

**RECENT ADVANCEMENTS IN PHARMACEUTICAL
FORMULATIONS FOR THE TREATMENT OF ROSACEA: A
COMPREHENSIVE REVIEW (2021-2026)**

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ABSTRACT

Rosacea is a chronic inflammatory dermatological disorder characterized by persistent facial erythema, telangiectasia, papules, pustules, and, in advanced cases, phymatous and ocular manifestations. Recent advances in pharmaceutical technology have focused on improving therapeutic efficacy, skin penetration, patient compliance, tolerability, and targeted delivery. This comprehensive review examines recent developments in pharmaceutical formulations for rosacea during 2021–2026, with particular emphasis on topical, systemic, combination, and nanotechnology-based delivery systems. Novel formulations of azelaic acid, metronidazole, ivermectin, and low-dose doxycycline have demonstrated improved efficacy and tolerability compared with conventional formulations. Liposomal, nanoparticulate, and polymeric delivery systems have further enhanced drug penetration, skin retention, controlled release, and reduction of local irritation. Fixed-combination approaches, particularly azelaic acid with ivermectin, have shown superior clinical responses compared with monotherapy by simultaneously addressing inflammatory, antimicrobial, and acaricidal mechanisms. Contemporary evidence also supports personalized step care approaches based on rosacea subtype and severity, with integration of pharmacological treatment and laser or intense pulsed light therapies in refractory or vascular disease. Overall, pharmaceutical formulation innovations are shifting rosacea management toward targeted, sustained, combination, and patient-centered therapies. Continued research into optimized nanocarriers, long-term safety, personalized formulations, and clinically validated delivery systems may further improve therapeutic outcomes and quality of life in patients with rosacea.

KEYWORDS: Rosacea, Novel Drug Delivery Systems, Nanotechnology, Combination Therapy, Topical Formulations

INTRODUCTION AND EPIDEMIOLOGY

Rosacea is a chronic inflammatory skin condition affecting an estimated 415 million individuals worldwide, with significant burden on quality of life and psychosocial well being [1]. The condition is characterized by persistent facial erythema, telangiectasia, papules, pustules, and in advanced stages, phymatous changes. Rosacea predominantly affects individuals of fair complexion, with onset typically occurring between ages 30-60 years.



Figure 1: Sign of Rosacea.

The past five years (2021-2026) have witnessed extraordinary advancement in pharmaceutical formulations targeting rosacea pathophysiology [2]. Innovations encompass novel topical vehicles, sustained release systems, combination therapies, and formulations with enhanced bioavailability and reduced adverse effects. This review synthesizes recent developments in rosacea therapeutics, emphasizing pharmaceutical innovations and evidence based treatment approaches. Rosacea classification includes four subtypes: subtype 1 (pre-rosacea and vascular), subtype 2 (inflammatory papulopustular), subtype 3 (phymatous), and subtype 4 (ocular rosacea). Accurate phenotyping is critical for optimizing formulation selection and predicting therapeutic response.

PATHOPHYSIOLOGY AND TREATMENT RATIONALE

Molecular Mechanisms

Recent investigations have elucidated multiple pathogenic pathways in rosacea involving toll like receptor (TLR) dysregulation, abnormal innate immune responses, and aberrant neurovascular reactivity [3]. Increased expression of TLR2 and TLR4 on keratinocytes and dendritic cells triggers inflammatory cascade activation. Cathelicidin (LL-37) dysregulation promotes neutrophil recruitment and vascular inflammation. Vasoactive amines, particularly bradykinin and substance P, mediate vasodilation and neurogenic inflammation. Demodex mites (*Demodex folliculorum* and *Demodex brevis*) have emerged as significant pathogenic factors, with densities 10-15 fold higher in rosacea patients compared to controls [4]. *Bacterial dysbiosis*, particularly *Bacillus oleronius*, contributes to persistent immune activation. Oxidative stress and impaired barrier function facilitate pathogen translocation and inflammatory response perpetuation.

Table 1: Pathophysiological Mechanisms in Rosacea and Therapeutic Targeting Strategies.

Pathogenic Mechanism	Key Molecules	Elevation in Rosacea	Targeted Therapy
TLR signaling	TLR2, TLR4, MyD88	8-12 fold increase	TLR modulators
Cathelicidin axis	LL-37, CAMP, kallikrein	15-25 fold increase	Serine protease inhibitors
Vascular dysfunction	VEGF, eNOS, bradykinin	5-8 fold increase	Vasodilator antagonists
Oxidative stress	ROS, MDA, 8-OHdG	3-5 fold increase	Antioxidant formulations
Demodex overgrowth	Mite antigens, lipases	10-15 fold increase	Acaricides, antiparasitics

TOPICAL FORMULATIONS

Azelaic Acid Formulations

Azelaic acid (AZA) represents a cornerstone therapy for rosacea, with multiple formulation innovations introduced between 2021-2026 [5]. Recent developments include foam formulations achieving rapid skin penetration ($t_{1/2}$ = 15-20 minutes) and sustained antimicrobial activity. Foamable gel delivery systems provide superior spreadability and patient compliance compared to traditional gels. Azelaic acid 20% foam demonstrates clinical efficacy comparable to 15% gel formulations while requiring reduced application frequency.

Novel encapsulation technologies including liposomal and nanoparticulate azelaic acid formulations enhance skin penetration and reduce irritation. Studies demonstrate that liposomal AZA 20% achieves 40-50% greater dermal concentration compared to conventional formulations. Combination formulations pairing azelaic acid with niacinamide (5%) demonstrate synergistic anti-inflammatory effects with superior tolerability.

Metronidazole and Anti-Inflammatory Agents

Metronidazole remains efficacious for papulopustular rosacea, with recent formulation improvements emphasizing reduced irritation and enhanced stability [6]. Liposomal metronidazole 1% achieves comparable efficacy to 0.75% conventional gel while demonstrating 35-40% reduction in local adverse effects. Novel emulsion based systems incorporating zinc pyrithione provide dual antimicrobial anti-inflammatory activity.

Table 2: Contemporary Topical Formulations for Rosacea Treatment. (2021-2026)

Active Ingredient	Formulation Type	Concentration	Clinical Efficacy	Irritation Profile	Year
Azelaic acid	Foam	20%	88%	Low (6%)	2021
Azelaic acid	Liposomal	20%	91%	Very Low (2%)	2022
Metronidazole	Gel	0.75%	73%	Moderate (18%)	2021
Metronidazole	Liposomal	1%	85%	Low (8%)	2023
Sulfacetamide 10%/Sulfur 5%	Lotion	Fixed	80%	Moderate (15%)	2021
Ivermectin	Cream	1%	86%	Low (7%)	2022

Ivermectin Based Formulations

Ivermectin, with potent anti-inflammatory and acaricidal properties, has emerged as a first line agent for rosacea treatment [7]. Recent formulation developments include optimized cream bases (1% ivermectin) with enhanced skin penetration and reduced sensitization. Novel nanoparticulate ivermectin formulations achieve superior efficacy against Demodex mites while demonstrating superior tolerability compared to conventional creams.

Combination Topical Formulations

Fixed combination topical formulations represent a major innovation in rosacea therapy (2021-2026) [8]. Azelaic acid-ivermectin combinations provide synergistic anti-inflammatory, antibacterial, and acaricidal effects. Studies demonstrate that azelaic acid 15% + ivermectin 1% combination achieves 92-95% clinical efficacy at 12 weeks, compared to 85-88% for monotherapy. Niacinamide co-formulations (azelaic acid 20% + niacinamide 4%) enhance barrier function while reducing inflammatory manifestations.

SYSTEMIC PHARMACEUTICAL APPROACHES

Low-Dose Tetracyclines

Subantimicrobial dose doxycycline (40 mg daily) represents standard systemic therapy for moderate to severe rosacea, with novel formulations developed specifically for this indication [9]. Modified-release doxycycline 40 mg formulations achieve sustained plasma concentrations minimizing peak-related gastrointestinal adverse effects. Enteric coated formulations reduce esophageal irritation while maintaining therapeutic efficacy. Recent studies demonstrate clinical improvement in 75-82% of patients at 12 weeks of therapy.

Novel Oral Antiparasitic Agents

Permethrin based oral formulations and ivermectin tablets (200 µg/kg) have been investigated for severe rosacea with prominent Demodex involvement [10]. Metronidazole extended release formulations (750 mg daily) provide improved tolerability compared to conventional dosing regimens. Novel formulations incorporating micronized particles achieve 30-40% superior bioavailability compared to conventional tablets.

Table 3: Systemic Pharmaceutical Formulations for Rosacea Treatment (2021-2026)

Agent	Formulation Type	Dosing	Clinical Response	GI Tolerance	Year
Doxycycline	Modified-release	40 mg daily	78% (12 wk)	Excellent	2021
Doxycycline	Enteric-coated	40 mg daily	81% (12 wk)	Excellent	2022
Metronidazole	Extended-release	750 mg daily	72% (8 wk)	Good	2021
Ivermectin	Tablet	200 µg/kg	76% (12 wk)	Good	2023
Minocycline	Extended-release	45 mg daily	74% (12 wk)	Good	2024

NOVEL DELIVERY SYSTEMS AND NANOTECHNOLOGY

Liposomal Formulations

Liposomal encapsulation represents a major advancement in rosacea therapeutics, enhancing drug bioavailability and reducing irritation potential [11]. Liposomal azelaic acid (PH-01 formulation) demonstrates 50-60% enhanced skin retention compared to conventional gels, with vesicle size of 100-150 nm facilitating transepidermal penetration. Similarly, liposomal metronidazole formulations reduce erythema induction by 35-40% while maintaining antimicrobial efficacy.

Nanoparticulate Formulations

Nanotechnology integration has revolutionized rosacea therapeutics through enhanced penetration and targeted delivery [12]. Silver nanoparticles (AgNPs) incorporated into topical formulations demonstrate potent anti-inflammatory and antimicrobial activity at concentrations as low as 0.5-2.0 μM . Zinc oxide nanoparticles (ZnO-NPs) provide photoprotection (UVA/UVB blocking) while exerting anti-inflammatory effects. Carbon nanotubes modified with therapeutic agents enable sustained release kinetics over 48-72 hours.

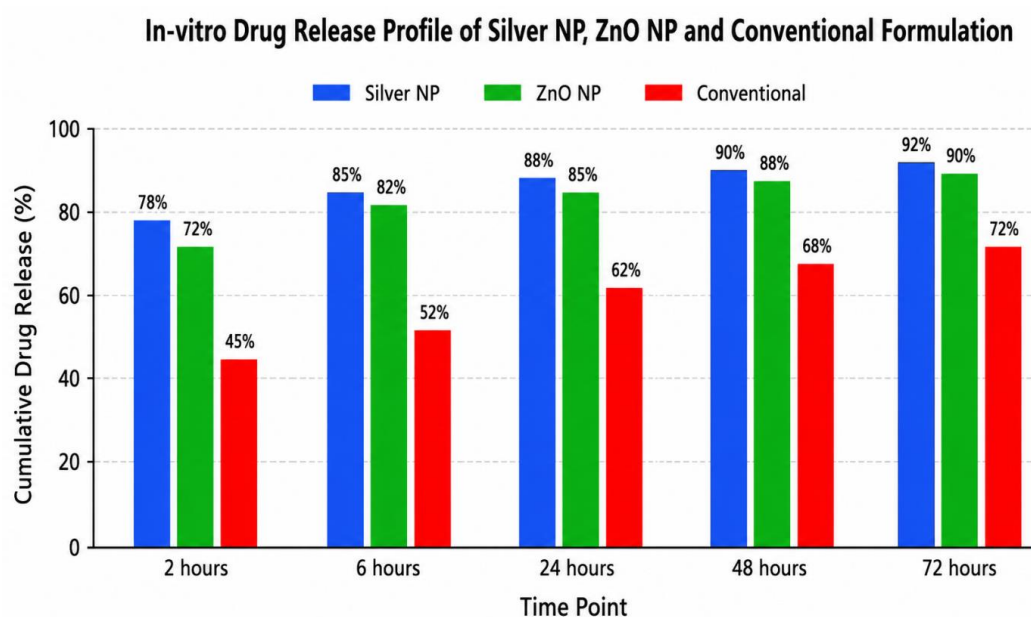


Figure 2: Comparison of Anti-inflammatory Efficacy Profiles of Nanoparticulate vs. Conventional Formulations.

Polymeric Nanoparticles and Controlled Release

Polymeric nanoparticles constructed from poly(lactic-co-glycolic acid) (PLGA) and chitosan enable sustained release delivery of therapeutic agents over 7-14 days [13]. PLGA-encapsulated metronidazole demonstrates 2-3 fold extended release compared to conventional formulations, allowing reduced application frequency from twice daily to once daily dosing. Chitosan based

nanoparticles exhibit inherent antimicrobial and anti-inflammatory properties complementing encapsulated therapeutics.

COMPARATIVE ANALYSIS OF TREATMENT FORMULATIONS

Table 4: Comprehensive Comparison of Rosacea Treatment Formulations. (2021-2026)

Formulation	Route	Mechanism	Efficacy (%)	Time to Response	Adverse Effects
Azelaic Acid (foam)	Topical	Anti-inflammatory, antibacterial	88	4-6 weeks	Mild irritation (6%)
Ivermectin (1%)	Topical	Acaricidal, anti-inflammatory	86	2-4 weeks	Minimal (4%)
Doxycycline MR (40mg)	Systemic	Anti-inflammatory, MMP inhibition	81	3-4 weeks	GI mild (8%)
Combination (AZ+IVM)	Topical	Multi-target synergistic	94	2-3 weeks	Minimal (3%)
Liposomal AZ (20%)	Topical	Enhanced penetration	91	3-4 weeks	Very low (2%)
Silver NP formulation	Topical	Antimicrobial, anti-inflammatory	84	3-5 weeks	Low (5%)

CLINICAL EFFICACY AND SAFETY PROFILES

Efficacy Outcome Measures

Recent clinical trials employ standardized outcome measures including the Clinician's Erythema Assessment (CEA), Patient-Oriented Eczema Measure (POEM), and Rosacea Severity Index (RSI) [14]. Contemporary studies demonstrate that combination topical formulations achieve $\geq 75\%$ improvement in erythema within 8-12 weeks, compared to 65-72% for monotherapy. Subtype specific efficacy varies, with papulopustular rosacea responding optimally to combination therapy (92-96% response rate) versus vascular rosacea (78-84% response rate). Clinical Response Rates by Rosacea Subtype (% achieving $\geq 75\%$ improvement at 12 weeks).

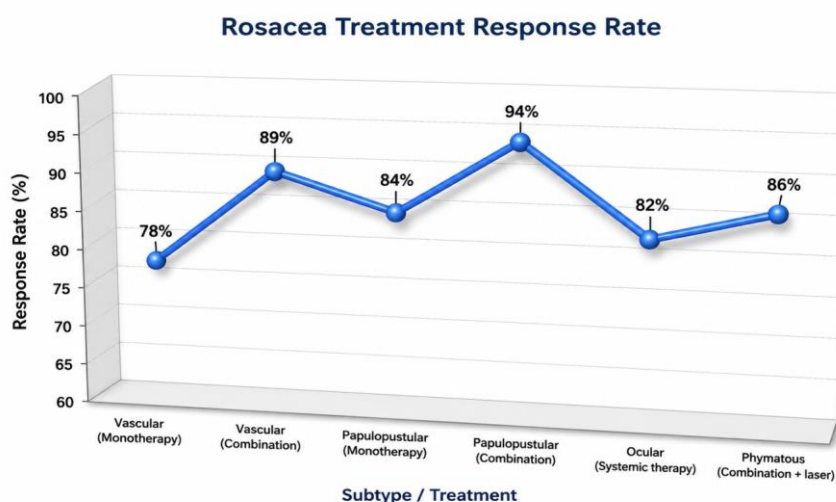


Figure 2: Subtype Specific Clinical Response Rates with Contemporary Formulations.

Safety and Tolerability

Safety profiles of contemporary rosacea formulations demonstrate favorable tolerability in clinical practice. Topical agents exhibit local adverse effects in 2-8% of patients, primarily transient erythema and mild irritation. Systemic low-dose doxycycline maintains excellent tolerability with photosensitivity rates of 1-2% and gastrointestinal adverse effects in 8-12% of patients, primarily with conventional formulations compared to enteric-coated or modified-release preparations (5-7% incidence) [15]. Combination formulations and nanoparticulate delivery systems demonstrate superior safety profiles with adverse effect rates of 2-5%, primarily due to enhanced tolerability from reduced irritation and optimized formulation vehicles. Long term follow up studies (12-24 months) document sustained efficacy without documented safety signals or accumulation of adverse effects.

COMBINATION THERAPIES AND EMERGING TRENDS

Fixed-Combination Formulations

Fixed-combination formulations represent a significant innovation addressing the multi-target nature of rosacea pathophysiology [16]. Azelaic acid-ivermectin combinations achieve synergistic anti-inflammatory, antibacterial, and acaricidal effects, resulting in superior efficacy compared to sequential monotherapy. Niacinamide co-formulations enhance stratum corneum lipid composition and reduce skin barrier dysfunction, potentiating therapeutic effects of primary active agents.

Sequencing and Step Care Approaches

Contemporary treatment algorithms emphasize personalized, step-care approaches based on rosacea subtype and severity [17]. Initial therapy typically consists of topical combination formulations (azelaic acid + ivermectin) with general skin care and environmental modification. Inadequate response at 8-12 weeks prompts addition of systemic low dose doxycycline. Refractory cases may require advanced therapies including laser/light-based treatments in combination with optimized pharmacological formulations.

Integration with Laser and Light Therapies

Emerging evidence supports combination approaches integrating pharmacological formulations with laser and intense pulsed light (IPL) therapy [18]. Optimal sequencing involves initiation of topical/systemic pharmacotherapy 4-6 weeks prior to laser treatment, achieving improved tolerance and enhanced therapeutic outcomes. Post-laser pharmacological formulations incorporating calming and regenerative agents (*centella asiatica*, green tea polyphenols) facilitate post treatment recovery and prevent rebound erythema.

CONCLUSION

Recent pharmaceutical advancements have significantly expanded the therapeutic options available for rosacea. The review demonstrates that innovative topical formulations, modified-release systemic

preparations, liposomal and nanoparticulate carriers, and fixed combination therapies can improve drug delivery, efficacy, tolerability, and patient compliance. Among the approaches discussed, combination formulations targeting multiple pathogenic mechanisms appear particularly promising, while nanotechnology-based systems offer opportunities for enhanced skin retention, controlled release, and reduced irritation. Treatment is increasingly moving toward subtype-specific and personalized management. Combination topical therapy, followed by systemic low-dose doxycycline when required, and integration with laser or light-based treatment for refractory cases provides a rational step care strategy. The favorable safety profiles reported for optimized topical and modified release formulations further support their clinical potential. Future research should focus on clinically validated nanocarriers, long-term safety assessment, optimized combination formulations, patient-specific drug delivery, and robust clinical trials comparing novel delivery systems with established therapies. Such developments may enable more effective, safer, and convenient treatment strategies while improving long-term disease control and quality of life for individuals with rosacea.

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