

# Chitosan-Based Hydrogels: Patent Analysis †

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**Abstract:** In this study, the state has been reviewed by introducing what has been patented concerning chitosan-based hydrogels. Four patent databases have been searched, and different keywords and related terms to chitosan-based hydrogels were used, and patents were searched according to title, abstract, and claims. The search was then filtered regarding publication dates, patent classifications, inventors, applicants, owners, and jurisdictions. During a search, 5734 patent documents were found until 31 December 2021. The United States was ranked first with 2332 patent documents, with a higher patent contribution per total of 40.67%. The year 2021 recorded the maximum number of 576 patent documents as well as the maximum number of 470 patent applications. The Massachusetts Institute of Technology, the University of California, and Harvard College are considered the top academic innovators in chitosan hydrogel-based research and development in the world. The patent classification codes reveal that most inventions are intended for compositions of polysaccharides or their derivatives, and macromolecular materials. Moreover, they are also intended for macromolecular gels and hydrogels or hydrocolloids. The knowledge clusters and expert driving factors of this patent analysis indicate that the research and development based on the formulation of chitosan-based hydrogels for biomedical use is concentrated in most patents.

**Keywords:** chitosan; hydrogel; innovation; patent data; patent analysis; patent classifications

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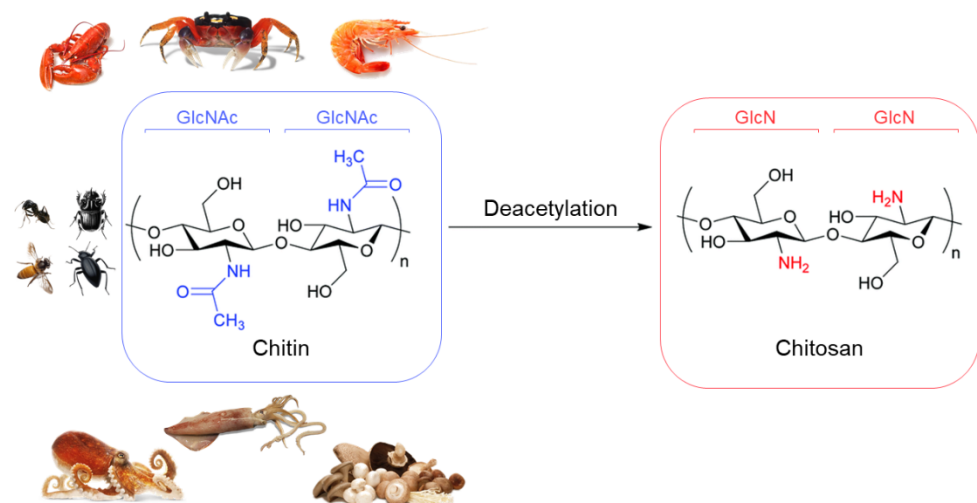
## 1. Introduction

Research on hydrogels, as a remarkable class of soft nanomaterials, is developing rapidly through the innovation and improvement of polymers, chemical synthesis, methods of preparation, formulations, and fabrication processes. This trend is justified by the several advantages that hydrogels offer for biofabrication [1] and biomedical applications [2].

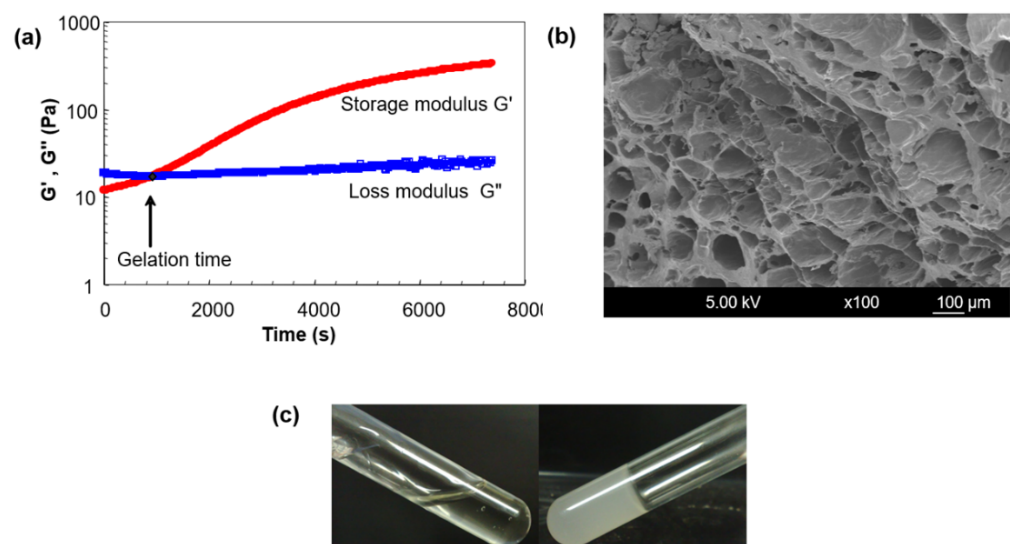
Hydrogels are synthetic matrices made up of a network of hydrophilic synthetic polymers or natural polymers (i.e., biopolymers) that absorb water and/or biological fluids. The current strategy to design and produce hydrogels involves a range of various biopolymers, among them chitosan. Chitosan's non-toxic, biocompatible, and biodegradable characteristics allow its use as a hydrogel in many successful applications within the biomedical and environmental fields [3–5]. Chitosan is a linear amino-polysaccharide of  $\beta(1\rightarrow4)$ -linked D-glucosamine and N-acetyl-D-glucosamine residues. Also called poly- $\beta(1\rightarrow4)$ -2-amino-2-deoxy- $\beta$ -D-glucose, it is a natural heteropolymer obtained by alkaline deacetylation of the amino acetyl groups of chitins, which is the main component of fungi and the exoskeleton of insects, crabs, shrimp, and krill (Figure 1) [6].

Typically, the design and fabrication of chitosan-based hydrogels is based on the association with glycerophosphate salt [7,8]. The mixture remains liquid at room temperature, and it gels quickly when heated to body temperature (i.e., 37 °C) at physiological pH (i.e., 7.4). Chitosan solutions heated in the presence of glycerophosphate salt will become

partly neutralized by transferring protons to glycerol phosphate and thereby reduce the repulsive forces among positively charged ammonium groups, allowing attractive inter-chain forces to form a physically crosslinked gel under the appropriate conditions [9]. The rheological properties during the gelation process of chitosan-based hydrogel could be determined immediately after mixing the two solutions (i.e., chitosan and glycerophosphate), and the time evolution of the storage ( $G'$ ) and loss ( $G''$ ) moduli measured at 37 °C within the linear viscoelastic region could confirm the hydrogel formation. At this step, a microscopic morphological observation should show chitosan-based hydrogels with a typical porous structure with interconnected pores, which has the necessary characteristics for the permeability for nutrients and biological waste for cells (Figure 2).



**Figure 1.** Origin of chitin and structure of chitosan (Dglucosamine (GlcN) residues) obtained by alkaline deacetylation of the amino acetyl groups of chitins (N-acetyl-D-glucosamine (GlcNAc) residues).



**Figure 2.** (a) Rheological properties of chitosan hydrogel displayed as storage and loss moduli as a function of time at 37 °C. (b) Morphological observation of chitosan hydrogel obtained by scanning electron microscope. (c) Photographs of chitosan hydrogel before and after gelation at 23 and 37 °C, respectively (Figures (a) and (b) are reprinted from Fatimi et al., 2012 [4], with permission from Elsevier Ltd. Published under license. Copyright 2012 Acta Materialia Inc.).

Although the concept of chitosan-based hydrogel formulations has been known for several years, the first patent application concerning this area was filed in 1983, and then granted in 1986 [10]. Through this patent, Widra has invented the first formulation of hydrophilic biopolymeric co-polyelectrolytes and biodegradable wound dressing comprising a chitosan hydrogel. The primary object of this invention was to provide a novel biomaterial (i.e., chitosan-based hydrogel) exhibiting the proper combination of properties, rendering it suitable for use as a dressing for burn wounds and other denuded tissue wound sites such as deep ulcers [10].

As a source of production of chitosan-based hydrogels, research and development in this area is developing rapidly through the innovation and improvement of raw materials, chemical synthesis, methods of preparation, formulations, and fabrication processes, as well as applications. This is evident also from the increase in the number of patent applications filed each year worldwide in this area of chitosan biopolymer research and development. For example, during the period from 2011 to 2021, patent applications related to chitosan biopolymer increased from 304 to 1169, respectively, with several organizations around the world that are currently involved in chitosan patent activity and filing [11].

This work, in the form of a patent analysis, which is a family of techniques for studying the information present within and attached to patents, describes the state by introducing what has been patented concerning chitosan-based hydrogels regarding preparation methods/processes, formulations, and applications. Furthermore, this work gives a competitive analysis of the past, present, and future trends in hydrogels and leads to various recommendations that could help one to plan and innovate a research strategy. It is established as a research planning tool in accordance with patent analysis standards [1,12]. The results are then analyzed by answering specific questions, such as those relating to patterns of patenting (e.g., who files applications, what is filed, and where?), by determining publication dates, patent classifications, inventors, applicants, owners, and jurisdictions.

## 2. Materials and Methods

The supported field codes used in this study were based on the Patentscope search service of the World Intellectual Property Organization (WIPO) [13], the Espacenet patent search of the European Patent Office (EPO) [14], the PatFT/AppFT Databases of the United States Patent and Trademark Office (USPTO) [15], and the Lens patent data set of the Cambia Institute [16]. During the search, different keywords and related terms were used, and patents were searched according to title, abstract, and claims. The search was then filtered to include only documents with a publication date until December 31<sup>st</sup>, 2021.

Hereinafter, the state of the art will be reviewed by introducing what has been patented in relation to chitosan-based hydrogels. A detailed analysis of patents for the used raw materials, extracting methods/processes, formulations, and applications will be provided following these sections:

- **Publication dates:** The date on which a patent document is published, thereby making it part of the state of the art [1].
- **Patent classifications:** The International Patent Classification (IPC) is a hierarchical system in the form of codes, which divides all technology areas into a range of sections, classes, subclasses, groups, and subgroups. It is an international classification system that provides standard information to categorize inventions and evaluate their technological uniqueness [17].
- **Inventors:** An inventor is a natural person designated for a patent application. In several cases, the inventor can also be the applicant, and there may be more than one inventor per patent application [18].
- **Applicants:** An applicant is a person (i.e., a natural person) or an organization (i.e., a legal entity) that has filed a patent application. In several cases, the applicant can also

be the inventor, and there may be more than one applicant per patent application [18].

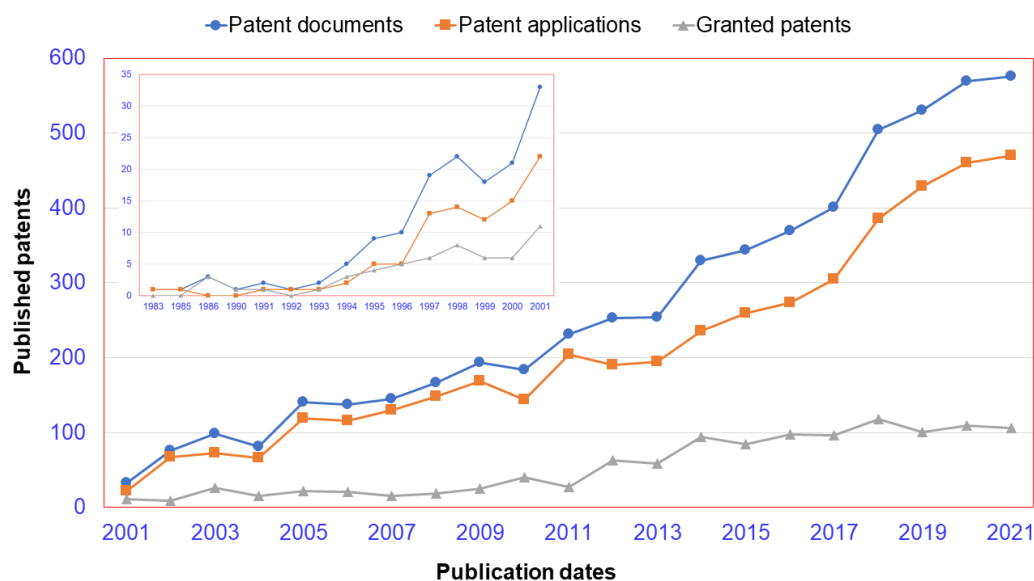
- **Owners:** An assignee, or patent owner, is a person (i.e., a natural person) or an organization (i.e., a legal entity) to whom the inventor or applicant assigned the right to a patent. The patent owner has the right, for a period limited to the duration of the patent term, to protect his brainchild. The patent system stops others from making, using, or selling the invention without the inventor's permission or requires others to use the invention under agreed terms with the inventor [18].
- **Jurisdictions:** An applicant, or a first-mentioned applicant in the case of joint applicants, can apply for a patent at the appropriate patent office (e.g., USPTO) under whose jurisdiction he normally resides, has his domicile, has a place of business, or the place from where the invention originated [19]. Under such regional systems, an applicant requests protection for an invention in one or more member states of the regional organization in question. The regional office (e.g., EPO) accepts these patent applications, which have the same effect as national applications, or grants patents, if all the criteria for the grant of such a regional patent are met [20].

### 3. Results and Discussion

#### 3.1. Publication Dates

Based on the early priority date of the above-described patent, the year 1983 is considered the first year of chitosan-based hydrogel patenting [10]. Between 1 January 1983 and 31 December 2021, a total of 5734 patent documents were found. Generally, it encompasses patent applications and granted patents. In relation to chitosan-based hydrogels, the found patent documents are classified as 4532 patent applications and 1202 granted patents.

Figure 3 presents the evolution of published patents as a function of the publication dates for chitosan-based hydrogels during the 1983–2021 period. The year 1983 saw the registration of only one patent application. However, the year 2021 recorded the maximum number of 576 patent documents as well as the maximum number of 470 patent applications. Furthermore, a maximum granted patent of 118 was recorded in 2018. Finally, it should be noted that from 2014 to 2021, a stable rate of about 100 per year was observed for granted patents.

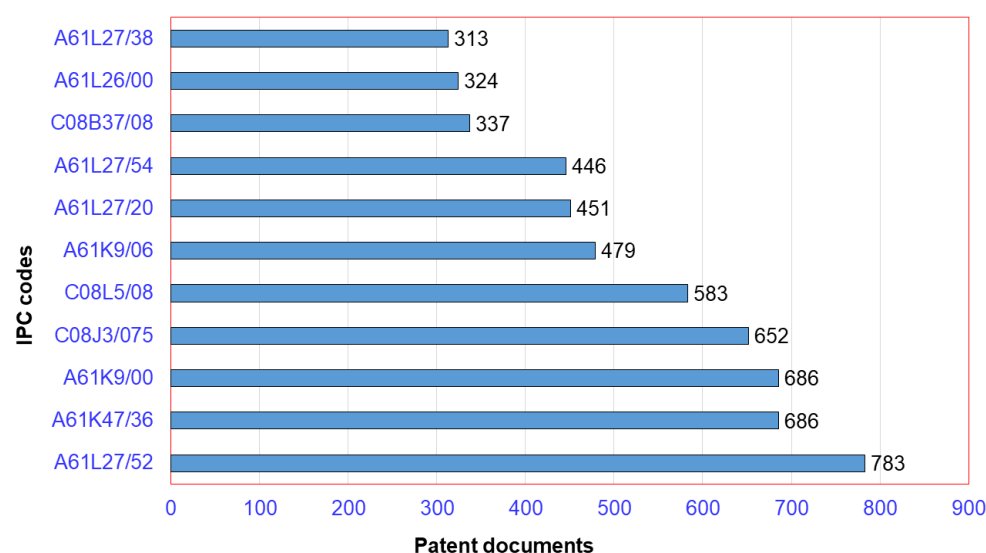


**Figure 3.** Evolution of published patents as a function of the publication dates for chitosan-based hydrogels during the 1983–2021 period.

In a previous study concerning chitosan biopolymer, only a total of 1169 patent documents were found through Patentscope [11]. Despite that the study included the formulation of chitosan biopolymer and its uses in the forms of nanoparticles, fibers, hydrogels, etc., the number of 1169 patent documents for chitosan biopolymer seems to be lower compared to 5734 patent documents for chitosan-based hydrogels. This lower number of patent documents found on the Patentscope compared to other databases could be explained by the difference in the services offered by each database. In fact, the Patentscope, as a research service of the WIPO, offers searches of international patent applications filed under the Patent Cooperation Treaty (PCT), as well as access to some national and regional collections, while other databases could be considered as a multicountry research service that has access to all patent applications at the international, regional, and national levels through databases provided by WIPO, regional offices, and national offices, respectively.

### 3.2. Patent Classifications

The top 10 IPC codes of patents concerning chitosan-based hydrogels between 1983 and 2021 are presented in Figure 4. The most IPC code corresponds to A61L27/52, which is a subgroup of hydrogels or hydrocolloids. This subgroup is present in 783 patent documents with a patent contribution per total of 13.65%. Secondly, the subgroup A61K47/36 concerns macromolecular organic or inorganic compounds such as polysaccharides and their derivatives. This subgroup is present in 686 patent documents with a patent contribution per total of 11.96%. The same patent contribution per total of 11.96% is registered for the group A61K9/00, which concerns medicinal preparations characterized by special physical form. Thirdly, the subgroup C08J3/075 concerns macromolecular gels and is present in 652 patent documents with a patent contribution per total of 11.37%. For more details concerning these top 10, a description of each IPC code is shown in Table 1.



**Figure 4.** IPC codes (top 10) of resultant patent documents for chitosan-based hydrogels.

Regarding the top 10 IPC codes of patents, the major synthesized hydrogels based on chitosan found in patents concern biomedical applications as well as tissue engineering (Table 2). Furthermore, the designed chitosan-based hydrogels have been obtained according to the following four Wichterle design criteria [21]:

- Avoid dissolving hydrogel macromolecules in biological fluids;
- Create a stable chemical and biochemical structure;
- Have a high permeability for nutrients and biological waste for cells; and
- Reproduce physical characteristics similar to natural biological tissues.

**Table 1.** Meaning of IPC codes (top 10) in relation to resultant patent documents for chitosan-based hydrogels (Adapted from IPC Publication list [17]. Copyright © 2022 WIPO under Creative Commons – Attribution (BY) 3.0 IGO – license).

IPC	Description
A61L27/52	Materials for prostheses or for coating prostheses, characterized by their function or physical properties: hydrogels or hydrocolloids
A61K47/36	Medicinal preparations characterized by their non-active ingredients: macromolecular organic or inorganic compounds such as polysaccharides and their derivatives
A61K9/00	Medicinal preparations characterized by special physical form
C08J3/075	Processes of treating or compounding macromolecular substances: macromolecular gels
C08L5/08	Compositions of polysaccharides or their derivatives: chitin, chondroitin sulfate, hyaluronic acid, and their derivatives
A61K9/06	Medicinal preparations characterized by special physical form: ointments
A61L27/20	Materials for prostheses or for coating prostheses: macromolecular materials such as polysaccharides
A61L27/54	Materials for prostheses or for coating prostheses, characterized by their function or physical properties: biologically active materials (e.g., therapeutic substances)
C08B37/08	Preparation of polysaccharides: chitin, chondroitin sulfate, hyaluronic acid, and their derivatives
A61L26/00	Chemical aspects of, or use of materials for, liquid bandages
A61L27/38	Materials for prostheses or for coating prostheses, containing ingredients such as animal cells for use in artificial skin

**Table 2.** Examples of patented chitosan-based hydrogels used in biomedical applications and tissue engineering [15].

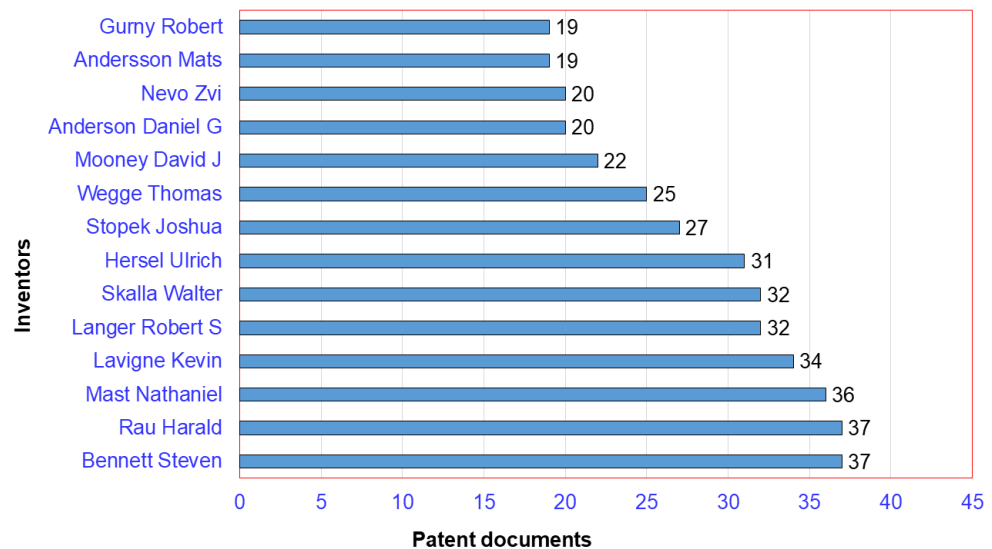
Application	Reference
Encapsulation of limbal stem cells	[22]
Prevention of intramammary infections	[23]
Treatment of transected peripheral nerve injuries	[24]
Aneurysm embolization and other endovascular therapies	[25]
Surgical and medical procedures for sealing biological tissues	[26]
Treatment of articular diseases	[27]
Drug delivery systems for anti-cancer therapies	[28]
Repair of nerve tissues	[29]
Intravenous amperometric biosensors	[30]
Repair and healing of skin lesions and wounds	[31]

### 3.3. Inventors, Applicants, and Owners

The top 10 inventors of patents concerning chitosan-based hydrogels between 1983 and 2021 are presented in Figure 5. The podium in first place, it is shared between the two inventors, Bennett Steven and Rau Harald, who have recorded 37 patent documents each. In second place, the inventor Mast Nathaniel has recorded 36 patent documents. Thirdly, the inventor, Lavigne Kevin, has recorded 34 patent documents. The patent documents of the three inventors, Bennett Steven, Mast Nathaniel, and Lavigne Kevin, are primarily concerned with the company Covidien LP (Mansfield, MA, USA). However, the patent documents of the inventor Rau Harald are primarily concerned with the company Ascendis Pharma AS (Hellerup, Denmark).

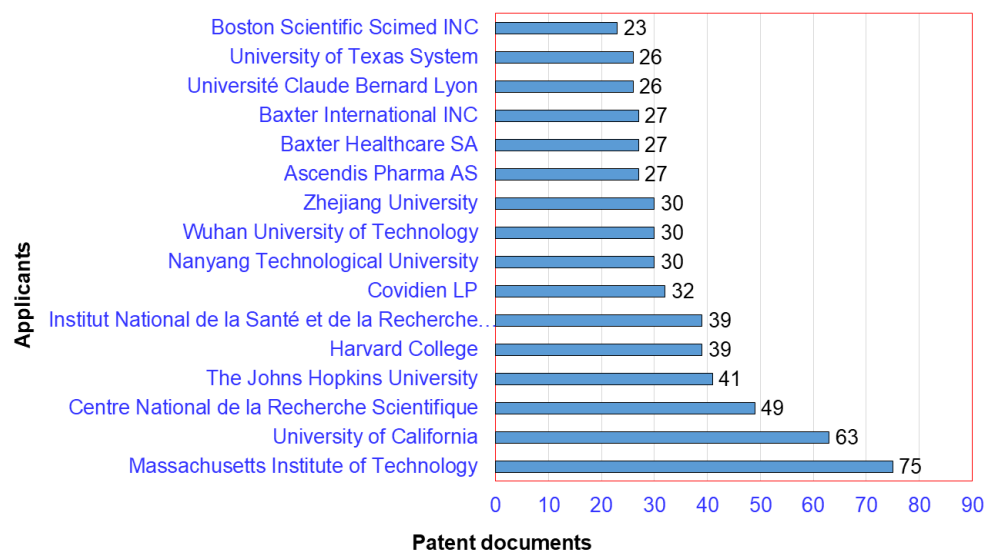
The top 10 applicants of patents concerning chitosan-based hydrogels between 1983 and 2021 are presented in Figure 6. As presented, all the top 10 applicants are organizations, either universities, academic institutions, or companies. As a legal entity, the Massachusetts Institute of Technology (Cambridge, MA, USA) is ranked as the first applicant who has recorded 75 patent documents. In second place, the University of California (Los Angeles, CA, USA), as a legal entity, has recorded 63 patent documents. As for the podium

of the third place, the Centre National de la Recherche Scientifique (Paris, France), as a legal entity, has recorded 49 patent applications.



**Figure 5.** Inventors (top 10) of resultant patent documents for chitosan-based hydrogels.

It should be noted that the Massachusetts Institute of Technology, the University of California, The Johns Hopkins University, and Harvard College are considered the top academic applicants for patents for biopolymer-based hydrogels as well as hydrogel-based research and development in the world [32,33]. Regarding the results of this study, the same tendency was obtained specifically for development and innovation in chitosan-based hydrogels.



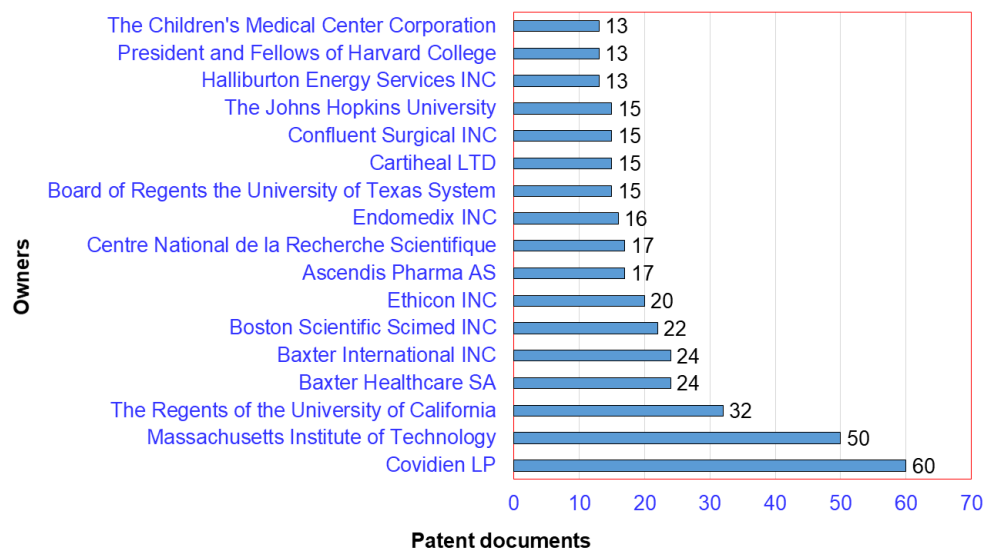
**Figure 6.** Applicants (top 10) of resultant patent documents for chitosan-based hydrogels.

The top 10 owners of patents concerning chitosan-based hydrogels between 1983 and 2021 are presented in Figure 7. As presented, all the top 10 owners are organizations, either universities, academic institutions, government bodies, or companies. As a legal entity, the company Covidien LP (Mansfield, MA, USA) is ranked as the first owner who has recorded 60 patent documents. In the second and third places, the owners, Massachusetts Institute of Technology (Cambridge, MA, USA), as a legal entity, and the Regents of



the University of California (Los Angeles, CA, USA), as a government body, have recorded 50 and 32 patent documents, respectively.

It should be noted that the Massachusetts Institute of Technology, the University of California, and Harvard College are considered the top academic owners of patents for biopolymer-based hydrogels [32]. Regarding the results of this study, the same tendency was obtained specifically for development and innovation in chitosan-based hydrogels.



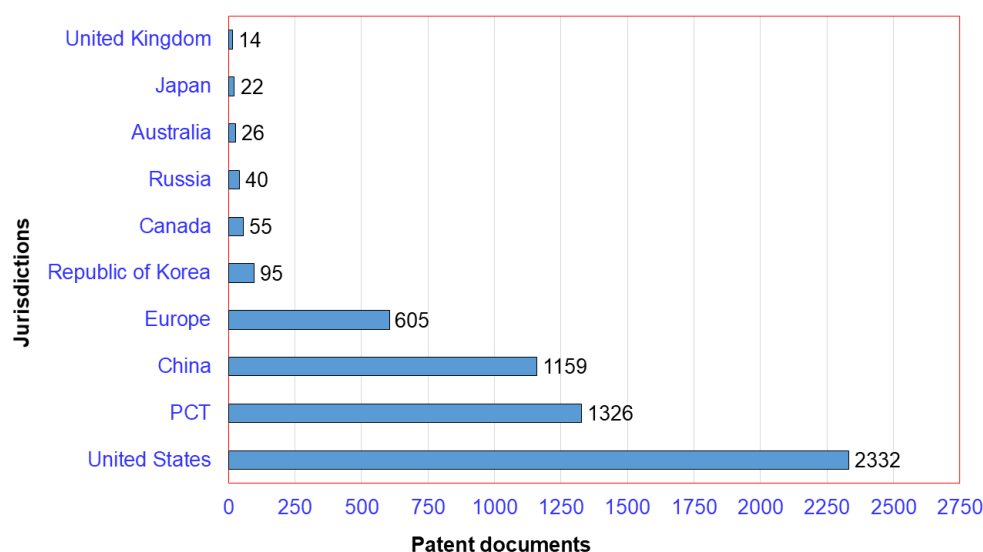
**Figure 7.** Owners (top 10) of resultant patent documents for chitosan-based hydrogels.

### 3.4. Jurisdictions

The top 10 jurisdictions of patents concerning chitosan-based hydrogels between 1983 and 2021 are presented in Figure 8. The United States through the USPTO encompasses 2332 patent documents, with a higher patent contribution per total of 40.67%. On the other hand, the global system for filing patent applications, known as the Patent Cooperation Treaty (PCT) and administered by WIPO, encompasses 1326 patent documents with a patent contribution per document total of 23.12%. Finally, China, through the CNIPA, encompasses 1159 patent documents with a patent contribution per total of 20.21%, as well as the EPO, through which patent applications are filed regionally (Europe), with 605 patent documents with a patent contribution per total of 10.55%.

It should be noted that the four cited jurisdictions are considered the top jurisdictions for the patent filing of chitosan biopolymer applications and biopolymer-based hydrogels in the world [11,32]. Regarding the results of this study, the same tendency was obtained specifically for development and innovation in chitosan-based hydrogels.





**Figure 8.** Jurisdictions (top 10) of resultant patent documents for chitosan-based hydrogels.

#### 4. Conclusions

This study provides a comprehensive overview of the patent situation for chitosan-based hydrogels. It was established according to standards of patent analysis. It was divided into two major parts: Firstly, the state of the art of chitosan formulation. Secondly, an analysis of the patentability of these chitosan-based hydrogels has been provided regarding publication dates, patent classifications, inventors, applicants, owners, and jurisdictions. The results are then analyzed by answering specific questions, such as those relating to patterns of patenting (e.g., who files applications, what is filed, and where?).

This patent analysis concerned only the innovation and improvement of chitosan-based hydrogels between 1 January 1983 and 31 December 2021. A detailed analysis of the patentability of formulations and the preparation process of chitosan-based hydrogels has been provided. During research, 5734 patent documents (4532 patent applications and 1202 granted patents) were found. The United States was ranked first with 2332 patent documents, and 2021 was the year with the maximum number of patent documents (576). The innovation and improvement of chitosan-based hydrogels concerns the innovation and improvement of polymers, chemical synthesis, methods of preparation, formulations, and fabrication processes, as well as applications. Based on the patent classification codes, all fully filed patents and inventions are intended for compositions of polysaccharides or their derivatives, and macromolecular materials. Moreover, they are also intended for macromolecular gels and hydrogels or hydrocolloids.

The knowledge clusters and expert driving factors of this patent analysis indicate that the research and development based on the formulation of macromolecular gels and hydrogels for use in biomedical applications is concentrated in most patents. More specifically, the research and development outlines concern: (i) materials for prostheses, or for coating prostheses, characterized by their function or physical properties; (ii) medicinal preparations characterized by the non-active ingredients; (iii) medicinal preparations characterized by special physical form; and (vi) processes of treating or compounding macromolecular substances.

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**Conflicts of Interest:** The author is a co-inventor on a patent family pertaining to chitosan–sodium tetradecyl sulfate hydrogel (Granted Patents: CA2704971C, US9731043B2, and US8840867B2; Patent Applications: US20140377187A1, US20110286925A1, and CA2704971A1). The author declares that the content of this article has no conflict of interest. The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this article.

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