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Application of Nano-niosomes in the Treatment of Skin Acne

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ABSTRACT

Acne is a multifactorial and sebaceous follicles disease. Sebaceous follicles are located in areas prone to acne (cheeks, nose, and forehead). There are many obstacles to the successful treatment of acne. In this study, the pathogenesis of acne and the effective ingredients in acne treatment were briefly explained. In this regard, the potential of nanoparticles in the skin treatment of acne was reviewed. Then, the nanoniosome as effective nanoparticles in the treatment of this disorder was explained. Finally, the components of the niosomal formulation, the factors affecting the formation of niosomes, and their application in acne treatment were briefly described. In the end, it was concluded that nanoniosomes increase the therapeutic effects of effective drugs in the treatment of acne by reducing the side effects of drugs, controlling the release of drugs into the skin, accelerating local penetration, and targeting follicles

Keywords: Acne, Niosome

1. INTRODUCTION

Acne is a disease with a primary pathological condition related to microcomedones [1] and disease of the sebaceous follicles. Sebaceous follicles are present in acne-prone areas. Acne lesions are divided into inflammatory and non-inflammatory lesions. Non-inflammatory lesions include open (blackhead) and closed (whitehead) comedones. Comedones enter the follicles due to the retention of sebum and creatine residues, leading to the expansion of hair follicles and the formation of comedones. Inflammatory acne is characterized by one or more of the following lesions: Papules, pustules, and nodules (cysts). Papules are inflammatory lesions less than 5 mm in diameter. Pustules are similar in size to papules, but they have a center of pus. Nodules are inflammatory lesions 5 mm or more in diameter (Fig. 1). These nodes possibly become purulent or bleeding. Nodular lesions, especially when purulent, are commonly called cysts because they resemble inflamed epidermal cysts [2].

Topical drug delivery has advantages such as topical drug delivery at the operation site and reducing side effects by minimizing systemic absorption. Drug delivery through the skin has high bioavailability because, in this way, the liver metabolism is prevented. It is non-invasive because there is no need for a needle. It prevents acidic and enzymatic degradation in the gastrointestinal tract and eliminates potential drug-food interactions. However, the use of the dermal route due to the weak penetration of drug molecules is the main barrier to drug uptake throughout the skin [3].

Commonly used forms such as creams, gels, and ointments have significant limitations, for example, they do not penetrate effectively into the pilosebaceous unit, and the effective drug concentration is not stable and uninterrupted [4]. Therefore, we have to look for a way to deliver drugs locally, which we found with studies that nanoparticles can solve these problems.

Design and fabrication of a material having at least one of its dimensions in the range of 1 to 100 nm; called nanotechnology that its application in medicine is known as nanomedicine; however, by definition, particles smaller than 100nm are called nanoparticles, in the field of drug delivery systems, particles up to 1000 nm in size are also used to transport drugs [5], [6]. The importance of nanoparticles in drug delivery is due to their small size and high surface-to-volume ratio. This high level allows the absorption, binding, and transport of drug compounds easily [7]. In this study, the pathogenesis of acne, effective drugs in the treatment of acne, the main barriers to the treatment of acne, the potential of nanoparticles in the treatment of acne, niosomes (their components and factors affecting their formation), skin penetration mechanisms of niosomes and finally their use in acne treatment were studied.

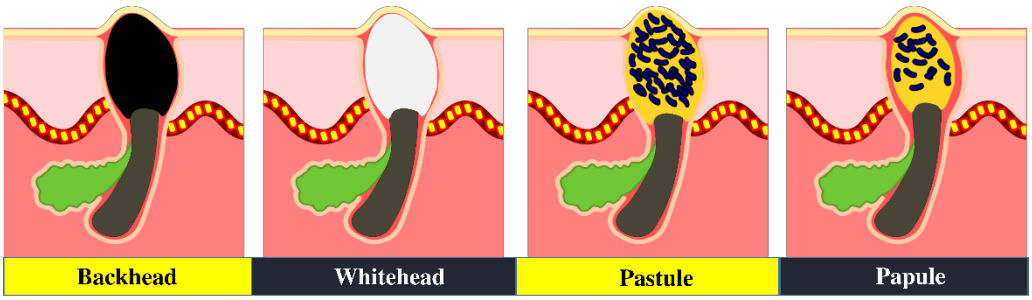

Fig. 1. Schematic of different types of acne

2. THE PATHOGENESIS OF ACNE

Four critical factors in the pathogenesis of acne are briefly described:

1. Increased androgen stimulation in sebum secretion resulting in sebum production.
2. Hyperkeratinization and obstruction of the sebaceous follicles result from abnormal shedding of the follicular epithelium.
3. Propionation of Propionibacterium acne (P.acne).
4. Inflammation [8].

2.1 Increased androgen stimulation in sebum secretion resulting in sebum production

Increased volume of sebaceous glands caused by androgens and excessive sebum production is an essential factor in the development of acne. Sebaceous glands are susceptible to androgens and are less sensitive to estrogens. Acne mainly starts with puberty, when androgen levels increase. The pituitary gland is the main factor in the hormonal control of the function of the sebaceous gland, which controls the hormonal interactions of the pilosebaceous units by acting on the adrenals and gonads [9].

2.2 Hyperkeratinization and obstruction of sebaceous follicles due to abnormal shedding of follicular epithelium

The reason for hyperkeratinization can be an overproduction of duct keratinocytes or a decrease in duct corneocytes [9].

2.3 Microbial proliferation

P.acne colonizes sebum-rich follicles on the skin of the face, chest, and back. P.acne is a gram-positive anaerobic bacterium that produces propionic and acetic acids. Comedones are anaerobic sites rich in lipids and suitable as a nutrient source for P.acne growth [9].

2.4 Inflammation

Inflammatory reactions are another factor involved in acne. Inflammatory acne occurs when the comedones rupture and excrete more contents into the dermis than the skin surface [8], [9].

3. DRUG AFFECTING THE TREATMENT OF ACNE

Topical treatment of retinoid on follicular keratinocytes works to prevent excessive cornification and obstruction of the follicle. It may also reduce the release of proinflammatory cytokines. The most common side effect is scaling. Topical antimicrobials are effective in treating inflammatory acne, benzoyl peroxide, and antibiotics. Benzoyl peroxide has anti-inflammatory properties and prevents the resistance of P. acne to antibiotics. Monotherapy with topical antibiotics develops bacterial resistance to P.acne one month after the start of treatment. Oral contraceptives containing estrogen are effective in treating women with acne. Combination therapy with topical agents or oral antibiotics can increase the effects of these agents. Isotretinoin alters abnormal keratinization of the follicle, reduces sebum production, reduces P. acne (colonization), and is anti-inflammatory [10].

4. SIGNIFICANT OBSTACLES TO SUCCESSFUL ACNE TREATMENT

The most significant obstacles to successful acne treatment are: First, the outermost layer of the epidermis is the stratum corneum, and it is a significant barrier to influence. This layer comprises brick-like corneocytes stacked together by a mortar of intercellular matrix materials. One of the main challenges is to achieve the ideal balance between the local penetration of the therapeutic agent and its retention at the desired location in the layers of the skin for a desirable period. Second, increasing the resistance of microorganisms such as P.acne and S.epidermis to common antibiotics prevents the successful treatment of acne. Third, the use of anti-acne drugs in conventional drug systems leads to undesirable side effects such as burning, redness, dryness, and sensitivity to light due to lack of targeted delivery to the pilosebaceous unit, which is the center of acne [11].

5. NANOPARTICLES

There are different types of nanoparticles; if we want to classify them based on their physical and chemical properties, these include nanoparticles based on carbon, metals, ceramics, semiconductors, polymers, and lipids [12]. Among the nanoparticles mentioned, lipid and polymer nanoparticles have been used and studied to transport drugs to the skin [13].

6. THE POTENTIAL OF NANOPARTICLES IN THE TREATMENT OF ACNE

Nanoparticles can transport the drug in which they are loaded to the desired location (in acne, hair follicles are the site of acne pathogenesis) [14]. In addition, the dermal metabolism of the drug is similar to that of primary hepatic metabolism. Nanoparticle delivery systems have been reported to be very useful for prescribing smaller amounts of drugs and protecting them against skin metabolism, and providing a stable release of drugs into the skin layers [15].

Lipid-based nanocarriers form a thin film on the skin's surface, thus preventing water loss throughout the epidermis and enhancing skin hydration. Increased hydration to the skin facilitates local penetration. Acne mainly affects the skin of the face, which is rich in hair follicles. The pathogenicity of acne requires the colonization of bacteria in the hair follicles. [70]. Smaller particle size is better for penetrating the skin and maintaining the formulation in the pilosebaceous units of the skin, which is the center of acne growth and a place for bacteria to load. The ideal particle size of nanocarriers for follicular penetration is in the range of 700-400 nm [11].

7. NIOSOME

Niosomes are a type of colloidal particle that can enclose active drugs and are an auspicious way to increase the bioavailability of drugs. In addition, niosomes are attracting much attention because of their advantages in various aspects, including biocompatibility, chemical stability, low cost and convenient storage of non-ionic surfactants, and a large number of surfactants available for niosome design [16], [17]. Niosomes can encapsulate hydrophilic and hydrophobic drugs in their structure. The enclosure of hydrophilic drugs in niosomes occurs in the central aqueous center or on the outer surface of the niosome. In comparison, hydrophobic drugs enter the bilayer structure [18]–[20].

8. FORMULATION COMPONENTS AND THEIR EFFECTS

The components of the niosome include surfactants and additives (cholesterol), each of which is briefly described [21].

8.1 Surfactants

Surfactants are amphiphilic molecules consisting of a lipophilic tail and a hydrophilic head. They are classified according to the charges in the hydrophilic groups, which are cationic, anionic, amphoteric, and non-ionic. Non-ionic surfactants are the main components of niosomes due to their low toxicity and biocompatibility compared to other types of surfactants [22], [23].

8.2 Additives

Cholesterol is the most important of the various additives used for niosomal membranes. Cholesterol interacts with surfactant molecules by creating a hydrogen bond between the hydroxyl groups and the alkyl chain. It increases the temperature of vesicle transport and improves stability by changing the fluidity of the chains in the niosomes. Cholesterol also improves drug confinement efficiency due to its membrane-stabilizing effect, as it fills the space of the niosomal bilayer, reduces membrane fluidity, and reduces drug secretion out of the niosome [23].

9. FORMULATION COMPONENTS AND THEIR EFFECTS

9.1 A critical parameter of packaging

The following equation (1) can express the critical packing parameter (CPP):

$$CPP = \frac{V}{a0 \times lc} \quad (1)$$

Where V is the volume of the hydrophobic group, a0 is the hydrophilic group's head area, and lc is the length of the hydrophobic group. From the amount of CPP, the type of micellar structure formed is determined. CPP less than 0.5 causes globular micelles to form. A CPP between 0.5 and 1 indicates the formation of bilayer micelles, and a CPP greater than 1 indicates the formation of reverse micelles [22].

9.2 Hydrophobic and lipophilic balance (HLB)

HLB is a practical term for the relationship between hydrophilic and hydrophobic groups of surfactants. Surfactants become more soluble in water as the number of HLB increases. Surfactants with HLB levels between 4 and 8 can form niosomes, while surfactants with HLB levels 6 or higher require the addition of cholesterol to form niosomes.

9.3 Gel liquid transition temperature (Tc)

The Tc of surfactants is an essential factor in the formation of niosomes. Shorter alkyl chains have lower Tc, which leads to the formation of leaky niosomes. Unsaturated bonds in the alkyl chain decrease Tc and increase chain fluidity and more membrane permeability. The temperature of the hydration medium should be higher than that of the surfactant Tc because it affects the formation of niosomes [23].

10. MECHANISM OF INCREASED SKIN PENETRATION THROUGH NIOSOMES

Several mechanisms have been proposed to explain the enhancing effects of niosomes (Fig.2). First, the adsorption and fusion of drug vesicles on the skin surface, leading to a gradient of high thermodynamic activity of the drug, acts as a driving force for the penetration of drugs through the SC. Second, penetration through skin appendages such as hair follicles. Third, non-ionic surfactants play a crucial role in improving penetration as penetration enhancers [23].

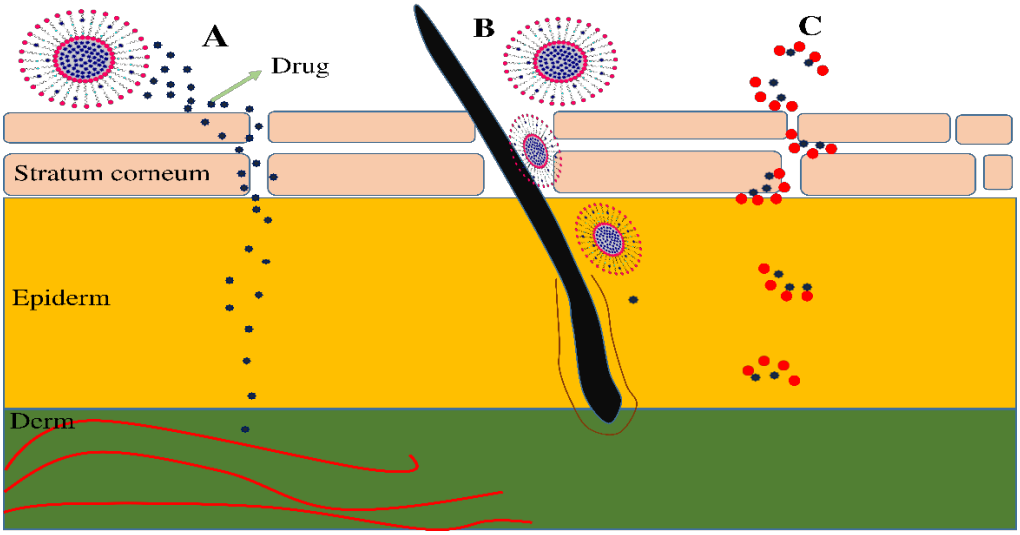

Fig. 2. A) Drug release from the niosome and its penetration into the skin layers. B) Penetration of drug-containing niosomes through hair follicles. C) The effect of niosomal surfactants as drug penetration enhancers.

11. APPLICATIONS OF NIOSOMES IN THE TREATMENT OF ACNE

In a study in 2010, A. Manosroi et al. loaded gallidermin to treat acne disorder in niosomal nanocarriers and evaluated the physicochemical properties of drug-containing nanocarriers. The most optimal samples of anionic niosomes consisting of twin 61, cholesterol, DI-acetyl phosphate, and gallidermin with specific concentrations, showed a size of about 149 nm, the zeta potential of about -50 mV, and a load efficiency of 45.06%; this research group also showed; The stability of the drug-loaded in the niosome is about 1.5 times higher than that of the free solution of gallidermin. However, the antibacterial activity of free gallidermin is about twice that of gallidermin loaded into the niosome. This study aimed to evaluate the increase in percutaneous uptake of gallidermin loaded into niosomes to evaluate their potential topical application to drugs [24].

In 2011, G. Goyal, T et al. loaded benzoyl peroxide (an anti-acne drug) into niosomal nanocarriers prepared by thin-film hydration. These nanocarriers reduced the side effects of topical use (dryness and redness) of the skin. Afterward, they evaluated the release profile, loading efficiency, stability evaluation at different temperatures for the prepared formulations. They showed that the drug is loaded into the niosomes, increases the release time and the retention of the drug in the skin, and improves penetration from the skin surface. From this study, we can conclude that the loading of benzoyl peroxide in niosomal nanocarriers is beneficial. These nanocarriers increased the penetration of the drug, controlled the drug release, prevented the destruction of benzoyl peroxide by protecting it from direct exposure to the environment, and reduces the side effects of skin irritation. It was shown in the *in vivo* study that the drug-containing niosome shows a more significant anti-inflammatory effect and further reduces the number of P.acne in the ears of mice than the free drug. Finally, they considered these drugs delivery systems to be sound systems for treating acne [25].

In a study conducted by A. Budhiraja and G. Dhingra in 2014; rosmarinic acid (ROA) was used to treat acne disorder in inverse nanoparticles prepared by reverse-phase evaporation method and different molar ratios of its constituents (surfactant span 85 and cholesterol) and evaluated and observed the physicochemical properties of drug-containing nanoparticles. These drug-containing nanocarriers have controlled and

continuous drug delivery to bacterial cells and good antibacterial activity against acne-prone bacteria such as P.acne and S. aureus compared to the free drug [26].

In 2017, a study was conducted by M. Jufri et al. they loaded betel pepper inside niosomal nanocarriers with different molar ratios of its components to treat acne and evaluated and compared properties such as particle size, loading efficiency, and stability of nanocarriers with different molar ratios prepared and compared. They conclude that the antibacterial activity of drug-containing niosomes has decreased compared to the free drug [27].

In a study by K. Begum et al., niosomes were used for topical use to increase skin penetration and improve skin retention of rifampicin. In thair study, three different niosomal formulations were prepared. The antibacterial activity of rifampicin niosomes against S.epidermidis and S. aureus showed that up to 96% of the bacteria were killed within 4 hours. This study demonstrated the potential of rifampin-containing niosomes to target bacteria in acne [28].

12. CONCLUSION

By loading effective drugs into niosomal nanoparticles in treating acne with lower drug concentrations, effective results can be achieved. These nanocarriers increase efficiency due to their targeted drug delivery, controlled drug release, accelerated local penetration, and dermal drug metabolism. In this way, bacterial resistance and adverse side effects on the skin can be reduced, and patient adaptation can be increased.

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