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(REVIEW ARTICLE)

An updated review on acne

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Abstract

Acne is a common chronic inflammatory skin disorder that affects individuals of all ages, particularly during adolescence. It is characterized by the formation of comedones, papules, pustules, and, in severe cases, nodules and cysts. While acne is primarily associated with the pilosebaceous unit, its pathogenesis involves multiple factors, including hormonal imbalances, increased sebum production, abnormal follicular keratinization, and the colonization of Propionibacterium acnes.This review aims to provide an updated understanding of acne, focusing on its pathogenesis, clinical presentation, and current management strategies. The pathogenesis of acne involves complex interactions between hormones, sebum production, follicular keratinization, and inflammation. Various predisposing factors, such as genetic susceptibility, diet, and environmental influences, also contribute to the development and exacerbation of acne. Management of acne encompasses a multifaceted approach, including topical and systemic therapies. Topical agents such as retinoids, benzoyl peroxide, and antibiotics target different aspects of acne pathogenesis, helping to normalize follicular keratinization, reduce inflammation, and inhibit bacterial growth. Systemic therapies, including oral antibiotics, hormonal agents, and isotretinoin, are often used for moderate to severe cases or those resistant to topical treatments. Additionally, this review highlights emerging therapies and advancements in acne management. Recent research has explored novel treatment options such as laser and light-based therapies, photodynamic therapy, and the use of probiotics and botanical extracts. These interventions show promise in targeting specific aspects of acne pathogenesis and reducing treatment-related adverse effects. Furthermore, the psychological impact of acne and its influence on quality of life are discussed. Acne can significantly affect an individual's self-esteem, body image, and social interactions, underscoring the importance of a holistic approach to patient care. In conclusion, this updated review provides a comprehensive overview of acne, including its pathogenesis, current treatment strategies, and emerging therapies. Understanding the multifactorial nature of acne and staying abreast of advancements in its management will help healthcare professionals provide effective and individualized care to patients suffering from this common dermatological condition.

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research has explored novel treatment options such as laser and light-based therapies, photodynamic therapy, and the use of probiotics and botanical extracts. These interventions show promise in targeting specific aspects of acne pathogenesis and reducing treatment-related adverse effects. Furthermore, the psychological impact of acne and its influence on quality of life are discussed. Acne can significantly affect an individual's self-esteem, body image, and social interactions, underscoring the importance of a holistic approach to patient care. In conclusion, this updated review provides a comprehensive overview of acne, including its pathogenesis, current treatment strategies, and emerging therapies. Understanding the multifactorial nature of acne and staying abreast of advancements in its management will help healthcare professionals provide effective and individualized care to patients suffering from this common dermatological condition.

Keywords: Acne vulgaris; Treatment of acne; Propionibacterium acne; Pathogenesis of acne; Management strategies of acne; Clinical presentation of acne; Psychological impact of acne

1. Introduction

1.1. Transdermal therapeutic drug delivery system

Transdermal drug delivery systems (TDDS), commonly referred to as "patches," are medication dosage forms that deliver a regulated distribution of an amount of medication across a patient's skin that is therapeutically effective. Due to its distinctive benefits, such as longer therapeutic efficacy, avoidance of first-pass metabolism, and simple therapy termination, TDDS has attracted intentional consideration for either local or systemic drug administration. Rate-controlling membranes, drugs, penetration enhancers, adhesives, backing laminates, release liners, etc. are the core elements of TDDS. TDDS are divided into reservoir, matrix, and microreservoir systems based on their architectural differences. [1]

People have applied substances to the skin for medicinal purposes for thousands of years, and in the modern period, numerous topical formulations have been created to address regional medical issues. [2]

It provides a number of benefits, including a longer therapeutic impact, fewer side effects, increased bioavailability, better patient compliance, and simple medication therapy cessation. The appendageal, transcellular, and intercellular pathways are the three main ways that drugs can enter the body. When giving medication by this route, it is important to consider the following aspects: skin age, condition, physicochemical characteristics, and environmental conditions. [3]

The phrase "transdermal delivery system" broadly refers to any medicine formulation applied topically with the goal of releasing the active component into the bloodstream. Transdermal therapy systems have been created to offer controlled continuous drug administration to the systemic circulation through the skin. [4]

This method has also been utilised to administer a variety of medications, including hydrophilic and hydrophobic substances. [5]

Drugs may be effectively made available throughout the body with TDDS. Transdermal patches are cutting-edge drug delivery methods that are applied to the skin to provide a systemic effect. The use of the TDDS system has various clinical advantages over alternative methods. [12]

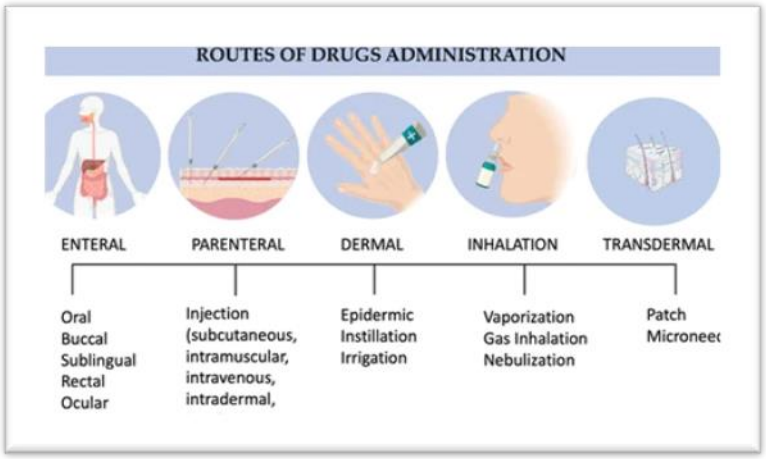

Figure 1 The principal drug administration routes. [12]

It offers reliable medication release, maintains a stable blood level profile, which might lessen systemic side effects, is practical, user-friendly, and helps to increase patient acceptance. Drugs that are continuously absorbed over an extended period of time don't need to be dosed as frequently, which improves patient compliance. [6]

In order to improve the transdermal delivery and dermal absorption of drugs, a variety of strategies have been used. These include increasing the effective concentration of the drug in the vehicle, improving the partitioning between the formulation, using chemical penetration enhancers, and using various physical enhancement techniques. The use of carrier systems such as liposomes, nanoparticles, and microparticles has also been investigated. [7,8]

Nanomaterials offer substitutes for common transdermal medication delivery methods, including patches, gels, sprays, and lotions, but it's important to comprehend how such methods work. [9]

Cutaneous formulation keeps drug levels within the therapeutic range for an extended length of time, making sure they don't drop below the minimum effective concentration or rise above the maximum effective concentration. [10]

Figure 2 Marketed available transdermal patches. [13]

A transdermal patch, also known as a skin patch, is an adhesive patch that is applied to the skin and contains medication that is intended to be absorbed into the bloodstream through the skin. The pace at which the liquid medicine housed in the reservoir within the patch can pass through the skin and into the bloodstream is controlled by a specific membrane used in skin patches. In order to utilise some medications in a skin patch, they must be mixed with other substances, such as alcohol, because alcohol increases their ability to permeate the skin. [11]

1.2. Advantages of transdermal therapeutic system [14,15,16]

- Preventing a drug's first-pass metabolism

- Transdermal drugs provide a consistent infusion of a medicament over a long period of time
- The streamlined drug schedule improves patient compliance, lowers side effects, and reduces both intra- and inter-patient variability.
- No disruption of the digestive and gastrointestinal fluids
- Keeps blood levels consistent, constant, and under control for a longer period of time.
- They can prevent problems with gastrointestinal medicine absorption.
- They can take the place of oral medicine administration when it is not appropriate.
- Limited side effects and a localised effect.
- Enhancing medication bioavailability and decreasing dosage frequency.
- Keeping medication delivery profiles constant
- Characteristics that are similar to those of intravenous infusion.

1.3. Disadvantages of transdermal therapeutic system [17]

- A number of drugs, particularly those with hydrophilic properties that penetrate the skin too slowly, may not be effective at therapeutic levels.
- Erythema, itching, and localised edema may be brought on by the medication, the adhesive, or any excipients in the patch formulation.
- The skin's barrier function varies with age, from one location to another on the same individual, and also from person to person.
- Ionic medicines cannot be delivered via TDDS.
- High drug levels cannot be achieved via TDDS in the blood or plasma.
- It is impossible to build TDDS for medications with enormous molecular weights.
- Pulsatile drug delivery is not possible with TDDS
- A medicine or formulation cannot be used to create TDDS if it irritates the skin.

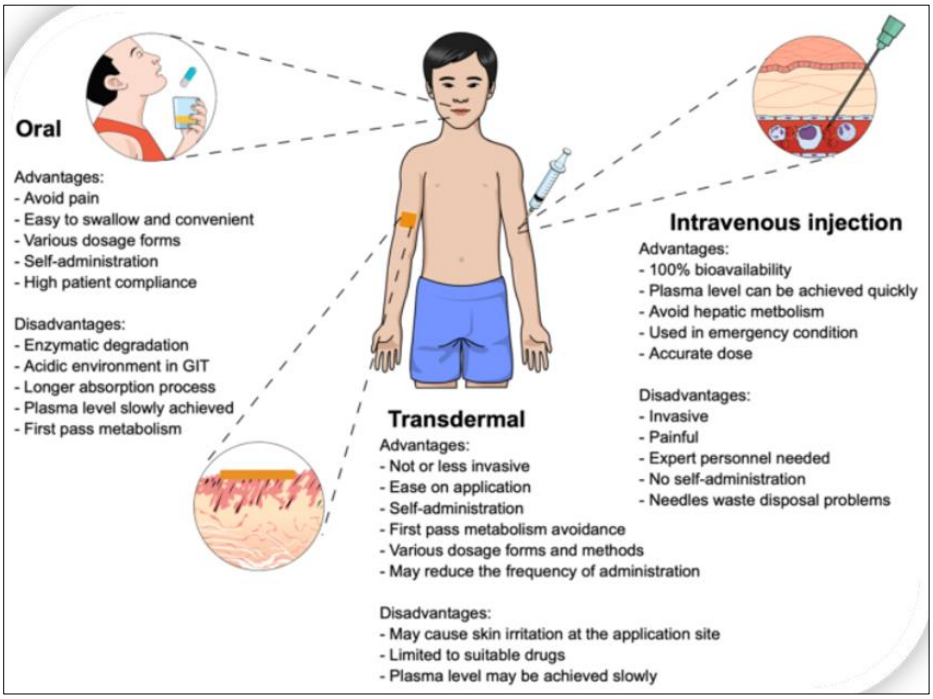

Figure 3 Comparison and Contrast of three different medication administration methods

Compares and contrasts the three different medication administration methods mentioned below in brief:

The following situations call for the usage of transdermal patches:

- When a patient experiences uncomfortable side effects including dysphagia and constipation.
- Any situation in which effective management could result in better pain control.

- It can be combined with other enhancing techniques to have an additive effect.

1.4. Transdermal drug penetration through skin [18,19,20]

1.4.1. Physiology of Skin

Despite being a big and sensible target for medication administration, the skin's utility for this purpose is limited by its fundamental activities. The skin's primary roles are to shield the body from outside threats (such dangerous substances and bacteria) and to hold all bodily fluids in place. It must be durable while still being pliable enough to allow for movement. Our skin's lipids act as weak electrical conductors and, if necessary, can shield us from electric current. The skin also aids in controlling body temperature.

The epidermis and dermis are two crucial layers of the human skin. Drugs must cross the two sublayers of the epidermis during transdermal administration in order to reach the dermis' microcirculation.

The stratum corneum, also known as the horny layer, is the skin's top layer and, depending on the area of the body, can range in thickness from 10 microns to several hundred microns. It is made up of layers of flattened, dead keratinocytes surrounded by a lipid matrix, which together form an impenetrable brick-and-mortar system.

The most important barrier to diffusion is provided by the stratum corneum. In fact, 90% of transdermal medication administrations are blocked by the stratum corneum. But almost all molecules manage to permeate it just a little bit. The viable epidermis is found underneath the stratum corneum. Although this layer is nearly 10 times as thick as the stratum corneum, diffusion moves through it considerably more quickly because the viable epidermis's living cells are more hydrated.

It contains Langerhans cells, which serve as the immune system's antigen-presenting cells. The distribution of vaccines by transdermal delivery will target these cells. The viable epidermis contains melanocytes, which give skin pigmentation. The dermis, which is located below the epidermis and is one millimetre thick, is 100 times thicker than the stratum corneum. The skin's microcirculation, which distributes medications into the systemic circulation and controls temperature, is a system that is found in the dermis. A lymphatic network and sensory neurons are also present in the dermis. There has not been a lot of study done on the lymphatic removal of medications that are applied transdermally.

The medications enter the systemic circulation via two primary routes that cross the skin. "Transcellular pathway" refers to the fastest path. Drugs cross the skin through this pathway by going right through the cytoplasm and phospholipid membranes of the dead keratinocytes that make up the stratum corneum. Despite being the fastest route, the medicines face a lot of resistance during penetration.

This is to ensure drugs can pass through each cell's lipophilic membrane, its hydrophilic keratin-containing interior, and finally its phospholipid bilayer one more time. To cover the entire thickness of the stratum corneum, this series of procedures is repeated several times. Some medicines have the ability to pass through this method.

The intercellular route is the more frequent method via the skin. The passage of drugs via the skin and the narrow gaps between the skin cells make this route more difficult. The actual diffusion path of the majority of molecules penetrating the skin is on the order of 400 m, despite the stratum corneum having a thickness of just approximately 20 m. The rate of drug penetration has been significantly reduced by the 20-fold increase in the real path of permeating molecules.

The follicular route to drug penetration is a less significant channel. The stratum corneum is penetrated by hair follicles, providing more direct access to the dermal microcirculation. However, just 1/1000 of the total skin surface is taken up by hair follicles. As a result, virtually little medication enters the body through the follicular pathway.

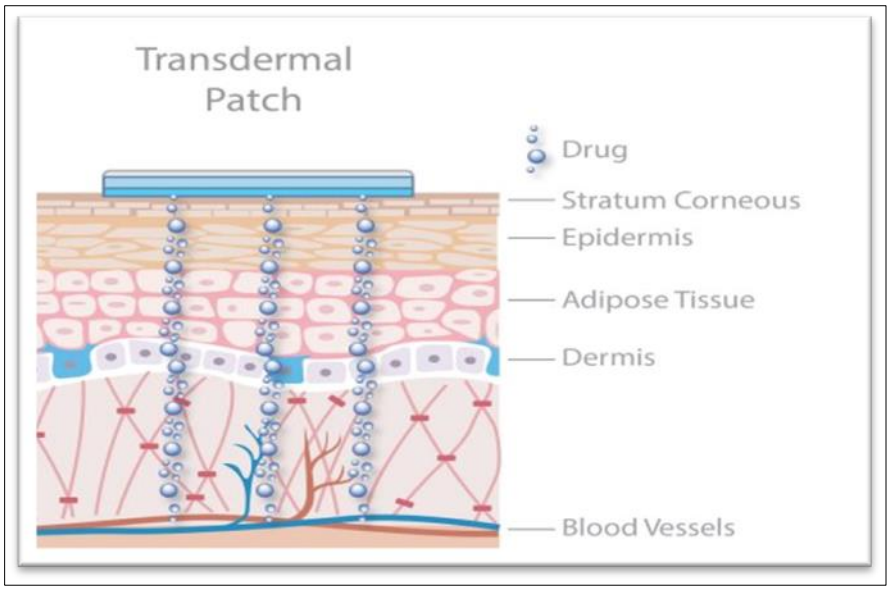

Figure 4 Diagram of Skin Along with Transdermal Patch

1.5. Types of transdermal patch [21]

1.5.1. Single layer drug in adhesive

In this form, the medicine is included in the sticky layer. The release of the medicine to the skin is accomplished by the adhesive layer, which also acts to cling the several layers together. There is a backer and a temporary liner around the adhesive layer.

1.5.2. Multi-layer drug in adhesive

This type is comparable to the single layer but includes an immediate drug release layer in addition to the adhesive layer, which makes it different from other layers that will have a controlled release.

Vapour patch

The adhesive layer in this kind of patch serves as an exchange, which is frequently utilized to release essential oils in decongestion, in addition to holding the other layers together.

1.5.3. Reservoir system

In this technique, a membrane that controls flow rate and an impervious backing layer are sandwiched together to form the drug reservoir. Only through the membrane that regulates release rate does the medication release. The medication can be in a solution, suspension, gel, or dispersed in a solid polymer matrix in the drug reservoir compartment.

1.6. Layers and materials of transdermal patches [22]

The layers that are frequently found in transdermal patches are listed below, along with the material factors for each layer:

1.6.1. Drug formulation

Let's begin with the drug formulation layer, which is composed of the medication or secondary compound that is absorbed into the skin by a transdermal patch. There are various ways to form the formulation:

In the typical reservoir design, the medication formulation is enclosed between the backing and membrane layers.

Formulations are separated by an additional membrane layer if numerous medications are required at various dosages or diffusion speeds.

Drug-in-adhesive patches combine the drug's dry powder with the adhesive.

A polymer matrix reservoir is yet another technique for delivering the medication directly to the skin.

The additional layers of the transdermal patch will be influenced by the kind and quantity of medication formulations.

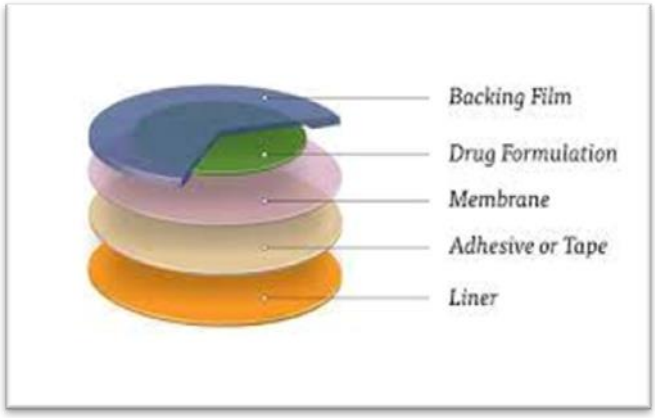

Figure 5 Layers of transdermal patch [22]

1.6.2. Backing

The backing's main function is to keep the patch's integrity safe. In effect, a pouch is formed around the drug formula layer by the material's sealing to the membrane layer. Additionally, the backing might have branding or product information printed on it.

We advise weighing factors including patient comfort, structural integrity, and aesthetic appeal when selecting a backing material.

1.6.3. Membrane

In transdermal patches with multiple layers or reservoirs, a membrane is frequently employed. The membrane regulates how quickly the drug formulation diffuses into the skin. Considerations to make when choosing materials for transdermal patch membranes include permeability, flexibility, thickness, history of use, and the ability to be directly fused to adhesives.

1.6.4. Skin tapes and adhesive

The transdermal patch's adhesive or tape layer is essential since adhering to skin can be difficult and delicate. Skin-friendly tapes offer dependable adherence and are biocompatible to shield the user from discomfort or harm. These are also known as medical adhesives or medical tapes.

1.6.5. Release liner

The transdermal patch's release liner has the responsibility of safeguarding the adhesive (and, in certain cases, the drug formulation) until the transdermal patch is prepared for application to the user. It is essential that the release liner is simple to remove and that the release is constant from lot to lot and throughout the lifespan of the product. Several skin-friendly adhesives, such as silicone, acrylate, and polyisobutylene (PIB), can be used with release lining materials. The release liner shouldn't interact in any way with the drug formulation in DIA transdermal patches.

1.7. Methods for preparation of transdermal drug delivery system

1.7.1. Asymmetric TPX membrane method

A heat sealable polyester paper (type 1009, 3 m) with a concave of 1 cm diameter will be employed as the backing membrane to create a prototype patch. Asymmetric TPX poly-(4-methyl-1-pentene) membrane is used to cover a concave membrane, which is subsequently attached using an adhesive. [23]

1.7.2. Circular Teflon mould method

Solutions with different ratios of polymers are utilised in an organic solvent. Half as much of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solvent is used to dissolve enhancers at various concentrations before they are applied. The plasticizer di-N butylphthalate is included in the drug polymer solution. The entire mixture is agitated for 12 hours before being placed into a Teflon mould. In a laminar flow hood model with a speed of 0.5 m/s, the moulds are put on a flat surface and covered with an inverted funnel to control solvent vaporisation. For 24 hours, the solvent is allowed to evaporate. Before evaluation, the dried films are kept for a further 24 hours at 250.5°C in a desiccator containing silica gel to remove ageing effects. [24]

1.7.3. Mercury substrate method

The technique involves dissolving the medication and plasticizer in a polymer solution. Pour the solution into a levelled mercury surface, cover with an inverted glass vial, and agitate for 10 to 15 minutes to create a homogeneous dispersion for managing the evaporation of solvent. [25]

1.7.4. IPM membrane method

This approach involves mixing the medicine with water and propylene glycol to dissolve it, then stirring the mixture for 12 hours in a magnetic stirrer. Triethanolamine is to be added in order to neutralise the dispersion and make it viscous. If the drug's solubility in aqueous solution is particularly poor, buffer pH 7.4 can be employed to create solution gel. The gel that has been created will be integrated into the IPM membrane. [26]

1.7.5. EVAC membrane method

1% Carbopol reservoir gel, polyethylene (PE), and ethylene vinyl acetate copolymer (EVAC) membranes can be employed as rate control membranes to prepare the target transdermal treatment system. Propylene glycol is used to make gel when the medication is not soluble in water. Propylene glycol is used to dissolve the drug, Carbopol resin is then added to the mixture, and the mixture is then neutralised using 5% sodium hydroxide solution. The medication is applied to a backing layer sheet that covers the designated region and is in the form of a gel. To create a leak-proof device, a rate-controlling membrane is placed over the gel, and the edges are heated to seal them. [27]

1.7.6. Aluminium backed adhesive film method

If the loading dose is larger than 10 mg, transdermal drug delivery systems may result in unstable matrices. The method of using adhesive film with aluminium backing is appropriate. Chloroform is the preferred solvent for its manufacture because it is soluble in the majority of medications and adhesives. The medicine is dissolved in chloroform, and then adhesive material is added and dissolved in the drug solution. Aluminium foil lines a custom-made aluminium former, which has its ends blanked off with tightly-fitting cork blocks. [28]

1.7.7. Preparation using proliposomes

Proliposomes are created utilising the film deposition technique and the carrier approach. The proliposomes are made by adding 5 mg of mannitol powder to a 100 ml round bottom flask that is heated to 60–70°C, rotating the flask at 80–90 rpm, and vacuum-drying the mannitol for 30 minutes. After drying, the water bath's temperature is set to 20–30 °C. In an appropriate organic solvent mixture, the drug and lecithin are dissolved. A 0.5 ml aliquot of the organic solution is added to the round-bottomed flask at 37°C, and when the solution has dried completely, a second 0.5 ml aliquot of the solution is to be added. Following the final loading, the flask containing the proliposomes is attached to a lyophilizer. The drug-loaded mannitol powders (proliposomes) are then put in a desiccator overnight and sieved through a 100mesh screen. the obtained powder is moved to a glass bottle and kept at a freezing temperature. [29]

1.7.8. Free film method

Coating on the surface of the mercury creates an open layer of cellulose acetate. Utilising chloroform, a 2% weight-to-weight polymer solution is to be created. Plasticizers must be added at a 40% weight-to-weight (w/w) concentration in the polymer. In a glass petri dish with mercury on the surface, 5 ml of polymer solution was added to a glass ring. An inverted funnel is positioned above the petri dish to control the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is observed to detect the film formation. The dried film will be sorted out and kept in a desiccator between the wax paper sheets until it is needed. The volume of the polymer solution can be changed to create free films of various thicknesses. [30]

1.8. Transdermal bioavailability-affacting factors [31,32]

1.8.1. Physical-chemical variables

Skin hydration

The permeability of skin rises dramatically when it comes into touch with water. The most crucial aspect in promoting skin permeability is hydration. Therefore, humectant usage occurs during transdermal administration.

1.8.2. Temperature and pH

With temperature change, drug permeability increases, with a drop-in temperature, the diffusion coefficient falls. Depending on the pH and pKa or pKb values, weak acids and bases separate. The amount of medication in skin is based on the percentage of unionized drug. Thus, a significant factor impacting medication penetration is temperature, along with pH.

1.8.3. Diffusion coefficient

Drug diffusion coefficient affects drug penetration. The features of the drug, the diffusion medium, and their interactions determine the drug's diffusion coefficient at a constant temperature.

1.8.4. Drug concentration

The flux is inversely correlated with the gradient of concentration across the barrier, and the gradient will be bigger if the drug concentration is higher across the barrier.

1.8.5. Partition coefficient

For effective action, the ideal partition coefficient (K) is needed. High K drugs are not yet ready to leave the lipid layer of skin. Additionally, low-K medicines won't permeate the body.

1.8.6. Molecular size and shape

Drug absorption and molecular weight are unfavourably associated; tiny molecules enter more quickly than large ones.

1.8.7. Biological factors

Skin condition

Acids, alkalis, and several solvents, including methanol and chloroform, harm skin cells and encourage penetration. Skin problems change depending on the patient's state of illness. Although the skin is a better barrier when it is intact, the aforementioned factors affect penetration.

Skin age

Younger skin is more porous than older skin. Children have more sensitive skin when it comes to toxin absorption. Consequently, one of the factors influencing medication penetration in TDDS is skin age.

Blood flow

Transdermal absorption may be influenced by changes in peripheral circulation.

Regional skin site

Site differences include differences in appendage density, stratum corneum type, and skin thickness. All of these variables have a big impact on penetration.

Skin metabolism

Steroids, hormones, chemical carcinogens, and some medicines are all processed by the skin. Therefore, skin metabolism determines how well a medicine penetrates the skin.

Species differences

The penetration is affected by the thickness, density, and keratinization of the skin, which differ from species to species.

Important characteristics of TDDS [33]

Table 1 Characteristics of TDDS

Properties	**Description**
Shelf life	2 years
Patch size	<40 cm^2
Dose frequency	Once daily or once a week
Aesthetic appeal	Transparent
Packaging	removing the release liner is simple, and applying it only requires a few steps.
Skin reaction	Neither irritating nor sensitive
Release	pharmacokinetic and pharmacodynamic features remain constant
Dose	Low
Half life	Less than 10
Molecular weight	< 400
Skin reaction	Non-irritant and non-sensitive
Therapeutic index	Low

2. Review of literature

2.1. Literature review regarding Transdermal Patches

Chudasama. Arpan, Patel. Vineet kumar, et.al, (2011), reported that: For topical distribution, a novel oil-in-water microemulsion-based (ME) gel with 1% itraconazole (ITZ) was created. The particle size distribution and morphology of the optimised microemulsion were examined. For easy application, the optimised microemulsion was added to polymeric gels made of Lutrol F127, Xanthan gum, and Carbopol 934, and its pH, drug content, viscosity, and spreadability were assessed. The optimised microemulsion's droplet size was discovered to be 100 nm. The pH range for the improved Lutrol F 127 ME gel was 5.68–0.02 and the spreadability was from 5.75–1.396 gcm/s. It was discovered that the viscosity of ME gel was 1805.535542.4 mPa s. ITZ was observed to permeate (flux) from the produced ME gel at a rate of 4.234 g/cm/h. The drug release from ME ITZ gel was demonstrated by the release profile as being controlled by diffusion. There was no erythema or edema, and the generated ME gels were non-irritating. With Lutrol F127 ME gel, ITZ's antifungal activity shown the largest zone of inhibition. These findings suggest that the investigated ME gel may provide promise as a topical delivery method for ITZ. [34]

Zeng. Wen-Sheng, Fang. Xia-Qin et.al, (2012), reported that: Itraconazole, a lipophilic medication, was used as a model drug in the preparation of drug-loading transfersomes so that the main factor influencing transfersome quality could be identified and evaluated. The film dispersion method was used to create drug-loading transfersomes. HPLC, a transmission electron microscopy, a particle size analyzer, and in vitro release were used to assess the transfersomes' quality. With a mean entrapment efficiency of about 80%, transfersomes were a translucent solution of an ivory white colour. The hollow vesicles exhibited a good transdermal action because of their spheroidal shape, which had a diameter of about 100 nm and a zeta potential of 45 mV. The quality of transfersomes is found to be highly influenced by solvent, salt ion concentration, homogenization pressure, and other factors, according to a single-factor analysis. The preparation technique developed through formulation and technology optimisation and screening is workable, and the quality can be managed. [35]

Wagh. Vijay D, Deshmukh. Onkar J et.al, (2012), reported that: Potential uses for niosomes include topical medication delivery systems. The formulation and assessment of the Itraconazole niosomes were the study's main goals. Utilising

a factorial design, the ratio of surfactant to cholesterol and the amount of ethanol utilised were investigated. The vesicle size, entrapment effectiveness, drug release, skin penetration, and antimycotic efficacy of synthesised niosomes were assessed. The ratio of surfactant to cholesterol and the amount of ethanol utilised had a significant impact on the size of the vesicles, entrapment effectiveness, and drug release. The formulation's cholesterol level has an impact on the drug's ability to pass through skin. When activity was tested against C. albicans, itraconazole niosomes had a greater zone of inhibition than the formulation that was commercially available. Due to their straightforward manufacturing, niosomes may be a potential carrier for the topical administration of itraconazole. [36]

Zeng. Wen-Sheng, Fang. Xia-Qin et.al, (2012), reported that: Itraconazole, a lipophilic medication, was used as a model drug in the preparation of drug-loading transfersomes so that the main factor influencing transfersome quality could be identified and evaluated. The film dispersion method was used to create drug-loading transfersomes. HPLC, a transmission electron microscopy, a particle size analyzer, and in vitro release were used to assess the transfersomes' quality. With a mean entrapment efficiency of about 80%, transfersomes were a translucent solution of an ivory white colour. The hollow vesicles exhibited a good transdermal action because of their spheroidal shape, which had a diameter of about 100 nm and a zeta potential of 45 mV. The quality of transfersomes is found to be highly influenced by solvent, salt ion concentration, homogenization pressure, and other factors, according to a single-factor analysis. The preparation technique developed through formulation and technology optimisation and screening is workable, and the quality can be managed. [37]

Mohamed. Salama, Eid. Masoud Mustafa Ahmad, et.al, (2013), reported that: This paper's preparation and evaluation of several polymeric films for the treatment of fungus infections was its main goal. By using the solvent casting approach, several Eudragit polymeric films containing the antifungal medication itraconazole were created. The phsico-mechanical characteristics of the produced films, such as tensile strength, physical endurance, elasticity, water vapour permeability, and water loss, were evaluated. It was investigated how Itraconazole was released from the produced medicated films. In comparison to alternative topical dosage forms, such as ointments and gels, the results showed that films created with Eudragit RL 100 containing hydroxyl propyl methyl cellulose caused the highest release of itraconazole both in vitro and in vivo. Additionally, the films serve as an easy and practical technique for treating numerous fungal infections. Itraconazole, a broad-spectrum antifungal medicine used to treat dermatophytosis, was included in polymeric films, and as a result, it showed more promising outcomes in the treatment of dermatophytosis. [38]

Sampathi. S, Mankala. S K, et.al, (2015), reported that: The goal of the current work was to create an itraconazole nanoemulsion and nanoemulsion-based hydrogel for transdermal delivery in the treatment of chomycosis. Lecithin and sodium cholate were used as the surfactant and co-surfactant in the creation of the nanoemulsions. The produced nanoemulsions were evaluated for zeta potential and particle size. To create a gel for easier superficial application, the optimised nanoemulsion was mixed with 3% carbopol-934 solution. Using a dialysis membrane and rat skin, in vitro and ex vivo drug penetration investigations of nanoemulsions and gels were conducted. The range of the particle size was between 223.9 nm and 154.3 nm. The nanoemulsions' and nanoemulsion gel's viscosities were discovered to be between 1964.89 mPa.S. and 1644.82 mPa.S. and 28.3 mPa.S. to 8.58 mPa.S., respectively. The very low polydispersibility value discovered indicates that the formulations' droplet sizes are homogenous. Gels had a drug concentration ranging from 86.2% to 98.26%. After 24 hours, it was discovered that the medication released between 44.33% and 73.6% with a permeation flux of between 296.3 and 203.1 (g/cm2/hr1). The findings suggested that hydrogels based on nanoemulsions are a potential delivery system for itraconazole. To determine whether it is appropriate for topical use, additional in vivo investigations must be carried out. [39]

Choudhury. Hira, Gorain. Bapi, (2017), reported that: Nanoemulgel, a new transdermal delivery method, has demonstrated unexpected advantages for lipophilic medicines over conventional formulations. The bulk of the more recent medications created in this day and age are lipophilic, which causes low oral bioavailability, unpredictable absorption, and pharmacokinetic changes. In order to prevent these disturbances, it has been demonstrated that this unique transdermal delivery technique is superior to traditional oral and topical drug administration methods. These nanoemulgels are essentially oil-in-water nanoemulsions that have been made to gel using a gelling agent. This formulation's gel phase is non-greasy, which encourages user compliance and stabilises the product by lowering surface and interfacial tension. Additionally, it can bypass first-pass metabolism, target the site of action more precisely, and free the user from gastric/systemic incompatibilities. This succinct review is focused on nanoemulgel as a superior topical drug delivery technology, including the screening of its components, the formulation process, and recent pharmacokinetic and pharmacodynamic development in research studies conducted by scientists all over the world. As a result, it can be concluded from the results of this study that nanoemulgel may be a more superior and efficient drug delivery mechanism for the topical system. [40]

Tejas. B Patel, Tushar. R Patel, et.al, (2018), reported that: The study's goal is to make it easier for itraconazole to pass through skin. Eucalyptus oil, tween 20, and methanol were used as the oil phase, surfactant, and co-surfactant in the preparation of the microemulsion, respectively. Pseudo-ternary phase diagrams were created to determine the ideal oil ratio: Water: Smix (surfactant: Co-Surfactant). The prepared microemulsion was optimised using a 32 complete factorial design. The microemulsion's globule size, zeta potential, in-vitro diffusion studies, etc. were all analysed. Zeta potential measurements and globule size results showed that ME7 had higher stability than other microemulsion formulations. Transdermal flux and%Q6 were chosen as dependent variables for the optimisation. The results of the optimisation investigation further showed that ME 7 was an optimised microemulsion for high skin permeability. Additionally, ME7 was contrasted with a commercially available isoniazid formulation (ITASPORE) and assessed using similarity factor F2. The fact that the F2value was nowhere close to 100 showed that the diffusion patterns of ME7 and ITASPORE are not identical. Thus, indirectly, it implies that the preparation of the microemulsion boosted the drug's permeability. [41]

Goyal. Kumar Manoj and Kureshi. Junaid (2019), reported that: Potential uses for niosomes include topical medication delivery systems. Since they can alter pharmacokinetics and bioavailability as well as lower toxicity, niosomes play an increasingly significant role in drug delivery. It can serve as a drug reservoir, and altering the vesicular composition or surface characteristics can change how quickly the drug is released and how affinely it binds to the target location. A triazole derivative called itraconazole is effective in treating a variety of fungus infections. This comprises paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, blastomycosis, and aspergillosis. It can be administered intravenously or orally. By employing cholesterol as a stable vesicle-forming ingredient and span 20, 40, 60 as a non-ionic surfactant, it was possible to create itraconazole niosomes. Different drug ratios were used in the synthesis of niosomes: cholesterol is a surfactant (1:1:1, 1:2:1, and 1:3:1). Vesicle size, surface appearance, % entrapment efficiency, drug content, and in vitro drug release were all assessed for the niosomal dispersion. Using a UV spectrophotometer, the entrapment effectiveness and drug content were determined at 262 nm. The entrapment efficiency for the formulations ITZ 20-3, ITZ 40-2, and ITZ 60-1 was determined to be 57.2%, 73.2%, and 61.2%, respectively. Utilising Carbopol 940, glycerol, triethanolamine, and distilled water, itraconazole niosomal gel was created. Physical appearance, pH, viscosity, drug content, entrapment effectiveness, and in-vitro permeation investigations were used to evaluate niosomal gel. For ITZG-2, 55.67% of the medication was observed to be released from the niosomal gel. The current study shows that when Itraconazole in is encapsulated in niosomal topical gel, the drug release is prolonged, the amount of drug retained in the skin increases, and the penetration of the drug across the skin is improved. [42]

Passos. Julia Sapienza, Martino. Luiza Capello de, et.al, (2020), reported that: We studied nanostructured lipid carriers (NLC) as topical delivery systems to increase itraconazole localization in skin lesions and link efficacy with decreased systemic exposure in light of the increased incidence of sporotrichosis and other fungal infections in rural and urban areas, as well as the limitations and side effects of oral itraconazole therapy. NLC therapy showed the ability to localise itraconazole within the skin by reducing trans epidermal water loss, an indicator of cutaneous barrier function, by 23–36% in intact skin and in tissues injured with a linear incision (to simulate lesions). According to values of 0.5 and 0.6 in HET-CAM models, respectively, and lack of toxicity (measured by survival and health index) on the Galleria mellonella larvae, the unloaded and itraconazole-loaded NLC were regarded as safe. On Sporothrix brasiliensis yeasts, 0.25 and 32 g/mL were found to be the minimal inhibitory concentration and minimum fungicidal concentration, respectively. Similar values were shown by the medication in solution, showing that encapsulation had no influence on the antifungal properties of itraconazole. The survival rate and health index of G. mellonella larvae infected with S. brasiliensis yeasts and C. albicans were both enhanced by NLC treatment, suggesting the effectiveness of the antifungal. When taken as a whole, itraconazole encapsulation in NLC is a workable method to improve cutaneous localization without reducing its effectiveness against fungus. [43]

Thakre Durgesh, Saxena Swati, et.al, (2020), reported that: The current study's objectives were to examine the potential of itraconazole transdermal distribution using transfersomal gel formulations and to assess the impact of lipid, ethanol, medication, and stirrer time concentrations. Using vesicle size, surface charge, entrapment effectiveness, and stability studies, transfersomes are characterised. Measurements of viscosity, pH, drug content, extrudability, spreadability, and in vitro drug diffusion are used to characterise transfersomes that include gel. The synthesised gel's viscosity was determined to be 3240cps, its extrudability to be 145g, and its spreadability to be 9.85 (g.cm/sec), respectively. Franz diffusion cell method was used to test the in vitro drug release from transfersomes, and results showed 92.230.21% in 12 hours. A slightly high 12.250.32% drug release occurred in the first 30 minutes. It was brought on by the free medication that had been present in the bag and had been leached from transfersomes. Very regulated and prolonged drug release from transferosomal formulations was observed. Itraconazole-loaded transfersomal formulation was added to the produced gel, which was then optimised for topical preparation of the antifungal effect. The outcomes demonstrated that transdermal delivery with targeted and sustained drug release using transfersomal gel was a potential choice. It also makes several medications more permeable via the skin. [44]

Kumar. Neeraj, Goindi. Shishu et.al (2021), reported that: A novel formulation of itraconazole-loaded nanosized liposomes (NLPs) for efficient topical delivery against superficial fungus infections was to be statistically developed as the study's main goal. Target formulation was created by thin-film hydration, and it was optimised using a two-step design of experiments (DoE) strategy, which included a fractional factorial design for screening 'vital few' factors and response surface mapping optimised with a fractional factorial and 32 full factorial designs of experiments. To produce the optimised ITZ loaded NLPs (OPT-NLPs) suspension, overlays of response maps for percent drug entrapment (PDE), vesicle size, ITZ skin retention, and penetration were done. To make the liposome suspension easier to apply topically, it was gelled. High PDE (78.69 3.17%) was demonstrated by the OPT-NLP formulation, and average vesicle sizes of 358.2 9.45 nm and mean zeta potentials of 20.66 0.74 mV were noted. Additionally, compared to ITZ conventional cream and oily solution, excised rat skin had considerably higher ITZ skin retention (44.39 1.32 g/cm2) and cumulative 6-h drug permeation (14.81 0.48 g/cm2). Additionally, a conventional Tinea pedis animal model was employed to assess the in vivo antifungal efficacy seen in terms of the physical symptoms, fungal-burden score, and histological profiles. Compared to animals treated with commercial topical and oral antifungal treatments, optimised hydrogel-treated animals showed a rapid reduction in infection. [45]

Sheridy. EL, Nabila. A, et.al, (2022), reported that: Skin cancer could potentially be treated orally with the antifungal medicine itraconazole (ITC), which also has anticancer properties. Topical ITC is clinically necessary to treat low-risk skin carcinogenesis. Our goal was to create ITC nanoformulations with improved antitumor effectiveness. The development of lipid Nano capsules (LNC), either unmodified (ITC/LNC) or modified with either the lipopeptide biosurfactant surfactin (ITC/SF-LNC) or the amphiphile miltefosine as bioactive additions. Small diameter (42–45 nm), good ITC entrapment effectiveness (>98%), and sustained ITC release were all characteristics of LNC formulations. An LNC formulations significantly improved ITC anticancer activity and selectivity for cancer cells, according to cytotoxicity experiments utilising malignant SCC 9 cells and normal human fibroblasts (NHF). These investigations also showed a synergistic ITC-amphiphile interaction that improved the performance of the combination. When intradermal tumor-bearing mice were treated with ITC nanoformulations gels as opposed to ITC and 5-FU gels, the tumour growth was significantly inhibited, and ITC/MF-LNC and ITC/SF-LNC also helped the skin architecture recover. The suppressive impact of LNC formulations on cytokeratins was superior to that of 5-FU, and it considerably reduced tumoral production of the proliferative proteins Ki-67 and cytokeratin. These results give additional evidence for effective topical therapy for low-risk skin carcinogenesis using several strategies, including medication repurposing, nanotechnology, and formulation-enhancing bioactive amphiphiles. [46]

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topical therapy for low-risk skin carcinogenesis using several strategies, including medication repurposing, nanotechnology, and formulation-enhancing bioactive amphiphiles. [48]

2.2. Literature Review regarding fungal Acne Vulgaris

Preneau S and Dreno B (2011), reported thatThe prevalence of female acne is rising; it is currently believed to be between 40% and 50%. This study's goal was to provide a comprehensive review of recent findings on the clinical and epidemiological dimensions of female acne in order to determine if female acne should be classified as a distinct subtype of acne from teenage acne. When discussing female acne, the age of 25 is most usually mentioned. Most frequently, the face is the main area affected by light to moderate acne. There are two distinct clinical forms: the inflammatory type, which is more common and characterized by papulo-pustules and nodules on the lower portion of the face, and the retentional form, which features blackheads and tiny cysts along with hyperseborrhoea. Regarding its evolution, it is divided into three subtypes, of which two are more common than the others: the most common form, known as "continue acne," which occurs from adolescence to adulthood, and the less common form, known as "late onset acne," which appears after the age of 25. Two basic theories can be put out at the physiopathological level. Female acne would require a specific global diagnostic and therapy protocol, and in the future, it would need to be evaluated independently from teenage acne when considering a new medicine. [49]

K. Bhate and H.C. Williams (2012) reported that: Observational studies must distinguish between characteristics that may be linked to acne's onset and those that have an impact on its severity, which could affect how it is treated. To support additional meta-analytical work in all elements of acne epidemiology work, it is necessary to examine the evidence of dietary factors in acne more closely in cohort and experimental studies. [50]

Vyas Amber, Kumar Sonker Avinesh, et.al, (2013), reported that: Conventional topical methods have a number of negative side effects. The negative effects of medications frequently used in the topical treatment of acne have been reduced by the use of novel drug delivery methods. Active pharmaceutical ingredients (API) used in topical acne treatment establish direct contact with the target location prior to entering the bloodstream, which lessens the systemic negative effects of parenteral or oral drug administration. Carrier system-based formulations offer effectiveness, tolerability, compliance, and cosmetic acceptability. The employment of cyclodextrin-based carriers and their delivery systems will be more advantageous in the future because it covers a dual strategy that takes advantage of both systems and results in the development of safe and efficient formulations that are affordable, save time and labor, and are cost-effective. [51]

Christos C and Zouboulis (2014), reported that: The severity and distribution of acne on the skin can fluctuate over time, and it can also be a physically (scars can form) and mentally destructive condition that lasts for years. It can be classified as a chronic disease under the standards of the World Health Organisation based on its clinical features. Acne is also a cardinal component of many systemic diseases or syndromes, such as congenital adrenal hyperplasia, seborrhea-acne-hirsutism-androgenetic alopecia syndrome, polycystic ovarian syndrome, hyperandrogenism-insulin resistance-acanthosis nigricans syndrome, Apert syndrome, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, and pyogenic arthritis-pyoderma gangrenosum-acne syndrome. [52]

Fox Lizelle, Csongradi Candice, et.al (2016), reported that: Four well-known pathogenic variables that contribute to acne are the focus of acne treatment. The use of complementary and alternative medicines (CAM) as well as topical (retinoids, antibiotics, and hormonal) and systemic (retinoids, antibiotics, and hormonal) treatments are all covered as therapy options for acne. Physical therapies include comedone removal, cryotherapy, electrocauterization, intralesional corticosteroids, and optical treatments are also an option. [53]

Souto Eliana B., Fernandes Ana Rita (2020) reported that: Dermatologic changes that develop as a result of exposure to environmental variables (such as chemical products, pollution, infrared, and ultraviolet radiations) or as a result of ageing that occurs naturally over time are referred to as dermatologic alterations. The primary structural proteins responsible for skin strength and elasticity, collagen and elastin, are produced less as we age, yet their participation in skin rejuvenation can have a wrinkle-reversing impact. The use of nanomaterials packed with cosmeceuticals (such as phytochemicals, vitamins, hyaluronic acid, and growth factors) has emerged as an intriguing alternative to traditional methods of tissue regeneration. A number of cosmeceutical and pharmaceutical products are currently on the market that attempt to reduce the indications of ageing skin. These products are based on their bioactivities and use various Nano formulations as effective delivery mechanisms. [54]

Sousa Filipa, Ferreira Domingos et.al, (2020), reported that: The most recent techniques that have been researched to enhance antifungal therapy and lessen the negative effects of traditional medications. It also explains the reciprocal

relationship between mycology and nanotechnology. The emphasis is also on novel marine compounds with demonstrated antifungal activity that may serve as platforms to identify drug-like properties, emphasising the difficulties in bringing these natural compounds into the clinical pipeline. [55]

Mejía Susana P and Sánchez Arturo (2021), reported that: Due to drug interactions during coinfections and the emergence of microbial resistance, which restricts the use of currently available medicines, infectious disorders brought on by intracellular microorganisms pose a substantial challenge to medical care. In order to tackle intracellular infections, itraconazole (ITZ) was encapsulated into useful polymeric nanoparticles for targeted and controlled release. Overall, in vitro tests demonstrated the effectiveness of the Nano system to destroy the Histoplasma capsulatum fungus and open the door to the development of extremely effective nanocarriers for the delivery of drugs against intracellular infections. [56]

Kaur Anureet and Kaur Lakhvir et.al, (2022), reported that: Although acne is not a dangerous condition, it has a significant impact on the physical and psychological well-being of patients due to their fear of developing permanent scars, decreased self-esteem, despair, avoidance of social situations, and even suicidal tendencies. The primary treatment for the majority of kinds of acne vulgaris is topical retinoids. Applications of retinoids for anti-acne therapy are restricted by poor water solubility in combination with physical or chemical instability. By increasing the solubility, stability, lowering skin irritation, promoting drug targeting, and increasing therapeutic efficacy, nano formulations of retinoids can solve several issues related to conventional retinoid formulations. This review elaborates on the formulation, characterisation, and in vivo/in vitro testing of specific nanoparticles loaded with retinoids with the goal of translating the results of the literature into prospective benefits. [57]

Judy Lalrengpuii and Kaisar Raza et.al, (2022) reported that: The skin condition known as acne vulgaris is brought on by the blockage of hair follicles with dead skin cells and skin oils. The primary treatment for the majority of kinds of acne vulgaris is topical retinoids. Applications of retinoids for anti-acne therapy are restricted by poor water solubility in combination with physical or chemical instability. By increasing the solubility, stability, lowering skin irritation, promoting drug targeting, and increasing therapeutic efficacy, nano formulations of retinoids can solve several issues related to conventional retinoid formulations. formulating, characterising, and evaluating specific nanoparticles loaded with retinoids in vivo and in vitro with the aim of interpreting the literature's findings into possible promises. [58]

3. Conclusion

A myriad of treatment choices is available to treat adult female patients with acne. Treatment options should be tailored to the individual patient with considerations for the patient's preferences, tolerability of the agent, and psychosocial factors. A relatively limited number of options are available for the management of acne during pregnancy and lactation. However, the level of evidence on the safety of any therapies during pregnancy and lactation is low. Novel agents continue to be developed to treat patients with AV, which will further enhance the clinician's care of patients with this impactful and prevalent disease.

Compliance with ethical standards

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Disclosure of Conflicts of interest

The authors have no conflicts of interest to declare.

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