Expert Opinion

Novel vesicular and particulate drug delivery systems for topical treatment of acne

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Background: The efficacy of the antiacne topical drugs is well established. The local side effects, however, mainly cutaneous irritation, erythema, dryness, peeling and scaling, remain major problems. Novel vesicular and particulate drug delivery systems have been proposed to reduce the side effects of drugs commonly used in the topical treatment of acne. *Objective*: This review focuses on the development and evaluation of antiacne drug-loaded vesicular and particulate delivery systems (liposomes, polymeric microspheres and solid lipid nanoparticles) for topical treatment, their advantages and challenges. *Methods*: All the literature available was reviewed to highlight the potential of these novel systems for the topical treatment of acne. *Conclusion*: The encapsulation of antiacne drugs in vesicular and particulate delivery systems represents an innovative alternative to minimize side effects, while preserving their efficacy. This can be obtained by the capacity of these systems to provide controlled release or to improve the drug penetration into skin or even into the pilosebaceous unit.

Keywords: acne, antiacne drugs, liposomes, polymeric microspheres, solid lipid nanoparticles, topical treatment

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1. Introduction

Acne is a common disease which affects approximately 40 – 50 million people in the United States alone. The prevalence of acne in adolescents can reach up to 80%, and it produces clinical conditions that can carry over into adulthood, creating a negative impact on quality of life [1,2]. Acne is a chronic inflammatory dermatosis of the pilosebaceous unit (PSU) and is characterized by several abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, inflammation and immunological host reactions [3-5]. Recent findings have shown the influence of genetic factors in the follicular environment that optimize *Propionibacterium acnes* proliferation: in sebum production enhancement as well as in the immunological host reaction [6,7].

According to the evolution, acne can be classified as mild, moderate or severe. Topical treatment is the first choice in mild and moderate acne, whereas systemic therapy is used to treat severe and moderate cases. The pathophysiological goal of acne treatment includes the normalization of keratinization, the reduction of interfollicular *P. acnes*, the reduction of inflammation, and the reduction of sebaceous gland activity. The options for the topical treatment of acne consist of agents with a primarily keratolytic action (retinoids and retinoid-like drugs, benzoyl peroxide, salicylic acid and azeilac acid) and antibiotics (clindamycin, erythromycin and erythromycin–zinc complex) (**Table 1**). Topical retinoids and similar drugs which include tretinoin, adapalene and tazarotene are the most

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Table 1. Spectrum of efficacy of topical agents in acne treatment.

	Reduction in comedones	Sebosuppressive	Antimicrobial	Anti-inflammatory
Tretinoin	++	–	–	–
Isotretinoin (topical)	++	–	–	(+)
Adapalene	++	–	–	+
Tazarotene	++	–	–	(+)
Azelaic acid	+	–	+	(+)
Erythromycin	(+)	–	++	+
Clinfamycin	(+)	–	++	+
Benzoyl peroxide	+	–	+++	(+)
Salicylic acid	(+)	–	–	–

*Only direct *in vivo* anti-inflammatory effects are mentioned. The spectrum of *in vitro* activity is different from this scoring.
+++: Very strong; ++: Strong; +: Moderate; (+): Weak; –: None.
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Table 2. Adverse drug reactions* of topical therapeutics in acne treatment.

	Erythema	Scaling	Burning	Flare	Resistance	Other
Tretinoin‡	+++	+++	++	++	–	–
Isotretinoin	++	++	+	+	–	–
Adapalene	+	+	+	+	–	–
Tazarotene	++	+	+	+	–	–
Azelaic acid	+	+	++	–	–	–
Benzoyl peroxide	++	++	+	+	–	Bleaches hair/clothes
Topical antibiotic	(+)	(+)	(+)	(+)	+++	

*Adverse reactions may vary due to skin type and sensitivity.
‡Depends on formulation.
+++: Most often; ++: Often; +: Occasional; (+): Very occasional; –: None.
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commonly used topical agents [8-10]. Nevertheless, some of these agents usually produce a high incidence of side effects, such as skin dryness, peeling and skin irritation or bacterial resistance (**Table 2**) [8,11-13]. These symptoms diminish patient compliance, compromising the efficacy of the therapy [14]. To reduce these side effects the use of lower concentrations of antiacne agents, as well as novel drug delivery systems, has been proposed [15,16]. While conventional formulations containing lower concentrations of antiacne agents can lead to less significant results [17], the novel delivery systems present the potential to reduce the side effects without reducing the efficacy [15,18]. Therefore, with novel delivery systems outstanding advantages can be noticed in comparison to conventional formulations.

Vesicular and particulate drug delivery systems such as liposomes, microspheres and solid lipid nanoparticles (SLNs) have the potential for controlled release. The application of these systems to the skin distributes the topical agents gradually and, in some cases, has demonstrated the ability to reduce the irritancy of some antiacne drugs, yet it maintains a similar efficacy when compared with conventional formulations [19]. In addition to the controlled release of the drug into the epidermis, these systems can also promote follicular targeting, creating high local concentrations of the active compounds in the PSU [20-23]. The vesicular and particulate drug delivery systems have the advantage of penetrating more efficiently into the hair follicles than do non-particulate systems, such as conventional formulations, so long as the size is selected in an appropriate manner. This provides a high local concentration over a prolonged period of time (**Figure 1**) [20,24,25].

The studies concerning novel drug delivery systems containing antiacne agents were recently updated. The authors have reviewed controlled (particulate and vesicular) and non-controlled drug delivery systems [16]. The present review focuses on particulate and vesicular drug delivery

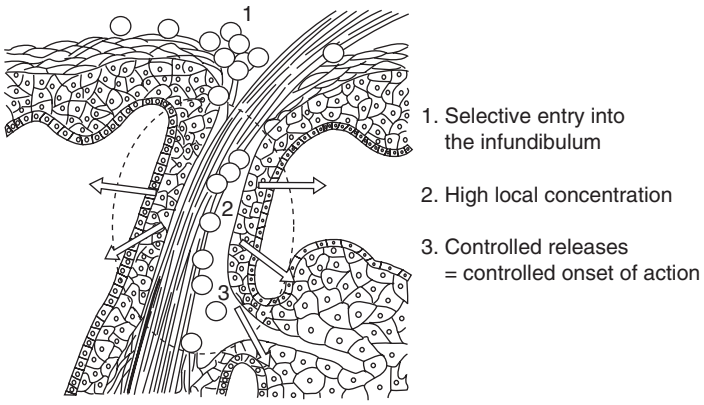

Figure 1. Microparticles enter selectively into the hair follicle and may yield high local concentrations of the active compound.
The controlled destabilization of the microspheres may allow a controlled release of the compounds. The penetration depth depends on the size of the particles and the size of the target.
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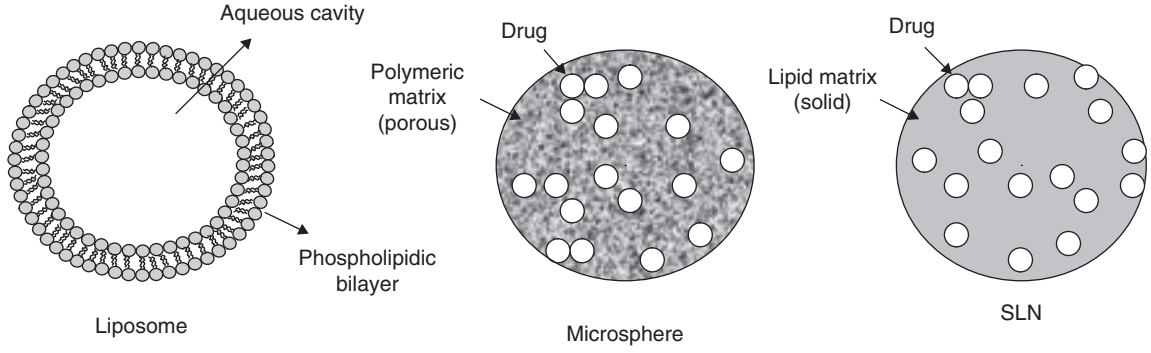

Figure 2. Schematic representation of liposomes, microspheres and solid lipid nanoparticles (SLNs).
Liposomes: Hydrophilic and lipophilic drugs can be entrapped in the aqueous cavity and phospholipidic bilayer, respectively; Microspheres: Drugs homogenously dispersed within the polymeric matrix; SLN: Drugs homogenously dissolved or dispersed within the lipid matrix or enriched within the outer shell.

systems (**Figure 2**), which have shown more advantages as carriers of antiacne agents for topical treatment than noncontrolled drug delivery systems. To date, however, the novel delivery systems for acne treatment have remained in a constant process of evolution, with the aim of not only enhancing skin penetration but also allowing for drug targeting to the skin or even to the PSU.

2. Liposomes

Liposomes are spherical vesicles that are basically formed of phospholipids that have associated themselves spontaneously in a bilayer containing a centralized aqueous cavity (**Figure 2**). They are most commonly formed by phospholipids of natural, synthetic or semisynthetic origin and possess great potential for the delivery of hydrophilic, lipophilic and amphiphilic drugs [26,27]. Lipid bilayers exhibit various phase transitions that could be used to trigger drug release. Bilayers can exist in a low-temperature solid-ordered phase and, above a certain temperature, in a fluid-disordered phase; the temperature of this phase transition can be tailored by selecting the proper lipids. The transition can be exploited to control drug leakage from liposomes [26].

Although early studies focused on the parenteral route, Mezei and Gulasekharam [28] reported the effectiveness of liposomes for skin delivery. In line with these studies, several research groups have been researching the possibility of liposomes producing improved topical delivery. Liposomes are able to enhance the accumulation of drugs at administration sites, even in the PSU [29,30]. Depending on the composition of the phospholipids (saturated or unsaturated) and the presence of co-surfactants (cholesterol, sodium cholate), rigid, fluid or elastic (the high deformable liposomes known as Transfersomes®; IDEA AG) vesicles can be obtained and dermal or transdermal delivery can be favoured [31,32].

Other lipid vesicles, such as niosomes, were also studied. The niosomes, as with liposomes, can be small unilamellar vesicles (SUVs) or multilamellar vesicles (MLVs), in which an aqueous solution is enclosed in a highly ordered bilayer. In contrast to liposomes, however, this bilayer is made up of nonionic surfactants [33,34]. Studies have shown the potential of this system for acne treatment [35-37].

The use of antiacne drug-loaded liposomes has been widely reported in the literature.

2.1 Clindamycin

Antibiotic therapy has been used in the management of inflammatory acne vulgaris for many years. Clindamycin is one of the most popular topical antibiotics for acne treatment [38]. In previous studies, lipid compositions have been evaluated in an attempt to improve the effectiveness of clindamycin-loaded multilamellar liposomes in acne treatment [39,40].

In one study, hostaphate liposomes presented sustained release when compared with lecithin liposomes. The efficacy of the clindamycin-loaded liposomes was compared with a free clindamycin lotion in a clinical trial in patients with acne (n = 30, 4-week treatment). The liposomal clindamycin proved to be much more effective in reducing the total number of comedones, papules and pustules [39]. In another study, significant differences were observed in the properties of different types of liposomes as regards skin penetration, with preparations composed of hydrogenated soya lecithin/cholesterol presenting the highest values of probe penetration among liposomal formulations. In a double-blind clinical trial (n = 76 patients, 6-week treatment), the efficacy of clindamycin liposomes to reduce open comedones (33.3%) was greater than that for the free clindamycin solution (8.3%), also appearing as therapeutically superior when closed comedones, papules and pustules were examined [40].

2.2 Tea tree oil

Tea tree oil, an antimicrobial agent that shows activity against *P. acnes* [41], has been efficient in the treatment of patients with mild to moderate acne [42]. The follicular uptake of tea tree oil from different formulations (colloidal bed, microemulsion, multiple emulsion, and liposomes) to bovine udder skin was determined by means of the cyanoacrylate method [43]. The accumulation of tea tree oil in the follicular casts (% milligram oil/gram of sebum plug) for microemulsion and liposomes (0.43 ± 0.01 and 0.41 ± 0.009, respectively) was approximately two-fold higher than that observed for multiple emulsions (0.21 ± 0.006) and colloidal beds (0.16 ± 0.005), suggesting follicular targeting.

2.3 Salicylic acid

Salicylic acid, a keratolytic agent with comedolytic activity in acne patients, has been efficiently used in the treatment of acne comedones [44,45]. Salicylic acid liposomes, when compared with free salicylic acid dispersion, not only prolonged the release of salicylic acid across the porcine skin but also enhanced its retention in the skin (about 10 times). After 12 weeks of storage at refrigeration temperature (4 – 5°C), the liposomes retained their normal structure and presented only 4.01% of salicylic acid leakage [46].

2.4 Topical antiandrogens

Enhanced dihydrotestoterone formation via 5α-reductase I, stimulating sebocyte proliferation and sebum production, is one of the factors involved in the acne vulgaris manifestation [47,48] and can be controlled through the application of antiandrogens. Moreover, the presence of androgen receptors in PSU keratinocytes suggests that androgens may influence PSU keratinization [49].

2.4.1 *Cyproterone acetate*

The efficacy of cyproterone acetate, a potent steroidal antiandrogen with progestational activity, in a topical liposomal cyproterone acetate lotion (2 mg cyproterone acetate/ml; n = 12) was compared with an oral formulation containing 0.035 mg of ethinyl estradiol, 2 mg cyproterone acetate (n = 12) and a placebo lotion (n = 16) [50]. After 3 months of topical cyproterone acetate application, lesion counts (total of comedones and inflammatory lesions) had decreased from of 35.9 to 9.1. Although a similar clinical response was observed with oral CA (45.4 – 15.5) and no subjective adverse effects were observed in either of the groups, the cyproterone acetate levels in serum were 10 times lower after topical application compared with orally administered cyproterone acetate. Thus, the liposomal cyproterone acetate lotion represents a suitable alternative for women with acne.

2.4.2 *Finasteride*

The encapsulation of finasteride, an antiandrogen that blocks the production of dihydrotestosterone from testosterone by competitively and specifically inhibiting the type II 5-α reductase isozyme, was also investigated [51,52].

The composition and physical state of liposomes and niosomes influenced the finasteride *in vitro* permeation through hamster flank skin as well as *in vivo* deposition in hamster ear skin. The *in vitro* permeation of ^{3}H-finasteride occurred at a faster rate when using a hydroalcoholic solution (0.13 μg/cm^2/h) compared with vesicles (0.025 – 0.058 μg/cm^2/h), while the *in vivo* deposition of finasteride liquid-state vesicles led to a deposition of 2.1% (dimyristoylphosphatidylcholine) or 2.3% (polyoxyethylene 10 oleyl ether : polyoxyethylene 10 stearyl) of the applied dose within the PSU, which was significantly higher than that obtained for gel-state vesicles (0.35 – 0.52%) or hydroalcoholic solution (0.76%). Thus, both *in vitro* permeation and *in vivo* deposition studies demonstrated the potential of liquid-state liposomes and niosomes to successfully deliver finasteride to the PSU [51].

The finasteride liposomal formulations also propitiated significantly higher skin permeation through mice skin (54 and 52.4% for liposomal suspension and gel, respectively) in comparison to solution (24%) and conventional gel (29%). Negatively charged small liposomes presented a higher permeation than that of the neutral liposomes with higher vesicle size. Liposomal finasteride formulations also showed a fivefold higher deposition of drugs into the skin (31.6 ± 3) than the drug solution (2.6 ± 1) and conventional gel (5.0 ± 1) [52].

2.4.3 *RU 58841*

RU 58841 is a new nonsteroidal antiandrogen that exhibits a strong topical efficacy on sebaceous gland activity in animal models [53]. After *in vitro* topical application on human skin, the liposomes considerably reduced the RU 58841 skin permeation compared with the alcohol solution (by a factor of 19 at 24 h and a factor of 10 after repeated applications). The *in vivo* cutaneous distribution studies on hairless rat skin showed that the highest amounts in epidermis and dermis were obtained with the solution over short time periods (3 and 6 h) and with liposomes over longer time periods (24 h after one and five applications). The liposomes also increased the drug concentration between 30 and 150 µm, indicating an accumulation in the sebaceous ducts and upper portion of the glands [54].

2.5 Benzoyl peroxide

Benzoyl peroxide has a mild keratolytic as well as bactericidal effect and is one of the most commonly used drugs in the treatment of acne. The main site of pharmacologic action is the PSU. Skin irritation, however, is a common side effect and a dose-related effect seems to exist between efficacy and irritation [55]. Theoretically, encapsulation in liposomes can be an interesting approach to improving efficacy and reducing the side effects associated with benzoyl peroxide topical application.

In a clinical trial (30 acne patients, 3-month treatment), liposomal benzoyl peroxide gels significantly improved therapeutic responses (about twofold) at all evaluation time intervals compared with those of the plain Benzoyl peroxide gel ($p < 0.05$). In addition, liposomal benzoyl peroxide gels showed much less irritation in the first 2 weeks of treatment, when it completely disappeared. No burning was observed throughout the studies. In contrast, the plain benzoyl peroxide gel showed high irritation through the eighth week of treatment and gradually decreased thereafter, whereas high burning was seen throughout the study. As it was more severe in the initial period of therapy, patients were tempted to discontinue the therapy. Benzoyl peroxide liposomes showed a better stability profile (almost 100% of drug retained, 90 days) at refrigeration temperature (2 – 8°C) compared with room temperature (25 ± 2°C) and body temperature (37°C). The Benzoyl peroxide liposomal gel, however, exhibited a reduction in drug leakage compared with benzoyl peroxide liposomal dispersions [17].

Benzoyl peroxide-loaded liposomes also promoted a significant antibacterial effect in the infundibula against both *Propionibacteria* and *Micrococcaceae* in acne patients (20 patients, 4-week treatment) when compared with other benzoyl peroxide formulations (pharmacopeial formulation and a commercial product). These results demonstrated the potential infundibular targeting of liposomal benzoyl peroxide [56].

2.6 All-*trans* retinoic acid

All-*trans* retinoic acid, or tretinoin, is an efficient drug used in the topical treatment of mild-to-moderate acne. Retinoic acid works both through comedolysis as well as by normalizing the maturation of the follicular epithelium so as to cease comedone formation [57,58]. Nevertheless, topical use of retinoic acid can cause local tolerability problems, such as irritation, mild-to-severe erythema, dryness, peeling and scaling [13,57]. These occurrences tend to diminish patient compliance, compromising the efficacy of the therapy [14]. To overcome these disadvantages and improve the effectiveness of retinoic acid after topical application, retinoic acid-loaded liposomes have come under study.

2.6.1 *In vitro and in vivo studies*

The morphological changes in reconstructed *in vitro* human epidermis after the application of liposomal and conventional retinoic acid were investigated. The changes, representing toxic dermatitis in the epidermis, were more marked by conventional forms than liposomal forms. It was suggested that these changes represent topically applied retinoic acid-induced inflammation. Changes representing efficacy, however, were similar for both formulations [59].

A number of studies have suggested improvement in skin penetration and decrease in the percutaneous absorption of retinoic acid encapsulated in liposomes. Retinoic acid *in vivo* distribution in hairless rats' skin epidermis (mainly stratum corneum) and dermis was significantly higher when using dipalmitoylphosphatidylcholine liposomes than when using the alcohol gel (41 and 13%, respectively, with liposomes versus 18 and 8% with the gel). By contrast, *in vitro* skin permeation was statically reduced for liposomes (1.6%) when compared with the gel (3.1%) [60]. Retinoic acid-loaded liposomes also produced significantly higher drug skin deposition (65.7 ± 1.6%) than did plain retinoic acid gel (33.6 ± 1.7%) in human skin [61]. Retinoic acid-loaded stratum corneum lipid liposomes (SCLLs) prolonged drug release through hairless rat skin and promoted greater amounts of the drug deposited into different skin layers (stratum corneum and epidermis plus dermis), increasing the retinoic acid concentration in these layers (about twofold) when compared with nonliposomal systems [62]. Moreover, the amounts of retinoic acid accumulated in newborn pig skin for liposomal formulations were enhanced by

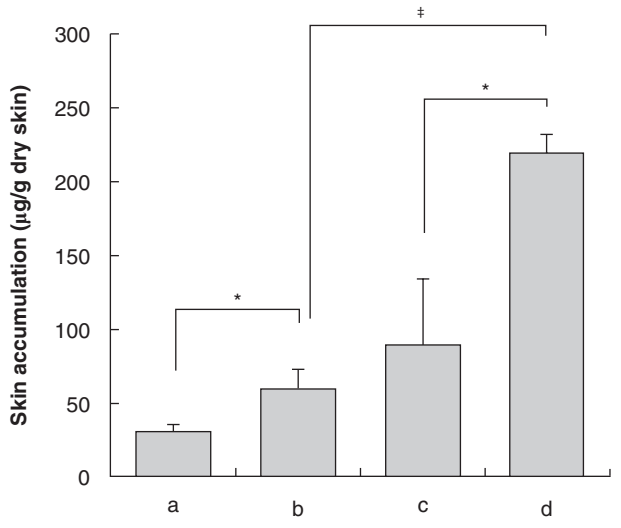

Figure 3. Effects of liposomes on the delivery of retinoic acid into skin.

a: isopropyl myristate solution; b: neutral liposome; c: cationic liposome (phosphatidylcholine:cationic surfactant, 3 : 1); d: cationic liposome (phosphatidylcholine:cationic surfactant, 1 : 1).

*$p < 0.01$ (differences between a and b and between c and d).

‡$p < 0.001$ (differences between b and d).

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factors of 1.5 – 2.8, 1.1 – 2.2 and 1.0 – 20.0 over Retin-A® (Ortho Dermatological Division, Ortho-McNeil Pharmaceutical, Inc.), hydroalcoholic solution, and oil solution, respectively [63].

Sinico *et al.* [63] also evaluated the influence of composition, lamellarity and vesicle charge on skin accumulation and retinoic acid permeation through the newborn pig skin. Lamellarity had no affect on retinoic acid delivery; however, positively charged or saturated phospholipid vesicles showed greater skin permeation than negatively charged or unsaturated phospholipid vesicles. Negatively charged vesicles strongly improved retinoic acid skin retention when compared with those which were positively charged. The influence of the membrane charge on retinoic acid skin permeation across human epidermal membranes was also investigated in another study performed by Montenegro *et al.* [64]. Positively charged liposomes, prepared with stearylamine, a lipid with an amine group of high pK_a, also provided greater retinoic acid permeation compared with neutral or negatively charged liposomes, but drug skin penetration was not evaluated.

Recently, the influence of neutral and cationic liposomes on the retinoic acid topical delivery in (penetration into) guinea-pig skin was investigated [65]. Neutral liposomes increased the retinoic acid topical delivery by approximately twofold when compared with an isopropyl myristate solution, while cationic liposomes further enhanced drug skin penetration (3.7-fold increase) (**Figure 3**). These data suggest the potential of cationic liposomes for the topical delivery of retinoic acid.

As an alternative to liposomes, retinoic acid-loaded niosomes have been studied. The retinoic acid release rate through a silicon membrane from niosomal and liposomal formulations was generally faster than from methanolic solutions and was mainly affected by the vesicular structure [MLV > large unilamellar vesicles (LUVs) > SUV] [37]. In a different study [35], retinoic acid skin permeation from MLV and SUV niosomes and liposomes through newborn pig skin was strongly affected by vesicle composition and drug thermodynamic activity (nonsaturated formulations showed negligible permeation) but not by the vesicle size nor lamellarity. While the highest retinoic acid permeation was obtained from positive vesicles (MLVs and SUVs), the highest accumulation values were obtained from negatively charged vesicles. The retinoic acid skin accumulation was also affected by vesicle structure (SUV > MLV) and composition (surfactants with lower hydrophile–lipophile balance enhanced skin penetration). The vesicular formulations enhanced the retinoic acid accumulation to a factor of 1 – 6.6 over Retin-A but the small, negatively charged niosomal formulations, which were saturated with retinoic acid, showed higher skin penetration than both liposomes and commercial formulation.

2.6.2 *Clinical studies*

In a double-blind clinical trial [15], 20 patients (uncomplicated acne) received retinoic acid liposomal gel (0.01%) on one side of the face and a commercial gel on the other (0.025 or 0.05%) once daily for 10 weeks. The global evaluation of efficacy (comedones, papules and pustules) indicated no differences between the areas receiving liposomal and conventional gels. Therefore, retinoic acid-loaded liposomes allowed for the reduction of drug concentration with no decline in efficacy. Liposomes, however, induced less burning (mean cumulative score 2.7 ± 1.2) than the 0.025% (16.1 ± 7.1) and 0.05% (9.7 ± 4.1) gels and less erythema (1.8 ± 0.7) than the 0.025% gel (11.4 ± 3.8; $p < 0.05$).

A double-blind study was conducted (30 patients, mild-to-moderate acne, 12 weeks) to compare the liposomal retinoic acid gel to the plain retinoic acid gel at the same concentration (both 0.025% retinoic acid) [61]. The liposomes showed better efficacy (about 1.5-fold) and, at all evaluation time intervals, the liposomal retinoic acid gel significantly improved the therapeutic response compared with the plain retinoic acid gel ($p < 0.05$). More remarkable improvement was observed in the treatment of comedones, with the mean percentage reduction in lesions increasing from 62.36% for plain retinoic acid gel to 94.17% for liposomal retinoic acid gel. All adverse symptoms, except scaling, were remarkably decreased with the use of liposomal retinoic acid gel compared with the plain retinoic acid gel ($p < 0.05$).

Considering that acne is a multifactorial disease, combination therapies using antiacne agents with different mechanisms of action are recognized as an effective strategy to treat this disease. A combination therapy with liposomal gels of retinoic acid (0.025%) and benzoyl peroxide (2.5%), in comparison with gels containing both drugs in free form, was performed in a double-blind study in mild-to-moderate acne patients (n = 30; 12-week treatment). An almost complete cure (100% reduction in skin lesions) was observed within 10 weeks for patients receiving the combination therapy using the liposomal gels, whereas only a 75 – 80% reduction in skin lesions was achieved with the gels containing free drugs even after prolonging the application of preparations for up to 12 weeks. Liposomal drug gels caused no adverse symptoms through the fourth week of treatment, while until the 12th week of treatment, with free drug gels, the severity of all adverse symptoms, except scaling and erythema (both of which were reduced), was high [66].

2.6.3 *Improved stability*

The liposomes developed by Patel *et al.* [61] showed only 2 – 4% of retinoic acid leakage after 90 days at refrigeration temperature, while at room temperature and body temperature the drug leakage was about 28 and 100%, respectively. In addition, reduced leakage was observed for liposomal retinoic acid gel in comparison with liposomal suspension at all temperature conditions. At room temperature the retinoic acid leakage in liposomal retinoic acid gel was decreased to 5% after 90 days.

The encapsulation of retinoic acid in liposomes also improved the drug photolability. When the liposomes developed by Brisaert *et al.* [67] were submitted to photo degradation (xenon lamp, 15 min), degradation constants in liposomes were approximately 1.8 times slower than in castor oil. These liposomes also presented a high stability for 1 year (about 95% retinoic acid retained), even when stored at 25°C.

In a study conducted according to the International Conference on Harmonization (ICH) Guidelines [68] using a xenon lamp (300 – 800 nm), retinoic acid and isotretinoin liposomes showed an increased stability when compared with the ethanol solutions. In particular for retinoic acid, a residual concentration of 60% was still present after light irradiance for 240 min (250 W/m^2 light power) versus a residual value of only 8% in ethanol solutions.

The retinoic acid-loaded niosomes also propitiated a higher retinoic acid chemical stability in comparison with a retinoic acid methanol solution when both were exposed to ultraviolet radiation and artificial daylight conditions. The photoprotection offered by vesicles varied as a function of vesicle structure and composition (3.5 to 11-fold higher). The best results were obtained with niosomes prepared from nonionic surfactants with an ethereal linkage [36].

3. Polymeric microspheres

Microencapsulation is a process through which the extremely fine coating of inert, natural and synthetic polymeric materials is deposited around solid and liquid micronized particles. The products formed are known as microparticles. The systems in which the core of the particle is a polymeric matrix that contains a drug which is homogeneously dispersed throughout this solid matrix are known as microspheres.

Microspheres offer numerous advantages when compared with the conventional formulations, highlighting their potential in the controlled release of administered drugs through the systemic pathway. Interest in their topical application has increased over the past few years, which can be explained by the fact that microspheres present a number of advantages in this context [25]: good stability when applied to the skin, easy to prepare with an average defined and homogeneous size, protection of the encapsulated drug against degradation (oxidation and hydrolysis), and controlled release.

Microspheres behave as a reservoir system for the active agent. When applied on the skin, the amount of free active agent in the formulation penetrates into the epidermis and this is compensated by a drug release from the microspheres. This will offer prolonged drug delivery without overloading the epidermis and subsequent increase of transdermal penetration [69].

The first studies showing the potential of polymeric microspheres for topical administration were published by Schaefer *et al.* [70], and Nacht and Katz [71]. Schaefer *et al.* demonstrated that microspheres with an average diameter of 3 – 10 µm selectively penetrate the PSU, while particles greater than 10 µm remain on the cutaneous surface and those smaller than 3 µm are randomly distributed on the PSU and the stratum corneum. Using microscopic techniques after the application of the microspheres containing fluorescent substances as markers, a number of studies have shown that, as long as the particle size is duly controlled, the follicular penetration can be favoured through the use of microspheres [22,25,72].

Systems similar to the microspheres, called Microsponges® (an allusion to a real sponge), were developed by Advanced Polymer Systems, Inc. [71,73]. Microsponges are made by means of suspension polymerization and typically consist of crosslinked polystyrene or polymethacrylates. Each microsphere (size ranging from 5 to 300 µm) presents a myriad of interconnecting voids within a noncollapsible structure with a large porous surface loaded with the active agent. When applied to the skin, the Microsponge releases the active agent according to a determined time mode but may also be released in response to other stimuli.

The preparation and evaluation of the 50 : 50 poly (DL-lactic-co-glycolic acid) microspheres containing adapalene were described by Rolland *et al.* [25]. The comedolytic

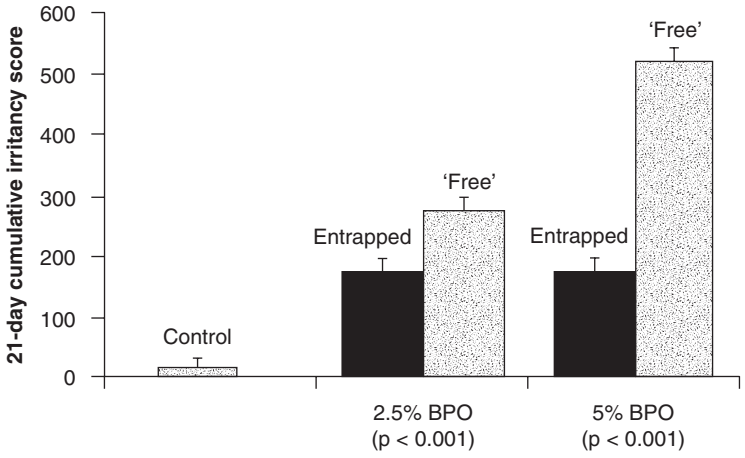

Figure 4. Cumulative irritancy induced in rabbits by topical benzoyl peroxide (BP) formulations containing either freely dispersed drug or entrapped in a Microsponge.
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Table 3. *In vivo* percutaneous absorption of benzoyl peroxide in the rhesus monkey.

Monkey	% Dose absorbed	
	Formulation A (freely dispersed)	Formulation B (entrapped)
1	16.7	8.5
2	15.3	9.7
3	13.9	8.4
4	13.4	7.7
Mean ± SD	14.8* ± 1.5	8.6* ± 0.8

*p = 0.002.
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activity of adapalene-loaded microspheres was evaluated through the rhino mouse model. A dose-dependent comedolytic activity of adapalene-loaded microspheres was observed. In addition, a reduction in the drug concentration (0.01%) or of the frequency of the administration (alternating days) showed that the efficacy of the adapalene-loaded microspheres was similar to that observed for the daily administration of an aqueous gel containing 0.1% of free adapalene. The majority of studies with antiacne drug-loaded microspheres, however, were conducted with benzoyl peroxide and retinoic acid.

3.1 Benzoyl peroxide

An extensive investigation of the potential of cutaneous irritation, percutaneous absorption *in vitro* and *in vivo*, and the efficacy of the encapsulated benzoyl peroxide in microspheres of divinylbenzene was conducted [74]. A 21-day cumulative irritancy study in rabbits showed that a lotion containing free benzoyl peroxide at 2.5 and 5% produced significantly greater irritation than that observed in entrapped benzoyl peroxide (**Figure 4**). A test on the backs of human volunteers confirmed this trend. Encapsulated benzoyl peroxide was also associated with a lesser percutaneous absorption *in vitro* and *in vivo* when compared with free benzoyl peroxide (**Table 3**). These data support the concept of the controlled release of benzoyl peroxide from the polymer system into and through the skin. This did not, however, compromise the efficacy of benzoyl peroxide.

Studies of antimicrobial efficacy *in vivo* in humans showed that encapsulated benzoyl peroxide significantly reduced the counts of *P. acnes* and aerobic bacteria [73,74]. Benzoyl peroxide-loaded Microsponges were evaluated for their ability to reduce noninflammatory and inflammatory acne lesions over a 12-week period. Benzoyl peroxide-loaded micropsonges presented similar results to those observed for commercial products containing free benzoyl peroxide.

More recently, a commercial formulation of entrapped benzoyl peroxide in methylacrylate microspheres showed a slightly better efficiency and greater tolerance compared with a gel containing free benzoyl peroxide in a clinical study with patients with light or moderate acne [69].

The preparation and characterization of the Microsponges of ethyl cellulose loaded with benzoyl peroxide were described by Jelvehgari *et al.* [75]. In an attempt to optimize the formulations, the influence of diverse parameters (drug/polymer ratio, stirring rates etc.) was evaluated. An increase in the drug/polymer ratio reduced the rate of release of BP, which was attributed to a reduced internal porosity of the microspheres. This same group investigated the factors that influenced the morphology and size of these microparticles using a scanning electron microscope. The studies showed that the Microsponges were spherical and porous [76].

Table 4. Effects of vehicle on the all-*trans* retinoic acid irritancy.

	0.1% TMG	0.1% RA cream	p-Value
Dryness	1.5	1.9	0.0004
Erythema	2.0	2.8	0.0004
Days to reach grade 3	8.4 ± 3.8*	6.1 ± 3.2*	0.0016

*Mean ± SD.

Irritancy of retinoic acid microsphere gel (TMG) and retinoic acid (RA) cream scored by clinical evaluation. Days to reach grade 3 is a measure of overall irritancy. Severity of irritation was measured on a 0 (none) to 4 (several) scale. Reprinted from [57], Copyright (1998), with permission from Elsevier Science Ltd.

3.2 All-*trans* retinoic acid

In an attempt to increase the profile of retinoic acid tolerance, a new formulation of the drug, based on Microsponges, was developed and evaluated. *In vitro* cutaneous permeation studies, through the hairless mouse skin, showed that the retinoic acid permeation from Microsponges was significantly lesser than that observed for a gel containing the free drug. The antiacne efficacy of this formulation was evaluated in a multicentre, double-blind, placebo-controlled, 12-week study. Compared with placebo, statistically significant reductions were observed in inflammatory and noninflammatory acne lesions treated using retinoic acid-loaded Microsponges [73].

These interesting findings constitute the rationale for the development and commercialization of a gel containing 0.1 or 0.04% retinoic acid-loaded microspheres (Retin-A, Micro™, Ortho Dermatological). A number of studies were conducted as part of this development and showed beneficial differences, especially regarding the profile of tolerance and irritation from retinoic acid-loaded microspheres [19]. A 21-day cumulative irritancy study of healthy volunteers showed that total scores for 0.1% retinoic acid microsphere gel (RAMG) were approximately two-thirds lower than for the 0.1% retinoic acid cream [69].

In an attempt to investigate the irritation potential even further, a half-face, double-blind randomized study was conducted [57,77]. The volunteers (women with sensitive skin, without acne) applied RAMG on one side of the face and the conventional cream containing 0.1% retinoic acid on the other side. At the end of the study, the dried skin and erythema were significantly less at sites treated with the microsphere gel than in the sites treated with the conventional cream (**Table 4**). In another study of facial tolerance [78], RAMG was significantly better tolerated than the conventional cream containing 0.1% retinoic acid.

Since the commercialization of this new formulation, many studies have been published comparing its tolerance and efficacy with other retinoic acid formulations and other retinoids (adapalene and tazorotene). RAMG was significantly more effective than the vehicle in reducing the severity of acne, evaluated by the reduction in the counts of acne lesions (**Table 5**) [57]. A half-face, double-blind study comparing 4 consecutive days of topical application of RAMG and 0.025% retinoic acid cream in 35 patients with acne vulgaris showed that the change from baseline facial oiliness (shine) was significantly greater on the sides treated with RAMG than on the sides treated with the drug cream [79]. In an intraindividual comparison study of the 21-day cumulative irritation potential, the 0.1% retinoic acid microsphere gel once again showed a significantly lower irritation potential than the 0.1% retinoic acid cream [80].

A number of studies have compared the efficacy and adverse reactions of the 0.1% adapalene gel with the conventional formulations containing retinoic acid. These studies suggest that the adapalene gel induces a lesser incidence of adverse reactions compared with conventional retinoic acid formulations. Nevertheless, when the adapalene gel was compared with RAMG, in a comparative clinical trial on the efficacy and safety in patients with moderate facial acne, a similar behaviour could be observed for both formulations regarding tolerance (erythema, stinging/burning and itching) and efficacy [10]. In contrast, in a similar clinical trial, the mean values for skin tolerance (erythema, peeling, dryness and stinging/burning) were significantly lower for patients treated with adapalene gel than for those treated with RAMG [81]. Furthermore, in intraindividual comparison studies, the 21-day cumulative irritation indices for the adapalene 0.1% gel were significantly lower than for those of the 0.1% retinoic acid microsphere [80,82].

Due to the tolerance of the 0.04% retinoic acid formulation, a study was conducted to evaluate the safety and efficacy of the 0.04% retinoic acid microsphere gel compared with the vehicle [83]. In the 12th week, patients treated with the 0.04% retinoic acid microsphere gel obtained a statistically significant reduction in the counts of inflammatory, noninflammatory and total lesions compared with the vehicle. All adverse reactions were of light to moderate intensity and, at the end of the study, no statistically significant difference among the groups (retinoic acid and vehicle) could be observed.

Finally, susceptibility to the photo degradation of retinoic acid under various light conditions is well known. Retinoic acid encapsulation in microspheres, however, offers marked protection against photo degradation, even in the presence of a strong oxidizing agent such as benzoyl peroxide, especially when compared with the conventional retinoic acid gel [84,85].

4. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs), originally developed for parenteral application, are particles made from solid lipids with a mean diameter of between approximately 50 and 1000 nm SLNs can be derived from the emulsions for parenteral nutrition simply by replacing the liquid lipid

Table 5. Mean percentage reduction in lesion counts.

	Retin-A Micro* (all-*trans* retinoic acid gel) microsphere, 0.1%		Vehicle gel	
	Study 1 (n = 72)	Study 2 (n = 71)	Study 1 (n = 72)	Study 2 (n = 67)
Noninflammatory lesion counts	49	32	22	03
Inflammatory lesion counts	37	29	18	24
Total lesion counts	45	32	23	16

*Prescribing information: Retin-A Micro (Ortho Dermatological, Raritan, NJ).
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(oil) of the emulsion droplets with a solid lipid. In contrast to emulsions for parenteral nutrition, however, which are normally stabilized by lecithin, SLNs can be stabilized by other surfactants or polymers and their mixtures [86].

Compared with vesicular and other particulate systems, SLNs have more advantages for drug delivery, such as good tolerability and biodegradation, high bioavailability, and sustained release due to their solid matrix. Moreover, SLNs are easily transposed to an industrial scale at a low cost and without the use of an organic solvent [86,87]. Some problems should be noted, however, such as limited encapsulation efficiency and drug expulsion from the carrier due to lipid polymorphic transformations [88,89].

The release from SLNs depends on the localization of the drug in the solid lipid matrix. If the drug is localized only in the outer shell, burst release will be observed and, probably, no controlled release will be achieved. If the drug is homogeneously distributed within the lipid matrix, however, controlled release can be achieved [86,89].

The first studies that evaluated the potential of SLNs for topical application were conducted by Jenning and coworkers [90]. This study showed that the retinol-loaded SLN application into porcine skin propitiated a high drug concentration in the upper skin layers. The potential for epidermal targeting and follicular delivery of SLNs was also recently reported [91,92]. To date, few studies with SLN-loaded antiacne drugs have been conducted.

4.1 Cyproterone acetate

The encapsulation of topical antiandrogens also promoted drug concentrations in the upper skin layers after SLN application [92,93]. The human skin penetration of cyproterone acetate (mainly within the first 100 μm) from drug-loaded SLNs increased at least fourfold compared with the uptake from creams and nanoemulsions, while the incorporation into nanostructured lipid carriers and microspheres resulted in a two- to threefold increase [93].

4.2 RU 58841

The encapsulation of the antiandrogen RU 58841-myristate (RUM) in SLNs propitiated only negligible permeation of RUM through reconstructed epidermis and excised porcine skin within 6 h Moreover, targeting to the PSU after the application of Nile Red labelled SLNs to human scalp skin was visualized using fluorescence microscopy, and 24 h after application to porcine skin, the intact silver labelled SLNs were detected by transmission electron microscopy [92].

4.3 Isotretinoin

Isotretinoin, a derivative of retinoic acid (13-*cis*-retinoic acid), has been used for the treatment of severe acne but with serious side effects after oral administration [94]. Liu *et al.* [91] investigated the potential of isotretinoin-loaded SLNs for the topical delivery of isotretinoin. The *in vitro* permeation of isotretinoin was evaluated from the SLN formulations through and into rat skin in comparison with a control tincture. These studies showed that all the isotretinoin-loaded SLN formulations avoided isotretinoin permeation across skin, however a high permeation rate (0.76 ± 0.30 μg/cm^2/h) was found for control tincture. Isotretinoin-loaded SLN formulations consisting of 3.0% lipid, 4.0% soybean lecithin, and 4.5% nonionic surfactant significantly increased the accumulative uptake of isotretinoin into the skin and showed a significantly enhanced skin targeting effect compared with tincture [91].

4.4 All-*trans* retinoic acid

The preparation and characterization of all-*trans* retinoic acid-loaded SLNs have been reported in the literature. The encapsulation rate of retinoic acid in SLNs is usually low (< 1% compared with the lipid mass) [95] unless a high surfactant/lipid ratio has been used [96,97]. This favours the interface location of the drug and could in turn compromise the benefits of drug encapsulation in the lipid matrix. To overcome this problem, a suitable approach could be the formation of an ion pairing between retinoic acid, an acid lipid, and a lipophilic amine, such as stearylamine, which would significantly increase the retinoic acid encapsulation in SLNs [98]. Nevertheless, the potential of these SLNs for acne topical treatment have yet to be investigated.

Interestingly, the skin irritation studies carried out on rabbits (Draize test) showed that retinoic acid SLN

gel was significantly less irritating to skin compared with the marketed retinoic acid cream (Retin-A). In addition, *in vitro* permeation studies through rat skin indicated that retinoic acid SLN gel presented a permeation profile comparable to that of the conventional retinoic acid cream. Furthermore, the SLNs also improved the retinoic acid photostability in comparison to methanolic retinoic acid solution when both formulations were exposed to 180 min of natural sunlight [99].

5. Expert opinion

The topical pharmacotherapy of acne includes a variety of drugs that can affect different aspects of the disease. The efficacy of the antiacne topical drugs is well established, however the local side effects, mainly cutaneous irritation, erythema, dryness, peeling and scaling, remain major problems. Unfortunately, both efficacy and side effects are dose related. The encapsulation of the antiacne drugs in vesicular and particulate delivery systems represents an innovative alternative to minimize side effects while preserving their efficacy. This is achieved by the capacity of these systems to provide controlled release or to improve the drug penetration into the skin or even into the PSU.

The studies showed that antiacne drug delivery systems (liposomes, polymeric microspheres and SLNs) provide an interesting alternative for topical treatment of acne. These delivery systems improve efficacy and decrease the incidence of side effects of antiacne drugs when compared with conventional formulations, thus improving patience compliance. Among many drug delivery systems, only liposomes, the most extensively investigated, provide improved efficacy, probably due to enhanced drug skin penetration, and decreased incidence of side effects, whereas the polymeric microspheres are generally associated with better tolerability, due to drug-controlled release but not necessarily with greater efficacy. Nevertheless, problems related to physical and chemical stability and large-scale production of liposomes constitute obstacles to their wider therapeutic use and only microspheres have a marketed formulation. In spite of its greater therapeutic potential, the advantages of SLNs over the vesicular and other particulate systems or conventional formulations still remain to be fully investigated.

Liposomes are the first generation of vesicular drug delivery systems. According to many investigators, these formulations enhance the accumulation of antiacne drugs in the skin, explaining their improved efficacy in comparison to that of conventional products, as demonstrated in some clinical trials. Liposomes also reduce antiacne drug-induced irritation when compared with conventional formulations, an advantage attributed to controlled release. Improved follicular penetration of liposomes has also been demonstrated. The high costs of production and physical stability problems, however, still represent a barrier to the development of a commercial product of antiacne drug-loaded liposomes. Moreover, only a few clinical studies, evaluating the response of a reduced number of patients, have been carried out to evaluate their efficacy in comparison to conventional formulations. Niosomes, a second-generation vesicular carrier, are an alternative to liposomes due to their higher chemical stability, enhanced encapsulation efficiency, intrinsic skin penetration-enhancing properties and lower cost of production. There are, however, fewer studies that have evaluated the dermal delivery of antiacne drugs from niosomes and no clinical studies have been carried out so far.

Among vesicular and particulate drug delivery systems for topical treatment of acne, only polymeric microspheres, presented as Microsponge, are currently marketed and, consequently, several clinical studies have been carried out with this new formulation. When compared with conventional formulations, Microsponge shows similar efficacy but with lower incidence of side effects, improving patient compliance. Generally, microspheres are more stable than liposomes. The large-scale production of microspheres, however, is still expensive and the use of organic solvent is a limiting factor.

SLNs are novel particulate drug delivery systems which have been introduced to combine the advantages of traditional colloidal drug carrier systems such as liposomes and polymeric microspheres, while reducing their drawbacks. These systems are easily produced on an industrial scale, do not require the use of organic solvents and may potentially be used in controlled release and follicular target formulations. Only few studies, however, have investigated the potential use of SLNs as antiacne drug delivery systems. Thus, the promising results obtained in some *in vitro* studies, which have shown that SLN formulations avoid permeation across the skin but increase penetration of the drug in the skin, must be further investigated.

The vesicular and particulate drug delivery systems presented herein (liposomes, microspheres and SLNs) showed potential to reduce the side effects associated with the topical pharmacotherapy of acne and this can be associated with a reduction of the free drug. To date, however, most studies have compared these systems with conventional formulations but no comparison among the three systems has been carried out. Considering the differences in composition and structure of these systems, their efficacy and tolerability are likely to vary. Furthermore, these systems showed potential for follicular penetration, but this aspect was only evaluated in normal skin. Could these systems improve follicular penetration after application on skin with acne, which presents virtually obstructed sebaceous follicles? What is the relevance of particle size and charge for this phenomenon?

Finally, these novel vesicular and particulate delivery systems for topical acne treatment may reduce side effects and consequently increasing patient compliance. Further investigations are needed, however, to allow the large-scale production of liposomes and polymeric microspheres at lower costs. Taking this factor into account, SLNs present clear advantages when compared with the other systems. Their potential as antiacne drug delivery systems, however, needs further investigation.

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Declaration of interest

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