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Recent advances for commedonal acne treatment by employing lipid nanocarriers topically

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***Abstract*---**Acne is one of the most common chronic inflammatory dermatological disorder associated with multifactorial pathogenesis. Approximately 95 % of the population suffers from it at some point in their lifetime. Antibiotics, acids, benzoyl peroxide, and retinoids are the most commonly drugs used for the treatment of acne. However, conventional formulations of these drugs are associated with undesirable toxicities, inadequate penetration across stratum corneum, short retention time of the drug in the target site, and poor aqueous solubility of drugs, that limited their medicinal applications. As a consequence pharmaceutical researchers are turning towards novel drug delivery systems to overcome these limitations. With respect to their small particle size, lipid occlusive nature and unique surface characteristics, lipid nanocarriers can promote skin hydration, enhance drug permeation, improve its targeting properties and retention time on the skin, increase drug solubility and protect it from

degradation, provide sustained drug release and reduce dosing frequency. The current review summarizes the better nanotechnological systems that can be used in future for better and effective treatment of acne.

***Keywords*---**recent advances, commedonal acne treatment, employing lipid nanocarriers topically.

Introduction

Acne vulgaris is a chronic inflammatory dermatological disorder ranking 8th globally in the list of dermatological disorders in prevalence(1). This infects over 90% of world population during their adoloscent periods which is caused due to rise in the level of testosterone hormone which manytimes continues into adulthood(2). Females are more prominent towards acne compared to males. 5% females of the world may show the presence of acne even after the age of forty(3). It rarely continues into adulthood with a negative impact on the quality of life(4). The emergence may be capable of result toward apprehension, low confidence, also in severe conditions despair(5). It is characterized by portions of skin with seborrhoea i.e scaly red skin, comedones i.e blackheads and whiteheads, papules i.e epinheads, nodules i.e large papules, pimples, and perhaps scarring with lesions occurring on face, neck, and back. Acne are classified into mild, moderate, and severe. Mild acne involves formation of small pimples, whiteheads and blackhead comedones devoid of inflammation. Moderate acne involves presence of blackheads, pustules, papules and slight swelling. Chronic acne comprises the formation of papules, pustules and aching cystic nodules, and may result in scar formation on skin. The pilosebaceous follicle inflammation canoccur due to several causes: 1) excessive sebum secretion from sebaceous glands, 2) hyperkeratinization and follicular plugging, 3) androgen-mediated effects, 4) inflammation and immunological host reactions, and 5) bacterial proliferation within the follicle(4). It results from relations between various factors. Androgens, particularly dehydroepiandrosterone sulfate (DHEAS), formed in the adrenal cortex, activate the sebaceous glands. The sebaceous glands are responsible for synthesizing more effective androgens from DHEAS, as they possess weakly androgenic activity. Firstly, microcomedones are formed in the pilosebaceous unit due to retention and hyperkeratosis and then they become larger easily visible to the naked eye. Feasible factors in this are as follows: Altered sebum composition, Bacterial metabolic products (lipase, protease, hyaluronidase), Inflammatory mediators (il-1α) Androgens Propionibacterium acnes (P.acne) is an anaerobic organism present in acne lesions. P acnes are mainly responsible for inflammation through a range of mechanisms. Proinflammatory mediators are produced that mainly diffuses through the follicle wall due to the stimulation of inflammation by P. acne bacteria. It stimulates the toll-like receptor 2 on monocytes and neutrophils. Multiple inflammatory tumor necrosis factor, lymphokine tumor mortification factors are produced due to the stimulus the protein cluster of differentiation(5). Other externalfactors, termed as “exposomes”, such as environmental factors, dietetic factors, emotional factors and various drug therapies, largely influence the incidence, duration and severity of acne(4). Most of the conventional formulations produce side effects that diminish the

patient compliance(6). Systemic utilization drugs can be accompanied with unwanted toxicities. Therefore , topical delivery of anti-acne drugs is preferred. Topical drug delivery allows: i) in bypassing first pass metabolism, ii) to prolong the duration of drug action by employing sustained release delivery systems which are more essential for the drugs that displays short half lives, iii) to lessen drug side effects, iv) to expect a better and effective therapeutical response by avoiding fluctuations of the blood concentration and inter- and intra-patient differentiation. Still , a higher patient acceptability could be expected due to the decreased side effects, the faster clinical effect and non-invasive application(7). therefore, topical delivery is disturbed by poor aqueous solubility of drug and inadequate penetration across stratum corneum(1).To overcome the disadvantages of conventional drug delivery systems, the evolution of lipid carrier based drug delivery came into existence. Nano-carrier based drug delivery reduces irritancy ofdrugs and improves penetration of drug into the hair follicles. The anti-acne therapeutics loadedlipid particulate system for topical application is more preferable compared to conventional available topical delivery system(6).Hence, nanocarriers used for topical drug-delivery strategies have gained interest in recent years. Dermal drug delivery via lipid-based nanocarriers (solid–lipid nanoparticles and nanostructured lipid carriers, vesicular nanocarriers including oleic acid vesicles, niosomes, transethosomes and spanlastics and microemulsions have been widely investigated. Although penetration of nanocarriers through the intact skin could be restricted, these carriers are particularly considered as feasible for the treatment of dermatological diseases in which the skin barrier is obstructed and also for follicular of drugs for management of skin disorders such as acne(8)

Pathophysiology

Acne is an intricate perplexing skin disorder associated with multifactorial pathogenesis , which can be divided into essential four stages: sebum overproduction , follicular hyper keratinization , proliferation of p. acne , and immune response (9). Androgenic hormones, especially testosterone , promote the excessive hypersecretion of sebum from sebaceous glands, which acts a basic role in disease development by creating appropriate environment for p. acnes growth(10). On the other hand, over keratinization of follicles disserves sebum flow to skin surface through pilosebaceous canal and this will lead to the formation of comodones which consists of oily sebum and keratinized cells(9). White heads are formed in case of closedcomedones where no reaction with oxygen whereas black heads are formed due to oxidation of open comedones(10). In this medium p.acnes (normally often exists on healthy human skin.)(11). proliferate rapidly, stimulating proinflammatory cytokines and inflammatory cells such as interleukin-1b (IL-1β),granulocyte– macrophage colony stimulating factor (GM-CSF), and (in particular IL-8, triggered through activation of TLR-2 by peptidoglycan present in cell wall of p. acne), resulting in recruitment of neutrophils and further proliferation of keratinocytes into the pilosebaceous community(4). As well P. acnes plays other role in follicles hyperproliferation and inflammation by inducing lipase enzyme which degrades triglycerides into free fatty acids such free oleic acid which increases P. acnes adherence and growth (13)(14). Genetic factors, decreased levels of linoleic acid and vitamin E (the main antioxidant sebum) in the skin surface could also be embroil in the onset of acne

pathology (15). Other contributing external factors responsible for acne include nutrition, high humidity, hair sprays, stress, depression, and different drug therapies, broadly influence the severity, durationand course of acne (16).

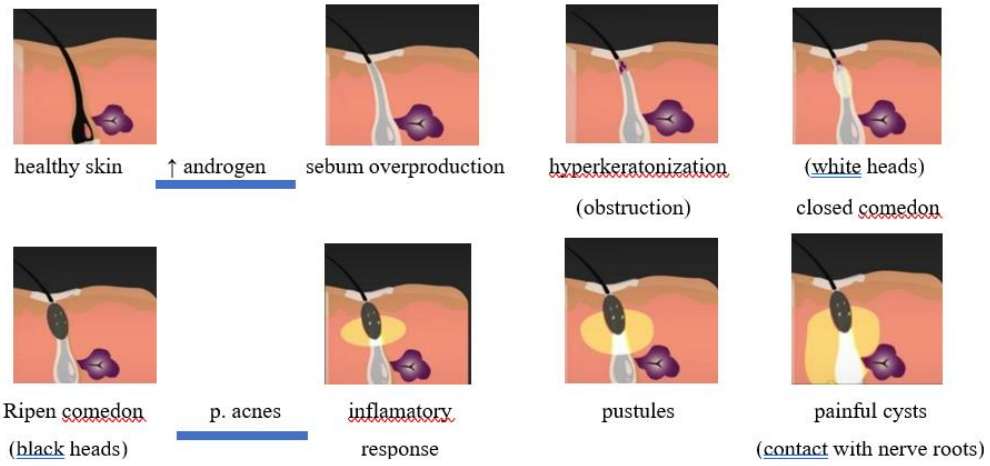

Figure (1): Basic mechanism involved in pathogenesis of acne.

Role of nanocarriers over conventionalforms

Relying on its intensity and development, acne cab be categorized into mild, moderate, and severe. Accordingly, treatment options of acne differs and it divided into:

Systemic treatment

Systemic therapy is the first-line treatment for the management of severe acne (3). It involves mainly oral antibiotics, retinoids, and hormonal treatments (4). Systemic medications are usually correlating to undesirable toxicities. Table (1) summarize various side effects of main conventional delivery systems used for acne treatment

Topical treatment

Topical therapy is the first-line treatment used for mild and moderate acne. Topical treatments base on antibiotics, acids, benzoyl peroxide, retinoids, herbal agents or a combination of topicaldrugs (6). Although topical treatments are safer than systemic, it has many adverse effects. Table (1) shows an overview of various side effects of main conventional delivery systems used for acne treatment. In addition to many several drawbacks related to topical administration of anti-acne agents, poor aqueous solubility of many drugs and deficiency in free drug penetration across stratum corneum considers important limitations of topical delivery (8). Table (1) summarize various side effects of main conventional delivery systems used for acnetreatment

Other treatments

These treatments include surgical removal of acne (comedone extraction), photodynamic treatment, Photothermal therapy, chemical peeling, laser therapy and other techniques associated to high cost and not available for all patients (16).

Table (1): Side effects of main conventional delivery systems used for acne treatment

Drugs	Drawback	Reference
Systemic treatments		
Oral antibiotics (Tetracycline, Doxycycline, Minocycline, Erythromycin, Azithromycin)	Gastrointestinal upset, vaginal candidiasis, pigment deposition in the skin & teeth	(6)
Hormonal treatment Spironolactone, Prednisone Dexamethasone, Cyproteroneacetate/ethinyl estradiol	Menstrual irregularities, contraindicated in pregnancy, Adrenal suppression, Vascular thrombosis, melasma, weight gain.	(16)
Oral retinoids (Isotretinoin)	Teratogenicity, skin dryness, and psychological disorders.	(1)
Topical treatments		
Topical antibiotics (Clindamycin, Erythromycin, Clarithromycin, Azithromycin, Nadifloxacin)	Erythema, peeling, itching, dryness, burning, bacterial resistance, cross resistance.	(6)
Topical retinoids (Tretinoin, Adapalene, Tazarotene, Isotretinoin, Metretinide)	Irritant dermatitis, erythema, scaling, burning sensation, dryness, stinging	(3)
Topical Herbal agents (Aloe vera, Curcuma longa, Melaleuca alternifolia (tea tree))	Skin irritation, allergy	(2)

Nanocarriers are materials in the range of 1 to 100 nm, but in novel medication conveyance frameworks, which ranges from 1 to 1000 nm in size and fabricate from an array of materials either organic (polymer and lipid-based nanoparticles) or inorganic (silica, calcium phosphate,metallic nanoparticles) which are normally biodegradable. The fundamental point in topical delivery for anti-acne agents is to carry the drug to the target site, improve its dermal localization (15). The ideal particle size to provide the highest follicular permeation, the target site in acne treatment, is found to be in the range of 400–700 nm, thus, Smart nanocarriers are able to reach the site of action easily, they endowed with diverse features which help to obtain the desired concentrations of API at the target site, provide controlled release of drug, and avoid side effects of systemic treatments which are the major objectives of topical treatment (9). Nanotechnological carriers have essential advantages over conventional treatments which overcome their undesired effects and address other challenges as following:

- They have high encapsulation efficiency EE
- Increase skin deposition and residence time of drug in the target site
- Act as penetration enhancers
- Protect the
- Maintain the physiochemical properties of encapsulated drug
- Provide local store for sustained release of drugs, thus decreasing dosing frequency
- Suitable for both lipophilic and hydrophilic drugs
- Provide follicular targeting
- With response to stimulus like pH, enzymes it delivers the anti-acne agents that are present at the target site, hence, decreasing side effects in non-targeted sites
- Take role in photothermal and photodynamic therapy of acne as through ruiningantibiotic resistant bacteria that cause acne

Besides particles size, lipophilicity of the nanocarrier plays important role in delivering the drug to the target site by helping crossing the stratum corneum and forming a drug reservoir in the hair follicles. Thus, lipid based nanocarriers are most suitable for topical therapy (6). Lipid nanoparticles are novel nanolipid carriers made from biocompatible lipid which reduces

toxicity; improve physical stability, skin hydration (due to their occlusive nature, they form a thin patch on skin surface thus reducing trans epidermal water loss) which facilitates topical penetration. Also, the lipid nanoparticles shield the encapsulated drug from degradation (6). Lipid nanocarriers refer to a large panel of drug delivery systems. Solid lipid nanoparticles and nanolipid carriers act by forming an occlusive layer on the skin leading to increased hydration and penetration of the drug. Vesicular carriers such as liposomes, niosomes, ethosomes vesicles etc. are also reported to enhance the penetration of the entrapped drugs in deeper layers of skin (15).

Solid lipid nanoparticles SLN

Solid lipid nanoparticles (SLN) were synthesized in the early 1990s as a substitute delivery systems to emulsions and polymeric nanoparticles . In comparison with lipid biocompatibility and versatility, SLN exhibit numerous advantages over polymeric and inorganic nanoparticles for the delivery of a group of drugs. Various advantages, such as higher loading capacity, improved safety ,chemical versatility, biodegradability of lipids, possibility of large-scale production, and a wide range of applications in various fields (22). Vijayan et al. evaluated the treatment of acne and pimples which showed improved skin elasticity by solid lipid nanoparticles (SLNs) loaded Neem oil which is employed as a natural agent that has been incorporated into SLNs, formulated by double emulsification method using different concentrations of lecithin and Tween 80. Results showed that the average particle size of Neem oil loaded SLNs decreased with increasing concentrationof surfactant.

SLNs of 221.6 nm having Polydispersity index of 0.948 were at higher concentration of lipid and surfactant. High entrapment efficiency of 82.10%

revealed the ability of solid lipid nanoparticles to incorporate a high quantity of Neem oil and the stability of SLNs with negligible drug leakage after 3 weeks (17). One of the chief retinoids employed for topical therapy of acne is Adapalene which is frequently associated with skin irritation. To overcome the skin irritation,

Rodrigues et al. proposed the encapsulation of AD in solid lipid nanoparticles (SLNs) using the ion pair strategy. The characterization studies were able to demonstrate that the proposed strategy effectively provided high AD encapsulation in SLNs and its incorporation into a hydrophilic gel. Sustained release, epidermal targeting, and less skin irritation were observed for SLN-AD gel in comparison to the marketed AD gel. The studies demonstrated that the encapsulation of AD in SLNs through the formation of an ion pair is a valuable alternative to diminish the adverse skin reactions caused by AD and can optimize patient adherence to treatment (18). Gupta et al. developed Isotretinoin (ITN) and α-tocopherol acetate (α- TA) loaded solid lipid nanoparticle topical gel for better skin sensitivity and potentiation of efficacy. ITN and α-TA loaded solid lipid nanoparticles (AE- SLN) were prepared by microemulsion method with glyceryl mono-stearate as lipid and tween 80: butanol as surfactant mixes and characterised. AE-SLN gel was evaluated for physicochemical characteristics, drug release, skin irritation and anti-acne activity in rats. AE- SLNs had mean particle size of 193.4nm (zeta-potential -29 mV) and entrapment efficiency for ITN and α-TA was found be 84%w/w and 77.4%w/w respectively. AE-SLN gel exhibited sustained drug release for 24 hours with final cumulative release of 95.8% w/w and 89.1%w/w for ITN and α-TA. AE-SLN gel showed no erythema or edema in rabbits but exhibited potent efficacy in rat model of acne (19).

Dhillon et al. tried to extend and sustain the erythromycin release by formulating a solid lipid nanoparticles (SLNs)-based gel formulation for zero toxicity effect in the treatment of acne. SLN's loaded with ERY were formulated , and various process variables were optimized with respect to average particle size, zeta potential, and entrapment efficiency,drug loading of optimized SLN (F4) using the Taguchi model. and were found to be 176.2±1.82 nm, 0.275±0.011, -34.0±0.84, 73.56%, and 69.74% respectively. The optimized SLN (F4) was successfully incorporated into the carbopol-based hydrogel. The comparison in vitro release of ERY from the SLN gel showed 90.94% and plain gel showed 87.94% .Therefore concluding that In vitro study of ERY-loaded SLN gel showed sustained delivery of drug from formulation thus enhancing the antimicrobial activity after 30 hours when compared to ERY plain gel (20).

Nanostructured lipid carrier (NLC)

second generation of lipid nanoparticles consisting of a blend of solid lipids and liquid lipids (oils) usually in the ratio of 70:30 up to a ratio of 99.9:0.1(7). These lipids are physiological, biodegradable and biocompatible lipids stabilized in aqueous dispersion using a surfactant or a mixture of surfactants and are accepted by regulatory authorities for implementation in pharmaceutical recrystallization of the solid lipid over storage, enhancing loading capacity for lipophilic drugs, providing thermodynamically stable system and furthermore, it can overcome the problem of drug expulsion in SLNs (14). Like SLNs, NLCs demonstrate controlled release fordifferent active molecules, and protect APIs that

are sensitive to light, oxidation or hydrolysis from degradation(7). NLCs can adhere well to skin lipids forming a very thin film increasing the skin hydration, which normalises the living conditions for the cells underneath. The film has also occlusive properties, which promotes penetration of many drugs into the skin layers and this occlusion effect can be enhanced by the small size of lipid nanoparticles(15) . The physiological biocompatible nature of NLC and their complete biodegradation have ensured them as safe nanocarriers and enhance skin tolerability (16). Due to their tendency to accumulate into the hair follicles expanding drug release, NLCs have been suggested as drug delivery systems for follicular targeting (17).These whole set of unique advantages offer supreme advantages of NLCS over other nanocarriers such nanoemulsions, polymeric nanoparticles, liposomes, SLN.. etc, and making it more flexible modification for drug release which thus makes NLC's for multilateral delivery system for several routes of administration, especially topical delivery systems(22). Isotretinoin, is an derivative of retinoic acid (13-cis- retinoic acid), is used in acne management. However, the topical convenience of IT is limited by several drawbacks, such skin irritation, very low water solubility, and photoinstability. Patwekar et al. prepared isotretinoin loaded nanostructured lipid carriers (NLC) gel using solid, liquid lipid, surfactant with gelling agent (Compritol 888 ATO, Oleic acid, Tween 80, Carbapol 974P) by the hot homogenization technique.The results emphasized that the optimized IT-NLC showed no irritation during 72 h, increasing in drug photostabilty due to high entrapment efficiency of IT into the carrier(91.85 ± 0.10%). IT-NLC increased drug water solubility and provided sustained drug release. Furthermore, zeta potential value (□23.3mv) shows better physical stability of the prepared IT-NLC (23). Curcumin is a phytochemical extract exhibited ability to suppress the nucular factor-κB, downregulate of IL- 1β, IL-6, and TNF-α which gave it high anti-inflammation properties. So, it has been proven to be good treatment for acne with a good safety profile. However, it has low water solubility, hence, Rapalli et al. designed curcumin loaded NLC gel by Hot emulsification followed by probe sonication method to improve its skin permeation and increase its retention in skin layers. In-vitro release studies revealed extended drug release up to 48 hours, ex-vivo skin permeation studies exhibited 3.24-fold better permeation and skin retention, no toxicity was observed towards keratinocyte cells with better cell uptake. Further, Curcumin NLC gel increased occlusive effect 3-fold due to small size of NLC and lipids presence that helps to form thin filmon the skin after application and provides an occlusive effect decreasing the percentage of waterloss and skin irritation (24). Because of its anti-infective and keratolytic properties, Salicylic acid (SA) have been reported to be used in acne treatment. Kovács et al. Optimized nanostructured lipid carriers containing salicylic acid to determine the ideal values of surfactant concentration, solid lipid/liquid lipid ratio and ultrasonication time that provides the best formulation. The results showed that an optimal formulation obtained when the surfactant concentration is set to 5%, the solid lipid/liquid lipid ratio is 7:3 and ultrasonication time is 20 minutes. The developed NLC SA showed narrow size distribution (0.857 ± 0.014) with a mean particle size of 114 ± 2.64 nm. In vitro studies exhibited the API released from the NLCs after 6 h was significantly higher than that released from the reference preparation (25).

Pinto et al. designed nanostructured lipid carriers for topical retinoids by miniemulsion methodology using central composite design (CCD) to predict

responses and construct 3D-response contour plots. The research group had selected the concentration of total lipids, solid lipid, surfactant, encapsulated retinoid and number of carbons on the solid lipid fatty acid chain length as the independent variables while the selected responses were the particle size, surface charge of the nanoparticles and the encapsulation efficiency (EE %) at 3 levels. The results showed that optimal composition was 2.5% of total lipids,(2.0% myristic acid and 0.5% of sunflower oil) and 1.5% of surfactant (1.4% of RP, and 0.1% of TRT and ADP). The developed RP-NLC, TRT-NLC and ADP-NLC formulations showed appropriate particle sizes (below b200 nm) which indicates high physical stability which were improved by using Span 80 as surfactant (its lipophilic nature improved the electrostatic and steric stabilization of the lipid nanoparticles that was confirmed by ZP values above −24.3 mV for all formulations).Moreover, high entrapment efficiency values were obtained for RP-NLC, TRT-NLC and ADP-NLC as 84.4 ± 3.0%, 84.1 ± 7.8% and 73.7 ± 3.3%, respectively with verywell-controlled release for the three delivery systems (26).

Liposomes

Liposomes are vesicles composed of amphiphilic molecules in a bilayer conformation. Phospholipids, exclusively used in liposomal preparation, having a cylindrical shape. It has a polar hydrophillic head and two non-polar hydrophobic tails. When subjected to aqueous medium, the molucules arranges itself on two sides of imaginary plane causing the hydrophobic moieties to interact with each other and are directed inside, and the hydrophilic portions are oriented outside, interacting with water. Lipid bilayer hydration tends to generate multilamellar vesicles (MLVs), which are essentially concentric bilayers separated by aqueous compartments. Therefore, various methods have been developed for the production of unilamellar vesicles and each generates distinct sized vesicles, allowing their classification in giant unilamellar vesicles (GUVs; 10-100 μm); large unilamellar vesicle (LUVs; ~100-500 nm) and small unilamellar vesicles (SUVs; ~30-50 nm). Due to their vesicular structure, liposomes resemble biological membranes, with the advantage of constituting a simplified system of controlled composition. Therefore, they are used as membrane models in the basic science (28). Liposome used in spray form to encapsulate and deliver 5-aminolevulinic acid (5-ALA) into the pilosebaceous unit decreases the concentration of 5-ALA to 0.5% in photodynamic therapy (PDT) for acne, with low post-treatment photosensitivity. Yeung et al. investigated the clinical outcome and side effects of PDT using intense pulsed light (IPL) and 0.5% 5-ALA spray for inflammatory facial acne in Asian skin. Twelve subjects of skin types IV–V suffering from facial acne received a full-face treatment at 3-week intervals with IPL. After 1hour of being spreayed with 5- ALA, the lesion counts were assessed using serial standardized photographs taken up to 6 months after treatment. Serial sebum measurement and subjective assessment was carried out. There were mean reductions in inflammatory lesions of 52% at 1 month (p= .02) and 65% at 6 months (p= .04) after treatment. Mean subjective acne score decreased from 6.6 to 4.5 (on a scale from 1 to 10) 1 month after treatment. Significant reduction in sebum production was noted only on the forehead. No significant side effects, including post inflammatory hyperpigmentation and phototoxicity, were observed. We can conclude that the use of 0.5% liposome-encapsulated 5- ALA spray with IPL

decreased inflammatory facial acne in Asians, with a low risk of persistent phototoxic effects after PDT in this pilot study (29).

Moftah et al. also studied the effect of PDT in truncal acne vulgaris using liposomal methylene blue (LMB) versus IPL alone. Thirty- five subjects having different levels of acne were treated with topical 0.1 % LMB hydrogel applied on the randomly selected one side of the back, and after 60 min the entire back was exposed to IPL. This approach was conducted weekly once in three sessions and subjects were re analysed 1 month after the third session by two independent dermatologists. Using Burton scale, the acne severity was graded. Patient satisfaction was recorded by using Cardiff Acne Disability Index (CADI) before and after treatment. On LMB-pretreated side, inflammatory acne lesion counts were significantly decreased by 56.40 % as compared to 34.06 % on IPL alone. Marked improvement was seen on LMB-pretreated side in 11.5 % of patients compared with 2.8 % on IPL alone. Then a correlation existed between CADI score and overall improvement. From the study, it was concluded that LMB-IPL has higher efficacy than IPL alone,providing a safe tolerable pain for treatment of acne vulgaris on the back. (30). Topical clindamycin are often used for their lesser efficacy and increased adverse effects. Therefore, liposomes is the first choice for the present work assuming that incorporation of Clindamycin into liposomes which may decrease the side effects associated with it. To overcome the potential risk of adverse effects and antibiotic resistance from prescribed therapeutics, traditional phytological medications have been extensively studied as alternative remedy for various dermatological disorders. Most widely known herbal medicationfor acne treatment is Green tea for their antibacterial properties.Drugs incorporated in liposomes were formulated using lipid film hydration method and the optimum ratios of the ingredients were recorded.The formulations F1 and F6 having highest encapsulation efficiency (69.5% and 66.2%) and in-vitro drug release (82.5 % and 82.2%) was achieved respectively, containing lipid: cholesterol inthe ratio of 1:1.

Carbopol gel base are incorporated in liposomal formulations and compared with non-liposomal marketed gel. The non-liposomal marketed gel exhibited higher release (90.5%) when compared with liposomal gel of clindamycin (77.5%) and green tea (74.8%) within 24 hours (31). Madan et al. studied the significance of co-application of bioactive components into liposomal gel formulations and their comparison to azithromycin for acne treatment. A Design of Experiments (DoE) technique was employed to obtain optimized liposomal formulation encapsulating curcumin, with size ~100 nm and zeta potential~ 14 mV respectively, characterized by DLS, HR-TEM, FESEM and AFM. The curcumin liposomal dispersion showed excellent stability for time period of 60 days, which was further converted to gel form using Carbopol. Pharmacokinetics of curcumin loaded liposomal gel exhibited the Tmax for curcumin which was achieved within 1 h of post application in both stratum corneum and skin, indicating quick penetration of nano-sized liposomes. Stratum corneum depicted Cmax of 688.3 ng/mL and AUC0-t of 5857.5 h×ng/mL, while the skin samples displayed Cmax of 203.3 ng/gm and AUC0-t of 2938.1 h×ng/gm. Lauric acid and azithromycin liposomal gel formulations were prepared as per the optimum parameters obtained by DoE. In antibacterial activity using agar diffusion assay, lauric acid gel formulation revealed ~1.5 fold improved antibacterial effect than curcumin gel

formulation. Notably, their coapplication (1:1) exhibited significantly enhanced antibacterial effect against both macrolide sensitive (1.81 vs 1.25 folds) and resistant strains of P. acnes (2.93 vs 1.22 folds) than their individual counterparts. The in vivo studies in rat ear model showed a ~2-fold reduction in comedones count and cytokines (TNF-α and IL-1β) on co-application with curcumin and lauric acid liposomal gel compared to placebo treated group (32)

Niosomes

Niosomes are microscopic synthetic vesicles consisting of an aqueous core bounded in bilayers comprises cholesterol and few non-ionic surfactants. Here, assessment of hydrated molecules of non-ionic surfactant forms vesicles. The drug is delivered directly towards the area of process, lead to depletion of medication toxicity. Niosomes are bio-degradable, noncarcinogenic and non-immunogenic. Niosomes is a nonionic surfactant-based vesicle. It assumes more significant to the drug delivery system. Niosomes were originally advanced as substitute to liposomes in form to dispatch their drawbacks: (cost effective and good stability). It increases the skin permeability of medication when locally administered. (33) The antibacterial effect of rosemarinic acid ROA causes nucleoid damage and thus increases genetic material condensation and spatial division. Resistance to current antimicrobial therapies suggested the need to explore new antimicrobial agents against acne. Budhiraja et al. prepared ROA-loaded niosomes and evaluated their in vitro antimicrobial against P. acne and S. aureus.

The research group developed niosomal gel of rosmarinic acid for sustained deliveryinto cells infected by bacteria. Niosomes of rosmarinic acid were prepared by reverse phase evaporation method using different ratio of span 85 and cholesterol. In vivo study of developedformulation was carried out on Swiss albino mice when compared to in plain drug solution along with marketed formulation of benzoyl peroxide. Niosomes of ROA were found to increase ROA retention in skin, facilitating prolong release. Drugs loaded in niosomes for dermal application interacts with epidermal tissue without showing strong systemic action. The plain gel of ROA was effective on first day against S. aureus and P. acne while no response was found on fourth day. Niosomal gel on application for 4 days was found effective on prolonged release. Therefore, it was concluded that ROA has stronger inhibitory potential against the P. acne and can be used as a possible therapy against this bacteria provided it should reach the deeper skin layers. Therefore, niosomes can be employed as a delivery medium for naturally occurring antimicrobial agents, in deeper tissues of skin (34).

Wang et al. endeavored in their study to develop a 3Dprinted niosomal hydrogel (3DP-NH) containing CPT as a topicaldelivery system for acne therapy. Specifically, CPT-loaded niosomes were prepared using a reverse phase evaporation method, and the formulation was optimized using a response surface methodology. In vitro characterization showed that optimized CPT-loaded niosomes were below 150 nm in size with an entrapment efficiency of between 67 and 71%. The CPT-loaded niosomes were added in a dropwise manner into the hydrogel to formulate CPT-loaded niosomal hydrogel (CPT-NH), Permeation and deposition experiments showed significantly higher rates of transdermal flux, Q24, and CPT deposition ($p <$

0.05) compared with 3D-printed CPT-loaded conventional hydrogel (3DP-CPT-CH), which did not contain niosomes. In vivo anti-acne activity evaluated through an acne rat model revealed that 3DPCPT-NH exhibited a greater anti-acne effect with enhanced skin hydration and no skin irritation (35). Benzoyl peroxide (BPO) is generally considered as first line treatment against acne. Low water solubility and formation of larger clusters and limited skin permeation upon topical application necessitates the application of high amount of drug for desired action which leads to induction of skin irritation.

Goyal et al. formulated BPO-loaded niosomal formulation to enhance its permeation through skin. The niosomes were incorporated in the carbopol gel to improve contact time. The outcomes for both retention and permeation studies of skin showed that niosomes can effectively enhance the drug permeation through skin. On Application of niosomal gel significantly decreased the bacterial load when treated for four days. Thus bacterial load was reduced on the inflammation creating minimal skin irritation compared with plain drug and the plain niosomal formulation (36). A combination of tretinoin (keratolytic agent) with benzoyl peroxide (BPO) (an effective antibacterial agent) was employed by niosomes as promising carriers for an effectual acne treatment by acting on the pathogenic site. In this section, niosomal gel formulation encapsulated drugs have been evaluated for in vitro, ex vivo, and in vivo, for their predetermined characteristics; and finally, the stability of the niosome gel was tested at different temperature conditions for understanding the storage conditions required for maintaining the quality of formulation attributes. The range prepared niosome was found to be 531 nm with a zeta potential of -43 mV;

The entrapment efficiencies of tretinoin (TRA) were found to be 96.25%±0.56% and for BPO niosomes was found to be 98.25%±1.75%. After 24 hours, the perfused amount of TRA was calculated as 6.25±0.14 µg/cm2 and BPO was calculated as 5.04±0.014 µg/cm2 both from the niosomal gel.

A comparative drug retention study was carried out in Wistar rat skin by employing 3 different formulations i.e., a cream , an alcoholic solution, and a niosomal gel. In cream the amount of TRA and BPO showed 11.54 µg and 68.85 µg respectively,In an alcoholic solution, the amount of TRA and BPO showed 2.68 µg and 59.98 µg respectively. While in a niosomal gel, the amount of TRA and BPO showed 15.54 µg 143.78 µg respectively. The amounts of TRA and BPO from various formulations were retained in different layers of skin.The niosomal gel was found to be more potent than the antiacne cream because niosomal gels with a 4.16-fold lower dose of BPO exhibited the same therapeutic index at specified sites with comparison to the antiacne cream. This was confirmed by conducting In vivo studies of TRA and BPO based niosomal gel and anti-acne cream. (37)

Ethosomes

Ethosomes are the lipid form of vesicles which contains phospholipids, alcohols as their main active agents and the other agents like polyglygols, cholesterols and dye. When compared to the liposomes, the ethosomal drug carrier have the greater penetration rate through the skin thus ethosomes can be usually used in

the place of liposomes. The main reason provided that is responsible for the penetration of drugs into deeper layers of skin might be due to its combined effect of both phospholipids and ethanol which is present in higher concentration in the ethosomal drug carrier (38). Tretinoin is a widely used retinoid for the topical treatment ofacne, photo-aged skin, psoriasis and skin cancer which makes it a proper ingredient for topical formulation. Still various side effects, like redness, swelling, peeling, blistering and, erythema, in addition to its high lipophilicity make it challenging. Drug loaded ethosomes had been prepared by employing phospholipid and ethanol. Then they are optimized and characterized for entrapment efficiency, vesicular size, shape, In-vitro skin permeation, skin retention, drug-membrane component interaction and stability. The ethosomal formulation having 0.5 %w/v of phospholipid and 20 %v/v of ethanol (F2) showing the greatest entrapment efficiency (80.25±0.23) with small particle size (205.40±2.31nm) was selected for further skin permeation studies. The skin permeation and skin retention studies were performed on ethosomal formulation, liposomal formulation (0.5 %w/v of phospholipid without alcohol), hydroethanolic drug solution and phosphate buffer saline (pH7.4) drug solution. Among them, ethosomal formulation showed higher cumulative percentage of drug permeation (93.36±0.45%) and 8 hours than the other formulations. Scanning electron microscopy confirmed the three-dimensional nature of ethosomes. Dynamic light scattering technique proved that the ethosomes has smaller vesicular size than the liposomes prepared without alcohol. FT-IR studies revealed no interaction between the drug and membrane components. The ethosomal vesicles were incorporated in carbopol gel base and its anti-acne was compared with the marketed gel. Our results suggest that the ethosomes are an efficient carrier for dermal and transdermal delivery of tretinoin (39). Biofilm is prepared by Propionibacterium acnes which are known to cause failure of anti-acne treatment. Conventional therapies for acne are generally inadequate.

Wang et al. evaluated the pharmacological efficiency of photodynamic therapy (PDT) using ethosomes (ESs) loaded with hexyl-amino levulinate (HAL) against the biofilms of P. acnes in vitro and P. acnes–induced inflammatory acne model in vivo. The antibacterial effects of HAL ESs were estimated by employing XTT colorimetric assays and scanning electron microscopic observations of morphological changes. P. acnes was intradermally administered into the ears of Sprague-Dawley rats, and the anti-inflammatory effects of HAL ESs were measured by determining changes in appearance, histology, and the antibacterial effects by P. acnes abundance in ear tissues were compared with blank control ethosomes, hexyl-amino levulinate alone, and 5-aminolevulinic acid alone. The maximum depletion in viability in P. acnes biofilms was noted when treated with 5 mg/mL HAL ESs. Mostly the blank control ESs showed significant inhibitory effects. Furthermore, HAL ESs has superior therapeutic effects on the rat model compared with HAL or ALA solutions. The observed therapeutic results of HAL ESs against P. acnes biofilms and P. acnes–induced inflammation propounded that PDT with HAL-loaded ESs shows significant potency of therapeutic effects for management of acne. (40).

Venugopal et al. prepared ethosomes containing tea tree oil by hot homogenization method and to evaluated its physical characteristics and in-vitro release pattern. The globule size and zeta potential were determined by Zetasizer, respectively. The

release kinetics was also studied by fitting into few mathematical models. All the formulations were showed spherical and unilamellar shape with globule size of 931 to 975 nm, the zeta potential in the range of – 40 to -52 mV and entrapment efficiency were 57 to 65 %. Finally, the invitro release studies showed burst in drug release from ethosomal vessicles at initial time followed by sustained release throughout the study. From the above evaluation studies, it was considered that the tea tree oil loaded ethosomal formulation F5 shows best globule size, zeta potential and entrapment efficiency. Ethosome loaded tea tree oil could be the best choice for topical application. (41). Garg et al. evaluated the ability of ethosomes for topical delivery of isotretinoin. The ethosomal vesicles were prepared with various concentrations of lecithin and ethanol by employing hot method. The ethosomal based isotretinoin gel (GEL-ES) was compared to that of marketed formulations isotretinoin (GEL-MF) by using hydrophobic hydroxyl propyl methyl cellulose as gel base. The physicochemical and stability of ethosomal based isotretinoin and a marketed gel (control) were evaluated for organoleptic properties, drug entrapment, drug content uniformity and in vitro drug release and skin permeation studies. F2 ethosomal vesicles containing 2%w/w lecithin and 30%w/w ethanol was found to exhibit the best entrapment percentage (99.21%) exhibited suitable physicochemical characteristics for topical administration. In vitro release studies showed that < 10% of isotretinoin reached the receptor compartment compared to GEL-MF till 8 h. On comparing F2 and F4 gel formulations, F2 gel exhibited better controlled release by in vitro drug release and in vitro skin permeation profile than F4 gel. However, the in vitro skin permeation was increased with the addition of enhancers. From the experimental data, it may be concluded that the ethosomal vesicles and enhancers, which enhances drug permeation and depot formation in skin(42).

Table (2): Role of nanocarrier-based drug delivery system to encountered the major challengesfaced by conventional therapy for the treatment of acne

Challenges	Composition	Method	Model	Pharmacokinetic/ Pharmacodynamic significance	Pharmacological significance
LIPOSOMES					
Scaling,	(PG 90G),	Thin-film	Swiss albino	PS 256.4 ± 9.3 nm with	↑dermal bioavailability
dryness,	cholesterol,	hydration	mice	PDI~ 0.2	(AD-2.1, 5.4; BPO-3.0,
erythema,	Sodium	technique		EE of >80% for BPO	7.83-fold) and ↓ skin
burning/stingi	deoxycholate and			and >70% for AD	irritation and papule
ng,	(SLES)				density in animal model
Contact					
dermatitis,					
pruritus,					
peeling,					
sunburn and					
so forth					
Local	1-Palmitoyl-2-	Film	Mice	P.S. 111.10 ± 8.02 nm;	Release of apis was
irritation,	linoleoyl-	formation	fibroblast	P.D.I.¼0.198 ± 0.03;	sustained for 24 hours

					with
elevated	snglycero-3-	method.	cells	Z.P.¼25.83 ± 0.40 mv)	released amounts of
Sensitivity to	phosphocholine,			with an EE more than	56.44% and 58.44% for
sunlight and	1,2-dipalmitoyl-			80% for both apis	tetracycline hcl and
stability	sn-glycero-3-				tretinoin, respectively
problems of	phosphocholine,				-no toxicity was observed
the active	And 1,2-				- ↑antibacterial efficacy
Ingredients	distearoyl-				-provided good stability
	racglycero-3-				for 6 months at 4 C and 25
	phosphocholine,				C
	(Transcutol P),				
	cholesterol, and				
	Carbopol 980				
Erythema,	L-alpha lecithin,	Modified	Partiacne	PS < 0.5 less than 0.5	Released amounts of 22%
peeling and	cholesterol and,	ether	patients	µm, EE from 38.2 % to	to 53 % after 5 h. Film
burning	Dicetyl phosphate	injecting		70.5 % for ether	hydration showed higher
Increased	(electric	method, thin		injection method, and	percentage release than
susceptibility	insulator),	film		from 51.3 % to 73.4 %	ether injection method.
to sunlight	Carbopol 934	hydration		for film hydration	
Limited		method		method, ZP of	
stability				- 41.2 ± 1.2 mv	
Poor water	Phosphatidylcholi	Modified	-	-EE%= (65.47 ± 1.7%)	-provided good stability
solubility	ne, cholesterol	ethanol		- P.S. (209.56 ± 4.8 nm)	when stored for 2 months
		injection		- Z.P.= (–41.19 ± 1.3	in dark at 4◦C as well as
		method		mv)	room Temperature
					-MIC and MBC values of
					liposomal formulation
					against 11 clinical isolates
					and reference strains
					ranged from 1 to 4 and from 4 to 64 μg/ml, respectively, while those of rhodomyrtone were 0.25–1 and 0.5–2 μg/ml, respectively
ETHOSOMES					
Low	Carbopol-934,	Thin film	Male Albino	Vesicle's size of 105.2	Antimicrobia and anti-
solubility, and	Phospholipid 90G	hydration	rat.	± 8.0 nm, entrapment	inflammatory activities
penetration,		method	Wistar rats	efficiency of 85.30 ±	were relatively tolerable,
stability				6.30% and flux of 65.40	Penetration depth 103.5

problems				± 7.6 µg/cm2 /h.	µm across rat skin,
					Considerable effect on
					sebaceous glands units by
					reducing its glands number
					and size. The formulation
					was safe, less irritation.
Scaling,	Soya	Hot	Male Albino	A vesicle size of 4.25 ±	As compared to
erythema,	phosphatidyl	Method,	rats	1.35 µm and	conventional gel and
dryness,	choline	Cold		entrapment efficiency	marketed cream it showed
stinging,	Cholesterol	Method and		of 91.86 ± 2.25%	sustained release, ↑ flux,
irritation,	Carbopol 934	Thin film			and it was
burning,		hydration			Non-irritan
itching, rash,		method			
pruritus and		using rotary			
sunburn.		evaporator.			
Low	Soya	Cold	Albino rats	A particle size of 192.3	↑ prolonged drug release
bioavailability	phosphatidylcholi	method	weighing	nm, PDI of 0.523, zeta	↑ AMOUNT OF DRUG
, permeability,	ne, cholesterol		between	potential of -49.5 and	RELEASED
drug release	45% ethanol		150-200 gm	entrapment efficiency	↑ permeation
and stability			of either sex	of 63.4%.	Skin retention values of
problems					75.96%
					Irritation free
Dryness, skin	(SPC, Lipoid		Rabbits	Vesicle size of 69.1 ±	↑ anti-acne effect
irritation and	S100)		(male,	1.9 nm with loading	Slight skin irritation.
photosensitivi	Oleic acid and		weighting	efficiency of 0.445 ±	↑ permeation
ty	Carbomer 974		about 2.5	0.007 mg/ ml and	Transdermal flux were 2.5
Low water			kg)	encapsulation	times of conventional gels
solubility and				efficiency 40.31 ±	Skin deposition were 2.1-
bioavailability				0.67%	times of conventional gels
of API					
Scaling,	Phospholipon 90	Thin-layer	_	EE 94.48 ± 0.14,	↑ Antibacterial activity
erythema,	G	hydration		P.S.= 179.3 ± 2.23 nm,	MIC and MBC of azelaic
dryness,	Ethanol 35%	method		P.D.I.= 0.665 ± 0.02,	acid ethosome-based
stinging,				and Z.P.= −34.87 ±	cream was 250 µg/ml

irritation,				0.35 mv. EE 94.48 ±	while the marketed cream
burning,				0.14%,	(Zelface® cream) was
itching, rash,					shown MIC of 250 µg/ml
pruritus and					and MBC of 500 µg/ml.
sunburn					
Erythema and irritation	(Brij® 58), Stearylamine (STE), (CHO), (EDTA), (BHT), Compritol® 888 ATO, Propyleneglycol	Hot melt homogenization method using an emulsification-ultrasound	In vitro growth inhibitory activity was determined by the double layer method,	EE= 94±7% for retinoic acid and 100±4% for lauric acid, P.S. = 150±1 nm, Z.P. =11±4 mv	↑growth inhibitory activityof p. Acne
NLC					
Erythema, dryness, irritation, scaling and peeling, poor skin penetration, low Bioavailability(5–8%), drug loss, and degradation	Oleic acid, precirol ATO5, tween 80, Carbopol®940	Melt emulsification comibined with sonication technique followed by its optimized by using Box Behnken statistical design	Adult Albino Wistar malerats weighing 150–200 g	PS= 136 ± 3.15 nm, PDI= 0.256 ± 0.10, Z.P.= −41.9 ± 0.99 Mv, EE= 80 ± 3.62%, DL= 13.26 ± 1.32%, Spherical shape of particles, ph = 6.14, maximum drug content = 99.68 ± 2.21%., viscosity = 931 ± 0.41 cps, hardness = 94.567g, spreadability= 95.109 gs	-Provide biphasic release pattern with initial burst release followed by Sustained release. -↑skin penetration, -↑ skin targeting, -↑skin retention - good physical stability incool and dry place -↓ skin irritation
Irritation, erythema, dryness, peeling, scaling	(OA) (liquid lipid), (GMS) (solid lipid), Stearic acid (SA), Sodium dihydrogen orthophosphate, orthophosphoricacid, Cremophor RH40(as surfactant) Aloevera basednanogel	Melt emulsification and ultra-sonication method	Rabbits (either sex,2.0-3.0 kg), Swiss albino mice (either sex, 25 ± 5 g)	P.S. ~50 nm,EE >80%,	Skin retention ↑ two foldshigher than marketed preparation, no irritation, oedema, redness or dryness, ↑ penetration to deeper layers of skin, ↑ retention for prolonged time periods, high inflammatory and microbial in comparison tomarkets drug, low toxicity (<10%) and safety profile, ↑efficacy and cutaneous targeting at lower concentration
Low water solubility, rritation,	Precirol ATO5(solid lipid), Labrafac	Emulsification/sonication method	Albino rats weighing	P.S. from 106.2±5.6 nm to 151.3±7.4 nm, EE from 76.5±3.8 % to	Weakened the stratum corneum and ↑permeation,

redness, itching and burning	Lipophile (liquid lipid) (Transcutol P), (CTAB), Tween 80, 0.5% lecithin (emulsifying agent)		180–200 g	91.1±3.9 %,	↑the amount of drug retained in the skin, enhance anti-rosace activity, a rounded to elliptical shape OF PARTICLES was observed, ↑ occlusive effects, no irritation or skin
Burning, Desquamation		hydration technique	moderate acne vulgaris of both genders aged between 12 to 30 years		infammatory and inflammatory lesions number respectivrly, reduction in lesions number over time was significant, improvement of QOL was observed, ↓ severity of side effects,
SLN					
Irritation, erythema, dryness, and itching, poor water solubility	Compritol® 888 ATO, MH, Tween 60, dcchol , (Brij® 58), (SA), Tetrahydrofuran ,trifluoroacetic acid and ethylenediamine tetraacetic acid	Hot emulsificati onultrasonic ation Method	Female mice(7 to 8 weeks old)	E.E. =101 ± 1 (%) P.S. =107 ± 0.5 nmPDI = 0.25 ± 0.01 Z.P. = +42 ± 6 mv Total AD 102 ± 3 %	-no significant change in mean physical parameterswere observed - Sustain drug release -provide epidermal targeting, -↓ skin irritation -↑ drug incorporation intothe hydrophilic gel -↑ drug retention in skin epidermal, -↓ opening keratinized corneocytes - ↑ uniform epidermal surface
Erythema and skin peeling, irritation, low permeability, stability, and skin retention	GMS, Tween 80, butanol	Microemuls ion method	Male New Zealand White rabbits weighing 2.5–3 kg, Femal e wistar rats weighi ng 180-220 g	Mean P.S. of 193.nm, Z.P.= -29 Mv E.E.of 84% w/w for ITN and 77.4% w/w forα-TA, ph = 6.8 , viscosity = 88×105 mpa s , spreadability = 5.8 g.cm/sec , Drug content of ITN and α-TA 97.2 % w/w and 95.3 % w/w respectively	Sustained drug release for24 hours, - cumulative release of 95.8% w/w and 89.1%w/wfor ITN and α-TA. -no signs of irritation or edema -↑ anti-acne activity
Skin dryness, Low solubilityand skin penetration	Precirol ATO 5, Gelucire 50/13, Carbopol 974, Span 20, tween	Microemuls ion technique	Male young Wistar rats	E.E.= 95.64±0.2% P.S.= 168.5 nm, P.D.I.= 0.335 Z.P.= -16.8±6.1 mv	Drug release of 61.1±0.6%after 8 h, Provide sustained release pattern

	20			↑ viscosity,	↑ drug permeation
Erythema, Pruritus, Burning, Desquamation	Glyceryl monostearate, Polaxomer 188, stearic Acid, Comparitol, Lecithin	Microemulsion technique	In vitro antimicrobial activity: Disk diffusion Method	P.S.= 176.2±1.82 nm, PDI= 0.275±0.011, Z.P.= -34.0±0.84, EE=73.56%, Drug loading of 69.74%, Mean spreadability = 19.51 gcm/sec, Mean Viscosity = 9563 Pa.s , Mean ph= 6.5	-in vitro release of drug 90.94% - *in vitro* release study of SLN gel followed Higuchi kinetics (R2 =0.981). -provide sustained drug release -↑ antimicrobial activity after 30 hours
NIOSOMES					
Low dermal bioavailability,skin erythema,dryness, and itching, Redness, desquamation, bleaches hair and clothes	SPAN 60, SPAN 40, SPAN 85, cholesterol,Stearic acid	Thin-film hydration method	In vivo study on rabbit ear	Percentage drug content from 84–97.86 %., EE is higher in F8 which contain long chain of alkyl of Carbopol with cholesterol, Cumulative amounts ofADP and BPO permeated from niosomal gel in 24 h (6.25 ± 0.14- 5.04 ± 0.014 µg/cm2) respectively	↑drug retention, ↑antiacne effects, ↑ drug penetration into theSC, ↑ sustained drug release, ↓skin irritation, no scaling,no lesions were observed even after 48 h, ↓ dosage frequency, and systemic toxicity, good stablility at refrigeration and room temperatures,
Skin dryness, Low solubilityand skin penetration	Spans (20, 40, 60 And 80) and cholesterol	Thin film hydration method	15 patients with mild to Moderate acne vulgaris	Z.P. (-29.97 mv), P.S. (3.65 µm), drug-loaded niosomes are almost spherical in shape, percentage of drug release 96.78% over 24 h.	Provide sustained drug delivery, highly significantdecrease in non- inflammatory and inflammatory lesions, ↓ erythema, ↑ penetration
Low dermal bioavailabilityand side effects Such as skin irritation, erythema, dryness, and itching, poor water solubility	Span 60 , Carbopol 934 ,	Modified ethanol injection method.		P.S. = 278 nm, Z.P. = -17.99 mv, and EE%= 86 %,	Provide controlled drug release up to 24 h , ↓skin irritation , ↑ retention timein stratum corneum 2.5-fold higher than marketeddrug
Low solubility, Erythema, scaling, burning.	Cholesterol, span80	Thin film hydration Method	In-vitro anti acne activity By diffusion method	EE % (78.85±0.25%), P.S. (212.4±0.32 nm), Viscosity (3350.2±10cps), drugcontent 99.4±0.23 %,PH of (6.80), Drug released after 12 h (96.65±0.32),	↑ anti acne activity where it showed zone of bacterialTazarotene loaded niosomal gel for effective acne treatment growth Inhibition (18.5±0.86mm) at concentration 10µg/ml, ↑ drug permeation, preventthe degradation of tazarotene by protecting it from the direct exposure to Environment, ↓ drug side effects.

Erythema, Pruritus,	Cholesterol,Span 60	Lipid thin film	70 patients with mild to		40% and 66.6% of subjectsshowed reduction in non -

Entrapment efficiency (EE) , PS particle size , ZP zeta potential , AD adapalene , polydispersity index (PDI) , Phospholipon 90G (PG 90G) , sodium lauryl ether sulfate (SLES) , Cetiol B R _ (Dibutyl adipate) and Acconon C-44 EP/NF (Lauroyl macrogol glycerides)1,2Diethylene glycol monoethyl ether(Transcutol P) , Soybean phosphatidy choline (SPC, Lipoid S100) , propyleneglycol dicaprylate/dicaprate (Miglyol® 840), Propylene glycol monocaprylate(Capryol™ 90), decyl glucoside (Plantacare® 2000 UP, P2000), propylene glycol (PG), Caprylic capric triglycerides(Saboderm TCC), glycerol monocaprylate (Imwitor® 988, I988), glycerol monocaprylate/caprate (Imwitor® 742, I742), Isopropyl myristate (IPM), diethylene glycol monoethyl ether (DEGEE) , Caprylocaproylmacrogoglycerides (Labrasol), Capryol 90 (Propylene glycol monocaprylate) and Diethylene glycol monoethyl ether (Transcutol P), maprotiline hydrochloride (MH) , 3β- [N-(Dimethylaminoethane) carbamoyl] cholesterol (dcchol®),, polyoxyl 20 cetyl ether (Brij® 58), stearylamine (SA), Glyceryl monostearate (GMS), Oleic acid (OA), stearic acid (SA), Glyceryl palmitostearate (Precirol ATO 5), caprylic/capric triglyceride (Labrafac lipophile) and diethylene glycol monoethyl ether (Transcutol P), Cetyltrimethylammonium bromide (CTAB), Cremophor RH 60 (PEG-60 hydrogenated castor oil;) , Miglyol 812(caprylic/capric triglyceride), Compritol 888 ATO (glyceryl behenate/dibehenate) ,polyoxyl20cetyl ether (Brij® 58), stearylamine (octadecylamine, STE), cholesterol (CHO), ethylenediaminetetraacetic acid (EDTA) and butylatedhydroxytoluene (BHT) , Compritol® 888 ATO [glycerylbehenate, mixture of mono, di and triacylglycerols of behenic acid (C22)]

Future aspects

The use of adjuvant skin care is now integral to the management of acne and natural compoundsare evolving into a real management option for dermatologists. They have very good safety profile compared to chemically synthesized counterparts. However, lack of adequate solubility, optimum permeability and stability makes them not a suitable source for product commercialization. Advanced drug delivery systems like nanocarriers are able to improve their therapeutic efficacy by modifying their physicochemical properties and pharmacokinetic properties. Further, complete clinical investigations need to be performed to establish the benefits of such nanotechnology-based herbal products. Though many reports advocate on the usefullness of nanotechnology in enhancing pharmacokinetic and pharmacodynamic characteristics of natural products, certain points, such as production cost, scale up feasibility, batch to batch uniformity, availability of suitable analytical characterization tools and toxicity of the materials used, need careful evaluation and selection for the successful delivery of natural products usingnanotechnology(42).

Conclusion

Lipid nanoparticles are novel nanolipid carriers made from biocompatible lipids, SLN and NLC are occlusive in nature and form a thin film on skin surface thus reducing trans epidermal waterloss and promoting skin hydration.As compared to conventional creams, lotions and solutions or free forms, liposomes are advantageous as they improve the amount of drug permeation into the stratum corneum. Also on liposomal composition modification, production of new nanovessicles are permitted which have improved chemical stability in niosomes and higher deformability in ethosomes. This versatility of the composition of nano systems could allow personalized therapy. The most suitable carrier can be chosen depending on the physicochemical characteristics and the site of action of the drug(s), the depth of the skin layers to be reached for acne treatment, and the need to deliver a single drug or a combination of drugs. Moreover, diverse adaptability nature of these nanocarriers in their flexible or deformable vesicles is confirmed by their stability when introduced in conventional formulations. The preparation of liposomal or transfersomal gels or creams for acne treatment combines the drug delivery capabilities of nano-formulations with the mechanical characteristics of the conventional formulation, such as viscousity, spreadability and ease of application, which should lead to patient acceptability. When compared to the numerous scientific studies confirming the efficacy and low toxicity of the aforesaid nanotechnological products in acne treatment currently in commerical availability. This is probably because of some aspects are still uncertain, such as the skin transfusion mechanism of ultradeformable vesicles or their localization in a specified skin layer. For this reason, the medical and life sciences researchers focus on anti-acne treatments, trying to convince the pharmaceutical market to trust more strongly in nanotechnoogical employment. Suitable nanosystems for acne treatment have yet to be realized. In our opinion, the nanosystem should maintain excellent characteristics of the described carriers, such as biocompatibility, better stability, sustained or extended drug release and good pharmacological effectiveness. Therefore, it should assure specific targeting providing better follicular bioavailability, as acne is an inflammatory disease involving the pilosebaceous follicles, which is required proper stimulating for in situ retention, thus avoiding reaching the deeper skin layers, which could lead to systemic side effects.

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