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Recent approaches in topical acne treatment and drug delivery

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ABSTRACT: Acne vulgaris is a widespread chronic disease of the hair follicles associated with the sebaceous glands. Disease factors include occlusion of follicles, hyperkeratinizations, keratin plug formation, enlargement of the sebum gland and increased sebum production. The selection of drugs to be applied in acne treatment is made according to criteria such as the degree of acne lesions, the preferred route of administration, and the patient's medical condition. With its large surface area, the skin is a high potential route for drug release, so topical agents have a wide range of uses. However, these agents often have disadvantages such as dry skin, peeling and skin irritation or bacterial resistance. In order to minimize these disadvantages, new drug delivery systems have been developed. Drug delivery systems are biocompatible systems that enable the transport of molecules for pharmaceutical applications. These systems are usually designed at nanometric and micrometric levels for purposes such as increasing site specificity and penetration. Topical drug delivery systems are preferred due to eliminating the need for systemic drug treatments, minimizing the total dose required to reach the targeted layers in the skin, and reducing side effects. Nanotechnological approaches such as particulate, vesicular, colloidal drug delivery systems and various other systems have an important place in the treatment of acne. These approaches offer significant opportunities for designing novel, low-dose and effective treatment systems to control acne. In this review, recent approaches to topical acne treatments and drug delivery have been overviewed.

KEYWORDS: Acne vulgaris, topical treatment, nanocarrier systems, drug delivery.

1. INTRODUCTION

Acne also known as acne vulgaris is a skin disorder that causes comedones, inflammatory lesions and scars. The pathogenesis stages of acne are excessive sebum secretion from sebaceous glands, excessive keratinization, growth of anaerobic bacteria in hair follicles, and inflammatory response (1)(2).

Topical therapy is the first-line treatment for all types of acne (3). Human skin plays a role as a strong barrier against the passage of externally applied drugs. Epidermis, dermis and hypodermis are the layers of the skin and the stratum corneum, which is the outermost layer of the epidermis, is a strong barrier to permeability. The main goal for drug treatment is achieving the topical penetration and retention of the drug at the desired skin layers (4). In case of drug treatment, structure of human skin restricts the active substances by physicochemical barriers that will pass through the barrier that required the drugs have sufficient lipophilicity and a Mw <500 Da (5). Therefore, a wide variety of ways to facilitate and increase the penetration of drugs for topical applications are being explored. Physical penetration enhancers or chemical enhancers like alcohols, polyalcohols, surfactants, fatty acids, esters, pyrrolidones, amines, amides, sulfoxides, terpenes, alkanes, and phospholipids can be useful to increase skin penetration (6).

Penetration enhancers aim to irritate the skin because of their destructive effects on the skin lipids. The concentration that the skin can tolerate is typically higher than the quantity of penetration enhancers

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needed to produce pharmacologically effective drug penetration rates. As an alternative, scientists have developed delivery systems for topical treatments using nanotechnology, in particular nanoparticles and nanofibers (2)(4).

In order to increase the efficacy of biotherapeutic agents in comparison to conventional dosage forms, innovative drug delivery systems aim to manufacture novel pharmaceutical forms with optimal qualities including reduced particle size, higher permeability parameters and specific site targeting (7).

Nanoparticles have several advantages over other conventional technologies when it comes to topical application. These benefits include making the medication more soluble and serving as a depot for controlled release. Additionally, they promote drug stability and give drug encapsulation a wider surface area to work with, reducing degradation. Additionally, nanoparticles can penetrate the subcutaneous layer, the principal barrier to drug release, increasing drug absorption and offering a reliable method of transdermal and topically administering all medications. They are well tolerated locally. Additionally, it has been claimed that they can reduce skin irritation brought on by conventional therapy approaches. The lipid, vesicular and the polymer based nanoparticles are the most extensively researched (8). On the way of the targetted tissue or locus of infection, micro- and nano-scale drug carriers pass through a variety of dynamics of biological tissues. Biological barriers which mediated the process include cellular absorption and intracellular exchange, immune system, mucus and bacterial biofilm formation and tissue barriers. Enhancing these factors is crucial to improving the effectiveness of the drug delivery mechanism (9). In the preference of a drug delivery system, features such as good biocompatibility, low cytotoxicity, high drug content, increasing drug stability and compatibility with the drug route of administration should be considered (10).

In this review, an overview of the active substances currently used in topical acne treatment and research based on new generation drug carriers is presented.

2. RECENT APPROACHES FOR TOPICAL MEDICATION OF ACNE VULGARIS

One of the simplest and safest treatments for acne is a topical medication that can be preferred for mild to moderate acne. It offers a lot of benefits. One of them involves applying directly to the lesion, which increases the treatment's exposure to the hair root follicles. It is advised to treat mild to moderately severe inflammatory acne with topical antibiotics. Topical antibiotics are believed to build up in hair follicles where they may have anti-inflammatory and antibacterial effects. The fact that topical antibiotics have very low irritating profiles is by far their most popular benefit where the significant drawback can be accepted as the occurrence of bacterial resistance against *Propionibacterium acnes (P. acnes) and Staphylococcus aureus (S. Aureus*). In Table 1, active substances used topically in acne, their mechanism of action and side effects are given (11)(12)(13)(14)(15)(16).

Table 1. Topically used active substances in acne, mechanisms of action and side effects.

Active Ingredient Name	Effect Mechanism	Side Effect
Retinoic acids (Tretinoin)	It increases the circulation of follicular epithelial cells and stimulates comedolysis.	Skin irritation, redness, and rash
Tazarotene	It prevents excessive proliferation of cells and has an anti-inflammatory effect.	Itching, peeling and stinging
Adapalene	It prevents excessive proliferation of follicular epithelial cells and has an anti-inflammatory effect.	Local erythema, dryness, pruritus
Dapsone	It has effective on *P. acnes* and *S. Epidermidis* with anti-inflammatory and antibacterial effects.	Local oiliness, erythema, itching and redness
Azelaic acid	It has effective on *P. acnes* and *S. Epidermidis* with anti-inflammatory and antibacterial effects and has a keratolytic effect on the skin.	Skin itching and burning
Benzoyl peroxide	It is bactericidal against *P. acnes.*	Discoloration, irritation and erythema of hair, sheets and feathers
Clindamycin Erythromycin	It has antibacterial and anti-inflammatory effects.	Local erythema, burning and dryness of the skin

3. RECENT STUDIES ON DRUG CARRIER SYSTEMS COMBINED ANTIACNE MOLECULES

According to the new generation drug delivery systems structures; vesicular systems and particulate systems, can be classified as colloidal and micellar systems. For topical treatment, anti-acne drug loaded vesicular and particulate delivery systems have advantages over the conventional current topical delivery system. The encapsulation of anti-acne drugs in vesicular and particle delivery systems represents an innovative approach to minimizing side effects and maintaining their effectiveness. In severe acne cases, drugs need to be prescribed for systemic use. Advances in new drug delivery systems may allow safer use of these agents by the topical route. (17). Vesicular systems are modulating drug delivery and targeting to improve efficacy and also safety. Liposomes, ethosomes, niosomes, transfersomes, pharmacosomes, colloidosomes, autosomes, invasomes and sphinosomes are vesicular drug delivery systems (18). Particulate drug delivery systems include systems like solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) (19). Nanotechnological systems for topical delivery for acne treatment are mainly; solid lipid nanoparticles and microspheres (particular systems), liposomes and niosomes (vesicular systems), microemulsion and nanoemulsion (colloidal systems), aerosol foams and microsponges. And those systems offer crucial possibilities for designing new, fewer dose, and more efficient treatments for acne management (20). Colloidal carrier systems include nano and microemulsions. Micellar carrier systems include micro and nanoparticles and polymeric nanoparticles, aerosol foams, carbon nanotubes, microsponge and nanosuspensions. The controlled drug release and subsequent biodegradation of these new carrier-based delivery systems are essential to developing successful formulations.

Nanotechnology is a subject where a lot of work is carried out, especially in the field of medicine and pharmacy, to develop and control materials in the desired molecular size range in a reproducible way (21). The main advantages of nano drug delivery systems are to provide improved bioavailability by increasing water solubility, increasing the duration of resistance in the body, and targeting the drug to the desired location in the body. These advantages result in a simultaneous reduction of the drug dose and thus dose-related undesirable, toxic effects, providing the safe delivery of toxic active agents and protecting non-target tissues and cells from serious adverse effects. A wide variety of carriers have been developed, consisting of different structures in terms of chemical and physical properties such as different material, size, shape and surface properties (22).

Novel drug carrier systems are successful in improving the release of anti-acne agents to the skin with increased dermal localization and reduced undesirable effects. They enable to direct drug loading, controlled release and subsequent biodegradation which are valuable advantages to developing successful dosage forms (20).

Topical retinoids which can be grouped as tretinoin, adapalene and tazarotene are frequently used topical active agents which unfortunately cause undesirable and adverse effects, such as skin dryness, peeling, and skin irritation or bacterial resistance. In order to reduce these undesirable effects, novel drug carrier systems including the lower dose of drugs have been used (23)(24). Another topical retinoid isotretinoin (ITN) has an anti-inflammatory effect, significant activity by various mechanisms by reducing cell cycle progression, cellular differentiation and apoptosis, and is also effective on comedogenesis by reducing sebum production. Besides those advantages, it causes local irritation, redness, peeling and burning at the application site and those limits its patient acceptance. In addition, ITN is extremely sensitive to oxidative degradation, which is another concern for the stability of the topical formulation (25). Due to the limitations of ITN in conventional topical applications, new delivery systems have been used. In the study of Gupta et al. (26), AE-SLN containing ITN and α-Tocopherol based gel is presented, which shows better efficacy compared to the traditional gel forms. With the combination of ITN and alpha-tocopherol acetate, a strong anti-acne effect was achieved while no skin irritation occurred. For this reason, it can be said that with this developed SLN carrier system, serious advantages are provided compared to traditional gel formulations.

Layegh et al. (27) developed ITN loaded SLN formulations with a size of approximately 60 nm. Stability results were observed to be good when these developed formulations were kept at 4 °C for 3 months. Next, the SLN efficacy was compared with one of the commercial products in 30 patients that resulted as SLN`s superior activity against lessions (both inflammatory and non-inflammatory) and good patient tolerability.

Adapalene as the third-generation retinoid, which is not extensively used due to its current available topical dosage forms has insufficient efficacy and patient compliance related to undesired effects like skin irritation, erythema, dryness and pruritus. Jain et al. (18) aimed to develop and characterize adapalene loaded SLNs for effective topical drug release. They tested the SLN-based adapalene gel they developed on rats and observed that it could provide the localization of adapalene in the epidermis without its systemic uptake in the skin layers. The enhanced adapalene loaded SLNs nanoparticulate system showed good therapeutic response and efficacy with minimal undesirable-adverse effects. The success of this study is an important development in the treatment of acne by targeting the drug to the skin layer mechanism.

Tretinoin (retinoic acid, RA), as well as ITN is widely preferred in the treatment of mild to moderate acne. However, in topical use of RA, undesired effects like sensitivity to sunlight, eczematous irritation, mild and severe erythema when applied simultaneously, and frequently observed interactions with other products are limiting factors for patient compliance, thus many new approaches have been developed to minimize these problems. One of these is the study of Silva et al. (28) in which they aimed to evaluate their antibacterial activities by developing SLNs including lauric acid and RA. The results of the study showed that lauric acid contributed to the incorporation of SLNs and retinoic acid, but stearylamine is required to provide the stability of the encapsulation. Retinoic acid-lauric acid included SLNs have been shown to offer an alternative for the topical treatment of acne vulgaris by showing growth inhibitory activity against *S. epidermidis*, *P. acnes* and *S. aureus*.

The system of nanolipid particles has also been studied in order to solve the irritation problem of the marketed gel form of RA and to provide a longer drug effect period (29). NLCs are modified SLNs in which the lipid phase contains both solid and liquid lipids at room temperature (30).

Ghate et al. (29) were succeeded in the development of RA-loaded NLCs incorporated with carbopol gels including oleic acid, stearic acid, Tween 80 and Span 60. Skin irritation test was studied with male Wister rats. NLCs loaded gel applied for 7 days and irritation or erythema on the skin wasn't observed. However, marketed RA gel showed irritation and slight erythema within 3 days. NLCs have been observed to prolong the release of the drug compared to conventional gel formulations. The results of the current study showed that NLCs are promising carriers for tretinoin.

The many advantages offered by NLC gels have led them to be used as a carrier system for isotretinoin, the main drug of acne treatment. Patwekar & Pedewad (31) tried to formulate the isotretinoin loaded NLC gel using the hot homogenization method to make ITN with poor water solubility more suitable for topical application. According to in vivo study, NLC-based ITN gel did not show skin irritation and edema. The irritation score of the test formulation on skin was 0 at the end of 48, 72 h. This formulation offered new approaches to the treatment of acne by reducing side effects and confirmed the potential of water-soluble drugs in nanostructured lipid form for topical application.

Dapsone, which is a sulfone, has low water solubility with anti-inflammatory and antibacterial properties. The topical administration of a 5% dapsone gel has recently been used for acne vulgaris and has

shown good efficacy and safety. It offers a tolerable treatment option especially for inflammatory acne lesions (32). Elmowafy et al. (32) investigated the potential benefits of NLCs to improve the topical release of dapsone. The formulation they prepared by embedding dapsone in the lipid matrix showed a significant improvement in skin localization, efficacy and safety of the drug. These findings conclusively confirm the safe and significant effects of cationic NLCs on dapsone topical drug release.

Liposomes are colloidal vesicles used as drug delivery systems. It is known that liposomes increase the penetration of encapsulated drugs into the skin well (33). Liposomes offer various benefits like biocompatibility, non-toxicity and flexibility, reduction of adverse effects of drugs, protection from the inactivating effect of external conditions and unique ability to deliver pharmaceutical agents into cells and even into individual cellular compartments (34). Honzak and Sentjurc (35) conducted studies based on the finding that liposome-encapsulated drugs have better penetration through the skin. For the topical treatment of acne vulgaris, they aimed to improve the effectiveness of the drug and eliminate its undesired effects with the development of a formulation containing clindamycin trapped in the liposome. Based on the clinical trial, they concluded that the liposomal clindamycin 1% formulation was much more effective than the conventional clindamycin 1% solution.

In a study, liposome formulations of RA were prepared for the treatment of acne. Since RA causes lipophilicity, instability and local irritation when applied topically, liposome is the most suitable delivery system to control these side effects. It has been reported that liposomes are superior to conventional topical preparations as drug delivery systems for topical therapy. Work on liposomes to target drugs to pilosebaceous units showed that liposomes are potent drug carrier systems for the treatment of hair follicle-related disorders such as acne (36). In this line, Rahman et al. (36) aimed to prepare RA liposomal gel in order to achieve lower skin irritation and better efficacy. They observed that the formulation they prepared had better skin tolerability against non-inflammatory acne lesions compared to conventional preparations. Patel et al. (37) also worked on developing the liposomal RA gel for the treatment of acne in patients. They achieved better efficacy with lower undesired effects (erythema and irritation) with liposomal RA gel compared to conventional gel. The findings of this study underline the benefits of liposomal RA gel in the treatment of acne.

Loading multiple drug substances into nanocarriers such as liposomes is also an interesting approach to achieve a synergistic efficacy and less complex dosing schedules in multidrug treatment regimens. Combination of drugs co-encapsulated in liposomes is also advantageous in overcoming the solubility and stability problems of drugs but may also have a potential synergistic therapeutic effect and reduce side effects. In the treatment of acne, liposomal drug release can improve drug efficacy, reduce side effects, and improve patient compliance through targeted delivery to pilosebaceous units (38). Therefore, Ingebrigtsen et al. (38) aimed to encapsulate benzoyl peroxide (BPO) and chloramphenicol (CAM) together in the liposome. For drugs that do not exhibit cytotoxicity, the toxicity of the carrier appears to be more important, while for more cytotoxic drugs, the carrier has a protective effect against the effect of the drug on cells. The presence of CAM in the formulations did not have a negative effect on cytotoxicity. This situation makes it an effective antibiotic for further administration in topical liposomal formulations. Antibiotics have been used for many years to treat acne. However, antibiotic resistance is common in acne. In order to overcome the problem of antibiotic resistance, it may be the right approach to increase the penetration of the drug into the lower layers of the skin with less dosing by using new drug carriers. Azithromycin, with its superior tissue distribution, is a macrolide antibiotic that is used both orally and topically as an anti-acne agent. The potential of topical liposomal antibiotics in the treatment of acne is well known. Curcumin therapeutic efficacy dates back to its notable anti-inflammatory, antibacterial, antioxidant effects and negligible undesired effects (39). Therefore, Madan et al. (39) developed a topical liposomal gel formulation due to anti-inflammatory and antibacterial activities of curcumin and lauric acid, respectively. This cationic liposomal gel formulation consisted of of lipids (Phospholipon 90 G and Phospholipon 90 H) and encapsulated drugs; curcumin, lauric acid and azithromycin. The study revealed the benefits of combined administration of active ingredients in liposomal gel forms and topical azithromycin administration for acne treatment.

Ethosomes are one of the modified liposome derivatives. In their structure, phospholipids are formable vesicles containing high concentrations (20-45%) of alcohol (ethanol) and water. The presence of ethanol, which is known to increase permeability well, helps the ethosomes to carry into deep layers of skin. The interdigitation effect of ethanol also helps the vesicles gain a flexible structure. So, they can get stuck and pass through the pores in the skin. In addition, the presence of ethanol helps drugs with different physicochemical properties to be included in the structure (40). Touitou et al. (41) studied on an ethosomal gel containing clindamycin and salicylic acid for acne treatment in an 8-week double-blind randomized

clinical trial on 40 patients. It was indicated that patients have mild to moderate symptoms showed good compliance with a significant reduction in the total number of inflammatory and non-inflammatory lesions observed following 8 weeks of treatment. Over 70% of the participants reported partial or complete recovery and over 80% of patients who had previously received non-ethosomal clindamycin and salicylic gel treatments reported that they experienced less burning, itching, erythema and photosensitivity reactions. This study showed the effectiveness and good patient compliance of ethosomal gel forms in acne treatment.

Studies have been conducted on the antibacterial activity of tea tree oil, against harmful bacteria without harming healthy skin bacteria. It has also been confirmed that this oil inhibits the growth of gram-positive bacteria (*P. acnes*) associated with acne. The topical application of the active ingredient also increases patient compliance by eliminating the side effects of this oil. However, the inability of tea tree oil formulations to penetrate the skin leads to low clinical efficacy (42). Therefore, Venugopal et al. (42) aimed to develop an improved ethosomal formulation with a high degree of permeability for the treatment of acne. They evaluated ethosomes that were prepared with small vesicular size and maximum oil retention properties as a suitable carrier system for topical application. They observed that the ethosomal formulations they prepared were a promising treatment option by releasing drugs at various points in the skin passageway.

Azelaic acid is an anti-acne drug with an antibacterial action against *P. acnes* that requires penetration from stratum corneum into the sebaceous tissue and through the thick peptidoglycan layer of *P. acnes* into the cytoplasm. Due to increasing the penetration of azelaic acid through the skin, Apriani et al. (43) first formulated azelaic acid as ethosome and then turned this etosomal azelaic acid into a cream. In their study, they observed that this cream showed anti-acne activity against *P. acnes* and was also more effective and safer compared to the conventional cream form on the market.

Transfersomes are elastic spherical vesicles, which are composed of one or more phospholipid bilayers and a single-chain surfactant (edge activator) with particle sizes ranging from 30 nm to several micrometers. Transfersomes are successful vesicles to improve the permeability by compressing themselves along the intercellular lipid of the stratum corneum (44). Effectively used to treat acne vulgaris in humans, adapalene has cutaneous undesirable effects such as irritation, erythema, peeling, and dryness. This reduces patient compliance, ultimately compromising the effectiveness of the drug. Vitamin C can be added to formulations to help eliminate side effects associated with conventional monotherapy of adapalene. Vitamin C, which has an antioxidant, collagen synthesis stimulating and depigmentation activity is also widely used in various cosmetic products. Vasanth et al. (45) formulated an adapalene-loaded transfersome gel containing vitamin C as a combination therapy for acne vulgaris. They found that the optimized adapalene-loaded transfersomal gel containing vitamin C had a better delivery system compared to the marketed gel version. Additionally, supplementation of vitamin C has been found to play an important role in improving the quality of treatment.

Niosomes, which are alternative to liposomes are monolayer or multilayered nonionic surfactant vesicles formed from synthetic nonionic surfactants by hydration. Patel et al. (46) aimed to load RA into niosome vesicles and also to incorporate it into Carbopol® 971 gel. They used Span 60 as a nonionic surfactant and cholesterol as a vesicle stabilizer. In their research, they compared skin irritation tests of RA niosomal gel, RA drug solution and RA gel. *In vivo* skin irritation tests revealed that the niosome formulation significantly reduced erythema, crusting, and lesions associated with RA treatment. They concluded from the present research that niosomes are versatile dosage forms and therefore require further investigation to improve its dosage forms.

Proniosomes are dry formulation prepared using suitable carrier coated with non-ionic surfactants. The formulation can be converted to niosomes by hydration before use. Proniosomes are more stable because they are a dry and free-flowing product. thus, they can extend the shelf life of drugs. Rahman et al. (47) aimed to develop a new formulation containing the proniosome carrier system for the topical application of RA which is frequently used in acne treatment. They prepared RA using proniosomes, which is successful carriers for an effective treatment of acne by acting on a pathogenic area. The formulation showed better efficacy and very low irritation potential when compared to marketed product in human volunteers.

Rosemarinic acid (ROA) is a naturally occurring caffeic acid ester, which has lipophilic nature with antibacterial and anti-inflammatory potential. ROA has low water solubility. In order to overcome its lipophilicity, Budhiraja & Dhingra (48) loaded ROA into niosomes to improve skin condition both by reducing transepidermal water loss and improving stratum corneum properties and by increasing smoothness by reloading lost skin lipids. This study revealed the preparation of ROA-loaded niosomes and

in vitro antimicrobial evaluation against *P. acnes* and *S. aureus*. The development of a niosomal gel of ROA for sustained release into bacteria-infected cells is also included in this study. Drug-loaded niosomes for topical application were absorbed from the epidermis without systemic effects. While the non-niosomal gel of ROA was effective against *S. aureus* and *P. acnes* on the first day, it lost its effectiveness on the 4th day. Despite that niosomal gel has been found to be effective for up to 4 days of application due to prolonged release. As a result of the study, it was found that ROA niosomes increase the retention of ROA in the skin and facilitate its prolonged release. Therefore, it was concluded that ROA has a strong inhibitory potential against *P. acnes* and can be used as a possible treatment against these bacteria, provided that it reaches the deeper layers of the skin.

Al Saba et al. (49) using varios Span (20, 40, 60 and 80) and cholesterol, prepared dapsone-loaded niosome formulations, which is an anti-acne agent, by thin-film hydration method. The niosomes were prolonged release up to 24 hours with good efficacy. Niosomes containing Span 60 showed a higher drug release after 24 hours and also higher entrapment efficiency compared to other formulations. This is thought to be because Span 60 has the longest alkyl chain, increasing drug release. In patients, both inflammatory and non-inflammatory lesions of acne vulgaris responded to once-daily topical application of dapsone niosomes, resulting in healing of the lesions, but negligible adverse effects such as mild erythema and post-inflammatory hyperpigmentation were also observed after topical application.

Goyal et al. (6) formulated BPO niosomes (308.9 nm in size and polydispersity index 0.332) in a Carbopol 934-based gel for the treatment of acne. Niosomes presented 72% drug release after 24 hours and niosomal gel showed 47% release after 24 hours. Niosomal gel provided superior skin absorption than plain gel, reduced side effects of skin irritation and showed greater skin deposition. After 4 days of treatment, it showed superior antibacterial activity against *S. aureus and P. acnes* than the conventional drug solution. As a result of the study, it was concluded that the niosomal formulation of BPO is more effective than conventional preparations.

Microemulsions (ME) are considered an effective carrier for dermal application as they offer increased drug solubility potential by providing a high concentration gradient toward the skin. ME have several benefits such as long-term stability, easy preparation, and significant capacity to dissolve various active agents, and their components can act as penetration enhancers by disrupting the stratum corneum structure and increasing the permeability of the drug through the skin (50).

ME are used primarily for transdermal formulations rather than their topical drug application potential due to their low viscosity and the presence of penetration enhancing surfactants and co-surfactants (51). Patel et al. (51) aimed to optimize the dermal deposition of ME. For this, they used the lipophilic tazarotene molecule, which is known to have an anti-acne effect. Tazarotene is a synthetic topical retinoid known to improve abnormal differentiation of keratinocytes and reduce their hyperproliferation by reducing inflammatory markers. Microemulsification method consisting of 10% Labrafac CC, mixed emulsifiers 15% Labrasol–Cremophor–RH 40 (1:1), 15% Capmul MCM. Moreover, ME-based gel was prepared with Carbopol®971P NF in optimized ME formulation having higher skin permeation rate. ME-based gel showed advantage over marketed formulation in improving the skin tolerability of tazarotene. It has been observed that the topical focused ME formulation in their studies can be beneficial in site-specific dermal treatment with minimum drug systemic availability and high skin tolerance. Therefore, they recommended that further studies be conducted on the treatment of acne in the future.

Miastkowska et al. (52) also studied to formulate a nanoemulsion as a carrier for topical release of ITN used in the anti-acne treatment and to determine the release kinetics of the active substance from the nanoemulsion. They obtained oil-in-water nanoemulsions loaded with ITN based on coconut oil and stabilized with Polysorbate 80. In the results of the study, positive effects of nanoemulsion on ITN release were observed. The profile of ITN release from nanoemulsion the best fit to zero order kinetic model. Controlled ITN release can minimize drug side effects due to a reduction in drug administration frequency. It has been concluded that nanoemulsions are effective tools for modified drug delivery with long-term dermatological effects and reduce side effects with this research.

In the study of Sabouri et al. (53) a RA-loaded nanoemulsion was developed to compare with the conventional RA 0.05% emulsion in acne vulgaris lesions. In a 6-week pilot clinical study with RA-loaded nanoemulsions, the acne lesions and the intensity of porphyrin production, a marker produced by *P. acnes* bacteria, were significantly reduced after topical application of nanoemulsion including RA. In addition, adverse effects such as side effects and slow release of the drug have been eliminated. The developed formulation showed the appropriate efficacy and high loading capacity of RA in the nanoemulsion system.

To improve the dermal application of adapalene, increase its effectiveness and minimize adverse effects, thereby providing better user compliance, Pajic et al. (54) aimed to develop ME formulations of adapalene based an alkyl polyglucoside. In their study, despite the lower in vitro drug release, the amount of adapalene penetrating the pig skin from ME was higher than the commercial product of adapalene. Adapalene deposition in hair follicles for 1 hour exposure ranged from 157.00 ng/cm^2 to 183.30 ng/cm^2 for skin areas treated with commercial cream and ME, respectively. Therefore, the use of MEs in the treatment of acne seems promising, as they provide higher adapalene delivery in the skin layer and more deposition in the hair follicles. In conclusion, this study showed that alkyl polyglucoside-based ME are systems worth exploring for the targeted application of adapalene in the treatment of acne.

Bhatia et al. (55) also aimed to prepare a ME for transfollicular administration of adapalene. A pseudoternary phase diagram was used for the ME consisting of oleic acid as oil phase, Tween 20 as surfactant, Transcutol as co-surfactant and deionized water. Differential band stripping and confocal laser scanning microscopy were used to determine the penetration of the ME through the hair follicles. Microscopy images showed that the hair follicle pathway is suitable for transfollicular passage of adapalene ME. The results showed that the ME penetrated the hair follicles and were found as promising for transfollicular drug release.

Nanofibers are fiber-shaped nanostructures that typically have two dimensions at the nanoscale. Nanofibers can be beneficial to solve many problems, like low solubility and loading efficiency, short circulation and plasma half-life of drugs. It is also successful to improve the bioavailability of drugs and growth factors, biological drugs such as DNA, RNA and the like. Owing to their high solubility and sustained drug release kinetics, nanofibers facilitate the local administration of a drug with the properties of preventing unwanted drug release and having excellent skin permeability (56).

Resveratrol, which has low water solubility is a potent antioxidant and successful at removing free radicals and binding metal ions. In case of topical administration, it shows antiviral, antimicrobial (*P. acnes*), anti-inflammatory and wound-healing effects. In order to increase the dermal permeability of the compound, both the stability of the trans form and its solubility in water should be increased (57). Karakucuk et al. (57) aimed to prepare dermal patches from resveratrol nanocrystals to improve these limiting properties of resveratrol. They found nanofibers as a suitable carrier system for resveratrol nanocrystals to develop dermal patches with high load capacity. Thus, the study revealed that the use of nanofiber patches as a dermal patch with protective and antimicrobial effects by exhibiting antibacterial activity against *P. acnes* was effective.

The combination of RA with erythromycin increases the efficacy of acne treatment. RA increases the skin penetration of erythromycin and increases its efficacy and antibacterial activity by reducing cellular adhesion. This results to the drainage of excess sebum and create an environment that can inhibit the growth of anaerobic bacteria, including *P. acnes*. Erythromycin and RA combination has also shown enhanced efficacy in *in vivo* models (58). In this line, Khoshbakht et al. (58) aimed to develop RA-loaded nanofibers as a potential anti-acne patch for the face and to investigate their physicochemical properties, including drug release and stability. With the use of RA-loaded polycaprolactone nanofibers, they found that the potential anti-acne patch mimics the natural hierarchical structure of tissues, can be used for a long time and has skin-targeting properties that can reduce the formation of adverse reactions and biomimetic scaffolds. The easy fabrication and cost-effective nature of the patch they developed made it a suitable delivery system for the on-demand delivery of RA, either alone or in combination with erythromycin and it was concluded that further studies needed to improve drug stability and release in terms of changes in excipients.

Polymers for drug delivery systems presented low toxicity, high biocompatibility and also interlocking polymeric networks such as hydrogels have been prepared to improve the physicochemical properties of these polymers. Natural polymers such as chitosan are widely used in these carrier systems. The most important advantages of chitosan nanoparticles are biocompatibility, low toxicity and low immunogenicity (59).

Sungkharak et al. (60) investigated the antibacterial activities of different molecular weight chitosans in solution and as nanoparticles against *P. acnes, S. aureus* and *S. epidermidis*. The results showed that the nanoparticle form of chitosan is more effective than chitosan in solution. Chitosan nanoparticles with smaller particle size create larger surface area so that they can be adsorbed tightly on the surface of bacterial cells and then cause leakage of intracellular components. This can disrupt the cell membrane. Particle size < 200 nm showed greater antibacterial activity than particles > 200 nm and this was attributed to the ability of smaller size and low molecular weight chitosan nanoparticles in solution to penetrate the bacterial cell membrane and interact with DNA, while high Mw chitosan and larger nanoparticles interact with the

bacterial cell surface. Considering the results of the study, it was seen that chitosan is a promising polymer in the use of nanocarriers for acne treatment due to its anti-inflammatory, moisturizing, sebum removal and wound healing properties.

Friedman et al. (61) prepared chitosan-alginate nanoparticles (341 nm in size) with antibacterial and anti-inflammatory properties. They found that the nanoparticles disrupted the cell membrane of *P. acnes* and inhibited *P. acnes*-induced pro-inflammatory cytokine formation in keratinocytes and human monocytes. In the study, with the inclusion of BPO in these nanoparticles, they achieved increased antimicrobial activity and reduced toxicity against *P. acnes*.

Tolentino et al (62) developed chitosan and hyaluronic acid nanoparticles to trap clindamycin, one of the antibiotics used in the treatment of acne. Regarding drug follicular deposition, chitosan nanoparticles provided a 4-fold reduction compared to a commercial formulation, while hyaluronic acid nanoparticles provided a similar clindamycin penetration to the commercial formulation in pilosebaceous units of the skin. As a result, they found that nanoparticles prepared with both chitosan and hyaluronic acid increased the targeting of clindamycin to the pilosebaceous structures of the skin. Chitosan nanoparticles restrict the penetration of the drug into all layers of the skin but allow about half of the total amount of drug (53%) penetrated to accumulate in the hair follicles, while hyaluronic acid nanoparticles promote drug accumulation (77%) for both the stratum corneum and pilosebaceous units. In the case of oily skin, a reduction in the penetration profile of clindamycin into the skin layers was observed in all formulations. However, drug penetration into pilosebaceous units remained the same in hyaluronic acid nanoparticles and increased in chitosan nanoparticles, while the amount of drug in pilosebaceous units decreased by half when commercial formulation was applied. Possibly due to the hydrophilic nature of drugs and polymers, the oil content may have provided both encapsulated drug and free drug release, affected stratum corneum interaction and cutaneous drug penetration, but failed to prevent nanoparticles from accumulating in the body. As fewer nanoparticles interact with the stratum corneum in pilosebaceous units, more particles accumulate in the appendage structures. When this study was evaluated, it was seen that clindamycin phosphate loaded nanoparticles prepared with both chitosan and hyaluronic acid were promising alternatives for the topical treatment of acne vulgaris.

Reis et al. (63) prepared azelaic acid loaded poly-dl-lactide/glycolide nanoparticles (< 400 nm in size) used in acne treatment. The developed nanoparticles showed a sustained release profile of up to 75 hours. Then, by incorporating polymeric nanoparticles into a carbopol-based gel, they created a topical form with successful spreadability and washability with water. By encapsulating azelaic acid in nanoparticle-loaded gel, they obtained similar antibacterial activity against *P. acnes* and *S. epidermidis* with conventional azelaic acid preparations. Excipients safety testing was performed after in vitro cytotoxicity assessment. The in vitro cytotoxicity of nanoparticles was evaluated in the Saccharomyces cerevisiae model. The results showed that the cytotoxicity of azelaic acid loaded nanoparticles was concentration dependent. Human safety studies of 12 healthy female volunteers were conducted to evaluate formulation excipients by the occluded patch test method. Two different samples were tested: one was gel base and the other was gel with empty nanoparticles. Samples were applied to the volunteers' backs and evaluated 48 hours later. No primary reaction was detected. It could be said that all excipients were safe.

BPO, which is a widely used active agent for the treatment of acne often causes skin irritation as an undesirable effect (64). The pharmacological activity of BPO is through penetration into the skin through follicular openings. Therefore, a controlled-release topical delivery system can reduce the percutaneous absorption of BPO without affecting its intrafollicular penetration. Thus, it can reduce the irritation of the skin without changing the effectiveness of the drug. For this reason, Jelvehgari et al. (63) developed BPO-loaded microsponge systems for use in acne treatment. The result of the study showed that the controlled release of BPO via microsponges can reduce its side effects on the skin and increase its percutaneous absorption.

In another study, Dimitrovska et al. (65) developed a microsponge system for clindamycin hydrochloride with anti-acne effect. Microsponge-based dosage form for acne treatment has the ability to absorb skin secretions and reduce their accumulation in the epidermis and dermis. Lactic acid (1%, w/v) and chitosan (2%, w/v) were used as gelling agent. According to release kinetic of the formulation, the main mechanism that indicates drug release is the Higuchi model. A high correlation coefficient (0.978) was found between the data obtained from *in vitro* drug release and *ex vivo* permeation studies. This demonstrates the permeability of the formulation through the skin layers and its effectiveness in treating acne. Stability studies show that the dosage forms developed under controlled conditions (25 ± 2°C, 60% ± 5% RH and 40 ± 2°C, 75% ± 5% RH) are stable over the long term.

It is common practice to prescribe RA with BPO or a BPO/antibiotic combination, but the RA molecule is unstable and can lead to BPO degradation, further complicating treatment regimens. Recently, formulation technology has been focused on enabling RA to penetrate the skin layers more efficiently so that lower RA concentrations can provide better tolerability and maintain efficacy (66). A micronized RA (0.05%) gel formulation was developed from Torok et al. (66) RA microsphere. With this formulation, RA delivery was achieved by optimum particle size, no degradation by BPO, and better tolerability in the skin. By using the microsphere carrier system, they provided more efficient delivery of RA to the skin.

RA also causes adverse effects such as skin irritation, edema and redness. These undesirable effects reduce patient compliance in the young population (67). Jorizzo et al. (67) also developed RA loaded microsphere gel formulations in order to minimize these side effects. The developed gel has been clinically studied on male and female adolescents aged 11-16 years. At the end of the study, it was seen that the microsphere gel was successful at reducing the lesions both inflammatory and non-inflammatory in 12 weeks compared to conventional RA gel. RA microsphere gel was better tolerated and more than 70% of patients experienced no cutaneous adverse events. RA microsphere gel was found to be effective in significantly reducing all types of acne lesions in adolescents aged 11-16 years with moderate facial acne and had a low incidence of cutaneous adverse events.

The physicochemical properties of adapalene limit its local bioavailability in skin layers and hair follicles (68). Ramezanli et al. (68) aimed to develop a new formulation in order to increase the bioavailability of adapalene in the topical treatment of acne. They researched the feasibility of polymeric nanocarriers based on tyrosine-derived nanospheres (TyroSpheres™) for adapalene release. They found that TyroSpheres effectively encapsulated adapalene and significantly increased the water solubility of the drug in the formulation. As a result, they developed an oil-free and alcohol-free water-based adapalene formulation that is potentially less irritating than the commercial dosage form and is suitable for application to oily skin. TyroSphere formulations with less drug content than the marketed commercial product was able to release comparable amounts of adapalene into the epidermis and hair follicles. Therefore, they concluded that the developed Adapalen-TyroSphere was an innovative alternative approach for the topical treatment of the early stages of acne.

Aggarwal et al. (69) developed tazarotene-loaded nanosponges (using ethyl cellulose and polyvinyl alcohol) and niosomes (using Tween 20 and cholesterol) to facilitate the topical release of tazarotene and reduce its undesirable effects. Nanosponge and niosomes are consisted of gel form to optimize the viscosity for topical applicable dosage form. *In vitro* permeability studies on rat skin showed higher drug absorption of nanosponge and niosome-based gel formulations compared to the conventional gel dosage form. This is a result of the ability of tazarotene-loaded vesicles to be absorbed into the deeper layers of the skin, and thus to the accumulation of the drug in the layers of the skin. Stability studies show that the nanosponge-based gel is stable for a long time and no changes were observed in drug content, pH, and *in vitro* permeation, but it was observed that the nanosponge-based gel had better diffusion than the niosome-based gel. In the light of this study, they showed that nanosponge gels with controlled drug release are promising in the treatment of acne.

Study examples of innovative drug delivery systems used in topical acne treatment are summarized in Table 2.

Table 2. Studies of novel drug carrier systems used in topical acne treatment.

Active Substance	Carrier System	Results	Reference
Isotretinoin	SLN	Non-irritating to the skin and stronger anti-acne effect compared to traditional isotretinoin gel	(26)
	SLN	Increased stability and stronger effectiveness	(27)
	NLC	Decreased skin irritation, increased patient compliance, increased solubility	(31)
	Nanoemulsion	Decreased side-effect profile, prolonged efficacy	(52)
Tretinoin	SLN	Inhibitory activity against *S. epidermidis, P. Acnes, S. aureus* Extended release	(28)
	NLC	Increased skin tolerability and increased patient compliance	(29)
	Liposome	Reduced erythema and irritation	(36)
	Liposome	Decreased side effect profile	(37)
	Nanoemulsion	Rapid release, reduced side-effect profile, high efficacy	(53)
	Nanofiber	Reduced cost, ease of manufacture, reduced side-effect profile	(58)
	Microsphere	Increased yield, better skin tolerability	(66)
	Microsphere	Good efficacy, reduced side-effect profile	(67)
	Microsponge	Significant reduction in lesions	(70)
Adapalene	SLN	Increased penetration, minimalized side effects	(18)
	Microemulsion	Increased skin permeability	(54)
	Microemulsion	Increased transfollicular transmission	(55)
	Nanosphere	Increased solubility, less irritation, increased release	(68)
Adapalene + Vitamin C	Transfersome	Increased treatment quality, better release profile	(45)
Tazarotene	Microemulsion	High skin tolerance	(51)
	Nanosponge	High drug absorption	(69)
Clindamycin	Liposome	Increased therapeutic efficacy, decreased side-effect profile	(35)
	Polimeric nanoparticle	Increased skin targeting	(62)
Clindamycin + salicylic acid	Ethosome	Decreased side effect profile, increased efficacy, better tolerability	(41)
Benzoyl peroxide + chloramphenicol	Liposome	Decreased cytotoxicity, increased synergistic effect	(38)
Benzoyl peroxide	Niosome	Superior skin absorption, increased efficacy	(6)
Benzoyl peroxide	Microsponge	Increased percutaneous absorption, decreased side-effect profile	(64)
Benzoyl peroxide	Polimeric nanoparticle	Increased antimicrobial activity, decreased toxicity	(61)
Azithromycin + curcumin + lauric acid	Liposome	Increased activity	(39)
Dapsone	NLC	Good efficacy and safety, improved topical release	(32)
	Niosome	Prolonged release, undesirable effects	(49)
Azelaic acid	Ethosome	Increased efficiency and security	(43)
	Polimeric nanoparticle	Increased release time	(63)

Rosmarinic acid	Niosome	Prolonged release, increased skin uptake	(48)
Resveratrol	Nanofiber	High solubility, increased skin permeability, good efficacy	(56)
Tea tree oil	Ethosome	Increased skin permeability	(42)

4. CONCLUSION

The skin is a high potential route for drug applications due to its large surface area. In systemic treatment, the drug does not only reach the target area, but also can cause adverse reactions in different parts of the body as it enters the circulation. In addition, the drug may undergo a first pass effect, and treatment may be difficult for patients who are not able to oral drugs. In topical treatment, on the other hand, target site specificity is provided, drugs do not undergo first-pass effects and their toxicity is greatly reduced. Patient compliance is high, and treatment costs can be reduced thanks to easy application. However, for topical applications, the drug is expected to pass through the layers of the skin. The most important limiting factor in penetration through the skin is the stratum corneum layer. In drugs that can pass this layer, low molecular weight and optimum water and lipid partition properties are sought. In addition, the drug to be applied should not cause irritation to the skin. It is very difficult to provide all these features together in traditional drug formulations. Today, innovative topical drug delivery systems are being developed in order to eliminate these negativities. Nanotechnology is also used for the reproducible development and control of these systems in desired molecular dimensions.

Novel drug carrier systems used in the treatment of acne are examined in this review; nanoparticles (SLNs and NLCs), liposomes, ethosomes, transfersomes, niosomes, nano and microemulsions, nanofibers, polymeric nanoparticles and microsponges. It has been observed that the drug release time is prolonged and the therapeutic efficacy increases in formulations obtained by loading traditional acne drugs into SLN and NLC systems. It has been observed that liposomal systems reduce the side-effect profile in treatment, increase patient compliance, increase the stability of drugs and increase their effectiveness by protecting drugs from external factors. Despite these advantages, their use is limited due to high production costs. Ethosomes are modified derivatives of liposomal systems. Its ethanol content facilitates the uptake of lipophilic drugs into the structure, and its skin permeability is quite high. Many studies have shown that ethosomes are safer and more effective than conventional formulations. Transfersomes are composed of a phospholipid bilayer and single-chain surfactants and are elastic derivatives of liposomes. It is one of the drug delivery systems with high potential with its low toxicity, effective release profiles and ability to encapsulate hydrophobic and hydrophilic drugs simultaneously. Niosomes are superior carrier systems to liposomes due to their high stability and low cost. The developed niosomal formulations were found to be more effective at lower doses than conventional acne medications. Micro and nanoemulsions are carrier systems with the advantages of long-term stability, ease of preparation and high skin permeability. In the developed anti-acne formulations, the side effects and slow drug release profiles of traditional delivery systems have also been eliminated. Nanofibers are ideal topical drug delivery systems with their high skin permeability and ability to prevent unwanted drug distribution. Nanofiber formulations of anti acne agents have been developed, and it has been observed that their effectiveness has increased. Polymeric nanoparticles are drug carrier system that are developed for the purposes of improving the penetration of active agents and masking their negative properties. They have advantages such as low toxicity and high biocompatibility. In the studies, the stability of the agents that can cause degradation when used together, are preserved and their efficiency is increased by transporting them in polymeric nanoparticles in a combined manner. Due to their structure, microsponges trap the drug particles and ensure their release for a long time. Microsponge formulations of effective agents in acne treatment have been developed, and it has been observed that the developed systems reduce side effects on the skin with controlled release. As a result, important steps have been taken for the treatment of acne with the advancement of nanotechnology and the development of innovative drug delivery systems. Although clinical studies are insufficient, this research demonstrates the potential of newly developed topical drug delivery systems.

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