How to Cite:
Bhandari, N., Raja, M. K. M. M., Singh, L. P., Kukreti, G., & Kaushik, S. (2022). A detailed overview on pharmaceutical dosage forms in treatment of acne. *International Journal of Health Sciences*, *6*(S4), 9916–9931. https://doi.org/10.53730/ijhs.v6nS4.10847

A detailed overview on pharmaceutical dosage forms in treatment of acne

Mr. Neeraj Bhandari
Head pharmacy, Arni school of Pharmacy, Arni university, kathgarh indora, District kangra Himachal Pradesh- 176401
Corresponding author email: bhandarineeraj786@gmail.com

Dr. M. K. Mohan Maruga Raja
Associate Professor, Parul Institute of Pharmacy & Research, Parul University,Vadodara, Gujarat, India

Laliteshwar Pratap Singh
Professor, Narayan Institute of Pharmacy, Gopal Narayan Singh University, Jamuhar, Rohtas, Bihar – 821305

Gauree Kukreti
Assistant Professor, School of Pharmaceutical Sciences and technology,Sardar Bhagwan Singh University, Balawala, Dehradun

Sumit Kaushik
Assistant Professor, Faculty of Pharmacy, Raja Balwant Singh Engineering Technical Campus, Bichpuri Agra, U.P.

***Abstract*---**Acne vulgaris is a skin condition characterized by an obstruction or inflammation of the oil glands, present on skin's surface, which are collectively termed as pilosebaceous units. The skin on face, back, and upper chest have a greater number of sebaceous follicles. Topical, systemic, or combination therapy can be used to treat acne, while mild and moderate acne are generally treated with topical therapy. Topical acne therapy has direct access to the target site (skin) prior to reaching the blood stream, thereby reducing the systemic adverse effects of delivery of drug via parenteral or oral routes. Oral antibiotics, on the other hand, are a crucial treatment for acne which have not improved with topical treatment and for inflammatory lesions, such as pustules, nodules, and papules. Due to their capability to improve dermal therapeutics by boosting therapeutic efficacy and lowering adverse effects, nanodelivery technologies, developed to address skin delivery difficulties, have been extensively investigated. The goal of this study

is to go through the many types of pharmacological dosage forms that are available for the treatment of acne.

Keywords---acne, treatment, dosage forms, topical treatment, systemic therapy**.**

Introduction

Acne vulgaris seems to be one of the most prevalent skin conditions, characterized by comedones or severe inflammatory lesions on skin areas having a significant number of sebaceous glands or follicles, such as the face, back, and chest and the disease's severity is linked to an increased level of sebum secretion (Vyas et al., 2014). It is a skin disorder involving pilosebaceous units, which comprises the hair follicle, sebaceous gland, and the erector pili muscle (Singh et al., 2019). The interaction of the following four events is assumed to be the pathophysiology of acne.

- The first irregularity is elevated sebum secretion because of hyperplasia of sebaceous glands.
- Follicular hyperkeratinization inhibits the follicular keratinocytes from shedding properly, clogging the follicle and forming an imperceptible microcomedo. Inside the clogged follicle, lipids and cell debris quickly build.
- This milieu supports Propionibacterium acnes proliferation, which triggers an immunological response by producing a slew of inflammatory mediators (Figure 1).
- Follicular burst and consequent release of lipids, bacteria, and cell debris into the dermal layer exacerbate inflammation (Tan et al., 2017).

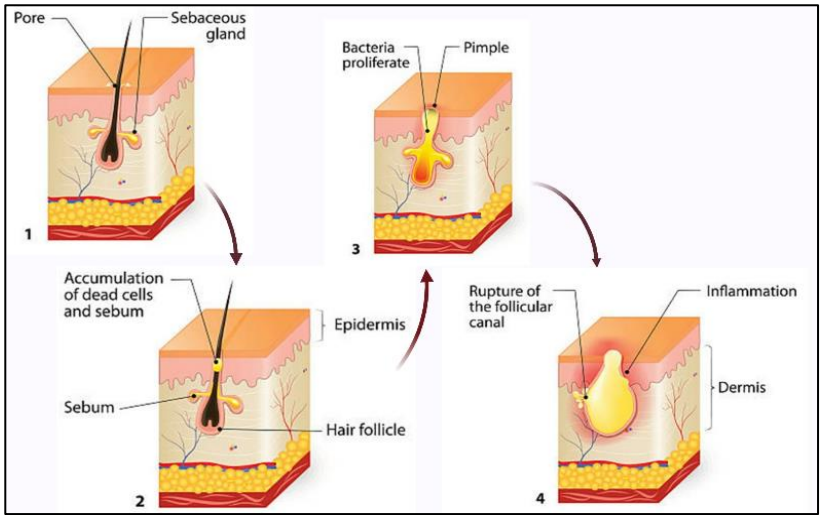

Figure 1: Pathophysiology of Acne

Treatment of acne

A range of topical and oral (systemic) drugs are used to treat acne pharmacologically. In patients having mild-to-moderate acne with comedones and papules/pustules, topical therapy, including benzoyl peroxide, topical antibiotics, and topical retinoids, are usually utilized as the first-line therapy (Benner et al., 2013). For moderate-to-severe acne, oral therapy such as oral antibiotics and hormone therapy can be utilized as first-line therapy in conjunction with a topical agent (Figure 2) (Baldwin H, 2020).

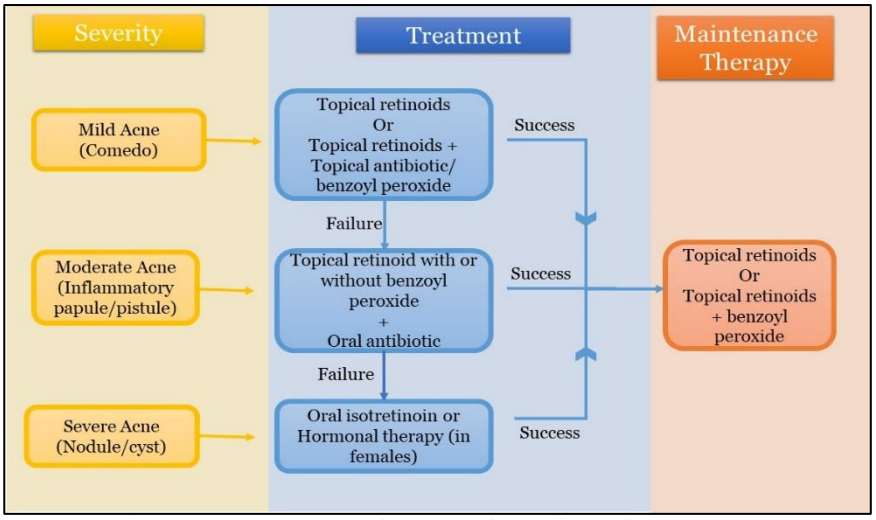

Figure 2: Treatment for acne based on the severity

Dosage forms for acne treatment

As a result, there is no straightforward therapeutic formulation, and treatment options differ depending on the level and severity of the condition. Acne can be classed as mild, moderate, or severe based on its progression (Dréno et al., 2013). The different dosage forms available for the treatment of acne are tabulated in Table 1.

Table 1: Different dosage forms used in acne treatment

Dosage form	Drugs	Features	References
Topical dosage form	Retinoids: adapalene, isotretinoin, motretinide, retinoyl-β-glucuronide, tazarotene, tretinoin Antibiotics: clindamycin, erythromycin Diverse: azelaic acid, benzoyl peroxide,	▪ Can be used externally on affected area; however, long-term usage is not advised.	Fox et al., 2016; Simonart T, 2012

	chemical peels, corticosteroids, dapsone, hydrogen peroxide, niacinamide, salicylic acid,		
Oral dosage form	Retinoids: isotretinoin Antibiotics: azithromycin, clindamycin, co-trimoxazole, doxycycline, erythromycin, levofloxacin, lymecycline, minocycline, roxithromycin Hormonal: contraceptives Diverse: clofazimine, corticosteroids, ibuprofen, zinc sulfate	▪ A significant degree of patient compliance ▪ Have side effects ▪ The drug must be consumed in huge quantities.	Ogé et al., 2019; Farrah et al., 2016
Particle-based formulations	Liposomes, solid lipid nanoparticles, microemulsions, nanostructured lipid carriers	▪ Efficacious than topical dosage forms ▪ Prolonged drug release	Paiva-Santos et al., 2021; Chakraborty et al., 2022
Light-based therapy	5-aminolevulinic acid (5-ALA) Endogenous porphyrins	▪ Less adverse effects ▪ Not a first-line therapy	Pei et al., 2015; Momen et al., 2015

Topical dosage form

Topical treatment is the most effective option for mild to severe acne. Topical treatment could also be employed as a supplement to systemic treatment in severe cases of acne. Retinoids, antibiotics, and herbal agents are examples of topical treatments that are available in the form of creams, gels, lotions , and ointments (Stuart et al., 2021) (Table 2). Topical therapies are only effective at the site of application, and a few of them induce skin irritation, which can be reduced by using smaller dose formulations (Otlewska et al., 2020). Numerous topical formulations are currently available, and the dermatologist recommends them based on the type of acne lesions found after clinical assessment. Patients generally receive a topical retinoid as the first-line treatment, considering the pivotal role of the microcomedo in the initial stages of non-inflammatory and inflammatory acne (Layton AM, 2006).

Retinoids such as adapalene, retinoic acid, isotretinoin, and tretinoin are often used alone or in combination with other topical antibiotics (Hsu et al., 2011). The most commonly used comedolytic drug is retinoic acid, which is available in 0.025

percent, 0.05 percent, 0.1 percent cream, and gel concentrations. Clindamycin 1% to 2% topical gel and lotion, nadifloxacin 1% gel and lotion, and azithromycin 1% gel and lotion are all available (Table 2) (Sandoval et al., 2014). Topical benzoyl peroxide in conjunction with adapalene forms a comedolytic and antibacterial formulation (Feneran et al., 2011). It's employed in gel bases in concentrations of 2.5%, 4%, and 5%. Azelaic acid is another antibacterial and comedolytic gel that is available in a 15% or 20% concentration, which is also prescribed to treat acne scars. In seborrhoea, comedonal acne, and also post-inflammatory hyperpigmentation, beta hydroxy acids such as salicylic acid are used in the form of 2% gel or a chemical peel of 10% - 20% (Sutaria et al., 2022).

Table 2: Types of topical anti-acne formulations

Category	Drug	Formulation	Reference
Topical Retinoids	Adapalene	0.1 % gel	Kolli et al., 2019; Yeh et al., 2016; Leyden et al., 2017; Feldman et al., 2004
		0.1 % Cream	
		0.1 % pledget	
		0.1% solution	
	Tretinoin	0.025% cream	
		0.05% cream	
		0.01% gel	
		0.1% cream	
		0.025% gel	
		0.05% solution	
	Tazarotene	0.05% gel	
		0.1% gel	
		0.05% cream	
		0.1% cream	
Topical antibiotics	Clindamycin	1% gel	Kosmadaki et al., 2017; Del Rosso JQ, 2016
		1% Lotion	
		1% Swab	
		1% Solution	
	Erythromycin	2% Gel	
		2% Solution	
Miscellaneous	Azelaic acid	20% cream	
	Benzoyl peroxide	2.5% gel	
		5% gel	
		10% gel	
		2.5% wash	
		5% wash	
		10% wash	
	Sulfur	5% lotion	
		10% lotion	
	Sulfacetamide	10% lotion	

Because of its various favorable functions in reducing sebum accumulation, lipid peroxidation, and oxygen radicals, inhibiting Cutibacterium acnes growth, and controlling inflammatory response, CleodermTM Clarifying Cream could be a significant method for formulating customized acne therapies (Palonini et al., 2021). Clascoterone 1% cream formulation has been proven to be a safer and more efficacious therapy alternative for acne vulgaris even in children over the age of 12. (Kalabalik-Hoganson et al., 2021, Hebert et al., 2020). NM itric oxide (NO)-producing gel has been found to be effective in treating acne vulgaris. There was a reduction in comedones and pustulae formation (Settelmeier et al., 2021). According to a study, latest preparations of tretinoin 0.05 percent lotion (Harper et al., 2020) and tazarotene 0.045 percent lotion (Tanghetti et al., 2020) show an extremely favorable pharmacological and toxicological profile in treating moderate-to-severe acne, with fewer side effects than those reported with earlier formulations.

Oral (systemic) dosage form

For moderate to severe acne, oral treatment is used. Isotretinoin, oral antibiotics such as doxycycline, tetracycline, erythromycin, etc., and hormone treatment are all utilized for systemic applications. In severe cases, a combination of more than one topical or oral drug is a standard option, as this strategy can address many pathogenic causes. For acne treatment, combination therapy has been demonstrated to be more effective than monotherapy (Najafi-Taher et al., 2017)

Tetracycline, doxycycline, and minocycline are commonly used oral antibiotics for the treatment of acne (Table 3). Among them, tetracycline has been used for the longest period. Minocycline is the primary anti-acne agent because it has higher lipophilicity and has better oral absorption and antibacterial activity against P. acnes than other oral antibiotics (Hsieh et al., 2011). The European Directive standardized isotretinoin systemic prescriptions across Europe. It should be emphasized, though, that systemic retinoids such as isotretinoin are not recommended during pregnancy or breastfeeding (Rigopoulos et al., 2010).

Table 3: Oral antibiotics available for acne treatment

Drug	Features	References
Doxycyclin	• Acceptable for use in patients with renal failure • Not recommended for pregnant women or children below 9 years • Side effects include gastrointestinal upset; phototoxicity	Kraft et al., 2011; Purdy et al., 2011)
Erythromycin	• Safe in pregnant women and children • Few adverse effects • Patients may acquire resistance	Chien et al., 2016
Minocyclin	• Not recommended for pregnant women or children below 9 years • Side effects include dizziness, pigment changes, hepatitis, lupus-like reactions	Ochsendorf F, 2010

Tetracyclin	• Chelated by antacids and milk; to be taken on an empty stomach • Not recommended for pregnant women or children below 9 years • Inexpensive	Graber EM, 2021; Armstrong et al., 2020

Microbiological profile of oral sarecycline, a tetracycline-class antibiotic, against clinical specimens of C. acnes was described by Zhanel et al., and the data confirm sarecycline as useful in acne therapy (Zhanel et al., 2019). R esearch found that combining probiotics, lactic acid bacteria (LAB) and curcuma longa extract (CLE) showed synergistic antibacterial activities against C. acnes, indicating that these formulations might be used to cure or relieve acne vulgaris (Kim et al., 2020). Oral zinc gluconate has also shown promising outcomes in the treatment of acne (Searle et al., 2022).

When compared to the oral administration of a drug, its topical use has far fewer side effects. When adopting a topical dosage of retinoids, for instance, the primary risk includes tolerability and skin irritation. Furthermore, topical antibiotics pose no significant risk (Krautheim et al., 2003). Whereas oral retinoids (isotretinoin) are known to cause a variety of adverse effects, including angular cheilitis, chapped lips, nasal bleeds, systemic infections, transient exacerbation of lesions, photosensitivity, and elevated serum levels of lipids (De Graaf et al., 2004). The development of resistance to antibiotics is an issue when antibiotics are used systemically. Topical anti-acne therapies, on the other hand, are relatively less efficient due to limited permeation across the skin. To address this issue, patients must take the drug for an extended period, which reduces treatment adherence. Furthermore, this might raise the possibility of bacterial resistance (Gupta et al., 2020). Such issues highlight the importance of creating new topical formulations that are more effective.

Light-based therapies

Acne may be treated using a variety of light-based techniques in addition to topical and oral drugs. These therapies are typically only useful in conjunction with drugs since they are unlikely to be as efficient as the drug. Under the care of a physician, the skin is exposed to (typically blue) light in light therapy. According to research, this can help with acne in the immediate term. However, because the studies had significant problems, the results are extremely untrustworthy. Under the care of a physician, the skin is irradiated using (typically blue) light in light therapy. According to studies, this can help with acne in the short term. However, because the studies had significant problems, the results are extremely untrustworthy. Light therapy may cause skin burning as an adverse reaction. The skin is irradiated by ultraviolet (UV) light in UV phototherapy. However, because of the dangers to the skin, this is not suggested for acne therapy (InformedHealth, 2013).

Greater efficiency, low irritation, speedy recovery, and outstanding aesthetic and therapeutic benefits have all been demonstrated with intense pulsed light (IPL). IPL was found to be safe and effective procedure for severe truncal acne (chest and back) in a research, with great cosmetic and therapeutic effects in 85% of

patients (Piccolo et al., 2022). For the treatment of acne, IPL devices have been conjungated with traditional topical and systemic treatments. Patients who are unable to receive oral acne therapy may benefit from IPL therapy with a dual-band filter (In Ryu et al., 2022). A research examined the performance of red light (RL) and blue light (BL) treatments in mild-to-moderate acne vulgaris, and showed each has significant efficiency. However, when compared to BL, RL had the benefit of having less adverse responses (Li et al., 2022). According to research, laser therapies can help with inflammatory acne in the short run. However, because there is a scarcity of high-quality studies on the long-term impacts of this strategy, it's unclear how successful it is.

Particle-based dosage forms

Liposomes, niosomes, microemulsions, lipid nanoparticles, and other innovative delivery methods are being developed for topical application in the treatment of acne. Increased solubility, absorption, and pharmacokinetics of poorly soluble drugs like isotretinoin have been achieved using a variety of modern technologies. The lipid-based and micronized formulation are two elements that have been used to increase isotretinoin bioavailability (Figure 3).

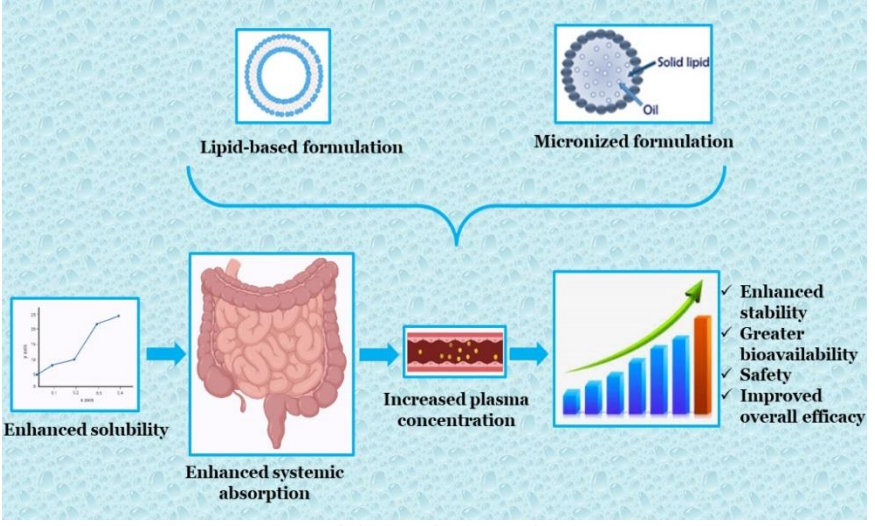

Figure 3: Novel formulations for isotretinoin

Table 4: Mechanism of novel drug formulations in acne treatment

Novel drug delivery system	Nanoformulation	Drug	Mechanism	References
Lipid-based systems	Nanoemulsions	Isotretinoin	Improved efficacy	Miastkowska et al., 2016
		Dapsone	Improved skin permeation	Borges et al., 2013
		Clindamycin phosphate + Adapalene	Improved stability, permeability, and efficacy	Sunilendu et al., 2013

	Solid Lipid Nanoparticles (SLNs)	Tretinoin	Enhanced permeation and reduced side effects	Shah et al., 2007
		Isotretinoin	Improved bioavailability and reduced side effects	Layegh et al., 2014
		Triclosan	Higher retention and permeation	Domínguez-delgado et al., 2011
	Nanostructured Lipid Carriers (NLCs)	Azelaic acid	Higher retention and lower side effects	Kumari et al., 2015
		Adapalene + Vitamin C	Improved therapeutic efficacy and safety profile	Jain et al., 2014
		Isotretinoin	Reduced photolytic degradation	Patwekar et al., 2017
Vesicular systems	Liposomal formulation	Benzoyl peroxide	enhanced the bactericidal efficacy and patient compliance	Fluhr et al., 1999
		Clindamycin	Sustained release and improved efficacy	Skalko et al., 1992; Honzak et al., 2000
		Isotretinoin	Reduced acne lesions increased efficacy and lesser side effects	Kaur et al., 2010
		Lauric acid	Enhanced the bactericidal efficacy against P. acne.	Yang et al., 2009
		Salicylic acid	Increased deposition	Bhalerao et al., 2003
		Tretinoin	Increased stability and drug retention	Rahman et al., 2016
	Niosomal formulation	Benzoyl peroxide	Minimized adverse effects and enhanced efficacy	Vyas et al., 2011
		Erythromycin	Sustained release and lesser adverse effects	Shilakari et al., 2013
		Tretinoin	Enhanced stability and minimized side effects	Varun et al., 2012; Qureshi et al., 2011

Nanoemulsions

Sunilendu et al. described a new nanoemulsion using clindamycin phosphate and adapalene as the active ingredients. The formulation had high therapeutic effectiveness as well as increased permeability (Sunilendu et al., 2013). A randomized clinical trial using the topical gel of this nanoemulsion revealed higher tolerability and effectiveness than the standard formulation. In another experiment, isopropyl myristate was used to make a nanoemulsion that demonstrated higher in-vitro epidermal absorption of dapsone, whereas n-methyl-pyrrolidone gave better solubility and improved drug release rate. When compared to clindamycin, nanoemulsions of lemongrass oil and oleic acid demonstrated enhanced zone inhibition characteristics against P. acnes. Clindamycin nanoemulsion demonstrated good physicochemical qualities as an anti-acne carrier in another investigation. The release kinetics of isotretinoin nanoemulsions were examined by Miastkowska et al. (Miastkowska et al., 2016).

Liposomes

In 1988, scientists accomplished the commercialization of liposomal gel for topical econazole administration after years of hard work. When it was discovered that liposomes can be used to target pilosebaceous units, the prospects of liposomes for effective acne therapy became clear. Ever since, there's been ongoing attempts to utilize liposomal encapsulation to provide topical antiacne drugs (Date et al., 2006).

Niosomes

Niosomes are vesicular nanosystems made up of cholesterol with non-ionic surfactants. Cholesterol is primarily employed to make the bilayer more stable. Niosomes are incredibly stable and also have the capacity to shield the enclosed drug from the environment, making them ideal for encapsulating unstable and delicate pharmaceuticals. Furthermore, they enable targeted drug delivery, resulting in a more effective therapeutic impact on the skin (Amer et al., 2019).

Lipid-nanoparticles (SLN and NLC)

Solid lipid nanoparticles (SLNs) are nano-sized colloidal systems varying in size between 50 and 1000 nm that are made up of lipids distributed in an aqueous surfactant solution to provide physical stability. SLNs have better tolerance since they use physiologically appropriate lipids. These carriers also have the following benefits: preservation of labile substances against chemical breakdowns, such as retinol and tocopherol. Furthermore, SLNs have the potential to bounce and disperse UV rays, acting as physical sunscreens and allowing photosensitive antiacne agents to be better protected. Cyproterone acetate, isotretinoin, retinoic acid, sphingosomes, tretinoin, and triclosan have all been studied as possible carriers in SLNs. Combination acne treatment has also been researched using lipid nanocarriers. The integration of tretinoin and tetracycline into nanostructured lipid carriers (NLCs) ranging in size from 200 nm produced considerably enhanced antibacterial activity against Staphylococcus aureus (Patel et al., 2020).

Miscellaneous Particle-based anti-acne formulations

Owing to the antibacterial and antioxidant properties of fullerene, it is a promising nanomaterial that might be a prospective option for treating acne. Chitosan-modified glycine-fullerene conjugate nanoparticles (Chi-Gly-Ful NPs) gel has been created to be used as a topical acne therapy (Ghabdian et al., 2021). According to an investigation, a solid lipid nanoparticle gel loaded with isotretinoin and α-tocopherol acetate can treat acne without causing skin irritation (Gupta et al., 2020). Tretinoin-loaded nanofibers have been proven as a possible anti-acne patch by Khoshbakht et al (Khoshbakht et al., 2020). Clinical studies revealed that nicotinamide-loaded chitosan nanoparticles can bring about 73 percent decrease in inflammatory acne lesions (Abd-Allah et al., 2020).

Conclusion

Although there has been great progress in the treatment of acne, the appropriate treatment method should provide a better possibility for rapid improvement with minimal side effects. Numerous topical and systemic drugs have previously demonstrated their efficacy against acne; yet, the condition's prevalence and resistant nature necessitate the development of novel dosage forms. While there has been substantial progress in treating acne, not all of it has been positive. An ideal formulation should be successful in that it is stable and enhances the uptake/permeation of active ingredients at their concentrations of efficacy; it should also be palatable and cost-efficient and should have no/negligible negative effects. Nanoformulations or the creation of nanotherapeutics with light-induced bactericidal and immunomodulatory properties might open up new avenues for the potential treatment of acne vulgaris.

References

1. Abd-Allah H, Abdel-Aziz RTA, Nasr M. Chitosan nanoparticles making their way to clinical practice: A feasibility study on their topical use for acne treatment. *Int J Biol Macromol.* 2020;156:262-270. doi:10.1016/j.ijbiomac.2020.04.040
2. Amer SS, Nasr M, Mamdouh W, Sammour O. Insights on the use of nanocarriers for acne alleviation. Current Drug Delivery. 2019 Jan 1;16(1):18-25.
3. Armstrong AW, Hekmatjah J, Kircik LH. Oral Tetracyclines and Acne: A Systematic Review for Dermatologists. Journal of Drugs in Dermatology: JDD. 2020 Nov 1;19(11):s6-13.
4. Baldwin H. Oral Antibiotic Treatment Options for Acne Vulgaris. *J Clin Aesthet Dermatol.* 2020;13(9):26-32.
5. Batara, R., Ardani, I. G. A. I., Wardani, I. A. K., Windiani, I. G. A. T., Adnyana, I. G. A. N. S., & Setiawati, Y. (2022). Psychogenic dysphagia in children, and the success of family-based treatment: Case report. *International Journal of Health & Medical Sciences*, *5*(1), 163-168. https://doi.org/10.21744/ijhms.v5n1.1894
6. Benner N, Sammons D. Overview of the treatment of acne vulgaris. Osteopathic Family Physician. 2013 Sep 1;5(5):185-90.

7. Bhalerao, S.S.; Raje, H.A. Preparation, optimization, characterization, and stability studies of salicylic acid liposomes. Drug Dev. Ind. Pharm., 2003, 29(4), 451-467.
8. Borges, V.R.; Simon, A.; Sena, A.R.; Cabral, L.M.; de Sousa, V.P. Nanoemulsion containing dapsone for topical administration: A study of in vitro release and epidermal permeation. Int. J. Nanomed., 2013, 8, 535-544.
9. Chakraborty N, Narayanan V, Gautam HK. Nano-Therapeutics to Treat Acne Vulgaris. Indian Journal of Microbiology. 2022 Jan 29:1-8.
10. Chien AL, Qi J, Rainer B, Sachs DL, Helfrich YR. Treatment of acne in pregnancy. The Journal of the American Board of Family Medicine. 2016 Mar 1;29(2):254-62.
11. Date AA, Naik B, Nagarsenker MS. Novel drug delivery systems: potential in improving topical delivery of antiacne agents. *Skin Pharmacol Physiol*. 2006;19(1):2-16. doi:10.1159/000089138
12. De Graaf YG, Euvrard S, Bouwes Bavinck JN. Systemic and topical retinoids in the management of skin cancer in organ transplant recipients. Dermatologic surgery. 2004 Apr;30(4p2):656-61.
13. Del Rosso JQ. Topical and oral antibiotics for acne vulgaris. , 35, 2. 2016 Jun 1;35(2):57-61.
14. Domínguez-delgado, C.L.; Rodríguez-cruz, I.M.; Escobar-chávez, J.J.; Calderón-lojero, I.O.; Quintanar-guerrero, D.; Ganem, A. Preparation and characterization of triclosan nanoparticles intended to be used for the treatment of acne. Eur. J. Pharm. Biopharm., 2011, 79(1), 102-107.
15. Dréno B, Layton A, Zouboulis CC, Lopez-Estebaranz JL, Zalewska-Janowska A, Bagatin E, Zampeli VA, Yutskovskaya Y, Harper JC. Adult female acne: a new paradigm. Journal of the European Academy of Dermatology and Venereology. 2013 Sep;27(9):1063-70.
16. Farrah G, Tan E. The use of oral antibiotics in treating acne vulgaris: a new approach. Dermatologic Therapy. 2016 Sep;29(5):377-84.
17. Feldman S, Careccia RE, Barham KL, Hancox JG. Diagnosis and treatment of acne. American Family Physician. 2004 May 1;69(9):2123-30.
18. Feneran AN, Kaufman WS, Dabade TS, Feldman SR. Retinoid plus antimicrobial combination treatments for acne. Clinical, Cosmetic and Investigational Dermatology. 2011;4:79.
19. Fluhr, J.W.; Barsom, O.; Gehring, W.; Gloor, M. Antibacterial efficacy of benzoyl peroxide in phospholipid liposomes. A vehiclecontrolled, comparative study in patients with papulopustular acne. Dermatology, 1999, 198(3), 273-277.
20. Fox L, Csongradi C, Aucamp M, Du Plessis J, Gerber M. Treatment modalities for acne. Molecules. 2016 Aug;21(8):1063.
21. Ghabdian Y, Taheri A, Jahanian-Najafabadi A. Development of novel topical formulation from fullerene with antibacterial activity against Propionibacterium acnes. Fullerenes, Nanotubes and Carbon Nanostructures. 2021 Feb 1;29(2):163-73.
22. Graber EM. Treating acne with the tetracycline class of antibiotics: A review. Dermatological Reviews. 2021 Dec;2(6):321-30.
23. Gupta S, Wairkar S, Bhatt LK. Isotretinoin and α-tocopherol acetate-loaded solid lipid nanoparticle topical gel for the treatment of acne. Journal of microencapsulation. 2020 Nov 16;37(8):557-65.

24. Harper JC, Roberts WE, Zeichner JA, Guenin E, Bhatt V, Pillai R. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. *J Dermatolog Treat*. 2020;31(2):160-167. doi:10.1080/09546634.2019.1587884
25. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients With Facial Acne: Two Phase 3 Randomized Clinical Trials. *JAMA Dermatol*. 2020;156(6):621-630. doi:10.1001/jamadermatol.2020.0465
26. Honzak, L.; Sentjurc, M. Development of liposome encapsulated clindamycin for treatment of acne vulgaris. Pflugers Arch., 2000, 440(Suppl 1), R044-R045.
27. Hsieh MF, Chen CH. Delivery of pharmaceutical agents to treat acne vulgaris: current status and perspectives. J Med Biol Eng. 2011;32(4):215-24.
28. Hsu P, Litman GI, Brodell RT. Overview of the treatment of acne vulgaris with topical retinoids. Postgraduate Medicine. 2011 May 1;123(3):153-61.
29. In Ryu S, Suh DH, Lee SJ, Kim KE, Jeong JY, Ryu HJ. Efficacy and safety of intense pulsed light using a dual-band filter for the treatment of facial acne vulgaris. Lasers in Medical Science. 2022 Feb;37(1):531-6.
30. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. Acne: Do lotions, tablets or light-based treatment help? 2013 Jan 13 [Updated 2019 Sep 26]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279210/
31. Jain, A.K.; Jain, A.; Garg, N.K.; Agarwal, A.; Jain, A.; Jain, S.A.; Tyagi, R.K.; Jain, R.K.; Agrawal, H.; Agrawal, G.P. Adapalene loaded solid lipid nanoparticles gel : An effective approach for acne treatment. Colloids. Surf. B. Biointerfaces., 2014, 121, 222- 229.
32. Kalabalik-Hoganson J, Frey KM, Ozdener-Poyraz AE, Slugocki M. Clascoterone: A novel topical androgen receptor inhibitor for the treatment of acne. Annals of Pharmacotherapy. 2021 Oct;55(10):1290-6.
33. Kaur, N.; Puri, R.; Jain, S.K. Drug-cyclodextrin-vesicles dual carrier approach for skin targeting of anti-acne agent. AAPS. Pharm. Sci. Tech., 2010, 11(2), 528-537.
34. Khoshbakht S, Asghari-Sana F, Fathi-Azarbayjani A, et al. Fabrication and characterization of tretinoin-loaded nanofiber for topical skin delivery. Biomater Res. 2020;24(1):8
35. Kim, J.; Kim, H.; Jeon, S.; Jo, J.; Kim, Y.; Kim, H. Synergistic Antibacterial Effects of Probiotic Lactic Acid Bacteria with Curcuma longa Rhizome Extract as Synbiotic against Cutibacterium acnes. Appl. Sci. 2020, 10, 8955
36. Kolli SS, Pecone D, Pona A, Cline A, Feldman SR. Topical retinoids in acne vulgaris: a systematic review. American Journal of Clinical Dermatology. 2019 Jun;20(3):345-65.
37. Kosmadaki M, Katsambas A. Topical treatments for acne. Clinics in dermatology. 2017 Mar 1;35(2):173-8.
38. Kraft J, Freiman A. Management of acne. *CMAJ*. 2011;183(7):E430-E435. doi:10.1503/cmaj.090374
39. Krautheim A, Gollnick H. Transdermal penetration of topical drugs used in the treatment of acne. Clinical pharmacokinetics. 2003 Dec;42(14):1287-304.
40. Kumari, S.; Pandita, D.; Poonia, N.; Lather, V. Nanostuctured lipid carriers for topical delivery of an anti-acne drug: Characterization and ex-vivo evaluation. Pharm. Nanotechnol., 2015, 3(2), 122-133.

41. Layegh, P.; Mosallaei, N.; Bagheri, D.; Jaafari, M.R.; Golmohammadzadeh, S. The efficacy of isotretinoin-loaded solid lipid nanoparticles in comparison to Isotrex ® on acne treatment. Nanomed. J., 2014, 1(1), 38-47
42. Layton AM. A review on the treatment of acne vulgaris. International journal of clinical practice. 2006 Jan;60(1):64-72.
43. Leyden J, Stein-Gold L, Weiss J. Why topical retinoids are mainstay of therapy for acne. Dermatology and therapy. 2017 Sep;7(3):293-304.
44. Li J, Li J, Zhang L, Liu X, Cao Y, Wang P, Wang X. Comparison of red light and blue light therapies for mild-to-moderate acne vulgaris: A randomized controlled clinical study. Photodermatology, photoimmunology & photomedicine. 2022 Jan 3.
45. Miastkowska, M.; Sikora, E.; Ogonowski, J.; Zielin, M.; udzik. A. The kinetic study of isotretinoin release from nanoemulsion. Colloids. Surf. A., 2016, 510, 63-68.
46. Momen S, Al-Niaimi F. Acne vulgaris and light-based therapies. Journal of Cosmetic and Laser Therapy. 2015 May 4;17(3):122-8.
47. Najafi-Taher R, Amani A. Nanoemulsions: colloidal topical delivery systems for antiacne agents-A Mini-Review. Nanomedicine Research Journal. 2017 Feb 1;2(1):49-56.
48. Ochsendorf F. Minocycline in acne vulgaris. American journal of clinical dermatology. 2010 Oct;11(5):327-41.
49. Ogé LK, Broussard A, Marshall MD. Acne vulgaris: diagnosis and treatment. American family physician. 2019 Oct 15;100(8):475-84.
50. Otlewska A, Baran W, Batycka-Baran A. Adverse events related to topical drug treatments for acne vulgaris. Expert Opinion on Drug Safety. 2020 Apr 2;19(4):513-21.
51. Paiva-Santos AC, Mascarenhas-Melo F, Coimbra SC, Pawar KD, Peixoto D, Chá-Chá R, Araujo AR, Cabral C, Pinto S, Veiga F. Nanotechnology-based formulations toward the improved topical delivery of anti-acne active ingredients. Expert opinion on drug delivery. 2021 Oct 3;18(10):1435-54.
52. Patel R, Prabhu P. Nanocarriers as versatile delivery systems for effective management of acne. International Journal of Pharmaceutics. 2020 Apr 15;579:119140.
53. Patwekar, S.L.; Pedewad, S.R.; Gattani, S. Development and evaluation of nanostructured lipid carriers-based gel of isotretinoin. Part. Sci. Technol., 2017, 35, 1-12.
54. Pei S, Inamadar AC, Adya KA, Tsoukas MM. Light-based therapies in acne treatment. Indian dermatology online journal. 2015 May;6(3):145.
55. Piccolo D, Kostaki D, Dianzani C, Crisman G, Conforti C. Effective Intense Pulsed Light Protocol in the Treatment of Moderate to Severe Acne Vulgaris of the Chest and Back. *J Clin Aesthet Dermatol*. 2022;15(3):22-25.
56. Polonini H, Zander C, Radke J. CleodermTM Clarifying Cream: A Novel, Topical Vehicle Using Plant-Based Excipients and Actives Targeting Acne and Oily Skin. Journal of Cosmetics, Dermatological Sciences and Applications. 2021 Nov 5;11(4):381-99.
57. Purdy S, de Berker D. Acne vulgaris. BMJ clinical evidence. 2011;2011.
58. Qureshi, S.R.; Sahni, Y.P.; Singh, S.K.; Bhat, M.A.; Dar, A.A.; Quadri, S.A. Nanotechnology based drug delivery system. J. Pharm. Res. Opin., 2011, 1, 161-165.

59. Rahman, S.A; Abdelmalak, N.S.; Badawi, A.; Elbayoumy, T.; Sabry, N.; El Ramly, A. Tretinoin-loaded liposomal formulations: from lab to comparative clinical study in acne patients. Drug. Deliv., 2016, 23(4), 1184-1193.
60. Rigopoulos D, Larios G, Katsambas AD. The role of isotretinoin in acne therapy: why not as first-line therapy? Facts and controversies. *Clin. Dermatol.*, 28: 24-30, 2010.
61. Sandoval LF, Hartel JK, Feldman SR. Current and future evidence-based acne treatment: a review. Expert opinion on pharmacotherapy. 2014 Feb 1;15(2):173-92.
62. Searle T, Ali FR, Al-Niaimi F. Zinc in dermatology. Journal of Dermatological Treatment. 2022 Apr 8:1-4.
63. Settelmeier S, Rassaf T, Hendgen-Cotta UB, Stoffels I. nitric oxide generating formulation as an innovative approach to topical skin care:An open-label pilot study. Cosmetics. 2021;8:16
64. Shah, K.A.; Date, A.A.; Joshi, M.D.; Patravale, V.B. Solid lipid nanoparticles (SLN) of tretinoin: Potential in topical delivery. Int. J. Pharm., 2007, 345(1-2), 163-171.
65. Shilakari, G.; Singh, D.; Asthana, A. Novel vesicular carriers for topical drug delivery and their application's. Int. J. Pharm. Sci. Rev. Res., 2013, 21(1), 77-86.
66. Simonart T. Newer approaches to the treatment of acne vulgaris. American journal of clinical dermatology. 2012 Dec;13(6):357-64.
67. Singh N, Singh M and Panwar S. An overview on Novel Drug Delivery Systems for Acne. Int. J. Res. Dev. Pharm. L. Sci. 2019; 8(4): 1- 12. doi: 10.13040/IJRDPL.2278-0238.8(4).1-12
68. Skalko, N.; Cajkovac, M.; Jalsenjak, I. Liposomes with clindamycin hydrochloride in the therapy of acne vulgaris. Int. J. Pharm., 1992, 85(1-3), 97-101.
69. Stuart B, Maund E, Wilcox C, Sridharan K, Sivaramakrishnan G, Regas C, Newell D, Soulsby I, Tang KF, Finlay AY, Bucher HC. Topical preparations for the treatment of mild-to-moderate acne vulgaris: systematic review and network meta-analysis. British Journal of Dermatology. 2021 Sep;185(3):512-25.
70. Sunilendu, B.R.; Kothari, J.S.; Shafiq, S.; Pancholi, J.S.; Patel, J.D.; Ravindra, M. Pharmaceutical compositions of anti-acne agents. U.S Patent 2013/0280308 A1, October 24, 2013.
71. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, *5*(3), x-xv. https://doi.org/10.53730/ijhs.v5n3.2938
72. Sutaria AH, Masood S, Schlessinger J. Acne Vulgaris. [Updated 2021 Aug 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459173/
73. Tan AU, Schlosser BJ, Paller AS. A review of diagnosis and treatment of acne in adult female patients. *Int J Womens Dermatol.* 2017;4(2):56-71. Published 2017 Dec 23. doi:10.1016/j.ijwd.2017.10.006
74. Tanghetti EA, Werschler WP, Lain T, Guenin E, Martin G, Pillai R. Tazarotene 0.045% Lotion for Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Results from Two Phase 3 Trials. *J Drugs Dermatol.* 2020;19(1):70-77. doi:10.36849/JDD.2020.3977

75. Varun, T.; Sonia, A.; Bharat, P.; Patil, V. Niosomes and liposomes - vesicular approach towards transdermal drug delivery. Int. J. Pharm. Chem. Sci., 2012, 1(3), 981-993.
76. Vyas A, Kumar Sonker A, Gidwani B. Carrier-based drug delivery system for treatment of acne. *ScientificWorldJournal*. 2014;2014:276260. Published 2014 Feb 9. doi:10.1155/2014/276260
77. Vyas, J.; Vyas, P.; Raval, D.; Paghdar, P. Development of topical niosomal gel of benzoyl peroxide. Int. Sch. Res. Notices. Nanotechnol., 2011, 2011, 1-6.
78. Yang, D.; Pornpattananangkul, D.; Nakatsuji, T.; Chan, M.; Carson, D.; Huang, C.M.; Zhang, L. The antimicrobial activity of liposomal lauric acids against Propionibacterium acnes. Biomaterials, 2009, 30(30), 6035-6040.
79. Yeh L, Bonati LM, Silverberg NB. Topical retinoids for acne, 35, 2. 2016 Jun 1;35(2):50-6.
80. Zhanel G, Critchley I, Lin L-Y, Alvandi N. Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris. *Antimicrob. Agents Chemother.* 63(1), e01297–e01218 (2019).