Various studies on azelaic acid to increase its permeability: A review

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Abstract

Azelaic acid (1,7-heptanedicarboxylic acid, $COOH(CH_2)_7COOH$) is a saturated, dicarboxylic acid, straight-chained organic compound with molecular weight of 188g/mol. Azelaic acid is used in the treatment of acne, rosacea, acne vulgaris, lentigo maligna, malignant melanoma. Azelaic acid shows a wide range of activities such as anti-bacterial, anti-inflammatory, anti-microbial and anti-keratinizing activity. The anti-inflammatory effect of AzA is based on suppression of the expression of pro-inflammatory cytokines. This effect is further supported by the ability of AzA to scavenge ROS as well as the suppression of ROS production by granulocytes. AzA inhibits the proliferation of a range of Gram-positive and Gram-negative microorganisms. In addition, AzA affects the disturbed follicular keratinization characteristic of acne. Its inhibitory effect on the formation of comedones is also well documented. As AzA addresses these three key pathophysiological mechanisms in acne vulgaris, it is a valuable option in the topical treatment of mild-to-moderate acne. Azelaic acid is a competitive inhibitor of tyrosinase enzyme, which is a key enzyme in melanin production, so azelaic acid is used in treatment of hyperpigmentation. This review has covered various studies and researches on azelaic acid.

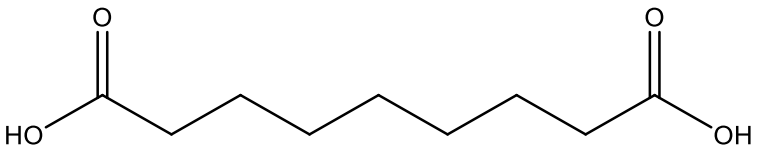
Keywords: *Azelaic acid, acne vulgaris, rosacea, tyrosinase, permeability.*

Introduction

Azelaic acid (1,7-heptanedicarboxylic acid) is a saturated, dicarboxylic acid, straight chained organic compound [1]. It possesses significant biological properties and has potential to act as a therapeutic agent. Azelaic Acid is a naturally occurring dicarboxylic acid produced by Malassezia furfur and it is found in whole grain, cereals, rye, barley and animal products. Azelaic acid possesses antibacterial, keratolytic, comedolytic, and anti-oxidant activity [2]. Azelaic acid is used in the treatment of acne, rosacea, acne vulgaris, lentigo maligna, malignant melanoma. Azelaic acid also possesses a direct anti-inflammatory effect due to its scavenger activity of free oxygen radical [2]. Azelaic acid is bactericidal against Propionibacterium acnes and Staphylococcus epidermidis due to its inhibitory effect on the synthesis of microbial cellular proteins. Both in vitro and in vivo it has an antimicrobial effect on both aerobic and anaerobic (Propionibacterium acnes) microorganisms [3]. Azelaic acid exerts its keratolytic and comedolytic effects by reducing the thickness of the stratum corneum and decreasing the number of keratohyalin granules by reducing the amount and distribution of filaggrin in epidermal layers. It also causes the induction of peroxisome proliferator-activated receptor-gamma (PPARG). PPARG is also called glitazone receptor which decreases the inflammatory responses [4]. This drug is used topically to reduce inflammation associated with acne and rosacea. Azelaic acid is a competitive inhibitor of tyrosinase enzyme, which is a key enzyme in the production of melanin, so AzA is used in the treatment of hyperpigmentation.

Chemistry of azelaic acid

Structure:



Chemical formula: $C_9H_{16}O_4$

Molecular weight: 188.22g/mol

Melting point: 106ºC-111ºC

Appearance: White solid

Solubility: Slightly soluble in ethyl ether, benzene, DMSO but soluble in hot water, ethanol, alcohol and organic solvents (acetone, methanol, ethanol).

Mechanism of action:

Anti-enzymatic and anti-mitochondrial activity: Azelaic acid is a reversible inhibitor of the activity of cytochrome P450 reductase and 5-alpha reductase in microsomal preparations supplemented with decreased nicotinamide adenine dinucleotide phosphate, in addition to being a competitive inhibitor of tyrosinase (NADPH). Azelaic acid can also inhibit several respiratory chain enzymes in a reversible manner (reduced nicotinamide adenine dinucleotide [NADH]-dehydrogenase, succinic acid dehydrogenase, reduced ubiquinone cytochrome c oxidoreductase) [3].

Anti-inflammatory activity: AzA inhibited UVB-induced interleukins IL-1 and IL-6, as well as TNF-messenger ribonucleic acid (mRNA) production and protein release, indicating that it has anti-inflammatory properties. UVB causes phosphorylation of the mitogen and stress-activated protein kinase p38, as well as the translocation of the redox-sensitive transcription factor B p65 subunit (NF-B p65) to the nucleus, where it activates the transcription of genes involved in the production of pro-inflammatory cytokines like IL-1, IL-6, and TNF. AzA was discovered to greatly block this process, as well as stimulate the expression of peroxisome proliferator-activated receptor-gamma (PPARG), which was accompanied with cell proliferation inhibition. PPARG, commonly known as glitazone receptor, is a glitazone receptor that reduces inflammatory reactions. AzA causes kallikrein 5 to be downregulated in epidermal keratinocytes, which causes cathelicidins to be downregulated, reducing inflammatory processes. This pathway appears to be particularly crucial for azelaic acid's anti-inflammatory effects in rosacea. AzA's anti-inflammatory properties are due to its ability to scavenge reactive oxygen species (ROS) in vitro, including as hydroxyl radicals and superoxide anions. AzA also inhibit the production of superoxide anions and hydroxyl radicals from neutrophils [5].

Anti-bacterial and anti-microbial activity: It has an antibacterial impact on both aerobic and anaerobic microbes in vitro and in vivo. It exhibits antimicrobial effect against both aerobic and anaerobic bacteria (Staphylococcus aureus, Proteus mirabilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans). It acts by inhibiting the DNA synthesis of bacteria and microbes. AzA works primarily on cellular protein synthesis in both aerobic and anaerobic bacteria, and it inhibits Propionibacterium proliferation [5].

Anti-keratinizing activity: AzA is an anti-keratinizing agent as well. Treatment with AzA causes epidermal keratinization to be altered, with a concomitant reduction in the size and number of keratohyalin granules and tonofilament bundles, especially in the terminal phases of epidermal differentiation. AzA also causes the mitochondria to inflate and the rough endoplasmic reticulum to expand. Filaggrin expression in the stratum granulosum of acne patients is similarly reduced by AzA

therapy. The thickness of the stratum corneum in the acroinfundibular zones is significantly diminished, and the cytoplasmic content of the cells in this stratum corneum layer is distributed in a wide and irregular pattern. AzA inhibited keratinocyte DNA synthesis in a dose- and time-dependent manner, as well as regulated human epidermal differentiation and the synthesis of particular 95 and 36 kDa proteins, indicating that AzA has reversible antiproliferative effects on keratinocytes. Reduced NADH dehydrogenase, succinic dehydrogenase, and reduced ubiquinone cytochrome c oxidoreductase are among the mitochondrial respiratory chain enzymes that inhibit by AzA. AzA's antikeratinizing action has been found to reduce the formation of comedones in people with mild to moderate acne [5].

Various studies on azelaic acid to increase its bioavailability and penetration in the skin:

1. **H.H. Amrutbhai, P.A. jaykumar and Narkhede Sachin B et al. (2019)** reported the synthesis of azelaic acid emulgel. Acne and hyperpigmentation are both treated with azelaic acid, which also lessens irritation and redness. However, because azelaic acid is poorly soluble and permeable, the goal of the current study was to improve these properties by creating an emulgel that would effectively treat acne and hyperpigmentation [6].

   Topical drug delivery makes it simple to provide medication through the cutaneous, vaginal, ophthalmic, and rectal channels. A topical delivery method's primary advantage is that it prevents first-pass metabolism. Additionally, it aids in avoiding intravenous difficulties as well as other problems such gastric emptying, enzyme presence, and pH fluctuations. The main components of gels are water or a hydroalcoholic liquid. However, because it is unable to improve penetration, emulsion is the best choice. By adding it into the gel, emulsion's stability issue can be avoided. A blend of emulsion and gel is called emulgel. Emulgels have many advantages, including being greaseless, environmentally friendly, translucent, appealing in appearance, easily spreadable, quickly removable, thixotropic, emollient, water-soluble, non-staining, and having a longer shelf life. [7].

   Acne vulgaris is one of the most prevalent chronic skin conditions. Acne vulgaris gradually develops from mild acne's initial stage. There are several acne treatments available, however they all cause scarring and skin pigmentation in the affected area. One sign of post-acne hyperpigmentation, a type of hyperpigmentation, is this darker skin. Acne and hyperpigmentation can be effectively treated with azelaic acid. Emulgel will be a good option as a cutting-edge pharmacological approach to address this issue, nevertheless, as Azelaic Acid is a Class IV drug with low permeability and solubility.

It's challenging to get the drug to work from a dosage due to the medication's restricted solubility and permeability. When this sort of medication is administered as a cream, ointment, lotion, or emulsion, stability and bioavailability problems develop. Only the gel formulation does not produce the desired outcomes. As a result, the unique emulgel concept is developed, which involves combining an emulsion with a gel to increase delivery and stability. Due to the drug's incorporation in the oil phase of the emulsion in emulgel and the emulsion's improved stabilization in the gel, the interaction of the two phases results in a controlled release effect that increases the medication's bioavailability. Emulgel has a number of characteristics that will expand the options for topical pharmaceutical distribution in the future, with improved efficacy and reduced production costs.

2. **S. J Berlitz, D. D Villa et al. (2019)** reported the synthesis of azelaic acid (AzA)-loaded nanoemulsion with hyaluronic acid (HA) as a double targeting strategy to increase drug retention and tyrosinase inhibition activity and development of new technologies that allow a deeper penetration in the skin while enhancing the efficacy of a safe and well-known dermatological active agent, like AzA, is a very promising alternative to improve the treatment of this disease.[10]

The vast majority of whitening medications used to treat melasma is tyrosinase inhibitors. An essential enzyme in the synthesis of melanin is tyrosinase [11-15]. To boost tyrosinase inhibition and, hence, decrease melanin synthesis, it is required for the depigmenting topical formulation to penetrate the stratum corneum (SC) barrier and regulate drug permeation/penetration and skin accumulation to the skin layer where melanocytes are present.

By controlling drug release, changing drug permeation/penetration behavior, and extending skin permanence, nanotechnology has the potential to enhance the development of whitening formulations [16]. However, the developed formulation must have acceptable Nano technical properties while maintaining stability, low toxicity, and presenting a suitable clinical sensory profile for the patient to comply with the treatment.

The antibacterial, anti-inflammatory, antikeratinizing, antioxidant, and depigmenting properties of azelaic acid make it a useful depigmenting agent. Melasma is treated with it. Additionally, it can be used to treat rosacea and acne [17-19]. While many depigmenting agents can aid with melasma, a difficult-to-treat hyperpigmentary disorder, there is presently no nanoscale formulation that is especially made to increase therapeutic efficacy and enhance medication skin retention. In order to bypass the stratum corneum (SC) barrier and improve drug skin retention, this research aims to develop a new treatment for hyperpigmentary skin disorders, particularly melasma, that uses an AzA-loaded nanoemulsion created

with nanotechnology and hyaluronic acid (HA). The HA in the formulation served as an adjuvant rather than being encapsulated. AzA's depigmenting effectiveness may be improved by the suggested nanosystem's improved drug retention in the viable epidermis and dermis.

A kind of hyperpigmentation that affects the skin is dermic melasma. Therefore, enhancing the efficacy of a safe and well-known dermatological active agent, such as AzA, while allowing for deeper penetration into the skin is a very promising approach for treating this disease.

Without inducing cytotoxicity, the developed nanoemulsion penetrated the skin, reached the epidermis, and reached the dermis. It also suppressed tyrosinase activity. According to the sensory evaluation profile, the product was easier to spread and left behind less whitening residue. The nanoemulsion demonstrated nanoscale characteristics, penetrating deeper skin layers, and improving in vitro tyrosinase inhibition, indicating that it would be a potential treatment for dermic melasma.

3. Hung W.H, Chen P.K, Fang C.W, Lin Y.C, Wu P.C et. al (2021) reported the method of preparation and evaluation of Azelaic acid topical microemulsion formulation. The design of oil in water (O/W) microemulsion formulations for the topical delivery of azelaic acid is demonstrated in this study. To evaluate the effectiveness of the created formulations, studies on the permeability of azelaic acid through rat skin and the anti-inflammatory properties of the formulations were done. Using O/W microemulsions as carriers greatly enhanced the permeability of azelaic acid [20].

Microemulsion is a promising nanocarrier for the topical delivery of insoluble therapeutic compounds [21-25]. With just a little gentle stirring, the formulation, which consists of the water phase, surfactant, and co-surfactant, can be formed. A combination of surfactants, co-surfactants, and co-solvents can be used to solubilize oil molecules in order to create spontaneously occurring oil in water (O/W) microemulsions [26,27]. The formulation is less greasy and simpler to remove from the applied locations because water makes up the continuous phase. In this study, azelaic acid solubilization was increased while skin permeability was raised by using O/W microemulsions as a drug carrier. In this study, drug carriers were utilized to increase the solubility and permeability of azelaic acid, including isopropyl myristate, cremophor EL, and trancutol microemulsions [28-31].

The permeability of azelaic acid was significantly improved by the microemulsion carrier. The microemulsion formulation's ingredients changed how well the medicine could penetrate the skin. The formulation of the drug-loaded microemulsion was extremely stable and did not significantly irritate the skin. The results suggest that the O/W microemulsion might work well as a topical drug delivery system for azelaic acid.

4. N. Khairudin, M. Basri, H.R Fard Masoumi et al. (2018) reported the methods of enhancing the bioconversion of azelaic acid to its derivatives by Response surface methodology**.** Acne and other

cutaneous hyperpigmentary disorders can both be successfully treated with azelaic acid (AzA) and its derivatives. Azelaic acid and lauryl alcohol (LA) were esterified to create dilaurylazelate utilising immobilised lipase B from Candida antarctica (Novozym 435). For the purpose of improving the reaction conditions, response surface methodology was used [32].

The efficacy of azelaic acid derivatives in the treatment of various dermatological and cosmetic disorders involving inflammation, bacterial and fungal infections can be achieved through the modification of azelaic acid, leading to the production of a derivative of azelaic acid (dilaurylazelate ester) with even better properties than the original starting material. The technical characteristics and functional performance of the modified azelaic acid have been enhanced by the covalent ester linkage and conversion of at least one carboxylic acid group into the ester group [33].

Modified azelaic acid was used as a prodrug to show the effectiveness of azelaic acid derivatives in the treatment of various cutaneous hyperpigmentary disorders and acne vulgaris. By changing the hydrophilic-lipophilic balance of the prodrug, the bioavailability of several drugs has been significantly increased. The development of numerous prodrugs has increased bioavailability [34]. Manipulation of physicochemical features to increase the rate of diffusion into the skin barrier would be one way to improve drug efficacy via the dermal route. The development of prodrugs [35,36] is a novel method. Prodrugs improve or facilitate drug transport over or into the skin by adding a cleavable chemical group to the drug, which often enhances its lipophilicity. Because the prodrug strategy is based on changing the structure of the drug, prodrugs rarely cause skin irritation [37].

The versatile and mostly used biocatalysts which are usually employed for the direct synthesis of esters are lipases [38]. The active site of lipases is protected by a helical oligopeptide unit known as the lid or flap. Serine, histidine, aspartate, and a carboxylic acid residue make up the active site (aspartic or glutamic acid). When a hydrophobic interface, such as a lipid droplet, interacts with the lid, it experiences a conformational change that exposes the catalytic site to complete access of the reaction substrate. Candida antarctica lipase B (CalB), on the other hand, has an open active site and no true lid. CalB therefore shows no interfacial activations or conformational changes in which a lid area is removed to reveal the active site. Candida antarctica lipase B has been discovered to have significant catalytic activity for esterification of dicarboxylic acids [39].

In general, a lipase Candida antarctica (Novozym 435) catalysed esterification reaction to produce dilaurylazelate ester was successfully optimised using the response surface technique. In the lab, a high conversion rate of 95.38 percent was achieved. In light of the economic and environmental concerns, it is possible to scale up the enzymatic synthesis of dilaurylazelate ester in the future employing RSM

techniques. The research showed that dilaurylazelate ester is interestingly antimicrobial and non-toxic when compared to AzA, making it safe for use in medical applications.

5. Sara Al-Marabeh, Enam Khalil, Mohammad Khanfar, Amal G. Al-Bakri & Muhammed Alzweiri et al. (2016) reported the prodrug approach to enhance azelaic acid percutaneous availability. It had never been documented to use prodrugs to improve azelaic acid diffusion via skin. To increase the percutaneous availability of azelaic acid, a lipophilic prodrug of the compound (diethyl azelate) was created and studied [40].

The prodrug technique has been frequently used to increase bioavailability by changing the hydrophilic-lipophilic balance of a medication. To improve the bioavailability of medications like acetylsalicylic acid, metronidazole, 5-fluorouracil, and others, numerous prodrugs have been created [41, 42, 43]. However, The impact of azelaic acid on topical diffusion throughout the skin was not mentioned. In this study, azelaic acid's ethanolic ester is made in order to study how it impacts azelaic acid diffusion through the skin. Calculations were made for the solubility and partition coefficient. The amount of prodrug that has penetrated is measured using a vertical Franz-diffusion cell. *In vitro* testing was done on the prodrug's and parent drug's antibacterial properties.

By controlling their pharmacokinetic properties, the use of a prodrug method enhanced the topical delivery of medications. According to the results of this investigation, a lipophilic azelaic acid prodrug can boost the topical administration of the parent medication. Azelaic acid permeability was successfully boosted by the DEA prodrug, according to a silicone membrane diffusion investigation. Because of this, azelaic acid therapeutic dosages may need to be reduced to have the same keratolytic effect. Chemical stability, cleavage susceptibility, and inactivity against microbes were all essential requirements met by DEA for a topical prodrug. Strong evidence suggests that DEA is kept inside the stratum corneum layer. To validate DEA depot development inside the SC, more research and in vivo clinical investigations are needed.

6. E. Burchacka, P. Potaczek, P. Paduszynski, K. Karlowicz-Bodalska, T. Han, S. Han et al. (2016) reported the formulation of azelaic acid liposomal gel with enhanced pharmaceutical bioavailability. This study compares the bioavailability of the active ingredient azelaic acid in newly created liposomal hydrogel (lipogel) versus commercially existing products. This study finds increased active substance bioavailability, stability, and antimicrobial preservation in the liposomal gel formulation of azelaic acid [44].

Azelaic acid's anti-inflammatory and anti-bacterial properties against acne bacteria (Propionibacterium acnes) invading skin pores are well recognized [45]. Additionally, azelaic acid decreases the production of neutrophil free radicals, which is advantageous for melasma and post-inflammatory hyperpigmentation. It is highly advantageous to incorporate active pharmaceutical ingredients into gel

formulations like hydrogels or liposomal hydrogels (lipogels). Such gel-formula formulations exhibit a number of advantages in clinical trials, with higher bioavailability appearing to be the most efficient in terms of supplemental active pharmaceutical ingredient (API) dose requirements [46]. Additional yet highly favourable characteristics of hydrogels for topical therapeutic use include a moderate chilling feeling when applied to the skin and their capacity to evaporate, resulting in a drying impact on the skin, which is particularly helpful in the treatment of acne infection [47]. The essential functional component of liposomal hydrogels are liposomes, small vesicles composed of various type of phospholipids, which have been used for many years to bring active ingredients into the skin [48-53]. These are frequently utilised as drug carriers that regulate the release of the therapeutic agent, but they can also deliver the medicine to specific skin appendages or generate a localised (API) deposit in the skin to reduce systemic effects [49].

Liposome-skin interactions and their effects on drug concentration permeability in the skin are influenced by the lipids that make up the liposome membrane and the particle size of liposomes [54-57]. Liposomes derived from soybean phospholipids were used for the azelaic acid lipogel composition disclosed in this report. This type of liposomal formulation is able to essentially increase the percutaneous absorption rate of API in the stratum corneum without uncontrolled skin penetration, as was previously reported for hydrocortisone-loaded liposomes, which when applied topically, could act as a selective drug delivery system with reduced adverse systemic effects [58].

The developed liposomal hydrogel formulations with azelaic acid as the active ingredient have excellent API bioavailability and the necessary stability for such preparations, making them suitable for use in a range of lipogel formulations for the treatment of skin diseases like rosacea, acne vulgaris, and skin hyperpigmentation. Liposomal formulations enable a significant drop in API concentration while maintaining the same therapeutic impact as other commercially available formulations due to their increased delivery efficacy.

According to this study, the formulation and content of liposomal gel containing azelaic acid exhibit higher pharmacological bioavailability when compared to a 20 percent cream. The created preparation was skin-friendly because it had appropriate physical qualities. No preservatives are necessary because antimicrobial preservation tests demonstrate that the formulation is appropriate. The formulation therefore functions effectively as an API carrier. The product's quality is influenced by the technological process used to create the formulation, according to the formulation's bioavailability results.

7. D.S. Malik, G. Kaur et al. (2018) reported the synthesis of nanostructured gel for topical delivery of azelaic acid: Designing, characterization, and in-vitro evaluation. In order to improve skin targeting, retention, and prolonged release while lowering drug-related adverse effects, this study focuses on the formulation, development, and testing of azelaic acid-loaded nanostructured lipid carriers (NLCs). Melt

emulsification and ultrasonication are used to create NLCs. The produced gel is found to be non-irritating, homogeneous, and to have the ideal moisture content, spreadability, and occlusivity. In-vitro penetration testing showed that NLC preparation considerably increased the dug's skin retention compared to drug suspended in gel and commercial preparations [59].

Various cosmeceutical treatments for acne (targeting one or more etiological factors) are available on the market, but none of them have been shown to be successful. These treatments range from retinoids, antibiotics, and benzoyl peroxides to contraceptives, steroids, and spironolactone. Their limited clinical use is due to the side effects of standard therapy, which include skin erythema, photosensitivity, bacterial resistance, hyperpigmentation, dryness, thrombosis, gastrointestinal distress, and adrenal suppression [60-66].

A novel technique will be needed to create a reliable system with enhanced medicine penetration and skin targeting. As a second-generation lipid carrier, NLCs are a stable, biodegradable system that can transport significant quantities of bioactives. According to these methods, medications are administered gradually, with better tissue targeting and little skin absorption, preventing adjuvant negative effects. The development of a secure and efficient delivery mechanism for the treatment of acne vulgaris may therefore benefit from azelaic acid-loaded NLCs.

For the purpose of developing a secure alternative preparation with enhanced therapeutic effect, this work comprises formulation, optimization, and evaluation of innovative nano systems (NLCs) loaded with azelaic acid. NLCs were modified using design expert software to achieve the lowest size and greatest entrapment. The optimised preparation was then added to the carbopol gel carrier made of aloe vera. The formulation was then subjected to physiological, morphological, stability, in-vitro permeation, and skin dispersion tests.

It is necessary to consider a number of formulation variables and their effects on particle properties when developing and optimizing NLCs. The researchers created an azelaic acid-loaded colloidal system using melt emulsification and ultrasonication (NLCs). The ability of the NLC formulation to permeate the skin and hold the medication there for a long time was proven by microscopic studies. Based on the study's findings, it can be said that NLC-based aloe-gels offer a great deal of potential for enhancing azelaic acid skin penetration and retention for effective acne vulgaris treatment.

Conclusion

Azelaic acid is a straight-chained, saturated, dicarboxylic acid. Acne, rosacea, acne vulgaris, lentigo maligna, and malignant melanoma are all treated with azelaic acid. Antibacterial, anti-inflammatory, anti-microbial, and anti-keratinizing properties are all demonstrated by azelaic acid. Acne and hyperpigmentation can be effectively treated with azelaic acid. However, because azelaic acid is a

medicine with low permeability, solubility and bioavailability. Several studies and experiments have been conducted in order to increase the permeability of azelaic acid and to overcome the problems associated with it. So, this review has covered various studies and researches on azelaic acid.

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