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Review

Visualizing the Knowledge Domain of Nanoparticle Drug Delivery Technologies: A Scientometric Review

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Abstract: The scientific literature of nanoparticle drug delivery technologies (NDDT) between 2005 and 2014 was reviewed. The visualized co-citation network of its knowledge domain was characterized in terms of thematic concentrations of co-cited references and emerging trends of surging keywords and citations to references through a scientometric review. The combined dataset of 25,171 bibliographic records were constructed through topic search and citation expansion to ensure adequate coverage of the field. While research in *gold nanoparticle* and *magnetic nanoparticle* remains the two most prominent knowledge domains in the NDDT field, research related to clinical and therapeutic applications has experienced a considerable growth. In particular, clinical and therapeutic developments in NDDT have demonstrated profound connections with the *mesoporous silica nanoparticle* research and *microcrystal* research. A rapid adaptation of mesoporous silica-based nanomaterials and rare earth fluoride nano-/microcrystal in NDDT is evident. Innovative strategies have been employed to exploit the multicomponent, chemical synthesis, surface modification, and controlled release imparting functionalized targeting capabilities. This study not only facilitated the connection of authors and research themes in the NDDT community, but also demonstrated how research interests and trends evolve over time, which greatly contributes to our understanding of the NDDT knowledge domains.

Keywords: drug delivery; nanoparticle; knowledge domain; scientometrics

1. Introduction

In recent years, increasing attention has paid to the development of novel drug delivery systems (NDDS), because the average cost and time for the development of a new chemical or biochemical entity are much higher than those required to develop a NDDS [1]. Moreover, incorporating an existing medicine into a NDDS can significantly improve its performance in terms of efficacy, safety, and improved patient compliance [2].

Among the various NDDS, a considerable attention has focused on the development of therapeutic nanoparticle technologies, because they have the potential to revolutionize the drug development manner and alter the landscape of the pharmaceutical industry [3]. As nanoparticle drug delivery technologies (NDDT) begin to gain traction over the next several decades, it is important to visualize its knowledge domains. In this context, this paper aimed to explore the knowledge domains associated with NDDT, quantifying research patterns and trends in NDDT. Using *CiteSpace* as a visualization tool to analyze the scientific literature retrieved from the Web of Science Core Collection (WoSCC) [4],

this paper reflected a number of remarkable connections and clusters of research in NDDT over the past decade (2005–2014).

2. The Visualization of Scientific Knowledge Domains

A knowledge domain is a particular field of study that creates a common ground and a sense of development of a common identity by affirming its purpose and value to members and stakeholders [5]. Moreover, intellectual relationships and collaboration networks are fundamental to a knowledge domain [6]. The visual representation of such "knowledge networks" contributes to the overall understanding of intellectual collaborations in a particular knowledge domain.

Scientific knowledge changes all the time. Most of the changes are incremental, but some are revolutionary and fundamental [7]. For example, in the field of NDDT, several subareas have formed through the years, ranging from drug incorporation and release, formulation stability and shelf life, biocompatibility, to biodistribution and targeting, and functionality [8]. With recent advances in computing power, scientific indexes, and bibliographic techniques, progress is being made and researchers are gradually piecing together this dilemma and exploring hidden connections and knowledge domains in the literature. In the next section, the process of exploring the knowledge domains associated with NDDT was described.

3. Method

3.1. Bibliographic Records

We collected the bibliographic records from the WoSCC of Thomson Reuters. We determined the time frame of this analysis to the last decade (2005–2014) due to a concerted effort to improve the clarity of derived results. The search consists of two subqueries about NDDT: "*nanoparticle* drug delivery*" in topic search and "*nanoparticle* drug delivery*" in title search. Two datasets of bibliographic records on NDDT were retrieved from the WoSCC, including both SSCI and SCI-Expanded subsidiary databases. The topic-search dataset is referred as the core dataset [9]. The query resulted in 1770 bibliographic records which includes 1178 original research articles. The expanded dataset is a superset of the core dataset with extra bibliographic records obtained by association through citation links. Any article citing at least one original article in the core set can be assumed that it may be thematically relevant to the subject matter underlying the core dataset [10]. The resultant expanded dataset consists of 23,993 unique records. Both datasets were merged as a whole for scientometric review. The whole bibliographic records were then exported to *CiteSpace* [11] for subsequent analysis.

3.2. CiteSpace

CiteSpace supports the visualization of a scientific field from bibliographic sources in terms of networks of several types of entities, including cited references, co-authors, and co-occurring keywords [12]. This paper centered on document co-citation networks and networks of co-occurring keywords in an effort to deliver more accurate and complete results for the NDDT knowledge domains. Individual nodes in the network can be aggregated into clusters based on their interconnectivity. Each cluster represents a distinct specialty or a thematic concentration. Other points of interest include highly cited landmark articles, articles with strong citation bursts, and keywords with a strong surge of frequency.

The aim of burst detection is to investigate whether the frequency of an entity increases abruptly with reference to its peers. If an article is found to have a steep increase of its citation counts, then the article is regarded as having a citation burst. Similarly, if the number of articles with a term in their titles or abstracts sharply increased at a much faster rate than other terms, then the term is defined as a burst term. For the purposes of this paper, we first identified key articles associated with NDDT. Next, we detected key clusters and emerging topics through citation bursts in the literature for exploring the knowledge domains of NDDT.

3.3. Network Analysis and Visualization

The data input of *CiteSpace* is a collection of scientific publications associated with a specific topic [4]. Through its network modeling and visualization, we can explore the knowledge domains in a specific topic. One of the important tools in *CiteSpace* helps identify betweenness centrality between pivotal points in the scientific literature [13]. The betweenness centrality of a node in a network functions as a measure to indicate the importance of nodes in a network.

Research fronts are a collection of articles that are actively cited by researchers and often display properties of domain specificity [14]. Research front terms generated by *CiteSpace* capture core concepts of co-citation clustering and provide a general overview of a knowledge domain and its associated network. Finally, time slices are powerful tools for providing a temporal perspective to the literature and identifying citation bursts [11].

4. Bibliographic Landscape

4.1. Document Co-Citation Analysis

The complete set of 25,171 bibliographic records combining both the core dataset and the expanded dataset were visualized and analyzed using *CiteSpace*. Next, the bibliographic records were extracted from the WoSCC and their document co-citation network was generated as shown in Figure 1.

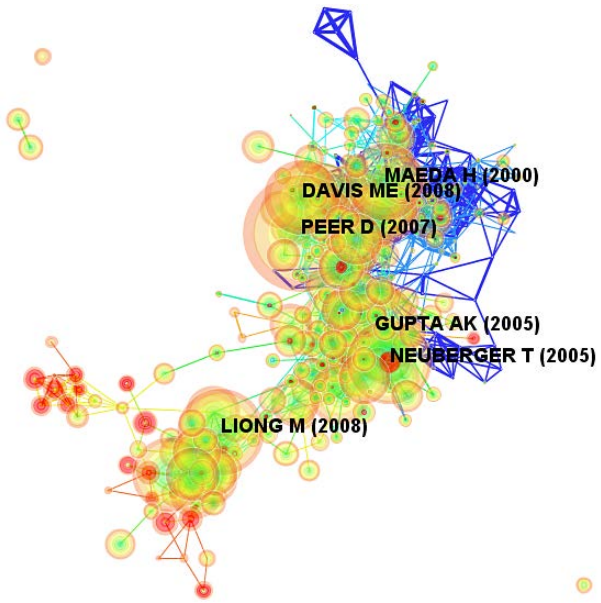

Figure 1. Key articles in nanoparticle drug delivery technologies.

In this network, there are 402 unique nodes and 2974 links for a one-year time slice. These nodes represent cited references from the collected articles, and the links in the network represent co-citation relationships. Each link colors correspond directly to each time slice. For example, blue links describe articles that were co-cited in 2005, and the most recent co-citation relationships are visualized as orange or red links. We can further conclude three focal points from Figure 1. First, larger node sizes imply that the article is an important one within the knowledge domain. Second, red rings around a node represent a citation burst. Third, purple rings indicate nodes that have a relatively high betweenness centrality in the network.

Table 1 presents the five top-cited articles associated with the term "nanoparticle drug delivery" between 2005 and 2014.

Table 1. Five critical articles in nanoparticle drug delivery technologies.

Cited Frequency	Title	Author	Year	Betweenness Centrality	Journal
1014	Nanocarriers as an emerging platform for cancer therapy	Peer *et al.*	2007	0.00	Nature Nanotechnology
829	Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications	Gupta and Gupta	2005	0.02	Biomaterials
764	Multifunctional inorganic nanoparticles for imaging, targeting, and drug delivery	Liong *et al.*	2008	0.00	ACS Nano
755	Superparamagnetic nanoparticles for biomedical applications: possibilities and limitations of a new drug delivery system	Neuberger *et al.*	2005	0.01	Journal of Magnetism and Magnetic Materials
712	Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review	Maeda *et al.*	2000	0.08	Journal of Controlled Release

The first is a paper by Peer *et al.* [15], which examined some of the approved formulations for clinical use and discussed the challenges in translating basic research to the clinic. The second is Gupta and Gupta [16] work, which discussed the synthetic chemistry, fluid stabilization and surface modification of superparamagnetic iron oxide nanoparticles. The other three papers focus on particular application areas or techniques. For example, Liong *et al.* [17] demonstrated the multifunctional inorganic nanoparticles can be monitored inside living cells by both magnetic resonance and fluorescence imaging methods. Neuberger *et al.* [18] discussed the characteristics and applications of superparamagnetic nanoparticles based on a core consisting of iron oxides (SPION). Finally, Maeda *et al.* [19] reviewed the basic characteristics of the enhanced permeability and retention (EPR) effect. In sum, regardless of the subareas, all five articles represent nanoparticle drug delivery as a key enabling technology for pursuing substantive research questions in physical or social environments.

4.2. Identification and Interpretation of Clusters

We used *CiteSpace* to explore research patterns and emerging trends in the body of knowledge in terms of key clusters of articles. Figure 2 shows clusters labeled with title terms. The size of a cluster's label is proportional to the size of the cluster.

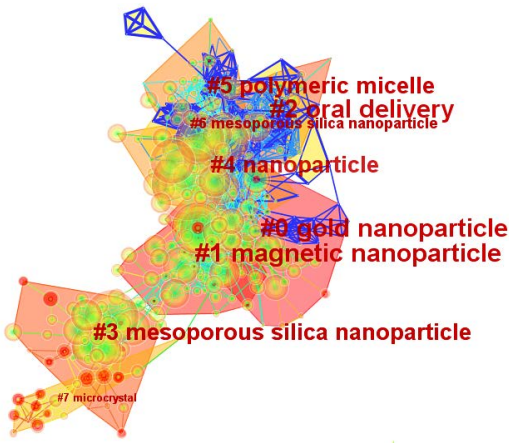

Figure 2. Clusters visualization based on a document co-citation network.

In this instance, there are total 55 clusters in the network. To characterize the nature of a cluster, *CiteSpace* can extract noun phrases from the titles of articles that cited the cluster based on three

specialized metrics—TF*IDF, log-likelihood tests (LLR) and mutual information tests (MI). LLR usually gives the best result in terms of the uniqueness and coverage of themes associated with a cluster. Table 2 details the top 11 clusters in rank order.

Table 2. Top-ranked clusters in nanoparticle drug delivery technologies.

ID	Size	Silhouette	Label (TF*IDF)	Label (LLR)	Label (MI)	Mean (Cited Year)
0	55	0.789	nano	gold nanoparticle	biomaterial-based technologies	2003
1	53	0.853	ion	magnetic nanoparticle	behavior	2003
2	51	0.776	nano	oral delivery	general strategy	2001
3	48	0.933	silica	mesoporous silica nanoparticle	anticancer drug delivery system	2007
4	46	0.704	nano	nanoparticle	drug discovery	2003
5	42	0.811	nano	polymeric micelle	nanofibrous scaffold	2001
6	23	0.890	nano	mesoporous silica nanoparticle	ouzo region	2002
7	13	0.972	upconversion	microcrystal	drug-delivery system	2010
8	8	1.000	plaque angiogenesis	nanomedicine strategies	mechanism	2002
9	8	0.954	nano	nanotechnology-based drug delivery	drug-delivery system	2000
10	5	0.998	carboxymethyl konjac	glucomannan-chitosan nanoparticle	drug delivery	1994

As shown in Figure 2, *gold nanoparticle* and *magnetic nanoparticle* are the two largest clusters. *Microcrystal* and *mesoporous silica nanoparticle* are the two youngest clusters, and *glucomannan-chitosan nanoparticle* is the oldest cluster. The values of the silhouettes for each cluster are greater than 0.5, suggesting robust and meaningful results. The largest cluster, *gold nanoparticle* (#0), consists of 55 members. The three most active citers in this cluster are Aswathy *et al.* [20], Alkilany and Murphy [21], and Chithrani [22]. According to the titles of these citers in this cluster, research works related to gold nanoparticle shape a foundation of the knowledge domain. Researchers interested in gold nanoparticle are particularly concerned with near-infrared quantum dot, toxicity, and biomaterial-based technologies. Not surprisingly, this cluster covers a range of interests, reflecting the interdisciplinary nature of NDDT and their use.

The second largest cluster (#1) in this knowledge domain, *magnetic nanoparticle*, has 53 member articles and an average publication year of 2003. The three most active citers to this cluster are Hao *et al.* [23],Veiseh *et al.* [24], and Faraji *et al.* [25] accordingly. Because of their remarkable magnetic properties and biologically comparable sizes, these magnetic nanoparticles are very beneficial for biomedical applications [23]. In addition, these magnetic nanoparticles can also respond resonantly to an alternating magnetic field and function as a heater, offering a promising therapeutic solution by magnetic fluid hyperthermia [25]. In recent years, the synthesis, design, and fabrication of multifunctional magnetic nanoparticles for biomedical applications has become one of the most active research areas in this knowledge domain [24]. As shown in Figures 1 and 2 this cluster has the top ranked burst item—Neuberger *et al.* [18] among all clusters, with bursts of 61.86. Thus, the magnetic nanoparticle cluster is essential to the literature represented by the datasets.

The third largest cluster (#2) is *oral delivery* which has 51 member articles and an average publication year of 2001. The three most active citers in this cluster are Ratzinger *et al.* [26], Roger *et al.* [27], and Patel *et al.* [28] accordingly. According to the titles of these citers in this cluster,

nanometric-sized drug delivery systems are being extensively studied and provide promising potential for oral drug delivery. Researchers interested in oral delivery focus particularly on how technological solutions can enhance the bioavailability or the targeting of anticancer drug after oral administration.

There are other clusters worth mentioning. For example, the cluster (#3) for *mesoporous silica nanoparticle* consists of 48 member articles and an average publication year of 2007. According to the major citing articles [29,30], it is not surprising that previous advances push *mesoporous silica nanoparticle* to the research forefront of drug delivery development.

Another major cluster corresponds to the terms *polymeric micelle*. In most instances, polymeric micelles play a significant role in the advancement of NDDT by providing controlled release of therapeutic agents in constant doses over long periods [31,32]. Thus, *polymeric micelle* has become a substantive knowledge domain in NDDT research field.

Finally, the term *microcrystal* also represents a cluster which has 13 member articles and an average publication year of 2010. This cluster is the newest one in which the three most active citers in this cluster are Li and Lin [33], Chen *et al.* [34], and Liu *et al.* [35] accordingly. Dramatic efforts have been dedicated to the chemical synthesis of rare earth fluoride nano-/microcrystals with uniform size and shapes [33]. Hence, research works related to *microcrystal* reflect the recent knowledge domain in NDDT research field.

An alternative approach for viewing these clusters and their relationships is with timeline visualization as shown in Figure 3.

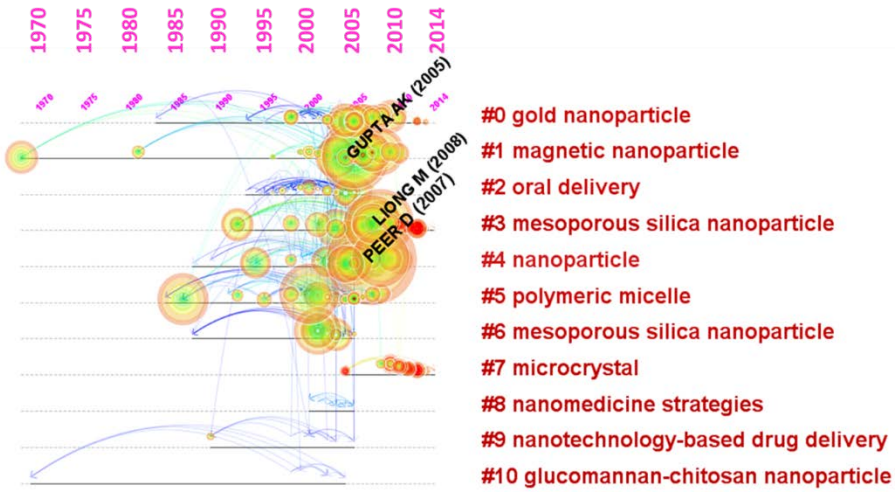

Figure 3. Timeline view for nanoparticle drug delivery technologies: 2005–2014.

The most obvious trend in Figure 3 is that most of the documents cited were published after 1985, roughly corresponding to the rise and deployment of an existing drug molecule from a classic type to a novel nanoparticle drug delivery system. Interestingly, the earliest cited document in the derived network was published before 1970 [36] and is found in the cluster of magnetic nanoparticle. Moreover, as shown in Figures 2 and 3 the top ranked item by centrality is Yoon *et al.* [37] in Cluster #1, with centrality of 0.26. The second one is Giri *et al.* [38] in Cluster #3, with centrality of 0.22. The third is Gao *et al.* [39] in Cluster #0, with centrality of 0.14. These nodes can be considered as pivotal points that provide important bridging connections between two research interests.

4.3. Most Active Clusters

Figure 3 shows two clusters, cluster #3 and cluster #7, with the strongest citation bursts. This means that cluster #3 and cluster #7 represent where the major efforts of the research in this field since 2010. Cluster #3 is labeled as *mesoporous silica nanoparticle*. Table 3 lists five articles in cluster #3 with the strongest citation bursts.

Table 3. Articles with the strongest citation bursts in cluster #3.

Citation	Burst	Author	Year	Title	Source
248	46.48	Tang *et al.* [40]	2012	Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery	ADV MATER
222	44.12	Yang *et al.* [41]	2012	Functionalized mesoporous silica materials for controlled drug delivery	CHEM SOC REV
238	41.45	Li *et al.* [42]	2012	Mesoporous silica nanoparticles in biomedical applications	CHEM SOC REV
127	20.30	Liong *et al.* [43]	2009	Mesostructured multifunctional nanoparticles for imaging and drug delivery	J MATER CHEM
297	13.07	Trewyn *et al.* [44]	2007	Mesoporous silica nanoparticle based controlled release, drug delivery, and biosensor systems	CHEM COMMUN

The title terms in Table 3 mainly include mesoporous silica nanoparticle, controlled release, and drug delivery. The highest bursted article in this cluster, Tang *et al.* [40], discussed the recent progress in the synthesis of mesoporous silica nanoparticles for drug delivery applications. The second highest bursted article in this cluster, Yang *et al.* [41], reviewed the most recent research progress on silica-based controlled drug delivery systems. The common theme in terms of the bursted articles to this cluster is the design, synthesis and functionalization of mesoporous silica nanoparticles for efficient drug delivery systems.

Cluster #7 is labeled as *microcrystal*. Table 4 lists five articles in cluster #7 with the strongest citation bursts.

Table 4. Articles with the strongest citation bursts in cluster #7.

Citation	Burst	Author	Year	Title	Source
200	37.79	Tian *et al.* [45]	2012	Mn^{2+} Dopant-Controlled Synthesis of $NaYF_4$: Yb/Er Upconversion Nanoparticles for *in vivo* Imaging and Drug Delivery	ADV MATER
186	24.91	Zhou *et al.* [46]	2012	Upconversion nanophosphors for small-animal imaging	CHEM SOC REV
178	19.64	Haase and Schäfer [47]	2011	Upconverting nanoparticles	ANGEW CHEM INT EDIT
233	19.44	Wang and Liu [48]	2009	Recent advances in the chemistry of lanthanide-doped upconversion nanocrystals	CHEM SOC REV
221	13.97	Wang *et al.* [49]	2010	Simultaneous phase and size control of upconversion nanocrystals through lanthanide doping	NATURE

The title terms in Table 4 mainly include nanocrystals, upconversion, and drug delivery. Tian *et al.* [45] has the strongest citation burst in the cluster. The work suggested that upconversion nanoparticles (UCNPs) could be used as potential bio-labels for *in vivo* imaging, and as promising drug carriers for intracellular drug delivery. The second highest bursted article in this cluster, Zhou *et al.* [46], considered a rational approach to obtain suitable UCNP nanoprobes for small animal bioimaging. A common theme among this group of articles appears to focus on applications of UCNP research for novel imaging agents and therapy.

4.4. References with Strong Citation Bursts

Significant increases of research interests within the NDDT knowledge domain are characterized by publications that experienced citation bursts. This was based on a total of 25,171 bibliographic records which were selected from 555,999 valid references. Figure 4 shows the top 30 references with the strongest citation bursts during the period between 2005 and 2014.

Top 30 References with Strongest Citation Bursts

References	Year	Strength	Begin	End	2005 - 2015
MORAWSKI AM, 2004, MAGNET RESON MED, V51, P480, DOI	2004	8.6328	2005	2006	
CHEN GH, 1995, NATURE, V373, P49, DOI	1995	8.0753	2005	2006	
LIU FT, 2003, J AM CHEM SOC, V125, P15059, DOI	2003	7.3831	2005	2007	
AHLIN P, 2002, INT J PHARM, V239, P113, DOI	2002	3.6539	2005	2006	
MCCLEAN S, 1998, EUR J PHARM SCI, V6, P153, DOI	1998	9.295	2005	2006	
SAKUMA S, 2001, ADV DRUG DELIVER REV, V47, P21, DOI	2001	8.4298	2005	2006	
FLORENCE AT, 1995, J CONTROL RELEASE, V36, P39, DOI	1995	3.2957	2005	2006	
KATO K, 1969, AGR BIOL CHEM TOKYO, V33, P1446	1969	13.1658	2005	2007	
DESAI MP, 1997, PHARMACEUT RES, V14, P1568, DOI	1997	3.1789	2005	2006	
CHOI Y, 2005, CELL CYCLE, V4, P669, DOI	2005	6.4054	2005	2008	
SALVAGE JP, 2005, J CONTROL RELEASE, V104, P259, DOI	2005	8.0753	2005	2006	
FENG SS, 2003, CHEM ENG SCI, V58, P4087, DOI	2003	4.8621	2005	2006	
KUMAR MNVR, 2004, EXPERT OPIN BIOL TH, V4, P1213	2004	12.4776	2005	2007	
CEGNAR M, 2004, EUR J PHARM SCI, V22, P357, DOI	2004	9.7946	2005	2006	
OH KS, 2005, BIOMACROMOLECULES, V6, P1062, DOI	2005	12.2368	2005	2007	
CSABA N, 2004, J BIOMAT SCI-POLYM E, V15, P1137, DOI	2004	7.7131	2005	2006	
FENG SS, 2004, CURR MED CHEM, V11, P413, DOI	2004	16.4733	2005	2006	
KREUTZER HJ, 2000, ACTA MOZARTIANA, V47, P65	2000	6.8475	2005	2006	
DOUGLAS SJ, 1987, CRIT REV THER DRUG, V3, P233	1987	3.6539	2005	2006	
SCHMIEDER AH, 2005, MAGNET RESON MED, V53, P621, DOI	2005	13.8707	2005	2006	
JUNG T, 2000, EUR J PHARM BIOPHARM, V50, P147, DOI	2000	10.7179	2005	2006	
ANDERSON SA, 2000, MAGNET RESON MED, V44, P433, DOI	2000	13.9537	2005	2007	
CHAW CS, 2004, BIOMATERIALS, V25, P4297, DOI	2004	19.6709	2005	2007	
DONG DC, 1984, CAN J CHEM, V62, P2560, DOI	1984	5.0238	2005	2006	
DOYLE PS, 2002, SCIENCE, V295, P2237, DOI	2002	9.2524	2005	2008	
EDLUND U, 2002, ADV POLYM SCI, V157, P67	2002	5.0238	2005	2006	
MALINGRE MM, 2001, INVEST NEW DRUG, V19, P155, DOI	2001	6.3465	2005	2006	
LIU XM, 2003, J COLLOID INTERF SCI, V266, P295, DOI	2003	15.227	2006	2007	
FLACKE S, 2001, CIRCULATION, V104, P1280, DOI	2001	8.5456	2006	2007	
LITTLE SR, 2004, P NATL ACAD SCI USA, V101, P9534, DOI	2004	6.5637	2007	2008	

Figure 4. Top 30 references with strong citation bursts.

As shown in Figure 4, most of the references started to burst in year 2005, two references started to burst in year 2006, and only one reference started to burst in year 2007. Table 5 shows the representative references for three groups by the beginning time of burst.

Table 5. Representative references with the strongest citation bursts.

References	Year	Citation Burst		
		Strength	Begin	End
Chaw *et al.* [50]	2004	19.67	2005	2007
Feng *et al.* [51]	2004	16.47	2005	2006
Anderson *et al.* [52]	2000	13.95	2005	2007
Liu *et al.* [53]	2003	15.23	2006	2007
Little *et al.* [54]	2004	6.56	2007	2008

In the group of year 2005, the top three references with the strongest citation bursts are Chaw *et al.* [50], Feng *et al.* [51], and Anderson *et al.* [52] accordingly. Chaw *et al.* [50] analyzed the drug-loading process for understanding the effect of various fabrication parameters on drug encapsulation efficiency. The burst lasted for three years from 2005 till 2007. Feng *et al.* [51] article indicated that nanoparticles of biodegradable polymers can provide an ideal solution to clinical administration with better efficacy and less side effects. Anderson *et al.* [52] article demonstrated a new MRI method for visualizing the endothelial $\alpha_v\beta_3$ integrin *in vivo* using an antibody-targeted, site-directed contrast agent.

In the group of year 2006 by the beginning time of burst, Liu *et al.* [53] reported the synthesis, characterization and temperature sensitivity of thermally responsive polymeric micellar nanoparticles that were self-assembled from cholesteryl end-capped random poly. The article published in 2003 has the third strongest citation burst in the entire dataset. The burst lasted for two years from 2006 till 2007. Little *et al.* [54] article published in 2004 has the strongest citation burst in the group of year 2007 by the beginning time of burst. They described a microparticle-based DNA delivery system which is composed of pH-sensitive poly-β amino ester and poly lactic-co-glycolic acid.

4.5. References Bursted Since 2013

Table 6 shows the references with the recent citation bursts from 2010 onward. In this subsection, we will review key articles with the most recent citation bursts starting from 2013. Citation bursts starting from 2013 are associated with the main three 2012 articles.

Table 6. References with the most recent citation bursts since 2010.

References	Year	Citation Burst			
		Strength	Begin	End	Duration
Liong *et al.* [43]	2009	20.3	2010	2011	
Jain *et al.* [55]	2008	6.2	2010	2011	
Winter *et al.* [56]	2003	3.7	2010	2011	
McCarthy and Weissleder [57]	2008	2.8	2010	2011	
Hood *et al.* [58]	2002	2.5	2010	2011	
Lu *et al.* [59]	2010	8.9	2012	2013	
Ashley *et al.* [60]	2011	8.5	2012	2015	
Vivero-Escoto *et al.* [61]	2010	7.7	2012	2013	
Meng *et al.* [62]	2010	3.3	2012	2015	
Tang *et al.* [40]	2012	46.5	2013	2015	
Yang *et al.* [41]	2012	44.1	2013	2015	
Li *et al.* [42]	2012	41.5	2013	2015	
Tian *et al.* [45]	2012	37.8	2013	2015	
Pan *et al.* [63]	2012	36.3	2013	2015	
Du *et al.* [64]	2011	35.1	2013	2015	
Liu *et al.* [65]	2011	34.2	2013	2015	
Albanese *et al.* [66]	2012	29.0	2013	2015	
Zhang *et al.* [67]	2012	25.8	2013	2015	
Zhou *et al.* [46]	2012	24.9	2013	2015	
Wang *et al.* [68]	2012	24.4	2013	2015	
Haase and Schäfer [47]	2011	19.6	2013	2015	
Wang *et al.* [69]	2011	19.6	2013	2015	
Wang and Liu [48]	2009	19.4	2013	2015	
Wang *et al.* [49]	2010	14.0	2013	2015	
Luo *et al.* [70]	2011	12.8	2013	2015	
Auzel [71]	2004	12.1	2013	2015	
He and Shi [72]	2011	10.6	2013	2015	
Thomas *et al.* [73]	2010	9.9	2013	2015	

Among the articles with strong citation bursts since 2013, Tang *et al.* [40] article, titled "Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery", has the strongest citation burst with a burst strength of 46.5. This article published in *Advanced Materials* discussed the biological barriers for nano-based targeted cancer therapy and mesoporous silica nanoparticle-based targeting strategies. The second article with the most recent citation burst studies the functionalized mesoporous silica materials [41]. The work reported several exciting achievements on mesoporous silica-based materials as sustained-release systems and stimuli-responsive controlled release systems. The third article that has drawn much attention is a 2012 article studied by Li *et al.* [42]. The authors described that the functionalization of mesoporous silica nanoparticles with molecular, supramolecular or polymer moieties provides the material with great versatility and makes the delivery operation highly controllable.

5. Conclusions

According to the network visualization and the document co-citation analysis supported by *CiteSpace*, we explored the key clusters of articles and identified research patterns and emerging trends in the literature. The top two clusters were labeled as *gold nanoparticle* and *magnetic nanoparticle*, suggesting that they are foundational to the knowledge domain. Not surprisingly, the two largest clusters cover a range of interests, reflecting the interdisciplinary nature of NDDT and their use. While research in *gold nanoparticle* and *magnetic nanoparticle* remains the two most prominent knowledge domains in the NDDT field, research related to clinical and therapeutic applications in NDDT has experienced a considerable growth. The detected surge of the two keywords—"mesoporous silica" and "microcrystal" in the literature of NDDT led us to investigate the nature and context of its use in NDDT. The investigation revealed a rapidly increasing number of studies that specifically used mesoporous silica-based nanomaterials and rare earth fluoride nano-/microcrystal in NDDT research. Similarly, a detected burst of citations underscores a fast-moving knowledge domain. For example, knowing exactly when citations to Chaw *et al.* [50] had surged (2005–2007) can improve our understanding of the complex adaptive behavior of the field. Knowing that Tang *et al.* [40] has been attracting much attention since 2012 can help us capitalize on the collective intelligence of the multidisciplinary scientific communities. The emergence of a new cluster indicates the beginning of a trend, for example, in *microcrystal*. A persistent cluster represents a continuation of an existing trend, for example, in *mesoporous silica nanoparticle*. In addition, the two most active clusters with the strongest citation since 2010 appear to *mesoporous silica nanoparticle* (cluster #3) and *microcrystal* (cluster #7). This means that both *mesoporous silica nanoparticle* and *microcrystal* represent where the major efforts of the research in this field.

Finally, considering the interdisciplinary characteristic of NDDT, it is not easy to obtain an overall picture of the research field. Hence, the contribution of this work was to explore an efficient and quantitative way of understanding the NDDT knowledge domain.

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