(Review Article)

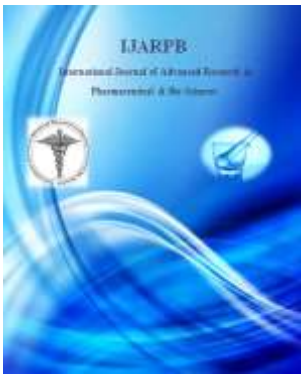
IJARPB
International Journal of Advanced Research in Pharmaceutical & Bio Sciences
(A peer reviewed International journal for Pharmaceutical and Bio Sciences)

Received on 05/02/2012; Revised on 23/02/2012; Accepted on 11/03/2012.

Topical approach expresses high level of potential in Acne

Surbhi Sharma

Research Scientist (R&D),Roha Dyechem PVT. LTD.



Corresponding Author:
Surbhi Sharma

Research Scientist (R&D),Roha Dyechem PVT. LTD.
Email:surbhi.horizon.rx@gmail.com

ABSTRACT

For centuries, skin and skin related problems is the most burning topic on everyone's tongue and mind. Whether its man or woman, everyone dreamt of a flawless and healthy skin, this emerges the science of dermatology dealing with the skin and its diseases, a unique specialty with both medicinal and surgical aspects. With the advent of time, new technologies and research revealed several skin related problems. Skin diseases are most common form of infections occurring in people of all ages. Skin disorders due to its ugliness and associated hardships are one of the hardest ailments to get accustomed to especially when it is located in a place that is difficult to conceal like the face. Some of the common diseases are Acne, Psoriasis, Eczema, Rosacea, Skin Cancer, Fungal Infections, and Inflammation etc. Out of these the most prevalent and commonest is the acne. Currently, research is aimed at the development of drug delivery system with maximum therapeutic benefits for safe and effective management of skin diseases. Topical (word derived from the ancient greek "topos", meaning place or location) approach has rapidly emerged as a new interdisciplinary sciences that offers novel approaches to the delivery of therapeutic agents in acne.

KEY WORDS: Acne Vulgaris, Sebum, Shunt Pathway, Stratum Corneum

(Review Article)

INTRODUCTION

During the past few years, interest in the development of Novel Drug Delivery Systems for existing drug molecules has been renewed. The development of a Novel Delivery System for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent.

When properly designed and developed for a particular drug, novel drug delivery system can overcome specific hurdles associated with conventional methods of delivery, e.g. drugs that undergo partial or complete degradation before reaching the site of action could be effectively delivered with improved bioavailability by using the novel concepts of timed, pulsatile, or targeted release[1].

Time is the fastest runner and as we are running in the 21st century, an era where the technology and research has enriched the quality of our life with the advancement in the pharmaceutical and medical science. This dedication has sorted out many health related problems. Here, we are focusing and dealing with Acne, the most common skin disease that occurs most commonly during adolescence, affecting more than 96% of teenagers, and frequently continues into adulthood.

Investigations and past research in the treatment of acne showed that the conventional administration of antimicrobials and antibiotics (creams, gels and lotions) are used to treat only mild to moderate form of acne but cannot be used in severe and nodulocystic form of acne. Additionally, the antibiotics and benzoyl peroxide nonspecifically reduce bacterial population on the skin, which imbalance the homeostasis and cause further complications such as promoting growth of antibiotic-resistant bacterial strains. Therefore, antibiotics are becoming less and less useful as resistant *P.acnes* are becoming more common. Acne return soon after the end of treatment –days later in the case of topical applications, and weeks later in the case of oral antibiotics. This shows that the conventional administration of drug sometimes prove to be insecure because of erratic response, overdosing and contrast monitoring. Therefore, it becomes a great responsibility on the shoulders of pharmacist to develop an effective dosage form enveloping the principle active moiety in treating the acne with minimum side-effects and maximum patient compliance. Currently, research is aimed at the development of drug delivery system with maximum therapeutic benefits for safe and effective management of the disease. New studies shows that the retinoids, derivative of vitamin A is a medication used for the treatment of severe and nodulocystic form of acne. The retinoids are given by both oral and topical route. Isotretinoin, a derivative of retinoic acid (13-cis-retinoic acid) has been commonly used for the treatment of severe acne and dermatological diseases[2]. However, it has obvious adverse side-effects by oral administration. This is the only disadvantage of administering oral isotretinoin. Therefore, topical approach, has rapidly emerged as a new interdisciplinary sciences that offers novel approaches to the delivery of

(Review Article)

therapeutic agents in acne and mainly combating the side-effects associated with the oral intake of retinoids.

Our prime objective is to harness such site-specific non-cellular carrier systems (containing Isotretinoin) which are essentially micron in size and may be particulate (SLN, Solid Lipid Nanoparticles) that will have a substantive impact on the treatment of acne and combating the side-effects, when used topically. The launched topical preparations such as, cream and gel also show systemic absorption[3]. So, it is necessary to improve the skin uptake and reduce systemic absorption of isotretinoin using a carrier with an ability of skin targeting.

In dermatologic treatment, improving the efficacy demands high drug levels in the skin. In an experiment with nanoparticle dispersion, it was found that a greater quantity of drug remained localized in the skin, with lesser amounts penetrating into the receptor compartment as compared with conventional gels. Thus, drug localizing effect in the skin seems possible with novel colloidal particulate carriers, such as solid lipid nanoparticles. The colloidal carrier, being submicron in size, enhances the drug penetration into the skin, and because of its lipoidal nature, the penetrated drug concentrates in the skin and remains localized for a longer period of time, thus enabling drug targeting to the skin[4]. The topical route has various advantages over other pathways, including avoiding hepatic first pass effects, delivering drugs continuously, fewer side-effects, and improving patient compliance[5]. However, stratum corneum is the main barrier of the skin; it not only prevents dehydration, but also hinders the penetration of various drugs. the intercellular lipids of the stratum corneum play a key role in establishing the permeability barrier of the skin[6].

The aim focuses on the formulation of topical preparations that could be localized in the stratum corneum, viable epidermis, and appendages but have reduced systemic absorption.

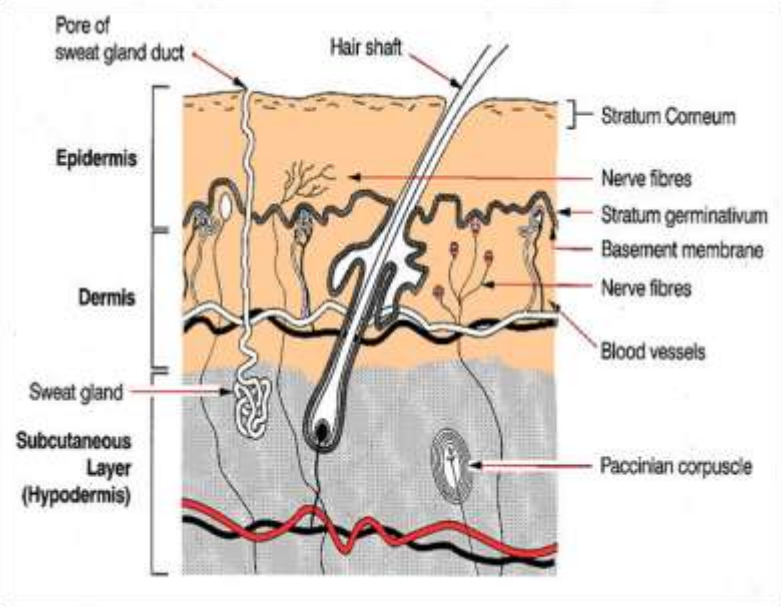


Figure 1: Showing mechanism of drug targeting in sebaceous glands

Acne Vulgaris

Acne vulgaris (commonly called acne) is a common human skin disease, characterized by areas of skin with multiple non-

(Review Article)

inflammatory
follicular papules or comedones and by inflammatory papules, pustules, and nodules in its more severe forms. Acne vulgaris mostly affects the areas of skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back. Severe acne is inflammatory, but acne can also manifest in noninflammatory forms[7]. Acne lesions are commonly referred to as pimples, blemishes, spots, zits, or simply acne. Acne lesions are caused by changes in pilosebaceous units, skin structures consisting of a hair follicle and its associated sebaceous gland, changes which require androgen stimulation.

In adolescence, acne is usually caused by an increase in male sex hormones, which people of both genders accure during puberty[8]. The face and upper neck are the most commonly affected, but the chest, back and shoulders may have acne as well. The upper arms can also have acne, but lesions found there are often keratosis pilaris, not acne. Typical acne lesions are comedones, inflammatory papules, pustules and nodules. Some of the large nodules were previously called "cysts" and the term *nodulocystic* has been used to describe severe cases of inflammatory acne[9]**.** The "cysts," or boils that accompany cystic acne, can appear on the buttocks, groin, and armpit area, and anywhere else where sweat collects in hair follicles and perspiration ducts.

Pathogenesis of Acne and Sebaceous Gland Function

Acne vulgaris is a skin disorder of the sebaceous follicles that commonly occurs in adolescence and in young adulthood. The major pathogenic factors involved are hyperkeratinization, obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium, stimulation of sebaceous gland secretion by androgens, and microbial colonization of pilosebaceous units by *Propionibacterium acnes*, which promotes perifollicular inflammation.

The clinical presentation of acne can range from a mild comedonal form to severe inflammatory cystic acne of the face, chest, and back. At the ultrastructural level, follicular keratinocytes in comedones can be seen to possess increased numbers of desmosomes and tonofilaments, which result in ductal hypercornification. The increased activity of sebaceous glands elicited by androgen causes proliferation of *P. acnes*, an anaerobe present within the retained sebum in the pilosebaceous ducts. The organism possesses a ribosome-rich cytoplasm and a relatively thick cell wall, and produces several biologically active mediators that may contribute to inflammation, for instance, by promoting leukocyte migration and follicular rupture. In inflamed lesions, numerous neutrophils and macrophages infiltrate around hair follicles and sometimes phagocytose *P. acnes*. The participation of neurogenic factors in the

(Review Article)

pathogenesis of acne, had quantitatively assessed the effects of neuropeptides on the morphology of sebaceous glands in vitro using electron microscopy. Substance P, which can be elicited by stress, promoted the development of cytoplasmic organelles in sebaceous cells, stimulated sebaceous germinative cells, and induced significant increases in the area of sebaceous glands. It also increased the size of individual sebaceous cells and the number of sebum vacuoles for each differentiated sebaceous cell, all of which suggests that substance P promotes both the proliferation and the differentiation of sebaceous glands.

Estrogens, glucocorticoids, and prolactin also influence sebaceous gland function. In addition, stress-sensing cutaneous signals lead to the production and release of corticotrophin-releasing hormone from dermal nerves and sebocytes with subsequent dose-dependent regulation of sebaceous nonpolar lipids. Among other lipid fractions, sebaceous glands have been shown to synthesize considerable amounts of free fatty acids without exogenous influence. Sebaceous lipids are responsible for the three-dimensional skin surface lipid organization. Contributing to the integrity of the skin barrier. They also exhibit strong innate antimicrobial activity, transport antioxidants to the skin surface, and express proinflammatory and anti-inflammatory properties[10].

Sebaceous gland

The sebaceous glands are microscopic glands in the skin which secrete an oily/waxy matter, called sebum, to lubricate the skin and hair of mammals[11]. In humans, they are found in greatest abundance on the face and scalp, though they are distributed throughout all skin sites except the palms and soles[12]. There are several related medical conditions including: acne, sebaceous cysts, hyperplasia, sebaceous adenoma and sebaceous gland carcinoma.

Sebum

Sebaceous glands secrete the oily, waxy substance called sebum (Latin, meaning fat or tallow) that is made of fat (lipids), wax, and the debris of dead fat- producing cells. In the glands, sebum is produced within specialized cells and is released as these cells burst; sebaceous glands are thus classified as holocrine glands. Sebum is odorless, but its bacterial breakdown can produce odors. Sebum is the cause of some people experiencing “oily” hair.

Function

Although it is commonly believed that sebum acts to protect and waterproof hair and skin, scientists have contended that “ low levels of sebaceous gland activity is not correlated with dry skin” and it may serve little or no purpose in modern humans[13].

(Review Article)

Composition

The composition of sebum varies between species. In humans, the lipid content is as Wax monoesters (25%), Triglycerides (41%), Free fatty acids (16%), and Squalene (12%). Sapienic acid is a sebum fatty acid that is unique to humans[14].

Anatomy of the Human Skin

The skin of an average adult body covers a surface area of approximately 2sq.m and receives about one-third of the blood circulating through the body and serves as a permeability barrier against the absorption of various chemical and biological agent. It is one of the most readily available organs of the body with a thickness of only a few millimeters[15,16,17,18].

THE SKIN

- Seperates the underlying blood circulation network from the outside environment.
- Serves as a barrier against physical, chemical and microbiological attacks.
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.

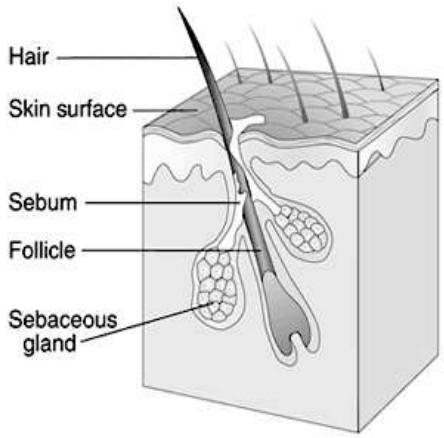


Figure 2: Schematic view of hair follicle and Sebaceous gland.

We can examine the structure and function of human skin categorized into three main layers.

The innermost subcutaneous fat layer (hypodermis).

The overlying dermis.

The viable epidermis, the outermost layer of the tissue (a non-viable epidermal layer) the stratum corneum.

The Subcutaneous Fat Layer

The Dermis

The dermis has numerous structures embedded within it; blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands), and sweat glands (eccrine and apocrine). Thus, provides physiological support for the epidermis. The dermis (or corium) is typically 3-5mm thick and is the major component of human skin. It is composed of

(Review Article)

a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility embedded in a mucopolysaccharide gel. The dermal barrier may be significant when delivering highly lipophilic molecules[18,19].

The Epidermis

The epidermis is approximately 150 micrometers thick in human being and may be further classified into a number of layers. The stratum germinavatum is the basal layer of the epidermis. Above the basal layer are the stratum spinosum, the stratum granulosum, the stratum lucidum, and, finally, the stratum corneum. The stratum corneum or horny layer is the rate limiting barrier that restricts the inward and outward movements of chemical substances consists of flattened keratin-filled cells (e.g. corneocytes). A penetrant must traverse both, the lipophilic environment of the stratum corneum & the aqueous environment of the underlying viable epidermis and upper dermis[18,19].

Basic Principle

Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum, the skin permeation barrier. Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway). In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat glands and then absorbed through the follicular epithelium and the sebaceous glands[20].

The Transfollicular (Shunt Pathway) Absorption

The skin's appendages offer secondary avenues for permeation. Sebaceous and eccrine glands are the only appendages which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. The follicular route remains an important avenue for percutaneous absorption since the opening of the follicular pore, where the hair shaft exit the skin, is relatively large and sebum aids in diffusion of penetrant. Partitioning into sebum, followed by diffusion through the sebum to the depth of epidermis, is the envisioned mechanism of permeation by this route.

Chemicals permeate the skin mainly through the intact epidermis (transepidermal pathway) in which the stratum corneum provides the major permeation barrier[21]. There are two pathways (intercellular and transcellular) available for permeation of drugs across the stratum corneum (Figure 1.8). The intercellular pathway, which is considered as main route for permeation of most drugs, is filled with a lipid-based lamellar liquid crystalline structure.[21,22,23]. The transcellular pathway includes protein-filled cell cytoplasm and a protein-lipid cellular envelope.[21]

(Review Article)

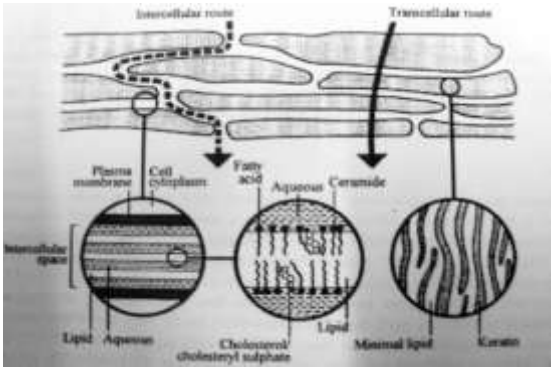


Figure 3: Schematic Representation of Stratum Corneum and its Intercellular and Transcellualar Pathways of Drug Permeation.

Causes of Acne

Acne develops as a result of blockages in follicles hyperkeratinization andformation of a plug of keratin and sebum (a microcomedo) is the earliest change. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen (DHEA-S) production at adrenarche. The microcomedo may enlarge to form an open comedone (blackhead) or closed comedone (whitehead). Whiteheads are the direct result of sebaceous gland becoming clogged with sebum, a naturally occurring oil, and dead skin cells.

In these conditions the naturally occurring largely commensal bacteria *propionobacteri umacnes* can cause inflammation, leading to inflammatory lesions (papules, infected pustules, or nodules) in the dermis around the microcomedo or comedone, which results in redness and may result in scarring or hyperpigmentation[24].

Propionibacterium acnes is a relatively slow growing, typically aerotolerant anaerobic gram positive bacterium (rod) that is linked to the skin condition acne; it can also cause chronic blepharitis and endophthalmitis, the latter particularly following intraocular surgery. The genome of the bacterium has been sequenced and a study has shown several genes that can generate enzymes for degrading skin and proteins that may be immunogenic (activate the immune system).

This bacteria is largely commensal and part of the skin flora present on most people's skin; and lives on fatty acids in the sebaceous glands on sebum secreted by follicles. It may also be found throughout the gastrointestinal tract in humans and many other animals. It is named after its ability to generate propionic acid.

Role in Disease

When a pore is blocked, this anaerobic bacterium overgrows and secretes chemicals that break down the wall of the pore, spilling bacteria such as Staphylococcus aureus into the skin, and forming an acne lesioin (folliculitis). It has also been found in corneal ulcers, and on very few occasions damaging heart valves leading to endocarditis, and infections of joints (septic arthritis) have been reported. Furthermore, propionibacterium have been found in ventriculostomy insertion sites, and areas subcutaneous to suture sites in

patients that have undergone craniotomy. Propionibacterium acnes can be found in bronchoalveolar lavage of approximately 70% patients with sarcoidosis and is associated with disease activity, however it can be also found in 23% of controls[25,26].

Antibiotic Sensitivity

P. acnes can be killed by benzoyl peroxide, tetracycline group and other antibiotics, and many antibacterial preparations, including clove oil[27]. tetracycline-resistant P. acnes is now quite common. Clindamycin is also frequently used. New facts show that P. acnes is sensitive to some macrolides such as azithromycin, which has a wide spectrum of action. It is normally prescribed 500mg by mouth, three times weekly for 4 to 6 weeks, but may have post-antibiotic effects by remaining concentrated in lung tissue for approximately 5 days after treatment stops. Fluoroquinolones may also be effective against P. acnes such as nadiflooxacin, ciprofloxacin, ofloxacin and levofloxacin. They are active against *P. acnes* and some other microorganisms that are also part of the poly-infection.

Phage sensitivity

P. acnes has known phages that can attack it, and these can be used to type it. Proposals exist to employ lytic phages for therapeutic purposes for acne vulgaris.

Photosensitivity

P. acnes glows orange when exposed to Wood's light[28] believed to be due to the presence of endogenous porphyrins. The bacterium is killed by ultraviolet light. *P. acnes* is also especially sensitive to light in the 405-420nm (near the ultraviolet) range due to an endogenic porphyrin-coporphyrin III. A total irradiance of 320 J/cm^2 is foun to inactivate this bacteria in vitro[29]. This fact is used in phototherapy. Its photosensitivity can be enhanced by pretreatment with aminolevulinic acid which boosts production of this chemical, although this causes significant side-effects in humans, and in practice was not significantly better than the light treatment alone.

Primary Causes

- Family/Genetic history. A family history of acne is associated with an earlier occurrence of acne and an increased number of retentional acne lesions[30].
- Hormonal activity, such as menstrual cycle and puberty. During puberty, an increase in male sex hormones called androgens cause the follicular glands to grow larger and make more sebum.
- Inflammation, skin irritation or scratching of any sort will activate inflammation.
- Stress. While the connection between acne and stress has been debated, scientific research indicates that "increased acne severity" is "significantly associated with increased stress levels.[31]" Hyperactive sebaceous gland,

secondary to the three hormone sources above.

- Bacteria in the pores. *Propionibacterium acnes(P.acnes)* is the anaerobic bacterium that causes acne. In-vitro resistance of *P. acnes* to commonly used antibiotics has been increasing.
- Use of anabolic steroids.[32]
- Exposure to certain chemical compounds. Chloracne is particularly linked to toxic exposure to chlorinated dioxins. .
- Several hormones have been linked to acne: testosterone, dihydrotestosterone and dehydroepiandrosterone sulfate, as well as insulin- like growth factor-1(IGF-1).

Diet Milk

Recently, epidemiological studies from the same group of scientists found an association between acne and consumption of partially skimmed milk, instant breakfast drink, sherbet, cottage cheese, and cream cheese.[33] The researchers hypothesize that the association may be caused by hormones (such as several sex hormones and bovine insulin-like growth factor-1 (IGF-1)) or even iodine[34] present in cow milk**.**

Carbohydrates

The recent low glycemic-load hypothesis postulates that rapidly digested carbohydrate foods (such as soft drinks, sweets, white bread) produce an overload in blood glucose (hyperglycemia) that stimulates the secretion of insulin, which in turn triggers the release of IGF-1[35]. IGF-1 has direct effects on the pilosebaceous unit (and insulin at high concentrations can also bind to the IGF-1 receptor)[36] and has been shown to stimulate hyperkeratosis and epidermal hyperplasia.[37] These events facilitate acne formation. Sugar consumption might also influence the activity of androgens via a decrease in sex-hormone binding globulin concentration.

Vitamins A and E

Studies have shown that newly diagnosed acne patients tend to have lower levels of Vitamin A circulating in their bloodstream than those who are acne free.[38] In addition people with severe acne also tend to have lower blood levels of Vitamin E.[39]

Treatment of Acne

In general treatments are believed to work in at least 4 different ways (with many of the best treatments providing multiple simultaneous effects):

- Normalising shedding into the pore to prevent blockage
- Killing *Propionibacterium acne*

(Review Article)

- Anti-inflammatory effects
- Hormonal manipulation

Topical Bactericidals

Widely available OTC bactericidal products containing benzoyl peroxide may be used in mild to moderate acne. The gel or cream containing benzoyl peroxide is applied, twice daily, into the pores over the affected region. Benzoyl peroxide also prevents new lesions by killing *P.acnes*. In one study, roughly 70% of participants using a 10% benzoyl peroxide solution experienced a reduction in acne lesions after six weeks[40]. Unlike antibiotics, benzoyl peroxide has the advantage of being a strong oxidizer and thus does not appear to generate bacterial resistance.

Disadvantages:

However, it routinely causes dryness, local irritation and redness. Care must be taken when using benzoyl peroxide, as it can very easily bleach any fabric or hair it comes in contact with.

Other antibacterials that have been used include triclosan, or chlorhexidine gluconate. Though these treatments are often less effective, they also have fewer side-effects.Products containing azeleic acid are also used in the treatment of *P.acnes*. It is available in the United States as a 20% concentration and does not generate bacterial resistance.[41].

Topical and Oral Antibiotics

Externally applied antibiotics such as erythromycin, clindamycin or tetracycline kill the bacteria that are harbored in the blocked follicles. Topical use of antibiotics may prove inefficient to apply over larger areas than just the face alone. Oral antibiotics used to treat acne include erythromycin or one of the tetracycline antibiotics, oxytetracycline, doxycycline, minocycline, Additionally, the antibiotics are becoming less and less useful as resistant *P. acnes* are becoming more common. Acne may return soon after the end of treatment—days later in the case of topical applications, and weeks later in the case of oral antibiotics. Furthermore, side effects of tetracycline antibiotics can include yellowing of the teeth and an imbalance of gut flora.

Hormonal Treatments

In females, acne can be improved with hormonal treatments. The common combined estrogen/progestogen methods of hormonal contraceptionhave some effect, but the antiandrogen, Cyproterone , in combination with an oestrogen (*Diane 35*) is particularly effective at reducing androgenic hormone levels. If a pimple is large and/or does not seem to be affected by other treatments, a dermatologist may administer an injection of cortisone directly into it, which will usually reduce redness and inflammation almost immediately. Side effects include a temporary whitening of the skin around the injection point; and occasionally a small depression forms,

(Review Article)

which may persist, although often fills eventually. This method also carries a much smaller risk of scarring than surgical removal.

Sulfur

Sulfur has an inhibitory effect on the growth of Propionibacterium acnes and, when combined with sodium sulfacetamide (5% and 10%, respectively) has been shown to reduce acne with only mild side effects.[42]

Oral Retinoids

An early, effective treatment of acne first used during the 1930s was high doses of the fat-soluble vitamin A (retinoic acid). At these dosage levels (sometimes 500,000 IU per day), sebum production is notably reduced, thwarting acne, but overly dry hair is a negative side effect, and such high doses can lead to vitamin A toxicity. Use of animal-based vitamin A at nutritive levels (where the upper limit dosage is 10,000 IU daily), taken over the course of a year, has also been shown to reduce acne. One positive side effect is that patients tend to be healthier, as present diets often do not include enough fat-soluble vitamin A. Building on the discovery that vitamin A can reduce sebum production at toxic dosages, the retinoic acid derivative isotretinoin (13-*cis*-retinoic acid) was developed and released in 1982 by Hoffmann-La-Roche. The advantage of the synthetic compound is an overall better success at treating acne, When compared to toxic dosages of Vitamin A, the side effects are reduced.A daily oral intake of vitamin A derivative Isotretinoin (marketed as Accutane, Amnesteem, Sotret, Claravis, Clarus) over a period of 4–6 months can cause long-term resolution or reduction of acne. It is believed that isotretinoin works primarily by[43] 1.)inhibition of sebaceous gland activity,(2) inhibition of the growth of *P. acnes* within the follicle.(3)alteration of the pattern of keratinization within the follicles.Isotretinoin has been shown to be very effective in treating severe acne and can either improve or clear well over 80% of patients. It is also effective for hidradenitis suppurativa and some cases of severe acne rosacea[44].

It can also be used to help treat harlequin ichthyosis, and is used in xeroderma pigmentosum cases to relieve keratoses. Isotretinoin has been used to treat the extremely rare condition Fibrodysplasia Ossificans Progressiva. It is also used for treatment of neuroblastoma, a form of brain cancer.

The most common side effects are dry skin and occasional nosebleeds (secondary to dry nasal mucosa). Oral retinoids also often cause an initial flare up of acne within a month or so, which can be severe. There are reports that the drug has damaged the liver of patients. The drug also causes birth defects if women become pregnant while taking it or take it while pregnant.

(Review Article)

Topical Retinoids

A group of medications for normalizing the follicle cell lifecycle are topical retinoids such as tretinoin (brand name Retin-A), adapalene (brand name Differin), and tazarotene (brand name Tazorac). Like isotretinoin, they are related to Vitamin A, but they are administered as topicals and generally have much milder side effects. The retinoids appear to influence the cell creation and death lifecycle of cells in the follicle lining. This helps prevent the hyperkeratinization of these cells that can create a blockage. Retinol, a form of vitamin A, has similar but milder effects and is used in many over-the-counter moisturizers and other topical products.

Topical retinoid therapy with 13-cis retinoic acid (13-cis RA) is an effective way of treating both inflammatory acne and non-niflammatory acne[45,46]. 13-cis RA, isotretinoin is thought to have an anti-comedonal effect, altering the epithelialization of the follicles[47]. In animals, topical application of retinoids has been shown to suppress sebum excreation, but this is not so in humans[48] owing to the known teratogenic effects of oral retinoids, studies have been conducted to detect the level of absorption, if any, of retinoids from topical formulations. Topical application of 13-cis RA gel has been shown to result in negligible absorption of the drug[49].

Other Treatments

- Dermabrasion
- Phototherapy
- Surgery
- Subcision
- Laser treatment

Penetration of Topical Preparations

Molecules can penetrate the skin[50] by three routes:

Through Intact Stratum corneum, Through the Sebaceous Follicles, Through sweat glands.

The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Passage through this outermost layer is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of concentration gradient, which provides the driving force for drug movement across the skin; release of drug from the vehicle (partition coefficient); and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 dalton), adequate solubility in oil and water, and a high partition coefficient[51]. Except for very small particles, water soluble ions and polar molecules do not penetrate intact stratum corneum. The relationship of these factors[52] to one another is summarized in the following equation:

(Review Article)

Where, **J** is the rate of absorption,

C_{veh} is the concentration of drug in vehicle,

K_m is the partition coefficient,

D is the diffusion coefficient, and

$$J = C_{veh} \cdot K_m \cdot D/X$$

X is the thickness of stratum corneum

Nanoparticulate Delivery Systems

Nanoparticulate delivery systems have been widely investigated as drug carriers because of advantages such as smaller size, controlled drug release potential, targeting ability, enhancement of therapeutic efficacy, and reduction of toxicity[53,54]. Lipid nanoparticles have recently received considerable attention as an alternative drug carriers to emulsions, liposomes and nanoparticles[55,56].The solid lipids used in nanoparticle preparation possess excellent stability, biocompatibility, biodegradation, and low cellular and systemic toxicity. This is the reason behind the selection of solid-lipid-nanoparticles as potential drug carriers in the present research.

Solid Lipid Nanoparticles

Solid-lipid nanoparticles (SLN) or lipospheres introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. SLN combine advantages of the traditional systems but avoid some of their major disadvantages. SLN are prepared from solid lipids. They represent novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system[57,58,59,60,61].

The solid-lipid nanoparticles (SLNs) are sub-micron colloidal carriers (50-1000nm). Generally, they are made of solid hydrophobic core having a monolayer of phospholipid coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipid are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics[62]. SLNs as colloidal drug carrier, combine advantages of polymeric nanoparticles, fat emulsions, liposomes and are simultaneously capable of avoiding some of their disadvantages. To overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced a solid lipid, which eventually transformed into solid lipid nanoparticles[58,63].

(Review Article)

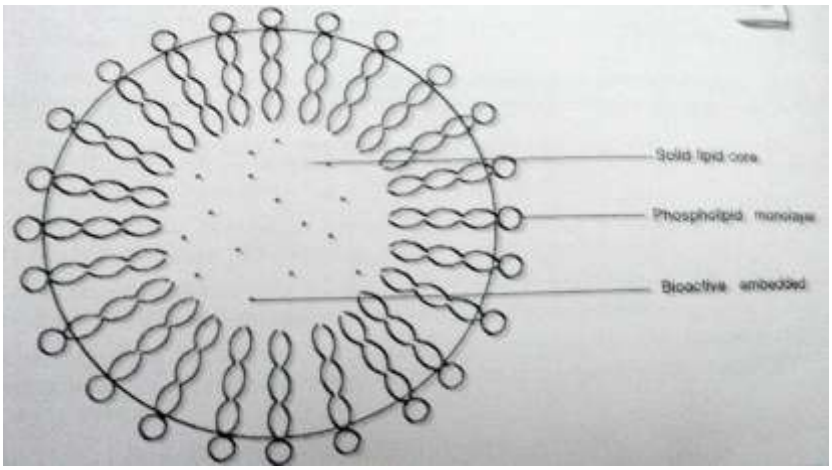


Figure 4: A Structural Representation of SLN is Shown.

Solid lipid nanoparticles (SLNs) or lipospheres are biodegradable and non-toxic, stable against coalescence, drug leakage, hydrolysis, particle growth often observed in lipid emulsion and liposome unlike lipid emulsion, which have a fluid core, they possess a solid matrix, which have the potential for allowing the drug release over a prolonged period. Other advantage includes low cost of ingredients, ease of preparation and scale-up, high dispensability in aqueous medium, high entrapment of hydrophobic drug, controlled particle size and extended release of entrapped drug after single injection from few hours to several days. They reported a prolonged in vitro release of upto 6 week for prednisolone.

Table1: Comparative Properties of Solid-Lipid Nanoparticles, Polymer Nanoparticles, Liposomes, Lipid Emulsions[64]

S.N0.	Property	SLN	Polymer Nanoparticle	Liposome	Lipid emulsion
1.	Systemic toxicity	Low	>or=to SLN	Low	Low
2.	Cytotoxity	Low	>=to SLN	Low	Low
3.	Residues from organic solvents	No	Yes	May or may not	No
4.	Large scale production	Yes	No	Yes	Yes
5.	Sterilization by autoclaving	Yes	No	No	Yes
6.	Sustained release	Yes	Yes	<or=toSLN	No
7.	Avoidance of RES	?	No	Yes	Yes

(Review Article)

Speiser, 1990 conducted the basic work in the area of SLNs a decade back. The lipid nanopellets were prepared by first melting the lipid and it was then dispersed in hot aqueous surfactant solution by stirring or ultrasonic treatment[65].

SLNs for Topical Application

An area of big potential for SLN and with a short time- to- market are topical products based on the SLN technology, that means pharmaceutical but also cosmetic formulations. SLN are considered as being the next generation of delivery systems after liposomes[66, 67]. Distinct advantages of SLN are their solid state of the particle matrix, the ability to protect chemically labile ingredients against chemical decomposition and the possibility to modulate drug release. Apart from technological benefits the solid state of SLN also an advantage with regard to the product registration for pharmaceuticals but also cosmetics. For example, in Japan even for cosmetic products it needs to be proven that liposomes are present not only qualitatively but also quantitatively. For liposomes, a qualitative proof is easy by electron microscopy, but extremely difficult to quantify them. In contrast to it quantitative analysis of SLN in creams is very easy and simple by DSC.

Similar to liposomes, SLNs are forming adhesive films onto the skin as the adhesiveness is the general property of very fine particles. Eg. Iced sugar. The recent study shows that under the pressure of application the SLNs form a coherent film. Such a lipid film formation will be able to restore a damaged protective lipid film on the skin. In addition such a film can have an occlusive effect.

A completely new, recently discovered area of application is the use of SLN in sun protective creams. Due to the reduction of the protective ozone layer there is a steep increase in skin cancer, melanoma is the form of cancer showing the strongest increase world-wide, especially in countries like Australia. Side-effects of molecular sunscreens (UV-blockers)[68] are penetration into the skin and consequently irritation. Particulate sunscreens like titanium dioxide were also found to possibly penetrate into the skin. This can be avoided by entrapping molecular and particulate sunscreens into the SLN matrix.

Surprisingly, it was found that the SLN themselves have also a sun-protective effect.

Advantages Over Others

- The SLNs offer some advantages compared to conventional particulate carriers[69,70,71] :
- Their small size and relatively narrow size distribution permits site-specific drug delivery.
- Controlled, Sustained release, and drug targeting.

- The incorporated drug is protected from the onslaughts of biochemical degradation.
- Can be sterilized by autoclaving or gamma irradiation.
- Can be lyophilized and spray dried.
- Do not generate any toxic metabolites.
- Relatively cheap and stable.
- Ease of industrial scale production by hot dispersion technique and high pressure homogenization technique.
- Surface modification can be easily performed.
- Avoidance of organic solvent.
- Incorporation of drug into SLN can reduce distinct side effects of drug.

CONCLUSION

In dermatologic treatment, improving the efficacy demands high drug levels in the skin. So, as in case of acne, where novel drug delivery carriers can be targeted effectively through topical route to the specific sweat glands, the incorporated drug acted on the targeted sites to relieve ailment and prevent systemic absorption of drug, which helps to reduce adverse effects. In this article we introduced Solid Lipid Nanoparticles as targeted drug delivery systems, which can favour drug penetration into the skins, maintain a sustained release to avoid systemic absorption, act as a UV sunscreen system, reduce irritation. It is evident that Solid Lipid Nanoparticles explore a novel formulation with skin targeting effect for the treatment of severe acne.

REFERENCE

1. Garg S, Kndarapu R, Kannan V, 2003, Pharm. Tech. 27(2), 74.
2. Katsambas A, Papakonstantinou A, Acne: systemic treatment. Clin. Dermatol. 2004, 22, 412-418.
3. Queille-Roussel C, Poncet M., Mesaros S, Clucas A, Baker M, Soloff A, Comparison of the cumulative irritation potential of Adapalene gel and cream with that of Erythromycin/Tretinoin solution and gel and Erythromycin/Isotretinoin gel. Clin. Therap. 2001, 23, 205-212.
4. Pople PV, Singh KK. Development and evaluation of topical formulation containing solid lipid nanoparticles of vitamin A. AAPS Pharm. Sci. Tech. 2006, 7, 91.
5. Maghraley GM, Williams AC, Barry BW, Skin delivery of oestradiol from lipid vesicles. importance of liposome structure. Int. J. Pharm. 2000, 159-169.
6. Elias PM. Lipids and the epidermal permeability barrier. Arch. Dermatol. Res. 1981, 270, 95-117.

(Review Article)

7. Harper JC, Acne vulgaris. e medicine, 2009.
8. James WD, Clinical practice: acne. N. Engl. J. Med, 2005, 352(14), 1463-1472.
9. Thiboutot DM, Strauss JS, Diseases of the sebaceous glands. Fitzpatrick's Dermatology in Gen. Med. 4th edition, 2003, 672-687.
10. Toyoda M, Morohashi M, Pathogenesis of acne. Pubmed, 2001, 34(1), 29-40.
11. Jo Ann CE, Brian LF, Dellman's Textbook of Veternary Histology, 2006, 29.
12. James WD, Berger T, Elston DM, Andrenus disease of skin. Clin. Dermatol. Saunders Elsevier P.T. 2006.
13. Dewing DT, Stewart ME, Wertz PW, Colton SW, Abraham W, Strauss JS, Skin lipids: an update. J. Invest. Derm. 1987, 88(3), 2S-6S.
14. Cheng JB, Russell DW, Mammalian wax biosynthesis .II. expression cloning of wax synthase cDNAs encoding a member of acyltransferase enzyme family. J. Bio. Chem. 2004, 279(36), 37798-37807.
15. Das SK, Chattaraj SC, Indian Drugs. 1989, 26(4), 135.
16. Shridevi S, Krishna DR, The Eastern Pharmacist. 1991, 34(406), 17.
17. Ghosh TK, Pfister WR, Transdermal and topical drug delivery systems. Inter. Pharm. Press. 3.
18. Walters KA, Robert MS, In; Walters, K.A., Eds., Dermatological and transdermal formulations. Marcel Dekker. New York. 119, 1-25.
19. Sharma SN, Popii H, The Eastern Pharmacist. 1990, 41-42.
20. Misra AN, Jain NK, Eds. Controlled and Novel Drug Delivery. I Edition. CBS Publishers and Distributors, New Delhi, 2002, 101-107.
21. Moghimi HR, Williams AC, Barry BW, Stratum corneum and barrier performance; a model lamellar structural approach, 1999, 5, 5-55.
22. Moghimi HR, Williams AC, Barry BW, A lamellar matrix model for stratum corneum intercellular lipids. V. Effects of terpene penetration enhancers on the structure and thermal behavior of the matrix. Int. J. Pharm. 1997, 146, 41-54.
23. Moghimi HR, Williams AC, Barry BW, A lamellar matrix model for stratum corneum intercellular lipids. IV. Effects of terpene penetration enhancers on the permeation of 5-fluoro-uracil and oestradiol through the matrix. Int. J. Pharm. 1996, 145, 49-59.
24. Simpson NB, Cunliffe WJ, Disorders of the sebaceous glands. Rook's Textbook of Dermatology. VII Edition, 2004, 43-75.

(Review Article)

25. Hiramatsu J, Kotaoko M, Nakata Y, Propionibacterium acnes DNA detected in bronchoalveolar lavage cells from patients with sarcoidosis. Sarcoidosis Vasc. Diffuse Lung Dis. 2003, 20(3), 197-203.

26. Inoue Y, Suga M, Granulomatous diseases and pathogenic micro-organism. Kekkaku. 2008, 83(2), 115-130.

27. Fu YJ, Chen LY, Zu YG, The antibacterial activity of clove essential oil against propionibacterium acnes and its mechanism of action. Arch. Dermatol. 2009,145(1), 86-88.

28. Eikone.com

29. Papageorgiou P, Katsambas A, Chu A, Phototherapy with blue (415nm) and red (660nm) light in the treatment of acne vulgaris. Br. J. Dermatol. 2000, 142(5), 973-978.

30. Ballangera, F, Baudrya, P, N'Guyenb, J.M, Khammaria A, Dreno B, Heredity: prognostic factor for acne, 2005.

31. Chiu A, Chon S.Y, Kimball A.B, The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress. Arc. Derm. 2003, 7, 139.

32. Melnik, B, Jansen T, Grabbe S, Abuse of anabolic-androgenic steroids and body-building acne: an underestimated health problem. J. Dtsch. Dermatol. Ges. 2007, 5(2), 110-117.

33. Adebamowo C A, Spiegelman D, Berkey C S, Milk consumption and acne in teenaged boys. J. Am. Acad. Dermatol. 2008, 58(5), 787-793.

34. Arbesman H,Dairy and acne the iodine connection. J. Am. Acad. Dermatol. 2005, 53(6), 1102.

35. Keri J E, Nijhawan R I, Diet and acne. Expert. Rev. Dermatol. 2008, 3(4), 437-440.

36. Deplewski D, Rosenfield R I, Role of hormones in pilosebaceous unit development. Endocr. 2000, Rev. 21(4), 363-392.

37. Digiovanni J, Bol D K, Wilker E, Constitutive expression of insulin-like growth factor-I in epidermal basal cells of transgenic mice leads to spontaneous tumor promotion. Cancer Res. 2000, 60(6), 1561-1570.

38. Naweko, S J, How does vitamin A prevent acne outbreaks. American Cronicals. 2007.

39. El Akawi Z., Abdel-latif, N, Abdul-razzak K, Does the plasma level of vitamins A and E affect acne condition? Clin. Exp. Dermatol. 2006, 31(3), 430-440.

40. Dogra A, Sood VK, Minocha YC, Comparative evaluation of retinoic acid, benzoyl peroxide and erythromycin lotion in acne vulgaris. Ind. Asso. of Dermat. Venereol. and Leprol. 1993, 59(5), 243-246.

(Review Article)

41. Antibiotic resistance of *P. acnes* in acne vulgaris. 2003.

42. Gupta AK, Nicol K, The use of sulfur in dermatology. J. Drugs Derm. 2004.

43. Klasco RK, Drugdex system, 2006, 128.

44. Plewig G, Nikolwski J, Wolff HH, Action of isotretinoin in acne rosacea and gram negative folliculitis. J. Am. Acad. Dermatol. 1982, 6(4), 766-785.

45. Chalker DK, Lesher JL, Smith JG, Efficacy of topical isotretinoin cream 0.05% in acne vulgaris: results of a multicenter, double-blind investigation. J. Am. Acad. Dermatol. 1987, 17, 251-254.

46. Langner A, Boorman G, Stupor V, Wolska H, Fraczykowska M, Isotretinoin cream 0.05% and 0.1% in the treatment of acne vulgaris. J. Dermatol. Treat. 1994, 5, 177-180.

47. Mills OH, Kligman AM, Therapeutic options in the management of acne and its variants. Semin. Dermatol. 1982, 1, 233-237.

48. Plewig G, Ruhfus A, Kloveborn W, Sebum suppression after topical application of retinoids (aretinoid and isotretinoin). J. Invest. Dermatol. 1983, 80, 357.

49. Jensen BK, Mc Gann LA, Kachersky V, Franz TJ, The negligible systemic availability of retinoids with multiple and excessive topical application of isotretinoin gel (Isotrex) in patients with acne vulgaris. J. Am. Acad. Dermatol. 1996, 24, 425-428.

50. Ebling FJG, Functions of the skin. In, Rook, Wilkinson. Ebling Textbook of Dermatology. Blackwell Scientific Publication, Oxford, England. 1993, 125-155.

51. Barry BW, Breaching the skin's barrier of drugs. Nature Biotech. 2004, 22, 165-167.

52. Piaquadio D, Kligman A, The critical role of the vehicle to therapeutic efficacy and patient compliance. J. Am. Acad. Dermatol. 1998, 39, 367-373.

53. Muller RH, Olbrich C, Solid-lipid nanoparticles: phagocytic uptake, in vitro cytotoxicity and in vitro biodegradation. Drugs Med. Ger. 1999, 42, 49-53.

54. Mehnert W, Mader K, Solid-lipid nanoparticles production, characterization and applications. Adv. Drug Deliv. Rev. 2001, 47, 165-196.

55. Schwarz C, Mehnert W, Lucks JS, Muller RH, Solid-lipid nanoparticles (SLN) for controlled drug delivery .I. production, characterization and sterilization. J. Control. Release. 1994, 30, 83-96.

56. Muller RH, Mehnert W, Lucks JS, Solid-lipid nanoparticles (SLN): an alternative colloidal drug carrier system for controlled drug delivery. Eur. J. Pharm. Biopharm. 1995, 41, 62-69.

(Review Article)

57. Muller RH, Lucks JS, German Patent Application, 1991, 562-566.

58. Muller RH, Lucks JS, European patent 0605497 B1. 1996.

59. Almeida AJ, Hunge S, Muller RH, Int. J. Pharm. 1997, 149, 255.

60. Zur muhlen A, Schwarz C, Mehnert W, Eur. J. Pharm. Biopharm. 1998, 45, 149.

61. Domb AJ, Lipospheres for controlled delivery of substances. U.S. Patent 5 1993, 188 837.

62. Muller RH, Schwarz C, Mehnert W, Lucks JS, Proc. Int. Symp. Control. Rel. Bioact. Mater, 1993, 20, 480.

63. Utreja S, Jain NK, Advances in Controlled and Novel Drug Delivery edited by N.K. Jain. I Edition. CBS Publication, 2001, 408-425.

64. Vyas SP, Khar RK, Targeted and Controlled Drug Delivery Novel Carrier System. I Edition. CBS Publication. 2002, 15, 346.

65. Muller RH, Dingler A, Feste lipid-nanopartikel (Lipopearls™)als neuartiger carrier fur kosmetische and dermatologische Wirkstoffe, Pharmazeutische Zestung Dermopharmazie. 1988, 11-15.

66. Muller RH, Dingler A, The next generation after the liposomes: solid lipid nanoparticles (SLN™, Lipopearls™) as dermal carrier in cosmetics, Eurocosmetics 1998, 7/8, 19-26.

67. Wissing S, Mader K, Rogarchewski S, Muller RH, Solid-lipid nanoparticles (SLN) - a novel carrier for UV- blockers. Int. J. Pharm. 2000.

68. Muller RH, Mehnert W, Lucks JS, Schwarz C, Zur muhlen, A., Weyhers, H., Freitas, C, Ruhl D, Eur. J. Pharm. Biopharm. 1995, 41, 62.

69. Zur muhlen A, Schwarz C, Mehnert W, Eur. J. Pharm. Biopharm. 1998, 45, 149.

70. Cavalli R, Gasco MR, Morel S, Behaviour of timolol incorporated in lipospheres in the presence of a series of phosphate esters, S.T.P. Pharma Sci. 1992, 2, 514-518.

71. Gasco MR, Cavalli R, Carlotti ME, Timolol in lipospheres. Pharmazie. 1992, 47, 119-121.