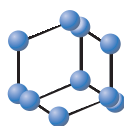


REVIEW ARTICLE


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Recent Patents Concerning the Use of Nanotechnology-Based Delivery Systems as Skin Penetration Enhancers



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Abstract: Nanotechnology-based delivery systems have been considered a promising approach for topical application, considering their characteristics of penetration into/across the skin. The present review aimed to evaluate the recent international scenario of patents concerning the use of nanotechnology-based delivery systems as skin penetration enhancers. A survey of recent patent documents was conducted by using the Espacenet patent database including the terms “skin” in the title and “promot* or enhanc* and penetrat* or absorp* or permeat*” and “nano*” with the truncation symbol (*) in the abstract of documents. A total of 110 patents were published from 2008 to 2018, with 94 technologies being considered. The results demonstrated an increase in innovations concerning nanotechnology-based delivery systems as skin penetration enhancers in recent years. Most patent applicants are from China (60.6%) and Korea (21.3%), and companies (68%) were the most prominent owners. The majority of patent applications (76%) were intended for cosmetic purposes; the types of products and nanostructures were also investigated. Overall results demonstrated the increased interest around the world in patenting products involving skin permeation promotion and nanotechnology for pharmaceutical and, mainly, for cosmetics purposes.

ARTICLE HISTORY

Received: August 30, 2019
Revised: October 01, 2019
Accepted: October 21, 2019

DOI:
10.2174/1872211313666191024112137



CrossMark

Keywords: Nanotechnology-based delivery systems, patents, penetration enhancers, skin delivery, cosmetic purposes, nanostructures.

1. INTRODUCTION

The skin is the largest organ in the human body. It is an important protective barrier against external agents (chemicals, microorganisms, ultraviolet radiation, and others) and contributes significantly to the human body's homeostasis. It is composed of three main functional layers: the epidermis (divided into the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale), dermis, and hypodermis. In particular, the structure of the stratum corneum in the epidermis is mainly formed from nonviable corneocytes rich in fatty acids, ceramides, cholesterol, and cholesterol esters, that altogether represent the main mechanism of the skin's protective barrier function, including the prevention of water loss [1-5].

On the other hand, although the stratum corneum is an important protective barrier in the skin, it also represents the

main limitation to compound penetration and drug absorption by this route [1-4]. In the last decade, the search for different strategies to overcome the stratum corneum barrier, in order to improve skin penetration or permeation and achieve dermal or transdermal delivery of drugs or actives for therapeutic/cosmetic purposes, has gained attention [6-13].

Skin penetration enhancement strategies include the use of physical (electroporation, iontophoresis, high-voltage, laser-light pulse sources, sonophoresis, and others) and chemical methods (cyclodextrins, lectin, fatty acids, urea, glycols, surfactants, terpenes, and others). Nevertheless, in many cases, these strategies are correlated with unexpected risks of skin irritation or sensitization [4, 9]. Recently, the use of nanotechnology-based delivery systems for pharmaceutical or cosmetic topical applications has been considered a promising approach, taking into account that the small size (nanometer scale) could facilitate passage through biological barriers such as skin [7, 14-16].

Considering their characteristics of penetration into/across the skin, nanostructures have been proposed as topical vehicles for a variety of therapeutic and cosmetic applications [17-19]. The main interest of using such vehicles

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is the potential for improvement of the percutaneous absorption of drugs and/or bioactive compounds [20]. The main types of nanostructures used in skin delivery are liposomes [21], nanoemulsions [14], lipid nanocapsules [22], solid lipid nanoparticles [23], and polymeric nanoparticles [4]. Different drugs/actives have been proposed, including anti-inflammatory drugs [24, 25], vitamins [26], antibacterials [27], antifungals [28], antioxidants [29], and sunscreens [30]. Besides the promotion of drug/active absorption, it has been claimed that nanostructures could also protect against drug/activity instability and could achieve prolonged and/or controlled sustained release, improving the effect in the skin [31].

As can be observed in the literature, many scientific articles have described skin penetration enhancers, including the use of nanotechnology delivery systems, highlighting their importance in the skin delivery field. Thus, numerous researchers have written review articles in order to assess the state of the art of the scientific use of nanotechnology-based delivery systems as skin permeation promoters [6, 14, 20, 21]. However, it is well-known that to evaluate the state of the art of a specific topic, the technologies protected through patents must also be investigated. Patents represent a fundamental tool for determining knowledge production and dissemination between the university and private sectors [32-

35]. Regarding the use of nanotechnology in skin penetration enhancers, to the best of our knowledge, no systematic review has been developed exploring this specific field.

In this context, the present study was conducted aiming to evaluate the recent international scenario of patent technologies concerning the use of nanotechnology-based delivery systems as skin penetration enhancers. The importance of this study is mainly justified as the state of the art regarding this field has not been completely explored, and technological innovations are particularly important in terms of the competitiveness of innovative delivery systems, supporting the Research and Development (R&D) of new products and avoiding the uncertainty of investment.

2. DATA SURVEY

As reported by Rother [36], seven steps are recommended for the elaboration of a systematic review, including question formulation, study location, data collection, critical evaluation of studies, data analysis and presentation, data interpretation, and review enhancement. Table 1 shows the methodology of the systematic review employed in the present study.

Table 1. Methodology of systematic review elaboration.

Steps	Answers
Question Formulation (Hypothesis)	How is the scenario of patent technologies involving nanotechnology-based delivery systems as skin penetration enhancers?
Study Location	International patents
Data Collection	Patent database: Espacenet (EPO) (Accessed on July 25 th , 2019) Scientific articles database: Web of Knowledge (Accessed on August 8 th , 2019) Strategies of search: 1) Keyword in the title: skin Keywords in abstract: promot* or enhanc* and penetrat* or absorp* or permeat* No time restriction 2) Keyword in the title: skin Keywords in abstract: promot* or enhanc* and penetrat* or absorp* or permeat* and nano* No time restriction 3) Keyword in the title: skin Keywords in abstract: promot* or enhanc* and penetrat* or absorp* or permeat* and nano* Period: 2008 - 2018
Critical Evaluation of Studies	Tabulation of patents of the third search strategy. Accounting by technology and not by patents (avoid repeated counting). Exclusion of patent technologies that do not fit the article purpose. Division of patent technologies by categories (year, country, type of applicants, types of products, types of nanostructure).
Data Analysis and Presentation	Graphs and tables elaboration. Discussion of results trying to understand the data obtained, and comparison with scenarios from other sources (scientific papers).
Review Enhancement	Search perspective every 5 years.

3. IMPORTANCE OF PATENTS

In order to explore the existing state of the art of a specific field, both scientific and technology indicators are important aspects to be investigated [34]. Technological innovation is recognized as a significant strategy for development and growth for all categories of companies. Intellectual Property (IP) is an important protection to inventors and industries from their innovations and creations being taken or explored by third parties in an unauthorized manner. One system to guarantee IP rights is patenting product or process [32, 35, 37, 38].

So, while scientific indicators are represented by published articles, technological indicators are commonly represented by patent data analysis [33]. Patents are one of the most significant innovation and inventive parameters attempted to devise the intrinsic value of an original technological invention [32, 37, 38]. Patent documents mainly comprise the application date and bibliographical details, as well as the novelties of the invention and its areas of application [35]. Technological changes have been found to have a critical impact on industry competitiveness, especially causing an impact in the industrial R&D sector [32, 37, 38].

4. OVERVIEW OF PATENTS TECHNOLOGIES

The first survey of patent documents using the international Espacenet (EPO) database included the terms "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat*" with the truncation symbol (*) in the abstract. A total of 3386 patents were found. Further, in order to analyze the patents that correlated to the use of nanotechnology-based delivery systems as skin penetration enhancers, a second analysis was performed crossing these results with the keyword "nano*" (representing all nanotechnologies involved). In this search without time restriction, a total of 142 patents were found. Of these, 77.43% were published between 2008 and 2018 (Fig. 1A), totalizing 110 patents. For comparison purposes, a search was also performed in the Web of Knowledge database using the same terms "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat*" with the truncation symbol (*) in the abstract, crossing these results with the keyword "nano*". For the period 2008 to 2018, 439 scientific articles were found, as shown in Fig. (1B).

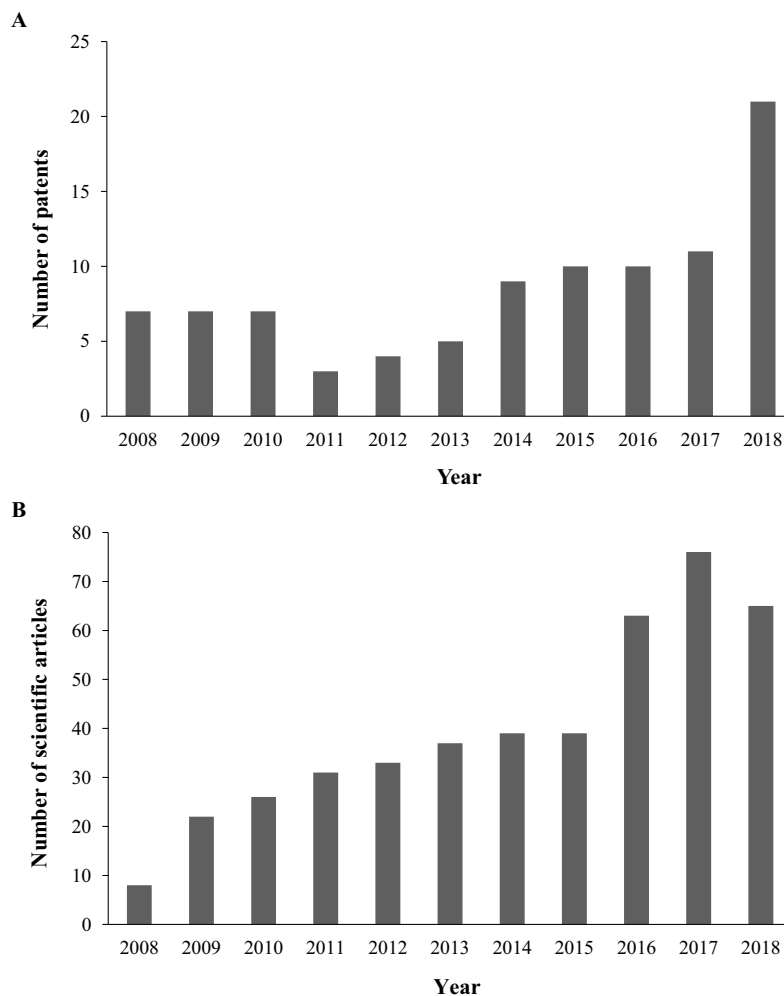


Fig. (1). Comparison between (A) annual distribution of patents with keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Espacenet (EPO) database between 2008 and 2018 and (B) number of scientific articles with title's keywords "skin" and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Web of Knowledge database between 2008 and 2018. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

In Fig. (1A), an increase in the number of patents published in recent years can be observed, although, we observed a constancy in the number of patents published in the first three years (2008-2010) and a slight decline in the following years. This low number may also be correlated with the low number of scientific articles published in the same period, as shown by Fig. (1B). From 2013 to 2017, the number of patents shows a slight growth, highlighting a jump in the number of patents filed from 2017 to 2018, doubling from 11 to 21 patents. This growth in the number of patents can also be explained by the significant increase in the number of scientific articles published during the same period, demonstrating the increased interest in researching and patenting products involving skin permeation promotion and nanotechnology [2, 9, 14, 39].

The abstracts from the 110 patents were analyzed, and those that did not represent the subject of interest of this study were excluded. A total of 10 patents were excluded, examples including patents that involve cellulose nanofibers for food or for enhancing the characteristics of construction material; to improve the leather tanning process; a nanocarrier polymer to improve the extraction method of a plant or the use of a nanometer in radiation. Also, patents from the same applicants and with the same contents were grouped and counted as one technology (Table 2). So, from 110 patents found between 2008 and 2018, 94 technologies were considered for the other steps of this study.

To visualize the most prominent countries involved in technological innovation regarding skin permeation promoters and nanotechnology, the 94 technologies were organized by the country in which patents were developed, as presented in Fig. (2). The results demonstrated that China and Korea were the most prominent countries, with 60.6% and 21.3% of technologies, respectively. Comparing these results with the recent data from World Intellectual Property Indicators (WIPO) con-

cerning the worldwide ranking of patents in various areas, the positions of these countries corroborate the world scenario, with few distinctions, given that the top 10 patent offices with the most filings in 2017 were, in the following order: China, United States of America, Japan, Korea, Germany, France, United Kingdom, Switzerland, Netherlands, and Italy. The data also reveal a very significant increase in the number of filings in China, in first place for patent filings, trademarks, utility models, industrial design, and cultivars, accounting for 43.6% of all patents filed in the world [40].

In order to better evaluate the types of patent applicants, the 94 technologies were also grouped according to the type of holder, divided into three categories: company, independent applicant and university. According to the results shown in Fig. (3), the most prominent applicants were companies, representing 68% of patent holdings. Following that were independent applicants (18%) and universities (14%).

Considering the company applicants, some companies stand out because they have more than one technology protected by patents. The Chinese Nantong Snakebite Therapy Res Inst[®] is the holder of patents from eight different technologies, all of them filed in China. The Japanese FujiFilm Corp.[®] is the holder of patents from three different technologies filed in countries other than Japan, such as the United States of America and in Europe. The Korean Hwajin Biosmetics Co. Ltd.[®] is the holder of patents from two technologies, both filed in Korea. The Chinese Beijing Laimi-ruike Technology Dev. Co. Ltd.[®] is the holder of patents from two technologies, both filed in China. Other companies that stand out are those that have one technology but filed in more than five patent offices, generating families of patents. Examples are Daewoong Co. Ltd.[®] from Korea, Euro Celtique SA[®] from Luxembourg, Sunev Pharma Solution Ltd.[®] from India, Sesvalia USA LLC[®] and JRX Biotechnology INC[®] from the United States of America.

Table 2. Patents with the same technologies found during the search in Espacenet with the keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract. Data from patents between 2008 and 2018.

Name of Technology	Patents Considered in Data Analysis	Patents not Considered Because are Repeated from the Same Technology	Applicant / Country
Nanoliposome using esterified lecithin and method for preparing the same, and composition for preventing or treating skin diseases comprising the same	TWI325325 (B)	US2009263473 (A1); US8685440 (B2)	DAEWOONG CO LTD [KR]
Systems and methods for skin rejuvenation	US8568749 (B2)	US2013345307 (A1); US9241887 (B2) US2016101029 (A1); US9782334 (B2)	SESVALIA USA LLC [US]
Multilamellar nanoliposome which contains skin lipid components, and preparation method therefor	KR20160106508 (A)	CN107405282 (A)	AMOREPACIFIC CORP [CN]
Approaches for improving skin hydration or moisturization	WO2017048807 (A1)	US2018256482 (A1)	JRX BIOTECHNOLOGY INC [US]
Topical herbal formulation for treatment of acne and skin disorders	CA2746566 (A1)	SG172455 (A1)	SUNEV PHARMA SOLUTION LTD [IN]

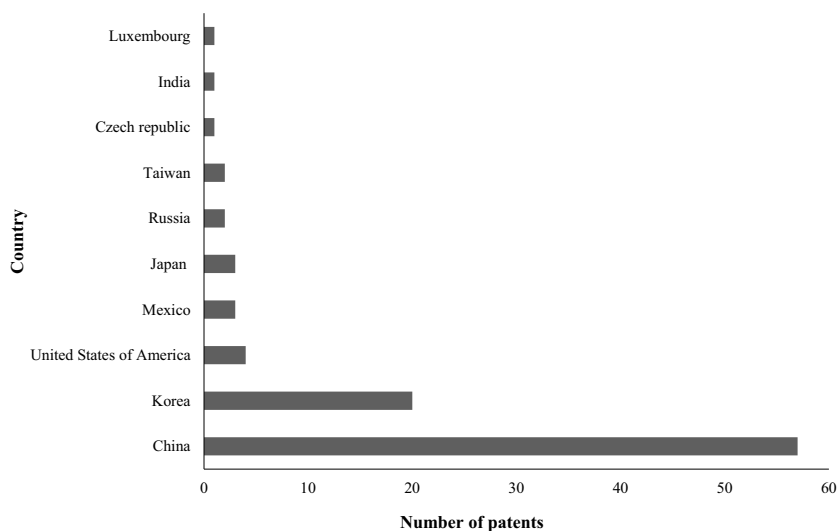


Fig. (2). Relationship between the number of technologies by depositing countries with the keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Espacenet (EPO) database between 2008 and 2018. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

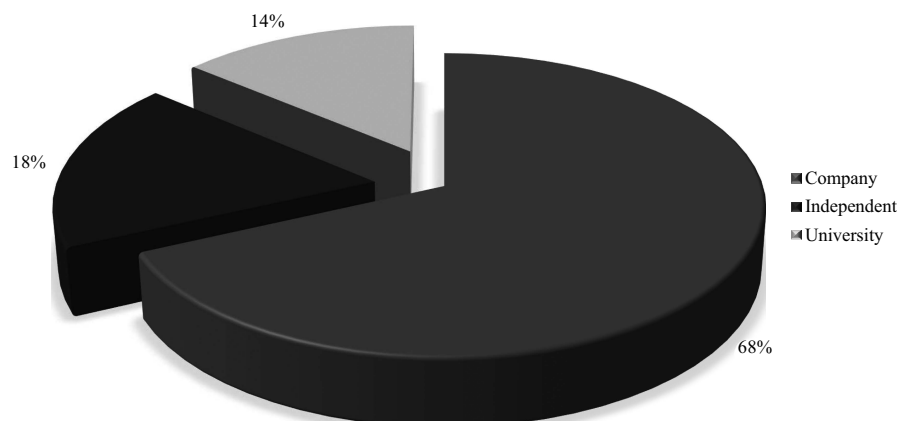


Fig. (3). Relationship between the number of technologies and applicants type for patents with keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Espacenet (EPO) database between 2008 and 2018. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Regarding university applicants, no institute presented more than one patent, and the technologies are not protected in the office of more than one country. Considering the localization of universities, eight are in China, one is in the United States of America, one from the Czech Republic, one in Korea, one in Russia, and one in Taiwan. Regarding independent applicants, only the inventor Wasserteil Raquel Lustbader presents more than one technology, representing three patents in total, all filed in Mexico.

The 94 technologies of the present survey were further organized into two major clusters according to their application: (1) cosmetics and (2) pharmaceutical purposes, presented in Table 3 and Fig. (4).

Analyzing the use of nanotechnology as skin penetration enhancers, the impact of the cosmetic segment is clear, showing that 76% of patents on technology filed in the last 10 years are for cosmetic use (Fig. 4). Cosmetics are legally defined as "any substance or mixture intended to be placed in contact with the external parts of the human body (epi-

dermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odors", according to the European Commission [41]. The cosmetic market has been increasingly promising for all segments of the economy as its growth in the last 20 years has been approximately 4.5% by year. This scenario proves its continued and consistent growth, even in unfavorable economic conditions [42-44].

So, to keep up with the evolution of this market, companies, independent applicants, and universities have also increasingly invested in research and innovation in this segment to stay ahead in this highly competitive universe, where more efficient options are expected by the consumer [45, 46]. According to the latest data published by Mintel (2018) in the cosmetics segment, the country leading the global market in product launches per year is the United States of

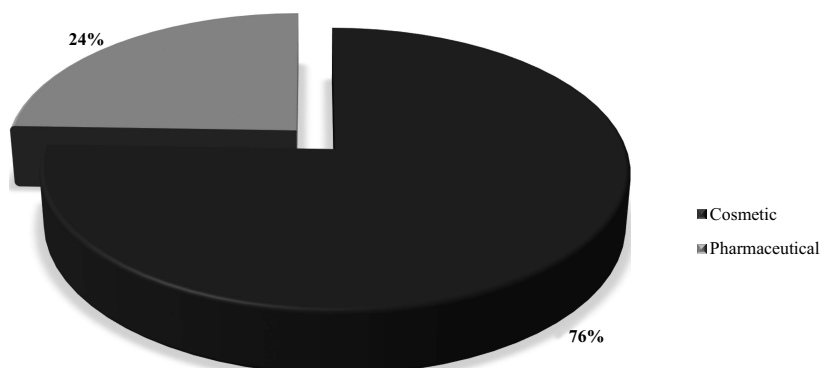


Fig. (4). Relationship of the number of technologies with keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Espacenet (EPO) database between 2008 and 2018 according to the *Clusters 1* (Cosmetic) and *Cluster 2* (Pharmaceutical). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 3. Patents separated by clusters after examination of abstract documents obtained in Espacenet database, between the years of 2008 - 2018 with interested keywords.

Cluster	Patent Number			
Cluster 1 Cosmetic	TWI325325 (B)	CN103142448 (A)	CN107281045 (A)	
	JP2008297241 (A)	CN103110534 (B)	CN206401924 (U)	
	JP2008255020 (A)	CN102988257 (B)	CN106860188 (A)	
	JP2008247814 (A)	CN102988200 (B)	KR101719811 (B1)	
	KR100912462 (B1)	CN104116651 (A)	WO2017048807 (A1)	
	KR100858628 (B1)	CN103966685 (B)	CN106474373 (A)	
	TW200914063 (A)	CN103565743 (B)	KR20180133237 (A)	
	KR101036961 (B1)	CN103520007 (A)	CN108938546 (A)	
	CN101474153 (A)	MX2014006945 (A)	KR101956553 (B1)	
	KR100958094 (B1)	TWI593426 (B)	CN108524411 (A)	
	CN101411678 (B)	CN105055186 (A)	CN108379204 (A)	
	CN101401775 (B)	KR101536996 (B1)	KR20180079673 (A)	
	CN101874762 (B)	CN104644459 (A)	CN108272670 (A)	
	US8568749 (B2)	CN104606078 (A)	KR20180067901 (A)	
	KR20100092922 (A)	CN104398395 (A)	KR101865841 (B1)	
	KR101023041 (B1)	KR101702482 (B1)	KR20180047152 (A)	
	CN101664372 (B)	CZ306274 (B6)	KR101850421 (B1)	
	CN202060058 (U)	KR20160106508 (A)	KR101860555 (B1)	
	CN102091013 (B)	CN105755817 (A)	CN107898699 (A)	
	CN102784084 (B)	MX2014009967 (A)	CN207044803 (U)	
	CN102579289 (A)	MX2014008660 (A)	CN206999797 (U)	
	CN102552073 (A)	CN105496886 (B)	CN107595715 (A)	
	KR101193606 (B1)	CN105473200 (A)	CN107582496 (A)	
	KR101337454 (B1)	CN105231999 (B)		
	Cluster 2 Pharmaceutical	CN101200816 (B)	CN103948960 (B)	CN206217260 (U)
		CA2723307 (C)	KR101419602 (B1)	CN106492278 (A)
CA2746566 (A1)		CN104987485 (A)	CN106427100 (A)	
WO2010039310 (A1)		RU2559938 (C2)	CN108998856 (A)	
CN102090904 (B)		CN204092654 (U)	CN108842222 (A)	
RU2554219 (C2)		CN105853335 (A)	CN207535410 (U)	
KR101437563 (B1)		CN107412882 (A)	CN107753747 (A)	
CN104055720 (A)		CN106691888 (A)		

America (1st place) followed by China (2nd place), which corroborates the results found for the top-ranking countries for nanotechnology patents as skin penetration enhancers [47].

The main purpose of patents in the cosmetic field is to treat recurrent skin problems and employ nanotechnology in order to promote transdermal absorption of the bioactive components, and occasionally to increase their stability. In general, protected technologies have as their target purpose: (a). treatment of acne; (b). treatment of hyperpigmentation of the skin; (c). sunscreen; (d). retarding the process of aging (anti-aging), (e). acting by fighting the production of free radicals (antioxidant); f. enhancing skin hydration or moisturization. These results are in accordance with the scientific literature, in which similar targets in the cosmetic segment have also been published [48-54].

Regarding pharmaceutical applications, the number of published patents is smaller than for the cosmetic segment, representing 24% of the total patent technologies. However, the development of pharmaceutical products using nanotechnology-based delivery systems as skin penetration enhancers and drug absorption skin promoter has been continuous over the years. The study and development of these delivery systems have allowed the release of drugs while providing one or more functionalities, including protecting the drug from the biological environment and, masking toxicity to cells and tissues, as well as, being able to promote prolonged and controlled release in order to accumulate the drug at the target site [55-57].

Analyzing the patents presented in Table 2, all protected technologies for pharmaceutical use are mainly concerned with the manufacture of products employing at least one of the following nanostructures: nanoemulsions, nanoparticles, nano-elements, or liposomes. In general, protected technologies have as their purpose the treatment of immune system dysfunctions that can cause different types of skin lesions such as psoriasis, allergies, eczema, and inflammatory processes of different natures. Another important use of these technologies is related to the treatment of different microbiological infections, presenting antifungal, antibacterial, and antiviral activity. Altogether, the pharmaceutical application technologies are in accordance with the scientific literature that also reports the relevance of nanotechnology in a wide range of skin diseases [18, 24, 28, 31, 58-63].

Other categorizations of the 94 technologies were performed, such as by the kind of products and the nanostructures used in the products. Fig. (5) shows the percentage of technologies classified as a formulation, skin adhesive, equipment, fiber, or artificial skin. Fig. (6) shows the percentage of technologies that use nano-elements, nanoemulsions, liposomes, nanocapsules, protein nanoparticles, carbon nanotubes, and others. It is important to mention that, for some technologies, there is no information about the type of nanostructure used in the abstract, and because of that they were classified as “non-explicated”.

The only invention classified in the group of “skin adhesive” corresponds to 1% of data, and the purpose of the product is to increase skin adhesiveness through interaction of the product and the skin lipid layer effectively collecting the active ingredient (KR20180133237 (A)). The nanostructure present in the product is nanocapsules with an amphiphilic block copolymer and a bionic surface-active agent and further comprising an additional useful active ingredient.

The patents classified as “equipment” represent 5% of technologies. The inventions are related to a skin massager (KR101036961 (B1)), a device for activating the ionic components of electrolytes in skin (KR101437563 (B1)), a skin laser (RU2559938 (C2)), electrode sensors (CN105231999 (B)), and a vibrating device (CN206401924 (U)). Most of them are involved in the enhancement of drug absorption, in which the substance could be present in the equipment or could be administered after the use of the equipment. Also, one of these technologies reports the use of a device for skin makeup purposes. The main nanostructures employed in equipment are carbon nanotubes and nanoelements.

Technologies involving skin tissue engineering were observed in patents classified as “artificial skin”, corresponding to 4% of technologies, and “fiber”, corresponding to 15% of technologies. Most innovations employed systems to enhance drug absorption, for which antimicrobial agents were the most cited, and to promote better skin lesion regeneration. A great number of these technologies employed nanoelements in the products.

Nanoelements represent the most patented nanostructures from the present survey (34.4%). According to the Commission Recommendation, a “nanomaterial means a natural,

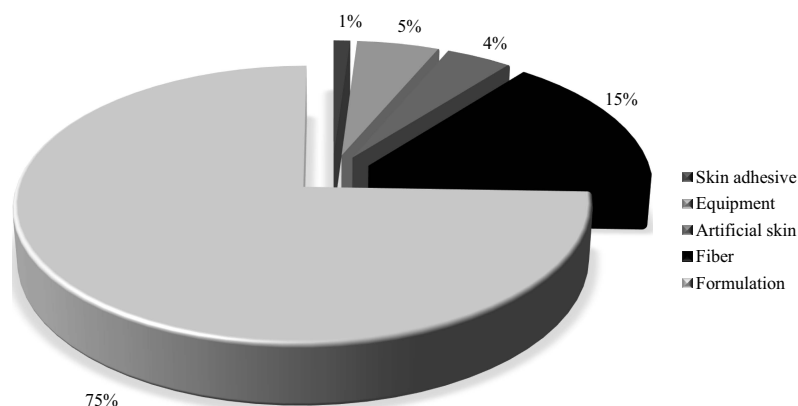


Fig. (5). Relationship of the number of technologies with keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Espacenet (EPO) database between 2008 and 2018 according to the kind of products. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

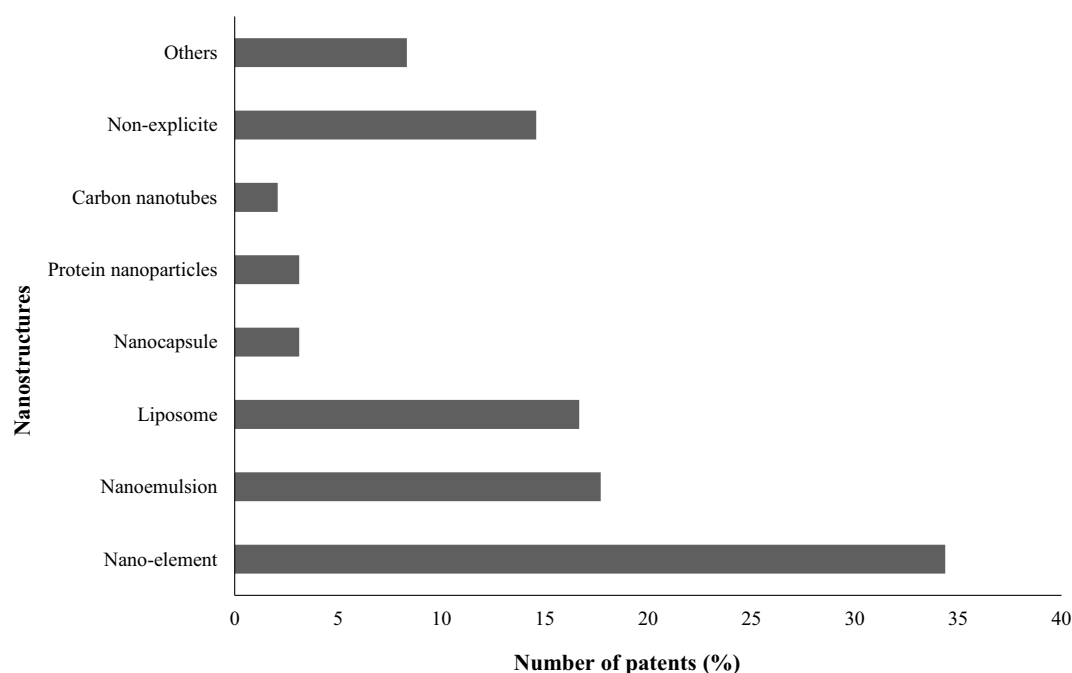


Fig. (6). Relationship of the number of technologies with keywords "skin" in the title and "promot* or enhanc* and penetrat* or absorp* or permeat* and nano*" in the abstract, found in the Espacenet (EPO) database between 2008 and 2018 according to the type of nanostructures used in the products. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm" [64]. Herein, included in this category were the technologies that employed nano-silver, nanocrystalline cellulose, nanometer pearl particles, nano-pearl fibers, nanometer collagen particles, nano-titanium dioxide, nano-selenium, nano-chitin, nano-calamine, and nano-zirconium phosphate, among others. The nanoelement most used in technologies was silver nanoparticles, important in the area of nanomedicine due to the antibacterial capacity of silver [65, 66]. Nano-silver can be incorporated into devices (dressings, bandages, catheters, and implants) as well as soaps for treating acne and dermatitis [65]. Among the protected technologies, silver nanoparticles are mainly developed for pharmaceutical purposes, in the form of artificial skin and fibers for antibacterial activity, but they were also present in other technologies belonging to the group of "formulations".

Finally, the greatest number of technologies was categorized as "formulation", corresponding to 75% of inventions. It is important to highlight that the composition of products depends on the interest of use, physical characteristics, and type of nanostructure employed [67]. Analyzing these technologies according to the nanostructure used in the composition, it is possible to verify the wide use of nanoemulsions, liposomes, nanocapsules and protein nanoparticles.

Nanoemulsions are Oil-in-Water (O/W) or Water-in-Oil (W/O) nanodispersion of two immiscible liquids stabilized by an amphiphilic surfactant system. Their droplet size ranges from 10 to 1000 nm, they are thermodynamically stable, optically clear with a milky white color. Such systems

have been considered as a potential lipid-nanotechnology-based delivery system for topical administration and an alternative to incorporating lipophilic drugs/actives [68-70]. Eighteen patents were found using nanoemulsions. Regarding pharmaceutical application, only two patents were found, one for eczema/ psoriasis (CA2746566 (A1)) and another for transdermal drug delivery (KR101419602 (B1)). The other 16 patents were correlated with cosmetic application, and indications include: anti-aging (CN101874762 (B); CN102784084 (B); CN107595715 (A); CN103110534 (B); KR101956553 (B1); CN106860188 (A); KR101850421 (B1); CA2746566 (A1); CN104644459 (A)), enhancement of skin permeation/absorption (TW200914063 (A); KR101719811 (B1); CN105473200 (A)), enhancement of skin hydration or moisturization (WO2017048807 (A1); CN107898699 (A); KR101956553 (B1)), whitening or lightening the skin (CN101401775 (B); CN104606078 (A); CN107898699 (A)), and antioxidant activity (CN101664372 (B); KR101850421 (B1)).

Liposomes are small vesicles comprising amphipathic lipids organized in one or more concentric bilayers, basically formed spontaneously when a lipid is brought into contact with an aqueous phase. Their size can range from 25 to 2500 nm; they are thermodynamically stable and lamellar structures mainly classified as multilamellar or unilamellar vesicles. Such systems are biocompatible, biodegradable, and present low toxicity. Additionally, they have been considered as suitable skin delivery systems to trap hydrophilic, hydrophobic, or amphipathic drugs/actives [21, 71, 72]. Sixteen patents were found using liposome, one for pharmaceutical application (transdermal drug vehicle KR101419602 (B1)) and 15 for cosmetics. Indications for use in cosmetics include: enhancement skin of permeation/absorption (TWI325325 (B); CN103520007 (A); KR20160106508 (A);

CN104116651 (A)), enhancement skin moisturization (KR101023041 (B1); TWI325325 (B); CN102988200 (B); MX2014009967 (A); CN105496886 (B); KR100912462 (B1); KR20160106508 (A)), minimizing skin irritation (KR100858628 (B1); CN102988257 (B)), anti-aging (MX2014006945 (A); KR100912462 (B1); KR20160106508 (A); MX2014008660 (A); KR100912462 (B1); KR100912462 (B1); KR20160106508 (A)), suppressing melanogenesis (KR100912462 (B1)), improving skin immunity and acne treatment (KR101702482 (B1)), and hair growing promotion (KR100912462 (B1)).

Nanocapsules are polymeric nanoparticles that present a typical core-shell structure wherein the drug is kept to a reservoir or within a cavity covered by a polymer. The loaded drug/active can be lipophilic or hydrophobic, and in liquid or solid form or as a molecular dispersion, with a high drug efficiency of encapsulation. Their particle size usually ranges from 100 to 500 nm, not exceeding 1,000 nm [73-75]. Concerning the types of nanostructures, only 2 patents use nanocapsules as a formulation, both being used for cosmetic purposes: one for skincare, to improve the permeability and selective absorption function of the skin (CN104398395 (A)), and the other for skin wrinkles (KR101865841 (B1)).

Another type of nanostructure also reported in the “formulation” technologies category is protein nanoparticles, which can derive from several nanomaterials. Protein nanoparticles have been actively used especially regarding their unique functionalities and properties, including biodegradability, metabolization, and capability to suffer surface modifications, that may facilitate attachment of the drug and targeting ligands (site-specific action) [76-78]. In total, only three patents were found using protein nanoparticles and all referred to cosmetic application, one indicated for acne treatment (JP2008297241 (A)), one for anti-aging (JP2008255020 (A)), and one for bleaching (JP2008247814 (A)), all from Japanese FujiFilm Corp.®.

The technologies of nanostructures cited only once were classified as “others” and include a nano-sponge sheet for a rapid allergic skin test detector (CN102090904 (B)), a nanolipid carrier for epidermal growth factor (CN101474153 (A)), a nanosuspension applied for skin moisturization and soothing (KR101337454 (B1)), lipid nanostructures applied for hair growth (KR101536996 (B1)), and solid lipid nanoparticles for skin lightening (KR101860555 (B1)).

CONCLUSION

The use of nanotechnology-based delivery systems as skin penetration/permeation enhancers can be considered an attractive strategy for pharmaceutical and, mainly, for cosmetics topical application.

CURRENT & FUTURE DEVELOPMENTS

Skin delivery still represents a great challenge due to the limited penetration and absorption by this route. In the last decade, various studies proposed different strategies to improve skin penetration/permeation and to achieve dermal or transdermal delivery of drugs or bioactive compounds for therapeutic/cosmetic purposes. Nanotechnology-based delivery systems have been suggested to overcome this feature. In

this study, a systematic review from recent patent technologies published from 2008 to 2018, concerning the use of nanotechnology-based delivery systems as skin penetration enhancers was performed for the first time. The overall data indicate an increase in the number of patents published in recent years, demonstrating the perspective for growth interest around the world in patenting products involving skin permeation promotion and nanotechnology for pharmaceutical and mainly for cosmetics purposes (anti-aging, antioxidant, moisturization, whitening, and others).

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The authors gratefully acknowledge Conselho Nacional de Desenvolvimento Científico e Tecnológico, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES - Finance Code 001) for the scholarships and the financial support.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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