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ADVANCES IN NANO DRUG DELIVERY FOR THE TREATMENT OF ACNE: A REVIEW

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ABSTRACT

Acne Vulgaris is inflammatory skin disorder by which approximately 95% of the population suffers at some point in their lifespan. Acne vulgaris, novel drug delivery, conventional system. This disorder is most common in adolescents but also effect prepubescent neonates, children's and adults. Topical treatments of Acne are associated with various side effects like skin Irritation, Dryness, Peeling, Itching etc. Novel drug delivery systems have been used to reduce the side effect of topically used Drugs. Topical treatment of acne makes direct contact with the target site before entering the systemic circulation which reduces the systemic side effect of the parenteral or oral administration of drug. The objective of the present review is to discuss the conventional delivery systems available for acne, their drawbacks, and limitations. Furthur, we also discuss the advantages, disadvantages, and outcome of using various micro/ Nanoparticulate delivery systems like liposomes, niosomes, solid lipid nanoparticles, and so forth, are explained. This paper emphasizes approaches to overcome the drawbacks and limitations associated with the conventional system and the advances and application that are poised to further enhance the efficacy of topical acne formulations, offering the possibility of simplified dosing regimen that may improve treatment outcomes using novel delivery system.

KEYWORDS: Acne vulgaris, novel drug delivery, conventional system.

INTRODUCTION

Acne vulgaris (acne) is a chronic inflammatory disease of pilosebaceous unit affecting seborrhoeic areas (mainly face, chest, back), characterized by the presence of comedones, papular and pustular eruptions, purulent cysts and scars.[1] Although it most often affects adolescents, *acne vulgaris* is not uncommon in adults and can be also seen in children. The current concept is that the pathogenesis of acne encompasses the interaction of several different pathogenic factors, namely follicular hyperkeratinization, hormonally determined overproduction of sebum and changes in microbial flora in addition to immunological factors and inflammatory processes. Increased sebum production and follicular hyperkeratosis result in the development of microcomedones, while changes in follicular milieu cause the intensive growth of *Propionibacterium acnes* (*P. acnes*).[2] In the emergence of acne, other factors such as androgens, Peroxisome proliferator-activated receptor (PPAR) ligands, insulin like growth factor-1 (IGF-1) signaling pathway, regulating neuropeptides and environmental factors are probably involved, which interrupt the natural cycling process in the sebaceous gland follicle and support the transition of microcomedones to comedones and inflammatory lesions.[3] Despite acne not being a life-threatening disease, it has significant physical and psychological consequences such as permanent scarring, reduced self-esteem, social inhibition, depression, anxiety and suicidal tendency.[4]

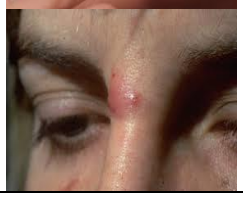
Since it can negatively affect the patients` quality of life, early and aggressive therapy is crucial, with successful treatment promoting much more than just cosmetic benefits. Up to date, various clinical guidelines for management of acne have been proposed. Different factors, such as age of the patient, site of involvement, extent and severity of disease and patient preference may influence the choice of the therapy.

A stepwise approach to acne management involves topical agents for mild to moderate acne (topical retinoid as mainstay and/or topical antibiotics) and escalation to oral agents for more resistant cases (oral antibiotics or hormonal agents in conjunction with a topical retinoid or oral isotretinoin alone for severe acne).[5]

In spite of various treatments for acne being available, many patients fail to respond adequately and often, the efficacy of the treatments is compromised.[6] The active substances and the conventional formulations for local acne treatment have numerous drawbacks, in terms of physico-chemical properties of the active ingredient, stability and limited possibility for penetration into the skin appendages. Numerous side-effects, such as skin irritation,

redness, dryness, severe desquamation and photosensitivity occur due to the incapacity for targeted drug delivery to the pilosebaceous units and achievement of optimal concentration at the site of action. These side-effects diminish the patients` compliance.[7]

Table 1: Types of acne lesions.[8]

S.No	Type	Indication	Clinical Representation
1.	Open Comedo (Non-inflammatory)	blackhead in which pigment is invariably visible and consist of dilated orifice.	
2.	Closed Comedo (Non-inflammatory)	Absence of orifice leads to inflammatory lesion in the dermis.	
3.	Pustule (Inflammatory)	A small inflammatory lesion emerging from the microcomedo & results in cap of pus.	
4.	Papule & Nodule (Inflammatory)	A rigid and more deep lesion than a pustule. Its results in more severe form of acne. A larger and still deeper inflammatory lesion that invariably produces a deep scar	 

Hence, the patients are in search of topical products for skin use that are not only safe and efficient, but are also cosmetically acceptable and easy to use. Novel delivery strategies for existing drugs and their modifications represent the recent changes in acne treatment, in addition to the development of new medications that target regulatory pathways involved in acne pathophysiology.[9] These novel drug delivery systems might minimize the problems associated with the conventional products in terms of penetration, retention, sustained release and therapeutic efficacy.

The micro/nanoparticulated systems have been widely researched both as carriers of active substances and as delivery systems for the cosmetic active ingredients. Encapsulating the active ingredient within these systems is anticipated to result in its protection, release of

smaller doses in a continuous period, as well as targeting the Pilosebaceous unit that would help achieve an efficient, relatively high local concentration at the site of action.[4] Beside controlled release of the encapsulated drug at the site of action, among the other main advantages of these carrier systems are: an improved stability of the active substance (e.g. active substances sensitive to oxidation, hydrolysis, thermal degradation), possibility for incorporation of incompatible substances, possibility for modification of the physicochemical and the organoleptic properties of the active substance, improved penetration (due to the defined size, structure, surface properties), improved skin tolerance, reduction of side-effects and satisfying aesthetic look of the product. Hence, these novel drug delivery systems are an innovative approach in the dermatological acne treatment and are expected to achieve a greater therapeutic efficacy with a possibility for a so-called size-dependent localization (especially in the hair follicle) and a possibility for diminution of the side-effects of the active ingredient, which makes them superior in comparison with the conventional preparations.

This review focuses on the so-far investigated contemporary carrier systems that are being used for acne treatment in terms of formulation and assessment of their efficacy and safety as well as the published patents concerning these systems.

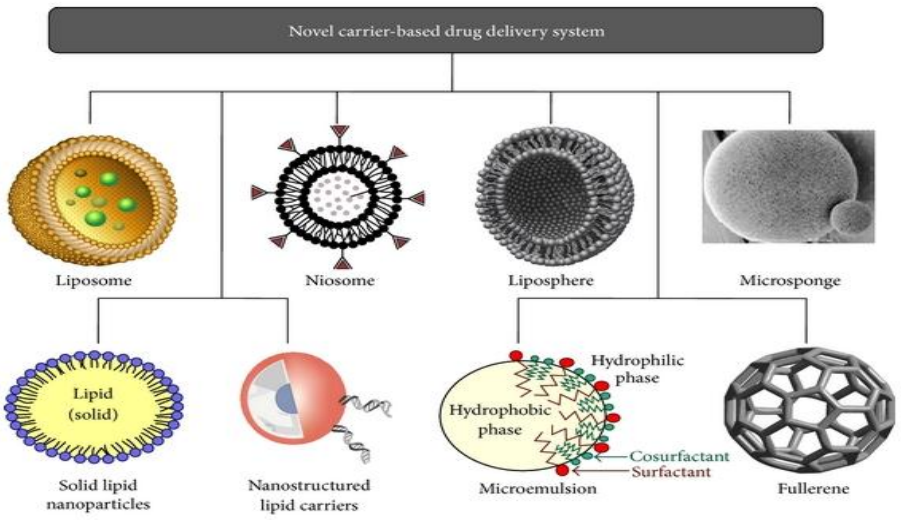


Fig 1: Different types of novel Carrier Based drug delivery system.

NIOSOME

Niosomes non-ionic surfactant vesicles are microscopic lamellar vesicles formed when non-ionic surfactants (mainly of alkyl or dialkyl polyglycerol ether class) are added to cholesterol with subsequent hydration in aqueous media. Vesicular systems such as liposomes and

niosomes are also widely used in cosmetic and skin care applications because of their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration Bacterial infection is one of the most continual and significant issue around the world especially Indians are genetically more prone to it.[10]

Niosomes are second-generation vesicular systems, whose design has helped overcome the disadvantages of conventional liposomes, such as the requirement for vigorous work conditions, limited encapsulation efficacy, instability and expensive production. These structures contain non-ionic surfactants instead of phospholipids, cholesterol which improves the rigidity of the bilayer and water phase and are therefore called non-ionic vesicles.[11] In their preparation, different non-ionic surfactants can be used such as polyoxyethylene alkyl ethers and esters, glucosyl dialkyl ethers, polyglycerol alkyl ethers, crown ethers and sorbitan esters.[4] Niosomes have a series of advantages such as biodegradability, non-toxicity and non-immunogenicity and they are able to encapsulate large amount of materials in a small volume of vesicles.[12] As a result of their composition and structure, niosomes improve the properties of stratum corneum by reducing the transepidermal water loss and restore the hydrolipid film.[6]

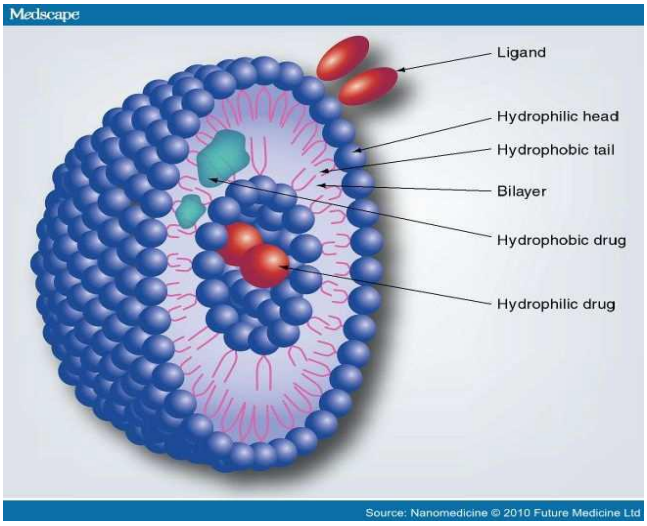


Fig 2: Structural composition of Niosome.

LIPOSOMES

The Liposomes are the micro-particular drug carrier one or more concentric phospholipids bi-layer separated by aqueous buffer compartments known as "Liposomes". Their diameter ranges from 25 nm to 5000 nm.

Liposomes is Greek words means

'**Lipo**' mean 'Fat' and
'**Somes**' mean 'Body'

liposome has an aqueous solution core surrounded by a hydrophobic membrane, in the form of a lipid bilayer; hydrophilic solutes dissolved in the core cannot readily pass through the bilayer. Hydrophobic chemicals associate with the bilayer.[13] A liposome can be hence loaded with hydrophobic and/or hydrophilic molecules. To deliver the molecules to a site of action, the lipid bilayer can fuse with other bilayers such as the cell membrane, thus delivering the liposome contents; this is a complex and non-spontaneous event, however. By preparing liposomes in a solution of DNA or drugs (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer, but are then typically distributed non-homogeneously. Liposomes are used as models for artificial cells. Liposomes can also be designed to deliver drugs in other ways. Liposomes that contain low (or high) pH can be constructed such that dissolved aqueous drugs will be charged in solution (i.e., the pH is outside the drug's pI range). As the pH naturally neutralizes within the liposome (protons can pass through some membranes), the drug will also be neutralized, allowing it to freely pass through a membrane. These liposomes work to deliver drug by diffusion rather than by direct cell fusion.[14]

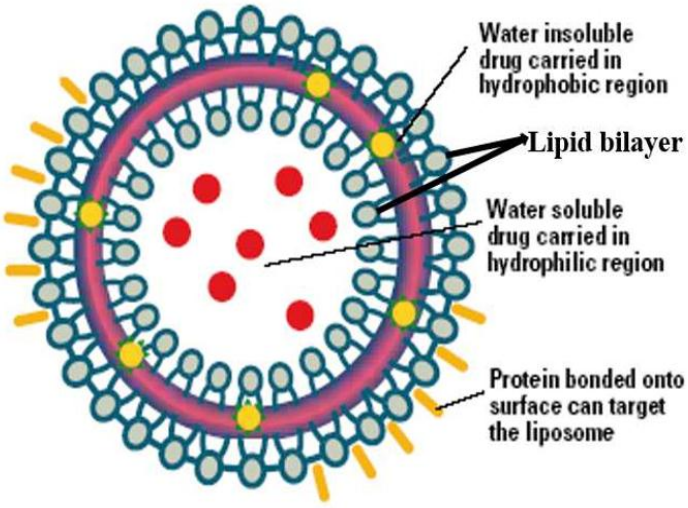


Fig 3: Structural organisation of Liposome.

INVASOMES

Invasomes are composed of unsaturated soybean lecithin (with high % PC), small amount of ethanol, and small amount of a mixture of terpenes (cineole, citral, and d-limonene). Unsaturated phospholipids were chosen as they, due to their low Tm, lead to the formation of

liposomes being in liquid crystalline thermodynamic state. The purpose of using terpenes was to impart deformability to the carrier. It was supposed that terpenes, which are used as penetration enhancers, as they increase the fluidity of SC lipid bilayers would also increase the fluidity of vesicles bilayers.[15] Namely, terpenes have been shown to be potent enhancers for a variety of drugs, such as nicardipine , lorazepam, clonazepam ,haloperidol, nicardipine, carbamazepine, tamoxifen etc. Investigations employing differential scanning calorimetry (DSC) and x-ray diffraction revealed that terpenes increase drug permeation by disrupting lipid packaging of the SC and/or disturbing the stacking of the bilayers.[16] Moreover, the enhanced skin penetration of various drugs is supposed to be a result of increased drug solubility in the SC treated by terpenes. The lipophilic drugs show increased penetration due to their increased partition coefficient SC/vehicle, and their penetration increases proportionally to their solubility in the enhancer. Regarding hydrophilic drugs, their penetration is assumed to be improved due to their increased diffusion coefficient.[17][18] Ethanol was added as it was believed that it would fluidize the vesicles' bilayers in the same manner as it fluidizes the SC lipid bilayers. Hence, it has been shown that ethanol is a potent penetration enhancer not only in combination with other chemical or physical penetration enhancers, but also in combination with liposomes due to their synergistic effect. In conclusion, the inventors of invasomes assumed that these potent penetration enhancers, ethanol and terpenes, would act synergistically on the fluidity and deformability of the vesicles' bilayers, as well as on disturbing the SC lipid bilayers. Further, these enhancers could act synergistically with liposomes in enhancing the drug penetration into the skin.[19]

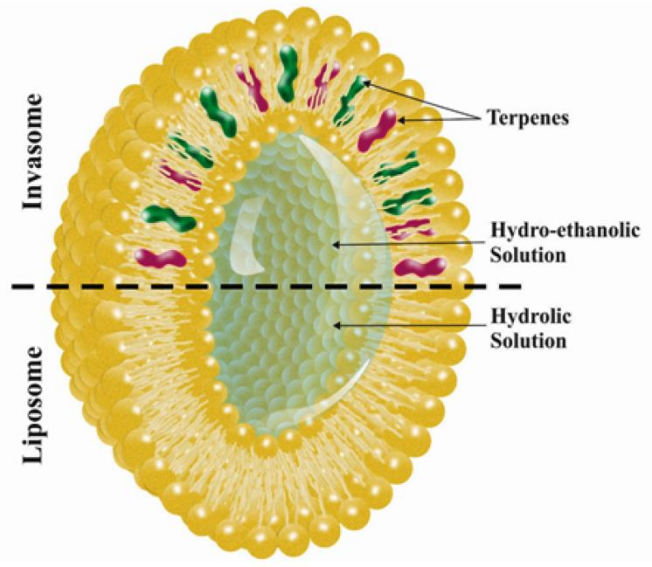


Fig 4: Structural comparsion between Invasome and Liposome.

MICROSPONGES

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The outer surface is typically porous, allowing a sustained flow of substances out of the sphere. Microsponges are porous, polymeric microspheres that are used mostly for topical use and have recently been used for oral administration. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.[20]

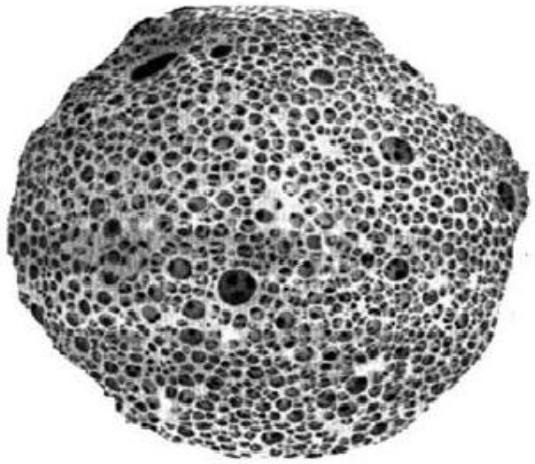


Fig 5: Highly porous structure of microsponge.

MICROSPHERES

It is well said “poor adherence is directly linked to poor treatment results and patient dissatisfaction”.[21] Irritation commonly associated with topical therapies is one of the most significant factors contributing to lack of adherence and therefore therapeutic withdrawal. Microspheres are small spherical shaped particles made of biodegradable polymer and is filled with drug substance that is dispersed homogenously throughout the core and these spheres when degraded, releases the drug for desired time. These microspheres act as a reservoir system for the active agent.[22] Microencapsulation technique is mainly used for the preparation of the microspheres which provide fine coating of inert, natural, and synthetic polymeric materials deposited around solid and liquid micronized particles.

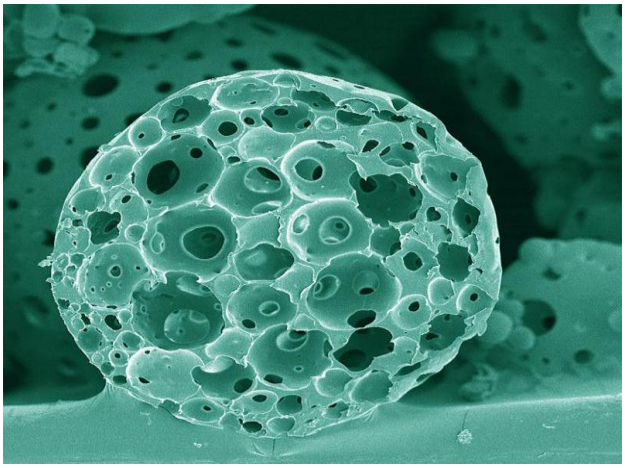


Fig 6: Image of Microsphere.

SOLID LIPID NANOPARTICLES (SLNS)

Solid lipid nanoparticles (SLN) were introduced in the year 1991 and they embody an alternative carrier system to tradition colloidal carriers such as emulsions, liposomes, and polymeric carriers. Solid lipid nanoparticles (SLNs) are particles made from solid lipids with a mean diameter between approximately 50 and 1000nm, which are normally stabilized by lecithin.[23] The reasons for the ever-increasing applications of lipid based system are many fold and include the following: lipids enhance the oral bioavailability and reduce plasma profile variability, better characterization of lipoid excipients, and an improved ability to address the key issues of technology transfer and manufacture scale-up.

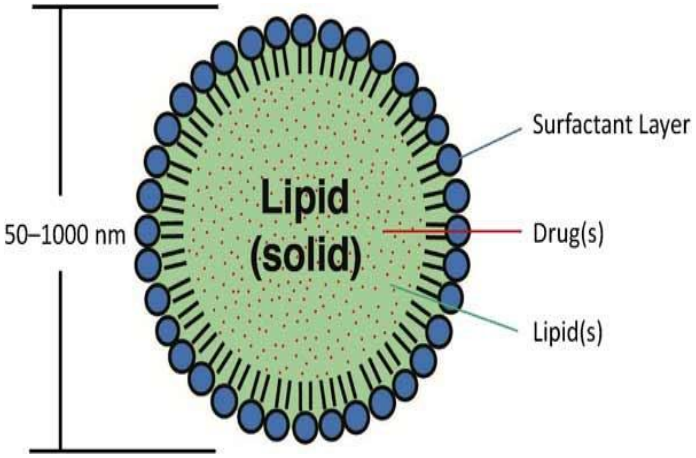


Fig 7: Structural composition and size of Solid lipid nanoparticles (SLN)

Cyclodextrins, Microemulsions, Hydrogels, Fullerenes and many other novel drug carriers were also used in effective treatment of acne.

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CONCLUSION

Adolescent stage is a complex life cycle characterized by many striking environmentally, mentally, physical, and social changes. It is a labile stage where most physical and mental development occurs, whereas low self-esteem is associated with anxiety, depression, and increased reports of general psychiatric morbidities. The physical changes of acne may have negative effect on the psychology, self-esteem, and quality of life of adolescents. Although many oral and topical medicaments have shown to be effective in the treatment of acne, the prevalence of the disease and its frequently resistant nature make the development of alternative therapies highly desirable. There has been significant progress over the past few years, but not all developments can be universally applied. An effective topical formulation must provide stability and enhanced penetration of active ingredients at optimal concentrations for efficacy and it should be acceptable and cheaper and should not add side effects of its own. The encapsulation of antiacne drugs in (vesicular and particulate) carrier delivery systems represents an innovative alternative to minimize the side effects, while preserving their efficacy. They can enhance the dermal and transdermal use and can alter the skin penetration. The penetration rate can increase or decrease depending on the nature of the active agent and the preparation. Novel carrier systems show good penetration through skin and also increases effectiveness of medicament by increase its concentration at the site of action. Each novel carrier have several advantages over conventational dosage form. Improved uptake is often linked with higher efficacy and minimizes the side effect. The capacity of these systems can provide controlled release to improve the drug penetration into skin or even into the Pilosebaceous unit. If the concentration of the active pharmaceutical ingredient is adjusted, local tolerability can be improved. Currently, only very few drugs based on microsized or nanosized application systems have been approved for topical use and introduced into the market. Much progress has been made to improve the performance of antiacne care products in recent years. These new formulations based on carrier system provide efficacy, tolerability, compliance, and cosmetic acceptability.

The use of various systems as carriers of active substances is becoming a handy in modern cosmetology, due to the need for formulation of efficient, Non toxic and acceptable cosmetic products. One of the recent focuses of research in the field of acne treatment has been the assessment of different novel drug delivery systems as carriers for anti-acne drugs. The novel drug delivery systems can help overcome the limitations of conventional formulations used in acne treatment, offering several advantages such as possibility for controlled release of the active substances, improved stability and reduction of side-effects, therefore, improving the patients` compliance to the treatment.

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