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REVIEW: ANTIBACTERIAL, ANTIFUNGAL AND WOUND HEALING ACTIVITY OF NANOEMULGEL FORMULATIONS AND PHYSICAL CHARACTERISTICS

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ABSTRACT

Nanoemulgel is an emulsion preparation with a droplet size of 1–100 nm suspended in a hydrogel. This review delves into the research on the impact of incorporating excipient components in nanoemulgel formulations to create products with specific physical attributes for different active ingredients with antifungal, antibacterial, and wound-healing properties. The research approach involves comparing articles on nanoemulgel preparation formulations with different combinations of active ingredients and excipients, as well as their pharmacological effects. Enhancing the level of active ingredients and altering the excipients can boost the effectiveness of nanoemulgel formulations in combating fungi, bacteria, and promoting wound healing. The review includes articles published within the past decade.

Keywords: Nanoemulgel, Pharmacological activity, Physical characteristics, Review

INTRODUCTION

The Nanoemulgel is a preparation that consists of an emulsion suspended in a hydrogel system, with particles ranging in size from 10–1000 nm (Reza, 2011). Nanoemulgel is a hybrid formulation that combines the properties of gel and emulsion for topical application on the skin. Nanoemulgel formulations are created by incorporating gelling agents into the aqueous phase, leading to modifications in the emulsion preparation. Nanoemulgel formulations address the limitations of emulsions by improving viscosity and spreadability for effective delivery of active ingredients (Eid et al., 2014).

The Nanoemulgel offers superior physical stability compared to traditional emulsion preparations because of its smaller particle size (<1000 nm) (Andini et al., 2023). Research by Singh *et al.* (2012), it was indicated that the size of particles can impact drug delivery by interacting with the skin barrier. Particles at the nanometer scale facilitate deeper skin penetration, leading to enhanced effectiveness (Chellapa et al., 2015). The excipient components in nanoemulgel formulas are crucial for enhancing the penetration and activity of active substances (Imanto et al., 2019).

The Nanoemulgel formula is composed of an active substance, oil, surfactant, cosurfactant, gelling agent, enhancer, and aqueous phase (Harshitha *et al.*, 2020). The diverse applications and different levels of active components and additives in nanoemulgel formulations may impact their physical properties and pharmacological effects (Mandal & Vishvakarma, 2023). So it is crucial to create efficient nanoemulgel dosage forms by incorporating active ingredients and suitable excipients to enhance physical properties and boost effectiveness. This review article was written to investigate how different components of nanoemulgel materials impact their effectiveness in treating fungal and bacterial infections as well as promoting wound healing.

RESEARCH METHOD

This review paper employs a literature review methodology based on research publications available online. Research articles searched by using keywords "Formula," "Nanoemulgel", "Characteristic", "Antibacterial", "Antifungal" and "Wound-healing" in ScienceDirect, Google Scholar, PubMed, and Semantic Scholar databases. Twenty articles were collected to review the physical features and pharmacological activity of nanoemulgel formulations, as the primary focus of this review study.

Tools and Materials

The search for research articles was conducted through ScienceDirect, Google Scholar, PubMed, and Semantic Scholar databases. The article was prepared using the auxiliary applications Publish or Perish and Mendeley.

Article Selection Criteria

This review includes research articles published between 2013 and 2023 that focus on the physical characteristics and antibacterial, antifungal, and wound-healing activities of nanoemulgel formulations containing different active pharmaceutical substances. The articles must be original and written in either Indonesian or English. The exclusion criteria for this evaluation include research studies in the form of a literature review, systematic review, meta-analysis, and research articles that are not available in full text.

Research Procedure

Four methodologies were employed in preparing this review. Initially, searches were carried out on the Google Scholar database, PubMed, and through manual searching with modified keywords. Secondly, the names of papers that aligned with the review's aims were evaluated. Thirdly, relevance screening is conducted based on the objectives of the review using the article abstracts collected. Fourth, obtain the free full text of the article relevancy screening findings. If unavailable, search for the full-text article (pdf) on Google. Figure 1 shows the search result.

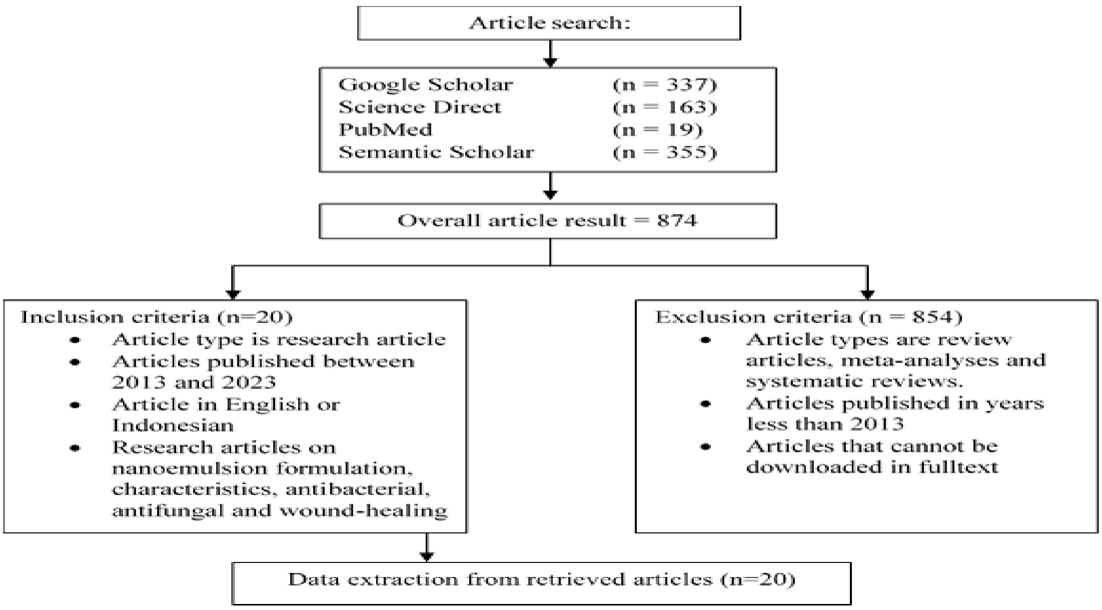

Figure 1. Process diagram of the literature search

RESULTS AND DISCUSSION

Review articles were conducted on 20 research articles focusing on the physical characteristics and activities of nanoemulgel formulations containing different active pharmaceutical substances. The following are the review results of the articles attached in

Different physical features can be achieved by producing nanoemulgel formulations with diverse active ingredients and excipients. The components of nanoemulgel formulations include oils, surfactants, cosurfactants, gelling agents, enhancers, and the water phase. Excipients in nanoemulgel formulations play a crucial role in determining the desired physical properties (Jivani et al., 2018; Sharma et al., 2023). The nanoemulgel preparation formula is evaluated for physical parameters such as pH, spreadability, adhesion, viscosity, particle size, and polydispersity index (PDI) (Harshitha et al., 2020).

The pH value obtained falls within the range suitable for topical treatments, which is between 4,5 and 8 (Setiawati et al., 2021). Testing the pH of the preparation is done to verify its safety and non-irritating properties when applied to the skin. The pH value of a preparation can be influenced by the kind and concentration of the active component. Pratiwi et al. (2023) found that increasing the content of *Phaleria macrocarpa* leaf extract led to a decrease in the pH of the preparation. Based on research by Imanto et al. (2019) found that as the quantity of the active substance increases, the pH value of the preparation decreases due to the acidity or basicity of the active substance, preservatives, temperature, and other substances.

The spreadability results meet the 5–7 cm standards (Suwarmi et al., 2022). Spreadability measurement assesses the capacity of nanoemulgel formulations to spread on the skin. The gelling agent is the main component influencing the dispersion of nanoemulgel. Increasing the concentration of the gelling agent results in a higher consistency of the preparation, leading to less spreadability. Gelling agents commonly mentioned in literature research include CMC Na, Carbopol 940, and HPMC (Hidayati et al., 2022; Saryanti et al., 2022). The adhesion result is greater than 1 second, indicating a high level of qualification. Adhesion testing assesses the nanoemulgel's ability to stick to the skin (Imanto et al., 2019). Gelling agents are factors that can influence the adhesive strength of the preparation. Increased concentration of gelling agent results in prolonged adhesion of the preparation to the skin (Saryanti et al., 2022; Suwarmi et al., 2022). The following characterisation pertains to the viscosity measurement of the preparation. The literature study revealed viscosity values ranging from 892 to 39300 centipoises. Viscosity values within the accepted range are 4000–40000 cPs (Indalifiany et al., 2021; Rahmatullah et al., 2020). Viscosity is a measurement that indicates the thickness of a fluid or liquid (Ratnapuri et al., 2019). The gelling agent can impact viscosity; increased concentration of the gelling agent leads to higher viscosity of the preparation. Augmenting the concentration of gelling chemicals can enhance the gel matrix and elevate the viscosity of the preparation (Ariani & Wulandari, 2021).

The following assessment pertains to particle size. Measuring particle size is a crucial factor in nanoemulgel formulations. Smaller particle sizes increase the contact area and the absorption of active chemicals into the skin, enhancing the desired impact. The literature review found that the particle size of nanoemulgel preparations ranged from 13,3 to 382,27 nm. The particle size measurements meet the specifications of 1–1000 nm (Reza, 2011). The nanometer-scale particle size is influenced by homogenization duration, stirring rate, and the presence of surfactants and cosurfactants in the formulation (Algahtani et al., 2021). The polydispersity index is nearly 0, indicating a high level of uniformity. A polydispersity index around 0 suggests an increase in particle size uniformity. The polydispersity index represents the variability in particle size inside a nanoemulgel, calculated as the standard deviation of the average particle size (Beandrade, 2018; Triani Olii et al., 2014).

Table I and Table II.

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Table I. Physical Properties of Nanoemulgel Formulation

Library	Active Substance	Excipient	Physical Characteristics					
			pH	Spreadability	Stickiness	Viscosity	Particle Size	PDI
(Pratiwi et al., 2023)	*Phaleria macrocarpa* leaf extract	1. Carbopol 940 2. TEA 3. Methyl paraben 4. Distilled water	5,02	-	-	1500 cPs	-	-
(Sanaji et al., 2019)	Ibuprofen	1.Carbopol/ Carbomer 940 2. PEG 400 3. VCO 4. Methyl paraben 5. Distilled water	6	-	3,15 ± 0,04	9173 cPs	123,6 nm	0,343
(Saryanti et al., 2022)	Sappan wood extract	1.Isopropyl myristate 2. PEG 400 3. Tween 80 4. CMC Na 5. Glycerin 6. Methyl paraben 7. Distilled water	6	20 ± 3,43 g.cm/s	3,96 ± 0,44	393,33 ± 11,55 dPas	-	-
(Dasawanti et al., 2022)	Clove leaf oil	1.Carbopol 940 2. PEG 400 3. Tween 80 4. TEA 5. Distilled water	6,25	-	-	3109 ± 7,54 M.Pas	13,3 nm	-
(Syahfitri et al., 2020)	Black cumin seed extract	1.Carbopol 940 2. Liquid paraffin 3. Tween 80 4. TEA 5. Sorbitol 6. Sodium carboxymethylcellul	-	-	-	3600 M.Pas	66,12 nm	-

		ose 7. Distilled water						
(Gadkari et al., 2019)	Tolnaftat	1. Almond oil 2. Propylene Glycol 3. Tween 80 4. BHT 5. Distilled water	6,60 ± 0,025	17,77 ± 0,025 g.cm/s	-	14960 cPs	100 nm	-
(Indalifiany et al., 2021)	*Petrosia Sp. sponge* extract	1.VCO 2. PEG 400 3. Tween 80 4. Carbopol 940 5. Methyl paraben 6. Glycerin 7. NaOH 8. Distilled water	5	5,7 cm	-	28000 cPs	23,9 nm	0,176
(Imanto et al., 2019)	Aloe vera powder	1.Carbopol 940 2. Chitosan 3. TEA 4. Ethanol 5. Methyl paraben 6. Acetic acid 7. NaOH 8. Distilled water	6	5 cm	5 seconds	326 dPaS	65,05 ± 13,49 nm	-
(Andini et al., 2023)	Black pepper fruit extract	1.Carbopol 940 2. TEA 3. Ethanol 4. Liquid paraffin 5. Tween 80 6. PEG 400 7. Methyl paraben	5,60 ± 0,01	6,42	-	5066 ± 61,28 cPs	59,37 nm	0,25

		8. Distilled water						
(Annaura et al., 2022)	Gambir extract	1.Carbomer/ carbopol 2. TEA 3. HPMC 4. Glycerin 5. BHT 6. Distilled water	6,23 ± 0,31	5,83 ± 0,15 (g.cm/sec)	7,33 ± 0,90 seconds	-	382,27 ± 72,28 nm	0,29 ± 0,14
(Hidayah et al., 2022)	Red algae extract	1.Coconut oil 2. Tween 80 3. HPMC 4. Glycerin 5. Propylene Glycol 6. Nipagin 7. Nipasol 8. Distilled water	-	-	-	-	24,3 nm	-
(Ermawati et al., 2020)	ZnO	1.Carbopol 940 2. TEA 3. Glycerin 4. Propylene Glycol 5. Nipagin 6. Distilled water	7,31 ± 0,04	5,4 cm	-	180 dPas	152,7 nm	0,58
(Jufri & Natalia, 2014)	Black cumin seed oil	1.Tween 80 2. Alcohol 3. Carbomer 940 4. Propylene Glycol 5. NaOH 6. Distilled water	6,6 5	-	-	4900 cPs	131,2 nm	-
(Hajrah et al., 2017)	Red pidada leaf extract	1.Carbopol 940 2. Viscolam MAC 10 3. Glycerin 4. Propylene Glycol 5. Distilled water	6,12 ± 0,07	-	-	3,10 ± 0,04 P.Sa	-	-

(Bashir et al., 2021)	Diflunisal	1.Eucalyptus Oil 2. Tween 80 3. Transcutol 4. Distilled water	6,14 ± 0,02	-	-	6268 ± 1,20 cPs	14,36 ± 0,10	-
(Algahtani et al., 2021)	Black cumin seed oil	1.Black cumin oil 2. Kolliphor 3. Transcutol 4. Distilled water	-	-	-	77,81 ± 1,55 dPas	48,45 ± 0,74 nm	0,052 ± 0,004
(Sultan et al., 2022)	Black cumin seed oil	1.Poly-ethylene Glycol 2. Methyl-cellulose 3. Distilled water	7,37	-	-	2343 cPs	342 ± 36,6 nm	-
(Viqhi et al., 2021)	Propolis extract	1.Carbopol 940 2.TEA 3.VCO 4.Oleic acid 5.Tween 80 6.Alcohol 7.Propylene Glycol 8.BHT 9.Distilled water	5,71 ± 0,03	5,77 ± 0,37	6–12 seconds	30266,7 ± 611,0 cPs	204,23 ± 11,61	-
(Ting et al., 2020)	Betel leaf oil	1.Carbopol 940 2.TEA 3.Tween 80 4.Soybean seed oil 5.Glycerol 6.Distilled water	6,60 ± 0,20	-	-	-	27,67 nm	-
(Hussain et al., 2016)	Amphotericin B	1.Carbopol 980 2.PEG 400 3.Propylene Glycol 4.Tween 80	7,4	-	-	892 ± 9,64 cPs	97,04 ± 7,4 nm	0,19± 0,01

5.Distilled water

Appropriate physical attributes will result in a high-quality nanoemulgel formulation. The pharmacological activity of nanoemulgel formulations was studied in addition to physical characterization in literature. The findings of the literature review are presented in Table II.

Table II. Nanoemulgel Formulations with Antibacterial, Antifungal, and Wound Healing Properties

Library	Active substance	Pharmacological Activity
(Dasawanti et al., 2022)	Clove leaf oil Excipients: 1. Carbopol 940 2. PEG 400 3. Tween 80 4. TEA 5. Propyl-paraben 6. Methyl-paraben 7. Distilled water	Increased concentration of the active ingredient results in stronger suppression of bacterial growth. The nanoemulgel formulations showed inhibitory zones of 18,96 ± 0,30 mm against *Staphylococcus epidermidis* and 18,03 ± 0,32 mm against *Propionibacterium acnes* bacteria.
(Syahfitri et al., 2020)	Black cumin seed extract Excipients: 1. Carbopol 940 2. Liquid paraffin 3. Tween 80 4. TEA 5. Sorbitol 6. Sodium carboxymethylcellulose 7. Distilled water	The rise in antibacterial effectiveness of nanoemulgel formulations containing black cumin seed extract correlates with the escalation in the active ingredient concentration. The nanoemulgel preparation exhibited inhibitory zones of (10,00±0.100; 8,43±0,153; 7,83±0,208) nm against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acne* germs, respectively.
(Gadkari et al., 2019)	Tolnaftat Excipients: 1. Almond oil 2. Propylene Glycol 3. Tween 80 4. Methyl-paraben 5. Propyl-paraben 6. BHT 7. Distilled water	The rise in antifungal effectiveness of Tolnaftate nanoemulgel formulation is directly related to the rise in almond oil concentration, which acts as a booster. The tolnaftat nanoemulgel preparation has antifungal properties against *Trichophyton rubrum*, resulting in an inhibitory zone measuring 24 mm.
(Hidayah et al., 2022)	Red algae extract Excipients: 1. Coconut oil 2. Tween 80 3. HPMC 4. Glycerin 5. Propylene Glycol 6. Nipagin 7. Nipasol 8. Distilled water	The nanoemulgel containing 5% red algae extract demonstrated superior wound healing activity by showing a higher number of fibroblast cells on day 5 in comparison to using only 5% red algae extract or gel basis.
(Ermawati et al., 2020)	ZnO Excipients: 1. Carbopol 940	ZnO nanoemulgel preparation functions as a sunscreen, demonstrated by its lower erythema score compared to the negative control and comparison group. A lower

	2. TEA 3. Glycerin 4. Propylene Glycol 5. Nipagin 6. Distilled water	erythema score suggests that the preparation is highly effective in shielding rat skin from radiation exposure. The erythema scores for the nanoemulgel formulation, comparator, and negative control were 1,74 ± 0,07 mm, 26,51 ± 0,26 mm, and 32,33 ± 0,14 mm, respectively.
(Jufri & Natalia, 2014)	Black cumin seed oil Excipients: 1. Tween 80 2. Alcohol 3. Carbomer 940 4. Propylene Glycol 5. NaOH 6. Distilled water	The enhanced antibacterial effect of black cumin seed oil nanoemulgel on *Staphylococcus aureus* bacteria correlates with the higher concentration of active compounds in the preparation. A notable difference ($p<0.01$) was seen in the antibacterial effectiveness of nanoemulgel formulations with 5, 10, and 20 µl of black cumin seed oil. The emulgel containing 20 µl of black cumin seed oil exhibited a bacterial suppression zone measuring 20,42 mm.
(Bashir et al., 2021)	Diflunisal Excipients: 1. Eucalyptus Oil 2. Tween 80 3. Transcutol 4. Distilled water	The anti-inflammatory and wound-healing effect of diflunisal nanoemulgel was enhanced using the formalin induction method, leading to a 75,20 ± 0,34% reduction in inflammation on the 13th day post-treatment.
(Algahtani et al., 2021)	Black cumin seed oil (thymoquinone) Excipients: 1. Black cumin oil *2. Kolliphor* 3. Transcutol 4. Distilled water	Thymoquinone nanoemulgel was prepared and shown wound healing effects in rats treated with Ketamine HCl. Thymoquinone nanoemulgel preparations enhanced wound healing activity, leading to quicker wound contraction and hastened healing compared to hydrogel preparations.
(Hidayah et al., 2022)	Red algae extract Excipients: 1. HPMC 4000 2. Glycerin 3. Ethanol 96% 4. Propylene glycol 5. Tween 80 6. Distilled water	Nanoemulgel of 5% red algae extract was most effective in increasing fibroblasts on day 5 of the traumatic ulcer healing process compared to 5% red algae extract gel, hyaluronic acid, and gel base.
(Tanjung et al., 2022)	*Artocarpus lakoocha* extract Excipients: 1. Carbopol 940 2. TEA 3. Tween 80 4. Isopropyl myristate 5. Propyl-paraben 6. Distilled water	This research demonstrates the wound-healing efficacy of nanoemulgels by adjusting *Artocarpus lakoocha* extract concentrations. In 14 days, there was a substantial increase in the percentage of wound diameter reduction and fibroblast cell value compared to the negative control ($p < 0,05$).

(Morsy et al., 2019)	Atorvastatin Excipients: 1. Carboxymethyl Cellulose 2. Tween 80 3. Liquid Paraffin 4. Propylene glycol 5. Distilled water	In vivo wound healing studies showed that Atorvastatin nanoemulgel exhibited the highest percent wound contraction. The histopathological evaluation revealed a significant enhancement in the histological structure of the skin following a 21 day therapy with Atorvastatin nanoemulgel.
(Sultan et al., 2022)	Black cumin seed oil Excipients: 1. Polyethylene Glycol 2. Methylcellulose 3. Distilled water	The antibacterial activity of black cumin seed oil nanoemulgel against *Staphylococcus aureus* bacteria was higher than that of black cumin seed oil. The nanoemulgel formulations exhibited a bacterial inhibition zone of 25 mm, while black cumin seed oil had a zone of 18 mm.
(Hussain et al., 2016)	Amphotericin B Excipients: 1. Carbopol 980 2. PEG 400 3. Propylene Glycol 4. Tween 80 5. Distilled wa ter	The enhanced antifungal effect of amphotericin B nanoemulgel formulations on *Candida albicans* correlates with the higher concentration of active ingredients in the formulation. The diameter of the inhibitory zone for the Amphotericin B nanoemulgel preparation was 4,3 ± 0,28 mm.

This review article discusses the pharmacological activity of nanoemulgel formulations, which include antifungal, antibacterial, and wound-healing properties. Studies in literature indicate that black cumin seed oil nanoemulgel preparations exhibit very strong antibacterial activity (>20 mm), whereas clove leaf oil nanoemulgel preparations show strong antibacterial activity (>10–20 mm) (Dasawanti *et al*., 2022; Jufri & Natalia, 2014; Sultan *et al*., 2022). Research by Gadkari *et al*. (2019) found that Tolnaftat is a potent antifungal agent against Trichophyton rubrum, exhibiting a 24 mm inhibitory zone, classified as very strong. Meanwhile, research by Algahtani *et al*. (2021) found that nanoemulgel preparations of black cumin seed oil have superior wound healing properties compared to hydrogel preparations.

The pharmacological effects of nanoemulgel formulations may vary based on the concentration of active ingredients and the choice of excipients in the formulation. The potency of the active ingredient impacts the pharmacological effects of the medication. Higher concentrations of the active substance lead to increased pharmacological activity, namely in terms of antifungal, antibacterial, and wound healing properties (Dasawanti *et al*., 2022; Jufri & Natalia, 2014). Utilizing excipients like surfactants can enhance the absorption of active compounds, thereby boosting pharmacological action. Surfactants included in nanoemulgel formulations include Transcutol, Tween 80, and Span 80. Nanoemulgel preparations containing surfactants work by disrupting the lipid bilayer in epithelial cells, leading to an increase in membrane permeability. Surfactants can disrupt the lipid bilayer by interacting with its polar region, altering the ionic and hydrophobic interactions, and incorporating their lipophilic molecules into the membrane to disrupt its integrity (Li et al., 2011). Tween 80, a surfactant, can hinder the removal of p-glycoprotein to enhance absorption. P-glycoprotein is a protein that can expel pharmaceuticals post-absorption and hinder cytochrome enzymes responsible for drug metabolism, hence enhancing the bioavailability of the active ingredient. Higher drug bioavailability leads to increased pharmacological activity (Avachat & Patel, 2015).

Nanoemulgel formulations containing nanoparticles with a nanoscale size have an increased contact surface area, which enhances interfacial interactions and speeds up the dissolution process (Mantena et al., 2015). Reducing particle size to nanometers can enhance the permeation of active substances and elevate medication concentrations at the desired location (Akhter *et al*., 2008; Syamala U., 2013). Utilizing enhancers in the formula can alter the stratum corneum's structure to facilitate the penetration of the active component. Enhancers found in nanoemulgel formulations include Transcutol, isopropyl myristate, and vegetable oils (Abd *et al*., 2016; Mandal & Vishvakarma, 2023).

CONCLUSION

Nanoemulgel is an emulsion preparation suspended in a hydrogel system with particle sizes <1000 nm. Formulation of nanoemulgels with different ingredient components results in variations in the preparation's physical characteristics and pharmacological activity. Increasing the concentration of active substances and varying excipients can improve the antifungal, antibacterial, and wound-healing activities of nanoemulgel preparations.

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