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A RESEARCH PROPOSAL: COMBINATORIAL NOVEL DRUG DELIVERY APPROACH OF THE MANAGEMENT OF ACNE-VULGARIS

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ABSTRACT

Chronic skin illness known as acne vulgaris is mostly brought on by obstructions in the sebaceous glands or inflammation in those glands, which are collectively referred to as pilosebaceous units. It mostly affects the face, back, and upper chest, which are the regions with the greatest concentration of sebaceous follicles. This illness may strike anyone of any age, although it mostly affects adolescents. These may manifest as non-inflammatory closed comedones (whiteheads), open comedones (blackheads), inflammatory pustules, papules, cysts, and nodules, or a combination of symptoms. It is most usual for practically everyone to have acne at some time in their life. There are 20–25 percent odds that acne may worsen to the point where it leaves permanent scars. Psychological issues including sadness, social isolation, poor self-esteem, and low self-confidence are brought on by these obstacles. The purpose of acne treatment is to avoid serious, long-term consequences. The innovative medication delivery methods for the treatment of acne are the main topic of this review. It also covers the limits of the traditional medicines that

are now on the market, as well as other approaches to get around them.

I. INTRODUCTION

Approximately 95% of the total population faces the problem of Acne in their lives for at least once. The Acne can be of any type either pustules, cysts, comedones, papules, and scarring can also be seen. Acne responds to hormones also either it is endogenous or exogenous. It is a chronic inflammatory disorder of the pilosebaceous units on the face and other regions comprising of the follicular canal and the bunch of sebaceous glands that surround the follicle.

Pathophysiology of Acne consists of differentiation in keratinocytes, hyperproliferation of Propionibacterium acne, increased sebum production, and inflammatory response initiated by any foreign material like antigens or cytokine, etc. Comedones on the face are formed by overproduction of androsterone and oilproducing glands in the face. The primary 2 types of noninflammatory comedones are 1) The closed comedones (whitehead) and 2) The ripen/open comedones (blackhead).

The main target of using Novel drug delivery system to the skin through topical agents is to minimize the risk of the irritant property of some anti-acne medicaments and also shows the great efficiency through it.



Fig. 1: Difference between regular skin and skin affected with acne

II. DIFFERENT TYPES OF ACNE

Minor acne can be cured at home or by using any over-the-counter (OTC) medicines. However, if the acne tends to go in severe cases or any long-term skin inflammation it should immediately get treated by any specialist or dermatologist. About 85% of teenagers and young adults deal with it. The commonly known types of acne are;

- 1) Whiteheads
- 2) Blackheads
- 3) Pustules, or commonly known as pimple
- 4) Nodules
- 5) Cysts
- 6) Papules

1. Non-inflammatory acne types

Whiteheads and Blackheads are two categories of noninflammatory acne. They are not very painful and do not cause any kind of swelling. They have less severe than others.

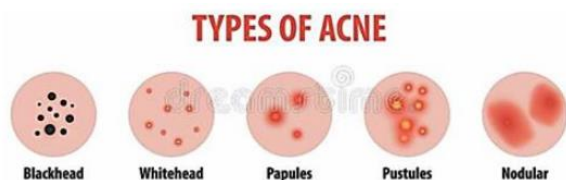


Fig. 2: Different types of Acne

1. Whiteheads

They are known as closed comedones in medical terms. They are small white, flesh-colored spots. The structure of the whitehead is somewhat like a white center around a red hole. Sometimes the hair emerges from the white center but in most cases, the hair can be seen trapped in the center. The skin around the whitehead gets tight or wrinkled especially when the whiteheads are big or are raised. They do not cause scarring.

2. Blackheads

They are known as ripening or open comedones. They are usually black or dark-colored spots that appear slightly raised. The skin surrounding the blackheads appears to be normal and blackheads are darker than its surroundings.

Treatment Option

One can use over-the-counter formulations available in the market in the form of gels, rinses, creams, toners, and moisturizers to treat comedones. Many ayurvedic and home remedies can also be used to treat them. Some basic daily routine can also help in minimizing and treating the comedones those are as follows;

- Wash the face with lukewarm water and soap 2 times a day.
- Reducing stress
- Eating a healthy and balanced diet.

3. Inflammatory Acne type

Inflammatory acne is:

- a) Papules
- b) Pustules
- c) Cysts
- d) Nodules

Minor to a mild form

• Papules- these are bumps present under the skin surface. They are solid, pink, tender, and raised. The skin around it mostly red or pinkish and is swollen.



• Pustules (pimples)- they look like an elongated whitehead which is inflamed.

Moderate to severe form

• Nodules- they are hard, inflamed, painful lump which is located deep with the skin. They are the severe form of acne and they can cause various skin problems like scarring and dark spots.

• Cysts- they are situated deep within the skin and generally the hard, painful and their color may be red or sometimes white. They are filled with pus. They are formed deeper within the skin even deeper than the nodules. They are the most severe case of acne and they also cause permanent skin complications.

Treatment options

a) Drainage and extraction to remove large cysts.

b) Use of steroidal injections

c) Use of topical corticosteroids

Mechanism and causes of acne

Pathogenesis

1. Occlusion of the pilosebaceous orifice
2. Increased sebum secretion
3. Microbial colonization
4. Release of inflammatory mediator

Epidemiology

Prevalence- affects most of the adolescent.

Age- between 12- 14 years.

Gender- in this both the sexes are equally affected but the nodulocystic type of acne is most common in males.

Morphology

Polymorphic eruption of all types of acne on the background of oiliness.

Causes

There are four major causes for any type of acne to occur those are as follows:

a) Excess oil production and retention of oil on the skin for a long time.

b) Hair follicles clogged by skin dead cells along with the presence of oils.

c) Bacteria

d) Excess secretion and activity of male hormone i.e. androgens.

III. STATUS OF ACNE

The seriousness of acne is measured according to the collective acne intensity classification. This categorized them into mild, moderate, and severe based on count and types of acne. According to research and surveys, the global market for acne was worth \$2800 million in 2009. Also, it was estimated to reach \$3020 million by 2016. The present market contains many different types of products that target acne through different factors even in the development of acne. In India, according to a report generated in 2009, the market of anti-acne products was 1.3 billion and is growing by the rate of 14% each year.

TREATMENT STRATEGIES USED FOR ACNE

The treatment option in this varies with the phase and degree of disease. No simple treatment can be given. To treat the mild and moderate form of acne the topical method is always the first choice and systemic treatment is given if the disease becomes severe or moderate. Treatment of acne is done by the following three ways:

a) Topical treatment- it only contains the usage of antibiotics, retinoids, or a combination of both medicaments. Topical medications are exasperating to the skin.

b) Systemic treatment- it contains oral antibiotics retinoids and hormonal treatment. This is given the case of severe or moderate acne types or when there is a resistant towards the topical treatment or if the acne is present in the area of the body.



c) Treatments are other than those which were not mentioned anywhere above. Two categories like resurfacing, chemical peels, xenografts, heterografts, and fat transplant.

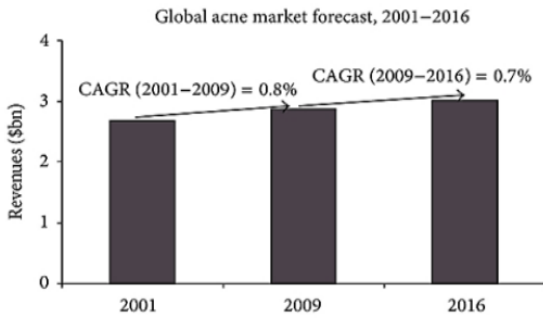


Fig. 3: Future Forecast of Acne

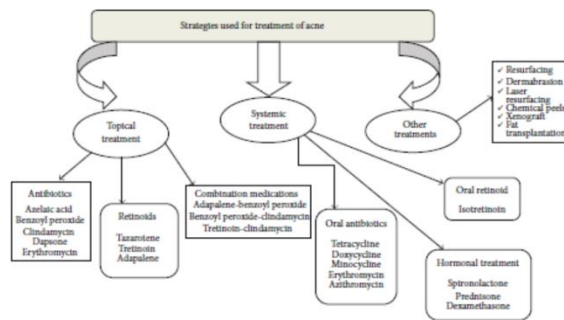


Fig. 4: Strategies to treat Acne

Table 1: Different type of Acne concerning their severity

S. No.	Type of acne	Features
1	Mild acne	Less than 20 comedones or less than 15 inflammatory lesions, or total lesion count lesser than 30
2	Moderate acne	20 to 100 comedones, or 10 to 50 inflammatory lesions, or a total of 30 to 125
3	Severe acne	More than 5 nodules, and if the total inflammatory count is greater than 50, or total lesion count is greater than 125

Table 2: Different types of Acne

S. No.	Types of Acne	Features	Reference
1	Comedones (non-inflammatory)	<i>Whitehead (closed)</i> : it is an obstructed skin opening that contains a hair follicle with sebum, keratin, and the bacteria. <i>Blackhead (open)</i> : it is a wide opening to the skin covered with the black mass of dead skin debris and contains a hair follicle with sebum, keratin, and bacteria.	[50]
2	Papulopustular (inflammatory)	<i>Papule</i> : small bump smaller than 5 mm in diameter. <i>Pustule</i> : smaller bump with a visible central core of purulent material.	[50]
3	Nodular (inflammatory)	<i>Nodule</i> : the size of the bump is greater than 5 mm in diameter	[50]

Table 3: Different types of antibiotics

Antibiotic	Name	Dose	Duration	Drawbacks	Reference
Antibiotics (oral)	Tetracycline, Oxytetracycline	250 to 500mg two times a day	4 to 6 months	The gastro-intestinal problem, vaginal candidiasis, development of resistance	[1]
Tetracyclines	Minocycline	50 to 100 mg two times a day	4 to 6 months	Vertigo, hyperpigmentation of skin and oral mucosa, the cost is high	[1]

Table 4: Treatment using Hormones

Name	Dose	Duration	Drawbacks	Reference
Spironolactone	25 to 100 mg two times a day	24 weeks	Menstrual irregularities, contraindication in pregnancy, loss of appetite, heartburn, trouble sleeping	[1]
Prednisone	2.5 to 5mg daily	Indefinitely	Adrenal suppression	[1]
Decamethasone	0.125 to 0.5mg daily	Indefinitely	Adrenal suppression	[1]
Cyproterone acetate/ethinyl Estradiol (oral contraceptives)	2mg/30 to 50µg	24 weeks	Vascular thrombosis, melasma, weight gain	[1]
Levonorgestrel/ethinyl estradiol	100 µg/20 µg	24 weeks	Vascular thrombosis, melasma, weight gain	[1]

CONVENTIONAL DELIVERY SYSTEM USED IN THE TREATMENT OF ACNE

In the early days, a conventional delivery system was used for treating acne. In around 1950, the use of antibiotics was increased as they were more effective because of the anti-inflammatory effect of tetracycline. In 1980, Accutane a type of vitamin A was made for reducing the oils in the skin and skin glands. In 1990 laser treatment was adopted to treat acne and later on it was observed that the use of laser technology is effective for the nodular and cystic type of acne. The conventional delivery system shows effect by using any of the four mechanisms namely; normalizing shedding into the pore to prevent blockage, killing bacteria responsible for acne, anti-inflammatory therapy, and hormonal treatment. Many patients fail to respond towards the treatment of acne despite having so many treatments or develop side effect that affects the patients and hinders the compliance and compromising the efficiency of therapy in patients. To reduce the risk of the above-mentioned side effects the development of novel drug delivery system came to existence. They decrease the irritant property of the moiety without altering the efficacy. The novel delivery system penetrates right into the skin more efficiently and goes straight towards the hair follicles.

IV. NOVEL DRUG DELIVERY SYSTEM USED TO TREAT ACNE

The use of the novel delivery system provides a better efficacy of the antiacne topical agents, but the adverse effects like irritation, redness, peeling, dryness, and scaling still are the major issues. The novel delivery systems are specially prepared to amplify the load ability of active

ingredients and decrease the side effects of it. The novel delivery systems which are under development for use topically in treating acne include liposomes, niosomes, microsponge, microemulsions, microsphere, hydrogel, aerosol, and so forth. The mechanisms of drug release in the novel carrier system are basically of two types: diffusion through the carrier matrix and erosion. Sometimes a combination of erosion and diffusion method is also present. As the novel carrier system is advantageous but it also carries some serious drawbacks which limit their usage. Drugs passively can lead to low drug loading efficacy, any error during preparation and preservation, and leakage.

Table 5: Side effects associated with the conventional formulations used.

Conventional delivery system	Drug	Side Effects	Reference
Lotion	Benzoyl peroxide	Peeling, itching, redness, drying.	[51]
	Clindamycin	Peeling, redness, dryness	[52]
	Tretinoin	Peeling, itching, redness.	[53]
	Erythromycin	Erythema, scaling, burning.	[54]
	Glycolic acid	Erythema, scaling, burning.	[55]
Cream	Adapalene	Erythema, scaling, dryness.	[56]
	Tazarotene	Erythema, scaling, burning.	[57]
	Azelaic acid	Itching, rash, pruritus.	[55]
	Tea oil	Burning, itching, irritation.	[58]
	Clindamycin	Erythema, desquamation.	[59]
Gel	Salicylic acid	Erythema, dryness, dermatitis.	[51; 60]
	Erythromycin	Dryness, erythema, peeling.	[54; 61]
	Benzoyl peroxide	Dryness, erythema, peeling, dermatitis.	[61]
	Dapsone	Erythema, scaling, dryness.	[62]
Emollient	Sodium sulfacetamide sulfur.	Dryness, irritation, redness, scaling, stinging, burning.	[63]

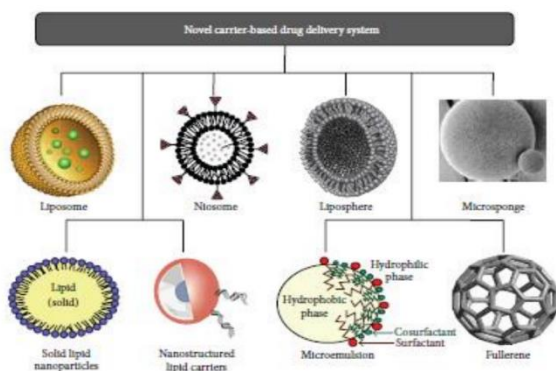


Fig. 5: Novel carrier-based drug delivery system for treatment of Acne

1) Liposomes

They are concentric bilayered vesicles in which there is an aqueous core that is enclosed in a membranous lipid bilayer mostly of natural or synthetic phospholipids. They are mainly used for treating diseases associated with hair

follicles like Acne. They are artificial vesicle which is spherical and they are made up from the non-toxic phospholipids. They are a promising system for drug delivery because of their size, hydrophobic and hydrophilic properties [28-30]. Their properties vary considerably with the difference in lipid composition, charge on the surface, size, or the process used for preparing the liposomes. Rigidity and fluid nature and the charge of the bilayer are solely depending on the components of the bilayers. For example; unsaturated phosphatidylcholine type from natural sources like eggs or soybean, they provide much permeable and a lesser stable bilayer, whereas saturated phospholipids having longer acyl chain, forms a rigid, or rather an impermeable structure [28-30]. Due to their promising properties like biocompatibility, biodegradability, lowered toxicity and tendency to trap both hydrophilic and hydrophobic drug molecules [31] and simplify the delivery of sitespecified drugs to tumor tissues they have both amplified rate in investigational system and commercially as drug delivery system [17,32].

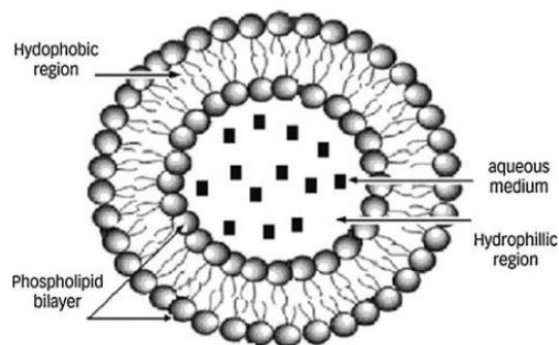


Fig. 6: Structure of Liposome

Advantage of Liposomes

When used topically, they can increase the deposition of the drug at the site of action within the skin, absorption in the systemic circulation is reduced that minimizes the adverse effect



thereby provides local effect and the direct target the skin appendages. The vesicular system leads to good results in treating the acne as a comparison to a conventional system by the release of the drug on target present in the skin and are more preferable for the lipophilic drug.

Disadvantages of Liposomes

The major demerit of this preparation type is its stability. Stability issues arise from several problems; formation of the ice crystals in the liposomes and instability in bilayers which leads to leakage of the enclosed material. Other reasons are oxidation of cholesterol and phospholipids which results in formulation instability. Hydrolysis and oxidation of lipids show the chemical instability. Destabilization is due to the exchange between the liposome and HDLs.

2) Niosomes

They are the unilamellar or multilamellar vesicles in which there is an aqueous core surrounded by bilayer made up of non-ionic surfactants. They are non-ionic surfactant vesicles because of which the skin penetration is increased in the skin. They are said to be the best carriers among the others [20]. The difference in the composition of the vesicle, lamellarity, surface charge, size, and concentration change the properties of the vesicle. The niosomes can accommodate drugs with an enormous range of solubility because of the presence of hydrophilic, amphiphilic, and lipophilic parts in the structure [21]. The therapeutic property of drugs can also be amplified by delayed clearance from the circulatory system that protects the drug from the environment and restricts the effects of affected cells [22]. The ideal properties of the surfactants that are used in the niosome formulation should be biocompatible, biodegradable, and non-immunogenic [26].

They are used to study the reaction of the immune system provoked by antigens [23]. They are also used as a carrier for hemoglobin [24,25]. The niosomal vesicular system provides better drug concentration by oral, parenteral, or topical routes at the site of action. The progress in the niosomal drug delivery system is still in the primitive stages, but it has shown a promising property in cancer chemotherapy and anti-leishmanial therapy [27,18].

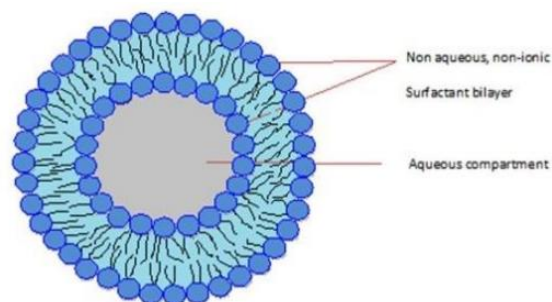


Fig. 7: Structure of Niosomes

Advantages of Niosomes

The systemic absorption of the drug can be reduced and the residence time of the drug in the epidermis and stratum corneum can be increased by using a niosomal preparation topically. Niosomes are used over liposomes because of the former exhibit high stability chemically and economy. The reason for the preparation of niosomes is that they have the higher chemical stability of the surfactants than that of phospholipids due to ester bond, phospholipids can be easily hydrolyzed.

Disadvantages of Niosomes

As niosomes are superior to liposomes, they still have some stability problems with them like physical stability of fusion, aggregation, sedimentation, and leakage on storage. The major issue is the hydrolysis of encapsulated



drugs which alters the shelf life of the dispersion in niosomes.

3) Microsponges

They are the patented polymeric drug delivery system that contains porous microspheres in which an enormous range of actives such as essential oils, anti-fungal, anti-inflammatory agents are easily enclosed. They have a true nature of a sponge that contains a myriad of interconnecting voids. Their size range varies from 5 – 300 μm in diameter that depends upon the intensity of after-feel required or smoothness needed for the end formula. They may vary in sizes but a typical 25 μm sphere has almost several pores up to 250000. The microsponges contain a huge reservoir within each of them that can be loaded up to its weight of the active agent. The porous nature of microsponges adds to its safety as it can entrap the bacterial contamination. Because of the smaller pore size, the bacteria ranging from 0.007 to 0.2 μm cannot penetrate the structure of microsponges [19,33].

Advantage of Microsponges

In this, the release of the drug can be controlled by diffusion or other parameters like pH, moisture, and friction, or skin temperature. They are also capable of enhancing the absorption of secretions of the skin, therefore, reducing the oiliness. These polymers tend to load a wide variety of APIs which provides the benefits of amplified efficacy along with mildness and tolerability. This system has ranged over pH 1-11 and temperature up to 130 Celsius and is compatible with most of the vehicles and ingredients, self-sterilizing average pore size is 0.25 μm .

4) Microemulsions

They are transparent dispersion of oil in water with the size of droplet about 100nm in diameter. They are stabilized with the film of surfactant and co-surfactant. They are thermodynamically stable, clear, and optically isotropic systems. They are prepared by step-wise mixing of suitable oil, water, and an amphiphile [35-38]. They were used to solubilize drugs and to enhance the availability of the drug [39]. It has said that they can dissolve the structure of lipids present in the stratum corneum which leads to the loss barrier properties of the skin [34,40].

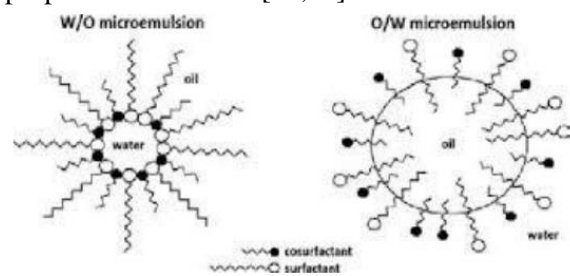


Fig. 8: Structure of Microemulsion

5) Nanoemulsion

They are a colloidal particulate system that is in the range of submicron size which acts as a carrier of the drug moiety. The size range varies from 10 to 1000 nm. They are negatively charged amorphous and lipophilic surfaces and are solid spheres. They are used as a drug delivery system because they have amplified therapeutic efficiency regarding the drug and minimize the side effects and toxic reactions in the body [41].

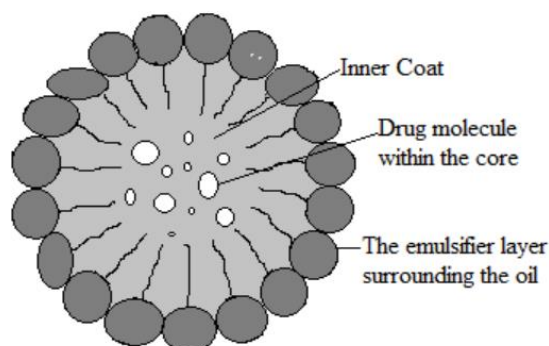


Fig. 9: Structure of Nanoemulsion

6) Microsphere

They are made up of biodegradable polymer and are spherical. It is filled with the drug substances and is dispersed and when it gets degraded to release the drug. The microencapsulation technique is used to prepare the microspheres. They can be prepared in a definite size and shape which by default improves delivery of the drug to the specified site. Porous microspheres are fabricated with either internal or external porosity, or even a combination of both, with or without interconnectivity for cell attachment. The Microspheres can be assembled into 3-Dimensional porous scaffolds or as a stand-alone product [42].

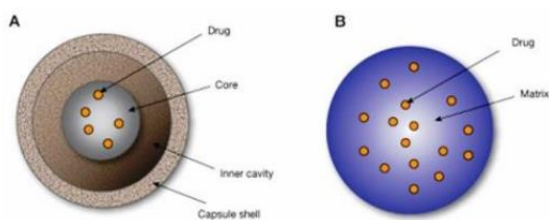


Fig. 10: Structure of Microsphere

Advantages of Microsphere

When administered in skin the free drug present in the preparation penetrates the epidermis layer and compensates by the release of drugs from the microsphere. The formulation of topical tretinoin and benzoyl peroxide has proven good efficiency and tolerability and is expected to

encourage adherence and therapeutic benefits. They absorb sebum from the skin surface reduces oiliness which is the most common complaint regarding acne.

V. CONCLUSION

The adolescent phase is a multifaceted life period marked by changes in the body, mind, and society. A person's self-esteem develops throughout this time, and it might be lowered by illnesses like anxiety, sadness, or any other issue that would need medical attention.

Teenagers' quality of life may be hampered by the obvious changes in their acne, which may also lower self-esteem and have psychological effects. Since standard oral and topical treatments for acne have been shown to be beneficial, it is imperative to discover novel therapies due to the prevalence of this condition and its resistance to treatment. While there has been progress in treating acne, not all of it is in the direction of what is ideal. A topical formulation has to be stable and have increased penetration of the active ingredients at their concentration of effectiveness in order to be considered effective. It also needs to be readily accessible, acceptable, and free of adverse effects.

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