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Pluronic F-127 hydrogel for stem cell research: a bibliometric analysis using Scopus database

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KEYWORDS

Pluronic F-127

Tissue engineering

Thermoresponsive hydrogel

Mesenchymal stem cells

Encapsulation

Regenerative medicine

ABSTRACT

Stem cell research holds immense promise in regenerative medicine. However, the successful utilization of stem cells relies on their inherent properties and the appropriate support matrix that provides an optimal environment for growth and differentiation. Optimizing their delivery and retention at the target site is crucial to enhance stem cell-based therapies' effectiveness. In recent years, hydrogels have emerged as a popular choice for culturing and delivering stem cells due to their unique properties, including biocompatibility, tunable physical and chemical characteristics, and mimicking the native extracellular matrix. Among the various hydrogels available, Pluronic F-127 (PF-127) has gained significant attention in stem cell research. This paper aims to study the publication trends of research that discuss the utilization of PF-127 hydrogel for stem cell research. The analysis is based on data extracted from the Scopus database using bibliometric methods. The results revealed the publication trends, collaboration patterns among authors and institutions, research areas, influential journals, funding agencies, and thematic connections in this field. By understanding the current state of research and identifying key areas of focus, this analysis provides valuable insights for researchers and practitioners interested in harnessing the potential of PF-127 hydrogel in regenerative medicine and tissue engineering.

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1 Introduction

Stem cell research holds immense potential in regenerative medicine (Sharun et al. 2020; Bist et al. 2021; Sharun et al. 2021; Peer et al. 2022; Sharun et al. 2022a; Sivanarayanan et al. 2023). However, the successful utilization of stem cells relies not only on their inherent properties but also on the appropriate support matrix that provides an optimal environment for their growth and differentiation (Bist et al. 2021; Peer et al. 2022; Sivanarayanan et al. 2023). In recent years, hydrogels have emerged as a popular choice for culturing and delivering stem cells due to their unique properties, including biocompatibility, tunable physical and chemical characteristics, and ability to mimic the native extracellular matrix (Tsou et al. 2016; Mantha et al. 2019). Among the various hydrogels available, PF-127 has gained significant attention in stem cell research (Sharun et al. 2023).

PF-127 is a thermosensitive and biocompatible hydrogel that exhibits a sol-gel transition at physiological temperatures, making it suitable for various biomedical applications (Sharun et al. 2023). Its unique thermoresponsive behaviour allows for easy gelation and subsequent encapsulation of stem cells, providing them with a supportive 3D microenvironment (Tsou et al. 2016; Mantha et al. 2019). Additionally, PF-127 hydrogel possesses excellent biodegradability and controllable release properties, making it an ideal candidate for controlled drug delivery and tissue engineering (Diniz et al. 2015). The use of PF-127 hydrogel in stem cell research offers numerous advantages. Its non-toxic nature and high-water content facilitate cell viability, proliferation, and differentiation. The hydrogel's porous structure facilitates efficient nutrient and oxygen exchange, promoting cell survival and functionality (Youn et al. 2021; García-Couce et al. 2022). Moreover, PF-127 can be easily modified to incorporate bioactive molecules, growth factors, and therapeutic agents, enhancing the bio functionality of the hydrogel and promoting specific cellular responses (Zhou et al. 2013; Kim et al. 2014).

It is necessary to explore the recent advancements and promising outcomes achieved using PF-127 hydrogel in regenerative medicine (Sharun et al. 2023). By understanding the capabilities and limitations of PF-127 hydrogel for stem cell research, we can unlock its full potential in harnessing the power of stem cells for therapeutic interventions. This knowledge will contribute to developing novel strategies for improving stem cell-based therapies and advancing regenerative medicine, bringing us closer to realizing effective clinical applications.

This paper aims to study the publication trends of research that discuss the utilization of PF-127 hydrogel for stem cell research. We will also address the challenges and future directions in the field, such as improving long-term cell viability, achieving controlled release kinetics, and enhancing tissue regeneration.

2 Materials and Methods

2.1 Data extraction

The data extraction was performed on June 21, 2023, using the Scopus database (Elsevier B.V) to identify the works of literature that use PF-127 in stem cell research. The search strategy aimed to collect the journal articles (research articles) data published to date while certain publication types such as reviews, editorials, conference papers, book chapters, letters, books, notes, short surveys, retracted papers, erratum, and reports are excluded (Sharun et al. 2022a; Sharun et al. 2022b). Articles published in any language were included in the analysis. The following search query was employed: TITLE-ABS-KEY [(poloxamer 407 OR "Pluronic F-127" OR pf-127 OR pluronic-f-127 OR "Pluronic™ F-127" OR "Plutonic F127" OR pf127 OR "Pluronic® F-127" OR "Pluronic® F127") AND ("stem cell" * OR "stromal cell" *) and (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SRCTYPE, "j")].

2.2 Analysis of variables

The extracted data file was further analyzed using R Studio and the bibliometrix package, a powerful open-source tool specifically designed for science mapping analysis within the R statistical programming language (Aria and Cuccurullo 2017). The extracted data were further analyzed, and interpretation was made based on the findings.

2.3 Visualization

The data was visualized using VOS viewer software (version 1.6.17) (van Eck and Waltman 2010). In addition, Biblioshiny, a web application framework that integrates with the R programming language, was also used for creating interactive and dynamic bibliographic data visualization tools (Aria and Cuccurullo 2017).

3 Results and Discussion

3.1 Overview of publication trends

The data presented encompasses the timespan from 2010 to 2020 and includes information from 17 documents. The annual growth rate for these documents is 0%, indicating a stable publication output over the specified period. The average age of the papers is 7.29 years, suggesting that the data primarily includes relatively recent research. On average, each document has been cited 33.86 times, indicating moderate impact and recognition within the scholarly community. Regarding document contents, the data includes 496 keywords identified as "Keywords Plus" and 63 author-provided keywords. The data involves 98 authors, with no single-authored documents among the 17 analyzed. The collaboration among authors is evident, with an average of 7.14 co-

authors per document, indicating a high level of cooperation in the field. Additionally, 28.57% of the co-authorships are international, reflecting a global perspective and collaboration within the research community. The document types included in the dataset are solely articles, indicating a focus on original research and scientific analysis.

3.2 Research areas

The subject areas in the Scopus database that have been published on PF-127 hydrogel in stem cell research vary in terms of the number of documents (Figure 1). Engineering appears to be the most prominent subject area, with 11 articles indicating a significant focus on the engineering aspects of using PF-127 hydrogel in stem cell research. The fields of Biochemistry, Genetics, Molecular Biology, Materials Science, and Medicine are equally represented with seven documents each, highlighting the interdisciplinary nature of this research topic. Additionally, Pharmacology, Toxicology, and Pharmaceutics have contributed three articles, indicating the interest in exploring the potential therapeutic applications of PF-127 hydrogel. Chemical Engineering has published two articles focusing on this hydrogel's engineering and manufacturing aspects. Lastly, Physics and Astronomy have contributed 1 document. This data reflects the multidisciplinary nature of PF-127 hydrogel research in stem cell studies involving various scientific disciplines and their collaborative efforts.

3.3 Analysis of keywords

The WordCloud illustrating the top 50 most frequent Keywords Plus is given in Figure 2a. Poloxamer (38), article (16), hydrogel (13), rats (13), cell survival (12), mesenchymal stromal cells (12), nonhuman (12), animal (11), animals (11), cell differentiation (11), chemistry (11), hydrogels (11), male (11), mesenchymal stem cell (11), and mesenchymal stroma cell (11) were some of the most frequently used Keywords Plus identified in this study. Similarly, Figure 2b presents the WordCloud of the top 50 authors' keywords used in their publications. Hydrogel (3), cell therapy (2), alginate/poloxamer systems (1), biocompatibility/soft tissue (1), bioprinting (1), biphilic (1), bmscs (1), bone (1), bone graft (1), and bone marrow mesenchymal stem cell (1) were some of the most frequently used authors keywords identified in this study.

3.4 Identification of top institutes and countries

Sun Yat-Sen University is the leading affiliation in productivity, with four publications dedicated to this subject. Université Paris Descartes follows closely behind with three publications, demonstrating its significant contributions to the scientific community's understanding of the intersection between PF-127 hydrogel and stem cell research. Several affiliations, including the Royal College of Surgeons in Ireland, Universidad de Santiago de Compostela, Saarland University Medical Center, Technical Institute of Physics and Chemistry, Universidade de Santiago de

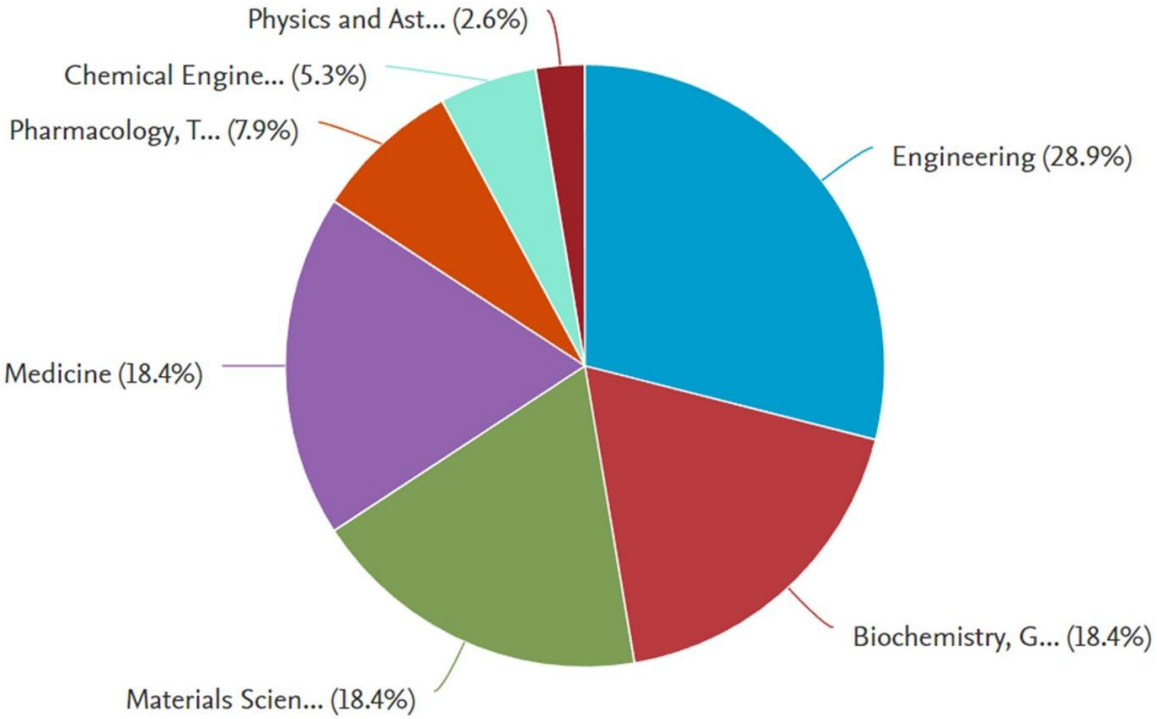

Figure 1 Pie chart illustrating the subject areas under which articles on Pluronic F-127 hydrogel for stem cell research are classified in the Scopus database.

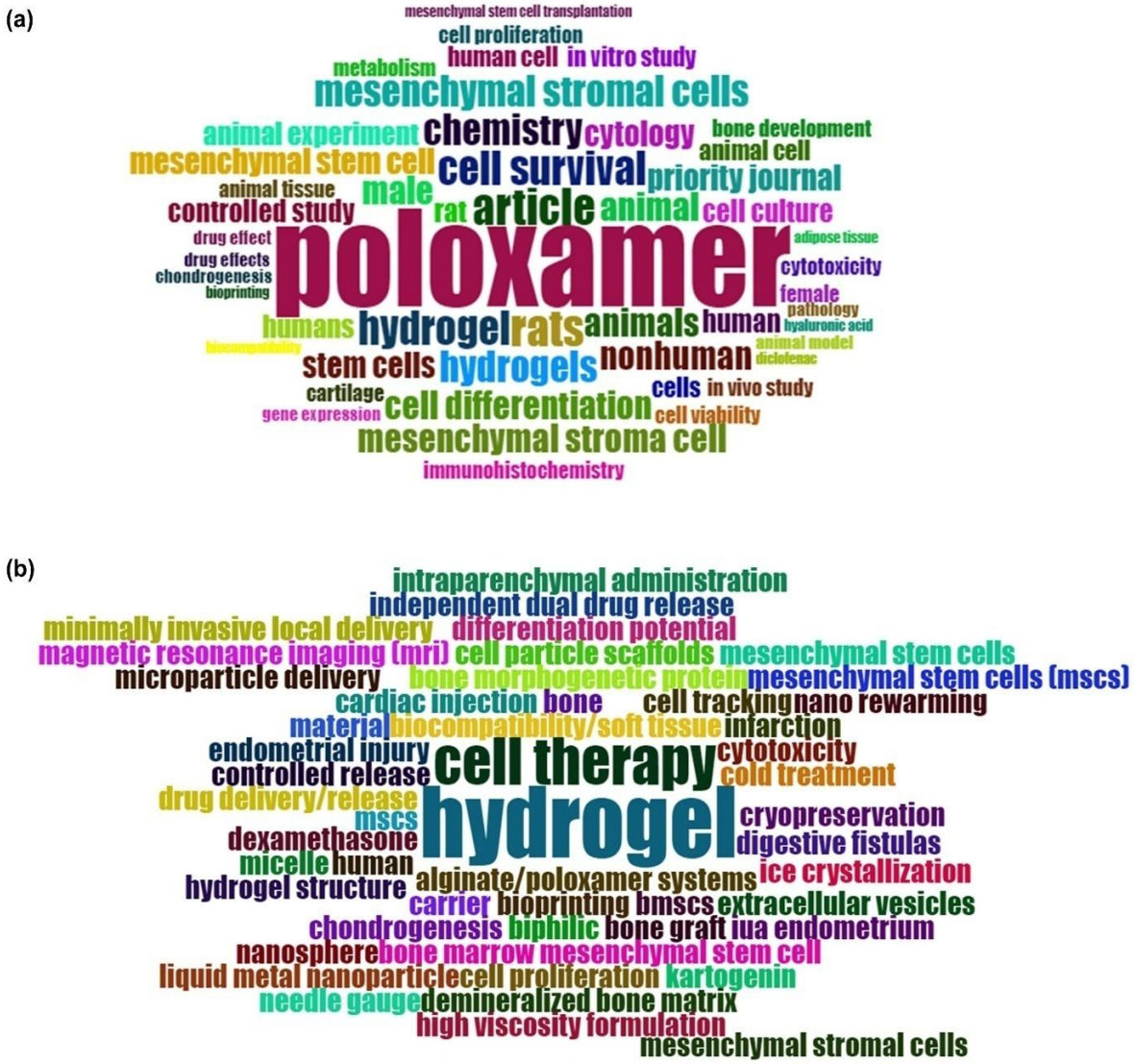

Figure 2 (a) Word Cloud illustrating the top 50 most frequent Keywords Plus (b) and 50 most frequent words by authors keywords.

Compostela, Trinity College Dublin, University of Iowa, and the University of Southern California, have all made notable contributions with two publications each. These affiliations represent a diverse range of research institutions from different countries, indicating the global interest in exploring the potential of PF-127 hydrogel in stem cell research. The collective efforts of these affiliations have enriched the scientific literature and furthered our understanding of the applications and implications of this hydrogel in the context of stem cells.

Among the countries, China is the most prolific, with 12 publications dedicated to this topic (Figure 3). China's strong presence in the field of PF-127 hydrogel research demonstrates its commitment to advancing stem cell studies and exploring the potential applications of this hydrogel in regenerative medicine. France and South Korea are closely behind China, contributing significantly with nine publications each. These countries have shown a substantial interest in the intersection of stem cell research and PF-127 hydrogel, contributing valuable insights to the scientific community. The United States, a leading hub of scientific research, has also made notable contributions with seven publications. Ireland and Spain demonstrate a commendable presence in the field, with five publications each indicating their active involvement in stem cell research involving PF-127 hydrogel. Other countries such as Belgium, Germany, the United Kingdom, Brazil, and Mexico have also made contributions with smaller numbers of publications. The collective efforts of these countries reflect the global interest in exploring the potential of PF-127 hydrogel in stem cell research and highlight the collaborative nature of scientific exploration in this field.

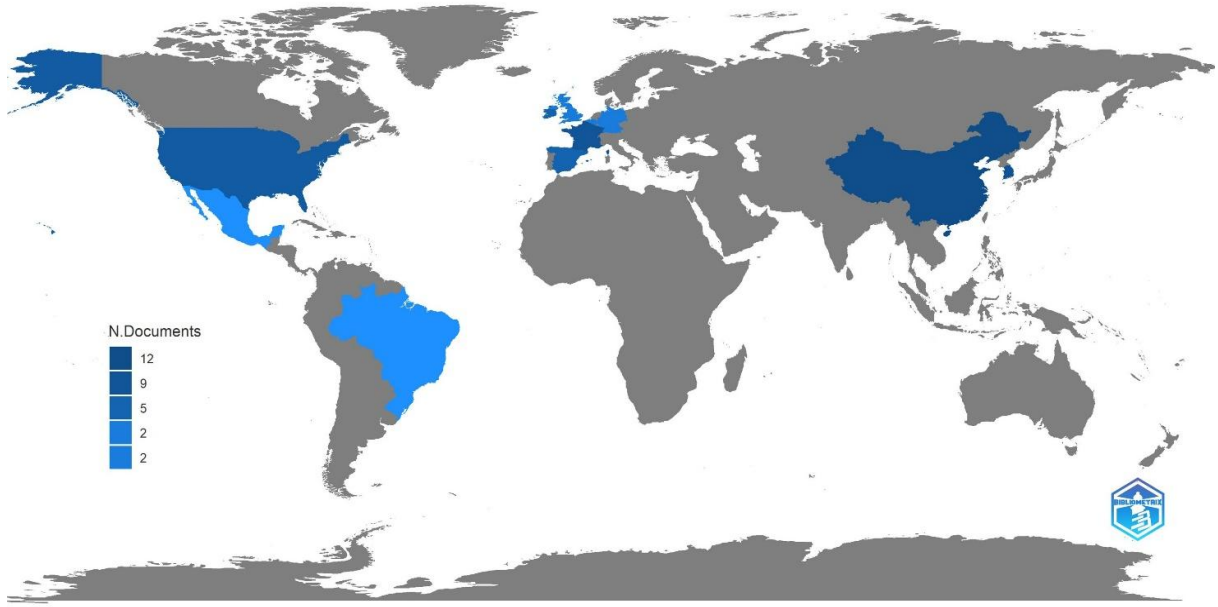

Figure 3 Map representing Country Scientific Production on Pluronic F-127 hydrogel for stem cell research across the globe.

3.5 Most cited countries

The data highlights the most cited countries and their corresponding total citations (TC) and average article citations. The United States (USA) leads the list with a total citation count of 172, indicating a high impact and recognition of research originating from the country. The average article citation for the USA is 57.30, suggesting that publications from the US receive a significant number of citations on average. Korea follows closely behind with a total citation count of 129 and an average article citation of 32.20, indicating a strong impact and influence of Korean research within the scholarly community. With a total citation count of 76 and an average article citation of 38.00, China demonstrates significant recognition and impact in the field. France has a total citation count of 49, with an average article citation of 49.00, reflecting a high average citation rate for publications originating from the country. Germany, the United Kingdom, Spain, and Ireland have lower total citation counts and average article citations, indicating a relatively lesser impact in citation numbers. Nevertheless, it is important to note that these values can vary depending on the specific research field and the time frame considered.

3.6 Identification of influential journals

The data provided showcases the most relevant journals publishing articles on PF-127 hydrogel in stem cell research and the corresponding number of published articles. Acta Biomaterialia, International Journal of Pharmaceutics, Chinese Journal of Tissue Engineering Research, and Journal of Biomedical Materials Research - Part B Applied Biomaterials emerge as the leading journals in this field, each publishing two articles on PF-127 hydrogel and its applications in stem cell research. These journals have established themselves as prominent platforms for disseminating research. Additionally, ACS Nano, Journal of Controlled Release, Cell Transplantation, CIOS Clinics in Orthopedic Surgery, Journal of Biomedical Materials Research - Part A, Stem Cell Research and Therapy, Journal of Materials Science: Materials in Medicine, West China Journal of Stomatology, and Tissue Engineering - Part C: Methods are also recognized as contributors to this field, each publishing one article on PF-127 hydrogel and its role in stem cell research. These journals serve as important outlets for researchers to share their findings and advancements, highlighting the diverse range of journals contributing to the body of knowledge in this area. Collectively, these publications contribute to the growing understanding of the applications and potential of PF-127 hydrogel in stem cell research.

Bradford's law is a bibliometric concept that suggests that scientific literature can be divided into zones based on the frequency of publication in certain journals. Zone 1, according to Bradford's law, represents the core journals that publish a significant portion of the articles in a particular field. In the given data, three journals, namely Acta Biomaterialia, Chinese Journal of Tissue Engineering Research, and International Journal of Pharmaceutics belong to zone 1 of Bradford's law. Overall, including Acta Biomaterialia, Chinese Journal of Tissue Engineering Research, and International Journal of Pharmaceutics in zone 1 of Bradford's law indicates their significance as core journals in their respective fields. These journals serve as important platforms for researchers to publish their findings related to PF-127 hydrogel and its applications, contributing to

advancing knowledge in biomaterials, tissue engineering, and pharmaceutical sciences.

3.7 Funding agencies

The data provided highlights the sponsorship of articles by various funding agencies. Among the mentioned agencies, most articles were sponsored by the National Natural Science Foundation of China, with three publications. The European Regional Development Fund and the National Research Foundation of Korea follow closely, each sponsoring two articles.

Several other funding agencies have sponsored one article each, including the Beijing Municipal Science and Technology Commission, Engineering and Physical Sciences Research Council, Fundación Pedro Barrié de la Maza, Institut National de la Santé et de la Recherche Médicale, Korea Institute of Science and Technology, Centre National de la Recherche Scientifique, Ministerio de Economía y Competitividad, National Key Research and Development Program of China, Ministerio de Educación, Cultura y Deporte, Ministry of Education, Science and Technology, Ministry of Health and Welfare, Ministry of Knowledge Economy, National Institute of Dental and Craniofacial Research, Instituto de Salud Carlos III, National Institutes of Health, Natural Science Foundation of Guangdong Province, Sun Yat-sen University, Université Paris Descartes, and Xunta de Galicia. This diverse range of funding agencies reflects the international nature of the research and the importance of financial support from various organizations in advancing scientific knowledge and innovation.

3.8 Thematic map

In bibliometric analysis, a thematic map containing development degree and relevance degree provides valuable insights into the distribution and characteristics of research topics within a specific field (Figure 4). The development degree indicates the research activity and output level in a particular research area or region. It reflects the quantity and growth of publications related to specific themes. A higher development degree suggests greater research output in that area. On the other hand, the relevance degree in a thematic map indicates the degree of interconnectedness or similarity between different research topics or areas. It helps identify clusters or groups of closely related research themes. A higher relevance degree indicates stronger thematic connections or shared characteristics among the topics.

The thematic map on PF-127 hydrogel in stem cell research is inserted in Figure 4. Researchers can gain a comprehensive understanding of the research landscape by considering both the development degree and relevance degree in a thematic map. They can identify hotspots of research activity, detect emerging trends, and uncover areas of high significance and potential for collaboration. This information can guide decision-making, resource allocation, and strategic planning in bibliometric analysis and research evaluation.

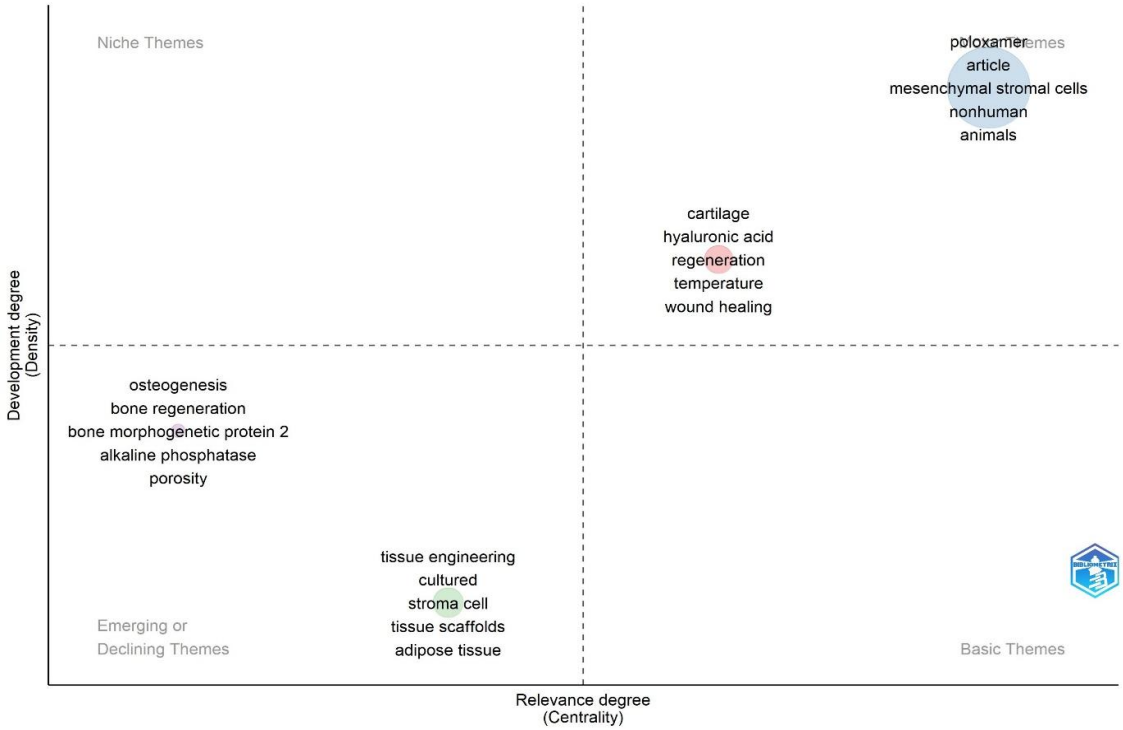

Figure 4 The thematic map on Pluronic F-127 hydrogel in stem cell research.

3.9 Network visualization map

The map indicates the connections between authors. Specifically, authors with at least one document were selected for inclusion in the map. Although 111 authors met this threshold, some were not connected; therefore, the most extensive set of connected items constituting 16 authors were illustrated (Figure 5a). Similarly, 4 countries of the 11 countries that met the threshold were illustrated since they formed the largest network (Fig. 5b).

3.10 Research on PF-127 hydrogel for stem cell research

The salient findings of the 17 papers published on the use of PF-127 hydrogel for stem cell research are presented in Table 1. Diniz et al. (2015) investigated the potential of dental pulp stem cells (DPSCs) to undergo differentiation into bone and fat tissues when encapsulated in a PF127 hydrogel scaffold. The viability, proliferation, and differentiation of DPSCs were assessed, and the results revealed that PF-127 hydrogel is a promising and safe scaffold for encapsulating DPSCs. These findings suggest that PF-127 hydrogel can be considered a potential candidate for delivering DPSCs in tissue engineering applications. Similarly, Kang et al. (2016) study describes the synthesis of F127/COS/KGNDCF nanospheres, which are composed of outer cross-linked PEO chains of dicarboxylate PF127 and chitosan oligosaccharide (COS) conjugated with kartogenin (KGN) and inner PPO chains of diclofenac (DCF) loaded PF127. Furthermore, the F127/COS/KGNDCF nanospheres were found to promote chondrogenic differentiation of human BMSCs, with enhanced effects observed upon cold shock treatment.

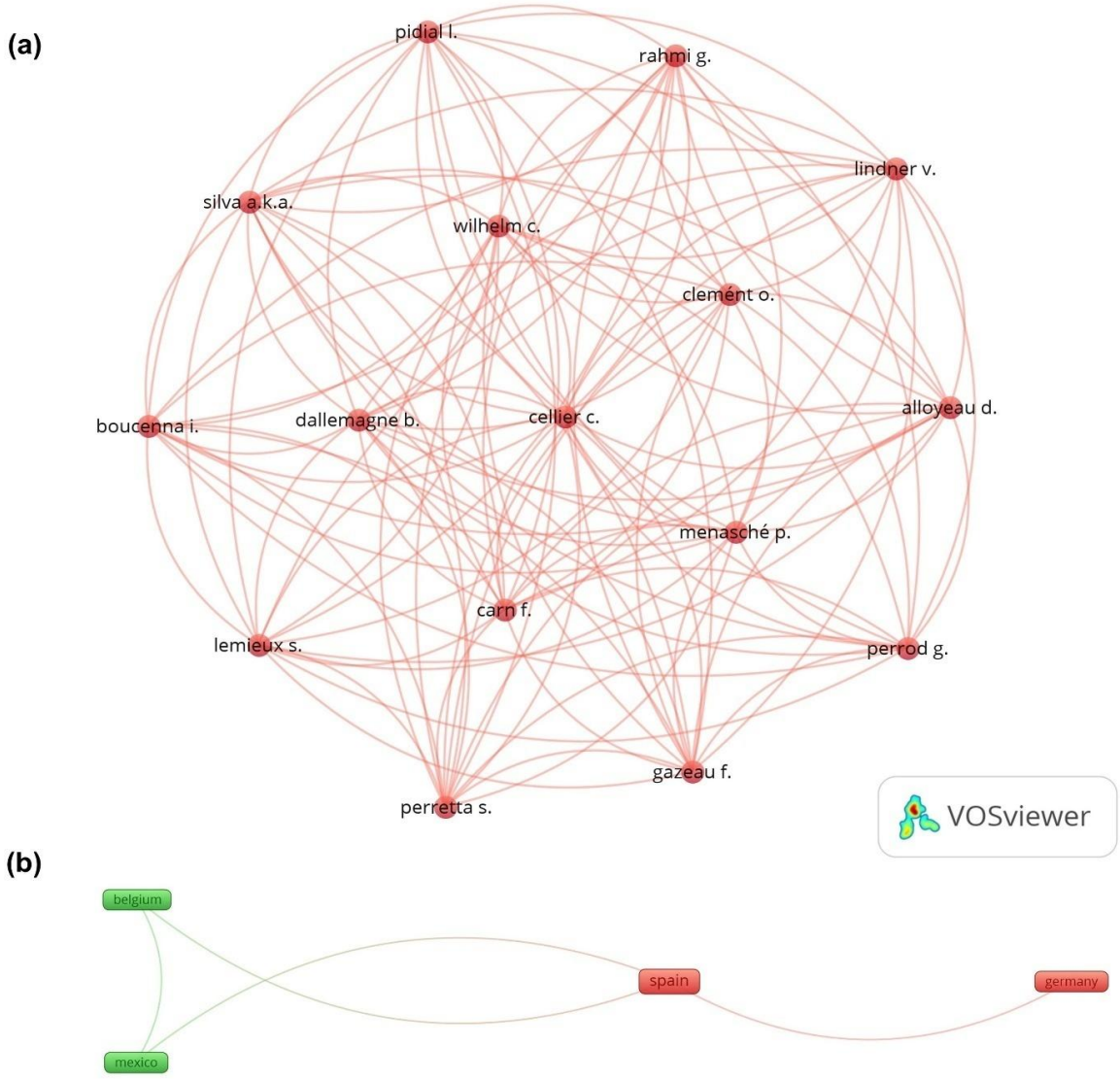

Figure 5 (a) The network visualization map indicating the connecting link between authors and (b) countries.

Table 1 Characteristics of the research articles that use Pluronic F-127 hydrogel in stem cell research.

Paper	DOI	Total Citations	TC per Year	Normalized TC
Diniz IM et al. Pluronic F-127 hydrogel as a promising scaffold for encapsulation of dental-derived mesenchymal stem cells. J Mater Sci Mater Med. 2015 Mar;26(3):153. PMID: 25773231; PMCID: PMC4477746.	10.1007/s10856-015-5493-4	124	13.78	1.65
Kang ML et al. Thermoresponsive nanospheres with independent dual drug release profiles for the treatment of osteoarthritis. Acta Biomater. 2016 Jul 15;39:65-78. PMID: 27155347.	10.1016/j.actbio.2016.05.005	79	9.88	1.84
Silva AKA, et al. Thermoresponsive Gel Embedded with Adipose Stem-Cell-Derived Extracellular Vesicles Promotes Esophageal Fistula Healing in a Thermo-Actuated Delivery Strategy. ACS Nano. 2018 Oct 23;12(10):9800-9814. PMID: 30231208.	10.1021/acsnano.8b00117	49	8.17	1.69
Yang H, et al. Vitamin C plus hydrogel facilitates bone marrow stromal cell-mediated endometrium regeneration in rats. Stem Cell Res Ther. 2017 Nov 21;8(1):267. PMID: 29157289; PMCID: PMC5697119.	10.1186/s13287-017-0718-8	46	6.57	1.89
Hou Y, et al. Soft liquid metal nanoparticles achieve reduced crystal nucleation and ultrarapid rewarming for human bone marrow stromal cell and blood vessel cryopreservation. Acta Biomater. 2020 Jan 15;102:403-415. PMID: 31734413.	10.1016/j.actbio.2019.11.023	30	7.50	1.00
Seol D, et al. Biocompatibility and preclinical feasibility tests of a temperature-sensitive hydrogel for the purpose of surgical wound pain control and cartilage repair. J Biomed Mater Res B ApplBiomater. 2013 Nov;101(8):1508-15. PMID: 24591226.	10.1002/jbm.b.32981	27	2.45	1.86
Díaz-Rodríguez P, et al. Effective genetic modification and differentiation of hMSCs upon controlled release of rAAV vectors using alginate/poloxamer composite systems. Int J Pharm. 2015 Dec 30;496(2):614-26. PMID: 26556623.	10.1016/j.ijpharm.2015.11.008	26	2.89	0.35
Bae SE, et al. Effect of temporally controlled release of dexamethasone on in vivo chondrogenic differentiation of mesenchymal stromal cells. J Control Release. 2010 Apr 2;143(1):23-30. PMID: 20056124.	10.1016/j.jconrel.2009.12.024	25	1.79	1.00
Gettler BC, et al. Formation of Adipose Stromal Vascular Fraction Cell-Laden Spheroids Using a Three-Dimensional Bioprinter and Superhydrophobic Surfaces. Tissue Eng Part C Methods. 2017 Sep;23(9):516-524. PMID: 28665236.	10.1089/ten.tec.2017.0056	21	3.00	0.86
Kim TH, et al. Bone morphogenetic proteins-immobilized polydioxanone porous particles as an artificial bone graft. J Biomed Mater Res A. 2014 May;102(5):1264-74. PMID: 23703875.	10.1002/jbm.a.34803	14	1.40	1.12
Lee JH, et al. The effect of poloxamer 407-based hydrogel on the osteoinductivity of demineralized bone matrix. Clin Orthop Surg. 2014 Dec;6(4):455-61. PMID: 25436071; PMCID: PMC4233226.	10.4055/cios.2014.6.4.455	11	1.10	0.88
Qutachi O, et al. Improved delivery of PLGA microparticles and microparticle-cell scaffolds in clinical needle gauges using modified viscosity formulations. Int J Pharm. 2018 Jul 30;546(1-2):272-278. PMID: 29753905.	10.1016/j.ijpharm.2018.05.025	9	1.50	0.31
Argibay B, et al. Easy and Efficient Cell Tagging with Block Copolymer-Based Contrast Agents for Sensitive MRI Detection in Vivo. Cell Transplant. 2016 Oct;25(10):1787-1800. PMID: 27093950.	10.3727/096368916X691303	7	0.88	0.16
Curley CJ, et al. An in vitro investigation to assess procedure parameters for injecting therapeutic hydrogels into the myocardium. J Biomed Mater Res B ApplBiomater. 2017 Nov;105(8):2618-2629. doi: 10.1002/jbm.b.33802. Epub 2016 Oct 20. PMID: 27764526.	10.1002/jbm.b.33802	6	0.86	0.25
Zhou N, et al. [Experimental study on transplantation of bone morphogenetic protein-2 gene transfected bone mesenchymal stem cells compounded with Pluronic F-127 for promoting bone regeneration in rabbit mandibular distraction]. Hua Xi Kou Qiang Yi Xue Za Zhi. 2013 Jun;31(3):247-52. Chinese. PMID: 23841294.	NA	2	0.18	0.14
Dong C, Xin J. Effect of kartogenin/pluronic f127 micelles on osteogenic differentiation of bone marrow mesenchymal stem cells. Chin J Tissue Eng Res. 2021;25(34):5473-7.	10.12307/2021.241	0	0.00	0.00
Yan L, et al. Hydrogel combined with bone marrow mesenchymal stem cells in the treatment of damaged endometrium in rats. Chin J Tissue Eng Res. 2022;26(31):4940-5.	10.12307/2022.776	0	0.00	0.00

Silva et al. (2018) explore the potential therapeutic application of allogenic extracellular vesicles (EVs) derived from ASCs for fistula healing. A local minimally invasive delivery strategy was employed, where the EVs were administered in a porcine fistula model using PF-127 gel. The gel was injected locally at 4 °C and gelled at body temperature, effectively retaining the EVs in the entire fistula tract. The results demonstrate the successful induction of a therapeutic effect in the swine fistula model through ASC-EV delivery within the PF-127 gel, highlighting its potential as a local minimally invasive approach. Yang et al. (2017) investigated the feasibility of using a combination of hydrogel PF-127, Vitamin C (Vc), and a mixture of BMSCs to enhance endometrial regeneration in a rat model of intrauterine adhesion (IUA) caused by mechanical damage. In vitro experiments showed that Vc improved the survival and health of PF-127-encapsulated BMSCs, counteracting the cytotoxic effects of PF-127 and promoting cell survival and growth. Therefore, a cell therapy approach combining a biomaterial scaffold, BMSCs, and Vc as modulatory factors were found to promote damaged IUA endometrium restoration.

Hou et al. (2020) reported that the PF-127-liquid metal nanoparticles (PLM NPs) demonstrated excellent characteristics, including uniform particle size, high photothermal conversion efficiency (52%), stable photothermal performance, and low cytotoxicity. The viability of human BMSCs after cryopreservation using PLM NPs reached 78±3%, three times higher than conventional warming methods (25±6%). Seol et al. (2013) investigated the safety and efficacy of a novel PF127 and hyaluronic acid-based hydrogel (HG) for therapeutic delivery. Standard in vitro cytotoxicity and drug release tests were performed, and *in-vivo* biocompatibility tests were conducted in a rat model. Additionally, the effectiveness of the HG as a stem cell carrier in a rat cartilage defect model was determined. The HG exhibited comparable levels of viability and biocompatibility to those reported for PF127 or hyaluronic acid individually. Stem cells encapsulated within the hydrogel remained in their original position and promoted cartilage regeneration in experimental defects.

Díaz-Rodríguez et al. (2015) developed hydrogel structures using alginate (AlgPH155) and poloxamer PF127 for encapsulating and releasing recombinant adeno-associated viral (rAAV) vectors. The different hydrogel systems exhibited high transduction efficiencies and gene expression levels in human mesenchymal stem cells, comparable to direct vector application. AlgPH155+PF127 demonstrated the most favourable results. Furthermore, no negative impact was observed on cell viability or chondrogenic differentiation potential. These findings suggest the potential of AlgPH155+PF127 hydrogel for the effective and safe delivery of rAAV vectors in stem cell applications. Bae et al. (2010) examined how the release of dexamethasone (Dex) from two groups of poly(lactic-co-glycolic acid) (PLGA) microspheres influenced the chondrogenic differentiation of MSCs in an in vivo setting. Each group of microspheres was incorporated into a composite hydrogel comprising hyaluronic acid (HA) and PF127, along with rabbit MSCs. The release profiles of Dex from each group of microspheres exhibited significant differences over time. The composite hydrogel underwent a sol-gel transition, forming a gel at body temperature. The hydrogel-containing nanoparticle microspheres (NPMS) demonstrated better in vitro cell viability than those with plain microspheres (PMS).

Gettler et al. (2017) utilized three-dimensional bioprinting technology, and this study successfully generated SVF cell-laden spheroids embedded in a collagen I biomatrix. The findings demonstrate that a biphilic surface can create a uniform and viable SVF-laden spheroids. By incorporating automation through a 3D bioprinter, the process becomes high throughput and suitable for point-of-care clinical applications. Additionally, using a water-soluble hydrophilic spot and the phase transition properties of PF-127 enable minimally disruptive spheroid removal, facilitating manipulation for various applications. These collagen-based SVF spheroids offer a potential strategy to enhance the therapeutic efficacy of cellular infusions in regenerative medicine by improving cellular localization and retention.

According to Kim et al. (2014) BMPs were immobilized onto polydioxanone (PDO)/PF127 porous particles to create a bone graft. Heparin and BMPs (BMP-2 and BMP-7, single or dual) were sequentially bound to the porous particles. The BMPs were successfully immobilized onto the particle surfaces via heparin binding and exhibited sustained release for up to 21 days, regardless of the BMP type. The BMP-immobilized particles effectively promoted in vitro osteogenesis of BMSCs. These BMP-immobilized PDO/PF-127 porous particles, whether containing BMP-2 alone or a combination of BMP-2 and BMP-7, hold promise as a bone graft option for clinical applications involving delayed or insufficient bone healing.

Further, Lee et al. (2014) suggested that demineralized bone matrix (DBM) possesses osteoinductivity that relies on an appropriate carrier for clinical use. This study evaluated the impact of using a poloxamer 407-based hydrogel as a carrier for DBM compared to sterile water. The findings indicate that the poloxamer 407-based hydrogel demonstrates potential as a DBM carrier, as it promotes ectopic bone formation. However, it negatively affects the osteoblastic differentiation in rat abdominal ectopic bone and MSCs.

Qutachi et al. (2018) investigated the impact of needle diameter on the delivery yield, and a modified viscosity formulation was developed to enhance microparticle delivery through clinically relevant needle diameters. A biocompatible formulation consisting of 0.25% PF-127 and 0.25% carboxymethyl cellulose was identified as optimal, leading to a 520% increase in delivery payload across needle gauges 21-30G. This optimized formulation was utilized to

improve the delivery yield of PLGA microparticles and PLGA-cell scaffolds that support viable MSCs. Notably, this study presents the first in vitro delivery of the PLGA-cell scaffold system.

Argibay et al. (2016) suggested that superparamagnetic iron oxide nanoparticles (MNPs) are widely used with MRI to track stem cells. However, commercial MNPs often require transfection agents and lengthy incubation periods for adequate cell labelling and subsequent in vivo cell detection. This study synthesized MNPs coated with PF-127 and tetronic 908 and was evaluated as contrast agents for MRI-based cell detection for MSCs and a mice-derived multipotent neural progenitor cell line (C17.2). These MNPs offer several advantages, including easy preparation, efficient cell labelling, and high sensitivity for in vivo cell detection. Curley et al. (2017) focus on optimizing parameters to effectively retain cell-loaded hydrogels after intramyocardial injection while maintaining cell viability. The research investigates the impact of mechanical factors on hydrogel retention and compares different needle designs. Results indicate that smaller-diameter needles have greater hydrogel retention. When human mesenchymal stem cells (hMSCs) embedded in fibrin hydrogel were injected using helical and 26G bevel needles, no significant difference in cell viability was observed at 48 hours. However, the helical group exhibited lower metabolic activity and decreased cell viability compared to the 26G bevel group over time. These findings emphasize the importance of considering biological and mechanical factors in localized stem cell delivery for myocardial regeneration. Zhou et al. (2013) evaluated the effectiveness of transplanting BMSCs transfected with the BMP-2 gene, combined with PF-127, for promoting bone regeneration in the mandibular distraction osteogenesis (DO) rabbit model. The findings indicate that the transplantation of BMP-2 gene transfected BMSCs combined with PF-127 effectively enhances bone regeneration in rabbit mandibular DO.

Chen and Jiang (2021) investigate the effect of Kartogenin/PF-127 micelles on the directional osteogenic differentiation of BMSCs. Kartogenin is known for its ability to activate the Smad4/Smad5 pathway and promote bone differentiation. However, its drug effect is limited. The study found that the Kartogenin/PF-127 micelles enhanced the osteogenic differentiation of BMSCs. Similarly, Yan et al. (2022) investigated the effect of combining hydrogel with BMSCs on endometrial reproduction in rats. The study results indicate that combining PF-127 hydrogel with BMSCs is feasible for treating endometrial injury. This finding provides new insights and potential strategies for endometrial repair.

Conclusion and Future Prospects

In conclusion, PF-127 hydrogel has shown great potential in various biomedical applications, particularly in regenerative medicine. Several studies have investigated its effectiveness as a scaffold material for encapsulating different types of stem cells, including DPSCs, BMSCs, and ASCs. The findings from these studies consistently indicate that PF-127 hydrogel provides a favourable environment for cell viability, proliferation, and differentiation. It has been demonstrated to support the differentiation of DPSCs into bone and fat tissues, BMSCs into chondrogenic and osteogenic lineages, and MSCs into various lineages such as osteoblasts and adipocytes.

Moreover, the hydrogel has been successfully utilized as a carrier for delivering therapeutic factors and gene vectors, enhancing their effectiveness in promoting tissue regeneration and healing. The thermoresponsive nature of PF-127 hydrogel, which undergoes sol-gel transition upon reaching body temperature, enables minimally invasive and localized delivery of cells and therapeutic agents. This property has been exploited in studies involving the local administration of hydrogel-encapsulated stem cells or extracellular vesicles, demonstrating its potential to improve therapeutic outcomes in tissue repair and regeneration models. Furthermore, PF-127 hydrogel has been combined with other biomaterials, such as alginate, hyaluronic acid, and PLGA, to enhance its properties and functionality. These composite hydrogels have shown improved cell viability, sustained release of therapeutic agents, and enhanced osteogenic or chondrogenic differentiation.

In addition to its applications in tissue engineering, PF-127 hydrogel has been investigated for its use in cell tracking and imaging studies. This advancement can significantly contribute to stem cell therapy by allowing non-invasive cell fate and distribution monitoring. Stem cells have garnered significant attention in regenerative medicine due to their remarkable potential to differentiate into different cell types and promote tissue regeneration. However, efficient and controlled delivery of stem cells to the target site is crucial for successful clinical translation. PF-127 hydrogel provides an ideal platform for stem cell encapsulation, offering numerous advantages that make it a favourable choice for researchers and clinicians.

One of the key features of PF-127 hydrogel is its thermoreversible property. This hydrogel transitions from a liquid state at low temperatures to a gel state at body temperature. This unique characteristic allows for easy handling and minimally invasive delivery. The liquid form facilitates cell encapsulation and homogeneous distribution, while the gel form provides a three-dimensional (3D) scaffold that supports cell proliferation and differentiation. The ability to encapsulate stem cells within the hydrogel matrix ensures their spatial confinement and protection from harsh external environments during transplantation.

Furthermore, PF-127 hydrogel exhibits excellent biocompatibility and biodegradability. It has been extensively studied and proven to be non-toxic to cells and tissues, minimizing the risk of adverse

reactions or inflammation. The hydrogel gradually degrades over time, allowing for the release of encapsulated stem cells and their secreted factors, which play a crucial role in tissue regeneration. This controlled release mechanism ensures sustained and localized delivery of stem cells, maximizing their therapeutic potential. The tunable mechanical properties of PF-127 hydrogel make it highly versatile for different tissue engineering applications. By adjusting the concentration of the hydrogel, the stiffness and elasticity can be modulated to match target tissue requirements. The ability of PF-127 hydrogel to mimic the native tissue properties enhances cell adhesion, migration, and integration into the host tissue, facilitating successful tissue regeneration. Moreover, PF-127 hydrogel can be easily functionalized and modified to incorporate bioactive molecules, growth factors, or extracellular matrix components. These modifications can further enhance the stem cell response and guide specific cellular behaviours. The hydrogel can release growth factors in a controlled manner, promoting stem cell differentiation towards desired lineages and facilitating tissue-specific regeneration. Additionally, incorporating bioactive molecules or ECM components can provide signalling cues that mimic the natural tissue microenvironment and improve the overall efficacy of stem cell therapy.

Overall, the studies reviewed demonstrate the promising potential of PF-127 hydrogel as a scaffold material in various stem cell-based applications. Its biocompatibility, thermoresponsive behaviour, and ability to support cell viability, proliferation, and differentiation make it an attractive choice for regenerative medicine applications and drug delivery. However, further research and optimization are still required to exploit its capabilities fully and address potential limitations in different clinical scenarios. Further research and development efforts are needed to optimize the formulation, design, and application of PF-127 hydrogel-based systems to harness the full therapeutic potential of stem cells in regenerative medicine. Overall, PF-127 hydrogel represents a valuable tool in stem cell research, offering a supportive and customizable microenvironment for stem cell growth, differentiation, and delivery. Its versatile properties and compatibility with various cell types make it a promising candidate for future biomedical applications.

Ethical approval

Not applicable.

Data statement

The authors confirm that the data supporting the findings of this study are available within the article.

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Declaration of Interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

Authors' contribution

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication

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