Transdermal Nanoparticle System for Anti-inflammatory drug

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***Abstract*—Inflammation is a natural immune response to infection or injury, but long-term inflammation can cause diseases such as autoimmune disorders, neurodegenerative diseases, and cancer. Many anti-inflammatory drugs like Aspirin and NSAIDs are available, and new treatments such as biological drugs, anti-cytokine therapies, and kinase inhibitors are being developed. Transdermal nanoparticle-based drug delivery systems are a promising method to improve treatment. Nanoparticles help drugs pass through the skin barrier, improve drug stability, and provide controlled drug release. This increases treatment effectiveness and reduces side effects. Nanoparticle-loaded Ibuprofen gels show better skin penetration, improved drug stability, and stronger anti-inflammatory effects compared to conventional formulations. Therefore, nanoparticle-based transdermal delivery systems are a promising approach for effective inflammation treatment. Future research will focus on developing safer and more advanced nanocarriers to improve drug delivery and patient compliance.**

***Index Terms*—Transdermal drug delivery, Nanoparticles, Anti-inflammatory drugs, Nanocarriers, skin, Permeation, Controlled drugs.**

I. INTRODUCTION

Inflammation is a slow, long-lasting process that can hang around for months or even years. How much it affects you usually depends on what caused the damage and how well your body can fix itself.[1] These events, along with the release of chemical signals that attract cells.[2] In the early stages of this response, the process is quickly started by signal triggers controlled by specific messenger proteins. The most important of these proteins are tumour necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6). These messengers turn on different pathways that help white blood cells stick to where they are needed and rush to the site of the problem.[3] Inflammatory diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease are characterized by excessive immune responses and chronic inflammation in affected tissues.[4] These diseases involve the release of inflammatory mediators such as cytokines and prostaglandins, which play a key role in the development and progression of inflammation.[5] Conventional oral or injectable anti-inflammatory therapies are commonly used for treatment; however, they often produce systemic side effects and may undergo first-pass metabolism in the liver, reducing drug bioavailability.[6]Anti-inflammatory drugs are widely used to reduce inflammation, relieve pain, and prevent tissue damage. These drugs work by inhibiting inflammatory mediators such as cytokines, prostaglandins, and leukotrienes that are responsible for the inflammatory response.[7] NSAIDs, like Ibuprofen and Aspirin, are common medicines used to reduce swelling and relieve pain. [8] New breakthroughs in medicine have created better ways to fight swelling and pain. Instead of general treatments, these new medicines called biological agents, cytokine inhibitors, and kinase inhibitors act like "precision tools." They target the specific parts of the body that cause redness and irritation. This gives people with long-term health issues much better options for feeling healthy.[9] Conventional routes of drug administration such as oral and injectable routes are widely used for the treatment of inflammatory diseases. However, these routes have several limitations that may reduce therapeutic effectiveness and patient compliance [10]

A. Gastrointestinal Side Effects: Taking anti-inflammatory medicines (like Ibuprofen or Aspirin) by mouth often causes problems in the stomach and

digestive tract. These issues include stomach irritation, the development of sores called ulcers, and even internal bleeding. This happens because the medicine blocks the body's ability to create "prostaglandins," which are natural chemicals that usually protect the stomach lining from its own acid. For example, drugs such as Aspirin and Ibuprofen can cause damage to the gastric mucosa when used for long periods.[11]

B. First-Pass Metabolism: When you swallow a pill, it doesn't go straight to the part of your body that hurts. Instead, it must first pass through your liver. The liver acts like a security guard or a filter, breaking down a large portion of the medicine before it ever reaches your bloodstream. This process is called first-pass metabolism. Because the liver "eats up" so much of the drug, the actual amount of medicine left to help you known as bioavailability is much lower than what you originally swallowed. To make up for this loss, doctors often have to give you a higher dose. However, taking a higher dose can be risky because it increases the chance of having bad side effects in other parts of your body.[12]

C. Poor Patient Compliance: Traditional ways of taking medicine often require people to take multiple doses throughout the day to keep enough of the drug in their system to work properly. Because of these busy schedules and the risk of unpleasant side effects, many patients find it difficult to stick to their treatment plan. This is especially challenging for people with long-term illnesses who must take medicine for months or years, as they are more likely to miss doses or stop the treatment altogether.[13] When people struggle to follow their treatment plan, the medicine becomes less effective, making it much harder to keep their illness under control. Because of the problems with traditional pills and shots, scientists are developing new ways to get medicine into the body, such as skin patches or tiny "nanoparticle" systems. These modern methods are designed to help more of the medicine reach the right spot, lower the risk of bad side effects, and make it much easier for patients to stay on track with their treatment.[14]

Transdermal Drug Delivery (TDD) is a painless way to deliver drugs to the whole body by applying a drug preparation on healthy, unbroken skin.[15] The drug first passes through the stratum corneum (outer skin layer), then moves through the deeper epidermis and dermis without collecting in the dermis. When it reaches the dermis, it enters the blood through the small blood vessels there and becomes available for absorption throughout the body [16] Transdermal drug delivery systems (TDDS), also called patches, are dosage forms made to deliver an effective amount of medicine through a patient's skin. To deliver medicine through human skin for effects in the whole body, the structure and physical and chemical properties of the skin must be considered. Transdermal delivery has advantages over injections and oral medicines because it improves patient comfort and avoids first-pass metabolism in the liver.[17] Transdermal delivery provides controlled and continuous delivery of a drug. It also allows continuous supply of drugs that have a short biological half-life and prevents sudden entry of large amounts of drug into the bloodstream, which can cause unwanted side effects. Because of this, different novel drug delivery systems were developed, such as Transdermal drug delivery systems (TDDS), controlled release systems, and transmucosal delivery systems.

Important advantages of transdermal drug delivery are:

1. avoiding first-pass metabolism in the liver
2. improving therapeutic effect
3. maintaining a steady drug level in the blood

The first transdermal system, Transderm Scōp, was approved by U.S. Food and Drug Administration in 1979 to prevent nausea and vomiting during travel, especially sea travel. Evidence that a drug is absorbed through the skin can be shown by: measurable drug levels in the blood detection of the drug and its metabolites in urine.[18]

Nanoparticles are extremely small particles produced by advanced technological modification of matter. Their size is only a few times larger than an atom, which results from molecular-level processing of materials. Because they have improved properties such as self-reactivity, stability, and the ability to self-assemble, they can easily adapt and be modified to obtain specific desired properties, such as a high surface area compared with conventional materials.[19] Nanotechnology is one of the fastest-growing fields of scientific research and development, with major progress being made in many applications. At present, nanotechnology is used in several areas such as electronics, energy, materials science, and

biomedicine. In electronics, researchers are studying nanoscale transistors and other tiny components to make devices smaller, faster, and more energy-efficient. In energy, nanotechnology helps develop new materials and devices for solar energy conversion, energy storage, and other uses. In biomedicine, it is used to create new diagnostic tools, treatments, and tissue engineering methods. Overall, nanotechnology is a highly active and rapidly developing field, with many new applications expected in the future. Nanoparticles and nanomaterials are also being widely studied for medical use. One of the most promising applications is drug delivery, where nanoparticles act as carriers to deliver drugs to specific cells or tissues in the body. Nanoparticles can be designed with special surface properties that help them target diseased cells while avoiding healthy cells, which improves drug effectiveness and reduces side effects. [20]

II. SKIN STRUCTURE AND BARRIER OF TRANSDERMAL DELIVERY

Think of your skin as a massive, multitasking shield it's the largest organ you have. Its main job is to protect you from things like germs and chemicals while keeping your body temperature steady and preventing you from getting dehydrated. In the world of medicine, we use Transdermal Drug Delivery (TDDS) to send medication through the skin so it can treat a specific area or enter your bloodstream. The catch? Your skin is actually too good at its job. Its tough outer layer acts like a security gate, making it very difficult for many drugs to pass through and get where they need to go.[21]

2.1. Structure of Skin: The skin is made up of three main layers: the epidermis, the dermis, and the hypodermis. Each of these layers has its own unique build and specific job, which together create the skin's protective wall and manage how it functions.[22]

2.1.1. The Epidermis:

The epidermis is the very top layer of your skin and is mostly made of cells called keratinocytes. It is actually built like a stack of several smaller layers: the stratum basale, stratum spinosum, stratum granulosum, and the tough surface layer called the stratum corneum. This entire section acts as a shield to protect you from the outside world and acts as a "security guard" that controls which substances can enter or leave your body.[23]

2.1.2. The Dermis

The dermis sits right under the epidermis and is made of connective tissue filled with collagen and elastin fibers, which give your skin its strength and stretchiness. This layer is also home to your blood vessels, nerves, sweat glands, and hair follicles. For medicine, this layer is a major goal: once a drug successfully travels deep enough to reach the dermis, it can be picked up by the tiny blood vessels (capillaries) and carried throughout your entire body. [24

2.1.3. The Hypodermis: The hypodermis, often called the subcutaneous tissue, is the deepest part of your skin. It is mostly made of fat (adipose tissue) and connective tissue. Its main jobs are to act as a layer of insulation to keep you warm, provide a soft cushion for your body, and offer physical support to the layers of skin sitting above it.[25]

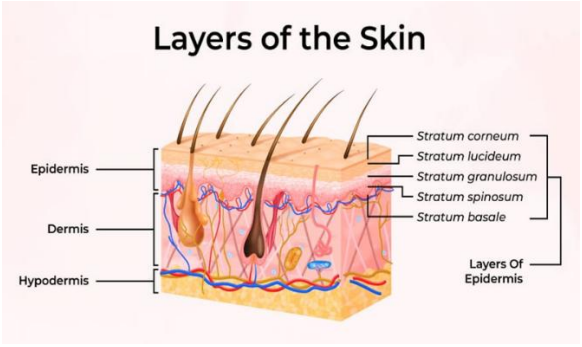

Fig.2.1 Structure and Layers of Skin [26]

2.2 The Skin Barrier

2.2.1. The Role of the Stratum Corneum:

The stratum corneum is the very top layer of your skin (the epidermis), and it acts as the main "security wall" that stops medicine from getting inside. You can think of its structure like a "brick and mortar" wall: the "bricks" are dead, tough skin cells, and the "mortar" is a layer of fats (lipids) that holds them together. This tight design makes it very hard for water-loving (hydrophilic) or large molecules to pass through, which is why it is the biggest obstacle for any skin-applied drug.[27] Because this wall is so effective, only certain types of drugs those that are the right size, can dissolve in fats, and are strong enough in small doses can get through on their own. To help other medicines cross this finish line, scientists use special

"keys" or tools. These include chemical enhancers to soften the barrier, nanoparticles to carry the drug, or microneedles to create tiny, painless paths through the surface.[28]

2.3 Drug Permeation Pathways:
Medicines can soak into the skin using different "routes" depending on what the drug is made of and how the medicine is designed.
2.3.1. The Transcellular Route (Through the Cells):
In this path, drug molecules go straight through the skin cells of the stratum corneum. This is a tough journey because the drug has to pass through both the watery (hydrophilic) and oily (lipophilic) parts of the cell. Because it has to switch between these different environments, it is considered a complicated way to travel.[29]
2.3.2. The Intercellular Route (Between the Cells):
In this path, drugs wiggle through the fatty "glue" (the lipid matrix) that sits in the spaces between the skin cells. This is usually the most common way for medicine to get through the skin's surface because it can follow these oily channels all the way down without having to break into the cells themselves.[30]
2.3.3. The Appendageal Route (Through Openings):
This route uses the skin's natural "back doors," like hair follicles and sweat glands, to get inside. Even though these openings cover only a tiny part of your total skin surface, they are very important for certain types of medicine and for tiny high-tech carriers called nanoparticles.[31]

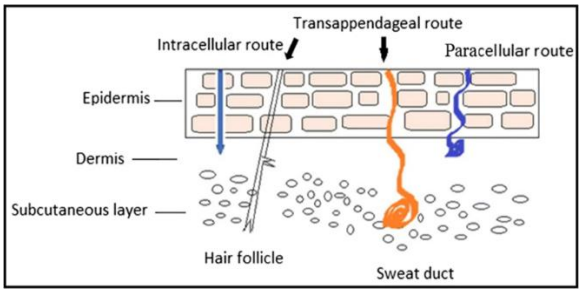

Fig.2.2 Drug permeation Pathways [32]

III. NANOPARTICLE SYSTEMS USED IN TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery means delivering medicine through the skin into systemic circulation. The main barrier is the Stratum corneum, which prevents many drugs from entering easily. Nanoparticles help by increasing penetration, improving stability, and controlling release of drugs.

3.1. Solid Lipid Nanoparticles (SLN)
SLN are very small particles made from lipids that remain solid at body temperature. The drug is trapped inside this solid lipid matrix.
Composition:
A) Solid lipids (glyceryl monostearate, stearic acid, cetyl palmitate)
B) Surfactants (polysorbate, lecithin)
C) Water

Advantages:
- Protect drug from degradation
- Controlled and sustained release
- Improve skin hydration by forming a thin lipid film

Application in anti-inflammatory drug delivery:
- SLN improve skin penetration of anti-inflammatory drugs such as:
- Diclofenac, Ibuprofen
- These formulations reduce gastric side effects and maintain drug action for longer. Nanoparticle Systems Used in Transdermal Drug Delivery [33]

3.2. Nanostructured Lipid Carrier (NLC)
NLC are improved lipid nanoparticles made by mixing solid lipid with liquid lipid (oil). This creates small imperfections inside the particle, allowing more drug to be loaded.
Composition:
A) Solid lipid
B) Liquid lipid (oil)
C) Surfactant

Advantages:
- Higher drug loading than SLN
- Less drug leakage
- Better skin penetration

Application:
Used for anti-inflammatory drugs like:
A) Celecoxib
B) Meloxicam [34]

3.3. Polymeric Nanoparticles
These nanoparticles are made from biodegradable polymers. Drug is either enclosed inside or attached to the polymer surface.

Composition:
A) Chitosan
B) PLGA
C) Alginate

Advantages:
- Controlled drug release
- Good stability
- Increased contact with skin
- Can target deeper skin layers

Application:
Useful for anti-inflammatory and antifungal drugs.[35]

3.4. Liposome & Niosome
Both are vesicles that carry drug inside tiny spherical structures.
Liposome: Made of phospholipids.
Niosome: Made of non-ionic surfactants.

Advantages:
- Carry both water-soluble and fat-soluble drugs
- Improve skin penetration
- Reduce toxicity
- Good local drug retention

Application:
Used for:
A) Hydrocortison
B) Diclofenac [36]

3.5. Nanoemulsion
Nanoemulsion is a very fine mixture of oil and water with very small droplets.
Composition:
A) Oil
B) Water
C) Surfactant
D) Co-surfactant

Advantages:
- Improves drug solubility
- Fast skin absorption
- Easy to prepare

Application:
Used for:
A) Ketoprofen
B) Diclofenac [37]

3.6. Dendrimers
Dendrimers are highly branched nano-sized polymers with many surface groups that can carry drug molecules.
Advantages:
- High drug loading
- Improve drug solubility
- Controlled release
- Surface can be modified easily

Application: Used in Anti- inflammatory and peptid Drug Delivery.[38]

IV. MECHANISM OF NANOPARTICLES IN ENHANCING SKIN PENETRATION

Think of nanoparticles as tiny delivery vehicles. Because they are so incredibly small and have special physical features, they are great at carrying medicine through the skin.
The biggest challenge for any cream or patch is the stratum corneum, which is the tough, waterproof outer layer of our skin that acts like a wall to keep things out. Nanoparticles are designed to get past this wall using a few different tricks. Some are small enough to slip through the tiny gaps between skin cells, while others interact with the skin's natural oils to soften the barrier, making it easier for the medicine to sink in deeper and work more effectively. [39] Nanoparticles are commonly used in skin creams and medical patches because their tiny size and special physical traits help medicine pass through the skin's surface. The stratum corneum (the tough outer layer of skin) usually acts like a wall that blocks medicine; however, nanoparticles are designed to get past this wall using several different methods.[40]

4.1. Increased Surface Area:
Because nanoparticles are incredibly small, they have a very large surface area compared to their volume. This increases the contact between the medicine carrier and the skin's surface. This better "stickiness" to the outer skin layer helps the medicine spread and sink into the deeper levels of the skin more effectively. Their tiny size also allows them to slip into hair follicles and small gaps between cells, which improves how well the medicine is delivered.[41]

4.2. Improved Drug Solubility:
Many medications used for skin conditions do not dissolve well in water, which makes it hard for the skin to absorb them. Nanoparticles help these drugs dissolve much faster and more easily. This creates a stronger "push" (concentration gradient) that helps the medicine move naturally through the skin barrier, making more of the drug available at the surface to sink into the deeper layers. [42]

4.3. Interaction with Skin Lipids:
Some nanoparticles, especially those made of fats (lipids), mix with the natural oils in your skin's outer layer. This interaction causes the skin's protective fats to "shuffle" or loosen, temporarily weakening the skin's shield so the medicine can pass through more effectively. They also form a thin, protective film on the surface that traps moisture, which hydrates the skin and further helps the penetration of medicine [43]

4.4. Controlled Drug Release:
Nanoparticles act like tiny storage tanks for medicine. Instead of the drug being used up all at once, the particles release it slowly and steadily over a long period. This keeps the medicine at the right level in your skin for a longer time, which makes the treatment work better and means you do not have to apply the medication as often.[41]

4.5. Targeted Delivery to Inflamed Tissue:
Nanoparticles are very good at gathering in skin that is red, swollen, or diseased because of their small size. They can settle specifically in hair follicles and oil glands, allowing the medicine to go exactly where the problem is such as in cases of acne or psoriasis. This targeted approach improves the results of the treatment while reducing the chance of side effects in the rest of the body. [44]

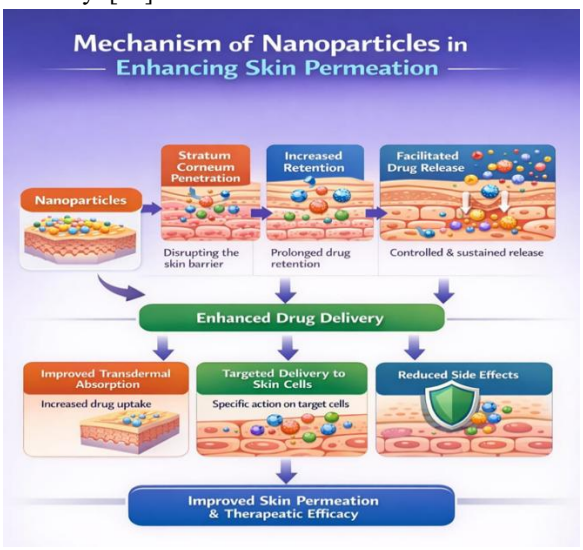

Fig.4.1 Mechanism of Nanoparticles in Enhancing Skin Penetration [45]

V. ANTI-INFLAMMATORY DRUG DELIVERED VIA NANOPATICLES

Examples:

Drug	Nanoparticle System	Therapeutic Application
1) Diclofenac	Solid Lipid Nanoparticles (SLN)	Improved skin penetration, prolonged release, effective in arthritis pain relief [46]
2) Ibuprofen	Nanoemulsion	Enhanced dermal absorption, faster pain relief, reduced gastric irritation [47]
3) Ketoprofen	Polymeric / lipid nanoparticles (commonly reported as SLN or PLGA systems)	Sustained release, reduced inflammation in rheumatoid arthritis [48]
4) Curcumin	Liposome	Improved bioavailability, strong anti-inflammatory and anti - oxidant action [49]
5) Naproxen	Solid lipid nanoparticles (SLN)	Improves bioavailability of poorly soluble naproxen. Enhances transdermal penetration. Provides sustained analgesic and anti-inflammatory action. Useful in arthritis and musculoskeletal inflammation [50]

6) Indomethacin	Nanostructured lipid carriers (NLC)	Increases skin penetration Decreases paw edema Reduces inflammatory mediators (TNF-α, IL-1β) Effective in rheumatoid arthritis [51]
7) Piroxicam	Solid lipid nanoparticles (SLN)	Sustained drug release Improved transdermal delivery Long-lasting anti-inflammatory effect Reduced systemic toxicity [52]
8) Ketoprofen	PLGA / polymeric nanoparticles	Controlled release up to long duration Improved solubility Reduced gastrointestinal irritation Effective in rheumatoid arthritis therapy [53]
9) Celecoxib	Polymeric nanoparticles	Improves dissolution of poorly water-soluble drug Sustained anti-inflammatory activity Reduced dosing frequency [54]

VI. EVALUATION OF NANOPARTICLE-BASED TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery systems (TDDS) are ways to send medicine through the skin and into the bloodstream. The biggest problem with regular skin patches or creams is the stratum corneum (the tough outer layer of the skin). This layer acts like a wall that stops many drugs from getting through. Recently, scientists have focused on using nanoparticles because they help medicine pass through this wall more easily, making the treatment more effective.[55] Nanoparticles are extremely tiny, usually between 10 and 200 nanometers in size. Because they are so small and have a large surface area, they help drugs dissolve better, stay stable, and reach the parts of the body where they are needed. Their tiny size allows them to get very close to the skin's layers, helping the medicine slip through the tough outer barrier.[56]

6.1 Particle Size and Zeta Potential:

Particle size is one of the most important parts of a nanoparticle mix. Smaller particles have more surface area, which helps the medicine spread and soak into the skin better. In these systems, particles are usually between 50 and 300 nm in size.[57] Zeta potential is the electric charge on the surface of the particles. It tells us how stable the mixture is. Particles with a charge higher than +30 mV or lower than -30 mV are usually stable because they push each other away, which stops them from clumping together.[58]

6.2 Drug Loading Efficiency:

Drug loading efficiency (also called entrapment efficiency) is the amount of medicine that successfully gets trapped inside the nanoparticles compared to the total amount used at the start.[59] It is better to have high efficiency so that enough medicine is delivered while using as little carrier material as possible. This efficiency depends on things like the type of material used, how well the medicine dissolves, and how the particles are made, Most of these systems trap between 60% and 90% of the drug.[60]

6.3 In-Vitro Drug Release:

In-vitro studies are lab tests done to see how the medicine leaves the nanoparticles. These tests are usually done using special filters or "Franz diffusion cells" under controlled condition.[61] This helps researchers understand if the medicine is released all at once or slowly over time. Nanoparticles usually release medicine slowly (sustained release), which helps keep a steady amount of the drug in the body for a longer time.[35]

6.4 Skin Permeation Studies:

These studies are done to see how well nanoparticles carry medicine across the skin barrier. They are usually tested in a lab using animal skin or artificial membranes. [62] Because they are tiny and help the medicine dissolve better, nanoparticles are much better at moving through the skin than traditional creams or patches. [57]

6.5 Stability Studies:
Stability studies are done to see how the formula holds up while it is stored on a shelf. Researchers check the particle size, the surface charge, and the medicine content under different conditions. [63]

VII. ADVANTAGES OF NANOPARTICLE-BASED TRANSDERMAL SYSTEMS

Improved Drug Permeability:
Nanoparticles help medicine soak through the tough outer layer of the skin (the stratum corneum) much better. They do this because they have more surface area to touch the skin and they help the drug dissolve more easily.[55]

Controlled Drug Release:
These tiny carriers can release the medicine slowly or at a steady speed. This makes the treatment last longer in the body and means the patient doesn't have to use the medicine as often. [35]

Reduced Systemic Side Effects:
Because the medicine is sent directly through the skin in precise, controlled amounts, it doesn't spread through the whole body in the same way as other methods. This helps lower the chance of unwanted side effects. [60]

Enhanced Therapeutic Efficacy:
By helping the drug pass through the skin better and releasing it slowly over time, nanoparticles make the overall treatment much more effective than traditional methods. [28]

Better Patient Compliance:
Nanoparticle skin systems are painless and easy to use compared to getting a shot (injections) or swallowing pills. Because they are so simple and comfortable to use, patients are more likely to stick to their treatment plan. [59]

VIII. LIMITATIONS AND CHALLENGES

8.1 Skin irritation potential:
Even though nanoparticle systems help medicine sink into the skin better, they can sometimes cause rashes or allergic reactions. Some of the materials used to make these tiny particles, along with the soaps (surfactants) and chemicals that help them penetrate, can mess with the natural oils in the skin's top layer. This can lead to redness, swelling, or soreness. Also, if nanoparticles stay on the skin for too long, they might damage the skin's natural shield or become toxic if the mix isn't made just right. [64] Because of this, scientists must be very careful when choosing the ingredients to make sure the treatment is safe and doesn't hurt the skin.[65]

8.2. Stability issue:
Keeping these tiny particles, stable is a big challenge. Over time, nanoparticles might clump together, sink to the bottom of the bottle, or let the medicine leak out before it's used. This changes how big the particles are and how well the medicine works. Things like heat, acidity (pH), and light can also ruin the formula. [59] To fix this, researchers have to run tests and find the best ways to package the medicine so it stays fresh and effective while sitting on a shelf.[66]

8.3. High Formulation cost:
Making nanoparticle medicines is expensive because it requires high-tech machines, special tools, and pricey raw materials. Creating these particles involves complex methods like high-pressure mixing or evaporating solvents, which need very precise control and fancy equipment. On top of that, making these in huge amounts for everyone to use is much harder and more costly than making regular creams or pills.[60]

8.4 Regulatory challenges:
Getting these products approved by the government is tricky because there aren't many standard rules for "nanomedicine" yet. Authorities need a massive amount of data to prove they are safe, won't be toxic, and won't cause long-term problems.[28] Also, because small changes in the size or surface of a nanoparticle can change how it works, it is hard to keep the quality exactly the same every time. Therefore, we need better global standards and very thorough testing to successfully bring these new treatments to the publish.[67]

IX. RECENT ADVANCE IN NANOPARTICLE TRANSDERMAL SYSTEM

9.1. Microneedle-assisted nanoparticle delivery:
Microneedle-assisted delivery is a new method created to get past the skin’s tough outer layer. These are tiny, microscopic needles that poke very small, temporary

holes in the skin. This allows nanoparticles and medicine to travel deeper into the middle and lower layers of the skin. This technique helps medicine get through more easily while causing almost no pain or damage to the skin. Research shows that using microneedles greatly improves how well nanoparticles like tiny fat bubbles or plastic-like particles move through the skin. [68] Additionally, some microneedles are made of special materials that dissolve once they are inside the skin, releasing the medicine directly where it is needed. This helps control how the drug is released and leads to better healing.[69]

9.2. Stimuli-responsive nanoparticles:
Stimuli-responsive nanoparticles are "smart" particles designed to release their medicine only when they sense a specific trigger. This trigger could be a change in temperature, acidity (pH), light, magnets, or even natural body chemicals called enzymes. Because these systems only release the drug when and where they are supposed to, the treatment works better and causes fewer side effects in the rest of the body. For instance, some particles release medicine when the skin gets warmer, while others react to changes in the skin's pH levels [70]

9.3. Smart nanocarriers:
Smart nanocarriers are advanced delivery systems that can target specific areas, control how fast medicine is released, and work safely with the body's natural tissues. These carriers include tiny fat spheres, solid wax-like particles, and branched structures that wrap up the medicine to keep it from breaking down.[71] Scientists can also "decorate" the surface of these carriers with special molecules that help them stick to or penetrate the skin better. Because they can do so many things at once, they are very promising for treating various skin conditions and internal diseases through the skin. [72]

9.4. Combination therapy approaches:
Combination therapy means using nanoparticle systems to deliver two or more different medicines at the same time. This strategy can make a treatment more powerful by attacking a disease from several different angles at once. Nanoparticles are great at holding different drugs together and letting them out in a steady way. For example, a single nanoparticle could carry both a swelling-reducer and a cell-protector to work together for a better result.[73] This approach is especially helpful for long-term illnesses, infections, and cancer, where using multiple drugs is often necessary to get the best results for the patient.[74]

X. FUTURE PERSPECTIVE

10.1 Personalized transdermal therapy:
Personalized transdermal therapy is all about making drug delivery systems that fit a specific person's body, their specific illness, and even their genetic makeup. Because of improvements in nanotechnology, scientists can now exactly control how fast a drug is released, how big the particles are, and where in the skin they should go to help a specific individual.[75] These custom-made nanoparticle systems can make treatments work much better while causing fewer side effects, which is especially helpful for long-term diseases, hormone treatments, and skin conditions.[76]

10.2. Nanotechnology integration with AI-based drug delivery system:
Combining artificial intelligence (AI) and machine learning with nanotechnology is expected to completely change how we deliver medicine through the skin. AI can predict the best ways to build a nanoparticle, how the drug will release, and how it will move through the skin, which allows researchers to design these systems much faster.[77] Machine learning can also help monitor how a patient is reacting to the medicine in real-time, allowing for a treatment that adapts to the person's needs. This teamwork between AI and nanotechnology could speed up the process of getting these advanced systems out of the lab and into the hands of patients.[78]

10.3. Advanced biodegradable nanocarriers:
Future nanocarriers will likely focus on being biodegradable and safe for the body, ensuring they don't cause long-term toxic effects or harm the environment. These advanced materials like special polymers, fats, or mixtures of both can hold medicine and release it slowly before naturally breaking down and disappearing once their job is done [59] These carriers can be designed to hit specific targets, react to triggers, or carry multiple medicines at once, making them a perfect choice for the next generation of skin-based medical treatments. [78]

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