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Development of Calcium Phosphate Cements for Bone Repair: An Overview Based on Patent Analysis †

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Abstract: The development of calcium phosphate cement (CaPC) has been regarded as a significant advance in the field of bone defect reconstruction. This patent analysis-based research concerns patent documents with an active legal status until 2022. The state of the art has been reviewed by introducing what has been patented concerning CaPCs for bone repair. As a result, 740 active patent documents were found, and 51% of them have been published during the last seven years. According to the findings, the United States ranked as the first jurisdiction, with academic institutions from France and the United States leading the patenting way. The Cooperative Patent Classification reveals that most inventions are intended for materials or treatments for tissue regeneration, such as the reconstruction of bones with weight-bearing implants, as well as inorganic materials for grafts or prostheses, such as phosphorus-containing materials.

Keywords: calcium phosphate cement; bone repair; bone tissue engineering; innovation; patent analysis

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1. Introduction

The development of calcium phosphate cement (CaPC) has been regarded as a significant advance in the field of bone defect reconstruction [1]. This bioceramic-based biomaterial is injected within the osseous cavity due to its bioactivity and rheological properties, which results in a very quick response to bone attachment and simultaneous regeneration [2]. Furthermore, CaPC may be useful as bone drug delivery systems, encapsulating cells for bone regeneration while also being capable of impregnating drugs for long-term release [3,4].

Active research on CaPCs for bone repair is focused on the development of an injectable, macroporous, and resorbable formula with a high compressive strength [5,6]. To prove the innovation in this way, we just need to see the increase in the number of patent applications filed each year in this area around the world [7].

The first granted patent in this field was filed in 1963 by "Biorex Laboratories LTD" (London, UK) and published in 1967 [8]. Through the claimed invention, Baxendale and Kirk proposed different dental fillers and bone cements. The compositions comprised collagen gel (doped with calcium and phosphate ions), calcium hydroxyapatite powder, an antibiotic, and an anti-inflammatory agent. In the board aspect of the invention, the inventors proposed the developed formulation for filling teeth or cementing bone [8].

This research, in the form of a patent analysis, focuses on patent documents relating to the development of CaPCs for bone repair, which have an active legal status until 2022.

It is established as a research planning tool to analyze what has been patented in this area in accordance with patent analysis standards [9–11]. Furthermore, we determine, through different patent databases, publication dates, applicants, owners, patent classifications, and patent jurisdictions. This type of research has already been demonstrated in various fields through several recent publications on hydrogel-based coatings [9], biocontrol agents [10], bioinks [11,12], hydrogels [13–15], biosensors [16], biofertilizers [17], and chemical molecules [18].

2. Resources and Methodology

Three patent databases were used in this study: Espacenet patent search [19], PatFT-AppFT databases [20], and Google Patents database [7]. Different terms and related keywords to CaPCs for bone repair were used, and the search was carried out on titles, abstracts, and claims. The search fields and queries used in this study were based on a previous study concerning the patent landscape [11]. The results were then filtered to include only patent documents (i.e., patent applications and granted patents) with publication dates until 2022 and which have an active legal status.

3. Results and Discussion

3.1. Patent Documents and Legal Status

During a search, 740 patent documents related to CaPCs for bone repair were found. It encompasses 394 patent applications and 346 granted patents. The legal status of the found patent documents is "active status", indicating that all granted patents are still in force. Moreover, if a patent application has been granted, all published patent documents associated with the application have the status "Active".

3.2. Publication Dates

Figure 1 shows the patent document record as a function of the publication dates. These publications concern only the active patent documents until 2022. 51% of them have been published during the last seven years. Furthermore, the maximum number of patent applications and granted patents were recorded in 2016 and 2018, with 35 and 38, respectively; however, the maximum number of patent documents was recorded in 2016 with 69.

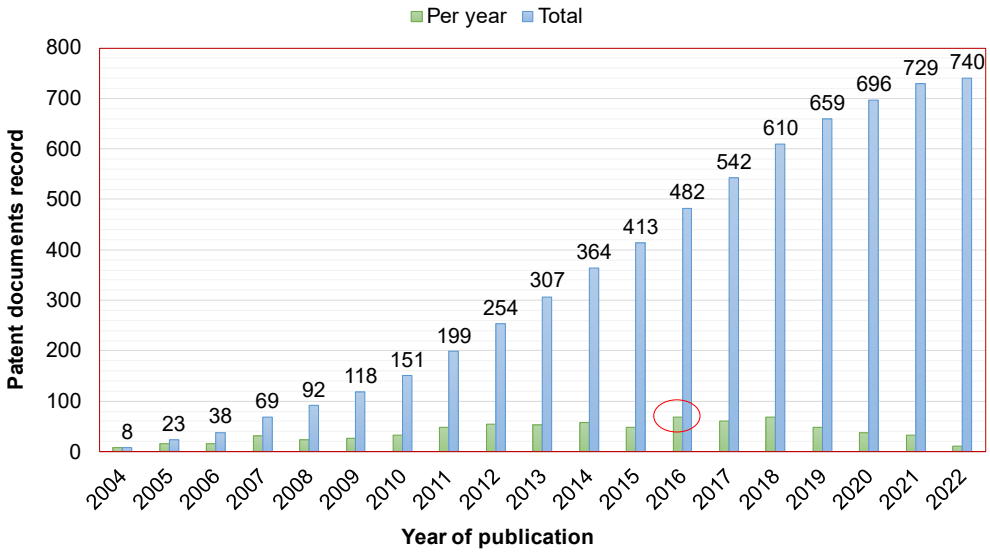

Figure 1. Publication dates of the active patent documents related to the development of CaPCs for bone repair.

3.3. Applicants and Owners

An applicant for a patent is a natural person or legal entity that seeks to obtain a patent from a patent office for a claimed invention [21].

The top 11 applicants of active patent documents related to the development of CaPCs for bone repair are displayed in Figure 2A. In the first instance, we note that these top 11 applicants include only legal entities from the United States, France, and Germany, which are considered companies, universities, or research institutions. "Warsaw Orthopedic INC" (Warsaw, IN, USA) is ranked as the first applicant, having recorded 24 patent documents. In second place, the applicant, "Agnovos Healthcare LLC" (Derwood, MD, USA), has recorded 20 patent documents. Thirdly, the "French National Centre for Scientific Research" (Paris, France), as a research institution, has recorded 18 patent documents.

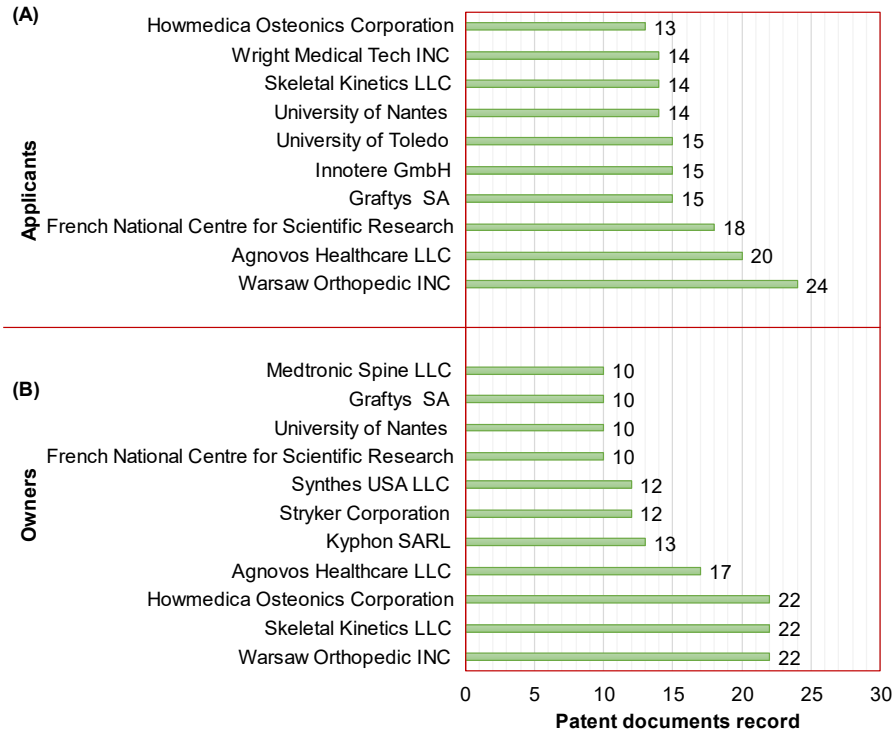

Figure 2. (**A**) Applicants (Top 11) and (**B**) Owners (Top 10) of active patent documents related to the development of CaPCs for bone repair.

An owner of a patent is a natural person or legal entity that holds the legal rights to the patent. This may be the inventor(s) and/or applicant(s) of the patent, or it may be an organization to which the inventor(s) and/or applicant(s) have assigned the rights to the patent [21].

The top 10 owners of active patent documents related to the development of CaPCs for bone repair are displayed in Figure 2B. In the first instance, we note that these top 10 owners include seven owners who are already classified as applicants. As owner, the parent organization Medtronic leads the patenting way with 45 patent documents through its branches or divisions: "Warsaw Orthopedic INC" (Warsaw, IN, USA), "Kyphon SARL" (Neuchâtel, Switzerland), and "Medtronic Spine LLC" (Sunnyvale, CA, USA). Stryker is another parent organization that is ranked as the second owner with 34 patent documents through its branches or divisions: "Howmedica Osteonics Corporation" (Mahwah, NJ, USA) and "Stryker Corporation" (Kalamazoo, MI, USA). Finally, the company "Skeletal Kinetics LLC" (Beach, FL, USA) is ranked as the third owner, having recorded 22 patent documents.

Further, academic institutions from France and the United States are leading the patenting way on the development of CaPCs for bone repair as applicants and/or owners. These institutions are the "University of Nantes" (Nantes, France) and the "University of Toledo" (Toledo, OH, USA).

3.4. Patent Classifications

Patent classifications are used to organize and classify patents according to the subject matter of the invention or technology described in the patent. There are several different patent classification systems in use around the world. Hereinafter we use the Cooperative Patent Classification (CPC) system that is used by the European Patent Office (EPO) and the United States Patent and Trademark Office (USPTO). It consists of a hierarchical structure of classes, subclasses, and groups, with each level of the hierarchy providing increasing levels of detail [21].

The top 10 CPC codes of active patent documents related to the development of CaPCs for bone repair are displayed in Figure 3. The most common code corresponds to A61L2430/02. It's a characteristic of materials or treatments for tissue regeneration, such as the reconstruction of bones with weight-bearing implants. This code was found in 396 patent documents (i.e., 53.5% of total patent documents). Secondly, the code A61L27/12 was found in 282 patent documents (i.e., 38.1% of total patent documents). It concerns inorganic materials for grafts or prostheses, such as phosphorus-containing materials. Thirdly, the code A61L24/02 was found in 220 patent documents (i.e., 29.7% of total patent documents). It concerns surgical adhesives or cement adhesives for colostomy devices containing inorganic materials. For the purpose of searching patent applications and granted patents related to the development of CaPCs for bone repair, Table 1 presents details concerning the description of the top 10 CPC codes.

Finally, it should be noted that applicants may use multiple CPC codes to further classify their patents, and more specifically if the patent document is related to interlinked fields or multidisciplinary sectors.

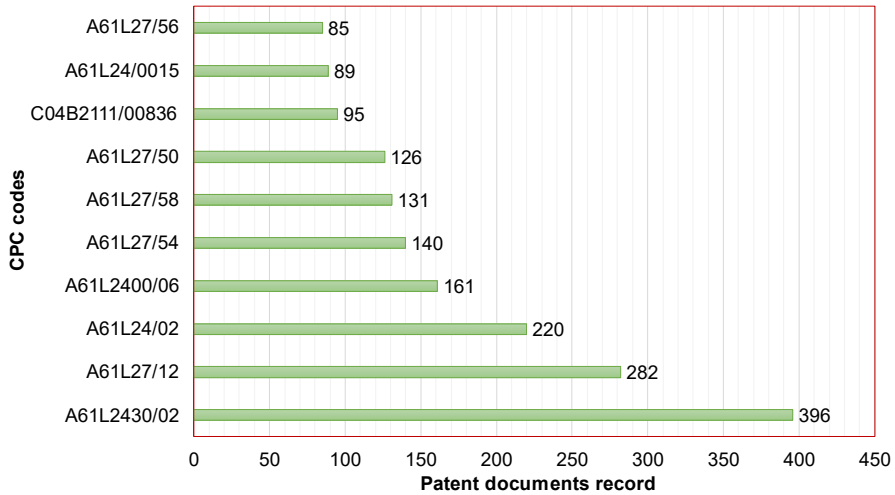

Figure 3. Cooperative Patent Classification (Top 10) of active patent documents related to the development of CaPCs for bone repair.

3.5. Patent Jurisdictions

Patent jurisdictions are the countries (i.e., national patent jurisdictions) or regions (i.e., regional patent jurisdictions) in which a patent is recognized and enforceable. However, there is an international system, administered by the World Intellectual Property

Organization (WIPO), that allows inventors to seek protection for their inventions in multiple countries worldwide by filing a single application under the Patent Cooperation Treaty (PCT) [21].

Table 1. Details of the top 10 CPC codes of active patent documents related to the development of CaPCs for bone repair [19,20].

CPC Code	Description
A61L2430/02	Materials or treatments for tissue regeneration, such as reconstruction of bones with weight-bearing implants
A61L27/12	Inorganic materials for grafts or prostheses, such as phosphorus-containing materials
A61L24/02	Surgical adhesives or cement adhesives for colostomy devices containing inorganic materials
A61L2400/06	Materials characterized by their function or physical properties, such as flowable or injectable implant compositions
A61L27/54	Biologically active materials (e.g., therapeutic substances)
A61L27/58	Materials characterized by their function or physical properties, such as materials that are at least partially resorbable by the body
A61L27/50	Materials characterized by their function or physical properties (e.g., injectable or lubricating compositions, shape-memory materials, surface-modified materials)
C04B2111/00836	Mortars, concrete or artificial stone, or preparation mixtures, distinguished by a specific function, property, or use in medical or dental applications
A61L24/0015	Surgical adhesives or cement adhesives, for colostomy devices, characterized by their function or physical properties, such as medicaments or biocides
A61L27/56	Materials characterized by their function or physical properties, such as porous materials (e.g., foams or sponges)

The jurisdictions of active patent documents related to the development of CaPCs for bone repair are displayed in Figure 4. The list includes 14 jurisdictions, one of which is a regional patent jurisdiction, Europe. The most patent-related jurisdictions correspond to the United States, Europe, and China. Firstly, the United States, through the USPTO, encapsulates 398 patent documents (i.e., 53.78% of total patent documents). Secondly, the Europe through the EPO encapsulates 125 patent documents (i.e., 16.89% of total patent documents). Thirdly, China, through the CNIPA (i.e., China National Intellectual Property Administration), encapsulates 117 patent documents (i.e., 15.81% of total patent documents).

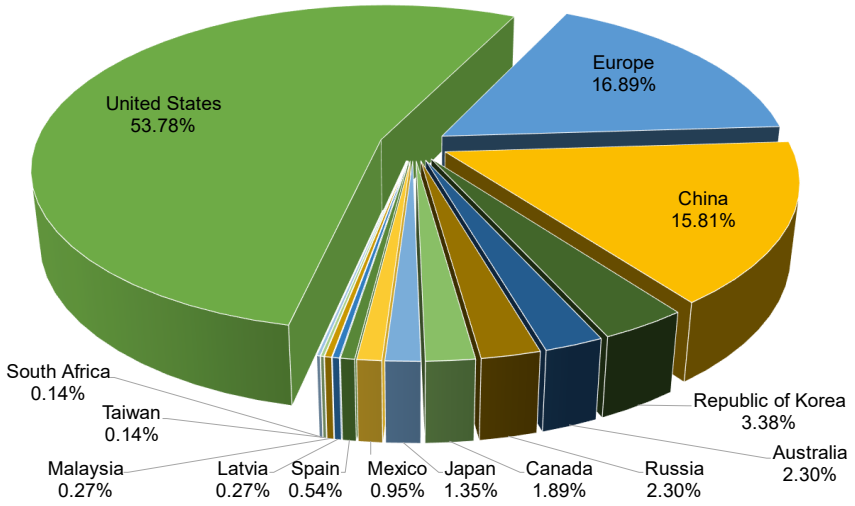

Figure 4. Jurisdictions of active patent documents related to the development of CaPCs for bone repair.

Relevant remarks coming from this jurisdiction's part should be highlighted hereinafter. They concern the absence of patent documents recognized and enforceable under the PCT international system. Furthermore, France is not presented above, although three leading organizations from this national patent jurisdiction (i.e., "French National Centre for Scientific Research", "Graftys SA", and "University of Nantes") are presented among applicants and owners. The majority of their patent documents are, in fact, recognized and enforceable in the United States and Europe (in member states of the European Patent Convention). The same remark also concerns the national patent jurisdictions of Germany and Switzerland. All patent documents of the companies "Innotere GmbH" and "Kyphon SARL" are, in fact, recognized and enforceable in the United States and Europe.

4. Conclusions

This study focused on patent documents for the development of CaPCs for bone repair that have an active legal status until 2022. The maximum number of patent documents recorded in 2016 was 69. On the other hand, 53.78% of the 740 active patent documents that have been found are from the United States. This justifies the fact that the United States shows great interest in developing bone substitutes. An overview of relevant patent documents related to the development of CaPCs for bone repair reveals that these common bioceramic material cements are used for a variety of purposes, including filling and sealing defects in bone, repairing damaged teeth, reinforcing bone tissue, and producing artificial joints as well as other medical devices. They are generally mixed with solutions to form a paste that can be molded and shaped into the desired form. They are then hardened by a chemical reaction with the solution, which results in the formation of a hard and stable material. According to findings in major patent documents, one of the main advantages of CaPCs is that they are injectable, self-hardening, biocompatible, and osteoconductive.

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References

1. Xu, H.H.K.; Wang, P.; Wang, L.; Bao, C.; Chen, Q.; Weir, M.D.; Chow, L.C.; Zhao, L.; Zhou, X.; Reynolds, M.A. Calcium phosphate cements for bone engineering and their biological properties. *Bone Res.* **2017**, *5*, 17056. https://doi.org/10.1038/boneres.2017.56.
2. Turnbull, G.; Clarke, J.; Picard, F.; Riches, P.; Jia, L.; Han, F.; Li, B.; Shu, W. 3D bioactive composite scaffolds for bone tissue engineering. *Bioact. Mater.* **2018**, *3*, 278–314. https://doi.org/10.1016/j.bioactmat.2017.10.001.
3. Song, Y.; Zhang, C.; Wang, P.; Wang, L.; Bao, C.; Weir, M.D.; Reynolds, M.A.; Ren, K.; Zhao, L.; Xu, H.H.K. Engineering bone regeneration with novel cell-laden hydrogel microfiber-injectable calcium phosphate scaffold. *Mater. Sci. Eng. C* **2017**, *75*, 895–905. https://doi.org/10.1016/j.msec.2017.02.158.
4. Verron, E.; Khairoun, I.; Guicheux, J.; Bouler, J.-M. Calcium phosphate biomaterials as bone drug delivery systems: A review. *Drug Discov. Today* **2010**, *15*, 547–552. https://doi.org/10.1016/j.drudis.2010.05.003.
5. Dorozhkin, S.V. Calcium Orthophosphate Cements and Concretes. *Materials* **2009**, *2*, 221–291. https://doi.org/10.3390/ma2010221.

6. Julien, M.; Khairoun, I.; LeGeros, R.Z.; Delplace, S.; Pilet, P.; Weiss, P.; Daculsi, G.; Bouler, J.M.; Guicheux, J. Physico-chemical–mechanical and in vitro biological properties of calcium phosphate cements with doped amorphous calcium phosphates. *Biomaterials* **2007**, *28*, 956–965. https://doi.org/10.1016/j.biomaterials.2006.10.018.
7. Google. Google Patents. Available online: https://patents.google.com (accessed on 5 January 2023).
8. Baxendale, L.; Kirk, E.E.J. Dental Fillers and Bone Cements Comprising Collagen. Granted Patent GB1068587A, UK, 1967.
9. Hachimi Alaoui, C.; Fatimi, A. A 20-year patent review and innovation trends on hydrogel-based coatings used for medical device biofabrication. *J. Biomater. Sci. Polym. Ed.* 2023, *in press*. https://doi.org/10.1080/09205063.2022.2161777.
10. Fatimi, A. A patent data analysis of the innovation trends in biological control agent formulations. Recent Advances in Food. *Nutr. Agric.* **2022**, *13*, 59–69. https://doi.org/10.2174/2772574X13666220831122154.
11. Fatimi, A. Exploring the patent landscape and innovation of hydrogel-based bioinks used for 3D bioprinting. *Recent Adv. Drug Deliv. Formul.* **2022**, *16*, 145–163. https://doi.org/10.2174/2667387816666220429095834.
12. Fatimi, A. Hydrogel-based bioinks for three-dimensional bioprinting: Patent analysis. *Mater. Proc.* **2021**, *7*, 3. https://doi.org/10.3390/IOCPS2021-11239.
13. Fatimi, A. Patentability of biopolymer-based hydrogels. *Chem. Proc.* **2021**, *8*, 39. https://doi.org/10.3390/ecsoc-25-11653.
14. Fatimi, A. Cellulose-based hydrogels: Patent analysis. *J. Res. Updat. Polym. Sci.* **2022**, *11*, 16–24. https://doi.org/10.6000/1929-5995.2022.11.03.
15. Fatimi, A. Chitosan-based hydrogels: Patent analysis. *Mater. Proc.* **2022**, *9*, 1. https://doi.org/10.3390/materproc2022009001.
16. Fatimi, A. Trends and recent patents on cellulose-based biosensors. *Eng. Proc.* **2022**, *16*, 12. https://doi.org/10.3390/IECB2022-12253.
17. Fatimi, A. Seaweed-based biofertilizers: A patent analysis. *Recent Pat. Biotechnol.* **2022**, *16*, 144–154. https://doi.org/10.2174/1872208316666220128105056.
18. Fatimi, A. Sodium tetradecyl sulfate molecule: Patent analysis based on chemical compounds search. *Eng. Proc.* **2022**, *19*, 4. https://doi.org/10.3390/ECP2022-12656.
19. European Patent Office. Espacenet Patent Search. Available online: https://worldwide.espacenet.com (accessed on 5 January 2023).
20. United States Patent and Trademark Office. USPTO Database (PatFT-AppFT). Available online: https://uspto.gov/patents/search (accessed on 5 January 2023).
21. European Patent Office. Espacenet Glossary. Available online: https://worldwide.espacenet.com/patent/help/espacenet-glossary (accessed on 5 January 2023).