry & molecular biology. These research areas could be roughly categorized into three groups: (I) pharmacological and toxicological aspects, about the in vivo processes of inhalable nano-systems (Liu et al. 2020); (II) material aspects, about the fabrication of inhalable nano-systems (Ma et al. 2021); (III) public environmental aspects, about the impact of nano-systems in the environment on human health (Creutzenberg et al. 2012). There were 1668, 784, and 569 documents associated with pharmacological and toxicological, material, and public environmental aspects, respectively. It was indicated that investigators from pharmacological, material, and public environmental fields paid much attention to such a topic.

According to Fig. 2, the majority of the 3362 documents were in English (3324, 98.87%), and a minority of them were in other languages (38, 1.13%, including Polish, German, Chinese, etc.). The use of English was favorable for international communication on the topic of inhalable nano-systems.

Subsequently, the contributing countries/regions for the documents were analyzed, and the results were illustrated in Fig. 3. For simplicity, countries/regions contributing at least 20 documents were listed. The USA contributed 1012 documents, ranking as the top 1 country/region. Germany (top 2) and China (top 3) published more than 400 items. The 4th ~ 14th countries/regions credited over 100 papers, and 20 ~ 100 papers were contributed by the 15th ~ 36th countries/regions. It was revealed that the main contributing centers were North America (representing countries/regions: USA and Canada), Europe (representing countries/regions: Germany and England), and East Asia (representing countries/regions: China and Japan). Some related but peripheral data could be found in Section 2 of Supplementary data.

The sum of documents contributed from each country/region was 4798, exceeding the total number of documents (3362). This suggested that a significant proportion of documents were co-contributed from more than one country/region. In other words, international collaboration might be a common phenomenon in the research area of inhalable nano-systems. The international collaboration situation was showcased in Fig. 3. The connecting lines between countries/regions meant there were cooperated papers, and the boldness of connecting lines was associated with the number of cooperated papers.

Evidently, the international collaboration was quite universal. Most countries/regions participated in the international collaboration, especially the top 10 contributors. For instance, 1st the USA, 2nd Germany, and 3rd China separately collaborated with over 10 countries/regions, and the 4th ~ 10th also established at least 3 international cooperation tiles. Other countries/regions, with very few exceptions, also participated in the global collaboration. Moreover, neighboring regions collaboration (e.g., USA and Canada), intracontinental collaboration (e.g., Romania and Poland), and intercontinental collaboration (e.g., China and UK) were observed. The most intense cooperation took place in China-Australia,

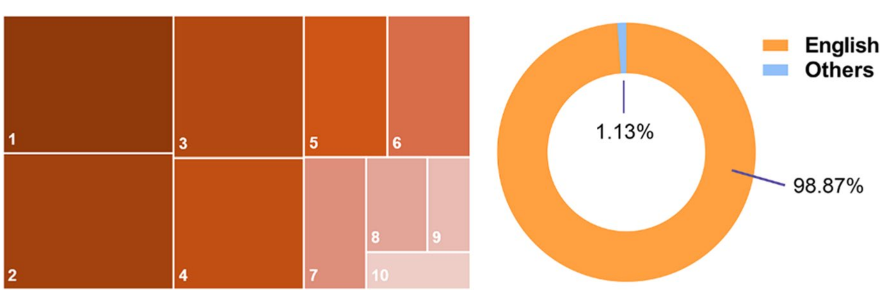

Fig. 2 Top 10 research areas (left; 1: toxicology, 2: pharmacology & pharmacy, 3: science & technology: other topics, 4: chemistry, 5: environmental sciences & ecology, 6: materials science, 7: engineering, 8: public environmental & occupational health, 9: physics, 10: biochemistry & molecular biology) and language distribution (right) of the retrieved 3362 documents

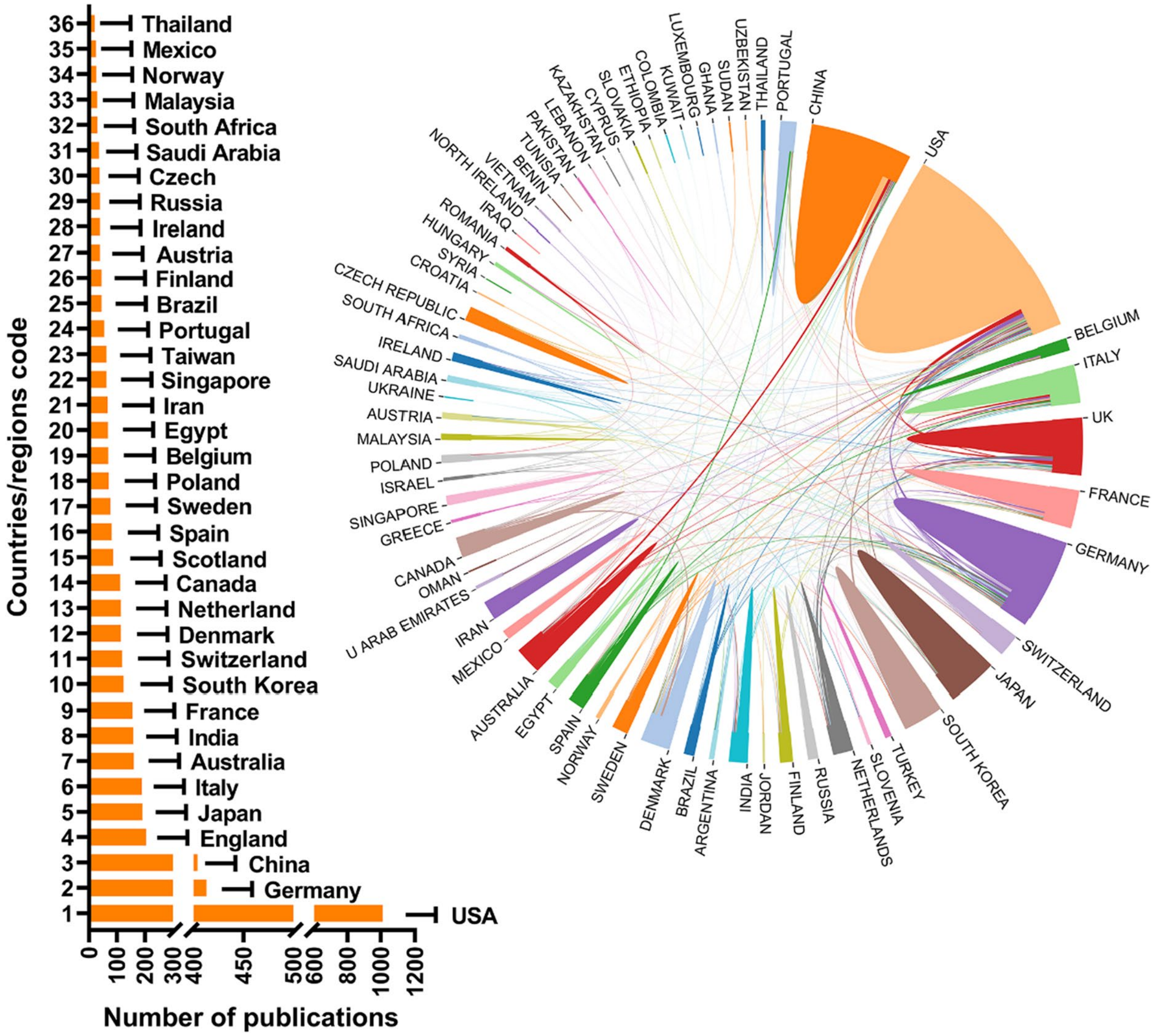

Fig. 3 The profile of countries/regions contributing at least 20 documents (left) and international collaboration in the topic (right) of the retrieved 3362 documents

Spain-Portugal, China-USA, USA-UK, USA-Germany, and UK-Netherlands. Overall, the investigators in this field tended to be willing to cooperate.

In each country/region, the documents were contributed by different organizations (universities, institutes, associations, and companies). In this case, the 3362 documents were contributed by 3008 organizations. Indicated by the active cooperation scenarios (Fig. 3), there were widespread collaborations among the 3008 organizations. The top 10 contributing organizations were shown in Table 1. Although the USA was the top 1 contributing country/region and National Institute for Occupational Safety & Health (NIOSH) ranked as top 1, only one organization of USA appeared in the top 10 list. Three organizations of Denmark ranked in the top 10, while Denmark was the 12th contributing country/region. Two organizations of Japan (2nd contributing country/region) were on the list. Other organizations were located in China, Australia, Germany, and Scotland. Interestingly, three organizations about occupational health were included in the top 10, i.e., NIOSH, National Research Centre for the Working Environment, and University of Occupational Environmental

Table 1 Top 10 contributing organizations of the retrieved 3362 documents (the country/region of an enterprise was determined by the location of its headquarter)

No	Organization name	Country/region	Number of documents	Percentage (%)
1	National Institute for Occupational Safety & Health (NIOSH)	USA	107	3.18
2	National Research Centre for the Working Environment	Denmark	79	2.35
3	Chinese Academy of Sciences	China	73	2.17
4	Technical University of Denmark	Denmark	60	1.78
5	University of Copenhagen	Denmark	57	1.70
6	The University of Sydney	Australia	46	1.37
7	National Institute of Advanced Industrial Science & Technology	Japan	45	1.34
8	University of Occupational Environmental Health	Japan	44	1.31
9	BASF SE	Germany	43	1.28
10	The University of Edinburgh	Scotland	42	1.25

Health, which indicated that the impact of inhalable nano-systems existing in the working environment on human health was a vital research focus.

The 3362 documents were published in 670 academic journals, 5.02 documents per journal averagely. Those source titles associated with 20 or more papers were listed in Fig. 4. The journals *Particle and Fiber Toxicology*, *Nanotoxicology* and *International Journal of Pharmaceutics* published over 100 papers, and *Inhalation Toxicology Journal of Nanoparticle Research*, *European Journal of Pharmaceutics and Biopharmaceutics*, *Journal of Controlled Release* and *International Journal of Nanomedicine* published 50 ~ 100 papers. It was

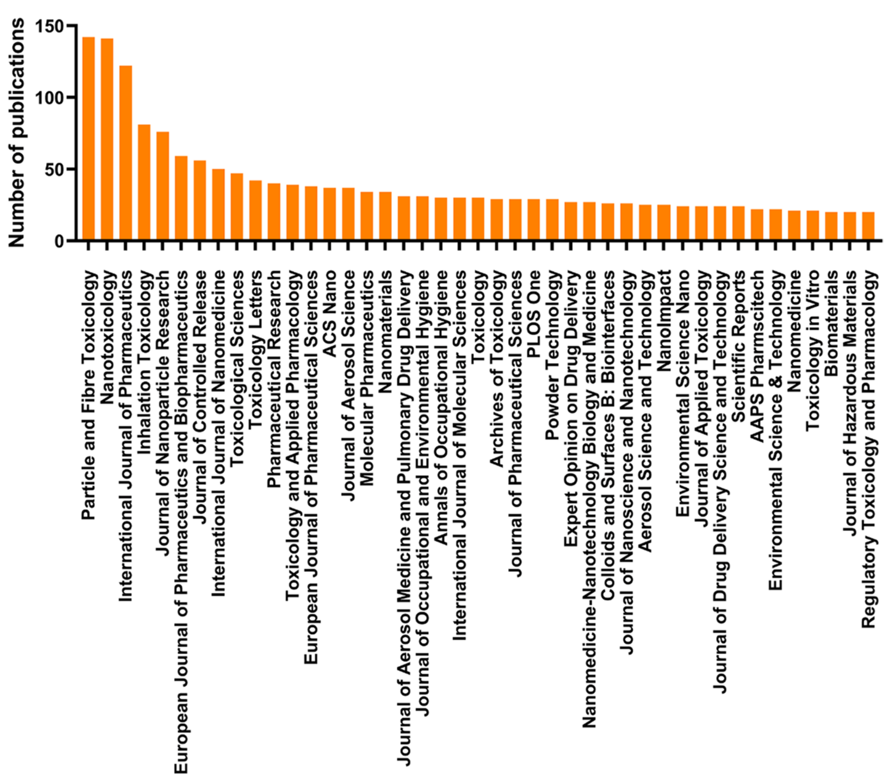

Fig. 4 The profile of source titles associated with at least 20 documents of the retrieved 3362 documents

exhibited that the source titles related to most documents were in the region of toxicology, pharmacy, and materials science. The rest of the journals published 20 ~ 50 papers, and those about public health and environmental health emerged herein. The research interests of the journals were basically in consistency with the major research areas displayed in Fig. 2. In addition, the 43 source titles in Fig. 4 were associated with 1741 documents, accounting for a percentage of 51.78%; the else 627 source titles occupied a proportion of 48.22%. Within the 43 journals, the top 10 published 816 papers, which was 46.87% of 1741 and 24.27% of 3362. The listed 43 journals, especially the top 10, could be viewed as the main publication platform for the researches on inhalable nano-systems. For future studies, it was advisable to choose these publication platforms.

In total, 12,059 researchers appeared on the author lists of the 3362 documents, which was 3.59 authors per document. Co-authorship was a common phenomenon in the field of inhalable nano-systems. This was in accordance with the active collaboration status between countries/regions and organizations. The authors contributing to at least 20 documents were summarized in Fig. 5. The number of documents contributed by each author did not vary at a large scale. Castranova V. (from West Virginia University, USA) and Vogel U. (from National Research Centre for the Working Environment, Denmark), as the top 2 authors, published over 50 papers, and the other authors contributed 20 ~ 50 papers.

Furthermore, the funding agencies of the 3362 documents were analyzed. The top 10 funding agencies were exhibited in Table 2. Six funding agencies

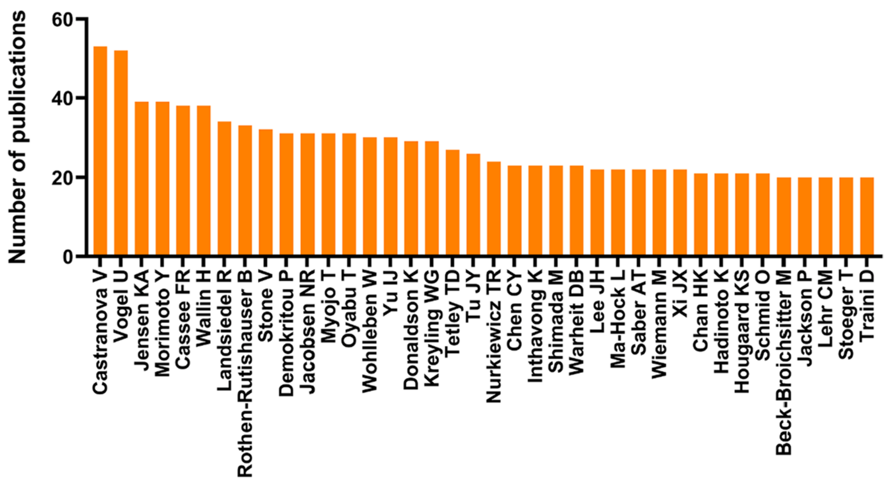

Fig. 5 The profile of authors publishing at least 20 documents of the retrieved 3362 documents

Table 2 Top 10 funding agencies of the retrieved 3362 documents

No	Funding agency name	Country/region	Number of documents	Percentage (%)
1	United States Department of Health Human Services	USA	464	13.80
2	National Institutes of Health (NIH)	USA	433	12.88
3	European Commission	Europe	277	8.24
4	National Natural Science Foundation of China (NSFC)	China	262	7.79
5	NIH National Institute of Environmental Health Sciences	USA	209	6.22
6	National Science Foundation	USA	149	4.43
7	NIH National Heart Lung Blood Institute	USA	109	3.24
8	UK Research Innovation	UK	90	2.68
9	Ministry of Education, Culture, Sports, Science and Technology	Japan	77	2.29
10	Centers for Disease Control and Prevention	USA	62	1.84

were in the USA, and the others were in Europe, China, the UK, and Japan. The firm financial supports from these agencies accounted for the fruitful contributions of the corresponding countries/regions.

Citation patterns

In addition, the *H*-index of the 3362 documents was 153, which was a high value in comparison (Chen et al. 2020; Lin et al. 2020 Sweileh and Moh'd Mansour A, 2020). According to the definition of the *H*-index (Bihari et al. 2021), 153 documents were cited for 153 times or more, and 3209 documents were cited for less than 153 times. Within Web of Science database, the documents were cited by 56,394 publications (16.77 citing publications per document).

The citing papers were firstly published in 2002 and continued increasing until 2020 (Fig. S6). Toxicological, pharmaceutical, and material journals were the main publication media for the citing papers, in parallel to the scenario of original papers; however, the weight of pharmaceutical and material journals increased and that of toxicological journals decreased (Tab. S1). These citing papers were contributed by the USA, China, India, Germany, Italy, England, South Korea, and France (the top 10 countries/regions in Fig. 3), and Iran, Spain, and other countries/regions (Tab. S2). As seen from Fig. S7, the top 10 research areas were basically in accordance with Fig. 2, but the focus shifted from toxicology to chemistry. For the top 10 contributing organizations (Tab. S3), 5 were Chinese organizations (Chinese Academy of Sciences, University of Chinese Academy of Sciences, Zhejiang University, Peking University and Southeast University), 2 were USA organizations (NIOSH and Harvard University), and 3 located in other countries/regions (King Saud University, National University of Singapore and University of Copenhagen). Over 99% of the citing publications were in English (Fig. S8). There were 3, 5, and 2 funding agencies ranking top 10 from China, the USA, and Europe, respectively (Tab. S4). The results of citation performance were shown in Section 3 of Supplementary data. Please refer to it for detailed information.

Comparing the profile of original and citing documents, two major differences were witnessed. First, the top emphases of original and citing papers were in toxicological and chemical aspects, respectively. Second, the USA made a dominant contribution to the original papers while the participation of China substantially enhanced in the citing papers.

Publication trends

With the purpose of mining the publication trends in the field of inhalable nano-systems, the keywords of the 3362 documents were extracted, and the time evolution of the frequency was plotted versus time, shown in Fig. 6. The term "frequency" was defined by the occurring time of a certain keyword divided by the total number of keywords. In this study, the 1st ~ 20th high-frequency keywords were included.

From Fig. 6, it could be seen that the keywords were related with toxicology (nano-toxicology, cytotoxicity, etc.), pharmacology (oxidative stress, inflammation, etc.), drug delivery (dry powder inhaler, spray dry, etc.), and materials science (nanomaterial, titanium dioxide, etc.). The toxicology evaluation and formulation design of inhalable nano-systems were hot topics. Noticeably, dry powder inhalers as the delivery approach of nano-systems (Dolatabadi et al. 2015) and titanium dioxide as the model inhalable nano-systems for toxicological tests (Grassian et al. 2007) were intensively reported.

The keyword "nanoparticle" maintained a high frequency within 2001 ~ 2020, the frequencies of "pulmonary delivery," "aerosol," "lung," and "drug delivery" were relatively high in the early period (2001 ~ 2003) but dropped after that, and else keywords showed a certain level of frequency since 2004. Although a quantitative evolution path was shown, information obtained from this analysis was to some extent limited. Many keywords in Fig. 6 were not meaningful for publication trends investigation, like "nanoparticle," "nanomaterial," and "inhalation" that were deviated words to the topic "inhalable nano-systems." Worse still, the frequencies in the recent decade were quite similar in every keyword except for "nanoparticle," and it was impractical to differentiate them. Therefore, further mining should be conducted to reveal the publication trends.

To this end, bibliometric clustering and mapping were performed via a Java-based VOSviewer program (Eck and Waltman 2010). The co-authorship, co-citation, bibliographic coupling, and co-occurrence (keywords or terms) were visualized. Herein, the number of items involved in the visualization was controlled

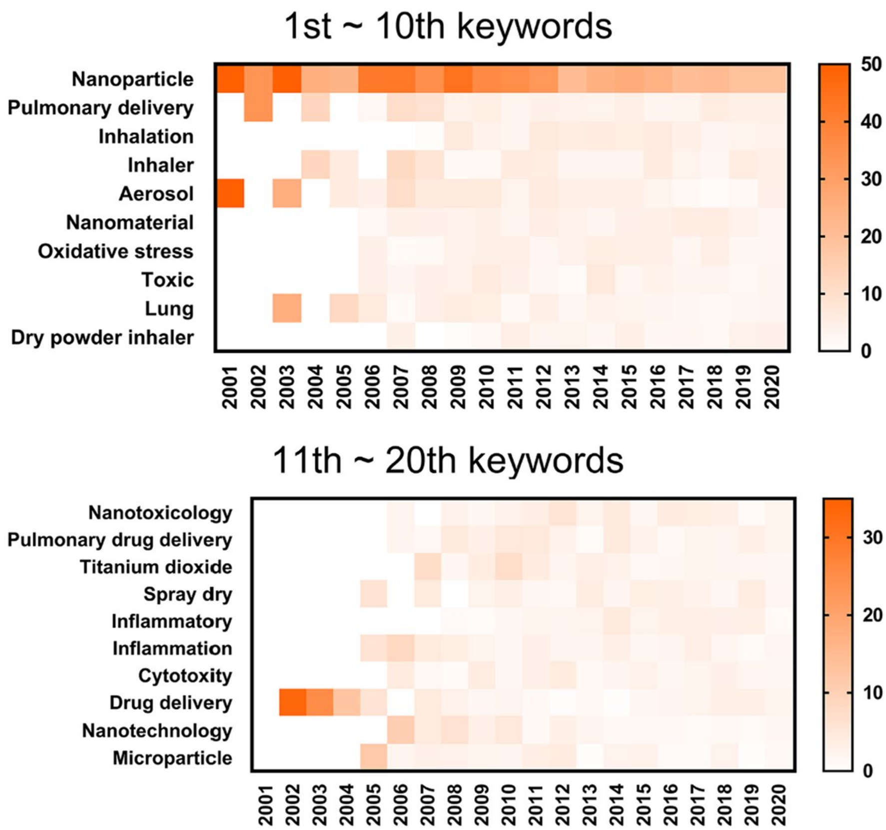

Fig. 6 The time evolution of the frequency (occurring time of a certain keyword divided by the total number of keywords) of 1st ~ 20th keywords of the retrieved 3362 documents (up: 1st ~ 10th; down: 11th ~ 20th)

to be 30 ~ 60, so as to assure the readability of figures. For the visualization results of all documents, please refer to Section 4 of Supplementary data.

The co-authorship profile was visualized in Fig. 7. The density of most zones of authors was high, which meant that these authors (Castranova V., Vogel U., et al.) published a considerable number of papers in this field. Warheit D.B. and Traini D. did not cooperate with other authors in Fig. 7, existing as isolated zones. Yu I.J. cooperated with Lee. J.H., but no other authors. Castranova V., Vogel U., Wang Y., Wohlleben W., and Inthavong K. et al. acted as the "connecter" of different clusters and actively participated in the cooperation.

It was worth mentioning that Castranova V. et al. had been in the community for a long period, Vogel U. et al. joint it later, and Inthavong K. et al. were new participants, according to the mean time overlay profile (Fig. 7, lower panel): 2012 for Castranova V. et al., 2016 for Vogel U. et al., and 2017 for Inthavong K. et al., respectively. It was shown that emerging investigators continuously took part in the study of inhalable nano-systems, which was an encouraging condition for sustainable development.

Co-citation clustering which unraveled the co-cited documents (including the provided set and external documents (Boyack and Klavans 2010)) was performed. In co-citation clustering, usually, the older documents whose citations had been accumulated for a longer period were included, and thus, the development foundation could be revealed. As depicted in Fig. 8, all documents were published in 2010 or earlier, and four high-density centers were observed, the zone of this literature (Bermudez et al. 2004; Kreyling et al. 2002; Nel et al. 2006; Oberdorster et al. 2005; Oberdorster et al. 2004; Patton and Byron 2007) (upper panel). These documents were frequently cited by other documents, indicating that they imposed critical inspiration for the study of inhalable nano-systems.

Correspondingly, four clusters were formed: clusters 1 (8 documents), 2 (8 documents), 3 (7 documents), and 4 (7 documents) were marked in red, green, blue, and yellow, respectively (Fig. 8, lower

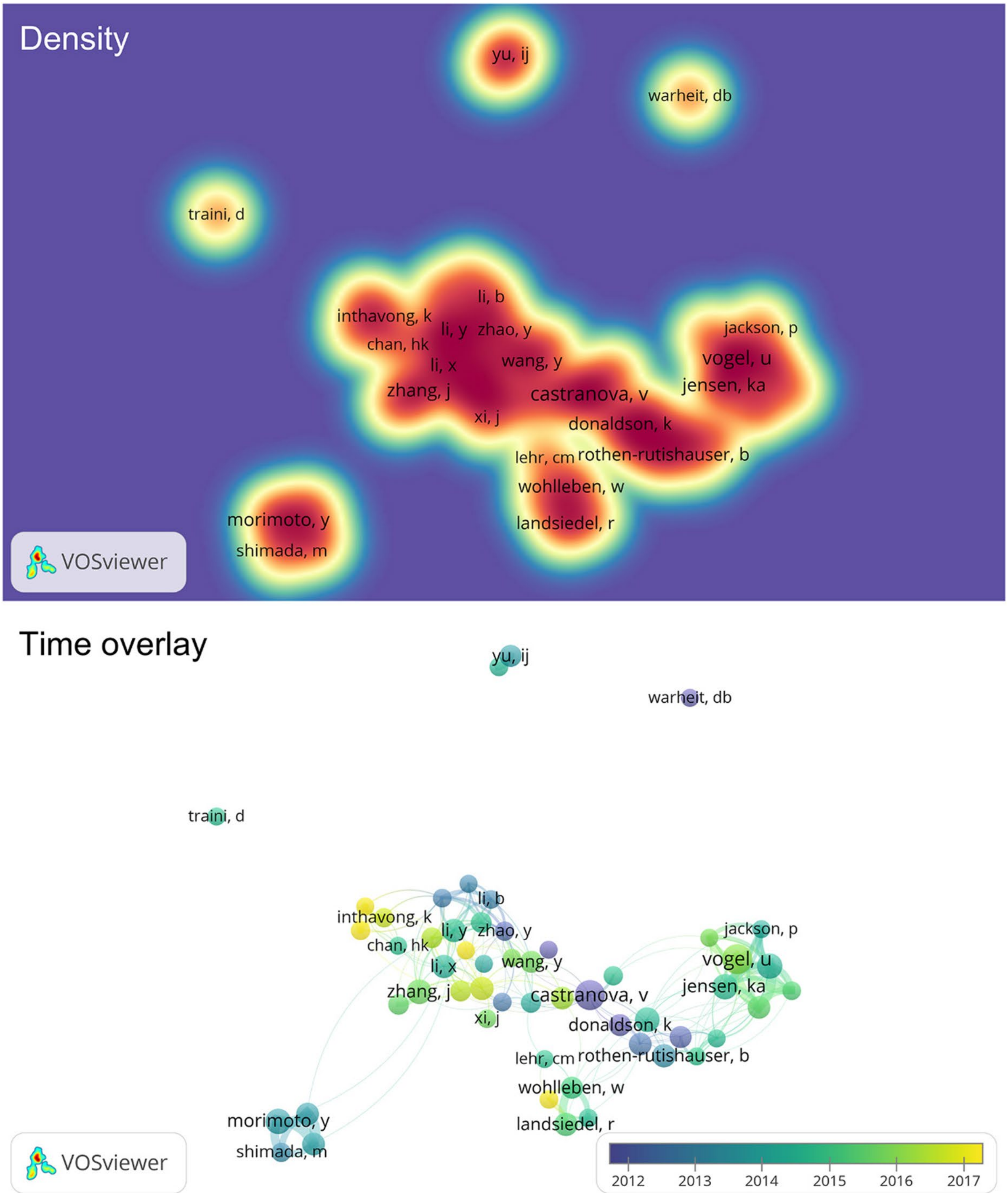

Fig. 7 Density (up; colored by the number of publications) and time overlay (down; colored by the mean publication time) visualization of co-authorship (54 items displayed)

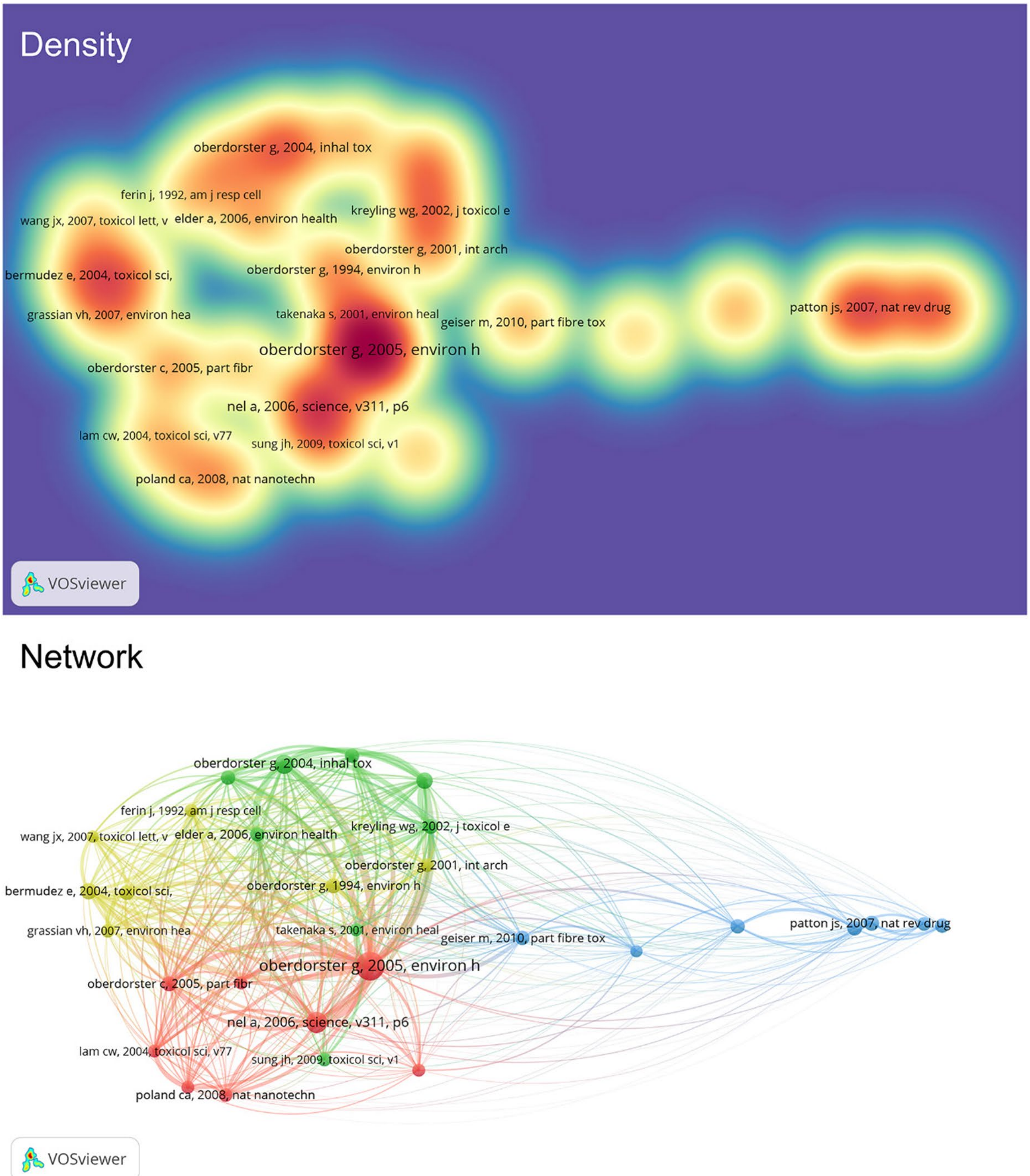

Fig. 8 Density (up; colored by the number of publications) and network (down; colored by the similarity of documents) visualization of co-citation (30 items displayed)

panel). Except for cluster 3 where the topic of pulmonary drug delivery was intensively discussed, the other three clusters were associated with toxicological studies. It was further envisioned that the documents citing them were in the field of toxicology and drug delivery.

To compensate for the flaw of co-citation clustering that mainly included older documents, the analysis for newer documents, bibliographic coupling was also conducted (Luo et al. 2020). Bibliographic coupling could be used to study the topic similarity and relationship among the documents and further showcase the evolutionary tendencies of the frontier (Li et al. 2017). The bibliographic coupling results of the researches on inhalable nano-systems were illustrated in Fig. 9. All documents revealed a certain degree of topic similarity, and the work of Nel A. in 2006 (Nel et al. 2006) that was a review in the field of toxicology exhibited a particularly high degree of connection with other documents, acting

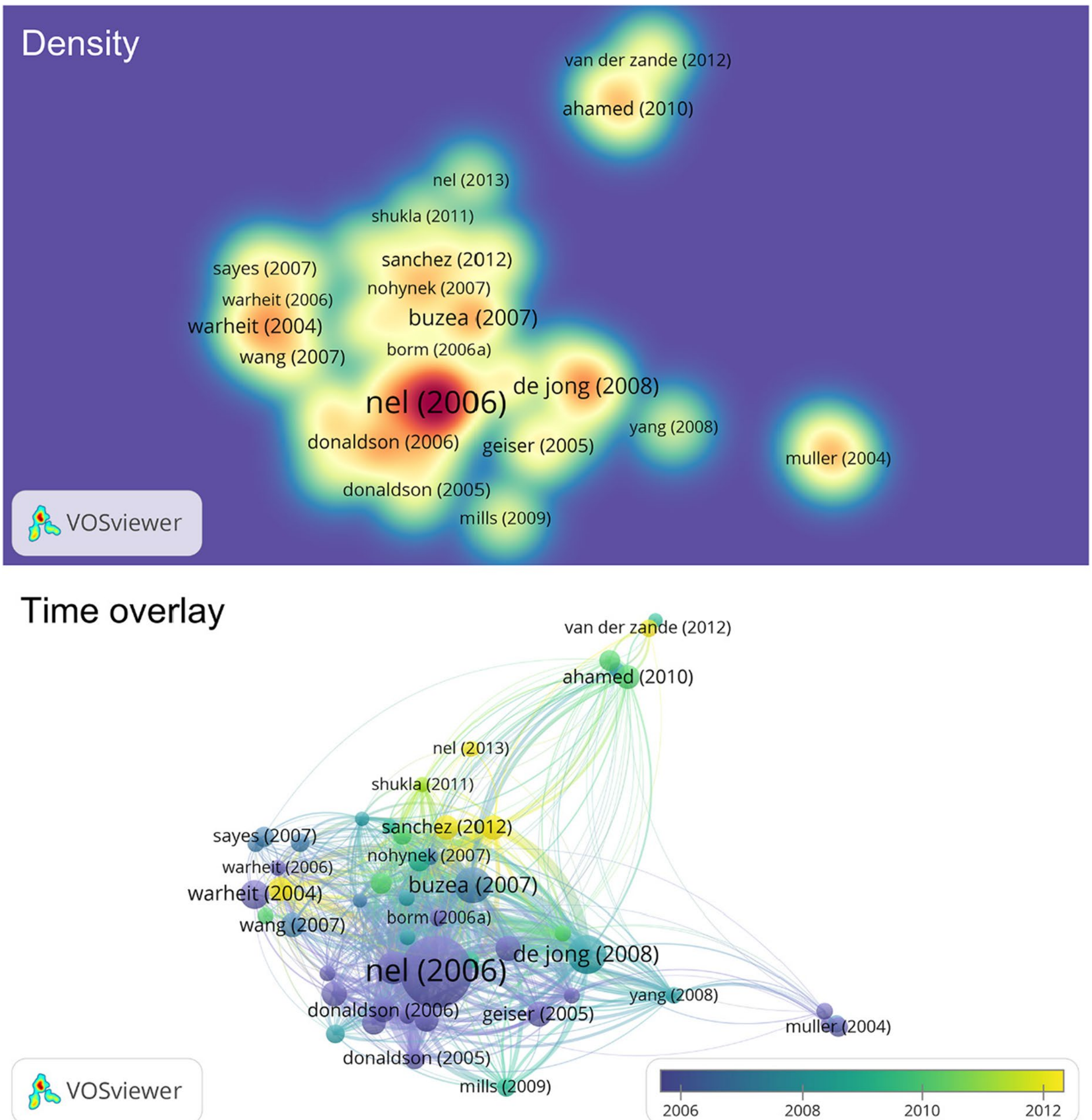

Fig. 9 Density (up; colored by the number of publications) and time overlay (down; colored by the mean publication time) visualization of bibliographic coupling (50 items displayed)

as the cluster core. In the proximity, the documents by Donaldson K. at 2005 (Donaldson et al. 2005) and at 2006 (Donaldson et al. 2006), and Borm P. at 2006 (Borm et al. 2006) were also toxicological articles or reviews. Furthermore, the documents like (Geiser et al. 2005) were in the pharmacological perspective. With a certain distance to the cluster core, the documents by De Jong W.H. (Jong and Borm 2008) and Mills N.I. (Sanchez et al. 2012) discussed the aspects of drug delivery and environmental health, respectively, but were still associated with safety concerns. Accordingly, the major topic in the field of inhalable nano-systems was the toxicity and safety issues, the impact of inhaled nanoparticles on the physiological pathways was also frequently studied, and drug delivery and environmental considerations were less involved.

From the time overlay profile in Fig. 9, it was revealed that the documents with intense coupling behaviors were mostly published before 2012. Similar topics had generated for a relatively long period in this field, which was mainly about the safety of inhaled nanoparticles. For the more recent documents marked in pale yellow, i.e., (Meike et al. 2012; Nel et al. 2012; Sanchez et al. 2012; Sharifi et al. 2012; Shi et al. 2013), the major topic was still toxicity. It could be concluded that the toxicity evaluations and the mechanisms thereof were comprehensively reported and achieved maturity.

Finally, the detailed evolution trends were evaluated by the co-occurrence of keywords and terms, and the results were shown in Fig. 10 and Fig. 11, respectively. In the keywords co-occurrence mapping (Fig. 10), there were three high-density centers: (I) nanoparticles, inhalation, particles, in vitro, and size. It meant that the in vitro assessment of inhalable nano-systems was widely reported, and the influence of size on the in vitro and in vivo performance was also discussed; (II) toxicity and ultrafine particles. “Ultrafine particles” was a previously used term for nanoparticles, and toxicity was a hotspot; (III) inflammation, exposure, and oxidative stress. The impact of inhalable nano-systems on the physiological pathways was intensively explored. Besides, the keywords “pulmonary delivery” and “drug-delivery” reflexed the studies on inhalable nano-systems for pulmonary drug delivery, and the keywords “mice” and “rat” suggested that rodents were the dominant animal models in related studies.

According to the lower panel of Fig. 10, most high-frequency keywords were marked in blue or green, suggesting that they were more frequently discussed in the early years (before 2015). The recently discussed keywords (marked in yellow) were inhalation toxicity, nanomaterials, titanium dioxide nanoparticles, silver nanoparticles, gold nanoparticles, and particulate matter. It was inferred that the types of model inhalable nano-systems were continuously expanding, and the toxicity of which was an enduring topic.

The co-occurrence of terms was visualized in Fig. 11. Basically, the density graph was bisected into two parts. The left part and right part were the terms about pharmacological tests and formulation development, respectively. There was a bridging section of these two parts, where the terms about the risk to human health of nanomaterials located, meaning that the safety issues were the common concern in the regions of pharmacology and drug delivery. Interestingly, in this analysis, the weight of the research area of drug delivery was significantly higher than all aforementioned examinations. The reason might be as follows. In the field of drug delivery, the weight was certainly high; in the field of materials science, most studies were to develop new systems for drug delivery; even in the fields of pharmacology and toxicology, the nanoparticulate drug delivery systems should be fabricated and then used in the in vitro studies and in vivo studies. The fabrication process was somehow associated with pharmaceutical development. Hence, the majority of documents would include drug delivery-related contents.

Regarding the time overlay profile in the lower panel of Fig. 11, the mean publication times were generally after 2014, and those of many terms were after 2015, revealing an emerging trend of the terms. The emerging terms after 2015 mainly included “review,” “development,” “treatment,” “administration,” and “expression.” It was suggested that (I) the formulation development of inhalable nano-systems; (II) the use of inhalable nano-systems in the disease therapy; and (III) the gene-level impact of inhalable nano-systems were hotspots in the area, and recently, some important review papers were published. Interestingly, “multi-wall carbon nanotubes (MWCNT)” was also an emerging term. Combined with the older terms like “silver nanoparticle”, it could be inferred that the type of nanomaterials subjected to the studies was also emphasized.

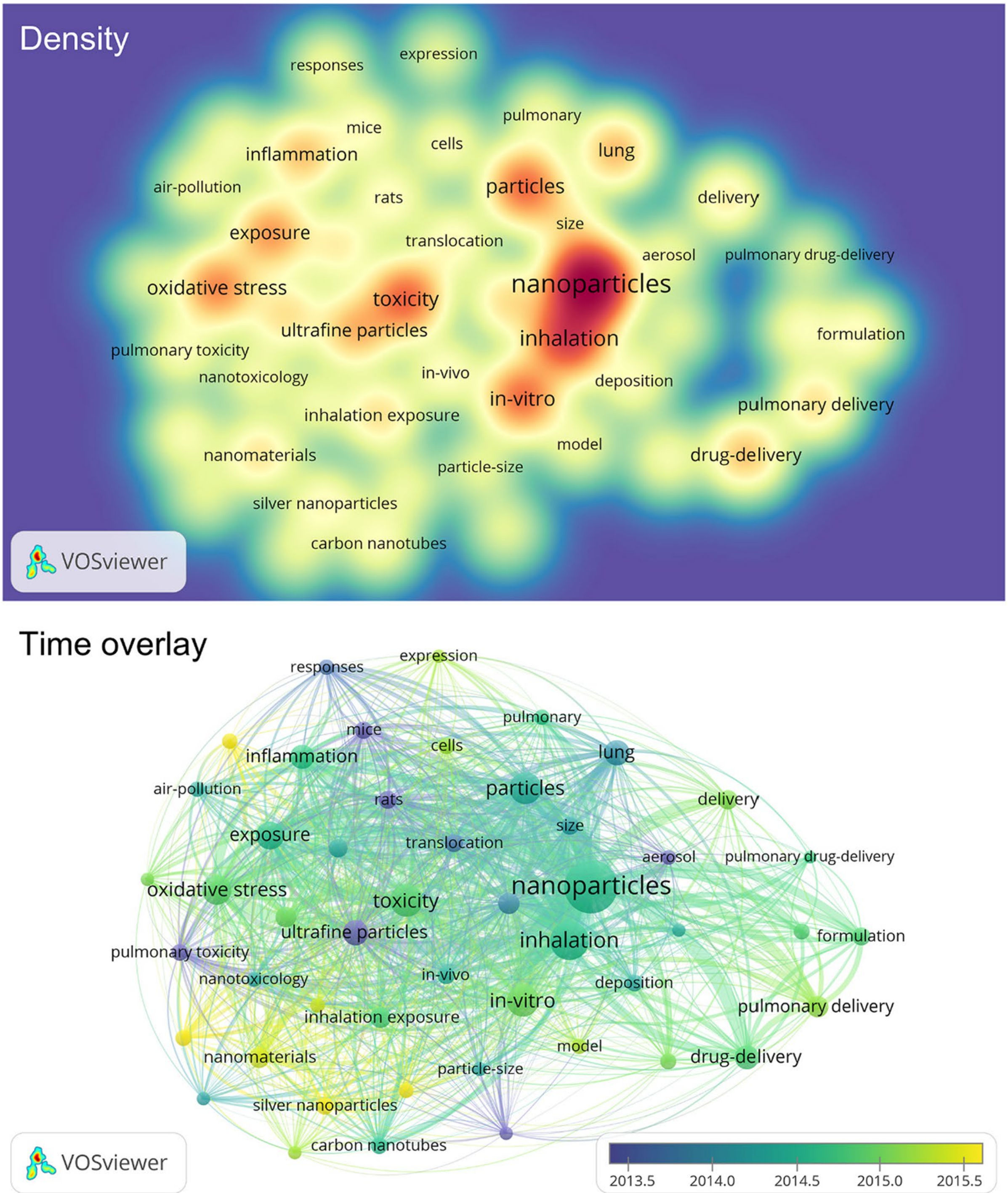

Fig. 10 Density (up; colored by the number of publications) and time overlay (down; colored by the mean publication time) visualization of keywords co-occurrence (49 items displayed)

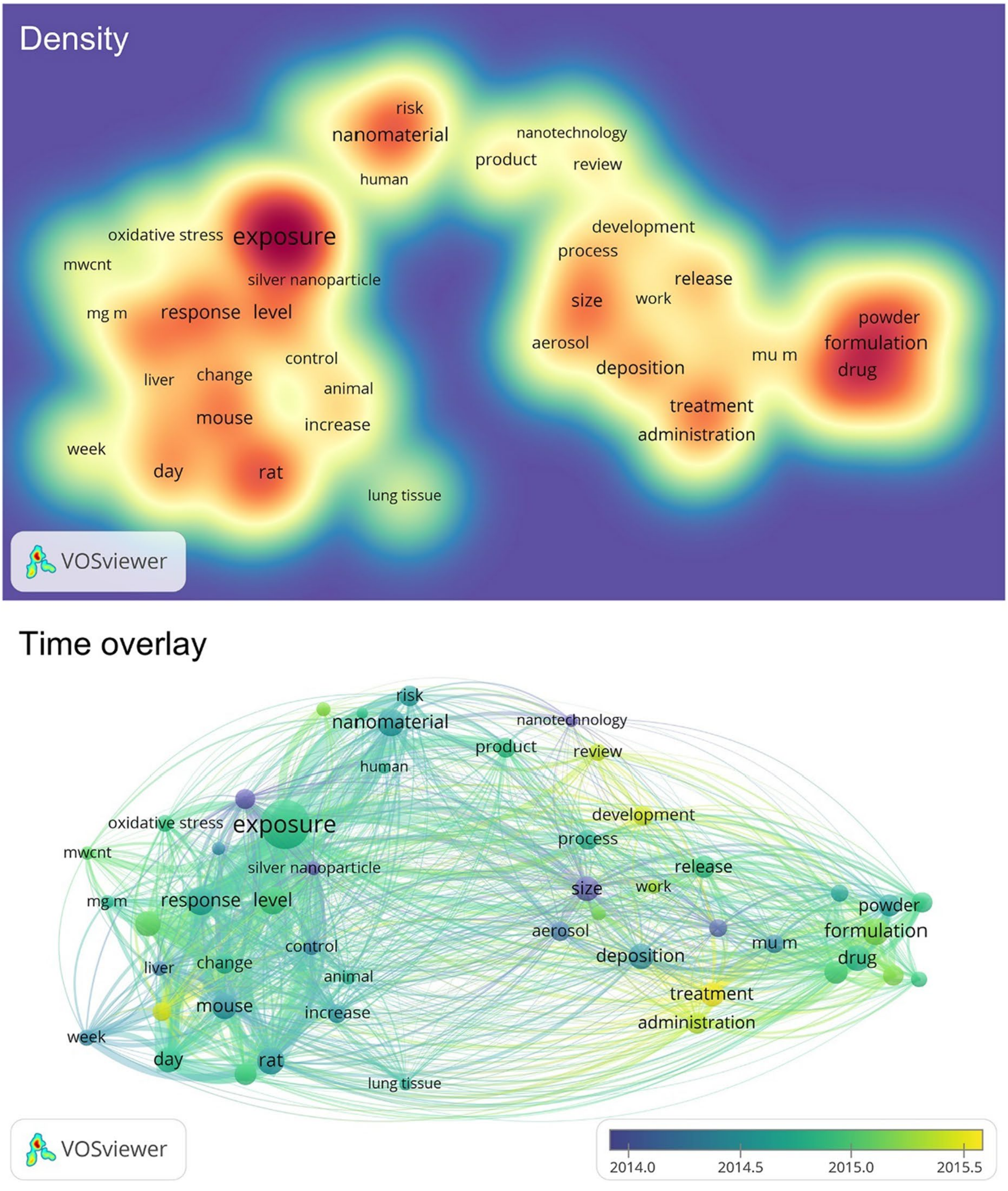

Fig. 11 Density (up; colored by the number of publications) and time overlay (down; colored by the mean publication time) visualization of terms co-occurrence (50 items displayed)

Discussion

Current status

In the former sections, the current status of the researches on inhalable nano-systems was scrutinized. It was clearly shown that the toxicology of inhalable nano-systems was the dominant topic in this field. Due to the low amount and activity of enzymes in the lung and the thin epithelium of alveoli (Ruaro et al. 2021), the inhaled nano-systems, either for drug delivery and non-biomedical use, might not undergo a significant degradation process in the lung region and be absorbed into the circulation. Besides, compared with other absorption sites, the lung was vulnerable to foreign stimuli. Therefore, safety risk would probably be induced by the inhaled nano-systems. This accounted for the high interest from the toxicology discipline. The current publishing hotspots included the in vitro and in vivo toxicity evaluation models, cell/gene/molecular-level toxicological pathways, and toxicity tests on different nanomaterials. Also, the environment discipline was involved, as there was an unneglectable number of nano-systems for non-biomedical use in the environment, which might enter the human bodies.

Inhalable nano-systems as drug delivery carriers were another hot topic in the field. The production, characterization, pharmacokinetics, and pharmacodynamics of the carriers were reported. These carriers were generally endowed with two kinds of functions, viz. lung retention to treat pulmonary diseases like lung cancer (Jin et al. 2021) and epithelium penetration to treat systemic diseases like diabetes (Al-Qadi et al. 2012). For both functions, the superiorities of enhanced solubility, improved stability, and controlled release of cargoes of inhalable nano-systems were utilized. The low-enzyme environment and thin epithelium in the lung facilitated lung retention and epithelium penetration, respectively. Hence, nano-systems were a prospective approach for drug delivery, which explained the related research interests.

A common research trend for both safety and drug delivery aspects was that more categories of nanomaterials were introduced to the list of inhalable nano-systems, e.g., MWCNT (Migliaccio et al. 2021) and metal–organic frameworks (MOF) (Fernández-Paz et al. 2021), whose toxicities and therapeutic efficacies were evaluated.

Promising topics

On the basis of the current status, several promising topics of inhalable nano-systems could be proposed. As the toxicological studies were quite mature in this field, the ideas that using inhalable nano-toxicology for disease therapy might be more attractive.

Firstly, lung cancer exhibited the highest mortality and second-highest morbidity among all cancer types (Sung et al. 2021), and the first-line remedy (like cisplatin) for lung cancer had encountered severe drug resistance (Peng et al. 2021). Strategies based on nano-systems should be developed to reverse the drug resistance in lung cancers and increase the therapeutic effects. For example, biomimetic nanoparticles based on cancer cell membrane enhanced the targeting capacity towards lung cancer cells and improve the cytotoxicity of loaded drugs (He et al. 2019); the encapsulation of small interfering ribonucleic acid (siRNA) into self-assembled nanocarriers effectively inhibit the drug resisting pathways in lung cancer cells (Wen et al. 2017); some nano-systems prepared by natural products demonstrated P-glycoprotein (P-gp) inhibiting activities, which were promising tools to reverse the drug resistance (Reshma et al. 2019). The combination of these strategies is also meaningful for lung cancer treatment.

Secondly, coronavirus disease 2019 (COVID-19) is now having a high infection rate across the world, with a reproductive number (R_0) of 3 ~ 7 (Viceconte and Petrosillo 2020). The main lesion site of COVID-19 was in the lung, and thus, theranostics by inhalable nano-systems might be appropriate. In addition, it would be meaningful to develop nanoparticle-based vaccines for COVID-19. Zhang Y. et al. prepared an I3-01v9 SApNP nano-system that showed longer retention, greater presentation on follicular dendritic cell dendrites, and stronger germinal center reactions in lymph node follicles (Zhang et al. 2021). REVC-128 nano-vaccine was fabricated by Gu M. et al., which protected hamster models against the virus challenge by stabilizing body weight, suppressing viral loads, and alleviating tissue damage (Gu et al. 2021). The two cases provided referencing values for the design and development of COVID-19 nano-vaccines.

Thirdly, the detailed in vivo fate of inhaled nano-systems was pending clarification. After pulmonary delivery, it was still ambiguous how nano-systems would be disposed of by the human body, and different conclusions were drawn (Huang et al. 2020a, b). The investigators were encouraged to adopt tracking methods with better resolution, and analyses on the cellular level, to unambiguously explore the biological fate of inhaled nano-systems. Labeling the nano-systems with environment-responsive fluorescent probes precluded the signals from detached probes and distinguished those from intact carriers, which was favorable for the biological fate investigations (Wang et al. 2021). For metal-based systems, visualization under microscopy was a convenient approach to trace the biodistribution profile (Miller et al. 2017). It was advisable to quantitatively determine the interaction between nano-systems with pulmonary surfactant by physicochemical methods, because such an interaction could mirror the in vivo fate after inhalation to a certain degree (Wan et al. 2019). Besides, one might use computational simulations to predict the biological fate of inhaled nano-systems in the preclinical stage (Vanaki and S, Holmes D, Suara K, Jayathilake PG, Brown R, 2020).

It should be noticed that bibliometric analysis is always a dynamic process (Huang et al. 2020a, b). New documents are still publishing in this field, and thus, there will be some limitations of this work in mining the future trends. The authors appeal to cooperate with the readers in continuously updating the literature survey and grasping the newest knowledge.

Conclusion

In this paper, bibliometrics analyses were used to describe the research framework of inhalable nano-systems from a new perspective. Firstly, the basic characteristics of bibliometrics were evaluated. The results showed that the inhalable nano-systems attracted increased attention worldwide and most of the literature was in the fields of toxicology, pharmacy, and materials science. Interestingly, international collaboration and co-authorship were common phenomena. Secondly, this paper analyzed the publication trend. It was found that most of the keywords were not well differentiated. Co-citation and bibliographic coupling showed the connection and similarity between documents. Hotspot mining was achieved by the analysis of high-frequency words and terms. The results denoted that the formulation development of inhalable nano-system, the application of inhalable nano-system in disease treatment, and the influence of inhalable nano-system on human health were the research hotspots. In general, this paper offered an overview of the researches on inhalable nano-systems and provided new ideas for the follow-up investigation in this field.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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