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Teaser This review provides a comprehensive perspective of the global research advances and frontiers in pharmaceutics from 1980 to 2014. Furthermore, a historical view and future prospects of drug delivery are discussed.

Big data analysis of global advances in pharmaceutics and drug delivery 1980–2014

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Introduction

Pharmaceutics, as an important discipline of pharmacy, relates to the science of pharmaceutical formulations and drug delivery, which prepare an active pharmaceutical ingredient (API) into a medication with safe and effective performance in patients. In fact, there is only a 60-year history for modern drug delivery systems. In 1952, SmithKline Beecham developed the first extended-release product with the Spansule® technology for 12-hour sustained-release [1]. After that, it was widely recognized that modern drug delivery systems (DDSs) could influence the therapeutic value of APIs [2]. Table 1 lists the landmark drug delivery systems [3] and a recent review discusses the history of drug delivery technologies and classified modern drug delivery technologies in two generations [4–6]. From 1950 to 1980, the first-generation (1G) oral and transdermal controlled-release formulations were developed, such as osmotic pump tablets and transdermal patches [4,6]. The second-generation (2G) drug delivery technologies from 1980 to 2010 were considered as advanced drug delivery systems, such as liposomes, biodegradable poly(lactic-*co*-glycolic acid) (PLGA) microspheres, nanoparticles and inhaled insulin [4,6]. However, 2G techniques were discussed as less successful owing to much fewer marketed products. Since the rapid development of novel pharmaceutical techniques and drug delivery systems, the past three decades have witnessed an upsurge of publications in the drug delivery field.

Mapping the knowledge domain is a newly emerging interdisciplinary area to chart, mine, analyze, sort and display knowledge [7]. Mapping the knowledge domain focuses on the analysis of the scientific knowledge to reveal the developing-process, research frontiers, knowledge structure, as well as the knowledge evolution in a visual way [7]. Thus, this technique provides a visual knowledge graph and knowledge sequence, such as individual activities, research groups, the knowledge structure and evolution. Lee *et al.* investigated thematic concentrations and emerging trends in nanoparticle drug delivery technologies (NDDT) by analyzing the co-citation visualization network of NDDT [8]. The results showed that gold nanoparticles and magnetic nanoparticles were two important topics in this area [8]. Another example was a scientometric review on global liposome research, which evaluated the global scientific outputs and characterized the development of liposome research [9]. The third example was the dynamic evolution of nanobiopharmaceuticals [10].

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TABLE 1

The landmark of key drug delivery technologies.

Year	Drug delivery systems	Refs
1952	The first sustained-release technology Spansule®	[1]
1950s	The first pressurized metered dose inhaler (MDI)	
1960s	The first dry powder inhalation (DPI)	[77]
1979	The first transdermal patch Transderm Scop®	[78]
1980s	The first elementary osmotic pump product Osmosin®	[79–81]
1984	The first Biodegradable microsphere VIVITROL®	[82]
1990	The first PEGylated protein Adagen®	[83]
1995	The first FDA-approved liposome Doxil®	[32]
2005	The first FDA-approved nanoparticle Abraxane®	[84]
2012	The first EU-approved gene therapy product Glybera®	[85]

The aim of the current research was to systematically evaluate research outputs in the drug delivery area and, retrospectively, global research advances by combined big data analysis and bibliometrics approaches. The objectives of this study were included as follows:

- To investigate the intellectual landscape of drug delivery systems from multiple perspectives including publications, countries and institutions.
- To evaluate international collaborations among main countries and institutions.
- To identify the knowledge structure and dynamic shift in pharmaceutics.

Data source and analysis

The reference data covered the total publications in all pharmaceutics periodicals with an impact factor of 1.0 or above. These relevant journals were extracted from the subject category of 'pharmacology and pharmacy' in the Science Citation Index Expanded (SCI-E) database via Web of Science from 1 January 1980 to 31 December 2014. Twenty-seven journals were identified (see Table S1 in the supplementary material online).

The original data of full records and cited references were downloaded from Web of Science, including the title, authors, source title, affiliations, abstract, publication date and citation number. There were two datasets: total publications (111 461) and high-cited publications with 100 citations or above (3242). The complete bibliographic records were imported into the visualization software including VOSviewer, GPSvisualizer and CiteSpace for further analysis. VOSviewer is a free visualization software package for constructing and visualizing bibliometric maps [11]. GPSvisualizer is an online utility used to create maps and profiles from geographic data (http://www.gpsvisualizer.com/). CiteSpace is a free visualization software package for the detection, analysis and visualization of the patterns and trends in scientific literature [12].

The total analysis included three parts: bibliographic landscape from global trends on publications, main active countries and institutions; the intellectual collaborations among main countries and institutions; and the knowledge structure and dynamic shift. Global intellectual collaborations among countries and institutions were estimated by analysis of 'co-authorship publications'. The research topics shift was captured by keyword burst-detection and the documents co-citation network analysis (for a list of the bibliometric technologies in this study see Table S2 in the supplementary material online). The parameters of visualization tools were shown as follows:

- Time slicing: 1980 to 2014.
- Years per slice: 5 years as the length of a single time slice.
- Threshold selection: top 100 references per time slice was selected to map the reference co-citation network in a standard graph and timeline view.
- Pruning and merging: the pathfinder approach was selected for the network pruning.

Bibliographic landscape of drug delivery

Analysis of annual publication number

A total of 111 461 publications and 3242 'high-cited' publications in pharmaceutics and drug delivery were identified in this study. As shown in Fig. 1, the publication number indicated the significant increase from 1585 in 1980 to 6111 in 2013. Moreover, it was obvious that there has been an upsurge in publication number in this area since 2000. In addition, data analysis showed that the publication types included 'research articles' (81%), review papers (8%) and others (11%). However, the review papers in 'high-cited' publications accounted for 42%, which indicated that review papers had more citations.

Analysis of main countries

Table 2 lists the top ten highly productive countries and institutions. As shown in Table 2 (left), the top ten countries published over 84% of papers. Japan with its global share of 26.08% had the largest contribution to pharmaceutical literature, followed by the USA (24.77%), UK (7.43%) and China (6.10%). However, the USA held nearly half of the 'high-cited' publications, followed by Japan (11.17%) and Germany (9.71%). Fig. 2 shows annual publications of the top five countries. In general, these leading countries showed an increase in yearly publication amount, except Japan. Japan ranked first before 2000, whereas the USA exceeded Japan after that. The reason was that Japan showed a steady decline after 1995. It was interesting that China has shown the most significant increase in the publication number in pharmaceutics since 2000. However, China did not show up in the top ten countries with 'high-cited' publications.

Analysis of main institutions

Table 2 (right) showed the top ten active institutions in pharmaceutics. The most productive institution was the University of London with 1891 publications during the period. In addition, international pharmaceutical enterprises, such as Pfizer (1741, 2nd) and GlaxoSmithKline (1070, 9th), also ranked among the top ten productive institutions, which showed strong R&D capability in this area. Additionally, Purdue University had the most 'high-cited' publications (56), followed by University of Utah (48) and Free University of Berlin (44).

Intellectual collaboration network

The global intellectual collaboration pattern in pharmaceutics is shown in Fig. 3a. Author affiliations are represented by white dots and their collaborations by the colored lines. Although pharma-

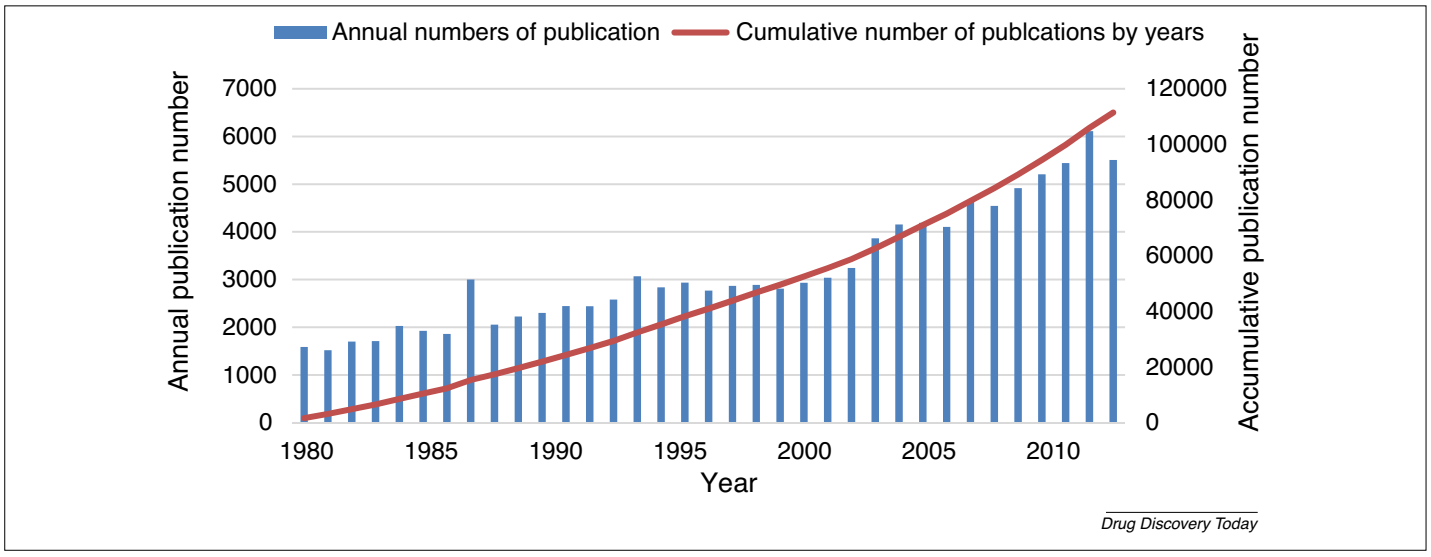

FIGURE 1

Annual publication number in pharmaceutics from 1980 to 2014. The blue column represents annual publication number; the red line represents the cumulative publication number.

ceutical research is widely distributed in the world, research collaborations are mainly located within the USA, Europe and Asia. The collaborations between the USA and Europe are much stronger than those among Asian countries. Australia has more collaborations with the USA and Europe than with Asian countries. Fig. 3b indicates the institutional collaboration network. The node size relates to the publication number, whereas the node link indicates the institutional collaboration. The institutions with the same circle color share a similar research theme. Obviously, Purdue University holds the largest number of 'high-citation' publications and is the most active institution in the collaboration. In addition, MIT and Harvard University are good partners.

Research frontier shift in pharmaceutics

The research frontier shift with time was analyzed by two approaches: documents co-citation network analysis and keyword burst detection. On the one hand, the co-citation network of the 'high-cited' publications was identified to reveal the most active research topics and research evolution over time. From 1980 to 2014, 13 major research topics were identified and these are listed in Table 3. On the other hand, keyword analysis could also be used to identify the research focus and research frontiers. Table 4 shows the keywords with the strongest citation burst. The time interval is depicted as a blue line, and the period with the keyword burst is marked as a red line segment. Higher strength of keyword burst is meant to be more active in this research field. For example; 'nanoparticle' with the burst period from 2011 to 2014 has the highest strength value of 331.08.

From Table 4 it is clearly shown that the leading topics before 1993 mainly focused on the preparation and characterization of conventional pharmaceutical techniques (e.g., solid dispersion, prodrug, permeability, metabolism and bioavailability) and biopharmaceuticals (e.g., vaccine, peptide and insulin). After 1993, however, advanced drug delivery systems and relevant applications have attracted more attention, such as liposomes, microcapsules, nanoparticles, gene delivery and cancer. The results indicated that pharmaceutical research from 1980 to 2014 gradually transferred from traditional pharmaceutical techniques to

TABLE 2

Top 10 countries (left) and institutions (right) in global publications.

Rank	Countries	Records	Rank	Institutions	Records
1	Japan	29 066	1	University of London	1891
2	USA	27 609	2	Pfizer	1741
3	UK	8276	3	Kyoto University	1470
4	China	6795	4	French National Center for Scientific Research (CNRS)	1183
5	Germany	4533	5	University Of Tokyo	1176
6	India	4134	6	University of California System	1143
7	France	4071	7	Toyama University	1076
8	South Korea	3456	8	Osaka University	1020
9	Italy	3283	9	GlaxoSmithKline	1007
10	Canada	2679	10	Kyoto Pharmaceutical University	992

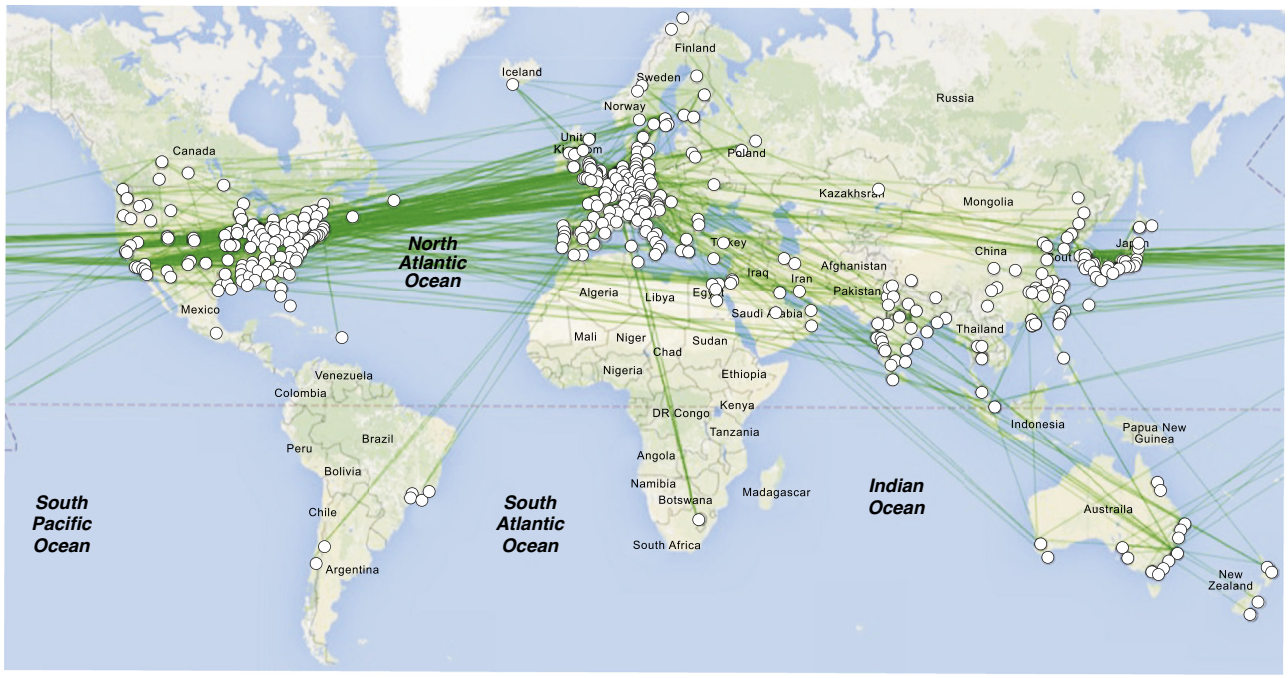

FIGURE 2

Annual publication number of top five most productive countries in pharmaceutics from 1980 to 2014.

advanced drug delivery systems, which was in agreement with the top-cited papers in the leading journal of pharmaceutics *Journal of Controlled Release* [6].

Historical view and future perspectives of drug delivery

The 1G from 1950 to 1980 focused on the fundamental drug release mechanisms of oral and transdermal dosage forms [4]. From 1950 to 1980 most oral and transdermal delivery systems had good understanding of the physicochemical properties of delivery systems to develop clinically successful products. Takeru Higuchi, who was considered 'the father of physical pharmacy' [13] made a pioneering contribution to this field. Also, the founding of ALZA in 1967 by Alejandro Zaffaroni had a significant influence on the controlled-release area [14]. ALZA brought the engineering and mechanistic view to design controlled-release drug delivery systems, such as osmotic pump tablets, transdermal delivery and ocular therapy. The Controlled Release Society (CRS) was established in 1978 to promote the field of controlled release (http://www.controlledreleasesociety.org). Another important in-

TABLE 3

Active thematic clusters in pharmaceutics from 1980 to 2014.

Year	Active thematic clusters
1980	Amorphous water-soluble solid dispersion
1981	Enantioselective
1981	Bioadhesive-based dosage form
1985	Vaccine
1989	Intestinal drug permeability
1992	Efflux transporter
1994	Biodegradable nanoparticle
1995	Gene delivery system
1997	Copolymer micelle
1998	Endosomal escape pathway
2003	Micellar drug delivery
2005	Inorganic nanoparticle
2005	pH-Sensitive degradable polymersome

TABLE 4

Keywords with the strongest citation burst in pharmaceutics from 1980 to 2014.

Keywords	Strength	Start	End	1980–2014[a]
Prodrug	32.07	1980	1997	
Metabolite	59.77	1980	1999	
Pharmacokinetics	34.10	1991	1993	
Peptide	15.26	1991	1995	
Bioavailability	6.57	1991	1992	
Kinetics	111.75	1991	1997	
Insulin	32.03	1992	1996	
Transport	24.42	1992	1999	
Microcapsule	46.15	1993	2002	
Liposome	32.52	1993	1996	
Absorption	3.84	1997	1998	
Percutaneous absorption	3.67	1998	1999	
Liver	5.52	1999	2000	
Paclitaxel	41.77	2009	2014	
Gene delivery	50.90	2009	2012	
Nanoparticle	331.08	2011	2014	
Breast cancer	76.85	2012	2014	
Cancer	78.00	2012	2014	

[a]Time interval was depicted as a blue line, whereas the period with the keyword burst was marked as red line segments.

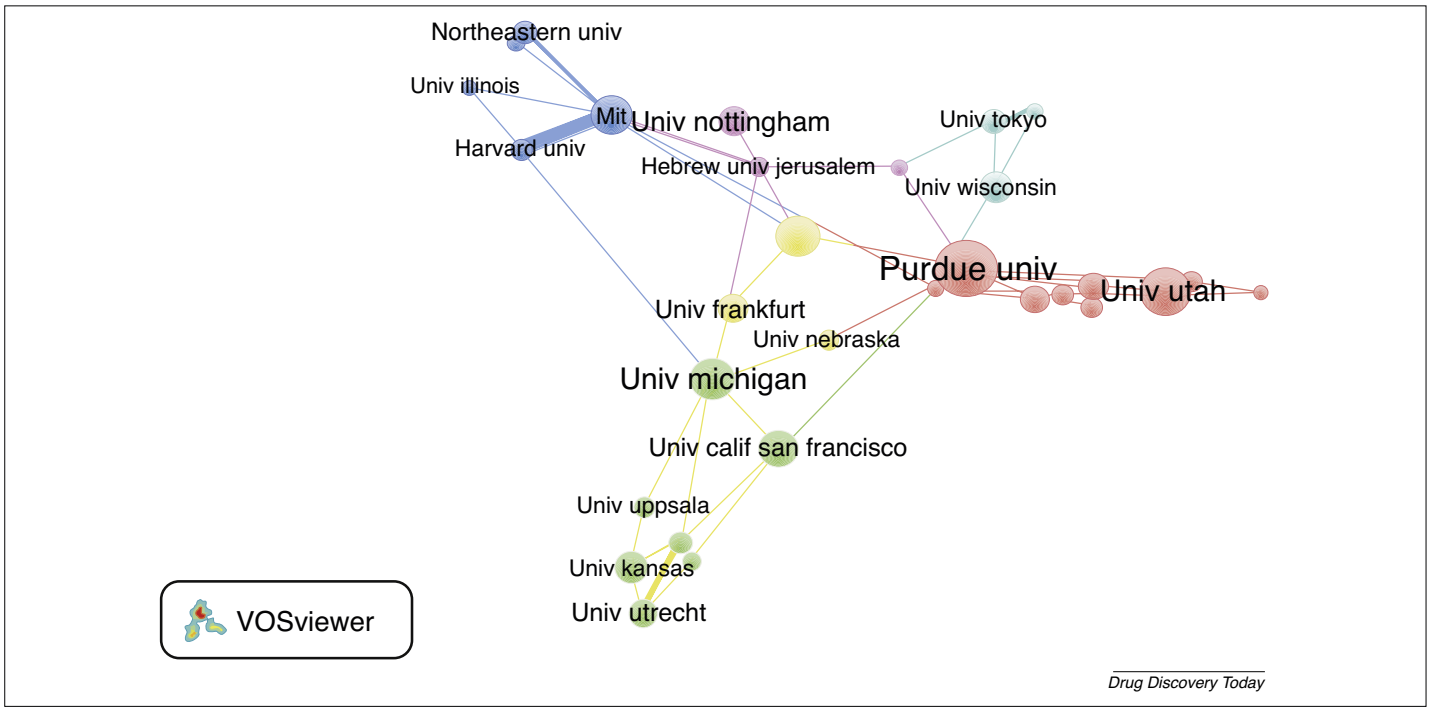

FIGURE 3

Intellectual collaboration network in pharmaceutics from 1980 to 2014. **(a)** Global collaboration network among countries: the node represents the author affiliation and the link between two nodes represents the authors' collaboration. **(b)** Institutional collaboration network: the size of the institution node represents the institution's publication number, the link between different institutions indicates the institutional collaboration and the institutions with the same circle color share a similar research theme. Abbreviations: calif, California; univ, university.

ternational organization of pharmaceutical sciences and pharmacy is the International Pharmaceutical Federation (FIP), which was founded in 1912 (https://www.fip.org/).

In the 1980s, the gastrointestinal (GI) absorption mechanism and bioavailability attracted more attention, which could be considered as the transition period between 1G and 2G delivery systems. Since the 1980s, pharmaceutical scientists paid more attention to formulation strategies (e.g., amorphous solid dispersion and prodrugs), absorption mechanisms (e.g., permeability) and their effect on *in vivo* pharmacokinetics (e.g., bioavailability and metabolism). Solid dispersion was one widely used method used to improve the solubility, dissolution rates and consequently the bioavailability of water-insoluble drugs [15,16]. Prodrugs were another key formulation strategy by enzymatically and/or chemically transforming a bioreversible molecule into an active parent drug *in vivo* for the desired pharmacological effect [17,18]. It was reported that ~5–7% approved drugs could be identified as prodrugs [19,20]. For the GI absorption mechanism, apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells were found to have a good correlation with oral drug absorption in humans [21]. After that, the biopharmaceutical classification system (BCS) was well established for *in-vitro–in-vivo* correlation and the estimation of oral drug absorption [22,23]. Now, the Caco-2 cell monolayer is widely used as a classic model for the drug permeability of the intestinal absorption.

In the 1980s the development of protein drugs and vaccines showed significant growth as a result of the discovery of the recombinant DNA technique in 1973 [24]. The first recombinant protein drug: human insulin, was approved in 1982. After that, dozens of protein and peptide drugs and vaccines have since been commercialized to the global market. These new biomolecules also presented many scientific and technical challenges to pharmaceutical scientists because the formulations, stability and characterization approaches of biomolecules were different from small-molecule drugs [25]. Thus, new delivery systems for biomolecules also attracted more attention at the next stage. Controlled-release delivery systems offered many advantages over immediate-release formulations for protein and peptide drugs [26]. Current controlled-release products on the market can deliver proteins or peptides up to once every 3 months [3].

Some advanced drug delivery techniques (e.g., liposome, nanoparticle and gene delivery) were raised during the period, which opened the door for 2G drug delivery systems. For example, liposomes were discovered in the middle of the 1960s [27] and their application as drug carriers started from the early 1970s [28–31]. As mentioned above, the first liposome product Doxil® was approved by the FDA in 1995 [32]. Currently, there have been ~15 FDA-approved liposome or lipid-based formulations [33,34]. Another important topic was gene delivery. In 1983 a bacterial gene with a retroviral vector was successfully delivered into mouse cells [35]. In 1990, the first successful gene therapy at the National Institutes of Health was trialed on a patient for adenosine deaminase deficiency using the viral vector [36]. In 1993 the first DNA–liposome formulation entered clinical trials for patients with stage IV melanoma [37]. Another important result in antitumor therapy was the discovery of the enhanced permeability and retention (EPR) effect [38]. The EPR effect is very important for nanoscale drug delivery systems to reach tumor tissues [39–42]. In addition, it should be mentioned that during the period two important journals in drug delivery: *Journal of Controlled Release* and *Advanced*

Drug Delivery Reviews, were first published in 1984 and 1987, respectively.

From 1993 to 2014 there were two hot research areas, including nanocarriers for cancer (e.g., nanoparticles and polymeric micelles) and gene delivery. Theoretically, the nanoscale drug delivery systems, such as the liposome [33,34], nanoparticle [43–46] or micelle [47,48], have great potential to enhance the therapeutic efficacy of an anticancer drug in the tumor site of the human body by the EPR effect [49]. The emergence of nanotechnology also offered an opportunity to diagnosis [50] or co-delivered therapeutic and imaging material together [51]. In the past 30 years, many approaches have also been tested to conquer biological barriers of gene delivery [52–56]. These approaches can be classified into three major types: physical methods, viral vector and nonviral vector, although each type has its own advantages and limitations. Physical approaches to gene delivery are still hampered by the issue of impracticality to the human body [57,58]. Viral carriers have excellent transfection efficiency but their inherent drawbacks include the stimulation of strong immune responses and oncogenesis [59,60]. During the past decades, nonviral vectors have achieved some progress in different areas, such as the liposome and polymeric delivery systems [55,61]. However, low transfection efficiency and toxicity issues of nonviral carriers still hamper their application in the clinic.

Different from 1G formulations, 2G drug delivery systems face strong challenges, leading to far fewer marketed products. For example, although there were thousands of publications about tumor-targeted nanoparticles and their animal experiments, very few drugs were approved by the FDA [62]. Many clinical trials about tumor-targeted nanoparticles have failed [5,63,64]. Some research has questioned that the EPR effect should only be appealed on a case-by-case basis from clinical evidence [65,66]. Currently, there have been over 2000 gene therapy clinical trials (until 2016) in the world (http://www.abedia.com/wiley/), but only one product has been approved in Europe. Another example was pulmonary delivery systems for insulin in clinical trials [67]. Multiple problems confounded the development of pulmonary insulin including lower bioavailability, unexpected side-effects and other factors. The only one product approved by the FDA had to be withdrawn from the market owing to limited market uptake and other financial reasons [68]. The main difficulties of 2G DDSs could be inadequate understanding of the effects of DDSs on the human body and the inability to overcome biological barriers by simply altering the physicochemical properties of DDSs [4,5].

Future pharmaceutical research should combine different disciplines (e.g., material science, engineering, biology, physiology and computer science) to overcome physicochemical and biological barriers for new drug delivery systems. New materials always attract lots of attention in the drug delivery area [69]. However, too complex a design of smart materials might not be a good choice in drug delivery and simplicity could be the better solution under better understanding of the biological mechanism [70,71]. Physical approaches and microdevices for drug delivery could also be a good choice to overcome some difficult biological barriers [72,73]. Precision medicine will also provide a new opportunity for nanomedicines [74]. With rapid development of computer and IT techniques the integration of computer modeling, big data and artificial intelligence techniques to drug delivery will revolutionize the formulation development and drug delivery, which is called 'computational pharmaceutics' [75]. It should always be remembered that the ultimate goal of drug delivery research is to develop the proper products for clinical use to patients. The future of drug delivery relies on the capability of the next generation of pharmaceutical scientists to identify the key fundamental and practical issues in the pharmaceutical field with honest, independent and self-critical attitudes, rather than blindly accepting the unproven assumption and simply following the crowd [5,6,76]. Even at the beginning of their career, the next generation of pharmaceutical scientists needs to think outside the box to see the whole forest, instead of an individual tree.

Concluding remarks

The current study has provided a comprehensive and systematic insight to the pharmaceutics field from a global view during three recent decades. The annual publication number showed a steady increase in the past three decades. Japan had the largest contribution to pharmaceutical publications, whereas there was a continued declining trend after 1995. The USA dominated the largest number of 'high-cited' publications. The University of London ranked first-most productive institution, whereas Pfizer and GlaxoSmithKline led the pharmaceutics industry. Major research institutions in the globalization landscape of pharmaceutics research were mainly located within the USA, Europe and Asia. The collaborations between the USA and Europe were much stronger than those within Asia. The research concentration on pharmaceutics transited from conventional techniques to advanced drug delivery systems. Big data analysis (e.g., patents, clinical trials and products) could further help us to get a deep insight to the field of pharmaceutics.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2017.05.012.

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