

Thymoquinone-Based Nanoemulgel for Enhanced Topical Delivery: Recent Advances and Therapeutic Potential

Aayush Rajput¹, Anshika Sharma², Nitanshu³, Nitish Kumar⁴, Chavi Mittal⁵

^{1,2,3,4}Research Scholar, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Naugaon, Dehradun, Uttarakhand, India

⁵Assistant Professor, School of Pharmacy and Research Dev Bhoomi, Uttarakhand University, Dehradun Uttarakhand 248007 India.

Corresponding Author: Chavi Mittal

E-mail: Chaviagggarwal2@gmail.com

ABSTRACT

Thymoquinone (TQ), the principal bioactive quinone associated with *Nigella sativa*, has attracted considerable attention because of its anti-inflammatory, antioxidant, antimicrobial, immunomodulatory and wound-healing activities. Its translation into topical products is, however, constrained by poor aqueous solubility, lipophilicity, photosensitivity, chemical instability and limited penetration across the stratum corneum. Nanotechnology-based topical systems have therefore been investigated to improve TQ solubilization, protection, release and skin deposition. Among these approaches, nanoemulgels are particularly attractive because they combine the high drug-solubilizing capacity and interfacial area of nanoemulsions with the viscosity, spreadability and residence time of a gel. This narrative review discusses the physicochemical and biopharmaceutical challenges of TQ, the rationale for topical nanoemulsion and nanoemulgel delivery, selection of oils, surfactants, co-surfactants and gelling polymers, formulation approaches, and critical characterization parameters including droplet size, polydispersity index, zeta potential, rheology, drug content, release, skin permeation and stability. Published topical TQ systems including nanoemulgels, liposomes, ethosomes, lipospheres, nanostructured lipid carriers and hybrid vesicles are critically compared. Available evidence consistently indicates improved solubilization, sustained release and enhanced dermal delivery relative to conventional TQ preparations; nevertheless, the field remains dominated by in-vitro, ex-vivo and animal studies. Standardized formulation protocols, robust stability programs, validated skin permeation models and human clinical evidence are major gaps that should be addressed before topical TQ nanoemulgels can progress toward clinical translation.

Keywords: Thymoquinone; *Nigella sativa*; nanoemulsion; nanoemulgel; topical drug delivery; skin permeation; Carbopol; nanocarrier

How to cite this article: Aayush Rajput. Thymoquinone-Based Nanoemulgel for Enhanced Topical Delivery: Recent Advances and Therapeutic Potential. *Int J Drug Deliv Technol.* 2026;16(81s):1056-1064. DOI: 10.25258/ijddt.16.81s.135.

INTRODUCTION

Thymoquinone (TQ; 2-isopropyl-5-methyl-1,4-benzoquinone) is a major pharmacologically active constituent of the volatile fraction of *Nigella sativa* seeds. A broad preclinical literature attributes antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, anticancer and tissue-protective actions to TQ [18-29]. These activities make it relevant to dermatological problems in which oxidative stress, inflammation, microbial burden and impaired barrier repair coexist. The pharmaceutical development of TQ is considerably more difficult than its pharmacological profile might suggest. TQ is lipophilic, poorly water-soluble and susceptible to degradation under unfavorable environmental conditions. Its poor biopharmaceutical properties have repeatedly been identified as barriers to reproducible exposure and clinical translation

[18-24]. Topical administration is attractive because it may provide high local drug concentration while minimizing systemic exposure; however, the stratum corneum is itself a formidable barrier to drug penetration [30-36]. Nano formulation has emerged as one strategy to bridge this gap. A range of TQ nanocarriers, including polymeric nanoparticles, nano structured lipid carriers, liposomes, ethosomes, lipospheres, hybrid vesicles and nano emulsions, have been investigated [1-14, 18-20]. Nanoemulgels are particularly relevant to lipophilic drugs because the drug can be maintained in a solubilized oil phase while the final semisolid dosage form remains convenient for topical application [15-17].

The purpose of this review is to integrate the available evidence specifically around TQ topical delivery and nanoemulgel development, with emphasis on formulation design, characterization, therapeutic evidence,

limitations and future research priorities

This article was prepared as a narrative review. Literature relevant to thymoquinone, *Nigella sativa*, topical delivery, nanoemulsion, nanoemulgel, liposomes, ethosomes, lipid vesicles, nanostructured lipid carriers, skin permeation and formulation characterization was identified from PubMed/PubMed Central and publisher databases, with emphasis on peer-reviewed research and review articles. Foundational drug-delivery references were included where they remain important for interpretation of skin transport, colloidal characterization, rheology and release testing. Recent TQ topical-nanocarrier studies were given greater weight in the critical comparison. This review is not presented as a PRISMA systematic review and does not claim exhaustive capture of every publication.

NANO EMULSION AND NANO EMULGEL

Nano emulsion

Nanoemulsions are kinetically stable dispersions with droplets typically in the submicron range. They differ from thermodynamically stable microemulsions and must not be defined solely by a single size cut-off [37-41]. Their pharmaceutical advantages include high loading of lipophilic drugs, large interfacial area, optical clarity in some compositions, and compatibility with multiple routes of administration.

Nanoemulgel

A nano emulgel is produced by incorporating a nanoemulsion into a gel matrix [15-17]. This hybrid design addresses one of the practical weaknesses of liquid nanoemulsions: low viscosity and short residence on the skin. The gel network can improve spreadability, non-greasy feel, local retention and dosing convenience while preserving the dispersed nano droplet system. For a poorly water-soluble compound such as TQ, this design is especially logical because the drug remains associated with a solubilizing oil phase while the final product has the handling properties expected of a topical semisolid.

Figure 1. Schematic architecture of thymoquinone - loaded nano emulgel.

2. THYMOQUINONE: SOURCE, CHEMISTRY AND PHARMACEUTICAL RELEVANCE

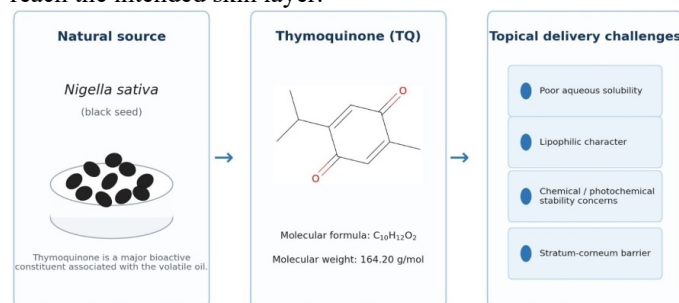
Source and chemical nature

TQ is a quinone-derived lipophilic molecule associated with the volatile oil of *Nigella*

sativa. The seed and its constituents have a long history of medicinal use, but modern pharmaceutical research has focused on TQ as one of the best-characterized active constituents [21-29]. The molecule's hydrophobicity favors partitioning into lipid environments, which is useful for incorporation into oils, lipid vesicles and other nanocarrier systems but problematic for aqueous dosage forms.

Pharmacological properties relevant to skin

Topical interest in TQ is driven mainly by anti-inflammatory, antioxidant, antimicrobial and immunomodulatory activity [18,21-24]. These actions are relevant to inflammatory dermatoses, acne, psoriasis, wounds and other skin conditions in which inflammatory mediators, oxidative stress and impaired barrier repair contribute to pathology. Importantly, promising pharmacology alone does not establish topical efficacy; sufficient drug must remain stable in the product, be released from the vehicle and reach the intended skin layer.



Bio pharmaceutical allimitations

Poor aqueous solubility, chemical and photochemical instability, and sub optimal bioavailability are recurrent limitations in the TQ literature [18-24]. For topical delivery, low water solubility can restrict

Figure 2. Source, chemical structure, and major challenges associated with the topical delivery of thymoquinone.

formulation options, while excessive affinity for the oil phase can also slow release if the vehicle is not appropriately designed. The formulation must therefore balance solubilization and thermodynamic driving force for partitioning into skin.

3. THE SKIN BARRIER AND CHALLENGES IN TOPICAL TQ DELIVERY

The outer stratum corneum is the principal resistance to per cutaneous transport [32-36]. Drug entry can occur through inter cellular

lipid pathways, transcellular route and appendageal structures such as hair follicles. Molecular size, lipophilicity, ionization, vehicle composition, skin hydration and the presence of penetration enhancers influence the amount of drug reaching deeper skin layers [30-36].

For TQ, topical formulation is a balancing problem. The drug needs adequate solubilization to prevent precipitation, but it must also partition out of the vehicle. Penetration-enhancing excipients such as fatty acids, glycols and selected surfactants can alter skin lipids or drug activity in the vehicle [14,32]. Nano emulsions provide a large interfacial area and can carry TQ in a lipid phase that is dispersed through water, while a gel network can improve residence time and patient handling.

4. FORMULATION COMPONENTS FOR TQ NANO EMULGEL

Oil phase

The oil phase is selected primarily on the basis of TQ solubility, safety for dermal use and ability to form a stable nano emulsion. Published TQ systems have employed black seed/ kalonji oil, oleic-acid-containing systems, Labrafil M2125 and other lipidic excipients [1-4,10]. Black seed oil is conceptually attractive because it is the natural matrix associated with TQ and may improve loading; however, batch variability and oxidation stability should be considered.

Surfactant

Nonionic surfactants such as poly sorbates are frequently used in topical nanoemulsions because of favorable emulsification properties and generally better tolerability than strongly ionic surfactants. Tween 80 appears repeatedly in TQ nanoformulation studies [1,3,4,11]. The minimum effective surfactant concentration should be targeted because excessive surfactant may increase irritation risk and alter drug release.

Co-surfactant

Co-surfactants such as Transcutol P, glycols or similar amphiphilic solvents can reduce interfacial tension, improve flexibility of the interfacial film and enlarge the nano emulsion region. Khan et al. Used Tween 80/ Transcutol – P with Kalonji oil in a TQ nano emulsion system [3]. The surfactant-to-co-surfactant ratio (S_{mix}) is commonly optimized rather than fixed empirically.

Gelling polymer

Carbomers, particularly Carbopol 934 and

940, are widely used in nano emulgels because they provide high viscosity at relatively low polymer concentration and can form clear gels after neutralization [1-4,44,45]. Their rheological behavior is sensitive to pH, electrolyte content, surfactant load and neutralization degree. Therefore, the gel base should be optimized together with the nano emulsion rather than treated as an independent final step.

5. FORMULATION APPROACHES

Low-energy methods

Low-energy emulsification methods exploit formulation composition and phase behavior. Aqueous micro titration and phase inversion approaches can form small droplets without intensive equipment when the oil/surfactant/co-surfactant ratios are favorable. Pseudo-ternary phase diagrams can be used to identify nano emulsion regions [15-17,37-41].

High-energy methods

High-energy techniques such as probe ultra sonication reduce droplet size through disruptive mechanical forces. Algahtani et al. showed that ultra sonication time significantly affected droplet size and PDI in TQ nano emulsions [1]. Khan et al. similarly employed ultra sonication and design-of-experiments optimization [3]. High-energy processing offers strong size control but can introduce heat, metal shedding from probes and degradation risks if not properly controlled.

Design of experiments

Factorial and response-surface approaches such as Box-Behnken design are increasingly used to quantify the effects of oil, surfactant/co-surfactant and process variables on particle size, PDI, entrapment and release [3,6,11]. This is more informative than one-factor-at-a-time experimentation and can reduce unnecessary batch numbers.

6. CRITICAL CHARACTERIZATION OF TQ NANO EMUL GEL

Droplet size and PDI

Dynamic light scattering (DLS) is the most common technique for measuring hydrodynamic droplet diameter and PDI [42,43]. PDI should be interpreted with size and raw distribution rather than used as a stand-alone quality label. Dilution medium, viscosity, scattering intensity and the presence of dust can substantially affect results.

Zeta potential

Zeta potential provides information about

electro kinetic surface behavior and may help explain colloidal stability, but a universal absolute-potential threshold should not be used mechanically, especially in sterically stabilized nonionic surfactant systems [42,43].

pH, rheology and spreadability

Atopical nanoemulgel should have a pH compatible with skin and exhibit rheological properties that allow extrusion from a container, easy spreading under shear and sufficient viscosity at rest [44,45]. Pseudo plastic and thixotropic behavior is often desirable because the formulation becomes less viscous during application and recovers after spreading.

Drug content and content uniformity

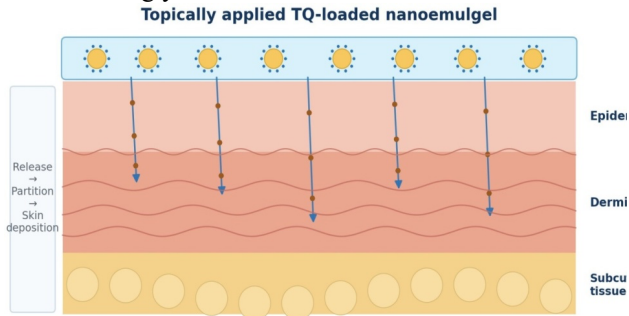
Drug-content analysis confirms that TQ is present at the intended dose and is uniformly distributed. The analytical method must be selective for TQ in the presence of oil, surfactant, polymer and degradation products.

In-vitro release

Franz diffusion cells are commonly used to compare drug release from topical semisolids [46,47]. When a synthetic membrane is used, the experiment primarily assesses release from the formulation; it should not be described as skin permeation. The receptor medium must maintain sink conditions and TQ stability.

Ex-vivo skin permeation and deposition

Ex-vivo skin studies can measure flux, cumulative permeation and drug retained in skin layers, providing strong evidence of topical delivery than synthetic-membrane release alone [14,30,31,33,46,47]. However, skin source, thickness, integrity, storage, receptor composition and extraction recovery can strongly affect the result.



Conceptual pathway: skin delivery depends on formulation composition, drug release and partitioning.

Figure 3. Conceptual pathway of thymoquinone release, skin partitioning, penetration, and deposition following topical application of nanoemulgel.

Release kinetics

Zero-order, first-order, Higuchi and Korsmeyer-

Peppas models are often fitted to released data [48-50]. Model fitting should be used descriptively and should not substitute for mechanistic evidence.

Stability

Physical and chemical stability is particularly important for TQ because of its sensitivity to environmental conditions. Appearance, phase separation, pH, viscosity, drug content, size and PDI are useful monitoring parameters. Formal shelf-life claims require appropriately designed stability studies rather than short academic observations [51].

7. PUBLISHED TOPICAL TQ NANO CARRIERS: CRITICAL COMPARISON

Study	Carrier	Key formulation feature	Approx. nanoscale finding	Evaluation	Main relevance
Algahtani et al., 2021 [1]	Nanoemulgel	Black seed oil; high-energy ultrasonication; gel conversion	Droplets <100 nm reported for optimized nanoemulsion	Rheology, skin penetration/deposition, wound model	Direct proof-of-concept for TQ nanoemulgel
Khan et al., 2022	TQ nanoemulgel	Kalonji oil + Tween 80 + Transcutol	~100 nm	SEM/TEM, FTIR/DRS, release, permeation	Strong formulation/optimization results

022 [3]	an o e m u l g e l c o m b i n a t i o n	l-P;Box- Behnke noptimi zation	orp hol ogy rep orte d		ference
An ura dha etal., 20 24[2]	Nanoe mulgel	Essentia l-oil- basedna noemul sion;Ca rbopol9 34	Na no sca le,l ow - PD Isy ste mr ep ort ed	Release, ex- vivoper meation, diabetic woundm odel	Recent direct TQnano emulgel evidenc e
Ala mo udi etal., 20 25[4]	Nanoe mulsio ngel	Labrafil M2125 +Tween 80 + Plurol Oleique; Carbopo 1934	NE~1 52nm; gel~1 72nm	Rheology , release, skinperm eation/der matokinet ics	Recen tcomp arative topica lstudy
Kau sare tal., 201 9[6]	Ethoso mes	Box- Behnke noptimi zedpho spholipi d/ethan olvesicl es	~105nm vesicles	Flux,co nfocalpe netration ,acne/inf lammatio nmodel s	S up po rts de ep sk in de li ve ry

					of T Q
Neg ieta 1,2 019 [7]	Ethoso malhy drogel	Flexi bleph ospho lipidv esicle s in hydro gel	Nanosiz edvesicl es	Skinret entiona ndanti- psoriati cmodel	Shows benefit ofvesic le-to- gelstra tegy
Jain etal., 20 17[8]	Liposp heres	Lipi d- bas edt opi caln ano carr ier	<70nm	Skin penetrat ion, slowrel ease,ps oriasis model	Strong precli nicalp soriasis sevide nce
Mo staf aeta 1,2 018 [5]	Liposo mes	Optimize dTQlipos omesfor topical use	Nanosca lelipos omes	Skinperm eationand anti- inflamma toryactivi ty	Supp ortsv esicu larT Qtopi calde live ry
Ala met al., 202 3[1 1]	NLC nanoge l	Tacr olim us+T Qco- loade dNLC s	~145nm ;PDI~0. 16	24- hrelea se,con focalp enetrat ion,ps oriasis studies	Demo nstrate scomb inatio nnano gelstra tegy
Pat hak etal., 20 25[12]	Ethoso malhy drogel	TQ- loaded nanosi zedeth osomes inCarb opol- typehy drogel	Nanosiz edethos omes	Release, ex-vivo permeati on, skin retention ,antimicr obial	Recen ttopic alanti micro bialevid ence

8. WHAT THE EVIDENCE COLLECTIVELY SHOWS

Across different carrier platforms, a consistent pattern is visible. Encapsulation of TQ within lipidic or nanoemulsion systems improves its pharmaceutical handling by keeping it in a solubilized state and protecting it from direct exposure to aqueous environments. Topical systems repeatedly report sustained release,

greater skin retention or deeper penetration, and improved pharmacodynamic activity compared with simple TQ dispersions or conventional gels [1-14].

The strongest evidence for the specific nanoemulgel concept comes from the direct TQ nanoemulgel studies [1-4]. These studies show that both high-energy and low-energy approaches can generate stable TQ nanoemulsions that can subsequently be gelled. They also show that final performance depends on formulation composition and not merely on achieving a small particle size.

However, comparison between studies is difficult because different oils, surfactants, TQ doses, membranes/skin sources, receptor media, animal models and outcome measures are used. A formulation with smaller droplets is not automatically superior if it requires a high surfactant concentration, has poor release, lacks stability or causes irritation.

9. ADVANTAGES OF TQ NANOEMULGEL

- Improved in incorporation of a lipophilic drug into an aqueous-compatible semisolid system.
- Large interfacial area and potential enhancement of release and dermal distribution.
- Possibility of combining solubilization and penetration-enhancing excipients within one system.
- Higher viscosity and residence time than a liquid nanoemulsion.
- Potential for sustained or controlled release depending on formulation composition.
- Convenient non-invasive topical administration and avoidance of gastrointestinal first-pass exposure.
- Compatibility with conventional pharmaceuticals characterization tools and scalable emulsification methods

10. LIMITATIONS AND SAFETY CONSIDERATIONS

Nanoemulgels also have important limitations. High surfactant concentrations may cause irritation; some co-solvents can disrupt the skin barrier excessively; physical stability may be sensitive to temperature and dilution; and chemical stability of TQ can still be affected by light, oxygen and pH. DLS data can be over interpreted, and apparent enhancement in synthetic-membrane release should not be equated with improved clinical efficacy.

Nanocarriers safety depends on the complete formulation rather than TQ alone. Irritation,

sensitization, long-term dermal tolerability, microbial quality and preservative effectiveness are relevant to a final topical product. The literature remains substantially preclinical, and this is a major limitation when translating promising animal or ex-vivo findings to human use [18-20].

11. RESEARCH GAPS

- Few direct head-to-head studies comparing TQ nanoemulgel with conventional TQ gel under identical conditions.
- Lack of standardized definitions and testing conditions across nanoemulsion/nanoemulgel studies.
- Limited long-term chemical stability data specifically quantifying TQ degradation products.
- Insufficient correlation between in-vitro release, ex-vivo skin deposition and pharmacodynamic response.
- Limited data on repeated-dose dermal irritations and sensitization.
- Very limited human clinical evidence for topical nano-TQ formulations.
- Need for scalable manufacturing and quality-by-design approaches defining critical material and process attributes.
- Need for validated analytical methods capable of distinguishing intact TQ from degradation products in complex semisolid matrices.

12. FUTURE PERSPECTIVES

Future TQ nanoemulgel research should move from proof-of-concept toward reproducible pharmaceutical development. Quality-by-design frameworks can define how oil level, S mix ratio, surfactant burden, Sonication energy and polymer concentration affect critical quality attributes. Stability-indicating HPLC methods should be preferred for advanced studies. Ex-vivo permeation should be complemented by drug-deposition measurements because the therapeutic target for many skin diseases lies within the skin rather than in systemic circulation.

For clinical translation, simplified formulations using well-characterized, pharmaceutically acceptable excipients are preferable to highly complex systems. Human-relevant skin models, irritation testing and controlled clinical studies will be necessary to establish whether the formulation advantages observed in vitro and in animals translate into meaningful therapeutic benefit.

13. CONCLUSION

Thymoquinone is a pharmacologically attractive but pharmaceutically challenging lipophilic molecule. Nanoemulgel technology offers a rational approach to topical TQ delivery by combining the solubilization and interfacial advantages of a nanoemulsion with the residence time and handling properties of a gel. Direct TQ nanoemulgel studies and related topical nano carrier research demonstrate improved drug release, dermal penetration or deposition and enhanced pre clinical therapeutic effects. Nevertheless, current evidence is dominated by formulation studies, ex-vivo experiments and animal models. Future work should prioritize standardized formulation design, chemical stability, robust skin-deposition methods, safety assessment and human clinical evaluation. On the basis of current evidence, TQ-loaded nanoemulgel is best considered a promising topical delivery platform with strong preclinical rationale but incomplete clinical validation.

14. REFERENCES

- Algahtani MS, Ahmad MZ, Shaikh IA, Abdel Wahab BA, Nourein IH, Ahmad J. Thymoquinone-loaded topical nanoemulgel for wound healing: formulation design and in-vivo evaluation. *Molecules*. 2021;26(13):3863. doi:10.3390/molecules26133863.
- Anuradha U, Bhavana V, Chary PS, et al. Thymoquinone-loaded nanoemulgel in streptozotocin-induced diabetic wound. *Nanomedicine (Lond)*. 2024;19(30):2577-2604. doi:10.1080/17435889.2024.2422805.
- Khan R, Mirza MA, Aqil M, et al. A pharmaco-technical investigation of thymoquinone and peat-sourced fulvic acid nanoemulgel: a combination therapy. *Gels*. 2022;8(11):733. doi:10.3390/gels8110733.
- Alamoudi MK, Ahmad N, Ansari KA, et al. A comparative dermatokinetic evaluation of thymoquinone-loaded nanoemulsion gel for enhanced wound healing and anti-inflammatory efficacy. *Polymer Bulletin*. 2025;82(14):9581-9621. doi:10.1007/s00289-025-05922-0.
- Mostafa M, Alaaeldin E, Aly UF, Sarhan HA. Optimization and characterization of thymoquinone-loaded liposomes with enhanced topical anti-inflammatory activity. *AAPS PharmSciTech*. 2018;19(8):3490-3500. doi:10.1208/s12249-018-1166-1.
- Kausar H, Mujeeb M, Ahad A, Moolakkadath T, Aqil M, Ahmad A, Akhter MH. Optimization of ethosomes for topical thymoquinone delivery for the treatment of skin acne. *J Drug Deliv Sci Technol*. 2019;49:177-187. doi:10.1016/j.jddst.2018.11.016.
- Negi P, Sharma I, Hemrajani C, Rathore C, Bisht A, Raza K, Katore OP. Thymoquinone-loaded lipid vesicles: a promising nanomedicine for psoriasis. *BMC Complement Altern Med*. 2019;19:334. doi:10.1186/s12906-019-2675-5.
- Jain A, Pooladanda V, Bulbake U, et al. Liposphere-mediated topical delivery of thymoquinone in the treatment of psoriasis. *Nanomedicine*. 2017;13(7):2251-2262. doi:10.1016/j.nano.2017.06.009.
- Trivedi S, Wadher K, Umekar M. Development of topical thymoquinone-loaded polymer-lipid hybrid vesicular gel: in-vitro and ex-vivo evaluation. *J Liposome Res*. 2022;32(3):224-236. doi:10.1080/08982104.2021.1929311.
- Bruno MC, Gagliardi A, Mancuso A, et al. Oleic acid-based vesicular nanocarriers for topical delivery of the natural drug thymoquinone: improvement of anti-inflammatory activity. *J Control Release*. 2022;352:74-86. doi:10.1016/j.jconrel.2022.10.011.
- Alam M, Rizwanullah M, Mir SR, Amin S. Statistically optimized tacrolimus and thymoquinone co-loaded nanostructured lipid carriers gel for improved topical treatment of psoriasis. *Gels*. 2023;9(7):515. doi:10.3390/gels9070515.
- Pathak P, Almalki WH, Alruwaili NK, et al. Thymoquinone-loaded nanosized ethosomal-based hydrogels: their preparation, characterization, in-vitro, ex-vivo, and antimicrobial evaluation against *Staphylococcus aureus*. *Curr Med Chem*. 2025;32(22):4585-4601. doi:10.2174/0109298673341004250101104428.
- Khatoon K, Ali A, Ahmad FJ, et al. Novel nanoemulsion gel containing triple natural bio-actives combination of curcumin, thymoquinone, and resveratrol improves psoriasis therapy: in-vitro and in-vivo studies. *Drug Deliv Transl Res*. 2021. doi:10.1007/s13346-020-00852-y.

14. Haq A, Michniak-Kohn B. Effects of solvents and penetration enhancers on transdermal delivery of thymoquinone: permeability and skin deposition study. *Drug Deliv.* 2018;25(1):1943-1949. doi:10.1080/10717544.2018.1523256.
15. Donthi MR, Munnangi SR, Krishna KV, Saha RN, Singhvi G, Dubey SK. Nanoemulgel: a novel nanocarrier as a tool for topical drug delivery. *Pharmaceutics.* 2023;15(1):164. doi:10.3390/pharmaceutics15010164.
16. Choudhury H, Gorain B, Pandey M, et al. Recent update on nanoemulgel as topical drug delivery system. *J Pharm Sci.* 2017;106(7):1736-1751. doi:10.1016/j.xphs.2017.03.042.
17. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. *Int J Pharm.* 2017;526(1-2):353-365. doi:10.1016/j.ijpharm.2017.04.068.
18. Modarresi Chahardehi A, Ojaghi HR, Motedayyeh H, Arefnezhad R. Nano-based formulations of thymoquinone are new approaches for psoriasis treatment: a literature review. *Front Immunol.* 2024;15:1416842. doi:10.3389/fimmu.2024.1416842.
19. Rathore C, Rathbone MJ, Chellappan DK, et al. Nanocarriers: more than tour de force for thymoquinone. *Expert Opin Drug Deliv.* 2020;17(4):479-494. doi:10.1080/17425247.2020.1730808.
20. El-Far AH, AlJaouni SK, Li W, Mousa SA. Protective roles of thymoquinone nanoformulations: potential nanonutraceuticals in human diseases. *Nutrients.* 2018;10(10):1369. doi:10.3390/nu10101369.
21. Darakhshan S, Bidmeshki Pour A, Hosseinzadeh Colagar A, Sisakhtnezhad S. Thymoquinone and its therapeutic potentials. *Pharmacol Res.* 2015;95-96:138-158. doi:10.1016/j.phrs.2015.03.011.
22. Goyal SN, Prajapati CP, Gore PR, et al. Therapeutic potential and pharmaceutical development of thymoquinone: a multitargeted molecule of natural origin. *Front Pharmacol.* 2017;8:656. doi:10.3389/fphar.2017.00656.
23. Amin B, Hosseinzadeh H. Black cumin (*Nigella sativa*) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects. *Planta Med.* 2016;82(1-2):8-16. doi:10.1055/s-0035-1557838.
24. Gholamnezhad Z, Havakhah S, Boskabady MH. Preclinical and clinical effects of *Nigella sativa* and its constituent, thymoquinone: a review. *J Ethnopharmacol.* 2016;190:372-386. doi:10.1016/j.jep.2016.06.061.
25. Ismail M, Al-Naqeeq G, Chan KW. *Nigella sativa* thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. *Free Radic Biol Med.* 2010;48(5):664-672.
26. Ali BH, Blunden G. Pharmacological and toxicological properties of *Nigella sativa*. *Phytother Res.* 2003;17(4):299-305. doi:10.1002/ptr.1309.
27. Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential of *Nigella sativa*: a miracle herb. *Asian Pac J Trop Biomed.* 2013;3(5):337-352. doi:10.1016/S2221-1691(13)60075-1.
28. Randhawa MA, Alghamdi MS. Anticancer activity of *Nigella sativa* (black seed): a review. *Am J Chin Med.* 2011;39(6):1075-1091.
29. Shuid AN, Mohamed N, Mohamed IN, et al. *Nigella sativa*: a potential antiosteoporotic agent. *Evid Based Complement Alternat Med.* 2012;2012:696230.
30. Nastiti CM, Ponto T, Abd E, Grice JE, Benson HAE, Roberts MS. Topical nano and microemulsions for skin delivery. *Pharmaceutics.* 2017;9(4):37. doi:10.3390/pharmaceutics9040037.
31. Roberts MS, Mohammed Y, Pastore MN, et al. Topical and cutaneous delivery using nanosystems. *J Control Release.* 2017;247:86-105. doi:10.1016/j.jconrel.2016.12.022.
32. Lane ME. Skin penetration enhancers. *Int J Pharm.* 2013;447(1-2):12-21. doi:10.1016/j.ijpharm.2013.02.040.
33. Flaten GE, Palac Z, Engesland A, Filipovic-Grcic J, Vanic Z, Skalko-Basnet N. In-vitro skin models as a tool in optimization of drug formulation. *Eur J Pharm Sci.* 2015;75:10-24.
34. Scheuplein RJ, Blank IH. Permeability of the skin. *Physiol Rev.* 1971;51(4):702-747.
35. Illel B, Schaefer H, Wepierre J, Doucet O. Follicles play an important role in percutaneous absorption. *J Pharm Sci.* 1991;80(5):424-427. doi:10.1002/jps.2600800505.

36. Golden GM, McKie JE, Potts RO. Role of stratum corneum lipid fluidity in transdermal drug flux. *J Pharm Sci.* 1987;76(1):25-28. doi:10.1002/jps.2600760108.
37. Anton N, Vandamme TF. Nano-emulsions and micro-emulsions: clarification of the critical differences. *Pharm Res.* 2011;28(5):978-985.
38. McClements DJ. Nanoemulsions versus microemulsions: terminology, differences, and similarities. *Soft Matter.* 2012;8:1719-1729.
39. Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ. Nano-emulsions. *Curr Opin Colloid Interface Sci.* 2005;10(3-4):102-110.
40. Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nano-emulsions. *Adv Colloid Interface Sci.* 2004;108-109:303-318.
41. Gupta A, Eral HB, Hatton TA, Doyle PS. Nanoemulsions: formation, properties and applications. *Soft Matter.* 2016;12:2826-2841.
42. Bhattacharjee S. DLS and zeta potential—what they are and what they are not? *J Control Release.* 2016;235:337-351.
43. Carvalho PM, Felicio MR, Santos NC, Goncalves S, Domingues MM. Application of light scattering techniques to nanoparticle characterization and development. *Front Chem.* 2018;6:237. doi:10.3389/fchem.2018.00237.
44. Islam MT, Rodriguez-Hornedo N, Ciotti S, Ackermann C. Rheological characterization of topical carbomer gels neutralized to different pH. *Pharm Res.* 2004;21(7):1192-1199.
45. Barreiro-Iglesias R, Alvarez-Lorenzo C, Concheiro A. Incorporation of small quantities of surfactants as a way to improve the rheological and diffusional behavior of Carbopol gels. *J Control Release.* 2001;77(1-2):59-75. doi:10.1016/S0168-3659(01)00458-8.
46. Franz TJ. Percutaneous absorption: on the relevance of in-vitro data. *J Invest Dermatol.* 1975;64(3):190-195.
47. Lehman PA, Franz TJ. In-vitro skin permeation methodology for over-the-counter topical dermatologic products. *J Clin Pharmacol.* 2019;59(Suppl 1):S28-S36.
48. Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci.* 1963;52:1145-1149.
49. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25-35.
50. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv.* 1985;60(4):110-111.
51. International Council for Harmonisation. ICH Q1A(R2): Stability testing of new drug substances and products. Geneva: International Council for Harmonisation; 2003.
52. Elmowafy M, Samy A, Raslan MA, et al. Enhancement of bioavailability and pharmacodynamic effects of thymoquinone via nanostructured lipid carrier formulation. *AAPS PharmSciTech.* 2016;17:663-672. doi:10.1208/s12249-015-0391-0.
53. Abdelwahab SI, Sheikh BY, Taha MME, et al. Thymoquinone-loaded nanostructured lipid carriers: preparation, gastroprotection, in-vitro toxicity, and pharmacokinetic properties after extravascular administration. *Int J Nanomedicine.* 2013;8:2163-2172. doi:10.2147/IJN.S44108.
54. Tubesha Z, Imam MU, Mahmud R, Ismail M. Study on the potential toxicity of a thymoquinone-rich fraction nanoemulsion in Sprague-Dawley rats. *Molecules.* 2013;18(7):7460-7472.
55. Kundu P, Das M, Tripathy K, Sahoo SK. Delivery of thymoquinone using nanocarriers: recent developments and future prospects. *Drug Deliv Transl Res.* 2022;12:1678-1701.
56. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. *Pharmaceutics* 2015;7(4):438-470. doi:10.3390/pharmaceutics7040438.