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Review article

Evolution of the scientific literature on drug delivery: A 1974–2015 bibliometric study

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ABSTRACT

This study charts the growth of the drug delivery literature published during 1974–2015 from journals indexed in the *Science Citation Index Expanded* database. The growth of publications on drug delivery paralleled the total scientific publications for three decades (1974–2003); however, from 2004 to 2015 it exploded fourfold, while the total increased only 1.75 fold. Industrialized countries (USA, UK, Germany, Japan, Italy, France and Canada) were the most prolific during the first decades, but in 2014–2015 China, India and South Korea ranked 1st, 3rd and 4th respectively among the productive countries. The number of participating countries increased fivefold (from 19 to 96). During the last 15 years, the journals targeted by drug delivery research increased nearly 2.4 fold (416 to 1001) and three journals (*Journal of Controlled Release, Advanced Drug Delivery Reviews,* and *International Journal of Pharmaceutics*) published nearly one-fifth of the drug delivery research in 2014–2015.

1. Introduction

Drug delivery (D.D.) concerns a large spectrum of approaches, formulations, technologies, and systems used to achieve and optimize the transport of pharmaceutical compounds in the human body by increasing their quantity and half-life in biological fluids while minimizing their adverse effects. One of the main benefits of D.D. systems is the opportunity to select the anatomical route through which drugs can be administered to the human body on the basis of the desired effect, the disease, and the type of molecule. The first D.D. devices were developed in the nineties and solely consisted of transdermal and oral delivery systems based on improving the drug release kinetics in order to obtain a constant rate over a certain period of time to enhance drug bioavailability, patient compliance, and decrease therapy costs [1]. Interestingly, since diseases such as cancer have been addressed as transport issues [2], there has been an increase in the exploitation of nanoparticles for medical applications. As a result, nanotechnology, whose conceptual foundations were laid down by Richard Feynman [3], has become one of the fastest growing research areas [4]. In particular, nanotherapeutics (i) improve the properties of drugs without affecting the carried molecules, (ii) provide the drugs with the ability to overcome several biological barriers that normally reduce the accumulation of therapeutics in the target area (iii) can consist in nanovectors loaded with various compounds such as two different drugs or a drug with an imaging agent in order to track the particles, (iv) increase the therapeutic impact by interacting with specific tissues and cells through surface functionalization and, (v) permit potential clinical application. Several types of nanovectors such as liposomes [5–7], polymeric nanoparticles [8], micelles [9,10], and iron based nanoparticles [11] have been exploited. Unfortunately, nanotechnology did not achieve the expected results, in fact a recent work showed that only a small portion of the injected dose accumulated at the target site [12] due to the presence of multiple biological barriers in the body that represent the main obstacles of D.D [13]. New technologies arise from a multidisciplinary approach that involves biology, chemistry, physics, and engineering based on the micro scale. Multistage discoidal vectors are an example of the next generation D.D. systems, and can be loaded with nanotherapeutics thereby overcoming biological barriers in a sequential manner to promote the accumulation at the site of interest [14,15]. In addition to injectable D.D. systems, other devices must be mentioned. Examples include the transdermal drug D.D., which is an effective alternative to the oral administration of various compounds

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[16], osmotic D.D. systems, that are suitable for implantation as well as for oral delivery by exploiting the movement of water through a selectively permeable membrane driven by a difference in osmotic pressure [17], and mucoadhesive D.D. systems which are tablets, polymer gels, and films that remain in close contact with the tissue such as the oral cavity, the eye, and the nasal cavity resulting in high drug accumulation at the site of release [18].

In addition, implantable D.D. systems are based on microfluidics and can exploit both micro- and nano-scale technologies. Such systems display some disadvantages such as higher cost and the necessity to be implanted with surgery, but at the same time they provide therapeutic drug concentrations over the whole treatment, even if it requires continuous or repeated administration [19–21].

External Medical devices play an important role in several therapies such as the therapies for pulmonary diseases. On the market there are several devices working with passive and active mechanisms such as dry powder inhalers (DPI) that make up a large part of the market [22]. It is important to stress that all this approaches, formulations, technologies, and systems arise from basic science or bench research and can potentially be translated into clinical applications.

During the last decades, qualitative evaluations of the progress in D.D. are available through the publication of numerous reviews [23,24]. Although such literature reviews provide readers updated and synthesized subject information, to our knowledge there is an absence of quantitative data describing the scientific publishing pattern of D.D. over time thus preventing scientists, physicians, decision-makers, politicians, and others a global view of scholarly communication in this field.

The aim of this study is to use bibliometric techniques to provide a 40 + year longitudinal view (1974 to 2015) of the evolution of the scientific literature on D.D. without focusing on a specific area. Two indicators were chosen to follow this evolution: the publishing outputs of D.D. research by countries, and the journals used to publish research on D.D.

2. Method

The data were collected between 20th October and 10th November 2016 from the *Science Citation Index Expanded* (SCI-E), a multidisciplinary index to the journal literature of science and technology, through the ISI *Web of Knowledge*™ (http://www.isiwebofknowledge.com/) – a part of the *Web of Science* (WoS) database.

The search strategy consisted of:

- all documents published in journals with at least one of the following keyphrases in the title: drug deliver*, drug release*, drug carr*, sustained release*, controlled release*, intranasal administra*, sustained deliver*, intelligent delivery system, pulsatile releas*, transdermal deliver*, drug nanocarr*, nasal deliver*, rectal deliver*, oral deliver*, buccal deliver*, drug nanopart*, nanopart* deliv*, nanopart* releas*, nanoparticule drug, with asterisks replacing characters following the word-stems;
- all documents published in the following journals: *Journal of Controlled Release, Advanced Drug Delivery Reviews, Expert Opinion on Drug Delivery, Drug Delivery, Journal of Drug Delivery Science and Technology, Current Drug Delivery, Critical Reviews in Therapeutic Drug Carrier Systems, Drug Delivery and Translational Research, Journal of Aerosol Medicine and Pulmonary Drug Delivery, Polymeric Drug Delivery I Particulate Drug, Cancer Drug Delivery, Polymeric Drug Delivery II Polymeric Matrix, Polysaccharides for Drug Delivery and Pharmaceutical Applications, Advances in Controlled Drug Delivery Science Technology and Products, Filled Elastomers Drug Delivery Systems*.

Only journal article and journal review-type publications (as defined in the SCI-E database) published during 1974–2015 were considered.

The 2015 impact factors (IF) were collected using the Thomson Scientific *Journal Citation Reports*. Downloaded documents were then analyzed by countries, and for each two-year period from 1974 to 2015 the following parameters were considered:

- the total number of publications authored or co-authored by researchers in each country – publications issued from more than one country were assigned equally to each contributing country – and,
- the top-10 most prolific journals publishing drug delivery research.

Publications originating from England, Wales, Scotland and Northern Ireland were assigned to the United Kingdom (UK), and the European Union (EU) was defined as the official member States registered on the 1st of January for each of the two year-periods considered. The set of BRICS countries includes Brazil, Russia, India, China and South Africa.

3. Results and discussion

3.1. Evolution of the drug delivery research

During the past 40 + years the scientific literature on D.D. emerged and has grown rapidly (Fig. 1). The global evolution of D.D. literature can be split into 2 parts. From 1974 to the start of the 2000s, the D.D. scientific literature grew slowly (from 63 publications published in 1974–1975 to 1750 publications in 2000–2001) paralleling the growth of the total WoS literature. However, from 2002 to 2015, the growth exploded: there was a fourfold increase of the D.D. literature (1848 D.D. publications published in 2002–2003 vs. 7823 in 2014–2015), while the total for the WoS literature only increased 1.75 fold.

3.2. Evolution of countries publishing drug delivery research

As shown in Table 1, from 1974 to 2015 the number of countries involved in D.D. research increased fivefold: 19 countries in the 1974–1975 period, 36 in 1984–1985, 52 in 1994–1995, 72 in 2004–2005, and 96 countries in 2014–2015.

In the first four of the five two-year periods analyzed the USA was by far the most productive country with a lead of 43.6% of the total share in 1984–1985; however, it ranked second in 2014–2015 with only 21.4% of the total publications. Some industrialized countries (UK, Japan, Germany, France, Netherlands and Canada) that were present among the leading countries in 1984–1985 slowly lost their high ranking positions, but remained among the leading countries in 2014–2015. These observations are in line with the domination (in terms of the number of publications) of these countries in various fields of Biology [25], Medicine [26,27], and in research fields more closely allied to D.D. research such as Nanotechnologies [28] and Liposomes

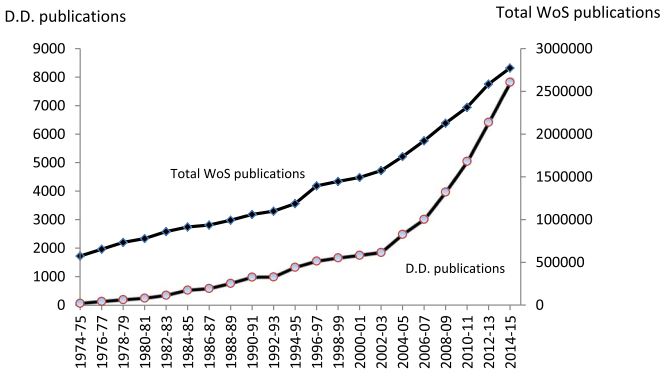

Fig. 1. Number of drug delivery and total WoS research articles and review publications: 1974–2015.

Table 1
The number of drug delivery research articles and review publications by countries, the EU countries, BRICS countries, and the World: 1974–1975, 1984–1985, 1994–1995, 2004–2005 and 2014–2015.

1974–1975			
Countries/territories	# publications	%	Rank
World	63	100.0	
EU	18	28.5	
USA	22	34.9	1
UK	12	19.0	2
Canada	4	6.3	3
Norway	3	4.7	4
Fed Rep Germany	2	3.1	5
Germany Dem Rep	2	3.1	5
Sweden	2	3.1	5
United Arab Rep	2	3.1	5
Belgium	1	1.6	9
Bulgaria	1	1.6	9
Denmark	1	1.6	9
Finland	1	1.6	9
India	1	1.6	9
Ireland	1	1.6	9
Israel	1	1.6	9
Netherlands	1	1.6	9
New Zealand	1	1.6	9
Switzerland	1	1.6	9
Trinidad & Tobago	1	1.6	9

1984–1985			
Countries/territories	# publications	%	Rank
World	527	100.0	
EU	169	32.0	
USA	230	43.6	1
UK	80	15.1	2
Japan	33	6.2	3
Fed Rep Germany	26	4.9	4
France	21	3.9	5
Netherlands	18	3.4	6
Canada	16	3.0	7
Israel	13	2.4	8
Denmark	11	2.0	9
Austria	10	1.8	10
India	10	1.8	10
Italy	10	1.8	10
Belgium	8	1.5	13
Australia	6	1.1	14
Switzerland	6	1.1	14
Egypt	5	0.9	16
Finland	4	0.7	17
Sweden	4	0.7	17
Turkey	4	0.7	17
Czechoslovakia	3	0.5	20
New Zealand	3	0.5	20
Poland	3	0.5	20
South Africa	3	0.5	20
Taiwan	3	0.5	20
Germany Dem Rep	2	0.3	25
Ireland	2	0.3	25
Jordan	2	0.3	25
Norway	2	0.3	25
Thailand	2	0.3	25
Argentina	1	0.1	30
Bahamas	1	0.1	30
Hungary	1	0.1	30
Kenya	1	0.1	30
Nigeria	1	0.1	30
Peoples R China	1	0.1	30

Table 1 *(continued)*

1984–1985			
Countries/territories	# publications	%	Rank
Philippines	1	0.1	30

1994–1995			
Countries/territories	# publications	%	Rank
World	1329	100.0	
BRICS	67	5.0	
EU	411	30.9	
USA	533	40.1	1
Japan	173	13.0	2
UK	150	11.2	3
France	62	4.6	4
Germany	60	4.5	5
Italy	57	4.2	6
Canada	52	3.9	7
Netherlands	42	3.1	8
Israel	41	3.0	9
India	36	2.7	10
Belgium	31	2.3	11
Sweden	23	1.7	12
Switzerland	17	1.2	13
Spain	17	1.2	13
Denmark	17	1.2	13
Finland	15	1.1	16
Peoples R China	15	1.1	16
Turkey	15	1.0	18
Australia	14	< 1	19
Egypt	12	< 1	20
Taiwan	12	< 1	20
South Africa	10	< 1	22
New Zealand	9	< 1	23
Austria	8	< 1	24
Czech Rep	7	< 1	25
Norway	6	< 1	26
Russia	6	< 1	26
South Korea	6	< 1	26
Saudi Arabia	5	< 1	29
Greece	4	< 1	30
Hungary	4	< 1	30
Iceland	4	< 1	30
Argentina	3	< 1	33
Bulgaria	3	< 1	33
Chile	3	< 1	33
Croatia	3	< 1	33
Hong Kong	2	< 1	37
Malaysia	2	< 1	37
Mexico	2	< 1	37
Nigeria	2	< 1	37
Portugal	2	< 1	37
Singapore	2	< 1	37
Thailand	2	< 1	37
Bangladesh	1	< 1	44
Estonia	1	< 1	44
Ireland	1	< 1	44
Jordan	1	< 1	44
Philippines	1	< 1	44
Poland	1	< 1	44
Romania	1	< 1	44
Slovenia	1	< 1	44
Ukraine	1	< 1	44

(continued on next page)

Table 1 *(continued)*

2004–2005			
Countries/territories	# publications	%	Rank
World	2485	100.0	
BRICS	373	15.0	
EU	833	33.5	
USA	746	30.0	1
Japan	262	10.5	2
UK	222	8.9	3
Peoples R China	169	6.8	4
Germany	153	6.1	5
India	146	5.8	6
South Korea	137	5.5	7
Italy	126	5.0	8
France	126	5.0	9
Canada	98	3.9	10
Spain	57	2.2	11
Switzerland	56	2.2	12
Netherlands	55	2.2	13
Australia	47	1.8	14
Belgium	46	1.8	15
Singapore	45	1.8	16
Taiwan	44	1.7	17
Israel	38	1.5	18
Turkey	36	1.4	19
Austria	33	1.3	20
Sweden	33	1.3	20
Brazil	31	1.2	22
Finland	23	< 1	23
Iran	23	< 1	23
Ireland	21	< 1	25
Denmark	17	< 1	26
Egypt	17	< 1	26
New Zealand	17	< 1	26
Russia	17	< 1	26
Portugal	16	< 1	30
Thailand	15	< 1	31
Czech Rep	13	< 1	32
South Africa	12	< 1	33
Norway	11	< 1	34
Romania	11	< 1	34
Argentina	8	< 1	36
Greece	8	< 1	36
Mexico	8	< 1	36
Malaysia	7	< 1	39
Croatia	6	< 1	40
Kuwait	6	< 1	40
Slovenia	6	< 1	40
Iceland	4	< 1	43
Philippines	4	< 1	43
Poland	4	< 1	43
Cuba	4	< 1	43
Hungary	3	< 1	47
Jordan	3	< 1	47
Nigeria	3	< 1	47
Pakistan	3	< 1	47
Saudi Arabia	3	< 1	47
Yugoslavia	3	< 1	47
Bulgaria	2	< 1	53
Estonia	2	< 1	53
Indonesia	2	< 1	53
U Arab Emirates	2	< 1	53
Bahrain	1	< 1	57
Chile	1	< 1	57
Kazakhstan	1	< 1	57
Latvia	1	< 1	57
Lebanon	1	< 1	57
Lithuania	1	< 1	57
Malta	1	< 1	57
Myanmar	1	< 1	57
Nepal	1	< 1	57
Rep Of Georgia	1	< 1	57
Serbia Montenegro	1	< 1	57
Slovakia	1	< 1	57
Tanzania	1	< 1	57

Table 1 *(continued)*

2004–2005			
Countries/territories	# publications	%	Rank
Tunisia	1	< 1	57
Ukraine	1	< 1	57
Uruguay	1	< 1	57

2014–2015			
Countries/territories	# publications	%	Rank
World	7824	100.0	
BRICS	3153	40.2	
EU	1924	20.5	
Peoples R China	2042	26.0	1
USA	1675	21.4	2
India	872	11.1	3
South Korea	408	5.2	4
UK	383	4.8	5
Germany	341	4.3	6
Japan	290	3.7	7
Italy	252	3.2	8
France	236	3.0	9
Iran	229	2.9	10
Spain	219	2.7	11
Australia	208	2.6	12
Canada	190	2.4	13
Brazil	146	1.8	14
Taiwan	144	1.8	15
Saudi Arabia	140	1.7	16
Egypt	139	1.7	17
Netherlands	123	1.5	18
Portugal	121	1.5	19
Singapore	119	1.5	20
Switzerland	113	1.4	21
Belgium	95	1.2	22
Malaysia	94	1.2	23
Israel	83	1.0	24
Denmark	71	< 1	25
Turkey	69	< 1	26
Thailand	65	< 1	27
Pakistan	62	< 1	28
Poland	61	< 1	29
Sweden	61	< 1	29
Russia	60	< 1	31
Romania	59	< 1	32
South Africa	54	< 1	33
Finland	52	< 1	34
Austria	48	< 1	35
Greece	48	< 1	35
Argentina	42	< 1	37
Ireland	42	< 1	37
Czech Rep	34	< 1	39
Hungary	34	< 1	39
Norway	34	< 1	41
New Zealand	29	< 1	42
Serbia	23	< 1	43
Slovenia	23	< 1	43
Mexico	22	< 1	45
Nigeria	22	< 1	45
Jordan	18	< 1	47
Chile	17	< 1	48
Vietnam	16	< 1	49
U Arab Emirates	11	< 1	50
Estonia	10	< 1	51
Bulgaria	8	< 1	52
Croatia	8	< 1	52
Indonesia	8	< 1	52
Bangladesh	6	< 1	55
Colombia	6	< 1	55
Iceland	6	< 1	55
Slovakia	6	< 1	55

(continued on next page)

Table 1 *(continued)*

2014–2015			
Countries/territories	# publications	%	Rank
Algeria	5	< 1	59
Cuba	5	< 1	59
Syria	5	< 1	59
Iraq	4	< 1	62
Mauritius	4	< 1	62
Tunisia	4	< 1	62
Cyprus	3	< 1	65
Lebano	3	< 1	65
Luxembourg	3	< 1	65
Morocco	3	< 1	65
Philippines	3	< 1	65
Qatar	3	< 1	65
Rep of Georgia	3	< 1	65
Byelarus	2	< 1	72
Ghana	2	< 1	72
Montenegro	2	< 1	72
Oman	2	< 1	72
Tanzania	2	< 1	72
Yemen	2	< 1	72
Azerbaijan	1	< 1	78
Benin	1	< 1	78
Brunei	1	< 1	78
Burkina Faso	1	< 1	78
Cameroon	1	< 1	78
Costa Rica	1	< 1	78
Ecuador	1	< 1	78
Ethiopia	1	< 1	78
Kenya	1	< 1	78
Kuwait	1	< 1	78
Libya	1	< 1	78
Macedonia	1	< 1	78
Myanmar	1	< 1	78
Nepal	1	< 1	78
Sudan	1	< 1	78
Uganda	1	< 1	78
Ukraine	1	< 1	78
Venezuela	1	< 1	78
Zimbabwe	1	< 1	78

[29]. Contrariwise, two Asian newcomers, China and South Korea, along with the continuous presence of India among the productive countries have progressively joined the industrialized countries in their D.D. research efforts: China from ranked 17th in 1994–1995, 4th in 2004–2005, to 1st in 2014–2015; and South Korea from ranked 28th in 1994–1995, 7th in 2004–2005, to 4th in 2014–2015.

The increasingly leading position of China is also supported by the fact that five of the ten most productive institutions in D.D. research are located in China (data not shown). The recent increase of Chinese D.D. publication (see Fig. 2) can be correlated to the explosion of publications authored by Chinese scientists in Pharmacology and Pharmacy journals [30]. More globally, it can be seen as a consequence of the

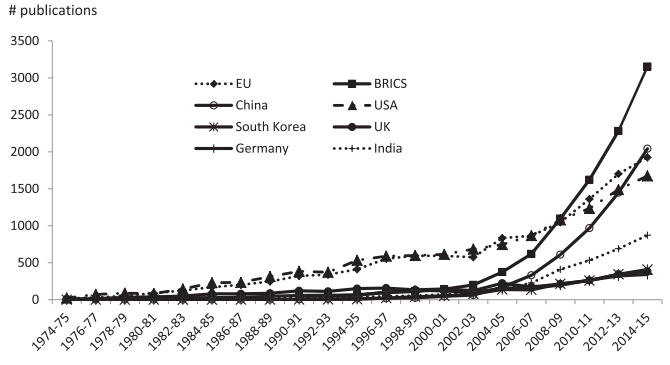

Fig. 2. Number of drug delivery research articles and review publications for top-producing countries, the EU countries and BRICS countries: 1974–2015.

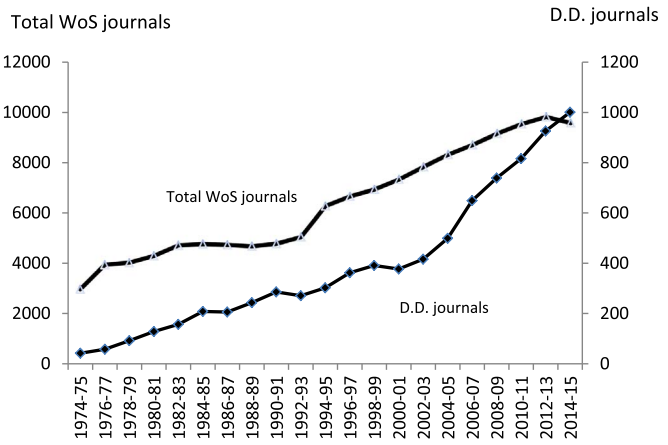

Fig. 3. Number of journals publishing drug delivery research articles and review publications: 1974–2015.

recent increase of China's total expenditure on Research and Development – on average 23% per annum over the last decade [31]. Additionally, the recent ascendancy of China over the USA was predicted in a report of the Royal Society [32].

While the share of D.D. publications among the EU countries remained stable from 1994 to 2005 (30.9% in 1994–1995, and 33.5% in 2004–2005) but decreased to 20.5% in 2014–2015; the share of the BRICS countries increased continuously (mainly due to the D.D. research output of China and India): 5.0% in 1994–1995, 15.0% in 2004–2005 and 40.2% in 2014–2015. As noted earlier, three members of BRICS (China, India and South Korea) were present in the top-ranking countries in 2004–2005 and in 2014–2015.

3.3. Evolution of journals publishing drug delivery research

During the 40 + years studied, the number of journals targeted by D.D. researchers increased in two trajectories (Fig. 3). From 1974 to the beginning of the 2000s, the increase of D.D. journals more or less paralleled that of the SCI-E database; however, from 2002 to 2015, the number of D.D. journals increased 2.4 fold (416 journals in 2002–2003 and 1001 for 2014–2015) while the total number of journals indexed in the SCI-E increased only 1.2 fold (7822 journals for 2002–2003 and 9550 for 2014–2015).

The top-10 most productive journals on D.D. research in each of the last four time periods are presented in Table 2. During the last three periods analyzed (1994–1995, 2004–2005 and 2014–2015) three journals (*Journal of Controlled Release, Advanced Drug Delivery Reviews,* and *International Journal of Pharmaceutics*) were ranked among the top-4 most productive journals; two other journals (*Drug Delivery* and *Journal of Drug Delivery Science and Technology*) were present among the top-10 most productive journals in the two most recent rankings (2004–2005 and 2014–2015). For the last time period studied, eight of the top-10 ranked journals had an IF > 3.00 with a maximum IF of 15.60 for the journal *Advanced Drug Delivery Reviews*.

Furthermore, during the same three time periods the distributions of publications in journals were markedly skewed:

- in 1994–1995, 1% (3 journals) of D.D journals concentrated 39.7% of the 1329 D.D. publications, while 91.3% (276 journals) of D.D. journals had ≤ 5 publications;
- in 2004–2005, 1% (5 journals) of D.D. journals concentrated 50% of the 2485 D.D. publications, while 91.5% (457 journals) of D.D. journals had ≤ 5 publications; and finally
- in 2014–2015, 1% (10 journals) of the journals concentrated 36.4% of the 7823 D.D. publications, while 81.9% (820 journals) of D.D. journals had ≤ 5 publications.

Table 2
The top-10 journals publishing drug delivery research articles and review publications: 1984–1985, 1994–1995, 2004–2005 and 2014–2015 (including 2015 IFs).

1984–1985

Source titles	# publications	% of 527	WoS category
Cancer Drug Delivery	53	10.0	n.a.
International Journal of Pharmaceutics	29	5.5	Pharmacology & Pharmacy
Drug Development and Industrial Pharmacy	18	3.4	Chemistral, Medicinal;Pharmacology & Pharmacy
Journal of Pharmaceutical Sciences	17	3.2	Chemistry, Multidisciplinary; Chemistry, Medicinal; Pharmacology & Pharmacy
British Journal of Clinical Pharmacology	15	2.8	Pharmacology & Pharmacy
Journal of Pharmacy and Pharmacology	11	2.0	Pharmacology & Pharmacy
International Journal of Clinical Pharmacology and Therapeutics	11	2.0	Pharmacology & Pharmacy
Chemical Pharmaceutical Bulletin	11	2.0	Chemistry, Multidisciplinary; Chemistry, Medicinal; Pharmacology & Pharmacy
American Journal of Medicine	8	1.5	Medicine, General & Internal
Pharmacy International	7	1.3	n.a.
Biopharmaceutics Drug Disposition	7	1.3	Pharmacology & Pharmacy
Annals of the New York Academy of Sciences	7	1.3	n.a.

1994–1995

Source titles	# publications	% of 1329	WoS category
Journal of Controlled Release	325	24.4	Chemistry, Multidisciplinary Pharmacology & Pharmacy
Advanced Drug Delivery Reviews	107	8.0	Pharmacology & Pharmacy
International Journal of Pharmaceutics	96	7.2	Pharmacology & Pharmacy
Drug Development and Industrial Pharmacy	65	4.8	Chemistral, Medicinal;Pharmacology & Pharmacy
Journal of Pharmaceutical Sciences	47	3.5	Chemistry, Multidisciplinary; Chemistry, Medicinal; Pharmacology & Pharmacy
Pharmaceutical Research	45	3.3	Chemistry, Multidisciplinary Pharmacology & Pharmacy
Chemical Pharmaceutical Bulletin	19	1.4	Chemistry, Multidisciplinary; Chemistry, Medicinal; Pharmacology & Pharmacy
STP Pharma Sciences	17	1.2	Pharmacology & Pharmacy
Journal of Pharmacy and Pharmacology	16	1.2	Pharmacology & Pharmacy
Journal of Drug Targeting	15	1.0	Pharmacology & Pharmacy
Journal of Clinical Pharmacology	15	1.0	Pharmacology & Pharmacy
Critical Reviews in Therapeutics Drug Carrier System	15	1.0	n.a.

2004–2005

Source titles	# publications	% of 2485	WoS category
Journal of Controlled Release	678	27.2	Chemistry, Multidisciplinary Pharmacology & Pharmacy
Advanced Drug Delivery Reviews	217	8.7	Pharmacology & Pharmacy
Journal of Drug Delivery Science and Technology	134	5.3	Pharmacology & Pharmacy
International Journal of Pharmaceutics	127	6.1	Pharmacology & Pharmacy
Drug Delivery	85	3.4	Pharmacology & Pharmacy
Biomaterials	46	1.8	Engineering, Biomedical; Materials Science, Biomaterials
Drug Development and Industrial Pharmacy	41	1.6	Chemistral, Medicinal;Pharmacology & Pharmacy
European Journal of Pharmaceutics and Biopharmaceutics	40	1.6	Pharmacology & Pharmacy
Pharmaceutical Research	31	1.2	Chemistry, Multidisciplinary Pharmacology & Pharmacy
Journal of Applied Polymer Science	31	1.2	Polymer Science

2014–2015

Source titles	# publications	% of 7823	IF (2015)	WoS category
Journal of Controlled Release	962	12.2	7.44	Chemistry, Multidisciplinary Pharmacology & Pharmacy
Advanced Drug Delivery Reviews	280	3.5	15.60	Pharmacology & Pharmacy
International Journal of Pharmaceutics	277	3.5	3.99	Pharmacology & Pharmacy
Expert Opinion on Drug Delivery	251	3.2	5.43	Pharmacology & Pharmacy
RSC Advances	228	2.9	3.28	Chemistry, Multidisciplinary
Journal of Drug Delivery Science and Technology	217	2.7	0.62	Pharmacology & Pharmacy
Journal of Materials Chemistry B	186	2.3	4.87	Materials Science, Biomaterials
Drug Delivery	179	2.2	4.84	Pharmacology & Pharmacy
Colloids and Surfaces B Biointerfaces	141	1.8	3.90	Biophysics; Chemistry, Physical; Materials Science, Biomaterials
Current Drug Delivery	128	1.6	1.44	Pharmacology & Pharmacy

With the rapid growth of the scientific literature, review publications are essential updating tools for researchers [33]. During the last fifteen years, the number of D.D. review publications increased 3.5 fold (347 reviews in 2000–2001 vs. 1220 in 2014–2015) while the total number of reviews in the SCI-E database only increased 2.6 fold (60,394 in 2000–2001 vs. 155,926 in 2014–2015). As in numerous scientific disciplines, a review journal, *Advanced Drug Delivery Reviews*, specifically dedicated to the field of D.D., was launched in 1987. This journal publishes approximately 150 publications per year, has a 2015 JCR impact factor of 15.60, and ranked 3rd (of 255) among the leading

journals in the *Pharmacology & Pharmacy* WoS category. Although this journal published most of the D.D. review publications, other review publications were scattered among a broad range of journals: prestigious journals such as *The Lancet* [34], *Nature* [35], *Nature Reviews Drug Discovery* [36] and more specialized journals [37,38]. Additionally, the increasing ratio of review publications/review + non-review publications from 1974 to 2000 and the stabilization since 2001 to 2015 from between 15% to 20% are indications of the evolving and maturing of the D.D. field.

Although two emblematic journals targeted by D.D. researchers began in the mid-1980s (*The Journal of Controlled Release* in 1984 and *Advanced Drug Delivery Reviews* in 1987), the recent explosion of the D.D. literature was accompanied by the launching of six more journals dedicated to D.D. in the 2000s: *The Journal of Drug Delivery Science Technology* (launched in 2004), *Expert Opinion on Drug Delivery* (2004), *Current Drug Delivery* (2004), *Drug Delivery* (2007), *Journal of Aerosol Medicine and Pulmonary Drug Delivery* (2008) and *Drug Delivery and Translational Research* (2011).

From 1974 to 2015 the scientific literature on D.D. spread among a broad range of scientific fields (WoS subject categories): 24 in 1974–1975; 70 in 1984–1985, 100 in 1994–1995; 124 in 2004–2005; and 144 in 2014–2015. During this period, the WoS subject category *Pharmacology & Pharmacy* was the most targeted field; some of the top-leading WoS fields (*Ophthalmology* and *Dermatology*) disappeared while other fields gained in importance: *Biochemistry Molecular Biology* in 1984–1985, *Materials Science Biomaterials*, *Polymer Science*, or *Engineering Biomedical* in 1994–1995, and *Nanoscience Nanotechnology* and *Chemistry Physical* in 2004–2005.

4. Conclusion

This brief bibliometric investigation on the evolution of the scientific literature on D.D. during 40 + years reveals three major trends: an explosion of D.D.-related publications (63 publications for 1974–1975 vs. 7824 for 2014–2015); the spread and distribution of publications among publishing countries (19 countries in 1974–1975 vs. 96 in 2014–2015); and an increase of the number of journals involved in D.D. publications (42 journals in 1974–1975 vs. 1001 in 2014–2015). Despite an overall increase in publications that seem to result in a rapid advancement of the field after an initial success achieved by the first D.D. systems, production of approved D.D. systems for clinical use slowed down in the following years. This happens because overcoming the physiochemical and biological barriers is still a challenge [39]. The development of new delivery systems that are able to address current challenges in medicine was often driven by discoveries in basic science. Specifically, biology gave a huge boost to the development of nanotechnologies with discoveries such as the enhanced permeability and retention (EPR) effect [40]. Likewise, chemistry and material sciences have had a tremendous impact on the development of all D.D. systems, while physics and mathematics have added to the understanding of transport through the organism. Therefore, it is easy to understand how the collaboration among different disciplines is fundamental and that it is critical to maintain a detached view from the major scientific trend to keep up with new scientific discoveries [41]. Overcoming such limits will have a great impact also on the healthcare economy by introducing new technologies. As an example, the commercialization of Doxil [42], the first approved nanoformulated drug, decreased the cost of treatment and hospitalization [43]. Furthermore, the economic investments play a critical role in the translation of basic research into the clinic. In particular, the funding management varies among countries. For example, there is a substantial difference in the funding approaches between the U.S. and China, which are the two leading countries in D.D. research. U.S. governmental agencies that provide research funding, such as the National Institutes of Health (NIH), promote the development of projects in which the translational aspect is a major component, thereby making the U.S. the leader in translational research. On the other hand, in the last few decades China has been investing most of its funds in basic sciences, which has led to a massive production of scientific publications less focused on translational science.

In the years to come there will be an increase in the development and the commercialization of D.D. systems thereby resulting in increased research activities worldwide and consequentially in an increased production of related scientific publications, probably with a similar trend observed in the last two decades among the countries considered.

We hope that our study will arouse interest in scientists, physicians, decision-makers, and politicians in extending this bibliometric study of the D.D. field.

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