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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

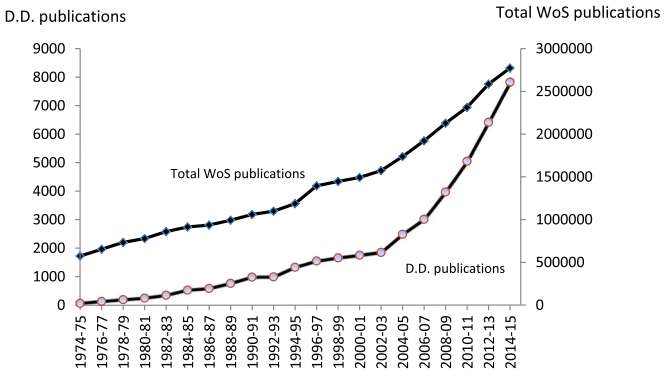

Fig. 1. Number of drug delivery and total WoS research articles and review publications: 1974–2015.