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Patentability of Biopolymer-Based Hydrogels †

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Abstract: The most of the scientific literature shows that the studies on biopolymer-based hydrogels have a bright future. This work, in the form of a patentability study, englobes information present within patents (i.e., patent applications and granted patents) related to biopolymer-based hydrogels. The patentability study describes the state of the art by introducing what has been patented in relation to biopolymer-based hydrogels regarding to preparation methods/process, formulations and applications. A detailed analysis is then given regarding to publication year, international patent classifications, inventors, applicants, owners, and jurisdiction. Furthermore, this work gives a competitive analysis of the past, present and future trends in the biopolymer-based hydrogels and leads to various recommendations that could help one to plan and innovate research strategy. The classification of patents reveals that most inventions intended for medicinal preparations characterized by special physical form, as well as materials characterized by their function or physical properties, such as hydrogels or hydrocolloids.

Keywords: biopolymers; hydrogels; formulation; innovation; patent; intellectual property

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1. Introduction

Biopolymers consist of biologically derived polymers synthesized by living organisms such as animals, plants, algae and microorganisms [1]. Owing to their chemical and biological in addition to their superior mechanical and thermal properties, biopolymers have become "the material of choice" in different applications such as health care and biomedical sciences [2].

Biopolymer-based hydrogels are used in the field of tissue engineering, in the form of matrix capable of sustaining the life of differentiated and non-differentiated cells in three-dimensional (3D) structure that they can develop there and produce all the compounds for which they are programmed [3]. Moreover, the elasticity of these structures and the presence of a large amount of water and the flexibility allow a resemblance to different living biological human/animal tissues [4]. The similarity to tissues, and their ability to form scaffolds for various tissues allow them to be employed in health care and in many biomedical applications (Table 1).

Biopolymer-based hydrogels can be created by supramolecular chemistry from a large number of water-soluble biologically derived polymers including proteins (e.g., collagen [5], gelatin [6], fibrin [7], etc.) and polysaccharides (e.g., cellulose [8], alginate [9], chitosan [10], etc.). The 3D structure of these hydrogels is due to crosslinking which forms an insoluble macromolecular network in the biofluid of the environment [11]. Furthermore, the network remains in equilibrium in an aqueous medium due to the balance of the elastic forces of the crosslinked polymer and the osmotic forces of the liquid [12]. The chemical composition and the crosslink density determine the swelling rate and the permeability of the structure. In addition, the crosslinking of hydrogels, which can either be covalent, ionic or physical gives them an elastic response to a given stress request [13].

Table 1. Properties and applications of some natural biopolymer-based hydrogels used in tissue engineering and regenerative medicine.

Hydrogel	Properties	Application
Collagen	Low immune response, good substrate for cell adhesion, chemotactic. Easily remodeled and degraded by cells. Chemical crosslinking decreases degradation and improves long-term mechanical properties.	*Corneal substitutes; Wound healing; Bone tissue engineering.*
Gelatin	Irreversibly hydrolyzed form of collagen. Presence of amino acidic sequences in the structure. Water soluble, non-toxic, inexpensive, and non-immunogenic material. Highly biocompatible and biodegradable in a physiological environment.	*Drug and cell delivery; Cell encapsulation; Wound healing; Skin substitute; Nerve regeneration; Bone repair.*
Fibrin	Stimulates cell migration, osteoconduction and vascularization. Fibrinolytic inhibitors, like aprotinin or aminocaproic acid, reduce in vitro degradation rates.	*Skin regeneration; Cardiac tissue engineering; Growth factors encapsulation.*
Silk	Low enzymatic degradation rate controlled by crystallinity and some concerns arise on potential cytotoxic effects. Intrinsic mechanical properties. Mechanics tailored by modifying concentration, crystallization, molecular weight, and scaffold size.	*Skin regeneration; Cardiac tissue engineering; Growth factors encapsulation.*
Alginate	Degradation through ionic exchange with surrounding media. Variations in local mechanical properties controlled by concentration of divalent cation (e.g., calcium ions).	*Microencapsulation of cells; Wound healing; Drug and cell delivery; Pulposous nucleus regeneration.*
Hyaluronic Acid	Minimal immune response and chemotactic combined with the adequate agents. Osteo-inductive and angiogenesis in combination with growth factors.	*Corneal wound healing; Bone and cartilage reparation; Spinal cord injury repair; Tumor models.*
Chitosan	Soluble only in acidic conditions, and insoluble in neutral and basic conditions. Hemostatic stimulates osteo-conduction and wound healing. Degradability and shape-ability to fit the defect site.	*Wound dressing; Drug delivery systems; Skin regeneration; Cartilage tissue engineering; Blood vessels embolization.*
Cellulose	Non-toxic and non-irritant material. Chemical crosslinking improves solubility and long-term mechanical properties. 3D interconnected structure suitable for cell maintenance and differentiation. Poor degradability.	*Wound dressing and transdermal patches; Ophthalmic preparations; Cartilage tissue engineering.*
Agarose	Slow degradation profile and the low mechanical properties. 3D scaffolds exhibiting soft and flexible structure suitable for cell maintenance and differentiation.	*Wound healing; Cell culture; Cartilage tissue engineering; Drug release.*
Carrageenan	Thermally, pH and cation concentration responsive material, in expensive and easy to manipulate. Effectiveness in maintaining the proliferative and chondrogenic potential of encapsulated cells.	*Controlled drug release; Tissue engineering; Skin regeneration; wound healing; Cartilage scaffold.*

The first patent application concerning biopolymer-based hydrogels was filled in 1935, and then granted in 1936 [14]. Through this patent, Julius has invented a chemical process to synthetize a protein-based hydrogel. The inventor has proposed and then proved the concept by treating fresh milk-proteins with lactic acid cultures to induce partial decomposition. The obtained protein-based hydrogel has been therefore proposed for the preparation of disinfectants, pest-exterminating agents, lubricants and other industrial dispersions [14].

To solve specific biological and medical difficulties, actual research on biopolymer-based hydrogels is based on the synthesis of new polymers or on the modification of existing ones [15]. More specifically, as a remarkable class of biomaterials, research on biopolymer-based hydrogels is developing rapidly through the innovation and improvement of raw materials (proteins or polysaccharides), synthesis and methods of preparation, formulations and fabrication process, as well as applications. This is evident also from the elevation in the number of patent applications filed each year worldwide in this area of biopolymer-based hydrogels research and development. For example, during the period from 2015 to 2020, patent applications related to biopolymer-based hydrogels have increased from 5331 to 8910, respectively, with more than 1000 organizations (universities, academic institutions, companies, foundations, governing bodies, etc.) around the world are currently involved in the biopolymer-based hydrogels patent activity and filing [16]. Moreover, the most of the scientific literature shows that the studies on biopolymer-based hydrogels have a bright future [13].

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 of the art by introducing what has been patented in relation to biopolymer-based hydrogels regarding to materials, methods/process, formulations and applications. Furthermore, this patentability study gives a competitive analysis of the past, present and future trends in the biopolymer-based hydrogels leads to various recommendations that could help one to plan and innovate research strategy.

2. Resources and Research Methods

The supported field codes used in this study was based on the Patentscope search service of the World Intellectual Property Organization (WIPO) [16,17] and The Lens patent data set [18]. During the search, different keywords and related terms (i.e., biopolymer hydrogel, polysaccharide hydrogel, protein hydrogel) were used and patents were searched according to title, abstract and claims. The search was then filtered to include only documents with the application date until 2020.

3. Analysis of the Patentability of Biopolymer-Based Hydrogels

After the search, 11,895 patent documents have been found. Generally, it encompasses patent applications and granted patents. For relation to biopolymer-based hydrogels the found patent documents are classed as: 8910 patent applications and 2985 granted patents.

Hereinafter we will review the state of the art by introducing what has been patented in relation to biopolymer-based hydrogels. We provide then a detailed analysis of the patentability of the raw materials (proteins or polysaccharides), synthesis and methods of preparation, formulations and fabrication process, as well as applications, following these sections: publication year, patent classification, inventors, applicants, owners, and jurisdiction.

3.1. Publication Year

Based on definitions of the terms used generally in the world of patent information, the publication is the step when the patent document (patent application, granted patent, etc.) made available to the public, to which a publication number and a publication date have been assigned by a patent authority. In other words, the publication date is the date on which a patent document is published, thereby making it part of the state of the art. In contrary, the filing date is the date when a patent application is first filed at a patent office [19].

For biopolymer-based hydrogels, 11,895 patent documents have been found until 2020. The year 1995 knew the registration of 51 patent documents only, with 25 patent applications and 26 granted patents, however the year 2020 recorded 934 patent documents, with 698 patent applications and 236 granted patents. Furtherer, the year 2017 was the year with the maximum granted patents with 254 (Figure 1).

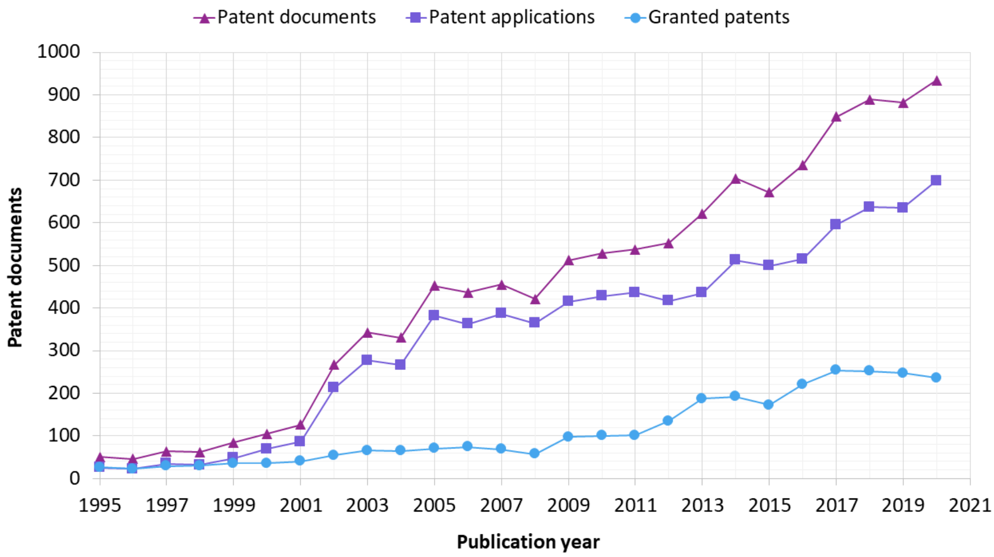

Figure 1. Evolution of patent documents (patent applications and granted patents) as a function of published date of biopolymer-based hydrogels.

3.2. International Patent Classification

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 to evaluate their technological uniqueness [20,21].

For biopolymer-based hydrogels, the top 10 of IPC codes until 2020 are presented in Figure 2. The most IPC code corresponds to A61K9/00 which is a group of preparations for medical, dental, or toilet purposes. More specifically, medicinal preparations characterized by special physical form. This group recorded it alone 1331 patent documents. The subgroups A61L27/52 (hydrogels or hydrocolloids) and A61K47/36 (polysaccharides and derivatives thereof) recorded 1179, and 743 patent documents, respectively. For mor details concerning the top 10, a description of each IPC code is shown in Table 2.

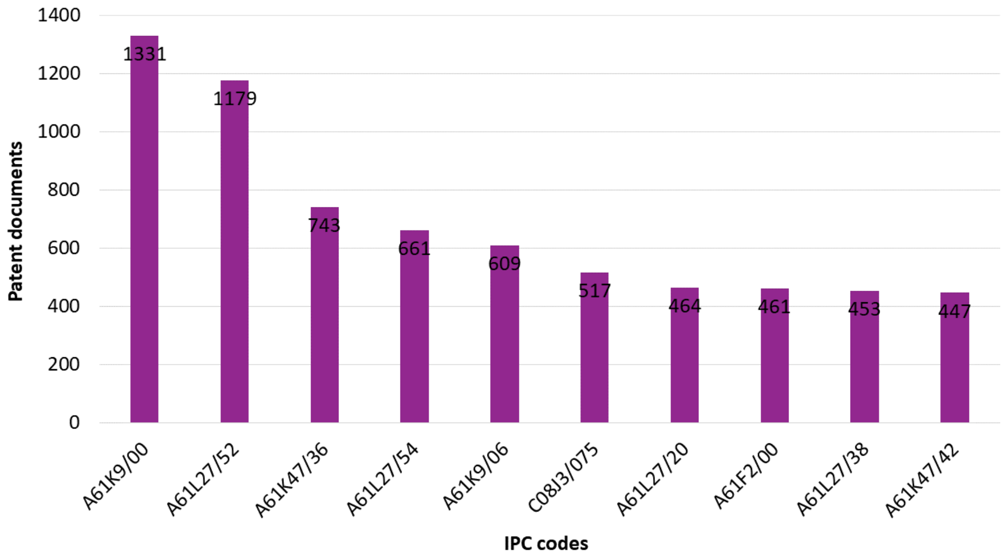

Figure 2. Top 10 of IPC codes of resulted patents as a function of patent documents of biopolymer-based hydrogels.

Table 2. Meaning of IPC codes (top 10) concerning the resulted patents of biopolymer-based hydrogels [20].

IPC	Description
A61K9/00	Preparations for medical, dental, or toilet purposes. More specifically, medicinal preparations characterized by special physical form.
A61L27/52	Materials characterized by their function or physical properties, such as hydrogels or hydrocolloids.
A61K47/36	Medicinal preparations characterized by the non-active ingredients used. More specifically, macromolecular organic or inorganic compounds, such as polysaccharides and derivatives thereof (e.g., gums, starch, alginate, dextrin, hyaluronic acid, chitosan, inulin, agar or pectin).
A61L27/54	Materials characterized by their function or physical properties, such as biologically active materials (e.g., therapeutic substances).
A61K9/06	Preparations for medical, dental, or toilet purposes. More specifically, medicinal preparations characterized by special physical form, such as ointments.
C08J3/075	Processes of treating or compounding macromolecular substances. More specifically, making solutions, dispersions, lattices or gels in aqueous media, such as macromolecular gels by other methods than by solution, emulsion or suspension polymerization techniques.
A61L27/20	Macromolecular materials for prostheses or for coating prostheses, such as polysaccharides.
A61F2/00	Filters implantable into blood vessels and prostheses (i.e., artificial substitutes or replacements for parts of the body), such as stents, artificial nails, dental prostheses, artificial kidneys and artificial hearts.
A61L27/38	Materials for prostheses or for coating prostheses containing ingredients of undetermined constitution or reaction products thereof, such as animal cells.
A61K47/42	Medicinal preparations characterized by the non-active ingredients used. More specifically, macromolecular organic or inorganic compounds, such as proteins and derivatives thereof (e.g., albumin, gelatin, oligopeptides or polyamino acids).

3.3. Inventors

Based on definitions of the terms used generally in the world of patent information, the inventor is a natural person designated for a patent application. In several cases, the inventor can also be the applicant, as well as there may be more than one inventor per patent application [19].

For biopolymer-based hydrogels, the top 10 of inventors until 2020 are presented in Figure 3. Langer Robert from United States is ranked as the first inventor who has recorded 92 patent documents. In the second place, the inventor Trieu Hai from United States has recorded 68 patent documents, and thirdly, the inventor Mooney David from United States has recorded 65 patent documents.

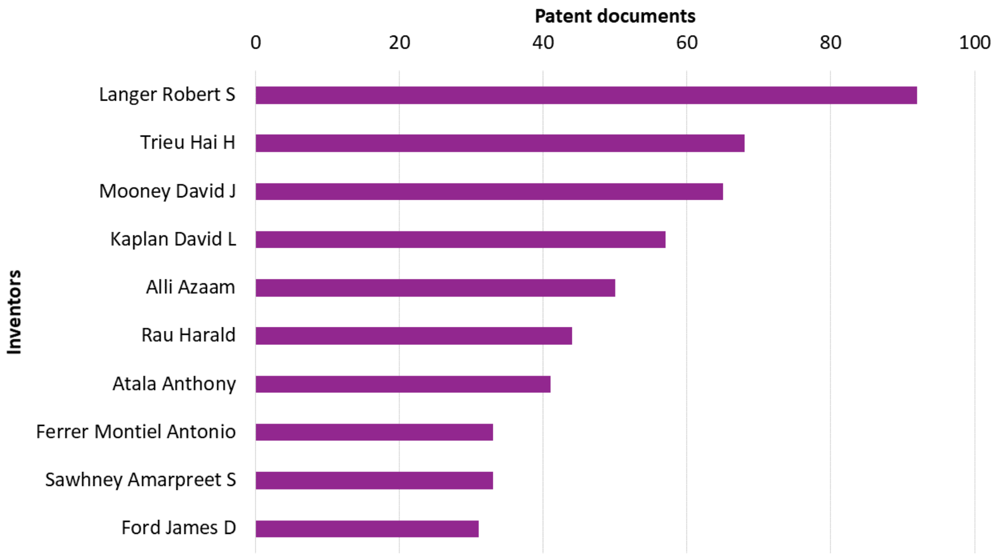

Figure 3. Top 10 of inventors of resulted patents as a function of patent documents of biopolymer-based hydrogels.

3.4. Applicants

Based on definitions of the terms used generally in the world of patent information, the applicant is a person (i.e., natural person) or an organization (i.e., legal entity) that has filed a patent application. In several cases, the applicant can also be the inventor, as well as there may be more than one applicant per patent application [19].

For biopolymer-based hydrogels, the top 10 of applicants until 2020 are presented in Figure 4. Massachusetts Institute of Technology (Cambridge, MA, United States), as a legal entity, is ranked as the first applicant which has recorded 211 patent documents. In the second place, University of California (Los Angeles, CA, United States), as a legal entity, has recorded 162 patent documents. As for the podium of the third place, Harvard College (Cambridge, MA, United States), as a legal entity, has recorded 129 patent documents.

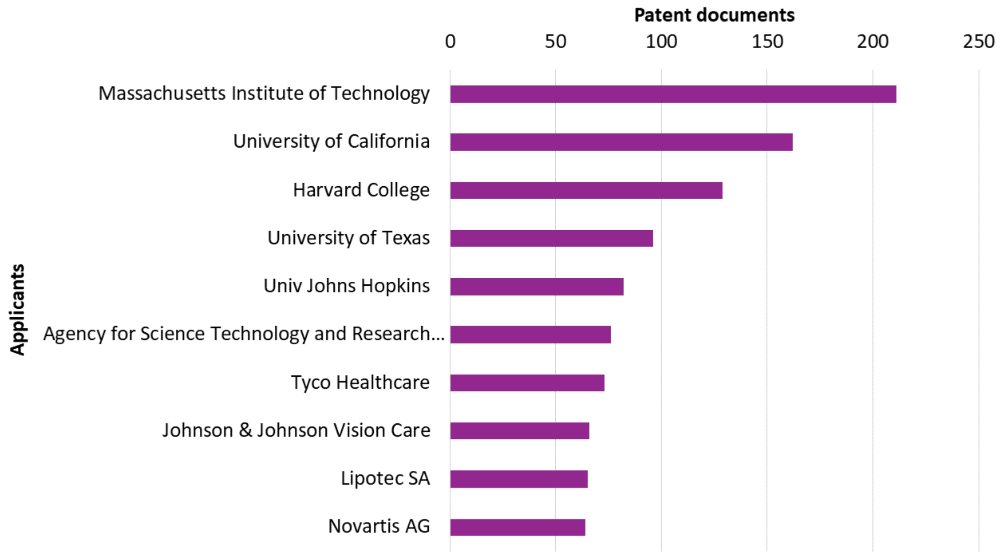

Figure 4. Top 10 of applicants of resulted patents as a function of patent documents of biopolymer-based hydrogels.

3.5. Owners

Assignee or patent owner is a person (i.e., natural person) or an organization (i.e., 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 his permission or requires others to use the invention under agreed terms with the inventor [22].

For biopolymer-based hydrogels, the top 10 of owners between are presented in Figure 5. Massachusetts Institute of Technology (Cambridge, MA, United States), as a university, is ranked as the first owner which has recorded 130 patent documents. In the second place, Covidien LP (Mansfield, TX, United States), as a company, has recorded 112 patent documents, and thirdly, the Regents of the University of California (Los Angeles, CA, United States), as a government body, has recorded 72 patent documents.

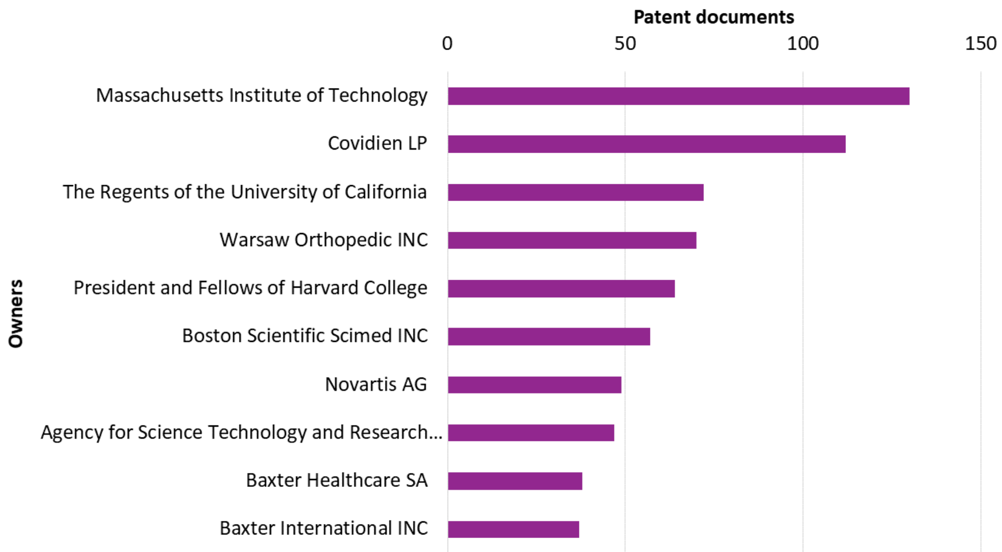

Figure 5. Top 10 of owners of resulted patents as a function of patent documents of biopolymer-based hydrogels.

3.6. Jurisdiction

An applicant or first mentioned applicant in case of joint applicants can file application for patent at the appropriate Patent Office (e.g., European Patent Office (EPO), United States Patent and Trademark Office (USPTO), China National Intellectual Property Administration (CNIPA), etc.) under whose jurisdiction he normally resides or has his domicile or has a place of business or the place from where the invention actually originated.

For biopolymer-based hydrogels, the top 10 of jurisdiction of filled patents until 2020 are presented in Table 3. United States through the USPTO encompasses 5865 patent documents with a higher patent contribution per total of 49.31%. On the other hand, the global system for filing patent applications, known as Patent Cooperation Treaty (PCT) and administered by WIPO encompasses 3266 patent documents with a patent contribution per total of 27.46%. Finally, the EPO, through where patent applications filled regionally (Europe), encompasses 1412 patent documents with a patent contribution per total of 11.87%.

Table 3. Patent contribution (%) as a function of jurisdiction (top 10) of filled patent applications and granted patents of biopolymer-based hydrogels.

Jurisdiction	Patent Documents	Patent Contribution (%)
United States	5865	49.65
PCT [1]	3266	27.65
Europe [2]	1412	11.95
China	681	5.77
Canada	166	1.41
Japan	137	1.16
Republic of Korea	137	1.16
Australia	85	0.72
Russia	43	0.36
Mexico	20	0.17

[1] International patents administered by WIPO through the Patent Cooperation Treaty. [2] European patents through the EPO.

4. Conclusions

This analysis of the patentability concerned only the innovation and improvement of biopolymer-based hydrogels until 2020. We provided a detailed analysis of the patentability of hydrogels based on both proteins or polysaccharides, regarding to publication year, patent classification, inventors, applicants, owners, and jurisdiction. During the search, 11895 patent documents have been found comprising of 8910 patent applications and 2985 granted patents. United States was ranked first with 5865 patent documents and 2017 was the year with the maximum granted patents (254).

The innovation and improvement of biopolymer-based hydrogels concerned the raw materials (proteins or polysaccharides), synthesis and methods of preparation, formulations and fabrication process, as well as applications. Based on the patent classification codes and areas, all filled patents and the most inventions intended for medicinal preparations characterized by special physical form, as well as materials characterized by their function or physical properties, such as hydrogels or hydrocolloids. Knowledge clusters and expert driving factors indicate that the research based on following areas is concentrated in the most patents: (i) Processes of treating or compounding macromolecular substances; (ii) Macromolecular organic or inorganic compounds, such as polysaccharides and derivatives thereof (e.g., gums, starch, alginate, dextrin, hyaluronic acid, chitosan, cellulose, agar, pectin, etc.), or proteins and derivatives thereof (e.g., collagen, gelatin, fibrin, oligopeptides, polyamino acids, etc.); (iii) Materials for prostheses or for coating prostheses; (iv) Prostheses and artificial substitutes or replacements for parts of the body.

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Conflicts of Interest: The author declares that this article content 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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