

A REVIEW ON ELEMENTAL NANOPARTICLES FOR TRANSDERMAL DRUG DELIVERY SYSTEM

Hitesh Mohanty¹, S. Swetha Malika Devi², S Rajarajan³, Beny Baby⁴ and K Ramesh⁵

1-2, 4-5 -Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore- 560064

3- Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore- 560064

ABSTRACT

Nanoparticles are known for their versatility as carriers, and it is providing drug stability, controlled drug release, and increased bioavailability. Transdermal drug distribution uses nanoparticles as a means of cross the skin barrier and allowing targeted as well as long-lasting drug release. Non-invasive transdermal delivery is an attractive option, encouraging patient compliance and comfort levels. Throughout this review, we look at current developments and challenges while employing nanoparticles to deliver transdermal drugs. The combination of nanoparticles with transdermal delivery has great potential to address barriers in traditional drug administration pathways, providing a path to personalized and effective therapeutic interventions for a wide range of medical conditions. As research advances, these advances may revolutionize drug delivery, opening new opportunities for better patient outcomes and improved healthcare practices.

Keywords: Elemental Nanoparticles, Transdermal Drug Delivery, Non-Invasive Drug Delivery

1. INTRODUCTION

One of the least invasive and patient-friendly ways to administer a therapeutic agent is through the transdermal route. Not only does it increase the bioavailability of medication by concentrating the drug molecules in a specific area of the skin, but it additionally minimizes the risk of potential undesirable side effects. Therefore, transdermal medication administration is a desirable substitute for oral administration and hypodermic administration¹. It could be used in more than just pharmaceuticals, it could be used in skin care, including cosmetics. Since it is mainly local administration, it prevents local accumulation of medication concentration as well as non-specific transport to bodily tissues that are not specifically targeted by the drug².

Skin diseases are among the most prevalent non-fungal disorders worldwide. TDDS is among the most effective medication delivery systems in relation to skin diseases owing to its elevated bioavailability and minimal toxicity to the system as well as improved patient compliance³. There are many different types of TDD systems under development, such as: microneedle injections, chemical Penetration Enhancers, Ultrasonic Penetration or Abrasion Physical Barrier Disruption Systems Nanocarriers⁴. This route of drug administration results in higher plasma concentrations and increased

bioavailability than other drug forms containing the same active ingredient⁵.

The benefits of transdermal administration are: No suffering, no blood loss, low dosage, easy self-administration and, high drug integrity. It lowers the risk of side effects from injectable or oral administration. When medications are applied transdermally, they penetrate the circulatory system gradually Prevent the liver's first-pass effect. Boost the healing outcome. Decrease the number of times that drugs are administered long term self-administration is possible Patients with inconvenient traditional administration⁶.

Nanoparticles can be encapsulated to enhance the physicochemical properties of medicines and control the release kinetics. Nanoparticles can improve the medicines pervasiveness through the stratospheric layer (SC) and improve retention in various skin layers⁷. The medication enters the bloodstream through the skin and travels across the body's systems before arriving at its intended location⁸.

Transdermal Drug Delivery with Nano Nanoparticles have grown in popularity in the medicine delivery industry. Nano particles have unique properties that allow them to improve the rate at which drugs pass through the skin's

barrier. Nano-based drug delivery systems offer several benefits, including controlled drug release better medication stability decreased greater medication efficacy systemic side effects characteristics of Sustained drug release improved patient compliance convenient drug administration⁹.

2. TYPES OF ELEMENTAL NANOPARTICLES

2.1. Metallic Silver Nanoparticles

Utilizing silver nanoparticles, there have been anthropogenic processes since ancient times. The low likelihood of certain mutations resulting in Ag-NP resistance has become crucial in the battle of microbiologists against an ever-increasing range of pathogens that are resistant to traditional antibiotics. Due to its relatively low toxicity, allergenicity, and good patient tolerance, Ag-NP

has become increasingly popular in many parts of the world¹⁰. AgNPs are known for their wide-ranging and highly effective anti-microbial and anti-cancer properties. Other biological activities have also been studied in AgNPs, such as immunogenicity, bone and wound healing enhancement in vaccinations, and antidiabetic effects¹¹. Transdermal medication delivery systems are among the many applications that have made extensive use of silver nanoparticles. Because their antibacterial qualities, these nanoparticles have been used to drug delivery systems to improve therapeutic outcomes⁷⁵. Studies have demonstrated that AgNPs capacity to penetrate skin varies depending on their form. AgNPs shape-dependent skin penetration emphasizes how crucial it is to take nanoparticles properties into account when creating topical medications with high efficacy and little systemic toxicity¹.

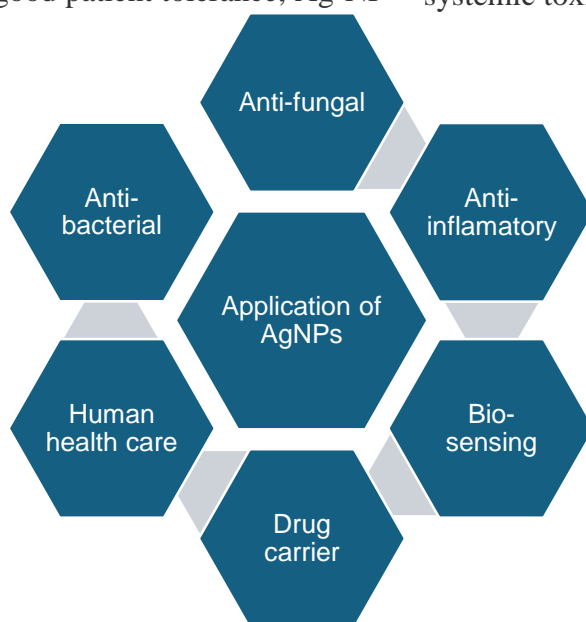


Figure 1: Application of silver nanoparticle

2.2. Gold Nanoparticles

Gold nanoparticles in the 18 to 37 nm range promoted severe toxicity to the spleen, liver, and lungs¹². AuNPs have a variety of chemical-physical properties that make them ideal for high-tech applications like sensing, optoelectronics, biotechnology, nanomedicine, diagnostics, therapeutics, drug delivery systems, and of course, their potential toxicity. One of gold nanoparticles primary benefits is that they can be fine-tuned in size, composition, and function, and thiol-based ligands can be used to create stable,

covalent, and chemically tuneable layers¹³. Transdermal patches are enhanced with gold nanoparticles to improve drug delivery with these cutting-edge methods, side effects are reduced, and medication efficacy is increased⁷⁶. Research aims to advance drug penetration through the skin by using them in transdermal patches. Gold nanoparticles increases medication delivery effectiveness by utilizing techniques including targeting skin lipids and forming microchannels⁷⁷.

2.3. Alloy Nanoparticles

Alloy nanoparticles differ in their structural properties from the bulk samples¹⁴. In Transdermal medication delivery alloy nanoparticles are becoming more and more popular. Alloy nanoparticles maximize therapeutic efficacy while reducing side effects by utilizing their special qualities such as controlled release and biocompatibility⁷⁸. With advantages including local targeting, lower toxicity, and avoiding hepatic metabolism, alloy nanoparticles tiny objects with a diameter of approximately 1-1000nm are becoming more and more popular in transdermal drug delivery⁷⁹.

2.4. Magnetic Nanoparticles

The magnetic drug delivery system works by delivering magnetic particles that are filled with drugs as to the tumour location affected by magnetic field outside the body. Magnetic nanoparticles offer the ability to be administered in a systematic manner nonetheless, focused to a particular location throughout the human body that is nonetheless locally specific through the application within a magnetic field¹⁵. Transdermal medication delivery is significantly aided by magnetic nanoparticles. Due to their intrinsic magnetism, which improves interactions with skin carriers and transdermal penetration, targeted drug administration is made possible⁸⁰. They present a promising option for meeting future medical demands because of their potential to transform clinical care. For medical applications, coating these nanoparticles is necessary to ensure safe medication release and reduce toxicity⁸¹.

2.5. Iron Oxide Nanoparticles

Fe₃O₄ nanoparticles are widely used in energy storage, magnetic fluids, biosensing, biotechnology, catalysis, separation methods, and environmental modification applications. In biotechnology, targeted drug/genetic delivery systems are used for targeted drug delivery, MRI, contrast enhancement, hyperthermia, bio photonics, detection, diagnosis, and magnetic field-assisted radiation therapy of cancerous cells¹⁶. Transdermal medication delivery has demonstrated the potential of super magnetic iron oxide nanoparticles⁸². Transdermal administration methods are non-invasive, and the

skin is easily accessible, which makes it a desirable strategy for achieving localized drug concentrations with minimal systemic toxicity⁸³. To overcome the limits of current treatment, a novel strategy is used that incorporates a microneedle transdermal patch loaded with iron nanoparticles for weekly iron supplement delivery⁸⁴.

3. FUNDAMENTALS OF TRANSDERMAL DRUG DELIVERY

3.1. Skin Barrier

Skin serves as the body's outermost layer, and it's exposed to an extensive range of external sources of oxidative stress, such as UV rays and contaminants¹⁷. Skin contributes significantly to the survival of both animals and humans. Human skin acts as a barrier against the environment; its beautifully designed structure allows for one-directional channelization. The primary functions of skin include protection, maintaining water levels, regulating body temperature, etc¹⁸.

3.2. Nanocarriers as skin Penetration

Largest organ in the human body is skin and performs several different functions like regulating body temperature, avoiding fluid and salt loss, and preventing the entry of pathogens like virus, bacteria, allergen, and toxic chemicals into the body. Skin penetration is a major area of research because of the advantages of skin such as easy accessibility, less systemic side effects and increased therapeutic efficacy. The SC function as a major impediment to the passage among molecules and nanoparticles throughout the skin. Nanoparticles (NPs) have been studied on a cellular level for a variety of biomedical applications. Smart nanoparticles that respond to external environmental conditions such as temperature or pH (by varying their hydrophilic/hydrophobic properties) have demonstrated promising results when addressing the multiple skin condition. However, due to the complex nature among the skin, it is important to tailor Nanoparticles to the chemical and physicochemical properties of the skin. Additionally, understanding how different cells and tissues react to nanoparticles within the skin

is essential for the use of Nanoparticles for pharmaceutical applications¹⁹.

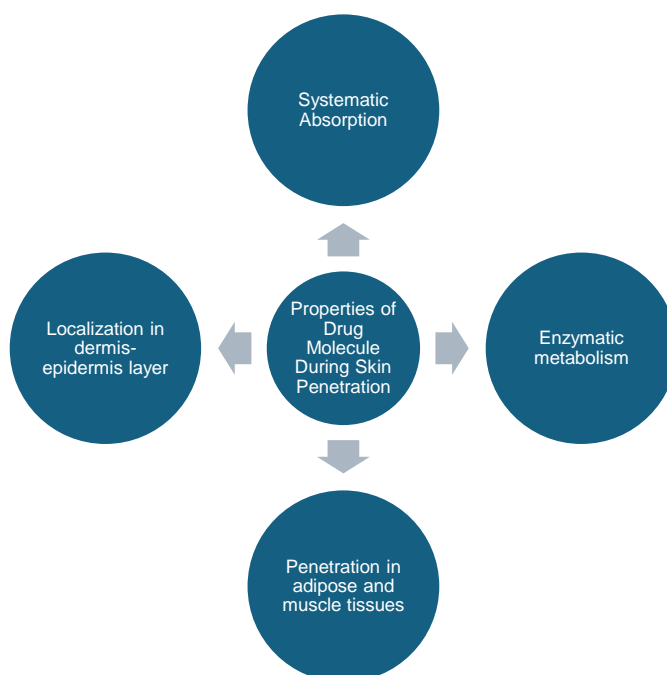


Figure 2: Drug Molecules during Skin Penetration

3.3. Skin Disease treatment with transdermal nanocarriers

Skin disorders are one among the most prevalent non-fungal disorders worldwide. The TDDS has shown to be successful treatment for skin diseases since it is so high bioavailability and low systemic toxicity as well as improved patient compliance. Both medical professionals and patients choose the TDDS to treat skin conditions according to previous studies. The advantages of using the TDDS greater than topical or oral medications include direct skin- contact effects without first-pass effects increased bioavailability in the liver; Maintains a stable blood volume with no peak or effects that peak or valley; low frequency of systemic side impacts; a high level of patient adherence Quick discontinuation of drug administration²⁰.

4. IMPORTANCE OF NANO BASED DDS

Drug delivery systems is a field that deliver medicinal substances or active substances derived from nature their intended site for the management of different illnesses has grown significantly in recent years. There are many

methods for delivering drugs that have been effectively employed lately. Nonetheless, there are still certain difficulties that need to be addressed and cutting-edge technologies must be created to bring medications to their intended locations. The medication delivery with a nanotechnology system is currently being researched to enable the advancement of drug delivery system²¹.

4.1. Fundamental of methods based on nanotechnology for creating drug

Nano systems can be used to deliver drugs at the illness's site to enhance the absorption of poorly soluble drugs, to target drugs to a particular location, as well as to enhance drug bioavailability. Since nanoparticles have a greater easily taken up by cells as opposed to larger molecular, they can be used as efficient delivery and transportation systems. For medicinal purposes, drugs can be incorporated within the matrix of particles or adhered to the surface of their particles. Nanoscale structures with diverse components in addition to bioactive qualities have been studied used for the delivery

of drugs and gens purposes. A successful strategy for reaching effective medication administration is to systematically create nano systems based on knowledge of how they interact with their target cell population, the biological environment, the target cell surface receptors, and modifications to

cell receptors as disease progresses, and the mechanisms and sites drugs action, drug retention, administration of numerous drugs, molecular processes, and the disease pathobiology with relation to consideration²².



Figure 3: Applications and objectives of nanomedicine in several biomedical research fields

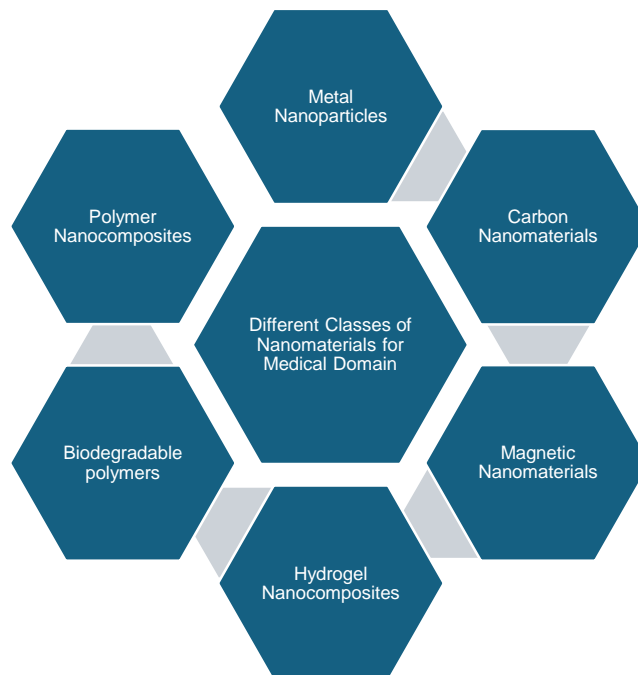


Figure 4: Classes of Nanomaterials for Medical Domain

4.2.1. Delivery of Drug

Initial nanoparticle-based drug delivery systems based on nanotechnology comprise one or more therapeutically active drugs that unite, scatter, or adsorbed on polymer matrix. Over the past few years, there has been significant

progress in the production of nano-drugs using imaging, treatments, or diagnostics. The primary objectives of nanomedicine systems

are to improve tissue delivery biological accessibility, extend the duration of injectable medicines, and administer medicinal products orally. Nano drugs are administered at low doses, resulting in significant improvements in their pharmacological properties and a decreased risk of health and side effects²³.

4.2.2. Diagnostic Techniques

In recent years, imaging has become one of the most powerful tools for diagnosing disease. Advancements in magnetic resonance imaging (MRIs) and computer tomography (CTIs) are impressive, but nanotechnology provides in vitro and in vivo diagnostic tools that are sensitive and highly precise, far beyond the capabilities of modern equipment. Like all advances in diagnostics, the goal is to enable doctors to diagnose disease early. It is expected that nanotechnology will enable cellular diagnostics and possibly sub-cellular diagnostics²⁴.

4.3. Method of Preparation

4.3.1. Method of Emulsion/ Solvent Evaporation

Evaporation of solvent involves the preparation of polymer solutions in volatiles and the formation of emulsions by evaporation of the solvent. Ethyl acetate was initially used as the solvent but has since been replaced by ethyl acetate due to its improved toxicity profile. The solvent is evaporated, and the emulsion converted into nanoparticle suspension. The solution is dispersed through the continuous emulsion phase using conventional methods such as single emulsion, such as oil in water and two-phase emulsion (water within water). Once the emulsion is formed, it is homogenized, and the solvent is evaporated. Continuous magnetic stirring can be done either at ambient temperature or with lower pressure can be used. After solidifying, the nanoparticles are gathered and cleaned to get rid of the surfactants. The final product is then lyophilised²⁵.

4.3.2. Double Emulsion and Solvent evaporation method

Double emulsions can be used for micronutrient delivery, mineral delivery, as well as medication administration because of special structure and encapsulation properties. Double emulsions offer several benefits over other encapsulation methods: They can be used directly as wet emulsions or mixed with other methods such as spray-drying to produce transportable powders. The double emulsion can be ready using a two-step or one-step process. The one-step method combines the oil and the watery phase in one step, often using microfluidics to control droplet size and form. The emulsion interface is engineered by selecting the appropriate ingredients to increase the stability of encapsulated components. Simulatively responsive block copolymers or nanoparticles can stabilize the emulsion, eliminating the need for separate emulsifiers and improving the process efficiency²⁶.

4.3.3. Salting out Method

The method of salting out uses the Salting-Out effect to precipitate nanoparticles. Because salts are present in the system, no solvent diffusion step is required. The organic phase of the emulsion includes the polymer in an aqueous water-machined a natural solvent. The solvent is dissolved in water while swirling the emulsion to reduce ionic strength and improve solvent diffusion. As the dissolver migrates transforming from the natural to the anhydrous phase, nanoparticles are precipitated in the dilution process. The filtering acrossflow removes the salting out agent and nanoparticles are extracted²⁷.

4.3.4. Emulsion Diffusion Method

Under the emulsion diffusion process, the polymer-containing solvent is dispersed from emulsion droplets to the external phase (typically water). Due to the solvent diffusion, nanoparticles are precipitated out of the solvent as the polymer changes solubility²⁸.

4.3.5. Method of Solvent Displacement and Precipitation

Using the solvent displacement approach, the addition within a polymer dissolved in an

aqueous semipolar organic solvent. The polymer is then precipitated into colloidal particles. The preferred method for nanoparticle preparation by solvent displacement is to quickly introduce the organic component of the solvent into the anhydrous phase. The faster the organic phase is mixed with the anhydrous, the smaller the colloidal particles will be. The speed at which the solvent that is organic passes using the interface determines the particle size. Higher velocities result in smaller nanoparticles²⁹.

4.4. Evaluation

4.4.1. Particle Sizes and Zetapotential

The scanning electrons microscope (SEM) was employed to measure the size of the particles in the nanoparticles. The polymer load affects the size of the particles and ranges between 350 and 600nm. Zeta potential and particle size were calculated using the Zetasizer³⁰.

4.4.2. Entrapment Efficiency

The difference between the total amount of drug utilized to generate the nanoparticles and the amount of drug present in the aqueous solution was used to calculate the amount of drug entrapped in the nanoparticles medium³¹.

4.4.3. Scanning Electron Microscopy (SEM)

Prepared nanoparticles are analysed for surface morphology using scanning electron microscope (SEM) analysis. All formulations were prepared by coating silica wafers with nanoparticle suspension, adhering to aluminium stubs fitted with sticky tapes, covered in gold sputter coat, and their morphology examined at 20 kV³².

4.4.4. Differential Scanning Calorimetry (DSC)

The data of DSC is obtained to understand the thermal behaviour of the medication in nanoparticles. Nanoparticles and polymers were deposited right into the various sealed aluminium pan of conventional size and were scanned at temperatures ranging from utilizing an empty aluminium pan as a heating pan, 25°C to 300°C with a heating rate of 10°C/min in a nitrogen environment³³.

4.4.5. Diffraction Analysis of X-rays

X-ray diffraction (XRD) is an effective method widely used to investigate the structure of components, including nanoparticles. When applied to nanoparticles, XRD provides valuable information about their crystal structure, size, and orientation³⁴.

4.4.6. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR in nanoparticles analyses infrared light absorption to reveal composition, surface modifications, and structural characteristics, aiding in quality control, synthesis optimization, and understanding interactions for diverse applications like drug delivery and nanomaterial research³⁵.

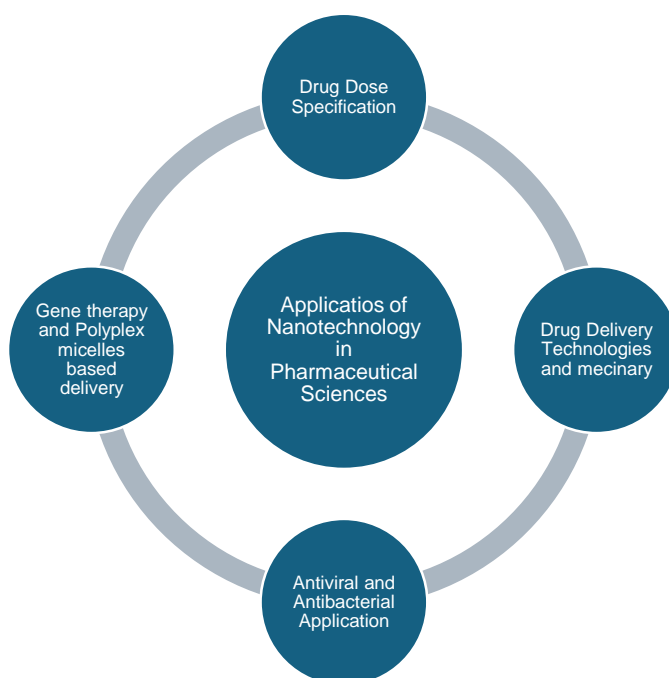
4.5. Applications of Nanotechnology in Pharmaceutical Sciences

Pharmaceutical Nanotechnology is concerned with the creation and evolution of nanostructures such as nano-atom, nano-molecule or nano-compound nanostructures with wavelengths ranging from 0.1 nm to 100 nanometres. Nanotechnology in pharmacy is helping to develop more sophisticated drug delivery systems and is therefore an important and effective alternative to traditional dosage forms such as tablets, capsules, etc. Pharmaceutical nanotechnology has significantly contributed to overcoming some of the drawbacks of traditional dosage forms³⁶. The field of nanotechnology has completely transformed pharmacology by enabling the creation of medication delivery methods that are more effective and less likely to cause adverse side effects. Recent developments and medication delivery applications highlight the potential use of nanotechnology in diagnosing and treating diseases. Nanomedicine utilizes nanotechnology to enhance drug delivery to target organs, enabling physicians to achieve optimal drug effectiveness and safety³⁷.

The emergence of nanotechnology over the past 35 years has opened many doors in medical science, particularly in drug delivery. Biotechnology has produced some powerful drugs, but many of them face challenges in

delivering them in biological systems. The nanotech and drug delivery market will have a

significant impact on the pharmaceutical industry³⁸.



4.2. Nanotechnology used in different medical field

5. NANOPARTICLES TDDS

5.1. Reservoir type Transdermal Patch

A reservoir TDDS has the capacity to disperse medication consistently and under control for an extended length of time³⁹. A reservoir- style transdermal drug delivery device is a patch with a liquid drug layer kept apart from the skin by a rate- regulating membrane. At a regulated pace the medication diffuses through the membrane and into the skin. By altering the membranes composition and thickness this kind of technology can simply be changed to deliver medications with various physicochemical qualities⁴⁰.

5.2. Matrix system

5.2.1. Drug Adhesive System

Drugs are delivered via adhesive patches used on the skin in the drug delivery method applied topically a revolutionary method⁴¹. In the Medication in Adhesive structure the drug is directly distributed throughout a sticky polymer, when applied to the skin, the drug permeates through the adhesive⁴².

5.2.2. Matrix Dispersion system

One kind of Transdermal drug delivery method is matrix dispersed system, which have a drug uniformly distributed within a polymer matrix⁴³. The medication permeates the skin barrier after diffusing from the matrix to the skin's surface⁴⁴.

5.3. Micro reservoirs type transdermal patch

The Micro-reservoir system is an intriguing method for transdermal medication administration⁴⁵. This technique uses small shapes as the supply of drugs, which are produced by stopping the use of drugs particles in an aqueous liquid polymer solution that dissolves in water. Next, utilizing a high shear mechanical stress, these micro-reservoirs are uniformly distributed throughout a lipophilic polymer⁴⁶.

5.4. Membrane matrix Hybrid type patch

The characteristics of both matrix and membrane-based Transdermal patches are combined in a membrane matrix hybrid type patch. It utilizes a matrix structure for ease of construction while incorporating a membrane to enhance drug delivery efficiency⁴⁷. The

purpose of these patches is to deliver medications under epidermal control. Membrane matrix hybrid provide improved drug release control, yet matrix patches are like build⁴⁸.

5.5. Regimens of TDDS

5.5.1. Patch application and Wear time

The process of applying patch involves cleaning and drying the area to be covered, removing the backing, and pressing the patch firmly into the skin. Depending on the medicine and patch, the wear period can vary, although it usually lasts anywhere from a few hours to several days⁴⁹. Current market patches have a wear time of seven to eight days, depending on the pharmaceutical kind and dosage. For example, once daily application of nitro-glycerine patches, which are worn for 12 to 14 hours before being removed⁵⁰.

5.5.2. Duration of Therapy

Achieving the desired therapeutic effects of Transdermal therapy, which applies medication via patches, depends on how long the treatment is administered for. A patient's unique circumstances, the drug being taken, and the illness being treated all influence how long therapy is advised to last. Transdermal patches often have a predetermined duration of use, such 72 hours, during which they are intended to administer medication gradually and then need to be replaced. Maintaining constant medication levels in the body and maximizing treatment effectiveness need adherence to the recommended therapy duration⁵¹.

5.5.3. Patch placement

The area of the upper arm, upper back, belly, chest, and thighs are where patches are placed. Based on variables including skin permeability, absorption site has special benefits. For optimal drug absorption and therapeutic results, the patch must be placed correctly⁵¹.

5.5.4. Monitoring and Adjustment

Drug Delivery and skin moisture are two areas where Transdermal patches must be monitored and adjusted⁵². Optimal therapy outcomes require constant monitoring and adjustments of Transdermal drug delivery system. Assessing drug absorption skin integrity and potential side effects are all part of routine monitoring. Patch placement adjustments, adhesion checks, and skin reaction management are a few examples of adjustments⁵³.

5.5.5. Adhesive properties and patch integrity

Pressure sensitive adhesives are the glue that transdermal drug delivery systems use to stick to the skin. These adhesives are vital for preserving patch integrity since they adhere with little pressure. The three main characteristics of an adhesive are peel adhesion, creep resistance, and tack⁵⁴. To stop drug leakage or dislodgment, the patch must also retain its integrity while being worn. Successful transdermal medication administration requires ensuring adequate adhesion and patch endurance⁵⁵.

6. EVALUATION OF NANOPARTICLES TDDS

6.1. Flux

The rate at which nanosized drug carriers can cross the skin's protective layer and reach the bloodstream is known as the flux of nano transdermal drug delivery⁵⁶. Several variables, including the drug's qualities, the skin's features, and size, shape, charge, and composition of the nanocarriers, affect the flow of nano transdermal drug delivery⁵⁷. Particularly for hydrophilic and macromolecular medications, nano transdermal drug administration can attain a greater drug flow than traditional techniques. Medicines to be delivered to the skin, precise management of flux guarantees efficient and regulated release, maximizing therapeutic benefits and reducing adverse effects⁵⁸.

6.2. Permeation Enhancers

Skin permeation enhancers are agents that can make the skin more permeable to medications applied topically using transdermal

nanocarriers⁵⁹. Enhancers of skin permeation are compounds that make the skin more permeable to medications deposited by nanocarriers⁶⁰. Drugs can be delivered via the skin barrier using a revolutionary technique called nano transdermal drug delivery, which makes use of nanocarriers such liposomes, nanoparticles, and dendrimers⁴⁸. Functional nano systems could increase drug concentration in the internal tissues⁶¹. And improve drug penetration across the skin barrier⁶¹. Drug can enter the skin and arrive at the target skin layers or the systemic circulation using skin penetration enhancers, which make the skin more permeable⁶².

6.3. Ex vivo

Ex vivo skin penetration is a technique use to assess a medications capacity to pass through the skin barrier after being administered Trans dermally. It entails putting the drug formulation typically delivered from human or animal sources to a section of skin that has been removed, then tacking how much of the medication eventually reaches the other side of

the skin⁶³. Usually, removed skin from humans or animals⁶⁴. It is used to evaluate the effectiveness and quality of products⁶⁵. Improve treatment efficacy by shedding light on the drug behaviour outside of the stratum corneum⁵⁷.

6.4. In vivo

In vivo Transdermal medication distribution refers to the application of medication via the skin, obviating the need for the digestive track. It provides better patient compliance and regulated discharge⁵⁷. Transdermal drug delivery in vivo research aims to penetrate the epidermal barrier for efficient administration of medicinal and cosmetic items⁶⁶. The permeation process is affected by variables like drug concentration partition coefficient, and molecule size⁶⁷. Studies conducted in vivo are essential for converting results from In vitro and Ex vivo research into practical applications because they shed light on the intricate relationships that exists between the medication, the skin, and the systemic circulation⁶⁸.

Table-1: Nanocarrier-based transdermal medication delivery.

Classification	Method of Penetration	Drugs	Treatable Illnesses	References
Dendrimers	Intercellular route	8-methoxypsoralene		69
Transferosomes	Intracellular Pathway	Dexamethasone	Skin Disease	70
SLNs	Accessory pathway	Fluconazole	Pityriasis rosea	71
NLCs	Accessory pathway	traconazole	Fungal infection	72
Nanoemulsions	Accessory pathway	Methotrexate	Psoriasis	73
Microemulsions	Accessory pathway	Retinol palmitate	Acne, skin aging, psoriasis	74

7. CURRENT & FUTURE PROSPECTS

In Future developments in nanotechnology in combination with personalized formulations will allow for the accurate regulation of medication release kinetics and giving idea to the new era of drug administration that is patient-centric and effective. Non-intrusive transdermal delivery approaches promise improved patient compliance. These approaches are essential for the future of healthcare and are expected to revolutionize drug administration.

8. CONCLUSION

According to this review Nanoparticles can be improve the stability and solubility as well as to improve bioavailability when it is encapsulated with the drug. Also, it gives unique advantages like improved medication stability, targeted distribution, and controlled release which can Significantly enhance the efficacy and safety of treatments. The main purpose of using Transdermal administration of medication is to provide a non-distant and convenient technique for medication administration. Also, this route allows for a sustained and controlled release of drugs, maintaining steady therapeutic levels and minimizing fluctuations. The combination of transdermal nanoparticles-based drug delivery gives an attractive option provides an extensive array of medical conditions. Also, this combination allows for exact regulation of medication release kinetics, prolonged healing effects, and reduced adverse consequence.

9. REFERENCE

1. Liu L, Zhao W, Ma Q, Gao Y, Wang W, Zhang X, Dong Y, Zhang T, Liang Y, Han S, Cao J. Functional nano-systems for transdermal drug delivery and skin therapy. *Nanoscale Advances*. 2023;5(6):1527-58.
2. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: A review. *Biomaterials research*. 2021 Dec; 25:1-5.
3. Cheng T, Tai Z, Shen M, Li Y, Yu J, Wang J, Zhu Q, Chen Z. Advance, and challenges in the treatment of skin diseases with the transdermal drug delivery system. *Pharmaceutics*. 2023 Aug 21;15(8):2165.
4. Palmer BC, DeLouise LA. Nanoparticle-enabled transdermal drug delivery systems for enhanced dose control and tissue targeting. *Molecules*. 2016 Dec 15;21(12):1719.
5. Reddy G, Durga G, Srilekha Y, Ratnakumari P. Review on Transdermal drug delivery system. *International Journal of Pharmaceutics and Drug Analysis*. 2021 Dec 31:236-40.
6. Li Z, Fang X, Yu D. Transdermal drug delivery systems and their use in obesity treatment. *International Journal of Molecular Sciences*. 2021 Nov 25;22(23):12754.
7. Madawi EA, Al Jayoush AR, Rawas-Qalaji M, Thu HE, Khan S, Sohail M, Mahmood A, Hussain Z. Polymeric nanoparticles as tunable nanocarriers for targeted delivery of drugs to skin tissues for treatment of topical skin diseases. *Pharmaceutics*. 2023 Feb 15;15(2):657.
8. Wong WF, Ang KP, Sethi G, Looi CY. Recent Advancement of Medical Patch for Transdermal Drug Delivery. *Medicina*. 2023 Apr 17;59(4):778.
9. Marzouk M, Elbakry AM, Elhosary R, Abd ElRahman NK. Polymeric Nanoparticles Based Transdermal Hydrogel of Terbutaline Sulphate: Formulation and Evaluation. *Azhar International Journal of Pharmaceutical and Medical Sciences*. 2023 Jun 1;3(2):20-9.
10. Mikhailov OV, Mikhailova EO. Elemental silver nanoparticles: biosynthesis and bio applications. *Materials*. 2019 Sep 27;12(19):3177.
11. Xu L, Wang YY, Huang J, Chen CY, Wang ZX, Xie H. Silver nanoparticles: Synthesis, medical applications, and biosafety. *Theranostics*. 2020;10(20):8996.
12. Hsiao PF, Peng S, Tang TC, Lin SY, Tsai HC. Enhancing the in vivo transdermal delivery of gold nanoparticles using poly (ethylene glycol) and its oleylamine conjugate. *International journal of nanomedicine*. 2016 May 2:1867-78.
13. Bessar H, Venditti I, Benassi L, Vaschieri C, Azzoni P, Pellacani G, Magnoni C, Botti E, Casagrande V, Federici M, Costanzo A. Functionalized gold nanoparticles for topical delivery of methotrexate for the possible treatment of psoriasis. *Colloids and Surfaces B: Biointerfaces*. 2016 May 1;141:141-7.
14. Kumari B. A Review on Nanoparticles: Their Preparation method and applications. *Ind Res J Pharm Sci*. 2018;5(2):1420.
15. Mody VV, Cox A, Shah S, Singh A, Bevins W, Parihar H. Magnetic nanoparticle drug delivery systems for targeting tumor. *Applied Nanoscience*. 2014 Apr;4:385-92.
16. Shen L, Li B, Qiao Y. Fe₃O₄ nanoparticles in targeted drug/gene delivery systems. *Materials*. 2018 Feb 23;11(2):324.
17. Vinardell MP, Mitjans M. Nanocarriers for delivery of antioxidants on the skin. *Cosmetics*. 2015 Oct 10;2(4):342-54.
18. Mishra DK, Pandey V, Maheshwari R, Ghode P, Tekade RK. Cutaneous and transdermal drug delivery: Techniques and delivery systems. In *Basic Fundamentals of Drug Delivery* 2019 Jan 1 (pp. 595-650).

19. Tiwari N, Osorio-Blanco ER, Sonzogni A, Esporrín-Ubieto D, Wang H, Calderón M. Nanocarriers for skin applications: where do we stand. *Angewandte Chemie International Edition*. 2022 Jan 17;61(3): e202107960.
20. Cheng T, Tai Z, Shen M, Li Y, Yu J, Wang J, Zhu Q, Chen Z. Advance and challenges in the treatment of skin diseases with the transdermal drug delivery system. *Pharmaceutics*. 2023 Aug 21;15(8):2165.
21. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez-Torres MD, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S. Nano based drug delivery systems: recent developments and future prospects. *Journal of nanobiotechnology*. 2018 Dec;16(1):1-33.
22. Groneberg DA, Fischer A. Occupational medicine and toxicology. *Journal of Occupational Medicine and Toxicology*. 2006 Dec; 1:1-2.
23. Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of Nanotechnology in Medical field. *Global Health Journal*. 2023 Feb 25.
24. Malik S, Muhammad K, Waheed Y. Emerging applications of nanotechnology in healthcare and medicine. *Molecules*. 2023 Sep 14;28(18):6624.
25. Tyagi S, Pandey VK. Research & Reviews: *Journal of Pharmaceutics and Nanotechnology*. JPN. 2016; 4:2-12.
26. Saffarionpour S. One-step preparation of double emulsions stabilized with amphiphilic and stimuli-responsive block copolymers and nanoparticles for nutraceuticals and drug delivery. *JCIS Open*. 2021 Oct 1; 3:100020.
27. Pulingam T, Foroozandeh P, Chuah JA, Sudesh K. Exploring various techniques for the chemical and biological synthesis of polymeric nanoparticles. *Nanomaterials*. 2022 Feb 8;12(3):576.
28. Pineda-Reyes AM, Delgado MH, de la Luz Zambrano-Zaragoza M, Leyva-Gómez G, Mendoza-Munoz N, Quintanar-Guerrero D. Implementation of the emulsification-diffusion method by solvent displacement for polystyrene nanoparticles prepared from recycled material. *RSC advances*. 2021;11(4):2226-34.
29. Beck-Broichsitter M, Rytting E, Leubhardt T, Wang X, Kissel T. Preparation of nanoparticles by solvent displacement for drug delivery: a shift in the “ouzo region” upon drug loading. *European Journal of Pharmaceutical Sciences*. 2010 Oct 9;41(2):244-53.
30. Rathod AV, Katekar VA, Deshmukh SP. A review: Recent advancement in the formulation and evaluation of the nanoparticles and its application. *GSC Biological and Pharmaceutical Sciences*. 2023;25(2):116-22.
31. Munjal M. Nanoparticles-Preparation, technology, evaluation and used in targeted drug delivery system. *Technology*. 2018; 14:15.
32. Sadozai SK, Khan SA, Karim N, Becker D, Steinbrück N, Gier S, Baseer A, Breinig F, Kickelbick G, Schneider M. Ketoconazole-loaded PLGA nanoparticles and their synergism against *Candida albicans* when combined with silver nanoparticles. *Journal of Drug Delivery Science and Technology*. 2020 Apr 1; 56:101574.
33. Chauhan m, Varma Ak. Indian Journal of Novel Drug Delivery. *Indian Journal of Novel Drug Delivery*. 2022 Jan;14(1):8-15.
34. Sharma R, Bisen DP, Shukla U, Sharma BG. X-ray diffraction: a powerful method of characterizing nanomaterials. *Recent Res Sci Technol*. 2012 Oct 19;4(8):77-9.
35. Faghhi Zadeh F, Anaya NM, Schiffman LA, Oyanedel-Craver V. Fourier transform infrared spectroscopy to assess molecular-level changes in microorganisms exposed to nanoparticles. *Nanotechnology for environmental engineering*. 2016 Dec; 1:1-6.
36. Swapna, G., Sree, P. T., & Mahitha, M. M. (2023). Applications of Nanotechnology in Drug Development. *Austin Pharmacol Pharm*, 7(1), 1024–1027.
37. Marquez O, Márquez J. Synthesis of electrocatalysts for electrochemistry in energy. In *Advanced Solid Catalysts for Renewable Energy Production 2018* (pp. 300-385).
38. Gazi AS, Krishna Sailaja A. Applications of Nanoparticles in Drug Delivery System: A Review. *Curr Trends Phyto-medicine Clin Ther*. 2019; 1:102.
39. Jayaprakash R, Hameed J, Anupriya A. An overview of transdermal delivery system. *Asian J Pharm Clin Res*. 2017;10(10):36-40.
40. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems. *Pharmaceutical technology*. 2002 May;26(5):62-81.
41. Waghulde S. Development, recent inventions, and evaluation techniques of transdermal drug delivery system-a review. *International Journal of Pharmaceutical and Phytopharmacological Research*. 2014 Feb 8;3(2).
42. Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: an overview. *Int J Pharm Sci Rev Res*. 2010 Jul;3(2):49-54.
43. Gandhi, K., Dahiya, A., Monika, Kalra, T., & Singh, K. (2012). Transdermal drug delivery - A review. *International Journal of Research in Pharmaceutical Sciences*, 3(3), 379–388.
44. Pathway, R., Cheraghali, R., Moradi, S., & Sepehrian, H. (2014). Research and Reviews: *Journal of Pharmaceutics and Nanotechnology*. *Journal of Pharmaceutics and Nanotechnology*, 2(2), 17–20.
45. Rao, V. S. V., Pravallika, M. P., & Jagathi, P. (2023). *Mini Review: Recent Trends in Transdermal Drug Delivery Systems*. 12(8), 8700–8713.
46. Upadhyay G, Verma S, Parvez N, Sharma PK. Recent trends in transdermal drug delivery system-a review. *Advances in biological research*. 2014;8(3):131-8.
47. Sharma N. A brief review on transdermal patches. *Organic & Medicinal Chemistry International Journal*. 2018;7(2):58-62.0
48. Sitaram, J. A., Jaydeep, P., & Sunil, P. (2023). *An Overview On transdermal patch-Past , Present and Future Perspective*. 8(2), 206–222.

49. He J, Zhang Y, Yu X, Xu C. Wearable patches for transdermal drug delivery. *Acta Pharmaceutica Sinica B*. 2023 May 15.
50. Rahman A, Ray B, Yadav S, Mishra S, Rai JK, Jena J. A Review on Transdermal Patch and Marketed Preparations.
51. Defraeye T, Bahrami F, Ding L, Malini RI, Terrier A, Rossi RM. Predicting transdermal fentanyl delivery using mechanistic simulations for tailored therapy. *Frontiers in pharmacology*. 2020 Sep 29;11:585393.
52. Lindley-Hatcher H, Wang J, Hernandez-Serrano AI, Hardwicke J, Nurumbetov G, Haddleton DM, Pickwell-MacPherson E. Monitoring the effect of transdermal drug delivery patches on the skin using terahertz sensing. *Pharmaceutics*. 2021 Dec 1;13(12):2052.
53. Bharadwaj S, Garg VK, Sharma PK, Bansa M, Kumar N. Recent advancement in transdermal drug delivery system. *International Journal of Pharma Professional's Research (IJPPR)*. 2011;2(1):212-9.
54. Bird D, Ravindra NM. Transdermal drug delivery and patches—An overview. *Medical Devices & Sensors*. 2020 Dec;3(6):e10069.
55. Lei Y, Yang G, Du F, Yi J, Quan L, Liu H, Zhou X, Gong W, Han J, Wang Y, Gao C. Formulation and Evaluation of a Drug-in-Adhesive Patch for Transdermal Delivery of Colchicine. *Pharmaceutics*. 2022 Oct 21;14(10):2245.
56. Valeveti sk, pashikanti s. Design, development, and evaluation of transdermal patches containing memantine hydrochloride. *Int j app pharm*. 2023;15(5):181-97.
57. Singh I, Sri P. Percutaneous penetration enhancement in transdermal drug delivery. *Asian Journal of Pharmaceutics (AJP)*. 2010;4(2).
58. Trivedi D, Goyal A. Formulation and evaluation of transdermal patches containing dexketoprofen trometamol. *Int. J. Pharm. Chem. Anal*. 2020;7(2):87-97.
59. Neupane R, Boddu SH, Renukuntla J, Babu RJ, Tiwari AK. Alternatives to biological skin in permeation studies: Current trends and possibilities. *Pharmaceutics*. 2020 Feb;12(2):152.
60. Sugumar V, Hayyan M, Madhavan P, Wong WF, Looi CY. Current Development of Chemical Penetration Enhancers for Transdermal Insulin Delivery. *Biomedicines*. 2023 Feb 22;11(3):664.
61. Damgalı Ş, Özdemir S, Kaya G, Demirkoz AB, Üner M. Development of monolithic matrix type transdermal patches containing cinnarizine: Physical characterization and permeation studies. *Brazilian Journal of Pharmaceutical Sciences*. 2022 Jul 13;58.
62. Mathur V, Satrawala Y, Rajput MS. Physical and chemical penetration enhancers in transdermal drug delivery system. *Asian Journal of Pharmaceutics (AJP)*. 2010;4(3).
63. Ezenwobodo, & Samuel, S. (2022). *International Journal of Research Publication and Reviews*. *International Journal of Research Publication and Reviews*, 04(01), 1806–1812.
64. Shirisha S, Joshi G, Sahoo SK, Rao YM. Preparation and evaluation of matrix type transdermal patches of domperidone maleate: In vitro and ex vivo Characterization. *Indian J Pharm Educ Res*. 2017 Oct 1;51(4):517-24.
65. Al Hanbali OA, Khan HM, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: Design and current approaches to painless drug delivery. *Acta Pharmaceutica*. 2019 Jun 30;69(2):197-215.
66. Defraeye, T., Bahrami, F., Ding, L., Malini, R. I., Terrier, A., & Rossi, R. M. (2020). Predicting Transdermal Fentanyl Delivery Using Mechanistic Simulations for Tailored Therapy. *Frontiers in Pharmacology*, 11(September), 1–23. <https://doi.org/10.3389/fphar.2020.585393>
67. Tanwar H, Sachdeva R. Transdermal drug delivery system: A review. *International journal of pharmaceutical sciences and research*. 2016 Jun 1;7(6):2274.
68. Alam MI, Alam N, Singh V, Alam MS, Ali MS, Anwer T, Safhi MM. Type, preparation and evaluation of transdermal patch: a review. *World journal of pharmacy and pharmaceutical sciences*. 2013 May 21;2(4):2199-233.
69. Borowska K, Wołowicz S, Rubaj A, Główniak K, Sieniawska E, Radej S. Effect of polyamidoamine dendrimer G3 and G4 on skin permeation of 8-methoxypsoralene—In vivo study. *International journal of pharmaceutics*. 2012 Apr 15;426(1-2):280-3.
70. Cevc G, Blume G. Hydrocortisone and dexamethasone in very deformable drug carriers have increased biological potency, prolonged effect, and reduced therapeutic dosage. *Biochimica et Biophysica Acta (BBA)-Biomembranes*. 2004 May 27;1663(1-2):61-73.
71. El-Housiny S, Shams Eldeen MA, El-Attar YA, Salem HA, Attia D, Bendas ER, El-Nabarawi MA. Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasis versicolor: formulation and clinical study. *Drug Delivery*. 2018 Jan 1;25(1):78-90.
72. Passos JS, de Martino LC, Dartora VF, de Araujo GL, Ishida K, Lopes LB. Development, skin targeting and antifungal efficacy of topical lipid nanoparticles containing itraconazole. *European Journal of Pharmaceutical Sciences*. 2020 Jun 15;149:105296.
73. Rashid SA, Bashir S, Naseem F, Farid A, Rather IA, Hakeem KR. Olive oil based methotrexate loaded topical nanoemulsion gel for the treatment of imiquimod induced psoriasis-like skin inflammation in an animal model. *Biology*. 2021 Oct 31;10(11):1121.
74. Algahtani MS, Ahmad MZ, Ahmad J. Nanoemulgel for improved topical delivery of retinyl palmitate: formulation design and stability evaluation. *Nanomaterials*. 2020 Apr 28;10(5):848.
75. Naves L, Dhand C, Almeida L, Rajamani L, Ramakrishna S, Soares G. Poly (lactic-co-glycolic) acid drug delivery systems through transdermal pathway: an overview. *Progress in biomaterials*. 2017 May;6:1-1.
76. Lee J, Kim J, Go J, Lee JH, Han DW, Hwang D, Lee J. Transdermal treatment of the surgical and burned wound skin via phytochemical-capped gold nanoparticles. *Colloids and Surfaces B: Biointerfaces*. 2015 Nov 1;135:166-74.

77. Friedman N, Dagan A, Elia J, Merims S, Benny O. Physical properties of gold nanoparticles affect skin penetration via hair follicles. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2021 Aug 1;36:102414.
78. Ting CK, Dhawan U, Tseng CL, Alex Gong CS, Liu WC, Tsai HD, Chung RJ. Hyperthermia-induced controlled local anesthesia administration using gelatin-coated iron–gold alloy nanoparticles. *Pharmaceutics*. 2020 Nov 16;12(11):1097.
79. Shanmugasundaram T, Radhakrishnan M, Gopikrishnan V, Kadirvelu K, Balagurunathan R. In vitro antimicrobial and in vivo wound healing effect of actinobacterially synthesised nanoparticles of silver, gold and their alloy. *RSC advances*. 2017;7(81):51729-43.
- 80-Chen AZ, Chen LQ, Wang SB, Wang YQ, Zha JZ. Study of magnetic silk fibroin nanoparticles for massage-like transdermal drug delivery. *International journal of nanomedicine*. 2015 Jul 21:4639-51.
81. Murthy SN, Sammeta SM, Bowers C. Magnetophoresis for enhancing transdermal drug delivery: Mechanistic studies and patch design. *Journal of Controlled Release*. 2010 Dec 1;148(2):197-203.
82. Arias LS, Pessan JP, Vieira AP, Lima TM, Delbem AC, Monteiro DR. Iron oxide nanoparticles for biomedical applications: a perspective on synthesis, drugs, antimicrobial activity, and toxicity. *Antibiotics*. 2018 Jun 9;7(2):46.
83. Gaharwar US, Paulraj R. Iron oxide nanoparticles induced oxidative damage in peripheral blood cells of rat. *Journal of Biomedical Science and Engineering*. 2015 Apr 7;8(04):274.
84. Coricovac DE, Moacă EA, Pinzaru I, Cîtu C, Mihali CV, Tsatsakis A. Biocompatible colloidal suspensions based on magnetic iron oxide nanoparticles: synthesis, characterization and toxicological profile. *Frontiers in Pharmacology*. 2017 Mar 28;8:244254.