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FORMULATION AND EVALUATION OF NANOEMULSION-BASED EYE DROPS TO ENHANCE THE BIOAVAILABILITY OF OPHTHALMIC DRUGS: A REVIEW

Annie Rahmatillah[1], Afnisyah Nurcahyati[1], Angelina da Costa Fernandes[2], Maria Margaretha Xan Xao[2]
[1]Universitas Duta Bangsa Surakarta, Jalan Ki Mangun Sarkoro Tegalmulyo, Nusukan, Banjarsari, Surakarta, Jawa Tengah 57135, Indonesia
[2]Instituto Superior Cristal, ISC Road Balide, Dili, Timor-Leste
*annie_rahmatillah@udb.ac.id

ABSTRACT
Eye drops are a common form of topical preparation used to treat ocular disorders such as conjunctivitis, glaucoma, and microbial infections. However, their effectiveness is often limited by low bioavailability due to rapid elimination by the tear fluid. To overcome this limitation, nanoemulsion technology has been developed, offering enhanced solubility, stability, and drug penetration into ocular tissues. This article presents a review of twenty scientific studies on the formulation and evaluation of nanoemulsion-based eye drop dosage form. The review findings indicate that the use of nanoemulsion technology, with appropriate selection of oil components, surfactants, and co-surfactants, as well as non-thermal formulation methods, significantly improves the efficacy and safety of topical ocular therapies. Evaluations include physicochemical parameters such as particle size, pH, viscosity, as well as stability and bioavailability tests. Moreover, several studies highlight the importance of patient education in optimising the effectiveness of eye drop use. Therefore, formulation innovation and user education are crucial for ensuring the safe and effective use of ophthalmic therapy.

Keywords: eye drop; bioavailability; drug delivery system; nanoemulsion; physicochemical evaluation

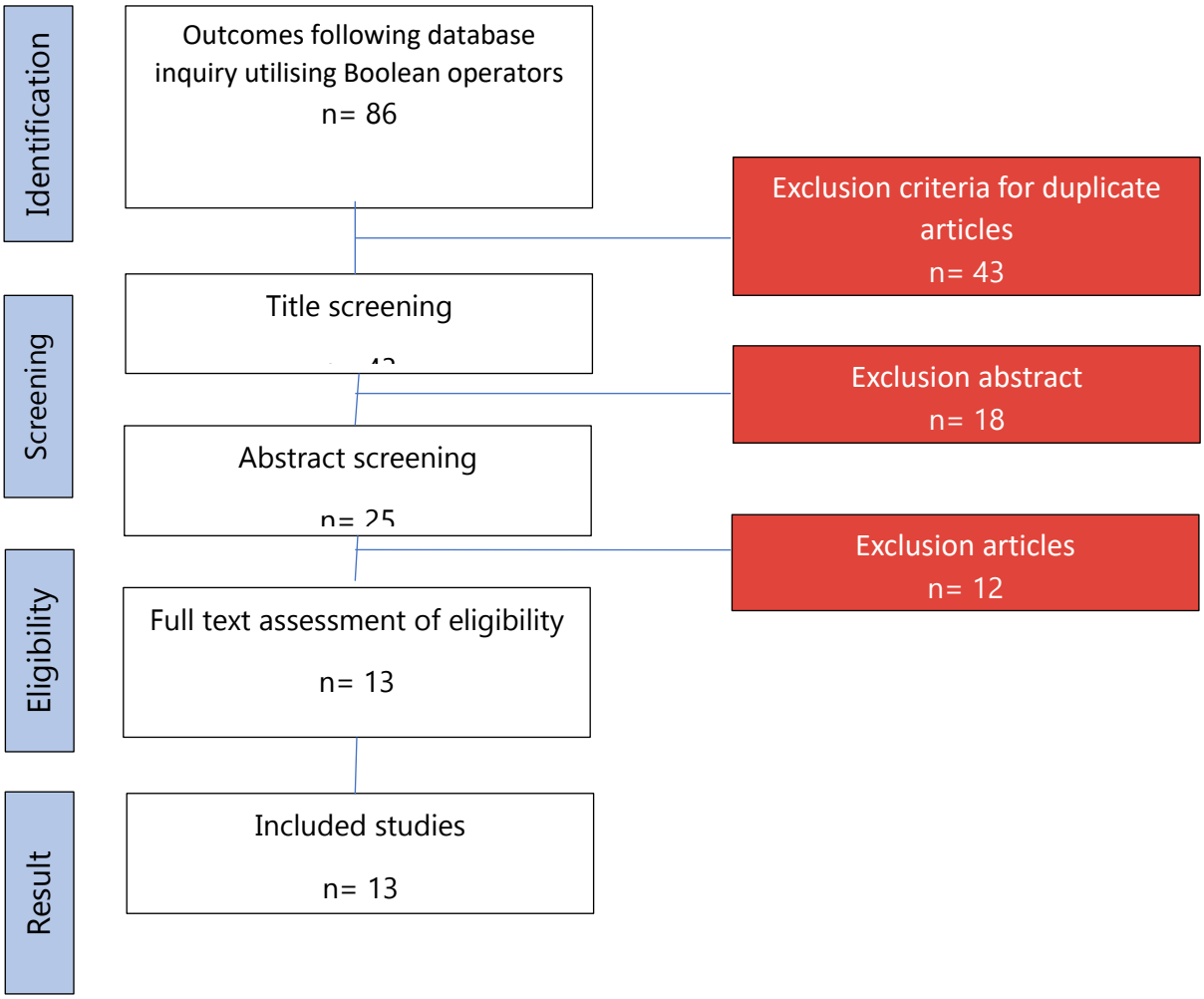
INTRODUCTION
Ocular conditions such as conjunctivitis, glaucoma, and microbial infections are prevalent health issues that necessitate effective and safe topical treatment. Ophthalmic solutions are the predominant dosage type in ocular therapy due to their straightforward administration and minimal systemic effects. The efficacy of eye drop therapy is frequently constrained by physiological aspects of the eye, including blinking, lacrimation, and tear flow, which swiftly remove medications from the ocular surface. These obstacles lead to diminished medication bioavailability, with typically only 1–5% of the injected dose reaching the intraocular space, resulting in inadequate clinical efficacy(Mofidfar et al., 2021). Diverse pharmaceutical technology methodologies have been devised to address these constraints, including hydrogel-based drug delivery systems, in situ gelling systems, and nanoparticle systems(Lin et al., 2025).

The nanoemulsion system has garnered significant attention for its capacity to enhance drug solubility, stability, and penetration into the cornea and other ocular tissues (Preeti et al., 2023). Nanoemulsions are colloidal dispersion systems comprising two immiscible phases (often oil in water or vice versa) with particle sizes between 20–200 nm, stabilized by surfactants(Mushtaq et al., 2023). As a drug delivery device, they enhance the therapeutic efficacy and mitigate the unwanted effects and toxic reactions of the delivered medicine (Dhahir, Al-Nima, & Al-Bazzaz, 2021). Research conducted by Daull, Garrigue, Liang, & Baudouin (2023) demonstrated that latanoprost nanoemulsions enhanced penetration and extended contact duration with the ocular surface, leading to a more pronounced decrease in intraocular pressure. Nevertheless, the majority of studies continue to focus on specific active compounds and formulations containing particular oil or surfactant components. This article introduces innovations in determining the ideal blend of oil, surfactant, and cosurfactant, along with a formulation approach utilizing low-energy emulsification techniques to prevent the degradation of heat-sensitive active ingredients. This study provides a comprehensive evaluation encompassing particle size, viscosity, pH, refractive index, stability, and in vitro permeation, aspects that have not been extensively reported in

prior similar research. This study also addresses the design and evaluation of a nanoemulsion-based eye drop formulation aimed at enhancing the bioavailability of ophthalmic drugs while maintaining stability and user comfort. The objective of this study is to develop and assess nanoemulsion-based eye drop formulations that exhibit optimal physicochemical and biopharmaceutical characteristics as a more effective and innovative alternative for topical eye therapy.

METHOD

This study employs the Systematic Literature Review (SLR) method to systematically identify, evaluate, and synthesize pertinent research findings related to the formulation and assessment of nanoemulsion-based eye drops aimed at enhancing the bioavailability of ophthalmic drugs. Data sources were acquired from multiple national and international scientific databases, including ScienceDirect, PubMed, Scopus, SpringerLink, Google Scholar, and DOAJ. The search utilized keywords such as "nanoemulsion eye drops," "ophthalmic drug delivery," "formulation and evaluation of ophthalmic nanoemulsion," "bioavailability," and "ocular drug delivery system," which were systematically combined using Boolean operators (AND/OR).



This review includes articles that meet specific inclusion criteria: original research published between 2017-2025, focusing on the formulation and/or evaluation of nanoemulsion-based eye drop preparations. The articles contain evaluation data, including bioavailability, particle size, physical stability, and

pharmacological efficacy, and are available in both English and Indonesian, with full-text access. Articles classified as reviews, opinion pieces, editorials, or those unrelated to the topic and lacking formulation evaluation data were excluded from the analysis. The selection process comprised three stages: screening of titles and abstracts, full-text review, and assessment of methodological quality. Out of the 86 identified articles, screening was performed based on the established criteria, resulting in 13 articles deemed eligible for analysis. The data from each article were systematically extracted into a table that encompassed the researcher's name, year of publication, active ingredient, nanoemulsion composition (including oil phase, surfactant, and cosurfactant), formulation method, evaluation method, bioavailability test results, and additional physicochemical parameters.

RESULT AND DISCUSSION

Table 1.
Article Analysis

No	Title of Article	Reference	Point of Result
1.	Nanoemulsion of Carrot Extract and Virgin Coconut Oil as Pro-Vitamin A Suplement to Prevent Vitamin A Deficiency	(Puspitasari, Rahmawati, Putri, & Fajar, 2022)	A high-quality nanoemulsion supplement was derived from HLB (hydrophylic-lipophylic balance) 10.3A, exhibiting a globule diameter of 65.9 nm, a polydispersity index of 0.311, a pH of 7.03, a turbidity of 0.46 cm-1, a viscosity of 2.4 cP, a beta-carotene concentration of 926.89 µg/100 g, and a potassium mineral content of 0.058 µg/L. Consequently, the resultant pro-vitamin A supplement possesses the capacity to avert vitamin A deficiency (VAD).
2.	Formulation Development and Evaluation of the Therapeutic Efficacy of Brinzolamide Containing Nanoemulsions	(Mahboobian, Seyfoddinb, Rupenthalc, Aboofazeli, & Foroutan, 2017)	The therapeutic efficacy of these formulations was evaluated by monitoring intraocular pressure following the instillation of the produced NEs in normotensive albino rabbit eyes.
3.	Formulation and evaluation of the effects of ophthalmic nanoemulsion of Nigella sativa seed extract on atropine-induced dry eye in mice	(Meshksar, Hadipour Jahromy, Qomi, Sami, & Faali, 2024)	The study shown that Nigella sativa seed extract nanoemulsion may positively influence tear production in atropine-induced dry eyes. Consequently, the utilization of this nanoemulsion warrants consideration in the management of dry eye.
4.	Achyranthis radix Extract-Loaded Eye Drop Formulation Development and Novel Evaluation Method for Dry Eye Treatment	(Kim et al., 2020)	Hyaluronic acid demonstrated a favourable impact on the formulation of eye drops utilising Achyranthis radix extracts for the treatment of dry eye condition.
5.	Effectiveness of cyclosporine nanoemulsion eye drops in patients with mild-to-moderate dry eyes: objective and subjective evaluation	(Moon et al., 2024)	the Schirmer I test showed no statistically significant change until week 12. Using the Symptom Assessment in Dry Eye (SANDE) score, both groups gradually showed significant improvement compared with baseline values. However, the Dry Eye-Related Quality-of-life Score Questionnaire (DEQS) showed no statistically significant change during the treatment period.
6.	Formulation and evaluation of ocular self-nanoemulsifying drug delivery system of brimonidine tartrate	(Vikash et al., 2023)	The improved SNEDDS with BRT exhibited exceptional stability during the storage period. The apparent permeability coefficient of the optimized SNEDDS was determined to be (7.078 ± 0.218 × 10−6 cm/s), in contrast to the marketed formulation, which exhibited (3.127 ± 0.173 × 10−6 cm/s).
7.	Comparing two mucin secretagogues for the treatment of dry eye disease: a prospective randomized crossover trial	(Jin, Seo, & Kim, 2024)	An elevation in Schirmer test scores was noted solely following rebamipide administration ($p = 0.007$). No substantial alterations were observed in tear osmolarity, MMP-9, and LLT subsequent to both treatments. Patients exhibited a marginally higher preference for diquafosol (46.4%) compared to rebamipide

No	Title of Article	Reference	Point of Result
			(36.7%), likely attributable to the bitter taste of rebamipide. The self-efficacy of both medications and overall satisfaction ratings were analogous. The results demonstrate that two mucin secretagogues shown similar efficacy in alleviating symptoms and enhancing indicators (TBUT, corneal and conjunctival staining) in individuals with DED.
8.	Experimental design, formulation and in vivo evaluation of a novel topical in situ gel system to treat ocular infections	(Nair et al., 2021)	in situ gel system (MH7) could offers a more effective and extended ophthalmic therapy of moxifloxacin in ocular infections when compared to conventional eye drops.
9.	Development of self-emulsifying oils for ophthalmic delivery of antibiotics instable in water	(Krzemińska & Sznitowska, 2023)	The developed formulations proved to be physically and chemically stable upon storage and are feasible to serve as the effective carriers for water-sensitive drugs.
10.	Ocular Distribution of Papaverine Using Non-aqueous Vehicles	(Agarwal, Behera, & Rupenthal, 2021)	This study demonstrated how diethyl glycol monoethyl ether (DGME) affects papaverine accumulation and distribution in the eyes.
11.	Suspensions of antibiotics in self-emulsifying oils as a novel approach to formulate eye drops with substances which undergo hydrolysis in aqueous environment	(Krzeminska, Sznitowska, Wroblewska, Wolska, & Winnicka, 2024)	SEO can be used as a novel carrier for the active substances which may not require improved solubility or absorption but need to be protected from moisture. This is a formulation that can be produced on industrial scale, with no limitation of stability or drug concentration.
12	Glycopeptide antibiotic drug stability in aqueous solution	(Jakaria, Budil, & Murtagh, 2022)	Enhancing the stability of heat-resistant glycopeptide pharmaceuticals in aqueous solutions by elucidating the degradation mechanisms of this therapeutic class, hence facilitating their accessibility in developing nations lacking cold chain infrastructure.
13	Olive leaf extract-based eye drop formulations for corneal wound healing	(Migone et al., 2025)	QA-Ch-MCD functions as an excipient that improves the therapeutic efficacy of OLE-GS, suggesting a viable strategy in ocular drug delivery systems for corneal wound healing.

The findings of a systematic review encompassing thirteen articles, as shown in Table 1, demonstrate that advancements in eye drop formulation are progressing swiftly, especially through contemporary pharmaceutical technologies including in situ gels, nanoemulsions, liposomal systems, and the incorporation of natural ingredients. Formulations of in situ gelling systems, as investigated by Nair et al. (2021), provide an advanced delivery mechanism that transitions from liquid to gel in the ocular environment, thus prolonging the drug's contact time with the target tissue. This significantly enhances bioavailability, moxifloxacin retention, and patient comfort, which are critical challenges in topical ophthalmic medicine. Articles authored by Migone et al. (2025) illustrate the significant potential of natural ingredients, such as olive leaf extract to enhance the therapeutic effects while improving the stability and efficacy of dry eye drops and those a viable strategy in ocular drug delivery system for corneal wound healing. This initiative aligns with the global trend of embracing herbal and lipid-based formulations as safer and more sustainable options in ocular care. Simultaneously, regarding the assessment and examination of preparation quality, several studies emphasize the importance of analytical techniques and physicochemical criteria in ensuring product safety and efficacy.

Research conducted by Mahboobian, Seyfoddinb, Rupenthalc, Aboofazeli, & Foroutan, (2017) explained that twelve formulations exhibiting the slowest release characteristics, as determined by initial release studies, were further analyzed for physicochemical properties including particle size, polydispersity index, pH, refractive index, osmolality, and viscosity. It indicated that physicochemical properties also

essential factors in the formulation and manufacturing of sterile preparations, including eye drops. The goal of the study that conducted by Krzeminska et al. (2024) was to create a new carrier that may be used to deliver medicines that are unstable in water to the eyes. This is the first study to demonstrate the potential of self-emulsifying oil (SEO) as a universal, easy-to-use, safe, and efficient carrier for the ocular administration of water-soluble antibiotics. The emulsion forms instantly after administration in vivo, and the antibiotic dissolves quickly. All papers examined in Table 1 substantially enhance comprehension of the formulation, assessment, and utilization of eye drop preparations from many scientific and practical viewpoints.

CONCLUSION

A systematic review of twenty articles concludes that the advancement of eye drop formulations is ongoing, utilizing technological approaches such as in situ gels, nanoemulsions, liposomes, and natural ingredients, which markedly enhance bioavailability, stability, and user comfort. The assessment of sterile preparations underscores the importance of thorough quality testing to ensure product safety, while educational initiatives have shown efficacy in increasing public awareness among eye drop users. The examined literature reveals significant advancements in the optimization of safe, efficacious, and practical topical ophthalmic treatments.

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