Revista da Sociedade Brasileira de Medicina Tropical
Journal of the Brazilian Society of Tropical Medicine
Vol.:52:e20180246: 2019
doi: 10.1590/0037-8682-0246-2018

Short Communication

Use of pharmaceutical nanotechnology for the treatment of leishmaniasis

***Carine Santana Ferreira Marques*[1],[2], *Jorge Barreto Machado Júnior*[1],[2], *Lucas Rannier de Melo Andrade*[1],[2], *Luciana Nalone Andrade*[1],[2], *André Luis Souza dos Santos*[3], *Maria do Socorro Pires e Cruz*[4], *Marco Chaud*[5], *Alini Tinoco Fricks*[1],[2] and *Patrícia Severino*[1],[2]**

[1]. Programa de Pós-Graduação em Biotecnologia Industrial, Universidade Tiradentes, Aracaju, SE, Brasil.
[2]. Laboratório de Nanotecnologia e Nanomedicina, Instituto de Tecnologia e Pesquisa, Aracaju, SE, Brasil.
[3]. Departamento de Microbiologia Geral, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil.
[4]. Faculdade de Veterinária, Universidade Federal do Piauí, Teresina, PI, Brasil.
[5]. Laboratório de Biomateriais e Nanotecnologia, Universidade de Sorocaba, Sorocaba, SP, Brasil.

Abstract

Introduction: Leishmaniasis is a global public health concern. Currently available treatments are associated with considerable side effects. The use of nanotechnology has shown promise for improving efficacy and bioavailability and minimizing side effects. **Methods:** This study investigated available literature, including patents and scientific articles, to identify advances in the use of nanotechnology for the treatment of leishmaniasis. **Results:** Our findings revealed a stable number of patents and scientific articles published over the past five years. **Conclusions:** There is a need to intensify research on the use of nanotechnology for the treatment of leishmaniasis.

Keywords: Leishmaniasis. Drugs. Nanotechnology. Treatment.

Neglected tropical diseases (NTDs) affect approximately 1 billion individuals living in social exclusion, thus posing considerable challenges to public health[1]. Leishmaniasis is the most common NTD[2], with 80% of cases occurring in populations with a daily family income of two dollars or less. An estimated 350 million people are at risk, with an incidence rate of approximately 2 million cases per year with varying clinical forms. Drugs currently used for leishmaniasis show limited efficacy[3].

Therapy with conventional formulations is limited because of the need for parenteral administration, collateral effects, parasite resistance, and treatment failure. In the current study, we identified few scientific articles and patents relating research into new treatments for leishmaniasis. Although this disease affects millions of people every year, treatment is based primarily on the use of N-methylglucamine antimoniate, pentamidine, and amphotericin B[4,5]. Chemotherapy triggers unfavorable reactions, including toxicity, low efficacy, and the need for long-term treatment. In addition, resistance to traditional conventional treatment is considered a major problem for disease control.

Accordingly, the World Health Organization has encouraged the development of new drugs to counter this disease. However, drug development is a time-consuming and expensive process[6]. Promising alternatives include the use of pharmaceutical technology in combination with different nanocarriers to minimize side effects and improve efficacy and bioavailability. Amphotericin B is an example of successful nanotechnology use. The active agent causes adverse effects such as fever, headache, nausea, vomiting, hyporexia, tremors, chills, phlebitis, cyanosis, hypotension, hypopotassemia, hypomagnesemia, anaphylaxis, seizure, and alteration of function[7]. Two forms of amphotericin B are currently commercially available: amphotericin B deoxycholate and liposomal amphotericin B. The liposomal form causes reduced toxicity and side effects, and increased quality of life for the patient.

Nanotechnology enables new approaches in drug delivery, optimizes pharmacokinetic properties, and improves drug absorption, distribution, and excretion[8]. Moreover, it is useful in

Corresponding author: Dra. Patrícia Severino.
e-mail: pattypharma@gmail.com / patricia_severino@itp.org.br
Orcid: 0000-0001-6527-6612
Received 19 June 2018
Accepted 29 November 2018

overcoming challenges such as low solubility, low permeability, high toxicity, and degradation of conventional drugs. Several studies have described the use of various nanocarriers for the treatment of leishmaniasis[9-11]. In particular, the use of cyclodextrin is highlighted[12-14] and has been applied in the pharmaceutical field primarily to increase solubility, chemical stability, and bioavailability. It may also be used to mask the unpleasant odors and flavors of certain drugs, reduce or eliminate ocular or gastrointestinal irritation, and prevent drug interactions[15].

For the development of new medicines that use nanotechnology for composition and processing, it is important to understand the performance of existing products[13]. Considering the growing volume of information and the increasing ease of access to knowledge, it is becoming necessary to use procedures and various sources of information and knowledge to aid in decision making, for example through prospective techniques. Among these, the analysis of patents is particularly important because of the electronic availability of large worldwide public databases, the important temporal retrospective available, and details about the inventions and technologies described in patents.

The objective of this study was to understand the dynamics of patenting related to the use of nanotechnology in the treatment of leishmaniasis by means of a prospective review of scientific articles and patents related to leishmaniasis, nanotechnology, and cyclodextrins. This enables us to correlate the potential development of new patents for products against neglected diseases and the temporal evolution of patents relating to nanotechnology and leishmaniasis.

This study investigated patents deposited at the following institutions: the Brazilian Patent Office (INPI), European Patent Office (ESPACENET), and World Intellectual Property Organization (WIPO). Data were collected in January 2018. For ESPACENET and WIPO, the following search terms were used: a) "leishmaniasis", b) "nanotechnology", c) "cyclodextrin", d) "leishmaniasis and nanotechnology", e) "leishmaniasis and cyclodextrin", f) "nanotechnology and cyclodextrin", and g) "leishmaniosis and nanotechnology and cyclodextrin". For INPI, the following search terms were used: "leishmaniose", "nanotecnologia", "ciclodextrina", "leishmaniose e nanotecnologia", "leishmaniose e ciclodextrina", "nanotecnologia e ciclodextrina", and "leishmaniose, nanotecnologia e ciclodextrina".

The aforementioned search terms were selected in the title/abstract fields and the Boolean operators "and" and "e" were adopted. The same search terms were used to search for publications in the Science Direct, PubMed, and Medline databases. The period of filing (2013–2017), the International Patent Classification status, and the country in which the patent was filed were taken into consideration to characterize the technological advancements of nanotechnology relating to the diagnosis and treatment of leishmaniasis.

In total, 12 855 patent deposits were identified using these search terms between January 1, 2013 and December 31, 2017 (**Table 1**). Although Brazil has a high prevalence of leishmaniasis, an initial search in the INPI database using the search term "leishmaniose" yielded only 47 deposited patents. In the ESPACENET and WIPO databases, a search using the term "leishmaniasis" yielded only 155 and 268 deposited patents, respectively.

Another search using the search terms "nanotechnology" and "nanotecnologia" yielded 21, 868, and 819 patent deposits in INPI, ESPACENET, and WIPO, respectively. Nanotechnology is widely used in the fields of biotechnology and biomedical sciences as it reduces toxicity and improves the bioavailability of drugs through the use of nanocarriers. However, only 21 patents were registered with INPI, which is less than that registered in the other databases.

TABLE 1: Total patent deposits in the Brazilian Patent Office (INPI), European Patent Office (ESPACENET), and World Intellectual Property Organization (WIPO) databases between 2013 and 2017.

Keywords	INPI	ESPACENET	WIPO	Total
Leishmaniasis or leishmaniose	47	155	268	**470**
Nanotechnology or nanotecnologia	21	868	819	**1,708**
Cyclodextrin or ciclodextrina	43	6,180	4,426	**10,649**
Leishmaniasis and nanotechnology or Leishmaniose e nanotecnologia	6	2	3	**11**
Leishmaniasis and cyclodextrin or Leishmaniose e ciclodextrina	0	0	0	**0**
Nanotechnology and cyclodextrin or Nanotecnologia e ciclodextrina	0	2	18	**20**
Leishmaniasis and nanotechnology and Cyclodextrin or leishmaniose e Nanotecnologia e ciclodextrina	0	0	0	**0**
Total	**117**	**7,207**	**5,531**	**12,855**

The search terms "ciclodextrina" and "cyclodextrin" identified 43, 6 180, and 4 426 patents in the INPI, ESPACENET, and WIPO databases, respectively. Of the 12 827 patents identified using the search terms "leishmaniose", "leishmaniasis," "nanotecnologia", "nanotechnology", "ciclodextrina", and cyclodextrin, only 470 (3.66%) patents referred to leishmaniasis.

Data crossing for the search terms "leishmaniasis" and "nanotechnology" highlighted the low representation of nanotechnological products/processes focusing on leishmaniasis treatment (0.044%). Of the 10 649 patents relating to the use of nanotechnology, <4.41% sought alternative diagnosis and treatment methods for leishmaniasis.

The highest number of patents identified using the search term "leishmaniasis" was observed in the Patent Cooperation Treaty (23.16%), followed by the United States of America (USA; 17.73%)[12], Brazil (11.11%), and the European Patent Organization (9.92%). The USA showed the highest percentage of published research on NTDs despite the low prevalence of these diseases in this country. In countries where leishmaniasis is endemic (incidence ≥100 000 cases per year[13]; such as Brazil, the percentage of published research was low (11.11%).

Another parameter evaluated was the International Classification of Patents deposited with INPI, ESPACENET, and WIPO using the search term "leishmaniasis." The data included A61K (preparations for medical, dental, or hygienic purposes), C07D (heterocyclic compounds), C07K (peptides), G01N (investigation or analysis of materials by determination of their chemical or physical properties), and C07C (therapeutic purpose). These results revealed that A61K was the most frequently filed category (with a total of 344 patents), followed by A6IP (209 patents), C07D (118 patents), C07K (75 patents), C07C (35 patents), and C12N (40 patents). Notably, B82Y, which is a class categorizing patents related to nanostructures, did not appear in this search.

Patent deposits are categorized chronologically in **Figure 1**. The highest number of patent registrations combining records from the ESPACENET and WIPO databases was observed in 2016. A significant increase in the number of patent registrations identified using the search term "nanotechnology" was observed from 2015 to 2016. A similar increase was observed in the number of scientific articles published between 2015 and 2016, thus indicating an increased interest in nanotechnology research during that period.

In this study, we searched for scientific articles exclusively in English in the Science Direct, PubMed, and Medline databases between 2013 and 2017. A total of 73 046 articles were identified (**Table 2**), which is considerably higher than the number of patent registrations (21 075).

A search using the term "leishmaniasis" yielded 936, 4,730, and 4 492 scientific articles in the Science Direct, PubMed, and Medline databases, respectively. Another search using the term "nanotechnology" yielded 1,876, 29 278, and 20 514 scientific articles in the same respective databases. Similarly, the search term "cyclodextrin" yielded 2,446, 4,714, and 4 040 results, respectively. Of the 87 061 scientific articles identified using the above search terms, 12 398 (14.24%) articles referred to leishmaniasis.

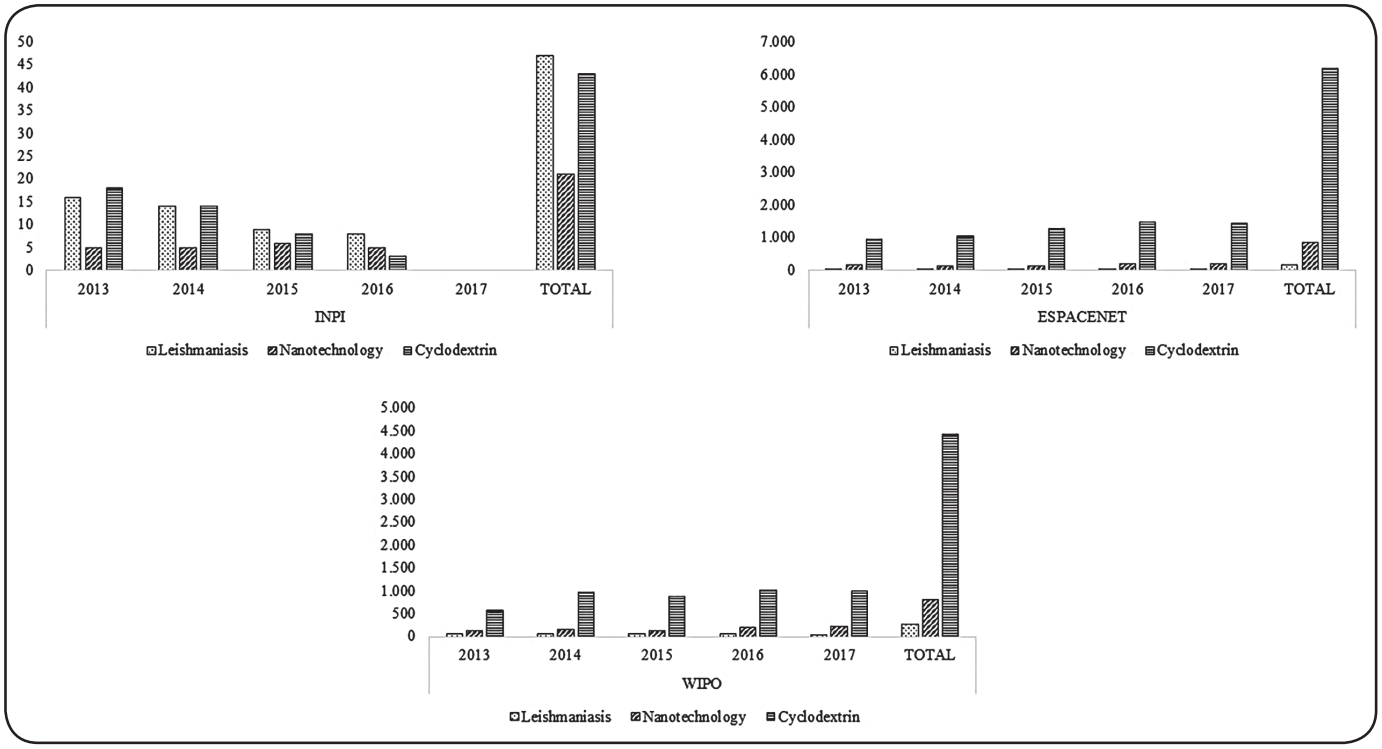

FIGURE 1: Patent deposited per year in **(A)** the Brazilian Patent Office (INPI), **(B)** the European Patent Office (ESPACENET), and **(C)** the World Intellectual Property Organization (WIPO) databases identified using the keywords nanotechnology, cyclodextrin, and leishmaniasis.

TABLE 2: Papers identified in the ScienceDirect, PubMed, and Medline databases between 2013 and 2017.

Keywords	Science Direct	Pubmed	Medline	Total
Leishmaniasis	1,087	5,575	4,492	12,398
Nanotechnology	1,690	34,376	26,052	62,118
Cyclodextrin	2,262	5,693	5,058	**13,013**
Leishmaniasis and nanotechnology	3	46	23	**72**
Leishmaniasis and cyclodextrin	3	3	3	**9**
Nanotechnology and cyclodextrin	6	264	117	**387**
Leishmaniasis, nanotechnology, and cyclodextrin	2	3	3	**0**
Total	**5,053**	**45,960**	**36,992**	**87,529**

Using the search term "leishmaniasis," a large number of articles published in 2014 relating to leishmaniasis were identified in the PubMed (1 191 articles) and Medline (1 258 articles) databases. Interestingly, in 2017, the number of relevant publications in PubMed was identical to that in 2014 (1 191 articles). The number of publications related to leishmaniasis remained constant between 2015 and 2017 (Science Direct, 1 087; PubMed, 5 575). Data crossing of the search terms "leishmaniasis" and "nanotechnology" highlighted the low representation of trials employing nanotechnology for NTD treatment (0.001%). Of the 62 118 scientific articles employing nanotechnology, <1% sought alternatives for the prevention, diagnosis, and treatment of leishmaniasis.

This study revealed the large number of patents/scientific articles related to nanotechnology. However, <1% of these were linked to leishmaniasis. These findings emphasize the need to intensify research on the development of new therapies for leishmaniasis employing the latest advances in pharmaceutical technology. The use of nanotechnology may be more cost-effective and faster than novel drug development. This need is greater in countries such as Brazil, which has a high epidemiological index for leishmaniasis.

Acknowledgments: The authors wish to acknowledge *Coordenação Aperfeiçoamento de Pessoal de Nivel Superior* (CAPES), *Fundação de Amparo à Pesquisa do Estado de Sergipe* (FAPITEC), *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq).

Conflict of interest: The authors declare that there is no conflict of interest.

Financial support : *Fundação de Apoio à Pesquisa e à Inovação Tecnológica do Estado de Sergipe* (FAPITEC/SE/88887.159533/2017-00).

REFERENCES

1. Hotez PJ, Pecoul B, Rijal S, Boehme C, Aksoy S, Malecela M, et al. Eliminating the neglected tropical diseases: translational science and new technologies. PLoS Negl Trop Dis. 2016;10(3):e0003895.
2. Abamor ES. Antileishmanial activities of caffeic acid phenethyl ester loaded PLGA nanoparticles against *Leishmania infantum* promastigotes and amastigotes *in vitro*. Asian Pac J Trop Med. 2017;10(1):25-34.
3. Ponte-Sucre A, Gamarro F, Dujardin J-C, Barrett MP, López-Vélez R, García-Hernández R, et al. Drug resistance and treatment failure in leishmaniasis: A 21st Century challenge. PLoS Negl Trop Dis. 2017;11(12):e0006052.
4. Dorlo TPC, Rijal S, Ostyn B, de Vries PJ, Singh R, Bhattarai N, et al. Failure of miltefosine in visceral leishmaniasis is associated with low drug exposure. J Infect Dis. 2014;210(1):146-53.
5. de Assis TSM, Rosa DCP, Teixeira EM, Cota G, Azeredo-da-Silva ALF, Werneck G, et al. The direct costs of treating human visceral leishmaniasis in Brazil. Rev Soc Bras Med Trop. 2017;50(4): 478-82.
6. Frézard F, Demicheli C, Da Silva SM, Azevedo EG, Ribeiro RR. Nanostructures for improved antimonial therapy of leishmaniasis. *In:* Andronescu E, Grumezescu A, editors. Nanostructures for Drug Delivery. Chapter 22. Philadelphia: Elsevier; 2017. p. 419-37.
7. Sundar S, Chakravarty J. An update on pharmacotherapy for leishmaniasis. Expert Opin Pharmacother. 2015;16(2):237-52.
8. Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm J. 2018; 26(1)64-70.
9. Fanti JR, Tomiotto-Pellissier F, Miranda-Sapla MM, Cataneo AHD, de Jesus Andrade CGT, Panis C, et al. Biogenic silver nanoparticles inducing *Leishmania amazonensis* promastigote and amastigote death *in vitro*. Acta Trop. 2018;178:46-54.
10. Noormehr H, Hosseini AZ, Soudi S, Beyzay F. Enhancement of Th1 immune response against *Leishmania* cysteine peptidase A, B by PLGA nanoparticle. Int immunopharmacol. 2018;59:97-105.
11. Chaubey P, Mishra B, Mudavath SL, Patel RR, Chaurasia S, Sundar S, et al. Mannose-conjugated curcumin-chitosan nanoparticles: efficacy and toxicity assessments against *Leishmania donovani*. Int J Biol Macromol. 2018; 111-109-20.
12. Kar N, Chakraborty S, De AK, Ghosh S, Bera T. Development and evaluation of a cedrol-loaded nanostructured lipid carrier system for *in vitro* and *in vivo* susceptibilities of wild and drug resistant *Leishmania donovani* amastigotes. Eur J Pharm Sci. 2017;104:196-211.
13. Leishmaniasis. Epidemiological situation. [Internet]; 2015. Available from: https://www.who.int/leishmaniasis/burden/en/

14. Kato KC, de Morais-Teixeira E, Islam A, Leite MF, Demicheli C, de Castro WV, et al. Efficacy of meglumine antimoniate under low polymerization state orally administrated in murine model of visceral leishmaniasis. Antimicrob Agents Chemother. 2018:62(8). pii:00539-18.

15. Akkari ACS, Munhoz IP, Tomioka J, Santos NMBF, Santos RF. Pharmaceutical innovation: differences between Europe, USA and 'pharmerging'countries. Gest Prod. 2016;23(2):365-80.

16. Vijayakumar S, Das P. Recent progress in drug targets and inhibitors towards combating leishmaniasis. Acta Trop. 2018;181(1):95-104.