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Review Article

A REVIEW ON: ADAPALENE IN COMBINATION WITH TEA TREE HERBAL OIL FOR ACNE TREATMENT

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Abstract:

Acne is the most common skin disease worldwide. Acne is estimated to affect 9.4% of the world's population, making it the eighth most common disease worldwide. Acne vulgaris is caused by disruption and inflammation of the pilosebaceous unit (hair follicles and sebaceous glands) leading to the formation of comedones, papules, pustules, nodules, and/or cysts. Acne appears on the face and upper body. It mostly affects young people. Adapalene binds to retinoic acid receptors (RAR)-beta and RAR-gamma; Retinoid activation is known to affect cell growth and differentiation, and adapalene has been shown to inhibit HeLa cell proliferation and human keratinocyte differentiation. These effects explain the anti-comedogenic and anti-inflammatory properties of adapalene. It acts as an anti-inflammatory agent, inhibits respiration and increases membrane permeability of microbial cells. Adapalene and herbal oil together create a synergistic effect. Adapalene and herbal oil will cause redness or swelling when taken alone, although not together, so the combination of adapalene and herbal oil will be effective in treating acne. Among herbal oils, some oils are used especially in the treatment of acne. Oils such as tea tree oil, neem oil and lemongrass oil have antibacterial properties and can help treat acne. tea tree oil has better effect along with adapalene for acne treatment. Niosomal gel preparation of adapalene in combination with tree oil will have potential effectiveness against acne.

Key words: Acne, Acne Vulgaris, Pilosebaceous gland, Comedones, Papules, Adapalene, Herbal oil, tea tree oil, niosomal gel.

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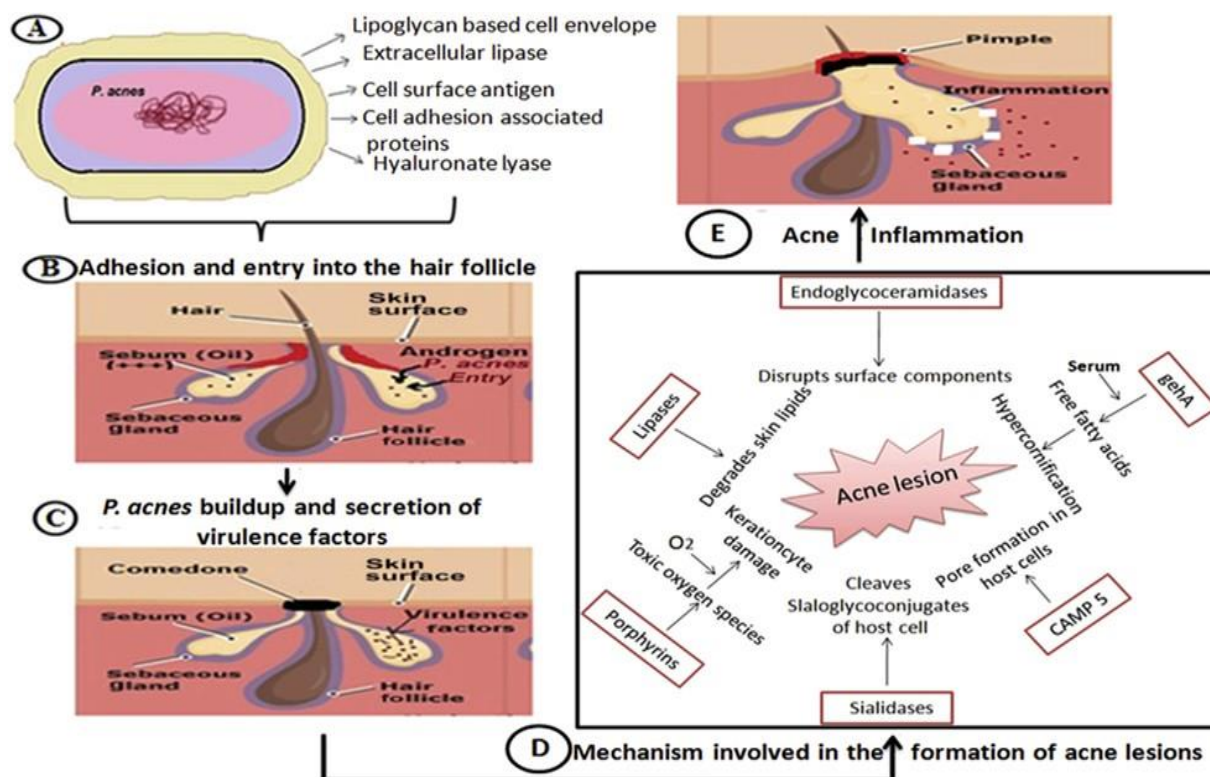
INTRODUCTION:

- Acne is the most common skin complaint worldwide.
- Acne is a skin condition that occurs when your hair follicles come plugged with oil and dead skin cells.
- Acne vulgaris is the conformation of comedones, pustules, papules, nodes, and/or excrescences as a result of inhibition and inflammation of pilosebaceous units(hair follicles and their coexisting sebaceous gland). Acne develops on the face and upper part. It most frequently affects adolescents.
- Acne is most common in teenagers and youthful grown-ups.
- Symptoms range from uninflamed papules to pus- filled pustules or large, red and tender bumps.
- Treatments include untoward creams and

cleaner, as well as traditional antibiotics.

EPIDEMIOLOGY

- Acne can begin in puberty and lasts until the early thirties.
- Males are more prone to get acne than females.
- The urban populace is more influenced than the country population.
- Around 20% of individuals with acne get scarring.
- Some races show up a bit more acne-prone than others. Asians and Africans are more inclined to extreme acne breakouts, while Westerners are more inclined to mellow acne.
- Hyperpigmentation is more common among populaces with darker skin.
- Acne can occur in newborns, but it ordinarily vanishes on its own.

PATHOPHYSIOLOGY

Acne is caused by the interaction of the following four factors:

1. Increased sebum production caused by androgenic stimulation of sebaceous glands in puberty or adulthood
2. Impairment of sebaceous follicle outflow due to abnormal keratinization process Especially with adhesion and transformation of hair follicle epithelial cells
3. Propionibacterium acnes is a type of anaerobic diphtheria bacteria that lives in the sebaceous glands of the hair follicle. Growth of P. acnes produces white blood cells that stimulate hair follicle expansion.
4. The disease is treated by the irritating effect of sebum entering the dermis and chemokines and pro-inflammatory mediators produced by Propionibacterium species. acne. This process causes the follicle wall to rupture, allowing P. acnes, sebum, hair, and dermal cells to come out. Penetration of comedone contents into the dermis causes acne swelling, including papules, pustules, nodules, and cysts. Although P. Acne is a disease that occurs when damage to the hair follicle occurs, which only exacerbates the inflammatory process. Therefore, acne is not a skin disease, but a harmless condition.

Types of acne

1. Blackheads (open comedones): little, dark, or dull brown spots that shape when a hair follicle gets to be clogged with oil and dead skin cells.
2. Whiteheads (closed comedones): little, flesh-colored or white bumps that shape when a hair follicle gets clogged with oil and dead skin cells, but remains closed.
3. Papules: little, ruddy, or pink bumps that are delicate to the touch.
4. Pustules: similar to papules, but with a white or yellow center that contains pus.
5. Nodules: expansive, agonizing bumps that are profoundly implanted in the skin.
6. Cysts: expansive, pus-filled bumps that are profoundly inserted in the skin and can lead to scarring.

Grades of acne

Grades of acne vulgaris are determined by the severity and types of lesions that are formed. Based on this there are two main classification systems which are the following:

1. The Global Acne Grading System (GAGS)
2. The Pillsbury scale is the two primary classification systems for acne vulgaris.

1. The global acne grading system (GAGS)

This system classifies acne into four categories:

- I. Grade 1 (Gentle): Non-inflammatory injuries, with few papules and pustules.
- II. Grade 2 (Direct): A blend of non-inflammatory and inflammatory injuries, such as comedones, papules, and pustules, but with less than 20-30 add up to lesions.
- III. Grade 3 (Modestly Serious): Various papules and pustules, as well as a few knobs, with 20-100 add up to lesions.
- IV. Grade 4 (Serious): Various knobs and sores, with more than 100 add up to lesions.

2. The Pillsbury scale

This scale classifies acne vulgaris based on the types of lesions present:

1. Grade 1 (Gentle): Comedones (clogged pores and whiteheads).
2. Grade 2 (Direct): Comedones and papules.
3. Grade 3 (Tolerably Serious): Comedones, papules, and pustules.
4. Grade 4 (Extreme): Comedones, papules, pustules, knobs, and cysts.

There are several factors that lead to acne, including:

- Diet: Dietary components cause acne to break out. For example, high glycaemic content in diets (i.e., diets that contain a high amount of sugar and refined carbohydrates) may worsen skin breakout by expanding insulin-like development factor-1 (IGF-1) levels, which can cause increased sebum generation and contribute to aggravation.

Dairy items have also been known to cause acne to break out, conceivably due to their high levels of hormones and development components.

- Hormones: Hormonal changes, such as those that happens during adolescence, menstrual cycle, pregnancy, and menopause, can trigger acne break out by expanding oil generation in the skin.
- Genetics: Acne breakout can be inheritable. There are higher chances of prevalence of acne in individuals with a family history of acne.
- Stress: Mental health has been known to cause acne break out in a few individuals, possibly because of activation of the hypothalamic-pituitary-adrenal (HPA) pivot and consequent increments in sebum generation and irritation.
- Medications: Corticosteroids, lithium, and certain anticonvulsants, can cause acne.
- Cosmetics: Certain beauty care products, particularly those that are sleek or oily, can clog pores and contribute to acne break out.

- **Bacteria:** The microscopic organisms *P. acnes* is actually present on the skin, but when it overgrows in hair follicles, it can contribute to acne break out.
- **Dysbiosis of the skin microbiome:** Some studies show that dysbiosis of the skin microbiome (the community of microorganisms that occupy the skin) can lead to the acne break out. Dysbiosis happens when there is an outgrowth of certain bacterial species that can trigger irritation and acne injuries.
- **Environmental components:** Introduction to certain natural toxins, such as polycyclic aromatic hydrocarbons (PAHs), has been found to be associated with acne break out. PAHs are found in cigarette smoke, air pollutants and certain related things, and may contribute to irritation and oxidative stretch in the skin.

Complications

While acne is not a life-threatening condition, it can have a severe effect on a person's self-esteem and quality of life. In expansion, serious acne break out can lead to a number of complications. A few of the conceivable complications of acne break out are following:

- **Scarring:** acne can cause lasting scars on the skin, which can have a noteworthy effect on a person's self-esteem and quality of life.
- **Post-inflammatory hyperpigmentation:** when the skin produces excess melanin in reaction to aggravation, it leads to hyperpigmentation. This can result in dark spots on the skin that can take months or indeed a long time to even out.
- **Psychological trouble:** acne break out can cause critical trouble, particularly in young people who are as of now battling with issues related to self-image and self-esteem.
- **Bacterial contaminations:** In serious cases, bacterial accumulation leads to painful pimples and cysts.
- **Secondary diseases:** Picking at acne causes injuries that can lead to secondary infection, which can be more troublesome to treat than the original acne.
- **Permanent changes in skin surface:** Acne can cause irreversible changes in the surface of the skin, including broadened pores and unpleasant or uneven skin. It can change the textures of the skin.
- **Delayed healing:** injuries caused by acne, can take a long time to heal, particularly if they are profound or cystic.

Treatment

A] Topical Retinoids

Retinoids are derivatives of vitamin A that smother comedone improvement by normalizing follicular epithelial desquamation. About 40% to 70%, all topical retinoids viably diminish the number of comedones and fiery lesions. The 3 fundamental topical retinoids are Tretinoin, Adapalene, and Tazarotene.

1. **Tretinoin:** It possesses anti-inflammatory properties. This medication is used to treat acne with other retinoids and to normalize the epithelial layer. It helps to prevent clogging of pores by oils, dead skin and bacteria and decreases sebum production. Tretinoin is available as a gel (0.01% and 0.025%), cream (0.025%, 0.05%, and 0.1%), liquid (0.05%). Tretinoin exhibits

dose-related side effects such as cutaneous erythema, skin peeling and edema.

2. **Adapalene:** It is a topical retinoid drug for treating mild-moderate acne patients. Adapalene has more advantages than tretinoin and tazarotene and is considered a first-line therapy for acne treatment. Gel causes less disturbance than tretinoin 0.05% gel, 0.1% microsphere gel, or 0.05% cream. It decreases hyperkeratinization of pilosebaceous follicles,

inflammation caused by acne. Adapalene 0.1% is available as a cream, gel, and arrangement, all with comparative viability. The side effects are minimal such as redness, irritation, and itching on the skin.

3. **Tazarotene:** It is one of the novel topical retinoids used for acne vulgaris treatment. If the patient isn't responding to tretinoin and adapalene, tazarotene is considered a second-line treatment. It decreases hyperkeratinization and hyperproliferation of *P. acnes* in the epithelial layer of skin. Tazarotene is accessible as 0.1% cream or gel formulations

B] Topical Antimicrobials: -

Topical antimicrobials include benzoyl peroxide and antibiotics like erythromycin and clindamycin have proven effective in the treatment of acne. At least 6 to 8 weeks of treatment is recommended.

In several controlled trials, it has been found that erythromycin and clindamycin help reduce inflammatory lesions by 46% to 70%. However, there is a risk of antibiotic-resistant strains of *Staphylococcus epidermidis* and *Staphylococcus aureus* emerging with monotherapy. Other adverse impacts of topical anti-microbials include erythema, peeling, dryness, and burning. Combining anti-microbial with benzoyl peroxide is the most common practice to

mitigate the issue of drug resistance. Benzoyl peroxide eliminates *P. acnes* by liberating oxygen within the follicle, thereby generating a bleaching effect. It also helps in curbing *P. acnes* resistance to antibiotic therapy, while also possessing moderate anti-inflammatory and comedolytic properties. It is used in various strengths, ranging from 2.5% to 10.0%.

C] Systemic Oral Antibiotics:

systemic antibiotics are often considered the next line of treatment in patients who do not respond or are intolerant to topical antibiotics, or in cases of moderate to severe acne, especially when the chest, back, and shoulders are involved.

The primary systemic anti-biotics utilized in acne vulgaris are tetracycline, doxycycline, minocycline, and erythromycin.

D] Hormonal Therapy

Hormone therapy is employed to address the impact of androgen on sebaceous glands due to their dependence on androgen. Typically, these hormones are administered in the form of oral contraceptive tablets. These contraceptive pills containing hormones work by suppressing sebum production, which is initially stimulated by testosterone.

They also elevate the production of sex hormone-binding globulin, leading to a reduction in the levels of physiologically active free testosterone in women's bodies. Acne in women can be managed using oral contraceptive pills either independently or in conjunction with other treatments. It's important to note that the beneficial effects of hormonal medications become noticeable only after a treatment duration of 3–6 months. Therefore, the recommended treatment duration for acne in females utilizing hormonal anti-androgens is typically at least 12 months. If there is no response to hormonal anti-androgens, then, spironolactone, an androgen receptor blocker, is often combined with oral contraceptives to alleviate inflammation caused by acne in females. Isotretinoin is suggested taken orally; a metabolite of vitamin A. It inhibits differentiation and proliferation of sebaceous gland resulting in reduction of sebaceous gland size. It helps in the normalization of follicular epithelial desquamation.

E] Electrotherapy

Recent investigations have examined the viability of electrotherapy in treating acne vulgaris, and a few

promising techniques mentioned below have been combined with other treatments for better acne treatment.

1] Radiofrequency (RF) therapy: RF treatment is a non-invasive strategy. It uses heat produced by high-frequency streams to boost collagen generation and rebuild tissue. RF treatment can be utilized in treating direct to extreme acne vulgaris by lessening the number of provocative injuries and progressing skin surface and appearance after 6 sessions.

2] Micro-needling: Micro-needling is a negligibly intrusive procedure that makes minor cut wounds in the skin to fortify collagen generation and enhance medicament delivery. Micro-needling, combined with other medications such as topical specialists and phototherapy, can appear critical enhancement in acne break-out injuries and scars.

3] Phototherapy: Phototherapy is a non-invasive strategy that employs light of particular wavelengths to treat different skin conditions, including acne vulgaris. It has appeared a critical diminishment in acne injuries and aggravation counting:

1. Blue light.

2. Red light.

3. Intense pulse light therapy.

4] Laser therapy: Laser treatments, are known to bring about a critical decrease in skin acne injuries and irritation. However, laser treatment is related to an increased risk of unfavorable side effects, such as post-inflammatory hyperpigmentation.

5] Microcurrent therapy: Microcurrent treatment employs low-level electrical streams to invigorate facial muscles and move forward circulation, which can help to decrease acne irritation and improve skin tone and surface texture.

Adapalene

Retinoids are the derivatives of vitamin A and are often classified into generations based on their increasing affinity for retinoic acid receptors (RAR). Third-generation retinoids, including adapalene, tazarotene, and bexarotene, offer advancements. Bexarotene, for instance, selectively binds to retinoid X receptors (RXR), while adapalene and tazarotene exhibit higher specificity for RAR-gamma and RAR-beta without interacting with RXRs, making them suitable for topical application with minimal systemic absorption.

Adapalene, a third-generation synthetic retinoid, was developed to mitigate side effects associated with tretinoin, a first-generation topical retinoid and it closely resembles the derivatives of vitamin A. Adapalene is quite a versatile and effective option in acne treatment, especially when compared to other

retinoids like tretinoin and tazarotene. Similarly, in the comparison with tazarotene, adapalene showed equivalent efficacy but with less irritation. This is significant as irritation can often lead to discontinuation of treatment or poor adherence by the patient. Moreover, the stability of adapalene allows for its use during daylight hours without concerns of photodegradation, which can be advantageous for patients who prefer daytime application or have outdoor activities. Overall, these findings suggest that adapalene is not only effective in treating acne but also offers advantages in terms of tolerability, stability, and compatibility with other acne medications, providing clinicians with a valuable option for managing acne, particularly in patients with moderate to severe inflammatory, non-nodulocystic acne.

Mechanism of action of adapalene on acne vulgaris

Adapalene plays a role in normalizing the shedding of follicular epithelial cells, thereby preventing microcomedone formation. Additionally, when applied topically, adapalene can penetrate hair follicles due to its lipophilic properties. Adapalene is believed to inhibit polymorphonuclear leukocyte chemotaxis and down-regulate 15-lipoxygenase and TLR-2, thus contributing to its anti-inflammatory effects. Adapalene's anti-inflammatory action is comparable to that of betamethasone-17-valerate and indomethacin.

Niosomes-

Niosomes exhibit a spherical structure comprising microscopic lamellar formations, whether unilamellar or multilamellar (as shown in the figure 4). Within niosomes, nonionic surfactants typically arrange themselves with their hydrophilic ends facing the outer aqueous phase and the hydrophobic ends facing inward to form a closed bilayer, effectively encapsulating solutes in an aqueous environment. The closed bilayer structure comprises hydrophilic inner and outer surfaces sandwiching a lipophilic interior. Forces such as van der Waals and repulsive forces among surfactant molecules maintain the vesicular structure.

Composition of Niosomes

These structures form bilayers and are composed of non-ionic surfactants, combined with cholesterol and charge inducers. The combinations of various surfactants, such as alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, and polyoxyethylene fatty acid esters, are utilized in varying proportions to create niosomes. The inclusion of cholesterol enhances bilayer rigidity, reducing niosomal leakage. Charge inducers contribute to vesicle stability and

increased drug entrapment efficacy, with negative charge inducers like dicetyl phosphate and dihexadecyl phosphate, and positive charge inducers such as stearylamine and cetylpyridinium chloride being utilized.

Classification of niosomes

Niosomes can be classified into three size-based categories:

1. small unilamellar vesicles (0.025–0.05 μ m),
2. multilamellar vesicles ($>$ 0.05 μ m), and
3. large unilamellar vesicles ($>$ 0.10 μ m).

Advantages of niosomes as a carrier for topical drug delivery

- Surfactants used in the preparation of niosomes are biodegradable, biocompatible, and non-immunogenic.
- Due to the chemical stability of their basic composition, handling and storage of niosomes do not require any special conditions.
- The physicochemical properties of niosomes, including their shape, elasticity, and size, can be easily manipulated by altering their basic composition and production method.
- Niosomes can encapsulate a large amount of material within a small vesicular volume.
- The structure of niosomes protects drug ingredients from external factors, enabling their use for delivering labile and sensitive drugs.
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase, allowing for modulation of drug delivery rates and facilitating administration of vesicles in an external non-aqueous environment.
- Utilization of a water-based vehicle for vesicle suspension enhances patient compliance compared to oily dosage forms.
- Niosomes exhibit osmotic activity and stability, contributing to the prolonged stability of entrapped drugs.
- Niosomes possess a versatile infrastructure comprising hydrophilic, amphiphilic, and lipophilic moieties, accommodating drug molecules with diverse solubilities.
- Characteristics of vesicle formulations are adjustable and controllable, including composition, size, lamellarity, tapped volume, surface charge, and concentration.
- Vesicles may function as depots, releasing

drugs in a controlled manner, prolonging therapeutic effects.

Methods of preparation for niosomes: -

The selection of preparation methods for niosomes should align with their intended use, as these methods significantly impact various characteristics such as the number of bilayers, size, size distribution, entrapment efficiency of the aqueous phase, and membrane permeability of the vesicles.

A. Ether/Ethanol Injection Method:

This method involves slowly introducing a surfactant solution dissolved in diethyl ether/ethanol into warm water maintained at 60°C. The injection of the surfactant mixture in ether/ethanol through a 14-gauge needle into an aqueous solution leads to the formation of single-layered vesicles. The diameter of these vesicles can range from 50 to 1000 nm depending on the conditions employed.

B. Hand Shaking Method (Thin Film Hydration Technique):

Ingredients for vesicle formation, such as surfactant and cholesterol, are dissolved in a volatile organic solvent (e.g., diethyl ether, chloroform, or methanol) in a round-bottom flask.

Removal of the organic solvent at room temperature leaves a thin solid layer deposited on the flask's wall. This dried surfactant film can be rehydrated with an aqueous phase at temperatures ranging from 0 to 60°C, resulting in the formation of typical multilamellar niosomes.

C. Sonication:

This method involves the sonication of a solution containing a drug and surfactant/cholesterol mixture in a glass vial. The mixture is probe-sonicated at 60°C for 3 minutes, yielding niosomes.

D. Microfluidization:

Utilizing the submerged jet principle, this technique generates unilamellar vesicles of defined size distribution. Two fluidized streams interact at ultra-high velocities within precisely defined microchannels, resulting in the formation of niosomes with greater uniformity, smaller size, and improved reproducibility.

E. Multiple Membrane Extrusion Method:

A mixture of surfactant, cholesterol, and dicetyl phosphate in chloroform is converted into a thin film by evaporation. The film is then hydrated

with an aqueous drug solution, and the resultant suspension is extruded through polycarbonate membranes placed in series for up to 8 passages, enabling control over niosome size.

F. Reverse Phase Evaporation Technique (REV):

Cholesterol and surfactant are dissolved in a mixture of ether and chloroform. An aqueous phase containing the drug is added, and the resulting two phases are sonicated at 4-5°C. The organic phase is removed under low pressure, yielding a viscous niosome suspension.

G. Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading):

Surfactant and cholesterol are dissolved in chloroform, and the solvent is evaporated to obtain a thin film on the flask wall. The film is hydrated with citric acid, and multilamellar vesicles are formed, followed by sonication. Aqueous solution containing the drug is added, and the pH is adjusted to 7.0-7.2 before heating to yield niosomes.

H. The "Bubble" Method:

This novel technique involves preparing liposomes and niosomes without using organic solvents. Cholesterol and surfactant are dispersed in a buffer at 70°C and mixed with high shear homogenizer. Nitrogen gas is then bubbled through the mixture at 70°C.

I. Formation of Niosomes from Proniosomes:

This method involves coating a water-soluble carrier such as sorbitol with surfactant, resulting in a dry formulation termed "proniosomes." Niosomes are formed by reconstitution with an aqueous phase at a temperature higher than the mean phase transition temperature (T_m) with brief agitation.

Adapalene alone:

Adapalene alone has side effects but if adapalene is given along with herbal oil like tea tree oil will not have any side effects

Herbal oil (Tea Tree oil):

Tea tree oil is effective against acne treatment, but have certain issues like it has slower rate of action, but it can be solved i.e its action can be potentiate along with other in combination (adapalene).

Adapalene & Herbal Oil (Tea tree oil) Niosomes:

Adapalene along with tea tree oil will have potentiated effects against acne. Niosomes possess a versatile

infrastructure comprising hydrophilic, amphiphilic, and lipophilic moieties, accommodating drug molecules with diverse solubilities. Adapalene and tea tree oil niosomes can be prepared by ethanol injection method.

Benefits:

- Can be gentle and effective in treating acne.
- Generally safe on most skin types more stable in UV light
- Adapalene niosomes with ethanol injection method can be prepared. In these niosomes along with adapalene herbal oil i.e tea tree oil can be added which will enhance effectivity against acne

Summary

The development of an adapalene niosomal gel utilising carbopol demonstrates a promising approach for enhanced drug delivery. The incorporation of adapalene into niosomes along with herbal oil i.e tea tree oil offers improved stability and prolonged release, potentially enhancing its therapeutic efficacy. Furthermore, the use of carbopol as a gelling agent provides favorable rheological properties for topical application. Overall, this formulation presents a viable strategy for optimizing Adapalene delivery, warranting further investigation for its clinical application in treating dermatological conditions.

Future Prospects

Further Refinement and optimization using systematic Design of experiment, detailed characterization including electronic microscopy, stability studies etc.

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