

# Bibliometric analysis of articles on nanoemulsion and/or in-situ gel for ocular drug delivery system published during the 2011–2021 period

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## Abstract

The bibliometric data were extracted from the Scopus database to investigate the conceptual framework of ocular nanoemulsion and/or in-situ gel drug delivery system using “ocular” AND “nanoemulsion” OR “in-situ gel” keywords. The data were evaluated with RStudio and VOSviewer program.

The results reveal that the publication trends tend to increase continually. India is the most impactful country, and the most constructive institution is Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University. International Journal of Pharmaceutics is the top influential source. Ali A is the most prolific author. The title of the most impactful article was In-situ gelling systems based on Pluronic F127/Pluronic F68 formulations for ocular drug delivery”. “Controlled release” is the most popular keyword.

These results provide insights for stimulating research collaborations and revealing open issues of controlled-release ocular preparation to overcome an ocular barrier and enhance patient compliance.

## Keywords

controlled release, drug delivery, RStudio, Scopus, VOSviewer

## Introduction

Ocular drugs can be used to treat various eye diseases such as cataracts, dry eye syndrome, inflammation, or glaucoma, where it is crucial for these drugs to penetrate the corneal barrier in order to reach the anterior segment of the eye (He et al. 2013). The corneal barrier comprises five distinct layers, epithelium, Bowman’s membrane, stroma, Descemet’s

membrane, and the endothelium; the increased hydrophobicity of the epithelium, combined with the presence of tight junction proteins between epithelial cells significantly limits the ability of hydrophilic drugs to penetrate the cornea. Furthermore, the hydrophilic environment of the stroma limits transportation of lipophilic drugs (Dinte et al. 2020). Additionally, issues such as tear formation, rapid nasolacrimal drainage, and corneal permeability prevent

ocular drugs from penetrating the corneal barrier. Consequently, only 1–3% of the ocular drug is able to penetrate the cornea and reach intraocular tissues (He et al. 2013).

Ocular nanoemulsion drug delivery systems are still under development to overcome the issue of absorption. Small droplets of nanoemulsions with particle sizes less than 100 nm can improve drug bioavailability by increasing absorption through the cornea and permeation through the aqueous humour. Thus, the drug's therapeutic window can be achieved with smaller doses, reducing systemic and ocular side effects. Additionally, this delivery system can also improve drug delivery to the target and provide sustained release drug profile to decrease the frequency of drug use. Furthermore, nanoemulsion protect active substance from degradation and oxidation (Huang et al. 2010; Patel et al. 2016; Yi et al. 2016; Singh et al. 2020).

However, the viscosity of nanoemulsions is similar to that of the conventional ophthalmic preparations, which implies that it can quickly be washed off when applied, decreasing the precorneal residence time (He et al. 2013). Extending the residence time in the eye area is possible with mucoadhesive preparations. An in-situ gel is an alternative ocular dosage form with mucoadhesive properties. In addition to minimizing the clearance of ocular drugs, an in-situ gel drug delivery system can prolong drug release. Various studies have shown that in-situ gels can be applied to the eye and can change from solution to gel form on the cul-de-sac of the eye owing to changes in pH, temperature, or ions present in the eye's environment (Dubald et al. 2018; Soliman et al. 2019; Wu et al. 2019).

Although nanoemulsions and in-situ gel ocular drug delivery systems are promising for the treatment of various eye diseases, only a few such drugs have been used in clinical trials. Unhealthy eye conditions can also increase variation in the ocular barrier, which affects the pharmacokinetic profile of the drug. However, these effects have not been reviewed by many studies. In addition, a majority of ocular nanoemulsions and in-situ gels have been formulated as a single active ingredient. In the future, the formulation of multi-target active ingredients will require a more appropriate strategy to treat various ocular diseases (Wu et al. 2019). A collaborative alliance between formulation scientists and clinicians could mean that they can further explore nanoemulsion and/or in-situ gel drug delivery systems (Singh et al. 2020).

However, several in-depth studies and exploration are required to develop the perfect ocular delivery system (Singh et al. 2020). Bibliometric analysis is a method for cumulatively describing and mapping scientific knowledge using unstructured data from numerous research. Bibliometric studies are beneficial for obtaining a comprehensive picture, identifying knowledge gaps, acquiring novel ideas, and determining the position of researchers' contributions to their research fields (Donthu et al. 2021). This analysis can also evaluate research results, authors, institutions, and published journals, including disseminating knowledge in specific topic areas (Arifaha et al. 2021).

From 2011 to 2021, there has been no comprehensive bibliometric analysis of the development of ocular

nanoemulsions and/or in-situ gel preparations. This bibliometric analysis aims to investigate the conceptual framework of ocular nanoemulsion and/or in-situ gel drug delivery systems from retrospective research based on publication trends, countries, institutions, sources, bibliographic coupling, papers, co-citation, keyword co-occurrence networks, and overlays. We believe that the bibliometric and network analysis approaches have the potential to contribute to future research on creating standardized preparations that meet clinical requirements with low toxicity and better drug absorption in the eye environment (Singh et al. 2020).

## Materials and methods

### Study technique and search strategy

Bibliometric analysis was carried out by collecting data from the Scopus search engine (<https://www-scopus-com>) on December 24, 2021. Searches for Scopus were carried out using the keywords “ocular” AND “nanoemulsion” OR “*in situ* gel.” The inclusion criteria for this search were articles published between 2011 and 2021 in English, with the type of document being articles. Then, the data were cleaned and rechecked to avoid data duplication and ensure that the data articles obtained discussed preparations of nanoemulsion for ocular drug delivery systems and/or *in situ* gels. Abstract and/or article searches were used to validate the right article. After that, the obtained data were exported in the form of a CSV Excel file.

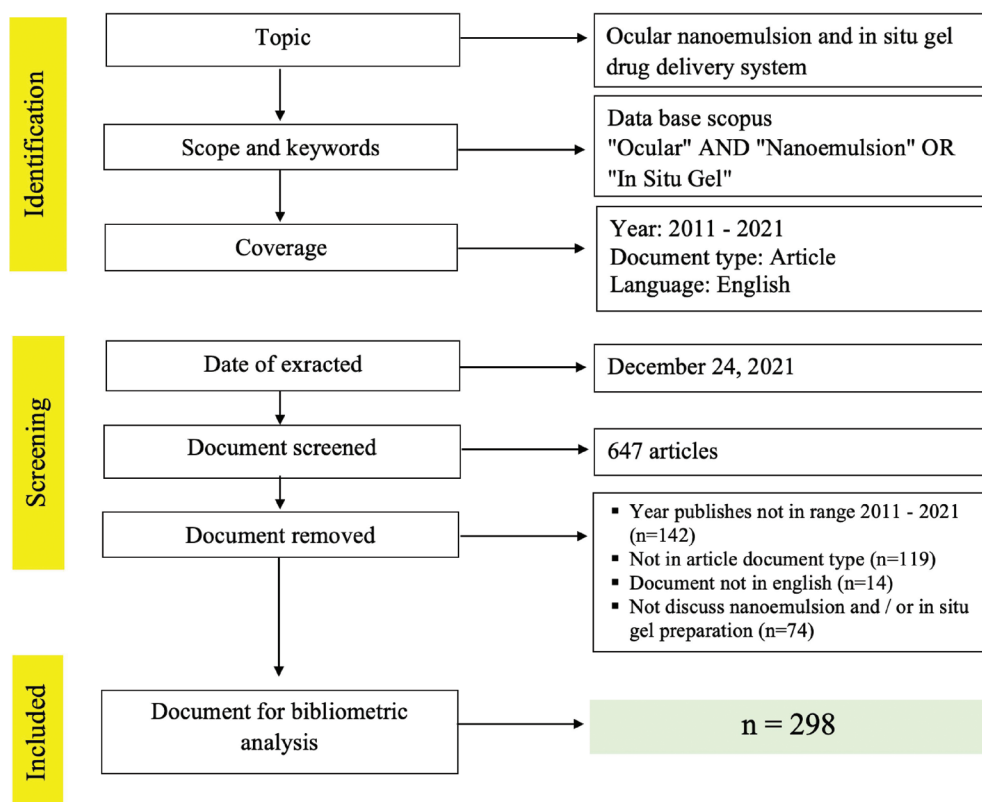
### Data analysis

The VOSviewer version 1.6.17 application from Centre for Science and Technology Studies, Leiden University, The Netherlands, which can be downloaded for free at <https://www.vosviewer.com/download>, was used to analyze the CSV export results. This application was used to examine contributing institutions, sources, authors, papers and co-citation, and keywords co-occurrence. Data cleaning was performed using the thesaurus program in Excel Office to avoid duplication of data or similar terms. Biblioshiny for bibliometrix (R version 4.1.2) from Department of Economics and Statistics, University of Naples Federico II, Italy was also used for data analysis with the Rstudio program, which can be downloaded for free at <https://www.rstudio.com/products/rstudio/download>. This program analyzes the publication trend, contributing country, contributing source, and contributing author.

## Results and discussion

### Data searches

The number of documents obtained after searching on the Scopus search engine with the keyword “ocular” AND “nanoemulsion” OR “*in situ* gel” was 647. The documents



**Figure 1.** Flow diagram of the steps of article search.

were then filtered using inclusion criteria, offering 372 articles. Following the process of ensuring that the filtered articles discussed ocular nanoemulsion preparations and/or in-situ gels, 298 articles were obtained, as shown in Table 1. Fig. 1 presents a flow diagram of the steps of article search.

**Table 1.** Data search results via Scopus search engine.

Search screening	Number of Article
Year publishes not in range 2011–2021	142
Not in article document type	119
Document not in English	14
Documents that do not discuss nanoemulsion and/or in-situ gel ocular preparations	74
Document with inclusion criteria	298
Total articles	647

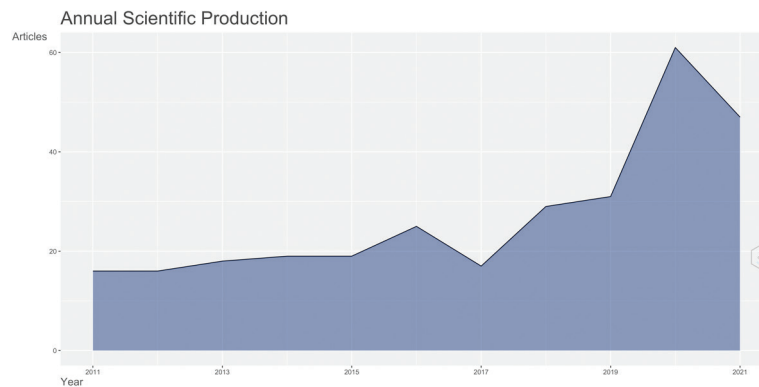
Bibliometric analysis of nanoemulsions and/or in-situ gel ocular preparations was performed to help describe and map knowledge concepts related to advancing research on ophthalmic drug delivery systems using nanoemulsions and/or in-situ gel drug delivery systems using the Scopus database. Performance analysis and science mapping are the two types of bibliometric processing techniques. Performance analysis considers the contributions of research participants from various countries, institutions, sources, and authors who contribute to the productivity of the produced articles (Donthu et al. 2021). Meanwhile, science mapping depicts the relationships between the intellectual aspects of research constituents, such as citation, co-citation, and keyword analyses, as well as bibliographic coupling (Kent Baker et al. 2020).

## Publication trend

As shown in Fig. 2, the number of articles appears to have increased in recent years. Table 2 depicts the publication data trends and the average number of citations per article. On average, 27 articles were produced each year, with a relatively high average of 21 citations per article. The highest number of articles on ocular nanoemulsion and in-situ gel preparations were published in 2020 (61), followed by 47 and 31 articles in 2021 and 2019, respectively. The highest average number of citations per article occurred in 2011 (35.4 points), indicating that the 16 articles published in 2011 were cited or used as a reference for 35.4 other research articles. The second-highest average citation per article was in 2016 (31.3 points), followed by the third highest in 2013 (30.8 points). A higher average citation value for each article

**Table 2.** RStudio-based publication data trend by year.

Year	Articles	Mean Total Citation per Art	Mean Total Citation per Year	Citable Years
2011	16	35.4	3.2	11
2012	16	18.8	1.9	10
2013	18	30.8	3.4	9
2014	19	29.0	3.6	8
2015	19	25.9	3.7	7
2016	25	31.3	5.2	6
2017	17	24.4	4.9	5
2018	29	16.5	4.1	4
2019	31	14.5	4.8	3
2020	61	6.6	3.3	2
2021	47	2.0	2.0	1
Average	27.09	21.4	3.7	6.0



**Figure 2.** Annual scientific production of papers since 2011–2021.

indicates that, in that year, many articles became references for researchers, and so did their articles in the following years.

### Analysis of the contributing country

Rstudio software was used to analyze the contributing countries. Fig. 3 reveals the collaboration map of the countries involved in the research of ocular nanoemulsions and/or in-situ gel preparations. The more intense the blue color on the map is, the more articles that were published during the 2011–2021 period. The pink line indicates the collaborative relationships of each author in different countries. Collaborative articles from two different countries with the highest frequency (seven times) were between Egypt and Saudi Arabia, India and Saudi Arabia, and the United Kingdom and New Zealand.

The greater the number of citations, the greater the country's dominance in article publication. Fig. 4 reveals a graph of the most cited countries from the authors' 39 countries of origin. The three countries with the most

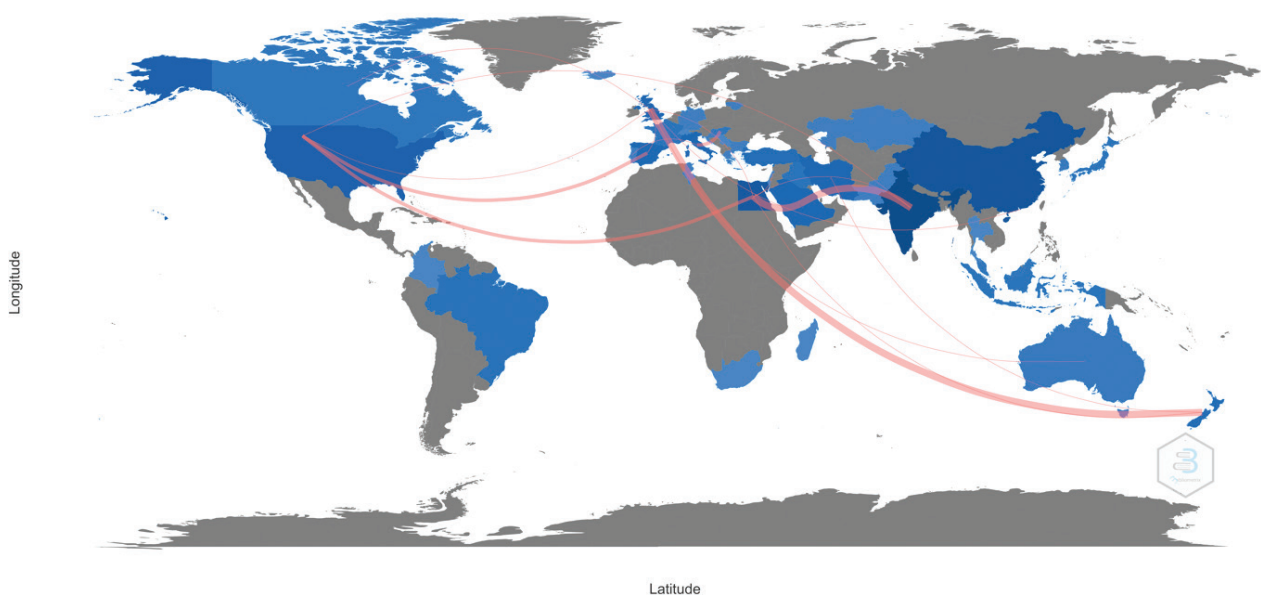
citations were India (1180 citations), China (1120 citations), and Egypt (560 citations), indicating these countries' strong focus on research on nanoemulsion ocular preparations and/or in-situ gels.

### Analysis of the contributing institution

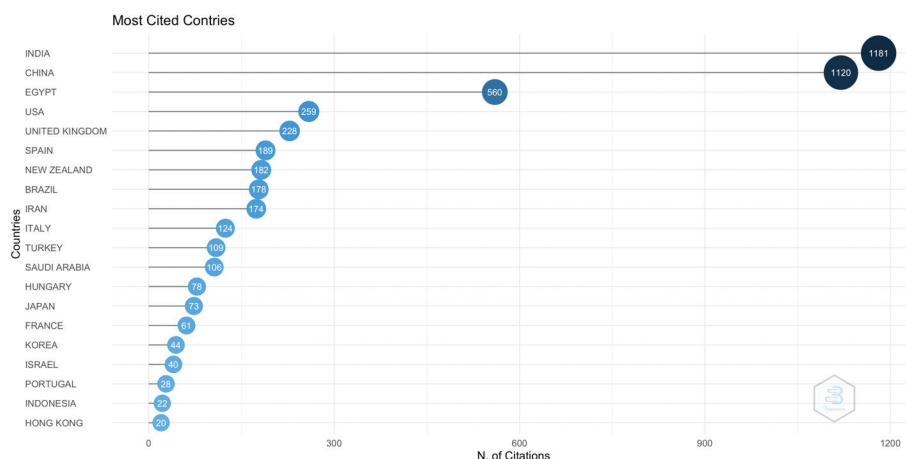
A bibliometric analysis of the contributing institutions was performed using VOSviewer. This analysis depicts the relationship between institutions that collaborate to produce an article. The total number of organizations or institutions involved in producing articles was 740. To avoid duplication, data cleaning was performed using a thesaurus, which resulted in 618 organizations.

Based on the full counting method, six organizations met the minimum of five (article) publication. These organizations are interconnected in publishing several articles, as shown in Table 3. The Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, presented the most articles (nine in total). This was followed by the Department of Pharmaceutics and

### Country Collaboration Map



**Figure 3.** Country collaboration map from 2011 to 2021 using Rstudio.



**Figure 4.** Most cited country from 2011–2021 using Rstudio.

**Table 3.** The most productive organization using the VOSviewer application.

No	Organization	Country	Documents	Citations	Average citation per publication
1	Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University	Egypt	9	351	39.00
2	Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi	USA	7	123	17.57
3	Research Institute of Pharmaceutical Sciences, University of Mississippi	USA	7	123	17.57
4	Department of Pharmaceutics, School of Pharmacy, Hamadan University of Medical Sciences	Iran	7	48	6.86
5	Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard University	India	5	156	31.20
6	Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University	China	5	84	16.80

Drug Delivery, School of Pharmacy, University of Mississippi; Research Institute of Pharmaceutical Sciences, University of Mississippi; and the Department of Pharmaceutics, School of Pharmacy, Hamadan University of Medical Sciences, which published seven articles in total. The Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, and the Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University published five articles each.

Furthermore, the Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, published the most influential articles when compared the other organizations. This organization had the most citations at 351. Following this were The Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard (156 citations); Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi (123 citations); and Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University (123 citations) as the most influential organizations.

## Analysis of the contributing source

According to the VOSviewer analysis, there are 120 sources or journals that publish articles on preparations of nanoemulsion and/or in-situ gels in ocular drug delivery systems. The more articles were published, the more relevant the source is for publishing articles on ocular nanoemulsion and/or in-situ gel preparation. Table 4 lists the top five data sources that published at least eight articles

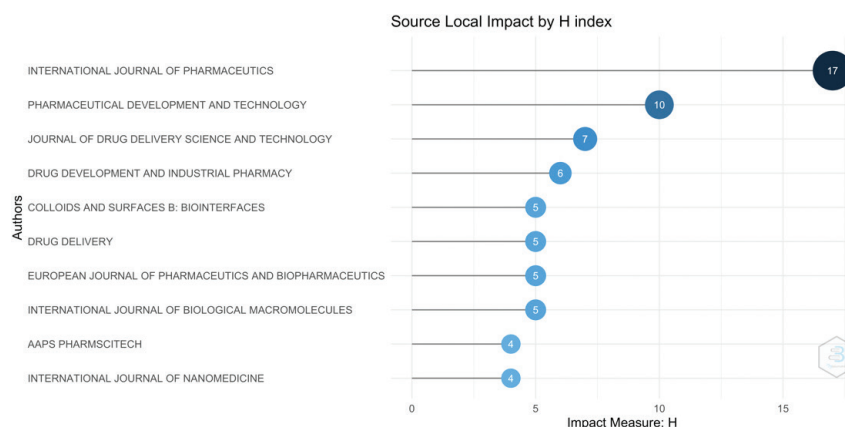
between 2011 and 2021, namely, the International Journal of Pharmaceutics (25 articles), the Journal of Drug Delivery Science and Technology (14 articles), Pharmaceutical Development & Technology and Pharmaceutics (10 articles), Drug Development and Industrial Pharmacy, and the European Journal of Pharmaceutics and Biopharmaceutics (8 articles). Information about the most relevant sources can assist researchers or scholars in submitting or publishing research reports that correspond to the topics provided in the source or journal (Arifaha et al. 2021).

The “International Journal of Pharmaceutics” had the greatest impact on the development of ocular nanoemulsions and/or in-situ gel preparations with the highest total

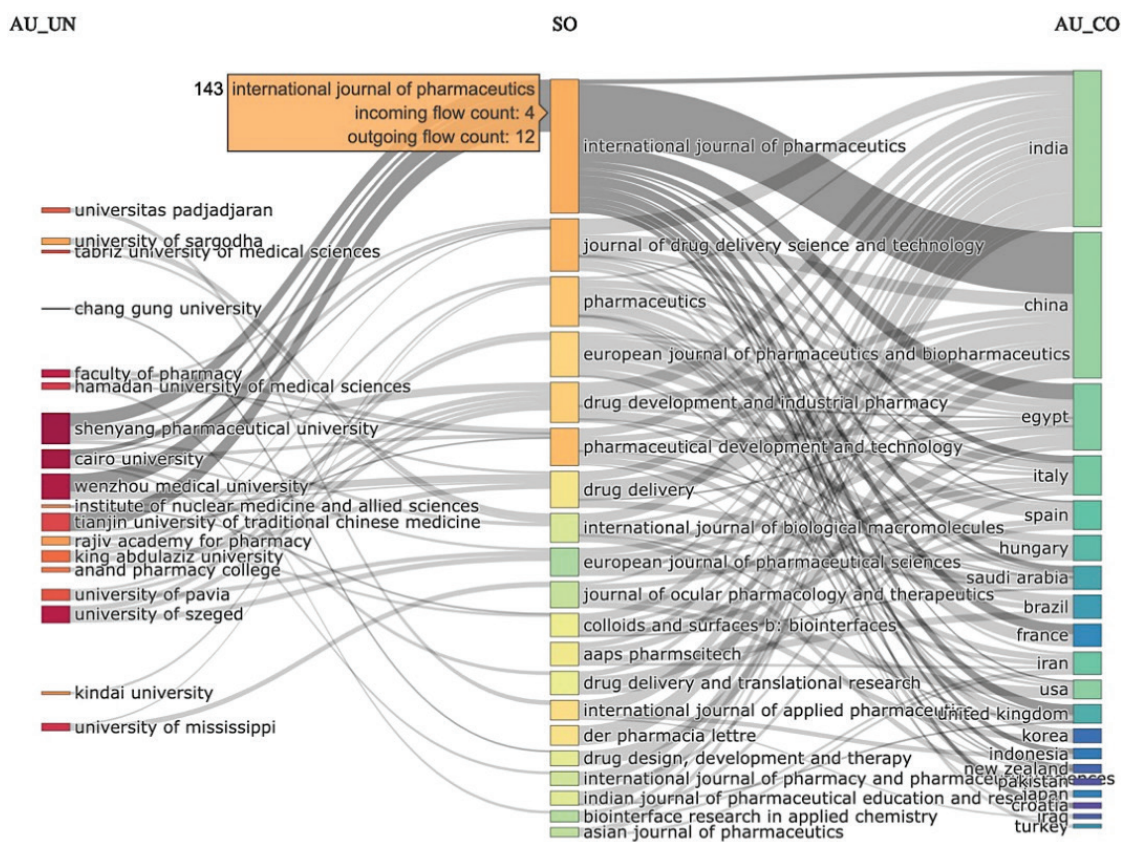
**Table 4.** The most productive source using the VOSviewer application.

Source	Documents	Citations	Average Citation Per Publication
International Journal of Pharmaceutics	25	1030	41.20
Journal of Drug Delivery Science and Technology	14	176	12.57
Pharmaceutical Development and Technology	10	194	19.40
Pharmaceutics	10	95	9.50
Drug Development and Industrial Pharmacy	8	174	21.75
European Journal of Pharmaceutics and Biopharmaceutics	8	287	35.86





**Figure 5.** Highest impact source for ocular nanoemulsion and or *in situ*-gel drug delivery system using Rstudio.



**Figure 6.** Three-fields plot between author affiliations (AU\_UN), Source (SO) and author country (AU\_CO) using Rstudio.

number of citations (1,030) and the highest average number of citations per article (41.20). This result is consistent with the prediction based on Rstudio analysis results, as shown in Fig. 5. According to the H-index, the “International Journal of Pharmaceutics” had the greatest impact, with an H-index of 17. This result indicates that 17 articles were cited at least 17 times by 17 other scholars. This was followed by “Pharmaceutical Development and Technology” with an H index of 10 and the “Journal of Drug Delivery Science and Technology” with an H index of 7.

Fig. 6 illustrate the correlations between author affiliations (AU UN), source (SO), and author's country of origin (AU CO) in a plot of three fields. This study focused on the top 20 author affiliations, top 20 sources, and top

20 countries of origin that published articles on ocular nanoemulsion and/or in-situ gel preparations. RStudio was used for the analysis using 20 items. A gray line connects the three fields. The size of rectangle indicates the number of related articles in each field. The greater the length of the rectangle is, the greater the number of articles associated with each field

In line with Table 4 and Fig. 5, Fig. 6 reveals that the International Journal of Pharmaceutics is the most influential journals in the 20 affiliations and 20 countries to publish articles on ocular nanoemulsion and/or in-situ gel preparations. Incoming flow analysis revealed that four of the top 20 affiliations—Shenang Pharmaceutical University, Wenzhou Medical University, Cairo University, and

Tianjin University of Traditional Chinese Medicine—submitted articles to this journal. Outgoing flow analysis revealed that this journal published articles by authors from 12 of the 20 most productive countries, namely India, China, Egypt, Spain, Italy, Saudi Arabia, France, the United States of America, the United Kingdom, Indonesia, New Zealand, and Croatia.

## Analysis of contributing author and bibliographic coupling

Analysis of the contributing author and bibliographic coupling was performed using the Rstudio application and VOSviewer program. The Rstudio application was used to analyze the contribution of the corresponding author and author impact. Corresponding authors submit articles to journal editors and correspond with them via an email address listed on the first page of the article, which is also accessible to other researchers (Peláez-Repiso et al. 2021). Table 5 shows that most of the corresponding authors were from India (82 articles). China (44 articles) and Egypt (28 articles) ranked second and third, respectively. Furthermore, a high number of corresponding authors in a country indicates that the research environment or the country's resources support the researchers with publishing on nanoemulsion and/or in-situ gels for ocular drug delivery systems.

**Table 5.** Top 10 corresponding author's country using Rstudio.

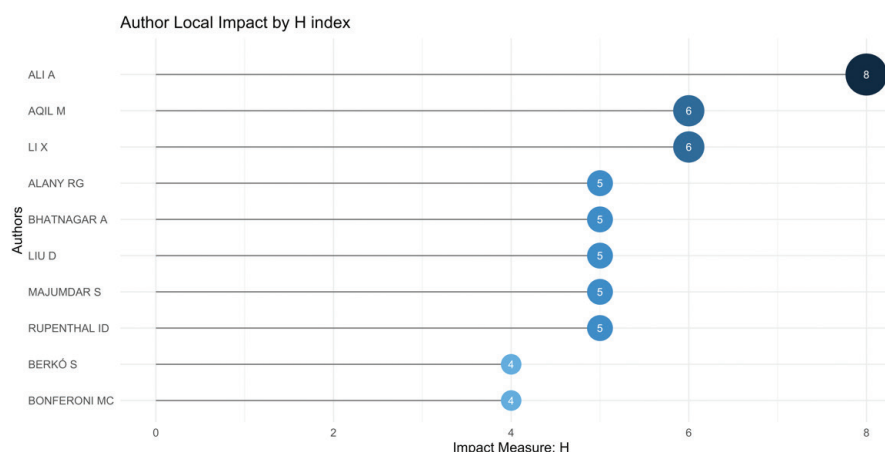
No	Country	Articles	SCP*	MCP*	MCP_Ratio*
1	India	82	76	6	0.07
2	China	44	43	1	0.02
3	Egypt	28	24	4	0.14
4	Iran	15	13	2	0.13
5	USA	15	12	3	0.20
6	Italy	9	9	0	0.00
7	Turkey	8	7	1	0.13
8	Saudi Arabia	7	0	7	1.00
9	Spain	7	6	1	0.14
10	Brazil	5	4	1	0.20

\*SCP: Single Country Publication, MCP: Multiple Country Publications, MCP Ratio = MCP/ Articles.

The countries with the most corresponding authors, India, and China, have the most human resources in the world, and so they are inextricably linked to the problem of ocular disease. India is a developing country with increasing urban migration and a large elderly population on the verge of a dry eye disease epidemic (Donthineni et al. 2019). Over the last two decades, China has seen an increase in the number of people with eye diseases who have lost their vision, and this may continue because of population growth and aging (Wang et al. 2018). As a result, it is not remarkable that these countries have published numerous articles on this subject.

Table 5 also represents the level of collaboration, which consists of intra-country collaboration, also known as single-country publication (SCP), and inter-country collaboration, also known as multiple-country publication (MCP). Corresponding authors from Saudi Arabia have the highest international collaboration and inter-country collaboration ratio of 1. All articles (seven articles) with a corresponding author from Saudi Arabia resulted from international collaborations. Following Saudi Arabia, India (six articles) and Egypt (four articles) had the most international collaborations. MCP paves the way for technological harmonization and expands research opportunities. Comparative studies can be used to investigate scientific production that has an enormous impact on solving global and local ocular problems. Compared to those of other countries, India (76 articles), China (43 articles), and Egypt (24 articles) had the highest intra-country collaborations.

In addition to the author's impact, Fig. 7 represents the author's influence, as indicated by the value of the H index. Ali A had the most influence on articles produced on ocular nanoemulsions and/or in-situ gel preparations, with the highest H index of 8, followed by Aqil M and Li X, with an H index of 6. Ali A's articles were mostly about ocular in-situ gel formulations with in-vitro, in-vivo, and ex-vivo profiles, including irritation tests (Gupta et al. 2013b, 2013a, 2015b, 2015a; Katiyar et al. 2014; Khan et al. 2015; Aslam et al. 2016; Ameenuzzafar et al. 2018a, 2018b). This information is significantly helpful for article writers, including researchers, in designing and discussing the impact of research results.



**Figure 7.** Author local impact based on H using with Rstudio.

**Table 6.** Top 5 most productive authors using VOSviewer.

No	Author	Title & Document Year
1	Ali A. ■ Total documents: 9 ■ Citations: 276 ■ Average Citation Per Document: 30,67 ■ Affiliation: Jamia Hamdard Faculty of Pharmacy, New Delhi, India	1 Preparation and evaluation of novel chitosan: gelrite ocular system containing besifloxacin for topical treatment of bacterial conjunctivitis: scintigraphy, ocular irritation and retention assessment (2018a)
		2 Formulation and optimization of levofloxacin loaded chitosan nanoparticle for ocular delivery: In-vitro characterization, ocular tolerance and antibacterial activity (2018b)
		3 Levofloxacin loaded gelrite-cellulose polymer based sustained ocular drug delivery: Formulation, optimization and biological study (2016)
		4 Physiologically active hydrogel ( <i>in situ</i> gel) of sparfloxacin and its evaluation for ocular retention using gamma scintigraphy (2015b)
		5 Development and evaluation of a novel <i>in situ</i> gel of sparfloxacin for sustained ocular drug delivery: <i>In vitro</i> and ex vivo characterization (2015)
		6 An alternative <i>in situ</i> gel-formulation of levofloxacin eye drops for prolong ocular retention (2015a)
		7 <i>In situ</i> gelling dorzolamide loaded chitosan nanoparticles for the treatment of glaucoma (2014)
		8 Nanoparticles laden <i>in situ</i> gel of levofloxacin for enhanced ocular retention (2013b)
		9 Nanoparticles laden <i>in situ</i> gel for sustained ocular drug delivery (2013a)
2	Mahboobian M.M. ■ Total documents: 8 ■ Citations: 61 ■ Average Citation Per Document: 7,63 ■ Affiliation: Hamadan University of Medical Sciences, Iran	1 Ocular toxicity assessment of nanoemulsion in-situ gel formulation of fluconazole (2021)
		2 Studying the ophthalmic toxicity potential of developed ketoconazole loaded nanoemulsion <i>in situ</i> gel formulation for ophthalmic administration (2021)
		3 Acyclovir-loaded nanoemulsions: preparation, characterization and irritancy studies for ophthalmic delivery (2021)
		4 Thermosensitive brinzolamide <i>in situ</i> gel nanoemulsions, <i>in vitro</i> and ex vivo evaluation (2021)
		5 Development of thermosensitive <i>in situ</i> gel nanoemulsions for ocular delivery of acyclovir (2020)
		6 Investigating the ocular toxicity potential and therapeutic efficiency of <i>in situ</i> gel nanoemulsion formulations of brinzolamide (2020)
		7 Brinzolamide-loaded nanoemulsions: ex vivo transcorneal permeation, cell viability and ocular irritation tests (2019)
		8 Formulation development and evaluation of the therapeutic efficacy of brinzolamide containing nanoemulsions (2017)
3	Majumdar S. ■ Total documents: 7 ■ Citations: 123 ■ Average Citation Per Document: 17,57 ■ Affiliation: University of Mississippi, University, United States	1 Design of topical ocular ciprofloxacin nanoemulsion for the management of bacterial keratitis (2021)
		2 Ciprofloxacin loaded nanostructured lipid carriers incorporated into in-situ gels to improve management of bacterial endophthalmitis (2020)
		3 $\Delta^9$ -tetrahydrocannabinol derivative-loaded nanoformulation lowers intraocular pressure in normotensive rabbits (2019b)
		4 Analog derivatization of cannabidiol for improved ocular permeation (2019a)
		5 Gellan gum based sol-to-gel transforming system of natamycin transfersomes improves topical ocular delivery (2019)
		6 <i>In situ</i> gel of triamcinolone acetone-loaded solid lipid nanoparticles for improved topical ocular delivery: Tear kinetics and ocular disposition studies (2019)
		7 Ion-sensitive <i>in situ</i> hydrogels of natamycin bilosomes for enhanced and prolonged ocular pharmacotherapy: <i>in vitro</i> permeability, cytotoxicity and <i>in vivo</i> evaluation (2018)
4	Pan W. ■ Total documents: 7 ■ Citations: 130 ■ Average Citation Per Document: 18,57 ■ Affiliation: Shenyang Pharmaceutical University, Shenyang, China	1 A novel carbon dots/thermo-sensitive <i>in situ</i> gel for a composite ocular drug delivery system: Characterization, ex-vivo imaging and <i>in vivo</i> evaluation (2021b)
		2 A composite system combining self-targeted carbon dots and thermosensitive hydrogels for challenging ocular drug delivery (2021a)
		3 A novel ion-activated <i>in situ</i> gelling ophthalmic delivery system based on $\kappa$ -carrageenan for acyclovir (2018)
		4 Development and characterization of nanostructured lipid carriers based chitosan thermosensitive hydrogel for delivery of dexamethasone (2017)
		5 A novel hydrogel with dual temperature and pH responsiveness based on a nanostructured lipid carrier as an ophthalmic delivery system: Enhanced trans-corneal permeability and bioavailability of nepafenac (2017)
		6 Liposome incorporated ion sensitive <i>in situ</i> gels for ophthalmic delivery of timolol maleate (2015)
		7 Optimized flurbiprofen cationic liposomes <i>in situ</i> gelling system of thermosensitive polymers for ocular delivery (2012)

The contributing author and research network analyses was carried out between the authors using bibliographic coupling with the full counting method in the VOSviewer application. The full counting method assigns one credit to each contributing author. If there are five authors in a single article, the total number of credits is five (Sivertsen et al. 2019). A bibliographic coupling analysis was performed on the contributing authors with at least two published articles that were linked with other authors; this approach was necessary because if the minimum criteria of one article was used or an analysis on all authors was

conducted, the results would indicate that not all authors were connected in the articles created. Consequently, 227 authors were selected based on this approach. There were ten indicated author clusters. Table 7 shows the number of authors in each cluster and the focus of the research themes conducted by the top three authors in each cluster.

A thesaurus was used to clean the data for author name duplication, post which, the number of authors reduced from 1,215 to 1,205. Table 6 shows the top authors who published the most articles that link with other authors about ocular nanoemulsions and in-situ gel preparations.



**Table 7.** Research focuses of the top 3 authors in each cluster using VOSviewer.

Cluster	Quantity of Author	Top 3 Author	Focus
Cluster 1	87	Ali a. (9 documents) Aqil m. (6 documents) Alany r.g. (6 documents)	Formulation, characterization of ocular nanoemulsion and or <i>in situ</i> gel, toxicity study, <i>in vitro</i> , <i>in vivo</i> , ex vivo, and pharmacodynamic study
Cluster 2	25	Nagai n. (4 document) Zhang y. (3 document) Wu h. (3 documents)	Prolonged of drug residence time and diffusion, enhance corneal permeability, absorption into the cornea and conjunctiva, sustained ophthalmic drug delivery
Cluster 3	23	Majumdar s. (7 documents) Dudhipala n. (4 documents) Tatke a. (3 documents)	Improve permeation, enhanced and prolonged ocular pharmacotherapy, cytotoxicity of antibacterial ocular delivery
Cluster 4	18	Kurniawansyah i.s. (4 documents) Yozgatli v. (4 documents) Üstündağ okur n. (4 documents)	<i>In situ</i> gel (thermosensitive gel, pH triggered <i>in situ</i> gel) formulation for ocular antifungal (chloramphenicol, voriconazole) and allergic (tetrahydrozoline) preparation.
Cluster 5	15	Rupenthal i.d. (5 documents) Mohammadi m. (6 documents) Mahboobian m.m (8 documents)	Ocular nanoemulsion and nanocarrier loaded to <i>in situ</i> gel
Cluster 6	15	Horvát g. (4 documents) Sandri g. (4 documents) Szilágyi a. (4 documents)	Preparation of ocular mucoadhesive of thiolated poly (aspartic acid) polymers
Cluster 7	13	Liu d. (5 documents) Yang x. (5 documents) Pan w. (7 documents)	Preparation of thermosensitive <i>in situ</i> gel
Cluster 8	11	Tan j. (2 documents) Yeu e. (2 documents) Liu h. (3 documents)	ocular nanoemulsion for dry eye disease
Cluster 9	10	Mignet n. (2 documents) Seguin j. (2 documents) Zeng n. (2 documents)	Cytotoxicity, <i>in vitro</i> , <i>in vivo</i> study of ophthalmic <i>in situ</i> gel
Cluster 10	10	Yu j. (2 documents) Chen h. (3 documents) Li x. (6 documents)	<i>In situ</i> hydrogel ocular formulation

In addition to producing the most influential articles, Ali A. from Jamia Hamdard Faculty of Pharmacy, New Delhi, India, published nine articles between 2011 and 2018, with an average of 30.67 citations per article, who was followed by Mahboobian M.M. from Hamadan University of Medical Sciences in Iran with eight articles (2017–2021). Majumdar S. from the University of Mississippi in the United States and Pan W from Shenyang Pharmaceutical University in China were third, with seven articles (2018–2021).

## Analysis of contributing paper and co-citation

The number of citations obtained from an article reveals the study with the most significant contribution. The more citations an article receives, the greater its influence on advancing research on preparations with nanoemulsion and/or *in-situ* gel for ocular drug delivery systems. A total of 298 papers contributed to research on ocular nanoemulsions and/or *in-situ* gel preparations. Based on the bibliographic coupling analysis with the document analysis unit in VOSviewer, the number of articles with a minimum of one citation was 265. Only 11.07% of articles were not cited by another article and most of these articles were published in 2021, implying that most articles influence those published following their publication.

Table 8 lists the top ten most-cited articles. The number of contributing papers is calculated by full counting

The most influential article, titled “*In situ* gelling systems based on Pluronic F127/Pluronic F68 formulations for ocular drug delivery,” was written by Al Khateb (2016). This study demonstrated that Pluronic F127 and Pluronic F68 at a concentration of 20% w/w in an *in-situ* gel drug delivery system does not cause mucosal tissue irritation, allowing their efficient application to the eyes; wherein Pluronic F127 20% w/w solution can form a transparent gel, increasing the drug’s residence time (Al Khateb et al. 2016).

“Enhancing and sustaining the topical ocular delivery of fluconazole using chitosan solution and poloxamer/chitosan *in-situ* forming gel” was the second most influential article with 119 citations (Gratieri et al. 2011). This study aimed to assess the *in-situ* delivery of a drug using poloxamer 407-chitosan gel to improve corneal permeation and sustained fluconazole release. Fluconazole was released from the poloxamer/chitosan formulation over time, according to the study’s *in-vitro* drug release evaluation. Ex vivo permeation evaluation of porcine corneas revealed increased permeation at chitosan concentrations ranging from 0.5 to 1.5 percent w/w. The chitosan solution alone demonstrated the highest ex vivo drug permeation. However, the poloxamer/chitosan combination was only comparable *in-vivo* to the 1.0% chitosan solution. Compared with the simple drug solution, both formulations demon-

**Table 8.** Most cited articles using VOSviewer.

No	Author	Title	Source	Total Citation
1	(Al Khateb et al. 2016)	<i>In situ</i> gelling systems based on Pluronic F127/Pluronic F68 formulations for ocular drug delivery	International Journal of Pharmaceutics	130
2	(Gratieri et al. 2011)	Enhancing and sustaining the topical ocular delivery of fluconazole using chitosan solution and poloxamer/chitosan <i>in situ</i> forming gel	European Journal of Pharmaceutics and Biopharmaceutics	119
3	(Tayel et al. 2013)	Promising ion-sensitive <i>in situ</i> ocular nanoemulsion gels of terbinafine hydrochloride: design, <i>in vitro</i> characterization and <i>in vivo</i> estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits	International Journal of Pharmaceutics	115
4	(Rupenthal et al. 2011b)	Comparison of ion-activated <i>in situ</i> gelling systems for ocular drug delivery. Part 2: Precorneal retention and <i>in vivo</i> pharmacodynamic study	International Journal of Pharmaceutics	109
5	(Morsi et al. 2017)	Nanoemulsion-based electrolyte triggered <i>in situ</i> gel for ocular delivery of acetazolamide	European Journal of Pharmaceutical Sciences	85
6	(Lai and Hsieh 2012)	A gelatin-g-poly(N-isopropylacrylamide) biodegradable <i>in situ</i> gelling delivery system for the intracameral administration of pilocarpine	Biomaterials	83
7	(Makwana et al. 2016)	Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride	Results in Pharma Sciences	82
8	(Duan et al. 2015)	Novel <i>in situ</i> gel systems based on P123/TPGS mixed micelles and gellan gum for ophthalmic delivery of curcumin	Colloids and Surfaces B: Biointerfaces	79
9	(M.A. Fathalla et al. 2017)	Poloxamer-based thermoresponsive ketorolac tromethamine <i>in situ</i> gel preparations: design, characterisation, toxicity and transcorneal permeation studies	European Journal of Pharmaceutics and Biopharmaceutics	76
10	(Lou et al. 2014)	Optimization and evaluation of a thermoresponsive ophthalmic <i>in situ</i> gel containing curcumin-loaded albumin nanoparticles	International Journal of Nanomedicine	74

strated sustained release and a 3.5-fold increase in total fluconazole absorption (Gratieri et al. 2011).

Meanwhile, the third most influential article was “Promising ion-sensitive in-situ ocular nanoemulsion gels of terbinafine hydrochloride: Design, in-vitro characterization, and in-vivo estimation of ocular irritation and drug pharmacokinetics in rabbit aqueous humor,” which had been cited 115 times (Tayel et al. 2013). This study aimed to prepare an in-situ gel nanoemulsion of terbinafine hydrochloride for use in ocular drug delivery systems. Drug-loaded nanoemulsions (0.5%, w/v) were dispersed in gellan gum solution (0.2%, w/w). The in-situ NE gel was transparent, pseudoplastic, and mucoadhesive with a slower zero-order drug release rate. Formula 31 (Miglyol 812-5% w/w, Cremophor EL 18.33% w/w, polyethylene glycol 400-36.67% w/w, gellan gum 0.2% w/w, and water) in-situ NE gel had the least ocular irritation potential and significantly ( $P, 0.01$ ) better  $C$  (max), delayed  $T$  (max), prolonged mean residence time, and increased bioavailability (Tayel et al. 2013).

Analysis of co-citation—when two papers are cited by a third paper—revealed the relationship between the cited articles that formed the basic theme of the research. The co-citation relationship between two papers becomes stronger with an increasing number of papers citing both of them (Bamel et al. 2020). Co-citation analysis helps identify the most influential published articles to form thematic clusters (Donthu et al. 2021). Co-citations were analyzed based on a unit analysis of the cited references. Fractional counting was used for this calculation. The co-authored publications were calculated fractionally for each author, with the overall weight of the publication equal to one (Bamel et al. 2020). Therefore, in fractional counting, each publication has the same overall weight to provide balance, consistency, and precision in bibliometric measurements (Sivertsen et al. 2019).

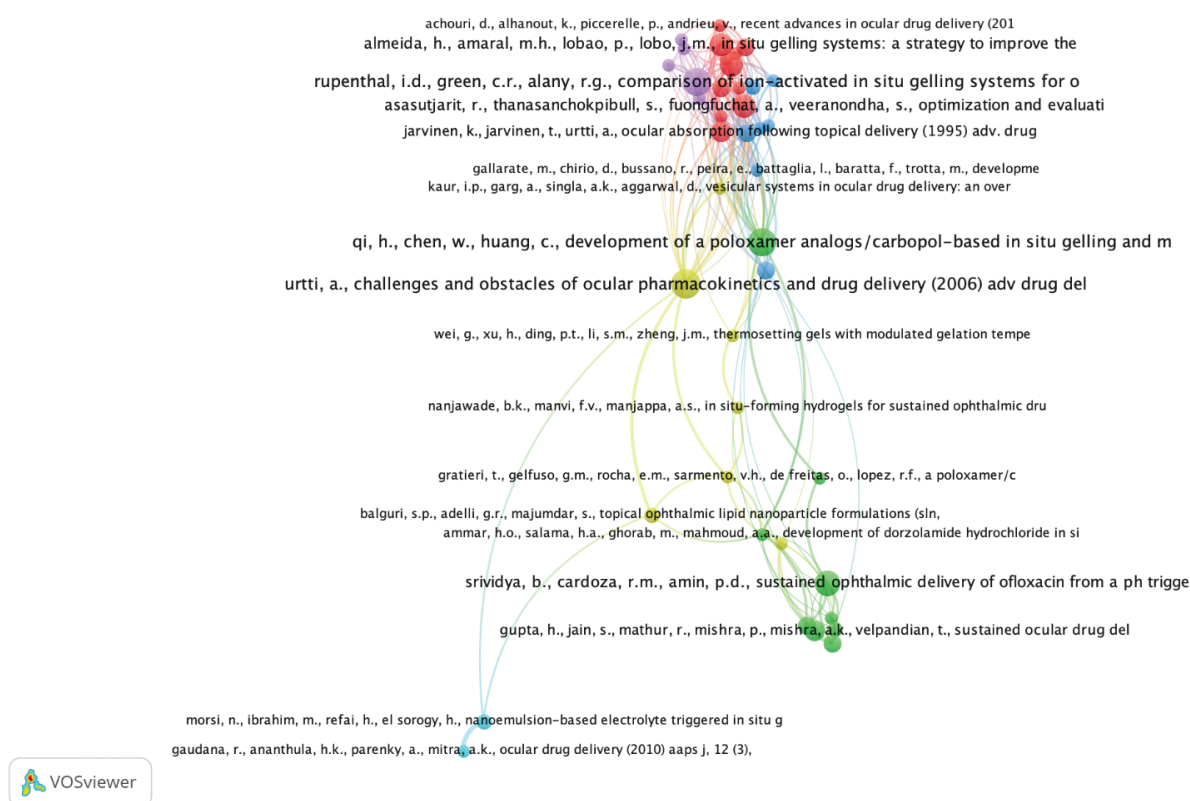
Based on the VOSviewer analysis, the total number of references cited was 11,338. At least one reference cited as

many as 504 references, but only 446 articles were connected with each other. Using at least one reference cited by three articles, 112 references were obtained; however, one reference was not connected to the other articles. Therefore, the analysis was carried out on references with a minimum of four citations by other articles to obtain 46 reference articles. As there was duplication of data in the analysis results, cleaning of the data was performed using a thesaurus and 41 articles remained. The top three reference articles that were most cited by articles on ocular nanoemulsions and/or in-situ gel preparation are shown in Table 9.

**Table 9.** Top 3 most cited co-citation reference using VOSviewer.

Authors	Title	Source	Cited number
(Urtti. 2006)	Challenges and obstacles of ocular pharmacokinetics and drug delivery	Advanced Drug Delivery Reviews, 58, pp. 1131–1135	11
(Qi et al. 2007)	Development of a poloxamer analogs/carbopol-based <i>in situ</i> gelling and mucoadhesive ophthalmic delivery system for puerarin	International Journal of Pharmaceutics, 337, pp. 178–187	10
(Rupenthal et al. 2011a)	Comparison of ion-activated <i>in situ</i> gelling systems for ocular drug delivery. Part 1: physicochemical characterisation and <i>in vitro</i> release	International Journal of Pharmaceutics, 411, pp. 69–77	10

The most co-citation reference belonged to Urtti (2006). The reference was about topical eye drops wearing off quickly from the eye's surface, revealing that the absorption time of the drug was short and thus impacting the bioavailability of the drug, which was less than 5%. As a solution, the dosage form can be designed for prolonged action; however, not many patients have received this form. In addition, absorption of the modified preparation



**Figure 8.** Co-citation network visualization using VOSviewer.

can be blocked by the corneal and conjunctival epithelium of the eye (Urtti 2006).

The reference articles were linked to other articles and were divided into six clusters, depicted in different colors on the circle in Fig. 8. Each cluster focuses on a different theme or area of research on ocular nanoemulsions and/or in-situ gel preparations. The red cluster is the largest (11 articles), while the blue cluster is the smallest (2 articles). The size of each circle represents the number of citations. The larger the circle, the more citations an article has received. The distance between the two circles indicates the similarity between their themes; the higher the similarity level, the closer the circles (Bamel et al. 2020). The research focuses on the top three co-citation authors in each cluster with VOSviewer, as shown in table 10.

## Analysis of keyword co-occurrence

The following analysis examined keyword co-occurrence across all keywords using VOSviewer. This analysis can be used to map current or future research topics on ocular nanoemulsion and/or *in situ* gel preparations based on the content of the articles written (Donthu et al. 2021). The number of documents that appear using a specific keyword is shown by occurrence. The calculation method used was full counting, so the number of occurrences of keywords in the analysis obtained represents the total occurrence of these keywords in all documents. The All keyword category is made up of author keywords (“article titles,” “abstracts,” and “full texts”) as well as indexed keywords (Arifaha et al. 2021).

The total number of keywords examined was 2,778. The number of keywords used after filtering with the thesau-

rus was 2,457. The filter process seeks to eliminate duplicate keywords with the same meaning, such as antioxidant and antioxidants, carbopol and carbopol, het-cam and hen’s egg test-cam, and so on. The number of keywords that appeared at least 30 times in the articles found was 68. Then, the manual selection was performed on unrelated or irrelevant to the article’s theme. The analysis did not include keywords of articles, female, human, male, non-human, priority journals, or procedures. The list of keywords and the interpretation of the results obtained can be seen in Table 11 and divided into 3 clusters.

Fig. 9 shows the co-occurrence network based on time division. The most used keyword was “controlled release” (183 occurrences), which appeared in mid-2017. This was followed by “drug delivery system” (170 occurrences) and “drug formulation” (159 occurrences), which began to appear in early 2017. “*In vitro* studies” began to increase in mid-2017 (141 occurrences) and “gels” appeared in mid-2016 (130 occurrences). **Controlled release** was the keyword that appeared the most. Prolonged action necessitates controlled drug release from the delivery system to prolong the ocular surface retention time. Controlled release or slow release and/or dissolution of drugs without prolonged retention on the ocular surface is ineffective because it results in poor ocular bioavailability. Therefore, the ocular delivery system must be designed to remain on the ocular surface for an extended period to effectively release the drug dose in the lacrimal fluid. Polymers that exhibit mucoadhesion based on electrostatic interactions or hydrogen bonding can be used to extend the retention time on the ocular surface (Subrizi et al. 2019).

**Table 10.** Research focus on top 3 co citation authors in each cluster using VOSviewer.

Cluster	Authors	Title	Year	Cited number	Theme
Cluster 1 (Red nodes, 11 items)	Almeida, H., Amaral, M.H., Lobao, P., Lobo, J.M.	<i>In situ</i> gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations	2014	8	When applied to the eye, <i>in situ</i> gel polymers (Pluronic F27, Pluronic F68, Carbopol 940) provide mucoadhesive liquid properties with a stimulus responsiveness mechanism, produce a transparent profile, suitable pH, and form a gel better than conventional preparations.
	Asasutjarit, R., Thanasanchokpibull, S., Fuongfuchat, A., Veeranondha, S.	Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic <i>in situ</i> gels	2011	8	
	Ludwig, A.	The use of mucoadhesive polymers in ocular drug delivery	2005	8	
Cluster 2 (Dark green nodes, 9 items)	Qi, H., Chen, W., Huang, C.	Development of a poloxamer analogs/ carbopol-based <i>in situ</i> gelling and mucoadhesive ophthalmic delivery system for puerarin	2007	10	Carbopol in combination with poloxamer (poloxamer 407, poloxamer 188), hydroxypropyl methylcellulose (HPMC), and chitosan can improve mucoadhesive properties, provide a sustained release profile, and increase residence time and drug penetration on the corneal membrane.
	Srividya, B., Cardoza, R.M., Amin, P.D.	Sustained ophthalmic delivery of ofloxacin from a pH triggered <i>in situ</i> gelling system	2001	9	
	Gupta, H., Jain, S., Mathur, R., Mishra, P., Mishra, A.K., Velpandian, T.	Sustained ocular drug delivery from a temperature and pH triggered novel <i>in situ</i> gel system	2007	7	
Cluster 3 (Dark blue nodes, 7 items)	Ammar, H.O., Salama, H.A., Ghorab, M., Mahmoud, A.A.	Nanoemulsion as A Potential Ophthalmic Delivery System for Dorzolamide Hydrochloride	2009	6	The delivery of nanoemulsions and nanoemulsions <i>in situ</i> gel can increase the contact time with the eye surface, thereby increasing therapeutic efficacy, accelerating the onset, and prolonging the effect of drugs compared to market products.
	Tayel, S.A., El-Nabarawi, M.A., Tadros, M.I., Abd-El salam, W.H.	Promising ion-sensitive <i>in situ</i> ocular nanoemulsion gels of terbinafine hydrochloride: design, <i>in vitro</i> characterization and <i>in vivo</i> estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits	2013	6	
	Edsman, K., Carlfors, J., Petersson, R.	Rheological evaluation of poloxamer as an <i>in situ</i> gel for ophthalmic use	1998	5	
Cluster 4 (Yellow nodes, 7 items)	Urtti, A.	Challenges and Obstacles of Ocular Pharmacokinetics and Drug Delivery	2006	11	The polymer composition and drug delivery of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) can improve the pharmacokinetic profile of drugs in the anterior and posterior segments of the eye.
	Balguri, S.P., Adelli, G.R., Majumdar, S.	Topical Ophthalmic Lipid Nanoparticle Formulations (SLN, NLC) of Indomethacin for Delivery to The Posterior Segment Ocular Tissues	2016	5	
	Gratieri, T., Gelfuso, G.M., De Freitas, O., Rocha, E.M., Lopez, R.F.	Enhancing and sustaining the topical ocular delivery of fluconazole using chitosan solution and poloxamer/chitosan <i>in situ</i> forming gel	2011	4	
Cluster 5 (Purple nodes, 5 items)	Rupenthal, I.D., Green, C.R., Alany, R.G.	Comparison of ion-activated <i>in situ</i> gelling systems for ocular drug delivery. Part 1: physicochemical characterisation and <i>in vitro</i> release	2011	10	Anionic polysaccharides (gellan gum, xanthan gum, carrageenan, and alginate), an uncharged (HPMC), and a positively charged (chitosan) polymer affect gelling behavior, rheological, textural properties, gel microstructure, contact angle, and <i>in vitro</i> release characteristics and that a high rate of the sol/gel transition results in long contact times.
	Carlfor, J., Edsman, K., Petersson, R., Jorning, K.	Rheological evaluation of gelrite <i>in situ</i> gels for ophthalmic use	1998	4	
	Morris, E.R., Nishinari, K., Rinaudo, M.	Gelation of gellan – A review	2012	4	
Cluster 6 (Ligth blue nodes, 2 items)	Morsi, N., Ibrahim, M., Refai, H., El Sorogy, H.	Nanoemulsion-based electrolyte triggered <i>in situ</i> gel for ocular delivery of acetazolamide	2017	5	An approach using bioadhesive gels and fibrin sealant-based has been developed to sustain drug levels at the target site, and nanoemulsion based <i>in situ</i> gels showed a significant, sustained drug release in comparison to the nanoemulsion.
	Gaudana, R., Ananthula, H.K., Parenky, A., Mitra, A.K.	Ocular drug delivery	2010	3	

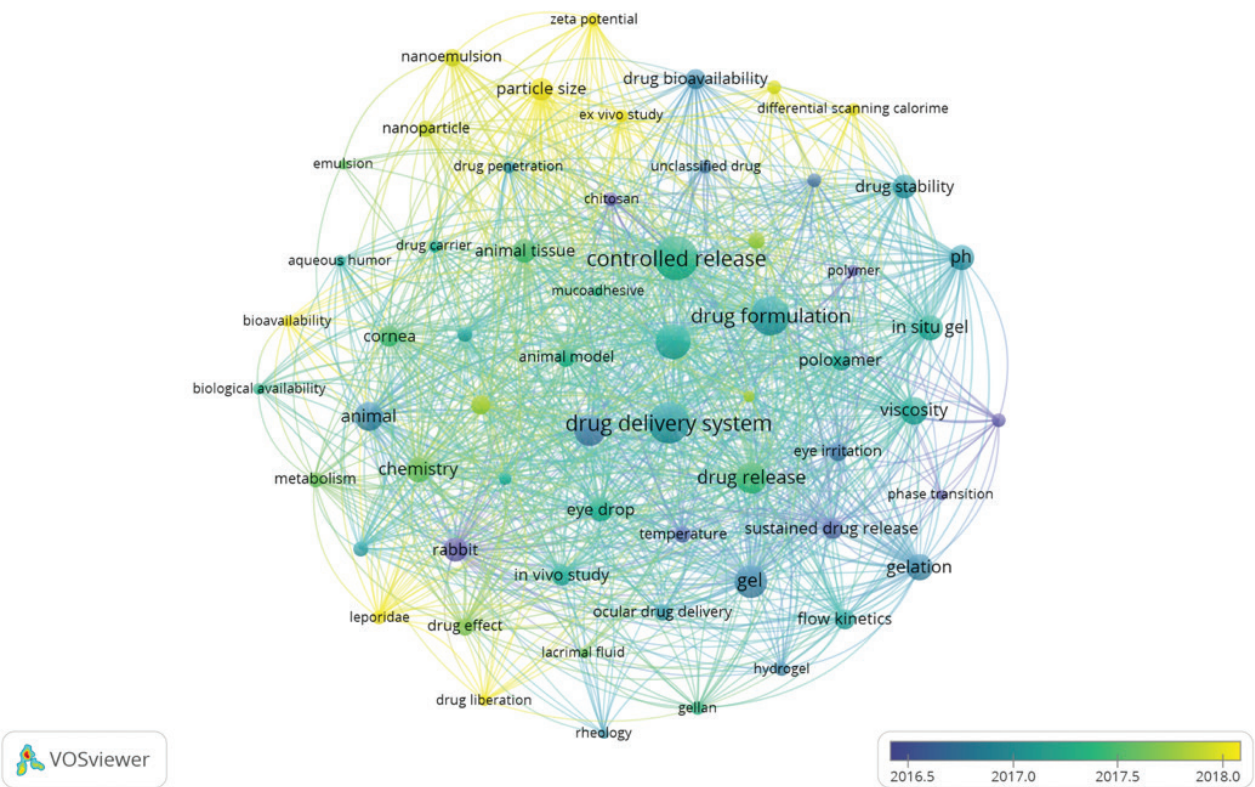
Fig. 10 shows the trend of the research topics each year based on author keywords that appeared at least five times in one year from 2011 to 2021 using RStudio. “Nanoemulsion drug delivery systems” began to appear more around 2018–2019, while “in-situ gel preparations” have often appeared since 2011. Low nanoemulsion viscosity can affect the residence time of the preparation on the ocular surface. Therefore, some researchers have modified the preparation by wrapping it in a gel or hydrogel. However, the drawback

of this hydrogel form is that the amount of active substance and homogeneity are limited, especially for hydrophobic drugs; therefore, the use of a nanoemulsion delivery system is expected to overcome these problems (Dubald et al. 2018). This has led to the development of ocular in-situ gel preparation research being more varied and dominated by identifying the right gelling agent. The most frequently developed gelling agents are sodium alginate (2014), carbopol (2015), poloxamer (2016), chitosan (2018), and gellan gum (2019).

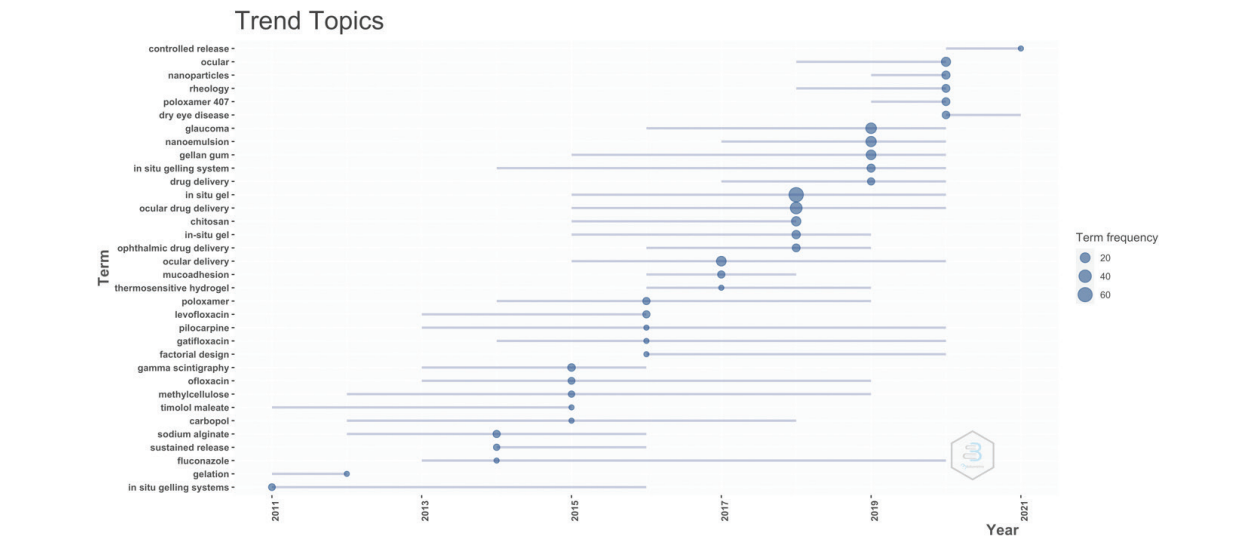


**Table 11.** Theme interpretation of keywords in each cluster using VOSviewer.

Cluster	Keywords	Theme interpretation
Cluster 1	controlled release; differential scanning calorimetry; drug bioavailability; drug delivery system; drug efficacy; drug formulation; drug release; drug solubility; drug stability; eye irritation; flow kinetics; gel; gelation; glaucoma; hydrogel; hydroxypropyl methyl cellulose; <i>in situ</i> gel; <i>in vitro</i> study; ocular drug delivery; pH; phase transition; physical chemistry; poloxamer; polymer; sustained drug release; temperature; unclassified drug; viscosity	This cluster illustrates the theme of ophthalmic preparations with a controlled release profile related to the preparation's bioavailability and efficacy, as well as the physicochemical characterization and <i>in vitro</i> profile, particularly in polymer matrices.
Cluster 2	administration, ophthalmic; animal; aqueous humor; area under the curve; bioavailability; biological availability; chemistry; cornea; drug effect; drug liberation; eye drop; gellan; <i>in vivo</i> study; intraocular drug administration; lacrimal fluid; leporidae; metabolism; mucoadhesive; ophthalmic solutions; rabbit; rheology	This cluster describes the drug release profile on the eye surface in eye drop preparations based on biological availability in test animals ( <i>in vivo</i> study).
Cluster 3	animal experiment; animal model; animal tissue; chitosan; drug carrier; drug penetration; emulsion; ex vivo study; nanoemulsion; nanoparticle; particle size; zeta potential	This cluster provides information about drug penetration in nanoemulsions and nanoparticles in a matrix gel in ex vivo model.



**Figure 9.** Overlay visualization of all keywords using VOSviewer.



**Figure 10.** Each year trend topic using RStudio.

Alginate is a brown seaweed-derived anionic, hydrophilic polysaccharide. It is composed of -D-mannuronic acid linked to R-L-guluronic acid units. When sodium alginate comes into contact with the cornea, it can interact with cations, such as  $\text{Ca}^{2+}$ , in the tear film to form a gel (Jumelle et al. 2020). In addition, sodium alginate and gellan gum have been used in conjunction with sodium carboxymethylcellulose (NaCMC) to deliver gatifloxacin against bacterial keratitis in an infected rabbit model. Compared with conventional eye drops, in-situ gel was found to be more effective in treating keratitis (redness, lacrimal secretion, mucoid discharge, response to visual stimulus, and swelling of eyelids) (Kesavan et al. 2016). Surprisingly, a gellan gum (Gelrite) and alginate in-situ gel combination demonstrated a greater capacity to retain a drug on the corneal surface than either gellan gum or alginate in-situ gel alone (Liu et al. 2010). These findings suggest that combining ion-sensitive polymers can improve gelation properties, allowing increased precorneal drug retention on the corneal surface (Jumelle et al. 2020).

Poloxamer 407 (P407) and poloxamer 188 (P188) are the two most frequently used poloxamers in ocular drug delivery owing to their high-water solubility, clarity of aqueous solutions, concentration-dependent viscosity, shear-thinning behavior patterns of the aqueous phase, and safety of use in ocular tissues. The percentage of corneal surface damage in eyes treated with 20% w/w P407 solution was not significantly different from that in eyes treated with saline solution (Soliman et al. 2019). Gupta and Samanta (2010) conducted in-vivo ocular tolerance tests on forskolin-loaded poloxamer-based in-situ gels instilled into rabbit eyes. Inflammatory responses were scored using a modified Draize test, and no significant macroscopic or microscopic reactions were observed in the tested eyes when compared with the contralateral eyes in the same animal.

The active ingredients often used for research on nanoemulsion and/or in-situ gel drug delivery systems are fluconazole (five times in 2014), timolol maleate (five times in 2015), ofloxacin (seven times in 2015), and pilocarpine (five times in 2015), and levofloxacin (8 times,

2016). Concurrently, the types of diseases that are often discussed in the article are glaucoma (25 times, in 2019) and dry eye disease (9 times, in 2020).

Glaucoma was the most studied disease in 2019. It is the leading cause of blindness and it requires long-term therapy (Sall 2000; Silver 2000a; Bhalerao et al. 2020), while 12% of the cases are preventable. It is expected that nearly four million Americans and 80 million people worldwide will have the disease by 2020 (Reeder et al. 2008; Gooch et al. 2012; Mahboobian et al. 2021). Owing to tearing turnover and nasolacrimal drainage, topical dosage forms of drug solutions and suspensions available for the treatment of glaucoma are rapidly eliminated from the precorneal tract, resulting in a drug bioavailability of less than 10% of the administered dose (DeSantis 2000; Silver 2000b; Lester 2008; Bhalerao et al. 2020).

Topical preparations must be used more frequently to overcome drug elimination from the precorneal tract and to achieve desired therapeutic efficacy (Wu et al. 2013; Zhang et al. 2013; Bhalerao et al. 2020). Azopt 1% is an ophthalmic suspension of brinzolamide administered to glaucoma patients every 8–12 hours or 2–3 times per day to effectively control intraocular pressure (Talaie et al. 2020). Patient compliance problems arise due to the required frequency of administration. Furthermore, this formulation has been linked to several side effects, including blurred vision, ocular discomfort (foreign body sensation), blepharitis, and dry eye (Chockalingam et al. 2019; Bhalerao et al. 2020; Talaie et al. 2020).

The in-situ gel-loaded nanoemulsion preparation can be used as an adequate and better alternative preparation than commercial eye drops, and it has exhibited higher permeation with a sustained-release drug profile. It can provide a prolonged therapeutic effect and improve patient compliance due to its less-frequent application and safety. In addition, the in-situ gelling polymer retains the drug for a longer period in the eye because it is not easily washed off or dissolved by tears (Pathak et al. 2013; Morsi et al. 2017). Several studies on nano-ocular preparations with in-situ gel-loaded nanoemulsion delivery systems are shown in Table 12.

**Table 12.** Findings of ocular nanoemulsion *in situ* gel preparation.

Author	Title	Findings
(Ge et al. 2020)	Penetrating modified lutein nanoemulsion <i>in-situ</i> gel for the treatment of age-related macular degeneration	Eye retention of penetrating nanoemulsion gel was longer (> 60 minutes) than penetrating nanoemulsion (approximately 25 min)
(Morsi et al. 2017)	Nanoemulsion-based electrolyte triggered <i>in situ</i> gel for ocular delivery of acetazolamide	Acetazolamide nanoemulsion based <i>in situ</i> gelling formulations had higher therapeutic efficacy than Azopt eye drops where showed the highest therapeutic activity with $\text{AUC}_{0-10}$ ( $189.15 \pm 10.18\% \cdot \text{h}$ ) higher than that of Azopt drops $\text{AUC}_{0-10}$ ( $82.51 \pm 7.53\% \cdot \text{h}$ )
(Patel et al. 2016)	Development of loteprednol etabonate-loaded (LE) cationic nanoemulsified <i>in-situ</i> ophthalmic gel for sustained delivery and enhanced ocular bioavailability	The mean $C_{\text{max}}$ values in nanoemulsion <i>in situ</i> gel higher (27.152 ng/ml) than marketed product (6.254 ng/ml) The delay $T_{\text{max}}$ of nanoemulsion <i>in situ</i> gel were 4 h as well as the prolongation in the mean residence time than the marketed $T_{\text{max}}$ (0.50 h) The increase in the ocular bioavailability of LE Nanoemulsion <i>in situ</i> gel, judged from the $\text{AUC}_{(0-10)}$ 37.43 ng h/mL, 2.45 fold higher than marketed product (14.7 ng/mL)
(Tayel et al. 2013)	Promising ion-sensitive <i>in situ</i> ocular nanoemulsion gels of terbinafine hydrochloride: Design, <i>in vitro</i> characterization and <i>in vivo</i> estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits	Mean residence time from 2.264h for oily solution to 3.839 h for the <i>in situ</i> nanoemulsion gel

## Conclusion

According to the analyses of our bibliometric study, there were 298 articles on ocular preparations with drug delivery systems in the form of nanoemulsions and/or in-situ gels. The average annual publication of articles each year was 27. The number of articles tends to increase every year. The average number of citations for each article published was reasonably high (21 citations).

Based on the performance analysis, the total number of authors who participated in the research was 1205 from 39 countries. Many research collaborations have been established in the authors' countries, but the number of inter-country collaborations or multiple country publication (MCP) remained far below the number of single-country publication (SCP). Cairo University's Department of Pharmaceutics and Industrial Pharmacy was the most influential institution, with an average of 39 citations per publication with nine articles published. The "International Journal of Pharmaceutics" was the most influential journal of the 120 journals, with an H-index value of 17. Ali A was the author with the highest influence, with the highest H index of 8. This bibliometric performance analysis is expected to trigger research partnerships with prolific authors, institutions, and countries to conduct future ocular research and submit research articles to supporting journals.

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According to science mapping, Al Kahteb (2016) was the most referenced study. Co-citation analysis showed that Urtti's article (2006) was the most widely used reference with its solution for designing preparations with prolonged action and controlled drug release. These findings correlate with the keywords that appeared the most, namely, **controlled release**. Bibliographic coupling results: A total of 227 authors were chosen from at least two interconnected publications. Ali A was the most productive author with nine articles correlating with other authors. This bibliometric science mapping analysis is beneficial for researchers in designing and discussing potential future research that meets the clinical requirements of low toxicity and better ocular drug absorption.

However, there were a few limitations in our study: only those articles published in English during the 2011–2021 period were included, and the keyword selection was based on the knowledge of the literature, which can affect the number and diversity of articles.

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